UNIVERSITY OF
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Reductive Homocoupling from Samarium to Ytterbium

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by

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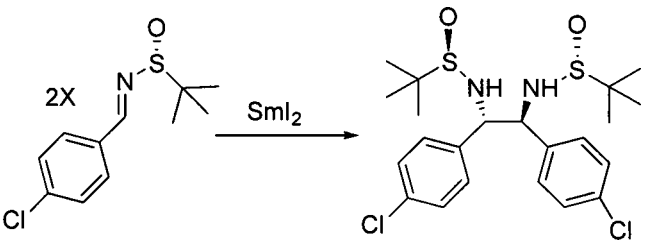
In loving memory of my mother

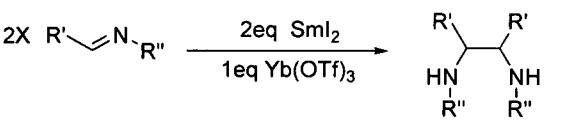
Abstract

Optically pure vicinal diamines are very important as they have several applications. Our study has started on samarium diiodide mediated homocoupling reaction to form vicinal diamines and we were attempting to use substoichiometric amount of SmI_2, along with a co-reductant, to obtain similar reported results where several eq of SmI_2 are being used. The first reaction studied was the reductive homocoupling of sulfinyl imines to synthesis vicinal diamines (scheme 1).



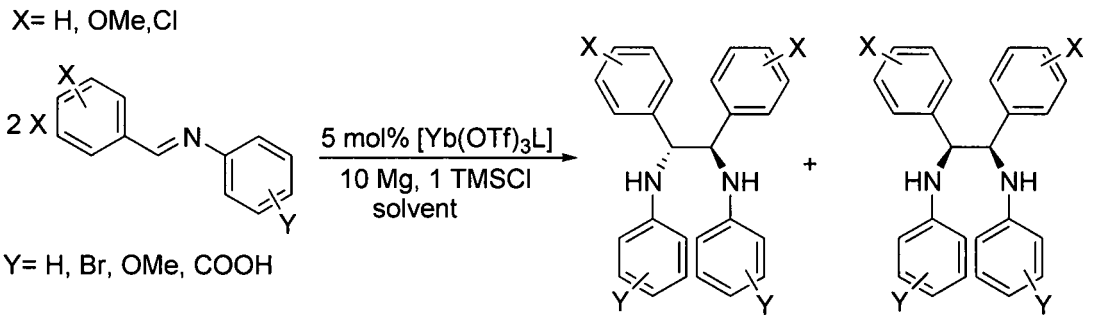
Scheme 1

The reductive homocoupling of the sulfinyl imines did not perform well with substoichiometric SmI_2 so alternative substrates were looked into and simple aromatic imines were chosen. Literature has reported the reductive homocoupling of aromatic imines, promoted by a $SmI_2/Yb(OTf)_3$ system (scheme 2).



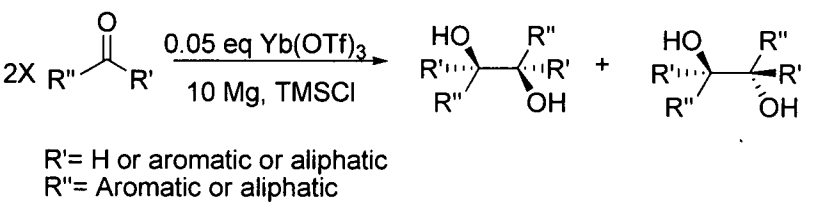
Scheme 2

In the course of our studies, it was seen that in the absence of SmI_2, the Lewis acid $Yb(OTf)_3$ (only 5 mol%) was an efficient catalyst, along with magnesium and TMSCl for the reductive homocoupling of imines (scheme 3). The reactions are simpler, requiring no inert atmosphere and/or anhydrous conditions. In order to increase the selectivity, a range of solvents and polyether complexes of $Yb(OTf)_3$ were used.



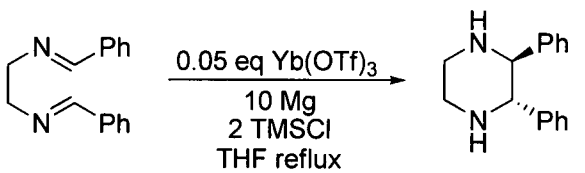
Scheme 3

The methodology has also been applied to other substrates like aromatic and aliphatic aldehydes and ketones (scheme 4) with the coupling of aldehydes being more selective compared to the ketones. Quantitative conversions of starting materials to coupled product were obtained without seeing the reduced monomer product.



Scheme 4

Intramolecular imine coupling from a diimine has also being successfully carried out with the $Yb(OTf)_3$/Mg/TMSCl system (scheme 5). The reaction was very selective as only the *d/l* piperazine was obtained.



Scheme 5

Content

List of Abbreviations

° C	degrees Celsius
15-C-5	15-Crown-5
18-C-6	18-Crown-6
add. time	addition time
bi-py	bi-pyridyl
br s	broad singlet
C.I.	chemical ionisation
CAM	ceric ammonium molybdate
Cbz	benzyloxycarbonyl
Cy	cyclohexyl
δ	chemical shift
d	doublet
DCM	dichloromethane
dd	doublet of doublets
E.I	electronic ionisation
eq	equivalent(s)
ES	electrospray
F.A.B	fast atom bombardment
GC	gas chromatography
GCMS	gas chromatography mass spectometry
h	hour(s)
HMPA	hexamethylphosphoramide
IR	infra red spectroscopy
L	ligand
lit.	literature
M	molar
m	multiplet
m	meta
m.p.	melting point

m/z	mass over charge
m-CPBA	*meta*-chloroperbenzoic acid
min	minute(s)
MS	molecular sieves
NMR	nuclear magnetic resonance spectroscopy
o	ortho
O/N	overnight
OTf	trifluoromethanesulfonate
p	para
Ph	phenyl
rt	room temperature
Rxn	reaction
s	singlet
t	tertiary
t	triplet
Temp	temperature
tetraglyme	tetraethylene glycol dimethyl ether
tlc	thin layer chromatography
TMS	tetramethylsilane
TMSCl	chlorotrimethylsilyl
TMSOTf	trimethylsilyltrifluoromethanesulfonate
tosyl	toluenesulfonic acid
triflic acid	trifluoromethanesulfonic acid
triglyme	triethylene glycol dimethyl ether

Chapter 1

1 Introduction to SmI_2 and vicinal diamines

1.1 Samarium (II) Iodide

Samarium (II) is a powerful, useful one electron reducing agent, with a reduction potential of -1.57 eV for the Sm^{2+}/Sm^{3+} system in water, as the Sm^{2+} readily reverts to the more stable Sm^{3+} oxidation state.[1] Samarium was isolated in 1879 by Boisbaudran and, as with other lanthanides; it has a strong oxophilicity and high electropositivity as well as being a good Lewis acid. Since the introduction of the efficient synthesis of samarium diiodide (scheme 1) in 1977 by Kagan *et al*,[2] many reactions have been developed with Sm(II), in which high levels of stereoselectivity and enantioselectivity with several functional groups are achieved under relatively mild conditions.[3] SmI_2 has been very popular in academia due to its reactivity and availability.[2]

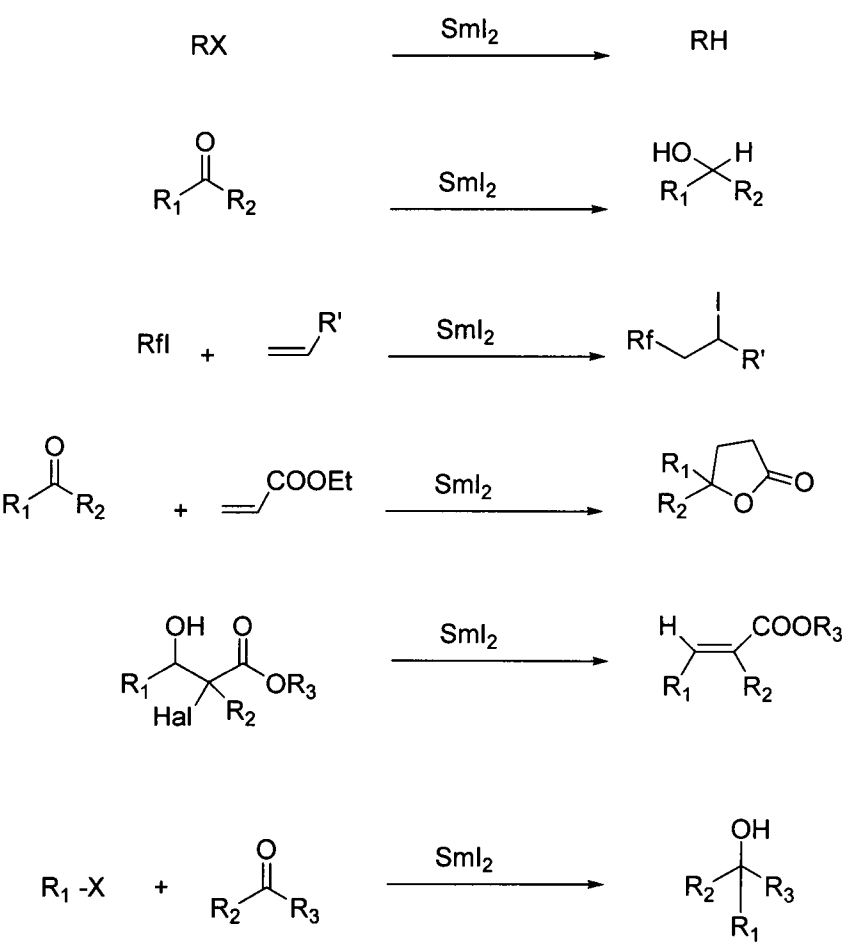
$$\text{Sm metal} + C_2H_4I_2 \xrightarrow{\text{THF}} SmI_2 + C_2H_4$$

Scheme 1

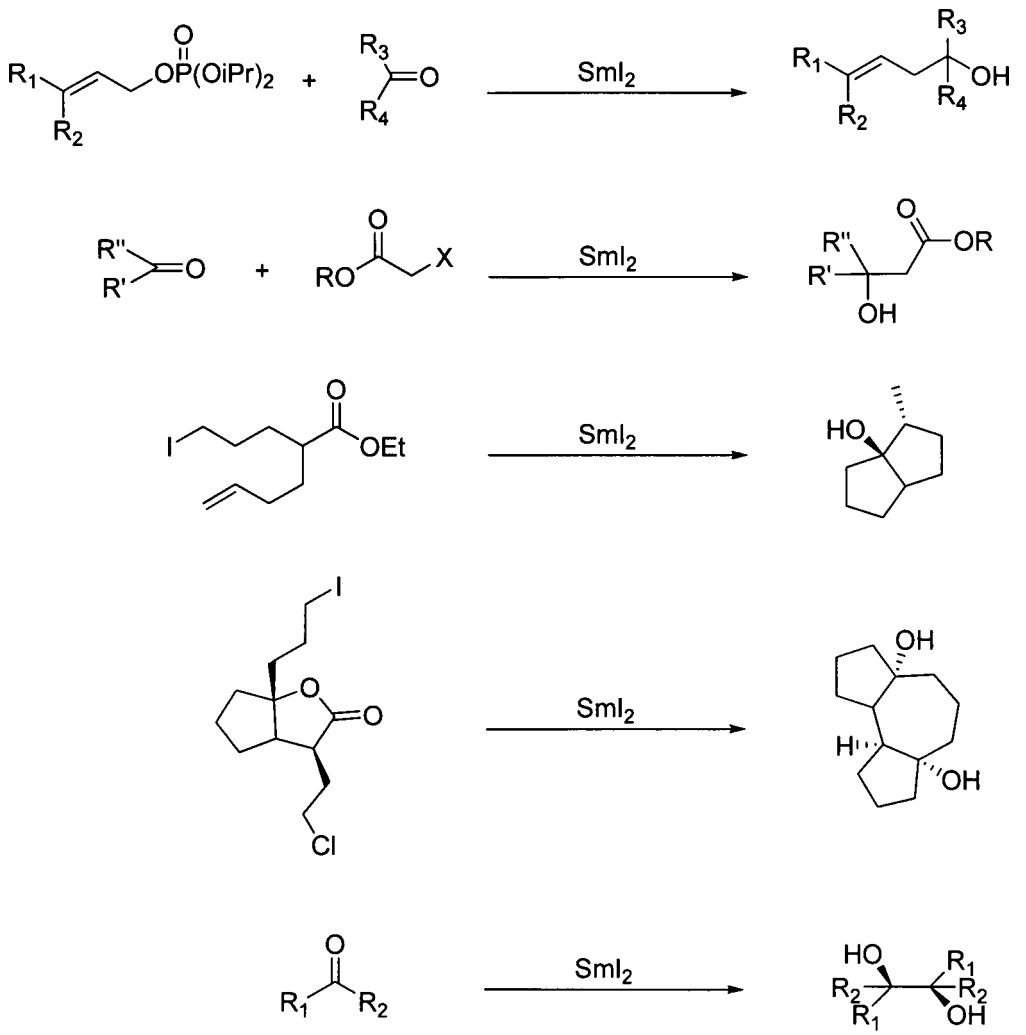
The high cost of Sm(II), its relative instability towards air as well the use in stoichiometric amounts have prevented the wide use of this reagent in industry. The development of cheaper Sm(II) reagent species combined with a catalytic method with Sm(II) would be favourable for its use in the pharmaceutical and fine chemical industries.

Due to its above mentioned properties, samarium diiodide is very reactive to organic substrates containing oxygen, halides or π–electrons. It is usually used in reduction of organic functional groups including conjugated double bonds, carboxylic acids, carbonyls, esters, amides, nitro and nitroso compounds, amine oxides, azo compounds, sulfoxides, sulfones, phosphine oxides, epoxides, halides, allyl acetates, pyridines, phenols and heterocyclic compounds[4] and also reductive coupling of halides with π–bonds,[5] ketyl-

olefin coupling,[6] β-elimination reactions,[7] Grignard and Barbier reactions,[8] Reformatsky reactions,[9] both intra- and intermolecular carbon-carbon bond-formation, and pinacol type couplings.[10,11] Samarium diiodide also exhibits excellent properties for sequential cascade organic reactions, requiring less time, effort and material compared to more traditional multi-step reactions.[12] Some of these reactions (schemes 2 and 3) are discussed in details in section 1.2 below.

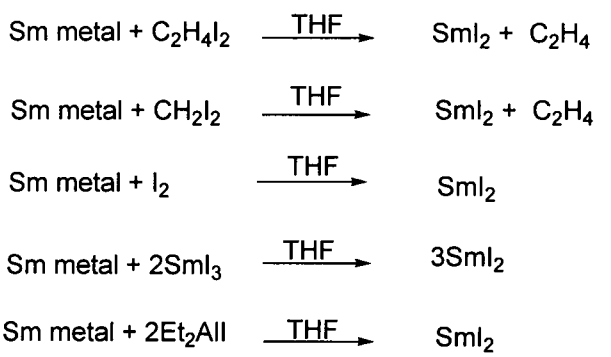


Scheme 2


R1
R2
OP(OiPr)2
O
+
R3
R4
O
SmI2
OH
R''
R'
RO
X
OR
I
OEt
HO
Cl
H
Scheme 3

1.1.1 Preparation of samarium(II) iodide

Samarium diiodide is available commercially as a 0.1 M solution in tetrahydrofuran (THF); however it can be easily prepared using metallic samarium with an iodine source. The first straightforward synthesis of samarium diiodide was published in 1977 by Kagan *et al* where a quantitative yield was obtained from reacting samarium metal and diiodoethane (scheme 1).[2] A deep blue solution with a concentration of 0.1M is obtained, after mixing both reagents in dry freshly distilled and degassed THF under an inert atmosphere (nitrogen or argon) at room temperature, after a few hours. This has enabled the use of Sm^{2+} with I^- acting as counterion. Other iodine sources (scheme 4) include diiodomethane, sodium iodide,[13] iodine, samarium triiodide[14] and diethylaluminium iodide.[15] Other reported samarium(II) equivalents include, samarium(II) triflate ($Sm(OTf)_2$), a deep purple solution in THF,[16] samarium dibromide ($SmBr_2$), a dark violet solution in THF,[17] and samarium dichloride ($SmCl_2$), a red solution in THF.[18]



Scheme 4

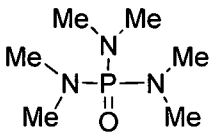
Recently the use of ultrasound with metallic samarium and iodoform (scheme 5) to increase the rate of the preparation, from a few hours to a few minutes, has been published by Concellón *et al.*[19]

Scheme 5

After being synthesised, SmI_2 is air sensitive and has to be handled using standard syringe techniques when transferred from one flask to another. SmI_2 can be kept for a long time in the laboratory under strictly anhydrous conditions in the dark and under an inert atmosphere. All reactions are carried out in freshly distilled dry degassed THF, which also acts as a H atom donor, but sometimes SmI_2 synthesis and reactions have been reported to be carried out in other solvents like alkylnitriles (especially pivalonitrile and octanenitrile)[20], tetrahydropyran (THP)[21] or benzene.[22,23] In nitriles, reactions are slower but are more selective.[20] On the other hand solvents like diethyl ether, *tert*-butyl methyl ether or dioxane cannot be used to prepare SmI_2.[21]

1.1.2 Factors affecting the reactivity of Sm (II)

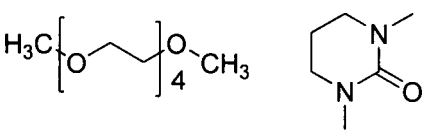
The use of proton donors e.g. water[24] or low molecular weight alcohols, is believed to increase the reactivity of SmI_2. These additives are generally put in a reaction as they are thought to protonate the basic organometallic key intermediate or end product. It is also thought that a mixture of methanol and water doubly acts as a proton source as well as activating the reagent by coordinating to the metal centre.[24] Several reagents with Lewis basic oxygen and/or nitrogen functionality or electron donors have also been used as additives. In order to enhance the reducing power of SmI_2, hexamethylphosphoramide (HMPA, figure 1) is used as the most common additive.[24-26]



hexamethylphosphoramide

Figure 1

Using 3 eq. of HMPA increases the redox potential of Sm^{+2}/Sm^{+3} system to -1.95 V, with 4 eq., the redox potential increases to -2.05 V but any increase above 4 eq. of HMPA does not increase the redox potential.[27] Not only does HMPA increase the rate of reaction, it also affects the stereochemical outcome as well, like reductive cyclisations [28] but it does not have any effect on the outcome of the reaction in alkylnitriles.[20] Due to the toxic (carcinogenic) nature of HMPA, other additives like 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) or tetraethylene glycol dimethyl ether (tetraglyme) (Figure 2 below) have been used as alternatives but larger amounts have had to be introduced to obtain similar results.[29] Attempts at substituting HMPA by alternative reagents have so far not led to a general solution.



Tetraglyme

DMPU

Figure 2

Various inorganic salts have also been used as additives.[30] An increase in reactivity and chemoselectivity of SmI_2 has been noted when lithium chloride and lithium bromide have been used as additives in the pinacol coupling of cyclohexanone. These lithium salts were forming Br^- and Cl^-, which were displacing the I^- from SmI_2 to produce more soluble and solvated $SmBr_2$ and $SmCl_2$.[31] It has also been reported that use of transition metal salts like nickel(II) iodide and some iron(III) salts have increased reactions rates of Barbier-type SmI_2 mediated reactions when they have been used as catalytic additives.[30] Nickel(II) iodide appears to be more effective than other transition metal salts, requiring ≤ 1 mol% to promote the coupling of imines[32]

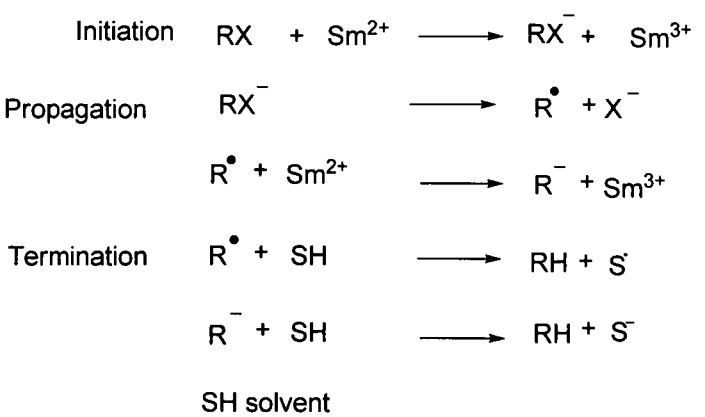
and intermolecular nucleophilic acylation of esters by acid chlorides.[33] The possibility of changing the reactivity and selectivity of Sm (II) by using additives or catalysts, have made it very popular and reactions conditions can be tailored for optimum results.

1.2 Reactions mediated or catalysed by samarium diiodide[34]

1.2.1 Reduction of organic functional groups

1.2.1.1 Reduction of organic halides[35,36]

Kagan *et al* reported that primary alkyl bromides and iodides can easily be converted to the corresponding alkanes by refluxing with two eq. of SmI_2 in THF, without any coupling reactions occurring.[36] A radical mechanism was put forward to explain this transformation as shown below (scheme 6). The alkane is obtained as the radical or anion is able to abstract hydrogen from THF. Reduction of benzylic or unsaturated halides with one eq. of SmI_2, gave primarily the coupled products at room temperature. The coupling arises as the radical formed from the above mentioned halides is stable enough to diffuse outside the coordination sphere of samarium.

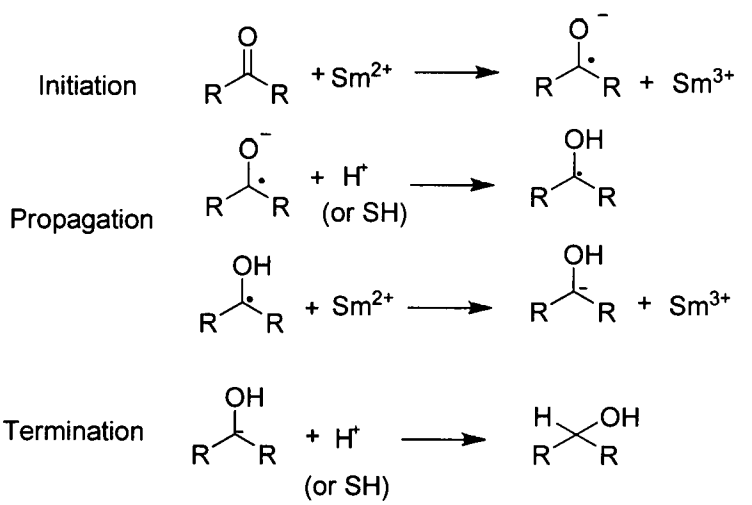


Radical mechanism proposed for reduction of organic halides

Scheme 6

1.2.1.2 Reduction of aldehydes and ketones[36]

The reduction of carbonyl groups by SmI_2 can be described *via* a radical mechanism (scheme 7) where SmI_2 acts as a one-electron donor as reported by Kagan *et al.*[36] The first step is the formation of the ketyl radical anion, where two eq. of SmI_2 and a proton source are required. The reduction of 2-octanone by SmI_2 in THF gave 2-octanol as main product with some pinacol product. When SmI_2 in THF/CH_3OD was used to reduce 1-octanal, the C-deuterated 1-octanol and a very small amount (10%) of the non C-deuterated 1-octanol were obtained. The same observations were noted when acetophenone was reduced with SmI_2 and D_2O in THF. This implies that THF is acting both as a solvent and H-atom donor.

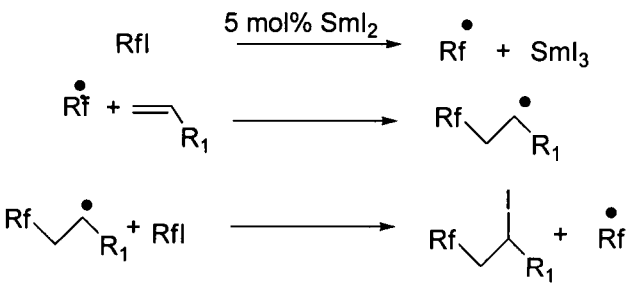


Radical mechanism proposed for reduction of carbonyls

Scheme 7

1.2.2 Reductive coupling of halides with π–bonds[5]

In 1988 Lu *et al* were the first to publish a reaction in which SmI_2 was used as a catalyst (5 mol%) to promote the coupling of fluoroalkyl iodides to olefins to synthesise organofluoro compounds. SmI_2 here was used as an initiator, forming a fluoroalkyl radical in the first step of the proposed mechanism (scheme 8). The fluoroalkyl radical then went on to add onto the double bond, giving another radical and so on. Yields were in the range of 55% to 91%. It was interesting to note that there was no reaction observed when allyl alcohols were used. Yields were also lower when disubstituted olefins were used and it may be explained by the steric effect as the sterically hindered radical may not easily abstract the bulky iodine atom from the fluoroalkyl iodide. The best conversion of 96% with an isolated yield of 95% was obtained when 1-octene reacted with β-chloroperfluorohexyliodide. Below is the proposed mechanism as reported (Scheme 8).

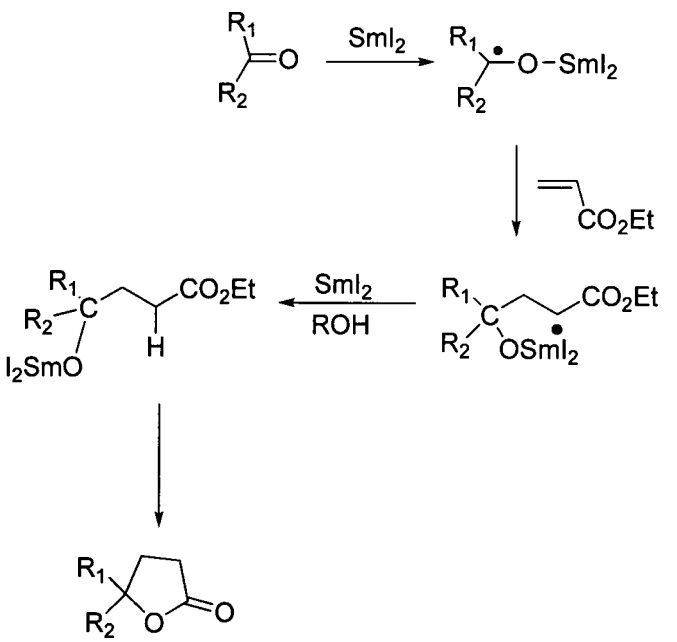


Radical mechanism proposed for reductive coupling of halides with π-bonds

Scheme 8

1.2.3 Ketyl-olefin coupling[6]

Fukuzawa *et al* published a reaction where SmI_2 was used to mediate the coupling reaction of ketones or aldehydes with electron deficient alkenes, thereby synthesising γ–lactones. A radical mechanism (scheme 9) was put forward to explain the reaction. SmI_2 being oxophillic, binds to the carbonyl oxygen, forming an organosamarium radical species. This radical then goes on to add on the double bond, forming another radical. The addition of another equivalent of SmI_2 with an alcohol quenches the radical, giving the γ–lactones after cyclisation. The reaction works for both aliphatic and aromatic carbonyl giving reasonable yields under mild conditions. It was found that when ^{t}butanol was used as proton donor, yields were better than with methanol and ethanol. On the other hand, yields were not improved when other additives like tetraglyme and tetramethylethylenediamine (TMEDA) were used.

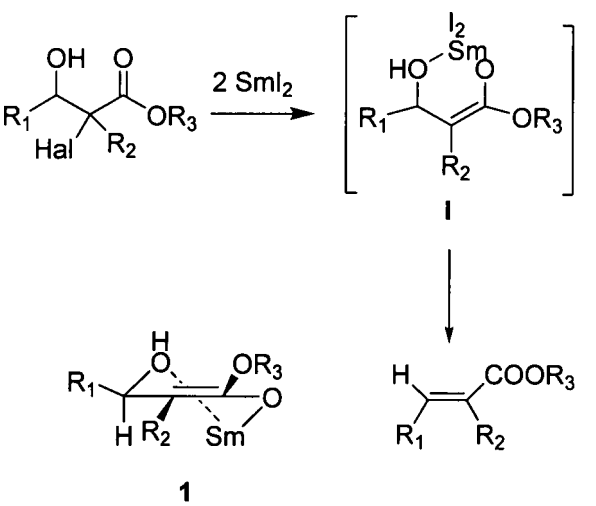


Proposed radical mechanism for ketyl-olefin coupling

Scheme 9

1.2.4 β-elimination reactions[7,37]

β-elimination reactions in 1,2-difunctionalised substrates are one of the main routes to synthesise a carbon-carbon double bond. Concellon *et al* described the synthesis of (*E*)-α,β-unsaturated esters and amides with total selectivity via a β-elimination route, mediated by SmI_2.[37] Two equivalents of samarium diiodide were used to mediate the elimination reaction of a 2-halo-3-hydroxyester (chloro and bromo compounds were used). The observed *E* stereoselectivity is explained by assuming a chelation-control model as transition state, where the SmI_2 coordinates to the oxygen atom from the carbonyl and the hydroxyl oxygen. This chelation between the 2 oxygen atoms gives a 6 membered ring (**1** in the scheme 10 below) and increases the ability of the hydroxyl group as a leaving group. The *E*-alkene is still obtained even when a diastereoisomeric mixture of the starting material was used as epimerization of the C(R^2) carbon centre occurs after reaction with SmI_2, giving the diastereoisomer with the appropriate conformation for coordination of the samarium centre with the hydroxyl oxygen. Yields went up to 90% with a de >98%, with a range of different substituents, aromatic, aliphatic and unsaturated, giving a carbon-carbon double bond which is di- or trisubstituted.

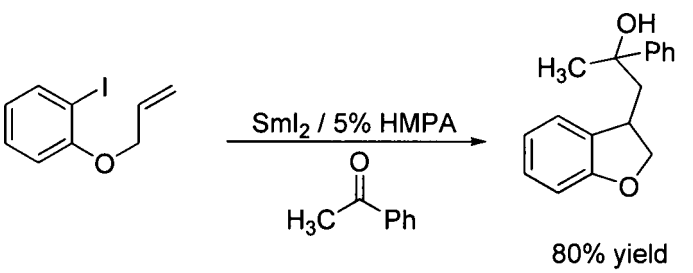


Mechanistic proposal for the synthesis of (*E*)-α,β-unsaturated esters via intermediate **I. 1** is the proposed transition state model

Scheme 10

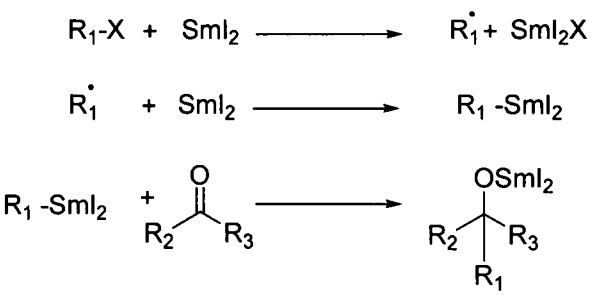
1.2.5 Barbier and Grignard type reactions[8,38]

Both samarium Barbier and samarium Grignard reactions have been reported in the literature. Curran *et al*, in 1992 have published a samarium Grignard reaction during which there is the *in situ* formation and reaction of primary and secondary alkyl samarium (III) reagents from *o*-allyl-2-iodophenol and acetophenone (scheme 11).[38] They have proposed a radical mechanism whereby the halides are reduced to radicals, ketones are reduced to ketyls and then coupling occurs between the radicals and ketyls. This above reaction is limited to only primary and secondary alkyl halides and even in these restricted cases, the reactions are capricious.



Scheme 11

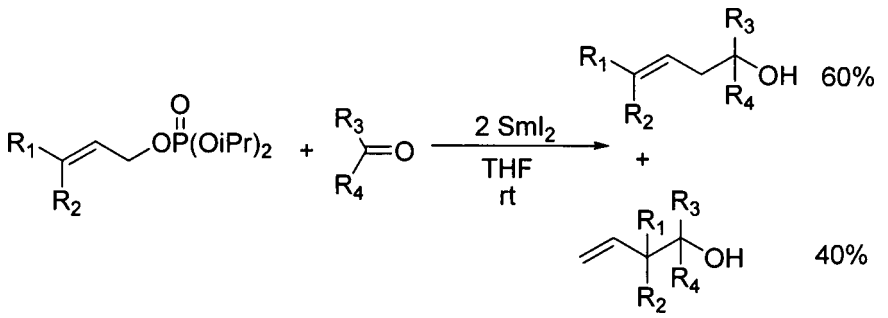
The following year, Curran reported a new approach involving an organosamarium intermediate to the samarium reaction.[39] This new mechanism starts with the reduction of the halide to give a radical which then gets reduced to form the organosamarium intermediate (scheme 12). This organosamarium intermediate then undergoes a 1,2-addition to a ketone and work up gives the desired alcohol product. The previous radical mechanism does not work for samarium Barbier reactions as the radical addition step is too slow.



modern mechanistic approach to the samarium Grignard reaction

Scheme 12

The samarium Barbier has been more successful and has even worked in cases where organolithium or organomagnesium chemistry has failed. Allylic, propargylic and benzylic halides are very reactive substrates in samarium Barbier reactions, reacting within minutes at ambient temperatures in THF. Butsugan *et al*[40] reported that allylic phosphates can be used as precursors (scheme 13). The reactions went to completion within an hour but reactions were limited as aldehydes and ketones (e.g. acetophenone and benzophenone) undergo competitive pinacol formation. Yields ranged from 23% for octanal up to 93% for 2-octanone. The couplings proceeded with the preservation of the olefin geometry but regioselectivity and stereoselectivity were not very high due to coupling occurring at either the α- or γ- positions of the allylic phosphates with a ratio of 3:2 in favour of the α product. Reaction of benzaldehyde (aromatic aldehyde) with prenyl phosphate gave 1,2-diphenyl-1,2-ethanediol in 80% yield with no cross coupling products. However reactions using α,β- unsaturated carbonyls gave a complex mixture of products.

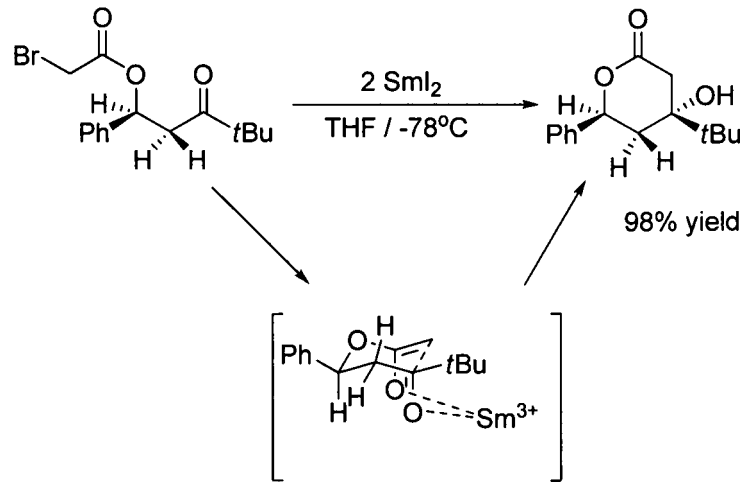


Reaction scheme for a samarium Barbier type reaction

Scheme 13

1.2.6 Reformatsky-type reactions

The Reformatsky reaction is the construction of a carbon to carbon bond by coupling or condensing α–haloesters to a carbonyl compound in the presence of metallic zinc forming a β–hydroxyester. Molander *et al* have reported an intramolecular reformatsky reaction of a β-bromoacetoxy carbonyl promoted by samarium diiodide.[41] Treatment of the β-bromoacetoxy carbonyls with Sm^{2+} generates the Sm^{3+} ester enolates which then cyclises to give the corresponding β-hydroxy δ-valerolacetones (scheme 14). The stereochemistry of the product is defined by the rigid cyclic transition state. The reaction had a wide range of substrates with yields ranging from 65% to 98%.



Scheme 14

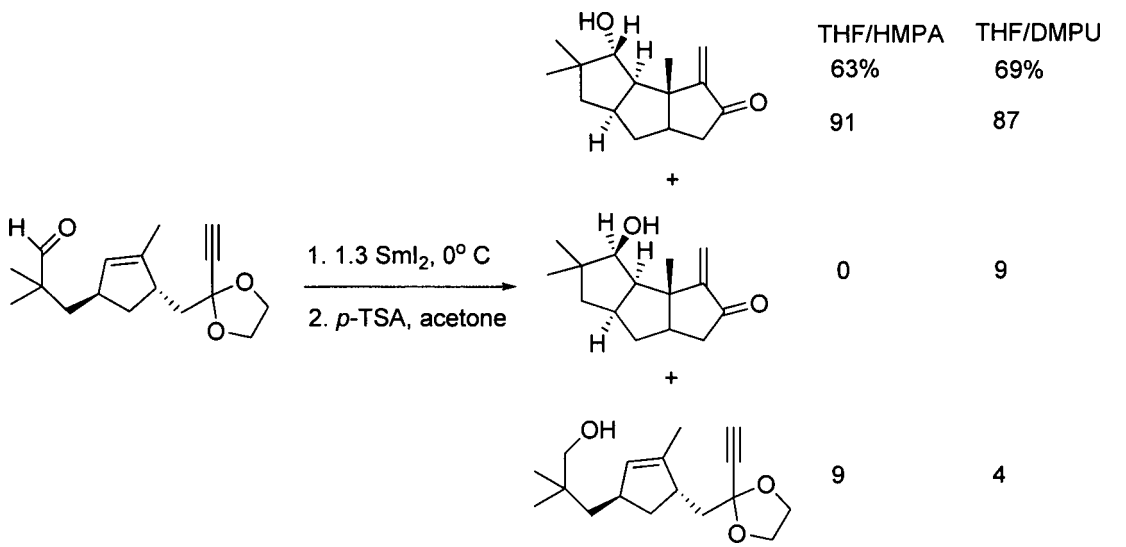
Samarium diiodide promoted Reformatsky reaction has also been used extensively to promote intramolecular Reformatsky reactions, leading to medium and large carbocycles.[42] Orsini *et al* have also reported a Reformatsky reaction promoted by catalytic amount of SmI_2 with magnesium acting as co-reductant (discussed in section 1.3).[9]

1.2.7 Sequential cascade organic reactions[12]

1.2.7.1 Sequential radical reactions[43]

The hydrides of tin and silicon have been widely used to promote sequential radical reactions. In 1988 Curran *et al* reported the first sequential radical reaction mediated by SmI_2. SmI_2 promoted a tandem bicyclisation, which was the key step in the synthesis of (±)-hypnophilin (scheme 15). This cyclisation required less than two eq. of SmI_2 (about 1.3 eq of SmI_2 in THF and HMPA), which shows that the reaction is initiated by a single-electron reduction of the aldehyde to form the ketyl which goes on to cyclise onto the cyclopentene double bond, forming another radical. This tertiary radical is stable enough under these reductive reaction conditions to add on to the terminal alkyne. During the terminating step, a H atom from THF is abstracted by the cyclopentylidene radical to give the final product. The use

of DMPU gave similar results to HMPA with respect to reaction rate and yield but there was the formation of a diastereoisomeric alcohol as side product, which was not seen when HMPA was used. The only limitation in a sequential radical process is that the radical intermediate must undergo cyclization faster than it can be reduced to the corresponding anion.



	THF/HMPA	THF/DMPU
	63%	69%
	91	87
	0	9
	9	4

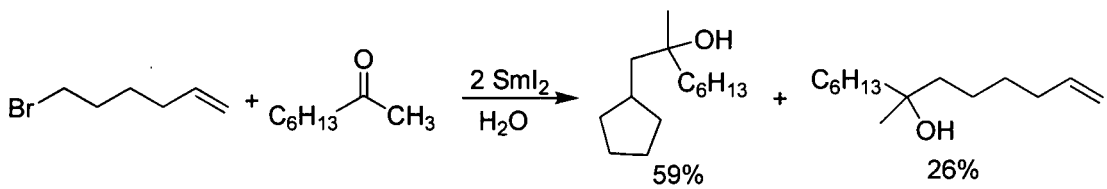
Reaction scheme and results of a sequential radical reaction

Scheme 15

1.2.7.2 Radical/Anionic sequences

The first radical reaction followed by an anionic reaction mediated by SmI_2 was reported in 1981 by Kagan *et al.*[36] Initially SmI_2 reacts with 1-bromohex-5-ene in the presence of 2-octanone to give a radical/anion cyclised product and the Barbier coupled product in 59% and 26% yields respectively (scheme 16). In this reaction the reduction of the 5-hexenyl radical competes with the cyclization of the radical on the double bond, hence the presence of two products. By lowering the concentration of SmI_2, it is possible to change the ratio of the products in favour of the cyclised product. Since the rate of

cyclization of the 5-hexenyl radical is slower than the reduction reaction, both the cyclised and the normal Barbier products are still formed. The radical anionic sequence will only work if the cyclization of the radical intermediate occurs faster than the rate of the reduction of the radical to the anion. These rates were later studied by Curran *et al.*[26] They recommend using 5 eq of HMPA and under these conditions, the rate constant of 7 x 10^6 $M^{-1}S^{-1}$ can be used to predict the product ratios.

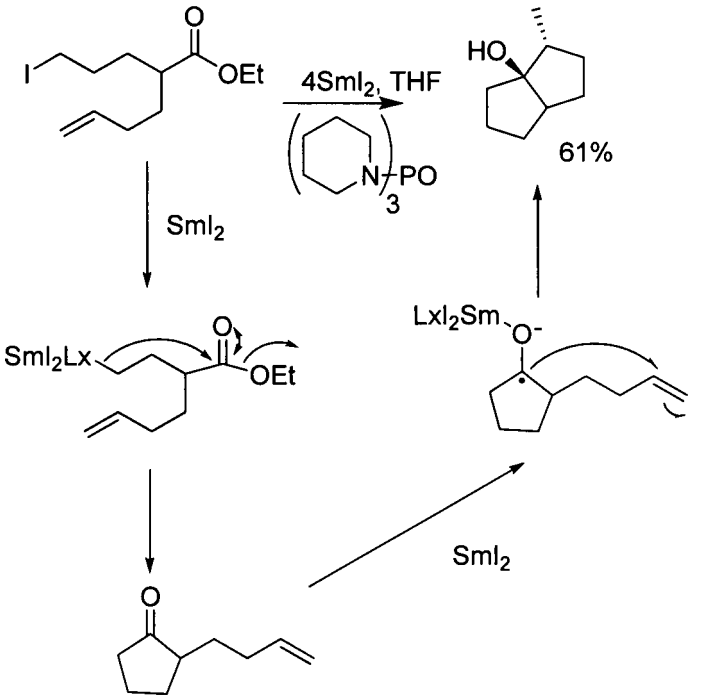


Reaction scheme of a sequential radical-anionic process

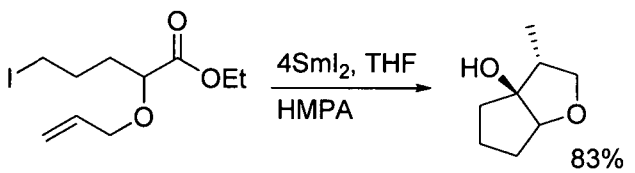
Scheme 16

1.2.7.3 Anionic/Radical sequences

SmI_2 can also promote an anionic reaction followed by a radical reaction, which can be represented by a ketyl olefin cyclization, preceded by nucleophilic acyl substitutions. Molander *et al* have reported such a reaction during which a ketone is formed in an intramolecular nucleophilic acyl substitution reaction (scheme 17).[44] This newly generated ketone reacts with SmI_2 to give a ketyl radical. This allows the process of a bicyclization sequence. The addition of tripiperidinophosphine oxide [$(C_5H_{10}N)_3PO$], which is increasing the redox potential of SmI_2, promoted the cyclization of all the substrates. α-Heterosubstituted esters can also be used to give heterocycles as shown in scheme 17 below, in high yields.



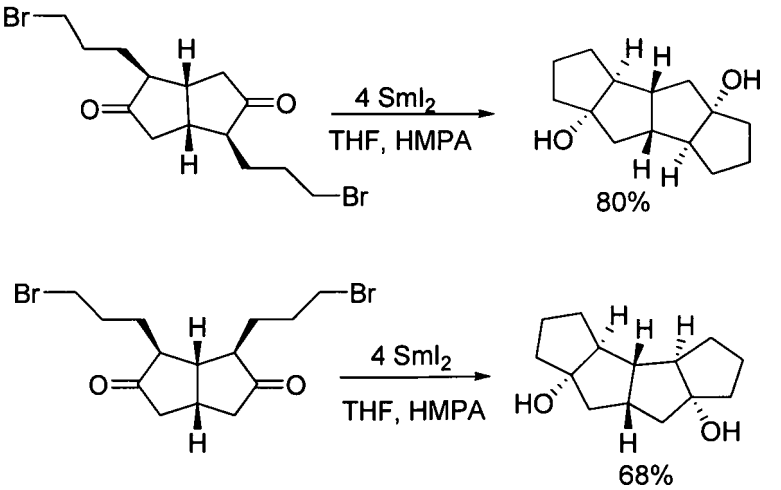
Sequential anionic/radical intramolecular cyclisation reaction



Scheme 17

1.2.7.4 Sequential anionic reactions

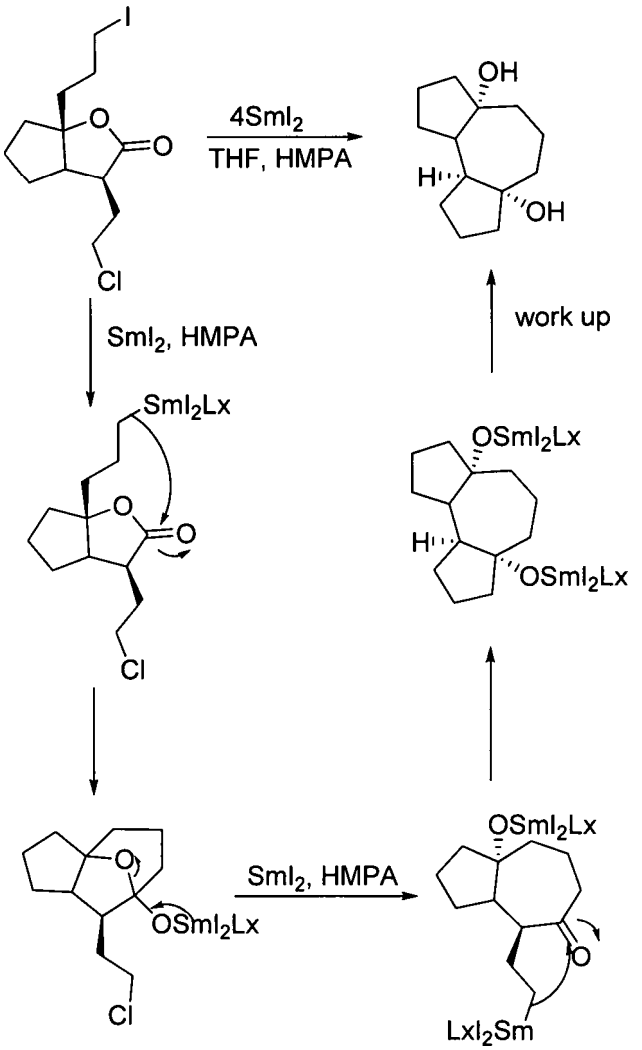
SmI_2 also promotes sequential anionic reactions. The easiest sequence is one where two intramolecular Barbier-type reactions occur in one pot. Cook *et al* have used this sequence in the key step during the synthesis of polyquinenes.[45,46] The dibromodione gave a mixture of stereoisomic tetracyclic diols after reaction with SmI_2 and HMPA as additive, as shown in scheme 18.



Sequential anionic intramolecular cyclisation

Scheme 18

Bicyclic and tricyclic systems can also be synthesised *via* this route, where a nucleophilic acyl substitution followed by a Barbier reaction has been used to form seven- and eight-membered rings (scheme 19).[44,47] The substrate needs to be designed to undergo nucleophilic acyl substitution to precede a Barbier-type reaction.



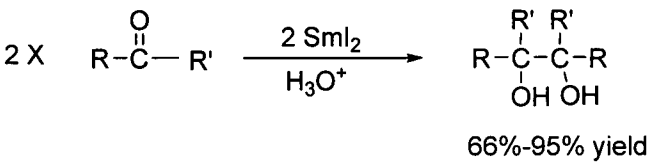
Formation of seven-membered ring via sequential anionic reactions

Scheme 19

1.2.8 Pinacol type couplings[11,48]

The pinacol coupling of aldehydes and ketones is a very useful intermolecular transformation. Samarium diiodide is an excellent reagent for aldehyde and/or ketone couplings. Kagan *et al* in 1983[11] found that aromatic aldehydes and aromatic ketones couple very rapidly with one equimolar amount of SmI_2 in the absence of any additives at room temperature in THF (scheme 20). The reaction is slower with aliphatic aldehydes, with a few

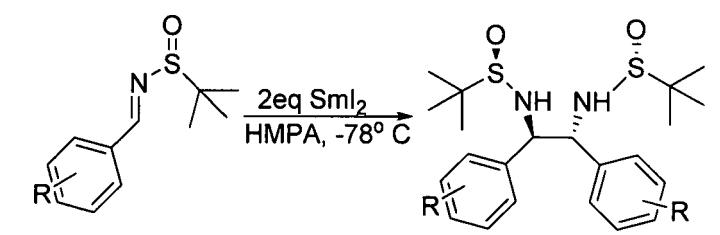
hours required before reaction is over. A day is required for aliphatic ketones. All reactions gave the diol as main product with good yields ranging from 66% to 95% but no diastereoselectivity was obtained. The reaction involves an initial electron transfer from SmI_2 with the formation of an organosamarium ketyl radical, which goes on to couple itself to another ketyl radical. Addition of aqueous acid will give the diol product.



