Learn Chemistry

Faster Greener Chemistry? Catalyst Synthesis and Evaluation

Tutor Guide

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Introduction - About context/problem based learning

Context/Problem Based Learning (C/PBL) is a teaching methodology that aims to increase student engagement with a subject by designing courses based on real-life applications of the principles, techniques and experiments students encounter in their undergraduate courses. These real world contexts are presented in the form of problem scenarios which are ill-defined and have a number of satisfactory solutions. Learners work collaboratively to solve problems and acquire new knowledge and then present the outcomes or product. This approach provides the opportunity to develop valuable transferable skills such as communication, team working and problem solving. Students are encouraged to take control of their learning and real world examples are used as an effective means to promote real learning. Academic staff adopt the role of facilitator or guide during this process. For further information, the following review on context and problem based learning can be consulted; T.L. Overton, Context and Problem-Based Learning, *New Directions*, Issue 3, Oct. 2007, pages 7-12.
(see http://www.heacademy.ac.uk/assets/ps/documents/new_directions/new_directions/newdir3_link.pdf)

About this learning resource

This case study focuses on the synthesis, characterisation and evaluation of a range of up to nine manganese(III) salen complexes that are employed as catalysts in the oxidation of alkenes to epoxides. Students adopt the role of chemists employed in a campus company that specialises in chemical catalysts, Chem Cat Ltd. Their company has been contracted to carry out some consultancy work for a large pharmaceutical multinational, HugePharma Ltd. Students work in teams and report to their laboratory manager in Chem Cat Ltd. Their brief is outlined in a letter to their Managing Director from the Chemical Development Manager in HugePharma Ltd. The pharmaceutical company have specifically requested that green chemistry (also known as sustainable chemistry) principles be implemented to their full potential in the epoxidation process, as they need to maintain their Integrated Pollution Prevention and Control (IPPC) licence.

The students are required to work as part of a team to:

1. Prepare and characterise one of a range of Mn-salen complexes using a two step synthesis.
2. Evaluate the performance of the catalyst in a reference reaction (epoxidation of stilbene).
3. Assess the relative costs and the environmental impact of this process and of alternative procedures with reference to suitable metrics.

To do this, they need to devise and perform several laboratory experiments to obtain the results required, research relevant information and make a recommendation to HugePharma Ltd.

The context is based on information from the literature, including journal articles and reviews, patents, textbooks, some articles in Chemistry World and Chemical & Engineering News, and environmental protection agency websites. Salts of Mn(III), particularly those that contain salen type ligands (salen is bis(salicylaldehyde)ethylene diamine), have been found to show catalytic activities of significant interest. The main application of these properties to date has been in the asymmetric epoxidation of alkenes (e.g. Jacobsen's catalyst) and oxidation of a variety of organic substrates. As a result, Mn-salens have been employed at commercial scale to oxidise a wide range of organic compounds. The process often uses sodium hypochlorite (bleach) as the oxidant. It is an environmentally friendly reagent as it breaks down into sodium chloride, water and oxygen. It is also inexpensive and has an efficient atom economy. Modifications are being investigated to reduce the environmental impact further as several of the catalysts can be recovered and recycled, and reactions in the absence of an organic solvent and in supercritical carbon

dioxide have been performed. Some useful references that provide more detail are listed in the literature review in the student briefing pack at the end of this guide. This case study resource aligns with the RSC Chemistry for Tomorrow's World priority areas of "Water and Air" and "Raw Materials and Feedstocks".

Who is the learning resource designed for?

The resource is designed for undergraduate students in the last two years of their degree. However, it could be modified to be suitable for students at an earlier stage by providing some additional supporting information on green chemistry principles and environmental legislation and adapting the assessment criteria and learning outcomes to suit the performance expected of learners at that stage.

There are also opportunities for further investigations at more advanced levels such as purification of the epoxide product by column chromatography, determination of the enantiomeric excess in the epoxidation product if chiral diamines were used to prepare the ligand, and variation of the metal (to Co or Fe). References are provided in relation to these other options in the literature review, but they are not dealt with in this guide.

Tutors are encouraged to use this guide as a flexible framework to produce a C/PBL student activity that is appropriate to their circumstances and meets their requirements. It is anticipated that the student contact hours available, prior knowledge of the students and the specific skills, knowledge and understanding to be developed will vary across cohorts and institutions. The tutor and student guides are provided as Microsoft® Word documents so that they can be modified to suit a particular situation and to allow the appropriate learning outcomes to be addressed. With this in mind, the developers have indicated which aspects of the delivery they consider to be core and which ones could be omitted or modified in the section that follows on 'Flexibility within this resource'.

How is the learning resource delivered?

The resource is designed to be delivered to students as a laboratory based course, with 8 three-hour sessions incorporated, four delivered in a laboratory setting, and four not, labelled as workshops. When combined with independent study and writing-up time, it is intended that this resource will require a total of 50 learning hours. (a total of 24 contact hours plus 26 hours of self study). As such it represents approximately 2.5 European Transfer Credit System (ECTS) or 5 UK credits of work or 1.5 US credits.

Some of the workshop sessions require access to computers for all students (Session 1 if some training on using wikis is provided and Session 6 when students are asked to find information on vendors and costing for raw materials). In each case, a one hour session in a computer laboratory would suffice and the remainder of the session can be spent in a classroom. A digital projector is required for Sessions 1 and 8. If possible, access to some computers during all sessions would be useful to allow students to input information into their wiki directly but this is not a requirement.

In addition to the group wikis that the students will produce, it is strongly recommended that a Virtual Learning Environment (or alternatively a 'central' wiki to which all of the students are invited) is used to support this case study. This will allow the tutor to host the Student Guide, supplementary material (presentations, journal articles) and any other information that is deemed appropriate, on a central resource that all of the students can access. It also provides a communication tool that may be useful in implementing the resource (providing general feedback, reminders of tasks to be completed and deadlines etc).

Navigating this tutor guide

A schedule for delivery which provides an overview of the resource is presented in Table 2. It contains a breakdown of what each lab and workshop session will entail, including aims and teaching and learning activities. Further details for each session are included in the relevant sections throughout this Tutor Guide. A simplified version of Table 2 can also be found in the accompanying Student Guide (also Table 2). Table 3 is a schedule of the weekly tasks to be completed by students which are aligned with the suggested tutor feedback / prompts / actions required. The Appendices to this guide contain the student briefing pack (Appendix 1) which is provided to students in the Student Guide for this resource. Appendix 2 deals with using wikis to facilitate and assess group collaboration and Appendix 3 summarises materials, apparatus and instrumentation requirements. The remaining Appendices 4-8 provide detailed tutor notes for Sessions 2-6 respectively and elements of these can serve as a sample answer when assessing student work.

This Tutor Guide in its entirety presents quite a daunting prospect because of its length. However, the Appendices account for almost two thirds of the content so it is recommended that the main body of the guide be printed separately for ease of use (It would also be useful to add the final page which lists the references). Appendices 1-4 would need to have been consulted before beginning this C/PBL case study and, thereafter, the relevant Appendix can be read before the previous session (e.g. read the tutor notes for Session 3 before Session 2). It is recommended that, for each session, the tutor brings along for reference the main body of the Tutor Guide, a copy of the Student Guide and the Appendices relevant to that session and to the next one.

Assessment

This case study resource has three main elements: planning laboratory experiments, conducting experiments and analysis of results and reporting of the data obtained. Therefore, assessment focuses on (i) the planning of the group project, most conveniently monitored using a wiki (see later in this section) (ii) student lab books on experiments conducted and (iii) the reporting, analysis and recommendations arising out of the data obtained. More details on assessment are provided at appropriate points in this guide and the assessment components and a guideline weighting are provided in Table 1 below. These are also presented in the Student Guide (Table 1) and introductory presentation, and can be adjusted if considered necessary.

Table 1: Assessment components

Activity	Group / individual	% mark allocation (guideline)
Contribution to group (based on effort and effective collaboration - evidenced by participation in lab and workshop sessions, summaries of meetings and contribution to group wiki)	Individual	10
Peer assessment by other group members* (based on frequency and quality of contributions, both online and face-to-face)	Individual	5
Lab notebook and individual work submitted on a weekly basis	Individual	30
Reflective piece (criteria are presentation, relevant content and structure, coherence and accuracy)	Individual	10
Final wiki report (Criteria are relevant content, accuracy, structure, clarity, literature references)	Group	30
Presentation - feedback from tutor and peers and assessment by tutor (criteria are visual impact, effectiveness of oral communication, relevant content, accuracy, structure, clarity, references to the literature and understanding).	Group	15

* Peer assessment is an optional but recommended assessment component and the weighting allocated (5%) is low to encourage its inclusion. The weighting can be increased if the tutor wishes to do so.
One option to consider for peer assessment of each member's contribution to the group is peer review software such as CATME (Comprehensive Assessment of Team Member Effectiveness), available to download for free at https://engineering.purdue.edu/CATME. This software was developed with support from the National Science Foundation. E-mail contacts for group members are uploaded by the tutor and a range of statements on team member contributions can be selected to be used.

Flexibility within this resource

The work that learners undertake for this activity focuses on the development of teamwork, communication and problem-solving skills as well as the synthesis and characterisation of organic and organometallic compounds. The context provided requires that the preparation and use of these compounds on a larger scale be evaluated on the basis of their "greenness" (the extent to which hazardous substances are generated or used). Therefore, a tutor can opt to focus more on the organic chemistry (ligands and alkene oxidations), the inorganic chemistry (catalyst complexes, oxidation reagents) or the green / industrial chemistry aspects involved. Alternatively, a collaborative approach could be employed between academics with organic, inorganic and green / industrial chemistry backgrounds. The green chemistry metrics employed in this activity are at an introductory level and, if students have prior knowledge in this area, it would be appropriate to extend what is required of them (further details are provided in the notes provided for Session 6). Consultation with the lecturing staff concerned would be recommended. In addition, a recent review on effective practices in teaching green chemistry by Andraos and Dicks is very informative on this topic.[1] They emphasise that there is no one correct "green" answer but instead there are a range of alternatives that need to be evaluated using criteria so that a decision can be made. This approach of considering multiple solutions and making decisions is quite challenging for most students but develops important key skills.
Some modifications that tutors may consider are:

- To combine Sessions 4 and 5 so that some students in the group carry out the standard epoxidation reaction and others use the alternative conditions during the same laboratory session.
- Not to carry out the alternative epoxidation reaction and use data from the literature instead.
- To ask students to prepare either a report or presentation on their findings and recommendations but not both.

It is important that learners are provided with sufficient time to perform the tasks assigned and to gain understanding. If the time available is less than that outlined here, some components of the case study will need to be removed and / or the associated tasks reduced.

Table 2: Schedule Showing the Aims and Teaching and Learning Activities for the Workshops (WS) and Laboratory (Lab) Sessions

Session (3 hrs)	Title	Aims	Activities (during and between sessions)
1 (WS 1)	Introduction to the project and planning for first synthetic step	Tutor aims: • To introduce the case-study and outline the learning outcomes, learning activities and assessment components and criteria. • To introduce the principles of green chemistry and environmental reporting requirements for commercial producers of fine chemicals. • To provide information on the literature references to be consulted to plan the first synthetic step in the production of a Mn-salen catalyst for alkene epoxidations. Each group of 2 to 3 students is assigned a different catalyst to prepare. • To obtain student e-mail addresses so that a wiki can be set up for each group (if not possible to do so before the first session).	• Introduction presentation and assignment into groups. • Discussion on green chemistry, environmental legislation (Annual Environmental Reports and Integrated Pollution Prevention and Control licences) and the role of catalysts and desirable properties they should have. • Discussion on selecting a suitable scale for the first step and preparation of a procedure. • Demonstration of a sample wiki if possible (adding and editing pages, uploading files, adding comments and checking page history).
Independent group and individual work in preparation before each lab session should take 1 – 3 hrs. Some guidance prompts are provided.			
2 (Lab 1)	First synthetic step (reaction of diamine and salicylaldehyde to form the ligand intermediate)	Learner aims: • To perform a suitable experimental procedure to prepare the ligand intermediate in the synthesis of the Mn-salen catalyst. • To characterise the intermediate prepared.	• Writing of procedure in advance. • Preparation of ligand intermediate. • Prediction of expected IR and NMR spectra for the salicylaldehyde starting material used and the intermediate prepared. • Begin group literature research on alternative procedures/oxidants. • Maintain independent lab book and group wiki.
3 (Lab 2)	Second synthetic step (preparation of catalyst)	Learner aims: • To prepare a suitable experimental procedure to be used to prepare the Mn-salen catalyst. • To characterise the Mn-salen catalyst prepared and determine the overall yield obtained. • To review information obtained on alternative epoxidation conditions using Mn-salens and recommend an experiment to be attempted.	• Writing of procedure in advance. • Preparation of catalyst. • Prediction of expected IR spectrum for the catalyst prepared. • Interpretation of IR and NMR spectra of the salicylaldehyde used and the intermediate prepared. • Preparation of a 1 page summary on literature research on alternative epoxidation conditions (recommend one experiment to be attempted) • Maintain independent lab book and group wiki.
4 (Lab 3)	Evaluation of catalyst performance in a reference reaction (epoxidation of *trans*-	Learner aims: • To prepare a suitable experimental procedure to be used to perform the epoxidation of stilbene oxide. • To perform the epoxidation of an alkene (*trans*-stilbene) using	• Writing of procedure in advance. • Epoxidation reaction using sodium hypochlorite in duplicate / triplicate. • Prediction of expected IR and NMR spectra for the

	stilbene)	sodium hypochlorite as the oxidant in duplicate or triplicate. • To characterise the epoxide product and determine the yield and conversion obtained. • To evaluate the alternative oxidation procedures found and recommend related future work.	alkene substrate used and the epoxide prepared. • Evaluation of alternative oxidation procedures found based on criteria provided and recommend which should be attempted in the future. • Interpretation of IR spectrum obtained of catalyst. • Maintain independent lab book and group wiki.
5 (Lab 4)	Evaluation of catalyst performance using alternative conditions	Learner aims: • To perform the epoxidation of an alkene using alternative conditions in duplicate or triplicate. • To characterise the epoxide product and determine the yield and conversion obtained. • To compare the effectiveness of all catalysts prepared in the reference reaction.	• Writing of procedure in advance. • Epoxidation reaction using alternative conditions • Complete catalyst performance evaluations. • Analyse data from all groups to determine the most effective catalyst in the reference reaction. • Maintain independent lab book and group wiki.
6 (WS 2)	Costing and assessment of environmental impact for oxidation procedures performed	Learner aims: • To cost the raw materials for two oxidation processes. • To compare the environmental impacts of two processes with reference to the appropriate metrics. • To plan for the scope of future development work on each process. • To compare the results obtained in the two epoxidation reactions.	• Use ChemSpider to find vendors and costings for raw materials and solvents for the synthesis of the catalyst and the epoxidation reactions. • Use guidelines on metrics and recommended reading sources to evaluate the environmental impact of each process as well as the potential for further development. • Analyse data from all groups to determine the most effective epoxidation conditions.
7 (WS 3)	Clinic for formative feedback on draft reports (on group wiki)	Tutor aims: • To provide learners with formative feedback on areas of the report they need to work on and on which aspects have been addressed satisfactorily. • To answer any student queries on the assignment and activities, and discuss any issues raised.	'Clinic' where each group: • has submitted a 1 page 'work in progress' summary in advance. • discusses any problems or queries. • receives feedback on their summary and on their wiki draft report as it is at that point.
Optional Additional Laboratories: purification of the epoxide product by column chromatography, determination of enantiomeric excess in the epoxidation product by chiral GC if chiral diamines were used to prepare the ligand, variation of the metal (to Co or Fe)			
8 (WS 4)	Oral presentations	Tutor aim: • To provide feedback to the learners on their presentation skills and the content of their presentation. Student aim: • To learn from each other's presentations and to ask each other questions.	• Presentation to peers summarising work undertaken and recommendations made followed by questions from the tutor, guest tutor (if present) and peers. • General oral feedback from tutor (optional written feedback to each group from peers and tutors). • Completion of wiki report (with feedback from presentation incorporated), individual reflective piece, and, if required, peer assessment of other group members.

A word about wikis

There are many advantages to using a wiki when collaboration on a group project is required and these are dealt with in more detail in Appendix 2. To summarise, it provides an effective and flexible means for learners to work as a team on a report, presentation or web page while generating an archive of all information used and of all previous versions of the final pages. The main benefit to a tutor is that the quality and quantity of contributions made by each student can be tracked relatively easily and that the process as well as the product can be assessed. Wikis are regularly used in organisations to allow groups to collaborate on projects and documents and to share knowledge and the ability to use one is a valuable transferable skill. For example, a wiki has been established to develop policy in the area of green chemistry in California (http://cagreenchem.wikidot.com/start).

Although it is recommended that a wiki be used as a component of this C/PBL activity, an alternative can be adopted if preferred. Some type of online interaction among a group such as a discussion board or online group is very useful and, if this has been set up by the tutor, there is the advantage that they will be able to monitor progress being made. If this option is not used, the weekly group meeting summaries that are required from each group can be used to monitor progress and to check that all members are making a contribution. To provide a facility similar to the wiki for organisation of the work being undertaken, it would be useful for groups to use a ringbinder with sections that correspond to the main parts of the report to which useful documents and draft work can be added. Under these circumstances, it is recommended that this draft work and supporting information is submitted as an appendix to the final report.

Resource learning outcomes

On completion of this C/PBL resource, the learner should be able to do the following, within the context provided:

1. Use a procedure from scientific literature to write a laboratory procedure, including a list of materials and equipment required, for the preparation of organic and organometallic compounds on a suitable scale.
2. Prepare a short chemical risk assessment for the experimental work to be undertaken.
3. Plan time in the laboratory effectively in order to complete the synthesis and evaluation of the catalyst assigned.
4. Keep an accurate and current record of experimental details and data in a laboratory notebook.
5. Interpret experimental data and predict and assign spectra to confirm the identity and purity of the products.
6. Use appropriate databases to find relevant information on raw material costing for the process and on recent developments to improve the environmental impact it has (e.g. alternative solvents and oxidants).
7. Evaluate the efficiency, relative costs and the environmental impact of the two oxidation procedures used for the epoxidation of *trans*-stilbene.
8. Identify aspects of each reaction performed that adhere to the principles of Green Chemistry and those that do not.
9. Use the results obtained for all catalysts evaluated to predict how catalyst structure and efficiency are related.
10. Produce a professional report, including an executive summary and an assessment of the scope for each step to be improved, that is supported by the relevant experimental data and a laboratory notebook as well as references to the literature.

11. Prepare an oral presentation on the findings from the study to present to the company that commissioned the project.
12. Prepare a short individual reflective statement on the group process, transferable skills developed, and the extent to which the stated learning outcomes were met.

Transferable skills development

Students will be asked to reflect on the development of the skills listed below at the end of the project. It is recommended that they record notes as they go along on the areas they are finding challenging as well as progress that they feel they are making to make this task easier. The specific ways in which it is intended that key skills will be developed during this C/PBL case study are described below:

- Team work: learners work in groups to complete the task assigned, use a wiki to facilitate collaboration and meet between sessions to review progress.
- Organisation and planning: learners prepare procedures on a suitable scale and plan their time in the laboratory effectively.
- Communication skills: Learners present (oral presentation) and report (wiki and final report) on the scientific work performed in keeping with the context.
- Drawing conclusions and recommendations from data: learners justify decisions, assumptions and conclusions made with reference to results from other groups and supporting literature in order to produce a logical and clearly reasoned scientific report.
- Numeracy: learners apply the relevant green chemistry metrics to their experimental results.
- Professional role and responsibilities: learners adopt the role of a professional chemist and are required to consider the environmental impact and costing of the processes they have been working on.
- Problem solving: learners work in groups to address the brief presented in the context scenario.
- Information technology skills: learners use a wiki to collaborate and develop their ability to use word-processing, spreadsheet, presentation, chemical drawing and library database software.
- Metacognition: learners reflect on the process involved in working on the brief given, the extent to which the stated learning outcomes were met and to which their transferable skills were developed.

Implementation: Class organisation

This resource is designed so that students work in small groups (typically three students) to complete the brief provided together. A recommended maximum number of students for one tutor is 15. If a second tutor is available, the maximum cohort size would be about 30. The assessment components (Table 1) require that each student submits a laboratory book as well as a short reflective summary for individual assessment at the end of the C/PBL activity. The assessed group work covers the presentation and report and the group wiki which provides a record of how the group collaborated and their rate of progress. The report can be generated directly from the wiki either by converting wiki pages to PDF files or by printing the pages (depending on the software used). Alternatively, you may want to request that the text can be cut and pasted into a Microsoft® Word document once all collaboration on the wiki is complete. This option allows a word count to be performed easily as well as additional formatting such as page numbers. Alternatively, you may opt to read the report as generated on the wiki and not require that a paper copy be submitted. This decision is left to the discretion of the tutor as it will depend on what format you prefer to correct and whether you feel it would be useful for learners to produce a written report in a conventional format.

Weekly feedback

Advice on monitoring and correcting wikis is provided in this guide, but, to summarise, the tutor should log into each group's wiki approximately once per week if possible and provide brief feedback on the progress reported (in the group meeting summary). Feedback is also provided on any components of the group report that are submitted in a given week (e.g. experimental procedure, cost analysis) and the draft group reports are reviewed before Workshop 7. The remaining correction time is spent on the presentation and the completed reports. In this manner, students receive feedback at various stages throughout the process. Students' email addresses should be collected at the outset of the module and used to set up each group wiki. At the latest, each student should be invited to join his or her group wiki just after Session 1. Suggested assessment criteria are provided in Table 1 and further information on assessing individual contributions to wikis is presented in Appendix 2.

A schedule of weekly work to be submitted by students and the suggested feedback provided is shown in Table 3, but it will be at a tutor's discretion to decide the extent of the feedback that is reasonable for them to provide. The assignment of weekly tasks as individual or group activities can also be adjusted as the tutor decides is appropriate. The weekly work is designed so that students are preparing elements of their final report as they go along. Other considerations for the tutor are whether all submitted work should be typed or not and whether weekly work should be handed in as a printed copy and/or added as a file to the wiki. One factor that can be variable is how quickly students can obtain NMR spectra of their compounds. It has been assumed that they may not have them until the lab session that follows the one in which the compound was made. If the turnaround time is shorter, the schedule of work in Table 3 (and the corresponding Table 3 in the student guide) can be modified.

Student workload

In general, there is a piece of individual work each week as well as group work. In this way, students get to learn about compiling safety information on chemicals and prediction of NMR and IR spectra by themselves initially but, in later weeks, this is assigned as a group activity. To allow students to work efficiently, it is suggested that they be allowed to paste any relevant material already prepared in an electronic format such as reaction schemes and safety information into their laboratory notebooks. It is recommended that students be asked to submit any previously corrected work that was returned to them as a hardcopy with their final report (for group assignments) or with their laboratory notebook (for individual assignments) so that the extent to which feedback was incorporated can be determined. The ideal turnaround time would be that material is submitted 2 to 3 days after the weekly session and it is returned at the session the following week but this may not always be feasible. The day of the week on which work is due can be added to Table 3 in the space provided.

Student cohorts vary as do their workloads and you may opt to reduce some of the weekly requirements and overall assessment components depending on the length of time that you estimate it will take them to complete the tasks assigned (see Flexibility Within this Resource section also). For example, prediction of the main features of NMR and IR spectra of the compounds involved is a very useful learning exercise but it could be removed and students could just be asked to characterise their products using the spectra recorded.

Whenever possible, the tutor should take a back seat and direct the students to the Student Guide and recommended resources to obtain relevant information. This encourages learners to read and engage fully with the materials provided. The distribution of the workload associated with the tasks should be assigned by the students in their groups.

Groups

The authors recommend a group size of 3 students, but this will depend on the class size, ability and prior learning. It is recommended that these groups be assigned before the start of the first session and it is useful to prepare a table listing the group members and the diamine and salicylaldehyde starting materials that they have been assigned to use to add to the Student Guide or bring to the first session. It is recommended that the tutor tries to ensure there is a range of abilities and skills in each group and, if possible, that students get an opportunity to work with people they may not know very well. One other important consideration is that each member of a group should have similar class contact timetables so that it is easy for them to arrange to meet. You may like to suggest that each group choose a name for their team as this has been found to work as a good ice-breaker and develops a sense of group identity. Advise the students that there are 3 roles that should be assigned to group members each week on a rotating basis: Chair, Reporter and Editor. The Chair will prepare the agenda for meetings, will lead/run the group meeting/discussions, listen with an open mind to all group members, and ensure that everyone in the group has the opportunity to contribute. The Reporter should prepare a summary of the action items arising from discussions and meetings and should post these on the group wiki by the day of the week that you specify (usually 2 days before the next session). The Editor will review the wiki content to ensure a consistent style, coherency and an overall structure and will also liaise with authors when changes to content are required. Each student should adopt each role at least once during the project and the group should nominate these roles during each session (note than an Editor is not required until Session 2). It is recommended that you remind the students to nominate these roles at the start of each new Session.

It is useful to ask the students to stop what they are doing about 15 minutes before the end of each session and to identify all tasks that need to be completed before the next session, to review the description of the following session and to arrange a date and time to meet outside of the class contact time. It may also be helpful to ask a spokesperson from each group to very briefly summarise the progress of their group to the class.

It is not easy to ensure that equal time is spent with each group due to the nature of the C/PBL approach and tutors must do their best to ensure this is the case. If involved in a particularly interesting discussion with one group that merits more time, it may be a good idea to open up this discussion up to the entire class and in that way include all students. If a group has a problem that requires a significant proportion of your attention (e.g. the group is not functioning as a team, the students do not understand the tasks), it may be wise to meet with that group outside of normal contact time.

The most significant problem we have encountered when implementing this type of activity has been the difficulties that can arise when students are asked to work as a group. This is a necessary evil as some conflict is inevitable when groups begin to try to work together. If some tensions become apparent in a group over a number of weeks, it is likely to be as a result of one member not contributing, a personality clash or one person working on their own and not collaboratively. The methods of assessment used (wiki contribution, requirement to minute weekly group meetings, peer assessment) ensure that those not contributing or collaborating effectively will lose marks and the class can be reminded of this. If the problem persists, it may be necessary to speak to the particular group. It is also useful to remind students that the context is representative of the challenges that exist in the workplace when participating in a team and is a valuable learning experience.

A good overview for students on effective group work is presented in Chapter 3 of “Study and Communication Skills for the Chemical Sciences”; Overton, T., Johnson, S., Scott, J.; Oxford University Press (2011).

Table 3: Work to be completed after each weekly session & associated suggested feedback

Stage	For submission after the session by the following (add day of week) at (add time)	Suggested feedback
Week 1 (Introduction) Date for completion of tasks:	**Group** • Modified experimental procedure for step 1 (catalyst ligand preparation).* • Summary of group meeting posted on group wiki. **Individual** • Short version of chemical safety assessment.* • Maintain group wiki and independent lab book. * The procedure and safety assessments should be typed and structures should be drawn using chemical drawing software.	Any required changes. Acknowledgement. Grade and give brief comment to individual. General feedback either at next session or posted online before it. Brief comment on wiki, sign and date lab book at next session.
Week 2 (Ligand preparation) Date for completion of tasks:	**Group** • Modified experimental procedure for step 2 (catalyst preparation). • Short version of chemical safety assessment. • Summary of group meeting posted on group wiki. • Begin research on alternative epoxidation conditions for Mn-salen catalysts. **Individual** • Predicted IR and ^{1}H NMR spectra for salicylaldehyde starting material and ligand intermediate. • Maintain group wiki and independent lab book.	Any required changes. Any required changes. Acknowledgement. Acknowledgement. Grade and give brief comment to individual. Give general feedback at next session or online before it. Brief comment on wiki, sign and date lab book at next session.
Week 3 (Catalyst preparation) Date for completion of tasks:	**Group** • Modified experimental procedure for epoxidation of stilbene using standard conditions. • Summary of group meeting posted on group wiki. • One page summary on research carried out (on alternative conditions for epoxidation of alkenes with Mn-salen catalysts and recommended experiment to try). • Short version of chemical safety assessment. • Predicted IR spectrum for catalyst with suggestion as to why NMR analysis of catalyst is not useful. **Individual** • Interpretation of IR and ^{1}H NMR spectra obtained of ligand intermediate and of salicylaldehyde starting material. • Maintain group wiki and independent lab book.	Any required changes. Acknowledgement. Grade and give brief comment to group. Give general feedback at next session or online before it. Any required changes. Grade and give brief comment to group. General feedback either at next session or posted online before it. Grade and give brief comment to individual. Give general feedback at next session or online before it.. Brief comment on wiki, sign and date lab book at next session.
Week 4 (Catalyst evaluation 1) Date for completion of tasks:	**Group** • Modified experimental procedure for epoxidation of stilbene with catalyst using alternative conditions. • Short version of chemical safety assessment. • Predicted ^{1}H NMR spectra for stilbene and stilbene oxide.	Need to have identified to students which alternative procedure is to be used (e.g. H_2O_2 as oxidant). Any required changes. Any required changes. Grade and give brief comment to group. General feedback either at

		next session or posted online before it.
	• Evaluate alternative oxidation procedures found based on criteria provided (yield, catalyst loading, solvent, type of oxidant, complexity of the procedure) and recommend which should be attempted in the future.	Grade and give brief comment to individual. General feedback either at next session or posted online before it.
	• Summary of group meeting posted on group wiki.	Acknowledgement.
	Individual	
	• Interpretation of IR spectrum obtained of catalyst.	Grade and give brief comment to individual. General feedback either at next session or posted online before it.
	• Maintain group wiki and independent lab book.	Brief comment on wiki, sign and date lab book at next session.
Week 5 (Catalyst evaluation 2, alternative conditions) Date for completion of tasks:	**Group**	
	• Compilation and sharing of data on group results (yields and conversions) for reference epoxidation reaction (using sodium hypochlorite).	Any required changes.
	• Determination of most effective catalyst based on this data for the reference reaction and prediction of how catalyst structure & efficiency are related.	Any required changes.
	• Summary of group meeting posted on group wiki.	Acknowledgement.
	Individual	
	• Interpretation of ^{1}H NMR spectra obtained of crude product from stilbene epoxidation using sodium hypochlorite.	Grade and give brief comment to individual. General feedback either at next session or posted online before it.
	• Maintain group wiki and independent lab book.	Brief comment on wiki, sign and date lab book at next session.
Week 6 (Costing and green metrics workshop) Date for completion of tasks:	**Group**	
	• Analysis of ^{1}H NMR spectra obtained of crude products from alternative stilbene epoxidation to determine percentage conversion.	Check conversion determined and state any required changes.
	• Compilation and sharing of data on group results for alternative epoxidation reaction.	Any required changes.
	• Comparison of results for the reference and alternative oxidation reactions.	Any required changes.
	• Costing of raw materials and solvents for synthesis (including work up) of the catalysts prepared, and for their epoxidation reactions. Identify any resulting issues (most and least expensive materials).	Any required changes.
	• Evaluation of the environmental impact of each process with reference to appropriate metrics and provide recommendations for further development.	Any required changes (it should be possible to give feedback during the workshop session)
	• Draft group report on wiki ready for preliminary review.	Review before next session and prepare short summary on aspects dealt with well and those that need more work. Check to see if anyone has not been contributing at all.
	• Work in progress summary on draft group report posted on group wiki (provide link from Table of Contents).	
	• Summary of group meeting posted on group wiki.	Acknowledgement.
	Individual	
	• Maintain group wiki and independent lab book.	Brief comment on wiki.

Week 7 (Clinic for formative feedback) Date for completion of tasks:	**Group** • Incorporation of feedback from clinic workshop into the group's wiki report. • Consideration of the scope for each synthesis step to be improved and recommendations for future work. • Practise group presentation to ensure it is coherent, structured, accurate and meets the time requirements (the wiki itself can be used as a visual aid or, alternatively, it may be preferred that PowerPoint slides be prepared). • Summary of group meeting posted on group wiki. • Maintain group wiki.	Any required changes. Provide oral and brief written feedback after presentation at next session. Acknowledgement. Brief comment on wiki.
Week 8 (Oral presentations) Date for completion of tasks:	**Group** • Incorporation of feedback from presentation into the group's wiki report. • Final editing and completion of group's wiki report. • Submission of wiki report **Note for tutor:** inform students on final report format required (PDFs, Microsoft® Word or wiki), if it should be printed and whether to submit it for checking by plagiarism detection software. **Individual** • Reflective piece to be submitted. • Lab book to be submitted. • Peer assessment of other students in the group (optional).	Provide spoken and written feedback during session - use criteria in Table 1. Grade using criteria in Table 1 (see Appendix 2 also) and give optional general feedback or group specific feedback added to wikis. Grade and add some comments. Grade and add some comments. (Using CATME software would automate this process.)

Why do it? The philosophy and rationale for this case study

In designing this case study, we wanted to put learners in a position where there is an existing framework (a proposed synthetic procedure that addresses some green chemistry principles) but to provide an opportunity to investigate potential improvements. As this is a constantly developing field, flexibility to incorporate alternative procedures that become available for using Mn-salen catalysts to epoxidise alkenes has been built in. The intention is to allow students to develop an appreciation of what scientific research involves and to gain some experience of this approach in a group project. The expectation is that they will have a better understanding of what is expected of them when they go on to undertake an individual final year research project. In the authors' experience, this has been the case as students have been observed to be able to work effectively as soon as they begin their final year projects, particularly in relation to planning their work, finding relevant information and evaluating results obtained in order to decide what should be done next.

Additional anticipated benefits are (i) that learners will appreciate the holistic nature of their subject as the case study interlinks the applications of organic, inorganic, industrial/process chemistry and green/sustainable chemistry, (ii) that students develop a sense of identity as a future professional chemist and (iii) that an opportunity to be involved in and reflect on working as part of a team is provided.

Session 1 (Workshop 1): Introduction to the project and to the first synthetic step

The purpose of the introduction session is to:

1. Introduce learners to the case study context and outline the schedule of work, the learning outcomes, and assessment components and criteria.
2. Introduce or revise the principles of green chemistry and environmental reporting requirements for commercial producers of fine chemicals (Annual Environmental Reports and Integrated Pollution Prevention and Control licences) as well as the role of catalysts and desirable properties they should have.
3. Provide information on the literature references to be consulted to plan the first synthetic step in the production of a Mn-salen catalyst for alkene epoxidations. Each group of students is assigned a different catalyst to prepare.
4. If possible, demonstrate how to use a sample wiki (adding and editing pages, uploading files, adding comments and accessing page histories).

If student e-mails are obtained in advance, they can have been invited to join their group wiki before the session.

Further Information

A PowerPoint induction / introduction presentation covering the items listed above has been prepared. It is important to refer to Tables 2 and 3 so that students can familiarise themselves with what will happen in each session and so that they can check what work they are required to submit each week.

In their guidebook, the students will be presented with a project briefing pack from HugePharma Ltd. (included here in Appendix 1). The original journal article describing the synthesis of the catalysts should also be provided: Asymmetric Olefin Epoxidation with Sodium Hypochlorite Catalyzed by Easily Prepared Chiral Mn(III) Salen Complexes, Zhang, W., Jacobsen, E.N., Journal of Organic Chemistry, 1991, 56, 2296-2298.

Ligand synthesis procedure

Students should then move into their teams to begin planning their work (a procedure on a suitable scale for the catalyst they have been allocated). Some time will need to be spent considering what might be a suitable scale to ensure there is enough material for characterisation, to evaluate the catalyst in duplicate or triplicate and to use it in an alternative oxidation process. **The scale recommended requires that each group synthesise 0.5 g of the catalyst assuming a 70% yield in each of the two steps involved.**

The Appendix to this guide contains tutor notes on preparing the catalyst ligand which detail the chemicals required as well as calculations on quantities of starting materials needed and expected yields to allow the tutor to plan for the upcoming sessions and to check the work submitted relatively easily. It is recommended that the tutor prints the appropriate section from the Appendix on the experiment being done each week and brings it to the laboratory session so that they can refer to this supporting data.

The students should compile a list of actions, people responsible and dates due for their group and arrange a time when the group will have a short meeting to review progress before the next workshop. A chair (who will prepare a short agenda) and recorder (who will prepare a short summary of decisions made and progress reported in the meeting, and post it on the wiki) should be selected. These positions rotate each week.

It can be anticipated that, if the C/PBL approach is unfamiliar to students, they will need some encouragement to begin working on the laboratory procedure and other tasks for the following week. In general, progress can be slow during the first week or two but improves once learners develop some confidence and begin to appreciate the real world element of their work.

Demonstration on using wikis

If possible, it is recommended that 15 to 20 minutes of the workshop be used to show students how to perform the basic wiki functions required. Ideally, they would have been sent an invitation to their group wiki in advance of this session. If this was not possible, student e-mail addresses should be obtained to allow their group wikis to be set up just after this workshop session. It is recommended that students be shown how to do the following;

- Set up a new page and link it to another one and how to upload files and link them to a wiki page. Remind students to write a brief comment on every file that they link to a page stating what it is and why it is relevant and to summarise changes made to a page when saving them to allow members of the group to keep track of each individual contribution and group progress.
- Use 'Page History' to monitor individual contributions.

Ensure that students are using the guidelines provided in Appendix 1 in the Student Guide to identify recommended headings for the pages of their wiki (see the screenshots in Appendix 2 of this guide).

Remind the students that the wiki will become the final report and so the content should reflect that of the final report. Note that most wiki software allows wikis to be converted to a PDF format, but you should check this is the case with the wiki software that you are using. However, you may request that the final proposal be submitted in the form of a Word® document by cutting and pasting the appropriate sections from the wiki if that is your preference (this would allow a word count and page numbering if your wiki software does not, for example).

Note: An alternative approach is to arrange wiki training for you and the students by a third party through the Learning and Teaching Centre or equivalent at your institution.

Student guidelines

Guidelines are provided in the appendix of the student guide for:

- Using a wiki
- Preparing laboratory procedures
- Compiling chemical safety information
- IR and NMR spectra prediction
- Writing up a lab notebook
- Preparing presentations
- Writing a reflective piece
- Writing an executive summary
- Plagiarism

These should be consulted when appropriate and adhered to.

Group planning and roles

About 15 minutes before the end of the workshop, pause activities and ask each group to identify all tasks that need to be completed before the next session, to review the description of the following session and to arrange a date and time to meet outside of their class contact time. They should also assign the group Chair and Recorder role for the coming week. It is recommended that this be done each week towards the end of the session.

