UNIVERSITY OF SOUTHAMPTON

ABSTRACT

Doctor of Philosophy

Optimisation of Catalytic Systems using Design of Experiment Methodologies

by Catherine Anne McNamara

A Sharpless ligand with a novel triazene core was synthesised in two simple, high yielding steps from cheap, readily available starting materials. The ligand showed good selectivity in the asymmetric dihydroxylation of alkenes, and its optimisation was undertaken in collaboration with Dr D. C. Woods and Professor S. M. Lewis of Southampton Unversity's Statistical Sciences Research Institute. Using a number of statistical designs and experimental methods, the results showed that the conditions reported and currently used were optimal. In the process of the investigation a greater understanding of the factors affecting the reaction was obtained.

In a second example, C-C bond formation was optimised using a supported palladium catalyst. Four different sulfur containing pincer ligands were synthesized and attached to four different solid supports. Subsequent complexation with palladium gave 16 different polymer supported catalysts which were active catalysts in the Heck reaction. The optimisation of this system with regards to both conversion and palladium leaching was undertaken using the experimental design software, MODDE which showed that solvent had the largest effect on both responses. The cHexyl thiol moiety was superior to its phenyl counterpart which is most commonly adopted. In the Heck reaction of 4-bromo acetophenone the conversion was improved from 30 % with large observable leaching to 88 % with no observable leaching varying 6 factors corresponding to 5760 possibilities.

To Mum, Dad, and Fliss.

Contents

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Finally and most importantly I would like to thank my family, Mum, Dad, Fliss (and Tom). Your love and constant support is also why I'm here. This could not have been achieved without you and I gratefully dedicate this thesis to you.

Abbreviations

AIBN	1,2'-Azobix(2-methylpropionitrile)
ALK	Alkaloid
ANOVA	Analysis of Variance
Boc	*tert*-butoxycarbonyl
Bu	butyl
cat	catalytic
CCC	Circumscribed Central Composite
CCF	Face centred Central Composite
CCI	Inscribed Central Composite
COST	Changing One Single Factor at a Time
δ	chemical shift
d	doublet
dd	doublet of doublets
dba	dibenzylideneactone
DBU	1,8-diazabicylo[5.4.0]undec-7-ene
DCM	dichloromethane
df	degrees of freedom
DHP	dihydropyran
DIC	1,3-diisopropylcarbodiimide
DIPEA	*N*-ethyldiisopropylamine
DMAP	4-(*N*-*N*-dimethylamino)pyridine
DMF	dimethylformamide
DoE	Design Of Experiments
D-Optimal	Determinant Optimal
DVB	divinylbenzene
e.e.	enantiomeric excess
Et	ethyl
Equiv	equivalents
Fmoc	fluoren-9-ylmethoxycarbonyl
h	hour(s)
HMBA	4-hydroxymethyl benzoic acid
HOBt	1-hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
HQD	hydroquinidine
HQN	hydroquinine
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infra-red
J	coupling constant
L	litres
LC	Liquid Chromatography
m	multiplet
Me	methyl
mins	minutes
MS	mean sum of squares
MS	mass spectrometry
MsCl	methanesulfonyl chloride
NMO	*N*-methylmorpholine *N*-oxide

NMR	nuclear magnetic resonance
o/n	overnight
OVAT	One Variable at a Time
PEG	polyethylene glycol
Ph	phenyl
PHAL	phthalazine
PS	polystyrene
*p*PTS	*p*-pyridinium toluenesulfonate
*p*TsOH	*p*-toluene sulfonic acid
PTC	phase transfer catalyst
QN	quinine
QD	quinidine
press	pressure
quant	quantitative
quar	quartet
r.t.	room temperature
s	singlet
SS	sum of squares
SSE	sum of squares for error
SST	sum of squares for treatments
t	triplet
TBDMS	*tert*butyldimethylsilyl
^{t}Bu	*tert*Butyl
temp	temperature
TFA	trifluoroacetic acid
Tf	triflate
THP	tetrahydropyran
THF	tetrahydrofuran
TLC	thin layer chromatography
TPAP	*tetra-N*-propylammonium perruthenate
TREAT.HF	triethylamine trihydrofluoride
TRZ	triazene

1 Introduction

1.1 Combinatorial Chemistry and the Design of Experiments

Over the last decade combinatorial chemistry has been one of the most rapidly expanding areas within the pharmaceutical industry enabling the parallel synthesis and screening of thousands of compounds. This technology, coupled with advances in automation,[1-3] and the development of polymer supported catalysts and reagents, have massively increased the efficiency of the chemist in the drug discovery process.

All library syntheses' rely on the efficient conversion of reactants into products, which can involve numerous different possibilities of reagents and reaction conditions. Indeed, the development of a reaction to be carried out in a high throughput fashion can often be far more time consuming and problematic than carrying out the whole process of identifying a lead compound from a library array.[4]

When a new reaction is carried out for the first time is very rare that all desirable criteria e.g. yield, by-product formation, temperature, or time are optimal in the first instance, in fact, in most cases, the optimum may never be reached, or may require several stages of experimentation. Often there is little or insufficient data in the literature and observations and knowledge concerning the reaction must come from experimentation, which can be extremely lengthy and laborious.

1.2 The Classical Approch

Traditionally, chemists in all disciplines have varied factors sequentially in a serial fashion to optimise reactions. Entitled the OVAT (One Variable at A Time) or the COST (Changing One Single Factor at a Time) this limited technique is illustrated below.[5]

Consider a process which is affected by temperature and pressure, with two classic series' of experiments conducted to optimise the yield. In the first

instance the temperature is held at 50 °C and the pressure varied, in the second the pressure is fixed (at the established maxima of 100 bar) and the temperature varied to give the results are shown in Figure 1.

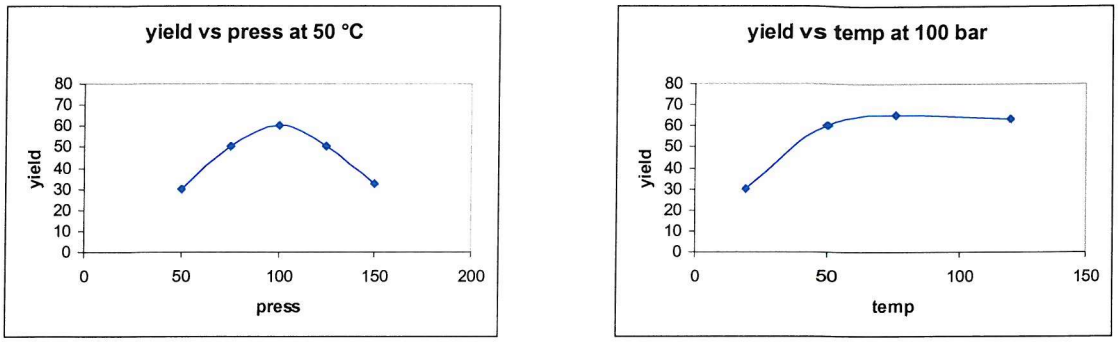


Figure 1 Yield vs Pressure and Temperature Plots

From this it can be concluded that the optimum operating conditions for the process are 100 bar and 75 °C. However this approach has made limited use of the design space of the reaction and in reality the true situation may be that shown in Figure 2.

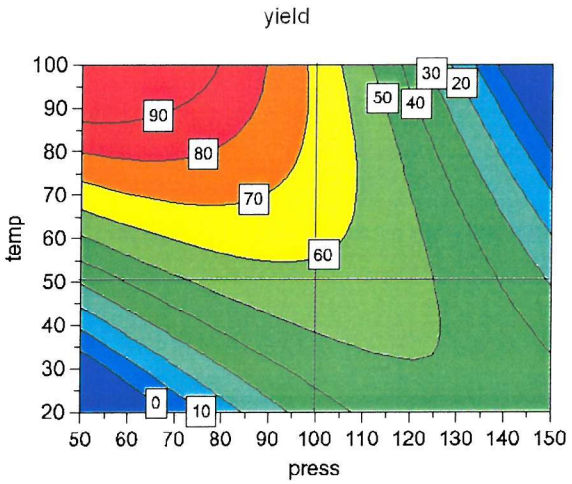


Figure 2 Contour Plot for Temperature Pressure Effects

Because of the interaction between a lower pressure and a higher temperature a local optima is present, which because of the poor occupation of the design space in this experiment conventional screening would fail to discover or predict the optimum conditions.

1.3 The Design of Experiments Approach

Design of experiment (DoE) techniques aim to devise a small set of experiments, over which all the factors which are considered important to a reaction are varied systematically, to yield the maximum amount of information from the minimum number of experiments. At least four stages of experimentation are generally carried out namely; pilot or scoping experiments, screening experiments, optimisation experiments and verification experiments. These are discussed in sections 1.3.1 - 1.3.4. When using DoE it is important that experimental errors occur randomly and not over a certain factor range and therefore experiments should be carried out in a random order. This is mainly because: (a) experimental skill is improved with time, (b) some reagents may have limited lifetimes, (c) the performance of the equipment may degrade with time and (d) if more than one chemist is performing the experiments they may have different levels of skill.

1.3.1 Pilot/Scoping Experiments

One or several scoping or pilot experiments, which should contain several replicates, are carried out to assess the experimental procedure. Reactions and analysis should be carried out exactly as they are to be carried out in the real experiment. As well as being an "equipment reliability test" this stage serves as a way of identifying problematic procedures, e.g. transfer or reagents or the removal of aliquots for sampling, in the experiment, which may have to be altered. Reactants can also be selected at this stage.

1.3.2 Screening Experiments

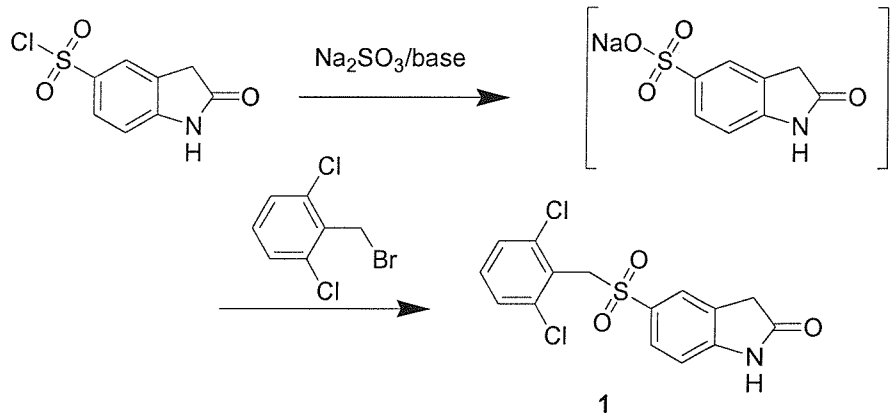
The aim of this stage is to advance from a position where little is known about the importance of the factors to one where an approximate "direction in which to proceed" can be established. Factors which have a real influence on the results are identified and therefore all factors to be considered must be included in this phase of experimentation. A larger screening experiment with a greater number of factors is far superior to a series' of experiments where factors are sequentially added to create smaller sets of experiments. Depending upon the

number of factors and the type of design, interactions between the factors can also be assessed.[5]

1.3.2.1 2 Level Full Factorial Designs.

Due to their simplicity, ease of construction, and the wealth of information acquired two level Factorial and Fractional Factorial Designs are most commonly used in screening in Experiments. These designs involve carrying out reactions which have coefficients at the extreme vertices of the "reaction space" i.e. factors are generally set at both their highest and lowest levels and combined with other factors also in their high and low states. Construction and analysis of a full factorial design is demonstrated by a recent account from Chen[6] which is given below.

Sulfone **1** was required on a kilogram scale, preferably via a one pot procedure for the preparation of an active pharmaceutical ingredient. The authors settled on a cheap, two-step, sodium sulfite mediated procedure as shown in Scheme 1 which initially resulted in only 30 % overall yield.



Scheme 1 Synthesis of Sulfonate **1**

Various scoping experiments had shown that the alkylation step (step 2) was facile and attention was therefore focussed on optimising step 1. Three factors were judged to have the greatest impact on this step: equivalents of sulfite (**A**), time (**B**) and temperature (**C**) and are shown in Table 1 with their high and low

levels denoted by 1 and -1 respectively (Table 1A). Systematic variation of the factors to include all high and low possibilities result in the shown design matrix (Table 1B) from which reactions 1 – 8 are formulated as the experiments to fulfil the design criterion (Table 1C). Centre points can be added to the design (Table 1C, line C) which are values at the mid-point of the factor settings and are used for predicting curvature i.e. to see if the relationship between a factor setting e.g. temperature and a response e.g. conversion is linear or curved (Figure 3), centre points also add balance to a design.

A

Factors/ levels			
	A	**B**	**C**
1	4	24	100
-1	2	6	60

A = equivalents of sulfite
B = time (hours)
C = temperature (°C)

B

Design matrix		
A	**B**	**C**
1	-1	-1
1	1	-1
1	1	1
1	-1	1
-1	1	1
-1	-1	1
-1	-1	-1
-1	1	-1

C

Experiments			
	A	**B**	**C**
1	4	6	60
2	4	24	60
3	4	24	100
4	4	6	100
5	2	24	100
6	2	6	100
7	2	6	60
8	2	24	60
C	3	18	80

Table 1 Design Matrix for Optimisation of the Synthesis of Sulfone **1**

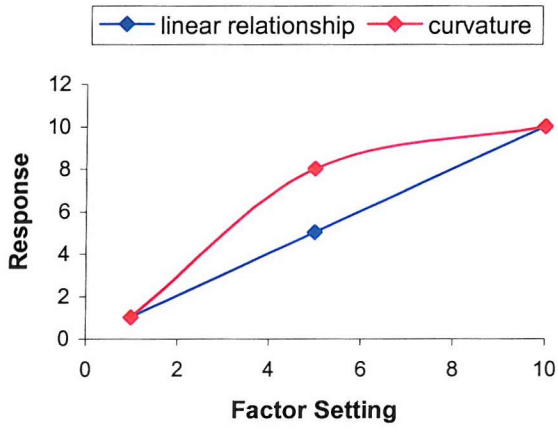


Figure 3 Linear and Curved Relationship between Factor Setting and Response

The design matrix and centre points are depicted pictorially in Figure 4, with the volume of the cube representing the reaction space. A diagram of the reaction space explored using an OVAT approach is also included for comparison.

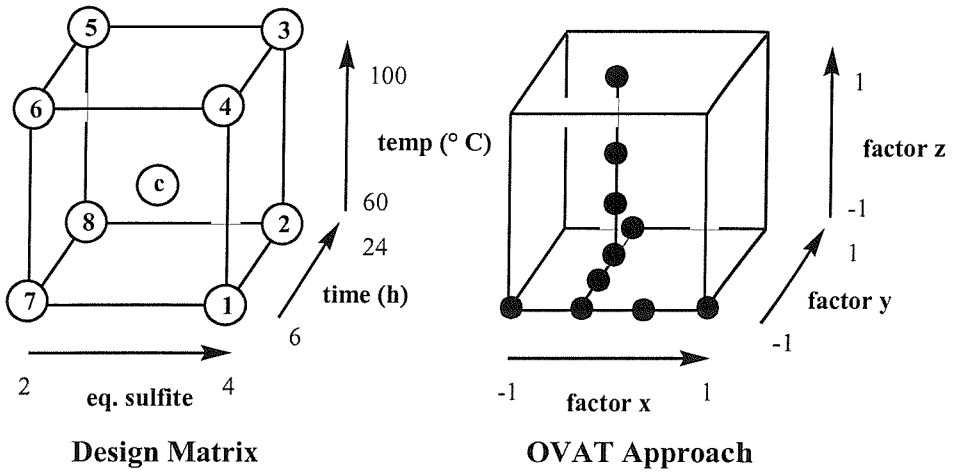


Figure 4 Pictoral Representation of the Design Space Explored by a DoE and an OVAT Approach

When more than three variables are studied the number of cubes is doubled for each additional variable.[4]

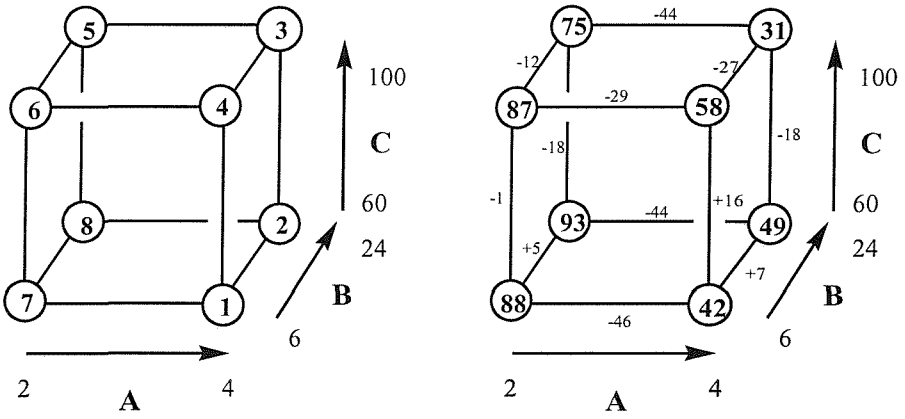
1.3.2.2 Calculation of Effects

For a full factorial examples, all main effects, two factor interactions, and multi factor interactions can be determined.[5]

The experiments which fulfilled the design matrix were carried out and are shown in Table 2. This data is however more conveniently visualised on the corners of a cube (Figure 5).

	eq. of sulfite (A)	Time (hours) (B)	Temp (°C) (C)	yield
1	4	6	60	42
2	4	24	60	49
3	4	24	100	31
4	4	6	100	58
5	2	24	100	75
6	2	6	100	87
7	2	6	60	88
8	2	24	60	93

Table 2 Results for the Optimisation of Sulfone **1**



Values represent experiment Number (Table 2)

Values represent yields (Table 2)

A = equivalents of sulfite, **B** = time (hours), **C** = temperature (°C)

Figure 5 Results for the Optimisation of Sulfone **1**

Immediately some independent factors are evident such as:

(a) The numbers on the right face are lower than those on the left; which indicates that increasing the equivalents of sulfite has a negative effect on the yield,

(b) The numbers on the top face are in most cases lower than those on the bottom; which indicates that an increased temperature has a negative effect on the yield,

(c) The numbers on the back faces are in half of the cases lower, and half of the cases higher than those of the front face, however overall the numbers are higher on the front face: which indicates that an increased time has a negative effect on the yield but a smaller effect than the two previously mentioned. The effects can be computed as follows.

A Main Effects

e.g. Equivalents of sulfite (A). The yield values at the low level of the response i.e. the left hand side of the cube (Figure 5) are subtracted from those at the high level of the response i.e. the right hand side of the cube and the total divided by the number of values (in this case four).

i.e.:

$$\frac{((42-88)+(49-93)+(58-87)+(31-75))}{4} = -40.75$$

In a similar fashion, for time (B), the values on the back face are subtracted from the values on the front face and divided by four, and for temperature (C) the values on the top face are subtracted by the values on the bottom face and divided by four which gives -6.75 and -5.25 respectively. The negative sign indicates that increasing the level of the factor has a negative effect on the yield.

B Interaction Effects

Two Factor Interaction Effects

For a full factorial design, all two factor interactions can be calculated; in this case there are three: equivalents of sulfite and time (AB), equivalents of sulfite and temperature (AC) and time and temperature (BC)

The equivalents of sulfite and time interaction (AB), is defined as ½ the difference between the average equivalents of sulfite effect at both levels of time and is calculated as follows.

At the high level of B, (the back face) the values on the right face (high level of A) are subtracted from those on the left face (low level of A) and divided by the number of values i.e. 2. This is then repeated for the low level of B (the bottom face).

$$A_{B+} = \frac{((49-93)+(31-75))}{2} = -44$$

$$A_{B-} = \frac{((42-88)+(58-87))}{2} = -37.5$$

The difference between the two is then calculated (-6.5) and divided by the number of values i.e. two to give the AB interaction.

$$AB = \frac{-6.5}{2} = -3.25$$

The other two factors are calculated in an analogous manner: for the AC interaction the numbers on the right face (high level of A) are subtracted from the numbers on the left face (low level of A) on the top face of the square (i.e. 58-87 and 31-75) and divided by two to give the A_{C+} interaction, which is then repeated for the bottom face (low level of C), (42-88 and 49-93) to give the A_{C-} interaction. Calculation of the difference and division by two in a similar fashion gives the AC interaction as 4.25. For the BC interaction, to find B_{C+}, on the top face (high level of C), the numbers on the front face are subtracted from the numbers on the back face (31-58 and 75-87), B_{C-} is found by subtracting the numbers on the front face from the numbers on the back face, for numbers on the bottom face (49-42 and 93-88). A similar treatment of the difference gives the interaction as -12.75.

Three Factor Interaction Effects

In this case there is only one three factor interaction, the ABC interaction. This measures the consistency of one of the factors with respect to the other two e.g. the equivalents of sulfite and time (AC) for both levels of temperature (B+ and B-), in this case, instead of adding the values together and dividing them the values are subtracted and then divided by the number of values (2). Thus AC_{B+} is calculated by considering the back face (high level of B) and subtracting each value on the left face from each value on the right face, the found values are then subtracted from each other; this is then repeated for the values on the bottom face to calculate AC_{B-}, both are then divided by two.

$$AC_{B+} \frac{((31-75)-(49-93))}{2} = 0$$

$$AC_{B-} \frac{((58-87)-(42-88))}{2} = -8.5$$

The difference is then calculated and again divided by the number of values, to give the three factor interaction.

$$\frac{-8.5}{2} = -4.25$$

This interaction is symmetric for all factors. It could well have been defined by any factor with respect to the other two i.e. AB at both levels of C and BC at both levels of A.

Calculation for all effects using this method is laborious, especially for more than three factors but serves as a useful illustration of where the effects originate. Using the design matrix is a much more efficient way of calculating the effects[5] whereby the effects can be calculated by simply adding or subtracting the yield value as denoted by the matrix and dividing by half the number of values i.e. 4, thus column A, Table 3 would become:

$$A = \frac{(+42+49+31+58-75-87-88-93)}{4} = -40.75$$

The full model matrix is shown in Table 3 with the values for all effects shown in the final row; the data can then be more conveniently displayed in an effects plot such as that shown in Figure 6.

Expt	A	B	C	AB	AC	BC	ABC	yield
1	1	-1	-1	-1	-1	1	1	42
2	1	1	-1	1	-1	-1	-1	49
3	1	1	1	1	1	1	1	31
4	1	-1	1	-1	1	-1	-1	58
5	-1	1	1	-1	-1	1	-1	75
6	-1	-1	1	1	-1	-1	1	87
7	-1	-1	-1	1	1	1	-1	88
8	-1	1	-1	-1	1	-1	1	93
Effect	**-40.75**	**-6.75**	**-5.25**	**-3.25**	**4.25**	**-12.75**	**-4.25**	

Table 3 Calculation of Main Effects from the Design Matrix

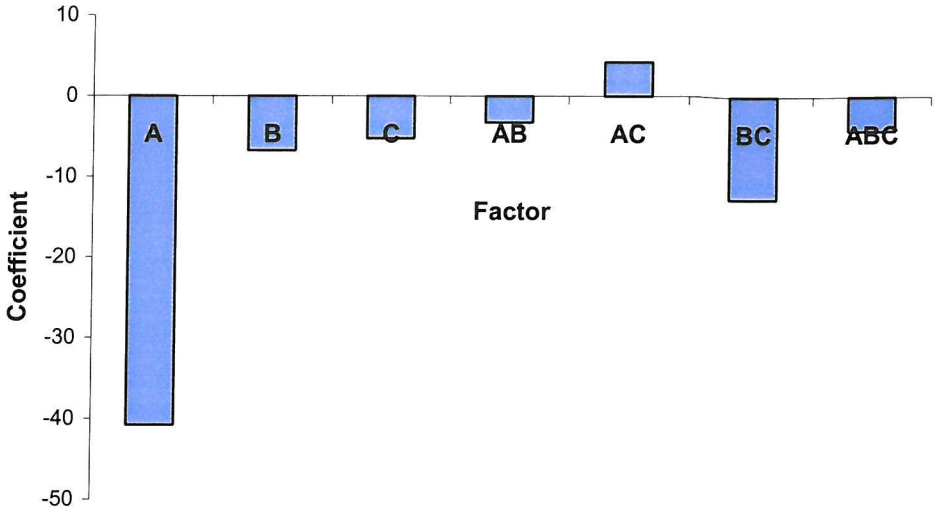


Figure 6 Effects Plot for the Optimisation of Sulfone **1**

Statisticians commonly represent effect data as a normal probability effects plot (Figure 7).[5] In this plot the effects are sorted from the smallest (largest negative) to the largest (highest positive). The cumulative probability for each is then calculated by dividing the total cumulative probability (100) by the number of factor terms (7), 100/7 = 14.3. The first co-efficient i.e. -40.75 is then plotted against the midpoint of the first interval i.e. 14.3/2 = 7.15 giving points (-40.75, 7.15). The second co-efficient is then plotted against the second midpoint i.e. 7.15 + 14.3 = 21.45 giving the second point as (-12.75, 21.45); the other five points are plotted in an analogous manner, the final point being (4.25, 92.8). A line is then drawn which passes through the maximum number of points. Effects far away from the line are deemed to be real and significant and are those which should be further investigated.

In this case the equivalents of sulfite (A) was found to be the factor with the largest effect, the authors concluded that less sodium sulfite gave a greater yield. The interaction BC (time and temperature) showed that reactions carried out at a higher temperature required less time than those at a lower temperature. The highest yields were 88 % and 93 % for reactions with 2 equivalents of sulfite, at 60 ° C for reaction times of 6 and 24 hours respectively.

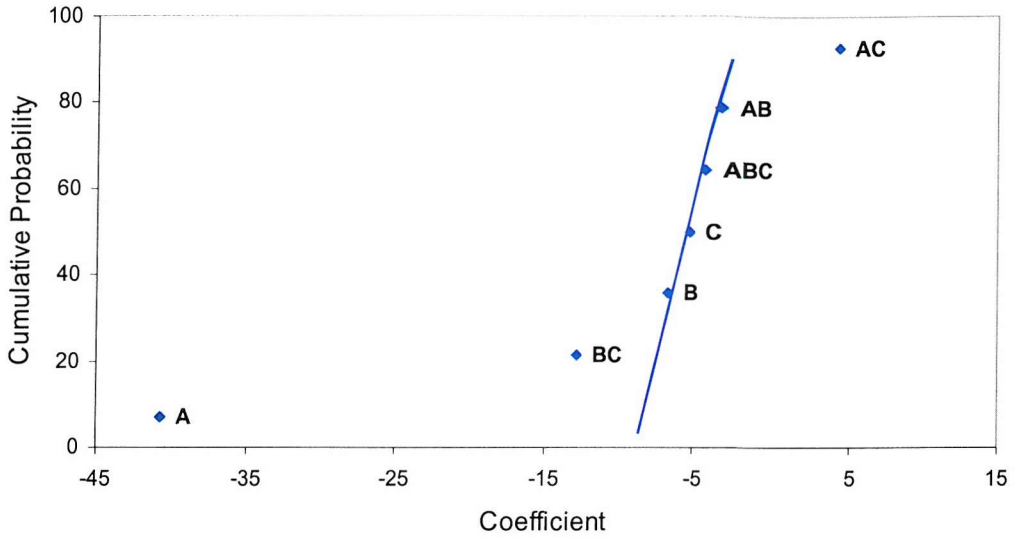


Figure 7 Normal Probability Plot of Effects

1.3.2.3 2 Level Fractional Factorial Designs

The above example illustrates a full or complete factorial design, where for 2 levels of each factor, 2^n (where n is the number of factors) experiments must be performed. When more factors are involved this can generate more experiments than are feasible to carry out, therefore the experimenter may consider a fractional factorial design, where design runs are strategically picked from the complete factorial design.

Thus considering the full factorial example shown in Table 1, the design matrix can be altered such that the third column i.e. C, is the product of columns 1 and 2 i.e. A*B, replicates can then be removed from the design which effectively removes half of the number of experiments. In this case experiments 2, 4, 5, and 7 are omitted. Addition of a centre point then generates 5 experiments instead of the original 9 (Table 4).

Modified full design matrix		
A	**B**	**AB**
1	-1	-1
1	1	1
1	*1*	*1*
1	*-1*	*-1*
-1	1	-1
-1	-1	1
-1	*-1*	*1*
-1	*1*	*-1*

modified design matrix		
A	**B**	**AB**
1	-1	-1
1	1	1
-1	1	-1
-1	-1	1

Experiments			
	A	**B**	**AB**
1	4	6	60
3	4	24	100
8	2	24	60
6	2	6	100
c	3	15	80

Table 4 Construction of a Fractional Factorial Experiment with an Additional Centre Point Included

An alternative way of considering this is to include all experiments where C is the product of A and B and disregard the rest, upon re-examination of the design matrix in Table 1 it is evident that the same experiments would be included. The design matrix is unique, in that each column is the product of the other columns i.e. A can be defined as BC, B as AC and C as AB.

This is an example of a half fractional factorial design and may be denoted as a 2^{3-1} fractional factorial design (2 is the number of levels, 3 is the number of factors, 1 is the fractionation, in this case ½, 2 would indicate ¼). Figure 8 shows the design region, outlined in red, offered by this design. It is evident that it is the shape of a tetrahedron, which is the largest volume of space which can be constructed with four points.[5]

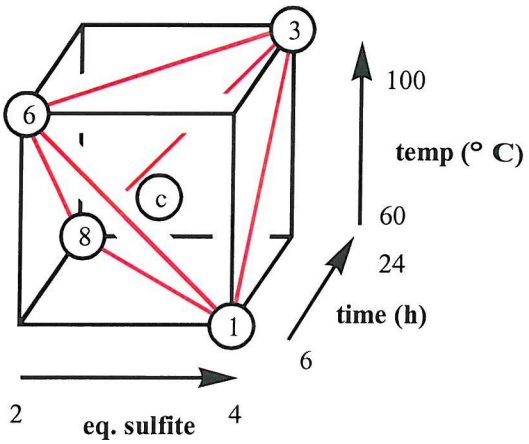
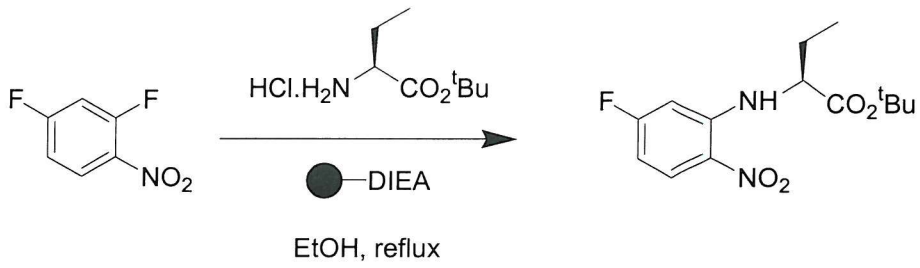


Figure 8 Design Region Explored by the Half Factorial Experiment

In practice these methods for the construction of factorial designs with a greater number of factors than three are laborious. Another method which is most commonly used for the generation of such designs is to consider the full factorial for n-1 factors and generate the n^{th} condition by multiplication of all the columns, this can be illustrated by an example reported by Jamieson[7] who reported the use of ReactArray Robotics and DoE to optimise the S_N-Ar displacement reaction between 2,4 difluoronitrobenzene and an amino acid (Scheme 2).



Scheme 2 Displacement Reaction between 2,4 difluoronitrobenzene and an amino acid

Prior to optimisation the desired aniline could only be isolated in ~ 40 % yield and chromatographic purification was required to remove the unreacted starting materials. A 2^{4-1} factorial experiment was undertaken to assess the factors shown in Table 5.

	Factors/levels			
	Equivalents of amino acid (A)	**Equivalents of PS-DIEA (B)**	**Time (hours) (C)**	**Concentration (volumes) (D)**
high (+1)	2	4	2	50
low (-1)	1	2	4	25

Table 5 Factors Investigated in the Aryl Displacement Reaction by Jamieson

The design matrix was constructed as shown in Table 6, thus initially the full design matrix for a 2^3 full factorial experiment, which involves 8 runs was assigned to factors A to C, multiplication of the three columns gave the setting for the fourth factor, D. Again it can be seen that each column is the product of the other three columns. In this case 2 repeated centre points were added which gave a total of 10 experiments.

Experiment	**A (BCD)**	**B (ACD)**	**C (ABD)**	*	**D (ABC)**
1	1	1	1	→	1
2	1	1	-1	→	-1
3	1	-1	-1	→	1
4	-1	-1	1	→	1
5	-1	1	1	→	-1
6	-1	-1	-1	→	-1
7	1	-1	1	→	-1
8	-1	1	-1	→	1
9	0	0	0	→	0
10	0	0	0	→	0
					Multiplication gives the setting for factor D

Table 6 Construction of the 2^{4-1} Fractional Factorial from the 2^3 Full Factorial Experiment

1.3.2.4 Confounding and Calculation of Effects

In the fractional design, as previously mentioned, each column is the product of all the other columns and the effects can be described as "confounded" or as "aliases" of each other i.e. A is confounded with or is an alias of BCD, B with ACD, C with ABD and D with ABC, thus A is actually the effect of A and BCD added together, B the effect of B and ACD added together etc. The effect estimates are therefore "sums of the true effects". This is however not such a serious drawback as interaction effects, especially higher order interaction effects are often negligible.[8] The two-factor interactions are also confounded with other two factor interactions giving the full design matrix as shown in Table 7, which also shows the results of the experiments, the corresponding normal probability plot is shown in Figure 9.

Expt	A (BCD)	B (ACD)	C (ABD)	D (ABC)	AB (CD)	AC (BD)	AD (BC)	yield
1	1	1	1	1	1	1	1	89.7
2	1	1	-1	-1	1	-1	-1	92.7
3	1	-1	-1	1	-1	-1	1	63.5
4	-1	-1	1	1	1	-1	-1	43.8
5	-1	1	1	-1	-1	-1	1	54.5
6	-1	-1	-1	-1	1	1	1	41.9
7	1	-1	1	-1	-1	1	-1	83.3
8	-1	1	-1	1	-1	1	-1	43.4
9	0	0	0	0	0	0	0	64.7
10	0	0	0	0	0	0	0	64.4
effect	**36.4**	**11.95**	**7.45**	**-8**	**5.85**	**0.95**	**-3.4**	

Table 7 Confounding of Effects and Results of the Fractional Factorial Experiment

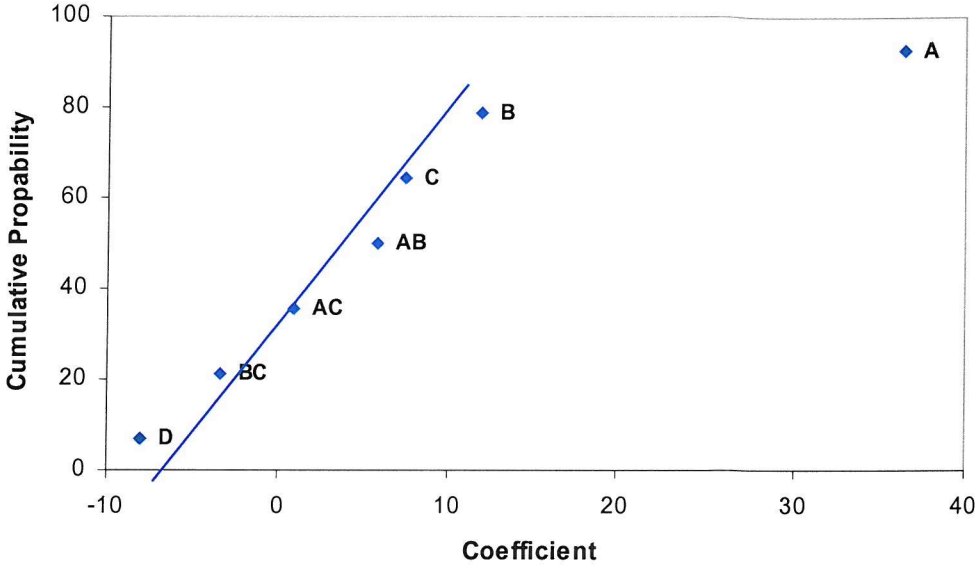


Figure 9 Normal Probability Plot

Analysis was aided with Design Expert 5 Software, which indicated that A was the most significant factor, B had a smaller effect and C and D were found to be the least important. The optimum conditions were calculated to be when 2 equivalents of amino acid and 4 equivalents of DIEA were employed, time and concentration were set at convenient levels, (18 hours and 37.5 volumes respectively). Under these conditions the desired nitro aniline was isolated in 91 % yield with greater than 98 % purity.

In this example main effects were confounded with the 3 factor interactions and the 2 factor interactions with other 2 factor interactions, therefore this experiment can only be used to estimate the former. The resolution of a design is used to describe the level of confounding.[5]

- In Resolution III designs main effects are confounded with 2 factor interactions. This is the case for the 2^{3-1} factorial shown in Table 4.
- In Resolution IV designs no main effects are confounded with 2 factor interactions, but 2 factor interactions are aliased with each other. This was the case in the 2^{4-1} factorial example shown in Table 6.
- In Resolution V designs no main effects or 2 factor interactions are aliased with other main effects or 2 factor interactions, but 2 factor interactions are

aliased with 3 factor interactions. An example of this is the 2^{5-1} factorial examples, one of the most efficient fractional factorial experiments. In this experiment of 16 runs, the main effects are confounded with the four factor interactions and the two factor interactions with the three factor interactions. Hence from this experiment both main effects and 2 factor interaction effects can be estimated with a high degree of precision from only 16 experiments.

In most cases higher-order interaction effects are negligible therefore fractional designs can be used to give good estimates of true effects. Fractionation can heavily outweigh the extra effort required in running the other halves of the experiment, which can always be run at a later date.

For both types of factorial experiment a model is then calculated from a series of matrix calculations, this model can be used for assessing the correlation of results and predictions.

1.3.3 Optimisation

In many cases a model involving only main effects and interactions may be sufficient to describe a process. Principally if, the results revealed no evidence of curvature (see below), or if the experiment was run at the limits of the factor settings of the process.

In many cases as the level of the factor increases the measured response either increases or decreases in a linear fashion and the response of the centre point experiments corresponds to that of the average of the responses (see linear series, Figure 10). However in some cases the behaviour of going from the high to the low factor setting may be more similar to those shown in the quadratic and cubic series' shown indicating that a Response Surface Modelling (RSM) experiment is required.[5]

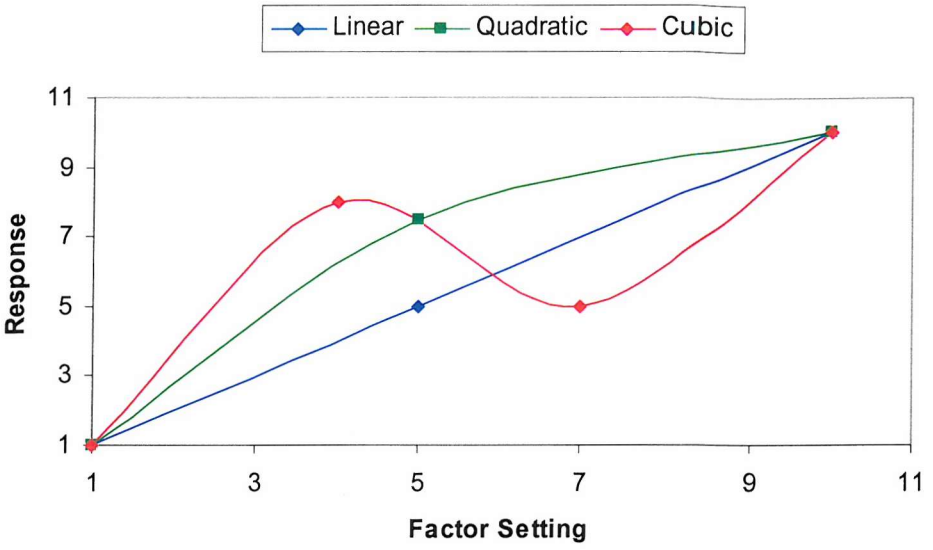


Figure 10 Possible Response/Factor Relationships

To estimate these effects three level and even four level factorial designs would be required however, very quickly these become too large for practical applications and their construction and analysis is significantly more complex than their 2 level counterparts. Other designs include Box-Wilson Central composite designs (CCDs) where factorial or fractional factorial designs are augmented with star points to estimate curvature. Central composite designs always contain twice as many star points as factors in the design and are illustrated in Figure 11 for a 2 level factorial design with three factors. The star points are situated at distances from the centre depending on the number and properties of the factors in the design.[5]

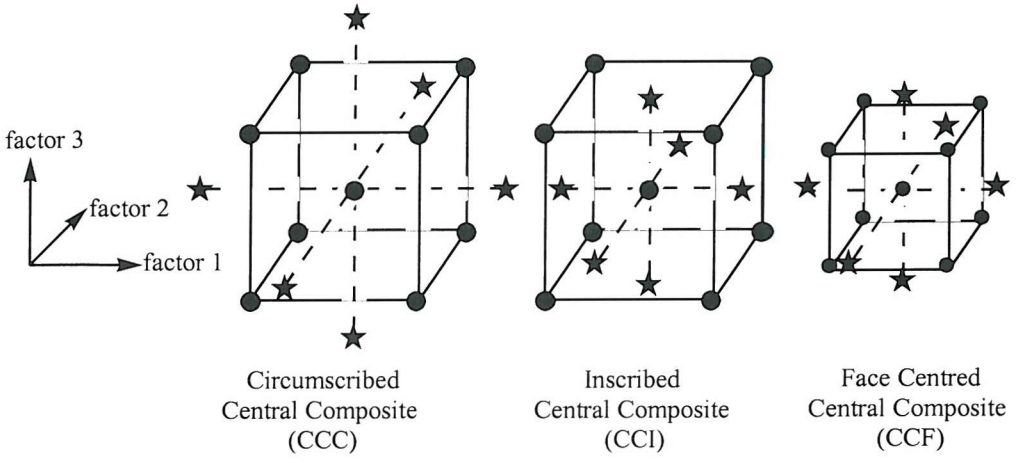
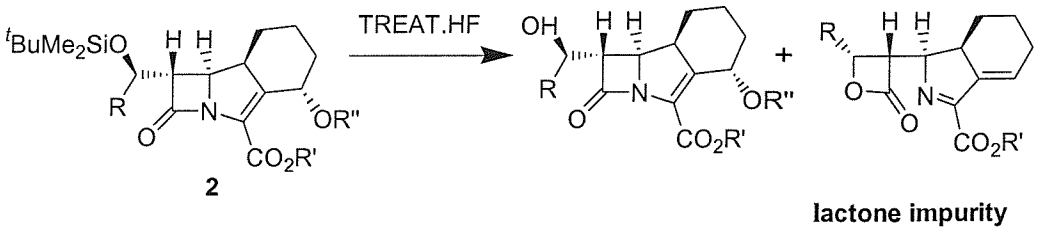


Figure 11 Central Composite Designs

Owen[9] used a Face Centred Central Composite design to demonstrate a step by step approach in the optimisation of deprotection of silyl ether **2** varying the factors shown in Table 8. The product was required on a 1000 L scale and was complicated by the formation of a lactone side product.



Scheme 3 Deprotection Reaction of Silyl Ether **2**

	Factors/levels			
	temperature (° C)	**time (hours)**	**concentration (volumes)**	**$Et_3N.3HF$ (equiv)**
high (+1)	30	31	7	1.67
low (-1)	10	19	3	1

Table 8 Factors Varied in the Deprotection of Silyl Ether **2**

Sufficient resources were available and scoping experiments carried out to proceed directly with a response surface modelling design. This involved 30 experiments; 16 corner points, 8 star points and 6 replicated centre points, although in practice only 20 experiments were carried out as some experiments could be sampled more than once at different times. The authors noted that if resources were tighter a fractional factorial study with as few as 8 experiments could have initially been performed.

Using Design Expert 5 a highly predictive model was obtained which when interrogated under various constraints (Table 9 - in all cases maximising the product yield was included as the target) showed a high degree of correlation between the observed and predicted yield, for the calculated conditions. (Figure

12 - results are shown for product yield but equal correlation was achieved for the yield of the impurity).

	Target/Constraint	Temp	Time	Conc.	$Et_3N.3HF$
1		19	31	3.6	1.42
2	limit on lactone (< 2 %)	17	31	4.8	1.5
3	limit on lactone (< 1.1 %)	16	29	5.3	1.68
4	limit on lactone (, 2 %) solvent (>3.5 volumes)	14	31	3.45	1.58
5	limit on lactone (, 2 %) TREAT.HF (<1.18 equiv)	28	19.5	7	1.17
6	limit on lactone (, 2 %) time (< 23 hours)	24	23	6.3	1.41

Table 9 Constrained Conditions for Prediction of Maximum Product Yield

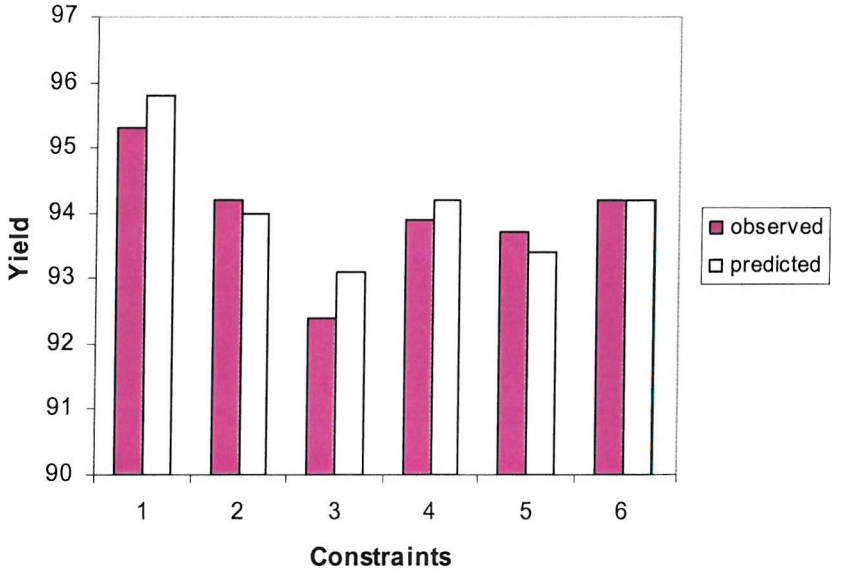


Figure 12 Predicted and Actual Yields for Constrained Conditions (see Table 9)

The authors concluded that "*Reactions are often more complex than intuition would suggest*" and that "*Woolly statements can be quantified and the effect of*

several (often conflicting) responses can be visualised". As a result of the modelling which showed how sensitive the reaction was to temperature the thermal control of the manufacturing plant was improved at a cost of £10,000 which was felt to be justified in light of the results.

1.3.4 Verification

The Verification stage tests the reliability of the optimised conditions, thus factors may be varied at +/- 10 - 20 % of their optimised levels or merely repeated to establish the robustness of the found optima.

1.3.5 D-Optimal Designs

Factorial and fraction factorial designs are all D-Optimal (D = Determinant) designs but these can be constructed by hand. In general D-Optimal designs are applied when classical designs are not feasible. This may be due to: (a) constraints in the experimental domain i.e. if not all combinations of factor settings are feasible, (b) a non-linear model is required, (c) a response surface modelling design is required in the presence of qualitative factors, (d) the presence of a large number of factors including those on more than 2 levels or (e) when classical designs require too many experiments for the given time or resources.

1.3.6 DoE vs OVAT

Assessing the effect of 1 factor by keeping all other conditions constant severely restricts the evaluation of interactions between factors and robustness and an incomplete picture of the effect of the factors is obtained. In contrast a DoE approach, where factors are examined over the full range of reactions space, allows the generation of a model which can be used for prediction and optimisation. A better understanding of the process is thus obtained.[9]

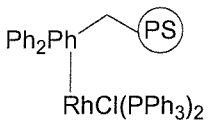
As well as the previously mentioned examples there are few other reports where DoE has been used to optimise chemical processes. Ley[10] optimised an amide

bond formation using a polymer supported carbodiimide and Gooding[11] used the technique for the optimisation of a PS supported *N*-hydroxybenzotriazole resin. Other applications where the use of DoE has been used to optimise processes, recently reported in the chemical literature include the optimisation of semipreparative LC and LC/MS methods[12] and water-compatible molecularly imprinted polymers.[13]

1.4 Solid Supported Catalysts

The use of catalysts in all areas of synthetic chemistry is widespread, as their application often enhances reactivity and selectivity in otherwise slow or unselective processes.

The development of catalysts tethered to solid supports has received massive acclaim over the last decade, although the technique was actually first reported in the early 1970's, not so long after Merrifield's pioneering work on peptide synthesis.[14] In 1971 Grubbs used the polymer-supported rhodium catalyst **3** in the presence of hydrogen gas to effect the quantitative hydrogenation of a variety of different sized, acyclic and cyclic alkenes.[15]



3

Figure 13 Polymer Supported Rhodium Catalyst **3**

The catalyst which was easily recovered by filtration could be reused, over ten cycles and activity varied by only +/- 5 % and this demonstrates the utility of heterogenisation, with the ability to recover catalysts by simple filtration facilitating work-up and recycling. In many cases reaction yields and purities may be increased and the need for time-consuming, laborious purification steps such as chromatography, distillation and crystallization are eradicated. The cost and time of synthesizing and purchasing expensive or synthetically challenging ligands is reduced and in some cases the handling of toxic or malodorous

compounds simplified.[16] In this day, their amenability to automation and library synthesis is of significant value to the drug discovery industry.

In addition to these practical advantages, in some instances the unique microenvironment created by the polymer matrix exerts its own influence on the catalytic behaviour: improved catalyst stability,[17] increased selectivity for intramolecular reactions,[18] enhanced regioselelectivity due to steric hindrance[19] and superior activity of supported chiral catalysts due to site cooperation[20] have all been reported.

Although there are many reports of supported catalysts on inorganic materials such as zeolites, aluminas, zirconia, ZnO and clay[21] the remainder of this introduction will focus on organic polymers.

1.4.1 Properties of a Good Solid Phase

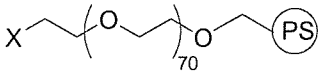
In selecting a solid support there are a number of desirable properties that the support must possess, in general it must (a) be mechanically, thermally and chemically stable, (b) have a clear, definable loading, (c) have suitable functionality, (d) be easy to derivatise and (e) be inexpensive to produce and dispose of with regards to both financial and environmental considerations

In general, except for biological applications, a higher loading is usually of more use to the organic and peptide chemist although for catalytic based applications this is not always true.

From their very first utility in the synthesis of a tetrapeptide,[14] lightly divinylbenzene (DVB) cross-linked polystyrenes (PS) have been one of the most widely used insoluble polymer supports. These supports, prepared with between 1 and 2 % DVB are termed microporous or gel type resins and require solvent swelling, where solvents literally enter the polymer matrix and partially dissolve it allowing sufficient access and diffusion of reactants into the active sites.

For PS resins this has sometimes proved to be problematic, especially with highly polar solvents and indeed PS resins are incompatible with alcoholic solvents and water. Incorporation of a solvent (poragen) and increasing the levels of the cross-linker to typically greater than 10 %, results in beads with a rigid, permanent pore structure. Termed macroporous, these beads do not undergo significant swelling in solvents; reactants just simply fill the pores regardless of the solvent. These resins do however suffer from poor loading capacity and brittleness and their preparation must be carefully controlled to fix pore size and volume.[22]

In one approach poly(ethylene glycol) (PEG) is grafted onto the PS backbone. One such example is commercially available TentaGel (**4**, Figure 14); this resin shows much improved compatibility with polar solvents.



$X = NH_2$, OH

4

Figure 14 TentaGel, **4**

In some cases the activity of solid-supported catalysts does not equate to that of the solution-phase counterpart due to their heterogeneous character. Various groups have addressed this, by the use of non-crosslinked resins i.e. linear PS and PEG.[23-25] Although reaction rates may be improved the polymers are not so easy to recover, requiring precipitation or centrifugation, which sometimes results in contamination of the resultant products.

1.4.2 Attachment to the Solid Support

Four main immobilization methods are generally used being a) covalent attachment, b) physical adsorption, c) encapsulation and d) ion-pair formation. These are illustrated with relevant examples below.

1.4.2.1 Covalent Bonding

This is by far the most commonly used method to attach catalysts to polymer matrixes as the robust covalent bonds formed ensures stable catalyst attachment and minimizes leaching. Binding can be effected in two ways a) by co-polymerization of active monomers or b) by grafting of the functional moiety onto the support.

Chiral catalysts are often prepared by these methods and 2,2'-(bis)-(diphenylphosphino)-1,1'-binaphthyl (BINAP) derivatives have been prepared by both routes (Figure 15).

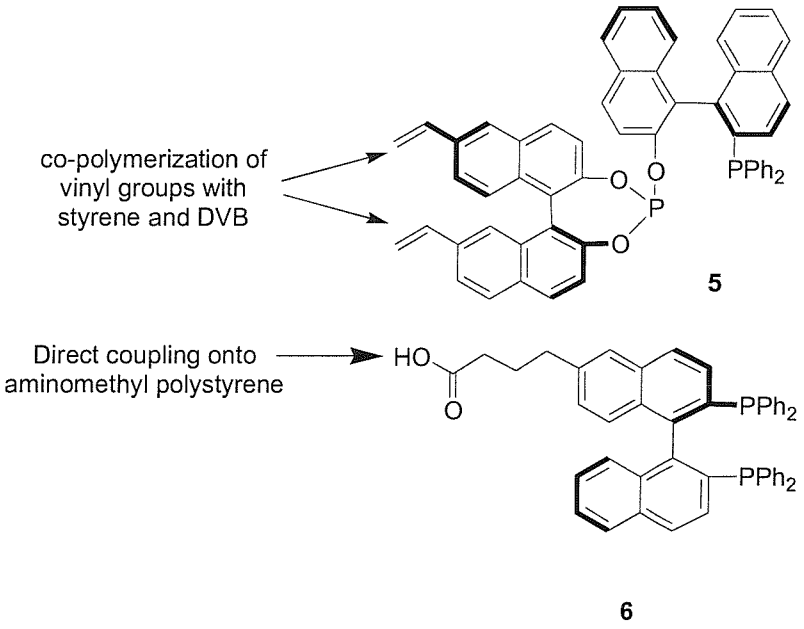
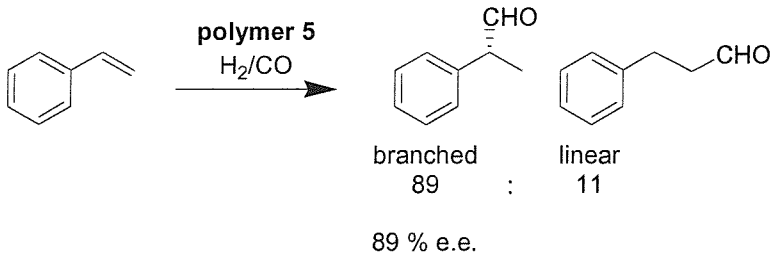


Figure 15 BINAP Moieties Derivatized for Immobilization

Nozaki[26] reported the preparation of vinyl phosphine-phosphite-BINAP **5**, which contains two polymerizable vinyl groups. Copolymerisation of these (3%) with various percentages of styrene and DVB followed by treatment with $Rh(acac)(CO)_2$ afforded highly cross-linked polymers, which in the presence of hydrogen and carbon monoxide, efficiently catalyzed the asymmetric hydroformylation of styrene with a branched:linear ratio of 89:11 and an e.e. of 89 % (Scheme 4).



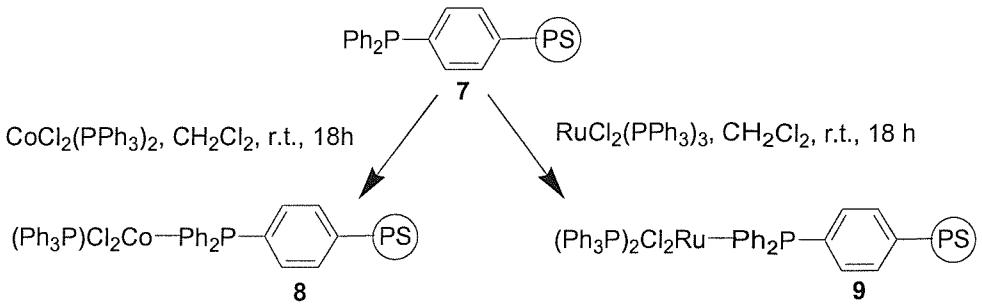
Scheme 4 Hydroformylation of Styrene

Bayston[27] described the preparation of BINAP derivative, **6**, which was coupled onto standard aminomethyl PS. Activation of the catalyst with (cyclo-octadiene)Ru(*bis*-methallyl) in acetone afforded an active hydrogenation catalyst which was found to be effective in the enantioselective reduction of alkenes and β-keto esters to the corresponding alkanes and β-hydroxy esters. A drop of only 2 % in e.e. was observed on going to a heterogeneous system for the reduction of ethyl acetoacetate and the catalyst could be reused with only minimal loss of activity.

1.4.2.2 Physical Adsorption

Metal complexes are commonly attached to solid supports using this method. The polymeric supports are often initially functionalized with ligands that have a lone pair on the central atom e.g. N, S, or P which can be donated to a metal centre; the latter two can also act as π acids. Attachment of metals is often achieved by a ligand substitution reaction with complexes such as $Pd(PPh_3)_4$, $Ni(PPh_3)_4$, and $RuCl_2(PPh_3)_3$ or by reaction with an organometallic precursor such as a Grignard or lithium reagent. Much of the work in this area has focused on polymer supported analogues of triphenylphosphine (**7**) as it is both easily prepared and commercially available. A variety of metal complexes including Cu, Ni, Mn, Pd, Rh, Pd, Os, Ir, Co, Cr and Pt can be used to functionalize the support.[28] Leadbeater prepared PS-bound cobalt and ruthenium phosphine catalysts, **8** and **9** by stirring resin **7** with a DCM solution of the corresponding metal complex.[29,30] **8** was an active catalyst in the oxidation of benzylic and allylic alcohols with *tert*-butyl hydroperoxide as the

stoichiometric oxidant and **9** catalyzed both transfer hydrogenation of alcohols and hydrocarbon oxidation.



Scheme 5 Polymer Supported Cobalt and Ruthenium Complexes

1.4.2.3 Encapsulation

Predominant in this field is the work of Kobayahsi.[31] Catalysts were physically enveloped in polymer films, subsequent π interactions between the PS backbone resulted in the formation of stable catalytic complexes. The encapsulated polymer was prepared by adding the homogenous catalyst to a stirred solution of linear PS in cyclohexane. After cooling to 0 °C the polymer was found to coascervate around the unsupported catalyst, leading to the formation of soft microcapsules which were hardened by the addition of hexane and dried. Microencapsulated $Sc(OTf)_3$ for use in Lewis acid catalysed C-C bond formation, $Pd(PPh_3)_4$ for use in Heck Suzuki and allylic substitution reactions, arene-ruthenium complexes for use in ring closing metathesis reactions, and OsO_4 dihydroxylation catalysts have all been successfully prepared and show good activities in their respective reactions.[31] In all cases the polymers were successfully recovered and recycled and no metal leaching was observed.

1.4.2.4 Ion Pair Formation

Although this technique is widespread in the formation of polymer supported reagents e.g. polymer supported borohydride complexes, it is one of the least common methods for catalyst immobilization. One example was reported by Ley[32] who developed an immobilized variant of TPAP (**10**, Figure 16). The resin-bound analogue was obtained by addition of Amberlyst ion-exchange resin

(IR 27) to an aqueous solution of potassium perruthenate, followed by ultrasonification. The resulting PS-TPAP resin was used in a series of alcohol reactions with NMO or trimethylamine *N*-oxide as the stoichiometric oxidant,

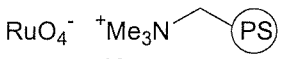


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Figure 16 Tetra-n-propylammonium perruthenate Immobilized on Amberlyst Ion Exchange Resin

1.5 Scope of the Study

During the time course of this PhD project two catalytic systems were studied. The first concerned chiral catalysis and the Sharpless asymmetric dihydroxylation of alkenes, the second concerned C-C bond formation and the Heck reaction catalyzed by polymer supported, sulfur containing palladacycles. The remainder of this report will focus on these reactions.

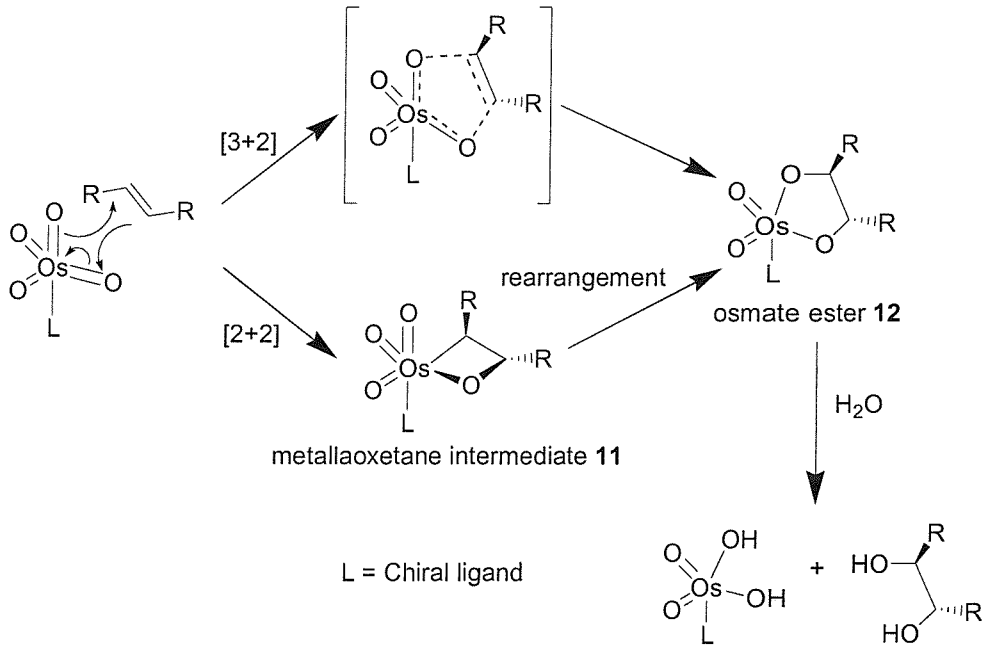
1.6 Asymmetric Dihydroxylation

1.6.1 Mechanism and Conditions

The cycloaddition reaction of osmium tetroxide to alkenes allows access to a wide variety of vicinal diols; its use is widespread because of its generality and mildness. Whether the alkene geometry is E or Z, the addition of osmium tetroxide occurs in a *syn* fashion and has been the subject of extensive mechanistic studies. Two different pathways have been suggested, these include a concerted [3+2] cycloaddition mechanism, proposed by Criegee[33] and a step-wise mechanism proposed by Sharpless.[34,35] Both pathways are shown in Scheme 6 for the stereospecific oxidation catalyzed by a chiral ligand. Despite the two different mechanistic schemes the two pathways are kinetically indistinguishable[36] and no definitive evidence for the metallaoxetane intermediate (**11**) exists. Opinion on which pathway the cycloaddition follows is divided,[37-40] although for both the final product is the osmate ester **12**. The

reaction is commonly carried out in a 1:1 organic solvent, H_2O mixture which hydrolyses the osmate ester to the diol product.

