Copper-catalysed conjugate addition to sulfinimines

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Abstract

The synthesis of a series of α,β-unsaturated sulfinimines is described. Their reaction in the presence of copper-based nucleophiles to yield 1,4-addition products is analysed in terms of yield and *d.r.* values and reported herein. After an introductory chapter, the first section of this thesis describes the synthesis and reaction of (*R*)-(*E*)-*N*-((*E*)-but-2'-en-1'-ylidene)-2-methylpropane-2-sulfinamide in the presence of a series of copper-based nucleophiles – most notably *Gilman* nucleophiles – displaying yields of up to 54% and 3:2 *d.r.* values.

The second section of this thesis describes the synthesis of a range of cinnamaldehyde-derived sulfinimines and their reaction in the presence of copper-based nucleophiles – this time derived from alkyl aluminium reagents. Up to quantitative yields and *d.r.* values of 1:>20 are reported.

In addition, methodology for the synthesis of cinnamaldehyde precursor derivatives *via* a Meyer-Schuster rearrangement is discussed along with the qualitative identification of competing reactions.

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Abbreviations

acac	acetylacetonate
THF	Tetrahydrofuran, Oxolane
DCM	Dichloromethane, CH_2Cl_2
DCE	1,2-Dichloroethane, CH_2ClCH_2Cl
HMQC	Heteronuclear Multiple-Bond Correlation
DEPT	Distortionless Enhancement by Polarization Transfer
BINOL	1,1'-bi-2-naphthol
OTf	trifluoromethanesulfonate
TC	thiophene-2-carboxylate
p-TSA	*para*-toluenesulfonic acid
MMPP	Magnesium monoperoxyphthalate
D_a	Dalton
MTBE	Methyl *tert*-butyl ether
coe	*cis*-cyclooctene
dppbenz	1,2-Bis(diphenylphosphino)benzene

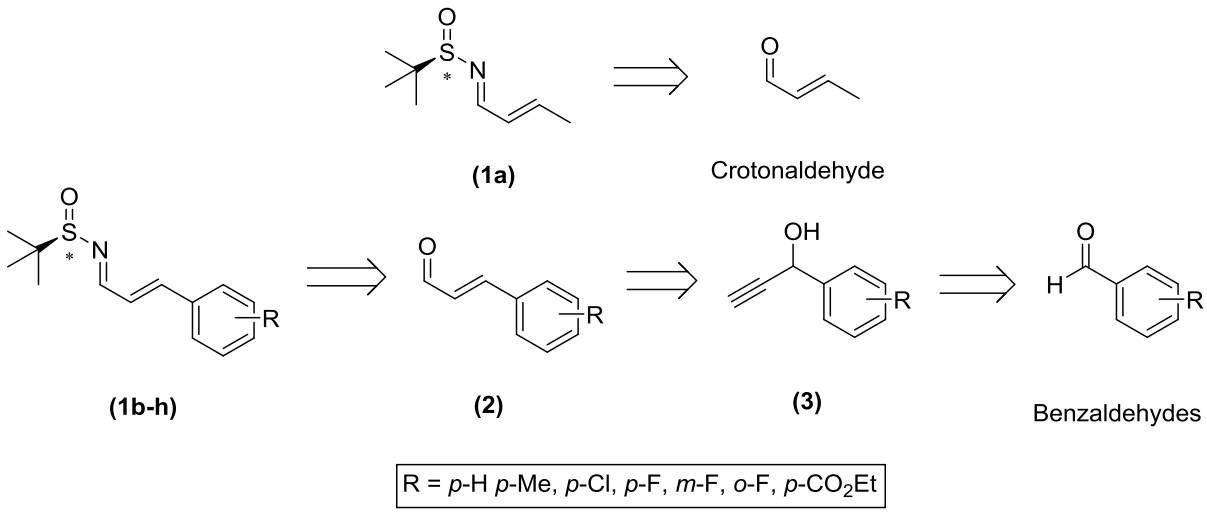
All other abbreviations that are used are given in the standard abbreviations list for the *Journal of the American Chemical Society* at the time of writing.

Chapter One

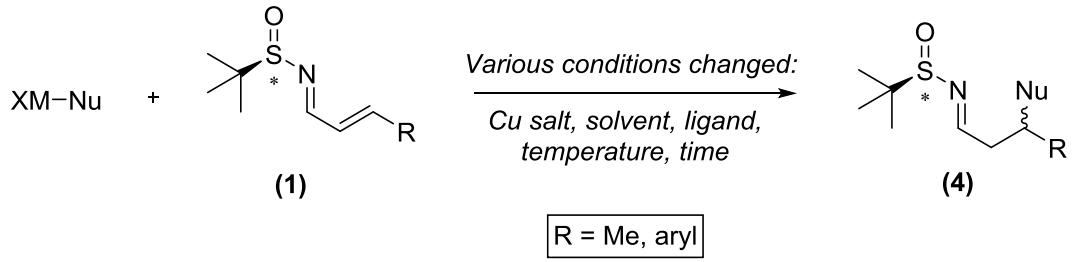
Introduction

1.1 Opening remarks

This Thesis details the preparation of sulfinimine **(1a)** and sulfinimines of the type **(1b-h)** (Scheme 1) and their reaction with organometallic nucleophiles in the presence of copper catalysts (Scheme 2) to give 1,4-addition compounds **(4)**. Sulfinimine **(1a)** was synthesised *via* condensation of crotonaldehyde with commercially available enantiopure (*R*)-*tert*-butyl sulfinamide. Sulfinimines **(1b-h)** were similarly synthesised by condensation of the corresponding aldehydes **(2)** with enantiopure (*R*)-*tert*-butyl sulfinamide. It was postulated that the aldehydes **(2)** could be accessed *via* a Meyer-Schuster rearrangement from substituted propargyl alcohols **(3)**, themselves accessible *via* 1,2-addition to benzaldehyde derivatives.



Scheme 1: Preparation of enantiopure sulfinimines



Scheme 2: Proposed 1,4-conjugate addition

The aim of this project was to establish methodology for stereoselective copper-catalysed 1,4-conjugate addition to compounds **(1)** to demonstrate the use of sulfinimines as chiral auxiliaries. Therefore, this opening Chapter will review research in the areas relevant to this study in the period 1970-2015, and this is presented in the following sections and throughout.

1.2 Reactions and use of chiral sulfinimines

1.2.1 Introduction to chiral sulfinimines

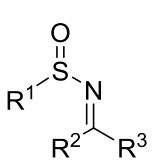
A sulfinimine is defined as a compound possessing the *N*-sulfinyl-imine functional group **(5)** (Figure 1).[1-3] This functional group possesses one stereogenic centre at the sulfur atom that is formally in a +4 oxidation state. The sulfur atom is bonded to a nitrogen atom that is in turn doubly bonded to a carbon atom which boasts a high stereomutation barrier.[4,5] The functional group provides an opportunity to tune the reactivity and selectivity of the desired reaction *via* the remaining substituent directly bonded to the sulfur atom (Figure 1, **(5)**, R^1). The common conformations of *tert*-butyl sulfinimines have been studied[6] and can provide explanations for observed reactivity in some cases (See Figure 7, Section 1.2.3.2).

A short chronology of the emergence of sulfinimines is now given below, before specific areas pertinent to this Thesis are discussed in detail.

Sulfinimines were first synthesised in 1974 *via* the oxidation of sulfenimines with *m*-CPBA from achiral starting materials by Davis *et al.*[4] These sulfinimines **(6)** possessed aryl groups bonded to the sulfur and were made in good yields as racemates with the exception of **(6b)** that was obtained as a single diastereomer (Figure 1) for which no explanation was given. A reliable synthesis of enantiomerically pure sulfinimines was then reported in 1982[5] using enantiomerically pure **(7)** (Figure 1, Andersen reagent) in the presence of magnesium ketimines, yielding good quantities of a range of *p*-tolyl sulfinimines (See Scheme 6, Section

1.2.2.2). These were then reduced with achiral metal hydrides to yield chiral amines, demonstrating the use of sulfinimines as chiral auxiliaries for the first time.

There was then a lull in the research until 1995, when Davis *et al.* reported[7] a synthesis of optically pure (*R*)-(+)-*β*-phenylester **(8)** from (*S*)-(+)-benzylidene-*p*-toluenesulfinamide and was able to regenerate the precursor sulfinimine *via* chiral crystallisation in 60% yield as a single enantiomer. The ability to recycle what was then a difficult auxiliary to prepare coupled with the potential of the group as a chiral directing group made this paper noteworthy.



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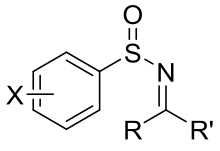
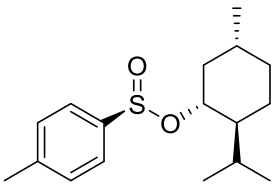


(6)
(a) X = H; R = R' = CH_3
(b) X = H; R = H; R' = Ph
(**c**) X = *p*-Cl; R = H; R' = Ph
(**d**) X = *m*-NO_2; R = H; R' = CH_3
(**e**) X = *m*-NO_2; R = H; R' = Ph



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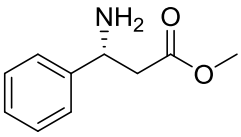
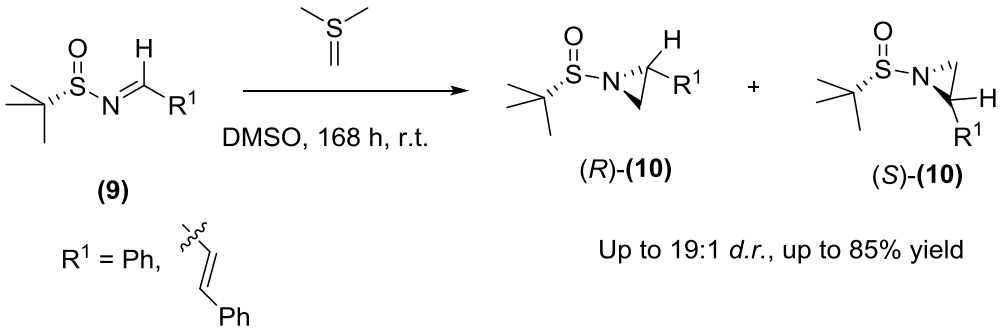


(8)

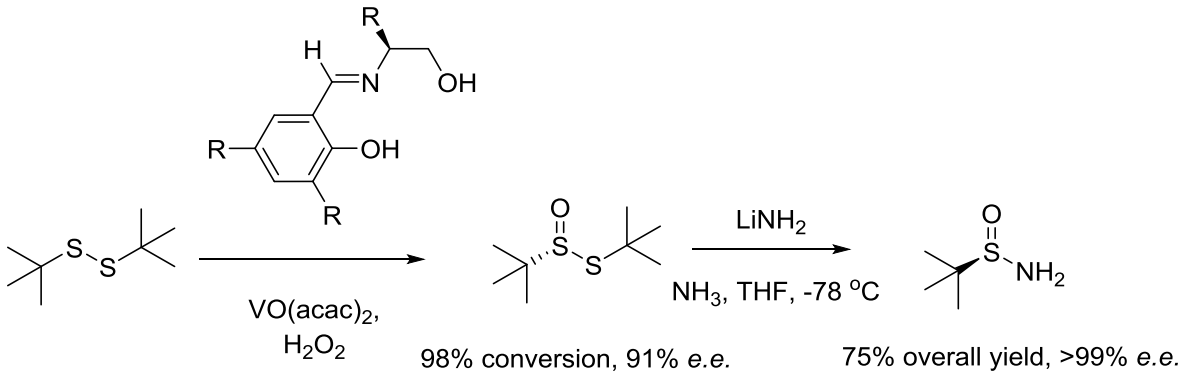
Figure 1 – Compounds of early interest with regards to sulfinimine chemistry

Shortly afterwards in 1996, Ruano *et al.* reporting improved selectivity in the aziridination of sulfinimines using *tert*-butanesulfinimines **(9)** and dimethylsulfonium methylide, allowing either azide enantiomer **(10)** to be selected by altering the precursor sulfinimine chirality (Scheme 3).[8]



Scheme 3 – Enantiomeric control in the aziridination of sulfinimines

The potential of *tert*-butanesulfinimines, but the lack of an easy synthesis of this class of compounds, prompted a paper from Ellman *et al.*[9] in 1997, detailing the quantitative and enantioselective synthesis of *tert*-butyl sulfinamide (Scheme 4). This paper also included the condensation of *tert*-butyl sulfinamide with aldehydes, and the addition of Grignard reagents to the resultant sulfinimines. The reactions proceeded in high yield and excellent selectivity.



Scheme 4 – Catalytic synthesis of (*S*)-*tert*-butane sulfinamide

For the synthetic chemist, the 1997 Ellman paper marks the first time that these chiral auxiliaries were available in large quantity and *via* easy preparation from simple starting materials. The has been a surge of interest in sulfinimines after 1995, which have been applied to areas such as: synthesis of 1,2-amino alcohols;[10] 1,3-amino alcohols *via* enamine addition;[11,12] piperidines *via* 1,4-conjugate enamine addition;[13] β-amino carbonyl compounds;[14,15] aziridination;[16-19] as ligands in palladium-catalysed cross-coupling;[20]

iridium-catalysed hydrogenation;[21] as thiourea organocatalysts;[22] as electrophiles in the 1,2-addition of organometallic reagents;[23-25] and as electrophiles in the 1,4-conjugate addition of organometallic reagents.[26] This list is not exhaustive, but indicates the largest areas of research which will now be discussed in more detail.

1.2.2 Synthesis of chiral sulfinimines

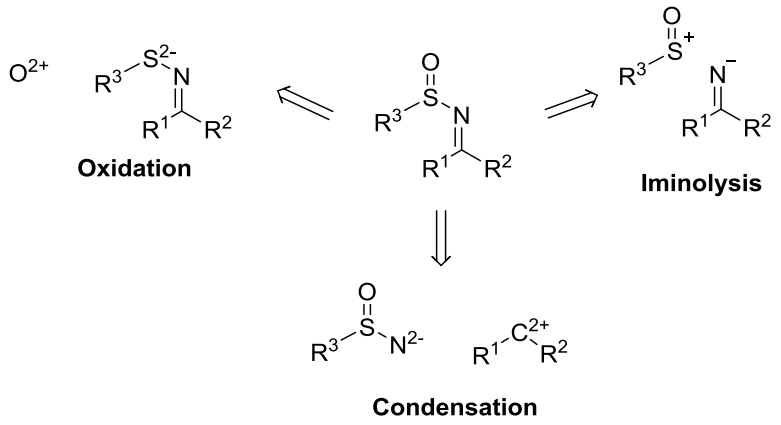
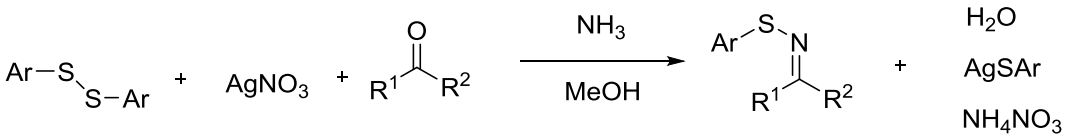


Figure 2: Retrosynthetic analysis of a generic sulfinimine showing synthons

Figure 2 shows the three most obvious retrosynthetic routes towards the synthesis of a sulfinimine. In contemporary synthesis, it is likely that one of the commercially available sulfinamides would be used for the condensation of aldehydes or ketones to form a sulfinimine. However, to access commercially unavailable sulfinimines, other methods need to be employed.

1.2.2.1 Synthesis of sulfinimines by oxidation

The first reported oxidation of sulfenimines to sulfinimines appeared in 1974.[4] This built on previous work by Davis *et al.* in the synthesis of sulfenimines *via* silver-promoted disulfide bond cleavage (Scheme 5).[27]



Scheme 5: Silver-promoted sulfenimine synthesis

This was an oxidation with achiral components, and it was not until 1992 that an oxidation of sulfenimines using chiral components was published, again by Davis *et al.*[28] This used the chiral oxidants **(11)** (Figure 3) to provide the desired sulfinimines in high yields (72-95%) and modest to good *e.r.* values (up to 90%).

Unfortunately, this required the use of difficult to synthesise *N*-sulfonylcamphorimines[29] and although the method has general application, the approach of using chiral oxidants with sulfenimines does not appear to have been widely used.

Another approach to chiral oxidation of sulfenimines is to use chiral substrates with achiral oxidants. Teng-Kuei Yang *et al.*[30] published the synthesis of a range of camphor-based sulfenimines **(12)** that were then oxidised using *m*-CPBA or MMPP to yield chiral sulfinimines with up to >99:1 *d.r.* values in up to 99% yields. Although the reaction terminus is at sulfur, the use of a camphor-derived auxiliary was reported to be sufficient to transmit chiral information to the sulfur centre to synthesise sulfinimines **(13)**.

Again, the difficulty associated with the synthesis of compounds **(12)** appears to have prevented this method from receiving continued interest.

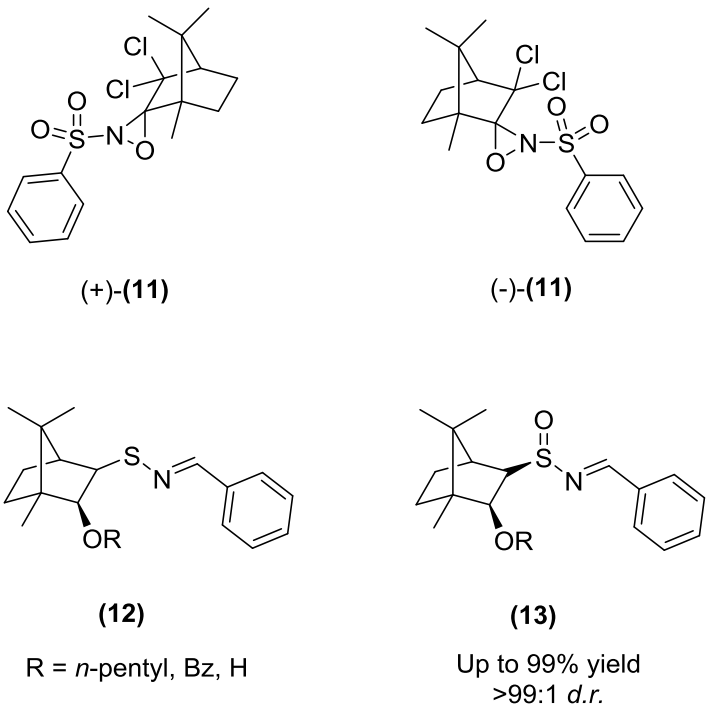
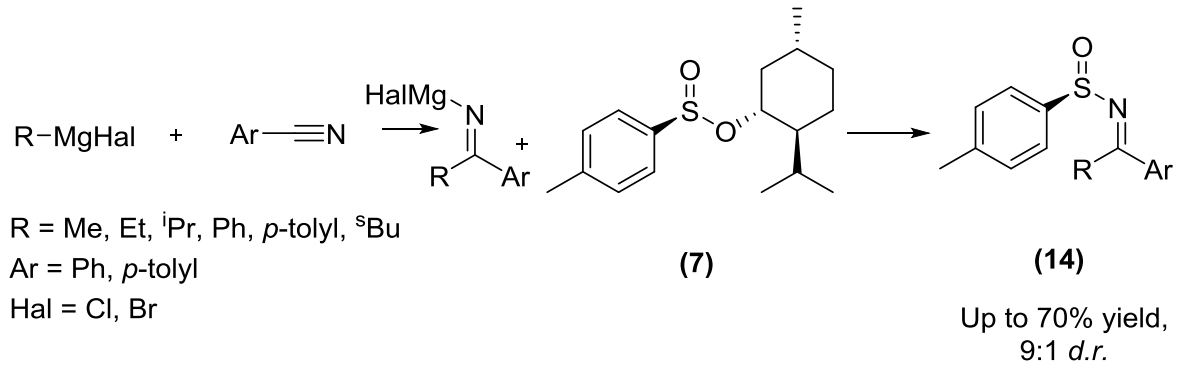


Figure 3 – Substrates of interest in the oxidation of sulfenimines

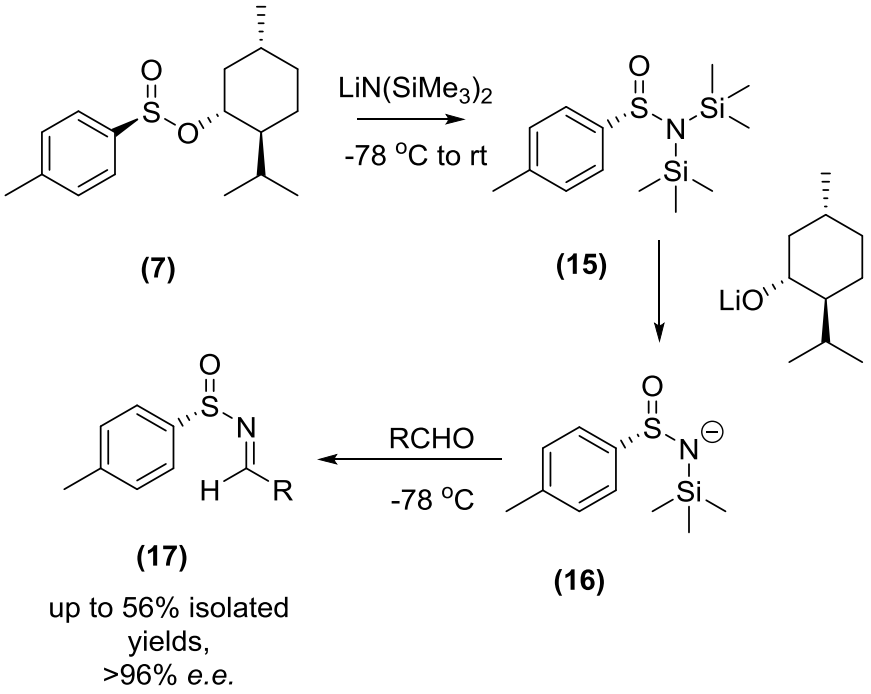
1.2.2.2 Synthesis of sulfinimines by iminolysis

The first addition of an imine nucleophile to a chiral sulfur was published by Cinquini *et al.* in 1982.[5] Addition of magnesium ketimines to the Andersen reagent **(7)** provided the desired sulfinimines **(14)** in yields of up to 70% and up to 9:1 *d.r.* values. This was only demonstrated on aryl ketimines, not alkyl ketimines or aldimines (Ar = H), limiting the scope of this method.



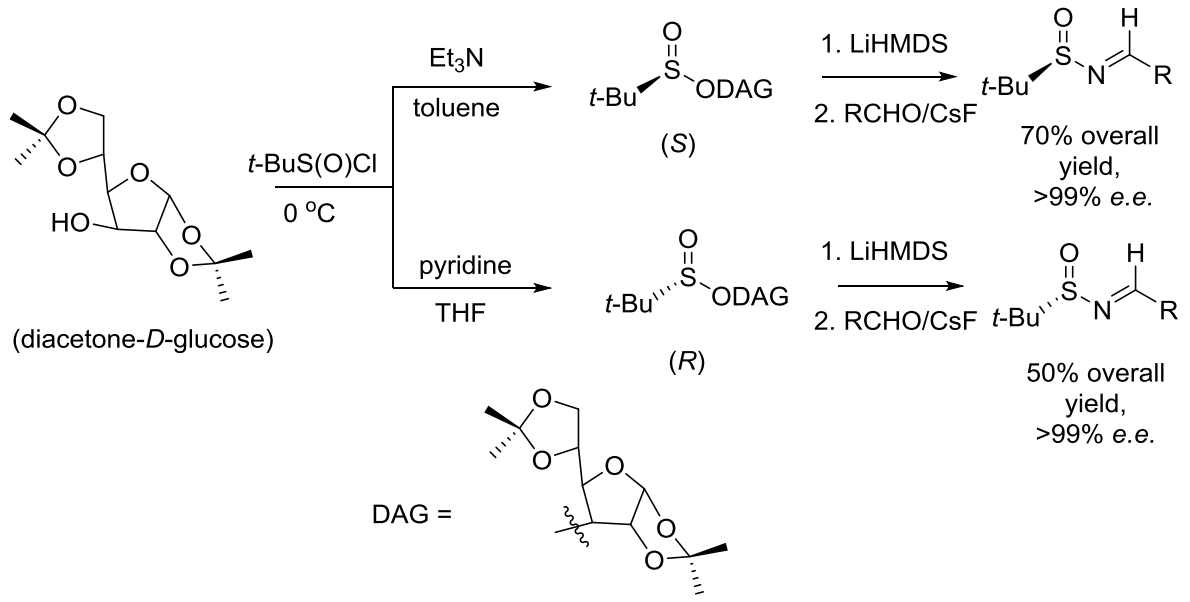
Scheme 6: Ketimine addition to Andersen reagent (7)

To get around this limitation, Davis *et al.*[31] prepared the sulfinamide **(15)** and were able to successfully react it with a range of aldehydes *via* the intermediate **(16)** generated *in situ*, marking the first synthesis of aldehyde-derived sulfinimines **(17)** from readily available and relatively easy to handle reagents.



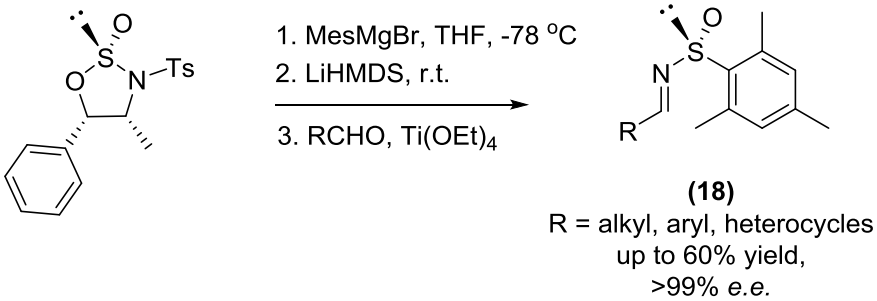
Scheme 7 – Sulfinimines synthesised by chiral iminolysis

Enantiopure *tert*-butyl sulfinimines can be prepared through an intermediate similar to **(16)**. By alteration of base and solvent in the presence of diacetone-*D*-glucose as the chiral transfer reagent, *tert*-butylsulfinyl chloride can be used to form desired aldehyde-derived sulfinimines (Scheme 8).[8] This method was developed by Fernandez *et al.*[32] and later Garcia *et al.*[8] and is known as the 'DAG' method.