Scheme 20

1.2.9 Reductive homocoupling of *t*-butanesulfinyl imines

Xu *et al* reported the synthesis of symmetrical vicinal diamines *via* the reductive homocoupling of N-*tert*-butanesulfinyl imines, mediated by two eq of SmI_2 with HMPA used as additive (scheme 21).[49] Addition of two eq of HMPA gave only *anti* product. Good yields were obtained with the best isolated yield of 99% obtained with the 4-chlorobenzaldehyde derivative. These coupling reactions have provided a route to synthesise symmetrical vicinal diamines, which were obtained by cleaving the *tert*-butanesulfinyl groups under acidic conditions.



R= H, F, Cl, Br, Me OAc, OMe

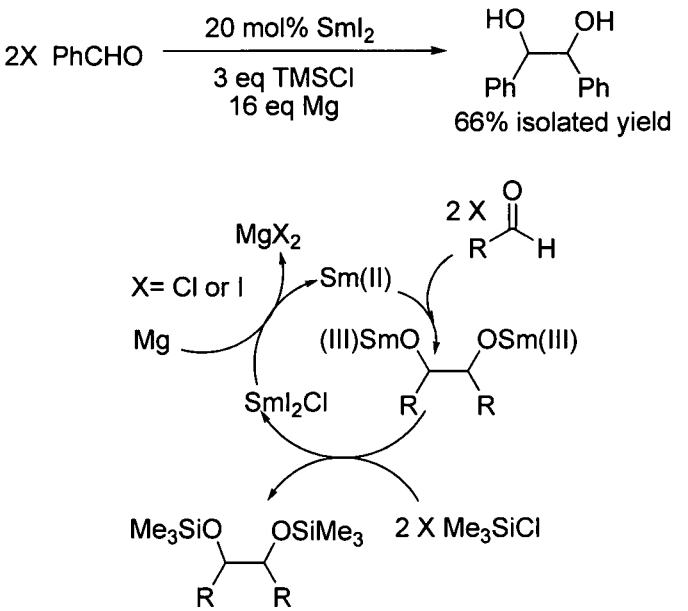
Scheme 21

1.3 Catalytic SmI_2

As mentioned in section 1.1, SmI_2 is quite an expensive reagent and in order to mimise the cost of reactions involving SmI_2, it is desirable to reduce the amount of SmI_2 used. When used in a catalytic amount, the Sm^{2+} has to be regenerated back from the Sm^{3+} in a catalytic cycle by a co-reductant. The choice of this co-reductant is very important as its redox potential must be high enough to reduce Sm^{3+} to Sm^{2+} but it must not enhance or perform the reaction; for example, magnesium metal, in stoichiometric amounts, can promote the pinacol coupling, however very low selectivity is obtained.[50] Endo *et al* pioneered a SmI_2 catalysed pinacol coupling reaction using magnesium as co-reductant.[51] This reaction required 10 mol% SmI_2, 1.5 mol eq TMSCl with an excess of magnesium in THF. This catalytic cycle is described in scheme 22, Sm^{2+} reduces the carbonyl and after the coupling of the organosamarium species, TMSCl replaces Sm^{3+} to form a silyl ether. The Sm^{3+} gets reduced by the magnesium to give the Sm^{2+} which can again reduce a carbonyl. The reaction was made catalytic with the use of TMSCl and magnesium acting as co-reductant, reducing the Sm^{3+} back to the active Sm^{2+}, while formation of strong Si-O bond liberates the Sm^{3+}, which can complete the catalytic cycle. TMSCl has also been found to generate SmI_2Cl and promotes the reduction to Sm^{2+}, which is easier than the corresponding reduction of the Sm(III) pinacolate. The corresponding diol was obtained in good yields but with no diastereoselectivity.

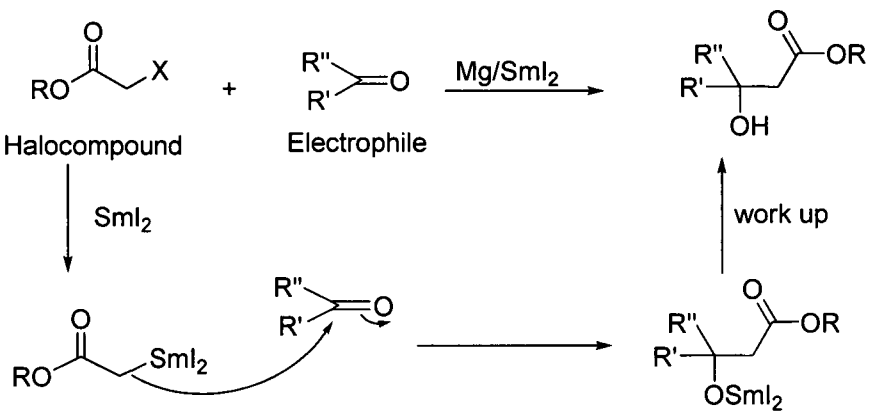
Endo based his samarium diiodide catalytic cycle on a pinacol coupling reaction proposed by Hirao *et al,* where a low-valent vanadium species, $CpV(CO)_4$, was used as catalyst with zinc metal acting as co-reductant and TMSCl.[52] Other metal/co-reductant/silane promoter systems of pinacol coupling include Cp_2TiCl_2/Zn/TMSCl,[53,54] ethylenebis-(η^5-tetrahydroindenyl)$TiCl_2$/Zn/TMSCl,[55] $CrCl_2$/Mn/TMSCl,[56] $NiCl_2$/Mg/TMSCl,[57] $InCl_3$/Mg/TMSCl[58] and $Ce(O^iPr)_3/Et_2Zn$/TMSCl.[59] It has also been found that the addition of a silane helps in the activation of the co-reductant surface and the carbonyl by forming a Lewis-base adduct and also facilitates the transfer

of a single electron to the carbonyl.[60,61] Gansauer *et al* have also reported that silanes with bulkier groups can affect the diastereoselectivity outcome of the pinacol coupling but slower coupling rates were obtained and the formation of the mono-alcohol was quite significant.[62]



Scheme 22

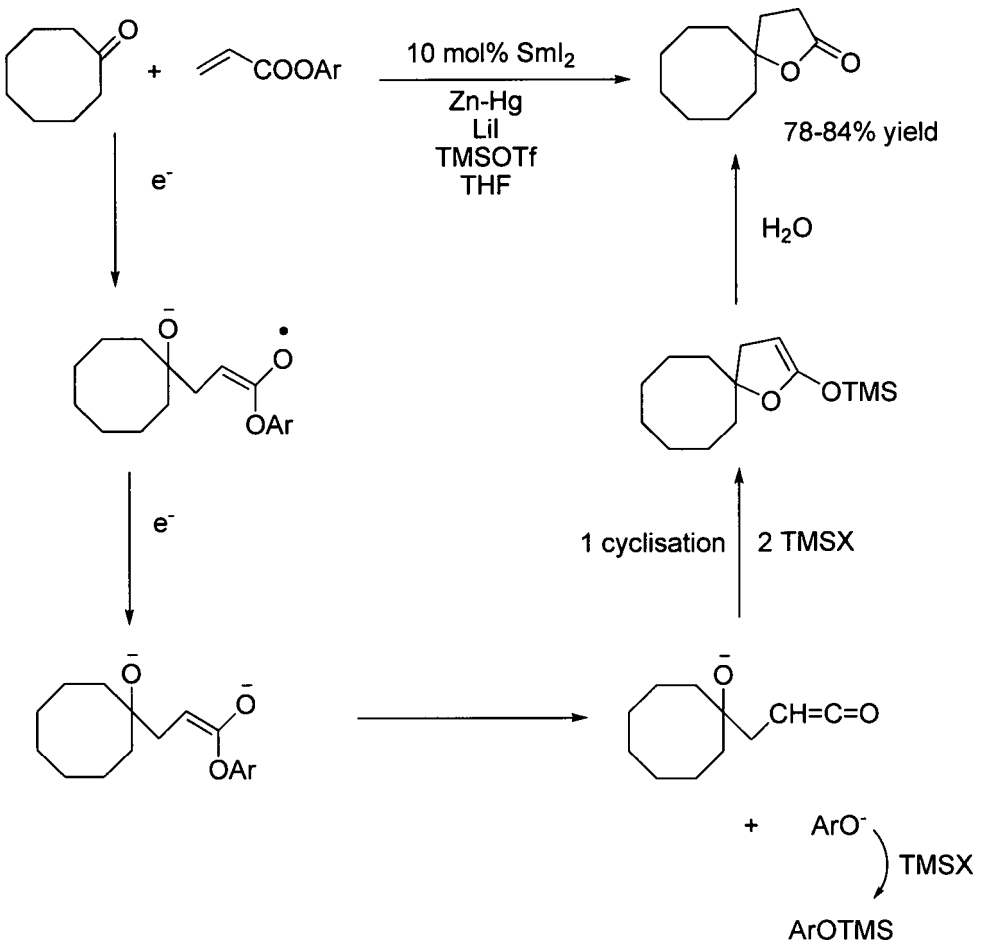
Orsini *et al*, reported a Reformatsky reaction (scheme 23) promoted by SmI_2/Mg where a substoichiometric amount of SmI_2 was used (10%).[9] The magnesium is acting as co-reductant in this reaction, reducing the Sm (III) back to Sm (II) which can thus start the catalytic cycle again. The reaction goes *via* a radical pathway, the samarium (II) binds to the carbonyl oxygen of the haloester and forms the halide radical and an organosamarium species. This organosamarium species then goes on to add onto the carbonyl compound. The addition product was obtained in good yields when an α-bromoester and a carbonyl compound were used. Aromatic α-bromoketones and α-bromoacetonitrile gave lower yields.



Reaction scheme of a Reformatsky reaction catalysed by SmI_2

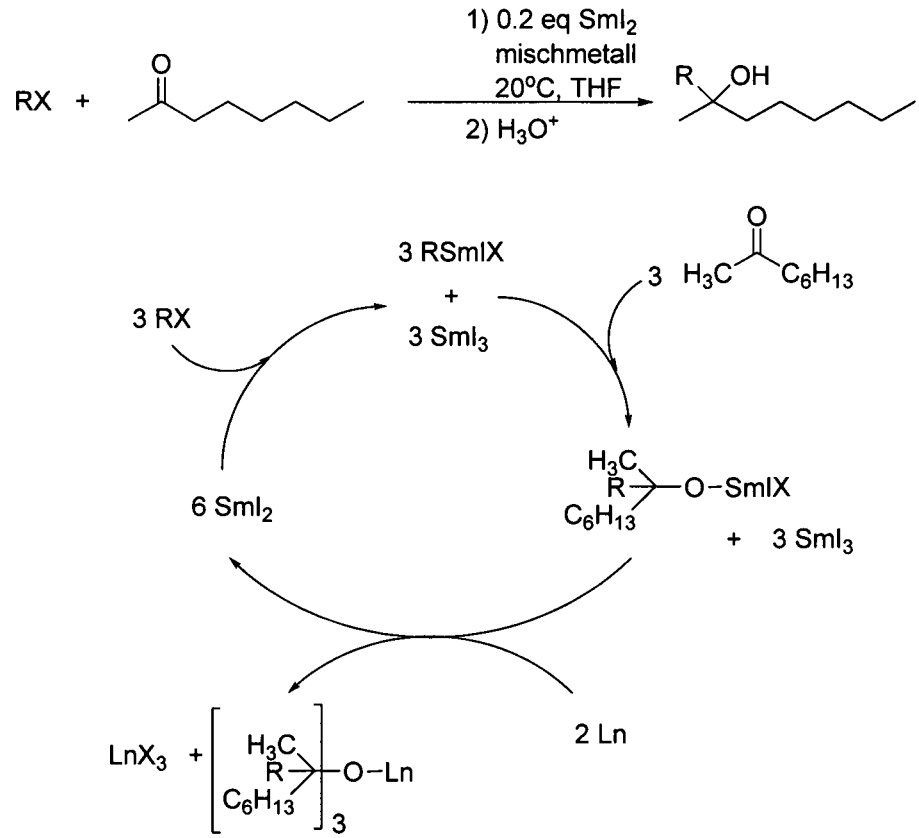
Scheme 23

In 1997, Corey *et al* reported a series of SmI_2 catalysed reactions, the annulation of ketones to γ-lactones, the deoxygenation of oxiranes to olefins and a radical π-cyclisation.[63] Amalgated zinc was used as co-reductant with 10 mol% of SmI_2 while TMSOTf and LiI were used to generate SmI_3 (scheme 24).



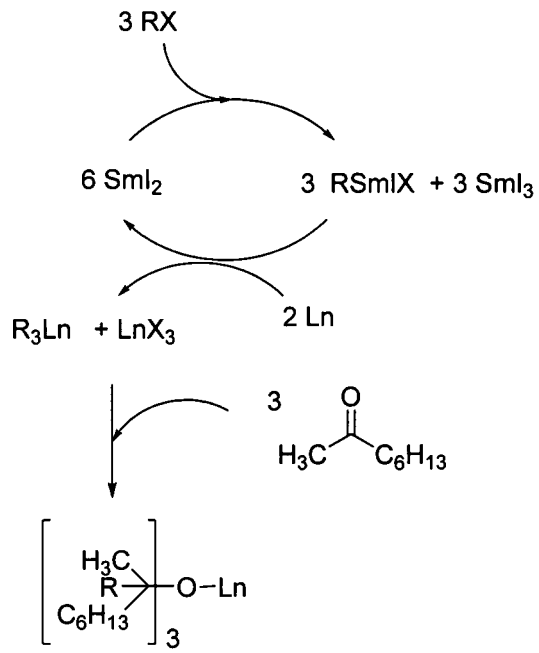
Scheme 24

Namy *et al* proposed a Barbier type reaction catalysed by 10 mol% SmI_2 with 1.4 eq Mischmetall, a cheap lanthanide alloy, acting as co-reductant.[64] Allyl iodide, benzyl bromide and ethyl iodide were used with 2-Octanone and the corresponding tertiary alcohol was obtained in yields ranging from 52%-91%. Two mechanisms have been put forward by Namy for the catalytic cycle. In the first catalytic Mischmetall (Ln) substitutes Sm^{3+} and reduces it to Sm^{2+} (scheme 25). This route goes *via* an organosamarium compound, which forms a Sm(III) alkoxide and SmI_3 and both are then reduced by Mischmetall. This mechanism is supported by the fact that when Mischmetall is added to a yellow suspension of (*t*-Bu)OSmI_2, there is a rapid colour change to the deep blue SmI_2.



Scheme 25

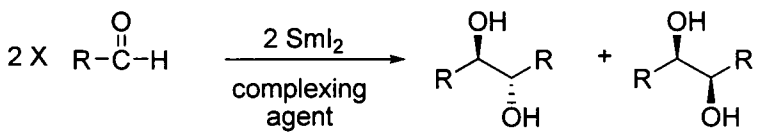
The second mechanism proceeds with the reduction of the organic halide to give an alkyl samarium species, which then gets reduced by the Mischmetall to give an organolanthanide reagent. This organolanthanide then reacts with the ketone to give the tertiary Ln(III) alkoxide. The Sm^{3+} also gets reduced by the mischmetall to give the Sm^{2+} (scheme 26). The addition of TMSCl was not required to free the Sm^{3+} as Mischmetall can cleave the Sm-O bond.



Scheme 26

This SmI_2/mischmetall system has also been applied in the pinacol coupling of acetophenone and acid chlorides,[64] Barbier/Grignard allylation[65] and Barbier/Grignard-type reactions of lactones and esters.[66]

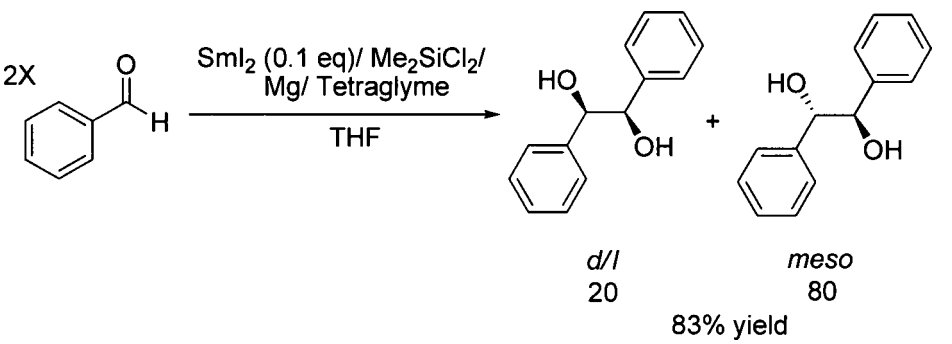
In order to improve the diastereoselectivity of reactions, Skrydstrup *et al* have proposed the addition of chelating ligands in a SmI_2 mediated pinacol coupling reaction (scheme 27).[67,68] Addition of one eq of polyether ligands like diglyme, triglyme and tetraglyme has greatly improved the diastereoselectivity outcome when SmI_2 was used to promote the pinacol coupling of benzaldehyde and cyclohexanecarboxaldehyde. On the other hand, ligands like 18-crown-6 (insolubility of resulting Sm complex) and triethylene glycol di-2-naphthyl ether (no Sm complex formed) were not very effective. In the absence of any ligand, a *meso* to *d/l* ratio of 1:1.3 was obtained with benzaldehyde and this ratio increased to 4.8:1 when 4 eq of diglyme was added. The diastereoselectivity was increased to 6.4:1 in favour of the *meso* diol product when 4 eq of triglyme or 2 eq of tetraglyme were added. A 1:1.1 *meso* to *d/l* ratio was obtained in the absence of ligand with cyclohexanecarboxaldehyde. This ratio was increased to 10:1 in favour of the *d/l* diol was obtained when 1 eq of triglyme was added to the reaction.



		meso	*d/l*	yield
R = Ph	2 eq Tetraglyme	86	14	63%
R = Cy	1 eq Triglyme	9	91	25%

Scheme 27

Greeves *et al* have reported that the use of chelating ligands along with catalytic SmI_2 (10 mol%) influences the diastereoselectivity in pinacol coupling reactions, a *d/l*:*meso* ratio of 20:80 was obtained when one eq of tetraglyme was used in the coupling of benzaldehyde (scheme 28).[10] De values of up to 99% have also been achieved in intramolecular pinacol coupling reactions using catalytic amounts of SmI_2 with tetraglyme acting as chelating ligand. Magnesium was used as co-reductant and Me_2SiCl_2 has allowed the amount of SmI_2 to be reduced to 10 mol%.



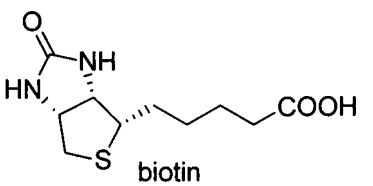
d/l 20 | *meso* 80

83% yield

Scheme 28

1.4 Vicinal diamines[49,69,70]

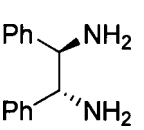
Optically pure vicinal diamines or the 1,2-diamine functionality are very important in organic chemistry as they can be used as building blocks for synthesising biologically active compounds like biotin (also known as vitamin H or vitamin B_7) and can be used as chiral ligands or chiral auxiliaries for asymmetric synthesis.[70]



biotin

Figure 3

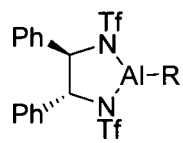
1,2-Diamino compounds are useful synthetic intermediates for the preparation of heterocycles including nitrogen-containing macrocycles and diazacrown ether analogues, which could be used in asymmetric synthesis as chiral ligands.[71] Diamines like tetramethylethylenediamine (TMEDA) are commonly used as additives to stabilize and activate organometallic reagents and inorganic salts.[72] Several chiral auxiliaries with C_2 symmetry derived from 1,2 diamines have been used in highly stereoselective reactions.[73] Symmetrical vicinal diamines are also used for racemate resolution, like (*R,R*)-1,2-diphenylethylenediamine (or stein) is used to resolve atropisomeric binaphthols.[74]



Stein

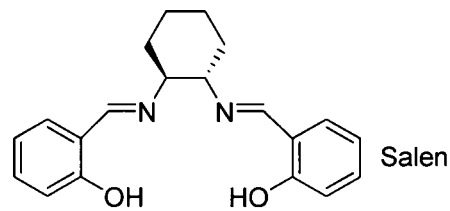
Figure 4

As previously mentioned, 1,2-diamines are also used as ligands. The most widely used ligands incorporating a vicinal diamine moiety are derivatives of 1,2-diphenylethylenediamine and of 1,2-diaminocyclohexane and can be grouped in categories. Firstly Lewis acid derivatives usually with electron withdrawing groups substituted on them, secondly ligands from aromatic aldehydes (e.g. salen) and thirdly simple ligands, as shown with examples below. These chiral ligands are used in a range of reactions including alkylation of aldehydes,[75] aldol reactions,[76] conjugate addition of organometallics to α,β–unsaturated carbonyls,[77] Diels-Alder reactions.[78,79] The Lewis acid **A** (figure 5) has been used by Corey *et al* for the cycloaddition of cyclopentadiene to activated dienophiles.[80] The Salen **B** has been used as a manganese complex by Katsuki *et al* to epoxidise simple olefins with enantionemric excesses >90%,[81] while the simple ligand **C** (figure 5) is used in the enantioselective reduction of ketones.[82]



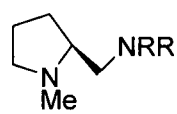
A

Lewis acid derivative



B

Aromatic aldehyde derivative



Simple ligands

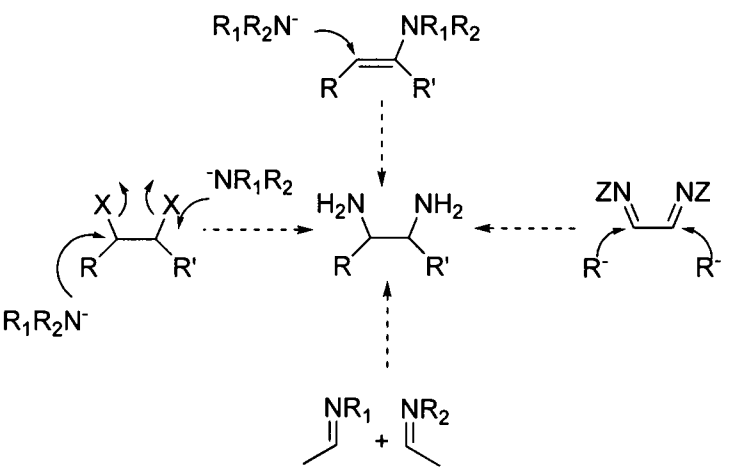
C

Some diamine ligands

Figure 5

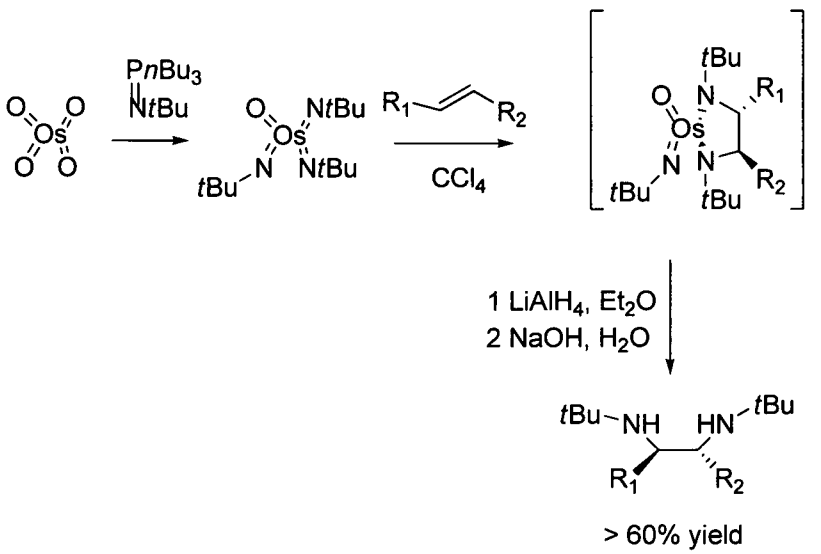
1.4.1 Routes to synthesise vicinal diamines

The most common and simplest route to prepare diamines is the aminolysis of the corresponding vicinal dihalide. This route was first applied to synthesise ethylenediamine. The main drawback of this method is the formation of elimination products in complex systems.[83] There are various ways of synthesising these diamines and they can be classified into four main groups as shown in the scheme 29 below. Firstly the two nitrogen atoms are added onto the carbon skeleton, secondly starting with a compound which already has one of the final nitrogen atoms, thirdly starting with materials which already contain both nitrogen atoms and lastly, starting from two nitrogen-containing substrates and this route involves the formation of the C1-C2 bond.



Scheme 29

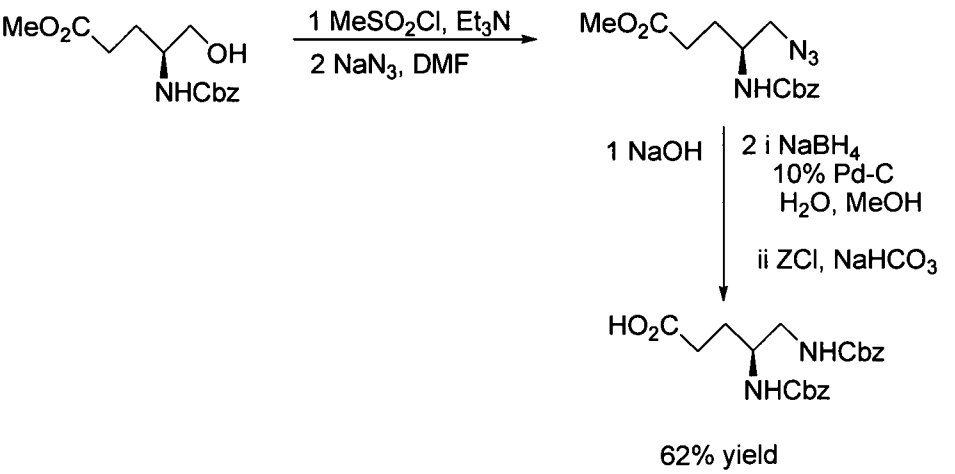
Vicinal diamines can be made from alkenes by direct introduction of the two nitrogen atoms, using mainly organometallic reagents. Sharpless *et al* in 1977 have reported the use of a triimidoosmium complex with mono- or disubstituted alkenes to give diamines in good to excellent yields via a *cis* addition mechanism (scheme 30).[84] It is a costly route for diamines as the osmium complex has to be synthesised from osmium tetraoxide and the reaction requires stoichiometric amounts.



Direct diamination of alkenes with a diimidoosmium complex

Scheme 30

The second method for synthesising vicinal diamines is by starting with a compound which already has one of the final nitrogen atom for example from a β–amino alcohol or a β-halogenoalkynamine. This route consists of introducing a second amino group on the substrate. Kokotos *et al* have reported such a reaction where they have synthesised several chiral protected diamines and triamines (scheme 31).[85] As described below, the Cbz-protected 4,5-diaminopentoic acid was prepared from a Cbz-protected β–amino alcohol derived from glutamic acid. The synthetic sequence involved the nucleophilic displacement of the hydroxyl group by sodium azide.

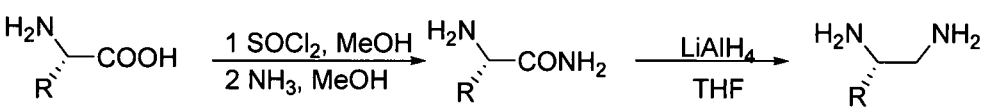


62% yield

Synthesis of a Cbz protected 4,5-diaminopentanoic acid

Scheme 31

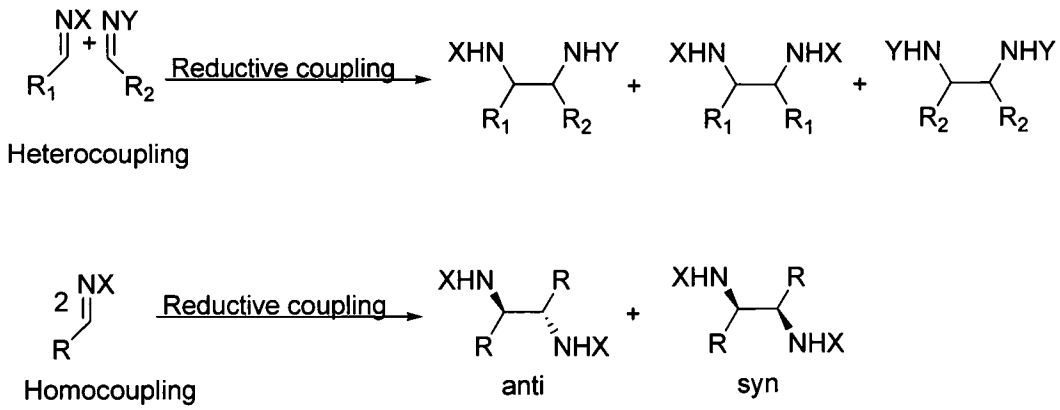
The third commonly used route to make diamines is starting with materials which already contain both nitrogen atoms. Brunner *et al* have used the reduction of amides derived from naturally occurring α–amino acids like leucine, valine, isoleucine, L-phenylalanine and methionine to synthesise monosubstituted vicinal diamines (scheme 32).[86] These diamines were used in the synthesis of platinum complexes.



23%-69% yield

Scheme 32

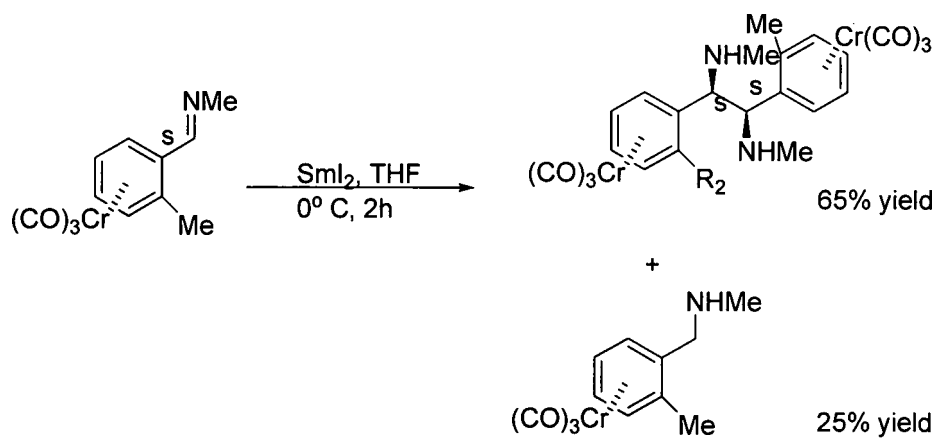
Vicinal diamines are also prepared starting from two nitrogen-containing substrates coupling them, hence forming a carbon to carbon bond. The easiest and most obvious route is the reductive coupling of imines to either give symmetrical or unsymmetrical diamines. A mixture of products is usually obtained from this route as illustrated in the scheme 33 below. The mixture arises due to the fact that homocoupling also takes place alongside the heterocoupling.



Reductive couplings of imines

Scheme 33

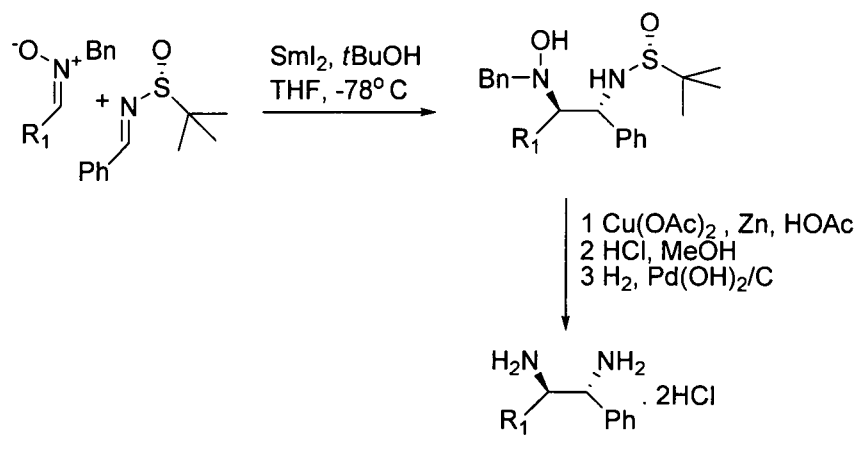
Various conditions have been used to couple imines which have given variable proportions of *anti-* and *syn*-diamines. Uemera *et al* have reported the synthesis of *syn*-diamines exclusively using a SmI_2 mediated homocoupling of enantiomerically pure tricarbonyl(benzaldimine)chromium complex (scheme 34).[87] The reduced monomer is the other by-product of the reaction.



SmI_2 mediated reductive coupling of enantiomerically pure tricarbonyl(benzaldimine)chromium complexes

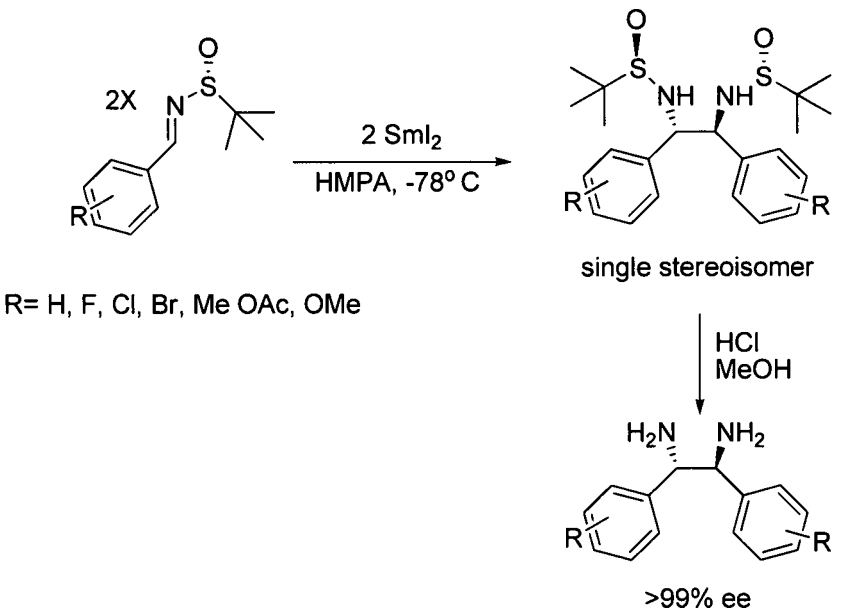
Scheme 34

Xu *et al* have reported the synthesis of optically pure unsymmetrical vicinal diamines by the reductive cross coupling of nitrones with N-*t*-butylsulfinyl imines, with >99% ee, *via* a SmI_2 mediated (between 1 eq and 1.5 eq of SmI_2) reaction (Scheme 35).[69] The cross-coupling product was obtained in good to moderate yields and was then converted to the free diamine in a 3 step reaction sequence, starting by the deoxygenation of the hydroxylamino group by treatment with $Zn/Cu(OAc)_2$ then the removal of the sulfinyl and benzyl groups afforded the optically pure (*R,R*)-3-ethyl-1-phenyl-butane-1,2-diamine. After reporting the reductive cross coupling of nitrones with N-*t*-butylsulfinyl imines, Xu *et al* reported the synthesis of symmetrical vicinal diamines *via* the reductive homocoupling of chiral N-*t*-butylsulfinyl imines, mediated by 2eq of SmI_2 with HMPA used as additive (Scheme 36).[49] These coupling reactions have provided a route to synthesise enantiomerically pure vicinal unsymmetrical and symmetrical diamines.



Reductive cross coupling of nitrones with N-*t*-butylsulfinyl imines to give diamines

Scheme 35

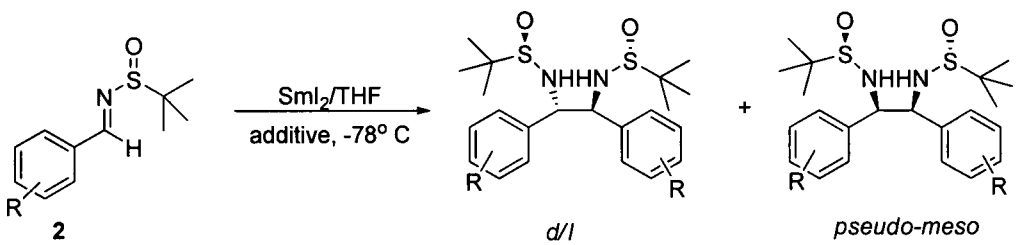


Reductive Homocoupling of chiral N-*t*-butylsulfinyl imines

Scheme 36

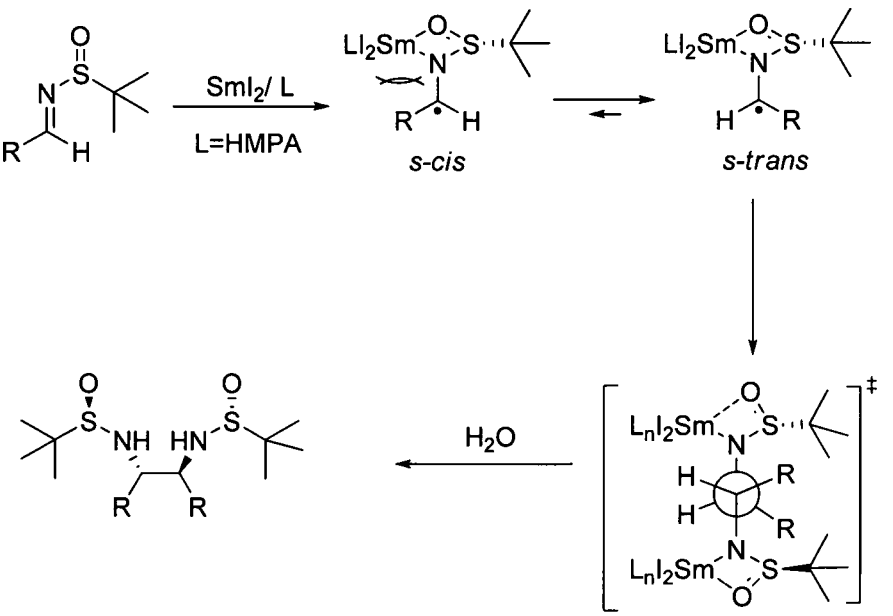
Chapter 2

2 Homocoupling of N-*t*-butylsulfinyl imines



Scheme 37

The aim of this work is the study of published reactions where several equivalents of SmI_2 are being used to try and obtain similar results using a substoichiometric amount of SmI_2 and along with a co-reductant and a non toxic ligand to improve stereoselectivity. We aimed to develop a SmI_2 catalytic system, which will deliver high diastereoselectivity as well as high yields. The reductive homocoupling of aromatic N-*t*-butylsulfinyl imines to form vicinal diamines has been reported by Xu *et al* [49] (scheme 21), using two equivalents of SmI_2 with HMPA used as additive. We have tried using smaller equivalents of SmI_2 along with magnesium acting as a co-reductant and other non toxic additives. The original reaction gave both *d/l* and *pseudo-meso*-adduct in good to excellent yields (52-99%) with both electron-withdrawing and electron-donating substituents on the aromatic ring (scheme 37). The homocoupling products were easily converted to the free amines by cleavage of the N-*t*-butylsulfinyl group under acidic conditions. The proposed mechanism as reported is shown below (scheme 38).

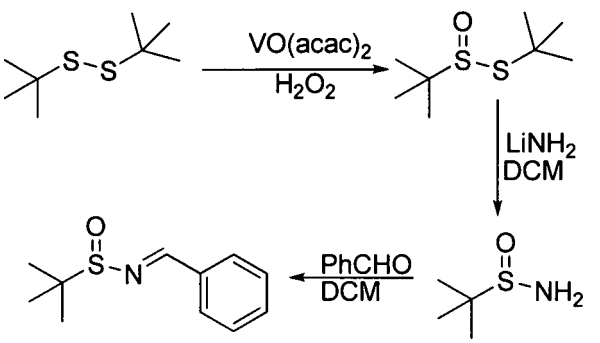


Scheme 38

After complexing with the imine by the bulky samarium/HMPA complex, the *s-cis* radical isomer reverts to the more stable *s-trans* intermediate before undergoing homocoupling. The *s-trans* intermediate is more favoured during homocoupling to reduce steric repulsion between the bulky *t*-butylsulfinyl group and the samarium ligand sphere, which occur in the *s-cis* intermediate. The coupled diamine is obtained after an aqueous quench.

2.1 Homocoupling of benzylidene-*t*-butyl-sulfinimine

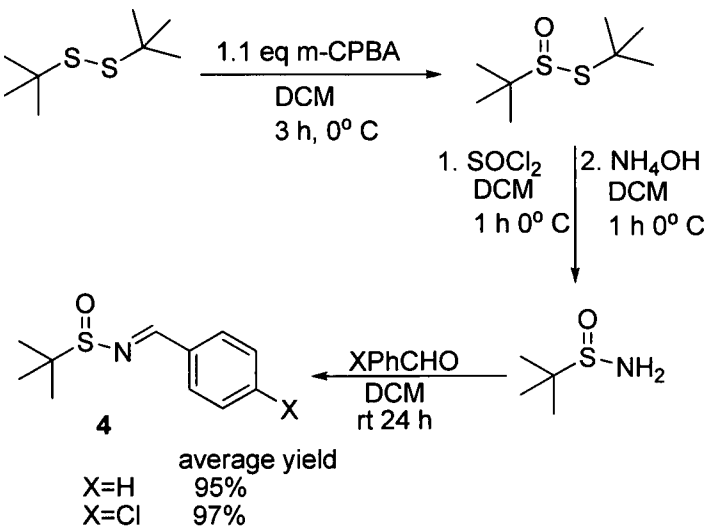
We tried replicating the reaction by using the benzaldehyde derivative of N-*t*-butylsulfinyl imine (R = H, scheme 30) and we decided to investigate the trend and outcomes if smaller amounts of SmI_2 along with a coreductant and different non toxic additives, were used. The sulfinyl imine material was synthesised *via* a different route from that published by Xu *et al* as it was not possible to make the sulfamine in the second step of their reported synthesis.[69,88] They started with the oxidation of *t*-butyldisulfide using hydrogen peroxide, followed by the amination of the thiosulfinate, using liquid ammonia and lithium metal and finally formation of the sulfinyl imine by coupling the sulfamine with an aldehyde (scheme 39).[89]



4

Scheme 39

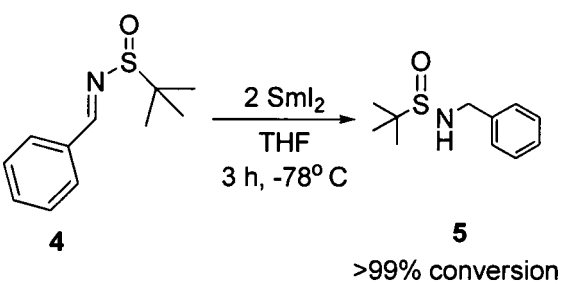
The yield of the oxidation step was quite low (yields were below 50%) and the amination step of this synthesis proved to be hard to reproduce. Thus an alternative pathway was found (scheme 40), starting with *t*-butyldisulfide and *meta*-chloroperbenzoic acid to form the sulfoxide and this oxidation route was much more successful with yields of ≥ 99%.[90] The thiosulfinate was then reacted with sulfuryl chloride and ammonium hydroxide to form the sulfamine material which was then coupled with an aldehyde to give the sulfinyl imine.



Reaction scheme for synthesis of sulfinyl imine

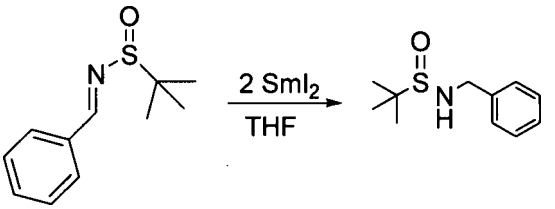
Scheme 40

After having successfully synthesised a sulfinyl imine (benzylidene-*t*-butyl-sulfinimine), the homocoupling reaction was then carried out using two equivalents of SmI_2 as reported in literature. Benzylidene-*t*-butyl-sulfinimine was chosen as substrate as benzaldehyde was easily available and was synthesised in an average yield of 95%. This homocoupling reaction had not been successful. It was reported that this substrate has a coupling yield of 30%, this coupled product was not synthesised and isolated *via* this reaction pathway. Instead the reduced monomer was obtained with >99% conversion as determined by the 1H NMR of the crude reaction mixture (scheme 41).



Scheme 41

Initially the reaction was carried out in a more dilute solution of SmI_2 in THF (1 mmol in 9 mL of THF) than reported in the paper and when a solution of the imine in THF was added dropwise over 30 minutes, no visible change occurred at -78° C (entry 1, table 1).[49] Using same concentration of SmI_2 in THF (1 mmol in 5 mL of THF), only the reduced monomer sulfinamide was obtained as product after 3 hours at -78° C but no coupling product was observed (entry 2, table 1). The sulfinamide was isolated and purified by flash chromatography using a solvent system consisting of 1:6 hexane: ethyl acetate. In order to allow the radical to couple, a reaction was repeated with a longer reaction time of 5 hours at -78° C (an increase of 2 hours over reported reaction time). Again no coupled product was observed (entry 3, table 1). No coupled adduct was observed when the reaction was carried out -25° C for 3 hours and 5 hours, only the reduced monomer was present (entries 4 and 5, table 1). The same result was obtained when the reaction was carried out at 0° C for 5 hours (entry 6, table 1). There was no reduction or change when the homocoupling reaction was carried out in presence of two equivalents of *t*BuOH in SmI_2 at -78° C (entry 7, table 1). As an alternative to the reported toxic HMPA, the same reaction was carried out with tetraglyme at room temperature for 3 hours; but as with *t*BuOH, no reaction occurred (entry 8, table 1). All reaction crudes were analysed by 250 MHz NMR to see whether any change occurred. All the results are summarised in the table (table 1) below and with the exception of entry 1 (1 mmol of SmI_2 in 9 mL of THF), all experiments were carried out using ½ mmol of sulfinyl with 1 mmol of SmI_2 in 5 mL of THF.



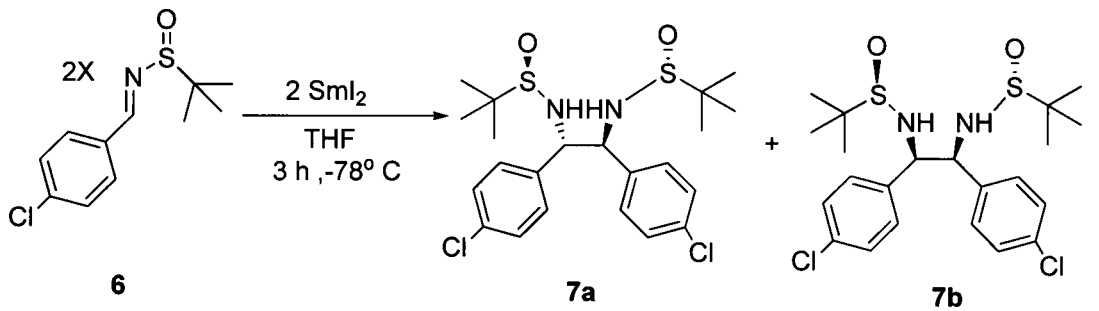
4 5

entry	time	Temp	outcome	additive	conversion
1	3 h	-78° C	no reaction	-	-
2	3 h	-78° C	reduction [a]	-	>99%
3	5 h	-78° C	reduction	-	>99%
4	3 h	-25° C	reduction	-	>99%
5	5 h	-25° C	reduction	-	>99%
6	5 h	0° C	reduction	-	>99%
7	3 h	-78° C	no reaction	*t*BuOH	-
8	3 h	rt	no reaction	tetraglyme	-

Table 1

[a] reaction was carried out more concentrated

2.2 Homocoupling of 4-chlorobenzaldehyde derivative with catalytic amounts of SmI_2



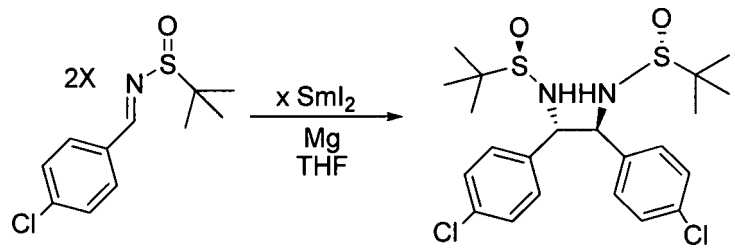
6 7a 7b

Scheme 42

Xu *et al* used the 4-chlorobenzaldehyde imine derivative to study the reductive homocoupling reaction and claimed that in the presence of two equivalents of SmI_2, this imine will undergo coupling to give the dimer in 81% yield with a ratio of *d/l* and *pseudo-meso* coupled products in 1.4:1 (scheme 42). We first tried to replicate the published reaction under the same

conditions without the use of HMPA. The imine was dissolved in dry degassed THF and was added dropwise over 30 minutes to a solution of SmI_2 in THF and the reaction was monitored by tlc. After flash chromatography, the coupled amine product was isolated in 24% yield with only one stereoisomer (entry 1, table 2), the *d/l* product (compared to 81% as published) as reported in the literature by comparison with ^1H and ^{13}C NMR.[49] The same reaction was then carried out using 1.5 eq of SmI_2 and 10 eq of magnesium under the same conditions. After 5 hours at -78° C there was no presence of coupled product (entry 2, table 2). The reaction was left overnight to gradually reach room temperature but again no coupling has occurred. The tlc of the crude showed only the presence of unreacted starting material and no reduced imine. The same reaction was then repeated with an addition time of the imine over 1 hour but was again unsuccessful. The homocoupling was then repeated at a higher temperature of -40° C with an addition time of the imine over 1 hour (entry 3, table 2). After addition of the imine, the SmI_2 turned from dark blue to greenish blue and colour was slowly fading to yellow. After 3 hours, a tlc was carried out on a sample of the reacting mixture and it showed presence of both starting material monomer as well as coupled product. The reaction was left for another 3 hours (total reaction time of 6 hours) at -50° C before work up. This reaction yielded 18% of the coupled product. Only one isomer, the *d/l* adduct was obtained (entry 4, table 2). A series of reactions, using 1.5 and 1.0 eq of SmI_2 were carried out at various temperatures and it was found that the homocoupling only occurred between -50° C and -25° C (entries 4 to 7, table 2). No reaction occurred at 0°C or room temperature, even though reaction was left to stir overnight (entries 8 to 11, table 2). The results of these reactions are shown in table 2 below, so far it was seen that the best yield (30%) was obtained when the reaction used one eq of SmI_2 at a temperature of -40° C for 6 hours, which is an improvement in yield from the reaction using two eq of SmI_2 (entry 5, table 2). The remaining material recovered after each reaction consisted of the starting material imine **6** only. No solution can be put forward as to why the homocoupling using less than two eq of SmI_2 does not occur below -50° C or above -25° C. One possible reason may be at -78° C, magnesium is not reactive enough to reduce Sm^{3+}

to Sm^{2+} but then homocoupling would have been expected to perform much better at higher temperatures. The organosamarium radical intermediate may not be stable enough at higher temperatures and hence reduction was favoured.