During the oxidation one equivalent of osmium tetroxide is consumed, which is undesirable as osmium tetroxide is both a toxic and expensive reagent. Fortuitously though, the process can be made catalytic by the introduction of a stoichiometric co-oxidant, NMO (described in 1988 by Sharpless[41]) and Fe(III) in the form of $K_3Fe(CN)_6$ (described by Sharpless in 1990[42]) are commonly used. The latter has shown to improve the enantioselectivity of the diols formed due to the presence of a biphasic solvent system which precludes a competing secondary cycle where alkenes are dihydroxylated by an osmium species without the chiral ligand co-ordinated which results in diols of lower enantioselectivity.



Scheme 6 Concerted [3+2] and stepwise [2+2] Mechanisms

When NMO is used as the secondary oxidant it is normally used in 1.5 excess, with 1 equivalent of $Et_4N^+(H_2O)_3$ as a base in a 1:1 acetone/water mixture. When $K_3Fe(CN)_6$ is employed the base is K_2CO_3, 3 equivalents of each are commonly used in a $^tBuOH/H_2O$ solvent system. For the former system as little as 1.5 % OsO_4 can be used. One equivalent of methane sulfonamide is routinely

added to the reaction mixture for all classes of alkenes except for those which are mono- or 1,1- disubstituted. It has been demonstrated that addition of this additive accelerates the rate of hydrolysis of the osmium glycolate products hence allowing higher catalytic turnovers.[43]

1.6.2 Asymmetric Dihydroxylation

The development of chiral ligands which effect the transformation enantioselectively have been widely reported. The most successful of these are cinchona alkaloid derivatives reported by Sharpless and these are discussed in more detail below. Other systems include chiral diamines which have been reported by various groups such as Corey and Hanessian[44] although these can suffer from poor *in situ* recycling of the spent osmium reagent because of the bidentate nature of the ligands, which forms a stable chelate complex with the osmium glycolate products and reactions often have to be carried out using both stoichiometric osmium and chiral ligand. In contrast cinchona alkaloids can be used catalytically with respect to both chiral ligand and osmium.

1.6.2.1 First Generation Ligands

In 1980 Hentges and Sharpless reported the use of cinchona alkaloid derivatives in the preparation of chiral diols using both the chiral ligand and OsO_4 stoichiometrically.[35] Griffith had previously shown that 3° alkyl bridgehead amines such as quinuclidene (**13**) formed stable complexes with OsO_4[45] which led Hentges and Sharpless to postulate that chiral quinuclidene moieties could induce chirality in the diol products. Thus samples of hydroquinine (HQn) acetate (**15**) and hydroquinidine (HQd) acetate (**17**), on the basis that they contained chiral centers adjacent to the co-ordination sites, were prepared. In the asymmetric dihydroxylation of stilbene at –78 °C, the corresponding diol was obtained in 90 % e.e.

15 and **17** are pseudoenantiomers of each other which afford diols of the opposite configuration when used independently as chiral catalysts in the asymmetric dihydroxylation reaction. Hydroquinine (**14**), hydroquinidine (**16**)

and their dehydro-derivatives quinine (**18**) and quinidine (**19**) are commercially available (Figure 17).

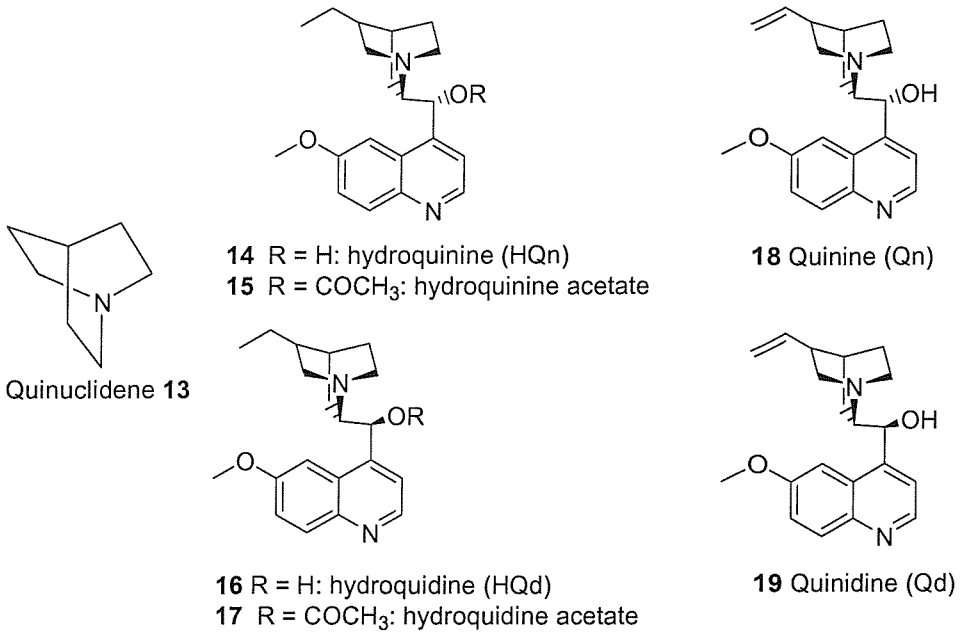


Figure 17 Hydroquinine, Hydroquinidine Chiral Moieties and their Derivatives

Attachment of these 'first generation' type ligands onto a variety of polymeric supports has been reported and their use in asymmetric dihydroxylation well documented,[46-51] the immobilized ligands are most commonly prepared by polymerization of the Qn and QdN moieties or their vinylic derivatives with various monomers.

1.6.2.2 Second Generation Ligands and their Immobilization

In 1992 Sharpless reported the synthesis and use of 'second generation' ligands, which further improved the e.e. of diols obtained.[52] These utilized the same HQn and HQd alkaloids attached to a phthalazine (PHAL) heterocyclic ring spacer (**20** Alk^1 = Alk^2 = HQd, Figure 18). In order to assess the role of the two quinuclidene rings the mono and bis benzyl-quaternary salts were prepared and their activity in the asymmetric dihydroxylation of 1-decene studied. The former was found to be just as effective as the parent ligand, whereas the latter gave only the racemic diol[53] which led to the conclusion that the quinuclidene

moieties operated independently during the dihydroxylation cycle. Other spacer groups which have been utilized are shown in
Figure 18.

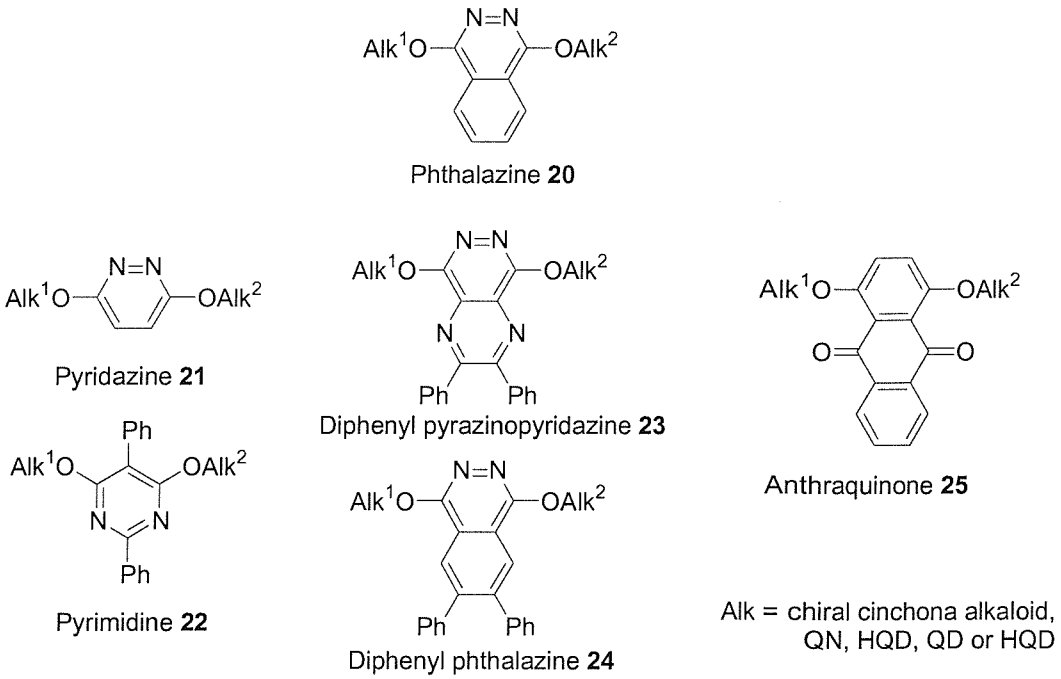


Figure 18 Second Generation Ligands

Diphenyl pyrimidine ligands (**22**, Alk^1 = Alk^2 = HQd), the synthesis and immobilization of which is discussed in more detail in Chapter 2, were reported in 1993[54] as giving improved selectivity in the dihydroxylation of terminal alkenes. For example in the asymmetric dihydroxylation of vinyl cyclohexane an e.e. of 96 % was achieved compared to 88 % for the phthalazine ligand, they are thus the ligand of choice for this class of substrates.

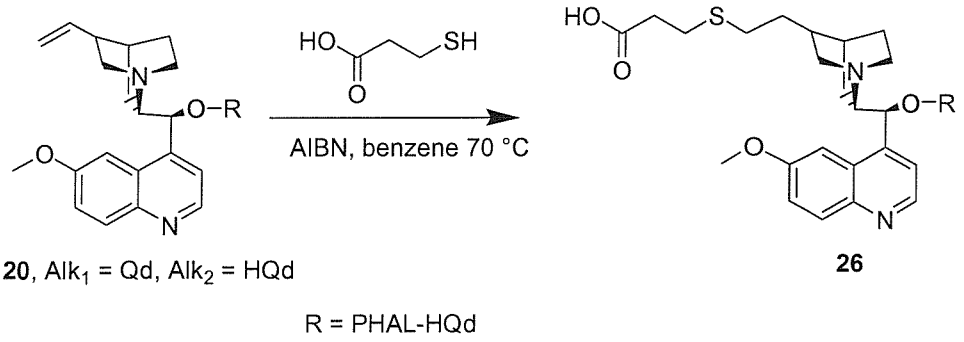
Diphenyl pyrazinopyridazine (**23**, Alk^1 = Alk^2 = HQd) and phthalazine ligands (**24**, Alk^1 = Alk^2 = HQd), reported in 1995[55] were found to give comparable or greater e.e.'s than ligands **20** or **22** for most classes of substrates, most noteworthy they were found to improve e.e.'s in the dihydroxylation of *cis* alkenes, which had always been a problematic class of alkene from which to obtain high e.e.'s. For example in the asymmetric dihydroxylation of indene the

e.e. achieved was 53 % using ligand **24** compared to 42 % and 35 % for **20** and **22** respectively and the e.e. of the diol product of *cis* β-methyl styrene was 63 %, compared to 35 % achieved with **20**.

Anthraquinone derivatives (**25**, Alk^1 = Alk^2 = HQd) reported in 1996,[56] were a further addition to a family of ligands, from which the dihydroxylation of most alkene substrates can now proceed with good to excellent enantioselectivity. This class of ligand showed substantial improvement in the asymmetric dihydroxylation of vinyl substrates, which had previously given unreliable and inconsistent results.

The immobilization of *bis* pyridazine derivatives (**21**, Alk^1 = Qn, Alk^2 = HQn) was reported in 1994 by Lohray.[57] Immobilization was achieved by synthesis of an unsymmetric ligand containing one quinine moiety and one hydroquinine moiety on each arm of the spacer group and polymerising it with ethyleneglycol dimethacrylate. Although this ligand generally gave slightly inferior e.e.'s to the PHAL derivatives it is considerably cheaper, hence industrially offers an attractive alternative.[54]

Song has reported the polymerization of *bis* phthalazine derivatives (**20,** Alk^1 = Alk^2 = Qn) with methyl methacrylate, 2-hydroxylethyl methacrylate[58] and mercaptopropylsilanized silica gel,[59] all showed excellent enantioselectivity in the asymmetric dihydroxylation of *trans*-stilbene and methyl *trans*-cinnimate. The silica gel supported ligands could be reused without further addition of OsO_4, with no significant loss in selelectivity. The phthalazine ligands were also immobilized by Janda who synthesized an unsymmetric version analogous that of Lohray's pyridazine (**20**, Alk^1 = Qd, Alk^2 = HQd). The vinyl quinidine moiety was treated with mercaptopriopionic acid and AIBN which give acid **26** which was subsequently coupled onto MeO-PEG.



Scheme 7 Janda's Immobilization Approach

The polymer was totally soluble in the ^{t}BuOH/H_2O solvent mixtures which allowed the study of homogeneous reactions. E.e.'s were equal to or greater than the free ligand suggesting that the MeO-PEG backbone did not alter the activity and after the reaction the polymer was recovered in virtually quantitative yield by ether precipitation.[60]

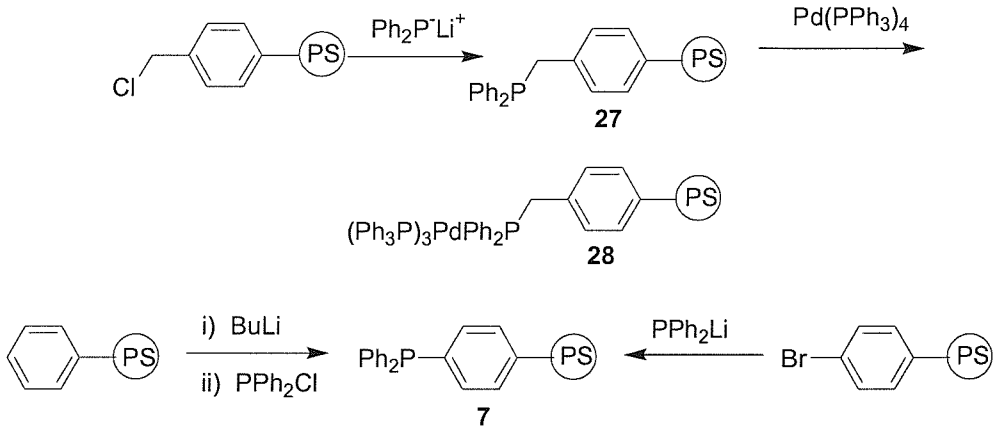
Bolm and Maischak reported the immobilization of anthraquinone-type ligands onto both soluble (MeO-PEG) and insoluble (silica gel) supports. Immobilization was effected either *via* the quinidyl vinyl group in a manner similar to that of Janda, described above, or via a remote position of the anthraquinone core, the latter resulted in a larger distance between the catalytically active sites and the polymer backbone. E.e.'s for the soluble ligands compared well with those for the unsupported analogue and could be recycled with no loss in selectivity, although a slightly lower e.e. was observed for the silica-supported version. Interestingly the site of attachment showed no significant influence on the enantioselectivity.[61] The same group also reported the synthesis and use of silica bound pyrimidine and pyrazino-pyridazine ligands.[62]

1.7 Polymer Supported Palladium Complexes

Palladium cross-coupling reactions have received massive attention over the years as carbon-carbon bonds can be formed under relatively mild conditions from a variety of substrates. Most common are the reactions between halogen containing compounds with boronic acids, organostannanes, alkene or alkyne

acceptors, the so-called Suzuki,[63] Stille,[64] Heck and Sonagashira[65] coupling reactions respectively. As the palladium metal complexes are often expensive to purchase or prepare substantial research into their immobilization and recycling has been undertaken.

Much of the earlier work was concentrated on the immobilisation of palladium complexes onto phosphinated resins such as **7** and **27**, (Scheme 8). The latter was produced by the reaction of bromo or chloromethylated resins with $LiPPh_2$ or $KPPh_2$ and the former by either lithiation of polystyrene followed by reaction with PPh_2Cl or by reacting brominated resins with PPh_2Li. Attachment of the metal was then achieved by ligand exchange with a complex such as $Pd(PPh_3)_4$.[28]



Scheme 8 Common Approach in the Immobilization of Palladium Complexes

In 1997 Jang[66] reported the use of polystyrene bound palladium catalyst **28** for the Suzuki coupling reaction. The reactions between a number of organoboranes with alkenyl, bromides, iodobenzene and aryl triflates were studied which gave isolated yields between 78 – 96 %. Catalytic activity was found to be superior to that of homogeneous $Pd(PPh_3)_4$ and the catalyst could be reused more than 10 times without loss in activity.

Since then, these simple $Pd(PPh_3)_4$ analogues have developed into more elaborate structures containing mono, bis and tri dentate phosphine ligands, with

some containing chiral moieties for asymmetric reactions. A variety of transformations such as hydrogenations, cyclisations, aminations and asymmetric additions have all been achieved.[28]

1.8 The Heck Reaction

The Heck reaction, discovered independently in the late 1960's by Heck[67,68] and Mizoroki,[69] is a useful reaction in organic and organometallic synthesis involving the coupling of an alkene with a halide or a triflate to form a new alkene, the former can be mono- or di- substituted and can be electron rich, neutral or poor, although the latter are more reactive. The halide moiety must not contain β-hydrogen atoms, otherwise β-hydride elimination can compete with the desired coupling reaction.

The rapid development of new protocols has expanded the scope of the initial, small molecule couplings, to complex intramolecular annelations with high regioselectivity and stereoselectivity.[70] The most accepted mechanism, which is summarised in
Figure 19, is believed to proceed *via* Pd (0) and Pd (II) species' and consists of four discrete steps (Figure 19).[71]

In the first step the catalytically active coordinatively unsaturated complex (**29**) which is formed *in situ* from a stable complex such as $Pd(PPh_3)_4$, undergoes **oxidative addition** with the halide component to give species **30**. Although intermediate **30** possesses an available co-ordination site, the loss of a neutral donor ligand precedes **alkene insertion** to give **31** which undergoes a simple bond rotation to setup the necessary *syn* relationship between a β-hydrogen and the transition metal (**32**). The reaction-terminating step: ***syn*-β-hydrogen elimination** affords the coupling product and the hydridopalladium complex **33** which undergoes base-assisted **reductive elimination** to regenerate complex **29** which re-enters the catalytic cycle.

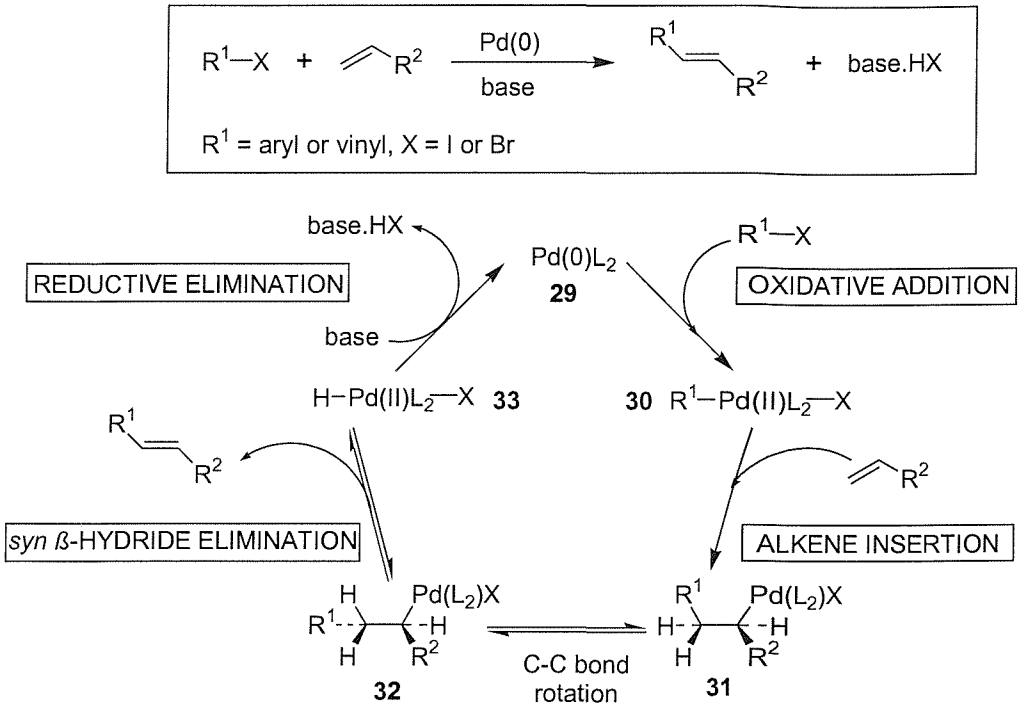


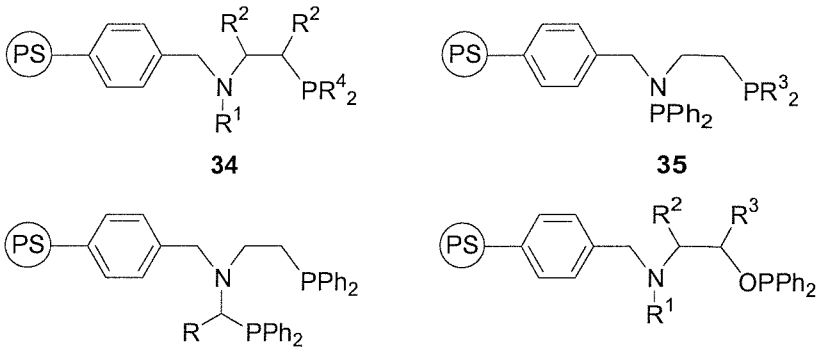
Figure 19 Mechanism of the Heck Reaction

1.9 Immobilization of Palladium Catalysts for the Heck Reaction

As early as 1985 Hallberg[72] prepared supported analogues of $PdCl_2$ bound to resin polymer-supported triphenylphosphine resins which were found to give very high activity in the arylation of methyl acrylate and styrene with iodobenzene.

More recently Portnoy [73] synthesised a diverse set of phosphorous ligands (**34** – **37**) from amino-alcohol templates. Following complexation with $Pd(OAc)_2$ the ligands were screened in the Heck reaction of iodobenzene with methyl acrylate, surprisingly all ligands were equally efficient giving a yield of ~90 %. However, when the reaction with bromobenzene was investigated, clear differences in the ligands were observed, with the bi-dentate and phosphine moieties being superior to the mono-dentate and phosphinite counterparts. Ligand **34** (R^1=R^3=H, R^2=CH_2PPh_2, R^4=Ph) gave the best conversion of 63 %. The difference between the selectivity observed for the different halide

substrates was attributed to the fact that in the case of the iodides, Pd(0) metal particles, resulting from coagulation and precipitation from the resin are the most active catalyst, the reaction therefore becomes "ligand-independent". These particles are not sufficiently reactive to promote the reaction for bromoarenes hence the reaction became ligand sensitive.



R^1, R^2 and R^2 = H, Ph, Bn, Me, ^{t}but, CH_2OH or CH_2PPh_2

R^4 = Ph, or *o*-Tol

Figure 20 Amino Alcohol Phosphine and Phospite Ligands **34** - **37**

The same group have also reported the use of a dendronised support (**38**)[74] for the Heck reaction. The systems exhibited remarkable superiority over their homogeneous nondendritic analogues with the reaction between bromobenzene and methyl acrylate proceeding in 100 % yield, after 72 hours at 80 ° C.

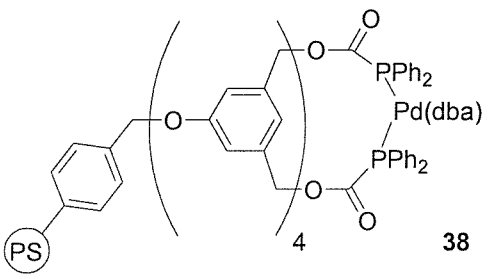
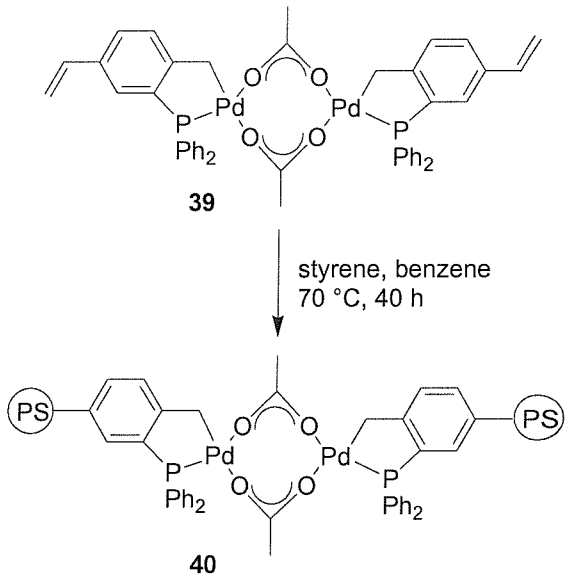


Figure 21 Dendronized Support **38**

Finally Luo[75] reported the synthesis of palladacyle **40** *via* copolymerization of monomer **39** with styrene (Scheme 9). The catalyst was found to be very

effective in the Heck reaction of aryl bromides, in the cross-coupling reaction between bromobenzonitrile and methyl acrylate, the desired product was obtained after only 10 hours at 100 °C in quantitative yield.



Scheme 9 Synthesis of Palladacycle **40**

1.10 Sulfur Containing Palladacycles

Palladacycles are an important class of organometallic compound which have been successfully used in a wide range of areas including the synthesis of metallodendrimers and new materials such as liquid crystals and non-linear optics. Due to their ease of synthesis and modification of the properties of the complex by simply changing (a) the size of the metallacyclic ring (b) the nature of the metallated carbon atom (c) the type of donor group and its substituents, and (d) the nature of the coordinated ligands, the scope of these compound is vast.[76]

Although sulfur-containing palladacylces were synthesized and characterized in 1980 by Shaw and co-workers[77] it was in 1999 when they were first used in catalysis by Bergbreiter,[78] who found that palladacyle **41** was capable of promoting the Heck reaction of a range of aryl iodides with different alkene acceptors, the catalyst was however, found to be much less active with aryl bromides.

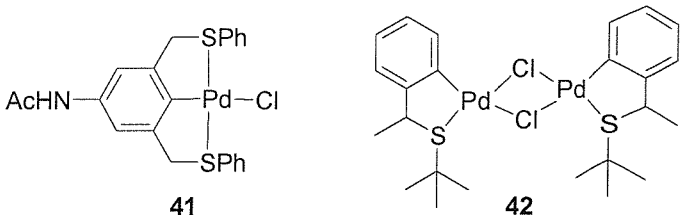


Figure 22 Sufur Containing Palladacycles **41** and **42**

Other research in this area involves mainly the work of Dupont who has reported the synthesis of palladacycles such as **42** for use in Heck, Suzuki and homo coupling reactions.[76,79-82]

1.11 Conclusion and Aims of the Study

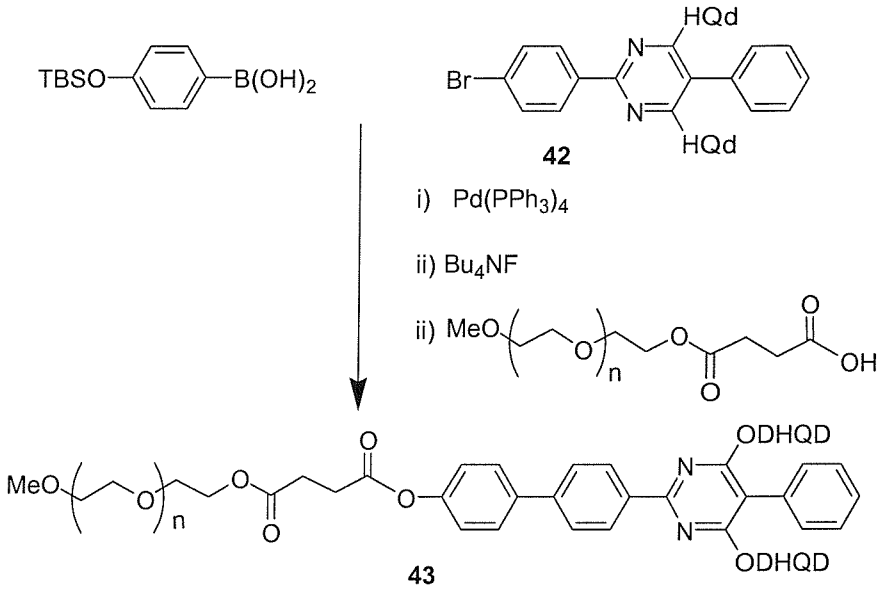
The use of DoE techniques, aim to not only optimise a process but enable its thorough understanding. The aim of the study was to select two different catalytic systems, the first concerned with chiral catalysis (Sharpless asymmetric dihydroxylation) and the second with C-C bond formation (the Heck reaction), and attempt to optimise them in this statistical, rational fashion and evaluate the proficiency of the approach. This would be achieved by two methods, (1) by collaboration with two statisticians, Dr D. C. Woods and Professor S. M. Lewis from Southampton University's Statistical Sciences Research Institute and (b) by use of experimental design software MODDE.

2 A Triazine Based Catalyst for the Asymmetric Dihydroxylation of Alkenes

2.1 Introduction

Various groups have reported dimeric ligands with a variety of spacer groups for the asymmetric dihydroxylation of alkenes and these have been attached to a number of different polymeric supports and their chemistries investigated. Two main areas have generally been explored for the attachment of ligands to solid supports; *via* the C-1 vinyl group of the quinine and quinidine moieties or at a site on the heterocyclic spacer.

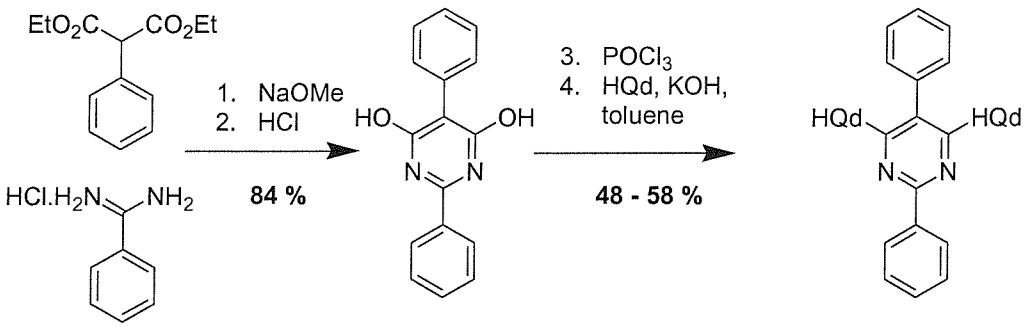
Since an extensive investigation of the asymmetric dihydroxylation of alkenes was to be undertaken a ligand that could be easily synthesized on a large scale from cheap, readily available starting materials was sought. The use of the phthalizine spacer group was therefore rejected as it is very expensive and its immobilization has been well documented. In another example Bolm and Gerlach[83] reported the immobilization of a pyrimidine-based ligand onto acylated PEG (**43**, Scheme 10), although attachment was *via* a labile phenolic ester and the synthesis of **42** required three steps (Scheme 11).



Scheme 10 Bolm and Gerlach PEG supported Pyrimidine Ligand

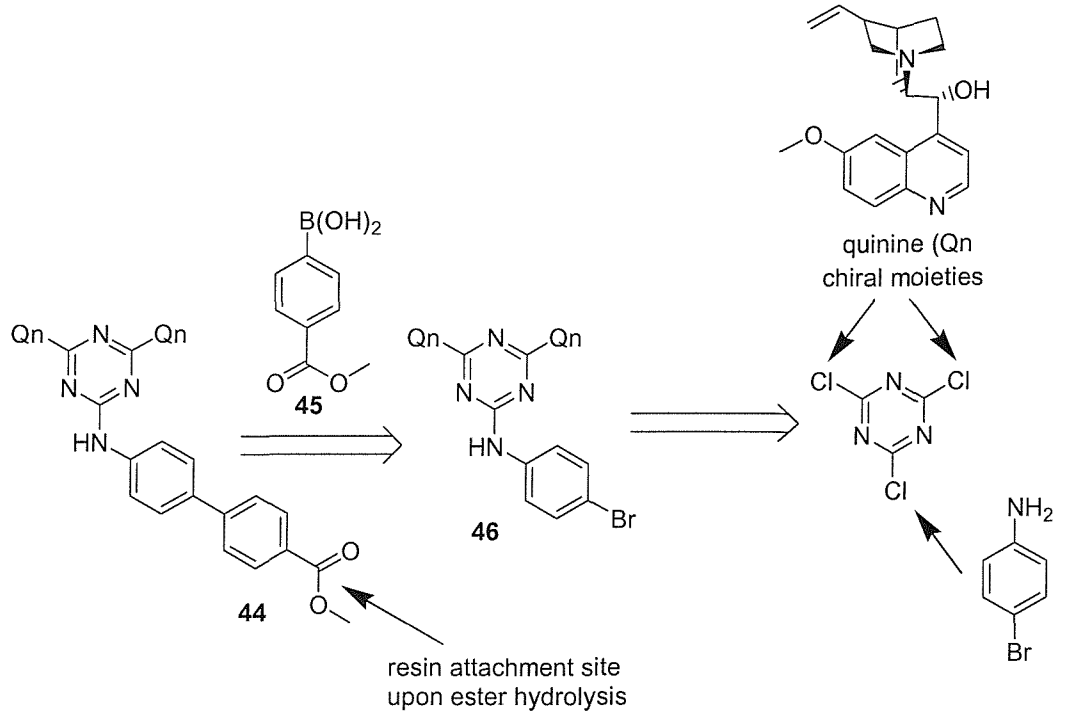
2.2 Scope of Study

The synthesis of pyrimidine based ligands was considered complex, but a brief study of their synthesis (Scheme 11) led to the notion that cyanuric chloride could be used a spacer group. The possibility of selective substitution of the chlorine atoms at different temperatures is well documented,[84,85] and would allow displacement with a suitable functionality for resin attachment, and with chiral quinine moieties. As this highly reactive heterocyle already had three chlorine atoms in place, the need for a chlorination step as in the pyrimidine synthesis (Scheme 11) was eliminated. Therefore it was envisaged that using this route the desired *bis*-ligand would be afforded in few steps and in higher yield (Scheme 12).



Scheme 11 Synthesis of Pyrimidine Ligands

It was decided to embark on a synthetic approach similar to that described by Bolm, in which a bromo compound bearing both chiral groups analgous to **42**, in this case **46** (Scheme 12) could be coupled under Suzuki conditions to a boronic acid suitably functionalised with a resin attachment site. Synthesis of **46** was envisaged *via* displacement of cyanuric chloride with 4-bromo aniline and subsequently with the chiral quinine moieties (Scheme 12).

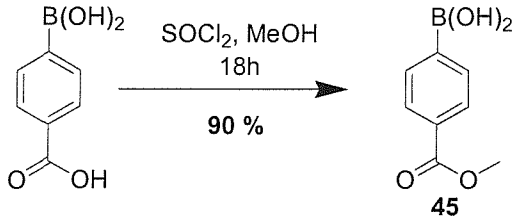


Scheme 12 Proposed Strategy with Cyanuric Chloride

2.3 Attempted Solid Phase Synthesis of Triazine Catalysts

2.3.1 Suzuki Coupling Strategy

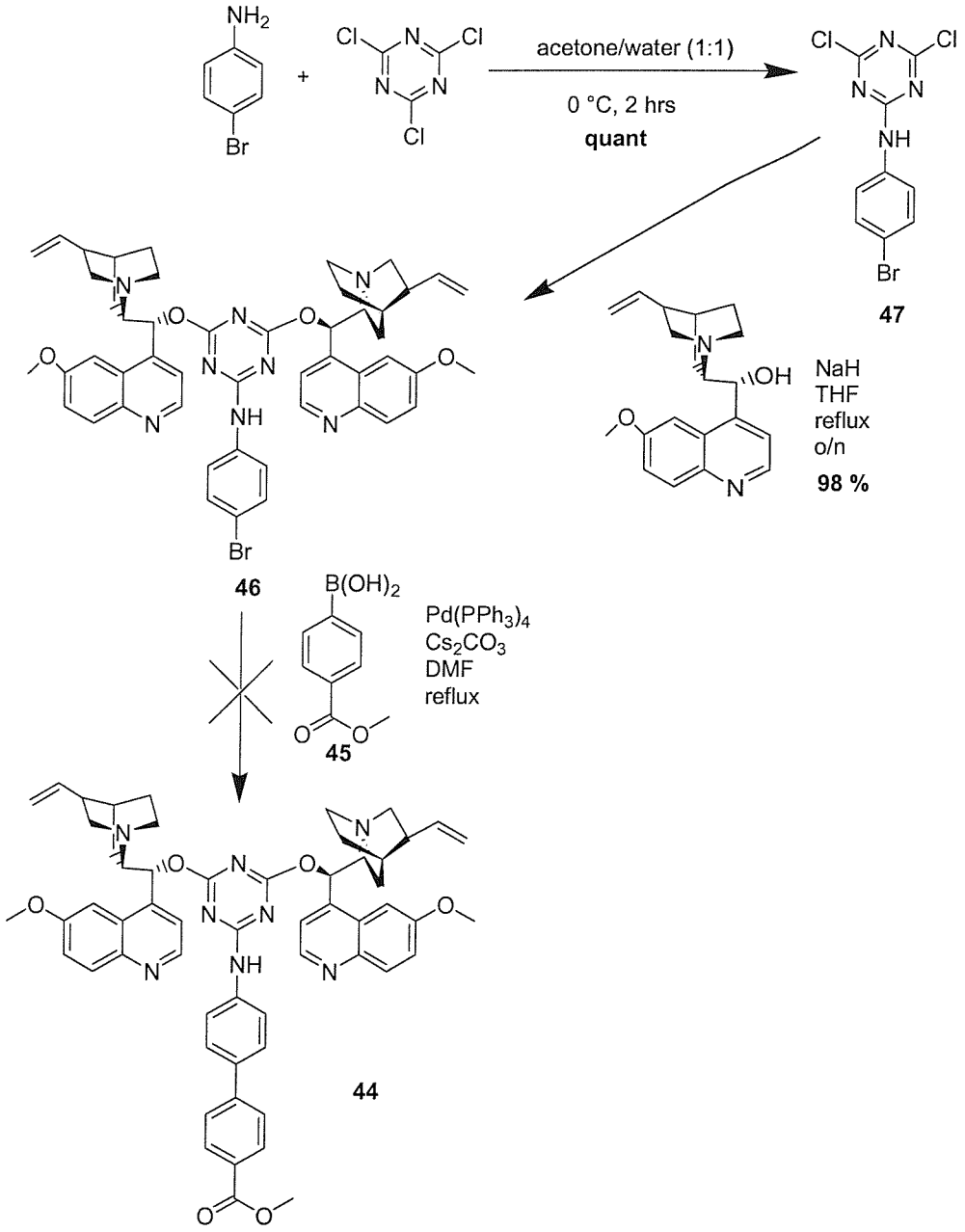
Carboxyphenyl-boronic acid was efficiently converted to the corresponding methyl ester (**45**) by treatment with thionyl chloride in methanol (Scheme 13).



Scheme 13 Esterification of carboxyphenyl-boronic acid

Cyanuric chloride was successfully reacted with bromo-aniline to give the di-chloro intermediate (**47**) in quantitative yield, after 2 hours, on both 1 and 10 g

scale. Subsequent reaction of this with two equivalents of quinine gave tri-substituted triazine, **46** in excellent yield. Unfortunately Suzuki coupling of this with ester **45** was unsuccessful (Scheme 14) and therefore investigation of other, more reactive palladium complexes and ligands was undertaken.



Scheme 14 Synthesis of tri-Substituted Triazine **46** and Attempted Suzuki Coupling with **45**

Fu[86] has reported a mild procedure for the Suzuki coupling of unactivated halogen substrates, including aryl chlorides, using a highly reactive palladium/phosphine complex prepared *in* situ from $Pd_2(dba)_3$ and $P(^tBu)_3$ and it was decided to attempt the coupling adopting these conditions. Table 10 shows the combination of palladium, ligands, solvents, bases and reaction conditions attempted. No product formation was observed for any attempt except **4**, where molecular ions corresponding to the desired product, the starting material and the de-brominated compound were observed by LC-MS although the desired product could not be isolated.

attempt	palladium source/ligand	base	solvent/Conditions
1	$Pd_2(dba)_3$, $P(^tBu)_3$	KF	THF/r.t.
2	$Pd_2(dba)_3$, $P(^tBu)_3$	KF	THF/reflux
3	$Pd(PPh_3)_4$	NEt_3	THF/reflux
4	$Pd(PPh_3)_4$	Cs_2CO_3	DMF/100 °C
5	$Pd(PPh_3)_4$	Cs_2CO_3	Dioxane:water (4:1) /reflux

Table 10 Suzuki Coupling Conditions Attempted

All Suzuki couplings so far had been carried out in a serial fashion. In a final attempt to obtain the desired product, 12 Suzuki reactions with aryl bromide **46** were carried out in a parallel fashion on a small scale and the conditions used are shown in Table 11.

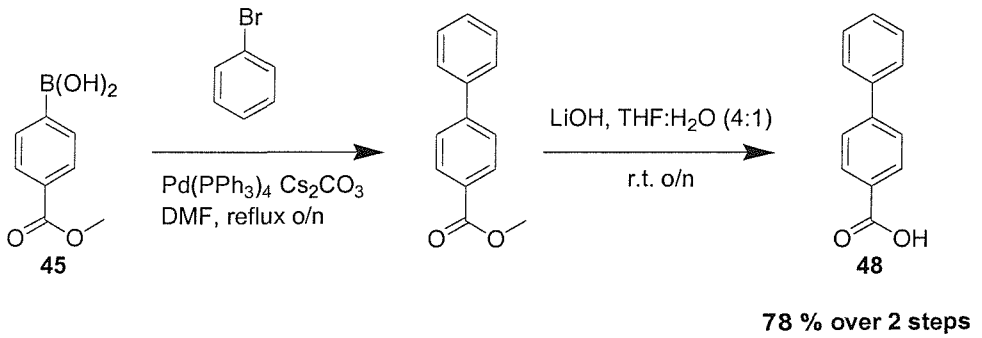
	Ligand/ Phosphine	base (3eq)	Solvent		Ligand/ phosphine	base (3eq)	Solvent
1	A	KF	DMF	7	A	KF	Acetone
2	A	KF	Dioxane	8	B	KF	DMF
3	A	Cs_2CO_3	Benzene	9	B	KF	Dioxane
4	A	KF	Benzene	10	B	Cs_2CO_3	Benzene
5	A	KF	THF	11	B	KF	Benzene
6	A	$CsCO_3$	Acetone	12	B	KF	THF

A= $Pd_2dba_3/P(^tBu)_3$, B=$Pd(PPh_3)_4$

Table 11 Conditions used for the 12 Parallel Suzuki Reactions

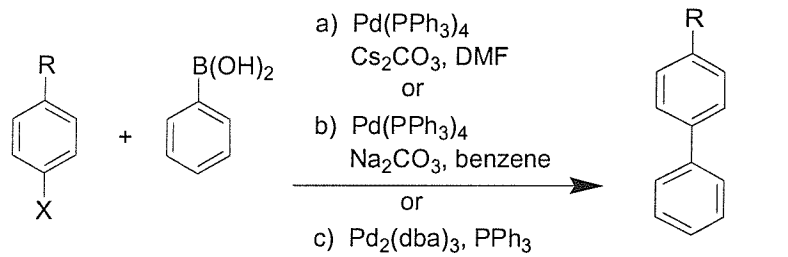
This originally seemed promising as crude reactions mixtures from entries 2 and 3 appeared to contain peaks in the mass spectra corresponding to the desired product. Purification by column chromatrography proved problematic and NMR did not indicate the desired compound. When reaction 2 was repeated on a larger scale to isolate more material less than 50 % of the starting material had been consumed after 1 week and TLC appeared to show the formation of many different products.

As a test reaction ester **45** was successfully coupled with bromobenzene and subsequent deprotection with LiOH gave the desired biaryl as a white solid in 78 % yield over the two steps. This confirmed the viability of the boronate as a Suzuki coupling componenent (Scheme 15).



Scheme 15 Test Reaction with Bromobenzene

As this route to performing the biaryl system was not feasible it was decided to embark on a different strategy where the biphenyl moiety was constructed in the first part of the sequence. Three different haloarene substituents, which provided attachment sites for cyanuric chloride, were selected: a Boc protected aniline, a nitro compound, and a phenol. For the former two, TFA deprotection or hydrogenation repectively would afford the desired aniline, and for the latter, it has already been shown that phenols react well with triazines.[87] Bromo and iodo variants of all three were also used giving six different substrates (**49** – **54**, Scheme 16), each of which was coupled under two of three different reaction conditions (Table 12) with phenyl boronic acid, which was used as a model compound as it was substantially cheaper and more readily available than ester **45**.



49 R = NHBOC, X = Br
50 R = NHBOC, X = I
51 R = NO_2, X = Br
52 R = NO_2, X = I
53 R = OH, X = Br
54 R = OH, X = I

55 R = NHBOC
56 R = NO_2
57 R = OH

Scheme 16 Substrates and Conditions used in the Synthesis of Biaryls

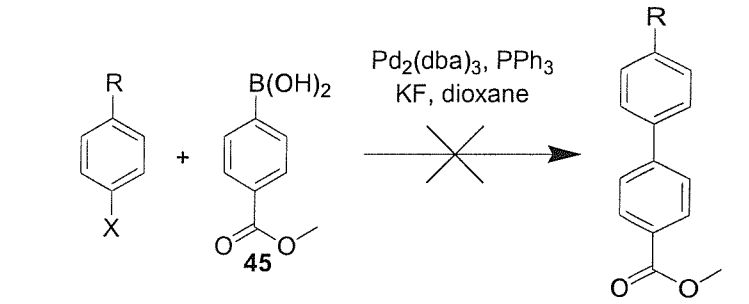
Reaction	Substrate	Method[a]	Reaction	Substrate	Method[a]
1	**49**	a	2	**49**	c
3	**50**	a	4	**50**	c
5	**51**	c	6	**51**	b
7	**52**	c	8	**52**	b
9	**53**	a	10	**53**	c
11	**54**	a	12	**54**	c

[a]See Scheme 16

Table 12 Methods Used in the Synthesis of Biaryls

After two days reflux reactions 7 and 10 exhibited the highest yield by HPLC and NMR. The crude product from reaction 7 was purified by column chromatography to afford **56** in 74 % yield. Column chromatography of reaction mixture 10 did not sufficiently purify the desired biaryl; although purification was easily achieved by recrystallisation of the residue from hexane/ethyl acetate to give **57** in 62 % yield.

These reactions were then repeated using ester **45**, however after one weeks reflux in dioxane there were no signs of product formation by TLC or HPLC.



52 R = NO_2, X = I
53 R = OH, X = Br

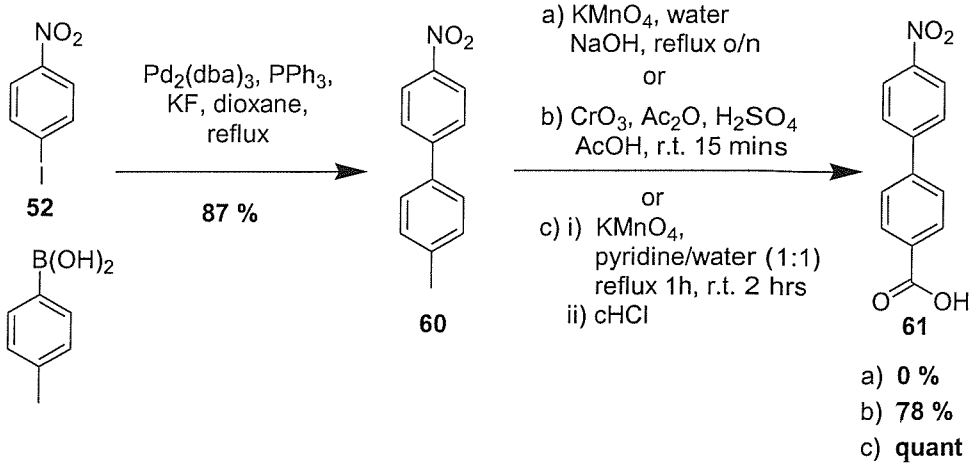
58 R = NO_2
59 R = OH

Scheme 17 Reaction of Optimum Halide Substrates with Ester **45**

2.3.2 Tolyl Oxidation Strategy

This was both puzzling and discouraging therefore a new strategy was devised. As halides **52** and **53** had both successfully reacted with phenyl boronic acid it was postulated that they would react with tolyl-boronic acid which could then be oxidised to the corresponding acid and esterified to give a resin attachment site. It was decided to undertake the synthesis with nitro compound **52** as this had been the most straightforward to purify, had afforded the desired compound in high yield and its reduction to an aniline was considered facile, this functionality had previously been used for the selective substitution of cyanuric chloride. The tolyl group could then be oxidised to the corresponding acid, esterified, and the nitro compound reduced to afford the desired bi-aryl aniline which could then be reacted with cyanuric chloride and quinine. Subsequent hydrolysis of the ester would give an acid which could be coupled onto aminomethyl resin.

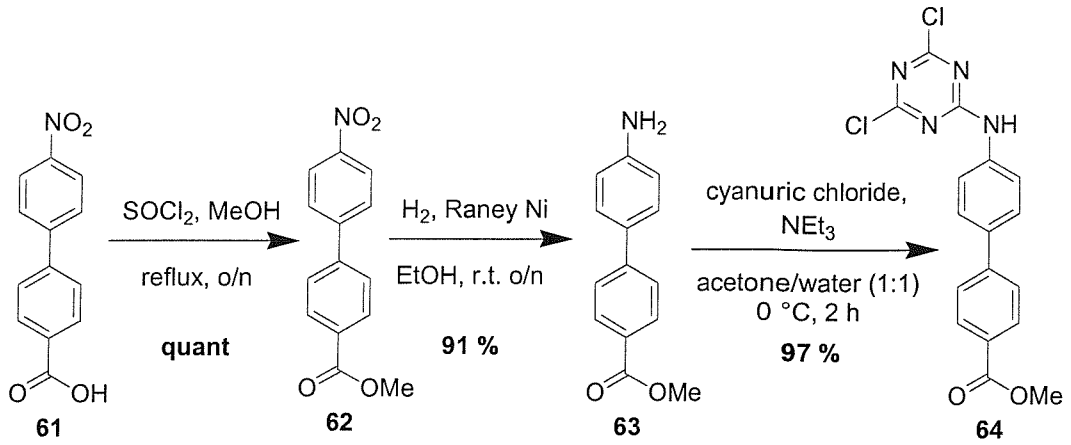
The Suzuki coupling of nitro compound **52**, with tolyl boronic acid, to afford **60** proceeded in 87 % yield (Scheme 18).



Scheme 18 Strategy with Tolyl Boronic acid Followed by Oxidation

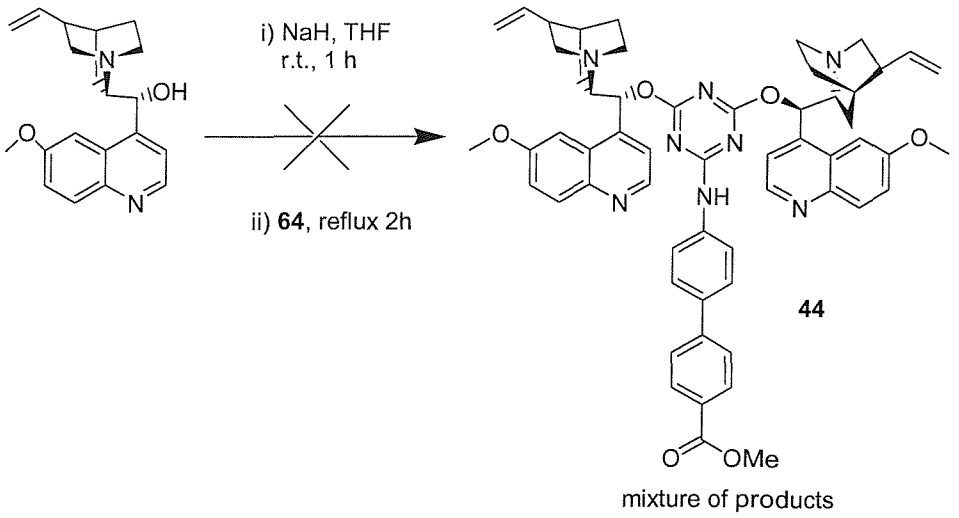
Initial attempts to oxidise the tolyl moiety with potassium permanganate were unsuccessful, probably due to the insolubility of **60** in the selected reaction media (H_2O/NaOH), but the second attempt with chromium trioxide in acetic acid gave the desired compound in 78 % yield. Although the latter proceeded in an acceptable yield, use of this reagent to effect the transformation on a larger scale was considered highly undesirable, as chromium complexes are highly toxic and difficult to dispose of. They are also known for emulsion formation upon work-up, which was indeed observed in this case. Isolation of **61** was problematic as it was not amenable to column chromatography, due to its intrinsic insolubility and high polarity and the product was isolated as a brown solid, believed to be contaminated with chromium residues. However, upon changing the solvent system for the permanganate mediated oxidation to pyridine/water, the oxidation proceeded, albeit under harsh, refluxing conditions, in quantitative yield after only 3 hours. The acid product was easily isolated by precipitation with cHCl and filtration and pyridine salts were washed away with copious amounts of hot water.

Esterification of **61** in refluxing methanol with thionyl chloride followed by hydrogenation of the nitro group with Raney nickel afforded bi-aryl **63** which underwent selective displacement of one chlorine moiety of cyanuric chloride in excellent yield (Scheme 19).



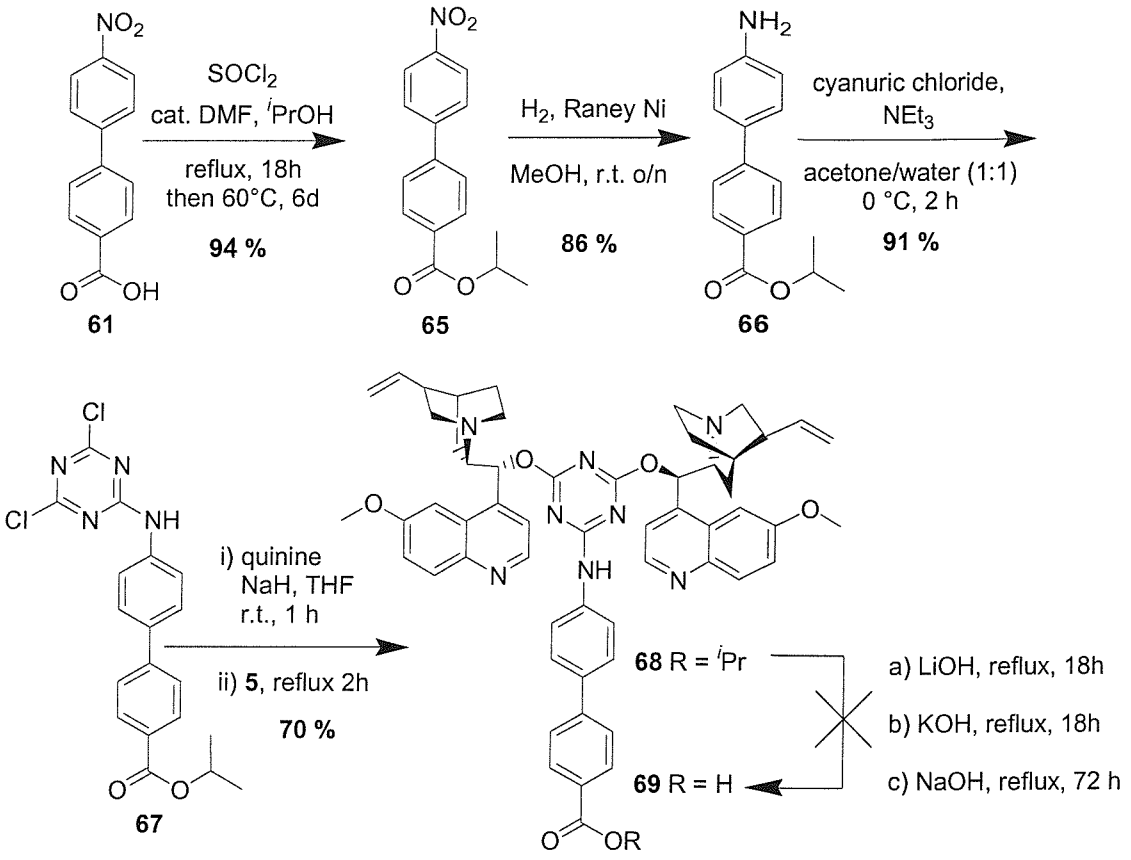
Scheme 19 Synthesis of Mono Substituted Triazine **64**

After prolonged drying of **64** under vacuum, attention was then turned to the displacement of the final two moieties with quinine. Thus the anions of quinine were formed by reaction with NaH in dry THF and reacted with **64**. Unfortunately this gave rise to a complex mixture of products, one of which appeared to be the hydrolysed product. Although the acid was the target compound attempts to isolate it, including purification by crystallisation, trituration and ion-exchange resin, failed due in part to the very poor solubility of the crude mixture.



Scheme 20 Attempted Synthesis of Tri Substituted Triazine **44**

It was therefore concluded that the methyl ester was not sufficiently stable to withstand the reaction conditions for attachment of the quinine moieties hence the synthesis was repeated substituting the methyl for an *iso*-propyl ester. Tri-substituted Triazine **68** was readily achieved following a similar synthetic sequence (Scheme 21), most reactions proceeded in high yield and this time, reaction of the mono-substituted triazine **67** with quinine afforded the desired product with no evidence of ester hydrolysis in reasonable yield. Subsequent deprotection of **68** was however, more problematic than expected. The ester was initially stirred with 1.1 equivalents of LiOH at room temperature overnight and then at reflux overnight but no reaction took place. The reaction was re-attempted with 5 equivalents of KOH and NaOH, for both after 72 hours reflux no reaction had taken place (Scheme 21).



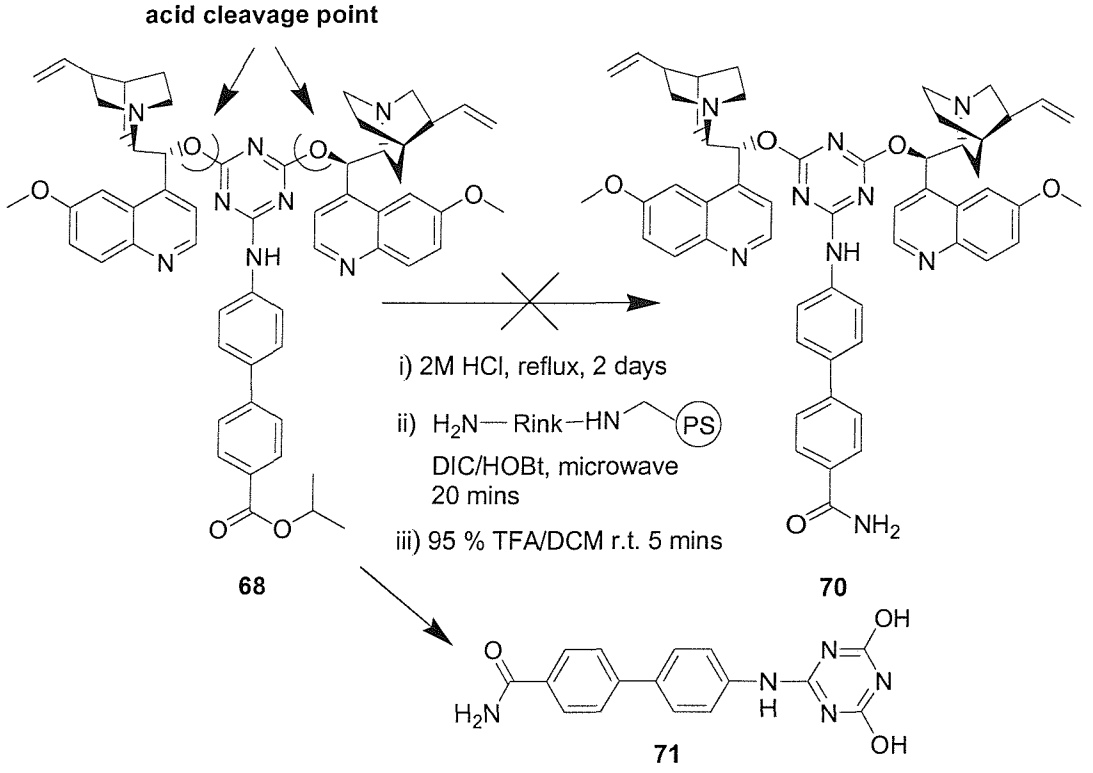
Scheme 21 Synthesis with Iso Propyl Ester

Acid deprotection was then attempted, **68** was refluxed overnight in 2 M HCl and the solvent removed *in vacuo*. ^{1}H and ^{13}C crude NMR showed disappearance of the *iso*-propyl groups and it was thus concluded that the reaction had gone to completion.

Believing that acid **69** was in hand, attachment of the ligand to aminomethyl polystyrene using DIC/HOBt chemistry was attempted. To effect complete conversion (negative, qualitative ninhydrin test) it was necessary to perform two couplings under microwave irradiation at 140 °C for 1 hour. Combustion analysis results showed much a lower nitrogen content than expected, which suggested that the ligand had not been attached to the resin, even though the qualitative ninhydrin test had shown that no more primary amine functionality remained. Ester **68** and amino-methyl resin were both separately subjected to 2 hours heating in the microwave in the presence of DIC and HOBt. These

stability tests showed that a) the catalyst did not decompose and b) no loss of amine functionality (quantitative ninhydrin test positive) occurred under the coupling conditions.

