JOHANNES GUTENBERG UNIVERSITÄT MAINZ

Enantioselective Desymmetrisation of Prochiral Four Membered Carbocycles

Dissertation

for the degree of "Doctor of Natural Sciences"

in the doctoral subject chemistry

at the Faculty of Chemistry, Pharmaceutical Sciences,

Geography and Geosciences

of the Johannes Gutenberg University Mainz

Marius Tenberge

Born in Münster

Mainz, June 2023

Dean: [redacted]

1. Examiner: [redacted]

2. Examiner: [redacted]

Day of the oral exam: 04.08.2023

Acknowledgements

[redacted]

„*Es könnt' alles so einfach sein, ist es aber nicht*"

– Die Fantastischen Vier feat. Herbert Grönemeyer

Table of contents

Abstract

Over the course of this work, three new methods for the enantioselective desymmetrisation of prochiral four-membered carbocycles have been investigated.

In the first research project a method for the enantioselective one-carbon ring expansion of prochiral cyclobutanones has been developed. The optimisation of reaction conditions revealed Scandium triflate as a potent *Lewis* acid catalyst using silyl diazomethanes as one-carbon synthons. Enantioinduction was achieved by the evolution of the employed chiral bis(oxazoline) ligands. Thereby, enantioselective access to β-substituted cyclopentanones was enabled, which was demonstrated for a number of examples including ones bearing all-carbon quaternary stereocentres.

A second part of the work dealt with oxidative ring expanding *Wacker-Tsuji* oxidation of prochiral methylenecyclobutanes. The substrate scope for functionalised methylenecyclobutanes was explored and stereochemical analysis of the reaction provided support for the assumed reaction pathway. Furthermore, the existing reaction conditions were adapted to enable the use of chiral pyridine-oxazoline ligands. The application of weakly coordinating anions as ligands for the chiral palladium catalyst resulted in the achievement of the first enantioselective *Wacker-Tsuji* oxidation of 1,1-distubstituted alkenes.

A third research project was the desymmetrisation of prochiral methylenecyclobutanes *via Mizoroki-Heck* arylation. Successive optimisation of the reaction conditions was conducted for methylenecyclobutane model substrates bearing tertiary as well as quaternary carbon centres in 3-position. High dependency of the electronic nature of the employed phosphine ligands was found. Furthermore, the addition of silver(I) salts forcing a cationic pathway of the reaction was found crucial to obtain reasonable yields. Initial attempts to use chiral ligands to achieve enantioinduction were not successful so far.

Zusammenfassung

Im Rahmen dieser Arbeit wurden drei neue Methoden für die enantioselektive Desymmetrisierung von prochiralen viergliedrigen Cycloalkanen untersucht.

Im ersten Forschungsprojekt wurde eine Methode zur enantioselektiven Ein-Kohlenstoff-Ringerweiterung von prochiralen Cyclobutanonen entwickelt. Die Optimierung der Reaktionsbedingungen zeigte, dass Scandiumtriflat als potenter *Lewis*-Säurekatalysator unter Verwendung von Silyldiazomethanen als C1-Baustein fungiert. Durch die Weiterentwicklung der verwendeten Bis(oxazolin)-Liganden konnte eine Enantioinduktion erreicht werden. Die entwickelte Methode ermöglicht somit einen enantioselektiven Zugang zu β-substituierten Cyclopentanonen. Dies konnte für eine Reihe von Beispielen demonstriert werden, einschließlich solcher mit quaternären Stereozentren.

Ein zweiter Teil der Arbeit befasste sich mit der oxidativen ringerweiternden *Wacker-Tsuji*-Oxidation von prochiralen Methylencyclobutanen. Der Substratbereich für funktionalisierte Methylencyclobutane wurde erforscht und die stereochemische Analyse der Reaktion bestätigte den bisher angenommenen Reaktionsweg. Darüber hinaus wurden die bestehenden Reaktionsbedingungen angepasst, um die Verwendung chiraler Pyridin-Oxazolin-Liganden zu ermöglichen. Durch den Einsatz von schwach koordinierenden Anionen als Liganden für den verwenden chiralen Palladium Katalysator wurde die erste enantioselektive *Wacker-Tsuji*-Oxidation von 1,1-distubstituierten Alkenen erreicht.

Ein drittes Forschungsprojekt war die Desymmetrisierung von prochiralen Methylencyclobutanen mittels *Mizoroki-Heck*-Arylierung. Die sukzessive Optimierung der Reaktionsbedingungen wurde für Methylencyclobutan-Modellsubstrate durchgeführt, die sowohl tertiäre als auch quaternäre Kohlenstoffzentren in 3-Position tragen. Es zeigte sich eine hohe Abhängigkeit vom Elektronenreichtum der eingesetzten Phosphinliganden. Darüber hinaus erwies sich die Zugabe von Silber(I)-Salzen als entscheidend. Durch das Erzwingen eines kationischen Reaktionsweges konnten so angemessene Ausbeuten erzielt werden. Erste Versuche unter Verwendung chiraler Liganden eine Enantioinduktion zu erreichen waren bisher nicht erfolgreich.

Publications

Parts of this work have been published:

- **Lewis Acid Catalysed Asymmetric One-Carbon Ring-Expansion of Prochiral Cyclobutanones**
  M. Tenberge, J. M. Wahl, *Synthesis* **2023**, 55, 892 – 898.
- **Wacker Oxidation of Methylenecyclobutanes: Scope and Selectivity in an Unusual Setting**
  J. Sietmann,[#] M. Tenberge,[#] J. M. Wahl, *Angew. Chem. Int. Ed.* **2023**, 62, e202215381.
  [#] These authors contributed equally to this work

Poster presentations

Parts of this work have been presented at the following scientific conferences:

- 47th National Organic Chemistry Symposium 2022 – 26 – 30.06.2022, La Jolla, CA, USA
  Enantioselective Desymmetrisation of prochiral Cyclobutanones towards Cyclopentanones
  M. Tenberge, J. M. Wahl

- ORCHEM 2022 – 22nd Lecture Conference – 05 – 07.09.2022, Münster, Germany
  Enantioselective Desymmetrisation of prochiral Cyclobutanones towards Cyclopentanones
  M. Tenberge, J. M. Wahl

Declaration on the work of others contained herein

In the course of this work, several collaborations with others have occurred, their individual contributions are discussed in more detail below.

Parts of the initial experiments for the proof of concept of the asymmetric Sc(III)-catalysed one-carbon ring expansion of prochiral cyclobutanones (s. chapter 2) were performed by [redacted]. He conducted the experiments revealing $Sc(OTf)_3$ as a potent catalyst and bis(oxazoline)-ligands as a promising ligand motive for the envisioned enantioinduction, which then led to further optimisation and development of the method described in chapter 2.3.

[redacted] synthesised BINOL-ligand **38** and performed the corresponding ring expansion reaction employing it in combination with an aluminium *Lewis* acid in the context of a research internship.

As part of her bachelor's thesis, [redacted] contributed with the synthesis of the box ligand **50**, which was later employed as a chiral ligand for Sc(III) in the screening for a suitable ligand for the asymmetric ring extension of prochiral cyclobutanones (s. chapter2.3).

In the course of their own work [redacted] and [redacted] synthesised the cyclobutanones **3**, **4** and **148** and cyclobutanone **6**, respectively, which were used as substrates for the exploration of the scope of the asymmetric ring extension of prochiral cyclobutanones described in chapter 2.3.

The development of the *Wacker* oxidation of methylenecyclobutanes discussed in chapter 3 was performed in collaboration with [redacted] His work focused on the optimisation of the racemic reaction conditions as well as a major part of the exploration of the substrate scope. Furthermore, he conducted several experiments towards the stereochemical analysis of the reaction (s. chapter 3.3).

The contributions of the respective persons have been clearly stated in the corresponding places.

Index of abbreviations

AFC	automated flash chromatography
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
BiOx	bi(oxazoline)
BiPyBox	bis(oxazolinyl)bipyridine
bomen	bis(oxazolin-2-ylmethyl)ethane-1,2-diamine
Box	bis(oxazoline)
BoxAx	2,2'-bis(oxazolinyl)-1,1'-binaphthyl
BQ	benzoquinone
CAM	cerium ammonium molybdate
CBone	cyclobutanone
CPone	cyclopentanone
CyHex	cyclohexane
DBFox	dibenzofuran-4,6-bis(oxazoline)
DIPEA	*N,N*-diisopropylethylamine
DMA	*N,N*-dimethyl acetamide
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethyl formamide
DMPSD	dimethylphenylsilyl diazomethane
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EI	electron ionisation
ELN	electronic lab notebook
eq.	equivalent
er	enantiomeric ratio
EtOAc	ethyl acetate
FC	flash column chromatography
GC	gas chromatography
hfac	hexafluoroacetylacetonate
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared
LA	*Lewis* acid
LiHMDS	lithium bis(trimethylsilyl)amide
M.P.	melting point
MCB	methylenecyclobutane
MDPSD	methyldiphenylsilyl diazomethane
Ms	mesyl
MS	mass spectrometry
MTBE	methyl tert-butyl ether
NMM	*N*-methyl morpholine
NMR	nuclear magnetic resonance
PHOX	phosphinooxazoline

PMA	phosphomolybdic acid
ppm	part per million
p-Ts	*p*-tosyl
PyBox	pyridine-2,6-bis(oxazoline)
PyOx	pyridine-oxazoline
quinox	quinolinyl oxazoline
RLS	rate-limiting-step
rr	regioisomeric ratio
rt	room temperature
salen	bis(salicyliden)ethylendiamine
TBAB	tetrabutylammonium bromide
TCAC	trichloroacetyl chloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSD	trimethylsilyl diazomethane
trisox	tris(oxazoline)
vs.	versus

1 Introduction

Nature and the life on earth have evolved to a diverse construct of molecular complexity. Complex molecules are responsible for many fundamental processes in living organisms. Therefore, it is of major importance not only to identify, isolate and characterise such molecules, but further to be able to synthesise and modify those. Hence, an insight into their role in the corresponding processes and their properties can be obtained. That knowledge can then be used to develop and improve molecules important for the every-day-life, such as drug agents or agrochemicals.

A molecule's properties in regard of complexity are vastly increased by chirality. A large number of natural products, drug agents and other biologically active substances possess stereogenic elements – most commonly a carbon stereocentre. The fact that the two enantiomers of a structure can have significantly different biological activity was very tragically demonstrated with the prescription and use of the sedative contergan in the late 1950s and early 1960s. In that case one enantiomer caused the desired effect and the other one led to major birth defects due to its teratogenic properties.[1] This underlines the need for research and development of enantioselective synthetic methods, in an ideal case giving rise to both enantiomers selectively. Over the last decades especially the field of asymmetric synthesis gained significant attention in the scientific community. Different methodologies to gain access to enantioenriched compounds have been developed, including kinetic resolution of racemates and the employment of chiral auxiliaries. Drawbacks like limited yields or the need for stoichiometric amounts of a chiral auxiliary were overcome by asymmetric catalysis. The use of a chiral catalyst – oftentimes derived from natures chiral pool – renders this approach especially powerful. Only minor quantities of enantiopure material are needed to transfer the chiral information to the newly formed product and generate stereocentres enantioselectively.

1.1 Desymmetrisation

In asymmetric catalysis two different scenarios – deracemisation[2] and desymmetrisation[3,4] – can be distinguished. The former describes the conversion of a racemic mixture of a molecule to one enantiomer of that precise molecule, for example *via* deprotonation of a stereocentre and enantioselective re-protonation. In contrast,

the latter represents a reaction on a molecule causing the loss of a symmetry element.[5] In the case of a prochiral molecule thereby a new stereogenic element is generated, while in case of a *meso*-compound a pre-existing stereocentre is modified resulting in the formation of a chiral molecule (Figure 1).

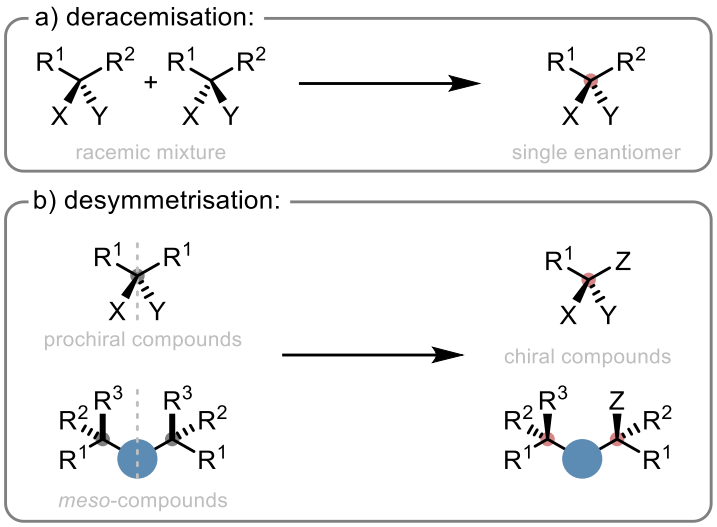


Figure 1: Two possible scenarios in asymmetric catalysis: a) deracemisation of a racemic mixture and b) desymmetrisation of prochiral or *meso*-compounds.

A desymmetrisation itself is generally not enantioselective as both enantiomers of the modified or newly formed stereocentre can be formed in a corresponding transformation.[6] However, in a chiral surrounding enantioinduction is enabled. This type of reaction does not necessarily have to be a catalysed one, yet it is particularly useful and efficient when a chiral catalyst is employed to facilitate the reaction and establish a chiral surrounding.

