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Complexes salen supportés sur rGO : catalyseurs énanti sélectifs recyclables

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rGO-supported salen complexes as efficient and recyclable enantioselective catalysts

Complexes salen supportés sur rGO : Catalyseurs énantiosélectifs recyclables

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Thèse soutenue à Beyrouth, le 07 décembre 2021, par

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Titre : Complexes salen supportés sur rGO: Catalyseurs énantiosélectifs recyclables

Mots clés : Hétérogénéisation, catalyse asymétrique, oxyde de graphène réduit, recyclage, catalyseurs supportés, catalyse coopérative.

Résumé : Les matériaux à base de carbone sont largement utilisés comme supports très stables pour immobiliser plusieurs catalyseurs organométalliques et favoriser ainsi les transformations catalytiques hétérogènes. En outre, l'immobilisation par interactions non covalentes sur ces supports a également été utilisée pour améliorer la coopérativité entre les complexes en catalyse et pour le recyclage. D'autre part, et malgré tout l'intérêt que représentent de telles procédures, elles ont très peu été utilisées pour réaliser de la catalyse asymétrique. Dans ce contexte et vue la grande importance et l'énorme application des complexes chiraux dérivés de ligands salen « privilégiés », l'hétérogénéisation de ces précieux catalyseurs énantio-purs via des interactions non covalentes avec des matériaux à base de carbone représente un moyen efficace d'effectuer de la catalyse asymétrique supportée avec la possibilité de récupérer à la fois le catalyseur chiral et le support. L'objectif de ces travaux de thèse est donc de préparer de nouveaux complexes chiraux de salen supportés et de tester leur activité et leur aptitude au recyclage en catalyse hétérogène.

Une réaction click a été réalisée pour introduire des groupes pyrène et ainsi, de nouveaux ligands de salen marqués mono comme bis-pyrène, avec deux longueurs d'espaceurs différentes, bis-pyrène, avec deux longueurs d'espaceurs différentes, ont été préparés avec des rendements élevés.

Les complexes de chrome correspondants ont été synthétisés et testés dans la réaction asymétrique d'ouverture du cycle (ARO) de l'oxyde de cyclohexène avec l'azide de triméthylsilyle et la réaction d'hétéro-Diels-Alder (HDA) de divers aldéhydes avec le diène de Danishefsky. D'autre part, les analogues des complexes de manganèse ont été testés dans l'époxydation asymétrique des oléfines. Grâce aux interactions de type π - π entre les groupes pyrène et l'oxyde de graphène réduit (rGO) utilisé comme support, la première immobilisation des complexes chiraux de salen de chrome est réalisée, offrant un catalyseur supporté très robuste pour promouvoir la catalyse asymétrique dans des cycles répétés (jusqu'à 10 cycles). Le catalyseur au chrome supporté s'est en outre avéré parfaitement compatible pour la catalyse hétérogène de type multi-substrats. De même, l'époxydation asymétrique hétérogène a été rapportée. L'étude des procédures d'immobilisation et de désorption a également été rapportée. De plus, des premiers tests pour effectuer un processus de multicatalyse avec une réaction séquentielle d'époxydation-ouverture asymétrique ont été réalisés.

Title : rGO-supported salen complexes as efficient and recyclable enantioselective catalysts

Keywords : Heterogenization, asymmetric catalysis, reduced graphene oxide, recycling, supported catalysts, cooperative catalysis.

Abstract : Carbon materials are widely used as highly stable supports for immobilizing several organometallic catalysts and thus promoting heterogenized catalytic transformations. Furthermore, non-covalent anchoring onto such supports was also used to enhance cooperativity between complexes for catalysis and recycling. However, despite all the interest they represent, they have not been the subject of many studies in the field of enantioselective catalysis. In this context and regarding the great importance and the huge application of chiral complexes derived from "privileged" salen ligands, the heterogenization of such precious enantiopure catalysts via non-covalent interactions to carbon-based materials represents an efficient way to perform supported asymmetric catalysis with the opportunity to recover both the chiral catalyst and the support. The aim of this work is to prepare new supported chiral salen complexes and test their activity and recycling aptitude in heterogeneous catalysis.

A click reaction was performed to introduce pyrene groups and thus, novel mono as bis-pyrene tagged salen ligands, with two different spacer's lengths, have been prepared with high yields.

The corresponding chromium complexes were synthesized and engaged in the asymmetric ring opening reaction (ARO) of cyclohexene oxide with trimethylsilyl azide and the hetero-Diels-Alder (HDA) of various aldehydes with Danishefsky's diene. In the other hand, the analogous manganese complexes were tested in the asymmetric epoxidation of olefins. Thanks to π - π type interactions between the pyrene groups and reduced graphene oxide (rGO) chosen as support, the first immobilization of chiral chromium salen complexes is achieved, offering a very robust supported catalyst to promote efficient asymmetric catalysis in repeated cycles (up to 10 runs). The supported chromium catalyst was furthermore found very compatible for multi-substrate type heterogeneous catalysis. Similarly, supported asymmetric epoxidation of various alkenes was reported. The study of the immobilization and the desorption procedures was also reported. Moreover, attempts to perform multicatalysis process with a sequential epoxidation-ring opening reaction has been investigated.

Résumé étendu en français

La catalyse, qu'elle soit homogène ou hétérogène, est avant tout un processus moléculaire impliquant un catalyseur qui offre une voie beaucoup plus énergétiquement favorable à la réaction avec une énergie d'activation inférieure à celle de la réaction non catalysée. La catalyse est actuellement l'un des sujets importants en sciences appliquées, et elle a trouvé des applications répandues dans les processus chimiques et biochimiques industriels. De nos jours, la catalyse est la technologie la plus importante sur laquelle repose la protection de l'environnement.

L'accès aux composés optiquement actifs reste un défi très important pour les chimistes dans les domaines académiques et industriels. Leur importance vient du rôle important de la reconnaissance des énantiomères dans l'activité biologique, conduisant ainsi à un rôle vital dans la découverte et le développement de médicaments, de produits agrochimiques et de matériaux innovants. Parmi les différentes stratégies développées pour obtenir des composés énantiopurs, la catalyse asymétrique est devenue le meilleur choix pour la préparation de produits à fort excès énantiomère. L'utilisation de catalyseurs chiraux en petites quantités peut transmettre la chiralité aux substrats et permet de réduire les quantités de réactifs et d'énergie, et de séparer facilement les produits en augmentant la valeur de sélectivité.

Dans le contexte de la chimie verte qui est basée sur 12 principes représentant une ligne directrice pour aider les chimistes à atteindre l'objectif de durabilité en évitant la formation de produits dangereux, en minimisant l'utilisation de solvants toxiques et en les remplaçant par des solvants plus verts, et en développant la catalyse verte. Un grand défi prend place entre les chercheurs et donc les industries visant à réaliser des processus plus respectueux de l'environnement. Pour atteindre cet objectif, les chimistes se sont concentrés sur la conception de catalyseurs verts qui devraient avoir une activité plus élevée, une sélectivité plus élevée et une récupération efficace et une durabilité.

À cet égard, et dans la plupart des cas, les catalyseurs existants sont modifiés en fonction des connaissances mécanistes, de l'intuition chimique et des résultats d'expériences de dépistage dans le but de respecter ces règles vertes. Dans ce contexte, l'hétérogénéisation de catalyseurs chiraux homogènes précieux est apparue comme une solution intéressante pour les récupérer tout en conservant l'activité et la sélectivité, combinant, ainsi, des avantages de catalyse homogène et hétérogène.

Les dérivés chiraux de la famille salen ont démontré leur énorme application en tant que ligands pour la catalyse asymétrique car ils sont capables de promouvoir la formation de diverses liaisons carbone-carbone, carbone-hétéroatome ou hétéroatome-hétéroatome en raison de leur capacité à coordonner

une grande variété de sels métalliques. Ces ligands possédant une symétrie C₂, appartiennent à la famille des ligands essentiels, avec les bis(oxazolines) et les dérivés de la série BIMAP, car ils sont capables d'induire des niveaux d'énantiosélectivité bons à excellents dans diverses réactions. Certains synthons cibles hautement énantioenrichés ont même été préparés à l'échelle industrielle avec l'utilisation de complexes de salen

En outre, des complexes métal-salen ont été impliqués dans la multicatalyse, en particulier dans la catalyse coopérative, via la formation d'espèces multimétalliques, ainsi que des processus en tandem. En catalyse coopérative, les complexes salen peuvent agir comme un acide de Lewis et une base de Lewis pour activer à la fois l'électrophile et le nucléophile respectivement.

Un grand nombre de recherches ont été développées pour l'hétérogénéisation des complexes de salen afin d'optimiser leur coopérativité et d'améliorer leur recyclage.

Les matériaux à base de carbone sont largement utilisés comme supports très stables pour immobiliser plusieurs catalyseurs organométalliques et favoriser ainsi les transformations catalytiques hétérogènes. En outre, l'immobilisation par interactions non covalentes sur ces supports a également été utilisée pour améliorer la coopérativité entre les complexes en catalyse et pour le recyclage. D'autre part, et malgré tout l'intérêt que représentent de telles procédures, elles ont très peu été utilisées dans le domaine de la catalyse asymétrique.

En se basant sur tous les concepts mentionnés ci-dessus, et de travaux antérieurs réalisés au Laboratoire de Catalyse Moléculaire, l'objectif de cette thèse est de développer une nouvelle génération de complexes de salen marqués à des groupes pyrène pour étudier leur activité en catalyse homogène coopérative ainsi que des transformations catalytiques en tandem. De plus, grâce aux interactions non covalentes de type π - π entre les groupements pyrène polyaromatiques et l'oxyde de graphène réduit (rGO), un nouveau complexe de salen marqué pyrène est prêt à favoriser des réactions catalytiques asymétriques hétérogènes et à être récupéré après plusieurs cycles. Ainsi, les complexes salen correspondants du chrome et du manganèse sont synthétisés, testés et comparés au complexe de Jacobsen qui est considéré comme une référence de catalyseur.

Sur la base de la capacité des groupes pyrène à se lier aux surfaces graphitiques, des ligands de salen marqués mono comme bis-pyrène ont été synthétisés. Le lien entre le groupe pyrène et la fraction salen a été construit à la position para du phénol par une réaction dite Click de cycloaddition 1,3-dipolaire (CuAAC) qui s'est produite entre les alcynes marqués au pyrène et l'azidosalicylaldéhyde. Par conséquent, à partir de deux dérivés du pyrène avec des chaînes alkyles différentes, quatre salen marqués au pyrène ont été préparés, y compris des ligands symétriques portant deux groupes pyrène et des ligands dissymétriques avec un seul groupe pyrène, tous avec de très bons rendements. Les

complexes de chrome et de manganèse correspondants ont été synthétisés en rendements quantitatifs et leurs propriétés catalytiques ont été évaluées dans la réaction asymétrique d'ouverture du cycle (ARO) de l'oxyde de cyclohexène avec l'azide de triméthylsilyle et la réaction d'hétéro-Diels-Alder (HDA) de divers aldéhydes avec le diène de Danishefsky et l'époxydation asymétrique des oléfines.

Les complexes de salen de chrome marqués au pyrène ont catalysé efficacement les réactions ARO et HDA. Cependant, les complexes symétriques se sont révélés moins énantiosélectifs que les analogues dissymétriques, probablement en raison de l'absence des groupes tert-butyle volumineux en position para du phénol, qui sont cruciaux pour une énantiosélectivité élevée. De plus, la forte activité associée à la meilleure énantiosélectivité a été attribuée au complexe Cr-salen dissymétrique marqué au pyrène Unsym-C1-Cr, dérivé du méthanol pyrène. Nous avons suggéré que cela était dû à sa structure plus rigide.

L'immobilisation de tous les complexes marqués au pyrène sur le rGO a été réalisée avec succès grâce à l'imprégnation de la suspension rGO avec une solution des catalyseurs dans le DCM avec un rapport massique de 4:1.

À notre connaissance, il s'agit de la première immobilisation médiée par les interactions π - π de complexes de salen à la surface des matériaux carbonés. Le complexe supporté Unsym-C1-Cr @rGO a montré une efficacité, une stabilité et une robustesse élevées en catalysant l'ARO hétérogène de l'oxyde de cyclohexène avec TMSN₃, avec des valeurs d'activité et d'énantiosélectivité similaires à celles obtenues dans des conditions homogènes. Il a été recyclé et réutilisé pour 10 cycles successifs, sans montrer de perte notable d'activité ou de sélectivité. La même efficacité a été observée pour la réaction HDA avec le cyclohexane carboxaldéhyde et également dans un processus multisubstrat dans lequel différents aldéhydes ont été testés.

De plus, le catalyseur analogue au manganèse favorisait l'époxydation asymétrique (AE) de diverses oléfines en présence de PhIO ou de mCPBA/NMO comme oxydants. Les résultats en termes d'activité et d'énantiosélectivité dépendaient fortement de la structure des substrats et de la nature de l'oxydant utilisé. L'AE hétérogène de l'indène, du styrène et du CN-chromène a été réalisée, ce qui a conduit à des résultats prometteurs qui doivent être améliorés pour explorer davantage la procédure de recyclage dans des conditions optimales.

Enfin, un processus de réaction séquentielle à un pot consistant en une époxydation suivie d'une réaction d'ouverture de cycle a été tenté en présence d'un complexe de manganèse marqué au pyrène pour la première étape et suivi de l'ajout d'un complexe du chrome marqué au pyrène dans des conditions homogènes. Dans le cas du CN-chromène, la réaction séquentielle n'a pas été aussi difficile puisque l'étape d'époxydation était hautement énantiosélective offrant l'époxyde avec 96%

d'ee, qui réagira certainement dans l'étape suivante menant au produit désiré avec une valeur élevée d'ee.

D'autre part, une réaction plus difficile était attendue à partir de l'indene. Dans ce cas, nous avons prévu d'effectuer un dédoublement cinétique pour le mélange d'époxyde résultant de la première étape avec un ee modeste (60%). Cela aurait dû conduire, dans le cas d'une sélectivité élevée pour la réaction d'ouverture de l'époxyde, à une augmentation du rendement des produits à la fin du processus. Malheureusement, la résolution n'a pas réussi car la dernière étape était lente et non énantiosélective.

L'étude du processus de réaction séquentielle devrait être poursuivie. D'autres expériences étudiant l'énantiosélectivité de la réaction d'ouverture de l'anneau doivent être effectuées dans la dernière étape pour comprendre les résultats obtenus et atteindre l'objectif de ce travail. Ainsi, il est possible d'utiliser l'autre énantiomère du complexe dans la dernière étape et de comparer ensuite les résultats obtenus, ou de le remplacer par un autre complexe salen avec une structure différente et de comparer l'énantioselectivité. En outre, il est important de prouver le rôle de l'acide m-chlorobenzoïque résiduel dans cette réaction. Enfin, tous ces résultats et ces suggestions préliminaires sont prometteurs pour développer un système catalytique multimétallique original avec des complexes Mn et Cr salen marqués au pyrène co-immobilisés sur rGO, comme une plateforme efficace pour promouvoir la catalyse séquentielle et tandem à un pot. De plus, les complexes de salen marqués au pyrène avec d'autres centres métalliques (Al, Co,..) pourraient être préparés à promouvoir d'autres transformations catalytiques homogènes et supportées pour effectuer différents processus séquentiels multimétalliques.

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Abbreviations

%wt: percentage in weight

ACN: Acetonitrile

AcOEt: Ethyl Acetate

AE: Asymmetric Epoxidation

AFM: Atomic force microscopy

AKR: Aminolysis Kinetic Resolution

ARO: Asymmetric Ring Opening

BET: Brunauer-Emmett-Teller

BINOL: 1,1'-Bi-2-naphthol

BPPM: (2*S*,4*S*)-4-(Diphénylphosphino)-2-[(diphénylphosphino)méthyl]-1-pyrrolidinecarboxylate de 2-méthyl-2-propanyle

CC: Column Chromatography

CNT: Carbon Nanotubes

COF: Covalent Organic Frameworks

Conv: conversion

CuAAC: Copper catalyzed Azide Alkyne Cycloaddition

DCM: Dichloromethane

DIOP: 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis (diphénylphosphino) butane

DIPEA: *N,N*-Diisopropylethylamine

DMF: Dimethylformamide

EDTA: Ethylenediaminetetraacetic acid

ee: enantiomeric excess

equiv, eq: Equivalent

Et₂O: Diethyl ether

EtOH: Ethanol

FT-IR, IR: Fourier Transform InfraRed

GC: Gas Chromatography

h: hour

H₂O₂: Hydrogen Peroxide

HDA: Hetero-Diels-Alder

HKR: Hydrolytic Kinetic Resolution

HPLC: High-performance liquid chromatography

HRTEM: High-Resolution Transmission Electron Microscopy

ICP-MS: Inductively Coupled Plasma Mass Spectrometry

ITQ-2: Zeolite

IUPAC: International Union of Pure and Applied Chemistry

K : Kelvin

M: Molar

MALDI-TOF: Matrix-Assisted Laser Desorption/Ionization-Time Of Flight

MCM-41: Mobil Composition of Matter n°41

MCM-48: Mobil Composition of Matter n°48

m-CPBA: *meta*-Chloroperoxybenzoic acid

MeTHF: Methyl Tetrahydrofuran

min: minutes

MOF: Metal Organic Frameworks

MS: Mass Spectrometry

MTBE: methyl-*tert*butyl ether

MWCNT: Multi-Walled Carbon Nanotubes

NaOCl: Sodium hypochlorite

NHC: *N*-Heterocyclic Carbene

NMO: *N*-Methylmorpholine *N*-oxide

NMR: Nuclear Magnetic Resonance

PAMAM: Poly(amidoamine)

PhIO: Iodosobenzene

PyNO: Pyridine *N*-oxide

rGO: Reduced Graphene Oxide

rt: room temperature

SBA-15: Ordered Mesoporous Silica

SWCNT: Single-Walled Carbon Nanotubes

*t*Bu: *tert*butyl

TFA: Trifluoroacetic Acid

TGA: Thermal Gravimetric Analysis

THF: Tetrahydrofuran

UV-Vis: Ultraviolet-Visible

XPS: X-ray photoelectron spectroscopy

XRD: X-Ray Diffraction

Introduction

“It is, then, proved that several simple or compound bodies, soluble and insoluble, have the property of exercising on other bodies an action very different from chemical affinity. By means of this action they produce, in these bodies, decompositions of their elements and different recombination of these same elements to which they remain indifferent.”

Using these rational findings, Berzelius had given the first recognition of the word “catalysis” in 1835 as the decomposition of bodies by the catalytic force.¹ In 1895, Ostwald proposed the concept of catalysis as a universal dynamic phenomenon and defined the catalyst as a material accelerating a chemical reaction without affecting the position of the equilibrium.²

Catalysis whether homogeneous or heterogeneous, is above all, a molecular process implying a catalyst which offers a much more energetically favorable path for the reaction with lower activation energy than the uncatalyzed reaction. Catalysis is currently one of the important topics in applied science, and it has found widespread applications in industrial chemical and biochemical processes. Nowadays, catalysis is the most important technology on which is based the environmental protection.³

The access to optically active compounds remains a very important challenge to chemists in academic and industrial fields. Their importance stems from the central role of enantiomer recognition in biological activity, leading thus to a vital enabling role in the discovery and the development of innovative medicines, agrochemicals, and materials.⁴ Among the different strategies developed to obtain enantiopure compounds, asymmetric catalysis has become the best choice for the preparation of products with high enantiomeric excess. The use of chiral catalysts in small amounts can transmit chirality to substrates and allows to reduce the quantities of reactants and energy, and to easily separate the products by increasing the selectivity value.

At the beginning of the 90s, the term “green chemistry” was formulated to introduce the concept of non-polluting manufacturing process. It has been based on 12 principles representing a guideline to help chemists reach the goal of sustainability⁵ by avoiding the formation of hazardous products, minimizing the use of toxic solvents and replacing them with safer ones, designing green chemicals,

¹ J. Hagen, *Industrial Catalysis: A Practical Approach*, John Wiley & Sons, **2015**.

² P. W. N. M. van Leeuwen, *Homogeneous Catalysis: Understanding the Art*. Springer, **2004**.

³ K. Kakaei, M. D. Esrafil, and A. Ehsani, ‘Introduction to Catalysis’, in *Interface Science and Technology*, Elsevier, **2019**, 27, 1–21.

⁴ T. Kégl and L. Kollár, ‘Chiral Phosphorous Ligands in Asymmetric Catalysis’, in *Comprehensive Inorganic Chemistry II*, Elsevier, **2013**, 271–308.

⁵ S.L. Tang, R.L. Smith, M. Poliakoff, *Green Chem.* **2005**, 7 761-762.

and developing green catalysis. This latter gained a great importance and contributed to a big challenge between researchers and thus industries aiming to perform more environmentally friendly processes. To achieve this goal, chemists focused on the design of green catalysts that should have higher activity, higher selectivity, and should show efficient recovery, and durability.

In this regard, and in most cases, existing catalysts are modified based on mechanistic knowledge, chemical intuition, and the results of screening experiments with the aim of respecting these green rules. In this context, the heterogenization of precious homogeneous chiral catalysts emerged as an attractive solution to recover catalysts while retaining the activity and the selectivity⁶, combining, thus, homogeneous and heterogeneous catalysis advantages.

Schiff base ligands are considered as privileged ligands because they are easily prepared by a condensation between aldehydes and amines.⁷ The condensation of salicylaldehyde derivatives with 1,2 diamines leads to the formation of one extremely important class of ligands, generally known as “Salens”⁸ (Figure 1).

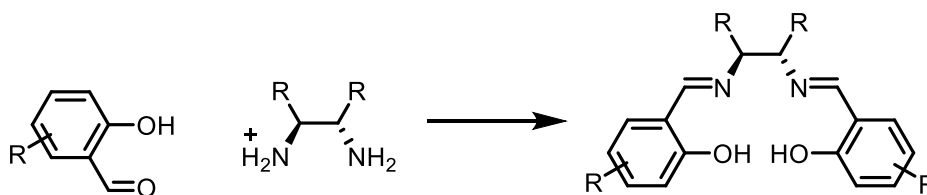


Figure 1: structure of salen ligands.

Chiral salen derivatives have demonstrated their huge application as ligands for asymmetric catalysis since they were able to promote formation of various carbon-carbon, carbon-heteroatom or heteroatom-heteroatom bonds due to their ability to coordinate a large variety of metal salts.⁸ These ligands possessing a C_2 symmetry belong to the family of essential ligands, together with bis(oxazolines) and derivatives from the BIMAP series, since they are able to induce good to excellent enantioselectivity levels in various reactions. Some highly enantioenriched target synthons have even been prepared at the industrial scale with use of salen complexes.^{9,10}

⁶ P. McMorn and G. J. Hutchings, *Chem. Soc. Rev.* **2004**, 33, 108–122

⁷ H. Schiff, *Ann. Suppl.*, **1864**, 3, 343.

⁸ P. G. Cozzi, *Chem. Soc. Rev.*, **2004**, 33, 410–421.

⁹ J. F. Larrow, P. F. Quigley, Industrial Applications of the Jacobsen Hydrolytic Kinetic Resolution Technology. In *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H., Eds.; Elsevier: Amsterdam, **2012**, 129–146.

¹⁰ H.-U. Blaser, H.-J. Federsel, *In Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*; 2nd Ed., WILEY-VCH, Weinheim, **2010**.

Furthermore, metal-salen complexes have been implied in multicatalysis, specifically in cooperative catalysis, via formation of multi-metallic species, as well as tandem processes.¹¹ In cooperative catalysis, salen complexes may act as a Lewis acid and a Lewis base to activate both the electrophile and the nucleophile respectively.¹²

A great number of research was developed for the heterogenization of salen complexes to optimize their cooperativity and enhance their recycling. As an illustration, salen complexes were grafted on organic as inorganic supports, condensed in linear polymers as macrocyclic scaffolds, combined via non-covalent interactions, and introduced in metal organic frameworks (MOF) as covalent organic frameworks (COF).

Carbon materials have recently emerged as highly stable supports for immobilizing several organometallic catalysts and thus promoting catalytic transformations under heterogeneous conditions.¹³ Non-covalent anchoring onto carbon supports was also used to enhance cooperativity between complexes for catalysis and recycling.¹⁴

Based on all the concepts mentioned above, and previous works done in the Laboratory of Molecular Catalysis, the aim of this thesis is to develop a new generation of salen complexes tagged to pyrene groups to study their activity behaviour in homogeneous cooperative as tandem catalytic transformations. In addition, thanks to non-covalent π - π type interactions between the polyaromatic pyrene moieties and reduced graphene oxide (rGO), a new supported pyrene-tagged salen complex is ready to promote heterogeneous asymmetric catalytic reactions and to be recovered after several runs. Thus, chromium and manganese pyrene-tagged salen complexes are synthesized, tested, and compared to Jacobsen complex which is considered as catalyst reference.

This manuscript, divided into four chapters, describes our approach towards the elaboration of modified salen complexes which are tested as homogeneous catalysts to promote various important cooperative catalytic transformations and our attempts to perform tandem catalytic process, the immobilization procedure of these catalysts onto the rGO surface and their recycling and reuses conditions.

¹¹ a) M. Abd El Sater, N. Jaber, E. Schulz, *ChemCatChem*. **2019**, *11*, 3662–3687. b) A. Zulauf, M. Mellah, X. Hong, E. Schulz, *Dalton Trans.* **2010**, *39*, 6911–6935.

¹² M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936–938

¹³ M. R. Axet, O. Dechy-Cabaret, J. Durand, M. Gouygou, P. Serp, *Coord. Chem. Rev.* **2016**, *308*, 236–345.

¹⁴ a) H. Nasrallah, S. Germain, P. Queval, C. Bouvier, M. Mauduit, C. Crévisy, E. Schulz, *J. Mol. Cat. A: Chemical*, **2016**, *425*, 136–146. b) D. Didier, E. Schulz, *Tetrahedron: Asymmetry*. **2013**, *24*, 769–775.

First, chapter 1 highlights the different methods described in the literature to immobilize organometallic complexes and more specifically the reports on the heterogenization of metal-salen complexes and the use of rGO and other carbon materials as supports in catalysis.

Next, the synthesis of chromium and manganese pyrene-tagged salen complexes and their immobilization onto rGO will be detailed in chapter 2.

Then, chapter 3 focuses on the study of the activity of the chromium salen complexes in the cyclohexene oxide ring-opening with trimethylsilyl azide, and the hetero-Diels-Alder cycloaddition between various aldehydes and Danishefsky's diene under homogeneous and heterogeneous conditions.

Finally, enantioselective epoxidation of various alkenes catalysed by manganese salen complexes is detailed in chapter 4. Besides, tests on tandem epoxidation-ring opening reaction of alkenes are described.

Chapter 1: Heterogenization of Organometallic Complexes: State of the art



I. Chapter 1: Heterogenization of Organometallic Complexes: State of the art

This chapter is divided in three main parts. First, the general methods used for the heterogenization of organometallic complexes are described. The second section outlines the literature on the heterogenization of salen complexes and the current developments of polymetallic salen complexes used in asymmetric heterogeneous catalysis. Finally, a general view on carbon materials, and their use as supports to immobilize catalysts with recent examples will be detailed in the last section of this chapter

A. Immobilization of chiral organometallic catalysts

Organometallic compounds used as homogeneous catalysts for a large variety of catalytic transformations, have demonstrated a very high activity, selectivity, and ability to act in mild reaction conditions. On the other hand, their application at the industrial scale remains limited due to the difficulty of their separation and elimination from the products and their impossible recovery and reuse.

In order to optimize the use of the costly chiral homogeneous catalysts and ensure their recoverability, efforts have been realized to immobilize these species onto solids as a solution to combine the merits of homogeneous and heterogeneous catalysis.⁶ Consequently, the system is regarded as heterogenized homogeneous catalyst also known in the literature as “hybrid catalyst”; this term has been quite frequently referenced to define a supported catalyst with its catalytically active molecules combined in a matrix, being thus heterogeneous with respect to the reaction medium.¹⁵ Accordingly, the heterogenized catalyst should be chemically a homogeneous, and physically a heterogeneous catalyst.

Several materials were used as supports to immobilize organometallic compounds and especially chiral catalysts. However, the most common ones are inorganic materials such as silica, mesoporous silicious materials and zeolites. Depending on the support's type and the link that connects it to the chiral catalyst, many consequences can arise affecting its activity and its conformation. This can then

¹⁵ a) Y. I. Yermakovt, Y. A. Ryndin, O. S. Alekseev, D. I. Kochubey, V. A. Shmachkov, N. I. Gergert, *J. Mol. Catal.* **1989**, *49*, 121–132. b) A. Choplin, F. Quignard, *Coord. Chem. Rev.* **1998**, *178-180*, 1679–1702. c) B. Pugin, *J. Mol. Catal.* **1996**, *107*, 273–279.

lead to a different selectivity and sometimes to an improvement of the chemo- or the enantioselectivity.¹⁶

The immobilization of a chiral catalyst is a subject with serious consequences from an economic point of view. Depending on the mode of tethering between the catalyst and the support, different methods of immobilization can be distinguished: the covalent tethering and the non-covalent immobilization.

1. Covalent tethering

The most widely used method for immobilizing chiral catalysts is the formation of covalent bonds between the support and the chiral ligand. This method requires the functionalization of the support or of the ligand and sometimes both of them. In all cases, a bifunctional ligand has to be employed, for tethering to the metal centre and to the support. Therefore, two approaches can be described. In the first one, the chiral ligand bearing a functional group is anchored to the support surface, usually containing the proper other complementary functional group, forming a new supported ligand L' which then will be coordinated to the metal centre as active site. The second approach consists of the tethering of the bifunctional ligand to the metal centre of the homogeneous catalyst first and then, this new complex is immobilized on the support surface via a specific reaction between the complementary functional groups. The ligand backbone is usually an alkyl group playing the role of a spacer which exerts an effect on the mobility of the complex and its bulk, thus leading, depending on its length, to different activity and selectivity.^{15b}

Covalent tethering represents a convenient method to obtain a stable supported catalyst due to the strong covalent bonds formed. Silicious materials are largely used in this method thanks to the hydroxyl groups found on their surface; the binding of the ligand with these groups is easy to achieve via a siloxane-forming reaction with several functional groups. The same strategy can be employed with other supports such as carbon materials, which are in this case modified by an oxidation reaction to form anchoring groups.

To sum up, immobilization using covalent bonds is very convenient to maintain a stable linkage between the chiral ligand and the support. On the other hand, the required functionalization of the ligand and/or the support increases the cost of the final chiral catalysts and thus limits their application in industrial fields. Furthermore, any changes in the conformation of the original homogeneous

¹⁶ M. C. Román-Martínez and C. Salinas-Martínez de Lecea, 'Chapter 3 - Heterogenization of Homogeneous Catalysts on Carbon Materials', in *New and Future Developments in Catalysis*, Elsevier, 2013, 55–78.

catalyst can lead to an unpredictable effect on the enantioselectivity. Finally, using this method, only the supported catalyst may be recovered; the recovery of both the homogeneous catalyst and the support separately is not possible.

2. Noncovalent immobilization

This part describes the immobilization procedures implying noncovalent interactions to build the link between the ligand and the chosen support. Different strategies are included starting from the electrostatic interaction, the adsorption, the trapping of the catalyst into cavities and the use of supported liquid phase catalysts (SLPC).

This method ensures the immobilization of the homogeneous catalysts and mostly without any need to perform prior structural modifications, offering an efficient way to recover the chiral catalyst from the reaction medium. In addition, thanks to these noncovalent reversible interactions, the recovery of both the support and the catalyst is possible. Another important advantage is that most of these methods are simple and there are some possibilities to control the stereochemical outcome of the catalytic process due to the relative position of the catalyst with respect to the support.¹⁷

a) *Electrostatic interaction*

According to its name, this type of interaction occurs between ionic species. Generally, cationic complexes require a counteranion and in this case, the support surface may act as the negatively charged counteranion for the complex and an ion-exchange phenomenon is supposed to take place.

Fraile *et al.*¹⁷ have indicated two routes to carry out this type of immobilization which was probably the first noncovalent immobilization method described in the literature: the direct cationic exchange of the complex performed in solution and the formation of the complex on a pre-exchanged metal center. In the first case, a well characterized complex is formed in solution and then exchanged on the support. The addition of an excess of ligand to the pre-exchanged metal in the other case forces the formation of the complex (Figure 2)

¹⁷ J. M. Fraile, J. I García, J. A. Mayoral, *Chem. Rev.* **2009**, *109*, 360–417.

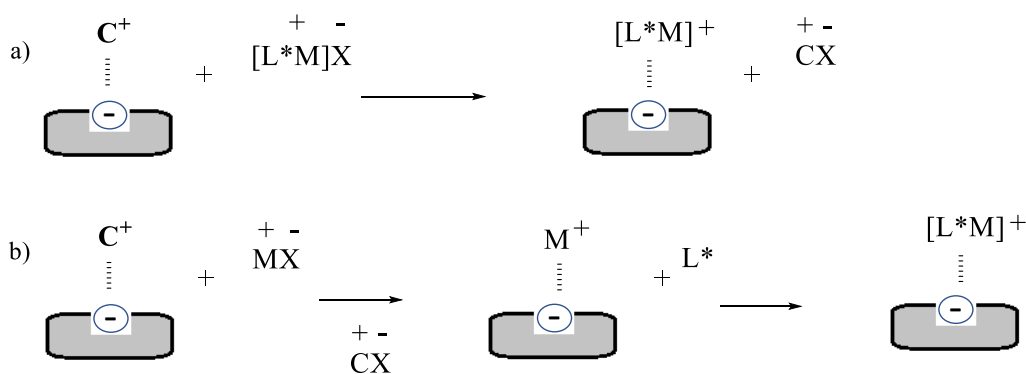


Figure 2: Electrostatic interaction a) Cationic exchange b) Complex formation.

This method is effective, provided that the catalytic species remain charged throughout the catalytic cycle, but factors such as the exchange solvent and the size of the ligand are very important affecting the ion mobility and thus the exchange ratios. Among the supports used in this method, we can mention mineral clays,¹⁸ cation exchange resins,¹⁹ zeolites and mesoporous crystalline materials like MCM-41.²⁰

b) Adsorption

Immobilizing a catalyst by adsorption is based on the Van Der Waals interactions known in some cases as hydrophobic interactions, also using hydrogen interactions. This kind of immobilization was explored for the first time in 1983 by Inoue *et al.*²¹ who performed the adsorption of [(DIOP)Rh(cod)Cl] and [(BPPM)-Rh(cod)Cl] neutral complexes on charcoal. Because of the weakness of the Van Der Waals interactions, partial leaching of the catalyst can occur and usually adsorption is replaced by electrostatic or polar interactions.

c) Encapsulation

Entrapment, intercalation, structural immobilization, and encapsulation are different terms to describe the trapping of homogeneous catalysts into the pores, the cavities, or the voids of the support structure as a method to heterogenize it without the need for additional support-complex interactions. This

¹⁸ T. Sento, S. Shimazu, N. Ichikuni, T. Uematsu, *J. Mol. Catal. A: Chem.* **1999**, *137*, 263–267.

¹⁹ P. Barbaro, C. Bianchini, G. Giambastiani, W. Oberhauser, L. M. Bonzi, F. Rossi, V. D. Santo, *Dalton Trans.* **2004**, *12*, 1783–1784.

²⁰ G.-J. Kim, S.-H Kim, *Catal. Lett.* **1999**, *57*, 139–143.

²¹ M. Inoue, K. Ohta, N. Ishizuka, S. Enamoto, *Chem. Pharm. Bull.* **1983**, *31*, 3371.

trapping can be performed by the introduction of the complex inside the pore of the support²² or by using it as a reactant in the synthesis of the support.²³ This kind of immobilization makes it possible to avoid the dimerization or aggregation of catalytic species. The size of the support pore is very important and has to be optimized to ensure the entrance of the catalyst inside. In case of too narrow pores, a “ship in a bottle” strategy performed by reacting the complex during the support synthesis can be envisaged.

d) *Supported Liquid Phase Catalysts SLPC*

This strategy is very related to the catalysis in biphasic media. Liquid phase catalysts are dispersed as a thin film onto the surface of the support giving thus a large interphase and a recoverable system. This approach was originally used for reactions in the gas phase.

When the supported film is water, a supported aqueous phase catalysts SAPC is obtained.²⁴ Thanks to hydrogen bonds between water and the surface groups, the hydrophilic catalyst is thus supported, and remains immiscible with the organic phase containing the reactants and products. Recently, supported ionic liquid phase catalysts (SILPC) gained a significant attention because it represents an alternative to homogeneous catalysis.²⁵

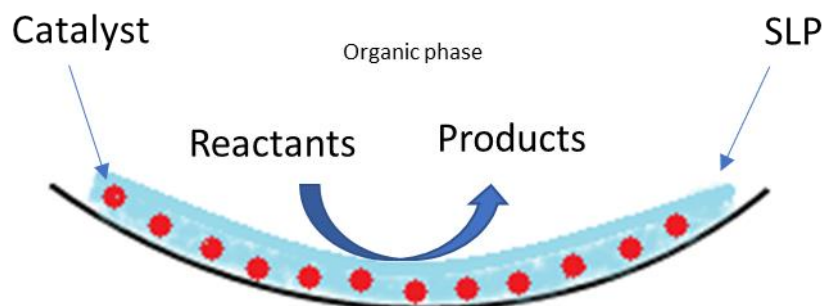


Figure 3: Supported Liquid Catalyst (SLP).

²² H. Yang, L. Zhang, W. Su, Q. Yang, C. Li, *Chem. Comm.*, **2007**, 10, 1086–1088.

²³ H. Yang, L. Zhang, W. Su, Q. Yang, C. Li, *J. Catal.* **2007**, 248, 204–212.

²⁴ J. P. Arhancet, M. E. Davis, J. S. Merola, B. E. Hanson, *Nature*, **1989**, 339, 454.

²⁵ C. P. Mehnert, R. A. Cook, N. C. Dispenziere, M. Afeworki, *J. Am. Chem. Soc.* **2002**, 124, 12932–1293.

B. Heterogenization of metal salen complexes

Chiral salen complexes are well known as versatile catalysts in the field of asymmetric catalysis. Salen ligands which are easily obtained from a condensation reaction between salicylaldehyde derivatives and an enantiopure diamine, have catalyzed various asymmetric transformations, all depending on the nature of the complexed metal.⁸

Based on their huge importance and their application in asymmetric catalysis, and the great importance of the recovery of these enantioselective catalysts, several reports have studied their heterogenization. Almost all the procedures described above were used, including their immobilization by covalent bonds and noncovalent interactions onto inorganic and organic supports, their polymerization, their assembly in macrocyclic structures, and their introduction into MOFs and COFs frameworks.¹⁰

Accordingly, examples from the literature will be detailed following the same classification.

1. Covalent tethering

a) *Inorganic supports*

Salen complexes were largely immobilized via covalent bonds on inorganic supports such as silica-based materials and specifically mesoporous siliceous supports such as MCM-41, MCM-48 and SBA-15.²⁶

In this context, Bhaumik, Islam *et al.*²⁷ described the immobilisation of an iron (III) salen complex on the surface of SBA-15 which was modified by using 3-aminopropyl triethoxysilane (3-APTES). The obtained salen Fe@SBSAL was tested to promote the asymmetric ring opening (ARO) of terminal and *meso*-epoxides with aniline and substituted anilines under solvent-free conditions, to obtain the corresponding β -aminoalcohols in high yields (up to 98%) and excellent enantiomeric excesses (up to 99%) (Figure 4).

²⁶ R. Ji, K. Yu, L. L. Lou, S. Liu, *J. Mol. Catal. A* **2013**, 378, 7–16.

²⁷ S. Roy, P. Bhanja, S. S. Islam, A Bhaumik, S. M. Islam, *Chem. Commun.* **2016**, 52, 1871–1874.

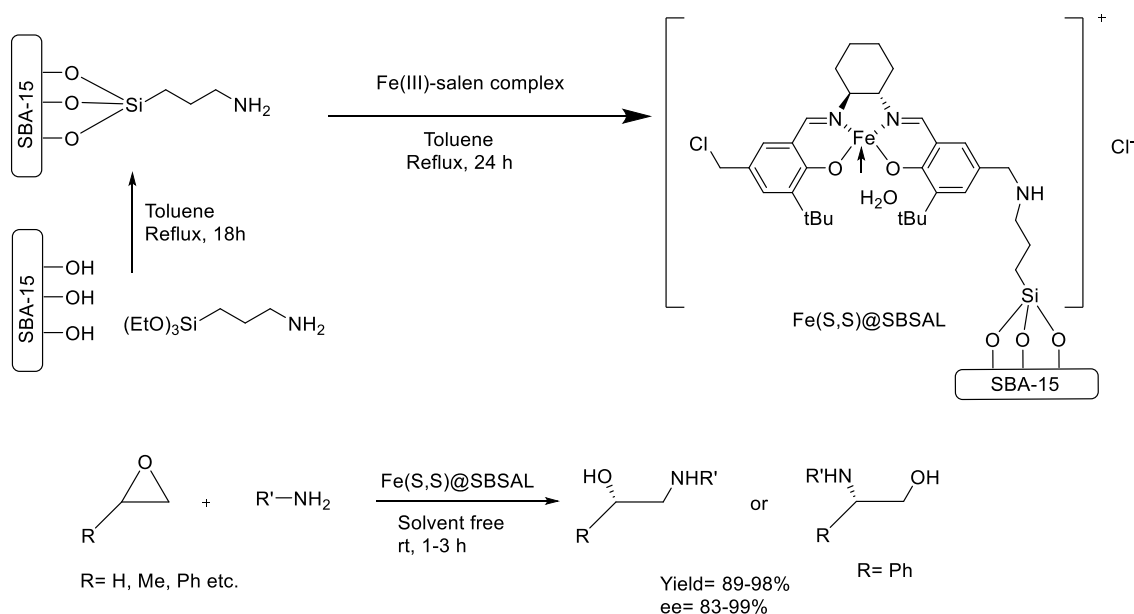


Figure 4: Regio- and enantioselective ARO of terminal and meso-epoxides catalyzed by $\text{Fe(III)salen@SBSAL}$.

Other supports such as glass beads were used to heterogenize Mn-salen complexes,²⁸ and the supported catalyst was reused up to 4 times in the asymmetric epoxidation of alkenes, leading to the desired epoxides with excellent yields and good enantioselectivity (**a**, Figure 5). Furthermore, Mn-salen complexes were also immobilized onto membranes.²⁹ Epoxidation of styrene was carried out for 4 runs using a functionalized Mn-salen complex supported onto a 3-aminopropyltriethoxysilane modified ceramic membrane (**b**, Figure 5).

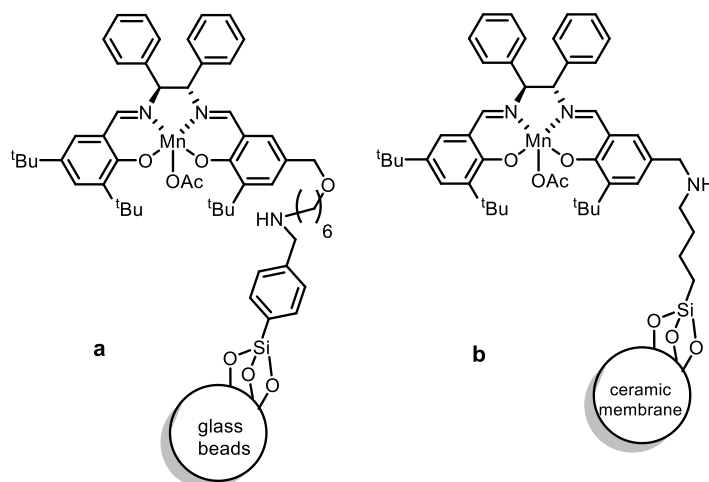


Figure 5: Immobilization of modified Mn-salen complexes onto different supports via covalent bonds.

²⁸ G. Trusso Sfrassetto, S. Millesi, A. Pappalardo, R. M. Toscano, F. P. Ballistreri, G. A. Tomaselli, A. Gulino, *Cat. Sci. Technol.* **2015**, *5*, 673–679.

²⁹ M. Liu, Z.-P. Zhao, K.-C. Chen, W.-F. Liu, *Catal. Commun.* **2015**, *64*, 70–74.

In another example, a chiral Mn(III) salen complex has been covalently supported on modified ZPS-PVPA (zirconium poly(styrene-phenylvinylphosphonate)) and ZPS-IPPA (zirconium poly(styrene-isopropenyl phosphonate)).³⁰ The resulting supported catalysts showed high activity and enhanced enantioselectivity with respect to the homogeneous analogue in the asymmetric epoxidation of α -methylstyrene, styrene and indene in the presence of 4-phenylpyridine *N*-oxide (PPNO) as axial base using NaClO as an oxidant (up to 99% conversion, up to 99% ee). It was found that the ZCMPS-PVPA-based supported catalyst, with larger pore diameter and surface area, was more active than the ZPS-IPPA-based catalyst. The increase in enantioselectivity was suggested to be due to the microenvironment effects induced by the supports. Besides, the heterogeneous catalysts have been recycled by centrifugation and reused for eight runs without no important decrease in yield or enantioselectivity.

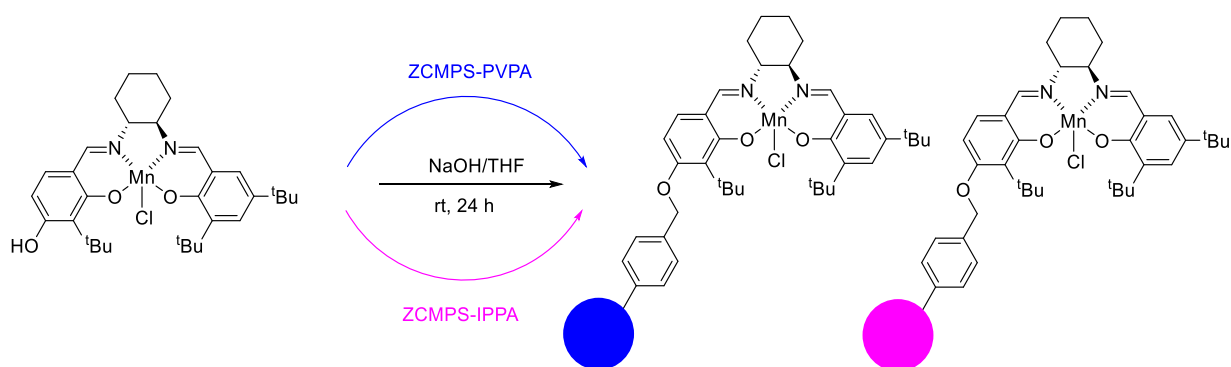


Figure 6: Mn-salen complexes covalently supported on ZPS-PVPA and ZPS-IPPA.

We mentioned some examples illustrating the immobilization of salen complexes on inorganic supports in particular silica-based ones which are very widely known and used for their stability, their high resistance and their availability. However, this kind of immobilization on inorganic supports are currently less frequent and innovations are now devoted towards the use of other supports with developed shapes and characteristics allowing to perform more stable and efficient immobilization.

b) Organic supports

(1) Pre-existing organic supports

Besides, salen complexes have indeed not only been immobilized onto inorganic materials but also on organic supports such as organic polymers and specifically of polystyrene-type,^{11,31} due to their modular properties. Recently, Merrifield and JandaJel resins were used to covalently immobilize V- and Al-salen complexes.³² The activity of these catalysts, that were fully characterized by analytical

³⁰ X. Zou, C. Wang, Y. Wang, K. Shi, Z. Wang, D. Li, X. Fu, *Polymers* **2017**, *9*, 108.

³¹ C. Baleizão, H. Garcia, *Chem. Rev.* **2006**, *106*, 3987–4043.

³² M. A. Esteves, B. Gigante, C. Santos, A. M. Guerreiro, C. Baleizão, *Catal. Today* **2013**, *218–219*, 65–69.

and spectroscopic techniques, was tested in the asymmetric addition of hydrogen cyanide to *N*-benzyl benzylamine, *i.e.* in a Strecker-type reaction. The vanadium supported salen complexes were found to be more efficient than the aluminum analogues, in line with their homogeneous catalysts counterparts. In addition, the Janda-V(V) was used for 3 runs without a significant loss of activity or enantioselectivity (Figure 7).

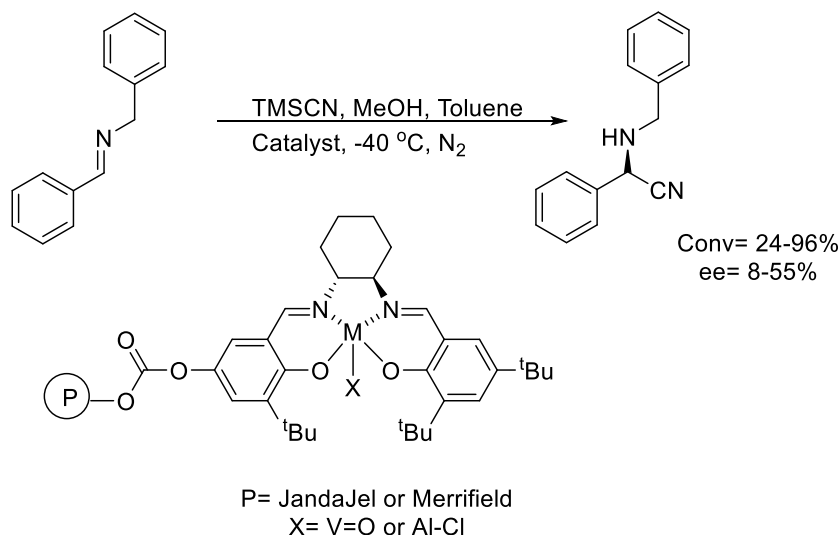


Figure 7: Immobilization of V and Al-salen complexes onto polystyrene type supports.

Another example is the preparation of dendritic Ti-salen complexes attached covalently on a polyamidoamine (PAMAM) dendrimer through a flexible ionic-liquid linker.³³ The imidazole groups of this latter were alkylated by functionalized salen ligands for a covalent grafting. The supported Ti(IV)-salen complexes resulting from the addition of titanium precursor and water, with the favored formed μ -oxo-bridged dimeric species, catalysed the asymmetric sulfoxidation reaction of methyl aryl sulfides with H_2O_2 . Very good results in terms of activity and enantioselectivity were observed, highlighting thus the intramolecular cooperativity achieved in this case (Figure 8).

Moreover, Schulz *et al.*³⁴ reported the immobilization of Co-salen complexes on a calix[8]arene platform via a flexible linker in order to study its reactivity in the hydrolytic kinetic resolution (HKR) of various epoxides. The supported system containing eight Co-salen units demonstrated an efficient cooperative bimetallic process and an enhancement of activity compared to the homogeneous

³³ Y. Chen, R. Tan, Y. Zhang, G. Zhao, D. Yin, *ChemCatChem* **2015**, *7*, 4066–4075.

³⁴ I. Abdellah, C. Martini, A. Dos Santos, D. Dragoe, V. Guérineau, V. Huc, E. Schulz, *ChemCatChem* **2018**, *10*, 4761–4767.

analogue. Being insoluble, its recovery was realized by simple filtration for 4 successive runs without any loss of activity or selectivity or release of cobalt traces in the final products.

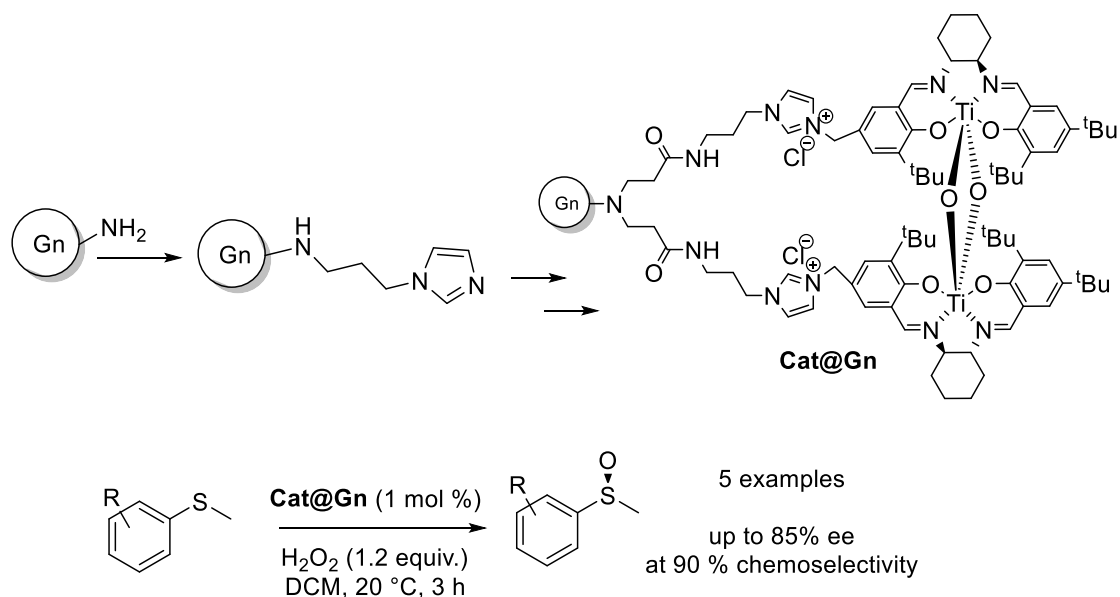


Figure 8: Ti(IV)-salen complexes supported on PAMAM dendrimers.

Polystyrene-type polymers or their analogues are no longer frequently used to support salen complexes. Even if the structure of such support has been modified to respond to the targeted catalytic reactions requirements, the amount of catalyst used in this approach remains important. Hence, recent examples are directed towards the preparation of new organic polymers with convenient structures, aiming at reducing the mass ratio of the support with regard to the active catalyst.

(2) Polymerization of salen complexes

In addition to the use of pre-existing organic supports, the preparation of new organic polymers has recently gained attention as a convenient solution to reduce the amount of the introduced supported catalyst. To illustrate these procedures, we can mention the work reported by Roger *et al.*³⁵ on the atom transfer radical polymerization (ATRP) of styryl functionalized salen ligands. The control of polymerization was possible only when the salen monomer was introduced in less than 10 mol%. The corresponding Co-salen complexes were tested in the HKR of epibromohydrin leading to good activity and enantioselectivity (Figure 9).

³⁵ N. Zidelmal, N. Aubry-Barroca, B. Lepoittevin, M. Mellah, L. Costa, F. Ozanam, A. -C. Gouget-Laemmel, E. Schulz, P. Roger, *Polymer* **2018**, *135*, 261-270.

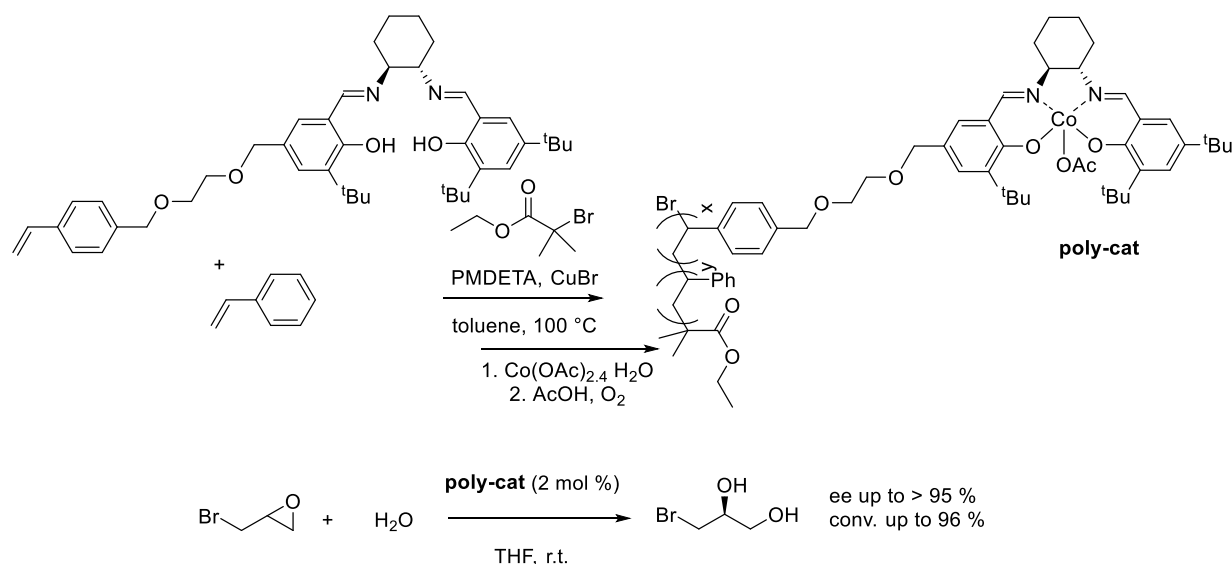


Figure 9: ATRP of salen monomers for the HKR of epibromohydrin.

On the other hand, Weck *et al.*³⁶ reported the preparation of oligomerized salen complexes via the original ring-opening metathesis polymerization of cyclooctene-modified salen monomers. The corresponding cobalt-based-salen oligomers Co(II) and Co(III) were engaged in the Henry reaction and their efficiency was compared to monomeric and salen derivatives analogues (Figure 10). The Co(II)-salen oligomers displayed a better activity than the monomers proving the preferred bimetallic pathway in this case, while no differences in activity were observed in the case of the Co(III) species since they act in a monometallic pathway. In addition, the enantioselectivity was reversed using the salen analogues probably due to a different geometry, an increased basicity of the *N*-atoms and the possibility of hydrogen bond formation.

³⁶ X. Zheng, C. W. Jones, M. Weck, *J. Am. Chem. Soc.* **2007**, *129*, 1105–1112.

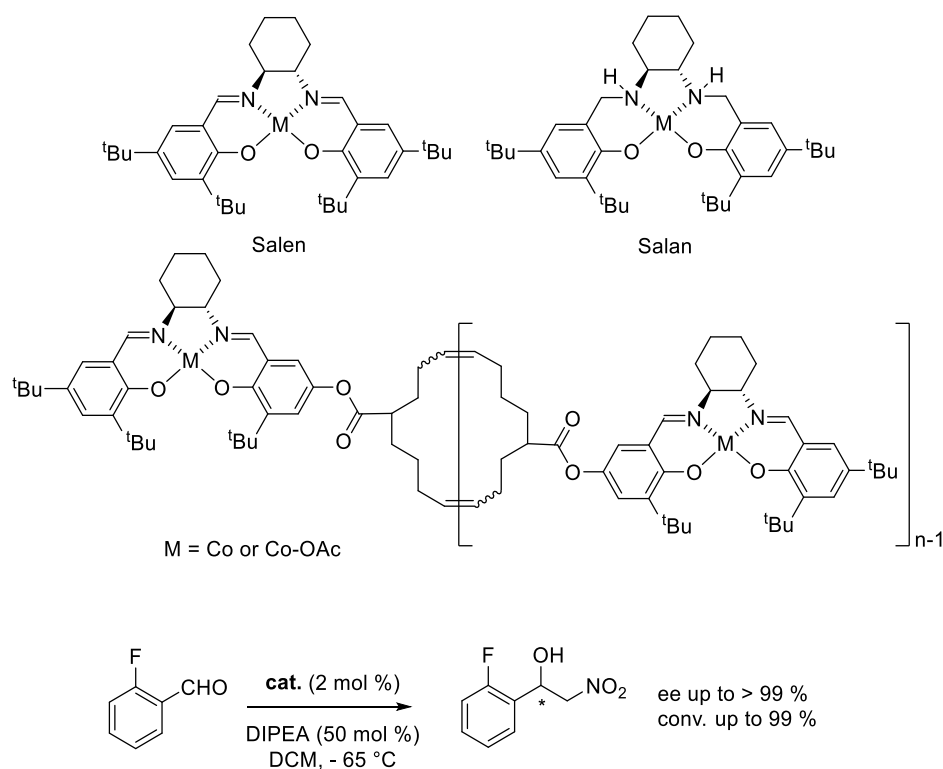


Figure 10: The nitro-aldol reaction catalysed by Co-salen oligomers and salan derivatives.

Recently, the preparation of a single-chain polymeric nanoparticles (SCPNS) containing a chiral Ti(IV) salen complex in their hydrophobic cavity was reported.³⁷ Their preparation was realized via a copolymerization reaction between a vinylimidazolium-modified chiral Ti-salen complex and *N*-isopropylacrylamide (NIPAAm) leading to a thermo-responsive polymer able to undergo reversible single chain self-folding in water. The polymeric catalyst was used in a 0.5 mol% loading to promote asymmetric sulfoxidation reaction in water showing an increased activity and enantioselectivity over the homogeneous analogue (Figure 11). An important protecting effect of the active sites by the hydrophobic core occurred indeed, together with a beneficial effect of the Ti-salen motifs confinement for cooperative catalysis of alkyl-aryl sulfides oxidation. The polymer catalyst was easily recovered from the aqueous solution by thermo-controlled separation due to the thermo-responsive properties and was thus easily precipitated out from the reaction system. It demonstrated a high stability for its reuse in seven consecutive cycles.

³⁷ Y. Zhang, R. Tan, M. Gao, P. Hao, D. Yin, *Green Chem.* **2017**, *19*, 1182–1193.

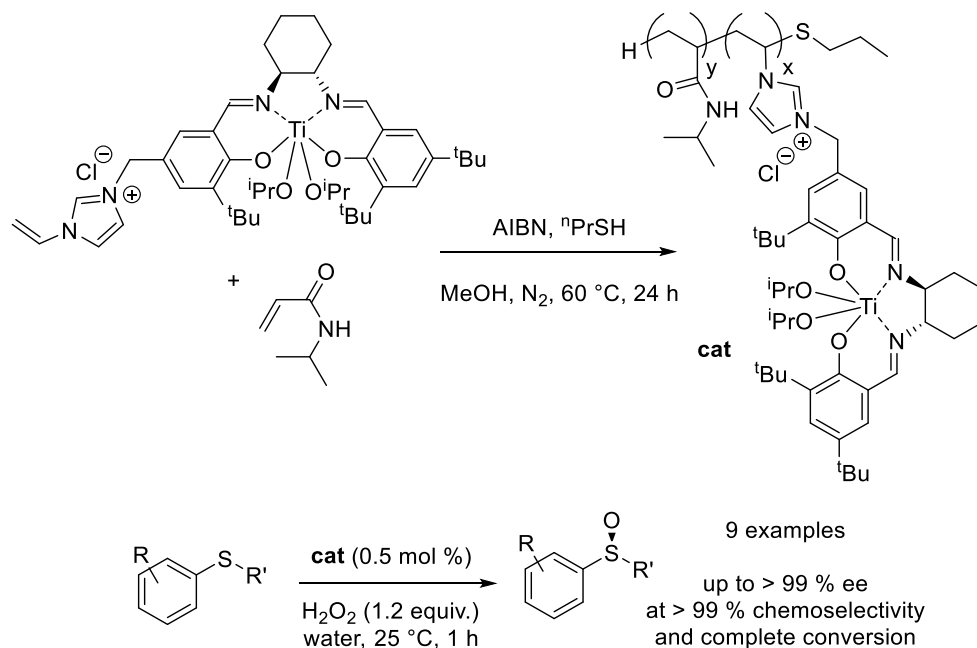


Figure 11: Ambiphilic Ti-salen copolymer for sulfoxidation in water.

In the previous examples, the salen ligands have been attached to oligomers and polymers as a pendant group on the main chain. This kind of polymers preparation allows to control the properties of the resulting polymer and the density of catalytic sites by the control of the structure and the amount of each co-monomer respectively. Another approach to prepare organic polymers was developed, in which the salen moieties constitute an integral part of the polymer main chain. In this context, some of us prepared salen complexes tagged to thiophene groups which could be electropolymerized under a constant current to generate insoluble polymer complexes. The electrochemical polymerization was performed on a platinum grid and the insoluble polymeric complex was recovered from the electrode surface. Accordingly, the corresponding Co-salen polymer was engaged in the hydrolytic kinetic resolution of epibromohydrin yielding the diol with complete conversion and a high enantiomeric excess. This insoluble polymer was recycled and reused for 11 runs without any loss of activity or enantioselectivity (Figure 12). On the other hand, the chemical-promoted oxidative polymerization of thiophene-based Co-salen complexes was achieved using chemical oxidants such as FeCl_3 or NOBF_4 . Hence, the copolymerization of a 50/50 mixture of salen monomers possessing Co-OAc or Co-BF_4 active sites led again to a very stable catalyst which was dispersed in an octadecyl carbon chain (C18) bonded silica and reused in a flow procedure for up to five cycles.³⁸

³⁸ X. Hong, L. Billon, M. Mellah, E. Schulz, *Catal. Sci. Technol.* **2013**, 3, 723–729.