6 7a

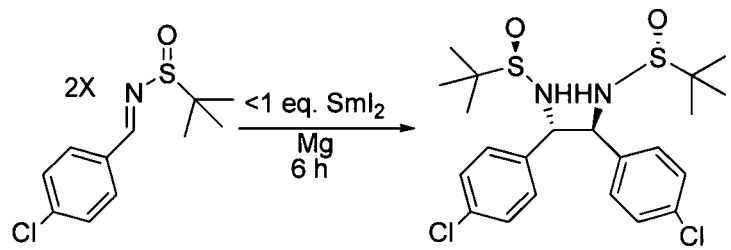
Scheme 43

entry	SmI_2	Temp	time	yield
1	2.0 eq	-78° C	3 h	24%
2	1.5 eq	-78° C	O/N	0%
3	1.0 eq	-78° C	O/N	0%
4	1.5 eq	-40° C	6 h	18%
5	**1.0 eq**	**-40°C**	**6 h**	**30%**
6	1.5 eq	-25° C	6 h	28%
7	1.0 eq	-25° C	6 h	13%
8	1.5 eq	0° C	O/N	0%
9	1.0 eq	0° C	O/N	0%
10	1.5 eq	rt	O/N	0%
11	1.0 eq	rt	O/N	0%

Table 2

The homocoupling of the 4-chlorobenzaldehyde derivative was then carried out with substoichiometric amounts of SmI_2 from 0.75 eq to 0.1 eq along with magnesium acting as coreductant. All reactions were carried out with 1 mmol of sulfinyl imine **6**. All reactions were carried out for 6 hours. Some of the yields were comparable to those carried out with higher amounts of SmI_2 and only the *d/l* isomer was obtained. The remaining material recovered after each reaction consisted of the starting material imine **6** only. All of them were carried out at -40° C and -25° C. Generally yields were slightly higher for the reactions carried out at -25°C. Coupling was also observed with as little as 0.1 eq of SmI_2 (entries 7 and 8, table 3). To investigate whether SmI_2 was

involved in the reaction, the reaction was carried with magnesium only at -40° C and -25° C (entries 9 and 10, table 3). In these experiments, the sulfinyl imine was recovered unchanged, showing that SmI_2 was important in promoting the reductive homocoupling. The yields are shown in table 3 below.



6 **7a**

Scheme 44

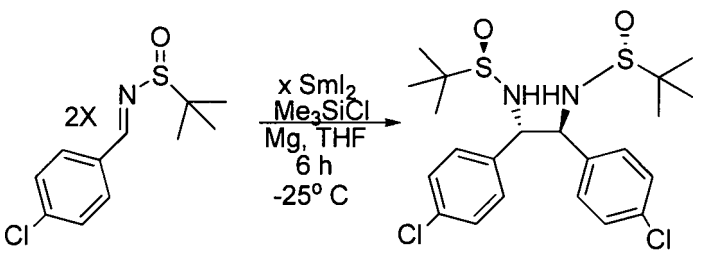
entry	SmI_2	Temp	yield
1	0.75 eq	-40° C	17%
2	0.75 eq	-25° C	10%
3	0.5 eq	-40° C	21%
4	0.5 eq	-25° C	25%
5	0.25 eq	-40° C	9%
6	0.25 eq	-25° C	16%
7	0.1 eq	-40° C	6%
8	0.1 eq	-25° C	10%
9	0 eq	-40° C	0%
10	0 eq	-25° C	0%

Table 3

2.2.2 Homocoupling using SmI_2, Me_3SiCl and Mg

In order to improve the yield of the homocoupling reaction, it is essential for the samarium-substrate bond to break after reduction and coupling in order to allow the samarium to reduce more substrate. Trimethylchlorosilane (TMSCl) was introduced in the reaction so that a Si-O bond could be formed and hence free the Sm (III), which could then be reduced by the magnesium[10,91] to Sm (II) and then continue the catalytic cycle. A reaction was carried out at -25° C, using one eq of SmI_2 with one eq TMSCl (entry 2, table 4). The TMSCl was added to both the substrate in THF and the

SmI_2/Mg mixture. There was a visible change when the silane was mixed with the imine in THF (solution change from colourless to pale yellow with emission of some fumes). This reaction yielded 11% of the *d/l* coupled product only. The same conditions were applied for a second reaction but this time the TMSCl was added to the SmI_2/Mg mixture in one go at the beginning of the reaction (entry 3, table 4). This time 75% of coupled product was isolated. This is the highest yield obtained so far with 100% conversion of starting material to coupled final product. The table below compares the results of these reactions and the remaining material recovered after each reaction consisted of the starting material imine **6** only. It can be seen that adding the silane to the SmI_2 mixture, greatly improves the yield. A series of reactions were carried out using substoichiometric amounts of SmI_2 with and without trimethylchlorosilane. All results are shown in the table 4 below.



6 **7a**

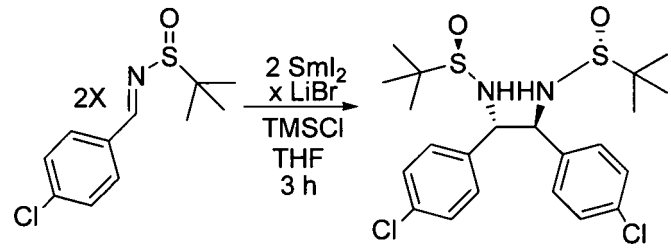
Scheme 45

entry	SmI_2	TMSCl [a]	yield
1	1.0 eq	-	13%
2	1.0 eq	imine	11%
3	**1.0 eq**	**SmI_2**	**75%**
4	0.75 eq	-	10%
5	0.75 eq	SmI_2	44%
6	0.5 eq	-	25%
7	0.5 eq	SmI_2	38%

Table 4

[a] added to either imine or SmI_2

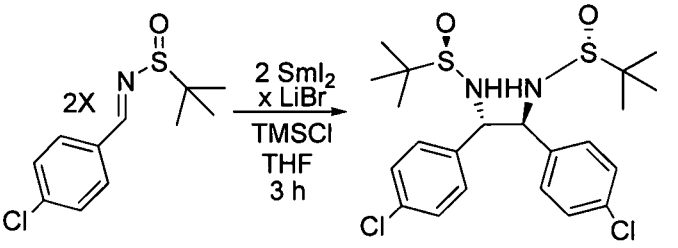
2.2.3 Homocoupling using LiBr as additive



6 **7a**

Scheme 46

Flowers *et al* have found that the addition of LiBr and LiCl to SmI_2 has greatly improved the outcome of the pinacol coupling of cyclohexanone.[31,92] These lithium salts were forming Br^- and Cl^-, which were displacing the I^- from SmI_2 to produce more soluble and solvated $SmBr_2$ and $SmCl_2$. A series of homocoupling reactions of the 4-chlorobenzaldehyde sulfinyl imine was carried out using two eq of SmI_2 with 4 eq, 8 eq and 12 eq of LiBr (scheme 46). The amount of LiBr used was proportional to the concentration of SmI_2. There is an immediate colour change from dark blue to deep purple on addition of SmI_2 to LiBr. The yield of the reaction which was carried out without LiBr was 24% (entry 1, table 5) and with four eq of LiBr, there was no improvement (entry 2, table 5). On using twice the amount of LiBr (8 eq), the same reaction (entry 5, table 5), gave a yield of 61% and with 12 eq of LiBr, the yield was 40% (entry 8, table 5). From these results, reactions using 4 eq, 8 eq and 12 eq of LiBr were carried out at different temperatures to see whether a trend could be found. It was noted that with 4 eq of LiBr, an increase in temperature from -78° C to -40° C gave a slight decrease in yield but on increasing temperature to -25° C, increased the yield to 61% (entries 2 to 4, table 5). When using 8.0 eq (entries 5 to 7, table 5) and 12 eq (entries 8 to 10, table 5) of LiBr were used, an increase in temperature brought about a general decrease in yield. LiBr has not affected stereoselectivity of reaction as only the *d/l* isomer was obtained in each case. Yields are given in table 5 below and the remaining material recovered after each reaction consisted of the starting material imine **6** only.



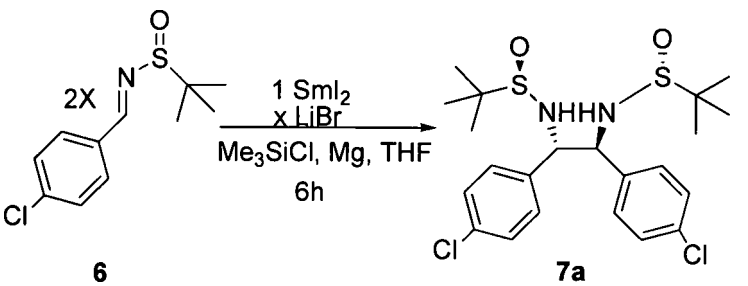
6 **7a**

Scheme 47

entry	LiBr	Temp	yield
1	-	-78° C	24%
2	4 eq	-78° C	23%
3	4 eq	-40° C	17%
4	**4 eq**	**-25° C**	**61%**
5	**8 eq**	**-78° C**	**64%**
6	8 eq	-40° C	16%
7	8 eq	-25° C	20%
8	12 eq	-78° C	40%
9	12 eq	-40° C	38%
10	12 eq	-25° C	27%

Table 5

2.2.4 Homocoupling using LiBr, Me_3SiCl and Mg



6 **7a**

Scheme 48

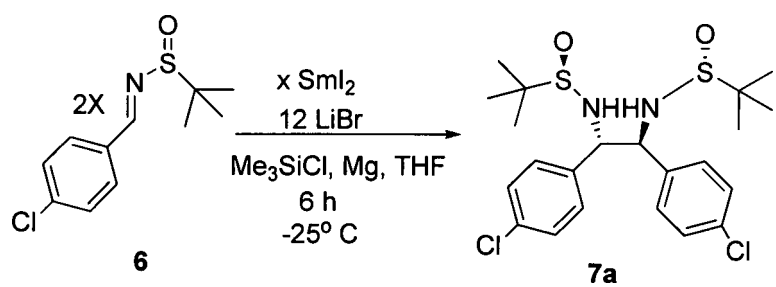
A series of homocoupling reactions were also carried out using one eq of SmI_2 and one eq TMSCl with 4 eq, 8 eq and 12 eq of LiBr at -78° C, -40° C and -25° C (scheme 48). With the 4 eq and 8 eq of LiBr, it was seen that increasing the temperature from -78° C to -40° C increased the yield but a further increase in temperature to -25° C, brought a decrease in the yields

(entries 3 to 8, table 6). The yield of the reactions with 12 eq of LiBr on the other hand is linked to temperature; an increase in temperature has produced a rise in yield (entries 9 to 11, table 6). The optimum conditions for the use of SmI_2 with LiBr are 12.0 eq of LiBr at -25° C. The remaining material recovered after each reaction consisted of the starting material imine **6** only.

entry	LiBr	Temp	yield
1	-	-40° C	30%
2	-	-25° C	13%
3	4 eq	-78° C	6%
4	4 eq	-40° C	37%
5	4 eq	-25° C	27%
6	8 eq	-78° C	18%
7	8 eq	-40° C	37%
8	8 eq	-25° C	22%
9	12 eq	-78° C	29%
10	12 eq	-40° C	31%
11	**12 eq**	**-25° C**	**51%**

Table 6

2.2.5 Homocoupling using catalytic SmI_2, LiBr and Mg



Scheme 49

As previously seen, the highest yield was obtained when 12 eq of LiBr as additive with one eq of SmI_2 at -25° C. A series of reactions were carried out at these conditions using substoichiometric amounts of SmI_2 (scheme 49).

Catalyst equivalents ranging from 0.75 and 0.25 were used and yields ranged from 20% to 34% (entries 2 to 4, table 7). Lowering the amount of SmI_2 has lowered the overall yields of the reactions. All yields are summarised in table 7 below.

entry	SmI_2	yield
1	1 eq	51%
2	0.75 eq	31%
3	0.50 eq	34%
4	0.25 eq	20%

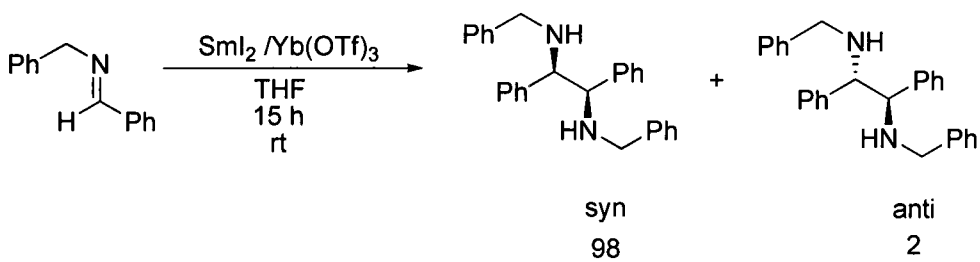
Table 7

2.2.6 Conclusion of the reductive homocoupling of N-*t*-butylsulfinyl imines

The reductive homocoupling of these butylsulfinyl imines have not perfomed very well with catalytic amounts of SmI_2. Even the presence of additives like LiBr has not greatly enhanced the reaction. Addition of TMSCl has up to some extent improved the yield (entry 3, table 4). The addition of HMPA as reported in the literature must be the crucial element for the reductive homocoupling to occur.

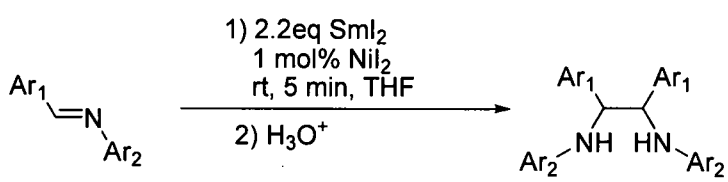
2.3 Reductive homocoupling of imines

As the reductive homocoupling of sulfinyl imines was not very successful, other reductive homocoupling reactions promoted by samarium diiodide reported in literature were investigated. Annunziata *et al* [93] reported a $SmI_2/Yb(OTf)_3$ system to allow the efficient and stereoselective synthesis of 1,2 diamines, whereby the Lewis acid, $Yb(OTf)_3$ was activating the imines towards nucleophilic attack at carbon (scheme 42). It was reported that the homocoupling of *N*-benzyl benzaldimine had to be carried out with SmI_2 in refluxing THF for 15 hrs and yielded a 53% of coupled diamine with 57/43 *syn/anti* mixture of isomers in the absence of $Yb(OTf)_3$. But in the presence of the $SmI_2/Yb(OTf)_3$ system in THF under reflux, the reaction gave an 84% yield of the coupled product with a 63/37 ratio of *syn/anti.* Better selectivity was obtained when the reaction was carrired out at room temperature to give 81% yield with the *syn* isomer as major product in a 98:2 ratio (scheme 50).



Scheme 50

Later in the same year, Namy *et al* [32] reported a similar reaction where a SmI_2/NiI_2 system was used to promote the reductive homocoupling of aromatic imines at room temperature in 5 minutes, giving approximately a 1:1 ratio of isomers (scheme 51).



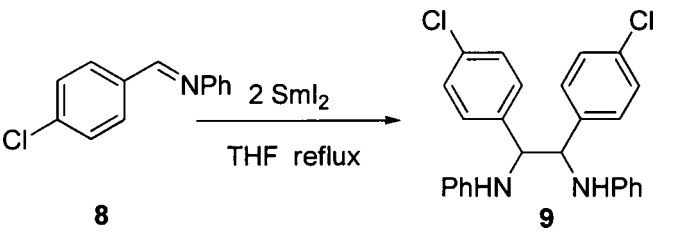
Scheme 51

As Namy's conditions were easier to work with, 4-chlorobenzaldehyde phenyl imine was synthesised and a reaction was carried out using 2.2 eq of

SmI_2 with 1 mol% NiI_2. After 5 minutes, the reaction was stopped but no coupled product was isolated. It was then decided to leave the reaction longer and after 24 hours at room temperature, no change has occurred. The same reaction was repeated under reflux and was completed after 17 hours. Another reaction was carried out with SmI_2 only and this reaction took 19 hours to go to completion. In order to favour coupling, the reaction was repeated with NiI_2 but using less solvent, 2 mmol of SmI_2 were prepared in 10 mL of THF, instead of 16 mL (entry 4, table 8). This reaction took longer to go to completion. An increase in temperature had no effect on the reaction rate (entry 5, table 8); reaction was over in 19 hours when carried out in dimethoxyethane under reflux. Addition of LiBr had no effect on this reaction (entry 6, table 8).

Annunziata's conditions were then used for the reductive homocoupling reaction, using two eq of SmI_2 and one eq of $Yb(OTf)_3$ in THF under reflux. Coupling occurred with formation of both stereoisomers as expected. On addition of SmI_2 to $Yb(OTf)_3$, the dark blue SmI_2 colour faded to green and dark brown. After 23 hours, reaction was completed (entry 7, table 8). It was then thought that the presence of the water on the hydrated $Yb(OTf)_3$ was inhibiting the reaction, hence giving colour change when SmI_2 was added. Another reaction was then carried out using a sample of an anhydrous $Yb(OTf)_3$, which was dried at 130° C for 3 hours under reduced pressure prior to reaction. Again the colour change was noted on addition of SmI_2 to $Yb(OTf)_3$ and the reaction took longer to go to completion (entry 8, table 8). This colour change can only be due to the reduction of Yb (III) to Yb (II) by SmI_2. In order to confirm the catalytic role $Yb(OTf)_3$ in this reaction, a test reaction was carried out with a sample of anhydrous $Eu(OTf)_3$. The redox potential of the Eu^{2+}/Eu^{3+} (redox potential is -0.941 V) [94] is greater than the Sm^{2+}/Sm^{3+}, so no reduction of the lanthanide triflate will hinder the reaction. There was no loss of dark blue colour on addition of SmI_2 to $Eu(OTf)_3$ and this reaction took 48 hours to go to completion (entry 9, table 8). This showed that $Yb(OTf)_3$ was catalysing the reaction. A reaction was then carried out in absence of SmI_2 with Mg acting as reductant. The reaction was

completed in 1 hour under reflux (entry 10, table 8). The results of the above mentioned reactions are summarised in the table 8 below.



8 9

Scheme 52

entry	additive	time
1	NiI_2 at rt	-
2	NiI_2	17 h
3	none	19 h
4	NiI_2 [b]	23 h
5	NiI_2 in DME	19 h
6	LiBr	18 h
7	1 eq $Yb(OTf)_3$ [c]	23 h
8	1 eq dry $Yb(OTf)_3$	28 h
9	1 eq dry $Eu(OTf)_3$	48 h
10	**1 eq dry $Yb(OTf)_3$ + Mg** [d]	**1 h**

Table 8

[b] Reaction was carried out using a more concentrated solution of SmI_2 in THF. [c] hydrated $Yb(OTf)_3$ was used. [d] in absence of SmI_2

Chapter 3

3 Introduction to ytterbium(III) triflate

3.1 Ytterbium (III) triflate

Ytterbium is element 70 and is another rare earth lanthanide metal, discovered by Marignac in 1878 and was isolated in 1907 by Urbain. Ytterbium (III) triflate is a stable and water compatible Lewis acid due to its hard character, relatively small ionic radius of Yb^{3+} (100.8 pm),[95] which is among the smallest of the Ln^{3+} and strong affinity for oxygen.[96,97] It is very electrophilic due to the presence of the three electron-withdrawing trifluoromethanesulfonyl groups, which also enhances the Lewis acidity. Yb(II) is a weaker Lewis acid due to its larger ionic radius (116.0 ppm). The relative Lewis acidity is related to the competitive ligand dissociation from the complex as proposed by Imamoto *et al* using tandem mass spectrometry and was calculated by the peak intensities of the product ion.[98,99] Unlike other conventional Lewis acids like BCl_3 and $SnCl_4$, which react with any trace of water, it is active in both organic and aqueous media.[100] This offers the advantage of using water as solvent instead of organic solvents. Even though it is very environmentally friendly, water is not often used as reaction media due to either insolubility of reactants or low reactivity of reagents. The hydrated ytterbium triflate is easily prepared by heating ytterbium oxide with trifluoromethanesulfonic acid in water.[101,102] Ytterbium oxide is used in a slight excess and the unreacted oxide is then filtered off and the triflate is obtained after evaporation of water. Alternatively silver triflate can also be used with ytterbium chloride to generate ytterbium triflate (scheme 53).

$$Yb_2O_3 + 6\,CF_3SO_3H \xrightarrow[\text{heat}]{H_2O} 2\,Yb(OTf)_3 + 3\,H_2O$$

$$YbCl_3 + 3\,CF_3SO_3H \xrightarrow[\text{heat}]{H_2O} Yb(OTf)_3 + 3\,HCl$$

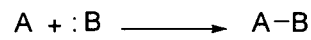
$$YbCl_3 + 3\,Ag(OTf) \xrightarrow[\text{heat}]{H_2O} Yb(OTf)_3 + 3\,AgCl$$

Scheme 53

Each hydrated ytterbium triflate complex $[Yb(H_2O)_9]^{3+}(OTf)_3$ contains up to 9 molecules of water and is air and moisture stable. Anhydrous samples are obtained by heating under vacuum at 140° C for 3 to 4 hours. The anhydrous triflate has to be kept in a vacuum dessicator as it is very hygroscopic.[103]

3.1.1 Ytterbium triflate and Lewis acidity

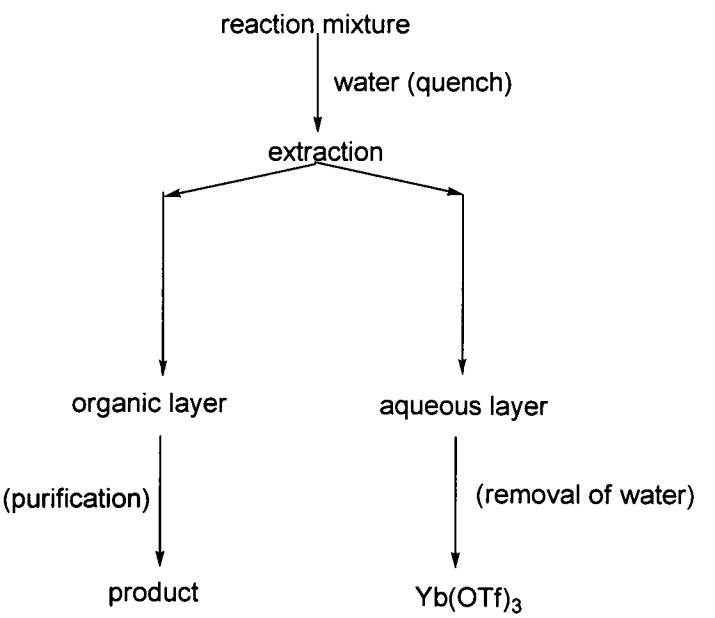
Lewis acid catalysed reactions are very important as they give good selectivities under mild reaction conditions. Lewis acids were first proposed by Lewis in 1923,[104] based on the redistribution of the reactants' valence electrons rather than the characteristic ions formed in the reaction.[105] So from this definition, the Lewis acid is an electron pair acceptor and the Lewis base is an electron pair donor (scheme 54).



Scheme 54

The modern view of a Lewis acid is an ionic or molecular species that has an empty orbital of low energy, LUMO (Lowest Unoccupied Molecular Orbital), which can accommodate a pair of electrons.[106] So a typical Lewis acid will be an electrophile, which can form a cation to react with a nucleophile, for example $AlCl_3$, $TiCl_4$, BF_3 and B_2H_6. Lewis acids can further be classified as "hard" or "soft" depending on their characteristics. The term "hard" applies to species which are small, have high charge states, high electronegativity, high LUMO's and are weakly polarisable like H^+ and Cr^{6+} whereas the term "soft" is used for species which are big, have low charge states, low electronegativity, low LUMO's and are strongly polarisable for example Au^+. This concept was put forward by Pearson in 1962 and is known as the "Hard and Soft Acids and Bases" theory (HSAB) and is used to explain stability of compounds and reaction mechanisms.[107] This is important in coordination chemistry, where there are hard-hard and soft-soft interactions between the metal centre and the ligands.

Usually only catalytic amounts (≤ 20 mol%) of ytterbium triflate are required compared to other conventional Lewis acids (examples discussed in section 3.2), which have to be used in stoichiometric or greater amounts and it can be used alongside several Lewis bases containing nitrogen, oxygen, phosphorus and sulphur.[108] It can be easily recovered after the reaction and reused without lost of catalytic activity. Other ytterbium compounds used as Lewis acids include ytterbium(III) chloride,[109] ytterbium(III) bis(trifluoromethylsulfonyl)amide,[110] ytterbium(III) perfluorooctanoate,[111] ytterbium(III) perfluorooctanesulfonate,[112] and ytterbium(III) acetate.[113] Ytterbium triflate is generally more soluble in water than in organic solvents like dichloromethane and can thus be recovered from the aqueous layer during the work up after a reaction (scheme 55).[96] This is a step towards green chemistry and it is also expected that lanthanide triflates are going to solve some severe waste problems induced by Lewis acid promoted reactions in the chemistry industry.[114]



Scheme 55

Due to the above mentioned properties, ytterbium triflate has been reported in the literature to catalyse and promote a whole range of reactions, namely C-C bond formation like aldol,[115] Mannich,[116] Diels-Alder,[117] ene, Friedel-Crafts (acylation and alkylation),[118] Allylation,[119] Baylis-Hillman,[120] Reformatsky,[121] cyanation,[122] pinacol couplings[123] and Michael reactions,[124]

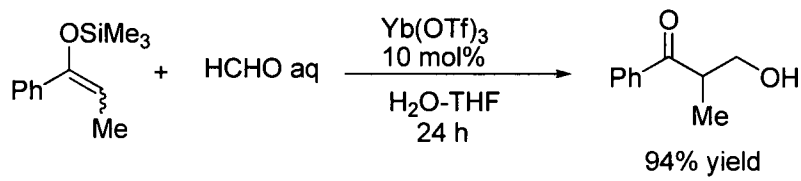
C-X bond formation,[125-127] where X= N, O, P, S etc..., polymerisation,[128] oxidation[129] and reduction,[130] radical additions,[131] rearrangements,[132] protection[133] and deprotection,[134] cycloadditions,[135] cyclisations[136] and ring openings.[137] Some of these reactions are discussed in section 3.2 below.

3.2 Reactions catalysed by ytterbium triflate

3.2.1 C-C bond formation

3.2.1.1 Mukaiyama Aldol

Mukaiyama Aldol reactions are usually performed under strictly anhydrous conditions as the presence of water, even in a trace amount is detrimental to the reaction due to decomposition or hydrolysis of the silyl enol ethers. $Yb(OTf)_3$ can be used in the hydroxymethylation of silyl enol ethers with commercial formaldehyde as reported by Kobayashi *et al* (scheme 56).[115]

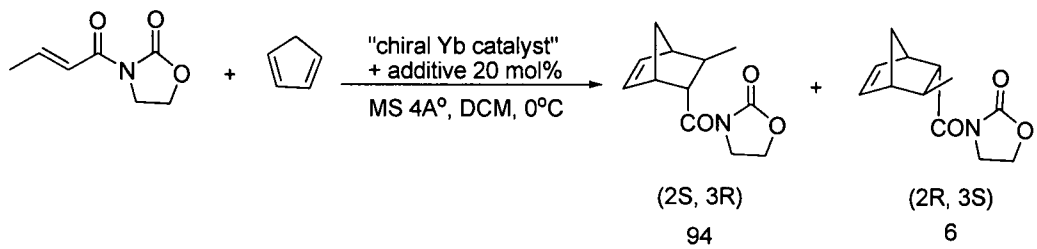


Scheme 56

Commercial formaldehyde is an aqueous solution of 37% formaldehyde and 10% methanol. It is easier to handle than anhydrous formaldehyde, which has to be generated from paraformaldehyde *via* thermal depolymerisation. Several silyl enol ethers were reacted with commercial formaldehyde giving the aldol products in high yields. High enantioselectivities were obtained with sterically hindered silyl enol ethers. Other water soluble aldehydes like acetaldehyde, acrolein and chloroacetaldehyde also reacted smoothly with the silyl enol ether of propiophenone to give cross aldol product in high yields with moderate diastereoselectivities.[138] The ytterbium triflate was easily recovered and recycled without loss of catalytic activity noted. Addition of water was also found to be beneficial to the yield of the reaction.

3.2.1.2 Diels-Alder

The Diels-Alder reaction is useful for generating unsaturated six-membered rings. Lewis acids have been employed to promote Diels-Alder reactions, where they can help to improve the selectivity and extent of *endo* addition. Kobayashi *et al* have successfully used a chiral $Yb(OTf)_3$ complex generated *in situ* to promote the reaction below (scheme 57).[117]

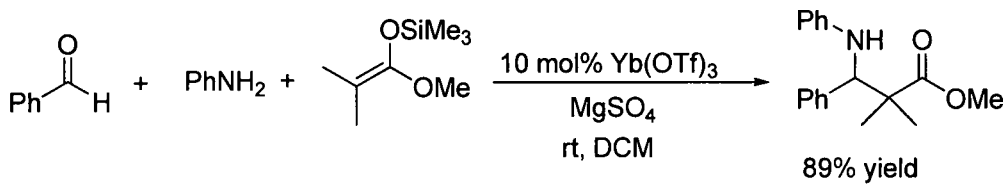


Scheme 57

$Yb(OTf)_3$ was treated with 1.2 eq of (*R*)-(+)-binaphthol ((*R*)-(+)-BINOL) and 2.4 eq of a tertiary amine at 0° C in dichloromethane and molecular sieves to form a chiral complex. The generated chiral $Yb(OTf)_3$ was more soluble and the Diels-Alder reaction proceeded at room temperature. The Diels-Alder adduct was formed in 87% yield with the *endo* adduct giving a 33% enantiomeric excess when 3-(2-butenoyl)-1,3-oxazolidin-2-one and cyclopentadiene were reacted. It was also found that the nature of the amine greatly influenced the outcome of the reaction. Generally bulky amines gave better results and ee's of up to 75% were obtained with *cis*-2,6-dimethylpiperidine. Presence of molecular sieves also increased ee's and ee was further increased to 95% when reaction was carried out at 0° C.

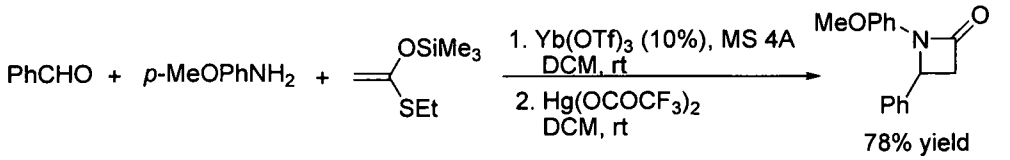
3.2.1.3 Mannich type reaction

In the preparation of β–amino esters, stoichiometric amounts of $TiCl_4$ are usually required and side reactions are common. Small amounts of TMSOTf[139] or FeI_2[140] have been found to promote the reaction but have to be used under strict anhydrous conditions. One of the reaction components, the imines are not very compatible with Lewis acids due to their hygroscopic nature. They have to be generated *in situ* from the corresponding aldehyde and amine as they cannot be easily purified by distillation or chromatographic methods. The condensation of aldehydes and amines generates water as by-product and hence limits the activity of conventional Lewis acids. Kobayashi *et al* have reported the use of catalytic ytterbium triflate in a one-pot synthesis of β–amino esters in high yields (scheme 58).[116]



Scheme 58

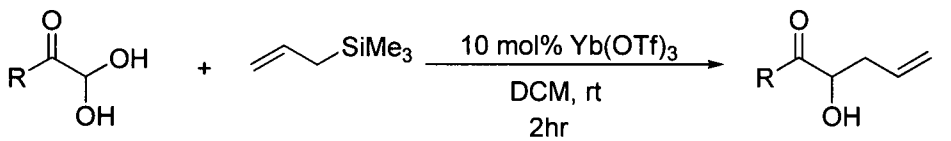
The aldehyde was added to the amine and $Yb(OTf)_3$ before addition of silyl enol ether. Magnesium sulfate or molecular sieves are used as additive to drive the imine formation. The reaction works well with several aromatic and aliphatic aldehydes as well as aromatic and aliphatic amines and most reactions gave the corresponding β–amino ester in high yield. Silyl enolates derived from esters, ketones or thioesters have also been successfully reacted to give the β–amino esters. It was also noted that $TiCl_4$ and TMSOTf yielded only trace amounts of the desired β–amino esters even when used in stoichiometric amounts in the one-pot reaction. This reaction system has also been successfully applied in the synthesis of a β-lactam in 78% yield from benzaldehyde, *p*-anisidine and a silyl enolate in the presence of $Hg(OCOCF_3)_2$ (scheme 59).



Scheme 59

3.2.1.4 Allylation

The allylation of carbonyl compounds with allylsilanes is an important C-C bond forming route in chemistry. It has been found that stoichiometric amounts of Lewis acids have to be used to promote the reaction due to the low nucleophilicity of the allylsilanes. The strong attraction between the Lewis acid and homoallylic alkoxide also makes the catalytic use of the Lewis acid more difficult. Wang *et al* have reported the use of substoichiometric amounts of $Yb(OTf)_3$ to catalyse the allylation of α–keto aldehyde hydrates with the allyltrimethylsilane as shown in the scheme 60 below.[119]



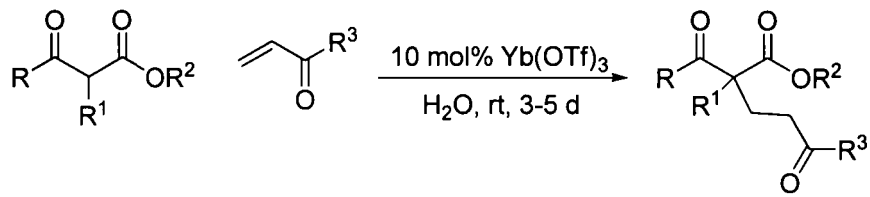
Scheme 60

The reaction proceeded at room temperature, the hydrate and $Yb(OTf)_3$ were allowed to mix prior addition of the allylsilane. The reaction works with glyoxylate hydrates as well and in both cases the homoallylic alcohol was obtained good yields. They have to be converted to the corresponding α-keto aldehyde before reaction with a Lewis acid to limit interaction with hydroxyl group. $Yb(OTf)_3$ does not seem to be affected by the presence of the hydroxyl groups as reaction proceeded smoothly to yield the allyl alcohol. Wang *et al* have also found that the solvent played an important role in the reaction. Some biologically active natural compounds like antibiotics can be

made from precursor compounds with α-keto and α-ester homoallylic alcohol moieties.[141]

3.2.1.5 Michael reaction

The Lewis acid catalysed Michael reaction allows the use of base sensitive Michael acceptors while reducing 1,2-addition. They also give β-quaternary centres in high yields. The reactions are catalysed in non-aqueous conditions and the Michael addition of β-ketoesters is not very favourable when carried out under neutral conditions in water.[142] Feringa *et al* reported the Michael addition of β-ketoesters to β-unsubstituted α,β-unsaturated enones and enals in water, catalysed by 10 mol% $Yb(OTf)_3$ as Lewis acid (scheme 61).[124]



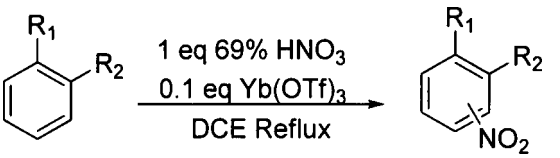
Scheme 61

No acid-catalysed hydrolysis of the ester functionality was seen and the reaction did not work very well in organic solvents like DCM, THF and dioxane. Quantitative yields of Michael adduct was obtained in a 1,4 addition of β-ketoesters to methyl vinyl ketones with 10 mol% of $Yb(OTf)_3$ in water at room temperature. Reaction time ranged from 3 to 5 days and reaction was successful with both cyclic and acyclic β-ketoesters. In the absence of $Yb(OTf)_3$, the reaction gave a 40% conversion after 14 days. The desired Michael adduct was obtained as sole product and no purification was necessary after reaction. The solubility of β-ketoesters did not affect the reaction as high conversion to the corresponding Michael adducts was still observed even when the β-ketoesters did not form a homogenous solution on water.

3.2.2 C-X bond formation

3.2.2.1 Nitration

Aromatic nitrates are useful intermediates as they can used to make compounds for the pharmaceutical, dye, plastic and perfume industries. Their synthesis involves the use of concentrated or fuming nitric and sulphuric acids which can be hard to dispose of.[143] Nitric acid can also be used alongside a strong Lewis acid but has to be used in more than stoichiometric amounts and the excess is lost during the quenching of reaction.[144] Only 10 mol% of $Yb(OTf)_3$ is enough to act as catalyst to promote an aromatic nitration reaction using only one eq of 69% nitric acid as proposed by Waller *et al* (scheme 62).[125]

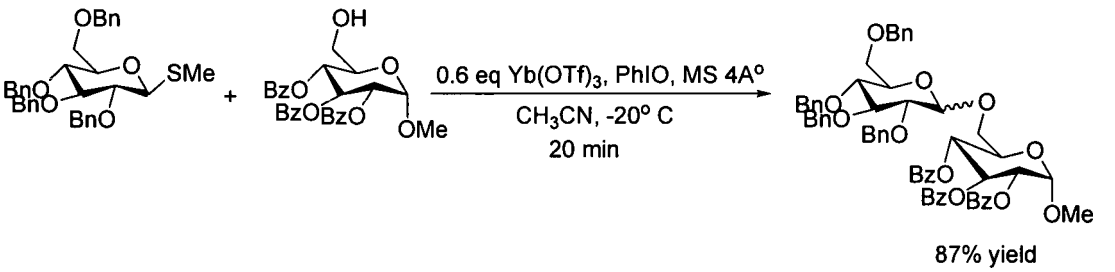


Scheme 62

Nitric acid reacts cleanly with electron rich arenes in refluxing dichloroethane to give the corresponding aromatic nitro compound in good to excellent yields, but the reaction does not work with nitrobenzene. The reaction is very efficient as no other side products like dinitrated compounds were observed in the reaction. Catalyst loading as low as 1 mol% of $Yb(OTf)_3$ still promoted the reaction, the nitration of *m*-xylene was over in 12 hours with an 80% conversion to products. Water is the only by-product and the ytterbium triflate was easily recovered by simple evaporation techniques. The $Yb(OTf)_3$ was still active after 4 runs, giving a conversion rate of 88%.

3.2.2.2 C-O bond formation

Glycosidation is an important reaction due to the presence of several oligosaccharides as part of different natural compounds.[145] Fukase *et al* have put forward a reaction using a iodosobenzene (PhIO)/$Yb(OTf)_3$ system to generate a hypervalent iodine reagent as catalyst to promote the reaction with thioglycosides as glycosyl donors to give disaccharides in good yields and selectivities (scheme 63).[126]

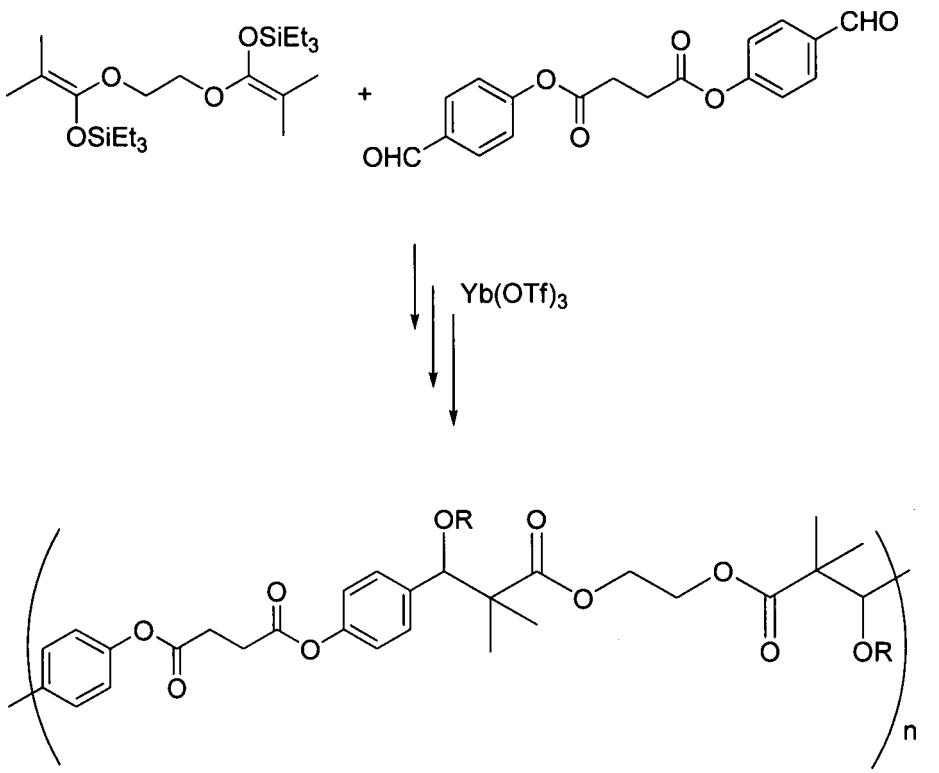


Scheme 63

When $Yb(OTf)_3$ was used as catalyst, β-selective glycosidation was favoured when 2-O-benzoylated or 2-O-acetylated donors were used due to solvent effect of acetonitrile, which attacks the axial position first and neighbouring group participation. Reaction time was less than 20 mins in acetonitrile with a yield of 87% and an α:β ratio of 7:93 for the above reaction. Combination of PhIO with $SnCl_2$-$AgClO_4$ or $BiCl_3$-$AgClO_4$ favoured α-glucosidation.

3.2.3 Polymerisation

Catalytic amounts of $Yb(OTf)_3$ can be used to promote aldol reactions to give polymers with high molecular weights. Itsuno *et al* have reported a repetitive Mukaiyama aldol reaction between a bis-silyl ketene acetal and a dialdehyde to give a polyhydroxy ester (scheme 64).[128]



Scheme 64

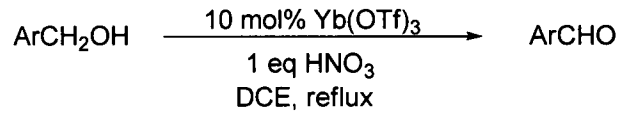
20 mol% of $Yb(OTf)_3$ was very effective for the above aldol reaction. Other Lewis acids like $TiCl_4$ and $ZnBr_2$ required at least two eq to give similar results. Polymers with a main structure having polyhydroxyl esters have been successfully synthesised and this reaction system can also be applied in the generation of optically active polymers when a chirally-modified $Yb(OTf)_3$ is used as catalyst.

3.2.4 Oxidation and reduction

3.2.4.1 Oxidation

Selective oxidation of alcohols to aldehydes is an important transformation and can be carried out using a wide range of reagents but in a lot of cases, heavy toxic metals like chromium, manganese and selenium are involved in more than stoichiometric amounts.[146] Waller *et al* have reported the use of

$Yb(OTf)_3$ as catalyst to promote the oxidation of benzylic alcohols to benzaldehydes with one eq of nitric acid (scheme 65).[129]

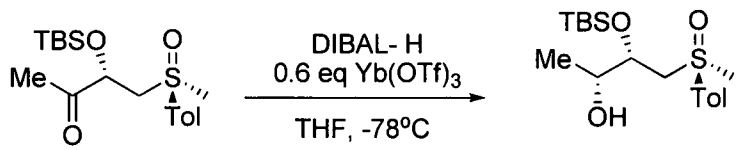


Scheme 65

The use of nitric acid has already been described earlier by McKillop *et al* in 1972 but a minimum of three equivalents of nitric acid was needed and neutralisation of the excess acid was required at the end to quench the reaction.[147] Waller *et al* have optimised the reaction and found that only 10 mol% of $Yb(OTf)_3$ was enough when used alongside one eq of commercial nitric acid (69% w/w) to oxidise one eq of benzyl alcohol to benzaldehyde in 91% yield within 30 minutes in dicholoroethane under reflux. A wide range of alcohols have been studied and the corresponding benzaldehydes were successfully obtained in good to excellent yields with reaction time ranging from 0.5 hour for substituents like Cl, Br and Me to 24 hours for more electron withdrawing substituents like NO_2. Even though presence of NO_2 group slowed down reaction, a 70% conversion was obtained for nitrobenzaldehyde from the nitro benzylalcohol and in the absence of $Yb(OTf)_3$, no corresponding aldehyde was obtained. The $Yb(OTf)_3$/nitric acid system does not work with electron rich arenes as nitration of the aromatic ring occurred as side reaction. The $Yb(OTf)_3$ was recycled and no loss of catalytic activity was observed after 3 runs.

3.2.4.2 Stereoselective reduction

Functionalised diols are useful intermediates as they can used to make natural compounds. Solladié *et al* have proposed a stereoselective sulfoxide directed reduction of β-silyloxy γ-ketosulfoxides to give enantiomerically pure *syn* and *anti* 1,2-diols using DIBAL-H as catalyst alongside $Yb(OTf)_3$ and ZnI_2 (scheme 66).[130]



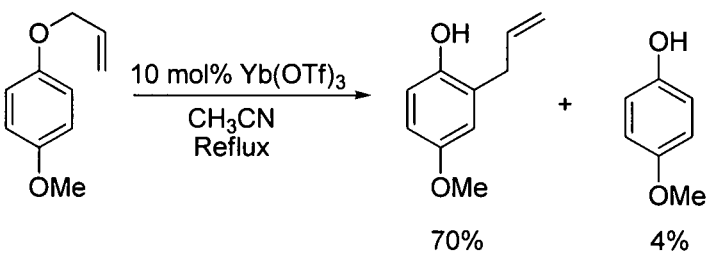
96% yield, de > 90%

Scheme 66

Addition of 0.6 eq of ytterbium triflate has modified the yield, reaction time and selectivity in the DIBAL-H reduction of the β-silyloxy γ-ketosulfoxide to the corresponding 1,2 diol after deprotection. $Yb(OTf)_3$ gives the *syn* product only in 92% yield and reduces the reaction time from 12 hours to 2 hours. In the absence of $Yb(OTf)_3$ a 87/13 ratio of *syn/anti* products is obtained in 60% yield after 12 hours. While $Yb(OTf)_3$ gives only the *syn* product, addition of ZnI_2 to DIBAL-H gives the *anti* product in 3 hours due to chelation of the ZnI_2. The system also works well for allyl, vinyl and phenyl β-silyloxy γ-ketosulfoxides. $Zn(OTf)_2$, $ZnCl_2$ and $ZnBr_2$ gave lower diastereoselectivity. This system has also been applied in the synthesis of natural products Goniobutenolides A.

3.2.5 Rearrangement

The Claisen rearrangement is usually driven by high temperatures. The heating of an allyl vinyl ether will initiate a [3,3] sigmatropic rearrangement to give a γ,δ-unsaturated carbonyl. It was previously reported that presence of a Lewis acid affects the yield and stereoselectivity of the Claisen adduct in the rearrangement of an allylic amine, but the reaction had to be carried out under strict anhydrous conditions.[148] Sharma *et al* have reported the use of catalytic ytterbium triflate to promote the Claisen migration to transform allylic aryl ethers to allylic phenols (scheme 67).[149]

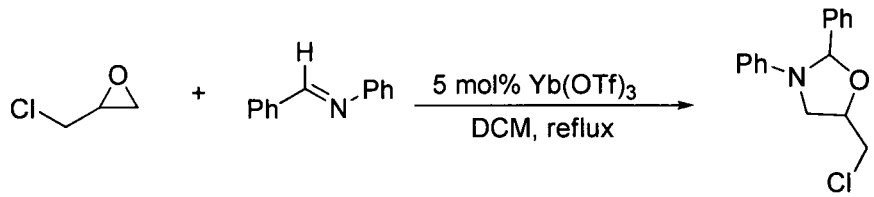


Scheme 67

Only 10 mol% of $Yb(OTf)_3$ was sufficient to promote the Claisen rearrangement of allyl ethers in 48-72 hours. The ortho product was obtained in 70% yield in acetonitrile under reflux with 1-allyloxy-4-methoxybenzene. The reaction was successful with several substituents on the phenyl ring. The system also works for crotyl and prenyl aryl ethers. Crotyl ethers had shorter reaction time of 3 hours. It was also found that the solvent played a role in the reaction as deprotection occurred when nitromethane and dioxane were used while methanol and benzene gave a sluggish reaction mixture.