Considering the desymmetrisation of a prochiral molecule, transformations proceeding proximal or distal with respect to the corresponding prochiral centre can be differentiated. Following a proximal desymmetrisation the newly formed stereocentre is located at the centre directly involved in the bond formation, while in a distal desymmetrisation the former prochiral centre is not directly involved in a transformation (Figure 2).[7,8]

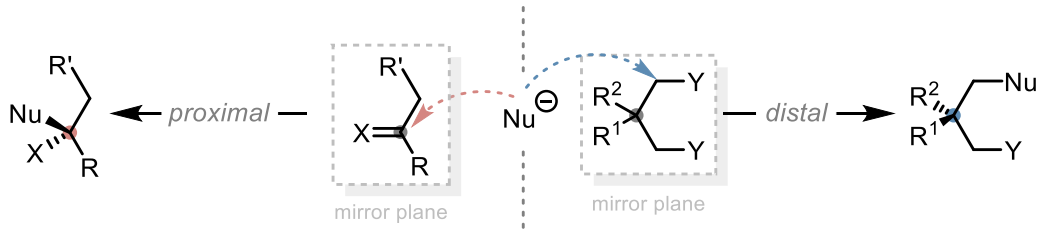


Figure 2: Exemplified comparison of proximal and distal desymmetrisation of prochiral molecules.

A very prominent example of an enantioselective desymmetrisation was presented with the synthesis of the *Wieland-Miescher* ketone *via* the *Hajos-Parrish-Eder-Sauer-Wiechert* reaction in 1971 employing (*S*)-proline as an organocatalyst (Figure 3).[9–11]

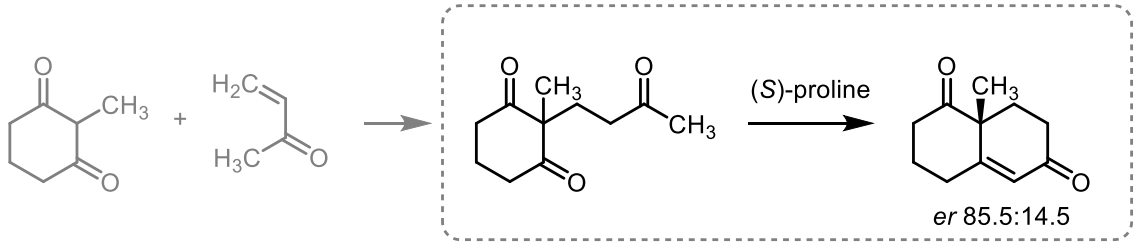


Figure 3: Synthesis of the *Wieland-Miescher* ketone *via* enantioselective desymmetrisation of 2-methyl-2-(3-oxobutyl)cyclohexane-1,3-dione in a *Hajos-Parrish-Eder-Sauer-Wiechert* reaction.[9–11]

The *Wieland-Miescher* ketone as well as its 5,6-fused bicyclic analogue, the *Hajos-Parrish* ketone, are key building block for the synthesis of steroids and other terpenoids nicely presenting the potential of enantioselective desymmetrisation for the synthesis of complex molecules.[12] A particularly interesting setting for the enantioselective desymmetrisation is the application on strained molecules – especially cyclic molecules – as starting materials. The loss of ring strain energy can act as an additional driving force rendering transformations at least thermodynamically downhill.

1.2 Ring strain

The strain energy of a molecule is defined as the difference $\Delta\Delta H_f^\circ$ between its theoretical estimated heat of formation ΔH_f° and its experimentally observed value of ΔH_f°. The heat of formation is the total enthalpy ΔH° for the formation of a molecule from its containing elements in their standard state. Although ΔH_f° is not easily measurable, it can be derived simply from the heat of combustion of the respective molecule. This corresponds to the enthalpy of the complete combustion of a molecule with oxygen and has been determined for many organic molecules especially hydrocarbons. As the values of ΔH_f° for CO_2 and H_2O are known, the ΔH_f° of a respective molecule can be calculated from its measured heat of combustion.[13] The theoretical heat of formation of a molecule can be determined by the group increment method. Through comparison of the ΔH_f° values of a set of structurally related compounds, e.g., a series of *n*-alkanes, the contribution of different structural groups to the heat of formation can be derived. The group increment values for most

fundamental groups of organic molecules have been determined and tabulated. For example, the group increment of a CH_2-group is found to be −4.93 kcal/mol. Through addition of individual group increments of a molecule its theoretical heat of formation can be calculated.[13]

Especially for cyclic hydrocarbons with small or medium ring sizes significant differences $\Delta\Delta H_f^\circ$ are found comparing their theoretical and experimental heat of formation, thus implying that these contain a certain strain energy. The origin of this ring strain energy can be subdivided into different components, although one should keep in mind that such partitioning is not necessarily supported by the underlining quantum mechanics defining the bonding situation and that these components are usually interdependent.[13,14]

Ring strain has three major contributions. One being torsional strain, also called *Pitzer* strain,[5] resulting from repulsive interactions of eclipsed groups attached to adjacent atoms, which are dependent on the respective C–C–C–C torsional angle. Another component is angle strain, also called *Baeyer* strain, which originates from the distortion of bond angles from the geometrical optimum, e.g., 109.5° for a sp^3 hybridised carbon atom. A third component is transannular strain or *Prelog* strain, arising from repulsive interaction of groups attached to non-adjacent atoms of the ring. This type of strain is especially observed for the hydrogen atoms of medium sized rings facing to the centre of the ring.[5,13–15]

Considering the homologous series of simple cycloalkanes, the highest strain energy is found for cyclopropane with 27.5 kcal/mol. Compared to cyclobutane the change in strain energy is surprisingly low with about 1 kcal/mol. The reason for this are stabilising factors present in cyclopropane reducing its total amount of strain, such as the absence of 1,3-repulsive interactions. Taking into account the considerably high angle strain and torsional strain, that cannot be relieved anyway, its strain energy would otherwise be even higher. (Figure 4).[15]

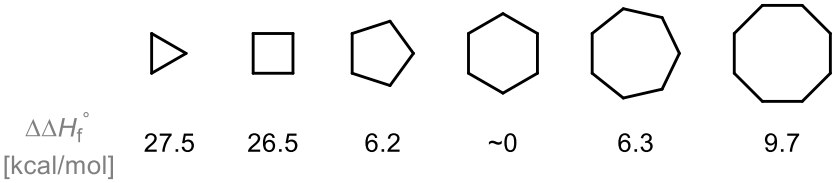


Figure 4: Strain energies for cycloalkanes cyclopropane to cyclooctane in kcal/mol.[15]

Further following the series, the strain energy lowers to 6.2 kcal/mol for cyclopentane towards cyclohexane with a strain energy of about 0 kcal/mol as the bonding

situation in cyclohexane is, at least in its most favourable chair conformation, rather close to the hypothetical optimum. Continuing to the medium sized rings cycloheptane and cyclooctane, strain energy rises again as a result of the increase of the interaction outlined above.[13,15]

1.3 Desymmetrisation of prochiral four-membered carbocycles

Prochiral four-membered carbocycles represent a potent class of precursors for enantioselective desymmetrisation.[4,7,16] Considering their structural properties, several transformations resulting in their desymmetrisation are possible, thus opening the door for the development of new enantioselective methods (Figure 5). A monosubstituted cyclobutane derivative is prochiral, if the functional group X opposite to the substituted position is symmetrical thus sharing a mirror plane with the rest of the molecule. Besides X = CH_2, this is the case, for example, if X is a ketone (C=O) or an equally substituted alkene ($C=CR_2$).

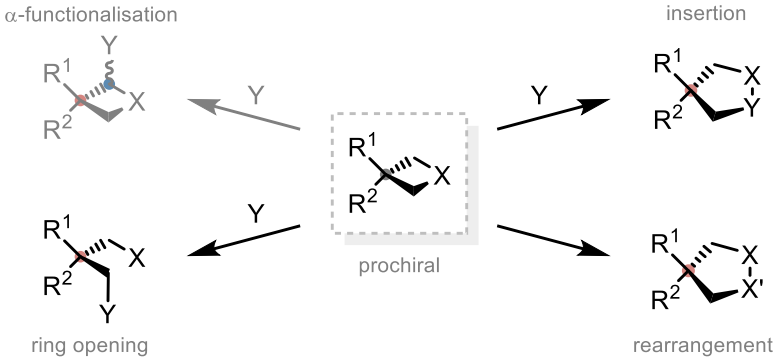


Figure 5: Possible exemplified transformations leading to a desymmetrisation of a substituted cyclobutane derivative. X = carbon-based functional group possessing a mirror plane, e.g., CH_2, C=O, $C=CH_2$.

In contrast to the other depicted transformations, the α-functionalisation of such molecule does not result in the release of its ring strain energy. While the ring opening would release the total amount of ring strain providing a major driving force, the ring expansion would result in only partial release of ring strain, keeping the molecular skeleton widely intact. Thereby, ring expansion can either occur through an insertion of a second molecule or group Y (*cf.* chapter 2) or *via* rearrangement leading to the incorporation of an atom X' already present in the precursor into the cycle (*cf.* chapter 3). Assuming appropriate choice for X and Y, such ring expansions can result in the formation of functionalised five-membered rings, which are valuable building blocks for organic synthesis as they resemble an ubiquitous structural motif in

nature.[17,18] Especially, 3-substituted cyclobutanones (CBones) and methylenecyclobutanes[1] (MCBs) are interesting substrates for those transformations.

1.3.1 Properties and synthesis of cyclobutanones

Not surprisingly, the amount of ring strain energy of cyclobutanone is about 26 kcal/mol and thereby in the same magnitude as that of cyclobutane as its parent structure.[19] To relieve some strain, cyclobutanes as well as cyclobutanones usually exist in a slightly puckered shape.[13,20] CBones are rendered prochiral when substituted in 3-position, as the molecule then possesses a mirror plane (Figure 6).

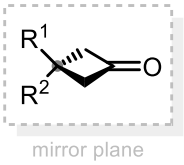


Figure 6: General structure of a prochiral 3-substituted CBone.

Most commonly 3-substituted CBones are synthesised *via* [2+2] cycloaddition of an alkene – as feedstock chemicals a large number of simple alkenes is commercially available – and a usually in situ generated ketene or keteniminium species. In contrast to the [2+2] cycloaddition of two alkenes, which is thermally forbidden due to orbital symmetry, the thermal [2+2] cycloaddition of an alkene with allenes or ketenes are allowed.[13] For the synthesis of 3-substituted CBones several different protocols have been developed using highly reactive dichloroketene for subsequent [2+2] cycloaddition (Figure 7, left).

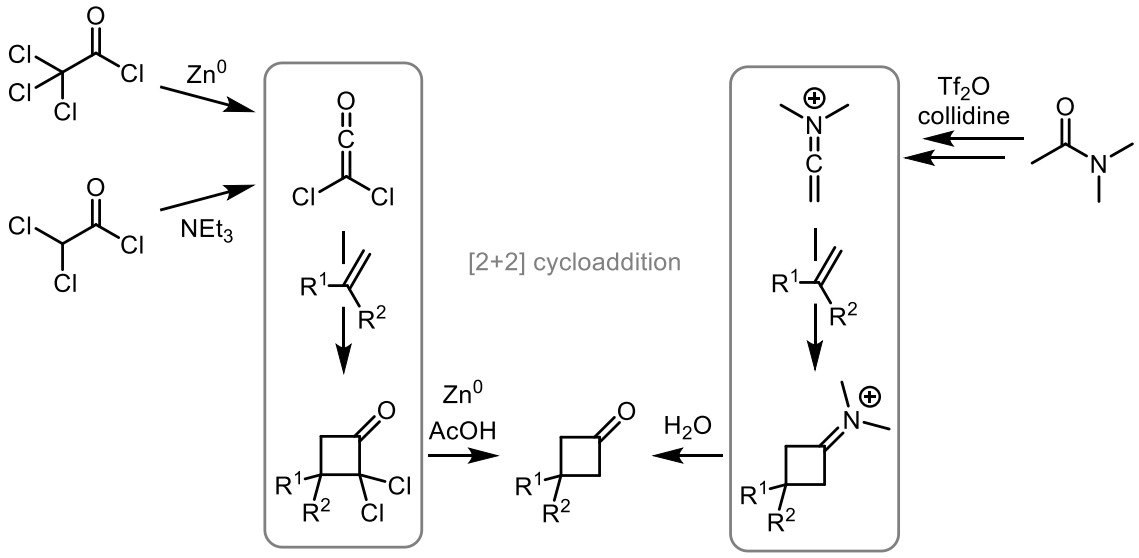


Figure 7: Commonly used routes for the synthesis of 3-substitued CBones either proceeding *via* dichloroketene or a keteniminium species for subsequent [2+2] cycloaddition with a respective alkene.

[1] The numbering of MCBs herein is analogous to that of CBones to avoid confusion due to the varying numbering of MCBs depending on their respective substituent according to IUPAC.

Dichloroketene is commonly generated *via* zinc-mediated dehalogenation of trichloroacetyl chloride (TCAC) or *via* deprotonation of dichloroacetyl chloride.[21,22] Thereby, an α,α-dichloro-CBone is generated, which can be dehalogenated using Zn^0 in acidic media affording the desired CBone. it was further found that the use of $POCl_3$ as additive or conducting the reaction under ultrasonication facilitates the zinc-mediated generation of dichloroketene.[22,23,24,25]

Another frequently employed method is the use of a keteniminium species as counterpart to the alkene in the [2+2] cycloaddition (Figure 7, right).[26,27,28] Commonly, *N,N*-dimethylketeniminium triflate is used, generated *in situ* by triflation of *N,N*-dimethyl acetamide (DMA) followed by base-induced elimination.[27,29] The resulting cyclobutylideneammonium salts can then be hydrolysed to yield the desired CBone.[27,28]

1.3.2 Properties and synthesis of methylenecyclobutanes

MCBs are rather similar to CBones regarding their structural shape and ring strain, which is about 27 kcal/mol (Figure 8).[15,30] A number of synthetic methods have been employed for the synthesis of MCBs (Figure 10, *vide infra*). First to mention is the [2+2] cycloaddition of alkenes with allene, suffering from elaborate reaction conditions due to the use of gaseous allene and often poor regioselectivity unless electron poor alkenes are used.[31] The [2+2] cycloaddition of allenoates with alkenes offers milder reaction conditions, thus necessarily giving higher substituted MCBs.[32] Given a substitution in the 3-position of the cyclobutane ring, those are usually already chiral structures as they then possess a stereogenic axis (Figure 9). Although this axial chirality is an interesting property,[5,33] this method is therefore of lesser importance for the synthesis of prochiral MCBs.

