

The development of novel copper-based catalysts for the oxidative transformation of organic substrates

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Thesis accepted in fulfilment of the requirements for the degree
Doctor of Philosophy in Science with Chemistry at the North-
West University

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Graduation May 2021

23459093

Abstract

A series of novel pyrazolylpyridineimine, (E)-*N*-(2-(1*H*-pyrazol-1-yl)ethyl)-1-(pyridine-2-yl)methanimine (imine-**L01**), (E)-*N*-(2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl)-1-(pyridine-2-yl)methanimine (imine-**L02**), and -amine ligands, 2-(1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L01**), 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L02**), *N*-methyl-2-(1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L03**) and 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-methyl-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L04**) were synthesised through the Schiff base condensation, reductive amination and methylation reaction steps. These ligands were characterised by FT-IR and NMR [^1H and $^{13}\text{C}\{^1\text{H}\}$] spectroscopy as well as APCI mass spectrometry. The (**L01**)/[Cu(MeCN) $_4$]BF $_4$ /CsOH catalyst system was optimised through the evaluation of pyrazolylpyridineamine ligands **L01** to **L04**, Cu $^{\text{I}}$ /Cu $^{\text{II}}$ -precursors and hydroxide bases for the hydroxylation of 4-iodotoluene to *p*-cresol. A shortened induction period was possible with the initial *in situ* formation of the proposed [(**L01**)Cu-OH] intermediate. This resulted in a rapid increase in the conversion during the initial 23 min, while complete conversion to *p*-cresol was obtained within 1 h. Moreover, an excellent turnover number (TON) value of 1952 was obtained when employing the above-mentioned catalyst system for the hydroxylation of 4-iodotoluene at a lower catalyst loading of 0.05 mol%, due to the shortened induction period. This is an improvement on the TON value of 1640 obtained by the benchmark catalyst system. Lastly, moderate to excellent conversions were obtained for the hydroxylation of various aryl iodide and bromide substrates.

The potential application of the pyrazolylpyridineimine (imine-**L01** and imine-**L02**) and -amine ligands (**L01-L04**) was expanded by evaluating them with a Cu $^{\text{I}}$ /Cu $^{\text{II}}$ -precursor and H $_2$ O $_2$ during the optimisation of the (**L03**)CuCl $_2$ ·2H $_2$ O/H $_2$ O $_2$ catalyst system for the peroxidation of various cyclic and linear alkanes. Cyclohexane peroxidation resulted in excellent product yields of > 90 % with an alcohol selectivity of 44 % within 3 h. The rate of cyclohexyl hydroperoxide formation exhibits first-order dependence on [LCu] and [H $_2$ O $_2$] and zero-order dependence on [substrate]. Cyclohexyl ($\cdot\text{Cy}$) and hydroxyl ($\cdot\text{OH}$) radical formation and the nature of the active Cu-based species were investigated by evaluating toluene as substrate or performing the reactions in the presence of radical trapping agents. These results, in combination with the relative ease of C-H bond activation for 2,4-di-*tert*-butylphenol, and the electrochemical studies, support the reversible transformation between Cu $^{\text{II}}$ and Cu $^{\text{I}}$, with the proposed formation of the LCu $^{\text{II}}$ -OOH intermediate, followed by the formation of LCu $^{\text{II}}$ -hydroxyl (LCu $^{\text{II}}$ -OH) and LCu $^{\text{II}}$ -oxyl (LCu $^{\text{II}}$ -O $\cdot$) active species during the rate-determining step. Hydroxyl radicals are involved in the H-atom abstraction step and the reduction of H $_2$ O $_2$ resulted in the regeneration of Cu $^{\text{I}}$ species, which is consistent with the proposed mechanistic pathway.

Novel bifunctional α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene, α,α' -bis[*N*-(2-pyrazolyl)ethylimino]-*m*-xylene (imine-**L05**), α,α' -bis[*N*-(2-(3,5-dimethylpyrazolyl))ethylimino]-*m*-xylene (imine-**L06**), and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene, α,α' -bis[*N*-(2-pyrazolyl)ethylamino]-*m*-xylene (**L05**), α,α' -bis[*N*-(2-(3,5-dimethylpyrazolyl))ethylamino]-*m*-xylene (**L06**), α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene (**L07**) and α,α' -bis[(*N*-methyl-2-(3,5-dimethylpyrazolyl))ethylamino]-*m*-xylene (**L08**) ligands were successfully synthesised and characterised via a similar synthesis route, as indicated above for the pyrazolylpyridineimine and -amine ligands. Experimental evidence supported the bifunctionality of our ligands to accommodate two copper centres. These bifunctional ligands in combination with $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ -precursors and H_2O_2 were evaluated during the optimisation of the (**L05**)[Cu(MeCN)₄]PF₆/H₂O₂ catalyst system for the peroxidation of cyclic and linear alkanes. Remarkable product yields of > 88 % were obtained for cyclohexane peroxidation in 3 h. Reactions were performed in the presence of radical trapping agents, while toluene was also evaluated as substrate. These results, in combination with the first-order dependence on [LCu] and [H₂O₂] and zero-order dependence on [substrate], supported the formation of C-centred and O-centred radical species and the LCu^{II}-OH and LCu^{II}-O[•] species. This is consistent with the findings for the above-mentioned (**L01**)CuCl₂·2H₂O/H₂O₂ catalyst system.

Lastly, the imine-**L01**, imine-**L02** and **L01-L04** ligands, in combination with a $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ -precursor, H_2O_2 and NEt₃, were evaluated as LPMO mimics for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside in H₂O. UV/vis studies were employed to monitor *p*-nitrophenol formation at 405 nm and exceptionally good rate constants of 0.1026 to 0.3588 s⁻¹ were obtained during the initial 0.2 s, while a maximum product yield of 69 % was possible for the [Cu(MeCN)₄]OTf/**L03**/H₂O₂/NEt₃ catalyst system after 15 min at 27 °C. An increase in the absorbance at 375 nm supported the formation of the LCu^{II}-OOH intermediate in the absence of the substrate. Decreased rate constants for *p*-nitrophenyl formation were obtained for reactions performed in the presence of radical trapping agents, supporting the formation of C- and O-centred radical species. The rate of *p*-nitrophenol formation exhibits first-order dependence on [LCu], [H₂O₂], and [substrate], with zero-order dependence on [NEt₃]. These results, in combination with the electrochemical studies, support the oxidation of Cu^I to Cu^{II} due to the formation of the LCu^{II}-OOH intermediate, followed by the formation of LCu^{II}-O[•] and [•]OH radical species for substrate activation. The reduction of H₂O₂ resulted in the regeneration of Cu^I species. Lastly, selectivity towards oxidative cleavage reactions was observed, since the oxidation of primary and secondary alcohols resulted in poor to no conversions.

Keywords: Oxidative transformation, hydroxylation, peroxidation, pyrazolylpyridineamine ligands, bifunctional ligands, lytic polysaccharide monooxygenase (LPMO), mechanistic pathway

Acknowledgements

I thank my Heavenly Father for blessing me in more ways than I could ever deserve. I cherish every moment and opportunity that He has given me, because without His grace and mercy, none of this would be possible.

So many people contributed to my success in completing this degree and in keeping my sanity while doing it. Firstly, I would like to express all my gratitude to my promotor, Prof. Andrew Swarts and Prof. Manie Vosloo for believing in me and allowing me the opportunity to complete this research project under your supervision. Thank you for your mentorship, guidance, incredible scientific contributions and the general support whenever I encountered challenges throughout my studies.

A special thank you to my loving parents, Willie and Susan Marais, for their advice, love, support and encouragement. Thank you for the financial support throughout, for believing in me and helping me to get where I am today. Arlene Marais, thank you for your love and motivation and for being the best sister ever. I am forever grateful to have you all in my life.

I would like to express my deep gratitude towards the Chemical Resource Beneficiation (CRB) and in particular the Catalysis and Synthesis Research Group, for their assistance and laboratory space. To the staff members and the students, thank you for all the scientific discussions and exciting group meetings. I am also grateful for Dr. Johan Jordaan and Dr. Danie Otto from the Laboratory of Analytical Services (LAS) for their assistance with the analytical techniques such as NMR and UV/vis spectroscopy.

My appreciation goes to my lab partner, Tshilidzi Makhado, for her support and assistance with the electrochemical analyses and the interpretation thereof. Tanya Botha, thank you for the great moments we shared, your support and encouragement during our studies. I also thank all my other friends who believed in me and who motivated and supported me when I needed it most. I wish you all success and happiness in whatever you pursue in life.

I also want to thank Mrs. Hestelle Stoppel for her assistance with the administrative matters, technical help, moral support and motivation throughout. Mrs. Cecile van Zyl, thank you for your assistance with the language editing and technicality of the thesis, I appreciate it a lot.

The financial support from the National Research Foundation of South Africa (Unique Grant No. 112545 and 117869) and North-West University is gratefully acknowledged.

Finally, COVID-19 and the nationwide lockdown kept my last year of studies interesting. This won't be forgotten.

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Preface

Format of thesis

The thesis is submitted in article format, as allowed by the North-West University (NWU). Various manuscripts (published and unpublished) have been prepared which form part of the study on the development of copper-based catalysts for oxidative transformation reactions. In addition to these manuscripts, an introduction and problem statement for the study (Chapter 1), the literature study (Chapter 2, review article) and a summary of findings and concluding remarks (Chapter 7) have been included in the thesis. Some of this information has already been presented in the manuscripts, which will result in the repetition of ideas.

According to the Quality Manual 2020 for the Faculty of Natural and Agricultural Sciences at the NWU, the publication of the manuscripts is not a prerequisite for submitting a PhD thesis in article format; however, at least one of the manuscripts should have been accepted for publication. Therefore, the prerequisite of the NWU was exceeded.

Format of numbering and referencing

It should be noted that the formatting, referencing style, the numbering of tables, figures and schemes, re-numbering of the ligands and complexes and the general outline of the manuscripts were adapted to ensure uniformity throughout the thesis. The format of manuscripts which have been submitted and/or published adheres to the author guidelines as stipulated by the editor of each journal and may appear in a different format to what is presented in this thesis. The headings and original technical content of the manuscripts were not modified from the submitted and/or published versions, and only minor spelling and typographical errors were corrected.

Statement from co-authors

To whom it may concern,

The listed co-authors hereby give consent that **Lindie Marais** may submit the following published and unpublished manuscripts as part of her thesis entitled: **The development of novel copper-based catalysts for the oxidative transformation of organic substrates**, for the degree *Philosophiae Doctor in Science with Chemistry*, at the North-West University:

L. Marais, H.C.M. Vosloo and A.J. Swarts. Homogeneous oxidative transformations mediated by copper catalyst systems. *Coord. Chem. Rev.*, **2021**, 440, 213958. DOI: [10.1016/j.ccr.2021.213958](https://doi.org/10.1016/j.ccr.2021.213958)

L. Marais, H.C.M. Vosloo and A.J. Swarts. The development of a Cu(I)/pyrazolylpyridineamine catalyst system for the hydroxylation of aryl halides. *Mol. Catal.*, **2020**, 486, 110839. DOI: [10.1016/j.mcat.2020.110839](https://doi.org/10.1016/j.mcat.2020.110839)

L. Marais, H.C.M. Vosloo and A.J. Swarts. Highly efficient alkane peroxidation mediated by a copper(II)/pyrazolylpyridineamine catalyst system. Manuscript in preparation.

L. Marais, H.C.M. Vosloo and A.J. Swarts. A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions. Manuscript in preparation.

L. Marais, H.C.M. Vosloo and A.J. Swarts. Synthetic LPMO mimics: A copper/pyrazolylpyridineamine catalyst system for the highly efficient oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside. Manuscript in preparation.

The contributions to the manuscripts were as follow: The experimental work and writing of the manuscripts were executed by myself, Lindie Marais, with conceptual ideas, recommendations and corrections by A.J. Swarts (promoter) and H.C.M. Vosloo (co-promoter).

Signed at Potchefstroom

Andrew J. Swarts

Date

Hermanus C.M. Vosloo

Date

Conference contributions

Poster contributions:

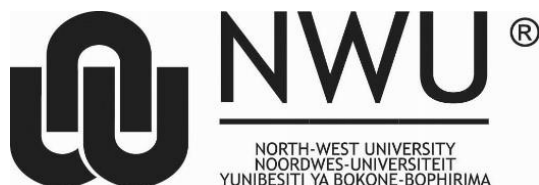
Lindie Marais, H. C. M. Vosloo and A. J. Swarts.

The development of a Cu(I)/alkyl-linked pyrazole-pyridine catalyst system for the hydroxylation of aryl halides. *Proceedings of the Catalysis Society of South Africa (CATSA) conference*, Club Mykonos, Langebaan, November 2019 (*Poster*)

A Cu(I)/alkyl-linked pyrazole-pyridine catalyst system for the hydroxylation of 4-iodotoluene. *Proceedings of the Royal Society of Chemistry (RSC) Twitter conference*, March 2019 (*Poster*)

A Cu(I)/alkyl-linked pyrazole-pyridine catalyst system for the hydroxylation of 4-iodotoluene. *Proceedings of the CATSA conference*, Legends Golf and Safari Resort, Mokopane, November 2018 (*Poster*)

Ethics Certificate



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ETHICS APPROVAL LETTER OF STUDY

Based on the review by the **Faculty of Natural and Agricultural Sciences Ethics Committee (FNAS-REC)**, the Committee hereby clears your study as no ethical risk. This implies that the FNASREC grants permission that, provided the general conditions specified below are met, the study may be initiated, using the ethics number below.

Study title: The development of novel copper-based catalysts for the oxidative transformation of organic substrates

Study Leader/Supervisor: Dr A Swarts

Student: L Marais

Ethics number:

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Institution

Study Number

Year

Status

Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation

No Risk

Application type: Single

Risk Category:

General conditions:

The following general terms and conditions apply:

- The commencement date indicates the date when the study may be started.
- In the interest of ethical responsibility, the NWU-SCRE and FNASREC reserves the right to:
 - request access to any information or data at any time during the course or after completion of the study;
 - to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process;
 - withdraw or postpone approval if:
 - any unethical principles or practices of the study are revealed or suspected;
 - it becomes apparent that any relevant information was withheld from the FNASREC or that information has been false or misrepresented;
 - submission of the annual (or otherwise stipulated) monitoring report, the required amendments, or reporting of adverse events or incidents was not done in a timely manner and accurately; and / or
 - new institutional rules, national legislation or international conventions deem it necessary.
- FNASREC can be contacted for further information or any report templates via Roelof.Burger@nwu.ac.za 018 299 4269

The FNASREC would like to remain at your service as scientist and researcher, and wishes you well with your study. Please do not hesitate to contact the FNASREC or the NWU-SCRE for any further enquiries or requests for assistance.

Yours sincerely,

Prof Roelof Burger

Chairperson Faculty of Natural and Agricultural Sciences Ethics Committee (FNASREC)

List of Abbreviations

ABNO [•]	9-azabicyclo[3.3.1]nonane- <i>N</i> -oxyl
AHBA	Arylhydrazone of barbituric acid
AIE	Aggregation-induced emission
APCI	Atmospheric-pressure chemical ionisation
Ar	Argon
BDPG	<i>N,N</i> -bis-(2-pyridylmethyl)- β -alanineamide
BDE	Bond dissociation energy
BF ₄ ⁻	Tetrafluoroborate anion
BOH	Hydroxide base; B: K, Na, Cs
Bpy	2,2'-bipyridine
Bu ₄ NPF ₆	Tetrabutylammonium hexafluorophosphate
BzO	Benzaldehyde
BzOH	Benzyl alcohol
CAPS	3-(cyclohexylamino)-1-propanesulfonic acid
CBM	Carbohydrate-binding module
CBrCl ₃	Bromotrichloromethane
CCl ₄	Carbon tetrachloride
CHP	Cumene hydroperoxide
ClO ₄	Perchlorate
CsOH	Cesium hydroxide
Cu(acac) ₂	Copper(II) acetylacetonate
Cubpdpo	<i>N,N'</i> -1,3-bis[(pyridine-2-ylmethyl)amino]propan-2-ol copper(II) diperchlorate
[Cu ^I (bpy) ₂] ⁺	Bis(2,2'-bipyridine)copper(I)

List of Abbreviations

CuBr	Copper(I) bromide
CuBr ₂	Copper(II) bromide
CuCl	Copper(I) chloride
Cu(ClO ₄) ₂ ·6H ₂ O	Copper(II) perchlorate hexahydrate
CuI	Copper(I) iodide
[Cu(MeCN) ₄]BF ₄	Tetrakis(acetonitrile)copper(I) tetrafluoroborate
[[Cu(MeCN) ₄]PF ₆	Tetrakis(acetonitrile)copper(I) hexafluorophosphate
CuNCs	Copper nanoclusters
Cu(NO ₃) ₂ ·2.5H ₂ O	Copper(II) nitrate hydrate
CuO	Copper(II) oxide
Cu ^{II} -O·	Cu ^{II} -oxyl
Cu ^{II} -OO·	Cu ^{II} -superoxo
Cu ^{II} -OH	Cu ^{II} -hydroxo
Cu ^{II} -OOH	Cu ^{II} -hydroperoxo
Cu ₄ O ₄	Cubane core
Cu(OAc) ₂ ·2H ₂ O	Copper(II) acetate dihydrate
Cu(OH) ₂	Copper(II) hydroxide
Cu(OTf) ₂	Copper(II) triflate
Cu(salen)	<i>N,N'</i> -(1,2-ethylene)-bis(salicylaldamine)-copper(II)
CuSO ₄ ·5H ₂ O	Copper(II) sulfate pentahydrate
Cu ₂ bpdbo	<i>N,N'</i> -{bis(2-pyridylmethyl)-1,4-diaminobutan-2-ol}ato dicopper(II) (μ-acetato) diperchlorate
Cu ₂ bpdpo	<i>N,N'</i> -{1,3-bis[(pyridine-2-ylmethyl)amino]propan-2-ol}ato dicopper(II) (μ-acetato) diperchlorate

List of Abbreviations

Cu ₂ EGbsdpo	{ <i>N,N'</i> -1,3-bis[{2-hydroxy-4-(2-methoxyethoxy)}benzylideneamino]propan-2-ol}ato dicopper(II) (μ-acetato)
Cu ₂ TEGbsdpo	<i>N,N'</i> -{1,3-bis[{2-hydroxy-4-[2-(2-methoxyethoxy)-ethoxyl]ethoxy}benzylideneamino]-propan-2-ol}ato dicopper(II) (μ-acetate)
Cu ₂ VBbpdpo	<i>N,N'</i> -{bis((3-(4-vinylbenzyloxy)-2-pyridylmethyl)-1,3-diaminopropan-2-ol}ato dicopper(II) (μ-acetato) diperchlorate
Cu ₂ VBbsdpo	<i>N,N'</i> -{1,3-bis[(2-hydroxy-4-(p-vinylbenzyloxy))-benzylideneamino]-propan-2-ol}ato dicopper(II) (μ-acetate)
CV	Cyclic voltammetry
•Cy	Cyclohexyl radical
CyO	Cycloketone
CyOH	Cycloalcohol
CyOO•	Cycloalkyl hydroperoxo radical
CyOOH	Cycloalkyl hydroperoxide
DAB	1,4-diaminobutane
DBADH ₂	Di- <i>tert</i> -butylazodicarboxylic acid
DCM	Dichloromethane
DFT	Density functional theory
DMAP	Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
EDTA	Ethylenediaminetetraacetic acid
E _{pa}	Electrochemical potential of the anodic peak
E _{pc}	Electrochemical potential of the cathodic peak
EPR	Electron paramagnetic resonance spectroscopy
FT-IR	Fourier-transform Infrared spectroscopy
Gal	Galactose

List of Abbreviations

GC	Gas chromatography
GC-MS	Gas chromatography mass spectrometry
GH	Glycoside hydrolase
Glu	Glucose
GOase	Galactose oxidase
H ₂ bdca	4,4'-biphenyldicarboxylic acid
H ₂ bdea	<i>N</i> -butyldiethanolamine
H ₂ O ₂	Hydrogen peroxide
H ₂ pmal	Phenylmalonic acid
H ₂ sal	Salicylic acid
H ₂ SO ₄	Sulphuric acid
H ₄ edte	<i>N,N,N',N'</i> -tetrakis(2-hydroxyethyl)ethylenediamine
Haca	9-anthracenecarboxylic acid
Hbdea	<i>N</i> -butyldiethanolamine
Hbdca	4,4'-biphenyldicarboxylic acid
HCl	Hydrochloric acid
Hhba	4-hydroxybenzoic acid
HNO ₃	Nitric acid
Im	Imidazole
IMes	<i>N,N'</i> -bis-[2,4,6-(trimethyl)phenyl]imidazol-2-ylidene
E _{pa}	Electrochemical current of the anodic peak
E _{pc}	Electrochemical current of the cathodic peak
IPr	<i>N,N'</i> -bis[2,6-(di- <i>iso</i> -propyl)phenyl]imidazol-2-ylidene
<i>K</i> _{obs}	Rate constant
KHSO ₅	Potassium peroxymonosulfate

List of Abbreviations

KI	Potassium iodide
KOH	Potassium hydroxide
K ₂ CO ₃	Potassium carbonate
L01	(E)- <i>N</i> -(2-(1 <i>H</i> -pyrazol-1-yl)ethyl)-1-(pyridine-2-yl)methanimine
L02	(E)- <i>N</i> -(2-(1 <i>H</i> -pyrazol-1-yl)ethyl)-1-(pyridine-2-yl)methanimine
L03	2-(1 <i>H</i> -pyrazol-1-yl)- <i>N</i> -(pyridine-2-ylmethyl)ethan-1-amine
L04	2-(3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)- <i>N</i> -(pyridine-2-ylmethyl)ethan-1-amine
L05	<i>N</i> -methyl-2-(1 <i>H</i> -pyrazol-1-yl)- <i>N</i> -(pyridine-2-ylmethyl)ethan-1-amine
L06	2-(3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)- <i>N</i> -methyl- <i>N</i> -(pyridine-2-ylmethyl)ethan-1-amine
L07	α,α'-bis[<i>N</i> -(2-pyrazolyl)ethylimino]- <i>m</i> -xylene
L08	α,α'-bis[<i>N</i> -(2-(3,5-dimethylpyrazolyl))ethylimino]- <i>m</i> -xylene
L09	α,α'-bis[<i>N</i> -(2-pyrazolyl)ethylamino]- <i>m</i> -xylene
L10	α,α'-bis[<i>N</i> -(2-(3,5-dimethylpyrazolyl))ethylamino]- <i>m</i> -xylene
L11	α,α'-bis[(<i>N</i> -methyl-2-pyrazolyl)ethylamino]- <i>m</i> -xylene
L12	α,α'-bis[(<i>N</i> -methyl-2-(3,5-dimethylpyrazolyl))ethylamino]- <i>m</i> -xylene
L_A	Ligands for alcohol oxidation with O ₂
L_B	Ligands for hydroxylation reactions
L_C	Ligands for peroxidation reactions
L_D-L_G	Ligands for oxidative cleavage reactions with O ₂ as oxidant
L_H	Ligands for oxidative cleavage reactions with H ₂ O ₂ as oxidant
LiOH·H ₂ O	Lithium hydroxide monohydrate
LMCT	Ligand-to-metal charge transfer
LPMO	Lytic polysaccharide monooxygenase
MeCN	Acetonitrile
MS	Mass spectrometry

List of Abbreviations

ms	Molecular sieves
$n\text{-Bu}_4\text{NOH}\cdot 5\text{H}_2\text{O}$	Tetrabutylammonium hydroxide pentahydrate
N_2	Nitrogen
NaBH_4	Sodium borohydride
NaIO_4	Sodium periodate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NEt_3	Triethylamine
NHE	Normal hydrogen electrode
NH_2NH_2	Hydrazine hydrate
NHC(s)	<i>N</i> -heterocyclic carbene(s)
NMI	<i>N</i> -methylimidazole
NMR	Nuclear magnetic resonance
O_2	Molecular oxygen
$\cdot\text{OH}$	Hydroxyl radical
OTf	Triflate
PAA	Peroxyacetic acid
PC	Phthalocyanines
PCET	Proton-coupled electron transfer
PhX	Aryl halide
PF_6^-	Hexafluorophosphate anion
Pol	Polymeric
PPh_3	Triphenylphosphine
PPI	Poly(propylene-imine)

List of Abbreviations

Pt	Platinum
Py ₂ SSPy ₂	Bis{2-[<i>N,N</i> -bis(2-pyridylethyl)amino]-1,1-dimethylethyl} disulphide
Pz	Pyrazolate
·R	Substrate radical
R ¹ -dtpy	Furan-2-yl; 2,6-di(thiazol-2-yl)pyridine derivative
ROH	Alcohol
R=O	Aldehyde
ROOH	Peroxide
ROS	Reactive oxygen species
(<i>R,R</i>)-BPBP	(2 <i>R</i> ,2 <i>R'</i>)-1,1'-bis(2-pyridinylmethyl)-2,2'-bipyrrolidine
SIMes	<i>N,N'</i> -bis[2,4,6-(trimethyl)phenyl]-imidazolidin-2-ylidene
SIPr	<i>N,N'</i> -bis[2,6-(di- <i>iso</i> -propyl)phenyl]imidazolidin-2-ylidene
<i>t</i> -BuOH	<i>tert</i> -butanol
TBAB	Tetrabutylammonium bromide
TBHP	<i>tert</i> -butyl hydroperoxide
TEA	Triethanolamine
TEMPO·	2,2,6,6-tetramethylpiperidine- <i>N</i> -oxyl
TFA	Trifluoroacetic acid
TMA	Trimethyl acetate
TPMA	Tris(2-pyridylmethyl)-amine
TOF	Turnover frequency
TON	Turnover number
Tp	Hydrotrispyrazolylborate
UV/vis	Ultraviolet-visible spectroscopy

1.1 Literature background

Oxygenated products such as alcohols, ketones and aldehydes are valuable and important intermediates in the pharmaceutical and chemical industries. Previously, the Hock and Dow processes, the non-oxidative Sandmeyer reaction, nucleophilic aromatic substitution and oxidation reactions were employed for the synthesis of these oxygenates. However, these synthesis methods lead to low product yields and poor selectivity due to the need for harsh reaction conditions such as high temperatures, the inclusion of expensive catalysts or strong oxidants, and an inert atmosphere during the reactions. These drawbacks resulted in the growing demand to develop alternative synthesis methods of which one is *via* the oxidative transformation of a series of organic substrates. Initially, the focus was on various transition metals, as precursors, but the advantages of lower toxicity and higher economic benefits of copper metal have led to the development of several Cu-based catalyst systems to afford the oxygenated products.

Much work has been done to develop Cu-based catalytic oxidation systems to understand the functionality of natural enzymes, such as galactose oxidase (GOase), by mimicking the active sites during oxidation reactions. The active sites of GOase consist of a copper centre in combination with a redox active phenolate/phenoxy radical ligand [1]. The alcohol substrate then coordinates to the active site with a resulting hydrogen abstraction step to afford the aldehyde product. The ability to mimic the geometries of the Cu-based active site, with the radical co-catalyst, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO[•]), has led to the development of a number of Cu/TEMPO[•] catalyst systems for the oxidation of alcohols to the corresponding aldehyde products [2-7]. However, the bulky structure of TEMPO[•] hinders the approach of the alcohol substrate to coordinate with the active copper centre, and therefore limits the substrate scope to primary alcohols. Stahl and co-workers replaced TEMPO[•] with a sterically smaller 9-azabicyclo[3.3.1]nonane-*N*-oxyl (ABNO[•]) co-catalyst, thereby expanding the substrate scope to primary and secondary alcohols [8]. Unfortunately, both of these co-catalysts are very expensive and resulted in the development of Cu-based catalyst systems for different oxidative transformation reactions, which can operate in the absence of an *N*-oxide co-catalyst.

Oxidative transformation reactions include *N*-oxide co-catalyst-free oxidation, hydroxylation and peroxidation reactions, as well as Cu-based lytic polysaccharide monooxygenase (LPMO) mimics for oxidative cleavage reactions to afford the oxygenated products. These reactions involve an H-atom abstraction step or the substitution of either a halogen (-X) or hydrogen (-H) atom with a hydroperoxide (-OOH) or a hydroxyl (-OH) group using a Cu-based pre-catalyst in combination with a hydroxide base or an oxidant such as H₂O₂. Alternatively, Cu-

based catalyst systems are also employed as LPMO mimics for the oxidative cleavage of recalcitrant polysaccharides in the presence of H_2O_2 as the oxidant.

Several Cu-based catalyst systems have been reported for the oxidation of primary and secondary alcohols in the absence of an *N*-oxide radical co-catalyst. Either O_2 (aerobic oxidation) or peroxides such as H_2O_2 or *tert*-butyl hydroperoxide (TBHP; peroxidative oxidation) may be employed as the oxidant [9]. However, these catalyst systems are usually limited to the oxidation of activated alcohols such as allylic and benzylic alcohols. The hydroxyl groups of these alcohols are better leaving groups and the resulting carbocation is resonance-stabilised, thereby promoting the reactivity of activated alcohols during oxidation reactions. Unfortunately, this does not form part of the scope of this study, but will be kept in mind for future investigations.

Cu-based catalyst systems have also been employed for the hydroxylation of aryl halides to afford the resulting phenolic products. However, these catalyst systems usually require high catalyst loadings, extremely high reaction temperatures and an inert atmosphere. Cazin and co-workers improved on these drawbacks by decreasing the catalyst loading for their $[\text{CuCl}(\text{SIPr})]/\text{CsOH}$ catalyst system (SIPr: (*N,N'*-bis[2,6-(*di-iso*-propyl)phenyl]imidazolidin-2-ylidene) during the hydroxylation of iodobenzene, and they obtained turnover numbers (TON) of 1640 [10]. However, their catalyst system still requires an inert atmosphere and a temperature of 130 °C for successful conversions.

The focus of recent research efforts have been on the inclusion of copper as metal precursor, due to its lower toxicity, with H_2O_2 as oxidant for the peroxidation of cycloalkanes to the corresponding cycloalkyl hydroperoxide, alcohol and ketone products. Previous catalyst systems resulted in low product yields, while high reaction temperatures and the addition of additives are often required. The current benchmark catalyst system for cyclohexane peroxidation was reported by Garcia-Bosch and co-workers, which showed remarkable efficiency, alcohol selectivity and a product yield of 56 % [11]. Furthermore, previous studies have shown that the reversible transformation of the copper oxidation states and a sufficient amount of initial H_2O_2 determine the preferred mechanistic pathway [11-14]. However, due to the lack in experimental proof for these copper oxidation states, the need to further investigate the mechanistic pathway for hydrocarbon peroxidation reactions arises.

Cu-based catalyst systems can also serve as LPMO mimics during the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside to afford *p*-nitrophenol and D-allose as products, using H_2O_2 as the oxidant. These mononuclear enzymes consist of an unusual surface-exposed active site, which is coordinated to the copper centre for substrate activation. Mayilmurugan and co-workers reported on the combination of Cu^{II} complexes, consisting of copper(II)

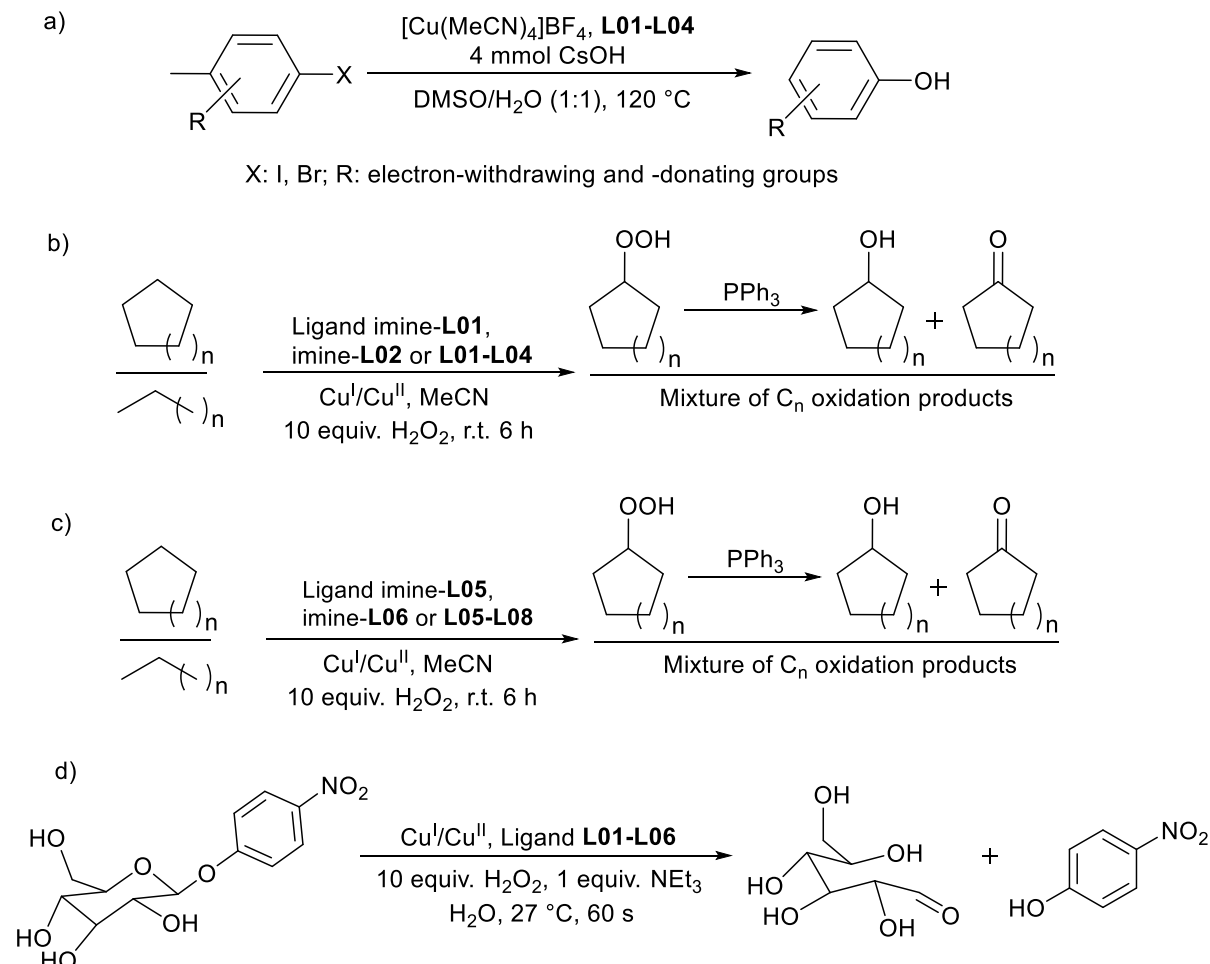
perchlorate hexahydrate ($\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$) and pyridinoyl-substituted cyclic 1,4-diazepane 3*N*-ligands, with H_2O_2 and NEt_3 for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside [15]. They obtained rate constants of 1.61 ± 0.2 to $9.06 \pm 0.1 \times 10^{-3} \text{ s}^{-1}$ for *p*-nitrophenol formation while a maximum isolated yield of 78 % (reported TON: 300, actual TON: 63) was possible in 2 h at 60 °C. The current state-of-the-art Cu-based catalyst system, for the oxidative cleavage of *p*-nitrophenyl-derivatised glucose and galactose mono- and disaccharides, was recently reported by Cowen and co-workers [16]. They employed mono-, bi- and tetranuclear Cu^{II} complexes, bearing a di(2-picoly)amine ligand and rate constants of 0.3 to 0.56 min^{-1} were obtained for monosaccharide substrates using the mononuclear Cu^{II} complex. A two-fold increase in the rate constant was observed for disaccharide substrates (1.1 to 1.4 min^{-1}), while a further increase was obtained when employing the tetranuclear Cu^{II} complexes (3.0 to 15.3 min^{-1}). Only a few Cu-based LPMO mimics have recently been developed for oxidative cleavage of recalcitrant polysaccharide substrates. However, these catalyst systems still require elevated reaction temperatures, while the addition of additives are required in some cases.

In conclusion, a variety of Cu-based catalyst systems have previously been reported for the above-mentioned oxidative transformation reactions to afford the respective oxygenated products. However, the need still exists to develop Cu-based catalyst systems with the inclusion of novel and efficient ligand sets for the oxidative transformation of organic substrates that can operate under mild reaction conditions, open to air and result in excellent product yields and product selectivity. I envisage that the nature of the ligands as well as the oxidation state of the copper metal centre will have an effect on the reactivity of the *in situ* formed pre-catalysts for these oxidative transformation reactions.

1.2 Aims of the study

With the focus on the development of novel Cu-based catalyst systems for oxidative transformation reactions, in the absence of an *N*-oxide radical co-catalyst, I propose several catalyst systems for the hydroxylation of aryl halides, peroxidation of cyclic and linear alkanes and to serve as LPMO mimics for the oxidative cleavage of polysaccharides, under ambient air (Scheme 1.1). These catalyst systems involve the inclusion of a $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ -precursor in combination with a pyrazolylpyridineimine (imine-**L01** and imine-**L02**), -amine (**L01-L04**), α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene (imine-**L05** and imine-**L06**) or α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene (**L05-L08**) ligand and a hydroxide base or H_2O_2 as the oxidant. These ligands include imine groups or substituents on either the pyrazole ring or the ethyl-linked *N*-atom and they may accommodate one or two copper centres during the *in situ* formation of the pre-catalysts. The aim is to determine the effect of substituents on the

two ligand sets, the difference between tridentate and *m*-xylene bridged ligands, as well as varying nuclearity of the pre-catalysts on the various oxidative transformation reactions. Furthermore, the improvement of the product yields, at low catalyst loadings, ambient temperatures and open to air is of importance in this study.



Scheme 1.1: A summary of the Cu-based catalyst systems that will be optimised for the various oxidative transformation reactions. This study will focus on the hydroxylation of aryl halides (a), peroxidation of cyclic and linear alkanes (b and c) and the oxidative cleavage of polysaccharides (d).

1.3 Objectives

The objectives for this study include:

- The synthesis and characterisation of the novel pyrazolylpyridineimine, -amine, α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene ligand frameworks. Different spectroscopic and analytical techniques were employed during the characterisation of these novel ligands.

- The novel ligand sets, in combination with copper precursors, were evaluated during the optimisation of alternative catalyst systems for the hydroxylation of aryl halides, the peroxidation of cyclic and linear alkanes and to serve as LPMO mimics for the oxidative cleavage of polysaccharides (Scheme 1.1).
- The optimisation of these Cu-based catalyst systems includes the evaluation of the effect of mono- and bifunctional ligands, Cu^I/Cu^{II}-precursors, pre-catalyst concentration, oxidant concentration and substrate concentration.
- Oxidative transformation reactions were also performed in the presence of radical trapping agents to evaluate the effect of radical species on the efficiency of the reaction and to investigate the nature of active metal species.
- Kinetic studies were performed and the effect of the initial concentration of various reaction parameters on the rate of product formation was evaluated.
- The substrate scope of these Cu-based catalyst systems were also investigated.
- Lastly, the proposed mechanistic pathways for these oxidative transformation reactions were assessed.

1.4 Outline of thesis

The development of Cu-based catalyst systems for the oxidative transformation of organic substrates, in the absence of a radical co-catalyst, are highlighted in the review article in **Chapter 2**. Oxidative transformation reactions include *N*-oxide co-catalyst-free alcohol oxidation, the hydroxylation of aryl halides, peroxidation of cyclic and linear alkanes as well as Cu-based LPMO mimics for the oxidative cleavage of recalcitrant polysaccharides. Specifically the differences, advantages and disadvantages for the various Cu-based catalyst systems are reported. Furthermore, the effects of the nature of the ligand and copper oxidation states on the efficiency of these reactions are investigated. Lastly, the mechanistic aspects of the oxidative transformation reactions are discussed.

Chapter 3, a peer-reviewed article, involves the evaluation of novel pyrazolylpyridineamine ligands, in combination with a Cu-precursor and CsOH, during the optimisation of the (L01)[Cu(MeCN)₄]BF₄/CsOH catalyst system for the hydroxylation of aryl halides. The effects of the optimised reaction conditions and the initial *in situ* formation of a [(L01)Cu-OH] intermediate on the hydroxylation of 4-iodotoluene to *p*-cresol are evaluated. Lastly, the substrate scope was investigated by evaluating different aryl iodides and bromides.

The application of the pyrazolylpyridineimine and -amine ligands, in combination with a copper precursor and H₂O₂, for the peroxidation of various cyclic and linear alkanes are reported in the manuscript in **Chapter 4**. Kinetic studies are performed to evaluate the effect of initial

concentrations of **LCu**, H_2O_2 and substrate on the rate of cyclohexyl hydroperoxide formation. Various experimental methods, such as the addition of radical trapping agents and the evaluation of toluene as substrate, are employed to determine the effect of radical species on the peroxidation reaction and to investigate the nature of the active Cu-based intermediates. The reversible transformations of the oxidation state of copper, the effect of various pyrazolylpyridineimine and -amine ligands as well as added H_2O_2 on the redox potentials are investigated using cyclic voltammetry. Lastly, the obtained experimental results are employed to propose a plausible mechanistic pathway for hydrocarbon peroxidation reactions.

The manuscript in **Chapter 5** involves the synthesis, characterisation and evaluation of novel α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene and α,α' -bis[(*N*-methyl-2-pyrazolyl)-ethylamino]-*m*-xylene ligands, in combination with a copper precursor and H_2O_2 , during cyclohexane peroxidation. The peroxidation of various cyclic and linear alkanes are also evaluated. Kinetic assessments are done to determine the effect of the initial concentrations of **LCu**, H_2O_2 and substrate on the rate of cyclohexyl hydroperoxide formation. Radical formation and the nature of the active metal species are investigated using various experimental methods, such as the addition of radical trapping agents or by employing toluene as the substrate.

The development of a Cu-based catalyst system that can serve as an LPMO mimic for the oxidative cleavage of recalcitrant polysaccharides are described in the manuscript in **Chapter 6**. The pyrazolylpyridineimine and -amine ligands, in combination with a copper precursor, H_2O_2 and NEt_3 , are evaluated for the oxidative cleavage of *p*-nitrophenol- β -D-glucopyranoside. UV/vis spectroscopic studies are employed to monitor the kinetics and conversions of the reaction in water and the absorption band for the formation of *p*-nitrophenol at 405 nm is followed. UV/vis studies are also employed to provide evidence for the presence of the **LCu^{II}**-OOH intermediate (absorbance at 375 nm) in the absence of the substrate. The effect of radical trapping agents on the rate of product formation supports the formation of both C- and O-centred radical species. Electrochemical studies are employed to evaluate the effect of scan rates, varying pyrazolylpyridineimine and -amine ligands and the addition of NEt_3 and H_2O_2 on the redox potentials. These experimental results are employed to identify the optimal mechanistic pathway for the **(L03)** $[\text{Cu}(\text{MeCN})_4]\text{OTf}/\text{H}_2\text{O}_2/\text{NEt}_3$ catalyst system. Lastly, the selectivity of the Cu-based catalyst system towards oxidative cleavage reactions is evaluated.

Concluding remarks related to this study, which is focused on oxidative transformation reactions, my scientific contributions as well as recommendations for future work, are reported in **Chapter 7**.

1.5 References

- [1] B. Xu, J.P. Lumb, B.A. Arndtsen, *Angew. Chem. Int. Ed.*, 54 (2015) 4208-4211.
 - [2] A. Dijksman, I.W.C.E. Arends, R.A. Sheldon, *Org. Biomol. Chem.*, 1 (2003) 3232-3237.
 - [3] E.T. Kumpulainen, A.M. Koskinen, *Chem. Eur. J.*, 15 (2009) 10901-10911.
 - [4] J.M. Hoover, S.S. Stahl, *J. Am. Chem. Soc.*, 133 (2011) 16901-16910.
 - [5] L. Wang, Z. Bie, S. Shang, Y. Lv, G. Li, J. Niu, S. Gao, *RSC Adv.*, 6 (2016) 35008-35013.
 - [6] L. Marais, J. Bures, J.H.L. Jordaan, S. Mapolie, A.J. Swarts, *Org. Biomol. Chem.*, 15 (2017) 6926-6933.
 - [7] T.F. Silva, L.M. Martins, *Molecules*, 25 (2020) 748.
 - [8] J.E. Steves, S.S. Stahl, *J. Am. Chem. Soc.*, 135 (2013) 15742-15745.
 - [9] R. Trammell, K. Rajabimoghadam, I. Garcia-Bosch, *Chem. Rev.*, 119 (2019) 2954-3031.
 - [10] O. Songis, P. Boulens, C.G. Benson, C.S. Cazin, *RSC Adv.*, 2 (2012) 11675-11677.
 - [11] I. Garcia-Bosch, M.A. Siegler, *Angew. Chem. Int. Ed.*, 55 (2016) 12873-12876.
 - [12] M.V. Kirillova, A.M. Kirillov, M.F.C. Guedes da Silva, A.J.L. Pombeiro, *Eur. J. Inorg. Chem.*, 2008 (2008) 3423-3427.
 - [13] G.B. Shul'pin, J. Gradinaru, Y.N. Kozlov, *Org. Biomol. Chem.*, 1 (2003) 3611-3617.
 - [14] G.B. Shul'pin, G.V. Nizova, Y.N. Kozlov, L. Gonzalez Cuervo, G. Süss-Fink, *Adv. Synth. Catal.*, 346 (2004) 317-332.
 - [15] S. Muthuramalingam, D. Maheshwaran, M. Velusamy, R. Mayilmurugan, *J. Catal.*, 372 (2019) 352-361.
 - [16] Z. Yu, Z. Thompson, S.L. Behnke, K.D. Fenk, D. Huang, H.S. Shafaat, J.A. Cowan, *Inorg. Chem.*, 59 (2020) 11218-11222.
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Homogeneous oxidative transformations mediated by copper catalyst systems

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Highlights

- State of the art copper-catalysed oxidative transformations is described.
- Hydroxylation, peroxidation and oxidative cleavage reactions are reviewed as radical co-catalyst-free transformations.
- Key differences in the mechanistic pathways are discussed with insights from experimental and theoretical aspects.

Oxidative transformations involve the conversion of organic substrates through various processes to obtain oxygenated products such as alcohols, ketones and aldehydes, which can be used in the pharmaceutical and chemistry industries. These reactions include, but are not exclusive to, the radical co-catalyst-free oxidation of activated alcohols, hydroxylation of aryl halides, peroxidation of hydrocarbons, and lastly, lytic polysaccharide monooxygenase (LPMO) mimics for oxidative cleavage of polysaccharides. The lower toxicity of copper as a metal pre-catalyst, has received considerable attention during the development of various catalyst systems to generate oxygenates. The mechanistic pathway for these Cu-based catalyst systems has been investigated, and the major differences involve the initial oxidation state of copper, the reversibility of the transformation of these oxidation states, and the nature of the Cu-based active species. Herein, we discuss the development and the mechanistic pathways for the oxidative transformation reactions.

Keywords: oxidative transformations, oxidation, hydroxylation, peroxidation, lytic polysaccharide monooxygenase (LPMO), copper catalysis, mechanistic pathways.

2.1 Introduction

Oxygenates such as alcohols, ketones and aldehydes are high-value building blocks in the pharmaceutical and chemical industries. Several methods have been developed to prepare these oxygenated products from various organic substrates. The initial focus was on the application of a variety of transition metals as pre-catalysts for oxygenate syntheses. Copper has emerged as a pre-catalyst of choice due to its low economic cost, low toxicity and widespread availability in nature [1, 2].

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Cu-based catalyst systems have provided key insights into the understanding of natural enzymes such as galactose oxidase (GOase), a type-II mononuclear Cu-based enzyme for aerobic alcohol oxidation to afford the corresponding aldehydes [3, 4]. The ability to mimic the Cu-based active centre of the enzyme by the interaction with the radical co-catalyst, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO[•]), led to the development of several promising Cu-based homogeneous catalyst systems. The inclusion of the radical co-catalyst, similar to the radical ligand of the enzyme, is important for optimal activity with these catalyst systems, and it can either be added intentionally, such as TEMPO[•] or created *in situ* during the reaction.

A number of Cu/TEMPO[•] catalyst systems have been reported for the aerobic oxidation of alcohols to the corresponding aldehydes [5-11]. The high cost and bulky structure of TEMPO[•] and the preference for primary over secondary alcohols led to further investigations to replace TEMPO[•] with a sterically smaller co-catalyst such as 9-azabicyclo[3.3.1]nonane-*N*-oxyl (ABNO[•]) [12]. Even though the oxidation of both primary and secondary alcohols was possible, ABNO[•] is more expensive. As such, the development of Cu-based catalyst systems for alcohol oxidation in the absence of an *N*-oxide co-catalyst is of importance in an attempt to overcome the above-mentioned drawbacks for GOase mimics (see Section 2.2.1).

Phenolic compounds were initially synthesised through the decomposition of cumene hydroperoxide (CHP), mediated by sulphuric acid (Hock process), and the reaction between benzene and a hydroxide base to afford a phenoxide salt, followed by the acidification thereof (Dow process) [13]. The non-oxidative Sandmeyer and nucleophilic aromatic substitution reactions were also employed in later years [14-17]. Several limitations such as ineffective energy use and harsh reaction conditions are, however, associated with these synthesis methods, which results in low product yields and poor selectivity. Another alternative synthesis method that has received great attention is the hydroxylation of aryl halides to afford oxygenated compounds. Even though several late-transition metals have initially been employed as catalysts, copper as a catalyst has a high potential interest due to its lower toxicity and better product selectivity during the reaction (see Section 2.2.2).

Oxygenated compounds could also be obtained through the oxidative cleavage of recalcitrant polysaccharides. Several Cu-based catalyst systems have been reported to mimic the active site of lytic polysaccharide monooxygenases (LPMOs). The generation of an active Cu-based species during the reaction is responsible for the H-atom abstraction from the substrate, followed by substrate hydroxylation [18-22]. Moreover, oxidative cleavage as synthesis method has not yet received much attention, since the first Cu-based catalyst system was only reported in 2010 [23]. As such, the opportunity arises to develop an optimal Cu-based LPMO

mimic for the oxidative cleavage of polysaccharides under ambient reaction conditions (see Section 2.2.4).

Lastly, oxygenates can be obtained by the peroxidation of hydrocarbons, but these reactions usually require harsh reaction conditions and high economic costs, which lead to low product yields and low selectivity. Various Cu-based catalyst systems have recently been reported for these reactions, but they still suffer from the aforementioned drawbacks (see Section 2.2.3) [24-28]. This review provides a critical assessment of copper-based oxidative transformations to afford oxygenates as well as the proposed mechanistic pathways for these reactions. Alternative oxidants and the employment of other transition metals as pre-catalysts are mentioned, but not discussed in detail.

2.2 Cu-based oxidative transformation reactions

The oxidative transformation of organic substrates include the aerobic oxidation of primary and secondary alcohols, hydroxylation of aryl halides and the peroxidation of hydrocarbons. These reactions involve an H-atom abstraction step or the substitution of either a halogen (-X) or hydrogen (-H) atom with a hydroperoxide (-OOH) or a hydroxyl (-OH) group. The reaction occurs in the presence of a Cu-based pre-catalyst in combination with a hydroxide base or an oxidant, such as H_2O_2 . Alternatively, Cu-based catalyst systems that can serve as LPMO mimics are also employed for the oxidative cleavage of recalcitrant polysaccharides in the presence of an oxidant such as molecular oxygen (O_2) or H_2O_2 . The development of these Cu-catalysed oxidative transformations is discussed in the following sub-sections.

2.2.1 N-oxide radical co-catalyst-free oxidation reactions

The oxidation of primary and/or secondary alcohols is important since it affords the corresponding aldehydes and ketones, which can be employed in the pharmaceutical industry or as intermediates for fine chemistry [7, 29, 30]. An optimal catalyst system will involve low O_2 pressures or low amounts of peroxide (ROOH) as the oxidant, mild reaction conditions with a preference of room temperature, low catalyst loadings and in the absence of costly or toxic additives as co-catalysts. Several transition metals such as platinum, vanadium, nickel, ruthenium, chromium, manganese and iron have been employed in the oxidation of alcohols, operating under the above-mentioned conditions [31-41]. However, the inclusion of copper as a metal pre-catalyst has attracted interest, even though fewer studies have recently been reported for Cu-based catalyst systems where either O_2 (aerobic oxidation) or peroxides (peroxidative oxidation) were employed as the oxidant [20]. The aerobic oxidation involves oxidative dehydrogenation catalysed by late-transition metals, while the peroxidative alcohol

oxidation involves an early transition metal with a high oxidation state and the formation of active peroxymetal species [10]. These oxidation methods are described in the next sub-sections.

2.2.1.1 Alcohol oxidation with molecular oxygen

Several studies have previously focused on the aerobic oxidation of alcohols, using a Cu/TEMPO[•] catalyst system, which can serve as a GOase mimic. However, these catalyst systems have a limited substrate scope as well as a preference for primary over secondary alcohols. As such, other sterically less demanding *N*-oxide co-catalysts were also evaluated during the oxidation reactions in an attempt to improve on the substrate scope [12, 42]. Even though these co-catalysts revealed improved catalytic efficiency, they are also the most expensive component of the catalyst system. The focus in this sub-section is on the catalyst systems that can operate in the absence of an *N*-oxide co-catalyst such as TEMPO[•], by employing O₂ as the oxidant while forming H₂O and H₂O₂ as by-products [10]. These aerobic alcohol oxidation reactions involve two half-reactions; the oxidation of alcohols to aldehydes or ketones, and the reduction of O₂ to H₂O₂. Unfortunately, these *N*-oxide-free catalyst systems are usually limited to activated alcohols and they require higher temperatures and high O₂ pressures [43].

One of the first *N*-oxide-free catalyst systems was reported by Stack and co-workers in 1998 [44]. They employed Cu^{II}-complexes, such as **C2.1** (Figure 2.1), bearing a multi-functional ligand with a bidentate *N*-atom unit, a phenyl group as well as a TEMPO[•] moiety, during the oxidation of primary alcohols. Their catalyst system could still serve as a GOase mimic, even though no *N*-oxide co-catalyst, similar to the radical ligand of the enzyme, was present.

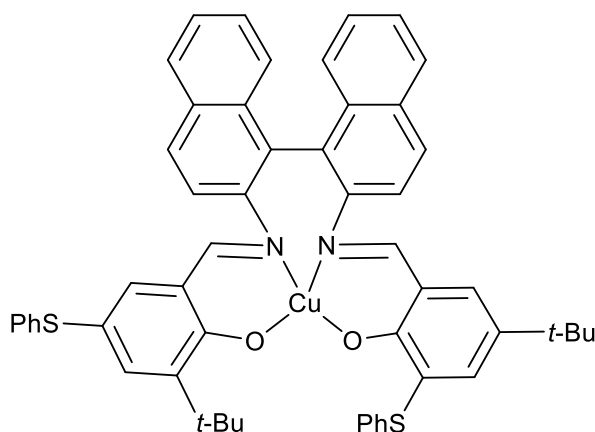
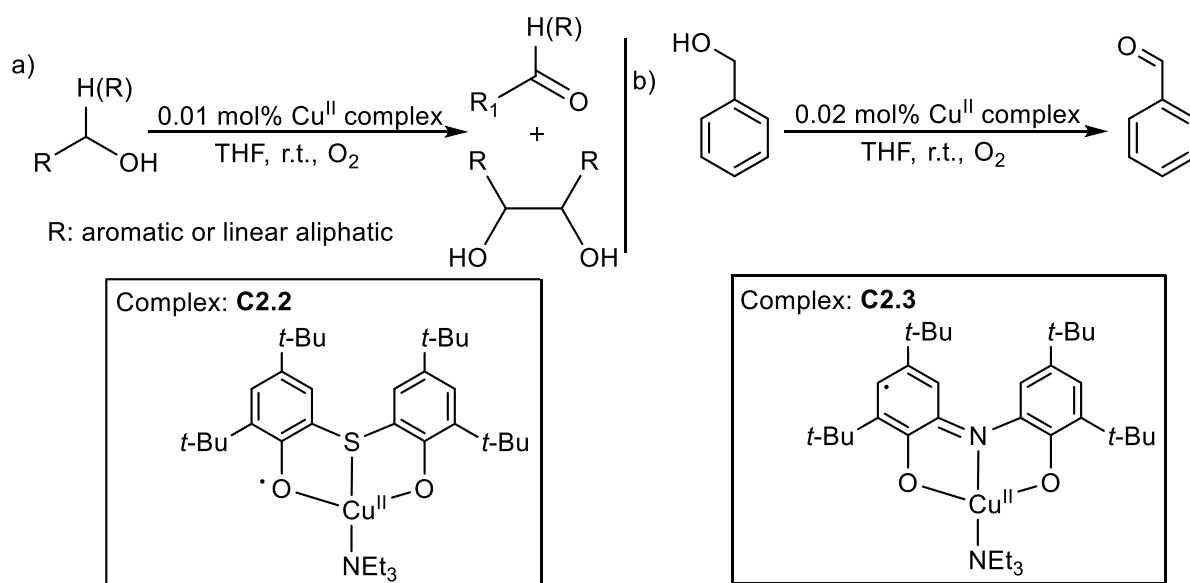


Figure 2.1: The application of the Cu^{II} complex, **C2.1**, in the absence of an *N*-oxide co-catalyst for the oxidation of alcohols [44].

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Independently, Chaudhuri and Wieghardt were able to improve on this catalyst system with the development of another mononuclear Cu^{II} complex, $[\text{L2.1Cu}^{\text{II}}(\text{NEt}_3)]$ (**C2.2**), bearing doubly deprotonated 2,2'-thio-bis(4,6-di-*tert*-butylphenol) (**L2.1**) and triethylamine (NEt_3) as another GOase mimic for the oxidation of primary and secondary alcohols (Scheme 2.1, reaction a) [45]. Binuclear Cu^{II} -phenoxyl active species were generated from complex **C2.2** when a stream of dry O_2 was passed through the reaction mixture. These species were suggested to be responsible for the rate-determining H-atom abstraction step from either one or two alcohol substrates. This afforded the corresponding aldehydes, ketones and traces of ethylene glycol derived products, while H_2O_2 is generated as a by-product. Moderate conversions of 60 to 68 % were obtained after 12 h under mild reaction conditions. No benzophenone product was observed during the oxidation of diphenylmethanol; instead, the formation of benzopinacol was rather observed. They also observed that mixtures of the binuclear Cu^{II} species in the presence of H_2O_2 and an excess of an aldehyde such as acetaldehyde are stable in the air, since no over-oxidation of the aldehyde to the carboxylic acid product occurs, the H_2O_2 oxidant remains intact and no C-C coupling products were observed. A separate mechanistic pathway was followed for the formation of ethylene glycol derivatives, which is not included in this review.



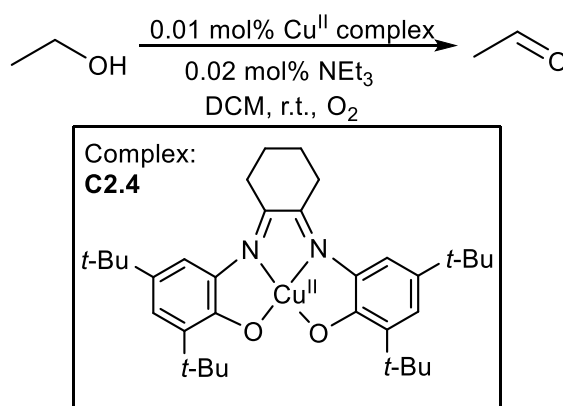
Scheme 2.1: Cu^{II} complexes, **C2.2** and **C2.3**, were employed for the oxidation of alcohols to the corresponding aldehydes [45, 46].

In 1999, another mononuclear Cu^{II} -iminosemiquinone complex, $[\text{Cu}^{\text{II}}\text{L2.2}(\text{NEt}_3)]$ (**C2.3**), bearing doubly deprotonated *N,N*-bis(2-hydroxy-3,5-di-*tert*-butylphenyl)ammonium (**L2.2**) and NEt_3 ligands, was evaluated in the O_2 -mediated oxidation of benzyl alcohol and ethanol to obtain benzaldehyde and acetaldehyde with a conversion of 55 % for both substrates after

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20 h at room temperature (Scheme 2.1, reaction b) [46]. Formation of the corresponding carboxylic acids or oxidative C-C coupling products was not observed nor did disproportionation of H_2O_2 occur. The rate of aldehyde formation increased with an increase in the concentration of NEt_3 until a maximum was reached, where after a decrease in the rate was observed because an excess inhibits the catalytic activity of the reaction. They were unfortunately still unable to convert secondary alcohols with their catalyst system.

An additional Cu^{II} (**C2.4**) complex bearing a doubly deprotonated tetradentate *N,N'*-bis-(3,5-di-*tert*-butyl-2-hydroxyphenyl)-1,2-phenylenediamine ligand was employed in combination with NEt_3 in the oxidation of primary alcohols such as methanol, ethanol and benzyl alcohol using O_2 as the oxidant (Scheme 2.2) [47]. The oxidation of ethanol to acetaldehyde resulted in a conversion of 50 % at 22 °C. They found that ethanol can coordinate to the active Cu^{II} -diimine-phenoxyphenolate species, which is responsible for the rate-determining H-atom abstraction step. A reaction with O_2 results in the regeneration of the active species. No disproportionation of H_2O_2 was observed. A first-order dependence on the initial catalyst concentration was observed, which suggests the involvement of mononuclear complexes as active species. Unfortunately, the oxidation of secondary alcohols was not successful with their optimised catalyst system. These Cu-based GOase mimics could be used in the oxidation of mostly primary alcohols under aerobic and/or anaerobic reaction conditions with moderate conversions to the aldehyde product. No over-oxidation to the corresponding carboxylic acid or C-C coupling products was observed.

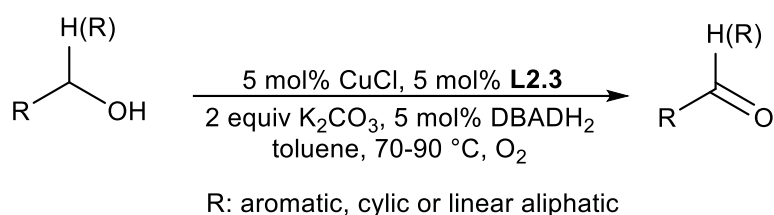


Scheme 2.2: The application of complex **C2.4** and NEt_3 in the oxidation of ethanol to acetaldehyde in 40 h [47].

The limitation in terms of the substrate scope was addressed in the following Cu-based catalyst systems. Markó and co-workers reported the application of copper(I) chloride (CuCl), 1,10-phenanthroline (**L2.3**), di-*tert*-butylazodicarboxylic acid (DBADH_2) and potassium carbonate (K_2CO_3) in the oxidation of a wide range of primary and secondary alcohols to the

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corresponding aldehydes and ketones (65 to 93 %) at 70 to 90 °C by using O₂ as the oxidant (Scheme 2.3) [48, 49]. They proposed that K₂CO₃ serves as a base that can react with the hydrochloric acid (HCl) that was generated during the replacement of the chloride anion with the alcohol substrate [49]. Furthermore, their experimental results revealed that K₂CO₃ may also serve as a solid support where the copper pre-catalyst can be anchored. Lastly, it may also act as an H₂O scavenger, since H₂O is released during the reaction. This is one of the first synthetically relevant Cu-based catalyst systems, but the high amount and nature of the required base were a concern.



Scheme 2.3: The CuCl/**L2.3**/K₂CO₃/DBADH₂ catalyst system for the oxidation of benzylic, aliphatic and cyclic alcohols to the corresponding aldehydes and ketones [48, 49].

In 2004, Repo and co-workers used 9,10-diaminophenanthrene (**L2.4**), *N,N,N',N'*-tetramethylethylenediamine (**L2.5**) and *rac*-1,2-diaminocyclohexane (**L2.6**) as ligands (Figure 2.2) for the *in situ* formation of Cu^{II} complexes [50, 51]. These *in situ* formed complexes were evaluated for the oxidation of benzylic alcohols to the corresponding aldehydes by using O₂ as the oxidant. The water-soluble 3,4-dimethoxybenzyl alcohol (veratryl alcohol) was employed during their kinetic studies and they obtained full conversion to 3,4-dimethoxybenzaldehyde (veratric aldehyde) when employing ligand **L2.4** in combination with a Cu^{II}-precursor; however, this was not possible for **L2.5** or **L2.6**. Overall, the oxidation reaction is linearly dependent on the initial catalyst and substrate concentration; however, the reaction with ligand **L2.6** is independent of the initial substrate concentration. The rate-limiting factor at low substrate concentrations is the interaction between the substrate and Cu-based active species, but the reaction itself becomes rate-limiting with an increase in the substrate and the turnover frequencies (TOF) were the highest when employing ligand **L2.4**.

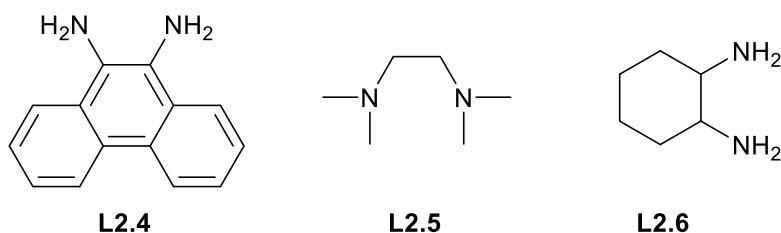
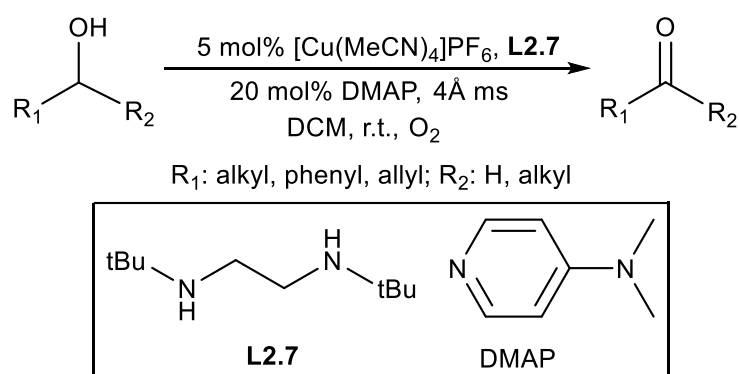


Figure 2.2: Ligands **L2.4**, **L2.5** and **L2.6** were employed in the *in situ* formation of Cu^{II} complexes for alcohol oxidation [51].

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Furthermore, Repo and co-workers also observed that veratric aldehyde and traces of veratric acid hinder the approach of the substrate by coordinating to the catalyst or by influencing the equilibrium [51]. The effect of these products on the reaction was probed by adding more thereof during the reaction. Almost no effect was observed for veratric acid, but veratric aldehyde has a dramatic negative influence on the reaction. When employing **L2.6**, the catalytic activity was not only inhibited, but they also observed an increase in the amount of the initial veratryl alcohol [51]. This was not possible when replacing the ligand with **L2.4** or **L2.5**. Mass spectrometric (MS) studies were also employed to observe the degradation of the **L2.4** and **L2.5** ligands due to condensation with the veratric aldehyde during the reaction, while **L2.6** might decompose by dimerisation. Moreover, the ligand decomposition and the resulting release of copper, led to the formation of a $\text{Cu}(\text{OH})_2$ precipitate, which is then transformed to CuO in the presence of O_2 and neither of these Cu-based species is able to catalyse the oxidation reaction.

In 2015, Arndtsen and co-workers reported the application of tetrakis(acetonitrile)copper(I) hexafluorophosphate ($[\text{Cu}(\text{MeCN})_4]\text{PF}_6$) and *N,N'*-di-*tert*-butylethylenediamine (**L2.7**) in the oxidation of a diverse range of activated (reaction time: 1 h) and non-activated (reaction time: 6 h) alcohols using O_2 as the oxidant [52]. Even though their catalyst system could be employed for the oxidation of primary and secondary alcohols, preference for secondary over primary alcohols was observed. *N*-containing bases such as pyridine, *N*-methylimidazole (NMI) and dimethylaminopyridine (DMAP) have an effect on the catalytic activity of the reaction and DMAP was identified as the optimal base. As such, they employed their $\text{Cu}/\text{L7}/\text{DMAP}/\text{O}_2$ catalyst system for the oxidation of 1-octanol to 1-octanal with a conversion of 92 % in 3 h (Scheme 2.4) [52].



Scheme 2.4: The $\text{Cu}/\text{L2.7}/\text{DMAP}/\text{O}_2$ catalyst system was employed in the oxidation of activated and non-activated alcohols [52].

Molecular sieves (ms) were added to the reaction to absorb H_2O that was formed during the reaction. An extremely low conversion of 14 % was obtained when copper(II) triflate ($\text{Cu}(\text{OTf})_2$)

was rather employed in the oxidation of 1-octanol. No aldehyde products were observed in the absence of **L2.7**, which confirms the high reactivity of the Cu_2/O_2 species that was generated during the reaction [48, 53]. Their catalyst system was found to be less sensitive towards steric influences from the substrates than TEMPO $\cdot$ -based catalyst systems. Initially, they believed that their catalyst system could serve as a tyrosinase mimic during alcohol oxidation in the absence of a co-catalyst. However, their mechanistic studies revealed similar results to the Cu/nitroxyl catalyst systems due to the formation of an oxygenated version of **L2.7**, as a co-catalyst for the reaction [54].

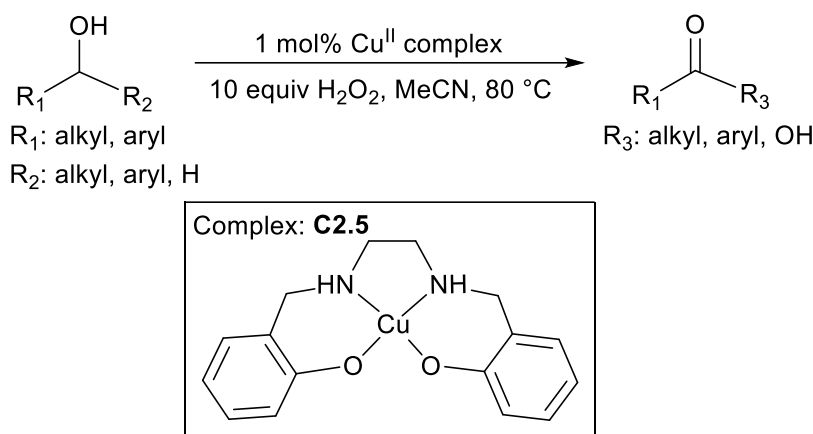
Even though O_2 can be employed as an oxidant in the absence of an *N*-oxide co-catalyst, these reactions usually require harsh reaction conditions such as high temperatures and high O_2 pressure, while poor selectivity is observed. As an alternative, studies have also focused on the evaluation of peroxides as an oxidant during the peroxidative oxidation of alcohols.

2.2.1.2 Alcohol oxidation with peroxides

Peroxides such as H_2O_2 or *tert*-butyl hydroperoxide (TBHP) as inexpensive oxidants were evaluated in the oxidation of alcohols in neat water or an organic solvent [10]. The employment of TBHP as oxidant was found to be an economic alternative, and many Cu-based catalyst systems have recently been reported [55-58]. However, these reactions usually result in the formation of butan-1-ol as a by-product and they require the addition of other additives such as nitric acid (HNO_3), TEMPO $\cdot$ or K_2CO_3 . Hydrogen peroxide is therefore preferred due to its green chemical practices and the generation of H_2O as the only by-product [10, 35, 36]. It needs to be borne in mind that high reaction temperatures may lead to the decomposition of H_2O_2 . Our focus for this sub-section is on the development of Cu-based catalyst systems that contain H_2O_2 , instead of other peroxides, in either H_2O or an organic solvent such as MeCN.

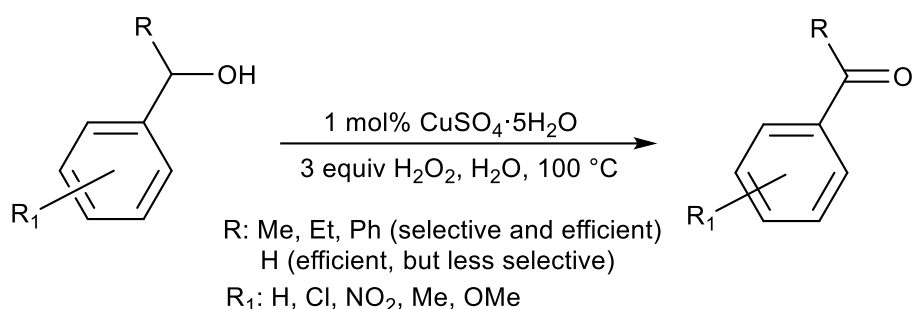
The first example of a Cu-based catalyst system with H_2O_2 was reported by Punniyamurthy and co-workers in 2003 [59]. They evaluated a Cu^{II} complex (**C2.5**) in combination with H_2O_2 (30 % in H_2O) in the oxidation of 4-chlorobenzyl alcohol in MeCN, under ambient reaction conditions to obtain a conversion of 30 %, which consists of a mixture of 4-chlorobenzaldehyde and 4-chlorobenzoic acid (ratio of 2:1) at 60 °C (Scheme 2.5). However, when the temperature was increased to 80 °C, the conversion also increased to 95 % in 4.5 h. Lower conversions of 30 and 65 % were obtained when the catalyst was replaced with copper(II) acetate dihydrate ($\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$) or $\text{Cu}^{\text{II}}(\text{salen})$, respectively. Furthermore, the oxidation reaction did not proceed in the absence of the catalyst or when O_2 was employed as the oxidant. Their catalyst system was also amenable to the oxidation of primary and secondary alcohols, yielding the corresponding carboxylic acids and ketones, respectively.

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Scheme 2.5: The application of complex **C2.5** in combination with H₂O₂ in the oxidation of aromatic and aliphatic alcohols at 80 °C [60].

In 2012, Repo and co-workers reported two Cu-based catalyst systems [61]. In the first catalyst system, they evaluated various copper salts, in combination with 2-*N*-(*p*-fluorophenyl)-pyrrolecarbalimine (ratio of 1:2), TEMPO[•] and H₂O₂ (30 % in H₂O) at 60 °C. High conversions were obtained, except for copper(II) bromide (CuBr₂), possibly due to the formation of copper(I) oxide (CuO) or Cu(OH)₂ during the reaction. Copper(II) sulfate pentahydrate (CuSO₄·5H₂O) was determined as the most efficient copper salt, while an increase in selectivity towards the formation of the aldehyde product was observed in the presence of TEMPO[•]. They were able to oxidise both primary and secondary alcohols with a high selectivity towards the corresponding aldehyde products, but high efficiency and conversions are only obtained for the primary alcohols. Our focus, however, is on their second catalyst system, which only consists of CuSO₄·5H₂O in combination with H₂O₂, in the absence of TEMPO[•]. They evaluated their CuSO₄·5H₂O/H₂O₂ catalyst system for the oxidation of benzylic alcohols in an aqueous solution at 100 °C (Scheme 2.6) [61].



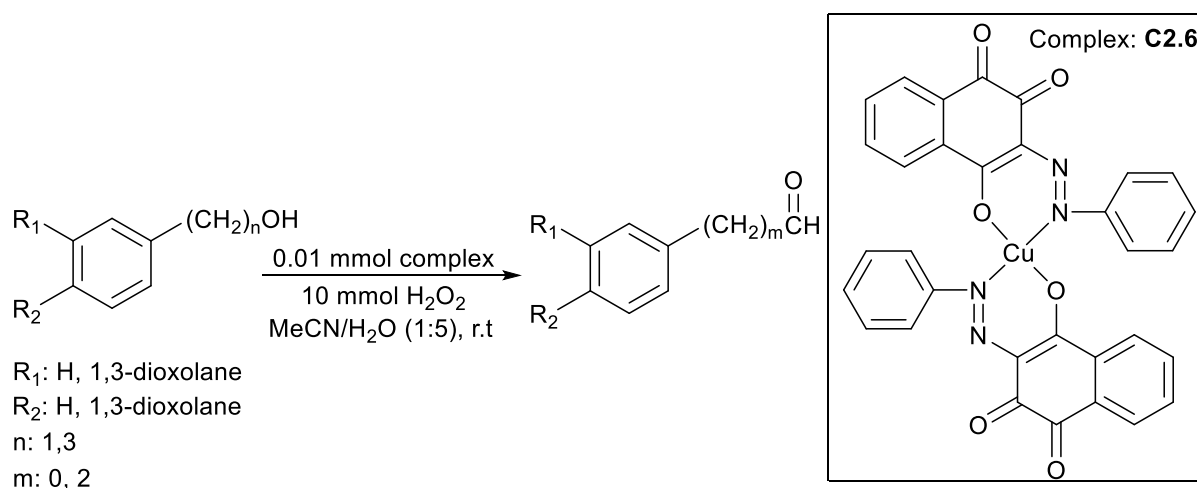
Scheme 2.6: The CuSO₄·5H₂O/H₂O₂ catalyst system for the oxidation of benzylic alcohols in H₂O at 100 °C [61].

The oxidation of benzyl alcohol to benzaldehyde exhibited a conversion of 98 % within 15 min (90 % in 90 min at 80 °C). Even though benzaldehyde was obtained as the major product,

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traces of benzoic acid and benzaldehyde-derived products were also present. This selectivity problem could not be solved with changes in the reaction time, temperature or varying concentrations of reaction parameters. The oxidation of both primary and secondary benzylic alcohols with high efficiencies was possible, but a high selectivity towards the corresponding ketones was only observed for secondary alcohols. Alcohol substrates with electron-donating groups exhibited a selectivity of 70 to 80 %, while those bearing electron-withdrawing groups were over-oxidised to the corresponding carboxylic acid. The catalyst can be recovered from the reaction mixture and reused for a second time without loss of selectivity, but a decrease in the conversion from 92 to 70 % was observed. Kinetic studies showed a first-order dependence for $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and H_2O_2 , while the substrate showed a second-order dependence.

Shoair reported the use of Cu^{II} complexes bearing substituted 4-hydroxyl-1,2-naphthoquinone ligands in combination with H_2O_2 (30 % in H_2O) for the oxidation of benzyl alcohol (conversion of 90 %), piperonyl alcohol (80 %) and cinnamyl alcohol (75 %) in an $\text{MeCN}/\text{H}_2\text{O}$ (ratio of 1:5) solvent system for 2 h, at ambient temperature (Scheme 2.7) [62]. The compound 3-(*p*-H)-4-hydroxyl-1,2-naphthoquinone (**L2.8**) was found to be the optimal ligand for the complex $[(\text{L2.8})_2\text{Cu}] \cdot \text{H}_2\text{O}$ (**C2.6**), resulting in high selectivity towards the formation of the corresponding aldehyde products. Low conversions of less than 5 % were obtained for the oxidation of benzyl alcohol to benzaldehyde in the absence of the catalyst or by employing alternative oxidants such as sodium periodate (NaIO_4), due to the formation of precipitates (NaIO_3) as by-products interfering with the work-up.



Scheme 2.7: The application of the **C2.6**/ H_2O_2 catalyst system for the oxidation of benzyl, piperonyl and cinnamyl alcohol at ambient temperature [62].

Shul'pin and co-workers evaluated Cu^{II} complexes, bearing functionalised 2,2':6',2''-terpyridine (**C2.7-C2.9**) and 2,6-di(thiazol-2-yl)pyridine (**C2.10-C2.12**) ligands for the oxidation of secondary benzylic and cyclic alcohols (Figure 2.3) [63].

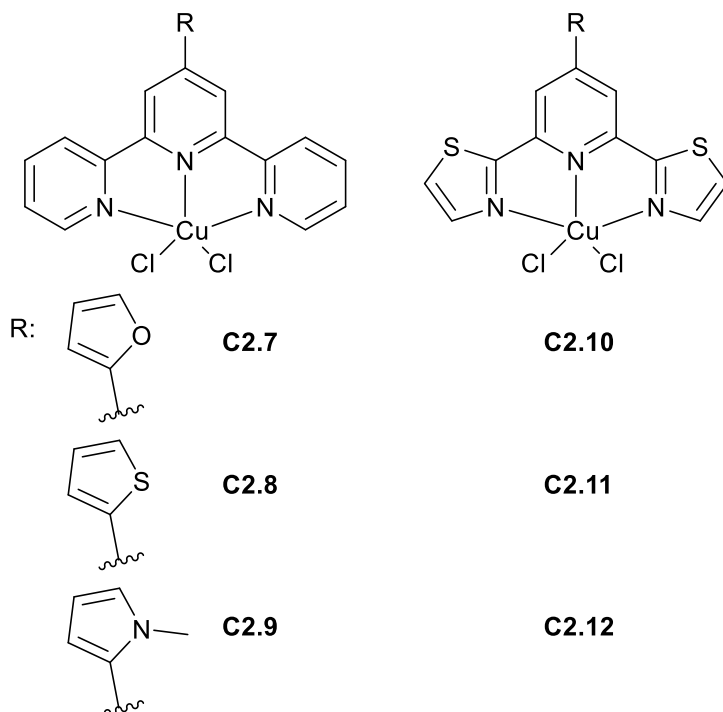
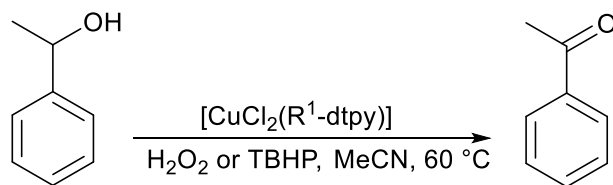


Figure 2.3: Complexes **C2.7-C2.12** were evaluated for alcohol oxidation reactions [63].

The oxidation of 1-phenylethanol to acetophenone was possible when using H_2O_2 (30 % in H_2O) or TBHP in combination with $[\text{CuCl}_2(\text{R}^1\text{-dtpy})]$ (**C2.10**; R^1 : furan-2-yl, dtpy: 2,6-di(thiazol-2-yl)pyridine derivative), and a maximum conversion of 98 % with a turnover number (TON) of 630 was obtained after 5 h at 60 °C (Scheme 2.8). They were also able to oxidise cyclohexanol to cyclohexanone with a conversion of 71 % and a TON of 580, under the same reaction conditions.

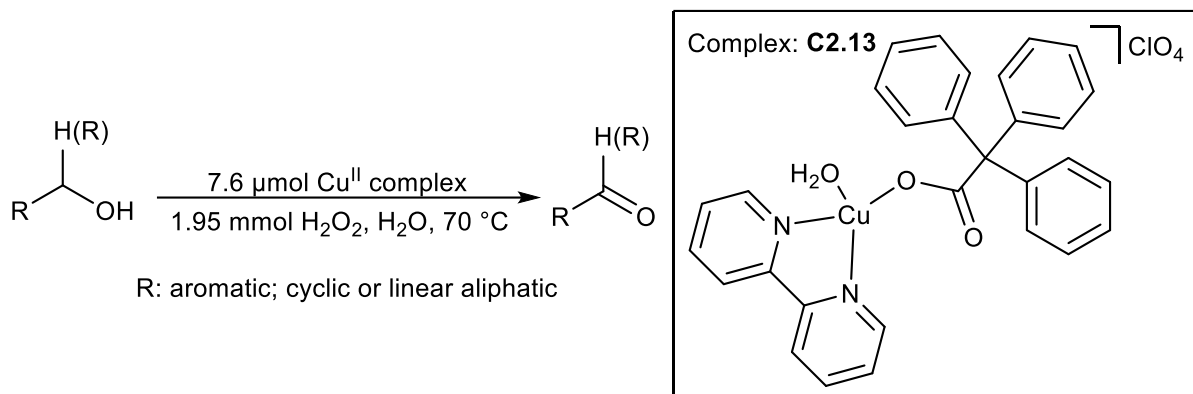


Scheme 2.8: The combination of $[\text{CuCl}_2(\text{R}^1\text{-dtpy})]$ (**C2.10**) and H_2O_2 or TBHP for the oxidation of 1-phenylethanol in 5 h at 60 °C [63].

Independently, Kani and co-workers reported on the application of the water-soluble mononuclear Cu^{II} complex, $[\text{Cu}(\eta^1\text{-O}_2\text{CCPh}_3)(\text{bpy})(\text{H}_2\text{O})][\text{ClO}_4]$ (**C2.13**) for the oxidation of primary and secondary alcohols, using H_2O_2 (30 % in H_2O) in an aqueous solution at 70 °C (Scheme 2.9) [64]. A high conversion of 97 % was obtained for the oxidation of benzyl alcohol

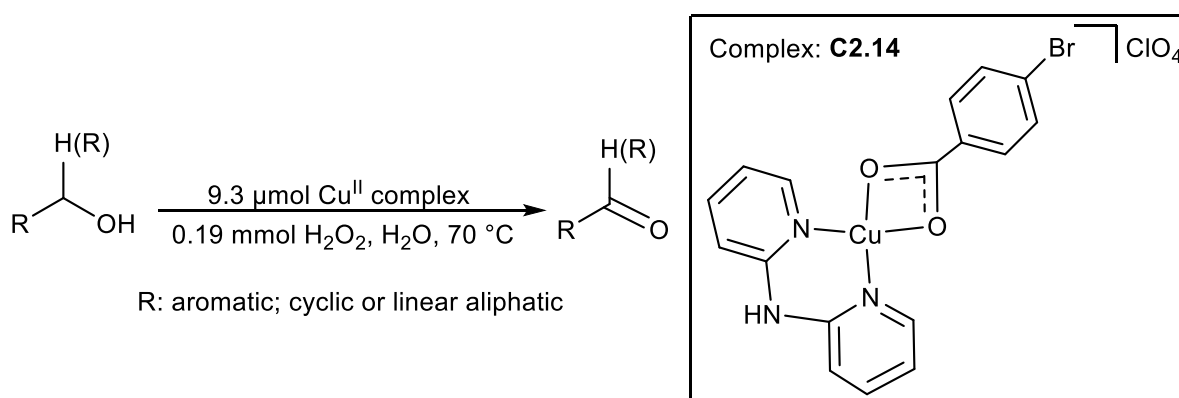
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in 6 h, with benzaldehyde as the sole product, while low conversions of 28 and 12 % were obtained for the oxidation of cyclohexanol and heptan-1-ol to cyclohexanone and heptan-1-al, respectively. No over-oxidation to the corresponding carboxylic acids was observed.



Scheme 2.9: The application of complex **C2.13** and H_2O_2 for the oxidation of primary and secondary alcohols at 70 °C [64].

Low product yields of 11 to 29 % were obtained for secondary aliphatic alcohols, while 1-phenylethanol resulted in a moderate product yield of 73%. An increase in the catalytic activity for the secondary alcohols was possible at longer reaction times of 24 h without a C-C chain cleavage reaction. They further extended their investigation, by employing a new water-soluble Cu^{II} complex, $[\text{Cu}(\eta^2\text{-O}_2\text{C(4-BrC}_6\text{H}_4\text{))}(\text{C}_{10}\text{H}_9\text{N}_3)](\text{ClO}_4)$ (**C2.14**) in combination with H_2O_2 (30 % in H_2O) for the oxidation of primary and secondary alcohols at 70 °C (Scheme 2.10) [65]. Even though a lower conversion of 71 % was obtained for the oxidation of benzyl alcohol, similar results for the oxidation of secondary alcohols were observed, relative to their first water-soluble Cu^{II} complex, **C2.13**.

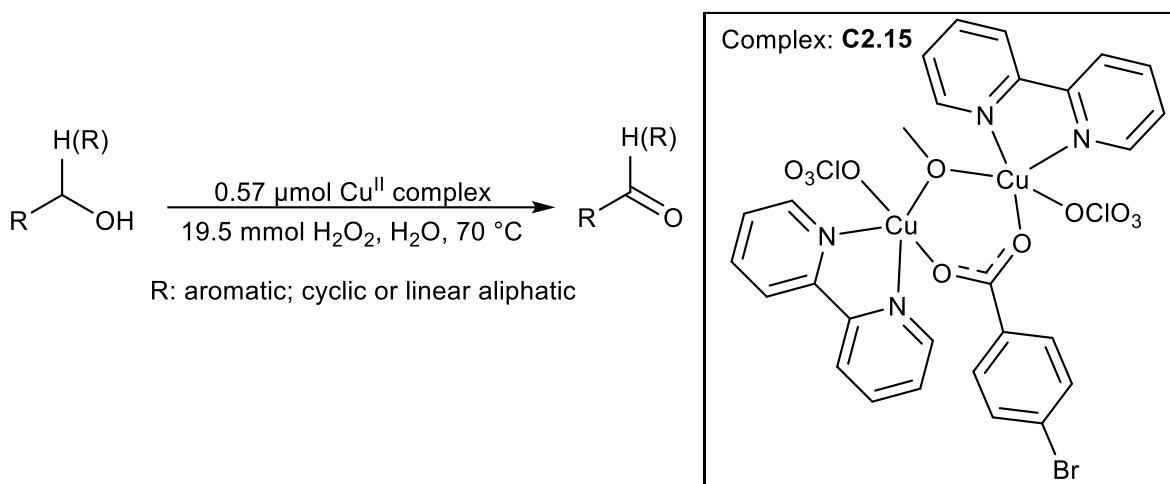


Scheme 2.10: The application of complex **C2.14** and H_2O_2 for the oxidation of primary and secondary alcohols at 70 °C [65].

In 2018, Ünver reported the application of another water-soluble binuclear Cu^{II} complex, $[\text{Cu}_2(\eta^2\text{-O}_2\text{C(4-BrC}_6\text{H}_4\text{))}(\text{OCH}_3)(\text{bpy})_2](\text{ClO}_4)_2$ (**C2.15**) for the oxidation of primary and

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secondary alcohols, with H_2O_2 (30 % in H_2O ; Scheme 2.11) [66]. Excellent product yields of 100 % were obtained for the oxidation of benzyl alcohol, 1-phenylethanol and butan-2-ol to benzaldehyde, acetophenone and butan-2-one, respectively, in 6 h without over-oxidation. The binuclear complex **C2.15** was found to be active for benzylic, cyclic and secondary aliphatic alcohols, while low product yields were obtained for primary aliphatic alcohol substrates [67].



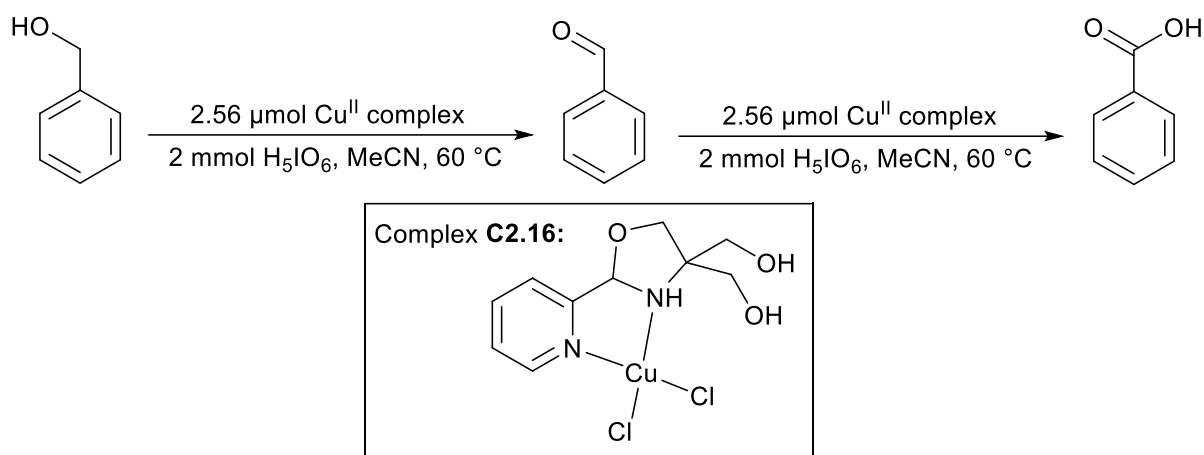
Scheme 2.11: The application of complex **C2.15** and H_2O_2 for the oxidation of primary and secondary alcohols at 70°C [66].

Bikas and co-workers evaluated a Cu^{II} complex, $[\text{Cu}(\text{L2.9})\text{Cl}_2]$ (**C2.16**), bearing the 1,3-oxazolidine-based (2-pyridin-2-yl-1,3-oxazolidine-4,4-diyl)dimethanol (**L2.9**) ligand, for the oxidation of alcohols, using either H_2O_2 (30 % in H_2O) or TBHP as oxidant [68]. They obtained a conversion of 96 % for the oxidation of benzyl alcohol to benzaldehyde in 120 min by employing their **C2.16**/ H_2O_2 catalyst system (Scheme 2.12). An alternative Cu^{II} complex, $[\text{Cu}(\text{L2.9})_2]\cdot 2\text{Cl}$ (**C2.17**), was also evaluated, but a lower conversion of 88 % was observed, due to its octahedral geometry vs a square-pyramidal geometry for **C2.16** and steric hindrance of the ligand, which limits the interaction between the copper centre and the oxidant and substrate. This steric hindrance resulted in the preference of benzaldehyde as a product.

Over-oxidation occurs while kinetic studies revealed an increase in the formation of benzaldehyde after 2 h, after which saturation was reached. No oxidation products were observed in the absence of the catalyst or oxidant. They also evaluated TBHP as the oxidant to confirm the effect of the nature of the oxidant on the catalytic activity [68]. Increased conversions of 98 and 92 % for the respective ligands were obtained due to the weaker O-O bond as well as the steric hindrance of TBHP to rather afford benzaldehyde as the product. Their catalyst system could also be employed for the oxidation of various chloro-substituted benzyl alcohols with conversions of 72 to 82 % with selectivity for the corresponding aldehyde

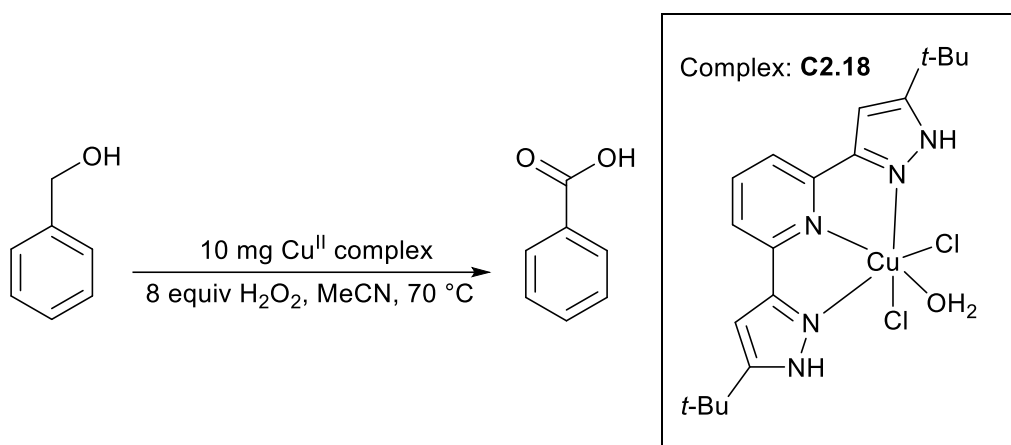
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products. They observed that the selectivity and efficiency of the catalyst system are dependent on the electronic and steric demands of the chlorine group since *ortho*-positioned chlorine substituents showed lower activity relative to the *meta*- and *para*-substituted substrates.



Scheme 2.12: The **C2.16**/H₂O₂ catalyst system was employed for the oxidation of benzyl alcohol in 2 h at 60 °C [68].

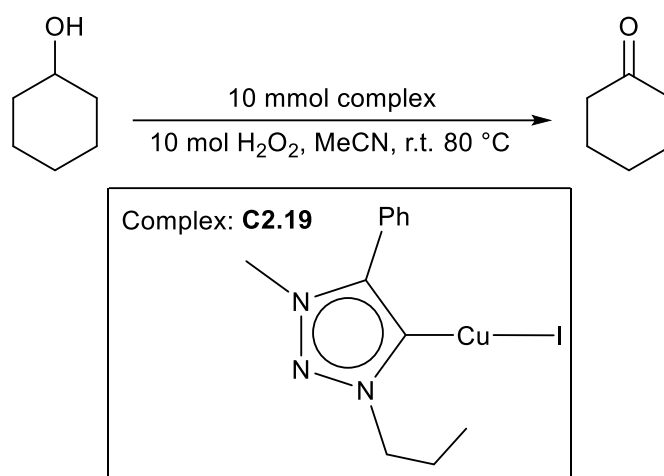
In 2019, Hu and co-workers reported on the application of a mononuclear Cu^{II} complex (**C2.18**) for the oxidation of aromatic alcohols, using H₂O₂ (30 % in H₂O) as the oxidant in 1 to 4 h at 70 °C, with conversions of > 95 % (Scheme 2.13) [69]. Benzoic acid was obtained as the major product with a conversion of 97 % (selectivity of 96 %) during the oxidation of benzyl alcohol in 1 h, which is in contrast to the benzaldehyde product obtained in previous reports. Their catalyst system could also be employed for the oxidation of alkenes, such as styrene and ethylbenzene.



Scheme 2.13: The application of complex **C2.18**, in combination with H₂O₂, for the oxidation of benzyl alcohol to benzaldehyde at 70 °C [69].

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Mncube and Bala reported the application of *in situ* synthesised Cu^I complexes, consisting of Cu^I in combination with NHC-triazolylidene ligands in a ratio of 1.1:1, and H₂O₂ on the peroxidation of cyclohexane [70]. These reactions will be discussed later in this review (see Section 2.2.3 for peroxidation reactions). They also investigated the oxidation of alcohol substrates, using their optimised reaction conditions. The oxidation of cyclohexanol resulted in a maximum conversion of 91 % to cyclohexanone in 24 h at 80 °C by employing complex **C2.19** and H₂O₂ as the oxidant (Scheme 2.14). They observed an increase in the reactivity of phenolic and benzylic alcohols relative to the aliphatic alcohols. Furthermore, they also observed higher catalytic activity for secondary aliphatic alcohols than for primary alcohols, thereby suggesting that reactions at the secondary C-atom of aliphatic alcohols are more facile than terminal or primary C-atoms. This is possibly due to easier access for secondary aliphatic alcohols to coordinate to the copper centre.



Scheme 2.14: The **C2.19**/H₂O₂ catalyst system was employed for the oxidation of cyclohexanol in 24h at 80 °C [70].

In conclusion, a number of Cu-based catalyst systems with either O₂ or H₂O₂ as the oxidant have recently been reported for the oxidation of primary and secondary alcohols. However, these catalyst systems are mostly limited to the oxidation of activated alcohols. The next subsection details the mechanistic pathways for this oxidation reaction.

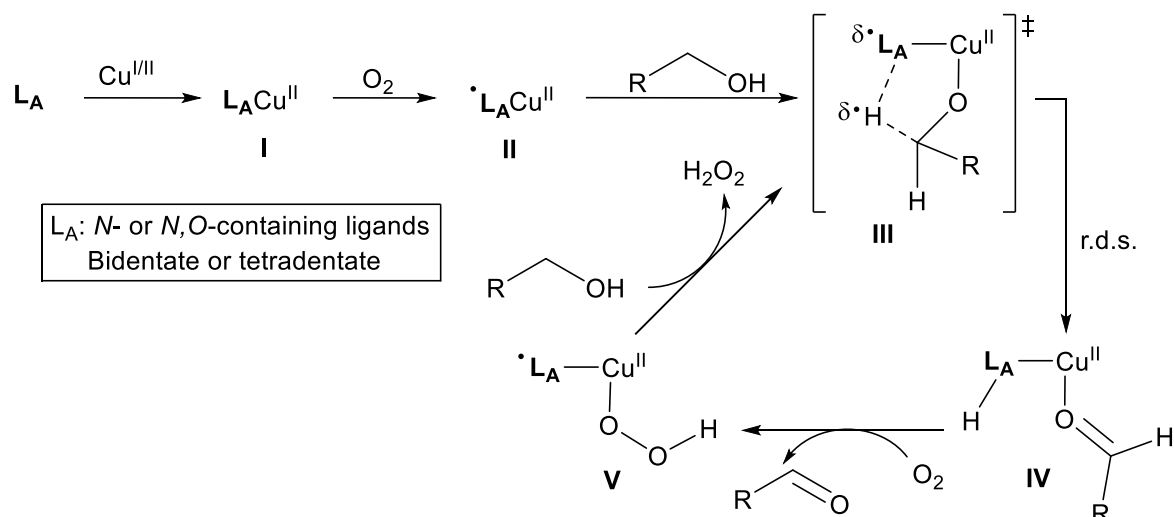
2.2.1.3 Mechanistic aspects

2.2.1.3.1 O₂ as oxidant

The groups of Arndtsen, Stahl and Stack proposed a mechanistic pathway for the oxidation of alcohols in the presence of O₂, which involves both oxygenase- and oxidase-type reactivity [44, 54, 71]. Stack and co-workers employed electron paramagnetic resonance (EPR) spectroscopy to investigate the oxidation reaction and they proposed a mechanistic pathway,

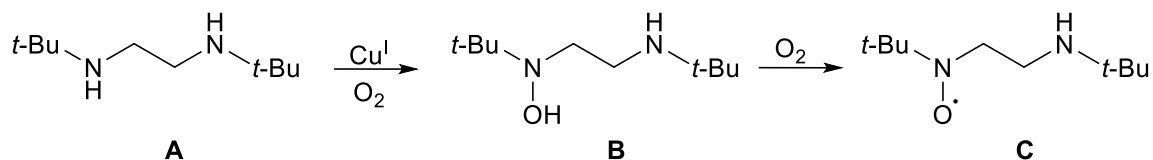
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where ligand L_A (L_A : possible ligands, Scheme 2.15) coordinates to either Cu^I or Cu^{II} to afford $L_A Cu^{II}$, **I**, followed by ligand oxygenation via an *in situ* oxidative self-processing step in the presence of O_2 (aerobic conditions) to afford a radical species, $\cdot L_A Cu^{II}$, **II** (Scheme 2.15). The oxygenated ligand serves as a co-catalyst to promote the catalytic activity during the oxidation reaction, similarly to Cu/nitroxyl catalyst systems [3, 5, 72, 73].



Scheme 2.15: The proposed mechanistic pathway for Cu-based aerobic alcohol oxidation with O_2 as the oxidant. Adapted from the groups of Stahl and Stack [44, 54, 71].