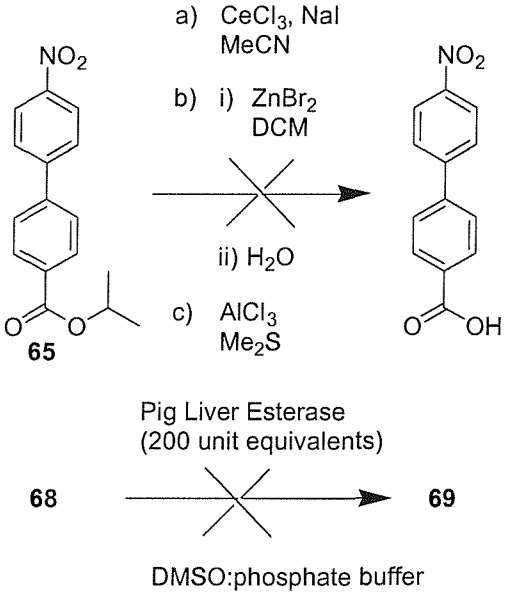
To establish what was being incorporated onto the resin, the coupling was repeated using the same conditions onto Rink amide resin (Scheme 22). Upon thorough washing and cleavage with 95 % TFA in DCM it was realized that the resin product was not amide **70** but de-alkylated product **71**. Upon further inspection of the deprotection product it was evident that the harsh acidic conditions had effected ether cleavage (Scheme 22).



Scheme 22 Coupling of Ligand onto Rink Amide Resin

Using catalyst precursor **65**, three chemical methods for the deprotection of esters, taken from the literature,[88-90] and enzymatic cleavage of **68** with Pig liver esterase were unsuccessfully attempted. The failure of the latter was attributed

to its insolubility, even with only 1 % water in DMSO, a consequence of seven aromatic rings in the structure.

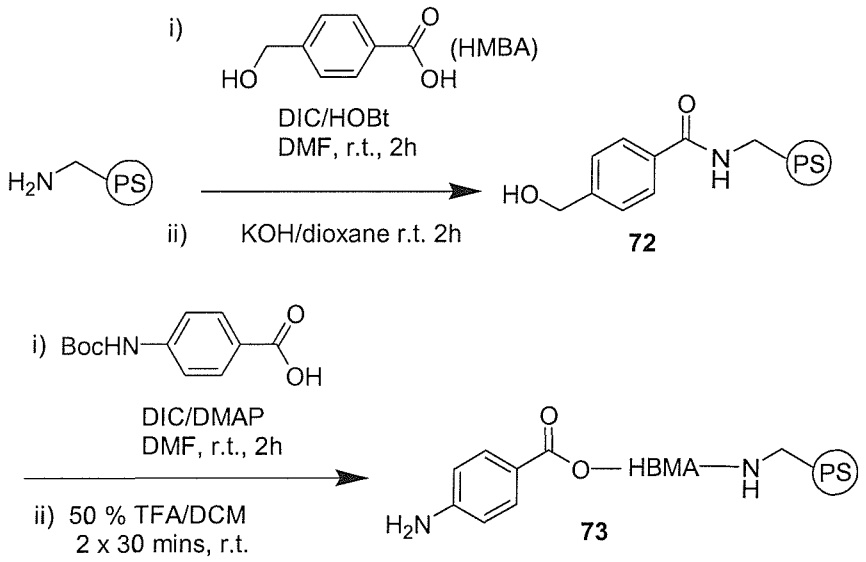


Scheme 23 Attempted Chemical Deprotection of Catalyst Precursor **65** and Enzymatic Cleavage of **68**

2.3.3 Direct Solid Phase Construction Strategy

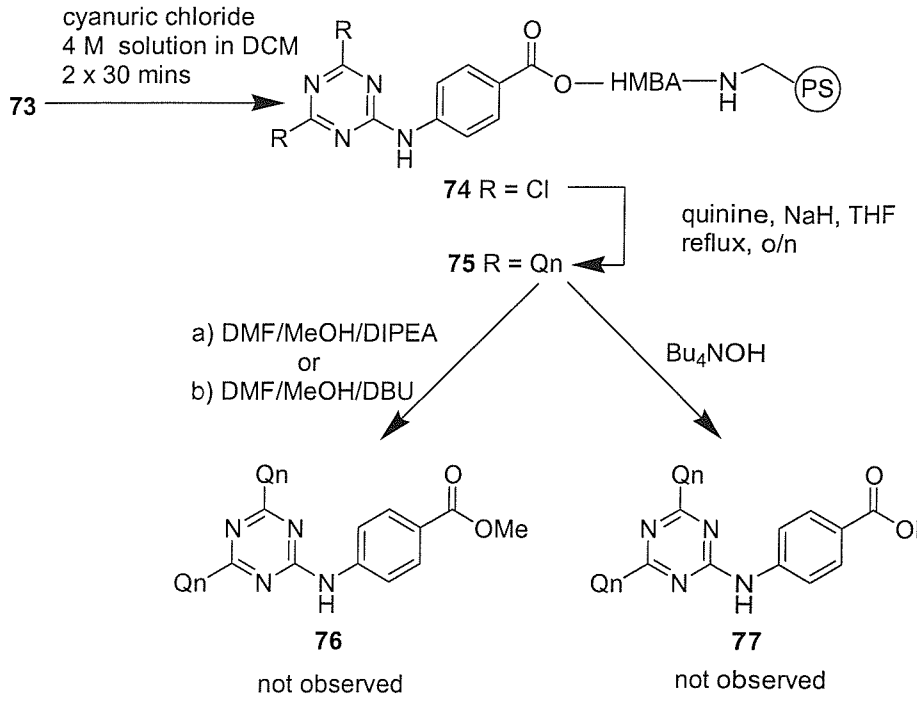
As a final strategy to achieve the resin bound triazine catalyst it was decided to synthesize the catalyst in a step-wise manner directly onto polystyrene resin, functionalised with an aniline-containing moiety onto a resin pre-loaded with a suitable linker for cleavage and product analysis.

Thus as shown in Scheme 24, aminomethyl polystyrene was loaded with the HMBA linker, which was selected because of its ready availability, low cost and its ability to be cleaved under conditions to yield an ester product.[91] Subsequent treatment with KOH in dioxane gave resin **72** which was coupled with N-Boc-amino benozoic acid, TFA deprotection afforded aniline resin **73,** suitably functionalised for cyanuric chloride displacement.



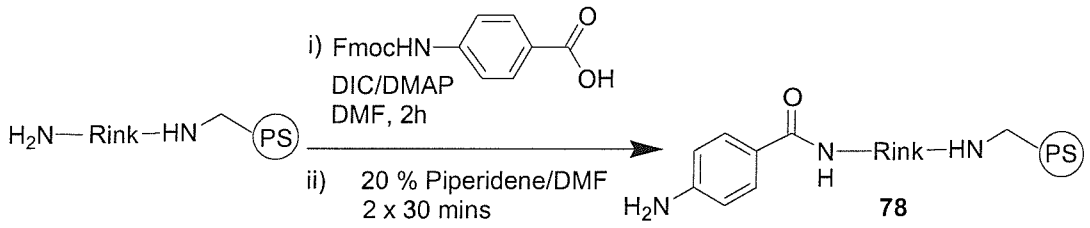
Scheme 24 Synthesis of Aniline, HMBA Resin

Resin **73** was treated with cyanuric chloride in the form of a 4 M solution in DCM (Scheme 25) which was then reacted with 4 equivalents of quinine which was deprotonated as in the solution phase reaction using NaH. Cleavage of the ligand from the resin was effected using a literature procedure of a 5:5:1 cocktail of DMF/MeOH/DIPEA,[91] although after overnight shaking no cleavage was observed by analysis of the resin by IR spectroscopy. A stronger base, DBU was then used on a separate portion of resin, IR spectroscopy showed regeneration of HMBA resin **72**, effectively showing that cleavage had taken place. HPLC showed the presence of many different products, although none corresponded to the correct product, **76**. Cleavage was then effected by basic hydrolysis, using tetrabutylammonium hydroxide although again HPLC suggested the presence of at least four different compounds and the correct molecular ion was not observed by mass spectrometry.



Scheme 25 Attempted Synthesis on HMBA Aniline Resin

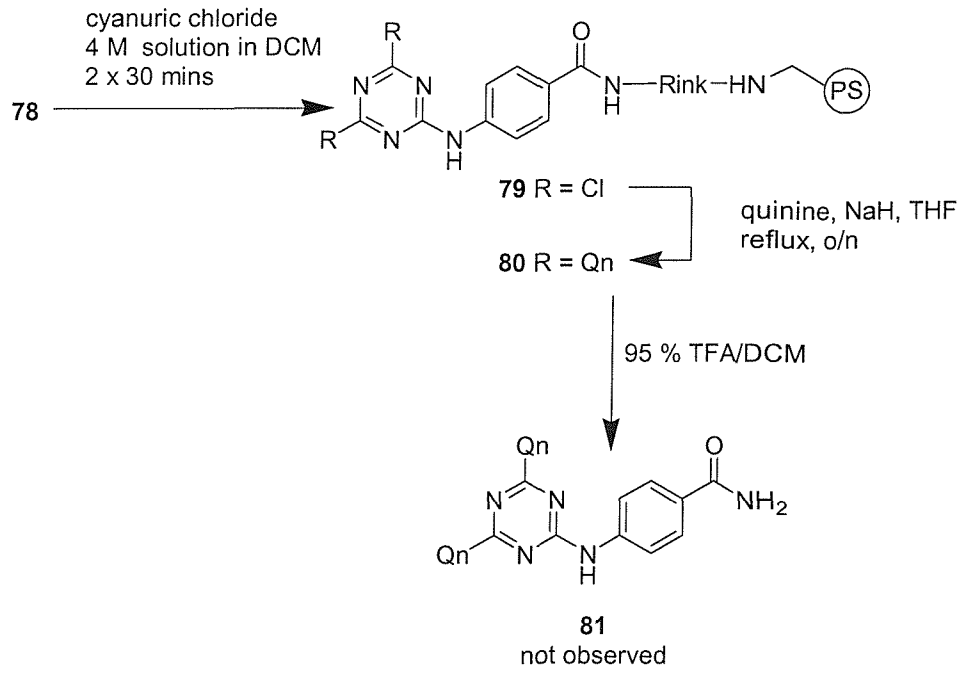
The synthesis was then repeated on Rink amide resin, which was initially coupled with Fmoc amino benzoic acid, subsequent cleavage with 20 % piperidine in DMF afforded resin **78**, which, in analogy to resin **73**, contained an aniline functionality suitable for cyanuric chloride displacement.



Scheme 26 Synthesis of Aniline, Rink resin

The attempted synthesis was carried out in a manner analogous to that of the HMBA resin (Scheme 27). Thus the resin was again treated with a 4 M solution of cyanuric chloride in DCM followed by reaction with an excess of quinine. Again, disappointingly upon cleavage of the resin, many compounds were

present in the HPLC chromatogram and the molecular ion corresponding to desired product **81** was not observed by mass spectrometry.

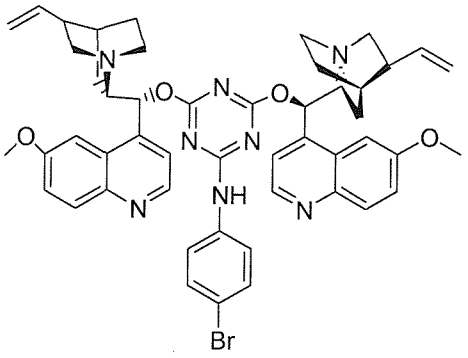


Scheme 27 Attempted Synthesis on Rink Amide Resin

2.4 Solution Phase Studies

Unfortunately all attempts to synthesize a solid supported triazine catalyst had been unsuccessful and attention was then turned to optimise the solution phase analogue.

As previously described solution phase ligand **46** (Figure 23) was synthesized in two, facile, high yielding steps from inexpensive starting materials, bromoaniline, cyanuric chloride and quinine (Scheme 12) on a multigram scale.



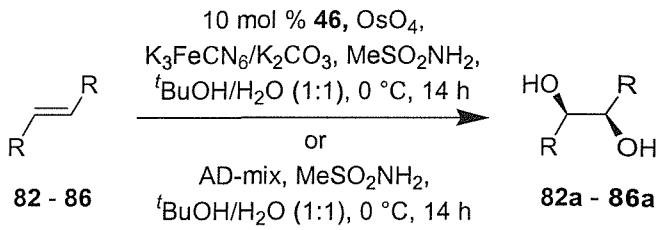
46

Figure 23 Solution Phase Ligand **46**

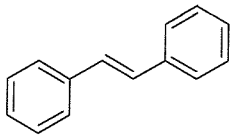
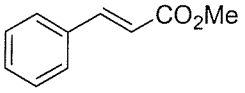
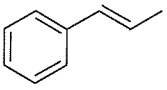
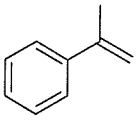
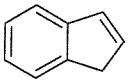
2.4.1 Use of the Triazine Catalyst in the Asymmetric Dihydroxylation of Alkenes

Use of **47** in the asymmetric dihydroxylation of different alkene substrates, **82** – **86**, to afford the corresponding diols (**82a** – **86a**) showed that it was indeed a viable ligand to effect the transformation in an enantioelective fashion. Table 13 shows the isolated yield and e.e.'s, for three different classes of alkenes. For comparison the e.e. achieved under our system using the Sharpless, *bis*-phthalazine derivative, which was utilised in the form of AD-mix and a literature e.e. reference, are included.

It is evident that the ligand is most selective for *trans*-substituted alkenes, which all gave greater than 90 % e.e. For the first entries, the ligand was found to be superior to that of the Sharpless ligand under our conditions and equal to, or greater than that reported in the literature. The highly stereoselective, asymmetric dihydroxylation of **83** is highly desirable as this forms the first step, in a published synthesis of the C-13 side chain of Taxol,[92] which is considered to be an extremely promising cancer chemotherapeutic agent.



82 - 86 **82a - 86a**

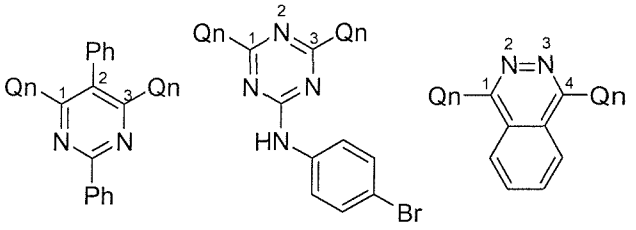
	Alkene	Yield	e.e.[a]	AD mix	Sharpless ref[43]
82		75 %	**> 99 %**	91 %	>99 %
83		quant[b]	**> 99 %**	94 %	97 %[c]
84		78 %	**93 %**	96 %	97 %
85		85 %	**64 %**	91 %	94 %
86		90 %	**26 %**	29 %	42 %

[a] Determined by chiral HPLC on Chiralpak AD-RH column, 20 % MeCN/H_2O, flow rate 0.5 ml/min; [b]Carried out at room temperature; [c]Value quoted for the ethyl ester

Table 13 Asymmetric Dihydroxylation Results

On consultation of the literature it was found that the e.e. results obtained were similar to those Sharpless obtained with his pyrimidine based ligand,[54] as for this ligand the e.e. achieved for alkene **85** was 69 % and for alkene **86**, 35 %, thus a similar reduction with this ligand was observed. On inspection of the

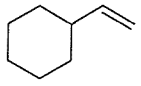
respective structures this is not so surprising as they both have a 1,3-relationship between the two quinine moieties whereas the phthalazine ligand has a 1,4- relationship (Figure 24).



Pyrimidine Ligand Triazene Ligand Phthalazine Ligand

Figure 24 1,3 and 1,4 Quinine Relationships in Various Ligands

Pyrimidine ligands show improved enantioselectivities in the asymmetric dihydroxylation of terminal alkenes over their phthalazine counterparts, for example the dihydroxylation of vinyl cyclohexene (Table 14), however when this reaction was undertaken the e.e. was found to be lower than that of the Pyrimidine ligand, although equal to that of the phthalazine ligand.

Alkene	Pyrimidine Ligand	Phthalazine Ligand	Triazine[a,b] Ligand
 **87**	96 %	88 %	88 %

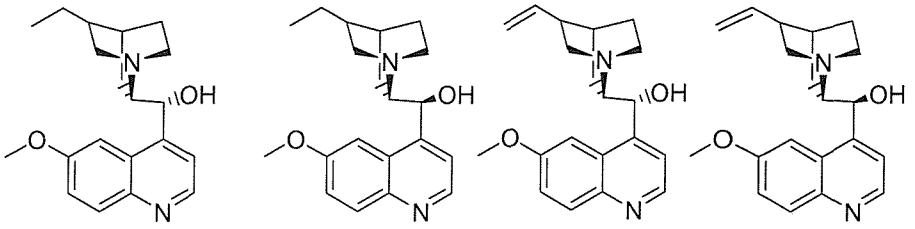
[a]Determined by comparison in ^{1}H NMR of the *bis*-Moshers ester; [b]using dihydrquinidyl ligand.

Table 14 E.e.'s for the Asymmetric Dihydroxylation of Terminal Alkenes.

It was therefore concluded from this series of experiments that the optimum substrates for the triazine ligand were those which were *trans* substituted, which considering that most commercially available alkenes are of this orientation was very positive.

2.4.2 Studies on Different Alkaloid Moieties

As mentioned in Chapter one, there are four possible alkaloid moieties which can be incorporated onto the heterocyclic ring spacers, these are quinine (**18**) and its pseudo-enantiomer quinidine (**19**), and their dihydro analogues hydroquinine (**14**) and hydroquinidine (**16**), (Figure 25).

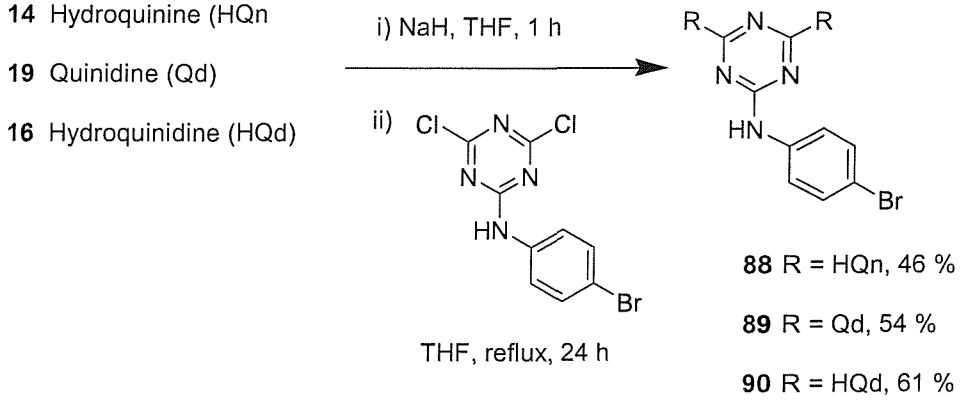


14 Hydroquinine (HQn) | **16** Hydroquinidine (HQd) | **18** Quinine (Qn) | **19** Quinidine (Qd)

Figure 25 Alkaloid Moieties

The quinine and quinidine moieties are substantially less expensive than their dihydro derivatives, as are pseudoenantiomers **14** and **18** compared to **16** and **19**. For this reason in this study, the results shown in Table 13 were carried out with the quinine moiety attached to the triazine spacer.

For ligands with different heterocyclic spacer groups, in some cases differences in e.e. have been observed with different alkaloids.[52,55,56] The synthesis of the other three *bis*-alkaloid ligands was therefore undertaken in a similar fashion to that for the quinine moiety (Scheme 28) to see if any differences in e.e. resulted.



Scheme 28 Synthesis of Triazine Ligands

Alkenes **84** – **86** were then subjected to asymmetric dihydroxylation using the conditions described in Table 13 with ligands **88** – **90** and the results are given in Table 15 which shows that overall there were no significant differences in the overall behaviour of the ligands. This is in contrast to the anthraquinone[56] and pyrimidine[54] catalysts where ligands based on pseudoenantiomer **16** gave higher e.e.'s that those based on **14**, although for the phthalazine ligands Sharpless noted that the quinine and quinidine anlogues were virtually identical in effectiveness to their dihydro analogues despite the fact that the operative ligands were the corresponding tetrols formed by rapid *in situ* dihydroxylation of the vinyl groups.[52]

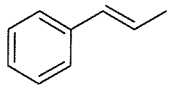
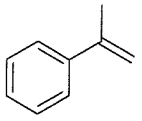
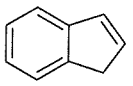
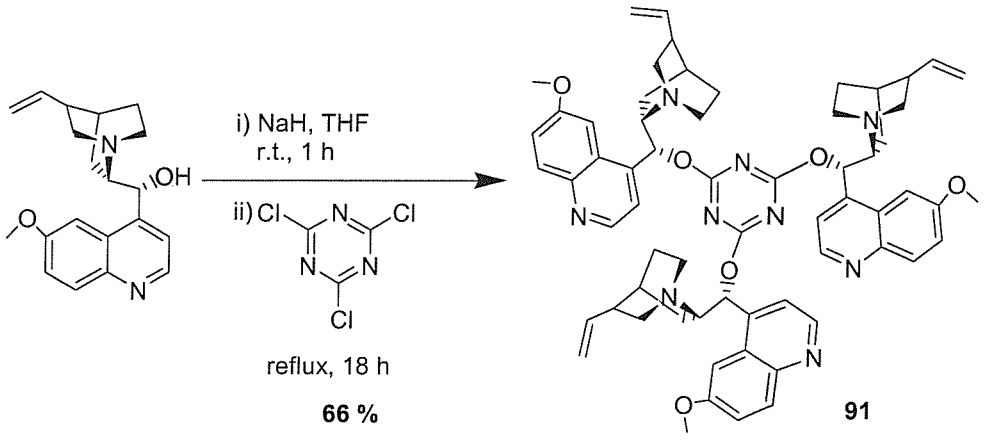
	Alkene	$BA(Qn)_2TRZ$ (47)	$BA(HQn)_2TRZ$ (88)	$BA(Qd)_2TRZ$ (89)	$BA(HQd)_2TRZ$ (90)
84		93 %	94 %	86 %	92 %
85		64 %	64 %	64 %	74 %
56		26 %	24 %	29 %	22 %

Table 15 Asymmetric Dihydroxylation Results with Chiral Ligands **88** – **90**

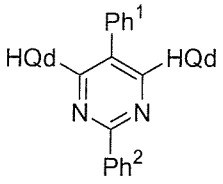
2.4.3 Synthesis of a C-3 Symmetric Ligand – Evidence In Support of a Binding Pocket

To assess the performance of a C-3 symmetric ligand, **91** (Scheme 29) was synthesized in 66 % yield in a manner similar to all the other quinuclidene-triazine complexes.



Scheme 29 Synthesis of Tri-Substituted Triazine **91**

This showed to have a disastrous result on the catalytic activity; e.e.'s dropped from 64 % to 42 %, 94 % to 76 % and 24 % to 2 % for α-methyl styrene, β-methyl styrene and indene respectively. This is similar to that observed by Sharpless for the pyrimidine ligand[54] where substitution of the 1-phenyl group (Figure 26) with a ^{t}Bu group gave results similar to that of **22** whereas the same substitution of the 2-phenyl had a similar disastrous effect. This can be explained as the disruption of a necessary binding cavity into which the alkene fits to undergo dihydroxylation in an asymmetric fashion.



22

Figure 26 Pyrimidine Ligand **22**

Although there have been various proposals on the active catalytic species involved in the asymmetric dihydroxylation by various groups[93-101] it is now universally accepted that only one quinuclidene moiety is actively involved in the catalytic cycle.[53,93,98,100] Sharpless found that quaternization of one of the quinuclidene groups with benzyl bromide gave a mono-quat salt which proved

just as effective in the asymmetric dihydroxylation of styrene and 1-decene.[100] He then reported the presence of an L-shaped binding cleft where an aromatic alkene underwent attractive face to face interactions with the phthalazine ring and edge to face interactions with the other, so-called bystander alkaloid moiety. This enabled the alkene to fit neatly into a binding platform in the desired conformation for asymmetric dihydroxylation and explained the difference in e.e. observed for styrene (97 %) and vinyl cyclohexane (88 %).[99,101] Lohray had previously reported that the alkene could be held over the π-cloud of the asymmetric ligand which would mean that one side underwent steric repulsion.[94] Although there are various suggestions on the geometry of the binding cleft, for example Corey believes it to be U-Shaped formed by stacking interactions between the two quinoline rings,[95,98,102,103] there is no doubt that such a cavity exists and it appears that this is also true for the triazine ligand. The aromatic aniline moiety assists in the assembly of the necessary arrangement of quinuclidene moieties and triazine spacer group to undergo the dihydroxylation in an asymmetric fashion, it's function therefore is not simply as a steric block.

2.5 Conclusion

A Sharpless type asymmetric dihydroxylation ligand with a novel triazine core was synthesized in two, easy, high yielding steps from cheap, ready available starting materials. Although attempts to form an immobilized version were unsuccessful, the solution phase ligand was found to be active in the asymmetric dihydroxylation of alkenes, especially those of the most common, *trans* geometry. No significant difference on the incorporation of different alkaloid moieties was observed. Synthesis of the C-3 symmetric analogue confirmed that which has been previously reported, that the assembly of a binding pocket is vital to effect the transformation stereospecifically.

As cyanuric chloride can be easily and selectively reacted with a variety of nucleophiles including thiols, phenols[87] and Grignard reagents,[104] upon further investigation it could serve as an extremely useful spacer group to further extend the scope of the asymmetric dihydroxylation reaction.

3 Use of Experimental Design to Optimise Sharpless Asymmetric Dihydroxylation Using the Triazine Ligand

3.1 Introduction

In the previous chapter, asymmetric dihydroxylation mediated by ligand **47** was described using potassium ferricyanide as the secondary oxidant, and it was shown that the ligand was reasonably selective in the asymmetric dihydroxylation of several alkenes, especially those of the *trans* geometry. Here its optimisation using a DoE approach was undertaken.

This was carried out in collaboration with statisticians: Professor S. M. Lewis and Dr D. C. Woods from Southampton University's Statistical Sciences Research Institute, who designed the experiments from the given factors and carried out model fitting and analyses.

3.2 Optimization of the Asymmetric Dihydroxylation Reaction

Following an extensive scoping phase this study was carried out in a classical manner; initially, a large screening experiment, encompassing all factors to be varied was undertaken. This was followed by applying a response surface design to the most important factors to fully optimise the reactions.

3.2.1 Scoping

This stage involved the development of a method for implementation and analysis of the asymmetric dihydroxylation reactions and to select viable substrates.

3.2.1.1 Method Development

A successful DoE investigation requires an efficient, reproducible method, in this case encompassing both implementation and analysis of each reaction. For the former this entailed the transfer of six different components (alkene substrate, osmium tetroxide, secondary oxidant, base, chiral catalyst and the methane sulfonamide additive) and the solvent, as well as a requirement for suitable agitation and maintenance of a low (0 °C) temperature. For the latter, as well as actual sampling, both conversion and e.e. were the desired responses; therefore a method to enable both of these responses to be accurately determined was required.

Reactions were carried out in screw-top vials; which were agitated on a horizontal shaker; the lower level of temperature was achieved by placing the vials in ice boxes. Each vial was equipped with a transponder in order that each reaction could be easily identified. The chiral catalyst and methane sulfonamide additive were hand-weighed into each vial as unfortunately due to the intrinsic insolubility of both, preparation of stock solutions was not feasible. Stock solutions of the secondary oxidant and both bases could however be prepared and were dispensed using a Hewlett Packard Multiprobe liquid handler. The volumes required were calculated directly applying "IF" functions to the design matrix in an Excel spreadsheet, which were subsequently incorporated as CSV files into the liquid handler. Direct calculation of the required volume from the design matrix in this fashion ensured higher accuracy.

The solvent and osmium tetroxide were then added manually by micropipette. From this time, due to osmium tetroxide's high toxicity it was essential that the reactions remained in a ventilated fume hood and therefore the liquid handler could no longer be used. The reactions were agitated for 1 hour prior to substrate addition and shaken at the desired temperatures overnight.

Conversion and e.e. were measured using RP-HPLC on a Hewlett Packard 1100 Chemstation equipped with an HP 220 automated fraction collector (absorbance 220 nm). Upon consideration of how the experiment was to be analysed two

main issues arose. It was discovered that the chiral ligand, which contained seven aromatic rings, completely dominated the HPLC trace at 220 nm, thus reactants and products could not be distinguished from the ligand. Fortuitously the catalyst could be efficiently scavenged using Amberlyst A-15 ion-exchange resin (Figure 27). Another concern was how to determine the e.e., as chiral columns are extremely expensive and sensitive, an aliquot of the crude reaction mixture could not merely be applied to a chiral column. Therefore a purification step was deemed necessary. This was simply resolved using the fraction collector to collect the column eluent at the retention time corresponding to that of the diol products, although this did add 6 minutes analysis time to each reaction (Figure 28). Thus after 16 hours reaction an aliquot was taken from each reaction and added to thoroughly washed ion-exchange resin[105] which had been placed into a 2 ml 96 deep well filter plate, which was positioned on top of a 2 ml, 96 deep well receiver plate (Figure 27). The latter plate contained a stock solution of at least one equivalent of Na_2SO_3 to neutralise the osmium tetroxide. The ion exchange resin was then washed with a MeCN/H_2O (1:1) solution; this ratio was found to be crucial as its replacement by MeOH or a higher percentage of MeCN led to extremely poor chromatography.

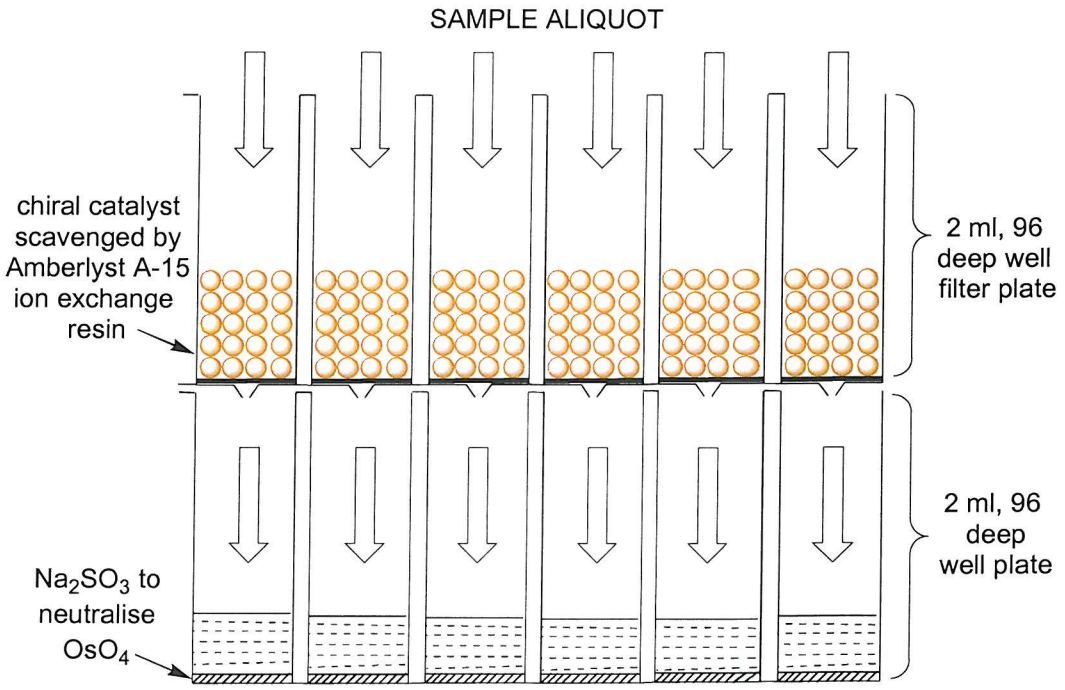


Figure 27 Sample Preparation

From each sample two injections were taken, the first was to determine the level of conversion and the second, the e.e. The HP220 robot was programmed to take a 50 μl injection from each sample which was analysed using a 6 minute gradient on a 5 cm, RP-C18 column, which following a calibration study could be used to calculate conversion. To determine e.e. another injection, this time of 500 μl was taken and applied to the same C-18 column. The retention time of the diol products was found to be between 2 and 2.5 minutes and the HP220 was programmed to collect the column eluent between these times into another 96, deep well plate. Maintenance of a sample and fraction position relationship at this stage was crucial. The RP-C18 column was changed for a ChiralPak AD-RH column and the purified diol applied to the column for e.e. determination. Analysis time for each reaction was therefore 24 minutes, which considering two responses were measured, one of them being e.e. which is notoriously laborious and sometimes takes up to an hour per sample was deemed highly satisfactory (Figure 28).

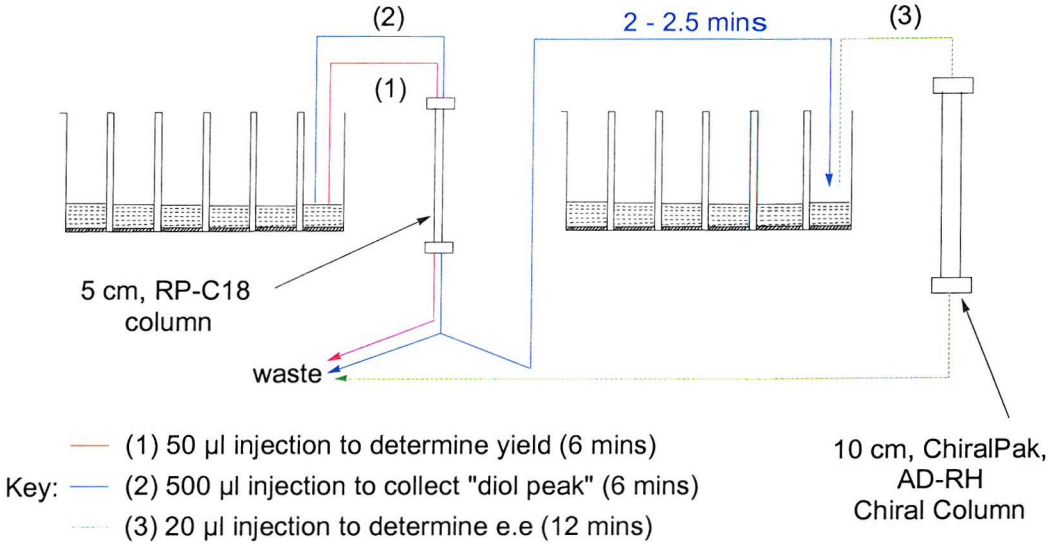
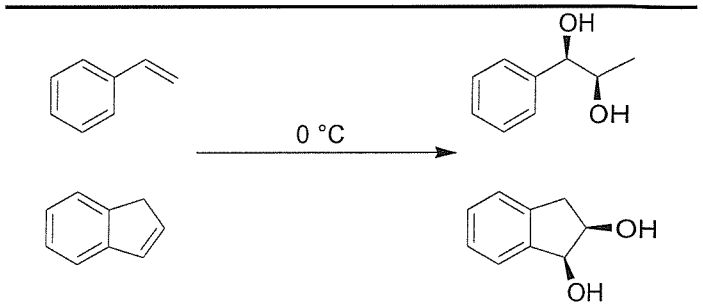


Figure 28 HP220 Programming to Determine Conversion and e.e.

3.2.1.2 Reproducibility

In order to test the reproducibility the asymmetric dihydroxylation of both β-methyl styrene and indene under standard conditions was repeated five times

(Table 16). These substrates were selected as they had previously been observed to give very different e.e.'s; 96 % and 24 % and it was necessary to clarify that the reaction conditions were suitable to distinguish between diols of both low and high enantioselectivity. These reactions were carried out on a 3 mmol scale. Quantities of reactants are summarized in Table 16 and the results are displayed in Figure 29.



Component	Weight/Volume
alkene	35 μl
chiral catalyst **46**	29 mg
OsO_4	46 μl[a]/1.1mg
K_3FeCN_6	294 mg
K_2CO_3	124 mg
$MeSO_2NH_2$	29 mg
$^tBuOH/H_2O$ (1:1)	6 ml

[a]1.5 % solution in ^{t}BuOH

Table 16 Dihydroxylation conditions for the Reproducibility Experiment

The mean and standard deviation for each treatment (substrate) are shown in Table 17. Standard deviations measure how widely dispersed the values are from the mean and are calculated by averaging the square of the difference of each value from the mean (see Appendix for calculation). In this case, the standard deviations were significantly smaller than the means, suggesting that reproducibility was good.

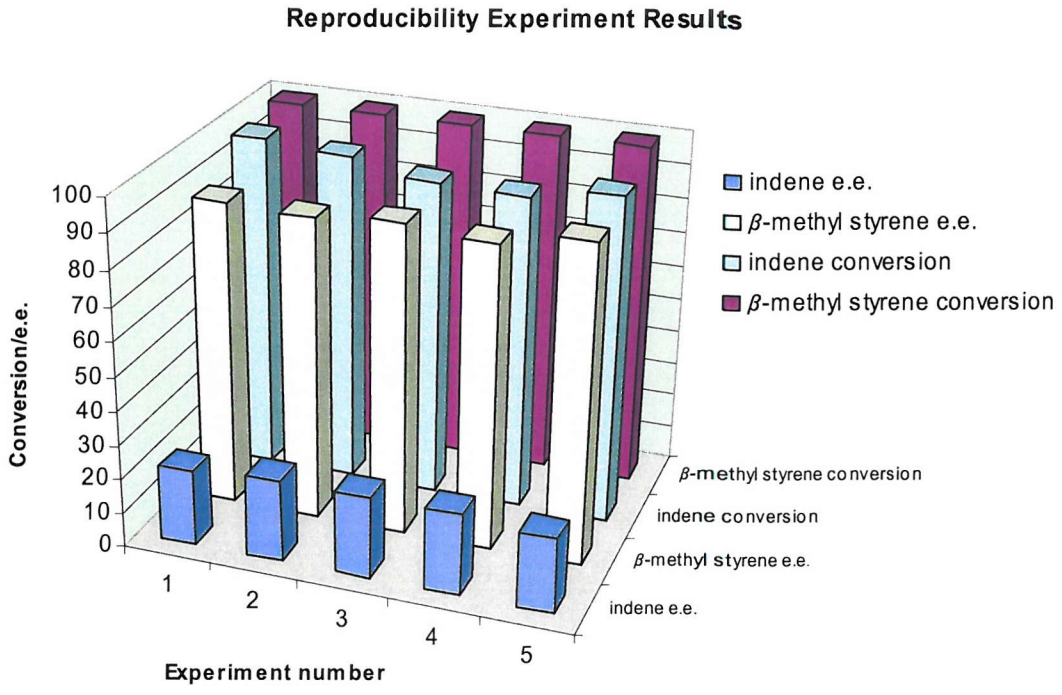


Figure 29 Results of the Reproducibility Experiment

Alkene	Indene		β-methyl styrene	
Response	**conversion**	**e.e.**	**conversion**	**e.e.**
Mean	94.7	23.2	100.0	89.4
Standard Deviation	2.9	0.8	0.0	1.9

Table 17 Mean and Standard Deviation Results of the Reproducibility Experiment

Although the mean and standard deviation gave a good statistical summary of the results, this information alone is not sufficient. ANOVA (Analysis Of Variance) was therefore also applied.

The purpose of ANOVA is to test the null hypothesis that the treatment means (in this case the treatment is the substrate) are equal, against the alternative hypothesis that the treatment means differ. This is achieved by comparing the difference between the treatment means to the variability within the treatments. If the variation of the values within the treatments is large relative to the

difference in the means the null hypothesis may be favoured. In contrast if the variation of the values within the treatments is small relative to the difference in the means the null hypothesis may be rejected and the alternative hypothesis favoured.

The target value of the analyses, the *F*-ratio, (which can be calculated manually, see statistical appendix, which also details the assumptions for the analysis, and by computer programmes e.g. Microsoft Excel) is thus, the ratio of the variability between and within the treatment means. Values near 1 indicate that the two sources of variation are equal providing little support for the alternative hypothesis. In contrast values well in excess of 1 indicate that the variation between the means well exceeds that of the variation within the means, supporting the alternative hypothesis.

To ascertain at which value of F the alternative hypothesis may be accepted the *F*-ratio is then compared with a critical *F* value which is obtained from a table of significance. **For the difference in the results to be significant the *F*-ratio must be greater than the critical *F* value.** The critical *F* value depends on (a) the number of treatments, (b) the number of values within each treatment and (c) the degree of confidence required. Tables of significance exist for various confidence levels including 0.001 level = 99.9 %, 0.01 level = 99 % or 0.05 level = 95 %, although statisticians generally use a cut off point of 0.05 for statistical significance.[106]

The *P*-value is the lowest confidence level at which the difference is significant. Traditionally these were obtained from the previously mentioned tables of significance although this is limited in that exact values could not be calculated. Computer programmes have addressed this and *P*-values can be calculated in Microsoft Excel. **Thus in order for the null hypothesis to be rejected the P value must be small** (less that 0.005).

Table 18 and 19 show ANOVA tables for the e.e. and conversion respectively. Upon inspection of the tables, it is immediately obvious that the difference in e.e. between the substrates is far greater than the conversion and this is reflected

in the *F*-ratios and *P*-values. The former is much larger for e.e. than conversion, although the latter still shows a significant difference for the different substrates, thus for both responses the null hypothesis would be rejected. The *P*-value of 0.003 for conversion indicates that the null hypothesis would be rejected at a confidence level of 0.003 or greater (0.3 %) implying that the difference between the two treatments is highly significant.

Anova: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Treatment 1	5.00	115.83	23.17	0.61
Treatment 2	5.00	447.12	89.42	3.54

ANOVA

Source of Variation	*SS*	*df*	*MS*	***F*-ratio**	***P-value***	***F crit***
Model	10975.53	1.00	10975.53	**5293.82**	**1.42E-12**	**5.32**
Error	16.59	8.00	2.07			
Corrected Total	10992.12	9.00				

Table 18 Anova Table for e.e.

Anova: Single Factor

SUMMARY

Groups	*Count*	*Sum*	*Average*	*Variance*
Treatment 1	5.00	473.47	94.69	8.39
Treatment 2	5.00	500.00	100.00	0.00

ANOVA

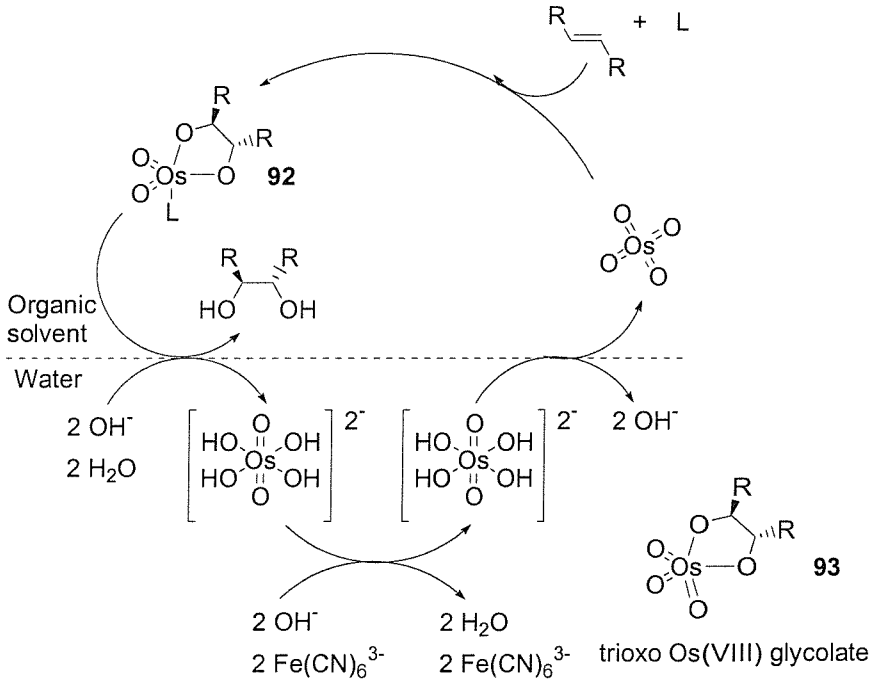
Source of Variation	*SS*	*df*	*MS*	***F*-ratio**	***P-value***	***F crit***
Model	70.36	1.00	70.36	**16.77**	**0.003**	**5.32**
Error	33.56	8.00	4.20			
Corrected Total	103.92	9.00				

Table 19 Anova Table for Conversion

The results for the repeatability experiment showed that the experimental procedure was reproducible; ANOVA data showed that the effect of changing the substrate was much larger than the overall random variation.

3.2.1.3 Factor Variation

With the method in hand, attention was then turned to deciding upon which factors would be investigated. Scheme 30 shows the mechanism of the process from which the factors to be varied in the experiment were selected. Upon examination it was apparent that a catalytic amount of osmium tetroxide (typically 1.5 – 4 %) was used in the presence of two equivalents of the secondary oxidant (K_3FeCN_6) and base (K_2CO_3) to effect the transformation. The reaction was carried out in a 1:1 solvent mixture of ^tBuOH:H_2O and one equivalent of methane sulfonamide was routinely added to the reaction mixture for all classes of alkenes except for those which are mono or 1,1- disubstituted. It has been demonstrated that addition of this additive accelerates the rate of hydrolysis of the osmium glycolate products hence allows higher catalytic turnovers.[43]



Scheme 30 Asymmetric Dihydroxylation Mechanism

Crucial to the success of the reaction is the biphasic solvent system which precludes a competitive secondary cycle which can occur under homogeneous conditions, when **92** undergoes oxidation and ligand loss to give the trioxo Os(VII) glycolate **93**. This species can then react with another molecule of alkene, as the ligand is no longer co-ordinated, in a less selective fashion. In

contrast under these bi-phasic conditions **92** must enter the aqueous phase to be re-oxidised and is therefore the only oxidising species in the organic layer. Alkenes are consequently dihydroxylated with higher enantioselectivity. It was decided to investigate the following seven factors (a) temperature, (b) type of base, (c) equivalents of base, (d) equivalents of secondary oxidant, (e) addition of additive, (f) solvent, and (g) substrate. The percentage of catalyst and OsO_4 were kept constant at 10 and 1.5 % respectively. These are discussed in more detail with the levels decided upon below.

(a) Temperature

The reaction is generally carried out at 0 °C, except in the case of substrates which react sluggishly such as cinnimates, in which case it is carried out at room temperature. This factor was varied at these two levels - room temperature and 0 °C.

(b) Type of base

The base most widely used is K_2CO_3. It has been shown that when this is entirely replaced with $NaHCO_3$ the reaction does not proceed.[43] This observation and the mechanism outlined in Scheme 30, which involves OH^- suggests that the pKa of the conjugate acid used must be relatively high. Base was therefore considered as a qualitative factor and varied on two levels, K_2CO_3 and KOH.

(c) and (d) Equivalents of base and secondary oxidant.

Two equivalents of each are required for one molecule of alkene and three are commonly used. They can be varied independently of each other and in this experiment these were included as quantitative factors.

(e) Addition of additive

As previously mentioned the addition of methane sulfonamide has been reported to enhance the rate of the catalytic cycle. This factor was included as "present" or "absent".

(f) Solvent

The solvent generally used is a 1:1 solvent mixture of water:^{t}BuOH, the importance of this solvent mixture can be seen in Scheme 30. As described earlier, the bi-phasic nature of this system ensures that only one oxidising species is present in the organic layer and thus diols of higher enantioselectivity are formed. Upon consideration of which solvents were to be incorporated into the experimental design it was evident that selection of an appropriate solvent parameter was crucial.

Carlson[5] listed 9 physio-chemical properties (melting point, boiling point, dielectric constant, dipole moment, refractive index, the normalized Reichardt-Dimroth parameter, lipophilicity and water solubility) for 103 different solvents. Musumarra[107] later extended this to 113 solvents by incorporation of a further 10 ethereal solvents and also corrected erroneous values. In this study the nine chemical descriptors described by Musumarra were each considered, and four selected as the most important – the dielectric constant and dipole moment (indicative of the solvent polarity) and lipophilicity and water solubility (as the reaction is carried out in a 1:1 solvent:water mixture). Upon examination of the parameters, a high correlation between the latter two was observed, which is undesirable in statistical model building hence lipophilicity was disregarded, leaving three solvent parameters.

In an initial attempt to condense the data set of 113 solvents, a limit of 170 °C was set for the boiling point as anything higher than this was deemed to reduce the synthetic utility of the method; eliminating 30 solvents. Further solvents were then removed on the basis of incompatible reactivity or the presence of a chromophore which would hamper HPLC analysis (18 removed); missing values (15 removed); toxicity (8 removed) and poor availability. This led to a final shortlist of 29 solvents for consideration which are shown in Table 20.

Solvent[a]		Descriptors[b]			
		3	4	8	9
4	methanol	32.66	5.5	-0.77	1.393
8	2-methoxyethanol	16.93	6.8	-0.77	1.103
10	ethanol	24.55	5.8	-0.31	1.231
14	1-propanol	20.45	5.5	0.25	1.126
15	1-butanol	17.51	5.8	0.88	0.125
16	2-methyl-1-propanol	17.93	6	0.76	0.176
17	2-propanol	19.92	5.5	0.05	1.117
18	2-butanol	16.56	5.5	0.61	0.176
19	3-methyl-1-butanol	15.19	6.1	1.22	-0.518
23	nitromethane	35.94	11.9	-0.35	0.235
24	acetonitrile	35.94	11.8	-0.34	1.282
30	2-methyl-2-propanol	12.47	5.5	0.35	-1.057
31	N-N-dimethylformamide	36.71	10.8	-1.01	1.112
32	N-N-dimethylacetamide	37.78	12.4	-0.77	1.11
35	acetone	20.56	9	-0.24	1.134
43	dichloromethane	8.93	5.2	1.25	-0.699
53	chloroform	4.81	3.8	1.97	-1.246
58	ethyl acetate	6.02	6.1	0.73	-0.041
63	tetrahydrofuran	7.58	5.8	0.46	1.142
67	1,4-dioxane	2.21	1.5	-0.27	1.07
71	diethyl ether	4.2	3.8	0.89	0.076
73	di-isopropyl ether	3.88	4.2	1.52	-0.198
75	dibutyl ether	3.08	3.9	3.21	-1.941
81	cyclohexane	2.02	0	3.44	-3.069
82	hexane	1.88	0	3.98	-3.359
84	1-pentanol	13.9	5.7	1.56	-0.631
89	3-methyl-2-butanone	15.87	9.2	0.56	-0.164
102	n-heptane	1.92	0	4.57	-4.046
103	n-pentane	1.84	0	3.39	-3.129

[a]Solvent number corresponds to that of Musumarra
[b]Descriptors: 3 = dielectric constant, 4 = dipole moment, 8 = lipophilicity (logP), 9 = water solubility

Table 20 29 Solvents with Descriptors Used in the DoE Investigation

(g) Substrate

This was varied to examine the scope and utility of the optimisation process. In general asymmetric dihydroxylation is a very robust process and can be applied to all classes of alkenes. For HPLC analysis a UV chromophore was required and therefore a substructure search of molecules containing the styrene moiety was carried out. This search resulted in over 400 hits which were either selected or rejected on the basis of poor availability; the presence of more than one double bond; incompatible reactivity (for example a vinyl halide which could undergo epoxide formation); or if they were incompatible with HPLC conditions. Prior to this investigation it was known that the racemic diols of styrene were inseparable by chiral HPLC and therefore styrenes with ring substituents were also rejected.

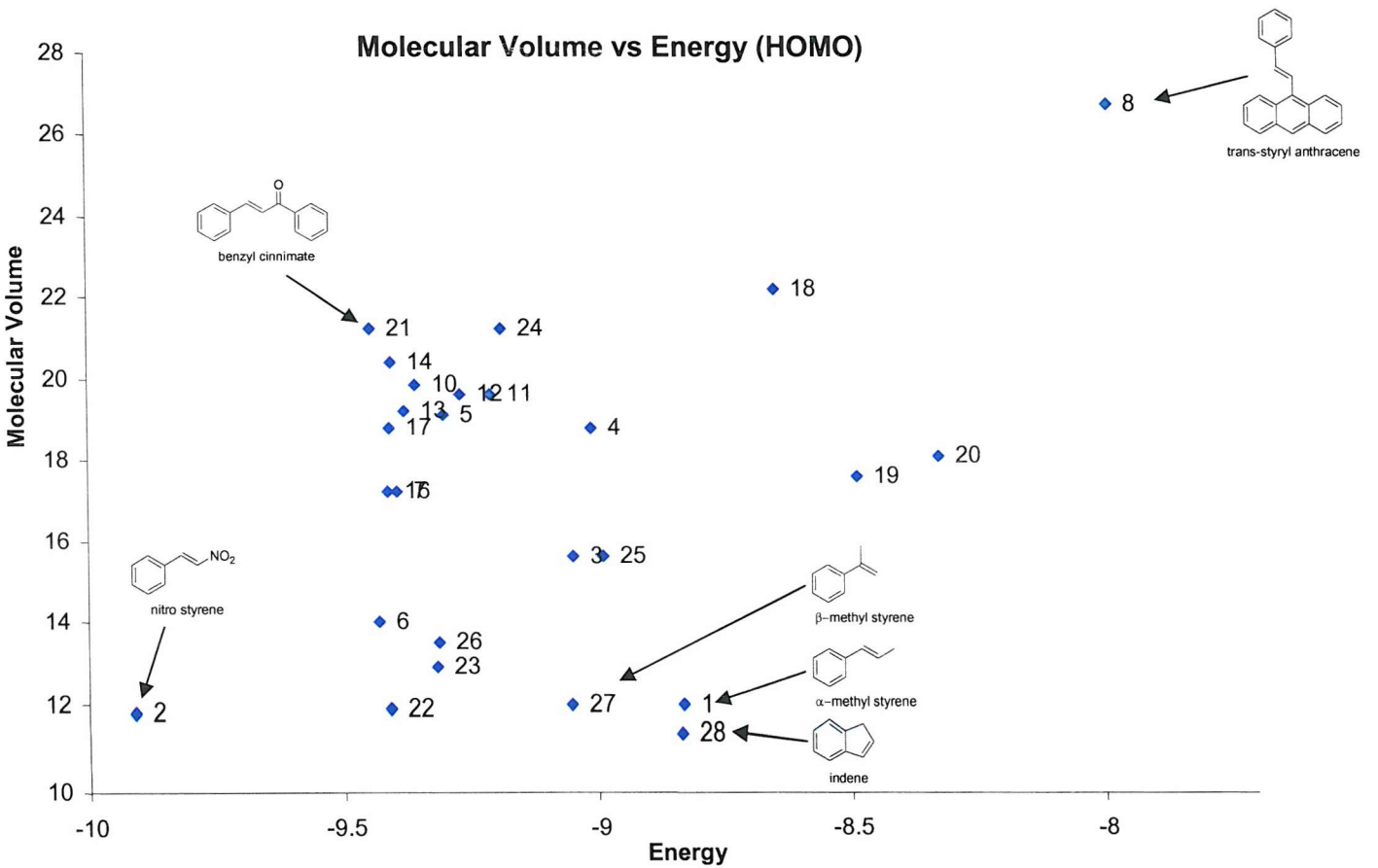
Consideration of other heterocycles was not feasible as it had previously been noted that the racemic diols of vinyl pyridine and indeed vinyl pyridine itself eluted from the C-18 reverse phase column too rapidly and thus separation of the starting material and product for conversion analysis and the racemate for e.e. analysis was deemed impossible.

3.2.1.4 Substrate Scoping

In the selection of alkenes for incorporation into the DoE investigation it was first necessary to ascertain that that they were viable substrates and that their racemic diol products were separable by chiral HPLC. If these were both successful the reaction would then have to be repeated on a large scale for characterisation and calibration studies. It was thus decided to undertake a substrate scoping experiment in a manner similar to that for the reproducibility experiment. The substrate search resulted in 28 feasible molecules with all but two being of the *trans* geometry. Two parameters were then calculated for each – the molecular volume (calculated in Dragon) and the HOMO energy (calculated in Chem3D). The former was considered important as it was previously shown, in Chapter 2, that the formation of a binding cavity for the alkene was necessary for asymmetric induction and it was postulated that the setup of this cavity would differ for different sized alkenes which could affect

the enantioselelectivity of the diols formed. As dihydroxylation is an oxidation process it was thought that the energy value of the HOMO may affect the reaction and this parameter was also considered. A plot of both is shown in Figure 30. Thus for the initial substrate screening experiment four substrates, from the extreme corners of the graph were selected; benzyl cinnimate, nitro styrene, trans styryl anthracene and indene. In this experiment it was also decided to determine the viability of using KOH as a base. Thus for each substrate five reactions were performed: one without catalyst to determine whether the racemate was separable by chiral HPLC, two with K_2CO_3 as the base and two with KOH. To check the experimental procedure α-methyl styrene and β-methyl styrene were both also included, thus giving a total of 30 experiments.

Unfortunately none of the three new substrates were viable. Reaction with nitro-styrene was unsuccessful, probably because of its electron deficiency; it has previously been observed that some electron poor alkenes such as cinnimates react sluggishly. For benzyl cinnimate and *trans*-styryl anthracene, reactions did occur but their large molecular volume meant that they were insoluble in the water/MeCN washing solution and precipitated upon catalyst scavenging with the Amberlyst ion-exchange resin. Different washing solutions were attempted but this always resulted in poor chromatography and the two substrates were therefore disregarded. Reactions with indene, α and β-methyl styrene were however successful with both bases and their results are shown in Figure 31 and the ANOVA plot for e.e. in Table 21. Again it was evident that the substrate had the largest effect on e.e., although the type of base was on the borderline of statistical significance.



1	*β-methyl styrene*
2	*nitrostyrene*
3	*methyl-trans-styryl acetate*
4	*iso-propyl trans-styryl acetate*
5	*chalcone*
6	*methyl cinnimate*
7	*isopropyl cinnimate*
8	*trans styryl anthracene*
10	*4-chlorochalcone*
11	*2-hydroxychalcone*
12	*4-hydroxychalcone*
13	*4-fluorochalcone*
14	*isoamyl cinnimate*
15	*isobutyl cinnimate*
16	*propyl cinnimate*
17	*butyl cinnimate*
18	*cinammyl anthranilate*
19	*trans stilbene*
20	*hydroxystilbene*
21	*benzyl cinnimate*
22	*cinnamaldehyde*
23	*cinnamamide*
24	*4-methoxy chalcone*
25	*cinnamyl acetate*
26	*benzylidene acetone*
27	*α-methyl styrene*
28	*indene*

Figure 30 Substrates Considered for the Asymmetric Dihydroxylation Invesigation

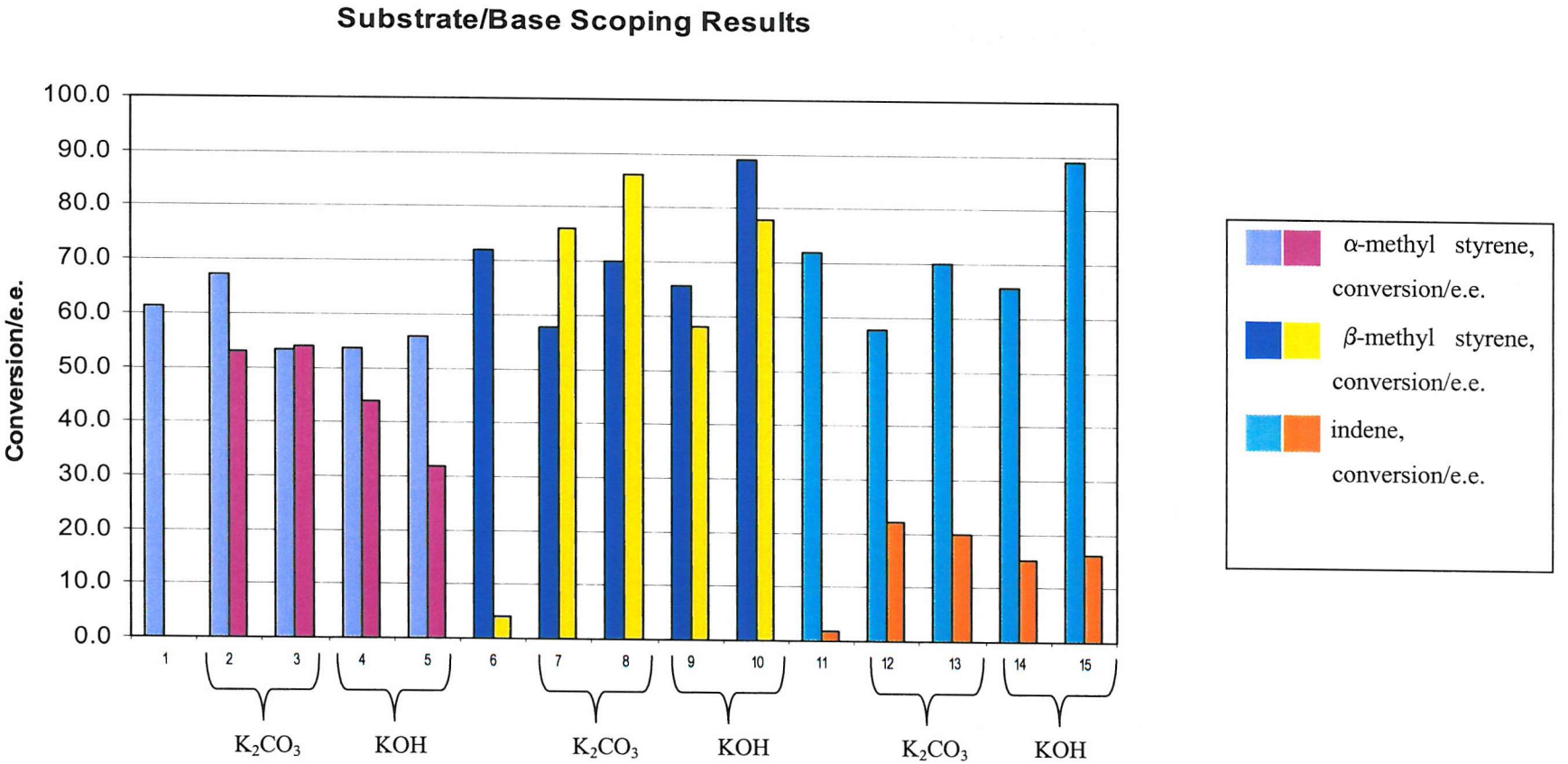


Figure 31 Results for the Substrate/Base Screening Experiment, entries 1, 6 and 11 are for those without the chiral catalyst.