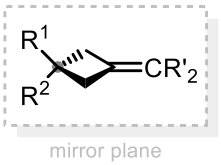


Figure 8: Structure of prochiral 3-substituted MCBs.

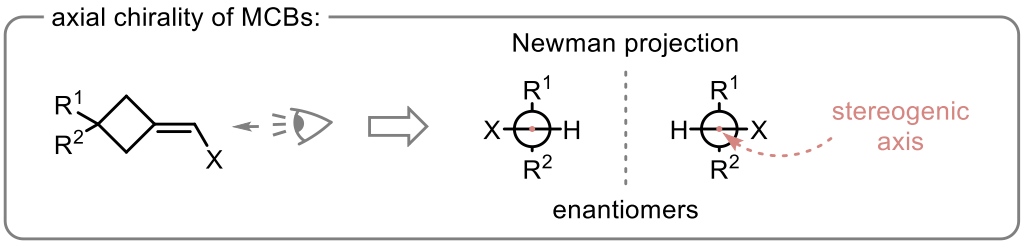


Figure 9: Axial chirality of substituted MCBs visualised in a corresponding Newman projection of a respective MCB.

Another method yielding prochiral MCBs is the ring opening of bicyclo[1.1.1.]pentane moieties.[34] Thus, affording the synthesis of rather complex starting materials. Furthermore, elimination of 3-substituted iodomethylcyclobutanes can afford prochiral MCBs. Nevertheless, strongly basic conditions are required.[35]

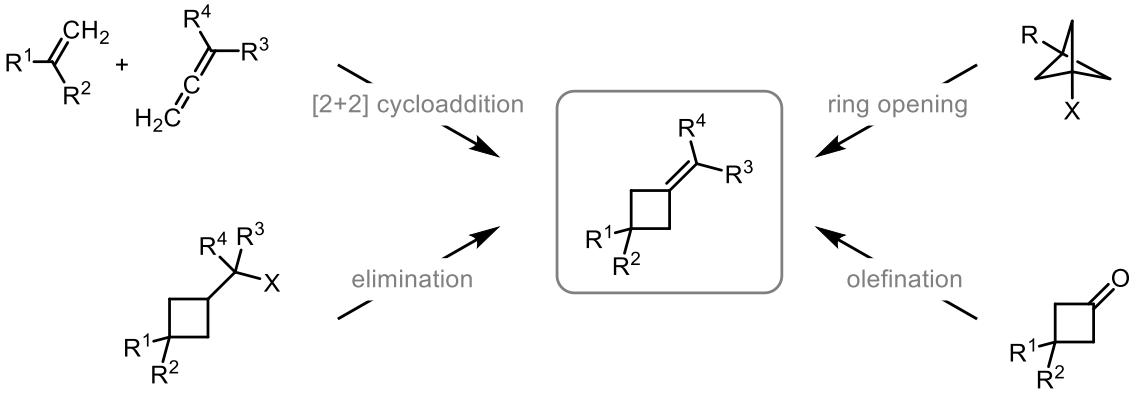


Figure 10: Strategies employed for the synthesis of MCBs.

The most useful method for the synthesis of prochiral MCBs for laboratory scale is the olefination of prochiral CBones, discussed in the previous chapter. Several olefination methods are feasible, however, the *Wittig*-Olefination is the most widely applied reaction.[36,37]

2 Asymmetric desymmetrisation of prochiral cyclobutanones *via* ring expansion

2.1 Introduction

Enantioenriched cyclopentanones (CPones) are an ubiquitous structural motif in natural products such as jasmonoids,[38] prostaglandins[18,39] or steroids[40] and therefore resemble valuable building blocks in organic synthesis (Figure 11).

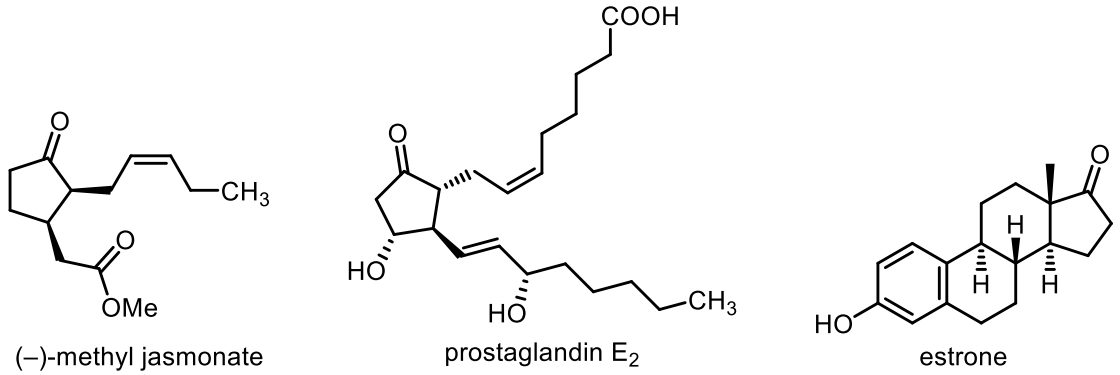


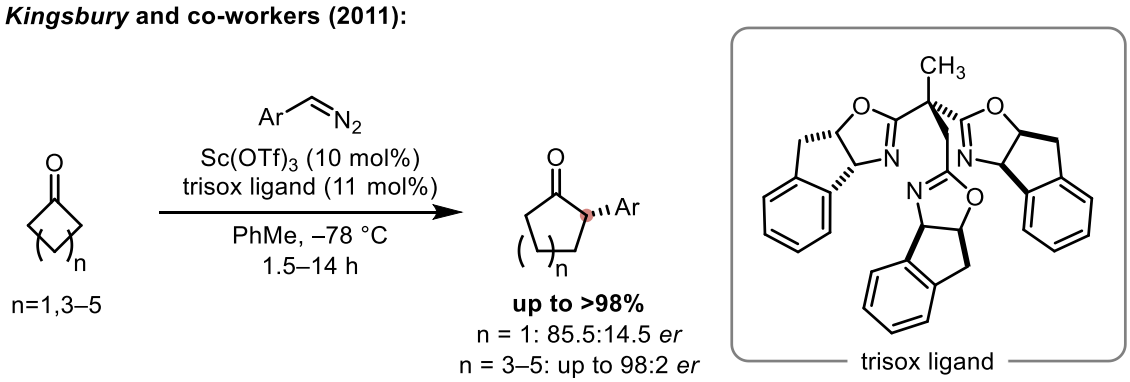
Figure 11: Representative examples of natural products from the group of jasmonoids, prostaglandins and steroids containing cyclopentanone moieties.

Gaining access to those enantioselectively from simple precursors is of significant interest for the synthetic organic community. As outlined in chapter 1, the enantioselective desymmetrisation of prochiral four-membered carbocycles is a method with enormous potential. This was brilliantly demonstrated for the synthesis of enantioenriched γ-lactones *via* asymmetric *Baeyer-Villiger* oxidation of cyclobutanones.[41,42] The enantioselective ring expansion of prochiral cyclobutanones would resemble an ideal strategy for tackling the asymmetric synthesis of substituted CPones. However, the asymmetric one-carbon ring expansion of prochiral cyclobutanones towards β-substituted CPones was not possible prior to this study.[43]

In the homologation chemistry of carbonyl compounds diazomethane and its derivatives emerged as powerful C1-building blocks from decades of studies.[44,45] Arising from these studies, the asymmetric homologation of cyclic ketones, especially of cyclohexanones, has been studied much more intensively, in contrast to the transformation mentioned above.

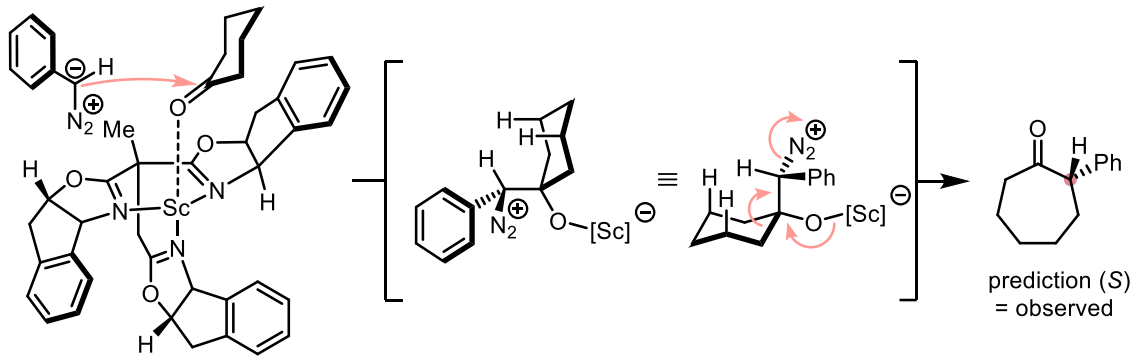
2.1.1 Asymmetric homologation of cyclic ketones – state of the art

Important pioneering work was presented by *Yamamoto* and co-workers in 1994 with the diastereoselective ring expansion of 4-*tert*-butylcyclohexanone using diazomethane and methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) as a bulky *Lewis* acid for carbonyl activation.[46,47] Years later, this work was extended by *Maruoka* and co-workers towards the use of substituted diazomethanes and further a camphorsultam-substituted diazomethane following a chiral auxiliary approach.[48] Likewise, *Kingsbury* and co-workers did intensive work on *Lewis* acid catalysed ring expansion on acyclic as well as cyclic ketones. After preliminary work on racemic protocols,[49,50] they presented the asymmetric *Lewis* acid catalysed ring expansion of cyclic ketones with diazoalkanes in 2011.[51] By employing a chiral tris(oxazoline) (trisox) ligand for Scandium(III) as *Lewis* acid catalyst, they were able to synthesise α-aryl substituted cycloheptanones and their higher homologues with high enantiomeric ratio (*er*) from the corresponding achiral cyclic ketones using aryl diazomethanes (Scheme 1).



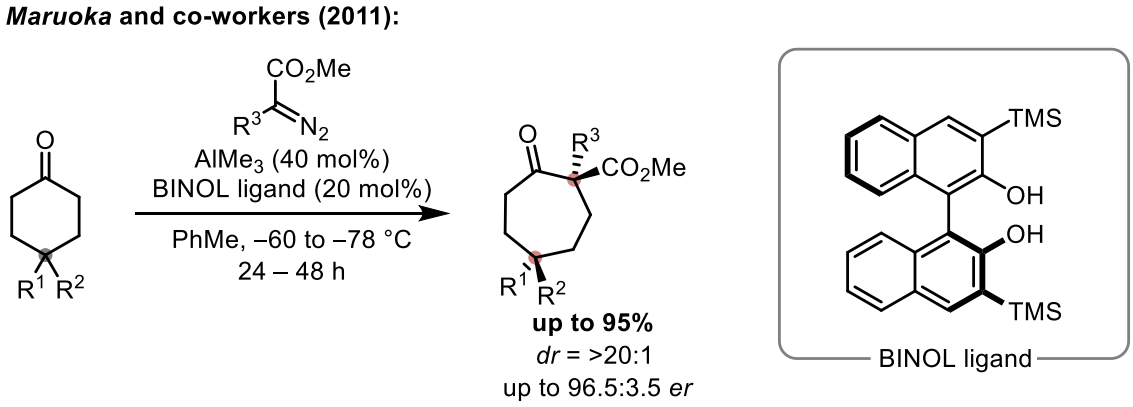
Scheme 1: *Kingsbury's* enantioselective ring expansion of cyclic ketones using a chiral Scandium *Lewis* acid.[51]

Further, one example for the enantioselective ring expansion of cyclobutanone to α-phenyl CPone with a moderate *er* of 85.5:14.5 was presented. In the same publication the authors reported the desymmetrisation of 3-*tert*-butyl cyclohexanone under the developed conditions affording the *anti*-product in high diastereo- and enantioselectivity. These results are in line with *Yamamoto's* earlier findings.[46] The observed enantiomeric ratios were further rationalised with the proposal of a corresponding induction model relying on an axial attack of the nucleophile with its larger substituent facing away from the chiral pocket and subsequent least motion collapse of the formed betaine intermediate (Scheme 2).



Scheme 2: Model for the enantiofacial discrimination of the employed aryl diazomethanes proposed by *Kingsbury* and co-workers. Triflate ligands omitted for clarity.[51]

Simultaneously, *Maruoka* and co-workers reported the enantioselective desymmetrisation of cyclohexanones *via Lewis* acid catalysed ring expansion.[52] Using α-substituted α-diazoacetates and a chiral aluminium based *Lewis* acid, the synthesis of substituted cycloheptanones in highly diastereo- and enantioselective fashion was presented (Scheme 3).