The Cu/O_2 adduct that is responsible for the oxygenation and coordination steps, is similar to the one used in amine oxygenation [74, 75]. Stahl and co-workers employed EPR studies to identify a small Cu^{II} signal in the absence of the alcohol substrate [52, 54]. An organic radical signal, similar to that obtained for nitroxyl radicals such as TEMPO $\cdot$ and ABNO $\cdot$, was observed and the intensity thereof increased during the oxidase-type reaction [76, 77]. As such, they also proposed the formation of an oxygenated ligand, derived from their initial DBED ligand (Scheme 2.16, **A** and **B**). **B** was synthesised and evaluated in the oxidation reaction under the same reaction conditions and a significantly shorter induction period was observed [3]. EPR spectroscopic studies revealed the formation of a radical ligand, **C**, in the presence of O_2 , which is analogous to species **II** ($\cdot L_A Cu^{II}$, Scheme 2.15).



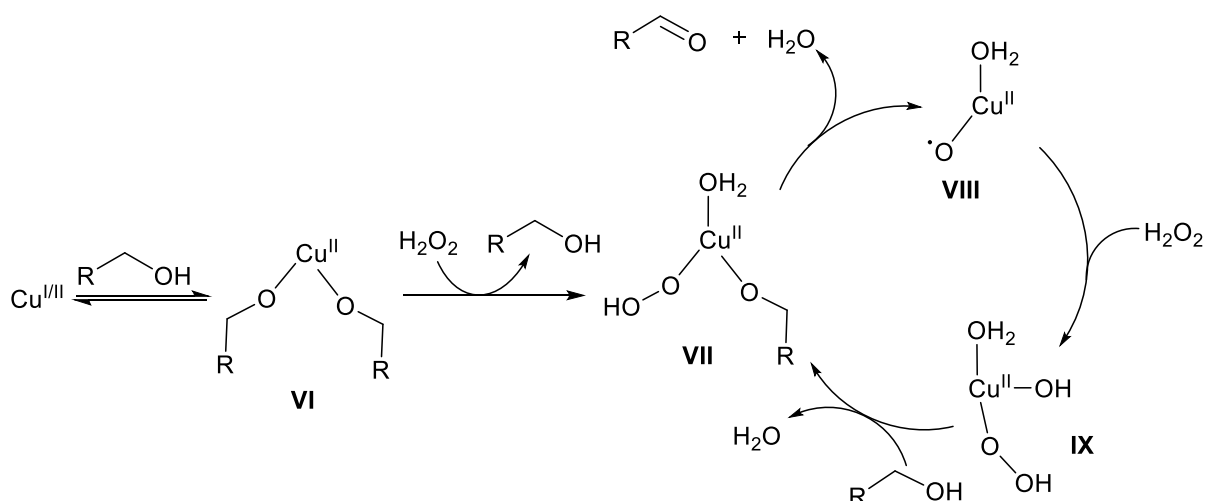
Scheme 2.16: The oxygenation of DBED to afford a radical derivative of DBED, similar to nitroxyl radicals [54].

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The alcohol substrate (ROH) then coordinates to **II** during the formation of $\cdot\text{L}_A\text{Cu}^{\text{II}}\text{-OR}$, **III**, (Scheme 2.15) [44, 71]. The radical species, **III**, is responsible for the H-atom abstraction step from the substrate during the rate-determining step to afford $\text{L}_A\text{Cu}^{\text{I}}\text{-O=R}$, **IV**, in the presence of the bounded aldehyde product [44, 49, 71]. Under anaerobic reaction conditions, species **I** is regenerated from **IV** via a one-electron transfer step. Alternatively, the aldehyde product (RO) is released from **IV** in the presence of O_2 to afford $\cdot\text{L}_A\text{Cu}^{\text{II}}\text{-OOH}$, **V**. The last step involves the production of H_2O_2 upon substrate coordination to afford species **III**. A similar mechanistic pathway was also proposed by Chaudhuri and Wieghardt even though they suggested the formation of binuclear Cu^{II} complexes, which can accommodate one or two alcohol substrates during the reaction [45-47].

2.2.1.3.2 H_2O_2 as oxidant

Previous studies have proposed that the oxidation of organic substrates, in the presence of H_2O_2 , proceeds via a free-radical mechanistic pathway (see Section 2.2.3.1.2). Repo and co-workers added radical traps such as TEMPO $\cdot$ and hydroquinone during the alcohol oxidation reaction, but no change in the catalytic activity was observed [61]. Their results suggest that the reaction rather proceeded via an ionic mechanistic pathway, in the absence of a ligand. UV/vis spectroscopic studies were employed to investigate the oxidation state of copper under argon atmosphere. An absorption band peak was initially observed at 834 nm, which confirms the presence of Cu^{II} species. Alcohol substrate and H_2O_2 were added sequentially at 100 °C. The initial Cu^{II} bis-alkoxide species, **VI**, is transformed into Cu^{II} -hydroperoxy species, **VII** (Scheme 2.17) [61, 68].



Scheme 2.17: The proposed mechanistic pathway for the oxidation of alcohols when H_2O_2 is employed as the oxidant. Reproduced from Repo and co-workers [61].

The Cu^{II}-hydroperoxy species, **VII**, has previously been suggested to be the active species in various catalytic reactions [78-80]. The intramolecular abstraction of a β -hydrogen from the alkoxide substrate affords an aldehyde product as well as the formation of Cu^{II}-oxyl (Cu^{II}-O $\cdot$) species, **VIII** [81, 82]. The addition of excess H₂O₂ converts the Cu^{II}-oxyl species to the Cu^{II}-perhydroxide species, **IX**, while the initial Cu^{II}-hydroperoxy species, **VII**, is regenerated in the presence of the alcohol substrate. A similar mechanistic pathway was also proposed by Hu and co-workers, except that they observed the formation of both aldehyde and epoxide products [69]. The next section details progress in the development and understanding of the copper-catalysed hydroxylation of aryl halides.

2.2.2 Hydroxylation reactions

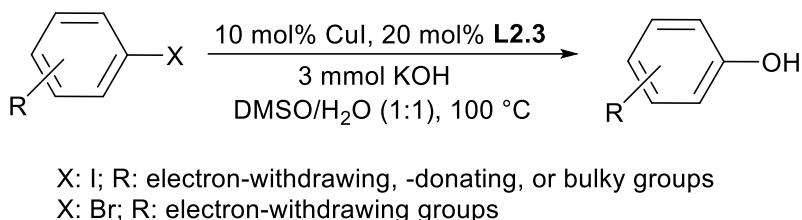
Hydroxylation reactions generally involve the introduction of a hydroxyl group to an organic compound. In this section, the focus is specifically on the substitution of the halogen atom (-X; X: I, Br, Cl) of aryl halide substrates with a hydroxyl group to afford the corresponding phenolic compounds. These are high-value intermediates in the chemical and pharmaceutical industries [83, 84]. Traditionally, the Hock and Dow processes, the non-oxidative Sandmeyer reaction as well as the nucleophilic aromatic substitution of compounds such as aryl halides were employed for the synthesis of substituted phenols [13-17]. These synthesis methods, however, involve harsh reaction conditions and inefficient energy use, leading to low product yields and a limited substrate scope. In an attempt to overcome these limitations, alternative synthesis methods have been developed. One of these synthesis methods is the metal-catalysed aryl halide hydroxylation.

Various metal-based catalyst systems have previously been reported for the hydroxylation of aryl halides. Initially, iridium- and palladium-catalysed aryl halide hydroxylations were utilised as milder and more applicable synthesis routes [85-92]. However, several drawbacks were identified for these catalyst systems. These include the use of expensive catalysts with air- and moisture-sensitivity, high toxicity and low product selectivity. In an attempt to circumvent these issues, several Cu-based catalyst systems have been reported for aryl halide hydroxylation [93-99].

Ma and co-workers developed a catalyst system, consisting of copper(I) iodide (CuI) and L-proline, which was evaluated by Kormos and Leadbeater in the hydroxylation of activated aryl halides [100, 101]. Potassium hydroxide (KOH) was employed as the base in near-critical (300 °C) water by using microwave heating. Their catalyst system required high catalyst loadings, long reaction times and high temperatures, while a limitation on the substrate scope was observed [102, 103]. More efficient Cu-based catalyst systems were reported in ensuing

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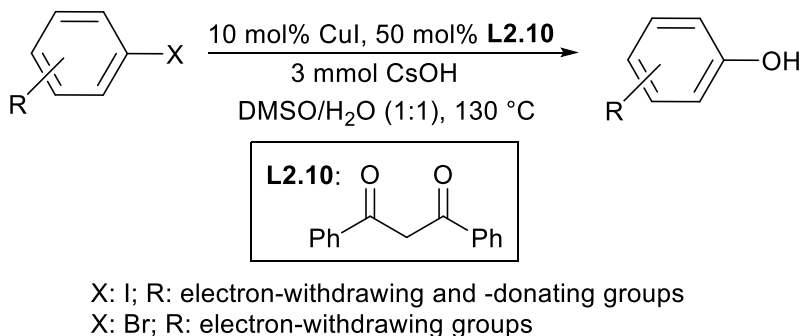
years and one of the first catalyst systems for the hydroxylation of 4-iodotoluene, operating without microwave heating, was reported by You and co-workers in 2009 [93]. They observed the direct coupling between aryl halides and KOH, using mild reaction conditions and commercially available pre-catalysts to obtain a conversion of 96 % to *p*-cresol in 24 h with their CuI/**L2.3**/KOH catalyst system (Scheme 2.18).



Scheme 2.18: The CuI/**L2.3**/KOH catalyst system in DMSO/H₂O (ratio of 1:1) for the hydroxylation of aryl iodides and bromides at 100 °C [93].

The above-mentioned catalyst system of You and co-workers could be used for the successful hydroxylation of activated, non-activated and sterically demanding aryl iodides to afford good to excellent conversions of the corresponding phenolic products. The hydroxylation of aryl bromides possessing electron-withdrawing groups to the corresponding phenols proceeded with excellent conversions of 76 to 92 %. Moreover, their catalyst system showed good chemoselectivity between the iodide, bromide and chloride substituents of the aryl halide.

Independently, Taillefer and co-workers reported a CuI/dibenzoylmethane (**L2.10**) catalyst system in combination with cesium hydroxide (CsOH), in 2009, for the hydroxylation of 4-iodotoluene and iodobenzene resulting in conversions of 82 % and 97 % to *p*-cresol and phenol, respectively, in 24 h at 130 °C (Scheme 2.19) [95]. Evaluating various β -diketone ligands in the reaction, they observed that ligands with decreased steric hindrance resulted in lower conversions. Sterically hindered 2,2,6,6-tetramethyl-3,5-heptanedione and ligand **L2.10** were the most effective with excellent conversions of 95 and 97 %, respectively. No arylation of the diketone ligands was observed during the reaction.

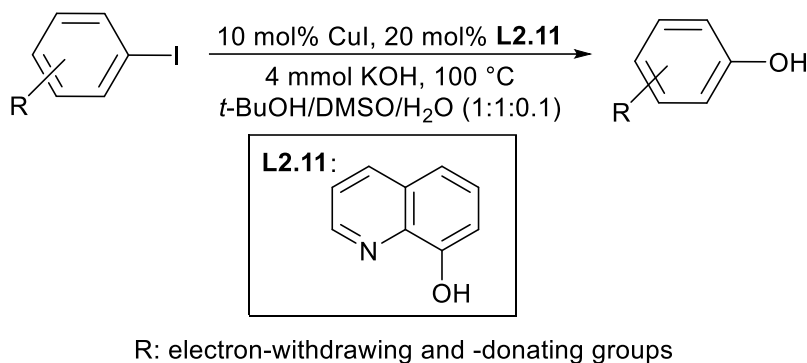


Scheme 2.19: The CuI/**L2.10**/CsOH catalyst system for the hydroxylation of aryl iodides and bromides at 130 °C [95].

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The ratio of H₂O/base/co-solvent was found to have a higher impact on the efficiency of the reaction, since a higher concentration of H₂O, in combination with dimethyl sulfoxide (DMSO), will improve the solubility of CsOH and thereby improve its nucleophilicity. Lastly, their catalyst system could be employed in the hydroxylation of activated and non-activated aryl iodides as well as activated aryl bromides with good to excellent yields.

In 2010, Ma and co-workers modified their previous catalyst system by employing CuI in combination with 8-hydroxyquinoline (**L2.11**), instead of L-proline, and KOH (Scheme 2.20) [104]. Various ligands such as *trans*-4-hydroxy-L-proline, pipecolinic acid and picolinic acid were also evaluated in the hydroxylation of 4-iodoanisole, and conversions of 83 to 89 % were obtained in 48 h at 100 °C. The best conversion (96 %) was obtained when employing ligand **L2.11**.



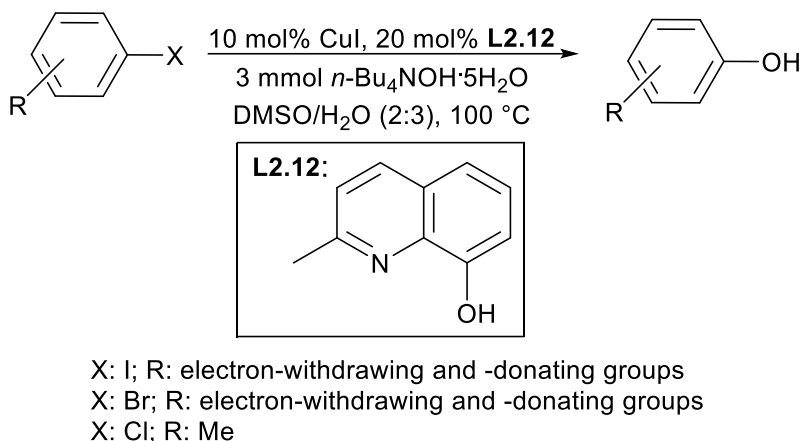
Scheme 2.20: The CuI/**L2.11**/KOH catalyst system for the hydroxylation of aryl iodides at 100 °C [104].

Ma and co-workers also attempted the hydroxylation of aryl bromides, but only low conversions were possible, even with longer reaction times [104]. The solvent system influences the hydroxylation reaction since the wrong solvent system allows for the sublimation of the substrate, resulting in lower conversions. Evaluating various solvent systems, they found that the addition of sterically hindered *tert*-butanol (*t*-BuOH) as a co-solvent to the DMSO/H₂O solvent system (in a ratio of 1:1:0.1) prevents substrate sublimation, while the hydroxylation reaction was still possible, without the formation of by-products [105]. Cu-based catalyst systems have been reported using only water as the solvent system [13, 102, 106]. However, high catalyst loadings of 5 to 10 mol%, longer reaction times, the need for an inert atmosphere and high loadings of phase-transfer catalysts such as tetrabutylammonium bromide (TBAB) were required during the hydroxylation reactions. Furthermore, decreased substrate solubility and the formation of a biaryl ether by-product were also observed.

Punniyamurthy and co-workers employed an alternative base, tetrabutylammonium hydroxide pentahydrate (*n*-Bu₄NOH·5H₂O), in their CuI/8-hydroxy-quinoline (**L2.12**) catalyst system, using a DMSO/H₂O solvent system (ratio of 2:3), for the hydroxylation of 4-iodotoluene with a

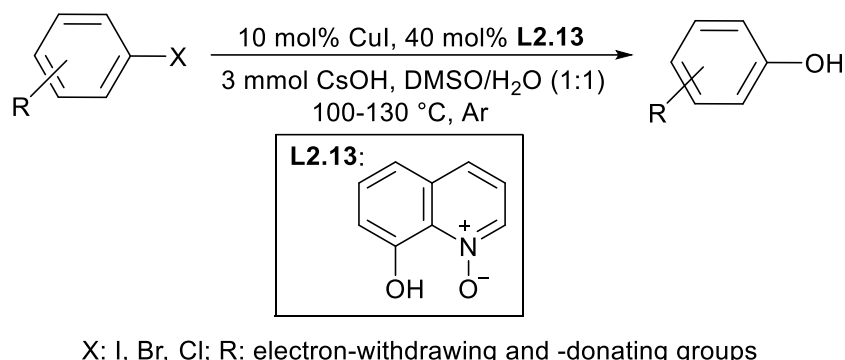
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conversion of 97 % in 7 h at 100 °C (Scheme 2.21) [96]. Their catalyst system could be used for the hydroxylation of activated and non-activated aryl iodides and bromides with excellent conversions, while 4-chlorotoluene resulted in an extremely low conversion. Activated aryl iodides such as 1-iodo-4-nitrobenzene require a lower reaction temperature of 70 °C and a shorter reaction time of 5 h for optimal conversions of 95 to 98 %.



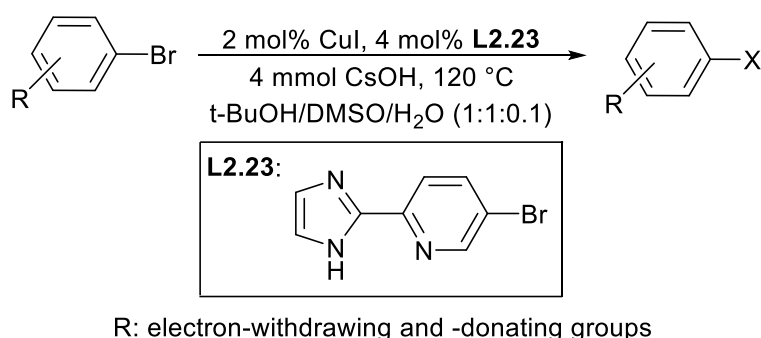
Scheme 2.21: The CuI/**L2.12**/*n*-Bu₄NOH·5H₂O catalyst system for the hydroxylation of aryl iodides, bromides and chlorides at 100 °C [96].

In 2011, Jiang and co-workers improved the reactivity of the hydroxylation reaction for aryl bromides and chlorides, even though high catalyst loadings were required for their CuI/8-hydroxyquinoline-*N*-oxide (**L2.13**) catalyst system in combination with CsOH (Scheme 2.22) [94]. Different solvent systems were evaluated and DMSO/H₂O (ratio of 1:1) was identified as the optimal system for the hydroxylation of 4-iodotoluene with a conversion of 93 % to *p*-cresol in 18 h at 100 °C. Moreover, the success of the hydroxylation reaction was influenced by the nature of the copper salts since decreases of 7 and 8 % in the conversions were obtained when CuI was replaced with copper(I) bromide (CuBr) and CuCl, respectively. An even lower conversion of 75 % was obtained for CuBr₂. The hydroxylation of sterically hindered aryl iodide substrates resulted in the formation of coupling products.



Scheme 2.22: The CuI/**L2.13**/CsOH catalyst system for the hydroxylation of aryl iodides (100 °C), bromides (110 °C) and chlorides (130 °C) [94].

Even though good to excellent conversions were possible for the above-mentioned Cu-based catalyst systems with bidentate ligands, high catalyst loadings (5 to 10 mol% copper and 10 to 20 mol% ligand), harsh operating conditions (up to 140 °C) and the need for an inert atmosphere of nitrogen (N₂) or argon (Ar) were often required [93-96, 99]. Ma and co-workers attempted to improve on the limitation of high catalyst loadings with their CuI/5-bromo-2-(1H-imidazol-2-yl)pyridine (**L2.23**) catalyst system operating at a catalyst loading of 2 mol% copper and 4 mol% ligand. In combination with CsOH and a *t*-BuOH/DMSO/H₂O (ratio of 1:1:0.1) solvent system, aryl bromides could be hydroxylated with moderate to excellent yields of 68 to 93 % in 24 h at 120 °C (Scheme 2.23) [107].



Scheme 2.23: The CuI/**L2.23**/CsOH catalyst system for the hydroxylation of aryl bromides at 120 °C [107].

Different substituted 2-pyridin-2-yl-1H-benzimidazole (**L2.14-L2.21** and **L2.25**) and 2-(1H-imidazol-2-yl)pyridine (**L2.22-L2.24**) ligands were evaluated during the hydroxylation of 4-bromoanisole (Figure 2.4) [107]. No phenolic compounds were obtained for 2-pyridin-2-yl-1H-benzimidazole (**L2.14**) and the substituted versions (**L2.19** and **L2.16**). The efficiency of the ligands increased with the introduction of electron-donating substituents on the pyridine ring (**L2.17-L2.20**). Furthermore, the availability of the free NH-group on the benzimidazole is essential, since the absence thereof resulted in inactive ligands **L2.21** and **L2.25**. Similarly, a

moderate conversion was obtained for the unsubstituted pyridine-based ligand **L2.22**, while the introduction of electron-donating substituents (**L2.23** and **L2.24**) resulted in excellent conversions. Their results suggested ligand **L2.23** as the optimal ligand for their catalyst system during the hydroxylation reactions.

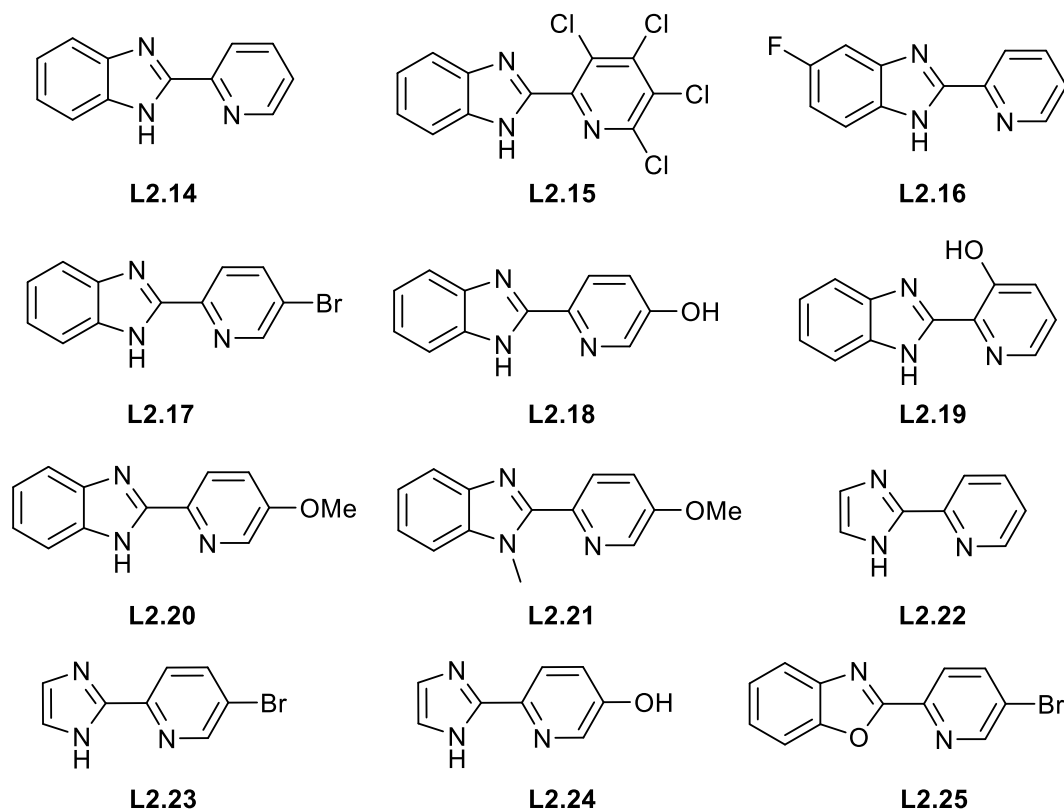
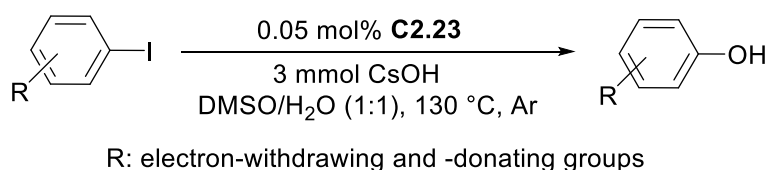


Figure 2.4: The effect of substituted 2-pyridin-2-yl-1H-benzimidazole (**L2.14-L2.21** and **L2.25**) and 2-(1H-imidazol-2-yl)pyridine (**L2.22-L2.24**) ligands on the hydroxylation of 4-bromoanisole were evaluated [107].

In 2012, Cazin and co-workers further decreased the catalyst loading to an extremely low 0.05 mol% when they employed the Cu^I complex, [CuCl(SIPr)] (**C2.23**), bearing *N,N'*-bis[2,6-(di-*iso*-propyl)phenyl]imidazolidin-2-ylidene (SIPr), in combination with CsOH during the hydroxylation of aryl iodides in 24 h at 130 °C, under an inert atmosphere (Scheme 2.24) [97]. They obtained conversions of 99 and 82 % and TON values of 1 980 and 1 640 for the hydroxylation of iodobenzene and 4-iodotoluene, respectively.



Scheme 2.24: The **C2.23**/CsOH catalyst system for the hydroxylation of aryl iodides at 130 °C and under an inert atmosphere [97].

N-heterocyclic carbenes (NHCs), such as *N,N'*-bis-[2,4,6-(trimethyl)phenyl]imidazol-2-ylidene (IMes); *N,N'*-bis[2,4,6-(trimethyl)phenyl]-imidazolidin-2-ylidene (SIMes); *N,N'*-bis[2,6-(di-*iso*-propyl)phenyl]imidazol-2-ylidene (IPr) and SIPr, were employed in the synthesis of Cu^I complexes, **C2.20-C2.23**. These complexes were evaluated in aryl iodide hydroxylation and they found that the NHC ligands only have a moderate influence on the activity of the catalyst under their reaction conditions (Figure 2.5). A solvent system of DMSO/H₂O (ratio of 1:1) was found to be optimal due to the immiscibility of the aryl iodide substrates in water as well as the poor solubility of CsOH in DMSO. They also observed that the conversions were negatively influenced when a base other than CsOH was used [97, 99].

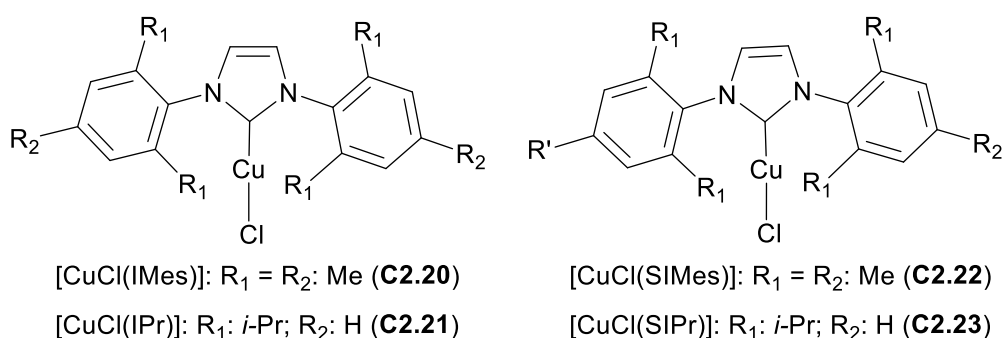
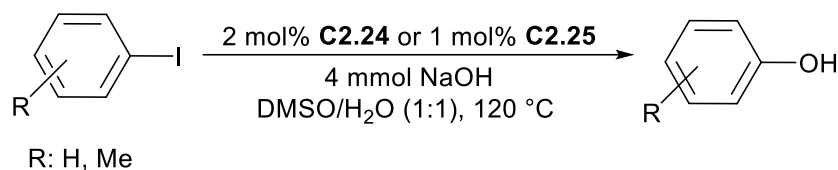


Figure 2.5: Various Cu^I complexes (**C2.20-C2.23**), with *N*-heterocyclic carbene (NHC) ligands, were evaluated in the hydroxylation of aryl iodides [97].

In 2016, Swarts and co-workers reported the application of their Cu^I-based complexes with sodium hydroxide (NaOH) as the base and they obtained a GC-yield of 100 % for the hydroxylation of 4-iodotoluene to *p*-cresol in 3 h at 120 °C (Scheme 2.25) [98]. Various Cu^I complexes (1 or 2 mol%), bearing *N*-propyliminopyridine ligands, were evaluated for the hydroxylation of aryl iodides and they found that an increase in the solubility of the complexes en route to the formation of the active species has a positive influence on the activity of the complexes, since an increased conversion to the phenolic product was possible. Furthermore, a complex with a non-coordinating anion displayed higher activity than those with coordinating anions, because they promote the oxidative addition step during the reaction. The best conversion was obtained for the mononuclear complex, [Cu{(6-Br-C₅H₃N)CH=N(*n*Pr)-κ²-*N,N*}₂][BF₄] (**C2.24**). When the mononuclear complexes were replaced with Cu^I iminopyridine metallodendrimers, similar conversions were obtained in a shorter reaction time and with lower catalyst loadings due to the stabilisation effect of the dendritic ligand on the active copper species. Furthermore, increasing dendrimer generation led to an increase in the catalyst activity. The unsubstituted iminopyridyl Cu^I metallodendrimer complex, [DAB-G₂-PPI-(Cu{(6-Me-C₅H₃N)-κ²-*N,N*}₂)₄][BF₄]₄ (**C2.25**; DAB: 1,4-diaminobutane, PPI: poly(propylene-imine)), could operate in neat water as the solvent to afford *p*-cresol from 4-iodotoluene with a GC-

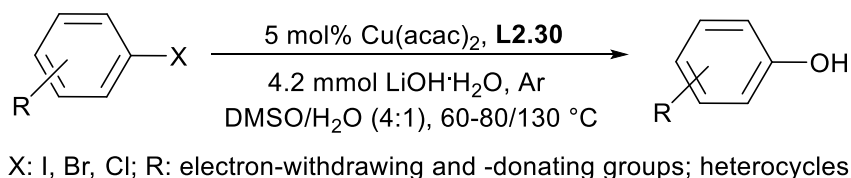
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yield of 55 % after 12 h and 100 % after 24 h. No biaryl ether by-product formation was observed due to the inclusion of a strong base [13, 108].



Scheme 2.25: Evaluation of the mononuclear complex **C2.24** or the iminopyridine metallodendrimer **C2.25** for the hydroxylation of aryl iodides at 120 °C [98].

In a separate study, Ma and co-workers reported on the combination of copper(II) acetylacetonate ($\text{Cu}(\text{acac})_2$), *N,N'*-bis(4-hydroxy-2,6-dimethylphenyl)-oxalamide (**L2.30**) and lithium hydroxide monohydrate ($\text{LiOH}\cdot\text{H}_2\text{O}$) for the hydroxylation of (hetero)aryl iodides, bromides and chlorides (Scheme 2.26) [109]. They obtained a conversion of 87 % for the hydroxylation of 4-chloroanisole to 4-methoxyphenol in 24 h under an inert atmosphere. In contrast to previous reports, lower conversions were obtained when a stronger base such as NaOH or KOH was employed, attributed to the instability of ligand **L2.30** [94, 97, 107, 110]. A higher reaction temperature and catalyst loading of 5 mol% were required for optimal results in a DMSO/H₂O solvent system (ratio of 4:1). Water as co-solvent prevents the coupling between the phenol product and the aryl chloride, while DMSO enhances the solubility of the aryl chloride and intermediates during the reaction.



Scheme 2.26: The $\text{Cu}(\text{acac})_2$ /**L2.30**/ $\text{LiOH}\cdot\text{H}_2\text{O}$ catalyst system for the hydroxylation of (hetero)aryl iodides (60 °C), bromides (80 °C) and chlorides (130 °C) [109].

A series of *N,N'*-disubstituted oxalamide ligands was evaluated during the hydroxylation of 4-chloroanisole (Figure 2.6). Ligands **L2.26** to **L2.28** resulted in no conversion, but an improvement was observed for the 2,6-dimethylaniline derived amide, **L2.29**. Furthermore, a poor conversion was obtained for the methoxy-analogue (**L2.31**) of ligand **L2.29**, while the hydroxyl-analogue (**L2.30**, optimal ligand) resulted in the best conversion to the phenolic product due to the high efficiency and electron-donating ability of the free hydroxyl group within the ligand. Other known ligands, which have found application in the hydroxylation of aryl iodides and bromides, were also evaluated for the aryl chloride substrates, but very poor, if any, conversions were obtained [94, 95, 106, 107]. Their catalyst system could be employed for the successful hydroxylation of (hetero)aryl chlorides at 130 °C, while lower reaction

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temperatures of 60 to 80 °C and catalyst loadings of 0.5 mol% were sufficient for (hetero)aryl iodides and bromides [109]. Better conversions were obtained for more reactive hetero(aryl) iodides using KOH instead of LiOH·H₂O due to the stronger ability of KOH to deprotonate the ligand during the reaction.

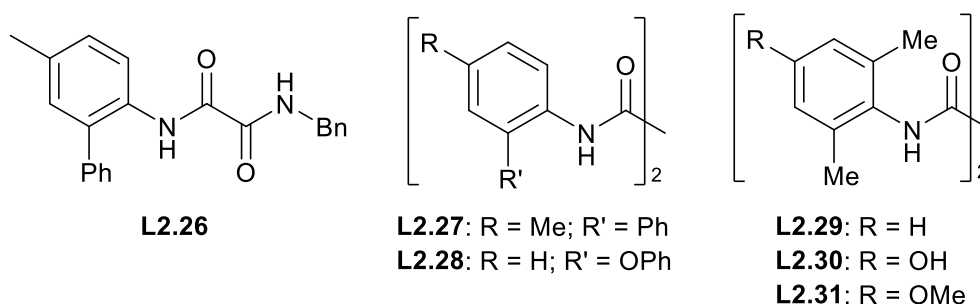
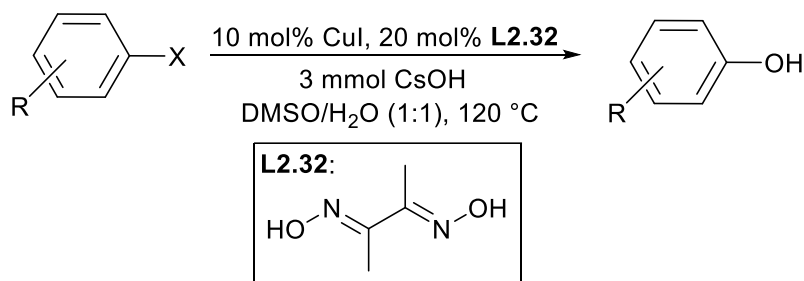


Figure 2.6: The evaluation of *N,N'*-disubstituted oxalamide ligands (**L2.26-L2.31**), in combination with Cu(acac)₂, in the hydroxylation of 4-chloroanisole [109].

In 2018, Shendage and co-workers had to increase the catalyst loading (10 to 20 mol%) for the application of CuI with an inexpensive dimethylglyoxime (**L2.32**) ligand and CsOH in a DMSO/H₂O (ratio of 1:1) solvent system during the hydroxylation of aryl iodides and bromides (Scheme 2.27) [111]. Longer reaction times were required when evaluating aryl bromides as substrates. Conversions of 96 % (10 h) and 89 % (12 h) were obtained for the hydroxylation of iodobenzene and 4-iodotoluene, respectively.



X: I, Br; R: electron-withdrawing and -donating groups; bulky groups

Scheme 2.27: The CuI/**L2.32**/CsOH catalyst system for the hydroxylation of aryl iodides and bromides at 120 °C [111].

Recently, we evaluated Cu^I in combination with novel pyrazolylpyridineamine ligands as pre-catalysts for the hydroxylation of aryl iodides and bromides when using NaOH as the base (Figure 2.7 and Chapter 3) [112]. The *N*-unsubstituted pyrazole-based ligands (**L2.33** and **L2.34**) gave conversions of 86 and 65 %, respectively, whereas the *N*-methyl substituted derivatives (**L2.35** and **L2.36**) resulted in lower conversions of 62 and 34 %. As such, both the steric and electronic effects of the methyl groups on the pyrazole ring of the ligand and the

availability of the NH-proton have a greater negative influence on the success of the reaction, than the substituents on the ethyl-linked *N*-atom [3, 9, 107, 110, 113].

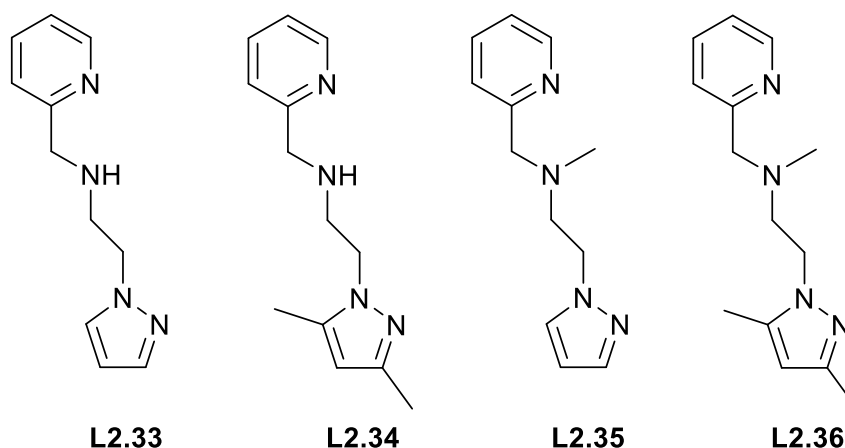
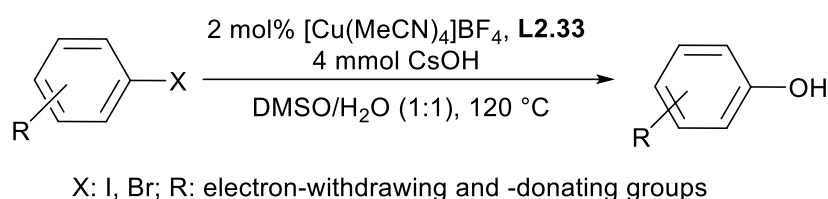


Figure 2.7: Novel pyrazolylpyridineamine ligands, **L2.33-L2.36**, were synthesised and evaluated, in combination with Cu^I, in the hydroxylation of 4-iodotoluene [112].

Our [Cu(MeCN)₄]BF₄/**L2.33**/CsOH catalyst system could be used for the hydroxylation of a selection of aryl iodides (conversion: 70 to 96 %), while lower conversions of 41 to 68 % were obtained for the less reactive aryl bromide substrates under ambient air at 120 °C (Scheme 2.28). No phenolic product was observed in the absence of the copper precursor, while extremely low conversions of 2 to 12 % were obtained in the absence of a base. We identified an induction period that could be drastically shortened by the pre-reaction of ligand, precursor and base.



Scheme 2.28: The [Cu(MeCN)₄]BF₄/**L2.33**/CsOH catalyst system for the hydroxylation of aryl iodides and bromides at 120 °C [112].

In conclusion, high conversions to the corresponding phenolic compounds were possible for the Cu-based catalyst systems described above, yet they still suffer from the traditional drawbacks. Optimal catalyst systems were reported by the groups of Cazin, Ma and Swarts, where excellent conversions were obtained for the hydroxylation of aryl halides, each of which has eliminated these drawbacks to a certain extent. The next section details studies of the reversible Cu^I/Cu^{III}/Cu^I and Cu^{II}/Cu^{III}/Cu^I couples implicated in the various mechanistic pathways for the hydroxylation of aryl halides.

2.2.2.1 Mechanistic aspects

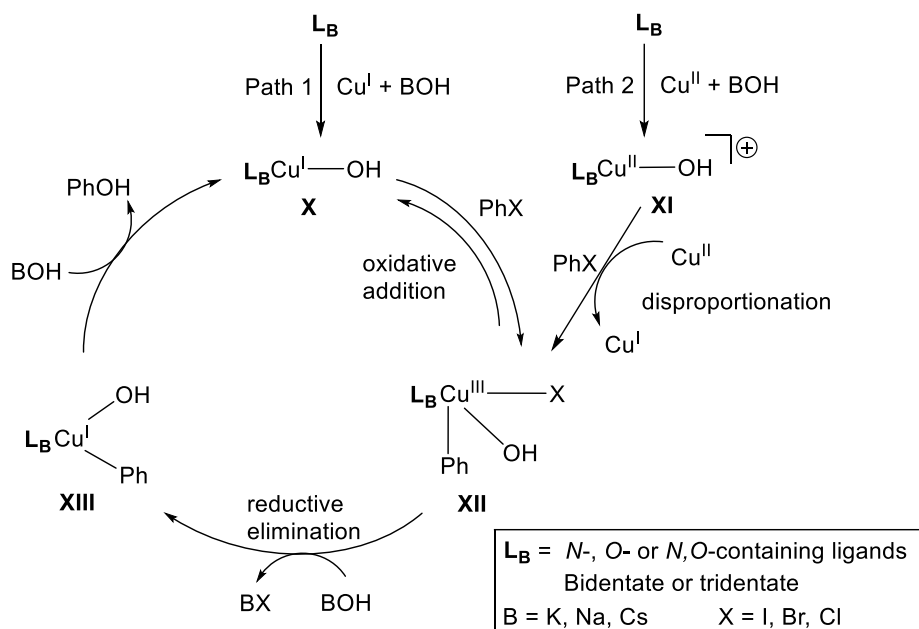
Taillefer, Ciofini and co-workers employed computational DFT and cyclic voltammetry (CV) studies to investigate the mechanistic pathway for the Cu-catalysed hydroxylation of aryl halides [108, 114, 115]. The reaction between Cu^{I} and ligand L_{B} (possible ligands for hydroxylation reactions) affords $\text{L}_{\text{B}}\text{Cu}^{\text{I}}$, which then reacts with a hydroxide base, BOH (B: K, Na, Cs), to afford $\text{L}_{\text{B}}\text{Cu}^{\text{I}}\text{-OH}$, **X** (Scheme 2.29) [103]. Cazin and co-workers have also hypothesised the formation of an $(\text{NHC})\text{Cu-OH}$ complex during the reaction [97]. They evaluated the well-defined $(\text{IPr})\text{Cu-OH}$ complex to support their hypothesis, which resulted in a lower conversion, relative to the obtained conversion for the **C2.21**/CsOH catalyst system. As such, they suggested slow dosing of this active species during the hydroxylation reaction for optimal catalytic activity.

Alternatively, our group has also suggested the formation of a Cu-hydroxo species. This was confirmed by allowing the *in situ* formation of the $[(\text{L2.33})\text{Cu-OH}]$ active species before the addition of the aryl halide substrate [112]. Our group observed an induction period of 90 min under the optimised reaction conditions with a catalyst loading of 2 mol%; however, a significantly shorter induction period was observed in the initial presence of $[(\text{L2.33})\text{Cu-OH}]$ and complete conversion was obtained in a shorter reaction time of 1 h. Computational and EPR studies revealed that the type of Cu-hydroxo species is influenced by the pH of the reaction [116, 117]. As such, both $\text{L}_{\text{B}}\text{Cu}^{\text{II}}\text{-OH}$ and the $\text{L}_{\text{B}}\text{Cu}^{\text{II}}\text{-OH}$ dimer may be present in the reaction due to the high pH of 15 to 16. However, the deactivating nature of the dimeric species, as previously reported, allowed us to assume the presence of only monomeric $\text{L}_{\text{B}}\text{Cu}^{\text{II}}\text{-OH}$ species [118].

The oxidative addition of the aryl halide substrate to **X** revealed the formation of the Cu^{III} intermediate, **XII** (Scheme 2.29, Path 1). Alternatively, the reaction between Cu^{II} , L_{B} and BOH is also possible to generate $\text{L}_{\text{B}}\text{Cu}^{\text{II}}\text{-OH}$ species, **XI**. Similar observations were previously proposed for reactions such as cross-coupling with boronic acids, arene hydroxylation and nitration [119-122]. These $\text{Cu}^{\text{II}}\text{-hydroxo}$ species then react with another Cu^{II} group during a disproportionation reaction, in the presence of PhX , to afford Cu^{I} and the Cu^{III} intermediate, **XII** (Scheme 2.29, Path 2). The electrochemical analysis did not reveal the presence of a Cu^{III} intermediate, but several groups have proposed the formation thereof, using experimental and DFT studies [119, 123, 124]. The rapid elimination of the halogen from **XII**, followed by a reduction step, affords $\text{L}_{\text{B}}\text{Cu}^{\text{I}}(\text{OH})\text{Ph}$, **XIII**. The regeneration of $\text{L}_{\text{B}}\text{Cu}^{\text{I}}\text{-OH}$, **X** was possible when the phenolic product was released [125-127]. In conclusion, the hydroxylation of aryl halides proceeds via two mechanistic pathways, differing only in the initial oxidation state of

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the copper precursor. Both pathways involve the formation of Cu^{III} species during the reaction. The synthesis of cyclic alcohols and ketones via the peroxidation of cyclohexane is described in the next section.



Scheme 2.29: The proposed $\text{Cu}^{\text{I}}/\text{Cu}^{\text{III}}/\text{Cu}^{\text{I}}$ or $\text{Cu}^{\text{II}}/\text{Cu}^{\text{III}}/\text{Cu}^{\text{I}}$ mechanistic pathways for the hydroxylation of aryl halides. Adapted from the groups of Wang, Taillefer and Ciofini [103, 108, 115].

2.2.3 Peroxidation reactions

Alkanes have limited use due to the inertness of its C-H bonds towards chemical transformations, which have received great attention. These inexpensive hydrocarbons can be oxidised to value-added products such as alcohols, ketones and aldehydes, which are more reactive than alkanes. One of the first methods to oxidise hydrocarbons into oxygenates is the DuPont process, which uses a Co^{III} naphthalene catalyst [128, 129]. This two-step process involves an air oxidation step to convert cyclohexane to cyclohexanol or cyclohexanone, followed by nitric acid-assisted oxidation to afford adipic acid. The involvement of a corrosive acid as the oxidant is a concern for this process, since extremely low product yields and selectivities are obtained under these harsh reaction conditions. Alternatively, hydrocarbon oxidation may also involve a peroxidation reaction under mild reaction conditions using H_2O_2 as oxidant. During these reactions, a hydrogen atom of an organic compound is replaced with a hydroperoxide group, which could then either terminate the peroxidation reaction or undergo a homolytic cleavage reaction to obtain the corresponding alcohol and ketone products. In this review, the focus is on the peroxidation of hydrocarbons such as cyclo- and linear alkanes to valuable pharmaceutical and chemical compounds.

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Hydrocarbon activation under mild reaction conditions can be accomplished using Gif systems, which include an electron source or reductant (copper or zinc powder), O_2 as the oxidant and an iron-based catalyst, to obtain product yields of 10 to 25 % with ketones as the major product [130-132]. Gif chemistry involves the fast oxidation of saturated hydrocarbons to obtain the corresponding ketone products. The characteristics of these systems can be maintained while varying the reductant, solvent and oxidant. However, low amounts of oxidation products are obtained with these systems due to competitive solvent oxidation and ketonisation of the substrate [133, 134]. One of the first examples of a Cu-based catalyst system that shares properties with the Gif system was reported by Barton and co-workers in 1992 [24]. They combined copper powder, pyridine, acetic acid and H_2O_2 (30 % in H_2O) for the peroxidation of cyclohexane, but a very low product yield of less than 5 % was obtained after 24 h [133]. Initially, they thought that their catalyst system involves a non-radical mechanistic pathway, similar to the Gif system, but experimental work suggested the involvement of radical species during the peroxidation of cycloalkanes [24, 135]. They also observed that the basicity of pyridine facilitates the elimination of H_2O from H_2O_2 , leading to cyclohexanone formation as the major product.

A similar method was employed by Sawyer and co-workers in 1993 where they investigated the activation of either H_2O_2 (50 % in H_2O) or TBHP in the bis(2,2'-bipyridine)copper(I) ($[Cu^I(bpy)_2]^+$, **C2.26**) catalyst system with a solvent system of acetonitrile (MeCN)/pyridine (ratio of 4:1) [136]. The addition of an oxidation-resistant co-solvent such as MeCN has numerous advantages. These include stabilisation of the Cu-based pre-catalyst via MeCN coordination, increased solubility of the hydrocarbon substrate and oxidised products and lastly an increase in the overall reaction stability leading to fewer side-reactions [24]. The efficiency of the peroxidation reaction increased when employing TBHP as oxidant, instead of H_2O_2 and they could improve on the initial product yield of < 5 % to obtain 15 % in 3 h with their **C2.26**/TBHP/ O_2 catalyst system. They were able to employ their catalyst system for the peroxidation of cyclohexane, methylcyclohexane and adamantane, where the ketone product was observed as the major product in all cases.

In ensuing years, several transition metals such as iron, manganese, vanadium and cobalt have been employed as catalysts for the peroxidation of cycloalkanes. The inclusion of copper to this list has high potential interest due to its widespread availability and low cost [20, 25, 134, 137-145]. A mixed solvent system of MeCN/ H_2O is crucial for the solubilisation of the catalyst and the hydrocarbon substrate [146]. In addition, it was observed that H_2O , as a sole solvent, suppresses the catalytic activity of the Cu-based catalyst system. Various mononuclear Cu^I -/ Cu^{II} -based catalyst systems have been reported between 1997 and 2003

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for cyclohexane peroxidation; however, they usually require high reaction temperatures with extremely low product yields of 4 to 18 % (Table 2.1) [60, 137, 147-150].

Table 2.1: A summary of some of the first Cu^I-/Cu^{II}-based catalyst systems, which usually require high reaction temperatures, for cyclohexane peroxidation with extremely low product yields. These catalyst systems were reported between 1997 and 2003.

Catalyst	Oxidant	Temp (°C)	Time (h)	Product yield (%)	Ref
[Cu(MeCN) ₄]BF ₄ ^a	TBHP/PAA	60	5	12	[147]
[Cu ₂ (Py ₂ SSPy ₂)](ClO ₄) ₂ ^b	H ₂ O ₂ /TBHP	25	0.5	4	[149]
[Cu(salen)] ^c	H ₂ O ₂ [*]	80	5	18	[60]
[Cu(tma) ₂] ^d	TBHP	70	24	11	[137]
[CuCl ₁₆ Pc] ^e	O ₂ /TBHP	70	8	12	[151]
[Cu(bdpg)Cl]Cl ^f	H ₂ O ₂ [*]	25	2	7	[150]
[(CuCl ₂) ₄ (18-crown-6) ₂ (H ₂ O) ₂] ^g	O ₂	70	24	4	[152]
Cu(OH) ₂	O ₂	20	24	4	[153]
Cu-SiO ₂	TBHP	75	24	4	[148]
Cu(NC ₃)Si-MCM-41	H ₂ O ₂	100	12	5	[154]

^a [Cu(MeCN)₄]BF₄: tetrakis(acetonitrile)copper(I) tetrafluoroborate; PAA: peroxyacetic acid. ^b Py₂SSPy₂: bis{2-[N,N-bis(2-pyridylethyl)amino]-1,1-dimethylethyl} disulfide. ^c Cu(salen): N,N'-(1,2-ethylene)-bis(salicylaldamine)-copper(II). ^d tma: trimethyl acetate. ^e PC: phthalocyanines. ^f bdpg: N,N-bis-(2-pyridylmethyl)-β-alanineamide. ^g In the presence of acetaldehyde additive. * 30 % in H₂O.

In the following years, several Cu-based catalyst systems were reported with improved product yields for hydrocarbon peroxidation. These catalyst systems are summarised in Table 2.2 and described in more detail. An excess of H₂O₂ (8 to 10 equiv.) as the oxidant is required for the optimal cycloalkyl hydroperoxide formation; however, extreme amounts might lead to over-oxidation [146].

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Table 2.2: The development of mono- and multinuclear Cu-based catalyst systems for the peroxidation of cyclohexane and/or cyclooctane.^a

Entry	Catalyst/Complex	n	Yield (%)	C-OH (%)	C=O (%)	Ref
1 ^b	[Cu ₄ (tea) ₄ -(BOH) ₄ (μ-O)][(BF ₄) ₂] (C2.27) ^c	2	38.5	24.3	14.2	[128]
2 ^b	[Cu ₃ (μ ₃ -OH)(μ-pz) ₃ (EtCO ₂) ₂ (H ₂ O)] (C2.28) ^d	2	32	23.6	8.6	[155]
3 ^e	[Cu(μ-dipic) ₂ {Na ₂ (μ-H ₂ O) ₄ }] _n ·2nH ₂ O (C2.29)	2	11.1	9.3	1.8	[156]
4 ^f	[Tp ^{Br3} Cu(NCMe)] (C2.30) ^g	2	24.5	9.3	14	[27]
		4	11	0	9.8	
5 ^{e,h,i}	[Cu ₄ (μ ₄ -Hedte) ₂ (Hpma) ₂ (H ₂ O)] (C2.31)	2	16.2	-	-	[157]
		4	19.3	-	-	
6	[Cu(L2.37)(H ₂ O)(im)]·3H ₂ O (C2.32) ^j	2	23	21.7	1.3	[158]
		4	20	18.1	1.9	
7	[Cu(TMPA)(NCMe)][PF ₆] (C2.33) ^k	4	47	43	4	[25]
8	[Cu(<i>R,R</i>)-(BPBP)][PF ₆] (C2.34) ^l	2	56	50	6	[25]
9 ^{m,n}	[CuCl ₂ (R ¹ -dtpy)] (C2.10)	2	23	-	-	[63]
10 ^o	NHC-Cu-I (C2.19) ^p	2	39 ^q	24.6	14.4	[70]
11 ^{e,l,n}	[Cu ₂ (μ-Hbdea) ₂ (μ-bdca)] _n (C2.40)	2	21.1	10.8	10.3	[28]
		4	16.2	3.5	12.7	
12 ^{e,i}	Cu ^{II} -complex (C2.41)	2	15	10	5	[159]
13 ^{b,r}	[Cu ₂ (L2.40) ₂ (μ ₂ -Cl)Cl] (C2.42) ^s	2	48.2	29.8	18.4	[160]

^a Time: 6 h; room temp; oxidant: H₂O₂, unless stated otherwise. ^b Additive: HNO₃. ^c Tea: triethanolamine.

^d Pz: pyrazolate. ^e Temp: 50 °C. ^f Traces of dehydrogenation by-products. ^g Tp: hydrotrispyrazolylborate.

^h Time 3 h. ⁱ Additive: Trifluoroacetic acid (TFA). ^j **L2.37**: 5-(2-(2-hydroxyphenyl)hydrazono)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione; im: imidazole. ^k TMPA: tris(2-pyridylmethyl)-amine. ^l (*R,R*)-BPBP: (2*R*,2*R'*)-1,1'-bis(2-pyridinylmethyl)-2,2'-bipyrrrolidine.

^m Temp: 60 °C; oxidant: H₂O₂/TBHP. ⁿ Time: 2 h. ^o Temp: 80 °C; time: 24 h. ^p Triazolylidene copper(I) catalysts. ^q Product yield and distribution: mol%.

^r Temp: 40 °C; time: 48 h. ^s **L2.40**: 1-((2-hydroxyethylimino)methyl)naphthalene-2-ol.

Even though several studies have focused on the evaluation of mononuclear Cu-based complexes in peroxidation catalysts, the same is not true for multinuclear Cu-based

complexes. Pombeiro and co-workers reported one of the first examples of a multinuclear Cu^{II}-based catalyst system in 2006. They evaluated a tetranuclear Cu^{II} complex, **C2.27**, with an excess of H₂O₂ (30 % in H₂O) and HNO₃ for the peroxidation of cyclohexane (Table 2.2, entry 1 and Figure 2.8) [128, 161]. An improved product yield of 39 % was obtained in 6 h.

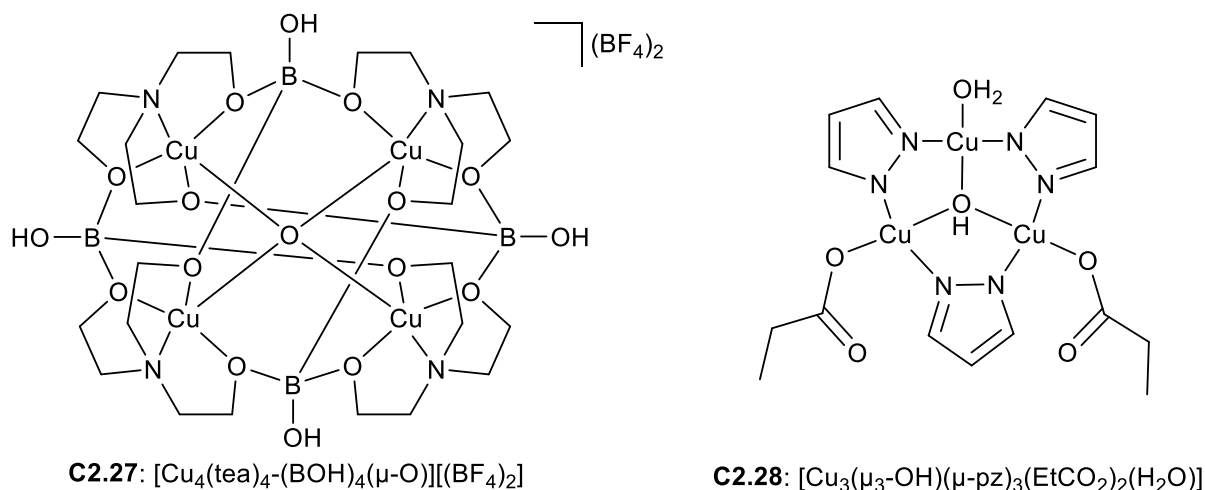
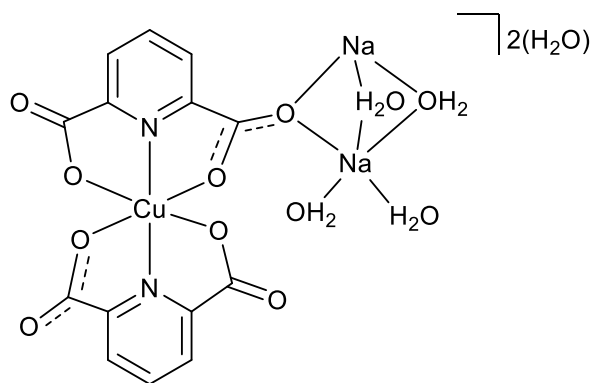


Figure 2.8: Complexes **C2.27** and **C2.28** have been employed in combination with H₂O₂ and HNO₃ for the peroxidation of cyclohexane [128, 155].

In 2007, Pettinari and co-workers reported the combination of trinuclear copper(II) complexes such as $[\text{Cu}_3(\mu_3\text{-OH})(\mu\text{-pz})_3(\text{EtCO}_2)_2(\text{H}_2\text{O})]$ (**C2.28**), bearing anionic pyrazolate (pz) and carboxylate ligands. Complex **C2.28**, with H₂O₂ (30 % in H₂O) and HNO₃, was used for the peroxidation of cyclohexane with a product yield of 32 % in 6 h (Table 2.2, entry 2 and Figure 2.8) [155, 162, 163]. A high selectivity towards the alcohol product was obtained, while no by-products were observed. Their catalyst system could also be employed for the peroxidation of cyclopentane with a product distribution (CyOH/CyO) of 22.6/8.4 % and a total product yield of 31 %. No reaction occurred in the absence of the Cu-based complex. The efficiency of the reaction depends on the concentration of HNO₃ and H₂O₂ since an increase in either of the two reaction parameters increased the product yields, but a decrease in the product yield was also observed in a highly acidic environment.

In 2008, Pombeiro and co-workers evaluated complex **C2.29** in combination with H₂O₂ (50 % in H₂O) for the peroxidation of cyclohexane at 50 °C and they obtained a product yield of 11 % (Table 2.2, entry 3 and Figure 2.9) [156]. Cyclopentane peroxidation was also possible and they obtained a product yield of 10 % with a product distribution (CyOH/CyO) of 9.1/0.8 %. No reaction occurs in the absence of the Cu-based catalyst. An advantage of their catalyst system is that it can operate in the absence of an acid promoter because the activity thereof is suppressed in the presence of HNO₃.



C2.29: $[\text{Cu}(\mu\text{-dipic})_2\{\text{Na}_2(\mu\text{-H}_2\text{O})_4\}]_n \cdot 2n\text{H}_2\text{O}$

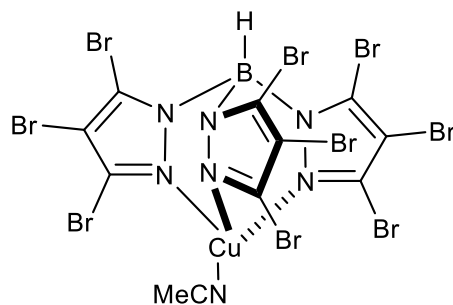
Figure 2.9: The application of complex **C2.29** in combination with H_2O_2 for hydrocarbon peroxidation [26, 156].

Pombeiro and co-workers further expanded their work in 2009 by including more novel trinuclear Cu^{II} -based complexes. However, none of these complexes could improve on the product yields obtained for the peroxidation of cyclohexane relative to using complex **C2.28** (Table 2.2, entry 2 and Figure 2.8) [26, 155]. Decreased product yields were obtained when the trinuclear Cu^{II} complexes were replaced with copper(II) carbonate or copper(II) 2-methylbutyrate, while no oxidation products were obtained in the absence of a Cu^{II} catalyst. An increase in the ratio of H_2O_2 :catalyst from 250 to 750 increased the product yield from 27 to 34 %. Furthermore, high amounts of H_2O_2 favour the decomposition of the cyclohexyl hydroperoxide product and it may also result in a change in the selectivity to rather afford cyclohexanone as the major product.

In conclusion, the efficiency of the peroxidation reactions depends on the amounts of Cu-based catalyst, oxidant and substrate, the type of solvent system, reaction time and temperature. Several studies have highlighted the importance of an acid co-catalyst to improve on the product yields; however, a decrease in the product yields was also observed in a highly acidic environment. The above-mentioned catalyst systems often require harsh reaction conditions such as high temperatures, the use of strong oxidants and sometimes environmentally unfriendly reagents, stoichiometric additives and the addition of an acidic medium [164]. These drawbacks lead to poor selectivity, low product yields and undesired environmental and economic costs during peroxidation reactions. More recent reports have shown that Cu-based peroxidation catalysts can also be active in the absence of an acid environment.

The application of $[\text{Tp}^{\text{X}}\text{Cu}(\text{NCMe})]$ (X: Br_3 , Br, Me_3 , Me_2 or Ph) complexes with H_2O_2 in the oxidation of benzene to phenol was reported by Pérez and co-workers in 2011 [165]. Later, in 2013, they expanded their research by evaluating complex **C2.30** in combination with H_2O_2

(30 % in H₂O) for the peroxidation of cyclohexane (25 %) and -octane (11 %, Table 2.2, entry 4 and Figure 2.10). Even though cyclohexanol and cyclohexanone (major product) were obtained as the products for cyclohexane peroxidation, they also found traces of the two dehydrogenation by-products, cyclohexene (1 %) and cyclohexene oxide (0.5 %) [27]. Similar results were observed for the peroxidation of cyclooctane.



C2.30: [Tp^{Br3}Cu(NCMe)]

Figure 2.10: Complex **C2.30** was used in combination with H₂O₂ for the peroxidation of cycloalkanes [27].

The formation of dehydrogenation products during peroxidation reactions was not observed previously for Cu-based catalyst systems where radical species are formed. However, the dehydrogenation of activated (benzylic) C-H bonds was previously observed with a manganese-catalysed system [166, 167]. As such, the authors proposed the formation of metal-oxo species, instead of the radical species, during the peroxidation reaction [27]. Their results revealed that long reaction times and high temperatures, close to the boiling point of the hydrocarbon substrate, have a negative influence on the peroxidation reaction because lower product yields were obtained. Less-reactive linear alkanes such as *n*-hexane were also evaluated and a product yield of 9 % was obtained in 3.5 h. The main products were internal alcohols as well as over-oxidised analogues.

Kirillov and co-workers further expanded on the application of tetranuclear Cu-based complexes, bearing a cubane core (Cu₄O₄), such as [Cu₄(μ₄-Hedte)₂(Hpmal)₂(H₂O)] (**C2.31**) for peroxidation reactions in 2015 (Figure 2.11) [157]. Various organic building blocks, *N,N,N',N'*-tetrakis(2-hydroxyethyl)ethylenediamine (H₄edte), salicylic acid (H₂sal) and phenylmalonic acid (H₂pmal), were employed during the synthesis of these tetranuclear Cu-based complexes. They evaluated **C2.31** in combination with H₂O₂ (50 % in H₂O) and TFA for the peroxidation of cyclohexane (16 %) and cyclooctane (19 %) in 3 h at 50 °C (Table 2.2, entry 5). Moreover, product yields of 9 and 20 % were obtained for the peroxidation of cyclopentane and -heptane, respectively. The distribution between the alcohol and ketone product is unclear for their catalyst system.

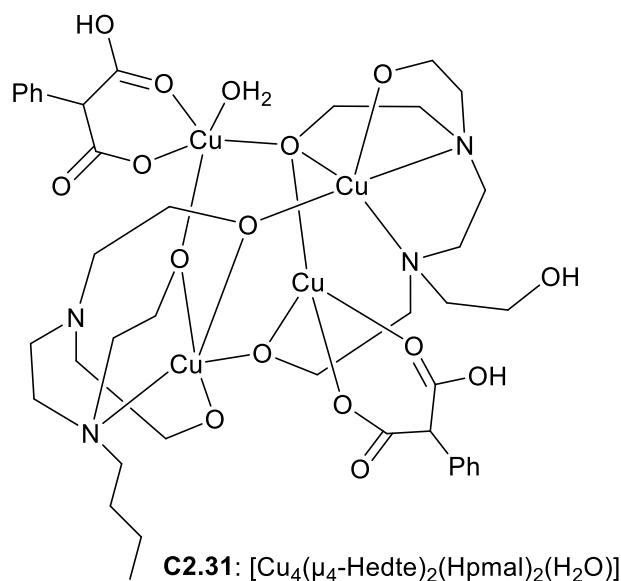


Figure 2.11: Complex **C2.31**, in combination with H_2O_2 and TFA, was evaluated for cycloalkane peroxidation reactions [157].

Decreased product yields were obtained in the absence of an acid promotor, which dropped to zero in the absence of **C2.31**. The type of acid promotor affects the catalytic efficiency with similar product yields of 15 % obtained for either TFA or HNO_3 . A longer reaction time was, however, required for sulphuric acid (H_2SO_4) to obtain the same product yield. When employing HCl, the reaction was completed in 3 min, with a comparable product yield of 13 %. The rate of H_2O_2 decomposition also decreased in the acidic environment. Their catalyst system could also be employed for the peroxidation of linear alkanes such as *n*-pentane, *n*-hexane, *n*-heptane and *n*-octane, but extremely low product yields of 3 to 10 % were obtained. Lastly, methylcyclohexane was also evaluated and they observed preferential oxidation of the 3° over the 2° C-atoms.

Later, in 2016, Pombeiro and co-workers synthesised water-soluble tetranuclear Cu^{II} complexes, which consist of copper(II) nitrate hydrate ($\text{Cu}(\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$) and an arylhydrazone of barbituric acid (AHBA) ligand [158]. Functionalised AHBA ligands with -OH, - SO_3H or - COOH substituted groups were previously reported for cyclohexane peroxidation and low product yields of 6 to 21 % were obtained, with selectivity (89 to 98 %) towards the formation of cyclohexanol [168]. They evaluated the tetranuclear Cu^{II} complex, **C2.32**, bearing 5-(2-(2-hydroxyphenyl)hydrazono)-pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**L2.37**), in combination with H_2O_2 (30 % in H_2O) and TFA as an acid promotor for the peroxidation of cyclohexane (23 %) and -octane (20 %) in 6 h (Table 2.2, entry 6 and Figure 2.12). Moreover, they also evaluated the peroxidation of cyclopentane (11 %) and -heptane (25 %) with a selectivity towards the corresponding alcohol products according to their respective product distributions

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(CyOH/CyO) of 9.8/1.2 % and 23.4/1.6 %. The importance of the ligand during the proton-transfer step was confirmed with a decrease in the product yield in the absence of the ligand [169].

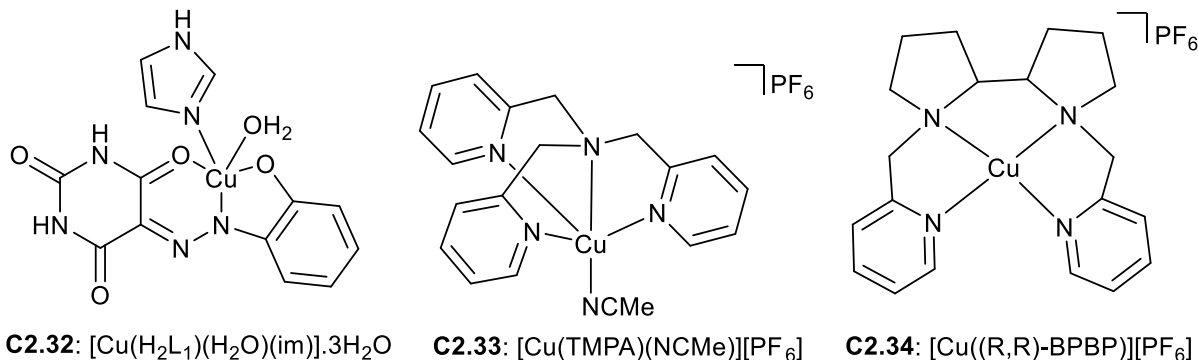


Figure 2.12: Complex **C2.32** and the *in situ* formed catalysts **C2.33** and **C2.34** were evaluated in combination with H₂O₂ and TFA for the peroxidation of cycloalkanes [25, 158].

In a separate study, Garcia-Bosch and co-workers investigated the effect of various tetra-, tri-, bi- and monodentate ligands such as (2*R*,2'*R*)-1,1'-bis(2-pyridinylmethyl)-2,2'-bipyrrolidine ((*R,R*)-BPBP, **L2.38**) and tris(2-pyridylmethyl)-amine (TPMA, **L2.39**) in combination with [Cu(MeCN)₄]⁺PF₆⁻ on peroxidation reactions. The Cu^I catalysts, [Cu(TPMA)(NMe)][PF₆] (**C2.33**) and [Cu(*R,R*)-BPBP][PF₆] (**C2.34**), were formed *in situ* before initiating the reaction, since no significant change in the product yield was observed when isolated complexes were employed as pre-catalysts (Figure 2.12). They were able to generate product yields of 56 and 47 % in 6 h for the peroxidation of cyclohexane and -octane, respectively (Table 2.2, entries 7 and 8) [25]. Cyclopentane (39 %) and -heptane (47 %) peroxidation was also possible with product distributions (CyOH/CyO) of 32/7 % and 39/8 %, respectively. This represents the current state-of-the-art for copper-catalysed peroxidation. Cyclohexyl hydroperoxide products were observed and they proposed that their catalysts can discriminate between the presence of H₂O₂ and these products, thereby preventing the formation of cyclohexane and cyclohexanone.

Evaluating the linear alkane, *n*-hexane, afforded a product yield of 20 to 30 %, which consists of a mixture of C1, C2 and C3 oxidation products. Internal C-H bonds, instead of terminal bonds, were preferentially activated during these reactions. Further experiments involve the confirmation of C-centred and O-centred radicals within the reaction. A mixture of *trans/cis* products was observed for the peroxidation of *cis*-1,2-dimethylcyclohexane, which confirmed the presence of C-centred radicals. Despite the low product yield of less than 10 % for the peroxidation of toluene, a mixture of oxidation products (*o*-, *m*-, *p*-cresol) was observed, which confirmed the presence of O-centred radicals. Lastly, the addition of radical traps such as

CCl_3Br to the reaction resulted in the formation of cyclohexyl bromide and -chloride products, instead of the hydroperoxo product, and the product yield was decreased to less than 30 %. These results further support the formation of radical species [25, 170].

In 2017, Shul'pin and co-workers reported on the application of a Cu^{II} complex, **C2.10**, in combination with H_2O_2 (30 % in H_2O) for the oxidation of activated alcohols or the peroxidation of hydrocarbons [63]. The peroxidation of cyclohexane mediated by their **C2.10**/ H_2O_2 catalyst system led to a product yield of 23 % in 2 h at 60 °C (Table 2.2, entry 9 and Figure 2.3). The product distribution was, however, unclear for their catalyst system. Their results for the peroxidation of linear and substituted cyclic alkanes confirmed the formation of radical species during the reaction.

The application of NHC-Cu^{I} complexes, bearing triazolyldiene (1-(*R*)-3-methyl-4-phenyl-1*H*-1,2,3-triazol-3-ium-5-yl) ligands, for the peroxidation of cyclohexane was reported by Mncube and Bala in 2018 [70]. The steric hindrance of the bulky aromatic substituents on the N_3 -atom of complexes **C2.35** (*R*: phenyl) and **C2.19** (*R*: propyl) has a negative influence on the catalytic activity leading to decreased product yields relative to complexes **C2.36** (*R*: mesitylenyl) and **C2.37** (*R*: hexyl), bearing aliphatic substituents on the N_3 -atom (Figure 2.13).

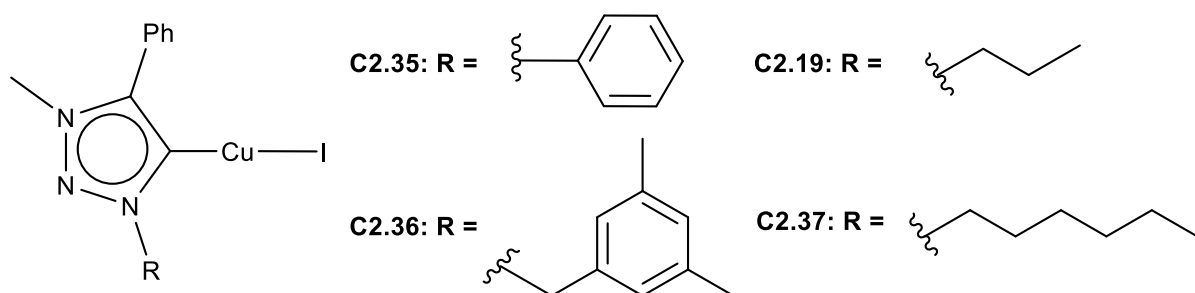


Figure 2.13: Various NHC- Cu^{I} complexes, **C2.19** and **C2.35-C2.37** (ratio of 1:1.1 for NHC:Cu), were evaluated for the peroxidation of cyclohexane [70].

Complex **C2.19**, in combination with H_2O_2 (30 % in H_2O), was used for cyclohexane peroxidation resulting in a product yield of 39 mol% in 24 h at 80 °C (Table 2.2, entry 10). Cyclohexyl hydroperoxide was observed as the major product before treatment with an excess of PPh_3 , which confirms the formation of radical species during the reaction. A change in the ratio of NHC:Cu from 1:1 to 1:2 had a negligible effect on the product yield, while increasing the selectivity towards cyclohexanone. The reaction proceeded with no induction period while no oxidation products were observed in the absence of the catalyst. Furthermore, their catalyst system could also be employed for the peroxidation of toluene and linear alcohols such as *n*-octane to obtain a mixture of oxidation products. These observations support the formation of radical species during the reaction, which was further confirmed by the suppression of the

catalytic activity in the presence of radical traps. Initial rate studies confirmed the gradual catalyst decomposition that was exacerbated in an acidic environment. The efficiency of the peroxidation reaction increased with an increase in the reaction temperature, but it was limited to 80 °C due to the volatility of cyclohexane as well as the solvent.

In 2019, Kirillov and co-workers reported on the synthesis and application of mono-([Cu(H_{1.5}bdea)₂](hba)·2H₂O, **C2.38**) and binuclear ([Cu₂(μ-Hbdea)₂(aca)₂]·4H₂O, **C2.39**) complexes as well as the 1D coordination polymer ([Cu₂(μ-Hbdea)₂(μ-bdca)]_n, **C2.40**) for peroxidation reactions at a lower reaction temperature and shorter reaction time (Figure 2.14) [28]. Building blocks and supporting ligands such as *N*-butyldiethanolamine (H₂bdea), 4-hydroxybenzoic acid (Hhba), 4,4'-biphenyldicarboxylic acid (H₂bdca) and 9-anthracenecarboxylic acid (Haca) were employed to generate *N,O*-containing ligands during the synthesis of these materials. They evaluated the **C2.40**/H₂O₂/TFA (50 % in H₂O) catalyst system for the peroxidation of cyclohexane (21 %) and -octane (16 %) in 2 h at 50 °C (Table 2.2, entry 11). No improvement in the product yields or over-oxidation was obtained in longer reaction times, while a preferential formation for the corresponding ketone products was observed, except in the case of cyclohexane. They were also able to employ their catalyst system in the peroxidation of cyclopentane (10 %) and -heptane (25 %) with product distributions (CyOH/CyO) of 3.5/6.6 % and 10/14.5 %, respectively. An increase in the concentration of the acid promoter increased the product yield [146, 157, 171]. Moreover, when TFA was replaced with HCl for cyclohexane peroxidation, they could speed up the reaction time from 2 h to only a few minutes, but a lower product yield of 16 % was obtained due to the possibility of the Cl⁻ anions to act as ligands to stabilise the Cu-peroxo intermediates or Cu^I oxidation state [146]. They observed a first-order dependence on the catalyst and H₂O concentration, which confirms the involvement of both Cu-based species and H₂O during the rate-limiting step of the peroxidation reaction. This is, however, in contrast with previous studies where the addition of H₂O leads to a lower reactivity due to a decrease in the concentration of H₂O₂ and substrate solubility [146].

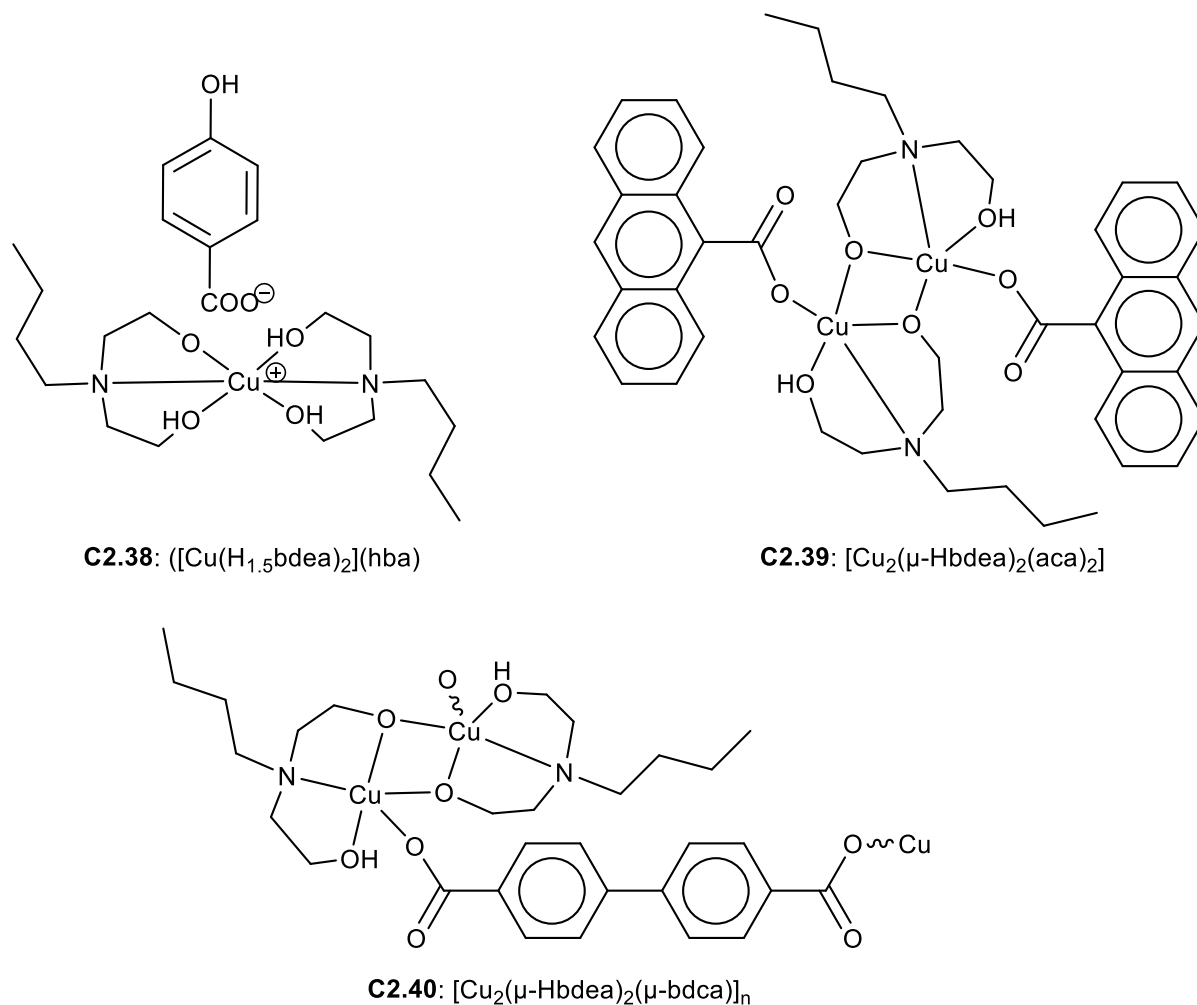


Figure 2.14: The mono- (**C2.38**) and binuclear (**C2.39**) complexes as well as the 1D coordination polymer (**C2.40**) were employed for hydrocarbon peroxidation reactions. The H_2O molecules as reported for the crystal structures of **C2.38** and **C2.39** are not included in this figure [28].

Firinci evaluated various Cu^{II} complexes such as **C2.41**, bearing a pyrimidine-2,4,6-trione ligand, in combination with H_2O_2 (30 % in H_2O) and TFA for cyclohexane peroxidation and a product yield of 15 % was obtained in 6 h at 50 °C (Table 2.2, entry 12 and Figure 2.15) [159]. Pombeiro and co-workers have previously reported on the application of Cu^{II} in combination with hydrazone-derived pyrimidine-2,4,6-trione ligands in the peroxidation of cyclohexane and they obtained product yields of 21 to 23 % [158, 168].

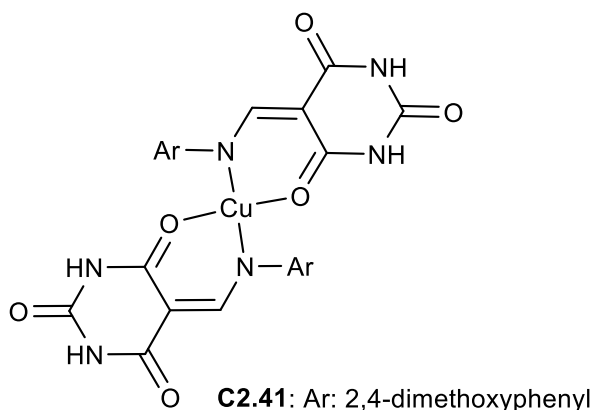


Figure 2.15: The application of complex **C2.41** in combination with H_2O_2 and TFA for cyclohexane peroxidation [159].

In 2019, Roy and co-workers reported on the application of a binuclear Cu^{II} complex, $[\text{Cu}_2(\text{L2.40})_2(\mu_2\text{-Cl})\text{Cl}] \cdot 2.5\text{H}_2\text{O}$ (**C2.42**), bearing a 1-((2-hydroxyethylimino)methyl)-naphthalene-2-ol (**L2.40**) ligand, in combination with H_2O_2 (30 % in H_2O) and HNO_3 in the peroxidation of cyclohexane in 48 h at 40 °C (Table 2.2, entry 13 and Figure 2.16) [160]. Product yields of 36 to 48 % were obtained for the peroxidation of cyclopentane (CyOH/CyO distribution of 19.1/16.7 %) and cyclohexane (29.8/18.4 %). The peroxidation of toluene resulted in a product yield of 40 %, with a product distribution (BzOH/BzO) of 23.8/15.9 %, while traces of benzoic acid were also observed due to over-oxidation. They observed that their binuclear Cu-based complex requires HNO_3 to increase the unsaturation at the metal centre, consistent with previous reports [146, 157, 158, 171, 172].

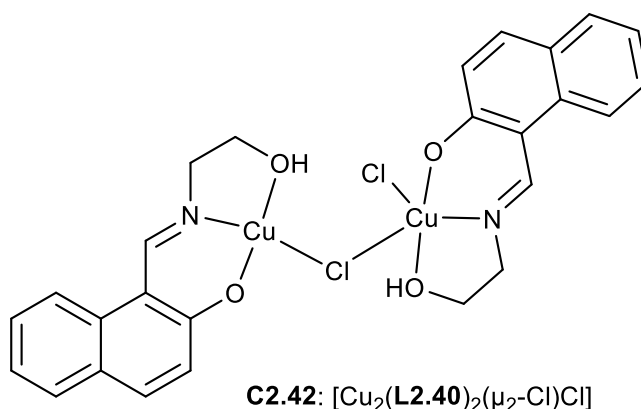


Figure 2.16: The application of complex **C2.42** in combination with H_2O_2 and HNO_3 for cyclohexane peroxidation of cyclohexane [160].

The above-mentioned Cu-based catalyst systems highlight that the following are required for an optimal catalyst system for the peroxidation of cycloalkanes: N-atom containing ligand sets, low coordination numbers for the Cu centre, high stability of the Cu centre and the solubility and stability of the catalyst in the solvent system. Unfortunately, these Cu-based catalyst

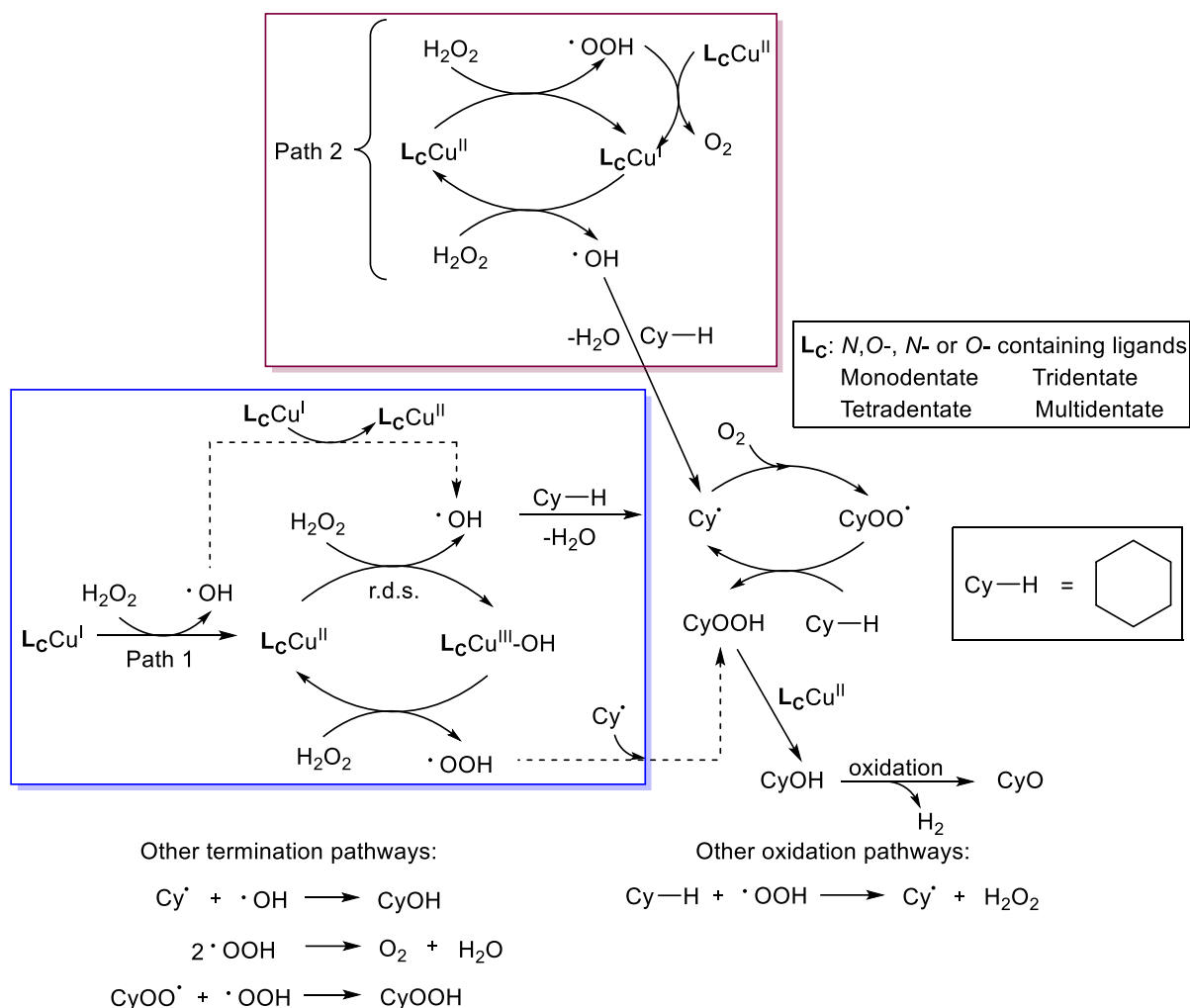
systems still require acid promoters, high amounts of H_2O_2 or high temperatures for optimal reactivity, since only low to moderate product yields were possible. As such, there is still room for improvement in catalyst design. The next section discusses the mechanistic aspects of copper-catalysed peroxidation.

2.2.3.1 Mechanistic aspects

Various possible radical-based mechanistic pathways have been proposed previously where cycloalkyl hydroperoxide is generated as the major product before the reaction was treated with an excess of PPh_3 to afford the corresponding alcohols and ketones as the final products. The initial changes in the oxidation state of copper during the formation of the active species are currently the only difference between these mechanistic pathways for hydrocarbon peroxidation. A variety of experimental, spectroscopic and computational DFT studies was employed to suggest possibilities for the nature of the active species and to identify possible Cu-based intermediates for the different radical-based mechanistic pathways. These investigations are described below.

2.2.3.1.1 Fenton-like radical mechanistic pathway

This mechanistic pathway was proposed by the groups of Karlin and Garcia-Bosch [25, 173]. UV/vis spectroscopy studies were employed to confirm the initial oxidation of the $\text{L}_\text{c}\text{Cu}^\text{I}$ (L_c : ligand for peroxidation reactions) complex with H_2O_2 , to afford the catalyst resting state, $\text{L}_\text{c}\text{Cu}^\text{II}$. A subsequent Fenton-like reaction of $\text{L}_\text{c}\text{Cu}^\text{II}$ with H_2O_2 affords $\text{L}_\text{c}\text{Cu}^\text{III}$ -OH and the hydroxyl radical ($\cdot\text{OH}$) during the rate-determining step (Scheme 2.30, Path 1). Roy and co-workers used electrochemistry to confirm the generation of $\text{L}_\text{c}\text{Cu}^\text{III}$ [160]. The resting-state was determined by UV/vis measurements, where they compared the crude catalytic reaction with an independently synthesised $\text{L}_\text{c}\text{Cu}^\text{II}$ complex [170]. $\text{L}_\text{c}\text{Cu}^\text{I}$ that might be present after H_2O_2 was added, will lead to the formation of $\text{L}_\text{c}\text{Cu}^\text{II}$ and $\cdot\text{OH}$. From here, the mechanistic pathway involves radical species and the reaction between $\cdot\text{OH}$ and the substrate to afford C-centred radical species ($\text{Cy}\cdot$) via an H-atom abstraction step. H_2O_2 assists in the reduction of $\text{L}_\text{c}\text{Cu}^\text{III}$ -OH to regenerate the resting state, $\text{L}_\text{c}\text{Cu}^\text{II}$, species and a cycloalkyl hydroperoxo ($\text{CyOO}\cdot$) radical. The formation of the cycloalkyl hydroperoxide (CyOOH) product, which was confirmed by various research groups, occurs either by the termination of the radical chain or H-atom abstraction from the cycloalkane, via the $\text{CyOO}\cdot$ intermediate. The cycloalkyl hydroperoxide is cleaved homolytically using $\text{L}_\text{c}\text{Cu}^\text{II}$, to obtain the corresponding alcohol (CyOH , H-atom abstraction from the substrate, using $\text{Cy}\cdot$) and ketone (CyO , decomposition of $\text{CyOO}\cdot$) products. A similar mechanistic pathway was proposed for the oxidation of benzene to phenol, using catalyst **C2.33** in an H_2O_2 /acetone solvent system (Figure 2.12) [173].



Scheme 2.30: The proposed mechanistic pathways (Path 1 and 2) for cycloalkane peroxidation. Adapted from the groups of Garcia-Bosch, Karlin, Shul'pin, Kirillova, Pombeiro, Mncube and Bala [25, 70, 144, 147, 156, 172-174].

2.2.3.1.2 Free-radical mechanistic pathway

A similar mechanistic pathway, as described in Section 2.2.3.1.1, was proposed by several groups; however, they did not observe LcCu^{III} species and rather suggested the reversible transformation between LcCu^{II} and LcCu^{I} [70, 144, 147, 156, 172, 174]. The reaction between Cu^{II} -precursor and Lc results in the formation of the pre-catalyst, LcCu^{II} , which is reduced to LcCu^{I} and $\cdot\text{OOH}$ in the presence of H_2O_2 (Scheme 2.30, Path 2). Alternatively, when LcCu^{I} is employed, the reaction thereof with H_2O_2 resulted in the formation of the resting state, LcCu^{II} , and $\cdot\text{OH}$ radicals. EPR studies have been employed in the solid-state and in aqueous solution to confirm the presence of LcCu^{II} and the intensity of the signal decreases dramatically with the addition of aqueous H_2O_2 , which suggests the formation of diamagnetic LcCu^{I} [156]. Furthermore, the LcCu^{II} signal does not disappear, which confirms that it is impossible to

convert all the LCu^{II} , even in the presence of excess H_2O_2 . As such, the $\cdot\text{OOH}$ then reacts with the remaining LCu^{II} to afford LCu^{I} and O_2 , while H_2O_2 assists in the oxidation of LCu^{I} to LCu^{II} and the formation of $\cdot\text{OH}$. From here, the same mechanistic pathway as proposed for the Fenton-like mechanistic pathway is operative. The substrate is activated by $\cdot\text{OH}$ through an H-atom abstraction step to afford $\text{Cy}^{\cdot}$ radicals [28]. Atmospheric oxygen then reacts with these radical species to generate $\text{CyOO}^{\cdot}$, which leads to the formation of the primary product, CyOOH . Mncube and Bala suggested that the generation of the $\text{CyOO}^{\cdot}$ species was the rate-determining step [70]. Alternatively, Roy and co-workers also proposed that the formation of CyOOH , as confirmed by UV/vis spectroscopic studies, may be due to the reaction between $\text{Cu}^{\text{II}}\text{-OOH}$ and the $\text{Cy}^{\cdot}$ [160]. The cycloalkyl hydroperoxide product is converted to the corresponding CyOH and CyO products, via the same method as described for the Fenton-like mechanistic pathway. The free-radical mechanistic pathway is further supported by the observed intense release of O_2 during the reaction and the initial colour change from pale blue to green-yellow with the addition of H_2O_2 to the reaction mixture [156].

In the mechanistic pathways described above, the key difference is in the oxidation states of copper. In the Fenton-like mechanistic pathway, the oxidation states cycles between LCu^{I} , LCu^{II} and LCu^{III} , while in the free-radical mechanistic pathway, the oxidation states cycles between LCu^{II} and LCu^{I} . Alternatively, Pérez and co-workers observed no change in their GC-MS chromatograms before and after the reaction was treated with an excess of PPh_3 , which confirmed the absence of radical species during the reaction [27]. As such, they postulated the involvement of metal-oxo species during the activation of the cycloalkane substrate, which is the topic of the next sub-section.

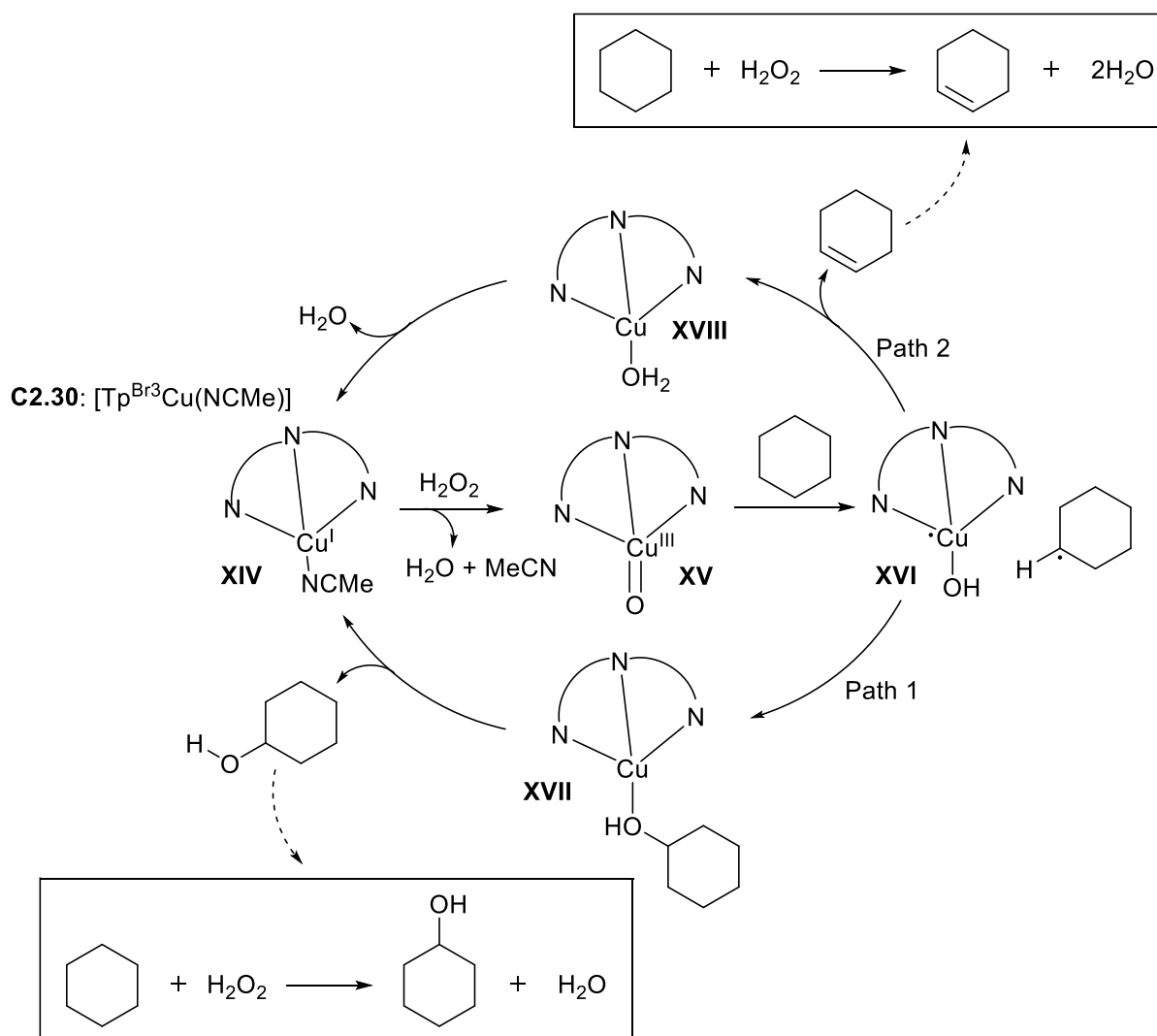
2.2.3.1.3 Metal-oxo mechanistic pathway

Pérez and co-workers did not only observe the oxidation products during the cycloalkane peroxidation, but also dehydrogenation products, which suggest the absence of free radical species during the reaction [27]. They rather proposed the involvement of metal-oxo species during the H-atom abstraction step (Scheme 2.31). The peroxidation of cyclohexane proceeded in the presence of complex **C2.30** and either oxone or H_2O_2 as the oxidant, and they obtained similar product yields and product distribution for both reactions. No variations in the product yields were observed for the peroxidation reactions under inert or ambient atmospheres. They also evaluated radical traps, without C-H bonds, such as carbon tetrachloride (CCl_4) to confirm the formation of the C-centred radical, $\text{Cy}^{\cdot}$, during the reaction. Cycloalkyl chloride was observed as one of the products due to the trapping of cycloalkyl radicals with halogenated reagents. These reactions are performed in the absence of O-centred radicals because the total product yield was not influenced by the presence of

radical trapping agents. Moreover, when CCl_4 was replaced with bromotrichloromethane (CBrCl_3), only bromocycloalkane was obtained. Similar observations were reported by Shaik, Nam and co-workers for their $\text{Fe}^{\text{IV}}=\text{O}$ complex where CBrCl_3 trapped the H-atom during the formation of the cycloalkyl radical [175]. These experimental findings support the formation of metal-oxo species, instead of the radical species [27].

Computational studies were then employed to investigate the proposed involvement of metal-oxo species during the peroxidation reaction. Oxone, containing potassium peroxymonosulfate (KHSO_5) was selected as the oxidant to prevent the formation of hydroxyl products, which supports their experimental findings [176]. Three different species are possible after the oxidation of the Cu-based pre-catalyst with H_2O_2 : Cu-oxo, -superoxo and -hydroperoxo species [177, 178]. The Cu-superoxo and Cu-hydroperoxo species were found to be less reactive than the Cu-oxo species, since more energy is required for the formation of these species. Moreover, when employing Cu-superoxo or Cu-hydroperoxo species during the substrate activation step, more energy is required relatively to the Cu-oxo species.

Complex **C2.30** (**XIV**) reacts with H_2O_2 to afford Cu^{III} -oxo species, **XV**, which has a strong oxyl character (Scheme 2.31). These Cu-oxo species then react with the substrate to afford $\text{Cy}^\bullet$ radicals and $\bullet\text{C2.30-OH}$, **XVI**, via an H-atom abstraction step. Two competitive pathways are possible: firstly, the hydroxylation pathway suggests that the cycloalkyl radical coordinates with **XVI** to afford **C2.30-OH-Cy**, **XVII**, and the resulting CyOH product (Scheme 2.31, Path 1). Secondly, a dehydrogenation reaction rather occurs where a second H-atom was abstracted from the α C-H of $\text{Cy}^\bullet$ to afford the corresponding CyO product and the formation of **C2.30-OH₂**, **XVIII** (Scheme 2.31, Path 2). The oxidant of the dehydrogenation reaction also acts as a hydrogen acceptor, which results in the production of two H_2O molecules from one molecule of H_2O_2 and cycloalkane substrate. Both species **XVII** and **XVIII** were converted to the initial **XIV** species to restart the peroxidation reaction.



Scheme 2.31: The proposed mechanistic pathway for the peroxidation of cycloalkanes, using metal-oxo species instead of radical species. Reproduced from Pérez and co-workers [27].

It becomes apparent from the above discussion that the mechanistic pathway, which is operative for a specific Cu-based catalyst system, is determined by the initial oxidation state of copper as well as whether radical species are generated during the reaction. The next section introduces oxidative cleavage reactions, in which Cu-based catalyst systems function as LPMO mimics for the synthesis of phenolic compounds.