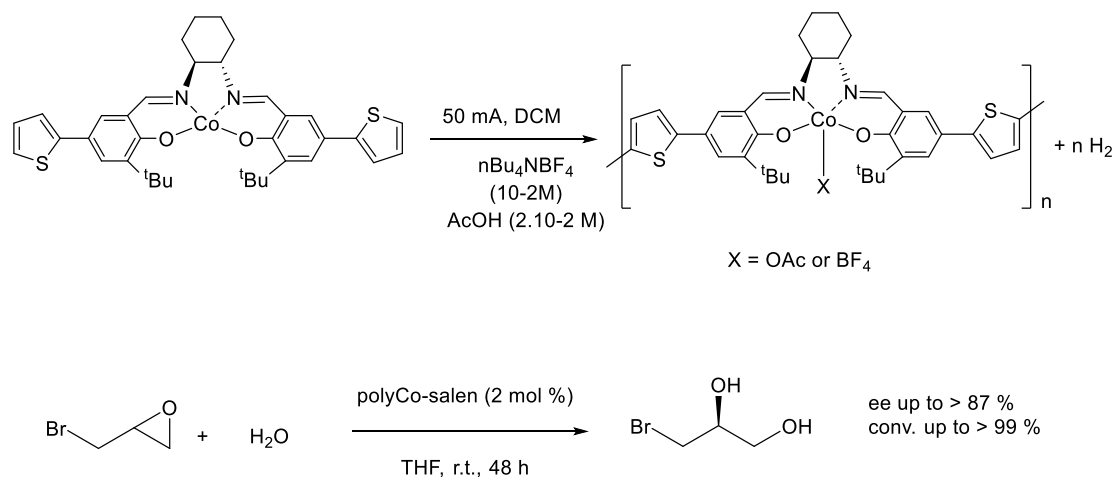


Figure 12: Electropolymerization of a chiral Co-thiophene-salen for the HKR of epibromohydrin.

Another approach consists in the preparation of the polymer via formation of the salen core itself by multiple imine bond formation between various salicylaldehyde derivatives and enantiopure diamine. Generally, disalicylaldehydes have been interconnected via numerous linkers in *para* position of the phenol while the *tert*-butyl groups were kept in the *ortho* position to maintain high enantioselectivity (Figure 13).

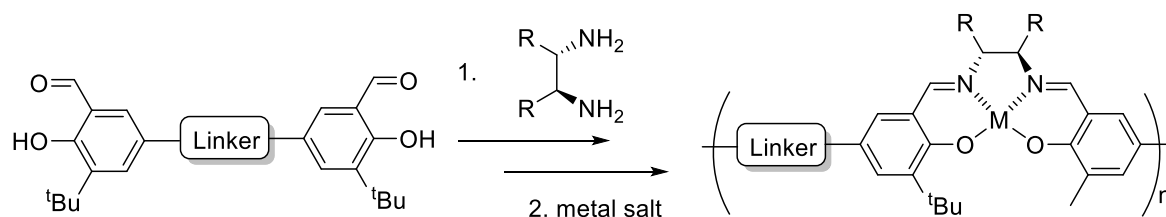


Figure 13: Polymerization via imine bond formation between dialdehydes.

In this context, Kureshy *et al.*³⁹ reported the preparation of recyclable chiral polymeric Co(III)-salen complexes derived from the condensation between dialdehydes modified with chiral (binaphthol or diethyltartrate derivatives) or achiral (piperazine and trigol) linkers with the enantiopure cyclohexyldiamine and followed by the introduction of cobalt salts. The linear Co-salen polymer was engaged in the asymmetric kinetic aminolysis of various epoxides (Figure 14). It was noticed that the stereochemistry of the products was driven by the chirality of the salen moiety. In addition, the distance between the salen units and their orientation were crucial factors affecting their activity in such cooperative bimetallic reactions. The best result was obtained using the catalyst bearing the binol linker for the reaction between phenoxypropane and *tert*-butyl carbamates as nucleophiles. The catalysts were recovered by precipitation after the addition of an apolar solvent and reused efficiently

³⁹ M. Kumar, R. I. Kureshy, A. K. Shah, A. Das, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *J. Org. Chem.* **2013**, 78, 9076–9084.

for 6 runs. The same polymeric systems were also used for a related catalytic transformation, the HKR of epoxides (21 examples).⁴⁰

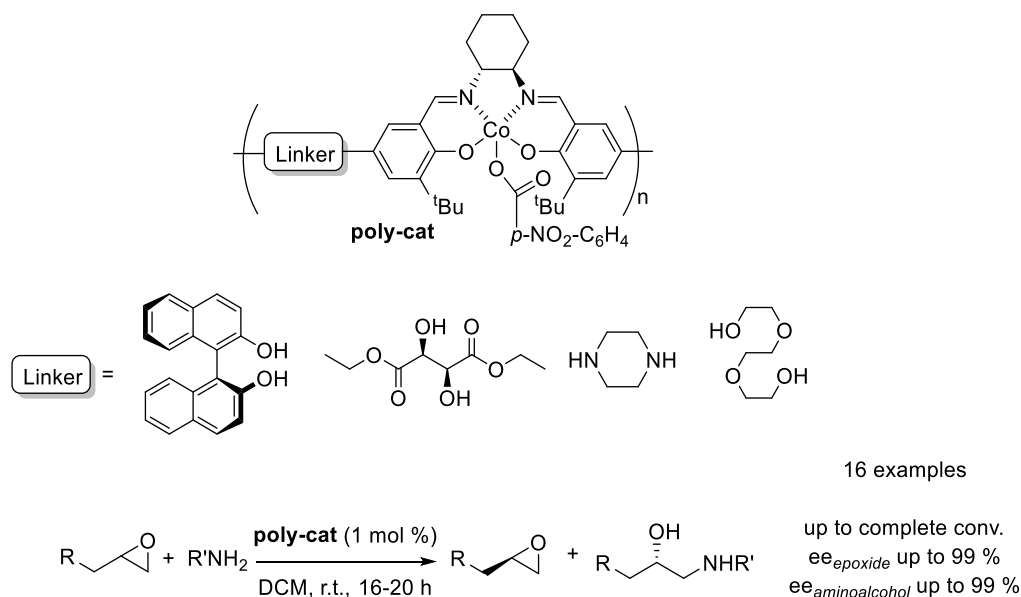


Figure 14: Linear polymeric Co-salen complexes for the kinetic aminolysis of epoxides.

Similarly, the same group prepared the manganese complexes analogues and tested them in the asymmetric epoxidation reaction of non-functionalized olefins.⁴¹ All the linear polymers showed good activity while the best result was observed in the epoxidation of indene with the polymer possessing a flexible trigol linker. The reactions have been performed in DCM at 0 °C in the presence of NaOCl as oxidant and PyNO as an axial base and the desired indene oxide was obtained with high yield and ee values (>99% yield, 70-92% ee). Moreover, polymers with a tritopic aldehyde as a spacer have been prepared and engaged in the asymmetric epoxidation of various alkenes showing high activity and delivering the desired epoxides with excellent enantioselectivity (Figure 15). Similarly, the Co-salen analogues were synthesized and tested in the asymmetric ring-opening of epoxides with CO₂ in the absence of usual co-catalysts.⁴² The reaction was performed at room temperature and 1 atm of CO₂ and the propylene carbonate was delivered in a modest yield with 74% ee (Figure 15). The catalyst was recovered and reused for 10 consecutive cycles without any loss of activity or enantioselectivity.

⁴⁰ T. Roy, S. Barik, M. Kumar, R. I. Kureshy, B. Ganguly, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *Catal. Sci. Technol.* **2014**, *4*, 3899–3908.

⁴¹ T. Roy, R. I. Kureshy, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *ChemPlusChem* **2015**, *80*, 1038–1044.

⁴² T. Roy, R. I. Kureshy, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *Catal. Sci. Technol.* **2013**, *3*, 2661–2667.

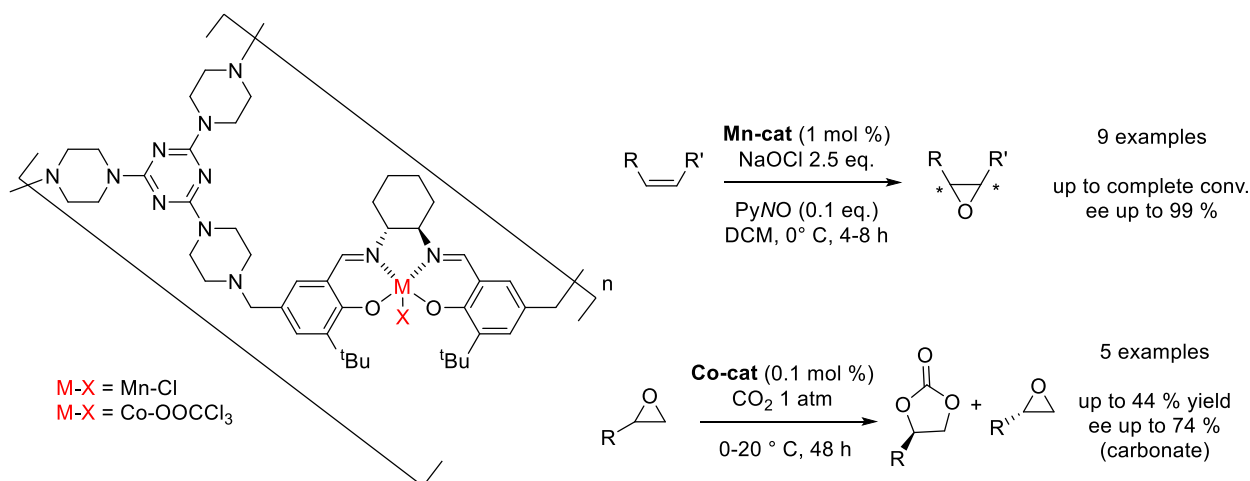


Figure 15: Polymeric Mn and Co-salen complexes with a tritopic spacer.

The heterogenization of salen complexes by forming linear salen-containing polymers was extensively studied, in which the salen could be introduced as a pendant group or incorporated in the main chain. The polymers issued from the first approach are mostly insoluble and thus their recovery is achieved by filtration, while the second types are in most cases soluble and their recovery requires the addition of an apolar solvent leading to their precipitation before filtration.

(3) Macrocyclization of salen complexes

The condensation of modified dialdehydes via the formation of imine bond allowed not only the preparation of linear polymers but also macrocyclic oligomers containing the salen complexes. This procedure, by privileging an optimal arrangement of the active sites, leads to the preparation of very active catalysts for the bimetallic cooperative based catalysis since cyclic dimers or a mixture of larger oligomers could be obtained. In this context, Jacobsen *et al.*⁴³ reported the first preparation of a cyclic oligomeric Co(OTf)-salen complex and used it in the asymmetric ring opening reaction of epoxides and in the kinetic resolution of terminal epoxides with various nucleophiles (Figure 16). The catalyst was soluble and leads to a high reactivity outperforming the monomer analogue.

⁴³ a) J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 2687–2688. b) J. M. Ready, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2002**, *41*, 1374–1377.

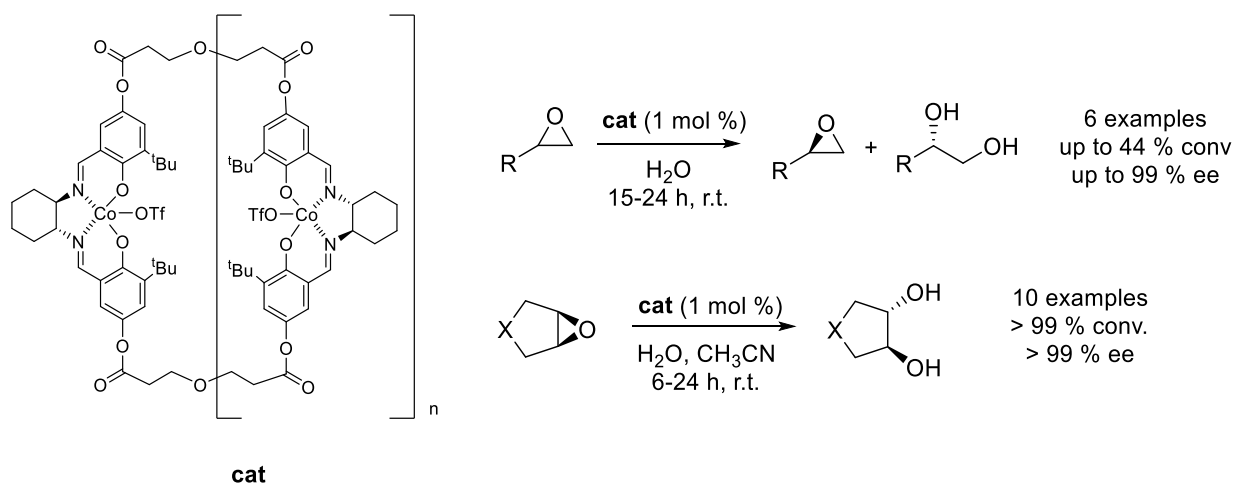


Figure 16: Cyclic oligomeric $\text{Co}(\text{OTf})$ -salen complexes.

In order to recover these modified-salen complexes, new series of recyclable macrocyclic oligomers have been developed, synthesized starting from stoichiometric amounts of dialdehydes with diamine, and linked through ethylene glycol derivatives, piperazine and diethyl tartrate linkers (Figure 17). The corresponding complexes catalysed efficiently various asymmetric transformations such as the cyanation reaction of aldimines,⁴⁴ the asymmetric cyanoethoxycarbonylation reaction of aldehydes,⁴⁵ the epoxidation of olefins and the kinetic resolution of secondary alcohols.⁴⁶

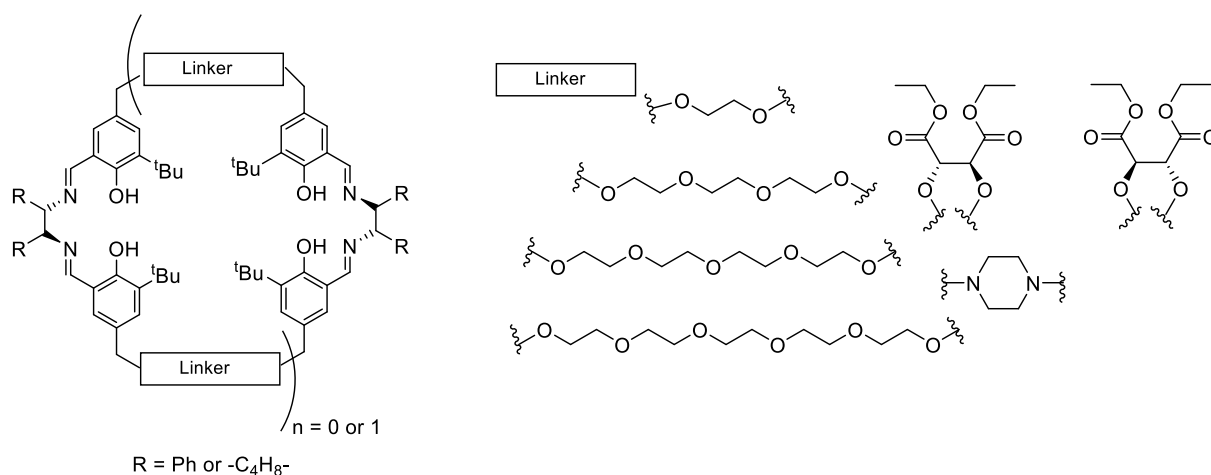


Figure 17: Recyclable oligomeric salen ligands

⁴⁴ S. Saravanan, N. H. Khan, P. K. Bera, R. I. Kureshy, S. H. R. Abdi, P. Kumari, H. C. Bajaj, *ChemCatChem* **2013**, *5*, 1374–1385.

⁴⁵ A. Sadhukhan, M. K. Choudary, N. H. Khan, R. I. Kureshy, S. H. R. Abdi, H. C. Bajaj, *ChemCatChem* **2013**, *5*, 1441–1448.

⁴⁶ N. C. Maity, P. K. Bera, S. Saravanan, S. H. R. Abdi, R. I. Kureshy, N. H. Khan, H. C. Bajaj, *ChemPlusChem* **2014**, *79*, 1426–1433.

Moreover, some of us prepared macrocyclic salen ligands, which were called calix-salen, via a polycondensation reaction between modified disalicylaldehydes and chiral diamines.⁴⁷ Consequently, the Henry reaction involving different aldehydes was evaluated using these Cr- and Co-calix-salen complexes and also tetrahydrosalen-based Cu-macrocycles (Figure 18, eq. a); this latter showed the best results for ten runs. On the other hand, Co-calix salen complexes were tested in the HKR of epibromohydrin (Figure 18, eq. c); in this case, the tetramer species was found to be more active and selective than the trimer analogue with an efficient recovery for 6 runs.⁴⁸ Furthermore, a matched effect was observed by using an equivalent catalytic mixture of Co- and Mn-calix-salen having the same salen configuration, in promoting the HKR of epibromohydrin, in the context of an heterobimetallic catalytic system (Figure 18, eq. b).⁴⁹

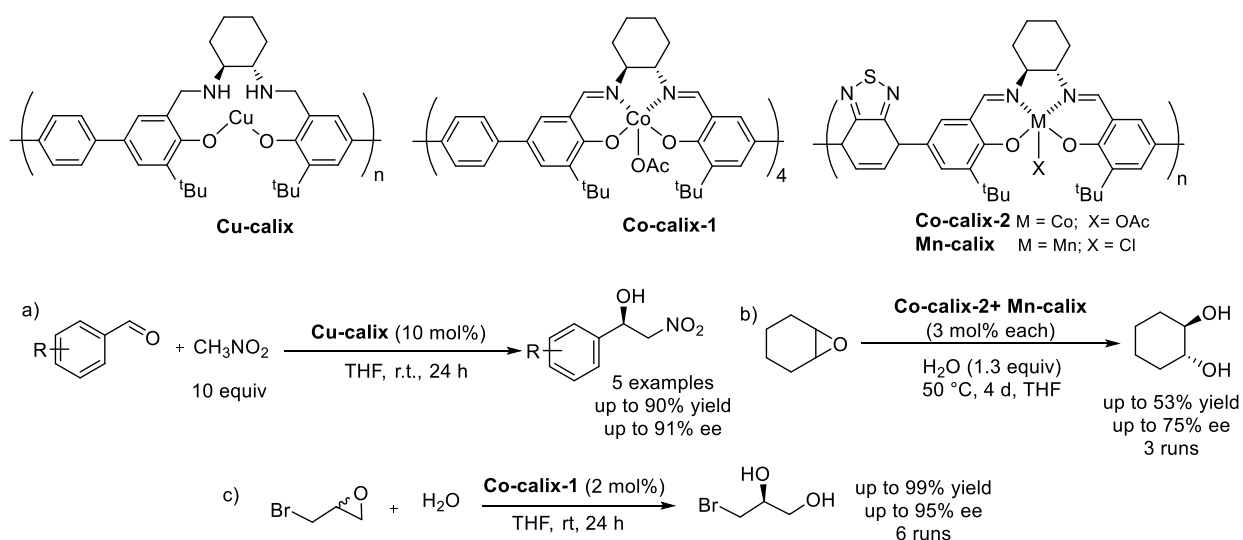


Figure 18: Macrocyclic calix salen complexes for various asymmetric transformations

Recently, Kureshy *et al.*⁵⁰ reported the synthesis of monometallic macrocyclic salen derivatives formed via additional chiral linkers. The corresponding Co-salen complex bearing a BINOL linker promotes efficiently the aminolytic kinetic resolution (AKR) with a variety of amines with high regioselectivity towards the attack of the nitrogen nucleophile, affording the unreacted epoxide and the ring-opened products in good yields and high enantioselectivity for the AKR (Figure 19). The

⁴⁷ a) F. Ibrahim, H. Nasrallah, X. Hong, M. Mellah, A. Hachem, G. Ibrahim, N. Jaber, E. Schulz, *Tetrahedron*, **2012**, *68*, 9954–9961. b) F. Ibrahim, N. Jaber, V. Guérineau, A. Hachem, G. Ibrahim, M. Mellah, E. Schulz, *Tetrahedron: Asymmetry*, **2013**, *24*, 1395–1401.

⁴⁸ H. Dandashi, H. Nasrallah, F. Ibrahim, X. Hong, M. Mellah, N. Jaber, E. Schulz, *J. Mol. Catal. A: Chem.* **2014**, *395*, 457–462.

⁴⁹ H. Dandashi, E. Zaborova, E. Kolodziej, O. R. P. David, J. Hannedouche, M. Mellah, N. Jaber, E. Schulz, *Tetrahedron: Asymmetry*. **2016**, *27*, 246–253.

⁵⁰ R. Tak, M. Kumar, T. Menapara, N. Gupta, R. I. Kureshy, N. H. Khan, E. Suresh, *Adv. Synth. Catal.* **2017**, *359*, 3990–4001.

catalysts were recovered and reused five times with a slight decrease in activity with constant selectivity. Following the same procedure, chiral oligomeric Cr-salen complexes have been prepared and engaged in the asymmetric aminolysis of internal epoxides with different anilines affording the β -amino- α -hydroxyl esters in very good yields and excellent ee values (Figure 19). The monomeric catalyst was recycled four times without any loss in catalytic properties.⁵¹

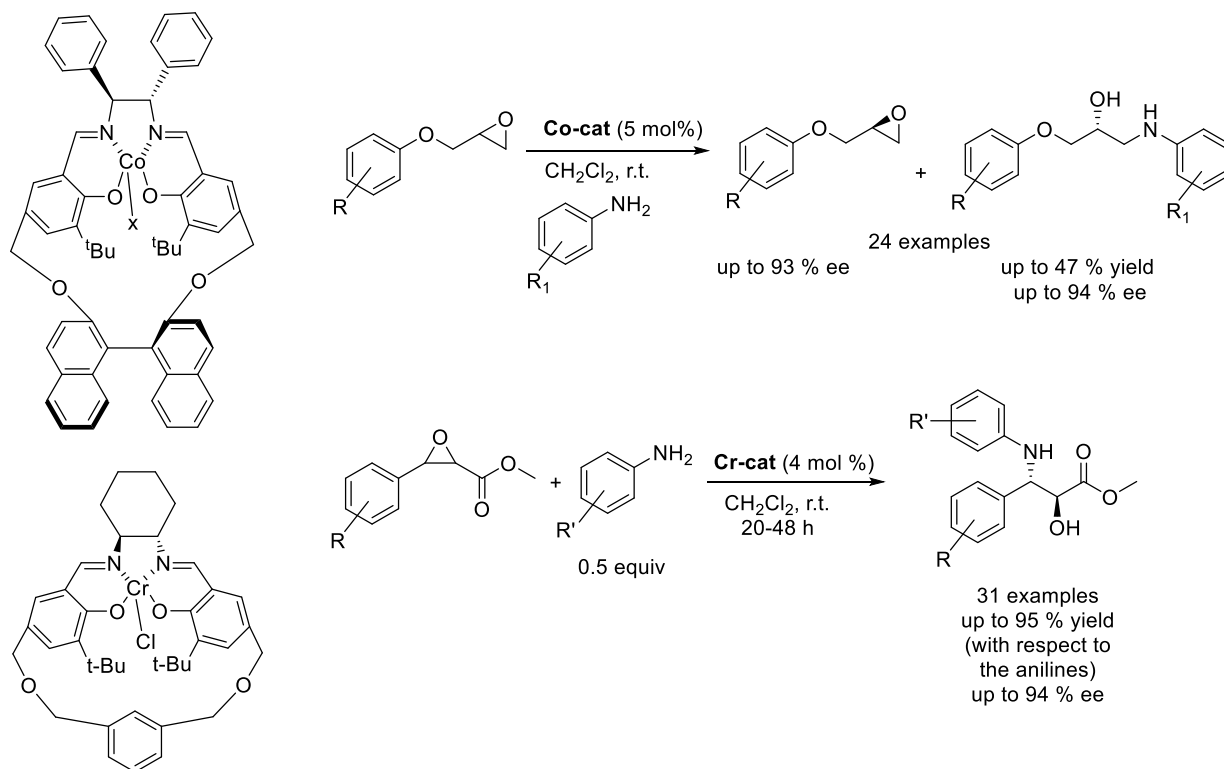


Figure 19: Monometallic macrocyclic salen complexes for the AKR reaction.

Hence, the preparation of macrocyclic salen derivatives depends on the structure of the linked dialdehydes and in some cases there is no need to purify a mixture of oligomers with different sizes in order to perform catalysis. The arrangement of salen derivatives in macrocyclic structures represents a very effective method to enhance the cooperative activity of active sites. Furthermore, these species are recyclable catalysts which are efficiently recovered by precipitation and filtration.

2. Noncovalent attachment

The use of non-covalent interactions for the assembly of salen derivatives and their heterogenization will be detailed in this part.

⁵¹ R. Tak, M. Kumar, T. Menapara, M. K. Choudhary, R. I. Kureshy, N. H. Khan, *ChemCatChem*. **2017**, *9*, 322–328.

a) Salen complexes assembled via non-covalent interaction to enhance cooperativity

The aromatic donor-acceptor interaction is one of the most challenging non-covalent interactions used in a variety of supramolecular assemblies.⁵² Such interactions have for instance already been used to assemble monophosphate⁵³ or monooxazoline⁵⁴ derivatives functionalized by electro-donor and electro-acceptor moieties, to promote enantioselective hydrogenations by generating bidentate rhodium complexes or copper species for Diels-Alder reactions, respectively.

Recently, Liang and coworkers⁵⁵ described the synthesis of three generations of Co(III)-salen complexes bearing aromatic 1,4,5,8-naphthalenediimide (NDI) groups as electron deficient moieties and studied the effect of the addition of an electron rich donor compound such as 1,5-dimethoxynaphthalene (DMN), pyrene, perylene and coronene (G1, Figure 20). The aromatic donor-acceptor interaction was verified by NMR titration experiments and UV-vis spectroscopy and the catalyst assemblies were involved in the HKR of epichlorohydrin. The different donor compounds were tested with the first generation of catalyst. The best result was obtained with pyrene as a donor partner (3.5 equiv) after an optimization series of reaction conditions while DMN, perylene and coronene led to a decreased reactivity. However, the catalytic system did not outperform Jacobsen's catalyst in terms of activity or enantioselectivity probably because of the rigid phenyl linker between the NDI and the Co(III)-salen core. So, two other generations of Co-salen complexes tagged to the NDI and pyromellitic diimide (PDI) as acceptor units with flexible alkyl ester linker were synthesized (G2 and G3, Figure 20) and tested in the same catalytic transformation under the previously optimized conditions; the best results were achieved using the combination **G3**-pyrene (52% conv after 10 hours, >99% ee).

⁵² A. Das, S. Ghosh, *Angew. Chem. Int. Ed.*, **2014**, *53*, 2038–2054.

⁵³ B. Lynikaite, J. Cvengros, U. Piarulli, C. Gennari, *Tetrahedron. Lett.* **2008**, *49*, 755–759.

⁵⁴ O. Chuzel, C. Magnier-Bouvier, E. Schulz, *Tetrahedron: Asymmetry*, **2008**, *19*, 1010–1019.

⁵⁵ D. R. Blechshmidt, M. D. Woodhouse, S. Inagaki, M. Whitfield, A. Ogunsanya, A. Yoder, D. Lilly, E. W. Heim, L. N. Soucie, J. Liang, Y. Liu, *Org. Biomol. Chem.* **2019**, *17*, 172–180.

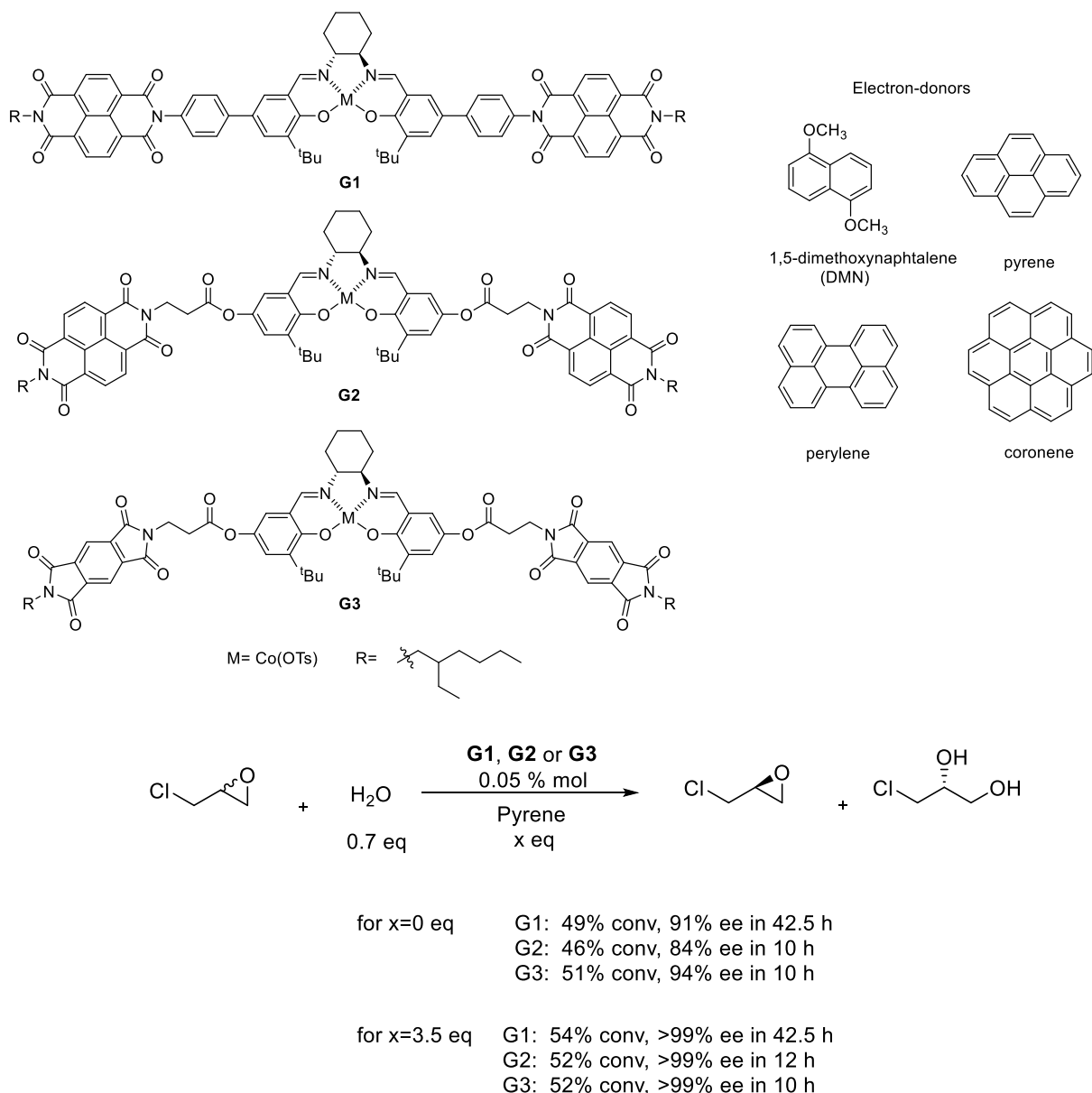


Figure 20: Bis-diimide functionalized Co-salen complexes and aromatic donor compounds.

Thus, aromatic non-covalent interactions promoted the cooperativity between two Co(III)-salen cores and led to a higher catalytic efficiency for all three generations of complexes, with the rate acceleration of the HKR of epichlorohydrin using the catalysts assemblies following the order **G3** > **G2** > **G1**.

The same group also designed a new model of Co(III)-salen assemblies, in which bis-substituted symmetrical or unsymmetrical complexes as well as their mono-substituted analogues were synthesized, and tested in the same catalytic reaction (Figure 21).⁵⁶ In this case, the selectivity and the reaction rate have been improved, and best results were obtained with the unsymmetrical Co(III)-

⁵⁶ J. Liang, L. N. Soucie, D. R. Blechschmidt, A. Yoder, A. Gustafson, Y. Liu, *Org. Lett.* **2019**, *21*, 513–518.

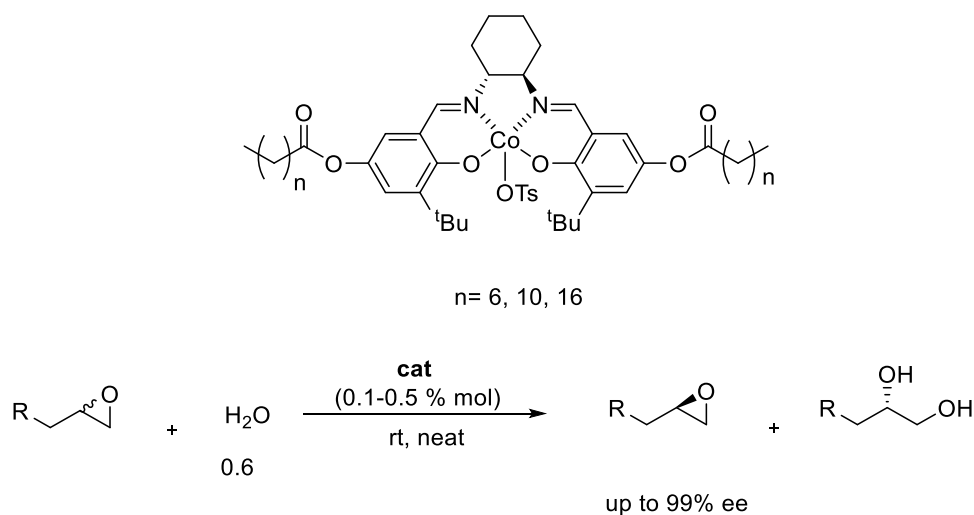


Figure 22: Amphiphilic Co-salen complexes for the HKR of terminal epoxides.

On the other hand, Hong and coworkers reported another non-covalent approach, where a dinuclear Co(III)-salen supramolecular catalyst was assembled via hydrogen bonding offered by the urea pairs flanked on, and achieving a rate acceleration in the HKR of epoxides⁵⁸, as a good example for the efficiency of another non-covalent interactions to promote cooperative catalysis by salen complexes.

To sum up, the use of non-covalent interactions directed by the presence of polyaromatic moieties, hydrogen bonding, or of hydrophobic interactions lead to the enhancement of the cooperativity between salen complexes and thus the improvement of their activity and sometimes in their selectivity.

b) Immobilization on inorganic supports

Noncovalent immobilization of salen complexes is recently a new interesting heterogenization method because only simple modifications of the engaged compounds are required. Among these procedures, coordinative, adsorptive, and trapping methods will be described.

In this context, mesoporous materials containing sulfonic acid groups were chosen as candidates for the immobilization of cationic chiral salen complexes. Homogeneous Co-salen complexes were thus immobilized onto a sulfonic acid-modified SBA-16 via electrostatic interactions,⁵⁹ and proved to be efficient catalysts for the ring opening of terminal epoxides with good enantiomeric excess values (up

⁵⁸ J. Park, K. Lang, K. A. Abboud, S. Hong, *Chem. Eur. J.* **2011**, *17*, 2236–2245.

⁵⁹ Y.-S Kim, X.-F. Guo, G.-J. Kim, *Chem. Commun.* **2009**, *28*, 4296–4298.

to 98%). The activity of the insoluble catalyst decreases by 5% after the third run in comparison with the first one, in the HKR of epichlorohydrin.

Moreover, salen complexes were noncovalently immobilized onto zeolites and mesoporous crystalline materials.⁶⁰

Following the strategy of supported ionic liquid phase, a solution of a dimeric Cr-salen complex was immobilized on silica and used in the asymmetric ring opening reaction of epoxides.⁶¹ The supported catalyst was reused efficiently for 4 runs and was engaged in a continuous flow process delivering the desired products with good ee values. Besides, a solution of Mn-salen in [bmim][PF₆] was supported on the surface of modified MCM-48 by grafting onto it 1-methyl-3-(3-trimethoxysilylpropyl) imidazolium hexafluorophosphate.⁶² This supported catalyst was found very efficient in the asymmetric epoxidation of several alkenes with *m*CPBA, giving similar or increased values of enantioselectivity probably due to the well-defined 3D topological structure of the support, limiting the free rotation of the reaction intermediates. The supported catalyst was reused for three runs after the solvent removal followed by the addition of hexane and further filtration.

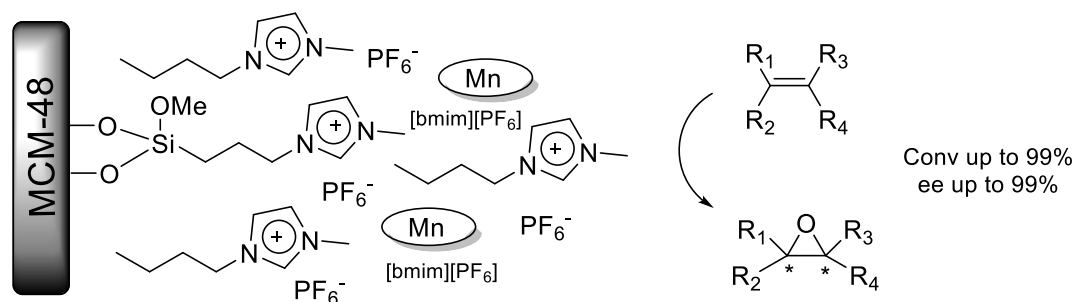


Figure 23: Supported ionic liquid phase Mn-salen on modified MCM-48.

Helical silica⁶³ was recently used as support to immobilize salen complexes. It was prepared in a sol-gel procedure, by alkali promoted hydrolysis of tetraethyl-orthosilicate, providing the shell of a chiral micelle, arising from quaternary ammonium surfactants associated to lactate anions; the thus formed helical packing was preserved through calcination. This helical support, after post-functionalization by phenylsulfonate groups, was used to anchor diverse Mn-salen complexes by coordination as axial ligand (Figure 24).⁶⁴ Achiral Mn catalysts have been anchored to helical silica and tested in the

⁶⁰ a) P. Piaggio, C. Langham, P. McMorn, D. Bethell, B. C. Bulman-Page, F. E. Hancock, C. Sly, O., G. J. Hutchings, *J. Chem. Soc.* **2000**, *Perkin trans 2*, 143-148. b) P. Piaggio, P. McMorn, D. Murphy, D. Bethell, B. C. Bulman-Page, F. E. Hancock, C. Sly, O. J. Kerton, G. J. Hutchings, *J. Chem. Soc.* **2000**, *Perkin trans 2*, 2008-2015.

⁶¹ B. Dioso, P. Jacobs, *J. Catal.* **2006**, *243*, 217-219.

⁶² L.-L. Lou, K. Yu, F. Ding, W. Zhou, X. Peng, S. Liu, *Tetrahedron. Lett.* **2006**, *47*, 6513-6516.

⁶³ S. Che, Z. Liu, T. Ohsuna, K. Sakamoto, O. Terasaki, T. Tatsumi, *Nature* **2004**, *429*, 281-284.

⁶⁴ L. Li, Y. Li, D. Pang, F. Liu, A. Zheng, G. Zhang, Y. Sun, *Tetrahedron* **2015**, *71*, 8096-8103.

asymmetric hetero Diels-Alder reactions affording the desired products in very good ee values. The use of a chiral salen catalyst afforded a synergistic effect, with the molecular catalyst being responsible for the product configuration and the chiral environment for an enhancement of the ee values. A major influence of the solvents was noticed with ionic liquids favoring the catalysts recyclability.

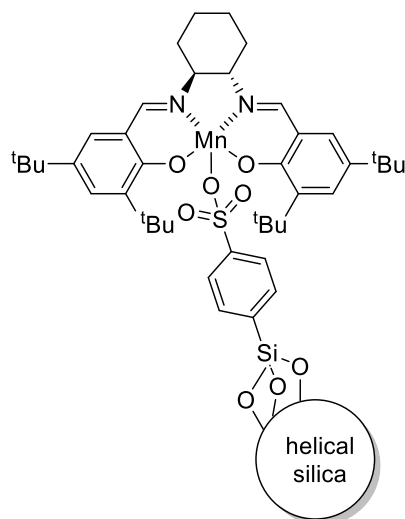


Figure 24: Chiral Mn-salen complex supported on helical silica.

Other silica-based supports have been employed to non-covalently anchor salen complexes such as MCM-41. Other examples will be detailed in the bibliographic part of the next chapters in relation to the catalytic transformations which have been studied in our work. This approach is mostly based on the use of electrostatic interactions as non-covalent interactions to build a link between the support and the salen complex.

c) Immobilization on organic supports

The non-covalent heterogenization of salen complexes onto organic supports such as polystyrene-based materials remains scarce and limited to electrostatic interactions and axial coordination. In this context, Zhang and coworkers⁶⁵ reported the immobilization of Mn-salen complexes onto polystyrene poly(styrene-divinylbenzene) (PS-DVB) previously modified by sulfonic and phenolic groups. The immobilization occurred via a cation exchange between the polymer sodium salts and an ethanolic solution of Mn(Cl)-salen complexes (Figure 25). The corresponding supported catalyst catalysed the asymmetric epoxidation of different alkenes using NaClO as oxidant affording the epoxides with

⁶⁵ H. Zhang, Y. Zhang, C. Li, *Tetrahedron: Asymmetry* **2005**, *16*, 2417–2423.

good yields and ee values. Interestingly, an enhancement of selectivity was observed for the epoxidation of *cis*-methylstyrene and α -methylstyrene.

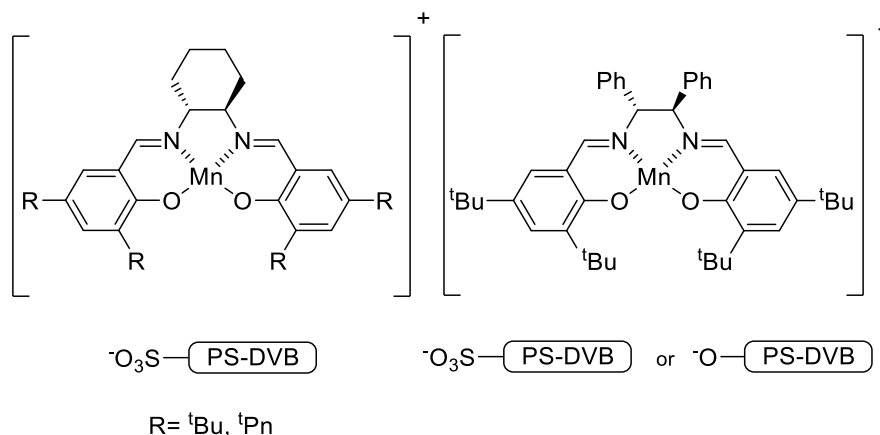


Figure 25: Mn-salen complexes immobilized in sulfonic or phenolic PS-DVB resins.

Another example is the immobilization of Mn-salen complexes by apical coordination to a PAMAM dendrimer with the phenolate ions present at the dendrimer border confirmed by FT-IR, UV-Vis and thermal analyses.⁶⁶ Different generations of the dendritic complexes were tested in the enantioselective epoxidation of alkenes in the presence of *m*CPBA (Figure 26). The best results were obtained in terms of selectivity for the first generation, G1, values which then decreased with the growth of the generation. G1 would indeed benefit from a positive dendritic effect for a high loading of the active sites but preventing from dimerization. On the contrary, higher generations led to dense packing of the active sites, creating therefore high steric hindrance, hampering their preferred conformation. G1 was recovered by simple phase-separation techniques thanks to solvents change in the reaction mixture, and efficiently recycled for five consecutive cycles.

⁶⁶ M. Peng, Y. Chen, R. Tan, W. Zheng, D. Yin, *RSC Adv.* **2013**, 3, 20684–20692.

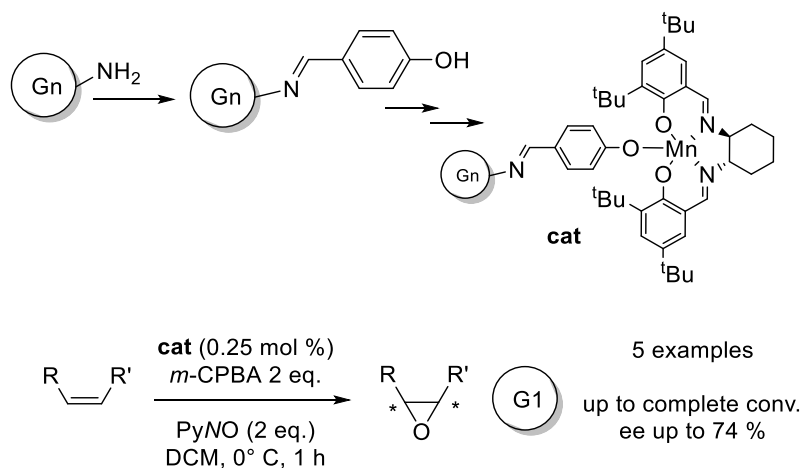


Figure 26: Dendrimer-supported Mn-salen complex via apical coordination.

d) Salen immobilized on metal organic frameworks (MOFs)

Salen complexes have been recently entrapped in metal organic frameworks (MOFs) which are ordered networks prepared from organic electron donor linkers and metal cations or clusters via non-covalent coordination interactions. Besides, these species can be considered as privileged heterogeneous catalysts with activity arising either from unsaturated metal coordination sites or from active linkers in between the metals, or from both together, specifically if those linkers are chiral salen complexes. Furthermore, the rich choice of available porous structures allows size- and shape-selective limitations through well-defined channels and pores. Thus, MOFs were already quite recently reported as efficient heterogeneous catalysts for numerous transformations, including enantioselective reactions.⁶⁷ Their visualization is possible due to their crystallinity leading thus to know the precise location of active sites and preventing their activity in cooperative and tandem catalysis processes. In this context, Liu, Cui *et al.*⁶⁸ reported the preparation of Cr-salen MOFs by heating the complex with CdI_2 and NaOAc . The structure of the resulted 3D Cr-salen MOF, the porosity and the enantioselective nature were confirmed using various analyses including circular dichroism, TGA, XPS and BET. The prepared heterogeneous catalyst was engaged in the the Nazarov reaction of alkoxydienones, affording functionalized cyclopentenones with high selectivity (Figure 27).

⁶⁷ L. Ma, C. Abney, W. Lin, *Chem. Soc. Rev.* **2009**, *38*, 1248–1256. b) L. Ma, J. M. Falkowski, C. Abney, W. Lin, *Nat. Chem.* **2010**, *2*, 838–846. c) M. Yoon, R. Srirambalaji, K. Kim, *Chem. Rev.* **2012**, *112*, 1196–1231; d) J. Gascon, A. Corma, F. Kapteijn, F. X. Llabrés i Xamena, *ACS Catal.* **2014**, *4*, 361–378. e) A. H. Chughtai, N. Ahmad, H. A. Younus, A. Laypkov, F. Verpoort, *Chem. Soc. Rev.* **2015**, *44*, 6804–6849; f) T. Drake, P. Ji, W. Lin, *Acc. Chem. Res.* **2018**, *51*, 2129–2138; g) G. Yuan, H. Jiang, L. Zhang, Y. Liu, Y. Cui, *Coord. Chem. Rev.* **2019**, *378*, 483–499.

⁶⁸ Q. Xia, Y. Liu, Z. Li, W. Gong, Y. A. Cui, *Chem. Commun.* **2016**, *52*, 13167–13170.

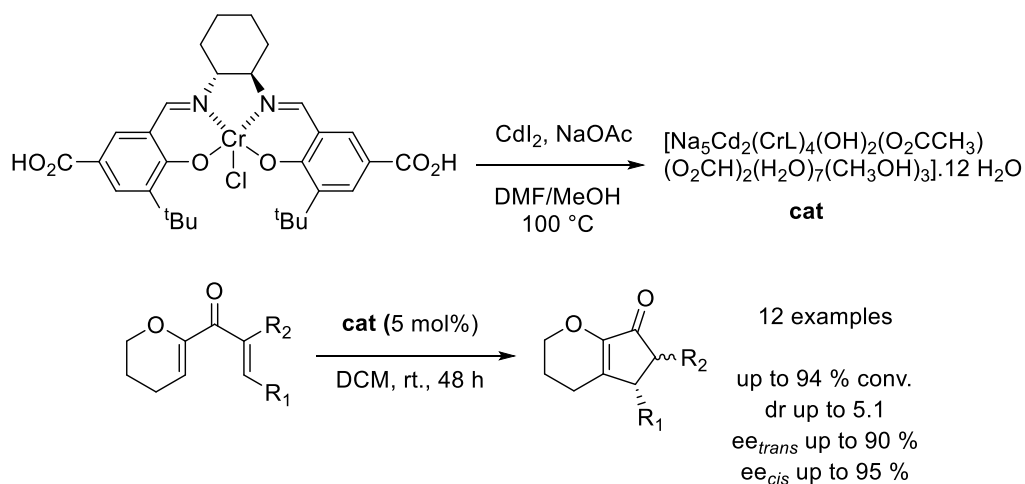


Figure 27: Cr-salen MOF for Nazarov cyclisation.

Moreover, this catalyst was tested in other catalytic transformations such as the asymmetric aminolysis of trans-stilbene, the Diels-Alder and hetero-Diels-Alder reactions affording high enantioselectivities. More interestingly, the size selectivity was also proved since a bulky benzaldehyde derivative could not undergo the hetero-Diels-Alder reaction, indicating thus a unique catalytic activity inside the pores of the MOF. The catalyst was reused in four catalytic aminolysis cycles showing a good stability.

Various heterogeneous MOFs catalysts could be obtained by changing the metal ions or clusters used as nodes, the structure of the salen moiety and the nature of the coordinating metal, enlarging thus the heterogeneous asymmetric catalysis field promoted by these species. Accordingly, Fe-salen complexes functionalized by pyridyl groups were assembled in MOFs.⁶⁹ A 3D framework resulted from the heating of the salen derivative in the presence of biphenyl-4,4'-dicarboxylic acid, as additional linker for porosity, and $\text{Cd}(\text{OAc})_2$. The heterogeneous framework was further used as efficient catalyst at a low loading in the oxidation of isopropyl phenyl sulfide with mesityl iodane. It was recovered by filtration and reused for 3 runs (Figure 28).

⁶⁹ Z. Yang, C. Zhu, Z. Li, Y. Liu, G. Liu, Y. Cui, *Chem. Commun.* **2014**, 50, 8775–8778.

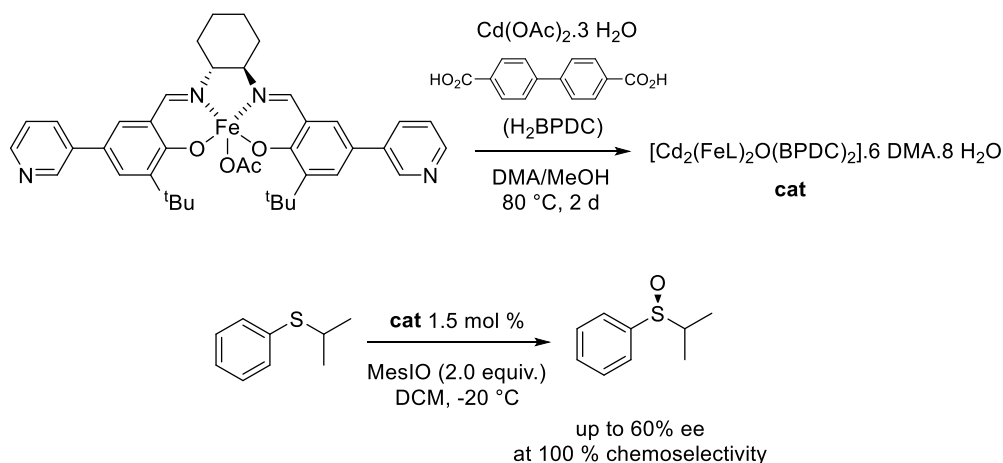


Figure 28: Fe-salen MOF catalyst for the sulfide oxidation.

On the other hand, some reports described the modification of the structure of the MOFs by a post-synthetic modification (PSM) in order to enhance the activity and the selectivity of the designed catalyst. In this context, Jiang *et al.*⁷⁰ prepared a 3D MOF network based on a tetracarboxyl-functionalized chiral Cu-salen complex which showed poor activity in catalysing the nitro-aldol reaction. For this reason, PSM was further performed by the reduction of the imine bonds into amino groups to increase both the basicity and flexibility of the corresponding catalyst. As expected, the recyclable catalyst was found to be more active and selective in the Henry reaction of various aldehydes.

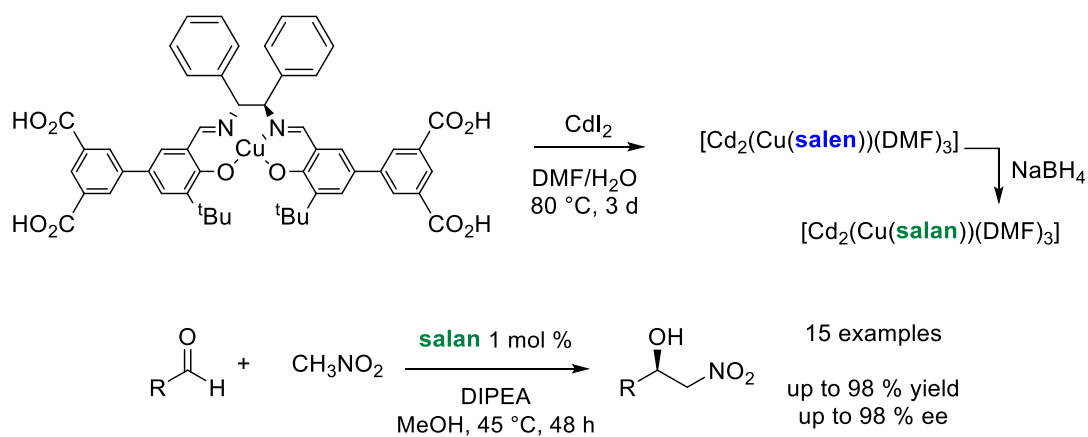


Figure 29: Enantiopure Cu-salan MOF by PSM.

Furthermore, and more interestingly, the crystalline MOFs networks were used as multimetallic catalysts. The introduction of various metal-salen complexes could be achieved by the cocrystallisation of multiple salen complexes leading to the formation of multivariate MOFs⁷¹.

⁷⁰ Y. Fan, Y. Ren, J. Li, C. Yue, H. Jiang, *Inorg. Chem.* **2018**, *57*, 11986–11994.

⁷¹ Q. Xia, Z. Li, C. Tan, Y. Liu, W. Gong, Y. Cui, *J. Am. Chem. Soc.* **2017**, *139*, 8259–8266.

Examples on the use of multimetallic MOFs in tandem sequential processes will be mentioned in chapter 4.

The immobilization of salen complexes via non-covalent interactions is not widely developed. Only few examples described the use of electrostatic interactions and more recently the coordination of salen moieties to ordered networks for their immobilization towards heterogeneous salen catalysts. To the best of our knowledge, the use of other non-covalent interactions such as π - π interactions have not been developed, yet.

C. Carbon materials as supports

1. Generality

As the clearly mentioned in their name, carbon materials are mainly constituted from the carbon element thanks to its extraordinary self-combination ability. Depending on the combination mode, different allotropic forms of carbon stacking exist such as cubic diamond, hexagonal graphite, and fullerene C₆₀. Many carbon materials are derived from different carbon allotropes. Activated carbon and carbon fibers for example are derived from graphite. Carbon nanotubes (CNT) and related nanostructures are considered as a rolled cylindrical single layer of graphene resembling on their end to a half-fullerene.⁷²

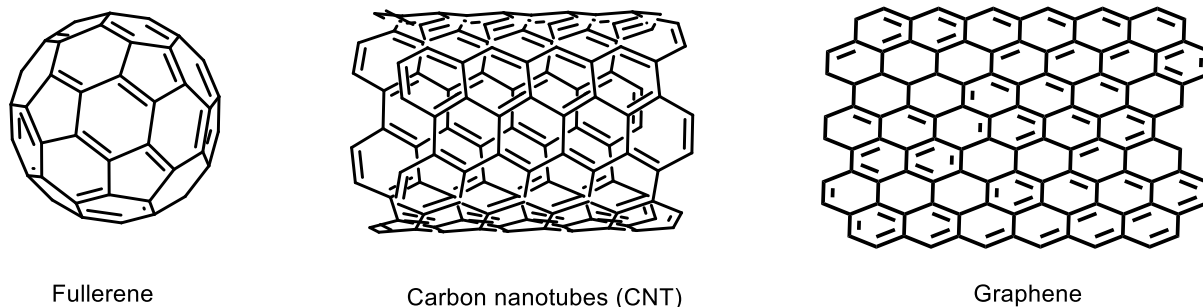


Figure 30: Fullerene, carbon nanotubes and graphene.

The different carbon materials possess interesting properties leading to their application in several field: mechanical, electrical, adsorption, reactivity and catalysis. Following the size of the surface pores, they could be classified by the IUPAC⁷³ into micropores (width < 2 nm), mesopores (2 nm < width < 50 nm) and macropores (width > 50 nm). Furthermore, their specific surface chemistry

⁷² S. Iijima, *Nature*, **1991**, 354, 56–58.

⁷³ K.S.W. Sing, D. H. Everett, R. A. W. Haul, L. Moscou, R. A. Pierotti, J. Rouquerol, K. Siemieniowska, *Pure Appl. Chem.* **1985**, 57, 603–619.

allows their functionalization, by which different heteroatoms can be introduced onto the carbon surface. Among the different heteroatoms that can be integrated, oxygen is the most frequent one, in terms of uses. Surface oxygen-containing functionalities include carboxylic acids, carbonyl groups, phenols and lactones that were created via oxidative treatment employing oxygen (air or ozone) and nitric acid, ammonium persulfate and hydrogen peroxide aqueous solutions.⁷⁴ The functionalization of carbon materials by heteroatoms allows their subsequent use as support to various molecules by covalent tethering.

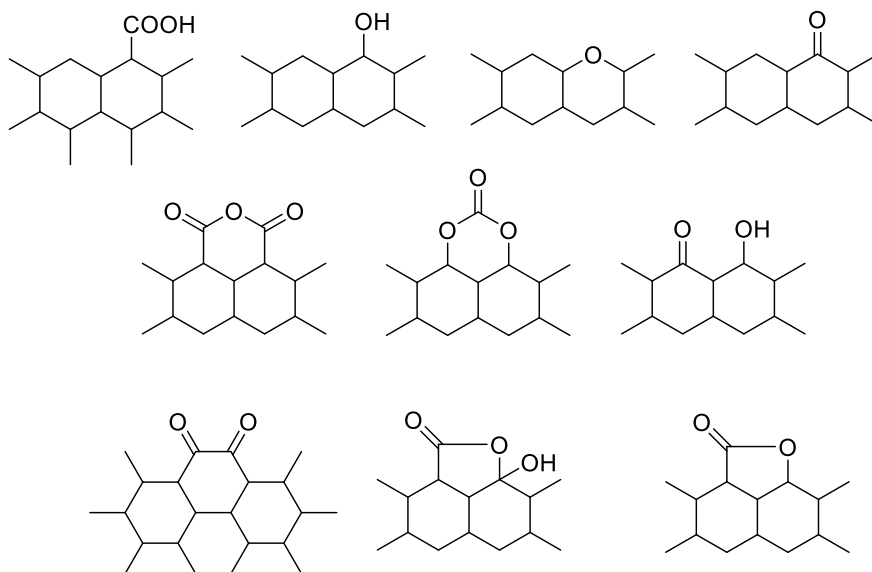


Figure 31: Different oxygen functionalities on the surface of carbon materials.

2. Suitability for supporting various catalysts

The particular characteristics that carbon materials possess satisfy most of the necessary conditions for a suitable catalyst support. Except their limitation to be used at high temperature ($T > 500$ K) which caused their gasification, several advantageous properties such as the chemical inertness, the mechanical resistance, the high surface area with optimum porosity and the suitable surface chemistry made these materials a very good choice to immobilize catalysts. Moreover, it should be noted that all these characteristics and especially the shape of the material and its surface chemistry have a strong influence on the catalyst activity, and they are a keystone for the design of interactions between catalyst and support.

⁷⁴ C. Moreno-Castilla, F. Carrasco-Marín, A. Mueden, *Carbon* **1997**, 35,1619–1626.

Several carbon materials have been used as supports to immobilize catalysts such as carbon black, activated carbon, graphite, carbon nanotubes, fullerene, and graphene derivatives. However, high surface area activated carbon and carbon black, together with graphite and graphitized material, have been the carbon materials of choice for most industrial carbon-supported catalysts.⁷⁵ Activated carbon has been, as well, the most used carbon support in research.⁷⁶ Recently, carbon nanotubes and carbon nanofibers are being also extensively used as catalysts supports in many research works.⁷⁷

The immobilization of catalysts onto the surface of carbon materials can be achieved via covalent tethering or non-covalent attachment thanks to different non-covalent interactions such as electrostatic and π -stacking interactions or also via supported liquid phase procedures.

3. Graphitic surfaces and immobilization

Graphite is a crystalline form of carbon element, and it consists of layers of graphene, interconnected for some of them. Graphene is a two-dimensional sp^2 -hybrid carbon, in a single-atom-thick sheet, combined in a honeycomb pattern. It is the thinnest, strongest, and most rigid material in the world, as well as an excellent conductor of both heat and electricity. Due to its wide important applications, this material is more promising than other nanostructured carbon allotropes. Graphene oxide (GO) and reduced graphene oxide (rGO) are derivatives of graphene. GO is obtained by an oxidizing treatment of graphite while rGO is prepared via a reduction treatment of GO. Reduced graphene oxide is cheaper than graphene with similar properties due to the presence of only small amounts of oxygen atoms. Hence, rGO shows high conductivity, stability, and the presence of defective sites which are chemically active making it a potential candidate in the application as an active material in biosensors.⁷⁸ Moreover, in addition to its ability to covalently attach molecules after a functionalization procedure, its sp^2 -hybridized surface make it an excellent electron-donor material allowing to perform π -type non-covalent interactions with specific compounds.

⁷⁵ E. Auer, A. Freund, J. Pietsch, T. Tacke, *Appl. Catal. A.* **1998**, *173*, 259–271

⁷⁶ V. Clavino-Casilda, A.J. López-Peinado, C. Durán-Valle, R.M. Martín-Aranda, *Chem. Rev.* **2011**, *52*, 325–386.

⁷⁷ P. Serp, M. Corrias, P. Kalck, *Appl. Catal. A.* **2003**, *253*, 337–358.

⁷⁸ J.T. Robinson, F.K. Perkins, E.S. Snow, Z. Wei, P.E. Sheehan, *Nano. Lett.* **2008**, *8*, 3137–3140

a) *Covalently immobilized catalysts*

Various organometallic complexes have been covalently immobilized onto the surface of different carbon materials after the pre-functionalization step via radical, cycloaddition or nucleophilic addition reactions.⁷⁹ Carbon nanotubes and fullerene are often used for this type of immobilization.

In this context, iron(III) porphyrin complexes have been immobilized onto the surface of pre-functionalized organosilylated multi-walled carbon nanotubes (MWCNT).⁸⁰ A quaternization reaction between the dimethylamine-tetrafluorophenyl groups of the metalloporphyrin and the bromoalkyl moieties attached on the nanotubes surface under microwave heating is responsible for the covalent tethering of the catalyst (Figure 32). The corresponding heterogeneous catalyst was characterized by XPS, TGA, FTIR, and XRD and it was tested in the epoxidation of *cis*-cyclooctene in the presence of hydrogen peroxide at room temperature. Almost complete conversion was obtained, and the catalyst was reused efficiently for three runs.

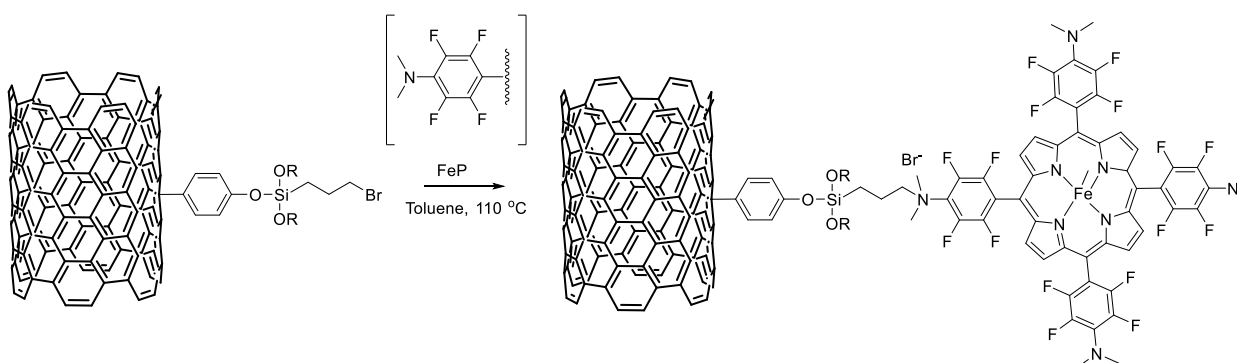


Figure 32: Fe(III) porphyrin complex immobilized onto MWCNT.