ANOVA

Source of Variation	*SS*	*df*	*MS*	***F*-ratio**	***P*-value**
Substrate	6555.2	2	3277.6	**56.67**	**0.000**
Base	341.3	1	341.3	**6.01**	**0.050**
Interaction	80.2	2	40.1	**0.71**	**0.531**
Error	341.0	6	56.8		
Total	7317.7	1			

Table 21 ANOVA table for the Substrate Scoping Experiment

Although it was disappointing that three of the substrates did not produce a response it was not considered a major hindrance as it is obvious that the three successful substrates have similar HOMO and molecular volume values but gave very different e.e.'s, suggesting that in fact the most important parameter was probably double bond orientation. Thus for the remainder of the investigation the substrate was considered as a qualitative factor varying at three levels.

3.2.2 Screening

3.2.2.1 Solvent Consideration

It was previously mentioned that three descriptors were selected for the quantification of the solvents – dielectric constant, dipole moment and water solubility. These were considered important and showed the least correlation (statistically, highly correlated factors are undesirable). The list of 29 solvents shown in Table 20 was "trimmed" by the statisticians which involved removing solvents which had the upper and lower 5 % of values for each of the three descriptors, this allowed solvents which were more representative of the population to be investigated although it also had the effect of reducing the correlations between the solvent descriptors. This resulted in 14 solvents for consideration in the screening experiment, scatter plots are shown in Appendix 1.

3.2.2.2 Factor Variation

With all factors decided upon attention was then turned to a screening experiment. The factors and their levels which were described in more detail in

Section 3.2.1.3 are summarized in Table 22. The experimental plan which was generated by the statisticians is shown in Table 23. Each of the 10 experiments was repeated for both levels of temperature (termed a whole plot factor) and the three substrates giving a total of 60 experiments.

The reactions were carried out in random order, a full table of results is shown in the experimental section, although this time the reactions were carried out on a smaller scale (0.06 mmol of alkene, with 1.2 ml of solvent, as in the previous experiments a large amount of waste had been generated, it was also desirable to reduce the amount of osmium tetroxide used. Unfortunately slightly lower conversions and e.e.'s resulted, perhaps because of different agitation efficiency. It was however assumed that the conclusions drawn would still be valid.

Factor	Description
Solvent	quantitative, described by three solvent parameters – dielectric constant, dipole moment and water solubility.
Temperature	0 °C and room temperature
Substrate	three levels, indene, α- and β-methyl styrene
Type of Base	qualitative – K_2CO_3 and KOH
Additive ($MeSO_2NH_2$)	0 (absent) or 1 (present)
Base Eq	quantitative, 2.2 and 4
2° Oxidant Eq	quantitative, 2.2 and 4

Table 22 Factors Varied in the Screening Experiment

Solvent		base[a]	Base Eq[b]	2° Oxidant Eq[b]	additive[c]
17	2-propanol	-1	1	-1	1
17	2-propanol	1	-1	1	-1
30	2-methyl-2-propanol	-1	1	1	-1
30	2-methyl-2-propanol	1	-1	-1	1
43	dichloromethane	-1	0	0	1
58	ethyl acetate	1	0	0	-1
71	diethyl ether	1	1	-1	-1
71	diethyl ether	-1	-1	1	1
89	3-methyl-2-butanone	1	1	1	1
89	3-methyl-2-butanone	-1	-1	-1	-1

[a] -1 = K_2CO_3, 1 = KOH
[b] -1 = 2.2 equivalents, 0 = 3 equivalents, 1 = 4 equivalents
[c] -1 = not present, 1 = present

Table 23 Experimental Plan for Each Substrate and Temperature Level

3.2.2.3 Analysis

The statisticians then analysed the data and fitted a main effects model. Residual plots, which are used to detect outliers and assess the normality of the results were inspected and found to be reasonable. For both responses the data was transformed using a logit function, which is often applied when the value of the response has limits i.e. in this case 0 to 100. All future analyses were then conducted on the transformed data

A summary plot for the effect of temperature, with all other affects averaged, on each substrate is shown in Figure 32, which shows that results were consistent with the scoping experiment, in that β-methyl styrene gave the highest e.e. and indene the lowest. The plots also show that on average the e.e. is slightly higher and less variable at 0 °C.

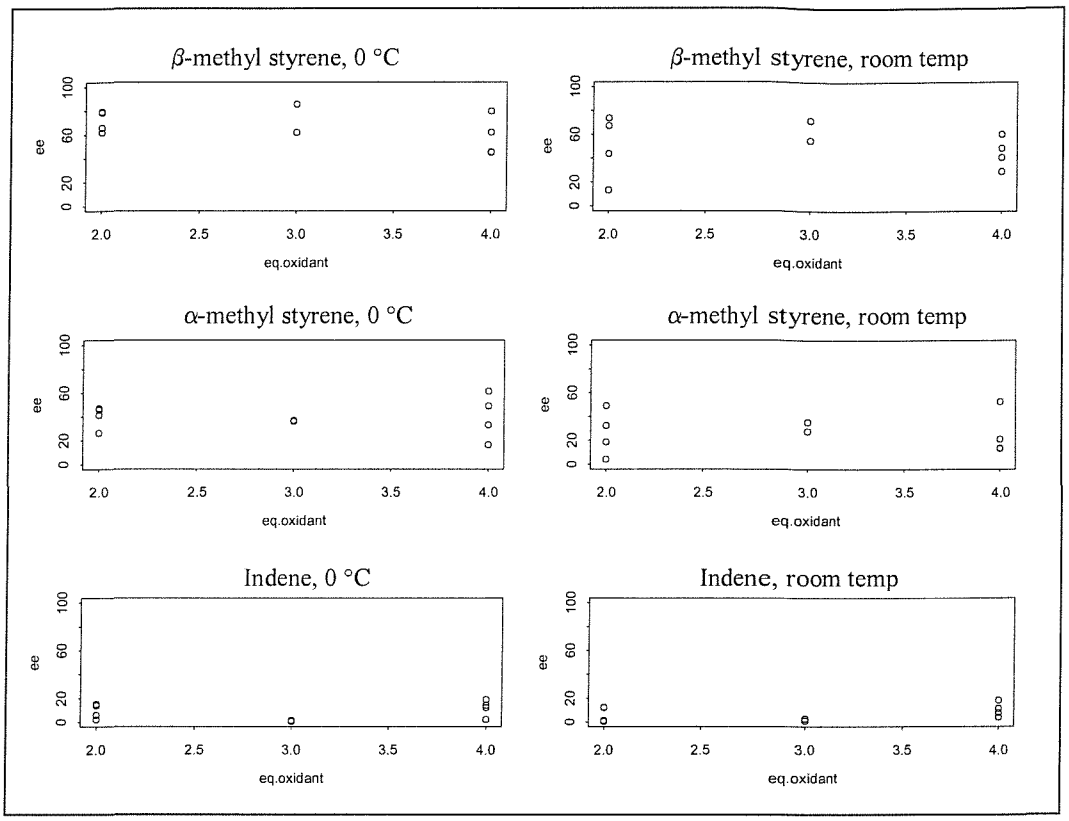


Figure 32 Summary Plot for temperature and substrate on e.e.

The data collected at the two different temperatures were analysed separately under the different conditions, *F*-ratios and *P*-values were used to ascertain the effect of the various factors. For both conversion and e.e. *F*-values were large enough to confirm that the temperature had a significant effect. However, whereas the model provided an excellent fit with an R^2 of 0.93 and 0.72 for e.e. and conversion respectively at 0 °C, the room temperature data showed a large degree of variation, with R^2 values of 0.58 and 0.46 for e.e. and conversion respectively. This may be have been due to (a) if the temperature had not remained constant over the 16 hours, or (b) if the formation of the binding cavity (described in Chapter 2) which is possibly more favourable at a lower temperature, was affected more by the changing conditions (solvent, type of base etc) at the higher level of temperature.

Thus, the main conclusion drawn at this stage was that the temperature had to be carefully controlled to produce meaningful results. The remainder of the

analysis was conducted on the data collected at 0 °C. ANOVA tables are shown in Table 24 and 25 and statistically significant values are shown in bold typeface. The tables show that for e.e. the three solvent descriptors and type of base were the most important terms, for conversion only water solubility was statistically significant. Interestingly the equivalents of base and secondary oxidant and the presence of the additive had no significant effect on either response. Salt precipitation, upon cooling an asymmetric dihydroxylation reaction to 0 °C has been observed[43] and it was therefore postulated that the three equivalents of base and secondary oxidant commonly used (reaction requires 2) were unnecessary.

Source	DF	SS	MS	F-value	P-value
Model	9	47.37	5.26	21.71	<0.0001
Eq. base	1	0.054	0.054	0.22	0.6439
Eq. oxidant	1	0.11	0.11	0.46	0.5105
Dielectric constant	1	2.65	2.65	**10.95**	**0.0052**
Dipole moment	1	5.89	5.89	**24.30**	**0.0002**
Water solubility	1	2.74	2.74	**11.31**	**0.0046**
Substrate	2	38.35	19.17	79.10	<0.0001
Base	1	2.48	2.48	**10.22**	**0.0065**
Additive	1	0.014	0.014	0.058	0.8133
Residual	14	1.95	0.33		
Corrected total	23	50.76			

Table 24 ANOVA Table for e.e. at 0 °C

Source	DF	SS	MS	*F*-value	*P*-value
Model	9	234.65	26.07	3.91	0.0113
Eq base	1	27.73	27.73	4.16	0.0607
Eq oxidant	1	19.21	19.21	2.88	0.1117
Dielectric constant	1	30.66	30.66	4.60	0.0500
Dipole moment	1	3.91	3.91	0.59	0.4565
Water solubility	1	105.34	105.34	**15.80**	**0.0014**
Substrate	2	18.95	9.48	1.42	0.2741
Base	1	29.37	29.37	4.41	0.0544
Additive	1	23.11	23.11	3.47	0.0837
Residual	14	93.32	6.67		
Corrected total	23	327.97			

Table 25 ANOVA Table for conversion at 0 °C

Figure 33 and 34 show the fitted surface plots for e.e. and conversion, the other factors were set to maximise the predicted e.e. (high dielectric constant, β-methyl styrene and K_2CO_3 as base). Surface plots are used to investigate which areas of the factor space should be investigated next to optimise the responses. Both of the responses show that the optimum settings are for both low dipole moment and low water solubility.

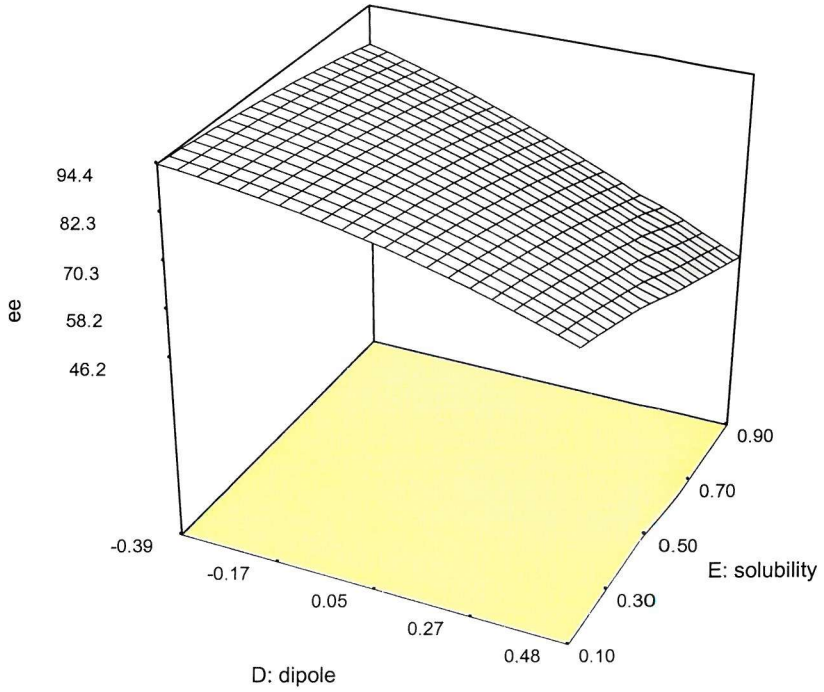


Figure 33 Predicted Surface Plot for e.e.

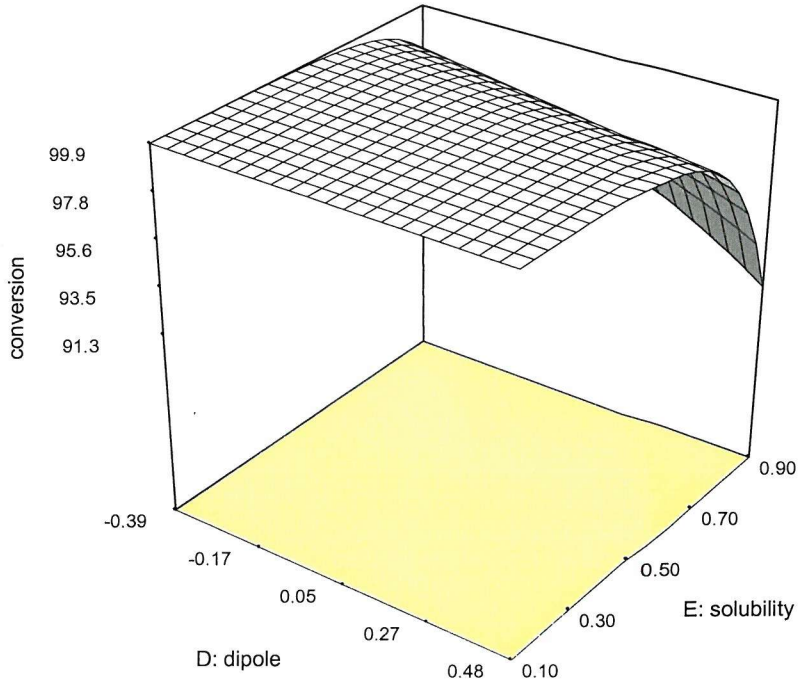


Figure 34 Predicted Surface Plot for Conversion

3.2.3 Response Surface Modelling Experiment

3.2.3.1 Solvent Consideration

Two plans for the investigation of the solvents were formulated by the statisticians. The first termed "the trimmed" design used the same solvents as for the screening experiment (3.2.2.1). The second was termed "the reduced" design and consisted of 14 solvents which satisfied two out of the three conditions decided upon from the screening experiment (low dipole moment, high dielectric constant and low water solubility).

3.2.3.2 Factor Variation

The screening experiment showed that maintenance of a low (0 °C) temperature was crucial for repeatable results. The equivalents of base and secondary oxidant and the presence of the additive, $MeSO_2NH_2$ had no statistical, significant effect on conversion or e.e. and K_2CO_3 had the best effect on both responses of the two bases. These factors were all set constant and two different designs considered to investigate the solvent descriptors in more detail. The levels of the factors for the response surface modelling are shown in Table 26.

Factor	Description
Solvent	quantitative, described by three solvent parameters – dielectric constant, dipole moment and water solubility.
Temperature	set at 0 °C
Substrate	set at β-methyl styrene
Type of Base	set at K_2CO_3
Additive ($MeSO_2NH_2$)	set at absent
Base Eq	set at 2.2
2° Oxidant Eq	set at 2.2

Table 26 Factors Varied in the Response Surface Experiment

26 experiments for each plan were necessary to fulfil the design criteria and although both were carried out (see experimental section for full table of results) the remainder of the analysis focuses on results from the first plan.

3.2.3.3 Analysis

The experimental results were analysed by the statisticians, as previously described for the screening experiment a logit transformation was applied and residual plots showed no evidence of model inadequacy.

Figure 35 shows the e.e. values for the 26 runs in plan 1 for the different solvents. The e.e. measurements were consistent and showed good reproducibility. R^2 and adjusted R^2 values of values showed that the model fitted best for the e.e. response (0.95 and 0.97 respectively).

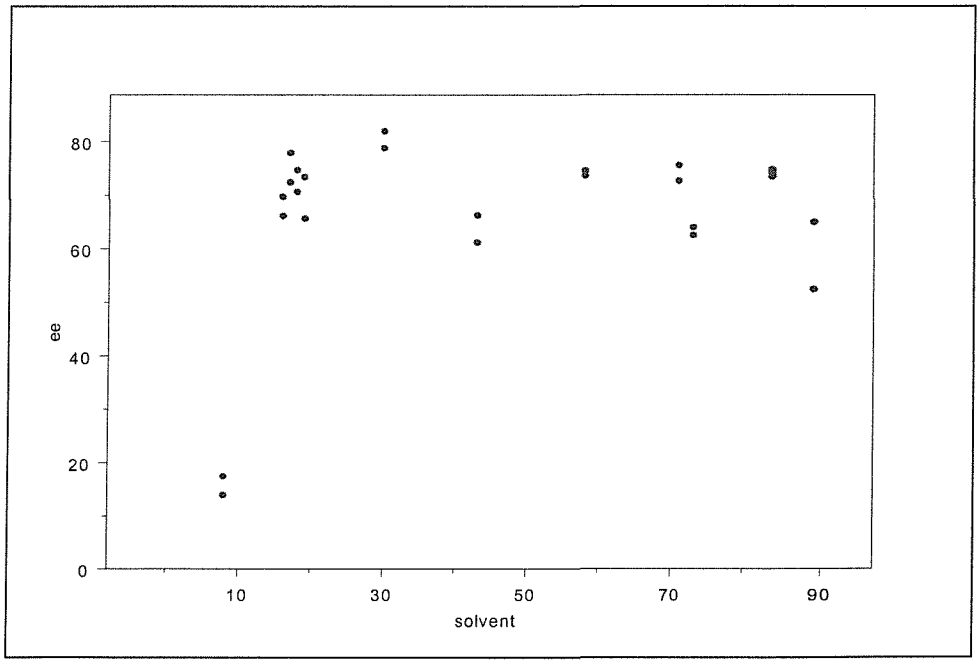


Figure 35 e.e. *vs* Solvent for the Response Surface Design

Table 27 shows the ANOVA table for the results after the logit transformation had been performed. It is clear that quadratic terms are needed and that interactions between the solvent parameters were significant. Quadratic terms

(denoted by square function in Table 27, e.g. A^2) imply that the optimum is not at an extreme of the factor setting, but somewhere between the extremes. The most significant effect was for the interaction between the dielectric constant and dipole moment, their relationship is shown in Figure 36.

Source	SS	df	MS	*F*-ratio	*P*-value
model	14.21	9	1.58	56.01	<0.0001
A	0.60	1	0.60	**21.15**	**0.0003**
B	0.071	1	0.071	2.51	0.1324
C	0.35	1	0.35	**12.53**	**0.0027**
A^2	0.47	1	0.47	**16.75**	**0.0008**
B^2	0.43	1	0.43	**15.41**	**0.0012**
C^2	0.17	1	0.17	6.07	0.0254
AB	0.77	1	0.77	**27.23**	**<0.0001**
AC	0.34	1	0.34	**11.96**	**0.0032**
BC	0.028	1	0.028	1.01	0.3301
Total	14.66	25			

A = Dielectric constant, B = Dipole Moment, C = Water Solubility

Table 27 ANOVA table for the Response Surface Design

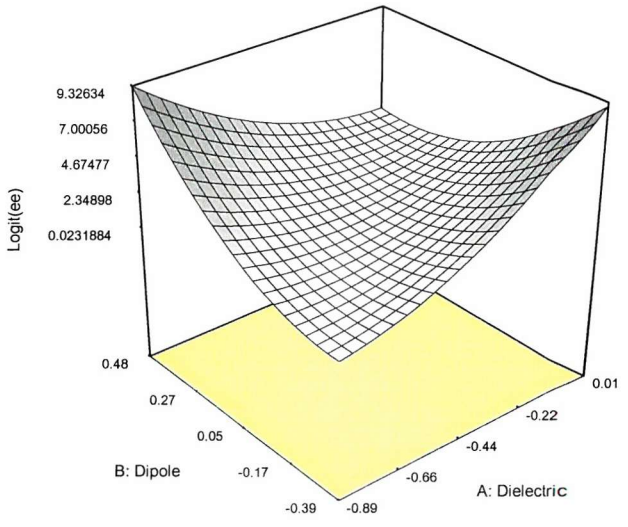


Figure 36 Response Surface Plot for e.e

The response surface plot clearly shows the relationship between the dipole moment and the dielectric constant, with solubility set to its lowest level it is also clear that the highest predicted e.e. occurs with either a low dielectric constant and high dipole moment or *vice versa* (the latter is in agreement with the screening experiment). This can be seen on comparison of the e.e. in MeOH and ^{t}BuOH of 4 and 70 % respectively, the former has a water solubility of 1.393 and the latter -1.057, confirming that indeed the biphasic nature of the solvent was indeed crucial. ^{t}BuOH has a higher dielectric constant than solvents such as DCM, dibutyl ether and hexane which also have low water solubilities, the e.e.'s achieved in these solvents was 59, 54 and 19 % showing that a higher dielectric constant was also necessary for high e.e's. The necessity for a high dielectric constant may be a consequence of the higher solubility of most organic compounds in such solvents.

Of the 13 solvents which lay in the design region explored by the plan, solvent 30 was predicted to; and; had given; the highest e.e. This turned out to be 2-methyl-2-propanol (^{t}BuOH), the solvent which has been used for over the past 2 decades and is the one currently used. Other solvents with high predicted e.e. were 17, 18 and 58 (2-propanol, 2-butanol and ethyl acetate), all solvents with low water solubilities.

3.3 Conclusion

Following an extensive DoE investigation into the Sharpless asymmetric dihydroxylation of alkenes, varying the solvent, base, addition of additive and equivalents of base and secondary oxidant it was found that the conditions reported and currently used are pretty optimal, although the reaction does not require the excesses of base and secondary oxidants. It should be clarified that the statisticians; Sue Lewis and Dave Woods were unaware of these conditions and thus to identify them from the large list of possibilities and for them to be the actual optima shows the power of the approach.

Consideration of the variables in this rational, statistical fashion leads not only to the optima but also a higher understanding and predictions for the future. In this case it was shown that a solvent with low water solubility, high dielectric constant and a low dipole moment would be most suitable although it was postulated that this would be difficult to achieve.

4 Synthesis of Polymer Supported Palladacycles

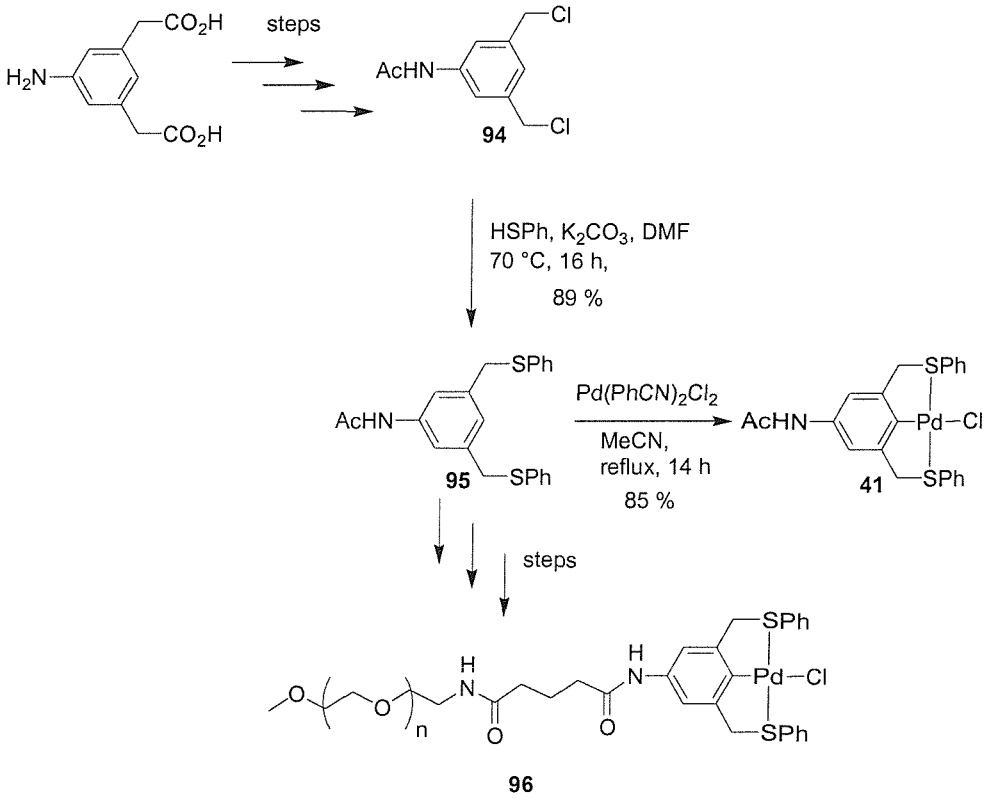
4.1 Introduction

As described in Chapter one, various groups have utilized experimental design for the identification of the most favourable reaction conditions to effect a chemical transformation. The aim here was to test the effectiveness of this approach for the optimisation of a polymer supported palladium complex; a system which has been shown to work reasonably effectively, but which offered scope for optimisation was sought. Such a system was known to be affected by several factors, which could be straightforwardly set at the required levels for experimental optimisation and would require facile attachment of the catalytic moiety onto the solid support.

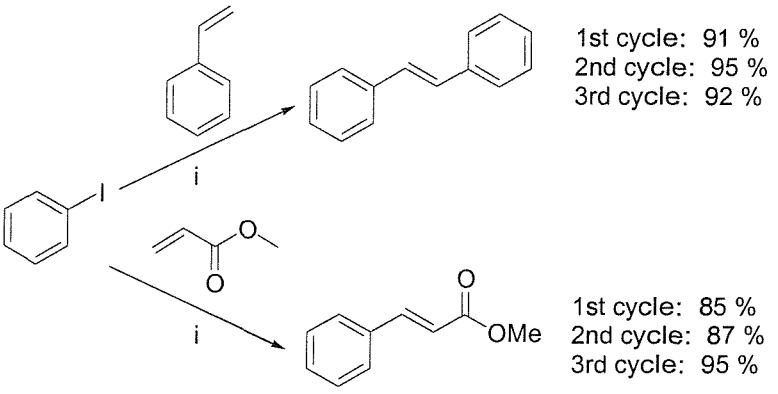
4.2 Sulfur Containing Palladacycles

In 1999 Bergbreiter[78] reported the synthesis of the soluble polymer-supported, tridentate, sulphur-containing palladacyle **96** from commercially available 5-aminoisophthalic acid *via* dichloride **94** and thioether **95** (Scheme 31).

96 was an efficient catalyst for the Heck reaction with 2 different alkene acceptors with iodobenzene and upon completion of the reaction the soluble polymer could be recovered by ether precipitation, and recycled (Scheme 32). The authors noted that the non-supported counterpart **41** was an ineffective catalyst for aryl bromides but did not report the use of **96** with this more challenging class of substrates.



Scheme 31 Bergbreiter's Synthesis of Supported Palladacycle **96**

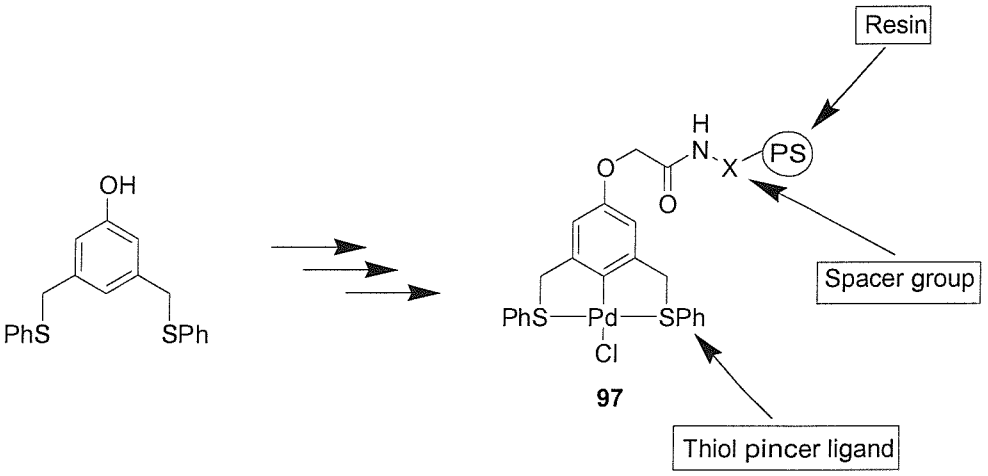


i) 1 mol % **96**, DMF, NEt_3, 115 °C

Scheme 32 Use of **96** to Promote the Heck Reaction

4.3 Scope of Study

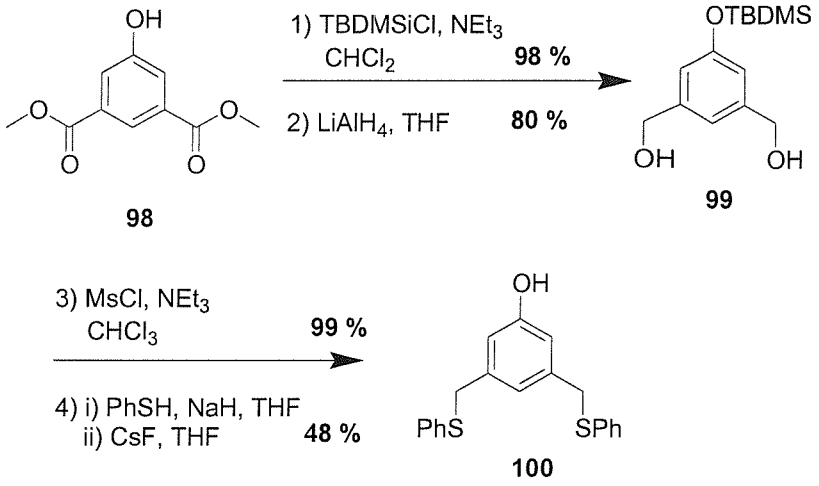
As previously mentioned, one of the most widely used and straightforward techniques for introducing small molecules onto solid supports is *via* coupling of a free acid with an aminomethylated support. Substitution of the aniline functionality in **41** for a phenol and the use of ethyl bromoacetate as a resin attachment moiety represented an ideal system for which to undertake an optimisation study as the resultant target, **97** had several sites for modification (Scheme 33).



Scheme 33 Modification of Bergbreiters Ligand with Potential sites of Variation

As well as these "support" characteristics, other variables which could be studied include: solvent, the presence of a phase transfer catalyst and the equivalence and type of base.

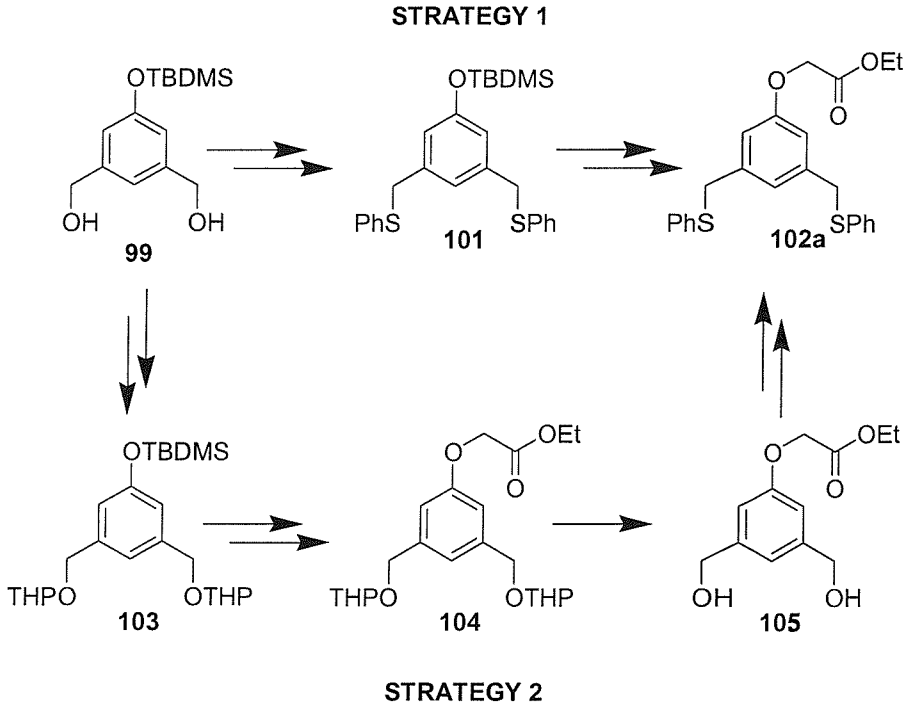
This strategy was found to be even more desirable on consultation of the literature as van Veggel[108] has reported the synthesis of thioether **100**, for the construction of metallodendrimers in four, simple, high yielding steps from diester **98** (Scheme 34).



Scheme 34 van Veggel's Synthesis of Phenol **100**

4.4 Synthetic Strategies

Thus ester **102a** (Scheme 35) was decided on as the catalyst precursor. Fu[86] and Buchwald[109] have both described the use of electron rich, bulky phosphine ligands which enhance palladium catalyzed reactions; it was therefore decided to investigate the effect of different thiol pincer groups. Two synthetic strategies for the synthesis of the catalyst precursor **102a**, both originating from common intermediate **99** were used (Scheme 35). The first strategy was based on that of van Veggel and involved direct activation and displacement of the two free hydroxy groups of **99** with the desired thiol, followed by silyl ether deprotection and alkylation of the resultant phenol with ethyl bromoacetate. Concerns were raised over this approach in that the thiol moieties might interfere with the alkylation step and that if strucutural analogues of **102a** with various thiol subsitituents were to be investigated, it would be desirable if the thiol-introducing step was near the end of the synthetic sequence.

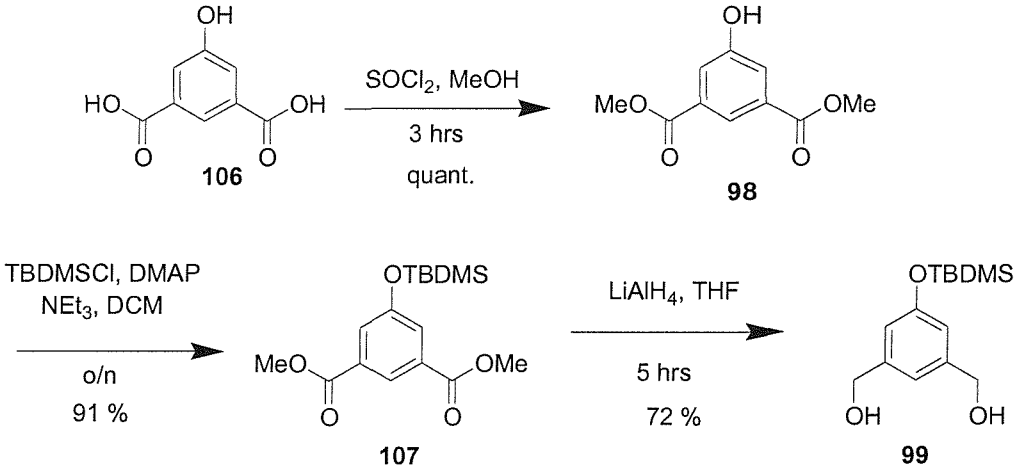


Scheme 35 Strategies formulated for the Synthesis of Catalyst Precursor **102a**

Strategy 2 involved initial protection of the free hydroxy groups, followed by silyl ether deprotection and alkylation of the resultant phenol with ethyl bromoacetate. Removal of the hydroxyl protecting groups and their subsequent activation would enable thiol displacement as the final step. For this route the choice of protecting group was crucial, it had to be stable under TBDMS cleavage conditions and could not be an ester as this functional group was to be introduced later in the sequence, accordingly it had to be resistant to basic hydrolysis, thus the THP group was selected. As well as fulfilling the afore mentioned criteria this protecting group is cheap, readily available, stable under subsequent chemical transformations and could be introduced and removed under mild conditions which were expected to be compatible with other functionality in the molecule. One minor drawback with the THP moiety was that its introduction created new stereogenic centres which were found to complicate NMR interpretation.

4.5 Synthesis

Protected diol **99** was prepared as shown in Scheme 36. Thus 5-hydroxy isophthalic acid (**106**) was converted to the corresponding diester in quantitative yield by stirring with thionyl chloride in MeOH at room temperature for 3 hours, Although **98** is commercially available, its synthesis from the diacid, which is considerably cheaper, was extremely facile and was therefore undertaken as the most favourable option for a large scale synthesis. TBDMS protection of **98** was accomplished by reaction with TBDMSCl and NEt_3 with catalytic DMAP to afford **107** in 91 % yield, which was reduced to the desired diol by $LiAlH_4$ in 72 % yield. For the latter two steps, yields were comparable with those reported by van Veggel.[108]

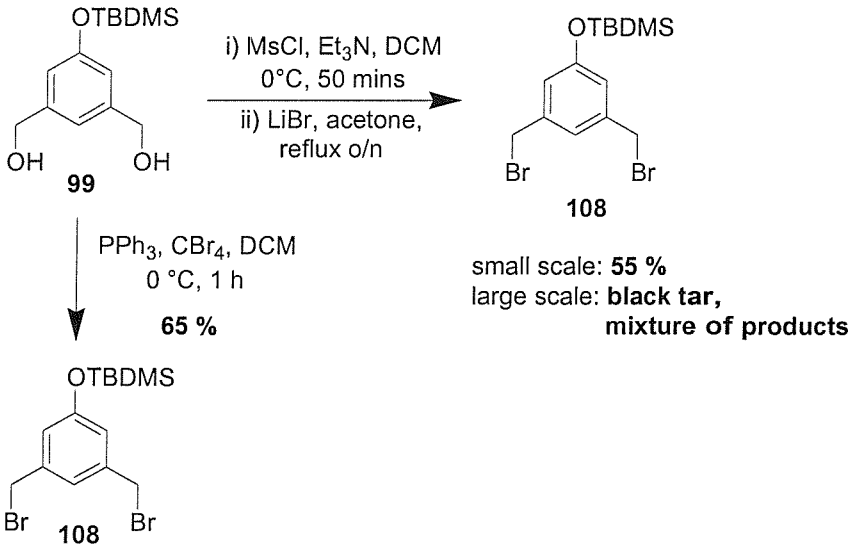


Scheme 36 Synthesis of Common Intermediate **99**

With diol **99** in hand, activation of the hydroxy moieties for displacement by thiophenol was embarked upon. Van Veggel achieved this by chlorination with MsCl at 50 °C overnight but when attempted this reaction was unsuccessful, with no isolation of the desired dichloride.

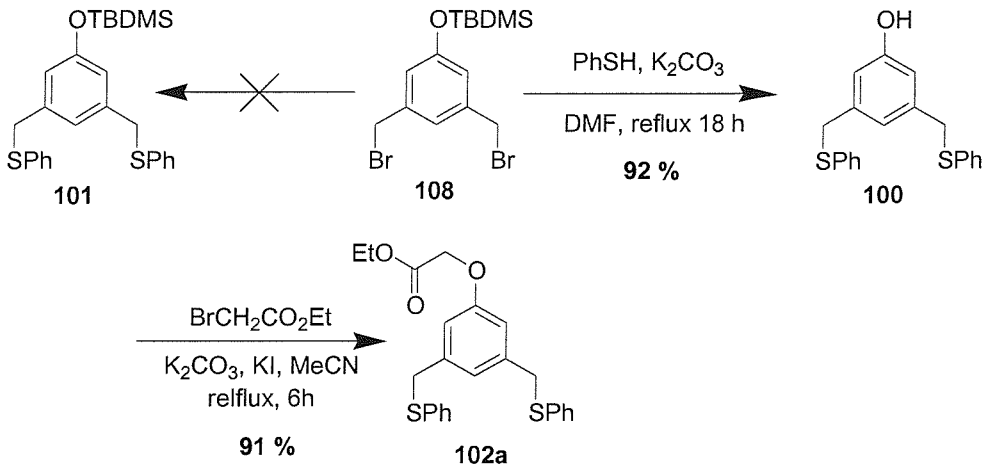
Dibromide **108** was instead prepared as shown in Scheme 37. Thus treatment of **99** with MsCl in dry DCM at 0 °C for 50 minutes followed by displacement with lithium bromide, gave the desired compound, albeit in low yield (55 %).

Disappointingly when the reaction was repeated on a larger scale the reaction was not successful, resulting in a black tar and mixture of products. However use of the milder procedure of PPh_3 and CBr_4 in DCM gave the desired compound in 65 % yield on a large scale (Scheme 37).



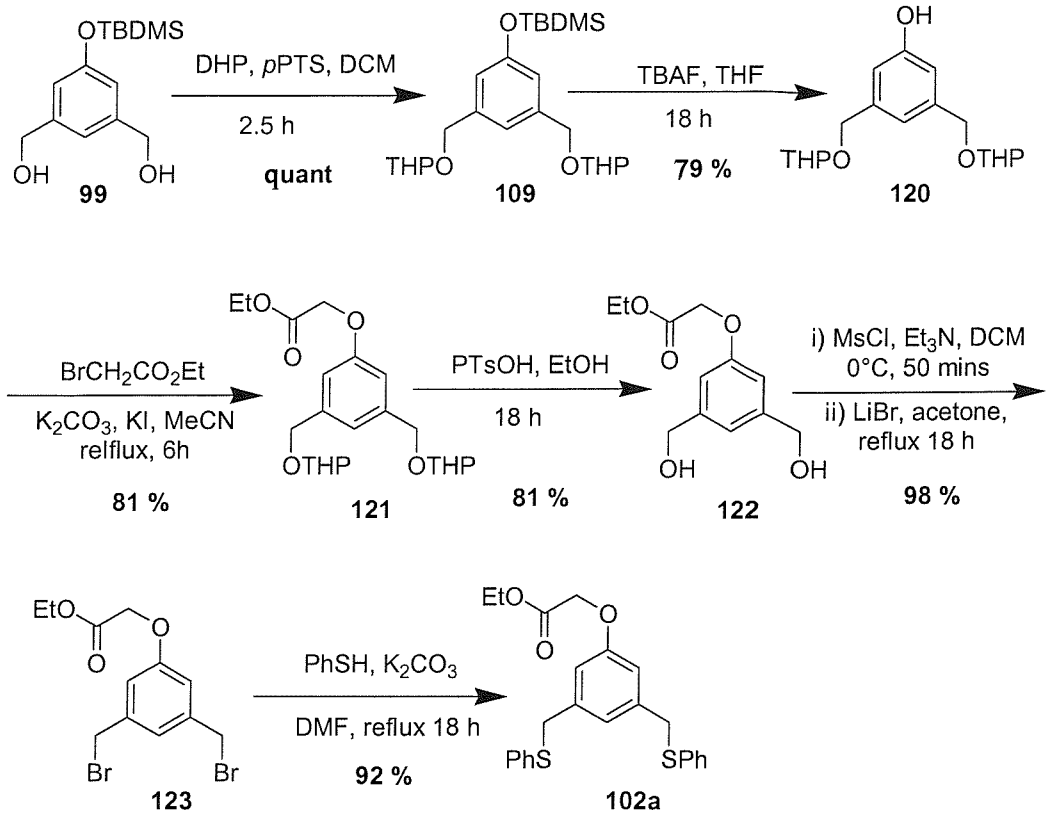
Scheme 37 Synthesis of Dibromide **108**

Van Veggel added the dichloride to the anion of benzene thiol (generated with NaH), subsequent removal of the TBDMS protecting group with CsF afforded the desired phenol in 48 % yield over two steps. The use of NaH was deemed unnecessary as the pKa of an aromatic thiol is only 8, therefore the method of Bergbreiter[78] was adopted where a dihalide, in this case dibromide, **108**, benzene thiol and K_2CO_3 were heated at 100 °C in DMF (Scheme 38). Fortuitously upon chromatography it was realised that the product was not the TBDMS ether **101** but the phenol **100** where TBDMS deprotection had occurred. Although unexpected, this was a useful result as it eliminated the requirement for fluoridolysis. Furthermore, alkylation of phenol **100** with ethyl bromoacetate proceeded in excellent yield after 7 hours with catalytic potassium iodide to give the target compound **102a** in excellent yield (91 %) with an overall yield of 54 % from diol **99**.



Scheme 38 Thiol Displacement of Bromide **108** and reaction with Ethyl Bromoacetate

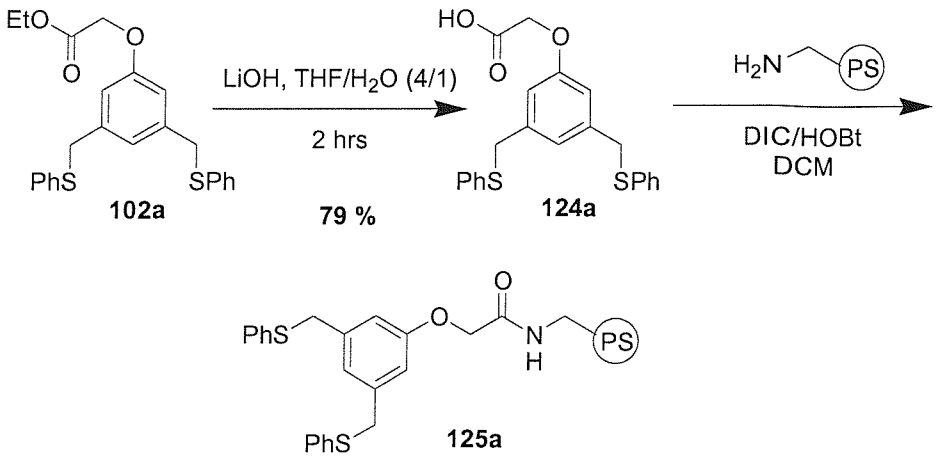
The second strategy began by protection of the two free hydroxy groups of **99** as THP ethers using DHP and catalytic *p*-pyridinium toluenesulfonate (*p*PTS) followed by fluoridolysis of the TBDMS ether. Phenol **120** was then alkylated with ethyl bromacetate, using the previously described procedure in high yield to afford ester **121**. Upon removal of the THP moieties with *p*TsOH the free hydroxy groups of **122** were efficiently transformed into the corresponding bromides using the previously unsuccessful method of mesylation followed by bromide displacement with LiBr. Finally displacement with benzene thiol gave ester **102a** in 92 % yield, 47 % from diol **99** (Scheme 39).



Scheme 39 Synthesis of **102a** by the Second Strategy

4.6 Attachment to the Solid Phase and Palladium Complexation

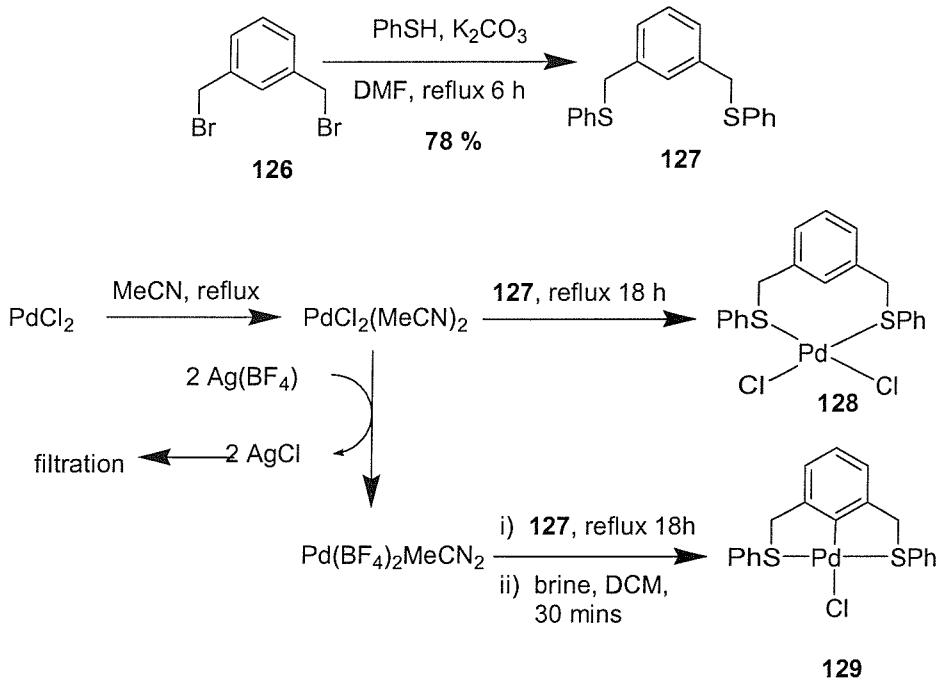
With ester **102a** in hand, work was focussed on its attachment to aminomethyl PS resin. This involved hydrolysis of the ester (LiOH in a 4:1 mixture of THF and water) in 79 % yield. Acid **124a** was then coupled to aminomethyl polystyrene resin with DIC/HOBt in DCM; after overnight agitation the resin gave a negative, qualitative ninhydrin test (Scheme 40).



Scheme 40 Hydrolysis of Ester and Attachment of **124a** to Aminomethyl Polystyrene

Resin **125a** was set up for palladium complexation. As this type of chemistry was previously unexplored, solution analogue **127** (Scheme 41) was prepared by benzene thiol displacement of commercially available α,α'-dibromo-*m*-xylene (**126**, Scheme 41). Two different methods of palladium introduction were explored. In the first, three equivalents of palladium chloride were refluxed in acetonitrile until complete dissolution had occurred (to form $PdCl_2(MeCN)_2$ *in situ*), to this solution one equivalent of **127** was added, immediately an orange solid precipitated. The reaction mixture was further refluxed overnight after which time **128** was isolated by filtration.

Van Veggel and Bergbreiter both reported the use of $Pd(MeCN)_2(BF_4)_2$ to form tridentate compounds such as **129**, the fluoroborate ligands activating the palladium to electrophilic attack. Its *in situ* preparation with silver tetrafluoroborate was thus attempted; palladium chloride (one equivalent) was refluxed in acetonitrile and silver tetrafluoroborate added in one portion. The dark red solution immediately became yellow, and a grey coloured solid precipitated (AgCl). The solution was refluxed for 1 hour after which time the silver chloride was removed by filtration and **127** added in one portion. After overnight reflux the solvent was removed *in vacuo* and the resultant orange solid resuspended in DCM/MeCN/brine (3:1:5). The biphasic solution was stirred at room temperature for 1 hour after which time the phases were separated. Evaporation of the organic solvent gave **129** as a yellow solid (Scheme 41).



Scheme 41 Synthesis of Solution Analogue **127** and its Complexation with Palladium

The differences in physical properties between **128** and **129** were remarkable. Whereas **128** was a completely insoluble orange solid, yellow solid **129** readily dissolved in organic solvents. Mass spectra proved to be a useful method of characterisation, in both cases, the $[M\text{-}Cl]^+$ was observed by positive electrospray. The palladium isotope pattern is unique and proved which structures were present. Finally crystals suitable for X-ray were obtained from an acetonitrile solution of **129** (Figure 37), unambiguously proving the formation of the tridentate species.

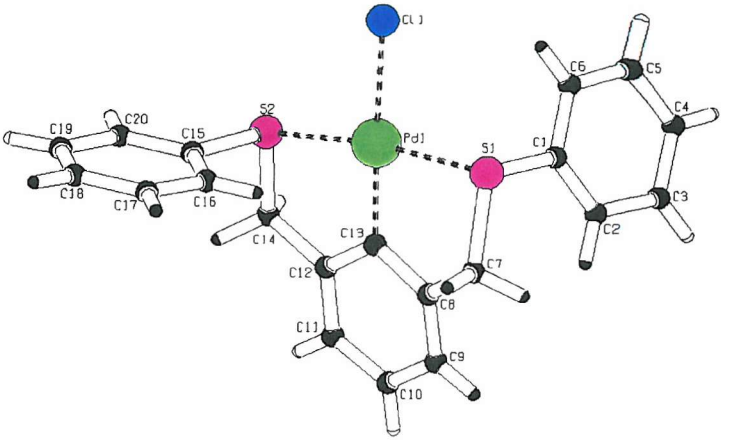
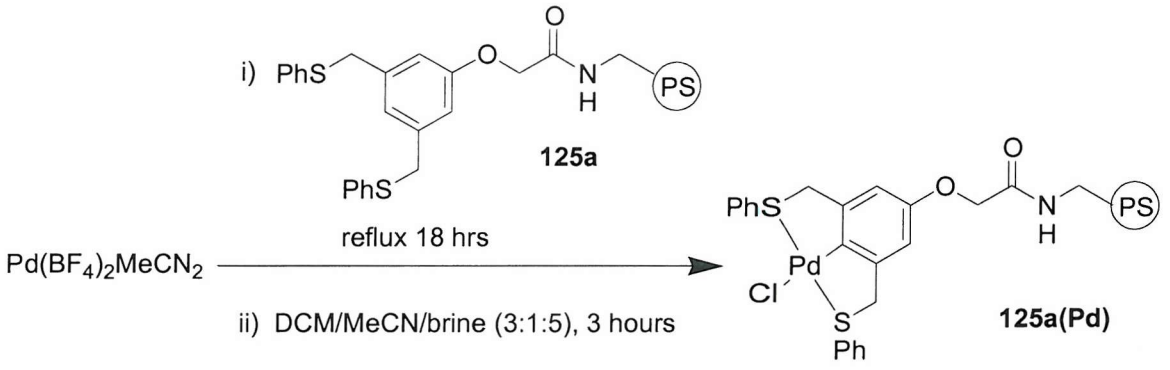


Figure 37 Crystal Structure of **129**

The tridentate, polymer supported palladium complex **125a(Pd)** was synthesized in a similar fashion as shown in Scheme 42 to give the desired compound as a bright orange coloured resin.



Scheme 42 Synthesis of Tridentate, Polymer Supported Palladium Complex **130**

4.7 Synthesis of 16 Different Catalytic Moieties

As four thiol analogues of **102a** and the investigation of various polymer supports were required the synthesis had to be repeated on a large scale. Thus the large scale synthesis *via* route 2, which involved introduction of the thiol moieties later in the synthetic sequence, was embarked upon.

Transformations from **106** (5-hydroxy isophthalic acid) to **121** proceeded smoothly, yields are shown in Table 28.

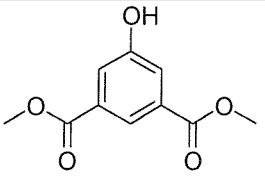
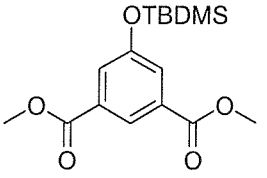
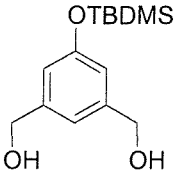
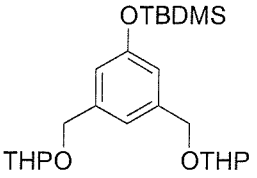
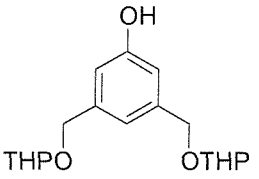
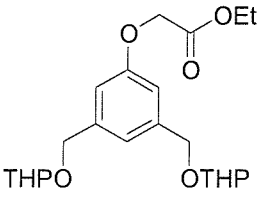
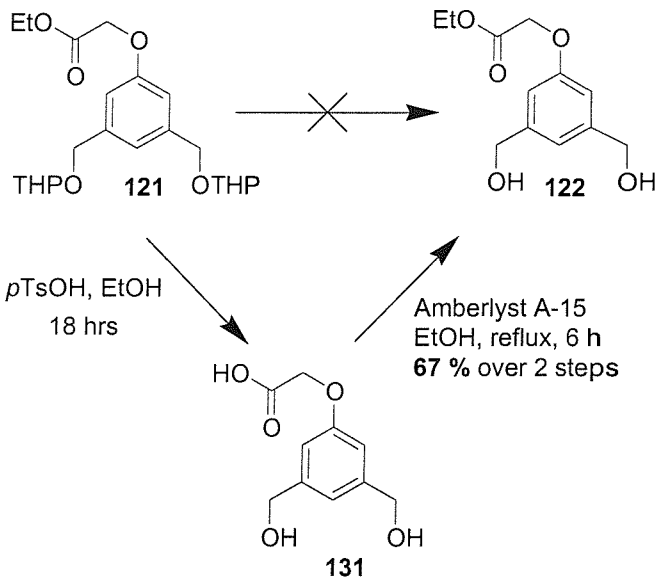
Transformation	Product	Scale/yield
methyl esterfication **106 → 98**		0.14 mol/88 %
TBDMS protection **98 → 107**		0.14 mol/quant
$LiAlH_4$ reduction **107 → 99**		0.1 mol/74 %
THP protection **99 → 109**		0.1 mol/quant
flyoridolysis **109 → 120**		0.08 mol/76 %
alkylation with $BrCH_2CO_2Et$ **120 → 121**		0.05 mol/68 %

Table 28 Scale and Yield for the Large Scale Synthesis

However, THP removal proved problematic, instead of obtaining a white solid as was previously observed, the main product was a brown oil and NMR and IR data suggested the formation of acid **131** (Scheme 43). Surprisingly **122** and

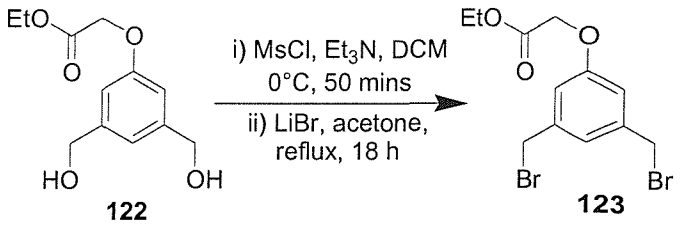
131 had almost exactly the same R_F, and could only be partially separated on long TLC plates. It was postulated that ester hydrolysis may have occurred upon removal of the solvent *in vacuo*, although only a catalytic amount of acid was employed and perhaps upon concentration of the residue the acid had been enough to effect hydrolysis.

Re-esterification, which was considered slightly tricky (formation of the acid may have led to polymerisation by attack of the free hydroxy groups) was considerably easier than expected using Amberlyst A-15 ion exchange resin. This allowed removal of the solid supported catalyst before concentration and when the residue was dissolved in ethyl acetate to undergo column chromatography it precipitated. The desired compound was therefore isolated by simple filtration and overall the two steps proceeded in 67 % yield.



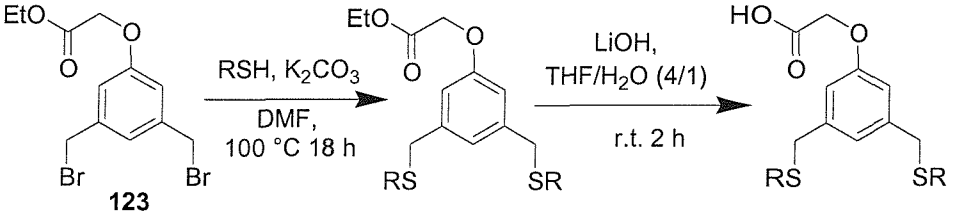
Scheme 43 Hydrolysis and subsequent re-esterification of ethyl ester

Bromination proceeded in 69 % yield after just 1 hour (Scheme 44). Although satisfactory this yield was lower than that achieved on a small scale, attributed to the increased complexity of column chromatography due to the presence of larger quantities of MsCl.



Scheme 44 Large Scale Bromination

With dibromide **123** in hand synthesis of the four thiol moieties was undertaken (Scheme 45). Using the previously described procedures acids **124a-d** were isolated in high yields.

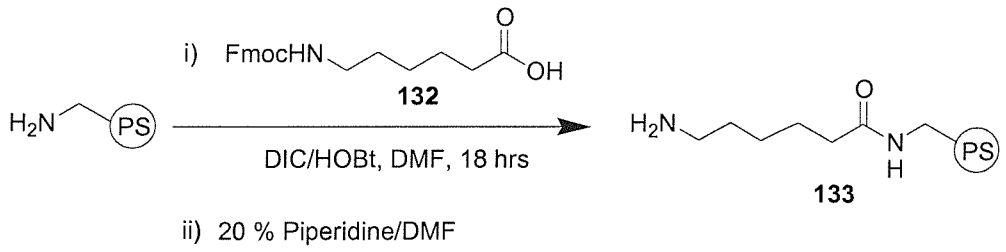


102a	R = Ph	**quant**	**124a**	R = Ph	**91 %**
102b	R = chex	**quant**	**124b**	R = chex	**94 %**
102c	R = ^{t}but	**93 %**	**124c**	R = ^{t}but	**95 %**
102d	R = Et	**82 %**	**124d**	R = Et	**82 %**

Scheme 45 Synthesis of Four Thioether Moieties

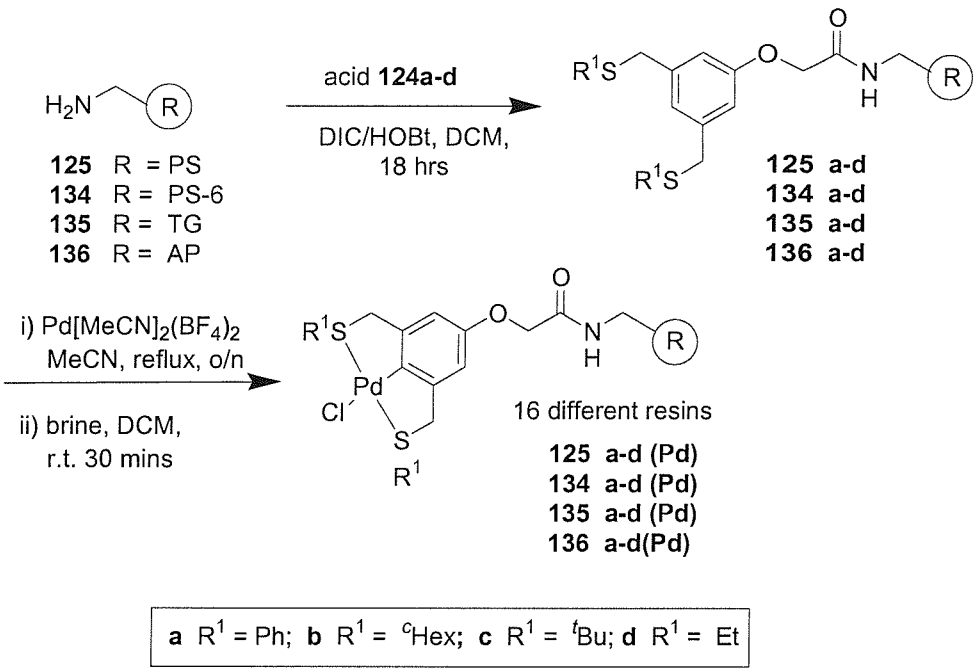
4.8 Attachment of Thiol Pincer Ligands to Solid Supports

As the effect of the polymer support on the catalytic activity was to be investigated, three different polymer supports were selected namely a standard, cross-linked polystyrene resin, a macroporous resin (ArgoPore) and a PEG grafted resin (TentaGel) (various advantages and disadvantages of these resins were discussed in Chapter 1). The effect of a spacer was also desired so aminomethyl polystyrene was treated with Fmoc-6-aminohexanoic acid (**132**) and the amino protecting group removed with 20 % piperidine in DMF to give a polystyrene resin with a 6 carbon spacer (PS-6, **133**, Scheme 46).