2.2.4 Oxidative cleavage reactions: LPMO mimics

An alternative oxidative transformation reaction for the synthesis of phenolic compounds is via the enzymatic oxidative cleavage of glycosidic bonds (glycosidic hydrolase) of recalcitrant polysaccharide biomass in the presence of an oxidant. The conversion of biomass has been expanded beyond the production of fuels because a wide range of other useful materials for energy, chemicals and other industries can also be derived from biomass [179]. Recalcitrant

polysaccharide biomass is resistant to degradation, and the enzymatic degradation thereof changed dramatically with the discovery of lytic polysaccharide monooxygenases (LPMOs) [18, 23, 180, 181]. These enzymes were initially classified into the glycoside hydrolase family (GH) and the carbohydrate-binding module family (CBM) for the fungal and bacterial enzymes, respectively. Cellulose-active enzymes were later described as 'lytic oxidases'; however, studies have shown that these enzymes could catalyse a Cu-dependent oxidative reaction, and therefore they were renamed as LPMOs [182-185]. The term 'lytic' refers to its ability to cleave and loosen polysaccharide chains [18]. LPMOs have been employed in the enzymatic conversion of lignocellulosic biomass to produce biofuels since 2010 [186]. The structure and coordination environment of the active centres of these enzymes are described below.

2.2.4.1 The active site of LPMOs

LPMO enzymes are isolated from cellulolytic fungi and actinomycete bacteria [21, 182, 187]. The active site of these enzymes exhibits a square pyramidal/pseudo-octahedral geometry with a single type II Cu-atom that is coordinated to three *N*-atoms as contributed by two histidine residues (Figure 2.17). The first histidine residue coordinates in an imidazole-bond fashion, while the second histidine residue is the methylated *N*-terminal one [23, 182, 187-191]. The latter is bound by the histidine-braced motif, which involves the main chain amino group and the side chain imidazole group. Lastly, two H₂O molecules complete the square pyramidal coordination of the Cu-based active centre. Studies proposed that the histidine brace might impose critical geometric and steric constraints on the active site [192].

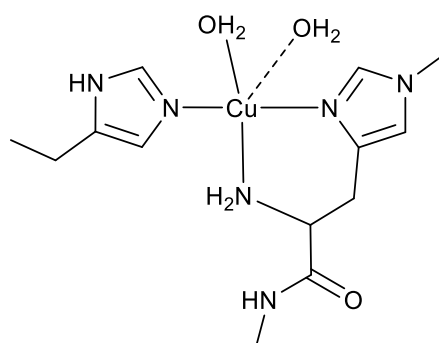


Figure 2.17: The active site of LPMOs consists of a mononuclear Cu-atom, which is coordinated to three *N*-atoms [184].

The specific role of the methylated *N*-terminal is still unclear, since some LPMO enzymes does not carry the methylated histidine. Walton and co-workers suggested that it may exude redox control of the metal site, thereby preventing the deprotonation of the histidine at the terminal position [191]. Furthermore, it may also be directly involved in the reaction as a redox-active partner or it can serve as a site for atom transfer. Contrastingly, Kim and co-workers used

computational studies and found that the methyl group does not have a significant impact on the catalytic activity of the enzyme [193].

Ligand sets with amine groups or *N*-atom containing heterocycles, such as pyrazole and pyridine, are usually employed in LPMOs to mimic the histidine groups of LPMO [195]. The unusual solvent-exposed Cu-based active site exists in the centre of a flat surface for easier interaction with the polysaccharide chains without the need to first isolate the chains from the crystalline form [23, 191, 192]. The active site can be used for the activation of O₂, which is in contrast to other Cu-based monooxygenases where two or three copper sites are used for the activation of O₂ through a multi-electron reduction step [196]. As such, the active site of LPMOs is responsible for the oxidative cleavage step, as described in the next section.

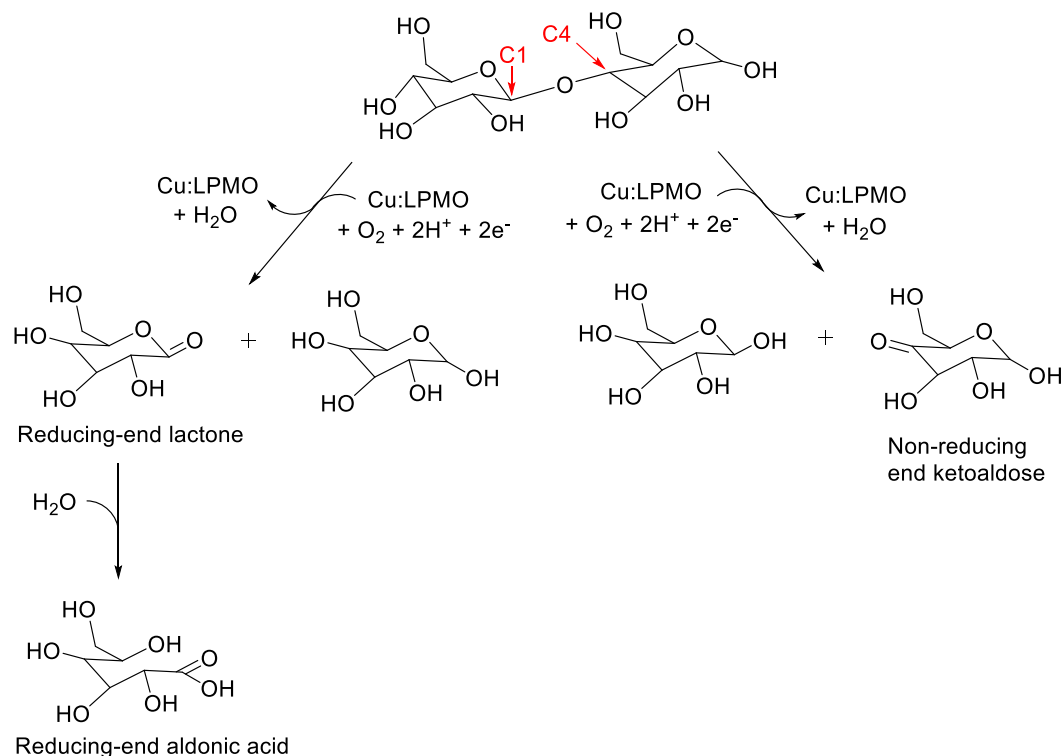
2.2.4.2 Possible oxidative cleavage positions for LPMO mimics

The Cu-based active site of LPMOs is responsible for the oxidative cleavage reaction in the presence of either O₂ or H₂O₂. Initially, the potential for H₂O₂ as a more active oxidant was overseen because LPMOs were performed in reaction conditions that promote the *in situ* formation of H₂O₂ in the absence of the polysaccharide substrate. Therefore, it is sometimes difficult to distinguish between oxygenase (O₂) and peroxygenase (H₂O₂) activity due to the presence of H₂O₂, which could then be employed during the reaction after substrate addition [197, 198]. The preference for H₂O₂ as the oxidant, instead of O₂ has resulted in the development of several catalyst systems for the oxidative cleavage of polysaccharides [22, 198-200]. Controlled addition of H₂O₂ is important because an overdose might damage the LPMOs. The difference between O₂ and H₂O₂ in the oxidative cleavage reaction has previously been evaluated and they observed that the consumption of H₂O₂, in the presence of a reductant, was much quicker than those reactions with O₂ [198, 201].

Substrate binding to the active centre is relatively weak, resulting in large amounts of unbound active centres at low substrate concentrations, and therefore more H₂O₂ is generated from the O₂ oxidant [202]. As such, the active site occupancy is crucial for oxygenase activity, which is sometimes difficult with insoluble substrates. Studies have shown that O₂ can be replaced with H₂O₂ as the oxidant; however, high O₂ concentrations may lead to oxidative damage to the LPMO enzyme [198]. These reactions of LPMO mimics typically involve two reduction steps. The oxidant activates the Cu^{II} active sites in the presence of electron donors to catalyse the regioselective hydroxylation of an inert C-H bond, leading to glycosidic bond cleavage [23, 198]. The oxidative cleavage may occur at C1 or C4 to afford either sugar lactones or ketoaldoses (Scheme 2.32) [18, 23, 180, 182, 184, 203-206]. Walton and co-workers suggested that the position of the enzyme on the surface of the polysaccharide substrate

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determines the oxidation position [191]. Furthermore, substrates are usually polymeric and sometimes insoluble, which may lead to challenges to investigate the interactions between the LPMO enzyme and the substrate [192].



Scheme 2.32: The oxidative cleavage of polysaccharides, using O₂, may occur at C1 to afford lactone, which is then hydrated to the aldonic acid; or at C4 for the formation of ketoaldose [18]. For this process, the O₂ + 2H⁺ + 2e⁻ step may also be replaced with H₂O₂.

The advantages of copper as a metal precursor within the active site resulted in the development of several Cu-catalysed LPMO mimics, using either O₂ or H₂O₂ as oxidant, where LCu^{II}-OO[•], LCu^{II}-OH or LCu^{II}-O[•] active species are generated and employed in the oxidative cleavage of C-H bonds during the synthesis of phenols [18-21]. These Cu-based LPMO mimics for the oxidative cleavage of polysaccharides are described in the next section.

2.2.4.3 The development of LPMO mimics

A seminal study by Striegler and co-workers in 2010 employed binuclear Cu^{II} complexes, *N,N'*-{1,3-bis[(pyridine-2-ylmethyl)amino]propan-2-ol}ato dicopper(II) (μ-acetato) diperchlorate (**C2.43a**, Cu₂bpdpo), *N,N'*-{bis(2-pyridylmethyl)-1,4-diaminobutan-2-ol}ato dicopper(II) (μ-acetato) diperchlorate (**C2.44**, Cu₂bpdbo) and *N,N'*-{1,3-bis[{2-hydroxy-4-[2-(2-methoxyethoxy)-ethoxy]ethoxy}benzylidene-amino]-propan-2-ol}ato dicopper(II) (μ-acetate) (**C2.45a**, Cu₂TEGbsdpo) for the hydrolysis of *p*-nitrophenyl-α-D-galactopyranoside, using a 3-(cyclohexylamino)-1-propanesulfonic acid (CAPS) buffer at pH 10.5 (Figure 2.18) [207].

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Their results revealed the preference for a pyridyl ring (complexes **C2.43a** and **C2.44**) over a phenoxy group (complex **C2.45a**), as well as for symmetrical (complex **C2.43a**) over unsymmetrical backbone ligands (complex **C2.44**) [207]. The importance of these backbone ligands was confirmed by evaluating Cu^{II} ions, in the absence of ligands, in the glycoside hydrolysis reaction, which led to precipitate formation at pH 10.5.

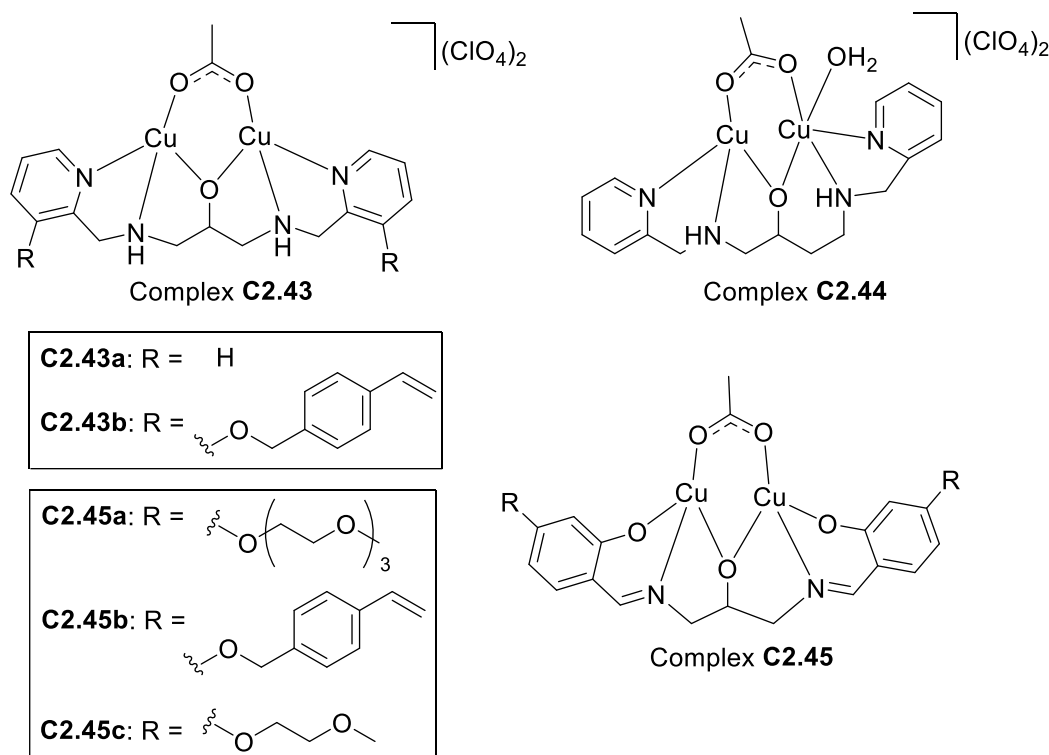
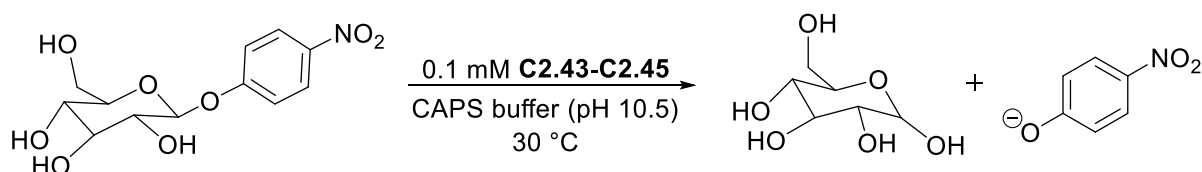


Figure 2.18: Various binuclear Cu^{II} complexes bearing pentadentate ligands were evaluated in the oxidative cleavage reaction [207].

UV/vis spectroscopic studies were employed to follow the formation of the yellow *p*-nitrophenoxide anion at 410 nm and Striegler and co-workers observed a linear dependency on the catalyst and substrate concentrations (Scheme 2.33) [207]. No catalyst deactivation, due to the coordination of *p*-nitrophenolate to the catalyst, was observed in the oxidative cleavage reactions of 26 h at 30 °C. Furthermore, no hydrolysis reaction was possible below pH 10.5, indicating the contribution of the metal-bound hydroxide ion in base catalysis.



Scheme 2.33: The Cu^{II} complexes, **C2.43-C2.45**, were employed in the hydrolysis of *p*-nitrophenyl- α -D-galactopyranoside at 30 °C, in the absence of an oxidant [207].

The rate constant (k_{obs} : $\times 10^{-4} \text{ min}^{-1}$) of **C2.43a** (k_{obs} : 43.4 ± 9.6) was the best for the hydrolysis of *p*-nitrophenyl- α -D-galactopyranoside, while complex **C2.45a** (k_{obs} : 12.7 ± 2.9) resulted in a similar rate constant relative to the reaction in the absence of a catalyst. This is possibly due to the formation of inactive species during the reaction. However, the rate constant for complex **C2.44** (k_{obs} : 2.5 ± 0.3) during the oxidative cleavage of *o*-nitrophenyl- α -D-galactopyranoside was significantly lower, relative to the *p*-analogue (k_{obs} for **C2.44**: 21.4 ± 3.3), possibly due to an increase in the possibility for autocatalytic hydrolysis of the substrate. They also employed either complexes **C2.43a** or **C2.44** in the evaluation of *p*-nitrophenyl- β -D-galactopyranoside (k_{cat} for **C2.44**: 20.0 ± 2.7), *p*-nitrophenyl- α -D-glucopyranoside (k_{obs} for **C2.43a**: 10.5 ± 4.5) and *p*-nitrophenyl- β -D-glucopyranoside (k_{obs} for **C2.44**: 2.4 ± 1.0), but low catalyst solubility in the aqueous solution limited their spectroscopic studies [207]. A mononuclear version of complex **C2.43a**, *N,N'*-1,3-bis[(pyridine-2-ylmethyl)amino]propan-2-ol copper(II) diperchlorate (Cubpdpo, k_{obs} : 3.0 ± 0.8) was also evaluated in the hydrolysis of *p*-nitrophenyl- α -D-galactopyranoside, but the reaction was significantly slower than for the binuclear complex **C2.43a** even though an increased catalyst concentration was used. Moreover, improved rate constants were possible for the binuclear complexes (**C2.43a**, **C2.44** and **C2.45a**) when the reactions were performed at a pH above 9.

In 2011, Striegler and co-workers further investigated the application of binuclear Cu^{II} complexes in the hydrolysis of *p*-nitrophenyl- α -D-galactopyranoside at pH 10.5 [208]. The binuclear complexes include *N,N'*-{bis((3-(4-vinylbenzyloxy)-2-pyridylmethyl)-1,3-diaminopropan-2-ol)}ato dicopper(II) (μ -acetato) diperchlorate (**C2.43b**, $\text{Cu}_2\text{VBbpdpo}$), *N,N'*-{1,3-bis[(2-hydroxy-4-(*p*-vinylbenzyloxy))-benzylideneamino]-propan-2-ol}ato dicopper(II) (μ -acetate) (**C2.45b**, $\text{Cu}_2\text{VBbsdpo}$) and {*N,N'*-1,3-bis[{2-hydroxy-4-(2-methoxyethoxy)}-benzylideneamino]propan-2-ol}ato dicopper(II) (μ -acetato) (**C2.45c**, $\text{Cu}_2\text{EGbsdpo}$; Figure 2.18). They also synthesised polymeric ligands, pol**L2.41** and pol**L2.42**, from miniemulsions that contain styrene and butyl acrylate and the ligands **L2.41** or **L2.42**. Ligands **L2.41** or **L2.42** were also employed in the synthesis of the binuclear Cu^{II} complexes **C2.43b** and **C2.45b** (Figures 2.18 and 2.19). The polymerised ligands, pol**L2.41** and pol**L2.42**, were employed in the synthesis of the macromolecular Cu^{II} complexes pol**Cu**₂**L2.41** (pol**C2.46**) and pol**Cu**₂**L2.42** (pol**C2.47**). High rate constants (k_{obs} : $\times 10^{-4} \text{ min}^{-1}$) were observed for the low molecular weight complexes **C2.43a** (k_{obs} : 43 ± 10) and **C2.45a** (k_{obs} : 13 ± 3), but a significant increase in the rate constant was possible for the macromolecular polymerisable complex pol**C2.46** (k_{cat} : 20 ± 1) [207, 208]. When employing the polymerisable complex pol**C2.47**, the rate constant was further increased to $350 \pm 60 \times 10^{-4} \text{ min}^{-1}$. High rate constants of 360 ± 44 to $380 \pm 20 \times 10^{-4} \text{ min}^{-1}$ were also obtained for the hydrolysis of *p*-nitrophenyl- β -D-galactopyranoside, *p*-nitrophenyl- α -D-glucopyranoside and *p*-nitrophenyl- β -D-

glucopyranoside, using complex **polC2.47**. Unfortunately, even though **polC2.47** showed excellent results, it could not be used to differentiate between α - and β -glycosidic linkages or even between the gluco- and galacto- configurations of the substrates. Similarly, macromolecular catalysts were also successfully employed in the catalytic oxidation of derived catechols to quinones [209].

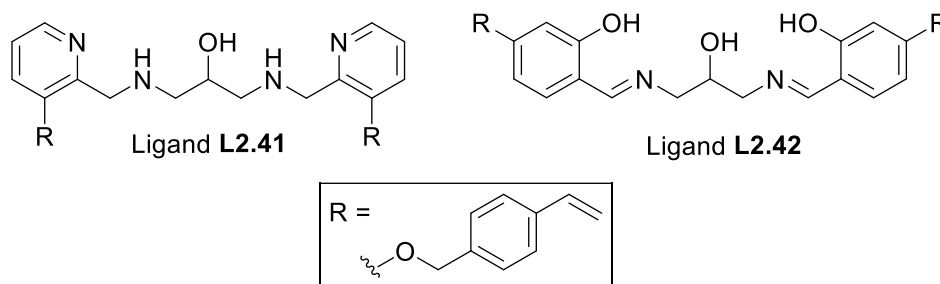


Figure 2.19: Ligands **L2.41** and **L2.42**, in combination with styrene and butyl acrylate, were employed in the synthesis of the polymerisable miniemulsions, **polL2.41** and **polL2.42** [208].

Striegler and co-workers further expanded the scope of their polymerisable Cu^{II} complexes in 2012 by focusing on the use of ligand **L2.41** (Figure 2.19) [210]. Glucose-templated (**polC2.48_{glu}**) and galactose-templated (**polC2.49_{gal}**) polymeric complexes were synthesised from the reaction between the polymerisable ligand **polL2.41**, $\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ and a carbohydrate (glucose (glu) or galactose (gal)). These sugar-templated Cu^{II} complexes were evaluated in the hydrolysis reaction. The rate constants (k_{obs} : $\times 10^{-4} \text{ min}^{-1}$) for the hydrolysis of *p*-nitrophenyl- α -D-galactopyranoside were found to be higher for the macromolecular complex **polC2.48** (k_{obs} : 350 ± 36), relative to **C2.43a** (k_{obs} : 40 ± 10), while even higher rate constants were possible for the sugar-templated polymerisable complexes **polC2.48_{glu}** (k_{obs} : 630 ± 40) and **polC2.49_{gal}** (k_{obs} : 1510 ± 10) [207, 208, 210]. Furthermore, they also evaluated their sugar-templated polymerisable complexes in the hydrolysis of *p*-nitrophenyl- β -D-galactopyranoside (k_{obs} for **polC2.49_{gal}**: 1260 ± 110), *p*-nitrophenyl- α -D-glucopyranoside (k_{obs} for **polC2.48_{glu}**: 1480 ± 10) and *p*-nitrophenyl- β -D-glucopyranoside (k_{obs} for **polC2.48_{glu}**: 1290 ± 490). Their result highlighted the positive effect that the macromolecular environment of the polymerisable sugar-templated complexes has on the catalytic performance [210]. The galactose-templated complex **polC2.49_{gal}** cannot distinguish between α - and β -glycosidic linkages and the rate constants for the reactions dropped when the substrate was changed from galacto- to the gluco- configuration. Moreover, no substrate differentiation was observed for complexes **C2.43a**, **C2.43b** or in the uncatalysed reactions. Similar results were observed for the glucose-templated complex **polC2.48_{glu}**.

Three Cu^{II} complexes, bearing the bis[(1-methyl-2-benzimidazolyl)ethyl]amine ligand (**L2.43**), were synthesised by Castillo and co-workers in 2014 as LPMO mimics (Figure 2.20) [194].

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The rationale behind their ligand design originated from the methylated *N*-atom of the terminal histidine imidazole and the secondary amine group from the LPMO enzyme, which can assist in the coordination of the substrate to the active site. EPR studies were employed to investigate the structure of the Cu^{II} complexes and they found that the strong coordination of fluoride in the $[\{\text{L2.43Cu}(\mu\text{-F})\}_2](\text{BF}_4)_2$ (**C2.50**) complex favours the square pyramidal geometry of LPMO, while the L2.43CuCl_2 (**C2.51**) and $[\text{L2.43Cu}(\text{H}_2\text{O})_2](\text{OTf})_2$ (**C2.52**) complexes rather exhibit a trigonal bipyramidal geometry. In all instances, the insolubility of the complexes prevented reactivity studies. As such, they further expanded the scope of their Cu-based complexes in 2019 by developing a more soluble $[\text{L2.43Cu}]\text{OTf}$ (**C2.53**) complex [195].

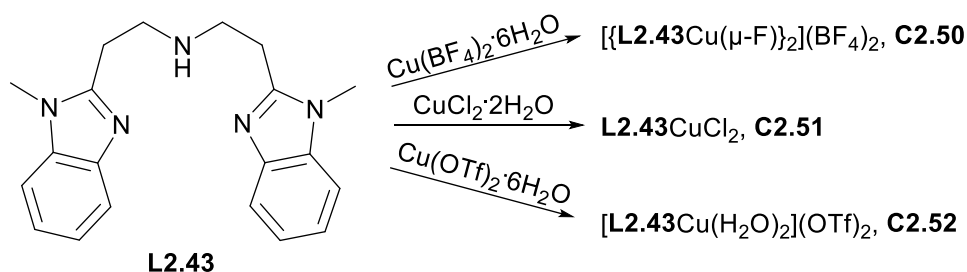
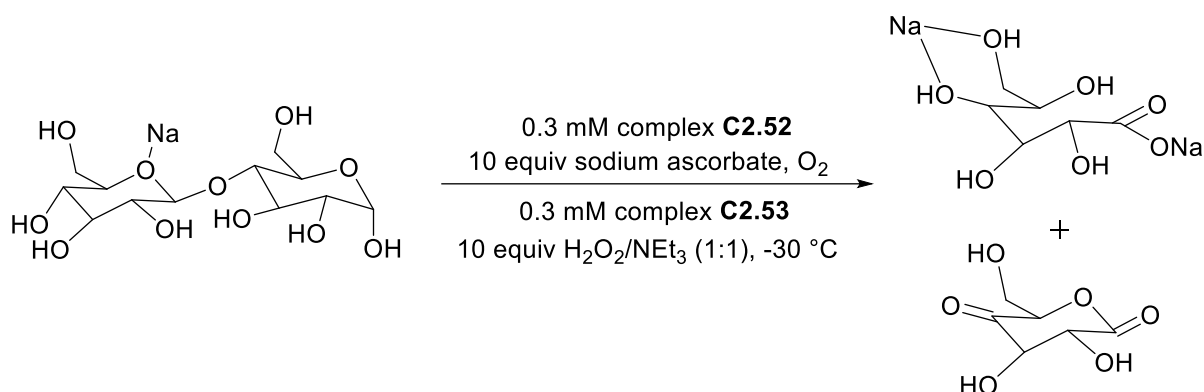


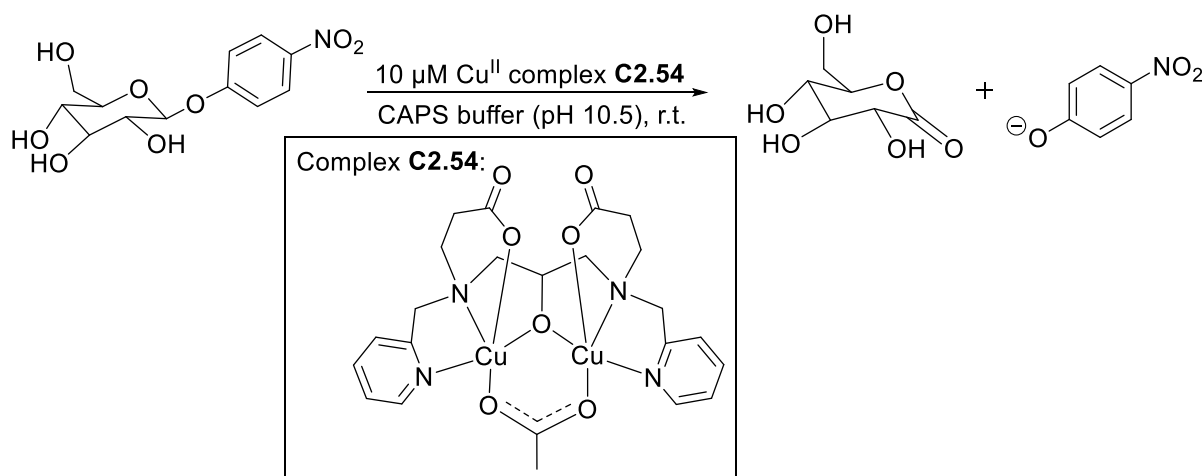
Figure 2.20: The Cu^{II} complexes, **C2.50-C2.52**, bearing a bis[(1-methyl-2-benzimidazolyl)ethyl]amine ligand (**L2.43**) have been evaluated in oxidative cleavage reactions [194].

Both **C2.52** and **C2.53** were evaluated in the oxidative cleavage of cellobiose at -30 °C (Scheme 2.34). The reactivity of complex **C2.53** and O₂ was evaluated using UV/vis spectroscopic studies at -30 °C. Castillo and co-workers observed a broad band at 360 nm and 680 nm, which is consistent with a ligand-to-metal charge transfer (LMCT) of copper-oxygen species and a d-d transition, respectively [195]. Molecular oxygen was then replaced with H₂O₂ as a stronger oxidising agent in the reaction with complex **C2.52** and similar spectroscopic results were observed. However, they observed spectral changes during the reaction between complex **C2.52** and H₂O₂/NEt₃ (ratio 1:1), signalling that the formation of a mixture of monomeric and dimeric Cu^{II} species was obtained. Acetonitrile solutions of complex **C2.52** with H₂O₂/NEt₃ were evaluated, while **C2.54** was generated *in situ* by reducing complex **C2.52** with sodium ascorbate while bubbling O₂ through the reaction. Product yields of 70 % (in MeCN) and 65 % (in H₂O) were obtained for the oxidative cleavage of cellobiose when employing different catalyst systems [195]. Higher catalytic activity was observed for complex **C2.52**, while better product selectivity was rather obtained with **C2.53**. Glucose was evaluated as substrate and the mono-oxidation product was obtained as the major product.



Scheme 2.34: The evaluation of complex **C2.52** with H₂O₂ /NEt₃ or *in situ* formed **C2.53** with sodium ascorbate and O₂ in the oxidative cleavage of cellobiose [195].

Bera and co-workers evaluated water-soluble binuclear Cu^{II} complexes in the oxidative cleavage of glycosidic bonds in 2014 (Scheme 2.35) [211]. Their Cu^{II} complexes consist of either Cu(OAc)₂·2H₂O or copper(II) perchlorate hexahydrate (Cu(ClO₄)₂·6H₂O) in combination with *N,N'*-bis(2-pyridylmethyl)-2-hydroxy-1,3-propanediamine-*N,N'*-dipropionic acid. One metal centre is responsible for the coordination to the substrate, while the other metal centre delivers an activated solvent nucleophile during the reaction, as confirmed by DFT studies [211].



Scheme 2.35: The application of complex **C2.54** in the oxidative cleavage of *p*-nitrophenyl-β-D-glucopyranoside [211].

Complex **C2.54** was evaluated in the oxidative cleavage of *p*-nitrophenyl-β-D-glucopyranoside in an aqueous solution (pH of 10.5). UV/vis spectroscopic studies showed a moderate increase in the absorption band peak at 410 nm, confirming the formation of the *p*-nitrophenolate product. They also observed a first-order dependence on both the catalyst and substrate concentration, with saturation at higher concentrations. Previous studies have found that the formation of *p*-nitrophenolate resulted in the inhibition of the Cu-based catalyst;

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however, they did not observe any inhibition of the catalytic activity, even during a longer reaction time of 30 h.

Later, in 2017, Simaan and co-workers reported on the application of Cu^{II} complexes, bearing ligands **L2.44** or **L2.45**, as one of the first functional models for LPMOs (Figure 2.21) [212]. These ligands consist of a methylated *N*-atom in the imidazole as well as an N₃-coordination sphere to coordinate to the copper centre, which is similar to the histidine moieties in the LPMO enzyme.

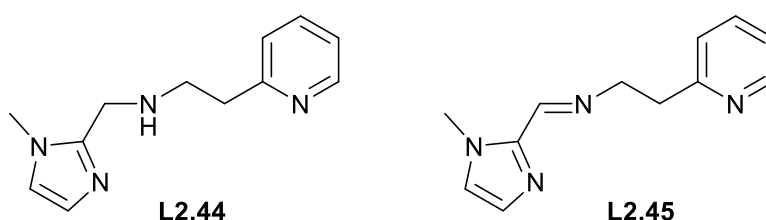
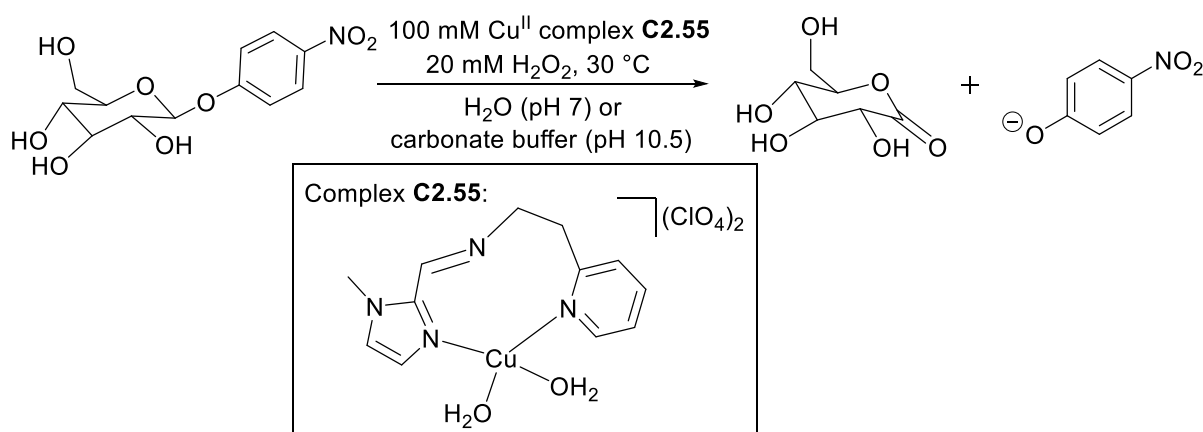


Figure 2.21: Ligands **L2.44** and **L2.45** were incorporated within the Cu^{II} complexes, as LPMO mimics, for the oxidative cleavage reaction [212].

Simaan and co-workers evaluated the Cu^{II} complex, [(**L2.45**)Cu(H₂O)₂][(ClO₄)₂] (**C2.55**), for the oxidative cleavage of *p*-nitrophenyl-β-D-glucopyranoside, using H₂O₂ as the oxygen source, and they obtained a *p*-nitrophenolate concentration of 50 μM with a TON of 50 in 24 h at 30 °C (Scheme 2.36). Lower product concentrations were obtained when the Cu^{II} complexes were replaced with CuSO₄·5H₂O.



Scheme 2.36: The **C2.55**/H₂O₂ catalyst system, in a carbonate buffer, for the oxidative cleavage of *p*-nitrophenyl-β-D-glucopyranoside in 24 h at 30 °C [212].

Low concentrations of *p*-nitrophenolate were obtained in the absence of H₂O₂ or the Cu^{II} complex, which confirms the oxidative process instead of a hydrolysis reaction. Moreover, gluconic acid was generated as a by-product during the reaction, which further supports an oxidative cleavage reaction, similar to LPMOs. The reaction rate was found to be dependent

on H_2O_2 and substrate concentrations since an increase led to increased product concentration [198, 212]. EPR studies and radical trapping experiments confirmed the presence of $\text{LCu}^{\text{II}}\text{-OOH}$ species, instead of radical species, during the reaction.

In a separate study, Feng and co-workers have employed *p*-methylthiophenol-protected copper nanoclusters (CuNCs) in the β -galactosidase reaction to generate *p*-nitrophenol, which led to the inactivation of the CuNCs [213]. This is in contrast to the findings of Bera and co-workers where they did not observe an inhibition of the catalytic activity [211]. Previously reported hydrophilic CuNCs possess bright luminescence in an acidic solution, which is switched off in neutral or alkaline solution. The luminescence is also sensitive to changes in the environmental temperature in the presence of H_2O_2 as oxidant [214-219]. This drawback was resolved by developing novel CuNC aggregation-induced emission (AIE) particles, bearing hydrophobic ligands, using hydrazine hydrate (NH_2NH_2) as the reducing agent to ensure optimal catalytic activity in various reaction conditions and environments (pH 2 to 12). They evaluated hydrophobic thiolated CuNCs with AIE enhancement, as stable and bright luminescence particles, in the β -galactosidase of *p*-nitrophenyl- β -D-galactopyranoside in H_2O to afford galactose and *p*-nitrophenol as products [213]. The *p*-nitrophenol then adsorbs onto the CuNC AIE particles, thereby quenching its luminescence and efficiency. A quenching efficiency of 80 % was obtained in the pH range of 6 to 7, but a decrease was observed at a higher pH value due to the strong interaction between *p*-nitrophenol and the CuNC AIE particles. Even though this Cu-based catalyst system could be employed for the formation of *p*-nitrophenol from *p*-methylthiophenol-protected CuNC cores, it is not feasible due to the quenching ability of the product when it adsorbs to the CuNC AIE particles.

In 2019, Mayilmurugan and co-workers reported three novel Cu^{II} based complexes that exhibit similar chemical and structural arrangements to the histidine brace and histidine residues of the active site of LPMO enzymes, in a distorted square-pyramidal coordination geometry [22]. The complexes **C2.56-C2.58**, prepared from $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ and pyridinoyl-substituted cyclic 1,4-diazepane 3*N*-ligands, were evaluated for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside and they observed that the steric hindrance of the 1,4-diazepene backbone facilitates faster formation of the desired product (Figure 2.22). Rate constants of (0.10 to 0.54 min^{-1}) were measured by UV/vis spectroscopic studies, when employing *p*-nitrophenyl- β -D-glucopyranoside as the substrate. The steric and electronic properties of the pyridyl arm of complex **C2.58** resulted in a higher rate constants relative to complexes **C2.56** and **C2.57** [220-223].

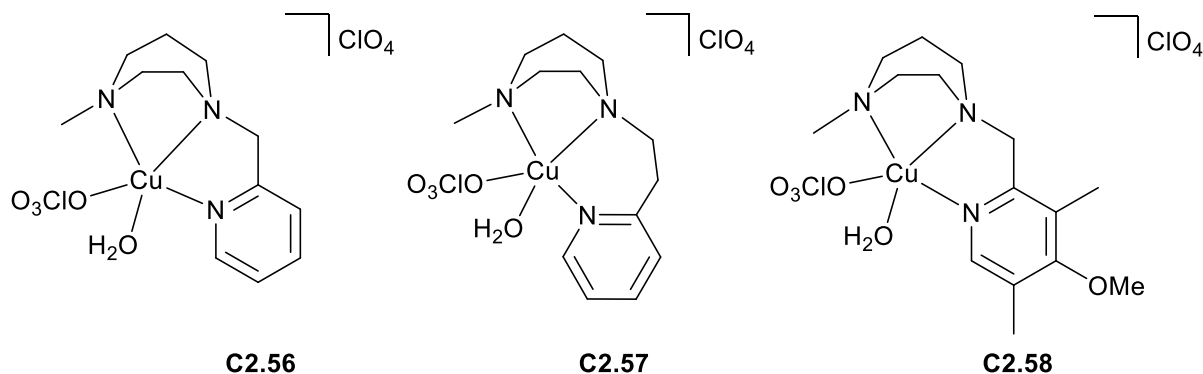
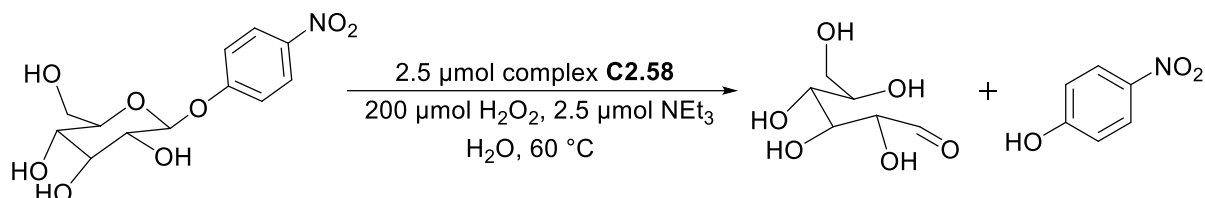


Figure 2.22: Various Cu^{II} complexes (**C2.56**–**C2.58**), bearing cyclic 1,4-diazepane 3*N*-ligands, have been evaluated in oxidative cleavage reactions [22].

Preparative scale catalytic reactions were also conducted at 60 °C, using **C2.58** in combination with H₂O₂ (30 % in H₂O) and NEt₃ (Scheme 2.37). They obtained *p*-nitrophenol product yields of 49 to 65 % and TON values of 202 to 249 [22, 212]. Lower reaction temperatures resulted in lower product yields and TON values, while no conversion was possible in the absence of the catalyst, H₂O₂ or NEt₃. An increase in H₂O₂ increased product yields, with a maximum isolated yield of 78 % (reported TON: 300, actual TON: 63). Their catalyst system was also employed during the oxidative cleavage of primary and secondary alcohols, but no oxidised products were observed.



Scheme 2.37: Oxidative cleavage of *p*-nitrophenyl-β-D-glucopyranoside, using complex **C2.58** in combination with H₂O₂ and NEt₃ to obtain *p*-nitrophenol as the product in 2 h at 60 °C [22].

Efficient oxidative cleavage reactions are usually mediated by mononuclear Cu-based complexes through the Cu^{II}/Cu^I redox couple, at a pH of 10.5 [212]. As such, in 2020, Cowan and co-workers synthesised novel mono- (**C2.59**), bi- (**C2.60** and **C2.61**) and tetranuclear (**C2.62**) Cu-based complexes, bearing the di(2-picolyl)amine ligand, which promotes the Cu^{II}/Cu^I redox activity for oxidative cleavage reactions (Figure 2.23) [224]. Complexes **C2.61** to **C2.62**, in combination with H₂O₂ and ascorbate, were used for the oxidative cleavage of various *p*-nitrophenyl-derivatised glucose and galactose mono- and disaccharides. These reactions were monitored, following the absorbance band for the formation of the *p*-nitrophenolate product. They highlighted the importance of the complex for these reactions since no activity was observed in the absence thereof. Complex **C2.59** resulted in a rate

constant of 0.3 to 0.56 min⁻¹ for the monosaccharides, while a two-fold increase in the rate constants was obtained for the disaccharides (1.1 to 1.4 min⁻¹) [224]. A further increase (3.0 to 15.3 min⁻¹) was obtained for **C2.60** and **C2.61** due to the effect of the interaction between the two Cu-centres on the formation of Cu-based active species or to facilitate substrate binding. The steric hindrance or orientation of the Cu-centres to the substrate for **C2.62** only resulted in a slight increase in the rate constant (5.8 to 15.6 min⁻¹) for the mono- and disaccharides. As such, their Cu-based catalyst system serves as the current state-of-the-art for the oxidative cleavage reactions. Moreover, while no preference towards the α - or β -glycosidic bonds was observed for the mononuclear complex, higher rate constants were obtained towards the cleavage of α -substrates for binuclear complexes and β -substrates for the tetranuclear complex. The orientation of the Cu-centres or the steric hindrance of benzidine may have an influence on the preference for glycosidic linkage.

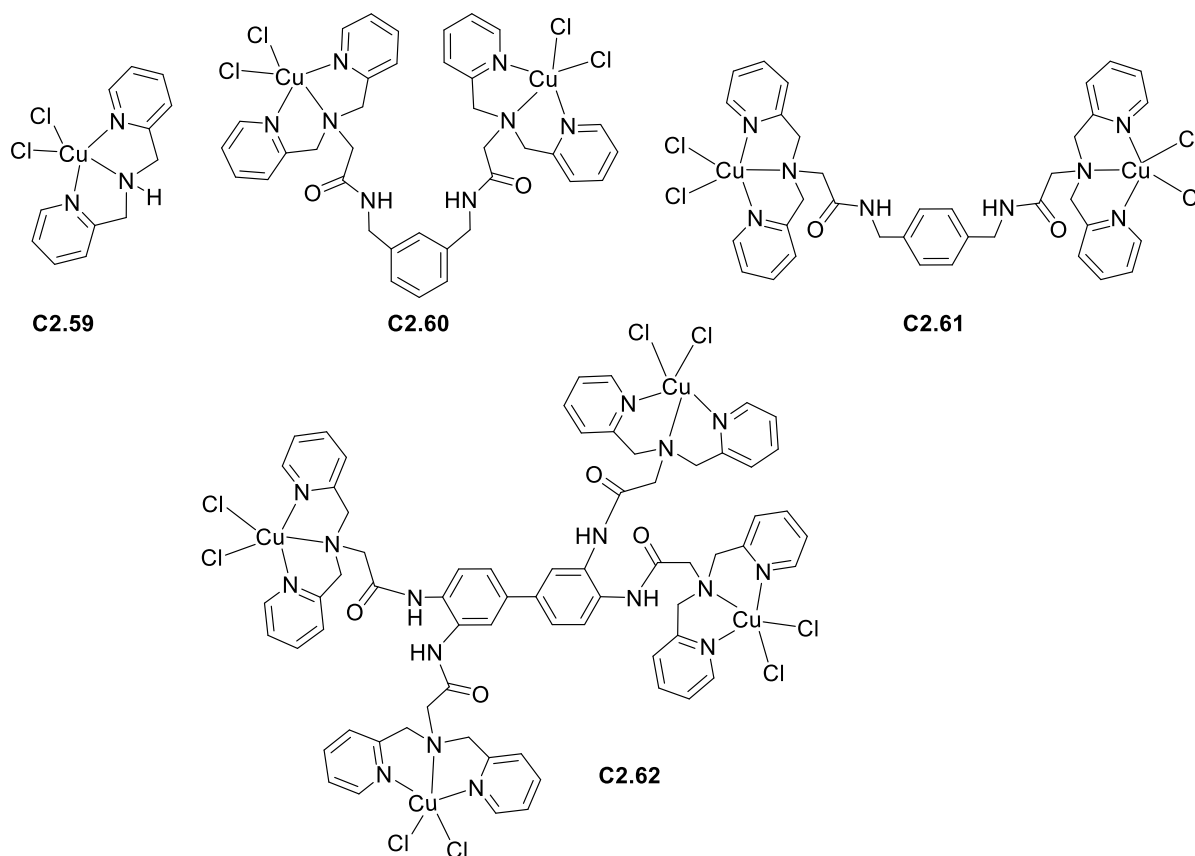


Figure 2.23: Mono- (**C2.59**), bi- (**C2.60** and **C2.61**) and tetranuclear (**C2.62**) Cu-based complexes were evaluated in the oxidative cleavage of mono- and disaccharide substrates [224].

In conclusion, only a few reports of Cu-based catalyst systems that can serve as LPMO mimics have recently been developed for the oxidative cleavage of recalcitrant polysaccharide substrates. Unfortunately, these catalyst systems still require moderate reaction temperatures and in some cases the addition of additives, for optimal catalytic activity. Several mechanistic

pathways have recently been proposed for the oxidative cleavage reaction with experimental, spectroscopic and computational evidence to highlight the changes in the oxidation state of copper and the structures of the active species. The differences in these mechanistic pathways are described in the section below.

2.2.4.4 Mechanistic aspects

Spectroscopic, crystallographic and computational DFT studies have allowed for the postulation of possible mechanistic pathways for the oxidative cleavage of polysaccharides, using either O_2 or H_2O_2 as the oxidant to afford copper-oxygen species [193, 197, 204]. The exact nature of the active species is still up for debate, since previous groups have proposed the inclusion of various active species during the H-atom abstraction step from the polysaccharide substrate. Similarities in the proposed mechanistic pathways include the initial formation of the LCu^{II} -superoxo as well as the regeneration of LCu^I . The reaction between LCu^I and an oxidant results in the formation of LCu^{II} -superoxo species in the absence of the polysaccharide substrate. Eijssink and co-workers have also proposed that when the reaction proceeds from the resting state, LCu^{II} , a one-electron reduction step generates the catalytically active LCu^I species, which then reacts with the oxidant to afford LCu^{II} -superoxo species [199]. This was further supported by the computational studies of Bruschi, Bortolotti and co-workers, which revealed no binding between LCu^{II} and O_2 [200].

Several mechanistic pathways have been previously proposed to rationalise proceedings from the LCu^{II} -superoxo species in the presence of O_2 as oxidant [189]. Firstly, the LCu^{II} -superoxo species itself is responsible for this step to afford LCu^{II} -hydroperoxo species (see Section 2.2.4.4.1 and Scheme 2.38). Secondly, the reduction and a double protonation of the LCu^{II} -superoxo species, followed by the homolytic cleavage of the O-O bond and the dissociation of H_2O , result in the formation of LCu^{II} -oxyl species for the H-atom abstraction step to afford LCu^{II} -hydroxo species (see Section 2.2.4.4.2 and Scheme 2.39). Thirdly, LCu^{II} -oxyl species are generated from the LCu^{II} -superoxo species, after which it is protonated to afford LCu^{II} -hydroxo species for the H-atom abstraction step leading to LCu^{II} - OH_2 species (see Section 2.2.4.4.3 and Scheme 2.40). Lastly, the protonation of the LCu^{II} -superoxo species resulted in the formation of LCu^{II} -hydroperoxo species, which can then perform the H-atom abstraction step to afford LCu^{II} -oxyl species (see Section 2.2.4.4.4 and Scheme 2.41). Alternatively, two mechanistic pathways have previously been proposed for the oxidative cleavage reactions using H_2O_2 as the oxidant. LCu^I -hydroperoxo species are formed, after which either LCu^{II} -oxyl species or hydroxyl radicals are generated to serve as the active species for the H-atom abstraction step (see Section 2.2.4.4.5 and Scheme 2.42). These

partially different mechanistic pathways are discussed in detail in the next sections, with support from experiments and theory.

2.2.4.4.1 $L_D Cu^{II}$ -superoxo mechanistic pathway

Several groups proposed the involvement of these $L_D Cu^{II}$ -superoxo (L_D : possible ligands, Scheme 2.38) species during the H-atom abstraction step [225-227]. Crystallographic results have previously shown the similarities between the electronic continuum of certain $L_D Cu^{II}$ -superoxo species and $L_D Cu^{III}$ -peroxo species (Figure 2.24) [53, 228-230]. Moreover, the computational results obtained by Cowley and co-workers indicate that end-on $L_D Cu^{II}$ -superoxo species possess lower energy barriers for the H-atom abstraction step, relative to their side-on counterparts [193, 231]. These $L_D Cu^{II}$ -superoxo species are usually stabilised by ligands with bulky or strong electron-donating substituents in a four-coordinate tetrahedral geometry [53, 229, 230, 232]. However, Itoh and co-workers reported on the development of mononuclear $L_D Cu^{II}$ -superoxo complexes bearing a 1,5-diazacyclooctane ligand with a 2-(pyridyn-2-yl)ethyl donor group lacking both bulky or strong electron-donating substituents [226].

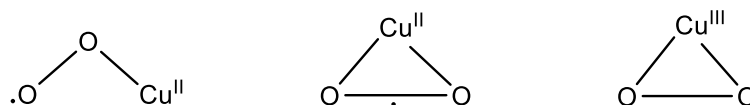
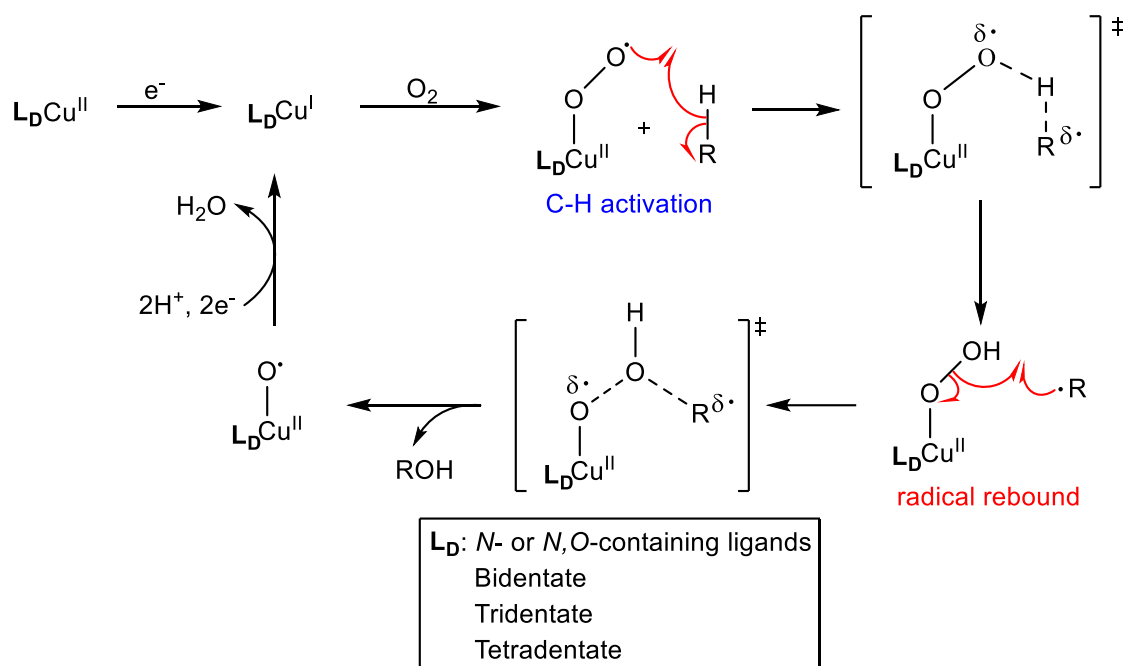


Figure 2.24: The different electronic structures of the Cu^{II} -superoxo species, with one that is similar to the electronic structure of the Cu^{III} -peroxo species [53, 225, 228-230, 233].

Kjaergaard and co-workers used computational studies to confirm the rapid oxidation of $L_E Cu^I$ with O_2 to obtain $L_D Cu^{II}$ -superoxo ($L_D Cu^{II}-OO\cdot$) species (Scheme 2.38) [197]. These $L_E Cu^{II}-OO\cdot$ species can easily coordinate to another $L_D Cu^I$ complex to afford μ -peroxide binuclear Cu^{II} complexes, but this was only observed by a few groups [53, 230]. The $L_D Cu^{II}-OO\cdot$ species is then responsible for the H-atom abstraction step from the polysaccharide substrate to afford $L_D Cu^{II}$ -hydroperoxo ($L_D Cu^{II}-OOH$) species and the substrate radical ($\cdot R$) [193, 197, 228]. A radical rebound step occurs with the homolytic cleavage of the O-O bond and the trapping of $\cdot R$ via the formation of the hydroxylated substrate ($R-OH$), while $L_D Cu^{II}$ -oxyl ($L_D Cu^{II}-O\cdot$) species are formed.

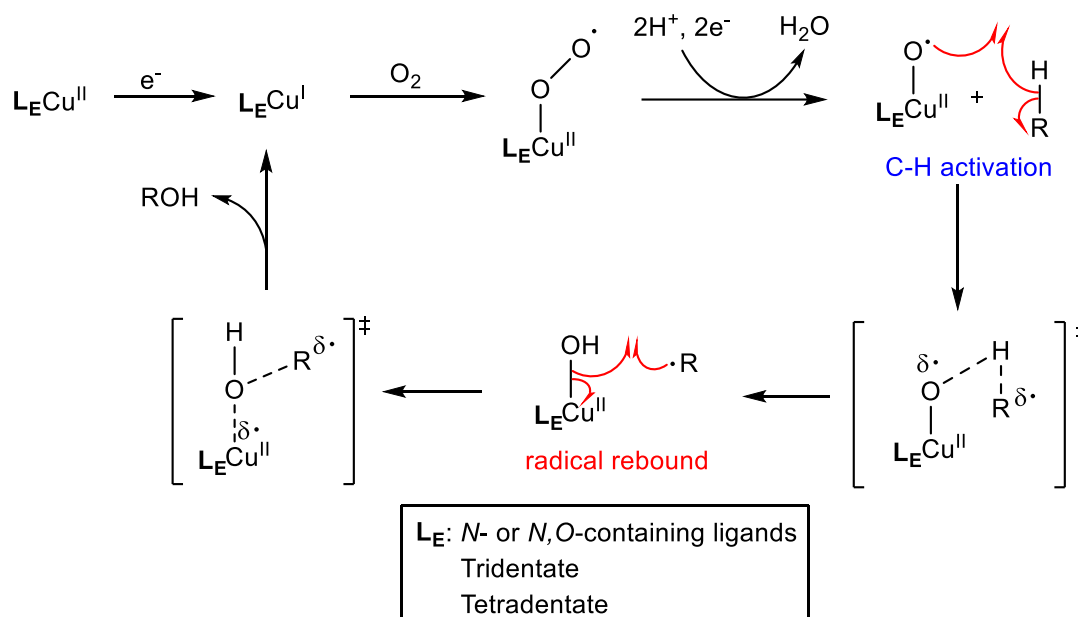


Scheme 2.38: The proposed mechanistic pathway for the oxidative cleavage of polysaccharides where $L_D Cu^{II}$ -superoxo species is involved in the H-atom abstraction step. Adapted from the groups of Tolman, Hemsworth and Beckham [190, 193, 197].

Studies have shown that the combination of the H-atom abstraction step and the transfer of the hydroxyl radical ($\cdot OH$) to $\cdot R$, is the rate-limiting step [193]. The $L_D Cu^{II}-O\cdot$ species is reduced back to $L_D Cu^I$ via proton-coupled electron transfer (PCET) in the presence of a reducing agent such as ascorbic acid. The involvement of $L_D Cu^{II}$ -superoxo species in the H-atom abstraction step is, however, currently in doubt, due to the high energy barrier required for this step [193].

2.2.4.4.2 $L_E Cu$ -oxyl mechanistic pathway

Bruschi, Bortolotti and co-workers employed computational studies to investigate the mechanistic pathway for the oxidative cleavage reaction and their results suggested the involvement of the powerful oxidant, $L_E Cu^{II}$ -oxyl, (L_E : possible ligands, Scheme 2.39) instead of the previously proposed Cu^{II} -superoxo species [200]. Similar observations have been proposed previously [178, 193, 206, 225, 233, 234].



Scheme 2.39: The proposed mechanistic pathway for the oxidative cleavage of polysaccharides where $L_E Cu^{II}$ -oxyl species is suggested to be responsible for the H-atom abstraction step. Adapted from the groups of Bruschi, Bortolotti, Beckham, Hedegård, Marletta and Tolman [190, 193, 200, 235, 236].

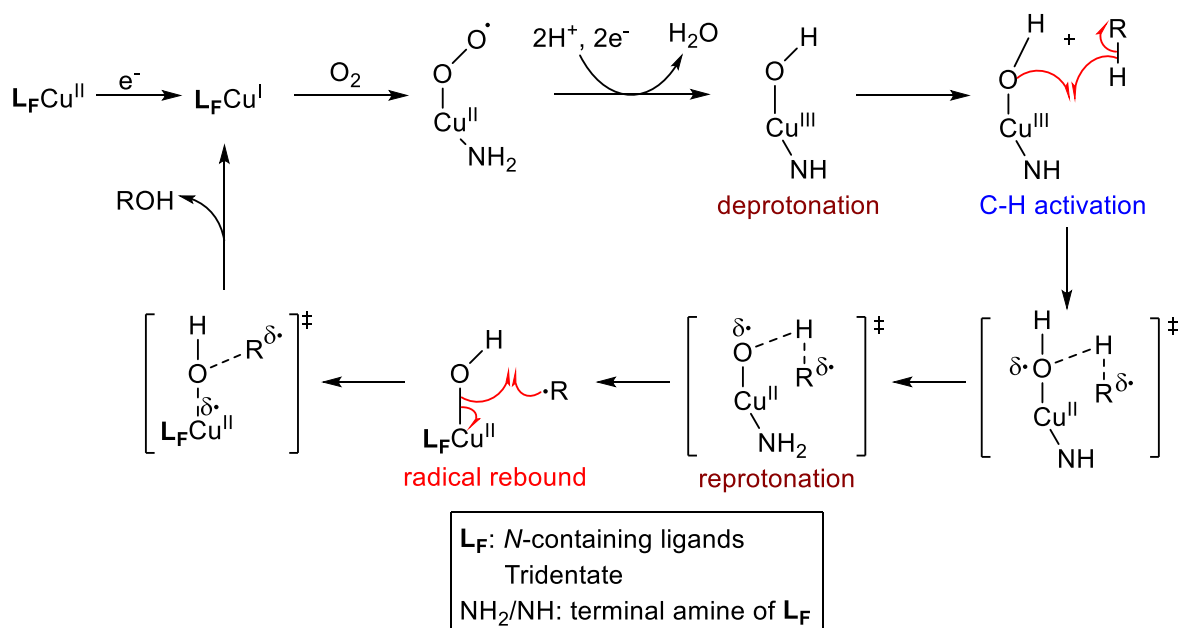
The presence of Cu^{II} -oxyl species in the absence and presence of a supporting ligand framework was previously reported, using MS studies [234, 237]. They focused on the reaction between $L_E Cu^I$ and O_2 to afford $L_E Cu^{II}$ -superoxo species, which can then also be converted to $L_E Cu^{II}$ -oxyl and $L_E Cu^{II}$ -hydroperoxo species. EPR and DFT studies revealed that $L_E Cu^{II}$ -superoxo and $L_E Cu^{II}$ -hydroperoxo species may not be responsible for the H-atom abstraction step [193, 200, 235]. Instead, the $L_E Cu^{II}$ -oxyl species is considered as the active species that is similar to the oxoferryl intermediate in P_{450} monooxygenases with a heme Fe-centre [238]. The homolytic cleavage of the O-O bond of $L_E Cu^{II}$ -superoxo species results in the formation of $L_E Cu^{II}$ -oxyl species prior to the H-atom abstraction step [227, 235, 236]. Two possible $L_E Cu$ -oxyl species can be generated, depending on whether a single- or two-electron transfer occurs. Firstly, the single-electron transfer to afford $L_E Cu^{III}-O\cdot$ species and H_2O , and secondly, the two-electron reduction results in the release in H_2O , while the active site remains the same, $L_E Cu^{II}-O\cdot$ [200, 206].

The $L_E Cu^{II}-O\cdot$ species easily abstracts the H-atom from the substrate, during the rate-limiting step, to afford $L_E Cu^{II}-OH$ species and $\cdot R$. Alternatively, the generation of $L_E Cu^{II}-OH$ species may also occur through further protonation of the $L_E Cu^{II}-O\cdot$ species if the H-atom abstraction step does not occur rapidly, which may then be responsible for the abstraction step (see Section 2.2.4.4.3 and Scheme 2.40) [239, 240]. The migration of $\cdot OH$ from $L_E Cu^{II}-OH$ to $\cdot R$ result in the formation of ROH and the regeneration of $L_E Cu^I$, through an oxygen-rebound

mechanism [22, 193, 198]. A similar mechanistic pathway was also proposed for the oxidation of methane to methanol, catalysed by methane monooxygenase and they found that the dissociation of H₂O plays an important role in the assistance with the L_FCu-OH bond cleavage as well as the formation of the new ROH bond during the rebound mechanistic pathway [241].

2.2.4.4.3 L_FCu^{III}-OH mechanistic pathway

Recently, experimental and computational studies have also suggested the involvement of the protonated version of the Cu^{II}-oxyl species, the L_FCu^{III}-OH (L_F: possible ligands, Scheme 2.40) species, during the H-atom abstraction step [233, 239, 240, 242, 243]. Instead of being the active species, it may also be a precursor for the formation of L_FCu^{II}-oxyl species during the reaction [225]. The reaction between L_FCu^I and the oxidant resulted in the formation of L_FCu^{II}-OO[•] species, where after the NH- of the histidine brace in LPMO can be deprotonated in the absence of the polysaccharide substrate to afford L_FCu^{III}-OH species [242]. The deprotonated *N*-atom then assists in the stabilisation of the newly formed L_FCu^{III}-OH species, which is responsible for the H-atom abstraction step from the substrate to generate L_FCu^{II}-OH₂ species (Scheme 2.40).



Scheme 2.40: The proposed mechanistic pathway for the oxidative cleavage of polysaccharides where L_FCu^{II}-hydroxo species is suggested to be responsible for the H-atom abstraction step. Adapted from the groups of Eijssink, Hedegård and Tolman [190, 233, 236, 239, 242].

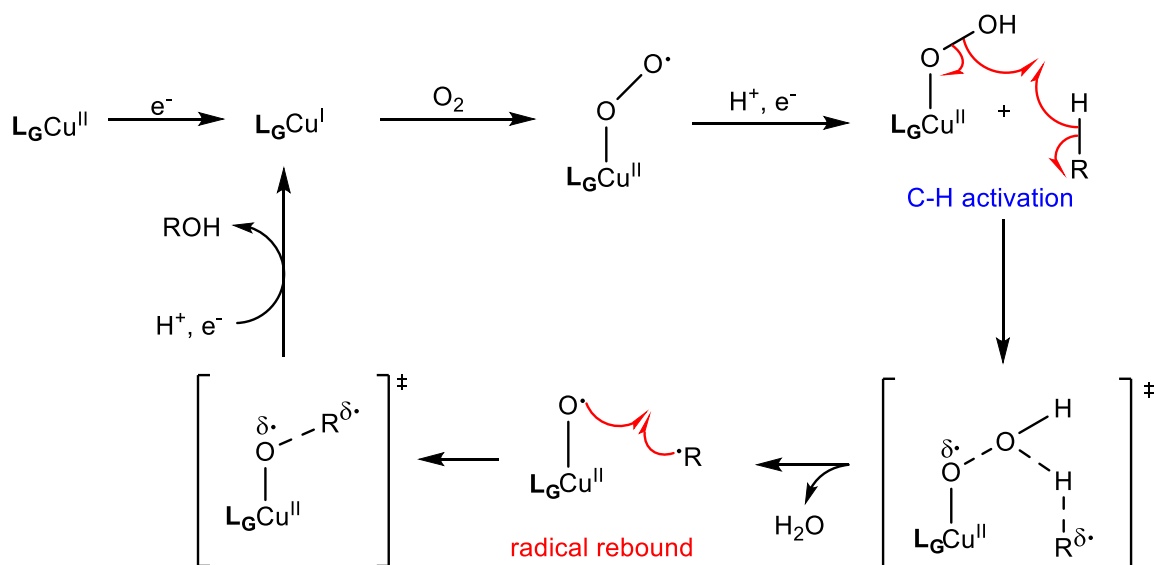
Studies have shown that the hydroxyl radical would have to be well positioned over the substrate to rapidly abstract the H-atom from the substrate [198]. The reprotoation of the *N*-

atom is responsible for the formation of $L_F Cu^{II}-OH$ species and the migration of the $\cdot OH$ radical to $\cdot R$, through a radical rebound reaction, leads to the formation of ROH and the regeneration of $L_F Cu^I$ species occurs. The radical rebound reaction may not always occur to regenerate the $L_F Cu^I$ species, and therefore the involvement of $L_F Cu^{III}-OH$ species during the oxidative cleavage reaction needs to be reconsidered.

Castillo and co-workers employed EPR studies during the oxidative cleavage reaction and proposed the formation of both Cu^{II} -superoxo (reaction between $L_F Cu^I$ and O_2) and binuclear Cu^{II} -peroxo-bridged species, $[{L_F Cu^{II}}]_2(\mu-\eta^2:\eta^2-O_2)]^{2+}$, (reaction between $L_F Cu^I$ and H_2O_2/NEt_3) [195]. Spectral changes and computational studies supported the formation of these peroxo-bridged species. EPR active $L_F Cu^{II}-OOH$ and ${L_F Cu^{II}}_2(\mu-OH)_2$ species were obtained upon H-atom abstraction from either the substrate or the solvent, and both reactions generated the $L_F Cu^{II}-OH$ species. However, due to the lack of sufficient experimental or computational evidence for the formation of peroxo-bridged species, we decided to eliminate the possibility for the formation thereof. Peroxo-bridged species are rather observed for Cu-based tyrosinase mimics [244, 245].

2.2.4.4.4 $L_G Cu^{II}-OOH$ mechanistic pathway

The reaction between $L_G Cu^I$ (L_G : possible ligands, Scheme 2.41) and an oxidant results in the formation of $L_G Cu^{II}-OO\cdot$ species, which was protonated to afford $L_G Cu^{II}-OOH$ species. EPR and computational studies supported the presence of copper-oxygen and $L_G Cu^{II}-OOH$ species [246-248].



Scheme 2.41: The proposed mechanistic pathway for the oxidative cleavage reaction where $L_G Cu^{II}$ -hydroperoxo species is involved in the H-atom abstraction step. Adapted from the groups of Marletta, Tolman and Wada [190, 235, 246].

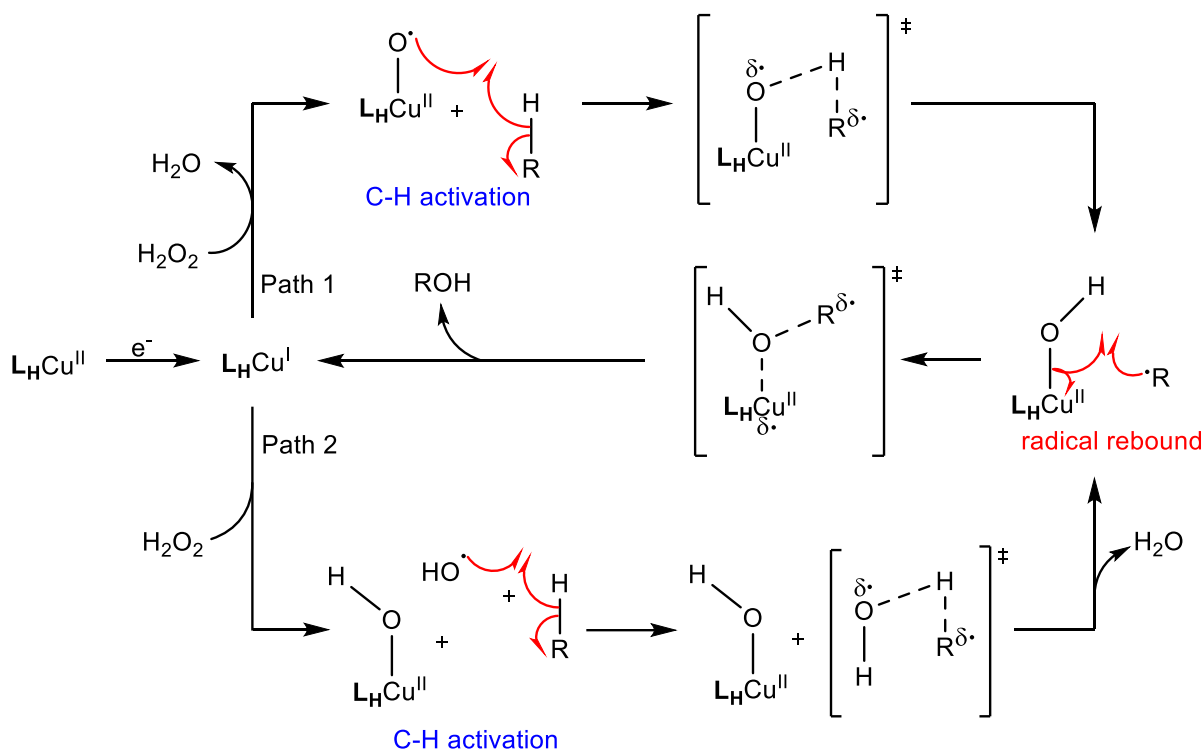
These studies proposed the involvement of $L_C Cu^{II}-OOH$ during the H-atom abstraction step to afford $L_C Cu^{II}-O^{\bullet}$ species and $\cdot R$, which then coordinates during the radical rebound step to afford $L_C Cu^{II}-OR$ species. The hydroxylated substrate and the initial $L_C Cu^I$ species are generated after a protonation reaction. Previous groups suggested that the cleavage of the intact O-O bond for the $L_C Cu^{II}-OOH$ species is not energetically feasible and should therefore be reconsidered to serve as active species [193, 236].

2.2.4.4.5 Possible mechanistic pathways with H_2O_2

Oxidative cleavage reactions may also occur in the presence of H_2O_2 as the oxidant, instead of O_2 , where H_2O is eliminated during the substrate hydroxylation reaction. This is particularly relevant since previous studies have observed the preference for H_2O_2 , instead of O_2 [22, 195, 198-200, 224]. Two extra protons and electrons are required for the reaction between $L_H Cu^I$ and O_2 , while H_2O_2 can operate without additional protons and electrons and result in oxygen-independent oxidation, even in the presence of O_2 [192, 198, 200]. High H_2O_2 concentrations, however, can result in catalyst deactivation [198, 199]. Mayilmurugan and co-workers found that the presence of NEt_3 facilitates the binding of H_2O_2 to the Cu-centre [22]. Two possible mechanistic pathways may be followed for the oxidative cleavage reaction using H_2O_2 as the oxidant. Firstly, the binding of H_2O_2 to the Cu-based active site is followed by intramolecular proton transfer from the coordinated to the distal O-atom of H_2O_2 and the dissociation of H_2O to afford $L_H Cu^{II}-O^{\bullet}$ species, which is then responsible for the H-atom abstraction step from the substrate to generate $L_H Cu^{II}-OH$ and $\cdot R$ (Scheme 2.42, Path 1). The migration of the $\cdot OH$ radical from $L_H Cu^{II}-OH$ to $\cdot R$, through a radical rebound reaction, leads to the formation of ROH and the regeneration of $L_H Cu^I$ species occurs. Mayilmurugan and co-workers performed the oxidative cleavage reactions in the presence of a radical trapping agent such as TEMPO $\cdot$ and no changes in the results were observed. Therefore, their studies support this part of the mechanistic pathway due to the absence of radical formation during the reaction [22].

The second pathway rather suggests the formation of $L_H Cu^{II}-OH$ and $\cdot OH$ radical species in the presence of the substrate (Scheme 2.42, Path 2) [224]. The $\cdot OH$ radical is then responsible for the H-atom abstraction step from the substrate to afford $\cdot R$. Cowan and co-workers employed UV/vis studies to follow the reduction of copper, facilitated by ascorbate when active species scavengers or enhancers were added to the reaction. A significant decrease in the cleavage rate (> 90 %) in the presence of DMSO (1 %) or potassium iodide (KI, 5 mM) was observed, which confirms the formation of $\cdot OH$ and peroxide. Superoxide dismutase was also added to the reaction to determine whether Cu^{II} -superoxide can serve as the active species. No significant inhibition was observed for **C2.58**, but a significant decrease of 40 to 50 % in the cleavage rate was obtained for complexes **C2.59-C2.61**, which further supports the

formation of hydroxyl radicals [224]. Similar to the first pathway, the migration of the $\cdot\text{OH}$ radical from $\text{L}_\text{H}\text{Cu}^\text{II}\text{-OH}$ to $\cdot\text{R}$, through a radical rebound reaction, leads to the formation of ROH and the regeneration of $\text{L}_\text{H}\text{Cu}^\text{I}$ species occurs.



Scheme 2.42: The proposed mechanistic pathway for the oxidative cleavage reaction using H_2O_2 as the oxidant. Either $\text{L}_\text{H}\text{Cu}^\text{II}\text{-oxyl}$ or $\cdot\text{OH}$ radical species is formed that can serve as the active species for the H-atom abstraction step. Adapted from the groups of Bissaro and Cowan [198, 224].

In conclusion, experimental, spectroscopic and computational studies have informed possible mechanistic pathways that may be operative during the oxidative cleavage reaction. The most important step during these mechanistic pathways is the H-atom abstraction step from the C-H bond in position C1 or C4 of the polysaccharide substrate. However, the nature of the Cu-based active species that is responsible for this step, is still in doubt since some groups have proposed the involvement of Cu^II -superoxo species [190, 193, 197, 228], while others have suggested the involvement of Cu^II -oxyl species [190, 193, 200, 235, 236] when using O_2 as the oxidant. Less experimental and/or computational evidence is available for the proposed involvement of Cu^II -hydroxo [190, 233, 236, 239] and Cu^II -hydroperoxo [190, 235, 246] species. Moreover, the involvement of either Cu^II -oxyl or Cu^II -hydroxo and $\cdot\text{OH}$ radical species has also been proposed in the presence of H_2O_2 as the oxidant [198, 224].

2.3 Summary

Various copper-catalysed oxidative transformation reactions have been reported for the synthesis of oxygenates such as alcohols, ketones and aldehydes. These reactions include the oxidation of activated alcohols in the absence of an *N*-oxide co-catalyst, the hydroxylation of aryl halides, the peroxidation of hydrocarbons and oxidative cleavage of polysaccharides. The advantages, disadvantages and variables associated with reported Cu-based catalyst systems for these reactions have been discussed. Unfortunately, many Cu-based catalyst systems still require high temperatures, long reaction times, high catalyst loadings and the addition of expensive or toxic additives. Therefore, potential developments for these reactions include Cu-based catalyst systems that can operate at room- to moderate reaction temperatures, without an inert atmosphere or additives. Proposed mechanistic pathways for these oxidative transformation reactions have been discussed in detail, with the major differences involving the initial oxidation state of copper, redox dynamism and the nature of the Cu-based active species that is responsible for substrate activation during the reaction. It is clear that even though several Cu-based catalyst systems have been reported for these oxidative transformation reactions, the majority still require harsh reaction conditions, which may also influence the product yields. As such, the focus remains to develop novel Cu-based catalyst systems to improve on these drawbacks and limitations and to better understand the specific mechanistic pathway for each reaction, especially the nature of the active species.

2.4 Acknowledgements

This work is based on the research supported by the National Research Foundation of South Africa (Unique Grant No. 112545 and 117869) and the North-West University. Any opinion, finding and conclusion or recommendation expressed in this material is that of the authors and the NRF does not accept any liability in this regard. The infrastructure support provided by the Focus Area for Chemical Resource Beneficiation (CRB) and in particular the Catalysis and Synthesis Research Group, at the NWU, is gratefully acknowledged.

2.5 References

- [1] L.Q. Hatcher, K.D. Karlin, *Adv. Inorg. Chem.*, 58 (2006) 131-184.
- [2] C. Sambiasi, S.P. Marsden, A.J. Blacker, P.C. McGowan, *Chem. Soc. Rev.*, 43 (2014) 3525-3550.
- [3] J.M. Hoover, B.L. Ryland, S.S. Stahl, *J. Am. Chem. Soc.*, 135 (2013) 2357-2367.
- [4] J.W. Whittaker, *Chem. Rev.*, 103 (2003) 2347-2364.
- [5] A. Dijkman, I.W.C.E. Arends, R.A. Sheldon, *Org. Biomol. Chem.*, 1 (2003) 3232-3237.
- [6] E.T. Kumpulainen, A.M. Koskinen, *Chem. Eur. J.*, 15 (2009) 10901-10911.
- [7] J.M. Hoover, S.S. Stahl, *J. Am. Chem. Soc.*, 133 (2011) 16901-16910.
- [8] L. Wang, Z. Bie, S. Shang, Y. Lv, G. Li, J. Niu, S. Gao, *RSC Adv.*, 6 (2016) 35008-35013.
- [9] L. Marais, J. Bures, J.H.L. Jordaan, S. Mapolie, A.J. Swarts, *Org. Biomol. Chem.*, 15 (2017) 6926-6933.
- [10] T.F. Silva, L.M. Martins, *Molecules*, 25 (2020) 748.
- [11] L. Marais, A.J. Swarts, *Catalysts*, 9 (2019) 395.
- [12] J.E. Steves, S.S. Stahl, *J. Am. Chem. Soc.*, 135 (2013) 15742-15745.
- [13] Y. Wang, C. Zhou, R. Wang, *Green Chem.*, 17 (2015) 3910-3915.
- [14] C. Hoarau, T.R. Pettus, *Synlett.*, 2003 (2003) 0127-0137.
- [15] P. Hanson, J.R. Jones, A.B. Taylor, P.H. Walton, A.W. Timms, *J. Chem. Soc., Perkin Trans. 2*, (2002) 1135-1150.
- [16] K. Inamoto, K. Nozawa, M. Yonemoto, Y. Kondo, *Chem. Commun.*, 47 (2011) 11775-11777.
- [17] J. Xu, X. Wang, C. Shao, D. Su, G. Cheng, Y. Hu, *Org. Lett.*, 12 (2010) 1964-1967.
- [18] G.R. Hemsworth, E.M. Johnston, G.J. Davies, P.H. Walton, *Trends Biotechnol.*, 33 (2015) 747-761.
- [19] G.R. Hemsworth, B. Henrissat, G.J. Davies, P.H. Walton, *Nat. Chem. Biol.*, 10 (2014) 122.
- [20] R. Trammell, K. Rajabimoghadam, I. Garcia-Bosch, *Chem. Rev.*, 119 (2019) 2954-3031.
- [21] P.K. Busk, L. Lange, *BMC Genomics*, 16 (2015) 368.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [22] S. Muthuramalingam, D. Maheshwaran, M. Velusamy, R. Mayilmurugan, *J. Catal.*, 372 (2019) 352-361.
- [23] G. Vaaje-Kolstad, B. Westereng, S.J. Horn, Z. Liu, H. Zhai, M. Sørli, V.G. Eijsink, *Science*, 330 (2010) 219-222.
- [24] D.H. Barton, S.D. Bévère, W. Chavasiri, É. Csuhai, D. Doller, *Tetrahedron*, 48 (1992) 2895-2910.
- [25] I. Garcia-Bosch, M.A. Siegler, *Angew. Chem. Int. Ed.*, 55 (2016) 12873-12876.
- [26] C. Di Nicola, F. Garau, Y.Y. Karabach, L.M. Martins, M. Monari, L. Pandolfo, C. Pettinari, A.J. Pombeiro, *Eur. J. Inorg. Chem.*, 2009 (2009) 666-676.
- [27] A. Conde, L. Vilella, D. Balcells, M.M. Díaz-Requejo, A. Lledós, P.J. Pérez, *J. Am. Chem. Soc.*, 135 (2013) 3887-3896.
- [28] M.V. Kirillova, T.A. Fernandes, V. André, A.M. Kirillov, *Org. Biomol. Chem.*, 17 (2019) 7706-7714.
- [29] Q. Cao, L.M. Dornan, L. Rogan, N.L. Hughes, M.J. Muldoon, *Chem. Commun.*, 50 (2014) 4524-4543.
- [30] P. Gamez, I.W.C.E. Arends, J. Reedijk, R.A. Sheldon, *Chem. Commun.*, 0 (2003) 2414-2415.
- [31] G. Sarmah, S.K. Bharadwaj, A. Dewan, A. Gogoi, U. Bora, *Tetrahedron Lett.*, 55 (2014) 5029-5032.
- [32] S. Chibani, C. Michel, F. Delbecq, C. Pinel, M. Besson, *Catalysis Science & Technology*, 3 (2013) 339-350.
- [33] B. Choudary, M.L. Kantam, A. Rahman, C.V. Reddy, K.K. Rao, *Angew. Chem. Int. Ed.*, 40 (2001) 763-766.
- [34] T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.*, 105 (2005) 2329-2364.
- [35] Q. Yan, Y.C. Fang, Y.X. Jia, X.H. Duan, *New J. Chem.*, 41 (2017) 2372-2377.
- [36] M.M. Heravi, N. Ghalavand, E. Hashemi, *Chemistry*, 2 (2020) 101-178.
- [37] J.-X. Wang, X.-T. Zhou, Q. Han, X.-X. Guo, X.-H. Liu, C. Xue, H.-B. Ji, *New J. Chem.*, 43 (2019) 19415-19421.
- [38] N. Noshiranzadeh, R. Bikas, K. Ślepokura, M. Mayeli, T. Lis, *Inorg. Chim. Acta*, 421 (2014) 176-182.
- [39] K. Marui, Y. Higashiura, S. Kodama, S. Hashidate, A. Nomoto, S. Yano, M. Ueshima, A. Ogawa, *Tetrahedron*, 70 (2014) 2431-2438.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [40] M.T. Räisänen, A. Al-Hunaiti, E. Atosuo, M. Kemell, M. Leskelä, T. Repo, *Catalysis Science & Technology*, 4 (2014) 2564-2573.
- [41] N. Noshiranzadeh, M. Mayeli, R. Bikas, K. Šlepokura, T. Lis, *Transition Met. Chem.*, 39 (2014) 33-39.
- [42] Y. Sasano, S. Nagasawa, M. Yamazaki, M. Shibuya, J. Park, Y. Iwabuchi, *Angew. Chem. Int. Ed.*, 53 (2014) 3236-3240.
- [43] S.E. Allen, R.R. Walvoord, R. Padilla-Salinas, M.C. Kozlowski, *Chem. Rev.*, 113 (2013) 6234-6458.
- [44] Y. Wang, J.L. DuBois, B. Hedman, K.O. Hodgson, T. Stack, *Science*, 279 (1998) 537-540.
- [45] P. Chaudhuri, M. Hess, U. Flörke, K. Wieghardt, *Angew. Chem. Int. Ed.*, 37 (1998) 2217-2220.
- [46] P. Chaudhuri, M. Hess, T. Weyhermüller, K. Wieghardt, *Angew. Chem. Int. Ed.*, 38 (1999) 1095-1098.
- [47] P. Chaudhuri, M. Hess, J. Müller, K. Hildenbrand, E. Bill, T. Weyhermüller, K. Wieghardt, *J. Am. Chem. Soc.*, 121 (1999) 9599-9610.
- [48] I.E. Marko, P.R. Giles, M. Tsukazaki, S.M. Brown, C.J. Urch, *Science*, 274 (1996) 2044-2046.
- [49] I.E. Markó, A. Gautier, I. Chellé-Regnaut, P.R. Giles, M. Tsukazaki, C.J. Urch, S.M. Brown, *The Journal of Organic Chemistry*, 63 (1998) 7576-7577.
- [50] P. Lahtinen, H. Korpi, E. Haavisto, M. Leskelä, T. Repo, *J. Comb. Chem.*, 6 (2004) 967-973.
- [51] P. Lahtinen, E. Lankinen, M. Leskelä, T. Repo, *Appl. Catal., A*, 295 (2005) 177-184.
- [52] B. Xu, J.P. Lumb, B.A. Arndtsen, *Angew. Chem. Int. Ed.*, 54 (2015) 4208-4211.
- [53] E.A. Lewis, W.B. Tolman, *Chem. Rev.*, 104 (2004) 1047-1076.
- [54] S.D. McCann, J.-P. Lumb, B.A. Arndtsen, S.S. Stahl, *ACS Cent. Sci.*, (2017).
- [55] A.N. Kulakova, A.N. Bilyachenko, M.M. Levitsky, V.N. Khrustalev, A.A. Korlyukov, Y.V. Zubavichus, P.V. Dorovatovskii, F.d.r. Lamaty, X. Bantreil, B. Villemejeanne, *Inorg. Chem.*, 56 (2017) 15026-15040.
- [56] A.N. Kulakova, V.N. Khrustalev, Y.V. Zubavichus, L.S. Shul'pina, E.S. Shubina, M.M. Levitsky, N.S. Ikonnikov, A.N. Bilyachenko, Y.N. Kozlov, G.B. Shul'pin, *Catalysts*, 9 (2019) 154.
- [57] A.N. Kulakova, A.A. Korlyukov, Y.V. Zubavichus, V.N. Khrustalev, X. Bantreil, L.S. Shul'Pina, M.M. Levitsky, N.S. Ikonnikov, E.S. Shubina, F. Lamaty, *J. Organomet. Chem.*, 884 (2019) 17-28.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [58] O.V. Nesterova, D.S. Nesterov, A. Krogul-Sobczak, M.F.C.G. da Silva, A.J. Pombeiro, J. Mol. Catal. A: Chem., 426 (2017) 506-515.
- [59] S. Velusamy, T. Punniyamurthy, Eur. J. Org. Chem., 2003 (2003) 3913-3915.
- [60] S. Velusamy, T. Punniyamurthy, Tetrahedron Lett., 44 (2003) 8955-8957.
- [61] J.U. Ahmad, M.T. Räisänen, M. Leskelä, T. Repo, Appl. Catal., A, 411 (2012) 180-187.
- [62] A.G.F. Shoair, J. Coord. Chem., 65 (2012) 3511-3518.
- [63] K. Czerwińska, B. Machura, S. Kula, S. Krompiec, K. Erfurt, C. Roma-Rodrigues, A.R. Fernandes, L.S. Shul'pina, N.S. Ikonnikov, G.B. Shul'pin, Dalton Trans., 46 (2017) 9591-9604.
- [64] H. Ünver, I. Kani, Polyhedron, 134 (2017) 257-262.
- [65] H. Ünver, I. Kani, J. Chem. Sci., 130 (2018) 33.
- [66] H. Ünver, Transition Met. Chem., 43 (2018) 641-646.
- [67] K. Kaneda, T. Yamashita, T. Matsushita, K. Ebitani, The Journal of Organic Chemistry, 63 (1998) 1750-1751.
- [68] R. Bikas, F. Ajormal, M. Emami, N. Noshiranzadeh, A. Kozakiewicz, Inorg. Chim. Acta, 478 (2018) 77-87.
- [69] C. Wu, B. Liu, X. Geng, Z. Zhang, S. Liu, Q. Hu, Polyhedron, 158 (2019) 334-341.
- [70] S.G. Mncube, M.D. Bala, Transition Met. Chem., 44 (2019) 145-151.
- [71] Y. Wang, T. Stack, J. Am. Chem. Soc., 118 (1996) 13097-13098.
- [72] P. Belanzoni, C. Michel, E.J. Baerends, Inorg. Chem., 50 (2011) 11896-11904.
- [73] B.L. Ryland, S.D. McCann, T.C. Brunold, S.S. Stahl, J. Am. Chem. Soc., 136 (2014) 12166-12173.
- [74] L. Chaloner, A. Khomutovskaya, F. Thomas, X. Ottenwaelder, Dalton Trans., 45 (2016) 11109-11119.
- [75] C.X. Zhang, H.-C. Liang, E.-i. Kim, Q.-F. Gan, Z. Tyeklár, K.-C. Lam, A.L. Rheingold, S. Kaderli, A.D. Zuberbühler, K.D. Karlin, Chem. Commun., 0 (2001) 631-632.
- [76] J. Windle, Journal of Magnetic Resonance (1969), 45 (1981) 432-439.
- [77] G. Mendenhall, K. Ingold, J. Am. Chem. Soc., 95 (1973) 6395-6400.
- [78] V.K. Bansal, P.P. Thankachan, R. Prasad, Appl. Catal., A, 381 (2010) 8-17.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [79] J.P. Klinman, *Chem. Rev.*, 96 (1996) 2541-2562.
- [80] J.-q. Xie, J.-z. Li, X.-g. Meng, C.-w. Hu, X.-c. Zeng, S.-x. Li, *Transition Met. Chem.*, 29 (2004) 388-393.
- [81] J. Wang, L. Yan, G. Li, X. Wang, Y. Ding, J. Suo, *Tetrahedron Lett.*, 46 (2005) 7023-7027.
- [82] A. Corma, P. Esteve, A. Martinez, *Appl. Catal., A*, 143 (1996) 87-100.
- [83] J.H. Tyman, *Elsevier.*, 52 (1996).
- [84] R. Bal, M. Tada, T. Sasaki, Y. Iwasawa, *Angew. Chem. Int. Ed.*, 45 (2006) 448-452.
- [85] R.E. Maleczka, F. Shi, D. Holmes, M.R. Smith, *J. Am. Chem. Soc.*, 125 (2003) 7792-7793.
- [86] K.W. Anderson, T. Ikawa, R.E. Tundel, S.L. Buchwald, *J. Am. Chem. Soc.*, 128 (2006) 10694-10695.
- [87] M.C. Willis, *Angew. Chem. Int. Ed.*, 46 (2007) 3402-3404.
- [88] G. Chen, A.S. Chan, F.Y. Kwong, *Tetrahedron Lett.*, 48 (2007) 473-476.
- [89] B.J. Gallon, R.W. Kojima, R.B. Kaner, P.L. Diaconescu, *Angew. Chem. Int. Ed.*, 46 (2007) 7251-7254.
- [90] A.G. Sergeev, T. Schulz, C. Torborg, A. Spannenberg, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.*, 48 (2009) 7595-7599.
- [91] T. Schulz, C. Torborg, B. Schöffner, J. Huang, A. Zapf, R. Kadyrov, A. Börner, M. Beller, *Angew. Chem. Int. Ed.*, 48 (2009) 918-921.
- [92] C.-W. Yu, G.S. Chen, C.-W. Huang, J.-W. Chern, *Org. Lett.*, 14 (2012) 3688-3691.
- [93] D. Zhao, N. Wu, S. Zhang, P. Xi, X. Su, J. Lan, J. You, *Angew. Chem. Int. Ed.*, 48 (2009) 8729-8732.
- [94] K. Yang, Z. Li, Z. Wang, Z. Yao, S. Jiang, *Org. Lett.*, 13 (2011) 4340-4343.
- [95] A. Tlili, N. Xia, F. Monnier, M. Taillefer, *Angew. Chem.*, 121 (2009) 8881-8884.
- [96] R. Paul, M.A. Ali, T. Punniyamurthy, *Synthesis*, 2010 (2010) 4268-4272.
- [97] O. Songis, P. Boulens, C.G. Benson, C.S. Cazin, *RSC Adv.*, 2 (2012) 11675-11677.
- [98] N. Mketo, J.H.L. Jordaan, A. Jordaan, A.J. Swarts, S.F. Mapolie, *Eur. J. Inorg. Chem.*, 2016 (2016) 3781-3790.
- [99] P.J. Amal Joseph, S. Priyadarshini, *Org. Process Res. Dev.*, 21 (2017) 1889-1924.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [100] C.M. Kormos, N.E. Leadbeater, *Tetrahedron*, 62 (2006) 4728-4732.
- [101] D. Ma, Q. Cai, H. Zhang, *Org. Lett.*, 5 (2003) 2453-2455.
- [102] L. Jing, J. Wei, L. Zhou, Z. Huang, Z. Li, X. Zhou, *Chem. Commun.*, 46 (2010) 4767-4769.
- [103] D. Wang, D. Kuang, F. Zhang, S. Tang, W. Jiang, *Eur. J. Org. Chem.*, 2014 (2014) 315-318.
- [104] S. Maurer, W. Liu, X. Zhang, Y. Jiang, D. Ma, *Synlett.*, 2010 (2010) 976-978.
- [105] K.H. Shaughnessy, *Chem. Rev.*, 109 (2009) 643-710.
- [106] D. Yang, H. Fu, *Chemistry—A European Journal*, 16 (2010) 2366-2370.
- [107] J. Jia, C. Jiang, X. Zhang, Y. Jiang, D. Ma, *Tetrahedron Lett.*, 52 (2011) 5593-5595.
- [108] G. Lefèvre, A. Tlili, M. Taillefer, C. Adamo, I. Ciofini, A. Jutand, *Dalton Trans.*, 42 (2013) 5348-5354.
- [109] S. Xia, L. Gan, K. Wang, Z. Li, D. Ma, *J. Am. Chem. Soc.*, 138 (2016) 13493-13496.
- [110] A.J. Swarts, F. Zheng, V.J. Smith, E. Nordlander, S.F. Mapolie, *Organometallics*, 33 (2014) 2247-2256.
- [111] S.S. Shendage, *J. Chem. Sci.*, 130 (2018) 1-4.
- [112] L. Marais, H.C.M. Vosloo, A.J. Swarts, *Mol. Catal.*, 486 (2020) 110839.
- [113] A.J. Swarts, S.F. Mapolie, *Dalton Trans.*, 43 (2014) 9892-9900.
- [114] G. Lefèvre, G.g. Franc, C. Adamo, A. Jutand, I. Ciofini, *Organometallics*, 31 (2012) 914-920.
- [115] G. Franc, Q. Cacciuttolo, G. Lefèvre, C. Adamo, I. Ciofini, A. Jutand, *ChemCatChem*, 3 (2011) 305-309.
- [116] E. Garribba, G. Micera, D. Sanna, L. Strinna-Erre, *Inorg. Chim. Acta*, 299 (2000) 253-261.
- [117] S.J. Koepke, K.M. Light, P.E. VanNatta, K.M. Wiley, M.T. Kieber-Emmons, *J. Am. Chem. Soc.*, 139 (2017) 8586-8600.
- [118] J.M. Hoover, B.L. Ryland, S.S. Stahl, *ACS Catal.*, 3 (2013) 2599-2605.
- [119] A. Casitas, A.E. King, T. Parella, M. Costas, S.S. Stahl, X. Ribas, *Chem. Sci.*, 1 (2010) 326-330.
- [120] J.X. Qiao, P.Y. Lam, *Synthesis*, 2011 (2011) 829-856.
- [121] H. Zhang, L. Zhao, D.-X. Wang, M.-X. Wang, *Org. Lett.*, 15 (2013) 3836-3839.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [122] X. Ribas, D.A. Jackson, B. Donnadieu, J. Mahía, T. Parella, R. Xifra, B. Hedman, K.O. Hodgson, A. Llobet, T.D.P. Stack, *Angew. Chem. Int. Ed.*, 41 (2002) 2991-2994.
- [123] A. Casitas, X. Ribas, *Chem. Sci.*, 4 (2013) 2301-2318.
- [124] N. Yoshikai, E. Nakamura, *Chem. Rev.*, 112 (2012) 2339-2372.
- [125] A. Annunziata, C. Galli, M. Marinelli, T. Pau, *Eur. J. Org. Chem.*, 2001 (2001) 1323-1329.
- [126] R.A. Altman, E.D. Koval, S.L. Buchwald, *The Journal of Organic Chemistry*, 72 (2007) 6190-6199.
- [127] H.-Z. Yu, Y.-Y. Jiang, Y. Fu, L. Liu, *J. Am. Chem. Soc.*, 132 (2010) 18078-18091.
- [128] A.M. Kirillov, M.N. Kopylovich, M.V. Kirillova, E.Y. Karabach, M. Haukka, M.F.C.G. da Silva, A.J. Pombeiro, *Adv. Synth. Catal.*, 348 (2006) 159-174.
- [129] J. Steeman, S. Kaarsemaker, P. Hoftyzer, *Chem. Eng. Sci.*, 14 (1961) 139-149.
- [130] D.H. Barton, M.J. Gastiger, W.B. Motherwell, *J. Chem. Soc., Chem. Commun.*, (1983) 41-43.
- [131] D.H. Barton, F. Halley, N. Ozbalik, M. Schmitt, E. Young, G. Balavoine, *J. Am. Chem. Soc.*, 111 (1989) 7144-7149.
- [132] Y.V. Geletii, V.V. Lavrushko, G.V. Lubimova, *J. Chem. Soc., Chem. Commun.*, (1988) 936-937.
- [133] D.H. Barton, D. Doller, Y.V. Geletii, *Mendeleev Commun.*, 1 (1991) 115-116.
- [134] G.B. Shul'pin, *Catalysts*, 6 (2016) 50-90.
- [135] P. Stavropoulos, R. Çelenligil-Çetin, A.E. Tapper, *Acc. Chem. Res.*, 34 (2001) 745-752.
- [136] A. Sobkowiak, A. Qui, X. Liu, A. Llobet, D.T. Sawyer, *J. Am. Chem. Soc.*, 115 (1993) 609-614.
- [137] U. Schuchardt, R. Pereira, M.c. Rufo, *J. Mol. Catal. A: Chem.*, 135 (1998) 257-262.
- [138] K. Pamin, E. Tabor, S. Górecka, W.W. Kubiak, D. Rutkowska-Zbik, J. Połtowicz, *ChemSusChem*, 12 (2019) 684-691.
- [139] J. Połtowicz, E. Tabor, K. Pamin, J. Haber, *Inorg. Chem. Commun.*, 8 (2005) 1125-1127.
- [140] M.S. Chen, M.C. White, *Science*, 318 (2007) 783-787.
- [141] A.M. Zima, O.Y. Lyakin, K.P. Bryliakov, E.P. Talsi, *Mol. Catal.*, 455 (2018) 6-13.
- [142] C. Pavan, J. Legros, C. Bolm, *Adv. Synth. Catal.*, 347 (2005) 703-705.
- [143] M. Sutradhar, L.M. Martins, T.R. Barman, M.L. Kuznetsov, M.F.C.G. da Silva, A.J. Pombeiro, *New J. Chem.*, 43 (2019) 17557-17570.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [144] G.B. Shul'pin, G.V. Nizova, Y.N. Kozlov, L. Gonzalez Cuervo, G. Süss-Fink, *Adv. Synth. Catal.*, 346 (2004) 317-332.
- [145] I. Tabushi, T. Nakajima, K. Seto, *Tetrahedron Lett.*, 21 (1980) 2565-2568.
- [146] A.M. Kirillov, M.V. Kirillova, A.J. Pombeiro, *Coord. Chem. Rev.*, 256 (2012) 2741-2759.
- [147] G.B. Shul'pin, J. Gradinaru, Y.N. Kozlov, *Org. Biomol. Chem.*, 1 (2003) 3611-3617.
- [148] R.S.d. Cruz, J.M.d.S. Silva, U. Arnold, M.S. Sercheli, U. Schuchardt, *J. Braz. Chem. Soc.*, 13 (2002) 170-176.
- [149] T. Ohta, T. Tachiyama, K. Yoshizawa, T. Yamabe, T. Uchida, T. Kitagawa, *Inorg. Chem.*, 39 (2000) 4358-4369.
- [150] T. Okuno, S. Ohba, Y. Nishida, *Polyhedron*, 16 (1997) 3765-3774.
- [151] R. Raja, P. Ratnasamy, *Catal. Lett.*, 48 (1997) 1-10.
- [152] N. Komiya, T. Naota, Y. Oda, S.-I. Murahashi, *J. Mol. Catal. A: Chem.*, 117 (1997) 21-37.
- [153] S.-I. Murahashi, N. Komiya, Y. Hayashi, T. Kumano, *Pure Appl. Chem.*, 73 (2001) 311-314.
- [154] W.A. Carvalho, M. Wallau, U. Schuchardt, *J. Mol. Catal. A: Chem.*, 144 (1999) 91-99.
- [155] C. Di Nicola, Y.Y. Karabach, A.M. Kirillov, M. Monari, L. Pandolfo, C. Pettinari, A.J. Pombeiro, *Inorg. Chem.*, 46 (2007) 221-230.
- [156] M.V. Kirillova, A.M. Kirillov, M.F.C. Guedes da Silva, A.J.L. Pombeiro, *Eur. J. Inorg. Chem.*, 2008 (2008) 3423-3427.
- [157] S.S. Dias, M.V. Kirillova, V.n. André, J. Klak, A.M. Kirillov, *Inorg. Chem.*, 54 (2015) 5204-5212.
- [158] M. Sutradhar, E.C. Alegria, T.R. Barman, M.F.C.G. da Silva, K.T. Mahmudov, F.I. Guseynov, A.J. Pombeiro, *Polyhedron*, 117 (2016) 666-671.
- [159] E. Firinci, *J. Mol. Struct.*, 1193 (2019) 125-130.
- [160] A. Bhattacharjee, S. Dey, P. Roy, *Inorg. Chim. Acta*, 490 (2019) 93-103.
- [161] A.M. Kirillov, M.N. Kopylovich, M.V. Kirillova, M. Haukka, M.F.C.G. da Silva, A.J. Pombeiro, *Angew. Chem. Int. Ed.*, 44 (2005) 4345-4349.
- [162] M. Casarin, C. Corvaja, C. Di Nicola, D. Falcomer, L. Franco, M. Monari, L. Pandolfo, C. Pettinari, F. Piccinelli, *Inorg. Chem.*, 44 (2005) 6265-6276.
- [163] M. Casarin, C. Corvaja, C. di Nicola, D. Falcomer, L. Franco, M. Monari, L. Pandolfo, C. Pettinari, F. Piccinelli, P. Tagliatesta, *Inorg. Chem.*, 43 (2004) 5865-5876.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [164] M.T. Musser, Ullmann's Encyclopedia of Industrial Chemistry, 6th ed., Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011; Vol. 11.
- [165] A. Conde, M.M. Diaz-Requejo, P.J. Pérez, Chem. Commun., 47 (2011) 8154-8156.
- [166] J.F. Hull, D. Balcells, E.L. Sauer, C. Raynaud, G.W. Brudvig, R.H. Crabtree, O. Eisenstein, J. Am. Chem. Soc., 132 (2010) 7605-7616.
- [167] S. Shi, Y. Wang, A. Xu, H. Wang, D. Zhu, S.B. Roy, T.A. Jackson, D.H. Busch, G. Yin, Angew. Chem. Int. Ed., 50 (2011) 7321-7324.
- [168] J. Palmucci, K.T. Mahmudov, M.F.C.G. da Silva, L.M. Martins, F. Marchetti, C. Pettinari, A.J. Pombeiro, RSC Adv., 5 (2015) 84142-84152.
- [169] G.B. Shul'pin, J. Mol. Catal. A: Chem., 189 (2002) 39-66.
- [170] I. Garcia-Bosch, Synlett., 28 (2017) 1237-1243.
- [171] A.M. Kirillov, G.B. Shul'pin, Coord. Chem. Rev., 257 (2013) 732-754.
- [172] M.V. Kirillova, Y.N. Kozlov, L.S. Shul'pina, O.Y. Lyakin, A.M. Kirillov, E.P. Talsi, A.J. Pombeiro, G.B. Shul'pin, J. Catal., 268 (2009) 26-38.
- [173] M. Yamada, K.D. Karlin, S. Fukuzumi, Chem. Sci., 7 (2016) 2856-2863.
- [174] M.N. Kopylovich, K.T. Mahmudov, M.F.t.C. Guedes da Silva, P.J. Figiel, Y.Y. Karabach, M.L. Kuznetsov, K.V. Luzyanin, A.J. Pombeiro, Inorg. Chem., 50 (2011) 918-931.
- [175] K.-B. Cho, X. Wu, Y.-M. Lee, Y.H. Kwon, S. Shaik, W. Nam, J. Am. Chem. Soc., 134 (2012) 20222-20225.
- [176] T.W.-S. Chow, Y. Liu, C.-M. Che, Chem. Commun., 47 (2011) 11204-11206.
- [177] I. Garcia-Bosch, X. Ribas, M. Costas, Chemistry—A European Journal, 18 (2012) 2113-2122.
- [178] K. Yoshizawa, N. Kihara, T. Kamachi, Y. Shiota, Inorg. Chem., 45 (2006) 3034-3041.
- [179] M.D. Sweeney, F. Xu, Catalysts, 2 (2012) 244-263.
- [180] W.T. Beeson, V.V. Vu, E.A. Span, C.M. Phillips, M.A. Marletta, Annu. Rev. Biochem, 84 (2015) 923-946.
- [181] P.V. Harris, D. Welner, K. McFarland, E. Re, J.-C. Navarro Poulsen, K. Brown, R. Salbo, H. Ding, E. Vlasenko, S. Merino, Biochemistry, 49 (2010) 3305-3316.
- [182] S.J. Horn, G. Vaaje-Kolstad, B. Westereng, V. Eijsink, Biotechnol. Biofuels, 5 (2012) 45.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [183] F.M. Medie, G.J. Davies, M. Drancourt, B. Henrissat, *Nature Reviews Microbiology*, 10 (2012) 227-234.
- [184] R.J. Quinlan, M.D. Sweeney, L.L. Leggio, H. Otten, J.-C.N. Poulsen, K.S. Johansen, K.B. Krogh, C.I. Jørgensen, M. Tovborg, A. Anthonsen, T. Tryfona, C.P. Walter, P. Dupree, F. Xu, G.J. Davies, P.H. Walton, *PNAS*, 108 (2011) 15079-15084.
- [185] C.M. Phillips, W.T. Beeson IV, J.H. Cate, M.A. Marletta, *ACS Chemical Biology*, 6 (2011) 1399-1406.
- [186] M.E. Himmel, S.-Y. Ding, D.K. Johnson, W.S. Adney, M.R. Nimlos, J.W. Brady, T.D. Foust, *Science*, 315 (2007) 804-807.
- [187] M. Dimarogona, E. Topakas, P. Christakopoulos, *Appl. Microbiol. Biotechnol.*, 97 (2013) 8455-8465.
- [188] C.E. Elwell, N.L. Gagnon, B.D. Neisen, D. Dhar, A.D. Spaeth, G.M. Yee, W.B. Tolman, *Chem. Rev.*, 117 (2017) 2059-2107.
- [189] E.D. Larsson, G. Dong, V. Veryazov, U. Ryde, E.D. Hedegård, *Dalton Trans.*, 49 (2020) 1501-1512.
- [190] B.D. Neisen, N.L. Gagnon, D. Dhar, A.D. Spaeth, W.B. Tolman, *J. Am. Chem. Soc.*, 139 (2017) 10220-10223.
- [191] G.R. Hemsworth, G.J. Davies, P.H. Walton, *Curr. Opin. Struct. Biol.*, 23 (2013) 660-668.
- [192] K.K. Meier, S.M. Jones, T. Kaper, H. Hansson, M.J. Koetsier, S. Karkehabadi, E.I. Solomon, M. Sandgren, B. Kelemen, *Chem. Rev.*, 118 (2017) 2593-2635.
- [193] S. Kim, J. Ståhlberg, M. Sandgren, R.S. Paton, G.T. Beckham, *PNAS*, 111 (2014) 149-154.
- [194] I. Castillo, A.C. Neira, E. Nordlander, E. Zeglio, *Inorg. Chim. Acta*, 422 (2014) 152-157.
- [195] A.C. Neira, P.R. Martínez-Alanis, G. Aullón, M. Flores-Alamo, P. Zerón, A. Company, J. Chen, J.B. Kasper, W.R. Browne, E. Nordlander, I. Castillo, *ACS Omega*, 4 (2019) 10729-10740.
- [196] E.I. Solomon, D.E. Heppner, E.M. Johnston, J.W. Ginsbach, J. Cirera, M. Qayyum, M.T. Kieber-Emmons, C.H. Kjaergaard, R.G. Hadt, L. Tian, *Chem. Rev.*, 114 (2014) 3659-3853.
- [197] C.H. Kjaergaard, M.F. Qayyum, S.D. Wong, F. Xu, G.R. Hemsworth, D.J. Walton, N.A. Young, G.J. Davies, P.H. Walton, K.S. Johansen, *PNAS*, 111 (2014) 8797-8802.
- [198] B. Bissaro, Å.K. Røhr, G. Müller, P. Chylenski, M. Skaugen, Z. Forsberg, S.J. Horn, G. Vaaje-Kolstad, V.G. Eijsink, *Nat. Chem. Biol.*, 13 (2017) 1123-1131.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [199] G. Müller, P. Chylenski, B. Bissaro, V.G. Eijssink, S.J. Horn, *Biotechnol. Biofuels*, **11** (2018) 209.
- [200] L. Bertini, R. Breglia, M. Lambrugh, P. Fantucci, L. De Gioia, M. Borsari, M. Sola, C.A. Bortolotti, M. Bruschi, *Inorg. Chem.*, **57** (2018) 86-97.
- [201] J.A. Hangasky, A.T. Iavarone, M.A. Marletta, *PNAS*, **115** (2018) 4915-4920.
- [202] G. Courtade, R. Wimmer, Å.K. Røhr, M. Preims, A.K. Felice, M. Dimarogona, G. Vaaje-Kolstad, M. Sørli, M. Sandgren, R. Ludwig, *PNAS*, **113** (2016) 5922-5927.
- [203] W.T. Beeson, C.M. Phillips, J.H. Cate, M.A. Marletta, *J. Am. Chem. Soc.*, **134** (2012) 890-892.
- [204] X. Li, W.T. Beeson IV, C.M. Phillips, M.A. Marletta, J.H. Cate, *Structure*, **20** (2012) 1051-1061.
- [205] B. Westereng, T. Ishida, G. Vaaje-Kolstad, M. Wu, V. Eijssink, K. Igarashi, M. Samejima, J. Stahlberg, S. Horn, M. Sandgren, *PloS one*, **6** (2011) e27807.
- [206] J.J. Liu, D.E. Diaz, D.A. Quist, K.D. Karlin, *Isr. J. Chem.*, **56** (2016) 738-755.
- [207] S. Striegler, N.A. Dunaway, M.G. Gichinga, J.D. Barnett, A.-G.D. Nelson, *Inorg. Chem.*, **49** (2010) 2639-2648.
- [208] S. Striegler, M. Dittel, R. Kanso, N.A. Alonso, E.C. Duin, *Inorg. Chem.*, **50** (2011) 8869-8878.
- [209] S. Striegler, M.G. Gichinga, *Chem. Commun.*, (2008) 5930-5932.
- [210] S. Striegler, J.D. Barnett, N.A. Dunaway, *ACS Catal.*, **2** (2012) 50-55.
- [211] S. Halder, A. Patra, M. Bera, *RSC Adv.*, **4** (2014) 62851-62861.
- [212] A.L. Concia, M.R. Beccia, M. Orio, F.T. Ferre, M. Scarpellini, F.d.r. Biaso, B. Guigliarelli, M. Réglie, A.J. Simaan, *Inorg. Chem.*, **56** (2017) 1023-1026.
- [213] M. Zhao, Z. Qian, M. Zhong, Z. Chen, H. Ao, H. Feng, *ACS Applied Materials & Interfaces*, **9** (2017) 32887-32895.
- [214] Z. Wu, J. Liu, Y. Gao, H. Liu, T. Li, H. Zou, Z. Wang, K. Zhang, Y. Wang, H. Zhang, *J. Am. Chem. Soc.*, **137** (2015) 12906-12913.
- [215] C. Wang, L. Ling, Y. Yao, Q. Song, *Nano Research*, **8** (2015) 1975-1986.
- [216] T. Long, Y. Guo, M. Lin, M. Yuan, Z. Liu, C. Huang, *Nanoscale*, **8** (2016) 9764-9770.
- [217] Y. Huang, W. Liu, H. Feng, Y. Ye, C. Tang, H. Ao, M. Zhao, G. Chen, J. Chen, Z. Qian, *Anal. Chem.*, **88** (2016) 7429-7434.
- [218] P.-C. Chen, Y.-C. Li, J.-Y. Ma, J.-Y. Huang, C.-F. Chen, H.-T. Chang, *Sci. Rep.*, **6** (2016) 1-9.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [219] X. Su, J. Liu, *ACS Applied Materials & Interfaces*, 9 (2017) 3902-3910.
- [220] T. Dhanalakshmi, E. Suresh, H. Stoeckli-Evans, M. Palaniandavar, *Eur. J. Inorg. Chem.*, 2006 (2006) 4687-4695.
- [221] S. Muthuramalingam, T. Khamrang, M. Velusamy, R. Mayilmurugan, *Dalton Trans.*, 46 (2017) 16065-16076.
- [222] S.V. Kryatov, S. Taktak, I.V. Korendovych, E.V. Rybak-Akimova, J. Kaizer, S. Torelli, X. Shan, S. Mandal, V.L. MacMurdo, A. Mairata i Payeras, *Inorg. Chem.*, 44 (2005) 85-99.
- [223] M. Velusamy, R. Mayilmurugan, M. Palaniandavar, *Inorg. Chem.*, 43 (2004) 6284-6293.
- [224] Z. Yu, Z. Thompson, S.L. Behnke, K.D. Fenk, D. Huang, H.S. Shafaat, J.A. Cowan, *Inorg. Chem.*, 59 (2020) 11218-11222.
- [225] S. Itoh, *Acc. Chem. Res.*, 48 (2015) 2066-2074.
- [226] A. Kunishita, M. Kubo, H. Sugimoto, T. Ogura, K. Sato, T. Takui, S. Itoh, *J. Am. Chem. Soc.*, 131 (2009) 2788-2789.
- [227] V.V. Vu, S.T. Ngo, *Coord. Chem. Rev.*, 368 (2018) 134-157.
- [228] A.M. Reynolds, B.F. Gherman, C.J. Cramer, W.B. Tolman, *Inorg. Chem.*, 44 (2005) 6989-6997.
- [229] N.W. Aboeella, S.V. Kryatov, B.F. Gherman, W.W. Brennessel, V.G. Young, R. Sarangi, E.V. Rybak-Akimova, K.O. Hodgson, B. Hedman, E.I. Solomon, *J. Am. Chem. Soc.*, 126 (2004) 16896-16911.
- [230] L.M. Mirica, X. Ottenwaelder, T.D.P. Stack, *Chem. Rev.*, 104 (2004) 1013-1046.
- [231] R.E. Cowley, L. Tian, E.I. Solomon, *PNAS*, 113 (2016) 12035-12040.
- [232] N.W. Aboeella, E.A. Lewis, A.M. Reynolds, W.W. Brennessel, C.J. Cramer, W.B. Tolman, *J. Am. Chem. Soc.*, 124 (2002) 10660-10661.
- [233] N. Gagnon, W.B. Tolman, *Acc. Chem. Res.*, 48 (2015) 2126-2131.
- [234] N. Dietl, C. van der Linde, M. Schlangen, M.K. Beyer, H. Schwarz, *Angew. Chem. Int. Ed.*, 50 (2011) 4966-4969.
- [235] E.A. Span, D.L. Suess, M.C. Deller, R.D. Britt, M.A. Marletta, *ACS Chemical Biology*, 12 (2017) 1095-1103.
- [236] E.D. Hedegård, U. Ryde, *J. Biol. Inorg. Chem.*, 22 (2017) 1029-1037.
- [237] D. Schröder, M.C. Holthausen, H. Schwarz, *J. Phys. Chem. B*, 108 (2004) 14407-14416.