Planning for the Next Session

The Appendix to this guide contains tutor notes on preparing the ligand which detail the chemicals required, as well as calculations on quantities of starting materials needed and expected yields. It is recommended

that the tutor prints the appropriate section from the Appendix on the experiment being done each week and brings it to the laboratory session so that they can refer to the relevant supporting data.

Tasks for Students to Complete Before Session 2

- Review the assessment criteria and schedules provided (Tables 1 to 3).
- Become familiar with how to navigate the group wiki and how to add and edit pages, add files and add comments. Add a Table of Contents and a Group Planning and Communication main page (see Appendix 1).
- Meet as a group to review progress on the list of actions for their group. The Chair will have prepared a short agenda and the Recorder will post a short meeting summary (of decisions made and progress reported) on the wiki by the day specified by the tutor.
- Submit a group experimental procedure for the preparation of the salen ligand on a suitable scale (via the wiki and/or directly to the tutor). These should be typed and structures should be drawn using a chemical drawing package (Accelyrs Draw and ChemSketch are both available to download free of charge). Students will not be allowed to begin lab work in Session 2 until this task has been satisfactorily completed.
- Individually submit a short chemical safety assessment for the synthesis procedure.
- Add information available in advance on the first experiment (materials, equipment, literature reference etc.) to their lab notebooks.

Desired learning outcomes

On completion of this session and the related independent learning hours the students will be able to:

- Understand the context based scenario and be aware of how the module will be assessed.
- Prepare an experimental procedure on a suitable scale and identify materials and equipment required as well as any chemical safety issues.

Session 2 (Laboratory 1): First synthetic step - Reaction of a diamine and a salicylaldehyde derivative to generate a catalyst ligand

Experimental data are included in the tutor notes for this session in the Appendix.

Aim / Goal of this Laboratory session:

The primary goal of this session is to carry out the experimental procedure to synthesise and isolate the salen ligand assigned. It should take about two hours from set-up to isolation of the product. This allows time to discuss writing the procedure for the following week, and to carry out characterisation afterwards by TLC, melting point, ^{1}H NMR, ^{13}C NMR (if required) and FT-IR spectroscopy.

Further Information

Yields obtained in our hands for these ligands ranged from 82 to 99 %.

Samples of each salicylaldehyde starting material should be characterised by ^{1}H NMR and FT-IR spectrocopic analysis during this session.

Students should be writing up their lab books as they go along. It is recommended that the tutor signs and dates the lab book each week (but does not correct it) so that it is obvious how much work has been done on an ongoing basis by each student.

Student guidelines for presenting the IR and ^{1}H NMR predictions are provided in the student guide.

It has been assumed that students may not obtain ^{1}H NMR spectra (and ^{13}C spectra if required) of their compounds until the week after they have submitted their samples as the systems in place vary between institutions. This timeframe also allows for FT-IR and other characterisation to be completed the week after a compound has been prepared and the work to be completed each week listed in Table 3 reflects this.

It is useful to refer to Table 3 in the student guide to ensure that students are clear as to what work should be submitted that week and to also refer to Table 2 so that they are aware of what is involved in the session next week.

Planning for the Next Session

You may like to direct the students to read the supporting information for the Journal of Chemical Education Paper referred to in the literature review as it gives considerable detail on the system to use for bubbling air through the reaction when preparing a Mn-salen catalyst. (Hanson, J., *Journal of Chemical Education*, 2001, 9, 1266-1268).

It should be pointed out to students that when they are preparing their catalyst preparation procedure for the next session that they will notice that HugePharma Ltd. have indicated that sodium chloride can be used in this procedure instead of lithium chloride which was the reagent stated in the original Jacobsen paper. Students can be asked to propose reasons as to why this substitution was made (cost, health and safety, environmental considerations) and it could be suggested that they check whether LiCl or NaCl is used in the patents referred to in the literature review supplied.

The Appendix to this guide contains tutor notes on preparing the catalyst which detail the chemicals required, as well as calculations on quantities of starting materials needed and expected yields. It is

recommended that the tutor prints the appropriate section from the Appendix on the experiment being done each week and brings it to the laboratory session so that they can refer to the relevant supporting data.

Tasks for Students to Complete Before Session 3

- Meet as a group to review progress on the list of actions for their group. The Chair will have prepared a short agenda, and the Recorder will post a short summary of decisions made and progress reported on the wiki by the day specified by the tutor.
- Submit a group experimental procedure for the preparation of the Mn-salen catalyst on a suitable scale, as well as a short chemical safety assessment (via the wiki and/or directly to the tutor). These should be typed and structures should be drawn using a chemical drawing package. Students will not be allowed to begin lab work in Session 3 until this task has been satisfactorily completed.
- Begin research on alternative epoxidation conditions for Mn-salen catalysts.
- Individually submit a prediction of the expected IR and NMR spectral characteristics of the salicylaldehyde starting material used and the ligand intermediate prepared.
- Add information on the characterisation and yield for their first synthetic step to their lab notebook. Add information available in advance on the second synthetic step (materials, equipment, literature reference etc.) to their lab notebooks.

Desired learning outcomes:

On completion of this session and the related independent learning hours the students will be able to:

- Prepare an experimental procedure on a suitable scale, and identify materials and equipment required as well as any chemical safety issues.
- Predict the IR and NMR spectral characteristics of the compounds they will be preparing and the starting material used.
- Collaborate in a face-to-face meeting and using a wiki.

Session 3 (Laboratory 2): Preparation of a Mn-salen catalyst

Experimental data are included in the notes in the Appendix.

Aim / Goal of this Laboratory session:

The primary goal of this session is to carry out the experimental procedure to synthesise and isolate the Mn-salen catalyst assigned. It should take almost 3 hours from set-up to tidy-up. The procedure requires that air be bubbled through the reaction mixture to allow in situ oxidation from Mn(II) to Mn(III).

Further Information

Yields obtained in our hands for these catalysts ranged from 58 to 94 %. A significant variation is expected as the conditions used are generic and have not been optimised for each specific catalyst. Disappearance of the ligand starting material from the TLC is taken as confirmation of product formation. As the reaction generally takes almost 3 hours to complete, it is likely that any analysis and characterisation required will not be performed until session 4. The product is paramagnetic, and therefore characterisation by NMR is difficult as the spectrum is not readily interpretable. Also, all of the products have melting points above 300 ^{o}C and, in many cases, this will be beyond the maximum operating temperature of a melting point apparatus, although it can be stated that a melting point of ≥300°C is generally a good indication of product purity. Elemental analysis or ESI (electrospray ionisation) mass spectrometry analysis can be performed if these facilities are available and time allows.

There should be a little time available during the session (e.g. while the initial reflux is on) to discuss writing the epoxidation procedure for the following week. In addition, the requirement for each group to perform some research on alternative alkene oxidation conditions that can be used with Mn-salen catalysts, either by looking at some of the references in the literature review provided or conducting a search on a scientific database using keywords should be discussed. It may be useful to refer to relevant local library resources on information retrieval and to databases such as Web of Knowledge, Scifinder or Reaxys or you may prefer to get students to focus on the literature review supplied. It is also useful to suggest to students that they try to extract some information on the oxidation reaction conditions employed from the patents listed in the literature review provided as this can be quite challenging but is an important skill to develop.

Students should be writing up their lab books as they go along. It is recommended that the tutor signs and dates the lab book each week so that it is obvious how much work on it has been done on an ongoing basis by each student.

Planning for the Next Session

The Appendix to this guide contains tutor notes on carrying out the oxidation of stilbene using sodium hypochlorite with each catalyst which detail the chemicals required as well as calculations on quantities of starting materials needed. It is recommended that students be reminded that they will be carrying out a reaction individually the following week.

Tasks for Students to Complete Before Session 4

- Meet as a group to review progress on the list of actions for their group. The Chair will have prepared a short agenda and the Recorder will post a short summary of decisions made and progress reported on the wiki by the day specified by the tutor. The Editor should be reviewing any page content that is being uploaded.
- Submit a prediction from the group of the expected IR spectral characteristics of the catalyst prepared and suggest why NMR analysis will not be useful.
- Submit a group experimental procedure for the oxidation of stilbene using the Mn-salen catalyst they prepared on a suitable scale as well as a short chemical safety assessment (via the wiki and/or directly to the tutor). These should be typed and structures should be drawn using a chemical drawing package. Students will not be allowed to begin lab work in Session 4 until this task has been satisfactorily completed.
- Carry out research as part of their group on alternative alkene oxidation conditions using Mn-salen catalysts, either by looking at some of the suggested references or conducting their own search on a scientific database using keywords selected. Each group should have posted a summary of the research carried out and information obtained with references used (one page maximum) on their group wiki in advance of the next session.
- Individually submit an interpretation of their IR and ^{1}H NMR spectra obtained of the ligand intermediate and of the salicylaldehyde starting material.
- Add information on the characterisation and yield for their second synthesis step to their lab notebook. Add information available in advance on the epoxidation reaction (materials, equipment, literature reference etc.) to their lab notebooks.

Desired learning outcomes:

On completion of this session and the related independent learning hours the students will be able to:

- Determine the overall yield of catalyst obtained.
- Perform literature research to identify alternative oxidation conditions.
- Prepare an experimental procedure on a suitable scale for the oxidation of *trans*-stilbene and identify materials and equipment required as well as any chemical safety issues.
- Characterise the salicylaldehyde starting material used and the salen ligand prepared
- Predict the IR spectral characteristics of the catalyst prepared
- Collaborate in a face-to-face meeting and using a wiki.

Session 4 (Laboratory 3): Evaluation of the catalyst performance in a reference reaction - epoxidation of *trans*-stilbene

Experimental data are included in the notes in the Appendix.

Aim / Goal of this Laboratory session:

The primary goal of this session is to carry out the experimental procedure to epoxidise *trans*-stilbene with sodium hypochlorite to give *trans*-stilbene oxide using the Mn-salen catalyst assigned.

Further Information

If possible, each student in the group should carry out the reaction individually as this data will allow for a more informative evaluation of the catalyst using this reference reaction and addresses the requirements in the project brief.

It is also useful to ask one student to carry out the reaction without any catalyst present to check if any conversion to product occurs.

The experiment takes about three hours from set-up to tidy-up if the reaction is left stirring for 2 hours. Therefore, it is likely that any analysis and characterisation required will not be performed until session 5.

Please note:

- It is very important that a fresh bottle of hypochlorite solution is purchased shortly before it is needed for this oxidation step and that it is kept refrigerated. If not, the reaction will not proceed as it should.
- Reaction progress is monitored by TLC and a ceric stain was used (details for preparation are in the Appendix).
- The level of conversion in the crude product is determined by comparing ^{1}H NMR integral values for the non-aromatic protons. Examples are shown in the Appendix.
- Column chromatography can be carried out to isolate the pure product if the time and equipment is available. We have not done this but a detailed procedure for this purification can be found in "Synthesis and Use of Jacobsen's Catalyst: Enantioselective Epoxidation in the Introductory Organic Laboratory"; John Hanson; *Journal of Chemical Education*, Vol. 78 No. 9, 1266-1268. This reference also provides information on GC analysis of the product using a chiral column to determine the enantiomeric excess if a chiral Mn-salen catalyst has been utilised. Students could be asked to consider the cost and environmental repercussions of using column chromatography to purify the epoxide and to suggest alternative methods of purification that are suitable for solid products.

Crude yields obtained in our hands for these catalysts ranged from 18 to 74 % for crude products, and conversion rates varied from 5 to 81 %.

There should be some time available while the reaction mixture is stirring for two hours to discuss the criteria for the selection of a suitable alternative oxidation procedure (yield, solvent, complexity of the procedure, catalyst loading, potential for catalyst recovery and type of oxidant) and to inform groups which literature method they should use the following week. It may not be feasible to attempt all of the alternative procedures that show potential as the necessary reagents might not be available and a chemical risk assessment would be required. For this reason, details have been provided in the Appendices on one such alternative so that the materials and any chemical risk assessments can be made ready in advance. The alternative oxidation conditions that we have tried are those reported by Liu and Nocera[2] which require lower catalyst loading and the use of hydrogen peroxide as an oxidant, and this article can be provided to the students at this point if

you wish (S.Y. Liu and D.G. Nocera, *Tetrahedron Letters*, 2006, **47**, 1923-1926). This reaction is performed on a very small scale (1 mmole of *trans*-stilbene) and the authors report some concern in relation to the incompatibility of DMF with strong oxidising agents. For this reason, we have not attempted to perform this reaction on a larger scale than that specified.

Students should be writing up their lab books as they go along. It is recommended that you sign and date the lab book each week at the end of the student's work, so that it is obvious how much work has been done on an ongoing basis by each student.

Planning for the Next Session

As discussed, the Appendix to this guide contains tutor notes on carrying out the oxidation of stilbene using hydrogen peroxide as an alternative oxidant which detail the chemicals required, as well as calculations on quantities of starting materials needed.

Tasks for Students to Complete Before Session 5

- Meet as a group to review progress on the list of actions for their group. The Chair will have prepared a short agenda, and the Recorder will post a short summary of decisions made and progress reported on the wiki by the day specified by the tutor. The Editor should be reviewing any page content that is being uploaded.
- Submit a prediction from the group of the expected IR and NMR spectral characteristics of the stilbene starting material and stilbene oxide product.
- Submit a group experimental procedure for the oxidation of stilbene under alternative conditions using the Mn-salen catalyst they prepared on a suitable scale as well as a short chemical safety assessment (via the wiki and/or directly to the tutor). Structures should be drawn using a chemical drawing package. Students will not be allowed to begin lab work in Session 5 until this task has been satisfactorily completed.
- As a group, evaluate all alternative oxidation procedures found based on the criteria provided in the company brief supplied (yield, solvent, complexity of the procedure, catalyst loading, potential for catalyst recovery and type of oxidant) and recommend which should be attempted in the future.
- On an individual basis, interpret the IR spectrum obtained of the Mn-salen catalyst.
- Add information on the characterisation and yield for their third experiment (oxidation of *trans*-stilbene) to their lab notebook. Add information available in advance on the next experiment on oxidation of *trans*-stilbene under alternative conditions (materials, equipment, literature reference etc.) to their lab notebooks.

Desired learning outcomes:

On completion of this session and the related independent learning hours the students will be able to:

- Perform the epoxidation of *trans*-stilbene with sodium hypochlorite using the catalyst prepared.
- Characterise the catalyst prepared using IR spectroscopy.
- Predict the NMR and IR spectral characteristics of the organic compounds being used in Session 4.
- Evaluate the alternative oxidation methods found the previous week, and recommend which should be attempted in the future.
- Prepare an experimental procedure on a suitable scale for the Mn-salen catalysed oxidation of *trans*-stilbene using alternative conditions (e.g. hydrogen peroxide as the oxidant), and identify materials and equipment required as well as any chemical safety issues.
- Collaborate in a face-to-face meeting and using a wiki.

Session 5 (Laboratory 4): Alternative method for epoxidation of *trans*-stilbene using the catalyst

Experimental data for the reaction using hydrogen peroxide are included in the notes in the Appendix.

Aim / Goal of this Laboratory session:

The primary goal of this session is to carry out the alternative experimental procedure (e.g. using hydrogen peroxide as the oxidant) to epoxidise *trans*-stilbene to *trans*-stilbene oxide using a Mn-salen catalyst.

Further Information

There should be some time available while the reactions are in progress to discuss compiling the results for all of the catalysts prepared (yield of catalyst from the two step preparation and average yield and conversion for the reference epoxidation reactions) and how to consider how the catalyst structure and efficiency might be related, based on the results from the reference epoxidation reactions in Session 4. Some suggestions are provided in the student guide to recommend that, if the epoxidation reaction was performed in duplicate or triplicate, the crude yield and percentage conversion results should be used to calculate actual yields and the mean and standard deviation of these actual yields can then be calculated. Students are requested to examine whether the following structural changes have resulted in any variations in the actual yields;

1. The nature of the diamine used to generate the catalyst ligand (ethylene or cyclohexane).
2. Electronic effects of substituents at the 5 and 5' position.

Students should be writing up their lab books as they go along. It is recommended that the tutor signs and dates the lab book each week so that it is obvious how much work on it has been done on an ongoing basis by each student.

Planning for the Next Session

The section describing the next session and the related tutor notes in the Appendix to this guide provides sample calculations for the reaction metrics that are examined and a template that it is suggested be used for costings. Access to computers is required for the first part of the session when students access the ChemSpider website to get costings for raw materials.

Tasks for Students to Complete Before Session 6

- Meet as a group to review progress on the list of actions for their group. The Chair will have prepared a short agenda, and the Recorder will post a short summary of decisions made and progress reported on the wiki by the day specified by the tutor. The Editor should be reviewing any page content that is being uploaded.
- Submit a group analysis of the results for all of the catalysts prepared (yield of catalyst from the two step preparation, average yield and conversion for the reference epoxidation reaction using sodium hypochlorite). This will require the determination of the percentage conversion to stilbene oxide based on the NMR data obtained.
- Produce a prediction of how catalyst structure and efficiency might be related, based on the results from the reference reactions and supporting literature references.
- On an individual basis, interpret the ^{1}H NMR spectra obtained of the crude products from the first stilbene epoxidation (using hypochlorite).

- Add information on the characterisation and yield for their fourth experiment (epoxidation using alternative conditions) to their lab notebook.

Desired learning outcomes:

On completion of this session and the related independent learning hours the students will be able to:

- Perform the epoxidation of *trans*-stilbene using the catalyst previously prepared under alternative conditions (e.g. using hydrogen peroxide as the oxidant).
- Characterise the stilbene epoxide product from the previous week, and determine the crude yield and the extent of conversion based on NMR analysis.
- Compare the effectiveness of all catalysts prepared in the reference reaction, and predict how structure is related to efficiency.
- Collaborate in a face-to-face meeting and using a wiki.

Session 6 (Workshop 2): Assessing cost, performance & environmental impact of reactions performed

Aim / Goal of this Laboratory session:

The purpose of this workshop session is to show students how to:

1. Use ChemSpider (www.chemspider.com) to find vendors and costings for raw materials for the synthesis of the catalyst and the epoxidation reaction.
2. Use recommended reading sources and the guidelines provided on metrics to evaluate the environmental impact of each process and the potential for further development.

Further Information

Full reaction metrics calculations are included in the notes in Appendix 8 and the results are summarised here. The sample calculations provided below for oxidation using mCPBA (*meta*-chloroperoxybenzoic acid) are provided as a worked example in the student guide and can be used as a basis of comparison to measure improvements made by applying the catalytic methods used.

Students will be given a deadline for submission of the draft wiki report and work in progress summary, which will be during or shortly after this workshop session.

Guidelines on Costing

Students are required to prepare an estimate for the cost of synthesising 100 g of *trans*-stilbene oxide by the original and alternative methods using the catalyst they synthesised. The costing should include solvents and materials needed for the work-up and they can assume a yield of 90% for each synthetic step, but students should also note the actual yield they obtained. They have been asked to include Valued Added Tax (20 %) on all raw materials to be purchased as well as a rough estimate of overhead costs (add 25 % to the raw material subtotal if the synthesis will take 2 days and then add an extra 10% for each additional day needed). Any of these values can be adjusted by you if you prefer an alternative, as the actual VAT rate in operation may be different, and a more sophisticated method for calculating overheads and including other costs may be preferred (see Active Pharmaceutical Ingredients, Development, Manufacturing and Regulation, 2nd Edition, Ed. S. H. Nusim, Informa Healthcare, New York 2010, pages 326-328).

ChemSpider includes a chemical vendors category for all compounds listed. Students should be reminded to consider whether a vendor will have to ship materials a long distance, the grade/specification for the chemical and the unit sizes that can be supplied. This costing is based on a modest scale (100 g), but you may like to refer students to the ChemMarket Reporter website where information on bulk prices for some common solvents and raw materials is provided so that they can make comparisons: http://www.icis.com/chemicals/channel-info-chemicals-a-z/. The template shown below is available as an Excel file.

Template for Costing for Synthesis of 100 g of Target Compound								
Name of Chemical	Name of Vendor	Purity Grade and Product Number	Quantity Required (g or ml)	Unit Size	Cost per Unit (€ or £)	No. of Units Required	Total Cost Including VAT*	Actual Cost to Produce 100 g of Target Compound (€ or £)
Example only- Acetone	Jupiter Chemicals	Reagent grade, >99.5%, Prod. no. 179124	450 ml	500 ml	23.80	1	28.56	25.70
							Subtotal:	
							Overheads:**	
* Value Added Tax = 20%							Total Cost per 100 g:	
**Including labour, consumables, utilities - Add 25% to the subtotal if the process will take 2 days and add an extra 10% for each additional day if needed.								

The overall cost per 100 g can be used to compare the original and alternative oxidation reactions carried out in sessions 4 and 5 and, if required, to discriminate between catalysts that show similar conversion rates and environmental impact. Useful information that should be noted is which raw materials are most and least expensive in the quantities required. Although not a green chemistry consideration, this information is important to be aware of in a commercial environment. Students will need to cost the synthesis of the amount of catalyst needed to produce 100 g of *trans*-stilbene oxide as it can be considered to be a raw material. If they are assuming that the catalyst can be reused for a particular number of batches, this should be stated but the calculation may be easier initially if it is done on the basis of no reuse.

Guidelines on Green Chemistry Metrics

Reaction metrics are used to measure the "green credentials" of a reaction, and provide a useful comparison tool to quantify improvements made when altering reaction conditions. By focusing only on product yield, chemists may miss the opportunity to improve the environmental credentials of a synthesis. A green chemist should influence the behaviour of synthetic chemists to move away from solely focusing on yield, and routinely consider environmental impacts. Table 4 shows how the application of green chemistry principles can deliver both economic and environmental benefits.

Table 4: Economic and environmental benefits from the application of green chemistry principles[3]

Process Improvement	Environmental Benefit	Economic Benefit
Atom economy	Less by-products and waste formed	Incorporate more of inputs into output, improving cost efficiency
Solvent reduction	Use lower volumes of potentially hazardous materials and have less solvent waste	Reduced volume means lower storage requirements and less energy to heat process
Reagent optimisation	Use catalysts rather than solely stoichiometric reagents to reduce inputs and recycle components	Improved selectivity and efficiency
Energy Reduction	Lower emissions related to power generation and use	Reduced costs
In situ analysis	Lower risk of exposure or release of analyte into environment.	Real time data increases efficiency, avoiding down time by detecting problems promptly
Safety	Use of non-hazardous materials and improved safety procedures lower the risk of environmental exposure, spillages, fire or explosions.	Increases worker safety and less downtime due to accidents

Reaction yield, atom economy, and mass intensity will be used to examine the reactions set out in this case study. The ideal value for atom economy and yield is 100 %, while for mass intensity it is 1.[4] Reaction yield will affect the mass of product obtained and therefore a low yield will result in a poorer mass intensity value.

$$\text{Atom economy} = \frac{\text{molecular weight of product}}{\text{sum of molecular weight of reactants}} \times 100$$

$$\text{Mass intensity} = \frac{\text{total mass used in process (kg)}}{\text{mass of product (kg)}} \times 100$$

$$\text{Percentage yield} = \frac{\text{actual yield of product}}{\text{theoretical yield of product}} \times 100$$

Metrics should be calculated for the reactions that follow. You may decide to ask each group to look at one or two of these steps rather than all four, depending on their level of familiarity with this type of calculation.

- Synthesis of salen ligand (see Figure 1)
- Preparation of manganese salen catalyst (see Figure 2)
- Epoxidation using a Mn-salen catalyst and hypochlorite solution (see Figure 5)
- Epoxidation using a Mn-salen catalyst and hydrogen peroxide or other alternative conditions examined (see Figure 6)

The metrics for the existing standard epoxidation method used by HugePharma Ltd. have been provided to students as a worked example for reference purposes. In the following pages, a summary of the data obtained from the analysis of the reactions involved in this project using green metrics is provided. Further detail is provided in the appendix (see Appendix 8).

As well as analysing some green chemistry metrics, it is recommended that learners are encouraged to take a holistic approach during this session and are asked to consider the following questions;[5]

- What is green about the process?
- What is not green?
- How can it be made greener?

The solvent used in a process has a critical influence on its environmental effects and Pfizer have developed a solvent selection guide for their medicinal chemists as well as a solvent replacement table which students should be prompted to consult when they are considering these questions.[6]

Metrics for catalyst synthesis

Table 5 shows the atom economy and mass intensity values calculated for step 1 (ligand synthesis) and step 2 (catalyst synthesis). The atom economy in the first step is relatively good in all cases (approximately 90%) as it involves a condensation reaction between the diamine and salicylaldehyde reactants.

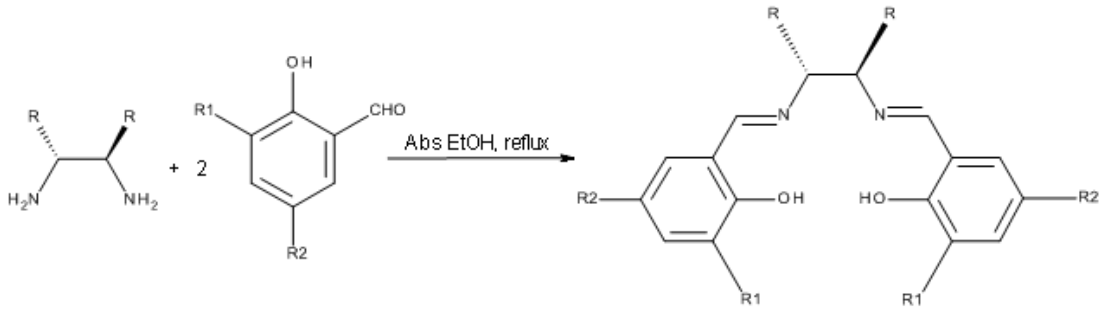


Figure 1: Step 1 - Reaction of diamine and salicylaldehyde derivative to form a salen ligand[7]

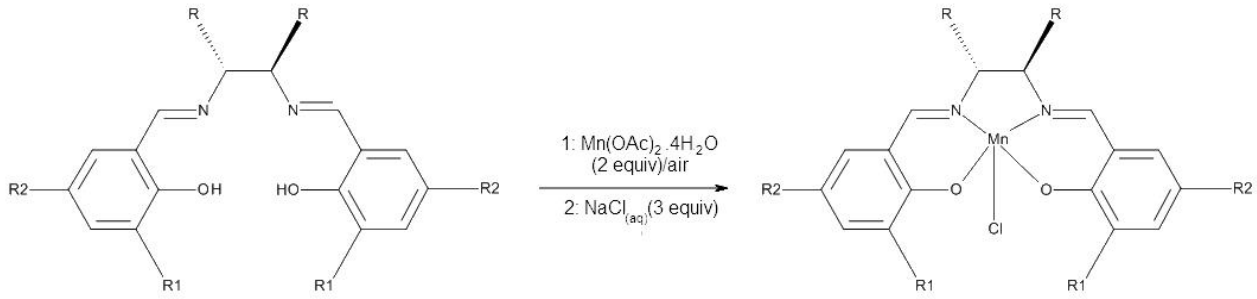
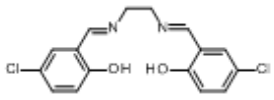
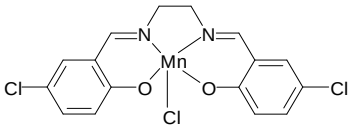
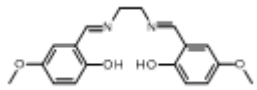
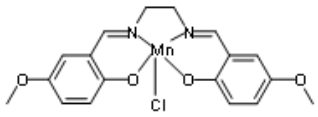
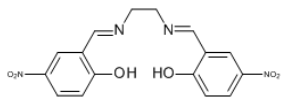
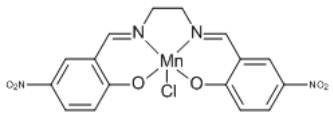
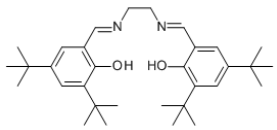
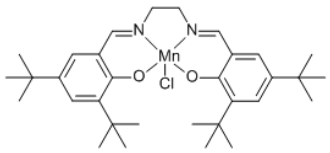
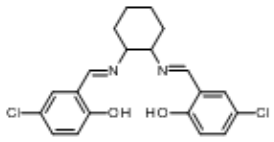
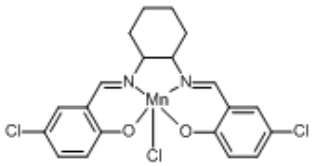
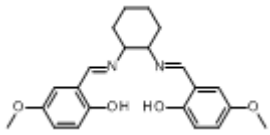
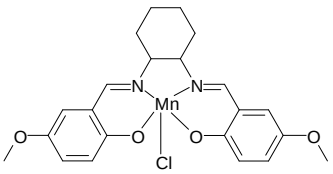
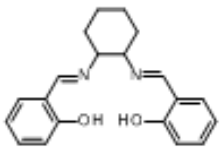
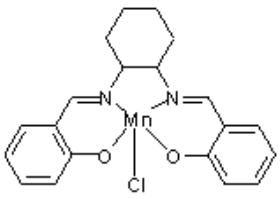
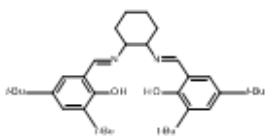
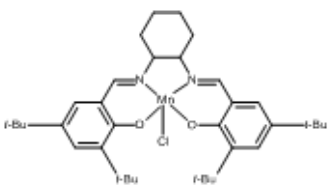
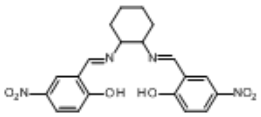
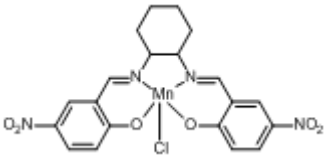


Figure 2: Step 2 - Synthesis of a manganese salen catalyst[7]

Table 5: Atom economy and mass intensity calculated for ligand and catalyst production

(see assumptions on previous page)

Product	Atom economy (%)	Mass intensity	Product	Atom economy (%)	Mass intensity
	90.34	12.81		42.44	20.90
	90.11	13.12		41.93	21.32
	90.86	12.11		43.63	19.87
	93.19	9.08		50.17	15.52
	91.57	11.17		45.39	18.65
	91.39	11.42		44.39	18.98
	89.95	13.35		41.58	21.61
	93.82	8.32		52.40	14.34

	91.97	9.90		46.46	17.87

Several assumptions have been made when performing these calculations as follows:

- Mass intensity calculations are based on producing 1 kg of product in 100 % yield and thus can be modified according to the actual percentage yield obtained.
- Chemicals used in the product work-up are not included.
- Water is not included in mass intensity calculations. (Process Mass Intensity, an alternative metric, does include process water).

Extending the green chemistry metrics used

The green chemistry metrics used here are at an introductory level and, if students have prior knowledge in this area, it would be appropriate to extend what is required of them. Consultation with the lecturing staff concerned is recommended and a recent review on effective practices in teaching green chemistry by Andraos and Dicks[1] is also very helpful. One way in which the assessment of each process can be developed is to ask students to include the materials used in the work-up as this gives a more accurate indication of its "greenness". In addition, Andraos and Sayed[8] have provided details on an Excel format suitable for analysis of reaction mass efficiency (which takes into account atom economy and material recovery) and raw material cost, and Ribeiro and Machado[9] describe the application of a global metric, the green star, which incorporates all 12 green chemistry principles, in a teaching context.

Epoxidation reactions

A brief review on some methods that have been reported in the literature for epoxidation of alkenes is provided below and it is followed by a comparison of the reaction metrics and other sustainable chemistry issues for those methods used in this case study.

Current epoxidation method:[11]

The established epoxidation method referred to by HugePharma Ltd. utilises a peroxyacid (*meta*-chloroperoxybenzoic acid (mCPBA)) as the oxidant for the conversion of an alkene to an epoxide. mCPBA is the preferred peroxy acid because of its relative ease of handling. The reaction scheme for epoxidation of *trans*-stilbene is shown in Figure 3. This procedure is not enantioselective.

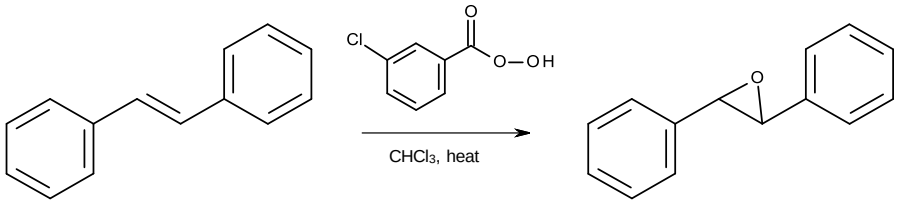


Figure 3: Peracid epoxidation of stilbene[11]

Catalytic asymmetric epoxidation methods:

The area of asymmetric epoxidation was initially pioneered by Sharpless[12] using catalysts based on titanium tetraisopropoxide and chiral dialkyl tartrate, forming an enantiomerically enriched product depending on the enantiomeric form (+ or -) of tartrate used (Figure 4). The oxidant used is *tert*-butyl hydroperoxide.

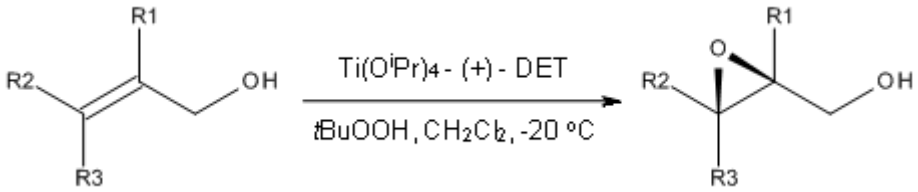


Figure 4: Sharpless epoxidation of allylic alcohols[12]

This method has proven effective for the production of complex carbohydrates but requires an allylic alcohol starting material. Oxidation of simple olefins shows very little enantioselectivity, therefore this method is not suitable for the epoxidation of stilbene.

In 1991, Jacobsen *et al.* published details of their epoxidation catalysts based on chiral Schiff base ligands around a manganese centre (Figure 5).[7] When used in the presence of sodium hypochlorite (bleach), these catalysts have been shown to efficiently transform a wide range of alkene substrates in high yields, and enantiomeric excesses in the region of 90 %.

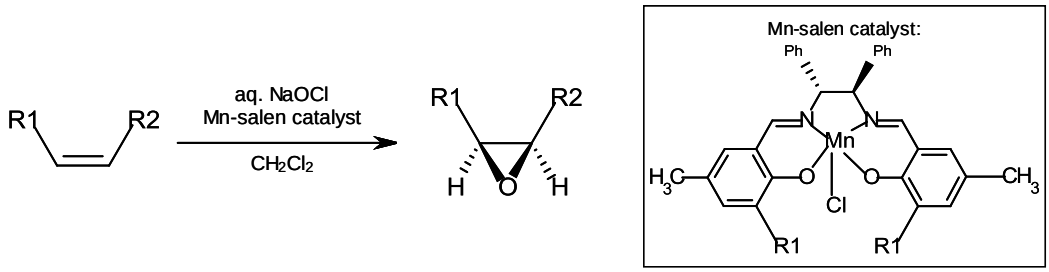


Figure 5: Epoxidation of alkenes with sodium hypochlorite using a Mn-salen catalyst (e.g. Jacobsen's catalyst)[7]

Catalytic asymmetric epoxidation method using hydrogen peroxide with Mn-salen catalyst:

An alternative method has been reported by Liu and Nocera[2] using Jacobsen's catalyst in the presence of hydrogen peroxide to perform the epoxidation of alkenes (Figure 6). This procedure is reported to employ

"green" methods through the use of this simple and cheap oxidising agent which should significantly improve the atom economy.

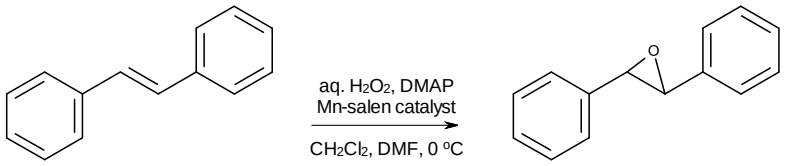


Figure 6: Epoxidation of stilbene with hydrogen peroxide using a Mn-salen catalyst (e.g. Jacobsen's catalyst)[2]

Table 6 which follows compares the green chemistry metrics and conditions for the three oxidation methods that are relevant to this case study. The other issues listed for each reaction in Table 6 should become apparent to students when they consult the literature review material provided in their briefing pack and from any additional information research they undertake.

Table 6: Comparison of reaction metrics and conditions used for epoxidation of *trans*-stilbene

Reaction	mCPBA as oxidant (Figure 3)	Mn-salen catalyst with sodium hypochlorite (Figure 5)	Mn-salen catalyst with hydrogen peroxide (Figure 6)
Atom economy (%)	55.62	77.05	91.59
Mass intensity	15.59	29.45	41.38
Other issues to be considered	Heat required to maintain operating temperature – energy input required. Chloroform as solvent – carcinogen, restrictions on use. mCPBA is shock sensitive – safety hazard on large scale. Cannot be used to produce one enantiomer over another.	Low operating temperature – varies from -78 °C to 5 °C to get good product resolution on commercial scale demanding high energy input to maintain[13] Dichloromethane as solvent – toxic, regulated by EU solvent directive. Catalyst needs to be recycled.	Use of additives – related expense and toxicity. DMF may form explosive mixture with H_2O_2 on larger scale. DMF can be difficult to remove from final product. Dichloromethane as co-solvent – toxic, regulated by EU solvent directive. Catalyst needs to be recycled.

Planning for the Next Session

Remind students that this is the last task and that they should now have all the information required to complete their wiki and report. Ask them to review the guidelines for the report and their progress and identify any areas that need further attention. Before the end of the workshop, pause activities and ask each group to review the tasks completed and those that need to be addressed before the next session. Ask the groups to feed back to the class if there is sufficient time.

At the next session, you will be providing formal feedback on each group's draft report and so you should set a deadline for submission that will give you adequate time to review them. It is recommended that a hard copy (i.e. a PDF version of the wiki) is submitted in order that students can continue to update the wiki in the meantime and to allow them to practise conversion of the wiki to a hard copy.