Scheme 46 Synthesis of Polystyrene resin with a 6 Carbon Spacer (PS-6)

The four different pincer ligands were then attached to the polymer supports and complexed with palladium as previously described to give the 16 different catalysts.



Scheme 47 Synthesis of 16 different catalysts

4.9 Conclusion

In conclusion, sulfur pincer ligand **102a** was synthesized *via* 2 synthetic strategies through common intermediate, diol **99**. The most straightforward strategy was selected and a large scale synthesis achieved, incorporating four different thiol moieties. The eleven step sequence, which was achieved in 14 %

overall yield from 5-hydroxy isophthalic acid, afforded acids **124a-d** which were attached to four different solid supports to afford 16 different polymer supported, sulfur containing palladacycles upon which a DoE investigation was carried out.

5 Use of Experimental Design Software to Optimise a Heck Reaction

5.1 Introduction

With the 16 resin bound species in hand, their investigation in a Heck reactions using a DoE approach was undertaken and experimental design software investigated.

Initially the software package Multisimplex[110] was considered. This highly intuitive programme was found to be very straightforward to use, aided by thorough step-by-step instructions and help menus. It was able to handle many factor and response settings and a useful feature of the application was that it allowed the allocation of an "importance weighting" to the responses. However, the application could only process quantitative variables, qualitative variables such as resin type and thiol could therefore not be considered and the use of this software was rejected.

Two other commercial packages considered were MODDE[111] and Design Expert[112]. Use of the latter is well documented in the literature and it is a generally accepted industry standard. The capabilities and applicability of both were similar but a single user licence for Design Experts was very expensive, in contrast to a departmental licence for MODDE and it was this programme which was selected.

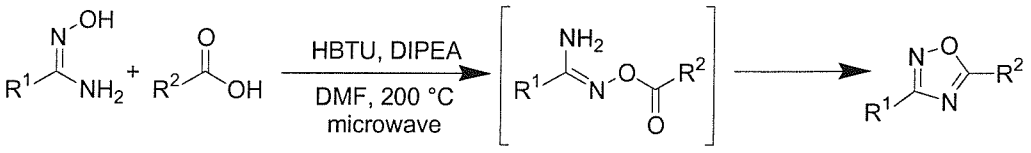
5.2 MODDE Experimental Design Software

MODDE 7 is able to generate designs, analyses, models and predictions for up to 32 factors and both qualitative and quantitative factors can be handled, while a variety of designs and plots were available for results analysis. The software required a basic understanding of statistical methods, but a new feature of the latest version is an "analysis advisor" which was found to efficiently aid analyses methods and plot interpretation.

There are few reports of the use of this software in the literature. In the first example, reported in 1995, Roebuck[113] used a 2 level factorial design to determine the optimum temperature and pH for the growth of *pachysden tannophilus*, a yeast capable of fermenting hexose and pentose sugars to ethanol or xylitol. There was much disparity in the literature in that the range of experimental conditions was broad: temperatures between 24 and 35 °C and pH between 2.5 and 5.5. The results of a response surface modelling experiment indicated that growth maxima was at pH 3.7 with a temperature of 31.5 °C, conditions that were determined with much greater precision that those previously described. In addition to obtaining the optimum conditions, the authors concluded that at the optima the growth response was more sensitive to a change in one pH unit than one temperature unit. The use of this approach thus afforded, a greater, overall understanding of the process.

Another two examples include an exploration of the effects of aeration in an immoblized primary fermentation[114] on the flavour compounds in beer and the optimisation of operating parameters for the determination of metallic elements in Millipore or brackish water by atomic absorption spectroscopy[115].

More recently Nicewonger[116] used MODDE to generate a central composite, face centred design and a quadratic model for its analysis to optimise the synthesis of 1,2,4-oxadiazoles using microwave irradiation (Scheme 48), varying the reaction time (2 -10 minutes), temperature (110 - 200 °C) and DIPEA equivalents (0 – 4.14).



Scheme 48 Synthesis of 1,2,4-oxadiazoles

The surface map showed a quadratic dependence upon the equivalents of DIPEA suggesting the optimum value was not at either of the extremes of the factor settings, but somewhere in the middle and that the reaction had an inverse

time-temperature relationship. This was the same observation reported by Chen[6], which was discussed in chapter one, were reactions carried out at a higher temperature required less time than those at a lower temperature. The optimum conditions were found to be: 2 minutes at 200 °C with 2.85 equivalents of DIPEA. To validate these conditions the temperature and DIPEA equivalents were varied by +/- 20 %. Results suggested that there was no significant difference among the different sets of conditions.

Finally, the scope of the method was confirmed by preparing a library of 24 compounds. The crude ELSD purities ranged from 21 to 93 % with the conversion of the majority of the samples corresponding to > 90 %. In all cases the products were purified by HPLC-MS giving recovered yields of 15 – 41 %.

5.3 Optimization of a Heck Reaction

As described in Chapter 1 a DoE investigation is normally conducted in 4 stages namely: scoping, screening, optimization and verification. The purpose of this study was to examine the effect of a large number of variables on the Heck reaction. Therefore two screening experiments were conducted followed by an optimisation experiment using a response surface modelling design. The findings were then verified by repetition of the optimized conditions.

5.3.1 Scoping

This stage involved the selection of a reaction for optimization and the development of a method for carrying out and analysing the results of the experiment.

5.3.1.1 Reaction Vessel

The first consideration was a reaction vessel which needed to incorporate heating, a reflux condenser, slow stirring and a 1 ml capacity, while the capability to perform multiple reactions was essential. A Radleys carousel unit was selected which allowed 12 reactions to be performed simultaneously. Standard tubes for the equipment were found to be unsuitable as they were

designed to accommodate 20 ml but modified tubes were designed (Figure 38) which satisfied all the the desired requirements

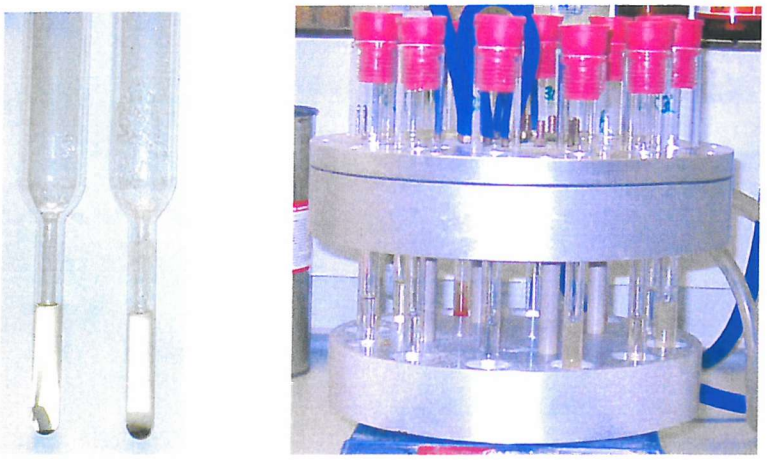
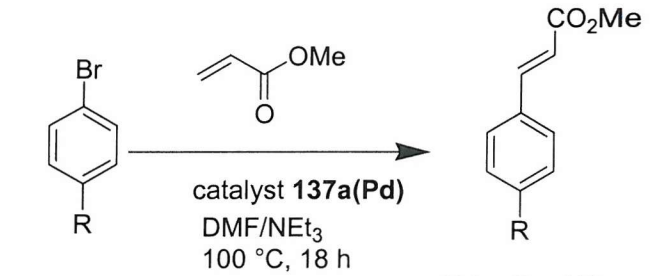


Figure 38 Specially Constructed Radleys Carousel Tubes

5.3.1.2 Selection of Substrates

A range of bromo-substrates (**138** – **141**) were investigated and four trial reactions were undertaken with methyl acrylate as the alkene acceptor, using NEt_3 as the base and DMF as the solvent. Conversion of the starting material was assessed by RP-HPLC at 254 nm after 18 hours (Scheme 49). During these experiments the solutions turned dark brown, corresponding to "leached" palladium, this led to the incorporation of a visually screening test for 'Pd' loss described in section 5.3.2.2.



138 R = NO_2
139 R = H
140 R = Me
141 R = OMe

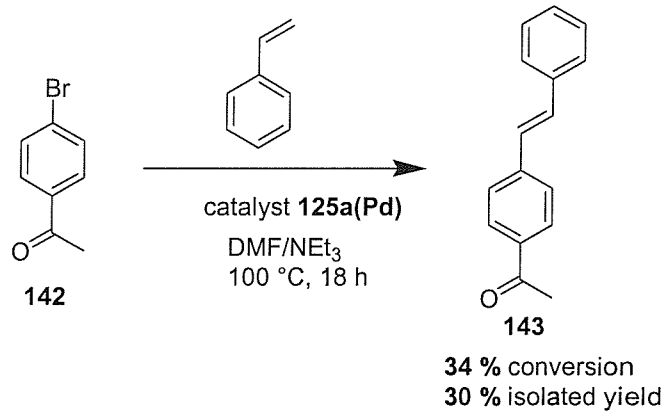
138a R = NO_2 89 %
139a R = H 78 %
140a R = Me 70 %
141a R = OMe >10 %

Scheme 49 Scoping Substrate Test

These reactions corresponded to expected trends, in that the more electron poor bromides reacted far superiorly to their electron rich counterparts; although none

of these reactions were considered as the ideal substrate for the investigation as a conversion of 20 - 50 % was sought for optimization.

Use of the less reactive alkene acceptor, styrene was considered and a further scoping experiment undertaken. From the previous experiment the nitro compound was considered too reactive and the anisole too unreactive and were disregarded. The phenyl and tolyl bromides had similar reactivity and therefore it was decided to consider just one of these. As bromobenzene is a liquid at room temperature it was decided to proceed with this substrate as this would have eased dispensing. However bromobenzene and stilbene, the coupling product, were found to be inseparable by HPLC therefore bromoacetophenone (**142**) was also considered as a substrate (Scheme 50).



Scheme 50 Second Scoping Substrate Experiment

Fortunately bromoacetophenone and **143** were separable by HPLC and upon column chromatography **143** was isolated in 30 % yield. A calibration study of **142** and **143** was then undertaken in order that accurate conversions could be determined. The 30 % isolated yield corresponded to an HPLC conversion of 34 %. Analyses were carried out by RP-HPLC, at a wavelength of 282 nm, which corresponded to the wavelength at which both the starting material and product had good absorbance.

5.3.2 First Screening Experiment

5.3.2.1 Factor Variation

With the reaction to be optimized decided upon and the experimental procedure verified the choice of factors was considered. As previously mentioned the nature of the resin and thiol pincer ligand had already been decided on as factors. Following an in-depth consideration of the Heck reaction four other factors were considered: the type of base, the equivalents of base; the presence of a phase transfer catalyst and the solvent. It was decided to fix the time and percentage of catalyst.

One problem often encountered in the use of experimental design is the quantification of variables. Although base is normally quantified by pKa this was considered to be an unsuitable measurement for this experiment as it is well known that the pKa of an acid or base varies dramatically with temperature and solvent. Therefore a less common approach was undertaken in this experiment, with most of the variables being considered in a qualitative fashion.

The use of different bases in the Heck reaction has been documented[82] and for this experiment base was set at four qualitative levels: NaOH, NaOAc, Na_2CO_3, and NEt_3. This was considered to encompass a range of strong, medium and weak inorganic and soluble bases. The equivalents of base was considered as a quantitative factor varying between 1 and 4.

The combination of tetraalkylammonium salts (phase-transfer catalysts) and insoluble bases has been shown to accelerate the Heck reaction. There are various explanations for this enhancement, Jeffrey[117] proposes the "*assistance of tetraalkylammonium salts in the regeneration of a zerovalent palladium catalyst*" whereas Amatore[118] believed it to be based on the fact that palladium complexes are stabilized by the coordination of halide ions. In this study tetrabutylammonium bromide was used as a phase transfer catalyst and treated as a quantitative factor set at a maximum of 2 equivalents.

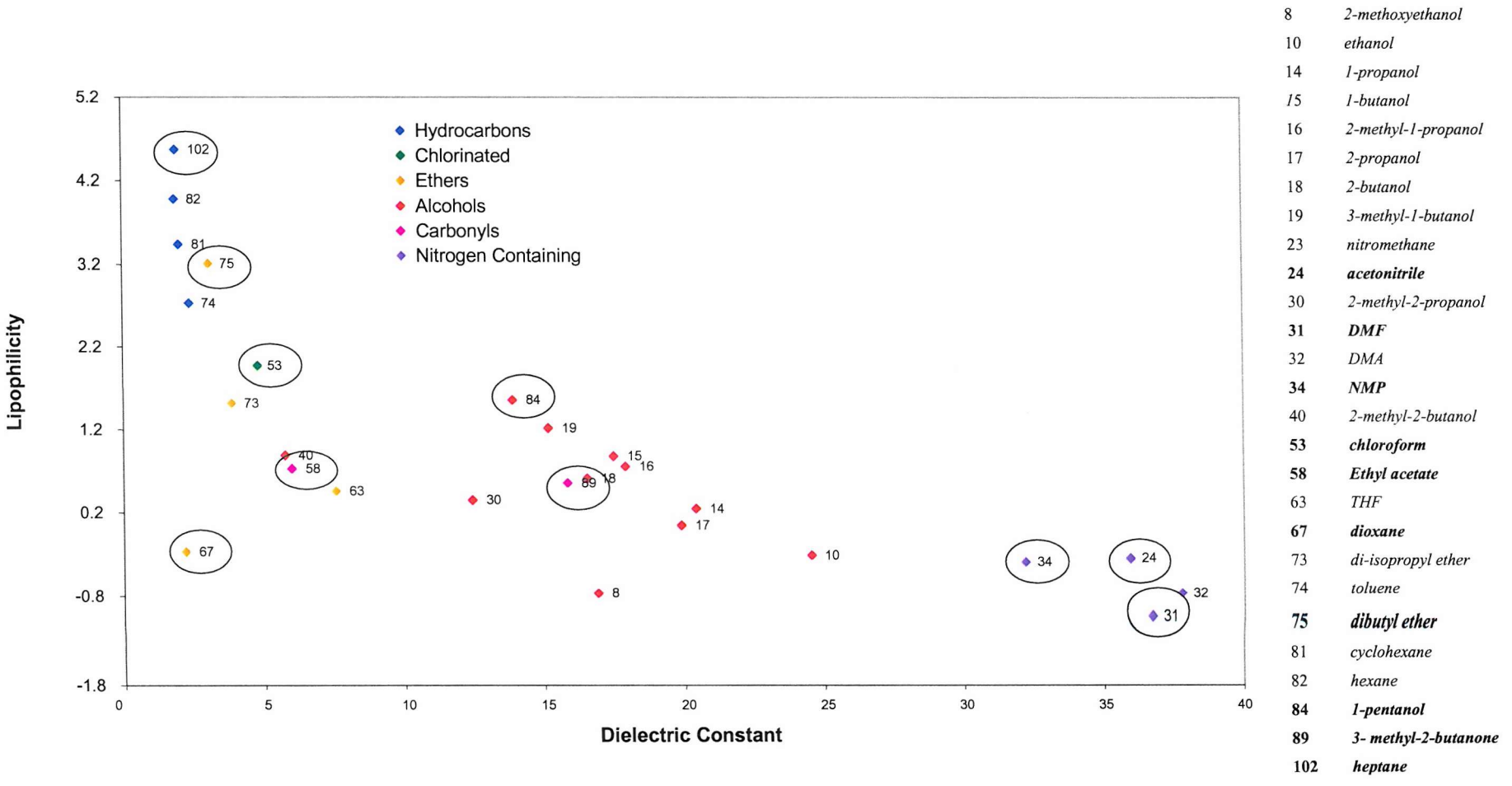
The most common way of quantifying a solvent is by its dielectric constant, although there are many other parameters which can be used. Most reports of the use of DoE do not consider the solvent as a factor; indeed the quantification of solvent is generally seen as a major obstacle. Some groups have applied the technique of principal component analysis, where a mathematical procedure or computer programme is used to transform a large number of correlated variables into a smaller number, which account for as much variability as possible. Carlson derived two parameters t1 and t2 which were indicative of the polarity and polarizing ability of the solvent from 9 physio-chemical descriptors (melting point, boiling point, dielectric constant, dipole moment, refractive index, the normalized Reichardt-Dimroth parameter, lipophilicity and water solubility), these parameters accounted for 69 % of the variation of these descriptors and were listed for 103 different solvents.[5] Ley used these values as solvent descriptors in the optimization of a polymer supported carbodiimide.[9] Musumarra[107] later extended this to 113 solvents and Sarbu[119] devised two components which accounted for 74 % of the total variance of the 9 parameters for 50 solvents used in liquid chromatography.

Quantification of solvent in this investigation would involve selection of the appropriate parameter and incorporation of it as a quantitative, multi-level factor (where the user specifies the level of each factor, as each solvent has a discrete value which does not necessarily correspond to that required for the quantitative factor). However with many parameters available it was difficult to select which of these were appropriate. This is clearly demonstrated in Figure 39, solvents 102 (heptane) and 67 (dioxane) have almost identical dielectric constants, 1.92 and 2.2 respectively but it is well known that these solvents have completely different properties, one being a hydrocarbon, the other an ether, one being water immiscible, the other miscible and so on, these huge differences resulting from solvents with the same common, fundamental descriptor. In this case lipophilicity may be a better measurement but does this does not take into account the huge number of other differences between the two solvents for example the co-ordination of ions and hydrogen bond donor abilities of dioxane. Even considering two parameters of lipophilicity and dielectric constant it is

evident that very different solvents can have similar values e.g. 89 (3-methyl-2-butanone) and 18 (2-butanol) or 40 (2-methyl-2-butanol) and 58 (Ethyl acetate).

It is highly likely that most of the time the effect of a solvent is due to a multitude of factors. If quantification of solvent by one of these methods had been undertaken it was postulated that a possible conclusion could be that the reaction was dependent upon the quantified solvent factor, but no indication of whether the correct parameter had been selected would be provided.

It was therefore decided to undertake a different approach in this study and treat solvents as qualitative variables. This meant that the resulting coefficients for the solvents would not be associated with a number i.e. would be unweighted. It was postulated that relationships would perhaps be established, with results in hand, post experiment rather than before.



8	*2-methoxyethanol*
10	*ethanol*
14	*1-propanol*
15	*1-butanol*
16	*2-methyl-1-propanol*
17	*2-propanol*
18	*2-butanol*
19	*3-methyl-1-butanol*
23	*nitromethane*
24	***acetonitrile***
30	*2-methyl-2-propanol*
31	***DMF***
32	*DMA*
34	***NMP***
40	*2-methyl-2-butanol*
53	***chloroform***
58	***Ethyl acetate***
63	*THF*
67	***dioxane***
73	*di-isopropyl ether*
74	*toluene*
75	***dibutyl ether***
81	*cyclohexane*
82	*hexane*
84	***1-pentanol***
89	***3- methyl-2-butanone***
102	***heptane***

Figure 39 Solvent Selection Parameters

The plot of lipophilicity *vs* dielectric constant was used to select the solvents for the DoE investigation (Figure 39). Although it was previously stated that this did not explain the full variation, these values corresponded to those which were considered the most important and those with the least correlation (e.g. dielectric constant is highly correlated to both the dipole moment and Reichard Dimroth parameter). Solvents were also classified according to a certain, functional group types (marked in different colours on the graph). Solvents were then selected across the whole range of values. As well as considering novel Heck reaction solvents such as pentanol and 3-methyl-2-butanone it was considered important to include those in which the reaction has been conducted before e.g. DMF and NMP. Unfortunately toluene, a popular non-co-ordinating solvent in which to carry out palladium catalysed reactions highlighted by Fu[86] could not be included as its UV chromophore was found to complicate HPLC measurements. The 10 solvents chosen with their reason for selection are shown in Table 29.

Solvent		Reason
34	NMP	extreme of graph, nitrogen containing examples, used previously.
31	DMF	
24	MeCN	
53	Chloroform	chlorinated solvent example
58	Ethyl acetate	carbonyl solvent example
67	Dioxane	used previously and extreme of graph
75	Dibutylether	ether example
84	1-pentanol	middle of graph, alcohol example
89	3-methyl-2-butanone	middle of graph, another carbonyl example
102	heptane	extreme of graph, hydrocarbon example

Table 29 Solvent Selection with Explanation

In conclusion it was decided to vary the factors as shown in Table 30. If each quantitative variable represented 3 levels this would correspond to a maximum number of 5760 possibilities.

Factor	Type	Levels	
Resin	qualitative	4	PS-0, PS-6, TentaGel, ArgoPore
Thiol	qualitative	4	Ethyl, cHexyl, tButyl, Phenyl
Base	qualitative	4	NaOH, Na_2CO_3, NaOAc, NEt_3
Eq of Base	quantitative		1 and 4
Eq of PTC	quantitative		0 and 2
solvent	qualitative	10	heptane, dibutyl ether, chloroform, Ethyl acetate, dioxane, 1-pentanol, 3-methyl-2-butanone, NMP, DMF, acetonitrile.

Table 30 Factors varied in the First Screening Experiment

The above factors and the response (conversion) were entered into the design wizard in MODDE 7 and a D-Optimal design with a total of 40 experiments (3 replicated centre points) generated. MODDE displayed the experiments to fulfil the design criteria in the form of a worksheet. A full table of results for these experiments, which were carried out in blocks of 12, in random order are shown in the experimental section.

5.3.2.2 Development of a Leaching Assessment Screen

As previously mentioned in Section 5.3.1.2 it was observed that when the Heck reaction of various substrates with the polymer-supported palladacycle were initially conducted a large amount of leaching was observed. In this screening experiment a large variation in the amount of leaching was observed and a visual screen formulated where the colour of the solution was assigned a value according to Figure 40. Initially the lightest solution was allocated 0 and the darkest 10, however this complicated analysis as when the coefficients were assessed, for conversion a positive, and for leaching a negative response were sought. Reversing the scale meant that for both responses positive coefficients

were required (thus in the remainder of this chapter a positive responses indicates a low observed level of leaching and *vice versa*). In addition to this MODDE could not perform some transformations on null responses, therefore one was added to each assessment, giving a final scale of 1 to 11.

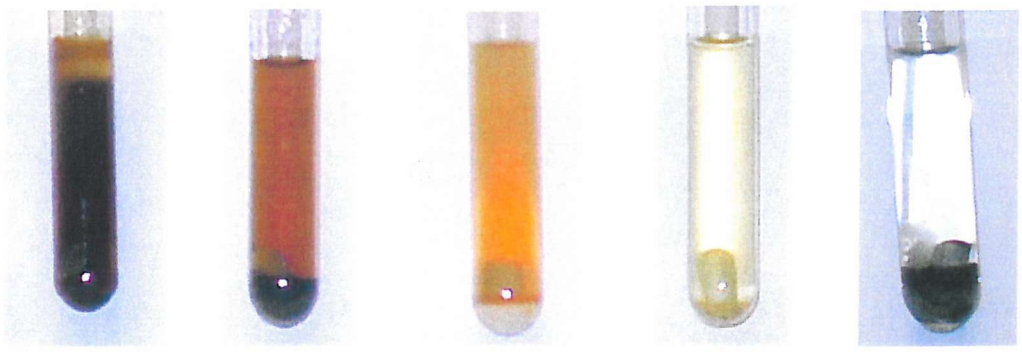


Figure 40 Scale for Assessment of Palladium Leaching

5.3.2.3 Analysis of Results

The results were entered into MODDE which immediately fitted a model to the data and a variety of plots were available for analysis. Although results were collected for conversion and leaching after both 6 and 24 hours, to aid simplification some plots only contain data for 24 hours as no significant difference in the effects between these two times was observed.

Sometimes it was necessary to perform a transformation on the responses for example if the spread of values was not uniform or if the responses to changing the levels of the factors were not linear, (they could for example be logarithmic). In this case a logit transformation was performed.

The first analysis plot is shown in Figure 41 where observed *versus* predicted values are plotted against each other. With good models all points fall on a 45 ° line, high R^2 and adjusted R^2 values are desirable. R^2 can therefore be described as a measure of how well the model fits the data although merely adding variables to the model can cause it to increase. The adjusted R^2 is R^2 adjusted for the number of degrees of freedom thus minimizing variance associated with the addition of more variables.

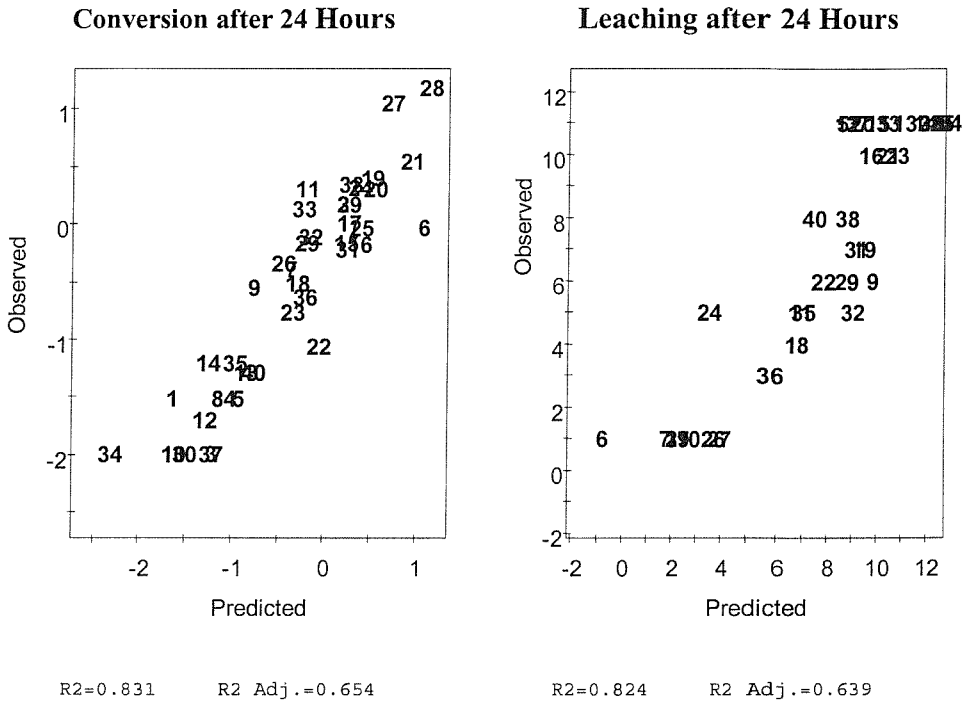


Figure 41 Observed *vs* Predicted Plot for the First Screening Experiment (numbers correspond to the experiment number)

In this case the values of R^2 of 0.83 and 0.82 and adjusted R^2 of 0.65 and 0.64 for conversion and leaching respectively were considered reasonable (Figure 41).

This plot could also be used to detect outliers – points far away from the line, which could signify errors or highly unpredictable, positive or negative responses. In this case no points were considered outliers. MODDE offers the

possibility of excluding the results of outliers but for this whole investigation this was deemed unnecessary.

Two other useful plots are shown in Figure 42 and 6, Normal Effects and Coefficient overview plots; their derivation was described in Chapter 1.

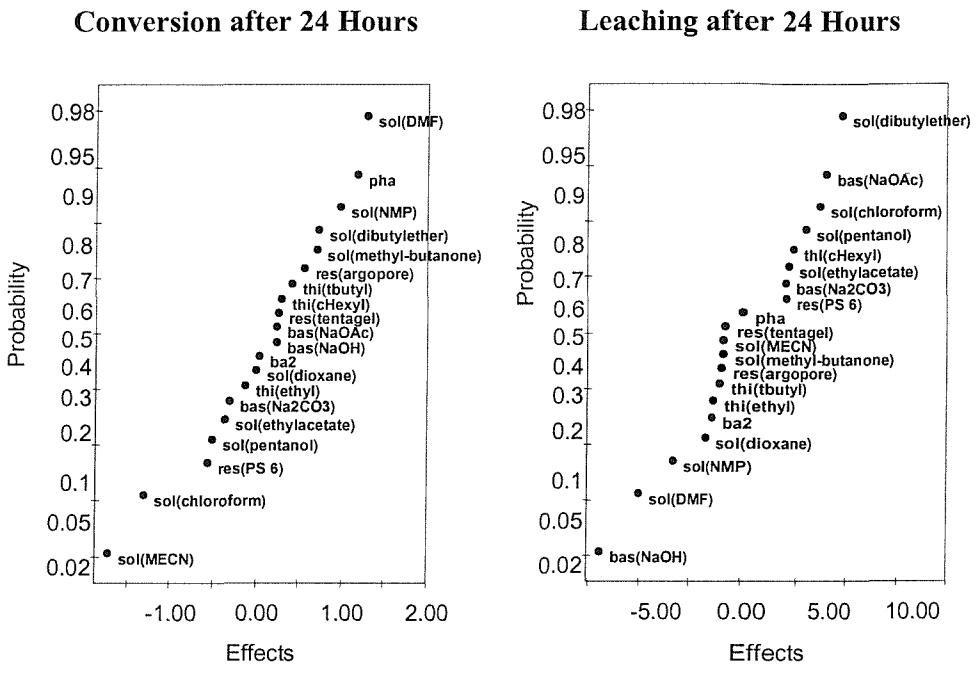


Figure 42 Normal Effects Plot for the First Screening Experiment

The Normal Effects plot is the most common plot that statisticians use to assess the importance of variables; in this experiment, due to the high number of qualitative variables the coefficient overview plot (Figure 43) was found to complement this analysis.

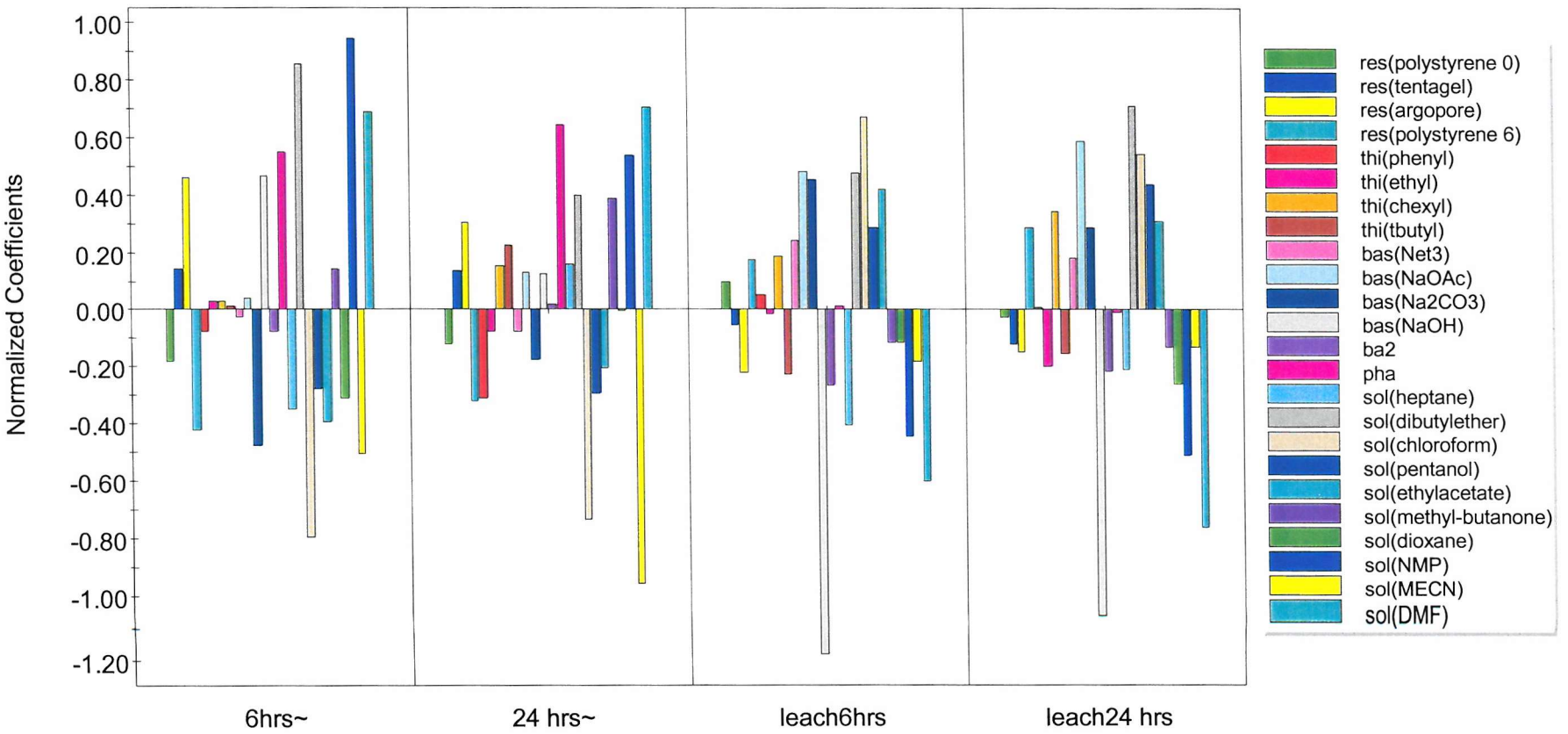
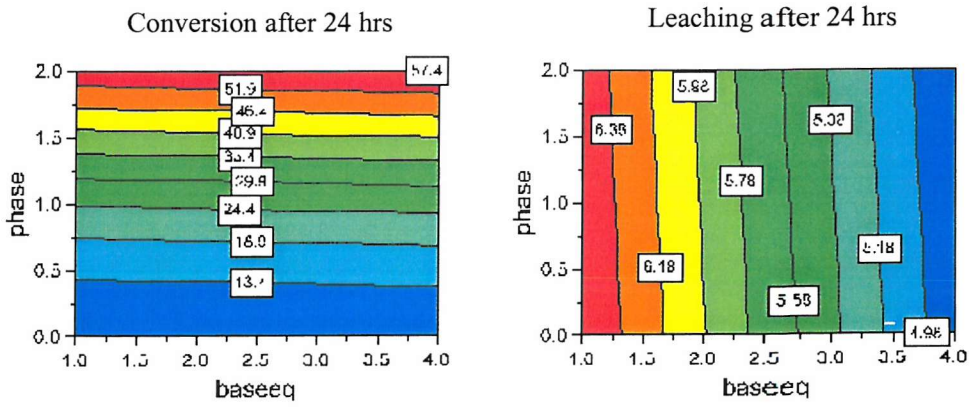


Figure 43 Normalized Coefficient Overview Plot for the First Screening Experiment

These plots indicate that after 24 hours the most positive significant factor on conversion was the use of DMF as solvent, however this corresponded to the second largest negative effect on leaching. The most significant, positive, effect on leaching was dibutylether as solvent; NaOH as base gave the worst response, with high levels of observed leaching.

2D contour and surface plots as shown in Figure 44 were used to evaluate the importance of quantitative variables and to predict the response at selected settings. Curvature from the incorporation of centre points can also be assessed.

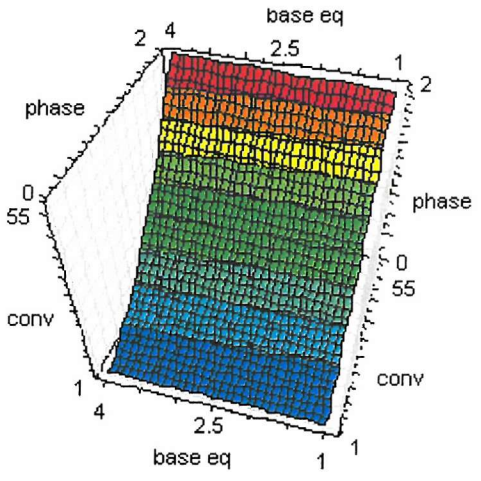
These contour and surface plots indicated that the presence of a phase transfer catalyst had a positive effect on the conversion, as had been suggested by Amatore and Jeffrey but no effect on the leaching, although at this stage it was unclear what effect the phase transfer catalyst had on this reaction and it was decided to investigate this in further experiments. In contrast the equivalents of base had no effect on the conversion but led to increased leaching. The effect on conversion was as would have been expected as the reaction scheme only involves one mole of base per mole of substrate and it was postulated that the negative effect on leaching may have occurred if the basic anions complexed the polymer bound palladium, causing it to be removed from the resin. A contour plot was available for every resin with every combination of thiol, base and solvent. Each showed the same general pattern and for simplicity only one is shown (Figure 44).



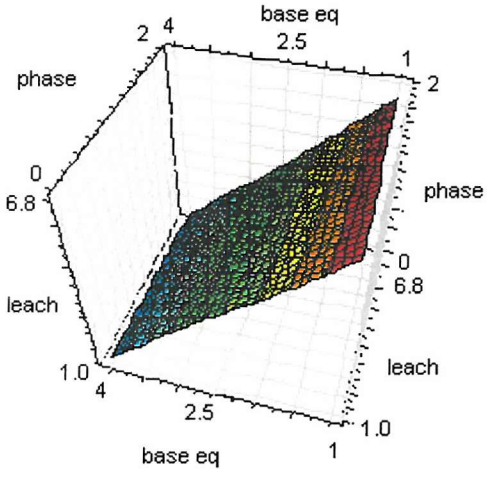
resin = PS0; thiol = phenyl; base = NEt_3; solvent = DMF

Figure 44 2D Contour Plots for the First Screening Experiment

conversion after 24 hours



leaching after 24 hours



resin = PS(0), thiol = phenyl, base = NEt_3, solvent = DMF

Figure 45 Surface Plots for the First Screening Experiment

The main conclusions drawn from this experiment were that overall the solvent had the greatest effect on both responses, for conversion this was followed by the presence of the phase transfer catalyst. The use of NaOH as a base had the most significant effect on leaching; only a small positive effect on conversion was observed with a large amount of leaching. In comparison, all other bases showed a positive effect with respect to leaching, although their effect on conversion was fairly insignificant.

Although minor, the effect of the thiol pincer group showed that the electron rich, bulky; cHexyl and tButyl thiols gave better conversions than their smaller (Ethyl) and electron poor (phenyl) counterparts, with the lowest levels of leaching observed for the cHexyl moiety. Finally ArgoPore and TentaGel supported catalysts gave higher conversions than those immobilized on PS; however these also gave the highest levels of leaching. PS-6 gave the least leaching but also the lowest conversion response.

5.3.3 Second Screening Experiment

In most DoE investigations, following a screening stage to identify the important factors, a response surface modelling experiment is typically undertaken to establish the best operating conditions for the process. These types of designs require far more experimental runs and therefore the number of variables should be kept to a minimum.

In this study, the investigation of a large number of factors had been embarked upon and one screening experiment was not deemed sufficient to identify all of the critical factors and a second screening experiment was therefore undertaken. For this it was decided to proceed with approximately half the number of variables from the original experiment.

5.3.3.1 Factor Variation

It was decided to keep all levels of the thiol pincer group, as some differences in their activity had been observed, and to investigate their effect in more depth. The type of resin had also shown subtle differences hence it was decided to retain PS-0, TengaGel and ArgoPore resins. PS-6 was excluded as this had the most negative coefficient for conversion.

As the equivalents of base has been shown to have no effect on conversion and a negative effect on leaching this factor was set at 1. In contrast the type of base had very different effects on both factors. NaOH was removed as it led to a high degree of leaching and NaOAc was retained as it had a positive effect on both responses. This left the choice of NEt_3 and Na_2CO_3; it was decided to retain the former because it had a less negative response on conversion.

Analysis of the results indicated that the presence of the phase transfer catalysts had a positive effect on the conversion. In this experiment the levels had been set at 0 and 2 for the lowest and highest levels respectively, therefore except for in the case of the centre points when present it had been used in stoichiometric excess (2 equivalents). It was deemed desirable to investigate the use of this material catalytically and for the second screening stage this factor was set at levels of 0.1 and 1.

By considering the solvent as a qualitative factor it had been hoped that correlations between the model coefficients and their physio-chemical properties could be established in order that predictions for the desirable parameters could be made. Unfortunately no such relationships could be detected although some conclusions could be drawn for example that the reaction proceeded in a wide range of solvents with different functionalities, although the reaction did not proceed well in $CHCl_3$, the only chlorinated solvent. The leaching coefficients were lowest for nitrogen-containing solvents with a high dielectric constant, although it could not be ascertained which of these parameters was responsible for this as there were no nitrogen containing solvents with a low dielectric constant used. A plot of the leaching coefficient *vs* dielectric constant gave an R^2 of only 0.33 reinforcing the view stated earlier that effects may be due to a combination of factors. It was therefore decided to consider solvent as a qualitative variable for the remainder of the investigation.

For the second screening stage it was decided to select five out of the initial 10 solvents; chloroform, pentanol, ethyl acetate and MeCN were disregarded because of their negative effect on conversion. DMF was retained because of its positive effect on conversion although NMP was omitted because it was considered similar to DMF. Heptane, dibutyl ether, methyl-butanone, dioxane and DMF were therefore set for solvent. The factors varied and their levels are summarized in Table 31.

Factor	Type	Levels	
Resin	qualitative	3	PS-0, TengaGel, ArgoPore
Thiol	qualitative	4	Ethyl, cHexyl, tButyl, Phenyl
Base	qualitative	2	Na_2CO_3 and NaOAc
Eq of PTC	quantitative		0.1 and 1
solvent	qualitative	5	heptane, dibutyl ether, dioxane, 3-methyl-2-butanone, DMF.

Table 31 Factors varied in the Second Screening Experiment

As previously described, the above factors were entered into the design wizard in MODDE 7 and a D-Optimal design generated. A full table of results for these experiments, which were again carried out in blocks of 12, in random order are shown in the experimental section. In this case a power transformation of 2 was applied.

5.3.3.2 Analysis of Results

The observed *vs* predicted plots are shown in Figure 46, the R^2 and R^2 adjusted values were similar to those of the previous screening experiment and were again considered reasonable from which conclusions could be drawn. No points were considered as significant outliers.

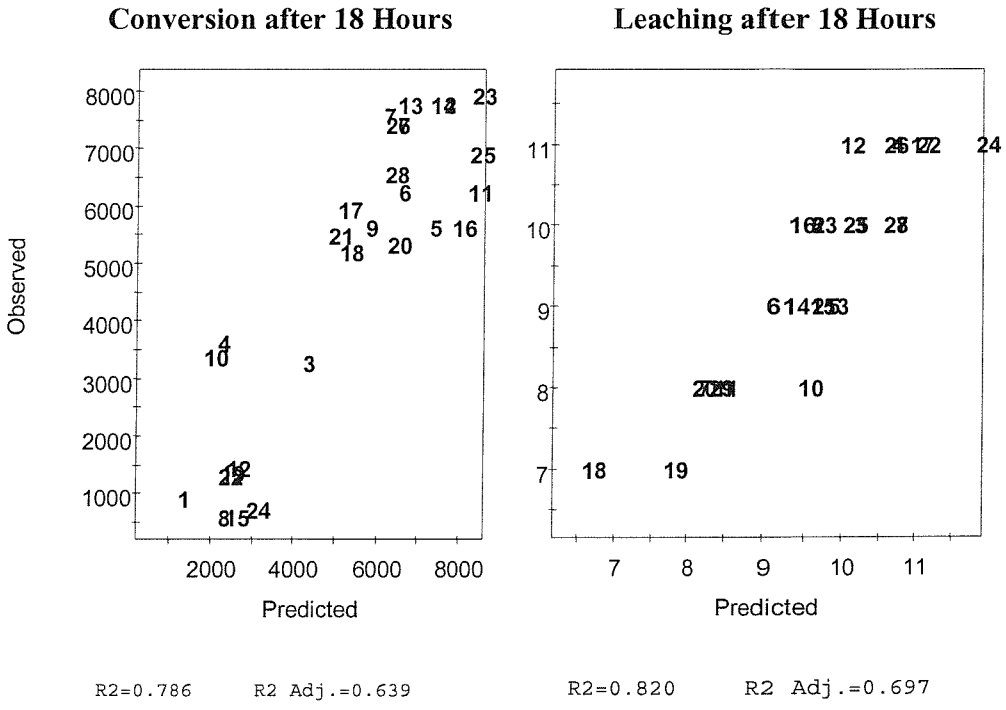


Figure 46 Observed *vs* Predicted Plot for the 2nd Screening Experiment (numbers correspond to the experiment number)

The Normal Effects plot (Figure 47) and coefficient overview plot (Figure 48) indicated that for conversion the most significant effect, which was fortuitously positive, was the increased amount of phase transfer catalyst, this was closely followed by the use of the cHexyl thiol pincer group. The most significant effect on leaching, which was a negative effect, was the use of DMF as solvent, which interestingly, in this experiment had a slight, negative effect on conversion. This was followed by the positive effect observed with the use of heptane as the solvent.

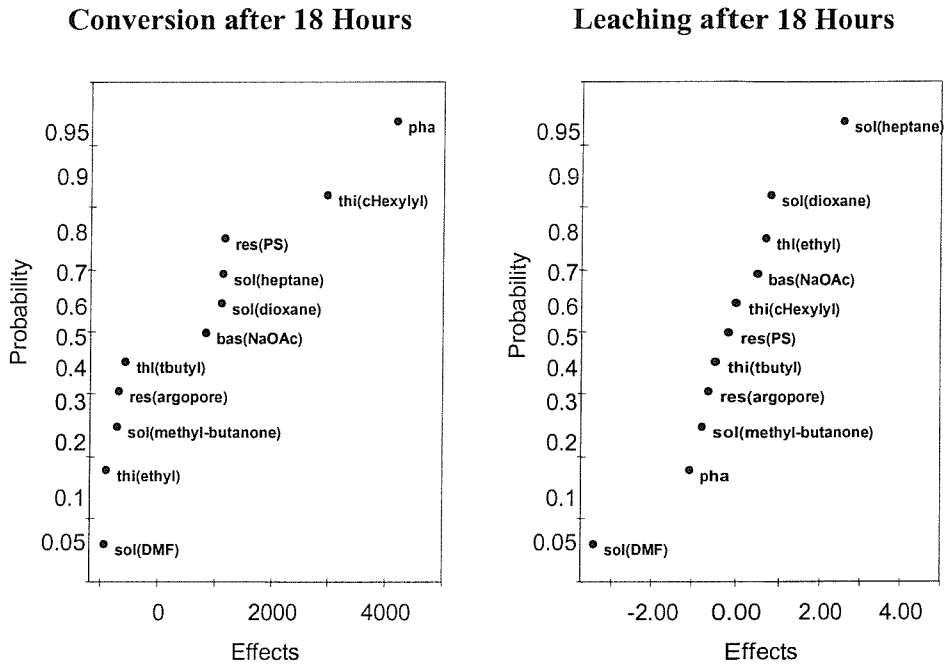


Figure 47 Normal Effect Plot for the Second Screening Experiment

Of the three resins, the only positive response for conversion was for PS, TentaGel gave the only positive effect on leaching and with regard to the four thiols only cHexyl and Ethyl had positive effects on conversion and leaching respectively; the others showed negative effects. Interestingly the Phenyl pincer which is most commonly used had the most negative effect on both responses.

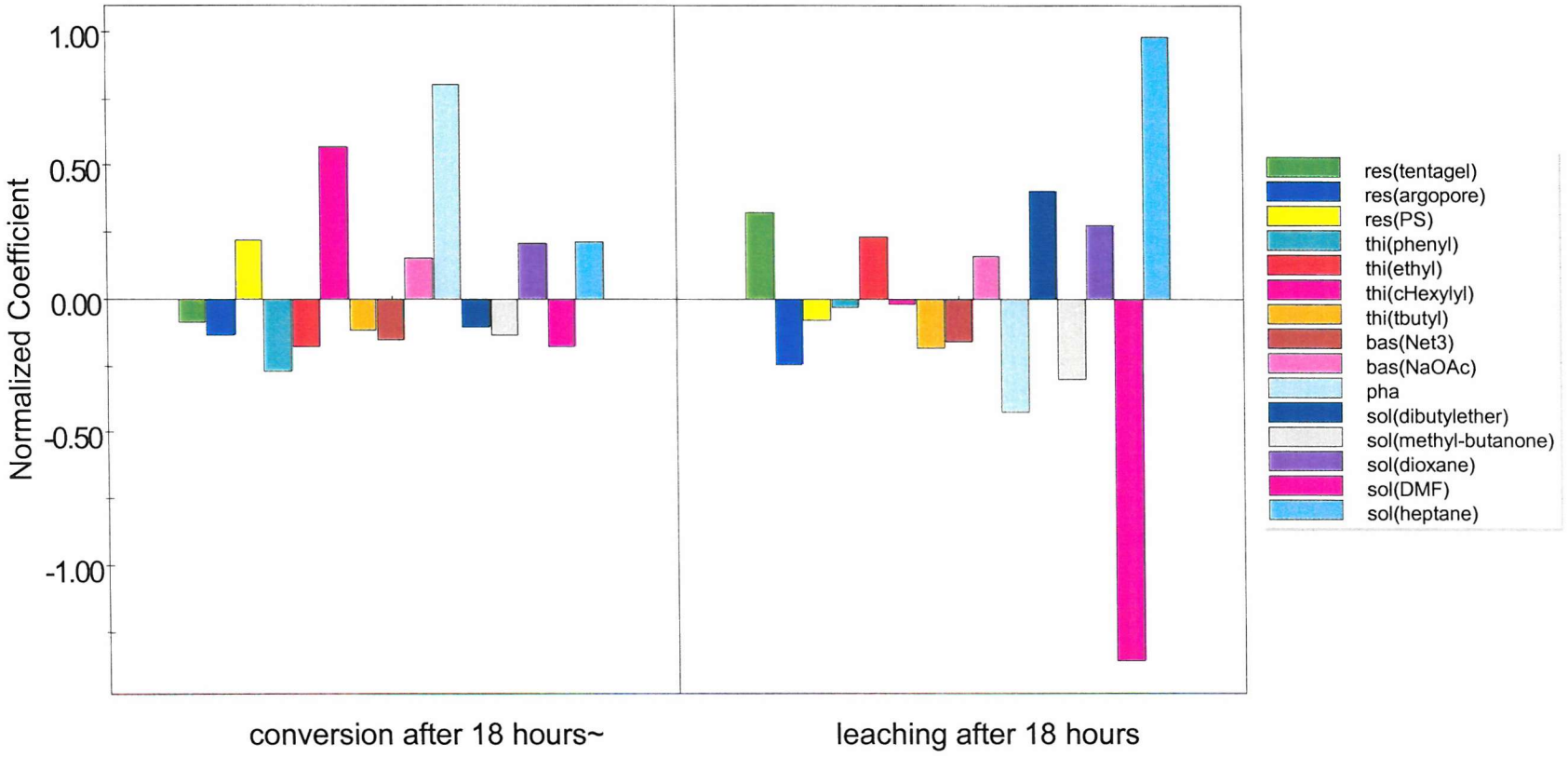


Figure 48 Normalized Coefficients for the Second Screening Experiment

5.3.4 Optimisation

The screening experiment was deemed to be highly conclusive for the selection of three suitable factors, to be varied at two levels for a response surface experiment.

5.3.4.1 Factor Variation

From the previous set of experiments it was decided to fix the resin as PS as this gave the most positive effect on conversion, the fact that this resin had proved the most successful was highly advantageous as PS is considerably cheaper than the other two and had a far superior loading. The other factor which was set constant was the use of NaOAc as the base.

From the results of the second screening experiment it was clear that the cHexyl thiol was far superior to the other three thiol pincer groups and therefore this was retained for the final experiment, tButyl was set as the other level as this had the second highest conversion coefficient. The solvents selected were dioxane and heptane as these had positive conversion coefficients. Phase transfer catalyst, again as a quantitative factor was included to investigate under these reduced factor settings. The factors investigated are summarized in Table 32.

Factor	Type	Levels	
thiol	qualitative	+1	cHexyl
		-1	^{t}Butyl
PTC	quantitative	+1	1
		-1	0.1
solvent	qualitative	+1	dioxane
		-1	heptane

Table 32 Factors to be Varied in the Optimisation Experiment

5.3.4.2 Analysis of Results

The factors and their levels were again entered into MODDE which produced the worksheet shown in Table 33. Experiments were carried out in 2 blocks of 8 in random order, in this case no leaching assessment was undertaken as almost no leaching, corresponding to levels 10 or 11 was observed. Figure 49 shows the observed *vs* predicted plot, in this case the model had an R^2 and adjusted R^2 of 0.81 and 0.73 respectively.

Run	thiol	phase	solvent	conv 18 hrs
1	cHexyl	0.55	heptane	76
2	cHexyl	0.55	heptane	70
3	cHexyl	0.1	dioxane	61
4	tButyl	1	heptane	69
5	cHexyl	0.1	heptane	50
6	cHexyl	0.55	dioxane	91
7	tButyl	0.55	dioxane	85
8	cHexyl	1	dioxane	73
9	cHexyl	1	heptane	85
10	tButyl	0.55	heptane	79
11	cHexyl	0.55	heptane	69
12	tButyl	1	dioxane	48
13	cHexyl	0.1	dioxane	42
14	cHexyl	0.55	heptane	88
15	tButyl	0.1	dioxane	25
16	tButyl	0.1	heptane	7

Table 33 Results for the Optimisation Experiment

The results shown in Table 3 can be conveniently displayed on the corners of a cube (Figure 50). Immediately some responses are evident, in that the cHexyl, thiol pincer group (left and right faces compared), the incorporation of a phase transfer catalyst (front and back faces compared) and the use of dioxane as a solvent) top and bottom faces compared) led to higher conversions. However for the phase transfer catalyst, strong evidence of curvature i.e. a quadratic dependence was observed, conversion peaked at intermediate levels of the

catalyst. All of these observations are displayed graphically on the prediction plot shown in Figure 51.

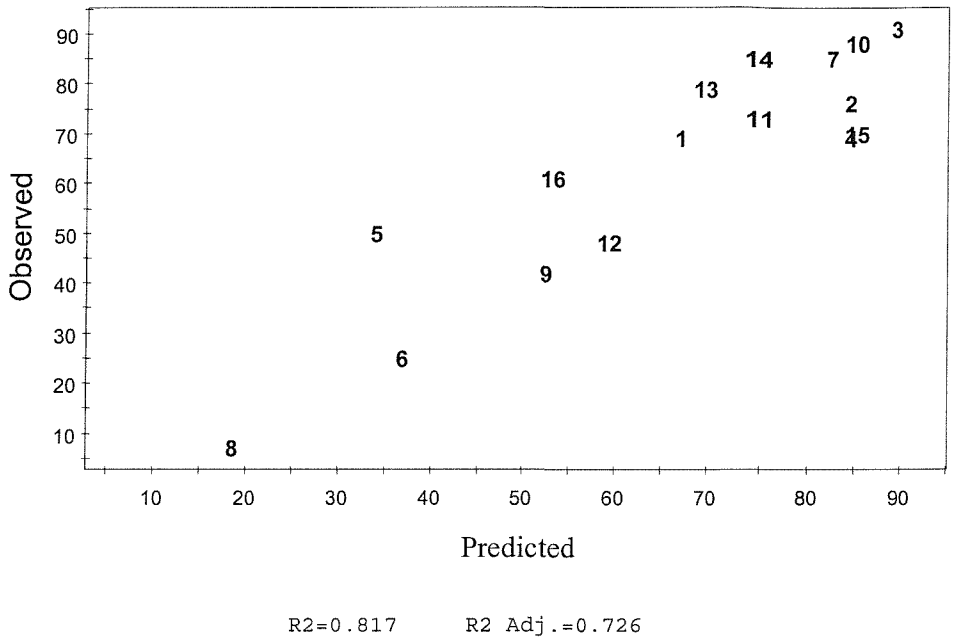


Figure 49 Observed vs Predicted Plot for Conversion for the Optimisation Experiment

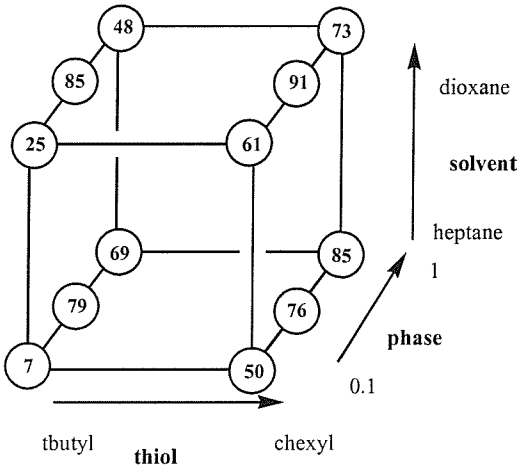


Figure 50 Results shown on the Corners of a Cube

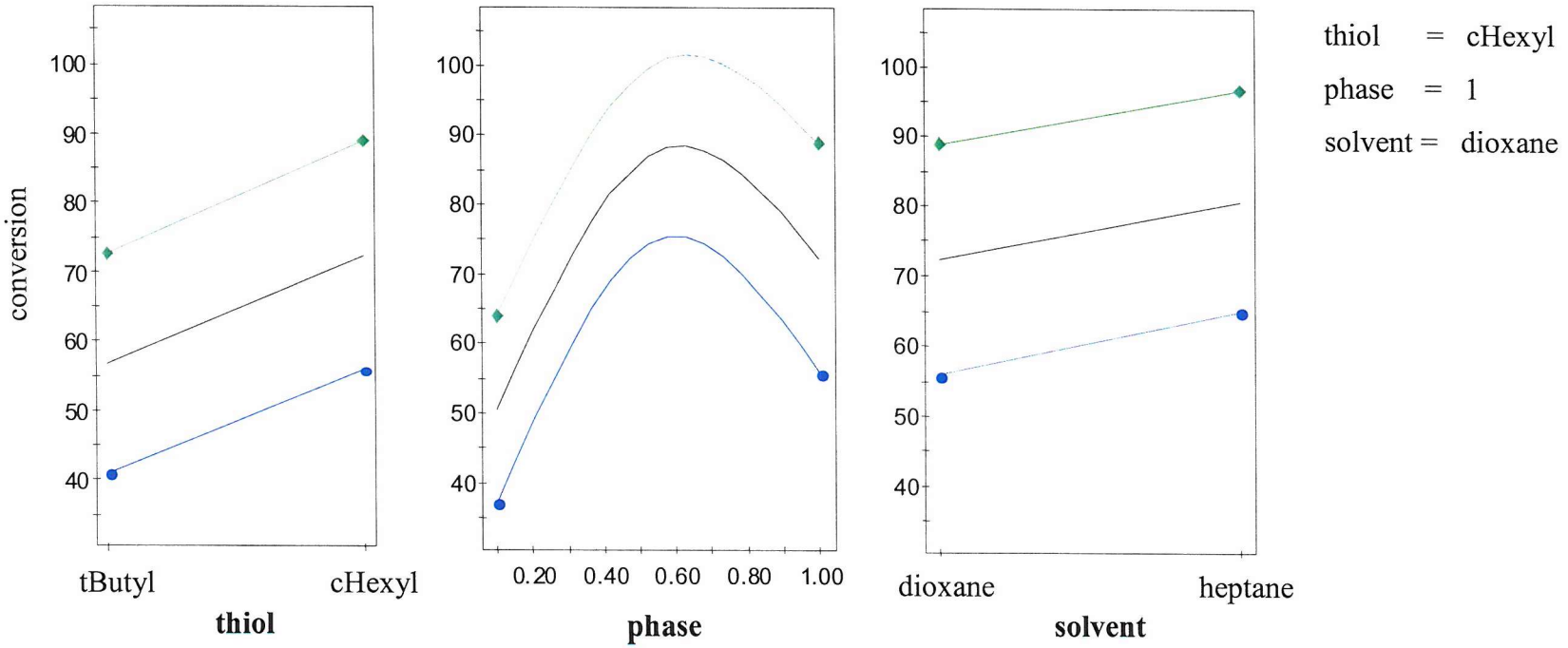


Figure 51 Curvature and Prediction Plots for the Optimisation Experiment with upper (green) and lower (blue) confidence levels of 95 %

The quadratic dependence was verified by the normal effects (Figure 52) and the coefficient overview plot (Figure 53) where phase transfer catalyst and the square of phase transfer catalyst were the most significant factors on conversion.

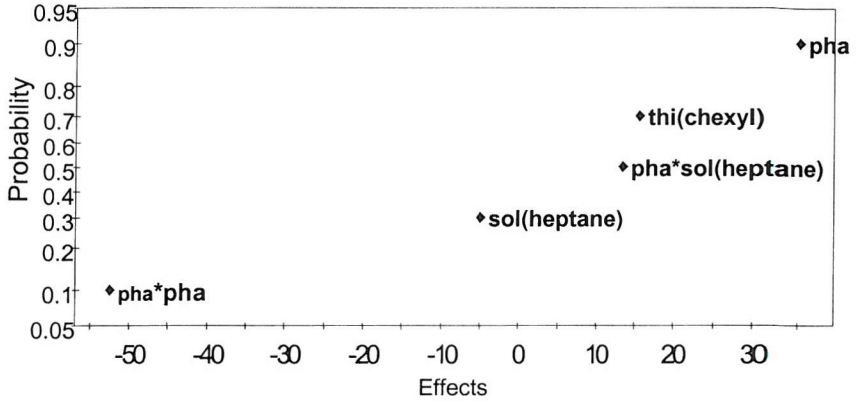


Figure 52 Normal Effect Plot for the Optimisation Experiment

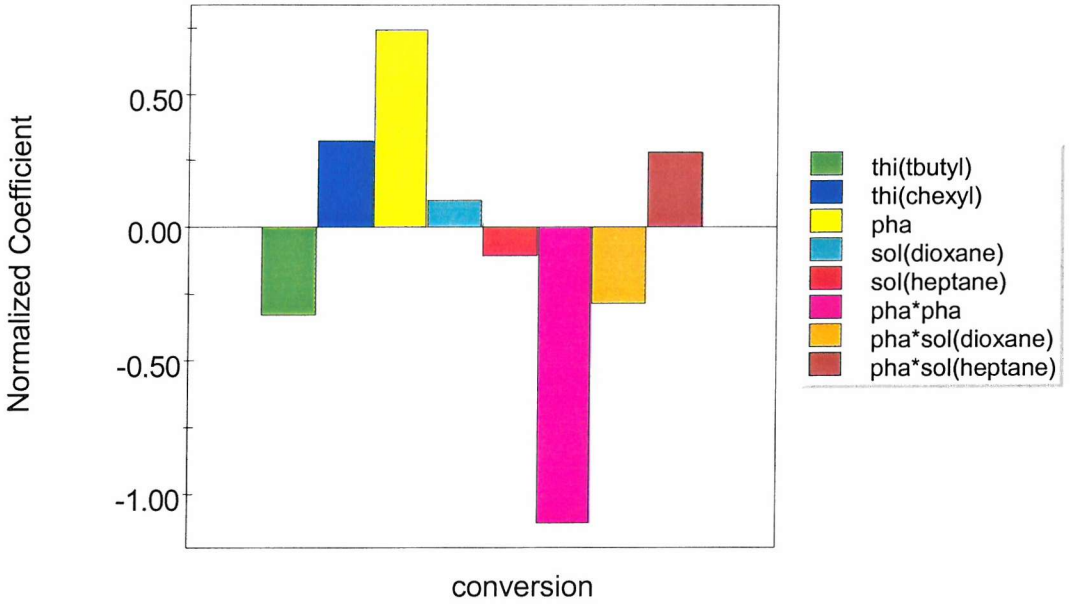


Figure 53 Normalized Coefficient Overview Plot for the Screening Experiment

From the Normalized Coefficients plot in Figure 53 it is also evident that the effect of the phase transfer catalyst depended on the solvent, in that increased levels caused conversion levels to increase with heptane being better than

dioxane. This is demonstrated clearly in Figure 54 where prediction plots show the effect of the phase transfer catalyst in the two solvents. In the first plot, for heptane, the conversion plateaus whereas in the second plot, for dioxane there is a significant decrease in conversion upon increased catalyst levels.