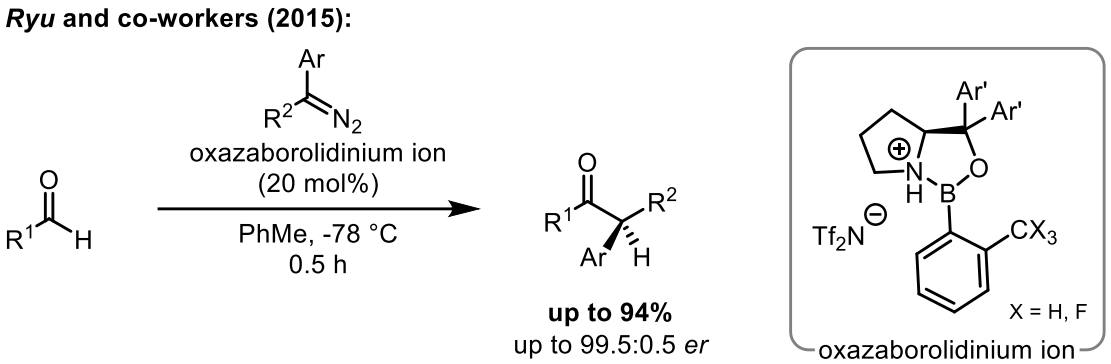


Scheme 3: *Maruoka's* asymmetric desymmetrisation of prochiral cyclohexanones using a chiral aluminium *Lewis* acid.[52]

Interestingly, the authors found the optimal ratio of $AlMe_3$ to ligand to be 2:1, indicating a bis-aluminium complex to be the active catalyst.[45] Similar to *Kingsbury's* work, the authors found cyclobutanone to be a viable substrate to the developed protocol as well. However, the respective CPone was received in low yield and a low *er* of 59.5:40.5.

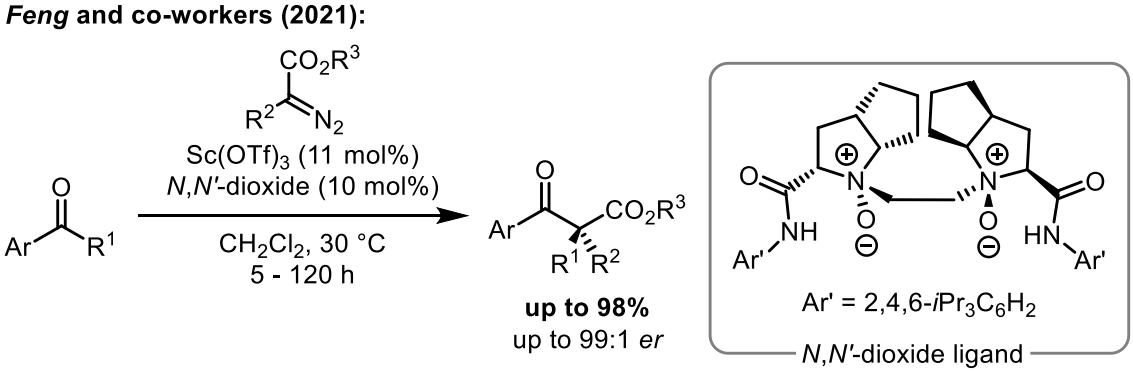
Even though not exclusively performed on cyclic ketones but methodologically closely related, the work of *Ryu* and co-workers has to be mentioned here. Over the course of several studies the authors found oxazaborolidinium complexes to be potent *Lewis* acid catalysts for the homologation of ketones and aldehydes with diazomethanes.[53–56] Using chiral oxazaborolidinium cations asymmetric transform-

ations were realised, for example, the enantioselective homologation of aldehyde towards α-tertiary aryl ketones (Scheme 4).[55]



Scheme 4: *Ryu's* asymmetric homologation of aldehydes using a chiral oxazaborolidinium ion catalysts.[55]

Additionally, *Feng* and co-workers did extensive research on the use of *N*,*N*'-dioxide type ligands in *Lewis* acid catalysis.[42,57,58] Especially, in combination with $Sc(OTf)_3$ the author used these chiral ligands also for asymmetric homologation of ketones (Scheme 5).[59,60]



Scheme 5: *Feng's* asymmetric homologation of ketone catalysed by chiral Sc(III)-*N*,*N*'-dioxide *Lewis acid*.[59]

2.1.2 Bis(oxazoline) ligands

Originally derived from C_2-symmetric semicorrins pioneered by *Pfaltz* and co-workers,[61] bis(oxazoline) (Box) ligands have emerged to a diverse class of bidentate N,N-ligands.[62–64] Since their application in pioneering work from *Masamune*,[65,66] *Corey*[67] and *Evans*[68] in the early 1990s, Box ligands are widely used in numerous fields of asymmetric catalysis. For example, Box ligands have been designed and applied in asymmetric transformations such as cyclopropanations,[65,66,68–70] *Diels-Alder* and hetero-*Diels-Alder* reactions,[67,71,72] allylic substitutions and oxidations,[73] aziridinations,[74] *Mukaiyama* aldol reactions[75] and others.[62–64]

Although the name bis(oxazoline) ligand does not explicitly exclude specific derivatives according to their linking moiety connecting the two oxazolines, Box ligands are usually referred to as corresponding bis(oxazolines) connected by a symmetrically substituted methylene unit (Figure 12). Other bis(oxazoline) ligand classes are usually differentiated by the use of specific abbreviations such as BiOx for two directly connected oxazoline rings or PyBox for pyridinyl-linked derivatives.[76]

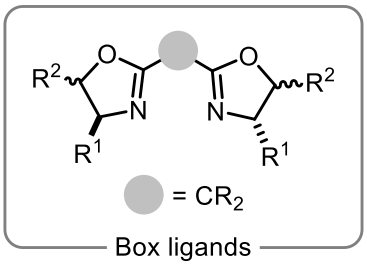
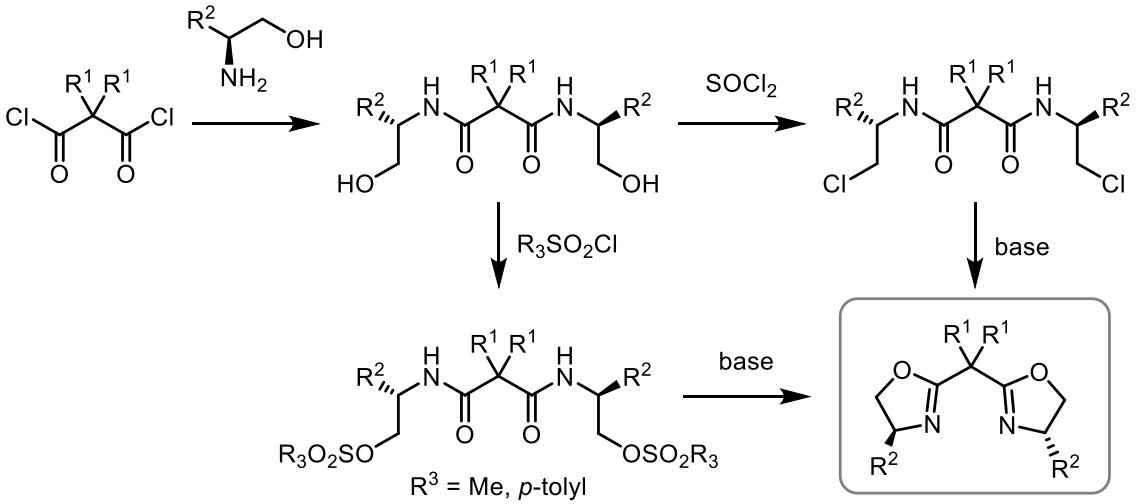


Figure 12: General structure of Box ligands.

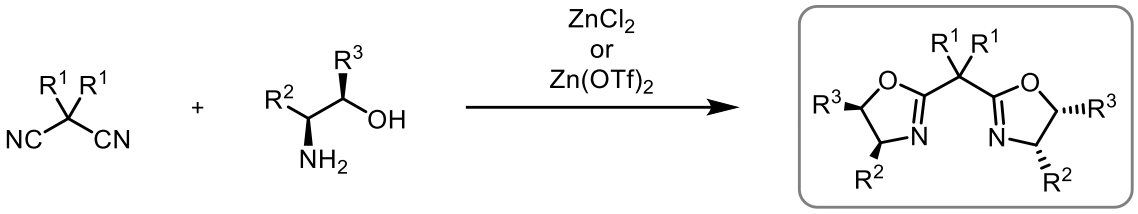
In over 30 years of application, several routes for the synthesis of Box ligands have been developed. The most frequently used ones will be discussed shortly in the following. A major benefit for the synthesis of Box ligands is the possibility of implementing the chiral information by employing enantiopure amino alcohols, in specific cases also amino esters, derived from natures chiral pool.[62–64]

The most versatile method (approach **I**) starts with the condensation of a malonyl dichloride with an amino alcohol to form a corresponding bis(hydroxy)amide. The hydroxyl groups of this bis(hydroxy)amide can then be activated as leaving groups *via* chlorination, mesylation or tosylation. The resulting intermediate can then be cyclised under basic conditions usually without prior purification (Scheme 6).[67,68,77] Direct cyclisation of the bis(hydroxy)amide is possible under certain conditions as well, but less frequently used.[65,66,78,79]



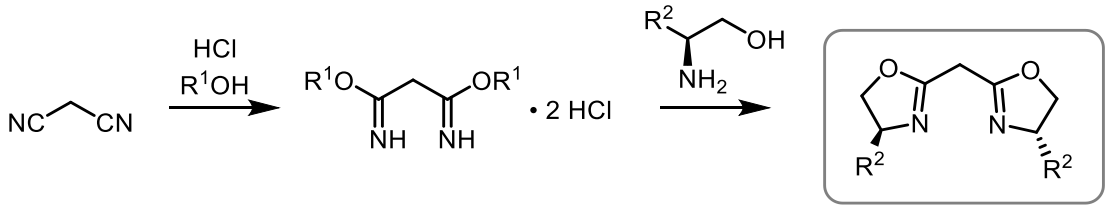
Scheme 6: Strategy for stepwise construction of Box ligands starting from a malonyl dichloride forming a bis(hydroxy)amide as key intermediate by condensation with a chiral amino alcohol (approach **I**).

A second frequently used method (approach **II**) is the direct condensation of a malononitrile with an amino alcohol mediated by zinc chloride or triflate. Although this method requires only one step, it suffers from high reaction temperature, long reaction time and often only moderate yields (Scheme 7).[80,81]



Scheme 7: Reaction scheme for the synthesis of Box ligands *via* direct condensation of a chiral amino alcohol with a malononitrile under zinc(II) mediation (approach **II**).

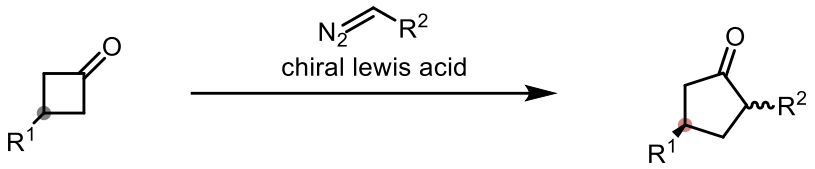
A third method (approach **III**) especially used for Box ligands with an unsubstituted methylene linker is the condensation of a bisimidate dichloride, easily prepared *via Pinner* reaction from a corresponding malononitrile, with an amino alcohol (Scheme 8).[72,82] This method is also used frequently when a more complex modification on the linking methylene unit is desired.[83,84]



Scheme 8: Reaction scheme for condensation of a *Pinner* salt, easily prepared from malononitrile, with a chiral amino alcohol affording the respective Box ligand (approach **III**).

2.1.3 Motivation and aim

As outlined above the enantioselective desymmetrisation of cyclic ketones is a potent strategy for the synthesis of chiral cyclic ketones of different ring sizes and substitution patterns. Taking the long history of research on ring expansions of cyclic ketones into account, it is remarkable that the asymmetric one-carbon ring expansion of prochiral CBones was poorly studied, although beneficial through partial release of inherent ring strain. Therefore, it was sought to gain further insight to such method and to develop a corresponding protocol. Considering the literature precedent, it seemed most reasonable to use diazomethane derivatives, further harnessing the entropic driving force of releasing N_2 throughout the reaction. Chiral *Lewis* acid catalysis appeared to be a promising strategy to realise the one-carbon ring expansion of prochiral 3-substituted CBones in asymmetric fashion (Scheme 9). The results on this endeavour are discussed in the following.

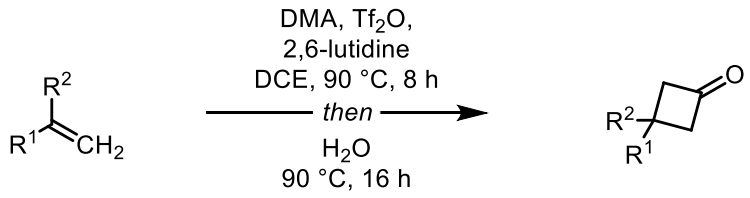


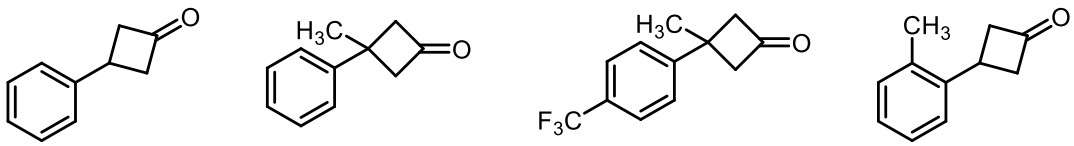
Scheme 9: Reaction scheme for desired enantioselective desymmetrisation of prochiral CBones *via* ring expansion with diazomethanes catalysed by a chiral *Lewis* acid.