Chapter 2: Homogeneous oxidative transformations mediated by copper catalyst systems

- [238] J.Y. Lee, K.D. Karlin, *Curr. Opin. Chem. Biol.*, 25 (2015) 184-193.
- [239] D. Dhar, W.B. Tolman, *J. Am. Chem. Soc.*, 137 (2015) 1322-1329.
- [240] D. Dhar, G.M. Yee, T.F. Markle, J.M. Mayer, W.B. Tolman, *Chem. Sci.*, 8 (2017) 1075-1085.
- [241] M.-H. Baik, M. Newcomb, R.A. Friesner, S.J. Lippard, *Chem. Rev.*, 103 (2003) 2385-2420.
- [242] J.-P. Bacik, S. Mekasha, Z. Forsberg, A.Y. Kovalevsky, G. Vaaje-Kolstad, V.G. Eijssink, J.C. Nix, L. Coates, M.J. Cuneo, C.J. Unkefer, *Biochemistry*, 56 (2017) 2529-2532.
- [243] D. Maiti, D.H. Lee, K. Gaoutchenova, C. Würtele, M.C. Holthausen, A.A. Narducci Sarjeant, J. Sundermeyer, S. Schindler, K.D. Karlin, *Angew. Chem. Int. Ed.*, 47 (2008) 82-85.
- [244] J.N. Hamann, F. Tucek, *Chem. Commun.*, 50 (2014) 2298-2300.
- [245] O. Kwon, K.V.N. Esguerra, M. Glazerman, L. Petitjean, Y. Xu, X. Ottenwaelder, J.-P. Lumb, *Synlett.*, 28 (2017) 1548-1553.
- [246] A. Wada, M. Harata, K. Hasegawa, K. Jitsukawa, H. Masuda, M. Mukai, T. Kitagawa, H. Einaga, *Angew. Chem. Int. Ed.*, 37 (1998) 798-799.
- [247] E.A. Span, M.A. Marletta, *Curr. Opin. Struct. Biol.*, 35 (2015) 93-99.
- [248] S. Kim, J.W. Ginsbach, J.Y. Lee, R.L. Peterson, J.J. Liu, M.A. Siegler, A.A. Sarjeant, E.I. Solomon, K.D. Karlin, *J. Am. Chem. Soc.*, 137 (2015) 2867-2874.
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The development of a Cu(I)/pyrazolylpyridineamine catalyst system for the hydroxylation of aryl halides

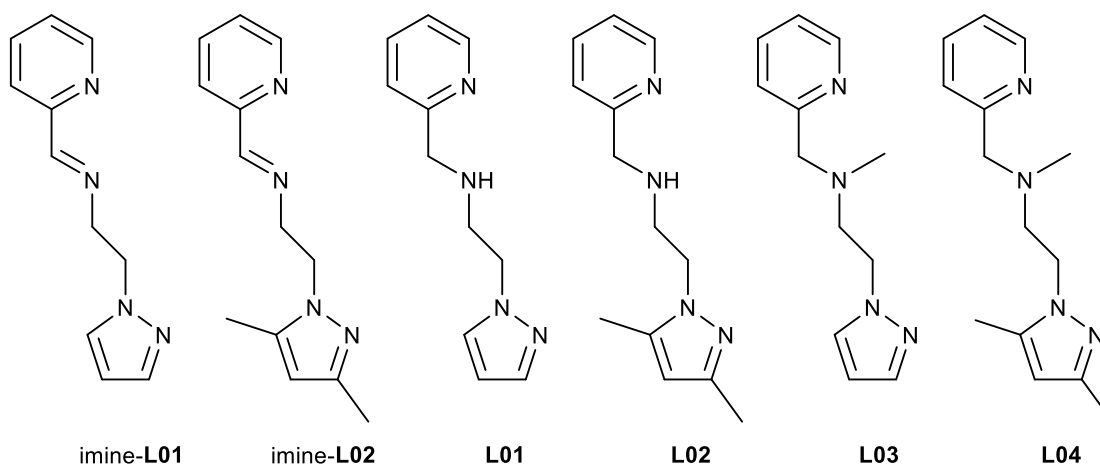
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Note to Examiners:

- Following the comprehensive review of the literature presented in **Chapter 2**, some repetition may occur in **Chapters 3 to 6**.
- For consistency purposes, ligands **L2.33-L2.36** in **Chapter 2**, has the following descriptors in **Chapters 3, 4 and 6**:
 - Secondary and tertiary amine ligands: **L01-L04**
- The imine-derivatives of these ligands were also evaluated in **Chapters 4 and 6**
 - imine-**L01** and imine-**L02**



A catalyst system comprising of pyrazolylpyridineamine/Cu^I/CsOH is reported for the hydroxylation of aryl iodides and bromides with moderate to outstanding yields, without the use of an inert atmosphere. A comprehensive parameter optimisation study established optimum component concentrations: [Cu(MeCN)₄]BF₄ and 2-(1H-pyrazol-1-yl)-N-(pyridine-2-ylmethyl)ethan-1-amine (**L01**) (2 mol%), substrate (1 mmol), CsOH (4 mmol) and DMSO:H₂O (1:1, 3 mL). Monitoring substrate conversion as a function of time revealed an induction period of 90 minutes, which could be eliminated through the initial *in situ* formation of the proposed [(**L01**)Cu-OH] intermediate. Eliminating the induction period resulted in complete conversion within one hour, with turnover numbers exceeding that of the benchmark catalyst system operating at an optimal catalyst loading of 0.05 mol%.

Keywords: Hydroxylation, pyrazolylpyridineamine ligands, copper catalysis, substrate scope

3.1 Introduction

Phenolic compounds are utilised as intermediates during the synthesis of several natural products and polymeric materials, as well as in the pharmaceutical industry [1]. The Hock and Dow processes were initially used for the preparation of these phenolic compounds [2]. These processes involve the sulphuric acid-mediated decomposition of cumene hydroperoxide (CHP) and the treatment of benzene with a hydroxide base and the acidification of the phenoxide salt, respectively. Some of the drawbacks of these processes involve the low yields and ineffective energy use, and therefore alternative methods were developed for the syntheses of these functional phenolic compounds. These methods include the non-oxidative Sandmeyer reaction as well as nucleophilic aromatic substitution. Several limitations are associated with these processes, such as harsh reaction conditions, a limited substrate scope, as well as difficulties to obtain the required starting materials [3-7]. These limitations resulted in the growing demand to develop alternative synthesis methods for these phenolic compounds. One of these methods involves the hydroxylation of aryl halides.

A number of varying metal-based catalyst systems have previously been reported for these hydroxylation reactions. Initially, the focus was on iridium- and palladium-based catalyst systems to provide a milder and more applicable synthesis route for the conversion of aryl halides [8-15]. However, several drawbacks were identified for these synthetic routes, which involve the employment of expensive catalysts with air- and moisture sensitivity, as well as high toxicity. Furthermore, these routes involve problems with product selectivity because they also resulted in C-O coupling by-product formation. These drawbacks resulted in the development of Cu-based catalyst systems, as a result of their economical attractiveness, low toxicity as well as better selectivity control during the reactions. As such, in recent years, several Cu-based catalyst systems were reported for the hydroxylation of aryl halides [16-21].

A variety of ligands have been previously evaluated in Cu-based catalyst systems for the hydroxylation of aryl halides. You and co-workers obtained a conversion of 92 % to *p*-cresol in 24 h with their CuI/phenanthroline/KOH catalyst system [16]. Independently, Yang and co-workers obtained a slightly lower conversion of 82 % to *p*-cresol in 18 h, using their CuI/8-hydroxyquinoline *N*-oxide/CsOH catalyst system [17]. Taillefer and co-workers reported a CuI/1,3-diphenylpropane-1,3-dione/CsOH catalyst system, which resulted in a conversion of 82 % to *p*-cresol in 24 h [18]. Unfortunately, even though excellent conversions were achieved for these catalyst systems, high catalyst loadings (5 to 10 mol% copper and 10 to 20 mol% ligand), harsh operating conditions (140 °C) and the need for an inert atmosphere are often required [16-19, 22].

Ma and co-workers decreased the catalyst loading to 2 mol% copper and 4 mol% ligand in the development of their Cu^I/CsOH catalyst system, in combination with substituted 2-pyridin-2-yl-1*H*-benzoimidazole and 2-(1*H*-imidazol-2-yl)pyridine ligands, for the hydroxylation of aryl bromides [23]. The electronic nature of the pyridine ring, as well as the availability of a free NH-group within the ligand, is of extreme importance for the success of these reactions [23]. Furthermore, Cazin and co-workers further decreased the catalyst loading to 0.05 mol% for their reported [CuCl(NHC)]/CsOH catalyst system for the hydroxylation of iodobenzene [20]. They obtained turnover numbers (TON) of 1640 when they perform their reactions at 130 °C, under an inert atmosphere, and they also found that the conversions were negatively influenced when a base other than CsOH was used [20, 22]. Unfortunately, not all the above-mentioned drawbacks have been addressed yet. Therefore, the need still exists to develop an alternative Cu-based catalyst system, in combination with a variety of efficient ligands that can operate open to air.

We have recently reported a Cu^I-based catalyst system, using substituted iminopyridine or quinoline ligands and NaOH as base to obtain complete conversion to *p*-cresol in 3 h, with an increased catalyst loading of 4 mol% [21]. Unfortunately, the limitations of this catalyst system were tested and it could only be employed for aryl iodides. Recently, pyrazolylpyridineamine ligands, coordinated to a nickel precursor, have been employed in the catalytic oligomerisation and polymerisation of ethylene [24, 25]. This ligand framework has not been exploited in Cu-catalysed hydroxylation reactions. Herein, we report the synthesis, characterisation and evaluation of similar pyrazolylpyridineamine ligands, 2-(1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L01**), 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L02**), *N*-methyl-2-(1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L03**) and 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-methyl-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L04**, Figure 3.1), in combination with copper, as pre-catalysts for the hydroxylation of aryl halides. The effects of both the optimised reaction conditions and the initial *in situ* formation of a [(**L01**)Cu-OH] intermediate on the hydroxylation of 4-iodotoluene to *p*-cresol were evaluated. Finally, we determined the substrate scope of our catalyst system after the evaluation of aryl iodides and bromides.

3.2 Results and discussion

3.2.1 Synthesis and characterisation of the pyrazolylpyridineamine ligands

The pyrazolylpyridineamine ligands, **L01-L04**, were prepared by means of the alkylation of substituted and unsubstituted pyrazole derivatives, after which reductive amination (**L01** and

L02) and methylation of the imines (**L03** and **L04**) were performed. The synthesis of ligand **L02** has been reported previously [24, 25], while ligands **L01**, **L03** and **L04** are novel.

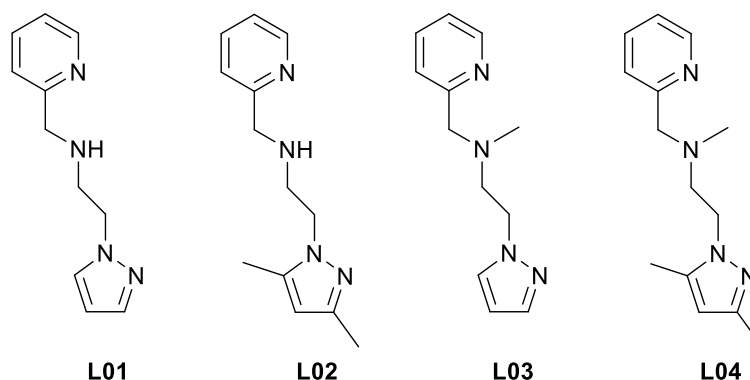
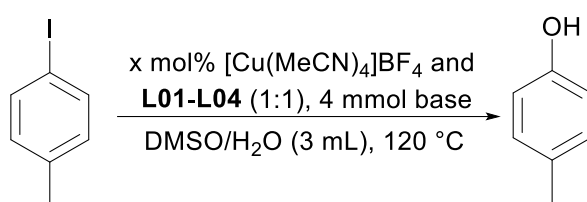


Figure 3.1: The novel pyrazolylpyridineamine ligands (**L01**, **L03** and **L04**) and ligand **L02** were successfully synthesised and characterised.

The ligands were obtained as light yellow or yellow-brown oils that display solubility in most organic solvents such as dichloromethane (DCM), dimethyl sulfoxide (DMSO), acetonitrile (MeCN), alcohols, as well as water. Furthermore, these ligands can be stored without any precaution due to their stability. Several spectroscopic and analytical techniques were employed to characterise these pyrazolylpyridineamine ligands. FT-IR spectroscopy showed an absorption band at 3303 cm^{-1} , consistent with the formation of a secondary amine during the reduction step (**L01**). Alternatively, an absorption band was observed more downfield in the regions 3383 to 3394 cm^{-1} and 2946 to 2947 cm^{-1} , which confirmed the successful methylation of the secondary amine to afford the tertiary amine analogues (**L03** and **L04**). Similarly, the ^1H NMR spectroscopic analysis of the ligands provided useful information on the structure of all compounds. We observed the secondary amine proton resonance at δ 4.74 ppm, while the tertiary amine (N-CH_3) singlet resonance was observed more upfield in the range δ 2.31 to 2.33 ppm (Figures S3.1-S3.6 in the Supporting Information). The introduction of methyl groups on the pyrazole ring for ligand **L04** was observed in the range δ 2.17 to 2.19 ppm, as a singlet resonance. Furthermore, the $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic analysis confirmed the substitution of methyl groups on the ethyl-linked N -atom (**L03** and **L04**) and on the pyrazole ring (**L04**) in the range δ 42.56 to 42.86 ppm and δ 11.07 to 13.48 ppm, respectively. The purity of these novel pyrazolylpyridineamine ligands (**L01-L04**) was confirmed with APCI mass spectrometry (APCI-MS; Figures S3.7-S3.10 in the Supporting Information).

3.2.2 Optimisation of the (**L01**)[Cu(MeCN)₄]BF₄/CsOH catalyst system

Hydroxylation reactions were carried out employing 4-iodotoluene as model substrate, at previously reported reaction conditions, followed by an acidic workup (Scheme 3.1) [20, 21]. These reactions were initially evaluated using the Radley's carousel reactor, to ensure the same reaction conditions for multiple reactions, but the obtained results were not reproducible. A white solid sublimed in the cooled area of the reaction tube with concomitant loss of activity. Similar observations of sublimation were previously reported by Ma and co-workers [26]. Repeating the reactions in a small reactor flask (5 mL) in an oil bath circumvented the reproducibility issues.



Scheme 3.1: A representative Cu-based catalyst system (before optimisation) for the hydroxylation of 4-iodotoluene.

As a point of departure, we evaluated different catalyst loadings (Cu:L) on the hydroxylation of 4-iodotoluene, using the reduced pyrazolylpyridineamine ligand (**L01**), in combination with [Cu(MeCN)₄]BF₄, under previously reported reaction conditions [20, 21]. The copper precursor and ligand were stirred for 30 minutes to allow the *in situ* formation of the pre-catalyst before the addition of the substrate and hydroxide base. Excellent conversions were observed with a catalyst loading of 2 and 4 mol%, even at a decreased reaction time of 6 h (Table 3.1, entries 1-3). When the catalyst loading was decreased to 1 and 0.5 mol%, significantly lower conversions were obtained (Table 3.1, entries 4-5). As such, an optimal catalyst loading of 2 mol% was identified for our catalyst system.

Next, we evaluated various pyrazolylpyridineamine ligands, bearing either a hydrogen or methyl group on the pyrazole ring as well as on the ethyl-linked *N*-atom, **L01-L04**, in the hydroxylation of 4-iodotoluene (Table 3.1, entries 6-11 and Figure S3.11 in the Supporting Information). The observed activity, expressed as the conversion of 4-iodotoluene to *p*-cresol, highlights the fact that the methyl groups on the pyrazole ring have a more pronounced effect on the success of the hydroxylation reaction, than the substituents on the ethyl-linked *N*-atom. Comparable conversions were obtained for the unsubstituted pyrazole-based ligands after 24 h, but a slight difference was observed at a decreased reaction time of 6 h (**L01** and **L02**, Table 3.1, entries 2-3 and 6-7). However, the introduction of methyl groups on the pyrazole ring resulted in lower conversions to *p*-cresol, irrespective of the reaction time (**L03** and **L04**,

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Table 3.1, entries 8-11). The hydroxylation reaction was also performed without a ligand and a conversion of 11 % to the corresponding *p*-cresol was found (Table 3.1, entry 12). Other groups also highlighted the importance of a ligand for successful hydroxylation reactions [19, 27].

Table 3.1: Evaluation of the effect of different catalyst loadings (Cu:L) as well as different pyrazolylpyridineamine ligands on the hydroxylation of 4-iodotoluene to afford *p*-cresol.^a

Entry	Catalyst load (mol%)	Ligand	Time (h)	Conversion (%) ^b	TON
1	4	L01	24	100	25.3
2	2	L01	24	100	49.9
3	2	L01	6	86	43.1
4	1	L01	24	52	51.6
5	0.5	L01	24	27	54.1
6	2	L02	24	83	41.7
7	2	L02	6	65	32.4
8	2	L03	24	99	49.5
9	2	L03	6	62	31.0
10	2	L04	24	63	31.6
11	2	L04	6	34	17.0
12	2	-	6	11	5.5

^a 4-iodotoluene (1.0 mmol), Cu(MeCN)₄BF₄ (x mol%), **L01-L04** (x mol%), NaOH (4 mmol, 4 equiv.), DMSO/H₂O (1:1, 3 mL), 120 ± 2 °C. ^b GC conversions for the phenolic product were determined, using a calibration curve (internal standard: biphenyl). Average conversions obtained for the two independent runs are summarised in the table.

The varying reactivity may be due to the availability of a free NH-group within the ligand and the ability to remove the proton during the hydroxylation reaction. Similar observations were reported by Ma and co-workers [23]. Furthermore, the steric and electronic effects of the methyl groups on the pyrazole ring also resulted in lower conversions. These methyl groups hinder the approach of the aryl halide substrate during the formation of the appropriate Cu-based active intermediate. Furthermore, the methyl groups also resulted in the lower electrophilicity of the copper metal centre due to the electron-donating ability of the methyl groups [28-31].

The above-mentioned conversion results are comparable with that obtained in previous literature reports, using higher catalyst loadings of up to 20 mol% [16-19, 21]. However, even though our catalyst system displayed excellent conversions at relatively low catalyst loadings

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and shorter reaction times, it could still not be compared to the activity reported by Cazin and co-workers, where they observed TON values of 1640 [20]. They employed an inert atmosphere for the hydroxylation reactions, while our reactions were performed in a closed reactor tube, under ambient air, to prevent evaporation of the solvent at high temperatures. In conclusion, both ligands **L01** and **L02** could be used for the successful hydroxylation of 4-iodotoluene in a reaction time of 6 h and were employed in further optimisation studies.

Next, we evaluated the effect of varying hydroxide bases on the hydroxylation of 4-iodotoluene to *p*-cresol, using either ligand **L01** or **L02** (Table 3.2 and Figure S3.12 in the Supporting Information). Sodium hydroxide (NaOH) as base resulted in conversions of 86 % and 62 %, respectively (Table 3.2, entries 1 and 4). When the base was replaced with potassium hydroxide (KOH), conversions of 100 % and 66 % were obtained, respectively (Table 3.2, entries 2 and 5), while the employment of cesium hydroxide (CsOH) as base resulted in similar conversions of 100 % and 98 %, respectively (Table 3.2, entries 3 and 6). As a result, both KOH and CsOH displayed excellent conversions, using ligand **L01**, while for ligand **L02**, only the reaction with CsOH displayed complete conversion.

Table 3.2: The evaluation of the effect of varying hydroxide bases on the hydroxylation of 4-iodotoluene, using either ligand **L01** or **L02**.^a

Entry	Ligand	Base	Conversion (%) ^b	TON
1	L01	NaOH	86	43.1
2	L01	KOH	100	50.1
3	L01	CsOH	100	50.2
4	L02	NaOH	62	31.0
5	L02	KOH	66	33.2
6	L02	CsOH	98	49.2

^a 4-iodotoluene (1.0 mmol), Cu(MeCN)₄BF₄ (2 mol%), **L01** or **L02** (2 mol%), base (4 mmol, 4 equiv.), DMSO/H₂O (1:1, 3 mL), 120 ± 2 °C, reaction time: 6 h. ^b GC conversions for the phenolic product were determined, using a calibration curve (internal standard: biphenyl). Average conversions obtained for the two independent runs are summarised in the table.

The next step was to evaluate the amount of base (KOH and CsOH) on the hydroxylation of 4-iodotoluene, using either ligand **L01** or **L02** (Table 3.3 and Figure S3.13 in the Supporting Information). The reaction time for these reactions was 4 h, instead of the optimised 6 h to determine whether the amount of base has an influence on the hydroxylation of 4-iodotoluene. Similar conversions to *p*-cresol were obtained with the standard reaction conditions of 4 mmol CsOH or KOH as base when either ligand **L01** or **L02** was employed (Table 3.3, entries 1-4).

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With a decrease in the amount of CsOH to 2 mmol, slightly lower conversions were obtained (Table 3.3, entries 5-6), while a significant decrease in the conversion to *p*-cresol was observed, using KOH as base (Table 3.3, entries 7-8). Finally, the hydroxylation of 4-iodotoluene was also performed in the absence of base, which resulted in low conversions of between 2 and 12 % for ligands **L01** and **L02**, respectively (Table 3.3, entries 9-10).

In conclusion, the introduction of CsOH as base resulted in better conversions to *p*-cresol for both ligands, while only average conversions were obtained for ligand **L02** when KOH was employed. Even though KOH is a less expensive base than CsOH, the conversion to *p*-cresol was slightly lower. Previous reports found that the selectivity towards the phenolic product decreases when a weaker base such as KOH was employed [2, 18, 32]. The conversion of 4-iodotoluene was possible with a lower amount of base, but it was decided that ligand **L01** and CsOH (4 mmol) as base were optimal.

Table 3.3: The effect of the amount of base (mmol) on the hydroxylation of 4-iodotoluene, using either ligand **L01** or **L02**.^a

Entry	Ligand	Base	Base (mmol)	Conversion (%) ^b	TON
1	L01	CsOH	4	100	50.2
2	L02	CsOH	4	98	49.2
3	L01	KOH	4	100	50.1
4	L02	KOH	4	66	33.2
5	L01	CsOH	2	84	42.1
6	L02	CsOH	2	63	31.7
7	L01	KOH	2	54	26.9
8	L02	KOH	2	24	12.0
9	L01	-	0	2	1.0
10	L02	-	0	12	6.2

^a 4-iodotoluene (1.0 mmol), Cu(MeCN)₄BF₄ (2 mol%), **L01** or **L02** (2 mol%), CsOH or KOH (x mmol), DMSO/H₂O (1:1, 3 mL), 120 ± 2 °C, reaction time: 6 h. ^b GC conversions for the phenolic product were determined, using a calibration curve (internal standard: biphenyl). Average conversions obtained for the two independent runs are summarised in the table. The reaction time for these reactions was 4 h, instead of the optimal 6 h.

Lastly, we evaluated different Cu^I-/Cu^{II}-precursors, using ligand **L01**, for the hydroxylation of 4-iodotoluene (Table 3.4 and Figure S3.14 in the Supporting Information). These reactions were allowed to run for 4 h, instead of the optimised 6 h, to determine the effect of both the counter anion as well as the oxidation state of the varying Cu-precursors. We evaluated Cu^I-

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precursors containing non-coordinating anions such as tetrafluoroborate (BF_4^-) or triflate (OTf^-), which resulted in higher conversions than those with the coordinating anions such as copper(I) chloride (CuCl) or -bromide (CuBr , Table 3.4, entries 1-2 and 4-5). An exception, however, was found when the non-coordinating anion was replaced with the hexafluorophosphate anion (PF_6^-), because almost no conversion to *p*-cresol was obtained (Table 3.4, entry 3). This Cu-precursor has never been used in previous hydroxylation reactions and this observation is in contrast with our previous findings where $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ was employed as Cu-precursor in aerobic alcohol oxidation reactions [31]. It is still unclear why $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$, as Cu-precursor, resulted in low conversions to *p*-cresol. The use of Cu^{II} -precursors (Table 3.4, entries 6-10) displayed comparable conversions, relative to the Cu^{I} -precursors. Interestingly, relatively good conversions to *p*-cresol were obtained for the Cu^{II} -precursors, which are hydrates (Table 3.4, entries 8-10). Lastly, the hydroxylation of 4-iodotoluene without a Cu-precursor resulted in no conversion to *p*-cresol (Table 3.4, entry 11).

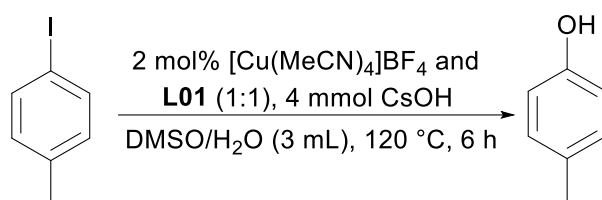
Table 3.4: Evaluation of various Cu^{I} -/ Cu^{II} -precursors, using ligand **L01**, for the hydroxylation of 4-iodotoluene to afford *p*-cresol.^a

Entry	Cu-precursor	Conversion (%) ^b	TON
1	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	100	50.2
2	$\text{Cu}(\text{MeCN})_4\text{OTf}$	79	39.5
3	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	1	0.5
4	CuCl	38	18.8
5	CuBr	38	19.1
6	$\text{Cu}(\text{BF}_4)_2 \cdot x\text{H}_2\text{O}$	71	35.6
7	$\text{Cu}(\text{OTf})_2$	48	23.8
8	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	87	43.7
9	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	99	49.6
10	$\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$	77	38.7
11	-	0	0

^a 4-iodotoluene (1.0 mmol), Cu^{I} -/ Cu^{II} -precursor (2 mol%), ligand **L01** (2 mol%), CsOH (4 mmol, 4 equiv.), $\text{DMSO}/\text{H}_2\text{O}$ (1:1, 3 mL), $120 \pm 2^\circ\text{C}$, reaction time: 6 h. ^b GC conversions for the phenolic product were determined, using a calibration curve (internal standard: biphenyl). Average conversions obtained for the two independent runs are summarised in the table. The reaction time for these reactions was 4 h, instead of the optimal 6 h.

We observe a higher catalytic activity, relative to previously reported results, which may be a result of the Cu-precursor's nature. Studies on the nature of the counter anion have been previously reported for Cu-based alcohol oxidation reactions [31, 33-35]. Several previously

reported catalyst systems focused on a Cu-precursor with a coordinating counter anion, whereas our focus rather shifts to a Cu-precursor with the non-coordinating anion, BF_4^- . The faster dissociation of the non-coordinating anions, relative to the coordinating anions, facilitates the approach of the aryl halide to coordinate with the copper centre. This leads to the promotion of the oxidative addition steps, which supports the findings of Mketo and co-workers [21]. Even though a Cu^{II} -precursor resulted in relatively good conversions, it is clear that a Cu^{I} -precursor is needed for these reactions and $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ was found to be the optimal Cu-precursor for the hydroxylation of aryl halides. In conclusion, our alternative Cu-based catalyst system could be fully optimised for the hydroxylation of 4-iodotoluene to *p*-cresol (Scheme 3.2).



Scheme 3.2: The optimised Cu-based catalyst system for the hydroxylation of 4-iodotoluene to *p*-cresol.

3.2.3 Effect of the presence of the *in situ* formed Cu-intermediate

After our optimisation studies, we evaluated the hydroxylation of 4-iodotoluene over time (Figure 3.2 and Table S3.1 in the Supporting Information). Separate hydroxylation reactions were employed and analysed after an acidic workup, for the varying reaction times. Initially, an induction period of approximately 90 minutes was observed, after which the conversion to *p*-cresol started to increase until a plateau was reached between 4 and 6 h. The induction period is possibly due to the absence of an active Cu-based intermediate that can initiate the hydroxylation reactions. Llobet and co-workers reported a Cu-based catalyst system for water oxidation, using tetradentate amidate acyclic ligands and their results suggested the formation of $[(\text{L1})\text{Cu}(\text{OH})]$ species during the reaction [36]. Similarly, the formation of Cu-hydroxo intermediates during the hydroxylation of aryl halides has been previously proposed [20, 32, 37, 38]. In 2012, Cazin and co-workers proposed the formation of $[\text{Cu}(\text{OH})-(\text{NHC})]$ as an active intermediate, which was evaluated using a well-defined $[\text{Cu}(\text{OH})(\text{IPr})]$ ($\text{IPr} = N,N'$ -bis-[2,6-(di-*iso*-propyl)phenyl]imidazole-2-ylidene) complex, but the reaction resulted in lower conversions to the phenolic products [20]. Separately, in 2013, Jutand and co-workers used cyclic voltammetry (CV) studies for the characterisation of the proposed Cu-OH key intermediate [32]. They proposed that this key intermediate will react with the aryl halide substrate.

However, the effect of this Cu-OH key intermediate on the hydroxylation reaction, as well as when the intermediate is formed during the reaction, is still unknown.

Computational and electron paramagnetic resonance (EPR) studies have shown that the pH of the reaction determines the type of Cu-OH intermediates that might form during the reaction [38, 39]. At a pH below 8, only $[\text{LCu}^{\text{II}}\text{-OH}_2]$ is present, while $[\text{LCu}^{\text{II}}\text{-OH}_2]$, $[\text{LCu}^{\text{II}}\text{-OH}]$ and the $[\text{LCu}^{\text{II}}\text{-OH}]$ dimer are present in the pH range of 8 to 10. Furthermore, with the pH above 10, a combination of $[\text{LCu}^{\text{II}}\text{-OH}]$ and the $[\text{LCu}^{\text{II}}\text{-OH}]$ dimer are observed. However, previous groups highlighted the formation of an off-cycle Cu-hydroxide dimeric species as a catalyst deactivator [40-44]. The pH of the hydroxylation reaction, using our optimised Cu-based catalyst system, was between 15 and 16, which resulted in the possibility that both $[\text{LCu}^{\text{II}}\text{-OH}]$ and the $[\text{LCu}^{\text{II}}\text{-OH}]$ dimer are present within the system. However, due to the possible deactivating ability of the dimeric species, we assume that only the monomeric $[\text{LCu}^{\text{II}}\text{-OH}]$ intermediate is present during the hydroxylation reaction.

To our knowledge, however, the initial *in situ* synthesis and evaluation of the effect of the $[(\text{L01})\text{Cu-OH}]$ intermediate on the hydroxylation reaction have not been investigated previously. We postulate that the initial presence of the $[(\text{L01})\text{Cu-OH}]$ intermediate, instead of the formation thereof during the reaction, would result in a shortened induction period and thereby speed up the reaction time for complete conversion to the corresponding phenolic products. A similar observation in alcohol oxidation was reported by Stahl and co-workers, where they used a hydroxide-containing intermediate, $[(\text{bpy})\text{Cu}(\text{OH})_2(\text{OTf})_2]$, which was dissociated to the monomeric $(\text{bpy})\text{Cu}(\text{II})(\text{OH})(\text{OTf})$ species, to shorten the induction period during the reaction [44].

Additional experiments were employed to determine whether the initial *in situ* formation of the $[(\text{L01})\text{Cu-OH}]$ intermediate has an influence on the activity of the hydroxylation reactions, as a function of time (Figure 3.2 and Table S3.2 in the Supporting Information). We found that the induction period of these reactions was drastically shortened, because conversion to *p*-cresol was observed after only 23 minutes. Complete conversion to *p*-cresol was obtained in approximately 1 h. As a result, higher conversions were observed in a shorter reaction time for the latter reaction conditions relative to those where the optimised reaction conditions were employed. In conclusion, we now have experimental evidence for the effect of the initial *in situ* formed $[(\text{L01})\text{Cu-OH}]$ intermediate on the hydroxylation of 4-iodotoluene.

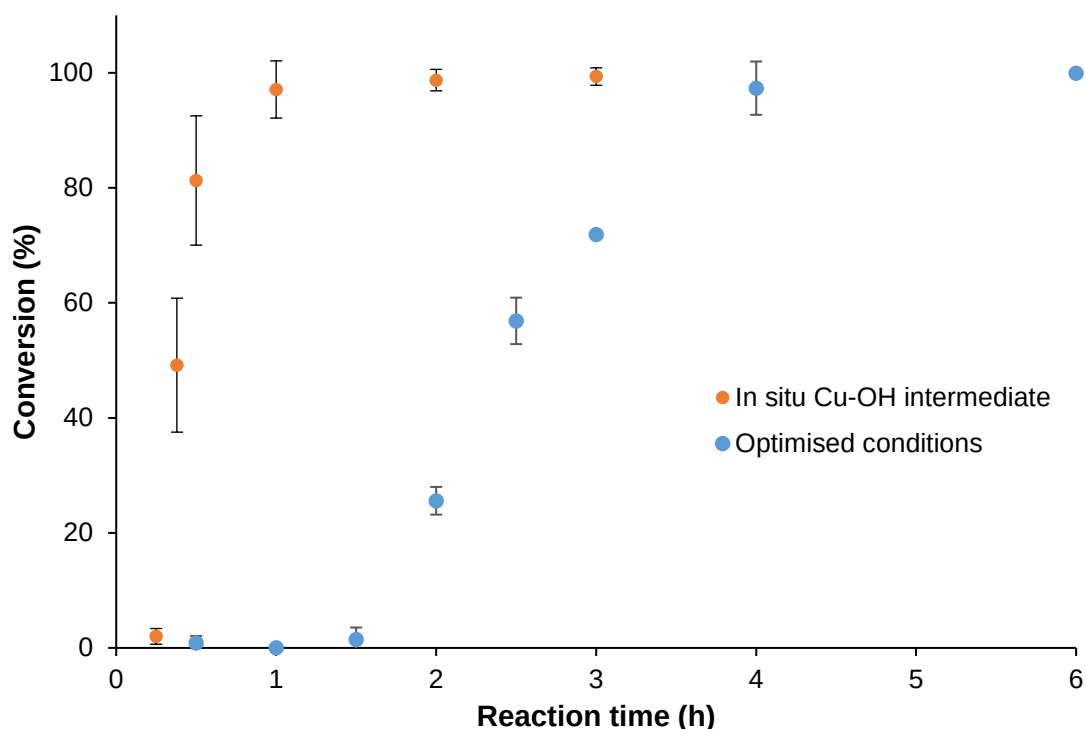


Figure 3.2: Evaluation of the conversion of 4-iodotoluene to *p*-cresol as a function of reaction time, using either the optimised reaction conditions or the initial *in situ* formation of the [(**L01**)Cu-OH] intermediate. Standard reaction conditions: [Cu(MeCN)₄]BF₄ and ligand **L01** (2 mol%), 4-iodotoluene (1 mmol), CsOH (4 mmol), DMSO:H₂O (1:1, 3 mL), 120 ± 2 °C.

Similar hydroxylation reactions, with the initial presence of the [(**L01**)Cu-OH] intermediate, were performed to determine whether conversions to *p*-cresol were possible at lower catalyst loadings due to the shorter induction period (Table 3.5). Conversions to *p*-cresol of 98 % and 8 % to *p*-cresol and TON values of 1952 and 819 were obtained, respectively for our catalyst system for a reaction time of 24 h (Table 3.5, entries 1 and 2). As such, with the initial *in situ* synthesis of the [(**L01**)Cu-OH] intermediate, we were not only able to eliminate the induction period of the reaction, but we could also improve on our previous results obtained for the varying catalyst loadings during the optimisation of our catalyst system (Table 3.1, entries 1-5). Furthermore, these results were also compared with the benchmark catalyst system, reported by Cazin and co-workers, where they obtained a conversion of 82 % to *p*-cresol with an optimal catalyst loading of 0.05 mol%, under an inert atmosphere (Table 3.5, entry 3) [20]. In conclusion, we could improve on the conversion results and TON values as reported for the benchmark catalyst system. To our knowledge, these conversions to *p*-cresol are currently the highest and most promising results, especially when employing a low catalyst loading and in the absence of an inert atmosphere.

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Table 3.5: Evaluation of varying catalyst loadings on the conversion of 4-iodotoluene to *p*-cresol, using the initial *in situ* formation of the [(**L01**)Cu-OH] intermediate.

Entry	Catalyst load (mol%)	Ligand	Time (h)	Conversion (%) ^b	TON
1 ^a	0.05	L01	24	98	1952
2 ^a	0.01	L01	24	8	819
3 ^b	0.05	SIPr ^c	24	82	1640
4 ^{b, d}	0.01	SIPr ^c	24	25	2500

^a Reaction conditions: [Cu(MeCN)₄]BF₄ and ligand **L01** (*x* mol%), CsOH (4 mmol), 4-iodotoluene (1 mmol), DMSO:H₂O (1:1, 3 mL), 120 ± 2 °C. ^b Benchmark catalyst system: reported by Cazin and co-workers. ^c SIPr = (*N,N'*-bis[2,6-(di-*iso*-propyl)phenyl]imidazolidin-2-ylidene). ^d Bromobenzene was evaluated as substrate.

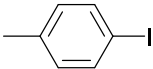
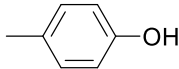
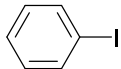
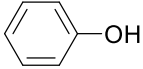
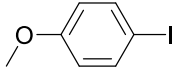
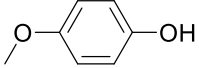
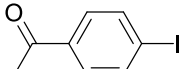
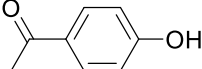
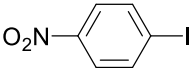
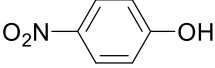
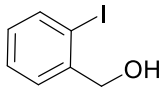
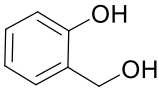
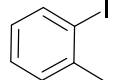
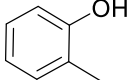
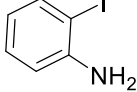
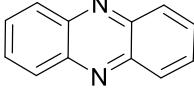
3.2.4 Substrate scope of the (**L01**)[Cu(MeCN)₄]BF₄/CsOH catalyst system

Our optimised Cu-based catalyst system was employed in the evaluation of the substrate scope for the hydroxylation reactions (Scheme 3.2). Table 3.6 summarises the capability of our catalyst system to convert a variety of aryl iodides with moderate to outstanding yields of the phenolic compounds, ranging from 70 to 96 %. These aryl iodides include those with electron-donating substituents (Table 3.6, entries 1-3) as well as those with electron-withdrawing substituents (Table 3.6, entries 4-6). The activity of the hydroxylation reaction was enhanced when substrates bearing electron-withdrawing substituents were used.

Our Cu-based catalyst system was tolerant towards a great selection of functional groups, including methyl, alkoxy, acetyl, nitro and alcohol substituents in the absence of an inert atmosphere. By comparing our results with those previously reported, it is evident that we could improve on the yields, decrease the catalyst loadings and/or reduce the reaction times [16-18, 20, 21, 45]. The electronic nature of the para-positioned substituents had no significant effect on the hydroxylation reaction. Furthermore, even though a longer reaction time was required for the successful conversion of the sterically hindered 2-iodotoluene to *o*-cresol (Table 3.6, entry 7), we were still unable to convert 2-iodoaniline to the corresponding phenolic compound (Table 3.6, entry 8). This observation is due to the regioselective conversion of iodoaniline to the corresponding phenazine product. Gendrineau and co-workers reported a Pd-based catalyst system for the synthesis of substituted phenazines, by employing phosphine ligands [46].

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Table 3.6: Evaluation of a variety of aryl iodides with our (**L01**)[Cu(MeCN)₄]BF₄/CsOH catalyst system.

Entry	Substrate	Product	Time	Isolated yield
1			6 h	70 %
2			6 h	100 % GC yield 47 % isolated
3			15 h	75 %
4			6 h	96 %
5			6 h	84 %
6			6 h	93 %
7			15 h	76 %
8			15 h	No phenol-based product

Optimal reaction conditions: [Cu(MeCN)₄]BF₄ and ligand **L01** (2 mol%), CsOH (4 mmol), substrate (1 mmol), DMSO:H₂O (1:1, 3 mL), 120 ± 2 °C

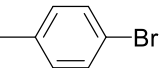
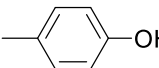
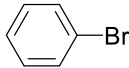
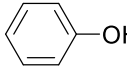
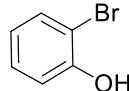
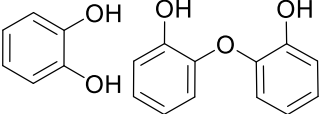
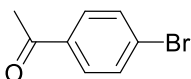
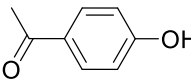
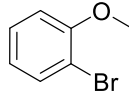
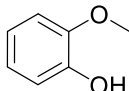
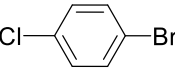
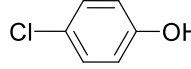
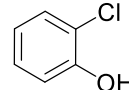
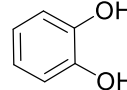
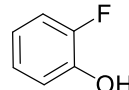
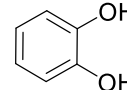
We were also capable of converting a variety of less reactive electrophiles such as the aryl bromides (Table 3.7, entries 1-4). The products of these reactions are important in industrial applications. We were able to convert 2-bromophenol, a substrate that was not previously evaluated, to catechol with an isolated yield of 68 % (Table 3.7, entry 3). Several previous reports confirmed the formation of biaryl ether by-products during the hydroxylation reactions, when performed in neat water [2, 17, 18]. However, Mketo and co-workers highlighted the excellent chemoselectivity of their catalyst system for hydroxylation reactions without the formation of any biaryl ether by-products [21]. With the exception of 2-bromophenol, we did not observe the formation of by-products during the hydroxylation of aryl halides.

A limitation of our catalyst system is the inability to successfully convert the sterically hindered 2-bromoanisole during the hydroxylation reaction and a complex mixture of products was generated (Table 3.7, entry 5). In conclusion, the conversions to the corresponding phenolic products were slightly higher for the aryl iodides relative to those employing aryl bromides.

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Unfortunately, we were not able to use our catalyst system for the hydroxylation of aryl chloride and fluoride substrates (Table 3.7, entries 6-8).

Table 3.7: Evaluation of a variety of aryl bromides with our **(L01)**[Cu(MeCN)₄]BF₄/CsOH catalyst system.

Entry	Substrate	Product	Time	Isolated yield
1			18 h	100 % GC yield 58 % isolated
2			18 h	100 % GC yield 41 % isolated
3			18 h	68 %
4			24 h	68 %
5		 and a complex mixture of products	24 h	-
6			24 h	-
7			24 h	-
8			24 h	-

Optimal reaction conditions: [Cu(MeCN)₄]BF₄ and ligand **L01** (2 mol%), CsOH (4 mmol), substrate (1 mmol), DMSO:H₂O (1:1, 3 mL), 120 ± 2 °C

3.3 Conclusions

We have successfully synthesised and characterised different novel pyrazolylpyridineamine ligands (Figure 3.1). These ligands, in combination with [Cu(MeCN)₄]BF₄ and CsOH, were evaluated as pre-catalysts in the hydroxylation of a variety of aryl halides to their corresponding phenolic products, operating under ambient reaction conditions. The optimisation of the **(L01)**/[Cu(MeCN)₄]BF₄/CsOH catalyst system was accomplished by evaluating the catalyst loading, different pyrazolylpyridineamine ligands, hydroxide bases and Cu^I-/Cu^{II}-precursors on the hydroxylation of 4-iodotoluene to *p*-cresol. The evaluation of the optimised reaction conditions allowed us to identify an induction period of 90 minutes. With the initial *in situ* formation of the proposed [(**L01**)Cu-OH] intermediate, we could drastically

shorten the induction period and thereby speed up the hydroxylation reaction for complete conversion within 1 h. Furthermore, we could also improve on the conversion results of the benchmark catalyst system at an optimal catalyst loading of 0.05 mol%. Lastly, the evaluation of the substrate scope of our Cu-based catalyst system revealed that we were able to convert a variety of aryl iodide and bromide substrates with moderate to outstanding conversions. Unfortunately, we were not able to use our catalyst system for the hydroxylation of aryl chloride and fluoride substrates. Future work should be focused on the identification and isolation of key Cu-based intermediates as well as the evaluation of the mechanistic pathway for these hydroxylation reactions.

3.4 Experimental section

3.4.1 General considerations

The commercially available reagents were obtained from Sigma-Aldrich and/or Merck and used as received. A literature procedure was employed for the synthesis of 2-(3,5-dimethyl-1H-pyrazol-1-yl)-N-(pyridine-2-ylmethyl)ethan-1-amine (**L02**) [24, 25]. NMR [^1H and $^{13}\text{C}\{^1\text{H}\}$] spectra were recorded on a Bruker Ultrashield Plus spectrometer at 600 MHz and 150 MHz, respectively. The chemical shifts (δ) are shown in parts per million (ppm) and referenced by using the residual protons of the deuterated solvent signal [47]. The coupling constants are reported in Hz. IR spectra were recorded on neat oils with a BrukerAlpha-P range FT-IR spectrometer, equipped with an ATR accessory. APCI (positive ion mode) spectra were recorded on a Bruker microTOF-Q II spectrometer. GC analyses were performed on an Agilent 6890 Series GC system with an HP-5 column, and samples (0.2 mL) were analysed with biphenyl as internal standard. GC-MS analyses were performed on an Agilent 6890 N Series GC system with a mass selective (5973) detector and an HP-5-MSUI column, and samples were analysed in the absence of an internal standard to confirm complete conversion. Duplicate hydroxylation reactions were performed to obtain average conversions and standard deviations. Complete phenol conversion was identified at the end of the hydroxylation reaction, after acidic workup and extraction with EtOAc.

3.4.2 Synthesis of the pyrazolylpyridineamine ligands (**L01**, **L03** and **L04**)

The synthesis methods for the initial primary amine and imine derivatives for the pyrazolylpyridineamine ligands are described in the Supporting Information.

2-(1H-pyrazol-1-yl)-N-(pyridine-2-ylmethyl)ethan-1-amine (L01): A modified method was used for the reduction of the ligands [48]. The unsubstituted pyrazole imine (0.17 g, 1.5 mmol)

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was dissolved in ethanol (6 mL) and cooled down in an ice bath for 30 minutes. Separately, sodium borohydride (NaBH_4 , 0.29 g, 7.66 mmol in 1 mL ethanol), was added to a 100 mL round-bottom flask which was also cooled down in the ice bath. After the allotted time, NaBH_4 was added to the pyrazole imine, where after the reaction mixture was stirred for 1 h and then refluxed for another hour. The solvent was removed *in vacuo* before DCM (20 mL) was added. The organic phase was washed with water (2 x 5 mL), dried over anhydrous sodium sulfate (Na_2SO_4) and filtered. The solvent was removed *in vacuo* to obtain the product as a dark brown oil (**L01**). Yield: 82 mg (97 %). ^1H NMR (600 MHz, CDCl_3): δ 8.50 (d, J = 4.6 Hz, 1H, H_{Ar}), 7.60 (t, J = 7.7, 1.4 Hz, 1H, H_{Ar}), 7.50 (s, 1H, H_{Ar}), 7.43 (d, J = 1.8 Hz, 1H, H_{Ar}), 7.25-7.22 (t, 1H, H_{Ar}), 7.13 (t, J = 7.2, 5.2 Hz, 1H, H_{Ar}), 6.23 (s, 1H, H_{Ar}), 4.74 (s, 1H, NH), 4.26 (t, J = 6.0 Hz, 2H, NCH_2CH_2), 3.86 (s, 2H, NHCH_2), 3.08 (t, J = 6.0 Hz, 2H, NCH_2CH_2). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 159.37 (C_{Ar}), δ 149.30 (C_{Ar}), δ 139.62 (C_{Ar}), δ 136.61 (C_{Ar}), δ 129.75 (C_{Ar}), δ 122.23 (C_{Ar}), δ 122.08 (C_{Ar}), δ 105.45 (C_{Ar}), δ 54.75 (NHCH_2), δ 52.15 (NCH_2CH_2), δ 49.04 (NCH_2CH_2) (Figures S3.1 and S3.2 in the Supporting Information). FT-IR (cm^{-1}): ν 3303 (NH and C-H (CH_2)), ν 2984 (CH_2), ν 1650 (C-C and C-H in pyridine ring), ν 1592 (C=C and C-H in pyrazole ring). APCI-MS (positive ion mode): mass fragment at m/z 203.13 (MW: 202.26 g/mol, Figure S3.7 in the Supporting Information).

***N*-methyl-2-(1H-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine (L03):** A modified method was used for the methylation of the secondary amine analogue (**L01**) [48]. Ligand **L01** (0.10 g, 0.5 mmol) was dissolved in MeCN (5 mL) in a 100 mL round bottom flask. The solution was allowed to stir during the addition of 100 % formaldehyde (0.436 g, 5.54 mmol) and glacial acetic acid (0.75 mL), after which it was stirred for 30 minutes. NaBH_4 (0.08 g, 2.1 mmol) was slowly added to the reaction mixture and stirred for 72 hours at room temperature. The MeCN solvent was removed *in vacuo* and 2 M KOH was added to increase the pH above 10. The reaction mixture was extracted with DCM (3 x 10 mL) and dried over anhydrous Na_2SO_4 . The solvent was removed *in vacuo* to obtain the product as a dark brown oil (**L03**). Yield: 63 mg (58 %). ^1H NMR (600 MHz, CDCl_3): δ 8.50 (d, J = 4.5 Hz, 1H, H_{Ar}), δ 7.60 - 7.57 (t, J = 7.6 Hz, 1H, H_{Ar}), δ 7.48 (s, 1H, H_{Ar}), δ 7.43 (s, 1H, H_{Ar}), δ 7.19-7.18 (d, J = 7.8 Hz, 1H, H_{Ar}), δ 7.14-7.12 (t, 1H, H_{Ar}), δ 6.23 (s, 1H, H_{Ar}), δ 4.27-4.25 (t, J = 6.5 Hz, 2H, NCH_2CH_2), δ 3.68 (s, 2H, N(Me)CH_2), δ 2.90-2.88 (t, J = 6.5 Hz, 2H, NCH_2CH_2), δ 2.31 (s, 3H, NCH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 158.97 (C_{Ar}), δ 149.03 (C_{Ar}), δ 139.18 (C_{Ar}), δ 136.57 (C_{Ar}), δ 129.61 (C_{Ar}), δ 122.93 (C_{Ar}), δ 122.11 (C_{Ar}), δ 105.33 (C_{Ar}), δ 63.87 (NCH_2CH_2), δ 57.20 (NCH_2CH_2), δ 50.17 (N(Me)CH_2), δ 42.56 (NCH_3) (Figures S3.3 and S3.4 in the Supporting Information). FT-IR (cm^{-1}): ν 3394 (C-H (N-CH_3 , CH_2 , pyridine ring)), ν 2947 (C-H (N-CH_3 , CH_2)), ν 1668 (C-N and C-H in pyridine ring), ν 1589 (C=C and C-H in pyrazole ring).

APCI-MS (positive ion mode): mass fragment at m/z 217.15 (MW: 216.29 g/mol, Figure S3.9 in the Supporting Information).

The same synthesis method was used for ligand **L04**, as described in the Supporting Information.

3.4.3 Optimisation of our Cu-based catalyst system

The optimisation of our catalyst system was performed by varying the catalyst loading (Cu:L), reaction time, Cu^I/Cu^{II}-precursors, pyrazolylpyridineamine ligands and bases in the hydroxylation of 4-iodotoluene. A solution of the Cu-precursor ([Cu(MeCN)₄]BF₄, [Cu(MeCN)₄]OTf, [Cu(MeCN)₄]PF₆, CuCl, CuBr, Cu(BF₄)₂·xH₂O, Cu(OTf)₂, CuCl₂·2H₂O, CuSO₄·5H₂O and Cu(OAc)₂·2H₂O, x mol%, in 0.5 mL DMSO) and ligand (**L01-L04**, x mol%, in 0.5 mL DMSO) was stirred in a small, closed reactor flask for 30 minutes at room temperature. 4-iodotoluene (1 mmol, in 0.5 mL DMSO) and hydroxide base (NaOH, KOH or CsOH (4 mmol, in 1.5 mL H₂O)) were added to the green complex mixture, where after the reaction was stirred for 6 or 24 h at 120 ± 2 °C. During the reaction, it changed from dark green to a milky yellow colour and then again to a clear yellow-orange colour. After the allotted time, the mixture was cooled down and acidified with 0.1 M hydrochloric acid (HCl, 25 mL). The acidified solvent was extracted with EtOAc (10 mL) and the organic layer was dried over anhydrous Na₂SO₄. After the solvent was filtered through a syringe filter, a sample (0.2 mL) was analysed by GC with biphenyl (50 µL) as internal standard.

3.4.4 Effect of the presence of the *in situ* formed Cu-intermediate

The hydroxylation of 4-iodotoluene was evaluated over a range of reaction times (0.5 to 6 h), using either the optimised reaction conditions or the initial *in situ* formation of the [(**L01**)Cu-OH] intermediate. The alternative reaction conditions involve: A solution of [Cu(MeCN)₄]BF₄ (2 mol%, in 0.5 mL DMSO), ligand **L01** (2 mol%, in 0.5 mL DMSO) and CsOH (4 mmol, in 1.5 mL H₂O) were stirred in a small reactor flask, for 5 minutes at 120 ± 2 °C, open to air. 4-iodotoluene (1 mmol, in 0.5 mL DMSO) was added to the milky orange complex mixture, closed and the reaction was stirred for 0.5 to 6 h at 120 ± 2 °C. The reaction mixture changed to a milky light yellow and later a clear light grey colour. After the allotted time, the mixture was cooled down to room temperature and then acidified with 0.1 M HCl (25 mL). The acidified solvent was extracted with EtOAc (10 mL) and the organic layer was dried over Na₂SO₄. After the solvent was filtered through a syringe filter, a sample (0.2 mL) was analysed by GC with biphenyl (50 µL) as internal standard.

These reactions were performed in duplicate and the varying reaction times, conversions (%) and the standard deviations are summarised in the Supporting Information, Tables S3.1 and S3.2.

3.4.5 Evaluation of catalyst loading: Alternative reaction conditions

The same method as mentioned above was used, but the catalyst loading was varied between 0.01 and 0.05 mol%. The reaction mixture was acidified, extracted with EtOAc and filtered through a silica plug. A sample (0.2 mL) was analysed by GC with biphenyl (50 μ L) as internal standard.

3.4.6 Evaluation of the substrate scope for the hydroxylation reactions

A solution of the $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (2 mol%, in 0.5 mL DMSO) and ligand **L01** (2 mol%, in 0.5 mL DMSO) was stirred in a small reactor flask, for 30 minutes at room temperature. Aryl halides (different aryl iodides and bromides, 1 mmol, in 0.5 mL DMSO) and CsOH (4 mmol, in 1.5 mL H_2O) were added to the green complex mixture and the reaction was stirred for varying reaction times at 120 ± 2 °C. The reaction mixture changed from dark green to a yellow milky colour and then a clear yellow-orange colour. After the allotted time, the mixture was cooled down and acidified with 0.1 M HCl (25 mL). Extraction was done with EtOAc (3 x 10 mL) and the organic layer was dried over Na_2SO_4 , filtered and the solvent was removed *in vacuo*. The phenolic product was flushed through a silica plug, using petroleum spirit/EtOAc as eluent, to remove residual DMSO.

3.5 Acknowledgments

This work is part of the research that is supported by the National Research Foundation of South Africa (Unique Grant No. 112545 and 117869) as well as North-West University. Any opinion, finding and conclusion or recommendation expressed in this material is that of the author(s) and the NRF does not accept any liability in this regard. The Focus Area for Chemical Resource Beneficiation (CRB) and specifically the Catalysis and Synthesis Research Group, at the NWU, is gratefully acknowledged for the infrastructure support.

3.6 References

- [1] R. Bal, M. Tada, T. Sasaki, Y. Iwasawa, *Angew. Chem. Int. Ed.*, 45 (2006) 448-452.
- [2] Y. Wang, C. Zhou, R. Wang, *Green Chem.*, 17 (2015) 3910-3915.
- [3] C. Hoarau, T.R. Pettus, *Synlett.*, 2003 (2003) 0127-0137.
- [4] T. George, R. Mabon, G. Sweeney, J.B. Sweeney, A. Tavassoli, *J. Chem. Soc., Perkin Trans. 1*, (2000) 2529-2574.
- [5] P. Hanson, J.R. Jones, A.B. Taylor, P.H. Walton, A.W. Timms, *J. Chem. Soc., Perkin Trans. 2*, (2002) 1135-1150.
- [6] J. Xu, X. Wang, C. Shao, D. Su, G. Cheng, Y. Hu, *Org. Lett.*, 12 (2010) 1964-1967.
- [7] K. Inamoto, K. Nozawa, M. Yonemoto, Y. Kondo, *Chem. Commun.*, 47 (2011) 11775-11777.
- [8] R.E. Maleczka, F. Shi, D. Holmes, M.R. Smith, *J. Am. Chem. Soc.*, 125 (2003) 7792-7793.
- [9] K.W. Anderson, T. Ikawa, R.E. Tundel, S.L. Buchwald, *J. Am. Chem. Soc.*, 128 (2006) 10694-10695.
- [10] M.C. Willis, *Angew. Chem. Int. Ed.*, 46 (2007) 3402-3404.
- [11] G. Chen, A.S. Chan, F.Y. Kwong, *Tetrahedron Lett.*, 48 (2007) 473-476.
- [12] B.J. Gallon, R.W. Kojima, R.B. Kaner, P.L. Diaconescu, *Angew. Chem. Int. Ed.*, 46 (2007) 7251-7254.
- [13] A.G. Sergeev, T. Schulz, C. Torborg, A. Spannenberg, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.*, 48 (2009) 7595-7599.
- [14] T. Schulz, C. Torborg, B. Schöffner, J. Huang, A. Zapf, R. Kadyrov, A. Börner, M. Beller, *Angew. Chem. Int. Ed.*, 48 (2009) 918-921.
- [15] C.-W. Yu, G.S. Chen, C.-W. Huang, J.-W. Chern, *Org. Lett.*, 14 (2012) 3688-3691.
- [16] D. Zhao, N. Wu, S. Zhang, P. Xi, X. Su, J. Lan, J. You, *Angew. Chem. Int. Ed.*, 48 (2009) 8729-8732.
- [17] K. Yang, Z. Li, Z. Wang, Z. Yao, S. Jiang, *Org. Lett.*, 13 (2011) 4340-4343.
- [18] A. Tlili, N. Xia, F. Monnier, M. Taillefer, *Angew. Chem.*, 121 (2009) 8881-8884.
- [19] R. Paul, M.A. Ali, T. Punniyamurthy, *Synthesis*, 2010 (2010) 4268-4272.
- [20] O. Songis, P. Boulens, C.G. Benson, C.S. Cazin, *RSC Adv.*, 2 (2012) 11675-11677.

Chapter 3: The development of a Cu(I)/pyrazolylpyridineamine catalyst system for the hydroxylation of aryl halides

- [21] N. Mketo, J.H.L. Jordaan, A. Jordaan, A.J. Swarts, S.F. Mapolie, *Eur. J. Inorg. Chem.*, 2016 (2016) 3781-3790.
- [22] P.J. Amal Joseph, S. Priyadarshini, *Org. Process Res. Dev.*, 21 (2017) 1889-1924.
- [23] J. Jia, C. Jiang, X. Zhang, Y. Jiang, D. Ma, *Tetrahedron Lett.*, 52 (2011) 5593-5595.
- [24] C. Obuah, M.K. Ainooson, S. Boltina, I.A. Guzei, K. Nozaki, J. Darkwa, *Organometallics*, 32 (2013) 980-988.
- [25] C. Obuah, B. Omondi, K. Nozaki, J. Darkwa, *J. Mol. Catal. A: Chem.*, 382 (2014) 31-40.
- [26] S. Maurer, W. Liu, X. Zhang, Y. Jiang, D. Ma, *Synlett.*, 2010 (2010) 976-978.
- [27] S.S. Shendage, *J. Chem. Sci.*, 130 (2018) 13.
- [28] J.M. Hoover, B.L. Ryland, S.S. Stahl, *J. Am. Chem. Soc.*, 135 (2013) 2357-2367.
- [29] A.J. Swarts, S.F. Mapolie, *Dalton Trans.*, 43 (2014) 9892-9900.
- [30] A.J. Swarts, F. Zheng, V.J. Smith, E. Nordlander, S.F. Mapolie, *Organometallics*, 33 (2014) 2247-2256.
- [31] L. Marais, J. Bures, J.H.L. Jordaan, S. Mapolie, A.J. Swarts, *Org. Biomol. Chem.*, 15 (2017) 6926-6933.
- [32] G. Lefèvre, A. Tlili, M. Taillefer, C. Adamo, I. Ciofini, A. Jutand, *Dalton Trans.*, 42 (2013) 5348-5354.
- [33] P. Gamez, I.W.C.E. Arends, R.A. Sheldon, J. Reedijk, *Adv. Synth. Catal.*, 346 (2004) 805-811.
- [34] E.T. Kumpulainen, A.M. Koskinen, *Chem. Eur. J.*, 15 (2009) 10901-10911.
- [35] J.M. Hoover, S.S. Stahl, *J. Am. Chem. Soc.*, 133 (2011) 16901-16910.
- [36] P. Garrido-Barros, I. Funes-Ardoiz, S. Drouet, J. Benet-Buchholz, F. Maseras, A. Llobet, *J. Am. Chem. Soc.*, 137 (2015) 6758-6761.
- [37] D. Wang, D. Kuang, F. Zhang, S. Tang, W. Jiang, *Eur. J. Org. Chem.*, 2014 (2014) 315-318.
- [38] E. Garribba, G. Micera, D. Sanna, L. Strinna-Erre, *Inorg. Chim. Acta*, 299 (2000) 253-261.
- [39] S.J. Koepke, K.M. Light, P.E. VanNatta, K.M. Wiley, M.T. Kieber-Emmons, *J. Am. Chem. Soc.*, 139 (2017) 8586-8600.
- [40] G.A. van Albada, I. Mutikainen, O. Roubeau, U. Turpeinen, J. Reedijk, *Inorg. Chim. Acta*, 331 (2002) 208-215.

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- [41] Y.-Q. Zheng, J.-L. Lin, Z. Anorg. Allg. Chem., 629 (2003) 1622-1626.
- [42] S.P. Perlepes, J.C. Huffman, G. Christou, Polyhedron, 11 (1992) 1471-1479.
- [43] G.A. van Albada, I. Mutikainen, U. Turpeinen, J. Reedijk, Inorg. Chim. Acta, 324 (2001) 273-277.
- [44] J.M. Hoover, B.L. Ryland, S.S. Stahl, ACS Catal., 3 (2013) 2599-2605.
- [45] L. Jing, J. Wei, L. Zhou, Z. Huang, Z. Li, X. Zhou, Chem. Commun., 46 (2010) 4767-4769.
- [46] J.D. Winkler, B.M. Twenter, T. Gendrineau, Heterocycles, 84 (2012).
- [47] H.E. Gottlieb, V. Kotlyar, A. Nudelman, J. Org. Chem., 62 (1997) 7512-7515.
- [48] R.V. Ottenbacher, K.P. Bryliakov, E.P. Talsi, Inorg. Chem., 49 (2010) 8620-8628.

Supporting Information for

The development of a Cu(I)/pyrazolylpyridineamine catalyst system for the hydroxylation of aryl halides

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S3.1 General considerations

S3.1.1 Instrumentation

NMR [^1H and $^{13}\text{C}\{^1\text{H}\}$] spectra were recorded on a Bruker Ultrashield Plus spectrometer at 600 MHz and 150 MHz respectively. The chemical shifts (δ) are given in parts per million (ppm) and externally referenced according to the residual protons of the deuterated solvent signal [1]. Coupling constants are reported in Hz. IR spectra were recorded as neat oils with a BrukerAlpha-P range FT-IR spectrometer equipped with an ATR accessory. APCI (positive ion mode) spectra were recorded on a Bruker microTOF-Q II spectrometer. GC analyses were performed on an Agilent 6890 Series GC system with an HP-5 column (30 m x 0.320 mm x 0.25 mm). N_2 served as the carrier gas, ethyl acetate (EtOAc) and dichloromethane (DCM) were used as the rinsing solutions and samples (0.2 mL) were analysed with biphenyl as internal standard. GC-MS analyses were performed on an Agilent 6890 N Series GC system equipped with a mass selective (5973) detector and an HP-5-MSUI column (30 m x 0.320 mm x 0.25 mm). Helium served as the carrier gas, EtOAc and DCM were used as the rinsing solutions and samples were analysed in the absence of an internal standard to confirm complete conversion. The hydroxylation reactions were done in duplicate to determine an average conversion value as well as the standard deviation. Complete phenol conversion was identified at the end of the hydroxylation reaction, after acidic workup and extraction with EtOAc. The phenolic products were isolated as described below.

S3.2 Synthesis of the pyrazolypyridineamine ligands

Primary amine precursors: Step 1: In a Schlenk tube, a suspension of 2-chloroethylamine hydrochloride (5.0 g, 43.2 mmol) and dry MeCN (7.5 mL), was stirred in an ice bath, under an inert atmosphere (N_2). Triethylamine (NEt_3 , 6.0 mL, 43.2 mmol) was added dropwise over 60 min after which the milky slurry was allowed to stir for another 5 min, while still in an ice bath. The Schlenk tube was sealed and stored in the fridge. Step 2: Pyrazole (1.47 g, 21.6 mmol) was added to a three-neck round-bottom flask and dissolved in dry MeCN (30 mL), under an inert atmosphere (N_2). NaOH (2.59 g, 64.7 mmol) and anhydrous Na_2SO_4 (spatula tip) were added to the reaction mixture while stirring at room temperature for 30 minutes. In the meantime, the product from step 1 was filtered and washed with dry MeCN (2 x 5 mL). The reaction mixture was stirred in an oil bath, at reflux temperature, and then the product from step 1 was added dropwise over 60 minutes. The reaction mixture was allowed to reflux for another 6 h, after which it was cooled down, filtered and washed with dry MeCN. Most of the solvent was removed *in vacuo*, the light yellow liquid was filtered and the last

solvent was allowed to slowly evaporate. The precursor was obtained as a light yellow oil. Yield: 770 mg, 32 %. ^1H NMR (600 MHz, MeOD): δ 7.66 (s, 1H, H_{Ar}), δ 7.54 (d, J = 1.4 Hz, 1H, H_{Ar}), δ 6.32 (s, 1H, H_{Ar}), δ 4.24-4.12 (t, 2H, NCH_2), δ 3.08-3.06 (t, 2H, CH_2NH_2), δ 1.96 (s, 2H, NH_2). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, MeOD): δ 140.58 (C_{Ar}), δ 131.73 (C_{Ar}), δ 106.51 (C_{Ar}), δ 54.77 (CH_2NH_2), δ 42.75 (NCH_2). FT-IR (cm^{-1}): ν 3361 and ν 750 (NH_2), ν 2941 (CH_2), ν 1597 ($\text{C}=\text{N}$).

The same synthesis method was used for the synthesis of the substituted primary amine precursor, but 3,5-dimethylpyrazole (2.07 g, 21.6 mmol) was used instead of pyrazole. The precursor was obtained as a light yellow oil. Yield: 2 g, 70 %. ^1H NMR (600 MHz, MeOD): δ 5.86 (s, 1H, H_{Ar}), 4.04 (t, J = 6.5 Hz, 2H, NCH_2), 2.99 (t, J = 6.5 Hz, 2H, CH_2NH_2), 2.27 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 1.95 (s, 2H, NH_2). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, MeOD): δ 148.98 (C_{Ar}), δ 141.49 (C_{Ar}), δ 106.10 (C_{Ar}), δ 51.06 (CH_2NH_2), δ 42.49 (NCH_2), δ 13.23 (CH_3), δ 10.89 (CH_3). FT-IR (cm^{-1}): ν 3358 and ν 773 (NH_2), ν 2927 (CH_2 and CH_3), ν 1551 ($\text{C}=\text{N}$).

Imine derivatives: A modified method was used to synthesise the imine products [2]. The pyrazole amine (0.17 g, 1.5 mmol) was dissolved in ethanol (5 mL) in a 100 mL round bottom flask. Separately, 2-pyridinecarboxaldehyde (0.11 mL, 1 mmol) was dissolved in ethanol (2 mL) and added to the amine solution. The reaction mixture was refluxed for 15 h where after the solvent was removed *in vacuo*. DCM (20 mL) was added to the brown oil which was extracted with H_2O (2 x 5 mL), dried, filtered and the solvent was removed *in vacuo* to obtain the product as a dark brown oil (imine-**L01**). Yield: 119 mg (35 %). ^1H NMR (600 MHz, CDCl_3): δ 8.61 (d, J = 4.1 Hz, 1H, H_{Ar}), δ 8.13 (s, 1H, NCH), δ 7.89 (d, J = 7.9 Hz, 1H, H_{Ar}), δ 7.73 (t, J = 7.7 Hz, 1H, H_{Ar}), δ 7.50 (s, 1H, H_{Ar}), δ 7.36 (d, J = 2.0 Hz, 1H, H_{Ar}), δ 7.30 (dd, J = 6.3, 4.9 Hz, 1H, H_{Ar}), δ 6.15 (t, 1H, CH), δ 4.50 (t, J = 5.9 Hz, 2H, NCH_2), δ 4.08 (t, J = 5.3 Hz, 2H, CH_2NC). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 164.06 (C_{Ar}), δ 154.01 (C_{Ar}), δ 149.57 (CH), δ 139.67 (C_{Ar}), δ 136.63 (C_{Ar}), δ 129.97 (C_{Ar}), δ 124.98 (C_{Ar}), δ 121.52 (C_{Ar}), δ 105.22 (C_{Ar}), δ 60.72 (CH_2NC), δ 52.33 (NCH_2). FT-IR (cm^{-1}): ν 3361 (C-H, pyridine ring), ν 2941 (CH_2), ν 1597 ($\text{C}=\text{N}$).

The same synthesis procedure as mentioned above were used, except for using 3,5-dimethylpyrazole amine (0.21 g, 1.5 mmol) instead of the pyrazole amine as reagent. The product was obtained as a dark brown oil (imine-**L02**). Yield: 101 mg (58 %) ^1H NMR (600 MHz, CDCl_3): δ 8.61 (d, J = 4.5 Hz, 1H, H_{Ar}), δ 8.14 (s, 1H, NCH), δ 7.89 (d, J = 7.9 Hz, 1H, H_{Ar}), δ 7.73 (dd, J = 7.6, 1.4 Hz, 1H, H_{Ar}), δ 7.30 (t, J = 7.4, 4.8, 1.0 Hz, 1H, H_{Ar}), δ 5.68 (s, 1H, H_{Ar}), δ 4.31 (t, J = 6.1 Hz, 2H, NCH_2), δ 4.05 (t, J = 5.5 Hz, 2H, CH_2NC), δ 2.19 (s, 3H, CH_3), δ 2.18 (s, 3H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 162.84 (C_{Ar}), δ 153.15 (C_{Ar}), δ 148.53 (C_{Ar}), δ 146.78 (NCH), δ 138.64 (C_{Ar}), δ 135.58 (C_{Ar}), δ 123.88 (C_{Ar}), δ 120.28 (C_{Ar}),

δ 103.74 (C_{Ar}), δ 60.20 (NCH_2), δ 47.73 (CH_2NC), δ 12.50 (CH_3), δ 10.10 (CH_3). FT-IR (cm^{-1}): ν 3390 (C-H, pyridine ring), ν 2918 (CH_2), ν 1649 (C=N).

2-(3,5-dimethyl-1H-pyrazol-1-yl)-N-methyl-N-(pyridine-2-ylmethyl)ethan-1-amine (L04):

The same synthesis procedure as for ligand **L03** was used for the synthesis of ligand **L04**, except for using the secondary 3,5-dimethylpyrazolylamine (**L02**, 0.12 g, 0.5 mmol) instead of ligand **L01** as reagent. The product was obtained as a dark brown oil. Yield: 69 mg (62 %). ^1H NMR (600 MHz, $CDCl_3$): δ 8.50 (d, $J = 4.5$ Hz, 1H, H_{Ar}), δ 7.58 (s, 1H, H_{Ar}), δ 7.20-7.19 (d, $J = 7.8$ Hz, 1H, H_{Ar}), δ 7.13 (s, 1H, H_{Ar}), δ 5.75 (s, 1H, H_{Ar}), δ 4.09-4.06 (t, $J = 7.0$ Hz, 2H, NCH_2CH_2), δ 3.68 (s, 2H, $N(Me)CH_2$), δ 2.81-2.78 (t, $J = 7.0$ Hz, 2H, NCH_2CH_2), δ 2.33 (s, 3H, NCH_3), δ 2.19 (s, 3H, CH_3), δ 2.17 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 159.04 (C_{Ar}), δ 149.02 (C_{Ar}), δ 147.29 (C_{Ar}), δ 139.04 (C_{Ar}), δ 136.49 (C_{Ar}), δ 122.95 (C_{Ar}), δ 122.05 (C_{Ar}), δ 104.86 (C_{Ar}), δ 64.01 (NCH_2CH_2), δ 57.06 (NCH_2CH_2), δ 46.79 ($N(Me)CH_2$), δ 42.86 (NCH_3), δ 13.48 (CH_3), δ 11.07 (CH_3) (Figures S3.5 and S3.6). FT-IR (cm^{-1}): ν 3383 (C-H (N-CH₃, CH₂, CH₃, pyridine ring)), ν 2947 (C-H (N-CH₃, CH₂)), ν 1656 (C-N and C-H in pyridine ring), ν 1590 (C=C and C-H in pyrazole ring, C-H (CH₃)). APCI-MS (positive ion mode): mass fragment at m/z 245.18 (MW: 244.34 g/mol, Figure S3.10 in the Supporting Information).

S3.2.1 ^1H and $^{13}C\{^1H\}$ NMR spectra for ligands L01, L03 and L04

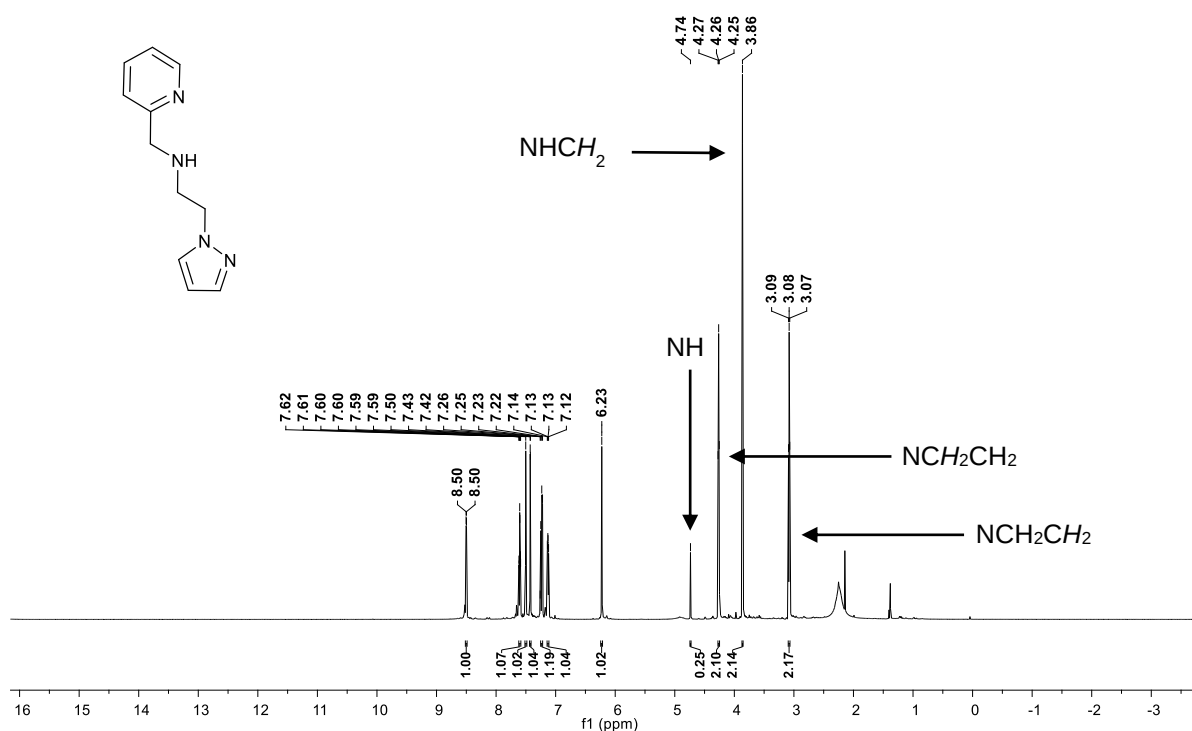


Figure S3.1: ^1H NMR (600 MHz, $CDCl_3$) spectrum for ligand **L01**.

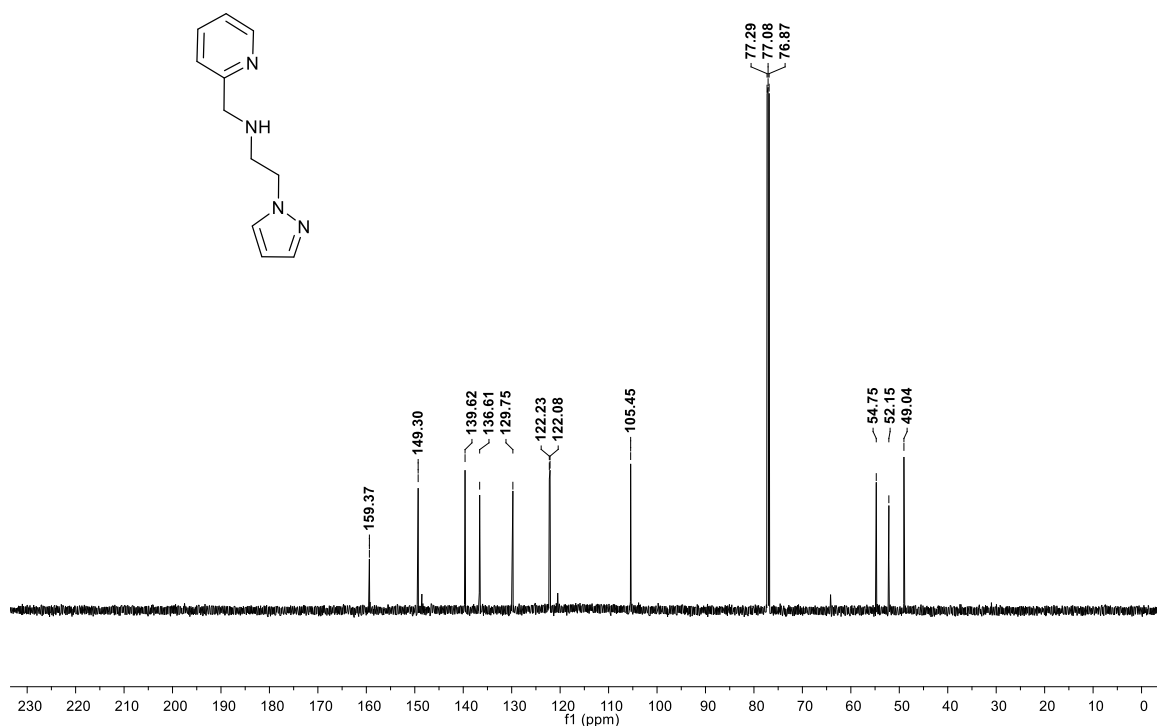


Figure S3.2: ¹³C{¹H} NMR (150 MHz, CDCl₃) spectrum for ligand **L01**.

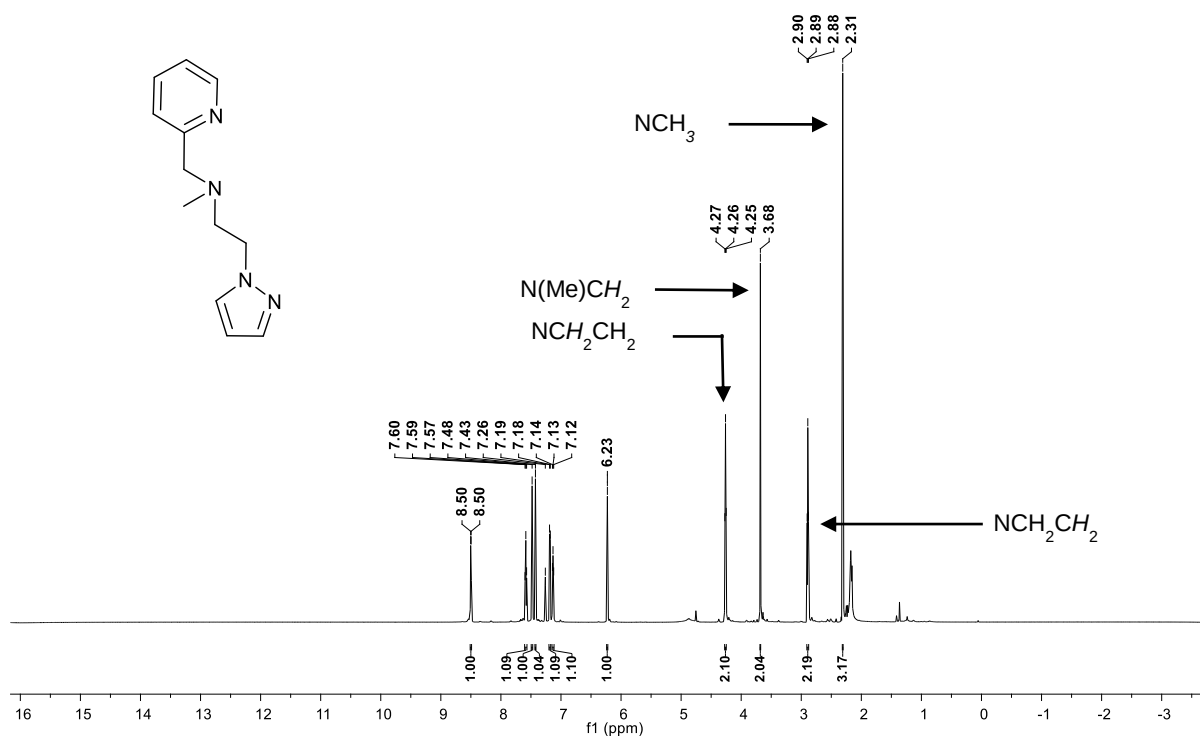


Figure S3.3: ¹H NMR (600 MHz, CDCl₃) spectrum for ligand **L03**.

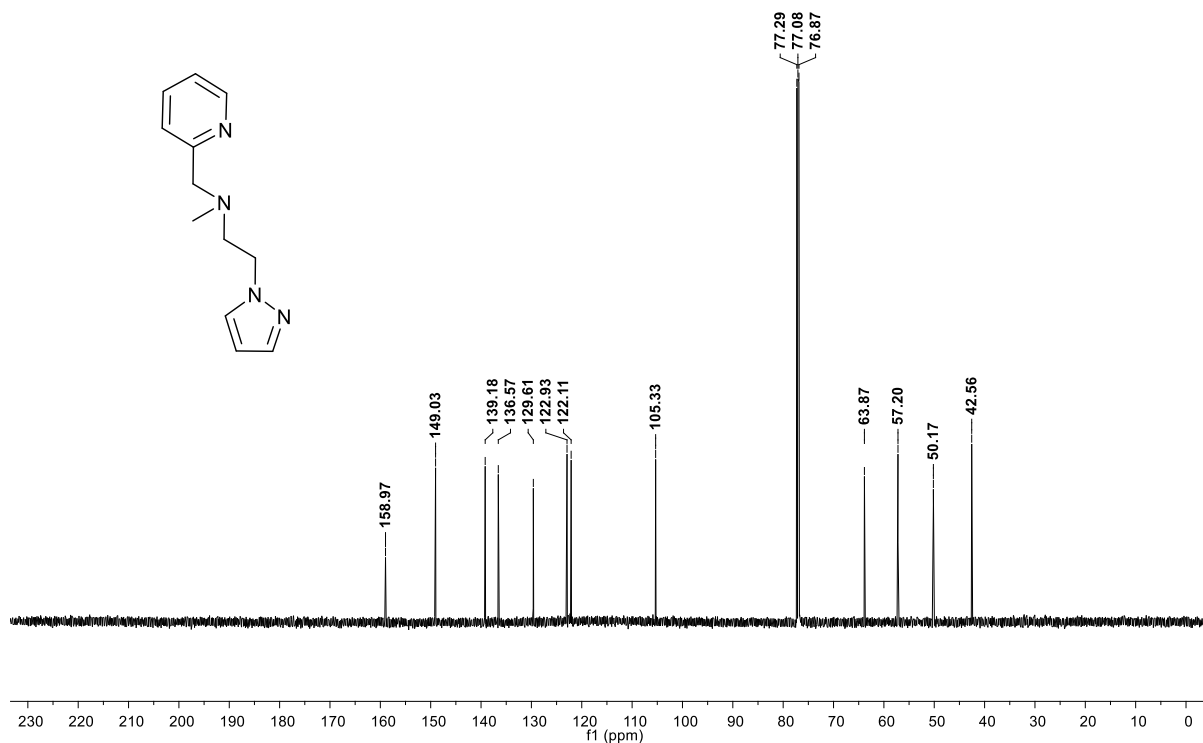


Figure S3.4: ¹³C{¹H} NMR (150 MHz, CDCl₃) spectrum for ligand **L03**.

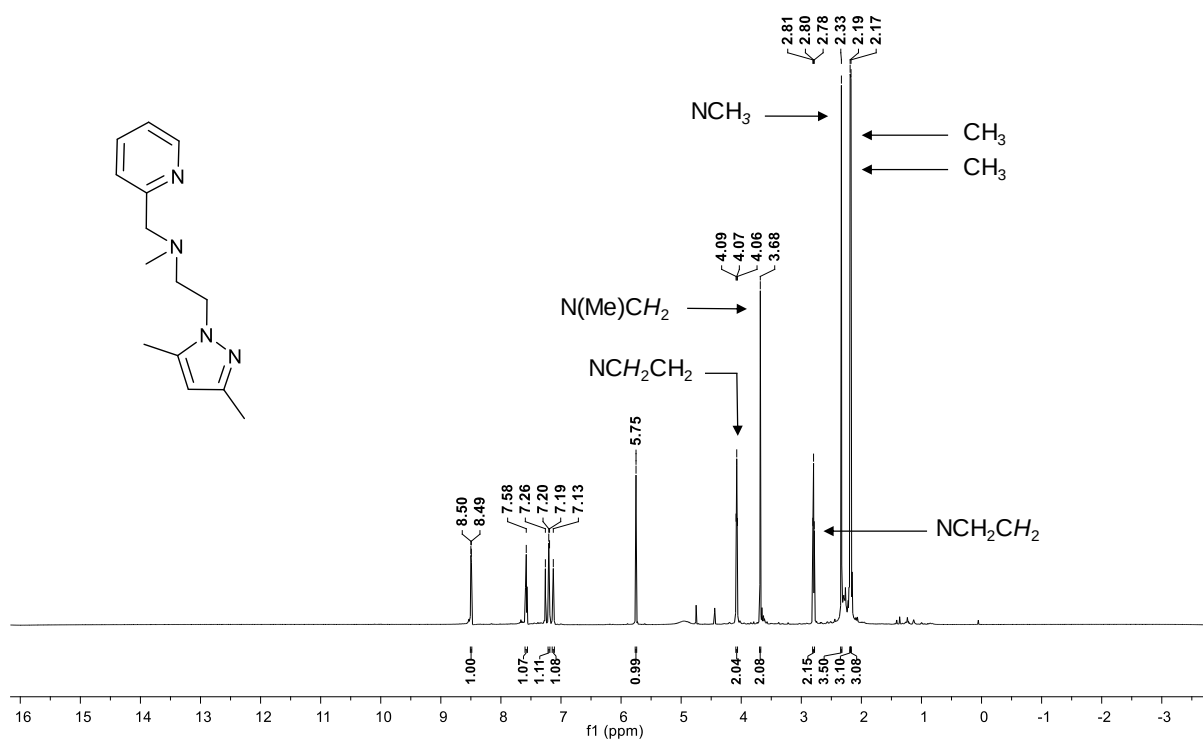


Figure S3.5: ¹H NMR (600 MHz, CDCl₃) spectrum for ligand **L04**.