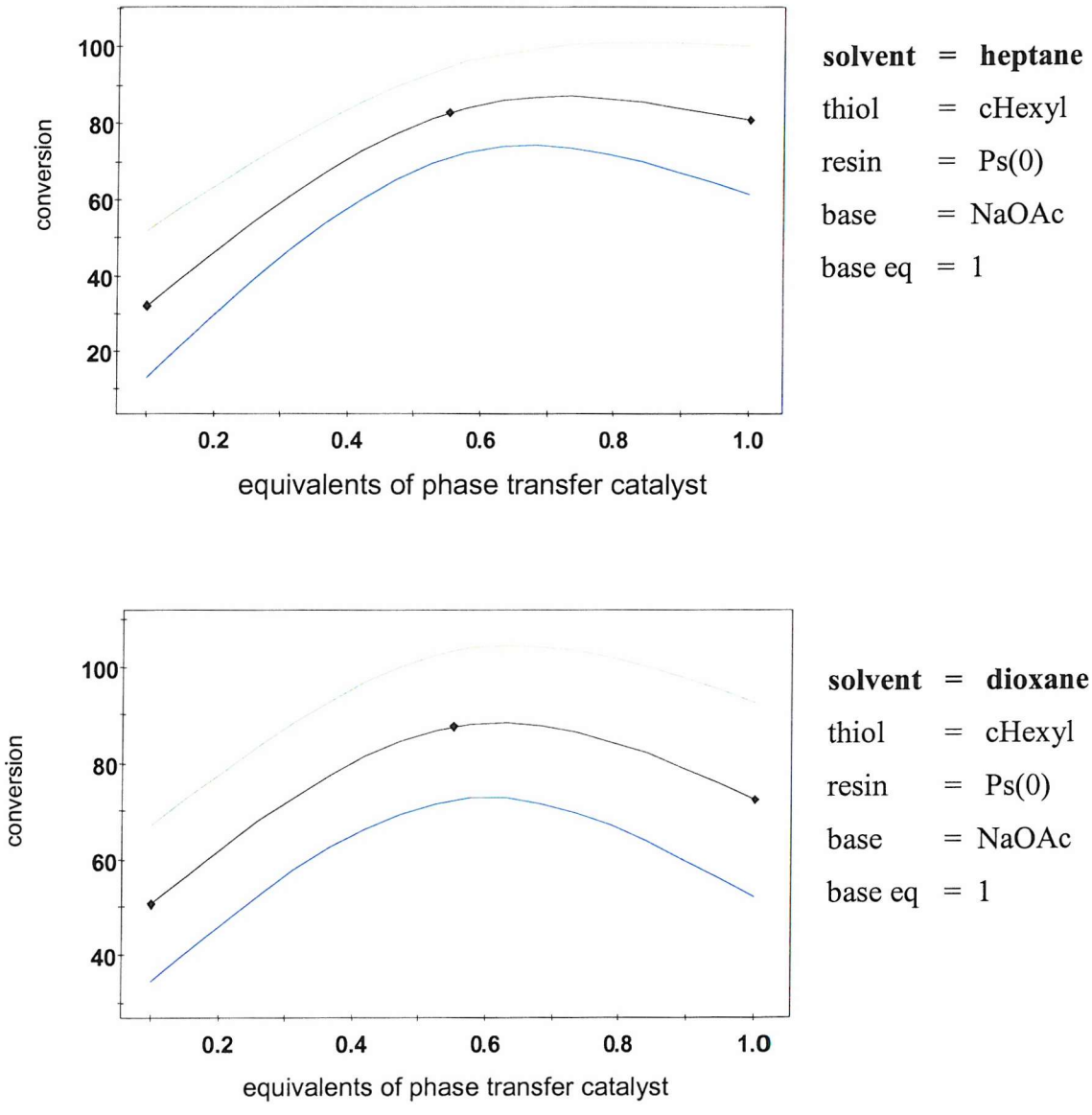


Figure 54 Prediction Plots for the Effect of the Phase Transfer Catalyst in Different Solvents

With such a high dependence upon solvent and the quadratic dependence whose maxima appears to be at about 0.6 equivalents it was postulated that the tetrabutylammonium bromide behaved as a true phase transfer catalyst, thereby

aiding dissolution of the insoluble base in the organic solvent. It may also have exerted some effect with regard to the active, catalytic, palladium species, although this was not determined.

5.3.5 Verification

From the optimisation experiment it was clear that the best conditions were with the cHexyl thiol pincer ligand in dioxane and MODDE predicted the optimum equivalents of phase transfer catalyst to be 0.65 and that under these conditions the predicted yield was 89 %.

Thus the reaction was repeated three times under the conditions shown in Table 34, to give yields of 87, 88 and 91 %, compared to the initial conversion of 34 %.

Factor	Level
Resin	PS-O
Thiol	cHexyl
Base	NaOAc,
Eq of Base	1
Eq of PTC	0.65
solvent	dioxane

Table 34 Verification, Optimised Conditions

5.4 Conclusion

Following an extensive DoE investigation, varying 6 factors at a total of 28 different levels, corresponding to 5760 different possibilities the Heck reaction of 4-bromo acetophenone with styrene was improved from 30 % conversion in a DMF/NEt_3 system with large observable leaching to 88 % with no observable leaching in a dioxane/NaOAc system. Although overall fairly insignificant the choice of resin was PS and the incorporation of the cHexyl thiol pincer group proved far superior to its phenyl counterpart. The reaction showed a quadratic

dependence concerning the level of tetrabutylammonium bromide, which suggests that the main function of this additive was as a true phase transfer catalyst. Consideration of the factors using this approach not only afforded substantially improved conditions but also led to an overall, higher understanding of this reaction.

6 Experimental

6.1 General Experimental

6.1.1 Instrumentation

^{1}H NMR were recorded at 300 MHz on a Bruker AC-300 FT, or at 400 MHz on a Bruker DPX-400 FT. Chemical shifts (δ_H) are quoted in ppm relative to TMS with the residual, non-deuterated solvent peak as the internal reference. **^{13}C NMR** were recorded at 75 or 100 MHz and where necessary Dept, COSY and HMQC 2 dimensional spectra were used to aid assignment. **Mass Spectrometry.** Electrospray spectra were recorded from acetonitrile solutions introduced into a Fisons VG platform through a Hewlett Packard 1050 HPLC system. High resolution ES mass spectra were recorded on an FT-ICR ES-MS Brucker Apex III. EI spectra were recorded using a ThermoQuest Trace MS gas chromatography configured for open access operation. **Infra red spectra** were recorded either neat or as a crushed resin sample on a Bio-Rad FTS-135 Fourier transform spectrometer equipped with a 'Golden Gate' attenuated total reflection (ATR) sample stage. Only selected absorbtions ($\nu_{max.}$) are quoted. **Melting points** were determined on an Electrothermal hot stage apparatus and are uncorrected. **HPLC.** Reverse phase HPLC analyses were performed on an Agilent Technologies 1100 modular HPLC equipped with a HP 220 automated fraction collector. Methods, gradients and columns used are mentioned in the appropriate section of the experimental section.

6.1.2 General Procedures

Reagents were purchased from Aldrich, Acros and Avocado.

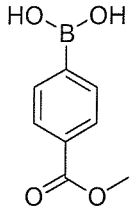
DCM was distilled from CaH_2 under N_2 **THF** was distilled from sodium/benzophenone under N_2 both immediately prior to use. All other solvents were used as received.

Solution phase reactions were monitored by TLC (Merck silica gel aluminium backed 60 F_{254} plates) and visualised by UV fluorescence (254 nm). Amide couplings were monitored on resin beads using the Kaiser ninhydrin test. Flash

chromatography was performed on a silica column using Keiselgel 60 230-400 mesh as supplied by Merck unless otherwise stated.

6.2 Experimental to Chapter 2

6.2.1 Synthesis of 4-(methoxycarbonyl)phenylboronic acid (45)[119]



4-carboxyphenylboronic acid (1 g, 6.0 mmol) was stirred in methanol (10 ml) at room temperature for 10 minutes after which time thionyl chloride (0.5 ml, 6.6 mmol) was added at 0°C. The reaction mixture was warmed to room temperature and stirred overnight after which time brine (20 ml) and 5% $NaHCO_3$ (20 ml) were added. The product was extracted with EtOAc (3 x 20 ml) and the combined organic phases were washed with 5% $NaHCO_3$ (25 ml), 1% $KHSO_4$ (25 ml), brine (25 ml) and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford the title compound as a white solid (974 mg, 5.4 mmol, 90 %).

^{1}H (400 MHz, $CDCl_3$) δ = 3.76 (3H, s, $OC\underline{H}_3$); 7.60 (2H, d, J = 8 Hz, $Ar^2C\underline{H}$); 7.80, (2H, d, J = 8 Hz, $Ar^3C\underline{H}$).

^{13}C (100 MHz, $CDCl_3$) δ = 52.6 ($O\underline{C}H_3$); 129.1 ($\underline{C}B(OH)_2$); 133.7 ($Ar^2\underline{C}H$); 134.0 ($Ar^3\underline{C}H$); 135.8 ($Ar\underline{C}CO_2Me$); 170.1 ($\underline{C}O_2Me$).

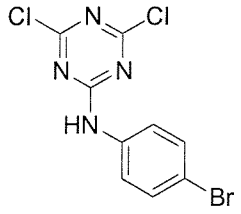
M/z (ES-): 293.0 $[M+TFA-H]^-$ 100%.

IR (ν_{max}/cm^{-1}): 1723 (s, C=O); 1340 (vs, B-O); 1264 (vs).

R_F: 0.4 (10% MeOH: $CHCl_3$).

m.p.: 236 – 238 °C (lit., 232 – 234 °C).[120]

6.2.2 Synthesis of (4-bromo-phenyl)-(4',6'-dichloro-[1',3',5']triazin-2'-yl)-amine (47)



A solution of cyanuric chloride (10.0 g, 5.4 mmol) in acetone (100 ml) was heated to 50 ° C and added to a stirred crushed ice/water mixture (200 ml). To the resulting fine white slurry 4-bromo-aniline (18.7g, 10.8 mmol) dissolved in an acetone/water mixture (1:1, 100 ml) was added drop wise with vigorous stirring. After stirring for 2 hours at 0 °C the resulting yellow suspension was filtered, washed with cold water (20 ml) and dried under vacuum to afford the title compound as a pale yellow solid (17.1 g, 53.9 mmol, 99 %). This compound was either used directly or stored under vacuum.

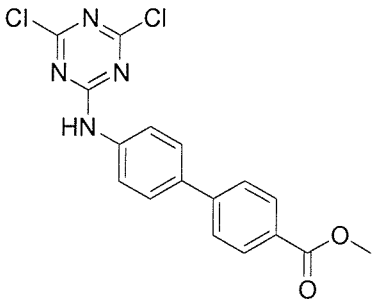
^{1}H (400 MHz, $CDCl_3$) δ = 7.45 (2H, d, *J* = 9 Hz, $Ar^2C\underline{H}$); 7.53 (2H, d, *J* = 9 Hz, $Ar^3C\underline{H}$); 7.60 (1H, s, N$\underline{H}$).

^{13}C (100 MHz, $CDCl_3$) δ = 117.7 ($Ar^4\underline{C}Br$); 121.7 ($Ar^2\underline{C}H$); 131.2 ($Ar^3\underline{C}H$); 133.7 ($Ar^1\underline{C}NH$); 162.9, 168.9, 170.3.

IR (ν_{max}/cm^{-1}): 1603 (s); 1543 (vs, aryl C-H).

m.p.: 184 – 186 °C.

6.2.3 Synthesis of methyl 4-(4'-(4'',6''-dichloro-[1'',3'',5'']-triazin-2''-yl)amino phenyl) benzoate (64)

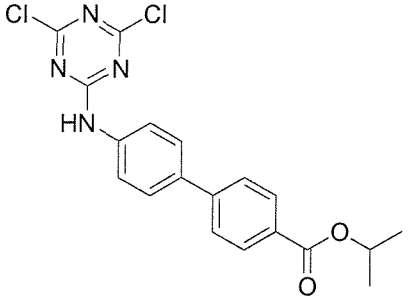


A solution of cyanuric chloride (2.44 g, 13.2 mmol) in acetone (100 ml) was heated to 50°C and added to a crushed ice-water mixture (200 ml). To the resulting fine white slurry, **63** (3 g, 13.2 mmol) and NEt_3 (2 ml, 14.4 mmol) dissolved in an acetone/water mixture (1:1, 100 ml) was added drop wise with vigorous stirring. After stirring for 2 hours at 0 °C the resulting white suspension was filtered, washed with cold water (25 ml) and dried under vacuum to afford the title compound as a white solid (4.84 g, 12.9 mmol, 97 %). This compound was either used directly or stored under vacuum.

^{1}H (300 MHz, $(CD_3)_2SO$) δ = 3.9 (2H, s $OC\underline{H}_3$); 7.8 (6H, m, $Ar^{3,2',3'}C\underline{H}$); 8.03 (2H, d, J = 8 Hz, $Ar^2C\underline{H}$); 11.3 (1H, s, $N\underline{H}$).
^{13}C (100 MHz, $(CD_3)_2SO$) δ = 52.6 ($O\underline{C}H_3$); 122.2 ($Ar^{3'}\underline{C}H$), 127.0 ($Ar^{2'}\underline{C}H$), 127.9 ($Ar^3\underline{C}H$); 128.7 ($Ar\underline{C}CO_2Me$); 130.3 ($Ar^2\underline{C}H$); 135.4 ($Ar^{1'}\underline{C}$); 137.7 ($Ar\underline{C}NH$); 144.3 ($Ar^4\underline{C}$); 164.2 (triazenyl$^{4''}\underline{C}Cl$); 166.5 (triazenyl$^{2''}\underline{C}NH$); 170.2 ($\underline{C}O_2Me$).

IR (ν_{max}/cm^{-1}): 1687 (s, C=O); 1542 (vs).
m.p.: 172 decomp.

6.2.4 Synthesis of isopropyl 4-(4'-(4'',6''-dichloro-[1'',3'',5'']-triazin-2''-yl)aminophenyl)benzoate (67)



The title compound was prepared as described for **64**, from **66** (4 g, 15.6 mmol), to afford **67** as a white solid (5.69 g, 14.2 mmol, 91 %).

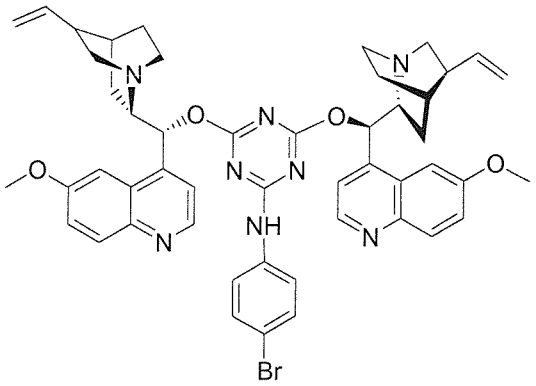
^{1}H (300 MHz, $CDCl_3$ + 1 drop $(CD_3)_2SO$) δ = 1.33 (6H, m, J = 6 Hz, $CH(C\underline{H}_3)_2$); 5.15 (1H, sept, J = 6Hz, $C\underline{H}(CH_3)_2$); 7.8 (6H, m, $Ar^{3,2',3'}C\underline{H}$); 8.01 (2H, d, J = 8 Hz, $Ar^2C\underline{H}$); 11.30 (1H, s, $N\underline{H}$).

^{13}**C** (75 MHz, $CDCl_3$ + 1 drop $(CD_3)_2SO$) δ = 21.5 ($\underline{C}H_3$); 67.9 ($\underline{C}H(CH_3)_2$); 121.3 ($Ar^{3'}\underline{C}H$), 126.1 ($Ar^{2'}\underline{C}H$), 127.2 ($Ar^{3}\underline{C}H$); 129.0 ($Ar\underline{C}CO_2Me$); 129.6 ($Ar^{2}\underline{C}H$); 135.8 ($Ar^{1'}\underline{C}$); 136.7 ($Ar\underline{C}NH$); 144.1 ($Ar^{4}\underline{C}$); 163.5 (triazenyl$^{4''}\underline{C}Cl$); 165.4 (triazenyl$^{2''}\underline{C}NH$).

IR (ν_{max}/cm^{-1}): 1686 (C=O); 1603 (m); 1542 (vs)

m.p.: 187 °C decompm

6.2.5 Synthesis of (*R*)-(4',6'-bis-((6'''-methoxy-quinolin-4'''-yl)-(5''-vinyl-1''-aza-bicyclo[2.2.2]oct-2''-yl)-methoxy)-[1',3',5'] triazin-2'-yl)-(4-bromo-phenyl)-amine (46)



Quinine (36.4 g, 54 mmol) and NaH (60% dispersion in mineral oil) (6.5 g, 0.17 mol) were dissolved in dry THF (250 ml) and stirred under a nitrogen atmosphere at 0 °C for 1 hour. After this time the solution was allowed to warm to room temperature and stirred overnight. **47** (17.1 g, 53.9 mmol) was dissolved in dry THF (200 ml) and added to the resultant green solution *via* canula. The reaction mixture was stirred at room temperature overnight and then refluxed for 5 hours. The reaction mixture was allowed to cool to room temperature and quenched by transfer onto saturated NH_4Cl (100 ml). The phases were separated, the product extracted into ethyl acetate (3 x 200 ml) and the solvent removed in *vacuo* to afford a yellow solid which was chromatographed in ethyl acetate on base activated alumina to give the title compound as a white solid (47.3 g, 53 mmol, 98 %).

^{1}**H** (400 MHz, DMSO, 373K) δ = 1.8 (6H, m, $^{3''}$C$\underline{H}_2$ (2) and $^{8''}$C$\underline{H}_2$ (4)); 1.9 (4H, m, $^{3''}$C$\underline{H}$, (2) and $^{4'''}$C$\underline{H}$); 2.3 (2H, m, $^{5''}$C$\underline{H}$); 2.7 (4H, m, $^{6''}$C$\underline{H}_2$ (2) and $^{7''}$CH$_2$ (2)); 3.1 (4H, m, $^{6''}$C$\underline{H}_2$ (2) and $^{7''}$CH$_2$ (2)); 3.5 (2H, m, $^{2''}$C$\underline{H}$); 4.0 (6H, s, OC$\underline{H}_3$); 5.1 (4H, m, vinyl C$\underline{H}_2$); 6.0 (2H, m, vinyl C$\underline{H}$); 6.6 (2H, d, J = 7 Hz, OC$\underline{H}$); 7.3 (2H, d, J = 9 Hz, Ar^{3}C$\underline{H}$); 7.4 (4H, m, Ar^{2}C$\underline{H}$ and $^{3'''}$C$\underline{H}$); 7.5 (2H, dd, J = 3 and 9 Hz, Ar$^{7'''}$C$\underline{H}$); 7.6 (2H, d, J = 3 Hz, Ar$^{5'''}$C$\underline{H}$); 8.1 (2H, d, J = 9 Hz, Ar$^{8'''}$C$\underline{H}$); 8.7 (2H, d, J = 4 Hz, Ar$^{2'''}$C$\underline{H}$); 9.9 (1H, s, N$\underline{H}$).

^{13}**C** (100 MHz, DMSO, 373K) δ = 24.6 ($^{3''}$C$\underline{H}_2$); 28.3 ($^{4''}$C$\underline{H}$); 28.4 ($^{8''}$C$\underline{H}_2$); 40.2 ($^{5''}$C$\underline{H}$); 43.1 ($^{7''}$C$\underline{H}_2$); 56.6 (OC$\underline{H}_3$); 57.2 ($^{6''}$C$\underline{H}_2$); 60.5 ($^{2''}$C$\underline{H}$); 78.2 (OC$\underline{H}$); 104.1 (Ar$^{5'''}$C$\underline{H}$); 115.0 (vinyl C$\underline{H}_2$); 119.8 (Ar$^{3'''}$C$\underline{H}$); 121.9 (Ar$^{7'''}$C$\underline{H}$); 123.9 (Ar^{2}C$\underline{H}$); 127.6 (Ar$^{4a'''}$C); 132.0 (Ar^{3}C$\underline{H}$); 132.5 (Ar$^{8'''}$C$\underline{H}$); 138.5 (ArCNH); 143.5 (vinyl C$\underline{H}$); 144.6 (Ar$^{4a'}$C); 145.3 (ArCOMe); 148.3 (Ar$^{2'''}$C$\underline{H}$); 158.5 (Ar$^{8a'}$C); 167.0 (triazenyl CNH); 172.3 (triazenyl CO).

M/z (ES+): 895.2 [^{78}Br M+H]$^{+}$ 70%, 897.2 [^{80}Br M+H]$^{+}$ 70%

HRMS: calcd for ($C_{49}H_{52}BrN_8O_4$) [^{78}Br M+H]$^{+}$ 895.3295, found 895.3289.

IR (ν_{max}/cm^{-1}): 1706 (w); 1568 (s); 1413 (m); 1351 (s).

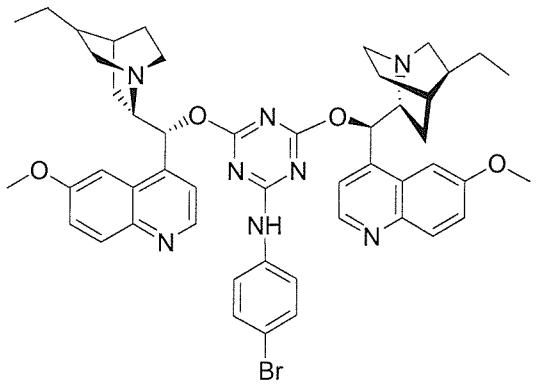
R_F: 0.5 (10% MeOH, 1 % NEt_3, $CHCl_3$).

Anal: calcd for ($C_{49}H_{51}BrN_8O_4$): C, 65.69; H, 5.74; N, 12.50 found C, 64.94; H, 6.07; N, 11.81, (Sharpless has previously observed that the *bis* alkaloid ligands crystallise with solvent molecules).[53]

m.p.: 208 – 210 °C.

$[\alpha]_D^{22}$: 219° (c = 0.5, $CHCl_3$)

6.2.6 Synthesis of (*R*)-(4',6'-bis-((6'''-methoxy-quinolin-4'''-yl)-(5''-ethyl-1''-aza-bicyclo[2.2.2]oct-2''-yl)-methoxy)-[1',3',5'] triazin-2'-yl)-(4-bromo-phenyl)-amine (88)



The title compound was prepared as described for compound **46**; from **47** (800 mg, 2.5 mmol) and hydroquinine (1.73 g, 5.3 mmol) to afford the title compound as a white solid (1.03 g, 1.1 mmol) 46 %).

^{1}H (400 MHz, DMSO, 373K) δ = 0.65 (6H, t, J = 7 Hz, $C\underline{H}_3CH_2$); 1.17 (8H, m, $CH_3C\underline{H}_2$, $^{5''}C\underline{H}$ and $^{8''}C\underline{H}_2$ (2)); 1.35 (2H, m, $^{3'''}C\underline{H}_2$ (2)); 1.42 (2H, M, $^{8'''}C\underline{H}_2$ (2)); 1.56 (4H, m, $^{3'''}C\underline{H}_2$ (2) and $^{4'''}C\underline{H}$); 2.08 (2H, m, $^{6''}C\underline{H}_2$ (2)) 2.37 (2H, m, $^{7'''}C\underline{H}_2$ (2)); 2.76 (2H, m, $^{6''}C\underline{H}_2$ (2)); 2.85 (2H, m, $^{7'''}C\underline{H}_2$ (2)) 3.22 ($^{2'''}C\underline{H}$); 3.76 (6H, s, $OC\underline{H}_3$); 6.47 (2H, d, *J* = 6 Hz, $OC\underline{H}$); 7.03 (2H, d, *J* = 9 Hz, $Ar^3C\underline{H}$); 7.16 (4H, m, $Ar^2C\underline{H}$ and $^{3'''}C\underline{H}$); 7.31 (2H, dd, *J* = 9 and 1 Hz, $Ar^{7'''}C\underline{H}$); 7.41 (2H, bs, $Ar^{5'''}C\underline{H}$); 7.85 (2H, d, *J* = 9 Hz, $Ar^{8'''}C\underline{H}$); 8.50 (2H, d, *J* = 4 Hz, $Ar^{2'''}C\underline{H}$); 9.74 (1H, s, N$\underline{H}$).

^{13}C (100 MHz, DMSO, 373K) δ = 12.2 ($C\underline{H}_3CH_2$); 23.8 ($^{3''}\underline{C}H_2$); 25.6 ($^{4''}\underline{C}H_2$); 27.4 ($CH_3C\underline{H}_2$); 28.5 ($^{8''}\underline{C}H_2$); 37.6 ($^{5''}\underline{C}H$); 42.6 ($^{7''}\underline{C}H_2$); 56.0 ($O\underline{C}H_3$); 58.2 ($^{6''}\underline{C}H_2$); 59.8 ($^{2''}\underline{C}H$); 77.6 ($O\underline{C}H$); 103.4 ($Ar^{5'''}\underline{C}H$); 115.8 (C-Br); 119.3 ($Ar^{3'''}\underline{C}H$); 121.4 ($Ar^{7'''}\underline{C}H$); 123.2 ($Ar^2\underline{C}H$); 127.0 ($Ar^{4a'''}\underline{C}$); 131.5 ($Ar^3\underline{C}H$); 131.9 ($Ar^{8'''}\underline{C}H$); 138.0 ($Ar\underline{C}NH$); 144.1 ($Ar^{4a'}\underline{C}$); 144.7 ($Ar\underline{C}OMe$); 147.8 ($Ar^{2'''}\underline{C}H$); 158.0 ($Ar^{8a'}\underline{C}$); 166.6 (triazenyl $\underline{C}NH$); 171.7 (triazenyl $\underline{C}O$).

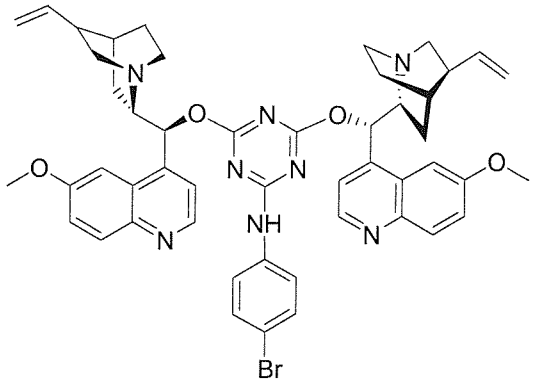
M/z (ES+): 899.0 [^{78}Br M+H]$^+$ 70%, 901.1 [^{80}Br M+H]$^+$ 70%

R_F: 0.5 (10% MeOH, 1 % NEt_3, $CHCl_3$).

m.p.: 213 – 215 °C

$[\alpha]_D^{22}$: 223° (c = 0.5, $CHCl_3$)

6.2.7 Synthesis of (*S*)-(4',6'-bis-((6'''-methoxy-quinolin-4'''-yl)-(5''-vinyl-1''-aza-bicyclo[2.2.2]oct-2''-yl)-methoxy)-[1',3',5'] triazin-2'-yl)-(4-bromo-phenyl)-amine (89)



The title compound was prepared as described for compound **46**; from **47** (800 mg, 2.5 mmol) and quinidine (1.71 g, 5.3 mmol) to afford the title compound as a white solid (1.22 g, 1.4 mmol) 54 %).

^{1}H (400 MHz, DMSO, 373K) δ = 1.37 (4H, m, $CH_3C\underline{H}_2$, $^{3''}C\underline{H}_2$ (2), $^{8''}C\underline{H}_2$); 1.57 (2H, m, $^{4'''}C\underline{H}$); 1.72 (2H, m, $^{3''}C\underline{H}_2$ (2)); 2.08 (2H, m, $^{5'}C\underline{H}$); 2.36 - 2.37 (8H, m, $^{6''}C\underline{H}_2$ and $^{7'''}C\underline{H}_2$) 3.21 ($^{2'''}C\underline{H}$); 3.75 (6H, s, $OC\underline{H}_3$); 4.90 (4H, m, vinyl $C\underline{H}_2$); 4.86 (2H, m, vinyl C<u>H</u>); 6.51 (2H, d, *J* = 7 Hz, OC<u>H</u>); 7.02 (2H, d, *J* = 5 Hz, $Ar^3C\underline{H}$); 7.13 (4H, m, $Ar^2C\underline{H}$ and $^{3'''}C\underline{H}$); 7.31 (2H, dd, *J* = 9 and 3 Hz, $Ar^{7'''}C\underline{H}$); 7.40 (2H, bs, $Ar^{5'''}C\underline{H}$); 7.84 (2H, d, *J* = 9 Hz, $Ar^{8'''}C\underline{H}$); 8.50 (2H, d, *J* = 5 Hz, $Ar^{2'''}C\underline{H}$); 9.72 (1H, s, N<u>H</u>).

^{13}C (100 MHz, DMSO, 373K) δ = 23.5 ($^{3''}\underline{C}H_2$); 26.5 ($^{8''}\underline{C}H_2$); 28.2 ($^{4''}\underline{C}H$); 39.8 ($^{5''}\underline{C}H$); 49.0 ($^{7''}\underline{C}H_2$); 49.7 ($^{6''}\underline{C}H_2$); 56.0 ($O\underline{C}H_3$); 59.7 ($^{2''}\underline{C}H$); 77.4 (O<u>C</u>H); 103.5 ($Ar^{5'''}\underline{C}H$); 114.9 (vinyl $\underline{C}H_2$); 115.8 (C-Br); 119.3 ($Ar^{3'''}\underline{C}H$); 121.4 ($Ar^{7'''}\underline{C}H$); 123.3 ($Ar^2\underline{C}H$); 127.0 ($Ar^{4a'''}\underline{C}$); 131.5 ($Ar^3\underline{C}H$); 131.9 ($Ar^{8'''}\underline{C}H$); 137.9 (Ar<u>C</u>NH); 141.2 (vinyl <u>C</u>H); 144.1 ($Ar^{4a'}\underline{C}$); 144.7

(ArCOMe); 147.8 ($Ar^{2'''}$CH); 158.0 ($Ar^{8a'}$C); 166.5 (triazenyl CNH); 171.8 (triazenyl CO).

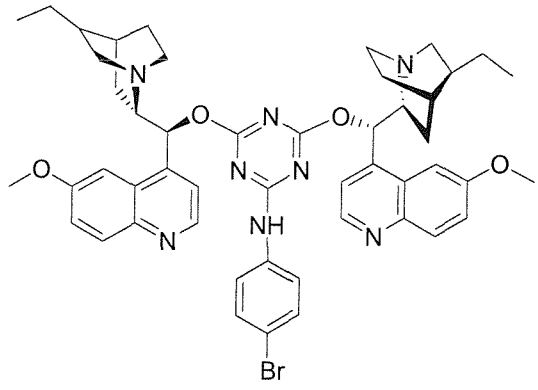
M/z (ES+): 895.0 [^{78}Br M+H]$^+$ 80 %, 896.8 [^{80}Br M+H]$^+$ 100%

R_F: 0.5 (10% MeOH, 1 % NEt_3, $CHCl_3$).

m.p.: 210 – 212 °C

$[\alpha]_D^{22}$: -114° (c = 0.5, $CHCl_3$)

6.2.8 Synthesis of (*S*)-(4',6'-bis-((6'''-methoxy-quinolin-4'''-yl)-(5''-ethyl-1''-aza-bicyclo[2.2.2]oct-2''-yl)-methoxy)-[1',3',5'] triazin-2'-yl)-(4-bromo-phenyl)-amine (90)



The title compound was prepared as described for compound **46,** from **47** (800 mg, 2.5 mmol) and hydroquinidine (1.73 g, 5.3 mmol) to afford the title compound as a white solid (1.37 g, 1.5 mmol) 61 %).

^{1}H (400 MHz, DMSO, 373K) δ = 0.74 (6H, t, J = 7 Hz, CH_3CH_2); 1.29 (10H, m, CH_3CH_2, $^{3''}CH_2$ (2), $^{5''}$CH and $^{8''}CH_2$ (2)); 1.43(2H, m, $^{8'''}CH_2$); 1.55 (2H, M, $^{4'''}$CH); 1.67 (2H, m, $^{3''}CH_2$ (2)); 2.4 - 2.7 (8H, m, $^{6''}CH_2$ and $^{7'''}CH_2$) 3.20 ($^{2'''}$CH); 3.77 (6H, s, OCH_3); 6.51 (2H, d, *J* = 7 Hz, OCH); 7.05 (2H, d, *J* = 9 Hz, Ar^3CH); 7.17 (4H, m, Ar^2CH and $^{3'''}$CH); 7.34 (2H, dd, *J* = 9 and 3 Hz, $Ar^{7'''}$CH); 7.42 (2H, bs, $Ar^{5'''}$CH); 7.86 (2H, d, *J* = 9 Hz, $Ar^{8'''}$CH); 8.52 (2H, d, *J* = 5 Hz, $Ar^{2'''}$CH); 9.74 (1H, s, NH).

^{13}**C** (100 MHz, DMSO, 373K) δ = 12.2 ($C\underline{H}_3CH_2$); 23.4 ($^{3''}\underline{C}H_2$); 24.3 ($CH_3C\underline{H}_2$); 26.2 ($^{4''}\underline{C}H_2$); 27.4 ($^{8''}\underline{C}H_2$); 37.5 ($^{5''}\underline{C}H$); 49.8 ($^{7''}\underline{C}H_2$); 50.7 ($^{6''}\underline{C}H_2$); 55.9 ($O\underline{C}H_3$); 60.0 ($^{2''}\underline{C}H$); 77.4 ($O\underline{C}H$); 103.6 ($Ar^{5'''}\underline{C}H$); 115.8 (C-Br); 119.3 ($Ar^{3'''}\underline{C}H$); 121.4 ($Ar^{7'''}\underline{C}H$); 123.3 ($Ar^{2}\underline{C}H$); 127.1 ($Ar^{4a'''}\underline{C}$); 131.5 ($Ar^{3}\underline{C}H$); 131.9 ($Ar^{8'''}\underline{C}H$); 138.0 (Ar<u>C</u>NH); 144.3 ($Ar^{4a'}\underline{C}$); 144.7 (Ar<u>C</u>OMe); 147.8 ($Ar^{2'''}\underline{C}H$); 157.8 ($Ar^{8a'}\underline{C}$); 166.5 (triazenyl <u>C</u>NH); 171.8 (triazenyl <u>C</u>O).

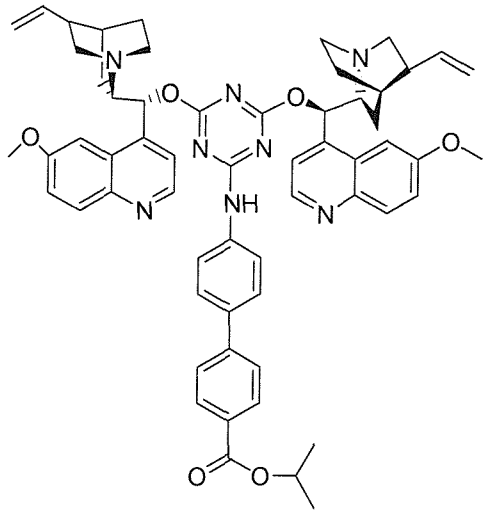
M/z (ES+): 899.0 [^{78}Br M+H]$^+$ 75 %, 901.0 [^{80}Br M+H]$^+$ 100%

R_F: 0.5 (10% MeOH, 1 % NEt_3, $CHCl_3$).

m.p.: 212 – 214 °C

$[\alpha]_D^{22}$: -118° (c = 0.5, $CHCl_3$)

6.2.9 Synthesis of isopropyl-(4-(4'-(4'',6''-bis-((6''''-methoxy-quinolin-4''''-yl)-(5'''-vinyl-1'''-aza-bicyclo [2.2.2]oct-2'''-yl)-methoxy)-[1'',3'',5'']triazin-2''-yl)aminophenyl)benzoate (68)



The title compound was prepared as described for **46**, from **67** (5.5 g, 13.7 mmol), quinine (9.3 g, 28.7 mmol) and NaH (60% dispersion in mineral oil, 1.1 g, 28.7 mmol) to afford the title compound as a yellow solid.

^{1}**H** (400 MHz, $(CD_3)_2SO$, 353K): δ 1.21 (6H, d, J = 6 Hz, $CH(C\underline{H}_3)_3$); 1.33 (2H, m, $^{8'''}C\underline{H}_2$ (2)); 1.46 (4H, m, $^{3'''}C\underline{H}_2$ (2) and $^{8'''}C\underline{H}_2$ (2)); 1.63 (4H, m, $^{3'''}C\underline{H}_2$ and $^{4,''''}C\underline{H}$); 2.10 (2H, m, $^{5'''}C\underline{H}$); 2.40 (4H, m, $^{6'''}C\underline{H}_2$ (2) and $^{7'''}C\underline{H}_2$); 2.81

(2H, m, $^{6'''}C\underline{H}_2$ (2)); 3.00 (2H, m, $^{7'''}C\underline{H}_2$); 3.26 (2H, m, $^{2'''}C\underline{H}$); 3.74 (6H, s, $OC\underline{H}_3$); 4.82 (4H, m, vinyl $C\underline{H}_2$); 5.05 (1H, sept, J = 6 Hz, $C\underline{H}(CH_3)_3$); 5.72 (2H, m, vinyl C$\underline{H}$) 6.53 (2H, d, J = 7 Hz OC$\underline{H}$); 7.16 (2H, bs, $^{3''''}C\underline{H}$); 7.22 (2H, d, J = 9 Hz, $Ar^{2'}C\underline{H}$); 7.31 (4H, 2d, m, $Ar^{7''''}C\underline{H}$ and $Ar^{3'}C\underline{H}$); 7.44 (2H, s, $^{5''''}C\underline{H}$); 7.54 (2H, d, J = 8 Hz, $Ar^{3}C\underline{H}$); 7.85 (2H, d, J = 9 Hz, $Ar^{8''''}C\underline{H}$); 7.88 (2H, d, J = 8Hz, $Ar^{2}C\underline{H}$); 8.51 (2H, d, J = 5Hz, $Ar^{2''''}C\underline{H}$); 9.79 (1H, s, N$\underline{H}$).

^{13}C (100 MHz, $(CD_3)_2SO$, 353K): δ 21.9 ($CH(\underline{C}H_3)_3$); 23.7 ($^{3'''}\underline{C}H_2$); 27.6 ($^{4'''}\underline{C}H$); 28.0 ($^{8'''}\underline{C}H_2$); 39.5 ($^{5'''}\underline{C}H$); 42.5 ($^{7'''}\underline{C}H_2$); 56.4 ($O\underline{C}H_3$); 59.8 ($^{6'''}\underline{C}H_2$); 68.4 ($\underline{C}H(CH_3)_3$); 77.4 (O$\underline{C}$H); 103.3 ($Ar^{5''''}\underline{C}H$); 114.4 (vinyl $\underline{C}H_2$); 119.2 ($Ar^{3''''}\underline{C}H$); 121.4 ($Ar^{7''''}\underline{C}H$ and $Ar^{3'}\underline{C}H$); 126.5, 127.0, 127.1 ($Ar^{3}\underline{C}H$, $Ar^{2'}\underline{C}H$ and $Ar^{4a}\underline{C}$); 129.4 ($Ar^{8''''}\underline{C}H$); 129.9 (Ar$\underline{C}CO_2{}^{i}$Pr); 130.1 ($Ar^{2}\underline{C}H$); 134.2 ($Ar^{1'}\underline{C}$); 138.8 (Ar$\underline{C}$NH); 142.4 (vinyl $\underline{C}$H); 143.9 ($Ar^{4}\underline{C}$); 144.3 ($Ar^{4a''''}\underline{C}$); 144.6 (Ar$\underline{C}$OMe); 147.7 ($Ar^{2''''}\underline{C}H$); 157.9 ($Ar^{8a''''}\underline{C}$); 165.5 ($\underline{C}O_2{}^{i}$Pr); 166.5 (triazine $\underline{C}$NH); 171.6 (triazine $\underline{C}$O).

M/z (ES+): 979.6 $[M+H]^+$ (100 %)

HRMS: calcd for ($C_{59}H_{63}N_8O_6$) $[M+H]^+$ 979.4871, found 979.4844

IR (ν_{max}/cm^{-1}): 1708 (C=O)

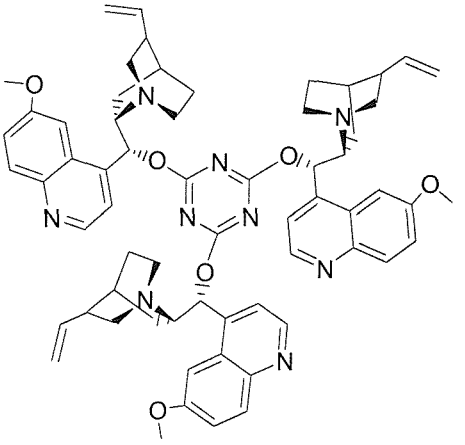
Anal: calcd for ($C_{59}H_{26}N_8O_6$): C, 72.37; H, 6.38; N, 11.44 found C, 70.93; H, 6.55; N, 11.08, (Sharpless has previously observed that the *bis* alkaloid ligands crystallise with solvent molecules).[53]

R_F: 0.5 (10% MeOH, 1 % NEt_3, $CHCl_3$).

m.p.: 245 °C (decomp).

$[\alpha]_D^{22}$: +131° (c = 0.5, $CHCl_3$).

6.2.10 Synthesis of (*R*)-(2,4,6-tris(6''-methoxy-quinolin-4''-yl)-(5'-vinyl-1'-aza-bicyclo[2.2.2]oct-2'-yl)-methoxy)-[1,3,5] triazine (91)



Quinine (600 mg, 1.8 mmol) and NaH (60% dispersion in mineral oil) (86 mg, 2.25 mmol mol) were dissolved in dry THF (50 ml) and stirred under a nitrogen atmosphere at room temperature for 1 hour. Cyanuric chloride (83 mg, 0.45 mmol) was dissolved in THF (10 ml) and added to the resulting white suspension in one portion and the reaction mixture refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature and quenched by transfer onto saturated NH_4Cl (20 ml). The phases were separated, the product extracted into ethyl acetate (3 x 20 ml) and the solvent removed in *vacuo* to afford a yellow solid which was chromatographed in ethyl acetate on base activated alumina to afford the title compound as a white solid (593 mg, 0.56 mmol, 66 %).

^{1}H (100 MHz, $CDCl_3$) δ = 1.36-1.67 (15H, m, $^{3'}C\underline{H}_2$, $^{4''}CH$ and $^{8'}CH_2$); 2.1 (3H, m, $^{5'}C\underline{H}$); 2.45 (6H, m, $^{6'}C\underline{H}_2$ (2) and $^{7'}CH_2$ (2)); 2.71 (3H, m, $^{6'}C\underline{H}_2$ (2)) 2.91 (3H, m, $^{7'}CH_2$ (2)); 3.22 (3H, m, $^{2'}C\underline{H}$); 3.78 (9H, s, $OC\underline{H}_3$); 4.86 (6H, m, vinyl $C\underline{H}_2$); 5.63 (3H, m, vinyl $C\underline{H}$); 6.24 (2H, d, J = 7 Hz, $OC\underline{H}$); 7.03 (3H, m, $^{3''}C\underline{H}$); 7.30 (6H, m, Ar $^{5''}C\underline{H}$ and $Ar^{7''}C\underline{H}$); 7.94 (3H, m, $Ar^{8''}C\underline{H}$); 8.56 (3H, m, $Ar^{2''}C\underline{H}$).

^{13}C (100 MHz, $CDCl_3$) δ = 23.7 ($^{3'}\underline{C}H_2$); 27.8 ($^{8'}\underline{C}H_2$); 27.9 ($^{4'}\underline{C}H$); 39.9 ($^{5'}\underline{C}H$); 42.9 ($^{7'}\underline{C}H_2$); 56.1 ($O\underline{C}H_3$); 57.0 ($^{6'}\underline{C}H_2$); 59.4 ($^{2'}\underline{C}H$); 79.7 ($O\underline{C}H$); 102.2

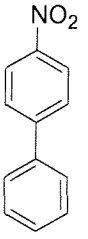
($Ar^{5''}\underline{C}H$); 114.9 (vinyl $\underline{C}H_2$); 119.9 ($Ar^{3''}\underline{C}H$); 122.1 ($Ar^{7''}\underline{C}H$); 127.6 ($Ar^{4a''}\underline{C}$); 132.3 ($Ar^{8''}\underline{C}H$); 142.0 (vinyl $\underline{C}H$); 143.1 ($Ar^{4a'}\underline{C}$); 145.1 (Ar$\underline{C}$OMe); 147.8 ($Ar^{2''}\underline{C}H$); 158.3 ($Ar^{8a'}\underline{C}$); 172.9 (triazenyl $\underline{C}O$).

M/z (ES+): 582.0 $[(M+TFA+H)/2]^+$ (100 %)

R_F: 0.5 (10% MeOH, 1 % NEt_3, $CHCl_3$).

m.p.: 197 °C

6.2.11 Synthesis of 1-nitro-4-phenylbenzene (56)[120]



p-iodo nitrobenzene (214 mg, 1.23 mmol), phenyl boronic acid (150 mg, 1.2 mmol), $Pd_2(dba)_3$ (17 mg, 0.02 mmol), $(PPh_3)_4$ (10 mg, 0.04 mmol) and potassium fluoride (214 mg, 3.6 mmol) were refluxed in freshly distilled dioxane (15 ml) for 48 hours under a nitrogen atmosphere. The resultant brown solution was filtered through celite and the solvent removed *in vacuo*. Ether and water were added to the residue, the phases separated and the aqueous phase extracted with ether (3 x 25 ml). The combined organic extracts were washed with water (25 ml), brine (25 ml), and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* followed by column chromatography using EtOAc/hexane as eluent gave the title compound as a yellow solid (180 mg, 0.9 mmol, 74 %).

^{1}H (400 MHz, $(CD_3)_2CO$) δ = 7.48 (1H, d, *J* = 8 Hz, $Ar^{4'}C\underline{H}$); 7.52 (2H, t, *J* = 8 Hz, $Ar^{3'}C\underline{H}$); 7.77, (2H, d, *J* = 8 Hz, $Ar^{2'}C\underline{H}$); 7.94 (2H, d, *J* = 9 Hz, $Ar^{3}C\underline{H}$); 8.32 (2H, d, J = 9 Hz, $Ar^{2}C\underline{H}$).

^{13}C (100 MHz, $(CD_3)_2CO$) δ = 123.5 ($Ar^{2}\underline{C}H$); 126.8 ($Ar^{2'}\underline{C}H$); 127.3 ($Ar^{3}\underline{C}H$) 128.4 ($Ar^{4'}\underline{C}H$); 128.7 ($Ar^{3'}\underline{C}H$); 138.1 ($Ar^{1'}\underline{C}$); 146.7 and 146.9 ($Ar^{1}\underline{C}$ and $Ar^{4}\underline{C}$).

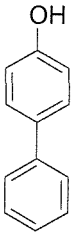
M/z (CIMS): 199.2 ([$M^{+\cdot}$], 51 %); 169.2, (100 %); 152.2, (97 %).

IR (ν_{max}/cm^{-1}): 1593 (m, aryl C-H);1509 and 1338 (s, NO_2).

R_F: 0.2 (10% EtOAc: hexane).

m.p.: 112 - 114 °C (lit., 112 – 114 °C).[121]

6.2.12 Synthesis of 4-phenylphenol (57)[121]



The title compound was prepared according to the procedure described for **56** from *p*-bromo phenol (212 mg, 1.23 mmol). The crude product was purified by column chromatography (10 % EtOAc/hexane) and recrystallised from hexane/ ethyl acetate to afford the title compound as a white solid (130 mg, 0.9 mmol, 62 %).

^{1}H (400 MHz, $(CD_3)_2CO$) δ = 6.93 (2H, d, *J* = 9 Hz, $Ar^2C\underline{H}$); 7.27 (1H; t, *J* = 8 Hz, $Ar^{4'}C\underline{H}$); 7.40 (2H, t, *J* = 8 Hz, $Ar^{3'}C\underline{H}$); 7.50 (2H, d, *J* = 9 Hz, $Ar^3C\underline{H}$); 7.57 (2H, d, *J* = 8 Hz , $Ar^{2'}C\underline{H}$)

13C (100 MHz, $(CD_3)_2CO$) δ = 116.9 ($Ar^2\underline{C}H$); 127.5 ($Ar^{2'}\underline{C}H$); 127.6 ($Ar^{4'}\underline{C}H$); 129.2 ($Ar^3\underline{C}$); 129.9 ($Ar^{3'}\underline{C}H$); 133.6 ($Ar^1\underline{C}OH$); 142.2 ($Ar^{1'}\underline{C}$); 158.4 (Ar^4C).

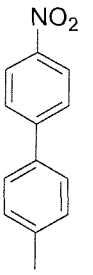
M/z (CIMS): 170.0 ([$M^{+\cdot}$] 100%); 141.1 (62 %); 139.1 (65 %).

IR (ν_{max}/cm^{-1}): 3387.8 (b,OH); 3038; 1596 (m, aryl C-H).

R_F: 0.3 (10% EtOAc: hexane).

m.p.: 167 - 168 °C (hexane/EtOAc) (lit., 165 °C).[122]

6.2.13 Synthesis of 4-(4'-methylphenyl)-1-nitrobenzene (60)[122]



The title compound was prepared according to the procedure described for **56** from *p*-nitro iodobenzene (3.8 g, 15.2 mmol). The crude product was purified by column chromatography (10 % EtOAc in hexane) and recrystallised from hexane to afford the title compound as yellow needles. (2.8 g, 13.2 mmol, 87 %).

^{1}H (300 MHz, (CD_3Cl_3) δ = 2.40 (3H, s, $ArC\underline{H}_3$); 7.32 (2H, d, *J* = 8 Hz, $Ar^{3'}C\underline{H}$); 7.55, (2H, d, *J* = 8 Hz, $Ar^{2'}C\underline{H}$); 7.74 (2H, d, *J* = 9 Hz, $Ar^{3}C\underline{H}$); 8.32 (2H, d, *J* = 9 Hz, $Ar^{2}C\underline{H}$).

13C (75 MHz, ($CDCl_3$) δ = 21.4 ($Ar\underline{C}H_3$); 124.3 ($Ar^{2}\underline{C}H$); 127.4 ($Ar^{2'}\underline{C}H$); 127.6 ($Ar^{3}\underline{C}H$) 130.0 ($Ar^{3'}\underline{C}H$); 136.0 ($Ar\underline{C}CH_3$); 139.3 ($Ar^{1'}\underline{C}$); 147.0 ($Ar^{4}\underline{C}$); 147.7 ($Ar^{1}\underline{C}$).

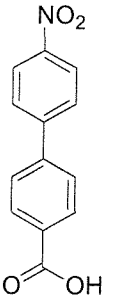
M/z (EIMS): 213.2 ([$M^{+\cdot}$] (60 %); 183.2 (100 %); 165.2 (66%).

IR (ν_{max}/cm^{-1}): 1593 (s, aryl C-H); 1509 and 1338 (s, NO_2).

R_F: 0.4 (2.5 % EtOAc: hexane)

m.p.: 133 - 135 °C (hexane) (lit. 140 - 141 °C (methanol))[123]

6.2.14 Synthesis of 4-(4'-nitrophenyl)benzoic acid (61)[123]

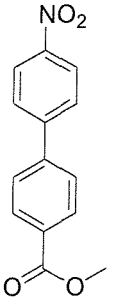


60 (11 g, 51.6 mmol) was suspended in pyridine (350 ml) and water (350 ml) and the heterogeneous mixture heated to reflux. Potassium permanganate (41 g, 0.26 mol) was added in three portions and the resulting purple solution refluxed for 30 minutes and then stirred at room temperature for 1 hour. The reaction mixture was filtered hot and the resultant brown MnO_2 precipitate washed with hot water (100 ml). The yellow filtrate was acidified with c.HCl and the resultant white solid collected by filtration, washed with hot water and dried under vacuum to afford the title compound as a white solid (12.1 g, 51.3 mmol, 99%).

^{1}H (400 MHz, $(CD_3)_2SO$) δ = 8.01 (2H, d, J = 8 Hz, $Ar^3C\underline{H}$); 8.12, (2H, d, J = 9 Hz, $Ar^{2'}C\underline{H}$); 8.17 (2H, d, J = 8 Hz, $Ar^2C\underline{H}$); 8.43 (2H, d, J = 9 Hz, $Ar^{3'}C\underline{H}$).
13C (100 MHz, $(CD_3)_2SO$) δ = 124.2 ($Ar^{3'}\underline{C}H$); 127.6 ($Ar^3\underline{C}H$); 128.3 ($Ar^{2'}\underline{C}H$) 130.2 ($Ar^2\underline{C}H$); 131.1 ($Ar\underline{C}CO_2H$); 141.9 ($Ar^4\underline{C}$); 145.5 ($Ar^{1'}\underline{C}$); 147.2 ($Ar\underline{C}NO_2$); 167.0 ($Ar\underline{C}O_2H$).

M/z (ES-): 356.1 $[M+TFA-H]^-$ 100 %.
IR (ν_{max}/cm^{-1}): 2544-2948 (b, OH); 1677 (vs, C=O); 1513 and 1342 (s, NO_2).
R_F: 0.2 (50 % EtOAc: hexane).
m.p.: >250 °C (lit. 339 – 340 °C).[124]

6.2.15 Synthesis of methyl 4-(4'-nitrophenyl)benzoate (62)[124]



61 (550 mg, 2.26 mmol) was stirred in methanol (50 ml) at room temperature for 10 minutes after which time thionyl chloride (0.2 ml, 2.71 mmol) was added dropwise. The reaction mixture was refluxed overnight after which time the

solvent was removed *in vacuo*. The residue was treated with 5% $NaHCO_3$ (50 ml) and EtOAc (50 ml) and the phases separated. The aqueous phase was extracted with EtOAC (3 x 40 ml) and the organic phases combined and washed with 5% $NaHCO_3$ (25 ml), 1% $KHSO_4$ (25 ml), brine (25 ml) and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford the title compound as an off white solid (580 mg, 2.25 mmol, 99 %).

^{1}H (300 MHz, ($CDCl_3$) δ = 3.97 (3H, s, $OC\underline{H}_3$) 7.71 (2H, d, J = 8 Hz, $Ar^3C\underline{H}$); 7.79, (2H, d, J = 9 Hz, $Ar^{2'}C\underline{H}$); 8.16 (2H, d, J = 8 Hz, $Ar^2C\underline{H}$); 8.34 (2H, d, J = 9 Hz, $Ar^{3'}C\underline{H}$).

13C (75 MHz, ($CDCl_3$) δ = 52.5 ($OC\underline{H}_3$) 124.4 ($Ar^{3'}\underline{C}H$); 127.6 ($Ar^3\underline{C}H$); 128.3 ($Ar^{2'}\underline{C}H$) 130.5 ($Ar^2\underline{C}H$) and ($Ar\underline{C}CO_2Me$); 143.2 ($Ar^4\underline{C}$); 146.5 ($Ar^{1'}\underline{C}$); 147.7 ($Ar\underline{C}NO_2$); 166.7 ($ArC\underline{C}O_2Me$).

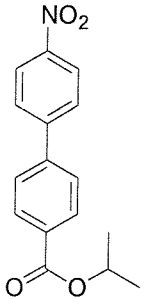
M/z (CIMS): 257 ([$M^{+\cdot}$] 48%); 228 (100 %).

IR (ν_{max}/cm^{-1}): 1712.3 (s. C=O); 1595 (s, aryl C-H); 1508 and 1338 (s, NO_2).

R_F: 0.8 (50 % EtOAc: hexane).

m.p.: 188 – 190 °C (lit. 189 – 190 °C).[125]

6.2.16 Synthesis of isopropyl-4-(4'-nitrophenyl)benzoate (65)

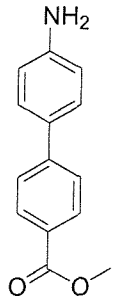


61 (5.5g, 22 mmol) was stirred in iso-propanol (500 ml) at room temperature for 10 minutes after which time thionyl chloride (8.2 ml, 0.1 mol) and catalytic DMF (3 drops) were added. The reaction mixture was refluxed overnight after which time the solution had become homogenous. The reaction mixture was refluxed for a further 6 days after which time the solvent was *in vacuo* to afford the title compound as a peach solid (6.1 g, 22 mmol, 99 %).

^{1}**H** (400 MHz, $CDCl_3$ + 1 drop $(CD_3)_2SO$): δ 1.33 (6H, d, J = 6 Hz, C$\underline{H}_3$); 5.20 (1H, sept, J = 6 Hz C$\underline{H}$(CH$_3$)$_2$); 7.63 (2H, d, J = 9 Hz, Ar^{3}C$\underline{H}$); 7.73 (2H, d, J = 9 Hz, Ar$^{2'}$C$\underline{H}$); 8.06 (2H, d, J = 9Hz, Ar^{2}C$\underline{H}$); 8.24 (2H, d, J = 9 Hz Ar$^{3'}$C$\underline{H}$).
^{13}**C** (75 MHz, $CDCl_3$ + 1 drop $(CD_3)_2SO$): δ 21.5 ($\underline{C}H_3$); 68.3 ($\underline{C}H(CH_3)_2$); 123.7 (Ar$^{3'}\underline{C}$H); 126.8 (Ar$^3\underline{C}$H); 127.6 (Ar$^{2'}\underline{C}$H); 129.7 (Ar$^2\underline{C}$H); 130.5 (Ar$\underline{C}CO_2{}^i$Pr); 142.2 (Ar$^4\underline{C}$); 145.8 (Ar$^{1'}\underline{C}$); 146.9 (Ar$\underline{C}NO_2$); 164.9 (ArC$\underline{C}O_2{}^i$Pr).

M/z (EIMS): 285.07 ([M$^{+\cdot}$] 15 %); 243.1 (42 %); 226.1 (49 %); 213.1 (56 %); 152.0 (100 %).
HRMS: calcd for ($C_{16}H_{15}ONO_4$) [M$^{+\cdot}$] 285.1001, found 285.1002
IR (ν_{max}/cm^{-1}): 1706 (s, C=O); 1519 and 1344 (s, NO_2)
R_F: 0.6 (EtOAc:Hexane (1:1)
m.p.: 73 – 75 °C

6.2.17 Synthesis of methyl-4-(4'-aminophenyl)benzoate (63)[126]



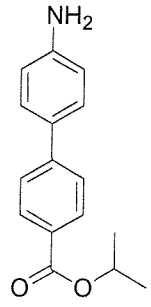
Raney nickel (20 ml of a 50% slurry in water) was filtered, washed and re-suspended in methanol (10 ml). **62** (4.14g, 16.1 mmol) was dissolved in methanol (600 ml) and combined with the nickel slurry. The flask was evacuated and a hydrogen atmosphere introduced *via* balloon. The yellow solution was stirred overnight after which time it was filtered through a plug of silica and the solvent removed *in vacuo*. The resultant brown solid was treated with triethylamine (100ml) and water (100 ml). The aqueous phase was extracted with chloroform (3 x 100 ml) and the combined organic phases washed with water (3 x 100 ml), brine (1 x 100 ml), dried over $MgSO_4$ and the

solvent removed *in vacuo* to afford the title compound as a brown solid. (3.32 g, 14.6 mmol, 91 %).

^{1}H (300 MHz, $CDCl_3$) δ = 3.79 (2H, bs, $N\underline{H}_2$); 3.85 (3H, s, $OC\underline{H}_3$); 6.77 (2H, d, J = 8 Hz, $Ar^{3'}C\underline{H}$); 7.5 (2H, d, J = 8. Hz, $Ar^{2'}C\underline{H}$); 7.6 (2H, d, J = 8 Hz, $Ar^{3}C\underline{H}$); 8.1 (2H, d, J = 8 Hz, $Ar^{2}C\underline{H}$).
^{13}C (75 MHz, $CDCl_3$) δ = 52.0 ($OC\underline{H}_3$); 115.5 ($Ar^{3'}\underline{C}H$); 126.0 ($Ar^{2'}\underline{C}H$); 128.0 ($Ar^{1'}\underline{C}$); 128.4 ($Ar^{3}\underline{C}H$); 130.1 ($Ar\underline{C}CO_2Me$); 130.2 ($Ar^{2}\underline{C}H$); 145.7 ($Ar\underline{C}NH_2$); 146.9 ($Ar^{4}\underline{C}$) 167.3 ($ArC\underline{C}O_2Me$).

M/z (ES+): 269.1 [M+MeCN+H] 100%.
IR (ν_{max}/cm^{-1}): 3436.2 and 3357.8 (m, NH_2); 1685.9 (s, C=O).
R_F: 0.8 (50 % EtOAc: hexane).
m.p.: 187 – 189 °C.

6.2.18 Synthesis of isopropyl-4-(4'-aminophenyl)benzoate (66)



The title compound was prepared as described for compound **63**; from **65** (5.9 g, 20.6 mmol). After work up and column chromatography (25 % EtOAc:Hexane) on silica gel, **66** was isolated as a brown oil, which solidified on standing (4.5 g, 17.6 mmol, 86 %).