Tasks for Students to Complete Before Session 7

- Meet as a group to review progress on the list of actions for their group. The Chair will have prepared a short agenda, and the recorder will post a short summary of decisions made and progress reported on the wiki specified by the tutor. The Editor should be reviewing any page content that is being uploaded.
- As a group, analyse the ^{1}H NMR spectra obtained of the crude products from alternative stilbene epoxidation to determine the percentage conversion.
- Prepare a group analysis comparing the results (yield and conversion) for the reference and alternative oxidation reactions for all catalysts.
- Prepare a group analysis of the costing for the raw materials and materials required for work up for the two oxidation processes carried out (including catalyst preparation) for production of 100 g of *trans*-stilbene oxide and identify any issues (e.g. which materials are most and least expensive in the quantities required).
- Prepare a group analysis of the environmental impacts of the two oxidation processes with reference to green chemistry metrics including recommendations for improvements that may be possible.
- Submit a draft wiki report and a work in progress summary describing which areas of the final report the group feel they have addressed and which ones they have yet to complete with details on who is responsible and due dates. Any clarifications required or queries that students have should also be noted.
- Ensure the experimental details in their lab notebooks have been completed (characterisation and conclusions).

Desired learning outcomes:

On completion of this session and the related independent learning hours the students will be able to:

- Plan for the scope of future development work on each process.
- Compare the results obtained in the epoxidation reactions they performed (using hypochlorite and hydrogen peroxide).
- Cost the raw materials for two oxidation processes.
- Compare the environmental impacts of each oxidation process with reference to the appropriate metrics.
- Prepare a draft report including a work in progress summary.
- Collaborate in a face-to-face meeting and using a wiki.

Session 7 (Workshop 3): Clinic for Formative Feedback on Draft Reports

Aim / Goal of this Session:

The purpose of this workshop session is to:

1. Answer any student queries on the assignment and activities, and discuss any issues raised.
2. Provide learners with formative feedback (as an entire class and as an individual group) on which areas of the report they need to work on, and which ones have been addressed satisfactorily.
3. Identify the tasks remaining, and plan for when they will be achieved.

Further Information

In this workshop, students have the opportunity to receive formal feedback from their tutor who will highlight any areas that require work, address any misunderstandings and identify the strengths of the work produced to date. It also allows learners to review their work as a group, and to complete any tasks they have not been able to finish to date while you are speaking to other groups. It is probably best to speak to the entire cohort first and deal with any general issues, and then speak to each group individually in turn. It may be worth reminding students to take some notes on what you say.
Some specific guidelines for the final presentation that will take place in Session 8 should be provided. General guidelines for preparing presentations are provided in the appendices to the student guide. You will need to indicate to the students whether peer evaluation will take place, how long the presentation should last and whether it should be in a PowerPoint format or presented directly from the wiki pages. **If there are a lot of groups, you may decide to ask each group to focus on one particular section of the report only**. Students should be reminded to refer back to the original brief from HugePharma Ltd. to ensure that their presentation and report are addressing all aspects.
During the time when you are speaking to an individual group, the other groups will be able to plan the work required to produce and give their presentation and any other work that still remains.

Remind students that now the main body of the proposal has been prepared, they should focus on ensuring a good structure, coherence and consistency of style and formatting of the final proposal. If the executive summary was not submitted with the draft, they now need attention.
If you have not done so already, give a deadline for submission of the final proposal and the reflective piece.

Planning for the Next Session

If you are incorporating peer feedback for the presentations, students should be briefed a week in advance and shown the forms to be used. Students are asked to identify strengths and weaknesses and it should be explained that any criticism should be constructive.

Presentation Skills Evaluation Forms are included with the information for Session 8 in this guide and can be printed two to a page. Both tutors and students can use this form to provide written feedback. Each student should be given one of the forms and should write his or her name in the Speaker/Group position and on the back of the form. Students should then be asked to swap forms with a person from another group so that each student will be providing feedback to one other person. The system can be kept anonymous if preferred. In this case, the tutor should collect the forms once the student has written his or her name on it (this is probably best done at the end of Session 7 to save time in Session 8). The tutor can distribute the forms randomly at the beginning of Session 8, and then collects them following the presentations and returns them to the person named on the back.

Tasks for Students to Complete Before Session 8:

- Incorporate feedback from the tutor into group report and presentation.
- Add information to the wiki on their consideration of the scope for each synthesis step to be improved and recommendations for future work.
- Meet as a group to finalise their presentation. Practise it several times as a "dry run" and ensure it meets the time requirement and is relevant, coherent, structured and accurate.
- Post information on who attended any meetings as well as the tasks completed at them on the wiki.
- Continue to update and edit the wiki by uploading files and summaries, drafting sections of the proposal, and responding to contributions from other group members.
- The structure, coherence and consistency of style and formatting of the final report are important considerations at this stage.
- If the executive summary was not submitted with the draft report, it now needs attention.

Desired Learning Outcomes:

On completion of this session and the related independent learning hours the student will be able to:

- Communicate effectively when receiving formative feedback to ensure that the maximum benefit is obtained.
- Act on constructive criticism and suggestions.
- Prioritise the remaining work to be done.
- Prepare and present an informative and visually engaging presentation on their group project that encapsulates their findings.
- Collaborate in a face-to-face meeting and using a wiki.

Session 8 (Workshop 4): Oral presentations

Aim / Goal of this Session:

The purpose of this workshop session is to:

1. Have students present their group's work to their peers and tutor by summarising the work undertaken and their recommendations and to answer any questions the audience may have.
2. Provide oral feedback to students (with optional written feedback on each presentation from the tutor and peers)
3. Allow students to learn about alternative approaches to the project from the other presentations, while providing a supportive audience and constructive feedback to their peers.

Further Information

Presentations

In this workshop, each group will present their work and their recommendations to HugePharma Ltd., and will listen to and assess the presentations of the other groups. You may opt to invite some guest tutors who have a background in green chemistry, or who work or have worked in industry to provide additional feedback. It is helpful to monitor the time and give each group a warning when they have one minute left.

It is important to emphasise to students that they have an essential role as an audience member for their peers. It is recommended that they are asked to provide a supportive environment by listening attentively, making some eye contact with the presenter, asking any questions they have in a respectful and non-confrontational way, and (if requested to) making some constructive comments on the peer feedback forms for the student assigned. These guidelines are based on the system used in the Toastmasters organisation, as are the feedback forms at the end of this section. Students should also be reminded that listening to the other group's presentations provides a very useful opportunity to see how others approached the same project and to assess what they might incorporate from their methods in the future. Learners should be prepared to receive constructive feedback from their peers and tutor, and be ready to take some notes on any corrections or recommendations.

It is at your discretion to decide whether to give each group some feedback in front of the entire group after they have presented or to give general feedback at the end. It is recommended that the feedback form at the end of this section be used to give some written feedback to each group member, and that some strengths should be noted as well as areas for improvement. The forms can be printed two to a page.

Final report

Students should be reminded about the deadline for the submission of their final report and the format required. It can be generated from the wiki by printing it directly or converting to PDFs and then printing or it can be generated as a Microsoft® Word document by cutting and pasting from the wiki. (Word has some added functionality such as insertion of page numbers and performing a word count). It is expected that any feedback (oral or written) relevant to the report provided by the tutor after the presentation will have been incorporated. Indicate whether you want students to have submitted the report through a plagiarism detection system prior to submission and whether any individual and group work that has been previously corrected by you and returned should be handed in again to allow you to check whether the feedback given was acted on in the report.

Reflective piece
Students should also be reminded about the deadline for submission of their reflective statement which will usually be several days after that for the group report. Guidelines for the reflective piece are given in the student guide appendices.

Peer assessment
If you have opted to include peer assessment by each group member of each individual's contribution, they should be asked to complete a form on which they rate the frequency and quality of contributions to the group of each member, including themselves. Another option is to use peer review software such as CATME (Comprehensive Assessment of Team Member Effectiveness) which is available to download for free at https://engineering.purdue.edu/CATME.

Tasks for students to complete by the end of the module:

- Incorporation of feedback from the presentation into the group report.
- Final editing and completion of group's wiki report.
- Printing out and submitting the final report in the format specified (wiki or PDFs or Microsoft® Word). They may also be required to submit the report for checking by plagiarism detection software.
- Lab book to be submitted by the deadline provided.
- Preparing and submitting their individual reflective piece.
- Peer assessment of the other students in their group based on frequency and quality of contributions to the group (optional).
- If requested, submission of any marked group or individual work in hard copy that was returned previously.

Desired learning outcomes:

On completion of this session and the related independent learning hours, the student should be able to:

- Present findings in a professional manner
- Evaluate their work and the work of others.
- Provide a supportive audience and constructive feedback to their peers
- Act on feedback provided that is relevant to their written report
- Produce a professional report, including an executive summary and an assessment of the scope for each step to be improved. This should be supported by the relevant experimental data and a laboratory notebook, as well as references to the literature.
- Prepare a short individual reflective statement on the group process, transferable skills developed, and the extent to which the stated learning outcomes were met.

PRESENTATION SKILLS EVALUATION FORM

Speaker/ Group:

What I liked:

Suggestions:

Date **Signed (Optional):**

PRESENTATION SKILLS EVALUATION FORM

Speaker/ Group:

What I liked:

Suggestions:

Date **Signed (Optional):**

Appendices

Appendix 1 – Student briefing pack

Appendix 2 – Tutor notes on using wikis

Appendix 3 – Materials, apparatus and instrumentation requirements for laboratory sessions

Appendix 4 – Tutor notes on formation of salen ligand (Session 2)

Appendix 5 – Tutor notes on formation of Mn-salen catalyst (Session 3)

Appendix 6 – Tutor notes on epoxidation of *trans*-stilbene using manganese salen catalysts under standard conditions (Session 4)

Appendix 7- Tutor notes on epoxidation of *trans*-stilbene with H_2O_2 using manganese salen catalysts (Session 5)

Appendix 8 - Tutor notes on Green Chemistry metrics calculations (Session 6)

Appendix 1 – Student briefing pack

HugePharma Ltd.,
Chemical Development Department (Europe Division)
Warner Industrial Park, Gladwell Road, Carrigstown

Project Briefing Pack

- Letter from Chemical Development Manager
- Guidelines for structure of scientific report
- Twelve Principles of Green Chemistry
- Current epoxidation method
- Epoxidation route to be examined
- Literature review

HugePharma Ltd.,
Chemical Development Department (Europe Division)
Warner Industrial Park, Gladwell Road, Carrigstown

To: Managing Director, Chem Cat Ltd., University Industry Centre, Bridgeford.
Re: Consultancy project – Synthesis and Evaluation of Manganese(III) Salen Catalysts

Further to our meeting last week, we would like to confirm that HugePharma Ltd. are engaging the services of Chem Cat Ltd. to undertake consultancy work on a project to synthesise and evaluate Mn(III) salen catalysts suitable for epoxidation of alkenes. As you are aware, we require a process that implements Green Chemistry principles to their full potential to ensure that we comply with environmental legislation and maintain our Integrated Pollution Prevention and Control (IPPC) licence.

As previously agreed, the following deliverables are required to be completed within a two month period:

- Preparation on a lab scale and characterisation of up to nine Mn-salen complexes using the two step procedure described in the original literature reference (W. Zhang and E. N. Jacobsen, *Journal of Organic Chemistry*, 1991, **56**, 2296-2298).
- Evaluation of the relative performance of each catalyst using a reference reaction (the epoxidation of *trans*-stilbene). Criteria for catalyst evaluation are: (i) the yield and purity of the catalyst prepared, (ii) conversion to and yield of *trans*-stilbene epoxide (based on crude product). The results should be shown to be reproducible by performing the reference reaction in duplicate or triplicate.
- Prediction of how catalyst structure and efficiency are related based on the results from the reference reactions.
- Evaluation of the relative costs and the environmental impact of the procedure used and of at least one alternative epoxidation procedure (different oxidant or reaction conditions). If time allows, it would be useful if the alternative conditions could be trialled. Environmental impact evaluations should include a comparison with our current method of alkene epoxidation using mCPBA (P. L. Robinson, C. N. Barry, J. W. Kelly and S. A. Evans Jr., *J. Am. Chem. Soc.*, 1985, **107**, page 5217).
- A scientific report on the findings from the study (including an executive summary for non-technical management staff). Information on the scope for each synthesis step to be improved and recommendations for future work should be provided. We are particularly interested in modifications to the oxidation reaction and yield, solvent, cost of raw materials (in reaction and work up), complexity of the procedure, catalyst loading, potential for catalyst recovery and type of oxidant are all important considerations.
- We may also require that some of your staff give an oral presentation on the report after it has been submitted.

I have attached our corporate guidelines for the structure of scientific reports. A copy of the relevant literature review work carried out by one of our Chemical Development teams and of the contract for your signature will be sent to your office by courier today.

Chem Cat Ltd. has a good reputation in this field and therefore I look forward to receiving the scientific report prepared by your staff in due course. As discussed at our meeting, further work on this project may be commissioned based on the findings from this initial work.

Yours sincerely,

Josephine Buckley

Dr. J. Buckley,

Chemical Development Director.

HugePharma Ltd.,
Chemical Development Department (Europe Division)
Warner Industrial Park, Gladwell Road, Carrigstown

Guidelines for Structure of Scientific Reports

Reports should be a maximum of 2,000 words (not including figures, tables etc.) and should contain the following elements:

1. Report title, date submitted and author name(s).
2. An executive summary (aimed at a non-technical audience, maximum 200 words)
3. The main body of the report to include:
   - Aims and objectives
   - Background information and related previous work
   - Experimental details
   - Results and discussion
   - Conclusion including recommendations
   - Glossary of definitions for any unfamiliar terminology used to ensure clarity.
4. References should be formatted according to the Royal Society of Chemistry Publishing author guidelines format. (See page eleven of the document at this link: http://www.rsc.org/images/Guidelines_tcm18-186308.pdf)

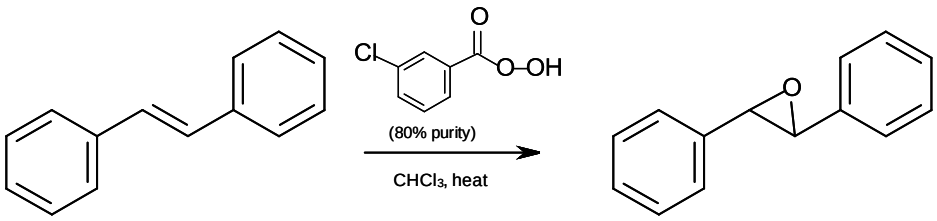
Any alternative epoxidation methods should align with the Twelve Principles of Green Chemistry as set out by P. Anastas and J. Warner, in Green Chemistry: Theory and Practice (Oxford University Press: New York, 1998).

The Twelve Principles of Green Chemistry:

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances should be made unnecessary wherever possible, and innocuous when used.
6. Energy requirements should be recognised for their environmental and economic impacts, and should be minimised. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatisation should be avoided whenever possible.
9. Catalytic reagents are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimise the potential for chemical accidents.

Current method:

The established epoxidation method uses a peroxyacid (*meta*-chloroperoxybenzoic acid (mCPBA)) as the oxidant in the conversion of an alkene to the corresponding epoxide. mCPBA is the peroxy acid employed because of its relative ease of handling. The reaction scheme for epoxidation of stilbene is shown below. This procedure is not enantioselective and gives a yield of 90 % for the conversion of *trans*-stilbene.



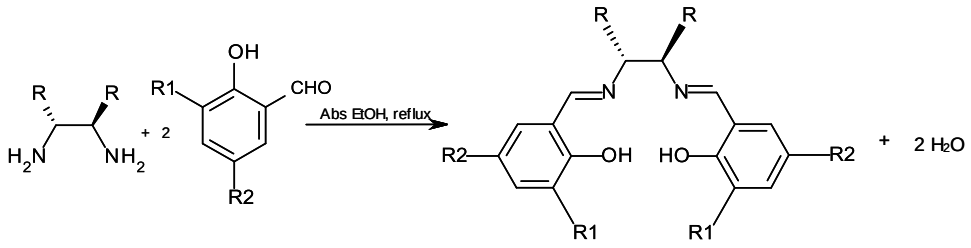
Reference: P.L. Robinson, C.N. Barry, J.W. Kelly, S.A. Evans Jr., *J. Am. Chem. Soc.*, 1985, **107**, 5210–19.

It is requested that Chem Cat Ltd. investigate the use of Jacobsen's catalyst to carry out a "greener" epoxidation of the model compound *trans*-stilbene. This alternative method would also facilitate enantioselective epoxidations to be performed should the need arise.

Epoxidation route to be examined:[7]

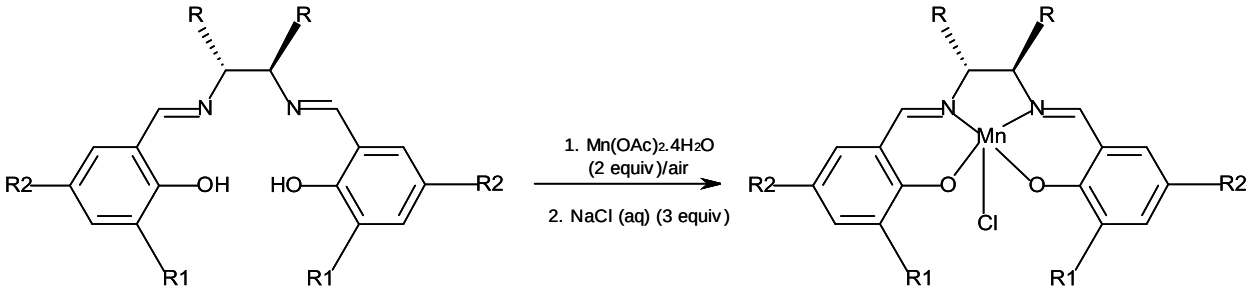
Reference: W. Zhang and E. N. Jacobsen, *Journal of Organic Chemistry*, 1991, 56, 2296-2298

Step 1- Synthesis of catalyst ligand:



(R=H or $–CH_2CH_2CH_2CH_2$-, R1=H or *t*-butyl, R2= Cl, OMe, H, *t*-butyl, or NO_2)

Step 2- Synthesis of Mn-salen catalyst complex:



(R=H or $–CH_2CH_2CH_2CH_2$-, R1=H or *t*-butyl, R2= Cl, OMe, H, *t*-butyl, or NO_2)

Step 3 – Epoxidation of trans-stilbene using the Mn-salen catalyst:

Literature review - annotated bibliography

Key to superscripts used to classify texts:

A: General topic reading – directly related

B: General topic reading – not directly related

C: Specific reference to Mn-salen catalysed epoxidation reaction

News stories

Herbert C. Brown Award For Creative Work In Synthetic Methods [A]

Yarnell, A.; Chemical & Engineering News, January 21, 2008, 86 (3), 57

Citing him as "the preeminent developer of synthetic methods of his generation," this article reports the conferring of an American Chemical Society award on Prof. Eric Jacobsen. His discovery and use of catalysts for enantioselective catalytic reactions, including epoxidation, have garnered him great respect. Jacobsen's chiral metal salen catalysts have widespread use in academic and industrial applications for the enantioselective epoxidation of olefins. The preparation of a key intermediate in the synthesis of Indinavir (Crixivan®), a HIV protease inhibitor drug, is given as an example of use on a multiton commercial scale.

Chiral Chemistry [B]

Stinson, S.C.; Chemical & Engineering News, May 14 2001, 79(30), 45-57

and Rouhi, A.M., Chemical & Engineering News, June 14 2004, 82 (24), 47-62

These articles discuss the ever increasing demand and sales of single-enantiomer chiral compounds. While the references to applications may be dated, this does provide a useful overview of the importance of these compounds in the pharmaceutical industry. A number of applications and synthetic routes are discussed throughout the reports.

Epoxidation Catalyst Immobilized In Ionic Liquid [A]

Freemantle, M.; Chemical & Engineering News, May 22 2000, 78 (21), 8-9

Chemists in South Korea immobilised Jacobsen’s catalyst in a room temperature ionic liquid in order to improve ease of recovery and recycling of the homogeneous chiral catalyst in asymmetric epoxidation of alkenes. They showed that the immobilised catalyst can be recycled five times with only a slight decrease in enantioselectivity and activity.

Enzymes at Work [B]

Thayer, A.M.; Chemical & Engineering News, August 14 2006, 84 (33), 15-25

This report discusses the option of using enzymes as alternative catalysts for epoxidation. The benefits of this technology are considered along with the reluctance of chemists to apply the technology.

Text books

Green Chemistry: Theory and Practice[A]

Anastas, P.T., Warner, J.C., Oxford University Press, 1998

This text book defines green chemistry and the tools used to achieve it. It sets out the twelve principles, exploring each principle individually. Tools for the evaluation of effects of chemistry, feedstocks and starting materials, reaction types and methods of improving reactions are also provided alongside examples of green chemistry in action. While this text book is over 10 years old, it is a key text written by authors who first conceived the principles of this approach.

Green Chemistry: An Introductory Text (2nd Edition) [A]

Lancaster, M., RSC Publishing, 2010

This updated edition of Mike Lancaster's textbook discusses a number of key green chemistry topics including waste minimisation, feedstocks, green metrics, efficient processes, catalysis, and greener solvents. There is a strong focus on new green methods which have been commercialised, and comparing new synthetic pathways with those used in the past. Chapters of particular relevance include Ch.1: Principles and Concepts of Green Chemistry (22 pages), Ch. 3: Measuring and Controlling Environmental Performance (28 pages), Ch. 4: Catalysis and Green Chemistry (48 pages), Ch. 8: Designing Green Processes (24 pages), and Ch. 9: Industrial Case Studies (31 pages).

Sustainable Solutions for Modern Economies[B]

Höfer, R. (Ed.), Royal Society of Chemistry, 2009

Giving an overview of the topic of sustainable solutions for development, this text book sets a useful context for the overall project. In particular, the introductory chapters cover the history of the concept of sustainability and its economic importance. Case studies showing applications of sustainable industrial processes should also be useful to give an impression of changes occurring in industry due to this important consideration.

Organic Chemistry[C]

Clayden, J., Greeves, N., Warren, S., 2nd edition, Oxford University Press, 2012.

Chapter 43 describes the application of Jacobsen's catalyst to the synthesis of Indinavir (Crixivan®), a HIV protease inhibitor drug and, in chapter 41, the conditions under which the catalyst is applied in organic synthesis are discussed.

Oxford Chemistry Primers 96: Applied Organometallic Chemistry and Catalysis[C]

Whyman, R., Evans, J. (Ed.), Oxford University Press, 2001

This primer provides an overview of homogeneous and heterogeneous organometallic catalysis, providing an account of the principal commercial applications in industry. Section 7.6 focuses on asymmetric

epoxidation including the Sharpless method and use of Jacobsen's catalyst. Applications of the Jacobsen catalyst in production of enantiomerically pure amino-alcohols as precursors for HIV and cancer treatments are mentioned along with potential barriers to commercialisation such as availability of ligands and catalyst stability on a large scale.

Modern Oxidation Methods (2nd Edition) [A,C]

Bäckvall, J.E. (Ed.), WILEY-VCH Verlag GmbH & Co. KGaA, 2010, pages 37 - 80, 371 - 421

This text book would be of use when researching new methods of oxidation. Of particular interest are the discussions in Chapter 2 on transition metal catalysed epoxidations of alkenes and information in Chapter 11 on manganese catalysed oxidation with hydrogen peroxide. This provides a useful context for comparison of different methods of epoxidation.

Methods and Reagents for Green Chemistry: An Introduction [A,C]

Tundo, P., Perosa, A., Zecchini, F. (Eds), John Wiley & Sons, 2007, pages 191 - 229

Part 3 of this text book covers "Green catalysis and biocatalysis", giving an over view of the importance of catalysis in green chemistry, waste minimisation and sustainable development. Chapter 11 focuses on metal catalysed enantioselective oxidation processes, reporting results based on use of Jacobsen's catalyst and related catalytic species. Substitution of groups at almost all positions on the catalyst structure have been investigated for the influence on yield and enantioselectivity of the catalyst, although no clear conclusion is drawn on this topic. This chapter also reports the industrial use of manganese salen catalysts for production of a potassium channel activator (BRL 55834), which has potential to be used as a bronchodilator, as shown in the scheme below (Figure A).

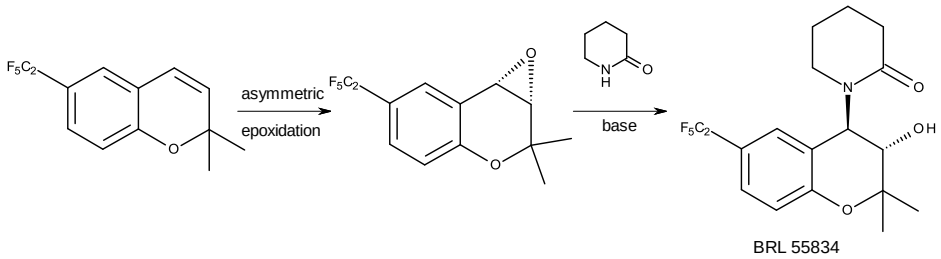


Figure A: Asymmetric epoxidation in the production of a pharmaceutical ingredient

Process Chemistry in the Pharmaceutical Industry. Chapter 19: Chiral (Salen)Mn(III) complexes in Asymmetrc Epoxidations: Practical Synthesis of *cis*-Aminoindanol and Its Applications to Enantiopure Drug Synthesis [A,C]

Editor: Gadamasetti,K.G., Chapter authors: Senanayake, C.H., Jacobsen, E.N.; Marcel Dekker Inc., 1999, pages 347-368

Two enantiomers of a chiral drug often display different biological activity; therefore a practical and reliable route for production is important to the pharmaceutical industry. This chapter focuses on the development of a practical chiral (salen)Mn catalyst for asymmetric epoxidation of unfunctionalised alkenes, and a practical application of salen(Mn)-based epoxidation methodology to the synthesis of enantiopure *cis*-aminoindanol and its applications in drug synthesis. Chiral salen complexes of all the first row transition metals have been prepared, with Mn(III) derivatives displaying superior selectivity and the highest turnover in epoxidation of most alkenes. The synthesis of (salen)Mn(III) complexes is readily accomplished by heating an ethanolic solution of a salen ligand to reflux with two equivalents of $Mn(OAc)_2.4H_2O$ in air (see Figure B).

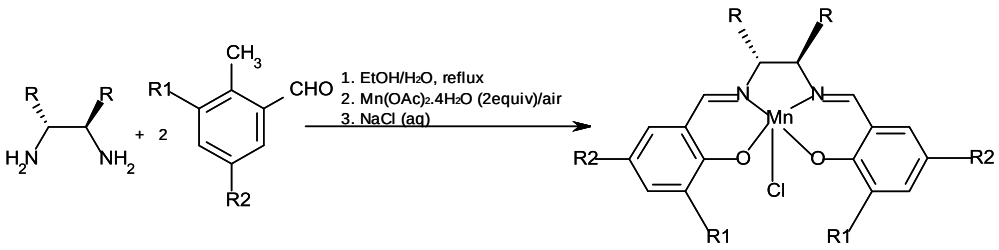


Figure B: Summary of synthesis procedure for Jacobsen's catalyst

It was reported that good enantioselectivity in olefin epoxidation requires 1) a dissymmetric diimine bridge derived from a C2 symmetric 1,2-diamine, and 2) bulky substituents on the 3 and 3' positions of the salicylide ligand. In general, electron donating or sterically demanding substituents on the 5 and 5' position also improve enantioselectivity. The most widely used catalyst in this class uses a *t*-butyl substituent at the 3 and 3' position.

A variety of stoichiometric oxidants are effective for (salen)Mn-catalysed epoxidations, but aqueous sodium hypochlorite was found to be a practical option. Conditions have been developed involving a two-phase system, with an aqueous phase containing commercial bleach and an organic phase containing a solution of substrate and catalyst in a suitable solvent. On lab scale, the reaction is carried out within a few hours in dichloromethane at 0^oC. Alternative solvents include 1,2-dichloroethane, *tert*-butyl methyl ether, ethyl acetate and toluene. Work-up is accomplished by phase separation and epoxide isolation by recrystallisation, distillation or chromatography. In general, complete substrate conversion can be achieved using 0.1 to 5 mol% of catalyst.

This system has been further developed by the Merck[14] and Sepracor[15] research groups for the production of *cis*-1-amino-2 indanol, an important pharmaceutical precursor. Applications for this in drug synthesis could include HIV protease inhibitors, synthesis of (S)-oxybutynin (Diropan®) which is a prescribed muscarinic receptor antagonist and production of (R)-Ketoprofen, a non-steroidal anti-inflammatory drug (NSAID).

Green Chemistry Metrics - Measuring and Monitoring Sustainable Processes. Chapter 5: Mass Balances and Life Cycle Assessment [A,C]

Lapkin, A, Constable, D. J.C., (Chapter authors: Eissen, M., Geisler, G., Bühler, B., Fischer, C., Hungerbühler, K., Schmid, A., Carreira, E. M.), John Wiley & Sons, 2008.

Chapter 5 of this book examines mass balances and life cycle assessment, focusing on enantioselective epoxidation of styrene as a case study (section 5.3.2). This comparison gives a useful introduction to the complexity of the number of different considerations which must be taken into account when evaluating a reaction. The use of Jacobsen's catalyst is compared to enzymatic conversion of styrene to styrene oxide. Mass intensity, environmental (E-) factor and cost index are calculated for both processes. The results found the enzymatic process to be greener although many factors must be balanced by the writers before reaching this conclusion.

Research Papers

Asymmetric Olefin Epoxidation with Sodium Hypochlorite Catalyzed by Easily Prepared Chiral Mn(III) Salen Complexes[A,C]

Zhang, W., Jacobsen, E.N., Journal of Organic Chemistry, 1991, 56, 2296-2298.

This is the original paper published by Jacobsen *et al.* reporting the effectiveness of manganese salen catalysts for the epoxidation of asymmetric olefins to give enantiopure products. The described synthesis is simpler than those previously reported and is a highly practical procedure using commercial bleach as the stoichiometric oxidant (see Figure C).

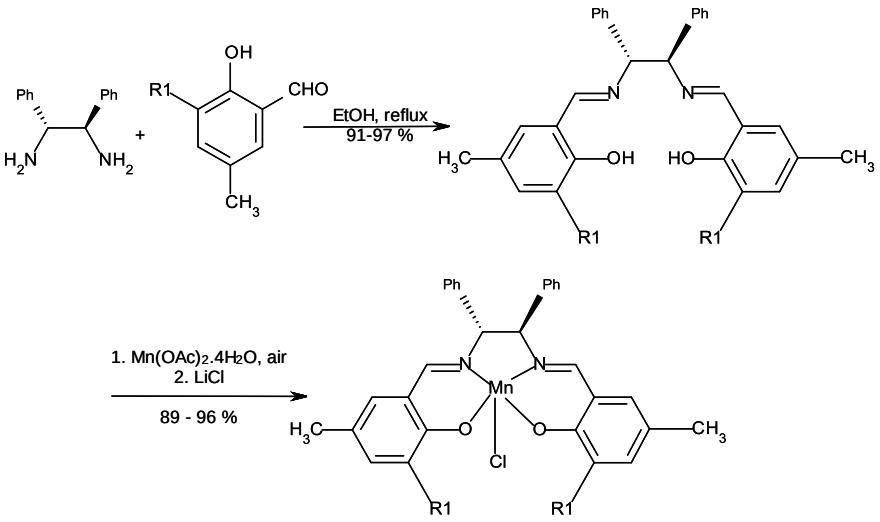


Figure C: Synthesis of Jacobsen's catalyst using conditions stated in the original reference

The catalyst is isolated in excellent yields and can be stored for prolonged periods of time without any precautions to exclude light, air or moisture. This route for olefin epoxidation claims to embody several appealing features, such as good isolated yields of epoxide, inexpensive reagents, and mild conditions.

Synthesis and Use of Jacobsen's Catalyst: Enantioselective Epoxidation in the Introductory Organic Laboratory[A,C]

Hanson, J., *Journal of Chemical Education*, 2001, 9, 1266-1268

This paper describes the use of Jacobsen's catalyst in an undergraduate teaching environment. The preparation was used to introduce students to a new synthetic method, to teach common techniques used in running reactions and characterising compounds, and to reinforce concepts learned in the accompanying lecture course. The methodology was reported to be reliable, safe, and inexpensive enough to be performed by large numbers of relatively inexperienced students. The paper and accompanying supplementary information provide a detailed description of the practicalities associated with implementing this laboratory session. The enantioselectivity of the catalyst, an aspect not addressed in this project, was also examined.

Asymmetric Processes Catalyzed by Chiral (Salen) Metal Complexes[A,C]

Larrow, J.F., Jacobsen, E.N., *Topics in Organometallic Chemistry*, 2004, 6, 123-152

This chapter reviews progress in the application of chiral salen ligands in asymmetric transformations, comparing the use of different metal catalysts. It is reported that the ligands are relatively simple to produce, display high enantioselectivities and are active on a broad range of substrates. In this comprehenensive review, a number of topics are covered including salen ligand synthesis, epoxidation reactions, epoxide ring opening reactions, carbonyl addition processes and cycloaddition processes.

A Simple and Versatile Method for Alkene Epoxidation Using Aqueous Hydrogen Peroxide and Manganese Salophen Catalysts[A,C]

Liu, S.Y., Nocera, D.G., *Tetrahedron Letters*, 2006, 47, 1923–1926

This paper and the accompanying supplementary information describes a versatile method for the catalytic epoxidation of a range of olefins using manganese salophen catalysts. This method varies from that reported by Jacobsen *et al.*, in that aqueous H_2O_2 is used as the oxidising agent in the presence of an organic additive. This system claims low catalyst loading, short reaction times, and a simple reaction procedure.

Recoverable chiral salen complexes for asymmetric catalysis: recent progress[A,C]

Zulauf, A., Mellah, M., Hong, X., Schulz, E.; *Dalton Trans*., 2010, 39, 6911–6935

This review reports on the various metal centred chiral salen-type complexes (including Jacobsen's catalyst) which have already been reported as asymmetric catalysts for the preparation of a wide range of enantioenriched products. When these complexes are efficiently recovered and recycled, the procedures have proven positive in terms of atom economy and overall economical savings. The paper summarises recent results (2006–2009) dealing with the use of recyclable chiral salen complexes.

Manganese-Based Organic and Bioinorganic Transformations[A,C]

Melikyan, G.G., *Aldrichimica Acta*, 1998, 31, 50-64

This review covers a number of applications of manganese compounds in synthetic chemistry including radical bond formation, manganese salen complexes, manganese porphyrins, and DNA-cleaving agents. Providing a overview of each use, this provides background reading for the use of Mn salen complexes in catalytic asymmetric epoxidation and related reactions, giving a large number of relevant citations.

Chromium- and Manganese-salen Promoted Epoxidation of Alkenes[A,C]

McGarrigle, E.M., Gilheany, D.G., *Chemical Reviews*, 2005, 105, 1563-1602

This review (40 pages) comprehensively covers the development of Cr(salen) and Mn(salen) mediated asymmetric epoxidation focusing in particular on progress between 1999 and March 2004. The review only considers salen complexes with a particular general structure which Jacobsen's catalyst shares. Heterogeneous and supported catalysts are not included. Pages 1569 – 1589 focus on manganese catalysed asymmetric epoxidation, discussing early results in this field, subsequent modifications and the reaction mechanism.

Practical Asymmetric Synthesis[A,C]

Davies, I. W., Reider, P. J., *Chemistry and Industry*, 1996, 11, 412-415

This article discusses several case studies on asymmetric synthesis strategies performed on a commercial scale. The first example discussed is the production of Indinavir (Crixivan®), a HIV protease inhibitor by Merck. The conditions under which Jacobsen's catalyst was utilised in this synthesis and some process improvements that were made are discussed.

Metal Acetylacetonate Synthesis Experiments: Which Is Greener? [B]

Ribeiro, M.G.T.C., Machado, A.A.S.C., *Journal of Chemical Education*, 2011, 88, 947–953

This paper describes a scenario in which learners are asked to carry out a synthetic procedure, calculate its green chemistry metrics and suggest improvements. In this case, the students are challenged to use the 12 principles to review and modify metal acetylacetonate synthesis. A "green star" metric is used alongside conventional green chemistry mass metrics to evaluate the improvement in greenness. This metric helps students to become familiar with both the 12 principles and green chemistry mass metrics and to gain experience in modifying synthetic chemistry to improve its greenness.

Patents[C]

U.S. Patent No. 5,637,739 Chiral Catalysts and Epoxidation Reactions Catalyzed Thereby

and U.S. Patent No. 5,663,393 Chiral Catalysts and Epoxidation Reactions

Jacobsen, E.N., Zhang, W., Deng, L.; 1997

These patents cover the use of chiral catalysts for enantioselective epoxidation and oxidation of prochiral alkenes. The catalyst described is Jacobsen's catalyst or a structurally similar Mn(salen) complex.

US Patent No. 6,031,115: Process for Preparing Epoxides **and** International Patent No. WO 93/1706 Process for Preparing Enantiomerically Pure Fluorinated Epoxychromans

Bell, D., Fedouloff, M., Turner, G.; 2000; SmithKline Beecham plc

This patent covers the use of Jacobsen type catalysts for the production of pharmaceutical grade ingredients.

Website[B]

The Green Chemistry Network website; http://www.greenchemistrynetwork.org/

This body aims to promote awareness and facilitate education, training and practice of Green Chemistry in industry, government, academia and schools. The main page has a useful links menu that includes a section on Educational Resources and on Environmental Agencies and Commissions.

Some additional sources that may be useful:

The following texts contain some information on environmental management and control in organisations;

- N. Stanley, Active Pharmaceutical Ingredients – Development, Manufacturing and Regulation, 2nd edition, Informa Healthcare, 2010 (see chapter on Environmental Control)
- M.K. Theodore and L. Theodore, Introduction to Environmental Management, CRC Press, 2009
- C. Sheldon and M. Yoxon, Environmental Management Systems, 3rd edition, Routledge, 2006

Appendix 2 - Tutor notes on using wikis

A wiki is “a collaborative website consisting of one or more pages that allow authorised users to contribute to or edit page content.” (source: http://usermanual.pbworks.com/Glossary)

Note that although many wikis are open access, those described for this project are secure and only people invited to join the group / wiki by the tutor administrator will have access.

Why use a wiki?