Scheme 8 – The 'DAG' methodology

More recently, in 2007 Stockman *et al.* reported a one pot synthesis of mesityl sulfinimines which built upon the work done by Davis *et al.* on sulfinamide formation[31] (Scheme 7) and the work done by Senanayake *et al.*[33] on sulfoxide formation to give aldehyde-derived sulfinimines **(18)** in up to 60% yields as a single enantiomer (Scheme 9). This methodology also offers the option to isolate the mesityl sulfinamide for use in a stepwise synthesis.

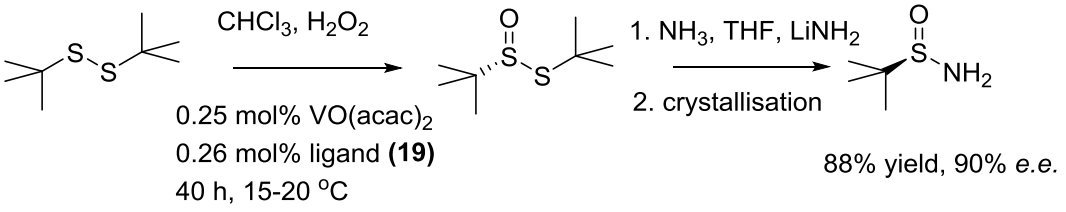


Scheme 9 – Mesityl sulfinimines as synthesised by the Stockman group

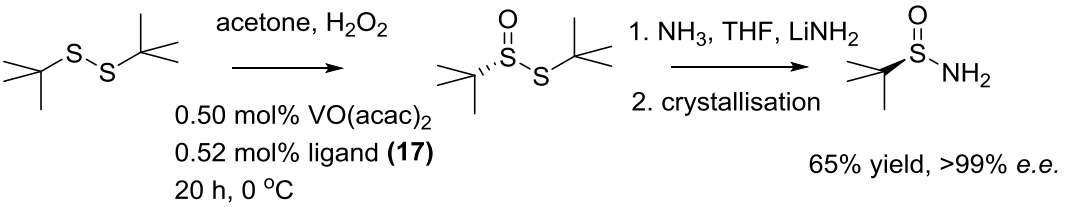
1.2.2.3 Synthesis of sulfinimines by condensation

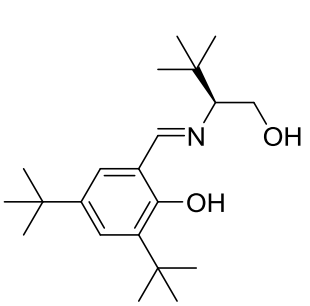
Schemes 7 and 8 show a condensation with *N*-sulfinyl silazane intermediates coupling with carbonyls, but better condensation methodology has been developed which avoids the use of extremely air- and moisture-sensitive reagents. In order to synthesise sulfinimines *via*

condensation, the corresponding sulfinamides must first be made. If the method is to be generalised, the sulfinamides must be isolable and enantiopure. Though initially mentioned as a side product by Davis *et al.* in 1997,[31] it was Ellman *et al.* who first developed methodology for preparation of sulfinamides at scale in 1997 (Scheme 10),[9] which was then improved on in 2003 (Scheme 11).[34] The original preparation of *tert*-butyl sulfinamides was limited by its biphasic nature and access to only one enantiomer, but these problems were alleviated in the follow-up 2003 paper, allowing synthesis on kilogram scales. The chiral ligand **(20)** is easily prepared from inexpensive starting materials in either enantiomer, which is a key factor in the commercialisation of *tert*-butyl sulfinamides.



Scheme 10 – Sulfinimine synthesis at a large scale





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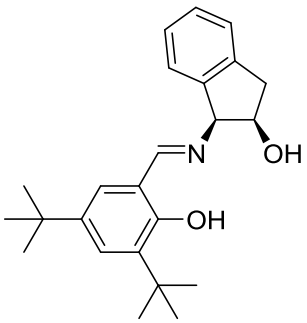

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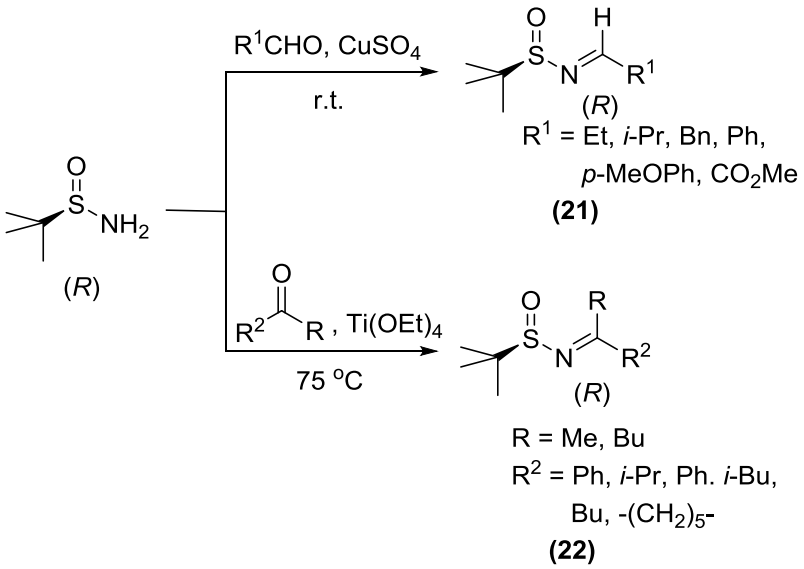
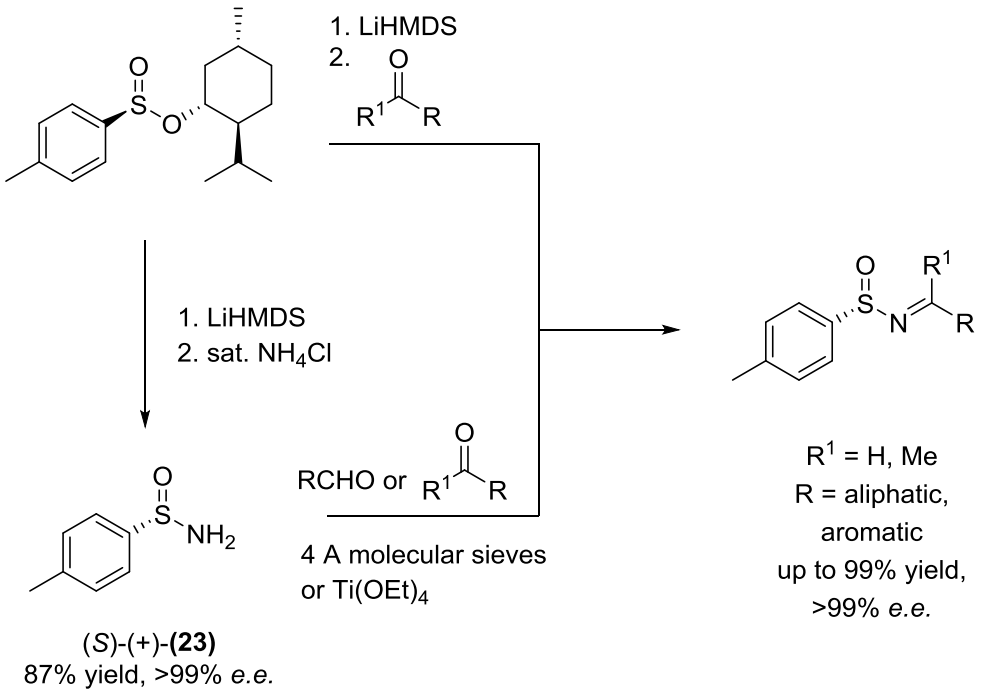
Scheme 11 – Improvement upon the initial large scale synthesis

With (*R*)-*tert*-butyl sulfinamide available, Ellman *et al.* then investigated its condensation with aldehydes and ketones.[35] A few different dehydration conditions were tested, and it was found that for aldehydes, the use of copper sulfate or magnesium sulfate was enough to afford desired sulfinimines **(21)**. However, in the case of ketones a much stronger Lewis acid was required. Various titanium salts were screened, but the optimum conditions were obtained using $Ti(OEt)_4$, forming sulfinimines **(22)** in up to 89% yield as a single enantiomer (Scheme 12).



Scheme 12 – Various dessicants and substrates used in the condensation reaction to form sulfinimines

An important result from this study is that the stereochemistry of the sulfur atom is retained through the condensation reaction. Davis *et al.* concurrently demonstrated in 1999 that *p*-tolyl sulfinimines are readily available through condensation and built upon previous work (Scheme 7)[31] to isolate the *p*-tolyl sulfinamide **(23)** (Scheme 13) in 87% yield as a single enantiomer. This added cleanly to alkyl or aryl carbonyl compounds that were either aldehydes or ketones under conditions similar to those reported by Ellman *et al.* in up to 99% yield with no observed sulfur-centred racemisation.



Scheme 13 – *p*-Tolyl sulfinimine synthesis by condensation

At the turn of the millennium, both *p*-tolyl and *tert*-butyl sulfinimines were accessible through simple condensation with inexpensive reagents, easy purification and access to both enantiomers, and finally a methodology that applied to ketimines and aldimines alike. Other dehydrating agents have been used for this imine condensation including caesium carbonate,[36] ytterbium triflate,[37] and even hydroxide/*tert*-butoxide[38] but the lion's share of research has used the conditions demonstrated by Ellman *et al.* and Davis *et al.*

Owing to the stability of the starting sulfinimines and the generality of these methods, the primary way to make sulfinimines for study is condensation from precursor sulfinamides.

1.2.3 Reactions of chiral sulfinimines

1.2.3.1 Reduction of the C=N bond

Additions across an imine double bond are a simple and potentially powerful method for the synthesis of chiral nitrogen-containing compounds. In 1982, Cinquini *et al.* reduced *p*-tolyl sulfinimines using metal hydrides, and proposed a transition state as shown (Figure 4) to explain the observed selectivity.[5]

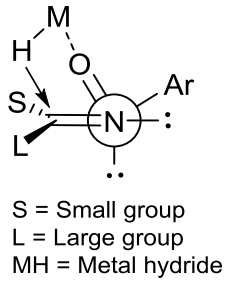
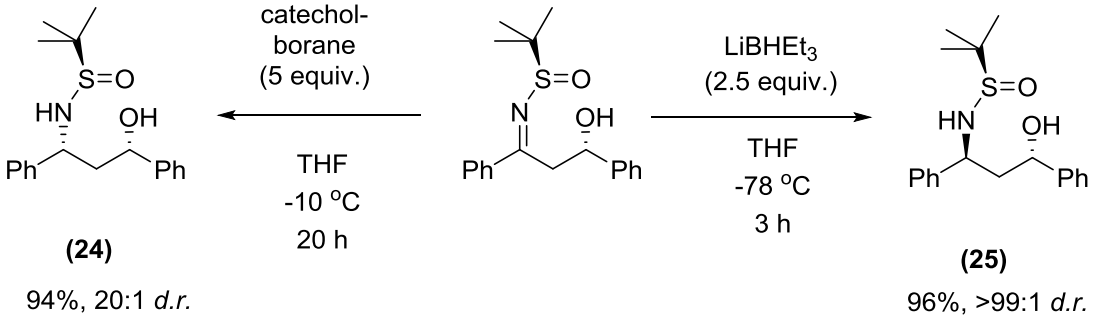


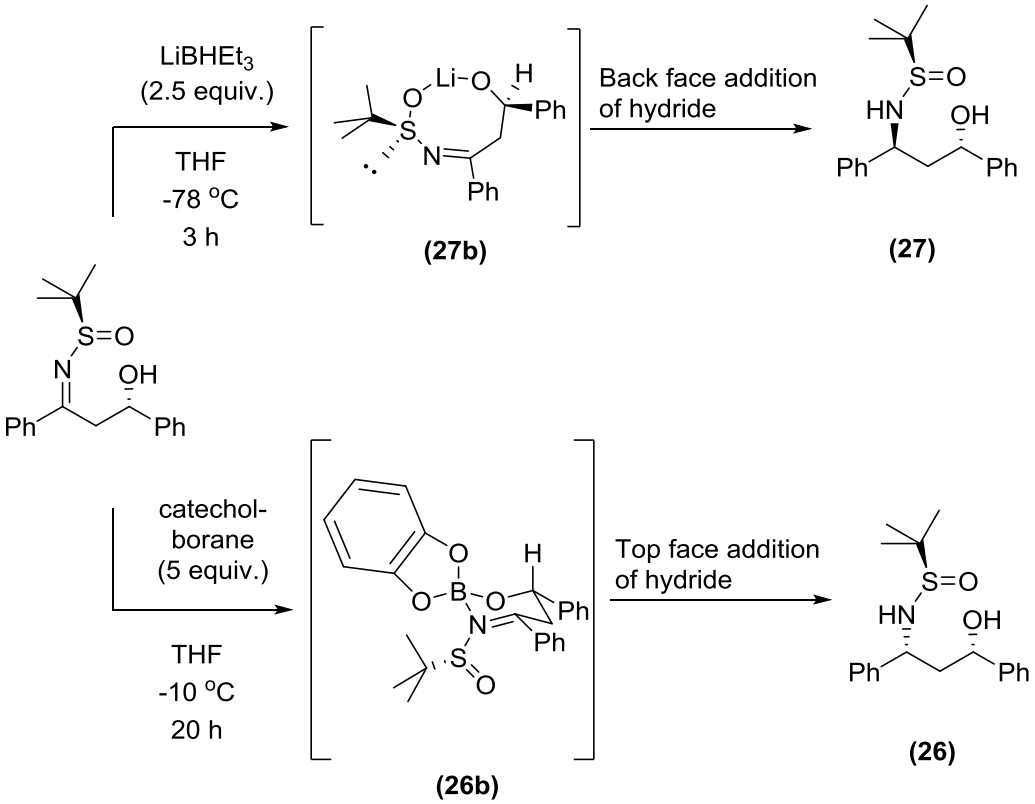
Figure 4 – Model C=N bond reduction

In this conformation, the large and bulky aryl group points away from the pendant groups attached to the imine carbon atom and therefore avoids steric clash, lowering the energy barrier of the transition state. Ellman *et al.* then applied this chemistry in the synthesis of 1,3-amino alcohols,[11] and demonstrated that *syn* or *anti* (*N*)-sulfinyl-1,3-amino alcohols **(24)** and **(25)** can be selectively synthesised by alteration of conditions (Scheme 14).



Scheme 14 – Stereocontrol in amino alcohol synthesis

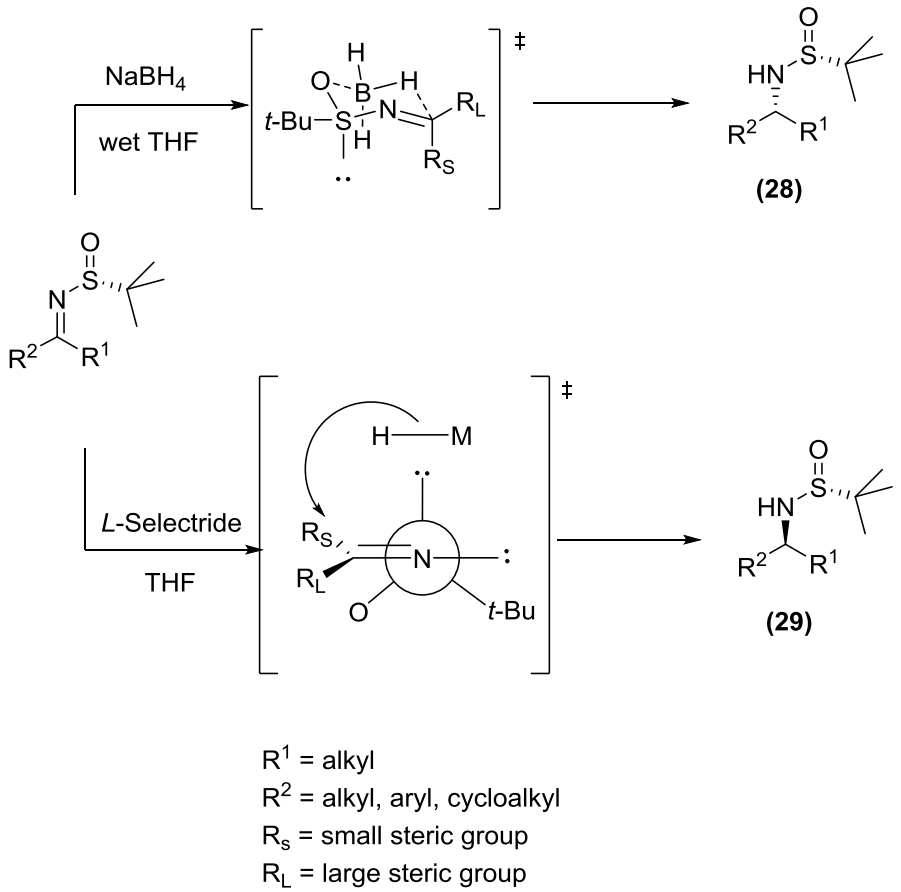
An explanation for this observation was also provided (Scheme 15). For the reducing agent $LiBHEt_3$, it was proposed that *in situ* formation of eight-membered ring intermediate **(27b)** explains the *anti* selectivity, but for the more strongly co-ordinating catechol borane reducing agent, the six membered intermediate **(26b)** is formed *in situ* and causes *syn* selectivity.



Scheme 15 – Explanation for stereocontrol in amino alcohol synthesis

Colyer *et al.*[39] built on this in 2006 by screening a series of solvents and reducing agents to reduce ketone-derived sulfinimines (Scheme 16), forming either enantiomer in a predictable way. It was claimed that the reactions involving $NaBH_4$ proceeds *via* a closed 6-membered transition state to form enantiomer **(28)** (after forming borane *in situ*), but weakly co-ordinating, hindered *L*-Selectride proceeds in a more classical open transition state, allowing nucleophile approach from the unhindered face to form enantiomer **(29)**. These results seem to agree with Ellman and co-worker's results from 2003[11] and 2004,[40] which pleasingly

demonstrates predictability in reduction reactions involving *tert*-butyl sulfinimines irrespective of intervening proximal chiral centres.

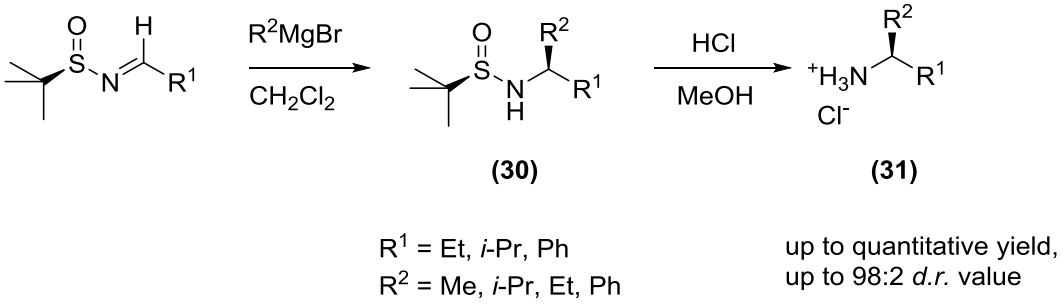


Scheme 16 – Explanation for stereocontrol in C=N reduction

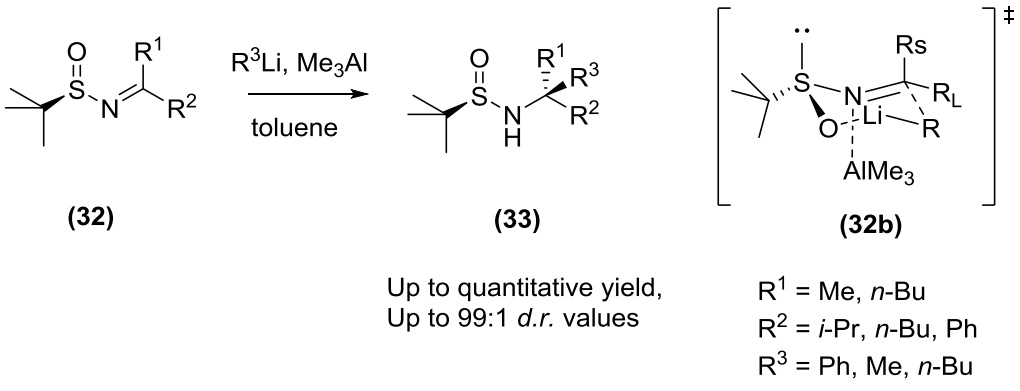
1.2.3.2 1,2-Nucleophilic additions

Ellman demonstrated in his 1997[9] paper that aldehyde-derived sulfinimines readily undergo 1,2-addition reactions with Grignard nucleophiles (Scheme 17). All the reactions proceed in near quantitative yield to form essentially optically pure products. Analysis of the Mosher amides of amine hydrochlorides **(31)** confirmed that addition proceeded from the same face in all cases. Further work from Ellman in 1999[41] produced a methodology for Me_3Al-promoted-1,2-addition of organolithium nucleophiles to sulfinimines (Scheme 18). The improved yields and *d.r.* values (up to quantitative yield and 99:1 *d.r.* values) were

rationalised by six-membered closed transition state (**32b)**. The proposal states that the bulkiest groups – *tert*-butyl and R_L – are placed equatorial to avoid 1,3-diaxial clash as is usual for six-membered ring conformations thereby allowing approach to the *si* face of the sulfinimine. Also, the use of ethereal solvents dramatically reduced the yield and selectivity observed therefore implying that some necessary co-ordination complexes are formed *in situ* that are destroyed by ethereal solvation.



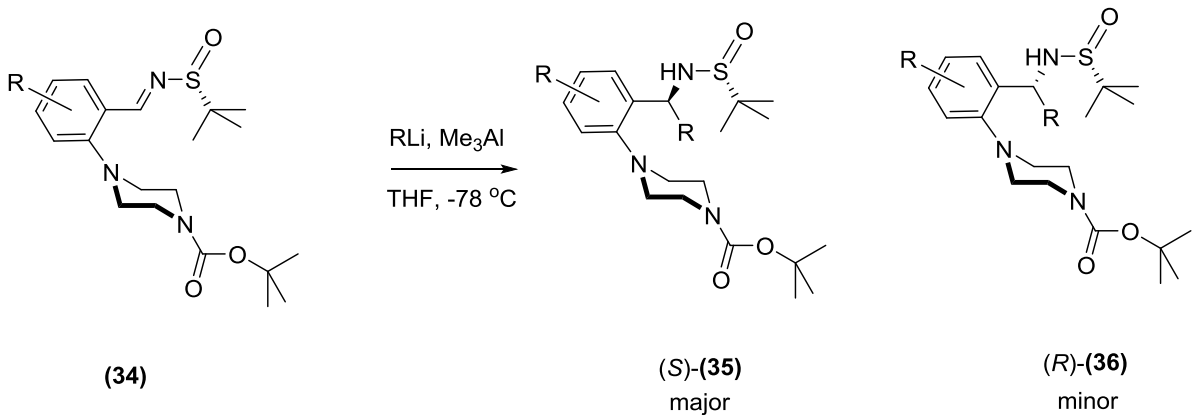
Scheme 3 – 1,2-Addition reactions of sulfinimines with Grignard reagents



Scheme 18 – 1,2-Addition reactions promoted by trimethyl aluminium

This model is contradicted by Jiang *et al.*[42] in their paper published in 2005 that finds an inversion of stereoselectivity when sulfinimines **(34)** are reacted with organolithium nucleophiles in the presence of Me_3Al (Scheme 19). An alternative rationalisation is provided for the observed selectivity (Figure 5). The authors propose that the trajectory that runs parallel to the sulfur lone pair is the least hindered and most favourable path for an incoming

nucleophile. There is a small amount of research supporting this model with regards to triorganozincates, although the authors do not specifically propose a rationalisation.[24] It should be noted that Jiang *et al*. use co-ordinating THF as a solvent as opposed to toluene, therefore facilitating the open transition state depicted in Figure 5.



Scheme 4 – Demonstration of inversion of selectivity in the presence of trimethyl aluminium

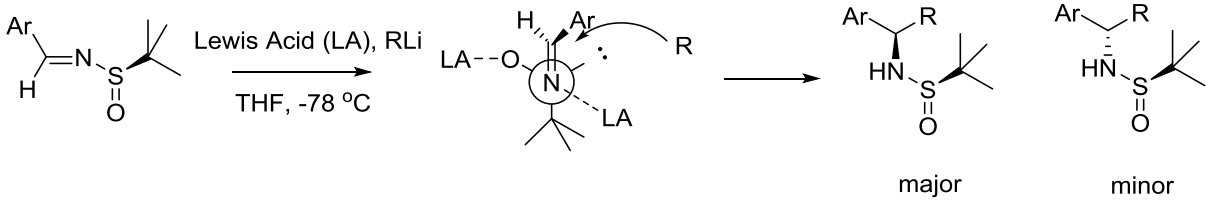
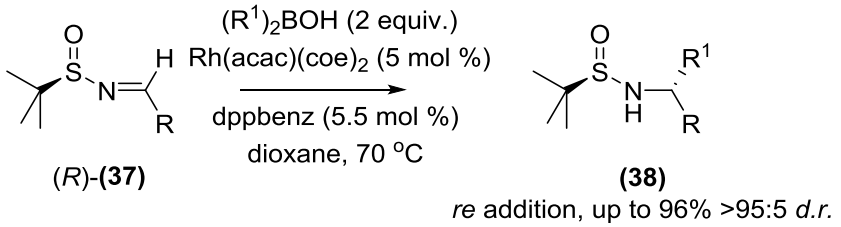


Figure 5 – "Yamamoto-type" addition of alkyllithium reagents to *N-tert*-butylsulfinyl imines

Although no explanation has been given by its authors, carbanion nucleophiles can also be delivered by boronic acids in the presence of rhodium catalysts.[43] Good to excellent yields and *d.r.* values are observed after condition screening (Scheme 20).



Scheme 5 – Rhodium-catalysed boron-nucleophile 1,2-Addition reaction

Shortly after Ellman's 1999 work, a second paper was published by Ellman in 1999 that demonstrated the addition of allyl nucleophiles to sulfinimines. The transition state, Ellman claims, forms *via* a 4,6-bicyclic 8-membered metallocycle that bonds the metal involved to both oxygen and nitrogen and contains a 6-membered ring in a chair conformation, causing the increased yields and selectivity observed (Figure 6).