3.2.6 Cycloaddition

1,3-oxazolidines can be used as ligands on metals for asymmetric synthesis and have been known to show some biological activity.[150,151] Su *et al* have reported the [3+2] cyclo addition of *N*-arylimines and epoxides catalysed by ytterbium triflate under solvent free conditions to give 1,3-oxazolidines (scheme 68).[135]



81% yield

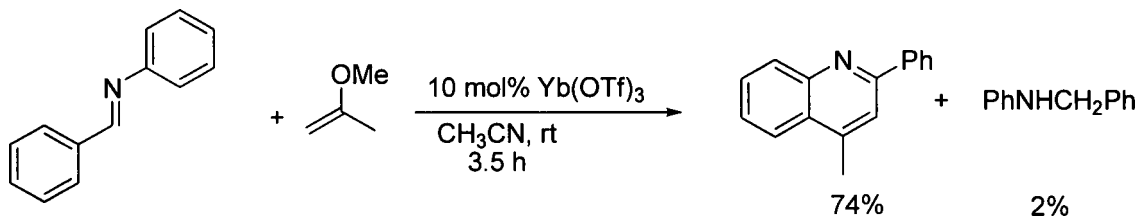
Scheme 68

A few Lewis acids were screened, like $Mg(OTf)_2$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Eu(OTf)_3$, $Y(OTf)_3$ and $AlCl_3$ in the studies and $Yb(OTf)_3$ gave the highest yield in shortest reaction time, 2 hours compared to 4 hours for the other Lewis acids. No desired oxazolidine was seen with $AlCl_3$. It was also found that 5 mol% $Yb(OTf)_3$ gave higher yield than 10 mol% under solvent free conditions. There was no effect on the outcome of the reaction when substituent groups on the *N*-arylimines were changed, yields ranged from 77% to 93%. The system also promotes the reaction between epoxides and ketimines.

3.2.7 Cyclisation

The Diels-Alder reaction of imines or aza-Diels-Alder is an efficient method to synthesise nitrogen containing six-membered rings. Lewis acids like $BF_3.OEt_2$ have been used to promote the reaction.[152] These reactions have not been successful in terms of yield and the Lewis acid had to be used in

more than stoichiometric amounts due to the strong coordination to the nitrogen atoms. Takaki *et al* have reported the use of ytterbium triflate to promote the synthesis of quinoline derivatives from N-arylaldimines and vinyl ethers *via* a [4+2] cycloaddition (scheme 69).[127]

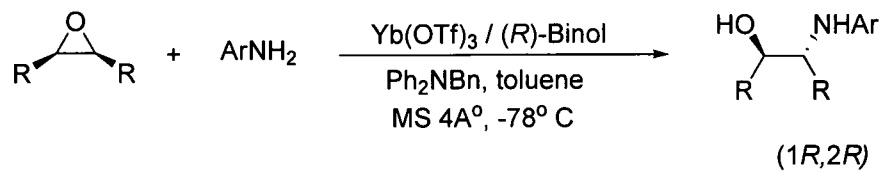


Scheme 69

$Yb(OTf)_3$ showed the highest activity out of the other Lewis acids screened, with a yield of 74% at room temperature in the reaction between benzylideneaniline and 2-methoxypropene whereas YCl_3, $Yb(fod)_3$ and $Yb(OAc)_3$ did not show much activity. A wide range of substituents, used on the arylaldimines like OMe, Me and Cl have been successfully reacted with 2-methoxypropene to give the corresponding quinoline with electron donating or withdrawing groups on the 2- and 6- position of the quinoline ring. The reaction system also works well for the reaction of arylimines with ethyl vinyl ether, dihydrofurans, trimethylsilyl enol ethers and ketene trimethylsilyl acetals, giving the corresponding quinoline derivatives in good to excellent yields. It was also found that the order of addition of reactants and presence of molecular sieves have affected the outcome of the reaction. In some cases, adding all reactants with $Yb(OTf)_3$ gave better yields or mixing of $Yb(OTf)_3$ with vinyl ether followed by arylaldimine or mixing of $Yb(OTf)_3$ with arylaldimine followed by addition of vinyl ether with or without molecular sieves.

3.2.8 Ring opening

β-Amino alcohols are important compounds as they can be used as chiral auxiliaries in diastereoselective reactions and as ligands for metal catalysed reactions and are common structural components of several naturally occurring and synthetic molecules.[153,154] Hou *et al* have proposed an asymmetric ring opening reaction of *meso*-epoxides with anilines promoted by chiral BINOL-Yb(OTf)$_3$ complex generated *in situ* to give β-amino alcohols (scheme 70).[137]



Scheme 70

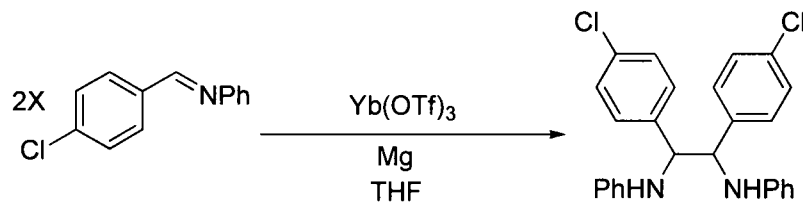
The *in situ* generated BINOL-Yb(OTf)$_3$ complex was very efficient and the corresponding β-amino alcohols were obtained in good yields with good enantiomeric excesses. The reaction has worked well with different substituents of the aniline like OMe, OEt, Cl and Br, though Cl and Br have given better ee values. The range of epoxide substituents included 5 to 8 membered rings, phenyl, methyl and propyl. 1,2-diphenyl epoxide and 1,5-cyclooctadiene monoxide gave better ee's at room temperature compared to -78° C. The enantioselectivity was also increased when a tertiary amine was used as additive over primary and secondary amines.

Chapter 4

4 Other promoters for reductive homocoupling

The reductive homocoupling of imines is an important route to make vicinal diamines as previously discussed in section 1.3.3. Usually metals like sodium,[155] zirconium,[156] aluminium,[157] manganese[158] and zinc[159] or metallic complexes like niobium (IV)[160] and low valent titanium[161] are used to promote the reaction. Photoreduction[162] and electrolysis[163] have also been employed to give coupled product in good yields. These routes have their own advantages as well as limitations.[164] We decided to investigate the potential of $Yb(OTf)_3$ as a catalyst for the reductive homocoupling of imines

4.1 Homocoupling of imines using $Yb(OTf)_3$



81% yield

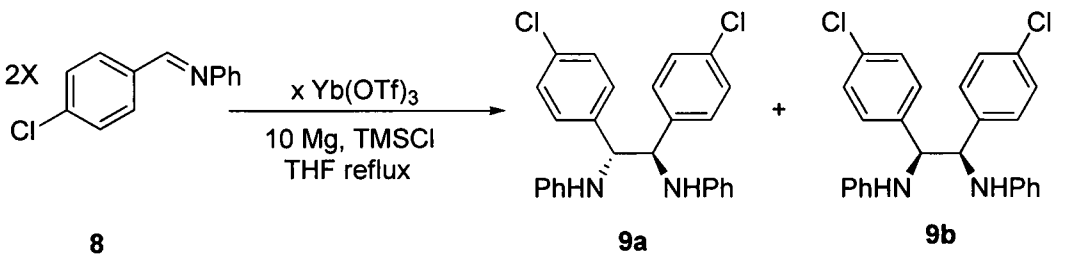
8 **9**

Scheme 71

As previously mentioned in chapter 2, one equivalent of $Yb(OTf)_3$ on its own when used alongside magnesium can promote the reductive homocoupling of imines to give vicinal diamines in THF under reflux (scheme 71). The reaction was carried out in dry distilled THF under an argon atmosphere, using imine **8** as substrate and magnesium as co-reductant. The diamine **9** was obtained in 81% yield in a mixture of both *d/l* and *meso* isomers in a 47:53 ratio after 1 hour. With this result, the aim of the project was again focused on making the reaction catalytic in lanthanide and we hoped that selectivity outcome of the reaction could be improved.

4.2 $Yb(OTf)_3$ as catalyst for imine homocoupling

Diamine **9** was obtained in 81% yield in a mixture of both *d/l* and *meso* isomers in a 47:53 ratio (determined by ^1H NMR of crude reaction mixture) in favour of the *meso* isomer after 1 hour when the reaction was carried out in THF under reflux (entry 1, table 9). The same reaction was carried out at a lower temperature (in an oil bath kept at 40° C) in an attempt to improve selectivity. The reaction was very slow and reaction was stopped after 7 hours when presence of starting material imine **8** was no longer observed by tlc. A mixture of products was obtained but none of the desired coupled diamine was isolated (entry 2, table 9). Reaction time was reduced to 40 minutes when one eq of hydrated $Yb(OTf)_3$ was used and an isomeric ratio of 65:35 in favour of the *d/l* isomer was obtained (entry 3, table 9). The reaction took 3 days to go to completion when the amount of $Yb(OTf)_3$ was lowered to 0.5 eq (entry 4, table 9). Addition of TMSCl to the reaction using 0.5 eq of hydrated $Yb(OTf)_3$ reduced the reaction time to 2 hours (entry 5, table 9). Isolated yields of both isomers were still obtained when 0.01 eq of hydrated $Yb(OTf)_3$ was used with TMSCl with a reaction time of under 5½ hours (entry 9, table 9). Substoichiometric amounts of anhydrous $Yb(OTf)_3$ gave longer reaction time compared to hydrated $Yb(OTf)_3$ (entries 7 and 8, table 9). Trimethylsilyl trifluoromethanesulfonate was not as efficient as chlorotrimethylsilane in promoting the reductive homocoupling coupling reaction, giving a lower yield with a longer reaction time and a slight selectivity towards the *meso* isomer (entry 10, table 9). All the above data is summarised in table 9.



8 **9a** **9b**

Scheme 72

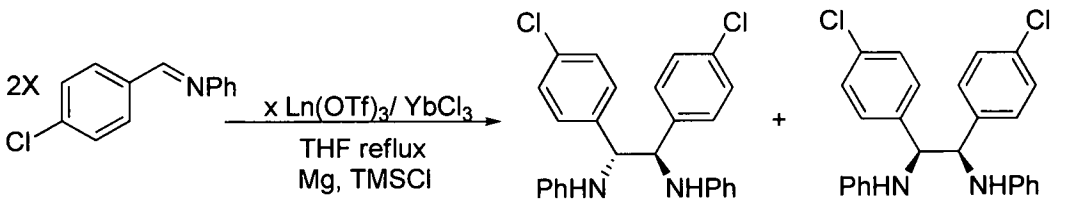
entry	catalyst	state	time	yield	*d/l:meso*
1	1 eq $Yb(OTf)_3$ [e]	anhydrous	1 h	81%	47:53
2	1 eq $Yb(OTf)_3$ [e,f]	anhydrous	7 h	NPI [g]	-
3	**1 eq $Yb(OTf)_3$ [e]**	**hydrated**	**40 min**	**81%**	65:35
4	0.5 eq $Yb(OTf)_3$ [e]	hydrated	>3 days	69%	64:36
5	0.5 eq $Yb(OTf)_3$	hydrated	2 h	64%	63:37
6	0.1 eq $Yb(OTf)_3$	hydrated	2½ h	80%	65:35
7	0.05 eq $Yb(OTf)_3$	anhydrous	4¼ h	NPI [g]	-
8	**0.05 eq $Yb(OTf)_3$**	**hydrated**	**¾ h**	**77%**	59:41
9	0.01 eq $Yb(OTf)_3$	hydrated	5½ h	60%	63:37
10	0.05 eq $Yb(OTf)_3$ [h]	hydrated	3 h	55%	48:52

Table 9

[e] in absence of TMSCl. [f] reaction carried out at 40° C. [g] NPI, no product isolated. [h] reaction used TMSOTf instead of TMSCl

4.2.1 Effect of other lanthanide triflates on the reductive homocoupling of imines

One eq of $Yb(OTf)_3$ reacted with imine **8** in 1 hour, in the presence of magnesium, to give diamine **9** in 81% yield and 0.05 eq $Yb(OTf)_3$ reacted in 45 minutes with a 77% isolated yield (entry 1, table 9). Other lanthanide triflates (Er, Sc, Sm and Y) were then synthesised and screened as potential catalysts for the reductive homocoupling reaction (scheme 73). It was found that $Eu(OTf)_3$, $Er(OTf)_3$ and $Sm(OTf)_3$ do not catalyse this reaction. After about 24 hours, a lot of amine side products were obtained from these reactions but the desired diamine 9 was not isolated (entries 3, 5, 6, 8 and 9, table 10). These reactions were monitored by tlc and the reactions were stopped when there was no starting material left. It was also found that $YbCl_3$ is not as efficient as $Yb(OTf)_3$ in promoting the reaction. 0.05 eq of $YbCl_3$ catalysed the reaction in 4 hours and diamine **9** was isolated in 61% yield with a *d/l*:*meso* ratio of 64:36 in favour of the *d/l* isomer (entry 2, table 10). 0.05 eq $Y(OTf)_3$ has catalysed the reaction. Hydrated $Y(OTf)_3$ reacted in 75 minutes with 70% yield of the desired diamine **9** in a 65:35 ratio in favour of the *d/l* isomer (entry 10, table 10). Dry $Y(OTf)_3$ catalysed the reaction in 5½ hours with formation of several side products and none of the desired coupled amine was isolated (entry 7, table 10). A reaction using $Sc(OTf)_3$ to promote the reductive homocoupling did not give the desired coupled product after 2 hours (entry 11, table 10). These results show that among the lanthanide triflates screened, $Yb(OTf)_3$ was the most efficient catalyst for the reductive homocoupling of imines. We have also seen that $YbCl_3$ was not as efficient as $Yb(OTf)_3$ in promoting the reductive homocoupling of imines. All these above mentioned results are summarised in table 10.



8 **9a** **9b**

Scheme 73

entry	catalyst	state	time	yield	*d/l:meso*
1	1 eq $Yb(OTf)_3$ [i]	anhydrous	1 h	74%	47:53
2	0.05 eq $YbCl_3$	anhydrous	4 h	61%	64:36
3	1 eq $Eu(OTf)_3$ [i,j]	anhydrous	-	-	-
4	0.05 eq $Yb(OTf)_3$	anhydrous	4½ h	NPI [k]	-
5	0.05 eq $Er(OTf)_3$	anhydrous	22 h	NPI [k]	-
6	0.05 eq $Sm(OTf)_3$	anhydrous	27 h	NPI [k]	-
7	0.05 eq $Y(OTf)_3$	anhydrous	5½ h	NPI [k]	-
8	0.05 eq $Er(OTf)_3$	hydrated	24 h	NPI [k]	-
9	0.05 eq $Sm(OTf)_3$	hydrated	24 h	NPI [k]	-
10	0.05 eq $Y(OTf)_3$	hydrated	1¼ h	70%	65:35
11	0.05 eq $Sc(OTf)_3$	hydrated	2 h	NPI [k]	-

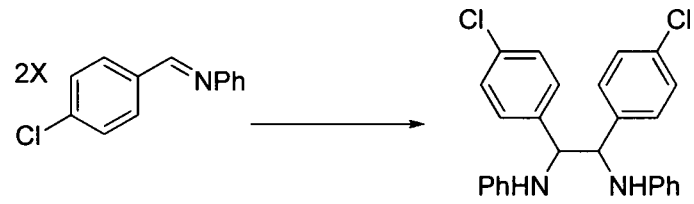
Table 10

[i] in absence of TMSCl. [j] reaction was left for 4 days. [k] NPI, no product isolated

4.2.2 Lewis acid or Brønsted acid catalysed?

As discussed previously in section 4.2.1 not all lanthanide triflates were efficient at promoting the reductive homocoupling reaction. In order to optimise the reaction, it was necessary to confirm the role of the $Yb(OTf)_3$. As a large excess of magnesium is used, it could be that Yb^{2+} is the actual catalyst. Yb(II) was generated *in situ* by reducing $Yb(OTf)_3$ with EtMgBr.[123] In the presence of one eq of $Yb(OTf)_3$, one eq of EtMgBr and 10 eq of magnesium, reaction gave 75% yield in 90 minutes (entry 1, table 11). The reaction did not occur when one eq of $Yb(OTf)_3$ and one eq of EtMgBr were used on their own (entry 2, table 11). No reaction occured when 0.05 eq triflic

acid or 0.05 eq tosyl acid were used along with 10 eq magnesium and one eq of TMSCl (entries 3 and 4, table 11). Magnesium does not promote the reaction on its own even in the presence of TMSCl (entries 5 and 7, table 11). One eq of TMSCl also does not promote the reaction (entry 6, table 11). All these results show that the reaction is not Brønsted acid catalysed but Lewis acid catalysed, shown by the fact that Yb(II) cannot promote reaction. This can be explained as the Lewis acidity of Yb(II) is less compared to Yb(III) due to the larger ionic radius of Yb^{2+} compared to Yb^{3+}.



8 **9**

Scheme 74

entry	conditions	time	yield
1	1 eq $Yb(OTf)_3$ + EtMgBr + Mg	1½ h	75%
2	1 eq $Yb(OTf)_3$ + EtMgBr	no reaction	-
3	0.05 eq Tosyl acid + Mg + TMSCl	no reaction	-
4	0.05 eq Triflic acid + Mg + TMSCl	no reaction	-
5	Mg + TMSCl	no reaction	-
6	TMSCl only	no reaction	-
7	Mg only	no reaction	-

Table 11

Coordination of the imine substrate to the ytterbium centre has also been demonstrated by ^1H NMR spectroscopy. When a sample using one eq of $Yb(OTf)_3$ and one eq of 4-chlorobenzaldehyde phenylimine in d^8 THF was analysed by ^1H NMR, all the peaks were shifted (diagrams 1 and 2). Three samples were prepared and analysed, the first sample is made from one eq of $Y(OTf)_3$ and one eq of imine **8** (blue spectra on diagrams 1 and 2), the second sample is imine **8** only (red spectra on diagrams 1 and 2) and the third sample is made from one eq of $Yb(OTf)_3$ and one eq of imine **8** (green spectra on diagrams 1 and 2). All three samples were in d^8 THF and were referenced to the THF multiplet peaks at 1.85 ppm. The singlet from the imine proton has been shifted from 8.58 ppm to 8.71 ppm in the presence of

$Yb(OTf)_3$. The distance between this singlet to the first doublet on the right to it has also been changed. In the sample with $Y(OTf)_3$ and the sample of the imine, this distance is about 0.58 ppm, when $Yb(OTf)_3$ was present, this distance was increased to 0.64 ppm. This doublet has also shifted by 0.08 ppm, in the presence of $Yb(OTf)_3$, the doublet appears at 8.08 ppm while in the absence of $Yb(OTf)_3$, the doublet is at 8.00 ppm. This shows that the imine is probably complexing to the ytterbium cation prior to coupling.

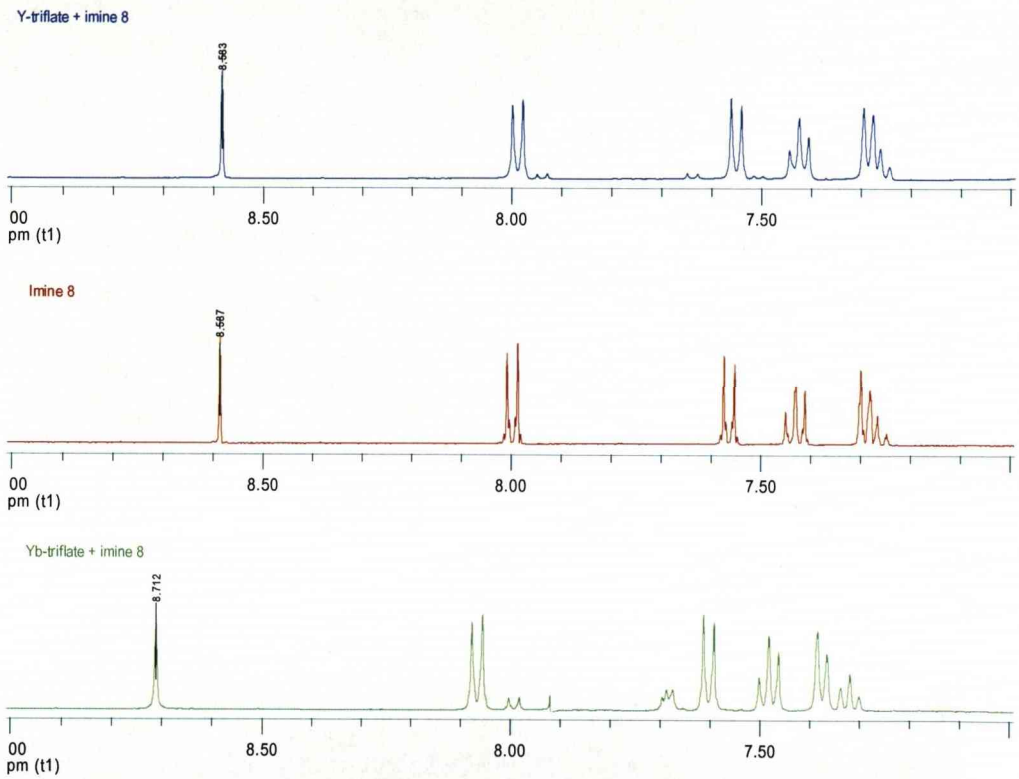


Diagram 1

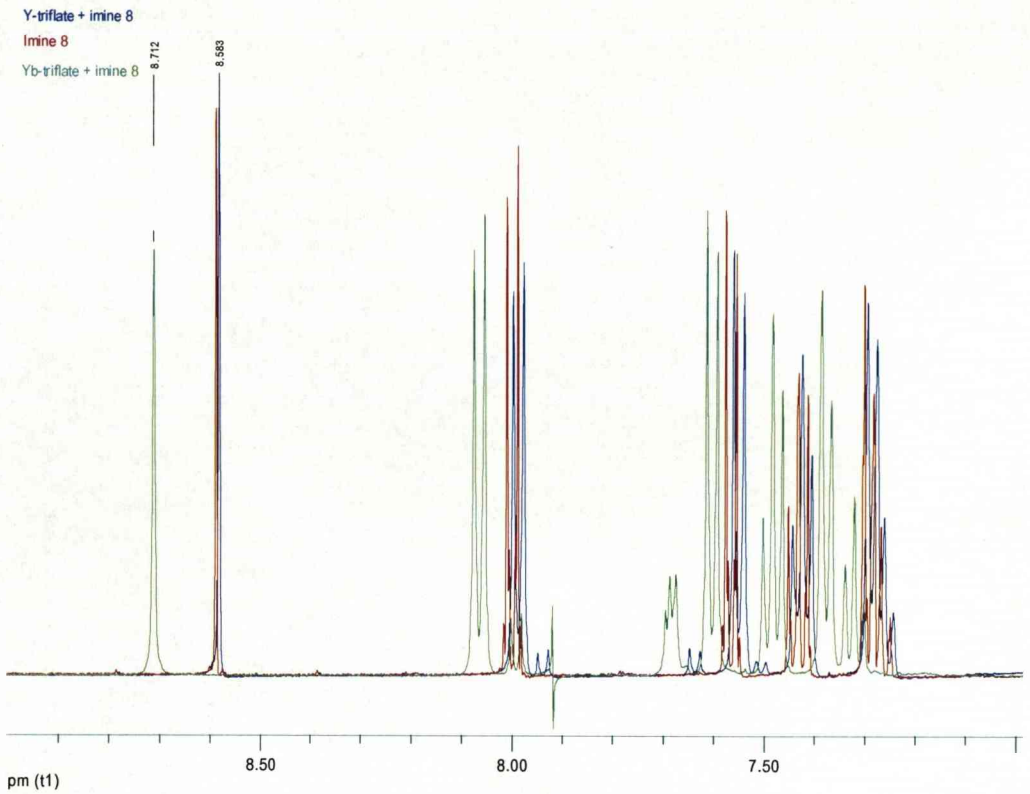
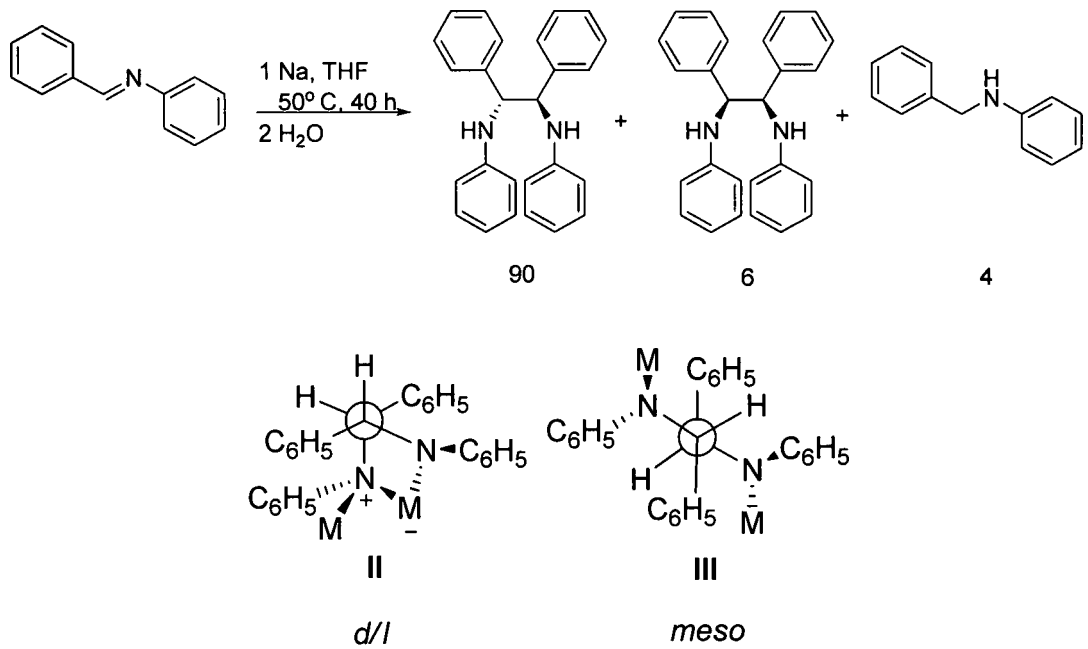


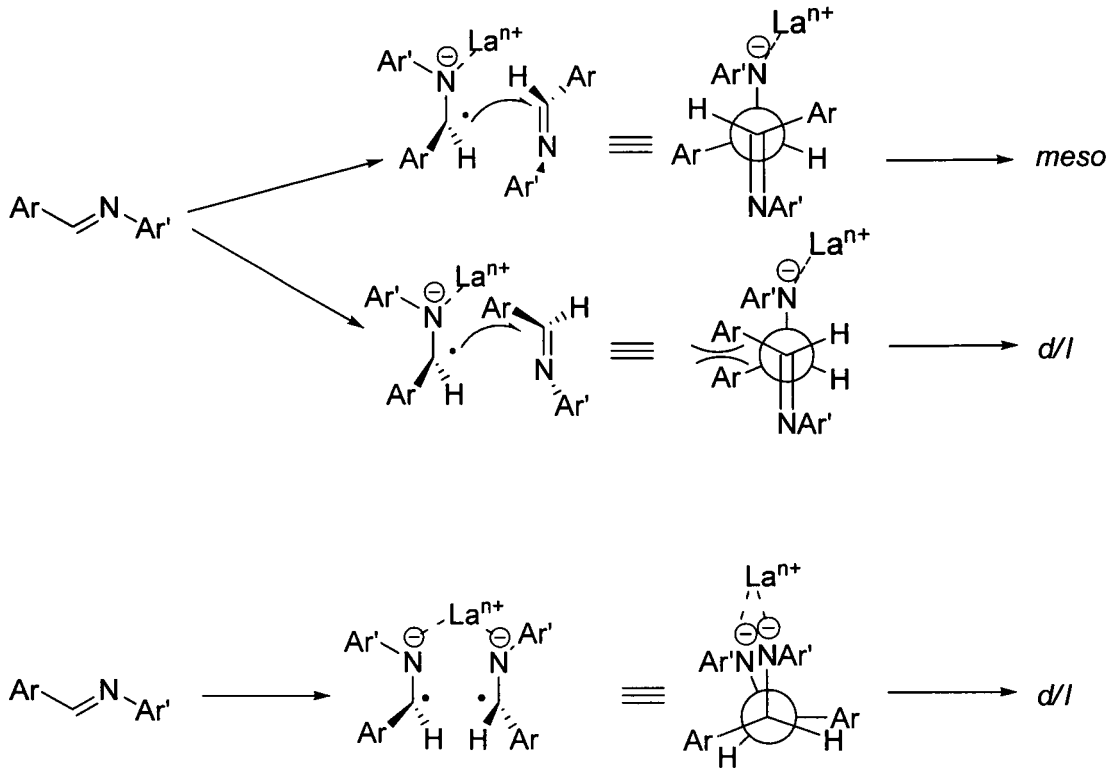
Diagram 2

Peterson *et al* put forward a mechanism to explain the formation of the *d/l* and *meso* diamines.[155] They studied the reductive homocoupling of benzaldehyde phenylimine (scheme 74) *via* a radical pathway promoted by various metals (lithium, sodium, magnesium, barium and aluminium/mercury) in different solvents (benzene, ether, THF and *N*-methylpyrrolidine). The *d/l* isomer was the major product in every case studied and its formation can be explained by steric factors. When two metal-anion pairs are attracted to each other, the bulky phenyl groups in the ion cluster tend to place themselves as far apart as possible before formation of the central carbon-carbon bond (scheme 75, **II**). The *meso* configuration occurs when two radicals fuse together unsymmetrically with the bulky phenyl groups *trans* to each other to form the carbon-carbon bond (scheme 75, **III**). They also found that ratios of both isomers were not affected by the activity or the size of the metal. The best selectivity 90:6 in favour of the *d/l* isomer was obtained when sodium was used to promote the reaction in THF at 45-50° C for 40 hours.



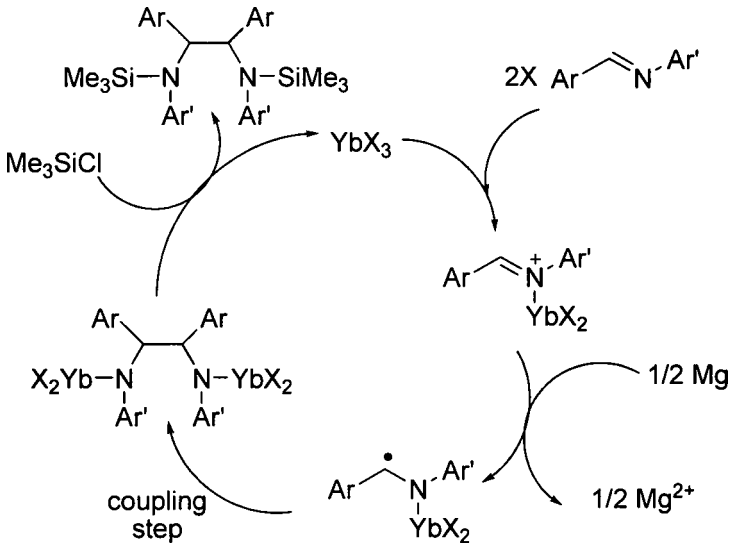
Scheme 75

Sonoda *et al* have also studied the reductive dimerisation of imines using lanthanum metal as promoter (scheme 76).[165] When the reaction was carried out with one eq of lanthanum metal only in THF, no coupled product was observed. Coupling occurred only when a catalytic amount of iodine (0.2 eq) was added to the reaction. They noted that the *meso* diamine was formed *via* a single electron transfer from lanthanum to the carbon-nitrogen double bond of another imine and was the major product when 0.5 eq of lanthanum metal was used. Thus the *meso* diamine is obtained after the addition of the ketyl like intermediate to the carbon-nitrogen double bond of another imine (scheme 76). This route does not favour the *d/l* diamine due to steric repulsion between 2 phenyl groups. They also observed that the *d/l* diamine was favoured when two eq of lanthanum metal were used. Hence they claimed that the *d/l* diamine is formed from 2 separate radicals joined by a lanthanum cation prior central carbon-carbon bond formation. A ratio of 1:1 was obtained when one eq of lanthanum was used. Their proposed mechanism is described in the scheme 76.



Scheme 76

We propose a catalytic cycle to explain the role of the Yb(III) in promoting the reductive homocoupling of imines. The Lewis acid Yb(III) coordinates to the nitrogen of the imine and this new Yb-imino complex is reduced by magnesium. The Yb-imino complex is easier to reduce and forms a radical due to an electron transfer from the magnesium. The radical amino anion then dimerises with another radical amino anion or adds itself to another imine to give the diamine product. The exact coupling mechanism is not clear at the moment and is further discussed in section 4.4. Addition of TMSCl will form a N-Si bond and hence free the Yb(III), which can then start a new catalytic cycle (Scheme 77).



Scheme 77

4.2.3 Effect of ligands on selectivity of the reaction

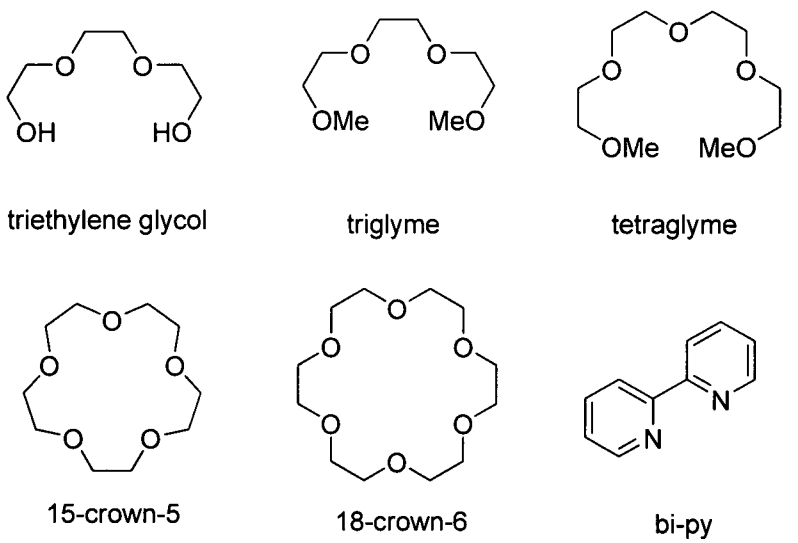
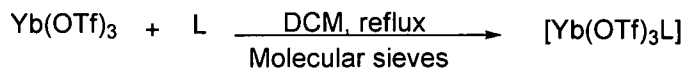


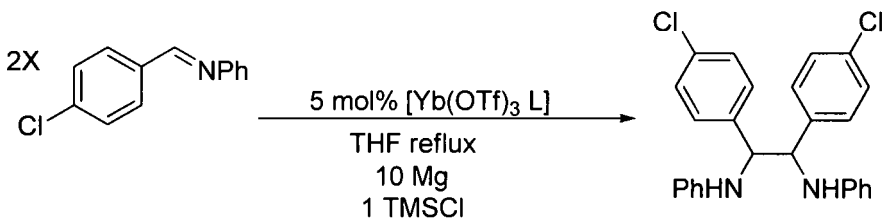
Figure 6

In an attempt to increase the selectivity of the reductive homocoupling reaction, simple polyether ligands like triglyme, triethylene glycol, tetraglyme, 15-crown-5 and 18-crown-6, were incorporated onto the ytterbium triflate to form complexes. A complex from 2,2-bi-pyridyl was also synthesised. These complexes were prepared by refluxing the polyether and $Yb(OTf)_3$ in DCM and water was removed from the azeotrope by using a soxhlet thimble filled with molecular sieves (scheme 78).



Scheme 78

All the ytterbium complexes catalysed the reductive homocoupling of imine **8** to give the desired coupled diamine **9** in isolated yields ranging from 59% to 81% (table 12). Both isomers were obtained and all reactions were run in THF under reflux with 10 eq of magnesium and one eq of TMSCl (scheme 78). Anhydrous complexes gave lower yields with longer reaction times compared to the corresponding hydrated complexes and a lot of side products were formed (entries 2 and 4, table 12). The anhydrous triethylene glycol complex reacted at similar rates compared to the hydrated triethylene glycol complex as the presence of the two OH's acted like water (entries 3 and 4, table 12). The *d/l* isomer was the major product for all the reactions from the ytterbium complexes with the best selectivity obtained with the tetraglyme complex (entry 5, table 12).



8 **9**

Scheme 79

entry	ligand	time	yield	*d/l:meso*
1	triglyme	< 1 h	68%	65:35
2	triglyme [I]	4½ h	59%	57:43
3	triethylene glycol	< 1 h	81%	67:33
4	triethylene glycol [I]	1½ h	62%	66:34
5	tetraglyme	<1 h	69%	69:31
6	bi-py	<1 h	51%	68:32
7	15C5	<1 h	73%	58:42
8	18C6	<1 h	60%	64:36

Table 12

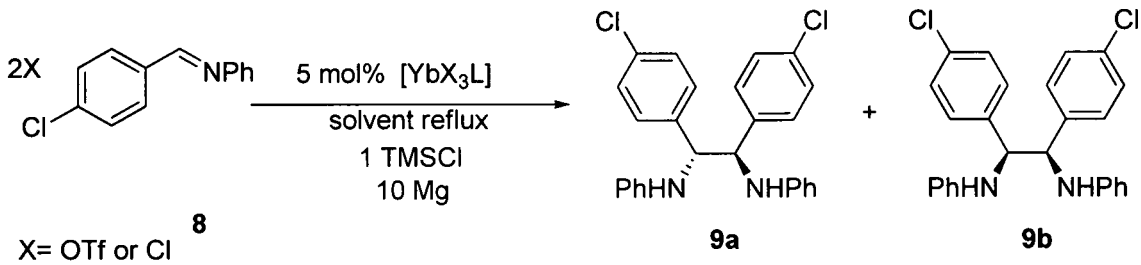
[I] anhydrous complex was used.

4.2.4 Solvent effect in the reaction

In an attempt to improve the selectivity of the reaction, a study of solvents was carried out. It was found that non-coordinating solvents like DCM, chloroform and toluene did not allow the reaction to proceed due to the poor solubility of $Yb(OTf)_3$ in these solvents (entries 1, 2 and 3, table 13). The reaction occurred in another coordinating solvent, acetonitrile. The reaction using 5 mol% of $Yb(OTf)_3$ in acetonitrile gave an isolated yield of 65% in under 1 hour (entry 4, table 13). In comparison to the reaction using 5 mol% of $Yb(OTf)_3$ in THF (entry 8, table 9), the yield and selectivity was lower with a longer reaction time. Complexes gave higher yields in shorter reaction time (entries 5 and 6, table 13). All the above mentioned reactions were carried out under reflux, except for the reaction in toluene which was carried out in an oil bath kept at 75° C.

Annunziata *et al* have claimed that selectivity towards the *meso* isomer is greatly improved when the reductive homocoupling using the $SmI_2/Yb(OTf)_3$ system was carried out at rt.[93] As previously discussed, the reaction did not occur in DCM under reflux (entry 1, table 13) nor in THF at 40° C (entry 2, table 9). Yamanaka *et al* have reported that using a solvent mixture of 4:1 DCM/THF have allowed an $Yb(OTf)_3$ catalysed reaction proceed at rt.[166] This mixture of DCM and THF (non-coordinating and coordinating solvents) allowed the reductive homocoupling reaction to go in 3½ hours at rt with an isolated yield of 70% (entry 7, table 13). Under reflux this solvent mixture gave a reduced reaction time of 30 minutes with 77% yield (entry 8, table 13). Both reactions gave poor selectivities. The $Yb(OTf)_3$ was dissolved in THF and a solution of the imine in DCM was then added. The reaction catalysed by the 15-crown-5 complex in the DCM/THF mixture went to completion in 3 hours with an isolated yield of 70% with the *d/l* isomer as major product in a ratio of 68:32 over the *meso* (entry 9 table 13). The $YbCl_3$ catalysed reaction was slower compared to $Yb(OTf)_3$ in this solvent mixture, with a lower yield of 66% and a lower selectivity at rt (entry 11, table 13). Under reflux, $YbCl_3$ promoted the reaction in 2½ hours with a yield of 73% and a better selectivity for the *d/l* isomer (entry 10, table 13). A complex

made from $YbCl_3$ and 15-crown-5, generated *in situ,* was used in the DCM/THF solvent mixture. This reaction went to completion in 5 hours with an isolated yield of 72% and a ratio of 62:38 in favour of the *d/l* isomer over the *meso* (entry 12, table 13). These results show that the presence of a coordinating solvent was essential to promote the reaction but the solvent was not affecting the selectivity. All the results for the above mentioned reactions are summarised in table 13 below.



X= OTf or Cl **8** **9a** **9b**

Scheme 80

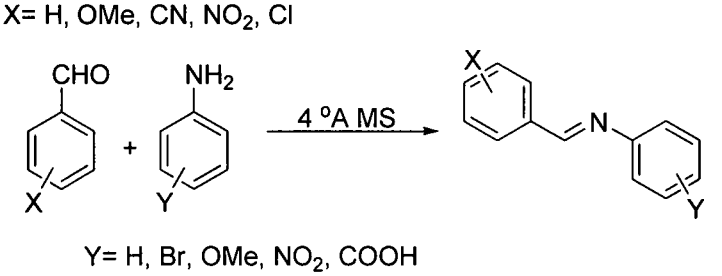
entry	catalyst	solvent	time	yield	*d/l:meso*
1	$Yb(OTf)_3$	DCM	-	-	-
2	$Yb(OTf)_3$	$CHCl_3$	-	-	-
3	$Yb(OTf)_3$ [m]	Toluene	-	-	-
4	$Yb(OTf)_3$	MeCN	<1h	65%	56:44
5	15C5 complex	MeCN	½ h	81%	62:38
6	triethylene glycol complex	MeCN	¾ h	67%	60:40
7	$Yb(OTf)_3$ [n]	DCM/THF	3½ h	70%	65:35
8	$Yb(OTf)_3$	DCM/THF	½ h	77%	66:34
9	15C5 complex [n]	DCM/THF	3 h	70%	68:32
10	$YbCl_3$	DCM/THF	2½ h	73%	68:32
11	$YbCl_3$ [n]	DCM/THF	3½ h	66%	58:42
12	$YbCl_3$/15C5 [n]	DCM/THF	5 h	72%	62:38

Table 13

[m] reaction was carried out at 75° C. [n] reaction was carried out at rt

4.3 Other imines

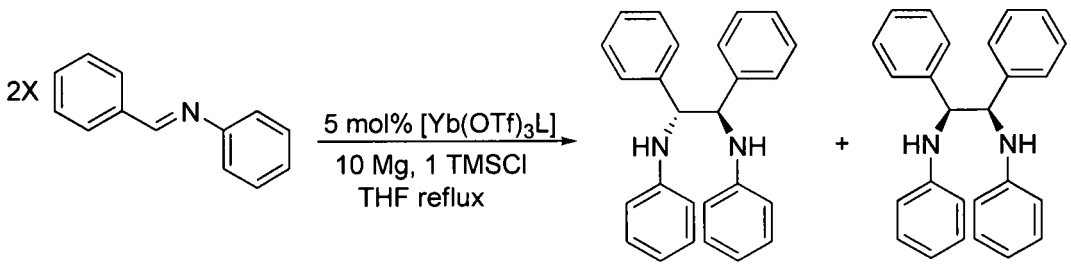
The reductive homocoupling, promoted by $Yb(OTf)_3$ and $[Yb(OTf)_3L]$ was carried out using a range of imines, synthesised from different substituted benzaldehydes and substituted anilines (scheme 81). The *d/l* to *meso* ratios were determined by ^1H NMR of crude reaction mixture. The results of these reductive homocoupling reactions are discussed below.



Scheme 81

4.3.1 Reductive homocoupling of benzaldehyde phenylimine

This imine was synthesised from benzaldehyde and aniline. It reacted with $Yb(OTf)_3$ and $[Yb(OTf)_3L]$ in THF under reflux to give both desired coupled diamines **11a** and **11b** (scheme 82) in good to excellent yields (table 14). Initially the reaction was carried out with one eq of $Yb(OTf)_3$ and 10 eq of magnesium in THF under reflux (entry 1, table 14). This reaction was over in 75 minutes with 84% yield and the *d/l* isomer was the major product in a 62:38 ratio over the *meso* product. The selectivity was reduced when 5 mol% of $Yb(OTf)_3$ was used along with 10 eq of magnesium and one eq of TMSCl (entry 2, table 14). Reactions using 5 mol% of $Yb(OTf)_3$ or $[Yb(OTf)_3L]$ complexes had slightly longer reaction times but yields were comparable to the reaction using stoichiometric $Yb(OTf)_3$. The best selectivity was obtained when the 15-crown-5 complex was used to promote the reaction in THF under reflux (entry 3, table 14). The *d/l* isomer was again the major product in a 91:9 ratio over the *meso*. The results of the reactions of benzaldehyde phenylimine are summarised in the table 14 below.



10 **11a** **11b**

Scheme 82

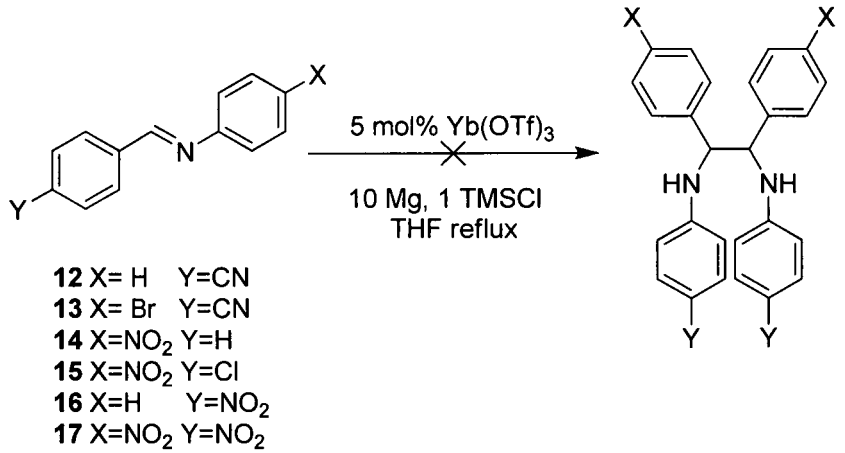
entry	catalyst	time	yield	*d/l:meso*
1	1 eq $Yb(OTf)_3$ °	1¼ h	84%	74:26
2	0.05 eq $Yb(OTf)_3$	2 h	77%	62:38
3	**0.05 eq 15-C-5 complex**	**2 h**	**76%**	**91: 9**
4	0.05 eq triethylene glycol complex	2 h	80%	68:32

Table 14

° in absence of TMSCl

4.3.2 Electron withdrawing substituents on phenyl ring

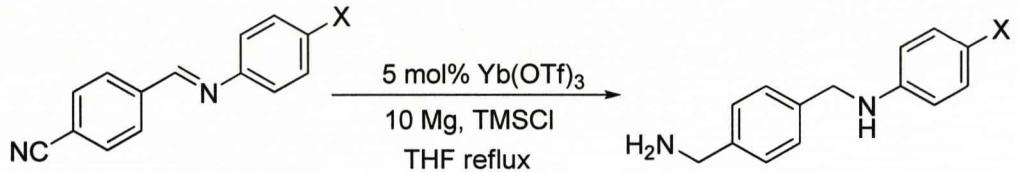
Six imines were synthesised from 4-cyanobenzaldehyde, 4-nitrobenzaldehyde and 4-nitroaniline and these imines reacted very differently compared to the previous substrates described. Three imines from 4-aminobenzoic acid were also synthesised. The results of the reductive homocoupling using these electron withdrawing substituents on the phenyl rings are described below.



12 X= H Y=CN
13 X= Br Y=CN
14 X=NO_2 Y=H
15 X=NO_2 Y=Cl
16 X=H Y=NO_2
17 X=NO_2 Y=NO_2

Scheme 83

When imines **12** and **13** reacted with 5 mol% of $Yb(OTf)_3$, 10 eq of magnesium and one eq of TMSCl in THF under reflux, none of the desired coupled diamines were obtained (scheme 83). Instead only reduction of the imine and cyano groups was obtained (scheme 84). These reactions were monitored by tlc and after 2 hours, there was no starting material. Reactions using $[Yb(OTf)_3L]$ also gave the reduced product only. The presence of a singlet at 4.32 ppm and 4.37 ppm was observed from the ^1H NMR of the reaction crudes. On the IR spectra, there was a broad peak at 3360 cm^{-1} (due to presence of NH groups) when the reaction crudes were analysed. The mass spec. of the crudes corresponds to the mass of the reduced product. The results of these analyses is summarised in the table 15 below.



12 X= H
13 X= Br

Scheme 84

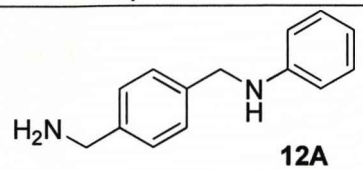
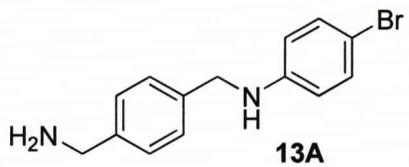
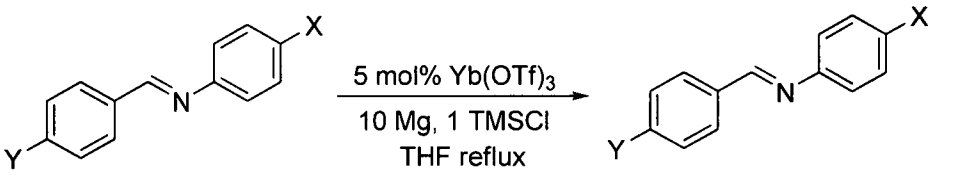
imine	^{1}H NMR	m/z	IR	product
12	4.32 ppm	210 $[M+H]^+$	3369.03 cm^{-1}	 **12A**
13	4.37 ppm	288 $[M+H]^+$ 290 $[M+H]^+$	3372.89 cm^{-1}	 **13A**

Table 15

Imines **14**, **15**, **16** and **17** also failed to give the desired coupled product when they reacted with 5 mol% $Yb(OTf)_3$, 10 eq magnesium and one eq of TMSCl (scheme 85). Like imines **12** and **13**, imines **14** to **17** offered reduction instead of reductive homocoupling (scheme 84). Unlike imines **12** and **13**, the Ph-N=CH in imines **14** to **17** was still intact after the reaction (reactions were left under reflux overnight) as shown by the presence of the singlet at about 8.4 ppm on the ^{1}H NMR of the reaction crudes. The nitro group was reduced to the NH_2 group as shown by the presence of a broad peak in the IR of the crudes at about 3300 cm^{-1}, which is not present in the spectra of the starting material. The mass spec also corresponds to the reduced amine product. The results of these analyses is summarised in the table 16.