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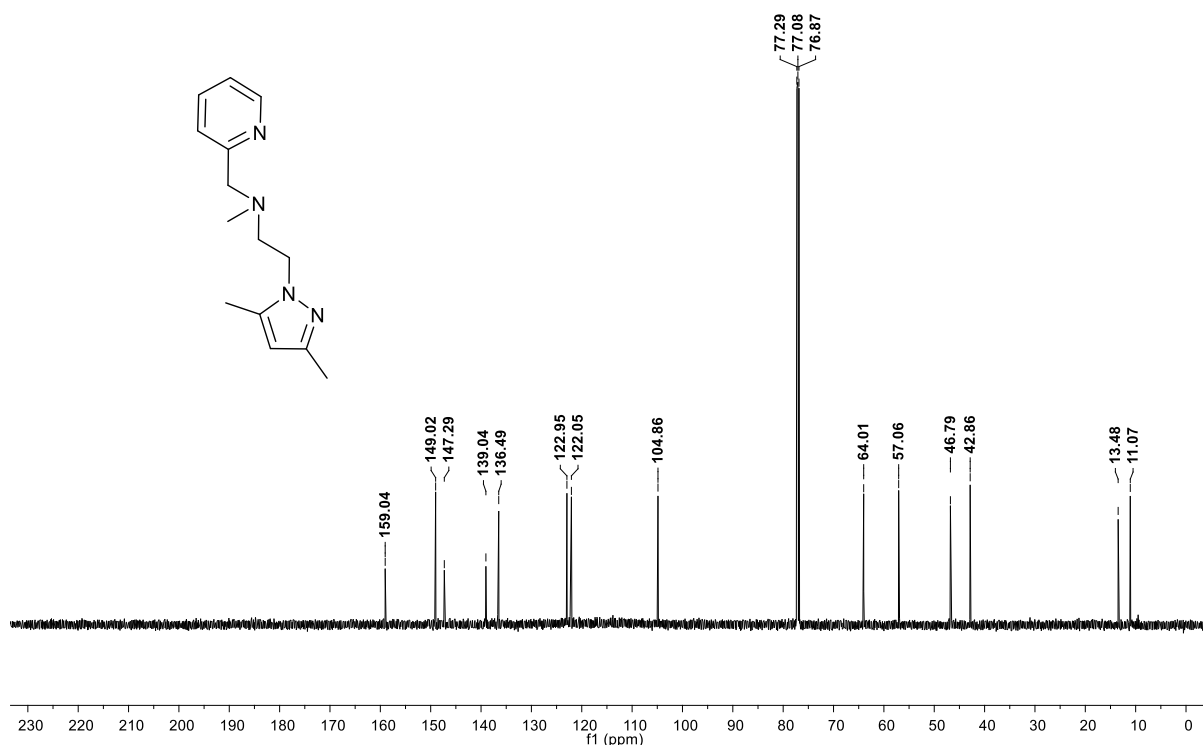


Figure S3.6: $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) spectrum for ligand **L04**.

S3.2.2 APCI-MS spectra for ligands **L01-L04**

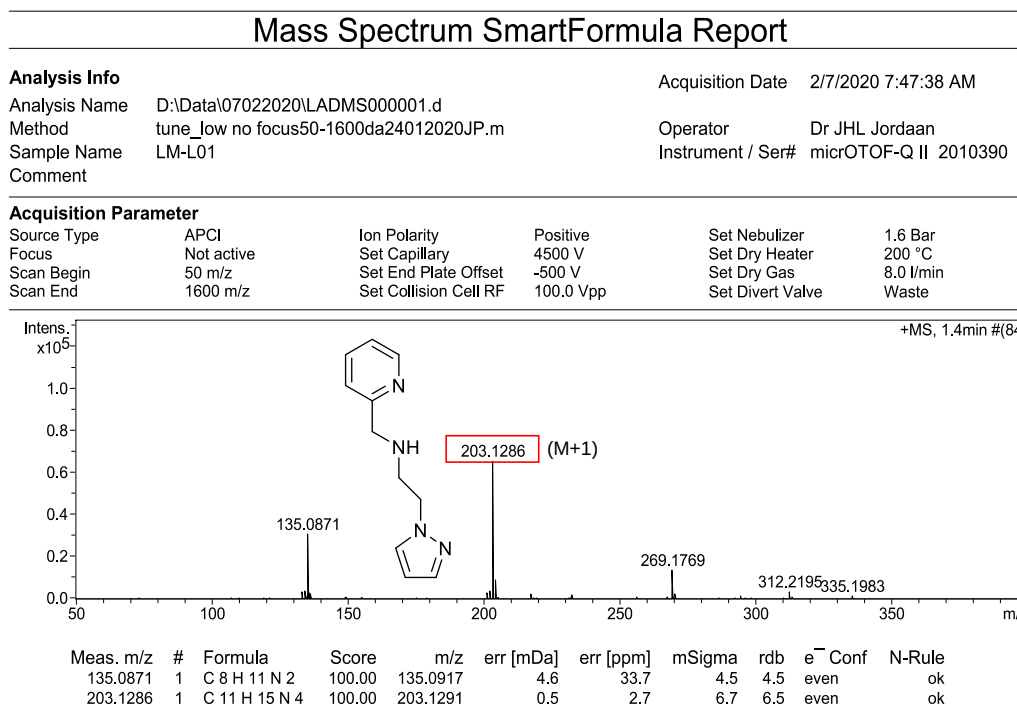


Figure S3.7: APCI-MS spectrum for ligand **L01** (MW: 202.26 g/mol). The spectrum revealed a mass fragment at m/z 203.13 which is consistent with the molar mass of the ligand (positive ion mode).

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Mass Spectrum SmartFormula Report

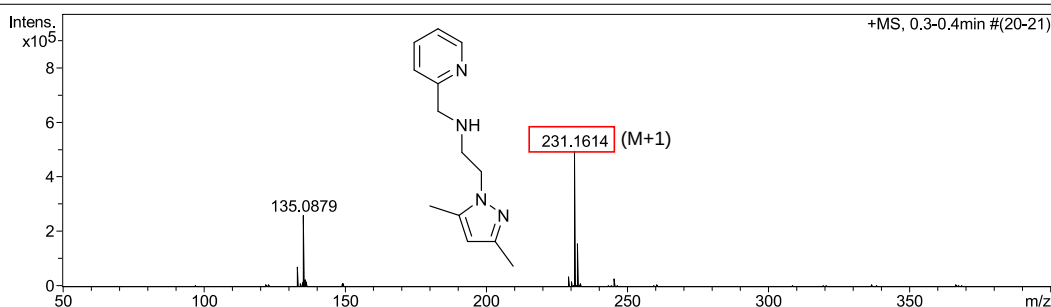
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Comment

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Operator Dr JHL Jordaan
Instrument / Ser# micrOTOF-Q II 2010390

Acquisition Parameter

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Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	8.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e ⁻ Conf	N-Rule
135.0879	1	C 8 H 11 N 2	100.00	135.0917	3.7	27.7	3.4	4.5	even	ok
231.1614	1	C 13 H 19 N 4	100.00	231.1604	-1.0	-4.4	95.1	6.5	even	ok

Figure S3.8: APCI-MS spectrum for ligand **L02** (MW: 230.32 g/mol). The spectrum revealed a mass fragment at m/z 231.16 which is consistent with the molar mass of the ligand (positive ion mode).

Mass Spectrum SmartFormula Report

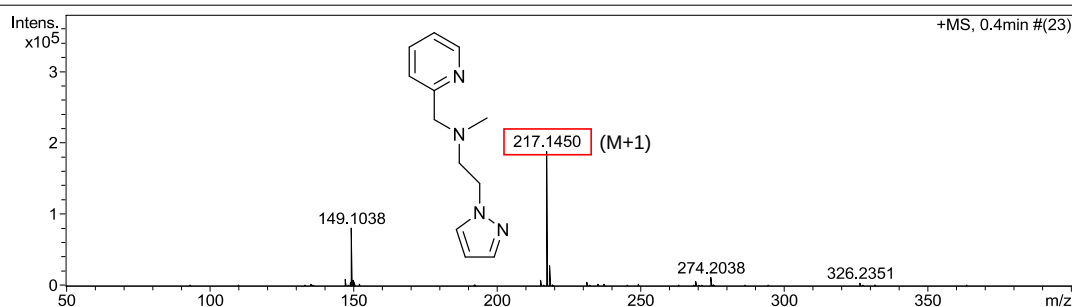
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Comment

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Operator Dr JHL Jordaan
Instrument / Ser# micrOTOF-Q II 2010390

Acquisition Parameter

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Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	8.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e ⁻ Conf	N-Rule
149.1038	1	C 9 H 13 N 2	100.00	149.1073	3.5	23.4	3.5	4.5	even	ok
217.1450	1	C 12 H 17 N 4	100.00	217.1448	-0.2	-1.0	4.4	6.5	even	ok

Figure S3.9: APCI-MS spectrum for ligand **L03** (MW: 216.29 g/mol). The spectrum revealed a mass fragment at m/z 217.15 which is consistent with the molar mass of the ligand (positive ion mode).

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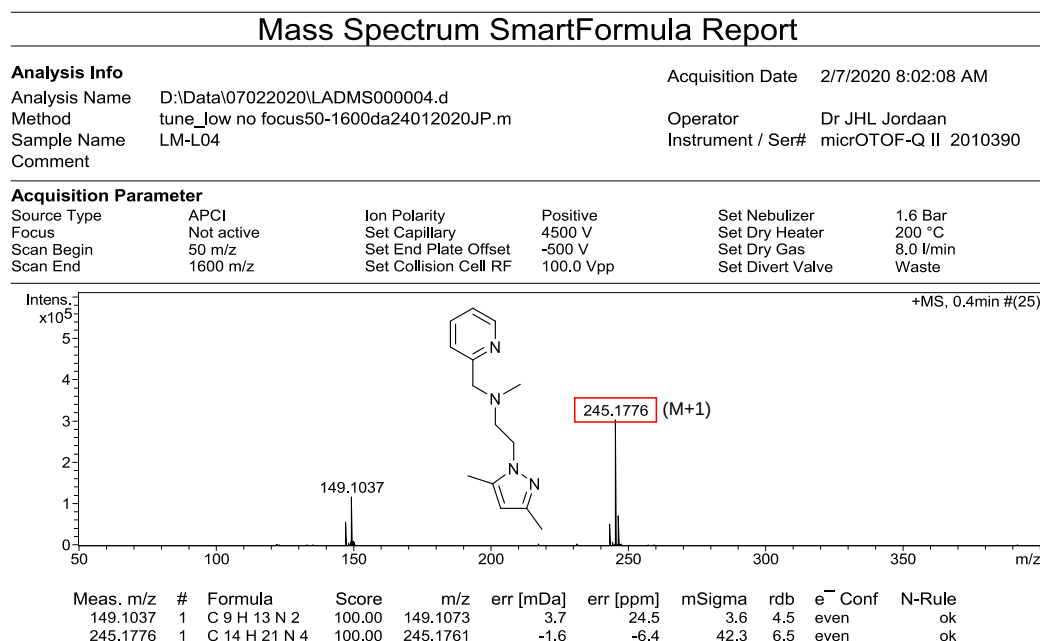


Figure S3.10: APCI-MS spectrum for ligand **L04** (MW: 244.34 g/mol). The spectrum revealed a mass fragment at m/z 245.18 which is consistent with the molar mass of the ligand (positive ion mode).

S3.3 Optimisation of the catalyst system

We evaluated the different pyrazolylpyridineamine ligands, **L01-L04**, in combination with $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ for the hydroxylation of 4-iodotoluene to *p*-cresol (Figure S3.11) [3].

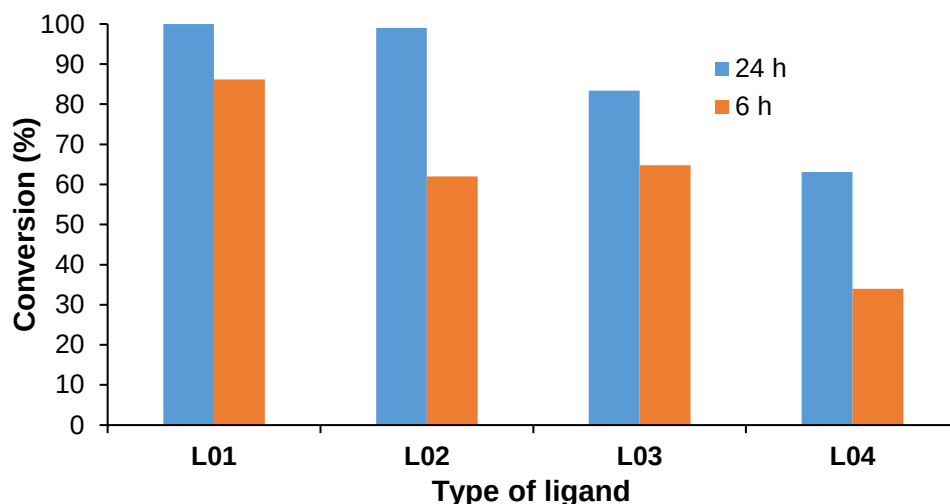


Figure S3.11: The observed conversion of 4-iodotoluene to *p*-cresol, using different pyrazolylpyridineamine ligands (**L01-L04**). **L01:** 2-(1H-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine; **L02:** 2-(3,5-dimethyl-1H-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine; **L03:** *N*-methyl-2-(1H-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine; **L04:** 2-(3,5-dimethyl-1H-pyrazol-1-yl)-*N*-methyl-*N*-(pyridine-2-ylmethyl)ethan-1-amine.

Next, we evaluated the effect of varying hydroxide bases on the hydroxylation of 4-iodotoluene to *p*-cresol (Figure S3.12).

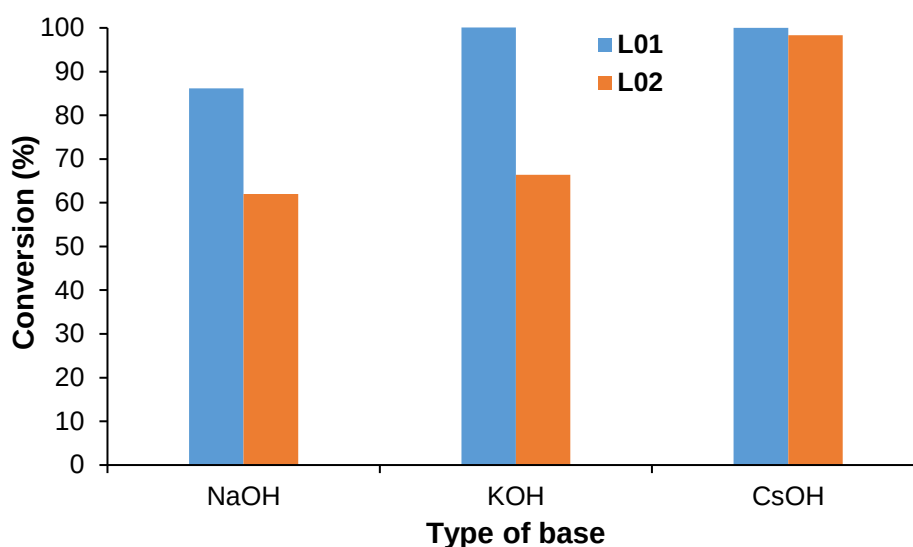


Figure S3.12: Evaluation of the effect of various bases on the hydroxylation of 4-iodotoluene to *p*-cresol, using either ligand **L01** or **L02**.

As a result, the next step was to evaluate the amount of base (KOH and CsOH) on the hydroxylation of 4-iodotoluene, using either ligand **L01** or **L02** (Figure S3.13).

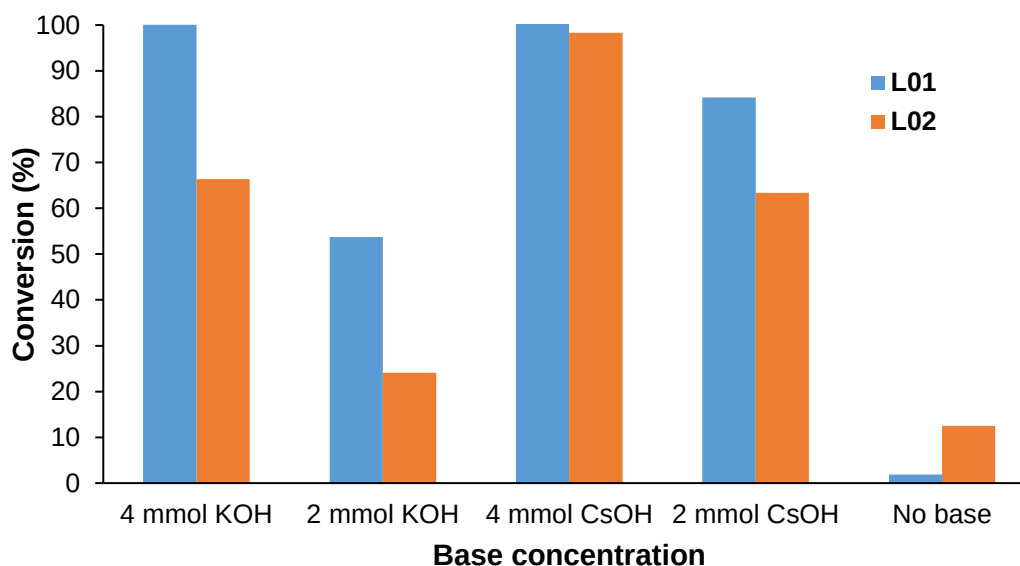


Figure S3.13: Evaluation of the amount of base (mmol) on the hydroxylation of 4-iodotoluene, using either ligand **L01** or **L02**.

We evaluated the effect of different Cu^I/Cu^{II}-precursors, in combination with ligand **L01**, for the hydroxylation of 4-iodotoluene to *p*-cresol (Figure S3.14).

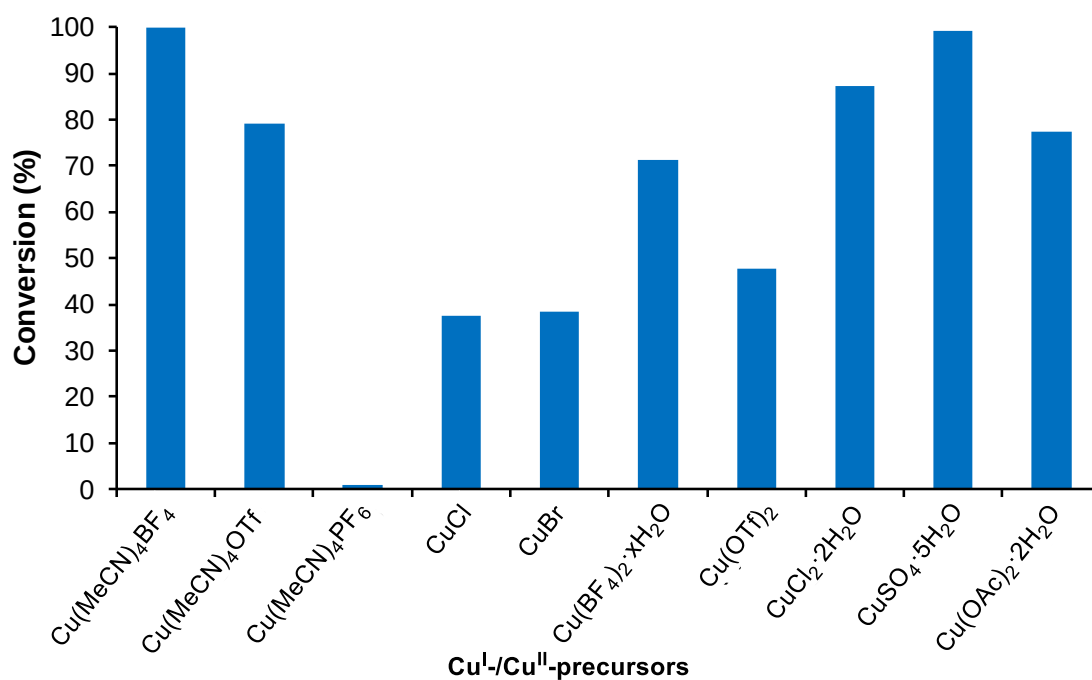


Figure S3.14: Evaluation of various Cu^I/Cu^{II}-precursors, in combination with ligand **L01**, for the hydroxylation of 4-iodotoluene to *p*-cresol, under optimal reaction conditions and a reaction time of 4 h.

S3.4 Effect of the presence of the *in situ* formed [(L01)Cu-OH] intermediate

With the optimised reaction conditions in hand, we evaluated the conversion of 4-iodotoluene to *p*-cresol, as a function of reaction time (Table S3.1). Initially an induction period was observed and conversion to *p*-cresol was only observed after a reaction time of 2 h. We postulated that the initial presence of a [(L01)Cu-OH] intermediate would shorten the induction period of the hydroxylation reaction and thereby speed up the reaction time until complete conversion (Table S3.2).

Table S3.1: Evaluation of the conversion of 4-iodotoluene to *p*-cresol as a function of reaction time, using the optimised reaction conditions. Standard reaction conditions: [Cu(MeCN)₄]BF₄ and ligand **L01** (2 mol%), 4-iodotoluene (1 mmol), CsOH (4 mmol), DMSO:H₂O (1:1, 3 mL), 120 ± 2 °C.

Reaction time (h)	Conversion (%)
0.5	1
1.0	0
1.5	1
2.0	26
2.5	57
3.0	72
4.0	97
6.0	100

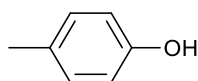
Table S3.2: Evaluation of the conversion of 4-iodotoluene to *p*-cresol as a function of reaction time, using the initial *in situ* formation of the [(L01)Cu-OH] intermediate. Reaction conditions: [Cu(MeCN)₄]BF₄ and ligand **L01** (2 mol%), 4-iodotoluene (1 mmol), CsOH (4 mmol), DMSO:H₂O (1:1, 3 mL), 120 ± 2 °C.

Reaction time (h)	Conversion (%)
0.25	2
0.38	49
0.5	81
1.0	97
2.0	99
3.0	99

S3.5 Conversion and characterisation of phenol-based products

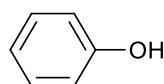
All aryl halides were obtained from Sigma-Aldrich and used as received and the obtained phenolic products were flushed through a silica plug, using petroleum spirit/EtOAc as eluent, to remove residual DMSO. The NMR [^1H and $^{13}\text{C}\{^1\text{H}\}$] spectral data were compared to those previously reported in literature.

p-Cresol



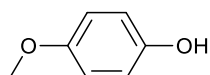
The reaction was performed in a small, closed reactor tube. After the allotted time (6 h or 18 h) the reaction mixture was cooled down, acidified with 0.1 M HCl, extracted with EtOAc (3 x 10 mL) and the solvent was removed *in vacuo*. The crude product was flushed through a silica plug, using petroleum spirit/EtOAc (8/2) as eluent, to remove residual DMSO. The product was obtained as a yellow-brown oil. Yield: 76 mg (70 %) for the iodide substrate and 63 mg (58 %) for the bromide substrate. ^1H NMR (600 MHz, CDCl_3): δ 7.05 (d, J = 8.1 Hz, 2H, H_{Ar}), 6.76 (d, J = 8.2 Hz, 2H, H_{Ar}), 5.28 (br s, 1H, OH), 2.28 (s, 3H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 153.6 (COH), 130.2 (C_{Ar}), 129.9 (C_{Ar}), 115.2 (C_{Ar}), 20.6 (CH_3). GC-MS: retention time = 5.60 min, MW: 107.2 g/mol. Spectral properties are consistent with literature values [4].

Phenol



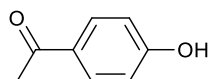
The reaction was performed in a small, closed reactor tube. After the allotted time (6 h or 18 h) the reaction mixture was cooled down, acidified with 0.1 M HCl, extracted with EtOAc (3 x 10 mL) and the solvent was removed *in vacuo*. The crude product was flushed through a silica plug, using petroleum spirit/EtOAc (8/2) as eluent, to remove residual DMSO. The product was obtained as a colourless oil. Yield: 45 mg (47 %) for the iodide substrate and 39 mg (41 %) for the bromide substrate. ^1H NMR (600 MHz, CDCl_3): δ 7.25 (t, J = 7.8 Hz, 2H, H_{Ar}), 6.95 (t, J = 7.3 Hz, 1H, H_{Ar}), 6.85 (d, J = 8.3 Hz, 2H, H_{Ar}), 5.15 (br s, 1H, OH). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 155.54 (C_{Ar}), 129.81 (C_{Ar}), 120.95 (C_{Ar}), 115.45 (C_{Ar}). GC-MS: retention time = 4.19 min, MW: 94.2 g/mol. Spectral properties are consistent with literature values [4].

***p*-Hydroxyanisole**



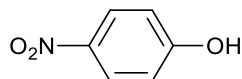
The reaction was performed in a small, closed reactor tube. After the allotted time (15 h) the reaction mixture was cooled down, acidified with 0.1 M HCl, extracted with EtOAc (3 x 10 mL) and the solvent was removed *in vacuo*. The crude product was flushed through a silica plug, using petroleum spirit/EtOAc (7/3) as eluent, to remove residual DMSO. The product was obtained as a brown solid. Yield: 94 mg (75 %). ^1H NMR (600 MHz, CDCl_3): δ 6.78 (m, J = 9.1 Hz, 4H, H_{Ar}), 5.13 (br s, 1H, OH), 3.77 (s, 3H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 153.7 (COH), 149.9 (C_{Ar}), 116.2 (C_{Ar}), 115.0 (C_{Ar}), 56.0 (CH_3). GC-MS: retention time = 7.22 min, MW: 124.1 g/mol. Spectral properties are consistent with literature values [4].

***p*-Hydroxyacetophenone**



The reaction was performed in a small, closed reactor tube. After the allotted time (6 h or 24 h) the reaction mixture was cooled down, acidified with 0.1 M HCl, extracted with EtOAc (3 x 10 mL) and the solvent was removed *in vacuo*. The crude product was flushed through a silica plug, using petroleum spirit/EtOAc (8/2, iodide) or (6/4, bromide) as eluent, to remove residual DMSO. The product was obtained as a brown solid. Yield: 130 mg (96 %) for the iodide substrate and 120 mg (88 %) for the bromide substrate. ^1H NMR (600 MHz, CDCl_3): δ 7.90 (d, J = 8.7 Hz, 2H, H_{Ar}), 7.69 (br s, 1H, OH), 6.95 (d, J = 8.7 Hz, 2H, H_{Ar}), 2.58 (s, 3H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 198.7 (C=O), 161.5 (COH), 131.4 (C_{Ar}), 129.8 (C_{Ar}), 115.7 (C_{Ar}), 26.4 (CH_3). GC-MS: retention time = 9.78 min, MW: 121.1 g/mol. Spectral properties are consistent with literature values [4].

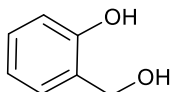
***p*-Nitrophenol**



The reaction was performed in a small, closed reactor tube. After the allotted time (6 h) the reaction mixture was cooled down, acidified with 0.1 M HCl, extracted with EtOAc (3 x 10 mL) and the solvent was removed *in vacuo*. The crude product was flushed through a silica plug, using petroleum spirit/EtOAc (8/2) as eluent, to remove residual DMSO. The product was obtained as a yellow-brown solid. Yield: 117 mg (84 %). ^1H NMR (600 MHz, CDCl_3): δ 8.17 (d, J = 9.1 Hz, 2H, H_{Ar}), 6.94 (d, J = 9.1 Hz, 2H, H_{Ar}), 6.63 (br s, 1H, OH). $^{13}\text{C}\{^1\text{H}\}$ NMR

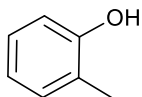
(150 MHz, CDCl₃): δ 161.9 (COH), 141.6 (CN), 126.4 (C_{Ar}), 115.9 (C_{Ar}). GC-MS: retention time = 10.24 min, MW: 139.1 g/mol. Spectral properties are consistent with literature values [4].

2-Hydroxybenzylalcohol



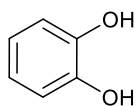
The reaction was performed in a small, closed reactor tube. After the allotted time (6 h) the reaction mixture was cooled down, acidified with 0.1 M HCl, extracted with EtOAc (3 x 10 mL) and the solvent was removed *in vacuo*. The crude product was flushed through a silica plug, using petroleum spirit/EtOAc (6/4) as eluent, to remove residual DMSO. The product was obtained as a white “glitter” solid. Yield: 116 mg (93 %). ¹H NMR (600 MHz, CDCl₃): δ 7.21 (t, *J* = 7.7 Hz, 1H, H_{Ar}), 7.04 (d, *J* = 7.4 Hz, 1H, H_{Ar}), 6.89 (d, *J* = 8.1 Hz, 1H, CH), 6.86 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 5.89 (br s, 1H, OH), 5.27 (br s, 1H, OH), 4.86 (s, 2H, CH₂). ¹³C{¹H} NMR (150 MHz, CDCl₃): δ 156.07 (COH), 129.40 (C_{Ar}), 128.09 (C_{Ar}), 125.27 (C_{Ar}), 120.09 (C_{Ar}), 116.46 (C_{Ar}), 64.22 (CH₂). GC-MS: retention time = 7.80 min, MW: 124.1 g/mol. Spectral properties are consistent with literature values.

o-Cresol



The reaction was performed in a small, closed reactor tube. After the allotted time (15 h) the reaction mixture was cooled down, acidified with 0.1 M HCl, extracted with EtOAc (3 x 10 mL) and the solvent was removed *in vacuo*. The crude product was flushed through a silica plug, using petroleum spirit/EtOAc (8/2) as eluent, to remove residual DMSO. The product was obtained as yellow-brown oil. Yield: 82 mg (76 %). ¹H NMR (600 MHz, CDCl₃): δ 7.14 (d, *J* = 7.4 Hz, 1H, H_{Ar}), 7.09 (t, *J* = 7.7 Hz, 1H, H_{Ar}), 6.86 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 6.78 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 4.74 (br s, 1H, OH), 2.28 (s, 3H, CH₃). ¹³C{¹H} NMR (150 MHz, CDCl₃): δ 153.91 (C_{Ar}), 131.15 (C_{Ar}), 127.23 (C_{Ar}), 123.88 (C_{Ar}), 120.84 (C_{Ar}), 115.02 (C_{Ar}), 15.84 (CH₃). GC-MS: retention time = 5.24 min, MW: 108.2 g/mol. Spectral properties are consistent with literature values [5].

Catechol



The reaction was performed in a small, closed reactor tube. After the allotted time (18 h) the reaction mixture was cooled down, acidified with 0.1 M HCl, extracted with EtOAc (3 x 10 mL) and the solvent was removed *in vacuo*. The crude product was flushed through a silica plug, using petroleum spirit/EtOAc (8/2) as eluent, to remove residual DMSO. The product was obtained as red-pink solid. Yield: 74 mg (68 %). ^1H NMR (600 MHz, CDCl_3): δ 6.88 (m, $J = 5.9$ and 3.6 Hz, 2H, H_{Ar}), 6.82 (m, $J = 5.9$ and 3.5 Hz, 2H, H_{Ar}), 5.26 (br s, 2H, OH). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 143.63 (COH), 121.43 (C_{Ar}), 115.67 (C_{Ar}). GC-MS: retention time = 7.14 min, MW: 110.1 g/mol.

S3.5.1 GC-MS and NMR spectral data of converted phenol products

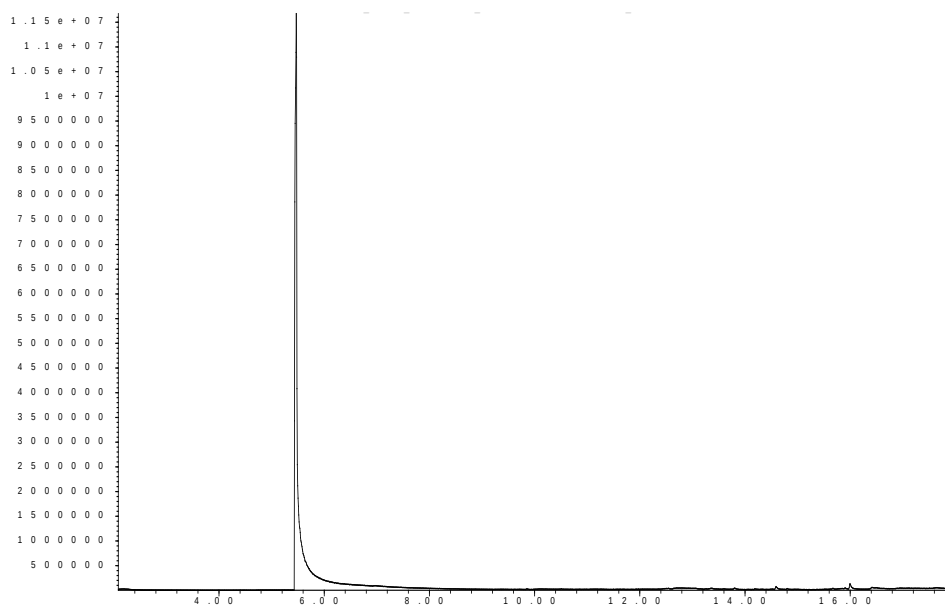


Figure S3.15: GC-MS spectrum for the hydroxylation of 4-iodo or 4-bromotoluene to afford ***p*-cresol** as product.

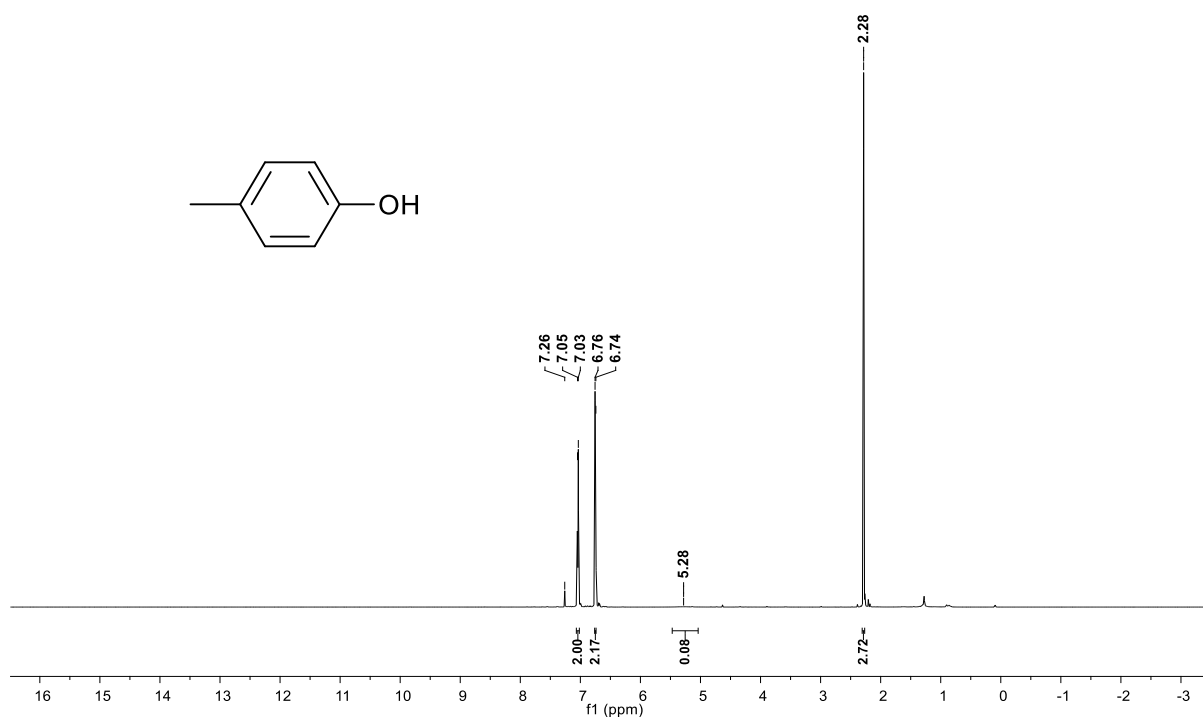


Figure S3.16: ¹H NMR (600 MHz, CDCl₃) spectrum for the hydroxylation of 4-iodo or 4-bromotoluene to afford *p*-cresol as product.

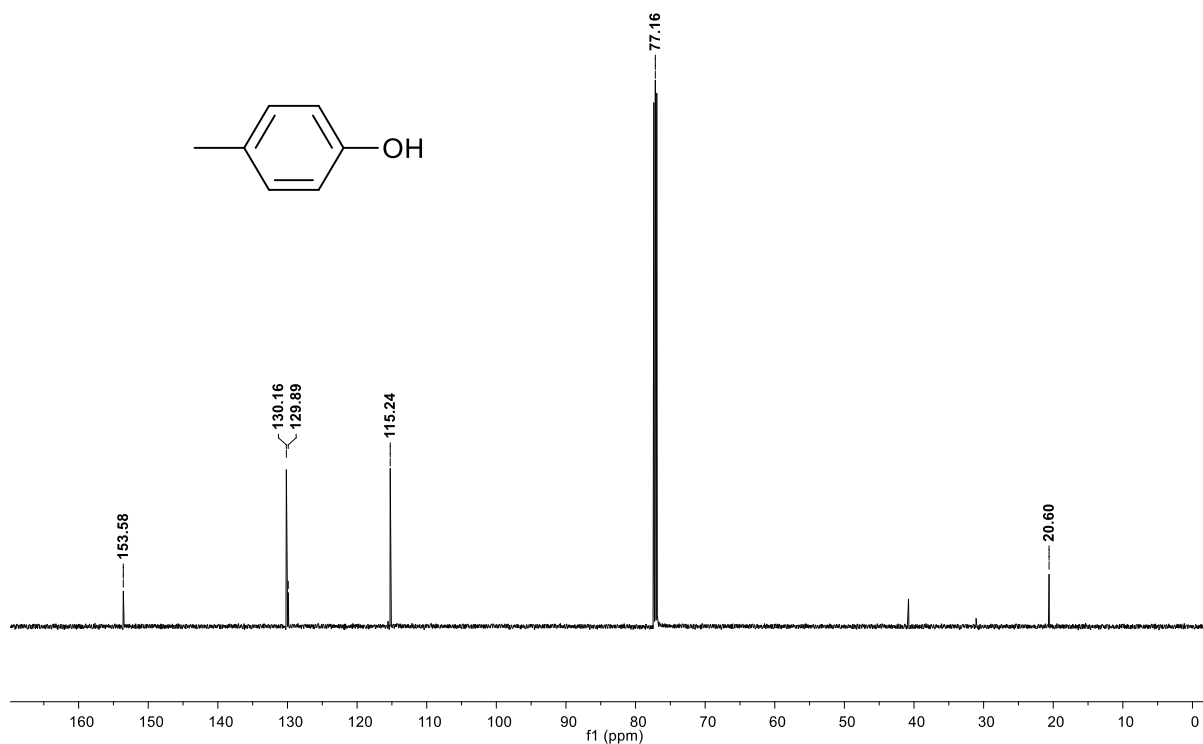


Figure S3.17: ¹³C{¹H} NMR (150 MHz, CDCl₃) spectrum for the hydroxylation of 4-iodo or 4-bromotoluene to afford *p*-cresol as product.

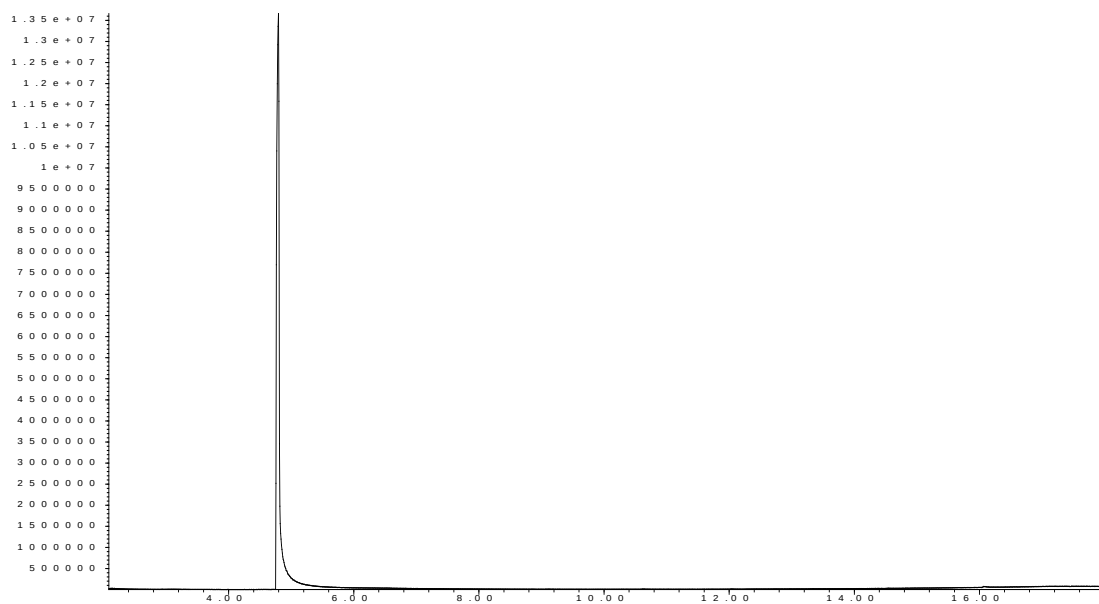


Figure S3.18: GC-MS spectrum for the hydroxylation of iodo- or bromobenzene to afford **phenol** as product.

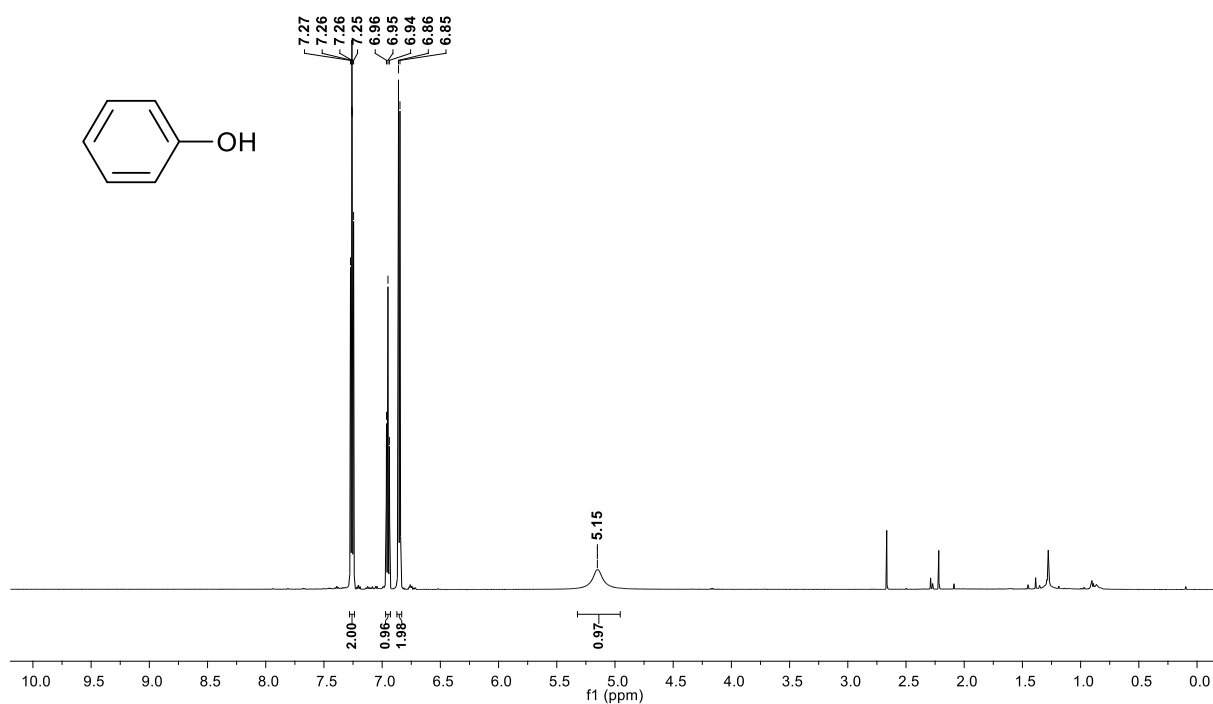


Figure S3.19: ¹H NMR (600 MHz, CDCl₃) spectrum for the hydroxylation of iodo- or bromobenzene to afford **phenol** as product.

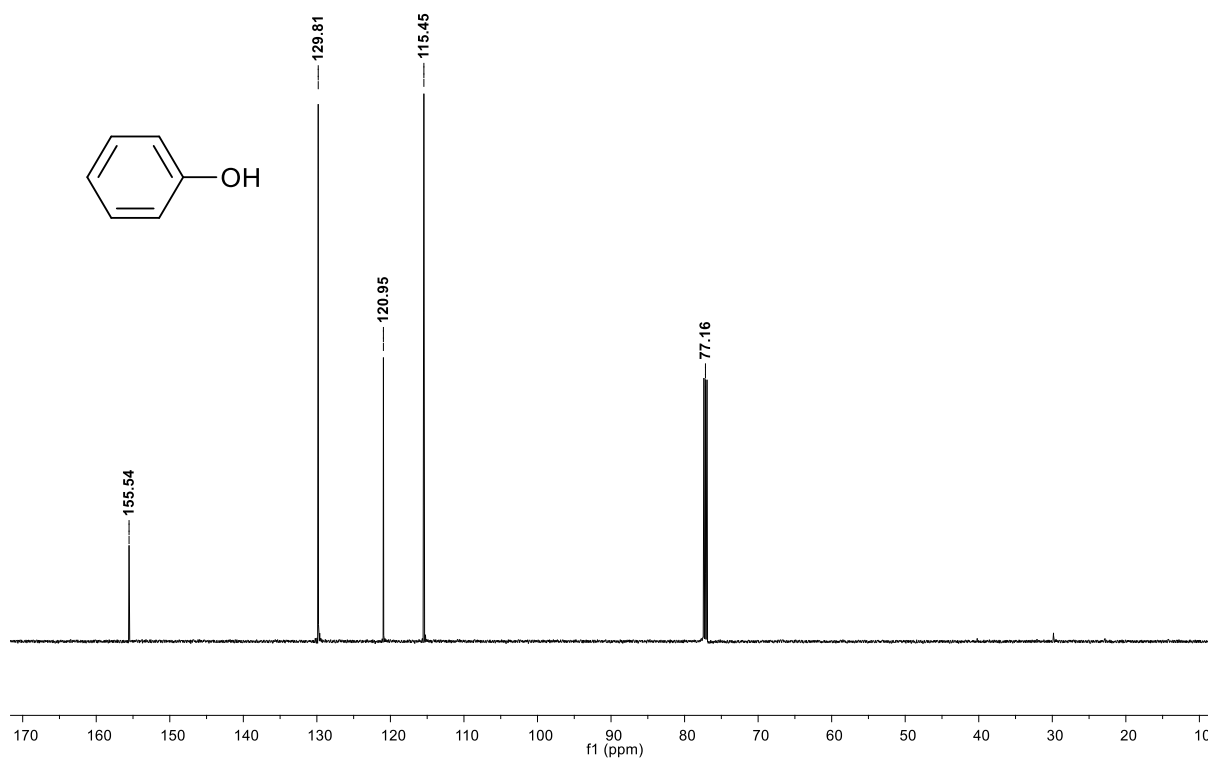


Figure S3.20: $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) spectrum for the hydroxylation of iodo- or bromobenzene to afford **phenol** as product.

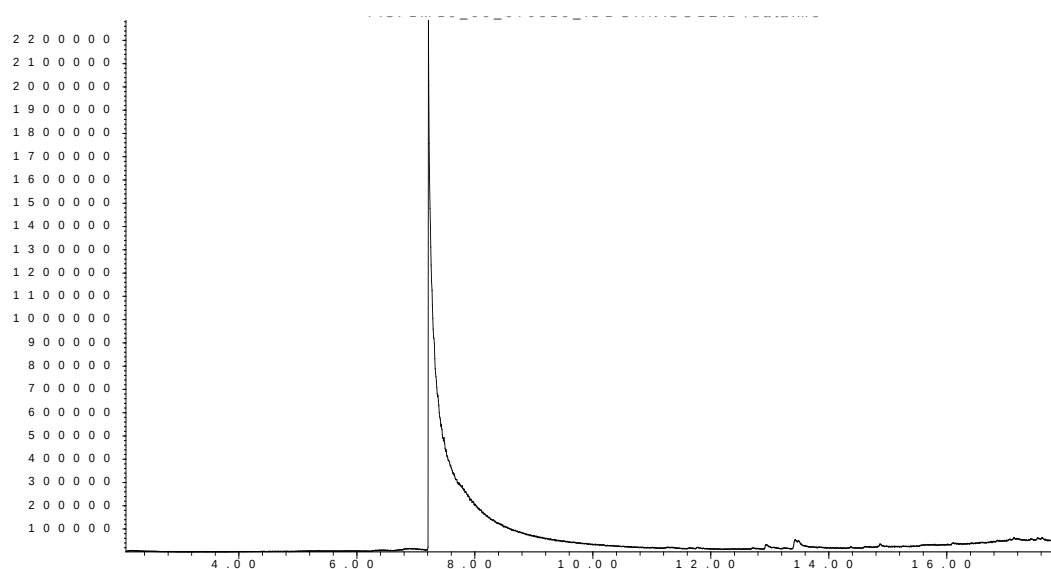


Figure S3.21: GC-MS spectrum for the hydroxylation of 4-iodoanisole to afford *p*-methoxyphenol (**mequinol**) as product.



Figure S3.22: ¹H NMR (600 MHz, CDCl₃) spectrum for the hydroxylation of 4-iodoanisole to afford *p*-methoxyphenol (mequinol) as product.

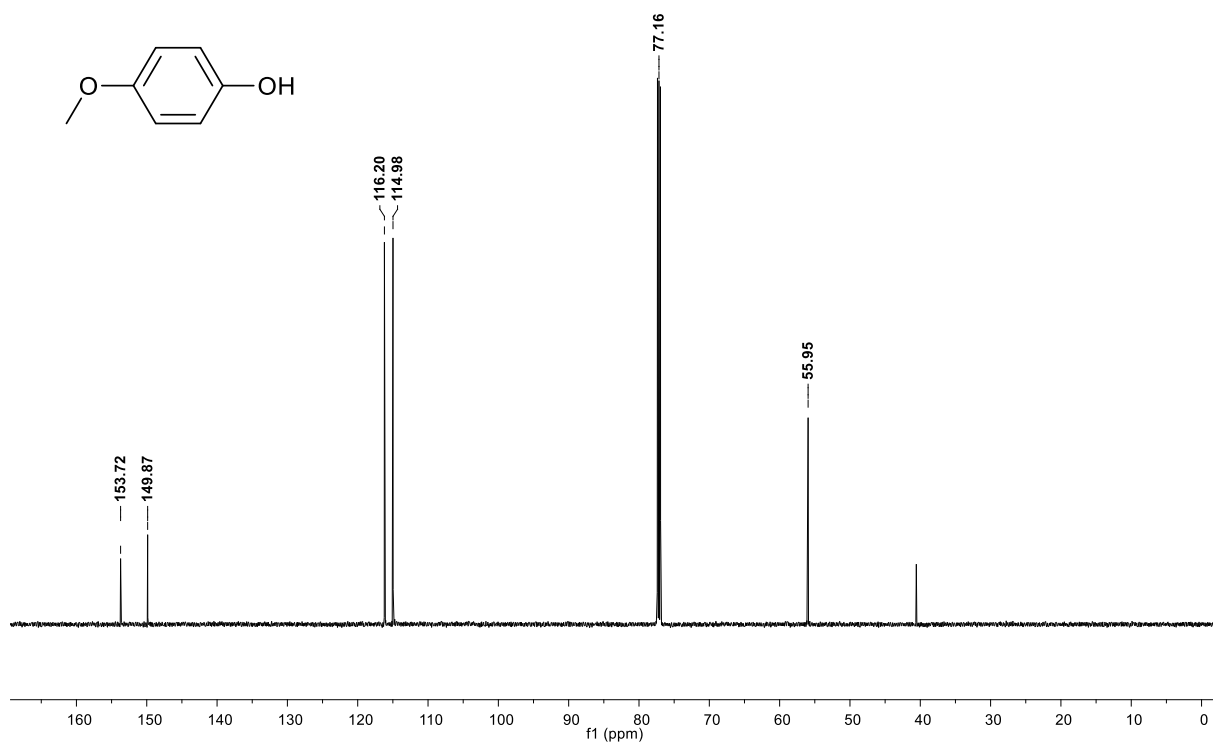


Figure S3.23: ¹³C{¹H} NMR (150 MHz, CDCl₃) spectrum for the hydroxylation of 4-iodoanisole to afford *p*-methoxyphenol (mequinol) as product.

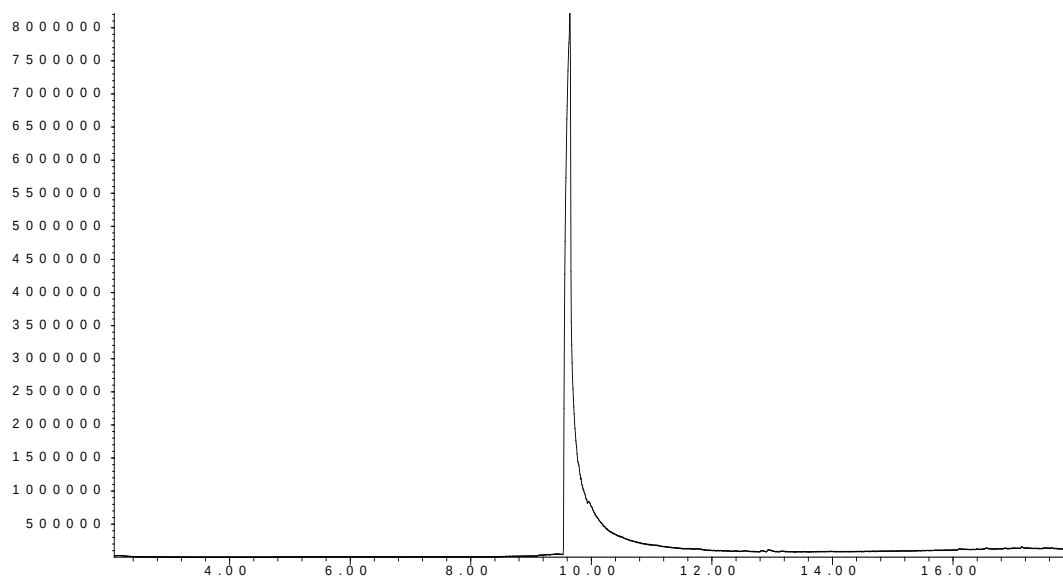


Figure S3.24: GC-MS spectrum for the hydroxylation of 4-iodo- or 4-bromoacetophenone to afford **piceol** as product.

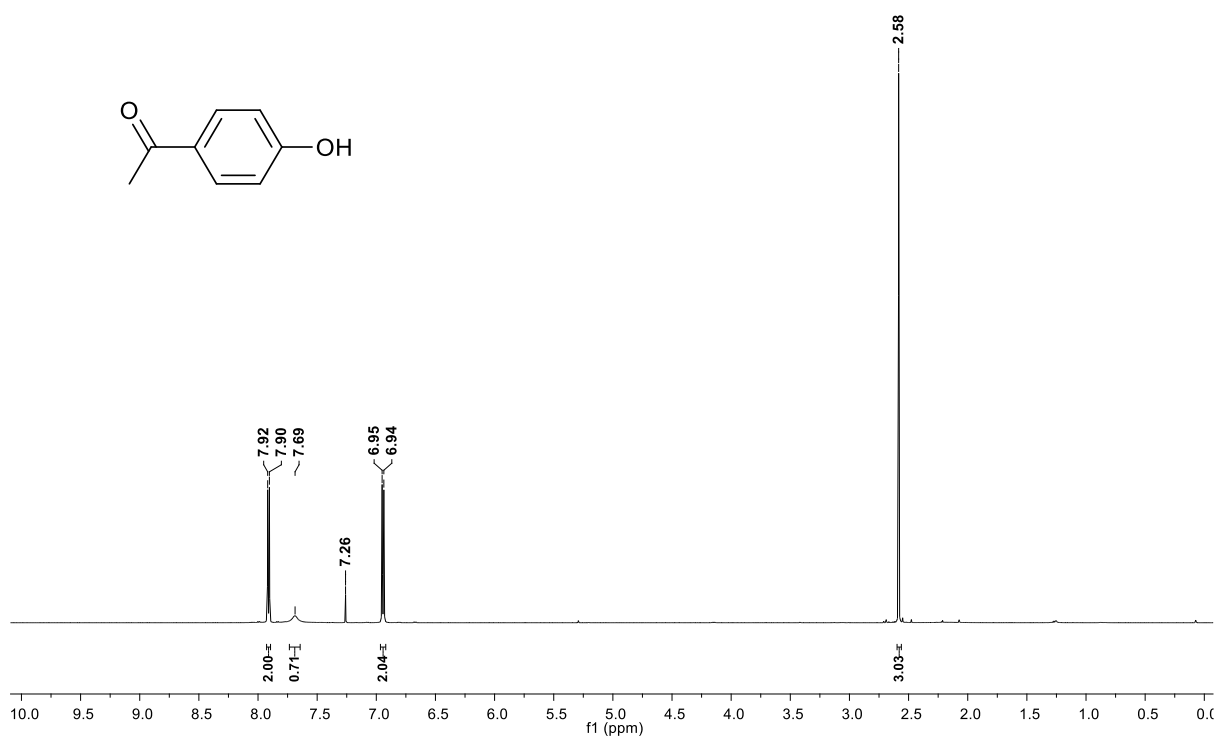


Figure S3.25: ¹H NMR (600 MHz, CDCl₃) spectrum for the hydroxylation of 4-iodo- or 4-bromoacetophenone to afford **piceol** as product.

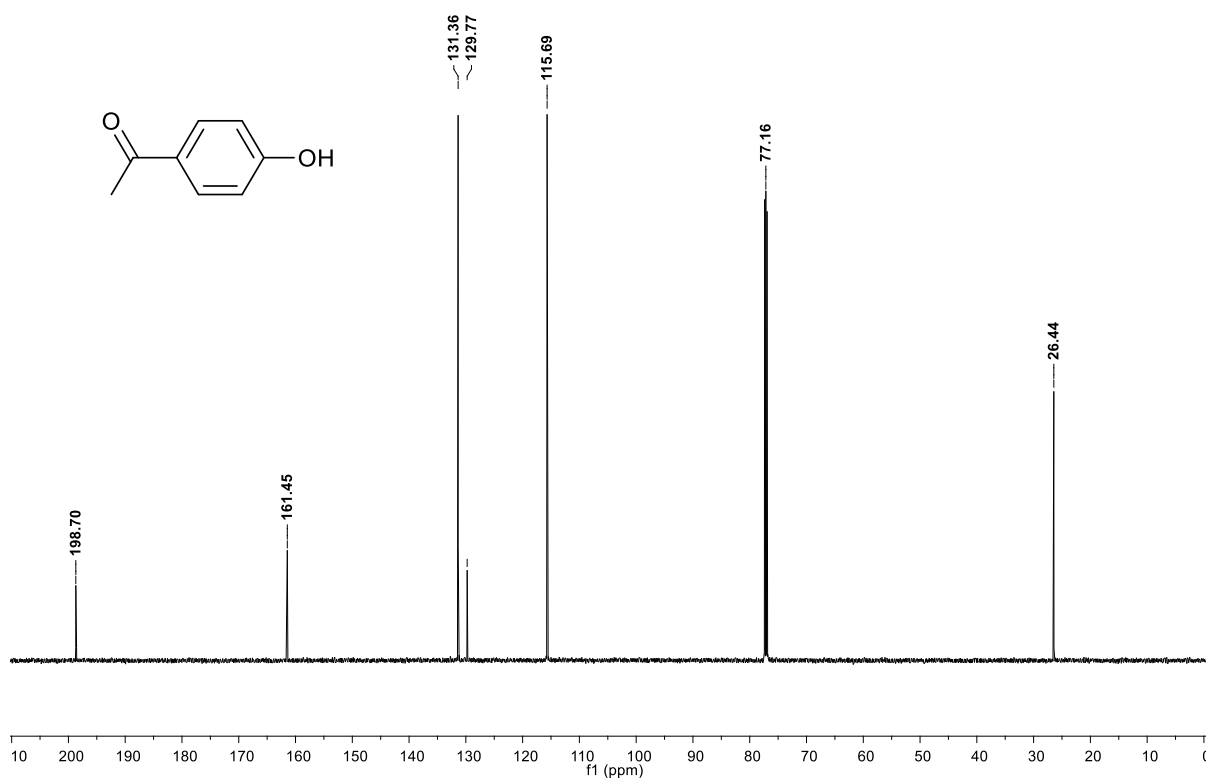


Figure S3.26: $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) spectrum for the hydroxylation of 4-iodo- or 4-bromoacetophenone to afford **piceol** as product.

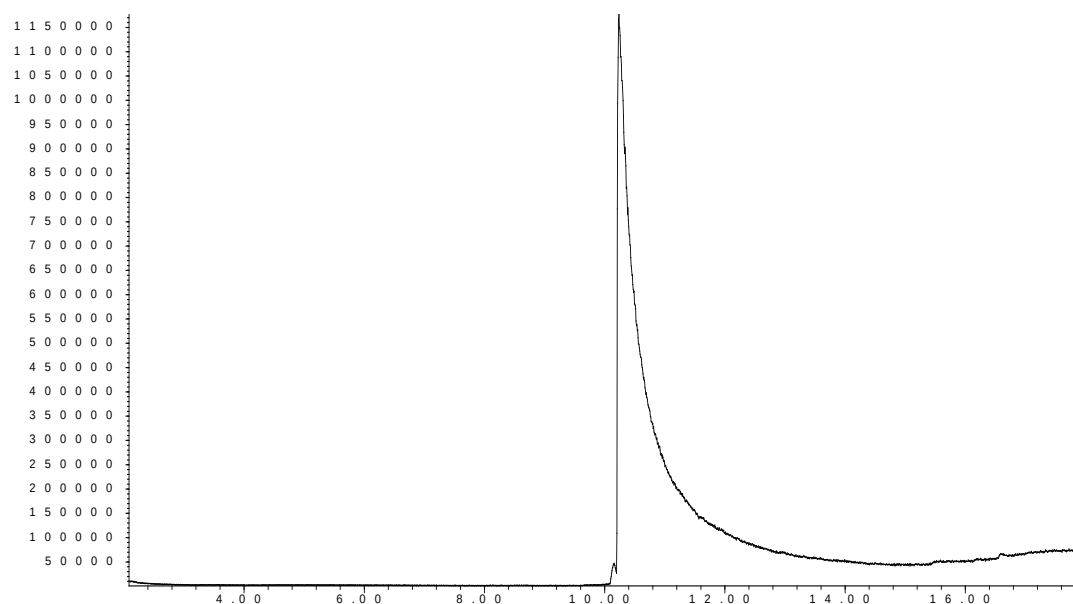


Figure S3.27: GC-MS spectrum for the hydroxylation of 1-iodo-4-nitrobenzene to afford *p*-nitrophenol as product.

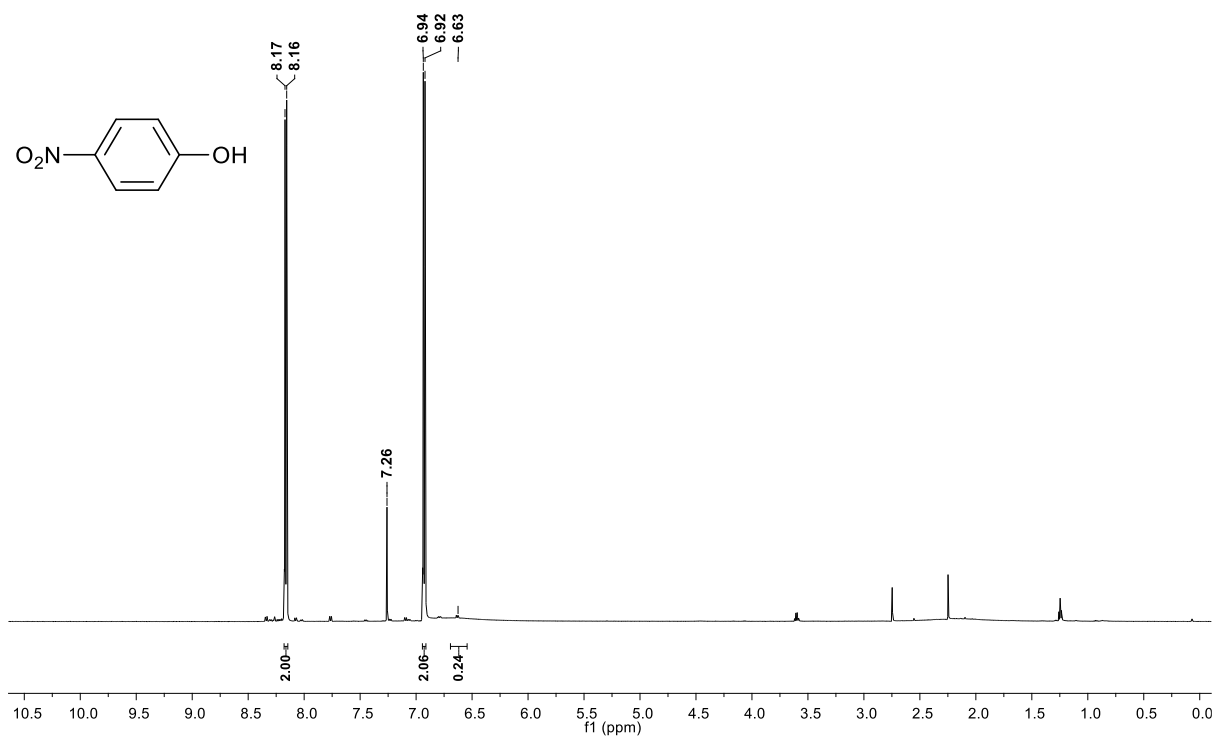


Figure S3.28: ¹H NMR (600 MHz, CDCl₃) spectrum for the hydroxylation of 1-iodo-4-nitrobenzene to afford *p*-nitrophenol as product.

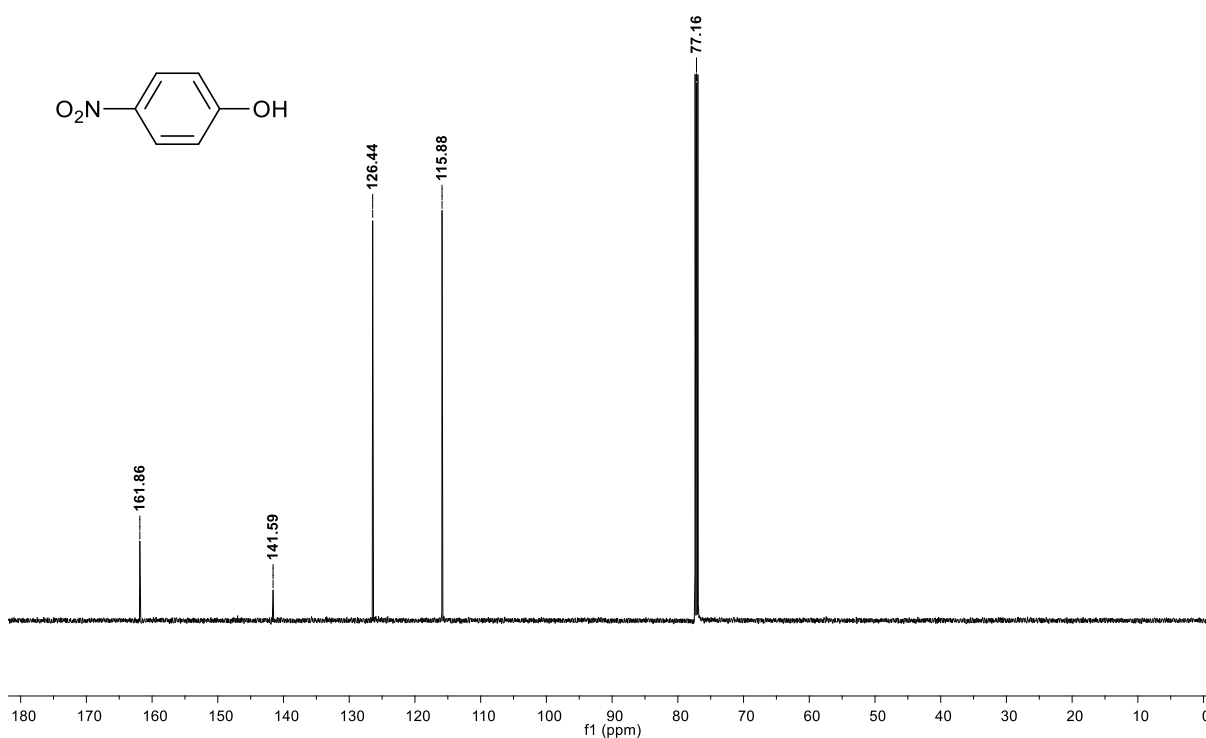


Figure S3.29: ¹³C{¹H} NMR (150 MHz, CDCl₃) spectrum for the hydroxylation of 1-iodo-4-nitrobenzene to afford *p*-nitrophenol as product.

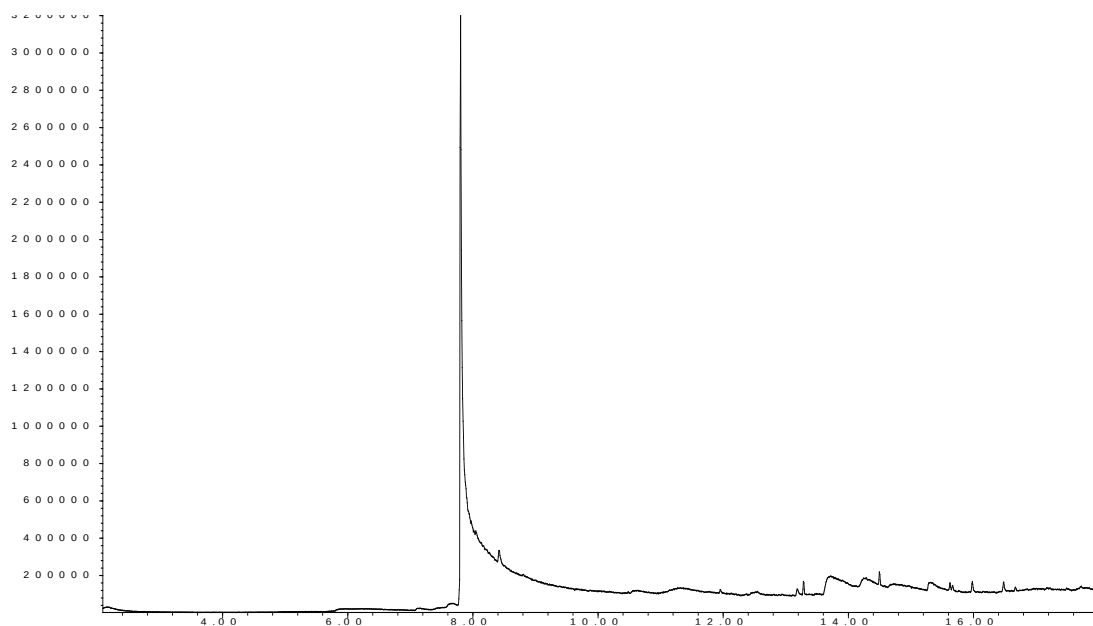


Figure S3.30: GC-MS spectrum for the hydroxylation of 2-iodobenzyl alcohol to afford **2-hydroxybenzyl alcohol** as product.

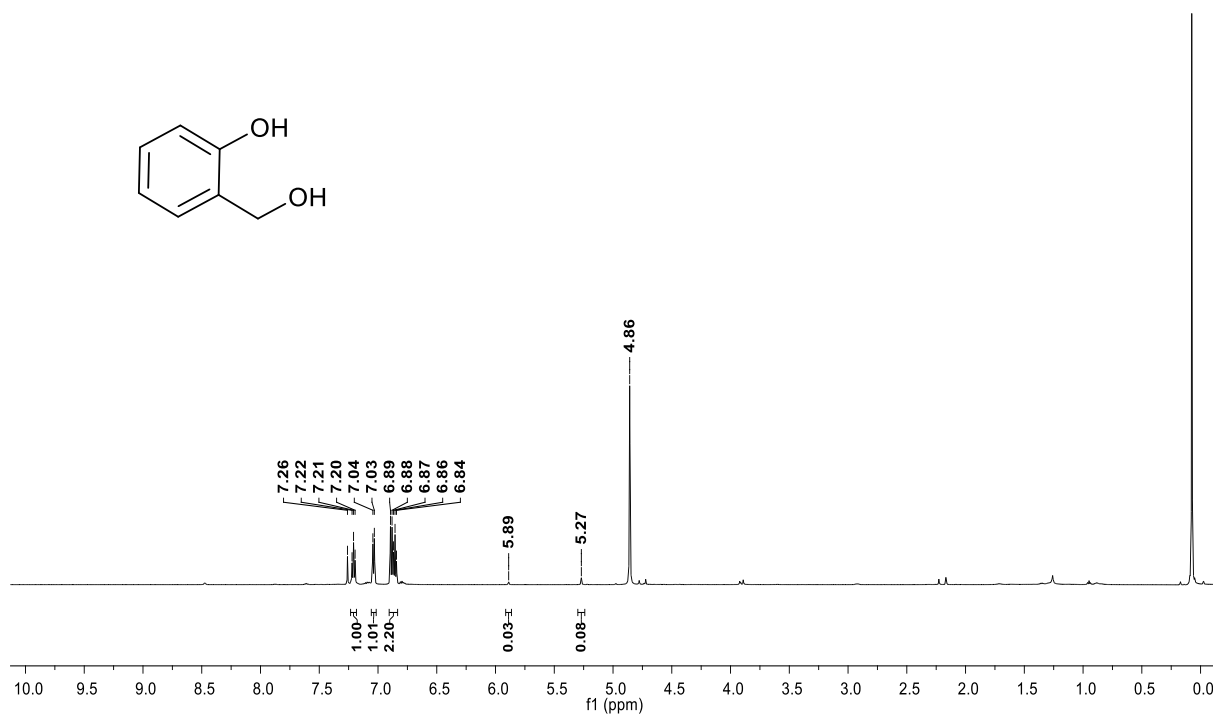


Figure S3.31: ¹H NMR (600 MHz, CDCl₃) spectrum for the hydroxylation of 2-iodobenzyl alcohol to afford **2-hydroxybenzyl alcohol** as product.

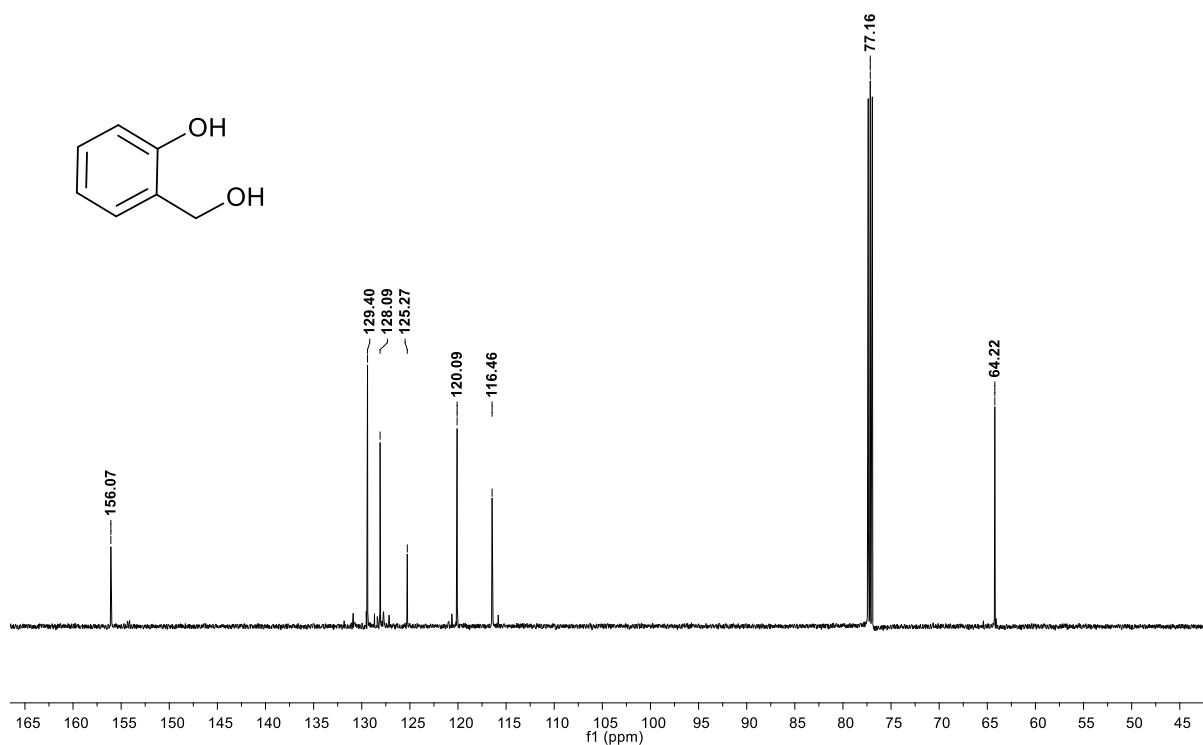


Figure S3.32: $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) spectrum for the hydroxylation of 2-iodobenzyl alcohol to afford **2-hydroxybenzyl alcohol** as product.

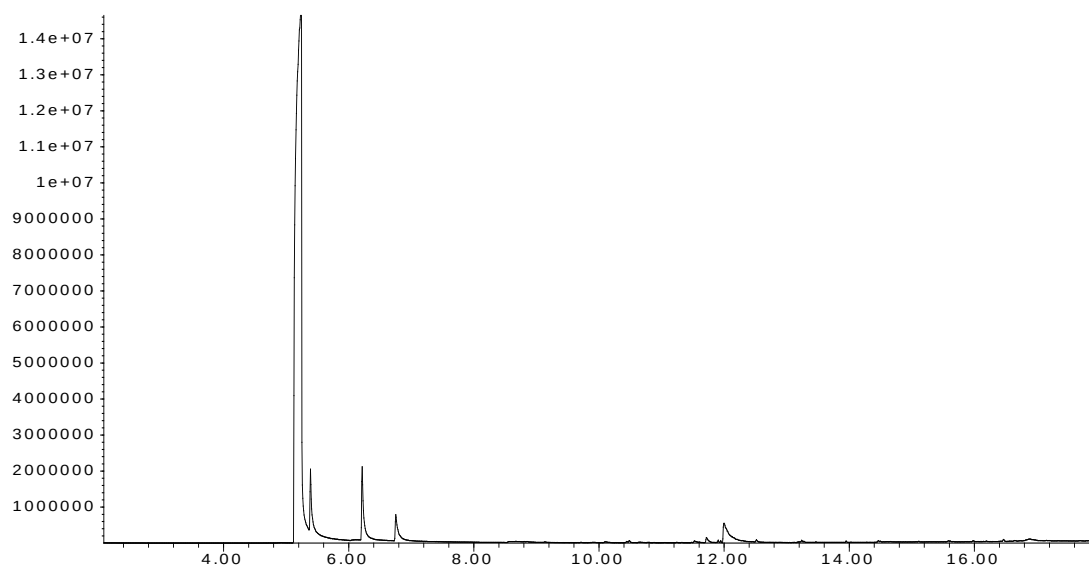


Figure S3.33: GC-MS spectrum for the hydroxylation of 2-iodotoluene to afford **o-cresol** as product.

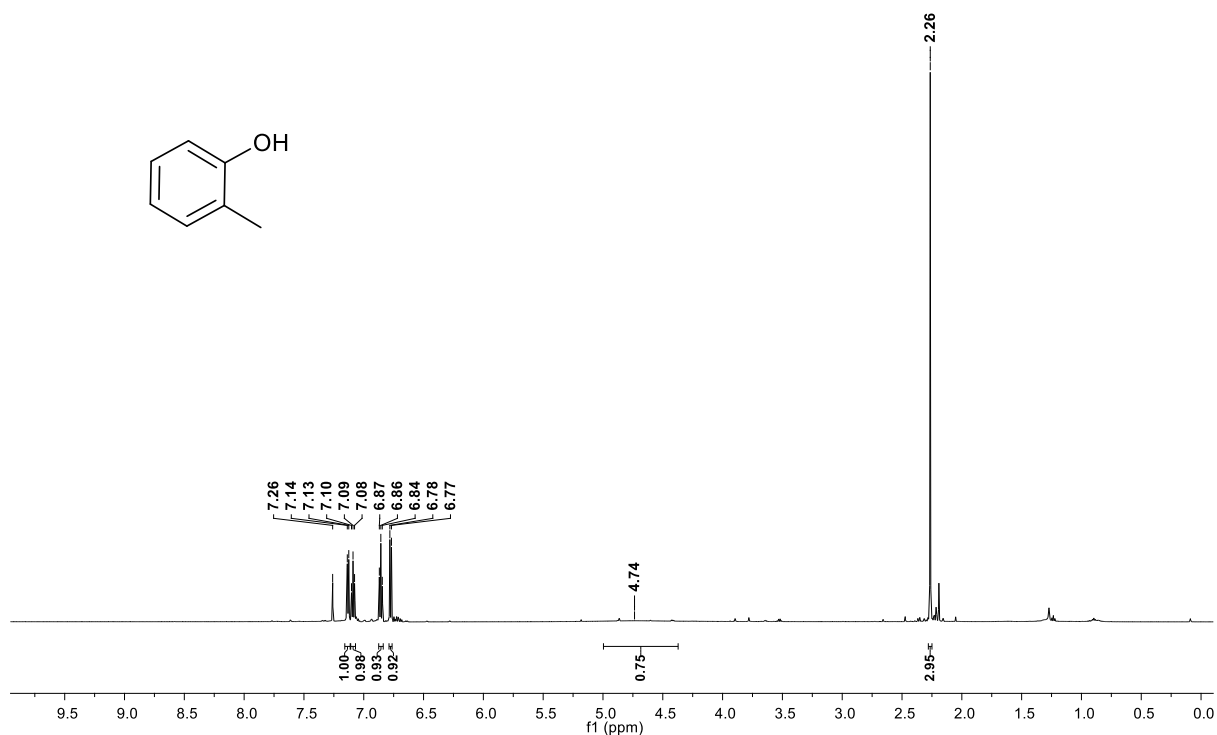


Figure S3.34: ¹H NMR (600 MHz, CDCl₃) spectrum for the hydroxylation of 2-iodotoluene to afford *o*-cresol as product.

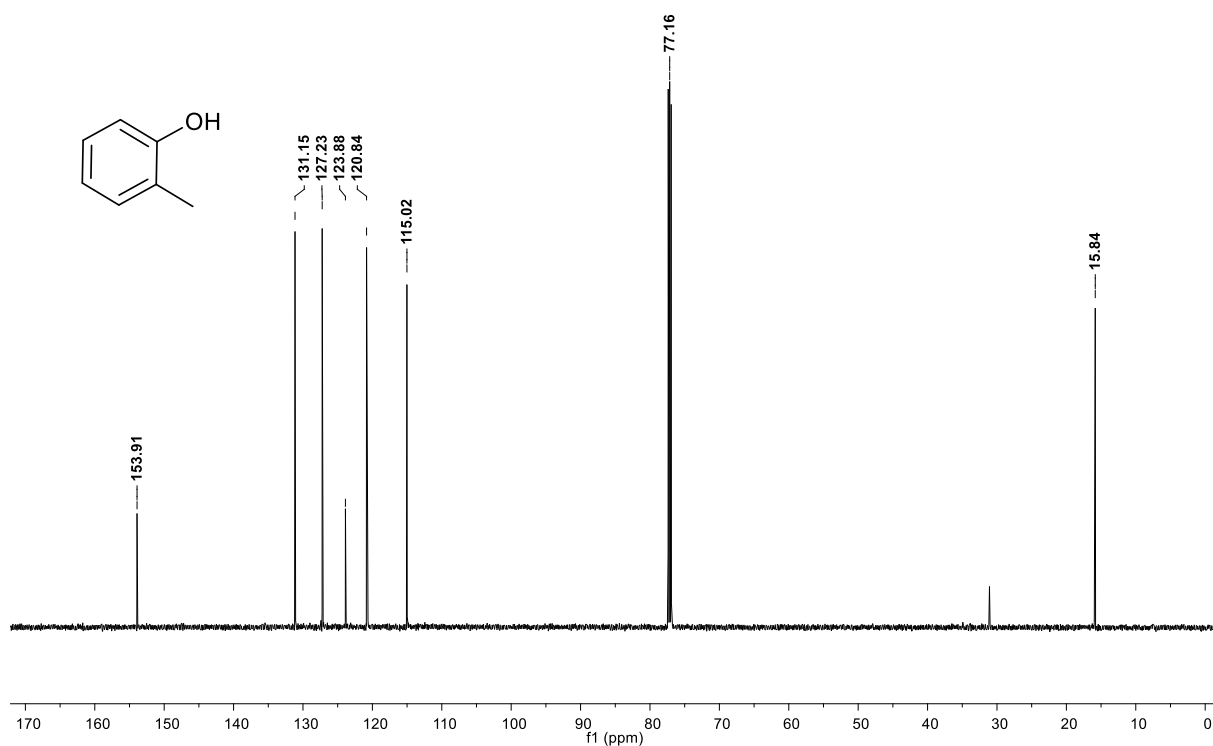


Figure S3.35: ¹³C{¹H} NMR (150 MHz, CDCl₃) spectrum for the hydroxylation of 2-iodotoluene to afford *o*-cresol as product.

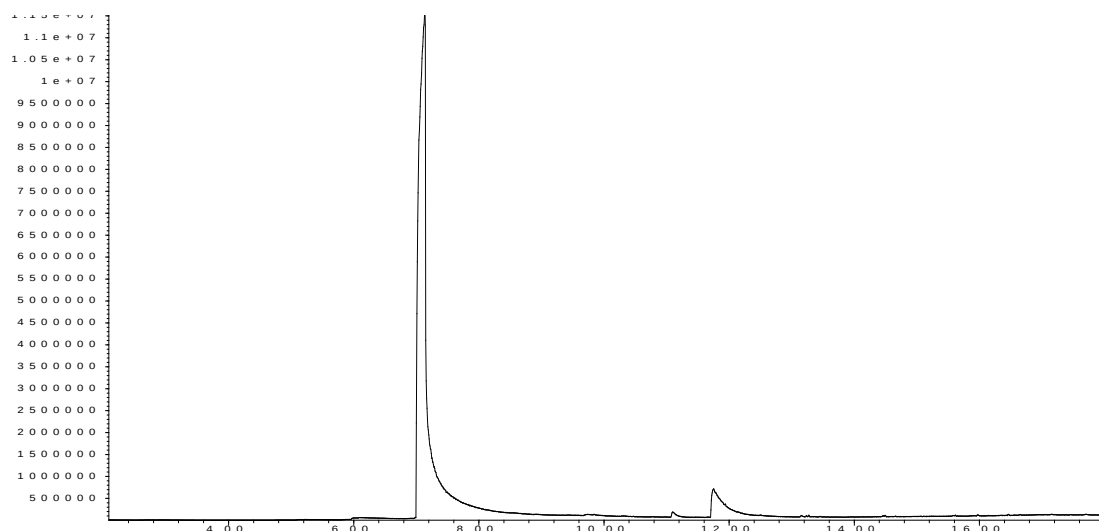


Figure S3.36: GC-MS spectrum for the hydroxylation of 2-bromophenol to afford **catechol** as product. An extra signal was observed, consistent with the coordination of two substrates to afford a by-product.

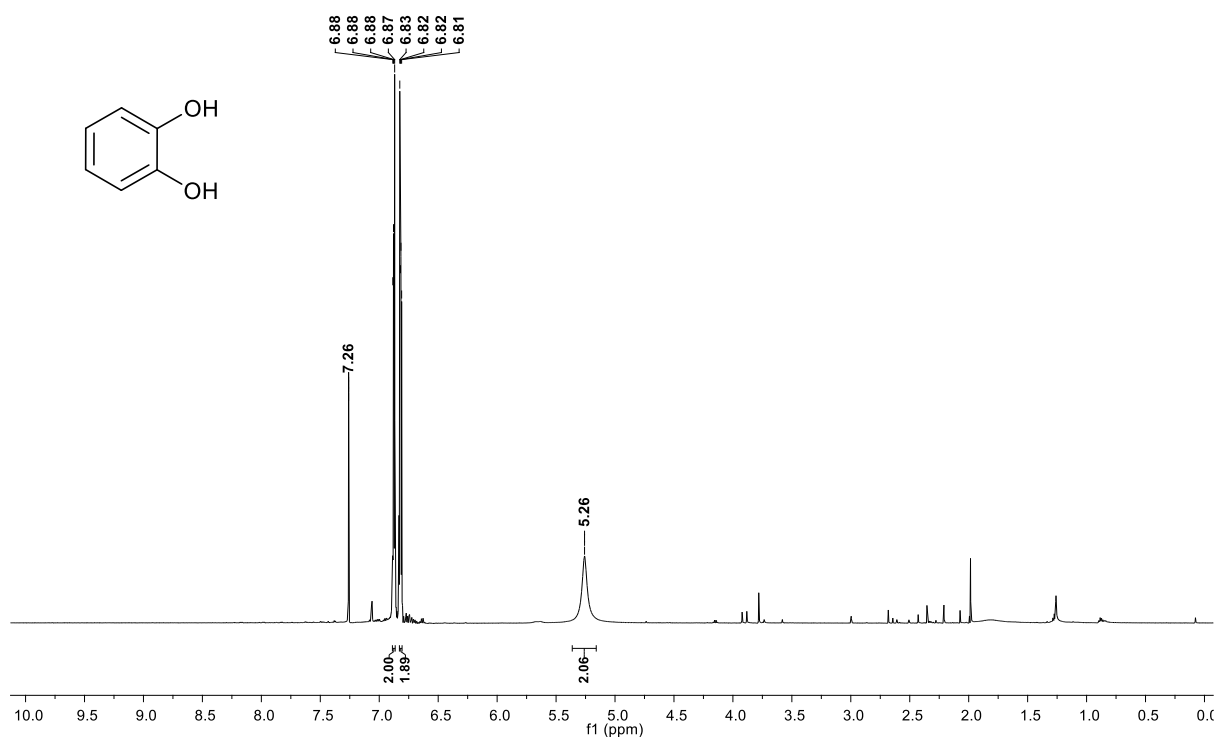


Figure S3.37: ¹H NMR (600 MHz, CDCl₃) spectrum for the hydroxylation of 2-bromophenol to afford **catechol** as product. Some impurities are present, but there is no clear evidence for the presence of the by-product.

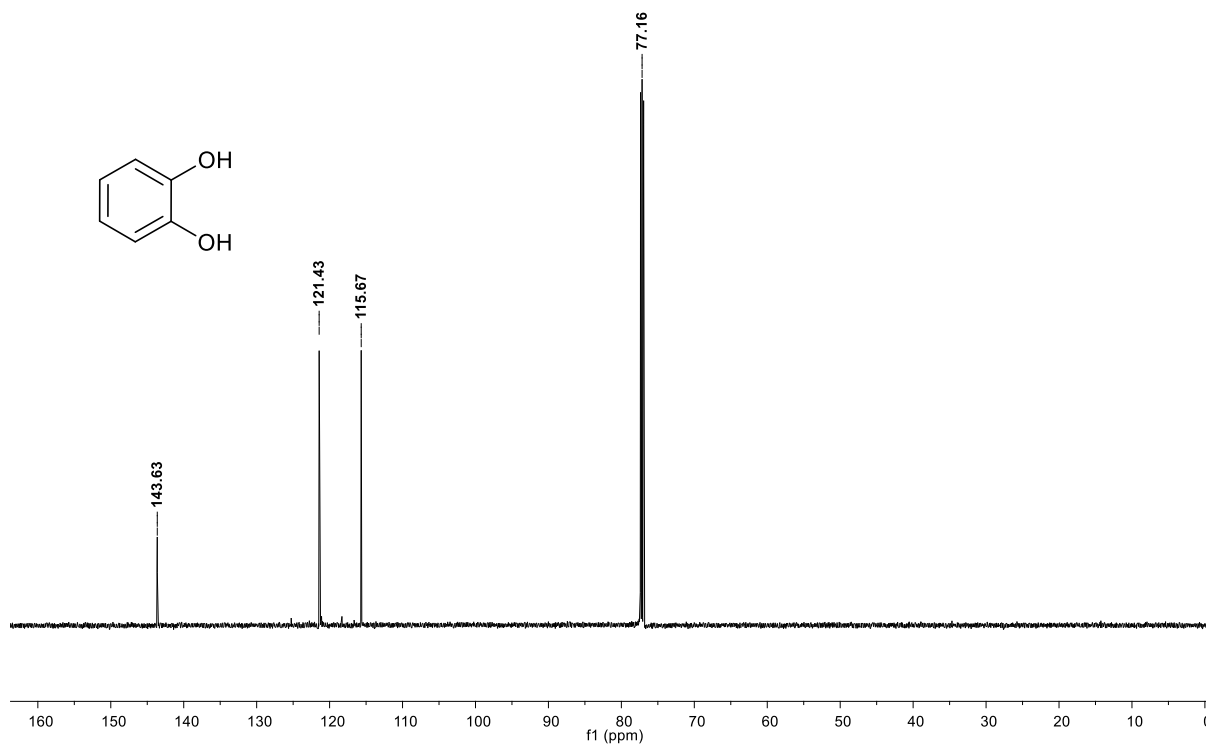


Figure S3.38: $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) spectrum for the hydroxylation of 2-bromophenol to afford **catechol** as product. Some impurities are present, but there is no clear evidence for the presence of the by-product.

S3.6 References

- [1] H.E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.*, 62 (1997) 7512-7515.
 - [2] J.N. Hamann, F. Tuzcek, *Chem. Commun.*, 50 (2014) 2298-2300.
 - [3] O. Songis, P. Boulens, C.G. Benson, C.S. Cazin, *RSC Adv.*, 2 (2012) 11675-11677.
 - [4] D. Zhao, N. Wu, S. Zhang, P. Xi, X. Su, J. Lan, J. You, *Angew. Chem. Int. Ed.*, 48 (2009) 8729-8732.
 - [5] A. Tlili, N. Xia, F. Monnier, M. Taillefer, *Angew. Chem.*, 121 (2009) 8881-8884.
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Highly efficient alkane peroxidation mediated by a copper(II)/pyrazolylpyridineamine catalyst system

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Pyrazolylpyridineimine (imine-**L01** and imine-**L02**) and -amine ligands (**L01-L04**), in combination with a Cu^I- or Cu^{II}-precursor and H₂O₂ as the oxidant, were employed in the peroxidation of cyclohexane with alcohol selectivity (44 %) and exceptional product yields of > 90 % in 3 h, which is a significant improvement on the product yields obtained by the benchmark catalyst system. The optimised reaction conditions were identified: CuCl₂·2H₂O and ligand **L03** (1 mol%), substrate (1 mmol), H₂O₂ (8 equiv.) and MeCN (3 mL), resulting in CyOOH as the major product. Our optimised catalyst system could be used for the successful peroxidation of various cyclic and linear alkanes with good to excellent product yields of 71 to 94 % and 75 %, respectively; however, the selectivity was shifted to the corresponding ketone products (28 to 64 %) for the cycloalkanes. Kinetic assessments for the rate of CyOOH formation exhibit a first-order dependence on [LCu] and [H₂O₂], while a zero-order dependence on [substrate] was obtained since cyclohexane is not involved during the rate-determining step. The proposed formation of C- and O-centred radical species was evaluated by conducting peroxidation reactions in the presence of the radical trapping agents, carbon tetrachloride (CCl₄) and 2,4-di-*tert*-butylphenol and significantly lower product yields of 29 and 33 % were obtained, respectively. Electrochemical studies support the reversible transformation between Cu^{II} and Cu^I species, while Cu^{III} species were only observed under applied potential. Hydrogen peroxide reduction resulted in the formation of H₂O, which undergoes Cu^{II}-catalysed electrochemically promoted oxidation to O₂, with the regeneration of Cu^I species. The kinetic, radical confirmation and electrochemical studies support the formation of C- and O-centred radical species as well as the formation of LCu^{II}-hydroxyl (LCu^{II}-OH) and LCu^{II}-oxyl (LCu^{II}-O•) species during the rate-determining step, which is consistent with our proposed mechanistic pathway.

Keywords: peroxidation, pyrazolylpyridineimine and -amine ligands, copper(II) catalysis, alkane peroxidation, radical traps, mechanistic pathway.

4.1 Introduction

The oxidation of alkanes is the first step in several industrial chemical syntheses; however, harsh reaction conditions such as high temperatures, the use of strong oxidants and stoichiometric additives are often required [1]. These reactions usually lead to poor selectivity, low yields and undesired environmental and economic costs. Several transition metals such

Chapter 4: Highly efficient alkane peroxidation mediated by a copper(II)/pyrazolylpyridineamine catalyst system

as iron, manganese and vanadium have been previously employed as catalysts for these peroxidation reactions [2-10]. However, the inclusion of copper to this list has received great attention due to the low costs involved as well as its widespread availability in nature.

One of the first examples of a Cu-based catalyst system was reported by Barton and co-workers, where they combined copper powder, pyridine, acetic acid and H_2O_2 [11]. A low product yield of < 5 % was obtained for cyclohexane peroxidation, and cyclohexanone (CyO) was identified as the major product, while cyclohexanol (CyOH) was also observed. Sawyer and co-workers investigated the activation of either H_2O_2 or *tert*-butyl hydroperoxide (TBHP) in combination with their $[\text{Cu}^{\text{I}}(\text{bpy})_2]\text{ClO}_4$ (bpy: 2,2'-bipyridine; ClO_4 : perchlorate) catalyst system in an acetonitrile (MeCN)/pyridine (ratio of 4:1) solvent system. They observed an increase in the efficiency of cyclohexane peroxidation when employing TBHP as the oxidant, and they were able to improve on the product yield (< 15 %) in 3 h, which consists of CyOH and CyO [12]. A further improvement in the product yield (39 %) was obtained by Pombeiro and co-workers when they evaluated the tetranuclear Cu^{II} complex, $([\text{Cu}_4(\text{tea})_4(\text{B}\{\text{OH}\})_4(\mu\text{-O})][(\text{BF}_4)_2]$; tea: triethanolamine), in combination with H_2O_2 and nitric acid (HNO_3) and they obtained a product distribution (CyOH/CyO) of 25/14 % [13, 14]. Pettinari and co-workers reported the application of trinuclear Cu^{II} complexes, such as $[\text{Cu}_3(\mu_3\text{-OH})(\mu\text{-pz})_3(\text{HCO}_2)_2(\text{Hpz})_2]\cdot\text{H}_2\text{O}$, bearing anionic pyrazolate (pz) and carboxylate ligands, in combination with H_2O_2 and HNO_3 [15]. However, they were unable to improve on previous results for cyclohexane peroxidation, since a product yield of 32 % (CyOH/CyO: 23/9 %) was obtained. Moreover, Pérez and co-workers evaluated mononuclear $[\text{Tp}^{\text{X}}\text{Cu}(\text{NCMe})]$ (X: Br_3 , Br, Me_3 , Me_2 or Ph) complexes, bearing tris(1,2,3-tribromopyrazolyl)borate ligands, in combination with H_2O_2 for the peroxidation of cyclohexane, and they obtained a product yield of 25 % [16]. Even though CyOH (9 %) and CyO (14.5 %, major product) were obtained as peroxidation products, they also found traces of the two dehydrogenation by-products, cyclohexene (1 %) and cyclohexene oxide (0.5 %).

These Cu-based catalyst systems usually require high temperatures, display considerably low product yields and require expensive additives. Recently, Garcia-Bosch and co-workers demonstrated the ability of tetrakis(copper(I) hexafluorophosphate $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$, in combination with either (2*R*,2'*R*)-1,1'-bis(2-pyridinylmethyl)-2,2'-bipyrrolidine [(*R,R*)-BPBP] or tris(2-pyridylmethyl)-amine (TMPA), and H_2O_2 for cyclohexane peroxidation [17]. Their $[\text{Cu}(\text{R,R})\text{-BPBP}]\text{PF}_6/\text{H}_2\text{O}_2$ catalyst system showed remarkable efficiency with an improved product yield of 56 % (CyOH/CyO: 50/6 %), which was identified as the current benchmark catalyst system. More recently, Kirillov and co-workers reported on the application of mono- and binuclear Cu^{II} complexes, as well as a 1D coordination polymer for peroxidation reactions

at a lower reaction temperature and shorter reaction time [18]. They employed $[\text{Cu}_2(\mu\text{-hbdea})_2(\mu\text{-bdca})]_n \cdot (\text{hbdea}: N\text{-butyldiethanolamine}; \text{H}_2\text{bdca}: 4,4'\text{-biphenylcarboxylic acid})$, in combination with H_2O_2 and trifluoroacetic acid (TFA) for cyclohexane peroxidation and obtained a product yield of 21 % (CyOH/CyO: 11/10 %) in 1 h, while no improvement was possible in longer reaction times. As a result, there is still a growing demand to develop an alternative Cu-based catalyst system for the peroxidation of cyclic and linear alkanes with improved product yields, without the need for an inert atmosphere.

Pyrazolypyridineamine ligands, in combination with a nickel catalyst, have been employed in the catalytic oligomerisation and polymerisation of ethylene [19, 20]. More recently, we reported the successful application of similar novel pyrazolypyridineamine ligands, in combination with a copper catalyst, for the hydroxylation of aryl iodides and bromides [21]. These pyrazolypyridineamine ligands have not been employed in peroxidation reactions before, and therefore we want to expand the potential application thereof. Herein, we report the evaluation of pyrazolypyridineimine, (E)-N-(2-(1H-pyrazol-1-yl)ethyl)-1-(pyridine-2-yl)methanimine (imine-**L01**), (E)-N-(2-(3,5-dimethyl-1H-pyrazol-1-yl)ethyl)-1-(pyridine-2-yl)methanimine (imine-**L02**), and -amine ligands, 2-(1H-pyrazol-1-yl)-N-(pyridine-2-ylmethyl)ethan-1-amine (**L01**), 2-(3,5-dimethyl-1H-pyrazol-1-yl)-N-(pyridine-2-ylmethyl)ethan-1-amine (**L02**), N-methyl-2-(1H-pyrazol-1-yl)-N-(pyridine-2-ylmethyl)ethan-1-amine (**L03**) and 2-(3,5-dimethyl-1H-pyrazol-1-yl)-N-methyl-N-(pyridine-2-ylmethyl)ethan-1-amine (**L04**, Scheme 4.1), in combination with copper, as *in situ* formed pre-catalysts for the peroxidation of various cyclic and linear alkanes. Kinetic studies were performed to evaluate the influence of varying $[\text{LCu}]$, $[\text{H}_2\text{O}_2]$ and $[\text{substrate}]$ on the rate of cyclohexyl hydroperoxide (CyOOH) formation during the peroxidation reaction. The effect of radical trapping agents on the obtained product yields was evaluated to indicate the formation of radical species and to investigate the nature of the active metal species. Electrochemical studies were employed to investigate the effect of various pyrazolypyridineimine or -amine ligands and the addition of H_2O_2 on the redox potentials. Our results allow us to propose a plausible mechanistic pathway for hydrocarbon peroxidation reactions mediated by our catalyst system.