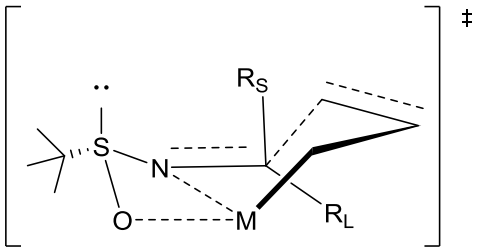
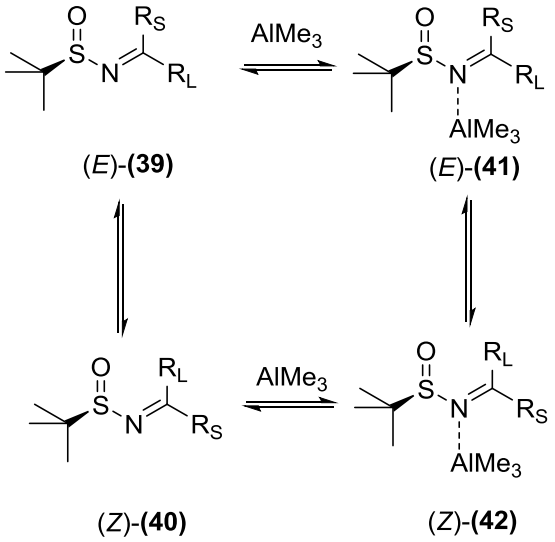


Figure 6 – Proposed 4,6-bicyclic 8-membered metallocycle transition state for the addition of allylic nucleophiles to sulfinimines

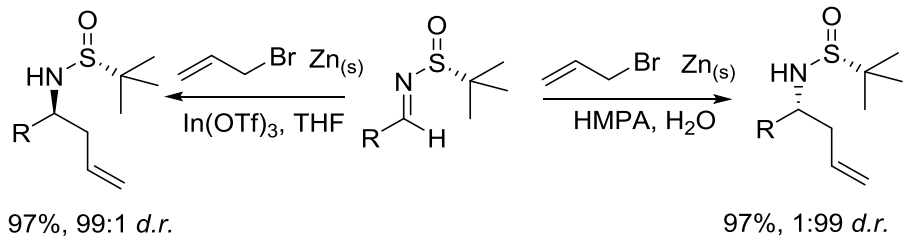
This paper also built upon the justification for the stereoselectivity observed with Me_3Al-promoted alkylations (Scheme 18), explaining that *p*-tolyl sulfinimines have a stereomutation barrier of ~17 kcal mol^{-1}, which is high enough to be stable for storage, but low enough to allow access to (*E*)/(*Z*) interchange (Scheme 21). If a similar stereomutation barrier applies to *tert*-butyl sulfinimines, and if one conformation is favoured to participate in the transition state **(32b)**, then interconversion of the C=N bond allows the most favourable conformation to be easily reached, leading to high yield and smooth reaction.



Scheme 6 – Proposed interchangability of (E)/(Z) isomers of sulfinimines promoted by trimethyl aluminium

Fueblo *et al.* concurred with this argument in 2004,[44] and went on to show that allyl indium complexes generated *in situ* showed the same behaviour.

Xing-Wen *et al.* studied allylic nucleophilic addition chemistry in 2006 and showed it to work with allylzinc bromide (Scheme 22).[45] In the case of zinc as a Lewis acid, they proposed a different transition state model, arguing that since the preferred conformer of *tert*-butyl sulfinimines is known to be as **C3** (Figure 7), and since they are using the strongly complexing solvent THF, an open acyclic transition state may be favoured instead of the one proposed by Ellman; the allyl nucleophile attacks in the expected manner from the less hindered, back-faced trajectory (Figure 8).



Scheme 7 – Allylzinc nucleophilic addition to sulfinimines

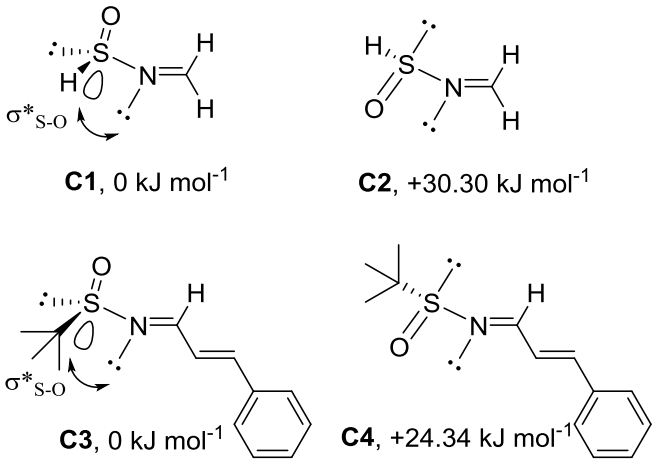


Figure 7 – Calculated lowest energy conformers of sulfinimines showing stabilising interaction between the nitrogen lone pair and the S-O antibonding orbital

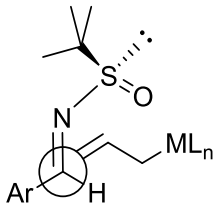
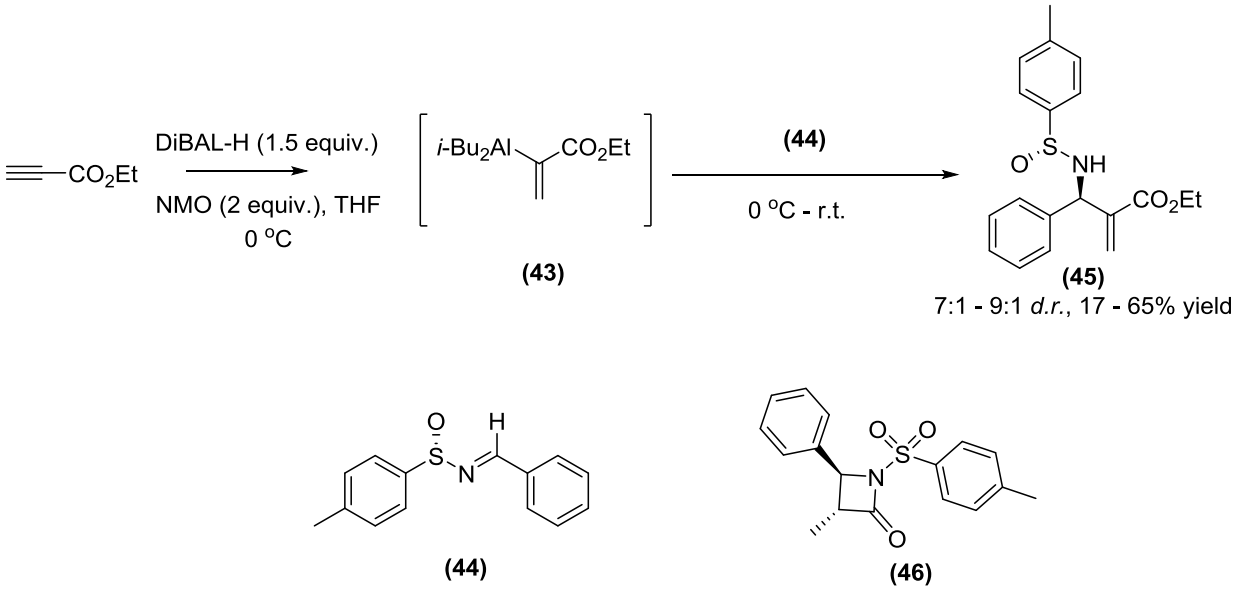


Figure 8 – Allylic addition to a sulfinimine in the C3 conformer – nucleophile approaches from the exposed back (*re*) face

An important outcome of this study is the observation that diastereomeric control can be switched completely by changing the solvent or with an addition of a proper amount of water. Though the authors concede that it is not known why water is crucial to the reaction, they offer the explanation that breaking up zinc chelates and aggregates with the sulfinimines by way of water is what drives the selectivity, fitting with the given transition state model (Figure 8).

Combining the work of Li *et al.*[46] on vinyl cuprate additions to *p*-tolyl sulfinimines and the work of Ramachandran *et al.*[47] on the synthesis of vinyl aluminates and their addition to aldehydes and ketones, Davis *et al.*[25] recently described methodology for the synthesis of vinyl alane **(43)** and their 1,2-addition to *p*-tolyl sulfinimine **(44)** (Scheme 23). The product

(45), an aza-Morita-Baylis-Hillman product, was used in the synthesis of lactam **(46)** where the sulfinimine moiety ultimately has become oxidised to a tosyl protecting group. The yield and selectivity for this transformation are modest (8:1, 63%), but the ability of the sulfinyl group to be oxidised to a protecting group potentially saves protection and deprotection steps later in the synthesis. The *si*-face addition is driven by simple steric control as opposed to chelation in this case.



Scheme 8 – 1,2-Addition to *p*-Tolyl sulfinimine (44) in the synthesis of (46)

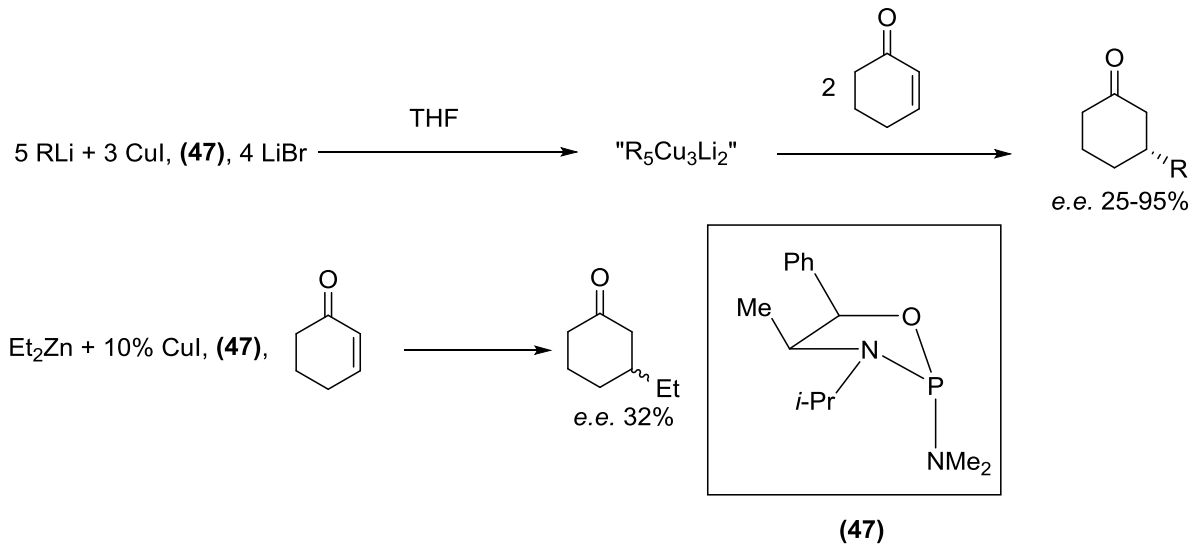
More esoteric nucleophilic addition to sulfinimines has been reported including: fluorosulfones,[48] ester enolates,[49] nitrile silanes,[50] phosphonate esters[51]. However, these transformations do not fall under the remit of this Thesis, and will not be discussed further here.

1.3 Copper catalysed 1,4-conjugate addition

With hundreds of papers being published per decade, copper-catalysed conjugate addition is one of the best known areas of study in modern chemistry.[52-58] This section will introduce key concepts relevant to the scope of this Thesis.

1.3.1 Organozinc nucleophiles

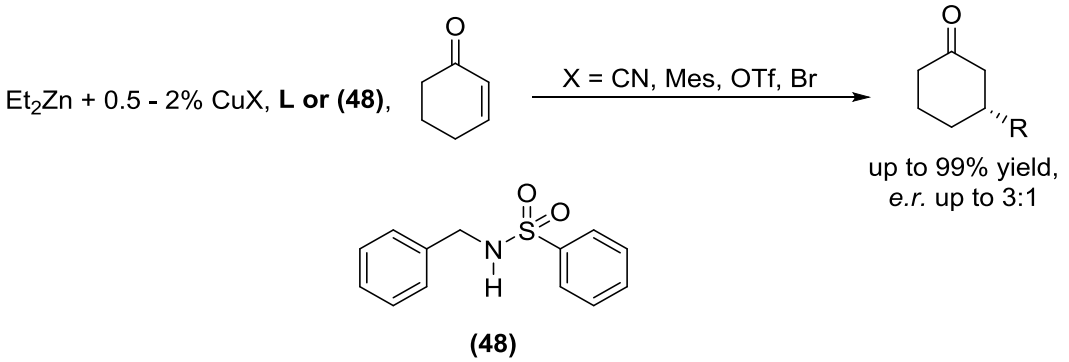
The pioneering paper in 1993 from Alexakis *et al.*[59] brought copper-based conjugate additions from the realms of stoichiometric cuprate nucleophiles (typically formed from organolithium or Grignard reagents) into catalytic methods using diorganic metal nucleophiles – in this case, diethylzinc (Scheme 24).



Scheme 9 – Catalytic copper-catalysed conjugate addition

Noyori *et al.*[60] followed this up by demonstrating that Cu^{I} salts do not in fact catalyse the conjugate addition of diethylzinc except in the presence of a ligand such as sulfonamide **(48)** (Table 1), prompting Alexakis *et al.* to then investigate the effect of various Cu^{I} salts and phosphite ligands on the reaction outcome.[61]

Table 1 – Variation of copper salt, ligand, temperature, and reaction time on the 1,4-addition reaction



(48)

Entry	Cu salt 0.5%	Ligand L 1%	Solvent	10 min 0 °C	1 h 0 °C	5 h 0 °C	12 h 20 °C
1	CuI	-	Toluene	-	-	-	-
2	CuCl	-	Toluene	-	-	-	-
3	$CuCl_2$	-	Toluene	-	-	-	-
4	CuCN	-	Toluene	-	21	77	100
5	$Cu(OTf)_2$	-	Toluene	-	28	78	100
6	CuCN	**(48)**	Toluene	52	88	100	
7	$Cu(OTf)_2$	**(48)**	Toluene	100			
8	$Cu(OTf)_2$	$P(NMe_2)_3$	Toluene	74	94	100	
9	CuCN	$P(OEt)_3$	Toluene	20	30	50	100
10	CuOTf	$P(OEt)_3$	Toluene	67	100		
11	$Cu(OTf)_2$	PBu_3	Toluene	100			
12	$Cu(OTf)_2$	$P(OEt)_3$	Toluene	100			
13	$Cu(OTf)_2$	$P(OEt)_3$	CH_2Cl_2	100			
14	$Cu(OTf)_2$	$P(OEt)_3$	Et_2O	100			
15	$Cu(OTf)_2$	$P(OEt)_3$	THF	41	100		
16	$Cu(OTf)_2$	$P(OEt)_3$	CH_3CN	23	30	36	80

The results summarised in Table 1 represent some of the most efficient methodology for organozinc conjugate addition with only 0.5% catalyst loading and 10 minutes reaction time for quantitative yields. Though the ligands used were achiral with one exception, the proof that ligand, solvent, and copper salt all have intimate effects on catalyst reactivity shaped future thought within copper catalysed conjugate addition discourse.

Some of the general families of ligands used for dialkylzinc conjugate additions are displayed in Figure 9.[62-69]

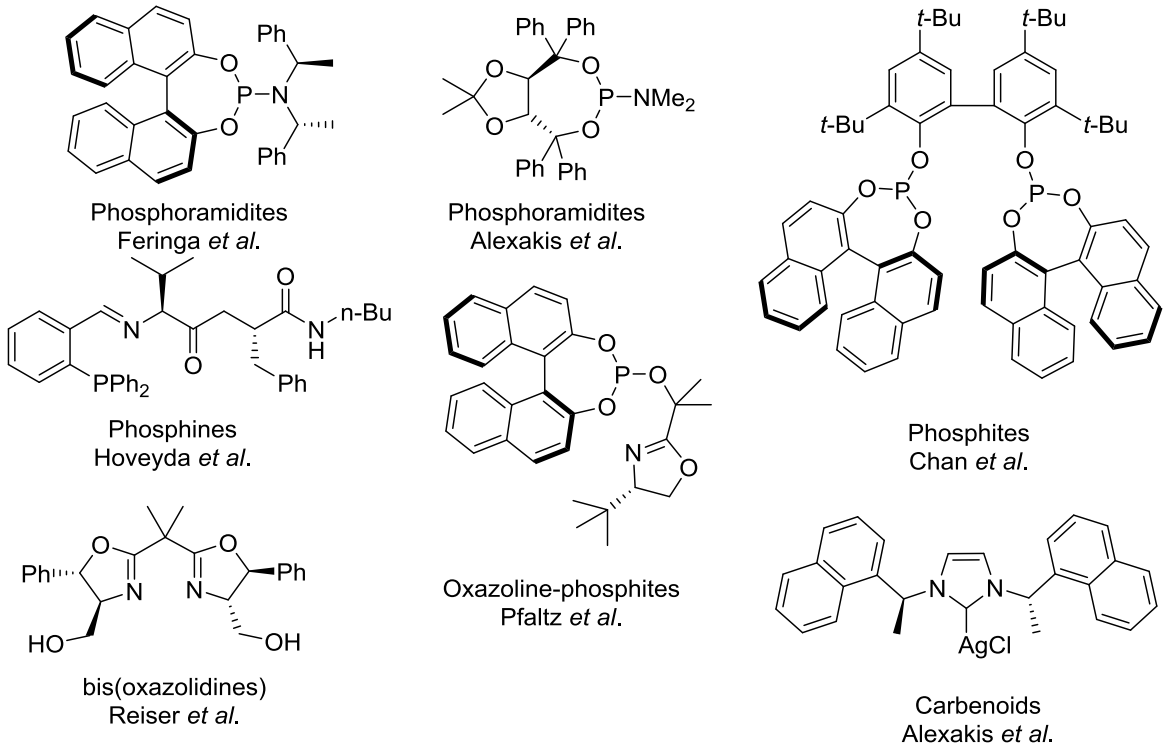


Figure 9 – Overview of some of the most commonly used ligands for copper catalysed conjugate addition

Discussion of all available ligands for copper-based conjugate addition falls well outside the scope of this thesis due to its huge range. However special attention will be given to the class of ligands known as 'Feringa ligands' in honour of their creator, Prof. Ben Feringa, in Section 1.3.4.

One widely accepted catalytic cycle for copper catalysed conjugate addition is provided in Figure 11.[52,70] It is worth mentioning at this time that the existence of a Cu^{III} intermediate **E** has long been postulated but until recently had not been detected outside of theoretical calculations.[71] Alternative suggestions exist such as carbocupration[72] as opposed to a Cu^{III} intermediate, but there is not space here to discuss fully the very nuanced area of thought on

copper catalyst intermediates and transition state structures. A square planar Cu^{III} intermediate has been examined computationally (Figure 10).[71]

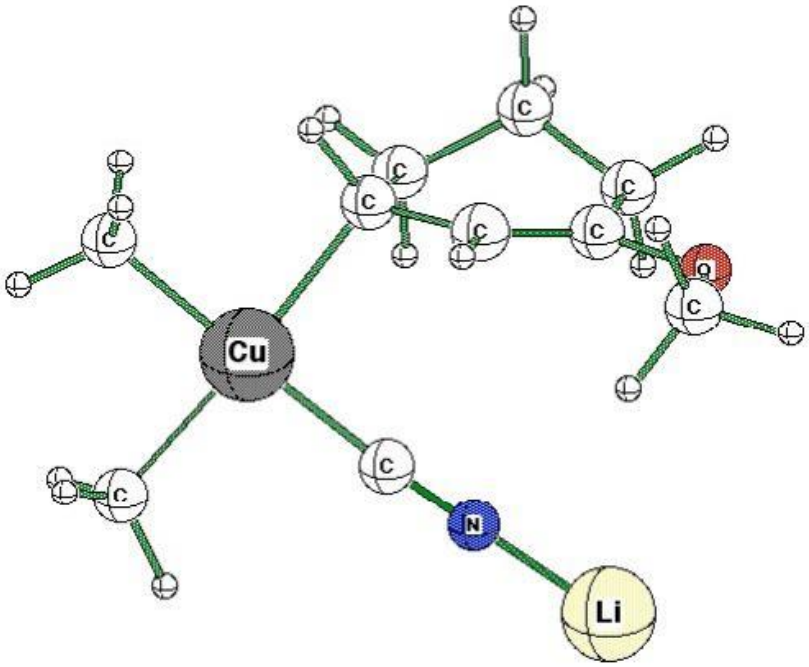


Figure 10 – Low energy DFT conformation of a calculated square planar Cu(III) complex as reported in the literature[71]

The cycle begins with the reduction of Cu^{II} salts to Cu^{I} salts by the organometallic reagent to form complex **A**. Insertion of the enone to the most oxophilic site (in this case, Zn) gives **B**. in order for the catalytic cycle to proceed, the *cuprate* (See Section 1.3.2) **C** must be formed from the stoichiometric nucleophile. Removal of the labile ligand **L** allows for π-co-ordination between the enone and the Cu atom to form **D**, followed by rapid oxidative addition to form **E** (formally a Cu^{III} species) and then reductive elimination through to enone complex **F**. Enolate dissociation returns complex **A** to the catalytic cycle to turn over again.

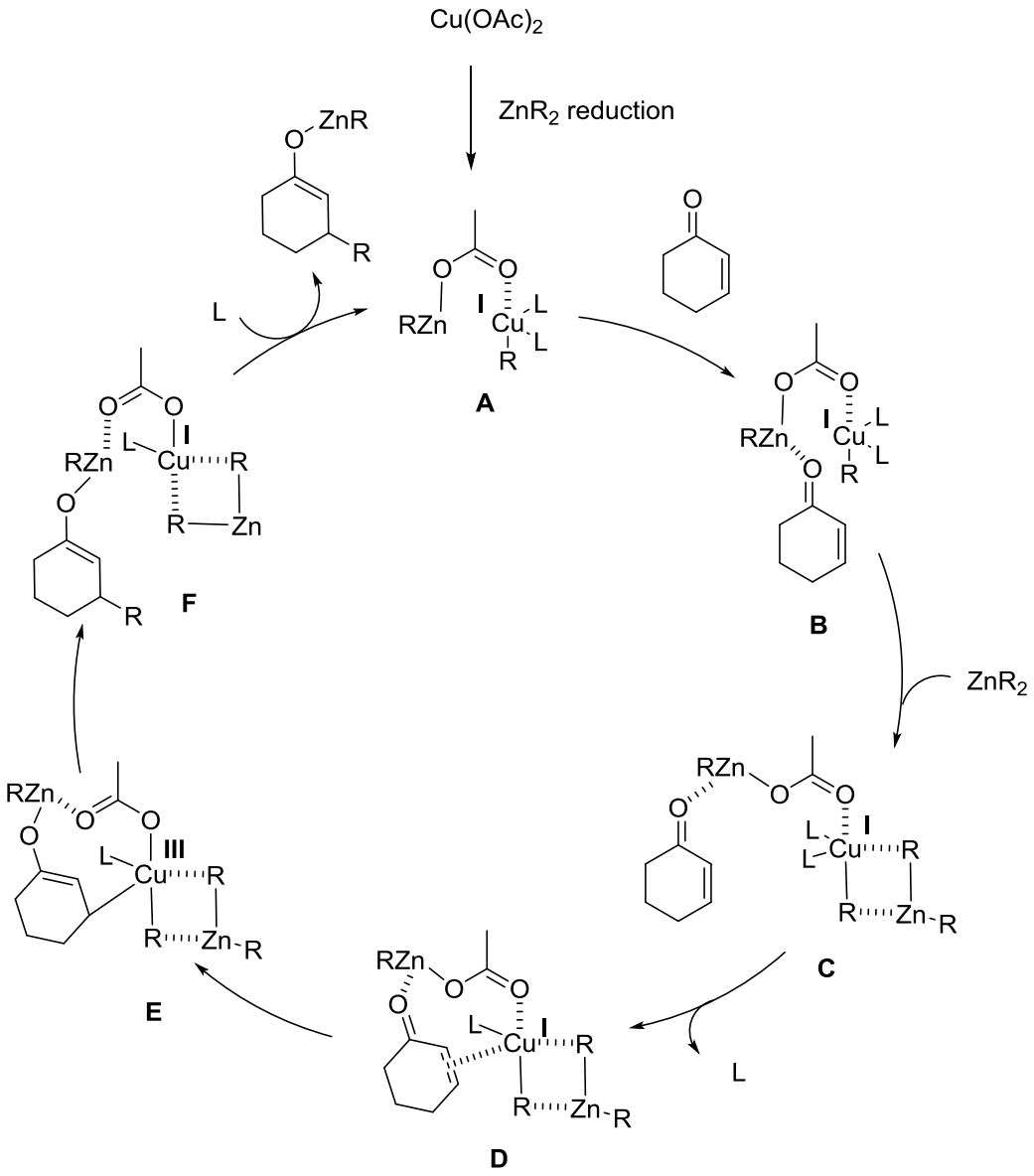


Figure 11 – The proposed catalytic cycle for copper-catalysed zinc-based conjugate addition to enones

Schrader *et al.* have shown that the rate determining step is the reductive elimination **E-F**[73] and for phosphorus ligands, the rate of reaction is directly correlated with the number of P-O bonds (as opposed to P-N or P-C). Section 1.3.4 discusses this in more detail in the context of phosphoramidite-based ligands.