^{1}H (300 MHz, $CDCl_3$): δ 1.39 (6H, d, J = 6 Hz, $C\underline{H}_3$); 3.82 (2H, bs, $N\underline{H}_2$) 5.28 (1H, sept, J = 6 Hz $C\underline{H}(CH_3)_2$); 6.77 (2H, d, J = 8 Hz, $Ar^{3'}C\underline{H}$); 7.47 (2H, d, J = 8 Hz, $Ar^{2'}C\underline{H}$); 7.60 (2H, d, J = 9Hz, $Ar^{3}C\underline{H}$); 8.06 (2H, d, J = 9 Hz $Ar^{2}C\underline{H}$).

^{13}**C** (75 MHz, $CDCl_3$): δ 22.2 ($\underline{C}H_3$); 68.3 ($\underline{C}H(CH_3)_2$); 115.5 ($Ar^{3'}\underline{C}H$); 126.1 ($Ar^{2'}\underline{C}H$); 128.4 ($Ar^{3}\underline{C}H$); 128.7 ($Ar^{1'}\underline{C}$); 130.2 ($Ar^{2}\underline{C}H$) and ($Ar\underline{C}CO_2{}^{i}Pr$); 145.5 ($Ar\underline{C}NH_2$); 146.8 ($Ar^{4}\underline{C}$); 166.3 ($ArC\underline{C}O_2{}^{i}Pr$).

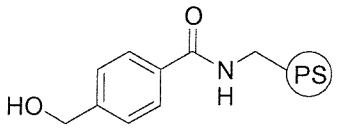
IR (ν_{max}/cm^{-1}): 3463 and 3371 (w, NH_2); 2979 (w, CH); 1697 (s, C=O); 1598 (vs); 1274 (vs).

M/z (ES+): 256.1 ($[M+H]^+$, 20 %); 297.1 ($[M+MeCN+H]^+$, 100 %).

R_F: 0.3 (Hexane:EtOAc 1:1)

m.p.: 99 – 101 °C

6.2.19 Synthesis of PS-HMBA Resin (72)

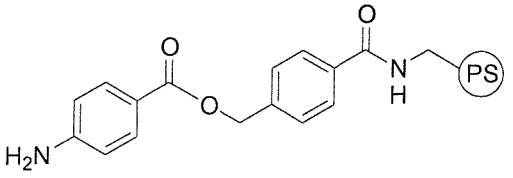


Aminomethyl PS (loading 1.65 mmol/g, 1 g, 1.65 mmol) was swollen in the minimum amount of DMF for 30 minutes. Hydroxymethyl benzoic acid (753 mg, 4.95 mmol) and HOBt (757 mg, 4.95 mmol) were stirred in DCM/DMF (50:1, 10ml) for 10 minutes after which time DIC (694 μl, 4.95 mmol) was added in one portion. The solution was stirred for a further 10 minutes before addition to the pre-swollen resin. The resin was then agitated for 4 hours to effect coupling; a qualitative ninhydrin test on a small portion of washed resin was negative. The resin was then washed with DCM and agitated for a further hour in a saturated solution of KOH in dioxane and washed with H_2O (3 x 25 ml), H_2O/DMF (1:1, 3 x 25 ml), DMF (3 x 20 ml), DCM (3 x 20 ml), MeOH (3 x 20 ml) Et_2O (3 x 20 ml) and dried under vacuum for 30 minutes.

Appearance: pale yellow resin

IR (ν_{max}/cm^{-1}): 3329 (w, OH); 2923 (m, aliphatic C-H); 1642 (s, NHC=O); 1493 (vs).

6.2.20 Synthesis of Aniline HMBA Resin (73)

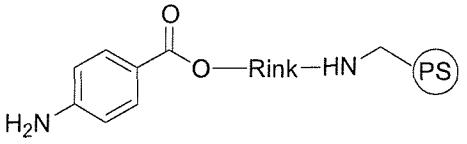


PS-HMBA resin **72** (loading 1.35 mmol/g, 250 mg, 0.33 mmol) was swollen in the minimum amount of DMF for 30 minutes. Boc-4-amino benzoic acid (237 mg, 1.0 mmol), DIC (159 μl, 1.0 mmol) and DMAP (10 mg, 0.08 mmol) were stirred in DCM (5 ml) for 10 minutes before addition to the pre-swollen resin. The resin was agitated for 6 hours to effect coupling, washed with DMF (3 x 15 ml) and suspended in 95 % TFA in DCM (10 ml) for 15 minutes, before being filtered and resuspended in a further portion of 95 % TFA in DCM (10 ml). After 15 minutes further shaking, the resin was filtered, washed with DMF (3 x 5 ml), DCM (3 x 5 ml), and MeOH (3 x 5 ml), Et_2O (3 x 5 ml) and dried under vacuum. A qualitative ninhydrin test was positive.

Appearance: pale yellow resin

IR (ν_{max}/cm^{-1}): 2928 (m, aliphatic C-H); 1721 (s, C=O); 1650 (s, NHC=O).

6.2.21 Synthesis of Aniline Rink Resin (78)



Rink aminomethyl PS (loading 1.1 mmol/g, 223 mg, 0.25 mmol) was swollen in the minimum amount of DCM for 30 minutes. Fmoc-amino benzoic acid (176 mg, 0.5 mmol) and HOBt (77 mg, 0.5 mmol) were stirred in DCM/DMF (50:1, 5 ml) for 10 minutes after which time DIC (78 μl, 0.5 mmol) was added in one portion. The solution was stirred for a further 10 minutes before addition to the pre-swollen resin. The resin was agitated for 6 hours to effect the coupling, a qualitative a qualitative ninhydrin test on a small portion of washed resin was

negative. The resin was then washed with DCM (3 x 15) and suspended in 20 % piperidine in DMF (10 ml), agitated for 15 minutes, filtered and resuspended in a further portion of 20 % piperidine in DMF (10 ml). After 15 minutes further shaking, the resin was filtered, washed with DMF (3 x 5 ml), DCM (3 x 5 ml), and MeOH (3 x 15 ml), Et_2O (3 x 15 ml) and dried under vacuum. A qualitative ninhydrin test was positive.

Appearance: pale yellow resin

IR (ν_{max}/cm^{-1}): 2928 (m, aliphatic C-H); 1721 (s, C=O); 1650 (s, NHC=O).

6.2.22 Asymmetric Dihydroxylation Procedures

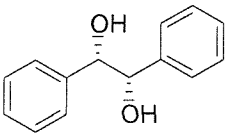
6.2.22.1 Using Triazine Catalyst (47)

47 (10 %) K_3FeCN_6 (3 eq), K_2CO_3 (3 eq), $MeSO_2NH_2$ (1.1 eq) and OsO_4 (1.5 % solution in ^{t}BuOH, 1.5 %) were stirred in ^{t}BuOH:water (1:1, 5.5 ml) at room temperature for 1 hour after which time the alkene (1 eq) was added in one portion. The reaction mixture was stirred for 18 hours at 0 °C and sodium sulfite (1.1 eq) added, the reaction mixture was stirred for a further hour after which time the brown/black solution was filtered and H_2O (20 ml) and DCM (20 ml) added. The phases were separated and the aqueous phase was extracted with DCM (3 x 20 ml), the organic extracts were combined, dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography on silica in DCM followed by Et_2O afforded the desired diol products.

6.2.22.2 Using AD mix

AD mix (2.32g based on 1.4 g per mmol of alkene) and $MeSO_2NH_2$ (158 mg, 1.66 mmol eq) were stirred in ^{t}BuOH:water (1:1, 5.5 ml) at room temperature for 1 hour after which time the alkene (1.66 mmol) was added in one portion. Work-up was carried out as described above.

6.2.23 Synthesis of (1*S*, 2*S*)-1,2-diphenylethane-1,2-diol (82a)[126]

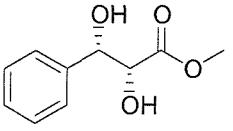


The title compound was prepared according to the procedure described above from *trans*-stilbene (300 mg, 1.66 mmol) to afford the title compound as a white solid (266 mg, 1.25 mmol, 75 %, 99% e.e.).

^{1}H (400 MHz, $CDCl_3$) δ = 2.90 (2H, bs, OH); 4.71 (2H, s, C<u>H</u>OH), 7.13 (4H, m, $Ar^2C\underline{H}$), 7.23 (6H, m $Ar^{3,4}C\underline{H}$).
^{13}C (100 MHz, $CDCl_3$) δ 79.5 (<u>C</u>HOH), 127.4 ($Ar^2\underline{C}H$), 128.4 ($Ar^4\underline{C}H$), 128.6 ($Ar^3\underline{C}H$), 140.2 (Ar<u>C</u>).

M/z (ES-): 327.1 $[M+TFA-H]^-$ (100%).
IR (ν_{max}/cm^{-1}): 3496 and 3387 (s, OH); 2894 (m, C-H).
R_F: 0.2 (10% MeOH:$CHCl_3$).
m.p.: 144 – 146 °C (148 – 150 Aldrich).
$[\alpha]_D^{22}$: -35° (c = 1, EtOH), (lit $[\alpha]_D$ = -36° (c = 1, EtOH).[127]

6.2.24 Synthesis of methyl-(2*R*,3*S*)-(2,3-Dihydroxy-3-phenyl-propionate (83a)



The title compound was prepared according to the procedure described above from methyl *trans* cinnimate (100 mg, 0.6 mmol), to afford the title compound as a colourless solid (266 mg, 1.25 mmol, 75 %, 94 % e.e.).

^{1}H (400 MHz, $CDCl_3$) δ = 3.62 (3H, s, $OC\underline{H}_3$); 4.26 (1H, s, C<u>H</u>(OH)CO_2Me), 4.98 (C<u>H</u>(OH)CH(OH)) 7.2 (5H, m, ArC<u>H</u>).

^{13}C (100 MHz, $CDCl_3$) δ 52.9 (OCH3); 74.7 (C̲H(OH)CH(OH)); 75.1 (C̲H(OH)CO_2Me); 126.4 (Ar^2C̲H); 128.2 (Ar^4C̲H); 128.6 (Ar^3C̲H); 140.1 (ArC̲); 173.4 (C̲O_2Me).

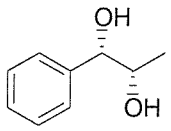
IR (ν_{max}/cm^{-1}): 3500 (b,s, OH); 1732 (s, C=O).

R_F: 0.3 (20% MeOH:$CHCl_3$).

m.p.: 88 – 89 °C (lit. 87 - 90).[92]

$[\alpha]_D^{22}$: +3.9 (c = 1.19, EtOH), (lit $[\alpha]_D$ = +3.4 (c = 1.19, EtOH).[92]

6.2.25 Synthesis of (1*S*, 2*S*)-1-Phenyl-propane-1,2-diol (84a)[126]



The title compound was prepared according to the procedure described above from β-methyl styrene (77 μl, 0.6 mmol) to afford the title compound as a colourless solid (71 mg, 0.47 mmol, 78 %, 96 % e.e.).

^{1}H (300 MHz, $(CD_3)_2CO$) δ = 1.00 (3H, d, J = 4 Hz C̲H_3); 3.74 (1H, m, CH_3C̲H(OH)); 3.88 (1H, d, J = 4 Hz, O̲H); 4.34 (1H, dd, J = 4 and 7 Hz C̲H(OH)$CHCH_3$); 4.40 (1H, d, J = 4 Hz, O̲H); 7.25 – 7.35 (5H, m, ArC̲H).

^{13}C (75 MHz, $(CD_3)_2CO$) δ = 19.0 (CH_3); 72.4 (CH_3C̲H(OH); 79.5 (C̲H(OH)$CHCH_3$); 127.7 (Ar^2C̲H); 127.9 (Ar^4CH); 128.5 (Ar^3C̲H); 143.4 (Ar^1C̲).

M/z (ES-): 265.1 $[M+TFA-H]^-$ (100%).

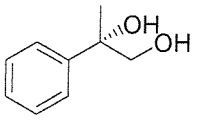
IR (ν_{max}/cm^{-1}): 3339 (vs, OH); 2999 (w, C-H).

R_F: 0.2 (10% MeOH:$CHCl_3$).

m.p.: 48 – 50 °C.

$[\alpha]_D^{22}$: +30° (c = 1.79, EtOH), (lit $[\alpha]_D$ = +31.1° (c = 1.79, EtOH).[127]

6.2.26 Synthesis of 2-(2*S*)-Phenyl-propane-1,2-diol (85a)[126]

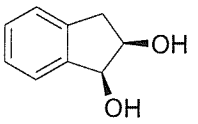


The title compound was prepared according to the procedure described above from α-methyl styrene (77 μl, 0.6 mmol) to afford the title compound as a colourless oil (77 mg, 0.51 mmol, 85 %, 91 % e.e.).

^{1}H (300 MHz, $(CD_3)_2SO$) δ = 1.39 (3H, s, $C\underline{H}_3$), 3.6 (1H, d, J = 7 Hz, $C\underline{H}_2$ (1)), 3.8 (1H, d, J = 7 Hz, $C\underline{H}_2$ (1)), 7.30 (1H, t, J = 7 Hz, $Ar^4C\underline{H}$), 7.41 (2H, t, J = 7 Hz, $Ar^3C\underline{H}$), 7.48 (2H, d, J = 7 Hz, $Ar^2C\underline{H}$).
^{13}C (75 MHz, DMSO) δ = 26.2 (CH_3), 70.5 ($CH_3\underline{C}H(OH)$), 73.7 ($CH(CH_3)\underline{C}H(OH)$), 125.5 ($Ar^3\underline{C}H$), 126.1 ($Ar^4\underline{C}H$), 127.6 ($Ar^3\underline{C}H$), 147.5 (Ar$\underline{C}$).

M/z (ES-): 266.1 $[M+TFA-H]^-$ (100%).
IR (ν_{max}/cm^{-1}): 3353 (vs, OH); 2999 (w, C-H).
R_F: 0.13 (10% MeOH:$CHCl_3$)
$[\alpha]_D^{22}$: +3 ° (c = 8.9, EtOH), (lit $[\alpha]_D$ = +5.4° (c = 8.9, EtOH).[127]

6.2.27 Synthesis of (1*R*,2*S*)-Indan-1,2-diol (86a)[126]



The title compound was prepared according to the procedure described above from indene (69 μl, 0.6 mmol) to afford the title compound as a colourless solid (81 mg, 0.54 mmol, 90 %, 29 % e.e.).

^{1}H (400 MHz, DMSO) δ = 2.76 (1H, dd J = 7 and 21 Hz $^4C\underline{H}$), 2.92 (1H, dd J = 5 and 21 Hz $^4C\underline{H}$), 4.26 (1H, m, $^5C\underline{H}$), 4.58 (1H, d, J = 6 Hz, $^6O\underline{H}$), 4.78 (1H, t, J = 6 Hz, $^8C\underline{H}$), 5.00 (1H, d, J = 9 Hz $^7O\underline{H}$), 7.3 (4H, m, $^{1,2,10,11}C\underline{H}$).

^{13}C (100 MHz, DMSO) δ 38.2 (^{4}C), 72.8 (^{5}C), 75.0 (^{8}C), 124.7, 2 signals (^{1,11}C), 126.2 (^{2}C), 127.5 (^{10}C), 140.5 (^{3}C), 143.9 (^{3}C)

M/z (ES-): 263.1 $[M+TFA-H]^-$ (100%).

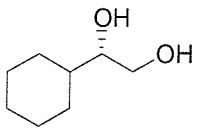
IR (ν_{max}/cm^{-1}): 3347,3265 O-H (b,s).

R_F: 0.13 (10% MeOH:$CHCl_3$).

m.p.: 103 – 105 °C (lit. 99 – 100).[128]

$[\alpha]_D^{22}$: -9° (c = 0.4, $CHCl_3$), (lit $[\alpha]_D$ = -51° (c = 0.4, $CHCl_3$).[127]

6.2.28 Synthesis of (S)-1-Cyclohexyl-ethane-1,2-diol (87a)



The title compound was prepared according to the procedure described above from vinyl cyclohexane (83 μl, 0.6 mmol) to afford the title compound as a colourless solid (88mg, 0.59mmol, 98%, 88 % e.e.).

^{1}H (400 MHz, $CDCl_3$) δ = 0.94 – 1.80 (11 H, m); 3.34 – 3.60 (5H, m).

^{13}C (100 MHz, $CDCl_3$) δ = 26.2, (2 signals, $\underline{C}H_2$); 28.8 ($\underline{C}H_2$); 29.1 ($\underline{C}H_2$); 40.8 ($\underline{C}H$); 64.8 ($\underline{C}H_2$); 76.6 ($\underline{C}H$).

M/z (EIMS): 127 ([M-CO] 15 %); 113.1 (67 %); 95.0 (100 %).

IR (ν_{max}/cm^{-1}): 3389 (b,m); 2922.03 (s) and 2852 (s), aliphatic C-H).

R_F: 0.2 (10% MeOH:$CHCl_3$).

m.p.: 50 °C (lit. 50 – 52).[129]

6.3 Experimental to Chapter 3

6.3.1 General Asymmetric Dihydroxylation Procedure

The methods used for implementation and analysis of the asymmetric dihydroxylation reactions described in Chapter 3 were achieved using conditions shown in Table 35 for the reproducibility experiments and Table 36 for the screening and response surface modelling experiments.

Reagent	Equiv	molar quantity (mmol)	mass/volume
α-methyl styrene	1	0.3	39 μl
β-methyl styrene	1	0.3	39 μl
indene	1	0.3	35 μl
chiral catalyst **5**	0.1	0.03	29 mg
OsO_4	0.015	0.0045	46 μl[a]
K_3FeCN_6	3	0.9	294 mg
K_2CO_3	3	0.9	124 mg
KOH	3	0.9	50 mg
$MeSO_2NH_2$	1	0.3	29 mg
$^tBuOH/H_2O$ (1:1)			6 ml

[a]1.5 % solution in ^{t}BuOH

Table 35 Quantities used in the Reproducibility Experiment

Reagent	Equiv	molar quantity (mmol)	mass/volume
α-methyl styrene	1	0.06	8 μl
β-methyl styrene	1	0.06	8 μl
indene	1	0.06	7 μl
chiral catalyst **5**	0.1	0.006	6 mg
OsO_4	0.015	0.0045	9 μl[a]
K_3FeCN_6	2	0.12	40 mg
	4	0.24	80 mg
K_2CO_3	2	0.12	16 mg
	4	0.24	32 mg
KOH	2	0.12	6 mg
	4	0.24	12 mg
$MeSO_2NH_2$	1	0.3	29 mg
$^tBuOH/H_2O$ (1:1)			6 ml

[a]1.5 % solution in ^{t}BuOH

Table 36 Quantities used in the Screening and Response Surface Modelling Experiment

Conversion was assessed using a Phenomonex C-18 Luna 50 x 4.6 mm 5 μm, C18 column with a flow rate of 1.5 ml/min and a solvent gradient as shown in Table 37.

Time	% MeCN
0	10
3	90
4	90
5	10
6	10

Table 37 HPLC Gradient for Assessment of Conversion

E.e. was determined on a ChiralPak AD-RH (150 mm), chiral column with a 12 minute isocratic gradient of 10 % MeCN/H_2O and flow rate of 0.5 ml/min

6.3.2 Asymmetric Dihydroxylation Results

Results for the Reproducibility Experiment, Screening Experiment and Response Surface modelling experiments are shown in Table 38 – 43 respectively.

indene		β-methyl styrene	
conversion (%)	e.e. (%)	conversion (%)	e.e. (%)
98	22	100	88
96	23	100	88
92	24	100	90
92	24	100	88
95	23	100	93

Table 38 Reproducibility Experiment

Temp	Substrate[a]	Solvent	Base	Eq Base	Eq Oxidant	Additive	e.e. (%)	Conversion (%)
ice	indene	17 2-propanol	K_2CO_3	4	2	1	14	74
room	β	89 3-methyl-2-butanone	KOH	4	4	1	49	100
room	β	71 diethyl ether	KOH	4	2	0	44	35
room	α	30 2-methyl-2-propanol	K_2CO_3	4	4	0	53	100
room	β	89 3-methyl-2-butanone	K_2CO_3	2	2	0	74	65
ice	indene	71 diethyl ether	K_2CO_3	2	4	1	14	70
ice	α	17 2-propanol	KOH	2	4	0	33	42
room	β	30 2-methyl-2-propanol	K_2CO_3	4	4	0	41	100
room	indene	58 ethyl acetate	KOH	3	3	0	3	93
room	α	89 3-methyl-2-butanone	KOH	4	4	1	14	84
ice	β	43 dichlormethane	K_2CO_3	3	3	1	62	64
ice	β	71 diethyl ether	KOH	4	2	0	62	69
ice	α	43 dichlormethane	K_2CO_3	3	3	1	36	100
ice	α	30 2-methyl-2-propanol	K_2CO_3	4	4	0	61	100
room	indene	43 dichlormethane	K_2CO_3	3	3	1	1	43
room	indene	71 diethyl ether	KOH	4	2	0	1	62

room	indene	17	2-propanol	KOH	2	4	0	8	42
room	β	17	2-propanol	KOH	2	4	0	29	50
ice	indene	30	2-methyl-2-propanol	KOH	2	2	1	15	90
room	α	43	dichlormethane	K_2CO_3	3	3	1	28	67
room	β	43	dichlormethane	K_2CO_3	3	3	1	72	100
room	α	71	diethyl ether	KOH	4	2	0	19	65
room	α	89	3-methyl-2-butanone	K_2CO_3	2	2	0	33	93
ice	α	71	diethyl ether	KOH	4	2	0	26	85
room	indene	17	2-propanol	K_2CO_3	4	2	1	12	65
ice	α	89	3-methyl-2-butanone	KOH	4	4	1	16	96
ice	α	30	2-methyl-2-propanol	KOH	2	2	1	41	90
ice	β	89	3-methyl-2-butanone	K_2CO_3	2	2	0	66	88
ice	β	58	ethyl acetate	KOH	3	3	0	86	37
room	α	71	diethyl ether	K_2CO_3	2	4	1	13	69
ice	indene	43	dichlormethane	K_2CO_3	3	3	1	1	97
ice	β	71	diethyl ether	K_2CO_3	2	4	1	62	43
room	α	30	2-methyl-2-propanol	KOH	2	2	1	4	99
room	α	58	ethyl acetate	KOH	3	3	0	35	55

ice	α	17	2-propanol	K_2CO_3	4	2	1	46	67
room	α	17	2-propanol	K_2CO_3	4	2	1	49	100
room	α	17	2-propanol	KOH	2	4	0	21	100
ice	indene	17	2-propanol	KOH	2	4	0	12	37
ice	indene	58	ethyl acetate	KOH	3	3	0	1	85
room	β	71	diethyl ether	K_2CO_3	2	4	1	60	49
ice	α	58	ethyl acetate	KOH	3	3	0	37	69
room	β	30	2-methyl-2-propanol	KOH	2	2	1	67	67
ice	β	30	2-methyl-2-propanol	K_2CO_3	4	4	0	80	100
room	indene	71	diethyl ether	K_2CO_3	2	4	1	11	100
room	β	17	2-propanol	K_2CO_3	4	2	1	13	12
room	indene	89	3-methyl-2-butanone	K_2CO_3	2	2	0	0	93
ice	β	17	2-propanol	K_2CO_3	4	2	1	79	78
ice	β	17	2-propanol	KOH	2	4	0	45	89
ice	indene	89	3-methyl-2-butanone	K_2CO_3	2	2	0	2	97
ice	α	71	diethyl ether	K_2CO_3	2	4	1	49	41
room	β	58	ethyl acetate	KOH	3	3	0	55	64
ice	β	89	3-methyl-2-butanone	KOH	4	4	1	45	95

ice	β	30	2-methyl-2-propanol	KOH	2	2	1	79	69
room	indene	89	3-methyl-2-butanone	KOH	4	4	1	4	84
ice	indene	71	diethyl ether	KOH	4	2	0	6	12
ice	α	89	3-methyl-2-butanone	K_2CO_3	2	2	0	47	96
ice	indene	30	2-methyl-2-propanol	K_2CO_3	4	4	0	19	86
ice	indene	89	3-methyl-2-butanone	KOH	4	4	1	2	87
room	indene	30	2-methyl-2-propanol	K_2CO_3	4	4	0	18	100
room	indene	30	2-methyl-2-propanol	KOH	2	2	1	12	76

[a] α = α-methyl styrene β = β-methyl styrene

Table 39 Results for the Screening experiment

Solvent	e.e. (%)	Conversion (%)
4 methanol	4	85
4 methanol	1	80
10 ethanol	37	53
10 ethanol	25	57
18 2-methyl-1-propanol	59	65
18 2-methyl-1-propanol	59	44
17 2-propanol	72	58
17 2-propanol	75	50
18 2-butanol	65	53
18 2-butanol	66	44
18 2-butanol	70	44
18 2-butanol	67	46
18 2-butanol	67	55
18 2-butanol	56	46
30 2-methyl-2-propanol	79	67
30 2-methyl-2-propanol	75	70
43 dichloromethane	80	82
43 dichloromethane	68	59
75 dibutyl ether	42	42
75 dibutyl ether	40	54
81 cyclohexane	10	25
81 cyclohexane	16	35
82 hexane	5	19
82 hexane	19	38
102 n-heptane	9	34
102 n-heptane	0	45

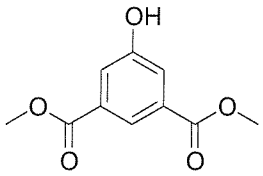
Table 40 Results for the Response Surface Modelling "Reduced" Plan

Solvent	e.e.	Conversion
8 2-methoxyethanol	17	74
8 2-methoxyethanol	14	83
18 2-methyl-1-propanol	66	40
18 2-methyl-1-propanol	70	39
17 2-propanol	78	56
17 2-propanol	72	49
18 2-butanol	75	46
18 2-butanol	71	41
19 3-methyl-1-butanol	73	46
19 3-methyl-1-butanol	66	33
30 2-methyl-2-propanol	82	85
30 2-methyl-2-propanol	79	69
43 dichloromethane	61	55
43 dichloromethane	66	53
58 ethyl acetate	74	69
58 ethyl acetate	75	69
71 diethyl ether	69	54
71 diethyl ether	71	52
73 di-isopropyl ether	63	78
73 di-isopropyl ether	64	77
84 1-pentanol	74	39
84 1-pentanol	73	46
84 1-pentanol	75	28
84 1-pentanol	75	53
88 3-methyl-2-butanone	65	49
88 3-methyl-2-butanone	52	54

Table 41 Results for the Response Surface Modelling "Trimmed" Plan

6.4 Experimental to Chapter 4

6.4.1 Synthesis of 3,5-dimethoxycarbonyl-phenol (98)[130]

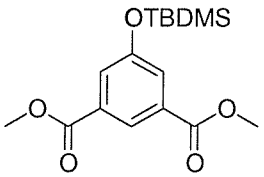


Thionyl chloride (2.4 ml, 33 mmol) was slowly added to an ice cold solution of 5-hydroxyisophthalic acid (2g, 11 mmol) in methanol (30 ml). The reaction mixture was stirred for 3 hours at room temperature after which time the solvent was removed *in vacuo* to afford the title compound as a white solid (2.29 g, 10.9 mmol, 99 %).

^{1}H (300 MHz, $CDCl_3$) δ = 3.86 (6H, s, $OC\underline{H}_3$); 7.55 (2H, s, $Ar^2C\underline{H}$); 7.93 (1H, s, $Ar^4C\underline{H}$); 10.34 (1H, s, $O\underline{H}$).
^{13}C (75 MHz, $CDCl_3$) 52.5 ($\underline{C}H_3$); 120.2 ($Ar^4\underline{C}H$); 120.3 ($Ar^2\underline{C}H$); 131.4 ($Ar\underline{C}CO_2Me$) (158.0 ($Ar\underline{C}$-OH); 165.5 ($\underline{C}$=O).

M/z (EIMS): 210.0 ([$M^{+\cdot}$] 45 %); 179.0 (96 %).
IR (ν_{max}/cm^{-1}): 3357 (s, O-H); 1724/1702 (s, C=O); 1599 (m, aryl C-C).
R_F: 0.5 (1:1 EtOAc:hexane)
m.p.: 161 - 162 °C (lit. 162 – 164 °C).[130]

6.4.2 Synthesis of *tert*-butyldimethyl(3,5-dimethoxycarbonyl-phenoxy)-silane (107)[108]



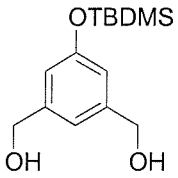
Using the procedure of van Veggel[108]

TBDMSiCl (1.08 g, 7.1 mmol) was dissolved in DCM (3 ml) and added dropwise to a stirred, ice cold solution of **98** (1g, 4.8 mmol), NEt_3, and DMAP (cat.) in DCM (10 ml). After stirring overnight at room temperature the mixture was diluted with DCM (15 ml) and washed with 2 M HCl (15 ml), sat. $NaHCO_3$ (15 ml), brine (20 ml), dried over $MgSO_4$, and the solvent removed *in vacuo.* Drying overnight and recrystallisation from hexane/DCM afforded the title compound as a white crystalline solid (1.4 g, 4.4 mmol, 91 %).

^{1}H (300 MHz, $CDCl_3$) δ = 0.24 (6H, s, $SiC\underline{H}_3$); 1.00 (9H, s, $C(C\underline{H}_3)_3$); 3.94 (6H, s, $OC\underline{H}_3$); 7.68 (2H, t, J = 1 Hz, $Ar^4C\underline{H}$); 8.30 (1H, s, $Ar^2C\underline{H}$).
^{13}C (75 MHz, $CDCl_3$) δ = -4.3 ($Si\underline{C}H_3$); 18.3 ($\underline{C}(CH_3)_3$); 25.7 ($C(\underline{C}H_3)_3$); 52.5 ($O\underline{C}H_3$); 123.9 ($Ar^4\underline{C}H$); 125.5 ($Ar^2\underline{C}H$); 131.0 ($Ar\underline{C}CO_2Me$); 156.1 ($Ar\underline{C}$-O); 166.3 ($\underline{C}$=O).

M/z (EIMS): 324.2 ([$M^{+\cdot}$] 23 %); 293.2 (36 %); 267.5 (100 %).
IR (ν_{max}/cm^{-1}): 1718 (s, C=O); 1024 (s, Si-O) 1596 (m, aryl C-H).
R_F: 0.6 (50 % EtOAc:hexane)
m.p.: 60 – 62 °C (hexane/DCM) (lit., 68 – 70 °C) [108]

6.4.3 Synthesis of *tert*-butyldimethyl-(3,5-dihydroxymethyl-phenoxy)-silane (99)[108]



Using a modified procedure of van Veggel.[108]

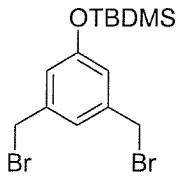
$LiAlH_4$, (1 M soln. in THF, 6 ml, 6.2 mmol) was slowly added to a stirred solution of the diester, **107** (1g, 3.1 mmol) in dry THF (6 ml), the reaction mixture was stirred for 5 hours under a nitrogen atmosphere. The reaction mixture was cooled to 0°C and quenched by careful addition of 2M HCl, and diluted with DCM (15 ml). The phases were separated and the aqueous phase

extracted with DCM (3 x 15 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the title compound as a white solid (600 mg, 2.2 mmol, 72 %).

^{1}H (300 MHz, $CDCl_3$) δ = 0.21 (6H, s, $SiC\underline{H}_3$); 1.00 (9H, s, $C(C\underline{H}_3)_3$); 1.95 (2H, s, O<u>H</u>); 4.63 (4H, s, $C\underline{H}_2O$); 6.77 (2H, t, J = 1 Hz, $Ar^2C\underline{H}$); 6.95 (1H, s, $Ar^4C\underline{H}$).
^{13}C (75 MHz, $CDCl_3$) δ = -4.2 ($SiCH_3$); 18.3 ($\underline{C}(CH_3)_3$); 25.8 ($C(\underline{C}H_3)_3$); 65.2 ($\underline{C}H_2O$); 117.8 ($Ar\underline{C}^2H$); 118.3 ($Ar\underline{C}^4H$); 142.9 ($Ar\underline{C}CH_2OH$); 156.2 ($Ar\underline{C}$-O).

M/z (EIMS): 268.2 ([$M^{+\cdot}$] 14 %) ; 211.1 (29 %) ; 193.1 (100 %).
IR (ν_{max}/cm^{-1}): 3265 (b, OH); 1056 (m, Si-O) 1596 (m, aryl C-H).
R_F: 0.3 (50 % EtOAc:hexane).
m.p.: 92 – 94 °C (Hexane/DCM) (lit., 99 – 100 °C).[108]

6.4.4 Synthesis of (3,5-Bis-bromomethyl-phenoxy)-tert-butyl-dimethyl-silane (108)



Triphenylphosphine (11.3 g, 43 mmol) followed by carbon *tetra*bromide (14 g, 43 mmol) were added slowly to a stirred solution of diol **99** (4.9 g, 18 mmol) in dry DCM (100 ml) at 0 °C. After 1 hour the solvent was removed *in vacuo* and the resultant white solid (product and triphenylphosphine oxide) chromatographed in hexane on silica gel to afford the title compound as a colourless oil (6.2 g, 16 mmol, 88 %).

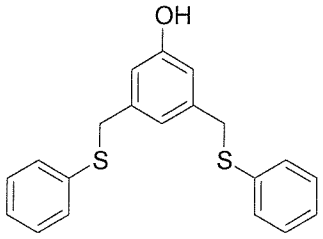
^{1}H (300 MHz, $CDCl_3$) δ = 0.23 (6H, s, $SiC\underline{H}_3$); 1.00 (9H, s, $C(C\underline{H}_3)_3$); 4.92 (4H, s, $C\underline{H}_2Br$); 6.81 (2H, s, $Ar^2C\underline{H}$); 6.95 (1H, s, $Ar^4C\underline{H}$).
^{13}C (75 MHz, $CDCl_3$) δ = -4.3 ($SiCH_3$); 18.5 ($\underline{C}(CH_3)_3$); 25.8 ($C(\underline{C}H_3)_3$); 32.9 ($\underline{C}H_2Br$); 120.9 ($Ar\underline{C}^2H$); 122.6 ($Ar\underline{C}^4H$); 139.7 ($Ar\underline{C}CH_2OH$); 156.4 ($Ar\underline{C}$-O).

M/z (EIMS): 394.0 ([^{79}Br ^{81}Br M] 30 %); 336.9 (70 %); 315.0 (67 %); 256.6 (100 %).

HRMS: calcd for ($C_{14}H_{22}O^{79}Br_2Si$) ([$M^{+\cdot}$] 391.9807, found 391.9803.

R_F: 0.8 (50 % EtOAc:hexane).

6.4.5 Synthesis of 3,5-Bis-phenylsulfanylmethyl-phenol (100)[131]



Dibromide **108** (936 mg, 2.3 mmol), K_2CO_3 (1g, 6.0 mmol) and thiophenol (495 μl, 4.81 mmol) were stirred overnight at 100 °C in DMF (20 ml). DCM (20 ml) and water (30 ml) were added to the resultant milky suspension and the phases separated, the aqueous phase was extracted with DCM (3 x 20 ml) and the solvent removed *in vacuo*. The resultant brown oil was chromatographed in DCM on silica gel to afford the title compound as colourless oil (718 mg, 2.1 mmol, 92 %).

^{1}H (300 MHz, $CDCl_3$) δ = 4.02 (4H, s, C$\underline{H}_2$SPh); 5.00 (1H,s, O$\underline{H}$); 6.66 (2H, s, Ar^{2}C$\underline{H}$); 6.82 (1H, s, Ar^{4}C$\underline{H}$); 7.22 (10H, m, SC$_6\underline{H}_5$).

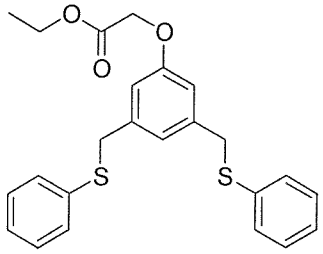
^{13}C (75 MHz, $CDCl_3$) δ = 38.9 ($\underline{C}H_2$SPh); 114.8 (Ar$^2\underline{C}$H); 122.0 (Ar$^4\underline{C}$H); 126.6 (SAr$^{4'}\underline{C}$H); 129.0 (SAr$^{2'}\underline{C}$H); 130.0 (SAr$^{3'}\underline{C}$H); 136.3 (SAr$^{1'}\underline{C}$); 139.6 (Ar$\underline{C}$CH$_2$SPh); 156.2 (Ar$\underline{C}$-O).

M/z (ES+ve): 361.1 ([M+Na]$^+$ 70 %).

IR (ν_{max}/cm^{-1}): 3431-3315 (b, OH); 1594 (s, aryl C-H).

R_F: 0.8 (50 % EtOAc:hexane).

6.4.6 Synthesis of ethyl(3,5-Bis-phenylsulfanylmethyl-phenoxy)-acetate (102a)



Procedure A, from Phenol **100**.

Phenol **100** (61 mg, 0.17 mmol), ethyl-bromoacetate (24 μl, 0.21 mmol), potassium carbonate (30 mg, 0.21 mmol) and potassium iodide (3 mg, 0.021 mmol) were refluxed in acetonitrile (5 ml) for 6 hours. After cooling the mixture was filtered, washed with DCM (15 ml) and the solvent removed *in vacuo*. The resulting residue was purified by column chromatography on silica gel (25 % EtOAc/hexane) to afford the title compound as a colourless oil (66 mg, 0.15 mmol, 91 %).

Procedure B, from dibromide **123**.

Dibromide **123** (1.5 g, 4.1 mmol), K_2CO_3 (2.2 g, 16 mmol) and thiophenol (926 μl, 9.02 mmol) were stirred overnight at 100 °C in DMF. DCM (20 ml) and water (30 ml) were added to the resultant milky suspension and the phases separated, the aqueous phase was extracted with DCM (3 x 20 ml) and the solvent removed *in vacuo*. The resultant brown oil was chromatographed in 10 % EtOAc/hexane on silica gel to afford the title compound as colourless oil (718 mg, 2.1 mmol, 92 %).

^{1}**H** (300 MHz, $CDCl_3$) δ = 1.30 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$); 4.04 (4H, s, $C\underline{H}_2SPh$); 4.26 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$); 4.52 (2H, s, $OC\underline{H}_2CO_2Et$); 6.74 (2H, s, $Ar^2C\underline{H}$); 6.89 (1H, s, $Ar^4C\underline{H}$); 7.20 (10H, m, $SC_6\underline{H}_5$).

^{13}**C** (75 MHz, $CDCl_3$) δ = 14.3 ($OCH_2\underline{C}H_3$); 39.1 ($\underline{C}H_2SPh$); 61.5 ($O\underline{C}H_2CH_3$); 65.6 ($O\underline{C}H_2CO_2Et$); 114.1 ($Ar^2\underline{C}H$); 122.9 ($Ar^4\underline{C}H$); 126.6 ($SAr^{4'}\underline{C}H$); 129.0

($SAr^{2'}\underline{C}H$); 130.1 ($SAr^{3'}\underline{C}H$); 136.2 ($SAr^{1'}\underline{C}$); 139.5 ($Ar\underline{C}CH_2SPh$); 158.2 ($Ar\underline{C}$-O); 168.9 ($CH_2\underline{C}O_2Et$).

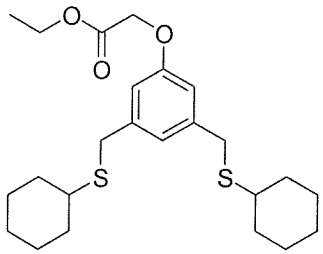
M/z (EIMS): 424.1 (([$M^{+\cdot}$] 37 %); 315.1 (33 %); 241.1 (41 %); 211.0 (100 %).

HRMS: calcd for ($C_{24}H_{24}O_3S_2$) [$M^{+\cdot}$] 424.1167, found 424.1169.

IR (ν_{max}/cm^{-1}): 1756 (s, C=O); 1593 (s, aryl C-H).

R_F: 0.5 (25 % EtOAc:Hexane)

6.4.7 Synthesis of Ethyl-(3,5-Bis-cyclohexylsulfanylmethyl-phenoxy)-acetate (102b)



The title compound was prepared according to procedure b, described above using cyclohexylthiol (1.1 ml, 9.02 mmol) as the sulfur source. The title compound was isolated as colourless oil (1.71 g, 4.06 mmol, 100 %).

^1H (300 MHz, $CDCl_3$) δ = 1.30 (13H, m, $OCH_2C\underline{H}_3$, $SCHC\underline{H}_2$ (x4); $SCHCH_2C\underline{H}_2$ (x4); $SCHCH_2CH_2C\underline{H}_2$ (x2)); 1.59 (2H, m, $SCHCH_2CH_2C\underline{H}_2$ (x2)); 1.73 (4H, m, $SCHCH_2C\underline{H}_2$ (x4)); 1.92 (4H, m, $SCHC\underline{H}_2$ (x4)); 3.70 (4H, s, $C\underline{H}_2$Schex); 4.27 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$); 4.61 (2H, s, $OC\underline{H}_2CO_2Et$); 6.77 (2H, s, $Ar^2C\underline{H}$); 6.91 (1H, s, $Ar^4C\underline{H}$).

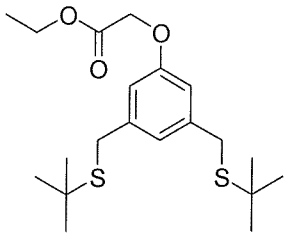
^{13}C (75 MHz, $CDCl_3$) δ = 12.9 ($OCH_2\underline{C}H_3$); 23.9 ($SCHCH_2CH_2\underline{C}H_2$); 24.0 ($SCHCH_2\underline{C}H_2$); 31.5 ($SCH\underline{C}H_2$); 32.6 ($\underline{C}H_2$Schex); 40.8 ($S\underline{C}H$) 59.5 ($O\underline{C}H_2CH_3$); 63.5 $O\underline{C}H_2CO_2Et$); 111.6 ($Ar^2\underline{C}H$); 120.8 ($Ar^4\underline{C}H$); 138.9 ($Ar\underline{C}CH_2$Schex); 156.1 ($Ar\underline{C}$-O); 167.0 ($CH_2\underline{C}O_2Et$).

HRMS: calcd for ($C_{24}H_{36}O_3S_2$) [$M^{+\cdot}$] 436.2106, found 436.2103.

IR (ν_{max}/cm^{-1}): 2952 and 2851 (m, aliphatic C-H); 1760 (s, C=O); 1593 (aryl C-H).

R_F: 0.4 (10 % EtOAc:Hexane)

6.4.8 Synthesis of Ethyl-(3,5-Bis-tert-butylsulfanylmethyl-phenoxy)-acetate (102c)

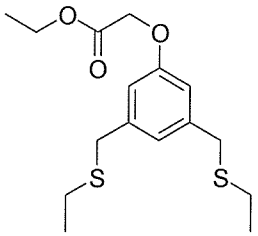


The title compound was prepared according to procedure b, described above using ^{t}butylthiol (1.01 ml, 9.02 mmol) as the sulfur source. The title compound was isolated as a white solid (1.46 g, 0.38 mmol, 93 %).

^{1}H (300 MHz, $CDCl_3$) δ = 1.34 (21H, s, $OCH_2C\underline{H}_3$ and $SC(C\underline{H}_3)_3$); 3.72 (4H, s, $C\underline{H}_2S^tBu$); 4.26 (2H, dq, J = 3 and 7 Hz, $OC\underline{H}_2CH_3$); 4.61 (2H, d, J = 3 Hz, $OC\underline{H}_2CO_2Et$); 6.80 (2H, s, $Ar^2C\underline{H}$); 7.00 (1H, s, $Ar^4C\underline{H}$).
^{13}C (75 MHz, $CDCl_3$) δ = 14.3 ($OCH_2\underline{C}H_3$); 31.1 ($C(\underline{C}H_3)_3$); 39.1 ($\underline{C}H_2S^tBu$); 43.1 ($\underline{C}(CH_3)_3$; 61.5 ($O\underline{C}H_2CH_3$); 65.6 ($O\underline{C}H_2CO_2Et$); 113.9 ($Ar^2\underline{C}H$); 123.1 ($Ar^4\underline{C}H$); 140.1 ($Ar\underline{C}CH_2S^tBu$); 158.1 ($Ar\underline{C}$-O); 169.0 ($CH_2\underline{C}O_2Et$).

HRMS: calcd for ($C_{20}H_{32}O_3S_2$) [$M^{+\cdot}$] 384.1793, found 384.1798.
IR (ν_{max}/cm^{-1}): 2960-2863 (m, aliphatic C-H); 1760 (s, C=O); 1593 (aryl C-H).
Anal: calcd for ($C_{20}H_{32}O_3S_2$): C, 62.46; H, 8.39 found C, 62.36, H, 8.41.
R_F: 0.4 (10 % EtOAc:Hexane).
m.p.: 66-67 °C.

6.4.9 Synthesis of Ethyl-(3,5-Bis-ethylsulfanylmethyl-phenoxy)-acetate (102d)

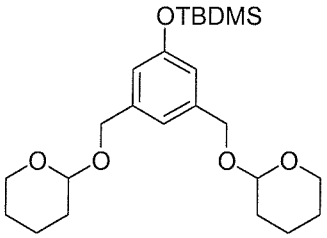


The title compound was prepared according to procedure b, described above using ethanethiol (680 µl, 9.02 mmol) as the sulfur source. The title compound was isolated as a colourless oil (1.27 g, 0.39 mmol, 95 %).

^{1}H (300 MHz, $CDCl_3$) δ = 1.21 (6H, t, J = 7 Hz, $SCH_2\underline{C}H_3$); 1.31 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$); 2.42 (2H, q, J = 7 Hz, $SC\underline{H}_2CH_3$); 3.66 (4H, s, $C\underline{H}_2SEt$); 4.28 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$); 4.63 (2H, s, $OC\underline{H}_2CO_2Et$); 6.77 (2H, s, $Ar^2C\underline{H}$); 6.90 (1H, s, $Ar^4C\underline{H}$).
^{13}C (75 MHz, $CDCl_3$) δ = 14.3 ($OCH_2\underline{C}H_3$); 14.5 ($SCH_2\underline{C}H_3$); 31.7 ($S\underline{C}H_2CH_3$); 35.9 ($\underline{C}H_2Et$); 61.5 ($O\underline{C}H_2CH_3$); 65.6 ($O\underline{C}H_2CO_2Et$); 113.8 ($Ar^2\underline{C}H$); 122.9 ($Ar^4\underline{C}H$); 140.6 ($Ar\underline{C}CH_2SEt$); 158.2 ($Ar\underline{C}$-O); 169.0 ($CH_2\underline{C}O_2Et$).

M/z (EIMS): 328.0 (([$M^{+\cdot}$] 89 %); 268.1 (86 %); 206.0 (100 %).
HRMS: calcd for ($C_{16}H_{24}O_3S_2$) [$M^{+\cdot}$] 328.1167, found 328.1166.
IR (ν_{max}/cm^{-1}): 2969-2871 (m, aliphatic C-H); 1758 (s, C=O); 1593 (aryl C-H).
R_F: 0.5 (10 % EtOAc:Hexane)

6.4.10 Synthesis of 3,5-di-(tetrahydro-pyran-2'-yloxymethyl)-phenoxy]-tert-butyl-dimethyl-silane (109)



Diol **99** (600 mg, 2.1 mmol), 3,4-Dihydro-2H-pyran (771 µl, 8.5 mmol) and *p*-pyridinium-toluenesulfonate (cat) were stirred in dry DCM (10 ml) at room temperature for 2 hours. After this time the reaction mixture was diluted with DCM (20 ml) and washed with a 50 % saturated brine solution (1 x 20 ml). The organic phase was separated and dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the title compound as a brown oil (926 mg, 2.1 mmol, 100 %).

^{1}H (300 MHz, $CDCl_3$) δ = 0.21 (6H, s, $SiC\underline{H}_3$); 1.00 (9H, s, $SiC(C\underline{H}_3)_3$); 1.57 (4H, m, $OCH_2C\underline{H}_2$ (x2) and $CH_2C\underline{H}_2CH_2$ (x2)); 1.63 (4H, m, $OCHC\underline{H}_2$ (x2) and $OCH_2C\underline{H}_2$ (x2)); 1.78 (2H, m, $OCHC\underline{H}_2$ (x2)); 1.87 (2H, m, $CH_2C\underline{H}_2CH_2$ (x2)); 3.55 (2H, m, $OC\underline{H}_2CH_2$ (x2)); 3.93 (2H, m, $OC\underline{H}_2CH_2$ (x2)); 4.47 (2H, m, $ArC\underline{H}_2O$ (x2); 4.71 (2H, t, J = 4 Hz, $OC\underline{H}O$); 4.74 (2H, m, $ArC\underline{H}_2O$ (x2)); 6.79 ($Ar^2C\underline{H}$); 7.00 ($Ar^4C\underline{H}$).

^{13}C (75 MHz, $CDCl_3$) δ = -4.2 ($Si\underline{C}H_3$); 18.4 ($\underline{C}(CH_3)_3$); 19.5 ($CH_2\underline{C}H_2CH_2$); 25.6 ($Si\underline{C}H_3$); 25.9 ($OCH_2\underline{C}H_2$); 30.7 ($OCH\underline{C}H_2$); 62.3 ($O\underline{C}H_2CH_2$); 68.6 ($Ar\underline{C}H_2O$); 97.7 ($O\underline{C}HO$); 118.5 ($Ar^2\underline{C}H$); 120.0 ($Ar^4\underline{C}H$); 140.0 ($Ar\underline{C}CH_2$); 155.9 ($Ar\underline{C}O$).

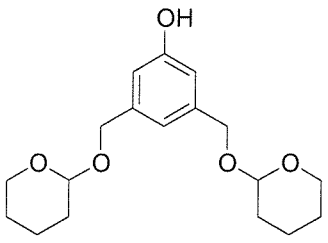
M/z (ES+ve): 895.3 [2M+Na^+] (100 %).

HRMS: calcd for ($C_{24}H_{40}O_5SiK$) [M+K]$^+$ 475.2277, found 475.2277.

IR (ν_{max}/cm^{-1}): 2941 (m, aliphatic C-H); 1598 (m, aryl C-H); 1024 (m, Si-O).

R_F: 0.7 (50% EtOAc:Hexane).

6.4.11 Synthesis of 3,5-di-(tetrahydro-pyran-2'-yloxymethyl)-phenol (120)



Silyl ether **109** (926 mg, 2.1 mmol) and TBAF (1.1 g, 4.2 mmol) were stirred in THF (20 ml) overnight. After this time THF was removed *in vacuo* and DCM

(20 ml) and water (25 ml) added to the resultant brown oil. The phases were separated and the aqueous phase extracted with DCM (3 x 20 ml). The combined organic extracts were washed with water, brine, dried over $MgSO_4$ and the solvent removed *in vauco.* The crude product was purified by column chromatography (1 % MeOH/DCM) to afford the title compound as a colourless oil (535 mg, 1.66 mmol, 79 %).

^{1}H (400 MHz, $CDCl_3$) δ = 1.46 (4H, m, $OCH_2C\underline{H}_2$ (x2) and $CH_2C\underline{H}_2CH_2$ (x2)); 1.56 (4H, m, $OCHC\underline{H}_2$ (x2) and $OCH_2C\underline{H}_2$ (x2)); 1.67 (2H, m, $OCHC\underline{H}_2$ (x2)); 1.70 (2H, m, $CH_2C\underline{H}_2CH_2$ (x2)); 3.48 (2H, m, $OC\underline{H}_2CH_2$ (x2)); 3.86 (2H, m, $OC\underline{H}_2CH_2$ (x2)); 4.37 (2H, d, J = 12 Hz, $ArC\underline{H}_2O$ (x2); 4.65 (2H, m, $OC\underline{H}O$); 4.66 (2H, d, J = 12 Hz, $ArC\underline{H}_2O$ (x2)); 6.29 (1H, bs, OH); 6.70 ($Ar^2C\underline{H}$); 7.20 ($Ar^4C\underline{H}$).

^{13}C (100 MHz, $CDCl_3$) δ = 20.0 ($CH_2\underline{C}H_2CH_2$); 26.1 ($OCH_2\underline{C}H_2$); 31.2 ($OCH\underline{C}H_2$); 62.8 ($O\underline{C}H_2CH_2$); 69.2 ($Ar\underline{C}H_2O$); 98.5 ($O\underline{C}HO$); 114.5 ($Ar^2\underline{C}H$); 120.0 ($Ar^4\underline{C}H$); 140.6 ($Ar\underline{C}CH_2$); 157.0 ($Ar\underline{C}O$).

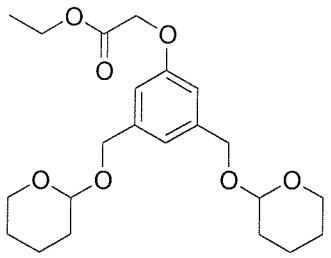
M/z (ES+ve): 667.3 [2M+Na^+] (100 %).

HRMS: calcd for ($C_{36}H_{52}O_{10}Na$) [2M+Na]$^+$ 667.3452, found 667.3464.

IR (ν_{max}/cm^{-1}): 3408 - 3270 (b, O-H); 2942 (s, aliphatic C-H); 1602 (aryl C-C).

R_F: 0.4 (50 % EtOAc:hexane)

6.4.12 Synthesis of ethyl-[3,5-Bis-(tetrahydro-pyran-2-yloxymethyl)-phenoxy]-acetate (121)



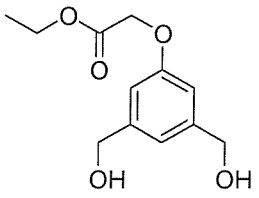
Phenol **120** (488 mg, 1.5 mmol), ethyl-bromoacetate (216 µl, 1.95 mmol), potassium carbonate (269 mg, 1.95 mmol) and potassium iodide (25 mg, 0.15

mmol) were refluxed in acetonitrile (15 ml) for 6 hours. After cooling the mixture was filtered, washed with DCM (30 ml) and the solvent removed *in vacuo*. The resulting residue was purified by column chromatography on silica gel (25 % EtOAc/hexane) to afford the title compound as a colourless oil (498 mg, 1.2 mmol, 81 %).

^{1}H (400 MHz, $CDCl_3$) δ = 1.3 (3H, t, J = 5 Hz, $C\underline{H}_3$); 1.56 (4H, m, $OCH_2C\underline{H}_2$ (x2) and $CH_2C\underline{H}_2CH_2$ (x2)); 1.66 (4H, m, $OCHC\underline{H}_2$ (x2) and $OCH_2C\underline{H}_2$ (x2)); 1.74 (2H, m, $OCHC\underline{H}_2$ (x2)); 1.8 (2H, m, $CH_2C\underline{H}_2CH_2$ (x2)); 3.54 (2H, m, $OC\underline{H}_2CH_2$ (x2)); 3.91 (2H, m, $OC\underline{H}_2CH_2$ (x2)); 4.27 (2H, quar, J = 5 Hz, $CH_3C\underline{H}_2$); 4.47 (2H, d, J = 12 Hz, $ArC\underline{H}_2O$ (x2); 4.62 (2H, s, $OC\underline{H}_2COO$); 4.70 (2H, t, J = 4 Hz, $OC\underline{H}O$); 4.75 (2H, d, J = 12 Hz, $ArC\underline{H}_2O$ (x2)); 6.86 ($Ar^2C\underline{H}$); 6.97 ($Ar^4C\underline{H}$).
^{13}C (100 MHz, $CDCl_3$) δ = 14.6 ($\underline{C}H_3$); 19.7 ($CH_2\underline{C}H_2CH_2$); 25.9 ($OCH_2\underline{C}H_2$); 31.0 ($OCH\underline{C}H_2$); 61.7 ($CH_3C\underline{H}_2$); 62.5 ($O\underline{C}H_2CH_2$); 65.9 ($O\underline{C}H_2COO$); 68.8 ($Ar\underline{C}H_2O$); 98.2 ($O\underline{C}HO$); 113.4 ($Ar^2\underline{C}H$); 120.6 ($Ar^4\underline{C}H$); 140.6 ($Ar\underline{C}CH_2$); 158.5 ($Ar\underline{C}O$); 169.3 ($CH_2\underline{C}O_2Et$).

M/z (ES+ve): 431.3 [M+ Na^+] (100 %).
HRMS: calcd for ($C_{22}H_{32}O_7K$) $[2M+K]^+$ 447.1780, found 447.1781.
IR (ν_{max}/cm^{-1}): 2940 (s, aliphatic C-H) ; 1761 (s, C=O) ; 1599 (m, aryl C-H).
R_F: 0.6 (50 % EtOAc:hexane).

6.4.13 Synthesis of ethyl-(3,5-Bis-hydroxymethyl-phenoxy)-acetate (122)



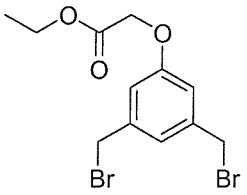
THP ether **121** (500 mg, 1.2 mmol) was stirred with *p*-toluene-sulfonic acid (11 mg, 0.06 mmol) in EtOH (15 ml) for 18 hours after which time the solvent was removed *in vacuo*. The resulting residue was purified by column

chromatography on silica gel (25 % EtOAc/hexane) to afford the title compound as a white solid (214 mg mg, 0.97 mmol, 81 %).

^{1}H (300 MHz, CD_3OD) δ = 1.29 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$); 4.25 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$); 4.57 (4H, s, $C\underline{H}_2OH$); 4.69 (2H, s, $OC\underline{H}_2CO_2Et$); 6.84 (2H, s, $Ar^2C\underline{H}$); 6.96 (1H, s, $Ar^4C\underline{H}$).
^{13}C (75 MHz, CD_3OD) δ = 14.4 ($OCH_2\underline{C}H_3$); 62.2 ($O\underline{C}H_2CH_3$); 64.8 ($\underline{C}H_2OH$); 66.1 ($O\underline{C}H_2CO_2Et$); 112.7 ($Ar^2\underline{C}H$); 119.3 ($Ar^4\underline{C}H$); 144.6 ($Ar\underline{C}CH_2OH$); 159.6 ($Ar\underline{C}$-O); 170.9 ($CH_2\underline{C}O_2Et$).

M/z (EIMS): 240.1 ([$M^{+\cdot}$] 100 %).
HRMS: calcd for ($C_{12}H_{16}O_5$) [$M^{+\cdot}$] 240.0998, found 240.0996.
IR (ν_{max}/cm^{-1}): 3510 – 3254 (b, O-H); 1740 (s, C=O); 1599 (aryl C-H).
Anal: calcd for ($C_{12}H_6O_5$): C, 59.99; H, 6.71 found C, 59.70, H, 6.63.
R_F: 0.6 (EtOAc).
m.p.: 74 - 76 °C.

6.4.14 Synthesis of ethyl-(3,5-Bis-bromomethyl-phenoxy)-acetate (123)



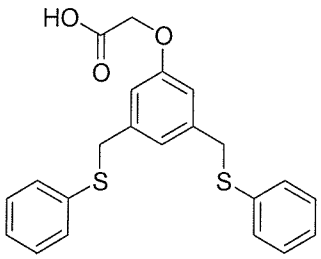
MsCl (57 μl, 0.37 mmol) was added dropwise to an ice-cold, stirred solution of diol **122** (80 mg, 0.33 mmol) and dry NEt_3 (146 μl, 0.53 mmol) in dry DCM (5 ml). The initial colourless solution, which immediately went bright yellow, was stirred for 50 minutes after which time LiBr (573 mg, 6.6 mmol) and acetone (10 ml) were added. The reaction was refluxed for 18 hours after which time the solvent was removed *in vacuo*. DCM (15 ml) and water (25 ml) were added, the phases separated and the aqueous phase extracted with DCM (3 x 20 ml). The combined organic extracts were washed with H_20 (1 x 20 ml), 1 M HCl (1 x 20 ml) and brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The

resulting yellow oil was chromatographed in 25 % EtOAc/hexane to give the title compound as a yellow oil (214 mg, 9.7 mmol).

^{1}H (300 MHz, CD_3Cl_3) δ = 1.30 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$); 4.28 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$); 4.42 (4H, s, $C\underline{H}_2Br$); 4.63 (2H, s, $OC\underline{H}_2CO_2Et$); 6.87 (2H, s, $Ar^2C\underline{H}$); 7.05 (1H, s, $Ar^4C\underline{H}$).
^{13}C (75 MHz, $CDCl_3$) δ = 14.3 ($OCH_2\underline{C}H_3$); 32.7 ($\underline{C}H_2Br$); 61.7 ($O\underline{C}H_2CH_3$); 65.6 ($O\underline{C}H_2CO_2Et$); 115.6 ($Ar^2\underline{C}H$); 123.0 ($Ar^4\underline{C}H$); 139.9 ($Ar\underline{C}CH_2OH$); 158.3 ($Ar\underline{C}$-O); 168.6 ($CH_2\underline{C}O_2Et$).

M/z (EIMS): 366.1 ([^{79}Br ^{81}Br $M^{+\cdot}$] 19 %); 285.2 (100 %).
HRMS: calcd for ($C_{12}H_{14}O_3{}^{79}Br_2$) [$M^{+\cdot}$] 363.9310, found 363.9308.
IR (ν_{max}/cm^{-1}): 1736 (s, C=O); 1599 (aryl C-H).
R_F: 0.7 (25 % EtOAc:hexane).

6.4.15 Synthesis of (3,5-Bis-phenylsulfanylmethyl-phenoxy)-acetic acid (124a)



Ester **102a** (784 mg, 1.9 mmol) and LiOH were stirred in THF:water (4:1, 15 ml) for 1 hour at room temperature. The organic solvent was removed *in vacuo* and the title compound precipitated as a white solid by dropwise addition of c.HCl to afford the desired compound as a white solid (595 mg, 1.5 mmol, 79 %).

^{1}H (300 MHz, CD_3OD) δ = 4.01 (4H, s, $C\underline{H}_2SPh$); 4.50 (2H, q, J = 7 Hz, $OC\underline{H}_2CO_2H$); 6.69 (2H, s, $Ar^2C\underline{H}$); 6.85 (1H, s, $Ar^4C\underline{H}$); 7.20 (10H, m, $SC_6\underline{H}_5$).
^{13}C (75 MHz, CD_3OD) 39.9 ($\underline{C}H_2SPh$); 66.4 ($O\underline{C}H_2CO_2Et$); 115.3 ($Ar^2\underline{C}H$); 124.2 ($Ar^4\underline{C}H$); 127.9 ($SAr^{4'}\underline{C}H$); 130.3 ($SAr^{2'}\underline{C}H$); 131.7 ($SAr^{3'}\underline{C}H$); 137.7 ($SAr^{1'}\underline{C}$); 141.5 ($Ar\underline{C}CH_2SPh$); 159.8 ($Ar\underline{C}$-O); 172.9 ($CH_2\underline{C}O_2H$).