- Wiki software is very easy to use and allows students to work and to write collaboratively to produce a report / presentation / webpage.
- The wiki is a means of generating a very useful archive of all of the information that is relevant to the assignment as the project proceeds.
- It provides the added flexibility of being able to work anywhere that a PC or laptop and internet connection are available at any time.
- All previous versions of each page can be accessed using the Page History function which means that no work can be permanently overwritten or deleted.
- Contributions made by each member can be easily tracked to assess their quality, quantity and whether they were made across the entire timeframe of the assignment.
- Peer feedback and review is facilitated by the comments and page editing option.
- The assignments and the feedback provided can be accessed easily and stored indefinitely for future reference and are available in a flexible format (pages can usually be saved as PDFs).
- Wikis are regularly used in organisations to allow groups to collaborate on projects and documents and to share knowledge and the ability to use one is a valuable transferable skill. For example, a wiki has been established to develop policy in the area of green chemistry in California (http://cagreenchem.wikidot.com/start) (further references on the use of wikis in organisations are provided towards the end of this Appendix under Further Reading / Viewing).

Available software

The authors have experience of using PBworks, but there are several other products and most virtual learning environments now have a built-in wiki. Should you wish to research options, www.wikimatrix.org allows the user to select the wiki platform which best suits their needs in terms of a number of features, including access control and security, advertising, file sharing, formatting etc.

PBworks has a basic version that is free to use (see https://plans.pbworks.com/academic to sign up and http://usermanual.pbworks.com/w/page/11632089/Home for help)

What do academic staff need to be able to do?

In advance:
The common tasks tutors perform initially are creating new wikis, adding group members to them and adding a message to the front page. Any training you request on how to do this from your local learning technology support staff should take less than an hour. You may decide to add some of the wiki pages the group will

need by adding new pages and naming them appropriately (e.g. Aims and Objectives, Experimental details, Results and discussion, References, Administration and Planning, Resources). However, it is less time consuming if the students are provided with a list of pages that they should add themselves instead and this is provided in the student guide in Appendix 1 on using wikis. It may also be helpful to create one central wiki that all groups have access to or use a virtual learning environment (VLE) so that assignment details and general feedback can be posted, and all technical / academic queries can be dealt with centrally. This will avoid duplication. Video files (e.g. tutorials on software) and audio files can also be added there if you wish to do so.

On an ongoing basis:
You may have to deal with some technical queries. It is recommended that students are required to confirm that they already asked a peer about their technical problem, and that they checked any guidelines they already have before they post a query to the tutor. Posting the answer in a central location accessible to all students saves considerable time, and builds up a "Frequently Asked Questions" page.

You should aim to provide some feedback on progress each week if possible. This would usually be posted as a comment on each group's page, although general feedback on a central wiki or VLE can also be used if similar issues are cropping up or if time is an issue. **The first week is particularly important** as students may be reticent about being the first to write on a page and often need encouragement. Students may find it useful to add files with their draft work in advance of their weekly group meeting, and then decide what will be added to the page at their meeting. A selection of tutor comments from previous wiki assignments have been added at the end of this section. You may want to cut and paste some of these and/or begin to save some of your own to a Microsoft Word file to make this process easier. Each group is required to post a short summary of their weekly meeting (decisions made and resulting actions, people responsible and dates to be completed) and, in this way, work undertaken that may not otherwise be apparent from the wiki is captured.

What do students need to be able to do?

The common tasks students will perform are adding and editing wiki pages, adding comments and links to pages and inserting tables and chemical schemes / structures. Note that most chemical drawing software allows for structures to be saved as images and the format required by the wiki for embedding an image directly will be specified in the help menu (for PBworks wikis, images need to be in a PNG, JPEG, or GIF format). If students have not used wikis before, it is recommended that time be booked in a computer lab to allow them to practice these tasks on the wiki you have set up for each group in Session 1.

This should only take 30 minutes maximum and requires you to have obtained student e-mail addresses in advance to set up the wikis.

Some issues with wikis

Netiquette and group interaction:

The concept of "netiquette" is discussed in the student guide, and is important to highlight at the outset, because of the lack of visual cues when not communicating face-to-face. Students should be respectful to each other and be conscious of not offending or insulting anyone. You may want to ask the students to suggest some ground rules about working in their groups, such as, remaining respectful towards a group member who is not contributing, providing constructive feedback to peers (e.g. posting a comment first before making changes to someone else's work), and consulting with all members of the group in relation to important decisions.

Plagiarism

Students may need to be reminded of the importance of providing references for information (and acknowledging the source of images), and of the need to use their own words to incorporate the ideas and information from the sources used into their report/presentation. Students can be asked to sign a declaration such as the one below (see also “A Handbook for Deterring Plagiarism in Higher Education”, Jude Carroll, Oxford Centre for Staff and Learning Development, Oxford, 2002).

Alternatively, they can be asked to submit their final report to plagiarism detection software.

Example of a statement of originality;

We hereby affirm that

1. the research and writing of this report/presentation is entirely our work;
2. we have not intentionally plagiarised any portion of the report/presentation

and have included quotation marks or references where required:

Signature: _____ Date: _____

Signature: _____ Date: _____

Signature: _____ Date: _____

Suggested assessment criteria for wikis

Assessment criteria that can be used by tutors for individual students are usually based on effort and collaboration. If used, peer assessment criteria can be based on the frequency and quality of contributions. (see this video of two staff from Swinburne University of Technology discussing using wikis in education for more details http://www.youtube.com/watch?v=gRj5ABJ-IPY&feature=related).

A detailed rubric for assessing individual contributions to a group wiki is provided on page 3 of the following reference and it is recommended that this rubric be modified as required and used: Learning to Teach Online, Case Study. Using wikis for student collaboration, Simon McIntyre, accessed 12 January 2012 at http://online.cofa.unsw.edu.au/sites/default/files/episode-pdf/CS_Wikis_LTTO.pdf

To summarise, aspects that can be considered for wiki assessment are:

Contribution to the Group (based on wiki, summaries of meetings and workshop participation)
Effort (based on wiki, summaries of meetings and workshop participation)
Optional - Peer Assessment (frequency and quality of contributions, both online and face-to-face)

West and West provide rubrics for assessing the process and outcomes of a wiki project on a group basis in Chapter 2 of their book. These could be used as they are presented to generate a group mark for collaboration or could be modified to incorporate an individual contribution also (West, J. A.; West, M. L., Using Wikis for Online Collaboration, Jossey-Bass, San Francisco, 2009).

Further Reading / Viewing:

A video showing how to set up a PBworks wiki for educational use:
http://www.youtube.com/watch?v=SZ5OV14v4xU

References on use of wikis in organisations:

- "Corporate Wiki Users: Results of a Survey", A. Majchrzak, C. Wagner & D. Yates, *WikiSym'06, Proceedings of the 2006 international symposium on Wikis*, D. Riehle, J. Noble, Eds. (ACM Press, 2006), vol. Odense, De, pp. 99-104, accessed 18 October 2011 at https://blog.itu.dk/MVOL-F2010/files/2010/02/corporate-wiki-users-results-of-a-survey.pdf
- A wiki to develop policy in the area of green chemistry in California is available here: http://cagreenchem.wikidot.com/start and here: http://cagreenchem.wikidot.com/welcome ; http://eponline.com/articles/2009/02/09/calif-launches-wiki-to-develop-green-chemistry-regulations.aspx
- Ganfyd wiki is a medical database that can be edited by registered medical practitioners and viewed by anyone: http://www.ganfyd.org/index.php?title=Main_Page
- Drug Discovery Today article on use of an in-house wiki by Hoffman La Roche to share medicinal chemistry knowledge: Mayweg, A., Hofer, U., Schnider, P., Agnetti, F., Galley, G., Mattei, P., Lucas, M., Boehm, H. J.; ROCK: the Roche medicinal chemistry knowledge application - design, use and impact. *Drug Discovery Today* **2011,** *16* (15-16), 691-696.

Use of wikis in teaching and learning chemistry

- Chemistry Education Research and Practice paper that discusses using wikis to support PBL in chemistry (see page 26): Williams, D. P., Woodward, J. R., Symons, S. L., Davies, D. L.; A Tiny Adventure: the introduction of problem based learning in an undergraduate chemistry course. *Chemistry Education Research and Practice* **2010,** *11* (1), 33-42.
- J Chem Ed article on using wikis to promote collaboration on online lab reports: Elliott, E. W., Fraiman, A.; Using Chem-Wiki To Increase Student Collaboration through Online Lab Reporting. *Journal of Chemical Education* **2010,** *87* (1), 54-56.
- Evans, M. J.; Moore, J. S., A Collaborative, Wiki-Based Organic Chemistry Project Incorporating Free Chemistry Software on the Web. *Journal of Chemical Education* **2011,** *88* (6), 764-768.

Some useful assessment and evaluation guidelines, learning factors and project design information:

- Tsai, W. T.; Li, W.; Elston, J.; Chen, Y. N., Collaborative Learning Using Wiki Web Sites for Computer Science Undergraduate Education: A Case Study. *Transactions on Education* **2011,** *54* (1), 114-124.

Textbook on the use of wikis in higher education:

- West, J. A.; West, M. L., Using Wikis for Online Collaboration, Jossey-Bass, San Francisco, **2009**.

Sample Front page of Wiki (input from tutor needed where highlighted)

Welcome to your Green Chemistry Group Assignment Wiki (Link to Index page)

Dear Group X,

Welcome to your wiki. You can begin to add relevant links and files on background material and your group meetings, and draft your report and /or presentation for your context/problem based learning assignment. Please take advantage of the **Help** link above to the right, and the links provided below by the software providers to ensure that you are using the wiki effectively. There are also some videos available on YouTube that show you how to carry out particular tasks.

Each group member can edit any wiki page or add a comment. The **Page History** link allows you to see previous versions of each page and recall portions of it if you want to do so. It also provides a permanent record of which group member did what. The **Pages & Files** tab on the top left has a number of existing templates that you can edit which you may find useful (e.g. meeting agenda). You can also create new pages with the formatting of your choice. Please use folders, link related pages, and name files and pages in a logical and structured way so that you can find information here easily. To help with this, your group are provided with names that should be used for the pages that will make up the main body of your report and/or presentation. **There is a space limit on each wiki page. If you find that a page is no longer accepting edits, you have probably reached this limit. You will need to add a new page, and link to this new page from the end of the existing one to continue that section.**

You should receive daily email notifications of changes made to your wiki, but you can change that to a different interval if you wish to do so by altering the "Notification Preferences" settings at the bottom of your log-in page.

Please make sure that all members of your group have access to this wiki. If there is a problem, ask the person who has not received an invitation to the wiki to e-mail me at tutorname@xxx to request access.

Also, remember that this wiki is for academic use only, that all changes are saved and traceable, and all entries made by a student are used to determine the grade obtained.

I'm looking forward to seeing the work that your group produce,

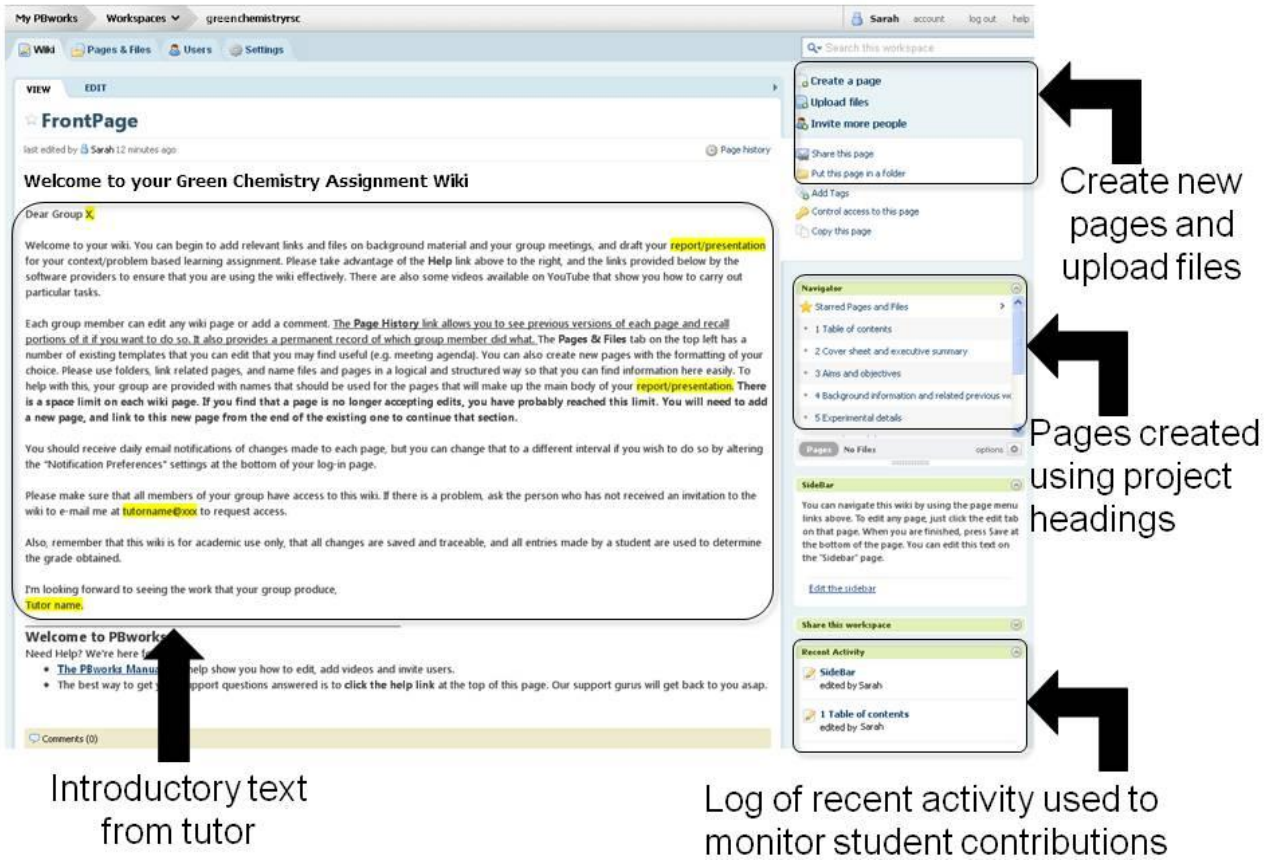
Tutor name.

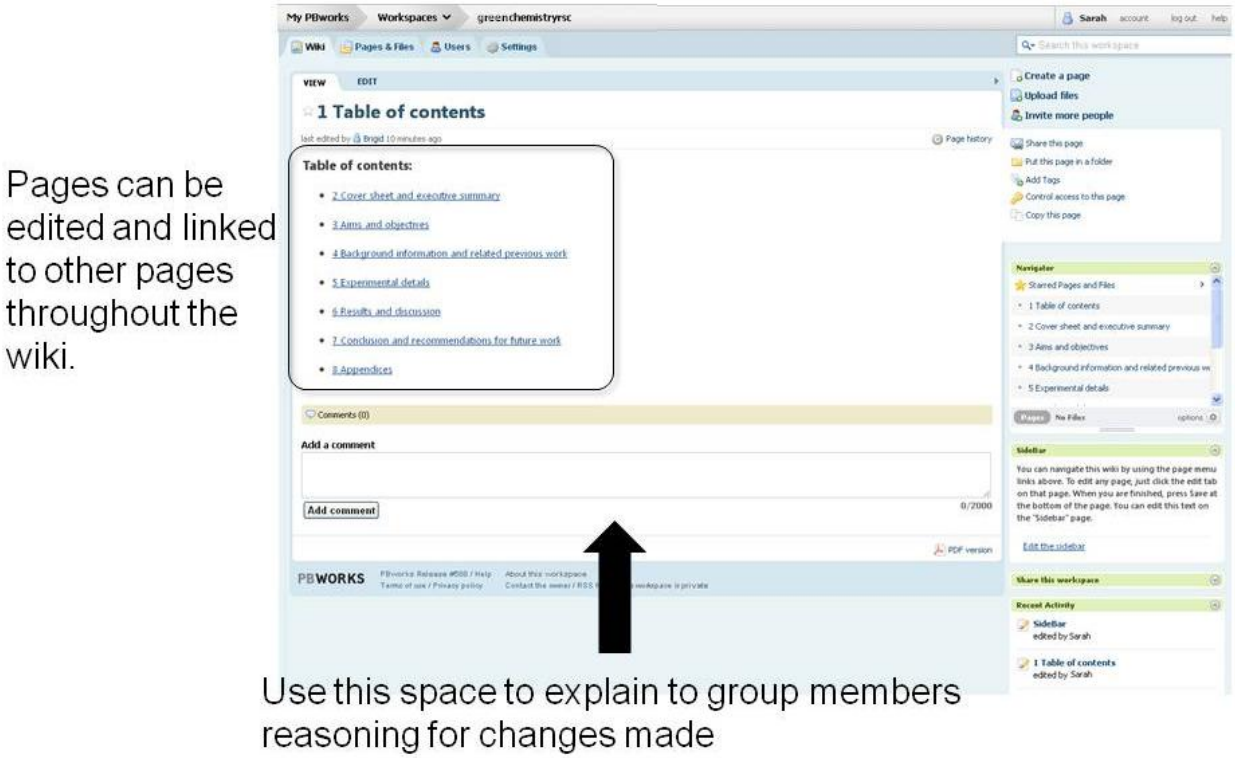
Welcome to PBworks

Need Help? We're here for you:

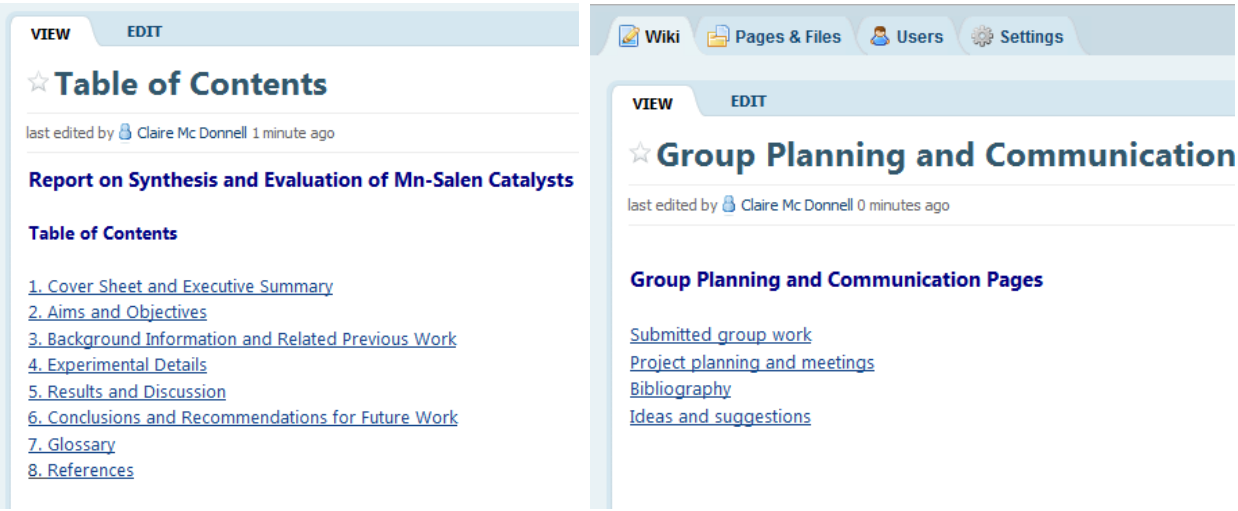
- **The PBworks Manual** can help show you how to edit, add videos and invite users.
- The best way to get your support questions answered is to **click the help link** at the top of this page. Our support gurus will get back to you asap.

Screenshots Showing Main Features of a Wiki





Screenshots of a Sample Wiki Showing Pages Linked to the Two Main Pages



Sample feedback comments from wikis used previously

Initial comments

- This is a reminder to start to use this wiki to plan your group assignment. Please make sure that you discuss it as a group (face to face or in an online chat) and post some minutes with a summary of group decisions as soon as possible. It is recommended to assign two roles in meetings that rotate each week - a "chair" (organises meetings, decides on agenda and running order, and deals with any differences of opinion), and a "recorder" (records a summary of the decisions made and resulting actions, people responsible, and dates to be completed meetings). Good luck with your assignment.
- You've made a good start here. I would hope that the other people in your group will also begin to contribute soon.
- This looks good so far. Can you add the reference numbers in below the relevant images though, and add them into the text where relevant too.
- The page is coming along very well. You've done a lot of research so far and found some interesting information.

Positive comments

- In general, the pages are well researched and referenced.
- Relevant schemes and images have been used, and they have been referred to in the main text.
- Well done on preparing a well researched and clearly structured report/presentation with relevant schemes and images that all team members contributed too.
- Your work has been carefully checked and proofread, and the wiki page history shows that you were all contributing effectively.

Room for improvement

As far as possible, any comment on an improvement that could be made was prefaced by a positive comment on another aspect of the wiki.

- There is some repetition of information - particularly about xxxxx.
- The overall report/presentation is quite long and is in need of a final edit - for structure and content and language errors.
- It is important that a group make sure they have time to review their work together towards the end, edit it to make sure that there is no repetition, and that all information can be clearly understood.
- Make sure that one or two people edit the whole report/presentation at the end so there is a "flow" between the sections and a similar style is used all the way through.
- Only include information that you understand yourself and explain all scientific and technical terms which would be unfamiliar to your peers.
- It would have be recommended to include more textbook references instead of websites.
- Where appropriate, add references for information you have given.
- Be careful that you have put all information in your own words and haven't plagiarised.
- A diagram/table/scheme in the section on xxxxxx would be helpful.
- Information on xxxxx was not included. Please add this before submission of the final version. Include a few more chemical structures.
- Look over where xxxxx is discussed. It could be made clearer.
- Give the information required in the correct format in the references e.g. article authors / journal name / place published for a text book.

General Feedback and Technical Support Comments

Please post any queries about any technical problems or general help you need on this page.

- Some of you put a lot of work into your procedures (well done) and some did not do as much. Please note that any feedback you get should be acted on by making changes to your second step procedure for next week (e.g. provide a list of glassware and equipment needed and the reaction scheme showing the starting material and product structure). Also, the final report should have the corrected version of these procedures and the safety information, and the original ones I corrected should be handed back then also.
- Most of you made a good attempt at predicting the IR and NMR spectra. The aspects that were often not included were: ...
- These requirements were mentioned on page xxxxx of your assignment guidelines and should be included in the final report.
- Give the references you used for the information about xxxxx.
- For the NMR interpretation, try to assign any extra signals (they are usually due to a solvent from the reaction, acetone, water, chloroform or remaining starting material), and discuss what you actually see, not what you expected (e.g. if you see 4 peaks and expected a doublet, note that extra coupling is taking place. We mentioned previously that this can be due to long range *meta* coupling in an aromatic ring.)

Appendix 3: Materials, apparatus and instrumentation requirements for laboratory sessions

Apparatus

Table 7 outlines the apparatus needed to complete each step of the experiment. Standard glassware such as conical flasks, graduated cylinders, Buchner funnels and separating funnels will also be needed at various times throughout the laboratory sessions.

Table 7: Apparatus requirements

Needed each week	Specific to step 1 (Session 2)	Specific to step 2 (Session 3)	Specific to step 3 (Session 4)
• boiling sticks or anti-bumping granules • heating mantles • water cooled condensers • retort stands and clamps	• 50 mL round bottom flask	• 3 necked 100 mL round bottom flask • thermometer & quickfit holder • air bubbler (Pasteur pipette attached to air cylinder or low pressure air pump e.g. fish tank air pump)	• ice bath • magnetic follower and stirrer plate • pH meter

Additional apparatus needed for optional epoxidation using H_2O_2 (Session 5)

- 10 mL disposable plastic syringe with needle
- rubber bung or lid with rubber septum or rubber septum
- glass sample bottle / reaction vessel (30 mL approximately) which can be sealed with a rubber bung or septum or a lid with a rubber septum

Instrumentation and characterisation methods

Products are characterised by melting point, FT-IR and NMR spectroscopy and, if available, differential scanning calorimetry (for catalysts which have melting points above 300 ^{o}C).

Access to a NMR spectrometer is essential for calculation of conversion in the epoxidation step.

TLC is used to monitor reaction progress and to provide an indication of product purity.

Depending on whether this case study is implemented as part of a module with a inorganic, organic or industrial chemistry focus, other methods of characterisation and analysis may also be employed.

Materials and reagents

Table 8 lists the materials and reagents for each synthetic step. Catalogue numbers and prices are given as a guideline only (information valid for Dec 2011). "Experiments per unit" indicates the number of reactions achievable with the given amount of the reagent. This should allow for easy scaling to suit different class sizes. Mass ratios are given in the experimental procedures.

Sodium hypochlorite solution should only be ordered in just before it is needed, to arrive one month or less before it will be used and should be stored in a refrigerator.

Table 8: Materials and reagents for laboratory sessions

Chemical	Sigma Aldrich catalogue number	Mass/volume	Price (excl. VAT)	Experiments per unit
Salen ligand production				
trans-1,2-Cyclohexanediamine	270016	250 mL	€166.50	675
ethylene diamine	03550	250 mL	€30.80	> 1000
5-Chlorosalicylaldehyde	447706	25 g	€136.50	26
5-Nitrosalicylaldehyde	275352	25 g	€109.00	26
2-Hydroxy-5-methoxybenzaldehyde	146862	10 g	€100.50	12
Salicylaldehyde	84160	100 mL	€36.50	135
3,5-Di-tert-butyl-salicylaldehyde	140414	25 g	€145.00	17
Absolute ethanol	459844	1 L	€ 50.80	58
Mn-salen catalyst production				
Manganese(II) acetate tetrahydrate	3537	250 g	€19.80	190
Sodium chloride	S9888	500 g	€30.00	> 1000
Sodium sulfate	17876	500 g	€19.30	> 200
Absolute ethanol	459844	1 L	€ 50.80	~ 37
Epoxidation of stilbene with sodium hypochlorite				
Sodium phosphate dibasic	S9763	100 g	€18.30	> 2000
10 – 15 % Sodium hypochlorite solution	425044	250 mL	€43.30	20
Sodium chloride	S9888	500 g	€30.00	> 100
trans-Stilbene	139939	100 g	€75.50	100
Sodium sulfate	17876	500 g	€19.30	>100
Cerium (III) sulfate	307688	50 g	€81.50	>100
Solvent	Dichloromethane (alternatively hexane or pentane can be used in work-up)			
Epoxidation of stilbene with hydrogen peroxide				
Dimethylformamide	319937	1 L	€51.70	158
4-(Dimethylamino) pyridine	107700	100 g	€115.50	175
Hydrogen peroxide	216763	500 mL	€32.50	175
Sodium chloride	S9888	500 g	€30.00	> 100
trans-Stilbene	139939	100 g	€75.50	380
Sodium sulfate	17876	500 g	€19.30	>100
Solvent	Dichloromethane			

Appendix 4 - Tutor notes on formation of salen ligand (Session 2)

Safety:

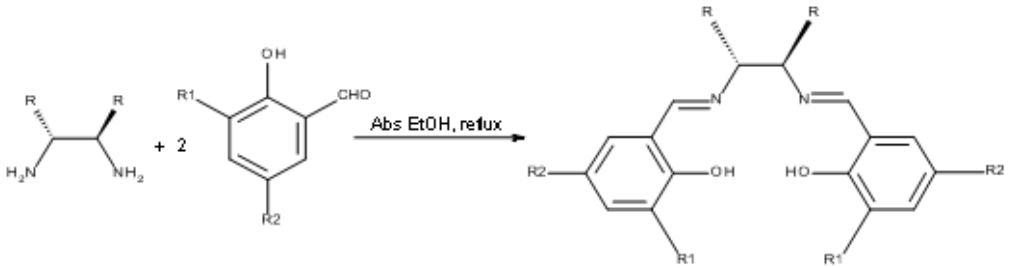
Table 9: Health and safety information for reagents used in salen ligand production

Substance name	CAS no	Hazard Classification	Hazard statement/Risk phrase	Route of exposure	OELV[i]
trans-1,2-diamino cyclohexane 	1121-22-8	Danger, skin corrosion, causes burns **DANGER**	H314 Causes severe skin burns and eye damage.	Skin Contact, Inhalation	
Ethylenediamine 	107-15-3	Flammable. Causes burns. Harmful in contact with skin and if swallowed. May cause sensitization by inhalation and skin contact. **DANGER**	H314 Causes severe skin burns and eye damage. H226 Flammable liquid and vapour. H302 Harmful if swallowed. H312 Harmful in contact with skin. H317 May cause an allergic skin reaction. H334 May cause allergy or asthma symptoms or breathing difficulties if inhaled.	Skin Contact, Inhalation	8 hr: 10 ppm or 25 mg/m^3
5-Chloro-salicylaldehyde 	35-93-8	Irritating to eyes, respiratory system and skin. **WARNING**	H315 Causes skin irritation. H319 Causes serious eye irritation. H335 May cause respiratory irritation. H400 Very toxic to aquatic life.	Skin Contact, Inhalation	
2 hydroxy-5-nitrobenzaldehyde 	97-51-8	Irritating to eyes, respiratory system and skin. **WARNING**	H302 Harmful if swallowed. H315 Causes skin irritation. H319 Causes serious eye	Skin Contact	

i OELV = occupational exposure limit as set down in the most up to date Code of Practice for the Chemical Agents Regulations.

			irritation. H335 May cause respiratory irritation		
2-Hydroxy-5-methoxy benzaldehyde 	672-13-9	Irritating to eyes, respiratory system and skin. **WARNING**	H315 Causes skin irritation. H319 Causes serious eye irritation. H335 May cause respiratory irritation.	Skin Contact, Inhalation.	
Salicylaldehyde 	90-02-8	Harmful in contact with skin and if swallowed. Possible risk of irreversible effects. Irritating to eyes and skin. Harmful to aquatic organisms. **DANGER**	H302 Harmful if swallowed. H311 Toxic in contact with skin. H315 Causes skin irritation. H319 Causes serious eye irritation. H341 Suspected of causing genetic defects.	Skin Contact, Inhalation.	
3,5-Di-tert-butyl-salicylaldehyde 	37942-07-7	Irritating to eyes, respiratory system and skin. **WARNING**	H315 Causes skin irritation. H319 Causes serious eye irritation. H335 May cause respiratory irritation.	Skin Contact, Inhalation.	
Ethanol [absolute] 	64-17-5	Highly flammable liquid and vapour **DANGER**	H225-Highly flammable liquid and vapour	Skin Contact, Inhalation.	8 hr: 1000 ppm or 1900 mg/m^3

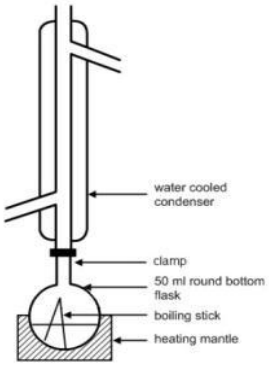
Reaction:



(R=H or $–CH_2CH_2CH_2CH_2$-, R1=H or *t*Butyl, R2= Cl, OMe, H, *t*Butyl, or NO_2)

Figure 7: Reaction scheme for synthesis of salen ligands

Apparatus:



- 50 mL round bottom flask
- boiling sticks (if not available use anti-bumping granules)
- heating mantle
- water cooled condenser
- retort stand and clamp

Figure 8: Experimental set up for production of salen ligand

Instructor notes:

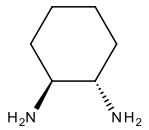
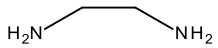
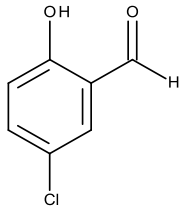
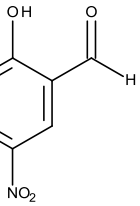
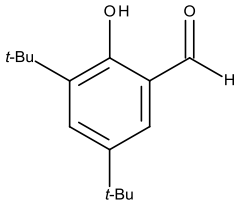
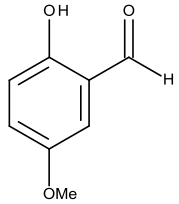
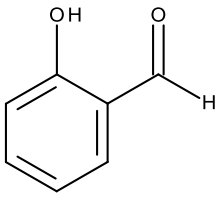
- Assuming a 70 % yield in each step, the masses listed in Table 10 produce about 0.5 g of Mn(salen) catalyst. If it is required that each student group produce an alternative amount of catalyst, it is recommended that an amount can be easily converted from 0.5 g be selected so that the quantities in Table 10 can be altered readily.
- Where possible, use boiling sticks rather than anti-bumping granules for ease of separation from the product.
- Due to the price of the salicylaldehyde derivatives, it may be useful to organise the students into groups of 3 for this stage. They can then work individually on the epoxidation stage, splitting the catalyst between them.
- See table 11 for individual observations on reactions.
- This reaction takes about two hours from set-up to isolation of product.
- Characterisation by melting point and ^{1}H NMR, ^{13}C NMR and FTIR spectroscopy was performed. Examples of spectra are included in the following pages so that they can be compared with those obtained by students.

Procedure:[7]

1. Add 2 equivalents of salicylaldehyde derivative to a 0.2 M solution of diamine in **absolute** ethanol (17 mL). See table 10 which follows for suggested masses and volumes to be used.
2. Reflux the bright yellow solution for 1 hour in the presence of boiling sticks.
3. Upon cooling add up to 5 mL deionised water drop-wise to encourage crystallisation of product from solution.
4. Separate the product from the solution by vacuum filtration, washing with 98 % ethanol.
5. Allow the product to air dry and record the yield.
6. Analyse the product by TLC (ethyl acetate:hexane, 1:4), melting point, FT-IR and ^{1}H NMR spectroscopy (^{13}C NMR is optional).

Table 10 which follows shows the recommended amounts of starting materials and Table 11 shows the R_f values and melting points recorded for each ligand.

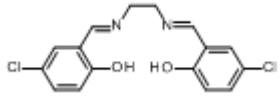
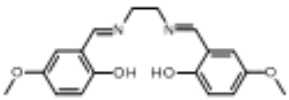
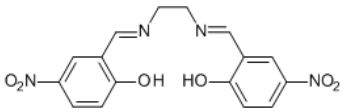
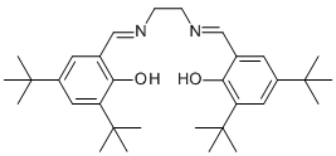
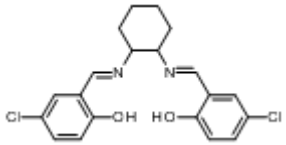
Table 10: Suggested masses of starting materials

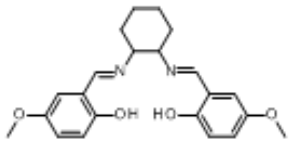
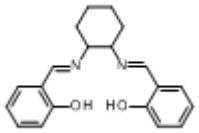
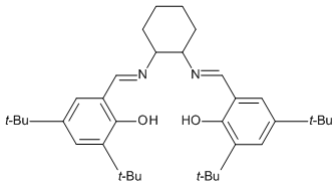
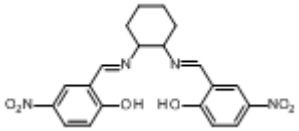
The volume of absolute ethanol used in all cases is 17 mL		
based on 6 mmol salicylaldehyde derivative	3 mmol  Molar mass = 114.19 g/mol Density = 0.951 g/mL	3 mmol  Molar mass = 60.1 g/mol Density = 0.899 g/mL
 Molar mass = 156.57 g/mol	Amine: 0.36 mL Salicylaldehyde derivative: 0.94 g	Amine: 0.20 mL Salicylaldehyde derivative: 0.94 g
 Molar mass = 167.12 g/mol	Amine: 0.36 mL Salicylaldehyde derivative: 1.0 g	Amine: 0.20 mL Salicylaldehyde derivative: 1.0 g
 Molar mass = 234.33 g/mol	Amine: 0.36 mL Salicylaldehyde derivative:1.41 g	Amine: 0.20 mL Salicylaldehyde derivative:1.41 g
 Molar mass = 152.15 g/mol Density = 1.221 g/mL	Amine: 0.36 mL Salicylaldehyde derivative: 0.76 mL	Amine: 0.20 mL Salicylaldehyde derivative: 0.76 mL
 Molar mass = 122.12 g/mol Density = 1.146 g/mL	Amine: 0.36 mL Salicylaldehyde derivative: 0.64 mL	

Results:

- All products were yellow solids.
- In most cases, no additional product was formed on addition of deionised water.
- See the note in Table 11 on ligand 1F; no solid was formed during the reaction. The solution was allowed to cool overnight and crystals were observed to have formed by morning.