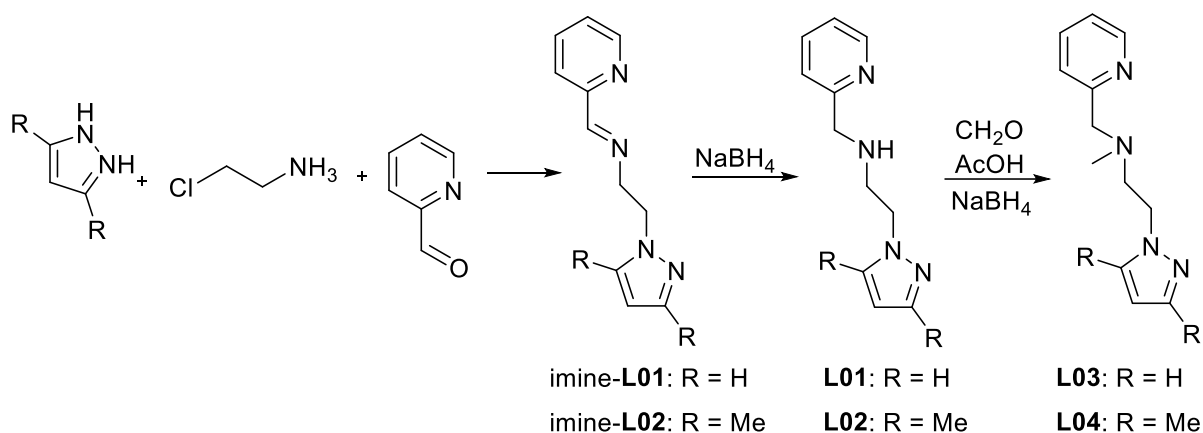
4.2 Results and discussion

4.2.1 Synthesis of the pyrazolypyridineimine and -amine ligands

Various pyrazolypyridineimine (imine-**L01** and imine-**L02**) and -amine ligands, **L01-L04**, were successfully synthesised via our previously reported synthesis route, which involves Schiff base condensation (imine-**L01** and imine-**L02**), followed by reductive amination (**L01-L02**) and methylation (**L03-L04**) reaction steps (Scheme 4.1) [21]. The Cu-based pre-catalysts were

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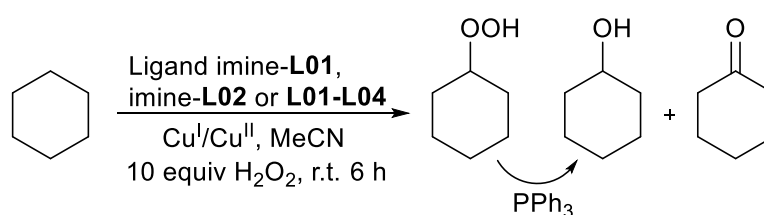
formed *in situ* prior to the reaction, and therefore no isolation of the copper complexes was required.



Scheme 4.1: The pyrazolylpyridineimine (imine-L01 and imine-L02) and -amine ligands (L01-L04) were successfully synthesised via our previously reported synthesis route [21].

4.2.2 Optimisation of the (L01)CuCl₂·2H₂O/H₂O₂ catalyst system

Cyclohexane was employed as the model substrate for peroxidation reactions, using previously reported reaction conditions (Scheme 4.2) [22, 23]. The peroxidation of cyclohexane resulted in three products, namely CyOOH (major), CyOH and CyO (Figure S4.1 in the Supporting Information). Cyclohexyl hydroperoxide can then be further converted to the alcohol (major product) and ketone products upon the addition of an excess of triphenylphosphine (PPh₃) to the peroxidation reactions [24]; however, complete conversion was not possible.



Scheme 4.2: A representative Cu-based catalyst system for the peroxidation of cyclohexane to afford CyOOH, CyOH and CyO as products.

We evaluated various pyrazolylpyridineimine (imine-L01 and imine-L02) and -amine ligands (L01-L04) in combination with [Cu(MeCN)₄]OTf (Table 4.1, entries 1-6 and Figure S4.2 in the Supporting Information). Good product yields of 73 to 75 % were obtained when employing the pyrazolylpyridineimine ligands, imine-L01 and imine-L02 (Table 4.1, entries 1 and 2); however, when replacing it with their secondary and tertiary amine analogues, slightly higher product yields of 80 to 89 % were possible (Table 4.1, entries 3-6). Similarly, alcohol selectivity

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increased with 14 to 18 % when the pyrazolypyridineimine ligands (imine-**L01** and imine-**L02**; 22 to 24 %) were replaced with their secondary and tertiary amine analogues (**L01**, **L03** and **L04**; 36 to 40 %), except for the lower alcohol selectivity of 28 % observed when employing ligand **L02**. Furthermore, the substituents on the ethyl-linked *N*-atom do not have a major influence on the peroxidation of cyclohexane, since similar product yields of 85 to 89 % were obtained for ligands **L01** and **L03** (Table 4.1, entries 3 and 5) [21, 25]. The steric and electronic effects of the methyl groups on the pyrazole ring as well as the lower electrophilicity of the copper metal centre have a negative influence on the peroxidation reaction since decreases of 5 to 12 % were observed for ligands **L02** and **L04** (Table 4.1, entries 4 and 6) [26-29]. A remarkably lower product yield of 39 % was obtained in the absence of a ligand (Table 4.1, entry 7). In conclusion, the above-mentioned product yields are significant improvements on previously reported product yields for cyclohexane peroxidation, using similar reaction conditions [11-14, 16, 17, 30]. Ligand **L01** resulted in the highest product yield (89 %) with the highest alcohol selectivity (40 %), and therefore it was employed in further studies.

Table 4.1: Evaluation of various pyrazolypyridineimine (imine-**L01** and imine-**L02**) and -amine ligands (**L01-L04**), in combination with [Cu(MeCN)₄]OTf, for cyclohexane peroxidation.^a

Entry	Ligand	Yield (%) ^b CyOH ^(CyOOH) /CyO	Total yield (%) ^b	Standard deviation (%)
1	imine- L01	24 ⁽³²⁾ /19	75	3.17
2	imine- L02	22 ⁽³³⁾ /17	73	3.75
3	L01	40 ⁽¹⁷⁾ /32	89	3.46
4	L02	28 ⁽²⁸⁾ /21	77	3.01
5	L03	36 ⁽²²⁾ /27	85	4.42
6	L04	37 ⁽¹⁵⁾ /28	80	0.70
7	-	7 ⁽²⁶⁾ /6	39	4.82

^a Cyclohexane (1 mmol), Cu(MeCN)₄OTf (1 mol%), imine-**L01**, imine-**L02** and **L01-L04** (1 mol%), H₂O₂ (10 mmol, 10 equiv.), MeCN (3 mL), reaction time: 6 h, 27 ± 2 °C. ^b GC yields of the products were determined with the use of a calibration curve (internal standard: biphenyl). The data reported are the average product yields obtained from two independent runs.

Next, we evaluated various Cu^I-/Cu^{II}-precursors for cyclohexane peroxidation using ligand **L01** (Table 4.2 and Figure S4.3 in the Supporting Information) [17]. The evaluation of Cu^I-precursors with non-coordinating anions, in combination with ligand **L01**, resulted in product yields of 84 to 89 %, with an alcohol selectivity of 31 to 40 % (Table 4.2, entries 1-3). Slightly lower product yields of 68 to 81 % were obtained when employing Cu^I-precursors bearing coordinating anions (Table 4.2, entries 4 and 5). Moreover, comparable product yields and

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alcohol selectivity of 75 to 95 % and 25 to 44 % were obtained, respectively when the Cu^I-precursors were replaced with Cu^{II}-precursors (Table 4.2, entries 8-10). However, when employing Cu(BF₄)₂·xH₂O, a slightly lower product yield of 62 % was obtained with a low alcohol selectivity of 14 % and increased amounts of the unconverted CyOOH product (36 %; Table 4.2, entry 6) [21]. In contrast with our findings, previous studies observed a slight decrease in product yields for hydrocarbon peroxidation and aerobic alcohol oxidation reactions when employing Cu^{II}- instead of Cu^I-precursors [17, 29, 31]. The inclusion of Cu^{II} pre-catalysts has previously been reported for peroxidation reactions and moderate product yields (< 50 %) were obtained [2, 18, 32, 33]. An extremely low product yield of 26 % was obtained for Cu(OAc)₂·2H₂O (Table 4.2, entry 7), while excellent product yields of 93 and 95 % and alcohol selectivity (37 to 44 %) were obtained when employing Cu(OTf)₂ and CuCl₂·2H₂O, respectively [33, 34]. Lastly, cyclohexane peroxidation was impossible in the absence of a Cu-precursor (Table 4.2, entry 13) [35].

Table 4.2: Evaluation of various Cu^I-/Cu^{II}-precursors, in combination with ligand **L01**, for cyclohexane peroxidation.^a

Entry	Cu ^I -/Cu ^{II} -precursor	Yield (%) ^b CyOH ^(CyOOH) /CyO	Total yield (%) ^b	Standard deviation (%)
1	Cu(MeCN) ₄ OTf	40 ⁽¹⁷⁾ /32	89	3.46
2	Cu(MeCN) ₄ BF ₄	32 ⁽²⁵⁾ /30	86	4.84
3	Cu(MeCN) ₄ PF ₆	31 ⁽²⁸⁾ /25	84	2.09
4	CuCl	28 ⁽²³⁾ /16	68	0.07
5	CuBr	30 ⁽²⁹⁾ /23	81	4.21
6	Cu(BF ₄) ₂ ·xH ₂ O	14 ⁽³⁶⁾ /12	62	5.45
7	Cu(OAc) ₂ ·2H ₂ O	5 ⁽¹⁸⁾ /3	26	1.53
8	Cu(OTf) ₂	37 ⁽²⁵⁾ /31	93	4.17
9	CuSO ₄ ·5H ₂ O	25 ⁽²⁸⁾ /23	75	2.18
10	CuCl ₂ ·2H ₂ O	44 ⁽¹⁶⁾ /35	95	1.19
11 ^c	CuCl ₂ ·2H ₂ O	40 ⁽²⁸⁾ /23	92	4.83
12 ^d	CuCl ₂ ·2H ₂ O	37 ⁽²⁵⁾ /25	87	4.97
13	-	0 ⁽⁰⁾ /0	0	-

^a Cyclohexane (1 mmol), various Cu^I-/Cu^{II}-precursors (1 mol%), **L01** (1 mol%), H₂O₂ (10 mmol, 10 equiv.), MeCN (3 mL), reaction time: 6 h, 27 ± 2 °C. ^b GC yields of the products were determined with the use of a calibration curve (internal standard: biphenyl). The data reported are the average product yields obtained from two independent runs. ^c Reaction time: 3 h, instead of 6 h. ^d Reaction time: 2 h.

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Our catalyst system displayed higher catalytic activity relative to previously reported studies, due to the nature of the ligands and the Cu-precursor employed. Even though both Cu^I- and Cu^{II}-precursors resulted in excellent product yields for cyclohexane peroxidation, the application of CuCl₂·2H₂O in combination with ligand **L01** was found to be optimal. This is due to the ability of the (**L01**)CuCl₂·2H₂O/H₂O₂ catalyst system to obtain a maximum product yield of 95 % with an alcohol selectivity of 44 %, while low amounts of the CyOOH product (16 %) were present.

The effect of reaction time on the obtained product yields was also investigated, using CuCl₂·2H₂O, in combination with ligand **L01**. A rapid increase in the product yield for cyclohexane peroxidation was observed since an excellent product yield of 87 % was obtained in 2 h, while an increase of only 5 to 8 % was obtained in the next 1 to 4 h (Table 4.2, entries 10-12). Therefore, we could not only improve on the product yield as obtained in the benchmark catalyst system (an increase of 39 %), but this could also be accomplished in a shorter reaction time [17]. The effect of varying [LCu], [H₂O₂] and [substrate] on cyclohexane peroxidation was evaluated, using CuCl₂·2H₂O in combination with ligand **L01**. An increase in either the LCu or H₂O₂ concentration increased the product yields until saturation was reached at high concentrations (Figures S4.4 and S4.5 in the Supporting Information) [15, 17]. Furthermore, even though similar product yields were obtained for low substrate concentrations, a decrease was observed at higher concentrations (Figure S4.6 in the Supporting Information).

Lastly, our optimised (**L01**)CuCl₂·2H₂O/H₂O₂ catalyst system was employed in the peroxidation of alternative cyclic and linear alkanes. Table 4.3, entries 2-4, shows our catalyst system was capable of converting cyclopentane, -heptane and -octane to the corresponding secondary alcohol and ketone products with remarkable product yields of 71 to 94 %. An alcohol selectivity of 44 % was obtained for cyclohexane peroxidation (Table 4.3, entry 1); however, a selectivity shift to the corresponding ketone products (28 to 64 %) was observed for the rest of the cycloalkane substrates (Table 4.3, entries 2-4). Garcia and co-workers employed several Cu- and Fe-based catalyst systems during their evaluation of cycloalkanes and they obtained moderate product yields of 36 to 56 % [17]. As such, we were able to improve on the product yields obtained for the peroxidation of various cycloalkanes with an order of cyclohexane > cycloheptane > cyclooctane > cyclopentane [3, 15, 18, 31, 36, 37].

The peroxidation of the linear alkane, *n*-octane, was also evaluated and a mixture of oxygenated C₈ products was obtained. A moderate product yield of 75 %, with a 67 % selectivity towards the octanone products, was possible (Table 4.3, entry 5). The regioselectivity in terms of C(1):C(2):C(3):C(4) was determined as 1:2:8:3, which confirmed

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the increased reactivity towards the internal C-H positions, and 3-octanone was identified as the major product. Kirillov and co-workers employed organic building blocks such as *N,N,N',N'*-tetrakis(2-hydroxyethyl)ethylenediamine (H₄edte) and phenylmalonic acid (H₂pmal) during the synthesis of their tetranuclear [Cu₄(μ₄-Hedte)₂(Hpmal)₂(H₂O)]·7.5H₂O complex [37]. This tetranuclear complex, in combination with H₂O₂ and TFA, were evaluated for *n*-octane peroxidation and they obtained an extremely low product yield of 5 %. Additionally, Bala and co-workers reported a product yield of 22 %, with 2-octanone as the most abundant product for their NHC-Cu^I complex, bearing a triazolylidene (1-(propyl)-3-methyl-4-phenyl-1*H*-1,2,3-triazol-3-ium-5-yl) ligand [35]. As such, we were able to improve on the above-mentioned product yields for the peroxidation of *n*-octane in 6 h, using our optimised reaction conditions.

Table 4.3: The evaluation of alternative cyclic and linear alkanes in peroxidation reactions, using our optimised (L01)CuCl₂·2H₂O/H₂O₂ catalyst system.^a

Entry	Substrate	Products	CyOH(CyOOH)/CyO (Yield: [%]) ^b	Yield [%] ^b
<u>Cyclic alkanes</u>				
1			44 ⁽¹⁶⁾ /35	95.3±1.19
2			8 ⁽³⁶⁾ /28	70.6±4.03
3			23 ⁽⁷⁾ /64	93.6±0.74
4			16 ⁽¹³⁾ /62	91.6±2.04
<u>Linear alkane</u>				
5		C(1) : C(2) : C(3) : C(4) Ketone, aldehyde and alcohol products	-	74.9±3.99

^a Reaction conditions: CuCl₂·2H₂O and ligand **L01** (1 mol%), H₂O₂ (8.5 mmol), substrate (1 mmol), MeCN (3 mL), 27 ± 2 °C. ^b GC yields of the products were determined with the use of a calibration curve (internal standard: biphenyl). The data reported are the average product yields obtained from two independent runs.

4.2.3 Kinetic behaviour of the (L01)CuCl₂·2H₂O/H₂O₂ catalyst system

Kinetic assessments were conducted and the initial rate data for the production of CyOOH were generated for varying [LCu], [H₂O₂] and [substrate] (Figure 4.1 and Table S4.1 in the Supporting Information). The initial rate studies was used for easier comparison with previous reported studies. First-order dependence on both the LCu catalyst and H₂O₂ oxidant concentrations was obtained, while a plateau was reached at high concentrations (Figure 4.1, A and B). These observations are consistent with those of previous groups for initial rate investigations at low concentrations, while the effect of higher concentrations was not included [9, 17, 18, 34]. This dependence suggests the involvement of a Cu-based catalytic species during the rate-limiting step of the reaction [18]. No proportionality was, however, observed between the rate of CyOOH formation and the initial concentration of cyclohexane, thereby indicating that the substrate is not involved during the rate-determining step (Figure 4.1, C) [17, 34].

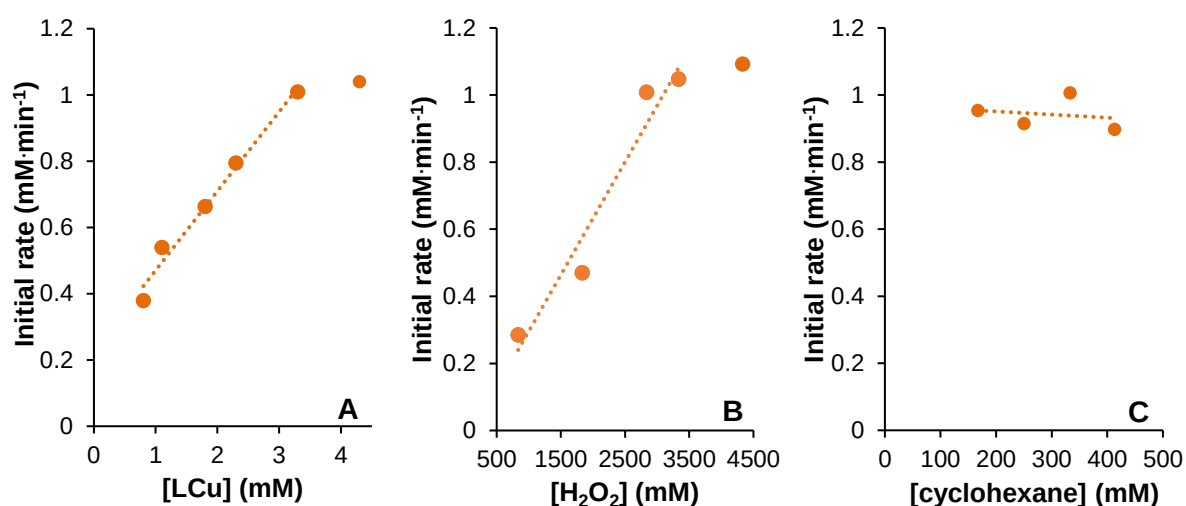


Figure 4.1: Kinetic data for the peroxidation of cyclohexane by (L03)CuCl₂·2H₂O/H₂O₂ assessing the kinetic dependence on [LCu] (A), [H₂O₂] (B) and [cyclohexane] (C).

4.2.4 Evaluating the formation of radical species for the (L01)CuCl₂·2H₂O/H₂O₂ catalyst system

Carbon tetrachloride (CCl₄, a ratio of 1:1 relative to H₂O₂ [17]) and 2,4-di-*tert*-butylphenol (a ratio of 1:300 relative to (L01)Cu^{II} [38]) were added to the peroxidation reactions as radical trapping agents to evaluate the effect thereof on the efficiency of the reaction (Table 4.4). When employing CCl₄ as the radical trap, a mixture of cyclohexyl chloride (CyCl), CyOH and CyO was observed, with CyCl as the major product (CyCl/(CyOH+CyO) ratio of 3.75, Table 4.4, entry 1) [17, 35, 36, 39]. This supports the formation of C-centred radical species during the H-atom abstraction step, while an extremely low product yield of 19 % (relative to

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95 %) is indicative of the formation of O-centred radical species. As such, these radical confirmation studies, in combination with the obtained zero-order dependence on the initial substrate concentration, indicate that the rate-determining step is substrate independent (see below). Moreover, a low product yield of 25 % (relative to 95 %) was obtained when employing 2,4-di-*tert*-butylphenol as the radical trap (Table 4.4, entry 2). GC-MS analysis confirmed the formation of 3,3',5,5'-tetra-*tert*-butylbiphenyl-2,2'-diol (major radical coupling product) and trace amounts of 3,5-di-*tert*-butylbenzene-1,2-diol (via *ortho*-hydroxylation) as by-products, while the expected CyOOH, CyOH and CyO products were also observed (Figure S4.7 in the Supporting Information). This observation is due to the lower bond dissociation energy (BDE) = 81.24 kcal/mol required to activate C-H bonds of 2,4-di-*tert*-butylphenol [40] relative to those of cyclohexane (BDE = 100 kcal/mol) [41]. The relative ease of C-H bond activation for 2,4-di-*tert*-butylphenol, as well as the resulting low product yield, supports the formation of LCu^{II} -hydroxyl ($\text{LCu}^{\text{II}}\text{-OH}$) and LCu^{II} -oxyl ($\text{LCu}^{\text{II}}\text{-O}^\bullet$) species during the rate-determining step, which was further supported by the obtained first-order dependence on $[\text{LCu}]$ [38].

Table 4.4: Evaluating the effect of radical trapping agents, toluene as substrate or an inert atmosphere on the total product yield for cyclohexane peroxidation.^a

Entry	Comment	Yield (%) ^b CyOH(CyOOH)/CyO	Total yield ^b (%)	Standard deviation (%)
1	Radical trap: CCl ₄	1/3/15 (3.75) ^c	19	7.25
2	Radical trap: 2,4-di- <i>tert</i> -butylphenol	10 ⁽¹¹⁾ /4 ^d	25	4.44
3	Substrate: Toluene	Mixture of oxidation products ^e	41	4.59
4	Inert atmosphere ^f	32 ⁽³⁸⁾ /23	93	1.03

^a Cyclohexane (1 mmol), CuCl₂·2H₂O and **L01** (1 mol%), H₂O₂ (8.5 mmol, 8.5 equiv.), MeCN (3 mL), reaction time: 6 h, 27 ± 2 °C. ^b GC yields of the products were determined using a calibration curve (internal standard: biphenyl). The data reported are the average obtained from two independent runs. ^c CyOH/CyO/CyCl (CyCl/(CyOH+CyO)). ^d The 3,3',5,5'-tetra-*tert*-butylbiphenyl-2,2'-diol (major radical coupling product) and trace amounts of 3,5-di-*tert*-butylbenzene-1,2-diol (via *ortho*-hydroxylation) by-products were observed. ^e The mixture consists of benzaldehyde (6 %), *p*-toluquinone (18 %) and *o*-/*m*-/*p*-cresols (8/3/6 %, in a ratio of 47:18:35). ^f Under nitrogen.

Finally, the formation of O-centred radical species is evident in the peroxidation of toluene [17, 35, 42]. Benzaldehyde, one of the products, is an important building block in the pharmaceutical industry and the synthesis of fine chemicals. Unfortunately, the peroxidation of toluene usually results in low aldehyde products, due to the possibility to activate the C-H

bonds of either the methyl group or those of the aromatic ring. As such, we decided to investigate toluene as substrate, using our (**L01**)CuCl₂·2H₂O/H₂O₂ catalyst system and we obtained a total product yield of 41 %. A mixture of oxidation products was observed with *p*-toluquinone as the major product, while benzaldehyde and *o*-/ *m*-/ *p*-cresols were obtained as minor products (Table 4.4, entry 3). As such, our results support the formation of O-centred radical species, while also improving on previously reported product yields. Lastly, reactions were performed under inert reaction conditions, but almost no change in the product yields (93 vs 95 %) were observed, while a decrease in alcohol selectivity was obtained (Table 4.4, entry 4). This observation indicates that H₂O₂ serves as the oxidant while the molecular oxygen, required for product formation, is generated during the reaction. In conclusion, these results support the formation of both C- and O-centred radical species, as well as the formation of LCu^{II}-OH and LCu^{II}-O[•] species during the rate-determining step, which is substrate independent. As such, the metal-oxo mechanistic pathway, as proposed by Pérez and co-workers, is not applicable for our catalyst system since they only proposed the formation of C-centred radical species [16].

4.2.5 Electrochemical studies of the (**L01**)CuCl₂·2H₂O catalyst system

Electrochemical studies were used to investigate the reversible transformation of the copper oxidation state in the absence of cyclohexane. The effects of various pyrazolylpyridineimine and -amine ligands on the redox potentials were evaluated. Voltammograms were obtained at a constant scan rate of 50 mV/s over a scanning potential window of -0.5 to +1.75 V (Figures 4.2 to 4.4). Tetrabutylammonium hexafluorophosphate (Bu₄NPF₆) was employed as the supporting electrolyte (*E*_{1/2}: -0.70 V [vs NHE (normal hydrogen electrode)]). When employing our optimised (**L01**)CuCl₂·2H₂O catalyst system, an anodic peak was observed at *E*_{pa} 0.18 V (vs NHE) and *I*_{pa} 0.002 mA in the forward scan, while the cathodic peak was observed at *E*_{pc} 0.04 V (vs NHE) and *I*_{pc} -0.02 mA in the reverse scan (Figure 4.2). This observation is consistent with the Cu^{II}/Cu^I redox couple (*E*_{1/2}: 0.11 V vs NHE), which shows a quasi-reversible one-electron oxidation process [39, 43-45]. Another anodic peak was observed at *E*_{pa} 0.79 V (vs NHE) and *I*_{pa} 0.02 mA with the cathodic counterpart at *E*_{pc} 0.65 V (vs NHE) and *I*_{pc} -0.02 mA, consistent with the quasi-reversible one-electron oxidation process for the Cu^{III}/Cu^{II} redox couple (*E*_{1/2}: 0.72 V vs NHE) [39, 43, 46-50]. Moreover, an irreversible one-electron ligand-centred oxidation (onset potential of 1.31 V vs NHE) was observed for ligand **L01** with a weak anodic peak at *E*_{pa} 1.35 V (vs NHE) and *I*_{pa} 0.01 mA.

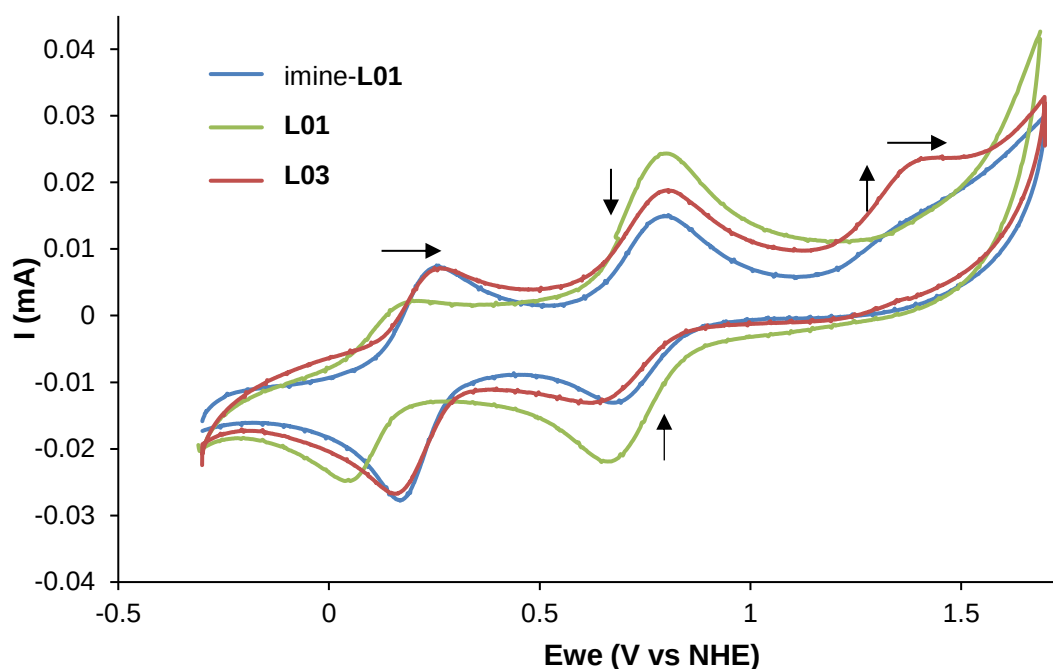


Figure 4.2: Cyclic voltammograms for various pyrazolylpyridineimine and -amine ligands in combination with $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, in the absence of cyclohexane. Voltammograms were recorded at a scan rate of 50 mV/s over the scanning potential of -0.5 to +1.75 V. Bu_4NPF_6 was employed as the supporting electrolyte ($E_{1/2}$: -0.70 V vs NHE). The $\rightarrow$ arrow denotes the gradual shifts in the $\text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}$ couple and the ligand-centred oxidation, while the $\uparrow$ and $\downarrow$ arrows denote the increase or decrease in the intensity of the $\text{Cu}^{\text{III}}/\text{Cu}^{\text{II}}$ redox couple and the ligand-centred oxidation.

The donor properties of ligands imine-**L01**, **L01** and **L03** in combination with $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ were evaluated, and a cathodic shift was observed for the $\text{Cu}^{\text{III}}/\text{Cu}^{\text{II}}$ redox couple when employing either imine-**L01** ($E_{1/2}$: 0.75 V vs NHE) or **L03** ($E_{1/2}$: 0.73 V vs NHE), relative to **L01** ($E_{1/2}$: 0.72 V vs NHE, Figure 4.2). Moreover, the intensity of the ligand-centred oxidation increased when **L01** was replaced with **L03**; however, a gradual shift to higher potentials was also observed. The obtained lower redox potential for the $\text{Cu}^{\text{III}}/\text{Cu}^{\text{II}}$ redox couple and the ligand-centred oxidation when employing **L01** support its stronger donor ability as well as the generation of a more electron-rich Cu-based intermediate [51].

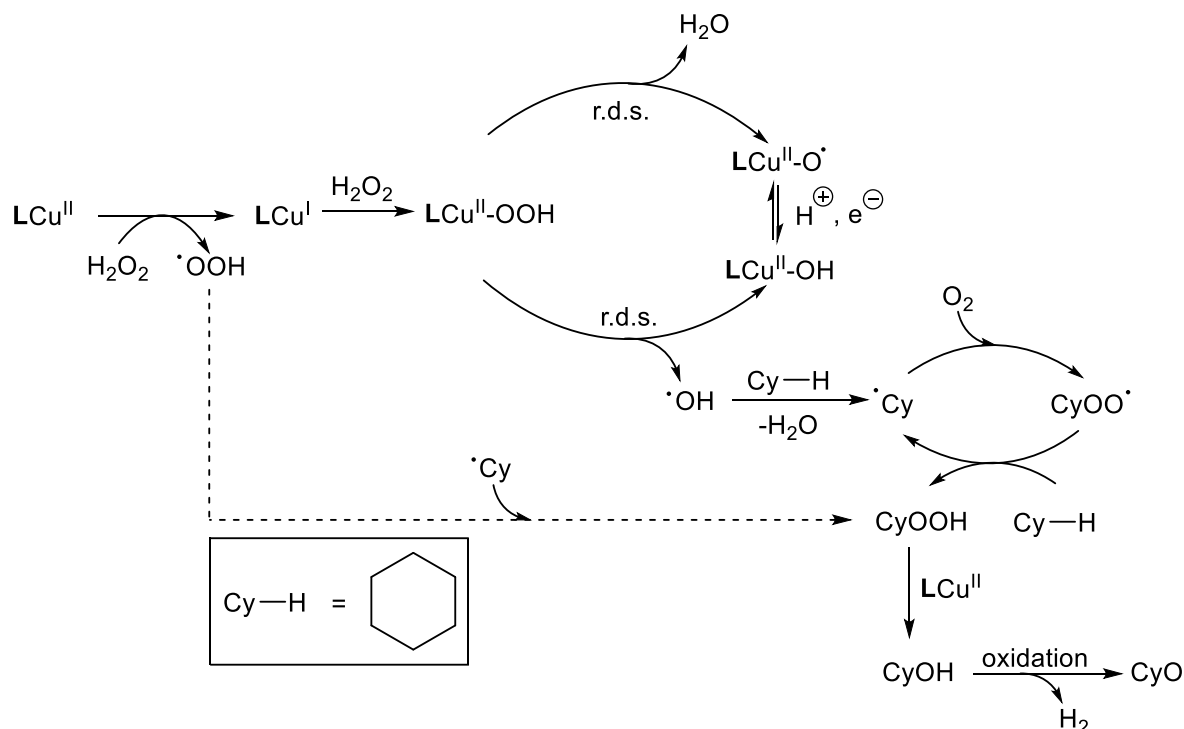
4.2.6 Mechanistic considerations

Two possible mechanistic pathways for hydrocarbon peroxidation have previously been proposed where $\cdot\text{OH}$ radical species are generated to participate in the substrate activation step [17, 34-36, 52-54]. The first mechanistic pathway involves the Fenton-like reaction between LCu^{II} and H_2O_2 to generate $\text{LCu}^{\text{III}}\text{-OH}$ and $\cdot\text{OH}$ radical species during the rate-determining step. The second pathway does not involve the formation of $\text{LCu}^{\text{III}}\text{-OH}$ species,

but rather the H_2O_2 -assisted reduction of LCu^{II} to LCu^{I} and the formation of hydroperoxo ($\cdot\text{OOH}$) radical species, followed by the oxidation of LCu^{I} to the initial LCu^{II} species to generate $\cdot\text{OH}$ radical species.

The oxidation of Cu^{II} to Cu^{III} species may be observed electrochemically under applied potential [39]; however, except for gas-phase methane activation studies, the formation of $\text{LCu}^{\text{III}}\text{-OH}$ species as proposed in the first mechanistic pathway is difficult to prove experimentally [34-36, 52, 53, 55-58]. Computational studies were therefore employed as an alternative method to obtain evidence of the formation of $\text{LCu}^{\text{III}}\text{-OH}$ species as the conjugated acid of the highly unstable $\text{LCu}^{\text{III}}\text{-O}\cdot$ species [59, 60]. The involvement of $\text{LCu}^{\text{III}}\text{-O}\cdot$ species during substrate activation was previously proposed [38, 61, 62]. As such, based on previous studies as well as the results obtained for our kinetic and radical confirmation studies, we propose an alternative mechanistic pathway for hydrocarbon peroxidation, where $\text{LCu}^{\text{II}}\text{-OH}$ and $\text{LCu}^{\text{II}}\text{-O}\cdot$ species are formed during the rate-limiting step, instead of the $\text{LCu}^{\text{III}}\text{-OH}$ species (Scheme 4.3). Even though $\text{LCu}^{\text{II}}\text{-OH}$ and $\text{LCu}^{\text{II}}\text{-O}\cdot$ species are present in the system, they are not involved during substrate activation, since the $\cdot\text{OH}$ radical species are responsible for the H-atom abstraction from the substrate.

The *in situ* formed LCu^{II} pre-catalyst reacts with H_2O_2 to afford LCu^{I} species and $\cdot\text{OOH}$ radical species, followed by the reaction between LCu^{I} and H_2O_2 to generate the $\text{LCu}^{\text{II}}\text{-hydroperoxo}$ ($\text{LCu}^{\text{II}}\text{-OOH}$) species in the absence of the substrate. Even though this was not previously observed for peroxidation reactions, we employed UV/vis studies to obtain experimental evidence for its formation under basic conditions (Figure S4.8 in the Supporting Information) [62]. The rate-determining step may either involve the dissociation of H_2O to afford $\text{LCu}^{\text{II}}\text{-O}\cdot$ species or the formation of $\text{LCu}^{\text{II}}\text{-OH}$ and $\cdot\text{OH}$ radical species. The $\text{LCu}^{\text{II}}\text{-O}\cdot$ and $\text{LCu}^{\text{II}}\text{-OH}$ species are in equilibrium with each other via proton-coupled electron transfer. The $\cdot\text{OH}$ radical species are then responsible for the H-atom abstraction step from the cyclohexane substrate to afford $\cdot\text{Cy}$ radical species (Scheme 4.3) [18]. Molecular O_2 reacts with $\cdot\text{Cy}$ to generate cyclohexylperoxyl radicals ($\text{CyOO}\cdot$), which leads to the formation of the primary CyOOH product. Homolytic cleavage of CyOOH resulted in the formation of CyOH and $\text{CyO}\cdot$, using the LCu^{II} species present in the system. The catalytic cycle is completed with the regeneration of the LCu^{I} species during the reduction of H_2O_2 , which was also supported by our electrochemical studies.



Scheme 4.3: The proposed mechanistic pathway for cycloalkane peroxidation where $\text{LCu}^{\text{II}}\text{-OH}$ and $\text{LCu}^{\text{II}}\text{-O}\cdot$ species are generated during the rate-determining step, while the $\cdot\text{OH}$ radical species are employed during the H-atom abstraction step.

4.3 Conclusions

Previously reported pyrazolylpyridineimine (imine-**L01** and imine-**L02**) and -amine ligands (**L01-L04**), in combination with a Cu-precursor, were evaluated as pre-catalysts in the peroxidation of cycloalkanes, under ambient reaction conditions using H_2O_2 as the oxidant. The optimisation of the (**L01**) $\text{CuCl}_2\cdot 2\text{H}_2\text{O}/\text{H}_2\text{O}_2$ catalyst system was accomplished by evaluating the effect of various ligands, $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ -precursors, $[\text{LCu}]$, $[\text{H}_2\text{O}_2]$ and $[\text{substrate}]$ on cyclohexane peroxidation. We could improve on the product yields (> 90 %) for cyclohexane peroxidation, in a shorter reaction time, relative to the benchmark catalyst system. Excellent product yields of 71 to 94 % and 75 % were obtained for the peroxidation of alternative cyclic and linear alkanes, respectively. Even though an alcohol selectivity of 44 % was obtained for cyclohexane peroxidation, a selectivity shift to the corresponding ketone products (28 to 64 %) was rather observed for the rest of the cycloalkanes. The rate of CyOOH formation exhibits a first-order dependence on $[\text{LCu}]$ and $[\text{H}_2\text{O}_2]$, while no proportionality was observed towards the initial concentration of the substrate since it is not involved during the rate-determining step. Reactions were performed in the presence of the radical trapping agents, CCl_4 or 2,4-di-*tert*-butylphenol and decreased product yields of 19 to 25 % were obtained, supporting the formation of C- and O-centred radical species. O-centred radical species

formation was further supported when the peroxidation of toluene resulted in a mixture of oxidation products with a product yield of 41 %. Electrochemical studies were employed and **L01** was identified as the optimal ligand due to its low redox potentials and strong donor ability to generate a more electron-rich Cu-based intermediate. As such, our radical confirmation, kinetic and electrochemical results support the reversible transformation between Cu^{II} and Cu^I species, with the proposed formation of the LCu^{II}-OOH intermediate, followed by the formation of LCu^{II}-OH and LCu^{II}-O[•] species during the substrate independent rate-determining step. Hydroxyl radical species are responsible for the H-atom abstraction step and the reduction of H₂O₂ resulted in the regeneration of LCu^I, consistent with our proposed mechanistic pathway. Future work in our group is focused on the development of a novel bifunctional ligand framework that can accommodate two copper centres to facilitate hydrocarbon peroxidation with improved product yields and alcohol selectivity.

4.4 Experimental section

4.4.1 General considerations

All commercially available reagents were obtained from Sigma-Aldrich and/or Merck and used as received. The pyrazolylpyridineimine (imine-**L01** and imine-**L02**) and -amine (**L01-L04**) ligands were synthesised according to a literature procedure [19-21]. GC analyses were performed on an Agilent 6890 Series GC system with an HP-5 column, and samples (0.2 mL) were analysed with biphenyl as the internal standard. The oxidation products were identified by comparing the GC retention times of commercial samples to our obtained retention times. GC-MS analyses were performed on an Agilent 6890 N Series GC system with a mass selective (5973) detector and an HP-5-MSUI column. Helium served as the carrier gas, EtOAc and DCM were used as the rinsing solutions and samples (0.2 mL) were analysed with biphenyl as the internal standard to confirm the identification of peaks. The peroxidation reactions were done in duplicate to determine an average product yield as well as the standard deviation.

4.4.2 Optimisation of our Cu-based catalyst system

The catalyst system was optimised by varying pyrazolylpyridineimine and -amine ligands and Cu^I-/Cu^{II}-precursors for the peroxidation of cyclohexane. A solution of Cu-precursor ([Cu(MeCN)₄]BF₄, [Cu(MeCN)₄]OTf, [Cu(MeCN)₄]PF₆, CuCl, CuBr, Cu(BF₄)₂·xH₂O, Cu(OTf)₂, CuCl₂·2H₂O, CuSO₄·5H₂O and Cu(OAc)₂·2H₂O, 10 μmol in 1.5 mL MeCN) and ligand (imine-**L01**, imine-**L02** and **L01-L04**, 10 μmol in 1.5 mL MeCN) was stirred in a small reactor flask. The oxidant, H₂O₂ (30 % in H₂O, 1.1 mL, 10 mmol) was added to the yellow complex mixture

and a colour change to blue-green was observed. Immediately after 5-10 s, cyclohexane (0.1 mL, 1 mmol) was added, the reactor flask was closed (to prevent evaporation of the substrate) and allowed to stir for 6 h at room temperature. After the allotted time, the reaction mixture was added to a 10 mL vial containing EtOAc (3 mL) and PPh₃ (0.20 g, 0.75 mmol) and placed in the fridge for 20 min to allow the conversion of CyOOH to CyOH and CyO (the excess H₂O₂ is converted to H₂O). A sample (0.18 mL) was analysed by GC with biphenyl (50 µL) as the internal standard.

4.4.3 Optimisation of the concentrations for each reaction parameter

The concentrations of each reaction parameter were optimised through the evaluation of the effect of varying [LCu], [H₂O₂] and [substrate] on the peroxidation reaction. The concentration of only one reaction parameter was varied while optimal reaction conditions were employed. A solution of CuCl₂·2H₂O (x µmol in 1.5 mL MeCN) and ligand **L01** (x µmol in 1.5 mL MeCN) was stirred in a small reactor flask. The oxidant, H₂O₂ (30 % in H₂O, x mL, x mmol) was added to the yellow complex mixture and a colour change to blue-green was observed. Immediately after 5-10 s, cyclohexane (x mL, x mmol) was added, the reactor flask was closed and allowed to stir for 6 h at room temperature. The above-mentioned workup process was used and a sample (0.18 mL) was analysed by GC with biphenyl (50 µL) as the internal standard.

4.4.4 Evaluation of the peroxidation of alternative cyclic and linear alkanes

A solution of CuCl₂·2H₂O (10 µmol in 1.5 mL MeCN) and ligand **L01** (10 µmol in 1.5 mL MeCN) was stirred in a small reactor flask. The oxidant, H₂O₂ (30 % in H₂O, 1 mL, 8.5 mmol) was added to the colourless or yellow complex mixture. Immediately after 5-10 s, one of the cyclic or linear alkanes (1 mmol) was added, the reactor flask was closed (to prevent evaporation of the substrate) and allowed to stir for 6 h at room temperature. After the allotted time, the reaction mixture was added to a 10 mL vial containing EtOAc (3 mL) and PPh₃ (0.20 g, 0.75 mmol) and placed in the fridge for 20 min to allow the conversion of CyOOH to CyOH and CyO (the excess H₂O₂ is converted to H₂O). A sample (0.18 mL) was analysed by GC with biphenyl (50 µL) as the internal standard.

4.4.5 Kinetic studies

The concentration of only one reaction parameter was varied while optimal reaction conditions were employed. A solution of CuCl₂·2H₂O (x µmol in 1.5 mL MeCN) and ligand **L01** (x µmol in 1.5 mL MeCN) was stirred in a small reactor flask. The oxidant, H₂O₂ (30 % in H₂O, x mL, x mmol) was added to the yellow complex mixture and a colour change to blue-green was

observed. Immediately after 5-10 s, cyclohexane (x mL, x mmol) was added, the reactor flask was closed and allowed to stir at room temperature. Samples (0.2 mL) were taken in varying reaction intervals of 20, 30, 40, 50, 60, 75, 90, 105, 120 and 135 min, which were added to a solution of EtOAc (0.2 mL) and PPh₃ (0.01 g, 0.38 mmol). A sample (0.18 mL) was analysed by GC with biphenyl (50 µL) as the internal standard.

4.4.6 Evaluating the formation of radical species formation

A solution of CuCl₂·2H₂O (10 µmol in 1.5 mL MeCN) and ligand **L01** (10 µmol in 1.5 mL MeCN) was stirred in a small reactor flask. The oxidant, H₂O₂ (30 % in H₂O, 1.0 mL, 8.5 mmol) was added to the yellow complex mixture and a colour change to blue-green was observed. Immediately after 5-10 s, cyclohexane (0.1 mL, 1 mmol) and either CCl₄ (0.77 mL, 8 mmol, a ratio of 1:1 relative to H₂O₂ [17]) or 2,4-di-*tert*-butylphenol (0.62 g, 3 mmol, a ratio of 1:300 relative to (**L01**)Cu^{II} [38]) were added, the reactor flask was closed and allowed to stir for 6 h at room temperature. A colour change to red-brown was observed with time. The above-mentioned work-up process was used and a sample (0.18 mL) was analysed by GC and GC-MS with biphenyl (50 µL) as the internal standard.

4.4.7 Electrochemical studies

Electrochemical studies were conducted on a BioLogic SP-150 potentiostat linked to a computer, utilising the EC Lab software. Measurements were done at 25 °C and the temperature was kept constant to within 0.5 °C. The measurements were performed on 1 mM solutions, dissolved in anhydrous MeCN as the solvent, containing 0.1 M tetrabutylammonium hexafluorophosphate (Bu₄NPF₆) as supporting electrolyte ($E_{1/2}$: -0.70 V [vs NHE (normal hydrogen electrode)]). A conventional three-electrode electrochemical cell was used, consisting of a platinum (Pt) wire as the counter-electrode, a glassy carbon working electrode with a geometrical area of 0.196 cm², as well as an Ag/AgCl (saturated KCl) reference electrode. The working electrode was polished with 0.5 M alumina suspension and washed with Milli-Q water, ethanol and isopropanol before it was assembled into a rotating disc electrode setup. The counter and reference electrodes were sonicated for two min in H₂O. Measurements were taken after N₂ was bubbled through the reaction mixture for at least 15 min. Voltammograms were recorded at a constant scan rate of 50 mV/s over a scanning potential window of -0.5 to +1.75 V. The measured redox potentials were converted to normal hydrogen electrode (NHE) values by adding +0.199 V to compare our results to related catalyst systems.

4.5 Acknowledgements

This work is based on the research supported by the National Research Foundation of South Africa (Unique Grant No. 112545 and 117869) and North-West University. Any opinion, finding and conclusion or recommendation expressed in this material is that of the author(s) and the NRF does not accept any liability in this regard. The infrastructure support provided by the Focus Area for Chemical Resource Beneficiation (CRB) and in particular the Catalysis and Synthesis Research Group, at the NWU, is gratefully acknowledged.

4.6 References

- [1] M.T. Musser, Ullmann's Encyclopedia of Industrial Chemistry, 6th ed., Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011; Vol. 11.
- [2] U. Schuchardt, R. Pereira, M.c. Rufo, J. Mol. Catal. A: Chem., 135 (1998) 257-262.
- [3] K. Pamin, E. Tabor, S. Górecka, W.W. Kubiak, D. Rutkowska-Zbik, J. Połtowicz, ChemSusChem, 12 (2019) 684-691.
- [4] J. Połtowicz, E. Tabor, K. Pamin, J. Haber, Inorg. Chem. Commun., 8 (2005) 1125-1127.
- [5] M.S. Chen, M.C. White, Science, 318 (2007) 783-787.
- [6] A.M. Zima, O.Y. Lyakin, K.P. Bryliakov, E.P. Talsi, Mol. Catal., 455 (2018) 6-13.
- [7] C. Pavan, J. Legros, C. Bolm, Adv. Synth. Catal., 347 (2005) 703-705.
- [8] M. Sutradhar, L.M. Martins, T.R. Barman, M.L. Kuznetsov, M.F.C.G. da Silva, A.J. Pombeiro, New J. Chem., 43 (2019) 17557-17570.
- [9] G.B. Shul'pin, G.V. Nizova, Y.N. Kozlov, L. Gonzalez Cuervo, G. Süß-Fink, Adv. Synth. Catal., 346 (2004) 317-332.
- [10] G.B. Shul'pin, Catalysts, 6 (2016) 50-90.
- [11] D.H. Barton, S.D. Bévière, W. Chavasiri, É. Csuhai, D. Doller, Tetrahedron, 48 (1992) 2895-2910.
- [12] A. Sobkowiak, A. Qui, X. Liu, A. Llobet, D.T. Sawyer, J. Am. Chem. Soc., 115 (1993) 609-614.
- [13] A.M. Kirillov, M.N. Kopylovich, M.V. Kirillova, M. Haukka, M.F.C.G. da Silva, A.J. Pombeiro, Angew. Chem. Int. Ed., 44 (2005) 4345-4349.
- [14] A.M. Kirillov, M.N. Kopylovich, M.V. Kirillova, E.Y. Karabach, M. Haukka, M.F.C.G. da Silva, A.J. Pombeiro, Adv. Synth. Catal., 348 (2006) 159-174.
- [15] C. Di Nicola, F. Garau, Y.Y. Karabach, L.M. Martins, M. Monari, L. Pandolfo, C. Pettinari, A.J. Pombeiro, Eur. J. Inorg. Chem., 2009 (2009) 666-676.
- [16] A. Conde, L. Vilella, D. Balcells, M.M. Díaz-Requejo, A. Lledós, P.J. Pérez, J. Am. Chem. Soc., 135 (2013) 3887-3896.
- [17] I. Garcia-Bosch, M.A. Siegler, Angew. Chem. Int. Ed., 55 (2016) 12873-12876.
- [18] M.V. Kirillova, T.A. Fernandes, V. André, A.M. Kirillov, Org. Biomol. Chem., 17 (2019) 7706-7714.
- [19] C. Obuah, M.K. Ainooson, S. Boltina, I.A. Guzei, K. Nozaki, J. Darkwa, Organometallics, 32 (2013) 980-988.

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- [20] C. Obuah, B. Omondi, K. Nozaki, J. Darkwa, J. Mol. Catal. A: Chem., 382 (2014) 31-40.
- [21] L. Marais, H.C.M. Vosloo, A.J. Swarts, Mol. Catal., 486 (2020) 110839-11087.
- [22] O. Songis, P. Boulens, C.G. Benson, C.S. Cazin, RSC Adv., 2 (2012) 11675-11677.
- [23] N. Mketo, J.H.L. Jordaan, A. Jordaan, A.J. Swarts, S.F. Mapolie, Eur. J. Inorg. Chem., 2016 (2016) 3781-3790.
- [24] G.B. Shul'pin, J. Mol. Catal. A: Chem., 189 (2002) 39-66.
- [25] J. Jia, C. Jiang, X. Zhang, Y. Jiang, D. Ma, Tetrahedron Lett., 52 (2011) 5593-5595.
- [26] J.M. Hoover, B.L. Ryland, S.S. Stahl, J. Am. Chem. Soc., 135 (2013) 2357-2367.
- [27] A.J. Swarts, S.F. Mapolie, Dalton Trans., 43 (2014) 9892-9900.
- [28] A.J. Swarts, F. Zheng, V.J. Smith, E. Nordlander, S.F. Mapolie, Organometallics, 33 (2014) 2247-2256.
- [29] L. Marais, J. Bures, J.H.L. Jordaan, S. Mapolie, A.J. Swarts, Org. Biomol. Chem., 15 (2017) 6926-6933.
- [30] D.H. Barton, D. Doller, Y.V. Geletii, Mendeleev Commun., 1 (1991) 115-116.
- [31] I. Garcia-Bosch, Synlett., 28 (2017) 1237-1243.
- [32] T. Okuno, S. Ohba, Y. Nishida, Polyhedron, 16 (1997) 3765-3774.
- [33] E. Firinci, J. Mol. Struct., 1193 (2019) 125-130.
- [34] G.B. Shul'pin, J. Gradinaru, Y.N. Kozlov, Org. Biomol. Chem., 1 (2003) 3611-3617.
- [35] S.G. Mncube, M.D. Bala, Transition Met. Chem., 44 (2019) 145-151.
- [36] M.V. Kirillova, A.M. Kirillov, M.F.C. Guedes da Silva, A.J.L. Pombeiro, Eur. J. Inorg. Chem., 2008 (2008) 3423-3427.
- [37] S.S. Dias, M.V. Kirillova, V.n. André, J. Klak, A.M. Kirillov, Inorg. Chem., 54 (2015) 5204-5212.
- [38] D.E. Diaz, M. Bhadra, K.D. Karlin, Inorg. Chem., 58 (2019) 13746-13750.
- [39] A. Bhattacharjee, S. Dey, P. Roy, Inorg. Chim. Acta, 490 (2019) 93-103.
- [40] M. Lucarini, P. Pedrielli, G.F. Pedulli, S. Cabiddu, C. Fattuoni, J. Org. Chem., 61 (1996) 9259-9263.
- [41] Z. Tian, A. Fattahi, L. Lis, S.R. Kass, J. Am. Chem. Soc., 128 (2006) 17087-17092.

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- [42] H. Marusawa, K. Ichikawa, N. Narita, H. Murakami, K. Ito, T. Tezuka, *Biorg. Med. Chem.*, 10 (2002) 2283-2290.
- [43] E. Chiyindiko, J. Conradie, *J. Electroanal. Chem.*, 837 (2019) 76-85.
- [44] G. Saha, K.K. Sarkar, T.K. Mondal, C. Sinha, *Inorg. Chim. Acta*, 387 (2012) 240-247.
- [45] M. Sarigul, S.E. Kariper, P. Deveci, H. Atabey, D. Karakas, M. Kurtoglu, *J. Mol. Struct.*, 1149 (2017) 520-529.
- [46] E. Franco, E. Lopez-Torres, M. Mendiola, M. Sevilla, *Polyhedron*, 19 (2000) 441-451.
- [47] M. Jeżowska-Bojczuk, W. Leśniak, W. Bal, H. Kozłowski, K. Gatner, A. Jezierski, J. Sobczak, S. Mangani, W. Meyer-Klaucke, *Chem. Res. Toxicol.*, 14 (2001) 1353-1362.
- [48] J.S. Pap, Ł. Szyrwił, *Comments Inorg. Chem.*, 37 (2017) 59-77.
- [49] Z. Wu, Z. Zhang, L. Liu, *Electrochim. Acta*, 42 (1997) 2719-2723.
- [50] J.P. Naskar, B. Guhathakurta, L. Lu, M. Zhu, *Polyhedron*, 43 (2012) 89-96.
- [51] M. Navarro, C.A. Smith, M. Li, S. Bernhard, M. Albrecht, *Chem. Eur. J.*, 24 (2018) 6386-6398.
- [52] M.N. Kopylovich, K.T. Mahmudov, M.F.t.C. Guedes da Silva, P.J. Figiel, Y.Y. Karabach, M.L. Kuznetsov, K.V. Luzyanin, A.J. Pombeiro, *Inorg. Chem.*, 50 (2011) 918-931.
- [53] M.V. Kirillova, Y.N. Kozlov, L.S. Shul'pina, O.Y. Lyakin, A.M. Kirillov, E.P. Talsi, A.J. Pombeiro, G.B. Shul'pin, *J. Catal.*, 268 (2009) 26-38.
- [54] M. Yamada, K.D. Karlin, S. Fukuzumi, *Chem. Sci.*, 7 (2016) 2856-2863.
- [55] D. Schröder, M.C. Holthausen, H. Schwarz, *J. Phys. Chem. B*, 108 (2004) 14407-14416.
- [56] N. Dietl, M. Schlangen, H. Schwarz, *Angew. Chem. Int. Ed.*, 51 (2012) 5544-5555.
- [57] N.J. Rijs, P. González-Navarrete, M. Schlangen, H. Schwarz, *J. Am. Chem. Soc.*, 138 (2016) 3125-3135.
- [58] M. Srnc, R. Navrátil, E. Andris, J. Jašík, J. Roithová, *Angew. Chem. Int. Ed.*, 57 (2018) 17053-17057.
- [59] D. Dhar, W.B. Tolman, *J. Am. Chem. Soc.*, 137 (2015) 1322-1329.
- [60] D. Dhar, G.M. Yee, T.F. Markle, J.M. Mayer, W.B. Tolman, *Chem. Sci.*, 8 (2017) 1075-1085.
- [61] B. Bissaro, Å.K. Røhr, G. Müller, P. Chylenski, M. Skaugen, Z. Forsberg, S.J. Horn, G. Vaaje-Kolstad, V.G. Eijsink, *Nat. Chem. Biol.*, 13 (2017) 1123-1131.

Chapter 4: Highly efficient alkane peroxidation mediated by a copper(II)/pyrazolylpyridineamine catalyst system

[62] L. Marais, H.C.M. Vosloo, A.J. Swarts, Synthetic LPMO mimics: a copper/pyrazolylpyridineamine catalyst system for the highly efficient oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside, Chapter 6, Manuscript in preparation, (2020).

Supporting Information for
Highly efficient alkane peroxidation mediated by a
Cu(II)/pyrazolylpyridineamine catalyst system

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S4.1 General considerations

S4.1.1 Instrumentation

GC analyses were performed on an Agilent 6890 Series GC system with an HP-5 column (30 m x 0.320 mm x 0.25 mm). N₂ served as the carrier gas, ethyl acetate (EtOAc) and dichloromethane (DCM) were used as the rinsing solutions and samples (0.2 mL) were analysed with biphenyl as the internal standard. GC-MS analyses were performed on an Agilent 6890 N Series GC system with a mass selective (5973) detector and an HP-5-MSUI column. Helium served as the carrier gas, EtOAc and DCM were used as the rinsing solutions and samples (0.2 mL) were analysed with biphenyl as the internal standard to confirm the identification of peaks. The peroxidation reactions were done in duplicate to determine an average yield as well as the standard deviation.

S4.2 Optimisation of the catalyst system

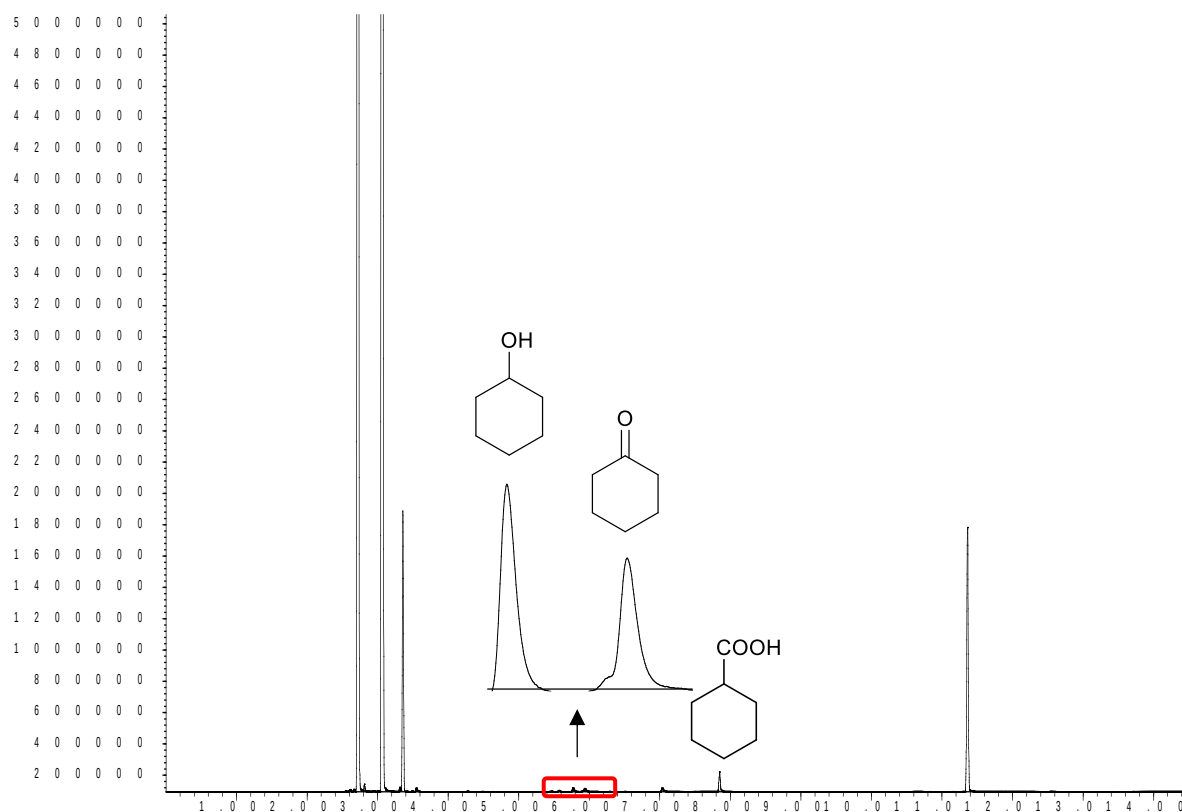


Figure S4.1: A visual representation of the GC spectrum for the peroxidation of cyclohexane (3.38 min). The formation of cyclohexanol (5.79 min), cyclohexanone (5.93 min) and cyclohexyl hydroperoxide (7.05 min) were observed as products relative to biphenyl (11.37 min) as the internal standard.

Various pyrazolylpyridineimine and -amine ligands, imine-**L01**, imine-**L02** and **L01-L04** with $[\text{Cu}(\text{MeCN})_4]\text{OTf}$ were evaluated for cyclohexane peroxidation (Figure S4.2) [1].

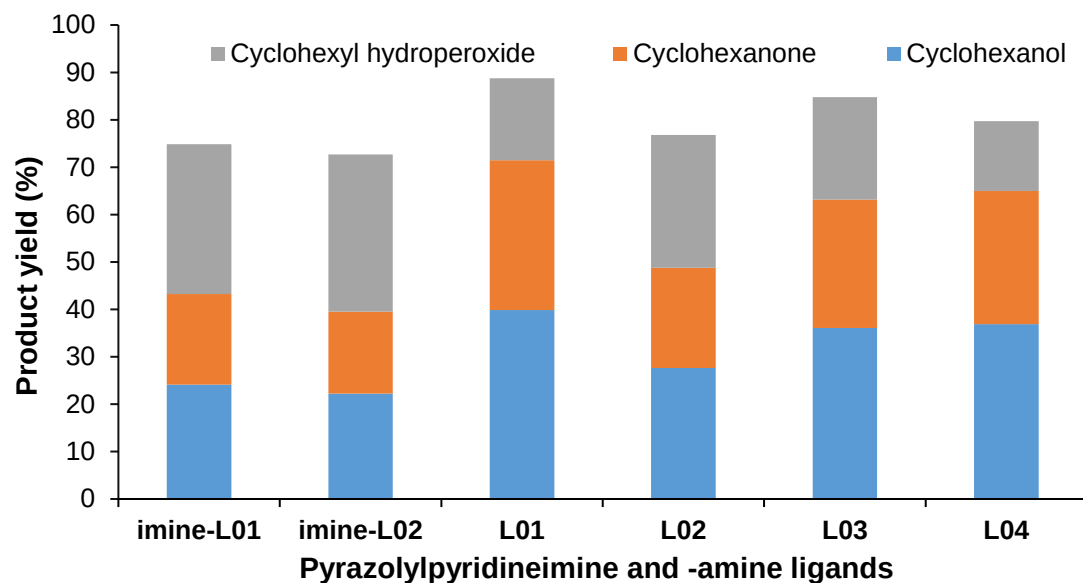


Figure S4.2: Various pyrazolypyridineimine: (E)-*N*-(2-(1*H*-pyrazol-1-yl)ethyl)-1-(pyridine-2-yl)methanimine (**imine-L01**), (E)-*N*-(2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl)-1-(pyridine-2-yl)methanimine (**imine-L02**) and -amine ligands 2-(1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L01**), 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L02**), *N*-methyl-2-(1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L03**) and 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-methyl-*N*-(pyridine-2-ylmethyl)ethan-1-amine (**L04**) were evaluated in cyclohexane peroxidation.

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Next, we evaluated various Cu^I-/Cu^{II}-precursors, in combination with ligand **L01**, for the peroxidation of cyclohexane (Figures S4.3).

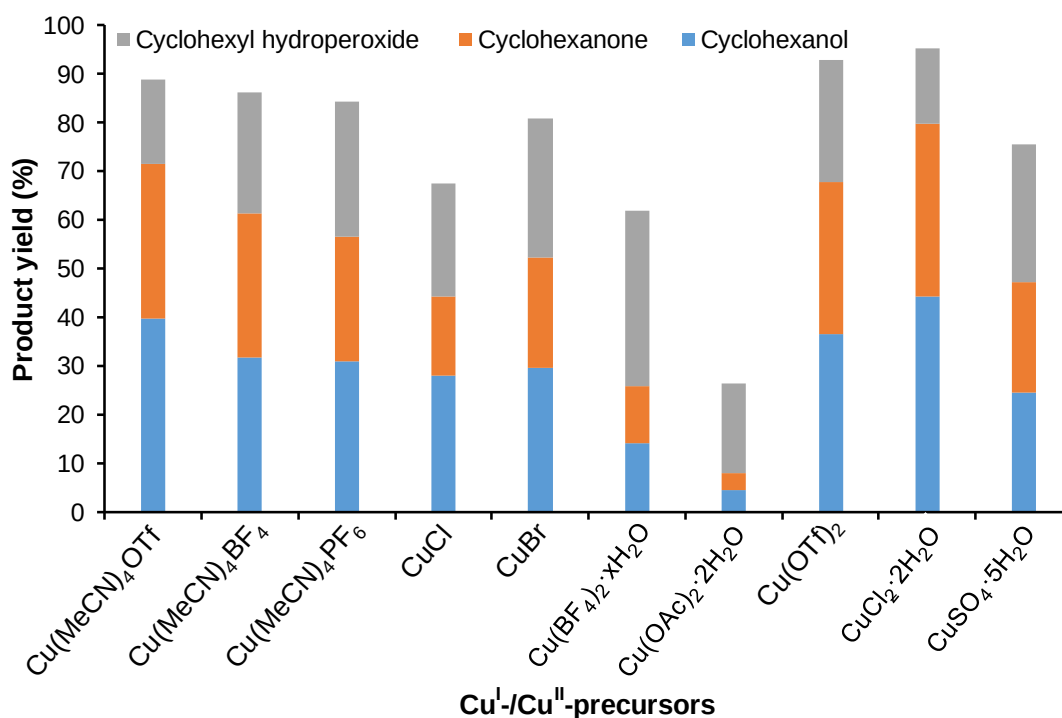


Figure S4.3: Evaluation of various Cu^I-/Cu^{II}-precursors, in combination with ligand **L01**, for the peroxidation of cyclohexane.

The effect of varying [LCu], [H₂O₂] and [substrate], using ligand **L01** in combination with CuCl₂·2H₂O, for cyclohexane peroxidation were evaluated. An increase in the concentration of LCu resulted in an increase in product yields (Figure S4.4).

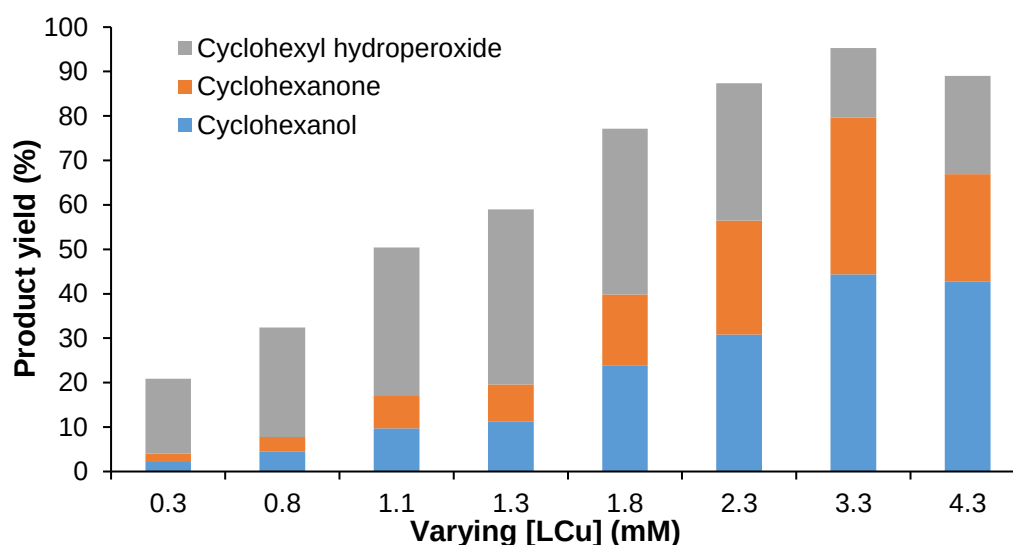


Figure S4.4: The evaluation of varying [LCu], using ligand **L01** and CuCl₂·2H₂O, for cyclohexane peroxidation.

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An increase in the concentration of H_2O_2 resulted in an increase in the product yields obtained during the peroxidation of cyclohexane (Figure S4.5).

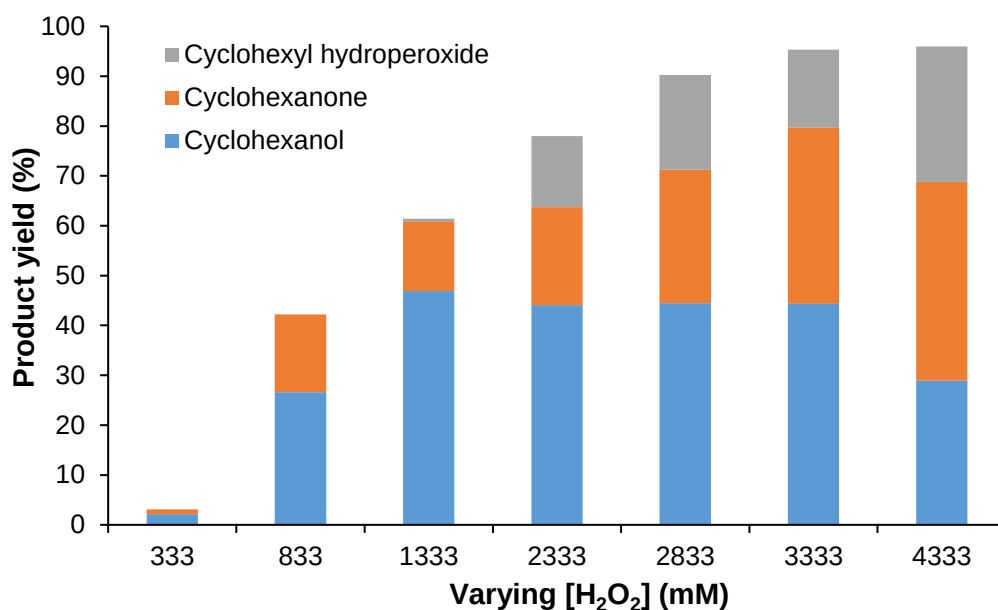


Figure S4.5: The evaluation of varying $[\text{H}_2\text{O}_2]$, using ligand **L01** and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, for the peroxidation of cyclohexane.

Similar product yields were obtained for the peroxidation of cyclohexane, even with an increase in the substrate (Figure S4.6).

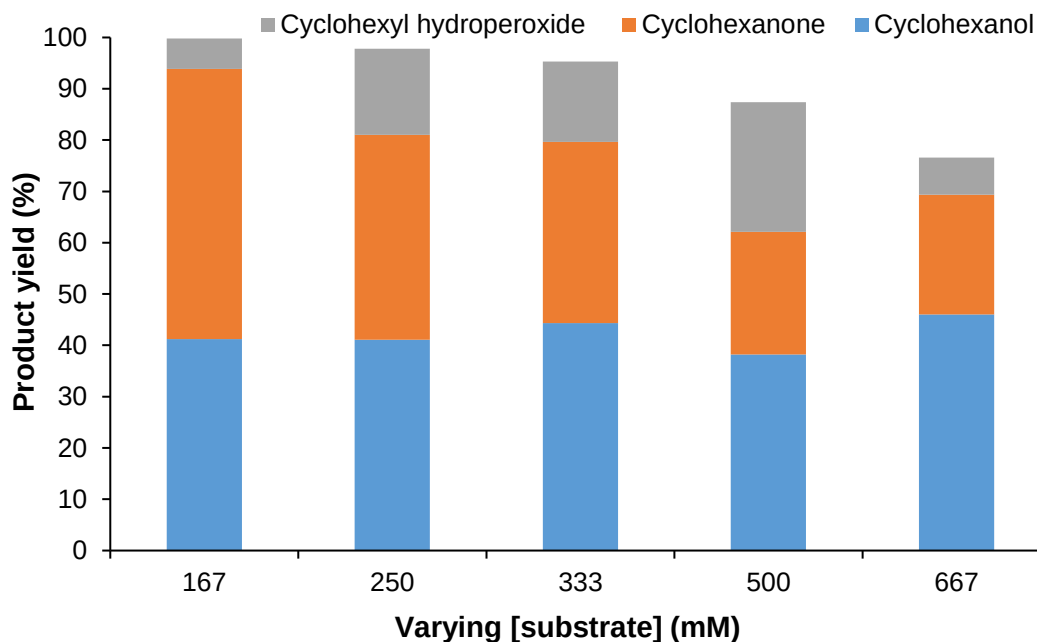


Figure S4.6: The evaluation of varying [substrate], using ligand **L03** and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, for the peroxidation of cyclohexane.

S4.3 Evaluating the formation of radical species

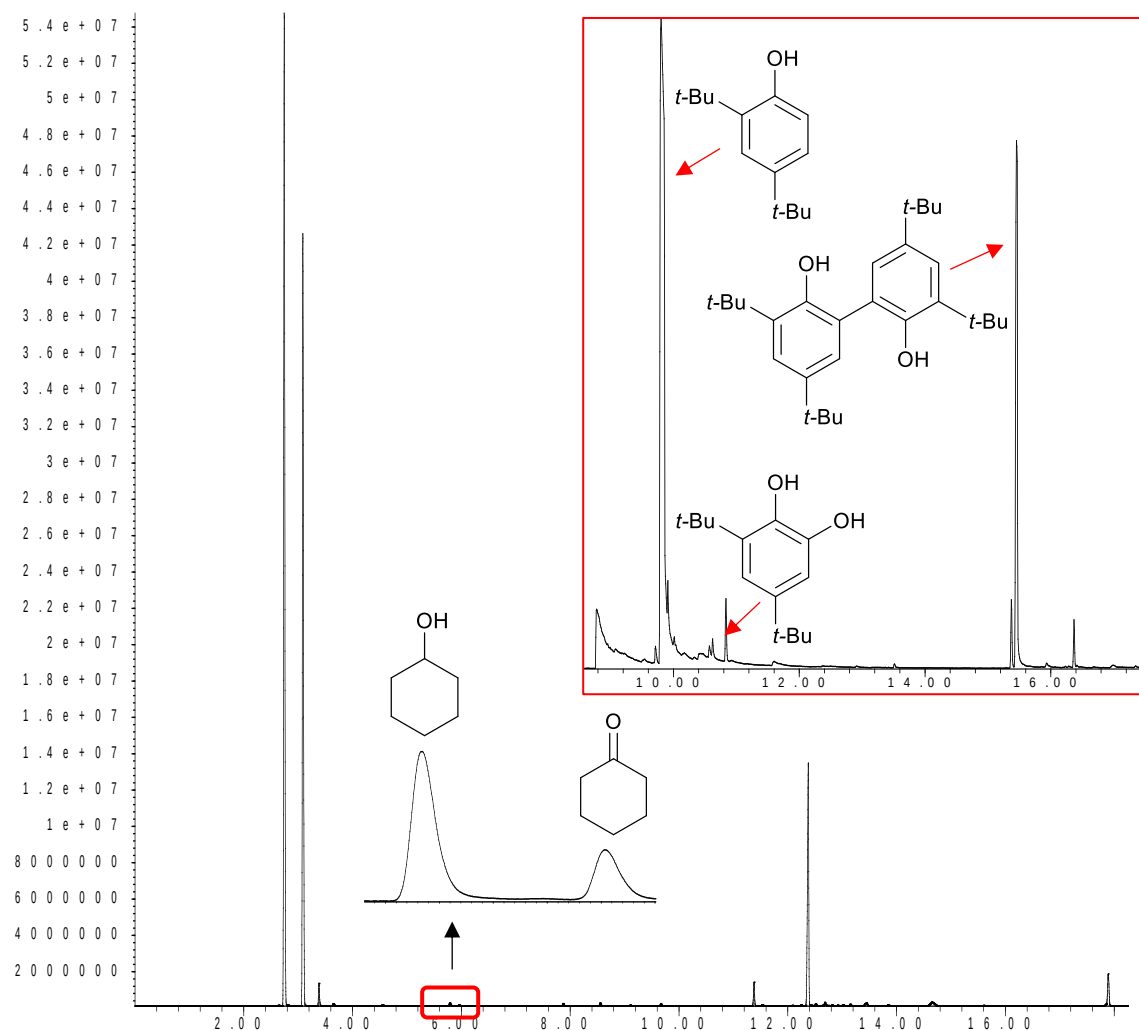


Figure S4.7: GC spectrum for cyclohexane peroxidation (3.38 min) in the presence of 2,4-di-*tert*-butylphenol as a radical trap, when employing our optimised (**L01**)CuCl₂·2H₂O/H₂O₂ catalyst system. Even though the formation of the cyclohexyl hydroperoxide (7.87 min), cyclohexanol (5.79 min) and cyclohexanone (5.93 min) products was observed, 3,3',5,5'-tetra-*tert*-butylbiphenyl-2,2'-diol (major radical coupling product) and 3,5-di-*tert*-butylbenzene-1,2-diol (trace amounts) were also identified by GC-MS (inset).

S4.4 Kinetic studies

Kinetic assessments were conducted for our optimised (**L01**)CuCl₂·2H₂O/H₂O₂ catalyst system. Initial rate data for the production of cyclohexyl hydroperoxide were generated for varying [LCu], [H₂O₂] and [substrate] (Table S4.1).

Table S4.1: Kinetic data for the peroxidation of cyclohexane by (**L01**)CuCl₂·2H₂O/H₂O₂, assessing the kinetic dependence on [LCu], [H₂O₂] and [cyclohexane].

Entry	[(L01)Cu ^{II}] (mM)	[H ₂ O ₂] (mM)	[Cyclohexane] (mM)	k _{initial} (mM·min ⁻¹)	Standard deviation
1	0.8	2833	333	0.3787	0.0088
2	1.1	2833	333	0.5392	0.0272
2	1.8	2833	333	0.6625	0.0029
3	2.3	2833	333	0.7946	0.1030
4	3.3	2833	333	1.0084	0.0689
5	4.3	2833	333	1.0396	0.1102
6	3.3	833	333	0.2847	0.0136
7	3.3	1833	333	0.4693	0.0010
8	3.3	2833	333	1.0084	0.0689
9	3.3	3333	333	1.0467	0.0113
10	3.3	4333	333	1.0918	0.0934
11	3.3	2833	167	0.9657	0.0183
12	3.3	2833	250	0.7410	0.0068
13	3.3	2833	333	1.0084	0.0689
14	3.3	2833	413	0.8966	0.0416

S4.5 Mechanistic considerations

UV/vis studies were employed to indicate the formation of the $\text{LCu}^{\text{II}}\text{-OOH}$ intermediate under basic conditions. Reactions were performed without the substrate to investigate the interaction between LCu and H_2O_2 , in the presence of NEt_3 [2]. An absorbance was observed at 375 nm, consistent with the formation of the $\text{LCu}^{\text{II}}\text{-OOH}$ intermediate (Figure S4.8) [3-5]. The reaction rate for the formation of this intermediate was calculated as 0.0337 s^{-1} over the initial 0.2 s, however, the formation of an off-cycle $[\text{Cu-hydroxo}]_2$ dimer then resulted in a significant decrease in the rate. Similar inactive dimeric species have been reported previously [6-11].

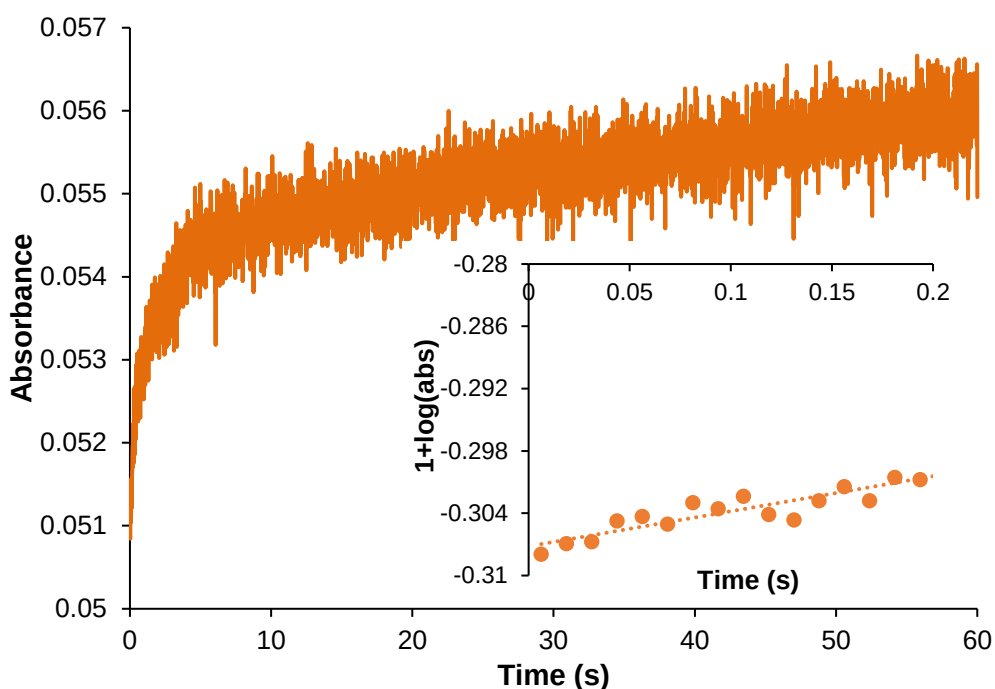


Figure S4.8: UV/vis studies were employed to follow the formation of the key intermediate, $\text{LCu}^{\text{II}}\text{-OOH}$, at 375 nm over a reaction time of 60 s, under basic conditions and in the absence of a substrate [2]. The rate constant (k_{obs}) for $\text{Cu}^{\text{II}}\text{-OOH}$ formation was calculated using $1+\log(\text{abs})$ vs time (s) for the initial 0.2 s (inset).

S4.6 References

- [1] I. Garcia-Bosch, M.A. Siegler, *Angew. Chem. Int. Ed.*, 55 (2016) 12873-12876.
- [2] L. Marais, H.C.M. Vosloo, A.J. Swarts, Synthetic LPMO mimics: a copper/pyrazolylpyridineamine catalyst system for the highly efficient oxidative cleavage of p-nitrophenyl- β -D-glucopyranoside, Chapter 6, Manuscript in preparation, (2021).
- [3] S. Muthuramalingam, D. Maheshwaran, M. Velusamy, R. Mayilmurugan, *J. Catal.*, 372 (2019) 352-361.
- [4] A.L. Concia, M.R. Beccia, M. Orio, F.T. Ferre, M. Scarpellini, F.d.r. Biaso, B. Guigliarelli, M. Réglér, A.J. Simaan, *Inorg. Chem.*, 56 (2017) 1023-1026.
- [5] B. Bissaro, Å.K. Røhr, G. Müller, P. Chylenski, M. Skaugen, Z. Forsberg, S.J. Horn, G. Vaaje-Kolstad, V.G. Eijsink, *Nat. Chem. Biol.*, 13 (2017) 1123-1131.
- [6] L. Marais, J. Bures, J.H.L. Jordaan, S. Mapolie, A.J. Swarts, *Org. Biomol. Chem.*, 15 (2017) 6926-6933.
- [7] J.M. Hoover, B.L. Ryland, S.S. Stahl, *ACS Catal.*, 3 (2013) 2599-2605.
- [8] G.A. van Albada, I. Mutikainen, O. Roubeau, U. Turpeinen, J. Reedijk, *Inorg. Chim. Acta*, 331 (2002) 208-215.
- [9] Y.-Q. Zheng, J.-L. Lin, *Z. Anorg. Allg. Chem.*, 629 (2003) 1622-1626.
- [10] S.P. Perlepes, J.C. Huffman, G. Christou, *Polyhedron*, 11 (1992) 1471-1479.
- [11] G.A. van Albada, I. Mutikainen, U. Turpeinen, J. Reedijk, *Inorg. Chim. Acta*, 324 (2001) 273-277.
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A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions

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Novel α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene (imine-**L05** and imine-**L06**) and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene (**L05-L08**) ligands have been successfully prepared and characterised, using several spectroscopic and analytical techniques. These ligands can coordinate with two Cu^I- or Cu^{II}-centres during the *in situ* formation of the pre-catalysts. Binuclear pre-catalysts, in combination with H₂O₂, were employed in the peroxidation of cyclohexane, with excellent product yields of > 88 % in 3 h. Cyclohexyl hydroperoxide (CyOOH) was observed as the major product. We have identified the optimised reaction conditions: [Cu(MeCN)₄]PF₆ and ligand **L05** (1 mol%), substrate (1 mmol), H₂O₂ (8 equiv.) and MeCN (3 mL). Our (**L05**)[Cu(MeCN)₄]PF₆/H₂O₂ catalyst system could be employed in the peroxidation of alternative cyclic and linear alkanes, and moderate to good product yields of 74 to 94 and 53 % were obtained, respectively. Kinetic assessments were performed and the rate of CyOOH formation exhibits a first-order dependence on [LCu] and [H₂O₂], while a zero-order dependence was obtained for [substrate]. Radical trap experiments with carbon tetrachloride (CCl₄) and 2,4-di-*tert*-butylphenol supported the formation of C- and O-centred radical species.

Keywords: peroxidation, bifunctional ligands, copper(I) catalysis, radical trap, alkanes.

5.1 Introduction

The oxidation of inexpensive alkanes is an important reaction due to the formation of more valuable oxygenated products such as alcohols, ketones, aldehydes and carboxylic acids [1]. Several reaction steps and harsh reaction conditions such as high temperatures, the addition of strong oxidants or additives, which result in poor selectivity and low yields, are often required during the activation of C-H bonds [2]. The economic attractiveness and widespread availability of copper have led to the development of a number of mononuclear Cu-based catalyst systems for the peroxidation of cycloalkanes [1, 3-14]. These catalyst systems, however, typically result in low product yields with low product selectivity and they require expensive additives. Garcia-Bosch and co-workers demonstrated the ability to apply Cu^I complexes, such as [Cu(*R,R*)-BPBP][PF₆] ((*R,R*)-BPBP: (2*R*,2'*R*)-1,1'-bis(2-pyridinylmethyl)-2,2'-bipyrrolidine), in combination with H₂O₂ for cyclohexane peroxidation with significantly improved product yields (56 % relative to < 5 %) and selectivity towards cyclohexanol [15].

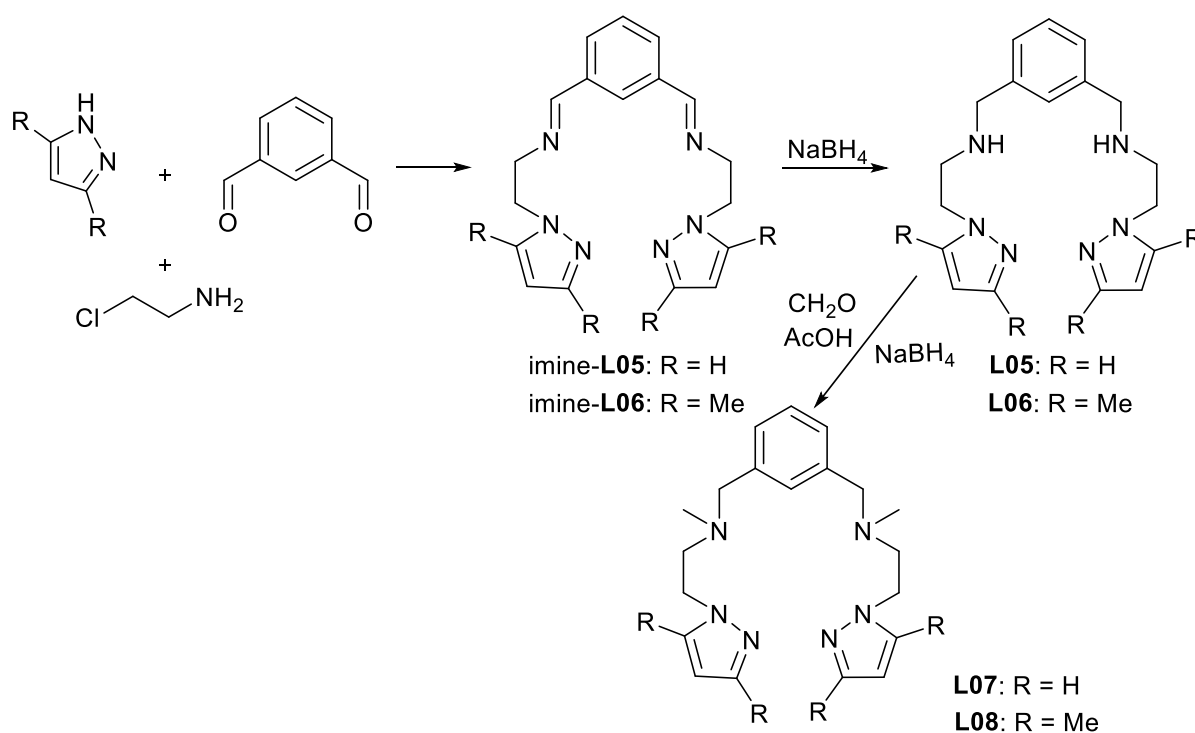
The application of pyrazolylpyridineamine ligands, in combination with a nickel precursor, in catalytic oligomerisation and polymerisation of ethylene was recently reported [16, 17]. Similar novel pyrazolylpyridineamine ligands, in combination with copper, have also found application in the hydroxylation of aryl halides and the peroxidation of hydrocarbons [18, 19]. These ligands can coordinate to one copper centre to afford mononuclear pre-catalysts; however, studies have also reported the application of bi- or multinuclear (> 2) Cu-based pre-catalysts for peroxidation reactions [5, 12]. Unfortunately, these catalyst systems still require high temperatures with resulting low product yields and the addition of additives, and therefore there is still a growing demand to develop an optimal binuclear Cu-based catalyst system for optimal peroxidation reactions.

Our pyrazolylpyridineimine and -amine ligand framework was expanded through the development of α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene ligands with two bidentate *N*-(2-pyrazolyl)ethylimino or *N*-(2-pyrazolyl)ethylamino units and a *m*-xylene bridge. We envisaged the ability of our novel ligand framework to be bifunctional in accommodating two copper centres, thereby facilitating the peroxidation of hydrocarbons with improved product yields and alcohol selectivity. Herein, we report the synthesis and characterisation of novel bifunctional α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene: α,α' -bis[*N*-(2-pyrazolyl)ethylimino]-*m*-xylene (imine-**L05**), α,α' -bis[*N*-(2-(3,5-dimethylpyrazolyl))ethylimino]-*m*-xylene (imine-**L06**) and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene ligands: α,α' -bis[*N*-(2-pyrazolyl)ethylamino]-*m*-xylene (**L05**), α,α' -bis[*N*-(2-(3,5-dimethylpyrazolyl))ethylamino]-*m*-xylene (**L06**), α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene (**L07**) and α,α' -bis[(*N*-methyl-2-(3,5-dimethylpyrazolyl))-ethylamino]-*m*-xylene (**L08**, Scheme 5.1). These *m*-xylene bridged ligands have never been employed in peroxidation reactions, and therefore the main goal of this study is to provide a detailed investigation of their application, in combination with Cu-precursors, as novel binuclear pre-catalysts for the peroxidation of various cyclic and linear alkanes. Reactions were performed in the presence of radical trapping agents to establish the nature of the active metal species and radical species formation. Lastly, kinetic studies were performed to evaluate the influence of varying [LCu], [H₂O₂] and [substrate] on the rate of cyclohexyl hydroperoxide formation.

5.2 Results and discussion

5.2.1 Synthesis and characterisation of the α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene ligands

Novel α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene (imine-**L05** and imine-**L06**) and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene ligands (**L05-L08**, Scheme 5.1) were successfully synthesised via a similar synthesis route as previously reported for our pyrazolylpyridineimine and -amine ligands [16, 18]. This synthesis route involves the Schiff base condensation (imine-**L05**, imine-**L06**), reductive amination (**L05-L06**) and methylation (**L07-L08**) reaction steps. Two copper centres coordinate to these ligands during the *in situ* formation of the bifunctional pre-catalysts, and therefore no complexes were isolated [20].



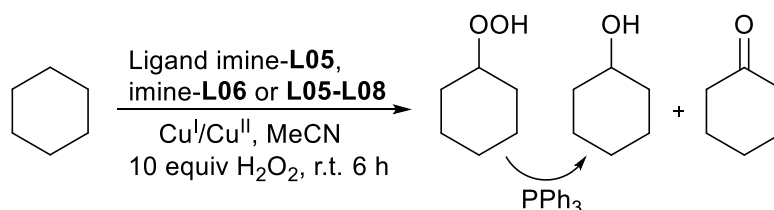
Scheme 5.1: Novel α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene (imine-**L05** and imine-**L06**) and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene ligands (**L05-L08**) were successfully synthesised and characterised.

Ligands imine-**L05**, imine-**L06** and **L05-L08** were isolated as light yellow or clear oils, soluble in polar organic solvents such as dichloromethane (DCM), acetonitrile (MeCN), dimethyl sulfoxide (DMSO), alcohols and water. These ligands are stable in air, and can therefore be stored without any precaution. Characterisation of the bifunctional ligands was done by employing several spectroscopic and analytical techniques. FT-IR spectroscopy showed the

presence of the imine (C=N) absorption band in the region 1644 to 1673 cm^{-1} for ligands imine-**L05** and imine-**L06**. This absorption band disappeared upon reduction, with the appearance of an absorption band either in the region 3291 to 3305 cm^{-1} , consistent with the formation of a secondary amine (**L05** and **L06**) or in the downfield regions of 3513 to 3535 cm^{-1} and 3145 to 3151 cm^{-1} , which confirmed the successful methylation of the secondary amines to afford the tertiary amine analogues, **L07** and **L08**. The ^1H NMR spectroscopic analysis of these ligands provides information on the structure of all compounds (Figures S5.1, S5.3, S5.5, S5.7, S5.9 and S5.11 in the Supporting Information). We observed the imine proton (CH=N) resonance as a singlet in the range δ 7.96 to 7.98 ppm, which disappeared upon reduction, while a new absorption band appeared more upfield in the ranges δ 5.38 to 6.16 ppm or δ 2.23 to 2.25 ppm, consistent with the secondary amine (N-H) or tertiary amine (N-CH₃) resonances, respectively. The introduction of methyl groups on the pyrazole ring for ligands imine-**L06**, **L06** and **L08** was observed as a singlet resonance in the range δ 2.14 to 2.27 ppm. Moreover, our $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopic analysis also confirmed the presence of an imine group (imine-**L05** and imine-**L06**) in the range δ 162.83 to 162.84 ppm; while the substitution of methyl groups on the ethyl-linked *N*-atom (**L07** and **L08**) and the pyrazole ring (imine-**L06**, **L06** and **L08**) was confirmed with resonances in the range δ 42.41 to 42.59 ppm and δ 11.11 to 13.63 ppm, respectively (Figures S5.2, S5.4, S5.6, S5.8, S5.10 and S5.12 in the Supporting Information). The purity of our novel bifunctional ligands, imine-**L05**, imine-**L06** and **L05-L08**, was confirmed with APCI mass spectrometry (APCI-MS; Figures S5.13-S5.18 in the Supporting Information).

5.2.2 Optimisation of the (**L05**)[Cu(MeCN)₄]PF₆/H₂O₂ catalyst system.

Our catalyst system was optimised for the peroxidation reaction by evaluating cyclohexane as the model substrate, using previously reported reaction conditions (Scheme 5.2) [21, 22]. The reaction was quenched with an excess of triphenylphosphine (PPh₃) to allow the conversion of most of the cyclohexyl hydroperoxide (CyOOH) product to afford the alcohol (CyOH, major product) and ketone (CyO) products (Figure S5.19 in the Supporting Information) [23]. It should be noted that complete conversion of CyOOH was impossible.



Scheme 5.2: The Cu-based catalyst system for the peroxidation of cyclohexane to afford CyOOH, CyOH and CyO as products, before optimisation.

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Our novel bifunctional ligands, imine-**L05**, imine-**L06** and **L05-L08**, in combination with [Cu(MeCN)₄]OTf, in a ratio of 0.5:1 (**L**:Cu) were employed during cyclohexane peroxidation (Table 5.1, entries 1-6 and Figure S5.20 in the Supporting Information) [21, 22]. Our hypothesis that these ligands accommodate two Cu-centres was confirmed, since similar product yields of 88 and 90 % were obtained for cyclohexane peroxidation, using (**L05**)Cu^I ratios of 0.5:1 and 1:1, respectively (Table 5.1, entries 3 and 7). Excellent product yields of 81 to 84 % were obtained in the presence of ligands imine-**L05** and imine-**L06** (Table 5.1, entries 1 and 2) as well as when employing their tertiary amine analogues, **L07** and **L08** (Table 5.1, entries 5 and 6). However, slightly higher product yields of 87 to 90 % were obtained when employing the secondary amine analogues (**L05** and **L06**, Table 5.1, entries 3 and 5). As expected, a low product yield of 39 % was obtained in the absence of a ligand (Table 5.1, entry 8).

Table 5.1: Evaluation of novel bifunctional ligands (imine-**L05**, imine-**L06** and **L05-L08**), in combination with [Cu(MeCN)₄]OTf, on the peroxidation of cyclohexane.^a

Entry	Ligand	Yield (%) ^b CyOH ^(CyOOH) /CyO	Total yield (%) ^b	Standard deviation (%)
1	imine- L05	28 ⁽³⁰⁾ /24	81	5.47
2	imine- L06	34 ⁽²³⁾ /27	84	2.08
3	L05	38 ⁽²⁰⁾ /32	90	2.88
4	L06	37 ⁽¹⁹⁾ /30	87	1.59
5	L07	29 ⁽³¹⁾ /23	84	6.83
6	L08	28 ⁽³⁰⁾ /23	82	5.30
7 ^c	L05	28 ⁽³⁸⁾ /23	88	4.07
8	-	7 ⁽²⁶⁾ /6	39	4.82

^a Cyclohexane (1.0 mmol), [Cu(MeCN)₄]OTf (1 mol%), imine-**L05**, imine-**L06** and **L05-L08** (1 mol %), H₂O₂ (10 mmol, 10 equiv.), MeCN (3 mL), reaction time: 6 h, 27 ± 2 °C. ^b GC yields of the products were determined with the use of a calibration curve (internal standard: biphenyl). The data reported are the average product yields obtained from two independent runs. ^c LCu ratio of 1:1 instead of 0.5:1.

The tertiary amine analogues, which do not contain a free NH-group, has a negative influence on the catalytic activity, while the substituents (hydrogen or methyl groups) on the pyrazole ring do not have a major influence, since almost no differences in the product yields were observed. This is, however, in contrast with previously reported results where they observed that the substituents on the pyrazole ring have a negative influence on the catalytic activity [24]. In conclusion, our obtained product yields are significant improvements on previously

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reported product yields for cyclohexane peroxidation employing both mononuclear and binuclear Cu-based catalyst systems [5, 7, 9-13, 15]. The optimal product yield was obtained in the presence of ligand **L05**, while CyOH was identified as the major product, and therefore it was employed in further studies.

Next, we evaluated various Cu^I/Cu^{II}-precursors in the peroxidation of cyclohexane using ligand **L05**, under previously reported reaction conditions (Table 5.2 and Figure S5.21 in the Supporting Information) [15]. Excellent product yields of 90 to 91 % were obtained when employing Cu^I-precursors with non-coordinating anions (Table 5.2, entries 1-3). In contrast, slightly lower product yields of 67 to 89 % were obtained for those bearing coordinating anions (Table 5.2, entries 4 and 5).

Table 5.2: Evaluation of various Cu^I/Cu^{II}-precursors, in combination with ligand **L05**, on the peroxidation of cyclohexane.^a

Entry	Cu ^I /Cu ^{II} -precursor	Yield (%) ^b CyOH ^(CyOOH) /CyO	Total yield (%) ^b	Standard deviation (%)
1	[Cu(MeCN) ₄]OTf	38 ⁽²⁰⁾ /32	90	2.11
2	[Cu(MeCN) ₄]BF ₄	35 ⁽²²⁾ /33	90	5.79
3	[Cu(MeCN) ₄]PF ₆	34 ⁽²⁶⁾ /31	91	2.65
4	CuCl	43 ⁽¹⁴⁾ /31	89	5.19
5	CuBr	23 ⁽²⁸⁾ /15	67	5.48
6	Cu(BF ₄) ₂ ·xH ₂ O	29 ⁽³²⁾ /25	85	3.85
7	Cu(OAc) ₂ ·2H ₂ O	1 ⁽⁵⁾ /1	6	2.29
8	Cu(OTf) ₂	34 ⁽²¹⁾ /29	84	7.10
9	CuCl ₂ ·2H ₂ O	38 ⁽²²⁾ /23	83	2.18
10	CuSO ₄ ·5H ₂ O	28 ⁽²⁹⁾ /23	79	1.44
11	-	0 ⁽⁰⁾ /0	0	-

^a Cyclohexane (1.0 mmol), various Cu^I/Cu^{II}-precursors (1 mol%), **L05** (1 mol %), H₂O₂ (10 mmol, 10 equiv.), MeCN (3 mL), reaction time: 6 h, 27 ± 2 °C. ^b GC yields of the products were determined with the use of a calibration curve (internal standard: biphenyl). The data reported are the average product yields obtained from two independent runs.

The evaluation of Cu^{II} pre-catalysts for cyclohexane peroxidation have previously been reported to proceed with moderate product yields of < 50 % [1, 8, 25, 26]. We obtained similar product yields when using either Cu^I- or Cu^{II}-precursors (79 to 85 %, Table 5.2, entries 6 and 8-10) [18], which is slightly in contrast to the findings of Garcia-Bosch and co-workers since they obtained a decrease in product yields when employing Cu^{II}-precursors [15, 27]. An exceptionally low product yield of 6 % was, however, obtained when employing

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$\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (Table 5.2, entry 7). No cyclohexane peroxidation was possible in the absence of a Cu-precursor (Table 5.2, entry 11) [14]. Pombeiro and co-workers reported a multinuclear Cu-based catalyst system with dimeric, trimeric, tetrameric and polymeric ligands, in an acidic medium, for cyclohexane peroxidation with moderate product yields of 15 to 31 %. Excellent product yields were possible when using either Cu^{I} - or Cu^{II} -precursors. Even though Cu^{I} -precursors with either coordinating or non-coordinating anions resulted in similar selectivity towards the formation of the alcohol product, the highest product yield was possible when employing $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ in combination with ligand **L05**, and was therefore employed in further studies.