M/z (ES-ve): 791.1 ([2M-H]$^-$ 100 %); 1186.9 ([3M-H]$^-$ 50 %)

HRMS: calcd for ($C_{22}H_{19}O_3S_2$) [M-H]$^-$ 395.0781, found 395.0784.

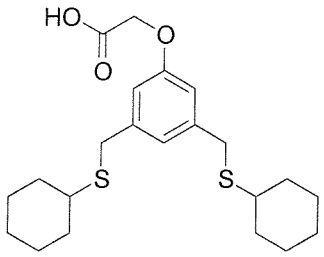
IR (ν_{max}/cm^{-1}): 3551 (w, OH) 1747 (s, C=O); 1587 (aryl C-C).

Anal: calcd for ($C_{22}H_{20}O_3S_2$): C, 66.64; H, 5.08 found C, 66.67, H, 5.15.

R_F: 0 (EtOAC)l

m.p.: 92 – 94 °C.

6.4.16 Ethyl-(3,5-Bis-cyclohexylsulfanylmethyl-phenoxy)-acetate (124b)



The title compound was prepared according to the procedure described above from ester **102b** (1.27 g, 0.39 mmol). The desired compound was isolated as a white solid (963 mg, 0.32 mmol, 82 %).

^{1}**H** (400 MHz, CD_3OD) δ = 1.24 (10H, m, SCHC$\underline{H}_2$ (x4); SCHCH$_2$C$\underline{H}_2$ (x4); SCHCH$_2$CH$_2$C$\underline{H}_2$ (x2)); 1.58 (2H, m, SCHCH$_2$CH$_2$C$\underline{H}_2$ (x2)); 1.72 (4H, m, SCHCH$_2$C$\underline{H}_2$ (x4)); 1.91 (4H, m, SCHC$\underline{H}_2$ (x4)); 3.68 (4H, s, C$\underline{H}_2$Schex); 4.63 (2H, s, OC$\underline{H}_2$CO$_2$H); 6.78 (2H, s, Ar^{2}C$\underline{H}$); 6.92 (1H, s, Ar^{4}C$\underline{H}$).

^{13}**C** (100 MHz, CD_3OD) δ = 27.4 (SCHCH$_2$CH$_2$C$\underline{H}_2$) and (SCHCH$_2$C$\underline{H}_2$); 35.0 (SCHC$\underline{H}_2$); 35.6 (C$\underline{H}_2$Schex); 44.3 (S$\underline{C}$H) 66.4 (O$\underline{C}$H$_2$CO$_2$H); 115.0 (Ar^{2}C$\underline{H}$); 124.1 (Ar^{4}C$\underline{H}$); 142.7 (Ar$\underline{C}$CH$_2$Schex); 160.0 (Ar$\underline{C}$-O); 173.1 (CH$_2\underline{C}$O$_2$H).

M/z (ES-ve): 1223.2 [3M-H]$^-$ (100 %).

HRMS: calcd for ($C_{22}H_{31}O_3S_2$) [M-H]$^-$ 407.1720, found 407.1711.

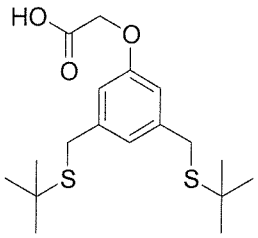
lR (ν_{max}/cm^{-1}): 2924-2850 (s, aliphatic C-H); 1741 (s, C=O); 1594 (aryl C-H).

Anal: calcd for ($C_{22}H_{32}O_3S_2$): C, 64.67; H, 7.89 found C, 64.6, H, 7.87.

R_F: 0 (EtOAC)

m.p.: 98-99 °C

6.4.17 (3,5-Bis-tert-butylsulfanylmethyl-phenoxy)-acetic acid (124c)



The title compound was prepared according to the procedure described above from ester **102c** (1.46 g, 0.38 mmol). The desired compound was isolated as a white solid (1.3 g, 0.36 mmol, 95 %).

^{1}H (300 MHz, CD_3OD) δ = 1.32 (18H, s, $C(C\underline{H}_3)_3$); 3.73 (4H, s, $C\underline{H}_2S^tBu$); 4.63 (2H, s, $OC\underline{H}_2CO_2H$); 6.79 (2H, s, $Ar^2C\underline{H}$); 6.96 (1H, s, $Ar^4C\underline{H}$).

^{13}C (75 MHz, CD_3OD) δ = 31.2 ($C(\underline{C}H_3)_3$) 34.0 ($\underline{C}H_2S^tBu$); 43.5 ($\underline{C}(CH_3)3$); 65.8 ($O\underline{C}H_2CO_2H$); 114.6 ($Ar^2\underline{C}H$); 123.9 ($Ar^4\underline{C}H$); 141.9 ($Ar\underline{C}CH_2S^tBu$); 159.4 ($Ar\underline{C}$-O); 172.6 ($CH_2\underline{C}O_2H$).

M/z (ES-ve): 711.5 $[2M-H]^-$ (100 %).

HRMS: calcd for ($C_{18}H_{27}O_3S_2$) $[M-H]^-$ 355.1407, found 355.1411.

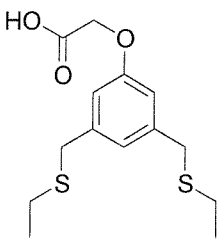
IR (ν_{max}/cm^{-1}): 2961-2862 (m, aliphatic C-H); 1738 (s, C=O); 1594 (aryl C-H).

Anal: calcd for ($C_{18}H_{28}O_3S_2$): C, 60.64; H, 7.92 found C, 60.84, H, 7.97.

R_F: 0 (EtOAC)

m.p.: 86-88 °C

6.4.18 (3,5-Bis-ethylsulfanylmethyl-phenoxy)-acetic acid (124d)

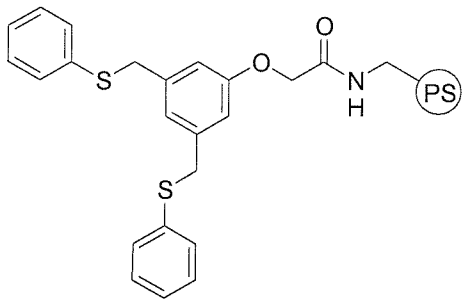


The title compound was prepared according to the procedure described above from ester **102d** (1.27 g, 0.39 mmol). The desired compound was isolated as a white solid (963 mg, 0.32 mmol, 82 %).

^{1}H (300 MHz, CD_3OD) δ = 1.20 (3H, t, J = 8 Hz, $SCH_2C\underline{H}_3$); 2.42 (2H, q, J = 8 Hz, $SC\underline{H}_2CH_3$); 3.8 (4H, s, $C\underline{H}_2SEt$); 4.64 (2H, s, $OC\underline{H}_2CO_2H$); 6.79 (2H, s, $Ar^2C\underline{H}$); 6.91 (1H, s, $Ar^4C\underline{H}$).
^{13}C (75 MHz, CD_3OD) δ = 14.7 ($SCH_2\underline{C}H_3$); 25.8 ($S\underline{C}H_2CH_3$); 36.2 ($\underline{C}H_2SEt$); 65.8 ($O\underline{C}H_2CO_2H$); 114.5 ($Ar^2\underline{C}H$); 123.6 ($Ar^4\underline{C}H$); 141.8 ($ArC\underline{C}H_2SEt$); 159.4 ($Ar\underline{C}$-O); 172.6 ($CH_2\underline{C}O_2H$).

M/z (ES-ve): 599.2 $[2M-H]^-$ (100 %).
HRMS: calcd for ($C_{14}H_{19}O_3S_2$) $[2M-Na]^-$ 299.0781, found 299.0776.
IR (ν_{max}/cm^{-1}): 2961 - 2873 (m, aliphatic C-H); 1737 (s, C=O); 1591 (aryl C-C).
Anal: calcd for ($C_{14}H_{20}O_3S_2$): C, 55.97; H, 6.71 found C, 55.59, H, 6.7.
R_F: 0 (EtOAC)
m.p.: 86-88 °C

6.4.19 Synthesis of (3,5-Bis-phenylsulfanylmethyl-phenoxy)-acetyl aminomethyl PS (125a)



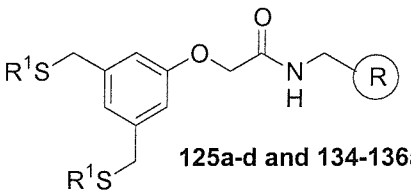
Aminomethyl PS (loading 1.65 mmol/g, 194 mg, 0.32 mmol) was swollen in the minimum amount of DMF for 30 minutes. Acid **124a** (178 mg, 0.45 mmol) and HOBt (81 mg, 0.6 mmol) were stirred in DCM/DMF (50:1, 5 ml) for 10 minutes after which time DIC (94 μl, 0.6 mmol) was added in one portion. The solution was stirred for a further 10 minutes before addition to the pre-swollen resin.

The resin was agitated overnight to effect coupling and washed with DMF (3 x 10 ml), DCM (3 x 10 ml), MeOH (3 x 10 ml) Et_2O (3 x 10 ml) and dried under vacuum for 30 minutes. A qualitative ninhydrin text was negative.

Appearance: *pale yellow resin*

IR (ν_{max}/cm^{-1}): 2923– 2954 (m, aliphatic C-H); 1675 (s, C=O); 1596 (aryl C-H).

6.4.20 Synthesis of Resins (125b-d) and (134-136 a-d)



125a-d and 134-136a-d

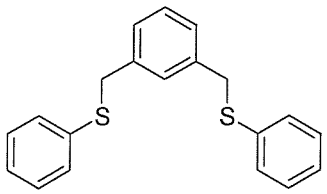
125	R = PS	**a**	R^1 = Ph
134	R = PS-6	**b**	R^1 = ^{c}hex
135	R = TG	**c**	R^1 = ^{t}Bu
136	R = AP	**d**	R^1 = Et

Resins **125b-d** and **134 a-d** were prepared in a similar fashion to that described previously for **125a** using the quantities outlined in Table 42. All resins were pale yellow in appearance.

Resin/Reagent	molar quantity (mmol)	mass/volume
PS (**125**) 1.65 mmol/g	0.32	194 mg
PS-6 (**134**) 1.39 mmol/g	0.32	230 mg
TG (**135**) 0.25 mmol/g	0.32	1.28 g
AP (**136**) 0.75 mmol/g	0.32	427 mg
Acid		
124a (Ph)	0.45	178 mg
124b (^{c}hex)	0.45	184 mg
124c (^{t}Bu)	0.45	160 mg
124d (Et)	0.45	135 mg
HOBt	0.6	81 mg
DIC	0.6	94 μl

Table 42 Quantities used in the Synthesis of Resins 125b-d and 134 a-d

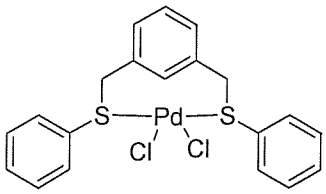
6.4.21 Synthesis of (3,5-Bis-phenylsulfanylmethyl)benzene (127)[131]



α-α'-dibromo-*m*-xylene (1.5 g, 5.6 mmol), K_2CO_3 (2.4 g, 14 mmol) and thiophenol (1.17 ml, 11.4 mmol) were stirred for 18 hours at 100 °C in DMF (20 ml). DCM (20 ml) and water (30 ml) were added to the resultant milky suspension and the phases separated. the aqueous phase was extracted with DCM (3 x 20 ml), the majority of the solvent was removed *in vacuo,* leaving 10 ml from which the title compound crystallised as a white crystalline solid upon standing for 18 hours (1.40 g, 4.3 mmol, 78 %).

^{1}H (400 MHz, $CDCl_3$) δ = 4.02 (4H, s, C$\underline{H}_2$SPh); 7.0 – 7.3 (13H, m, ArC$\underline{H}$).
^{13}C (100 MHz, $CDCl_3$) δ = 39.4 ($\underline{C}H_2$SPh); 126.8; 128.1; 129.0; 129.3; 129.8; 130.4 (Ar$\underline{C}$H); 136.7 (SAr$^{1'}\underline{C}$); 138.2 (Ar$\underline{C}CH_2$SPh).
M/z (EIMS): 322.2 (([$M^{+\cdot}$] 72 %); 213.11 (100 %); 179.2 (69 %).
R_F: 0.9 (50 % EtOAc:hexane)
m.p.: 73 – 75 °C(DCM/DMF) (lit., 72)[132]

6.4.22 Synthesis of Cyclopalladated Complex (128)[133]



Palladium chloride (165 mg, 0.93 mmol) was refluxed in MeCN (100 ml) for 3 hours, after which time complete dissolution of the palladium complex had occurred. **127** (300 mg, 0.93 mmol) was added to the resultant red solution in one portion and immediately the product precipitated as an orange solid. The

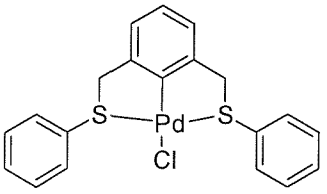
reaction mixture was refluxed for a further two hours after which time the product was isolated by filtration (460 mg, 0.93 mmol, quant).

This compound was too insoluble to record an NMR spectrum.

M/z (ES+ve): 465.0 ($[M\text{-}Cl]^+$ 80 %).

m.p.: >250 °C

6.4.23 Synthesis of Cyclopalladated Complex (129)[133]



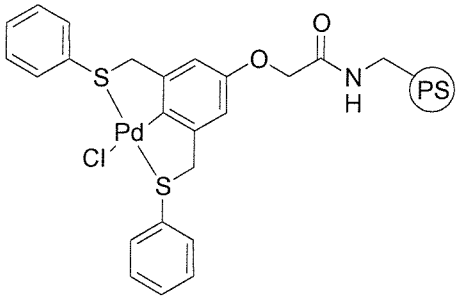
Palladium Chloride (27 mg, 0.15 mmol) was stirred in MeCN (20 ml) at reflux for 1 hour, after which time $AgBF_4$ (29 mg, 0.30 mmol) was added in one portion. Strong effervescence, precipitation of grey coloured AgCl and an immediate colour change of the dark red solution to bright yellow was observed. The reaction mixture was refluxed for 1 hour after which time it was filtered hot and immediately heated back to reflux. **127** (50 mg, 0.05 mmol) was then added in one portion. After a further four hours at reflux the solvent was removed in vacuo and the orange residue resuspended in a 3:1 mixture of MeCN, DCM (3 ml). Brine (3ml) was added and the biphasic solution stirred at room temperature for 1.5 hours. The phases were separated and the organic phase was allowed to stand at room temperature until the product precipitated as a yellow crystalline solid (92 mg, 0.2 mmol, 68 %).

An NMR spectra of this compound was recorded but was difficult to interpret as peaks were broad. In the ^{13}C NMR, the $\underline{C}H_2S$ peak was shifted from 39.4 ppm for the non-palladated compound **127** to 52.0 and a peak at 150.0 was present which has previously been reported to be a C-Pd chemical shift. The crystal structure obtained which is shown in the appendix confirms that the product was the tridentate species.

M/z (ES+ve): 465.0 ($[M-Cl]^+$ 80 %).

m.p.: >250 °C

6.4.24 Synthesis of (3,5-Bis-phenylsulfanylmethyl-phenoxy)-acetyl aminomethyl PS Palladium Complex (125a(Pd))



Palladium Chloride (54 mg, 0.31 mmol) was stirred in MeCN (30 ml) at reflux for 40 minutes, after which time $AgBF_4$ (122 mg, 0.62 mmol) was added in one portion. Strong effervescence, precipitation of grey coloured AgCl and an immediate colour change of the dark red solution to bright yellow was observed. The reaction mixture was refluxed for 1 hour after which time it was filtered hot and immediately heated back to reflux. Resin **124a** (100 mg, 0.31 mmol) was then added in one portion. After a further 18 hours at reflux the resin was filtered and a mixture of MeCN/DCM/brine (3:1:3, 10ml) added, the biphasic solution was then shaken at room temperature for 3 hours. After this time the resin was filtered, washed with H_2O, H_2O/MeCN (1:1), MeCN, DCM and dried under vacuum at 50 °C to afford the title compound as a dark orange resin

Appearance: dark orange resin

IR (ν_{max}/cm^{-1}): 2925 (m, aliphatic C-H); 1678 (s, C=O); 1596 (aryl C-H).

6.4.25 Synthesis of Resins 125b-d (Pd) and 134–136a-d(Pd)

Resins **125b–d(Pd)**, **a(Pd)-d(Pd)** were prepared in a similar fashion to that described previously for **30a(Pd)** (see section 6.4.24) using all of the resin from

the previous step, $PdCl_2$ (62 mg, 0.35 mmol) and $AgBF_4$ (137 mg, 0.7 mmol). Data is presented in Table 43-8.

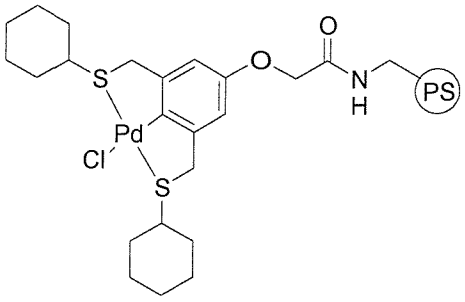
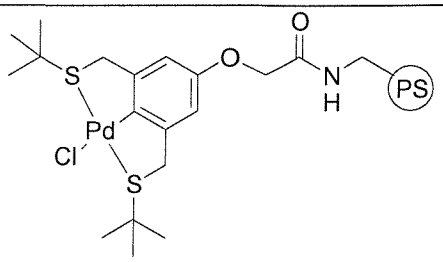
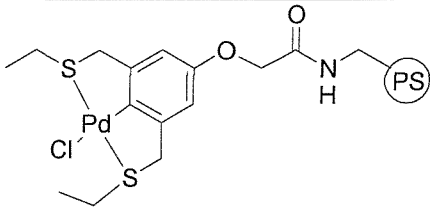
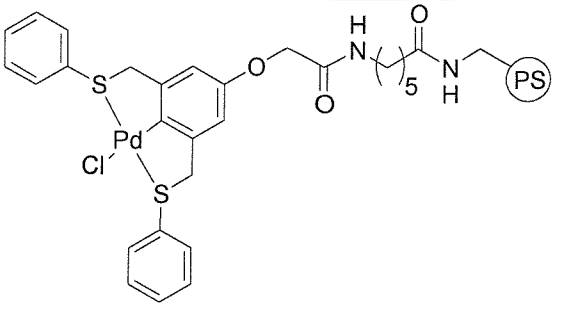
125b(Pd) **Appearance:** dark orange resin	
IR (ν_{max}/cm^{-1}): 2927 (s, aliphatic C-H); 1680 (s, C=O); 1449 (s).	
125c(Pd) **Appearance:** dark red resin	
IR (ν_{max}/cm^{-1}): 2921 (m, aliphatic C-H); 1680 (s, C=O); 1453 (s).	
125d(Pd) **Appearance:** dark red resin.	
IR (ν_{max}/cm^{-1}): 2925 (m, aliphatic C-H); 1678 (s, C=O); 1451 (s).	

Table 43 Data for PS(0) Catalysts

134a(Pd)

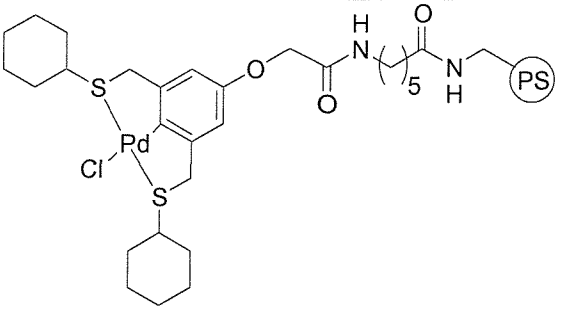
Appearance: light grey resin



IR (ν_{max}/cm^{-1}): 2926 (m, aliphatic C-H); 1658 (s, C=O); 1440 (m).

134b(Pd)

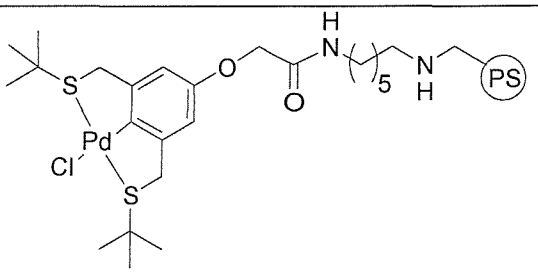
Appearance: brown resin.



IR (ν_{max}/cm^{-1}): 2926 (s, aliphatic C-H); 1664 (s, C=O); 1449 (s).

134c(Pd)

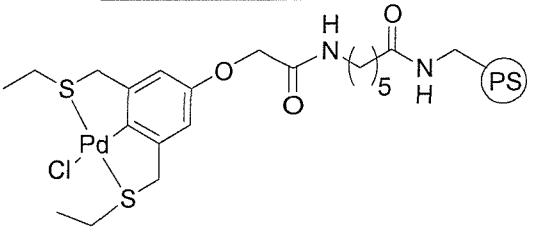
Appearance: dark red resin



IR (ν_{max}/cm^{-1}): 2926 (m, aliphatic C-H); 1658 (s, C=O); 1452 (s).

134d(Pd)

Appearance: light grey resin

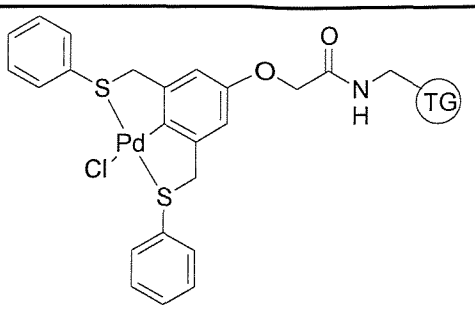


IR (ν_{max}/cm^{-1}): 2926 (m, aliphatic C-H); 1688 (s, C=O); 1451 (m).

Table 44 Data for PS(6) Catalysts

135a(Pd)

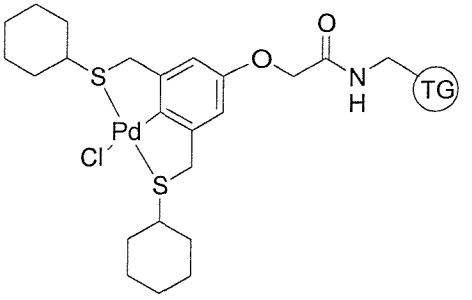
Appearance: light grey resin



IR (ν_{max}/cm^{-1}): 2900 (s, C-H(TG)); 1678 (w, C=O); 1453 (w); 1098 (s, C-O(TG)).

135b(Pd)

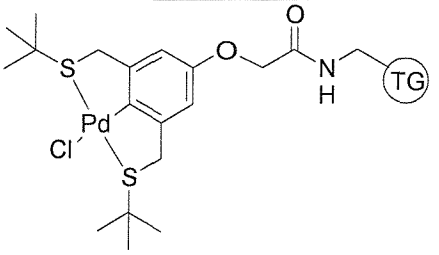
Appearance: pale brown resin



IR (ν_{max}/cm^{-1}): 2969 (s, C-H(TG)); 1670 (w, C=O); 1453 (w); 1096 (s, C-O(TG)).

135c(Pd)

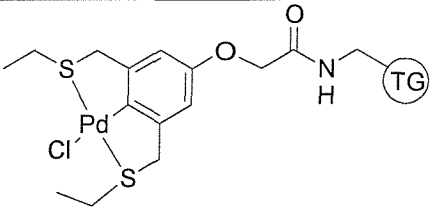
Appearance: dark red resin



IR (ν_{max}/cm^{-1}): 2923 (s, C-H(TG)); 1666 (w, C=O); 1453 (w); 1096 (s, C-O(TG)).

135d(Pd)

Appearance: pale brown resin

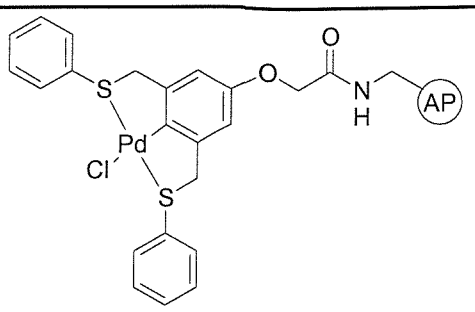


IR (ν_{max}/cm^{-1}): 2867 (s, C-H(TG)); 1672 (w, C=O); 1453 (w); 1096 (s, C-O(TG)).

Table 45 Data for TentaGel Catalysts

136a(Pd)

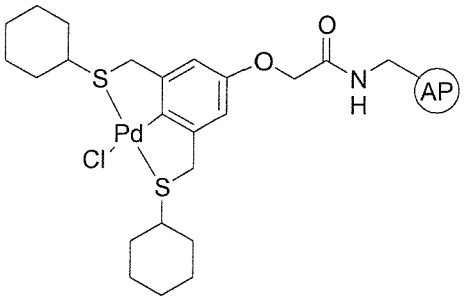
Appearance: dark orange resin



IR (ν_{max}/cm^{-1}): 2922 (s, C-H(AP)); 1681 (m, C=O); 1441 (s, (AP)).

136b(Pd)

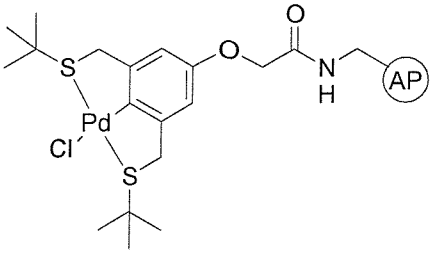
Appearance: orange resin.



IR (ν_{max}/cm^{-1}): 2926 (s, C-H(AP)); 1679 (m, C=O); 1447 (s, (AP)).

136c(Pd)

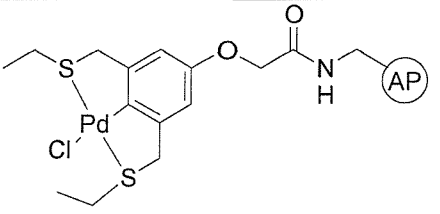
Appearance: dark orange resin



IR (ν_{max}/cm^{-1}): 2925 (s, C-H(AP)); 1682 (m, C=O); 1452 (s, (AP)).

136d(Pd)

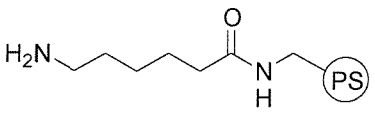
Appearance: dark orange resin



IR (ν_{max}/cm^{-1}): 2922 (s, C-H(AP)); 1681 (m, C=O); 1450 (s, (AP)).

Table 46 Experimental Data for Argopore Catalysts

6.4.26 Synthesis of PS(6) (133)



Aminomethyl PS (loading 1.65 mmol/g, 1.5 g, 2.5 mmol) was swollen in the minimum amount of DMF for 30 minutes. Meanwhile Fmoc-6-amino hexanoic acid (1.3 g, 3.7 mmol) and HOBt (567 mg, 4.2 mmol) were stirred in DMF (15 ml) for 10 minutes after which time DIC (663 μl, 4.2 mmol) was added in one portion. The solution was stirred for a further 10 minutes before addition to the pre-swollen resin. The resin was agitated overnight to effect coupling and washed with DMF (3 x 25 ml), DCM (3 x 25 ml), MeOH (3 x 25 ml) Et_2O (3 x 25 ml) and dried under vacuum for 30 minutes. A qualitative ninhydrin text was negative. The resin was then suspended in 20% piperidine in DMF (15 ml) and shaken for 5 minutes, then filtered, washed with DMF (3 x 10 mL) and resuspended in 20% piperidine in DMF (10 mL). After 15 minutes further shaking, the resin was filtered, washed with DMF (3 x 5 mL), DCM (3 x 5 mL), and MeOH (3 x 5 mL), Et_2O (3 x 5 mL) and dried under vacuum, a qualitative ninhydrin test was positive.

Appearance: pale yellow resin

IR (ν_{max}/cm^{-1}): 2925 (m, aliphatic C-H); 1678 (s, C=O); 1596 (aryl C-H).

6.5 Experimental to Chapter 5

6.5.1 General Heck Coupling Procedure

All Reagents were individually, manually weighed into the modified Radleys Carousel reaction tubes. Solvent (1 ml) was then added by micropipette. The reactions were heated at 70 °C for 24 or 18 hours as required. An aliquot of 10 μl was taken from each reaction vessel and combined with MeCN (1 ml). A 20 μl injection was taken from each reaction and analysed using a 21 minute HPLC gradient (see Table 48) on a Phenomonex Prodigy (150 x 4.6 mm 5 μm) C18 column with a flow rate of 0.5 ml/min.

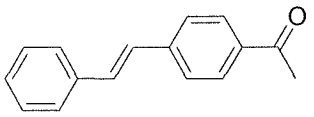
Resin/Reagent	Equiv	molar quantity (mmol)	mass/volume
bromo-acetophenone	1	0.5	100 mg
styrene	2	1	114 μl
PS(0) resins	0.01	0.005	5 mg
PS(6) resins	0.01	0.005	6 mg
TG resins	0.01	0.005	22 mg
AP resins	0.01	0.005	9 mg
NaOH	1	0.5	20 mg
NaOH	2.5	1.25	50 mg
NaOH	4	2	80 mg
Na_2CO_3	1	0.5	53 mg
Na_2CO_3	4	2	212 mg
NaOAc	1	0.5	41 mg
NaOAc	4	2	164 mg
NEt_3	1	0.5	63 μl
NEt_3	4	2	252 μl
$(C_4H_9)_4NBr$	0.1	0.05	16 mg
$(C_4H_9)_4NBr$	0.55	0.275	89 mg
$(C_4H_9)_4NBr$	0.65	0.35	112 mg
$(C_4H_9)_4NBr$	1	0.5	161 mg
$(C_4H_9)_4NBr$	1.05	0.525	169 mg
$(C_4H_9)_4NBr$	2	1	322 mg

Table 47 Quantities used in the Heck Reactions

Time	% MeCN
0	10
10	90
15	90
20	10
21	10

Table 48 *HPLC Gradient for the Analysis of the Heck Reactions*

6.5.2 Synthesis of 4-(1'-styryl)-ethanone (143)[134]



Bromoacetophenone (100 mg, 0.5mmol), styrene (114 μl, 1 mmol), PS-supported catalyst: **125a(Pd)** and NEt_3 (0.75 mmol, 94 μl) were heated at 70 °C for 24 hours in DMF (1 ml) with gentle stirring. The reaction mixture was poured onto H_20 (15 ml) and DCM (15 ml), the phases were separated and the aqueous phase extracted with DCM (3 x 20 ml). The combined organic extracts were washed with H_20 (15 ml), brine (15 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting yellow solid was purified by column chromatography on silica gel (10 % EtOAc/hexane) to afford the title compound as a white solid (45 mg, 0.2 mmol, 40 %).

^{1}H (400 MHz, $CDCl_3$) δ = 2.50 (1H, s, $C\underline{H}_3CO$); 7.02 (1H, d, J = 17 Hz, styryl C$\underline{H}$); 7.12 (1H, d, J = 17 Hz, styryl C$\underline{H}$); 7.21 (2H, d, J = 8 Hz, $Ar^{4'}C\underline{H}$); 7.28 (2H, t, J = 8 Hz, $Ar^{3'}C\underline{H}$); 7.43 (2H, d, J = 9 Hz, $Ar^{2'}C\underline{H}$); 7.48 (2H, d, J = 8 Hz, $Ar^3C\underline{H}$); 7.85 (2H, d, J = 8 Hz, $Ar^2C\underline{H}$).

^{13}C (75 MHz, $CDCl_3$) δ = 27.8 ($CO\underline{C}H_3$); 126.7 ($Ar^3\underline{C}H$); 127.0 ($Ar^{2'}\underline{C}H$) 127.6 (styryl $\underline{C}$H); 128.5 ($Ar^{4'}\underline{C}H$); 128.9 ($Ar^{3'}\underline{C}H$); 129.0 ($Ar^2\underline{C}H$); 136.1 (vinyl $\underline{C}$H); 136.8 (vinyl $\underline{C}$H); 142.1 ($Ar^1\underline{C}H$); 198.0 ($\underline{C}OCH_3$).

IR (ν_{max}/cm^{-1}): 1675 (s, C=O); 1594 (m, aryl C-H); 1261 (m)..

R_F: 0.3 (10 % EtOAc:hexane)

m.p.: 140 °C

6.5.3 Optimisation Results

Results for the DoE investigation are given in Table 49 and 50.

Run	resin	thiol	Base	baseeq	phase	solvent	yield 6hrs	yield 24 hrs	leach 6hrs	leach 24hrs
1	PS 0	Ethyl	Na_2CO_3	1	2	dioxane	7	44	10	5
2	TentaGel	tButyl	Na_2CO_3	1	0	DMF	11	67	9	5
3	PS 0	Ethyl	NaOAc	4	0	heptane	1	3	11	11
4	PS 6	cHexyl	Na_2CO_3	1	0	methyl-butanone	1	3	11	11
5	PS 6	cHexyl	Na_2CO_3	4	2	NMP	6	40	10	10
6	**PS 6**	**tButyl**	**NaOH**	**2.5**	**1**	**DMF**	**25**	**60**	**1**	**1**
7	PS 0	tButyl	NEt_3	1	2	methyl-butanone	7	67	11	11
8	PS 6	tButyl	NaOAc	4	2	dioxane	3	41	11	11
9	ArgoPore	cHexyl	NEt_3	1	2	MECN	14	15	11	10
10	TentaGel	Phenyl	NEt_3	1	0	dioxane	1	1	11	11
11	PS 0	tButyl	NaOH	4	0	MECN	1	1	1	1
12	TentaGel	Ethyl	NaOAc	1	0	pentanol	1	3	11	11
13	ArgoPore	cHexyl	NaOH	4	0	dioxane	10	32	1	1
14	PS 0	cHexyl	NaOAc	1	2	DMF	28	78	10	10
15	ArgoPore	tButyl	NaOAc	4	2	dibutylether	71	94	10	11
16	PS 0	Phenyl	Na_2CO_3	4	0	dibutylether	1	1	11	11
17	TentaGel	cHexyl	NaOAc	4	2	ethylacetate	9	49	11	11
18	**PS 6**	**tButyl**	**NaOH**	**2.5**	**1**	**DMF**	**51**	**60**	**1**	**1**
19	PS 6	Ethyl	NaOH	1	2	dibutylether	65	69	8	8
20	ArgoPore	tButyl	Na_2CO_3	1	0	ethylacetate	1	5	11	11

Run	resin	thiol	Base	baseeq	phase	solvent	yield 6hrs	yield 24 hrs	leach 6hrs	leach 24hrs
21	TentaGel	tButyl	NEt_3	4	0	NMP	17	19	5	3
22	TentaGel	cHexyl	NaOH	1	0	chloroform	2	2	11	11
23	ArgoPore	Phenyl	NaOAc	4	0	chloroform	1	1	11	11
24	ArgoPore	Phenyl	Na_2CO_3	4	2	pentanol	16	58	11	11
25	ArgoPore	Phenyl	NEt_3	1	2	heptane	21	38	7	7
26	PS 0	cHexyl	NEt_3	4	0	pentanol	4	6	11	11
27	ArgoPore	Ethyl	NaOAc	1	0	NMP	33	41	8	6
28	ArgoPore	Ethyl	NaOH	4	0	methyl-butanone	11	29	3	1
29	ArgoPore	Ethyl	NaOH	4	2	DMF	42	49	1	1
30	PS 6	Ethyl	NEt_3	4	0	Ethylacetate	1	3	11	11
31	PS 0	Ethyl	NEt_3	4	2	chloroform	4	22	9	6
32	TentaGel	Phenyl	NaOAc	4	2	methyl-butanone	38	72	8	7
33	TentaGel	cHexyl	NaOH	4	2	heptane	17	92	1	1
34	TentaGel	Ethyl	Na_2CO_3	4	2	MECN	4	5	9	8
35	**PS 6**	**tButyl**	**NaOH**	**2.5**	**1**	**DMF**	**23**	**51**	**1**	**1**
36	PS 6	tButyl	NaOH	1	2	pentanol	4	8	6	6
37	PS 6	Phenyl	NaOAc	1	0	MECN	1	1	11	11
38	PS 0	Phenyl	NaOH	1	2	NMP	69	68	5	5
39	PS 6	Phenyl	NEt_3	4	0	DMF	1	6	8	5
40	PS 0	Phenyl	NaOH	1	2	ethylacetate	13	24	8	4

Table 49 Results for the First Screening Experiment (entries in bold typeface denote the replicated centre points)

Run	resin	thiol	base	phase	solvent	yield 18 hrs	leach 18 hrs
1	PS	Ethyl	NEt_3	2	dioxane	88	9
2	TentaGel	cHexyl	NaOAc	0.1	dioxane	77	11
3	PS	Ethyl	NaOAc	2	dibutylether	75	9
4	PS	Phenyl	NaOAc	2	dioxane	75	10
5	TentaGel	Phenyl	NaOAc	0.1	heptane	27	11
6	TentaGel	cHexyl	NEt_3	2	dibutylether	88	9
7	**PS**	**tButyl**	**NaOAc**	**1.05**	**heptane**	**86**	**10**
8	ArgoPore	cHexyl	NEt_3	2	heptane	89	10
9	PS	tButyl	NaOAc	2	heptane	83	10
10	PS	cHexyl	NEt_3	0.1	dibutylether	57	10
11	ArgoPore	Ethyl	NEt_3	0.1	heptane	36	11
12	PS	tButyl	NEt_3	0.1	DMF	37	7
13	**PS**	**tButyl**	**NaOAc**	**1.05**	**heptane**	**81**	**10**
14	PS	Ethyl	NEt_3	0.1	methyl-butanone	24	10
15	ArgoPore	tButyl	NEt_3	0.1	dioxane	24	9
16	ArgoPore	tButyl	NaOAc	2	dibutylether	79	9
17	TentaGel	tButyl	NaOAc	0.1	methyl-butanone	38	11
18	**PS**	**tButyl**	**NaOAc**	**1.05**	**heptane**	**86**	**11**
19	ArgoPore	Ethyl	NaOAc	0.1	dibutylether	60	11
20	TentaGel	tButyl	NEt_3	2	methyl-butanone	75	8
21	PS	Phenyl	NEt_3	2	methyl-butanone	87	8
22	PS	cHexyl	NaOAc	0.1	DMF	74	8
23	TentaGel	Ethyl	NEt_3	2	dioxane	88	9
24	ArgoPore	Phenyl	NEt_3	2	DMF	72	7
25	TentaGel	Phenyl	NEt_3	0.1	dibutylether	30	11
26	ArgoPore	cHexyl	NaOAc	2	methyl-butanone	79	8
27	ArgoPore	Phenyl	NaOAc	0.1	methyl-butanone	58	8
28	TentaGel	Ethyl	NaOAc	2	DMF	73	8

Table 50 Results for the Second Screening Experiment (entries in bold typeface denote the replicated centre points)

7 Appendix

7.1 Calculation of Standard Deviation

This is a measure of how widely dispersed the values are, the example below shows calculation of the standard deviation for the conversion results of the reproducibility experiment for indene (Table 51).

Experiment	e.e.
1	88
2	88
3	89
4	88
5	92

Table 51 e.e. Results for Indene

The overall equation for standard deviation is given in Equation 1 where D is the deviation of each score from the mean and N is the number of scores.

$$SD = \sqrt{\left(\frac{\Sigma D^2}{N-1}\right)}$$

Equation 1 Standard Deviation

In practice it is common to calculate the standard deviation by putting the values in a table and follow the instructions below:

1. Calculate the mean.
2. Calculate the deviation from the mean.
3. Square each of the deviations.
4. Add the squared deviations up.
5. Divide by the number of deviations, minus one, in this case, 4.
6. Find the square root.

Experiment	e.e.	Mean	Deviation (D)	Deviation Squared (D^2)
1	98	94.69	3.71	13.77
2	96	94.69	1.68	2.82
3	92	94.69	-2.58	6.64
4	92	94.69	-3.19	10.19
5	95	94.69	0.38	0.14
Mean	94.69		Total (Σ)	33.56
			/ N-1 (4)	8.39
			$\sqrt{}$	2.90

Table 52 Calculation of Standard Deviation

7.2 Analysis of Variance and the *F*-ratio

As mentioned in Chapter 3, ANOVA is a useful method used to test the null hypothesis against the alternative hypothesis that the treatment means differ, it has three main assumptions: (1) that samples are selected randomly and independently (2) that population probability distributions are normal and (3) the population variances are equal.

This example shows the ANOVA of the e.e. results of the repeatability experiment, the analysis is shown in Table 53.

ANOVA

Source of Variation	*SS*	*df*	*MS*	***F*-ratio**	***P-value***	***F crit***
Model	10975.53	1.00	10975.53	**5293.82**	**1.42E-12**	**5.32**
Error	16.59	8.00	2.07			
Total	10992.12	9.00				

Table 53 Part of ANOVA table for e.e. of the Repeatability Experiment

The variance of the values is divided into two key components. The first is the variation between the treatment means and is measured by the **Sum of Squares for Treatments (SST)**. The second is the variability within the treatments; this is called

the **Sum of Squares for Error** (**SSE**) as it measures the variability around the treatment means that is attributed to sampling error. The equations for calculation of these values are shown in Equation 2 and 3, where X_1 is a value from group 1 and X_2 is a value from group 2 etc., n_1 is the number of values in group 1 and n_2 the number in group 2 etc. X_T is the total number of values in the group and n_T is the total number of values in all groups. Calculation of these values for the e.e.'s from the reproducibility experiment is demonstrated in Table 54 and 5.

$$SST = \frac{(\sum X_1)^2}{n_1} + \frac{(\sum X_2)^2}{n_2} - \frac{(\sum X_T)^2}{n_T}$$

Equation 2 Equation for **SST**

$$SSE = \left(\sum X_1^2 - \frac{(\sum X_1)^2}{n_1}\right) + \left(\sum X_2^2 - \frac{(\sum X_2)^2}{n_2}\right)$$

Equation 3 Equation for **SSE**

	e.e.		
	indene (X_1)	**β-methyl styrene(X_2)**	
	22.27	88.16	
	22.55	88.23	
	23.51	89.92	
	24.22	88.28	
	23.29	92.52	
totals	$(\sum X_1)$	$(\sum X_2)$	$(\sum X_T)$
	115.83	447.12	562.95
totals square	$((\sum X_1)^2)$	$((\sum X_2)^2)$	$((\sum X_T)^2)$
	13416.03	199917.19	316911.13
divide by number of values[a]	$\left(\frac{(\sum X_1)^2}{n_1}\right)$	$\left(\frac{(\sum X_2)^2}{n_2}\right)$	$\left(\frac{(\sum X_T)^2}{n_T}\right)$
	2683.21	39983.44	31691.11
	SST = 2683.21 + 39983.44 – 31691.11 = 10975.53		

[a] $n_1=n_2=5$, $n_T=10$)

Table 54 Calculation of **SST** for e.e.

	e.e.			
	indene (X_1)		β-methyl styrene(X_2)	
	X_1	X_1^2	X_2	X_2^2
	22.27	495.83	88.16	7772.22
	22.55	508.31	88.23	7784.89
	23.51	552.66	89.92	8086.25
	24.22	586.46	88.28	7794.14
	23.29	542.37	92.52	8560.10
totals	(ΣX_1)	(ΣX_1^2)	(ΣX_2)	(ΣX_2^2)
	115.83	2685.64	447.12	39997.59
totals square	$(\Sigma X_1)^2$		$(\Sigma X_2)^2$	
	13416.03		199917.19	
divide by number of values(5)	$\left(\frac{(\Sigma X_1)^2}{n_1}\right)$		$\left(\frac{(\Sigma X_2)^2}{n_2}\right)$	
	2683.21		39983.44	
	SSE = (2685.64 – 2683.21) + (39997.59 – 39983.44)			
	= 2.43 + 14.16			
	= 16.59			

Table 55 Calculation of **SSE** for e.e.

Each **SS** value is then converted to a mean square (**MS**) by dividing it by the degrees of freedom. For **SST**, the number of degrees of freedom is equal to the number of groups minus one (2-1 = 1), for **SSE**, it is the total number of observations, minus the number of groups (10-2 = 8).

Finally the *F*-ratio is achieved by dividing **MST** by **MSE**. The importance of the *F*-ratio was discussed in Chapter 3.

7.3 Solvent Scatter Plots

Scatter plots of the 29 solvents with the four chemical descriptors selected: dielectric constant, dipole moment, lipophilicity and water solubility are shown in Figure 55. The high correlation between the former two is immediately evident. As mentioned in Chapter 3, the statisticians chose to trim the solvent space by removing solvents with the upper and lower 5 % of values for each of the three descriptors resulting in the matrix scatter plot shown in Figure 56 with lipophilicity removed due to its high correlation with the water solubility.

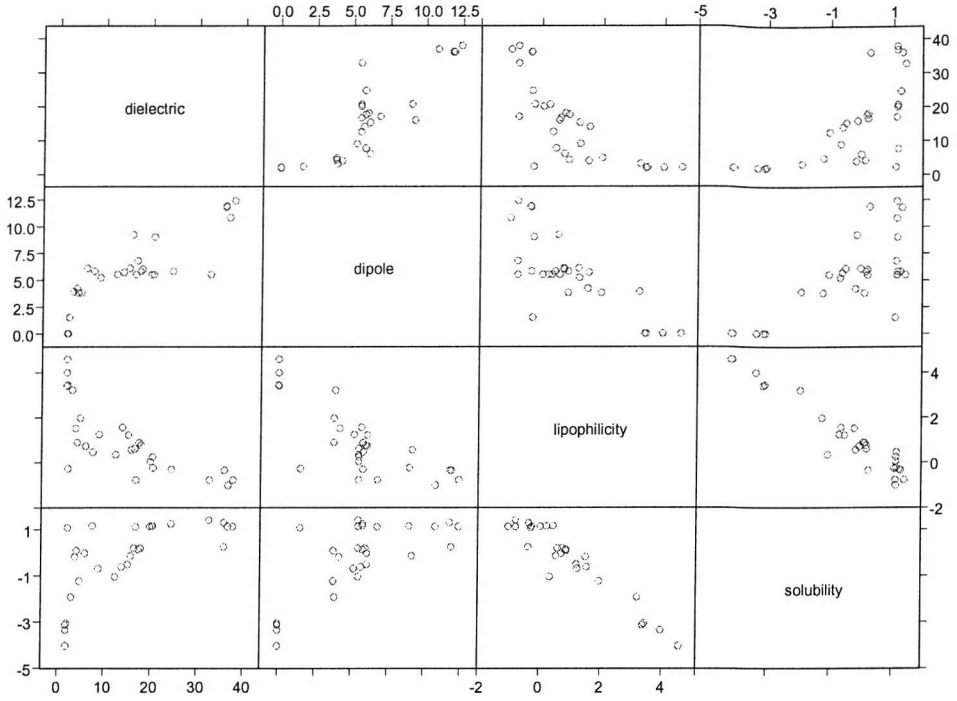


Figure 55 Matrix Scatter Plots of the 29 Solvents with the Four Chemical Descriptors

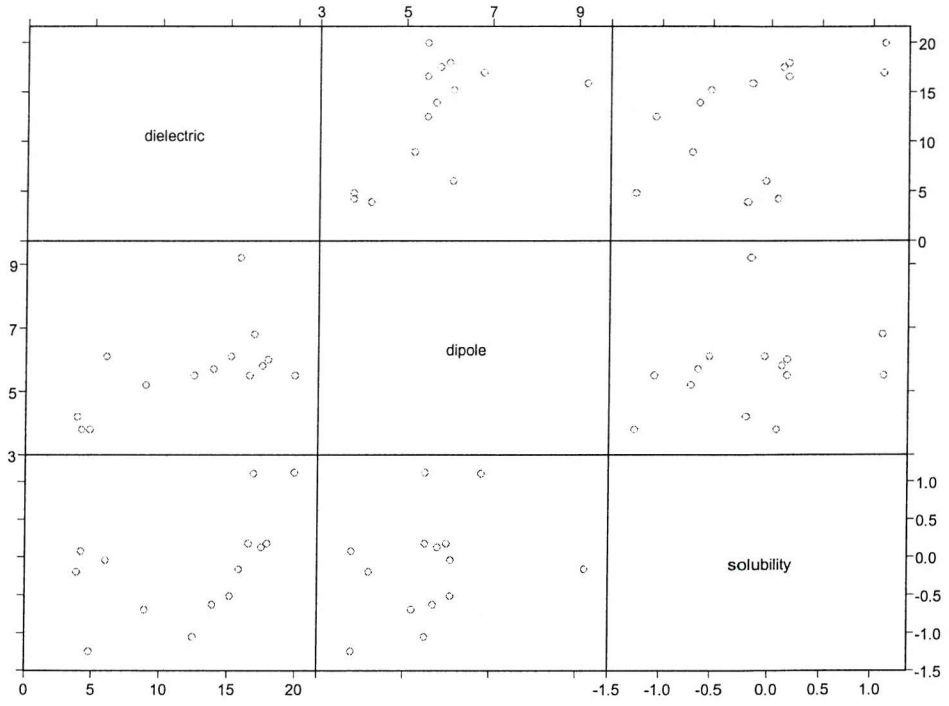


Figure 56 Matrix Scatter Plot of the "Trimmed" Solvents

7.4 Crystal Data for (129)

University of Southampton · Department of Chemistry

EPSRC National Crystallography Service

Table 1. Crystal data and structure refinement.

Identification code	**03sot035**	
Empirical formula	$C_{20}H_{17}ClPdS_2$	
Formula weight	463.31	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 9.8247(2) Å	α = 90°
	b = 18.1562(4) Å	β = 97.5190(10)°
	c = 10.0402(3) Å	γ = 90°
Volume	1775.56(8) Å^3	
Z	4	
Density (calculated)	1.733 Mg / m^3	
Absorption coefficient	1.429 mm^{-1}	
$F(000)$	928	
Crystal	Prism; pale yellow	
Crystal size	0.18 × 0.10 × 0.08 mm^3	
θ range for data collection	2.95 – 27.49°	
Index ranges	$-12 \le h \le 11$, $-23 \le k \le 22$, $-13 \le l \le 13$	
Reflections collected	20194	
Independent reflections	4025 [R_{int} = 0.0554]	
Completeness to θ = 27.49°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8943 and 0.7830	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4025 / 0 / 218	
Goodness-of-fit on F^2	1.044	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0284, $wR2$ = 0.0681	
R indices (all data)	$R1$ = 0.0340, $wR2$ = 0.0713	
Extinction coefficient	0.0022(4)	
Largest diff. peak and hole	0.660 and –0.857 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	9736(2)	2016(1)	3511(2)	15(1)	1
C2	9973(2)	2773(1)	3600(2)	19(1)	1
C3	10856(2)	3050(1)	4675(2)	21(1)	1
C4	11491(2)	2579(1)	5664(2)	20(1)	1
C5	11237(2)	1829(1)	5569(2)	21(1)	1
C6	10358(2)	1538(1)	4495(2)	17(1)	1
C7	7872(2)	2376(1)	1190(2)	20(1)	1
C8	6752(2)	2675(1)	1923(2)	16(1)	1
C9	6360(2)	3408(1)	1837(2)	20(1)	1
C10	5230(3)	3648(1)	2431(2)	23(1)	1
C11	4496(2)	3152(1)	3107(2)	20(1)	1
C12	4905(2)	2416(1)	3235(2)	16(1)	1
C13	6056(2)	2174(1)	2675(2)	15(1)	1
C14	4142(2)	1879(1)	4005(2)	16(1)	1
C15	3626(2)	567(1)	2527(2)	16(1)	1
C16	3918(2)	559(1)	1202(2)	20(1)	1
C17	3001(3)	227(1)	217(2)	24(1)	1
C18	1798(3)	−88(1)	548(3)	25(1)	1
C19	1495(3)	−67(1)	1862(3)	24(1)	1
C20	2423(2)	255(1)	2866(2)	19(1)	1
S1	8701(1)	1597(1)	2111(1)	16(1)	1
S2	4798(1)	938(1)	3873(1)	15(1)	1
Cl1	7818(1)	−20(1)	3473(1)	21(1)	1
Pd1	6815(1)	1171(1)	3023(1)	13(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C6	1.394(3)
C1–C2	1.396(3)
C1–S1	1.793(2)
C2–C3	1.387(3)
C2–H2	0.9500
C3–C4	1.394(3)
C3–H3	0.9500
C4–C5	1.386(4)
C4–H4	0.9500
C5–C6	1.394(3)
C5–H5	0.9500
C6–H6	0.9500
C7–C8	1.503(3)
C7–S1	1.823(2)
C7–H7A	0.9900
C7–H7B	0.9900
C8–C9	1.385(3)
C8–C13	1.415(3)
C9–C10	1.397(4)
C9–H9	0.9500
C10–C11	1.386(4)
C10–H10	0.9500
C11–C12	1.396(3)
C11–H11	0.9500
C12–C13	1.398(3)
C12–C14	1.504(3)
C13–Pd1	1.981(2)
C14–S2	1.836(2)
C14–H14A	0.9900
C14–H14B	0.9900
C15–C20	1.392(3)
C15–C16	1.397(3)
C15–S2	1.789(2)
C16–C17	1.385(3)
C16–H16	0.9500
C17–C18	1.392(4)
C17–H17	0.9500
C18–C19	1.391(4)
C18–H18	0.9500
C19–C20	1.396(3)
C19–H19	0.9500
C20–H20	0.9500
S1–Pd1	2.3051(6)
S2–Pd1	2.2977(6)
Cl1–Pd1	2.3936(6)
C6–C1–C2	120.9(2)
C6–C1–S1	116.27(17)
C2–C1–S1	122.76(17)
C3–C2–C1	119.3(2)
C3–C2–H2	120.4
C1–C2–H2	120.4
C2–C3–C4	120.5(2)
C2–C3–H3	119.8
C4–C3–H3	119.8
C5–C4–C3	119.6(2)
C5–C4–H4	120.2
C3–C4–H4	120.2

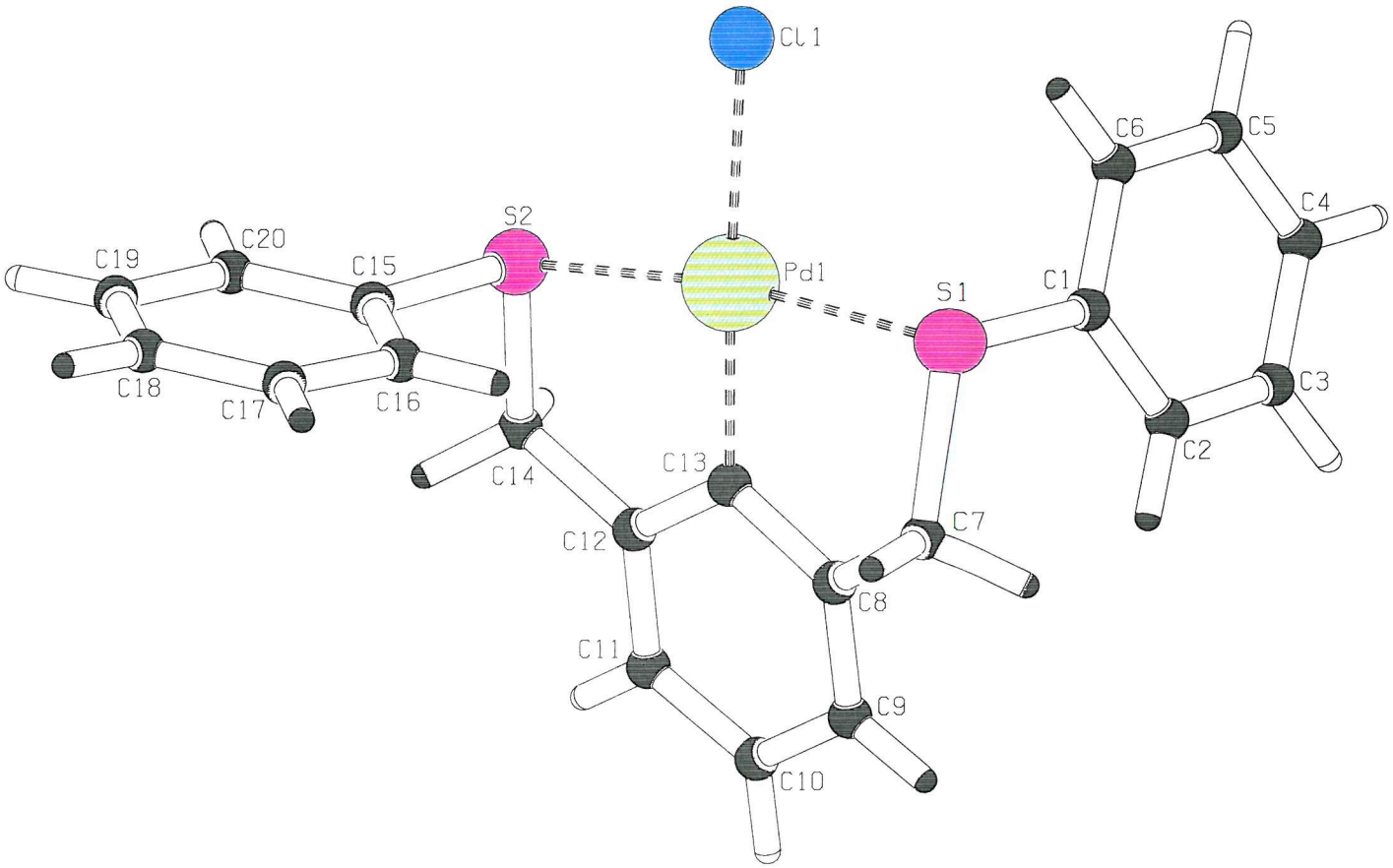
C4–C5–C6	120.9(2)
C4–C5–H5	119.6
C6–C5–H5	119.6
C5–C6–C1	118.8(2)
C5–C6–H6	120.6
C1–C6–H6	120.6
C8–C7–S1	109.83(16)
C8–C7–H7A	109.7
S1–C7–H7A	109.7
C8–C7–H7B	109.7
S1–C7–H7B	109.7
H7A–C7–H7B	108.2
C9–C8–C13	120.1(2)
C9–C8–C7	122.1(2)
C13–C8–C7	117.7(2)
C8–C9–C10	120.2(2)
C8–C9–H9	119.9
C10–C9–H9	119.9
C11–C10–C9	120.0(2)
C11–C10–H10	120.0
C9–C10–H10	120.0
C10–C11–C12	120.3(2)
C10–C11–H11	119.8
C12–C11–H11	119.8
C11–C12–C13	120.1(2)
C11–C12–C14	120.7(2)
C13–C12–C14	119.1(2)
C12–C13–C8	119.0(2)
C12–C13–Pd1	121.61(17)
C8–C13–Pd1	119.23(17)
C12–C14–S2	111.27(16)
C12–C14–H14A	109.4
S2–C14–H14A	109.4
C12–C14–H14B	109.4
S2–C14–H14B	109.4
H14A–C14–H14B	108.0
C20–C15–C16	121.1(2)
C20–C15–S2	116.82(18)
C16–C15–S2	122.06(18)
C17–C16–C15	119.2(2)
C17–C16–H16	120.4
C15–C16–H16	120.4
C16–C17–C18	120.1(2)
C16–C17–H17	119.9
C18–C17–H17	119.9
C19–C18–C17	120.6(2)
C19–C18–H18	119.7
C17–C18–H18	119.7
C18–C19–C20	119.8(2)
C18–C19–H19	120.1
C20–C19–H19	120.1
C15–C20–C19	119.2(2)
C15–C20–H20	120.4
C19–C20–H20	120.4
C1–S1–C7	103.80(11)
C1–S1–Pd1	103.51(7)
C7–S1–Pd1	97.63(8)
C15–S2–C14	102.00(10)
C15–S2–Pd1	106.84(8)
C14–S2–Pd1	100.61(8)

C13–Pd1–S2	84.89(7)
C13–Pd1–S1	85.72(7)
S2–Pd1–S1	170.60(2)
C13–Pd1–Cl1	177.76(6)
S2–Pd1–Cl1	96.77(2)
S1–Pd1–Cl1	92.62(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	12(1)	19(1)	14(1)	−3(1)	4(1)	−2(1)
C2	17(1)	20(1)	20(1)	2(1)	4(1)	−1(1)
C3	21(1)	16(1)	25(1)	−4(1)	7(1)	−4(1)
C4	13(1)	28(1)	19(1)	−8(1)	2(1)	−2(1)
C5	17(1)	28(1)	18(1)	0(1)	2(1)	4(1)
C6	14(1)	19(1)	19(1)	−1(1)	6(1)	2(1)
C7	19(1)	23(1)	16(1)	5(1)	2(1)	1(1)
C8	14(1)	20(1)	13(1)	0(1)	−2(1)	−2(1)
C9	23(1)	19(1)	18(1)	2(1)	−3(1)	−5(1)
C10	30(1)	13(1)	23(1)	−2(1)	−3(1)	3(1)
C11	19(1)	22(1)	19(1)	−5(1)	2(1)	2(1)
C12	15(1)	19(1)	14(1)	−4(1)	−2(1)	−1(1)
C13	14(1)	17(1)	14(1)	0(1)	−2(1)	−1(1)
C14	18(1)	18(1)	14(1)	−3(1)	4(1)	3(1)
C15	16(1)	14(1)	17(1)	1(1)	−1(1)	2(1)
C16	20(1)	24(1)	16(1)	0(1)	3(1)	2(1)
C17	25(1)	28(1)	18(1)	−5(1)	0(1)	7(1)
C18	23(1)	21(1)	28(1)	−9(1)	−7(1)	4(1)
C19	17(1)	20(1)	35(1)	−2(1)	0(1)	−2(1)
C20	18(1)	19(1)	21(1)	0(1)	3(1)	1(1)
S1	14(1)	19(1)	14(1)	−1(1)	3(1)	−1(1)
S2	15(1)	17(1)	13(1)	0(1)	2(1)	−2(1)
Cl1	24(1)	16(1)	22(1)	2(1)	2(1)	3(1)
Pd1	13(1)	14(1)	12(1)	0(1)	2(1)	−1(1)


Cl 1
Pd1
S1
S2
C1
C2
C3
C4
C5
C6
C7
C8
C9
C10
C11
C12
C13
C14
C15
C16
C17
C18
C19
C20

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