Moreover, Riant and coworkers⁸¹ reported the covalent immobilization of a gold complex [Tf₂NAuPPh₃CH₂NH₂] with an amine pendant group to the surface of modified MWCNT. The resulting catalyst showed better activity than the homogeneous analogue in the cyclization reaction of 1,6 enynes but with the same selectivity. The supported catalyst was recycled by filtration and reused for 6 runs with no significant loss of activity.

⁷⁹ A. Schaetz, M. Zeltner, W. J. Stark, *ACS Catal.* **2012**, 2, 1267–1284.

⁸⁰ M. Lipińska, S.H. Rebelo, C. Freire J. *Mater. Sci.* **2014**, 49, 1494–1505.

⁸¹ C. Vriamont, M. Devillers, O. Riant, S. Hermans, *Chem. Commun.* **2013**, 49, 10504–10506.

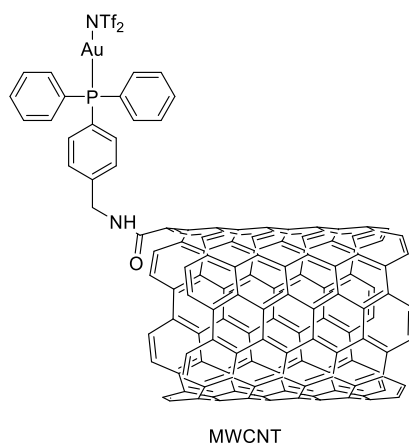


Figure 33: Gold complex immobilized onto the surface of MWCNT.

b) Non-covalently immobilized catalysts

As mentioned before, there are different ways to non-covalently immobilize catalysts on carbon materials. π - π interactions can take place between polyaromatic functions of a coordination compound with the graphitic sp^2 carbon network of carbon nanotubes or graphene. Such immobilization is usually carried out by solution mixing (stirring of a suspension/solution of the support and the complex, eventually upon sonication) or impregnation in the appropriate solvent, generally a polar one. Pyrene has been widely used as an efficient polyaromatic moiety to perform π - π stacking with CNTs, graphene or activated carbon (AC), allowing efficient immobilization of a wide range of chemical entities such as catalysts.

In this context, Peris *et al.*⁸² reported the synthesis of pyrene-tagged *N*-heterocyclic carbene complexes of rhodium (I) on reduced graphene oxide (Figure 34). The immobilization of both monometallic and bimetallic species was achieved by mixing catalysts with the support powder in dichloromethane DCM, and the mixture was further sonicated and stirred for 12 h. The exact amount of complex supported was determined by ICP-MS analysis (0.9% wt Rh for the monometallic and 1.11% wt Rh for the bimetallic complex). The supported catalysts were tested in the 1,4-addition of phenylboronic acid to cyclohex-2-one, and in the hydrosilylation of terminal alkynes. In both reactions, the bimetallic complex showed better activity and it was recovered for 5 runs in the 1,4-addition of phenylboronic acid to cyclohex-2-one without any loss of activity while a loss of activity was observed in the heterogeneous hydrosilylation of terminal alkynes.

⁸² S. Ruiz-Botella, E. Peris, *ChemCatChem* **2018**, *10*, 1874–1881.

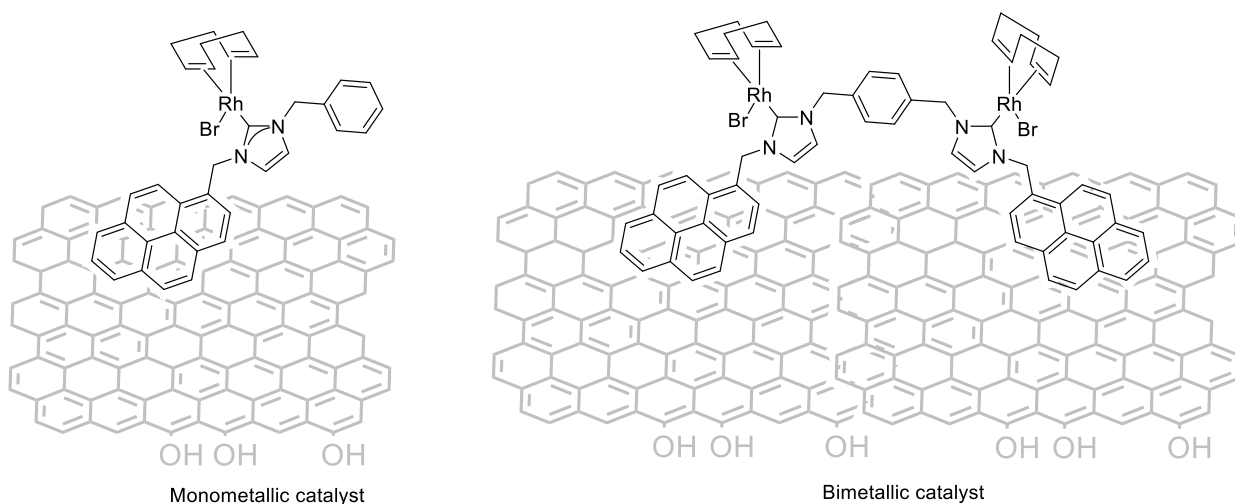


Figure 34: Pyrene-tagged *N*-heterocyclic carbene complexes of rhodium (I) on reduced graphene oxide.

Similarly, the co-immobilization of pyrene-tagged *N*-heterocyclic palladium and ruthenium complexes onto rGO was reported.⁸³ The immobilization was performed by mixing the molecular homogeneous complexes with the solid support powder in DCM and sonicating for 30 minutes followed by a stirring of the mixture for additional 10 h. The supported catalyst was characterized by UV-Vis, IR, AFM, and HRTEM analyses and the exact amount of supported palladium and ruthenium metals was determined using ICP-MS analysis. The obtained heterogeneous catalyst demonstrated a high efficiency in catalysing the hydrodefluorination reaction of a series of fluoroarenes, where the heterogeneous supported catalyst containing the two complexes outperformed the monometallic supported and the homogeneous analogues. This is an excellent example on the possible cooperativity between two supported catalysts even if it is not evident to know the exact distance between them. It was recovered by filtration and reused for 12 subsequent runs without any loss in activity.

⁸³ S. Sabater, J. A. Mata, E. Peris, *Organometallics* **2015**, *34*, 1186–1190.

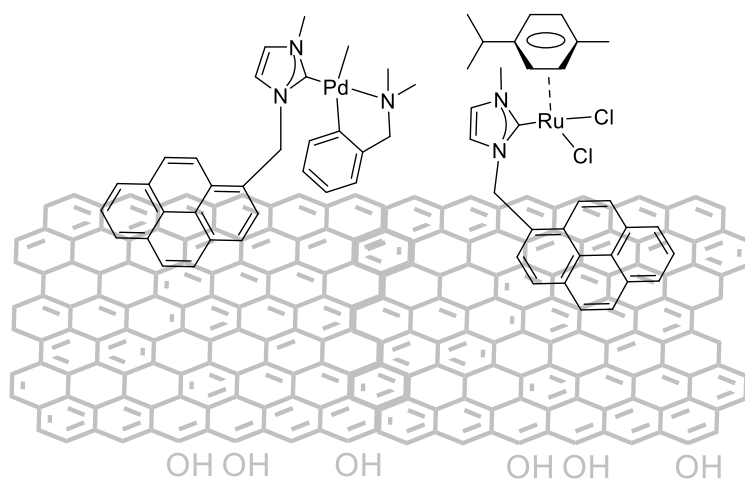


Figure 35: Pyrene-tagged NHC complexes of Pd and Ru co-immobilized onto rGO.

On the other hand, Perez *et al.*⁸⁴ prepared a *N*-heterocyclic carbene ligand modified with a pyrene group. After reacting the ligand with CuBr in a basic medium, the corresponding copper complex was immobilized onto rGO. The immobilization was done following the same procedure described in the previous example and confirmed using HRTEM, XPS, UV/Vis, and ICP/MS analyses. The supported catalyst displayed higher reaction rates and included higher yields than the soluble analogue in the functionalization of hydrocarbons such as *n*hexane, cyclohexane, and benzene by C-H insertion through incorporation of the CHCO₂Et unit from ethyl diazoacetate and could be reused for 3 runs. This improved activity could be explained by the increased electrophilicity of the metal center due to the electron flux induced by the support. This electronic effect was also observed by other groups which demonstrated that the substituents at the pyrene ring leads to a variation in the conductivity at graphene due to the electron transfer from or to pyrene.⁸⁵

Moreover, some of us prepared anthracene- and pyrene-tagged bis(oxazoline) ligands and immobilized them on charcoal, fullerene, and single-walled carbon nanotubes (SWCNT) through π - π interactions.^{14,b} The corresponding copper complexes have been used to promote heterogeneous asymmetric Henry and ene reactions (Figure 36). The best results, in terms of activity, selectivity, and stability toward the recycling procedure have been obtained with the pyrene/SWCNT system affording the desired products in high yield and good enantioselectivity. The catalysts were efficiently reused for 7 runs with no loss in catalytic activity and selectivity.

⁸⁴ P. Ballestin, D. Ventura-Espinosa, S. Martín, A. Caballero, J. A. Mata, P. J. Pérez *Chem. Eur. J.* **2019**, *25*, 9534–9539.

⁸⁵ J. Lee, E. Hwang, E. Lee, S. Seo, H. Lee, *Chem. Eur. J.* **2012**, *18*, 5155–5159.

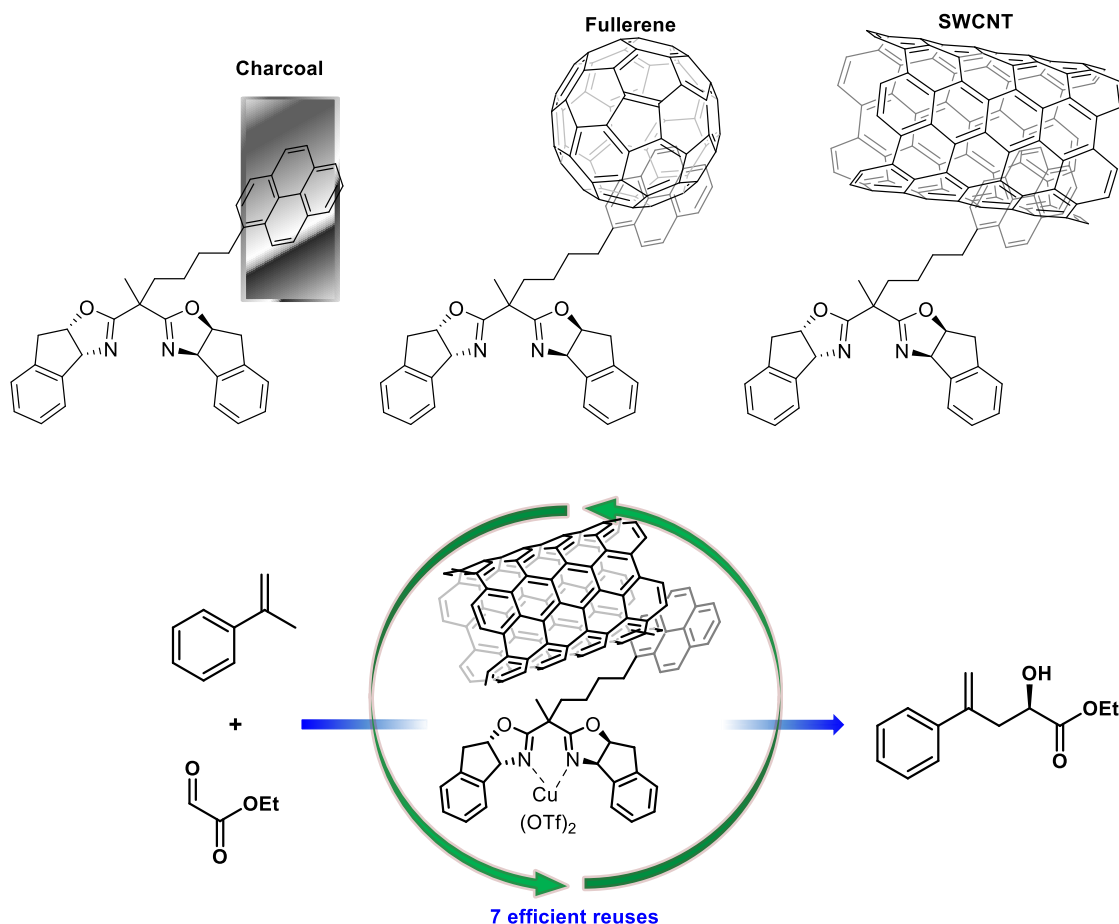


Figure 36: Pyrene-tagged bis(oxazoline) ligands immobilized on charcoal, fullerene and SWCNT.

Besides, some of us also prepared a Hoveyda-type ruthenium complex tagged to pyrene moieties on the NHC ligand and/or the benzylidene group.^{14,a} These complexes were successfully immobilized onto rGO and graphene and were used in metathesis reactions. The best result was obtained with the complex tagged to pyrene via the benzylidene moiety and supported to rGO. It was easily recovered by filtration and reused for five runs with an unavoidable loss of activity after the 4th run. Interestingly, the addition of pyrene-tagged styrenylether as supplementary ligand immobilized on rGO resulted in an important improvement of the catalytic results. This was suggested to a facilitated boomerang effect to stabilize the active ruthenium species from the solution, made possible by an increased concentration of benzylidene ligands on the support. Moreover, the same batch of supported catalyst/ligand was used to promote a multi-substrate process to transform different substrates in diene and ene-yne ring closing metathesis and it was reused for 4 runs.

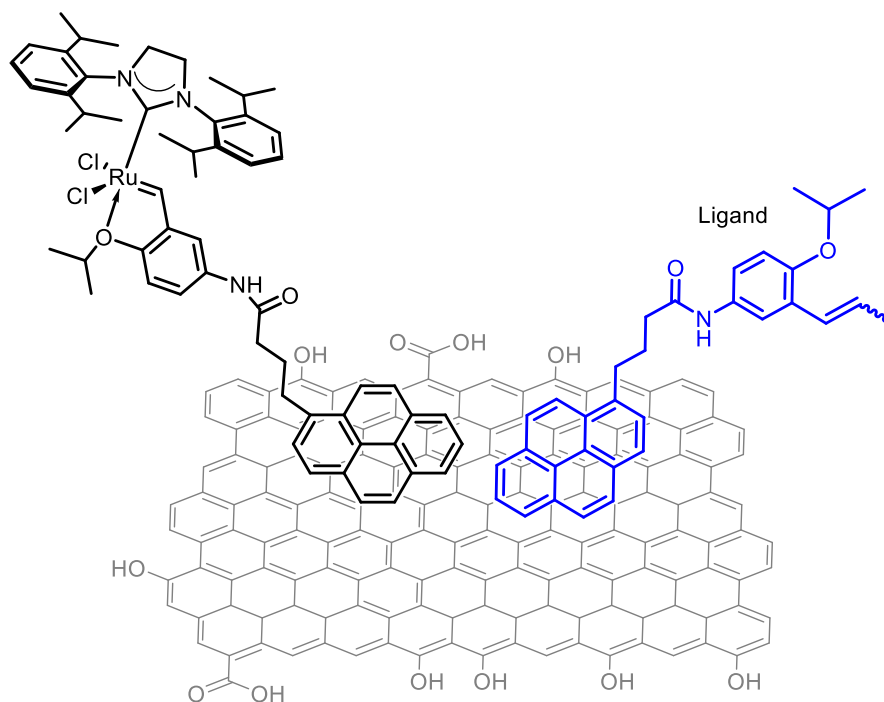


Figure 37: Co-immobilization of pyrene-tagged ligand and pyrene-tagged NHC based ruthenium complex onto rGO.

All the examples mentioned, illustrate the immobilization of organometallic catalysts via π - π interactions between pyrene groups linked to the ligand and the carbon material. Examples on the immobilisation of chiral catalysts via π - π interactions to carbon supports is scarce and such heterogenization method was never developed and used with chiral salen complexes. On the basis of the advantageous properties of carbon materials and the reversible efficient π - π interactions taken place between pyrene groups and graphitic surfaces, we aim in this PhD work to evaluate this immobilization method with chiral salen complexes and explore the effects of the required modifications and the presence of support on their catalytic properties in various asymmetric transformations. Therefore, the description of the synthesis of a novel pyrene-tagged salen derivatives and their immobilization will be detailed in the next chapter.

Chapter 2: Synthesis and Immobilization of Chromium and Manganese Salen Complexes



II. Chapter 2: Synthesis and Immobilization of Chromium and Manganese Salen Complexes

Introduction

The term salen is generally used to describe primarily bis-Schiff bases ligands derived from the condensation of salicylaldehyde derivatives with diamines. Enantiopure salen ligands are mostly obtained by incorporating enantiopure diamines. These C_2 -symmetric species tetradentate species are considered as privileged ligands which can coordinate various metals and thus promote asymmetric catalytic transformations leading to the preparation of scalemic synthons of great importance in pharmaceutical field.⁸

The heterogenization of such precious homogeneous enantiopure catalysts represents an ideal solution to recover them while maintaining as possible their high activity and selectivity.⁶ Among the different strategies developed to immobilize organometallic compounds that were described in the previous chapter, the use of noncovalent interactions to build the link between the ligand and the support is very interesting requiring in most cases simple modifications and allowing to control the location of the catalysts and their proximity.¹⁷

Carbon materials emerged as a useful support thanks to their valuable characteristics: chemical inertness, mechanical resistance, thermal stability, high surface area, optimum porosity, and suitable surface chemistry.⁷⁹ This latter allows their functionalization to perform covalent tethering or noncovalent bonding through π -type interactions with various aromatic molecules. Due to the inherent capability of pyrene, as polyaromatic compound, to stack onto the surface of graphitic surfaces through π -stacking interactions,⁸⁶ pyrene-tagged metal complexes have been efficiently supported to graphitized solids and some have been used in catalysis showing an interesting effect on catalytic activity.

Despite all the heterogenization methods reported to immobilize salen complexes, including their covalent grafting and non-covalent attachment, to the best of our knowledge, no examples describing their immobilization onto graphitic surfaces via π -stacking interactions can be found for instance. Furthermore, giving the wide versatility of these catalysts, efforts to promote multicatalysis processes

⁸⁶ a) L. Rodriguez-Perez, M. Angeles Herranz, N. Martin, *Chem. Commun.* **2013**, 49, 3721–3735. b) V. Georgakilas, M. Otyepka, A. B. Bourlinos, V. Chandra, N. Kim, K. C. Kemp, P. Hobza, R. Zboril and K. S. Kim, *Chem. Rev.* **2012**, 112, 6156–6214.

which include the use of different metal complexes to promote cooperative and tandem reactions are very appreciated. This type of catalysis presents an efficient way allowing to respect the atomic economy concept, to reduce the chemical wastes and promoting various catalytic transformations in a single pot without transient tedious purifications, or using flow procedures. Immobilizing different metal complexes via π -stacking interactions on graphitic materials is one of the important ways to perform mult catalysis processes, that we aim to explore.

Based on all the concepts mentioned above, we describe in this chapter the synthesis of mono and bis pyrene-tagged salen ligands, the preparation of the corresponding chromium and manganese salen complexes. These specific metallic derivatives have been chosen to promote the asymmetric ring opening reaction (ARO) of *meso*-epoxides and the hetero-Diels-Alder reaction (HDA) of various aldehydes but also the asymmetric epoxidation of alkenes. Their immobilization onto the surface of reduced graphene oxide (rGO) will also be reported. This chapter will be divided into two main parts: the complexes synthesis and their immobilization.

A. Synthesis of pyrene-tagged salen complexes

1. Synthesis by classical condensation strategy

Chiral symmetrical salen ligands are obtained from a condensation reaction between two equivalents of a salicylaldehyde derivative and an enantiopure 1,2-diamine. Structurally modified salen ligands can thus easily be obtained by performing modifications on the aldehyde and/or the diamine backbones.

In our project, the structural modifications to obtain a new generation of modified salen complexes are performed on the salicylaldehyde by introducing the pyrene moiety in the *para* position of the phenol group, and then preparing the pyrene-tagged salen with enantiopure (*S,S*)-1,2-cyclohexanediamine. This diamine has been chosen since it is used conventionally to prepare salen ligands, leading to highly efficient complexes. The *tert*-butyl group in the *ortho* position of the phenol moieties are maintained to keep the hindrance.

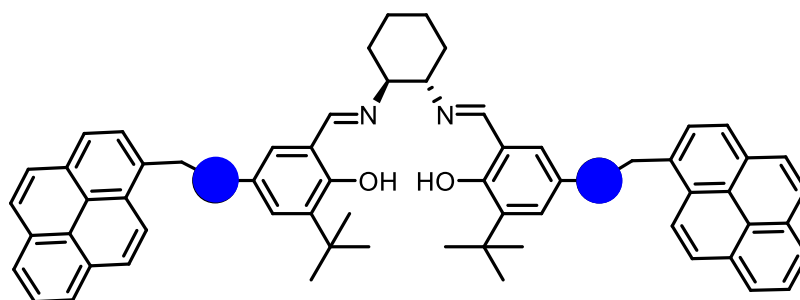


Figure 38: General structure of symmetrical pyrene-tagged salen ligands.

In our first attempt, the pyrene moiety has been introduced through a nucleophilic substitution of prepared 3-(*tert*-butyl)-5-(chloromethyl)-2-hydroxybenzaldehyde **1** with commercially available 1-pyrenebutanol in basic medium. Despite the series of reactions tested to optimize the conditions of the substitution, the formation of a by-product, a methylene bisphenyl derivative, is unavoidable (Figure 39). This side reaction decreased the formation yield of the desired salicylaldehyde and consequently, the total isolated yield of pyrene-tagged salen complexes. The appearance of this by-product, that we called dimer, in our reaction conditions was unexpected because such methylenebisphenol derivatives have always been obtained in acidic conditions, through a Friedel-Craft type alkylation starting from activated phenyl rings and chloromethylated salicylaldehydes.⁸⁷

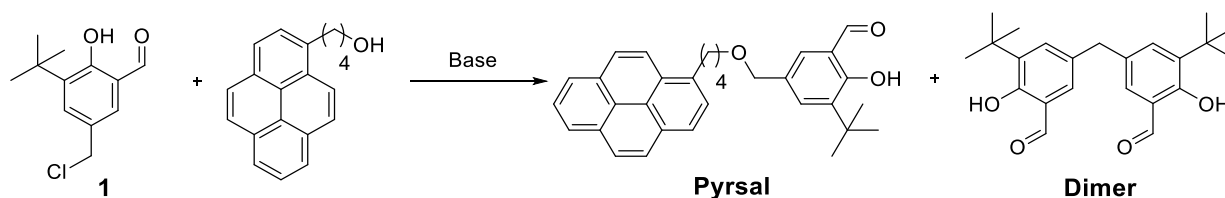


Figure 39: Substitution reaction with pyrene butanol and formation of dimer.

Results of all the tested reactions are given in Table 1. No reaction occurred when NaHCO_3 was used as base in THF (Entry 1). The dimer was obtained as main product with respect to the desired Pyrsal when potassium carbonate was engaged in polar non protic solvents such as DMF or ACN at 75 °C (entries 2, 3 and 4).

The best result leading to the target Pyrsal product (67 % NMR yield) was obtained using NaH (2.2 equiv) as base in THF at room temperature.

⁸⁷ S. Guieu, J. Rocha, A. M. S. Silva, *Synlett* **2013**, 24, 762–764.

Table 1: Optimization of Pyrsal formation reaction

Entry	1: pyrenebutanol (equiv)	Base (equiv)	Solvent	T (°C)	NMR yield (pyrsal:dimer) (%)
1	1:1.2	NaHCO ₃ (4)	THF	25	No reaction
2	1:1.3	K ₂ CO ₃ (5)	DMF	75	23:77
3	1:1.3	K ₂ CO ₃ (5)	ACN	75	44:56
4	1:1.2	K ₂ CO ₃ (3.3)	ACN	75	50:50
5	1.2:1	NaH (2.2)	THF	25	67:33

Due to the lack of time, we were not able to study the mechanism implied in the formation of this dimer in basic conditions. However, this seems like a very interesting subject that our lab will develop further in order to uncover this previously unknown reactivity.

In order to avoid the formation of the unexpected dimer and to enhance the yield formation of salen ligands, a new synthetic strategy was proposed based on the use of click chemistry to connect the pyrene group to the salicylaldehyde moiety.

To achieve this mission, we synthesized first the click reaction partners, then the pyrene-tagged aldehydes and finally the ligands. Pyrene butanol and pyrene methanol were used as pyrene group precursors. Following this synthetic strategy with both pyrene alcohols, it has been possible to study the effect of the spacer length on the performance of the complexes in catalysis. Furthermore, to evaluate the effect of the presence of the pyrene moiety, symmetrical ligands with two pyrene groups as unsymmetrical ones bearing only one pyrene group have been prepared. Consequently, a comparison of the catalytic reactivity of both symmetrical and unsymmetrical complexes will be evaluated. In addition, the effect of the pyrene moiety on the immobilization as recycling abilities of both catalysts will be studied.

The synthesis of all the precursors, ligands and complexes is described in this part.

2. Synthesis by click chemistry strategy

a) Click chemistry: generality

The concept of Click chemistry was introduced for the first time by Sharpless⁸⁸ and referred to a set of highly efficient, reliable, and stereoselective reactions that can be used to develop promising constructs using facile reaction conditions and easily available starting materials.⁸⁹ Click reactions can be classified in four different types: cycloaddition, nucleophilic substitution, carbonyl condensation and addition reactions. Thanks to its characteristics, respecting the fundamental principles of biorthogonal chemistry, click chemistry found a huge importance in the field of medicinal chemistry and drug discovery.^{90,91}

Cycloaddition reactions include the 1,3-dipolar cycloaddition and the hetero-Diels-Alder reactions.

The 1,3-dipolar cycloaddition between an azide and a terminal alkyne known as the cycloaddition of Huisgen,⁹¹ is a relatively slow reaction which requires elevated temperatures and often produces a mixture of 1,4-disubstituted and 1,5-disubstituted triazolic regioisomers in a 1:1 ratio approximately (Figure 40).⁹²

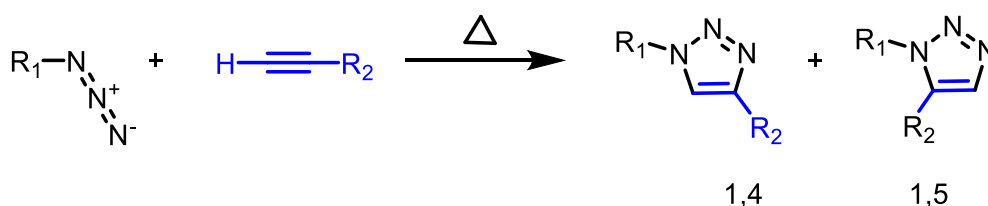


Figure 40: Thermal 1,3-cycloaddition of Huisgen

The copper(I)-catalysed 1,3-dipolar cycloaddition, discovered by Rostovtsev *et al.*,⁹² represents a very efficient alternative reaction to couple azides and terminal alkynes. This type of reaction can indeed be carried out at room temperature using a Cu(I) catalyst and leads to the unique formation of the 1,4-disubstituted triazole. Conversely, Ru(II) complexes are recently known as efficient catalysts catalysing this cycloaddition and regioselectively leading to the formation of the 1,5-disubstituted 1,2,3-triazoles, the opposite regioisomer.⁹³

⁸⁸ H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

⁸⁹ J. Kaur, M. Saxena, N. Rishi, *Bioconjugate Chem.* **2021**. <https://doi.org/10.1021/acs.bioconjchem.1c00247>.

⁹⁰ A. Rani, G. Singh, A. Singh, U. Maqbool, G. Kaur, J. Singh, *RSC Adv.* **2020**, *10*, 5610–5635.

⁹¹ R. Huisgen, *Proc. Chem. Soc.* **1961**, 357–396.

⁹² V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–22599.

⁹³ B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930.

1,2,3-Triazole rings are of great importance as preferred pharmacophores in medicinal chemistry and in the drug design of bioactive molecules analogues because of their ability to mimic different functional groups; they are thus often used as bioisosteres for the synthesis of new active molecules with various pharmaceutical applications.⁹⁰ The CuAAC (Copper catalyzed Azide Alkyne Cycloaddition) represents therefore one of the mostly used reactions to couple organic synthons and is of major acceptance in drug discovery.

The mandatory copper(I) catalyst can arise from various sources. The most regular catalytic system involves the use of copper sulfate together with a reducing agent such as sodium ascorbate or metallic Cu,⁹⁴ and tolerates toward aqueous medium and several solvent mixtures. An alternative way is the direct use of Cu(I) salts such as copper(I) bromide, copper(I) iodide, or copper(I) trifluoromethanesulfonate under inert atmosphere to avoid copper oxidation. Furthermore, nitrogen-based ligands and organic solvents have been used to stabilize the copper(I) state of the catalyst.⁹⁵

The mechanism of the CuAAC was first proposed by Sharpless and Fokin⁹⁶ involving only one copper unit to achieve the cycloaddition and consisting of the π -coordination of the alkyne to the copper centre in the first step; after deprotonation a copper(I) acetylide is formed. The azide moiety is further coordinated with departure of a ligand. Then a six-centre metallacycle with a copper(III) member is formed. Finally, the 1,4-disubstituted triazole cycle is obtained by reductive elimination and released by protolysis with copper(I) catalyst regeneration.

The mechanism of this 1,3 dipolar cycloaddition was widely studied and reported. Recently, it was proved that the mechanism requires the cooperation of two copper atoms working in concert. In this context, Fokin *et al.*⁹⁷ proposed the following mechanism (Figure 41): first, the σ -bound copper acetylide bearing the π -bound enriched copper atom reversibly coordinates an organic azide. In the formed complex, a nucleophilic attack at the N-3 of the azide by the β -carbon of the acetylide forms the first covalent C-N bond. A ligand exchange between two copper atoms results in a ring closure, the second copper atom acting as a stabilizing donor ligand to the otherwise highly energetic and unstable mononuclear metallacycle intermediate. Ring contraction to a triazolyl-copper derivative is followed by protonolysis that delivers the triazole product and closes the catalytic cycle.

⁹⁴ C. Spiteri, J. E. Moses, *Angew. Chem. Int. Ed.* **2010**, *49*, 31–33.

⁹⁵ C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064.

⁹⁶ F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210–216.

⁹⁷ B. T. Worell, J. A. Malik, V. V. Fokin, *Science*, **2013**, *340*, 457–460.

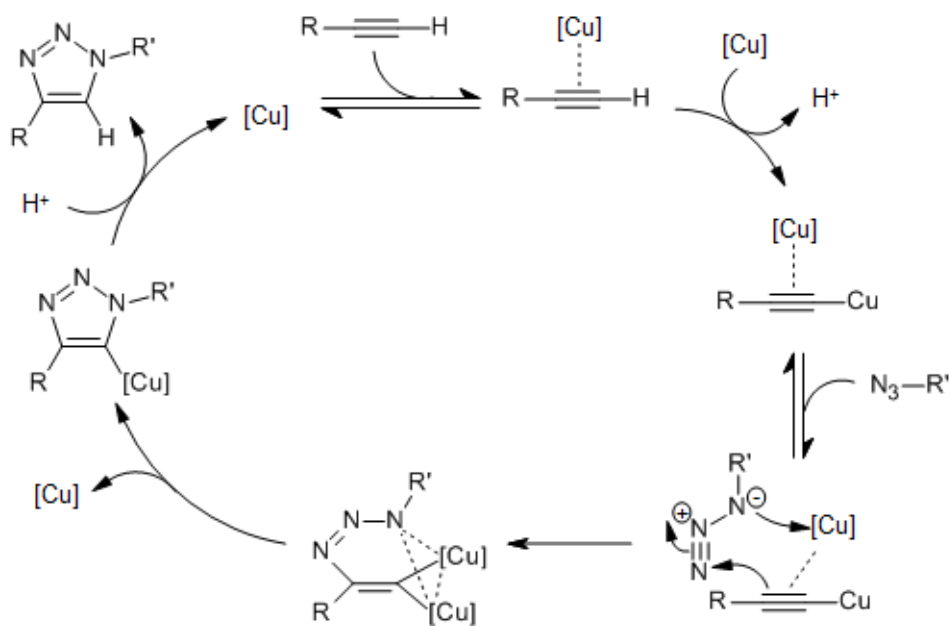


Figure 41: Proposed mechanism for CuAAC reaction.

b) Application to the synthesis of pyrene-tagged salen ligands

Accordingly, in our project we aim to use the CuAAC reaction to connect the pyrene moiety to the salicylaldehyde before its condensation with the diamine to prepare new modified salen complexes able to be immobilized onto the surface of reduced graphene oxide thanks to π -stacking interactions between pyrene groups and the carbon surface.

(1) Synthesis of aldehyde moiety

(a) Synthesis of 3-(*tert*-butyl)-5-(chloromethyl)-2-hydroxybenzaldehyde

The first step is the synthesis of 3-(*tert*-butyl)-5-(chloromethyl)-2-hydroxybenzaldehyde. Following the procedure described by Chen *et al.*,⁹⁸ the aldehyde **1** is obtained from a chloromethylation reaction between the commercially available 3-(*tert*-butyl)-2-hydroxybenzaldehyde and 1,3,5 trioxane (2.5 equiv) in the presence of an excess of hydrochloric acid HCl (37%). The reaction mixture is stirred for 2 days at 55 °C. After a quenching step with a saturated solution of sodium bicarbonate NaHCO₃ and several washings with diethyl ether, the desired chloromethyl salicylaldehyde is obtained in 89% yield without further purification.

⁹⁸ S. B. Salunke, N. S. Babu, C. T. Chen, *Adv. Synth. Catal.* **2011**, 353, 1234–1240

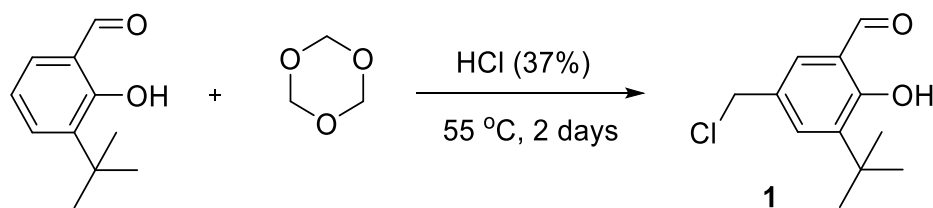


Figure 42: Synthesis of 3-(tert-butyl)-5-(chloromethyl)-2-hydroxybenzaldehyde **1**.

(b) Synthesis of 5-(azidomethyl)-3-(tert-butyl)-2-hydroxybenzaldehyde

The first partner of the click reaction is the salicylaldehyde bearing the azide group. It was prepared via a nucleophilic substitution reaction of the chloride in aldehyde **1** with an azide group, in the presence of sodium azide (1.1 equiv) in DMF at room temperature for 24 hours.⁹⁹ The 5-(azidomethyl)-3-(tert-butyl)-2-hydroxybenzaldehyde **2** was obtained as a brown oil with 71% yield.

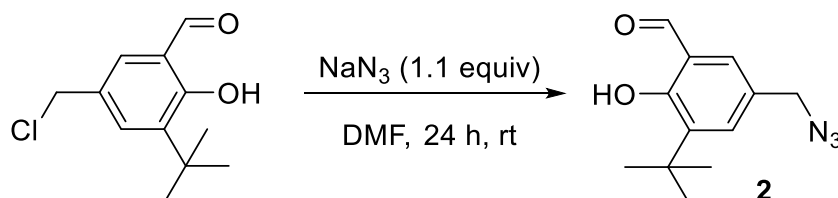


Figure 43: Synthesis of 5-(azidomethyl)-3-(tert-butyl)-2-hydroxybenzaldehyde.

(2) Synthesis of pyrene partners for click chemistry

(a) Synthesis of 1-((prop-2-yn-1-yloxy)methyl)pyrene

The pyrene-tagged alkyne **3** was first prepared following the procedure of Chen *et al.*¹⁰⁰ by reacting the pyrene methanol with propargyl bromide (1.2 equiv) in the presence of sodium hydride NaH (1.2 equiv) in acetonitrile at 70 °C. This nucleophilic substitution gave the desired product with 65% yield. A complete conversion has been obtained by increasing the amount of base and using THF as solvent at room temperature.¹⁰¹ Under these conditions, the alkyne was obtained as a brown powder in quantitative yield after a simple trituration in pentane (Table 2).

⁹⁹ C. G. Arellano, A. Corma, M. Iglesias, F. Sánchez, *Adv. Synth. Catal.* **2004**, 346, 1316–1328.

¹⁰⁰ K.-H. Chen, C. Y. Lu, H. J. Cheng, S. J. Chen, C. H. Hu, A. T. Wu, *Carbohydr. Res.* **2010**, 345, 2557–2561.

¹⁰¹ J. M. Lobe, T. M. Swager, *Angew. Chem. Int. Ed.* **2010**, 49, 95–98.

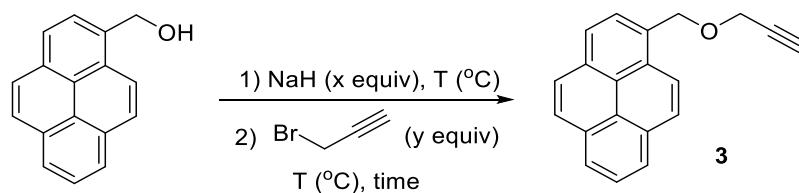


Table 2: Synthesis of 1-((prop-2-yn-1-yloxy)methyl)pyrene.

Entry	NaH (x equiv)	Solvent	Propargyl bromide (y equiv)	T °C	Time (h)	Yield (%)
1	1.2	CH ₃ CN	1.2	70	18	65 ^a
2	1.9	THF	2	0 then rt*	15	99 ^b

* Base and propargyl bromide are added at 0 °C. [a] isolated product with CC. [b] without CC.

(b) Synthesis of 1-(4-(prop-2-yn-1-yloxy)butyl)pyrene

Same procedures have been applied to synthesize the pyrene-tagged alkyne derived from pyrene butanol. Only 50% of conversion were obtained by performing the first method (Entry 1, Table 3), while the second yielded the isolated product as a brown powder in 69% yield (Entry 2, Table 3).

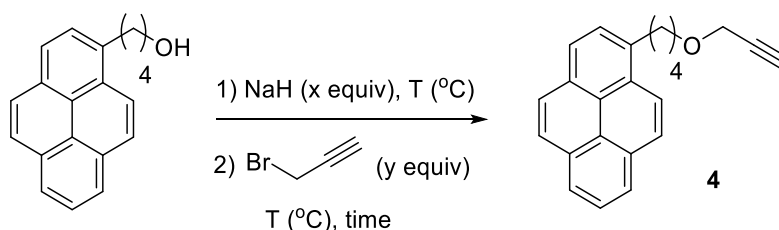


Table 3: Synthesis of 1-(4-(prop-2-yn-1-yloxy)butyl)pyrene.

Entry	NaH (x equiv)	Solvent	Propargyl bromide (y equiv)	T °C	Time (h)	Yield (%)
1	1.2	CH ₃ CN	1.2	70	18	50 ^a
2	1.9	THF	2	0 then rt*	15	69 ^b

* Base and propargyl bromide are added at 0 °C. [a] NMR conversion. [b] isolated yield with CC.

Finally, the two pyrene-tagged alkynes **3** and **4** were obtained in good yields even though their preparation was not optimized further, and they are ready to click with the azido-aldehyde **2**.

(3) Synthesis of pyrene-tagged salicylaldehyde via click reaction

Various methods have been tested to create the triazole moiety between the synthesized pyrene-tagged alkynes and the azido-aldehyde.

First, copper sulfate pentahydrate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$) and sodium ascorbate were used as a mixture to generate a copper(I) source, to promote the click reaction between alkyne **4** and azido aldehyde **2**. The reaction takes place under an argon atmosphere in a biphasic medium; the aqueous solution of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ /sodium ascorbate (0.3/0.9) was added to the click reactants which are soluble in DCM. The reaction mixture becomes green after a vigorous stirring at room temperature for 2 days. This method was not efficient to couple the click partners and gave the desired product in only 19% yield after a purification step by column chromatography (Entry 1; Table 4).

In a second attempt, an *N*-heterocyclic carbene copper(I) complex was tested to promote the same cycloaddition reaction. For this reason, (1,3-dimesityl-2,3-dihydro-1*H*-imidazol-2-yl)copper(I) bromide was prepared starting from commercially available 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride in two steps (Figure 44), and further used in a 30 mol% amount to catalyse the CuAAC between compounds **2** and **4** (Entry 2; Table 4).

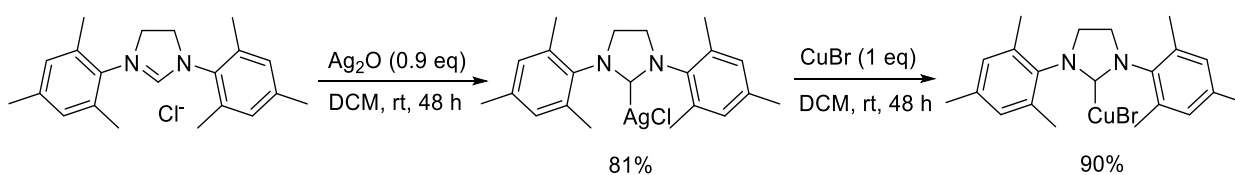


Figure 44: Synthesis of Cu(I)-NHC for CuAAC reaction.

The reaction was carried out in DCM and allowed to stir at room temperature for 2 days. The solution, initially yellow coloured, became green proving the presence of copper(II) ions in the medium. Only 32% of the desired isolated product was obtained by using this procedure.

Hence, other copper(I) salts such as copper bromide CuBr and copper iodide CuI were tested (entries 3 and 4; Table 4) with the reaction performed in degassed solvents and under strict argon atmosphere. The best result leading to a complete conversion was obtained by using CuI (5 mol%) in the presence of *N,N*-diisopropylethylamine DIPEA (3.5 equiv) in THF at 40 °C for 16 hours. Residual copper(II) salts were removed by washing the crude product with an EDTA (0.05 M in water) solution. The pyrene-tagged salicylaldehyde derived from pyrene butanol was thus isolated in 85% yield as a brown powder.

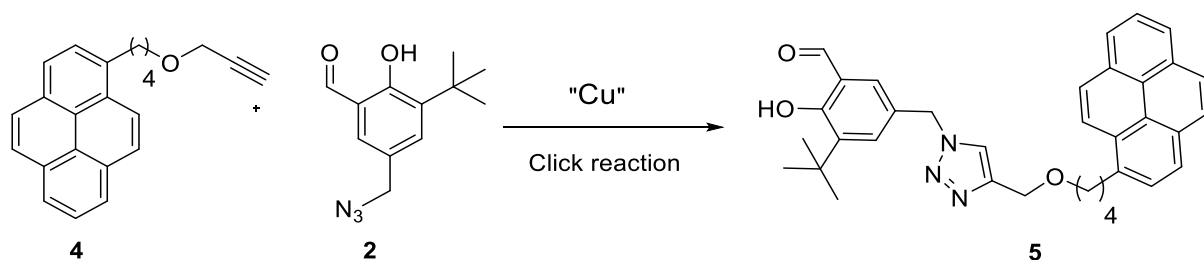
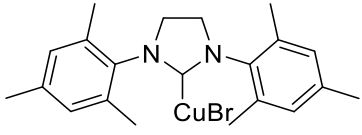


Table 4: Click reaction between pyrene butanol derived alkyne and azido-aldehyde

Entry	Cu source	Solvent	T (°C)	Time (h)	Yield (%)
1	CuSO ₄ ·5H ₂ O/sodium ascorbate (0.3/0.9)	DCM/ H ₂ O	rt	48	19
2	 30 mol%	DCM	rt	48	32
3	CuBr (15 mol%)	THF	40	36	65
4	CuI (5 mol%) DIPEA (3.5 equiv)	THF	40	16	85

Based on these results, the click product **6** implying the other alkyne **3** was obtained in 56% yield with CuBr while an enhanced yield of 86% was obtained by using CuI in the presence of DIPEA.

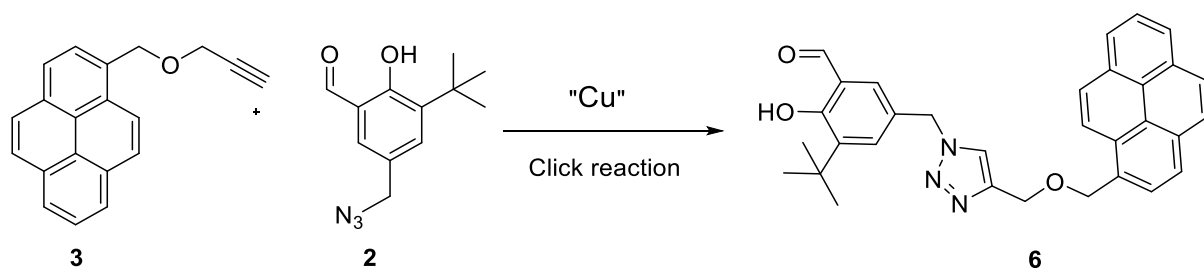


Table 5: Click reaction between pyrene methanol derived alkyne and azido-aldehyde.

Entry	Cu source	Solvent	T (°C)	Time (h)	Yield (%)
1	CuBr (15 mol%)	THF	40	36	56
2	CuI (5 mol%) DIPEA (3.5 equiv)	THF	40	16	86

(4) Synthesis of symmetrical pyrene-tagged ligands

The two symmetrical pyrene-tagged salen ligands sym-C1 and sym-C4 derived from the pyrene-tagged salicylaldehydes **6** and **5** respectively were prepared following the same procedure where two equivalents of the modified aldehydes were condensed with one equivalent of enantiopure (*S,S*)-1,2-cyclohexanediamine. Reactions were carried out under inert atmosphere; aldehydes **6** and **5**, dissolved in dry DCM or toluene respectively, were added to a solution of the diamine in dry ethanol. Reactions were refluxed for 4 hours, and a yellow precipitate was formed at the bottom of the flask in each case. After solvents removal, the symmetrical ligands sym-C1 **7** and sym-C4 **8** were obtained as yellow powders in 85% and 99% yield respectively.

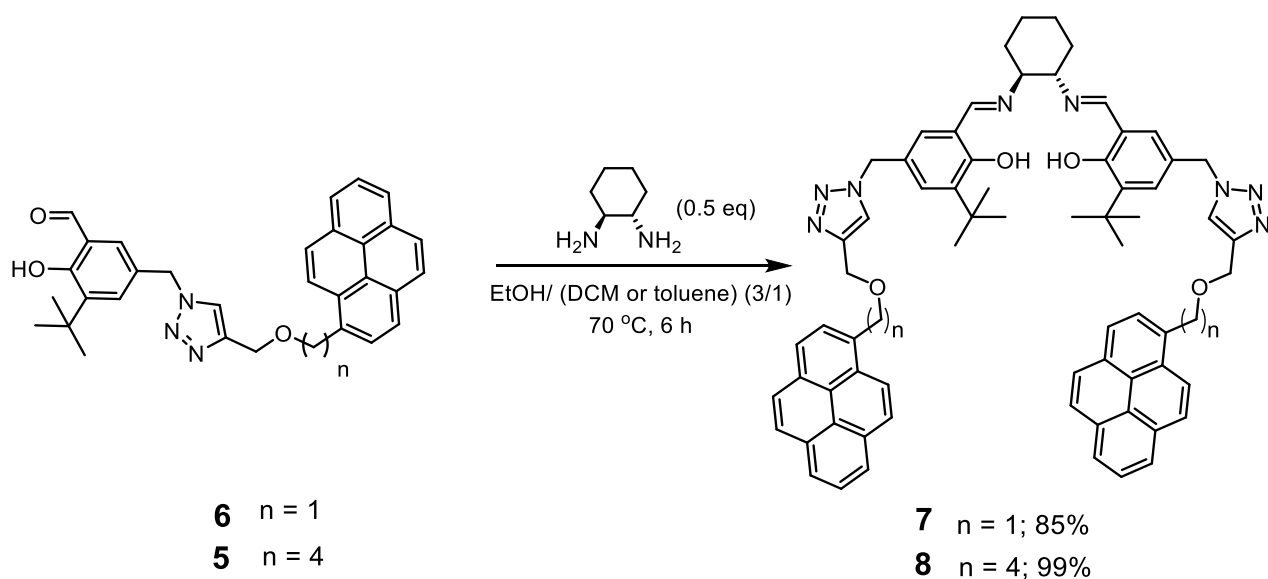


Figure 45: Synthesis of symmetrical pyrene-tagged ligands

(5) Synthesis of unsymmetrical pyrene-tagged ligands

The access to the unsymmetrical salen ligands with two different benzaldehyde moieties is more difficult than that of the standard symmetrical ones, due to the formation of unavoidable bis-imine products. Even if the diamine is introduced in a large excess, compared to the first aldehyde, the targeted imine as desired monocondensation product is obtained in only a small amount, together with the corresponding symmetrical salen derivative.¹⁰² The most effective method to obtain an unsymmetrical derivative consists in the preparation of the mono protected diamine followed by the stepwise condensation with two different benzaldehydes.¹⁰³

¹⁰² A. M. Daly, C.T. Dalton, M.F. Renehele, D.G. Gilheany, *Tetrahedron Lett.* **1999**, 40, 3617–3620.

¹⁰³ E. J. Campbell, S. T. Nguyen, *Tetrahedron Lett.* **2001**, 42, 1221–1225.

Nguyen *et al.*¹⁰³ reported the synthesis of various unsymmetrical salen ligands with high yields by using the diamine mono ammonium salt derived from the reaction of the enantiopure diamine with anhydrous hydrochloric acid. Being insoluble in ether, this salt is isolated and ready to react with one equivalent of the first salicylaldehyde. The mono-imine salt obtained with high yield is also isolated to react further with one equivalent of the other salicylaldehyde in the presence of triethylamine (Et₃N), leading to a large variety of modified unsymmetrical salen ligands with 60-87% yields (Figure 46).

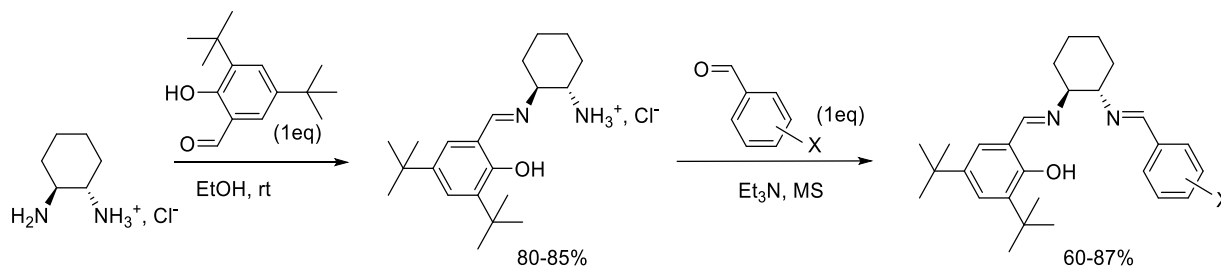


Figure 46: Two step preparation of unsymmetrical salen ligands

This strategy was further improved by Weck *et al.*¹⁰⁴ who described the practical one-pot synthesis of unsymmetrical salen ligands using a 1:1:1 mixture of the mono ammonium salt and each of the different salicylaldehydes. They prepared functionalized unsymmetrical ligands in high yields (60-85%) avoiding the need to isolate the intermediary mono imine salt. The reaction was efficient in terms of time and could be carried out in a multigram scale (Figure 47).

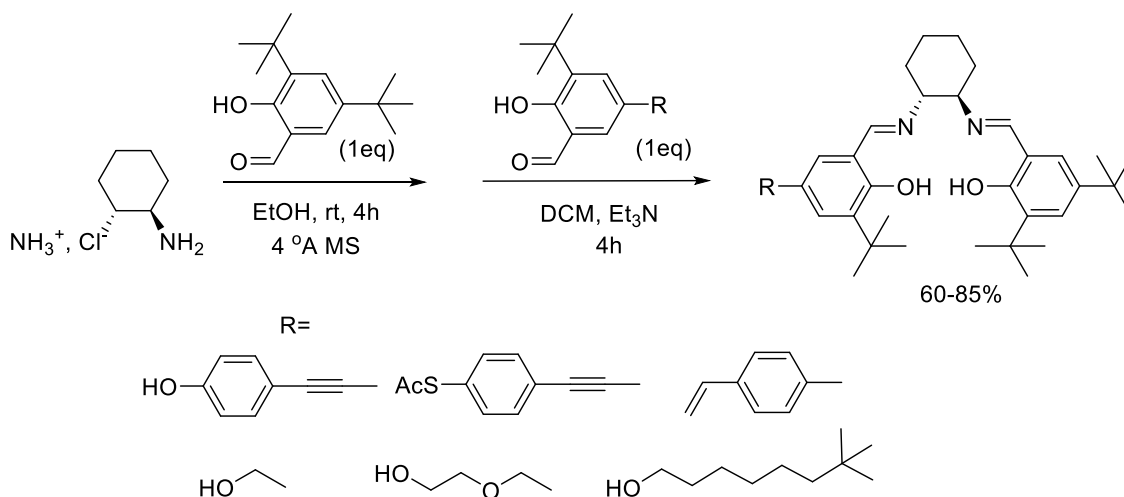


Figure 47: One-pot synthesis of unsymmetrical salen ligands

¹⁰⁴ M. Holbach, X. Zheng, C. Burd, C. W. Jones, M. Weck, *J. Org. Chem.* **2006**, *71*, 7, 2903–2906

Therefore, the two unsymmetrical mono-pyrene tagged salen ligands Unsym-C1 and unsym-C4 were synthesized following the procedure of Weck *et al.*¹⁰⁴ after a preliminary preparation of the diamine monoammonium salt **9**.

(a) Synthesis of monoprotected (*1S,2S*)-cyclohexane-1,2-diamine

One amine group of the enantiopure (*1S,2S*)-cyclohexane-1,2-diamine was protected using a hydrochloric acid solution (1 equiv, 2 M in ether). Being exothermic, the reaction was first performed at 0 °C in anhydrous ethanol with the dropwise addition of HCl, then stirred overnight at room temperature. The mono ammonium salt was then obtained as a white precipitate with 71% yield and further used as obtained after NMR characterization.

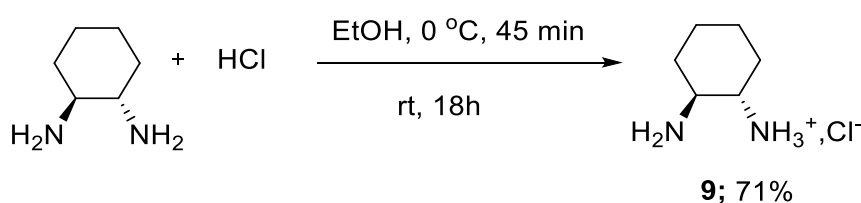


Figure 48: Synthesis of mono protected diamine.

(b) One-pot synthesis of mono-pyrene tagged ligands

Following the procedure mentioned above,¹⁰⁴ the ligands unsym-C1 and unsym-C4 derived from compounds **6** and **5** respectively were obtained in good yields (83% and 64% respectively) as yellow powders after purification by chromatographic columns in the presence of 1% of Et₃N.

Their preparation occurred by successively reacting 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde then **5** or **6**, in equimolar amounts.

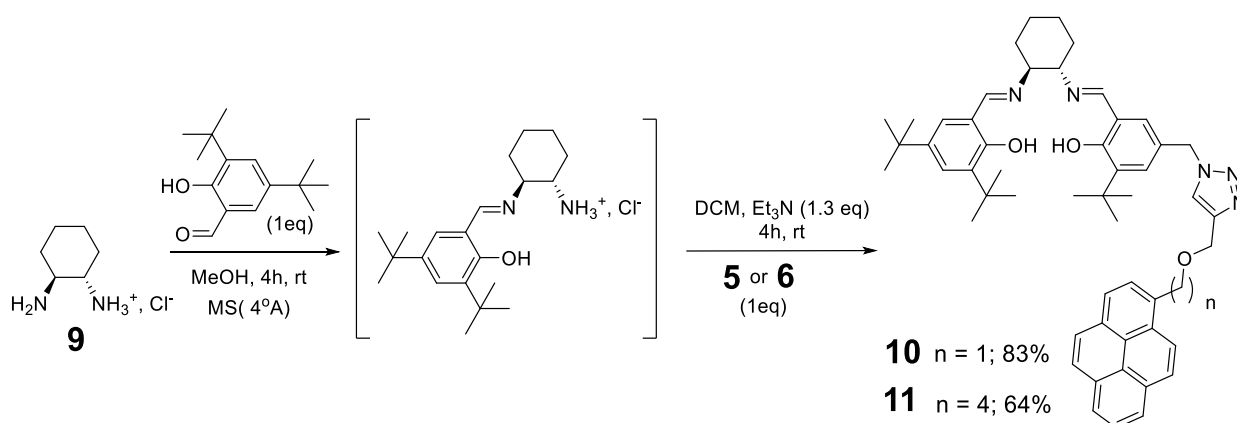


Figure 49: Synthesis of mono-pyrene tagged salen ligands.

The structures of all ligands have been verified using NMR, MS, IR, and UV-Vis analyses.

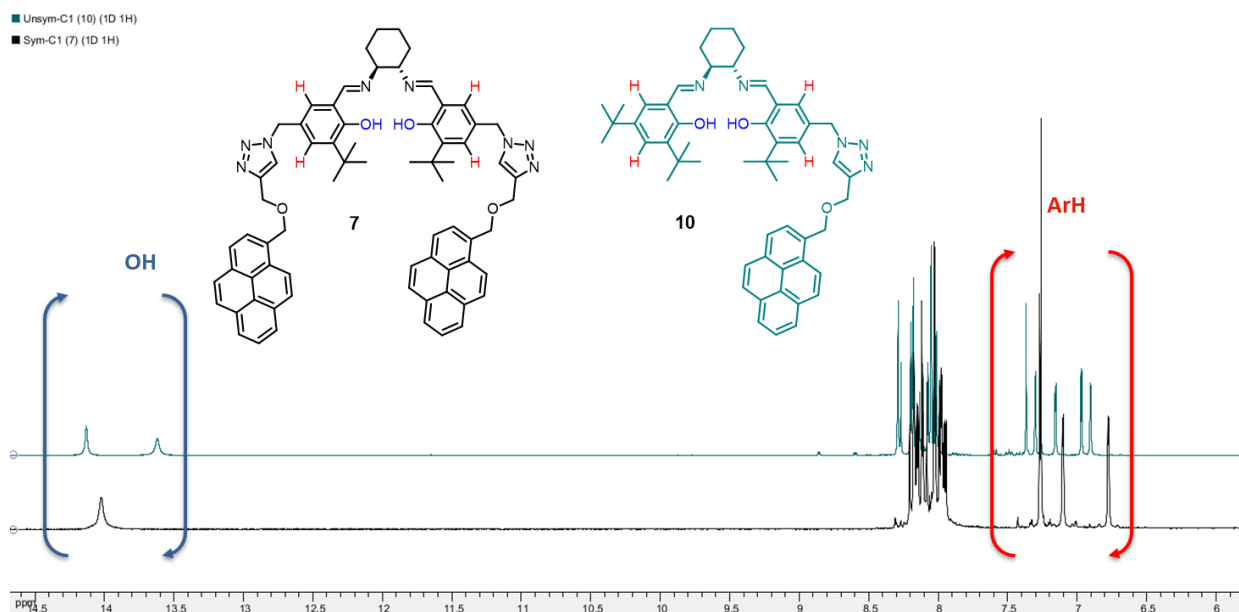


Figure 50: Comparison of ^1H NMR spectra of symmetrical and unsymmetrical ligands.

^1H NMR spectra clearly show the difference between the two kinds of ligands. For unsymmetrical ligand Unsym-C1 **10**, two peaks corresponding to the two differently surrounded hydroxyl groups are obtained at 13.6 and 14.1 ppm (green spectrum, Figure 50) while only one peak at 14 ppm is present for the symmetrical one Sym-C1 **7** (spectrum in black, Figure 50). Furthermore, for the aromatic protons (ArH) in *meta* position of the phenol, Sym-C1 **7** shows only two peaks (dd) at 6.7 and 7.1 ppm, while four peaks corresponding to four different protons are obtained in the case of Unsym-C1 **10**. Likely, for the protons of the imine groups, only one peak is obtained for **7** instead of two peaks for **10** but they are not easily distinguished due to the presence of the aromatic protons from the pyrene moieties.

B. Complexes synthesis

1. Synthesis of chromium pyrene-tagged salen complexes

We aim to prepare the corresponding pyrene-tagged complexes in order to evaluate their efficiency in supported asymmetric catalysis. For this reason, chromium metal was first chosen as the coordinating metal. Chromium salen complexes are known in the literature as very efficient catalysts for several transformations such as the asymmetric ring opening reaction (ARO) of epoxides,¹⁰⁵ the Diels-Alder (DA) as the hetero Diels-Alder reaction (HDA) of various aldehydes,¹⁰⁶ the aminolytic

¹⁰⁵ E. N. Jacobsen, *Acc. Chem. Res.* **2000**, 33, 421–431.

¹⁰⁶ M. Bandini, P. G. Cozzi, A. Umami-Ronchi, *Chem. Commun.* **2002**, 9, 919–927.

kinetic resolution (AKR) of epoxides,¹⁰⁷ the Nazarov cyclization,⁶⁸ the addition of dimethylzinc to aldehydes,¹⁰⁸ the Henry reaction,¹⁰⁹ and the kinetic oxidative resolution of secondary alcohols.¹¹⁰ In each case, these derivatives showed a high efficiency in terms of yield and enantioselectivity values at low catalytic amounts. Typically, metallo-salen complexes are obtained by mixing the ligands with the chosen metal salts. In this case, chromium complexes are prepared from reacting the prepared ligands with chromium chloride under inert atmosphere. Then the resulting chromium (II) complex is further oxidized by air to afford the stable Cr (III) species.

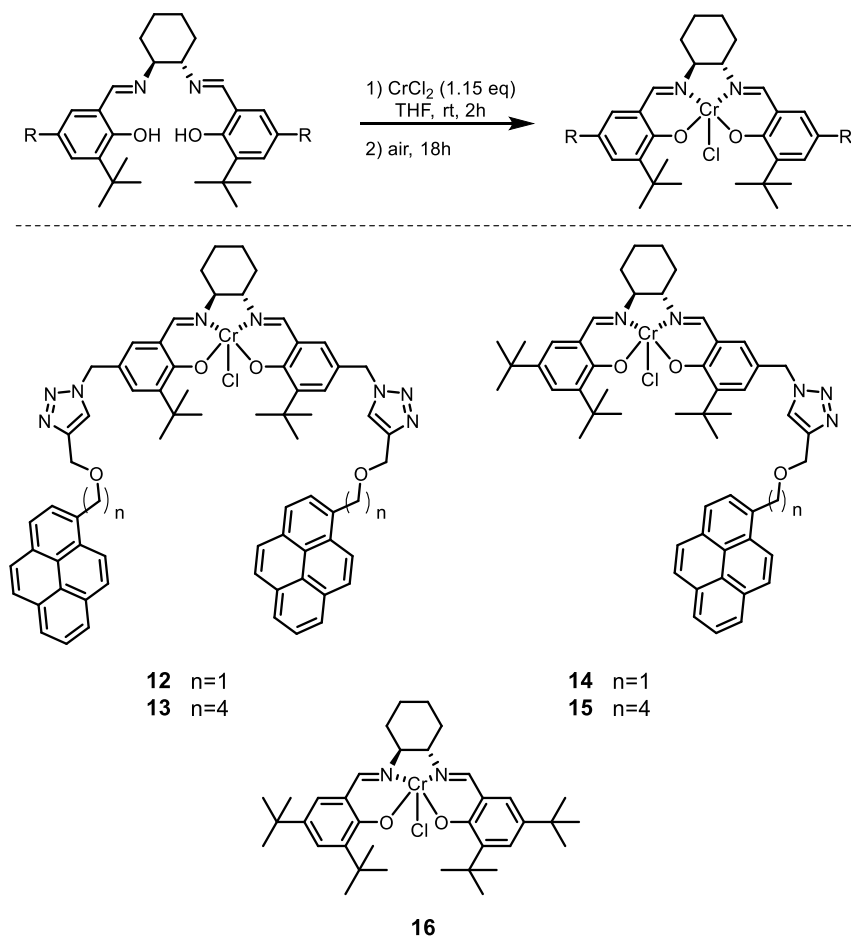


Figure 51: Synthesis of chromium salen complexes.

¹⁰⁷ R. I. Kureshy, S. Singh, N. H. Khan, S. H. R. Abdi, S. Agrawal, R. V. Jasra, *Tetrahedron: Asymmetry* **2006**, *17*, 1638–1643.

¹⁰⁸ P. G. Cozzi, P. Kotrusz, *J. Am. Chem. Soc.* **2006**, *128*, 4940–4941.