2.2 Synthesis of starting materials

2.2.1 Synthesis of prochiral cyclobutanones

Over the course of this study a number of 3-substituted CBones were used for the development of the described synthetic protocol and for the exploration of its substrate scope. Their synthesis was performed according to the methodologies described in chapter 1.3.1 and is therefore only discussed very shortly in the following: The CBones **1** – **4** were obtained *via* [2+2] cycloaddition of dimethyl keteniminium triflate, *in situ* generate from DMA, with the corresponding alkene following a modified procedure of *Chernykh et al.* (Scheme 10).[28]

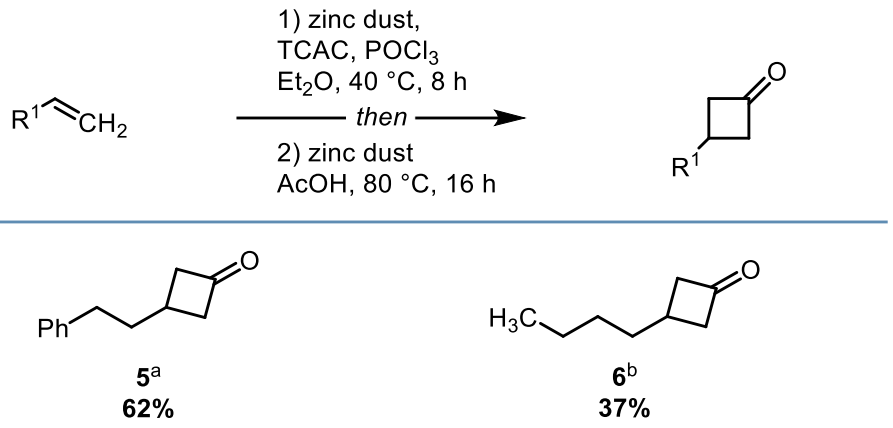




1[a] **78%** | **2**[b] **89%** | **3**[c] **54%** | **4**[c] **71%**

Scheme 10: CBones synthesised for this project *via* [2+2] cycloaddition of a respective alkene with *in situ* generated dimethyl keteniminium triflate. [a] Synthesis performed with slight alterations from shown conditions: 16 h reaction time in the first step and 8 h at 90 °C plus 2.5 d at rt for the second step. [b] Synthesis performed with slight alterations from shown conditions: 16 h reaction time in the first step and 20 h in the second step. [c] Synthesis performed by [redacted]

Furthermore, CBones **5** and **6** were synthesised by thermal [2+2] cycloaddition of the respective alkene with dichloroketene, *in situ* generated from TCAC, followed by zinc mediated dehalogenation according to a modified protocol by *Malkov et al.* (Scheme 11).[24]



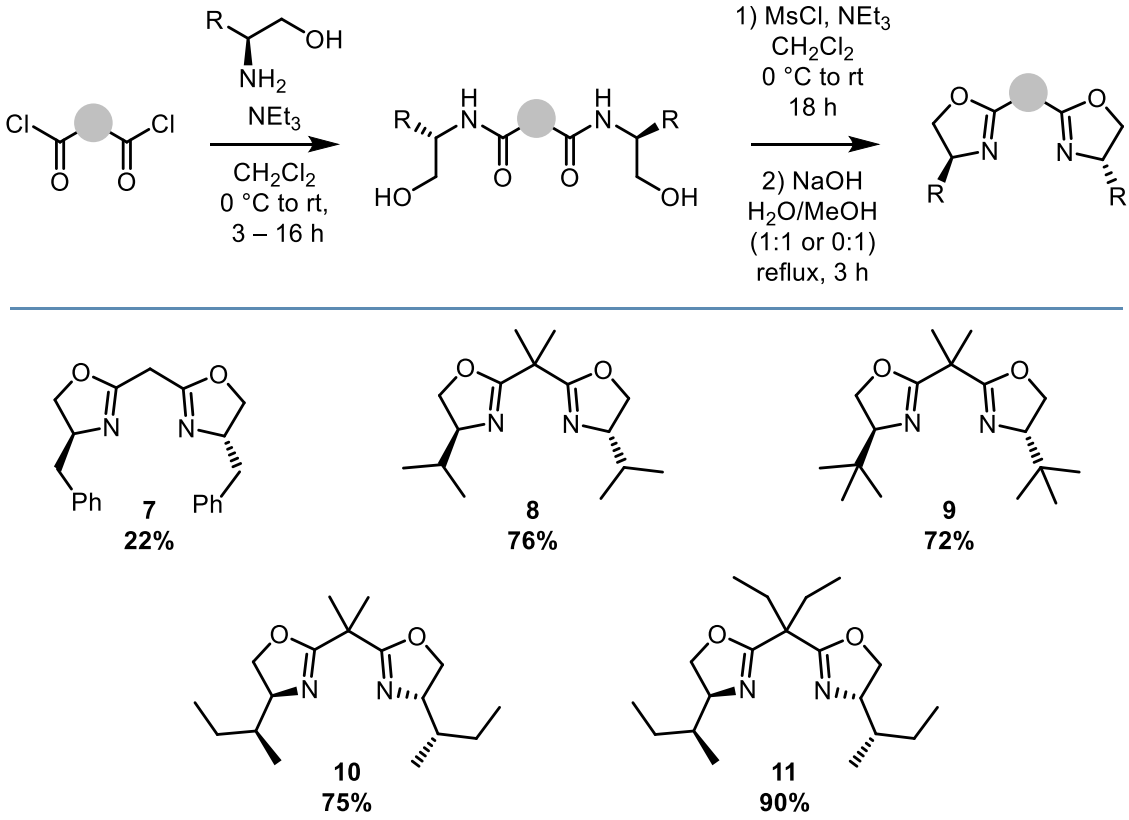
5[a] **62%** **6**[b] **37%**

Scheme 11: CBones synthesised for this project *via* [2+2] cycloaddition of a respective alkene with *in situ* generated dichloroketene. [a] Synthesis performed with slight alterations from shown conditions: Addition of $POCl_3$ was omitted, 3 h reaction time in the first step and 4 h in the second step. [b] Synthesis performed by [redacted]

2.2.2 Synthesis of ligands

During this work, many literature known as well as unknown ligands have been synthesised using several different synthetic approaches. These were applied in the search for a ligand able to facilitate sufficient enantioinduction in the desired transformation. Apart from a few exceptions, belonging to other ligand classes, most of the synthesised ligands were Box ligands:

The Box ligands **7** – **11** were synthesised following approach **I** (*cf.* chapter 2.1.2) in overall good to excellent yield (Scheme 12). In the case of ligand **7** the synthesis of the corresponding acid chloride, malonyl dichloride, failed. Therefore, the respective bis(hydroxy)amide was alternatively obtained *via* standard amide coupling of malonic acid with (*S*)-phenylalaninol.



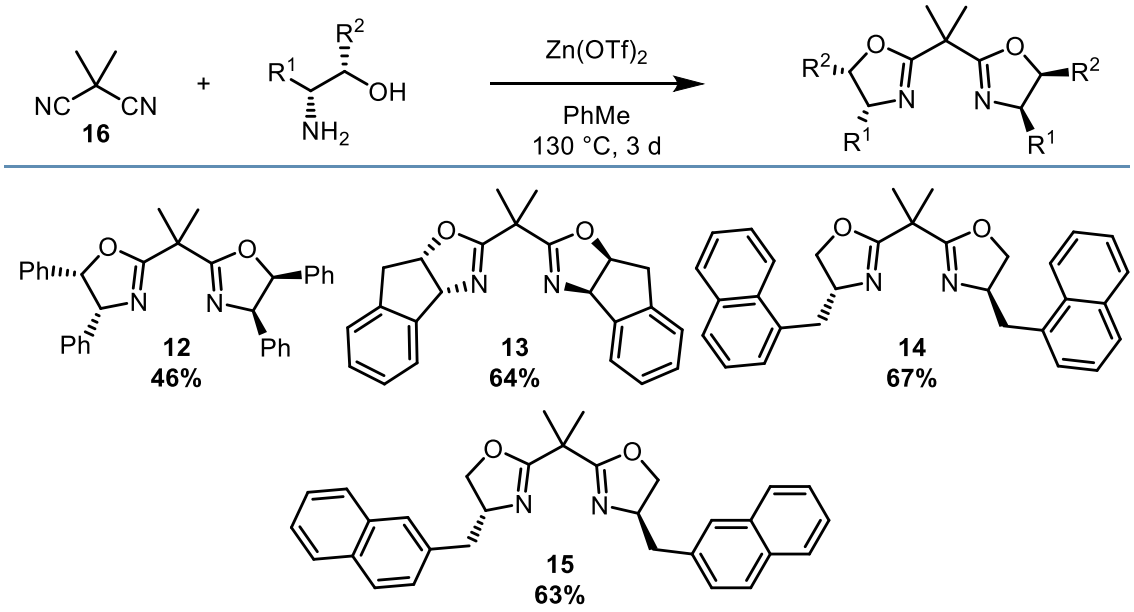
Scheme 12: Box ligands synthesised in this work following synthetic approach **I**, starting with the condensation of a malonyl dichloride with a respective chiral amino alcohol. The resulting bis(hydroxy)amide is then mesylated and subsequently cyclised under basic conditions in a one-pot procedure. Yields given over the two steps. [a] Yield of the second step.

The activation of the hydroxy groups of the bis(hydroxy)amides is usually achieved *via* tosylation with *para*-tosyl chloride (*p*-TsCl), according to literature.[62–64] Over the course of this work the use of *p*-TsCl in this step often led to unsatisfactory results, usually incomplete conversion towards the Box ligands. The respective monocyclised product was observed in the crude reaction mixture in some cases. These issues may result from weak activity of the used *p*-TsCl causing incomplete tosylation of the bis(hydroxy)amides. However, it was found that substituting *p*-TsCl with mesyl chloride (MsCl), even though way less frequently used in literature, led to complete conversion towards the Box ligand for all derivatives synthesised over this synthetic route.

The issues when using *p*-TsCl for activation of the bis(hydroxy)amides especially during an early stage of this work also encouraged a deepened examination on the possibilities of the isolation of the synthesised ligands from the reaction mixtures. Although literature often claims to isolate the Box ligands *via* silica column chromatography, this method was often rather ineffective, required several attempts or even failed completely. A possible explanation might be the high dependency on the

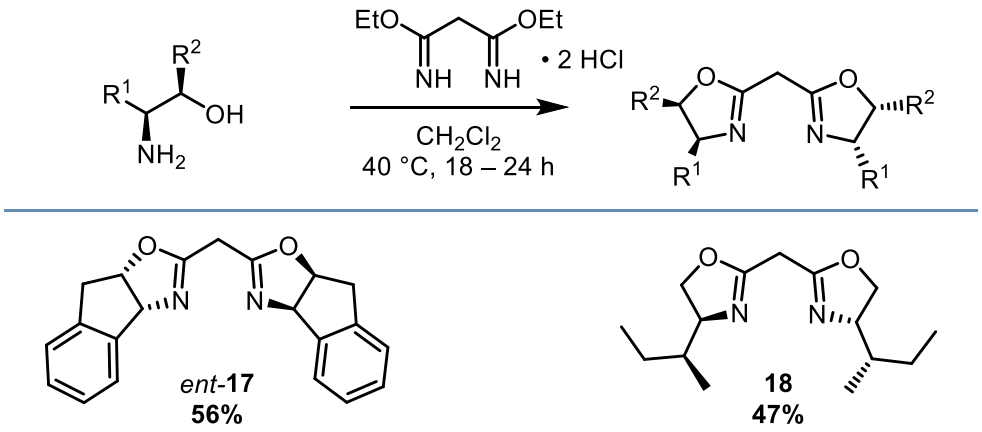
specific characteristics of the silica used. For example, the pH of the employed silica might strongly influence the retention of Box ligands due to their two *Lewis* basic nitrogen atoms, resulting in poor separation of by-products and reactants. However, it was found that for Box ligands appearing as oils Kugelrohr-distillation was the method of choice. For ligands appearing as solids or thick resins recrystallisation or crystallisation from solvent mixtures proved effective for their isolation. Further, when using MsCl for activation of the bis(hydroxy)amide, the desired ligands were obtained in high purity after aqueous work up, eliminating the need for additional purification steps.

Following approach **II,** the Box ligands **12** – **15** were synthesised *via* zinc(II) triflate mediated condensation of dimethyl malononitrile (**16**) with the corresponding amino alcohol (Scheme 13). In the case of ligands **14** and **15**, these were obtained by reduction of the respective commercially available amino acids with $LiAlH_4$.



Scheme 13: Box ligands synthesised in this work *via* zinc(II) triflate mediated condensation of nitrile **16** with the respective amino alcohols (approach **II**).

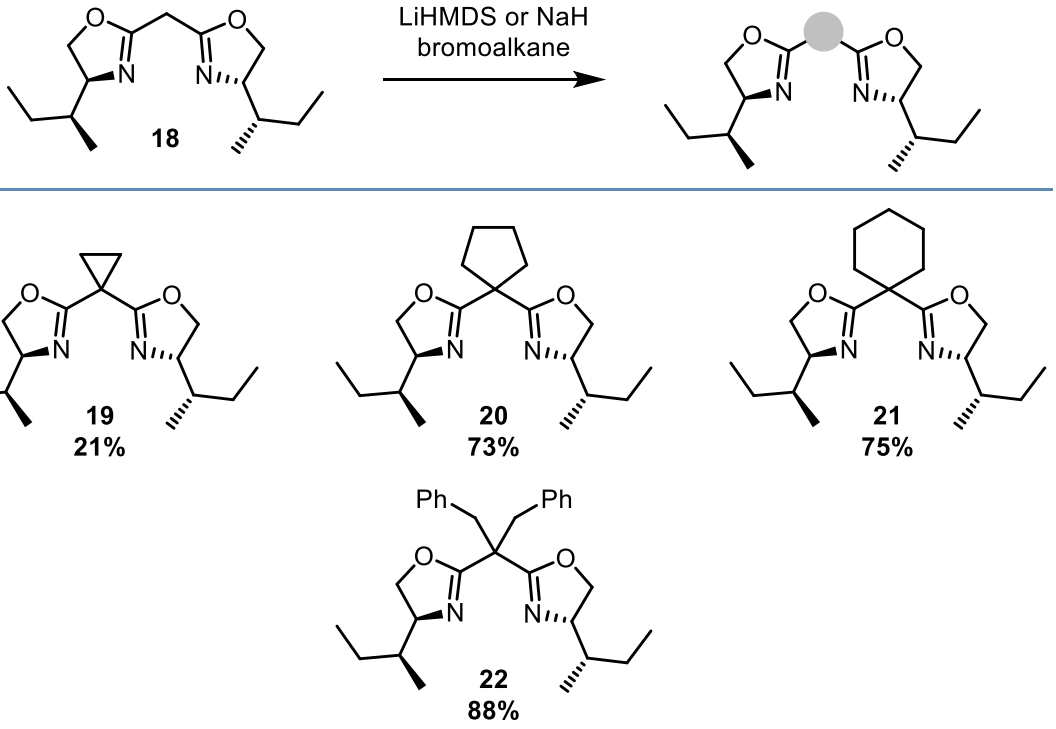
Furthermore, synthetic approach **III** was employed for the synthesis of Box ligands *ent*-**17** and **18.** The condensation of the corresponding amino alcohols with diethyl malonimidate dihydrochloride affording the desired ligands in moderate yield in a single step (Scheme 14).