Table 11: Results of ligand synthesis

Product: ID code, structure, IUPAC name, molar mass	Yield (%)	Observations and Characterisation
 1A: 4-chloro-2-[(E)-2-[(E)-(5-chloro-2-hydroxy-phenyl)methyleneamino]ethyliminomethyl]phenol Molar mass = 337.2 g/mol	93	Yellow product formed almost immediately on addition of chlorosalicylaldehyde to ethlyenediamine. TLC R_f = 0.02 (ethyl acetate:hexane, 1:4) Melting point: 179 - 181 ^oC
 1B: 2-[(E)-2-[(E)-(2-hydroxy-5-methoxy-phenyl) methyleneamino]ethyliminomethyl] -4-methoxy-phenol Molar mass = 328.36 g/mol	93	Yellow product formed almost immediately on addition of methoxysalicylaldehyde to ethylenediamine. TLC R_f = 0.14 (ethyl acetate:hexane, 1:4) Melting point: 161 - 164 ^oC
 1C: 2-[(E)-2-[(E)-(2-hydroxy-5-nitro-phenyl)methyleneamino]ethyliminomethyl]-4-nitro-phenol Molar mass = 358.30 g/mol	48	Yellow product formed quickly on addition of 5-nitrosalicylaldehyde to ethylenediamine. TLC R_f = 0.12 (ethyl acetate:hexane, 1:4) Melting point: 233 - 235 ^oC
 1D: 2,4-ditert-butyl-6-[(E)-2-[(E)-(3,5-ditert-butyl-2-hydroxy-phenyl)methyleneamino]ethyliminomethyl]phenol Molar mass = 492.74 g/mol	70	Yellow product formed quickly on addition of 3,5-di-tert-butyl-2hydroxybenzaldehyde to ethylenediamine. TLC R_f = 0.16 (ethyl acetate:hexane, 1:4) Melting point: 158 - 160 ^oC
 1E: 4-chloro-2-[(E)-[2-[(E)-(5-chloro-2-hydroxy-phenyl) methyleneamino]cyclohexyl] iminomethyl]phenol Molar mass = 391.29 g/mol	83	Yellow product formed almost immediately on addition of chlorosalicylaldehyde to cyclohexanediamine. Further product formed on cooling. TLC R_f = 0.42 (ethyl acetate:hexane, 1:4) Melting point: 158 - 159 ^oC

 1F: 2-[(E)-[2-[(E)-(2-hydroxy-5-methoxy-phenyl) methyleneamino]cyclohexyl] iminomethyl] -4-methoxy-phenol Molar mass = 382.45 g/mol	92	On addition of yellow methoxysalicylaldehyde to colourless cyclohexanediamine, the solution turned golden orange. **Note:** No solid was formed during the reaction. The solution was allowed to cool overnight and crystals were seen to have formed by morning. TLC R_f = 0.31 (ethyl acetate:hexane, 1:4) Melting point: 162 - 164 ^oC
 1G: 2-[(E)-[2-[(E)-(2-hydroxyphenyl)methyleneamino] cyclohexyl]iminomethyl]phenol Molar mass = 322.39 g/mol	87	On addition of colourless alicaldehyde to colourless cyclohexanediamine the solution turned yellow. No solid was formed during reaction. Product formed on addition of deionised water (14 ml H_2O to 16 ml of reaction solution). TLC R_f = 0.5 (ethyl acetate:hexane, 1:4) Melting point: 121 - 123 ^oC
 1H: 2,4-ditert-butyl-6-[(E)-[2-[(E)-(3,5-ditert-butyl-2-hydroxy-phenyl)methyleneamino]cyclohexyl] iminomethyl]phenol Molar mass = 546.85 g/mol	99	Yellow product formed quickly on addition of 3,5-di-tert-butyl-2hydroxybenzaldehyde to cyclohexanediamine. The isolated product had a very low density (approx two times less than other products). TLC R_f = 0.89 (ethyl acetate:hexane, 1:4) Melting point: 188 - 189 ^oC
 1I: 2-[(E)-[2-[(E)-(2-hydroxy-5-nitro-phenyl)methyleneamino]cyclohexyl]iminomethyl]-4-nitro-phenol Molar mass = 412.4 g/mol	45	Yellow product formed quickly on addition of 5-nitrosalicylaldehyde to cyclohexanediamine. TLC R_f = 0.08 (ethyl acetate:hexane, 1:4) Melting point: 203 - 206 ^oC

Characterisation

All NMR spectra were recorded on a 400 MHz instrument, acquiring 16 scans for proton and 1024 for carbon. The FT-IR and ^1H NMR spectra for most of the ligands synthesised are included in the following pages to allow them to be compared to those obtained by students. ^{13}C NMR spectra for two representative ligands, 1B and 1I, are provided. Spectra of the salicylaldehyde starting materials are not included but these are accessible from the Sigma-Aldrich website or the SDBS spectral database for organic compounds (see http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/cre_index.cgi?lang=eng).

Table 12 provides a general assignment for the absorption bands observed in the FT-IR spectra obtained.

The main features to note in the ^{1}H NMR spectra of these ligands are the singlet for the two imine protons at just above 8 ppm and the singlet due to the two phenol protons at about 13 ppm. The phenol protons are shifted downfield due to intramolecular hydrogen bonding to the imine nitrogens.

Table 12: FT-IR assignment

Wavenumber (cm^{-1})	Assignment	Wavenumber (cm^{-1})	Assignment
3100 - 3000	C-H aromatic ring (stretch)	3600 - 3200	O-H (stetch)
2960 - 2850	C-H alkane (stretch)	3500 - 3300	N-H (stretch)
1470 - 1350	C-H alkane (scissoring and bending)	1650 - 1580	N-H (bend)
1600, 1500	C=C aromatic (stretch)	1340 - 1020	C-N (stretch)
1760 - 1670	C=O (stretch)		