¹⁰⁹ a) R. Kowalczyk, Ł. Sidorowicz, J. Skarżewski, *Tetrahedron: Asymmetry*, **2007**, *18*, 2581–2586; b) R. Kowalczyk, P. Kwiatkowski, J. Skarżewski, J. Jurczak, *J. Org. Chem.* **2009**, *74*, 753–756. c) A. Zulauf, M. Mellah, E. Schulz, *Chem. Eur. J.* **2010**, *16*, 11108–11114.

¹¹⁰ a) R. I. Kureshy, I. Ahmad, K. Pathak, N. H. Khan, S. H. R. Abdi, J. K. Prathap, R. V. Jasra, *Chirality* **2007**, *19*, 352–357; b) K. Pathak, I. Ahmad, S. H. R. Abdi, R. I. Kureshy, N. H. Khan, R. V. Jasra, *J. Mol. Catal. A* **2007**, *274*, 120–126.

So, symmetrical (**12** and **13**), unsymmetrical (**14** and **15**), and the Jacobsen (**16**) chromium complexes have been synthesized in quantitative yields and fully characterized using MS, IR, and UV-Visible analyses. Since Cr-complexes are paramagnetic, it was not possible to characterize them by NMR.

However, IR spectra were realized for all ligands and reveal the presence of an elongation vibrational band corresponding to the imine bond C=N appearing between 1628-1630 cm^{-1} . After complexation with chromium metal, the spectra of Cr-complexes showed a clear shift of this band to 1620-1623 cm^{-1} , proving thus the complexation of Cr.

Figure 52 shows a comparison of the IR spectra of Unsym-C1 **10** and Unsym-C1-Cr **14**.

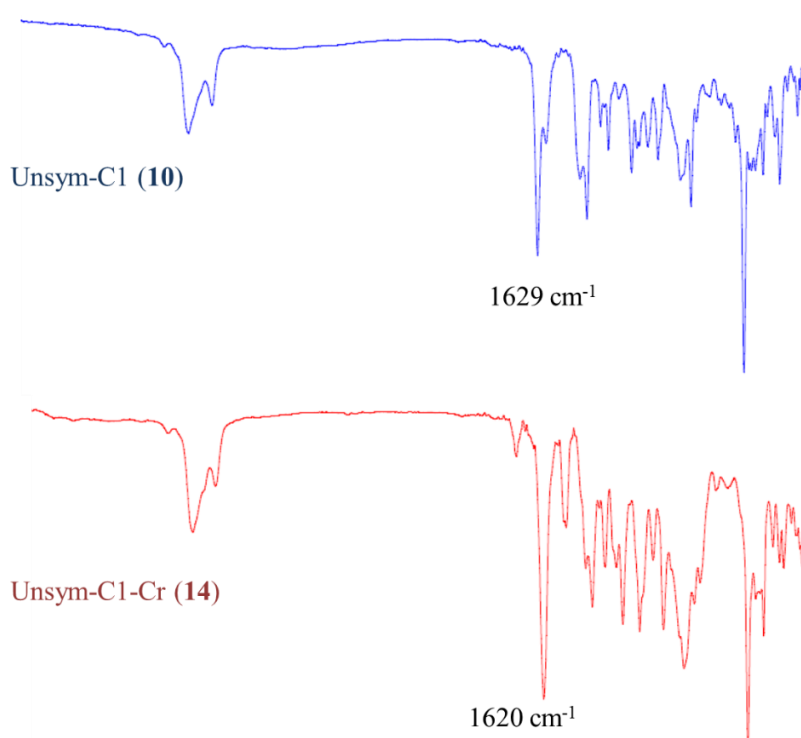


Figure 52: IR spectra of Unsym-C1 ligand and the corresponding Cr-complex.

2. Synthesis of manganese pyrene-tagged salen complexes

On the other hand, manganese salen complexes are also well known in asymmetric catalysis. They proved their efficiency in various asymmetric catalytic reactions and especially in the epoxidation and the acylazidation of olefins.^{111,112}

¹¹¹ E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064.

¹¹² L. Zhang, S. Liu, Z. Zhao, H. Su, J. Hao, Y. Wang, *Chem. Sci.* **2018**, *9*, 6085–6090.

In this case, only manganese complexes derived from the pyrene methanol-based ligand have been prepared. Mn(III)-unsymmetrical (**17**) and Mn(III)-Jacobsen (**18**) complexes were synthesized in quantitative yields by refluxing the corresponding ligands with manganese acetate pentahydrate $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ in a mixture of ethanol and toluene under an argon atmosphere for 5 h, followed by an oxidation step under air and an anion exchange occurred by adding an excess of NaCl.

Manganese complexes were also fully characterized using MS, IR and UV-Vis analyses. Similarly, IR spectra of Mn-complexes reveal the shift of the imine band after complexation from 1629 cm^{-1} to 1613 cm^{-1} proving thus the coordination of the metal.

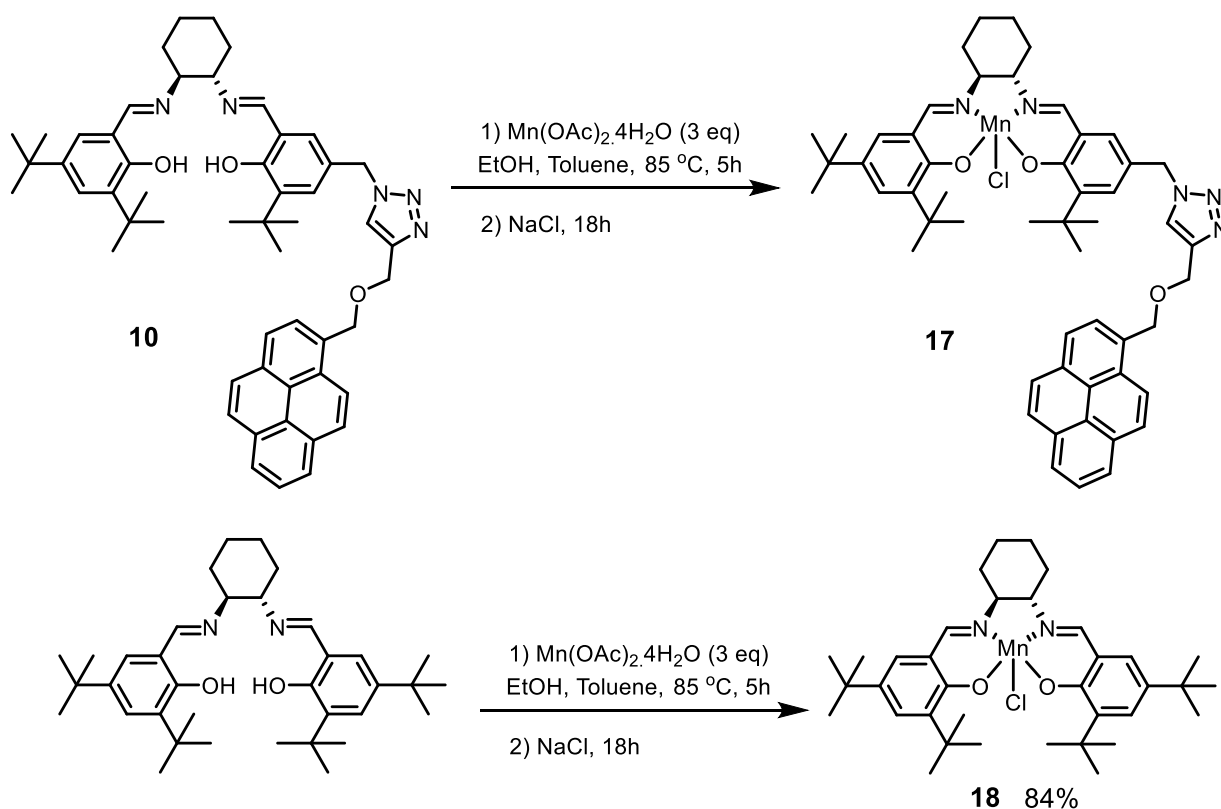


Figure 53: Synthesis of manganese salen complexes.

C. Immobilization of pyrene-tagged complexes

Carbon based materials have recently gained attention as convenient supports to immobilize catalysts. Regarding their physical and chemical properties, including their suitable surface area that could be modified covalently and non-covalently, all the carbon materials were mainly alused as a catalyst support. Due to the inherent ability of pyrene groups to stack onto the graphitic surfaces, modified tagged catalysts were prepared and immobilized leading to stable supported catalytic systems

showing an important efficiency in terms of activity and recyclability. In most cases, pyrene moieties are attached far away from the catalytic site to avoid any change on the accessibility and thus the reactivity.

Reduced graphene oxide rGO is one of most important carbon-based materials used in fundamental chemistry, which is cheaper than graphene with almost similar properties. Even though there are many reports on carbon-supported catalysis, only a few examples describe the use of such materials as supports to promote asymmetric catalytic transformations. Further detailed information about these results have been mentioned in chapter 1.

Consequently, we aim in our project to immobilize the new modified pyrene-tagged complexes onto rGO, to further test their catalytic activity in asymmetric ARO, HDA, and epoxidation reactions. The effect of immobilization on the catalysts reactivities will be evaluated. In addition, we aim to efficiently recover and reuse these precious enantiopure catalysts using this heterogenization method.

Immobilization procedures are strongly influenced by the temperature and the polarity of the solvents since these are factors affecting the reversible non-covalent interactions between the catalyst and the support. Immobilization is generally favourable in polar solvents, while non-polar solvents are the best medium to improve the desorption phenomenon. Furthermore, the increase of temperature can also enhance the desorption of attached molecules from the surface of support by making the π -interaction weaker.¹¹³

- Immobilization procedure

First, we tried to immobilize the complex **13** onto the surface of commercially available reduced graphene oxide rGO. Following the procedure described by Pérez *et al.*⁸⁴, a suspension of rGO powder in DCM, with a ratio $m(\text{mg})/V(\text{mL})$ of 25, was sonicated for 1 hour then the complex **13** was added. The mixture was sonicated for further five minutes and stirred at room temperature for 24 hours. A mass ratio of 4:1 was used to perform the immobilization and only 90% of **13** were completely immobilized. We assume that this mass ratio is optimal avoiding possible mass transfer problems in case of increasing the amount of rGO to immobilize the entire quantity of the added catalyst.

The amount of the immobilized catalyst was measured by UV-Vis analyses, where a calibration line was obtained by measuring the absorbance (Abs) of solutions of different concentrations at the λ_{max}

¹¹³ G. Liu, B. Wu, J. Zhang, X. Wang, M. Shao, J. Wang, *Inorg. Chem.* **2009**, *48*, 2383–2390.

(345 nm) and used to know the real concentration of **13** in the supernatant solution. Moreover, this result was confirmed by weighing the resulted solid which was filtered off, washed by DCM and dried under reduced pressures at room temperature.

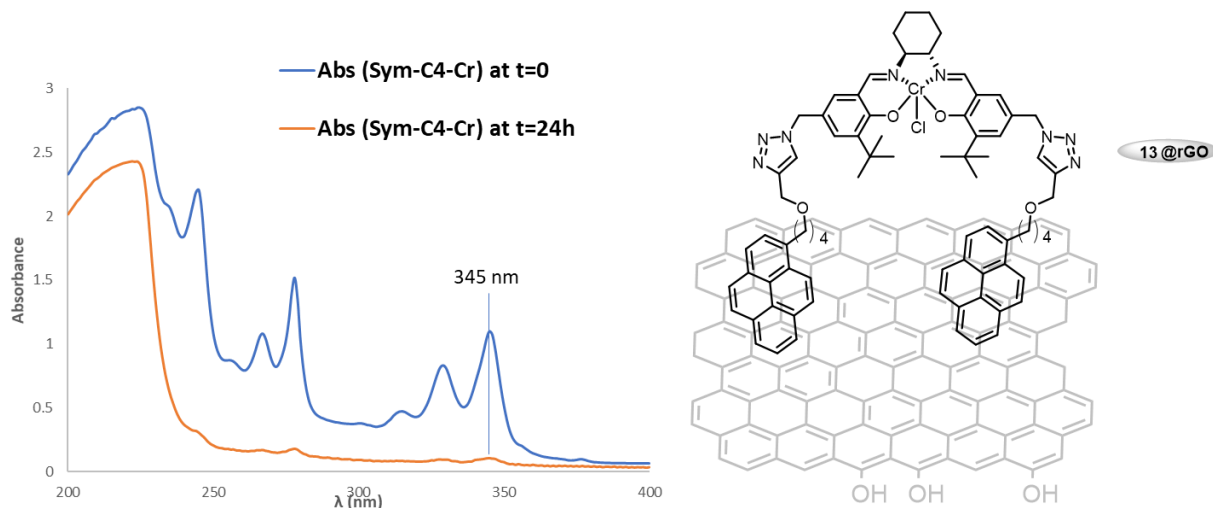


Figure 54: Immobilization of Sym-C4-Cr on rGO.

We succeed to immobilize all the pyrene-tagged salen chromium and manganese complexes including the symmetrical and the unsymmetrical species by following the same procedure.

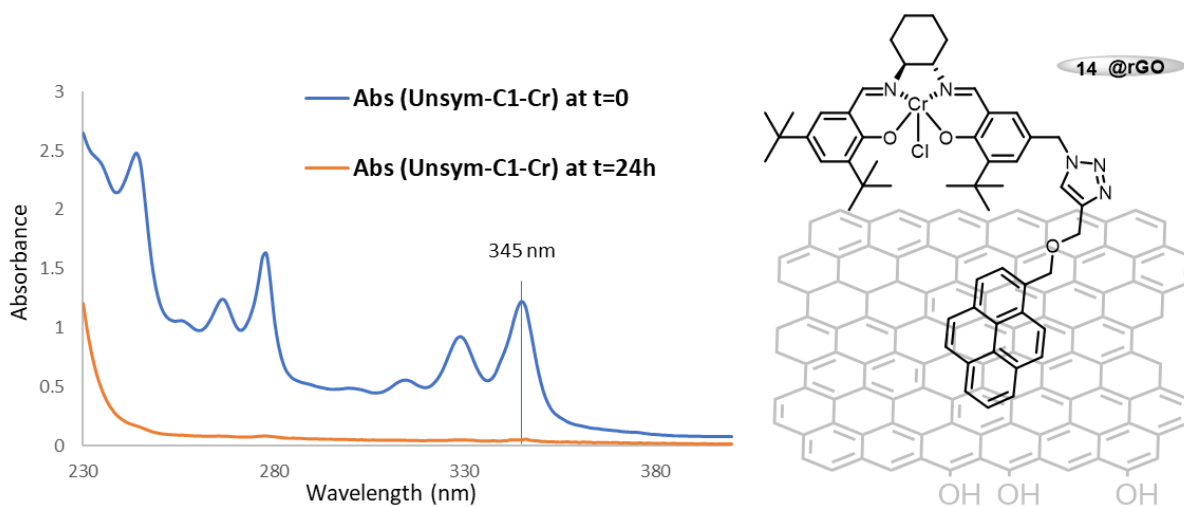


Figure 55: Immobilization of Unsym-C1-Cr on rGO.

Furthermore, X-ray photoelectron spectroscopy was conducted on powders of both unmodified rGO support and supported catalysts onto rGO. The wide-scan spectra clearly revealed the presence of signals arising from Cr2p, N1s and Cl2p core-levels proving that the catalysts had been successfully grafted. The narrow-scan spectra for Cr2p, N1s and Cl2p were then measured in both cases, which allowed to determine the position in energy of the three elements, as well as their atomic ratios.

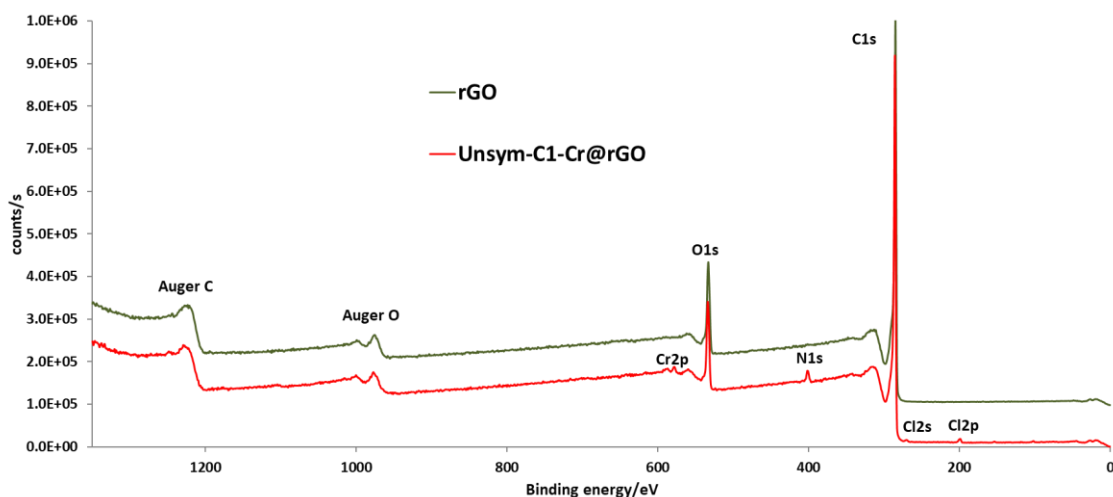


Figure 56: XPS of rGO and Unsym-C1-Cr **14**@rGO.

For Unsym-C1-Cr **14**, the Cr2p core-level spectrum consists of two main peaks corresponding to the spin-orbit components Cr2p_{3/2} and Cr2p_{1/2}, situated at 577.2 eV and 586.9 eV, respectively, and separated by 9.7 eV. These values allowed to assign the Cr³⁺ according to the literature.¹¹⁴ The Cl2p and N1s spectra are centered at 198.7 and 400.5 eV respectively. The experimental determination of the atomic ratios of the elements by XPS analyses proved the immobilization of the complexes onto the surface of rGO. Expected information on the values of the Cr/Cl and N/Cl contents was obtained in each case. These measured values are comparable to the theoretical ones, where the Cr/Cl is 1 for all the supported catalysts and the N/Cl ratio was 8 and 5 for the symmetrical and the unsymmetrical complexes respectively.

¹¹⁴ G. C. Allen, P. M. Tucker, *Inorg. Chim. Acta.* **1976**, *16*, 41–45.

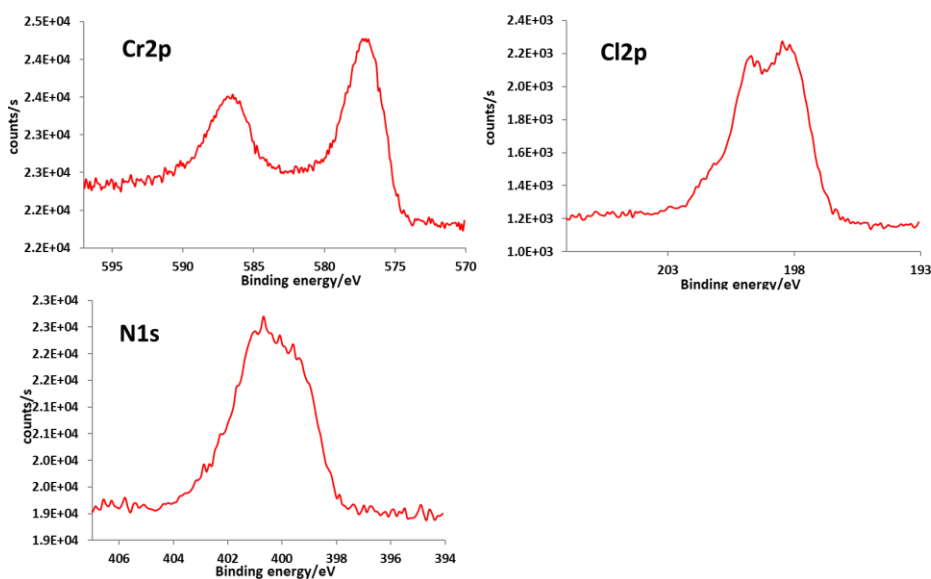


Figure 57: Narrow-scan spectra for Cr2p, N1s and Cl2p for Unsym-C1-Cr.

Similarly, the Mn-complex **17** was immobilized following the same procedure, and XPS analyses reveal the presence of signals arising from Mn2p, N1s and Cl2p core-levels. Again, the Mn/Cl ratio is 1 and N/Cl is 5, proving that the catalyst had been successfully grafted onto the rGO surface.

The number of pyrene moieties attached to the molecules did not affect the amount of supported catalyst onto the same quantity of rGO. In both cases, for symmetrical and unsymmetrical catalysts, we indeed tried to increase the amount of catalyst immobilized on the same quantity of rGO, in order to perform an immobilization procedure with a 2:1 mass ratio of rGO:catalyst. In all cases, only 9 mg of the chosen catalyst were immobilized onto 40 mg of rGO.

Thus, five supported catalytic systems were prepared and involved in heterogeneous asymmetric catalysis (their catalytic activities will be described in chapter 3 and 4).

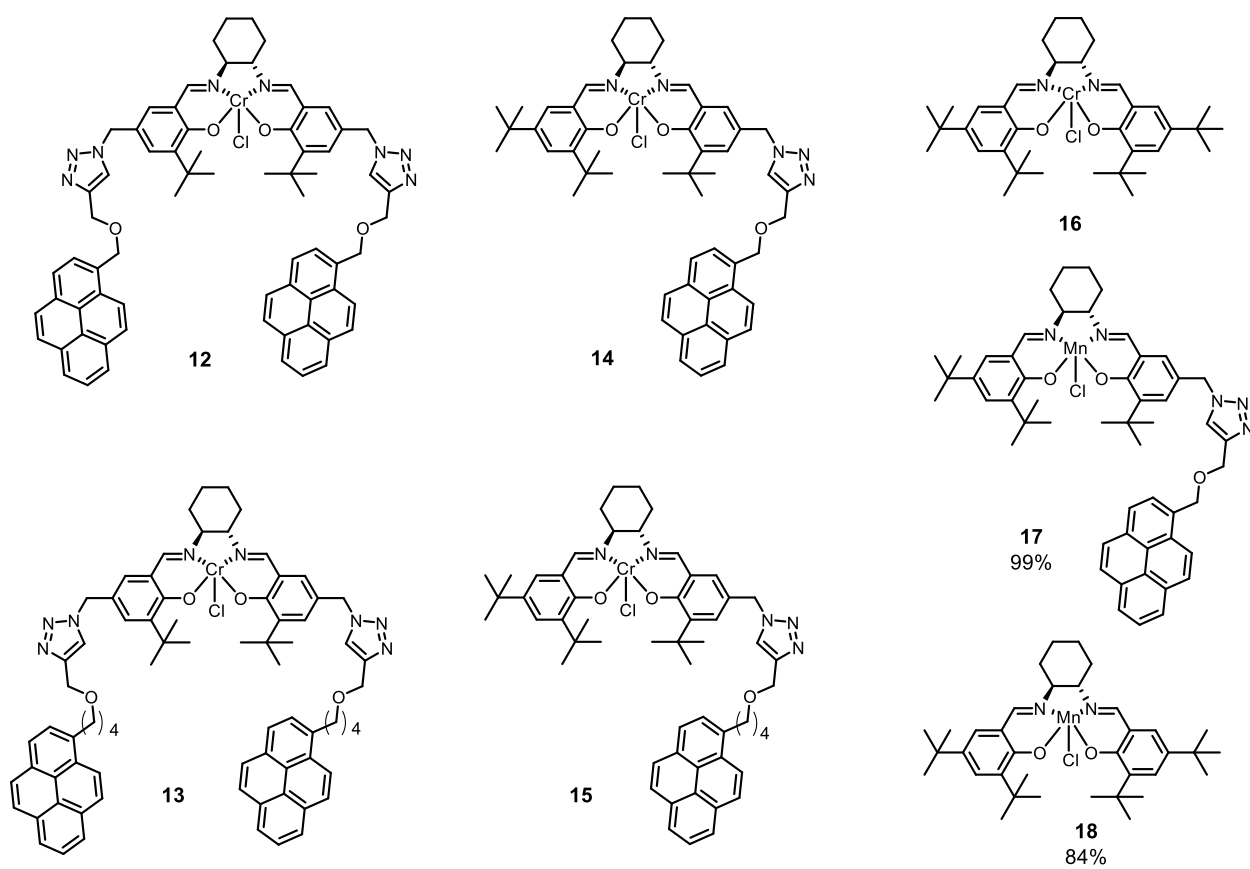
Conclusion

The synthesis of new modified salen ligands was described in chapter 2. Structural modifications have been performed on the salicylaldehyde by introducing a pyrene group in the *para* position of phenol following two synthetic strategies. The first one was achieved via a nucleophilic substitution reaction between pyrene alcohol and chloromethylated salicylaldehyde, which was not efficient due to the appearance of a methylene-bisphenol derivative as a side-product in majority, leading to the decrease of the overall yield formation of the desired salen ligand. The second strategy employed a click reaction (CuAAC) between the prepared pyrene-tagged alkyne and the azido salicylaldehyde. These synthetic routes were started from two pyrene alcohols with different carbon chain length (C1 and C4) and the two pyrene-tagged salicylaldehydes were obtained with excellent yields.

Then, the synthesis of the symmetrical ligands Sym-C1 **7** and Sym-C4 **8** was efficiently achieved by a simple condensation reaction with enantiopure (*S,S*)-1,2-cyclohexanediamine. In addition, the unsymmetrical analogues (**10** and **11**) have been prepared with good yields in a stepwise condensation reaction starting from the monoprotected form of the same enantiopure diamine. The corresponding chromium (**12**, **13**, **14** and **15**) and manganese complexes (**17** and **18**) were synthesized, according to the methods described in the literature, in quantitative yields and fully characterized by IR, UV-vis and MS analyses.

Finally, the non-covalent anchoring via π -stacking interactions of all pyrene-tagged salen complexes onto the surface of reduced graphene oxide was successfully achieved via a simple immobilization procedure in which 9 mg of each catalyst, whatever symmetrical with two pyrene groups or unsymmetrical with only one pyrene group, were immobilized onto 40 mg of rGO. The immobilization was confirmed by UV-vis measurements and with XPS analyses.

The structures of all the prepared complexes and the supported analogues are summarized in Figure 58 and Figure 59 respectively.



All Cr-complexes are obtained in quantitative yields

Figure 58: Synthesized Cr and Mn-complexes.

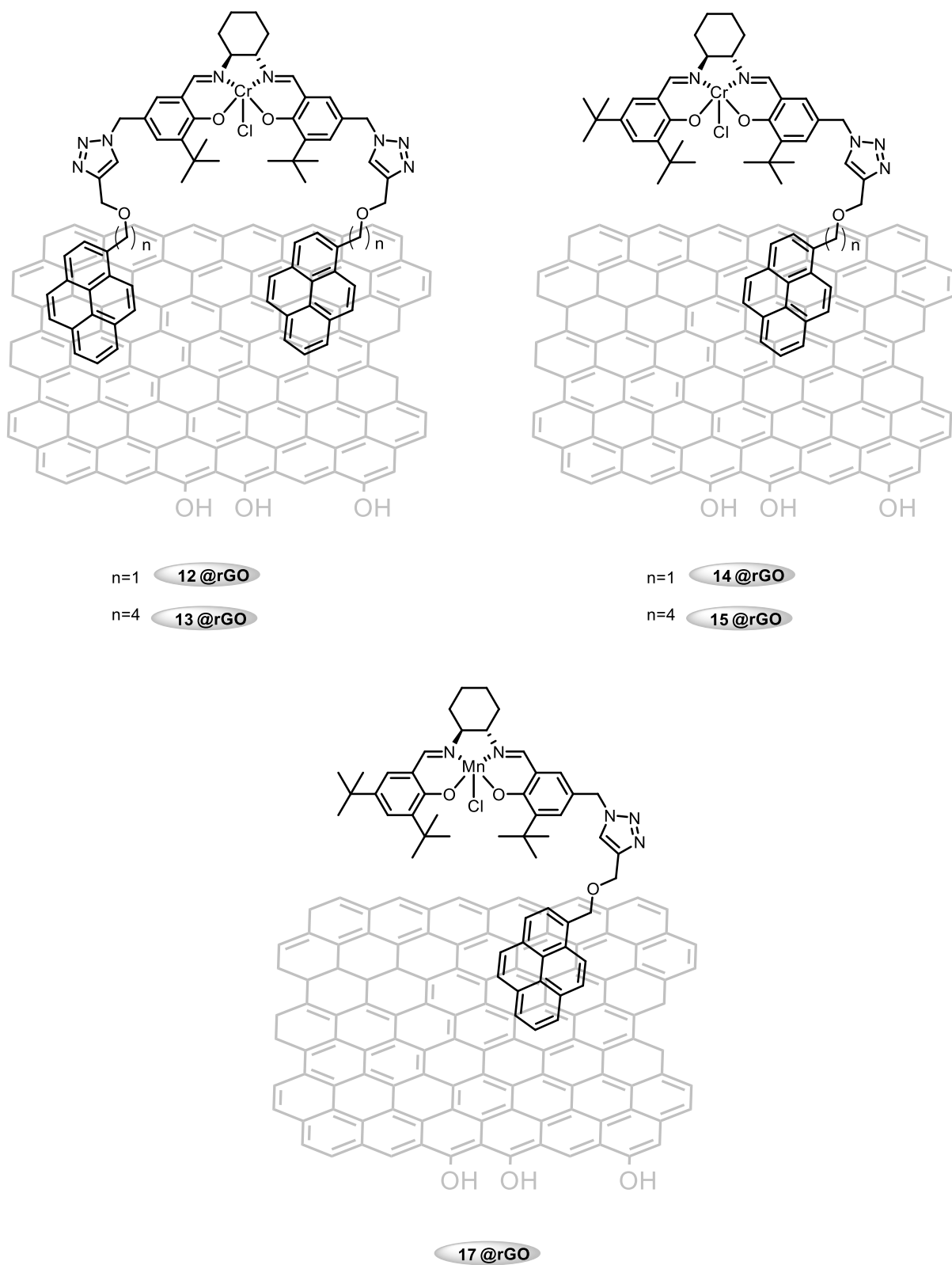


Figure 59: Supported Cr and Mn-pyrene tagged complexes on rGO.

Chapter 3: Catalytic Activity of Pyrene-tagged Chromium Salen complexes.



III. Chapter 3: Catalytic Activity of Pyrene-tagged Chromium Salen complexes.

A. Application in asymmetric ring opening reaction of *meso*-epoxides

Chromium salen complexes are widely used in various enantioselective catalytic reactions. They proved their high efficiency in catalysing the ARO of *meso*-epoxides with different nucleophiles.¹¹⁵ This reaction was found to be very important in asymmetric catalysis, leading to the formation of valuable synthons such as chiral β -amino alcohols when the nucleophile is a nitrogen-containing compound, which are intermediates for the preparation of a wide variety of biologically relevant molecules and chiral ligands.¹¹⁶

Trimethylsilyl azide TMSN₃ is one of the mostly used nucleophiles to open *meso*-epoxides, giving access to valuable β -amino alcohols. This reaction was extensively studied in the literature, and it implies a bimetallic mechanism where two chromium complexes units are involved. Chromium salen complexes act as a Lewis acid activating the electrophile, in this case the epoxide, and as a Lewis base activating the nucleophile, TMSN₃.

Based on all the above-mentioned properties and on the stability of chromium complexes, we aim in this chapter to describe our work on the use of the prepared pyrene-tagged salen complexes as catalysts for the ARO of cyclohexene oxide; this compound is indeed one of the typical substrates involved in such type of reactions, with TMSN₃ in homogeneous conditions as well as in supported catalysis. Cyclohexene oxide represents a challenging substrate due to its symmetrical structure and thus the difficulty to obtain a very good enantiofacial differentiation, the reason why the enantioselectivity toward this substrate remains modest.

¹¹⁵ L. E. Martinez, J. L. Leighton, D. H. Carsten, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5897–5898.

¹¹⁶ Y. Hayashi, J. J. Rohde, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 5502–5503.

1. State of art

Nucleophilic ring opening reactions of epoxides are of great importance due to their wide application in organic synthesis.

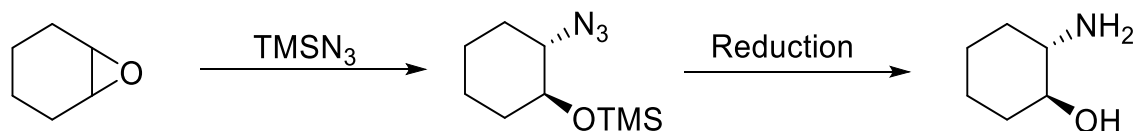


Figure 60: Access to *trans*-1,2-amino alcohol from ARO of cyclohexene oxide by TMSN₃ followed by a reduction step.

Jacobsen *et al.*³⁶ reported in 1995 the first use of chromium(III) salen complexes as efficient catalysts to promote the ARO of *meso*-epoxides with TMSN₃ and leading to high yields and enantiomeric excess (up to 98% ee). Other metallocen complexes (e. g. Co, Al, Ti, Mn) have been also tested to catalyse this reaction but remain less effective than Cr-complexes which possess an indefinite stability under ARO conditions. It was proven that high enantioselectivities were obtained for epoxides fused to five-membered rings, while the substrates bearing six-membered rings or the acyclic epoxides remained more difficult to transform with high enantioselectivities.

Mechanistic studies showed a second order kinetic dependence on catalyst concentration, meaning that two molecules of the catalyst are involved in a bimetallic cooperative mechanism.¹¹⁷ One Cr-salen unit acts as a Lewis acid to activate the epoxide while another is present as a Lewis base activating TMSN₃. Indeed, when salen-Cr-Cl is the catalyst, the active specie is the salen-Cr-N₃ formed directly after the addition of the nucleophile. Azide is delivered from one metal to the epoxide bonded to another metal to generate an azido alkoxide complex. After product dissociation and in presence of the nucleophile, the salen-Cr-N₃ is regenerated to further activate the epoxide and for the catalytic cycle to continue (Figure 61).

¹¹⁷ K. B. Hansen, J. L. Leighton, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 10924–10925.

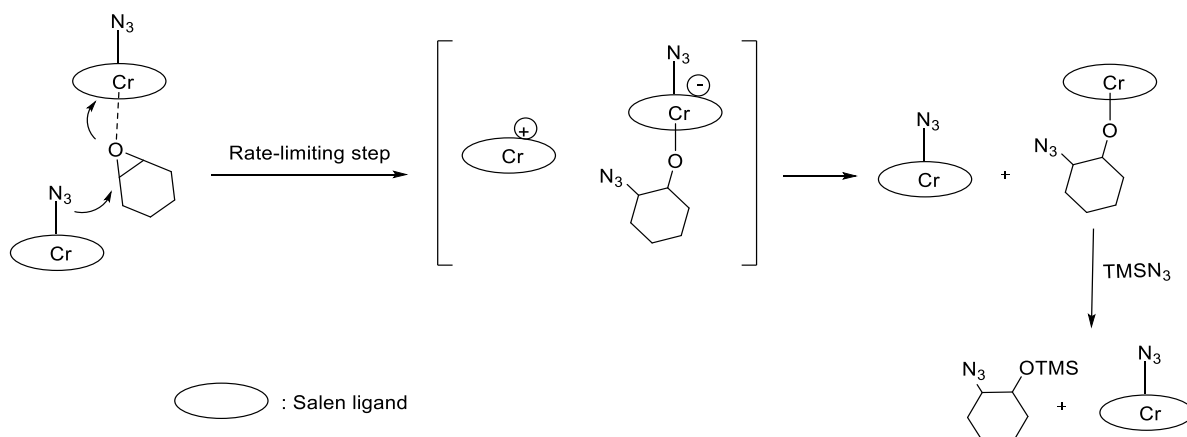


Figure 61: Mechanism of ARO of cyclohexene oxide with TMSN_3 .

Based on this second-order kinetic mechanism, efforts were devoted to develop new features of salen complexes with a particular design to favour the cooperativity between the catalytic active sites. Strategies have been oriented toward the synthesis of dimeric salen complexes linked to each other by a flexible linker, but also the association in macrocyclic scaffolds, the covalently attachment of complexes onto supports or even the use of a ship-in-a-bottle strategy.

In this context, Jacobsen *et al.*¹¹⁸ prepared covalently linked dimeric chromium salen complexes in order to enhance the cooperativity of two metal centers. First attempt was made by linking two salen moieties through the diamine backbone (Figure 62).

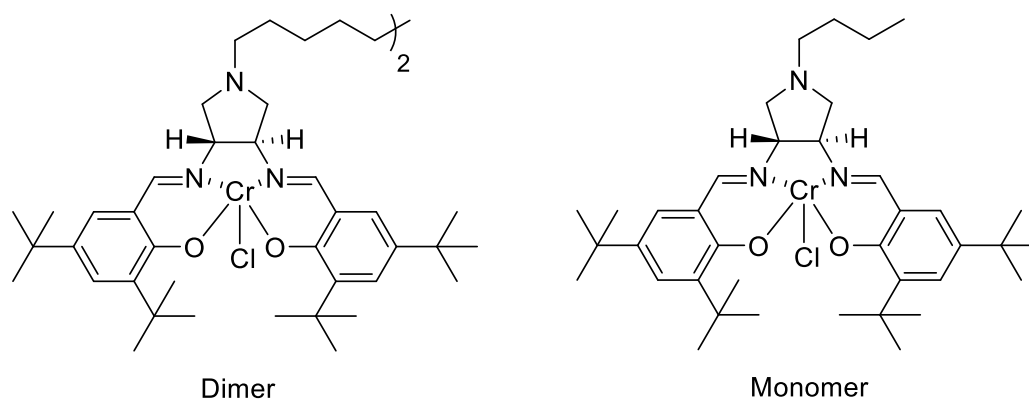


Figure 62: Dimeric Cr-salen complexes bridged via diamine backbone with its monomer analogue.

The resulting chromium complex as dimer achieved the ARO of cyclopentene oxide with TMSN_3 under solvent free conditions with an accelerating rate compared to its monomeric analogue. Importantly, however, the opening product was isolated with a dramatic loss in enantioselectivity

¹¹⁸ R. G. Konsler, J. Karl, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 10780-10781.

(8% ee vs 90% ee), which indicates that this dimer does not display a favourable transition state conformation to allow a good enantiodiscrimination of substrate.

Based on this result, different dimeric Cr-N₃ complexes linked through the phenol group were designed, prepared and engaged in the ARO of cyclopentene oxide (Figure 63). Effectively, corresponding dimeric chromium complexes were more reactive than the monomeric species and afforded the ring-opened product with comparable enantioselectivities, proving thus that the cooperative bimetallic mechanism occurred in this case with a suitable arrangement of catalytic sites leading to excellent ee values.

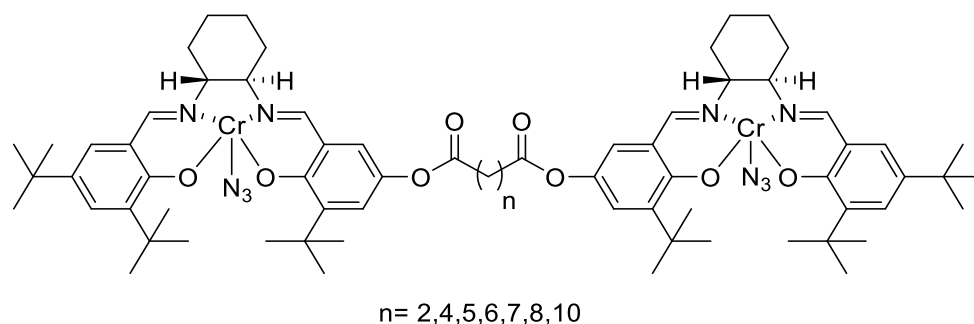


Figure 63: Dimeric Cr-salen complexes with different linker length favouring the bimetallic mechanism.

Moreover, in order to enhance the reactivity and enantioselectivity of the catalysts, Wärnmark *et al.*¹¹⁹ designed and synthesized several heterobimetallic dimeric complexes, based on the idea that some metallocen complexes might be more efficient to trigger the epoxide while others might be better activating the nucleophile. To prove this idea, the ARO of cyclohexene oxide with TMSN₃ was first conducted in the presence of different combinations 1:1 of monometallic salen complexes with different metal ions as catalysts. Indeed, synergistic effects in terms of reactivity and enantioselectivity were obtained when monomeric Mn or Co salen complexes have been combined with monomeric Cr salen complexes.

Accordingly, pseudo-C₂-symmetric [Cr-Co] and pseudo-C₂-symmetric [Cr-Mn] complexes have been synthesized (Figure 64) and tested in the ARO of cyclohexene oxide with TMSN₃. Reactions were carried out under solvent free conditions. The bis-salen Cr-Co showed the best results with excellent induced enantioselectivity (up to 99% yield and 94% ee), which was higher than that obtained with the monomeric analogue and the homobimetallic Cr-Cr dimer under the same reaction conditions. On the other hand, the bis-salen Cr-Mn displayed the highest TOF (183 h⁻¹) but with diminished ee (66%). The pseudo-C₂-symmetric [Cr-Co]-bissalen as highly efficient catalyst

¹¹⁹ D. -Y. Ma, Z. -Y. Xiao, J. Etxabe, K. Wärnmark, *ChemCatChem* **2012**, *4*, 1321–1329.

achieved the ARO of a range of different *meso*-epoxides with TMSN_3 , affording the ring-opened products with high enantioselectivity values at only 0.1 mol% catalyst loading under solvent-free reaction conditions.

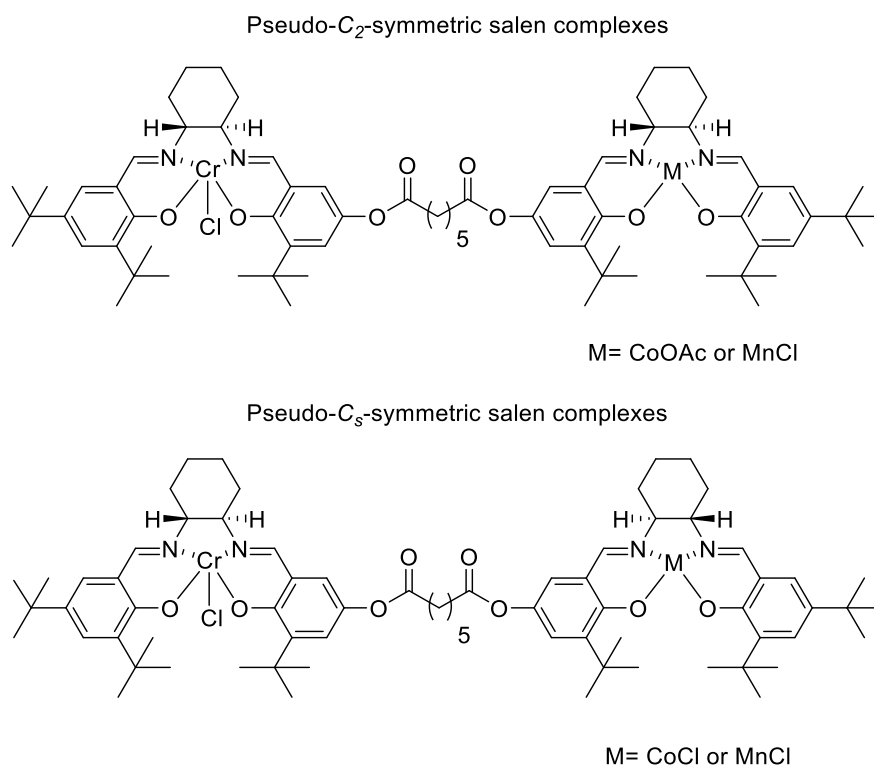


Figure 64: Pseudo- C_2 and pseudo- C_s -symmetric heterobimetallic bis-salen complexes.

Similarly, pseudo- C_s -symmetric [Cr-Co] and pseudo- C_s -symmetric [Cr-Mn] were designed and tested in the ARO of cyclopentene oxide with TMSN_3 .¹²⁰ Even if this kind of catalysts is achiral by itself, the chirality is induced by the insertion of metal ions; the designed pseudo- C_s -symmetric (Figure 64) afforded the ring-opened product in >99% yield and 63–76% ee.

Another way to exploit the cooperativity between two metal salen cores is by designing supramolecular complexes with specific proximity thanks to non-covalent interactions such as an hydrogen bond. In this context, Wärnmark and coworkers¹²¹ explored hydrogen-bonded supramolecular Cr-salen complexes as catalysts for the ARO of epoxides (A and B, Figure 65). Hydrogen bond was present between the 2-pyridone-containing isoquinolinone and quinolinone moieties.

¹²⁰ Y. Li, A. Lidskog, H. Armengol-Relats, T. H. Pham, A. Favraud, M. Nicolas, S. Dawaigher, Z. Xiao, D.-Y. Ma, E. Lindbäck, D. Strand, K. Wärnmark, *ChemCatChem* **2020**, *12*, 1575–1579.

¹²¹ D.-Y. Ma, H. Norouzi-Arasi, E. Sheibani, K. Wärnmark, *ChemCatChem* **2010**, *2*, 629–632.

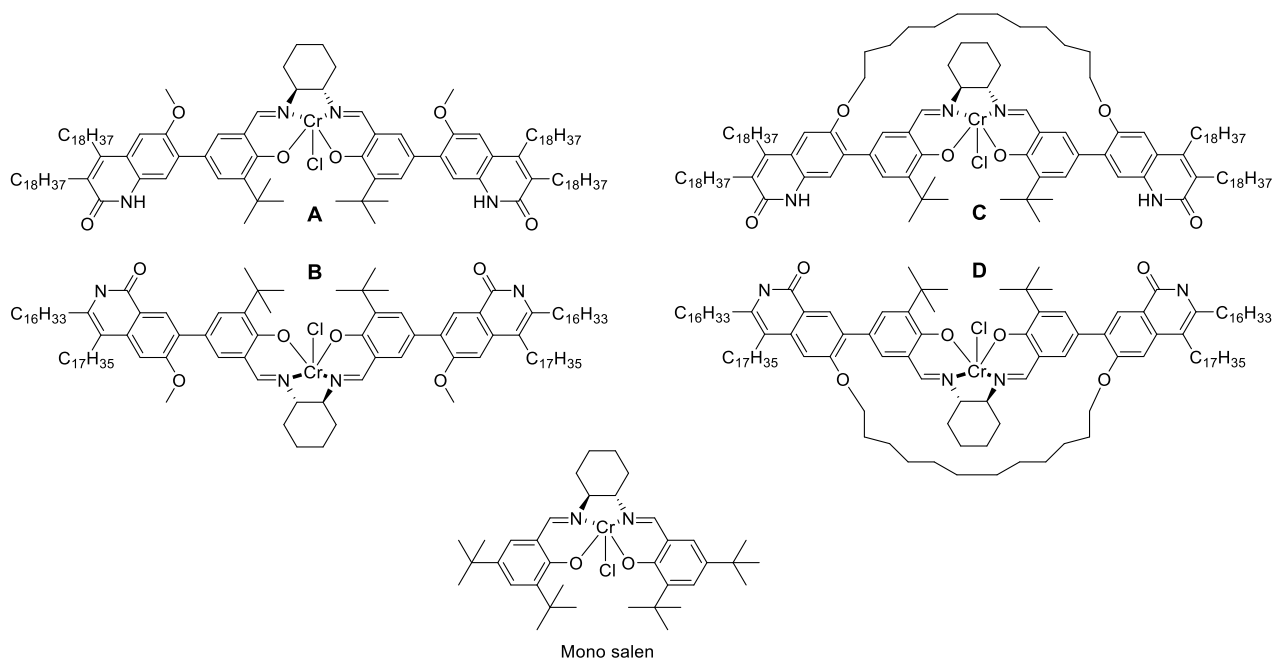


Figure 65: Dynamic supramolecular Cr-salen complexes

In addition, and to enhance the cooperativity by forcing the hydrogen-bonding moieties to take a favourable conformation to assist the aggregation of the desired cyclic heterodimer, an alkyl strap was introduced into catalysts A and B to deliver C and D. All these catalysts were involved in the ARO of cyclohexene oxide as that of cyclopentene oxide with TMSN_3 in toluene. Catalytic tests showed that the supramolecular systems A+B and C+D gave higher reaction rates than the mono salen analogs, with the strapped systems showing the highest catalytic efficiency. However, the enantioselectivity was significantly lower (<10% ee) proving that the transition states for the ring opening reaction using the supramolecular catalysts are not optimal for obtaining high ee values.

Besides, chromium salen complexes have been heterogenized following various immobilization methods to ensure their recovery and reuse at the end of each reaction.

One of the most used strategies to heterogenize salen complexes is their immobilization onto solid supports via covalent tethering and non-covalent electrostatic interactions. In this context, Garcia *et al.*¹²² prepared two series of solid catalysts in which a chiral chromium salen complex has been anchored on aminopropyl-functionalized SiO_2 , ITQ-2 or MCM-41 supports. Immobilization was performed following two methods; one by the coordination of the metal through its axial ligand and the other one by a covalent linkage of the ligand. The complexes anchored to the solid through coordination to the chromium catalyzed the ARO of cyclohexene oxide with TMSN_3 with high yield

¹²² C. Baleizão, B. Gigante, M. J. Sabater, H. Garcia, A. Corma, *Appl. Catal.*, **2002**, 228, 279–288.

(93–99%) and up to 70% ee but were found to undergo extensive leaching of the complex into the diethyl ether solution. In contrast, the covalently linked complexes showed no leaching but generated only moderate yields and low enantiomeric excesses in the ring-opening of cyclohexene oxide (43–66% yield and 8–18% ee). The decreased enantioselectivity compared to the homogeneous catalysts was attributed to a change in the reaction mechanism for which the authors proposed the occurrence of an unimolecular mechanism in such heterogeneous, highly crowded systems.

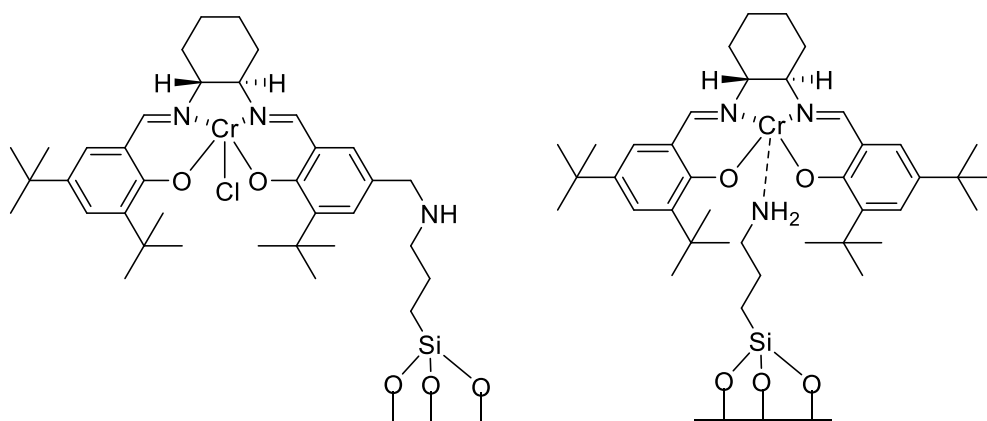


Figure 66: Cr-salen complexes anchored to functionalized silicates SiO_2 , ITQ-2 or MCM-41.

On the other hand, Jacobs *et al.*⁶¹ successfully immobilised a dimeric Cr-salen complex on a silica-supported ionic liquid [BMIM][PF₆]. The supported ionic liquid phase (SILP) catalyst was involved in the ARO with TMSN₃ of 1,2-epoxyhexane and of cyclohexene oxide as representative substrates for terminal and *meso*-epoxides respectively. The reaction was performed both under continuous flow conditions and in a stirred batch reactor. The supported catalyst (SILP) showed a better reactivity and selectivity than the Cr-salen complex immobilised by impregnation,¹²³ and afforded the ring-opened products with high conversions and ee values. This catalytic system was recovered for 4 consecutive runs when used in a batch reactor and for 3 runs in a flow reactor affording the desired products in almost stable conversion and ee values.

¹²³ B. M. L. Diosa, P. A. Jacobs, *Appl. Catal. A* **2005**, 282, 181–188.

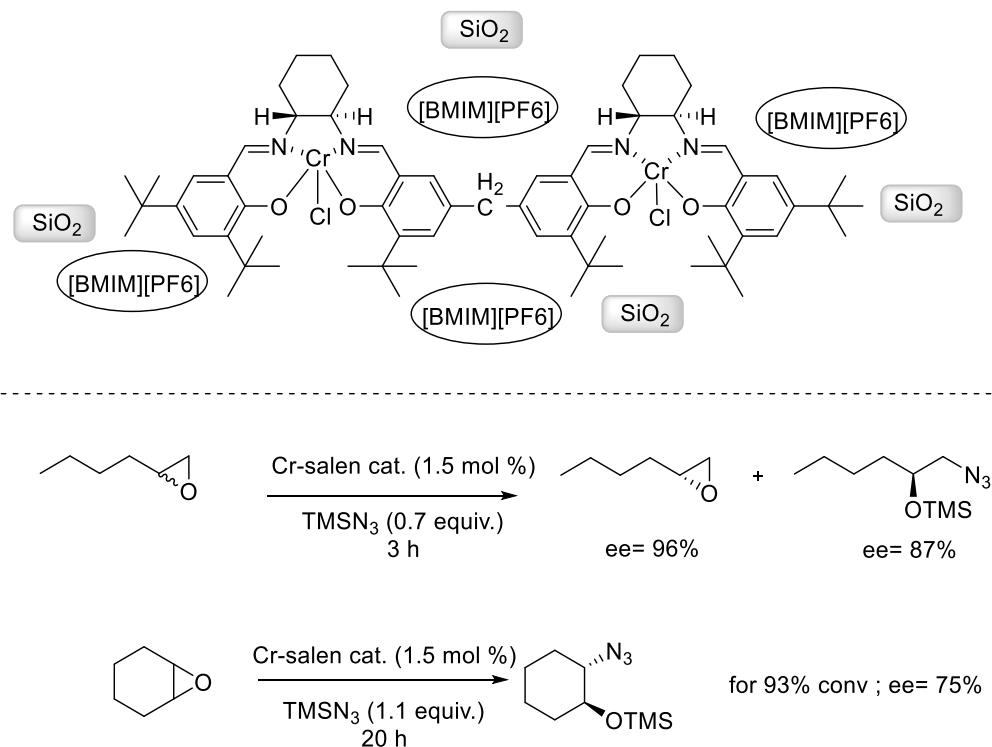


Figure 67: ARO of 1,2-epoxyhexane and cyclohexene oxide with TMSN_3 catalysed by dimeric-Cr SILP.

In another approach, in our group was prepared an electropolymerized chiral chromium thiophene-based salen complex.¹²⁴ The insoluble catalyst obtained by anodic polymerization at constant current of 50 mA and the monomer analogues were tested in various asymmetric catalytic transformations including the ARO of cyclohexene oxide with TMSN_3 in *tert*-butyl methyl ether (TBME) at room temperature (Figure 68). The reaction using both catalysts was slow, where 3 days were necessary to obtain 98% and 75% conversions in case of monomer and polymer catalysts respectively. However, the ring-opened product was isolated with low ee (49%) using the monomeric analogue and as racemic mixture when the electrogenerated catalyst was used. This latter, once used in a multi-catalytic reaction process in which the same batch of heterogeneous catalyst was used to promote successively different reaction, was efficiently recycled by simple filtration and reused for 9 runs.

¹²⁴ A. Zulauf, M. Mellah, E. Schulz, *Chem. Commun.* **2009**, 43, 6574–6576.

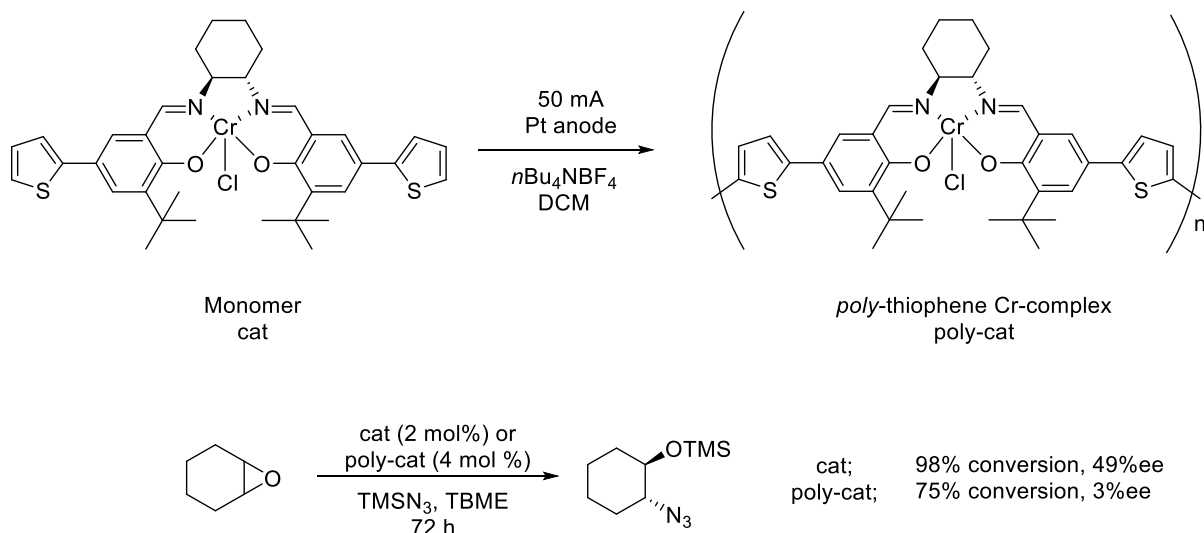


Figure 68: ARO of cyclohexene oxide catalysed by the electrogenerated heterogeneous Cr-thiophene based salen complex.

On the other hand, our group also prepared a calix-type Cr-salen complexes which contain 2 to 5 repeating thiophene-salen units and used them as an oligomeric mixture (Figure 69).^{109,c} The macrocyclic catalyst was employed in the heterogeneous ARO of cyclohexene oxide and 3,4-epoxytetrahydrofuran under the same previous conditions. It was recovered by filtration and reused for several times (up to 6 runs). The ring-opened products were obtained in good yields (62-90%) but with moderate enantioselectivities (42-62% ee). These results were comparable to those obtained with corresponding homogeneous analogues. In contrast, these macrocyclic catalysts proved to be much more selective than the analogous catalysts possessing a linear polymeric structure, thus confirming that their cyclic structure was more suitable for transformations involving a bimolecular activation mechanism.

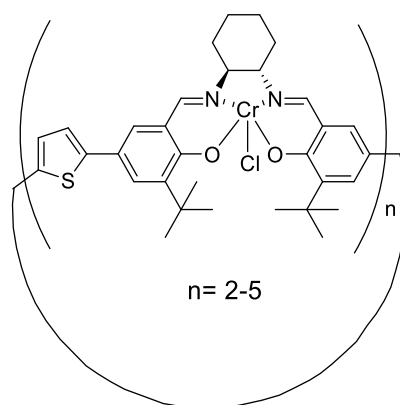


Figure 69: Macrocyclic calix-type thiophene based Cr salen complex.

Liu *et al.*¹²⁵ also studied the catalytic properties of macrocyclic oligomer-supported Cr-salen complexes in the ARO of cyclohexene oxide with TMSN_3 and in the kinetic resolution of terminal epoxides. This group synthesized three macrocyclic oligomeric cyclooctene-supported Cr-catalysts with different linker length (3, 8 and 12-bond linker; Figure 70). The formation of macrocycles was confirmed by NMR and MALDI-TOF spectroscopy. This latter showed that the macrocyclic ligands were obtained as a mixture of different ring size (dimers to decamers). The ARO reactions were carried out in diethyl ether with 0.2 mol% catalyst loading. It was noticed that the catalyst with the shortest linker showed the highest reaction rate (17 times higher initial TOF than Jacobsen's catalyst) while the catalyst with the longest one gave high enantioselectivity values (82% ee). The catalysts could be recovered by precipitation in acetone and recycled up to 5 times while maintaining high reactivity and selectivity. In this example, the length of the linker had two opposite roles playing on reactivity and enantioselectivity.

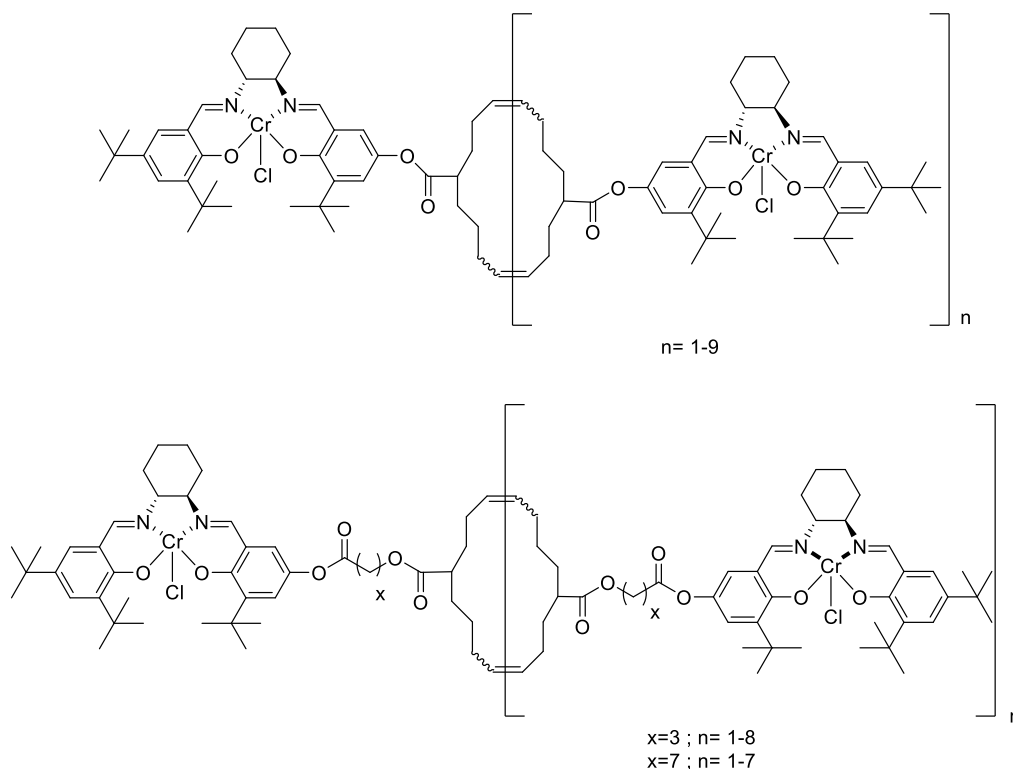


Figure 70: Macrocyclic oligomer-supported Cr-salen complexes.

In the first one the shortest linker enhances the cooperativity between two Cr-salen units, whereas in the second, a longer linker provided salen complexes with more flexibility to reach the optimal geometry and subsequent high enantioselectivity. In all reactions, the three supported catalysts

¹²⁵ K. Kinslow, A. M. Sevde, J. Liang, Y. Liu, *Tetrahedron: Asymmetry* **2015**, 26, 385–392.

outperformed homogeneous Jacobsen catalyst in terms of yield (conversion), thus indicating that the macrocyclic support promotes the bimetallic mechanism based catalysis by enhancing the cooperative interaction between neighboring Cr(III)–salen units.

Coordination cages have been widely explored for supramolecular catalysis. In this context, Cui and coworkers¹²⁶ prepared chiral such cages possessing metal–salen linkers. The prepared supramolecular nanoreactors consisted of six dicarboxylate linkers based on metal–salen complexes (with Mn(III), Cr(III), and Fe(III) metallic centres) and four Cp₃Zr₃ cluster vertices, giving a tetrahedral cage with a hydrophobic cavity. Remarkably, the mixed-linker cage containing both Mn–salen and Cr–salen linkers was tested in the sequential asymmetric epoxidation/ring-opening of 2,2-dimethyl-2*H*-chromene, affording the target product with high yield and enantioselectivity. The cage catalyst also allowed for very low catalyst loadings and remained active at a 0.005–0.01 mol% ratio. The reactions were performed under homogeneous conditions, but the catalyst could be recovered by precipitation through the addition of diethyl ether. It was recycled up to five times with only a slight decrease of enantioselectivity. The same group also explored metal-organic frameworks (MOFs) containing metal–salen linkers prepared by post-synthetic exchange of ligands. The mixed Cr–Mn MOFs catalyzed the sequential alkene epoxidation/ring-opening of 2,2-dimethyl-2*H*-chromene in good yield and enantioselectivity.¹²⁷

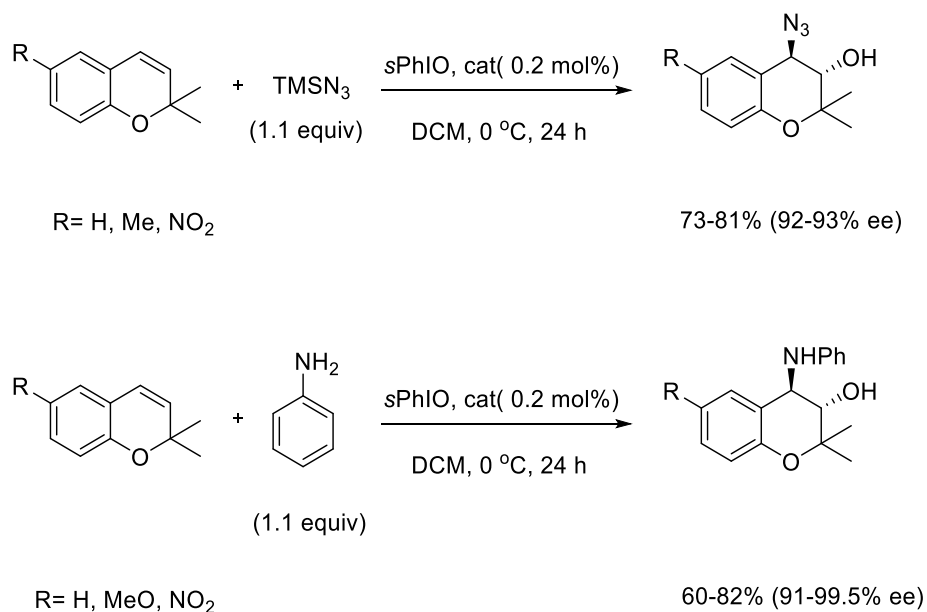


Figure 71: Sequential asymmetric epoxidation/ring opening of 2,2-dimethyl-2*H*-chromene catalyzed by mixed Mn–Cr coordination cage.