Lastly, we were able to employ our optimised (**L05**) $[\text{Cu}(\text{MeCN})_4]\text{PF}_6/\text{H}_2\text{O}_2$ catalyst system for the peroxidation of alternative cyclic and linear alkanes (Table 5.3).

Table 5.3: Our optimised (**L05**) $[\text{Cu}(\text{MeCN})_4]\text{PF}_6/\text{H}_2\text{O}_2$ catalyst system was employed in the peroxidation of various cyclic and linear alkanes.^a

Reaction scheme: $\text{C}_n \xrightarrow[8.5 \text{ equiv } \text{H}_2\text{O}_2, \text{ MeCN, r.t. 6h}]{10 \mu\text{mol } \text{L05} \& [\text{Cu}(\text{MeCN})_4]\text{PF}_6} \text{C}_n\text{OOH} \xrightarrow{\text{PPh}_3} \text{C}_n\text{OH} + \text{C}_n\text{O}$

Mixture of C_n oxidation products

Entry	Substrate	Products	$\text{CyOH}^{(\text{CyOOH})}/\text{CyO}$ (Yield: [%]) ^b	Yield [%] ^b
<u>Cyclic alkanes</u>				
1			35 ⁽²⁶⁾ /30	91.0±2.65
2			8 ⁽⁴²⁾ /26	76.0±2.85
3			53 ⁽²¹⁾ /20	94.3±2.38
4			26 ⁽³⁸⁾ /10	74.2±1.84
<u>Linear alkane</u>				
5		C(1) : C(2) : C(3) : C(4) Ketone, aldehyde and alcohol products	-	52.6±8.13

^a Reaction conditions: $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ and ligand **L05** (1 mol%), H_2O_2 (8.5 mmol), substrate (1 mmol), MeCN (3 mL), reaction time: 6 h, $27 \pm 2^\circ\text{C}$. ^b GC yields of the products were determined with the use of a calibration curve (internal standard: biphenyl). The data reported are the average product yields obtained from two independent runs.

A rapid increase in product yields was observed for cyclohexane peroxidation in the first 3 h (88 % total yield), after which an increase of only 3 % was obtained in the next 3 h (total product yield: 91 % in 6 h, Table 5.3, entry 1). Remarkable product yields of 74 to 94 % were obtained for the peroxidation of cyclopentane, cycloheptane and cyclooctane to the corresponding secondary alcohol and ketone products (Table 5.3, entries 2-4). Our results represent a significant improvement on previously reported product yields [12, 15, 25, 27-30]. The order of obtained product yields for the peroxidation reactions is: cycloheptane > cyclohexane > cyclopentane > cyclooctane.

Our catalyst system was also employed in the peroxidation of the linear alkane, *n*-octane, to afford a mixture of C₈ oxidation products and the regioselectivity in terms of C(1):C(2):C(3):C(4) was determined as 1:1:4:2 (Table 5.3, entry 5). We obtained a total product yield of 53 % and a selectivity of 66 % towards the octanone products, with 3-octanone as the major product. Previous groups have also evaluated *n*-octane as substrate during peroxidation reactions, and they observed an increased reactivity towards the internal C-H positions while low product yields of 5 to 23 % were obtained [14, 25, 30-32]. Our catalyst system displays enhanced activity for the peroxidation of *n*-octane.

5.2.3 Evaluating the formation of radical species in the (L05)[Cu(MeCN)₄]PF₆/H₂O₂ catalyst system

Cyclohexane peroxidation reactions were performed in the presence of the radical trapping agents, carbon tetrachloride (CCl₄, a ratio of 1:1 relative to H₂O₂ [15]) and 2,4-di-*tert*-butylphenol (a ratio of 1:300 relative to (L05)Cu^I [33]), to evaluate their effect on the obtained product yields. Even though CyOH and CyO were obtained as products when employing CCl₄ as the radical trap, an additional by-product, cyclohexyl chloride (CyCl) was also observed, with a CyCl/(CyOH+CyO) ratio of 2.3 (Table 5.4, entry 1). This supports the formation of C-centred radical species during the H-atom abstraction step [14, 15, 19, 28, 34, 35]. Moreover, a significant decrease in the product yield (33 vs 91 %) is indicative of the formation of O-centred radical species.

A remarkably low product yield of 29 % was obtained for cyclohexane peroxidation performed in the presence of 2,4-di-*tert*-butylphenol (Table 5.4, entry 2 and Figure S22 in the Supporting Information) and GC-MS analysis confirmed the formation of 3,3',5,5'-tetra-*tert*-butylbiphenyl-2,2'-diol as the major radical coupling product while traces of 3,5-di-*tert*-butylbenzene-1,2-diol (due to *ortho*-hydroxylation) were also observed. Our findings suggest the formation of LCu^{II}-hydroxyl (LCu^{II}-OH) and LCu^{II}-oxyl (LCu^{II}-O•) species during the rate-determining step, which is consistent with the first-order dependence on [LCu] [19, 33].

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The peroxidation of toluene usually results in low product yields, with a low probability to afford aldehyde products, since the C-H bonds of either the methyl group or the aromatic ring may be activated during the reaction [14, 15, 36]. As such, we employed our (L05)[Cu(MeCN)₄]PF₆/H₂O₂ catalyst system in toluene peroxidation and obtained a product yield of 44 %, with a mixture of oxidation products. *p*-Toluquinone was identified as the major product, while benzaldehyde and *o*-/ *m*-/ *p*-cresols were observed as minor products (Table 5.4, entry 3). This observation further supports the formation of O-centred radical species [19], while we were also able to improve on previously reported product yields. Lastly, inert reaction conditions were employed for cyclohexane peroxidation and a slight decrease in the product yield (83 vs 91 %) was observed (Table 5.4, entry 4). This suggests the conversion of H₂O₂ to O₂, which then reacts with the Cy[•] radical species to generate CyOOH.

Table 5.4: The formation of C- and O-centred radical species during peroxidation reactions was indicated using these experimental studies.^a

Entry	Comment	Yield (%) ^b CyOH(CyOOH)/CyO	Total yield ^b (%)	Standard deviation (%)
1	Radical trap: CCl ₄	3/7/23 (2.3) ^c	33	4.58
2	Radical trap: 2,4-di- <i>tert</i> butylphenol	12 ⁽¹²⁾ /5 ^d	29	3.42
3	Toluene as substrate	Mixture of oxidation products ^e	44	2.08
4	Inert atmosphere ^f	16 ⁽⁴⁷⁾ /21	83	5.27

^a Cyclohexane (1 mmol), [Cu(MeCN)₄]PF₆ and L05 (1 mol%), H₂O₂ (8.5 mmol, 8.5 equiv.), MeCN (3 mL), reaction time: 6 h, 27 ± 2 °C. ^b GC yields were determined using a calibration curve (internal standard: biphenyl). The data reported are the average conversions obtained from two independent runs. ^c CyOH/CyO/CyCl (CyCl/(CyOH+CyO)). ^d The 3,3',5,5'-tetra-*tert*-butylbiphenyl-2,2'-diol (major radical coupling product) and trace amounts of 3,5-di-*tert*-butylbenzene-1,2-diol (*via ortho*-hydroxylation) by-products were observed. ^e The mixture of products consists of benzaldehyde (7 %), *p*-toluquinone (20 %) and *o*-/ *m*-/ *p*-cresols (9/2/8 %, in a ratio of 47:10:41). ^f Under nitrogen.

5.2.4 Kinetic behaviour of the (L05)[Cu(MeCN)₄]PF₆/H₂O₂ catalyst system

Initial rate data for the formation of CyOOH were generated for varying [LCu], [H₂O₂] and [substrate], using our optimised reaction conditions (Figure 5.1 and Table S5.1 in the Supporting Information). First-order dependence on both the LCu catalyst and the H₂O₂ oxidant concentrations was obtained; however, while a plateau was reached at higher LCu concentrations, no loss in linearity was observed for H₂O₂ (Figure 5.1, A and B) [3, 15, 25, 37].

The rate of CyOOH formation exhibits no proportionality to the initial concentration of cyclohexane, consistent with the substrate not participating in the rate-determining step (Figure 5.1, C) [3, 15].

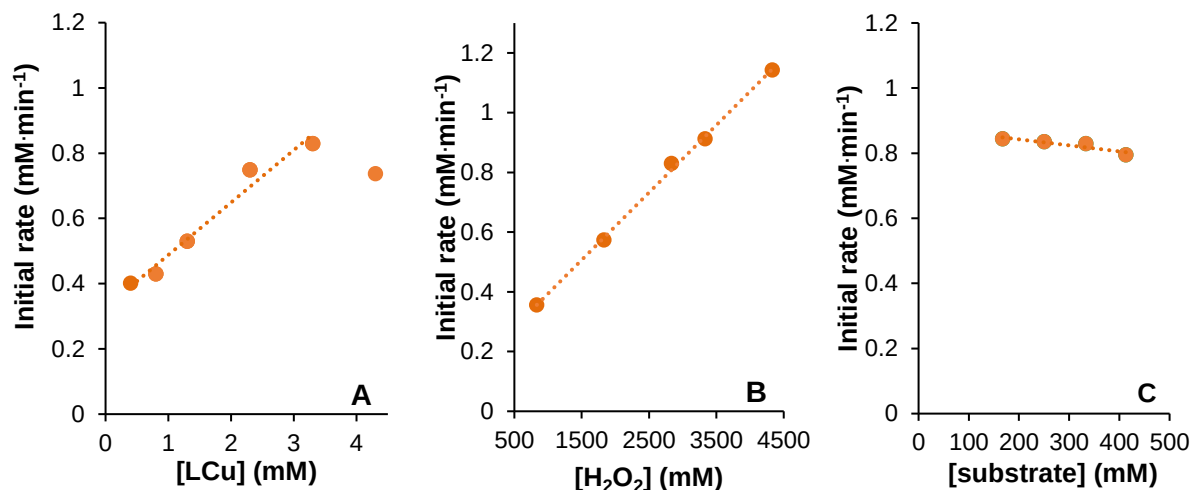


Figure 5.1: Kinetic assessments for varying [LCu] (A), [H₂O₂] (B) and [cyclohexane] (C) on the peroxidation of cyclohexane with our (L05)[Cu(MeCN)₄]PF₆/H₂O₂ catalyst system.

In conclusion, radical trap experiments and kinetic studies support the presence of both C- and O-centred radical species and the formation of both LCu^{II}-O[•] and LCu^{II}-OH species during the rate-determining step [33]. As such, these results support our previously reported findings for the application of *in situ* formed mononuclear Cu-based pre-catalysts, bearing pyrazolylpyridineamine ligands, for hydrocarbon peroxidation and the oxidative cleavage of polysaccharides [19, 35].

5.3 Conclusions

We have successfully synthesised our novel bifunctional α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene (imine-L05 and imine-L06) and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene (L05-L08) ligands following a similar synthesis route reported previously. Various analytical and spectroscopic techniques confirmed the preparation of our bifunctional ligands. These ligands consist of two bidentate *N*-(2-pyrazolyl)ethylimino or *N*-(2-pyrazolyl)ethylamino units with a *m*-xylene bridge, and can therefore accommodate two copper centres during the *in situ* formation of the pre-catalysts. This was confirmed when similar product yields were obtained for the LCu ratio of 1:1 and 0.5:1. Successful optimisation of our (L05)[Cu(MeCN)₄]PF₆/H₂O₂ catalyst system was achieved through the evaluation of various bifunctional ligands and Cu^I/Cu^{II}-precursors for cyclohexane peroxidation. Excellent product yields of > 88 % were obtained in 3 h, which is an improvement on the benchmark catalyst system. Our optimised catalyst system was further employed for the peroxidation of

alternative cyclic and linear alkanes and moderate to excellent product yields of 74 to 94 % and 53% were obtained, respectively. Significantly lower product yields of 29 to 33 % were obtained for reactions performed in the presence of the radical trapping agents, CCl₄ and 2,4-di-*tert*-butylphenol, supports the formation of C- and O-centred radical species. Moreover, the peroxidation of toluene resulted in a product yield of 44 %, which consists of a mixture of oxidation products. This further supports the formation of O-centred radical species. Kinetic studies were conducted and the rate of CyOOH formation exhibits a first-order dependence on [LCu] and [H₂O₂], while a zero-order dependence was obtained for [substrate]. As such, our radical confirmation and kinetic studies support the presence of C- and O-centred radical species, as well as the formation of both LCu^{II}-O[•] and LCu^{II}-OH species during the rate-determining step. This is consistent with our previously reported findings for *in situ* formed mononuclear Cu-based pre-catalysts, bearing a pyrazolylpyridineamine ligand, which confirmed that the nuclearity of the Cu-based catalyst system does not have a major influence on the efficiency of the peroxidation reactions. Even though high product yields were obtained for cyclohexane peroxidation, these reactions may also be further optimised to improve the alcohol selectivity, which forms part of current efforts in our laboratory.

5.4 Experimental section

5.4.1 General considerations

All commercially available reagents were obtained from Sigma-Aldrich and/or Merck and used as received. NMR [¹H and ¹³C{¹H}] spectra were recorded on a Bruker Ultrashield Plus spectrometer at 600 MHz and 150 MHz, respectively. The chemical shifts (δ) are given in parts per million (ppm) and externally referenced according to the residual protons of the deuterated solvent signal [38]. Coupling constants are reported in Hz. IR spectra were recorded as neat oils with a BrukerAlpha-P range FT-IR spectrometer equipped with an ATR accessory. APCI mass spectrometry (APCI-MS; positive ion mode) was recorded on a Bruker microTOF-Q II spectrometer. GC analyses were performed on an Agilent 6890 Series GC system with an HP-5 column, and samples (0.2 mL) were analysed with biphenyl as the internal standard. The oxidation products were identified by comparing their GC retention times to those of commercial samples. GC-MS analyses were performed on an Agilent 6890 N Series GC system with a mass selective (5973) detector and an HP-5-MSUI column. Helium served as the carrier gas, EtOAc and DCM were used as the rinsing solutions and samples (0.2 mL) were analysed with biphenyl as the internal standard to confirm the identification of peaks. The peroxidation reactions were done in duplicate to determine an average conversion value as well as the standard deviation.

5.4.2 Synthesis of the α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene ligands

The initial primary amine precursors were synthesised following our previously literature procedure [16-18]. The synthesis methods for the α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene ligands (imine-**L05** and imine-**L06**), are described in the Supporting Information.

α,α' -bis[*N*-(2-pyrazolyl)ethylamino]-*m*-xylene (L05**):** A modified method was used during the reduction of the ligands [39]. Ligand imine-**L05** (0.05 g, 0.16 mmol) was dissolved in ethanol (6 mL) and placed in an ice bath for 30 minutes. Simultaneously, a suspension of NaBH₄ (0.03 g, 0.80 mmol in 1 mL ethanol), in a 100 mL round-bottom flask, was also cooled down. Ligand imine-**L05** was slowly added to the round-bottom flask and the reaction mixture was stirred for 1 h at room temperature and then refluxed for another hour. The solvent was removed *in vacuo*, DCM (20 mL) was added and the organic phase was washed with water (2 x 5 mL), dried and filtered. The solvent was removed *in vacuo* to obtain the product as a light yellow oil (**L05**). Yield: 44 mg (87 %). ¹H NMR (600 MHz, CDCl₃): δ 7.51 (s, 2H, H_{Pyr}), 7.41 (d, *J* = 2.0 Hz, 2H, H_{Pyr}), 7.23 (t, *J* = 7.5 Hz, 1H, H_{Ar}), 7.17 (s, 1H, H_{Ar}), 7.13 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 6.23 (t, *J* = 1.9 Hz, 2H, H_{Pyr}), 6.16 (s, 1H, NH), 6.13 (s, 1H, NH), 4.25 (t, *J* = 5.8 Hz, 4H, NCH₂CH₂-Pyr), 3.75 (s, 4H, CH₂NH), 3.05 (t, *J* = 5.8 Hz, 4H, NCH₂CH₂-Pyr). ¹³C{¹H} NMR (150 MHz, CDCl₃): δ 140.16 (C_{Pyr}), δ 139.70 (C_{Ar}), δ 129.79 (C_{Pyr}), δ 128.65 (C_{Ar}), δ 127.83 (C_{Ar}), δ 126.91 (C_{Ar}), δ 105.53 (C_{Pyr}), δ 53.48 (NCH₂CH₂), δ 52.08 (NHCH₂-Pyr), δ 48.92 (NCH₂CH₂-Pyr) (Figures S5.1 and S5.2 in the Supporting Information). FT-IR (cm⁻¹): ν 3305 (NH and C-H (CH₂)), ν 2937 (CH₂), ν 1646 (C-C and C-H in pyridine ring), ν 1512 (C=C and C-H in pyrazole ring). APCI-MS (positive ion mode): mass fragment at *m/z* 325.22 (MW: 324.43 g/mol, Figure S5.15 in the Supporting Information).

The same synthesis method was used for ligand **L06**, as described in the Supporting Information.

α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene (L07**):** A modified method was used for the methylation of ligand **L05** [39]. In a 100 mL round-bottom flask, the reduced ligand **L05** (0.18 g, 0.79 mmol), dissolved in MeCN (5 mL), was allowed to stir during the addition of 100 % formaldehyde (0.75 mL, 8.75 mmol) and glacial acetic acid (0.75 mL). The reaction mixture was allowed to stir for 30 minutes before the slow addition of NaBH₄ (0.13 g, 3.31 mmol), after which the reaction mixture was stirred for another 72 hours at room temperature. The MeCN solvent was removed *in vacuo* and KOH (2 M) was added to the reaction mixture to increase the pH above 10. The aqueous phase was extracted with DCM (3 x 10 mL), the organic phase was dried over anhydrous Na₂SO₄ and the solvent was

removed *in vacuo* to obtain the product as a dark brown oil (**L07**). Yield: 47 mg (53 %). ^1H NMR (600 MHz, CDCl_3): δ 7.48 (d, J = 1.4 Hz, 2H, H_{Pyr}), δ 7.42 (d, J = 2.1 Hz, 2H, H_{Pyr}), δ 7.20 (t, J = 7.9 Hz, 1H, H_{Ar}), δ 7.10 (s, 1H, H_{Ar}), δ 7.09 (s, 2H, H_{Ar}), 6.22 (t, J = 1.9 Hz, 2H, H_{Pyr}), δ 4.23 (t, J = 6.6 Hz, 4H, $\text{NCH}_2\text{CH}_2\text{-Pyr}$), δ 3.49 (s, 4H, N(Me)CH_2), δ 2.84 (t, J = 6.6 Hz, 4H, $\text{NCH}_2\text{CH}_2\text{-Pyr}$), δ 2.23 (s, 6H, NCH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 139.21 (C_{Pyr}), δ 138.75 (C_{Ar}), δ 129.62 (C_{Pyr}), δ 129.44 (C_{Ar}), δ 128.34 (C_{Ar}), δ 127.78 (C_{Ar}), δ 105.38 (C_{Pyr}), δ 62.50 (N(Me)CH_2), δ 57.08 ($\text{NCH}_2\text{CH}_2\text{-Pyr}$), δ 50.38 ($\text{NCH}_2\text{CH}_2\text{-Pyr}$), δ 42.41 (NCH_3) (Figures S5.5 and S5.6 in the Supporting Information). FT-IR (cm^{-1}): ν 3513 (C-H (N-CH_3 , CH_2 , pyridine ring)), ν 3145 (C-H (N-CH_3 , CH_2)), ν 1638 (C-N and C-H in pyridine ring). APCI-MS (positive ion mode): mass fragment at m/z 353.24 (MW: 352.49 g/mol, Figure S5.17 in the Supporting Information).

The same synthesis method was used for ligand **L08**, as described in the Supporting Information.

5.4.3 Optimisation of our novel Cu-based catalyst system

The catalyst system was optimised by varying the ligands and the $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ -precursors in the peroxidation of cyclohexane. A solution of Cu-precursor ($[\text{Cu}(\text{MeCN})_4]\text{BF}_4$, $[\text{Cu}(\text{MeCN})_4]\text{OTf}$, $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$, CuCl , CuBr , $\text{Cu}(\text{BF}_4)_2 \cdot x\text{H}_2\text{O}$, $\text{Cu}(\text{OTf})_2$, $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and $\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$, 10 μmol in 1.5 mL MeCN) and ligand (imine-**L05**, imine-**L06** and **L05-L08**, 5 μmol in 1.5 mL MeCN) was stirred in a small reactor flask. The oxidant, H_2O_2 (30 % in H_2O , 1.1 mL, 10 mmol) was added to the colourless complex mixture. Immediately after 5-10 s, cyclohexane (0.11 mL, 1 mmol) was added, the reactor flask was closed (to prevent evaporation of the substrate) and allowed to stir for 6 h at room temperature. After the allotted time, the reaction mixture was added to a 10 mL vial containing EtOAc (3 mL) and PPh_3 (0.20 g, 0.75 mmol) and placed in the fridge for 20 min to allow the conversion of CyOOH to CyOH and CyO (the excess H_2O_2 is converted to H_2O). A sample (0.18 mL) was analysed by GC with biphenyl (50 μL) as the internal standard.

5.4.4 Evaluation of alternative cyclic and linear alkanes

A solution of $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ (10 μmol in 1.5 mL MeCN) and ligand **L05** (10 μmol in 1.5 mL MeCN) was stirred in a small reactor flask. The oxidant, H_2O_2 (30 % in H_2O , 1 mL, 8.5 mmol) was added to the colourless complex mixture. Immediately after 5-10 s, either a cyclic or linear alkane (1 mmol) was added, the reactor flask was closed (to prevent evaporation of the substrate) and allowed to stir for six hours at room temperature. After the allotted time, the reaction mixture was added to a 10 mL vial containing EtOAc (3 mL) and PPh_3 (0.20 g,

0.75 mmol) and placed in the fridge for 20 min to allow the conversion of CyOOH to CyOH and CyO. A sample (0.18 mL) was analysed by GC with biphenyl (50 μ L) as the internal standard.

5.4.5 Evaluating the formation of radical species formation

A solution of $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ (10 μ mol in 1.5 mL MeCN) and ligand **L05** (5 μ mol in 1.5 mL MeCN) was stirred in a small reactor flask. The oxidant, H_2O_2 (30 % in H_2O , 1.0 mL, 8.5 mmol) was added to the colourless complex mixture. Immediately after 5-10 s, cyclohexane (0.1 mL, 1 mmol) and either CCl_4 (0.77 mL, 8 mmol, a ratio of 1:1 relative to H_2O_2 [15]) or 2,4-di-*tert*-butylphenol (0.62 g, 3 mmol, a ratio of 1:300 relative to (**L05**)Cu^I [33]) were added, the reactor flask was closed and allowed to stir for 6 h at room temperature. A colour change to red-brown was observed with time. The above-mentioned workup process was used and a sample (0.18 mL) was analysed by GC and GC-MS with biphenyl (50 μ L) as the internal standard.

5.4.6 Kinetic studies

The concentration of only one reaction parameter was varied while the optimal reaction conditions were employed. A solution of $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ (x μ mol in 1.5 mL MeCN) and ligand **L05** (x μ mol in 1.5 mL MeCN) was stirred in a small reactor flask. The oxidant, H_2O_2 (30 % in H_2O , x mL, x mmol) was added to the colourless complex mixture. Immediately after 5-10 s, cyclohexane (x mL, x mmol) was added, the reactor flask was closed (to prevent evaporation of the substrate) and allowed to stir at room temperature. A sample (0.2 mL) was taken in varying reaction intervals of 20, 30, 40, 50, 60, 75, 90, 105, 120 and 135 min, which was added to a solution of PPh_3 (0.01 g, 0.38 mmol) in EtOAc (0.2 mL). A sample (0.18 mL) was analysed by GC with biphenyl (50 μ L) as internal standard.

5.5 Acknowledgements

This work is based on the research supported by the National Research Foundation of South Africa (Unique Grant No. 112545 and 117869) and North-West University. Any opinion, finding and conclusion or recommendation expressed in this material is that of the author(s) and the NRF does not accept any liability in this regard. The infrastructure support provided by the Focus Area for Chemical Resource Beneficiation (CRB) and in particular the Catalysis and Synthesis Research Group, at the NWU, is gratefully acknowledged.

5.6 References

- [1] U. Schuchardt, R. Pereira, M.c. Rufo, J. Mol. Catal. A: Chem., 135 (1998) 257-262.
- [2] M.T. Musser, Ullmann's Encyclopedia of Industrial Chemistry, 6th ed., Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011; Vol. 11.
- [3] G.B. Shul'pin, J. Gradinaru, Y.N. Kozlov, Org. Biomol. Chem., 1 (2003) 3611-3617.
- [4] R.S.d. Cruz, J.M.d.S. Silva, U. Arnold, M.S. Sercheli, U. Schuchardt, J. Braz. Chem. Soc., 13 (2002) 170-176.
- [5] T. Ohta, T. Tachiyama, K. Yoshizawa, T. Yamabe, T. Uchida, T. Kitagawa, Inorg. Chem., 39 (2000) 4358-4369.
- [6] S. Velusamy, T. Punniyamurthy, Tetrahedron Lett., 44 (2003) 8955-8957.
- [7] D.H. Barton, S.D. Bévière, W. Chavasiri, É. Csuhai, D. Doller, Tetrahedron, 48 (1992) 2895-2910.
- [8] T. Okuno, S. Ohba, Y. Nishida, Polyhedron, 16 (1997) 3765-3774.
- [9] D.H. Barton, D. Doller, Y.V. Geletii, Mendeleev Commun., 1 (1991) 115-116.
- [10] A. Sobkowiak, A. Qui, X. Liu, A. Llobet, D.T. Sawyer, J. Am. Chem. Soc., 115 (1993) 609-614.
- [11] A.M. Kirillov, M.N. Kopylovich, M.V. Kirillova, M. Haukka, M.F.C.G. da Silva, A.J. Pombeiro, Angew. Chem. Int. Ed., 44 (2005) 4345-4349.
- [12] A.M. Kirillov, M.N. Kopylovich, M.V. Kirillova, E.Y. Karabach, M. Haukka, M.F.C.G. da Silva, A.J. Pombeiro, Adv. Synth. Catal., 348 (2006) 159-174.
- [13] A. Conde, L. Vilella, D. Balcells, M.M. Díaz-Requejo, A. Lledós, P.J. Pérez, J. Am. Chem. Soc., 135 (2013) 3887-3896.
- [14] S.G. Mncube, M.D. Bala, Transition Met. Chem., 44 (2019) 145-151.
- [15] I. Garcia-Bosch, M.A. Siegler, Angew. Chem. Int. Ed., 55 (2016) 12873-12876.
- [16] C. Obuah, M.K. Ainooson, S. Boltina, I.A. Guzei, K. Nozaki, J. Darkwa, Organometallics, 32 (2013) 980-988.
- [17] C. Obuah, B. Omondi, K. Nozaki, J. Darkwa, J. Mol. Catal. A: Chem., 382 (2014) 31-40.
- [18] L. Marais, H.C.M. Vosloo, A.J. Swarts, Mol. Catal., 486 (2020) 110839.
- [19] L. Marais, H.C.M. Vosloo, A.J. Swarts, Highly efficient alkane peroxidation mediated by a copper(II)/pyrazolylpyridineamine catalyst system., Chapter 4, Manuscript to be submitted (2021).

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- [20] O. Gelling, F. Van Bolhuis, A. Meetsma, B.L. Feringa, J. Chem. Soc., Chem. Commun., (1988) 552-554.
- [21] O. Songis, P. Boulens, C.G. Benson, C.S. Cazin, RSC Adv., 2 (2012) 11675-11677.
- [22] N. Mketo, J.H.L. Jordaan, A. Jordaan, A.J. Swarts, S.F. Mapolie, Eur. J. Inorg. Chem., 2016 (2016) 3781-3790.
- [23] G.B. Shul'pin, J. Mol. Catal. A: Chem., 189 (2002) 39-66.
- [24] J. Jia, C. Jiang, X. Zhang, Y. Jiang, D. Ma, Tetrahedron Lett., 52 (2011) 5593-5595.
- [25] M.V. Kirillova, T.A. Fernandes, V. André, A.M. Kirillov, Org. Biomol. Chem., 17 (2019) 7706-7714.
- [26] E. Firinci, J. Mol. Struct., 1193 (2019) 125-130.
- [27] I. Garcia-Bosch, Synlett., 28 (2017) 1237-1243.
- [28] M.V. Kirillova, A.M. Kirillov, M.F.C. Guedes da Silva, A.J.L. Pombeiro, Eur. J. Inorg. Chem., 2008 (2008) 3423-3427.
- [29] C. Di Nicola, F. Garau, Y.Y. Karabach, L.M. Martins, M. Monari, L. Pandolfo, C. Pettinari, A.J. Pombeiro, Eur. J. Inorg. Chem., 2009 (2009) 666-676.
- [30] S.S. Dias, M.V. Kirillova, V.n. André, J. Klak, A.M. Kirillov, Inorg. Chem., 54 (2015) 5204-5212.
- [31] L. Soobramoney, M.D. Bala, H.B. Friedrich, Dalton Trans., 43 (2014) 15968-15978.
- [32] R. Chanerika, H.B. Friedrich, M.L. Shoji, Inorg. Chim. Acta, 495 (2019) 118992.
- [33] D.E. Diaz, M. Bhadra, K.D. Karlin, Inorg. Chem., 58 (2019) 13746-13750.
- [34] A. Bhattacharjee, S. Dey, P. Roy, Inorg. Chim. Acta, 490 (2019) 93-103.
- [35] L. Marais, H.C.M. Vosloo, A.J. Swarts, Synthetic LPMO mimics: a copper/pyrazolylpyridineamine catalyst system for the highly efficient oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside, Chapter 6, Manuscript in preparation, (2021).
- [36] H. Marusawa, K. Ichikawa, N. Narita, H. Murakami, K. Ito, T. Tezuka, Biorg. Med. Chem., 10 (2002) 2283-2290.
- [37] G.B. Shul'pin, G.V. Nizova, Y.N. Kozlov, L. Gonzalez Cuervo, G. Süß-Fink, Adv. Synth. Catal., 346 (2004) 317-332.
- [38] H.E. Gottlieb, V. Kotlyar, A. Nudelman, J. Org. Chem., 62 (1997) 7512-7515.
- [39] R.V. Ottenbacher, K.P. Bryliakov, E.P. Talsi, Inorg. Chem., 49 (2010) 8620-8628.

Supporting Information for

A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions

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S5.1 General considerations

S5.1.1 Instrumentation

NMR [¹H and ¹³C{¹H}] spectra were recorded on a Bruker Ultrashield Plus spectrometer at 600 MHz and 150 MHz, respectively. The chemical shifts (δ) are given in parts per million (ppm) and externally referenced according to the residual protons of the deuterated solvent signal [1]. Coupling constants are reported in Hz. IR spectra were recorded as neat oils with a BrukerAlpha-P range FT-IR spectrometer equipped with an ATR accessory. APCI mass spectrometry (APCI-MS; positive ion mode) was recorded on a Bruker microTOF-Q II

spectrometer. GC analyses were performed on an Agilent 6890 Series GC system with an HP-5 column (30 m x 0.320 mm x 0.25 mm). N₂ served as the carrier gas, ethyl acetate (EtOAc) and dichloromethane (DCM) were used as the rinsing solutions and samples (0.2 mL) were analysed with biphenyl as the internal standard. The oxidation products were identified by comparing their GC retention times to those of commercial samples. GC-MS analyses were performed on an Agilent 6890 N Series GC system with a mass selective (5973) detector and an HP-5-MSUI column. Helium served as the carrier gas, EtOAc and DCM were used as the rinsing solutions, and samples (0.2 mL) were analysed with biphenyl as the internal standard to confirm the identification of peaks. The peroxidation reactions were done in duplicate to determine an average yield as well as the standard deviation.

S5.2 Synthesis of the α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene ligands

The primary amine precursors (2-(1*H*-pyrazol-1-yl)ethan-1-amine and 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethan-1-amine) for these ligands were synthesised following our previously reported literature procedure [2-4].

α,α' -bis[*N*-(2-pyrazolyl)ethylimino]-*m*-xylene (imine-L05): A modified method was used to synthesise the imine ligands [5]. To a solution of isophthalaldehyde (0.12 g, 0.9 mmol) in DCM (10 mL) was added 2-(1*H*-pyrazol-1-yl)ethan-1-amine (0.20 g, 1.8 mmol) in a ratio of 1:2. The reaction mixture was stirred for 1 h, after which anhydrous Na₂SO₄ (1 g) was added and allowed to stir for another 30 min. After the allotted time, the reaction mixture was filtered and the solvent was removed *in vacuo* to obtain the crude product as a light yellow oil. Column chromatography was used to purify the crude oil, using EtOAc:MeOH (9:1) as eluent and 5 g silica gel. $Rf_{(\text{product})} = 0.47$, $Rf_{(\text{impurities})} = 0.20$. The product was isolated as a light yellow oil (imine-L05). Yield: 354 mg (75 %). ¹H NMR (600 MHz, CDCl₃): δ 7.98 (s, 2H, CHN), 7.87 (s, 1H, H_{Ar}), 7.71 (d, $J = 7.70$ Hz, 2H, H_{Ar}), 7.50 (s, 2H, H_{Pyr}), 7.40 (t, $J = 7.41$ Hz, 1H, H_{Ar}), 7.34 (s, 2H, H_{Pyr}), 6.13 (s, 2H, H_{Pyr}), 4.47 (t, $J = 4.47$ Hz, 4H, NCH₂CH₂-Pyr), 4.02 (t, $J = 4.01$ Hz, 4H, NCH₂CH₂-Pyr). ¹³C{¹H} NMR (150 MHz, CDCl₃): δ 162.83 (CHN), δ 139.73 (C_{Pyr}), δ 136.39 (C_{Ar}), δ 130.30 (C_{Pyr}), δ 130.23 (C_{Ar}), δ 129.05 (C_{Ar}), δ 128.02 (C_{Ar}), δ 105.20 (C_{Pyr}), δ 60.94 (NCH₂CH₂-Pyr), δ 52.52 (NCH₂CH₂-Pyr) (Figures S5.1 and S5.2). FT-IR (cm⁻¹): ν 3391 (C-H, pyridine ring), ν 2851 (CH₂), ν 1644 (C=N). APCI-MS (positive ion mode): mass fragment at m/z 321.18 (MW: 320.40 g/mol, Figure S5.13 in the Supporting Information).

Supporting Information for: A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions

α,α' -bis[*N*-(2-(3,5-dimethylpyrazolyl))ethylimino]-*m*-xylene (imine-L06): The same synthesis and purification methods as mentioned above were used, except for using 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethan-1-amine (0.28 g, 2 mmol) instead of the 2-(1*H*-pyrazol-1-yl)ethan-1-amine as reagent. The product was obtained as a yellow oil (imine-L06). Yield: 476 mg (53 %) ^1H NMR (600 MHz, CDCl_3): δ 7.96 (s, 2H, CHN), 7.84 (s, 1H, H_{Ar}), 7.71 (d, J = 8.50 Hz, 2H, H_{Ar}), 7.40 (t, J = 7.60 Hz, 1H, H_{Ar}), 5.66 (s, 2H, H_{Pyr}), 4.28 (t, J = 5.90 Hz, 4H, $\text{NCH}_2\text{CH}_2\text{-Pyr}$), 3.99 (t, J = 4.80 Hz, 4H, $\text{NCH}_2\text{CH}_2\text{-Pyr}$), 2.20 (s, 6H, CH_3), 2.14 (s, 6H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 162.84 (CHN), δ 147.84 (C_{Pyr}), δ 139.95 (C_{Pyr}), δ 136.50 (C_{Ar}), δ 130.11 (C_{Ar}), δ 129.06 (C_{Ar}), δ 128.13 (C_{Ar}), δ 104.74 (C_{Pyr}), δ 61.44 ($\text{NCH}_2\text{CH}_2\text{-Pyr}$), δ 48.87 ($\text{NCH}_2\text{CH}_2\text{-Pyr}$), δ 13.63 (CH_3), δ 11.21 (CH_3) (Figures S5.3 and S5.4). FT-IR (cm^{-1}): ν 3394 (C-H, pyridine ring), ν 2919 (CH_2), ν 1673 (C=N). APCI-MS (positive ion mode): mass fragment at m/z 377.25 (MW: 376.51 g/mol, Figure S5.14 in the Supporting Information).

α,α' -bis[*N*-(2-(3,5-dimethylpyrazolyl))ethylamino]-*m*-xylene (L06): The same synthesis procedure as for ligand L05 was used, except for using the substituted imine ligand imine-L06 (0.22 g, 0.6 mmol) as reagent. The product was obtained as a colourless oil (L06). Yield: 161 mg (70 %) ^1H NMR (600 MHz, CDCl_3): δ 7.34-7.29 (dd, J = 16.7 and 9.2 Hz, 2H, H_{Ar}), 7.21 (t, J = 7.5 Hz, 1H, H_{Ar}), 5.84 (s, 1H, H_{Pyr}), 5.38 (s, 1H, NH), 4.14 (t, J = 6.10 Hz, 4H, $\text{NCH}_2\text{CH}_2\text{-Pyr}$), 3.82 (s, 4H, CH_2NH), 3.07 (t, J = 6.2 Hz, 4H, $\text{NCH}_2\text{CH}_2\text{-Pyr}$), 2.28 (s, 6H, CH_3), 2.27 (s, 6H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 147.65 (C_{Pyr}), δ 140.30 (C_{Ar}), δ 139.25 (C_{Pyr}), δ 128.57 (C_{Ar}), δ 127.82 (C_{Ar}), δ 126.78 (C_{Ar}), δ 105.05 (C_{Pyr}), δ 53.59 ($\text{NCH}_2\text{CH}_2\text{-Pyr}$), δ 48.85 (CH_2NH), δ 48.43 ($\text{NCH}_2\text{CH}_2\text{-Pyr}$), δ 13.59 (CH_3), δ 11.19 (CH_3) (Figures S5.7 and S5.8). FT-IR (cm^{-1}): ν 3291 (NH and C-H (CH_2)), ν 2919 (CH_2), ν 1673 (C-C and C-H in pyridine ring), ν 1551 (C=C and C-H in pyrazole ring, C-C (pyr- CH_3)). APCI-MS (positive ion mode): mass fragment at m/z 381.28 (MW: 380.54 g/mol, Figure S5.16 in the Supporting Information).

α,α' -bis[*N*-methyl-2-(3,5-dimethylpyrazolyl))ethylamino]-*m*-xylene (L08): The same synthesis procedure as for ligand L07 was used, except for using the reduced ligand L06 (0.12 g, 0.5 mmol) as reagent. The product was obtained as a colourless oil (L08). Yield: 69 mg (62 %) ^1H NMR (600 MHz, CDCl_3): δ 7.19 (t, J = 7.5 Hz, 1H, H_{Ar}), δ 7.12 (d, J = 8.7 Hz, 2H, H_{Ar}), δ 7.10 (s, 1H, H_{Ar}), δ 5.74 (s, 2H, H_{Pyr}), δ 4.05 (s, 4H, $\text{NCH}_2\text{CH}_2\text{-Pyr}$), 3.50 (s, 4H, N(Me)CH_2), δ 2.75 (t, J = 6.6 Hz, 4H, $\text{NCH}_2\text{CH}_2\text{-Pyr}$), δ 2.25 (s, 6H, NCH_3), δ 2.18 (s, 6H, CH_3), δ 2.16 (s, 6H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 147.38 (C_{Pyr}), δ 139.07 (C_{Pyr}), δ 138.72 (C_{Ar}), δ 129.57 (C_{Ar}), δ 128.30 (C_{Ar}), δ 127.81 (C_{Ar}), δ 104.99 (C_{Pyr}), δ 62.62

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(N(Me)CH₂), δ 56.91 (NCH₂CH₂-Pyr), δ 47.08 (NCH₂CH₂-Pyr), δ 42.59 (NCH₃), δ 13.54 (CH₃), δ 11.11 (CH₃). (Figures S5.11 and S5.12). FT-IR (cm⁻¹): ν 3535 (C-H (N-CH₃, CH₂, CH₃, pyridine ring)), ν 3151 (C-H (N-CH₃, CH₂)), ν 1639 (C-N and C-H in pyridine ring), ν 1469 (C=C and C-H in pyrazole ring, C-H (CH₃)). APCI-MS (positive ion mode): mass fragment at m/z 409.31 (MW: 408.59 g/mol, Figure S5.18 in the Supporting Information).

S5.2.1 NMR spectra for the novel bifunctional ligands

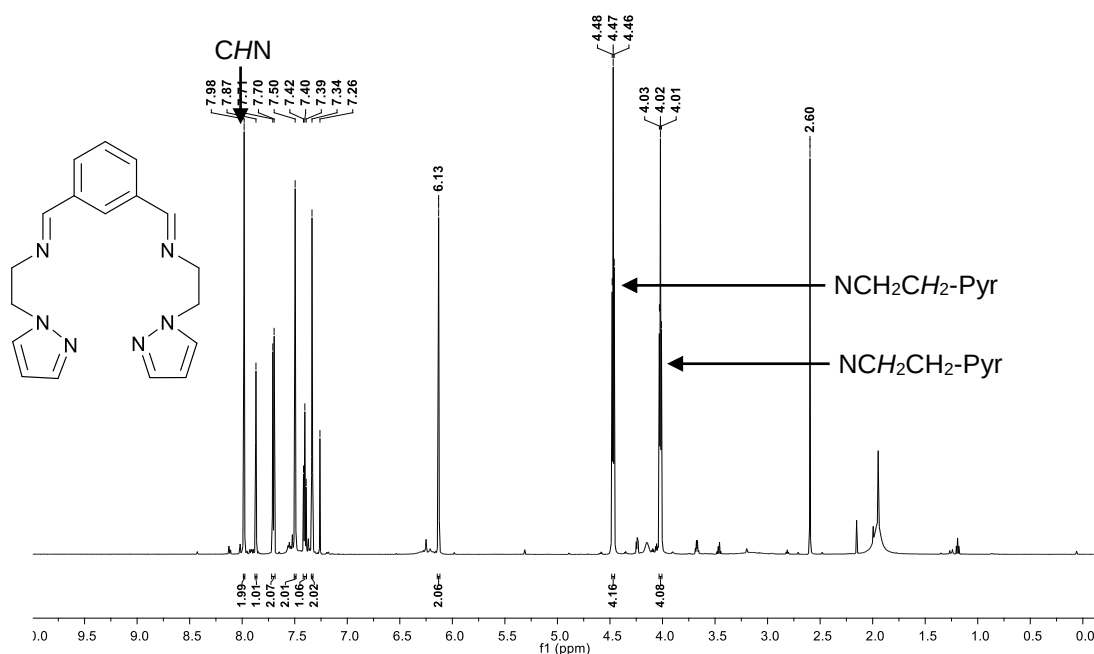


Figure S5.1: ¹H NMR (600 MHz, CDCl₃) spectrum for ligand imine-L05.

Supporting Information for: A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions

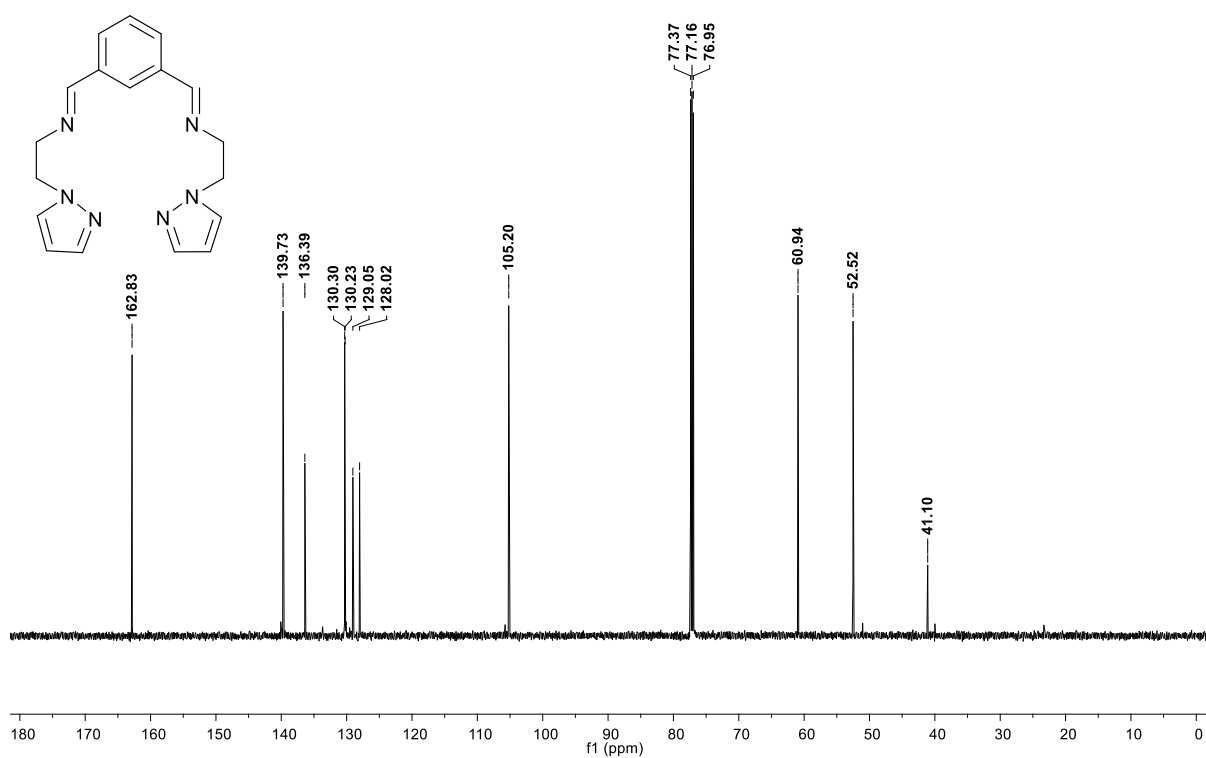


Figure S5.2: $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) spectrum for ligand imine-L05.

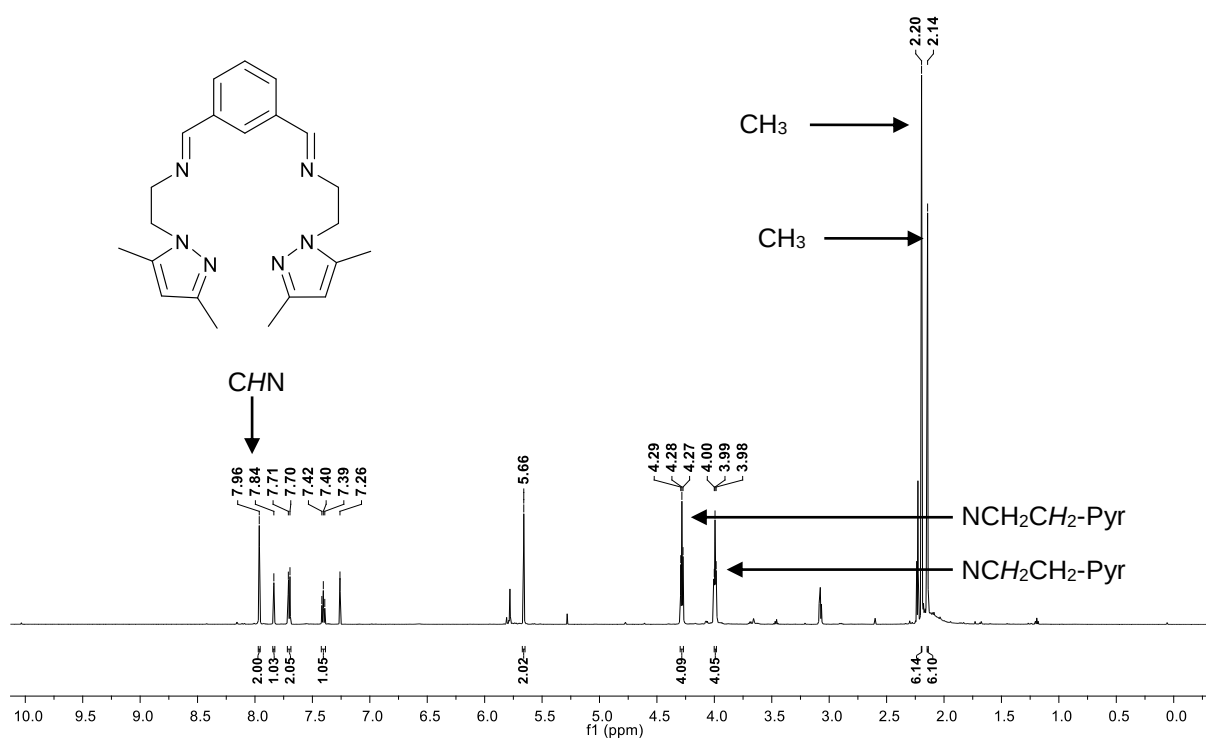
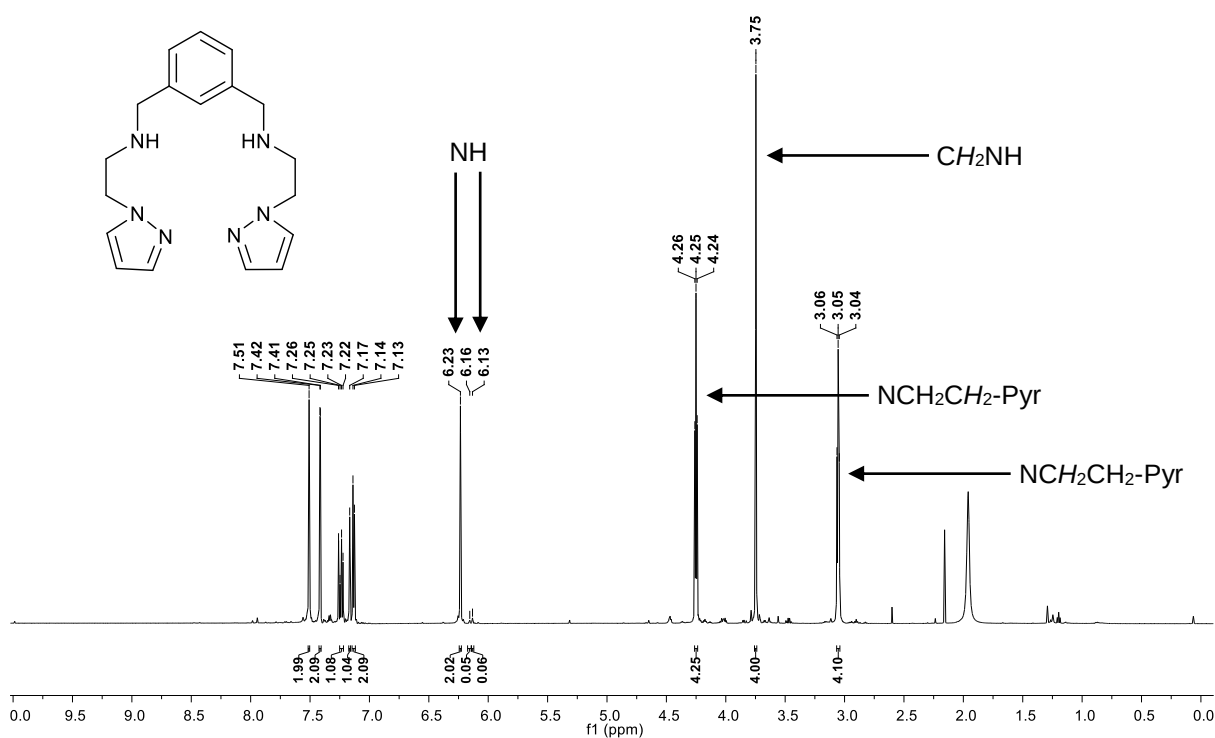
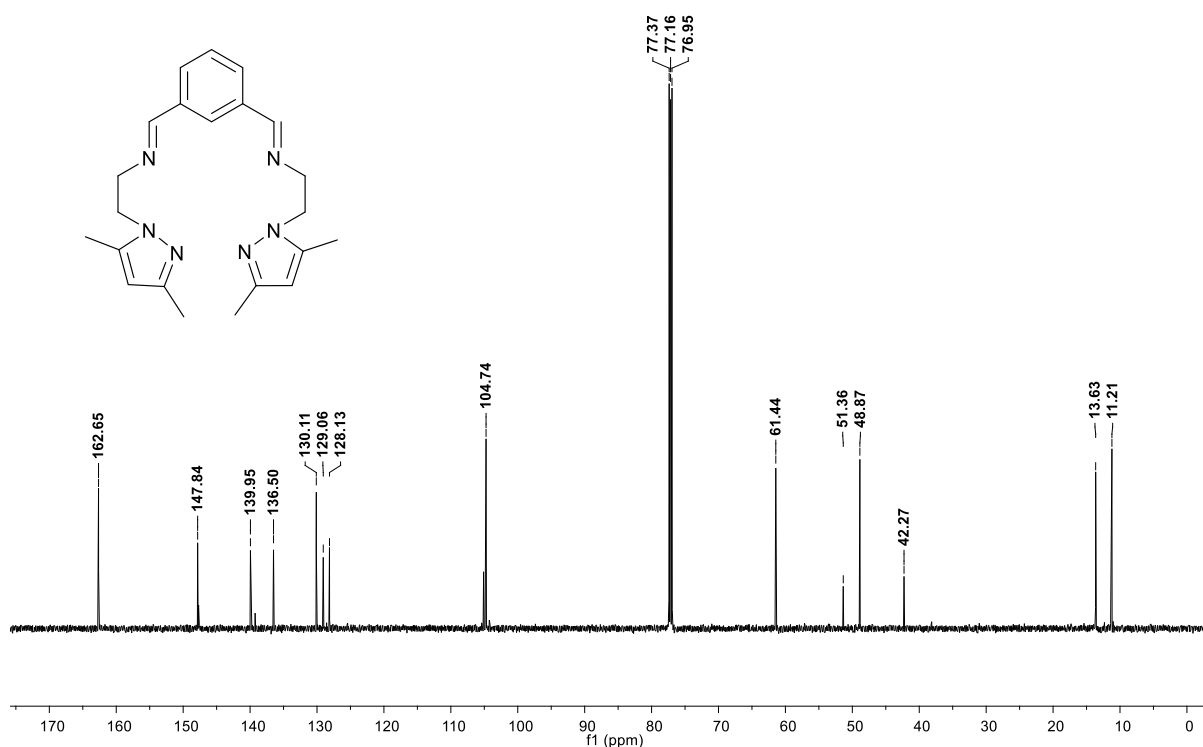


Figure S5.3: ^1H NMR (600 MHz, CDCl_3) spectrum for ligand imine-L06.

Supporting Information for: A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions



Supporting Information for: A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions

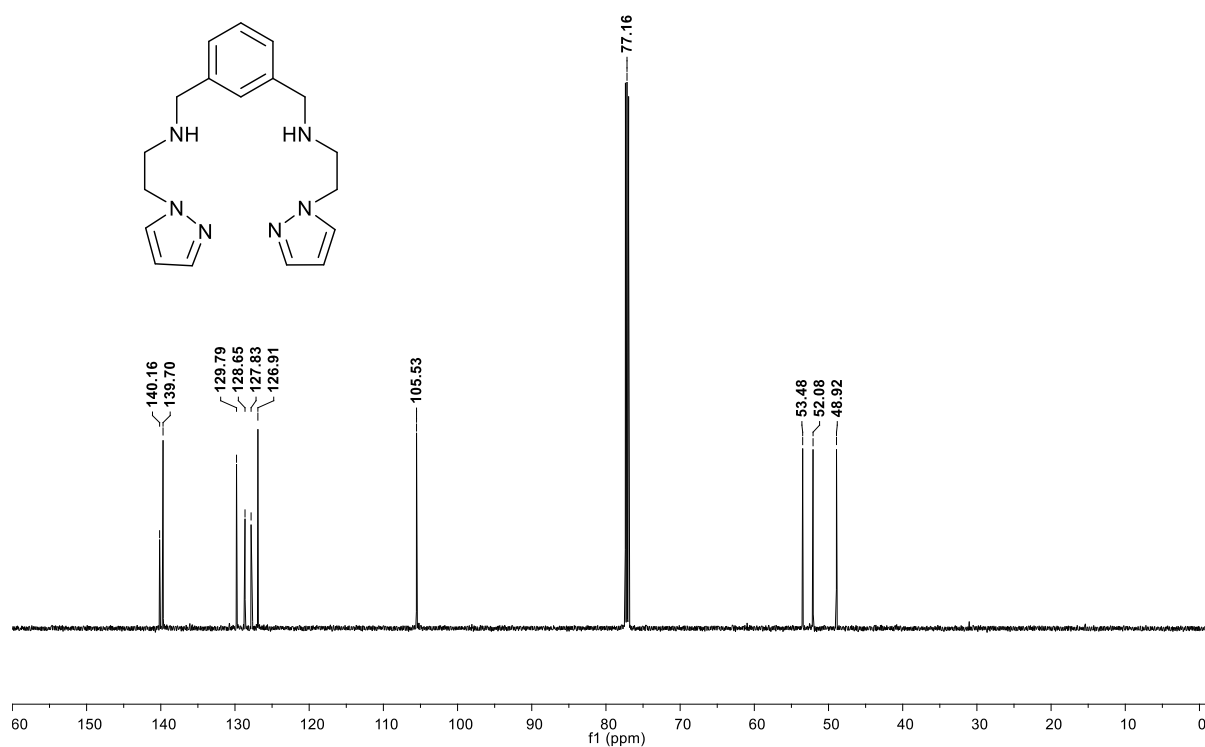


Figure S5.6: ¹³C{¹H} NMR (150 MHz, CDCl₃) spectrum for ligand L05.

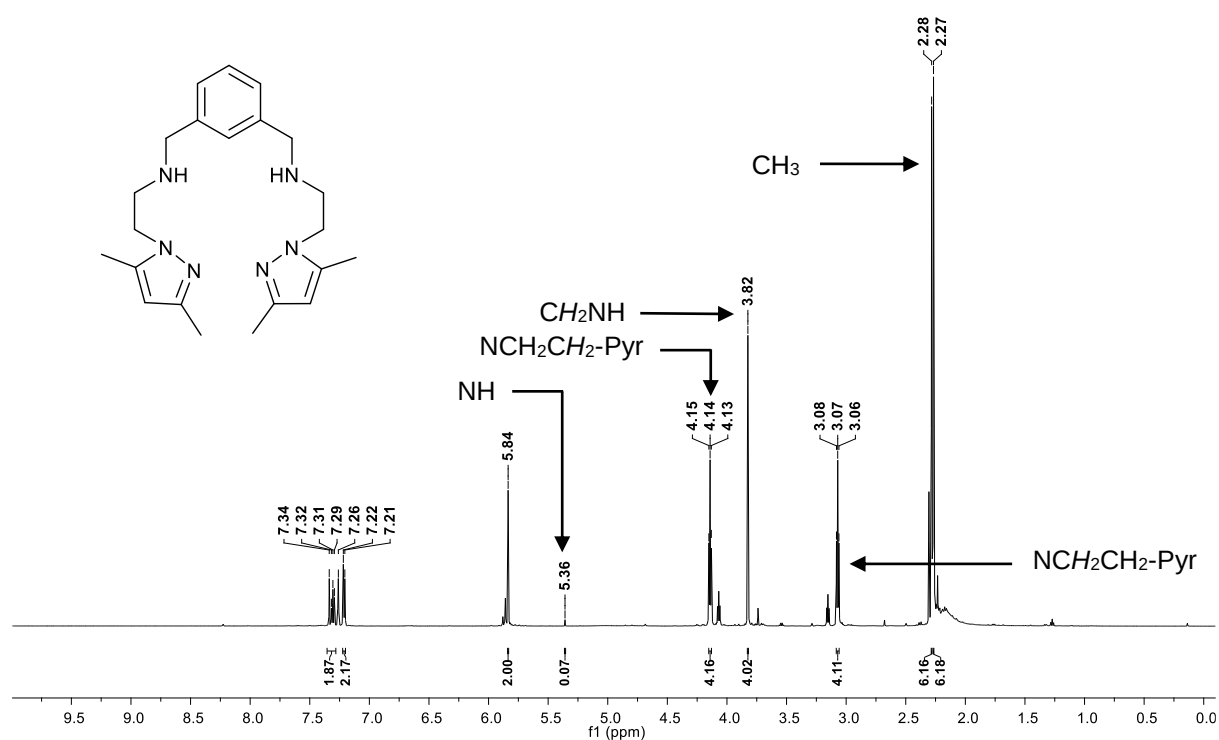


Figure S5.7: ¹H NMR (600 MHz, CDCl₃) spectrum for ligand L06.

Supporting Information for: A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions

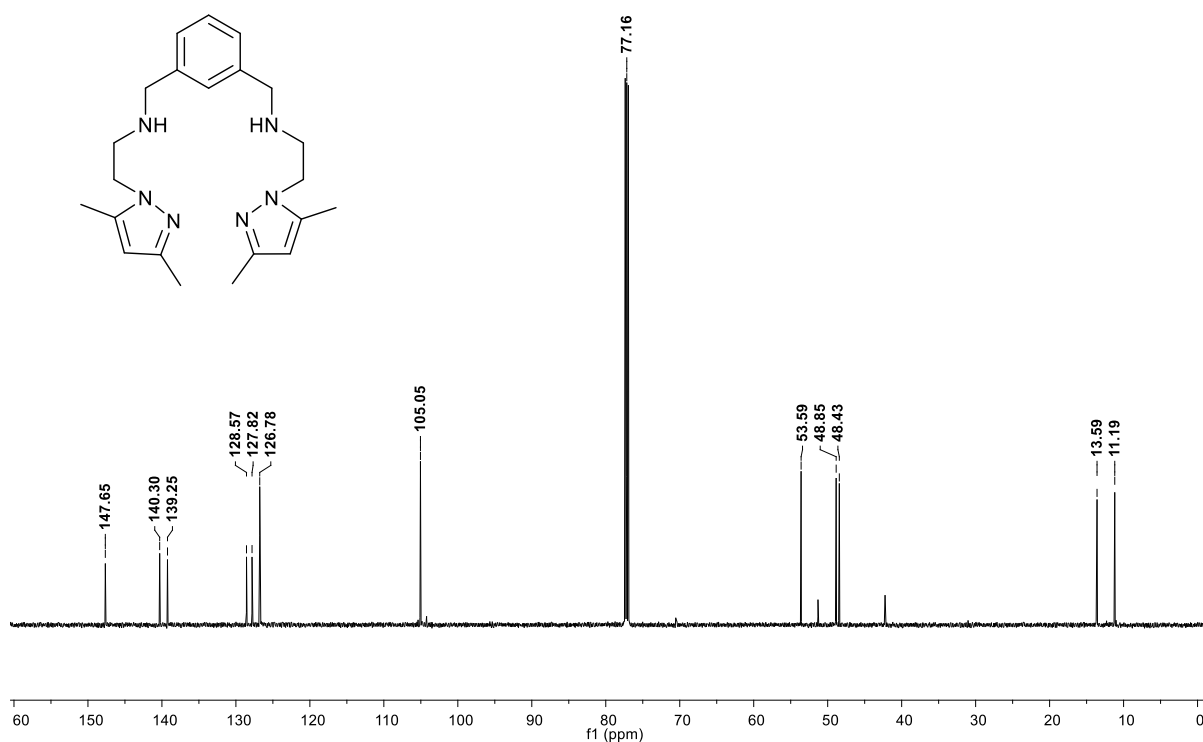


Figure S5.8: ¹³C{¹H} NMR (150 MHz, CDCl₃) spectrum for ligand **L06**.

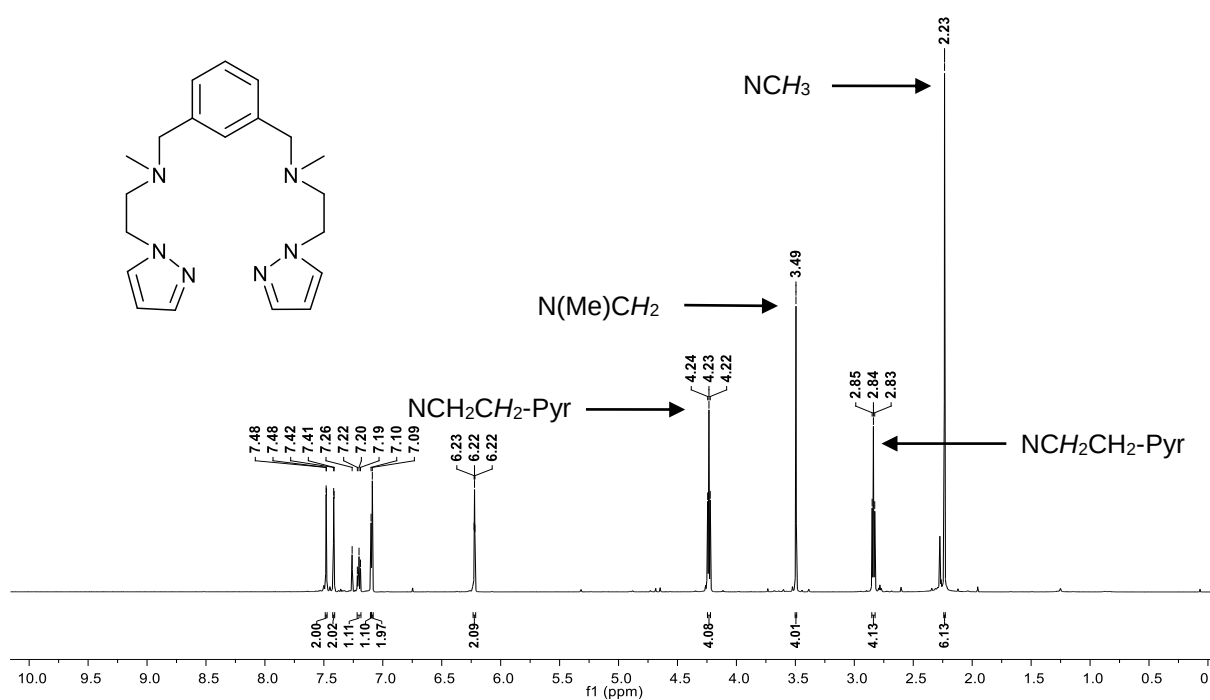


Figure S5.9: ¹H NMR (600 MHz, CDCl₃) spectrum for ligand **L07**.

Supporting Information for: A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions

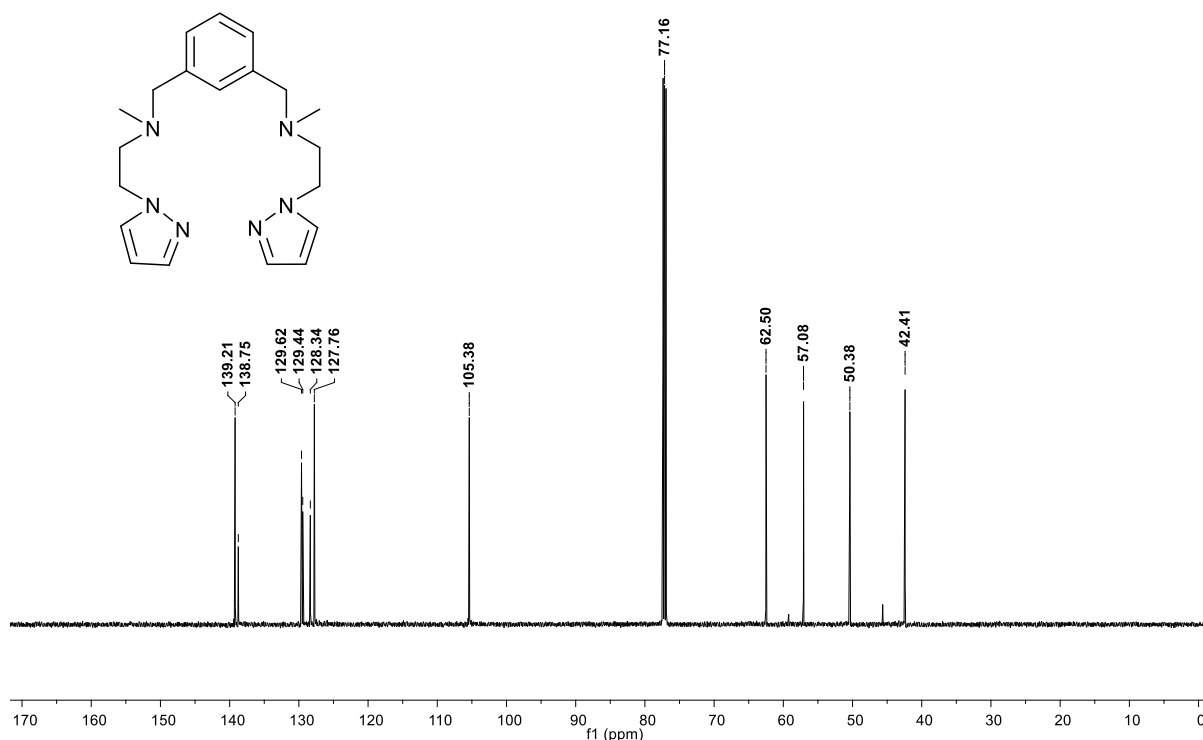


Figure S5.10: ¹³C{¹H} NMR (150 MHz, CDCl₃) spectrum for ligand L07.

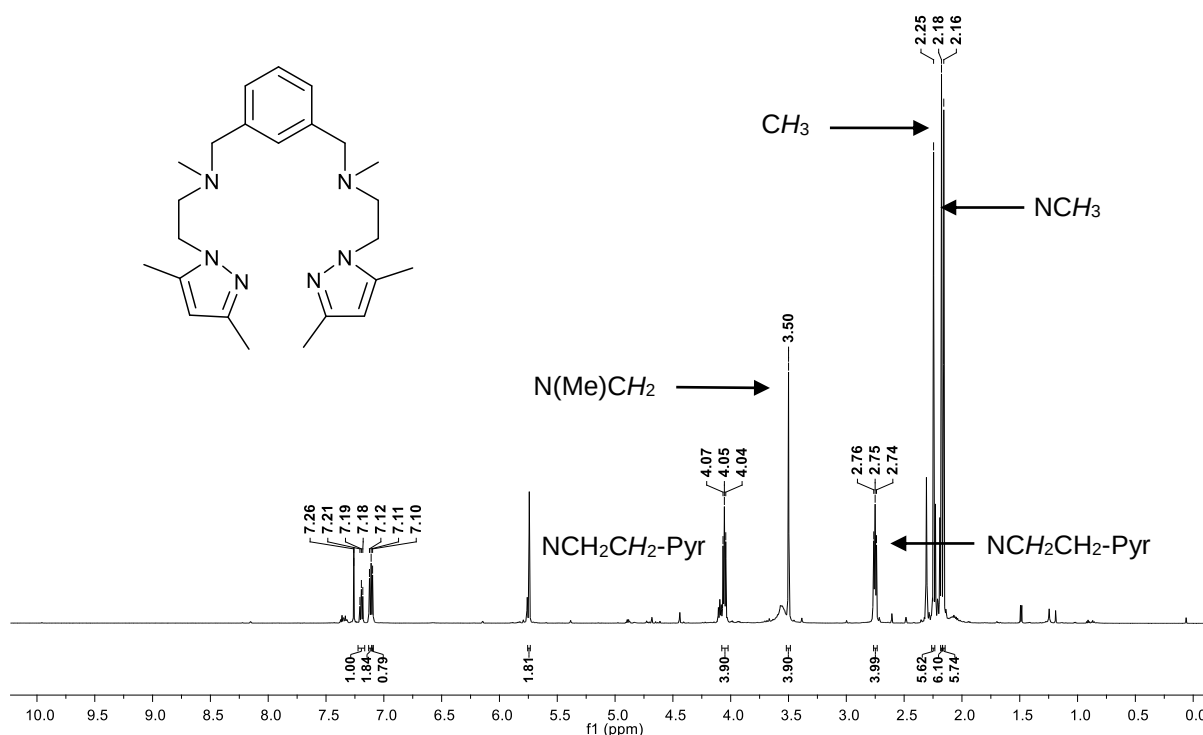


Figure S5.11: ¹H NMR (600 MHz, CDCl₃) spectrum for ligand L08.

Supporting Information for: A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions

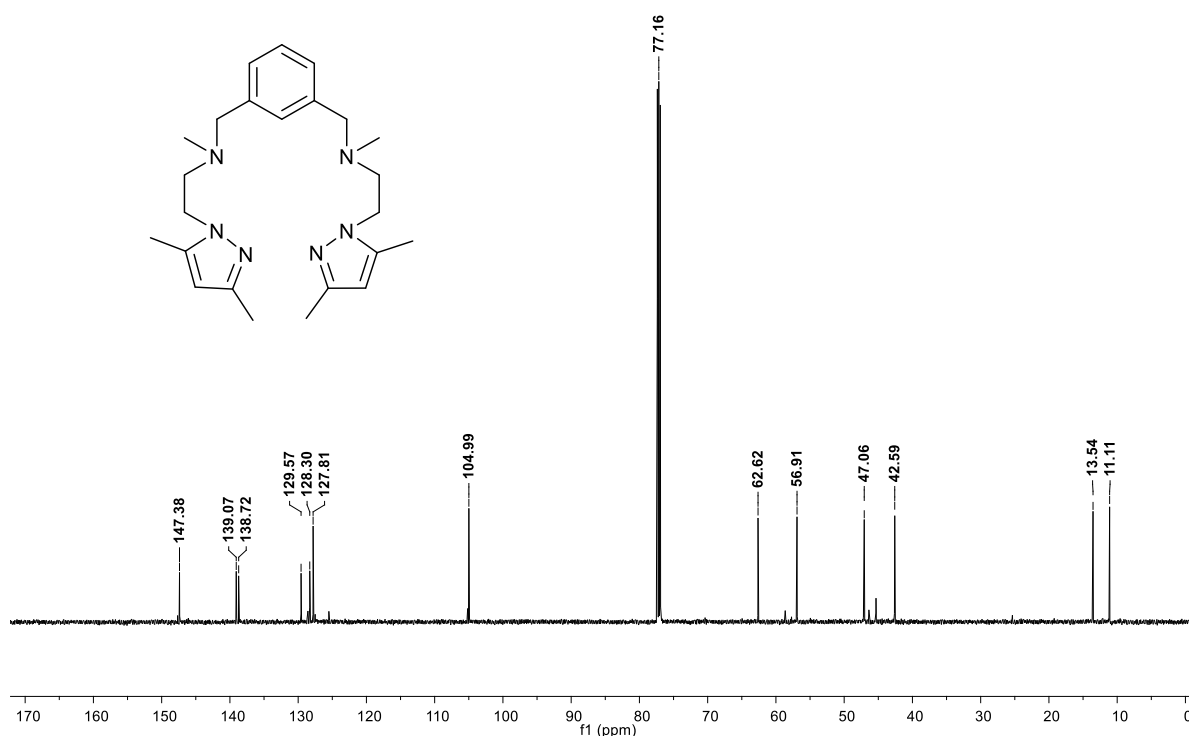


Figure S5.12: $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) spectrum for ligand **L08**.

S5.2.2 APCI-MS spectra for the bifunctional ligands

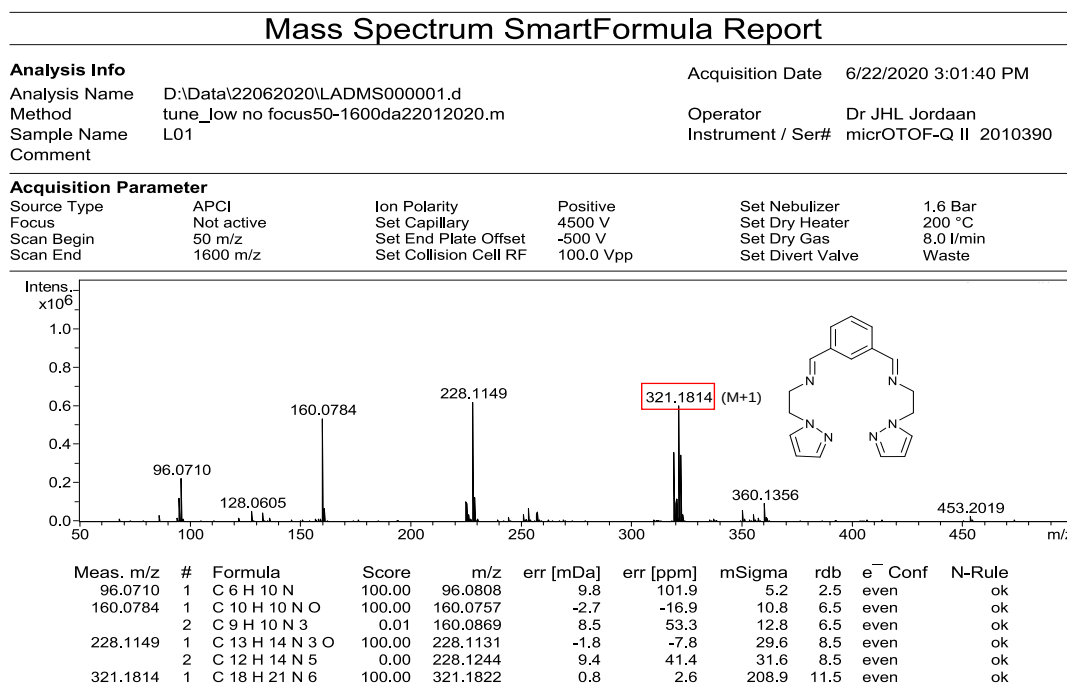


Figure S5.13: APCI-MS spectrum for imine-**L05** (MW: 320.40 g/mol). The spectrum revealed a mass fragment at m/z 321.18, consistent with the molar mass of the ligand (positive ion mode).

Supporting Information for: A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions

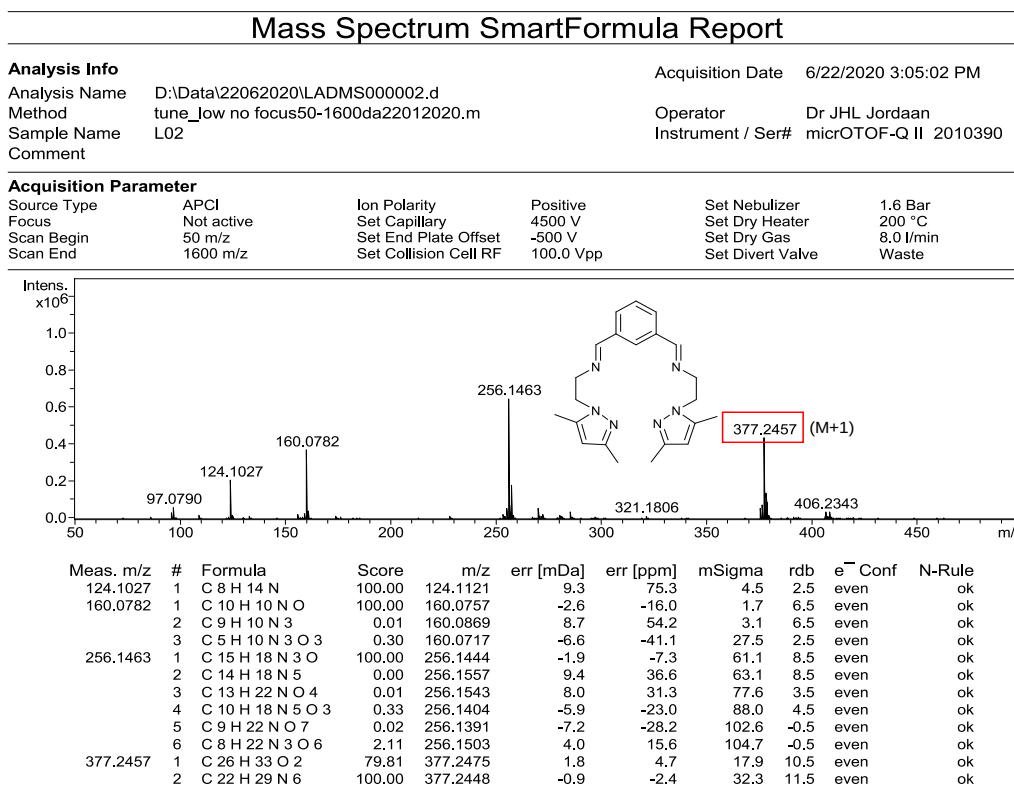


Figure S5.14: APCI-MS spectrum for imine-L06 (MW: 376.51 g/mol). The spectrum revealed a mass fragment at m/z 377.25, consistent with the molar mass of the ligand (positive ion mode).

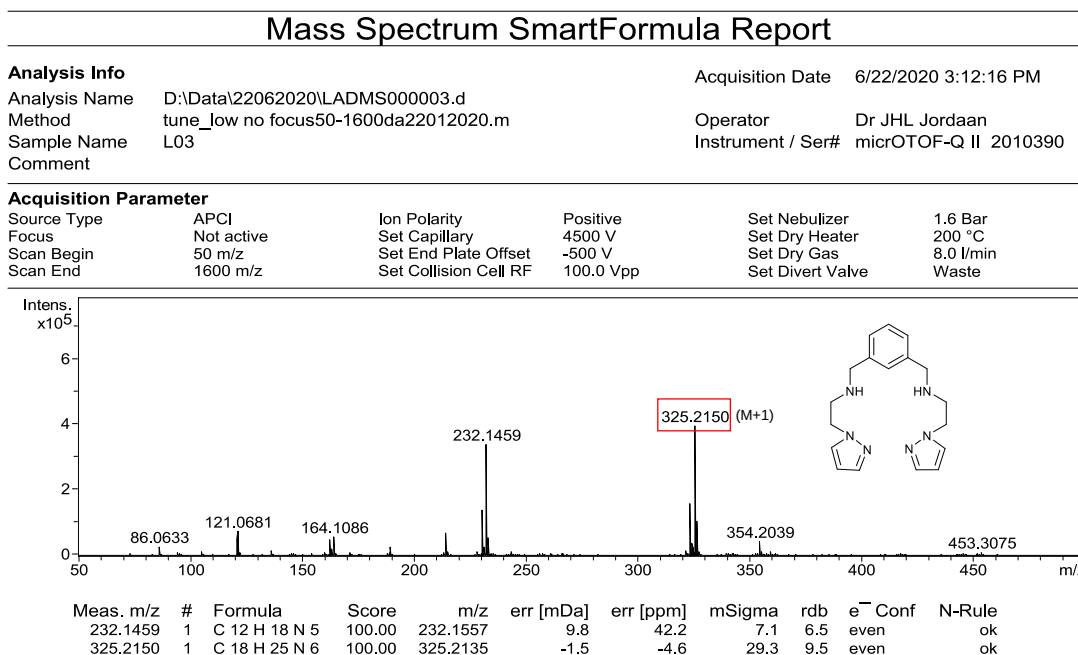


Figure S5.15: APCI-MS spectrum for L05 (MW: 324.43 g/mol). The spectrum revealed a mass fragment at m/z 325.22, consistent with the molar mass of the ligand (positive ion mode).

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Mass Spectrum SmartFormula Report

Analysis Info

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Method tune_low no focus50-1600da22012020.m
Sample Name L06
Comment

Acquisition Date 6/22/2020 3:21:50 PM

Operator Dr JHL Jordaan
Instrument / Ser# microTOF-Q II 2010390

Acquisition Parameter

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Scan End	1600 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste

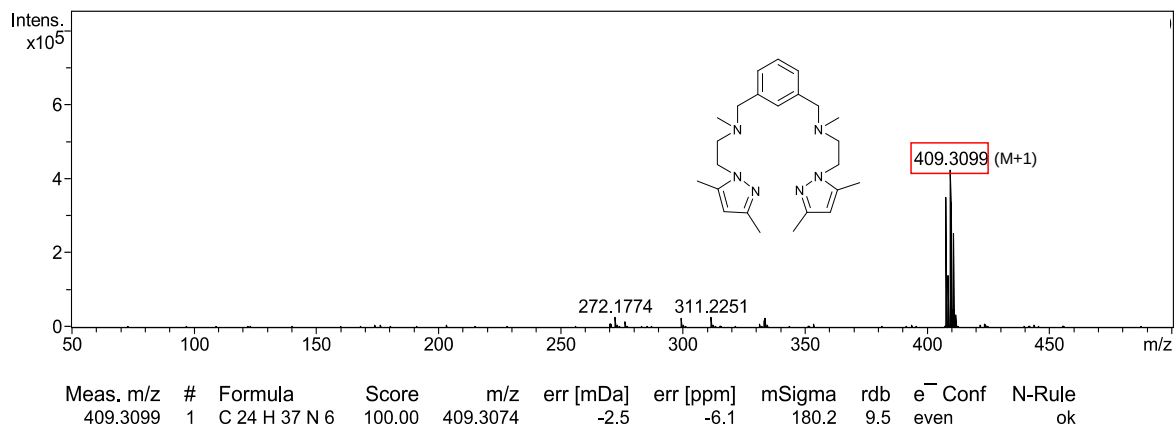


Figure S5.18: APCI-MS spectrum for **L08** (MW: 408.59 g/mol). The spectrum revealed a mass fragment at m/z 409.31, consistent with the molar mass of the ligand (positive ion mode).

S5.3 Optimisation of the catalyst system

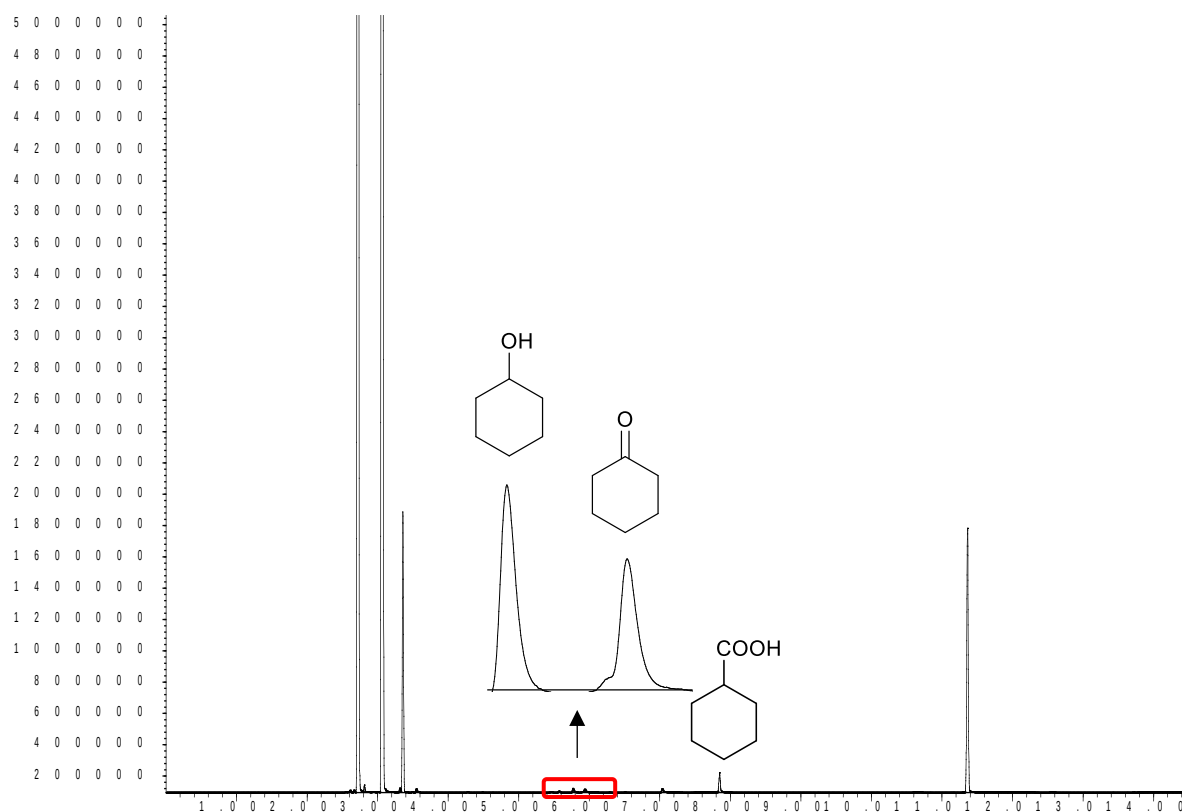


Figure S5.19: A visual representation of the GC spectrum for the peroxidation of cyclohexane (3.38 min). The formation of cyclohexanol (5.79 min), cyclohexanone (5.93 min) and cyclohexyl hydroperoxide (7.05 min) were observed as products relative to biphenyl (11.37 min) as the internal standard.

Novel α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene (imine-**L05**, imine-**L06**) and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene ligands (**L05-L08**) with $[\text{Cu}(\text{MeCN})_4]\text{OTf}$ were evaluated for cyclohexane peroxidation, using previously reported reaction conditions (Figure S5.20) [6].

Supporting Information for: A highly active copper(I)/ α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene catalyst system for alkane peroxidation under benign conditions

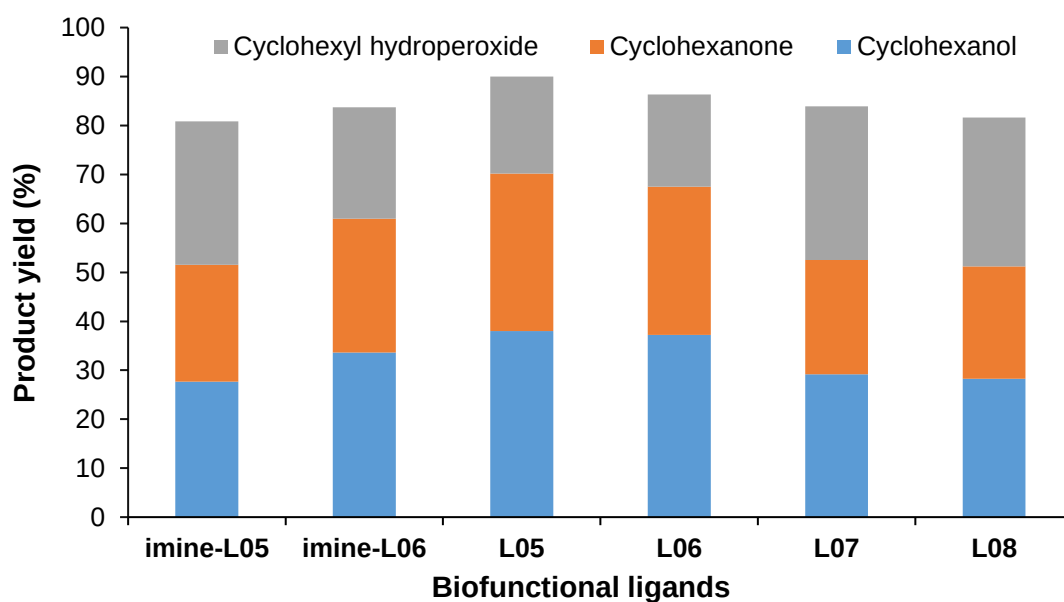


Figure S5.20: Product yields obtained for the peroxidation of cyclohexane, using bifunctional ligands: imine-**L05**: α,α' -bis[*N*-(2-pyrazolyl)ethyl-imino]-*m*-xylene; imine-**L06**: α,α' -bis[*N*-(2-(3,5-dimethylpyrazolyl))ethylimino]-*m*-xylene; **L05**: α,α' -bis[*N*-(2-pyrazolyl)ethylamino]-*m*-xylene; **L06**: α,α' -bis[*N*-(2-(3,5-dimethylpyrazolyl))ethylamino]-*m*-xylene; **L07**: α,α' -bis[(*N*-methyl-2-pyrazolyl)ethyl-amino]-*m*-xylene; **L08**: α,α' -bis[(*N*-methyl-2-(3,5-dimethylpyrazolyl))ethylamino]-*m*-xylene.

We evaluated various $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ -precursors with ligand **L05** for cyclohexane peroxidation (Figure S5.21).

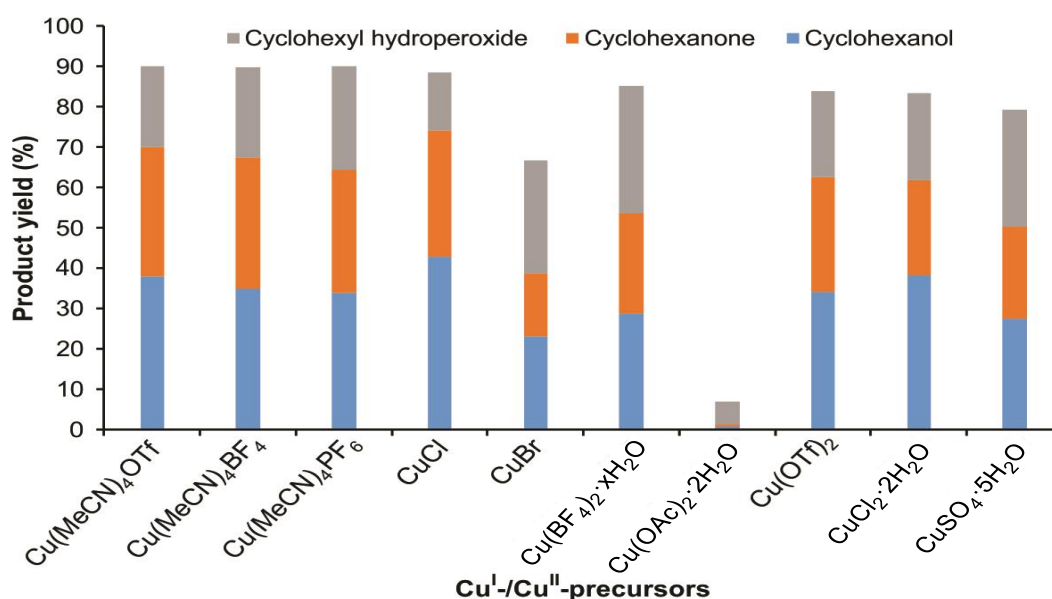


Figure S5.21: Evaluation of various $\text{Cu}^{\text{I}}/\text{Cu}^{\text{II}}$ -precursors, in combination with ligand **L05**, for cyclohexane peroxidation, under previously reported reaction conditions.

S5.4 Evaluating the formation of radical species

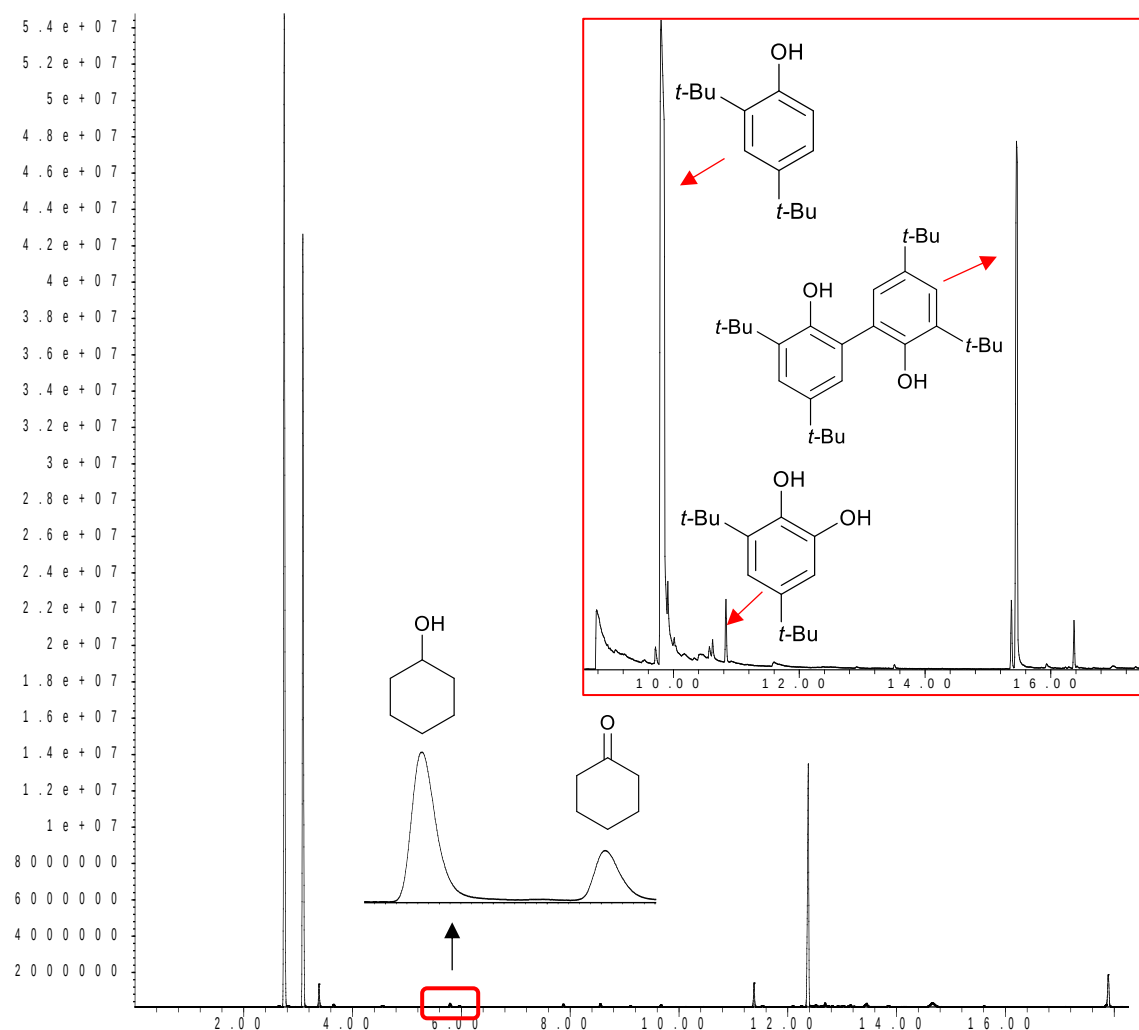


Figure S5.22: GC spectrum for the peroxidation of cyclohexane (3.38 min) using our (L05)[Cu(MeCN)₄]PF₆/H₂O₂ catalyst system in the presence of 2,4-di-*tert*-butylphenol as a radical trap. A decrease in cyclohexyl hydroperoxide (7.87 min) formation and the resulting cyclohexanol (5.79 min) and cyclohexanone (5.93 min) were observed. The formation of 3,3',5,5'-tetra-*tert*-butylbiphenyl-2,2'-diol (major radical coupling product) and 3,5-di-*tert*-butylbenzene-1,2-diol (trace amounts) as by-products were identified by GC-MS (inset).

S5.5 Kinetic studies

Initial rate profiles for the CyOOH formation were generated for varying [LCu], [H₂O₂] and [substrate], using our optimised reaction conditions (Figure 5.1 and Table S5.1). The rate of CyOOH formation exhibits a first-order dependence on [LCu] and [H₂O₂], while no proportionality was observed towards the initial concentration of cyclohexane.

Table S5.1: Kinetic data for the peroxidation of cyclohexane by (L05)[Cu(MeCN)₄]PF₆/H₂O₂, assessing the kinetic dependence on [LCu], [H₂O₂] and [cyclohexane].

Entry	[(L05)Cu] (mM)	[H ₂ O ₂] (mM)	[Cyclohexane] (mM)	k _{initial} (mM·min ⁻¹)	Standard deviation
1	0.4	2833	333	0.4009	0.0371
2	0.8	2833	333	0.4294	0
3	1.3	2833	333	0.5404	0.0423
4	2.3	2833	333	0.7354	0.0392
5	3.3	2833	333	0.8294	0.0035
6	4.3	2833	333	0.7394	0.0016
7	3.3	833	333	0.3554	0.0699
8	3.3	1833	333	0.5733	0.0658
9	3.3	2833	333	0.8294	0.0035
10	3.3	3333	333	0.9508	0.0684
11	3.3	4333	333	1.1424	0.0035
12	3.3	2833	167	0.8438	0.0808
13	3.3	2833	250	0.8004	0.0484
14	3.3	2833	333	0.8294	0.0035
15	3.3	2833	413	0.8038	0.0129

S5.6 References

- [1] H.E. Gottlieb, V. Kotlyar, A. Nudelman, J. Org. Chem., 62 (1997) 7512-7515.
- [2] C. Obuah, M.K. Ainooson, S. Boltina, I.A. Guzei, K. Nozaki, J. Darkwa, Organometallics, 32 (2013) 980-988.
- [3] C. Obuah, B. Omondi, K. Nozaki, J. Darkwa, J. Mol. Catal. A: Chem., 382 (2014) 31-40.
- [4] L. Marais, H.C.M. Vosloo, A.J. Swarts, Mol. Catal., 486 (2020) 110839-110847.
- [5] J.N. Hamann, F. Tuczek, Chem. Commun., 50 (2014) 2298-2300.
- [6] I. Garcia-Bosch, M.A. Siegler, Angew. Chem. Int. Ed., 55 (2016) 12873-12876.
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Chapter 6: Synthetic LPMO mimics: a copper/pyrazolylpyridineamine catalyst system for the highly efficient oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside

Synthetic LPMO mimics: a copper/pyrazolylpyridineamine catalyst system for the highly efficient oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside

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Pyrazolylpyridineimine (imine-**L01** and imine-**L02**) and -amine ligands (**L01-L04**), in combination with a Cu^I- or Cu^{II}-precursor, H₂O₂ and NEt₃, are reported as LPMO mimics for the oxidative cleavage of the model substrate, *p*-nitrophenyl- β -D-glucopyranoside, in H₂O. Our (**L03**)[Cu(MeCN)₄]OTf/H₂O₂/NEt₃ catalyst system resulted in a maximum rate constant (k_{obs}) of 0.3588 s⁻¹ in the initial 0.2 s, while a product yield of 69 % for *p*-nitrophenol formation was obtained in 15 min at 27 °C. The formation of LCu^{II}-OOH (k_{obs} : 0.0337 s⁻¹) was observed spectrophotometrically as an intermediate in the formation of LCu^{II}-O[•] and [•]OH active species for the H-atom abstraction step. Radical trapping experiments led to a decrease in *p*-nitrophenol formation (between 0.0933 and 0.1303 s⁻¹), supporting the presence of C- and O-centred radicals. Kinetic studies revealed first-order dependence on [LCu], [H₂O₂] and [substrate], while zero-order dependence was observed on [NEt₃]. Lastly, our optimised catalyst system is selective for oxidative cleavage reactions, since no or extremely low conversions were obtained for the oxidation of primary and secondary alcohols.

Keywords: lytic polysaccharide monooxygenase (LPMO), pyrazolylpyridineamine ligands, copper catalysis, UV/vis spectroscopic studies, kinetic studies, *p*-nitrophenol.