1.3.2 Organomagnesium and organolithium-derived nucleophiles

Organomagnesiums and organolithiums in the presence of copper salts form 'cuprate' species which are composed of fragments of the general formula $[M(CuR_2)]_n$ (M= Li, Mg).[72] The nature of the copper salt used to form the cuprate determines how many equivalents of precursor organometallic reagent are required to form the active cuprate. In the case of weakly binding counterions (CuX; X = Cl, Br, I, OTf etc.), two equivalents of organometallic reagent are required to form the reactive species $[M(CuR_2)]_n$ but in the case of strongly binding counterions (CuX; X = CN, RS, R_2P), $[M(CuRX)]_n$ is formed from only one equivalent of precursor organometallic reagent.[72] The initial discovery of these reagents comes from Gilman *et al.*[74] in 1952, where the synthesis of $[Li(CuMe_2)]$ is described. Compounds with the formula $[Li(CuR_2)]$ (R = alkyl, aryl) have been hitherto referred to as 'Gilman cuprates'. The two equivalents of methyl lithium required to form the Gilman cuprate were not used out of choice; initial efforts to isolate the insoluble yellow polymeric $[CuMe]_n$ ended in failure with the warning:

> *"When the methylcopper compound was dried and exposed to the air it exploded violently. It would probably be dangerous to isolate more than small quantities of the material."*

This, along with the observation that it decomposed to form metallic copper and ethane, steered cuprate research towards the more stable and easily used $[M(CuR_2)]_n$ complexes. The solid state structures of some cuprates have surfaced,[75] the most famous of which is the etherated complex $[Li(CuPh_2)\cdot(OEt_2)]_2$[76] generated from LiPh and CuI (Figure 12). The lability of the $[LiCuR_2]$ fragments of dimers of this kind in solution[77] is presumably the factor that causes cuprates to react in similar fashions to one another. That being said, it would be

remiss to ignore the effect of solvent, counterion, temperature etc. on the solid and solution structures and reactivity of cuprates and there exist reviews that attempt to address these differences.[72]

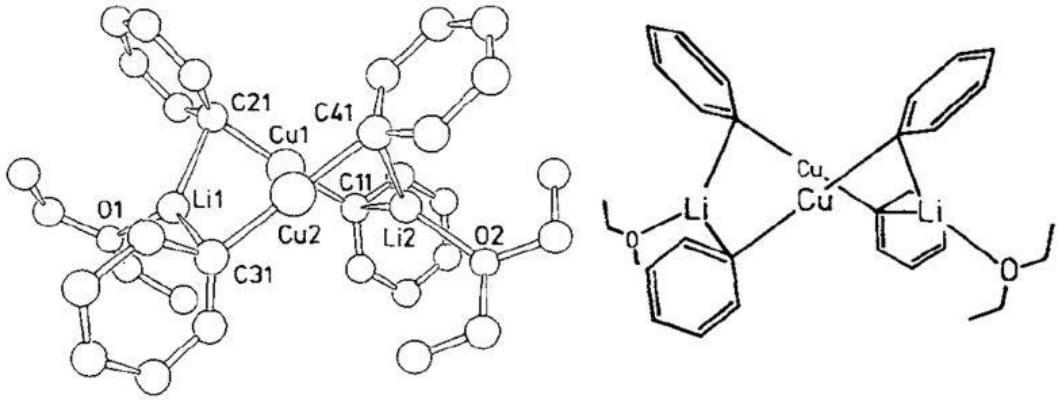
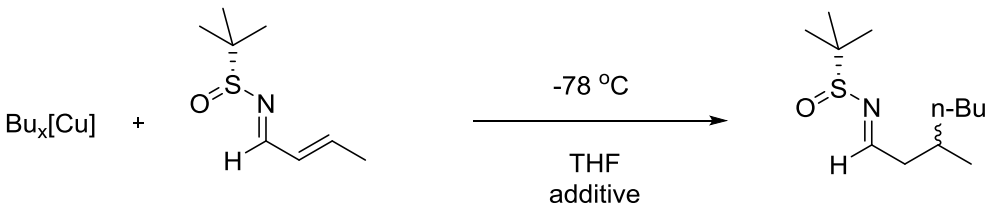


Figure 12 – Crystal structure of $[Li(CuPh_2)\cdot(OEt_2)]_2$ as reported in the literature[76]

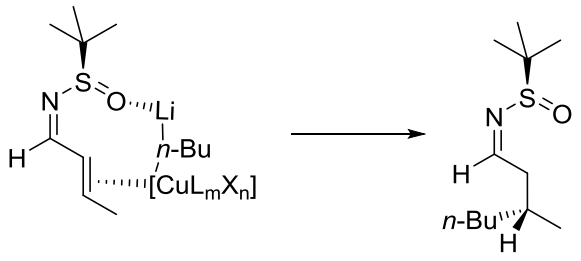
Organocuprate conjugate addition research has largely focused on the use of chiral electrophiles as opposed to chiral nucleophiles.[78] Sulfinimines themselves have been used as chiral electrophiles in the 1,4-conjugate addition of Gilman cuprates in 2005 by Ellman *et al.* (Scheme 26).[26] The results of this study show that copper-catalysed conjugate addition does indeed occur with sulfinimines in the presence of Gilman cuprates, albeit with moderate selectivities (Table 2, entries 10 and 17). These results were rationalised by an argument of simple facial selectivity (Scheme 27), although no explanation for inversion of selectivity with CuOAc was given (Table 2, entry 17).



Scheme 10 – 'Butyl' cuprate nucleophile addition to sulfinimines

Table 2 – Results of screening conditions for the addition of 'butyl' Gilman-type nucleophiles as reported by Ellman *et al*.[13]

entry	Cu salt	BuLi equiv.	additive	% yield	*d.r.*
1	CuI	2	None	52	1:1
2	CuI	2	$BF_3{\cdot}OEt_2$	78	3:1
3	CuI	1	$BF_3{\cdot}OEt_2$	15	7:3
4	CuCN	2	$BF_3{\cdot}OEt_2$	71	4:1
5	CuCN	1	$BF_3{\cdot}OEt_2$	62	4:1
6	CuBr	2	$BF_3{\cdot}OEt_2$	92	3:1
7	CuBr	1	$BF_3{\cdot}OEt_2$	48	4:1
8	$CuBr{\cdot}SMe_2$	2	$BF_3{\cdot}OEt_2$	64	3:1
9	$CuBr{\cdot}SMe_2$	1	$BF_3{\cdot}OEt_2$	4	3:2
10	CuCN	1	PBu_3	73	17:3
11	CuCN	2	PBu_3	65	7:3
12	CuCN	1	PCy_3	48	2:1
13	CuCN	1	PPh_3	52	3:1
14	CuI	1	PBu_3	59	3:1
15	$CuBr{\cdot}SMe_2$	1	PBu_3	15	3:1
16	$(CuOTf)_2{\cdot}$benzene	1	PBu_3	n.d.	
17	CuOAc	1	PBu_3	55	3:17
18	CuCN	1	PBu_3	57	2:1
19	CuCN	1	PBu_3	48	2:1

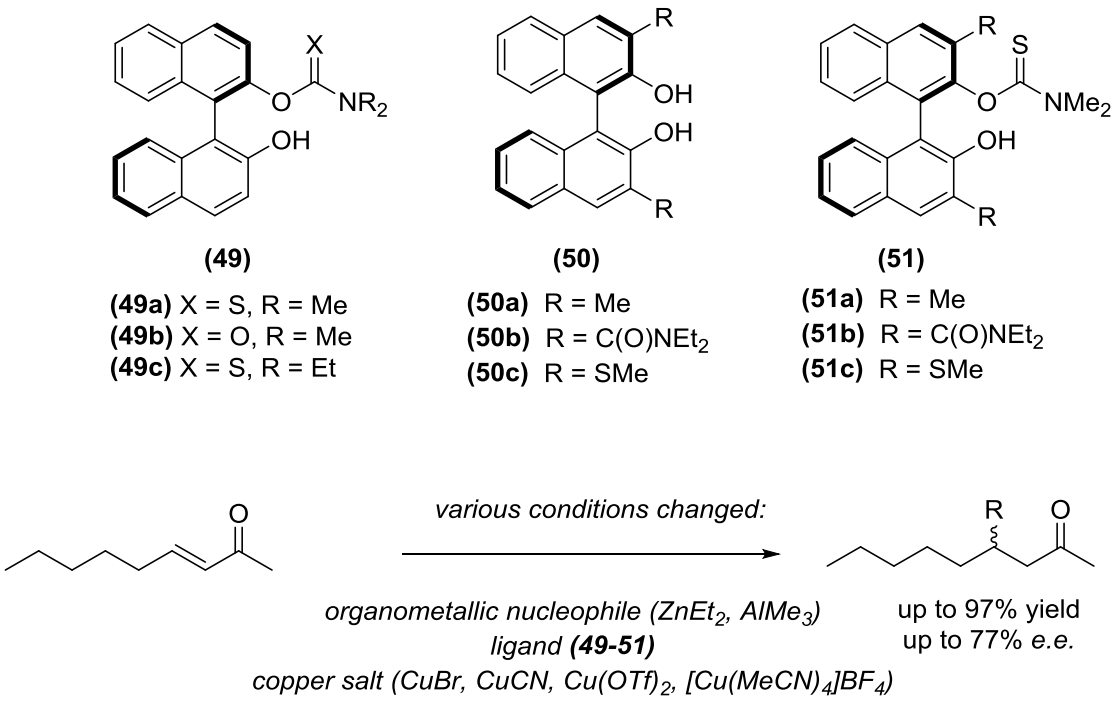


Scheme 11 – Rationalisation for observed selectivity

To our knowledge, this is the only example of a copper-catalysed conjugate addition of an unstabilised organometallic nucleophile to a sulfinimine that exists in the literature.

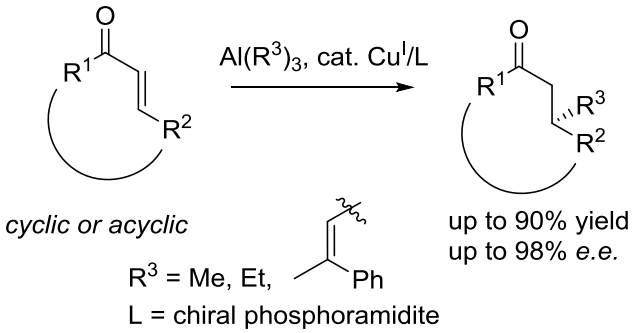
1.3.3 Organoaluminium nucleophiles

There has been a recent trend towards using organoaluminium nucleophiles instead of the more classic diorganiczinc or cuprate nucleophiles. Due to the strongly Lewis acidic aluminium, it may be expected that reaction rates are increased. In 2000, Woodward *et al.*[79] provided promising results for the addition of $AlMe_3$ (amongst other nucleophiles) to linear *trans*-3-nonen-2-one in the presence of BINOL-derived ligands (Scheme 28).



Scheme 12 – Ligand accelerated copper-catalysed conjugate addition to *trans*-3-nonen-2-one

This was followed up in 2005 by Woodward, Alexakis and co-workers,[80] to provide a more robust methodology that was applicable to cyclic and acyclic enones alike (Scheme 29). Additionally, this work included one of the first additions of a vinylalane nucleophile starting from a carboalumination, indicating a route towards the use of new and unconventional nucleophiles for copper-catalysed conjugate addition.



Scheme 13 – Expansion of substrate and nucleophile scope for aluminium-based copper-catalysed conjugate addition

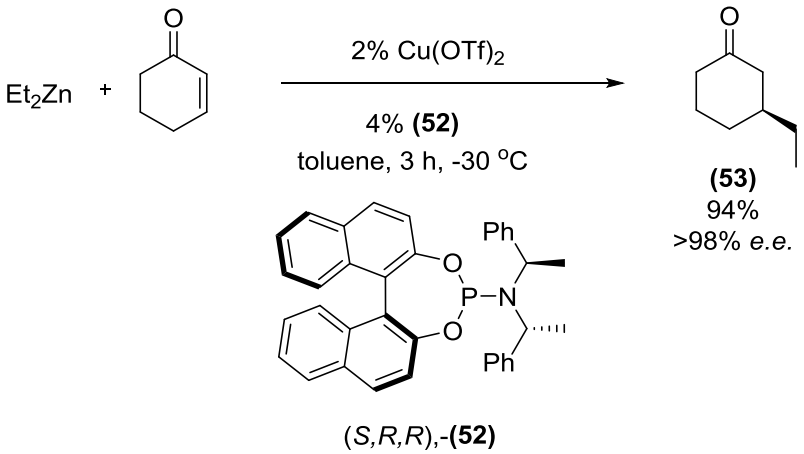
The substrate scope for copper-catalysed 1,4-conjugate addition of alkylaluminium reagents has continued to increase, albeit perhaps slowly. In 2015, Woodward *et al.*[81] built upon existing work and demonstrated that α-alkylidene cycloalkanones were appropriate electrophiles when paired with a phosphoramidite/Cu-based catalyst. The more synthetically relevant 'methyl' addition from trimethyl aluminium (up to 95% *e.e.*) was shown to be more successful than the 'ethyl' addition from triethyl aluminium.

Due to their ubiquity, it is now worth considering chiral phosphoramidites in more detail.

1.3.4 Chiral 2,2'-binapthol-derived phosphoramidites: 'Feringa ligands'

Feringa's phosphoramidites have an important place in the history of copper-catalysed conjugate addition. In 1997, it was demonstrated that complete stereocontrol could be achieved during the addition of diethyl zinc to cyclohexenone by incorporating the chiral and sterically demanding (*R, R*)-bis(1-phenylethyl)amine fragment together with *unsubstituted* (*S*)-2,2'-binapthol ((*S*)-BINOL) in a phosphoramidite (Scheme 30).[82] This resulted in a matched catalyst system that tolerated substituted cyclohexenones and alternative zinc nucleophiles. Considering the fact that at that time, Alexakis *et al.* had achieved *e.e.* values of only 33% with phosphoramidite-based copper-catalysed conjugate addition, it can be easily

seen how remarkable this class of ligands must be. In addition to providing ample opportunity for fine-tuning of the formed catalyst, Feringa ligands are easy to synthesise from simple starting materials allowing a synthetic chemist rapid access to a matched pair catalyst system.[63]



Scheme 14 – Application of Feringa lingands to asymmetric copper-catalysed conjugate addition

The X-ray structures of Feringa ligands and ligand-metal complexes have been published in recent years and all show similar features.[83-86] The geometry about the phosphorus and nitrogen atoms are tetrahedral and planar, respectively. This implies that formally the phosphorus atom is sp^3 hybridised, and the nitrogen atom is sp^2 hybridised. The M-P-N angle is typically between 113 – 117 ^{o}, and generally there is no C_2 symmetry anywhere in the molecule when a metal is not complexed. There is precedence for this lack of symmetry in the form of DFT calculations[87] that show that the ground state of Feringa's ligands **(52)** have a twisted P-N bond with asymmetrical arrangement of the phenyl groups of the amine fragment (Figure 13).

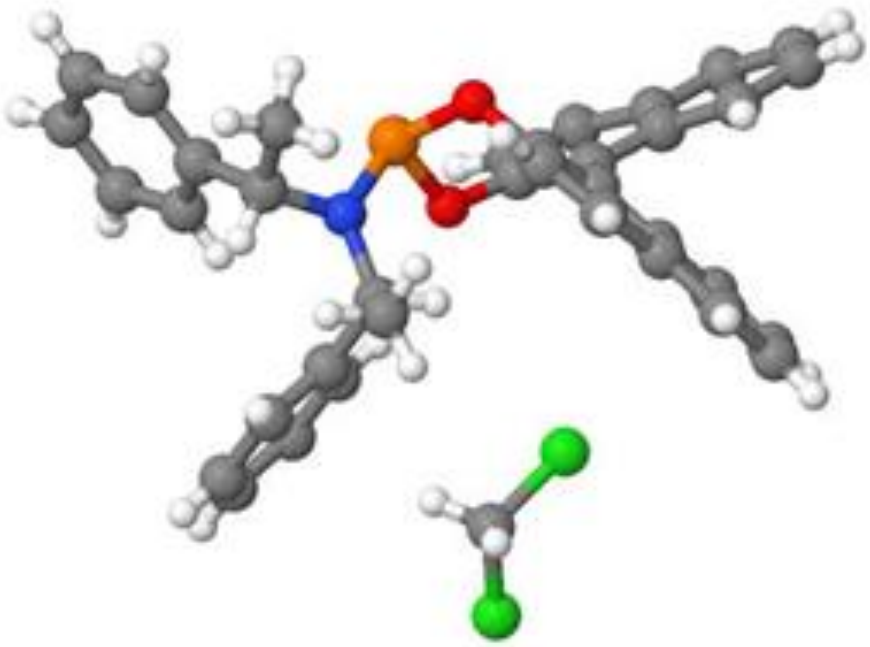


Figure 13 – Lowest calculated energy DFT conformmation of Feringa's ligand (52) as reported in the literature [81]

Finally, there exist some rhodium complexes (such as $[Rh(MonoPhos)_4]BF_4$) that *do* have C_2 symmetry and also feature a severe P-N bond twist together with alignment of the small dialkyl amine bonds with the P-Rh bond, indicating some degree of hyperconjugation (Figure 14).[84,85]

Electronically, Feringa ligands are both strong σ-donor and π-acceptor ligands.[88] Observing the C=O stretching frequencies of ligand complexes with transition metal carbonyls[89-91] reveals that phosphorus-based ligand σ- and π-acceptor ability is closely linked to the substituents that are directly bonded to the phosphorus atom.

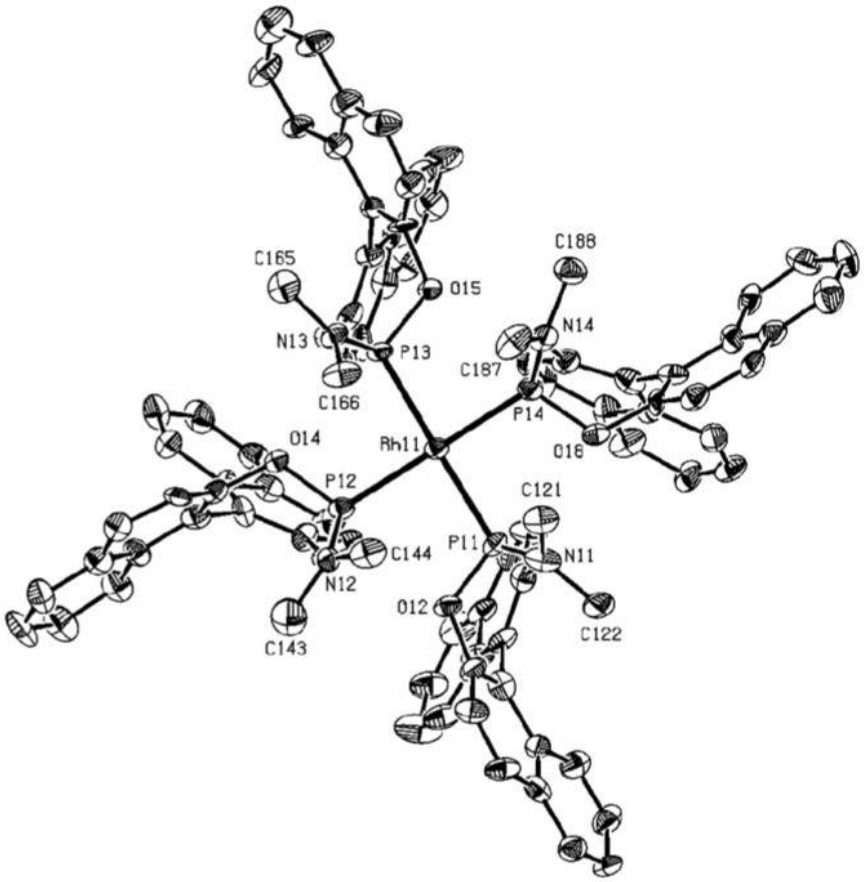


Figure 14 – Cystal structure of [Rh(MonoPhos)$_4$]BF$_4$ as reported in the literature[78, 79]

Tetrahedral, sp^3-hybridised phosphorus ligands are strong σ-donors.[91,92] Since Feringa ligands contain a tetrahedral phosphorus atom, it may be expected that phosphoramidites (2 × P-O bonds, 1 × P-N bond) are also strong σ-donors, but weaker σ-donors than their phosphine cousins (3 × P-C bonds, e.g. PBu_3) due to the electron withdrawing nature of the three electronegative elements directly bonded to the phosphorus atom.[91]

With regards to π-acceptor ability, phosphoramidites lie between weakly accepting phosphines (3 × P-C bonds) and strongly accepting phosphites (3 × P-O bonds), having closer kinship with their phosphite cousins.

Chapter Two

Addition of ‘ethyl’ nucleophiles to model sulfinimines

2.1 The model α,β-unsaturated sulfinimine

2.1.1 Choice of the precursor α,β-unsaturated substrate

The choice of initial substrate was not anticipated to be limited by issues with stability. Almost any sulfinimine precursors could have been chosen, but for the sake of simplicity the compounds **(54)** and **(55)** were chosen (Figure 15).

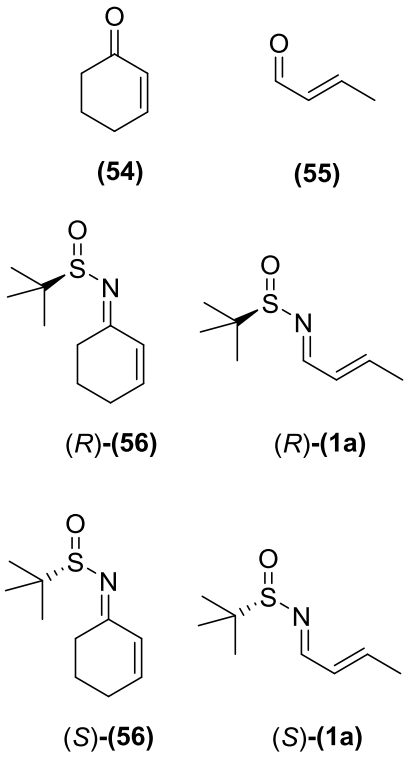


Figure 15 – Overview of target substrates

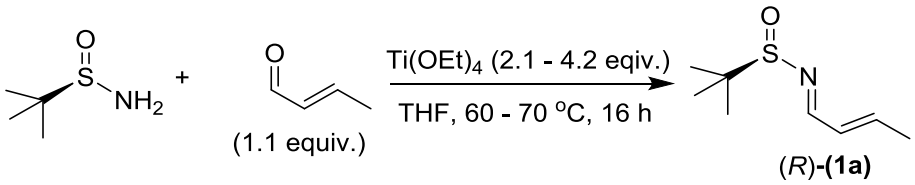
Compounds **(54)** and **(55)** are two of the simplest possible acyclic or cyclic prochiral Michael acceptors that are able to form a sulfinimine. Compounds **(56)** and **(1a)** contain no groups other than the sulfinimine moiety that are connected to the π-system in a conjugated manner. There can exist differences in reactivity between acyclic and cyclic enone Michael acceptors in copper-catalysed conjugate addition reactions, and it was thought that these differences would also be present in their substituent sulfinimines. Hence, both cyclic and acyclic targets

were selected. These sulfinimines are also known compounds, and their syntheses are reported in the literature.[26]

2.1.2 Synthesis of the α,β-unsaturated sulfinimines

Stocks of sulfinimines **(1)** and **(56)** first had to be prepared. An optimised process was obtained by altering the reaction temperature and $Ti(OEt)_4$ equivalents to increase yield to 61% (Table 3, entry 3), allowing a larger stock to be synthesised.

Table 3 – Condensation of crotonaldehyde with (*R*)-*tert*-butyl sulfinamide to form sulfinimine (*R*)-(1a)



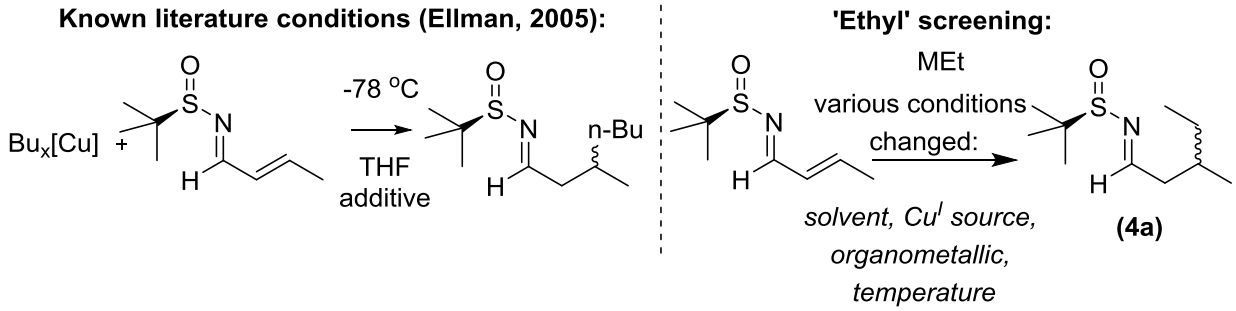
Entry	$Ti(OEt)_4$ equivs.	Temperature / °C	Pure yield of **(1a)** / %
1	2.1	60	45
2	2.1	70	52
3	4.2	60	61
4	4.2	70	58

When these conditions were applied to cyclohexenone, there were a number of difficulties. One major issue was the apparent low reactivity of cyclohexane with (*R*)-*tert*-butyl sulfinamide in the presence of very strong desiccants [e.g. $Ti(OEt)_4$] to drive the reaction to completion. A second major difficulty was that chromatographic separation proved detrimental due to the tendency of **(56)** to hydrolyse. Other purification methods (e.g. distillation and crystallisation) proved to be unfruitful and impractical in our hands. Synthesis of **(56)** was abandoned temporarily due to its associated failures, and since there was a large

quantity of **(1a)** available there was sufficient material to continue study on copper-catalysed conjugate addition.

2.2 Addition of 'ethyl' organometallic nucleophile

A comparison of the proposed screening vs. the known literature precedent is shown in Scheme 32.

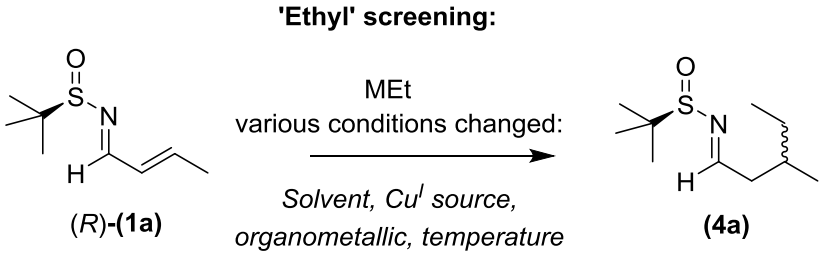


Scheme 15 – Comparison of conditions known in the literature with proposed conditions

With a stock of **(1a)** available, we were able to move on to the reaction of interest. Ellman's conditions for the addition of *n*-Bu nucleophiles are known,[26] and it was surmised that the addition of 'Et' nucleophiles could occur under similar conditions. It was decided that for this initial condition screening, no ligand would be present. The reasons for this were twofold: Firstly, the sulfinimine moiety is a chiral auxiliary and can act as a ligand itself.[93] Therefore, the chiral information had the possibility to be transmitted to the β-carbon *via* achiral materials. Secondly, Ellman's conditions used additives such as $BF_3{\cdot}OEt_2$ and PCy_3 and found little to no difference in reactivity.[26] Both polar (EtLi, EtMgBr) and more covalent ($ZnEt_2$, $AlEt_3$) nucleophiles were chosen and screened in conditions typical to those usually reported in the literature and the results are displayed in Table 4. Unless otherwise specified, 'traces' refers to <1% desired **(4a)** and significant returned starting material present in the

crude proton NMR spectrum. The full synthetic procedure is given in general procedures 3 and 4 (Chapter 3).