14 Y= H, X= NO_2
15 Y=Cl, X= NO_2
16 Y= NO_2, X=H
17 Y= NO_2, X= NO_2

14A Y= H, X= NH_2
15A Y=Cl, X= NH_2
16A Y= NH_2, X=H
17A Y= NH_2, X= NH_2

Scheme 85

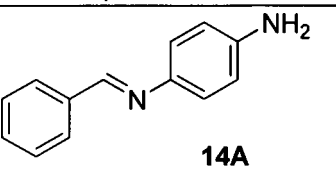
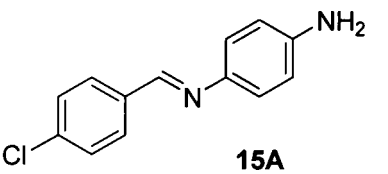
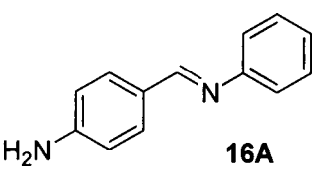
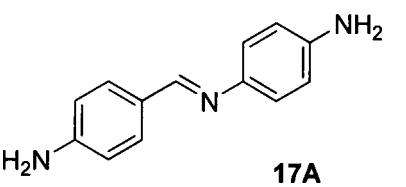
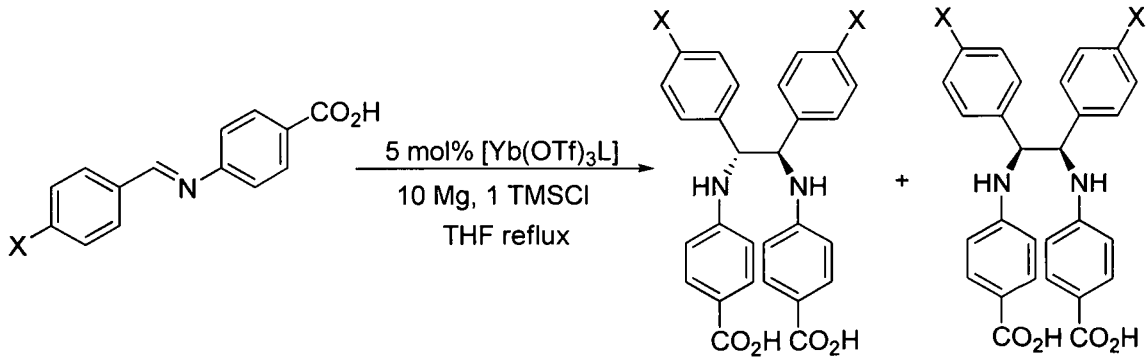
imine	^{1}H NMR	m/z	IR	product
14	8.48 ppm	197 $[M+H]^+$	3345.89 cm^{-1}	 **14A**
15	8.29 ppm	231 $[M+H]^+$ 233 $[M+H]^+$	3361.32 cm^{-1}	 **15A**
16	8.34 ppm	197 $[M+H]^+$	3370.96 cm^{-1}	 **16A**
17	8.54 ppm	212 $[M+H]^+$	3369.03 cm^{-1}	 **17A**

Table 16



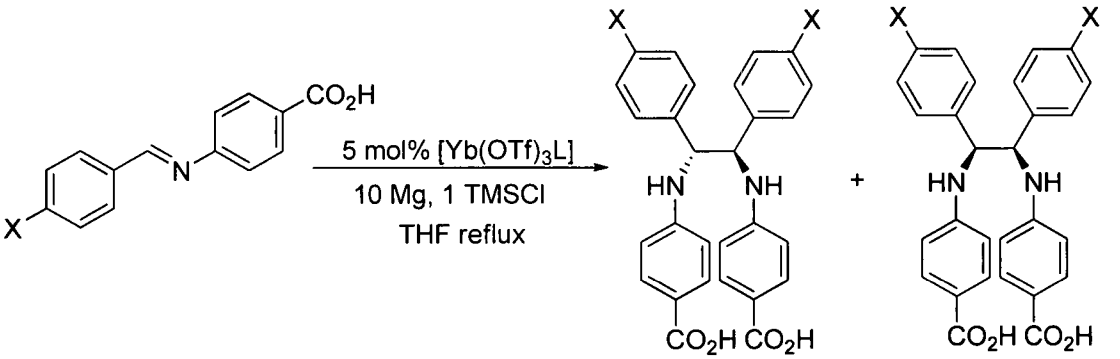
18 X= H,
19 X= Cl
20 X= OMe

21a X=H
22a X=Cl
23a X=OMe

21b X=H
22b X=Cl
23b X=OMe

Scheme 86

Imines **18**, **19** and **20** gave the corresponding coupled diamines *via* the reductive homocoupling reaction, promoted by $Yb(OTf)_3$ or $[Yb(OTf)_3L]$ (scheme 86). All reactions were monitored by tlc and reactions were completed after 7 hours when no starting material was observed. Due to the polar nature of these diamines, it was not possible to purify by flash chromatography, so no isolated yield was calculated. These diamines were recrystallised from diethyl ether and elemental analysis found traces of inorganic materials. The reaction using $Yb(OTf)_3$ with imine **18** gave the best selectivity, determined by ^1H NMR, for the *d/l* diamine with a ratio of 79:21 compared to the *meso* diamine (entry 1, table 17). The selectivity was reversed with imine **19**. The corresponding *meso* diamine **21** was the major product when $Yb(OTf)_3$ and the 15-crown-5 complex were used to promote the reductive homocoupling reaction (entries 4 and 5, table 17). Imine **20** took longer to react compared to the other imines with a COOH group (entries 7 to 9, table 17). This could be explained by the presence of the methoxy group which could be stabilising the radical intermediate species or higher energy LUMO. Table 17 summarises the results from the reductive homocoupling reaction of imines **18** to **20** promoted by $Yb(OTf)_3$ or $[Yb(OTf)_3L]$.



18 X= H,
19 X= Cl
20 X= OMe

21a X=H
22a X=Cl
23a X=OMe

21b X=H
22b X=Cl
23b X=OMe

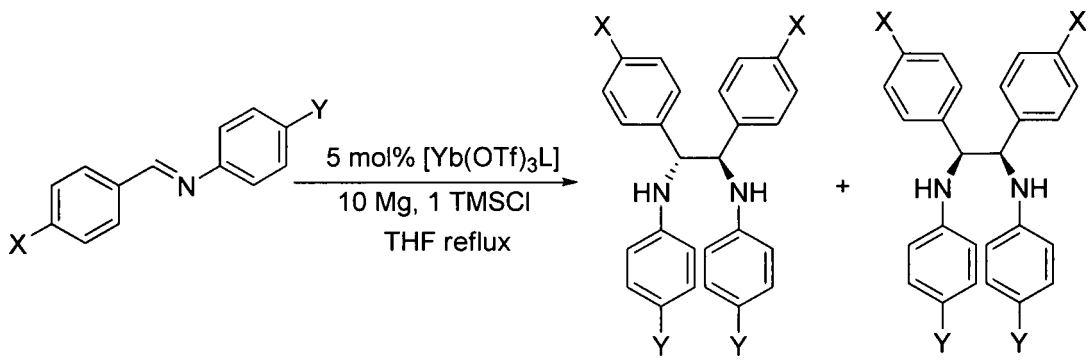
Scheme 86

entry	imine	ligand	time	*d/l:meso*
1	18	-	7 h	79:21
2	18	15-C-5	7 h	50:50
3	18	triethylene glycol	7 h	55:45
4	19	-	7 h	32:68
5	19	15-C-5	7 h	30:70
6	19	triethylene glycol	7 h	63:37
7	20	-	10 h	54:44
8	20	15-C-5	10 h	57:43
9	20	Triethylene glycol	10 h	54:46

Table 17

4.3.3 Electron donating substituents on phenyl ring

The range of the reductive homocoupling reaction of imines, promoted by $Yb(OTf)_3$ was extended to electron donating substituents on the phenyl rings (halides, *o*-methoxy and *p*-methoxy).



24 X=H Y=Br
26 X=Cl Y=Br

25a X=H Y=Br
27a X=Cl Y=Br

25b X=H Y=Br
27b X=Cl Y=Br

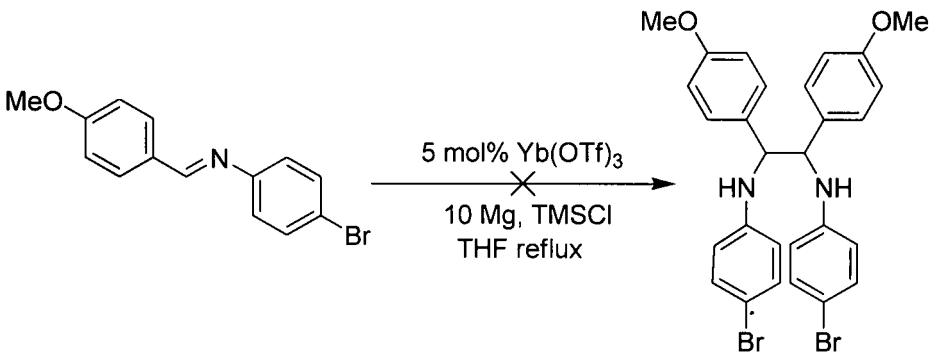
Scheme 87

Imines **24** and **26** gave the coupled corresponding diamines **25** and **27** in good to excellent yields with 5 mol% of $Yb(OTf)_3$ or $[Yb(OTf)_3L]$, 10 eq of magnesium and one eq of TMSCl in THF or acetonitrile under reflux (table 18). The *meso* product was the favoured isomer of the reactions of imine **24** except when triethylene glycol complex was used in THF under reflux. This reaction gave the *d/l* isomer as major product in a 56:44 ratio over the *meso* diamine (entry 3, table 21). The best selectivity was obtained when $Yb(OTf)_3$ was used in acetonitrile under reflux. The *meso* isomer was the major product in a 34:66 ratio over the *d/l* diamine (entry 4, table 18). Imine **26** is substituted on both phenyl rings on the *para* position by a halogen. The selectivity outcome from imine **26** was very low and both diamine isomers were obtained in a 1:1 ratio (entries 5 to 7, table 18).

entry	imine	ligand	solvent	time	yield	*d/l:meso*
1	24	-	THF	2½ h	69%	40:60
2	24	15-C-5	THF	3 h	74%	48:52
3	24	triethylene glycol	THF	3 h	70%	56:44
4	24	-	MeCN	3 h	79%	34:66
5	26	-	THF	2 h	81%	50:50
6	26	15-C-5	THF	2 h	83%	51:49
7	26	triethylene glycol	THF	2 h	79%	51:49

Table 18

The imines with methoxy substituents have generally given lower yields with longer reaction times, but similar conversions compared to the other imines used (except those synthesised from 4-aminobenzoic acid). Some of these electron rich imines underwent reductive homocoupling in presence of $Yb(OTf)_3$ or $[Yb(OTf)_3L]$ to give the desired corresponding coupled diamine.

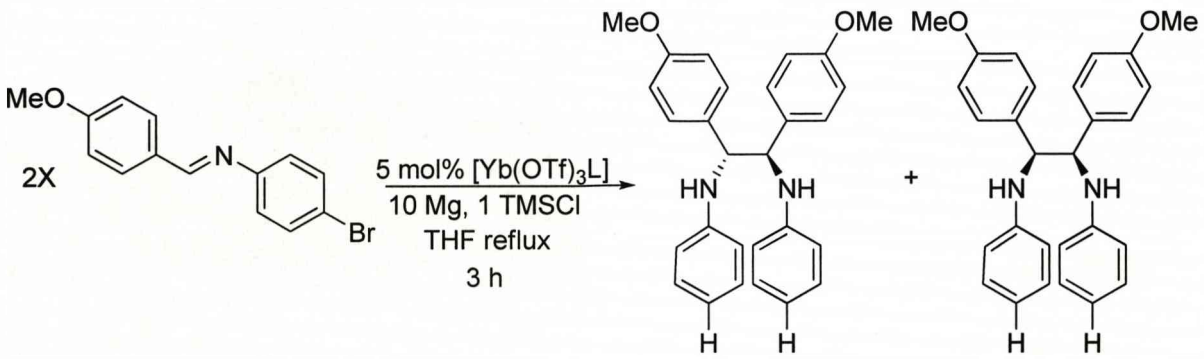


28 **28D**

Scheme 88

The expected corresponding coupled diamine **28D** was not obtained when imine **28** reacted with 5 mol% of $Yb(OTf)_3$ or $[Yb(OTf)_3L]$, 10 eq of magnesium and one eq of TMSCl in THF under reflux (scheme 88). Under these conditions, the methoxy group may have precipitated the loss of the bromine atoms. The main products from these reactions were diamines **30a** and **30b** (scheme 89). With $Yb(OTf)_3$, both isomers of the diamine were obtained in about 50:50 ratio (entry 1, table 23). The selectivity was

increased towards the *d/l* isomer when the [$Yb(OTf)_3L$] were used (entries 2 and 3, table 23). The best selectivity obtained from imine **28** was obtained when the triethylene glycol complex was used (entry 3, table 23). The results of these reactions are summarised in table 23 below.

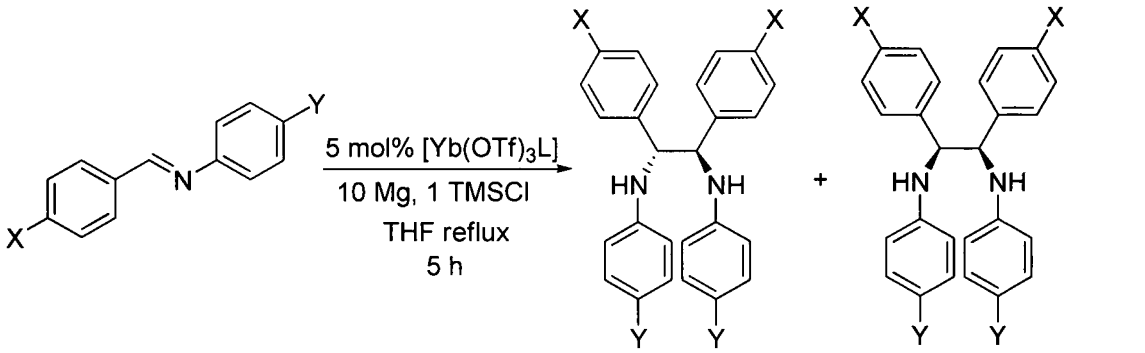


28 **30a** **30b**

Scheme 89

entry	ligand	yield	*d/l:meso*
1	-	64%	49:51
2	15-C-5	62%	58:42
3	triethylene glycol	67%	66:34

Table 19



29 X=OMe Y=H
31 X=H Y=OMe

30a X=OMe Y=H
32a X=H Y=OMe

30b X=OMe Y=H
32b X=H Y=OMe

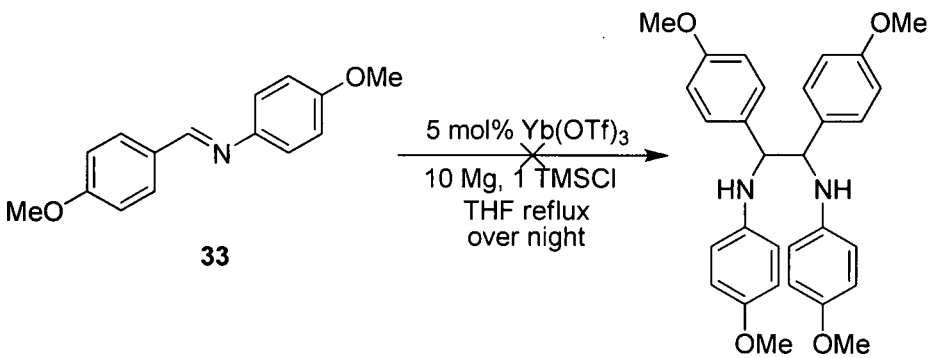
Scheme 90

Imines **29** and **31** gave the expected coupled diamines **30** and **32** when they reacted with 5 mol% of $Yb(OTf)_3$ or $[Yb(OTf)_3L]$, 10 eq of magnesium and one eq of TMSCl in THF under reflux after 5 hours (scheme 90). The selectivity outcome from the reaction using imine **29** with one eq of $Yb(OTf)_3$ was very low as nearly a 1:1 ratio of both diamines was obtained (entry 1, table 20) and was not improved when catalytic amounts of $[Yb(OTf)_3L]$ were used (entries 3 and 4, table 20). The selectivity was greatly improved towards the *d/l* diamine when catalytic amounts of $Yb(OTf)_3$ was used along with TMSCl. The *d/l* diamine was obtained in a 67:33 ratio over the *meso* diamine (entry 2, table 20). The *d/l* diamine **32** was obtained as major product in a 56:44 ratio over the *meso* diamine when $Yb(OTf)_3$ was used to promote the reductive homocoupling of imine **31** (entry 5, table 20). The selectivity was improved when $Yb(OTf)_3$ complexes were used to promote the reaction; the *meso* diamine was the major product over the *d/l* diamine (entries 6 and 7, table 20). The triethylene glycol complex has given the best selectivity for the *meso* diamine with a ratio of 21:79 over the *d/l* diamine (entry 3, table 20). The results are summarised in table 20 below.

entry	imine	catalyst	yield	*d/l:meso*
1	29	- [p]	63%	52:48
2	29	-	63%	67:33
3	29	15-C-5	65%	50:50
4	29	triethylene glycol	60%	56:44
5	31	-	56%	56:44
6	31	15-C-5	50%	35:65
7	31	triethylene glycol	45%	21:79

Table 20

[p] used 1 eq of $Yb(OTf)_3$ and no TMSCl.



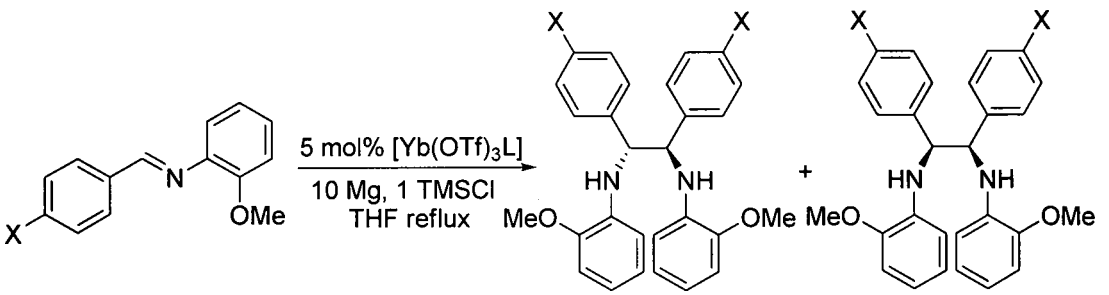
Scheme 91

Imine **33** was synthesised from *p*-anisaldehyde and *p*-anisidine. It is the most electron rich imine studied and it failed to give the desired corresponding diamine *via* the reductive homocoupling when it reacted with 5 mol% of $Yb(OTf)_3$ or $[Yb(OTf)_3L]$ with 10 eq of magnesium and one eq of TMSCl in THF under reflux (scheme 91). All reactions were left overnight for at least 18 hours. The ^1H NMR of the reaction crudes shows mainly unreacted starting imine. The diamine was detected only by mass spec, 507.2260 ($[M+Na]^+$), where $M=C_{30}H_{32}N_2O_4$. The presence of the 2 methoxy groups made the radical intermediate species very stable and increased the energy of the LUMO so it did not couple to form the diamine.

Imines **34** and **36** were synthesised from *o*-anisidine. As the reductive homocoupling occurs after coordination to the ytterbium centre, we thought that presence of a methoxy group at the *ortho* position would affect selectivity due to stronger coordination to the ytterbium centre. The diamines **35** and **37** were obtained in good yields after 4 hours when imines **34** and **36** reacted with 5 mol% of $Yb(OTf)_3$ or $[Yb(OTf)_3L]$, 10 eq of magnesium and one eq of TMSCl in THF under reflux (scheme 92). The *meso* diamine was the major product when $Yb(OTf)_3$ was used to promote the reductive homocoupling of imine **34**, in a ratio of 69:31 over the *d/l* diamine (entry 1, table 21). The selectivity was reversed in favour of the *d/l* diamine when $[Yb(OTf)_3L]$ were used (entries 2 and 3, table 21).

The best selectivity for the *meso* diamine was obtained when $Yb(OTf)_3$ was used to promote the reductive homocoupling of imine **36** (entry 4, table 21). This reaction gave a ratio of 76:24 in favour of the *meso* over the *d/l*. The selectivity was reversed when the triethylene glycol complex was used to prote the reaction; a ratio of 65:35 in favour of the *d/l* over the *meso* was obtained (entry 3, table 21).

Even though there is evidence of coordination to the ytterbium cation centre prior to coupling, the presence of a methoxy group at the *ortho* position on the aniline ring did not greatly improve the selectivity of the reaction. All the above mentioned results are summarised in table 21.



34 X=H
36 X=Cl

35a X=H
37a X=Cl

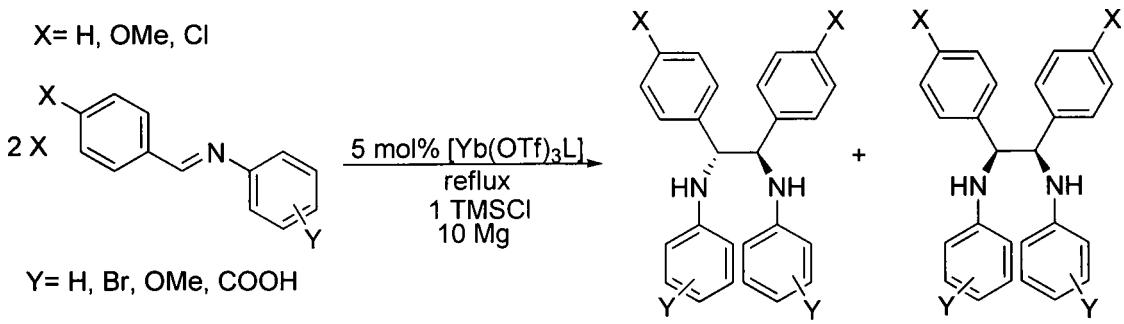
35b X=H
37b X=Cl

Scheme 92

entry	imine	ligand	time	yield	*d/l:meso*
1	34	-	4 h	63%	31:69
2	34	15-C-5	4 h	64%	62:38
3	34	triethylene glycol	4 h	60%	62:38
4	36	-	3½ h	49%	24:76
5	36	15-C-5	3½ h	50%	49:51
6	36	triethylene glycol	3½ h	50%	65:35

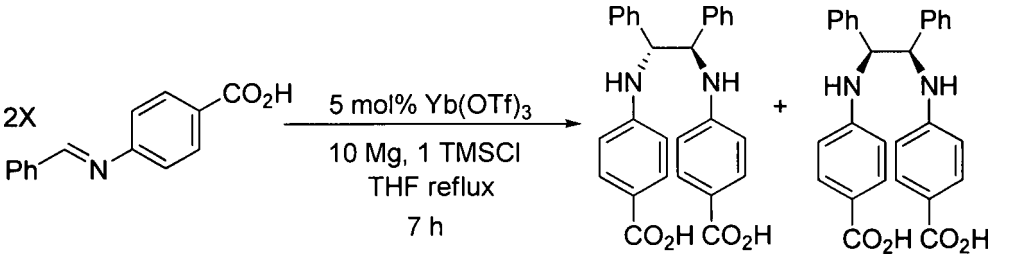
Table 21

4.4 Summary of results of homocoupling of imines



Scheme 93

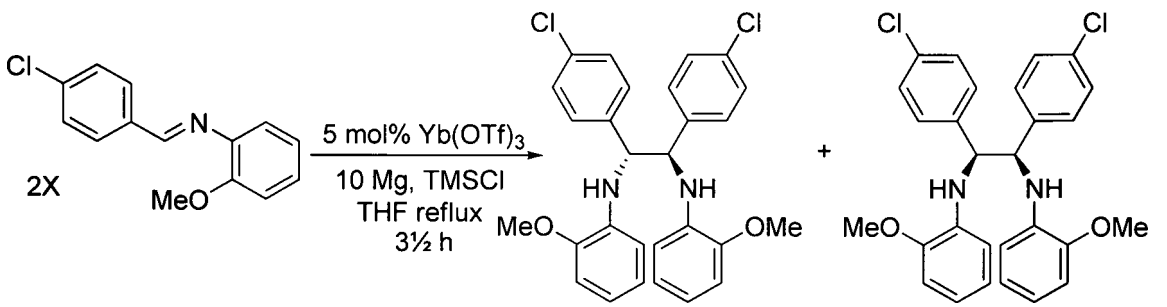
The reductive homocoupling has been applied to a range of aromatic imines, bearing different substituents. This reaction can be promoted by $Yb(OTf)_3$ or $[Yb(OTf)_3L]$ with magnesium acting as co-reductant and TMSCl. It was also seen that hydrated samples of $Yb(OTf)_3$ was a better catalyst compared to anhydrous material, giving faster reaction times (entries 1, 3, 5 and 7, table 9). Moderate selectivities were obtained from the reductive coupling of imines. Imine **8** gave the *d/l* diamine after 45 minutes in THF under reflux with a ratio of 59:41 over the *meso* when it reacted with $Yb(OTf)_3$ (entry 8, table 9). Imines **10**, **20** and **31** also gave the corresponding diamines in moderate selectivities when $Yb(OTf)_3$ was used in THF under reflux. Imine **10** gave better selectivity when stoichiometric $Yb(OTf)_3$ was used (entry 1, table 14), the *d/l* diamine was obtained in a ratio of 74:26 over the *meso*. The opposite was observed with imine **29**; no selectivity was obtained when 1 eq of $Yb(OTf)_3$ was used and it greatly improved towards the *d/l* diamine (entries 1 and 2, table 20), with a ratio of 67:33 with catalytic $Yb(OTf)_3$. No selectivity was obtained from imines **26** and **28**. Imine **18** gave better selectivity for the corresponding *d/l* diamine when it was reacted with 5 mol% of $Yb(OTf)_3$ in THF under reflux (scheme 94). A ratio of 79:21 in favour of the *d/l* diamine over the *meso* diamine was obtained after 7 hours (entry 1, table 17).



18 **21a** *d/l* 79 **21b** *meso* 21

Scheme 94

The selectivity was reversed in favour of the *meso* diamine when imines **19**, **24**, **34** and **36** reacted with $Yb(OTf)_3$ in THF under reflux. Imine **24** gave a ratio of 40:60 in favour of the *meso* diamine (entry 1, table 18). The selectivity for the *meso* diamine was increased to 34:66 when acetonitrile was used under reflux as reaction media (entry 4, table 18). The other 3 imines were more selective, imine **19** gave a ratio of 32:68 after 7 hours in THF under reflux (entry 5, table 17) while imine **34** gave a ratio of 31:69 after 5 hours (entry 1, table 21). The best selectivity for the *meso* diamine was obtained with imine **36**. The *meso* diamine was obtained in a ratio of 76:24 over the *d/l* after 3½ hours (scheme 95).



36 **37a** *d/l* 24 **37b** *meso* 76

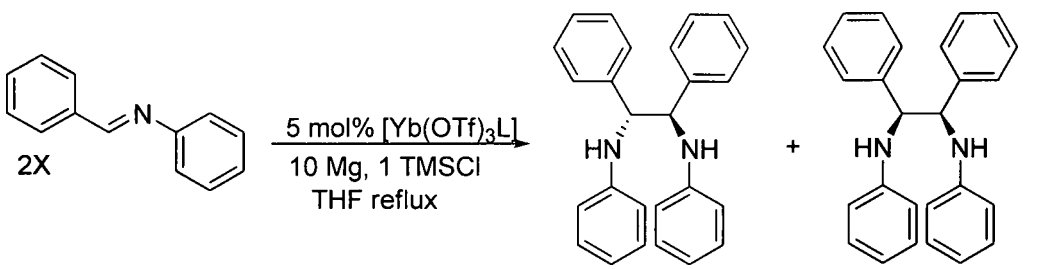
overall yield 49%

Scheme 95

In an attempt to increase the selectivity of the reductive homocoupling reaction of imines, we tried to used complexes of $Yb(OTf)_3$ to promote the reaction. 2,2-bi-pyridyl and polyether ligands including triglyme, triethylene

glycol, tetraglyme, 15-crown-5 and 18-crown-6, have been incorporated onto the ytterbium centre in order to form complexes. The 15-crown-5 complex gave cleaner reaction crudes and the triethylene glycol complex was found to be very efficient in promoting the reaction, due to the presence of the 2 OH groups, which may be acting like water.

The *d/l* diamine was the major product when 5 mol% of the triethylene glycol complex was used to promote the reductive homocoupling of imines **8**, **10**, **18**, **19**, **20**, **24**, **28**, **29**, **34** and **36**. Imine **26** gave no selectivity with the triethylene glycol complex in THF under reflux after 2 hours (entry 7, table 18). Moderate selectivities were obtained from imines **8**, **18**, **19**, **20**, **24**, **28**, **29**, **34** and **36**. The triethylene glycol complex reversed the selectivity of the outcome when it was used to promote the homocoupling of imine **19**. With $Yb(OTf)_3$ in THF, the *meso* diamine was the major product but *d/l* diamine was obtained in a ratio of 63:37 with the triethylene glycol complex (entries 6 and 6, table 17). The selectivity was also reversed with imines **34** and **36** (entries 1, 3, 4 and 6, table 21). The triethylene glycol complex gave better selectivity for the *d/l* diamine with imine **10**, compared to $Yb(OTf)_3$. The selectivity ratio was increased from 62:38 to 68:32 (entries 2 and 4, table 14). This was the highest ratio obtained with the triethylene glycol complex (scheme 96).



10

L= triethylene glycol

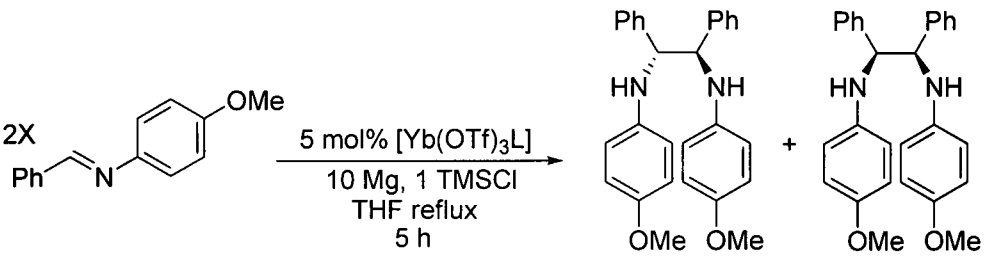
11a
d/l
68

11b
meso
32

overall yield 80%

Scheme 96

The selectivity was reversed when the triethylene glycol complex of $Yb(OTf)_3$ was used to promote the reductive homocoupling in THF under reflux of imine **31** (scheme 97). The meso diamine was obtained as major product after 5 hours in a 79:21 ratio over the *d/l* (entry 7, table 20).



31

L= triethylene glycol

32a

d/l
21

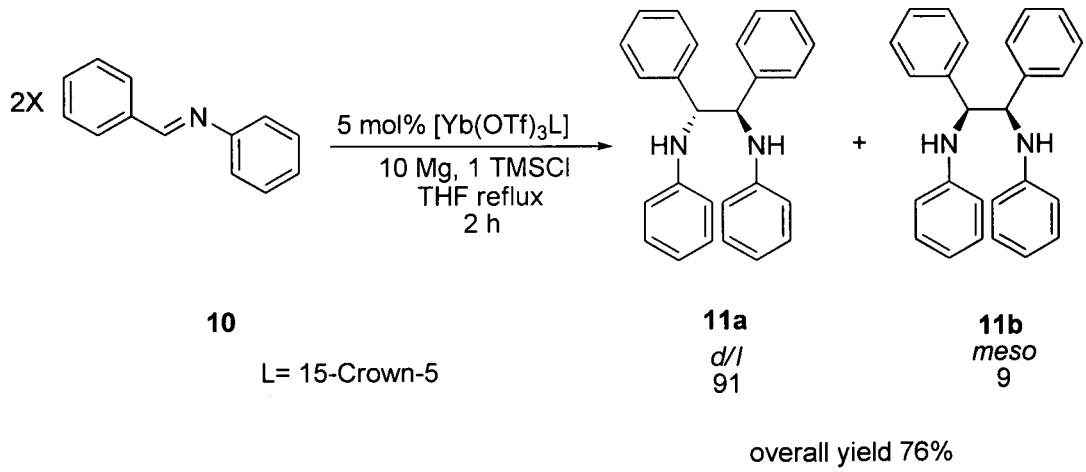
32b

meso
79

overall yield 45%

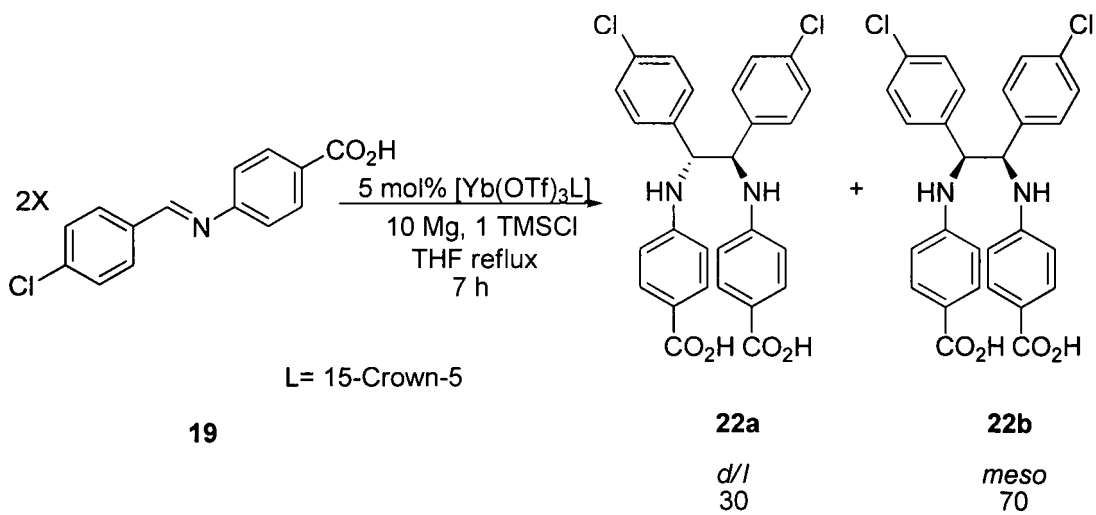
Scheme 97

The *d/l* diamine was the major product of the reductive homocoupling of 5 imines while the *meso* was the major product from 2 other imines when the 15-crown-5 complex was used as catalyst. Imines **18**, **24**, **26**, **29** and **36** were not selective when the 15-crown-5 complex was used to promote the reductive homocoupling in THF under reflux. Both isomers were obtained in a 1:1 ratio. Moderate selectivities towards the *d/l* were obtained from imines **8**, **20**, **28** and **34** in THF under reflux. In the case of imine **8**, an increase in selectivity was noted when the reaction was carried out in the DCM/THF solvent mixture at rt. In THF under reflux, a ratio of 58:42 (entry 7, table 12) in favour of the *d/l* was obtained and the DCM/THF solvent mixture at rt, the ratio was 68:32 (entry 9, table 13). The best selectivity for the *d/l* diamine was obtained from imine **10** (entry 3, table 14). The reductive homocoupling of imine **10**, promoted by the 15-crown-5 complex of $Yb(OTf)_3$ has given the *d/l* isomer in a ratio of 91:9 after 2 hours in THF under reflux (scheme 98).



Scheme 98

The 15-crown-5 complex of $Yb(OTf)_3$ gave the *meso* diamine when it was used to promote the reductive homocoupling reaction of imine **19** and **31**. The *meso* diamine was the major product with a ratio of 65:35 over the *d/l* with imine **31** (entry 6, table 20). The reaction with imine **19** was more selective as the meso diamine was obtained in a 70:30 ratio over the *d/l* diamine (entry 5, table 17). The reaction was carried out in THF under reflux and the diamines were obtained after 7 hours.

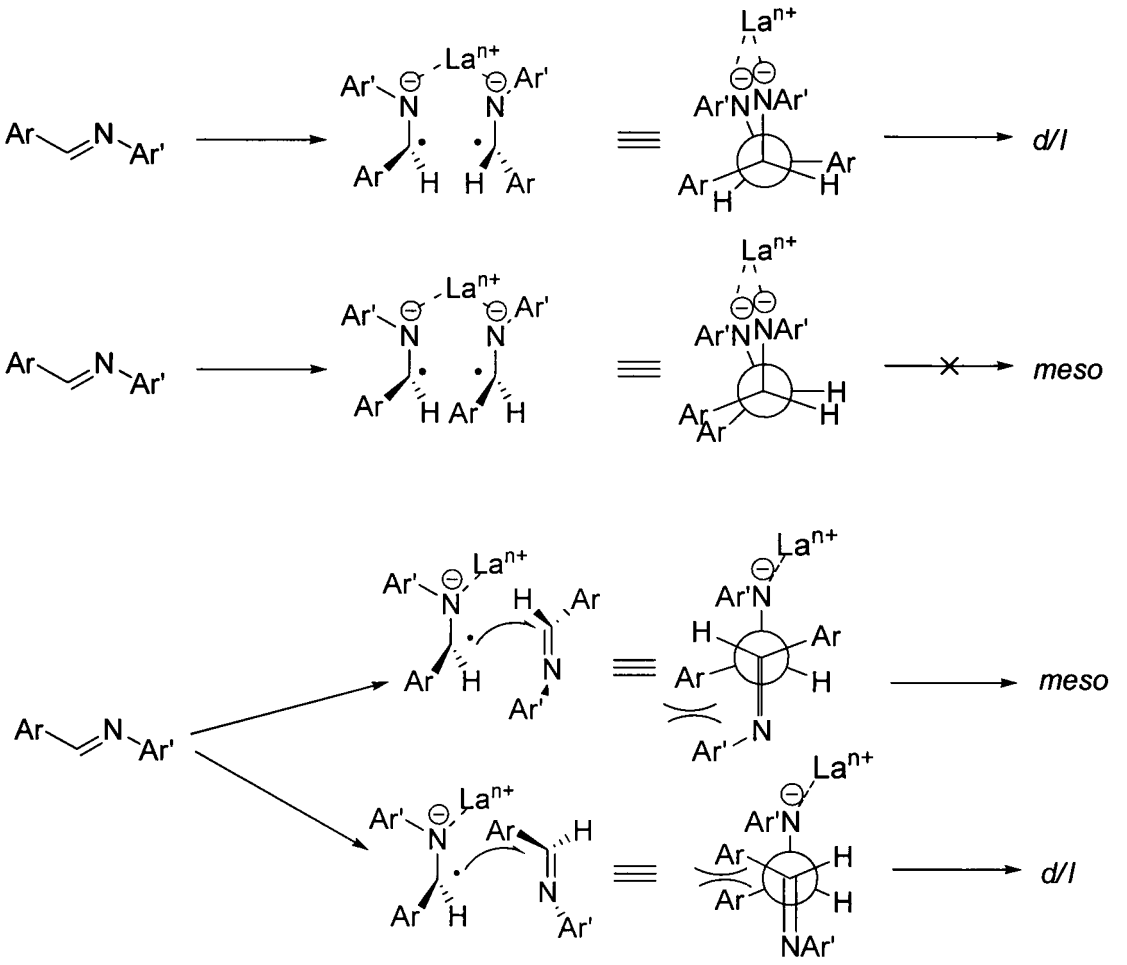


Scheme 99

Generally moderate selectivities were obtained when the reductive homocoupling of imines was promoted by $Yb(OTf)_3$ and $[Yb(OTf)_3L]$. As all the imines screened had a phenyl group on each end, it would imply that steric factors could not play a critical part in the selectivity outcome of this

reaction from these substrates. Except for a few cases, the *d/l* and *meso* diamines have been obtained in almost equal ratios. Unsymmetrical imines bearing one or two aliphatic groups need to be screened in order to extend the range of substrates in the reductive homocoupling reaction. This will also give a better insight to the mechanism *via* which this transformation is proceeding.

Following on to the proposed coupling pathway by Sonoda *et al*[165] it can be deduced from the results obtained with the reductive homocoupling reaction of imine promoted by $Yb(OTf)_3$ and $[Yb(OTf)_3L]$ does not go via a radical imino anion-radical imino anion coupling. This route is *d/l* selective only as shown in scheme 99. The *meso* conformation cannot be obtained *via* this route as it leads to an eclipsed aryl-aryl interaction, which is very disfavoured. The other option is that the radical imino anion couples itself to another imine. This route is not very selective as for the formation of both diastereoisomers, there are some aryl-aryl disfavoured steric interactions (scheme 100). The aryl-aryl interaction in the *d/l* formation is more significant, as the aryl groups are closer to each other, compared to the aryl-aryl interaction in the *meso* formation. This could explain why the reductive homocoupling promoted by $Yb(OTf)_3$ and $[Yb(OTf)_3L]$ has not been very selective towards either diastereoisomer.



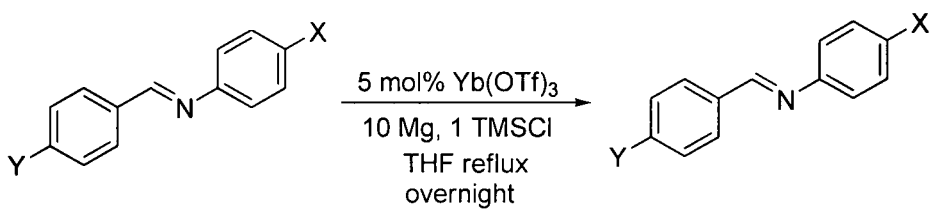
Scheme 100

Imines bearing *p*-cyano and *p*-nitro groups on the phenyl rings did not undergo reductive homocoupling when they reacted with 5 mol% of $Yb(OTf)_3$. Instead, the cyano and nitro groups were reduced to give the corresponding amine. When there was a cyano group substituent on the imine, both the HC=N and the cyano groups were reduced to CH_2NH and CH_2NH_2 (table 15).

The presence of the nitro group gave a different outcome to the cyano substituent. The nitro group (NO_2) was reduced to NH_2 (table 16). The imines bearing 1 or 2 nitro substituents were selectively reduced. Only the nitro groups were reduced while the imine moiety was intact, even after the

reaction was left for more than 16 hours in THF under reflux. The nitro group protected the imine after it was reduced by increasing the energy of the LUMO. This shows that electronic factors play a role in the promotion of the reductive homocoupling reaction.

Reduction of nitro compounds to amines can be achieved with iron, zinc or tin and hydrochloric acid.[167,168] The main problem of these routes is the waste disposal as there is the formation of a metal sludge at the end of the reaction and separation of the amine can be sometimes difficult. Recently Saha *et al* have reported the selective aromatic nitro reduction promoted by copper nanoparticles and ammonium formate.[169] This route requires three eq of copper nanoparticles and five eq of ammonium formate and is carried out in ethylene glycol at 120° C. The method is simple and can be applied to a wide range of aromatic substrates and reaction times varied from 8 to 12 hours with good to excellent yields. Kantam *et al* have also reported the selective reduction of aromatic and aliphatic nitro compounds using nanocrystalline magnesium oxide-stablised palladium.[170] This methodology requires 1.48 mol% of the nanocrystalline MgO stabilised Pd catalyst in THF and a hydrogen atmosphere. Reaction times varied from 1½ to 6½ hours at rt with excellent yields of the corresponding amine. The $Yb(OTf)_3$/Mg/TMSCl system, only requires 0.05 eq of $Yb(OTf)_3$ to catalyse the transformation in THF under reflux (scheme 85).

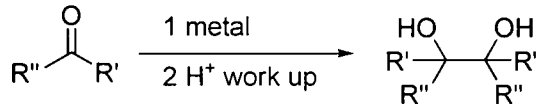


14 Y= H, X= NO_2
15 Y=Cl, X= NO_2
16 Y= NO_2, X=H
17 Y= NO_2, X= NO_2

14A Y= H, X= NH_2
15A Y=Cl, X= NH_2
16A Y= NH_2, X=H
17A Y= NH_2, X= NH_2

Scheme 85

4.5 Pinacol coupling of aldehydes and ketones[171]



R'= H or aromatic or aliphatic
R''= Aromatic or aliphatic

Scheme 101

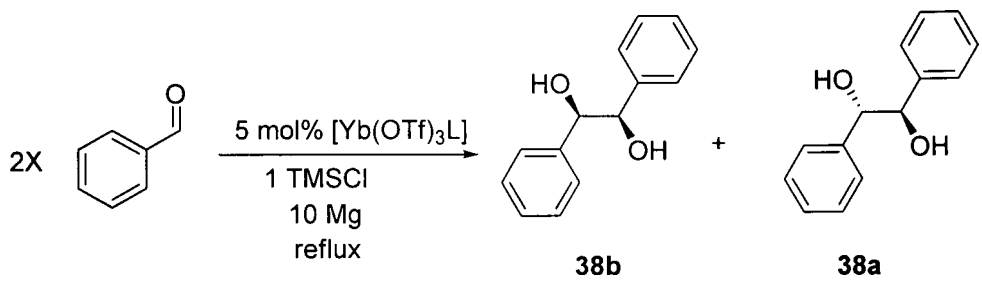
Since Fittig reported the pinacol coupling of acetone using sodium,[172] several other metals, like samarium, vanadium,[173] manganese,[174] zinc,[175] aluminium,[176] mercury[177] and cerium,[59] have been used for this carbon-carbon bond formation. Metal complexes, like SmI_2, low valent titanium,[178] lithium and $Fe_4S_4(SPh)_4$,[179] magnesium amalgam[180] and aluminium amalgam[181] have also been successfully used. The rate of the reaction is determined by the redox potential of the metal and the carbonyl substrate. Aromatic carbonyls have lower redox potential compared to aliphatic carbonyls; hence reaction involving aromatic aldehydes and ketones are generally much faster.[11] Some of these routes require stoichiometric amounts of the metal/metal complex to promote the reaction. Recently Greeves *et al* have reported the use of catalytic SmI_2 with magnesium acting as co-reductant and tetraglyme acting as chelating ligand to promote inter- and intramolecular pinacol coupling in good yields and diastereoseletivities (described in section 1.3).[10]

4.5.1 Pinacol coupling of benzaldehyde

As it was found that $Yb(OTf)_3$ could promote the reductive homocoupling of imines, the focus of the study was turned towards pinacol couplings. As previously mentioned, aromatic aldehydes react faster to form the corresponding diol as they have lower redox potential. So benzaldehyde was chosen as substrate and the same conditions used for the reductive homocoupling of imines were used (scheme 102). The corresponding diol was obtained in good to excellent yields.

When 5 mol% of $Yb(OTf)_3$ was used with 10 eq of magnesium and one eq of TMSCl in THF under reflux, the corresponding diols **38a** and **38b** were obtained after 90 minutes in 91% yield with the *d/l* isomer as major product in a 4:1 over the meso from benzaldehyde (entry 1, table 22). All crudes were analysed by GC to determine ratio of isomers and confirmed by GCMS. The selectivity was reversed when the same reaction and conditions were carried out in acetonitrile, with the *meso* diol being the major product in a 60:40 ratio over the *d/l* diol (entry 2, table 22). This reaction went to completion in 45 minutes with a yield of 95%. The selectivity was greatly improved when the same conditions were applied in the DCM/THF solvent mixture under reflux. The *meso* 1,2-diphenylethane-1,2-diol was the major product in a ratio of 96:4 over the *d/l* (entry 3, table 22). Surprisingly, the selectivity was lost when the reaction was carried out in the DCM/THF solvent mixture at rt (entry 4, table 22). The *meso* diol was still the major product but in a 63:27 ratio over the *d/l* diol. Very good selectivity towards the *meso* diol was obtained when the tetraglyme complex was used in acetonitrile and THF under reflux (entries 5 and 6, table 22). Selectivity was reduced when DCM/THF solvent mixture was used at rt (entry 7, table 22). $YbCl_3$ and the tetraglyme complex of $YbCl_3$ did not give good selectivity when they were used to promote the pinacol coupling in the DCM/THF solvent mixture at rt (entries 9 and 10, table 22). The Lewis acid $Sc(OTf)_3$ was not as efficient as $Yb(OTf)_3$ in promoting the pinacol coupling of benzaldehyde. The reaction

took 15 hours to go to completion with no selectivity (entry 11, table 22). $Yb(OTf)_3$ is an excellent catalyst for the pinacol coupling and very good selectivity for the *meso* diol was obtained with benzaldehyde. All the above mentioned results are summarised in the table 22 below.