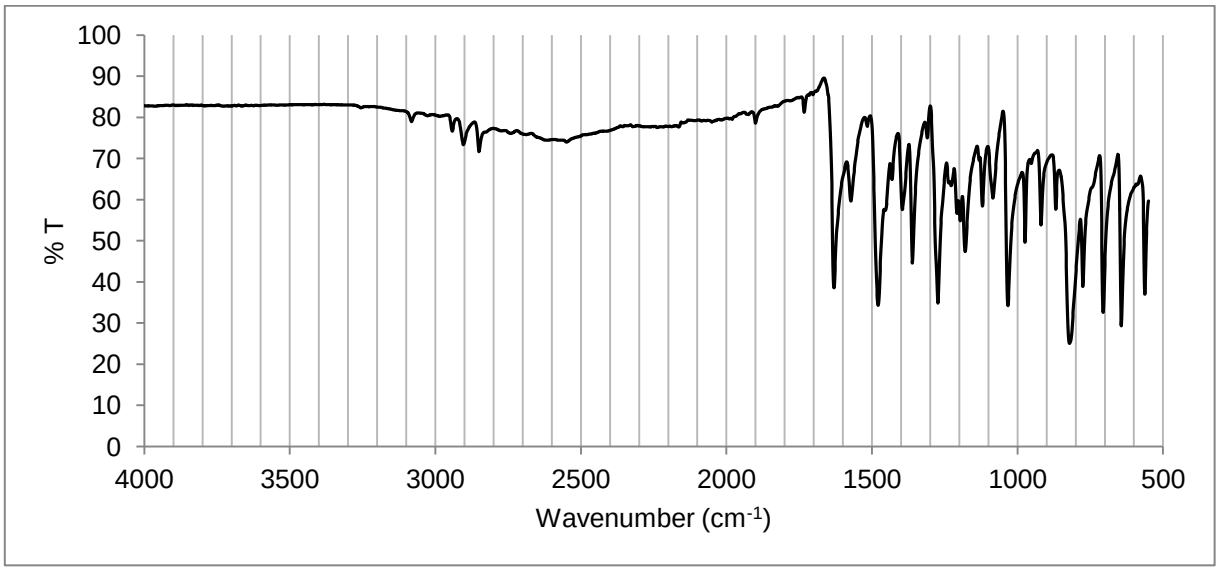


Figure 9: ATR IR Spectrum of 1A

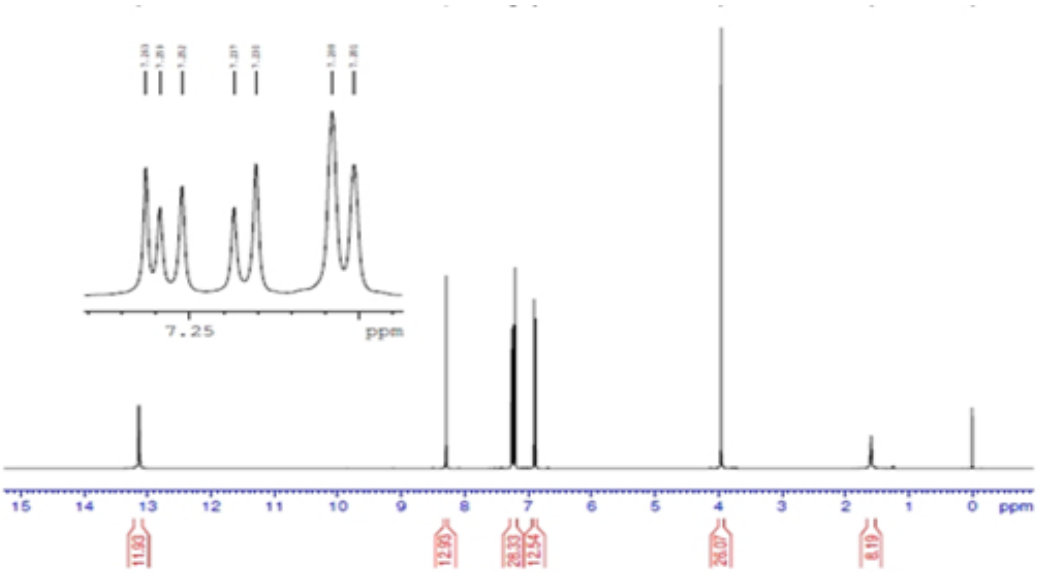


Figure 10: Proton NMR Spectrum of 1A in $CDCl_3$

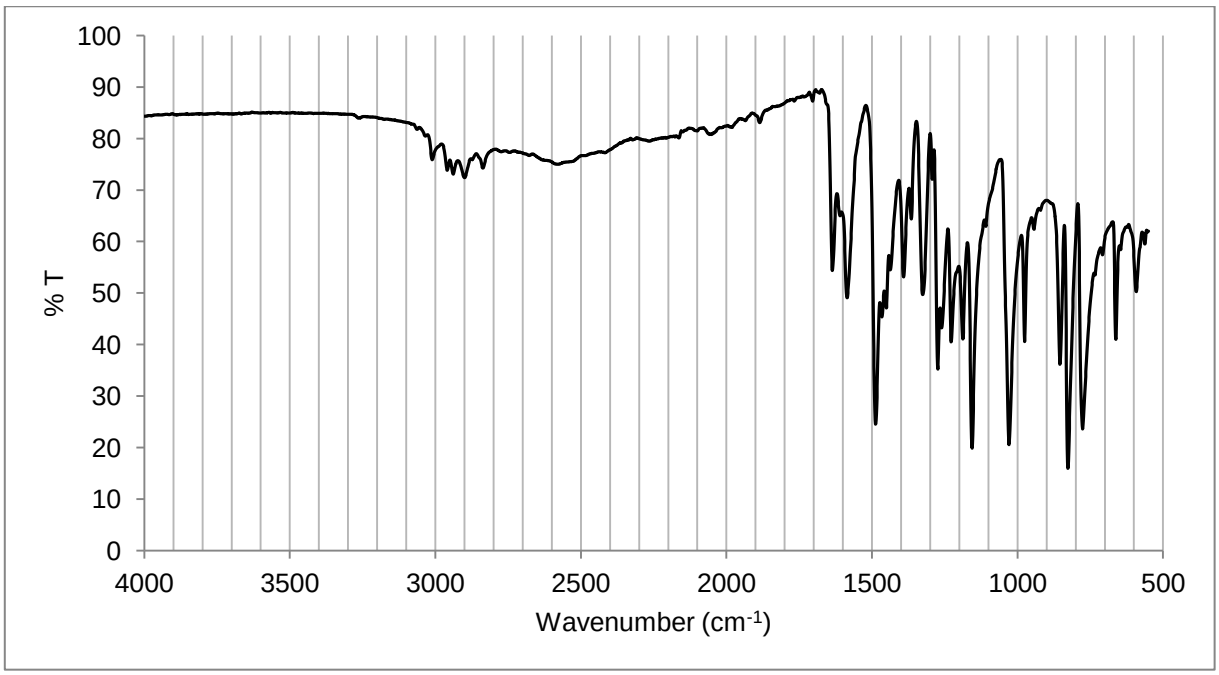


Figure 11: ATR IR Spectrum of 1B

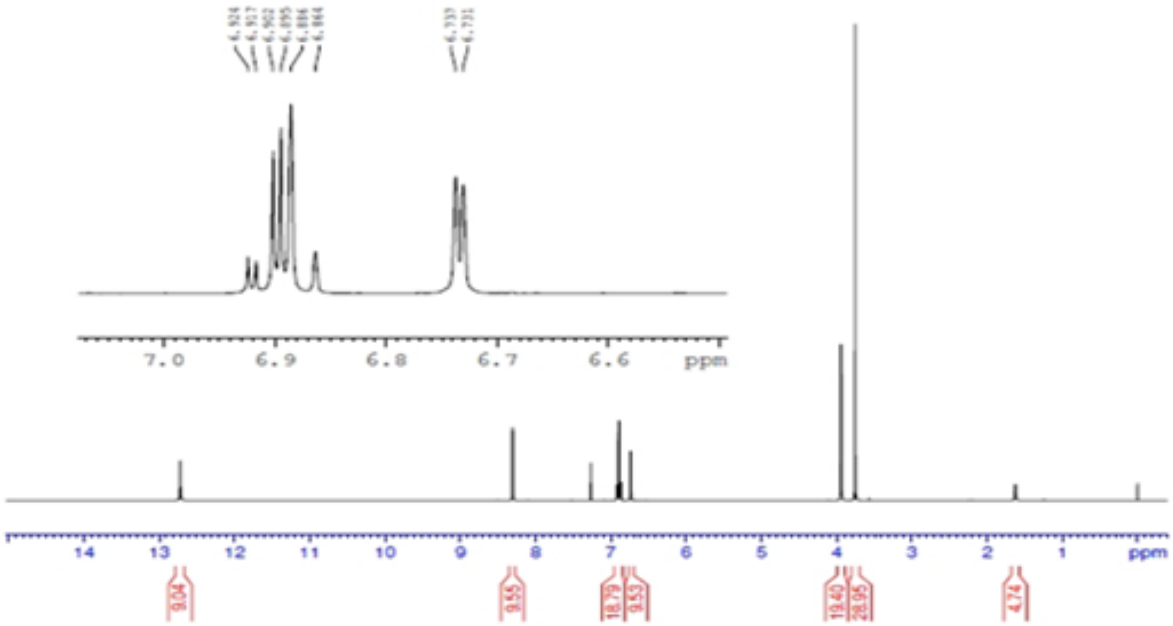


Figure 12: Proton NMR Spectrum of 1B in $CDCl_3$

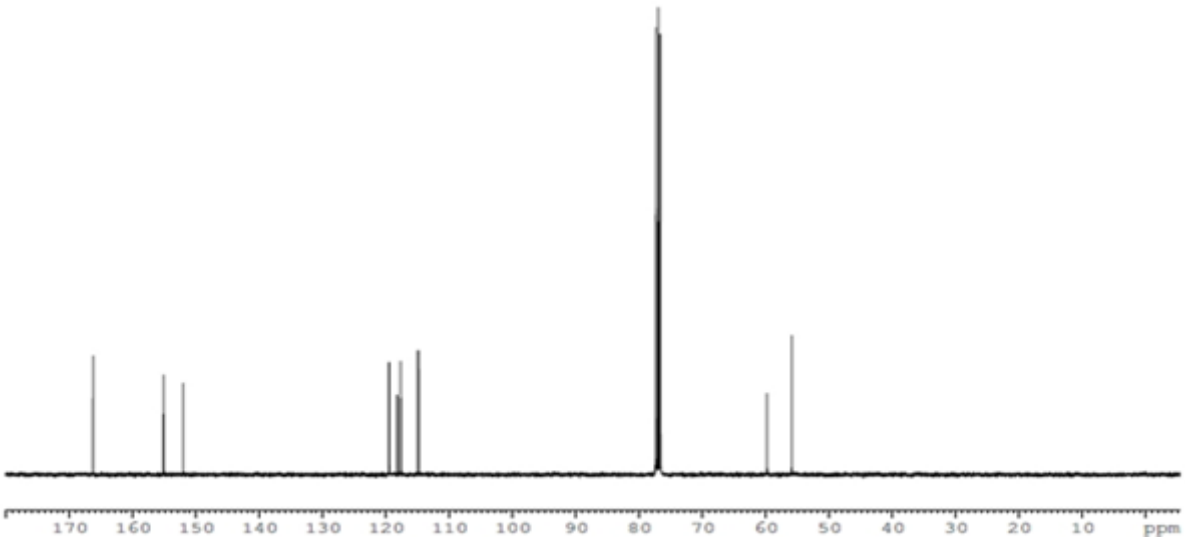


Figure 13: ^{13}C NMR Spectrum of 1B in $CDCl_3$

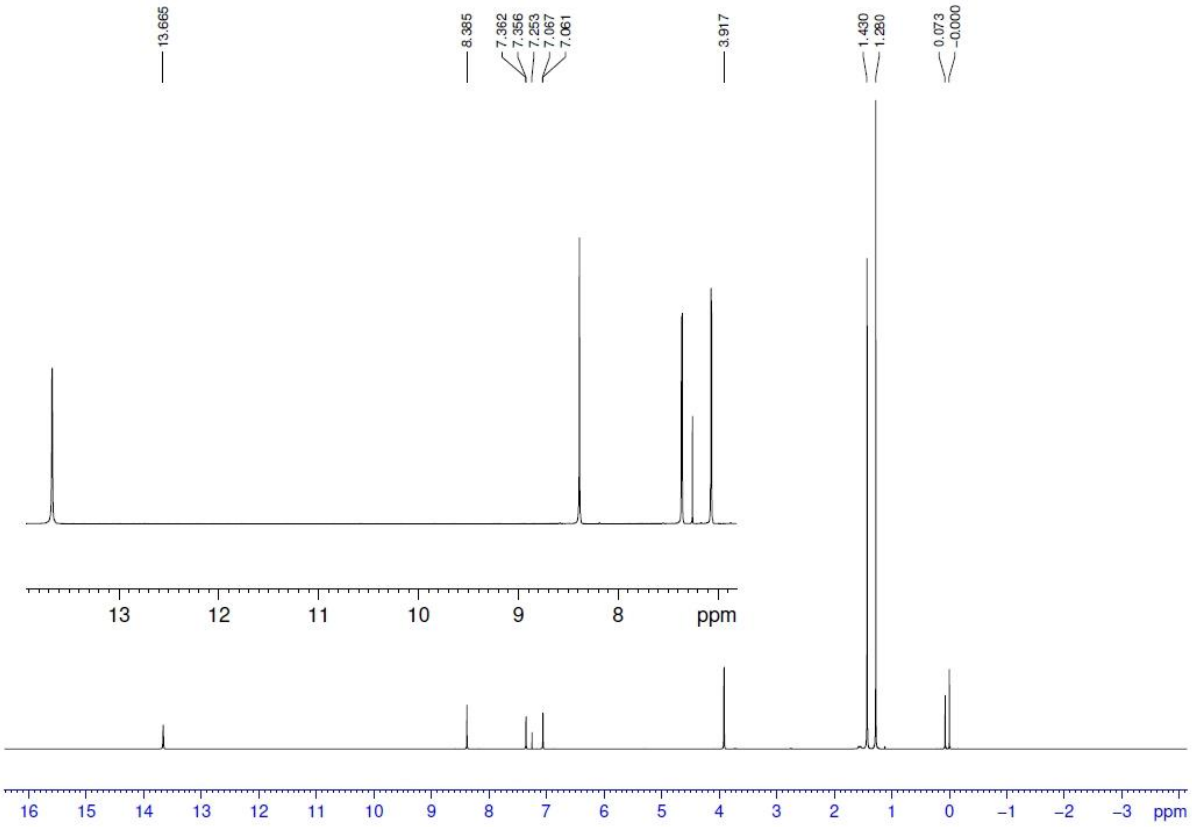


Figure 14: Proton NMR Spectrum of 1D in $CDCl_3$

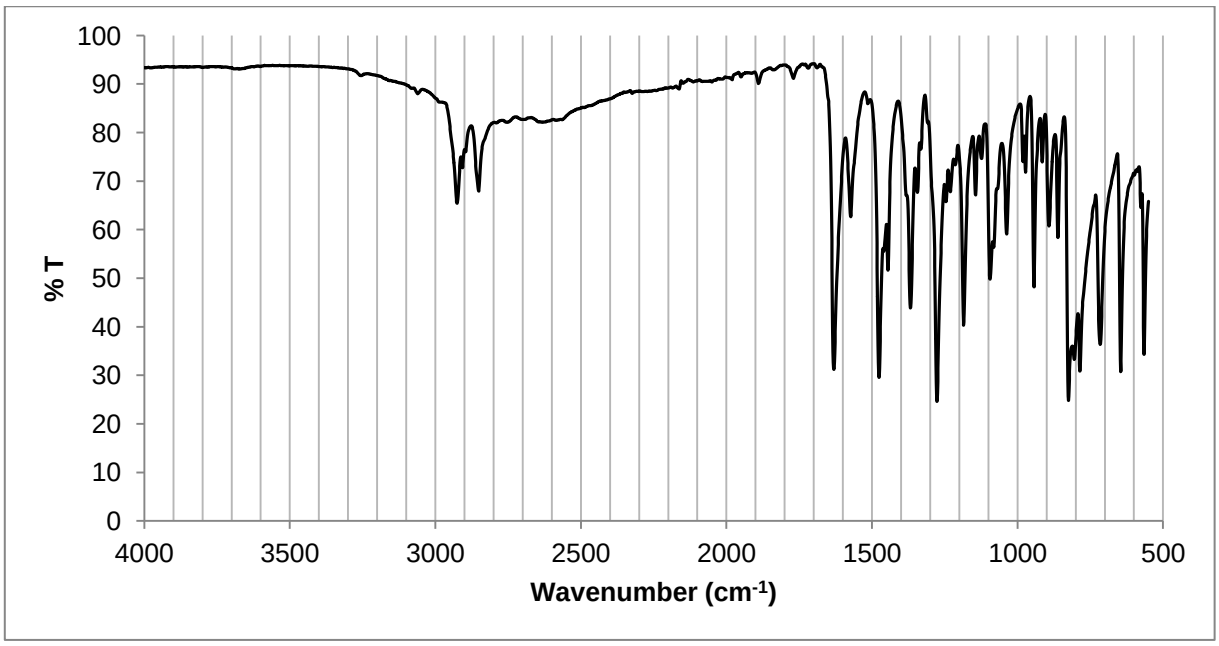


Figure 15: ATR IR Spectrum of 1E

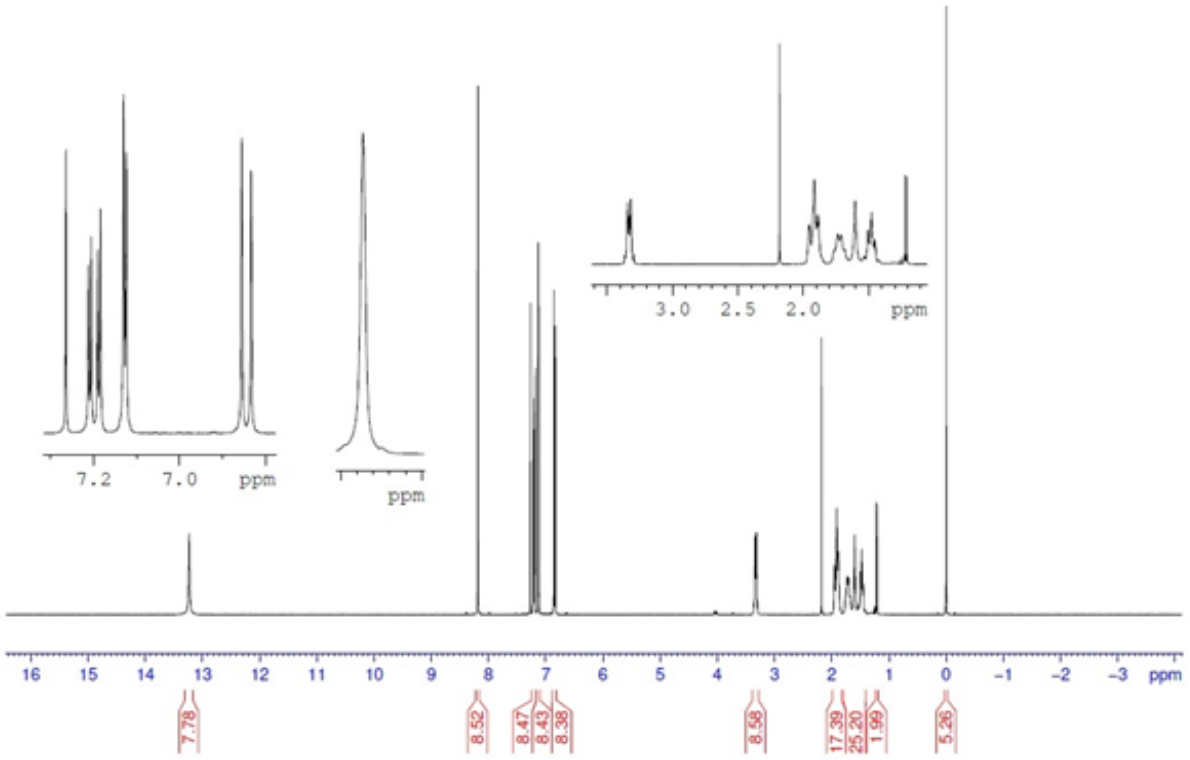


Figure 16: Proton NMR Spectrum of 1E in $CDCl_3$

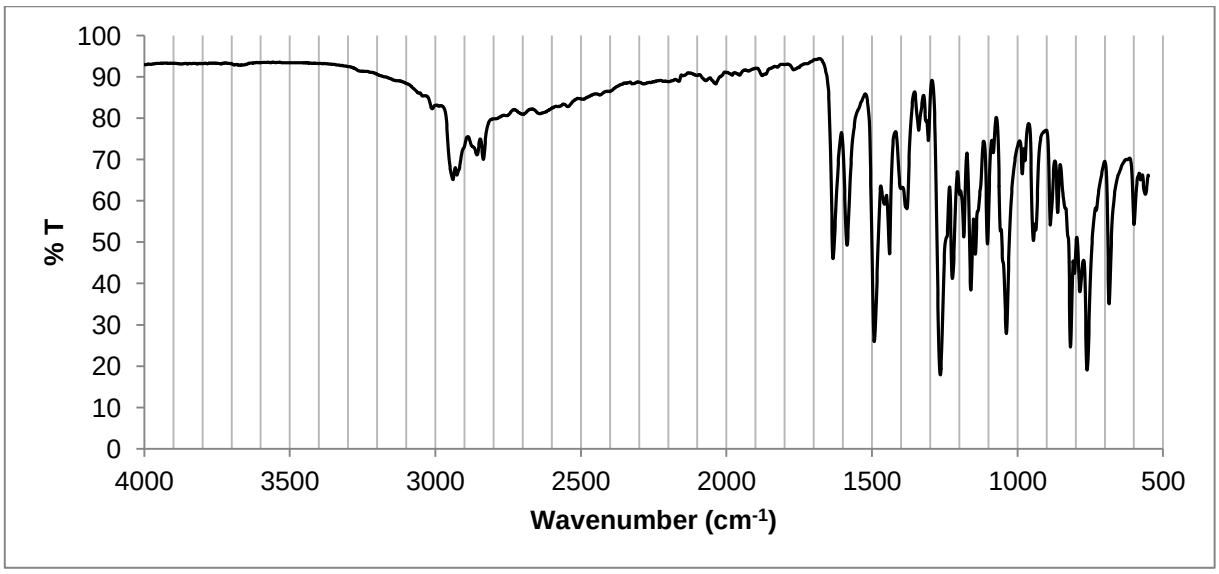


Figure 17: ATR IR Spectrum of 1F

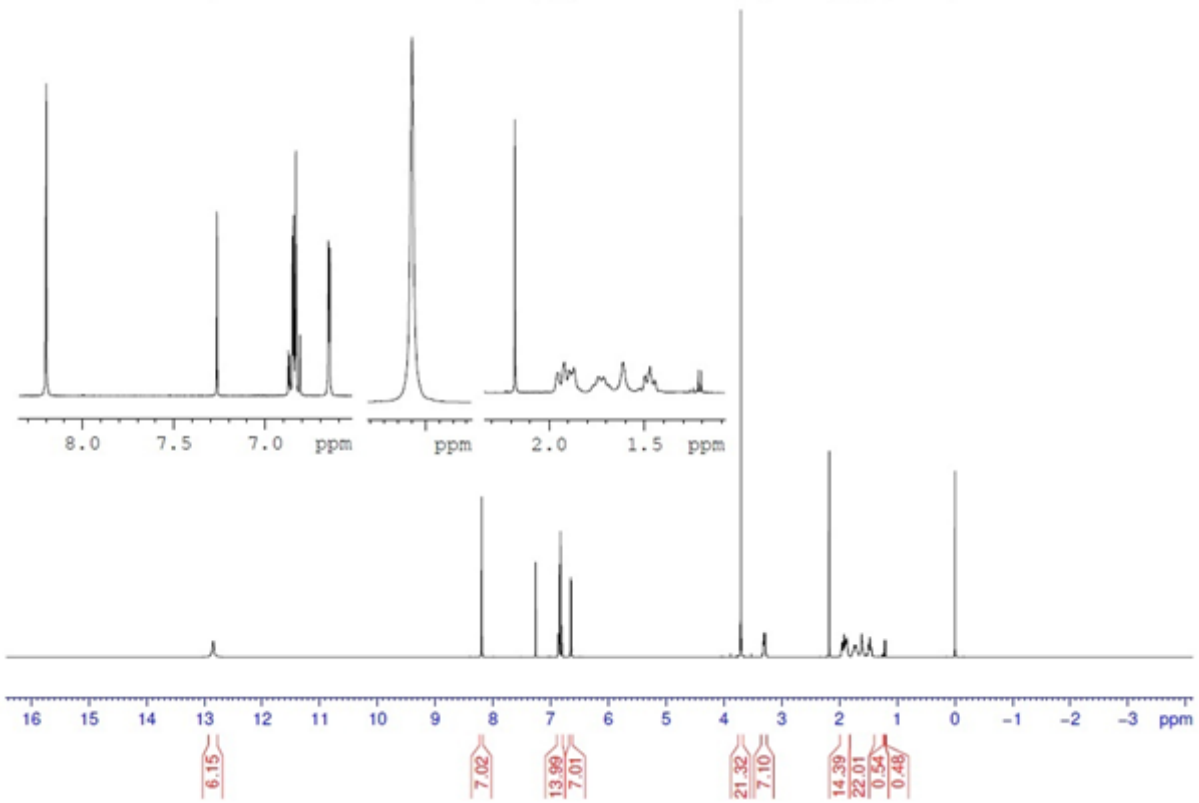


Figure 18: Proton NMR Spectrum of 1F in $CDCl_3$

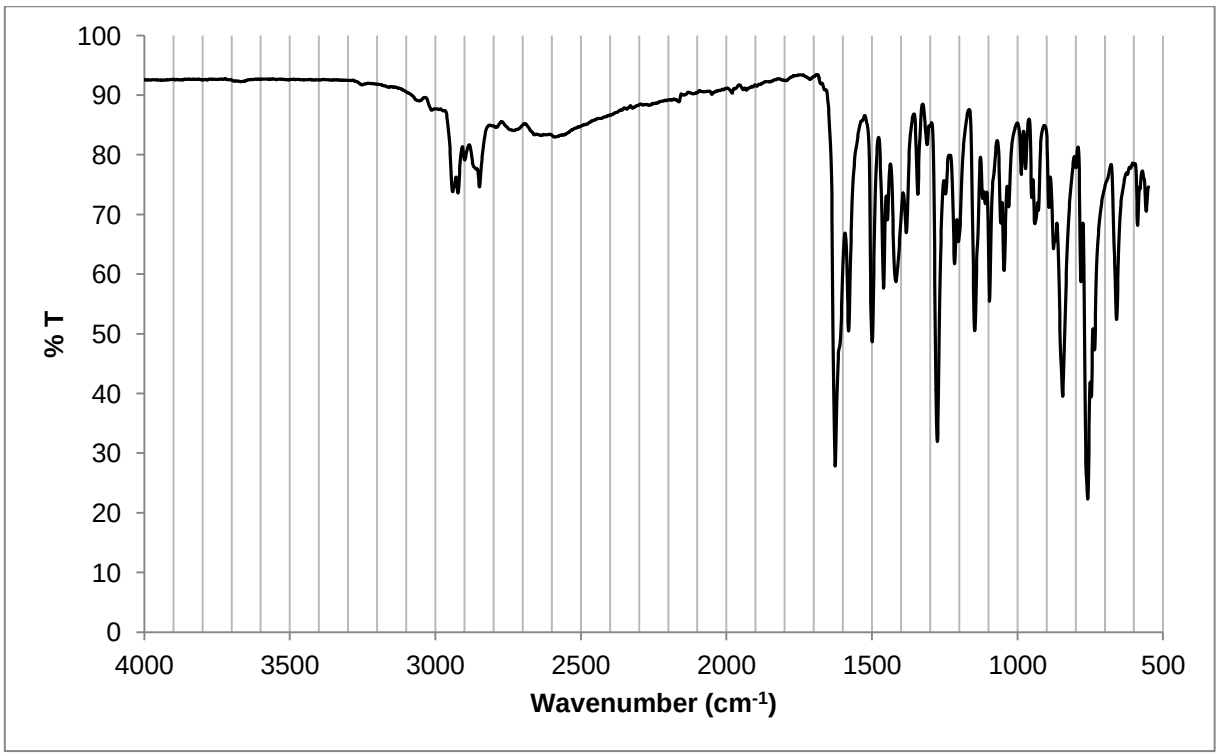


Figure 19: ATR IR Spectrum of 1G

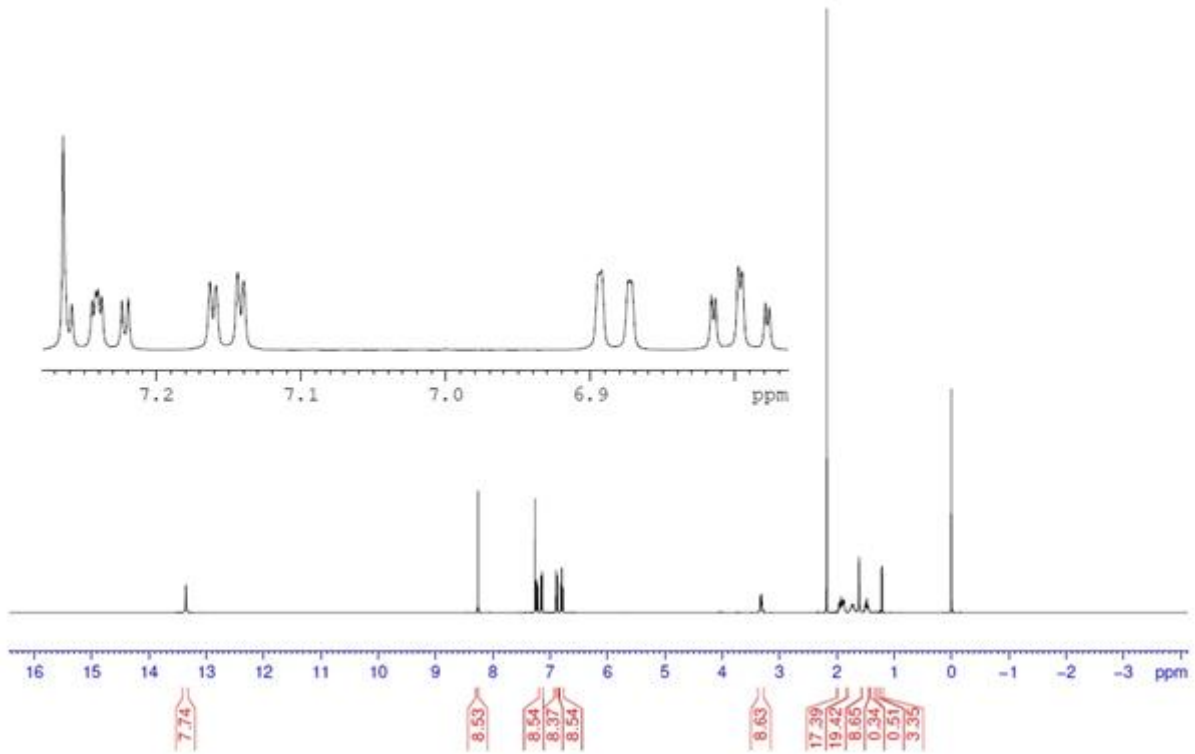


Figure 20: Proton NMR Spectrum of 1G in $CDCl_3$

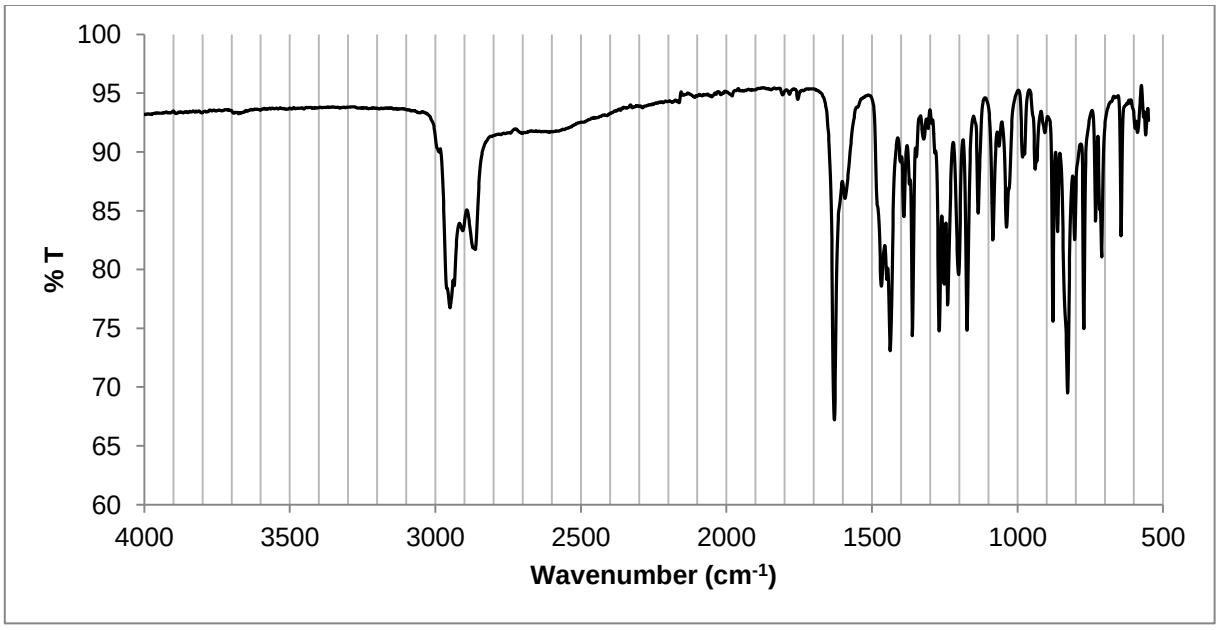


Figure 21: ATR IR Spectrum of 1H

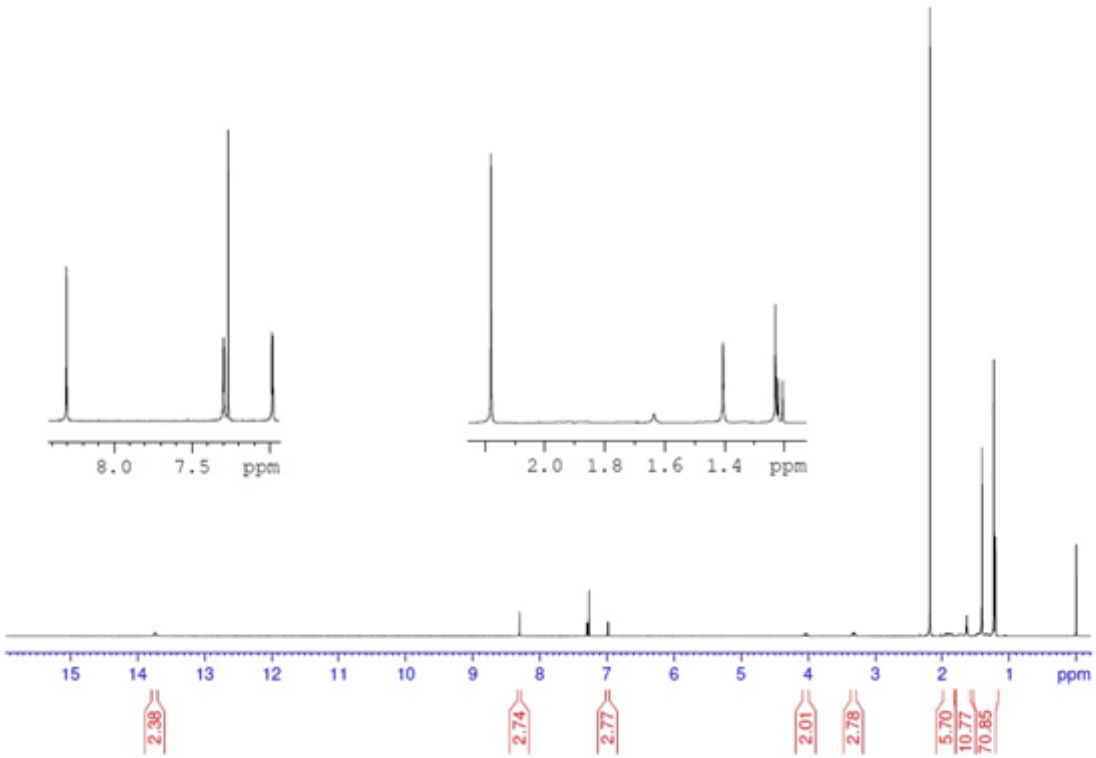


Figure 22: Proton NMR Spectrum of 1H in $CDCl_3$

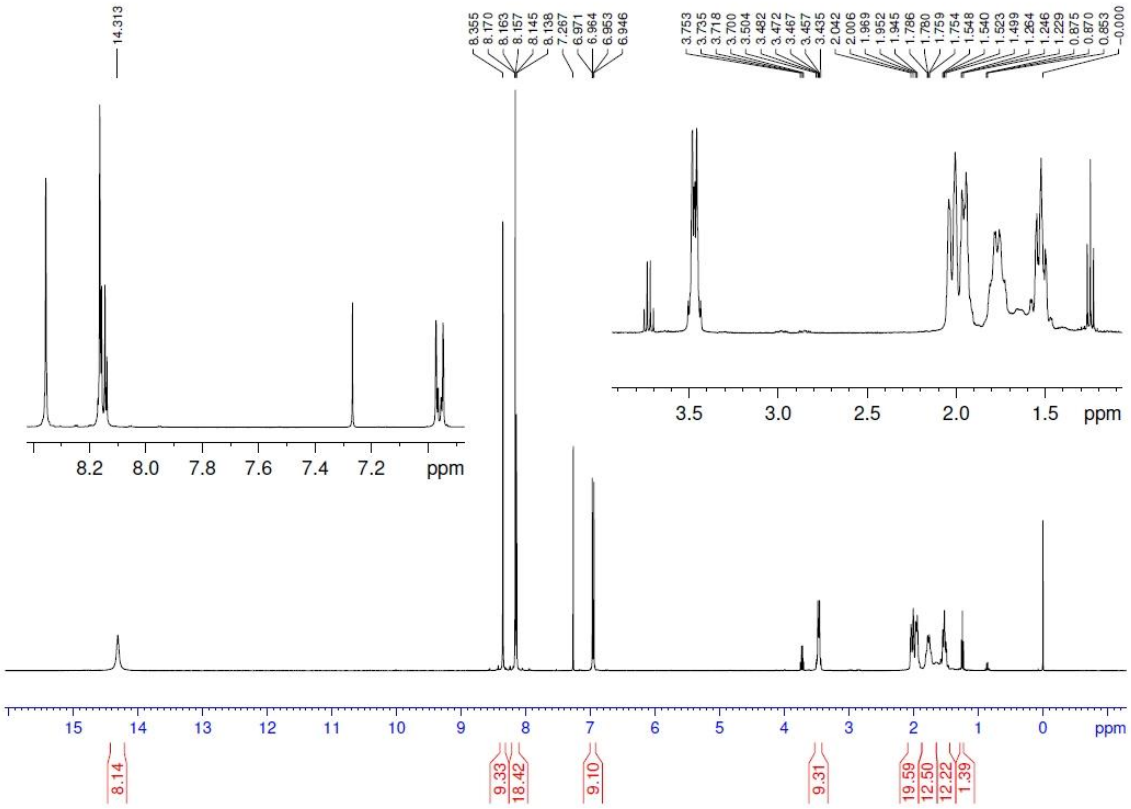


Figure 23: Proton NMR Spectrum of 1l in $CDCl_3$

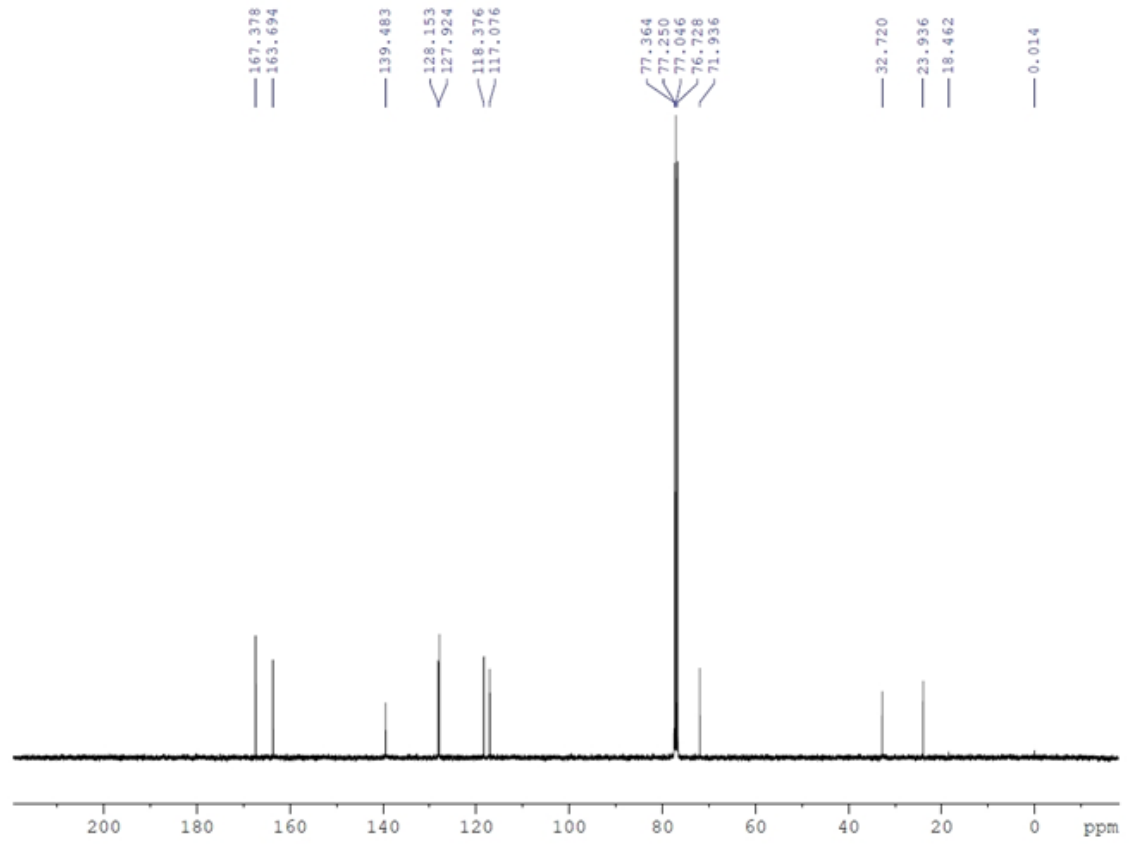
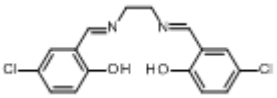
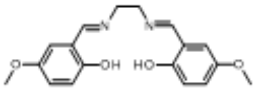


Figure 24: ^{13}C NMR Spectrum of 1l in $CDCl_3$

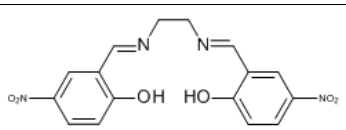
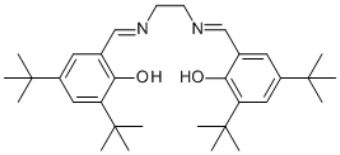
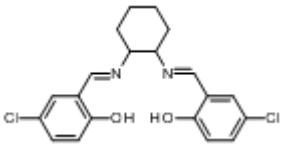
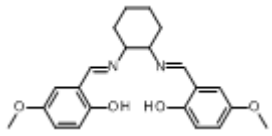
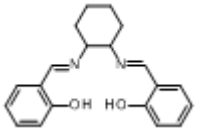
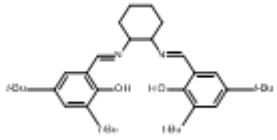
Appendix 5 - Tutor notes on formation of Mn-salen catalyst (Session 3)

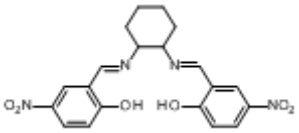
Safety Information:

Table 13: Health and safety information for reagents used in Mn-salen catalyst synthesis

Substance name	CAS no	Hazard Classification	Hazard statement/Risk phrase	Route of exposure	OELV[ii]
Manganese(II) acetate tetrahydrate 	6156-78-1	Irritating to eyes, respiratory system and skin. WARNING	H315 Causes skin irritation. H319 Causes serious eye irritation. H335 May cause respiratory irritation.	Skin contact, inhalation.	
Sodium chloride	7647-14-5	This substance is not hazardous	n/a	Skin contact, inhalation.	
Ethanol (absolute) 	64-17-5	Highly flammable liquid and vapour DANGER	H225-Highly flammable liquid and vapour	Skin contact, inhalation.	8hr period: 1000 ppm or 1900 mg/m^3
Salen ligand starting materials (CAS numbers unavailable):					
1A: [2,2'-{ethane-1,2-diylbis[nitrilo(E)methylylidene]} bis(4-chlorophenol)] 		Unknown – assume toxic	Unknown	Skin contact, inhalation.	
1B: [2,2'-{ethane-1,2-diylbis[nitrilo(E)methylylidene]} bis(4-methoxyphenol)] 		Unknown – assume toxic	Unknown	Skin contact, inhalation.	
1C: 2-[(E)-2-[(E)-(2-hydroxy-5-nitro-phenyl)methyleneamino]ethyliminomethyl]-4-nitro-phenol		Unknown – assume toxic	Unknown	Skin contact, inhalation.	

ii OELV = occupational exposure limit as set down in the most up to date Code of Practice for the Chemical Agents Regulations. If unavailable use TLV or equivalent

				
1D: 2,4-ditert-butyl-6-[(E)-2-[(E)-(3,5-ditert-butyl-2-hydroxy-phenyl)methyleneamino]ethyliminomethyl]phenol 	Unknown – assume toxic	Unknown	Skin contact, inhalation.	
1E: 2,2'- {cyclohexane-1,2-diylbis[nitrilo(E)methylylidene]} bis(4-chlorophenol) 	Unknown – assume toxic	Unknown	Skin contact, inhalation.	
1F: 2,2'- {cyclohexane-1,2-diylbis[nitrilo(E)methylylidene]} bis(4-methoxyphenol) 	Unknown – assume toxic	Unknown	Skin contact, inhalation.	
1G: N,N'-disalicylidene-1,2-cyclohexanediamine 	Unknown – assume toxic	Unknown	Skin contact, inhalation.	
1H: 2,4-ditert-butyl-6-[(E)-[2-[(E)-(3,5-ditert-butyl-2-hydroxy-phenyl)methyleneamino]cyclohexyl] iminomethyl]phenol 	Unknown – assume toxic	Unknown	Skin contact, inhalation.	

1l: [2,2'-{cyclohexane-1,2-diylbis[nitrilo(E)methylylidene]} bis(4-nitrophenol)] 	Unknown – assume toxic	Unknown	Skin contact, inhalation.	

Reaction:

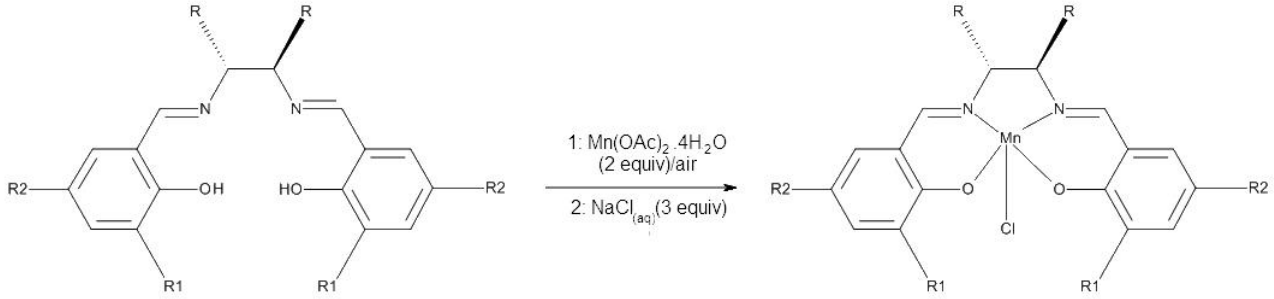
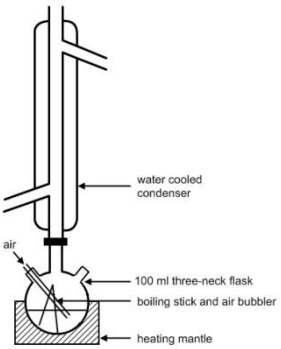


Figure 25: Synthesis of Mn-Salen catalyst

Apparatus:



- 3 necked 100 mL round bottomed flask
- boiling sticks (if not available, use anti-bumping granules)
- thermometer
- heating mantle
- water cooled condenser
- air bubbler (Pasteur pipette attached to air line or fish tank pump, see Figure 27 and J. Hanson, *J. Chem. Ed.*, 2001, **78**, 1266-1268.)
- retort stand and clamp

Figure 26: Experimental set up for synthesis of Mn Salen catalyst

Instructor notes:

- The supplementary information for J. Hanson, *Journal of Chemical Education*, 2001, 78, 1266-1268 is a very helpful reference when carrying out this step.[16] J.F. Larrow, E.N. Jacobsen, *Organic Syntheses, Vol. 75*; Wiley: New York, 1998; pp 1-11 is also useful.
- Where possible, use boiling sticks rather than anti-bumping granules for ease of separation from product.

- If an air line is not available, a fish tank air pump may be used to introduce air into the reaction mixture. The presence of air is required to oxidise Mn(II) to Mn(III). As shown in the picture below, the tubing from the air source may be branched as many times as needed. A disposable glass Pasteur pipette can be attached to the end of the tubing and inserted into the reaction mixture. To avoid the end of the tube blocking, it is useful to break off the end of the pipette to have a wider opening. If blocking does occur, change the pipette.

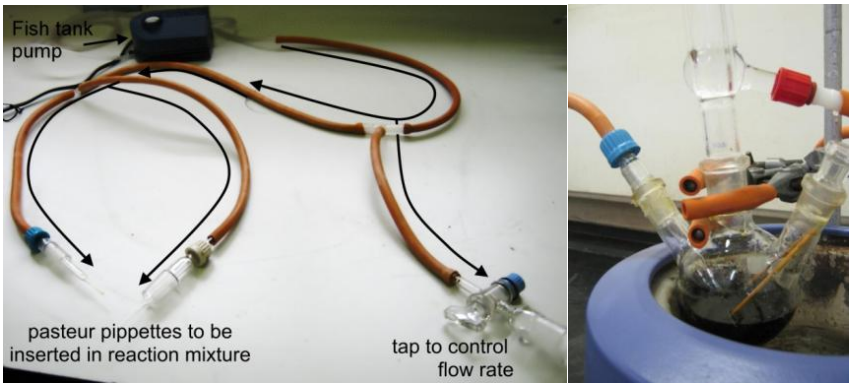


Figure 27: Introduction of air into reaction mixture

- It is important to set the bubbling rate relatively low to avoid ethanol evaporation of the ethanol solvent. Test the rate by bubbling through a small beaker containing some ethanol before starting.
- NaCl is used in this reaction instead of the LiCl which was employed by Jacobsen *et al*. in their original work. NaCl is cheaper and safer and waste produced is easier to dispose of. Most recent patents and papers report the use of NaCl.
- In all cases the product is a brown semicrystalline product.
- The product is paramagnetic and therefore characterisation by NMR is difficult. Disappearance of the starting material from the TLC is taken as confirmation of product formation. Some sample TLC plates showing the disappearance of starting material are shown below in Figure 28.

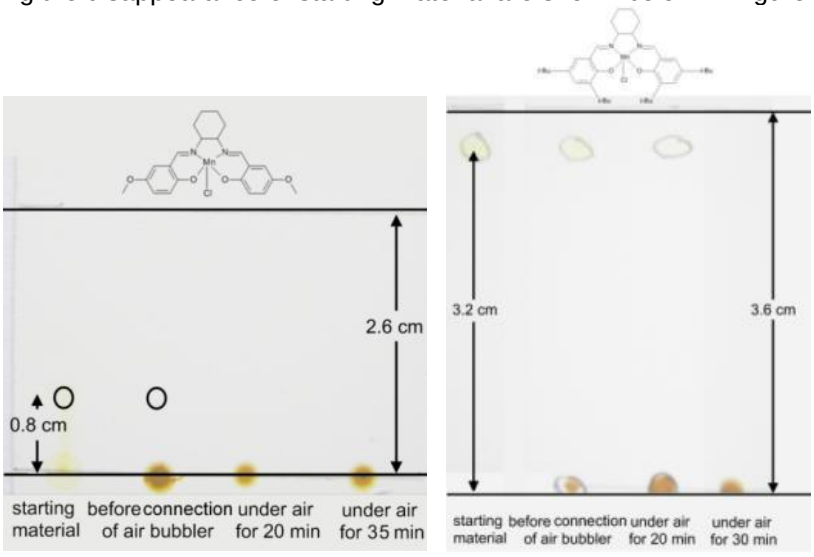


Figure 28: Examples of TLC analysis for catalyst synthesis reaction

- All of the catalyst products have melting points above 300 ^{o}C, making melting point determination difficult, although a melting point of ≥300°C is generally a good indication of product purity. If available, differential scanning calorimetry can be carried out to determine the melting point.

Elemental analysis or ESI (electrospray ionisation) mass spectrometry analysis are reported in the literature and can be performed if these facilities are available and time allows.

- This reaction usually takes a little under three hours from set-up to tidy up. The catalyst can be left to dry until the next session when it can be characterised.

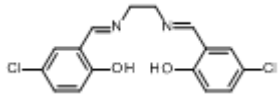
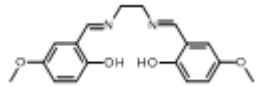
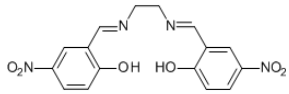
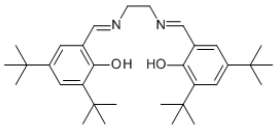
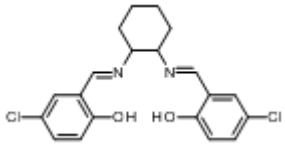
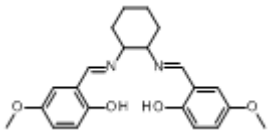
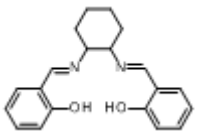
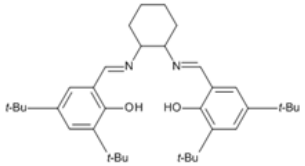
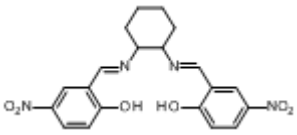
Procedure:[16]

1. Add the ligand prepared in the previous experiment to hot absolute ethanol to form a 0.1 M solution (see Table 14 for suggested quantities). Ensure that enough ligand has been retained to allow characterisation to be completed. **It is not a problem if the ligand does not fully dissolve, as it will go into solution during the experiment as it is being used up in the reaction.**
2. Heat the solution to reflux. Spot a sample as a starting reference for TLC analysis.
3. Add 2 molar equivalents of solid $Mn(OAc)_2.4H_2O$ to the hot solution in one portion, agitating the mixture to ensure full dissolution. The solution turns dark brown. Reflux for 30 minutes.
4. After 30 minutes, start bubbling air through the reaction mixture. Ensure to control a low rate of bubbling in order to minimise the evaporation of ethanol from the mixture. Follow the reaction by TLC analysis (eluent ethyl acetate/hexane 1:4).
5. Reflux in this manner for a further 30 minutes, or until all of the yellow solid (ligand) has disappeared. If TLC indicates that the reaction is complete and solid product remains, add absolute ethanol (~ 10 mL) to replace the solvent lost due to evaporation.
6. Once the reaction is complete, add 3 molar equivalents of solid NaCl to the solution, again agitating to ensure dissolution. Reflux for another 30 minutes.
7. Cool the solution to 0 ^{o}C to form a solid product.
8. Isolate by filtration. Add deionised water drop-wise to the mother liquor to encourage formation of further product. Re-filter the resulting solution and wash the products with deionised water. Dry in a desiccator or oven overnight to remove final water residues.
9. Analyse the product by TLC (ethyl acetate:hexane, 1:4) to ensure that no starting materials remains and by FT-IR spectroscopy and determine the melting point (a melting point of ≥300°C is expected). Elemental analysis or ESI (electrospray ionisation) mass spectrometry analysis can be performed if these facilities are available. It is also optional to use differential scanning calorimetry to determine the melting point.

Table 14 which follows summarises the quantities of each reagent required if 1 g of ligand is being used. In this way, the quantities can be multiplied across by the actual weight of ligand available to easily determine the quantities that students should have calculated.

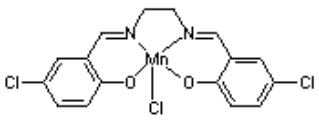
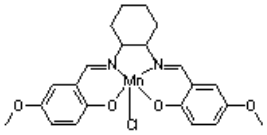
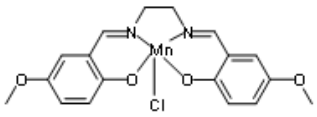
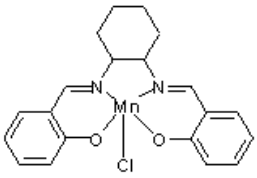
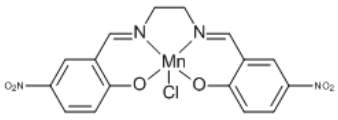
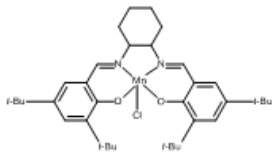
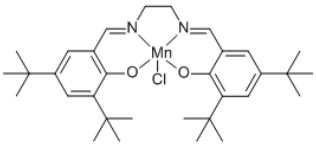
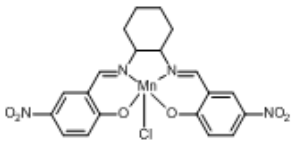
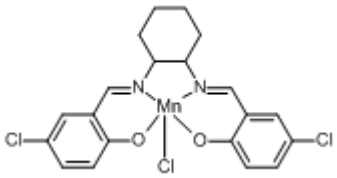
Table 15 summarises the yields and melting points obtained for each catalyst prepared. Melting points were measured on a standard melting point apparatus and were also checked by differential scanning calorimetry (DSC) in most cases. However, as stated previously, a melting point of greater than 300 ^{o}C can be taken as a good indication of product purity. Catalyst 2G had a lower melting point than expected (268 ^{o}C) and, on visual inspection, it was noted that some yellow ligand crystals were dispersed in this product. The catalyst was used in the epoxidation reactions successfully but it is evident that a longer reaction time than that used is required to convert all of the ligand starting material to catalyst in this case. This is not possible in a three hour laboratory session but would be a useful recommendation for future work from the students who prepare this catalyst.

Table 14: Suggested reagent quantities based on using 1 g of ligand input:

Ligand (1 g)	Volume of EtOH (mL)	Mass of $Mn(OAc)_2.4H_2O$ (g) (2 equivalents)	Mass of NaCl (g) (3 equivalents)
1A  Molar mass = 337.2 g/mol	29.6	1.45	0.52
1B  Molar mass= 328.36 g/mol	30.5	1.49	0.53
1C  Molar mass = 358.30 g/mol	27.9	1.37	0.49
1D  Molar mass = 492.74 g/mol	20.3	0.99	0.35
1E  Molar mass= 391.29 g/mol	25.6	1.25	0.45
1F  Molar mass= 382.45 g/mol	26.1	1.28	0.46
1G  Molar mass= 322.39 g/mol	31.0	1.49	0.53
1H  Molar mass= 546.85 g/mol	18.3	0.90	0.32
1I  Molar mass= 412.4 g/mol	24.2	1.18	0.42

Results:

Table 15: Results of catalyst synthesis

Product: ID code, structure, molar mass	Melting Point (°C)	Yield (%)	Product: ID code, structure, molar mass	Melting Point (°C)	Yield (%)
2A  425.59 g/mol	323	71	2F  470.84 g/mol	310	71
2B  416.75 g/mol	308	75	2G  410.79 g/mol	268	64
2C  446.70 g/mol	308	89	2H  635.29 g/mol	331	82
2D  581.13 g/mol	380	65	2I  500.79 g/mol	350	94
2E  479.68 g/mol	306	58			

A typical differential scanning calorimetry (DSC) trace is shown in Figure 29 (for catalyst 2D). The major peak at about 380 °C is assigned to the melting of the material, while the smaller, lower temperature peak corresponds to loss of associated water.

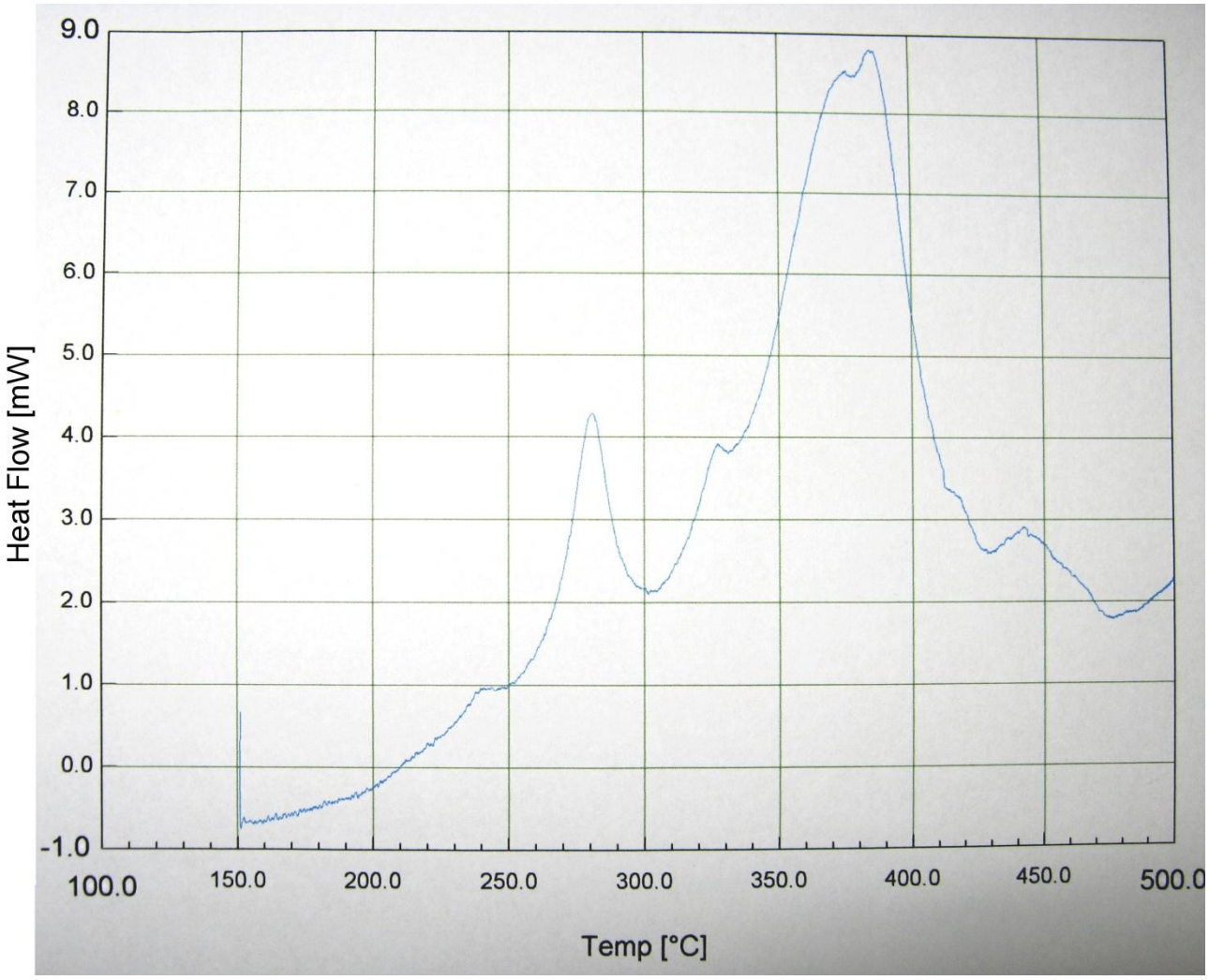


Figure 29: DSC trace indicating the melting point of catalyst 2D

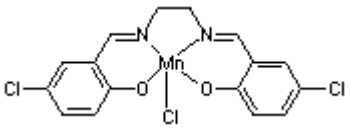
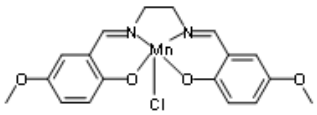
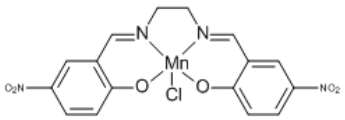
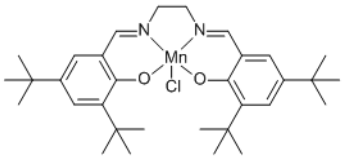
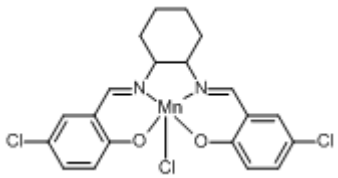
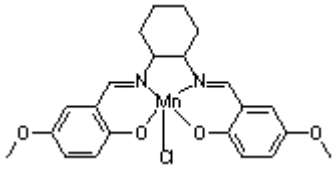
Appendix 6 - Tutor notes on epoxidation of *trans*-stilbene using manganese salen catalysts under standard conditions (Session 4)

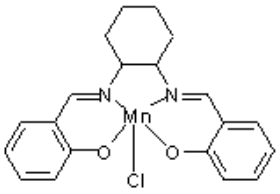
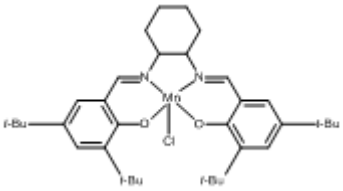
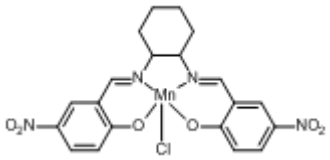
Safety:

Table 16: Health and safety information for reagents used in the epoxidation of stilbene with sodium hypochlorite

Substance name	CAS no	Hazard Classification	Hazard statement/Risk phrase	Route of exposure	OELV [iii]
Sodium phosphate dibasic	7558-79-4	Irritating to eyes, respiratory system and skin. WARNING	This substance is not classified as dangerous	n/a	
Sodium hypochlorite solution 	7681-52-9	Causes burns. Contact with acids liberates toxic gas. Very toxic to aquatic organisms. DANGER	H314 Causes severe skin burns and eye damage. H400 Very toxic to aquatic life	Skin contact, inhalation.	
Sodium chloride	7647-14-5	This substance is not hazardous	n/a	Skin contact, inhalation.	
Sodium hydroxide 	1310-73-2	Skin corrosion, causes burns. DANGER	H314 Causes severe skin burns and eye damage.	Skin contact, inhalation.	
trans-Stilbene 	103-30-0	Harmful if swallowed. Irritating to eyes. Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. WARNING	H302 Harmful if swallowed. H319 Causes serious eye irritation. H411 Toxic to aquatic life with long lasting effects.	Skin contact, inhalation.	
Sodium sulfate	7757-82-6	This substance is not hazardous	n/a	Skin contact, inhalation.	
Cerium sulfate 	13454-94-	Irritating to eyes, respiratory system and skin. WARNING	H315 Causes skin irritation. H319 Causes serious eye irritation. H335 May cause	Skin contact, inhalation.	

iii OELV = occupational exposure limit as set down in the most up to date Code of Practice for the Chemical Agents Regulations. If unavailable use TLV or equivalent

			respiratory irritation.		
Dichloromethane 	75-09-2	Limited evidence of a carcinogenic effect. WARNING	H351 Suspected of causing cancer.	Skin contact, inhalation.	8hr period: 174 mg/m^3
Catalysts (CAS numbers unavailable):					
2A 		Unknown – assume toxic	Unknown	Skin contact, inhalation.	
2B 		Unknown – assume toxic	Unknown	Skin contact, inhalation.	
2C 		Unknown – assume toxic	Unknown	Skin contact, inhalation.	
2D 		Unknown – assume toxic	Unknown	Skin contact, inhalation.	
2E 		Unknown – assume toxic	Unknown	Skin contact, inhalation.	
2F 		Unknown – assume toxic	Unknown	Skin contact, inhalation.	

2G 	Unknown – assume toxic	Unknown	Skin contact, inhalation.	
2H 	Unknown – assume toxic	Unknown	Skin contact, inhalation.	
2I 	Unknown – assume toxic	Unknown	Skin contact, inhalation.	
Product:				
Epoxystilbene	1439-07-2	Not a dangerous substance according to GHS.	Skin contact, inhalation.	

Reaction:

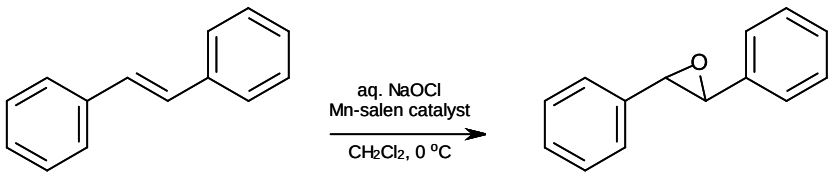
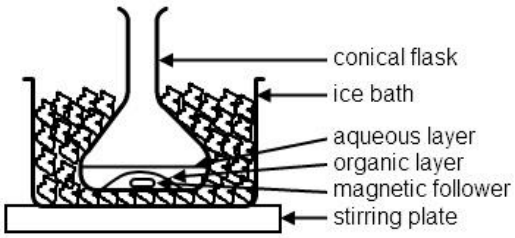


Figure 30: Epoxidation of *trans*-stilbene using sodium hypochlorite and Mn-salen catalyst

Apparatus:



- 2 x 50 mL conical flasks
- ice bath
- magnetic follower and stirrer plate
- retort stand and clamp
- pH meter

Figure 31: Experimental set up for epoxidation of stilbene with sodium hypochlorite

Instructor notes:

- It is important to purchase a fresh bottle of hypochlorite solution before use, and keep it refrigerated until needed. The reaction was repeated using hypochlorite which had been stored for 3 months and significantly lower yields were observed.
- In the referenced papers, the hypochlorite solution used was Chlorox, a strong domestic bleach). We attempted to use locally available domestic bleach but detergents present made the workup difficult.
- As the extent of conversion achieved using each catalyst is being compared, it is important that all reactions are left on for the same time (ideally 2 hours but 1 $^1/_2$ hours is sufficient if time is tight).
- It is useful to ask one student in the class to carry out the reaction in the absence of any catalyst to provide a comparison.
- The reaction can be easily scaled down to compensate for low yields of catalyst in the previous step.
- The catalyst mass is based on 0.2 mmol (4 % catalyst loading) as suggested in the procedure. The mass of *trans*-stilbene used for 100 mg of catalyst is given to allow for easy scaling if there is insufficient catalyst. Mass is calculated assuming 96 % purity stilbene.
- Hexane or pentane can be used instead of dichloromethane as the workup solvent.
- When monitoring the reaction by TLC, formation of some product was detected after 30 minutes.
- For TLC, we used aluminium-backed plates containing a fluorescent indicator (Sigma Aldrich 70643)
- TLC plates were developed using a ceric stain. The stain is a saturated solution of ceric sulfate in 15 % (v/v) aqueous H_2SO_4. The TLC plate is held with tweezers and dipped into the stain solution. The back of the plate should be wiped dry, and then the front heated with a heat gun. As the plate dries, spots will begin to appear. The starting material appears as a diffuse spot (Rf value ~ 0.7), while the product remains closer to the base line (R_f value ~ 0.15).
- Some of the phase separations proved difficult with an emulsion forming at the partition between the 2 layers (Figure 32). This usually separated over time. If not, addition of further salt to the brine layer should encourage separation.

Figure 32: Separation of layers

- The level of conversion is determined by comparing integral values in the ^{1}H NMR spectrum for the non-aromatic protons. Examples are shown in the NMR results section that follows.
- Pure stilbene oxide is a pale yellow solid, but product colour may vary depending on the amount of catalyst remaining in the product. In particular, the *tert*-Butyl substituted catalyst (2H) is highly soluble in dichloromethane and much of it remained in solution with the product. Column chromatography can be carried out to purify the crude product. A detailed procedure is available in "Synthesis and Use of Jacobsen's Catalyst: Enantioselective Epoxidation in the Introductory Organic Laboratory"; John Hanson; *Journal of Chemical Education*, Vol. 78 No. 9, 1266-1268.
- This experiment takes about three hours from set-up to tidy up.