Scheme 14: Synthesis of Box ligands *ent*-**17** and **18** using diethyl malonimidate dihydrochloride according to approach **III**.

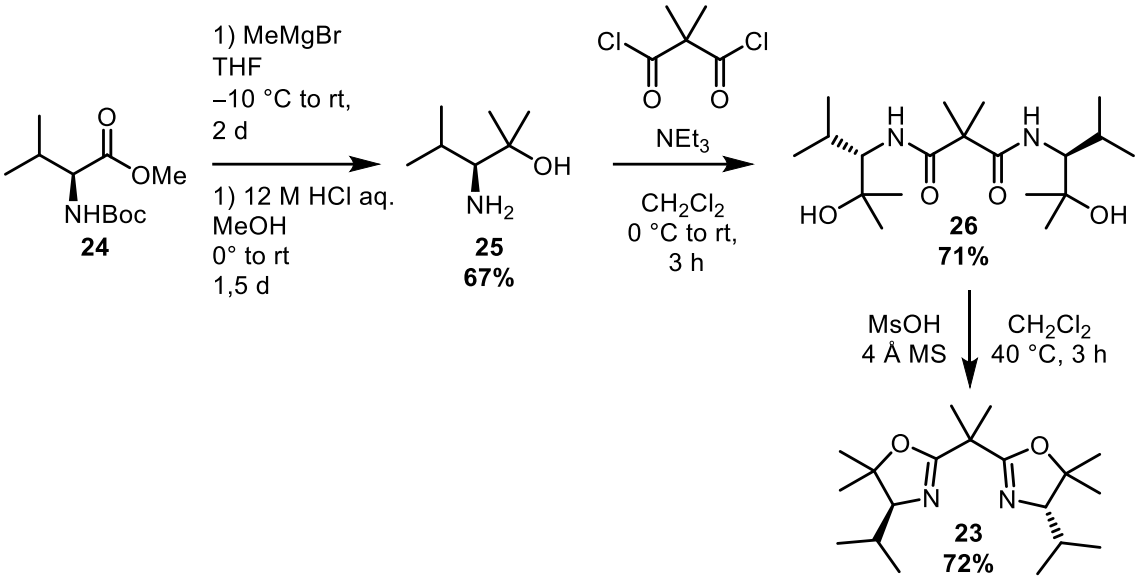
The single step synthesis of ligands *ent*-**17** and **18** was desirable, as both ligands were used as intermediates for the synthesis of other ligands with modifications on the linking methylene unit (*vide infra*).

Moreover, Box ligands **19** – **22** were synthesised *via* post-modification of the linking methylene unit of ligand **18**. Two different literature protocols were adapted for this purpose. Ligand **19** was synthesised following a slightly modified procedure by *Hofstra et al.*,[85] affording the desired ligand in a low yield. For the synthesis of ligands **20** – **22** a protocol by *Barnes et al.*[86] was adapted. Those ligands were isolated in overall good yields (Scheme 15).



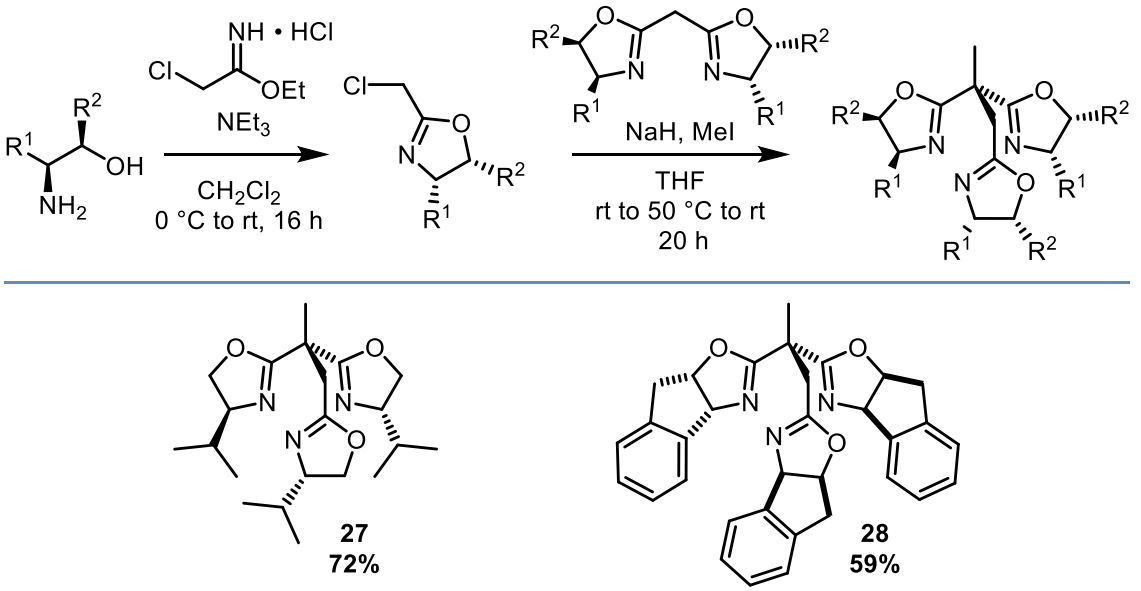
Scheme 15: Box ligands synthesised in this work *via* post-modification of the linking methylene unit of ligand **18**.

As another Box derivative, 5,5-dimethyl substituted Box ligand **23** was prepared over four steps from commercially available *N*-Boc-valine methyl ester (**24**). Doubled *Grignard* addition followed by Boc-deprotection afforded amino alcohol **25**, which was converted to bis(hydroxy)amide **26** using standard conditions. Ligand **23** was then obtained by dehydration under strongly acidic conditions (Scheme 16).



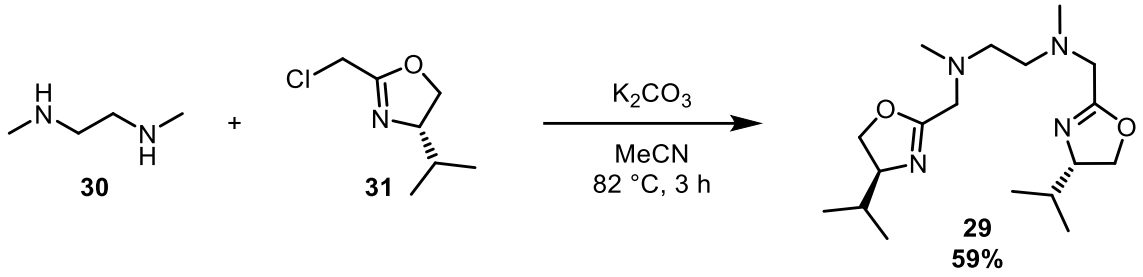
Scheme 16: Reaction scheme for the synthesis of ligand **23** starting from *N*-Boc-valine methyl ester (**24**).

Besides the previously discussed Box ligands, other ligands have been synthesised over the course of this work as well. The two trisox ligands **27** and **28** were obtained in good and moderate yield, respectively, by adapting procedures by *Snyder et al.*,[87] *Ye et al.*,[88] and *Rendina et al.* (Scheme 17).[51]



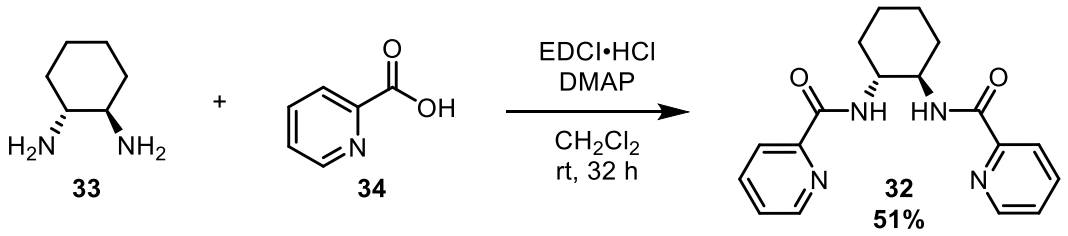
Scheme 17: Synthesis of trisox ligands **27** and **28** *via* subsequent alkylation of the corresponding Box ligand with methyl iodide and a respective chloromethyl oxazoline.

Furthermore, another oxazoline-based tetradentate bis(oxazolin-2-ylmethyl)ethane-1,2-diamine (bomen) ligand **29** was synthesised in moderate yield *via* alkylation of dimethyl ethylenediamine (**30**) with previously synthesised chloromethyl oxazoline **31** according to a procedure by *Guillemot et al.* (Scheme 18).[89]



Scheme 18: Reaction scheme for the synthesis of ligand **29** from amine **30** and oxazoline **31**.

Additionally, *Trost*-ligand **32** was obtained *via* amide coupling of cyclohexyl diamine **33** and 2-picolinic acid (**34**) in a moderate yield (Scheme 19).



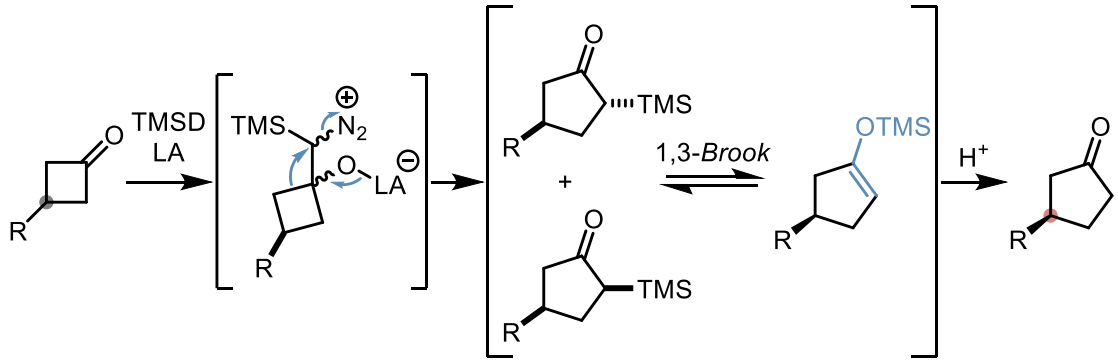
Scheme 19: Reaction scheme for the synthesis of *Trost*-ligand **32** from diamine **33** and picolinic acid (**34**).

Regarding the storage and stability of the synthesised ligands it was found that the shelf time of Box ligands is limited when stored in a regular laboratory cupboard at room temperature under air. For some examples partly or even complete hydrolysis to the corresponding bis(hydroxy)amide was observed. However, degradation over time was not observed for batches that were dried over P_2O_5 and subsequently stored under inert atmosphere in a glovebox.

2.3 Reaction development and substrate scope

As a starting point for the development of the desired method (*cf.* chapter 2.1.3) trimethylsilyl diazomethane (TMSD) was chosen as nucleophile for the initial optimisation of reaction conditions. It was envisioned that TMSD as commercially available and easy to handle diazomethane would be a potent one-carbon synthon for α-insertion into a prochiral CBone. The initial nucleophilic attack promoted by a respective *Lewis* acid would thereby form an isomeric mixture, which can then undergo ring expansion driven by the release of N_2 as well as large parts of the inherent ring

strain. It was anticipated that the close proximity of the *Lewis* acid during these steps would enable enantioinduction, when a chiral *Lewis* acid, e.g., by complexation with a chiral ligand, is employed. As a result, the corresponding α-silylated CPone would be generated, potentially as a diastereomeric mixture. The latter are known to undergo rapid 1,3-*Brook* rearrangement under strongly *Lewis* acidic conditions, which would form a silyl enol ether.[50,90] With the associated loss of the α-stereocentre, an enantiomeric mixture of the desired β-substituted CPone would be achieved after hydrolysis. The CPone would thereby be prevented from undergoing consecutive ring expansions rendering the TMSD not only a one-carbon synthon but further a traceless protecting agent (Scheme 20).

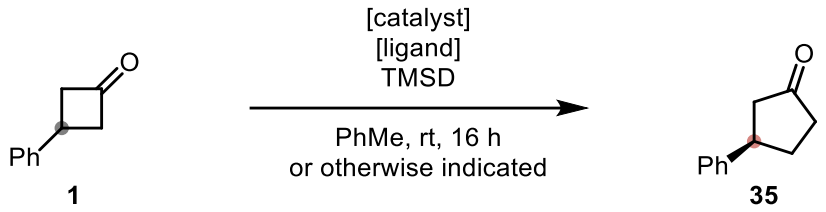


Scheme 20: Envisioned strategy for the ring expansion of 3-substituted CBones with TMSD employing a chiral *Lewis* acid (LA).