¹²⁶ J. Jiao, C. Tan, Z. Li, Y. Liu, X. Han, Y. Cui, *J. Am. Chem. Soc.* **2018**, *140*, 2251–2259.

¹²⁷ C. Tan, X. Han, Z. Li, Y. Liu, Y. Cui, *J. Am. Chem. Soc.* **2018**, *140*, 16229–16236.

All the examples mentioned illustrate the reports on the ARO of *meso*-epoxides with TMSN_3 , while many others have studied the ARO reactions with other nucleophiles such as anilines, amines, carbamates, thiols, selenols and with oxygen containing nucleophiles.

Using anilines and amines as nucleophile to open *meso*-epoxides appears to be a straightforward method to obtain vicinal amino alcohols instead of the use of TMSN_3 to form first the azido alcohol and then reduce it. Even though there is a possibility of coordination of amines acting as Lewis base to the metal salen complex and its deactivation, many successful strategies have been implemented to achieve high yields and ee values for such reactions.

To illustrate this point, we can mention the work performed by Kureshy and coworkers¹²⁸ using *in situ*-generated monomeric and polymeric Ti(V)-salen complexes (Figure 72) to promote the ARO of *cis*-stilbene oxide with aniline under a 20 mol% catalyst loading and in the presence of additives. The influence of the nature of the latter was evaluated, and the ring-opened product was obtained with high yield (99%) and excellent ee (>99%). The polymeric catalyst could be recovered by precipitation in hexane and reused for several times without significant loss of enantioselectivity.

The same group also reported the synthesis of a series of macrocyclic Cr-salen complexes with different counter ions and studied their catalytic properties in the ARO of a few cyclic and acyclic *meso*-epoxides with aniline, under optimized reaction conditions.¹²⁹ The catalyst bearing a chlorine atom as counter ion (Figure 72) gave the best results in terms of activity (98-99% yield) and enantioselectivity (up to 91% ee) and could be recovered by precipitation in a mixture of hexane/diethyl ether and reused for 5 runs without loss of reactivity or enantioselectivity.

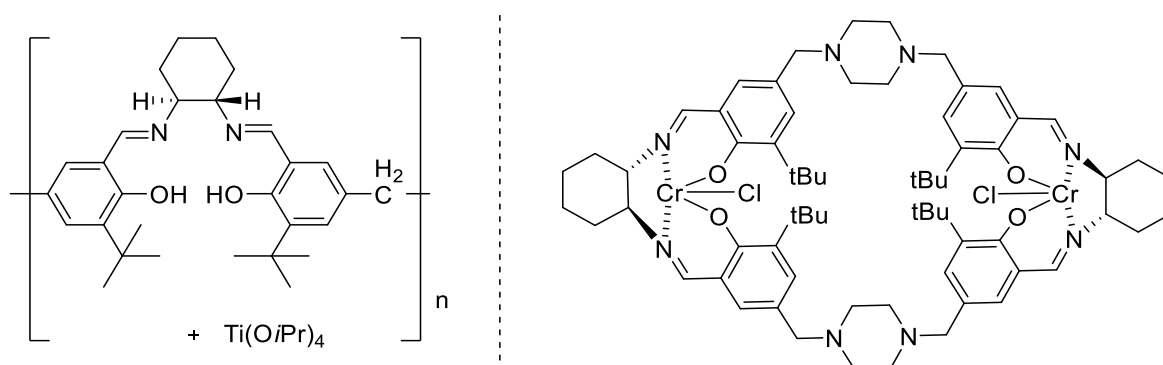


Figure 72: *In situ*-generated polymeric Ti(V)-salen complex and Macrocyclic Cr-salen complex with Cl⁻ as counter ion.

¹²⁸ R. I. Kureshy, M. Kumar, S. Agrawal, N.-U. H. Khan, B. Dangi, S. H. R. Abdi, H. C. Bajaj, *Chirality* **2011**, *23*, 76–83.

¹²⁹ R. I. Kureshy, K. J. Prathap, M. Kumar, P. K. Bera, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *Tetrahedron* **2011**, *67*, 8300–8307.

We summarized in this bibliographic part some reports on the design of salen complexes and particularly those possessing chromium as active site, embedded in different structures, to enhance the cooperative bimetallic mechanism between Cr-salen units for an increase of their reactivity in the ARO of *meso*-epoxides with nucleophiles especially TMSN_3 .

To our knowledge, there is no examples on the immobilization of such catalysts onto carbon materials via non-covalent π - π interactions. Such strategy looks very interesting to explore the effect of the carbon support such as graphitic materials, on the reactivity of the catalysts and the probable enantioselective induction in the ARO reaction of *meso*-epoxides. Furthermore, due to the hybrid character of such immobilized systems, it could be recovered and reused increasing thus the turnover number of such precious enantiopure catalysts.

2. Results and discussion

a) *Homogeneous catalysis*

The prepared chromium mono and bis-pyrene-tagged salen complexes have been thus engaged to promote the ARO of cyclohexene oxide with TMSN_3 (1.5 eq). They were used in a 2 mol% loading in all the catalytic tests (Figure 73). In all cases, the results have been compared to those obtained with the Jacobsen-Cr catalyst (**16**) prepared in our hands.

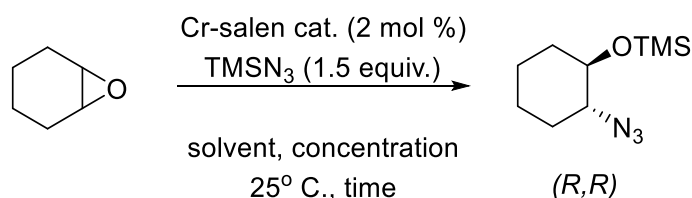


Figure 73: General scheme of the ARO reaction with TMSN_3 .

The study was first conducted using Sym-C4-Cr (**13**) as catalyst to promote the ARO of cyclohexene oxide with TMSN_3 in various solvents (Table 6). Reactions were carried out for 24 hours at 25 °C. Conversions and ee values were determined by GC using dodecane as internal standard. The absolute stereochemistry was assigned as *1R,2R* based on comparison with the literature.¹¹⁵

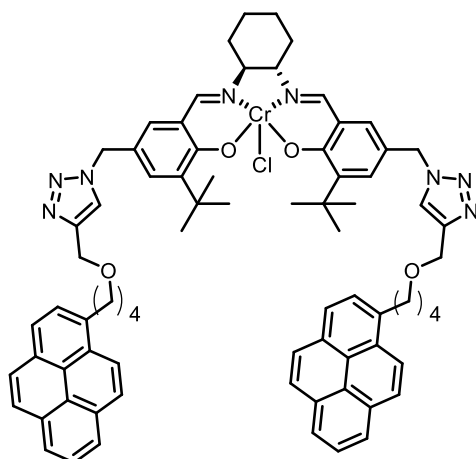


Figure 74: Symmetrical C4chromium pyrene-tagged salen complex Sym-C4-Cr 13.

Good conversions have been obtained after 24 hours (55-96%) but the enantiomeric excess was unstable with the reaction time, in which decreasing enantioselectivity values were observed in almost all solvents with this catalyst. In DCM, almost complete conversion was obtained but with only 14% ee for the target product after 24 hours.

Best results in terms of activity and selectivity were found in THF (93% conv, 52% ee), that was thus chosen as solvent for the next tests. Moreover, it was used to ensure the solubility of the catalysts and thus to allow a completely homogeneous reaction.

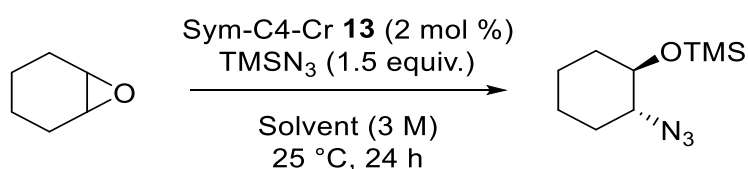


Table 6: Sym-C4-Cr (13) reactivity in various solvents.

Solvent	Time (h)	Conv (%)	ee (%)
DCM	7	56	24
	24	96	14
AcOEt	7	32	51
	24	82	27
Toluene	7	50	51
	24	55	56
Me-THF	7	37	59
	24	78	45
THF	7	61	68
	24	93	52

In our hands, Jacobsen's catalyst (**16**) led to only 33% conversion after 24 hours with 73% ee for the expected product when the reaction was performed at a quite high concentration (3M) in THF (Entry 1, Table 7). However, all pyrene-tagged complexes showed a much better activity compared to Jacobsen's catalyst with 91-96% conversion in the same reaction time but with diminished enantioselectivity values. The symmetrical complexes (**12** and **13**) were found to be much poorly enantioselective than the unsymmetrical analogues, for which only 56% and 52% ee were obtained respectively (Table 7, entries 2 and 4). This could be due to the absence of two *tert*-butyl groups in these complexes while three were present in the unsymmetrical species. These elements are known to be crucial to keep a favourable hindrance and to improve the enantioselectivity values. The catalyst Unsym-C1-Cr **14** approaches an enantioselectivity value similar to that obtained through the use of Jacobsen's catalyst, probably because of a more pronounced steric hindrance.

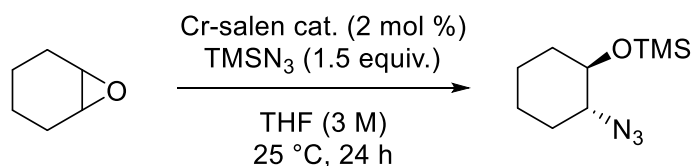


Table 7: Evaluation of catalysts activities in THF.

Entry	Catalyst	Conv (%)	ee (%)
1	Jacobsen (16)	33	73
2	Sym-C4 (13)	93	52
3	Unsym-C4 (15)	94	59
4	Sym-C1 (12)	91	56
5	Unsym-C1 (14)	96	70

In order to understand the behaviour of the pyrene-tagged complexes and to be able to compare results with the subsequent heterogeneous reactions, all the complexes were involved in the same catalytic reaction but at 0.9 M (Table 8). Indeed, the supported catalysis was firstly carried out at a low concentration, to ensure an efficient stirring.

Under these conditions, the symmetrical species (entries 1 and 3) showed better activities than the unsymmetrical complexes (entries 2 and 4). This could be explained by a favourable cooperative mechanism occurring between the symmetrical complexes due to their association thanks to π - π

interactions between pyrene moieties. The ee values are identical to those obtained at 3M, except in case of the symmetrical complex **12**, for which an improved ee was obtained (74%) probably due to its rigidity and its steric hindrance; in comparison, indeed, Sym-C4-Cr **13** is more flexible due to the longer carbon chain between the pyrene moiety and the ligand active site.

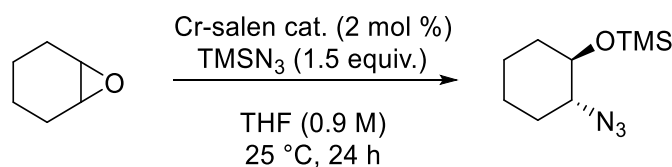


Table 8: Reactivity of all catalysts in THF at low concentration.

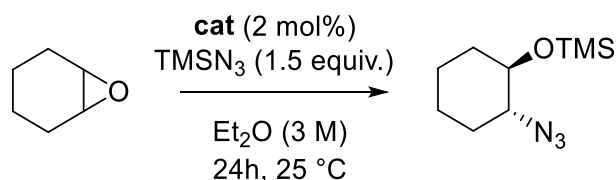
Entry	Catalyst	Conv (%)	ee (%)
1	Sym-C4 (13)	52	50
2	Unsym-C4 (15)	24	56
3	Sym-C1 (12)	62	74
4	Unsym-C1 (14)	31	73

When THF is used as solvent, the enantiomeric excess was unstable during time and during recycling for the heterogeneous catalysis (detailed below). In addition, the catalysts lose their reactivity and the reactions were not reproducible. Indeed, decreasing conversions values were obtained in repeated reactions and successive runs. This result could be explained by the fact that THF can act as an apical ligand coordinating to the complex and inhibiting thus the activation of cyclohexene oxide by the Cr-THF complex units.¹⁰⁵

For this reason, THF was replaced by diethyl ether which is a non-coordinating solvent used by Jacobsen for the ARO of *meso*-epoxides and leading to very good results in terms of yield and ee. Accordingly, all Cr-complexes were engaged in the ARO of cyclohexene oxide in ether at 3M. All catalysts were initially insoluble in Et₂O, but the reaction mixture became homogeneous with the product formation.

Jacobsen's catalyst **16** led to the desired product with 88% ee and 78% conversion after 24 hours, a much better result compared to the ones obtained by running the reaction in THF and closer to those reported in the literature.¹¹⁵ Different results were obtained depending on our catalysts structures. Again, and to our delight, all the pyrene-tagged complexes were found more active than the

Jacobsen's catalyst **16**, leading to almost complete conversions after 24 hours. We assume again that this is probably due to the association of pyrene-tagged complexes via non-covalent π -stacking interactions, enhancing the bimetallic cooperative mechanism between two chromium metal centres. The presence of non-covalent interactions between salen-based complexes was previously investigated and their influence on the cooperativity was also studied.¹³⁰

Table 9: Evaluation of catalysts activities in Et_2O

Entry	Catalyst	Conv (%)	ee (%)
1	Jacobsen (16)	78	88
2	Sym-C1 (12)	86	26
3	Unsym-C1 (14)	>99	81
4	Sym-C4 (13)	98	8
5	Unsym-C4 (15)	>99	70

Similarly, the symmetrical complexes **12** and **13** showed very low enantioselectivity values affording the product with 26% and 8% ee, respectively. This low selectivity with respect to the unsymmetrical analogues is suggested to be due to the bifunctionalization of these complexes by the pyrene groups and thus the lack of *t*Bu groups in the *para* position of phenol, as already proposed. Moreover, a possible intramolecular π -stacking interaction between two adjacent pyrene moieties could in this case constraint the access to the catalytic sites for a bimolecular mechanism and decrease thus the enantioselectivity for the symmetrical complexes. Catalyst **13** was found to be the much poorly enantioselective probably due to its high degree of flexibility with its four-carbon chain length.

¹³⁰ a) D. R. Blechschmidt, M. D. Woodhouse, S. Inagaki, M. Whitfield, A. Ogunsanya, A. Yoder, D. Lilly, E. W. Heim, L. N. Soucie, J. Liang, Y. Liu, *Org. Biomol. Chem.* **2018**, *17*, 172–180. b) J. Liang, L. N. Soucie, D. R. Blechschmidt, A. Yoder, A. Gustafson, Y. Liu, *Org. Lett.* **2019**, *21*, 513–518.

On the other hand, the unsymmetrical complexes **14** and **15** delivered better results (entries 3 and 5, Table 9). Unsym-C1-Cr **14** proved again his superiority over its more flexible analogue and led to complete conversion with 81% ee for the desired product, a very close value to that obtained with Jacobsen's catalyst **16**. Furthermore, additional experiments showed that a complete conversion was already achieved after only 6 h with this catalyst, with the same enantioselectivity value. The activity of this catalyst was further screened in various solvents (Table 10).

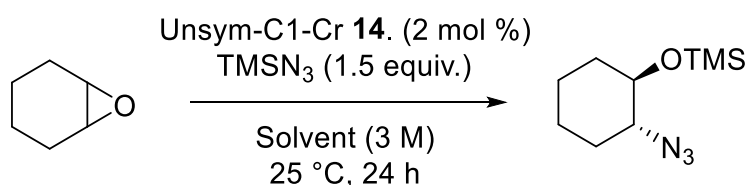


Table 10: Reactivity of Unsym-C4-Cr (**14**) reactivity in various solvents.

Solvent	Conv (%)	ee (%)
THF	96	70
DCM	74	40
AcOEt	100	81
Toluene	98	76
Me-THF	100	80
Et ₂ O	100	81

Similar results in terms of activity and enantioselectivity were found when ethyl acetate and methyl-THF are used instead of diethyl ether, while a poor ee (40%) is obtained in DCM and a slightly diminished ee (76%) is found in toluene.

To conclude, Cr-modified salen complexes are able to promote the ARO of cyclohexene oxide with TMSN₃ in homogeneous conditions, with high conversions and enantioselectivities values. They are all more active than Jacobsen's catalyst in various reaction conditions (concentration, solvent). Best and reproducible results were obtained in diethyl ether as non-coordinating solvent. Moreover, unsymmetrical complexes bearing only one pyrene group are more enantioselective than the symmetrical analogues, retaining the activity of the parent Cr-salen complex for this reaction, and thus are very good candidates to promote supported ARO.

b) Supported catalysis

The heterogeneous catalysis was then performed in the conditions matching those performed for the homogeneous catalytic tests. First, the supported catalyst Sym-C4-Cr **13@rGO** (Figure 75) was involved in the ARO of cyclohexene oxide in THF at 0.9M. We suppose that this catalyst, with a longer spacer between the support and the active site, is an optimal choice to avoid as possible any modification on the catalytic activity of the supported complex compared to the homogeneous one. Heterogeneous reactions were performed at low concentrations because of settling problems; THF was easily absorbed by rGO powders and thus stirring did not easily occur.

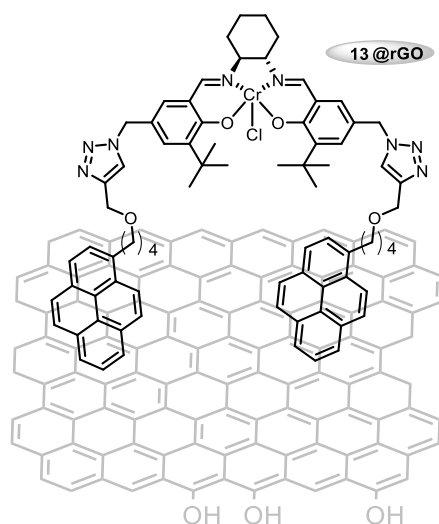


Figure 75: Supported Sym-C4-Cr **13@rGO**.

Consequently, a suspension of the supported catalyst corresponding to a 2 mol% catalytic ratio in THF was stirred at room temperature, then the epoxide together with the internal standard were added. Finally, TMSN_3 was added, and the heterogeneous mixture was stirred for 24 hours. Table 11 summarizes the first attempts of supported ARO using **13@rGO** as catalyst. Using the first batch of immobilized catalyst (entries 1 and 2), the first run led to 97% conversion with 45% ee after 24 h, which represents an excellent starting attempt proving that our supported catalytic system works without any detrimental effect of the rGO on the catalytic activity, even though there is an influence on the ee.

At the end of the reaction, the solid was filtered off, washed with DCM and vacuum dried to be further involved in the second run. An ^1H NMR analysis of the filtrate revealed the presence of a by-product with the desired opened product. We suppose that the desired product is not stable in DCM and a

possible hydrolysis reaction could occur in these conditions due to the acidity nature of DCM. An important decrease of conversion and ee was observed after the 2nd run (52% conv, 37% ee).

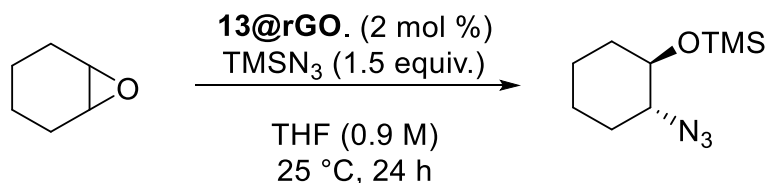


Table 11: Heterogeneous ARO of cyclohexene oxide with Sym-C4-Cr@rGO in THF at 0.9M

Entry	Run	Conv (%)	ee (%)
1	1	97	45
2	2	52	37
3	1	52	61
4	2	39	50
5	3	80	29
6	4	77	17

A new batch of **13@rGO** was prepared and engaged in a new catalytic cycle (Table 11, Entry 3). Only 52% conversion was obtained with 61% ee for the first run, confirming the difficulty to obtain of reproducible results in these conditions. The supported catalyst was filtered and washed with cold acetone in order to avoid any possible side reaction in DCM. Effectively in this case, the recovered filtrate contains only the desired product. We succeeded to recover the supported catalyst for four consecutive runs by using this recycling procedure, without any loss of the supported catalyst. It was indeed weighted at each run, after the vacuum drying, and its amount remained intact. Hence, Four runs were realized but an important decrease in ee values was observed, from 61% to 17%, while an unexpected variation of conversion was observed (entries 4 and 5).

Based on the results obtained under homogeneous and heterogeneous conditions using catalyst **13**, we concluded that it has a particular behaviour in the catalysis of this reaction due to its non-optimal structure and conformation, with a particular flexibility and catalytic site accessibility.

Consequently, and following the same reaction conditions, Unsym-C1-Cr **14@rGO**, in which the spacer between the anchoring moiety and the active site is smaller, was engaged in the catalysis, in THF at a low concentration. It was possible to recycle this heterogeneous species for 3 runs after filtration, subsequent washing by cold acetone and vacuum drying. An enhanced reactivity was observed in the first two runs compared to the homogeneous catalysis (52% and 60% conversions vs

31% in Table 12), while a diminished enantioselectivity was clearly obtained during all catalytic cycles (from 66% to 31% ee).

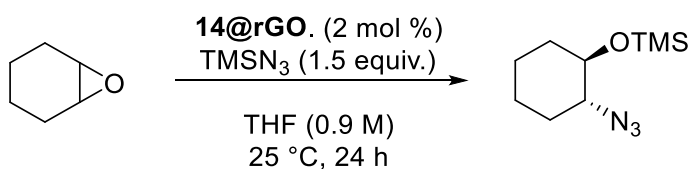
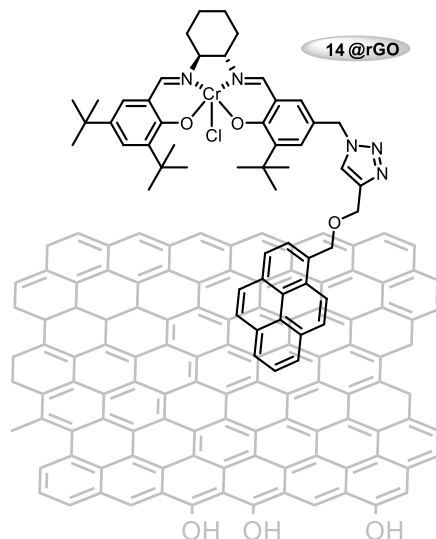


Table 12: Heterogeneous ARO of cyclohexene oxide with Unym-Cl-Cr@rGO in THF at 0.9M

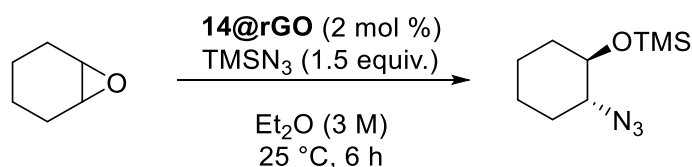
Run	Conv (%)	ee (%)
1	52	66
2	60	60
3	34	31



According to these results and our previously described observations when the catalysis was performed under homogeneous conditions, it was clear that THF was not the ideal solvent in which good activity and enantioselectivity could be afforded. It possesses obviously an inhibitor effect on all the pyrene-tagged complexes in homogeneous as supported ARO reactions.

Catalyst **14** seems to be the best catalyst affording the desired product with conversions and ee values very close to those obtained with Jacobsen's catalyst, at least when used in homogeneous conditions; it was therefore chosen to continue the study of the ARO reaction of cyclohexene oxide in a heterogeneous medium using Et₂O as solvent.

In this case, the reaction with a 3M concentration was carried out, however this led to non-ideal stirring conditions, with the formation of a slurry. Nevertheless, and pleasingly, the first run using **14@rGO** in a 2 mol% catalytic ratio showed complete conversion within 6 h, indicating that the support did not affect the activity of the immobilized catalyst. However, the ring-opened product was isolated with a slightly decreased ee of 63% (Table 13). After completion, the solid was filtered off, washed with diethyl ether (the reaction solvent) since the decantation of the solid before its filtration was difficult to achieve using cold acetone, vacuum dried and involved in a second catalytic run after adding again the substrate. A complete conversion was also obtained with an improved ee value of 75%.

Table 13: Heterogeneous ARO of cyclohexene oxide with Unym-C1-Cr@rGO in Et₂O at 3M

Run	Conv (%)	ee (%)
1	>99	63
2	>99	75
3	>99	75
4	>99	76
5	>99	79
6	>99	76
7	98	76
8	98	75
9	96	72
10	96	68

The second successful run, as the next ones, made it possible to reuse the same batch of supported catalyst 10 times without a significant loss of activity and with very good ee values reaching 79%. This result confirms the absence of any loss of catalyst during the recycling procedure, which was also proved by weighting the supported catalyst at the end of each run.

These results match those obtained with the non-supported catalyst **14** in the same reaction conditions, indicating that the immobilization of this complex did not alter its activity, which is often the case in heterogeneous reactions. Moreover, the enantioselectivity retained its high values by using this procedure. Despite the formation of a very thick reaction medium, it does not appear that difficult mass transfers operate which would slow down the reaction; the supported catalyst remains very accessible to the substrates.

In the same way, another test to prove the efficiency of this immobilization procedure was performed using the other supported unsymmetrical complex derived from pyrene butanol, Unsym-C4-Cr **15**. The reaction occurred in the same heterogeneous conditions used for the previous tests described in Et₂O. **15@rGO** was involved in 3 successful consecutive runs giving almost complete conversions. It was noticed that the ee retains its high value after the first run and reaches 70%, the same value as

obtained in homogeneous conditions. This recycling experiment proves the efficiency of our immobilization procedure and confirms its neutrality toward the catalyst's activity and selectivity.

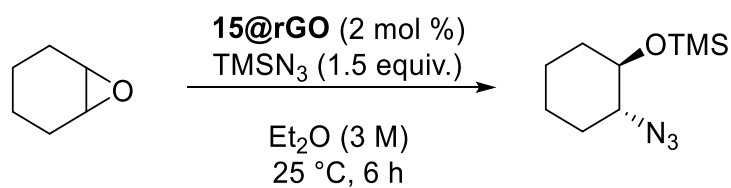
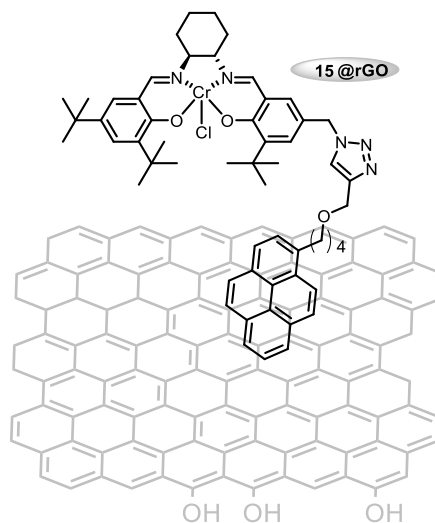


Table 14: Heterogeneous ARO of cyclohexene oxide with Unym-C1-Cr@rGO in Et₂O at 3M

Run	Conv (%)	ee (%)
1	>99	60
2	>99	70
3	>99	70



As noticed, the enantiomeric excess retained its high values only after the first run in case of both supported unsymmetrical complexes. This could be due to an effect of the washing solvent used in each case. Indeed, after the immobilization procedure, the supported catalyst has been washed with DCM while at the end of the first catalytic run, it was washed with diethyl ether; a more polar solvent. Therefore, we suggest that such polar solvent displayed a convenient medium for the dispersion of rGO sheets leading thus to a more favourable active sites accessibility.

Nevertheless, the unsymmetrical catalyst **14**, with a smaller spacer length between the pyrene moiety and the chromium active site, was found to be the best catalyst affording the ring-opened product with high conversions and ee values and outperforming all other pyrene-tagged complexes in homogeneous as in supported catalysis.

To sum up, the new modified chromium salen complexes bearing pyrene moieties are very efficient catalysts to promote the asymmetric ring opening reaction of cyclohexene oxide by TMSN₃. All the series were found more active than the parent Jacobsen's catalyst but remained less enantioselective. The unsymmetrical complexes, with only one pyrene group and one *t*Bu group in the *para* position of the phenol moiety, were more efficient than the symmetrical analogues. In addition, the unsymmetrical complex derived from pyrene methanol has outperformed other catalysts and approaches an enantioselectivity value similar to that of Jacobsen's catalyst.

A robust supported catalytic system was obtained with **14@rGO** showing a high activity and efficient recovery ability up to 10 times by simple filtration. As far as we know, this is the first example of

non-covalent immobilization of salen complexes via π -stacking interactions onto reduced graphene oxide as a support and the demonstration of the efficiency of the thus obtained heterogeneous complex.



Figure 76: Heterogeneous ARO of cyclohexene oxide with robust **14@rGO** supported catalyst.

B. Application in Hetero-Diels-Alder reaction

In addition to the ARO of *meso*-epoxides, chromium salen complexes are commonly known as efficient catalysts for the Hetero Diels-Alder reaction between aldehydes and diene with a heteroatom.

The asymmetric HDA reaction is one of the powerful reactions in organic synthesis leading to the formation of optically active six-membered heterocycles with large applications, especially in the synthesis of natural products and for medicinal chemistry.¹³¹ Indeed, the asymmetric HDA reaction, involving carbonyl compounds as the heterodienophiles or the heterodienes, has allowed the preparation of numerous chiral six-membered oxygen-containing heterocycles. This kind of reaction requires activation of the carbonyl compounds by a Lewis acid to facilitate the attack of the diene in a specific hindered environment to introduce the enantioselectivity. Therefore, several chiral Lewis acid complexes based on chromium, titanium, copper, aluminium, rhodium or even other metals have been developed to catalyse asymmetric HDA reactions.¹³² The formal HDA reaction between Danishefsky's diene and aldehydes has been efficiently catalysed by the chromium Jacobsen's catalyst giving access to enantioenriched dihydropyranones known for their utility in organic synthesis.¹³³

¹³¹ E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667.

¹³² H. Pellissier, *Tetrahedron* **2009**, *65*, 2839–2877.

¹³³ S. E. Schaus, J. Brånalt, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 403–405.

Thus, we aim in this part to study the catalytic properties of the novel pyrene-tagged chromium complexes and their supported analogues in the HDA of various aldehydes with Danishefsky's diene in homogeneous conditions and in heterogeneous ones. Furthermore, a multi-substrate supported catalysis is investigated, in which a different aldehyde will be introduced as reacting substrate in each run. By this way, the performance of the supported catalysts and their recyclability will be exploited.

1. State of art

In 1998, Jacobsen and coworkers⁵⁵ demonstrated that Cr(III)-salen complexes are efficient catalysts for the hetero-Diels-Alder reaction between various aldehydes and the Danishefsky's diene providing useful dihydropyranones with good yields and enantioselectivity values. After an optimization of the reaction conditions, and as the tested catalysts were cationic, it was proven that the ee is affected by the nature of the catalyst counterion; higher ee were obtained with more electronegative counterions such as azide and fluoride. Best results have been observed at low temperatures (-30 °C).

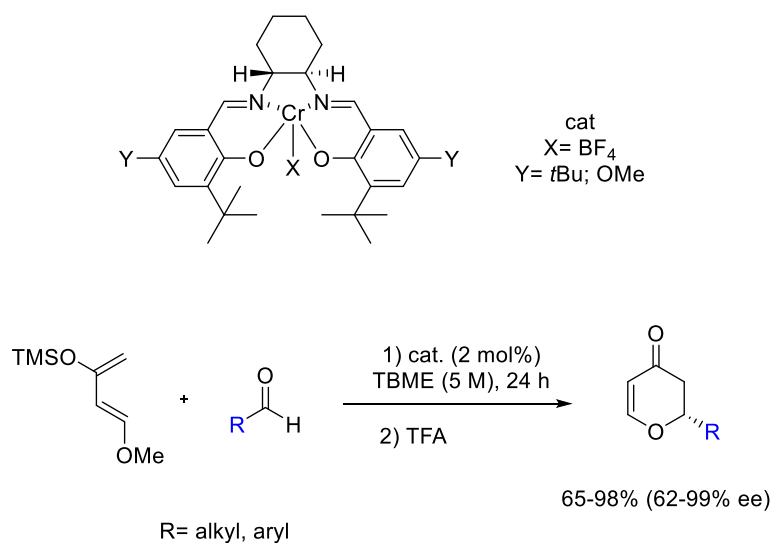


Figure 77: HDA of alkyl and aryl aldehydes catalysed by Jacobsen's catalyst.

Mechanistic studies showed that the salen-catalysed HDA is achieved by a concerted [4+2] cycloaddition rather than a Mukaiyama-aldol reaction.

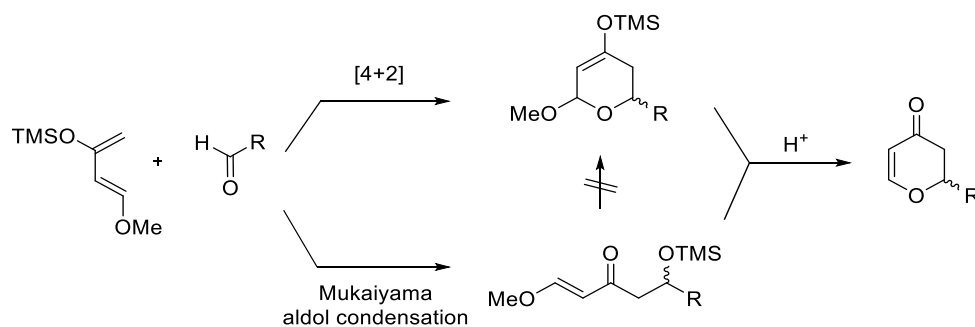


Figure 78: Mechanism of HDA reaction.

Katsuki *et al.*¹³⁴ reported the synthesis of a second generation of Cr and Mn salen complexes bearing a binaphthyl moiety as chiral auxiliary and catalysing the HDA of various aromatic aldehydes with Danishefsky's diene. The *R,R* diastereoisomer of each catalyst was the most suitable to efficiently promote the catalytic reaction. All catalysts were efficient Lewis acid catalysing the HDA with very good yields (up to 99%) and ee (up to 98%) and showed a different substrate specificity. It was noticed that, in the case of the Mn-salen complexes, the presence of polar *o*-substituent is responsible of a decrease of enantioselectivity probably due to their coordination to the Mn metal thus changing the catalysts conformation.

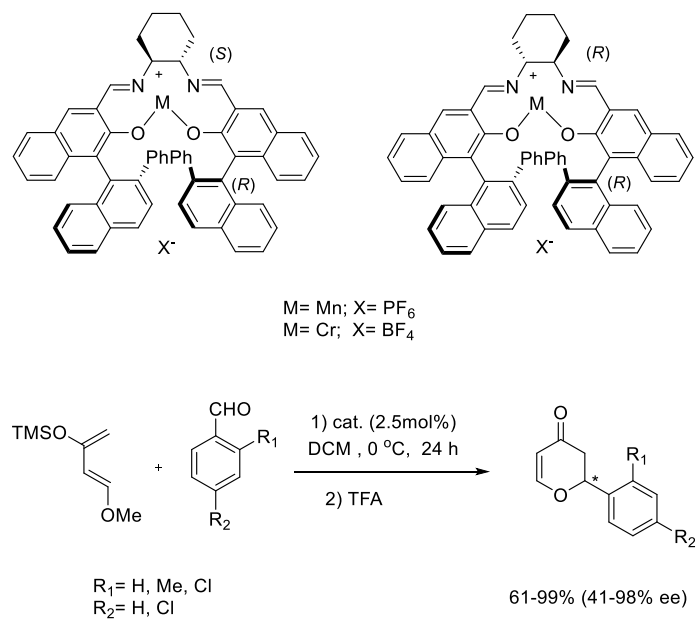


Figure 79: HDA reaction catalysed with second generation Mn and Cr-salen complexes.

Modifications of the structure of Jacobsen's catalyst have been performed in order to improve its enantioselectivity,¹³⁵ and to facilitate its recovery and reuse.

¹³⁴ K. Aikawa, R. Irie, T. Katsuki, *Tetrahedron* **2001**, *57*, 845–851.

¹³⁵ W. Chaładaj, P. Kwiatkowski, J. Jurczak, *Tetrahedron Letters* **2008**, *49*, 6810–6811.

Schulz and coworkers¹³⁶ prepared a chiral electropolymerized thiophene-based chromium salen complex as insoluble powder used as catalyst to promote the HDA of several aldehydes with Danishefsky's diene. The asymmetric HDA of various aliphatic and aromatic aldehydes was first promoted by the monomer thiophene-based complex; the desired dihydropyranones were obtained in good yields (up to 98%) and enantioselectivity (up to 82%), this latter was lower than that obtained with Jacobsen and Katsuki catalysts probably due to different electronic effects and steric hindrance caused by the thiophene substituents. The heterogeneous polymer catalyst was used and recycled via filtration for 15 runs without any loss of activity or enantioselectivity and engaged in a multi-substrate recycling procedure showing in both cases a high recycling stability and affording the target products with good yields and ee.

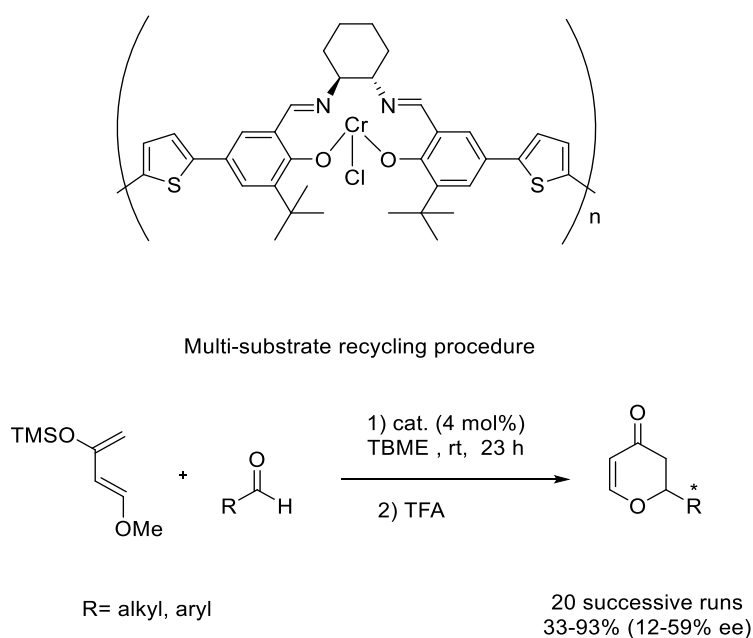


Figure 80: Multisubstrate catalytic system catalysed by Poly-thiophen based Cr-salen complex.

Moreover, Seebach *et al.*¹³⁷ reported the preparation of vinyl-substituted salen ligands and their immobilization on Me₃Si-hydrophobized silica gel (CPG: controlled-pore glass) via AIBN-mediated radical addition of mercaptopropyl substituent to styryl bound. The corresponding Cr-complexes were synthesized and engaged in the HDA reaction of caproaldehyde and benzaldehyde with Danishefsky's diene under heterogeneous conditions. CPG-immobilized catalysts conducted the HDA reaction affording the desired products with approximately similar performance as the

¹³⁶ A. Zulauf, M. Mellah, R. Guillot, E. Schulz, *Eur. J. Org. Chem.* **2008**, 2008, 2118–2129.

¹³⁷ A. Heckel, D. Seebach, *Helv. Chim. Acta.* **2002**, 85, 913–926.

homogeneous Jacobsen's catalyst (Figure 81). They could be reused up to eleven runs with decreased activity while a surprising increase in enantioselectivity has been observed during the first runs.

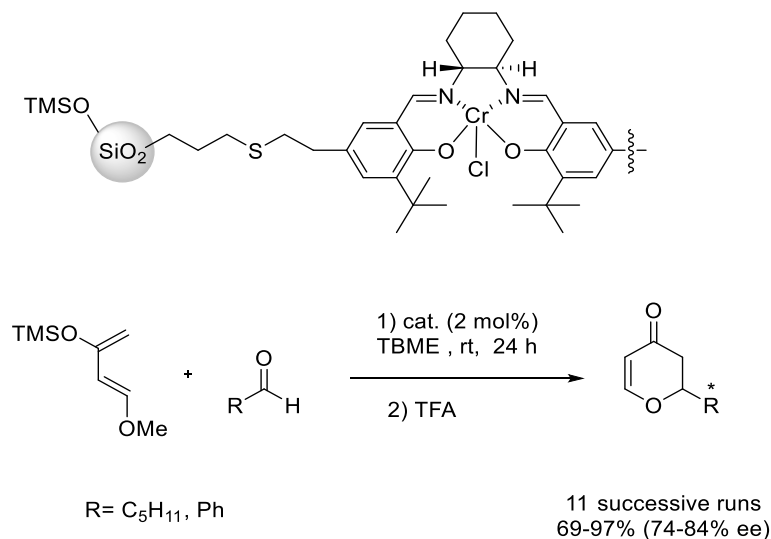


Figure 81: HDA of various aldehydes catalysed by CPG-immobilized Cr-salen complexes.

Furthermore, Hajji *et al.*¹³⁸ described the use of hyperbranched polyglycerol (PG) as support to covalently immobilize unsymmetrical salen ligand. In this case, one of the aldehyde moieties was anchored to the support and the synthesis was continued further via a condensation reaction with the prepared mono-imine salt. The resulting material was purified using preparative GPC. Various PG-supported Cr-salen complexes were prepared and tested in the HDA reaction of benzaldehyde and Danishefsky's diene leading to very good catalytic activity (up to 98% conversion) and enantioselectivity (up to 78% ee); results that were comparable to those obtained with Jacobsen's catalyst (Figure 82). The soluble PG-supported catalysts could be recovered by dialysis and reused for three runs with the same activity and a slightly diminished enantioselectivity.

¹³⁸ C. Hajji, S. Roller, M. Beigi, A. Liese, R. Haag, *Adv. Synth. Catal.* **2006**, *348*, 1760–1771.

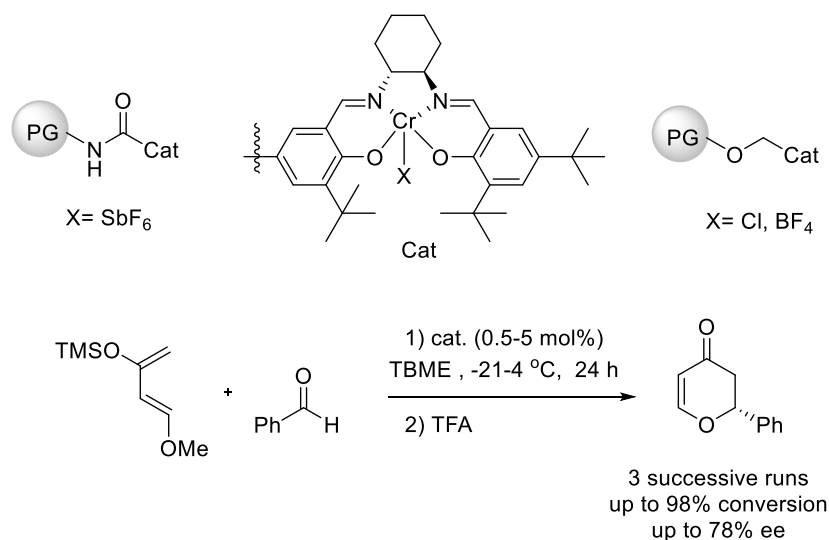


Figure 82: HDA of benzaldehyde catalysed by PG-supported Cr-salen complexes.

2. Results and discussion

a) Homogeneous catalysis

On the basis of the results obtained for the ARO of cyclohexene oxide with TMSN_3 and the excellent reactivity of Unsym-C1-Cr, only complexes of the generation derived from pyrene methanol were involved in the HDA reaction between various aldehydes and Danishefsky's diene.

Reactions were realized at room temperature in DCM at a 5M concentration, each time with a 2 mol% catalytic ratio. Then, a further deprotection step using trifluoroacetic acid TFA is required to obtain the corresponding dihydropyranone. Conversions and ee values were determined by GC with dodecane as internal standard. The configuration of the products was determined on the basis of those described in the literature.

First, the performances of both pyrene methanol-tagged complexes were tested in the HDA reaction of cyclohexane carboxaldehyde with the diene in a slight excess and compared to the results obtained in the presence of Jacobsen's catalyst **16** (Table 15).

The unsymmetrical catalyst **14** provided a similar activity and enantioselectivity as Jacobsen's catalyst and afforded the cycloaddition product with 73% conversion of the aldehyde and 78% ee in the product. In contrast, the symmetrical analogue was less active with only 23% conversion after 24 h.

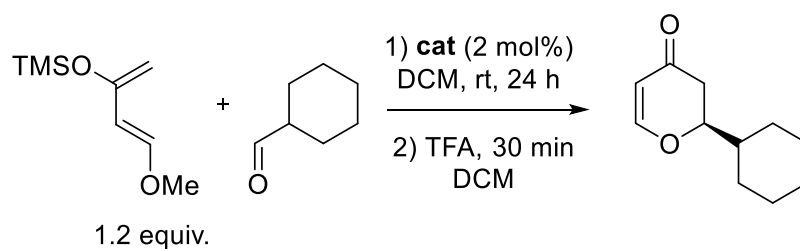


Table 15: Catalysts activities in the homogeneous HDA reaction

Catalyst	Conv (%)	Yield (%)	ee(%)
Jacobsen (16)	84	69	78
Sym-C1-Cr (12)	23	-	80
Unsym-C1-Cr (14)	73	61	78

For this reason, catalyst **14**, which is the best catalyst for the two tested catalytic reactions (ARO and HDA), was chosen for the rest of the study. A rapid screening of solvents was performed (Table 16). A slight loss of activity in ethereal solvents was observed, which seems however not to have any influence on the enantioselectivity of the reaction (78% ee). The study was thus pursued with the use of DCM as reaction solvent.

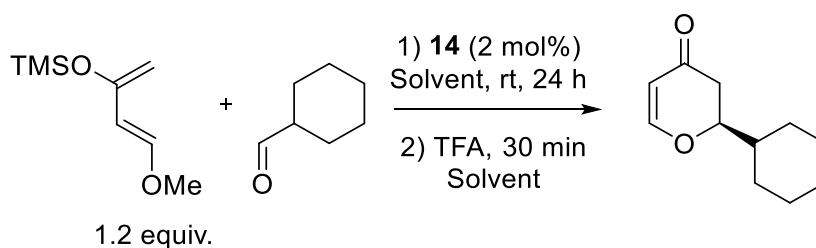


Table 16: Catalytic HDA of cyclohexane carboxaldehyde mediated by Unsym-C1-Cr 14 in various solvents.

Solvent	Conv (%)	ee (%)
DCM	73	78
Et ₂ O	67	78
Me-THF	61	78

Next, the activity of Unsym-C1-Cr **14** was tested in the HDA of various aromatic aldehydes (Table 17). Almost complete conversions were observed in this case with good ee values, these results are comparable to those obtained in the literature.¹³⁴ A better enantioselectivity was observed with the *o*-methoxybenzaldehyde (75% ee). These results prove the efficiency of Unsym-C1-Cr **14** as catalyst to promote the HDA reaction of various aldehydes, and thus the possibility to test a supported catalyst in multi-substrate process. This latter represents an original method in which a new substrate would be introduced in each run, leading to the use of the same batch of catalyst for several reactions involving different substrates with, if possible, no contamination of the products with the residual substrates and/or products of previous runs.

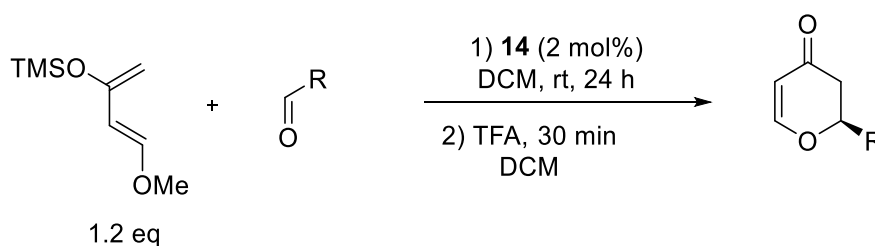


Table 17: Enantioselective HDA of various aldehydes using catalyst **14**.

Entry	Substrate	Conv (%) ^a	ee (%)
1		73	78 ^b
2		98	58 ^b
3		99	63 ^c
4		99	75 ^c

[a] Determined by GC with dodecane as internal standard. [b] determined by chiral GC. [c] determined by chiral HPLC.

b) Supported catalysis

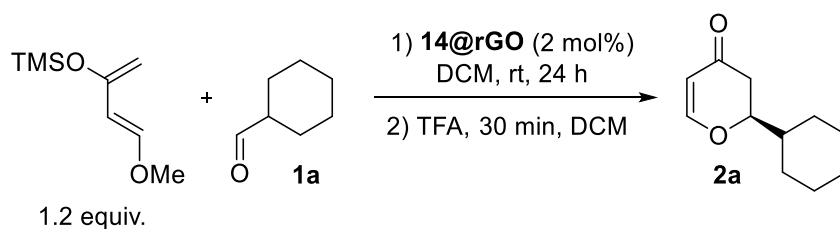
HDA reactions in heterogeneous conditions were performed under conditions exactly matching those used for the homogeneous catalytic tests. A black suspension of **14@rGO** corresponding to 2 mol% catalytic ratio with respect to the substrate was engaged in the HDA reaction of cyclohexane carboxaldehyde with Danishefsky's diene in DCM. Reactions were conducted for 24 hours.

The first run afforded the desired product with conversion and enantioselectivity values close to those obtained in homogeneous conditions (Entry 1, Table 18). This again confirms that the support has no detrimental effect on the catalyst's performance. Moreover, a test reaction was realized by using unmodified rGO in the same catalytic reaction, leading to no conversion after 24 hours of stirring; the absence of effect of the support on the reactivity is therefore well confirmed by this blank experiment.

After completion, the supported catalyst was filtered off, washed with cold DCM and vacuum dried to be ready for another catalytic run. At the same time, the recovered supernatant was further treated with TFA and purified using column chromatography to obtain the enantioselectivity value of the product by chiral GC or HPLC.

During the first four subsequent runs, an important decrease of the conversion values with each recycling was observed, while the selectivity of the supported catalyst was maintained. The very low conversion of 14% at the end of the 4th run prompted us to change the washing solvent and to use cold acetone instead of DCM. Interestingly, this resulted in the complete retention of activity and enantioselectivity for the next 4 runs (entries 5 to 8). We propose that acetone is both a polar solvent which promotes π -stacking type interactions, and a favourable medium for the dispersion of the rGO carbon sheets, which allows a better accessibility to the catalytic sites.¹¹³ The recycling procedure was not easy using cold acetone because the decantation of the solid in acetone before its filtration was difficult to achieve. Consequently, diethyl ether, in which the recycling procedure was more facilitated, was used instead and led to identical results in run 9.

A new batch of Unsym-C1-Cr **14@rGO** was consequently prepared and engaged in a new recycling experiment using diethyl ether as washing solvent from the first run (entries 10 to 16). Pleasingly, the supported catalyst showed great stability and efficiency, reproducing almost the same conversions and ee values for 7 subsequent runs.

Table 18: Heterogeneous HDA of cyclohexane carboxaldehyde using **14@rGO** in DCM.

Entry	Run	Conv (%)	ee (%)	Washing Solvent
1	1	55	81	DCM
2	2	61	81	DCM
3	3	49	81	DCM
4	4	14	71	Acetone
5	5	85	79	Acetone
6	6	82	81	Acetone
7	7	79	79	Acetone
8	8	79	79	Et ₂ O
9	9	79	80	-
10	1	82	80	Et ₂ O
11	2	85	81	Et ₂ O
12	3	86	80	Et ₂ O
13	4	78	80	Et ₂ O
14	5	74	81	Et ₂ O
15	6	76	81	Et ₂ O
16	7	68	81	-

Moreover, in order to evaluate the scope of the catalyst recovery via non-covalent interactions, another new batch of Unsym-C1-Cr **14@rGO** was prepared and used to catalyse the HDA of the four previously tested aldehydes (**1a-1d**) in a multi-substrate process. The structure of the engaged aldehyde was changed after each run (Table 19).

A first run was performed for the transformation of benzaldehyde **1b**, resulting in the isolation of the corresponding dihydropyranone **2b** with a good yield and an enantioselectivity value of 64 % ee, even slightly better than that obtained under homogeneous conditions. After washing with diethyl ether, the recovered catalyst was then engaged in the transformation of cyclohexane-carboxaldehyde **1a**, affording the product **1b** in 63% conversion and 81% ee. The conversion value was slightly decreased compared to that obtained with previous supported catalysis but the ee was the same.

The supported catalyst was finally engaged in further runs with other aromatic aldehydes (runs 3 and 4). It showed a slightly diminished activity compared to the homogeneous results but with similar

enantioselectivity levels. The product issued from each run was isolated, purified and it was not contaminated by any trace of the dihydropyranones obtained from the previous runs. Finally, recovered **14@rGO** after the 4th run was reassigned to the HDA of benzaldehyde (run 5), resulting interestingly in an enhanced activity and the same enantioselectivity for the target product **2b**. Recycling was continued again with the other three substrates (**1a**, **1c** and **1d**) while maintaining its efficiency (runs 6-8), as clear evidence of the stability of the procedure.

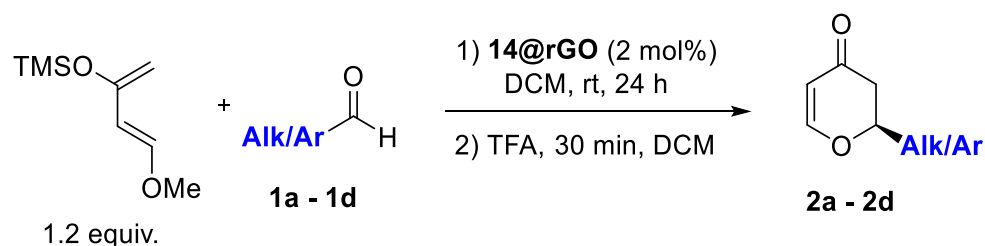


Table 19: Heterogeneous HDA of various aldehydes using **14@rGO** in multisubstrate recycling procedure.

	Run	Conv (%)	ee (%)	Yield (%)	Run	Conv (%)	ee (%)
	1	68	64	60	5	83	64
	2	63	81	30	6	70	81
	3	76	63	65	7	85	60
	4	75	64	71	8	84	63

The preparation of different batches of Unsym-C1-Cr **14@rGO** and their engagement in the same catalytic reactions for repeated times with the preservation of almost the same activity and selectivity

represents an important proof of the reproducibility of their synthesis as well as their excellent robustness in catalysis.

Regarding the stability of the used supported catalyst and that of obtained conversion and ee values during several runs, we can conclude that no leaching of catalytic species took place during the recycling procedure. Besides, recovered supported catalyst **14@rGO** was subjected to XPS analyses and as expected, the atomic ratio of the different elements remained similar to that measured for the fresh supported catalyst. In addition, the superposition of the narrow-scan spectra of Cr2p of both fresh and recovered **14@rGO** (Figure 83) showed the same signals of the two main peaks corresponding to the spin-orbit components Cr2p_{3/2} and Cr2p_{1/2}. These results allowed to prove the stability of the oxidation state of the Cr metal.

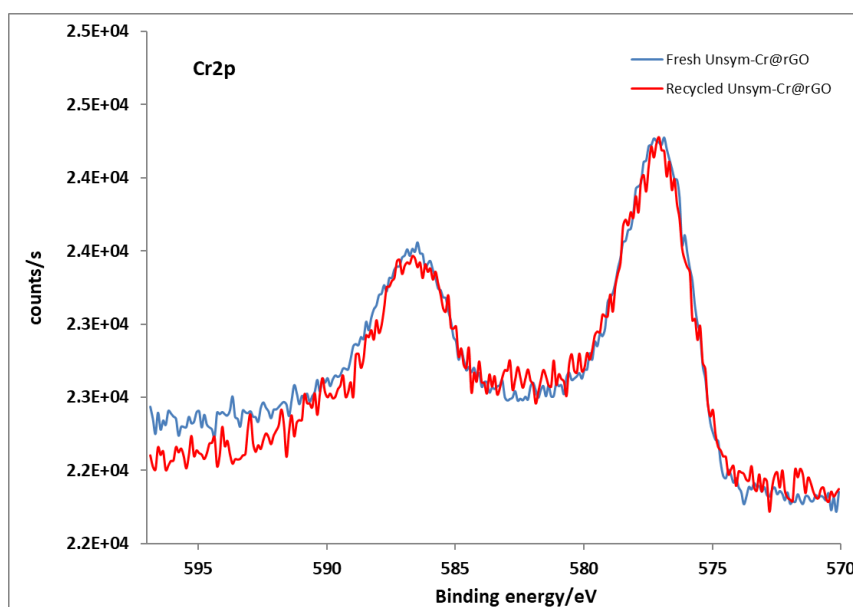


Figure 83: Comparison of chromium spectra in fresh and recycled **14@rGO**.

Furthermore, the heterogeneous nature of the catalysis has been proven as following: **14@rGO** was stirred in DCM for 18 h and then filtered off. To the resulting solution, substrates were added, and the mixture was allowed to stir for the same reaction time. No catalytic activity was observed proving thus that no release of catalytic species occurred in heterogeneous reaction.

c) Desorption tests

The term π - π interaction designates one of the weak non-covalent interactions taking place between aromatic molecules. Generally, the non-covalent interactions are not well understood and difficult to study experimentally due to the complexity of the systems in which they are involved and the possible

side interactions and solvent effects.¹³⁹ Carbon materials such as graphene and its derivatives are very well-known π -systems rich in electrons. Their special large surface area with suitable surface chemistry and other valuable characteristics made their functionalization possible in a covalent and non-covalent manner, as already previously discussed. Thus, graphitic surfaces represent a good choice to be used as supports to immobilize aromatic polycyclic compounds via non-covalent interactions and especially modified catalysts to perform supported catalysis. This method outperforms the covalent tethering in the capability to recover the catalyst and the support thanks to reversible attachment interactions.

In this context, Wang *et al.*¹¹³ studied the controlled reversible immobilization of a pyrene-tagged ruthenium carbene on the surface of single-walled carbon nanotubes (SWCNT). The authors proved that the π -stacking interaction between the pyrene moieties and the carbon support was strongly influenced by the temperature and the solvent polarity which made the immobilization reversible following these factors. Indeed, at room temperature and after 20 hours of stirring, the desorption of the complex was strongly favoured in non-polar solvents such as benzene and toluene and also in relatively polar solvents like THF and DCM. Furthermore, a small amount of catalyst was desorbed from the surface of SWCNT when more polar solvents were used such as acetone or ethyl acetate. Moreover, the amount of the desorbed catalyst increased with the increase of the temperature. When acetone was used as solvent, no desorption took place at room temperature, where only 7% were desorbed at 35 °C and 80% of the catalyst was desorbed after 24 hours at 56 °C. On the other hand, the sonication of the medium significantly affected the immobilization of the catalyst and accelerated its complete desorption in only 4 hours when THF or DCM were used as extracting solvents. More interestingly, the catalyst could be re-immobilized when the solvent was concentrated at low temperature. Besides, the authors recycled the catalyst by cooling down the temperature to 0 °C and reused it successfully for six consecutive runs in the heterogeneous ring closing metathesis of various substrates.

Based on the reversibility character of these π -stacking non-covalent interactions, we decided to explore the desorption ability of our supported catalytic system on rGO, for which, to the best of our knowledge, no study is reported. Several attempts were tried with playing on the temperature and the solvent. First, a recycled supported catalyst issued from the heterogeneous HDA reaction after 9 runs was chosen for the desorption test. Thus, a suspension of Unsym-C1-Cr **14@rGO**, in toluene was stirred at 40 °C for 4 hours. The solid was washed with hot toluene, filtered off, and dried. The

¹³⁹ M. O. Sinnokrot, C. D. Sherrill, *J. Phys. Chem. A* **2006**, *110*, 10656–10668.

resulting filtrate was concentrated, and only very small amount of solid (0.2 mg from 9 mg of catalyst initially immobilized) was obtained and subjected to IR analyses and MS spectroscopy. The two analyses proved the presence of desorbed catalyst with other unidentified compounds.

Next, a suspension of another batch of previously recovered supported catalyst **14@rGO** in DCM was stirred at 40 °C for 18 hours. No desorption of catalyst was detected by IR or MS. Consequently, THF was used as extracting solvent for a new supported batch and this time the mixture was sonicated for 4 hours. The solid was washed with THF and filtered off and the obtained filtrate was concentrated. Again, a very small amount of catalyst was desorbed and detected by MS. The recovered support was further engaged in the HDA of benzaldehyde with Danishefsky's diene, in the same conditions used for the previous described heterogeneous catalysis, and 50% conversion of the substrates were obtained after 24 hours, the desired product being isolated with 64% ee. This result confirms that the catalyst was always mainly immobilized on the surface of rGO and more importantly it was not deteriorated during the attempted desorption procedure because the ee value was equal to that obtained with the fresh supported catalyst (Table 19, Entry 1). Moreover, the same batch of supported catalyst was engaged in 3 successive desorption experiments via a sonication for 4 hours in THF, and no desorbed catalyst was detected. The solid support was then subjected to XPS which indicates, considering the precision limit of this technique, the presence of the signals arising from Cr2p, N1s and Cl2p core-levels with correct atomic ratios, proving that the catalyst **14** is always present onto the surface of rGO. Furthermore, the solid support was engaged one time again in the same catalytic transformation, and as expected, the same results in terms of conversion and enantioselectivity were observed (50% conversion, 64% ee).

All these experiments describing our attempts to desorb the catalyst from the rGO support were not successful proving the strong interaction between the pyrene moiety of the catalyst and the support and confirming that the complex was acting as heterogeneous catalyst in promoting thus supported asymmetric catalysis. We conclude that no catalyst leaching occurred during catalysis and a very stable, robust, and efficient supported catalyst was obtained with our pyrene-tagged salen complexes on rGO.

Conclusion

The catalytic properties of the prepared pyrene-tagged chromium complexes have been explored in two different enantioselective reactions: the ARO of cyclohexene oxide with TMSN_3 and the HDA of various aldehydes with Danishefsky's diene. For the homogeneous ARO reaction, performed with a 2 mol% catalyst loading, all the modified chromium salen complexes, including the symmetrical and the unsymmetrical species, showed a better activity than the reference Jacobsen's catalyst in various concentration and solvent conditions. They remained, however, less enantioselective. This enhancement of activity was attributed to the possible improvement in the cooperative bimetallic mechanism between the catalyst units due to non-covalent interactions between the pyrene moieties. Interestingly, the unsymmetrical complexes **14** and **15**, bearing only one pyrene group, were found to be more enantioselective than the symmetrical analogues and the best result was obtained using catalyst **14** (81% ee). Accordingly, the heterogeneous ARO was conducted in the same conditions, using supported Unsym-C1-Cr **14@rGO**. The supported catalyst approached the non-supported analogue in terms of activity and enantioselectivity and it was recovered by simple filtration and reused for 10 consecutive runs without significant loss of the catalytic properties. Subsequently, only the complexes with the shortest spacer length have been tested in the homogeneous HDA reaction of various aldehydes. Again, the catalyst **14** outperformed its symmetrical analogue in the HDA reaction of cyclohexane carboxaldehyde with Danishefsky's diene and showed activity and enantioselectivity values similar to those obtained with Jacobsen's catalyst (79% ee). Furthermore, **14@rGO** efficiently promoted the heterogeneous HDA reaction of cyclohexane carboxaldehyde and it was recovered and reused for 9 runs without any significant loss of activity or enantioselectivity. A very interesting effect of the recycling washing solvent was observed on the catalytic properties of the supported complex where the polar diethyl ether was found as the best choice for maintaining a favourable accessibility to the active sites on the carbon support. The very robust supported catalytic system was further engaged in a multisubstrate catalytic process, affording the desired dihydropyranones issued from each introduced aldehyde in very good yield and ee values.