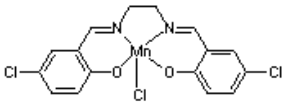
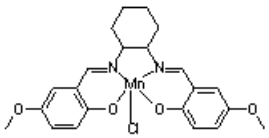
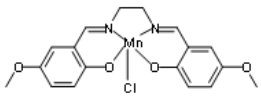
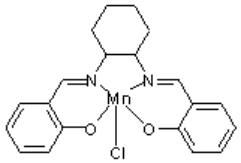
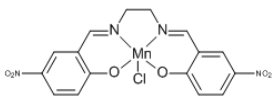
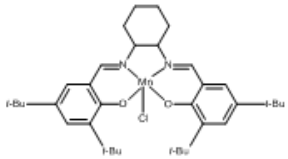
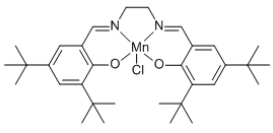
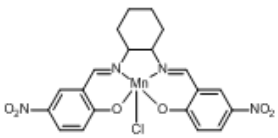
Procedure:[7,16]

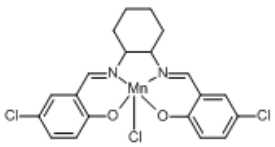
1. Dissolve *trans*-stilbene (0.94 g, 5 mmol, 96 %) and catalyst (0.2 mmol) in 5 mL of CH_2Cl_2 in a 50 mL conical flask containing a magnetic follower. Suggested catalyst quantities to be used are shown in Table 17.
2. Using an ice bath, cool the solution to below 4 ^oC.
3. In a separate 50 mL conical flask, add 5 mL of 0.05 M Na_2HPO_4 (7.1 g/L) to 12.5 mL of sodium hypochlorite solution (~0.55 M in NaOCl, 10-15 % w/w).
4. Using a pH meter to monitor changes, add 1M HCl or NaOH as appropriate dropwise to adjust the pH of the solution to 11.3.
5. The buffered bleach solution is then put on ice and cooled to below 4 ^oC.
6. Pour the cooled buffer solution into the flask containing the catalyst and *trans*-stilbene.

7. Place this flask in an ice bath in order to maintain a low temperature throughout the reaction mixture and stir the mixture vigorously ensuring none is splashed out of the conical flask.
8. Monitor the progress of the reaction by TLC. (Eluent: 40:60 CH_2Cl_2:hexane). To take a TLC sample, turn the stirrer off and let the two phases separate. Use a syringe or Pasteur pipette to remove a drop or two of solution from the lower organic layer. Place this solution in a small container and spot on the TLC plate. After running the TLC plate in the solvent mixture, the plate can be visualised using a "ceric stain" if it is available. A spot should be seen to develop close to the base line as product is formed.
9. After 2 hours remove the stir bar and add approximately 50 mL of dichloromethane.
10. Separate the brown organic phase, wash it twice with saturated NaCl solution, and dry it (Na_2SO_4). Filter and remove the solvent on a rotary evaporator.
11. Record the mass of crude product isolated.
12. Submit a sample for ^{1}H NMR analysis to determine the extent of conversion.

If students have difficulty weighing out the small amount of catalyst required when using 5 mmol of stilbene, it may be easier to ask them to use 100 mg of catalyst and vary the amount of stilbene accordingly while maintaining the correct ratios. Values for both are given in Table 17.

Table 17: Suggested masses of catalyst for epoxidation of *trans*-stilbene with sodium hypochlorite

Catalyst	Mass of catalyst used with 5 mmol of stilbene (mg)	Mass of stilbene used with 100 mg of catalyst (g)	Catalyst	Mass of catalyst used with 5 mmol of stilbene (mg)	Mass of stilbene used with 100 mg of catalyst (g)
2A  Molar mass: 425.59 g/mol	85	1.10	2F  Molar mass: 470.84 g/mol	94	0.10
2B  Molar mass: 416.75 g/mol	83	1.13	2G  Molar mass: 410.79 g/mol	82	1.14
2C  Molar mass: 446.70 g/mol	89	1.05	2H  Molar mass: 635.29 g/mol	127	0.74
2D  Molar mass: 581.13 g/mol	116	0.81	2I  Molar mass: 500.79 g/mol	100	0.94

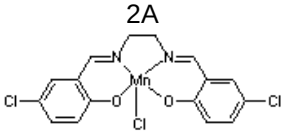
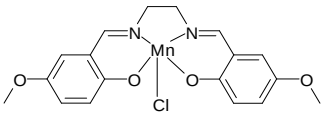
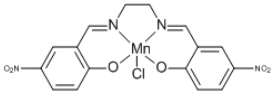
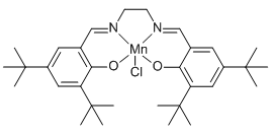
2E  Molar mass: 479.68 g/mol	96	0.98

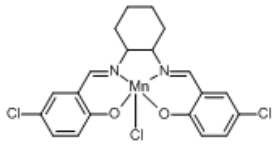
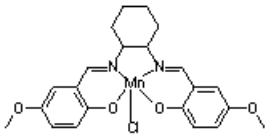
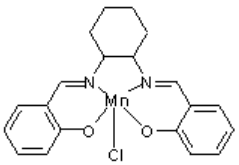
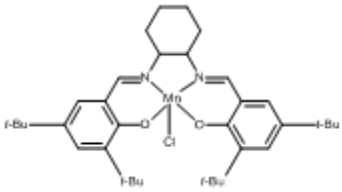
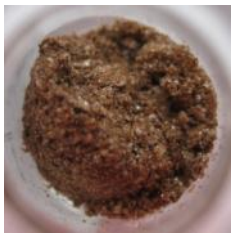
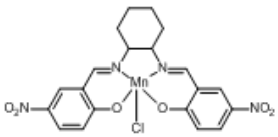
Results:

It was found that, in the absence of catalyst, no conversion occurs over the two hour reaction time.

Table 18 below shows the yields of crude product and percentage conversion to product obtained using each catalyst. The actual yield (crude yield x conversion) / 100 is also presented.

Table 18: Results from epoxidation of stilbene with sodium hypochlorite (yields of crude product and conversion to product)

Catalyst Used	Image	Crude Yield, Conversion and Actual Yield
2A  Molar mass: 425.59 g/mol		Yield of crude product = 18 % Molar conversion = 4.7 % Actual yield = 0.85 %
2B  Molar mass: 416.75 g/mol		Yield of crude product = 38 % Molar conversion = 8.5 % Actual yield = 3.23 %
2C  Molar mass: 446.70 g/mol		Yield of crude product = 74 % Molar conversion = 14.5 % Actual yield = 10.7 %
2D  Molar mass: 581.13 g/mol		Yield of crude product = 19 % Molar conversion = 48.2 % Actual yield = 9.16 %

2E  Molar mass: 479.68 g/mol		Yield of crude product = 42 % Molar conversion = 81.3 % Actual yield = 34.15 %
2F  Molar mass: 470.84 g/mol		Yield of crude product = 29 % Molar conversion = 6.5 % Actual yield = 1.88 %
2G  Molar mass: 410.79 g/mol		Yield of crude product = 34 % Molar conversion = 30.8 % Actual yield = 10.4 %
2H  Molar mass: 635.29 g/mol		Yield of crude product = 53 % Molar conversion = 14 % Actual yield = 7.42 %
2I  Molar mass: 500.79 g/mol		Yield of crude product = 63 % Molar conversion = 5.6 % Actual yield = 3.53 %

Relationship between catalyst structure and performance

As referred to in the literature review (Process Chemistry in the Pharmaceutical Industry, Gadamasetti, K.G.), good enantioselectivity in olefin epoxidation:

1. Requires a dissymmetric diimine bridge derived from a C2 symmetric 1,2-diamine
2. Requires bulky substituents on the 3 and 3' positions of the salicylide ligand
3. Is improved by electron donating or sterically demanding substituents at the 5 and 5' position.

In addition, in relation to conversion to product, Liu and Nocera[2] reported that the extent of epoxidation when using hydrogen peroxide as the oxidant was reduced significantly if a catalyst had an electron rich substituent at the 5 and 5' positions such as a methoxy group and that good reactivity could be achieved when less electron donating groups were present at these positions (-*t*-butyl, -Br).

If students have carried out the epoxidation reaction in duplicate or triplicate, the crude yield and percentage conversion results should be used to calculate actual yields and the mean and standard deviation of the

actual yields can be calculated. Results obtained by given student cohorts would be expected to show some variation but, as the expected trends have been reported in the literature, students can compile their combined class results and examine whether the following structural changes have resulted in any variations of the actual yields;

- The nature of the diamine used to generate the catalyst ligand (ethylene or cyclohexane).
- Electronic effects of substituents at the 5 and 5' position; (-Cl, -OMe, -NO_2 and –*t*-butyl were examined)

As shown in Table 19 below, the results obtained in the trials performed by the authors for the most part reflect the general trend that electron withdrawing groups at positions 5 and 5' show the best conversions. Also, catalysts derived from cyclohexanediamine showed better actual yields on average than those prepared from ethylene diamine. It has not been possible for us to perform reactions in duplicate or triplicate and the results presented are based on performing each epoxidation once only.

Some other considerations to factor in include that some crude yields will have been affected to a very minor extent by the presence of residual catalyst (e.g. 2H) and that GC analysis would have provided a more accurate determination of the percentage conversion than ^{1}H NMR spectroscopy. Also, the reaction and work up performed was a general procedure and was not optimised for the particular catalyst.

Table 19: Analysis of relationship between actual yields obtained and catalyst structure

Structural Modification to Catalyst	Effect Observed
Diamine used to prepare the ligand backbone linker (ethylene or cyclohexane)	Catalyst with cyclohexane linker shows better actual yields on average. 6 % average actual yield, range from 0.85 to 10.7 % for catalyst with ethylene linker; 11 % average actual yield, range from 1.88 to 34.1 % for catalyst with cyclohexane linker.
Substituents at 5 and 5' positions	For the cyclohexane diamine derived catalysts, the methoxy substituent resulted in the lowest actual yield (1.88 %) and the chloro substituent resulted in the highest actual yield (34.1 %) confirming the reported importance of an electron-donating group at this position.[2] For the ethylene diamine derived catalysts, the nitro and *tert*-butyl substituents gave the highest actual yields (10.7 % and 9.16 % respectively) however, the chloro substituent (0.85 %) showed a lower actual yield than the methoxy (3.23 %). It would be necessary to repeat the reaction with the chloro substituted catalyst before this particular result is considered further.

^{1}H NMR spectra of crude epoxide products for catalyst reference reactions

All NMR spectra were recorded on a 400 MHz instrument and 16 scans were acquired. Figures 33 to 41 show the ^{1}H NMR spectra of the crude product obtained from using each catalyst prepared to epoxidise trans-stilbene in the presence of sodium hypochlorite. Figure 33 shows structures of *trans*-stilbene and *trans*-stilbene oxide that are labelled to indicate how the protons are identified. The calculation based on the integration of the epoxide proton signal at approximately 4 ppm and the integration of the alkene protons at approximately 7 ppm to determine the conversion to epoxide product is shown in the top left corner of each spectrum.

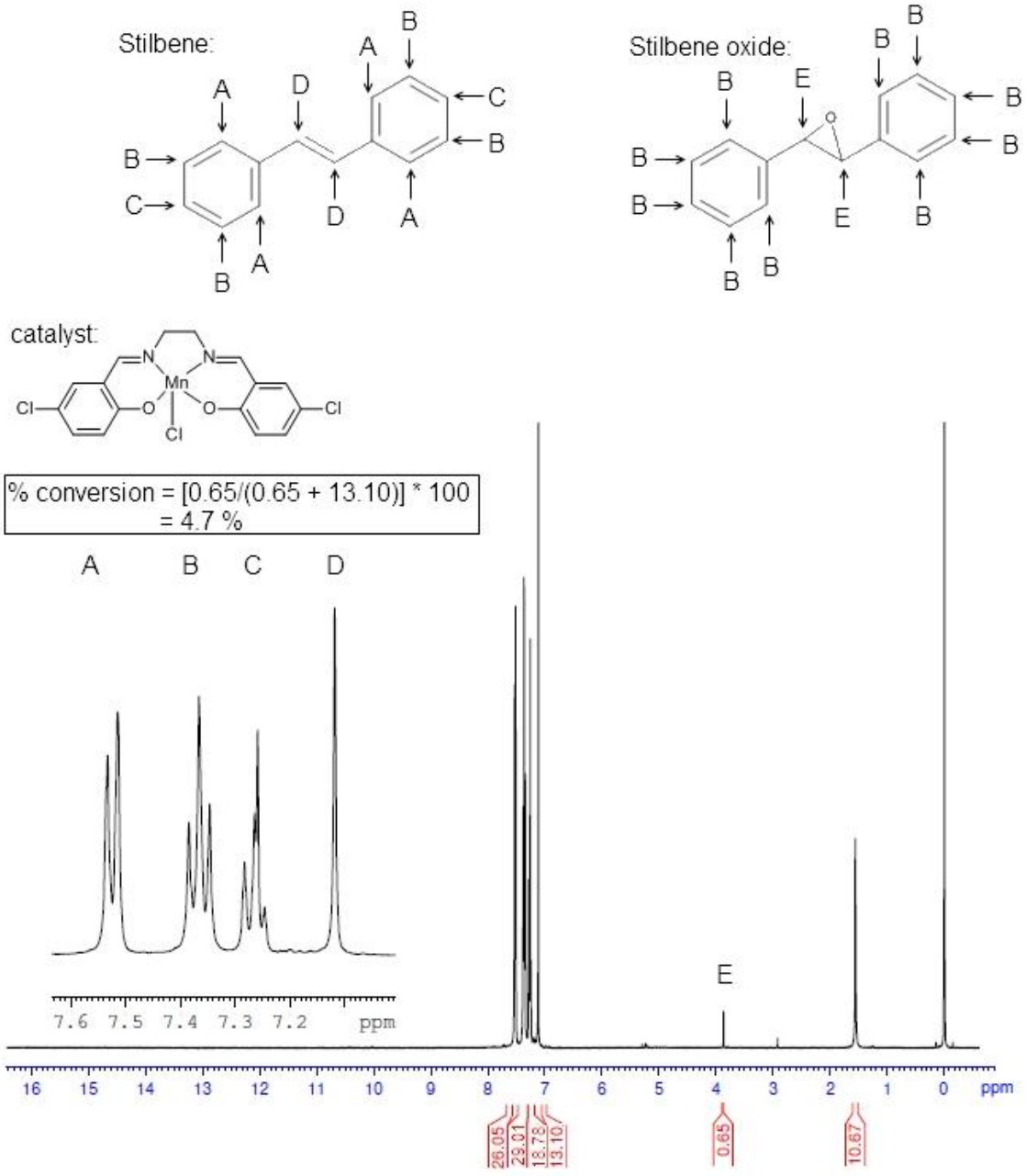


Figure 33: Proton NMR of crude product (in $CDCl_3$) from epoxidation using catalyst 2A showing peak assignment

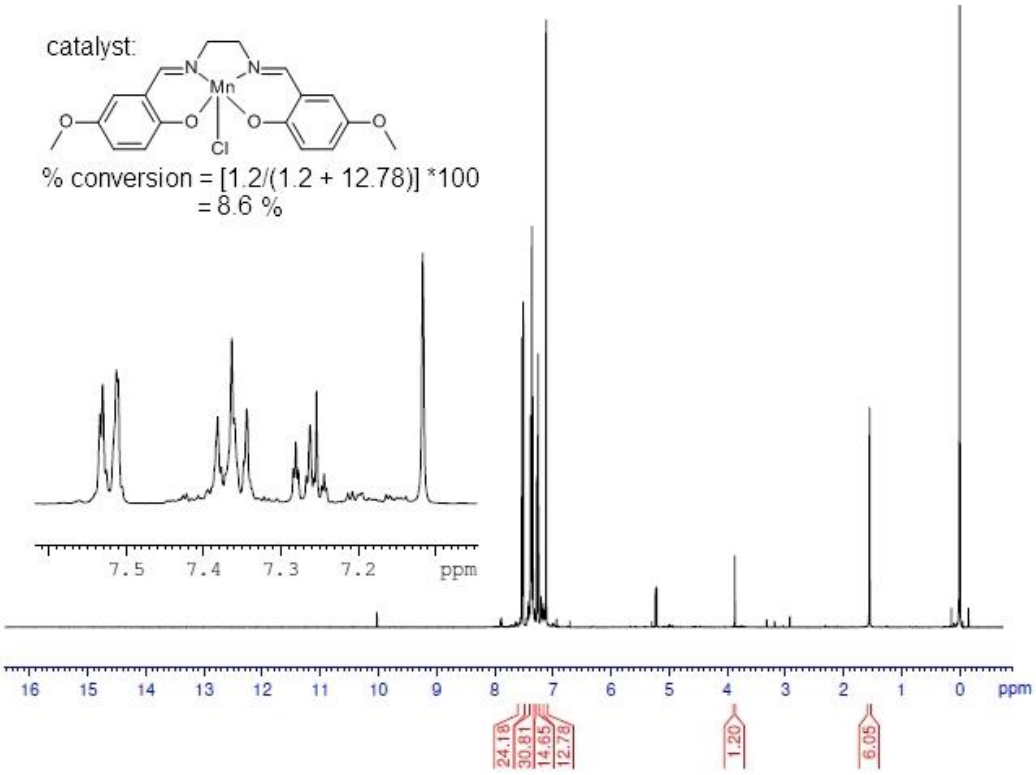


Figure 34: Proton NMR of crude product from epoxidation (in $CDCl_3$) using catalyst 2B

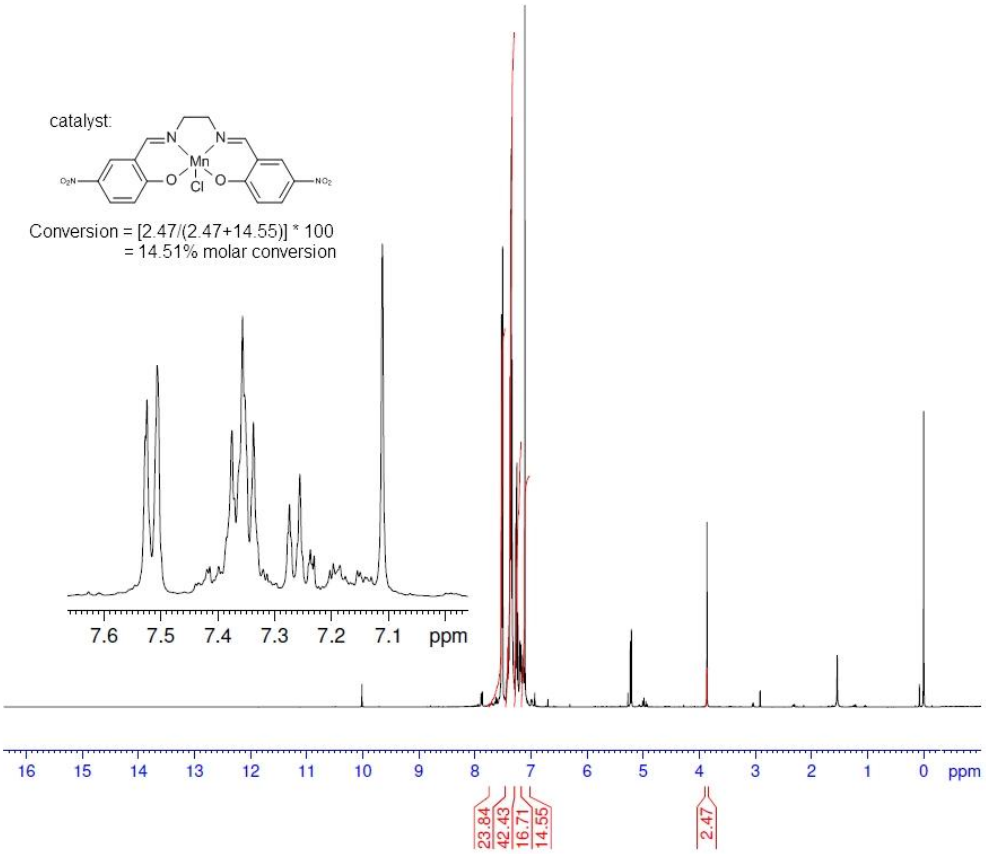


Figure 35: Proton NMR of crude product from epoxidation (in $CDCl_3$) using catalyst 2C

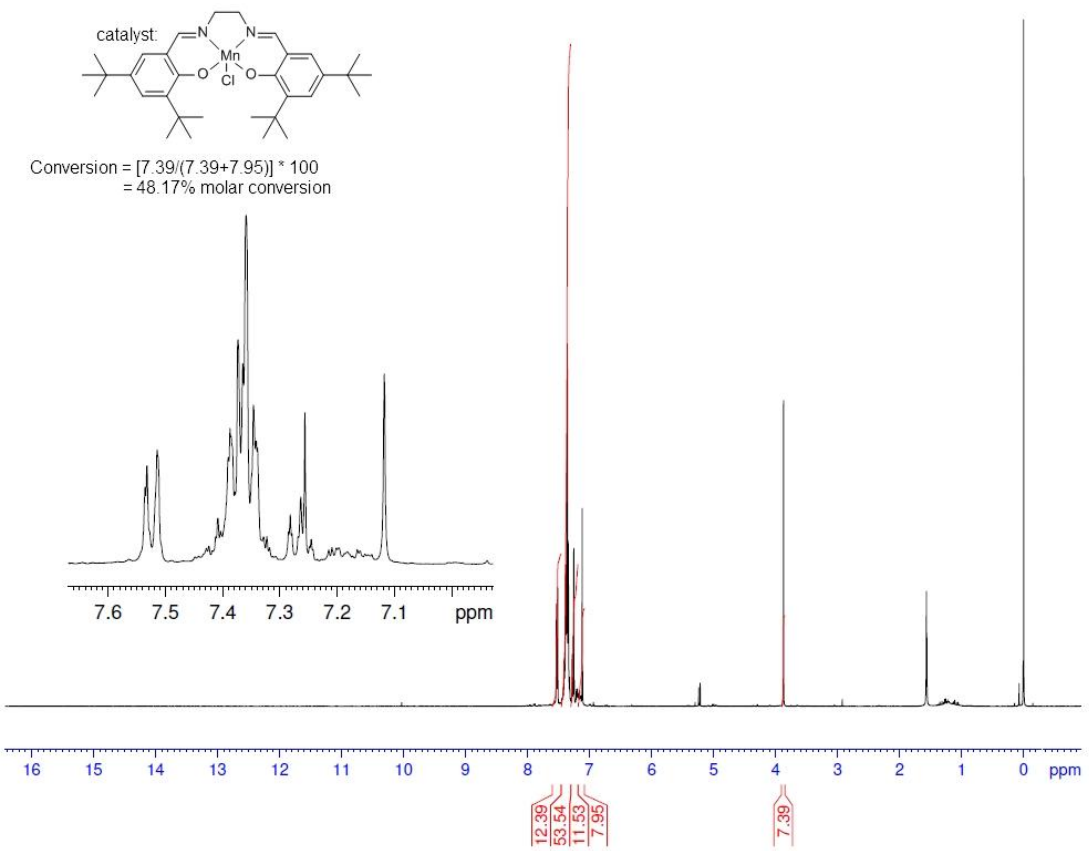


Figure 36: Proton NMR of crude product from epoxidation (in $CDCl_3$) using catalyst 2D

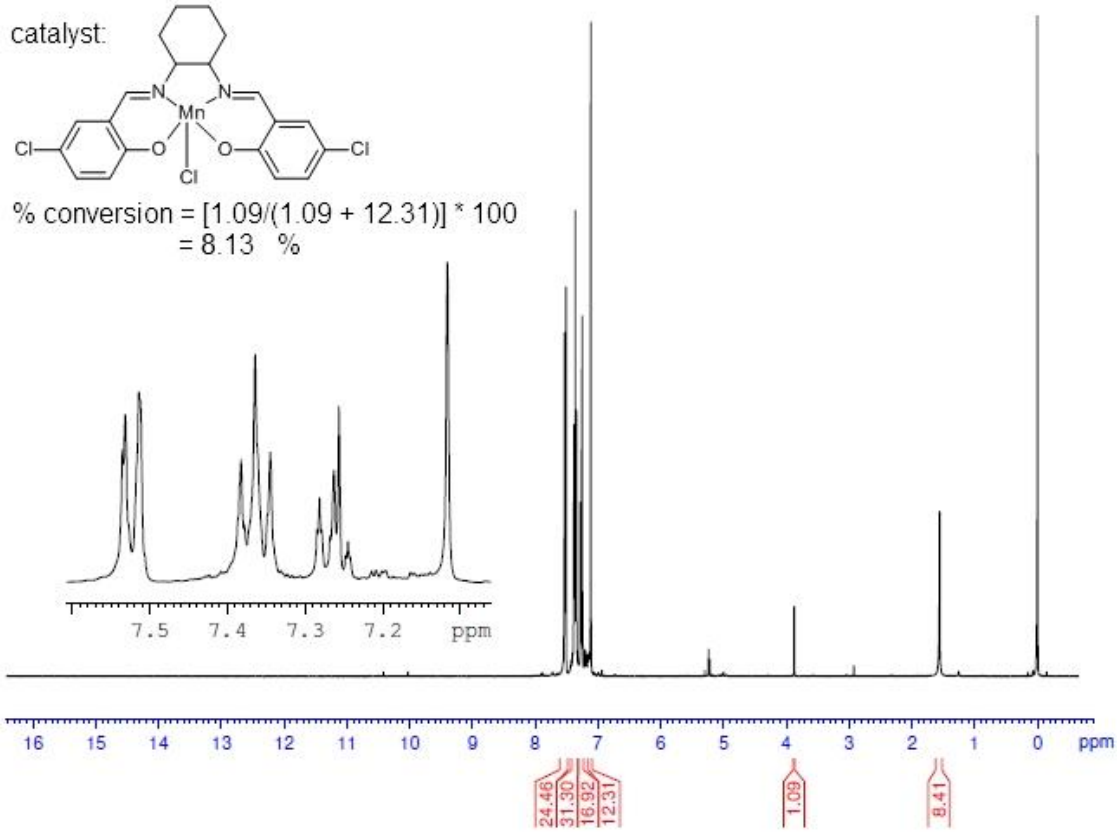


Figure 37: Proton NMR of crude product from epoxidation (in $CDCl_3$) using catalyst 2E

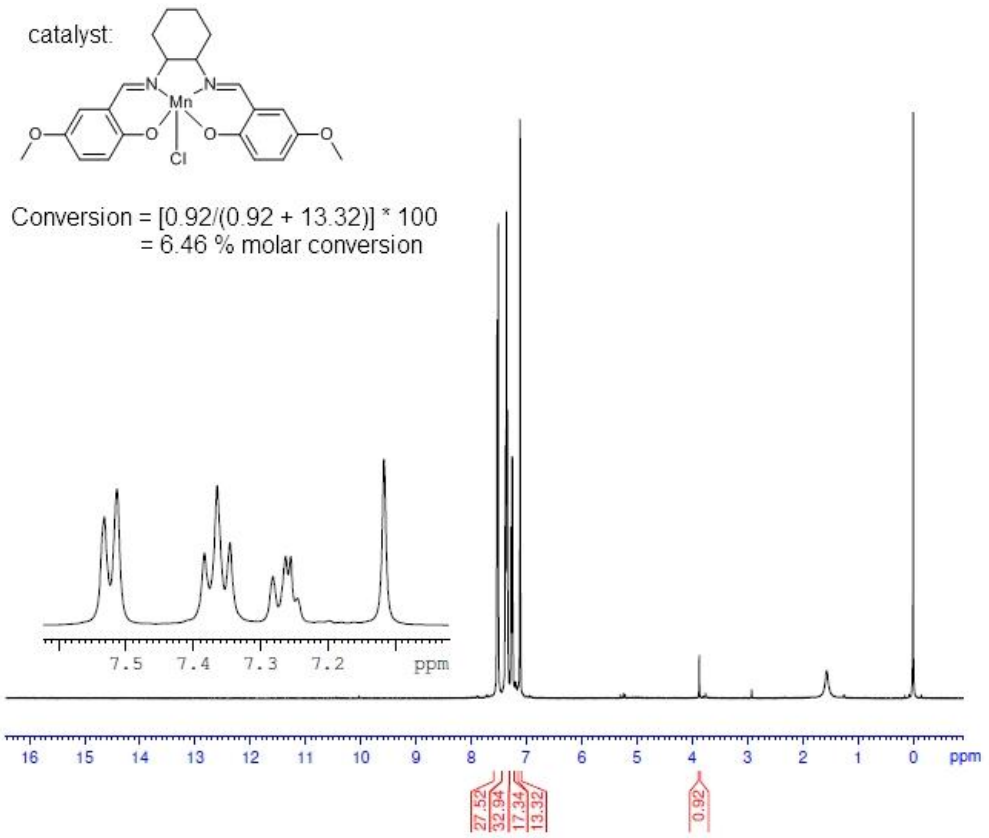


Figure 38: Proton NMR of crude product from epoxidation (in $CDCl_3$) using catalyst 2F

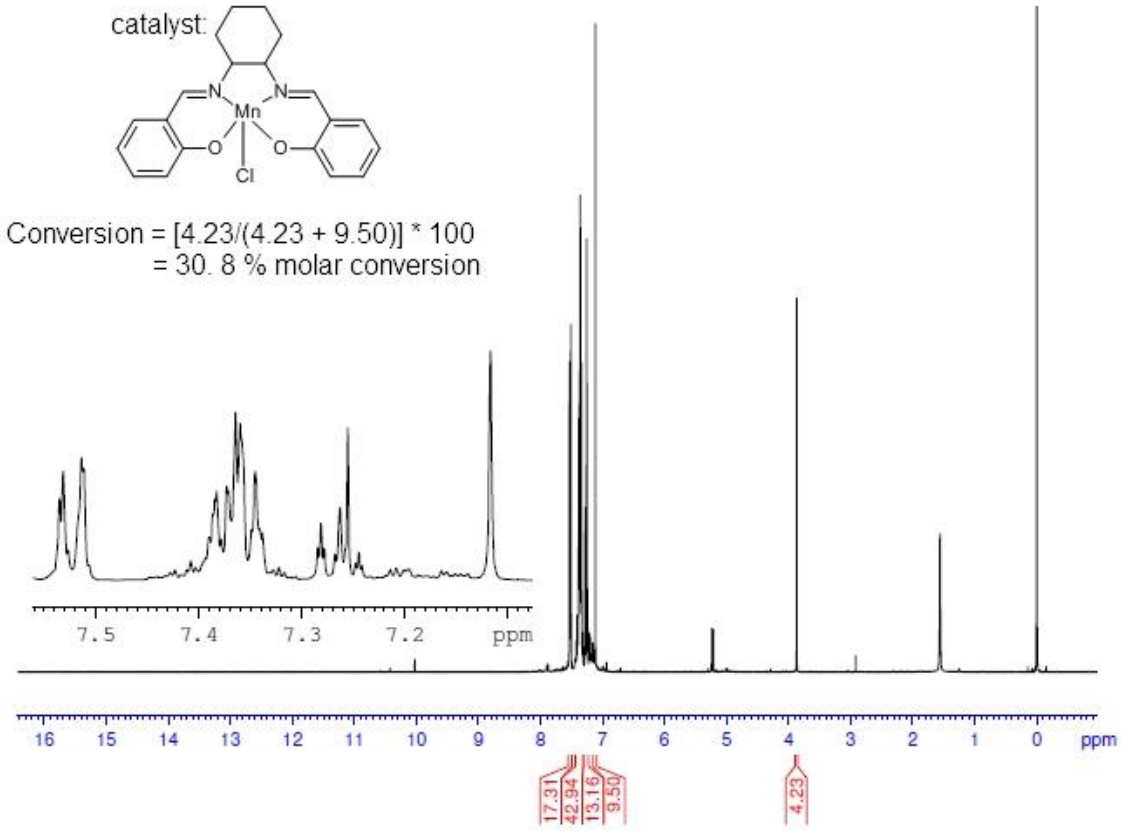


Figure 39: Proton NMR of crude product from epoxidation (in $CDCl_3$) using catalyst 2G

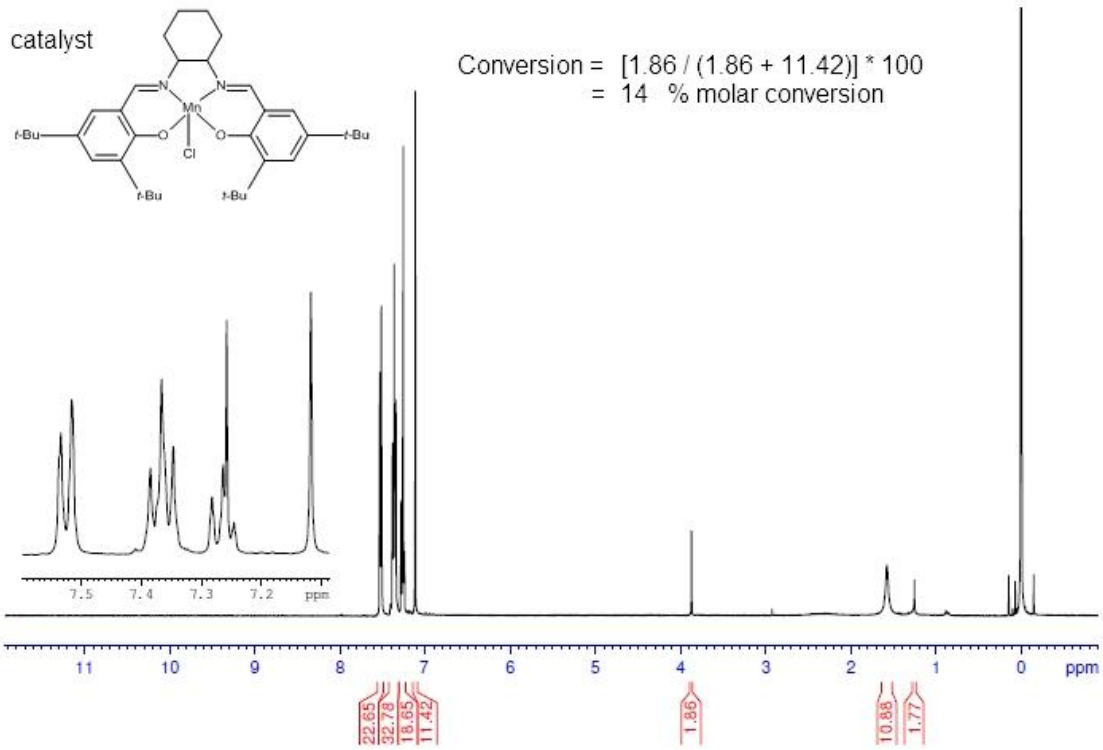


Figure 40: Proton NMR of crude product from epoxidation (in $CDCl_3$) using catalyst 2H

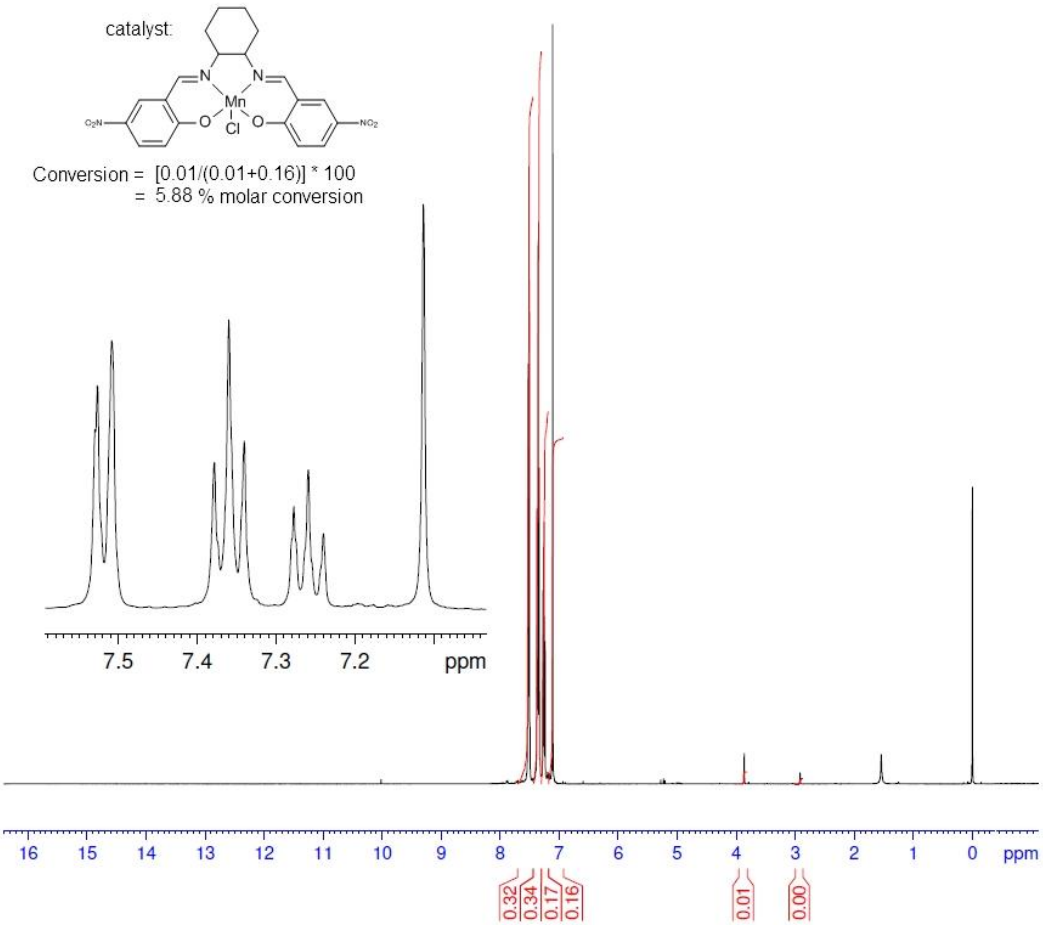


Figure 41: Proton NMR of crude product from epoxidation (in $CDCl_3$) using catalyst 2I

Appendix 7 - Tutor notes on epoxidation of *trans*-stilbene with H_2O_2 using manganese salen catalysts (Session 5)

Safety:

Table 20: Healthy and safety information for reagents used for epoxidation of *trans*-stilbene with hydrogen peroxide

Substance name	CAS no	Hazard Classification	Hazard statement/Risk phrase	Route of exposure	OELV [iv]
Dimethylformamide 	68-12-2	May cause harm to the unborn child. Harmful by inhalation and in contact with skin. Irritating to eyes. **DANGER**	H226 Flammable liquid and vapour. H319 Causes serious eye irritation. H312 Harmful in contact with skin. H332 Harmful if inhaled. H360D May damage the unborn child.	Skin Contact, Inhalation	8 hour reference period: 30 mg/ m^3
4-(Dimethylamino) pyridine 	1122-58-3	Toxic if swallowed. Very toxic in contact with skin. Irritating to eyes, respiratory system and skin. **DANGER**	H301 Toxic if swallowed. H310 Fatal in contact with skin. H315 Causes skin irritation. H319 Causes serious eye irritation. H335 May cause respiratory irritation.	Skin Contact, Inhalation	
Hydrogen peroxide (30%) 	7722-84-1	Harmful if swallowed. Risk of serious damage to eyes. **DANGER**	H302 Harmful if swallowed. H318 Causes serious eye damage.	Skin Contact, Inhalation	
Sodium chloride	7647-14-5	This substance is not hazardous	n/a	Skin Contact, Inhalation	
trans-Stilbene	103-30-0	Harmful if swallowed. Irritating to eyes. Toxic to aquatic organisms, may	H302 Harmful if swallowed. H319 Causes serious eye	Skin Contact, Inhalation	

iv OELV = occupational exposure limit as set down in the most up to date Code of Practice for the Chemical Agents Regulations. If unavailable use TLV or equivalent

		cause long-term adverse effects in the aquatic environment. **WARNING**	irritation. H411 Toxic to aquatic life with long lasting effects.		
Sodium sulfate	7757-82-6	This substance is not hazardous	n/a		
Catalysts (CAS numbers unavailable): see Table 16					
Product:					
Epoxystilbene		1439-07-2	Not a dangerous substance according to GHS.	Skin contact, inhalation.	