Table 4 – Screening of addition of 'ethyl' nucleophiles to substrate (*R*)-(1a)



Entry	Copper(I) iodide (equiv.)	MX (3 equiv.)	Solvent	Temperature/ ^{o}C	Yield of **(4a)**[a]/ %
1	0.05	EtMgBr	THF	-45	traces
2	1.5	EtMgBr	THF	-45	traces
3	1.5[d]	EtMgBr	THF	-45	traces
4	1.5	EtMgBr	THF	-78	traces
5	1.5	EtMgBr	THF	-10	traces[b]
6	0.03	$ZnEt_2$	THF	-45	n.d[c]
7	1.5	EtLi	THF	-45	traces
8	0.03	$AlEt_3$	THF	-45	10
9	1.5	EtMgBr	19:1 Toluene:THF	-45	54
10	1.5	EtMgBr	Et_2O	-45	27
11	1.5	EtLi	19:1 Benzene:THF	-45	19

[a] Isolated yield of 1,4-addition product. [b] Crude mixture contained significant amounts of 1,2-addition products. [c] The crude mixture was distinct from the starting sulfinimines but did not appear to be desired products nor 1,2-addition products. [d] ($CuBr{\cdot}SMe_2$) was used in place of CuI.

Entries 2, 4, and 5 show no difference in yield as the temperature was varied, however as the temperature was raised to -10 ^{o}C, the starting material (*R*)-**(1a)** was consumed and the crude ^{1}H NMR spectrum contained a broad new peak at ~4.0 ppm that could feasibly have been the sulfinamide 1,2-addition product. This would be as expected of Grignard-based copper-catalysed nucleophiles; enones typically display competing reactivity with alkyl lithium and

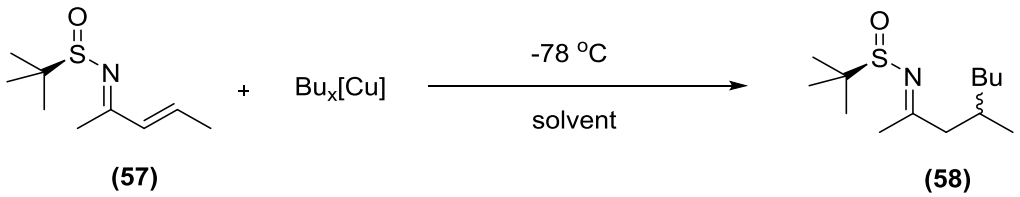
alkyl Grignard reagents at higher temperatures (-10 ^{o}C to r.t.), and by-product formation – including 1,2-additions – is common.[94] Entries 2, 6, 7, and 8 show a comparison between nucleophile sources. Zinc- and aluminium-based nucleophiles are not known to form Gilman cuprates, so only a catalytic quantity of copper salt was used. The cuprate formed from ethyl lithium did not change the yield of desired **(4a)** with comparison to that formed from ethyl magnesium to any significant degree.

The copper catalysed addition of diethyl zinc, however, did show a difference in reactivity as the starting (*R*)-**(1a)** was mostly consumed. Attempted chromatographic purification of entry 6 appeared not to separate the mixture, yielding no new tractable material and only reduced amounts of the impure starting material (*R*)-**(1a)** eluting at R_f ~0.45 (hexanes:EtOAc (4:1)) was recovered in a yield of 22 %. Given that metallic copper precipitated during this reaction, it can be assumed that the active catalyst either decomposed or did not form.

The first indication of success (Table 4, run 8) allowed the desired 1,4-addition product to be identified and an isolated yield of **(4a)** of 10% attained. This is noteworthy, as additions of alkyl aluminium reagents to Michael acceptors can be performed at much warmer temperatures, sometimes up to room temperature.[80,95]

Comparison of entries 2, 9, and 10 shows a strong effect on yield as a function of solvent polarity. The less polar Et_2O gives an isolable yield of 27% in comparison to THF which gave only traces of desired compound in the crude proton NMR spectrum. In turn, the even less polar toluene/THF mixture gives the highest isolable yield of 54%. Comparison of entries 11 and 7 concurs with this observation, showing a direct positive effect on the yield of **(4a)**. This is as expected, as main group organometallics often show increased Lewis acidity in less polar solvents which is reflected in their reactivity. Ellman's results for additions to ketimines are analogous in this regard, and also show an enhanced reactivity in less polar solvents (Table 5).[26]

Table 5 – Effect of solvent on the 'butyl' nucleophilic copper-catalysed 1,4-conjugate addition to ketimine (70)



(57) **(58)**

Entry	Cu salt	BuLi equiv.	Solvent	Yield of **(71)** /%	*d.r.*
1	CuI	2	Et_2O	71	2:1
2	CuI	2	THF	23	86:14

2.3 Initial conclusions

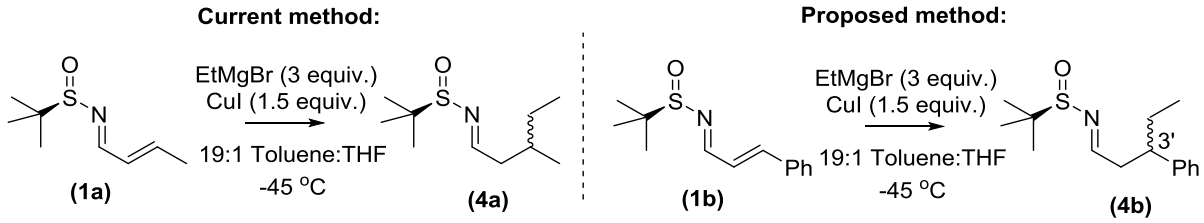
The results in Table 4 show some important observations. The use of magnesium-based cuprate nucleophiles has shown the highest success under these conditions. It appears that highly co-ordinating solvents have an extremely detrimental effect on the yield of the reaction. This may not be entirely unexpected, as the Lewis acidic counter ion has an activating effect upon enones in copper-catalysed conjugate addition, and the reaction is known not to proceed at all if the counter ion is sequestered.[72] The mild success of alkyl aluminium addition was extremely pleasing, and is indicative of an available alternative with substrates for which Gilman-type magnesium cuprates are not appropriate.

With comparison to Ellman's results (Table 2), the results in Table 4 show that 'ethyl' nucleophiles are significantly less reactive under almost identical conditions. The difference in reactivity was surprising, as the differences in M-C bond strength between M-$(CH_2)_nCH_3$ compounds does not differ to such a dramatic degree when n > 0.[96-98] The difference in reactivity that was observed is usually seen between n = 0 and n = 1 compounds, i.e. M-Me *versus* M-Et bond strengths. Nevertheless, similar yields were obtained in less polar solvents at higher temperatures.

For the compound **(4a)**, *d.r.* value determination was problematic – signal overlap meant that only approximate values could be attained. An approximate ratio of 3:2 was obtained (Table 4, entry 9), although without complete separation of the signals in the NMR and HPLC data this value remains only approximate.

2.4 Proposal for a new test substrate

It was clear that a substrate which gave more easily analysed diastereomeric ratio data was needed. Thus, the conditions used in entry 9, Table 4 were to be applied to a different model sulfinimine, **(1b)**.

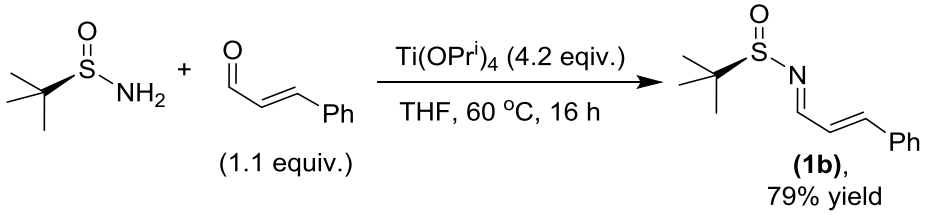


Scheme 16 – Proposed change of substrate to sulfinimine (4b)

The chiral centre generated in compound **(4b)** is significantly different to that attained in compound **(4a)** in terms of the magnetic environments of the diastereotopic protons. It was thought that the ring current[99-101] that is produced by the phenyl moiety would provide a significant enough shift in the ^{1}H NMR spectrum of the protons *geminal* and *vicinal* to the (3')C atom to allow accurate *d.r.* value determination from NMR alone. The compound **(4b)** is also 40.0 D_a heavier than **(4a)**. This normally leads to different elution times on a HPLC column, and so it opens up HPLC as a method for *d.r.* value determination.

2.4.1 Synthesis of (*R*)-(*E*)-*N*-((*E*)-3'-phenylprop-2'-en-1'-ylidene)-2-methylpropane-2-sulfinamide (*R*)-(1b) and addition of Gilman-type 'ethyl' nucleophile

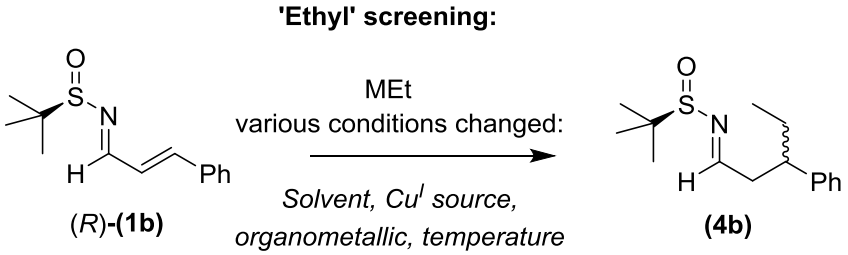
Synthesis of **(1b)** by the optimised conditions given in Section 2.1.2 (Table 3, General procedure 1) yielded 15 g of **(1b)** (79%) as brilliantly yellow, hazelnut-scented needles.



Scheme 17 – Condensation of cinnamaldehyde with (*R*)-*tert*-butyl sulfinamide to form sulfinimine (1b)

High throughput screening of the 'ethyl' addition using **(1b)** as the substrate and analysed by ^{1}H NMR spectroscopy, the results of which are presented in Table 6. Because clear high conversion to **(4b)** was sought, only qualitative data for less successful reactions were obtained.

Table 6[a] – Screening of addition of 'ethyl' nucleophiles to substrate (*R*)-(1b)



Entry	Copper(I) iodide (equiv.)	MX (3 equiv.)	Solvent	Temperature/ °C	Yield of **(4b)**/%
1	1.5	EtMgBr	Et_2O	-45	1
2	0.05 ($CuBr.SMe_2$)	EtMgBr	THF	-5	17
3	0.05 ($CuBr.SMe_2$)	EtLi	THF	-5	Complex mix[b]
4	0.05 ($CuBr.SMe_2$)	Et_2Zn	THF	-5	Complex mix

5	0.05 ($CuBr.SMe_2$)	Et_3Al	THF	-5	-[c]
6	1.5 ($CuBr.SMe_2$)	EtMgBr	THF	-5	Complex mix
7	1.5 ($CuBr.SMe_2$)	EtLi	THF	-5	-
8	1.5 ($CuBr.SMe_2$)	Et_2Zn	THF	-5	Trace[d]
9	1.5 ($CuBr.SMe_2$)	Et_3Al	THF	-5	-
10	3 ($CuBr.SMe_2$)	EtMgBr	THF	-5	Trace
11	3 ($CuBr.SMe_2$)	Et_2Zn	THF	-5	Trace[d]
12	3 ($CuBr.SMe_2$)	Et_3Al	THF	-5	-
13	1.5	EtMgBr	1:0 Toluene:THF	-20	-
14	1.5	EtMgBr	9:1 Toluene:THF	-20	Trace
15	1.5	EtMgBr	6:4 Toluene:THF	-20	Trace
16	1.5	EtMgBr	1:1 Toluene:THF	-20	-
17	1.5	EtMgBr	1:0 Toluene:THF	r.t.	Complex mix
18	1.5	EtMgBr	6:4 Toluene:THF	r.t.	Trace
19	1.5	EtMgBr	1:1 Toluene:THF	r.t.	-
20	1.5	EtMgBr	4:6 Toluene:THF	r.t.	-
21	1.5	EtMgBr	3:7 Toluene:THF	r.t.	-
22	1.5	EtMgBr	2:8 Toluene:THF	r.t.	-
23	1.5	EtMgBr	1:9 Toluene:THF	r.t.	Trace
24	1.5	EtMgBr	0:1 Toluene:THF	r.t.	-
25	1.5	EtMgBr	MTBE	r.t.	Trace

[a] 25 of >45 runs shown. When $CuBr.SMe_2$ is used instead of CuI, this is indicated. [b] 'Complex mix' refers to a resultant mixture that is neither starting material nor desired **(4b)**. [c] Dashed entries returned only starting **(1b)**. [d] Liberated a metallic copper mirror during reaction.

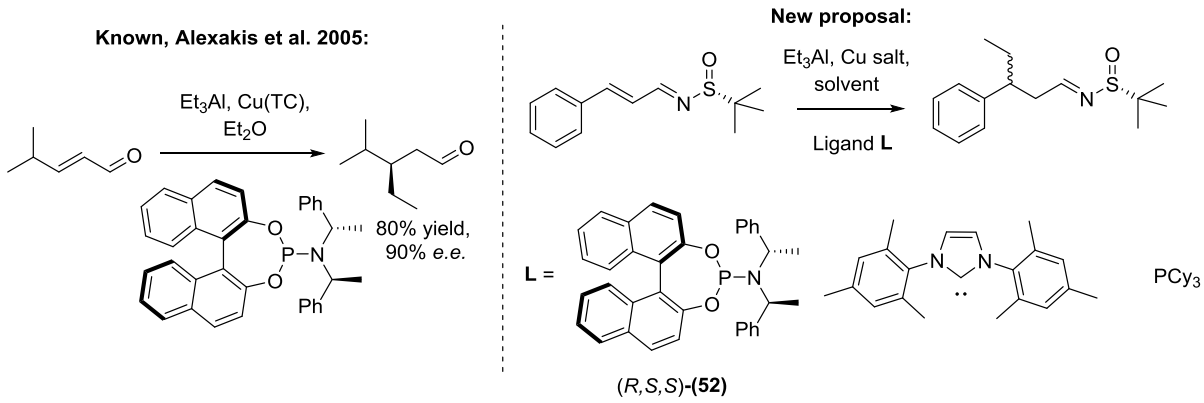
Within general procedures 3 and 4 (Chapter 3) are contained full procedural details.

Application of conditions used in Table 4, entry 9 did not yield any desired **(4b)**. Variation of copper salt, salt equivalents, temperature, nucleophile, and solvent all ended with either no reaction or an unintelligible, unpurifiable mixture that gave a mixture of poorly defined signals in the crude ^1H NMR spectrum. The highest obtained yield was the very low value of 17% (Table 6, Entry 2). Zinc-based nucleophiles – when in the presence of higher

equivalents of copper salts – caused the reduction of the copper salt to occur, precipitating a beautiful copper mirror. Unsurprisingly, as the temperature was increased to try to improve reactivity, competing 1,2-addition side reactions became more pronounced, with broad peaks appearing in the ^{1}H NMR spectrum in the region ~4.1 ppm that could feasibly have been the sulfinamide 1,2-addition product. Disappointingly, there appeared to be no enhanced reactivity with trialkyl aluminium nucleophiles. This methodology does not appear to be applicable to compound **(1b)**. It was thought that ligandless methodology produced 'ethyl' nucleophiles that were simply too unreactive with respect to 1,4-addition.

2.4.2 Application of triethyl aluminium nucleophiles to (*R*)-(*E*)-*N*-((*E*)-3'-phenylprop-2'-en-1'-ylidene)-2-methylpropane-2-sulfinamide (*R*)-(1b)

Taking note of the work done by Alexakis *et al*. (Scheme 38) in 2005,[80] a new set of screening conditions was proposed.



Scheme 18 – Comparison of known literature procedure with newly proposed conditions

Addition of triethyl aluminium nucleophiles to enones in the presence of Feringa ligand (*R,S,S*)-**(52)** is known to proceed in good yield and produce high enantiomeric excess values.

Compound **(1a)** showed at least some affinity for aluminium-based nucleophiles (Table 4, entry 8), so it was reasoned that a set of conditions focused solely on ligand-accelerated aluminium-based copper-catalysed conjugate addition may produce a positive result when applied to compound **(1b)**. Thus, the three ligands depicted in Scheme 38 were chosen due to their distinctly different properties and were reacted under the conditions given in Table 7. The yields and *d.r.* values were determined by crude ^{1}H NMR spectra integrated against an internal standard.

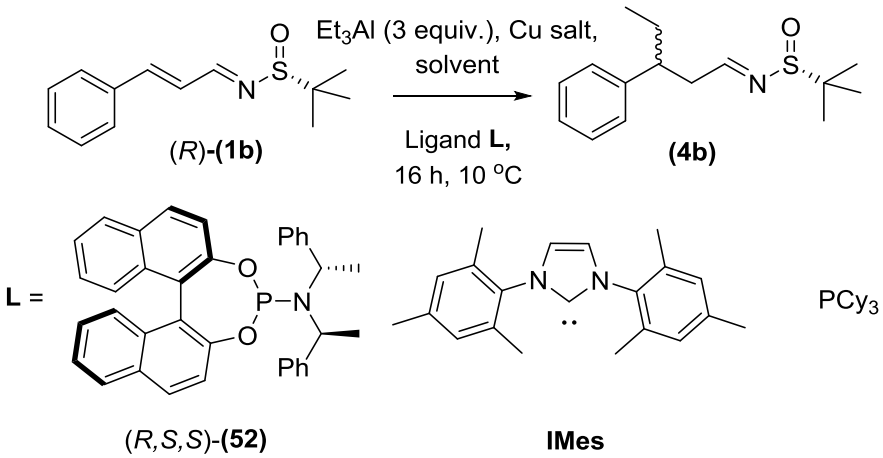
The variation of integrations of the triplet signal at 8.02 ppm and the double doublet signal at 7.97 ppm in the crude ^{1}H NMR spectra when integrated against an internal standard (a known amount of 1,3,5-trimethoxybenzene) was interpreted as the variation of the solution yields of (*R*)-**(4b)** and (*S*)-**(4b)** resulting from the copper-catalysed 1,4-conjugate addition to compound (*R*)-**(1b)**. With this method, it was estimated that the *d.r.* value could be obtained with an accuracy of $\pm$5%. The absolute configuration of each diastereomer was not determined. Reduction of the C=N bond and then stereo correlation of the resulting amines with an enantiopure Moscher's acid,[102] or X-ray crystallographic analysis of the initial product mixture would allow determination of absolute stereochemistry to be attained, but this has not yet been carried out.

It is immediately apparent that this methodology presents a successful route for conjugate addition to compound **(1b)**. Analysis of the results presented in Table 7 allows some conclusions to be drawn.

Broadly speaking, Et_2O is better than DCM in terms of yield and *d.r.* value. The ligand IMes is inferior when compared to the phosphoramidite (*R,S,S*)-**(52)** and PCy_3 in terms of yield and inferior to (*R,S,S*)-**(52)** in terms of diastereoselectivity. Both PCy_3 and (*R,S,S*)-**(52)** give excellent yields, but only (*R,S,S*)-**(52)** gives both excellent yield *and* an excellent *d.r.* value.

Comparison of entries 3 and 6 shows that the *Kubas* compound ($[Cu(MeCN)_4]BF_4$) provides the highest *d.r.* value, but the highest yield is furnished by Cu(TC).

Table 7 – Screening of ligand-accelerated aluminium-based nucleophilic 'ethyl' addition to (*R*)-(1b)

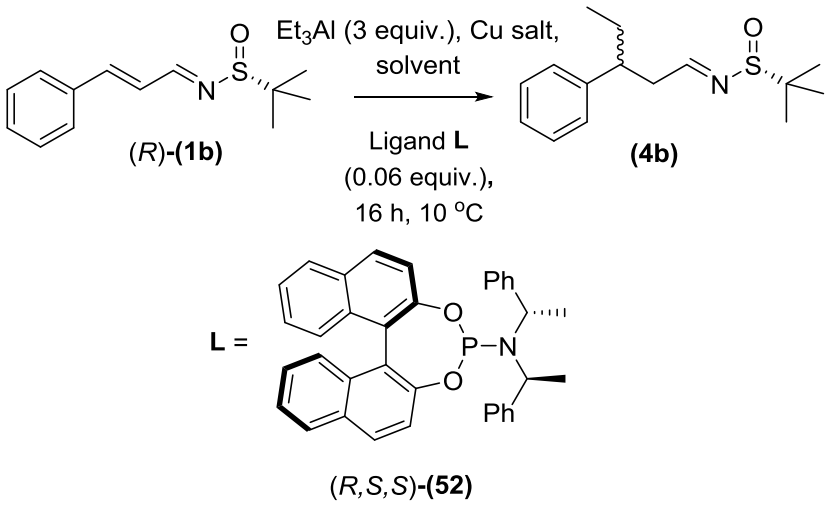


Entry	Copper source (0.04 equiv.)	L (0.06 equiv)	Solvent	Yield of **(4b)**[a]/%	*d.r.*[a]
1	$[Cu(MeCN)_4]BF_4$	PCy_3	Et_2O	95	1:2
2	$[Cu(MeCN)_4]BF_4$	IMes	Et_2O	70	1:2.7
3	$[Cu(MeCN)_4]BF_4$	(*R*,*S*,*S*)-**(69)**	Et_2O	90	1:9
4	Cu(TC)	PCy_3	Et_2O	Quant. (87)[b]	1:2
5	Cu(TC)	IMes	Et_2O	50	1:3
6	Cu(TC)	(*R*,*S*,*S*)-**(69)**	Et_2O	Quant.	1:7
7	$[Cu(MeCN)_4]BF_4$	PCy_3	DCM	5	1:1
8	$[Cu(MeCN)_4]BF_4$	IMes	DCM	Trace	3:1
19	$[Cu(MeCN)_4]BF_4$	(*R*,*S*,*S*)-**(69)**	DCM	60	1:5
10	Cu(TC)	PCy_3	DCM	90	4:5
11	Cu(TC)	IMes	DCM	Trace	2:1
12	Cu(TC)	(*R*,*S*,*S*)-**(69)**	DCM	60	1:8

[a] Determined by ^1H NMR spectroscopy against an internal standard. [b] Isolated yield in brackets. [c] Cu(TC) is copper(I) thiophene-2-caboxylate.

Working under these conclusions, further screening was proposed: The next round of conditions would investigate thoroughly solvent and copper salt dependency of the reaction outcome (Scheme 40). The results of this screening are presented in Table 8.

Table 8 – Screening of copper salt and solvent dependency in the formation of (4b) from (1b) and aluminium-based nucleophiles



Entry	Copper source (0.04 equiv.)	Solvent	Yield of **(4b)**/%	*d.r.*[b]
1	$Cu(OTf)_2$	Toluene	13	1.3:1
2	$Cu(OTf)_2$	DCM	22	1.3:1
3	$Cu(OTf)_2$	Et_2O	45	1:3
4	$Cu(OTf)_2$	MTBE	65	1:2
5	$Cu(OTf)_2$	THF	58	1:2
6	$Cu(OTf)_2$	DME	45	1:1.3
7	$Cu(OAc)_2$	Toluene	38	1:1
8	$Cu(OAc)_2$	DCM	S.M, Trace	1:1
9	$Cu(OAc)_2$	Et_2O	43	1:2
10	$Cu(OAc)_2$	MTBE	85	1:>20
11	$Cu(OAc)_2$	THF	30	1:3
12	$Cu(OAc)_2$	DME	37	1:3
13	Cu(TC)	Toluene	37	4:1
14	Cu(TC)	MTBE	Complex mix	-
15	Cu(TC)	DCM	28	2.5:1
16	Cu(TC)	Et_2O	9	1:2

17	Cu(TC)	THF	67	1:3
18	Cu(TC)	DME	55	1:10
19	$[Cu(MeCN)_4]BF_4$	Toluene	44	5:1
20	$[Cu(MeCN)_4]BF_4$	MTBE	18	1:1
21	$[Cu(MeCN)_4]BF_4$	DCM	Trace	1:1
22	$[Cu(MeCN)_4]BF_4$	Et_2O	Quant.	1:1[a]
23	$[Cu(MeCN)_4]BF_4$	THF	Trace	-
24	$[Cu(MeCN)_4]BF_4$	DME	49	1:3

[a] (*S*)-**(1b)** was used for this entry, not (*R*)-**(1b)**. [b]Yield and *d.r.* determined by ^{1}H NMR spectrum analysis containing an internal standard.

Three important observations can be drawn from these data:

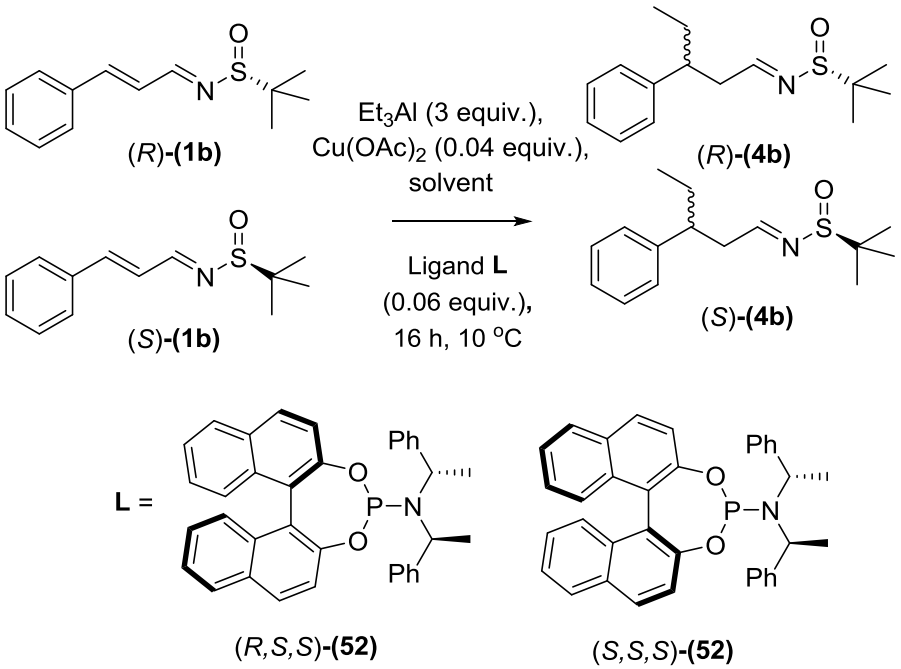
- The first is that the *d.r.* value is maximised within the bounds of experimental error when obtained *via* the conditions in entry 10 and represents an improvement upon the previous conditions.
- The second is that toluene as a solvent appears to confer an inversion of selectivity (Entries 13 and 19).
- The third is that when the *opposite enantiomer sulfinimine* is used – (*S*)-**(1b)** as opposed to (*R*)-**(1b)** – the stereoselectivity of the reaction is almost entirely degraded (entry 22, compared to entry 3).

To investigate this, a series of matched and mismatched pairs were synthesised.