Finally, several attempts have been realized in order to recover the catalyst from the support's surface including the treatment with different extraction solvents (toluene, DCM and THF) at different temperatures but no desorption of the catalyst was observed. The robustness and the stability of our supported catalytic system paves the way towards its applicability in other catalytic transformations and multicatalysis processes.

Chapter 4: Catalytic activity of Pyrene-tagged Manganese Salen



IV. Chapter 4: Catalytic activity of Pyrene-tagged Manganese Salen

Introduction

The catalytic activity of modified-salen chromium complexes has been studied in two asymmetric catalytic transformations: the ARO of cyclohexene oxide and the HDA of various aldehydes with Danishefsky's diene in homogeneous and supported catalysis conditions.

As described in chapter 2, manganese salen complexes have been also prepared. Given the results obtained in these other tested reactions with all the pyrene-tagged complexes, and the excellent activity and enantioselectivity of the unsymmetrical complex bearing only one pyrene group derived from pyrene methanol, only Unsym-C1-Mn (**17**) has been synthesized and chosen to promote the catalysis of enantioselective oxidation.

Chiral epoxides are very important building blocks for the synthesis of a large variety of enantiopure molecules, in particular biologically active compounds.¹⁴⁰ Catalytic asymmetric epoxidation is one of the most useful methods described for the preparation of enantioenriched epoxides, in which the enantiopure catalyst, engaged in a small amount, can transmit chirality to the products.

Catalytic asymmetric epoxidation of olefins has been widely studied using several metal-based catalysts such as chiral titanium and vanadium complexes developed by Sharpless, chiral metalloporphyrins with various metals (Fe, Ru, Mo, Mn), chiral BINOL-based metal complexes (La, Yb, Sm, Ca) and finally salen complexes developed by Jacobsen (Mn, Cr, Pd, Co, Ru).¹⁴¹ Manganese-based salen complexes are widely known as very efficient catalysts to promote asymmetric epoxidation of unfunctionalized olefins, leading to chiral epoxides with high yields and excellent ee.

Accordingly, we aim to explore the catalytic properties of our pyrene-tagged manganese salen complex in the epoxidation reaction of various alkenes in homogeneous medium and in supported catalysis. Furthermore, attempts have been dedicated to performing tandem catalysis, consisting of an olefin epoxidation reaction followed by an epoxide ring opening step with nitrogen-containing nucleophiles, without isolating the intermediate compound.

¹⁴⁰ P. Besse, H. Veschambre, *Tetrahedron* **1994**, *50*, 8885–8927.

¹⁴¹ Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K.-X. Su, *Chem. Rev.* **2005**, *105*, 1603–1662.

A. Asymmetric epoxidation of olefins: State of art

The asymmetric epoxidation (AE) of olefins catalysed by manganese salen complexes has been widely studied in the literature. In this bibliographic part, a brief reminder on the first reports describing the use of these catalysts for the epoxidation reaction, and some examples on the structural modifications studied for the heterogenization issue of such catalysts will be included.

The capacity of manganese-based salen complexes to catalyse efficiently the epoxidation of unfunctionalized olefins was pioneered independently in 1990 by Jacobsen¹⁴² and Katsuki¹⁴³ using iodosoarenes as oxidants. Jacobsen and coworkers¹⁴² reported the use of Mn(III)-salen complexes (Figure 84) for the epoxidation of alkyl and aryl-substituted olefins. The reactions were carried out in air with iodosylmesitylene as the oxidant and 1-8 mol % of the catalyst. Monosubstituted terminal and trisubstituted olefins but also *cis*-alkenes were epoxidized in good to excellent ee (57-93%), while *trans*- and 1,1'-disubstituted-alkenes were epoxidized with low ee (20-33%). The authors suggested that the degree of enantioselectivity could be explained by a side-on perpendicular approach of the olefin to the manganese-oxo bond of the putative Mn(V) intermediate, in which the more hindered terminus of the olefin was directed away from the sterically hindering *tert*-butyl group of the complex.

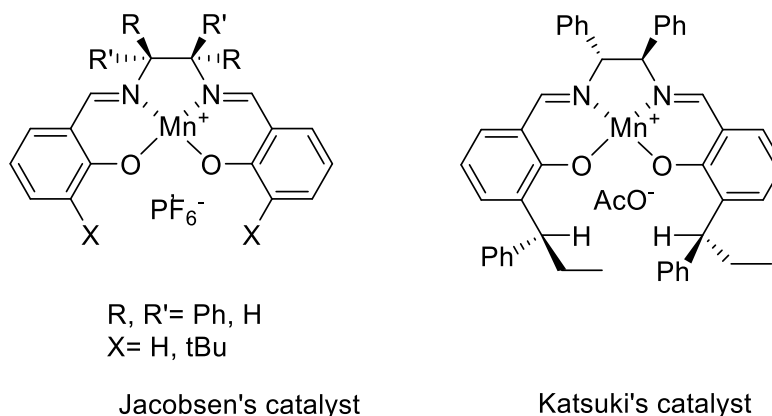


Figure 84: Mn-salen complexes used in the first asymmetric epoxidation of olefins by Jacobsen and Katsuki.

One year later, the group of Jacobsen described the use of a buffered bleach NaOCl solution as efficient oxidant in stoichiometric quantity with combination of Mn-salen complexes (5 mol%) to epoxidize various *cis*-substituted olefins in a biphasic medium.¹¹¹ The desired epoxides were obtained with high yields (up to 96%) and ee values (up to 98%). The presence of bulky groups such as *tert*-

¹⁴² W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801–2803.

¹⁴³ R. Irie, K. Noda, Y. Ito, N. Matsumoto, T. Katsuki, *Tetrahedron Lett.* **1990**, *31*, 7345–7348.

butyl groups in the *ortho* position of the phenol rings was crucial to the selectivity and stability of these catalysts (Figure 85). Moreover, they reported the first epoxidation of *cis*-methyl cinnamate as α,β -unsaturated carbonyl compound for which the addition of sub stoichiometric amounts of 4-phenylpyridine *N*-oxide was observed to improve both the catalyst selectivity and the turnover numbers.

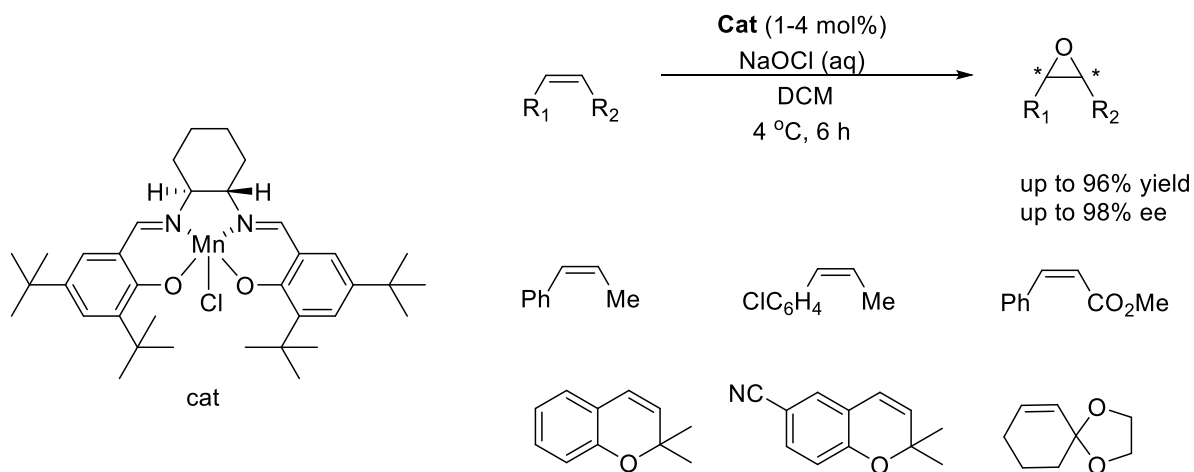


Figure 85: AE of *cis*-olefins using bleach solution.

On the other hand, in the same year, Katsuki and coworkers¹⁴⁴ described the enhancement of the enantioselectivity for the epoxidation reaction when donor ligands such as 2-methylimidazole, pyridine *N*-oxide, and lutidine *N*-oxide were added to the reaction mixture. Furthermore, the important role of these donor ligands was proven by Jacobsen¹⁴⁵ by adding 4-phenylpyridine *N*-oxide (4-PPNO) to the Mn-salen complex for the epoxidation of *cis*-ethyl cinnamate, where a significant increase in the enantioselectivity values was observed leading thus to the easy production of a Taxol side chain in a short, practical, and highly selective way. The active species for the asymmetric epoxidation is a $\text{Mn}^{\text{V}}(=\text{O})$ -salen complex, which may undergo a reversible coupling with a Mn^{III} -salen species to produce an inactive μ -oxo Mn^{IV} dimer. Jacobsen *et al.* thus proposed that the additive serves to increase the concentration into the active species by coordination to the unsaturated Mn^{III} species, thus minimizing the formation of the inactive dimer.

The mechanism of the oxygen transfer from the $\text{Mn}^{\text{V}}(=\text{O})$ -salen complex to the olefin was widely studied and different mechanisms have been proposed involving either radical¹⁴⁶ or metallooxetane intermediates.¹⁴⁷ Moreover, in some cases the enantioselectivity dependence was referred to the

¹⁴⁴ R. Irie, K. Noda, Y. Ito, N. Matsumoto, T. Katsuki, *Tetrahedron: Asymmetry* **1991**, 2, 481–494.

¹⁴⁵ L. Deng, E. N. Jacobsen, *J. Org. Chem.* **1992**, 57, 4320–4323.

¹⁴⁶ N. H. Lee, E. N. Jacobsen, *Tetrahedron Lett.* **1991**, 32, 6533–6536.

¹⁴⁷ T. Fukuda, T. Katsuki, *Tetrahedron Lett.* **1996**, 37, 4389–4392.

nature of oxidant used.¹⁴⁸ In this context, Jacobsen and coworkers¹⁴⁹ reported the asymmetric epoxidation of several terminal, di-substituted, and tri-substituted olefins in the presence of a combination of *m*-chloroperbenzoic acid (*m*CPBA) and *N*-methylmorpholine-*N*-oxide (NMO) as an effective anhydrous oxidant with the Mn-salen complex at low temperatures. High yields and ee values, were obtained for different alkenes proving the improvement of catalytic activity and enantioselectivity in the presence of this oxidizing system compared to the biphasic one employing buffered aqueous bleach solution (Figure 86).

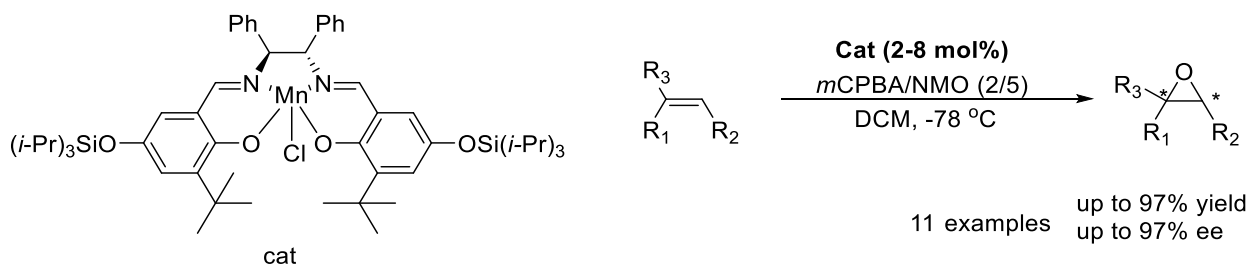


Figure 86: AE of various olefins using *m*CPBA/NMO as oxidant.

Several structural modifications on manganese Jacobsen's catalyst have been performed in order to improve the activity and enantioselectivity. More recent researches were directed towards performing structural modifications of these catalysts for their heterogenization to facilitate their recovery and avoid their dimerization. Older examples described the preparation of organic polymers of polystyrene type containing an optically active Mn-salen complex which, for instance, showed efficient reactivity when a combination of *m*-CPBA/NMO was used.¹⁵⁰ Moreover, immobilization of Mn-salen complexes on inorganic and organic supports has been studied. In this context, a manganese salen complex was modified by adding an alkene group to further ensure its grafting on mesoporous silica-based materials such as MCM-41, MCM-48 and SBA-15 modified by 3-mercaptopropyltrimethoxysilane²⁶ (Figure 87). Analytical studies proved the successful grafting on the inner surface without deterioration of the mesoporous structure. The supported catalysts have been tested in the AE of unfunctionalized alkenes using NaOCl as oxidant and better results in terms of activity and enantioselectivity have been found with the support having a large pore size (SBA-15) or a 3D pore structure, probably because they ensure a better diffusion of the substrates (4 examples).

¹⁴⁸ J. P. Collman, L. Zeng, J. I. Brauman, *Inorg. Chem.* **2004**, *43*, 2672–2679.

¹⁴⁹ M. Palucki, G. J. McCormick, E. N. Jacobsen, *Tetrahedron Lett.* **1995**, *36*, 5457–5460.

¹⁵⁰ F. Minutolo, D. Pini, P. Salvadori, *Tetrahedron Lett.* **1996**, *37*, 3375–3378.

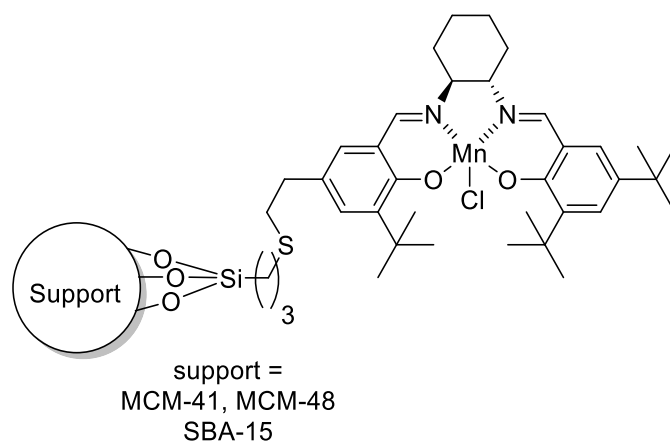


Figure 87: Mn-salen complex supported on mesoporous silica-based materials.

Furthermore, Mn-salen complexes have been immobilized onto the surface of organic polymer-inorganic hybrid materials. Fan *et al.*¹⁵¹ reacted oligo-styrenyl phosphonates with aluminum acetate and sodium dihydrogenophosphate under mild conditions. The layered crystalline hybrid material functionalized via a chloromethylation of the phenyl groups and nucleophilic substitution with diols possessing different spacers, was used as support for a chiral Mn-salen complex through an axial linkage (Figure 88). The supported catalyst, fully characterized by FT-IR, UV-vis, BET, XPS and X-ray diffraction analyses was engaged in the AE of α -methylstyrene and indene, in the presence of *m*CPBA. Whatever the spacer length, the desired epoxides were obtained in high yields and ee values and the heterogeneous catalyst was efficiently recovered by simple filtration and reused for 10 runs.

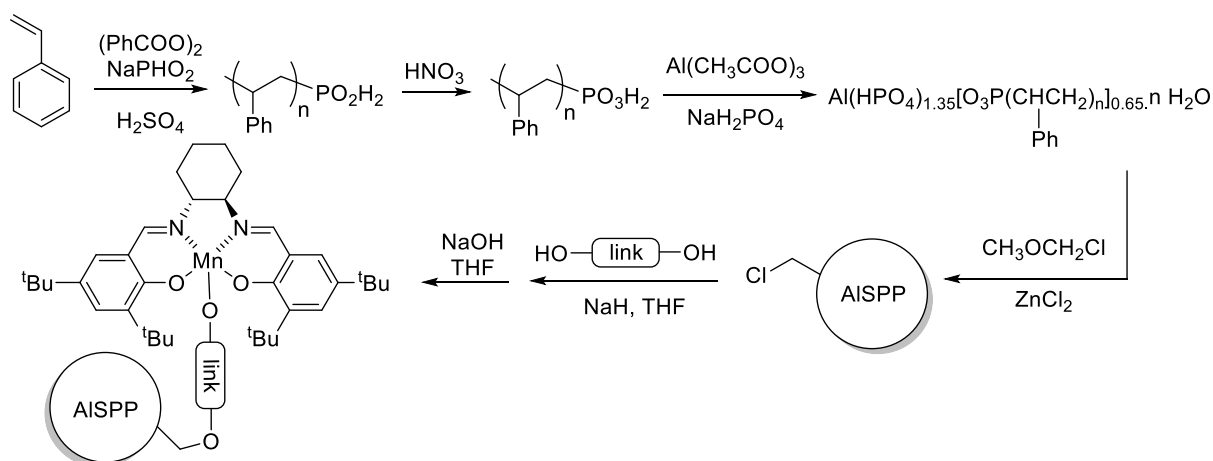


Figure 88: Chiral Mn-salen complex immobilized on organic polymer-inorganic hybrid material

In addition to the immobilization of Mn-salen complexes onto pre-existing supports, they have been modified towards their assembling in macrocyclic structures or even their own polymerization. In

¹⁵¹ X. Huang, X. Fu, Z. Jia, Q. Miao, G. Wang, *Catal. Sci. Technol.* **2013**, 3, 415–424.

this context, Kureshy's group¹⁵² synthesized a series of new chiral monomeric and dimeric macrocyclic Mn(III) salen complexes with trigol linker, and engaged them in the AE of styrene, *cis*- β -methyl styrene, indene, and chromenes in the presence of several *N*-oxides as axial ligands and NaOCl as an oxidant at 0 °C. The chiral dimeric macrocyclic catalyst used in a 2.5 mol% loading, afforded the epoxides in excellent yields (>99%) and high enantioselectivity values (ee up to 98% in selected cases). The recycling was demonstrated with the dimeric complex D (Figure 89) which was efficiently recyclable up to six times with retention of enantioselectivity in the AE of styrene.

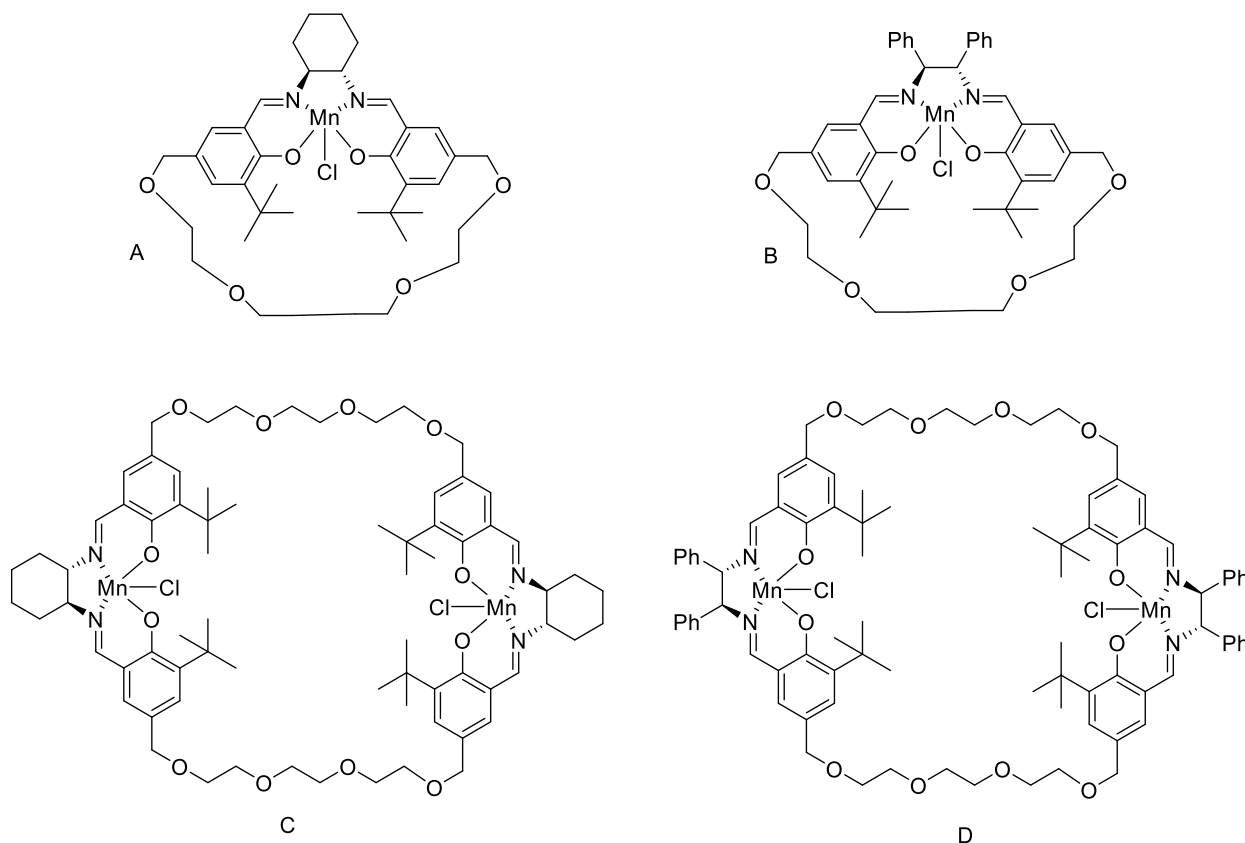


Figure 89: Macrocyclic Mn-salen complexes.

Tan *et al.*¹⁵³ prepared a polymer Mn-salen complex by bridging the chiral complex to polyethylene glycol-based diimidazole derivatives (Figure 90). FT-IR, UV-Vis and thermal analyses confirmed formation of a one-dimension polymer with alternation of Mn-salen species with PEG-dicationic imidazolium moieties. The prepared ionic liquid-containing polymers were engaged in the AE of unfunctionalized olefins with NaOCl in a biphasic reaction medium. The length of the PEG spacer was proved to be crucial with an optimal value of $n=3$, as the best compromise for the water solubility

¹⁵² R. I. Kureshy, T. Roy, N. H. Khan, S. H. R. Abdi, A. Sadhukhan, H. C. Bajaj, *J. Catal.* **2012**, 286, 41–50.

¹⁵³ Y. Chen, R. Tan, Y. Zhang, G. Zhao, W. Zheng, R. Luo, D. Yin, *Appl. Catal. A* **2015**, 491, 106–115.

of the catalyst. The corresponding catalyst showed an excellent activity and enantioselectivity with various substrates and it was recovered in consecutive runs by precipitation.

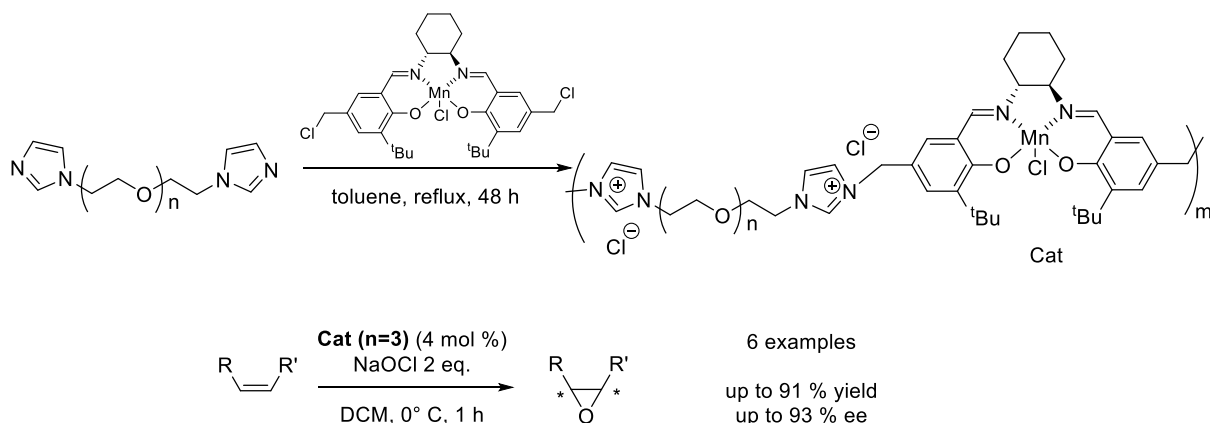


Figure 90: Epoxidation of olefins catalysed by Mn-salen polymers with phase transfer ability.

Recently, Mn-salen complexes have been incorporated in metal organic frameworks (MOFs) and covalent organic frameworks (COFs) to prepare crystalline porous stable structures used as heterogeneous catalysts in the AE of a range of olefins and more interestingly, crystals with various metals have been mixed and one-pot sequential reactions have been performed. The immobilization on MOFs and COFs was already detailed in chapter 1 and it will be farther discussed again in the part dealing with the sequential reaction tests (chapter 4).

To the best of our knowledge, no examples on the reversible immobilization of Mn-salen complexes have been reported, in particular the immobilization via non-covalent interactions on the surface of carbon materials. Hence, and on the basis of the excellent results obtained with the pyrene-tagged chromium salen complexes in the ARO and HDA reactions, an unsymmetrical pyrene-modified manganese salen complex has been prepared and ready to catalyse the AE of various olefins with different oxidants in homogeneous and in supported catalysis conditions.

B. Results and discussion

1. Homogeneous catalysis

For this part, and considering our previous results, the catalysts we used are Unsym-C1-Mn (**17**) and Jacobsen's catalyst prepared in our hands (**18**).

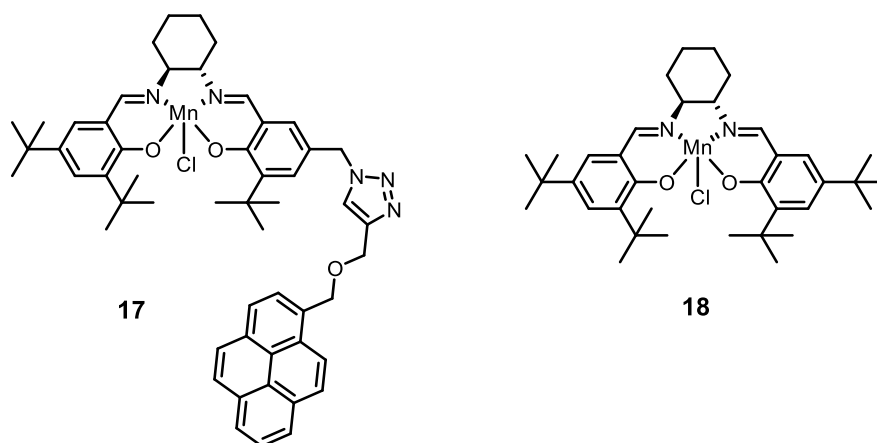


Figure 91: Manganese salen complexes used in this study.

Epoxidation reactions have been performed using two different oxidants: iodosobenzene (PhIO) prepared in our hands, and *m*-chloroperoxybenzoic acid (*m*CPBA) in the presence of *N*-methylmorpholine *N*-oxide (NMO). In addition, different substrates including challenging terminal olefins have been engaged in the reactions such as indene, styrene, allylbenzene and 2,2-dimethyl-2*H*-chromene-6-carbonitrile.

(1) Indene epoxidation

Indene oxide or 1,2-epoxyindane is the product of the epoxidation of indene. It represents one of the very important intermediates for the synthesis of valuable molecules for the pharmaceutical and agrochemical fields. For example, the asymmetric epoxidation of indene is a key step in the formation of 1-aminoindan-2-ol, a component of the HIV-protease inhibitor indinavir (Crixivan) (Figure 92).¹⁵⁴

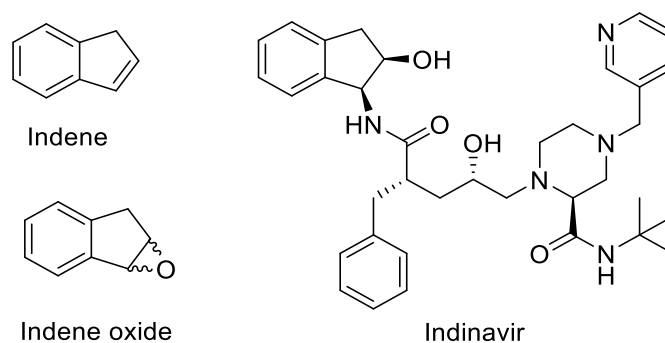


Figure 92: Structures of indene, indene oxide and Indinavir.

Jacobsen reported that indene could be epoxidized under anhydrous conditions in the presence of a combination of *m*CPBA/NMO (2/5) at low temperature (-78 °C) in DCM with the chiral Mn(III)-

¹⁵⁴ D. L. Hughes, G. B. Smith, J. Liu, G. C. Dezeny, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1997**, 62, 2222–2229.

salen complex (Figure 93), providing the product in 89% yield and 96% ee, while 88% ee were obtained when a buffered aqueous bleach solution (NaOCl) was used as an oxidant.¹⁴⁹

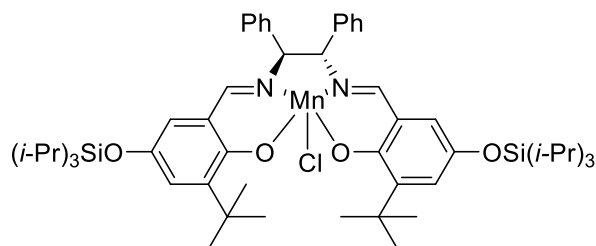


Figure 93: Jacobsen's Mn-salen catalyst

Our attempts for the epoxidation of indene were based on the use of two different oxidants: PhIO and a combination of *m*CPBA/NMO. Catalyst **17** was used in a 2 mol% loading, and reactions were performed in DCM as solvent at different temperatures. Reactions have been monitored using GC to calculate the conversion with help of an internal standard. Chiral HPLC analyses were performed to determine the ee values.

First, the combination of *m*CPBA/NMO (1/2.5) in the presence of Unsym-C1-Mn **17** was chosen as oxidant for the epoxidation of indene. The reaction was performed at -78 °C. A complete conversion was observed after only 2 h, and the isolated epoxide was obtained with an excellent ee value of 85%. This stimulating result prompted us to continue the study with this catalyst and to test other reaction conditions.

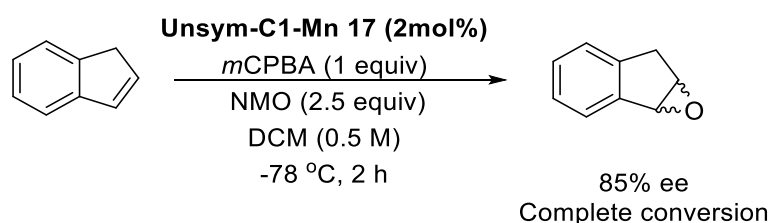


Figure 94: Epoxidation of indene catalysed by **17** using *m*CPBA/NMO as oxidant.

On the other hand, in order to ensure high atom economy and to reduce the amount of side products released during the epoxidation reaction, the oxidant was also replaced by iodosobenzene. This compound belongs to the family of hypervalent aryl- λ^3 -iodanes known as highly selective and environmentally friendly oxidizing reagents.¹⁵⁵ PhIO acts as an oxygen transfer agent and is therefore widely used in catalytic oxidation reactions.¹⁵⁶ It is advantageous over other oxidants because it only produces iodobenzene PhI as side product at the end of the oxidation reaction. In addition, PhIO is

¹⁵⁵ T. Wirth, *Angew. Chem. Int. Ed.* **2005**, *44*, 3656–3665.

¹⁵⁶ Y. Moro-oka, M. Akita, *Catal. Today* **1998**, *41*, 327–338.

used in a stoichiometric amount in most cases and reactions are performed in mild conditions without requiring low temperature as in the case with *m*CPBA systems. However, the fact that iodosobenzene is insoluble in almost all solvents, and possesses an explosive property under moderate heating conditions, make researchers look for other analogues with greater stability and solubility properties such as iodosylbenzene sulfate (PhIO)₃·SO₃.¹⁵⁷

Thus, the epoxidation of indene was then tested in the presence of PhIO (1.1 equiv) in DCM at -78 °C (Table 20, Entry 2). Unfortunately, only 35% of conversion were obtained after 2 hours. Based on the heterogeneous aspect of the mixture throughout and at the end of the reaction, we conclude that PhIO has not fully reacted and therefore has not been converted into soluble iodobenzene causing this low conversion value. The reaction at low temperature with PhIO was thus very slow compared to that involving *m*CPBA (Table 20, Entry 1). This was confirmed by performing the reaction at the same temperature and with increasing the concentration and the amount of PhIO (Table 20, Entry 3); a better conversion was obtained (63%) but remained lower than that observed with *m*CPBA (Entry 1). Nevertheless, the pyrene-tagged Mn-salen complex **17** showed a higher activity than Jacobsen's catalyst with 12% vs 2% conversions respectively after 2 hours at low temperature (entries 4 and 5).

Increasing the concentration and the temperature exerted an important influence on the activity of the catalyst and on the reactivity of PhIO. The catalyst **17** outperformed Jacobsen's catalyst prepared in our lab with 90% conversion after 2 h while only 35% conversion were obtained when the racemic Jacobsen catalyst was engaged in the presence of an excess of PhIO (Table 20, entries 7 and 8). The desired indene oxide was obtained in 60% ee with Unsym-C1-Mn **17** in the presence of PhIO as oxidant. This modest value represents an excellent result for us, allowing to do a challenging tandem reaction (detailed next).

¹⁵⁷ A. Y. Koposov, B. C. Netzel, M. S. Yusubov, V. N. Nemykin, A. Y. Nazarenko, V. V. Zhdankin, *Eur. J. Org. Chem.* **2007**, 2007, 4475–4478.

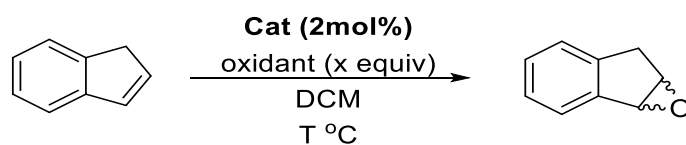


Table 20: Epoxidation of indene; optimization

Entry	Cat	Solvent	[conc] M	T ° C	Oxidant (equiv)	Conv %	ee (%)
1	17	DCM	0.5	-78	<i>m</i> CPBA/NMO (1/2.5)	>99	85
2	17	DCM	0.25	-78	PhIO (1.1)	35	--
3	17	DCM	0.5	-78	PhIO (2)	63	--
4	17	DCM	0.1	-78	PhIO (1.1)	12	
5	Jacobsen 18	DCM	0.1	-78	PhIO (1.1)	2	
6	17	Et ₂ O	0.5	rt	PhIO (1.1)	23	--
7	17	DCM	0.5	rt	PhIO (1.1)	90	60
8	Jacobsen (racemic)	DCM	0.5	rt	PhIO (1.5)	39	0

The epoxidation of indene was also tested in diethyl ether as solvent and only 23% conversion were observed (Table 20, entry 6). The ee values of the reactions in which the conversion remained low were not measured.

Therefore, the pyrene-tagged Mn-salen complex was more active than Jacobsen's catalyst in the epoxidation of indene in the presence of PhIO as oxidant.

(2) Styrene epoxidation

Styrene has been also tested in our epoxidation reaction conditions. Jacobsen performed the epoxidation of styrene using the Mn(III)-salen complex (Figure 93) in the presence of a combination of *m*CPBA/NMO (2/5) at low temperature (-78 °C) in DCM. The desired epoxide was isolated in 89% yield with 86% ee while 69% ee were obtained using a buffered aqueous NaOCl solution as oxidant.¹⁴⁹

Jacobsen's catalyst **18**, prepared in our hands, was used to catalyse the epoxidation of styrene in our reaction conditions. In the presence of a combination of *m*CPBA/NMO (1/2.5) at (-78 °C), styrene was almost completely converted (97%) after 2 h and styrene oxide was obtained with a modest ee of 47% (Table 21, entry 1). This ee value was lower than that described by Jacobsen (86% ee), however the structure of the complex is not the same and more importantly the amount of NMO, responsible for the activation and the stabilization of catalyst, used in our conditions was reduced to half compared to the literature, in order to ensure high atom economy and to avoid an excess of reactants when the reaction is performed in supported catalysis.

The epoxidation was then performed under the same conditions but using Unsym-C1-Mn **17** as catalyst, and 93% conversion were observed with 47% ee for the styrene oxide (Table 21, entry 2). The modified salen complex showed in this case the same reactivity and enantioselectivity as Jacobsen's catalyst **18**. In contrast, only 41% conversion with a very low ee of 10% of the expected product have been obtained when PhIO was used as oxidant with catalyst **17** (Entry 3).

It is clear from these results that the enantioselectivity and the activity of the catalysts are highly influenced by the nature of oxidant used. The *m*CPBA oxidative system in the presence of additives is the most efficient for the epoxidation of styrene, in an anhydrous media.

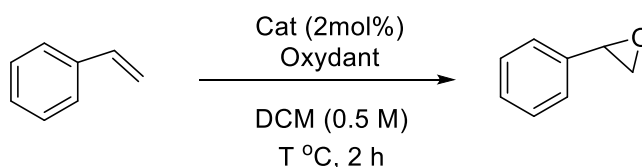


Table 21: Epoxidation of styrene.

Entry	Cat	T ° C	Oxidant (equiv)	Conv %	ee (%)
1	18	-78	<i>m</i> CPBA/NMO (1/2.5)	97	47
2	17	-78	<i>m</i> CPBA/NMO (1/2.5)	93	47
3	17	rt	PhIO (1.1)	41	10

(3) Epoxidation of 2,2-dimethyl-2*H*-chromene-6-carbonitrile

It is known that some 2,2-disubstituted 3,4-epoxychromane are convenient and useful intermediates in the synthesis of molecules with physiological activity such as cromakalim and related potassium channel openers (Figure 95).¹⁵⁸

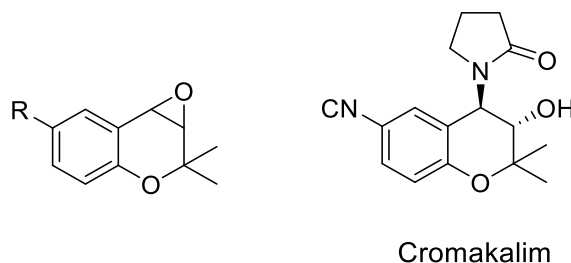


Figure 95: 2,2-disubstituted 3,4-epoxychromane and cromakalim.

The epoxidation of chromene derivatives with manganese salen complexes has been widely studied in the literature and lead to excellent yield and ee values.^{111,145,159} 2,2-dimethyl-2*H*-chromene-6-carbonitrile has been chosen as substrate for further epoxidation tests. First attempts were done by using the combination of *m*CPBA/NMO in DCM at different concentrations. Table 22 summarizes the different results obtained for those catalytic tests using Unsym-C1-Mn **17** and they are compared to those obtained with Jacobsen's catalyst. The conversion values were here again measured using GC analysis with dodecane as internal standard and the ee values were obtained from chiral HPLC

¹⁵⁸ D. R. Buckle, J. R. S. Arch, A. E. Fenwick, C. S. V. Houge-Frydrych, I. L. Pinto, D. G. Smith, S. G. Taylor, J. M. Tedder, *J. Med. Chem.* **1990**, *33*, 3028–3034.

¹⁵⁹ R. I. Kureshy, N. H. Khan, S. H. R. Abdi, S. Singh, I. Ahmed, R. S. Shukla, R. V. Jasra, *J. Catal.* **2003**, *219*, 1–7.

analyses. Reactions have been performed in DCM at $-78\text{ }^{\circ}\text{C}$. At a 0.1 M concentration in the presence of *m*CPBA/NMO (1/5), Jacobsen's catalyst **18** catalyses the epoxidation resulting in 45% conversion with an excellent ee value of 91% while Unsym-C1-Mn **17** showed a better activity (70% conversion) with a slightly better enantioselectivity (96% ee) (Table 22, entries 1 and 2). Unsym-C1-Mn **17** displayed a better activity than Jacobsen's catalyst **18** (80% versus 61% conversion) in a more concentrated medium even if the amount of NMO is reduced to 2.5 equivalents (Entries 3 and 4). The same enantioselectivity has been observed in both cases (96% ee). Increasing the temperature by allowing the reaction to stir for additional 21 h did not result in any increase of the conversion value.

Another test reaction was performed using catalyst **17** in the presence of *m*CPBA/NMO (1/5) but at room temperature. The conversion was very low compared to the reaction at low temperature and only 39% conversion were obtained after 24 h with diminished ee of 86% (Table 22, Entry 5). Thus, a low temperature is crucial to perform epoxidation reactions with *m*CPBA and NMO as oxidant. Again, the unsymmetrical pyrene-tagged salen complex outperformed Jacobsen's catalyst in the epoxidation of olefins in terms of activity and delivering the same enantioselectivity.

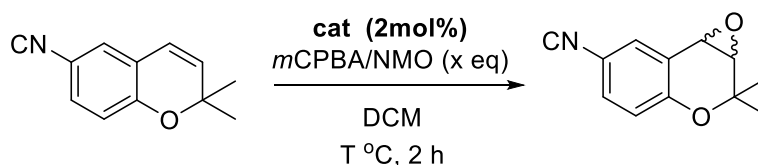


Table 22: Epoxidation of 2,2-dimethyl-2H-chromene-6-carbonitrile using *m*CPBA/NMO.

Entry	Catalyst	<i>m</i> CPBA/NMO (x equiv)	T ($^{\circ}\text{C}$)	[conc] M	Conv %	ee %
1	Unsym-C1 (17)	1/5	-78	0.1	70	96
2	Jacobsen (18)	1/5	-78	0.1	45	91
3	Jacobsen (18)	1/2.5	-78	0.5	61	96
4	Unsym-C1 (17)	1/2.5	-78	0.5	80	96
5	Unsym-C1 (17)	1/5	Rt	0.5	39 (24 h)	86

On the other hand, we tested the epoxidation with PhIO under different conditions.

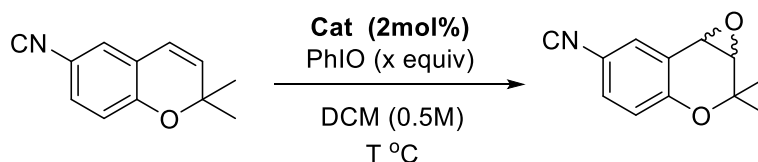


Table 23: Epoxidation of 2,2-dimethyl-2H-chromene-6-carbonitrile using PhIO.

Entry	Cat	Oxidant (equiv)	T (°C)	Time (h)	Conv %	ee %
1	18	1.1	-78	2	0	52
				19	0	
				24	2	
				48	9	
2	17	1.1	rt	2	33	79
				19	53	
				24	53	
3	18	1.1	rt	2	0	52
				19	5	
				24	6	
4	17	PhIO/NMO (1.6/5)	rt	2	49	89
				4	49	
				24	52	
				2	70 ^a	
				20	70 ^a	
5	17	(1.1) Added twice	rt	2	31	75
				3	33	
				2	55 ^b	
				3d	73 ^b	

^a after the addition of 0.5 equiv of PhIO. ^b after the second addition of PhIO.

Again, the modified salen complex Unsym-C1-Mn **17** catalyst showed better activity than Jacobsen's catalyst. Reactions performed at room temperature were not complete in both cases even after 24 hours, where only 6% and 53% of conversion have been observed when complex **18** and **17** were used as catalysts respectively (Table 23, entries 2 and 3). Interestingly, Unsym-C1-Mn **17** was found to be more enantioselective than Jacobsen's catalyst **18** (52% ee) under these conditions and afforded the desired epoxide with 79% ee. The addition of the axial base NMO (5 equiv) to the reaction mixture improves only the enantioselectivity of the reaction and the desired epoxide was obtained with 89%

ee instead of 79% (entries 2 and 4). Moreover, the addition of extra 0.5 equivalent of PhIO after 24 h, resulted in the increase of the conversion value (70%).

Finally, for an attempt to increase the activity and then the conversion value, the oxidant was added twice with 6 h of time interval. As expected, an improvement of activity was observed, and the conversion value increased and reached 73% with approximately the same enantioselectivity (75% ee) (Entry 5, Table 23).

Therefore, in both cases with the two oxidants, the Unsym-C1-Mn **17** outperformed Jacobsen's catalyst in terms of activity. The best result was obtained using *m*CPBA/NMO (1/2.5) combination as oxidant at low temperature. The epoxidation using PhIO was slow but in this case catalyst **17** afforded the epoxide with better enantioselectivity compared to that obtained with Jacobsen's catalyst **18**.

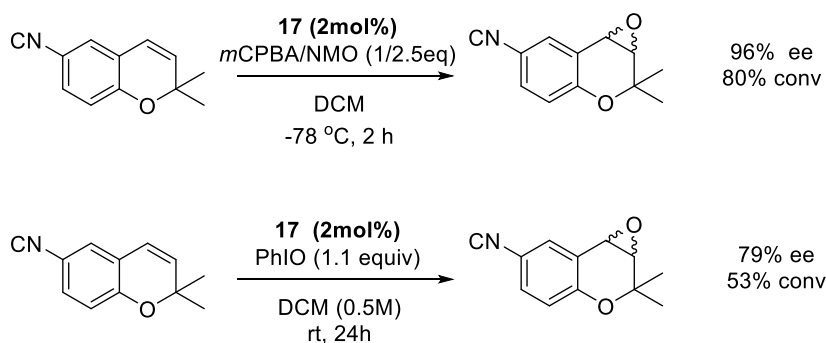


Figure 96: Epoxidation of CN chromene.

(4) Catalytic epoxidation of other olefins

Allylbenzene was also tested as substrate for the epoxidation reaction with our conditions. Unfortunately, catalyst **17** was not efficient for this catalytic reaction, and reactions have not been completed even after 24 hours with all oxidants. A better conversion value was obtained when *m*CPBA was used in combination with NMO in 2:5 ratio at 0.1 M (Table 24, Entry 2) instead of PhIO. Increasing the concentration with using only 1 equivalent of *m*CPBA and 2.5 equivalents of NMO at the same temperature did not increase the conversion value (Table 24, Entry 3) and only 30% conversion were obtained while the value was lower (20%) when PhIO was used as oxidant in 1.1 equivalent at room temperature. This alkene represents a hard substrate for the epoxidation reaction and based on the low conversion values obtained in all the tested reactions, the ee values of the products have not been determined.

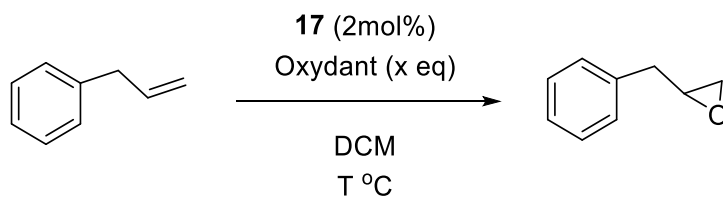


Table 24: Epoxidation of allylbenzene.

Entry	Oxidant	[conc] M	T °C	Time (h)	Conv %
1	PhIO (1.1 eq)	0.5	rt	2	6
				24	20
2	mCPBA/NMO (2/5)	0.1	-78	2	40
				24	45
3	mCPBA/NMO (1/2.5)	0.5	-78	2	26
				24	30

The epoxidation of allyloxybenzene was performed using catalyst **17** and PhIO as oxidant.

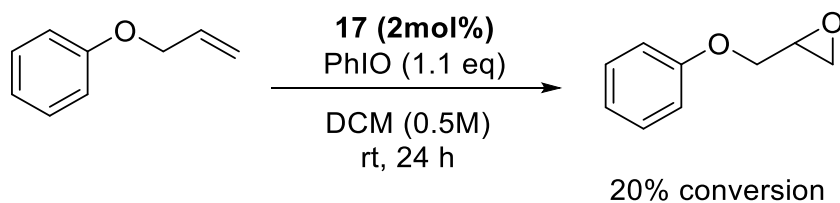


Figure 97: Epoxidation of (Allyloxy)benzene.

The epoxidation of allyloxybenzene was performed using catalyst **17** and PhIO as oxidant. Unfortunately, only 20% conversion were obtained after 24 hours. Considering the results obtained in the cases of styrene, allylbenzene and allyloxybenzene, we can conclude that the epoxidation of terminal alkenes using the modified salen complex was not efficient and especially when iodosobenzene was used as oxidant.

2. Heterogeneous catalysis

The heterogeneous epoxidation of indene, styrene, and CN-chromene was performed using the supported Mn-salen complex **17@rGO** (Figure 98) in a 2 mol% catalyst loading. The reactions were carried out in the optimal conditions found in homogeneous catalysis, for each substrate.

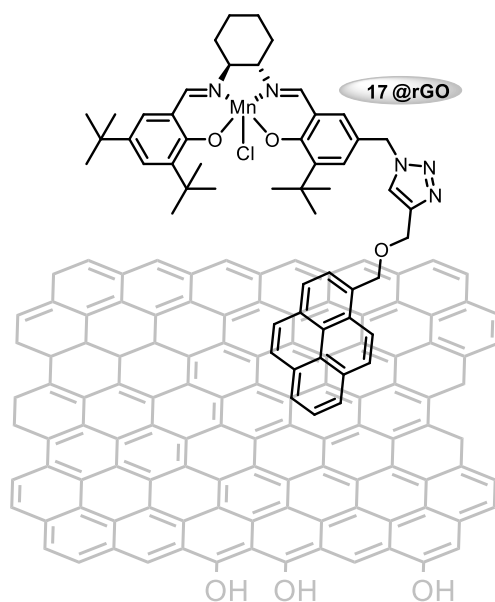
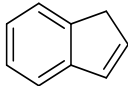
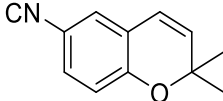
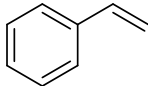


Figure 98: Supported pyrene-tagged Mn-salen complex **17@rGO**.

Table 25 summarizes the results of supported epoxidation reactions of all tested alkenes. The epoxidation of indene in the heterogeneous medium at room temperature led to 40% conversion after 24 hours but the desired product was not recovered. An unidentified product had been isolated, but its structure was not identified. On the other hand, the epoxidation of CN-chromene carried out at -78 °C with *m*CPBA/NMO in the presence of **17@rGO** proved to be less efficient than when it was performed with the homogeneous analogues (47% conversion). The target product was nevertheless isolated with a high 90% ee. It was noticed that at very low temperature, the stirring of the reaction mixture was difficult, and the supported catalyst was probably stacked. This limitation could probably be avoided by performing the reaction in diluted conditions. Moreover, **17@rGO** promoted the epoxidation of styrene with *m*CPBA/NMO leading to 63% conversion, and 40% ee for the desired styrene oxide.

Table 25: Heterogeneous epoxidation reaction of various alkenes

Alkene	Oxidant	T °C	Time (h)	Conv (%)	ee (%)
	PhIO (1.1)	rt	2 24	35 40	--
	<i>m</i> CPBA/NMO (1/2.5)	-78	4	47	90
	<i>m</i> CPBA/NMO (1/2.5)	-78	4	63	40

Unfortunately, due to the lack of time, the recovery of the supported catalyst after the epoxidation reaction was not performed. The optimization of the supported asymmetric epoxidation conditions is required to enhance the activity of catalyst. These attempts with our heterogeneous rGO-based catalyst represent a very promising results towards the efficiency of this catalytic system and the possible multi-functionalization of such support to promote supported one-pot sequential reaction processes.

C. Sequential reactions

1. Generality

Organic synthesis devoted towards the preparation of complex molecules, especially natural products and their derivatives and alternatives, requires a multistep procedure which at the end implies the use of important amount of reagents and solvents leading thus to the production of unavoidable amount of chemical wastes. The development of green and environmentally friendly chemical processes constitutes recently a necessary challenge aiming to reduce as possible chemical wastes and to highlight atomic economy. Accordingly, researchers are directed to explore new, faster and greener synthetic pathways, in particular using catalysis. One-pot catalytic processes represent an efficient way to perform sequential reactions implying multimetallic species and affording thus the desired products with minimizing wastes and processing time. One-pot procedures used to achieve at least two sequential reactions were described with many terms like: domino reaction, cascade reaction, and

tandem reaction.^{160,161} For simplicity, Figure 99 shows the distinctive classification of all the terms mentioned above.

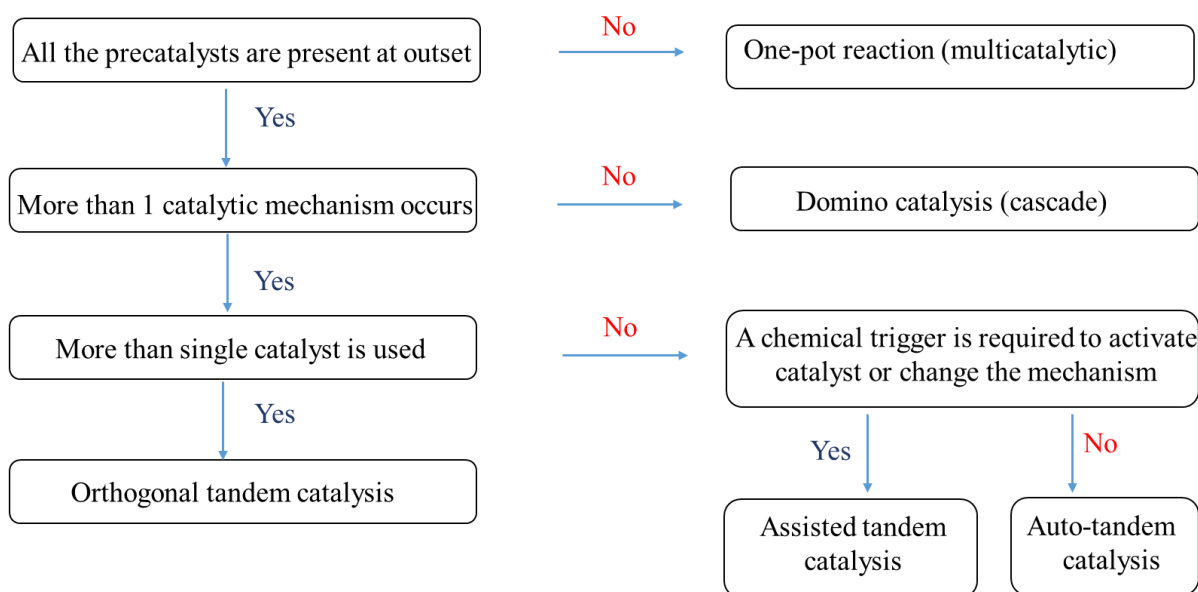


Figure 99: Classification of one-pot processes involving multiple catalytic transformations.

Salen-based complexes are considered as very useful platforms to conduct various transformations depending on the nature of the coordinated metal. Therefore, the use of different metal-based salen complexes in a one-pot reaction procedure represents a great solution to promote sequential catalytic transformations leading to the synthesis of enantioenriched final products. A huge number of reports and reviews described the multimetallic cooperativity between homometallic salen complexes in reactions requiring a bimetallic mechanism such as the ARO of epoxides (detailed in chapter 3), but only few examples are found recently studying the one-pot multicatalysis process using these catalysts, where two heterometallic salen complexes are involved.

Before citing the reports on the sequential one-pot process, it is very interesting to mention the work done by Jacobsen *et al.*¹⁶² on the synthesis of enantiopure 3-chlorostyrene oxide via an asymmetric epoxidation-hydrolytic kinetic resolution sequence. This example illustrates the use of two different salen complexes in a sequential epoxidation and HKR reaction; the Mn-based salen complex was used with various oxidants (NaOCl, *m*CPBA/NMO) to epoxidize 3-chlorostyrene, then the resulted mixture of two epoxides enantiomers was isolated and subjected to an HKR reaction in the presence of the Co-salen complex. Low ee values were obtained with aqueous NaOCl as oxidant (32% and

¹⁶⁰ L. F. Tietze, *Chem. Rev.* **1996**, 96, 115–136.

¹⁶¹ D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, 248, 2365–2379.

¹⁶² B. D. Brandes, E. N. Jacobsen, *Tetrahedron: Asymmetry* **1997**, 8, 3927–3933.

36% at 0 and -18 °C respectively) while 81% ee was observed in anhydrous medium. The amount of water added in the second step was adjusted to correspond to 1.1 equivalents of the minor epoxide issued from the first reaction. As expected, and interestingly, the diol and the epoxide were easily isolated by partitioning the products between pentane and water, and obtained with high ee (> 91%, >99% respectively), and with yields values in correlation with the overall yield obtained for the epoxidation step. Figure 100 shows only the reaction in which *m*CPBA/NMO was used as oxidant.

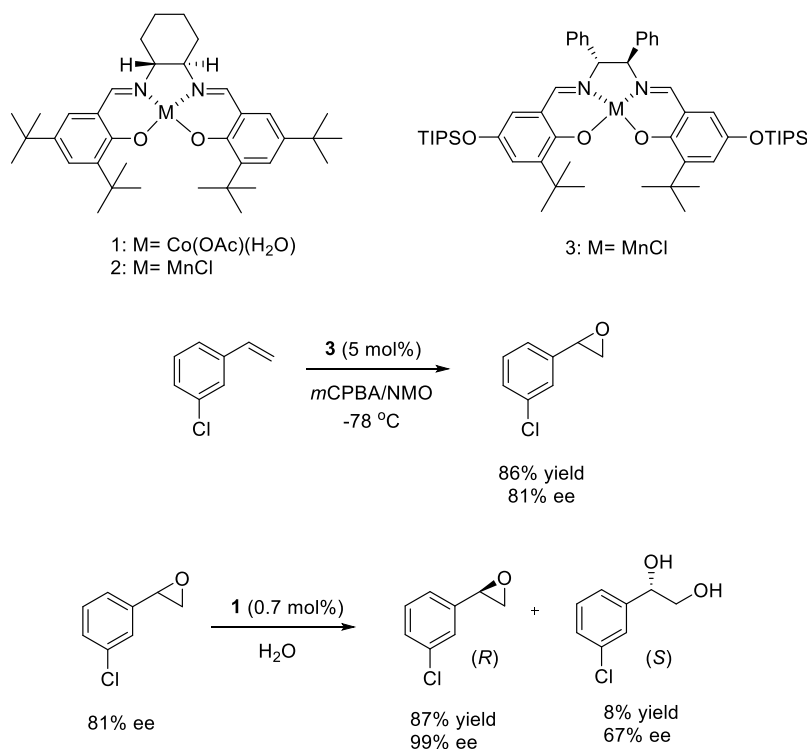


Figure 100: Epoxidation-HKR sequence of 3-chlorostyrene

The work done by Jacobsen does not represent a sequential reaction performed in a one-pot process but still a very interesting issue showing the importance of such a catalytic sequence to obtain separable enantioenriched products with high ee values. More recently, salen complexes have been incorporated as building blocks in the preparation of crystalline porous MOFs which were thus used as heterogeneous catalysts to promote asymmetric catalysis.¹⁶³ Moreover, MOFs platforms containing different metal salen derivatives were investigated to promote cooperative and tandem catalysis since their structures could be modified by solvent-assisted linker exchange (SALE).¹⁶⁴ Furthermore, multivariate (MTV) MOFs have been prepared via the cocrystallization of multiple salen complexes and used as heterogeneous catalysts to promote one-pot sequential catalysis. In this context, Lui *et al.*⁷¹ prepared a 2-fold interpenetrated 3D network starting from a carboxylic acid-

¹⁶³ F. Song, C. Wang, J. M. Falkowski, L. Ma, W. Lin, *J. Am. Chem. Soc.* **2010**, *132*, 15390–15398.

¹⁶⁴ O. Karagiari, W. Bury, J. E. Mondloch, J. T. Hupp, O. K. Farha, *Angew. Chem. Int. Ed.* **2014**, *53*, 4530–4540.

based Cu-salen link and $\text{Zn}(\text{NO}_3)_2$ where the Cu-salen units are in close proximity to each other. Then mixed crystals were obtained by mixing different metal-salen complexes. The binary MOFs conducted efficiently epoxidation reactions (Cu-Mn or Cu/Fe), cyanation of aldehydes (Cu/V), opening of epoxides (Cu/Cr or Cu/Co), and Diels-Alder reactions (Cu/Co). Interestingly, sequential reactions consisting in the epoxidation followed by the ARO with nucleophiles were performed using these platforms: Cu-Mn-Cr in the case of aniline or TMSN_3 and Cu-Mn-Co in the case of water. In both cases, the nucleophile used in one equivalent with respect to the starting olefin, was added once the epoxidation has been completed. Very high values in terms of activity and enantioselectivity have been obtained due to the important cooperativity of the different metallic units, in their conditions of proximity (Figure 101).

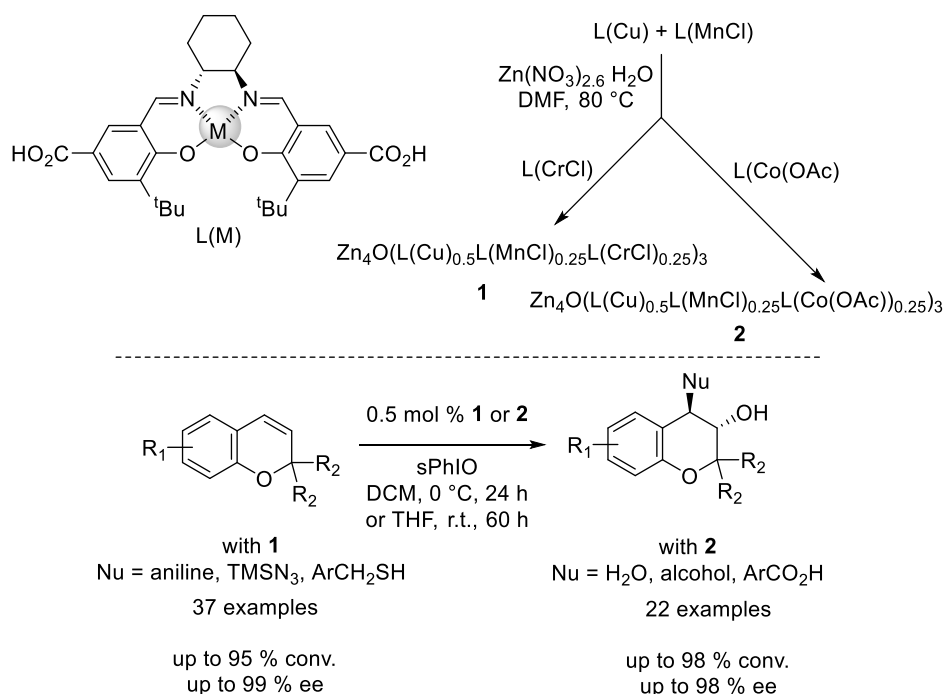


Figure 101: Multivariate MOFs with multimetallic salen complexes for sequential reactions.

In this case, the epoxidation step afforded the desired epoxides with high ee values, which led subsequently to the high enantioselectivity observed in the ring-opening reaction. The major epoxide (99% ee) issued from the first step indeed reacted delivering the corresponding ring-opened product with 99% ee. For this last step, an achiral catalyst would also be sufficient to lead to the same result.

Besides, Cui *et al.*¹⁶⁵ reported the one-step synthesis of stable, chiral crystalline COF via an imine condensation in the presence of zinc salts. COFs containing Cr-, Co-, Mn-, Fe- or V-salen complexes were easily obtained by a metal exchange procedure upon the introduction of saturated solutions of

¹⁶⁵ X. Han, Q. Xia, J. Huang, Y. Liu, C. Tan, Y. Cui, *J. Am. Chem. Soc.* **2017**, *139*, 8693–8697.

various metallic salts. Binary as ternary multimetallic based COFs were thus prepared and engaged in various catalytic transformations. Consequently, the mixed species containing Mn and Cr salen based units were engaged in a sequential epoxidation/ring opening reaction under mild conditions proving high activity and affording the desired products with high ee values (Figure 102).

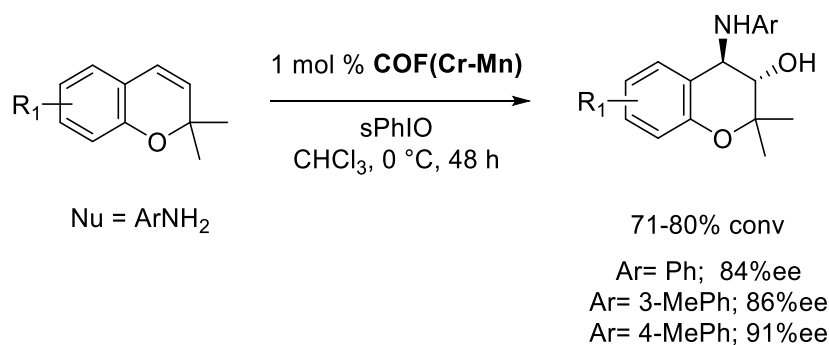


Figure 102: Sequential epoxidation/ARO of chromene derivatives catalyzed by multimetallic salen-based COFs.