For the optimisation of reaction conditions and the search for a potent *Lewis* acid, catalyst 3-phenyl CBone (**1**) was chosen as model substrate. Initially, several different *Lewis* acids were tested for activity in the reaction of CBone **1** with TMSD in toluene at room temperature (Table 1). While *Lewis* acids like zinc(II), copper(II) or magnesium(II) triflate were not able to facilitate the reaction (entries 1–3), the use of scandium(III) or hafnium(IV) triflate furnished the desired product **35** (entries 4–5). In terms of yield Scandium was clearly superior, which directly prompted working on a proof of concept for the desired enantioinduction. This was achieved by the use of the commercially available Box ligands **36** (entry 6) and **37** (entry 7) resulting in the formation of CPone **35** in a low *er* of 40:60 in the case of ligand **37** (Figure 13). The use of this ligand for hafnium(IV) did not result in any improvement (entry 8). Chiral aluminium- and boron-based catalyst systems were investigated as well to validate whether scandium was the catalyst of choice for further optimisation of the enantioinduction. The use of (salen)AlCl was not productive (entry 9) while employing *Maruoka's* catalyst system consisting of trimethyl aluminium complexed with 3,3'-TMS-BINOL **38** resulted in comparable yield and slightly lower *er*

compared to using the scandium-Box complex (entry 10).[2] However, this result was achieved already at a decreased reaction temperature. Compared to the similar results obtained with the chiral scandium complex, this approach was therefore less promising for the further optimisation towards better enantioinduction. Furthermore, chiral oxazoborolidinium ion **39** was tested showing inferior performance in yield and *er* (entry 11).

Table 1: Initial catalyst screening for the ring expansion of CBone **1** with TMSD.



Entry	Catalyst system	Change to conditions	NMR yield	Yield	*er*
1[a]	$Zn(OTf)_2$	-	-	-	-
2[a]	$Cu(OTf)_2$	-	-	-	-
3	$Mg(OTf)_2$	-	-	-	-
4[a]	$Sc(OTf)_3$	-	78%	69%	-
5	$Hf(OTf)_4$	-	51%	n.d.	-
6[a]	(Box **36**)Sc(III)	-	n.d.	40%	52:48
7	(Box **37**)Sc(III)	-	74%	69%	40:60
8	(Box **37**)Hf(IV)	-	70%	69%	49:51
9	(Salen)AlCl	20 mol% cat	<2%	n.d.	-
10[b]	(BINOL **38**)AlMe	40 mol% cat, 20 mol% Ligand, −78 °C, 48 h	79%	67%	58:42
11[a]	chiral oxazaborolidinium ion **39**[c]	−78 °C to rt	43%	n.d.	53:47

Reactions run on 0.1 mmol scale in dry solvent (0.1 M) under inert atmosphere using 10 mol% catalyst, 10 – 15 mol% ligand and 1.1 – 1.5 eq. TMSD. NMR yields determined *via* ^{1}H NMR using mesitylene as internal standard. *er* determined *via* HPLC using chiral stationary phases. [a] Reaction performed by [redacted] [b] Ligand synthesis and reaction performed by [redacted] [c] (*S*)-(−)-*o*-Tolyl-CBS-oxazaborolidinium bistriflimde, prepared by [redacted] according to a literature procedure.[53]

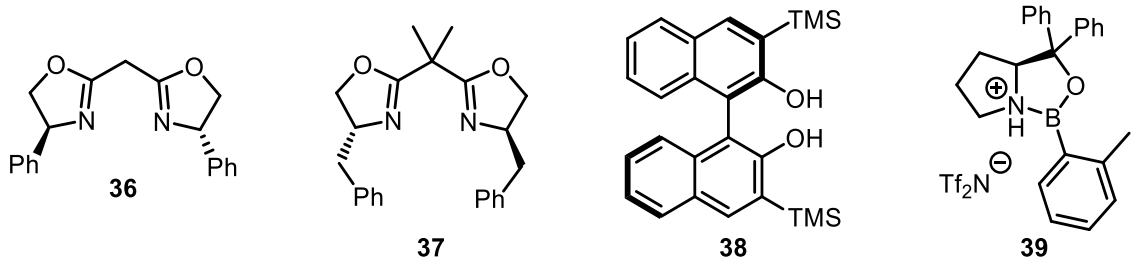


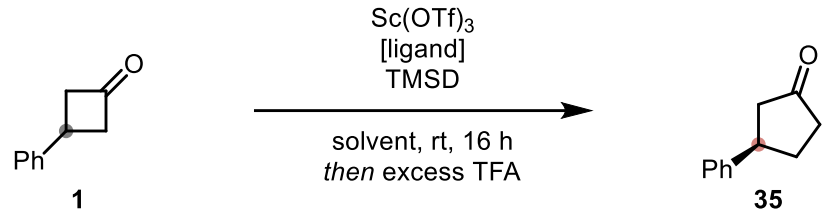
Figure 13: Structures of compounds **36** – **39** used during the initial catalyst screening.

Before profound studies on the optimisation of the employed ligand motif and their specific properties were undertaken, the impact of the solvent on the reaction

[2] Synthesis of ligand **38** and the respective reaction were performed by [redacted]

outcome was briefly elucidated (Table 2). Changing the solvent from toluene (entry 1) to *n*-heptane resulted in a significant drop in yield while an only minorly decreased *er* of 58:42 was measured (entry 2). Additionally, poor solubility of Box ligand and $Sc(OTf)_3$ was observed in this case. The use of more polar solvents like ethyl acetate (EtOAc) or tetrahydrofuran (THF) resulted in rather similar yields compared to when using toluene although the *er* further dropped (entries 3 and 4). It was therefore chosen to use toluene as solvent for the continued optimisation of the reaction conditions. At a later stage of the study using a revised ligand, it was also found that dichloromethane is an appropriate solvent as well, showing identical results to toluene.

Table 2: Solvent screening for the scandium(III) catalysed ring expansion of CBone **1** with TMSD.



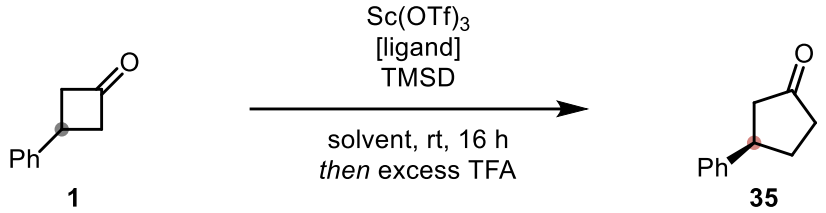
Entry	Ligand	Solvent	NMR yield	Yield	*er*
1	Box **37**	PhMe	80%	77%	40:60
2	Box **37**	*n*-Heptane	n.d.	60%	42:58
3	Box **37**	EtOAc	82%	75%	45:55
4	Box **37**	THF	83%	77%	48:52

Reactions run on 0.1 mmol scale in dry solvent (0.1 M) under inert atmosphere using 10 mol% catalyst, 11 mol% ligand and 1.1 eq. TMSD. NMR yields determined *via* ^{1}H NMR using mesitylene as internal standard. *er* determined *via* HPLC using chiral stationary phases.

The reaction parameters effecting enantioinduction were successively investigated while performing the reaction at room temperature to facilitate operational simplicity. Elucidation of the impact of reaction temperature for maximised enantiofacial discrimination of the two enantiotopic faces of the substrate was performed at a later stage of the study (*vide infra*). It was sought to find a ligand for scandium(III) more potent than Box **37** for enantioinduction in the desired transformation of CBone **1** towards CPone **35**. In an early stage of this search for an appropriate ligand several, different ligand motifs were tested (Table 3, Figure 14 & Figure 15). The use of other oxazoline-based ligand motifs such as BiOx **40**, PyBox **41**, BiPyBox **42**, bomen **29**, DBFox **43** or BoxAx **44** did not result in any considerable enantioinduction throughout the reaction (entries 1 – 6). Moreover, *Trost*-ligand **32**, *Feng's* N,N'-dioxide ligand **45**, salen ligand **46** as well as (*R*)-BINOL (**47**) or (+)-sparteine (**48**) proved ineffective for enantiofacial discrimination in the ring expansion of CBone **1**

using $Sc(OTf)_3$ as catalyst (entries 7 – 11). It was further observed that ligands containing a pyridine moiety or tertiary amines significantly reduced the catalytic activity resulting in decreased yield of product **35** in the model reaction compared to the initial result of the proof-of-concept.

Table 3: Ligand motif screening for the scandium(III) catalysed asymmetric ring expansion of CBone **1** towards CPone **35**.



Entry	Ligand	Yield	*er*	Entry	Ligand	Yield	*er*
1	BiOx **40**	77%	51:49	**7**	*Trost*-ligand **32**	n.d.	51:49
2	PyBox **41**	52%	52:48	**8**	N,N'-Dioxide **45**	69%	50:50
3	BiPyBox **42**	41%	50:50	**9**	Salen **46**	n.d.	51:49
4	Bomen **29**	29%	51:49	**10**	(*R*)-BINOL (**47**)	71%	50:50
5	DBFox **43**	74%	51:49	**11**	(+)-sparteine (**48**)	76%	51:49
6	BoxAx **44**	77%	50:50				

Reactions run on 0.1 mmol scale in dry toluene (0.1 M) under inert atmosphere using 10 mol% catalyst, 15 mol% ligand and 1.1 eq. TMSD. *er* determined *via* HPLC using chiral stationary phases.

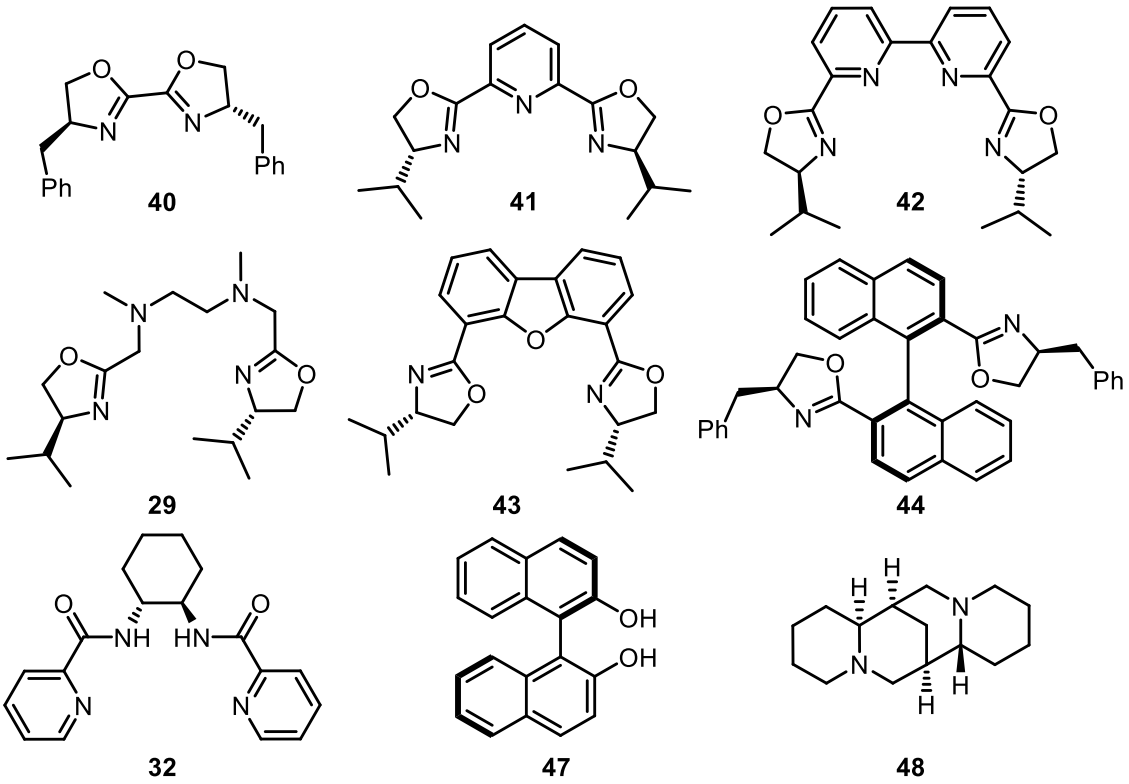


Figure 14: Structure of ligands tested during the ligand motif screening (part 1).

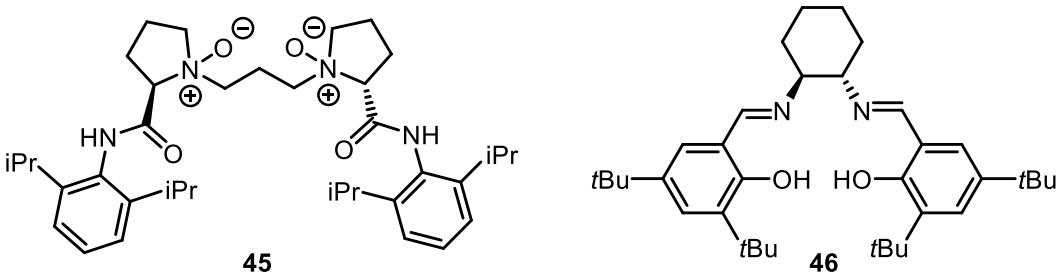


Figure 15: Structure of ligands tested during the ligand motif screening (part 2).