Table 9 contains the results of this investigation. The system in question has four chiral centres – the sulfur atom, the axis of chirality and the N-(CR_2)$_2$ atoms. Two of these centres come as a pair, so there are 2^3 permutations of this reaction that must be investigated in order to identify pair matching.

Path 2 (Table 10) is an exact enantiomer of Path 1. Therefore Path 2 will produce the exact same selectivity as Path 1, except mirrored, and so Path 1 was chosen and its data is depicted in Table 9 (Runs 1 – 4, 5 – 8).

Table 9 – Screening of ligand/substrate enantiomer pairings



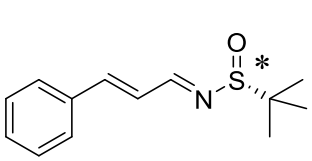
Entry	Sulfinimine chirality	L (0.06 equiv)	Solvent	Yield of **(4b)**/%	*d.r.*[a]
1	(*R*)	Feringa (*R*,*S*,*S*)	MTBE	Quant.	1:>20
2	(*S*)	Feringa (*R*,*S*,*S*)	MTBE	54	1:1
3	(*R*)	Feringa (*S*,*S*,*S*)	MTBE	57	1:1
4	(*S*)	Feringa (*S*,*S*,*S*)	MTBE	62	2:5
5	(*R*)	Feringa (*R*,*S*,*S*)	Toluene	Quant.	9:1
6	(*S*)	Feringa (*R*,*S*,*S*)	Toluene	85	5:1
7	(*R*)	Feringa (*S*,*S*,*S*)	Toluene	91	9:1
8	(*S*)	Feringa (*S*,*S*,*S*)	Toluene	98	2:1

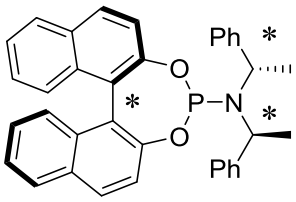
[a]Yield and *d.r.* determined by ^{1}H NMR spectrum analysis containing an internal standard.

Entry 1 (Table 9) clearly shows that the (*R*), (*R*,*S*,*S*) – system is the most successful and is the matched pairing. The runs using toluene as a solvent gave more interesting results. Only entry 8 is obviously a mismatched pair due to the low magnitude of the *d.r.* value. The value of 2:1 from entry 8 is comparable to those obtained earlier (Table 7, Entry 1 (1:2)) with respect to the magnitude of the value, and indicate that the ligand is not involved in the stereochemical outcome in this case. Entries 5, 6, and 7 (the runs in toluene) all show some enhanced

selectivity. This is at odds with the entries 2, 3, and 4 (the runs in MTBE) which show complete degradation of selectivity.

Table 10 – Possible enantiomeric pathways for the reaction presented in Table 9





Path 1			Path 2		
Sulfur chirality	Axis chirality	N-(CR_2)$_2$ chirality	Sulfur chirality	Axis chirality	N-(CR_2)$_2$ chirality
(*R*)	(*R*)	(*S*,*S*)	(*S*)	(*S*)	(*R*,*R*)
(*S*)	(*R*)	(*S*,*S*)	(*R*)	(*S*)	(*R*,*R*)
(*R*)	(*S*)	(*S*,*S*)	(*S*)	(*R*)	(*R*,*R*)
(*S*)	(*S*)	(*S*,*S*)	(*R*)	(*R*)	(*R*,*R*)

It is known that cinnamyl sulfinimine **(1b)** adopts a **C3**-like conformation as its preferred conformer.[6] In achiral media, the only source of chiral information comes from the sulfinimine itself and so it follows that the diastereoselectivity observed in these cases must be due to the sulfur centre alone (Figure 17). The methodologies involving achiral systems without toluene yield the same order of magnitude of diastereoselectivity and have the same bias towards a particular diastereomer. This diastereoselectivity is seemingly independent of solvent or nucleophile or copper source, so it is reasonable to assume that both of these systems proceed *via* an open transition state that is controlled predominantly by the spacial organisation of the groups bonded to the sulfur atom, taking into account the lowest energy conformation.

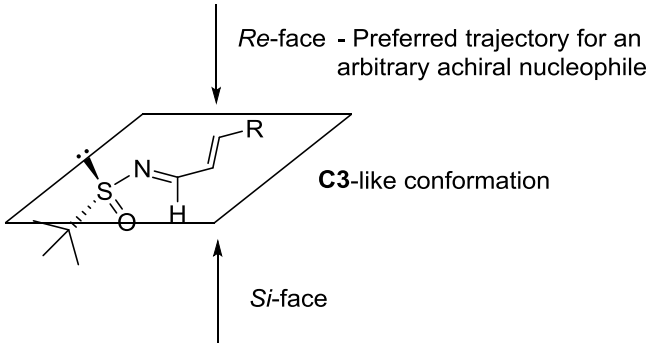


Figure 16 – Illustration of a potential open-transition state model to account for diastereoselectivity in achiral media

Therefore, if a solvent interferes in some manner with the formation of a closed transition state in an arbitrary system containing **(4b)**, the resulting mixture would contain diastereomers of an approximate ratio of 1:2, as the reaction proceeds instead *via* an open transition state.

If this reasoning holds true, then for the methodologies involving matched **(52)**/substrate pairs, and for methodologies in toluene, the enhanced selectivity can only be explained in terms of a closed transition state. The interesting implication from this data is that the transition states for Table 9, Entry 1 and Table 9, Entry 5 must be significantly different from one another as there is no other explanation for the presence of inversion – simple reversion to an open transition state would not yield the opposite enantiomer in the case of toluene.

In order to confirm if this is true, the conditions in Tables 8 and 9 would have to be repeated in the exact same manner but omitting any ligand. If it turned out that the *d.r.* values from such an investigation were 1:2, then it would confirm some of the hypotheses that have been suggested here.

Although it cannot be unequivocally argued, a tentative suggestion for the dominant transition state for the MTBE/**(52)** system is that it is similar to those postulated for the zinc-based copper-catalysed cycle. That is to say, the complexes **D** and **E** (Figure 11) are likely to

be analogous to complexes that would be formed within this reaction, and the transition state between them would likely be analogous as well (Figure 18).

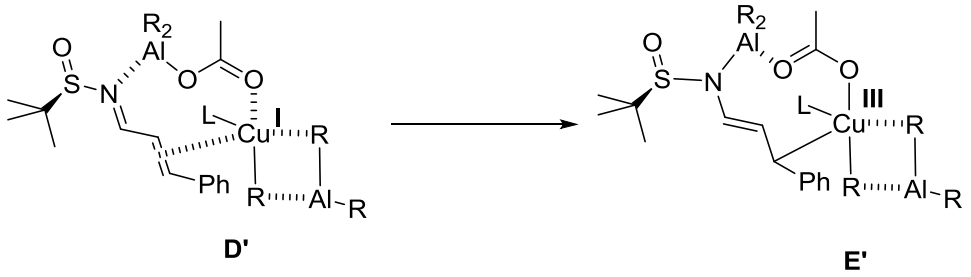


Figure 178 – Proposed analogous intermediates within the catalytic cycle with sulfinimines as the substrate. Bond angles and lengths are exaggerated for clarity

The problems with this are immediately apparent. It is difficult to argue that the sulfinyl oxygen atom would not be involved in the bonding to the complex's critical atoms, such as the proximal aluminium atom. However, the method developed here in this Thesis appears to be most responsive to the use of $Cu(OAc)_2$ as the copper salt which ultimately forms a catalytic complex, and so a reasonable assumption is that there exist similarities between this system and those of zinc-based systems previously reported in the literature.

With respect to the toluene/**(52)** system, it is more difficult to suggest what the transition state may look like. Toluene cannot form dative bonds in the same way that etherated and chlorinated solvents can. Because toluene does not have a large dipole moment (0.36 D compared to MTBE's 1.4 D), it is unlikely that solvent co-ordination to an arbitrary operator within this system is the driving force behind transition state formation. The fact that the reactions done in toluene produce the opposite enantiomer either implies that the closed transition state for that system does not have a **C3**-like conformation of the substrate or it disqualifies aggregative enhancement of reactivity for this system in low polarity solvents. If it were an effect of aggregation, and if the sulfinimine can freely tumble in solution, then the

diastereomeric ratio would be biased towards the same enantiomer as those present in the achiral systems. If it were an effect of aggregation that forces the sulfinimine to adopt a conformation unlike **C3**, then the solvent must be involved in the transition state and so the 'aggregative effect' is simply that a closed transition state may form in toluene that cannot in MTBE.

These data do not rule out the possibility of 'aggregation' due to low solubility being the cause of the inversion of selectivity entirely however, for it could be possible that the same reaction when repeated using pentane as a solvent produces the same result. It cannot be determined either way at this time.

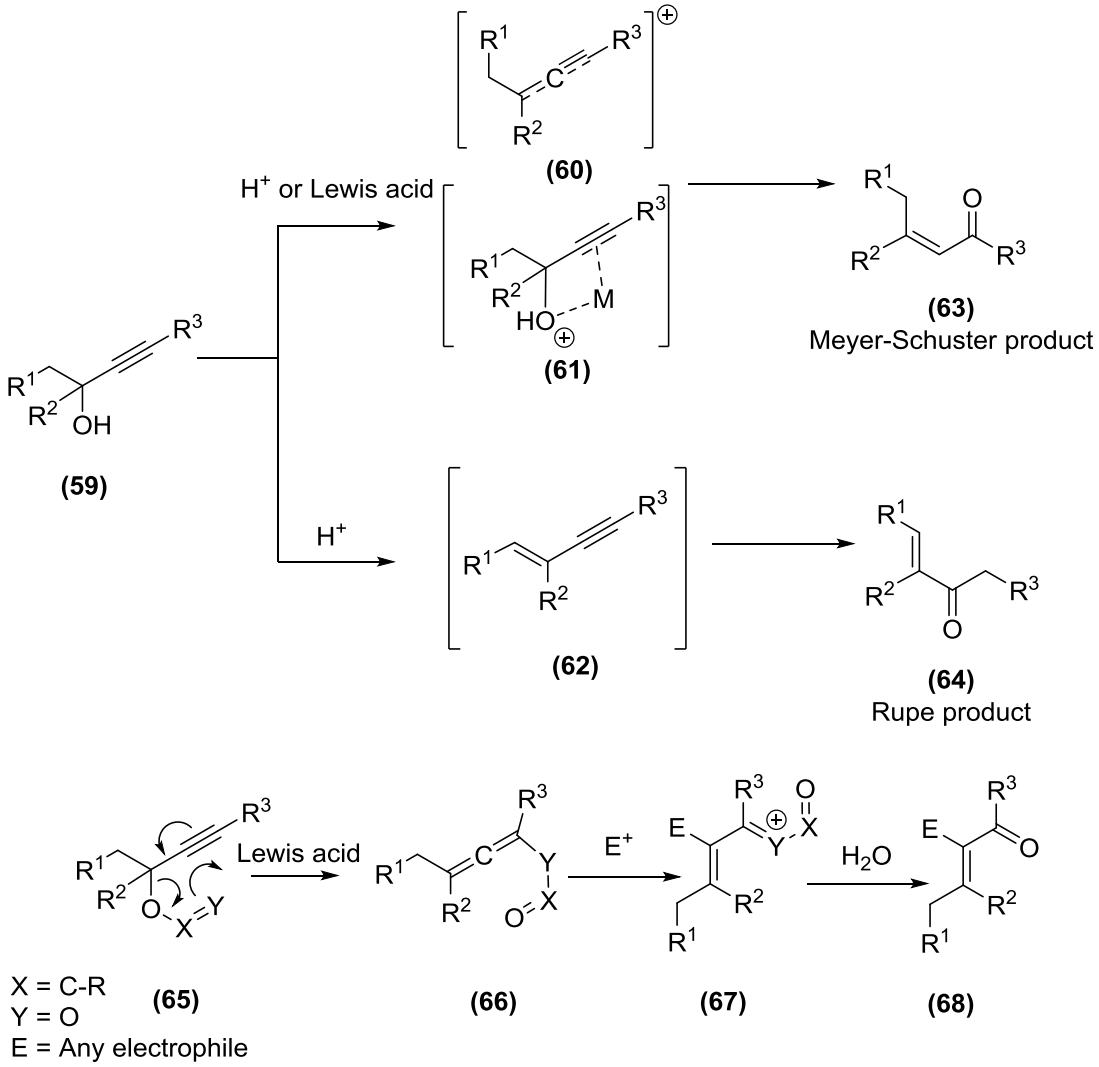
A unique property of aromatic solvents compared to classical solvents is the existence of π-stacking,[103-105] and the bond strength of the benzene dimer is calculated to be around 8-12 kJ/mol. When compared to 18 kJ/mol of the hydrogen bond of the hydronium ion in a water solvent shell ($H_2O\cdots H_3O^+$),[106] it can be speculated that the quadrupole-quadrupole and quadrupole-dipole interactions when using an aromatic solvent such as toluene play a very significant role.

With a successful set of conditions and method of analysis, the substrate scope was then investigated. Firstly, stocks of compounds **(1c-h)** had to be prepared.

2.5 Synthesis of sulfinimines (1c-1h) from benzaldehydes *via* cinnamaldehydes (2a-f), propargyl alcohols (3a-f)

The rearrangement shown in Scheme 39 leading to **(63)** was first reported in 1922 by Meyer and Schuster.[107] It is a reaction that is catalytic in acid with very high atom economy and can potentially use cheap and non-toxic reagents. Despite these attractive features, there are only 14 published papers in the period 1922-1990 that formally refer to the rearrangement. This may be due to the fact that the original paper used harshly acidic conditions that will not

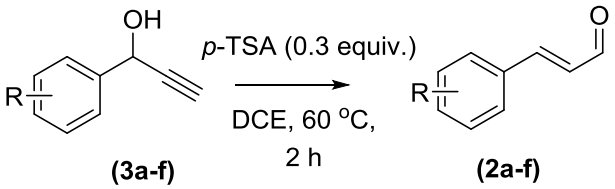
tolerate sensitive functional groups, compounded by the similarly acid-catalysed competing Rupe rearrangement leading to **(64)**.



Scheme 39 – Overview of the Meyer-Schuster and Rupe rearrangements with currently surmised intermediates

The mechanism of the Rupe rearrangement is generally accepted to be a dehydration-hydration mechanism that goes *via* enyne intermediates **(62)**. Such intermediates have been observed spectroscopically[108] and in some cases isolated.[109] The mechanism of the Meyer-Schuster rearrangement is less well understood, but is proposed to go *via* two distinct pathways. The first pathway is the pathway that the classic Meyer-Schuster reaction follows

under acid conditions and proceeds through cationic intermediates **(60)**[110] whereas the second pathway is proposed to go *via* activation of the alkyne by late transition metals (gold in particular)[111] forming intermediates **(61)**.[112,113] The enyne intermediate **(62)** is postulated to be lower in energy than cation **(60)**,[110] and therefore acid-catalysed Meyer-Schuster rearrangements are usually restricted to those that lack a β-proton. Gold is expensive, and there have been attempts to use other Lewis acid catalysts such as $InCl_3$, $Sc(OTf)_3$, $Ag(OTf)_2$, and $Cu(OTf)_2$,[114] but none seem to provide the reliability that is provided by gold catalysts. Though technically not a Meyer-Schuster rearrangement in the formal sense, the transformation of **(65)** to **(68)** shows an 'acetylenic Meyer-Schuster rearrangement' that forms similar products from similar starting materials under similar conditions.[112]



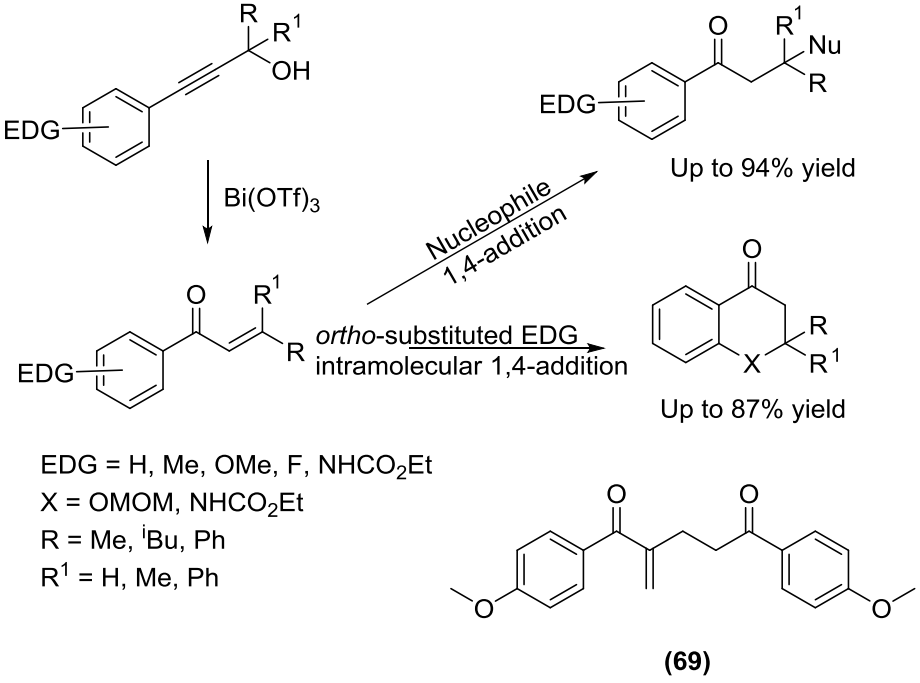
	R
(a)	*p*-Me
(b)	*p*-F
(c)	*o*-F
(d)	*m*-F
(e)	*p*-Cl
(f)	*p*-COOEt

Scheme 190 – Synthesis of cinnamaldehydes (2) under conditions published by Jungmin *et al*

Enals **(2)** are the key intermediates needed for the synthesis of the desired substrates **(1)** for this Thesis and are accessible from Meyer-Schuster chemistry. Compounds **(3)** lack a β-proton and so cannot undergo the Rupe rearrangement, so therefore a simple acid catalysis may be used to synthesise compounds **(2)**.

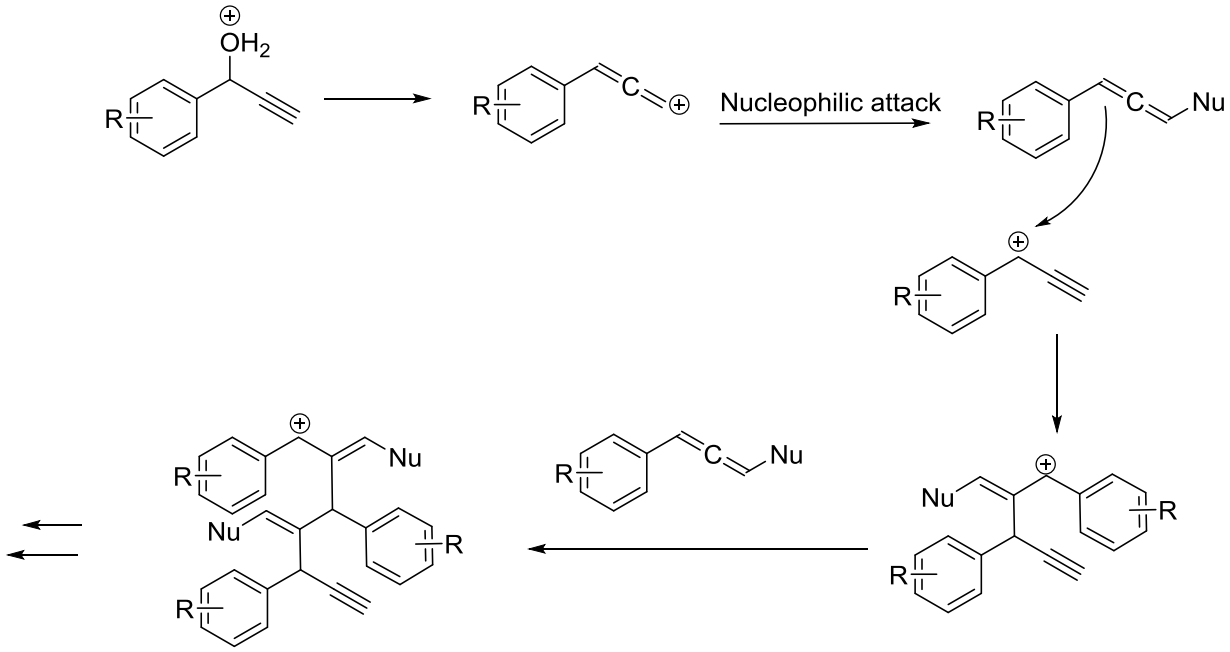
Propargyl alcohols **(3) a**re accessible from simple 1,2-addition from the respective aldehydes.

Compound **(2a)** was synthesised by the conditions given by Jungmin *et al.*[115] (Scheme 40) from **(3a)** and furnished the desired compound in quantitative yield as viscous brown oil. Purification of this oil was not possible using all of the techniques that were available (chromatographic separation, distillation, crystallisation, trituration, and sublimation). Curiously, there appeared to be nothing obviously unexpected to see in the ^{1}H NMR spectra, the ^{13}C NMR spectra, or the ESI+ MS of the cinnamaldehydes formed by the Meyer-Schuster reaction. There was quite clearly a competing side reaction forming undesired products, but the resultant materials from the Meyer-Schuster rearrangements were sufficient for use as crude starting material for the condensation of sulfinimines **(1)**. Indeed, purification could only be performed one step further along the synthetic pathway after sulfinimine formation, leaving behind a viscous brown oil which yielded only a collection of solvent peaks by spectroscopy. If this brown oil was not removed, the copper-catalysed 1,4-additions did not proceed at all. Quite recently, in 2014, Okamoto *et al.*[116] performed a variety of Meyer-Schuster rearrangements using $Bi(OTf)_3$ (Scheme 41).



Scheme 41 - Bismuth-catalysed Meyer-Schuster reaction

During the reaction, the dimerisation product **(69)** was isolated in up to 23% yield. It is interesting to note that **(69)** could still accept a nucleophile in a 1,4 manner. When considering the intermediates of the Meyer-Schuster reactions performed for this Thesis, one can posit some plausible ideas for potential polymerisation to account for the observed disappointing morphology and failed purification of the material obtained. The unknown compound does not seem to be observable by NMR spectrometry or by conventional Mass Spectrometry. A polymer with a high polydispersity index that is insoluble and has a high mass would fit both of these criteria, and would require techniques such as gel permeation chromatography or MALDI-TOF spectroscopy to identify. A suggestion for a potential pathway for polymerisation is given in Scheme 42.



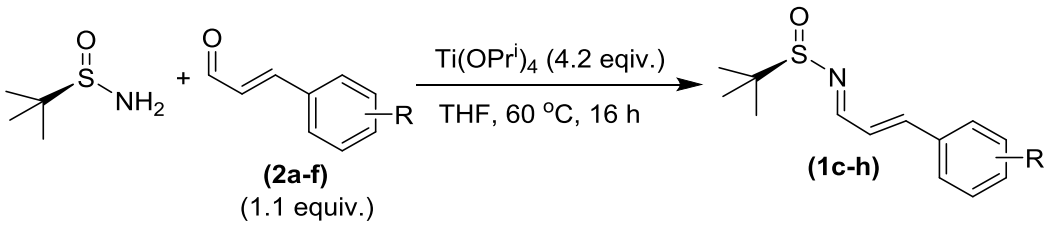
Scheme 42 – Proposed polymerisation pathway for Meyer-Schuster intermediates

There are many sources of nucleophile in a system like this which includes water, the propargyl alcohol starting material, and the aryl ring itself. The exact nature of the nucleophile is not necessarily important, as the salient point is that chain propagation under

these conditions is possible using these substrates and that is a reasonable explanation for the observed reactivity.

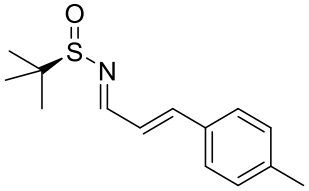
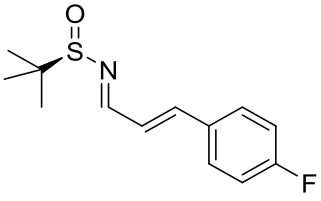
In order to push forward material, the reactions from benzaldehyde to sulfinimine were telescoped, and the experimental data collected for sulfinimines **(1)** confirms that the reaction pathway proceeded as expected beyond reasonable doubt. We had in hand sufficient material to synthesise sulfinimines **(1c-h)**, and the results of this are presented in Table 19.

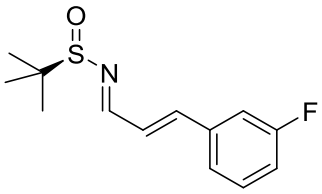
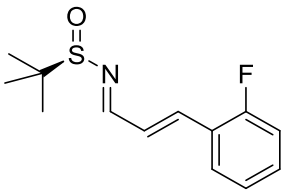
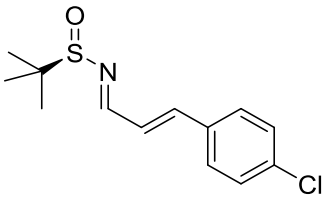
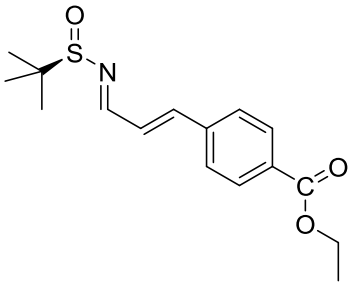
Table 19 – Condensation of enals (2a-f) with (*R*)-*tert*-butyl sulfinamide to form sulfinimines (1c-h)



	R
(2a)	*p*-Me
(2b)	*p*-F
(2c)	*o*-F
(2d)	*m*-F
(2e)	*p*-Cl
(2f)	*p*-COOEt

	R
(1a)	*p*-Me
(1b)	*p*-F
(1c)	*o*-F
(1d)	*m*-F
(1e)	*p*-Cl
(1f)	*p*-COOEt

Compound	Structure	Isolated yield[a] of **(1)**/%
(1c)		47
(1d)		93

(1e)		81
(1f)		99
(1g)		99
(1h)		67

2.6 Substrate scope of copper-catalysed aluminium-based 'ethyl' addition

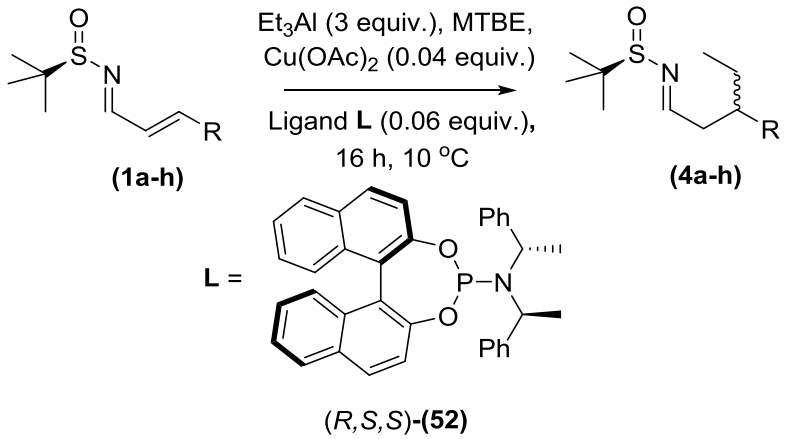
With adequate quantities of compounds **(1)** in hand, the conditions investigated in Section 2.4.2 were applied. The results are given in Table 20.