2. Results and discussion

Based on the mentioned examples, we aim to perform one-pot multicatalysis processes with the modified pyrene-tagged salen complexes in homogeneous as heterogeneous media. Using the Mn and the Cr pyrene-tagged salen complexes, we decided to perform the epoxidation of an olefin followed by the ARO of the resulted epoxide in a one-pot process.

First, CN-chromene was chosen as substrate. The epoxidation was conducted in the presence of Unsym-C1-Mn **17** under the same conditions as described previously and monitored using GC analysis. Then the catalyst Unsym-C1-Cr **14** was added followed by the addition of the nucleophile, in this case TMSN₃.

Table 26 summarizes the result of the first one-pot sequential reactions, in which PhIO was used as oxidant for the first step. In this case, 5 mol% of catalyst **17** was engaged. After 24 hours, 56% of conversion were observed, so additional 0.5 equivalents of oxidant were added to the reaction mixture in order to increase the conversion value; after additional 20 hours, the substrate was as expected converted with a high 90% conversion value.

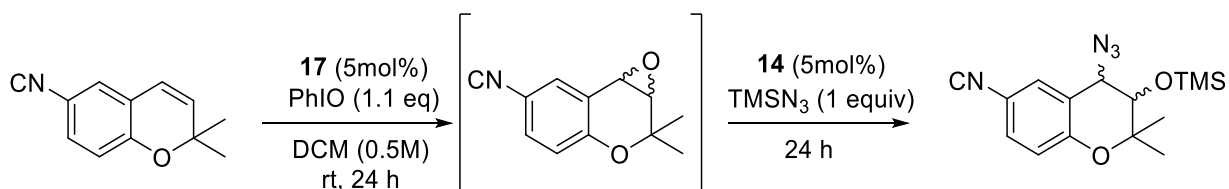


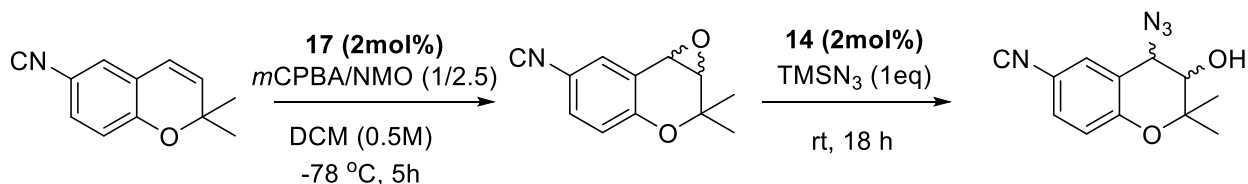
Table 26: Sequential epoxidation/ARO of CN-chromene in the presence of PhIO as oxidant.

Epoxidation reaction (catalyst 17)		ARO reaction (catalyst 14)		
Conv %	ee %	Conv %	ee (epoxide) %	ee (product) %
56	89	48	40	---
90*				

*After 20 hours of the addition of 0.5 equivalents of PhIO.

To the reaction mixture which contains the desired epoxide with 89% ee, the catalyst **14** was added (5 mol%) followed by the addition of one equivalent of TMSN₃ with respect to the obtained epoxide. The reaction was monitored by proton NMR and allowed to stir for 24 hours. Only 48% conversions were obtained. Unfortunately, the ee of the product was not measured due to the difficulty of its purification in these conditions. Moreover, only the peaks relative to the epoxide enantiomers could be identified using chiral HPLC and the ee was 40%. This unexpected result is not exploitable since if no enantioselectivity occurred in the last step, a high ee value for the residual epoxide (in the order of 80%) should be obtained. It could probably be explained by an analysis error due to the impurity of the obtained mixture.

On the other hand, using 2 mol% loading of Mn-salen complex **17** and *m*CPBA/NMO (1/2.5), the epoxidation of CN-chromene was carried out at -78 °C for 5 hours. 89% of conversion were obtained with 96% ee for the desired epoxide. Following the same procedure, catalyst **14** and the nucleophile were added. This time, the conversion calculated by NMR was 85% after 18 h but to afford the deprotected alcohol with 92% ee. The ee of the epoxide was also determined and it was diminished to 64% ee (Table 27).

Table 27: Sequential epoxidation/ARO of CN-chromene in the presence of *m*CPBA/NMO as oxidant.

Epoxidation reaction (catalyst 17)		ARO reaction (catalyst 14)		
Conv %	ee %	Conv %	ee (epoxide) %	ee (product) %
89	96	85	64	92

More interestingly, the same sequential reaction was carried out under the same conditions but without the addition of the Cr-salen catalyst in the second step. The same results in terms of activity (conversion) and enantioselectivity have been obtained (85% conversion and 92% ee), proving thus that there is no need for the addition of a chiral Cr-salen complex for the last step. Probably the residual *m*-chlorobenzoic acid is able to catalyse the ring opening reaction of CN-chromene oxide, as bronsted acid. Based on these results which are more consistent with the theoretical approaches, two hypotheses could be formulated: in the first one, only the main epoxide enantiomer obtained from the first step is reacting in the next ARO, leading to the decrease of the remaining epoxide ee at the end of the reaction, together with the ring-opened product in high ee. The second hypothesis consists of the absence of enantiodiscrimination in the last step, which will be further studied.

In order to understand the enantioselectivity value of the resulted epoxide after the sequential reactions, we performed the kinetic resolution of a racemic mixture of the corresponding isolated substrate. 51% of conversion have been observed after 4 days and the residual epoxide, as the ring-opened product, were obtained in a racemic way indicating that the pyrene-tagged Cr-salen complex was not enantioselective. The rate constant is therefore the same for the two enantiomers leading to the absence of competition and thus enantiodiscrimination between them.

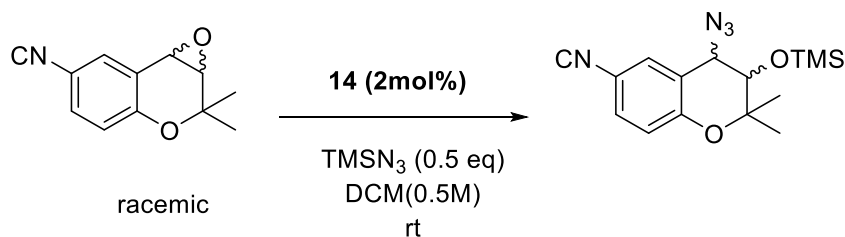


Table 28: Kinetic resolution of racemic mixture of CN-chromene oxide.

Solvent	Time (h)	Conv %	ee %	ee (epoxide)
DCM	6	24		
	24	36	racemic	racemic
	4d	51		

Moreover, the ARO of isolated enantioenriched epoxide (96% ee) was performed using catalyst **14** with 1 equivalent of TMSN₃ in DCM. No complete conversion was observed (58% after 24 hours) and the desired product was obtained with 96% ee and the residual epoxide in 91% ee. The ring-opening reaction catalysed with Unsym-C1-Cr **14** is thus slow and not enantioselective. The result confirms that the ARO in the sequential reaction (see Table 27) was mainly promoted by the *m*-chlorobenzoic acid as Bronsted acid in a faster reaction. Furthermore, all these results demonstrate that the enantioselectivity in the final product is strongly related to the first epoxidation step and that any achiral catalyst can be used for the ring-opening step leading to the same degree of enantioselectivity. Hence, the sequential reaction in this case is not as challenging because the epoxidation of CN-chromene was very enantioselective and the ring-opened product definitely can be obtained with excellent yield and excellent ee.

However, based on the concept described by Jacobsen¹⁶², we decided to promote a different sequential reaction with a more challenging substrate. It is known that the kinetic resolution (KR) of a racemic mixture is a good and efficient method to access to highly enantiopure molecules. However, with an ideal KR, it is possible to obtain products with high ee values but with only a maximum 50% yield (Figure 103).

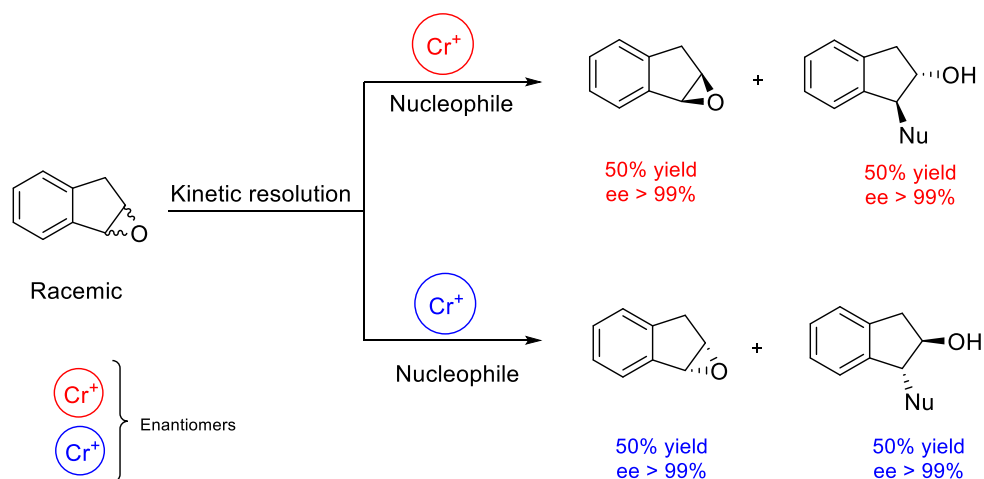


Figure 103: Illustration of a kinetic resolution of a racemic mixture of indene oxide.

Performing the kinetic resolution of a non-racemic mixture, but with a modest ee value, represents an alternative to obtain final products in high ee and in more than 50% yield. For example, if an epoxide delivered from the first enantioselective epoxidation step with 60% ee, is further engaged in the ARO reaction considered as a kinetic resolution of an enantioenriched mixture, and if the major epoxide reacts mainly with the ARO catalyst, it will be obtained in 80% yield and >99% ee (Figure 104).

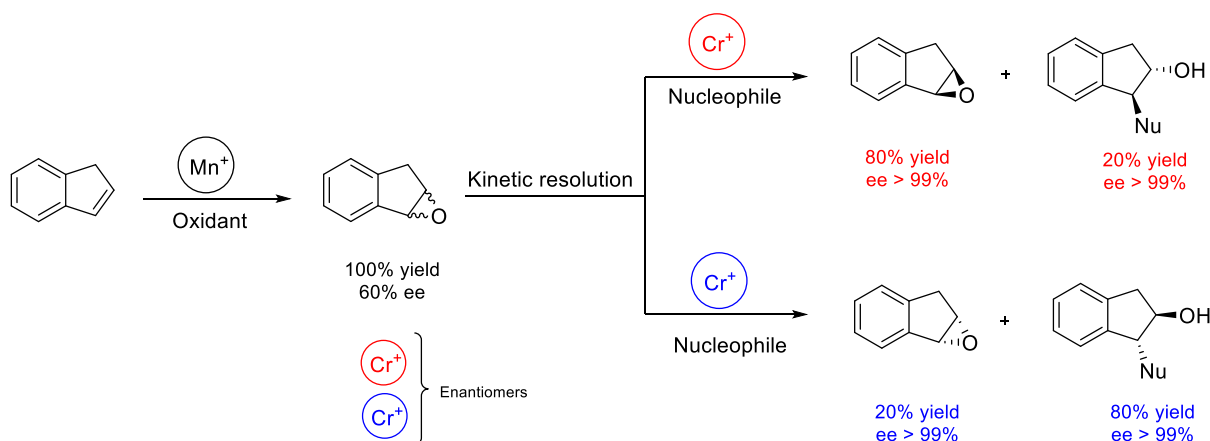


Figure 104: Representation of an asymmetric epoxidation reaction followed by a kinetic resolution.

In this context, and in order to perform more challenging sequential reaction processes outperforming the KR reaction, we decided to use indene as substrate. As described in the previous part, the epoxidation of indene using PhIO as an oxidant in the presence of **17** as catalyst afforded the indene oxide with 60% ee. The epoxidation reaction was carried out using PhIO as oxidant at room temperature in the presence of catalyst **17** in a 2 mol% loading affording the desired indene oxide with 60% ee. The ARO reaction was achieved by adding 2 mol% of catalyst **14** and 1 equivalent of the nucleophile to the thus obtained reaction mixture (Figure 105). Unfortunately, the desired ring-

opened product was obtained with 32% ee (16% yield) while the ee of the remaining epoxide was 56%.

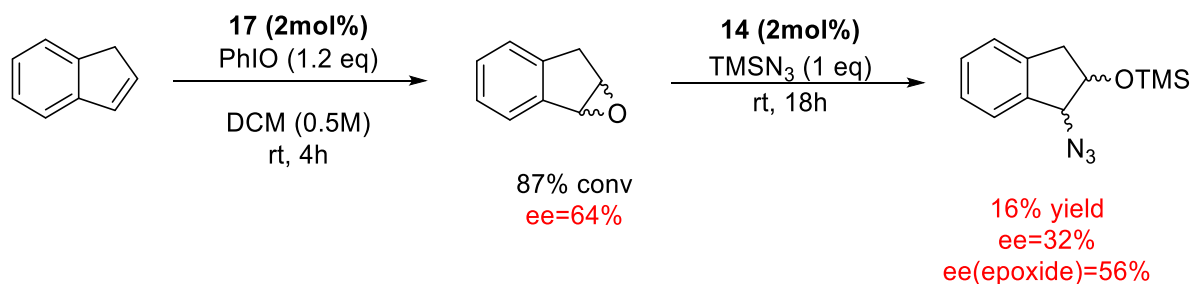


Figure 105: Sequential epoxidation/ARO of indene

This sequential reaction was not successful, and again catalyst **14** was inactive and non-selective in these conditions. Moreover, we tried to carry out the ARO of racemic indene oxide. Results are summarized in Table 29. 45% of conversion were observed after 72 hours in the kinetic resolution of the racemic mixture of indene oxide, and the desired product was afforded with only 10% ee, and 20% ee for the resting epoxide. This indicates that this reaction was not enantioselective. Furthermore, the use of 1 equivalent of TMNS_3 accelerates the reaction and 82% conversion were obtained after 72 hours, but with almost racemic product and very low ee for the epoxide (32%) (Table 29, Entry 2).

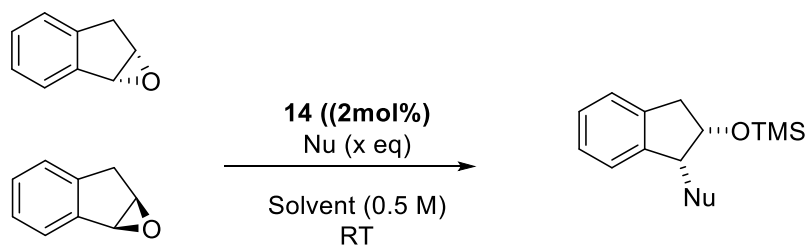


Table 29: KR and ARO of racemic indene oxide.

Entry	Solvent	Nu (eq)	Time (h)	Conv %	ee (product)	ee (epoxide)
1	DCM	TMSN_3 (0.5)	72	45	10	20
2	DCM	TMSN_3 (1)	24	58	9	12
			72	82	7	32
3	DCM	Aniline (1)	24	77	7	--

Aniline was further tested as nucleophile for this reaction, leading to almost the same results with racemic ring-opened product after 24 hours (Entry 3). These are our preliminary attempts to achieve the sequential reaction process with our pyrene-modified salen complexes. Even if they are not successful, modifications on the substrate nature and on the reaction conditions remain possible to optimize this process and to achieve an efficient one-pot multistep procedure.

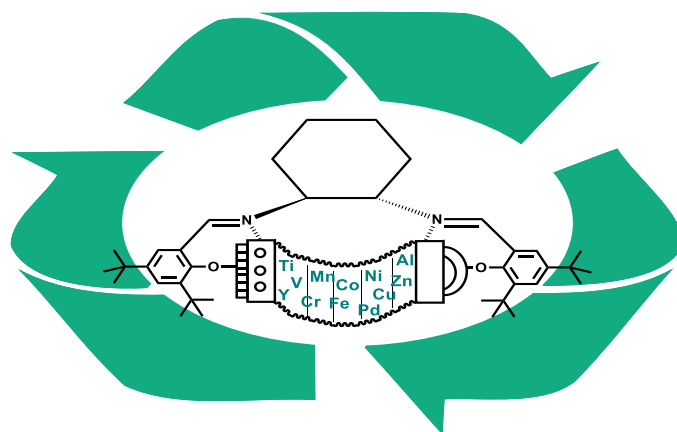
Conclusion

The application of the unsymmetrical pyrene-tagged Mn salen complex was tested in the asymmetric epoxidation of various alkenes. Depending on the nature of the olefins and of the oxidant used, different reactivities were observed. Unsym-C1-Mn **17** displayed a better activity than Jacobsen's catalyst **18** in the epoxidation of indene in the presence of PhIO as oxidant and delivered the corresponding epoxide with 60% ee. Under the same conditions, for the epoxidation of CN-chromene as substrate, catalyst **17** outperformed **18** in terms of activity and enantioselectivity (79% ee vs 52% ee). However, the best result for this reaction was obtained in the presence of mCPBA/NMO (1/2.5), in which again the pyrene-tagged Mn salen complex showed a better activity but a similar enantioselectivity with 96% ee for the desired epoxide. Terminal epoxides such as styrene, allylbenzene and (allyloxy)benzene have been also tested as substrates for the asymmetric epoxidation but in all cases very low conversions have been obtained. The supported Mn-salen complex **17**@rGO has been engaged in the heterogeneous AE of styrene, indene and CN-chromene. Good conversions and ee values were obtained, but in all cases, they remained lower than those obtained under homogeneous conditions.

A sequential one-pot asymmetric epoxidation-ring opening reaction using the pyrene-tagged Mn and Cr complexes (**17** and **14**) was tested using CN-chromene and indene as substrates. In the first case, based on the high enantioselective epoxidation first step, it was proven that there is no need for a chiral catalyst in the second step to obtain the final product with high ee values. However, the sequential reaction for indene is more challenging because the corresponding epoxide was obtained in only 60% ee. Unfortunately, the second step in this case showed a poor enantioselectivity affording the final ring-opened product with low yield, making the process unsuccessful.

General conclusion

The heterogenization of organometallic chiral complexes to facilitate their recovery remains an attractive method to benefit from the advantages of both homogeneous and heterogeneous catalysis in terms of activity, selectivity, and recovery of the catalysts. Based on this concept, the design of new modified chiral catalysts that are able to be immobilized, recycled and reused constitutes one of the most interesting subjects for chemists, particularly in the current global context of compliance with the rules of green chemistry. Our team is interested in the salen complexes chemistry and previous work has been carried out to study their heterogenization following different methods. At the beginning of this thesis, a review on recent methods of heterogenization of salen complexes and on the study of their cooperativity has been written and published.



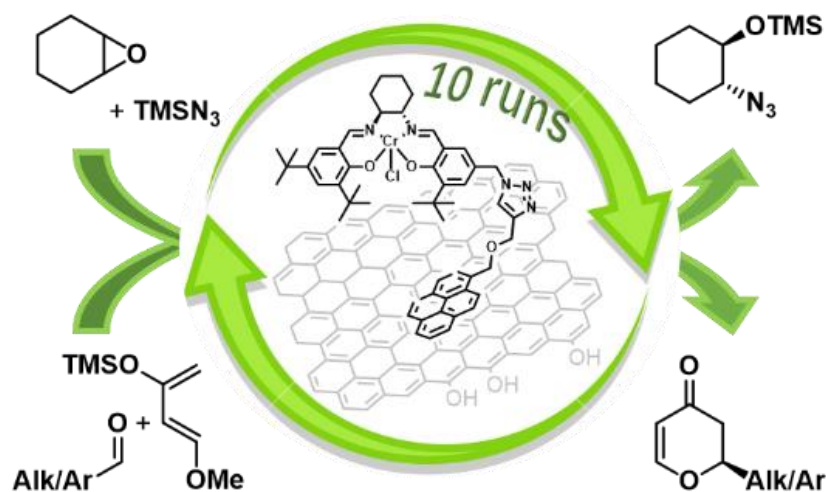
M. Abd El Sater, N. Jaber, E. Schulz, *ChemCatChem* **2019**, *11*, 3662–3687

We have deduced that the immobilization of salen complexes on organic supports by non-covalent interactions was very rare, whereas this type of immobilization is simple and should allow recovery of both the ligand and the support. Consequently, in this work, structural modifications have been performed on the salen ligands to ensure their immobilization onto reduced graphene oxide (rGO) via non-covalent π - π type interactions. Based on the capacity of pyrene groups to bind to graphitic surfaces, mono as bis-pyrene-tagged salen ligands have been synthesized. The bridge between the pyrene group and the salen moiety was built at the *para*-position of phenol ring through a 1,3-dipolar cycloaddition click reaction (CuAAC) which occurred between the pyrene-tagged alkynes and the azidosalicylaldehyde. Therefore, starting from two pyrene derivatives with different alkyl chains, four pyrene-tagged salen have been prepared including symmetrical ligands bearing two pyrene groups and unsymmetrical ones with only one pyrene group, all of them in very good yields. The corresponding chromium and manganese complexes were synthesized in quantitative yields and their catalytic properties were evaluated in the asymmetric ring opening reaction (ARO) of cyclohexene

oxide with TMSN_3 , the hetero-Diels-Alder reaction (HDA) of various aldehydes and the asymmetric epoxidation of olefins.

The pyrene-tagged chromium salen complexes promoted efficiently the ARO and the HDA reactions. However, the symmetrical complexes were found to be less enantioselective than the unsymmetrical analogues probably due to the absence of the bulky tert-butyl groups in the *para*-position of phenol, which are crucial for high enantioselectivity. Moreover, the high activity associated with the best enantioselectivity was assigned to the unsymmetrical pyrene-tagged Cr-salen complex Unsym-C1-Cr **14**, derived from pyrene methanol. We suggested that this was due to its more rigid structure.

The immobilization of all pyrene-tagged complexes onto rGO was successfully achieved via the impregnation of the rGO suspension with a solution of the catalysts in DCM with a mass ratio of 4:1. To our knowledge, this is the first π -stacking mediated immobilization of salen complexes onto the surface of any carbon materials. The Unsym-C1-Cr **14**@rGO showed a high efficiency, stability and robustness in catalysing the heterogeneous ARO of cyclohexene oxide with TMSN_3 , with activity and enantioselectivity values matching those obtained in homogeneous conditions. It was recycled and reused for 10 subsequent runs, without showing any notable loss of activity or selectivity. The same efficiency was observed for the HDA reaction with cyclohexane carboxaldehyde and also in a multisubstrate process.



M. Abd El Sater, M. Mellah, D. Dragoie, E. Kolodziej, N. Jaber, E. Schulz, *Chem. Eur. J.* **2021**, *27*, 9454–9460.

Moreover, the manganese analogue promoted the asymmetric epoxidation (AE) of various olefins in the presence of PhIO or *m*CPBA/NMO as oxidants. The results in terms of activity and enantioselectivity were highly dependent on the structure of the substrates and on the nature of

oxidant used. The heterogeneous AE of indene, styrene and CN-chromene was performed leading to promising results which must be improved to further explore the recycling procedure under optimal conditions.

Finally, a one-pot sequential reaction process consisting of an epoxidation followed by a ring-opening reaction was attempted in the presence of a pyrene-tagged Mn complex for the first step and followed by the addition of a pyrene-tagged Cr complex in homogeneous conditions. In the case of CN-chromene, the sequential reaction was not as challenging since the epoxidation step was highly enantioselective affording the epoxide with 96% ee, which will definitely react in the next step leading to the desired product with high ee value. On the other hand, a more challenging reaction was expected starting from indene. In this case, we planned to perform a kinetic resolution for the mixture of epoxide resulted from the first step with a modest ee (60%). It should have led, in the case of a high selectivity for the ring-opening reaction, to an increase in the yield of the products at the end of the process. Unfortunately, the resolution was not successful since the last step was slow and not enantioselective.

The study of the sequential reaction process should be continued. Further experiments studying the enantioselectivity of the ring-opening reaction must be performed in the last step to understand the results obtained and to reach the goal of this work. So, it is possible to use the other catalyst enantiomer in the last step and to compare then the obtained results, or to replace it by another salen complex with a different structure and compare the enantioselectivity. Furthermore, it is crucial to prove the role of the residual *m*-chlorobenzoic acid in this reaction. Finally, all these preliminary results and suggestions are promising to develop an original multimetallic supported catalytic system with pyrene-tagged Mn and Cr salen complexes co-immobilized onto rGO, as an efficient platform to promote one-pot sequential and tandem catalysis. Moreover, pyrene-tagged salen complexes with other metal centers (Al, Co,..) could be prepared to promote other catalytic transformations and immobilized to perform different multimetallic sequential processes.

General conclusion

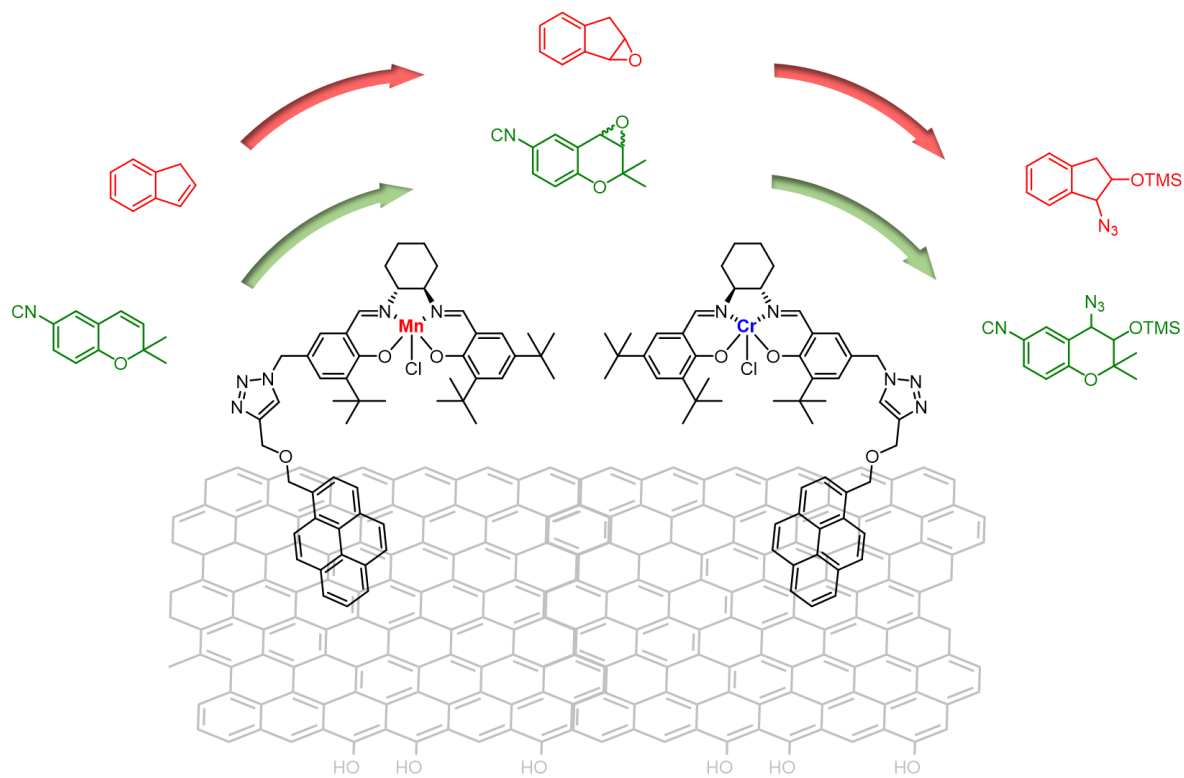


Figure 106: Co-immobilization of Mn and Cr-salen complexes for asymmetric tandem reaction

Experimental part

Experimental part

General remarks

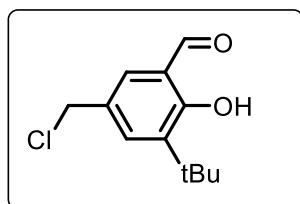
All reactions are carried under argon atmosphere. Catalytic reactions were performed in catalysis tubes with plastic septa.

Unless otherwise stated, all reagents are commercial and used without prior purification. Commercial reduced graphene oxide was purchased from Graphenea. All solvents were distilled before use. ^1H and ^{13}C NMR were recorded on Bruker AV360 (and 250, 300) spectrometer. ESI-HRMS was detected on Bruker MicroTOF-Q daltonics spectrometer. IR spectra were recorded on a Bruker Vertex 70 ATR-Germanium spectrometer. UV-Visible experiments were realized on Varian, Cary 300 bio spectrophotometer. GC analyses were performed on Shimadzu GC 2010-plus using chiraldex β -PM column (50m*0.25mm*0.12 μm). HPLC analyses were done on JASCO LC-NET II/ADC HPLC using chiral OD-H, OJ-H and IA columns. XPS analyses were performed using a ThermoFisher Scientific K-Alpha spectrometer.

XPS analysis was performed using a K-Alpha spectrometer from Thermo Fisher Scientific, with a monochromatic $\text{Al}_{\text{K}\alpha}$ source (1486.6 eV) with a spot size of 400 μm , and a hemispherical analyser (take-off angle 0°). The wide scan spectra were acquired at a pass energy of 200 eV and an energy step of 1 eV while the narrow scan spectra were recorded at 50 et 100 eV pass energies, with an energy step of 0.1 eV. Charge correction was accomplished by means of a dual beam source (electron energy of maximum 5 eV). The binding energy was calibrated using the sp^2C component considered at 284.5 eV. The spectra were treated by means of Avantage software provided by Thermo Fisher. A Shirley-type background was subtracted, and the peak areas were normalized using the Scofield sensitivity factors. Mixed Gaussian-Lorentzian (LG) functions (30%L) were considered as synthetic lineshapes for the symmetric peaks and an asymmetry was added for the fit of sp^2C signal.

I. Synthesis

3-(*tert*-butyl)-5-(chloromethyl)-2-hydroxybenzaldehyde (1)



Chemical Formula: C₁₂H₁₅ClO₂

Exact Mass: 226.08

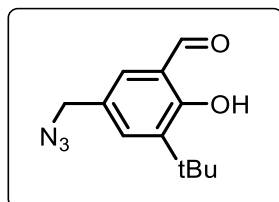
Molecular Weight: 226.70 g.mol⁻¹

3-*tert*-Butyl-2-hydroxybenzaldehyde (5 g, 28.05 mmol) reacted with 1,3,5-trioxane (2.5 equiv, 6.32 g) in 110 mL of concentrated HCl (37%) under vigorous stirring at 55 °C for 2 days. The reaction mixture was diluted with H₂O (80 mL) and extracted with diethyl ether (3x80 mL). The organic phase was separated and washed with a saturated NaHCO₃ solution (2x80 mL) and brine (3x80 mL). After drying on MgSO₄, the evaporation of the solvents afforded the product (5.6 g, 89 %).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 11.86 (s, 1H, OH), 9.87 (s, 1H, COH), 7.53 (d, 1H, *J* = 2.3 Hz, ArH), 7.44 (d, 1H, *J* = 2.3 Hz, ArH), 4.59 (s, 2H, CH₂), 1.43 (s, 9H, *t*Bu).

All other analytic data are identical to those described in previous works.¹⁶⁶

5-(azidomethyl)-3-(*tert*-butyl)-2-hydroxybenzaldehyde (2)



Chemical Formula: C₁₂H₁₅N₃O₂

Exact Mass: 233.12

Molecular Weight: 233.27 g.mol⁻¹

A 250 mL, two-necked, round-bottomed flask was charged with a solution of 3-(*tert*-butyl)-5-(chloromethyl)-2-hydroxybenzaldehyde (22.05 mmol, 5 g) in anhydrous DMF (96 mL). Sodium azide (1.1 equiv., 24.2 mmol, 1.58 g) was added in small portions under argon. The flask was wrapped with an aluminium foil and the reaction mixture was further stirred for 24 h at 25 °C.

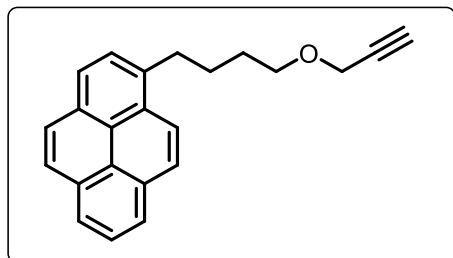
The resulting mixture was diluted with DCM (50 mL) and washed with water (3 x 50 mL). The organic layer was separated, dried over MgSO₄ and filtered, and the solvents were removed by rotary evaporation. A further extraction was needed to eliminate residual DMF by adding AcOEt (50 ml) and washing with water (6 x 60 ml). The product was obtained as a brown oil (3.66 g, 71% yield).

¹H NMR (360 MHz, CDCl₃) δ (ppm): 11.84 (s, 1H, OH), 9.89 (s, 1H, COH), 7.45 (d, *J* = 2.2 Hz, 1H, ArH), 7.36 (d, 1H, *J* = 2.2 Hz, ArH), 4.33 (s, 2H, CH₂), 1.43 (s, 9H, *t*Bu).

¹⁶⁶ F. Minutolo, D. Pini, A. Petri, P. Salvador, *Tetrahedron: Asymmetry*, **1996**, 7, 2293–2302.

All other analytic data are identical to those described in previous works.⁹⁹

1-(4-(prop-2-yn-1-yloxy)butyl)pyrene (4)



Chemical Formula: C₂₃H₂₀O

Exact Mass: 312.15

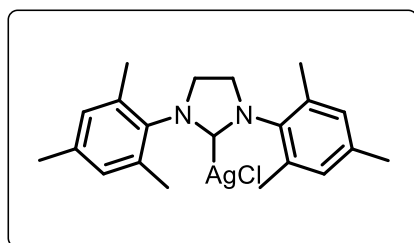
Molecular Weight: 312.41 g.mol⁻¹

A solution of 1-pyrenebutanol (1 g, 3.6 mmol) in anhydrous THF (8 mL), was added under argon to a suspension of NaH (1.9 equiv, 7 mmol, 277 mg) in THF (8 mL) at 0° C. The solution was stirred at 0° C for 1 h, and propargyl bromide (80 % in toluene, 2 equiv, 7.2 mmol, 835 μL) was added. The reaction was stirred at 0° C in the dark for 1 h, and then let warm to room temperature. After stirring for 15 h, the reaction was refluxed for 8 h, after which AcOEt (10 mL) and H₂O (10 mL) were added. The aqueous phase was extracted with AcOEt (2 x 15 mL). The combined organic phases were washed with H₂O (2 x 15 mL), and then with brine (2 x 15 mL) and dried over MgSO₄. After removal of solvents under vacuum, the crude was purified by column chromatography (cyclohexane/ AcOEt; 8/2). The product was obtained as pale-yellow powder (776 mg, 69 % yield).

¹H NMR (360 MHz, CDCl₃) δ (ppm): 8.29 (d, 1H, *J* = 9.7 Hz, ArH), 8.18-8.16 (m, 2H, ArH), 8.12-8.10 (m, 2H, ArH), 8.03-7.97 (m, 3H, ArH), 7.88 (d, 1H, *J* = 8.1 Hz, ArH), 4.15 (d, 2H, *J* = 2.4 Hz, CH₂-alkyne), 3.59 (t, 2H, *J* = 6.7 Hz, CH₂-O), 3.38 (t, 2H, *J* = 7.4 Hz, CH₂-pyrene), 2.43 (t, 1H, *J* = 2.4 Hz, CH), 2.00-1.92 (m, 2H, CH₂), 1.84-1.76 (m, 2H, CH₂).

All other data analyses are identical to those described in previous references.¹⁰¹

(1,3-dimesitylimidazolidin-2-yl)silver(II) chloride



Chemical Formula: C₂₁H₂₇AgClN₂

Exact Mass: 449.09

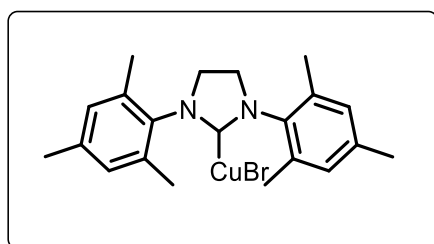
Molecular Weight: 450.77 g.mol⁻¹

Under argon, silver(I) oxide Ag₂O (135 mg, 0.58 mmol) was added to a solution of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (200 mg, 0.65 mmol) in anhydrous DCM (20 mL), and the reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was filtered

through a short pad of celite, and the celite was flushed with DCM. After solvent removing, the product was obtained as brown solid (236 mg, 81% yield).

¹H NMR (360 MHz, CDCl₃) δ (ppm): 6.94 (s, 4H, ArH), 3.99 (m, 4H, CH₂), 2.29 (s, 6H, CH₃), 2.28 (m, 12H, CH₃).

(1,3-dimesitylimidazolidin-2-yl)copper(I) bromide



Chemical Formula: C₂₁H₂₇BrCuN₂

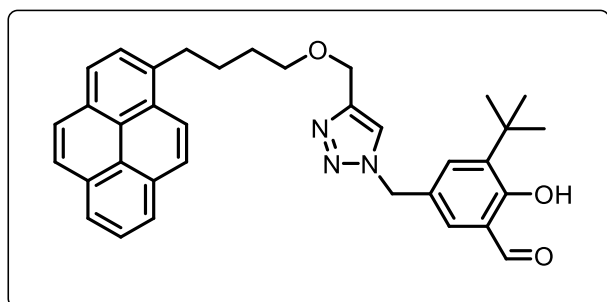
Exact Mass: 449.06

Molecular Weight: 450.91 g.mol⁻¹

Under argon, copper(I) bromide (70 mg, 0.49 mmol) was added to a solution of (1,3-dimesitylimidazolidin-2-yl)silver(II) chloride (220 mg, 0.49 mmol) in anhydrous DCM (15 mL), and the reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was filtered through a short pad of celite, and the celite was flushed with DCM. After solvent removing, the product was obtained as orange solid (220 mg, 90% yield).

¹H NMR (300 MHz, (CD₃)₂O) δ (ppm): 7.02 (s, 4H, ArH), 4.16 (m, 4H, CH₂), 2.38 (s, 12H, CH₃), 2.30 (m, 6H, CH₃).

3-(*tert*-butyl)-2-hydroxy-5-((4-((4-(pyren-1-yl)butoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzaldehyde (5)



Chemical Formula: C₃₅H₃₅N₃O₃

Exact Mass: 545.27

Molecular Weight: 545.68 g.mol⁻¹

Under argon, a Schlenk flask was charged with 5-(azidomethyl)-3-(*tert*-butyl)-2-hydroxybenzaldehyde (333 mg, 1.43 mmol), 1-(4-(prop-2-yn-1-yloxy)butyl)pyrene (1.1 equiv, 1.57 mmol, 490 mg) and CuI (0.05 equiv, 13.6 mg). Degassed THF was then added (13 mL), followed by anhydrous DIPEA (3.5 equiv, 0.84 mL) and the yellow solution was stirred at 40 °C for 16h. After removing the solvent under vacuum, the mixture was diluted in DCM (8 mL) and washed with an

EDTA solution (0.05 M). After drying the combined organic phases on MgSO₄, filtration and solvent evaporation, the product was obtained as a brown powder (661 mg, 85 % yield).

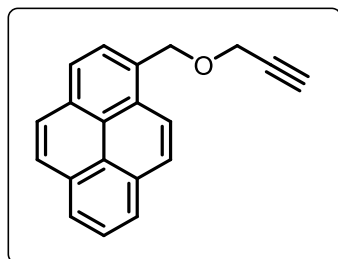
¹H NMR (360 MHz, CDCl₃) δ (ppm): 11.82 (s, 1H, OH), 9.73 (s, 1H, COH), 8.24 (d, 1H, *J* = 9 Hz, ArH), 8.15 (d, 2H, *J* = 7.8 Hz, ArH), 8.09-8.06 (m, 2H, ArH), 8.01-7.09 (m, 3H, ArH), 7.84 (d, 1H, *J* = 7.7 Hz, ArH), 7.41 (s, 1H, CH-triazole), 7.39 (d, 1H, *J* = 2.3 Hz, ArH), 7.20 (d, 1H, *J* = 2.3 Hz, ArH), 5.38 (s, 2H, CH₂-N), 4.60 (s, 2H, triazole-CH₂-O), 3.58 (t, 2H, *J* = 6.5 Hz, CH₂-O), 3.33 (t, 2H, *J* = 7.7 Hz, CH₂-pyrene), 1.96-1.87 (m, 2H, CH₂), 1.81-1.73 (m, 2H, CH₂), 1.36 (s, 9H, *t*Bu).

HRMS (ESI+): calcd for C₃₅H₃₆N₃O₃ (M+H⁺) 546.2751, found 546.2724

¹³C NMR (90 MHz, CDCl₃) δ (ppm): 196.77 (CH, COH), 161.44 (Cq), 139.59 (Cq), 136.77 (Cq), 133.82 (CH), 131.48 Cq), 131.34 (CH), 130.94-129.85-128.65 (Cq), 127.60-127.36-127.27-126.67-125.91 (CH), 125.39-125.12-125.07 (Cq), 124.95-124.88-124.76-123.50 (CH), 122.15-120.47 (Cq), 70.77 (CH₂), 64.49 (CH₂), 53.49 (CH₂), 35.03 (Cq), 33.32 (CH₂), 29.70 (CH₂), 29.12 (CH₃), 28.45 (CH₂). (one CH is lacking).

IR (ATR, ν cm⁻¹): 2958, 1649, 1436, 1383, 1099, 1048, 846.

1-((prop-2-yn-1-yloxy)methyl)pyrene (3)



Chemical Formula: C₂₀H₁₄O

Exact Mass: 270.10

Molecular Weight: 270.33 g.mol⁻¹

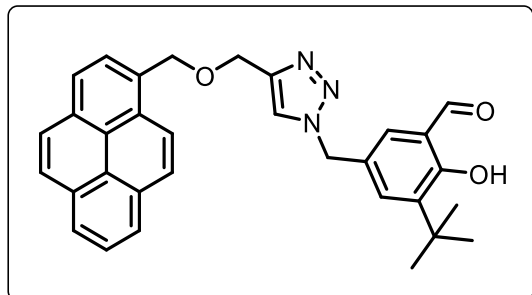
A solution of 1-pyrenemethanol (2 g, 8.61 mmol) in anhydrous THF (9 mL), was added under argon to a suspension of NaH (1.9 equiv, 16 mmol, 641 mg) in THF (9 mL) at 0 °C. The solution was stirred at 0 °C for 1 hour, and propargyl bromide (80 % in toluene, 2 equiv, 17.2 mmol, 983 μL) was added. The reaction was stirred at 0 °C in the dark for 1 h, and then let warm to room temperature. After stirring for 15 h, the reaction was complete (TLC control). The reaction mixture was quenched with brine (10 mL) carefully. The aqueous phase was extracted with AcOEt (3×10 mL). The combined organic fractions were washed with brine, dried (MgSO₄) and concentrated in vacuo. The product was obtained as a brown powder after a trituration with pentane (2.3 g, 99 % yield).

¹H NMR (360 MHz, CDCl₃) δ (ppm): 8.42 (d, 1H, *J* = 9.2 Hz, ArH), 8.23-8.15 (m, 4H, ArH), 8.07-8.00 (m, 4H, ArH), 5.34 (s, 2H, CH₂-O), 4.28 (d, 2H, *J* = 2.4 Hz, CH₂-alkyne), 2.57 (t, 1H, *J* = 2.4 Hz, CH).

HRMS (ESI+): calcd for C₂₀H₁₄NaO (M+Na⁺) 293.0937, found 293.0929

All other analytic data are identical to those described in previous references.¹⁰⁰

3-(*tert*-butyl)-2-hydroxy-5-((4-((pyren-1-ylmethoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzaldehyde (6)



Chemical Formula: C₃₂H₂₉N₃O₃

Exact Mass: 503.22

Molecular Weight: 503.60 g.mol⁻¹

Under argon, a Schlenk flask was charged with 5-(azidomethyl)-3-(*tert*-butyl)-2-hydroxybenzaldehyde (863 mg, 3.69 mmol), 1-((prop-2-yn-1-yloxy)methyl)pyrene (1.1 equiv, 4.06 mmol, 1.1 g) and CuI (0.05 equiv, 35 mg). Degassed THF was then added (35 mL), followed by anhydrous DIPEA (3.5 equiv, 2.2 mL) and the yellow solution was stirred at 40 °C for 16h. After removing the solvent under reduced pressure, followed by a trituration in Et₂O, the resulting solid was recovered after filtration. The mixture was then diluted in DCM (10 mL) and washed with an EDTA solution (0.05 M). After drying the combined organic phases on MgSO₄, filtration and solvent evaporation, the product was obtained as a brown powder (1.6 g, 86 % yield).

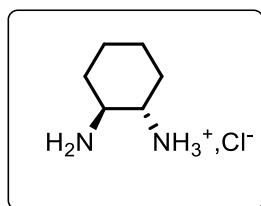
¹H NMR (360 MHz, CDCl₃) δ (ppm): 11.84 (s, 1H, OH), 9.73 (s, 1H, COH), 8.30 (d, 1H, *J* = 9.2 Hz, ArH), 8.18-8.16 (m, 2H, ArH), 8.12-7.98 (m, 6H, ArH), 7.42 (s, 1H, CH-triazole), 7.41 (d, 1H, *J* = 2.4 Hz, ArH), 7.20 (d, 1H, *J* = 2.4 Hz, ArH), 5.38 (s, 2H, CH₂-N), 5.29 (s, 2H, pyrene-CH₂-O), 4.79 (s, 2H, triazole-CH₂-O), 1.37 (s, 9H, *t*Bu).

¹³C NMR (90 MHz, CDCl₃) δ (ppm): 196.80 (CH, COH), 161.46 (Cq), 146.02 (Cq), 139.63 (Cq), 133.91 (CH), 131.46 (CH), 131.24-130.89-130.79-129.50 (Cq), 127.78-127.62-127.45-127.34 (CH), 126.10-125.40-125.37 (CH), 125.27-124.97-124.70 (Cq), 124.57-123.43-122.52 (CH), 120.47 (Cq), 71.32 (CH₂), 63.93 (CH₂), 53.57 (CH₂), 35.04 (Cq), 29.13 (CH₃). (one Cq is lacking).

HRMS (ESI⁺): calcd for C₃₂H₃₀N₃O₃ (M+H⁺) 504.2281, found 504.2267; calcd for C₃₂H₂₉N₃NaO₃ (M+Na⁺) 526.2101, found 526.2075

IR (ATR, ν cm⁻¹): 2959, 1648, 1437, 1384, 1074, 1048, 847.

Monoprotected (*1S,2S*)-cyclohexane-1,2-diamine (**9**)



Chemical Formula: C₆H₁₅ClN₂

Exact Mass: 150.09

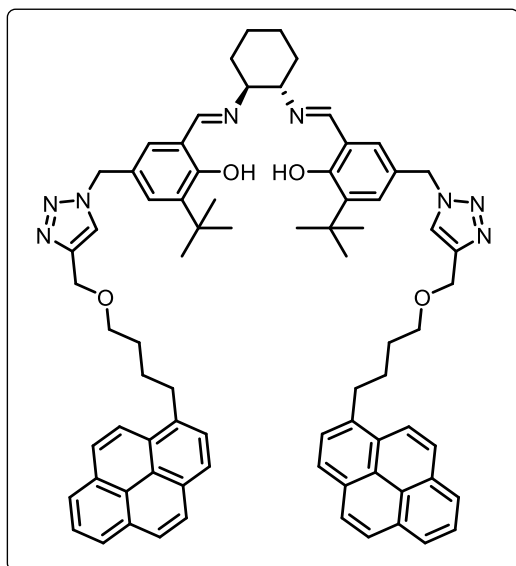
Molecular Weight: 150.65 g.mol⁻¹

(*1S,2S*)-cyclohexane-1,2-diamine (537 mg, 4.7 mmol) was dissolved in anhydrous ethanol (16 mL) under argon in a 100 mL three-necked flask equipped with a magnetic stir bar, an addition funnel, and a gas inlet. After cooling the solution to 0 °C with an ice/water bath, a solution of hydrogen chloride in ether (2M, 4.7 mmol, 2.35mL) was added dropwise through the addition funnel over a period of 45 min. The reaction was exothermic, and a white precipitate formed immediately. The reaction mixture was allowed to warm up to room temperature and stirring was continued overnight. The precipitate was collected by filtration, washed with dry Et₂O, and vacuum dried to afford the product as a colorless powder (500 mg, 71 %).

¹H NMR (300 MHz, D₂O) δ (ppm): 1.16-1.19 (m, 4H, -CH₂-), 1.63-1.64 (m, 2H, -CH₂-CH-(NH₂)), 1.86-1.89 (m, 2H, -CH₂-CH-NH₃⁺), 2.69-2.70 (m, 2H, -CH-).

6,6'-((1*E*,1'*E*)-(((1*S*,2*S*)-cyclohexane-1,2-diyl)bis(azanylylidene))bis(methanylylidene)) bis(2-(*tert*-butyl)-4-((4-((4-(pyren-1-yl)butoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl) phenol

Sym-C4 (**8**)



Chemical Formula: C₇₆H₈₀N₈O₄

Exact Mass: 1168.63

Molecular Weight: 1169.53 g.mol⁻¹

Under argon, to a solution of (*1S,2S*)-cyclohexane diamine (41.4 mg, 0.36 mmol) in anhydrous ethanol (1 mL) charged in a Schlenk, a solution of 3-(*tert*-butyl)-2-hydroxy-5-((4-((4-(pyren-1-yl)butoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzaldehyde (2 equiv, 397 mg, 0.72 mmol) in

anhydrous toluene (1 mL) was added. 1.5 ml of ethanol were added, and the solution was stirred at 70 °C for 4 hours. After cooling the solution, a brown oil was formed at the bottom of the Schlenk. Solvents were removed under reduced pressure. The obtained solid was dissolved in THF and then dried under reduced pressure. The product was obtained as a yellow powder (420 mg, 99% yield).

¹H NMR (360 MHz, CDCl₃) δ (ppm): 13.98 (s, 2H, OH), 8.22 (d, 2H, *J* = 9.4 Hz, ArH), 8.14-8.12 (m, 4H, ArH), 8.09-7.94 (m, 12H, ArH; CHN), 7.82 (d, 2H, *J* = 7.8 Hz, ArH), 7.29 (s, 2H, CH-triazole), 7.11 (d, 2H, *J* = 2.2 Hz, ArH), 6.84 (d, 2H, *J* = 2.2 Hz, ArH), 5.26 (s, 4H, CH₂-N), 4.55 (s, 4H, triazole-CH₂-O), 3.54 (t, 4H, *J* = 6.4 Hz, CH₂-O), 3.30 (t, 4H, *J* = 7.8 Hz, CH₂-pyrene), 3.20-3.17 (m, 2H, CH), 1.93-1.70 (m, 16H, CH₂), 1.32 (s, 18H, *t*Bu).

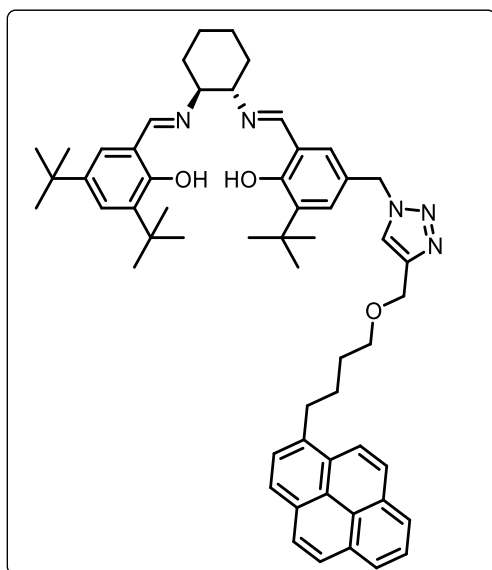
¹³C NMR (90 MHz, CDCl₃) δ (ppm): 164.82 (CH, CHN), 160.84 (Cq), 145.79 (Cq), 138.40 (Cq), 136.84 (Cq), 131.54 (Cq), 131.01 (Cq), 129.87 (Cq), 129.57-129.43 (CH), 128.70 (Cq), 127.64-127.37-127.30-126.67-125.91 (CH), 125.16-125.12 (Cq), 124.93-124.89-124.79-123.56-122.07 (CH), 118.65 (Cq), 72.15 (CH), 70.61 (CH₂), 64.49 (CH₂), 53.94 (CH₂), 34.95 (Cq), 33.30 (CH₂), 32.98 (CH₂), 29.71 (CH₂), 29.23 (CH₃), 28.43 (CH₂), 24.19 (CH₂). (one Cq is lacking).

HRMS (ESI+): calcd for C₇₆H₈₀N₈NaO₄ (M+Na⁺) 1191.6200, found 1191.6153

IR (ATR, ν cm⁻¹): 2931, 2862, 1630, 1443, 1376, 1098, 1047, 846.

2,4-di-*tert*-butyl-6-((*E*)-(((1*S*,2*S*)-2-(((*E*)-3-(*tert*-butyl)-2-hydroxy-5-(((4-((4-(pyren-1-yl)butoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzylidene)amino)cyclohexyl)imino) methyl) phenol

Unsym-C4 (11)



Chemical Formula: C₅₆H₆₇N₅O₃

Exact Mass: 857.52

Molecular Weight: 858.18 g.mol⁻¹

(1*S*,2*S*)-Cyclohexanediamine mono(hydrogen chloride) (82.5 mg, 0.55 mmol), 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (128.3 mg, 0.55 mmol), and 4 Å molecular sieves (0.44 g) were charged into

a Schlenk under argon. Anhydrous methanol (5 mL) was added, and the yellow solution was stirred at room temperature for 4 h. A solution of 3-(*tert*-butyl)-2-hydroxy-5-((4-((4-(pyren-1-yl)butoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzaldehyde (300 mg, 0.55 mmol) in anhydrous DCM (5 mL) and anhydrous NEt_3 (0.23 mL, 3 equiv) was added. The solution was stirred at room temperature for an additional 4 h. The reaction mixture was filtered through a short pad of celite, and the celite was flushed with DCM. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with NEt_3 (cyclohexane/ AcOEt: 7/3) to afford the product as a yellow powder (300 mg, 64% yield).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm): 14.18 (s, 1H, OH), 13.63 (s, 1H, OH), 8.30 (s, 1H, CHN), 8.27 (d, 1H, $J = 9.4$ Hz, ArH), 8.18-8.16 (m, 3H, ArH; CHN), 8.12-8.08 (m, 2H, ArH), 8.04-8.00 (m, 3H, ArH), 7.86 (d, 1H, $J = 7.6$ Hz, ArH), 7.34 (s, 1H, CH-triazole), 7.33 (d, 1H, $J = 2.5$ Hz, ArH), 7.15 (d, 1H, $J = 2.3$ Hz, ArH), 7.00 (d, 1H, $J = 2.5$ Hz, ArH), 6.90 (d, 1H, $J = 2.3$ Hz, ArH), 5.32 (s, 2H, $\text{CH}_2\text{-N}$), 4.59 (s, 2H, triazole- $\text{CH}_2\text{-O}$), 3.58 (t, 2H, $J = 3.4$ Hz, $\text{CH}_2\text{-O}$), 3.34 (t, 2H, $J = 7.6$ Hz, $\text{CH}_2\text{-pyrene}$), 3.29-3.21 (m, 2H, CH-cyclohexane), 1.97-1.72 (m, 12H, CH_2), 1.43 (s, 9H, *t*Bu), 1.37 (s, 9H, *t*Bu), 1.25 (s, 9H, *t*Bu).

$^{13}\text{C NMR}$ (90 MHz, CDCl_3) δ (ppm): 165.87 (CH, CHN), 164.79 (CH, CHN), 160.97 (Cq), 158.03 (Cq), 145.68-140.07-138.67-136.84-136.52 (Cq), 131.50-130.99-129.84 (Cq), 129.68-129.37 (CH), 128.68 (Cq), 127.61-127.37-127.27-126.93-126.64-126.06-125.90 (CH), 125.13 (Cq), 124.91-124.89-124.76-123.54 (CH), 123.40 (Cq), 122.13 (CH), 118.67-117.87 (Cq), 72.36-72.28 (CH), 70.54-64.41-53.97 (CH_2), 64.49 (CH_2), 53.94 (CH_2), 35.08-34.92-34.13 (Cq), 33.29-33.17 (CH_2), 31.16 (CH_3), 29.81-29.69 (CH_2), 29.52-29.29 (CH_3), 28.41 (CH_2).

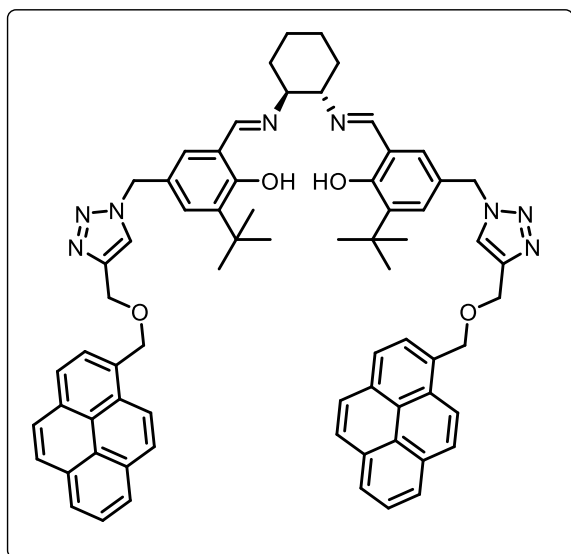
$\text{HRMS (ESI}^+\text{)}$: calcd for $\text{C}_{56}\text{H}_{68}\text{N}_5\text{O}_3$ ($\text{M}+\text{H}^+$) 858.5316, found 858.5282; calcd for $\text{C}_{56}\text{H}_{67}\text{N}_5\text{NaO}_3$ ($\text{M}+\text{Na}^+$) 880.5136, found 880.5100.

IR (ATR, ν cm^{-1}): 2960, 1628, 1530, 1442, 1360, 1091, 846

$[\alpha]^{20}_{\text{D}}$ +169 (THF, 1)

6,6'-((1E,1'E)-(((1S,2S)-cyclohexane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis (2-(tert-butyl)-4-((4-((pyren-1-ylmethoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl) phenol)

Sym-C1 (7)



Chemical Formula: C₇₀H₆₈N₈O₄

Exact Mass: 1084.54

Molecular Weight: 1085.37 g.mol⁻¹

Under argon, to a solution of (1S,2S)-cyclohexane diamine (63.4 mg, 0.55 mmol) in anhydrous ethanol (5 mL) charged in a Schlenk, a solution of 3-(tert-butyl)-2-hydroxy-5-((4-((pyren-1-ylmethoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzaldehyde (2 equiv, 560 mg, 1.11 mmol) in anhydrous DCM (2 mL) was added. The solution was stirred at 65 °C for 4 hours. After cooling the solution, a precipitate was formed at the bottom of the Schlenk. Solvents were removed under reduced pressure. The obtained solid was dissolved in THF and then dried under reduced pressure, and the product was obtained as a yellow powder (420 mg, 99% yield).

¹H NMR (360 MHz, CDCl₃) δ (ppm): 14.02 (s, 2H, OH), 8.20-7.94 (m, 20H ArH; CHN), 7.27 (s, 2H, CH), 7.10 (d, 2H, *J* = 2.1 Hz, ArH), 6.78 (d, 2H, *J* = 2.1 Hz, ArH), 5.23 (s, 4H, CH₂-N), 5.20 (s, 4H, CH₂-O), 4.73 (s, 4H, triazole-CH₂-O), 3.26-3.22 (m, 2H, CH), 1.90-1.81 (m, 4H, CH₂), 1.44-1.39 (m, 4H, CH₂), 1.31 (s, 18H, *t*Bu).

¹³C NMR: (90 MHz, CDCl₃) δ (ppm): 164.83 (CH, CHN), 160.77 (Cq), 145.52 (Cq), 138.38 (Cq), 131.38-131.22-130.93-130.77 (Cq), 129.51-129.43-127.74-127.51-127.41-127.29-125.98-125.29 (CH), 124.89-124.67 (Cq), 124.51 (CH), 123.49 (Cq), 123.33-122.22-118.52 (CH), 72.06 (CH), 70.89 (CH₂), 63.79 (CH₂), 53.82 (CH₂), 34.84 (Cq), 32.88 (CH₂), 29.19 (CH₃), 24.11 (CH₂). (one Cq is lacking).

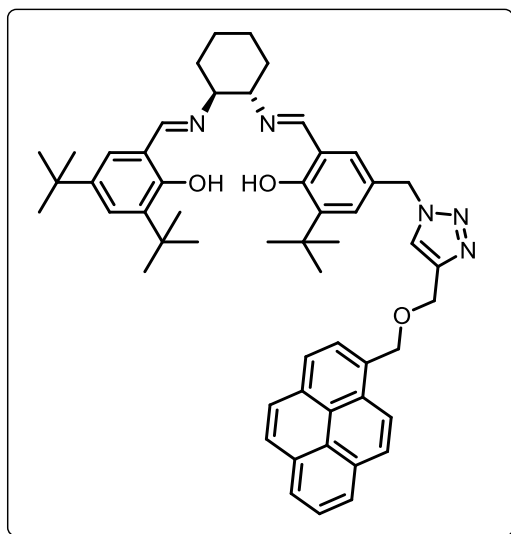
HRMS (ESI+): calcd for C₇₀H₆₈N₈NaO₄ (M+Na⁺) 1107.5256, found 1107.5220

IR (ATR, ν cm⁻¹): 2942, 2862, 1630, 1597, 1443, 1048, 847.

[α]²⁰_D +126 (THF, 1)

2,4-di-*tert*-butyl-6-((E)-(((1*S*,2*S*)-2-(((E)-3-(*tert*-butyl)-2-hydroxy-5-((4-((pyren-1-yl methoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzylidene)amino)cyclohexyl)imino) methyl) phenol

Unsym-C1 (10)



Chemical Formula: C₅₃H₆₁N₅O₃

Exact Mass: 815.48

Molecular Weight: 816.10 g.mol⁻¹

(1*S*,2*S*)-Cyclohexanediamine mono(hydrogen chloride) (150.6 mg, 1 mmol), 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (234.3 mg, 1 mmol), and 4 Å molecular sieves (0.8 g) were charged into a Schlenk under argon. Anhydrous methanol (9 mL) was added, and the yellow solution was stirred at room temperature for 4 h. A solution of 3-(*tert*-butyl)-2-hydroxy-5-((4-((pyren-1-yl)methoxy)methyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzaldehyde (503.6 mg, 1 mmol) in anhydrous DCM (9 mL) and anhydrous NEt₃ (0.42 mL, 3 equiv) was added. The solution was stirred at room temperature for an additional 18 h. The reaction mixture was filtered through a short pad of celite, and the celite was flushed with anhydrous DCM. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with NEt₃ (cyclohexane/ AcOEt: 7/3) to afford the product as a yellow powder (680 mg, 83 % yield).

¹H NMR (360 MHz, CDCl₃) δ (ppm): 14.11 (s, 1H, OH), 13.61 (s, 1H, OH), 8.30-8.26 (m, 2H, ArH; CHN), 8.20-8.17 (m, 3H, 2ArH; CHN), 8.13-7.98 (m, 6H, ArH), 7.36 (s, 1H, CH), 7.30 (d, 1H, *J* = 2.5 Hz, ArH), 7.16 (d, 1H, *J* = 2.2 Hz, ArH), 6.97 (d, 1H, *J* = 2.5 Hz, ArH), 6.90 (d, 1H, *J* = 2.2 Hz, ArH), 5.33 (s, 2H, CH₂-N), 5.27 (s, 2H, CH₂-O), 4.76 (s, 2H, triazole-CH₂-O), 3.33-3.24 (m, 2H, CH-cyclohexane), 1.96-1.86 (m, 4H, CH₂), 1.74-1.65 (m, 2H, CH₂), 1.48-1.42 (m, 2H, CH₂), 1.39 (s, 9H, *t*Bu), 1.36 (s, 9H, *t*Bu), 1.22 (s, 9H, *t*Bu).

¹³C NMR (90 MHz, CDCl₃) δ (ppm): 165.93 (CH, CHN), 164.88 (CH, CHN), 161.06 (Cq), 158.07 (Cq), 145.60-140.12-138.49-136.56 (Cq), 131.50-131.35-131.08-130.92 (Cq), 129.79(CH), 129.56 (Cq), 129.48-127.91-127.60-127.54-127.38-126.99 (CH), 126.09 (2 CH), 125.39 (2 CH), 125.04-

124.82 (Cq), 124.63-123.52 (CH), 123.42 (Cq), 122.45-118.76-117.90 (CH), 72.41 (2 CH), 71.07-63.88-54.09 (2 CH₂), 35.10-34.97-34.16 (Cq), 33.24 (CH₂), 31.52-29.52-29.32 (CH₃), 24.36 (2 CH₂).