6.1 Introduction

The enzymatic oxidative cleavage of glycosidic bonds of recalcitrant polysaccharide biomass has garnered significant recent research interest, since the resulting phenolic compounds are important in the pharmaceutical and chemical industries while providing novel beneficiation pathways. Initially, polysaccharide biomasses were considered highly resistant to degradation, however, the discovery of lytic polysaccharide monooxygenases (LPMOs) has improved the enzymatic degradation thereof through a Cu-dependent oxidative cleavage reaction [1-4]. The active site of LPMO enzymes consists of a single type-II Cu-atom, coordinated to three *N*-atoms from two histidine residues (Figure 6.1). The first histidine residue coordinates in an imidazole-bound fashion, while the second histidine residue is the methylated *N*-terminal one [4-10]. The latter is bound by the histidine-brace motif, which involves the main chain amino group and the side chain imidazole group. Lastly, two H₂O molecules complete the square pyramidal coordination geometry of the Cu-based active centre. Either O₂ or H₂O₂ may be

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employed as the oxidant, but the preference for H_2O_2 has led to the development of several catalyst systems for oxidative cleavage reactions [11-14]. The oxidant activates the Cu^{II} active sites in the presence of electron donors to catalyse the regioselective hydroxylation of an inert C-H bond, leading to glycosidic bond cleavage [4, 14]. The oxidative cleavage may occur at C1 or C4, and to a lesser extent at position C6 [1, 2, 4, 5, 15-19].

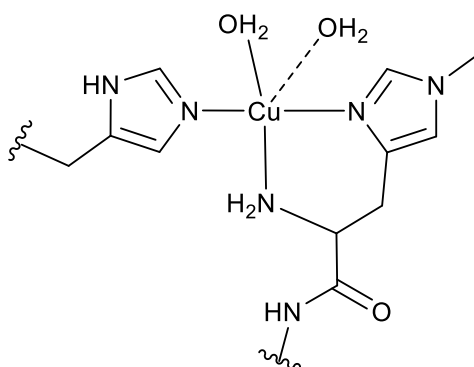


Figure 6.1: The active site of LPMOs consists of a mononuclear Cu-atom, which is coordinated to three N-atoms [20].

The advantages of copper as metal within the active site led to the development of several Cu-based LPMO mimics, using either O_2 or H_2O_2 as the oxidant for the formation of phenolic compounds [1, 21-23]. Striegler and co-workers reported the first Cu-based synthetic LPMO mimic in 2010 [24]. Various binuclear Cu^{II} complexes, bearing the *N,N'*-1,3-bis[(pyridine-2-ylmethyl)amino]propan-2-ol, *N,N'*-bis(2-pyridylmethyl)-1,4-diaminobutan-2-ol or *N,N'*-1,3-bis[2-hydroxy-4-[2-(2-methoxyethoxy)-ethoxy]-ethoxy-benzylidene-amino]-propan-2-ol ligand, were evaluated for the hydrolysis of *p*-nitrophenyl- β -D-glucopyranoside in 3-(cyclohexylamino)-1-propanesulfonic acid (CAPS) buffer at pH 10.5 and a maximum rate constant (k_{obs}) of $2.4 \pm 1.0 \times 10^{-4} \text{ min}^{-1}$ was obtained. The scope of their synthetic LPMO mimics was expanded further by evaluating *N,N'*-bis((3-(4-vinylbenzyloxy)-derived or *N,N'*-1,3-bis[2-hydroxy-4-(2-methoxyethoxy)-derived ligands [25]. Moreover, polymeric ligands bearing styrene, butyl acrylate and *N,N'*-1,3-bis[(2-hydroxy-4-(*p*-vinylbenzyloxy)-derived ligands, were employed in the synthesis of macromolecular Cu^{II} complexes. Lastly, the polymerisable Cu^{II} complexes were expanded by including polymerisable glucose- or galactose-templated Cu^{II} complexes, bearing an *N,N'*-1,3-bis[(2-hydroxy-4-(*p*-vinylbenzyloxy)-derived ligand [26]. These new additions to their Cu^{II} complexes allowed them to obtain increased rate constants of 375 ± 10 to $1290 \pm 490 \times 10^{-4} \text{ min}^{-1}$. A structural model of the active centre of LPMOs was reported by Castillo and co-workers, where they employed Cu^{II} complexes, bearing the bis[(1-methyl-2-benzimidazolyl)ethyl]amine ligand; however, reactivity studies were not performed [20]. Another Cu-based LPMO mimic was reported by Simaan and co-workers that consists

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of copper(II) perchlorate hexahydrate and N₃-coordinated ligands with a methylated *N*-atom in the imidazole, similarly to the histidine moieties of LPMO enzymes [27]. These complexes, in combination with H₂O₂, were evaluated for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside and they obtained a maximum turnover number (TON) of 50.

Mayilmurugan and co-workers reported the application of Cu^{II} complexes, bearing pyridinoyl-substituted cyclic 1,4-diazepane 3*N*-ligands, in combination with H₂O₂ and NEt₃ for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside to obtain rate constants of 1.61 ± 0.2 to $9.06 \pm 0.1 \times 10^{-3} \text{ s}^{-1}$ for *p*-nitrophenol formation [12]. These were correlated to a maximum isolated yield of 78 % (reported TON: 300, actual TON: 63) in 2 h at 60 °C. More recently, Cowen and co-workers reported the current state-of-the-art Cu-based catalyst system for the oxidative cleavage of *p*-nitrophenyl-derivatized glucose and galactose mono- and disaccharides [28]. Mono-, bi- and tetranuclear Cu^{II} complexes, bearing a di(2-picoyl)amine ligand, were prepared. Rate constants of 5.0 to $9.33 \times 10^{-3} \text{ s}^{-1}$ were obtained for monosaccharide substrates using the mononuclear Cu^{II} complex, while a two-fold increase was observed for disaccharide substrates (0.018 to 0.023 s^{-1}). A further increase in the rate constant (0.05 to 0.26 s^{-1}) was obtained when employing the tetranuclear Cu^{II} complexes. Reports suggest that either active LCu^{II}-oxyl species or hydroxyl radicals ($\cdot\text{OH}$) are generated from the LCu^{II}-OOH species for the H-atom abstraction step leading to more mechanistic uncertainty [14, 28].

Previous groups reported that ligands with amine groups or *N*-atom containing heterocycles, such as pyrazole and pyridine, are usually employed to mimic the histidine groups present in the active site of the LPMO enzyme [29]. As such, we expanded the application of our pyrazolylpyridineimine (imine-**L01** and imine-**L02**) and -amine ligands (**L01-L04**, Figure 6.2) [30], in combination with Cu^I-/Cu^{II}-precursors, as highly active pre-catalysts for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside to afford *p*-nitrophenol as the major product. Spectrophotometric, electrochemical and kinetic studies were performed to establish the optimum reaction parameters and better understand the mechanistic aspects associated with our catalyst system. Finally, we confirmed the selectivity of our catalyst system by evaluating the oxidation of some primary and secondary alcohols.

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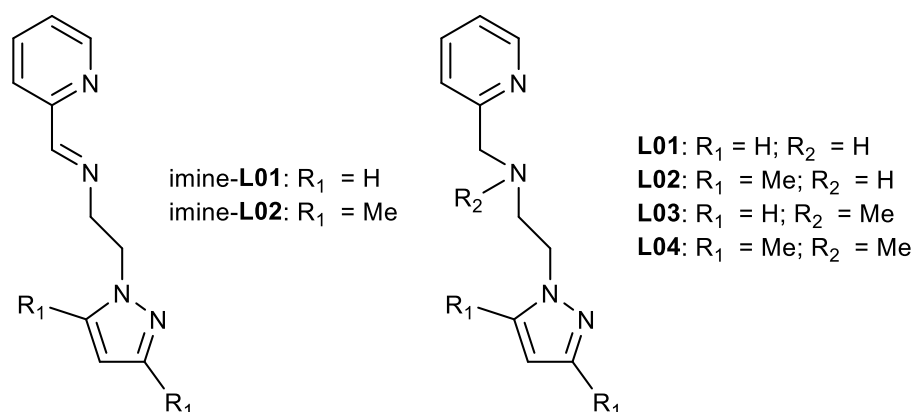
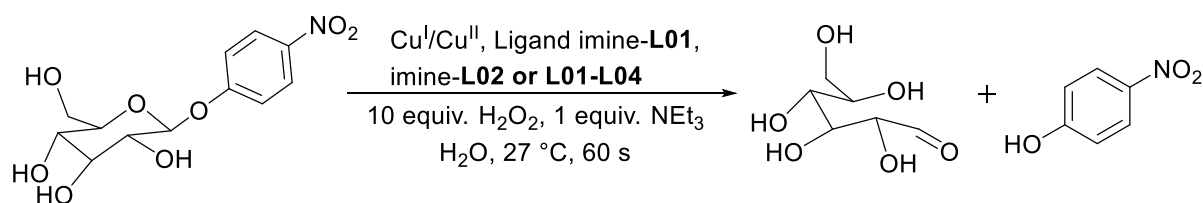


Figure 6.2: The pyrazolylpyridineimine (imine-**L01** and imine-**L02**) and -amine ligands (**L01-L04**) were employed for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside [30].

6.2 Results and discussion

6.2.1 Optimisation of the (**L03**)[Cu(MeCN)₄]OTf/H₂O₂/NEt₃ catalyst system

Various pyrazolylpyridineimine (imine-**L01** and imine-**L02**) and -amine ligands (**L01-L04**), in combination with copper, H₂O₂ (30 % in H₂O, 10 equiv.) as the oxidant and NEt₃ (1 equiv.) as the base, were evaluated as LPMO mimics for the oxidative cleavage of the model substrate, *p*-nitrophenyl- β -D-glucopyranoside (Scheme 6.1). These ligands were synthesised via our previously reported synthesis route, which involves Schiff base condensation (imine-**L01** and imine-**L02**), reductive amination (**L01-L02**) and methylation (**L03-L04**) [30]. Our catalyst system does not require the isolation of the pre-catalyst. The formation of the *p*-nitrophenol product was monitored spectrophotometrically.



Scheme 6.1: Cu^I/Cu^{II}-based catalyst system for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside to *p*-nitrophenol and D-allose at 27 °C.

The effects of imine-**L01**, imine-**L02** and **L01-L04** on the rate constants and obtained product yields for *p*-nitrophenol formation were evaluated using previously reported reaction conditions [12]. Table 6.1 summarises the rate constants, product yields, turnover number (TON) and turnover frequencies (TOF). Ligands without substituents on the pyrazole ring (imine-**L01**, **L01** and **L03**, Table 6.1, entries 1, 3 and 5) exhibited higher rate constants than those with methyl

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substituents (imine-**L02**, **L02** and **L04**, Table 6.1, entries 2, 4 and 6 and Figure S6.1 in the Supporting Information).

Table 6.1: Evaluation of various pyrazolylpyridineimine (imine-**L01** and imine-**L02**) and -amine ligands (**L01-L04**), in combination with [Cu(MeCN)₄]OTf, H₂O₂ and NEt₃, for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside. The *p*-nitrophenol formation was followed.^a

Entry	Ligand	k_{obs} (s ⁻¹) ^b	$t_{1/2}$ (s) ^c	Yield (%) ^d	TON ^e	TOF (min ⁻¹) ^e
1	imine- L01	0.2226	3.11	38	31	123
2	imine- L02	0.1778	3.90	56	45	180
3	L01	0.3202	2.16	43	35	138
4	L02	0.0951	7.29	53	42	168
5	L03	0.3588	1.93	69	55	222
6	L04	0.1026	6.75	31	25	99
7	-	0.0356	19.47	-	-	-
8	Benchmark: Cowan [28]	0.2600	2.67	-	-	-
9	Mayilmurugan [12]	0.0053	132	78 (45) ^f	300 (174) ^f	-

^a *p*-nitrophenyl- β -D-glucopyranoside (83 x 10⁻⁴ M), Cu(MeCN)₄OTf (1 x 10⁻⁴ M), imine-**L01**, imine-**L02** and **L01-L04** (1 x 10⁻⁴ M), H₂O₂ (10 equiv., 0.3 mmol) NEt₃ (1 equiv., 0.03 mmol), H₂O (3 mL), reaction time: 60 s, 27 ± 2 °C. ^b Rate constant ($k_{obs} = 1 + \log(\text{abs})$) measured over 0.2 s. ^c $t_{1/2} = 0.693/k_{obs}$. ^d Yield of *p*-nitrophenol after 15 min at 27 °C measured spectrophotometrically employing a calibration curve. ^e TON and TOF values after 15 min. ^f Isolated yield and reported TON values after 1 min at 60 °C (at 30 °C).

An increase in the rate constant was observed for the secondary (**L01**, 0.3202 s⁻¹) and tertiary (**L03**, 0.3588 s⁻¹) amine analogues of the pyrazole-derived ligands relative to ligand imine-**L01** (0.2226 s⁻¹). However, a decrease was observed when ligand imine-**L02** (0.1778 s⁻¹) was replaced with its secondary (**L02**, 0.0951 s⁻¹) or tertiary (**L04**, 0.1026 s⁻¹) amine analogues. Therefore, the steric and electronic properties of the methyl groups on the pyrazole ring present in imine-**L02**, **L02** and **L04** and the lower electrophilicity of the copper centre decrease the rate of *p*-nitrophenol formation. This is in contrast with the findings of several groups where they observed an increase in the rate constants for catalysts bearing sterically bulky and electron-donating substituents [12, 31-34]. A significant decrease in the rate constant (0.0356 s⁻¹) was observed when the oxidative cleavage reaction was performed in the absence

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of a ligand (Table 6.1, entry 7), consistent with the stabilising effect of the ligand framework [24, 35]. Ligand **L03** was identified as the optimal ligand. Our obtained rate constants of 0.1026 to 0.3588 s⁻¹ in 0.2 s at 27 °C represent a significant advance on previously reported catalyst systems, where a maximum rate constant of 0.26 s⁻¹ was obtained for reactions performed in a sodium phosphate buffer (pH 7.4) at 37 °C [12, 24-26, 28, 35].

Product yields of 31 to 69 % were obtained when employing imine-**L01**, imine-**L02** and **L01-L04** with the highest yield of *p*-nitrophenol obtained for **L03** (69 %; Table 6.1, entries 1-6). Longer reaction times resulted in a slight increase in the product yields when employing all ligand permutations. A similar trend in the product yields relative to the rate constants was observed for the unsubstituted ligands (imine-**L01**, **L01** and **L03**). However, no correlation was observed for the substituted ligands (imine-**L02**, **L02** and **L04**), since similar product yields were obtained when employing these ligands, irrespective of their rate constants. The groups of Simaan and Mayilmurugan obtained product yields of 500 μ M (TON of 50 in 24 h at 30 °C) and 78.4 % (reported TON: 300, actual TON: 63 in 2 h at 60 °C), respectively [12, 27]. While we obtained similar product yields (31 to 69 %), this was possible in a significantly shorter reaction time of 15 minutes, while performing the reactions at 27 °C, which from a synthetic perspective, is an improvement on previous studies.

Various Cu^I-/Cu^{II}-precursors were evaluated for the oxidative cleavage reaction using **L03** under previously reported reaction conditions (Table 6.2 and Figure S6.2 in the Supporting Information) [12]. The successful application of Cu^I and Cu^{II}-precursors have previously been reported for these reactions [24, 25, 27, 28, 35, 36]. Our results revealed similar rate constants for Cu^I- (Table 6.2, entries 1-5) and Cu^{II}-precursors (Table 6.2, entries 6-8). From these results, Cu(MeCN)₄OTf (0.3588 s⁻¹, Table 6.2, entry 1) and CuCl (0.3454 s⁻¹, Table 6.2, entry 4) exhibited the highest rate constants *p*-nitrophenol formation. However, a closer analysis of the CuCl-catalysed reaction revealed an initial burst in rate, after which the rate of the reaction decreased dramatically. This results in a lower rate of *p*-nitrophenol formation. Therefore, Cu(MeCN)₄OTf was chosen as the optimal precursor for further studies. A low rate constant of 0.0372 s⁻¹ was obtained when Cu(MeCN)₄OTf was replaced with the CuSO₄·5H₂O salt (Table 6.2, entry 9), consistent with previous reports [12, 27]. Lastly, reactions performed in an absence of the Cu-precursor, H₂O₂ or NEt₃ showed low rate constants of 0.0064 to 0.0909 s⁻¹ for *p*-nitrophenol formation (Table 6.2, entry 10).

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Table 6.2: Evaluation of Cu^I-/Cu^{II}-precursors, in combination with ligand **L03**, H₂O₂ and NEt₃, for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside.^a

Entry	Cu ^I -/Cu ^{II} -precursor	k_{obs} (s ⁻¹) ^b	$t_{1/2}$ (s) ^c
1	[Cu(MeCN) ₄]OTf	0.3588	1.93
2	[Cu(MeCN) ₄]PF ₆	0.2433	2.85
3	[Cu(MeCN) ₄]BF ₄	0.2839	2.44
4	CuCl	0.3454	2.01
5	CuBr	0.2882	2.40
6	Cu(BF ₄) ₂ ·xH ₂ O	0.2939	2.36
7	Cu(OTf) ₂	0.2743	2.53
8	CuCl ₂ ·2H ₂ O	0.2252	3.08
9 ^d	CuSO ₄ ·5H ₂ O	0.0372	18.63
10	-	0.0909	7.62

^a *p*-nitrophenyl- β -D-glucopyranoside (83 x 10⁻⁴ M), Cu^I-/Cu^{II}-precursors (1 x 10⁻⁴ M), **L03** (1 x 10⁻⁴ M), H₂O₂ (10 equiv.) NEt₃ (1 equiv.), H₂O (3 mL), reaction time: 60 s, 27 ± 2 °C. ^b Rate constant (k_{obs} = 1+log(abs)) measured over 0.2 s. ^c $t_{1/2}$ = $k_{obs}/0.693$. ^d Cu^{II} salt in the absence of **L03**.

The selectivity of our optimised (**L03**)[Cu(MeCN)₄]OTf/H₂O₂/NEt₃ catalyst system was confirmed by evaluating primary (benzyl alcohol) and secondary (1-phenylethanol) alcohols as substrates. Our catalyst system showed selectivity towards oxidative cleavage reactions.

6.2.2 Investigating the formation of LCu^{II}-OOH, LCu^{II}-O[•] and [•]OH species

Reactions were performed without the polysaccharide substrate to investigate the interaction between LCu and H₂O₂, in the presence of NEt₃. An absorbance was observed at 375 nm, consistent with the formation of the LCu^{II}-OOH intermediate (Figures S6.2 and S6.3 in the Supporting Information) [12, 14, 27]. The exact role of NEt₃ during this process is still unclear, but Mayilmurugan and co-workers proposed its involvement to facilitate the binding between H₂O₂ and the Cu^{II}-centre. The rate of formation of these species was calculated as 0.0337 s⁻¹ over the initial 0.2 s, where after a significant decrease in the rate was observed due to the possible formation of an off-cycle [Cu-hydroxo]₂ dimer in the absence of the substrate. Similar inactive dimeric species have been reported previously [37-42].

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Moreover, LCu^{II} -oxyl ($\text{LCu}^{\text{II}}\text{-O}\cdot$) and hydroxyl ($\cdot\text{OH}$) radical species may be derived from the $\text{LCu}^{\text{II}}\text{-OOH}$ intermediate to serve as the active species for the H-atom abstraction step during these reactions [27, 43, 44]. Oxidative cleavage reactions were performed in the presence of radical trapping agents, using our optimised reaction conditions, to evaluate its effect on the rate of *p*-nitrophenol formation (Scheme 6.2, Table 6.3 and Figure S6.4 in the Supporting Information). In particular, we sought to exploit the relative ease of C-H bond activation between 2,4-di-*tert*-butylphenol [bond dissociation energy (BDE) = 81.24 kcal/mol] [45] and *p*-nitrophenyl- β -D-glucopyranoside (BDE = 101.1 and 103.8 kcal/mol for C1 and C4, respectively, in the traditional polysaccharide substrate) [46, 47] as substrates. A significant decrease in the rate constant for *p*-nitrophenol formation was observed when employing either 2,2,6,6-tetramethylpiperidin-1-yl-oxyl ($\text{TEMPO}\cdot$, k_{obs} : 0.1303 s⁻¹, a ratio of 1:1 relative to H_2O_2 , Table 6.3, entry 2) or 2,4-di-*tert*-butylphenol (k_{obs} : 0.0933 s⁻¹, a ratio of 1:300 relative to L03Cu^{I} , Table 6.3, entry 3) as a radical trap. In the case of 2,4-di-*tert*-butylphenol, GC-MS analysis showed that 3,3',5,5'-tetra-*tert*-butylbiphenyl-2,2'-diol was formed as the major radical coupling product, with trace amounts of 3,5-di-*tert*-butylbenzene-1,2-diol (via *ortho*-hydroxylation) also observed, in the absence of the polysaccharide substrate (Figure S6.5 in the Supporting Information). It should be noted that no coupling or hydroxylation product was observed in the absence of L03Cu^{I} . These results support the formation of both C- and O-centred radical species [48]. Mayilmurugan and co-workers reported a decrease in the product yield for *p*-nitrophenol formation (64.5 % relative to 78.4 %) in the presence of $\text{TEMPO}\cdot$ despite stating that radical formation did not occur for their catalyst system [12].

Table 6.3: Evaluation of the effect of a radical trapping agent on the rate of *p*-nitrophenol formation using our (**L03**)[Cu(MeCN)₄]OTf/H₂O₂/NEt₃ catalyst system for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside.^a

Entry	Radical trap	k_{obs} (s ⁻¹) ^b	$t_{1/2}$ (s) ^c
1	None	0.3588	1.93
2	TEMPO $\cdot$	0.1303	5.32
3	2,4-di- <i>tert</i> -butylphenol	0.0932	7.44

^a *p*-nitrophenyl- β -D-glucopyranoside (83 x 10⁻⁴ M), [Cu(MeCN)₄]OTf (1 x 10⁻⁴ M), **L03** (1 x 10⁻⁴ M), H₂O₂ (10 equiv.) NEt₃ (1 equiv.), H₂O (3 mL), reaction time: 60 s, 27 ± 2 °C. ^b Rate constant ($k_{\text{obs}} = 1 + \log(\text{abs})$) measured over 0.2 s. ^c $t_{1/2} = 0.693/k_{\text{obs}}$.

6.2.3 Kinetic behaviour of the (L03)[Cu(MeCN)₄]OTf/H₂O₂/NEt₃ catalyst system

Initial rate data for the formation of *p*-nitrophenol at 405 nm were generated spectrophotometrically for [LCu], [H₂O₂], [NEt₃] and [substrate] over the initial 0.2 s (Figure 6.3 and Table S6.1 in the Supporting Information). A first-order dependence was observed on [LCu], [H₂O₂] and [substrate]; however, saturation was observed at concentrations above the optimal reaction conditions of 0.1 mM, 83 mM and 8.3 mM, respectively (Figure 6.3, A, B and D), consistent with previous reports [14, 24, 26, 27, 35]. Previous studies revealed that high concentrations of H₂O₂ may lead to enzyme inactivation, and this may also be applicable for Cu-based LPMO mimics [14]. Lastly, zero-order dependence was observed on [NEt₃] (Figure 6.3, C). This indicates the importance of NEt₃ during oxidative cleavage to assist with the coordination between H₂O₂ and the Cu-centre, but the reaction is independent of the initial concentration thereof [12].

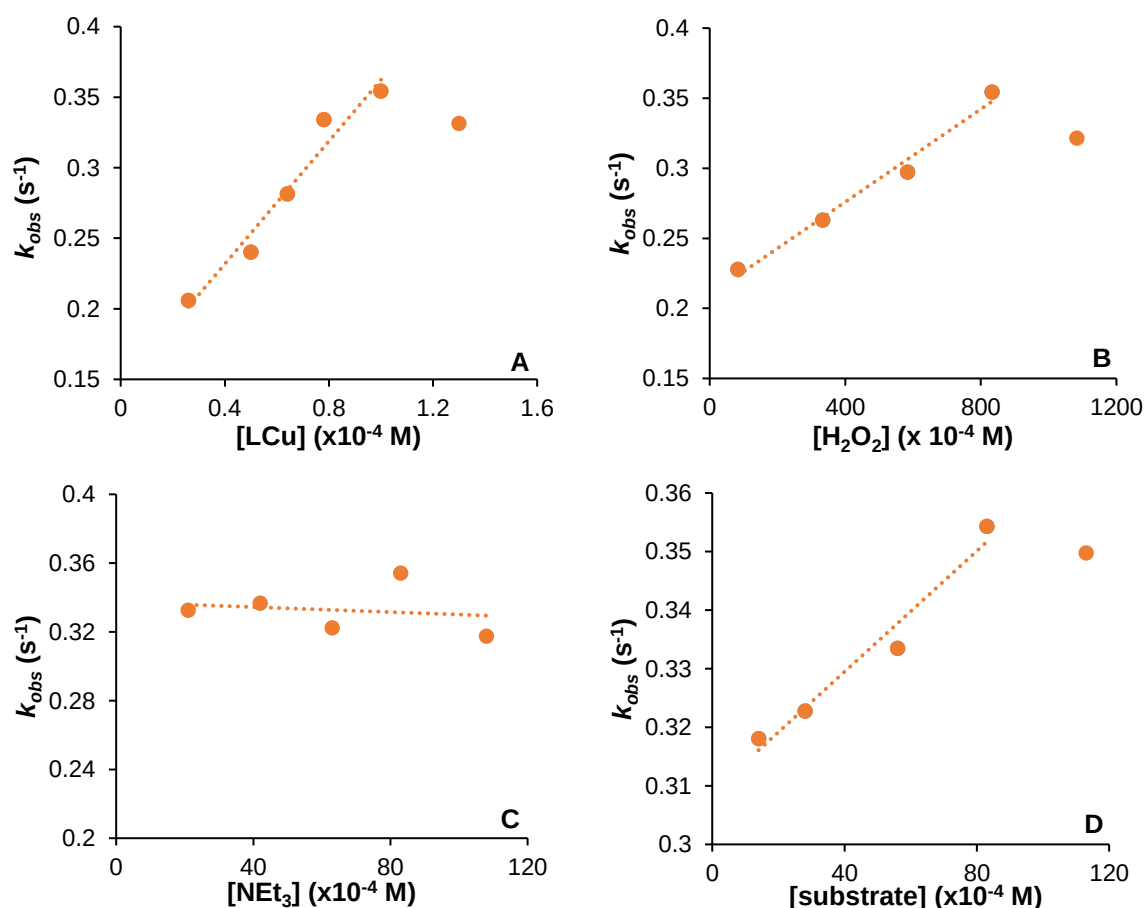
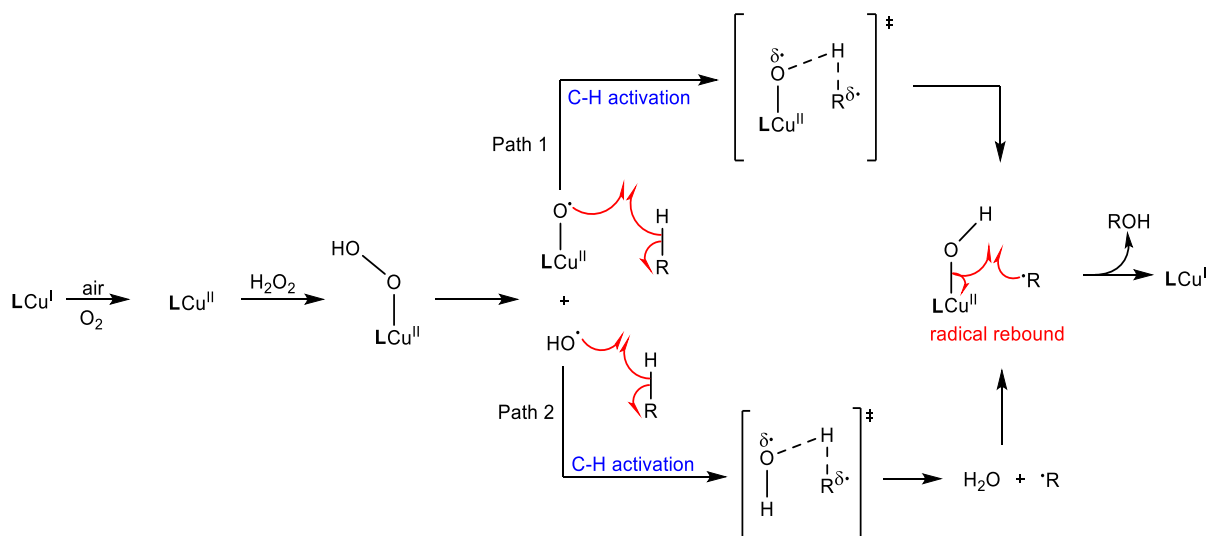


Figure 6.3: Kinetic data for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside by (L03)[Cu(MeCN)₄]OTf/H₂O₂/NEt₃ assessing the kinetic dependence on [LCu] (A), [H₂O₂] (B) [NEt₃] (C) and [substrate] (D).

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The reactions were performed open to air and therefore, the pre-catalyst, LCu^{I} , is rapidly oxidised to LCu^{II} which then reacts with H_2O_2 to afford the $\text{LCu}^{\text{II}}\text{-OOH}$ species in the absence of the substrate. This observation was also supported by our UV/vis studies. Both $\text{LCu}^{\text{II}}\text{-O}^\bullet$ and $^\bullet\text{OH}$ radical species are formed from the $\text{LCu}^{\text{II}}\text{-OOH}$ species, due to homolytic O-O bond cleavage, and either one may participate in the C-H activation step via two possible mechanistic pathways (Scheme 6.2). The first mechanistic pathway, Path 1, involves the reaction between $\text{LCu}^{\text{II}}\text{-O}^\bullet$ and the substrate (R-H) to afford the formation of $\text{LCu}^{\text{II}}\text{-OH}$ and an alkyl radical ($^\bullet\text{R}$) [14, 48]. Migration of the $^\bullet\text{OH}$ radical from $\text{LCu}^{\text{II}}\text{-OH}$ to $^\bullet\text{R}$, through the radical rebound reaction results in the formation of ROH and regenerates the LCu^{I} species. The second pathway, Path 2, proceeds via the reaction between $^\bullet\text{OH}$ and the substrate (C-H activation step), resulting in the formation of H_2O and $^\bullet\text{R}$ (Scheme 6.2) [14, 28]. Similar to the first pathway, the alkyl radicals may then react with the available $\text{LCu}^{\text{II}}\text{-OH}$ species from Path 1 during the radical rebound reaction to afford the formation of ROH and the regeneration of LCu^{I} species. Our kinetic studies and radical trapping experiments support the presence of the $\text{LCu}^{\text{II}}\text{-OOH}$ intermediate as well as the formation of both $\text{LCu}^{\text{II}}\text{-O}^\bullet$ and $^\bullet\text{OH}$ active species for substrate activation; however, we could not identify the optimal mechanistic pathway for our Cu-based catalyst system.



Scheme 6.2: The proposed mechanistic pathway for oxidative cleavage reactions. $\text{LCu}^{\text{II}}\text{-OOH}$ species is formed, followed by the formation of $\text{LCu}^{\text{II}}\text{-oxyl}$ and $^\bullet\text{OH}$ radical species for the H-atom abstraction step. Adapted from the groups of Bissaro and Cowan [14, 28].

6.2.4 Electrochemical studies of the **(L03)**[Cu(MeCN)₄]OTf/H₂O₂/NEt₃ catalyst system

Electrochemical studies were performed, in the absence of the substrate, to determine the various pyrazolylpyridineimine and -amine ligands on the Cu-based redox potentials. Voltammograms were obtained at a constant scan rate of 50 mV/s over a scanning potential window of -0.5 to +1.75 V (Figure 6.4). Tetrabutylammonium hexafluorophosphate (Bu₄NPF₆) was added to the reactions as a supporting electrolyte ($E_{1/2}$: -0.70 V [vs NHE (normal hydrogen electrode)]). When employing our optimised [Cu(MeCN)₄]OTf(**L03**) catalyst system, an anodic peak was observed at E_{pa} 0.47 V (vs NHE) and I_{pa} 0.01 mA in the forward scan, while the cathodic peak was observed at E_{pc} 0.19 V (vs NHE) and I_{pc} -0.02 mA in the reverse scan. This is consistent with a quasi-reversible one-electron oxidation process for the Cu^{II}/Cu^I redox couple [1, 2, 49, 50]. No redox potentials consistent with the Cu^{III}/Cu^{II} redox couple were observed between 0.5 and 1.0 V. Lastly, an irreversible one-electron ligand-centred oxidation for ligand **L03** (onset potential of 1.15 V vs NHE) was observed as a weak anodic peak at E_{pa} 1.30 V (vs NHE) and I_{pa} 0.01 mA.

Ligand **L03** was then replaced with imine-**L01** and **L01** and a cathodic shift was observed for the Cu^{II}/Cu^I redox couple employing imine-**L01** ($E_{1/2}$: 0.24 V vs NHE) and **L01** ($E_{1/2}$: 0.28 V vs NHE) relative to **L03** ($E_{1/2}$: 0.34 V vs NHE; Figure 6.4). This supports the increased donor ability of imine-**L01** and **L01** in comparison to **L03**. Moreover, the intensity of the irreversible ligand-centred oxidation increased when **L03** was replaced with either imine-**L01** or **L01**. As expected, imine-**L01** generates the most electron-rich copper intermediate in the series. The Cu^{II}/Cu^I redox potentials for imine-**L01**Cu^I, **L01**Cu^I and **L03**Cu^I are significantly higher than previously reported for both CuN₄ ($E_{1/2}$: -0.349 to -0.404 V) and CuN₃ (0.005 to 0.226 V vs NHE) complexes [12, 27, 29, 51]. Furthermore, our Cu^{II}/Cu^I redox potentials are comparable to those obtained for the LPMO enzyme (0.15 V to 0.37 V vs NHE) [1, 2, 49, 50]. This indicates the higher Lewis acidity of our *in situ* formed pre-catalysts, and therefore also the higher rate constants and faster conversions for *p*-nitrophenol formation, consistent with reactivity trends observed for putative high-valent copper-oxygen species.

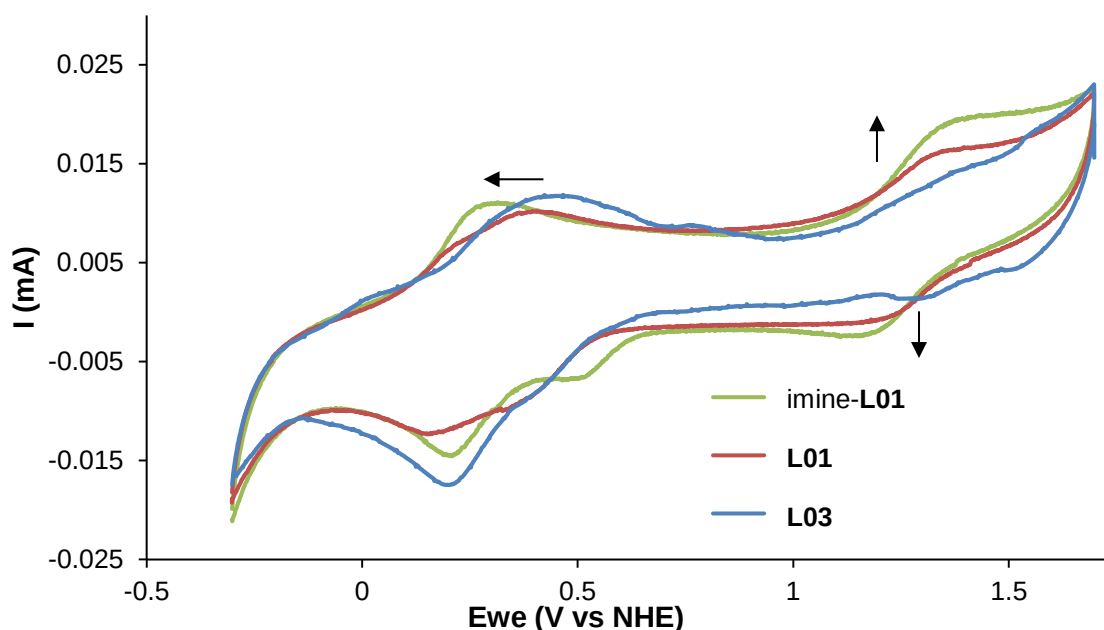


Figure 6.4: Cyclic voltammograms of various pyrazolylpyridineimine and -amine ligands, in combination with $[\text{Cu}(\text{MeCN})_4]\text{OTf}$, at a scan rate of 50 mV/s for the scanning potential of -0.5 to 1.75 V. Bu_4NPF_6 was added as the supporting electrolyte ($E_{1/2}$: -0.70 V vs NHE). The $\uparrow$ and $\downarrow$ arrows denote the increase in the intensity of the ligand-centred oxidation, while the $\leftarrow$ arrow denotes the gradual shift in the $\text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}$ couple.

6.3 Conclusions

Our previously reported tridentate pyrazolylpyridineimine and -amine ligands, imine-**L01**, imine-**L02** and **L01-L04**, in combination with Cu^{I} , H_2O_2 and NEt_3 , have been evaluated as LPMO mimics for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside in H_2O . The highest rate constant (k_{obs} : 0.3588 s^{-1}) was obtained for our (**L03**) $[\text{Cu}(\text{MeCN})_4]\text{OTf}/\text{H}_2\text{O}_2/\text{NEt}_3$ catalyst system, while a product yield of 69 % for *p*-nitrophenol formation was possible after 15 min at 27 °C. We observed the formation of $\text{Cu}^{\text{II}}\text{-OOH}$ species spectrophotometrically in the absence of the substrate. The addition of radical traps provided experimental evidence for the formation of both O- and C-centred radicals. Kinetic studies revealed first-order dependence in $[\text{LCu}]$, $[\text{H}_2\text{O}_2]$, and $[\text{substrate}]$, while zero-order dependence was obtained for $[\text{NEt}_3]$. Our catalytic and electrochemical studies confirmed **L03** as the optimal ligand for the oxidative cleavage reactions, due to the obtained high rate constant, high redox potentials and lower donor ability. Lastly, our catalyst system showed selectivity towards oxidative cleavage reactions since poor to no conversions were obtained during the oxidation of primary and secondary alcohols. Future studies include the further investigation of the efficiency of our (**L03**) $[\text{Cu}(\text{MeCN})_4]\text{OTf}/\text{H}_2\text{O}_2/\text{NEt}_3$ catalyst system toward the oxidative cleavage of naturally

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occurring gluco- and galacto-derived polysaccharides with either α - or β -glycosidic linkages, since exceptional activity was observed for the model substrate *p*-nitrophenyl- β -D-glucopyranoside.

6.4 Experimental section

6.4.1 General considerations

All commercially available reagents were obtained from Sigma-Aldrich and/or Merck and used as received. The pyrazolylpyridineimine and -amine ligands, imine-**L01**, imine-**L02** and **L01-L04**, were synthesised according to reported procedures [30, 66, 67]. Kinetic studies, product yields and spectrophotometric studies were obtained on an Agilent Technologies Cary 60 at 27 °C (controlled by the PCB 1500 Water Peltier System), either in 10 mm quartz cuvettes or using the Applied Photophysics RX2000 Rapid Stirring Accessory. GC analyses were performed on an Agilent 6890 Series GC system with an HP-5 column (30 m x 0.320 mm x 0.25 mm). N₂ served as the carrier gas, ethyl acetate (EtOAc) and dichloromethane (DCM) were used as the rinsing solutions, and samples (0.2 mL) were analysed with biphenyl as the internal standard. The oxidation products were identified by comparing the GC retention times of commercial samples to our obtained retention times. GC-MS analyses were performed on an Agilent 6890 N Series GC system with a mass selective (5973) detector and an HP-5-MSUI column. Helium served as the carrier gas, EtOAc and DCM were used as the rinsing solutions, and samples (0.2 mL) were analysed with biphenyl as the internal standard to confirm the identification of peaks. UV/vis studies of the oxidative cleavage reactions were done in duplicate to determine the rate constants as well as an average product yield in some cases.

6.4.2 Optimisation of our Cu-based catalyst system

Our catalyst system was optimised by stopped-flow UV/vis studies. The rapid stirring accessory was flushed twice with H₂O, after which the system was flushed twice with the reaction solutions. Solutions of **LCu** and substrate in H₂O (syringe one, 6 mL) and H₂O₂ and NEt₃ in H₂O (syringe two, 6 mL) were mixed in a 1:1 volume ratio at 27 °C. Reactions were repeated three to four times (approximately 120 μ L from each syringe are mixed, but only a final sample volume of 60 μ L is analysed) to condition the system and the data of the last run were used. The Cary WinUV Kinetics application (version 5.0.0.999) was used to follow the formation of *p*-nitrophenol at 405 nm over 60 s (fast scan rate). An increase in the absorbance was observed for the first 0.2 s, after which the rate of formation decreased. Good reproducibility was obtained between runs. Concentrations of all reagents are reported at the

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onset of the reaction (after mixing) and corrected for the 1:1 dilution. The rapid stirring accessory was flushed twice with H₂O after every analysis. The same method was employed for the kinetic studies as well as for the confirmation of the Cu-based intermediates.

The catalyst system was optimised by varying pyrazolylpyridineimine and -amine ligands and Cu^I-/Cu^{II}-precursors for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside in H₂O. A solution of Cu-precursor ([Cu(MeCN)₄]BF₄, [Cu(MeCN)₄]OTf, [Cu(MeCN)₄]PF₆, CuCl, CuBr, Cu(BF₄)₂·xH₂O, Cu(OTf)₂ and CuCl₂·2H₂O, 0.1 mM in 0.5 mL H₂O), ligand (imine-**L01**, imine-**L02** and **L01-L04**, 0.1 mM in 0.5 mL H₂O) and substrate (8.3 mM in 0.5 mL H₂O) was loaded in syringe one. Syringe two contains H₂O₂ (30 % in H₂O, 83 mM, 10 equiv.) and NEt₃ (8.3 mM, 1 equiv.) in H₂O (1.5 mL). The whole system was multiplied by four to obtain a total H₂O volume of 6 mL in each syringe.

6.4.3 Kinetic studies for our Cu-based catalyst system

The concentration of only one reaction parameter was varied, while optimal reaction conditions were employed. A solution of Cu(MeCN)₄]OTf (x mM in 0.5 mL H₂O), ligand **L03** (x mM in 0.5 mL H₂O) and substrate (x mM in 0.5 mL H₂O) was loaded in syringe one. Syringe two contains H₂O₂ (30 % in H₂O, x mM, x equiv.) and NEt₃ (x mM, x equiv.) in H₂O (1.5 mL). The whole system was multiplied by four to obtain a total H₂O volume of 6 mL in each syringe.

6.4.4 Oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside

A solution of [Cu(MeCN)₄]OTf (0.8 mM in 1.0 mL H₂O), ligand **L03** (0.8 mM in 1.0 mL H₂O), substrate (67 mM in 1.0 mL H₂O), H₂O₂ (30 % in H₂O, 670 mM, 10 equiv.) and NEt₃ (67 mM, 1 equiv.) was added to a small reactor flask and slowly mixed for 15 min at 27 °C before it was transferred to a quartz cuvette and analysed using UV/vis spectroscopic studies. Quantification of *p*-nitrophenol formation at 405 nm was done using a calibration curve with the Cary WinUV Concentration application (version 5.0.0.999).

6.4.5 Experimental evidence of the formation of the LCu^{II}-OOH intermediate

A solution of Cu(MeCN)₄]OTf (0.1 mM in 0.5 mL H₂O), ligand **L03** (0.1 mM in 0.5 mL H₂O) and an additional portion of H₂O (0.5 mL) was loaded in syringe one. Syringe two contains H₂O₂ (30 % in H₂O, 83 mM, 10 equiv.) and NEt₃ (8.3 mM, 1 equiv.) in H₂O (1.5 mL). The whole system was multiplied by four to obtain a total H₂O volume of 12 mL. The Cary WinUV Kinetics application was used to follow the formation of LCu^{II}-OOH, in the absence of the substrate, at

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375 nm over 60 s (fast scan rate). An increase in the absorbance was observed for the first 0.2 s, after which the rate of formation decreased dramatically.

6.4.6 Reactivity studies in the presence of a radical trapping agent

A radical trapping agent was added to the reaction to evaluate its effect on the rate of *p*-nitrophenol formation at 405 nm. A solution of $\text{Cu}(\text{MeCN})_4\text{OTf}$ (0.1 mM in 0.5 mL H_2O), ligand **L03** (0.1 mM in 0.5 mL H_2O) and substrate (8.3 mM in 0.5 mL H_2O) was loaded in syringe one. Syringe two contains H_2O_2 (30 % in H_2O , 83 mM, 10 equiv.), $\text{TEMPO}^\bullet$ (83 mM, 10 equiv., ratio of 1:1 relative to H_2O_2) and NEt_3 (8.3 mM, 1 equiv.) in H_2O (1.5 mL). The whole system was multiplied by four to obtain a total H_2O volume of 6 mL in each syringe.

Another radical trapping reaction was performed by replacing $\text{TEMPO}^\bullet$ with 2,4-di-*tert*-butylphenol. A solution of $\text{Cu}(\text{MeCN})_4\text{OTf}$ (0.1 mM in 0.5 mL MeCN), ligand **L03** (0.1 mM in 0.5 mL MeCN), substrate (8.3 mM in 0.25 mL H_2O for optimal solubility) and 2,4-di-*tert*-butylphenol (31 mM in 0.25 mL MeCN, ratio of 1:300 relative to **L03**Cu) was loaded in syringe one. Syringe two contains H_2O_2 (30 % in H_2O , 83 mM, 10 equiv.) and NEt_3 (8.3 mM, 1 equiv.) in MeCN (1.5 mL). The whole system was multiplied by four to obtain a total volume of 6 mL in each syringe.

Alternatively, the efficiency of our (**L03**) $[\text{Cu}(\text{MeCN})_4\text{OTf}/\text{H}_2\text{O}_2/\text{NEt}_3$ catalyst system towards 2,4-di-*tert*-butylphenol was also evaluated, in the absence of the *p*-nitrophenyl- β -D-glucopyranoside substrate. A solution of $\text{Cu}(\text{MeCN})_4\text{OTf}$ (0.8 mM in 1 mL MeCN), ligand **L03** (0.8 mM in 1 mL MeCN), 2,4-di-*tert*-butylphenol (250 mM in 1 mL MeCN, ratio of 1:300 relative to **L03**Cu), H_2O_2 (30 % in H_2O , 670 mM, 10 equiv.) and NEt_3 (67 mM, 1 equiv.) was added to a small reactor flask and stirred for 2 h at 27 °C. After the allotted time, the reaction mixture was filtered through a silica plug and a sample (0.18 mL) was analysed by GC-MS with biphenyl (50 μL) as the internal standard.

6.4.7 Electrochemical studies

Electrochemical studies were conducted on a BioLogic SP-150 potentiostat linked to a computer, utilising the EC Lab software. Measurements were done at 25 °C and the temperature was kept constant to within 0.5 °C. The measurements were performed on 1 mM solutions, dissolved in anhydrous MeCN as the solvent, containing 0.1 M tetrabutylammonium hexafluorophosphate (Bu_4NPF_6) as supporting electrolyte. A conventional three-electrode electrochemical cell was used, consisting of a platinum (Pt) wire as the counter-electrode, a glassy carbon working electrode with a geometrical area of 0.196 cm^2 , as well as an Ag/AgCl

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(saturated KCl) reference electrode. The working electrode was polished with 0.5 M alumina suspension and washed with Milli-Q water, ethanol and isopropanol before it was assembled into a rotating disc electrode setup. The counter and reference electrodes were sonicated for two min in H₂O. Measurements were taken after N₂ was bubbled through the reaction mixture for at least 15 min. Voltammograms were recorded with a scan rate of 50 mV/s (unless otherwise mentioned) for a scanning potential window of -0.5 to +1.75 V. The measured redox potentials were converted to normal hydrogen electrode (NHE) values by adding +0.199 V to compare our results to other LPMO mimics and related catalyst systems.

6.4.8 Evaluation of the selectivity of our catalyst system

The selectivity of our catalyst system for oxidative cleavage reactions was confirmed by evaluating the oxidation of primary and secondary alcohols. A solution of [Cu(MeCN)₄]OTf (0.8 mM in 1.0 mL H₂O), ligand **L03** (0.8 mM in 1.0 mL H₂O), benzyl alcohol or 1-phenylethanol (67 mM, 1.0 mL H₂O), H₂O₂ (30 % in H₂O, 667 mM, 10 equiv.) and NEt₃ (67 mM, 1 equiv.) was stirred in a small reactor flask for 2 h at 27 °C. After the allotted time, the reaction mixture was flushed through a silica plug and a sample (0.18 mL) was analysed by GC with biphenyl (50 μ L) as the internal standard.

6.5 Acknowledgements

This work is based on the research supported by the National Research Foundation of South Africa (Unique Grant No. 112545 and 117869) and North-West University. Any opinion, finding and conclusion or recommendation expressed in this material is that of the author(s) and the NRF does not accept any liability in this regard. The infrastructure support provided by the Focus Area for Chemical Resource Beneficiation (CRB) and in particular the Catalysis and Synthesis Research Group, at the NWU, is gratefully acknowledged.

6.6 References

- [1] G.R. Hemsworth, E.M. Johnston, G.J. Davies, P.H. Walton, Trends Biotechnol., 33 (2015) 747-761.
- [2] W.T. Beeson, V.V. Vu, E.A. Span, C.M. Phillips, M.A. Marletta, Annu. Rev. Biochem, 84 (2015) 923-946.
- [3] P.V. Harris, D. Welner, K. McFarland, E. Re, J.-C. Navarro Poulsen, K. Brown, R. Salbo, H. Ding, E. Vlasenko, S. Merino, Biochemistry, 49 (2010) 3305-3316.
- [4] G. Vaaje-Kolstad, B. Westereng, S.J. Horn, Z. Liu, H. Zhai, M. Sørlie, V.G. Eijsink, Science, 330 (2010) 219-222.
- [5] S.J. Horn, G. Vaaje-Kolstad, B. Westereng, V. Eijsink, Biotechnol. Biofuels, 5 (2012) 45-58.
- [6] M. Dimarogona, E. Topakas, P. Christakopoulos, Appl. Microbiol. Biotechnol., 97 (2013) 8455-8465.
- [7] C.E. Elwell, N.L. Gagnon, B.D. Neisen, D. Dhar, A.D. Spaeth, G.M. Yee, W.B. Tolman, Chem. Rev., 117 (2017) 2059-2107.
- [8] E.D. Larsson, G. Dong, V. Veryazov, U. Ryde, E.D. Hedegård, Dalton Trans., 49 (2020) 1501-1512.
- [9] B.D. Neisen, N.L. Gagnon, D. Dhar, A.D. Spaeth, W.B. Tolman, J. Am. Chem. Soc., 139 (2017) 10220-10223.
- [10] G.R. Hemsworth, G.J. Davies, P.H. Walton, Curr. Opin. Struct. Biol., 23 (2013) 660-668.
- [11] G. Müller, P. Chylenski, B. Bissaro, V.G. Eijsink, S.J. Horn, Biotechnol. Biofuels, 11 (2018) 209-226.
- [12] S. Muthuramalingam, D. Maheshwaran, M. Velusamy, R. Mayilmurugan, J. Catal., 372 (2019) 352-361.
- [13] L. Bertini, R. Breglia, M. Lambrugh, P. Fantucci, L. De Gioia, M. Borsari, M. Sola, C.A. Bortolotti, M. Bruschi, Inorg. Chem., 57 (2018) 86-97.
- [14] B. Bissaro, Å.K. Røhr, G. Müller, P. Chylenski, M. Skaugen, Z. Forsberg, S.J. Horn, G. Vaaje-Kolstad, V.G. Eijsink, Nat. Chem. Biol., 13 (2017) 1123-1131.
- [15] R.J. Quinlan, M.D. Sweeney, L.L. Leggio, H. Otten, J.-C.N. Poulsen, K.S. Johansen, K.B. Krogh, C.I. Jørgensen, M. Tovborg, A. Anthonsen, T. Tryfona, C.P. Walter, P. Dupree, F. Xu, G.J. Davies, P.H. Walton, PNAS, 108 (2011) 15079-15084.
- [16] W.T. Beeson, C.M. Phillips, J.H. Cate, M.A. Marletta, J. Am. Chem. Soc., 134 (2012) 890-892.
- [17] X. Li, W.T. Beeson IV, C.M. Phillips, M.A. Marletta, J.H. Cate, Structure, 20 (2012) 1051-1061.

Chapter 6: Synthetic LPMO mimics: a copper/pyrazolylpyridineamine catalyst system for the highly efficient oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside

- [18] B. Westereng, T. Ishida, G. Vaaje-Kolstad, M. Wu, V. Eijsink, K. Igarashi, M. Samejima, J. Stahlberg, S. Horn, M. Sandgren, *PloS one*, 6 (2011) e27807.
- [19] J.J. Liu, D.E. Diaz, D.A. Quist, K.D. Karlin, *Isr. J. Chem.*, 56 (2016) 738-755.
- [20] I. Castillo, A.C. Neira, E. Nordlander, E. Zeglio, *Inorg. Chim. Acta*, 422 (2014) 152-157.
- [21] G.R. Hemsworth, B. Henrissat, G.J. Davies, P.H. Walton, *Nat. Chem. Biol.*, 10 (2014) 122-126.
- [22] R. Trammell, K. Rajabimoghadam, I. Garcia-Bosch, *Chem. Rev.*, 119 (2019) 2954-3031.
- [23] P.K. Busk, L. Lange, *BMC Genomics*, 16 (2015) 368-381.
- [24] S. Striegler, N.A. Dunaway, M.G. Gichinga, J.D. Barnett, A.-G.D. Nelson, *Inorg. Chem.*, 49 (2010) 2639-2648.
- [25] S. Striegler, M. Dittel, R. Kanso, N.A. Alonso, E.C. Duin, *Inorg. Chem.*, 50 (2011) 8869-8878.
- [26] S. Striegler, J.D. Barnett, N.A. Dunaway, *ACS Catal.*, 2 (2012) 50-55.
- [27] A.L. Concia, M.R. Beccia, M. Orio, F.T. Ferre, M. Scarpellini, F.d.r. Biaso, B. Guigliarelli, M. Réglér, A.J. Simaan, *Inorg. Chem.*, 56 (2017) 1023-1026.
- [28] Z. Yu, Z. Thompson, S.L. Behnke, K.D. Fenk, D. Huang, H.S. Shafaat, J.A. Cowan, *Inorg. Chem.*, 59 (2020) 11218-11222.
- [29] A.C. Neira, P.R. Martínez-Alanis, G. Aullón, M. Flores-Alamo, P. Zerón, A. Company, J. Chen, J.B. Kasper, W.R. Browne, E. Nordlander, I. Castillo, *ACS Omega*, 4 (2019) 10729-10740.
- [30] L. Marais, H.C.M. Vosloo, A.J. Swarts, *Mol. Catal.*, 486 (2020) 110839-11047.
- [31] T. Dhanalakshmi, E. Suresh, H. Stoeckli-Evans, M. Palaniandavar, *Eur. J. Inorg. Chem.*, 2006 (2006) 4687-4695.
- [32] S. Muthuramalingam, T. Khamrang, M. Velusamy, R. Mayilmurugan, *Dalton Trans.*, 46 (2017) 16065-16076.
- [33] S.V. Kryatov, S. Taktak, I.V. Korendovych, E.V. Rybak-Akimova, J. Kaizer, S. Torelli, X. Shan, S. Mandal, V.L. MacMurdo, A. Mairata i Payeras, *Inorg. Chem.*, 44 (2005) 85-99.
- [34] M. Velusamy, R. Mayilmurugan, M. Palaniandavar, *Inorg. Chem.*, 43 (2004) 6284-6293.
- [35] S. Haldar, A. Patra, M. Bera, *RSC Adv.*, 4 (2014) 62851-62861.
- [36] S. Itoh, *Acc. Chem. Res.*, 48 (2015) 2066-2074.

Chapter 6: Synthetic LPMO mimics: a copper/pyrazolylpyridineamine catalyst system for the highly efficient oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside

- [37] L. Marais, J. Bures, J.H.L. Jordaan, S. Mapolie, A.J. Swarts, *Org. Biomol. Chem.*, 15 (2017) 6926-6933.
- [38] J.M. Hoover, B.L. Ryland, S.S. Stahl, *ACS Catal.*, 3 (2013) 2599-2605.
- [39] G.A. van Albada, I. Mutikainen, O. Roubeau, U. Turpeinen, J. Reedijk, *Inorg. Chim. Acta*, 331 (2002) 208-215.
- [40] Y.-Q. Zheng, J.-L. Lin, *Z. Anorg. Allg. Chem.*, 629 (2003) 1622-1626.
- [41] S.P. Perlepes, J.C. Huffman, G. Christou, *Polyhedron*, 11 (1992) 1471-1479.
- [42] G.A. van Albada, I. Mutikainen, U. Turpeinen, J. Reedijk, *Inorg. Chim. Acta*, 324 (2001) 273-277.
- [43] N. Gagnon, W.B. Tolman, *Acc. Chem. Res.*, 48 (2015) 2126-2131.
- [44] D. Dhar, G.M. Yee, T.F. Markle, J.M. Mayer, W.B. Tolman, *Chem. Sci.*, 8 (2017) 1075-1085.
- [45] M. Lucarini, P. Pedrielli, G.F. Pedulli, S. Cabiddu, C. Fattuoni, *J. Org. Chem.*, 61 (1996) 9259-9263.
- [46] K.K. Meier, S.M. Jones, T. Kaper, H. Hansson, M.J. Koetsier, S. Karkehabadi, E.I. Solomon, M. Sandgren, B. Kelemen, *Chem. Rev.*, 118 (2017) 2593-2635.
- [47] E.D. Hedegård, U. Ryde, *ACS Omega*, 2 (2017) 536-545.
- [48] D.E. Diaz, M. Bhadra, K.D. Karlin, *Inorg. Chem.*, 58 (2019) 13746-13750.
- [49] V.V. Vu, S.T. Ngo, *Coord. Chem. Rev.*, 368 (2018) 134-157.
- [50] S. Garajova, Y. Mathieu, M.R. Beccia, C. Bennati-Granier, F. Biaso, M. Fanuel, D. Ropartz, B. Guigliarelli, E. Record, H. Rogniaux, *Sci. Rep.*, 6 (2016) 28276-28285.
- [51] S. Muthuramalingam, S. Subramanian, T. Khamrang, M. Velusamy, R. Mayilmurugan, *ChemistrySelect*, 2 (2017) 940-948.
- [52] C. Obuah, M.K. Ainooson, S. Boltina, I.A. Guzei, K. Nozaki, J. Darkwa, *Organometallics*, 32 (2013) 980-988.
- [53] C. Obuah, B. Omondi, K. Nozaki, J. Darkwa, *J. Mol. Catal. A: Chem.*, 382 (2014) 31-40.

Supporting Information for

Synthetic LPMO mimics: a copper/pyrazolylpyridineamine catalyst system for the highly efficient oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside

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S6.1 General considerations

S6.1.1 Instrumentation

UV/vis spectroscopy were performed on an Agilent Technologies Cary 60 at 27 °C (controlled by the PCB 1500 Water Peltier System), either in 10 mm quartz cuvettes or using the Applied Photophysics RX2000 Rapid Stirring Accessory. GC analyses were performed on an Agilent 6890 Series GC system with an HP-5 column (30 m x 0.320 mm x 0.25 mm). N₂ served as the carrier gas, ethyl acetate (EtOAc) and dichloromethane (DCM) were used as the rinsing solutions and samples (0.2 mL) were analysed with biphenyl as the internal standard. The oxidation products were identified by comparing the GC retention times of commercial samples to our obtained retention times. GC-MS analyses were performed on an Agilent 6890 N Series GC system with a mass selective (5973) detector and an HP-5-MSUI column. Helium

served as the carrier gas, EtOAc and DCM were used as the rinsing solutions, and samples (0.2 mL) were analysed with biphenyl as the internal standard.

S6.2 Optimisation of the catalyst system

The effect of various pyrazolylpyridineimine and -amine ligands, imine-**L01**, imine-**L02** and **L01-L04** (Figure S6.1), on the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside was evaluated using UV/vis spectroscopic studies. The formation of *p*-nitrophenol was followed at an absorbance of 405 nm for a reaction time of 60 sec [1].

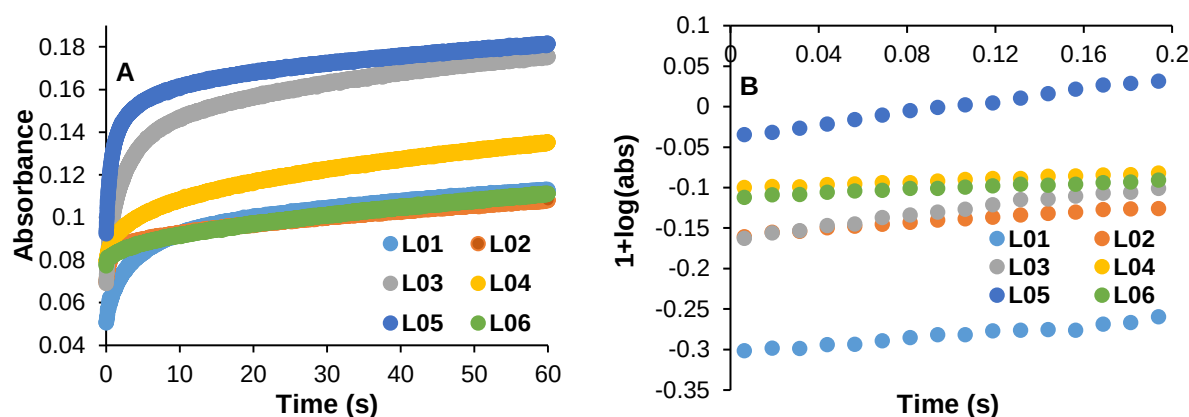


Figure S6.1: The formation of *p*-nitrophenol was followed at 405 nm over 60 s for ligands imine-**L01**, imine-**L02** and **L01-L04** (A). Rate constants (k_{obs}) were calculated using $1 + \log(\text{abs})$ vs time (s) for the first 0.2 s (B). imine-**L01**: (E)-*N*-(2-(1*H*-pyrazol-1-yl)ethyl)-1-(pyridine-2-yl)methanimine; imine-**L02**: (E)-*N*-(2-(3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl)-1-(pyridine-2-yl)methanimine; **L01**: 2-(1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine; **L02**: 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)-ethan-1-amine; **L03**: *N*-methyl-2-(1*H*-pyrazol-1-yl)-*N*-(pyridine-2-ylmethyl)ethan-1-amine; **L04**: 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-methyl-*N*-(pyridine-2-ylmethyl)ethan-1-amine.

S6.3 Formation of the $\text{LCu}^{\text{II}}\text{-OOH}$ intermediate

Reactions were performed without the polysaccharide substrate to investigate the interaction between LCu and H_2O_2 , in the presence of NEt_3 . An absorbance was observed at 375 nm, consistent with the formation of the $\text{LCu}^{\text{II}}\text{-OOH}$ key intermediate (Figures S6.2 and S6.3). The rate of formation of these species was calculated as 0.0337 s^{-1} over 0.2 s, after which a significant decrease in the rate constant was observed due to the possible formation of an off-cycle $[\text{Cu-hydroxo}]_2$ dimer in the absence of the substrate.

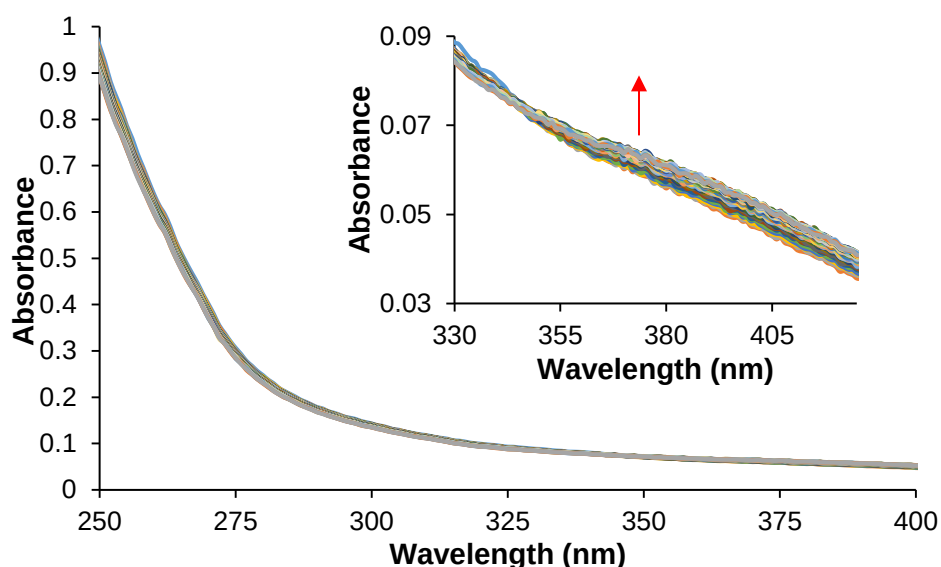


Figure S6.2: UV/vis studies were employed to follow the reaction in the absence of the polysaccharide substrate and the increased absorbance at 250 nm is due to the MeCN solvent. Inset: An increase in the absorbance was observed at 375 nm, which is consistent with the formation of the key intermediate, $\text{LCu}^{\text{II}}\text{-OOH}$.

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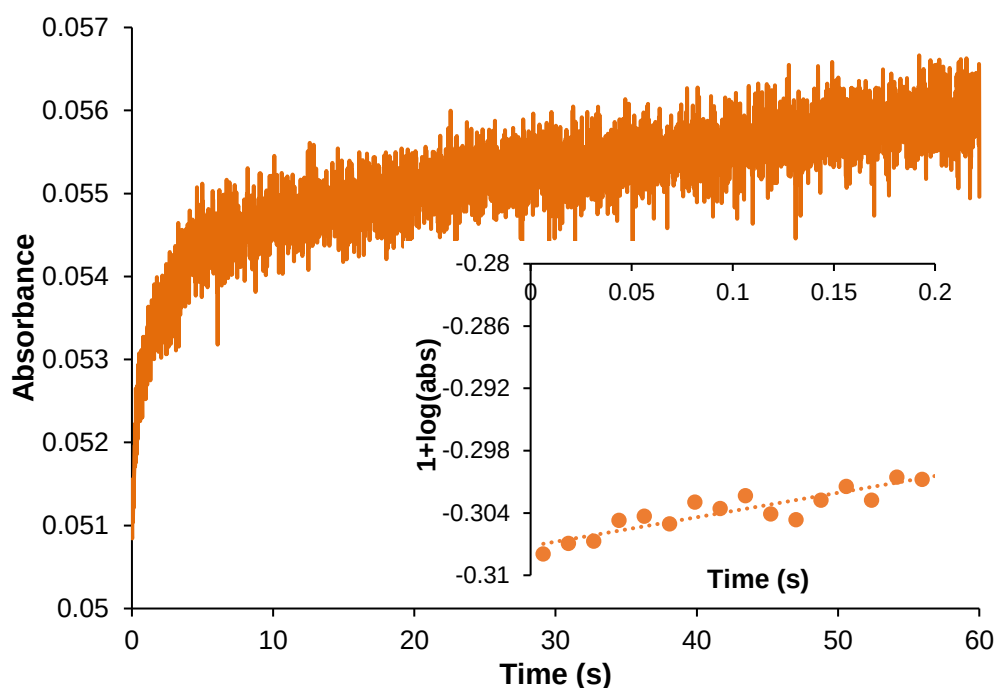


Figure S6.3: UV/vis studies were employed to follow the formation of the key intermediate, $\text{LCu}^{\text{II}}\text{-OOH}$, at 375 nm over a reaction time of 60 s, in the absence of the substrate. Inset: The rate constant (k_{obs}) for $\text{LCu}^{\text{II}}\text{-OOH}$ formation was calculated using $1+\log(\text{abs})$ vs time (s) for the initial 0.2 s.

S6.4 Experiments establishing radical species formation

LCu^{II}-oxyl (LCu^{II}-O[•]) and hydroxyl radical species may be derived from the LCu^{II}-OOH key intermediate to serve as active species for the H-atom abstraction step during these reactions. Oxidative cleavage reactions were performed in the presence of radical trapping agents, to determine its effect on the rate of *p*-nitrophenol formation (Table 6.3 and Figures S6.4 and S6.5). These results support the formation of both C- and O-centred radical species [2, 3].

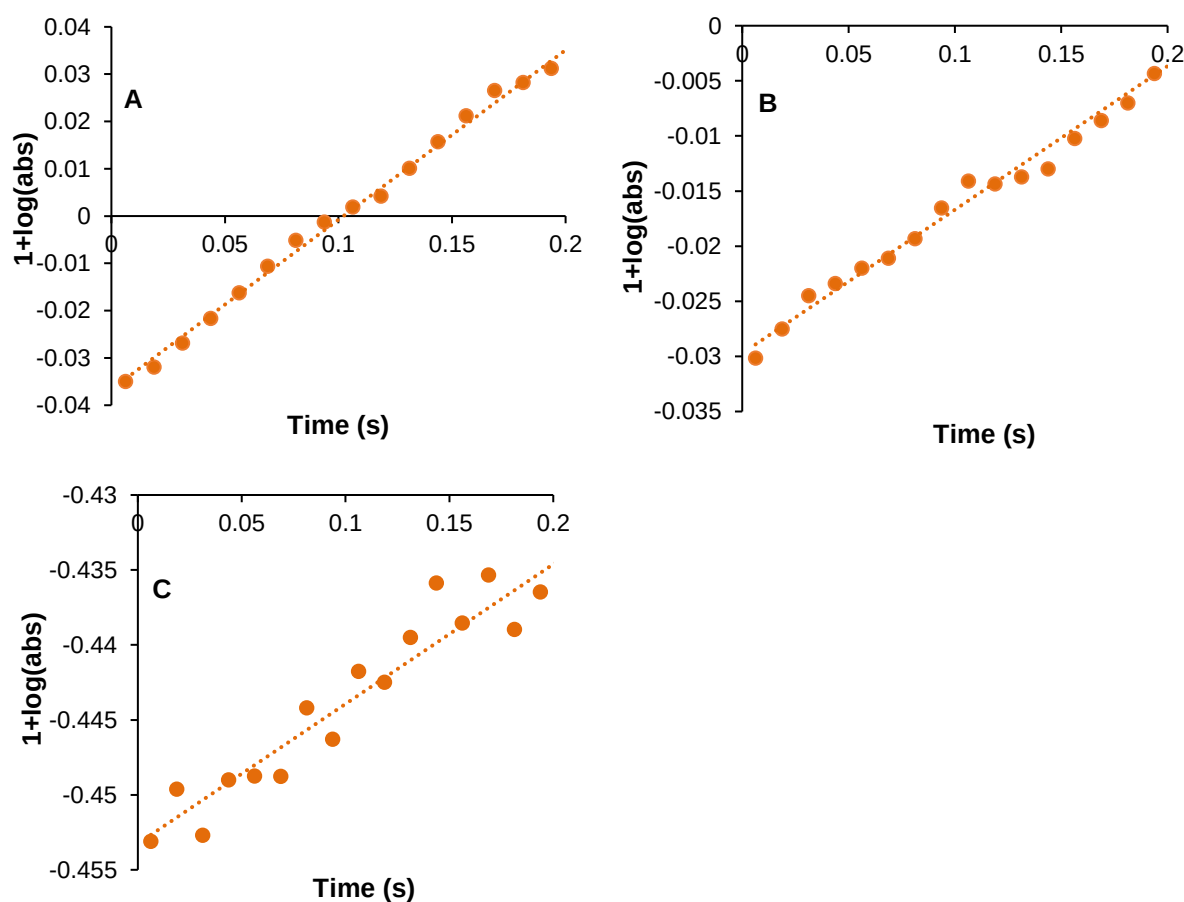


Figure S6.4: The formation of radical species was investigated using UV/vis spectroscopic studies. The rate constant (k_{obs} : 0.3588 s^{-1}) for *p*-nitrophenol formation at 405 nm was calculated using $1 + \log(\text{abs})$ vs time (s) in the absence of a radical trapping agent (**A**). A significant decrease in the rate constants was observed in the presence of a radical trapping agent such as TEMPO[•] (k_{obs} : 0.1303 s^{-1} , **B**) or 2,4-di-*tert*-butylphenol (k_{obs} : 0.0932 s^{-1} , **C**).

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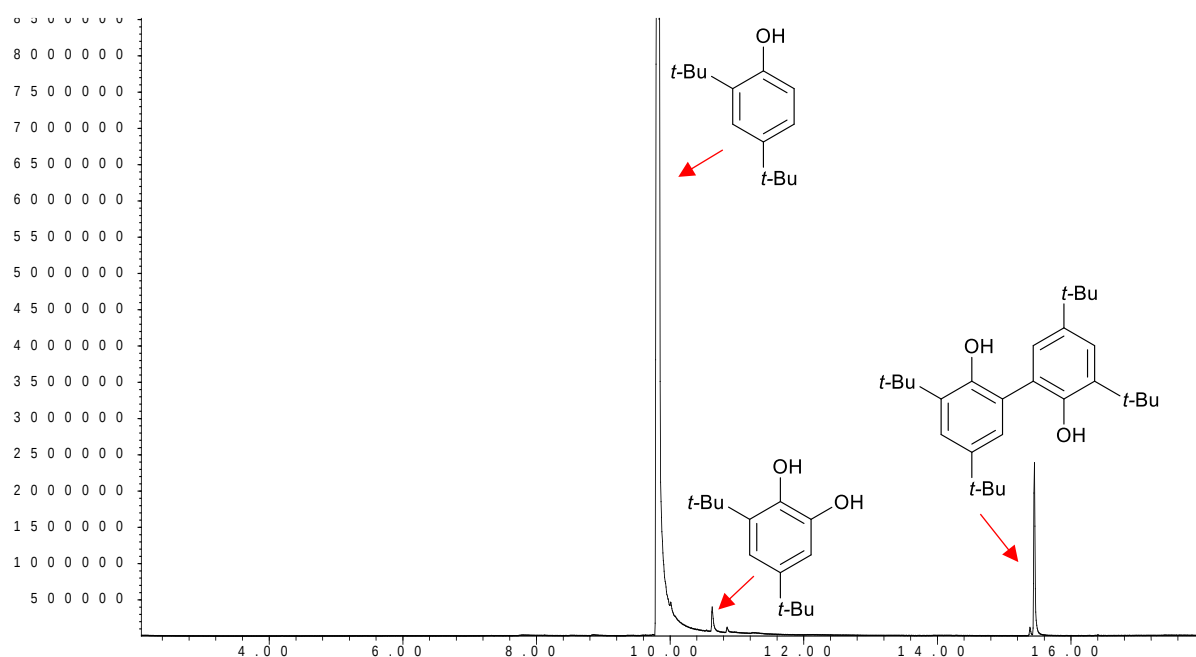


Figure S6.5: GC-MS spectrum for the efficiency of our (L03)[Cu(MeCN)₄]OTf/H₂O₂/NEt₃ catalyst system towards 2,4-di-*tert*-butylphenol, in the absence of *p*-nitrophenyl- β -D-glucopyranoside. The formation of 3,3',5,5'-tetra-*tert*-butylbiphenyl-2,2'-diol was formed as the major radical coupling product, while trace amounts of 3,5-di-*tert*-butylbenzene-1,2-diol (*ortho*-hydroxylation) were also observed.

S6.5 Kinetic studies

Kinetic assessments were conducted under synthetically relevant reaction conditions, using the rapid stirring accessory. The initial rate data for the *p*-nitrophenol formation at 405 nm was generated by varying [LCu], [H₂O₂], [NEt₃] and [substrate] during the initial 0.2 s (Figure 6.4 and Table S6.1). A first-order dependence was observed in [LCu], [H₂O₂] and [substrate], while a zero-order dependence was observed for [NEt₃].

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Table S6.1: Kinetic data for the oxidative cleavage of *p*-nitrophenyl-β-D-glucopyranoside by (L03)[Cu(MeCN)₄]OTf/H₂O₂/NEt₃, assessing the kinetic dependence on [LCu], [H₂O₂], [NEt₃] and [substrate].

Entry	[(L03)Cu] (x 10 ⁻⁴ M)	[H ₂ O ₂] (x 10 ⁻⁴ M)	[NEt ₃] (x 10 ⁻⁴ M)	[Substrate] (x 10 ⁻⁴ M)	<i>k</i> _{obs} (s ⁻¹)	<i>t</i> _{1/2} (s)
1	0.26	833	83	83	0.2059	3.21
2	0.5	833	83	83	0.2402	2.89
2	0.64	833	83	83	0.2813	2.46
3	0.78	833	83	83	0.3341	2.07
4	1.0	833	83	83	0.3543	1.96
5	1.3	833	83	83	0.3314	2.09
6	1.0	83	83	83	0.2269	3.05
7	1.0	333	83	83	0.2630	2.63
8	1.0	583	83	83	0.2972	2.33
9	1.0	833	83	83	0.3543	1.96
10	1.0	1083	83	83	0.3213	2.17
11	1.0	833	21	83	0.3327	2.08
12	1.0	833	42	83	0.3367	2.06
13	1.0	833	63	83	0.3225	2.15
14	1.0	833	83	83	0.3543	1.96
15	1.0	833	108	83	0.3175	2.18
16	1.0	833	83	14	0.3181	2.18
17	1.0	833	83	28	0.3228	2.15
18	1.0	833	83	56	0.3335	2.08
19	1.0	833	83	83	0.3543	1.96
20	1.0	833	83	113	0.3498	1.98

S6.6 References

- [1] S. Muthuramalingam, D. Maheshwaran, M. Velusamy, R. Mayilmurugan, J. Catal., 372 (2019) 352-361.
- [2] B. Bissaro, Å.K. Røhr, G. Müller, P. Chylenski, M. Skaugen, Z. Forsberg, S.J. Horn, G. Vaaje-Kolstad, V.G. Eijsink, Nat. Chem. Biol., 13 (2017) 1123-1131.
- [3] D.E. Diaz, M. Bhadra, K.D. Karlin, Inorg. Chem., 58 (2019) 13746-13750.
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7.1 Introduction

The oxidative transformation of organic substrates may be employed for the synthesis of alcohols, ketones and aldehydes as valuable oxygenated products to serve as building blocks in the pharmaceutical and chemical industries. These reactions include *N*-oxide co-catalyst-free oxidation, hydroxylation, peroxidation and oxidative cleavage reactions. Oxidative transformation reactions involve an H-atom abstraction step or the substitution of either a halogen (-X) or hydrogen (-H) atom with a hydroperoxide (-OOH) or a hydroxyl (-OH) group. A number of Cu-based catalyst systems have previously been reported for the above-mentioned oxidative transformation reactions to afford oxygenates. However, the need still exists to develop Cu-based catalyst systems with the inclusion of novel and efficient ligands for the oxidative transformation of organic substrates that can operate under mild reaction conditions, open to air, and result in excellent product yields and product selectivity.

This study aimed to develop novel Cu-based catalyst systems for the hydroxylation of aryl halides, peroxidation of cyclic and linear alkanes and the oxidative cleavage of polysaccharide surrogates that can operate under ambient air and in the absence of an *N*-oxide radical co-catalyst. These catalyst systems involve the inclusion of a Cu^I/Cu^{II}-precursor in combination with either a pyrazolylpyridineimine, -amine, α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene or α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene ligand and a hydroxide base or H₂O₂ as the oxidant. These ligands include imine groups or substituents on the pyrazole ring or the ethyl-linked *N*-atom, and they may accommodate one or two copper centres during the *in situ* formation of the pre-catalysts. We aim to determine the effect of substituents on the two ligand frameworks, the difference between tridentate and *m*-xylene bridged ligands, as well as varying nuclearity of the pre-catalysts on the various oxidative transformation reactions. Furthermore, we aim to improve on the product yields obtained, at low catalyst loadings, ambient temperatures and open to air.

7.2 Conclusions

Various novel pyrazolylpyridineimine and -amine ligands were prepared via the Schiff base condensation (imine-**L01** and imine-**L02**), reductive amination (**L01-L02**) and methylation (**L03-L04**) reaction steps [1-3]. The yellow or brown oily isolated ligands are stable and can be stored without any precaution. Spectroscopic and analytical techniques, such as FT-IR, [¹H and ¹³C{¹H}] NMR spectroscopy, were employed to characterise these ligands, while the purity thereof was confirmed with APCI mass spectrometry. Cu-based pre-catalysts were formed *in situ* prior to the reaction, and therefore no complexes were isolated. These

monofunctional ligands have found application in the hydroxylation of aryl halides, peroxidation of cyclic and linear alkanes, as well as the oxidative cleavage of polysaccharides.

The optimisation of our (**L01**)/[Cu(MeCN)₄]BF₄/CsOH catalyst system for the hydroxylation of 4-iodotoluene to *p*-cresol was accomplished by evaluating the catalyst loading, ligands **L01-L04**, hydroxide bases and Cu^I/Cu^{II}-precursors [1]. We observed a more pronounced effect on the efficiency of the reaction for the methyl groups on the pyrazole ring than the substituents on the ethyl-linked *N*-atom. Moderate conversions were obtained when employing ligands **L03** and **L04** due to the electron-donating ability of the methyl groups and the resulting lower electrophilicity of the copper metal centre [4-7]. Ligand **L01**, within the *in situ* formed copper pre-catalyst, was identified as a non-innocent ligand. This is due to the ability to remove the proton of the free NH-group during the pre-catalyst activation process. As such, **L01** in combination with [Cu(MeCN)₄]BF₄ was found to be optimal and high conversions to *p*-cresol were possible. Moreover, the observed induction period of 90 min could be shortened through the *in situ* formation of the proposed [(**L01**)Cu-OH] intermediate, accelerating the hydroxylation reaction for complete conversion within 1 h. As such, we obtained a turnover number (TON) value of 1952, which is an improvement on the TON value of 1640 obtained by the benchmark catalyst system when employing a low catalyst loading of 0.05 mol%. Lastly, our Cu-based catalyst system could be employed for the hydroxylation of a variety of aryl iodide and bromide substrates.

The application of our monofunctional ligands (**L01-L04**) was expanded by evaluating them, as well as the pyrazolylpyridineimine (imine-**L01** and imine-**L02**) ligands in the peroxidation of various cyclic and linear alkanes, using Cu^I/Cu^{II}-precursors and H₂O₂ as the oxidant. Higher product yields and alcohol selectivity were obtained when employing **L01-L04**, relative to imine-**L01** and imine-**L02** for cyclohexane peroxidation. Again, the effect of the methyl groups on the pyrazole ring has a more negative effect on the peroxidation reaction than the substituents on the ethyl-linked *N*-atom. The highest product yield and alcohol selectivity were obtained for ligand **L01**, in combination with CuCl₂·2H₂O, which was also supported by our cyclic voltammetry studies. The lower redox potentials for the Cu^{III}/Cu^{II} couple in the presence of **L01** indicate that **L01** is more easily oxidised under applied potential due to its strong donor ability and the generation of a more electron-rich Cu-based intermediate. Successful optimisation of our (**L01**)CuCl₂·2H₂O/H₂O₂ catalyst system was accomplished and exceptional product yields of > 90 %, with an alcohol selectivity of 44 %, were obtained in a shorter reaction time of 3 h, which is a significant improvement on the benchmark catalyst system [8]. Our kinetic, radical species confirmation and electrochemical studies support the formation of C- and O-centred radical species and the reversible transformation between Cu^{II} and Cu^I species, with the proposed formation of the LCu^{II}-OOH intermediate, followed by the formation

of LCu^{II} -hydroxyl (LCu^{II} -OH) and LCu^{II} -oxyl (LCu^{II} -O $\cdot$) species during the substrate independent rate-determining step. This is consistent with our proposed mechanistic pathway where the $\cdot\text{OH}$ radical species are involved in the H-atom abstraction step.

Our ligand framework was also expanded to investigate the effect of the nuclearity of Cu-based pre-catalysts on the peroxidation of cyclic and linear alkanes. As such, the above-mentioned synthesis route for the pyrazolylpyridineimine and -amine ligands was employed for the synthesis of our novel bifunctional α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene (imine-**L05** and imine-**L06**) and α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene (**L05-L08**) ligands [1, 2]. Identical analytical and spectroscopic techniques were employed to characterise these stable bifunctional ligands, which consist of two bidentate *N*-(2-pyrazolyl)ethylimino or *N*-(2-pyrazolyl)ethylamino units and a *m*-xylene bridge. These ligands can accommodate two copper centres during the *in situ* formation of the pre-catalysts and this was confirmed when similar product yields were obtained for the LCu ratio of 1:1 and 0.5:1. In contrast to our monofunctional ligands, we observed a more pronounced effect on the efficiency of the reaction for the methyl groups on the ethyl-linked *N*-atom, than for the substituents on the pyrazole ring, and the secondary amine ligand **L05** was identified as the optimal ligand. Excellent product yields of > 88 %, with alcohol selectivity, were obtained in 3 h for cyclohexane peroxidation when employing our optimised (**L05**)[Cu(MeCN)₄]PF₆/H₂O₂ catalyst system, which is an improvement on the benchmark catalyst system [8]. Kinetic and radical species confirmation studies were performed to investigate the nature of the active metal species and radical species formation, as mentioned above. These results are consistent with our findings for cyclohexane peroxidation when employing our (**L03**)CuCl₂·2H₂O/H₂O₂ catalyst system. This confirmed that the nuclearity of the *in situ* formed Cu-based pre-catalysts does not have a major influence on the efficiency of the peroxidation reactions [9].

Lastly, we evaluated our pyrazolylpyridineimine (imine-**L01** and imine-**L02**) and -amine ligands (**L01-L04**), in combination with Cu^I, H₂O₂ and NEt₃, as LPMO mimics for the oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside in H₂O. The formation of the *p*-nitrophenol product was monitored spectrophotometrically. Moderate rate constants for *p*-nitrophenol formation were obtained when employing ligands, imine-**L02**, **L02** and **L04**, due to the steric and electronic properties of the methyl groups on the pyrazole ring and the lower electrophilicity of the copper centre. Moreover, increased rate constants were obtained when employing the secondary (**L01**) and tertiary (**L03**) amine analogues of the unsubstituted pyrazole-derived ligands relative to ligand imine-**L01**. Ligand **L03**, in combination with [Cu(MeCN)₄]OTf, was found to be optimal, which was also suggested electrochemically. The higher redox potential for the Cu^{II}/Cu^I couple supported the lower oxidation potential of **L03** due to its weaker donor ability

and the formation of a less electron-rich copper intermediate. Moreover, our Cu^{II}/Cu^I redox potentials are comparable to those obtained for the LPMO enzyme [10-13]. A maximum rate constant of 0.3588 s⁻¹ was obtained during the initial 0.2 s of the reaction, while a product yield of 69 % for *p*-nitrophenol formation was possible for our optimised [Cu(MeCN)₄]OTf/L03/H₂O₂/NEt₃ catalyst system after 15 min at ambient temperatures. This is an improvement on the current state-of-the-art catalyst systems [14, 15]. UV/vis studies were employed to indicate the formation of the LCu^{II}-OOH intermediate at 375 nm, in the absence of the substrate. Both C- and O-centred radical species formation were confirmed when reactions were performed in the presence of radical trapping agents. These results, in combination with our kinetic and electrochemical studies, supported the oxidation of Cu^I to Cu^{II} due to the formation of the LCu^{II}-OOH intermediate, followed by the formation of LCu^{II}-O[•] and [•]OH radical species for substrate activation.

7.3 Scientific contributions

The following achievements are considered valuable additions to the current understanding of copper oxidation catalysis:

- Two novel ligand sets, pyrazolylpyridineimine and -amine, α,α'-bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene and α,α'-bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene, were successfully synthesised and characterised. These ligands, in combination with Cu^I-/Cu^{II}-precursors, find application in the hydroxylation of aryl halides [1], cycloalkane peroxidation [9], as well as the oxidative cleavage of polysaccharides [16].
- The initial *in situ* formation of the [(L01)Cu-OH] intermediate drastically shortened the previously observed induction period for the hydroxylation of 4-iodotoluene to *p*-cresol, and thereby accelerated the reaction [1]. An improved TON value of 1952 was possible at an optimal catalyst loading of 0.05 mol%, relative to the current benchmark catalyst system (TON: 1640) [17]. As such, this serves as experimental evidence for the effect of this intermediate, since the *in situ* formation and evaluation thereof have not been investigated previously.
- It was possible to improve on the product yields (90 and 88 %, respectively), with alcohol selectivity (44 and 40 %, respectively), for cyclohexane peroxidation in a shorter reaction time, when employing either the mono- or bifunctional ligand frameworks in combination with Cu^I-/Cu^{II}-precursors and H₂O₂. Improved product yields were also possible for the peroxidation of alternative cyclic and linear alkanes. No inert atmosphere or the addition of additives were required for these reactions.

- Two partially contradicting mechanistic pathways have previously been proposed for cycloalkane peroxidation reactions with the major difference in the reversible transformation of the copper oxidation states. Based on the findings in this study, it was possible to combine these mechanistic pathways in an attempt to propose a plausible mechanistic pathway, similar to the one proposed for the synthetic LPMO mimics [9, 16]. This mechanistic pathway supports the reversible transformation between Cu^{II} and Cu^I species, followed by the formation of the LCu^{II}-OOH intermediate and LCu^{II}-O[•] and LCu^{II}-OH species, instead of the previously proposed LCu^{III}-OH.
- The Cu(MeCN)₄OTf/L03/H₂O₂/NEt₃ catalyst system could be employed for the oxidative cleavage of *p*-nitrophenyl-β-D-glucopyranoside, and UV/vis studies were employed to follow the *p*-nitrophenol formation at 405 nm. Excellent rate constants (*k*_{obs}) of 0.1026 to 0.3588 s⁻¹ were obtained for the pyrazolylpyridineimine and -amine ligands during the initial 0.2 s at 27 °C, which is an improvement on the benchmark catalyst system where they obtained rate constants of 0.02 to 0.26 s⁻¹ at 37 °C [14].
- Lastly, product yields of 31 to 69 % for *p*-nitrophenol formation were obtained in 15 min at 27 °C. Similar yields were previously reported; however, these reactions were performed at 60 °C for 2 h [15]. Therefore, it was possible to obtain similar product yields in a shorter reaction time for reactions performed at a significantly lower reaction temperature.

7.4 Recommendations for future work

The current study on oxidative transformation reactions has generated some questions that may be addressed by future researchers.

7.4.1 Synthesis and characterisation of Cu-based complexes

The synthesis and characterisation of mononuclear and binuclear Cu-based complexes by employing our pyrazolylpyridineimine (imine-L01 and imine-L02), -amine (L01-L04), α,α'-bis[(*N*-methyl-2-pyrazolyl)ethylimino]-*m*-xylene (imine-L05 and imine-L06) or α,α'-bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene (L05-L08) ligand frameworks should be a key goal. We have previously attempted the synthesis and isolation of these complexes; however, the characterisation thereof was not successful. Even though our electrospray ionisation mass spectrometric (ESI-MS) studies showed mass fragments (positive mode), which may correspond to these complexes, no conclusive information of the bulk composition could be obtained when employing elemental analysis (EA). This may be due to the instability of these complexes in the solid state. Crystals were grown from these mono- and binuclear complexes; however, they transformed to oils when isolated from the solvent, even when handled under

inert conditions in the glove box. Therefore, single crystal X-ray diffraction analysis was not possible.

7.4.2 *N*-oxide radical co-catalyst-free alcohol oxidation

N-oxide co-catalyst-free alcohol oxidation was mentioned in **Chapter 1** of this study as another example of an oxidative transformation reaction to afford oxygenated products. However, further investigation of these oxidation reactions was not part of the scope of this study, but it may form part of future investigations. An optimal catalyst system will involve low amounts of peroxide (ROOH) as the oxidant, mild reaction conditions with a preference for room temperature, low catalyst loadings as well as performing the reactions in the absence of costly or toxic additives. Previous studies have reported Cu-based catalyst systems in combination with H₂O₂ for successful alcohol oxidation usually at high temperatures; however, these systems were mostly limited to the oxidation of activated alcohols [18-27]. As such, there is still a growing demand to develop a Cu-based catalyst system, which may be employed in the oxidation of a variety of alcohol substrates in the absence of an *N*-oxide co-catalyst. The application of our mono- or bifunctional ligand frameworks, in combination with a Cu-precursor, may therefore be further expanded by evaluating the *in situ* formed Cu-based pre-catalysts in the development of an optimal catalyst system for aerobic alcohol oxidation.

7.4.3 Hydroxylation of aryl halides

Even though our Cu-based catalyst system could be employed for the hydroxylation of aryl iodides and bromides, the hydroxylation of chloride- and fluoride-derived substrates was unsuccessful. Therefore, further optimisation of our catalyst system could expand the substrate scope to aryl chloride and fluorides, eliminating the current limitations thereof. These reactions may also be further expanded by including the hydroxylation of aromatic substrates without a halogen substituent, such as benzene.

Two mechanistic pathways, differing only in the initial oxidation state of the copper precursor, were previously reported [28-30]. Spectroscopic and analytical techniques may be employed to investigate the nature of key Cu-based intermediates and to evaluate the mechanistic pathway for these reactions.

7.4.4 Peroxidation of cyclic and linear alkanes

Both mono- and bifunctional ligands, in combination with Cu-precursors, were evaluated in the peroxidation of cyclohexane. We hypothesised the ability of our α,α' -bis[(*N*-methyl-2-pyrazolyl)ethylamino]-*m*-xylene ligands to be bifunctional in accommodating two copper

centres, and thereby facilitating hydrocarbon peroxidation with improved product yields and alcohol selectivity. However, exceptional product yields with alcohol selectivity were possible for both our mono- and bifunctional ligand sets, and therefore the nuclearity of the *in situ* formed pre-catalysts does not appear to have a major influence on the efficiency of the reaction. The reason for this observation is still unclear and future studies may involve further investigations, such as the synthesis and isolation of the binuclear complexes described above, before evaluating them in the peroxidation reactions. Moreover, our ligand framework may also be further expanded through the development of multifunctional ligands that accommodate more than two copper centres. The effect of these multinuclear pre-catalysts may be evaluated in an attempt to further improve on product yields or alcohol selectivity.

Similar alcohol selectivity was obtained when employing Cu^I-precursors, with coordinating or non-coordinating anions, in combination with our α,α' -bis[*N*-(2-pyrazolyl)ethylamino]-*m*-xylene ligand (**L05**). We identified [Cu(MeCN)₄]PF₆ as the optimal precursor due to the highest obtained product yield; however, its alcohol selectivity is comparable to other Cu^I-precursors where lower product yields were obtained (see Table 5.2). As such, the re-evaluation of Cu^I-precursors during further optimisation of our catalyst system may be required for a possible improvement in alcohol selectivity while still obtaining maximum product yields.

Peroxidation reactions were quenched with an excess of triphenylphosphine (PPh₃) to assist in the conversion of the cyclohexyl hydroperoxide product to obtain cyclohexanol and cyclohexanone [31]. Unfortunately, full conversion was not possible for our catalyst system, and may therefore be further optimised to promote alcohol selectivity.

The efficiency and limitations of our Cu-based catalyst system can be further investigated by extending the substrate scope to possibly include the highly stable methane substrate. The conversion of methane to methanol usually involves high pressures and temperatures, and therefore has high energy requirements [32, 33]. Some of these methods also involve expensive separation steps and the addition of strong oxidants. A direct conversion method instead of the indirect methods could also be used because it circumvents extremely expensive intermediate steps and has an economic advantage over the indirect methods [33]. Therefore, further optimisation of our Cu-based catalyst system may be necessary to directly convert methane to methanol with the highest activity and the lowest temperature and pressure.

7.4.5 Cu-based LPMO mimics

The efficiency of our Cu-based catalyst system can be further investigated by evaluating the oxidative cleavage of alternative gluco- and galacto-polysaccharides with α - or β -glycosidic linkages. An extended substrate scope was previously reported with moderate to good rate constants [14, 34-36]. Moreover, product yields for *p*-nitrophenol formation were obtained in a shorter reaction time using UV/vis studies and a calibration curve; however, product isolation and characterisation is possible and can be considered in future studies to provide evidence of successful oxidative cleavage. Lastly, we have evaluated the selectivity of our Cu-based LPMO mimic for the oxidation of primary and secondary alcohols using H_2O_2 as the oxidant. Extremely low oxidation products were obtained; however, this can be improved through further optimisation of the catalyst system, by focusing on increasing the catalyst load, the reaction time or by altering the H_2O_2 or NEt_3 concentrations.

7.5 References

- [1] L. Marais, H.C.M. Vosloo, A.J. Swarts, *Mol. Catal.*, 486 (2020) 110839-110848.
- [2] C. Obuah, M.K. Ainooson, S. Boltina, I.A. Guzei, K. Nozaki, J. Darkwa, *Organometallics*, 32 (2013) 980-988.
- [3] C. Obuah, B. Omondi, K. Nozaki, J. Darkwa, *J. Mol. Catal. A: Chem.*, 382 (2014) 31-40.
- [4] J.M. Hoover, B.L. Ryland, S.S. Stahl, *J. Am. Chem. Soc.*, 135 (2013) 2357-2367.
- [5] A.J. Swarts, S.F. Mapolie, *Dalton Trans.*, 43 (2014) 9892-9900.
- [6] A.J. Swarts, F. Zheng, V.J. Smith, E. Nordlander, S.F. Mapolie, *Organometallics*, 33 (2014) 2247-2256.
- [7] L. Marais, J. Bures, J.H.L. Jordaan, S. Mapolie, A.J. Swarts, *Org. Biomol. Chem.*, 15 (2017) 6926-6933.
- [8] I. Garcia-Bosch, M.A. Siegler, *Angew. Chem. Int. Ed.*, 55 (2016) 12873-12876.
- [9] L. Marais, H.C.M. Vosloo, A.J. Swarts, Highly efficient alkane peroxidation mediated by a copper(II)/pyrazolylpyridineamine catalyst system, Chapter 4, Manuscript to be submitted (2021).
- [10] G.R. Hemsworth, E.M. Johnston, G.J. Davies, P.H. Walton, *Trends Biotechnol.*, 33 (2015) 747-761.
- [11] V.V. Vu, S.T. Ngo, *Coord. Chem. Rev.*, 368 (2018) 134-157.
- [12] W.T. Beeson, V.V. Vu, E.A. Span, C.M. Phillips, M.A. Marletta, *Annu. Rev. Biochem.*, 84 (2015) 923-946.
- [13] S. Garajova, Y. Mathieu, M.R. Beccia, C. Bennati-Granier, F. Biaso, M. Fanuel, D. Ropartz, B. Guigliarelli, E. Record, H. Rogniaux, *Sci. Rep.*, 6 (2016) 28276.
- [14] Z. Yu, Z. Thompson, S.L. Behnke, K.D. Fenk, D. Huang, H.S. Shafaat, J.A. Cowan, *Inorg. Chem.*, 59 (2020) 11218-11222.
- [15] S. Muthuramalingam, D. Maheshwaran, M. Velusamy, R. Mayilmurugan, *J. Catal.*, 372 (2019) 352-361.
- [16] L. Marais, H.C.M. Vosloo, A.J. Swarts, Synthetic LPMO mimics: a copper/pyrazolylpyridineamine catalyst system for the highly efficient oxidative cleavage of *p*-nitrophenyl- β -D-glucopyranoside, Chapter 6, Manuscript in preparation, (2021).
- [17] O. Songis, P. Boulens, C.G. Benson, C.S. Cazin, *RSC Adv.*, 2 (2012) 11675-11677.

- [18] S. Velusamy, T. Punniyamurthy, *Eur. J. Org. Chem.*, 2003 (2003) 3913-3915.
- [19] J.U. Ahmad, M.T. Räisänen, M. Leskelä, T. Repo, *Appl. Catal., A*, 411 (2012) 180-187.
- [20] A.G.F. Shoaib, *J. Coord. Chem.*, 65 (2012) 3511-3518.
- [21] K. Czerwińska, B. Machura, S. Kula, S. Krompiec, K. Erfurt, C. Roma-Rodrigues, A.R. Fernandes, L.S. Shul'pina, N.S. Ikonnikov, G.B. Shul'pin, *Dalton Trans.*, 46 (2017) 9591-9604.
- [22] H. Ünver, I. Kani, *Polyhedron*, 134 (2017) 257-262.
- [23] H. Ünver, I. Kani, *J. Chem. Sci.*, 130 (2018) 33-41.
- [24] H. Ünver, *Transition Met. Chem.*, 43 (2018) 641-646.
- [25] R. Bikas, F. Ajormal, M. Emami, N. Noshiranzadeh, A. Kozakiewicz, *Inorg. Chim. Acta*, 478 (2018) 77-87.
- [26] C. Wu, B. Liu, X. Geng, Z. Zhang, S. Liu, Q. Hu, *Polyhedron*, 158 (2019) 334-341.
- [27] S.G. Mncube, M.D. Bala, *Transition Met. Chem.*, 44 (2019) 145-151.
- [28] D. Wang, D. Kuang, F. Zhang, S. Tang, W. Jiang, *Eur. J. Org. Chem.*, 2014 (2014) 315-318.
- [29] G. Lefèvre, A. Tlili, M. Taillefer, C. Adamo, I. Ciofini, A. Jutand, *Dalton Trans.*, 42 (2013) 5348-5354.
- [30] G. Franc, Q. Cacciuttolo, G. Lefèvre, C. Adamo, I. Ciofini, A. Jutand, *ChemCatChem*, 3 (2011) 305-309.
- [31] G.B. Shul'pin, *J. Mol. Catal. A: Chem.*, 189 (2002) 39-66.
- [32] Y. Hori, Y. Shiota, T. Tsuji, M. Kodaera, K. Yoshizawa, *Inorg. Chem.*, (2017) 8-11.
- [33] M. Alvarez-Galvan, N. Mota, M. Ojeda, S. Rojas, R. Navarro, J. Fierro, *Catal. Today*, 171 (2011) 15-23.
- [34] S. Striegler, J.D. Barnett, N.A. Dunaway, *ACS Catal.*, 2 (2012) 50-55.
- [35] S. Striegler, N.A. Dunaway, M.G. Gichinga, J.D. Barnett, A.-G.D. Nelson, *Inorg. Chem.*, 49 (2010) 2639-2648.
- [36] S. Striegler, M. Dittel, R. Kanso, N.A. Alonso, E.C. Duin, *Inorg. Chem.*, 50 (2011) 8869-8878.