The *para*-fluorocinnamyl sulfinimine **(1e)** gave the same excellent selectivity observed for cinnamyl sulfinimine **(1b)**. The *para*-methylcinnamyl sulfinimine **(1c)** gave good selectivity but only modest yields. The *ortho*- and *meta*-fluorocinnamyl sulfinimines **(1g)** and **(1f)** displayed a negative trend in both yield and *d.r.* value as the position of the fluorine atom became spatially closer to the reaction terminus.

2.7 Conclusions and future work

Methodology for the addition of 'ethyl' nucleophiles to sulfinimines **(1)** has been developed. Ligandless Gilman-like cuprate catalysis is not applicable for these substrates with 'ethyl' nucleophiles. In all cases, an 'ethyl' nucleophile could not produce results similar to those previously reported by Ellman *et al.* A matched pairing was identified with the (*R*), (*R,S,S*) system (Table 9, Entry 1). This system appears to be sensitive to substituents present on the

Table 20 – Substrate scope of ligand-accelerated aluminium-based 'ethyl' nucleophilic 1,4 addition to sulfinimines (1)

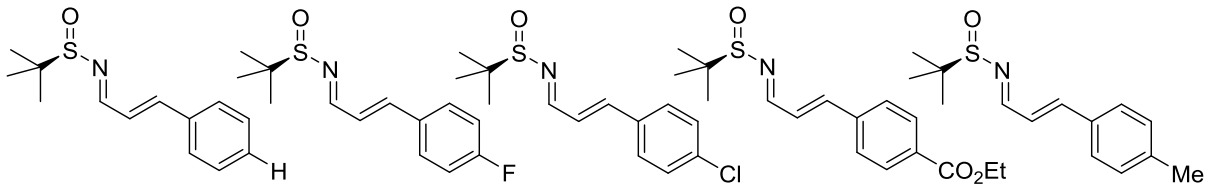


(*R,S,S*)-**(52)**

Entry	Sulfinimine chirality	Starting sulfinimine	Yield of **(4)**/%[a][b]	*d.r.*[a]
1	(*R*)	**(1a)**	32	1:1
2	(*R*)	**(1b)**	Quant.	1:>20
3	(*R*)	**(1c)**	54	1:7
4	(*R*)	**(1d)**	64	4:15
5	(*R*)	**(1e)**	73	1:>20
6	(*R*)	**(1f)**	44	1:5
7	(*R*)	**(1g)**	23	1:2
8	(*R*)	**(1h)**	81	2:1

[a] Determined from solution with an internal standard as described in Section 2.4.2. [b] Averaged value from two reactions.

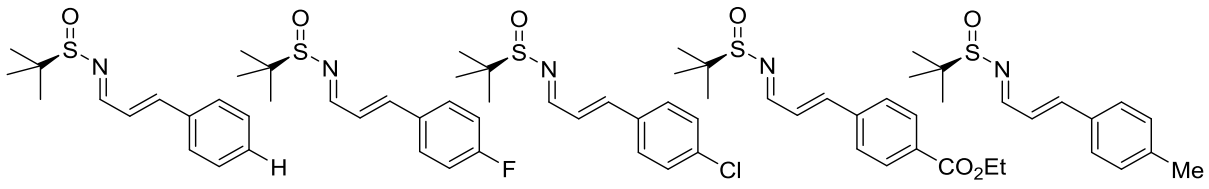
phenyl moeity. If it were a purely steric effect, then the *d.r.* pattern for substituents at the 4-position would be predictable with reference to their A-values.



A-value	0.000	0.15	0.43	1.20	1.70
d.r value	1:>20	1:>20	1:2	2:1	1:7

Figure 19 – Comparison of R-group A-values against outcome of *d.r.* value

Unsurprisingly, this does not appear to be the case.



σ_p	0.000	0.062	0.227	0.450	-0.170
d.r value	1:>20	1:>20	1:2	2:1	1:7

Figure 20 – Comparison of R-group Hammett parameters against outcome of *d.r.* value

Comparison of the Hammett parameters[117] (σ) for substituents in the *para*-position (σ_p) reveals a correlation between the increase in σ_p value (which can be assumed to be the electron withdrawing capacity) of the *para*-moeity and the *d.r.* values of the mixtures in Table 20. As σ_p increases, the *d.r.* values decrease even to the point of inversion (Table 20, entry 8). For electron-donating substituents ($-\sigma_p$ value) there also appears to be a decrease in *d.r.* value, although due to the comparably large A-value of the methyl unit (1.70) it may be the case that this decrease is simply due to steric effects. More data is needed to investigate this trend.

In the case of both sterics and electronics, the *para*-methyl compound **(1c)** is an outlier within this data set, as it is the only 'large' group with an A-value greater than 1.50 and is also the only group with a negative σ_p value. Indeed, omitting it from the plots of $\Delta G^{\Theta}(d.r.)$ = RTln(*d.r.*) against A-value and $\Delta G^{\Theta}(d.r.)$ = RTln(*d.r.*) against σ_p value produces graphs with reasonable linear correlation (Figure 21).

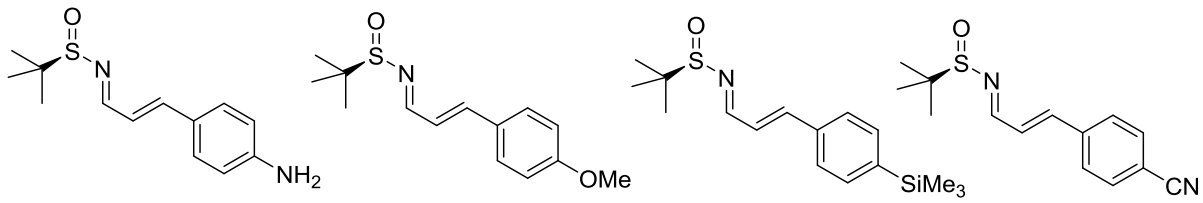
Although the R^2 values of both of these linear correlations are sub-optimal (below 0.995), it can clearly be seen that there is at least a weak correlation.

Using the Van der Waals radius of each moiety instead of the A-value again yields a weak correlation (Figure 22). Although the Van der Waals radius of a methyl group is small (21.58 Å) and so could be added to this data set without appearing as an outlier, for direct comparison it has been omitted.

The correlation for this data set is weaker than that for the A-values of the moieties. Since A-values are not an absolute standard for the steric size of the group and are instead representative of more 'real' data and the underlying effects that affect them, and since there is a stronger correlation for the results presented in Table 20 against the corresponding moiety's A-values, it would seem that for the data presented in this Thesis that the A-values are more important for prediction of diastereomeric ratio than are the Van der Waals radius values. The tentative conclusion from this is that the diastereoselectivity of this system decreases linearly with both increasing σ_p values and with increasing A-values of the moiety bonded at the *para* position with respect to the reaction terminus.

This work can be expanded on by increasing the range of substrates to which the optimised conditions are applied. Prime targets include the substrates already investigated but with their phenyl substituents in *ortho* or *meta* positions rather than *para*. Having those data would allow for a direct comparison between substituent positions to be obtained. A range of

electron-donating substituents would give a more complete picture of any electronic factors that are involved – in particular, substituents with low A-values and negative σ_p values.



σ_p	-0.66	-0.268	-0.07	0.660
A-value	1.2	0.60	0.74	0.17

Figure 183 – Potential attractive acceptors and their corresponding σ_p and A-values

The very apolar solvent toluene has a dramatic effect on the selectivity of the system. During the initial ligand screening, the solvents used were Et_2O and DCM. In order to investigate if the selectivity behaviour in toluene is unique to Feringa's ligands, it is worth repeating the conditions used in Table 7, but using toluene as a solvent and also the results in Tables 8 and 9 omitting the ligand. This will give a more complete picture about the role of solvent and ligand on the formation of closed transition states within the systems.

A natural extension of this work is trapping the intermediates formed in the reaction to electrophiles to form a new α-stereocentre, producing two chiral centres from one reaction with very high potential selectivity.

The Meyer-Schuster transformation presented in this Thesis appears to be retarded by an unknown competing reaction. Analysis of the brown residues by MALDI-TOF and/or GPC chromatography will elucidate whether or not there is a polymeric product forming. Determination of the repeating unit will give insight to the mechanism and may in turn allow for refinement of a potentially powerful, cheap, and easy-to-use methodology.

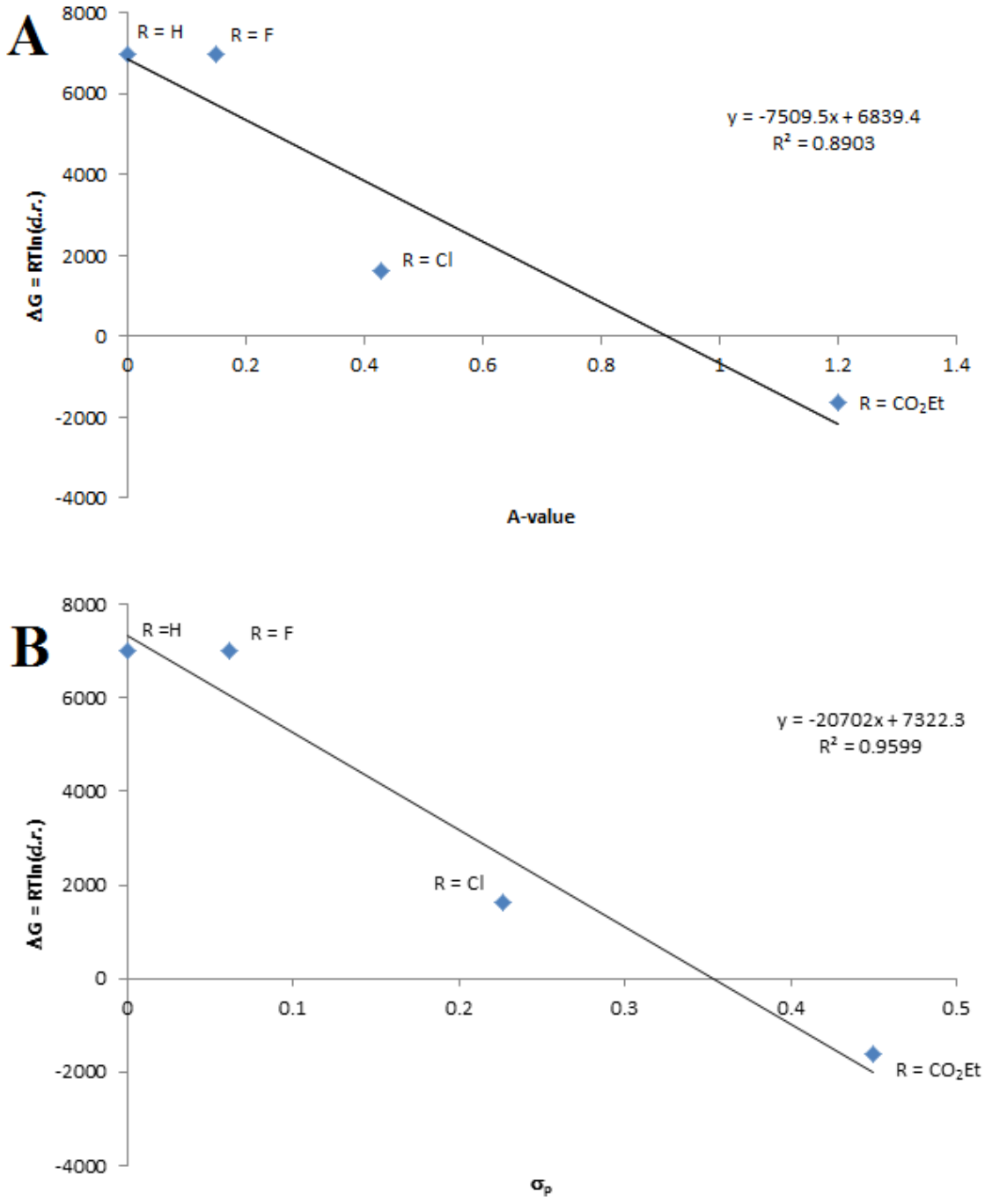


Figure 191 (A) A plot depicting the linear relationship for the plot of $\Delta G^{\Theta}(d.r.)$ = RTln(*d.r.*) against A-value. **(B)** A plot depicting the linear relationship for the plot of $\Delta G^{\Theta}(d.r.)$ = RTln(*d.r.*) against σ_p value. ΔG^{Θ} values are in Joules.

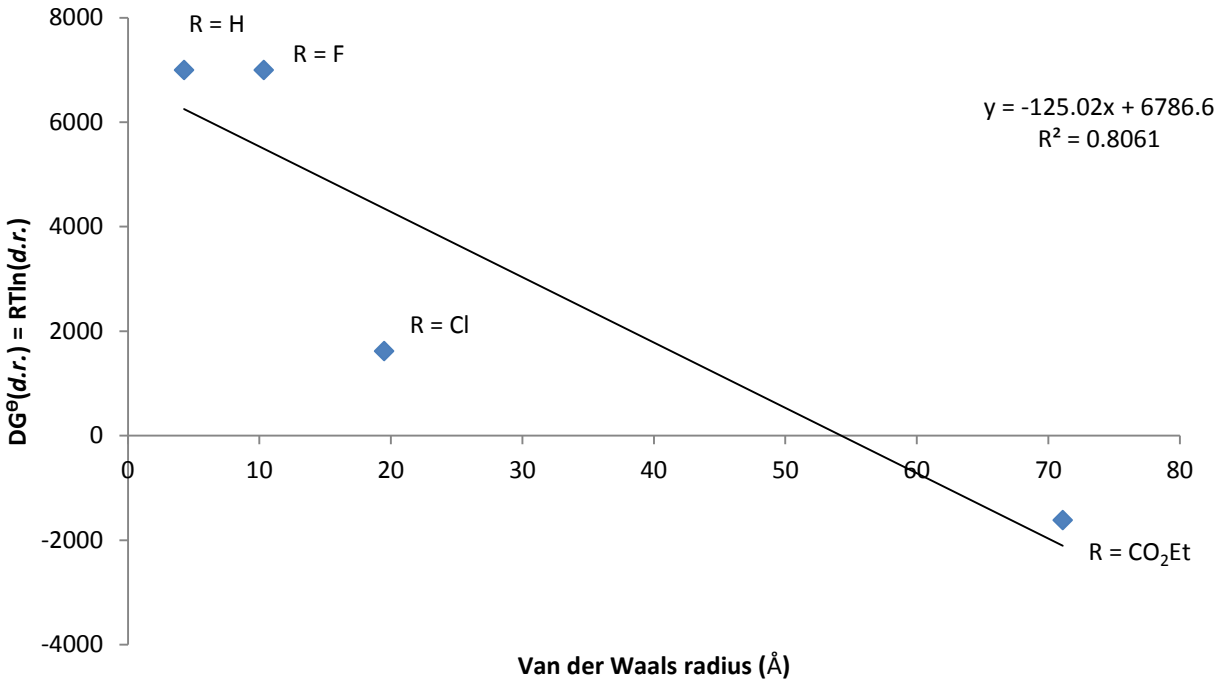


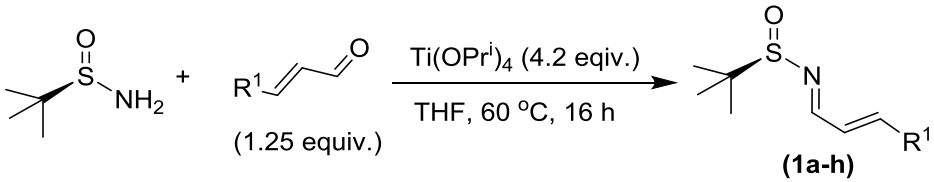
Figure 22 – A plot depicting the linear relationship between $\Delta G^{\Theta}(d.r.) = RT\ln(d.r.)$ and Van der Waals radius for moieties attached to the aryl system in compounds **(4)**. Methyl moiety omitted for direct comparison to Figure 21. The R^2 value when including the methyl in the data set is 0.8062. ΔG^{Θ} values are in Joules.

Alternative methods to perform Meyer-Schuster rearrangements (i.e. Lewis acid-catalysed) are also potential targets for analysis; the work done by Okamoto *et al.*[116] on bismuth(III) triflate-catalysed Meyer-Schuster transformations is work that is easy to test on the propargyl alcohols used in this Thesis. If successful, it would hold open this route towards cinnamaldehyde synthesis with a mind for more environmentally conscious chemistry, as bismuth(III) triflate itself is inexpensive, not harmful to the environment, and not toxic.

Chapter Three

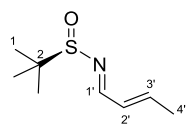
Experimental procedures

General procedure 1. Preparation of sulfinimines (1)



In a Schlenck tube neat $Ti(OEt)_4$ (35.2 mL, 38.3 g, 168 mmol, 4.2 equiv.) and precursor aldehyde (50 mmol, 1.25 equiv.) were combined and stirred at 60 ^oC (10 min). A solution of (*R*)-2-methylpropanesulfinamide (4.85 g, 40 mmol, 1 equiv.) in THF (100 mL) was added and the mixture stirred at 60 ^oC until the sulfinamide was completely consumed [R_f (hexanes:EtOAc (4:1)) of compounds **(1)** ~0.45, R_f of starting sulfinamide 0.05], typically 16-24 h. The reaction was cooled to -10 ^oC and quenched with pre-cooled saturated $NaHCO_{3(aq)}$ solution. The resulting suspension was filtered through a pad of Celite^{TM} which was washed with EtOAc (3 × 25 mL). The EtOAc fraction was separated, dried ($MgSO_4$), filtered, and evaporated to give the crude products as yellow oils. Alkyl sulfinimines were purified by Kugelrohr distillation (typically 55-65 ^oC, 0.01 mmHg). Aryl sulfinimines were purified by recrystallization from hexanes:Et_2O. Typically both provided pale yellow needle-like materials in 60-80% yield. Sulfinimines **(1a-1h)** are described below and are named using the nomenclature of *Chemical Abstracts*.

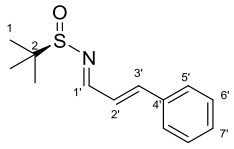
(*R*)-(*E*)-*N*-((*E*)-but-2'-en-1'-ylidene)-2-methylpropane-2-sulfinamide (*R*)-(1a)



Attained by general procedure 1 using crotonaldehyde (4.2 mL, 3.6 g, 51 mmol), $Ti(OEt)_4$, (36 mL, 39 g, 0.17 mol), and (*R*)-*tert*-butyl sulfinamide (5.0 g, 41 mmol). Kugelrohr distillation (58-60 ^oC at 0.075 mmHg,) gave (*R*)-**(1a)** as pale yellow needles (5.3 g, 61%) that melted at room temperature. **Mp** <20 ^oC. $\mathbf{[\alpha]_D^{20}}$ -557.1 (*c* = 1.0, $CHCl_3$). $\mathbf{R_f}$ (hexanes:EtOAc (4:1)): 0.51. ^{1}**H NMR** ($CDCl_3$, 400.1 MHz): δ 8.16 (1H, d, *J* = 9.1, $H^{1'}$), 6.54 (1H, dq *J* = 15.4, 13.1, 6.5, $H^{3'}$), 6.43 (1H, ddq, *J* = 15.3, 9.1, 1.3, $H^{2'}$), 1.96

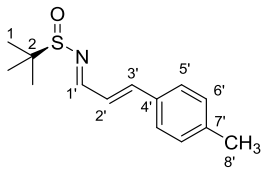
(dd, J = 6.7, 1.3, $H^{4'}$), 1.18 (9H, s, H^{1}). **^{13}C NMR** ($CDCl_3$, 73.7 MHz): δ 164.0 ($C^{1'}$), 146.5 ($C^{3'}$), 130.3 ($C^{2'}$), 57.11 (C^{2}), 22.4 ($C^{4'}$), 18.8 (C^{1}). **IR** ($CHCl_3$): ν 3034m, 2978, 2960m (3 × C-H), 1646s (C=N), 1581s, 1475s, 1458s, 1446m, 1362m, 1773m, 1081s (S=O), 996m, 963m, 934m cm^{-1}. **MS** (ESI+): *m/z* 196 $[M+Na]^+$; HRMS: found 196.0756, $C_8H_{15}NNaOS$ requires 196.0767 (σ 5.4 ppm). This data was concordant with literature values.[118]

(*R*)-(*E*)-*N*-((*E*)-3'-phenylprop-2'-en-1'-ylidene)-2-methylpropane-2-sulfinamide (*R*)-(1b)



Attained by general procedure 1 using cinnamaldehyde (13 mL, 12 g, 94 mmol), $Ti(OEt)_4$, (72 mL, 66 g, 0.29 mol), and (*R*)-*tert*-butyl sulfinamide (10 g, 83 mmol). Recrystallisation from Et_2O/hexanes *via* slow evaporation gave (*R*)-**(1b)** as bright yellow hexagonal needles (15 g, 79%). **Mp** 61-62 °C. **$[\alpha]_D^{19}$** -331.4 (*c* = 1.0, $CHCl_3$). **R_f** (hexanes:EtOAc (3:1)): 0.47. **^{1}H NMR** (400.1 MHz, $CDCl_3$): δ 8.38 (1H, d, J = 9.2, $H^{1'}$), 7.59 – 7.50 (2H, m, $H^{5'}$), 7.43 – 7.36 (3H, m, $H^{6',7'}$), 7.24 (1H, d, J = 15.8, $H^{3'}$), 7.09 (1H, dd, J = 15.8, 9.2, $H^{2'}$), 1.24 (9H, s, H^{1}). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 163.9 ($C^{1'}$), 146.5 ($C^{3'}$), 135.2 ($C^{4'}$), 130.4 ($C^{2'}$), 129.1 ($C^{5'}$), 128.0 ($C^{6'}$), 125.7 ($C^{7'}$), 57.7 (C^{2}), 22.6 (C^{1}). **IR** ($CHCl_3$): ν 2962m, 2927m, 2874m (3 × C-H), 1622s (C=N), 1494s, 1474s, 1454s, 1363s, 1184m, 1084s (S=O), 760s, 701s cm^{-1}. **MS** (ESI+): *m/z* 236 $[M+H]^+$; HRMS: found 236.1112, $C_{13}H_{18}NOS$ requires 236.1104 (σ 3.6 ppm). This data was concordant with literature values.[119]

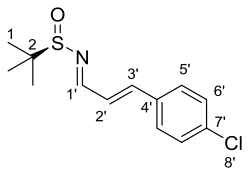
(*R*)-(*E*)-*N*-((*E*)-3'-(4-methylphenyl)prop-2'-en-1'-ylidene)-2-methylpropane-2-sulfinamide (*R*)-(1c)



Attained by general procedure 1 using *trans*-4-methylcinnamaldehyde (0.99 g, 6.7 mmol), $Ti(OEt)_4$, (5.1 mL, 5.5 g, 25 mmol), and (*R*)-*tert*-butyl sulfinamide (740 mg, 6.1 mmol). Recrystallisation from

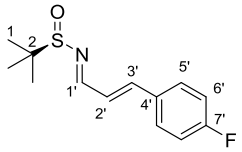
Et_2O/hexanes *via* slow evaporation gave (*R*)-**(1c)** as pale yellow needles (720 mg, 47%). **Mp** 59-61 °C. **$[\alpha]_D^{24}$** 252.2 (*c* = 1.0, $CHCl_3$). **R_f** (hexanes:EtOAc (3:1)): 0.42. **^{1}H NMR** ($CDCl_3$, 400.1 MHz) δ 8.36 (1H, d, *J* = 9.3 Hz, $H^{1'}$), 7.46 – 7.41 (2H, m, $H^{5'}$), 7.25 – 7.19 (3H, m, $H^{2',6'}$), 7.04 (1H, dd, *J* = 15.9, 9.3 Hz, $H^{3'}$), 2.38 (3H, s, $H^{8'}$), 1.23 (9H, s, H^1). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 164.1 ($C^{1'}$), 146.7 ($C^{3'}$), 140.9 ($C^{4'}$), 132.5 ($C^{2'}$), 129.9 ($C^{5'}$), 128.1 ($C^{6'}$), 124.8 ($C^{7'}$), 57.7 (C^2), 22.7 (C^1), 21.7 ($C^{8'}$). **IR** ($CHCl_3$): ν 3126, 3081, 3008, 2966, 2926, 2902, 2868 (C-H), 1624 (C=N), 1607, 1578, 1474, 1457, 1365, 1158, 1064 (S=O), 997, 944 cm^{-1}. **MS** (ESI+): *m/z* 250 $[M+H]^+$; HRMS: found 250.1266, C14H20NOS requires 250.1260 (σ 2.2 ppm). **CHN** %C, 67.1; %H, 7.72; %N, 5.50; $C_{14}H_{19}NOS$ requires %C, 67.4; %H, 7.7; %N, 5.6.

(*R*)-(*E*)-*N*-((*E*)-3'-(4-chlorophenyl)prop-2'-en-1'-ylidene)-2-methylpropane-2-sulfinamide (*R*)-(1d)



Attained by general procedure 1 using *trans*-4-chlorocinnamaldehyde (120 mg, 0.72 mmol), $Ti(OEt)_4$, (550 μL, 600 mg, 2.6 mmol), and (*R*)-*tert*-butyl sulfinamide (79 mg, 0.65 mmol). Recrystallisation from Et_2O/hexanes *via* slow evaporation gave (*R*)-**(1d)** as cuboid orange crystals (170 mg, 99%). **R_f** (hexanes:EtOAc(3:1)): 0.45. **^{1}H NMR** ($CDCl_3$, 400.1 MHz): δ 8.37 (1H, d, *J* = 9.0, $H^{1'}$), 7.48 (2H, d, *J* = 8.7 Hz, $H^{6'}$), 7.38 (2H, d, *J* = 8.7 Hz, $H^{5'}$), 7.19 (1H, d, *J* = 15.9, $H^{3'}$), 7.05 (1H, dd, *J* = 15.9, 9.1, $H^{2'}$), 1.24 (9H, s, H^1). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 163.6 ($C^{1'}$), 144.8 ($C^{3'}$), 129.4 ($C^{2'}$), 129.2 ($C^{6'}$), 126.2 ($C^{5'}$), 57.8 (C^2), 22.7 (C^1). **IR** ($CHCl_3$): ν 3053, 3005, 2966, 2928, 2903, 2869 (C-H), 1625 (C=N), 1577, 1492, 1475, 1457, 1407, 1365, 1180, 1089, 1067 (S=O), 1013, 995, 943 cm^{-1} **MS** (ESI+): *m/z* 270 $[M+H]^+$; HRMS: found 270.0721, C13H17ClNOS requires 270.0714 (σ 2.8 ppm). **CHN** %C, 57.6; %H, 6.13; %N, 5.08; $C_{13}H_{17}NOS$ requires %C, 57.9; %H, 6.0; %N, 5.2.