Scheme 102

entry	catalyst	ligand	solvent	time	yield	*d/l:meso*
1	$Yb(OTf)_3$	-	THF	1½ h	91%	80:20
2	$Yb(OTf)_3$	-	MeCN	¾ h	95%	40:60
3	**$Yb(OTf)_3$**	**-**	**DCM/THF**	**3 h**	**71%**	**4 :96**
4	$Yb(OTf)_3$	-	DCM/THF [q]	4 h	74%	27:63
5	$Yb(OTf)_3$	tetraglyme	THF	1½ h	80%	6 :94
6	**$Yb(OTf)_3$**	**tetraglyme**	**MeCN**	**¾ h**	**62%**	**5 :95**
7	$Yb(OTf)_3$	tetraglyme	DCM/THF [q]	4 h	69%	13:87
8	$Yb(OTf)_3$	triethylene glycol	THF	1½ h	63%	14:86
9	$YbCl_3$	-	DCM/THF [q]	4 h	68%	45:55
10	$YbCl_3$	tetraglyme	DCM/THF [q]	4½ h	80%	14:86
11	$Sc(OTf)_3$	-	THF	15 h	72%	50:50

Table 22

All crudes were analysed by GC to determine ratio of isomers and confirmed by GCMS[10]

[q] reaction ran at rt.

There is evidence that there is coordination to the ytterbium centre prior to coupling as some shifting is observed when the ^1H NMR spectra in d^8 THF of benzaldehyde and benzaldehyde with $Yb(OTf)_3$ are compared (diagrams 3 and 4). The first sample was benzaldehyde only (black spectra in diagrams 3 and 4) while the second sample was made up of one eq of $Yb(OTf)_3$ and one eq of benzaldehyde (blue spectra in diagrams 3 and 4). These spectra are

referenced to the THF multiplet peaks at 1.85 ppm. The singlet from the aldehyde proton was shifted by 0.22 ppm from 9.96 ppm in the absence of $Yb(OTf)_3$ to 10.21 ppm in the presence of $Yb(OTf)_3$. The distance between the singlet from the aldehyde proton and the multiplet has also changed from 2.10 ppm in the absence of $Yb(OTf)_3$ to 1.84 ppm with $Yb(OTf)_3$.

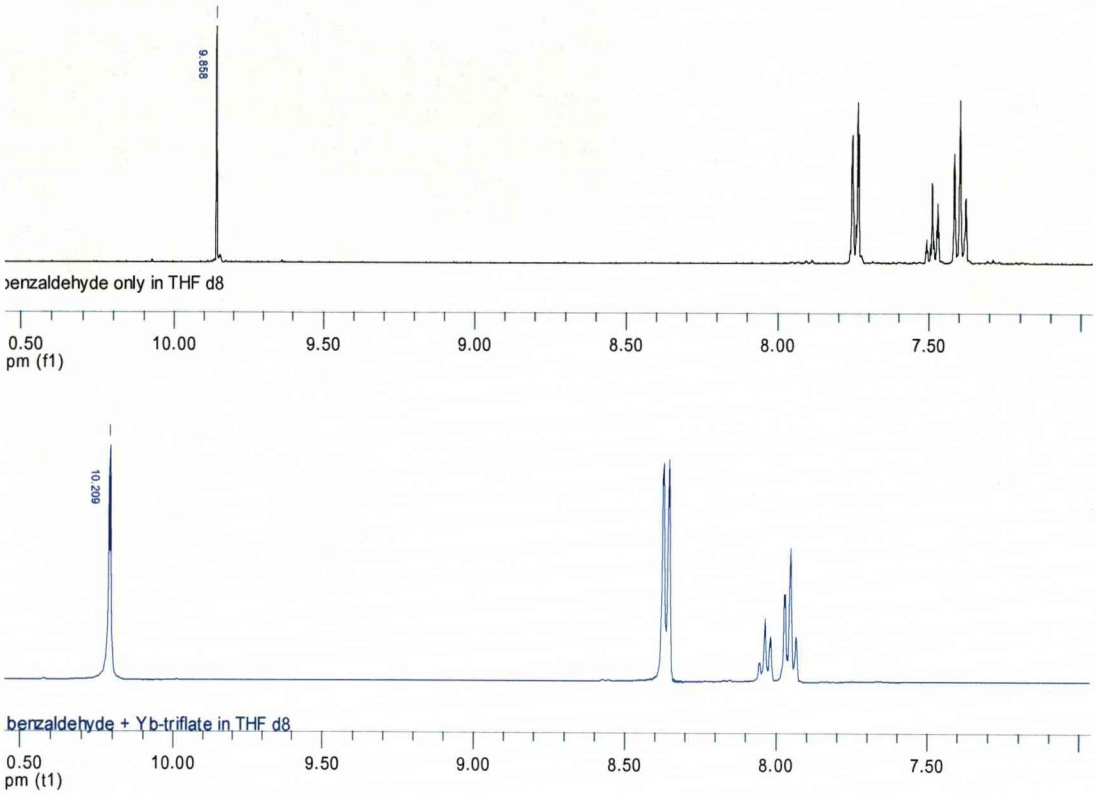


Diagram 3

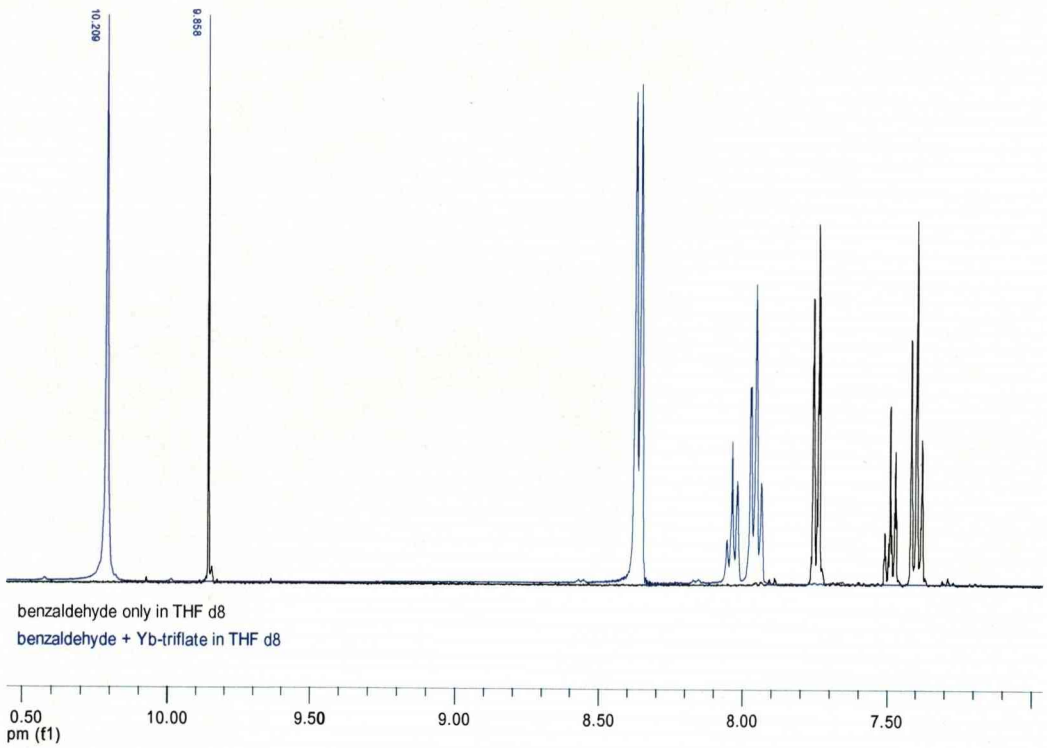
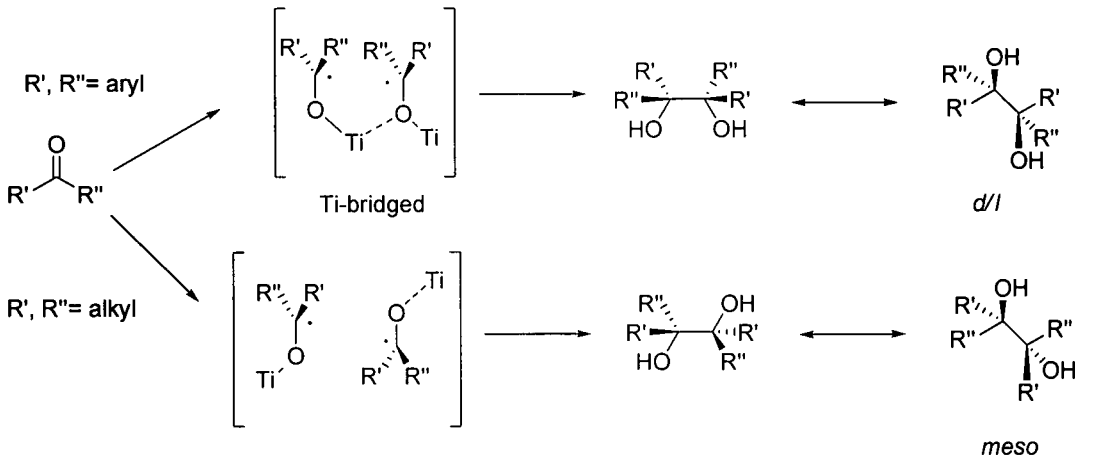


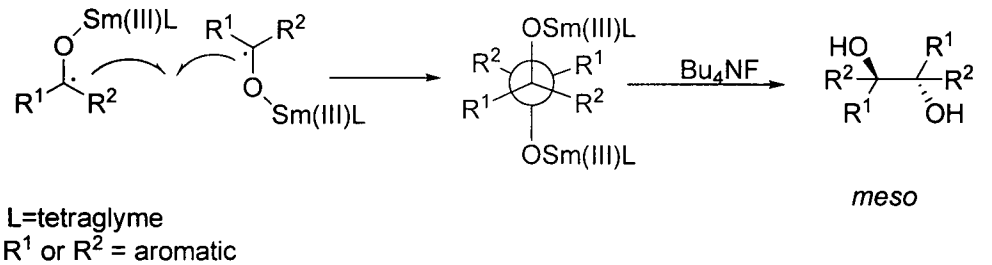
Diagram 4

The diastereoselectivity outcome can be explained in a similar manner for the reductive homocoupling of carbonyls or pinacol coupling. The diastereoselectivity from aliphatic carbonyls is often opposite to that obtained with aromatic carbonyls as shown in scheme 69. This was proposed by Mukaiyama *et al* when they used low valent titanium species to promote the pinacol coupling of aliphatic and aromatic ketones, based on the kinetic effect and Lewis acidity of the titanium species (scheme 103).[182] The radical intermediate species from aromatic carbonyls forms a bridged intermediate with the titanium, placing the 2 oxygen atoms on each side of the titanium and the 2 phenyl groups *anti* to each other. This leads to the formation of the *d/l* diol. The bridged intermediate arises due to the stronger Lewis acidity of the Ti^{3+}. The radical intermediate species from aliphatic carbonyl form an unsymmetrical intermediate with the titanium which couple to give the *meso* diol product, due to the weaker Ti-O interaction and the relative unstability of the ketyl radical. The size of the 2 and 2' substituents of the carbonyl group also affects selectivity.



Scheme 103

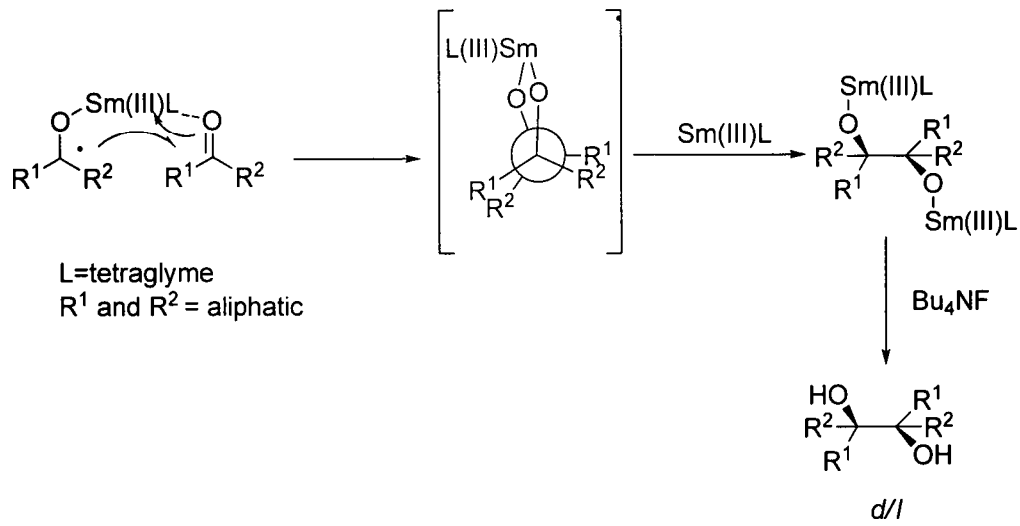
Greeves *et al* have also observed a reverse in diastereoselectivity between aromatic and aliphatic carbonyls when they used a samarium diiodide tetraglyme complex to promote the pinacol coupling (scheme 27).[10] This reverse in selectivity can be explained by the energy level of the LUMO's. The LUMO of an aromatic carbonyl is lower in energy compared to that of an aliphatic carbonyl and therefore formation of the Sm-ketyl radical is fast. The Sm-ketyl radical of aromatic carbonyl can easily undergo a one-electron reduction and the repulsion between the Sm centers during the transition state gives the *meso* diol (scheme 104).



Scheme 104

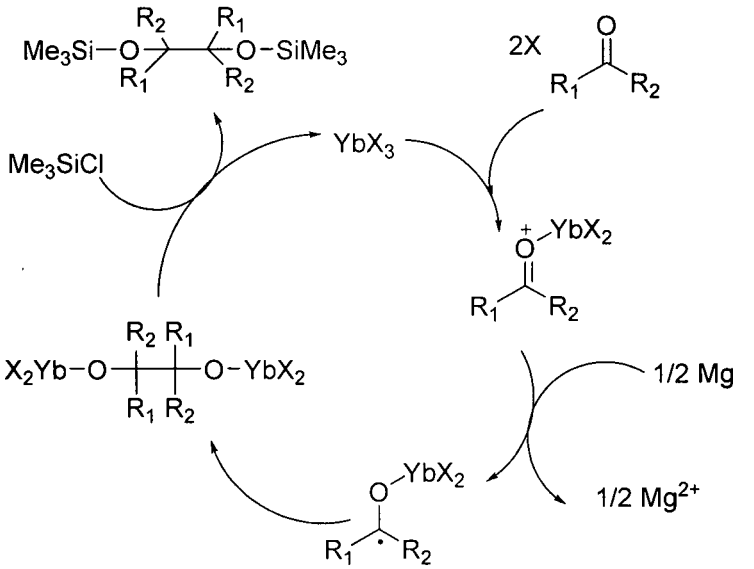
Aliphatic carbonyls will form the corresponding Sm-ketyl radical at a slower rate due to the higher energy level of their LUMO's. As a result of this slower formation rate, there is less Sm-ketyl radical present, this reduces the possibility of the dimerisation of the Sm(III)-bound ketyl radicals. So a second carbonyl substrate can bind itself to the Sm center and steric factors between the alkyl groups are determinant in the formation of the new bridged species.

The ketyl radical binds itself to the carbonyl to form the central carbon-carbon bond. The *d/l* diol is obtained after a second one-electron reduction by SmI_2 on the Sm(III)-bound ketyl (scheme 105).



Scheme 105

Similar diastereoselectivity as reported by Greeves *et al*, was observed when $Yb(OTf)_3$ and $[Yb(OTf)_3L]$ were used to promote the pinacol coupling of aldehydes and ketones (results are discussed in section 4.5). We propose a catalytic cycle to explain the role of the Yb(III) in promoting the pinacol coupling. The Lewis acid Yb(III) coordinates to the carbonyl oxygen and this new Yb-ketyl complex is reduced by magnesium. The Yb-ketyl complex is easier to reduce and forms a Yb-ketyl radical due to an electron transfer from the magnesium. The Yb-ketyl radical then dimerises with another Yb-ketyl radical or adds itself to another carbonyl to give the diol product. Addition of TMSCl will form a O-Si bond and hence free the Yb(III), which can then start a new catalytic cycle (Scheme 106).



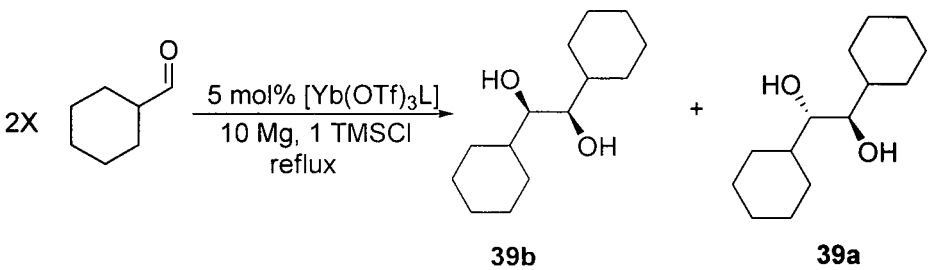
Scheme 106

4.5.2 Pinacol coupling of other aldehydes

After the pinacol coupling of benzaldehyde, other aliphatic aldehydes (cyclohexylcarboxaldehyde, octanal, cinnamaldehyde and pivaldehyde) were studied. The *d/l* to *meso* ratios were determined by GC of the crude reaction mixture and this was confirmed by GCMS.[10] The results of these pinacol coupling reactions are discussed below.

The coupled diols **39a** and **39b** were obtained when cyclohexylcarboxaldehyde reacted with 5 mol% $Yb(OTf)_3$ or $[Yb(OTf)_3L]$, 10 eq of magnesium and one eq of TMSCl. All reactions unless stated otherwise were carried out in THF under reflux. As expected, aliphatic aldehydes are slower to undergo pinacol coupling compared to aromatic aldehydes. The diol was obtained in good yields after 20 hours (scheme 107). The *d/l* isomer was the major product in all the pinacol couplings of cyclohexylcarboxaldehyde promoted by $Yb(OTf)_3$ (table 23). When 5 mol% of $Yb(OTf)_3$ was used in THF under reflux, the selectivity for the *d/l* diol was 75:25 over the *meso* diol (entry 1, table 23). This selectivity was lowered

when the reaction was carried out in acetonitrile under reflux or in the DCM/THF solvent mixture at rt (entries 3 and 4, table 23). The best selectivity from $Yb(OTf)_3$ was obtained when it was used in the DCM/THF solvent mixture under reflux, the *d/l* diol was obtained in a 93:7 ratio over the *meso* diol (entry 2, table 29). The *d/l* diol was still the major product when the tetraglyme complex and the triethylene glycol complex of $Yb(OTf)_3$ were used (entries 5 and 6, table 23). The tetraglyme complex was more selective than the triethylene glycol complex as the *d/l* diol was obtained in a 95:5 ratio over the *meso* diol in THF under reflux, which is the highest selectivity obtained from the pinacol coupling of cyclohexylcarboxaldehyde (entry 5, table 23). All the above mentioned results are summarised in the table 23 below.



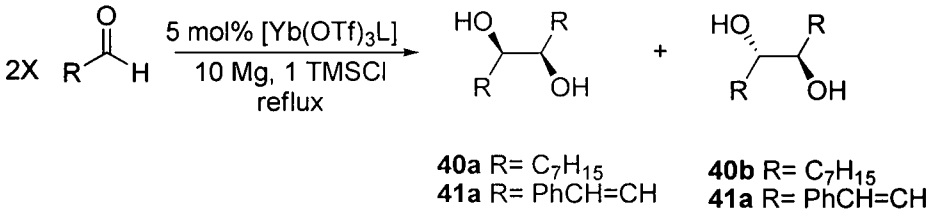
39b **39a**

Scheme 107

entry	ligand	solvent	time	yield	*d/l:meso*
1	-	THF	20 h	64%	75:25
2	**-**	**DCM/THF**	**24 h**	**65%**	**93: 7**
3	-	DCM/THF[r]	30 h	60%	60:40
4	-	MeCN	23 h	69%	60:40
5	**tetraglyme**	**THF**	**22 h**	**61%**	**95: 5**
6	triethylene glycol	THF	22 h	63%	83:17

Table 23

[r] reaction ran at rt.



Scheme 108

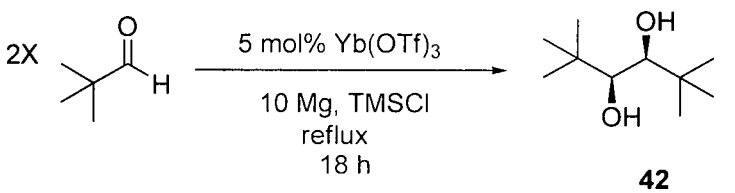
Octanal, a long chain aliphatic aldehyde, gave both isomers of the corresponding coupled diol in moderate to excellent yields when it reacted with $Yb(OTf)_3$ or the tetraglyme complex of $Yb(OTf)_3$ in either THF or the DCM/THF solvent mixture under reflux with 10 eq of magnesium and one eq of TMSCl (scheme 108). The *d/l* diol was isolated as major isomer from all the pinacol coupling reactions of octanal, after 15 hours (entries 1 to 4, table 24). $Yb(OTf)_3$ in THF under reflux gave the best selectivity for the *d/l* diol with a ratio of 69:31 over the *meso* diol (entry 1, table 24). The tetraglyme complex in THF under reflux gave better selectivity than in the DCM/THF solvent mixture under reflux.

Cinnamaldehyde, an α,β-unsaturated aldehyde, gave both isomers of the corresponding diol 41 in the pinacol coupling promoted by 5 mol% of $Yb(OTf)_3$ or the tetraglyme complex of $Yb(OTf)_3$ with 10 eq of magnesium and one eq of TMSCl (scheme 106). The *d/l* diol was isolated as the major product after 3½ hours in THF or DCM/THF solvent mixture under reflux (entries 5 to 8, table 24). The best selectivity for the *d/l* diol **41** was obtained when $Yb(OTf)_3$ was used in the DCM/THF solvent mixture under reflux (entry 6, table 24). The *d/l* diol was obtained in a 79:21 ratio over the *meso* diol. The selectivity was reduced when THF under reflux was used as solvent (entry 5, table 24). The selectivity was reversed when the tetraglyme complex was used. In the DCM/THF solvent mixture under reflux, the *d/l* over *meso* ratio was 62:38 in favour of the *d/l* (entry 8, table 24). This selectivity was increased to 76:24 when the tetraglyme complex was used in THF under reflux (entry 7, table 24). All the above mentioned results are summarised in the table below.

entry	ligand	solvent	time	yield	*d/l:meso*
1	-	THF	15 h	45%	69:31
2	tetraglyme	THF	15 h	60%	65:35
3	tetraglyme	DCM/THF	15 h	61%	56:44
4	-	DCM/THF	15 h	50%	60:40
5	-	THF	3½ h	55%	56:44
6	-	DCM/THF	3½ h	53%	79:21
7	tetraglyme	THF	3½ h	60%	76:24
8	tetraglyme	DCM/THF	3½ h	55%	62:38

Table 24

The pinacol coupling of pivaldehyde was very selective. Only the *d/l* diol was obtained when pivaldehyde was reacted with 5 mol% of $Yb(OTf)_3$ or the $Yb(OTf)_3$ tetraglyme complex and 10 eq of magnesium and one eq of TMSCl in either THF or DCM/THF solvent mixture under reflux (scheme 109). The reactions were completed in 18 hours and the *d/l* diol 42 was isolated in yields of over 90% (table 25). The results of the pinacol coupling of pivaldehyde is summarised in table 25 below.



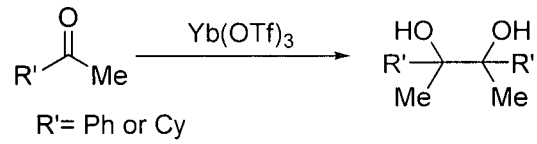
42

Scheme 109

entry	ligand	solvent	yield	*meso:d/l*
1	-	THF	95%	*d/l* only
2	-	DCM/THF	89%	*d/l only*
3	tetraglyme	THF	91%	*d/l* only
4	tetraglyme	DCM/THF	90%	*d/l only*

Table 25

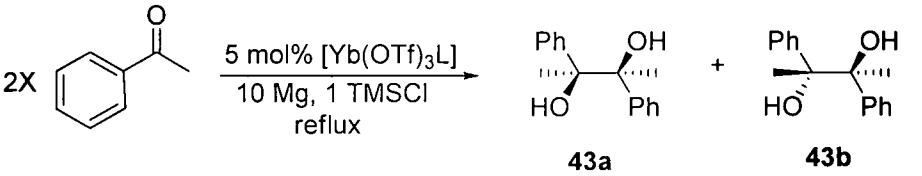
4.5.3 Pinacol coupling of ketones



Scheme 110

The pinacol coupling promoted by $Yb(OTf)_3$ or $[Yb(OTf)_3L]$ was also extended to ketones (acetophenone and cyclohexyl methyl ketone). The corresponding diols were obtained in moderate to excellent yields with the *d/l* diol being the major product. Reactions crudes were analysed by GC to determine ratio of isomers and this was confirmed by GCMS.[10] The results of the pinacol coupling of ketones are discussed below.

Both isomers of the corresponding coupled diol were obtained when acetophenone reacted with 5 mol% of $Yb(OTf)_3$ or $[Yb(OTf)_3$ L] with 10 eq of magnesium and one eq of TMSCl (scheme 111). All reactions gave the *d/l* isomer as major product (table 26). When 5 mol% of $Yb(OTf)_3$ was used in THF under reflux, the *d/l* isomer was obtained in a ratio of 67:33 over the *meso* isomer (entry 1, table 26). The selectivity was decreased when acetonitrile or DCM/THF solvent mixture were used under reflux (entries 2 and 4, table 26). The selectivity for the *d/l* isomer was not improved when $Yb(OTf)_3$ was used in the DCM/THF solvent mixture at rt (entry 3, table 26). The selectivity from the $[Yb(OTf)_3L]$ were slightly increased (entries 5 to 8, table 26). In THF under reflux, the tetraglyme complex gave a ratio of 64:36, which was decreased when acetonitrile under reflux was used (entries 5 and 6, table 26). The triethylene glycol complex and the 15-crown-5 complex in THF under reflux gave slightly better selectivity compared to the tetraglyme complex (entries 7 and 8, table 26). All reaction times were less than 3 hours and the diols were isolated in good to excellent yields. The results of these reactions is summarised in the table 26.



43a **43b**

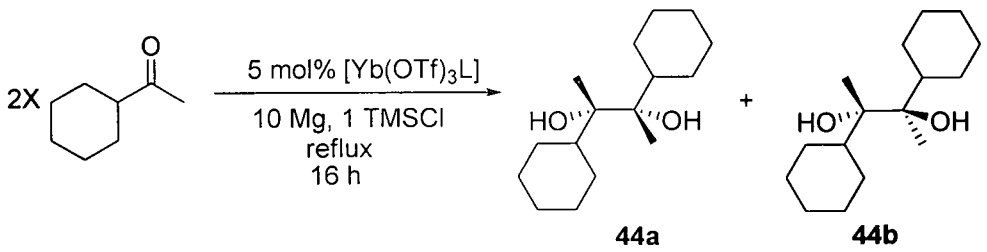
Scheme 111

entry	ligand	solvent	time	yield	*d/l:meso*
1	-	THF	1½ h	85%	67:33
2	-	DCM/THF	3 h	75%	55:45
3	-	DCM/THF [s]	3 h	73%	52:48
4	-	MeCN	2½ h	82%	52:48
5	tetraglyme	THF	3 h	65%	64:36
6	tetraglyme	MeCN	1½ h	77%	61:39
7	triethylene glycol	THF	2 h	85%	67:33
8	15-C-5	THF	3 h	70%	65:35

Table 26

[s] reaction ran at rt.

The pinacol coupling of cyclohexyl methyl ketone gave both diols **44a** and **44b**. The reactions were promoted by 5 mol% of $Yb(OTf)_3$ or the tetraglyme complex of $Yb(OTf)_3$ in THF or acetonitrile under reflux with 10 eq of magnesium and 1 eq of TMSCl (scheme 112). The *d/l* diol was the major product from all the pinacol coupling reactions of cyclohexyl methyl ketone and the best selectivity was obtained when $Yb(OTf)_3$ was used in THF under reflux (entry 1, table 27). The *d/l* diol was obtained in a 72:28 ratio over the *meso* diol. The selectivity was greatly decreased when acetonitrile under reflux was used as reaction media (entry 4, table 27). The same observation was noted with the tetraglyme complex (entries 2 and 3, table 27). A higher selectivity was obtained when THF under reflux was used (entry 2, table 27). The selectivity was reduced from 60:40 to 56:44 when acetonitrile under reflux was used (entry 3, table 27). All the above mentioned results are summarised in the table below.



44a **44b**

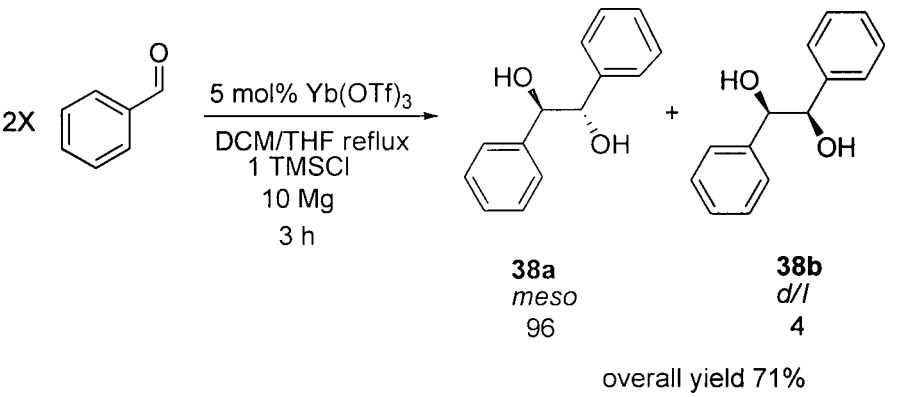
Scheme 112

entry	ligand	solvent	yield	*d/l:meso*
1	-	THF	48%	72:28
2	tetraglyme	THF	51%	60:40
3	tetraglyme	MeCN	55%	56:44
4	-	MeCN	50%	52:48

Table 27

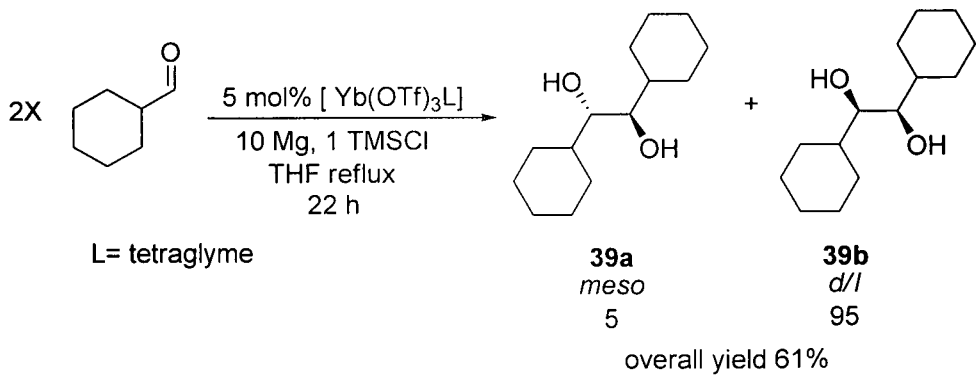
4.6 Summary of results of pinacol coupling

The pinacol coupling promoted by $Yb(OTf)_3$ or $[Yb(OTf)_3L]$ was applied to a range of aldehydes and ketones. Excellent selectivities were obtained in some instances, with aldehydes giving better selectivities compared to ketones. The aromatic aldehyde, benzaldehyde gave the corresponding *meso* diol product in 96:4 ratio over the *d/l* after 3 hours (scheme 113). High selectivity for the *meso* 1,2-diphenylethane-1,2-diol was also obtained when the tetraglyme complex was used to promote the pinacol coupling in acetonitrile under reflux (entry 6, table 22).



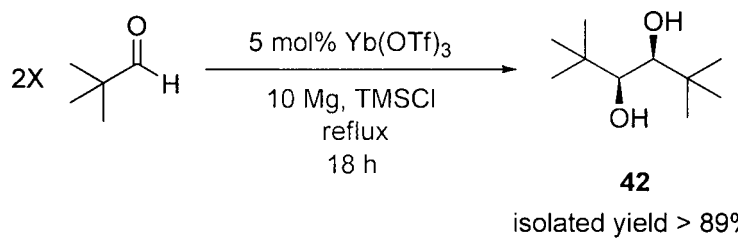
Scheme 113

The selectivity was reversed when aliphatic carbonyls were used. The *d/l* diol was formed predominantly. Very good selectivity was observed from the corresponding aliphatic aldehyde cyclohexyl carboxaldehyde; the *d/l* diol **39b** was obtained in a 95:5 ratio over the meso diol when the tetraglyme complex of $Yb(OTf)_3$ was used to promote the pinacol coupling (scheme 114). Excellent selectivity was also obtained when $Yb(OTf)_3$ in the DCM/THF mixture under reflux was used (entry 2, table 23).



Scheme 114

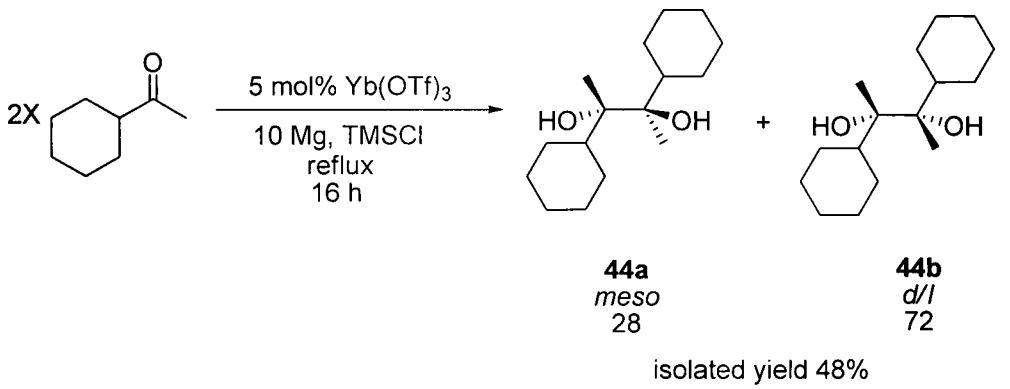
Octanal and cinnamaldehyde have also given the corresponding *d/l* diols in moderate to good selectivities (table 24). The pinacol coupling promoted by $Yb(OTf)_3$ or $[Yb(OTf)_3L]$ has been totally selective in the case of pivaldehyde towards *d/l* diol (scheme 115). The 2,2,5,5-tetramethyl-hexane-3,4-diol was isolated in excellent yields (table 25) after 18 hours when $Yb(OTf)_3$ or the tetraglyme complex of $Yb(OTf)_3$ were used in THF or DCM/THF solvent mixture under reflux.



Scheme 115

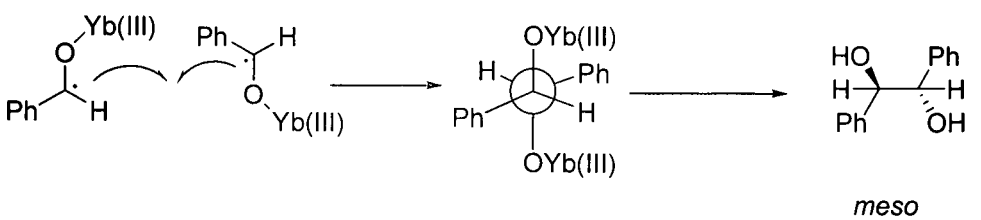
The pinacol coupling of acetophenone promoted by $Yb(OTf)_3$ or $[Yb(OTf)_3L]$ gave the *d/l* 2,3-diphenyl-butane-2,3-diol as major product in good to excellent yield after 1½-3 hours. The selectivity was not as high as those obtained with benzaldehyde, cyclohexylcarboxaldehyde and pivaldehyde. The best selectivity ratio from the pinacol coupling of acetophenone, 67:33 in favour of the *d/l* over the *meso* diol was obtained when $Yb(OTf)_3$ was used in THF under reflux (entry 1, table 26). The pinacol coupling of cyclohexylmethyl ketone was slightly more selective for the corresponding *d/l* diol (scheme 116). When $Yb(OTf)_3$ in THF under reflux was used to promote the pinacol coupling of cyclohexyl methyl ketone, the *d/l* 2,3-dicyclohexyl-

butane-2,3-diol was obtained with a ratio of 72:28 over the *meso* diol after 16 hours (entry 1, table 27).



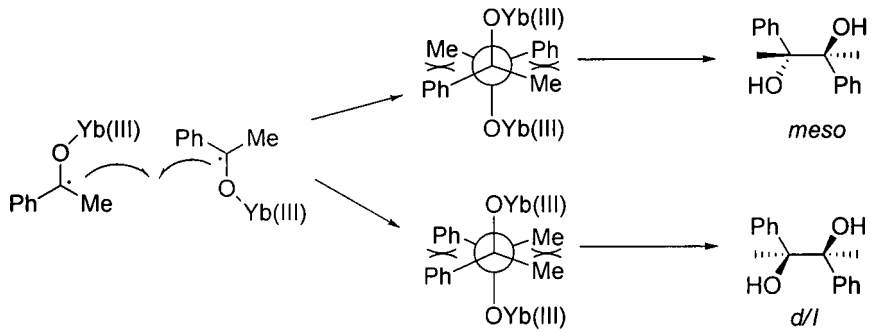
Scheme 116

Better selectivities in the pinacol coupling promoted by $Yb(OTf)_3$ and $[Yb(OTf)_3L]$ were obtained from aldehydes compared to ketones due to the diminished difference in bulkiness of the substituents on each side of the carbonyl. The reverse in selectivity obtained with benzaldehyde (aromatic aldehyde), with the corresponding *meso* diol favoured, while the *d/l* diol was favoured with aliphatic aldehydes, follows the results previously reported by Greeves *et al* when 0.1 eq of SmI_2 was used to promoted the pinacol coupling.[10] It can be assumed that like Sm, the formation of the Yb-ketyl from benzaldehyde is fast, due to the lower energy of the LUMO, and that the repulsion between the Yb centers and phenyl groups during the transition state will give the *meso* diol (scheme 117). The results of the pinacol coupling of aliphatic aldehydes also tend to show that coupling between an Yb-ketyl radical and another aldehyde molecule prevails to favour the corresponding *d/l* diol.



Scheme 117

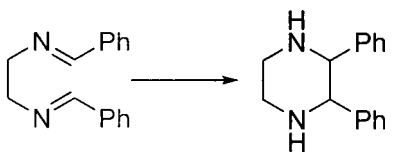
The selectivity for the *meso* diol was not very high with acetophenone as the methyl and phenyl interaction in the transition state was significant (scheme 118). Thus no stereoselectivity was obtained as both approaches of an Yb-ketyl radical to another Yb-ketyl radical gave rise to steric interactions, either Ph-Me interactions or Me-Me and Ph-Ph interactions. This could be used to explain the low selectivity obtained with the pinacol coupling of acetophenone.



Scheme 118

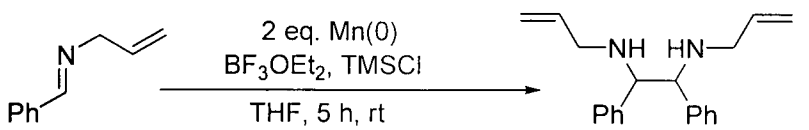
4.7 Intramolecular coupling

Piperazine rings are present in several natural products and can also be used as ligands on metals in asymmetric catalysis.[183,184] It is usually easier to prepare 2,5-disubstituted piperazines by reducing the corresponding diketopiperazines, compared to the 2,3-disubstituted piperazines.[185] An easy route to synthesise 2,3-disubstituted piperazines is the reductive cyclization of a bisimine (scheme 119).



Scheme 119

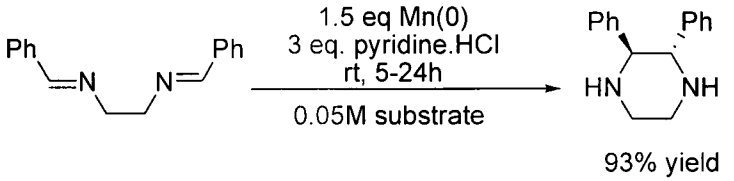
Sigman *et al* reported an intramolecular reduction of a bisimine using Mn(0) metal, a silyl chloride and a Lewis acid.[186] They started with an imine, *N*-benzylideneprop-2-en-1-amine as model substrate for their studies (scheme 120). After screening different Lewis acids and silyl chlorides, it was found that this system gave low diastereoselectivity for the useful *d/l* product. They then tried to substitute the Lewis acid and the silyl chloride with a single reagent and their focus was changed to Brønsted acids.



89% yield
d/l:*meso* 1: 0.55

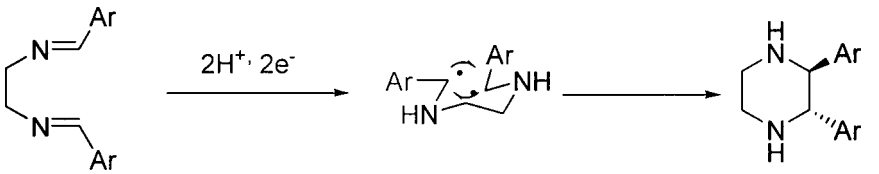
Scheme 120

After optimisation, they found that 10% toluene/acetonitrile gave best yield of 93% of the *trans* or *d/l* product, when 1.5 eq of Mn(0) and 3 eq of pyridine.HCl in acetonitrile and 10% toluene were used at room temperature in the intramolecular reductive coupling of a bisimine (1 eq) (scheme 121).



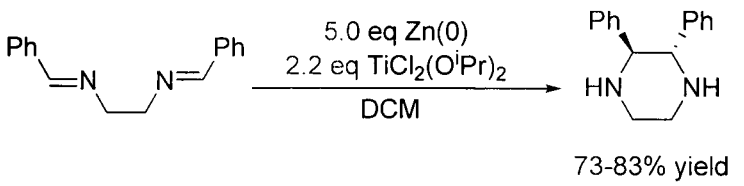
Scheme 121

This system also worked very well with trifluoroacetic acid as Brønsted acid and other substrates have included diimines made from different substituted benzaldehydes with yields > 76% of the desired *d/l* product. They have put forward that the cyclisation goes via an intramolecular termination of a diradical intermediate due to the observed diastereoselectivity.



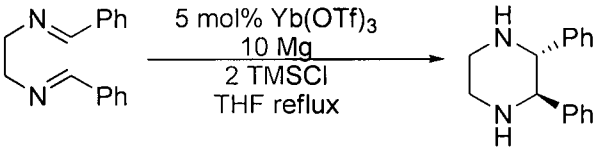
Scheme 122

Perisamy *et al* have also reported the synthesis of the *d/l* 2,3-diphenylpiperazine in >99% ee, using five eq of Zn with 2.2 eq of $TiCl_2(O^iPr)_2$ as Lewis acid in 73-83% yield (scheme 123). They found that yields were low when two eq of Zn was used.[187]



Scheme 123

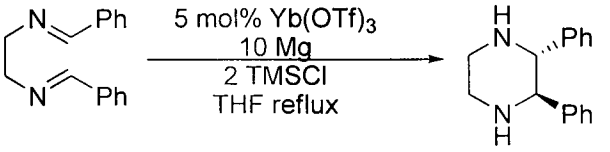
These methods both used several eq of the Lewis acid. Encouraged by the results of the $Yb(OTf)_3$/Mg/TMSCl system in the reductive homocoupling of imines, aldehydes and ketones, we carried out the intramolecular reductive coupling of a diimine (scheme 124), synthesised from benzaldehyde and ethylene diamine.



45 46

Scheme 124

Initially, the reaction was carried out using same conditions as for the homocoupling reaction, every reagent and substrate added in 8 mL of THF followed by heating under reflux. The piperazine product was not obtained; instead, oligomerisation occurred after 5 hours (entry 1, table 28). We then decided to increase the amount of THF used (decreasing concentration of reactants), in order to reduce oligomerisation. This reaction used 20 mL of THF and took longer to go to completion but again, no cyclisation occurred (entry 2, table 28). It was then decided to add the diimine dropwise in order to favour cyclisation over polymerisation (entry 3, table 28). This reaction was also unsuccessful at producing the cyclised product. In a further attempt to favour cyclisation, it was decided to add the TMSCl gradually. The reaction was carried out by adding 1eq of TMSCl with $Yb(OTf)_3$ in THF with magnesium and one eq of TMSCl added with diimine in THF. The oligomer was again obtained as main product along with a small trace of the piperazine adduct (entry 4, table 35) seen by NMR. The reaction was repeated but the diimine was added dropwise over a longer period of 2 hours (entry 5, table 28). Only one isomer of the piperazine was isolated in 85% and after characterisation by ^{1}H and ^{13}C NMR, it was found to be the *d/l* product.[186] All the above mentioned reactions were monitored by tlc and the results and shown in the table 35 below.



45 46

Scheme 124

entry	Add. time	Rxn time	Yield
1	0	5 h	0%
2	0 [t]	24 h	0%
3	1 h [u]	18 h	0%
4	1 h [v]	18 h	0%
5	2 h [v]	18 h	85%

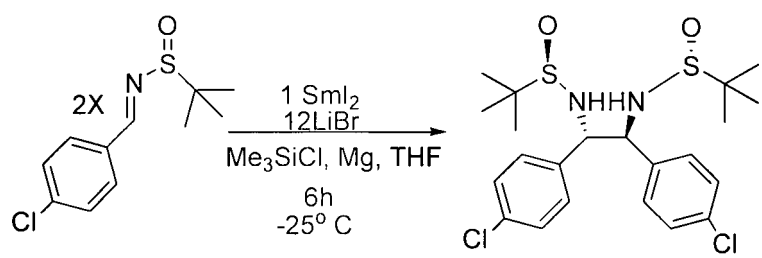
Table 28

[t] Reaction carried out with more solvent. [u] TMSCl added with $Yb(OTf)_3$ only.

[v] 1eq TMSCl added with $Yb(OTf)_3$ and 1 eq of TMSCl added with diimine

4.8 Conclusions

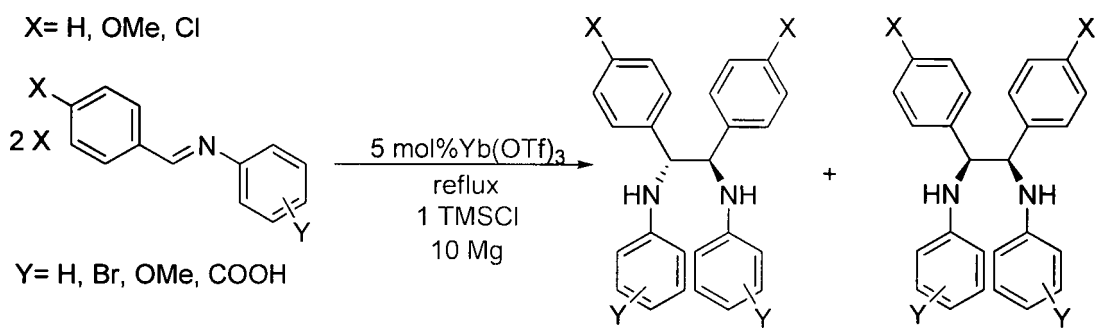
The results from the reductive homocoupling of sulfinyl imines have shown that HMPA is not important for stereoselectivity. Only the *d/l* isomer was obtained in all the reactions tried (results are detailed in chapter 2). LiBr/TMSCl/Mg were used with SmI_2 to promote the reductive homocoupling and even though the reaction has occurred with 0.25 eq of SmI_2, the yields were not very high. The best yield (51%) obtained was with one eq of SmI_2 with 12 eq of LiBr, 10 eq of magnesium and one eq of TMSCl at -25° C (scheme 125).



6 **7a** 51%

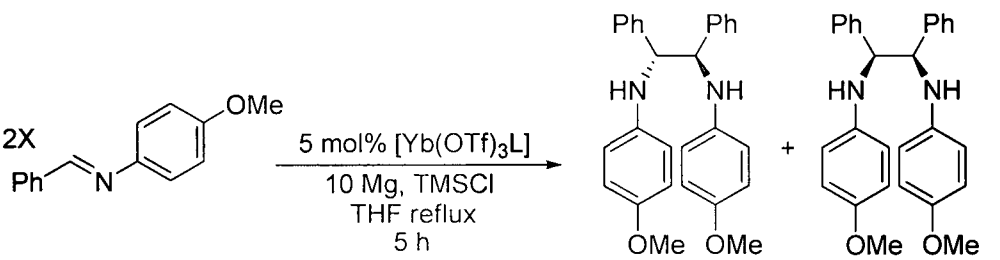
Scheme 125

This work also demonstrated that the reductive homocoupling of imines can proceed in the absence of SmI_2. The new methodology of $Yb(OTf)_3$/Mg/TMSCl, which needs only 5 mol% of $Yb(OTf)_3$, is very efficient at promoting the reaction and the corresponding coupled diamines were obtained in moderate to excellent yields. These reactions are simpler and require no inert atmosphere and/or anhydrous conditions (scheme 93).



Scheme 93

The reductive homocoupling of aromatic imines was moderately selective towards the *meso* diamine product. The triethylene glycol complex of $Yb(OTf)_3$ gave the *meso* diamine as major product in a 79:21 ratio over the *d/l* diamine when it was used to promote the reductive homocoupling reaction of benzaldehyde 4-methoxyphenylimine in THF under reflux (scheme 97)



31

L= triethylene glycol

32a

d/l
21

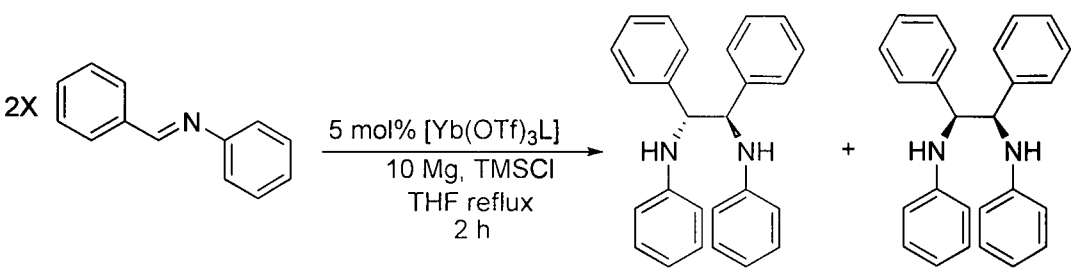
32b

meso
79

overall yield 45%

Scheme 97

The reductive homocoupling of imines was more selective towards the *d/l* diamine. When benzaldehyde phenylimine was used as substrate (scheme 98), the coupled *d/l* diamine was obtained in a 91:9 ratio over the *meso* isomer with the 15-crown-5 complex of $Yb(OTf)_3$ acting as catalyst for the reaction.