Reaction:[2]

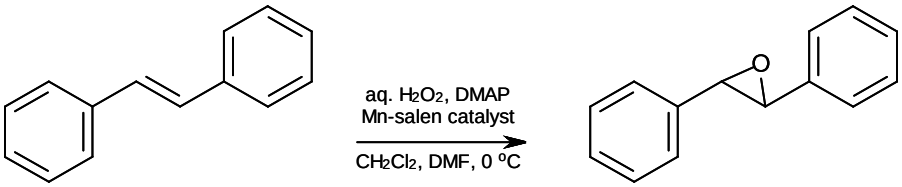
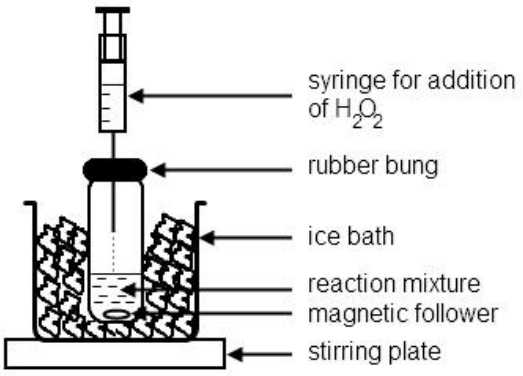


Figure 42: Epoxidation of stilbene with hydrogen peroxide

Apparatus:



- 10 mL plastic syringe
- rubber bung or lid with rubber septum or rubber septum
- glass sample bottle / reaction vessel (30 mL approximately) which can be sealed with a rubber bung or septum or a lid with a rubber septum
- ice bath
- magnetic follower and stirrer plate
- retort stand and clamp

Figure 43: Experimental set up for epoxidation of stilbene with 30 % hydrogen peroxide

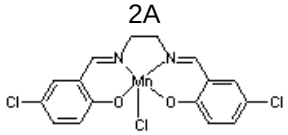
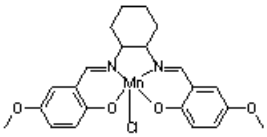
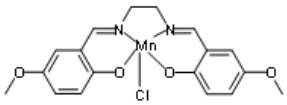
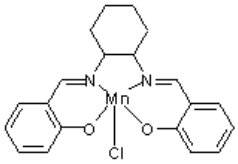
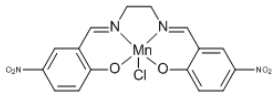
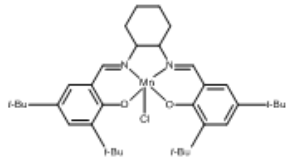
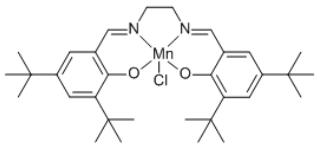
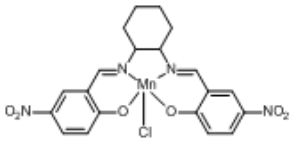
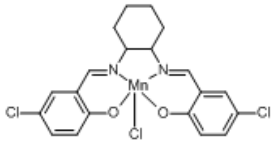
Instructor notes:

- If your students have found another procedure that employs Mn-salen catalysts under alternative conditions and you are satisfied that it is safe for them to carry out, you may wish to substitute their alternative for this reaction.
- This experiment is performed on a very small scale and requires accurate weighing and measurements which may be difficult in the undergraduate laboratory.
- H_2O_2 and DMF can form an explosive mixture. Take care to add the H_2O_2 slowly as specified in the original procedure.
- For TLC analysis, we used metal-backed plates containing a fluorescent indicator (Sigma Aldrich 70643)
- TLC plates were developed using a ceric stain. The stain is a saturated solution of ceric sulfate in 15 % aqueous H_2SO_4. The TLC plate is held with tweezers and dipped into the stain solution. The back of the plate should be wiped dry, and then heated with a heat gun. As the plate dries, spots will begin to appear. The starting material appears as a diffuse spot (Rf value ~ 0.7), while the product remains closer to the base line (Rf value ~ 0.15).
- It may be difficult to fully remove DMF during the work-up. If some remains, the product will be liquid. It should be removed by leaving on a rotary evaporator for several hours.
- The extent of conversion is determined by comparing integral values in the ^{1}H NMR for the non-aromatic protons.
- Pure *trans*-stilbene oxide is a pale yellow solid.
- This experiment takes about three hours from set-up to tidy up.

Procedure:[2]

1. Put 0.014 mmol of catalyst in a vial (30 mL approximate volume) which can be fitted with a rubber bung, and follow with 56 mg DMAP (dimethylaminopyridine). Catalyst masses to be used are given in Table 21.
2. Add a mixture of CH_2Cl_2/DMF (2.1/6.3 mL) to the vial followed by *trans*-stilbene (1.4 mmol, 262 mg) and a magnetic stirrer.
3. Place the flask in the bottom of an ice bath and surround it with ice, in order to maintain a low temperature throughout the reaction.
4. Place the ice bath on the stirred plate, clamping the top of the vial securely. The mixture should be stirred vigorously over the course of the reaction.
5. Add 400 µL of H_2O_2 (30 %) to the reaction mixture in one portion.
6. Close the vessel with a rubber bung (or a rubber septum or a lid containing a septum).
7. Use a disposable plastic syringe to slowly add an additional 2.8 mL of H_2O_2 (30 %) to the reaction mixture over an hour (approximately 1 drop per minute). It is important to add the oxidant slowly to prevent the risk of a very vigorous reaction.
8. Stir the mixture for a further 15 minutes after completing addition of the H_2O_2.
9. Confirm product formation by TLC (eluent: 40:60 CH_2Cl_2:hexane) and use a ceric stain to visualise the spots.
10. Add 10 mL CH_2Cl_2 to dilute the reaction mixture, followed by 2 mL pentane.
11. Wash the organic phase with water followed by saturated NaCl solution, and then dry it (Na_2SO_4). Filter and remove the solvent using the rotary evaporator.
12. Submit a sample for ^{1}H NMR analysis to determine level of conversion.

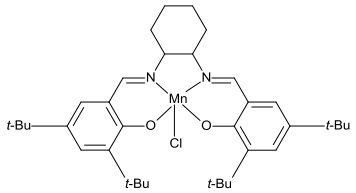
Table 21: Catalyst mass required based on procedure[2] (0.014 mmol)

Catalyst	0.014 mmol of catalyst (mg)	Catalyst	0.014 mmol of catalyst (mg)
2A  Molar mass: 425.59 g/mol	6	2F  Molar mass: 470.84 g/mol	7
2B  Molar mass: 416.75 g/mol	6	2G  Molar mass: 410.79 g/mol	6
2C  Molar mass: 446.70 g/mol	6	 2H Molar mass: 635.29 g/mol	9
2D  581.13 g/mol	8	2I  500.79 g/mol	7
2E  Molar mass: 479.68 g/mol	7		

Results:

The epoxidation of *trans*-stilbene with 30 % aqueous hydrogen peroxide has only been undertaken using one catalyst, 2H, and the resulting ^{1}H NMR spectrum is shown in Figure 44. Table 22 below presents the percentage conversion determined from this spectrum. A crude yield is not recorded as residual DMF remained in the product, as can be seen from the signals at 8 ppm and just below 3 ppm in the ^{1}H NMR spectrum. The conversion to product obtained is satisfactory and is would be anticipated that similar conversions would be reported for the other catalysts, expect those with methoxy substituents at the 5 and 5' positions. However, the scale that the reaction can be carried out is a severe limitation. The issue of safety considerations when using hydrogen peroxide in the presence of DMF and the impact on viability of using the reaction on a larger scale can be discussed with students.

Table 22: Results from epoxidation of *trans*-stilbene with 30 % hydrogen peroxide using catalyst 2H

Catalyst	Conversion
 2H Molar mass: 635.29 g/mole	Molar conversion = 60 %

The ^{1}H NMR spectrum of the crude product isolated from the reaction is shown below in Figure 44.

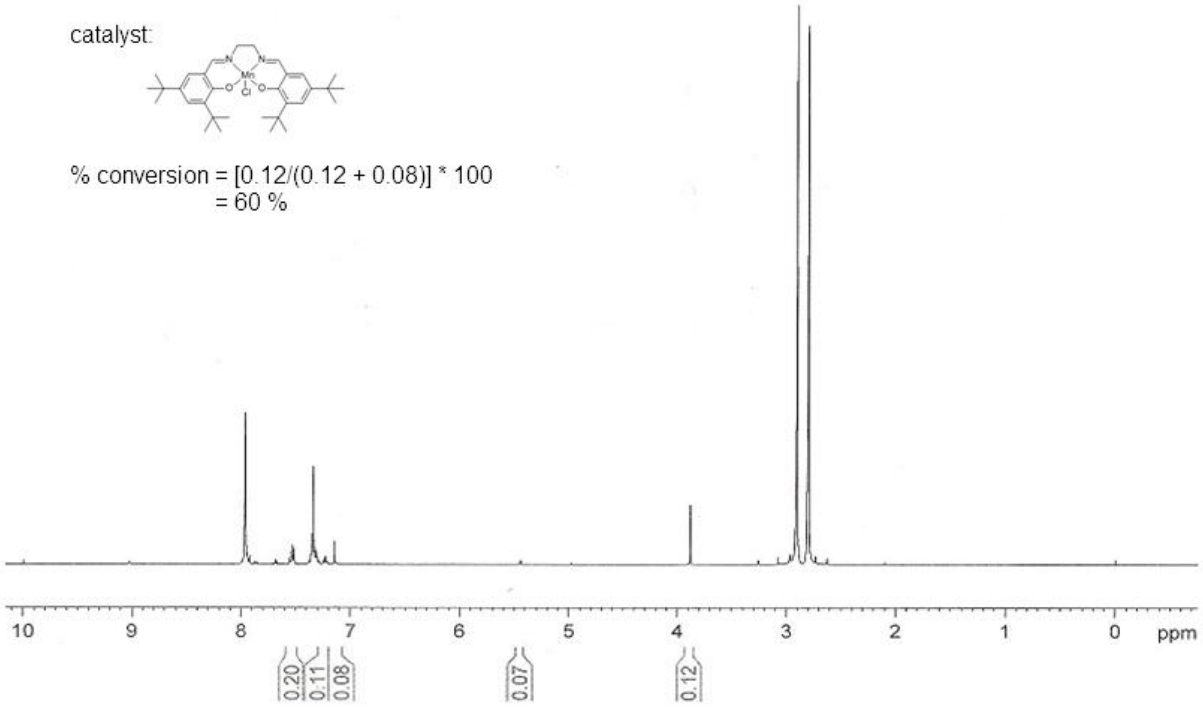


Figure 44: Proton NMR (in $CDCl_3$) of crude product from epoxidation with hydrogen peroxide using catalyst 2H

Appendix 8 - Tutor notes on Green Chemistry metrics calculations (Session 6)

An introduction to this topic has been provided earlier in the tutor notes on Session 6 (Workshop 2). The reaction metrics that have been calculated for the transformations in this case study are atom economy and mass intensity. Table 6 which appears earlier on presents the results of the reaction metrics calculations performed. Further details on these calculations and some worked examples are provided here in this Appendix.

$$\text{Atom economy} = \frac{\text{molecular weight of product}}{\text{sum of molecular weight of reactants}} \times 100$$

$$\text{Mass intensity} = \frac{\text{total mass used in process (kg)}}{\text{mass of product (kg)}} \times 100$$

$$\text{Percentage yield} = \frac{\text{actual yield of product}}{\text{theoretical yield of product}} \times 100$$

Step 1 of catalyst synthesis: ligand formation

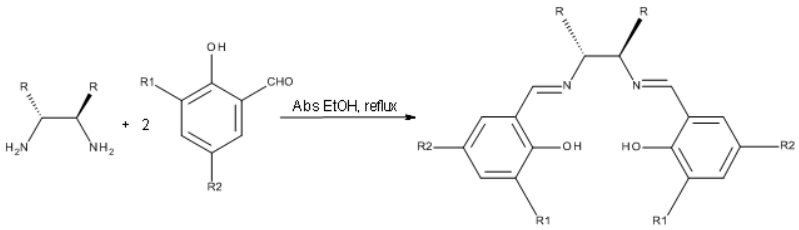
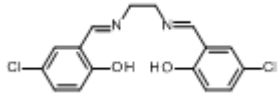
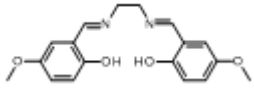


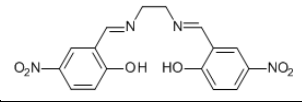
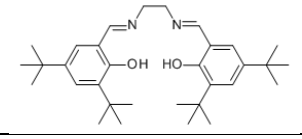
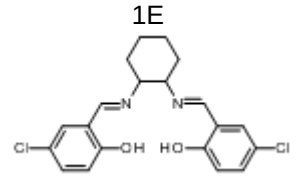
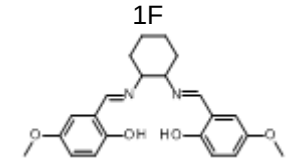
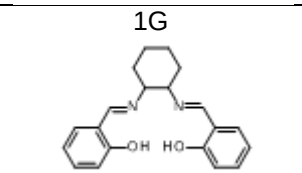
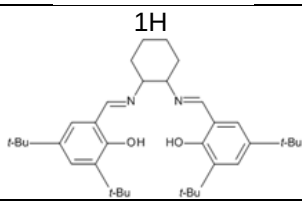
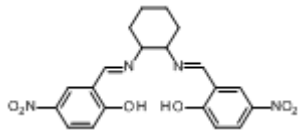
Figure 45: Salen ligand formation

Atom economy

$$\text{Atom economy} = \frac{\text{molecular weight of product}}{\text{molecular weight of diamine + 2(molecular weight of salicaldehyde derivative)}} \times 100$$

Table 22: Calculation of atom economy for salen ligand formation

Product	m.w. product	m.w. diamine	m.w. Salicylaldehyde	Atom economy (%)
1A 	337.2	60.1	156.57	90.34
1B 	328.36	60.1	152.15	90.11

1C 	358.30	60.1	167.12	90.86
1D 	492.74	60.1	234.33	93.19
1E 	391.29	114.19	156.57	91.57
1F 	382.45	114.19	152.15	91.39
1G 	322.39	114.19	122.12	89.95
1H 	546.85	114.19	234.33	93.82
1I 	412.4	114.19	167.12	91.97

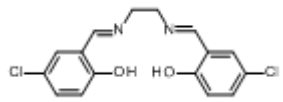
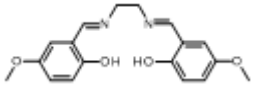
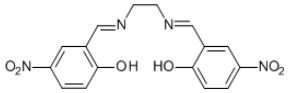
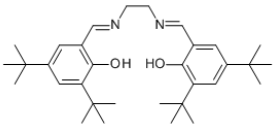
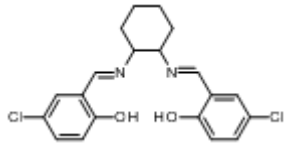
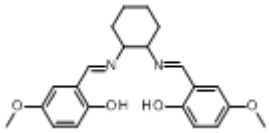
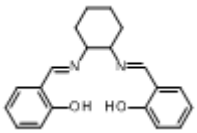
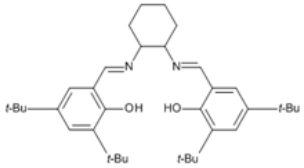
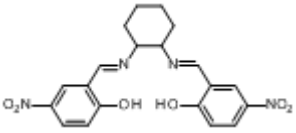
Mass intensity

$$\text{Mass intensity} = \frac{\text{mass of diamine} + \text{mass of salicaldhyde} + \text{mass of ethanol (kg)}}{\text{mass of product (kg)}}$$

Assumptions:

- Calculations are based on producing 1 kg of product and 100 % percentage yield.
- Chemicals used in product work-up are not included.
- Water is not included in mass intensity calculations. (Process Mass Intensity, an alternative metric, does include process water).

Table 23: Calculation of mass intensity for salen ligand formation

Product	mass of diamine (kg)	mass of salicylaldehyde derivative (kg)	mass of abs EtOH (kg)	Mass intensity (based on 1 kg of product)
1A  Molar mass = 337.2 g/mol	0.18	0.93	11.70	12.81
1B  Molar mass= 328.36 g/mol	0.18	0.93	12.01	13.12
1C  Molar mass = 358.30 g/mol	0.17	0.93	11.01	12.11
1D  Molar mass = 492.74 g/mol	0.12	0.95	8.01	9.08
1E  Molar mass= 391.29 g/mol	0.29	0.80	10.08	11.17
1F  Molar mass= 382.45 g/mol	0.30	0.80	10.32	11.42
1G  Molar mass= 322.39 g/mol	0.35	0.76	12.24	13.35
1H  Molar mass= 546.85 g/mol	0.21	0.86	7.25	8.32
1I  Molar mass= 412.4 g/mol	0.28	0.81	8.81	9.90

Step 2 of catalyst synthesis: formation of the Mn-salen complex

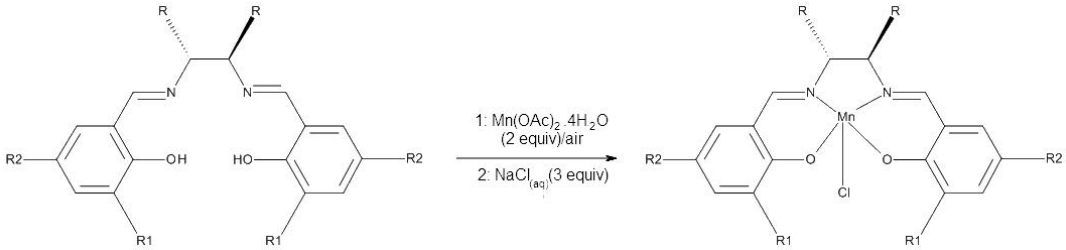
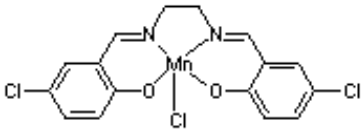
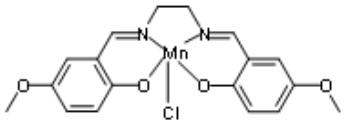
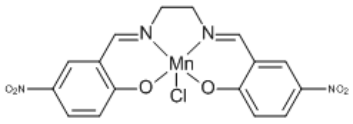
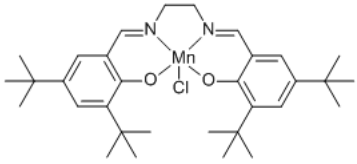


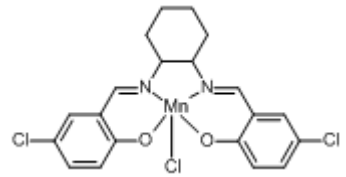
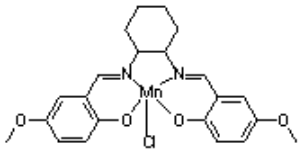
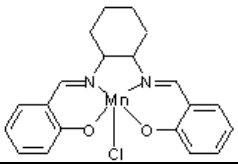
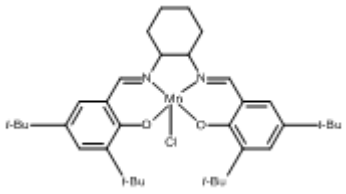
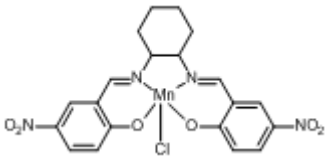
Figure 46: Formation of manganese salen catalyst

Atom economy

$$\text{Atom economy} = \frac{\text{molecular weight of product}}{\text{molecular weight of ligand} + 2(\text{molecular weight of } Mn(OAc)_2.4H_2O) + 3(\text{molecular weight of NaCl})} \times 100$$

Table 24: Calculation of atom economy for catalyst formation

Product	m.w. product	m.w. ligand	m.w. $Mn(OAc)_2.4H_2O$	m.w. NaCl	Atom economy
2A 	425.59	337.2	245.09	58.44	42.44
2B 	416.73	328.36	245.09	58.44	41.93
2C 	446.70	358.3	245.09	58.44	43.63
2D 	581.13	492.74	245.09	58.44	50.17

2E 	479.66	391.29	245.09	58.44	45.39
2F 	470.82	382.45	245.09	58.44	44.39
2G 	410.76	322.39	245.09	58.44	41.58
2H 	635.29	546.85	245.09	58.44	52.40
2I 	500.79	412.39	245.09	58.44	46.46

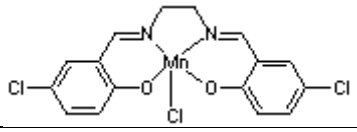
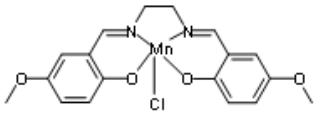
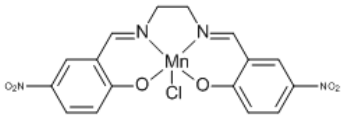
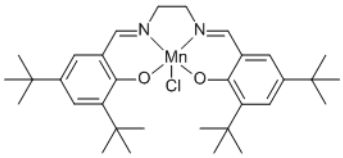
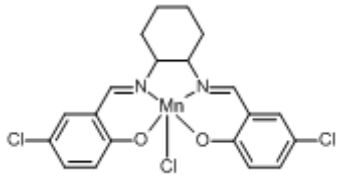
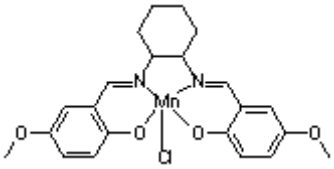
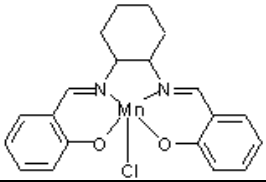
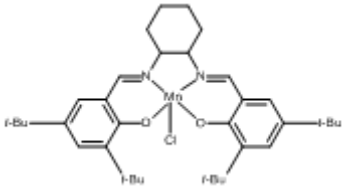
Mass intensity

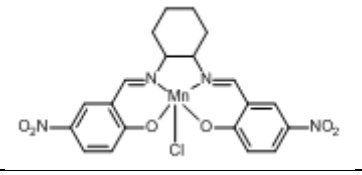
$$\text{Mass intensity} = \frac{\text{mass of ligand} + \text{mass of } Mn(OAc)_2.4H_2O + \text{mass of NaCl} + \text{mass of ethanol (kg)}}{\text{mass of product (kg)}}$$

Assumptions:

- Calculations are based on producing 1 kg of product in 100 % yield.
- Chemicals used in the product work-up are not included.
- Water is not included in mass intensity calculations. (Process Mass Intensity, an alternative metric, does include process water).

Table 25: Calculation of mass intensity for ligand formation

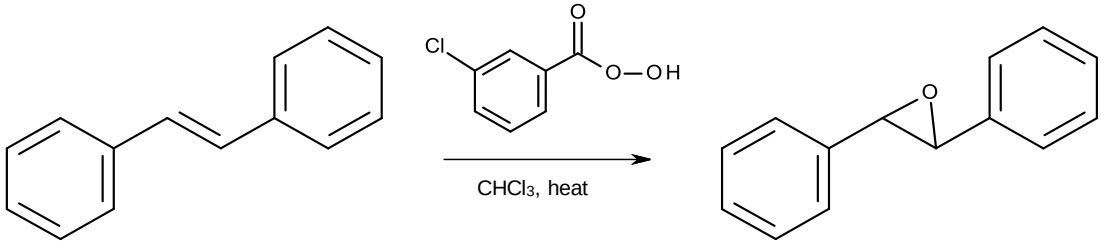
Product	mass of ligand (kg)	mass of $Mn(OAc)_2.4H_2O$ (kg)	mass of NaCl (kg)	mass of abs EtOH (kg)	Mass intensity (based on 1 kg of product)
2A 	0.79	1.15	0.41	18.55	20.90
2B 	0.79	1.18	0.42	18.93	21.32
2C 	0.80	1.10	0.39	17.58	19.87
2D 	0.85	0.84	0.30	13.53	15.52
2E 	0.82	1.02	0.36	16.45	18.65
2F 	0.81	1.04	0.37	16.76	18.98
2G 	0.78	1.19	0.43	19.21	21.61
2H 	0.86	0.77	0.28	12.43	14.34

2I 	0.82	0.98	0.35	15.72	17.87

Epoxidation methods

A) Standard existing epoxidation method:[11]

Stilbene oxide may be prepared by reacting 5.0 g (0.028 mol) *trans*-stilbene with *m*-CPBA (6.0 g, 0.028 mol, 80%) in 50 mL hot chloroform. This reaction is reported to occur with a 90 % product yield, as shown in Figure 47.



0.028 moles	0.028 moles	0.028 moles
m.w. 180.25	m.w. 172.57	m.w. 196.24

Figure 47: Peracid epoxidation of stilbene

Reaction metrics:

Atom economy = 55.62 %
Mass intensity = 15.59

Calculations:

Atom economy = [m.w. Stilbene oxide / (m.w. Stilbene + m.w. mCPBA)]*100

= [196.24/(180.25+172.57)]*100

= 55.62 %

Mass intensity

Assumptions:

- Calculations based on producing 1 kg of product in 100 % yield.
- Chemicals used in product work-up are not included.
- Water is not included in mass intensity calculations. (Process Mass Intensity, an alternative metric, does include process water).

1 kg stilbene oxide = 1000/196.24 moles

= 5.0958 moles therefore require 5.0958 moles of stilbene starting material

Scale factor = 5.0958 moles / 0.028 moles = 181.99

The mCPBA used has a specification of 80% purity

Mass of stilbene = 5.0958*180.25/1000 = 0.9185 kg

Mass of mCPBA = 181.99*(0.028*172.57) / 1000*0.80 = 1.099 kg

Density of $CHCl_3$ = 1.492 g mL^{-1}

Mass of $CHCl_3$ = 181.99*0.05*1.492 = 13.577 kg

Mass intensity (100 % yield)	= 0.9185 + 1.099 +13.577 = 15.5945

Mass intensity (90 % yield) = 17.33

(Note that the mCPBA used has a specification of 80% purity and the extra 20% mass has not been factored in here to keep the example relatively straightforward. If this extra 20% is included, 0.2748 kg should be added to the total and the mass intensity calculated is 15.87)

Issues with this method:

- Low atom economy
- Heat required to maintain operating temperature; energy input required.
- Chloroform as solvent; carcinogen, restrictions on use.
- mCPBA is shock sensitive; safety hazard on large scale
- Cannot be used to produce one enantiomer over another

B) Catalytic epoxidation of stilbene with sodium hypochlorite using Mn-salen catalyst[7]

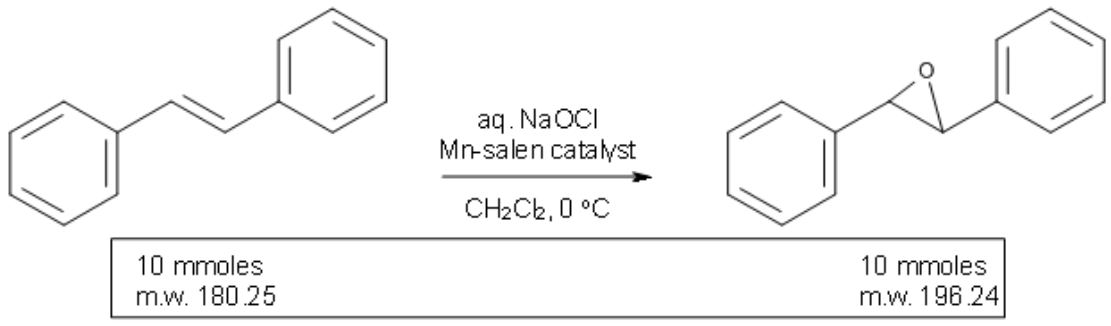


Figure 48: Epoxidation of stilbene with hypochlorite using Mn-salen catalyst

Reaction metrics:

Atom economy = 77.05 %

Mass intensity = 29.45

Calculations:

Atom economy = [m.w. Stilbene epoxide / (m.w. Stilbene + m.w. NaClO)] *100

= [196.24/(180.25 + 74.44)] *100

= 77.05 %

Mass intensity

Assumptions:

- Calculations based on producing 1 kg of product in 100 % yield
- Chemicals used in the product work-up are not included
- The mass of catalyst is excluded as it should be isolated and reused
- Density of Na_2HPO_4 and HCl aqueous solutions = 1 g mL^{-1}
- The quantities and ratios are based on using 10 mmol of stilbene substrate (5 mmol is the quantity used in the procedure used for this case study (see Appendix 6))

1 kg stilbene oxide = 1000 g / 196.24 g/mole

= 5.0958 moles therefore require 5.0958 moles of stilbene starting material

Scale factor = 5.0958 moles / 0.01 moles = 509.580106

Density of CH_2Cl_2 = 1.483 g mL^{-1}

Density NaClO (10-15%) = 1.206 g mL^{-1}

Mass of stilbene = 5.0958*180.25 g / 1000 = 0.9185 kg

Mass of NaClO = (509.5801*vol NaClO*density NaClO) /1000

= 509.5801*25*1.206/1000 = 15.3638 kg

Mass of Na_2HPO_4 = (509.5801*vol Na_2HPO_4*density Na_2HPO_4) / 1000)

= 509.5801*10*1/1000 = 5.0960 kg

Mass of HCl = (509.5801*vol HCl*density HCl) / 1000

= 509.5801*1*1/1000 = 0.5096 kg

Mass of CH_2Cl_2 = (509.5801*vol CH_2Cl_2*density CH_2Cl_2) / 1000

= 509.5801*10*1.483/1000 = 7.5571 kg

Mass intensity (100 % yield) = 0.9185 + 15.3638 + 5.0960 + 0.5096 + 7.5571

= 29.4450

Issues with method:

- Low operating temperature; varies from -78 ^oC to 5 ^oC to get good product resolution on commercial scale demanding high energy input to maintain[13]
- Dichloromethane as solvent; toxic, regulated by EU solvent directive.
- Catalyst needs to be recycled.

Catalytic epoxidation of stilbene with hydrogen peroxide using Mn-salen catalyst[2]

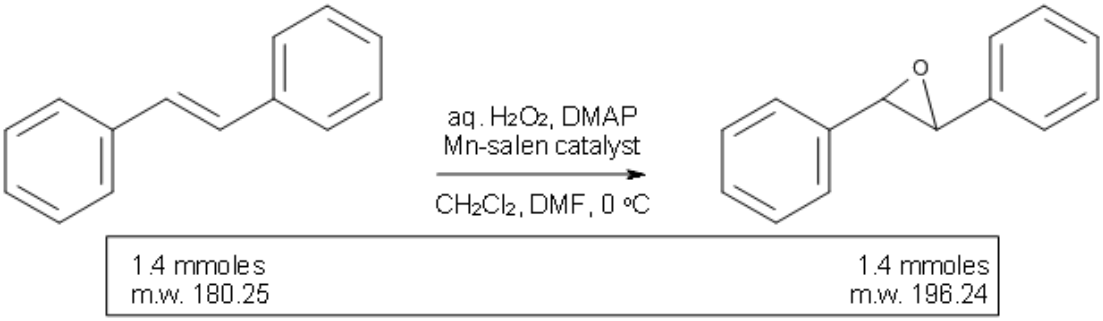


Figure 49: Epoxidation of stilbene with hydrogen peroxide using Mn-salen catalyst

Atom economy = 91.59 %
Mass intensity = 41.38

Calculations:

Atom economy = [m.w. Stilbene epoxide/(m.w. Stilbene + m.w. H_2O_2)]*100

= [196.24 / (180.25*34.015)]*100

= 91.5875 %

Mass intensity

Assumptions:

- Calculations are based on producing 1 kg of product
- Chemicals used in the product work-up are not included
- The mass of catalyst is excluded as it should be isolated and reused
- Quantities and ratios are taken from paper by Liu *et al*[2]

1 kg stilbene oxide	= 1000/196.24 moles	
	= 5.0958 moles	therefore require 5.0958 moles of stilbene starting material
Scale factor	= 5.0958/0.0014	= 3639.8579
Density of CH_2Cl_2	= 1.483 g mL^{-1}	
Density of 30% H_2O_2	= 1.11 g mL^{-1}	
Density of DMF	= 0.944 g mL^{-1}	

Mass of stilbene	= 5.0958*180.25/1000	= 0.9185 kg
Mass of DMAP	= 3639.86*mass DMAP/1000	
	= 3639.86*0.056/1000	= 0.2038 kg
Mass of CH_2Cl_2	= 3639.86*vol CH_2Cl_2*density CH_2Cl_2 / 1000	
	= 3639.86*2.1*1.483/1000	= 11.3356 kg

Mass of DMF = 3639.86*vol DMF/1000*density DMF

=3639.86*6.3*0.944 / 1000 = 21.6470 kg

Mass of H_2O_2 = 3639.86*vol H_2O_2*density H_2O_2 / 1000

= 3639.86*1.8004*1.11 / 1000 = 7.2741 kg

Mass intensity (100 % yield) = 0.9185 + 0.2038 + 11.3356 + 21.6470 + 7.2741

= 41.3790

Issues with method:

- Poor mass intensity
- Use of additives; related expense and toxicity.
- DMF may form an explosive mixture with H_2O_2 on a larger scale causing safety concerns and restricting ability to increase scale.
- DMF can be difficult to remove from the final product.
- Dichloromethane as co-solvent; toxic, regulated by EU solvent directive.
- Catalyst needs to be recycled.

Comparison of reaction metrics for epoxidation

Table 26: Summary of green chemistry metrics and related issues for epoxidation reactions performed on stilbene

Epoxidation reaction conditions	A) mCPBA as oxidant	B) Mn-salen catalyst with sodium hypochlorite	C) Mn-salen catalyst with hydrogen peroxide
Atom economy (%)	55.62	77.05	91.59
Mass intensity	15.59	29.45	41.38
Other issues to be considered	Heat required to maintain operating temperature – energy input required. Chloroform as solvent – carcinogen, restrictions on use. mCPBA is shock sensitive – safety hazard on large scale. Cannot be used to produce one enantiomer over another.	Low operating temperature – varies from -78 ^{o}C to 5 ^{o}C to get good product resolution on commercial scale demanding high energy input to maintain[13] Dichloromethane as solvent – toxic, regulated by EU solvent directive. Catalyst needs to be recycled.	Use of additives – related expense and toxicity. DMF may form explosive mixture with H_2O_2 on larger scale. DMF can be difficult to remove from final product. Dichloromethane as co-solvent – toxic, regulated by EU solvent directive. Catalyst needs to be recycled

References

1. J. Andraos and A. P. Dicks, *Chem. Educ. Res. Pract.*, 2012, **13**, 69 - 67.
2. S. Y. Liu and D. G. Nocera, *Tetrahedron Letters*, 2006, **47**, 1923-1926.
3. C. Jimenez-Gonzalez, D. J. C. Constable and C. S. Ponder, *Chemical Society Reviews*, 2012, **41**, 1485-1498.
4. P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice* Oxford University Press, USA, 2000.
5. T. E. Goodwin, *J. Chem. Educ.*, 2004, **81**, 1187-1190.
6. K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31 - 36.
7. W. Zhang and E. N. Jacobsen, *Journal of Organic Chemistry*, 1991, **56**, 2296-2298.
8. J. Andraos and M. Sayed, *J. Chem. Educ.*, 2007, **84**, 1004 - 1010.
9. M. G. T. C. Ribeiro and A. A. S. C. Machado, *J. Chem. Educ.*, 2011, **88**, 947-953.
10. H. Hibbert and P. Burt, *Organic Syntheses*, 1941, **Coll. Vol. 1**, 494.
11. P. L. Robinson, C. N. Barry, J. W. Kelly and S. A. Evans Jr., *J. Am. Chem. Soc.*, 1985, **107**, 5210-5219.
12. T. Katsuki and K. B. Sharpless, *Journal of the American Chemical Society*, 1980, **102**, 5974-5976.
13. M. Lancaster, *Green Chemistry: An Introductory Text*, Royal Society of Chemistry, 2010.
14. C. H. Senanayake, F. E. Roberts, L. M. DiMichele, K. M. Ryan, J. Liu, L. E. Fredenburgh, B. S. Foster, A. W. Douglas, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Letters*, 1995, **36**, 3993-3996.
15. Y. Gao, Y. Hong, X. Nie, R. P. Bakale, R. R. Feinberg and C. M. Zepp, *US Patent number: 5,616,808 Optically pure 1-amino-2-indanols*, 1997.
16. J. Hanson, *Journal of Chemical Education*, 2001, **78**, 1266-1268.