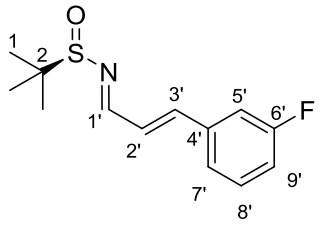
(*R*)-(*E*)-*N*-((*E*)-3'-(4-fluorophenyl)prop-2'-en-1'-ylidene)-2-methylpropane-2-sulfinamide (*R*)-(1e)



Attained by general procedure 1 using *trans*-4-fluorocinnamaldehyde (592 mg, 3.9 mmol), $Ti(OEt)_4$, (3.0 mL, 3.3 g, 14 mmol), and (*R*)-*tert*-butyl sulfinamide (435 mg, 3.6 mmol). Recrystallisation from Et_2O/hexanes *via* slow evaporation gave (*R*)-**(1e)** as colourless plates (928 mg, 93%). **Mp** 57-58 ^oC. **$[\alpha]_D^{24}$** -193.4 (*c* = 1.0, $CHCl_3$). **R_f** (hexanes:EtOAc(3:1)): 0.40. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.36 (1H, d, *J* = 9.2), 7.53 (2H, dd, *J* = 8.6, 5.4), 7.20 (d, 1H, J = 15.9), 7.09 (2H, tt, *J* = 2.1, 8.6), 7.00 (1H, dd, *J* = 15.9, 9.2), 1.23 (9H, s). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.0 (d, *J* = 251.7 $C^{7'}$), 163.7 ($C^{1'}$), 145.1 ($C^{3'}$), 131.4 (d, *J* = 3.5, $C^{4'}$), 129.9 (d, *J* = 8.5 $C^{5'}$), 125.5 (d, *J* = 2.2, $C^{2'}$), 116.3 (d, *J* = 22.0, $C^{6'}$), 57.7 (C^2), 22.6 (C^1). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.51 (tt, *J* = 8.4, 5.4). **^{19}F{H} NMR** (376 MHz, $CDCl_3$): δ -109.51. **IR** ($CHCl_3$): ν 3003, 2966, 2927, 2901, 2868, 1627 (C=N), 1603, 1457, 1297, 1157, 1013 (S=O), 996, 961 cm^{-1}. **MS** (ESI+): *m/z* 254 $[M+H]^+$; HRMS: found 254.1019, $C_{13}H_{17}FNOS$ requires 254.1009 (σ 3.6 ppm). **CHN** %C, 61.8; %H, 6.43; %N, 5.39; $C_{13}H_{16}FNOS$ requires %C, 61.6; %H, 6.4; %N, 5.5.

It is notable that this compound exhibits fluorine coupling for carbon $C^{2'}$ but not carbon $C^{3'}$.

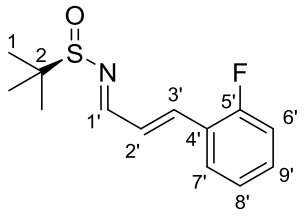
(*R*)-(*E*)-*N*-((*E*)-3'-(3-fluorophenyl)prop-2'-en-1'-ylidene)-2-methylpropane-2-sulfinamide (*R*)-(1f)



Attained by general procedure 1 using *trans*-3-fluorocinnamaldehyde (608 mg, 4.0 mmol), $Ti(OEt)_4$, (3.1 mL, 3.4 g, 15 mmol), and (*R*)-*tert*-butyl sulfinamide (440 mg, 3.7 mmol). Recrystallisation from Et_2O/hexanes *via* slow evaporation gave (*R*)-**(1f)** as pale orange cubes (835 mg, 81%). **R_f** (hexanes:EtOAc(3:1)): 0.41. **^{1}H NMR** ($CDCl_3$, 400.1 MHz): δ 8.37 (1H,

d, *J* = 9.1, $H^{1'}$), 7.41 – 7.25 (4H, m, $H^{5\text{-}8'}$), 7.20 (1H, d, *J* = 15.9, $H^{3'}$), 7.08 (1H, dd, *J* = 8.9, 15.9, $H^{2'}$), 1.24 (9H, s, H^{1}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 163.5 ($C^{1'}$), 163.2 (d, *J* = 246.9, $C^{6'}$), 144.8 (d, *J* = 2.8, $C^{3'}$), 137.4 (d, *J* = 7.8, $C^{4'}$), 130.6 (d, *J* = 8.2, $C8^{'}$), 126.9 ($C^{2'}$), 124.0 (d, *J* = 2.8, $C^{7'}$), 117.2 (d, *J* = 21.4, $C^{5'}$), 114.2 (d, *J* = 22.0, $C^{9'}$), 57.9 (C^{2}), 22.7 (C^{1}). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -112.41 (td, *J* = 9.0, 5.7). **^{19}F{H} NMR** (282 MHz, $CDCl_3$): δ -112.41. **MS** (ESI+): *m/z* 254 $[M+H]^+$; HRMS: found 254.1017, $C_{13}H_{17}FNOS$ requires 254.1009 (σ 3.0 ppm). **CHN** %C, 61.5; %H, 6.30; %N, 5.43; $C_{13}H_{16}$ FNOS requires %C, 61.6; %H, 6.4; %N, 5.5.

(*R*)-(*E*)-*N*-((*E*)-3'-(2-fluorophenyl)prop-2'-en-1'-ylidene)-2-methylpropane-2-sulfinamide (*R*)-(1g)

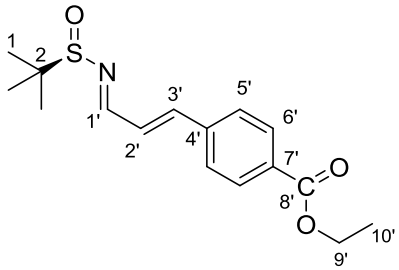


Attained by general procedure 1 using *trans*-2-fluorocinnamaldehyde (368 mg, 2.5 mmol), $Ti(OEt)_4$, (2.1 mL, 2.2 g, 9.8 mmol), and (*R*)-*tert*-butyl sulfinamide (270 mg, 2.2 mmol). Recrystallisation from Et_2O/hexanes *via* slow evaporation gave (*R*)-**(1g)** as deeply orange cubes (611 mg, 99%). **$[\alpha]_D^{23}$** -299.7 (*c* = 0.4, $CHCl_3$). **R_f** (hexanes:EtOAc(3:1)): 0.43. **^{1}H NMR** ($CDCl_3$, 400.1 MHz): δ 8.39 (1H, d, *J* = 9.2, $H^{1'}$) 7.58 (1H, td, *J* = 1.7, 7.7, H^{Ar}), 7.40 (1H, d, *J* = 16.2, $H^{3'}$) 7.35 – 7.10 (3H, m, H^{Ar}), 7.17 (1H, dd, *J* = 9.3, 16.1, $H^{2'}$), 1.24 (9H, s, H^{1}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.1 ($C^{1'}$), 161.2 (d, *J* = 253.8, $C^{5'}$), 138.8 (d, *J* = 3.2 $C^{3'}$), 131.8 (d, *J* = 8.7, $C^{7'}$), 128.6 (d, *J* = 2.8 $C^{8'}$), 127.9 (d, *J* = 6.0, $C^{9'}$), 124.7 (d, *J* = 3.7, $C^{2'}$), 123.3 (d, *J* = 11.7, $C^{4'}$)[1], 116.4 (d, *J* = 21.9, $C^{6'}$), 57.8 (C^{2}), 22.7 (C^{1}). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -114.91 (ddd, *J* = 10.7, 7.4, 5.3). **^{19}F{H} NMR** (282 MHz, $CDCl_3$): δ -114.91. **IR** ($CHCl_3$): ν 3048, 2978, 2926, 2902, 2868, 1698 (C=N), 1625, 1458, 1287, 1159, 1034 (S=O), 997, 964 cm^{-1}. **MS** (ESI+): *m/z* 254 $[M+H]^+$; HRMS: found 254.1012,

$C_{13}H_{17}FNOS$ requires 254.1009 (σ 1.2 ppm). **CHN** %C, 61.7; %H, 6.01; %N, 4.85; $C_{13}H_{16}$ FNOS requires %C, 61.6; %H, 6.4; %N, 5.5.

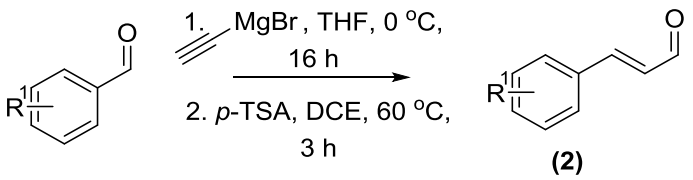
[1] This integration was weak as is typical of quaternary carbon signals, and so was assigned to carbon $C^{4'}$.

(*R*)-(*E*)-*N*-((*E*)-3'-(4-ethylbenzoate)prop-2'-en-1'-ylidene)-2-methylpropane-2-sulfinamide (*R*)-(1h)



Attained by general procedure 1 using *trans*-4-methoxycarbonylcinnamaldehyde (470 mg, 2.5 mmol), $Ti(OEt)_4$, (1.9 mL, 2.1 g, 9.0 mmol), and (*R*)-*tert*-butyl sulfinamide (270 mg, 2.3 mmol). Recrystallisation from refluxing hexanes gave (*R*)-**(1h)** as a pale yellow amorphous solid (510 mg, 67%). **Mp** 72-73 ^{o}C. $\mathbf{[\alpha]_D^{18}}$ -131.0 (*c* = 0.75, $CHCl_3$). $\mathbf{R_f}$ (hexanes:EtOAc (4:1)): 0.43. $^{\mathbf{1}}$**H** NMR ($CDCl_3$, 400.1 MHz) δ 8.40 (1H, d, *J* = 8.9, $H^{1'}$), 8.09 – 8.03 (2H, m, $H^{6'}$), 7.60 (2H, d, *J* = 8.4, $H^{5'}$), 7.26 (1H, d, *J* = 15.9, $H^{3'}$), 7.16 (1H, dd, *J* = 15.9, 8.9, $H^{2'}$), 4.40 (2H, q, *J* = 7.1, $H^{9'}$), 1.41 (3H, t, *J* = 7.1, $H^{10'}$), 1.25 (9H, s, H^{1}). $^{\mathbf{13}}$**C NMR** ($CDCl_3$, 101 MHz): δ 166.0 ($C^{8'}$), 163.3($C^{1'}$), 144.7 ($C^{3'}$), 139.1 ($C^{7'}$), 131.6 ($C^{4'}$), 130.1 ($C^{6'}$), 127.7 ($C^{5'}$), 127.5 ($C^{2'}$), 61.2 ($C^{9'}$), 57.8 (C^{2}), 22.5 (C^{1}), 14.3 ($C^{10'}$). **IR** ($CHCl_3$): ν 3009m, 2988m, 2966m (3 × C-H), 1714s (C=O), 1654 (C=N), 1625, 1609, 1392, 1281, 1180, 1068 (S=O), 1018, 876 cm^{-1}. **MS** (ESI+): *m/z* 308 $[M+H]^+$; HRMS: found 308.1320, $C_{16}H_{22}NO_3S$ requires 308.1315 (σ 1.6 ppm).

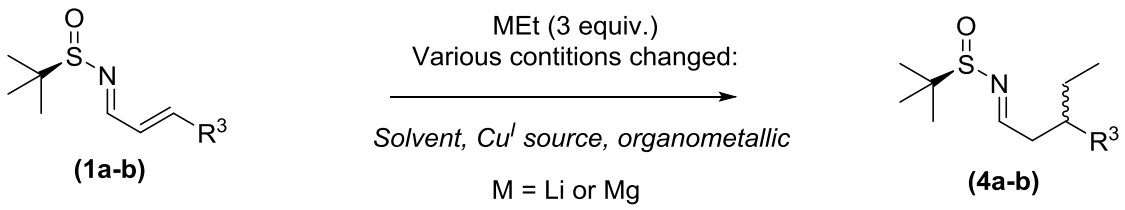
General procedure 2. Preparation of cinnamaldehydes (2)



(2)

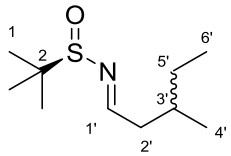
In a Schlenck tube freshly distilled, dry THF (32 mL) and precursor aldehyde (34 mmol, 1 equiv.) were combined and stirred at 0 ^{o}C (10 min). A solution of ethynylmagnesium bromide (75 mL of a 0.5 M THF solution, 37 mmol, 1.1 equiv.) was added and the mixture stirred at 0 ^{o}C overnight. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ solution and then extracted with EtOAc (3 × 30 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and evaporated to give the crude orange or brown oils. The oils were dissolved in DCE (15 mL) and combined with *p*-TSA·H_2O (0.75 g, 4.3 mmol, 0.3 equiv.) and stirred at 60 ^{o}C until the propargyl alcohol was completely consumed [R_f (hexanes:EtOAc (4:1)) of compounds **(2)** ~0.65, R_f of starting propargyl alcohols **(3)** ~0.35], typically 24-72 h. The reaction was cooled to 20 ^{o}C and quenched with $NaHCO_{3(aq)}$ solution. The resulting emulsion was washed with DCM (3 × 40 mL) and separated. The DCM fraction was dried ($MgSO_4$), filtered, and evaporated to give the crude products as black or brown oils. The oils were triturated with hot hexanes (3 x 50 ml) and the extracts re-evaporated to less dark oils. The procedure was repeated until no hexane insoluble residues remained (typically 3 iterations). This provided yellow or brown amorphous solids in 5-25% yield. The presence of cinnamaldehydes **(2)** was confirmed by ^{1}H NMR of the crude materials by identifying a signature doublet at ~9.5 ppm, and these were used without further purification.

General procedure 3. Synthesis of β–ethyl sulfinimines (4) *via* Gilman reagent



In a Schlenk flask solid Cu^I salt (0.87 mmol, 1.5 equiv.) and solvent (5 mL), and were combined and stirred at -45 ^oC (10 min.). To the solution was added ethyl organometallic reagent (Solutions in hexanes, 1.7 mmol, 3.0 equiv.) and then stirred at -45 ^oC (10 min). To the solution was added precursor sulfinimine **(1a-b)** (0.577 mmol, 1.0 equiv. solution in solvent (0.5 mL)) and stirred at -45 ^oC (5 h). The solution was warmed to 20 ^oC, quenched with saturated $NH_4Cl_{(aq)}$ solution, and then extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give the crude products as yellow oils. The yellow oils were further purified by preparative thin layer chromatography (2000 micron plates, hexanes:EtOAc (4:1), [R_f (hexanes:EtOAc (5:1)) of compounds **(4)** ~0.55, R_f of starting **(1)** ~0.45]). This provided yellow oils in up to 51% yield. See Chapter 2 for detailed yield information. Sulfinimines (**4a-b)** are described below and named using the nomenclature of *Chemical Abstracts*.

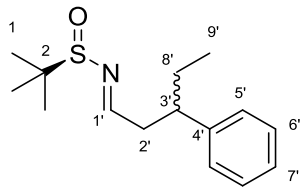
(*R*)-(*E*)-*N*-(3-methylpentylidene)propane-2-sulfinamide (4a)[2]



Obtained as a yellow oil. **R_f** (hexanes:EtOAc(3:1)): 0.51. **^{1}H NMR** ($CDCl_3$, 400.1 MHz): δ 8.06 (1H, m), 2.54 (1H, m), 2.34 (1H, m), 1.84 (1H, m), 1.42 (1.25H, m), 1.28 (n.d, m), 1.20 (9H, s), 0.96 (3H, d, *J* =

6.7), 0.91 (3H, t, *J* = 7.4). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 169.6, 56.5, 42.9, 32.4, 29.4, 22.4, 19.4, 11.3. **MS** (ESI+): *m/z* 204 $[M+H]^+$; HRMS: found 204.1433, $C_{10}H_{22}NOS$ requires 204.1422 (σ 4.0 ppm).

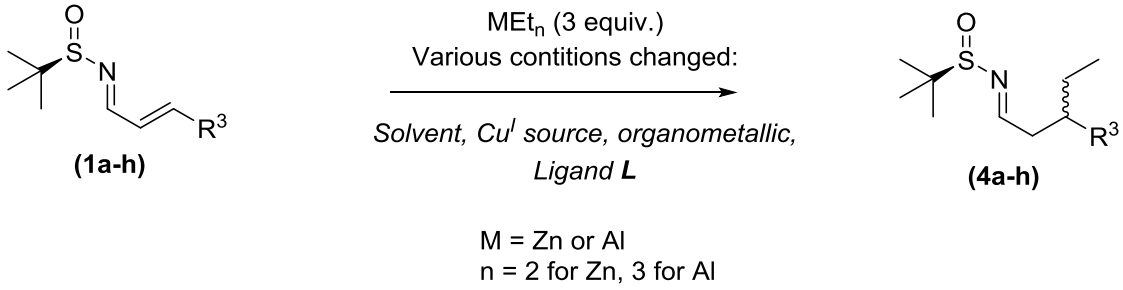
(*R*)-(*E*)-*N*-(3-phenylpentylidene)propane-2-sulfinamide (4b)[2]



Obtained as a yellow oil. **R_f** (hexanes:EtOAc(3:1)): 0.48. **^{1}H NMR** ($CDCl_3$, 400.1 MHz): δ 7.98 (1H, d, *J* = 4.4), 7.27 (m), 7.16 (m), 2.91 (m), 2.83 (m), 1.74 – 1.65 (m), 1.04 (9H, s), 0.80 (3H, d, *J* = 7.4). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 169.0, 143.9, 129.0, 128.1, 127.0, 56.9, 45.2, 43.2, 30.1, 22.6, 12.4. **MS** (ESI+): *m/z* 288 $[M+Na]^+$; HRMS: found 288.1390, $C_{15}H_{23}NNaOS$ requires 288.1393 (σ 0.7 ppm).

[2] For these compounds, NMR integration data was not informative. Only the major diastereomer is reported. See Sections 2.2 and 2.3 for further explanation.

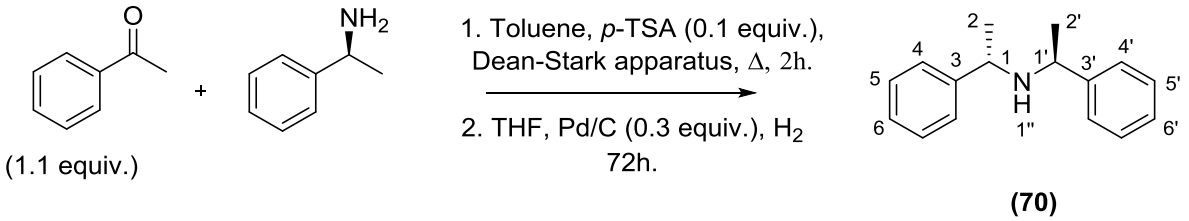
General procedure 4. Synthesis of β–ethyl sulfinimines (4) *via* catalytic copper nucleophiles



In a Schlenk flask solid Cu^I salt (0.023 mmol, 0.04 equiv.), solvent (5 mL), ligand **L** (0.035 mmol, 0.06 equiv., see Chapter 2) and precursor sulfinimine **(1a-h)** (0.577 mmol, 1.0 equiv.) were combined and stirred (-45 ^{o}C to 10 ^{o}C) for 10 min. To the solution was added ethyl organometallic reagent (Solutions in hexanes, 1.7 mmol, 3.0 equiv.) and then stirred (-45 ^{o}C

to 10 °C) for 16 h. The solution was warmed to 20 °C, quenched with methanol (1 mL), and then and evaporated to give the crude products as foul-smelling yellow oils. To the yellow oils was added 1,3,5-trimethoxybenzene (50 mg). Yield and *d.r.* value information was obtained from crude ^{1}H NMR spectra. See Section 2.4.2 for a detailed explanation.

Synthesis of (*S*)-*N*-((*S*)-1'-phenylethanyl)-1-phenylethan-1-amine (*S*,*S*)-(70)

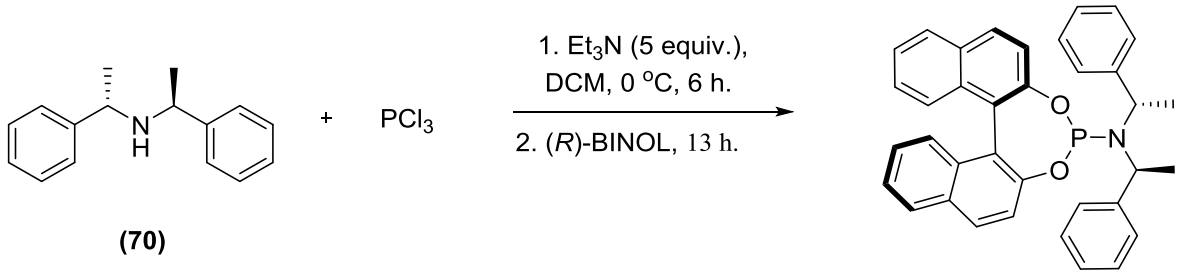


(70)

In a round bottomed flask equipped with a Dean-Stark adaptor freshly distilled toluene (50 mL), acetophenone (9.1 mL, 8.9 g, 71 mmol, 1.0 equiv.), and *p*-TSA·H_2O (0.5 g, 0.1 equiv.) were combined and stirred at 20 °C (5 min). Neat (*S*)-1-phenylethan-1-amine (10 mL, 9.8 g, 71 mmol, 1.0 equiv.) was added and the solution stirred at reflux until no more water was distilled (1.6 mL). The mixture was cooled to 20 °C then vacuum filtered and evaporated to provide a yellow oil (20 g, 110 %). To this oil was added freshly distilled THF (50 mL) and Pd/C (10 % w/w, 2 g) then stirred at 20 °C under an atmosphere of $H_{2(g)}$ until no further consumption of gas occurred (48 h, 1705 mL). This mixture was filtered and the residue washed with Et_2O (3 × 10 mL), then evaporated to provide crude (*S*)-**(70)** as a dark yellow oil. The crude product was diluted with Et_2O (50 mL) and sparged with $HCl_{(g)}$ to yield a white precipitate, then filtered and the residue washed with Et_2O (3 × 10 mL). The white powder was then recrystallized from refluxing EtOAc to yield solid white needles. Saturated $NaOH_{(aq)}$ solution (10 mL) was added to the needles and stirred at 20 °C until complete consumption of the solid occurred (2 h.). The resulting emulsion was washed with DCM (3 ×

20 mL) and separated. The DCM fraction was dried ($MgSO_4$), filtered, and evaporated to yield (*S,S*)-**(70)** as a pale yellow oil (6.6 g, 41%). **^{1}H NMR** (500.0 MHz, $CDCl_3$): δ 7.36 – 7.31 (m, 2H, $H^{4, 4'}$), 7.26 (dt, *J* = 4.4, 1.7, 1H, $H^{6, 6'}$), 7.25 – 7.20 (m, 2H, $H^{5, 5'}$), 3.51 (q, *J* = 6.7, 1H, $H^{1, 1'}$), 1.59 (s, 1H, $H^{1''}$), 1.28 (d, *J* = 6.7, 3H, $H^{2, 2'}$). **^{13}C NMR** ($CDCl_3$, 126 MHz): δ 146.4 ($C^{3, 3'}$), 129.0 ($C^{4,4'}$), 127.3 ($C^{6, 6'}$), 127.2 ($C^{5, 5'}$), 55.7 ($C^{1, 1'}$), 25.6 ($C^{2, 2'}$). **MS** (ESI+): *m/z* 248 $[M+Na]^+$; HRMS: found 248.1403, $C_{16}H_{19}NNa$ requires 248.1410 (σ 2.7 ppm). These data are concordant with the literature values.[120]

Synthesis of (*R,S,S)*-(52)



(70) **(52)**

In a round bottomed flask equipped with a reflux condenser freshly distilled DCM (43 mL) and freshly distilled PCl_3 (1.9 mL, 1.8 g, 22 mmol, 1.0 equiv.) were combined and stirred (10 min). Freshly distilled triethylamine (15 mL, 10 g, 108 mmol, 5.0 equiv.) was added to the solution and stirred at 0 °C until the white precipitate dissolved (30 min). Neat (*S,S*)-**(70)** (4.8 mL, 4.8 g, 21.5 mmol, 1.0 equiv.) was added and the solution stirred at 0 °C (6 h). Solid (*R*)-BINOL (6.2 g, 22 mmol, 1.0 equiv.) was added slowly over 10 min, then stirred (13 h). The reaction was quenched with water (3 × 20 mL) and separated. The DCM fraction was dried ($MgSO_4$), filtered, and evaporated to provide crude (*R,S,S)*-**(52)** as a yellow foam. The crude foam was filtered over neutral alumina and further eluted with DCM (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield a white

foam. The foam was further purified by crystallisation from a DCM solution layered with pentane to yield thick, clear, colourless, pentagonal crystals of (*R,S,S)*-**(52) (**8.2 g, 69%). **R_f** (hexanes:EtOAc(4:1)): 0.50. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.8, 2H), 7.92 – 7.87 (m, 2H), 7.59 (d, *J* = 8.8, 1H), 7.44 – 7.35 (m, 4H), 7.30 – 7.19 (m, 4H), 7.15 – 7.05 (m, 9H), 4.50 (q, *J* = 6.9, 2H), 1.72 (d, *J* = 7.1, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 150.0, 149.9, 142.7, 132.7, 131.3, 130.4, 130.2, 129.3, 128.2, 128.0, 127.8, 127.6, 127.1, 127.0, 126.5, 125.9, 124.7, 124.3, 122.3, 52.2, 52.1, 21.9. **MS** (ESI+): *m/z* 540 $[M+H]^+$; HRMS: found 540.2084, $C_{36}H_{31}NO_2P$ requires 540.2087 (σ 0.5 ppm). These data are concordant with the literature values.[121]

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