10

L= 15-Crown-5

11a

d/l
91

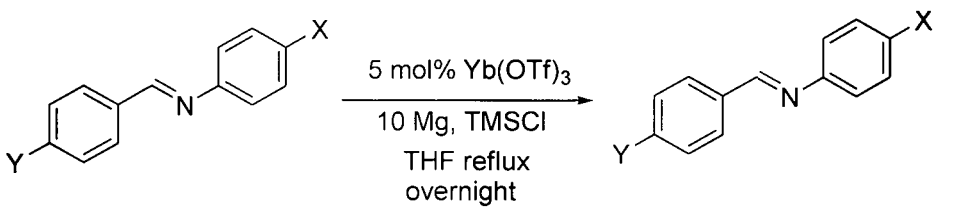
11b

meso
9

overall yield 76%

Scheme 98

Imines bearing a nitro group do not undergo reductive homocoupling but selective reduction of the nitro group only (scheme 85). Only 5 mol% of $Yb(OTf)_3$ were sufficient to promote this transformation in THF under reflux. Other reported routes require stoichiometric amounts of metal catalysts, which can be problematic with the disposal. The $Yb(OTf)_3$/Mg/TMSCl system gave complete conversion to the amine after 16 hours, with the imine moiety unaffected.

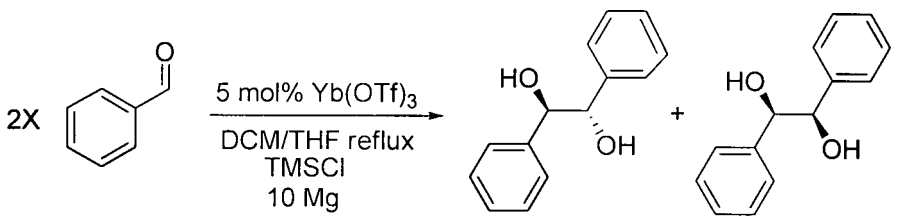


14 Y= H, X= NO_2
15 Y= Cl, X= NO_2
16 Y= NO_2, X=H
17 Y= NO_2, X= NO_2

14A Y= H, X= NH_2
15A Y= Cl, X= NH_2
16A Y= NH_2, X=H
17A Y= NH_2, X= NH_2

Scheme 85

The pinacol couplings were more selective than reductive homocoupling of imines. Excellent selectivity was obtained with benzaldehyde (aromatic aldehyde), with the *meso* 1,2-diphenylethane-1,2-diol obtained in 96:4 ratio over the *d/l* diol (scheme 113).



38a *meso* 96

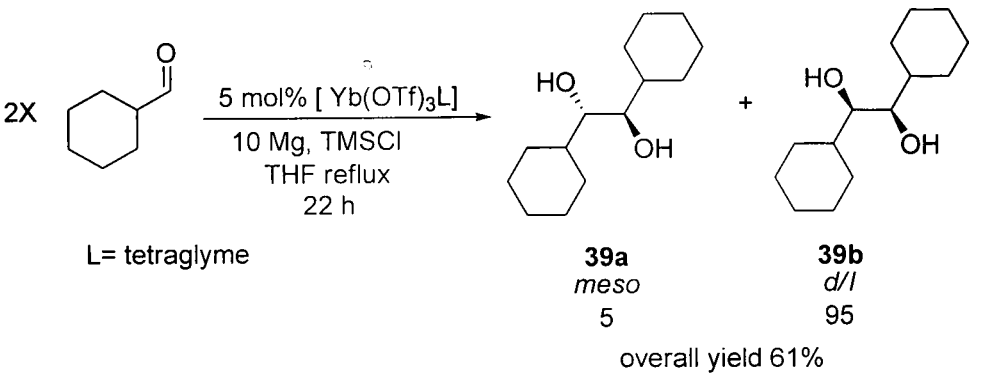
38b *d/l* 4

overall yield 71%

Scheme 113

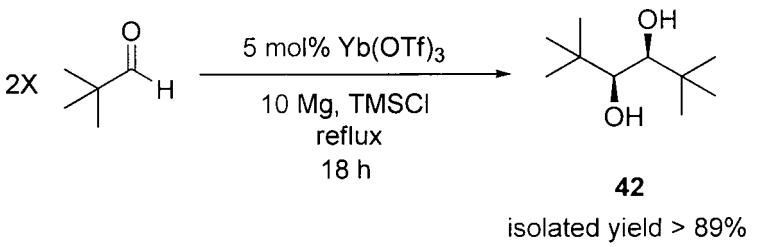
Aliphatic aldehydes like cyclohexyl carboxaldehyde were more selective towards the corresponding *d/l* diol. The tetraglyme complex of $Yb(OTf)_3$ gave

the *d/l* diol **39b** in a 95:5 ratio over the *meso* diol in THF under reflux after 22 hours (scheme 114).



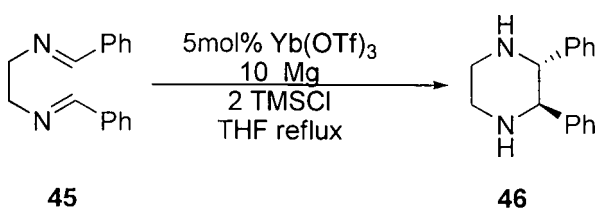
Scheme 114

The $Yb(OTf)_3$/Mg/TMSCl system was totally selective in the pinacol coupling of pivaldehyde. The *d/l* diol **42** was the only product from all the pinacol coupling reactions promoted by $Yb(OTf)_3$ and $[Yb(OTf)_3L]$ after 18 hours in isolated yields of > 89% (scheme 115).



Scheme 115

The intramolecular reductive coupling also gave excellent selectivity. The *d/l* piperazine **46** was the only product obtained after a reaction time of 18 hours (scheme 124). Only 5 mol% of $Yb(OTf)_3$ in THF under reflux were enough to promote the reaction, compared to other reported similar synthesis where several eq of metals were used.



Scheme 124

Chapter 5

5 Experimental

5.1 General techniques

Air and moisture sensitive reactions were performed under an inert atmosphere (argon or nitrogen) using standard Schlenk techniques.
Glassware was keep moisture free by storage in an oven at 160° C.
Molecular sieves used were 1.66mm pellets of 4Å pores. Prior use, they were kept in an oven at 170° C.
All chemicals were purchased from Acros or Aldrich or BDH.

5.2 Instrumentation

^{1}H NMR spectra were recorded on Bruker AC200, Bruker AC250 or Bruker Avance 400 spectrometers.
^{13}C NMR spectra were recorded on Bruker Avance 400 spectrometer.
Gas chromatography was performed with a SE 30 column.
Mass spectra were recorded on VG analytical 7070E and Fisions Trio 1000 spectrometers using electron ionisation (E.I.), chemical ionisation (C.I.) and fast atom bombardment (F.A.B.).
Elemental analysis (C, H, N and S) were recorded on Thermo-Flash EA1112 series CHNS analyser.
Syringe pump used was a Razel A-99.FZ.
Melting points were recorded using Stuart melting point apparatus SMP3.

5.3 TLC visualisation techniques

Silica gel 60 F_{254} on aluminium sheets were purchased from Merck.
Ultraviolet light: plates were visualised by spectroline EF-280C/F lamp.
Iodine vapours by treatment of the plate in a tank containing silica gel and some iodine crystals.
Ceric ammonium molybdate (CAM) dip, prepared by dissolving $(NH_4)_6Mo_7O_{24}$ (5 g), $Ce(SO_4)_2$ (0.2 g) and concentrated sulphuric acid (5 mL) in 100 mL of water.
Potassium permanganate dip, prepared by dissolving $KMnO_4$ (1 g), K_2CO_3 (6 g) and 5% NaOH solution (2 mL) in 100 mL of water.
Anisaldehyde dip, was prepared by mixing conc. sulfuric acid (87.5 mL) to ethanol (2325 mL) followed by glacial acetic acid (25 mL) and *p*-anisaldehyde (6.25 mL).
Ninhydrin dip, prepared by dissolving ninhydrin (3 g) in *n*-butanol (970 mL) and glacial acetic acid (30 mL).

5.4 Purification of solvents and reagents

All solvents used for reaction were distilled prior using and most reactions were carried out under an inert atmosphere, using either argon or nitrogen.

Tetrahydrofuran and dimethoxyethane were distilled under nitrogen from sodium benzophenone ketyl and were stored on molecular sieves under argon.
Acetonitrile, dichloromethane, ethanol and petroleum ether 40/60 were distilled under nitrogen from calcium hydride and were stored on molecular sieves under argon.
All liquid aldehydes, liquid ketones and liquid anilines used were distilled under vacuum using a Kugelrohr short-path distillation apparatus prior use.
Chlorotrimethylsilane was distilled under vacuum using a Kugelrohr short-path distillation apparatus.

meta-chloroperbenzoic acid (*m*-CPBA) was purified by washing with a buffer solution made from disodium hydrogen phosphate and potassium dihydrogen phosphate and was extracted in DCM.[188]

LiBr was kept in an oven at 130° C to remove any trace of moisture.

Magnesium powder was activated by stirring with a magnetic bar under an argon atmosphere for 24 hours. Once activated, the magnesium was kept under argon.

Diiodomethane was purified by drying over calcium chloride and fractionally distilled from copper powder.[188]

Diiodoethane was purified by dissolving in a minimum amount of diethyl ether and washing with a saturated aqueous solution of sodium thiosulfate ($Na_2S_2O_3$). The organic layer was separated and dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid, which was left to dry on a high vacuum pump for a few hours in a flask wrapped in aluminium foil.[188] The diiodoethane was kept in the fridge in a dark container wrapped in aluminium foil.

Tetraglyme and Triglyme were distilled from $LiAlH_4$, under reduced pressure.[188]

Triethylene glycol was dried over $CaSO_4$ for a few days before distillation under reduced pressure.[188]

All lanthanide(III) oxides, scandium(III) oxide, yttrium(III) oxide, 15-crown-5, 18-crown-6, 2,2-bi-pyridyl, trifluoromethanesulfonic acid, trimethylsilyl trifluoromethanesulfonate, di-*tert*-butyldisulfide, sulfuryl chloride, pyridinium *p*-toluenesulfonate, ethylene diamine, 2-methoxyaniline, 4-methoxyaniline, 4-bromoaniline, 4-nitroaniline, 4-aminobenzoic acid, 4-cyanobenzaldehyde, 4-nitrobenzaldehyde and 4-chlorobenzaldehyde were used without any purification.

5.5 Procedure for the synthesis of samarium diiodide

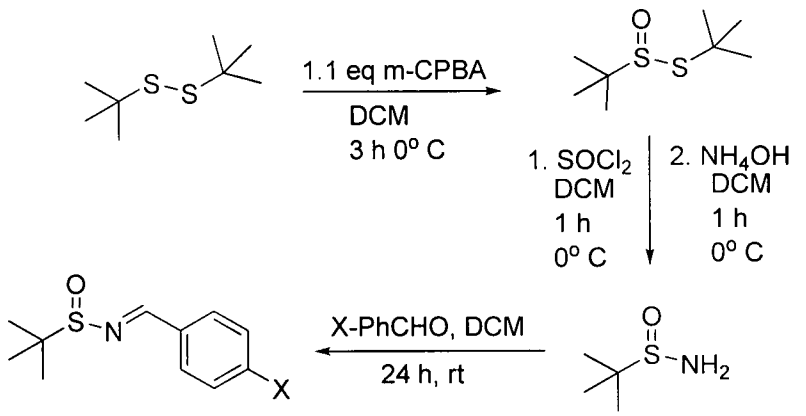
Samarium diiodide was prepared following Kagan's procedure.[2] Samarium chips (0.451 g, 3 mmol) and diiodoethane (0.846 g, 3mmol) were mixed in a Schlenk flask under vacuum using a magnetic stirrer bar. To remove any trace of air, the flask was then flushed with argon and left to stir for a few minutes before applying vacuum again. Freshly distilled, dry and degassed THF was then added to the Schlenk flask and mixture was allowed to stir vigorously at room temperature and pressure under an argon atmosphere. The initial pale yellow solution turned dark green and finally deep blue after a few hours.

St Jean *et al* have recently published an alternative method for the preparation of samarium diiodide.[189] Samarium chips (0.3 g, 2 mmol) were flame dried under vacuum in a Schlenk flask and were allowed to cool to rt under an argon atmosphere. Dry degassed THF was then added and the suspension was cooled to 0° C in an ice bath. Diiodomethane (0.8 mL, 0.6 g, 2 mmol) was then added and mixture was allowed to stir overnight at room temperature in a lighted fumecupboard.

It was also found that the deep blue solution of SmI_2 formed more rapidly if it was left to stir in a lighted fume cupboard. The SmI_2 would stay deep blue longer if it was kept stirring in a lighted fume cupboard.

If samarium metal was oxidised (the metal turns grey in colour), it had to be washed with a small amount of trifluoromethanesulfonic acid (triflic acid) in dry distilled THF and then washed three times with dry distilled THF. The metal was then left to dry under vacuum and kept under an argon atmosphere.

5.6 Synthesis of racemic *t*-butanesulfinyl imines [89,90]



Scheme 40

A solution of *m*-CPBA (1.4 g, 6.2 mmol) in DCM (10 mL) was added dropwise to a solution of *t*-butyldisulfide (1.0 g, 5.6 mmol) in DCM (2.5 mL) at 0° C over 15 minutes with constant stirring. The resulting solution was left to stir at 0° C for 30 minutes before allowing gradual increase to room temperature until reaction was complete. Reaction was monitored by tlc.

The reaction mixture was then poured into a separatory funnel containing DCM (20 mL) and saturated $NaHCO_3$ (15 mL). The organic layer was removed and washed with saturated $NaHCO_3$ (2 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

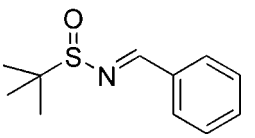
The material was used without any purification for the next step. It was dissolved in DCM (5 mL) and a solution of sulfuryl chloride (0.72 g, 5.3 mmol) in DCM (2 mL) was added dropwise over 15 minutes at 0° C. The resulting yellow solution was allowed to stir for 1 hour, with a gradual increase to room temperature. The excess sulfuryl chloride was removed under reduced pressure and the remaining solid residue was dissolved in DCM (10 mL).

Ammonium hydroxide (20 mL) was added dropwise over 30 minutes at 0° C. After stirring for an additional 30 minutes at rt, the reaction mixture was saturated with brine and extracted with DCM (3 X 20 mL). The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$ and concentrated *in vacuo* to give the crude sulfinamide.

The product was purified by flash chromatography using a solvent system consisting 12:1 dichloromethane: methanol.

A solution of the pure *t*-butanesulfinamide (1.0 g, 8.26 mmol) in dichloromethane (15 mL) was added to pyridinium *p*-toluenesulfonate (103 mg, 0.413 mmol), anhydrous $MgSO_4$ (4.97 g, 41.3 mmol) and aldehyde (24.78 mmol). The mixture was left to stir for 24 hours at rt. The $MgSO_4$ was filtered off through a pad of celite and washed well with DCM. The combined filtrate and washes were concentrated in *vacuo*. The product was purified by flash chromatography using a solvent system consisting of 5:95 hexane: dichloromethane.

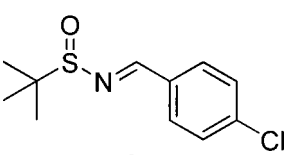
Analytical data for benzylidene-*t*-butyl-sulfinimine



4

Product was isolated as a colourless oil by flash chromatography on silica gel with a solvent system consisting of 5:95 hexane: dichloromethane with a R_f of 0.42. The data are consistent with the literature.[190] δ_H (400 MHz; $CDCl_3$; TMS) 1.27 (s, 9H, CH_3), 7.25-7.40 (m, 5H aromatic), 8.60 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 163.2, 134.5, 132.9, 129.7, 129.4, 58.2, 23.0; m/z (C.I.) 210 (100% $[M+H]^+$); $C_{11}H_{15}NOS$ requires C 63.12%, H 7.22%, N 6.69%, found C 63.21%, H 7.12%, N 6.59%

Analytical data for 4-chlorobenzylidene-2-methylpropane-2-sulfinamide

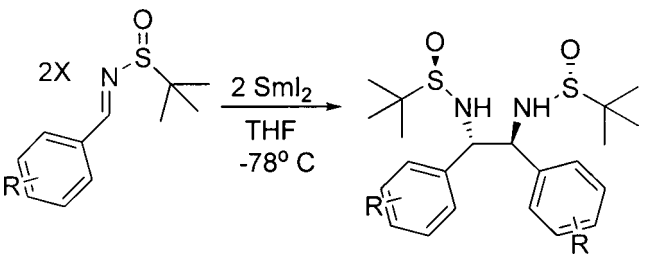


6

Product was isolated as a white solid by flash chromatography on silica gel with a solvent system consisting of 5:95 hexane: dichloromethane with a R_f

of 0.51. The data are consistent with the literature.[191] m.p. 39.8-41.3° C (lit. m.p. 38-40° C); δ_H (400 MHz; $CDCl_3$; TMS) 1.26 (s, 9H, CH_3), 7.44 (d, J 8.5 Hz, 2H aromatic), 7.79 (d, J 8.5 Hz, 2H aromatic), 8.55 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 161.9, 139.0, 133.0, 130.9, 129.7, 58.3, 23.0; m/z (C.I.) 244.06 (100% $[M+H]^+$); $C_{11}H_{14}NOSCl$ requires C 54.20%, H 5.71%, N 5.75%; found C 54.26%, H 5.71%, N 5.68%

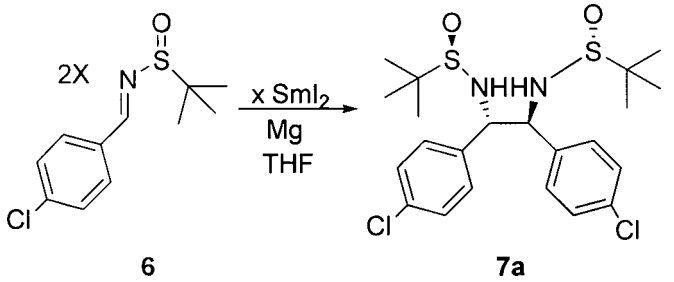
5.7 Homocoupling of *N*-*t*-butanesulfinyl imines[49]



Scheme 126

Under an argon atmosphere, a solution SmI_2 (1 mmol) in THF (5 mL) was cooled to -78° C in a Schlenk flask using acetone/CO_2. The sulfinyl imine (0.5 mmol) was dissolved in dry degassed distilled THF (6 mL) and was added dropwise over 30 minutes. The resulting solution was stirred at -78° C for about 3 hours. The reaction was monitored by tlc and was quenched with saturated $Na_2S_2O_3$ solution (5 mL). The crude product was extracted with ethyl acetate (3 X 20 mL). The combined ethyl acetate extracts were dried over magnesium sulfate and concentrated in *vacuo*. The crude product was purified by flash chromatography using hexane and ethyl acetate as eluent.

5.7.1 Homocoupling of 4-chlorobenzylidene-2-methylpropane-2-sulfinamide using catalytic SmI_2

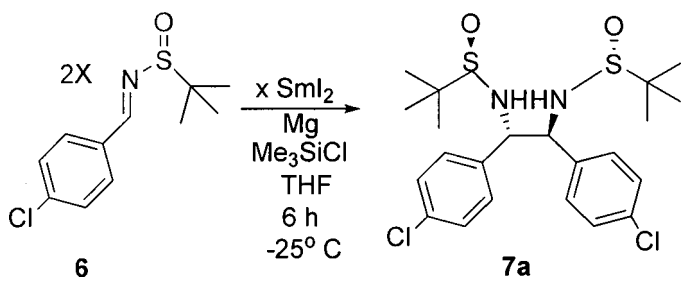


6 7a

Scheme 127

Under an argon atmosphere, a solution SmI_2 (1 mmol) in THF (5 mL) and activated magnesium powder were cooled in a Schlenk flask to the desired temperature using either ethylene glycol/CO_2 for -25° C or acetonitrile/CO_2 for -40° C. The sulfinyl imine was dissolved in dry degassed THF (6 mL) and was added dropwise over 30 minutes. The resulting solution was stirred for about 6 hours at the same temperature. The reaction was monitored by tlc and was quenched with saturated $Na_2S_2O_3$ solution (5 mL). The crude product was extracted with ethyl acetate (3 X 20 mL). The combined ethyl acetate extracts were dried over magnesium sulfate and dried in *vacuo.* The crude product was purified by flash chromatography using hexane and ethyl acetate as eluent.

5.7.2 Homocoupling of 4-chlorobenzylidene-2-methylpropane-2-sulfinamide with SmI_2, Me_3SiCl and Mg



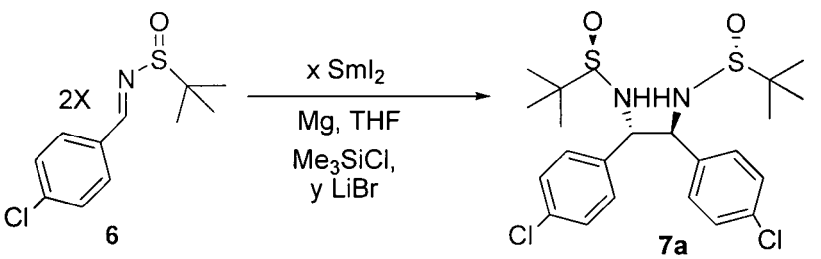
6 7a

Scheme 45

Under an argon atmosphere, TMSCl (1 eq. to sulfinyl imine) was added to a solution of SmI_2 (1 mmol) in THF (5 mL). This solution was then added to some activated magnesium powder in a Schlenk flask and this mixture was

cooled to the desired temperature using either ethylene glycol/CO_2 for -25° C or acetonitrile/CO_2 for -40° C. The sulfinyl imine was dissolved in dry degassed THF (6 mL) and was added dropwise over 30 minutes. The resulting solution was stirred for about 6 hours. The reaction was monitored by tlc and was quenched with saturated $Na_2S_2O_3$ solution (5 mL). The crude product was separated with ethyl acetate (3 X 20 ml). The combined ethyl acetate extracts were dried over magnesium sulfate and removed in *vacuo*. The crude product was purified by flash chromatography using hexane and ethyl acetate as eluent.

5.7.3 Homocoupling of 4-chlorobenzylidene-2-methylpropane-2-sulfinamide with SmI_2, LiBr, Me_3SiCl and Mg

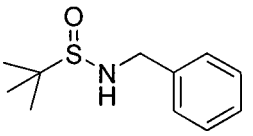


6 7a

Scheme 128

LiBr was heated at 125° C under vacuum in a Schlenk flask for at least 3 hrs. It was left to cool to room temperature under an argon atmosphere before addition of activated magnesium. SmI_2 and Me_3SiCl (0.1 mL, 0.5 mmol) was then added and mixture was stirred and cooled to the required temperature. The sulfinyl imine (0.5 mmol) was dissolved in dry degassed THF (2 mL) and was added dropwise over 1 hour. The resulting solution was stirred for about 6 hours. The reaction was monitored by tlc and was quenched with saturated $Na_2S_2O_3$ solution (5 mL). The crude product was separated with ethyl acetate (3 X 20 mL). The combined ethyl acetate extracts were dried over magnesium sulfate and removed in *vacuo*. The crude product was purified by flash chromatography using hexane and ethyl acetate as eluent.

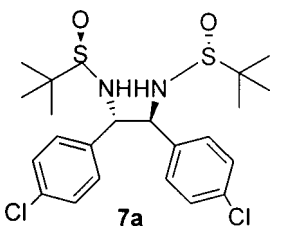
Analytical data for N-benzyl-*t*-butanesulfinamine



5

Product was isolated as a white solid by flash chromatography on silica gel using a solvent system of 1:6 hexane: ethyl acetate with a R_f of 0.35. The data are consistent with the literature.[192] m.p. 63.7-64.1° C (lit. m.p. 64-65° C); δ_H (400 MHz; $CDCl_3$; TMS) 1.27 (s, 9H, CH_3), 2.0 (br s, 1H, NH), 3.82 (s, 2H, CH_2), 7.25-7.40 (m, 5H aromatic); δ_C (100 MHz; $CDCl_3$) 140.2, 128.9, 128.7, 127.5, 58.2, 53.3, 23.1; m/z (C.I.) 198 (100% $[M+H]^+$); $C_{11}H_{17}NOS$ requires C 62.52%, H 8.11%, N 6.63%, found: C 62.69%, H 8.13%, N 6.55%; I.R. 1061.9 cm^{-1} (S=O), 1453.2 cm^{-1} (aromatic), 2924.5 cm^{-1} (C-H), 3292.8 cm^{-1} (N-H)

Analytical data for N,N'-(1,2-bis(4-chlorophenyl)ethane-1,2-diyl)bis(2-methylpropane-2-sulfinamide)



7a

Product was isolated as a white solid by flash chromatography on silica gel with a solvent system consisting of 1:1 hexane: ethyl acetate with a R_f of 0.3. The data are consistent with the literature.[49] m.p. 95.3-95.6° C (lit. m.p. 94-98° C) δ_H (400 MHz; $CDCl_3$; TMS) 1.12 (s, 18H, 6 CH_3), 4.85-4.87 (m, 2H, CH), 5.94 (s, 2H, NH), 7.08 (dd, J 1.8 Hz, 6.7 Hz, 4H aromatic), 7.20 (dd, J 1.9 Hz, 6.7 Hz, 4H aromatic); δ_C (100 MHz; $CDCl_3$) 137.4, 134.0, 130.4, 128.9, 60.3, 56.9, 23.8; m/z (ES+) 511.1 (100% $[M+Na]^+$); $C_{22}H_{30}Cl_2N_2O_2S_2$ requires C 53.98%, H 6.15%, N 5.72%; found C 54.17%, H 6.18%, N 5.66%

5.8 Procedure for the synthesis of lanthanide(III) triflates[193]

$$Ln_2O_3 + 6\,CF_3SO_3H \xrightarrow{H_2O} 2\,Ln(OTf)_3 + 3\,H_2O$$

Scheme 129

An excess of lanthanide oxide (1.1 eq) was stirred and heated to about 80-90° C in the minimum amount of water. Trifluoromethanesulfonic acid (triflic acid) (6 eq) was then added and the mixture was left to stir with boiling for 1 hour. After 1 hour, the excess lanthanide oxide was then filtered off and the filtrate was boiled to dryness. The lanthanide triflate was then heated under vacuum at 120° C for 1 hour to remove any excess water. The anhydrous triflate sample was obtained by further heating under vacuum at 140° C for a few more hours. The anhydrous crystals stored in a sealed Schlenk flask under nitrogen.

5.8.1 Procedure for the synthesis of polyether and polyethylene glycol complexes of $Yb(OTf)_3$ [194,195]

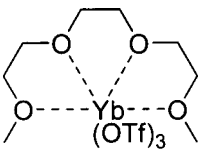
$$Yb(OTf)_3 + L \xrightarrow[\text{Molecular sieves}]{\text{DCM, reflux}} [Yb(OTf)_3L]$$

Scheme 78

$Yb(OTf)_3$ (1.57 g, 5 mmol) and ligand (5 mmol) were mixed in dry DCM (100 mL) and mixture was left to reflux overnight. A soxhlet extraction thimble filled with molecular sieves was fitted on top of apparatus to remove water from the DCM.H_2O azeotrope. The complex was then recrystallised using dry petroleum ether 40/60. Anhydrous complex was obtained by heating the hydrated complex to ca. 90-100° C under vacuum for 3 hour. The anhydrous complex was then kept in a dessicator under nitrogen.

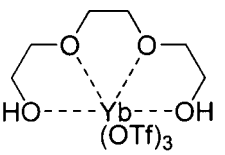
Due to the high fluorine content, it was not possible to carry out combustion analysis for carbon and hydrogen on these complexes. No NMR data is given as the complexes were not very soluble in non coordinating deuterated solvents.

Analytical data for triglyme complex of $Yb(OTf)_3$



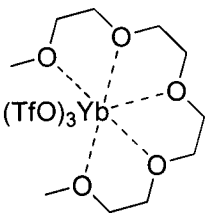
Product was isolated as a white solid by recrystallisation from DCM/pet ether 40/60. The data are consistent with the literature.[194] m/z (ES^+) 649.96 (100% $[M-(OTf)]^+$)

Analytical data for triethylene glycol complex of $Yb(OTf)_3$



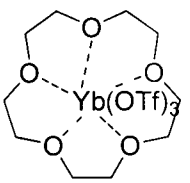
Product was isolated as a white solid by recrystallisation from DCM/pet ether 40/60. The data are consistent with the literature.[194] m/z (ES^+) 621.93 (100% $[M-(OTf)]^+$)

Analytical data for tetraglyme complex of $Yb(OTf)_3$



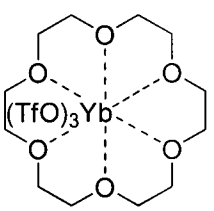
Product was isolated as a white solid by recrystallisation from DCM/pet ether 40/60. The data are consistent with the literature.[194] m/z (ES^+) 693.99 (100% $[M-(OTf)]^+$)

Analytical data for 15-crown-5 complex of $Yb(OTf)_3$



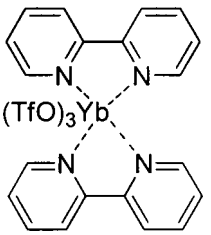
Product was isolated as a white solid by recrystallisation from DCM/pet ether 40/60. (ES^+) 691.97 (100% $[M-(OTf)]^+$).

Analytical data for 18-crown-6 complex of $Yb(OTf)_3$



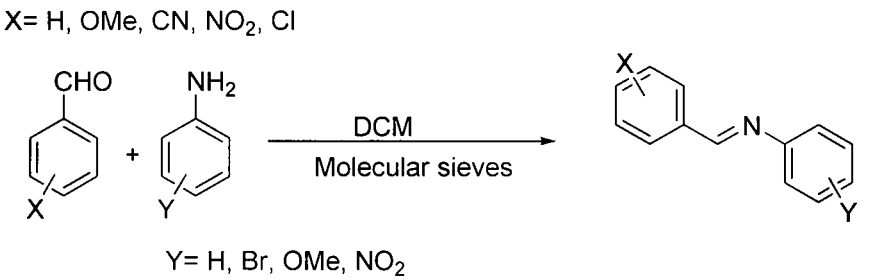
Product was isolated as a white solid by recrystallisation from DCM/pet ether 40/60. (ES^+) 735.98 (100% $[M-(OTf)]^+$)

Analytical data for $[Yb(OTf)_3(bipy)_2]$



Product was isolated as a white solid by recrystallisation from DCM/pet ether 40/60. m/z (ES^+) 783.98 (100% $[M-(OTf)]^+$)

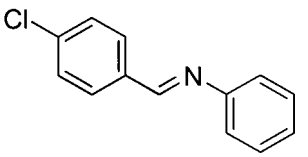
5.9 General procedure for imine synthesis[196]



Scheme 130

The aldehyde (10 mmol), aniline (10 mmol) and molecular sieves (10 g) were mixed in dry DCM (30 mL). Mixture was allowed to stir at rt and reaction was monitored by tlc. When reaction was completed, mixture was filtered through a pad of celite and residue was washed with dry DCM. Filtrate was collected and evaporated in *vacuo*. Imine was then dried under high vacuum and stored in a sealed container at rt.

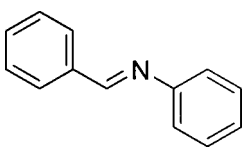
Analytical data for 4-chlorobenzaldehyde phenylimine



8

Product was isolated as a yellow solid. The data are consistent with the literature.[197] m.p. 62.8-63.3° C (lit. m.p. 63-64° C); δ_H (400 MHz; $CDCl_3$; TMS) 7.19-7.21(m, 2H aromatic), 7.23-7.25 (m, 1H aromatic), 7.37-7.39 (m, 2H aromatic), 7.45 (d, J 8.6 Hz, 2H aromatic), 7.84 (d, J 8.6 Hz, 2H aromatic), 8.42 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 159.2, 152.1, 137.8, 135.1, 130.3, 129.6, 129.5, 126.6, 121.2; m/z (C.I.) 216.1 (100% $[M+H]^+$); $C_{13}H_{11}ClN$ requires C 72.39%, H 4.67%, N 6.49%, found C 72.33%, H 4.65%, N 6.45%

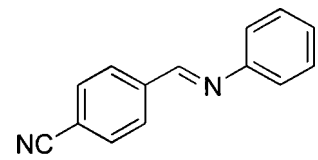
Analytical data for benzaldehyde phenylimine



10

Product was isolated as a very pale cream solid. The data are consistent with the literature.[197] m.p. 50.9-51.7° C (lit. m.p. 49-51° C); δ_H (400 MHz; $CDCl_3$; TMS) 7.20-7.24 (m, 3H aromatic), 7.37-7.40 (m, 2H aromatic), 7.46-7.88 (m, 3H aromatic), 7.89-7.92 (m, 2H aromatic), 8.45 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 160.9, 152.5, 136.6, 131.8, 129.6, 129.24, 129.21, 126.4, 121.3; m/z (CI+) 182.1 (100% $[M+H]^+$); $C_{13}H_{11}N$ requires C 86.15%, H 6.12%, N 7.73%, found C 86.67%, H 6.01%, N 7.32%

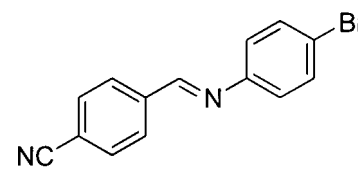
Analytical data for 4-cyanobenzaldehyde phenylimine



12

Product was isolated as a dark yellow solid. The data are consistent with the literature.[198] m.p. 94.0-94.8° C (lit. m.p. 93.5-94.5° C); δ_H (400 MHz; $CDCl_3$; TMS) 7.23-7.31 (m, 3H aromatic), 7.41-7.44 (m, 2H aromatic), 7.77 (d, J 8.4 Hz, 2H aromatic), 8.02 (d, J 8.4 Hz, 2H aromatic), 8.50 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 157.8, 151.0, 139.9, 132.5, 129.3, 129.1, 126.9, 120.9, 118.4, 114.4; m/z (C.I.) 207.1 (100% $[M+H]^+$); $C_{14}H_{10}N_2$ requires C 81.53%, H 4.89%, N 13.58%, found C 81.58%, H 4.88%, N 13.58%

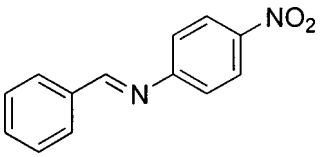
Analytical data for 4-cyanobenzaldehyde 4-bromophenylimine



13

Product was isolated as a yellow solid. The data are consistent with the literature.[199] m.p. 147.7-148.2° C (lit. m.p. 151-153° C); δ_H (400 MHz; $CDCl_3$; TMS) 7.12 (d, J 8.7 Hz, 2H aromatic), 7.54 (d, J 8.7 Hz, 2H aromatic), 7.77 (d, J 8.4 Hz, 2H aromatic), 8.0 (d, J 8.4 Hz, 2H aromatic), 8.48 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 158.2, 149.9, 139.6, 132.6, 132.4, 129.2, 122.6, 120.4, 118.3, 114.7 ; m/z (C.I.) 285.0 (100% $[M+H]^+$); $C_{14}H_9BrN_2$ requires C 58.97%, H 3.81%, N 9.82%, found C 58.90%, H 3.16%, N 9.79%

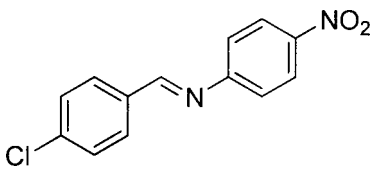
Analytical data for benzaldehyde 4-nitrophenyl imine



14

Product was isolated as a yellow solid. The data are consistent with the literature.[200] m.p. 139.9-141.0° C (lit. m.p. 138-140° C); δ_H (400 MHz; $CDCl_3$; TMS) 7.25 (d, J 8.9 Hz, 2H aromatic), 7.50-7.56 (m, 3H aromatic), 7.91-7.94 (m, 2H aromatic), 8.27 (d, J 8.9 Hz, 2H aromatic), 8.43 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 162.7, 157.9, 145.4, 135.3, 132.4, 129.3, 128.9, 125.0, 121.2; m/z (CI+) 272.1 (100% $[M+H]^+$); $C_{13}H_{10}N_2O_2$ requires C 69.02%, H 4.46%, N 12.38%, found C 68.91%, H 4.44%, N 12.41%

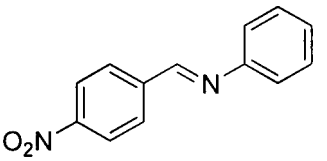
Analytical data for 4-chlorobenzaldehyde 4-nitrophenylimine



15

Product was isolated as a yellow solid. The data are consistent with the literature.[201] m.p. 164.5-165.7° C (lit. m.p. 168° C); δ_H (400 MHz; $CDCl_3$; TMS) 7.25 (d, J 9.0 Hz, 2H aromatic), 7.49 (d, J 8.5 Hz, 2H aromatic), 7.87 (d, J 8.5 Hz, 2H aromatic), 8.28 (d, J 9.0 Hz, 2H aromatic), 8.40 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 161.2, 157.5, 145.6, 138.5, 133.8, 130.4, 129.3, 125.1, 121.2; m/z (CI+) 261.0 (100% $[M+H]^+$); $C_{13}H_9ClN_2O_2$ requires C 59.9%, H 3.48%, N 10.75%, found C 59.74%, H 3.46%, N 10.82

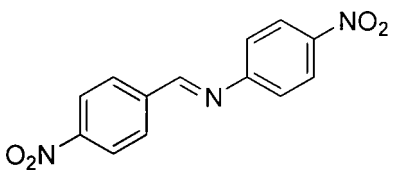
Analytical data for 4-nitrobenzaldehyde phenylimine



16

Product was isolated as a yellow solid. The data are consistent with the literature.[202,203] m.p. 117.1-117.3° C (lit. m.p. 117-118° C); δ_H (400 MHz; $CDCl_3$; TMS) 7.26-7.28 (m, 2H aromatic) 7.30-7.32 (m, 1H aromatic), 7.42-7.46 (m, 2H aromatic), 8.09 (d, J 8.8 Hz, 2H aromatic), 8.34 (d, J 8.8 Hz, 2H aromatic), 8.57 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 157.4, 150.9, 149.3, 141.6, 129.4, 129.3, 127.1, 124.0, 120.9 ; m/z (C.I.) 227.1 (100% $[M+H]^+$); $C_{13}H_{10}N_2O_2$ requires C 69.02%, H 4.46%, N 12.39%, found C 69.08%, H 4.45%, N 12.42%

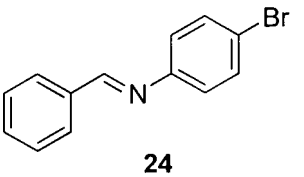
Analytical data for 4-nitrobenzaldehyde 4-nitrophenylimine



17

Product was isolated as a yellow solid. The data are consistent with the literature.[204] m.p. 197.4-199.0° C (lit. m.p. 191° C); δ_H (400 MHz; $CDCl_3$; TMS) 7.30 (d, J 9.0 Hz, 2H aromatic), 8.12 (d, J 8.8 Hz, 2H aromatic), 8.32 (d, J 9.0 Hz, 2H aromatic), 8.37 (d, J 8.8 Hz, 2H aromatic), 8.54 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 160.1, 156.6, 149.9, 146.1, 140.5, 129.9, 125.1, 124.1, 121.3; m/z (ES+) 272.1 (100% $[M+H]^+$); $C_{13}H_9N_3O_4$ requires C 57.57%, H 3.34%, N 15.49%, found C 57.53%, H 3.29%, N 15.53%

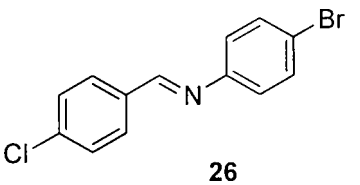
Analytical data for benzaldehyde 4-bromophenylimine



24

Product was isolated as a white/off white solid. The data are consistent with the literature.[200] m.p. 62.6-63.1° C (lit. m.p. 61-63° C); δ_H (400 MHz; $CDCl_3$; TMS) 7.09 (d, J 8.7 Hz, 2H aromatic), 7.48-7.52 (m, 5H aromatic), 7.88-7.91 (m, 2H aromatic), 8.43 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 161.2, 151.4, 136.3, 132.6, 132.1, 129.31, 129.26, 123.0, 119.7; m/z (CI+) 260.0 (100% $[M+H]^+$); $C_{13}H_{10}BrN$ requires C 60.02%, H 3.87%, N 5.38%, found C 60.29%, H 3.93%, N 5.34%

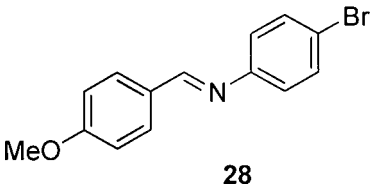
Analytical data for 4-chlorobenzaldehyde 4-bromophenylimine



26

Product was isolated as a very pale yellow solid. The data are consistent with the literature.[205] m.p. 118.3-119.1° C (lit. m.p. 117° C); δ_H (400 MHz; $CDCl_3$; TMS) 7.09 (d, J 8.7 Hz, 2H aromatic), 7.45 (d, J 8.5 Hz, 2H aromatic), 7.51 (d, J 8.7 Hz, 2H aromatic), 7.83 (d, J 8.5 Hz, 2H aromatic), 8.39 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 159.2, 150.6, 137.7, 134.4 132.2, 130.0, 129.1, 122.6. 119.6; m/z (CI+) 293.97 (100% $[M+H]^+$); $C_{13}H_9BrClN$ requires C 53.01%, H 3.08%, N 4.75%, found C 52.73%, H 3.03%, N 4.69%

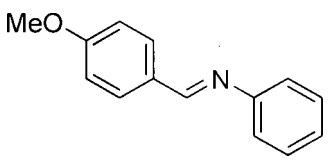
Analytical data for 4-methoxybenzaldehyde 4-bromophenylimine



28

Product was isolated as a very pale cream solid. The data are consistent with the literature.[206] m.p. 119.2-120.1° C (lit. m.p. 120° C); δ_H (400 MHz; $CDCl_3$; TMS) 3.89 (s, 3H, CH_3), 6.99 (d, J 8.7 Hz, 2H aromatic), 7.07 (d, J 8.6 Hz, 2H aromatic), 7.49 (d, J 8.6 Hz, 2H aromatic), 7.84 (d, J 8.7 Hz, 2H aromatic), 8.35 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 162.9, 160.5, 151.7, 132.5, 131.0, 129.4, 123.0, 119.3, 114.7, 55.9; m/z (CI+) 290.0 (100% $[M+H]^+$); $C_{14}H_{12}BrNO$ requires C 57.95%, H 4.17%, N 4.83%, found C 57.96%, H 4.15%, N 4.81%

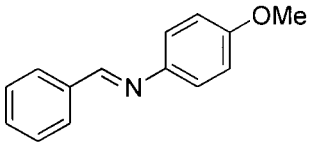
Analytical data for 4-methoxybenzaldehyde phenylimine



29

Product was isolated as a cream solid. The data are consistent with the literature.[197] m.p. 62.7-63.4° C (lit. m.p. 61-63° C); δ_H (400 MHz; $CDCl_3$; TMS) 3.87 (s, 3H, CH_3), 6.98 (d, J 8.7 Hz, 2H aromatic), 7.17-7.21 (m, 3H aromatic), 7.36-7.40 (m, 2H aromatic), 7.85 (d, J 8.7 Hz, 2H aromatic), 8.38 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 162.7, 160.1, 152.8, 130.9, 129.7, 129.5, 125.9, 121.3, 114.6, 55.8; m/z (CI+) 212.1 (100% $[M+H]^+$); $C_{14}H_{13}NO$ requires C 79.59%, H 6.20%, N 6.63%, found C 79.25%, H 6.21%, N 6.58%

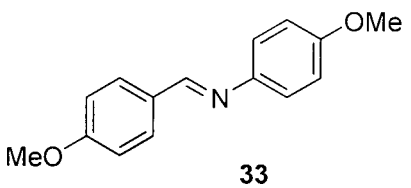
Analytical data for benzaldehyde 4-methoxyphenylimine



31

Product was isolated as an off white/pale grey solid. The data are consistent with the literature.[197] m.p. 68.5-69.7° C (lit. m.p. 69-70° C); δ_H (400 MHz; $CDCl_3$; TMS) 3.83 (s, 3H, CH_3), 6.94 (d, J 8.9 Hz, 2H aromatic), 7.24 (d, J 8.9 Hz, 2H aromatic), 7.45-7.47 (m, 3H aromatic), 7.88-7.90 (m, 2H aromatic), 8.48 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 158.3, 144.9, 136.4, 131.0, 128.7, 128.6, 122.2, 114.4, 55.5; m/z (CI+) 212.1 (100% $[M+H]^+$); $C_{14}H_{13}NO$ requires C 79.59%, H 6.20%, N 6.63%, found C 79.44%, H 6.25%, N 6.57%

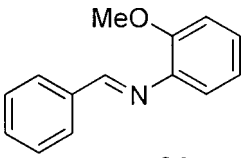
Analytical data for 4-methoxybenzaldehyde 4-methoxyphenylimine



33

Product was isolated as an off white/pale grey solid. The data are consistent with the literature.[207,208] m.p. 138.5-139.5° C (lit. not given); δ_H (400 MHz; $CDCl_3$; TMS) 3.81 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 6.92 (d, J 8.8 Hz, 2H aromatic), 6.96 (d, J 8.7 Hz, 2H aromatic), 7.20 (d, J 8.8 Hz, 2H aromatic), 7.8 (d, J 8.73 Hz, 2H aromatic), 8.39 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 161.9, 158.0, 157.9, 145.2, 130.2, 129.4, 122.0, 114.3, 114.1, 55.5, 55.4; m/z (CI+) 242.1 (100% $[M+H]^+$); $C_{15}H_{15}NO_2$ requires C 74.67%, H 6.27%, N 5.81%, found C 73.99%, H 6.62%, N 5.80%

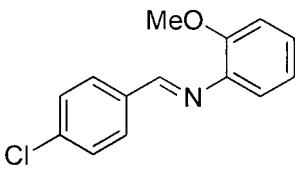
Analytical data for benzaldehyde 2-methoxyphenylimine



34

Product was isolated as a light brown solid. The data are consistent with the literature.[209] m.p. 61.8-62.5° C (lit. m.p. 62.5-64° C); δ_H (400 MHz; $CDCl_3$; TMS) 3.88 (s, 3H, CH_3), 6.70-6.81 (m, 2H aromatic), 6.94-7.02 (m, 1H aromatic), 7.16-7.21 (m, 1H aromatic), 7.45-7.47 (m, 3H aromatic), 7.91-7.94 (m, 2H aromatic), 8.45 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 161.3, 152.2, 141.9, 136.3, 131.3, 128.9, 128.7, 121.1, 120.3, 115.0, 55.9; m/z (C.I.) 212.1 (100% $[M+H]^+$); $C_{14}H_{13}NO$ requires C 79.59%, H 6.20%, N 6.63%, found C 79.60%, H 6.66%, N 8.11%

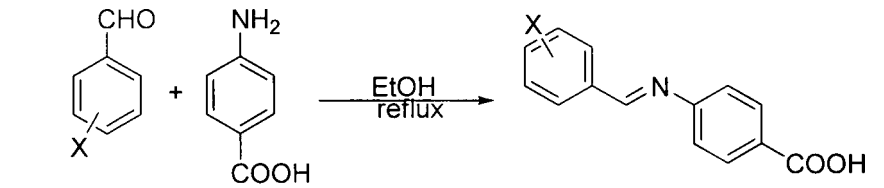
Analytical data for 4-chlorobenzaldehyde 2-methoxyphenylimine



36

Product was isolated as a yellow solid. m.p. 63.8-65.7° C; δ_H (400 MHz; $CDCl_3$; TMS) 3.88 (s, 3H, CH_3), 6.94-7.00 (m, 3H aromatic), 7.17-721 (m, 1H aromatic), 7.43 (d, J 8.5 Hz, 2H aromatic), 7.86 (d, J 8.5 Hz, 2H aromatic), 8.43 (s, 1H, CH); δ_C (100 MHz; $CDCl_3$) 159.8, 152.2, 141.5, 137.3, 134.9, 130.0, 129.0, 126.9, 121.0, 111.6, 55.9; m/z (C.I.) 246.1 (100% $[M+H]^+$); $C_{14}H_{12}ClNO$ requires C 68.44%, H 4.92%, N 5.70%, found C 68.39%, H 4.92%, N 5.70%; I.R. 738.6 cm^{-1} (C-Cl), 1168.65 cm^{-1} (C-O), 1241.9 cm^{-1} (C-N), 1490.7 cm^{-1} (C=C aromatic), 1650.99 cm^{-1} (C=N), 2979.5 cm^{-1} (C-H aromatic)

5.9.1 Procedure for imine synthesis starting with 4-aminobenzoic acid[210]

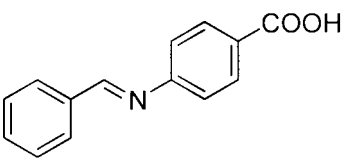


X= H, OMe, Cl

Scheme 131

The aldehyde (10 mmol) and 4-aminobenzoic acid (10 mmol) were mixed in dry ethanol (50 mL). Mixture was stirred under reflux and a soxhlet extraction thimble filled with dried molecular sieves was fitted on top of the flask. Reaction was left under reflux for about 4 hours. Ethanol was then removed under vacuum and imine was collected. It was then dried under high vacuum and stored in a sealed container at rt.