HRMS (ESI+): calcd for C₅₃H₆₂N₅O₃ (M+H⁺) 816.4847, found 816.4865

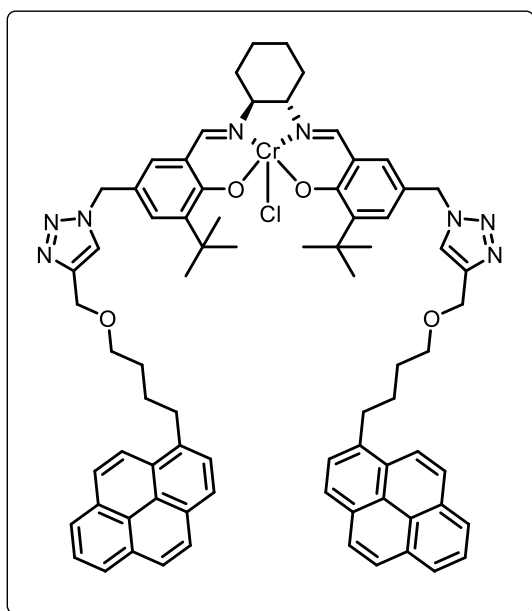
IR (ATR, ν cm⁻¹): 2952, 2863, 1629, 1597, 1442, 1047, 847.

[α]²⁰_D +176 (THF, 1)

General procedure for the synthesis of chromium complexes

Under argon atmosphere, a solution of the chiral ligand in dry, degassed THF (0.08 M) was added to a solution of anhydrous CrCl₂ (1.15 equiv) in dry, degassed THF (0.04 M). The resulting brown solution was stirred under argon for 2 hours and then in air for additional 18 hours. The solution was then diluted with DCM and washed with saturated NH₄Cl and brine. The combined organic layer was dried over MgSO₄, filtered and the solvents were removed under reduced pressure to afford the expected complex.

Chromium sym-pyr-but-salen: Sym-C4-Cr (13)



Chemical Formula: C₇₆H₇₈ClCrN₈O₄

Exact Mass: 1253.52

Molecular Weight: 1254.96 g.mol⁻¹

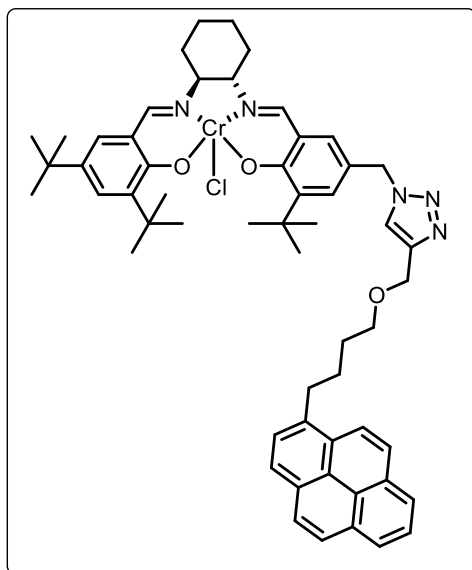
Starting from ligand Sym-C4 **8** (92 mg, 0.078 mmol) with CrCl₂ (11 mg, 0.09 mmol), complex Sym-C4-Cr was obtained as a brown solid in quantitative yield.

HRMS (ESI+): calcd for C₇₆H₇₈CrN₈O₄ (M-Cl)⁺ 1218.5548, found 1218.5490.

IR (ATR, ν cm⁻¹): 2927, 1623, 1542, 1320, 1047, 844.

$[\alpha]^{20}_{\text{D}} +283$ (THF, 1)

Chromium unsym-pyr-but-salen: Unsym-C4-Cr (15)



Chemical Formula: $\text{C}_{56}\text{H}_{65}\text{ClCrN}_5\text{O}_3$

Exact Mass: 942.42

Molecular Weight: $943.61 \text{ g}\cdot\text{mol}^{-1}$

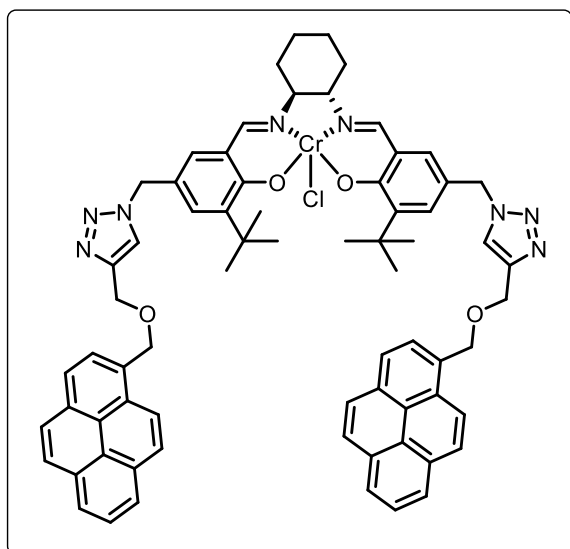
Starting from ligand Unsym-C4 **11** (100 mg, 0.116 mmol) with CrCl_2 (16.5 mg, 0.135 mmol), complex Unsym-C4-Cr was obtained as a brown solid in quantitative yield.

HRMS (ESI+): calcd for $\text{C}_{56}\text{H}_{65}\text{CrN}_5\text{O}_3$ (M-Cl)⁺ 907.4488, found 907.4455.

IR (ATR, $\nu \text{ cm}^{-1}$): 2950, 1620, 1435, 1083, 846.

$[\alpha]^{20}_{\text{D}} +490$ (THF, 1)

Chromium sym-pyr-met-salen: Sym-C1-Cr (12)



Chemical Formula: $C_{70}H_{66}ClCrN_8O_4$

Exact Mass: 1169.43

Molecular Weight: $1170.80 \text{ g}\cdot\text{mol}^{-1}$

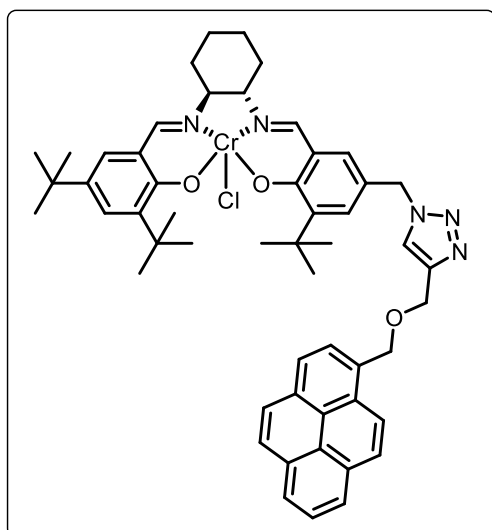
Starting from ligand Sym-C1 **7** (150 mg, 0.138 mmol) with CrCl_2 (19.5 mg, 0.158 mmol), complex Sym-C1-Cr was obtained as a brown solid with yield of 95%.

HRMS (ESI+): calcd for $C_{70}H_{66}CrN_8O_4$ (M-Cl)⁺ 1134.4609, found 1134.4588.

IR (ATR, $\nu \text{ cm}^{-1}$): 2940, 1621, 1545, 1384, 1320, 1048, 846.

$[\alpha]^{20}_D +510$ (THF, 1)

Chromium unsym-pyr-met-salen: Unsym-C1-Cr (14)



Chemical Formula: $C_{53}H_{59}ClCrN_5O_3$

Exact Mass: 900.37

Molecular Weight: $901.53 \text{ g}\cdot\text{mol}^{-1}$

Starting from ligand Unsym-C1 **10** (100 mg, 0.122 mmol) with CrCl_2 (17.3 mg, 0.141 mmol), complex Unsym-C1-Cr was obtained as a brown solid in quantitative yield.

HRMS (ESI+): calcd for $C_{53}H_{59}CrN_5O_3$ (M-Cl)⁺ 865.4019, found 865.3980.

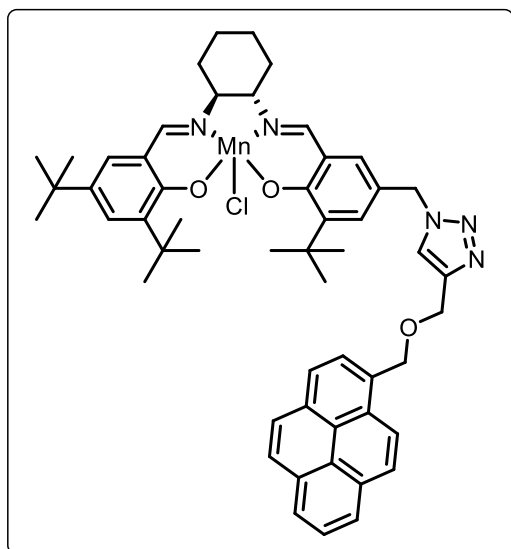
IR (ATR, ν cm^{-1}): 2950, 1620, 1535, 1435, 1320, 1256, 1166, 1088, 846.

$[\alpha]^{20}_D$ +790 (THF, 1).

General procedure for the synthesis of manganese complexes

Under argon atmosphere, a solution of manganese acetate pentahydrate $Mn(OAc)_4 \cdot 4H_2O$ (3 equiv) dissolved in anhydrous and degassed ethanol was added to a solution of the chiral ligand in dry, degassed toluene. The resulting solution was stirred under argon at 85 °C for 5 hours and then a saturated brine solution was added, and the reaction mixture was stirred at room temperature under air atmosphere for additional 18 hours. The solution was then diluted with DCM and washed with saturated brine solution. The combined organic layer was dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to afford the expected complex.

Manganese unsym-pyr-met-salen: Unsym-C1-Mn (17)



Chemical Formula: $C_{53}H_{59}ClMnN_5O_3$

Exact Mass: 903.36

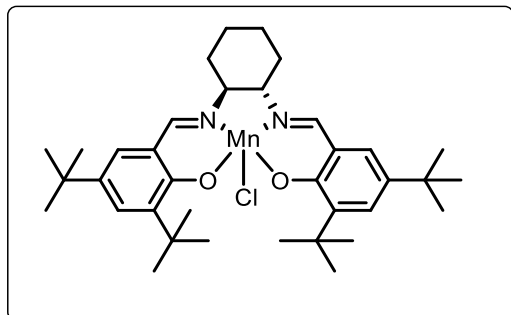
Molecular Weight: 904.47 $g \cdot mol^{-1}$

Starting from ligand Unsym-C1 **10** (500 mg, 0.55 mmol) with $Mn(OAc)_4 \cdot 4H_2O$ (450 mg, 1.65 mmol), complex Unsym-C1-Mn was obtained as a brown solid in quantitative yield.

HRMS (ESI+): calcd for $C_{53}H_{59}MnN_5O_3$ (M-Cl)⁺ 868.3993, found 868.3966.

IR (ATR, ν cm^{-1}): 2961, 1613, 1545, 1440, 1310, 1260, 1090, 1020, 847, 798.

Manganese Jacobsen's catalyst (**18**)



Chemical Formula: $C_{36}H_{52}ClMnN_2O_2$

Exact Mass: 634.30

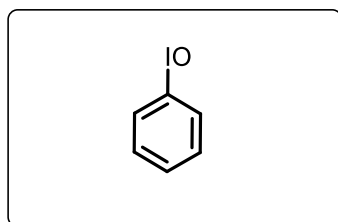
Molecular Weight: $635.21 \text{ g}\cdot\text{mol}^{-1}$

Starting from ligand (Jacobsen) (200 mg, 0.36 mmol) with $Mn(OAc)_4\cdot 4H_2O$ (269 mg, 1.09 mmol), complex Jacobsen-Mn (**18**) was obtained as a brown solid (195 mg, 84% yield)

HRMS (ESI+): calcd for $C_{36}H_{52}MnN_2O_2 (M-Cl)^+$ 599.3404, found 599.3379.

IR (ATR, $\nu \text{ cm}^{-1}$): 2952, 1630, 1608, 1535, 1450, 1361, 1315, 1253, 1175, 1135, 838.

Synthesis of iodosobenzene PhIO



Chemical Formula: C_6H_5IO

Exact Mass: 219.93

Molecular Weight: $220 \text{ g}\cdot\text{mol}^{-1}$

Finely ground iodosobenzene diacetate (4 g, 12 mmol) is placed in a 250-ml. beaker, and 18 mL of 3N sodium hydroxide is added over a 5-minute period with vigorous stirring. The lumps of solid formed were triturated with a stirring rod or spatula for 15 minutes, and the reaction mixture stands for an additional 45 minutes to complete the reaction. 12 mL of water is added, the mixture is stirred vigorously, and the crude, solid iodosobenzene is collected on a Büchner funnel. The wet solid is returned to the beaker and triturated in 24 mL of water. The solid is again collected on the Büchner funnel, washed there with 24 mL of water, and dried by maintaining suction. Final purification was realized by triturating the dried solid in 9 mL of chloroform in a beaker. The iodosobenzene is separated by filtration, vacuum dried, and obtained as a yellow powder (2.25 g, 85% yield).

HRMS (ESI+): calcd for $C_6H_6IO (M+H^+)$ 220.9457, found 220.9458; calcd for $C_6H_5INaO (M+Na^+)$ 242.92773, found 242.9271.

II. Immobilization

General procedure for pyrene-tagged salen complexes immobilization

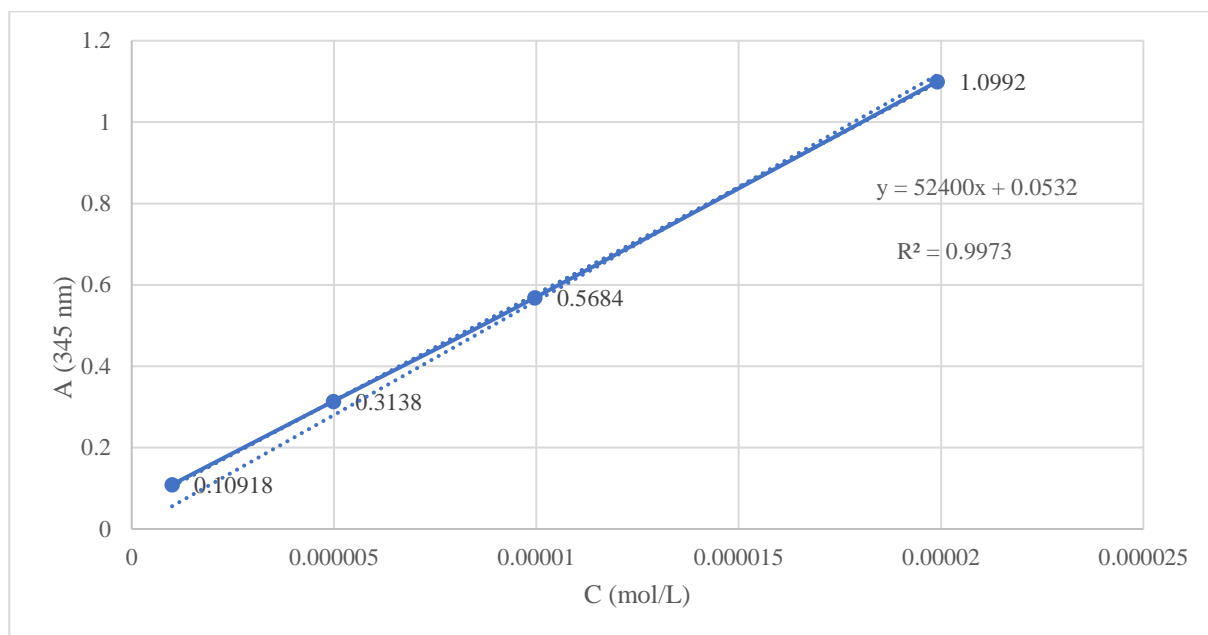
A glass vial with a screw cap septum top was charged with 80 mg of commercial reduced graphene oxide (rGO) and 3.2 mL of anhydrous DCM. The suspension was immersed in an ultrasound bath for 1 hour, then the chosen amount of catalyst was added, and the mixture was sonicated for another 5 minutes. After stirring for 24 hours at room temperature under air, the agitation was stopped and 10 μ L were taken from the supernatant solution, diluted in 20 mL of DCM and then subjected to UV-Vis detection. The supported catalyst was recovered by filtration and centrifugation and then washed with DCM (20 mL). Residual solvent was removed under reduced pressure without heating.

The immobilization was confirmed by UV-Vis and XPS analysis, and the exact amount of the immobilized catalyst was determined by UV-Vis. Furthermore, the mass of the obtained solid was equal to the sum of the mass of rGO and the mass of the introduced catalyst. The UV-visible analysis was performed using an UV-Vis spectrum scanning method (200-500 nm). A calibration line ($A=f(C)$) had been drawn for each compound by measuring the absorbances (A) of diverse solutions with different concentrations (C) at the λ_{max} (345 nm).

Supported Sym-C4-Cr@rGO (13@rGO)

In order to draw the calibration curve, a mother solution was prepared by dissolving 2.5 mg of the complex in 100 mL of DCM, from which three solutions were prepared by dilution. The table below shows the values of the concentrations of the different solutions and their corresponding absorbance measured values.

C (mol/L)	1.99E-05	9.96E-06	4.98E-06	9.96E-07
A (345 nm)	1.0992	0.5684	0.3138	0.10918

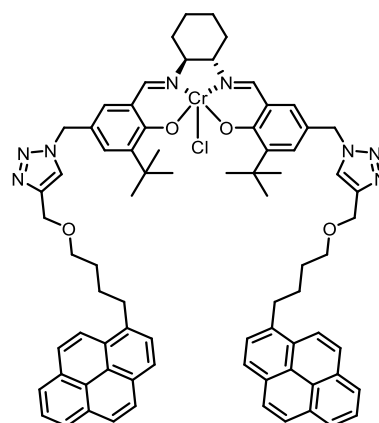
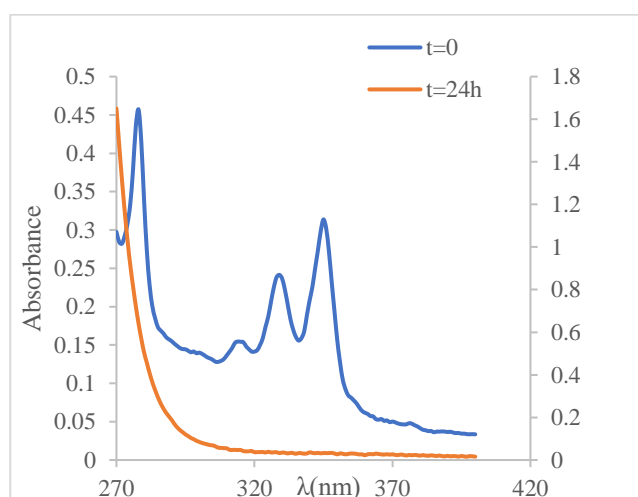


Calibration curve

After stirring for 24 hours at room temperature, the mixture was standing and 10 μL were taken from the supernatant solution, diluted in 20 mL of DCM and then subjected to UV detection. The concentration (in 20.01 mL) was calculated by replacing the value of the measured absorbance at 345 nm in the equation. From this value the concentration of the residual complex in the solution can be concluded.

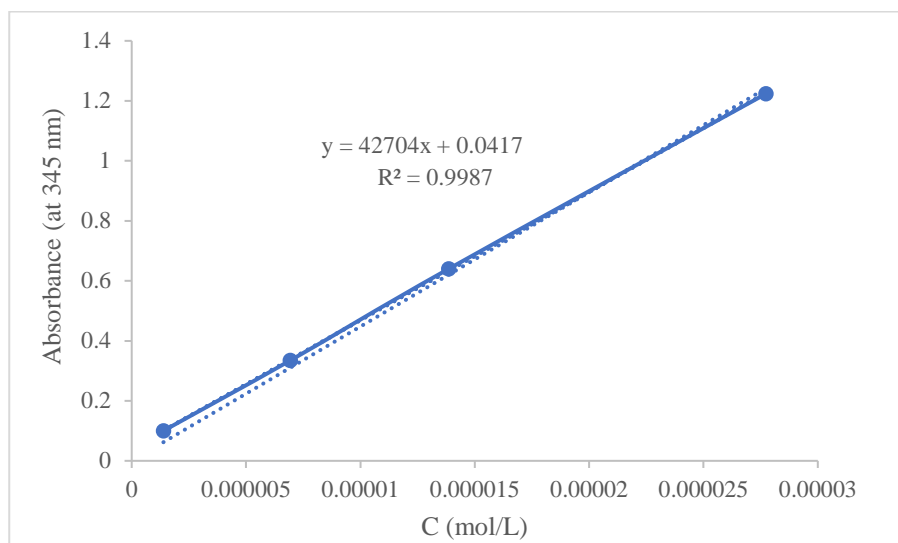
The same procedure was following for the other immobilized complexes.

18 mg of the complex were completely immobilized onto 80 mg of rGO, resulting in the recovery of 100 mg of a black solid.

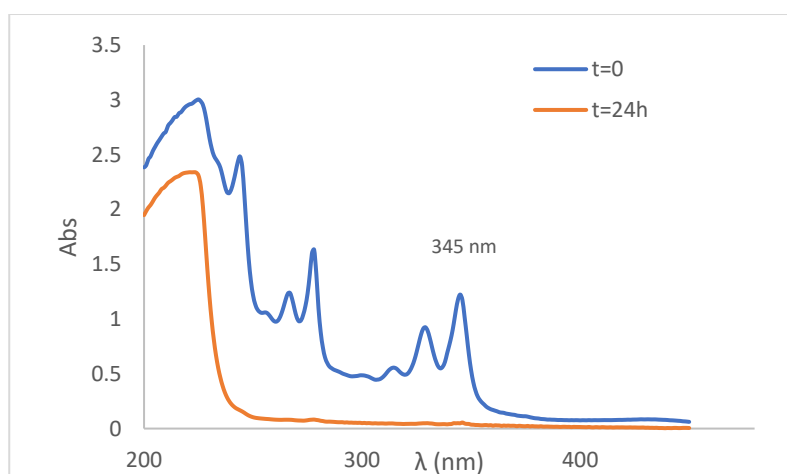


Supported Unsym-C1-Cr@rGO (14@rGO)

18 mg of the complex were completely immobilized onto 80 mg of rGO.



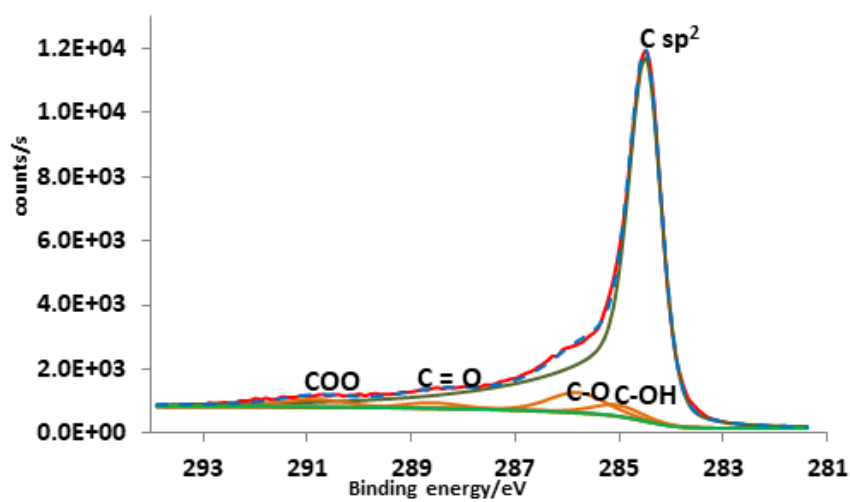
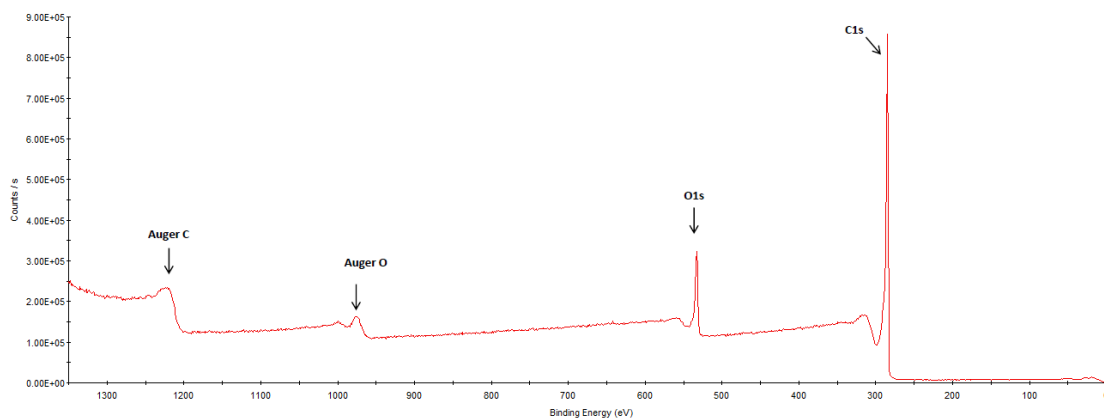
UV-Vis Calibration curve Abs=f [Unsym-Cr-A]



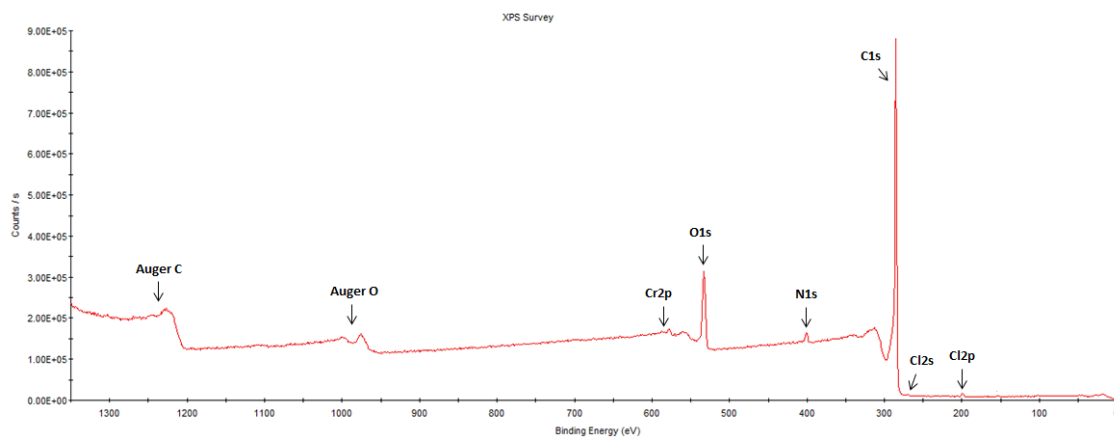
UV-Visible spectra of Unsym-Cr-A solution before and after immobilization.

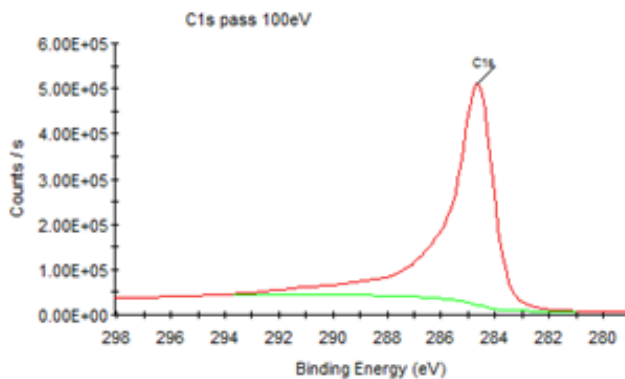
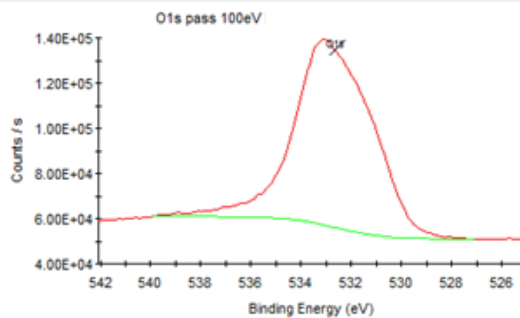
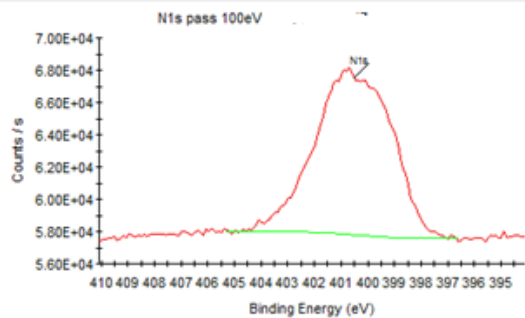
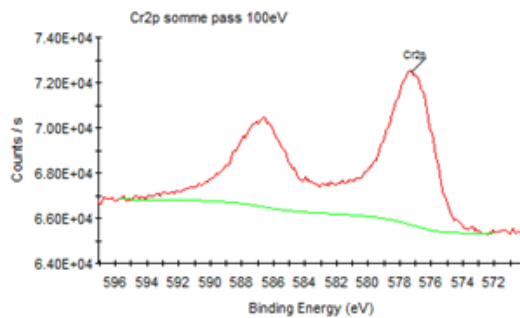
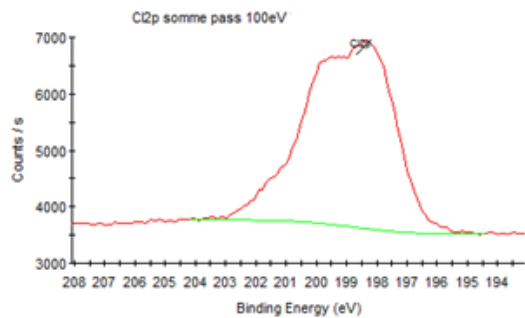
XPS Analyses

rGO support



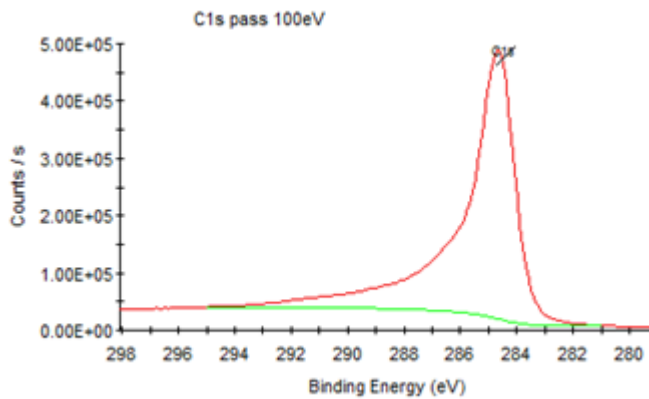
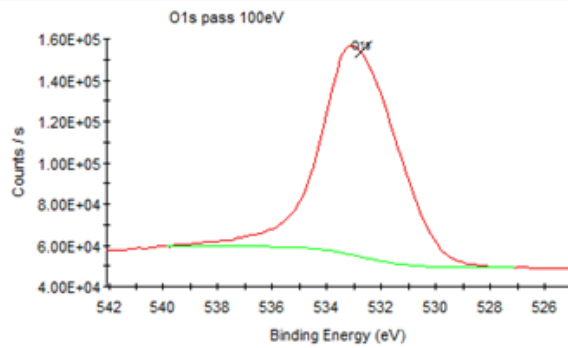
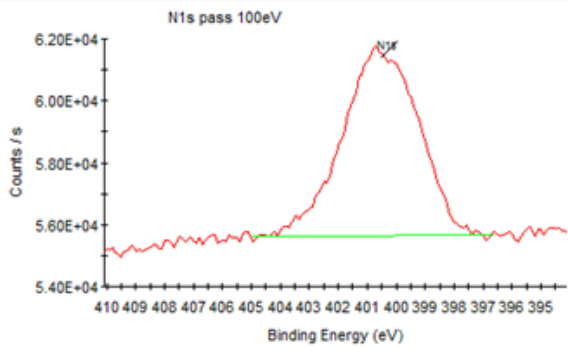
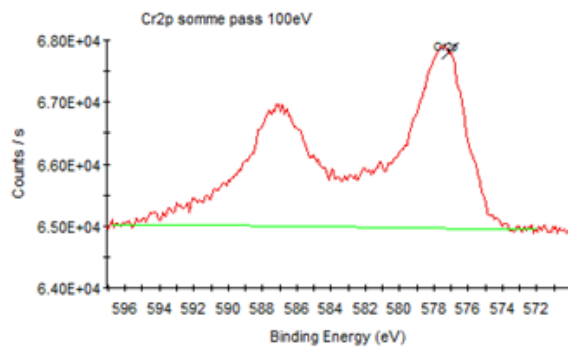
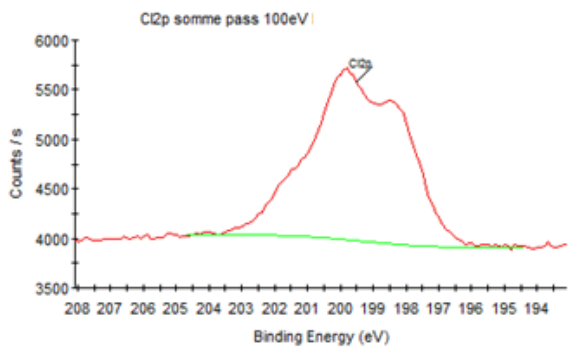
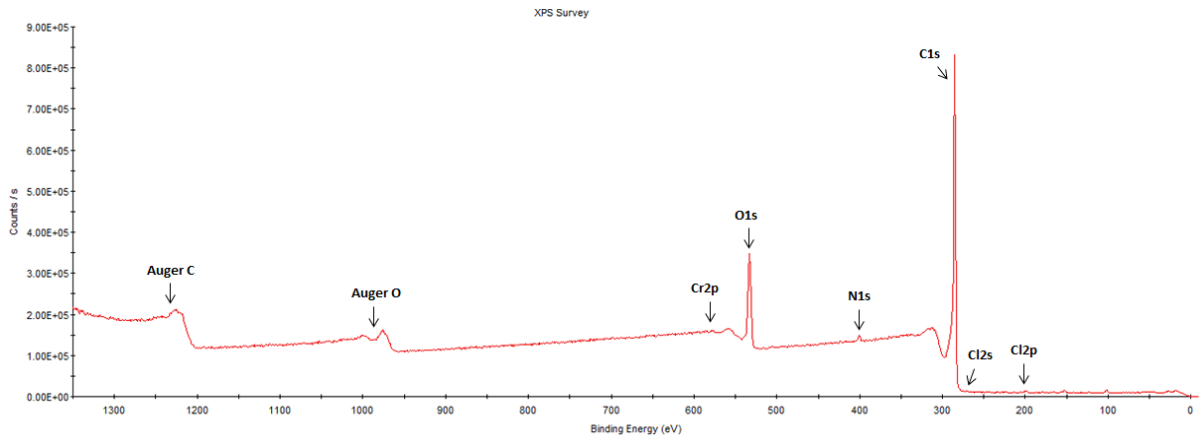
Fresh Unsym-C1-Cr 14@rGO





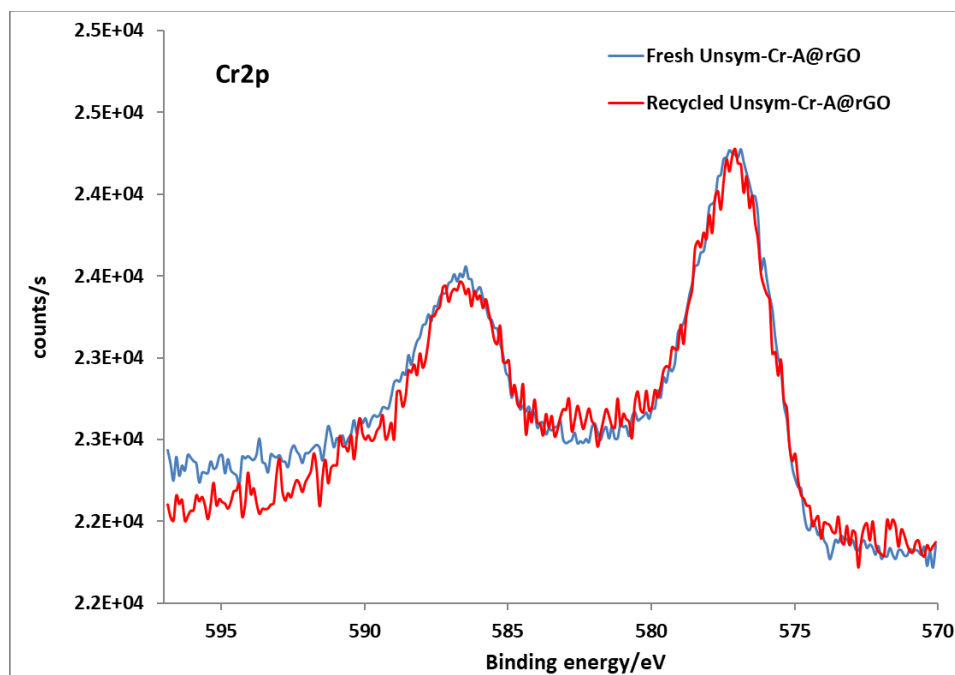
Name	Peak BE	FWHM eV	Area (P) CPS.eV	Area (N)	Atomic %
Cl2p	198.67	3.36	11707.16	69.76	0.4
Cr2p	577.23	3.35	45822.59	65.88	0.4
C1s	284.67	1.45	1027906.13	14588.42	87.3
N1s	400.52	3.29	35003.71	293.3	1.8
O1s	532.82	3.51	305194.37	1698.31	10.2

Recycled Unsym-C1-Cr 14@rGO



Name	Peak BE	FWHM eV	Area (P) CPS.eV	Area (N)	Atomic %
Cl2p	199.55	2.91	1886.72	11.25	0.2
Cr2p	577.37	3.37	7884.24	11.34	0.2
C1s	284.6	1.13	354840.2	5035.86	87.2
N1s	400.55	2.76	6535.97	54.77	1.0
O1s	532.89	2.96	118897.16	661.65	11.5

Comparison of chromium spectra between recycled Unsym-C1-Cr 14@rGO and fresh Unsym-C1-Cr 14@rGO



III. Catalysis

I. Catalytic procedure (ARO reaction) in homogeneous conditions

A tube was charged with catalyst (2 mol%) and maintained under argon. Solvent (165 μ L), cyclohexene oxide (0.5 mmol), and dodecane as internal standard (20 μ L) were then added. The reaction mixture was stirred for 10 minutes at 25 $^{\circ}$ C before adding the trimethylsilyl azide (197 μ L, 1.5 mmol), and then stirred for the corresponding amount of time. A sample was prepared to calculate conversion by GC (and ee).

II. Catalytic procedure (ARO reaction) in heterogeneous conditions

A tube was charged with supported catalyst (2 mol%) and maintained under argon. Solvent (165 μ L), cyclohexene oxide (0.5 mmol), and dodecane as internal standard (20 μ L) were then added. The

reaction mixture was stirred for 10 minutes at 25 °C before adding the trimethylsilyl azide (197 µL, 1.5 mmol), and then stirred for the corresponding amount of time. A sample was prepared to calculate conversion by GC (and ee). The supported catalyst was washed with ether (15 mL) at 0 °C, filtered and dried in the tube for its reuse in 10 runs.

III. Catalytic procedure (HDA reaction) in homogeneous conditions

A tube was charged with catalyst (2 mol%) and maintained under argon. DCM (100 µL), the aldehyde (0.5 mmol), dodecane as internal standard (20 µL) and Danishefky's diene (116 µL, 0.6 mmol) were then added. The reaction mixture was stirred at 25 °C for 24 hours then a sample was prepared to calculate conversion by GC (and ee). The reaction mixture was then diluted with DCM (1 mL) and treated with a drop of trifluoroacetic acid and further stirred for 30 mins. The solvents were removed under reduced pressure and the pure product was obtained after a chromatographic column.

IV. Catalytic procedure (HDA reaction) in heterogeneous conditions

Heterogeneous HDA reaction of cyclohexanecarboxaldehyde

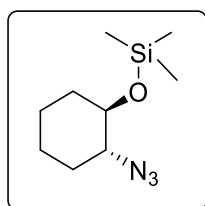
A tube was charged with supported catalyst **Unsym-C1-Cr 14@rGO** (2 mol%) and maintained under argon. DCM (100 µL), cyclohexanecarboxaldehyde (0.5 mmol), dodecane as internal standard (20 µL) and Danishefky's diene (116 µL, 0.6 mmol) were then added. The reaction mixture was stirred at 25 °C for 24 hours then a sample was prepared to calculate conversion by GC. The supported catalyst was washed with ether (15 mL) at 0 °C, filtered and dried in the tube for its reuse in 7 runs.

Heterogeneous multi-substrates HDA reaction

A tube was charged with supported catalyst **Unsym-C1-Cr 14@rGO** (2 mol%) and maintained under argon. DCM (165 µL), the aldehyde (0.83 mmol), dodecane as internal standard (33 µL) and Danishefky's diene (193 µL, 0.99 mmol) were then added. The reaction mixture was stirred at 25 °C for 24 hours then a sample was prepared to calculate conversion by GC. The supported catalyst was washed with ether (25 mL) at 0 °C, filtered and dried in the tube for its reuse. The solvents of the filtrate were removed under reduced pressure. The residue was diluted with DCM (1 mL), treated with a drop of trifluoroacetic acid and stirred for 30 mins. Solvent was removed and the residue was purified by chromatographic column for the determination of yield and the enantiomeric excess of the product

V. Description of ARO and HDA products

(((1*R*,2*R*)-2-azidocyclohexyl)oxy)trimethylsilane



Chemical Formula: C₉H₁₉ON₃Si

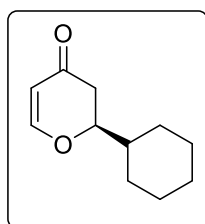
Exact Mass: 213.13

Molecular Weight: 213.35 g.mol⁻¹

The ee was determined by chiral GC (isothermal 110 °C), which resolved both enantiomers (tr maj= 10.9 min, tr min= 11.29 min). The absolute stereochemistry was assigned as *1R,2R* based on comparison with the literature.¹¹⁵

¹H NMR (360 MHz, CDCl₃) δ (ppm): 3.46-3.40 (m, 1H), 3.22-3.14 (m, 1H), 1.95-1.84 (m, 2H), 1.70-1.60 (m, 2H), 1.41-1.12 (m, 4H), 0.16 (s, 9H).

(*S*)-2-cyclohexyl-2,3-dihydro-4H-pyran-4-one



Chemical Formula: C₁₁H₁₆O₂

Exact Mass: 180.12

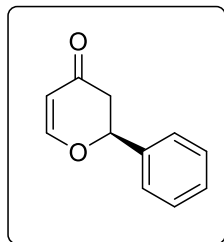
Molecular Weight: 180.24 g.mol⁻¹

Solvents for chromatographic column: pentane/ diethyl ether (1/1)

The ee was determined by chiral GC (isothermal 150 °C), which resolved both enantiomers (tr maj= 17.2 min, tr min= 17.6 min). The absolute stereochemistry was assigned as (+)-*S* based on comparison with the literature.¹³³

¹H NMR (360 MHz, CDCl₃) δ (ppm): 7.37 (dd, 1H, *J* = 9.5 Hz, 1.1 Hz), 5.38 (dd, 1H, *J* = 9.5 Hz, 1.1 Hz), 4.17 (ddd, 1H, *J* = 14.2 Hz, 5.5 Hz, 3.3 Hz), 2.54 (dd, 1H, *J* = 16.6 Hz, 14.2 Hz), 2.36 (dd, 1H, *J* = 16.6 Hz, 3.3 Hz), 1.9-1.50 (m, 5H, 1CH, 2CH₂), 1.35-1.00 (m, 6H, 3 CH₂).

(S)-2-phenyl-2,3-dihydro-4H-pyran-4-one



Chemical Formula: C₁₁H₁₀O₂

Exact Mass: 174.07

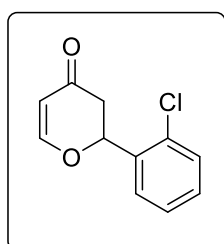
Molecular Weight: 174.19 g.mol⁻¹

Solvents for chromatographic column: heptane/ ethyl acetate (7/3)

The ee was determined by chiral GC (isothermal 150 °C), which resolved both enantiomers (tr maj= 20.2 min, tr min= 20.8 min). The absolute stereochemistry was assigned as (+)-S based on comparison with the literature. ¹

¹H NMR (360 MHz, CDCl₃) δ (ppm): 7.49 (d, 1H, *J* = 6.1 Hz), 7.44-7.37 (m, 5H, ArH), 5.54 (d, 1H, *J* = 6.1 Hz), 5.43 (dd, 1H, *J* = 14.4 Hz, 3.5 Hz), 2.92 (dd, 1H, *J* = 16.9 Hz, 14.4 Hz), 2.68 (dd, 1H, *J* = 16.9 Hz, 3.5 Hz).

2-(2-chlorophenyl)-2,3-dihydro-4H-pyran-4-one



Chemical Formula: C₁₁H₉ClO₂

Exact Mass: 208.03

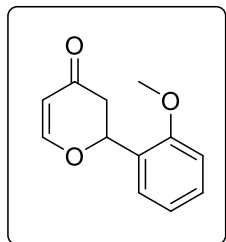
Molecular Weight: 208.64 g.mol⁻¹

Solvents for chromatographic column: pentane/ diethyl ether (7/3).

The ee was determined by chiral HPLC analysis using ODH column (flow rate= 0.5 mL.min⁻¹; 90% hexane, 10% isopropanol, 254 nm), which resolved both enantiomers (tr maj= 20.5 min, tr min= 22.9 min). The absolute stereochemistry was not determined.

¹H NMR (360 MHz, CDCl₃) δ (ppm): 7.61-7.51 (m, 2H, ArH), 7.42-7.29 (m, 3H, 2ArH: CH), 5.82 (dd, 1H, *J* = 4.4 Hz, 13.3 Hz), 5.56 (d, 1H, *J* = 4.4 Hz), 2.84-2.65 (m, 2H, CH₂).

2-(2-methoxyphenyl)-2,3-dihydro-4H-pyran-4-one



Chemical Formula: C₁₂H₁₂O₃

Exact Mass: 204.08

Molecular Weight: 204.22 g.mol⁻¹

Solvents for chromatographic column: pentane/ diethyl ether (7/3)

The ee was determined by chiral HPLC analysis using ODH column (flow rate= 0.5 mL.min⁻¹; 95% hexane, 5% isopropanol, 254 nm), which resolved both enantiomers (tr maj= 33.7 min, tr min= 35.7 min). The absolute stereochemistry was not determined.

¹H NMR (360 MHz, CDCl₃) δ (ppm): 7.51 (d, 1H, *J* = 5.9 Hz), 7.47 (dd, 1H, *J* = 7.6 Hz, 1.4 Hz), 7.30 (dd, 1H, *J* = 8.1 Hz, 1.3 Hz), 7.01 (dd, 1H, *J* = 0.9 Hz, 7.7Hz), 6.91 (d, 1H, *J* = 8.2 Hz), 5.79 (dd, 1H, *J* = 6.9 Hz, 10.8 Hz), 5.51 (d, 1H, *J* = 5.9 Hz), 3.83 (s, 3H, CH₃), 2.77-2.72 (m, 2H, CH₂).

VI. Catalytic procedure (epoxidation reaction) in homogeneous conditions (0.5 M)

- *m*CPBA/NMO as oxidant

To a solution of the catalyst (2 mol %) in DCM (1 mL), alkene (0.5 mmol) and internal standard (20 μL, 0.88 mmol) were added under continuous stirring. The temperature of the mixture was then decreased to -78 °C before the addition of NMO (293 mg, 2.5 equiv). *m*CPBA (112 mg, 0.5 mmol) was added to the mixture in portions for 10 minutes, and the resulting mixture was stirred at -78 °C for 2 hours. The conversion of the reaction was monitored by GC with the help of the internal standard and the ee of the product was determined by chiral GC or HPLC analyses.

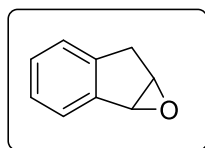
- PhIO as oxidant

To a solution of the catalyst (2 mol %) in DCM (1 mL), alkene (0.5 mmol) and internal standard (20 μL, 0.88 mmol) were added under continuous stirring. PhIO (121 mg, 0.55 mmol) was added to the mixture in portions for 1 hour, and the resulting mixture was stirred at room temperature for the specific time. The conversion of the reaction was monitored by GC with the help of the internal standard and the ee of the product was determined by chiral GC or HPLC analyses.

VII. Description of epoxidation products

Indene oxide

1a,6a-dihydro-6H-indeno[1,2-b]oxirene



Chemical Formula: C₉H₈O

Exact Mass: 132.06

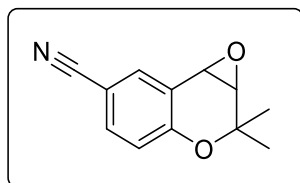
Molecular Weight: 132.16 g.mol⁻¹

The ee was determined by chiral HPLC analysis using OJ-H column (flow rate= 1 mL.min⁻¹; 95% hexane, 5% isopropanol, 215 nm), which resolved both enantiomers (tr min= 11.9 min, tr maj= 14.1 min). The absolute stereochemistry was not determined.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.52 (d, 1H, *J* = 7.4 Hz), 7.27-7.18 (m, 3H), 4.28 (dd, 1H, *J* = 2.6 Hz, 1.2 Hz), 4.15 (t, 1H, *J* = 2.8 Hz), 3.23 (d, 1H, *J* = 18.2 Hz), 3 (dd, 1H, *J* = 18.1 Hz, 2.9 Hz).

CN-Chromene oxide

2,2-dimethyl-1a,7b-dihydro-2H-oxireno[2,3-c]chromene-6-carbonitrile



Chemical Formula: C₁₂H₁₁NO₂

Exact Mass: 201.08

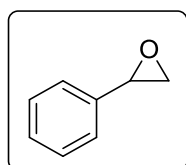
Molecular Weight: 201.22 g.mol⁻¹

The ee was determined by chiral HPLC analysis using OD-H column (flow rate= 1 mL.min⁻¹; 95% hexane, 5% ethanol, 220 nm), which resolved both enantiomers (tr min= 16.3 min, tr maj= 20.3 min). The absolute stereochemistry was not determined.

¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.65 (d, 1H, *J* = 2 Hz), 7.53 (dd, 1H, *J* = 8.7 Hz, 2.2 Hz), 6.87 (d, 1H, *J* = 8.3 Hz), 3.91 (d, 1H, *J* = 4.2 Hz), 3.54 (d, 1H, *J* = 4.2 Hz), 1.6 (s, 3H), 1.29 (s, 3H).

Styrene oxide

2-phenyloxirane



Chemical Formula: C₈H₈O

Exact Mass: 120.06

Molecular Weight: 120.15 g.mol⁻¹

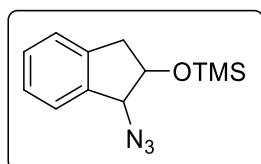
The ee was determined by chiral GC analysis using OD-H column (flow rate= 1 mL.min⁻¹; 95% hexane, 5% ethanol, 220 nm), which resolved both enantiomers (tr min= 11.9 min, tr maj= 14.1 min). The absolute stereochemistry was not determined.

VIII. Catalytic procedure (tandem) in homogeneous conditions (0.5 M)

After following the same procedure for epoxidation step (with PhIO or *m*CPBA/NMO as oxidant), Cr-salen complex (2 mol%) was added to the mixture which was stirred for 5 mins before the addition of 1 equivalent of the nucleophile (TMSN₃ or aniline) and the reaction mixture was allowed to stir for the specific time. After solvent removal, the catalysts were precipitated in ether, and the resulting solution was analysed by HPLC to measure the ee of the product.

IX. Description of tandem reaction products

((1-azido-2,3-dihydro-1H-inden-2-yl)oxy)trimethylsilane



Chemical Formula: C₁₂H₁₇N₃OSi

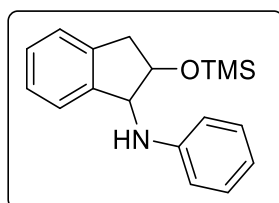
Exact Mass: 247.11

Molecular Weight: 247.37 g.mol⁻¹

The ee was determined by chiral HPLC analysis using OD-H column (flow rate= 1 mL.min⁻¹; 99% hexane, 1% ethanol, 215 nm), which resolved both enantiomers (tr min= 4.5 min, tr maj= 5.2 min). The absolute stereochemistry was not determined.

¹H NMR (360 MHz, CDCl₃) δ (ppm): 7.32-7.28 (m, 1H), 7.27-7.25 (m, 2H), 7.19-7.17 (m, 1H), 4.69 (d, 1H, *J* = 6.2 Hz), 4.45 (td, 1H, *J* = 7.3, 6.2 Hz), 3.20 (dd, 1H, *J* = 15.4, 7.1 Hz), 2.95 – 2.82 (m, 1H), 0.25 (s, 9H).

N-phenyl-2-((trimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-amine



Chemical Formula: C₁₈H₂₃NOSi

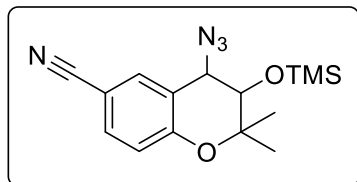
Exact Mass: 297.15

Molecular Weight: 297.47 g.mol⁻¹

The ee was determined by chiral HPLC analysis using IA column (flow rate= 1 mL.min⁻¹; 90% hexane, 10% isopropanol, 215 nm), which resolved both enantiomers (tr min= 13 min, tr maj= 14 min). The absolute stereochemistry was not determined.

¹H NMR (360 MHz, CDCl₃) δ (ppm): 7.37 – 7.16 (m, 6H), 6.84 – 6.71 (m, 3H), 4.85 (s, 1H), 4.46 (p, 1H, *J* = 5.2 Hz), 3.35 (dd, 1H, *J* = 16.0, 6.7 Hz), 2.91 (dd, 1H, *J* = 16.1, 5.6 Hz), 2.08 – 1.99 (m, 1H).

4-azido-2,2-dimethyl-3-((trimethylsilyl)oxy)chromane-6-carbonitrile



Chemical Formula: C₁₅H₂₀N₄O₂Si

Exact Mass: 316.14

Molecular Weight: 316.43 g.mol⁻¹

The ee was determined by chiral HPLC analysis using OD-H column (flow rate= 1 mL.min⁻¹; 95% hexane, 5% isopropanol, 220 nm), which resolved both enantiomers (tr min= 4.58 min, tr maj= 5.56 min). The absolute stereochemistry was not determined.

¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.70 (dd, 1H, *J* = 2.1, 1.1 Hz), 7.47 (dd, 1H, *J* = 8.6 Hz, 2 Hz), 6.85 (d, 1H, *J* = 8.5 Hz), 4.31 (d, 1H, *J* = 9 Hz), 3.66 (d, 1H, *J* = 9.1 Hz), 1.33 (s, 3H), 1.23 (s, 3H), 0.24 (s, 9H).

Annex

In the context of the research work conducted in our laboratory in collaboration with Dr. Olivier David at the Institut Lavoisier de Versailles, another subject on the heterogenization of organocatalysts has been studied in a one-year post-doctoral contract with Dr. Yu-chao Yun. He studied the structural modification of a chiral isothioureia to ensure its immobilization onto rGO and evaluate the recovery procedure. Therefore, the chiral organocatalyst (hyperBTM) was modified with a pyrene group as polyaromatic core via click chemistry and tested in the enantioselective formal [3+2] cycloaddition of ammonium enolates with oxaziridines to prepare the desired oxazolidine-4-ones, according to the work of Smith *et al.*¹⁶⁷ Thanks to strong π - π interactions present between the pyrene core and the carbon-based support, the first immobilization of the pyrene-hyperBTM was successfully achieved and the resulted stable supported catalyst was further engaged in the heterogeneous cycloaddition reaction and also in a multisubstrate process. I would like to explain in this annex part, what was my role in this work. I had the chance to participate to several scientific discussions done not only during the synthesis and the immobilization steps of the chosen organocatalyst, but also for the interpretation of results obtained during the recycling procedure and the kinetics of the catalysis. Furthermore, the synthetic procedure followed to prepare the pyrene-tagged ligand precursors via the click chemistry performed in my PhD work served as the basis for Dr. Yuan to prepare his pyrene-tagged organocatalyst under the same click reaction conditions (Figure 107). In addition, the immobilization of the pyrene-tagged hyper-BTM (**pyr-hyperBTM**) was achieved following the same procedure performed in the case of supported pyrene-tagged salen complexes. I participated in this immobilization procedure and in the UV characterization of its kinetic monitoring.

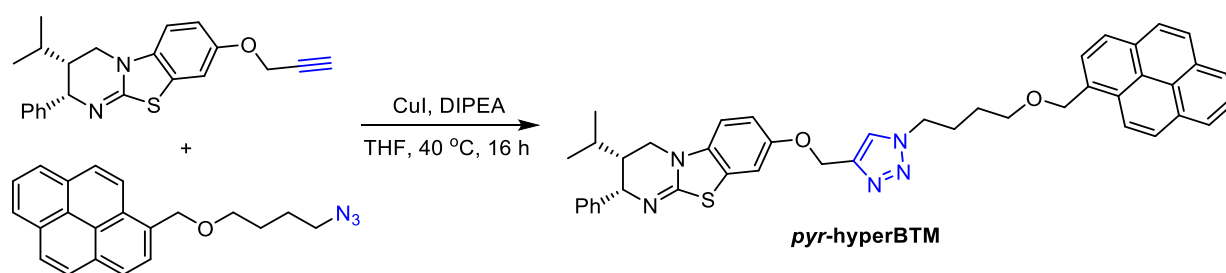


Figure 107: Synthesis of pyr-hyperBTM organocatalyst via click chemistry.

¹⁶⁷ S. R. Smith, C. Fallan, J. E. Taylor, R. McLennan, D. S. B. Daniels, L. C. Morrill, A. M. Z. Slawin and A. D. Smith, *Chem. Eur. J.* **2015**, *21*, 10530.

The modified hyper-BTM was first used as catalyst to promote the synthesis of oxazolidin-4-ones in homogeneous and heterogeneous conditions in the presence of either cesium carbonate Cs₂CO₃ or the Hünig base showing a very good activity and affording the *anti* and *syn* products in high yield and good enantioselectivity (Table 30).

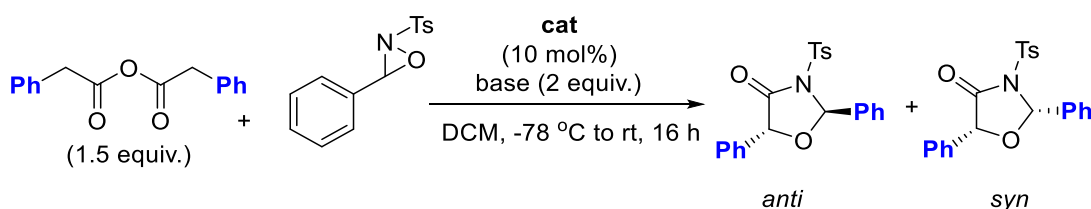


Table 30: Results reaction tests in homogeneous and heterogeneous condition.

Entry	Cat	Base	Yield ^a	d.r.		ee
				<i>anti/syn</i> ^b	<i>anti/syn</i> ^b	<i>anti/syn</i> ^b
1	<i>pyr-hyperBTM</i>	Cs ₂ CO ₃	74	61 / 39	96 / 98	
2		<i>i</i> Pr ₂ NEt	92	55 / 45	89 / 89	
3	<i>pyr-hyperBTM@rGO</i>	Cs ₂ CO ₃	64	69 / 31	87 / 81	
4		<i>i</i> Pr ₂ NEt	75	59 / 41	88 / 92	

^aisolated yield of *anti* + *syn* products. ^bdetermined by HPLC or SFC analysis with a chiral stationary phase.

Moreover, the recycling procedure in the presence of the inorganic base was not efficient because insoluble species accumulated on the solid support and a significant decrease in yield and in enantioselectivity was therefore observed. So, the supported catalysis was further conducted in the presence of the Hünig base. Effectively, the supported *pyr-hyperBTM* was engaged in seven successive runs delivering the desired product with good yield and enantioselectivity. A slight decrease in activity was observed after 6 runs which could be somehow restored by the addition of a small amount of fresh catalyst (Table 31).

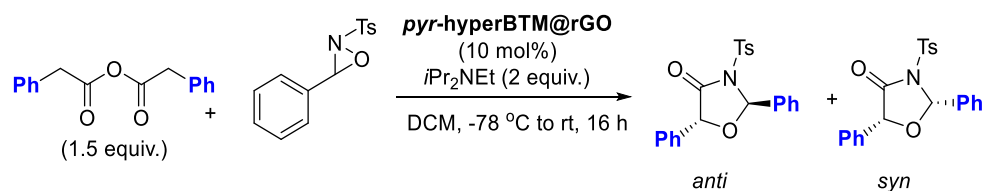


Table 31: Recycling tests with pyr-hyperBTM@rGO and *iPr*₂NEt as a base

	Yield ^a	d.r. ^{anti/syn} ^b	ee ^{anti/syn} ^b
1 st run	74	57/43	92/96
2 nd run	66	64/36	90/93
3 rd run	56	62/38	87/92
4 th run	40	66/34	85/87
5 th run	29	63/37	83/95
6 th run	20	68/32	74/89
7 th run ^c	51	67/33	91/93

^aisolated yield of *anti*+ *syn*. ^bdetermined by HPLC analysis with a chiral stationary phase. ^c2 mg of pyr-hyperBTM added to the spent supported catalyst before performing the 7th run.

Finally, the supported catalyst was engaged in a multisubstrate procedure and reused for 4 runs in which a new anhydride was introduced at each recycling (Table 32)

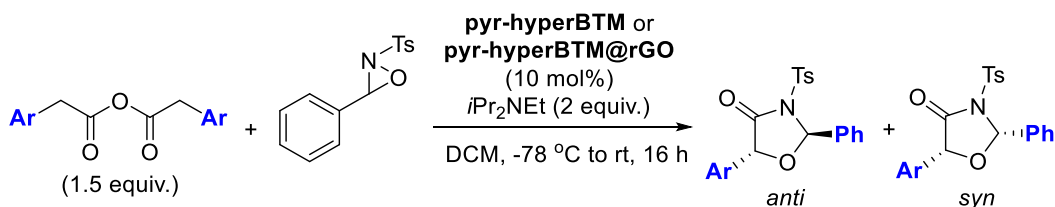
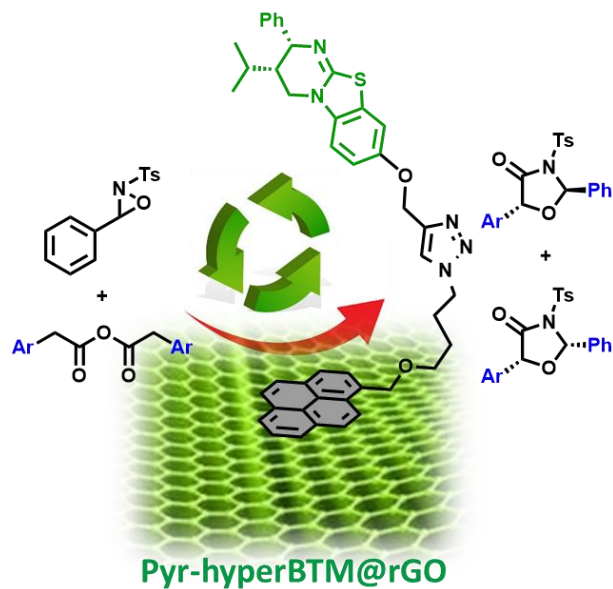


Table 32: Homoanhydride substrate scope and recycling tests with pyr-hyperBTM@rGO in a multi-substrate procedure.

Entry	Run	Cat	Ar	Yield ^a	d.r.		ee	
					<i>anti</i> / <i>syn</i> ^b	<i>anti</i> / <i>syn</i> ^b		
1	-		C₆H₅	92	55/45	89/89		
2	-	pyr-hyper	2-naphtyl	85	58/42	79/53		
3	-	BTM	<i>p</i>F-C₆H₄	82	63/37	85/60		
4	-		<i>p</i>OMe-C₆H₄	90	44/56	76/88		
5	1 st		C₆H₅	75	62/38	96/91		
6	2 nd	pyr-	2-naphtyl	65	80/20	86/69		
7	3 rd	hyperBTM	<i>p</i>F-C₆H₄	60	44/56	72/6 ^c		
8 ^d	4 th	@rGO	<i>p</i>OMe-C₆H₄	30	81/19	87/64		

^aisolated yield of *anti*-**10** + *syn*-**10**. ^bdetermined by HPLC or SFC analysis with a chiral stationary phase. ^c**10c** contaminated with an impurity preventing an accurate *ee* determination of *syn*-**10c**. ^dCs₂CO₃ is used as base.

Hence, the results obtained in this study have been recently published in a hot scientific paper in the Organic Chemical Frontiers journal (OCF).



Y.-C. Yuan, M. Abd El Sater, M. Mellah, N. Jaber, O. R. P. David, E. Schulz, *Org. Chem. Front.* **2021**, *8*, 4693–4699.

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