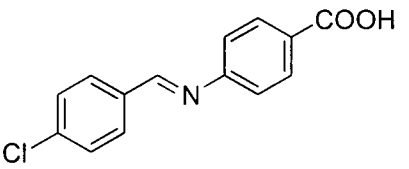
Analytical data for benzylidene-*p*-aminobenzoic acid



18

Product was isolated as a white solid. The data are consistent with the literature.[210] m.p. 184.7-184.9° C (lit. decomposition 185° C); δ_H (400 MHz; DMSO d^6; TMS) 7.34 (d, J 8.0 Hz, 2H aromatic), 7.55-7.65 (m, 3H aromatic), 7.97-7.99 (m, 2H aromatic), 8.0 (d, J 8.0 Hz, 2H aromatic), 8.65 (s, 1H, CH), 12.7 (br s, 1H, OH); δ_C (100 MHz; $CDCl_3$) 167.1, 162.4, 155.5, 135.7, 132.0, 131.3, 130.6, 129.0, 128.9, 121.0; m/z (CI+) 226.1 (100% $[M+H]^+$); $C_{14}H_{11}NO_2$ requires C 74.65%, H 4.92%, N 6.22%, found C 74.55%, H 4.84%, N 5.66%

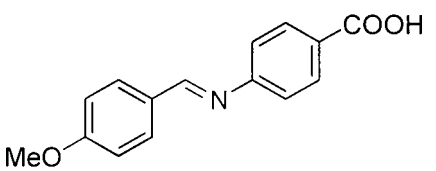
Analytical data for *p*-chlorobenzylidene-*p*-aminobenzoic acid



19

Product was isolated as a pale yellow solid. The data are consistent with the literature.[210] m.p. decomposition 263.0° C (lit. decomposition 269° C); δ_H (400 MHz; $CDCl_3$; TMS) 7.27 (d, J 8.4 Hz, 2H aromatic), 7.48 (d, J 8.4 Hz, 2H aromatic), 7.86 (d, J 8.4 Hz, 2H aromatic), 8.13 (d, J 8.4 Hz, 2H aromatic), 8.41 (s, 1H, CH), 12.9 (br s, 1H, OH); δ_C (100 MHz; $CDCl_3$) 167.1, 161.2, 155.0, 136.6, 134.6, 130.63, 130.56, 129.1, 128.9, 121.0 ; m/z (CI+) 261.0 (100% $[M+H]^+$); $C_{14}H_{10}ClNO_2$ requires C 64.75%, H 3.88%, N 5.39%, found C 64.33%, H 3.83%, N 5.42%

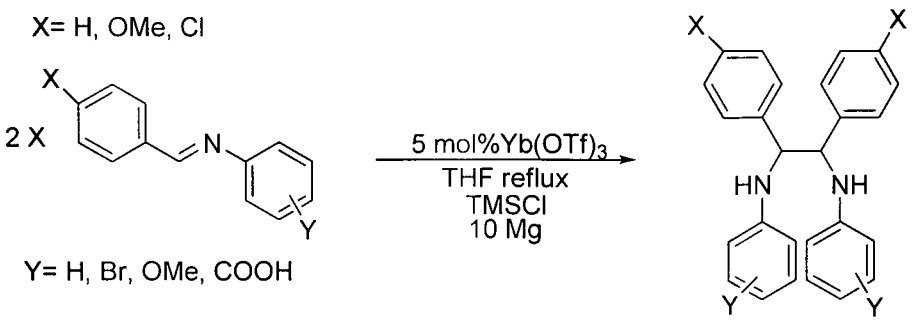
Analytical data for *p*-methoxybenzylidene-*p*-aminobenzoic acid



20

Product was isolated as an off white/pale yellow solid. The data are consistent with the literature.[211] m.p. 188.7-188.8° C (lit. m.p. 188-189° C); δ_H (400 MHz; DMSO d^6; TMS) 3.84 (s, 3H, CH_3), 7.08 (d, J 8.5 Hz, 2H aromatic), 7.28 (d, J 8.2 Hz, 2H aromatic), 7.91 (d, J 8.5 Hz, 2H aromatic), 7.96 (d, J 8.2 Hz, 2H aromatic), 8.55 (s, 1H, CH) 13.1 (br s, 1 H, OH); δ_C (100 MHz; DMSO d^6) 167.2, 162.3, 161.5, 155.7, 130.8, 130.6, 128.6, 127.8, 121.0, 114.4, 55.5 ; m/z (CI+) 256.1 (100% $[M+H]^+$); $C_{15}H_{13}NO_3$ requires C 70.58%, H 5.13%, N 5.49%, found C 69.93%, H 5.04%, N 5.24%

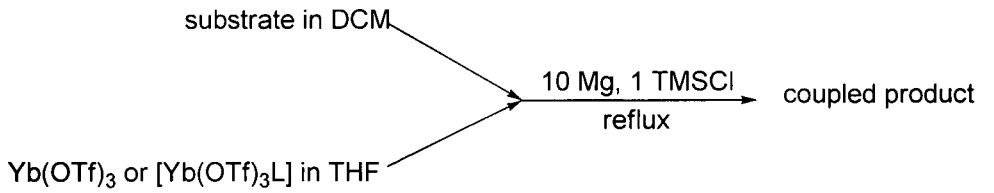
5.10 Procedure for homocoupling of imines using $Yb(OTf)_3$ and $Yb(OTf)_3$ complexes



Scheme 93

$Yb(OTf)_3$ or $Yb(OTf)_3$ complexes (5 mol%) and activated magnesium turnings (0.240 g, 10 mmol) and imine (1 mmol) were added to a Schlenk flask. The mixture was stirred under an inert atmosphere before addition of dry distilled THF. Chlorotrimethyl silane (0.2 mL, 1 mmol) was then added and the mixture was heated under reflux. Reaction was monitored by tlc and was quenched with saturated brine solution (20 mL). The crude product was extracted with ethyl acetate (3 X 20 mL). The combined ethyl acetate extracts were dried over magnesium sulfate. Crude diamine was purified by flash chromatography using hexane and diethyl ether over silica gel.

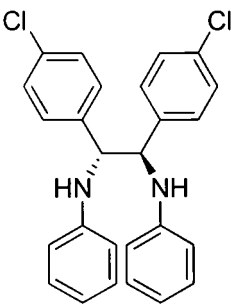
5.11 Procedure for reductive homocoupling using $Yb(OTf)_3$ and $Yb(OTf)_3$ complexes in mixed solvents



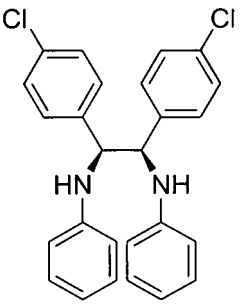
Scheme 132

$Yb(OTf)_3$ or $[Yb(OTf)_3L]$ (5 mol%) and activated magnesium turnings (0.240g, 10 mmol) were added to a Schlenk flask. The mixture was stirred under an inert atmosphere (argon or nitrogen) before addition of 2 mL of dry THF. A solution of the substrate (1 mmol) in dry DCM (8 mL) was then added with constant stirring. Chlorotrimethyl silane (0.2 mL, 1 mmol) was then added and mixture was heated under reflux. Reaction was monitored by tlc and was quenched with saturated brine solution (20 mL)(1M HCl (10 mL) was also added when diols were formed). The crude product was extracted with ethyl acetate (3 x 20 mL), which were combined and dried over magnesium sulfate. Product was purified by flash chromatography using hexane and diethyl ether.

Analytical data for *N,N'*-diphenyl-1,2-*bis*(4-chlorophenyl)-1,2-ethanediamine



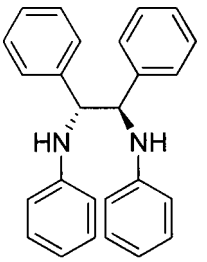
9a



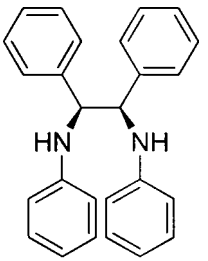
9b

Both isomers were isolated as white solids by flash chromatography on silica gel with a solvent system consisting of 97:3 hexane: diethyl ether with a R_f of 0.1. The data are consistent with the literature.[161,212] *d/l* isomer m.p. 139.1-139.3° C (lit. m.p. 137.0° C); δ_H (400 MHz; $CDCl_3$; TMS) 4.47 (br s, NH), 4.39 (s, 2H, CH) 6.42 (d, J 8.6 Hz, 4 H aromatic), 6.63 (t, J 7.4 Hz, 2H aromatic), 6.96 (d, J 8.5 Hz, 4H aromatic), 7.01 (dd, J 8.6 Hz, J 7.4, 4H aromatic), 7.11 (d, J 8.5 Hz, 4H aromatic); δ_C (100 MHz; $CDCl_3$) 146.5, 138.2, 133.4, 129.2, 128.7, 128.7, 118.6, 114.1, 63.4; *meso* isomer m.p. 195.3-195.4° C (lit. m.p. 198-199° C); δ_H (400 MHz; $CDCl_3$; TMS) 4.45 (s, NH), 4.92 (s, 2H, CH), 6.49 (d, J 8.6 Hz, 4H aromatic), 6.69 (t, J 7.4 Hz, 2H aromatic), 6.89 (d, J 8.5 Hz, 4H aromatic), 7.09 (dd, J 8.6 Hz, J 7.4 Hz, 4H aromatic), 7.21 (d, J 8.5 Hz, 4H aromatic); δ_C (100 MHz; $CDCl_3$) 145.9, 136.5, 133.6, 129.3, 128.8, 128.6, 118.3, 113.8, 61.3; m/z (ES^+) 433.12 (100% $[M+H]^+$); $C_{26}H_{22}N_2Cl_2$ requires C 72.06%, H 5.12%, N 6.64% found C 71.85%, H 5.18%, N 6.49%

Analytical data for *N,N'*-diphenyl-1,2-diphenyl-1,2-ethanediamine



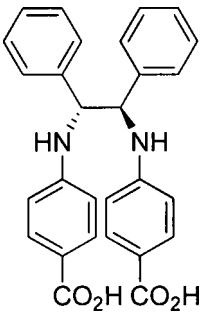
11a



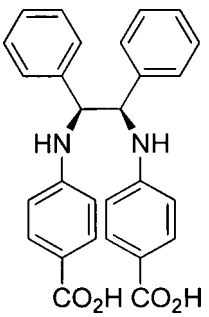
11b

Both isomers were isolated as white solids by flash chromatography on silica gel with a solvent system consisting of 97:3 hexane: diethyl ether with a R_f of 0.14. The data are consistent with the literature.[155,161,212] *d/l* isomer m.p. 150.5-150.7° C (lit. m.p. 151-152° C); δ_H (400 MHz; $CDCl_3$; TMS) 4.31 (s, 2H, NH), 4.55 (s, 2H, CH) 6.49-6.53 (m, 4 H aromatic), 6.66 (t, J 7.4, 2H aromatic), 7.04-7.09 (m, 4H aromatic), 7.11-7.14 (m, 6H aromatic), 7.17-7.19 (m, 4H aromatic); δ_C (100 MHz; $CDCl_3$) 147.0, 139.9, 129.1, 128.4, 127.5, 127.3, 118.1, 114.1, 64.0; *meso* isomer m.p. 170.4-170.5° C (lit. m.p. 169-170° C); δ_H (400 MHz; $CDCl_3$; TMS) 4.56 (s, 2H, NH), 4.96 (s, 2H, CH), 6.52 (d, J 7.56, 4H aromatic), 6.65 (t, J 7.3, 2H aromatic), 6.94-6.96 (m, 4H aromatic), 7.06-7.10 (m, 6H aromatic), 7.20-7.22 (m, 4H aromatic) δ_C (100 MHz; $CDCl_3$) 146.5, 138.2, 129.2, 128.2, 127.55, 127.51, 117.8, 113.7, 61.9; m/z (CI+) 365.20 (100% $[M+H]^+$); $C_{26}H_{24}N$ requires C 85.68%, H 6.64%, N 6.58%, found C 84.96%, H 7.05%, N 6.58%

Analytical data for *N,N'*-diphenyl-1,2-*bis*-phenyl-1,2-ethanediamine



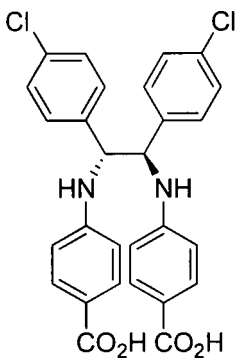
21a



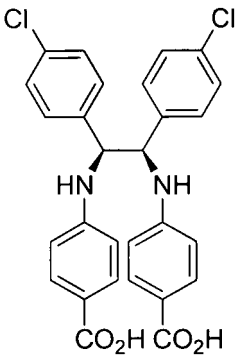
21b

Product was isolated as a very dark red solid by recrystallisation from diethyl ether. *d/l* isomer δ_H (400 MHz; CD_3CN; TMS) 5.62 (s, 2H, CH), 6.1 (br s, 2H, NH), 6.63 (d, J 8.8 Hz, 4H aromatic), 7.15-7.29 (m, 6H aromatic), 7.63-7.67 (m, 4H aromatic), 7.73 (d, J 8.8 Hz, 4H aromatic), 11.01 (br s, 2H, OH); δ_C (100 MHz; CD_3CN) 168.0, 152.1, 140.3, 132.1, 129.2, 128.5, 128.2, 117.9, 113.1, 63.5; *meso* isomer δ_H (400 MHz; CD_3CN; TMS) 4.97 (s, 2H, CH), 5.9 (br s, 2H, NH) 6.63 (d, J 8.8 Hz, 4H aromatic), 7.15-7.29 (m, 6H aromatic), 7.63-7.67 (m, 4H aromatic), 7.73 (d, J 8.8 Hz, 4H aromatic), 11.01 (br s, 2H, OH); δ_C (100 MHz; CD_3CN) 168.0, 152.1, 140.3, 132.5, 129.2, 128.5, 128.2, 117.9, 113.1, 62.0 m/z (ES+) 475.2 (100% $[M+Na]^+$); I.R. 1521.6 cm^{-1} (C=C aromatic), 1735.7 cm^{-1}(C=O), 2978.6 cm^{-1} (C-H aromatic), 3369.0 cm^{-1} (O-H) 3667.9 cm^{-1} (N-H).

Analytical data for *N,N'*-diphenyl-1,2-*bis*(4-chlorophenyl)1,2-ethanediamine



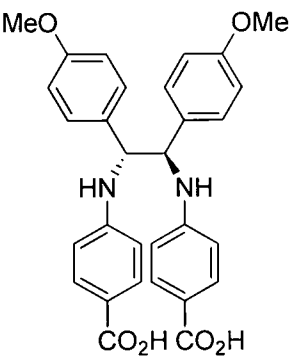
22a



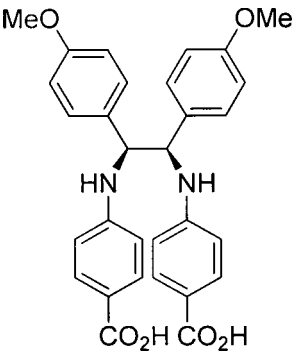
22b

Product was isolated as a dark red solid by recrystallisation from diethyl ether. *d/l* isomer δ_H (400 MHz; DMSO d^6; TMS) 4.82 (s, 2H, CH), 5.28 (br s, 2H, NH), 6.47 (d, J 8.4 Hz, 4H aromatic), 7.33 (d, J 8.32, 4H aromatic), 7.53 (d, J 8.3, 4H aromatic), 7.55 (d, J 8.4 Hz, 4H aromatic), 11.9 (br s, 2H, OH); δ_C (100 MHz; DMSO d^6) 167.3, 150.9, 140.2, 131.7, 130.9, 129.6, 128.0, 119.1, 111.7 68.8; *meso* isomer δ_H (400 MHz; DMSO d^6; TMS) 4.77 (s, 2H, CH), 5.85 (br s, 2H, NH), 6.47 (d, J 8.4 Hz, 4H aromatic), 7.33 (d, J 8.3, 4H aromatic), 7.53 (d, J 8.3, 4H aromatic), 7.55 (d, J 8.4 Hz, 4H aromatic), 11.9 (br s, 2H, OH); δ_C (100 MHz; DMSO d^6) 167.3, 150.9, 140.2, 131.7, 130.9, 129.6, 128.0, 119.1, 111.7, 64.9; m/z (ES+) 543.1 (100% $[M+Na]^+$); I.R. 734.7 cm^{-1} (C-Cl), 1737.6 cm^{-1} (C=O), 1498.4 cm^{-1} (C=C aromatic), 2970.5 cm^{-1} (C-H aromatic), 3359.4 cm^{-1} (O-H), 3666.0 cm^{-1} (N-H)

Analytical data for *N,N'*-diphenyl-1,2-*bis*(4-methoxyphenyl)-1,2-ethanediamine



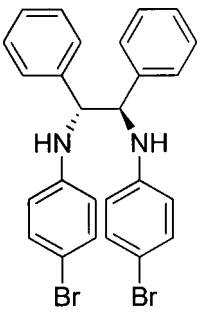
23a



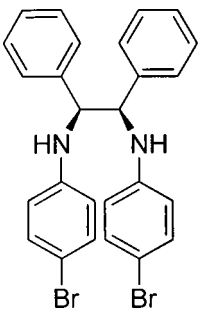
23b

Product was isolated as a bright terracota solid by recrystallisation with diethyl ether. *d/l* isomer δ_H (400 MHz; MeOD d^4; TMS) 3.58 (s, 6H, CH_3), 4.74 (s, 2H, CH), 4. 78 (br s, 2H, NH), 6.40 (d, J 8.8 Hz, 4 H aromatic), 6.71 (d, J 8.7 Hz, 4H aromatic), 7.04 (d, J 8.7 Hz, 4H aromatic), 7.55 (d, J 8.8 Hz, 4H aromatic), 11.6 (br s, 2H, OH) ; δ_C (100 MHz; MeOD d^4) 170.6, 160.5, 153.0, 138.2, 131.4, 129.9, 120.2, 114.3, 113.3, 63.8, 55.7; *meso* isomer δ_H (400 MHz; MeOD d^4; TMS) 3.56 (s, 6H, CH_3), 4.50 (s, 2H, CH), 4.78 (br s, 2H, NH), 6.43 (d, J 8.8 Hz, 4 H aromatic), 6.59 (d, J 8.7 Hz, 4 H aromatic), 6.90 (d, J 8.7 Hz, 4 H aromatic), 7.56 (d, J 8.8 Hz, 4H aromatic), 11.6 (br s, 2H, OH) ; δ_C (100 MHz; MeOD d^4) 170.6, 160.5, 153.0, 138.2, 131.4, 129.9, 120.2, 114.3, 113.3, 62.0, 55.6; m/z (ES+) 535.2 (100% $[M+Na]^+$); I.R. 1165.0 cm^{-1} (C-O), 1400.1 cm^{-1} (C=C aromatic), 2902.5 cm^{-1} (C-H aromatic), 3369.0 cm^{-1} (O-H), 3671.8 cm^{-1} (N-H)

Analytical data for *N,N'*-bis-(4-bromophenyl)- 1,2-diphenyl-1,2-ethanediamine



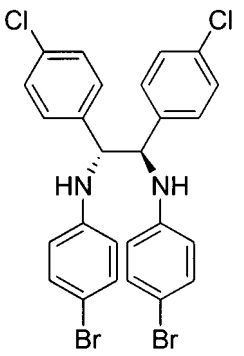
25a



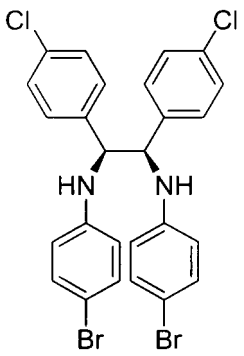
25b

Both isomers were isolated as very pale cream/yellow solids by flash chromatography on silica gel with a solvent system consisting of 97:3 hexane: diethyl ether with a R_f of 0.11. The data are consistent with the literature.[213] *d/l* isomer m.p. 133.4-133.6° C (lit. m.p. 131-132° C); δ_H (400 MHz; $CDCl_3$; TMS) 4.51 (s, 2H, CH), 4.60 (br s, 2H, NH), 6.37 (d, J 8.9 Hz, 4H aromatic), 7.08-7.11 (m, 6H aromatic), 7.13 (d, J 8.9 Hz, 4H aromatic), 7.21-7.24 (m, 4H aromatic); δ_C (100 MHz; $CDCl_3$) 145.8, 139.1, 131.8, 128.6, 127.8, 127.2, 115.7, 110.0, 63.8; *meso* isomer m.p. 210.7-210.8° C (lit. m.p. 210.5-211.5° C); δ_H (400 MHz; $CDCl_3$; TMS) 4.89 (s, 2H, CH), 4.57 (br s, 2H, NH), 6.39 (d, J 8.9 Hz, 4H aromatic), 6.89-6.91(m, 6H aromatic), 7.15 (d, J 8.9 Hz, 4H aromatic), 7.22-7.25 (m, 4H aromatic); δ_C (100 MHz; $CDCl_3$) 145.3, 137.4, 131.9, 128.4, 127.9, 127.4, 115.4, 109.7, 61.9; m/z (ES^-) 521.0 (100% $[M-H]^-$); $C_{26}H_{22}N_2Br_2$ requires C 59.79%, H 4.25%, N 5.36%, found C 60.01%, H 4.26%

Analytical data for *N,N'-bis*(4-bromophenyl)-1,2-*bis*(4-chlorophenyl)-1,2-ethanediamine



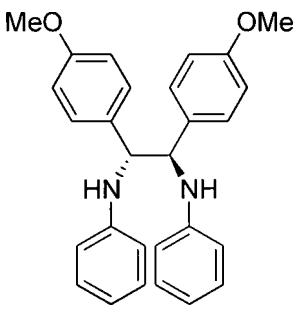
27a



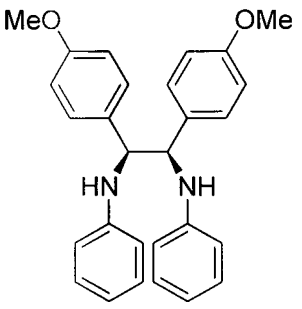
27b

Both isomers were isolated as very pale cream/off white solids by flash chromatography on silica gel with a solvent system consisting of 97:3 hexane: diethyl ether with a R_f of 0.1. *d/l* isomer m.p. 125.8-126.0° C; δ_H (400 MHz; $CDCl_3$; TMS) 4.52 (s, 2H, CH), 4.42 (br s, 2H, NH), 6.53 (d, J 8.9 Hz, 4H aromatic), 6.99 (d, J 8.5 Hz, 4H aromatic), 7.16 (d, J 8.9 Hz, 4H aromatic), 7.20 (d, J 8.5 Hz, 4H aromatic); δ_C (100 MHz; $CDCl_3$) 145.3, 133.8, 132.0, 128.9, 128.6, 127.2, 115.8, 110.5, 63.3; *meso* isomer m.p. 197.0-197.1° C; δ_H (400 MHz; $CDCl_3$; TMS) 4.86 (s, 2H, CH), 4.44 (br s, 2H NH), 6.36 (d, J 8.7 Hz, 4H aromatic), 6.85 (d, J 8.4 Hz, 4H aromatic), 7.17 (d, J 8.7 Hz, 4H aromatic), 7.23 (d, J 8.4 Hz, 4H aromatic): δ_C (100 MHz; $CDCl_3$) 144.8, 135.6, 133.9, 132.0, 128.8, 128.7, 115.4, 110.2, 61.2; m/z (ES^-) 588.9 (100% $[M-H]^-$); $C_{26}H_{20}N_2Br_2Cl_2$ requires C 52.82%, H 3.41%, N 4.74%, found C 52.29%, H 3.49%, N 4.44%; I.R. 650.0 cm^{-1} (C-Br), 811.9 cm^{-1} (C-Cl), 1486.9 cm^{-1} (C=C aromatic), 2910.3 cm^{-1} (C-H aromatic), 3361.4 cm^{-1} (O-H), 3666.0 cm^{-1} (N-H)

Analytical data for *N,N'*-diphenyl-1,2-*bis*(4-methoxyphenyl)-1,2-ethanediamine



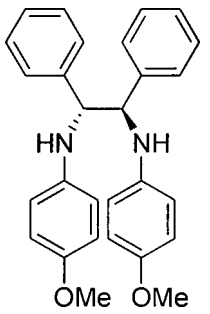
30a



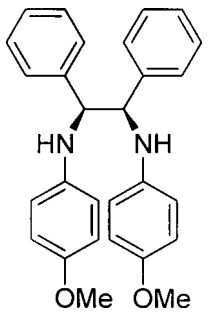
30b

Both isomers were isolated as pale pink solids by flash chromatography on silica gel with a solvent system consisting of 92:8 hexane: diethyl ether with a R_f of 0.2. The data are consistent with the literature.[214] *d/l* isomer m.p. 143.7-144.5° C (lit. m.p. 143-144° C); δ_H (400 MHz; $CDCl_3$; TMS) 3.76 (s, 6H, CH_3), 4.48 (s, 2H, CH), 4.45 (br s, 2H, NH), 6.63-6.67 (m, 4H aromatic), 6.73-6.76 (m, 2H aromatic), 6.87 (d, J 8.7 Hz, 4H aromatic), 7.02 (d, J 8.7 Hz, 4H aromatic), 7.04-7.09 (m, 4H aromatic); δ_C (100 MHz; $CDCl_3$) 158.8, 147.1, 131.8, 129.1, 128.4, 117.9, 114.0, 113.7, 63.2, 55.1; *meso* isomer m.p. 186.1-186.4° C (lit. m.p. 186-188° C); δ_H (400 MHz; $CDCl_3$; TMS) 3.74 (s, 6H, CH_3), 4.90 (s, 2H, CH), 4.46 (br s, 2H, NH), 6.63-6.67 (m, 4 H aromatic), 6.73-6.76 (m, 2H aromatic),), 6.87 (d, J 8.7 Hz, 4H aromatic), 7.02 (d, J 8.7 Hz, 4H aromatic), 7.04-7.09 (m, 4H aromatic); δ_C (100 MHz; $CDCl_3$) 158.9, 146.6, 130.1, 129.2, 128.6, 117.6, 113.7, 113.6, 61.4, 55.1; m/z (ES^+) 425.2 (100% $[M+H]^+$); $C_{28}H_{28}N_2O_2$ requires C 79.22%, H 6.65%, N 6.60%, found C 79.17%, H 6.68%, N 6.57%

Analytical data for *N,N'*-bis-(4-methoxyphenyl)-1,2-diphenyl-1,2-ethanediamine



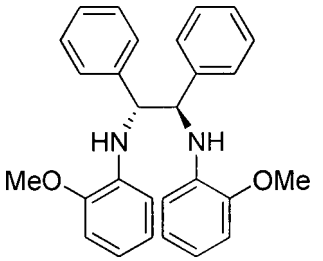
32a



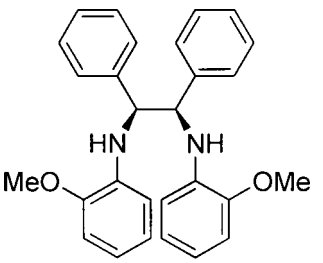
32b

Both isomers were isolated as off-white solids by flash chromatography on silica gel with a solvent system consisting of 92:8 hexane: diethyl ether with a R_f of 0.2. The data are consistent with the literature.[213,215] *d/l* isomer m.p. 137.2-137.4° C (lit. m.p. 137.5-139° C); δ_H (400 MHz; $CDCl_3$; TMS) 3.64 (s, 6H, CH_3), 4.42 (br s, 2H, NH), 4.31 (s, 2H, CH), 6.40 (d, J 7.5 Hz, 4H aromatic), 6.69 (d, J 7.5 Hz, 4H aromatic), 7.08-7.19 (m, 10H aromatic); δ_C (100 MHz; $CDCl_3$) 151.9, 142.5, 138.6, 128.7, 127.9, 127.3, 115.1, 114.7, 63.8, 55.7; *meso* isomer m.p. 196.5-196.7° C (lit. m.p. 199° C); δ_H (400 MHz; $CDCl_3$; TMS) 3.65 (s, 6H, CH_3), 4.20 (br s, 2H, NH), 4.80 (s, 2H, CH), 6.45 (d, J 7.5 Hz, 4 H aromatic), 6.65 (d, J 7.5 Hz, 4 H aromatic), 7.09-7.20 (m, 10 H aromatic); δ_C (100 MHz; $CDCl_3$) 152.2, 142.3, 138.9, 128.5, 127.6, 127.3, 115.0, 114.7, 62.3, 55.4; m/z (ES+) 447.2 (100% $[M+Na]^+$); $C_{28}H_{28}N_2O_2$ requires C 79.22%, H 6.65%, N 6.60%, found C 79.49%, H 6.63%, N 6.69%

Analytical data for *N,N'-bis*(2-methoxyphenyl)-1,2-diphenyl-1,2-ethanediamine



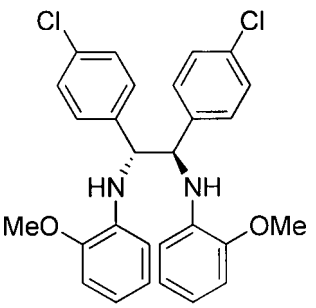
35a



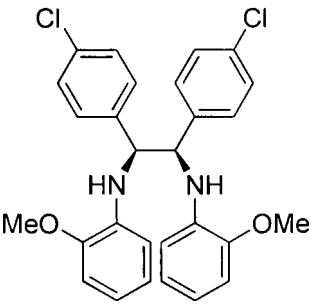
35b

Both isomers were isolated as dark yellow solids by flash chromatography on silica gel with a solvent system consisting of 95:5 hexane: diethyl ether with a R_f of 0.14. The data are consistent with the literature.[209] *d/l* isomer m.p. 136.1-136.3° C (lit. m.p. 135-138° C); δ_H (400 MHz; $CDCl_3$; TMS) 3.82 (s, 6H, CH_3), 4.58 (s, 2H, CH), 5.24 (br s, 2H, NH), 6.30-6.34 (m, 2H aromatic), 6.57-6.68 (m, 2H aromatic), 6.72-6.75 (m, 2H aromatic), 6.96-6.98 (m, 2H aromatic), 7.11-7.14 (m, 6H aromatic), 7.17-7.21 (m, 2H aromatic); δ_C (100 MHz; $CDCl_3$) 147.0, 140.3, 137.2, 128.2, 127.54, 127.3, 121.0, 116.9, 111.5, 109.6, 64.0, 55.6; *meso* isomer m.p. 195.2-195.4° C (lit. m.p. 198-201° C); δ_H (400 MHz; $CDCl_3$; TMS) 3.83 (s, 6H, CH_3), 4.97 (s, 2H, CH), 4.75 (br s, 2H, NH), 6.30-6.34 (m, 2H aromatic), 6.57-6.68 (m, 2H aromatic), 6.72-6.75 (m, 2H aromatic), 6.96-6.98 (m, 2H aromatic), 7.11-7.14 (m, 6H aromatic), 7.17-7.21 (m, 2H aromatic) ;δ_C (100 MHz; $CDCl_3$) 146.5, 138.7, 136.7, 128.1, 127.50, 127.4, 121.1, 116.6, 111.4, 109.5, 62.2, 55.5; m/z (ES^+) 447.2 (100% $[M+Na]^+$); $C_{28}H_{28}N_2O_2$ requires C 79.22%, H 6.65%, N 6.60%, found C 79.91%, H 6.58%, N 6.67%

Analytical data for *N,N'-bis*-(2-methoxyphenyl)-1,2-*bis*(4-chlorophenyl)-1,2-ethanediamine



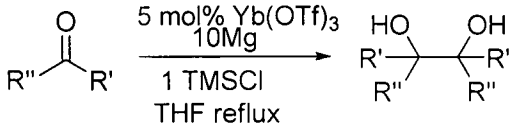
37a



37b

Both isomers were isolated as off white solid by flash chromatography on silica gel with a solvent system consisting of 95:5 hexane: diethyl ether with a R_f of 0.13. *d/l* isomer m.p. 134.7-135.2° C; δ_H (400 MHz; $CDCl_3$; TMS) 3.83 (s, 6H, CH_3), 4.92 (s, 2H, CH), 4.51 (br s, 2H, NH), 6.25-6.28 (m, 2 H aromatic), 6.64-6.67 (m, 4H aromatic), 6.74-6.76 (m, 2H aromatic) 7.03 (d, J 8.4 Hz, 4H aromatic), 7.17 (d, J 8.4 Hz, 4H aromatic); δ_C (100 MHz; $CDCl_3$) 147.2, 138.6, 136.6, 133.2, 128.8, 128.5, 121.0, 117.4, 111.5, 109.8, 63.4, 55.5; *meso* isomer m.p. 190.1-190.2° C; δ_H (400 MHz; $CDCl_3$; TMS) 3.84 (s, 6H, CH_3), 5.11 (s, 2H, CH), 5.19 (br s, 2H, NH), 6.64-6.67 (m, 4H aromatic), 6.75-6.77 (m, 2H aromatic), 6.90 (d, J 8.4 Hz, 4H aromatic), 7.20 (d, J 8.4 Hz, 4H aromatic); δ_C (100 MHz; $CDCl_3$) 147.0, 137.0, 136.1, 133.3, 128.9, 128.5, 121.0, 117.2, 111.4, 109.5, 61.6, 55.5; m/z (ES^+) 493.1 (100% $[M+H]^+$); $C_{28}H_{26}N_2O_2Cl_2$ requires C 68.16%, H 5.31%, N 5.68%, found C 67.94%, H 5.29%, N 5.64%; I.R. 734.7 cm^{-1} (C-Cl), 1174.4 cm^{-1} (C-O) 1498.4 cm^{-1} (C=C aromatic), 2979.5 cm^{-1} (C-H aromatic), 3388.3 cm^{-1} (N-H)

5.12 Procedure for homocoupling of aldehydes and ketones using $Yb(OTf)_3$ and $Yb(OTf)_3$ complexes

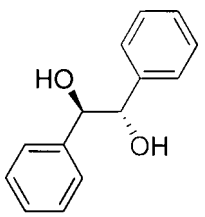


R'= H or aromatic or aliphatic
R''= Aromatic or aliphatic

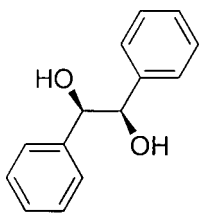
Scheme 133

$Yb(OTf)_3$ or $Yb(OTf)_3$ complexes (5 mol%) and activated magnesium powder (0.240g, 10 mmol) were added to a Schlenk flask. The mixture was stirred under an inert atmosphere (argon or nitrogen) before addition of dry distilled THF (8 mL). Aldehyde or ketone (1 mmol) was then added with constant stirring. Chlorotrimethyl silane (0.2 mL, 1 mmol) was then added and mixture was heated under reflux. Reaction was monitored by tlc and was quenched with saturated brine solution (20 mL) and 1M HCl (10 mL). The crude product was separated with ethyl acetate (3 X 30 mL). The combined ethyl acetate extracts were dried over magnesium sulfate. Crude diol was purified by flash chromatography using hexane and diethyl ether.

Analytical data for 1,2-diphenylethane-1,2-diol



38a

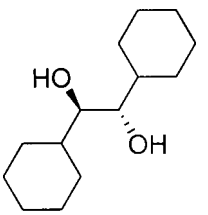


38b

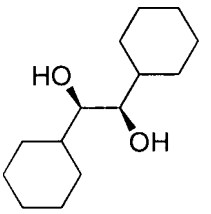
Both isomers were isolated as white solids by flash chromatography on silica gel with a solvent system starting with hexane then to 50:50 hexane: diethyl ether with a R_f of 0.2. The data are consistent with the literature.[216,217] *d/l* isomer m.p. 115.1-115.2° C (lit. m.p. 120-121° C); δ_H (400 MHz; $CDCl_3$; TMS) 2.90 (br s, 2H, OH), 4.60 (s, 2H, CH), 6.94-7.52 (m, 10 H aromatic); δ_C (100 MHz; $CDCl_3$) 139.9, 128.2, 128.1, 127.1, 78.1; *meso* isomer m.p. 134.7-134.8° C (lit. m.p. 135° C); δ_H (400 MHz; $CDCl_3$; TMS) 2.31(br s, 2H, OH),

4.73 (s, 2H, CH), 6.94-7.52 (m, 10 H aromatic); δ_C (100 MHz; $CDCl_3$) 139.8, 128.1, 127.9, 126.9, 79.1; m/z (CI+) 232.13 (100% $[M+NH_4]^+$); $C_{14}H_{14}O_2$ requires C 78.48%, H 6.59%, found C 78.80%, H 6.57%

Analytical data for 1,2-dicyclohexyl-ethane-1,2-diol



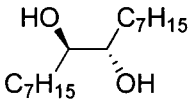
39a



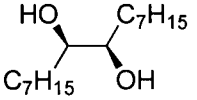
39b

Both isomers were isolated as white solids by flash chromatography on silica gel with a solvent system starting with hexane then to 50:50 hexane: diethyl ether with a R_f of 0.2. The data are consistent with the literature.[218,219] *d/l* isomer m.p. 134.7-134.8° C (lit. m.p. 136-137° C); δ_H (400 MHz; $CDCl_3$; TMS) 1.0-1.3 (m, 10 H), 1.5-1.9 (m, 14H), 2.17 (br s, 2H, OH), 3.35 (d, J 5.8, 2H, CH); δ_C (100 MHz; $CDCl_3$) 75.1, 40.4, 29.6, 28.2, 26.4, 26.2, 26.0; *meso* isomer m.p. 125.6-125.7° C; δ_H (400 MHz; $CDCl_3$; TMS) 1.0-1.3 (m, 10 H), 1.5-1.9 (m, 14H), 2.15 (br s, 2H, OH), 3.50 (d, J 6.6, 2H, CH); δ_C (100 MHz; $CDCl_3$) 75.1, 40.4, 29.6, 28.2, 26.4, 26.2, 26.0; m/z (CI+) 244.2 (100% $[M+NH_4]^+$); $C_{14}H_{26}O_2$ requires C 74.29%, H 11.58%, found C 74.53%, H 11.07%

Analytical data for hexadecane-8,9-diol



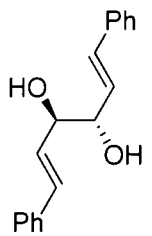
40a



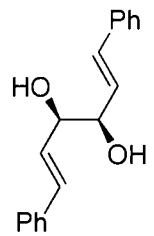
40b

Both isomers were isolated as white solids by flash chromatography on silica gel with a solvent system starting with hexane then to 50:50 hexane: diethyl ether with a R_f of 0.2. The data are consistent with the literature.[220] *d/l* isomer m.p. 121.5-121.6° C (lit. m.p. 132° C) δ_H (400 MHz; $CDCl_3$; TMS) 0.88 (t, J 6.8 Hz, 6H), 1.60-1.68 (m, 4 H), 1.26-1.34 (m, 20H), 2.19-2.29 (m, 2H, CH), 3.3 (br s, 2H, OH); δ_C (100 MHz; $CDCl_3$) 74.6, 31.6, 30.3, 29.1, 28.9, 24.7, 22.5, 14.0; *meso* isomer m.p. 73.3-73.5° C (lit. m.p. 70.5° C); δ_H (400 MHz; $CDCl_3$; TMS) 0.88 (t, J 6.8 Hz, 6H), 1.61-1.68 (m, 4 H), 1.26-1.34 (m, 20H), 2.19-2.29 (m, 2H, CH), 3.6 (br s, 2H, OH); δ_C (100 MHz; $CDCl_3$) 72.4, 31.6, 30.3, 29.0, 28.9, 24.7, 22.6, 14.0; m/z (CI+) 276.3 (100% $[M+NH_4]^+$); $C_{16}H_{34}O_2$ requires C 74.36%, H 13.26%, found C 74.16%, H 13.0%

Analytical data for 1,6-diphenyl-1,5 hexadiene-3,4-diol



41a

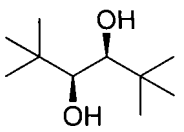


41b

Both isomers were isolated as white solids by flash chromatography on silica gel with a solvent system starting with hexane then to 50:50 hexane: diethyl ether with a R_f of 0.2. The data are consistent with the literature.[212] m.p. 122.8-122.9° C; *d/l* isomer δ_H (400 MHz; $CDCl_3$; TMS) 2.31 (br s, 2H, OH), 4.23 (d, J 5.6 Hz, 2H, CH), 6.25 (dd, J 5.6 Hz, 15.1 Hz, 2H, CH), 6.73 (d, J 15.1 Hz, 2H, CH), 7.20-7.41 (m, 10H aromatic); δ_C (100 MHz; $CDCl_3$) 135.7, 134.0, 130.7, 128.9, 128.6, 128.3, 75.7; *meso* isomer m.p. 126.2-126.3° C; δ_H (400 MHz; $CDCl_3$; TMS) 2.25 (br s, 2H, OH), 4.41 (d, J 5.9 Hz, 2H, CH),

6.29 (dd, J 5.9 Hz, 15 Hz, 2H, CH), 6.89 (d, J 15.1 Hz, 2H, CH), 7.15-7.35 (m, 10H aromatic); δ_C (100 MHz; $CDCl_3$) 135.7, 134.0, 130.7, 128.9, 128.6, 128.3, 71.3; m/z (CI+) 266.2 (100% $[(M+NH_4)-H_2O]^+$); $C_{18}H_{18}O_2$ requires C 81.17%, H 6.81%, found C 81.07%, H 6.73%

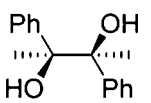
Analytical data for 2,2,5,5-tetramethyl-hexane-3,4-diol



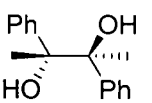
42

Product was isolated as a white solid by flash chromatography on silica gel with a solvent system starting with hexane then to 60:40 hexane: diethyl ether with a R_f of 0.2. The data are consistent with the literature.[216,221] m.p. 121.2-121.4° C (lit. m.p. 120° C) δ_H (400 MHz; $CDCl_3$; TMS) *d/l* 0.92 (s, 18H), 2.35 (br s, 2H, OH), 3.34 (d, J 5.0 Hz, 2H, CH); δ_C (100 MHz; $CDCl_3$) 74.9, 35.2, 25.8; m/z (CI+) 192.2 (100% $[M+NH_4]^+$); $C_{10}H_{22}O_2$ requires C 68.92%, H 12.72%, found C 68.95%, H 12.64%

Analytical data for 2,3-diphenyl-butane-2,3-diol



43a

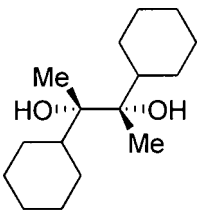


43b

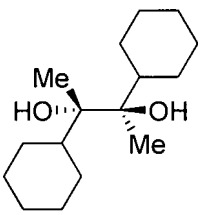
Both isomers were isolated as white solids by flash chromatography on silica gel with a solvent system starting with hexane then to 50:50 hexane: diethyl ether with a R_f of 0.2. The data are consistent with the literature.[212,222] *d/l* isomer m.p. 119.8-120.0° C (lit. m.p. 123-124° C); δ_H (400 MHz; $CDCl_3$; TMS) 1.49 (s, 6H, CH_3), 2.69 (br s, 2H, OH), 7.21-7.24 (m, 10 H aromatic); δ_C (100 MHz; $CDCl_3$) 143.4, 127.3, 127.1, 126.9, 78.5, 24.9; *meso* isomer m.p.128.1-128.2° C; δ_H (400 MHz; $CDCl_3$; TMS) 1.57 (s, 6H, CH_3), 2.55 (br s,

2H, OH), 7.17-7.20 (m, 10H aromatic); δ_C (100 MHz; $CDCl_3$) 143.7, 127.2, 127.0, 126.8, 77.3, 25.1; m/z (CI+) 260.2 (100% $[M+NH_4]^+$); $C_{16}H_{18}O_2$ requires C 79.31%, H 7.49%, found C 78.64%, H 7.68%

Analytical data for 2,3-dicyclohexyl-butane-2,3-diol



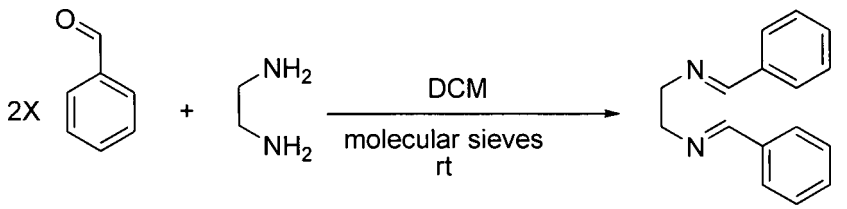
44a



44b

Both isomers were isolated as white solids by flash chromatography on silica gel with a solvent system starting with hexane then to 50:50 hexane: diethyl ether with a R_f of 0.2. The data are consistent with the literature.[182,223] *d/l* isomer m.p. 105.3-105.4° C (lit. m.p. 99-101° C); δ_H (400 MHz; $CDCl_3$; TMS) 0.95-1.21 (m, 8 H), 1.19 (s, 6H, CH_3), 1.63-1.89 (m, 12H), 2.05 (br s, 2H, OH); δ_C (100 MHz; $CDCl_3$) 19.6, 26.7, 27.3, 27.6, 28.4, 31.1, 46.7, 81.9; *meso* isomer m.p. 127.9-128.1° C (lit. m.p. 124-126° C); δ_H (400 MHz; $CDCl_3$; TMS) 0.95-1.21 (m, 8 H) 1.15 (s, 6H, CH_3), 1.63-1.89 (m, 12H), 2.25 (br s, 2H, OH); δ_C (100 MHz; $CDCl_3$) 21.9, 26.7, 26.9, 27.1, 28.0, 29.7, 44.0, 79.1; m/z (CI+) 254.2 (100% $[(M+NH_4)-H_2O]^+$); $C_{16}H_{30}O_2$ requires C 75.54%, H 11.89%, found C 75.74%, H 11.77%

5.13 Procedure for synthesis of *N,N'*-Bis(benzylidene)-1,2-diiminoethane



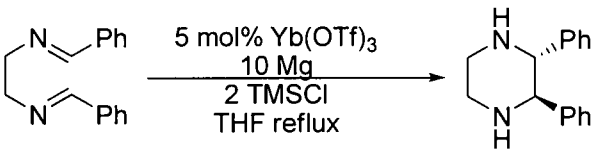
45

Scheme 134

Ethylene diamine (0.3 g, 0.33 mL, 5 mmol) and benzaldehyde (1.06g, 1.02 mL, 10 mmol) were mixed in dry DCM (20 mL) and molecular sieves (10 g) were added. Mixture was allowed to stir at rt for 3 hours and reaction was monitored by tlc. When reaction was completed, mixture was filtered through a pad of celite and residue was washed with dry DCM. Filtrate was collected and evaporated in *vacuo*. Diimine was then dried under high vacuum and stored in a sealed container at rt.

Diimine **45**, *N,N'*-Bis(benzylidene)-1,2-diiminoethane, was isolated as an off white/pale yellow solid. The data are consistent with the literature.[224] m.p. 53.9-54.1° C (lit. m.p. 55.1-56.4° C); δ_H (400 MHz; $CDCl_3$ TMS) 3.98 (s, 4H, CH_2), 7.38-7.41 (m, 6H aromatic), 7.68-7.71 (m, 4H aromatic), 8.29 (s, 2H, CH); δ_C (100 MHz; $CDCl_3$) 162.7, 136.1, 130.6, 128.5, 128.1, 61.6; m/z (CI+) 237.1 (100% $[M+H]^+$); $C_{16}H_{16}N_2$ requires C 81.32%, H 6.82%, N 11.85%, found C 81.70%, H 6.78%, N 11.77%

5.14 Procedure for intramolecular reductive coupling



45 **46**

Scheme 124

Dry distilled THF (7 mL) was added to $Yb(OTf)_3$ (0.039 g, 0.05 mmol), activated magnesium powder (0.240 g, 10 mmol) and chlorotrimethylsilane (0.2 mL, 1 mmol) in Schlenk flask under an inert atmosphere. The mixture was stirred and heated under reflux. A solution of diimine (0.236 g, 1 mmol) and chlorotrimethylsilane (0.2 mL, 1 mmol) in THF (10 mL) was then added dropwise over 2 hours with constant stirring while keeping reaction mixture still under reflux overnight. Reaction was monitored by tlc and was quenched with saturated brine solution (20 mL). The crude product was separated with ethyl acetate (3 X 30 mL). The combined ethyl acetate extracts were dried over magnesium sulfate. The crude piperazine was purified by recrystallisation from a mixture of hexane and diethyl ether with a yield of 85% (0.203 g, 0.85 mmol).

d/l 2,3-diphenylpiperazine **46** was isolated as an off white/pale yellow solid. The data are consistent with the literature.[184,187] m.p. 96.2-96.5° C (lit. m.p. 96-98° C); *d/l* isomer δ_H (400 MHz; $CDCl_3$ TMS) 2.1 (br s, NH), 3.10 (s, 4H, CH_2), 3.72 (s, 2H, CH), 7.04-7.14 (m, 10H aromatic); δ_C (100 MHz; $CDCl_3$) 140.5, 128.5, 127.8, 126.9, 65.8, 43.5; m/z (CI+) 239.2 (100% $[M+H]^+$); $C_{16}H_{18}N_2$ requires C 80.63%, H 7.61%, N 11.75%, found C 80.45%, H 7.40%, N 12.15%

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