Since solely the Box motif facilitated any enantioinduction in the scandium(III) catalysed ring expansion of CBone **1** with TMSD, the structural properties of the Box ligand were successively varied to investigate their impact on the reaction outcome. A variety of Box ligands was tested in the model reaction under variation of their substituents R^1 and R^2 as well as the linking methylene unit (Table 4, Figure 17; for general structure see chapter 2.1.2, Figure 12). Taking the result from proof-of-concept using Box ligand **37** with an *er* of 40:60 as a reference point (entry 1), it was found that the nature of the linking unit was crucial for achieving enantioinduction in the first place. Using ligand **7** bearing a methylene unit as linker, a noticeable drop in *er* was observed (entry 2). Similar results were also found for Box ligands bearing other substituents R^1 and R^2 while the linker was a CH_2 unit. The indanyl substituted ligand *ent*-**17** and 4-*sec*-butyl Box ligand **18** both showed decreased *er*s (entry 3 and 4, respectively) compared to their corresponding derivatives bearing a dimethyl substituted linking unit (entry 8 and 14, respectively; *vide infra*). These results strongly suggest that the *Thorpe-Ingold* effect of a *gem*-dialkyl group in the linking unit is necessary for achieving significant enantioinduction. The latter could be rationalised by the need for a certain bite angle of the ligand or the associated ligand-metal distance to form a chiral pocket appropriate for the desired transformation.

Scandium(III) is known to form complexes with coordination numbers between three and nine.[91] However, only a very limited number of scandium(III) complexes bearing oxazoline-based ligands have been characterised on the basis of a crystal structure.[92] For scandium complexes bearing PyBox ligands a pentagonal bipyramidal geometry was observed by *Evans et al*.[93] It is therefore assumed that a Sc(III)-Box complex would possess a bipyramidal geometry as well, thus forming a chiral pocket with the large Box ligand in the equatorial plane and the substrate coordinated in the axial position (Figure 16).

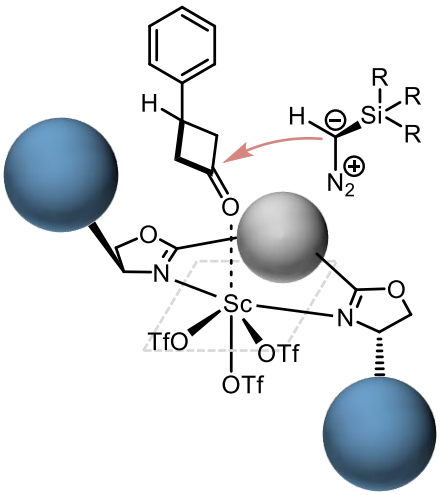


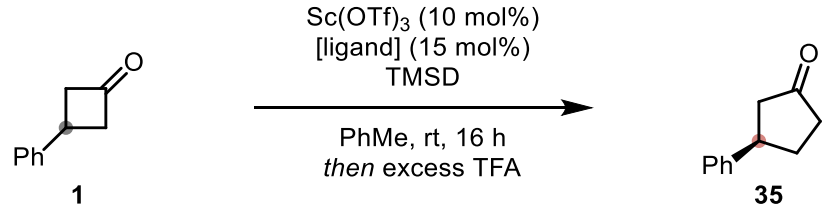
Figure 16: Schematised representation of a potential chiral pocket formed by a respective Box ligand coordinating the scandium centre.

It was anticipated that not only steric repulsion, but also π-π-interactions between ligand and substrate were important effects impacting the facial discrimination throughout the reaction. Therefore, several Box derivatives bearing aryl substituents were investigated. A 4-phenyl substitution instead of 4-benzyl was found to be deleterious resulting in the formation of almost racemic product (ligands **49** and **36**, entries 5 and 6, respectively). Additionally, 4,5-*syn*-diphenyl substituted Box ligand **12** was also not able to facilitate greater enantioinduction as again formation of almost racemic product was observed (entry 7). The more rigid indanyl substituted ligand **13** showed similar enantioinduction to ligand **37** furnishing the product in an *er* of 58:42 (entry 8). Furthermore, the two naphthyl substituted ligands **14** and **15** were investigated. While 1-naphthyl substituted ligand **14** was inferior, the use of 2-naphthyl substituted Box ligand **15** showed minorly improved results affording the desired product in 39:61 *er* (entries 9 and 10, respectively).

As no indication for anticipated importance of π-π-interactions for the enantioinduction was found, it was then sought to vary the steric bulk in the 4-position of the Box ligands using different alkyl substituents. The use of 4-isopropyl substituted Box **8** already resulted in a slight improvement with the product isolated in 63:37 *er* (entry 11). Introduction of an additional *gem*-dimethyl group in 3-position seemed to have no effect on the enantioinduction (ligand **23**, entry 12). Interestingly, when increasing the steric bulk further employing 4-*tert*-butyl substituted ligand **9** the product was furnished in significantly decreased *er* (entry 13). This could be attributed to a hindered complexation of the scandium cation with the ligand, resulting in uncomplexed $Sc(OTf)_3$ catalysing a racemic background reaction. Another plausible explanation would be the blocking of the favoured axial coordination side on the scandium centre by the ligand, leading to an equatorial coordination of the substrate facing away from the chiral pocket (*cf.* Figure 16). Therefore, a ligand with less bulk in close proximity to the metal centre but reaching more into the width of the ligand was anticipated to be beneficial. Employment of 4-*sec*-butyl substituted ligand **10** resulted in further improvement affording the product in 64:36 *er* (entry

14). The use of Box ligand **50** bearing even broader 4-heptyl substituents interestingly showed no further improvement as the product was isolated in a decreased *er* of 55:45 (entry 15).[3] It was then attempted to further optimise the so far best performing ligand **10** by modification of the linker and thereby changing the steric bulk in this part of the ligand as well as varying the bite-angle of the ligand. Further improvement was found when a diethyl substituted linking unit was installed. Utilisation of the corresponding Ligand **11** afforded CPone **35** in 88% yield and an *er* of 67:33 resembling the best result achieved under the given model conditions (entry 16). Further increase of the steric bulk at the spacer as well as variation of the bite-angle *via* a respective cycloalkyl substitution on the linking unit with ligands **19** – **22** was not effective showing identical or inferior results (entries 17 – 20). It was further anticipated that the formation of a more closed rigid chiral pocket could be important to achieve high amounts of enantioinduction throughout the reaction as both, substrate and nucleophile, are comparably small molecules. Furthermore, enantioinduction is desired in the distal position of the substrate, most likely facing away from the chiral centre. Therefore, trisox **27** and **28** were tested but did not lead to the desired success (entries 21 and 22, respectively).

Table 4: Result of the performed ligand screening for the ring expansion of CBone **1** with TMSD.



1 **35**

Entry	Ligand	Yield	*er*	Entry	Ligand	Yield	*er*
1	**37**	77%	40:60	**12**	**23**	87%	62:38
2	**7**	53%	47:53	**13**	**9**	78%	52:48
3	*ent*-**17**	88%	51:49	**14**	**10**	72%	64:36
4	**18**	40%	56:44	**15**[a]	**50**	75%	55:45
5	**49**	76%	51:49	**16**	**11**	88%	67:33
6	**36**	n.d.	52:48	**17**	**22**	81%	67:33
7	**12**	53%	53:47	**18**	**19**	87%	62:38
8	**13**	78%	58:42	**19**	**20**	81%	62:38
9	**14**	81%	46:54	**20**	**21**	78%	63:37
10	**15**	75%	39:61	**21**	**27**	71%	61:39
11	**8**	76%	63:37	**22**	**28**	49%	52:48

Reactions run on 0.1 mmol scale in dry toluene (0.1 M) under inert atmosphere using 10 mol% catalyst, 15 mol% ligand and 1.1 or 1.3 eq. TMSD. *er* determined *via* HPLC using chiral stationary phases. [a] Ligand synthesised by [redacted]

[3] Ligand **50** was synthesised by [redacted] [94].

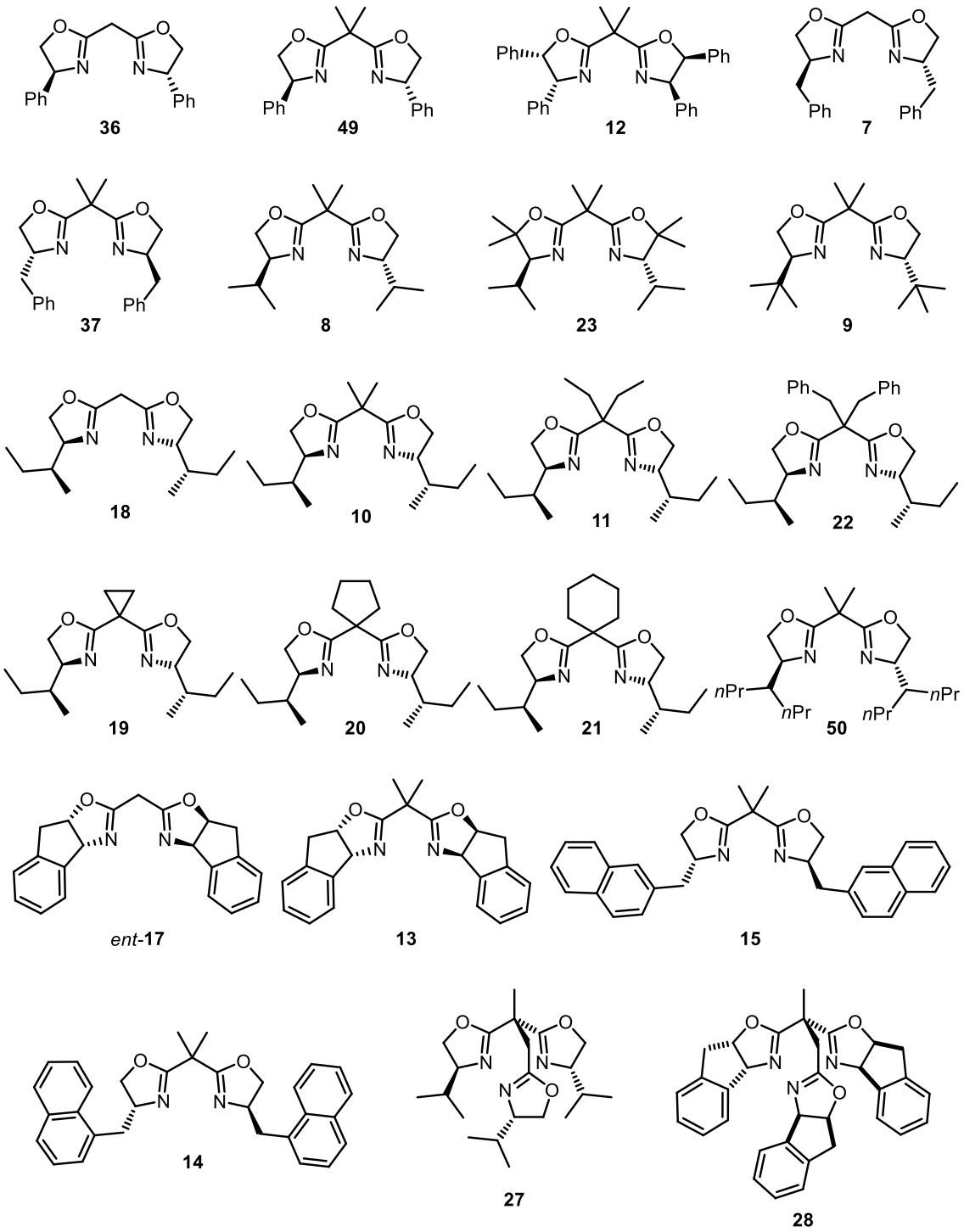


Figure 17: Structure of the ligands elucidated during the continued ligand screening.

During the above describe ligand evolution it became attentive that *Rendina* and *Kingsbury* described high dependency of achieving reproducibly high enantioinduction to the water content of their related ring expansion of cyclohexanones (*cf.* chapter 2.1.1).[51,95] To eliminate the possibility of residual water being an issue as far as possible, the used $Sc(OTf)_3$ as well as all ligands were rigorously dried over P_2O_5 under high vacuum and elevated temperatures, in addition to using dry solvent

under inert atmosphere as before. However, even in direct comparison, no noticeable differences were observed for the reaction described herein.

It was further observed that the reaction time could be reduced to one hour with no loss in yield when using Box ligand **37**. Nevertheless, the standard reaction time was kept at 16 h during optimisation of reaction conditions to ensure sufficient conversion even with potential reduced reaction rate due to the properties of a respective ligand.

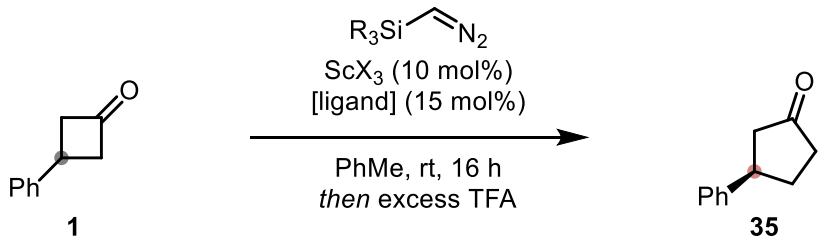
When it was realised that the evolution of the used ligand alone is most likely not sufficient to achieve high amounts of enantioinduction in the ring expansion of CBone **1** with TMSD catalysed by a chiral scandium(III) complex, simultaneous studies were directed towards the properties of the nucleophile as well as the impact of the reaction temperature.

It was envisioned that a larger nucleophile should facilitate the enantiofacial discrimination, thus suggesting that more bulky silyl diazomethanes might be promising derivatives. Subsequently, dimethylphenylsilyl diazomethane (DMPSD) and methyldiphenylsilyl diazomethane (MDPSD) were synthesised according to literature procedures,[56] and elucidated as nucleophiles in the desired transformation using Box Ligand **8** as a reference (Table 5). Utilisation of DMPSD resulted in isolation of the desired product in identical *er* although in higher yield (entry 2) compared to the use of TMSD (entry 1). A slightly increased *er* of 65:35 was observed when MDPSD was used (entry 3). Now, more potent ligand **11** was employed while using MDPSD as nucleophile affording the product in noticeably increased *er* of 70:30 (entry 4).

Furthermore, the impact of the reaction temperature on the enantioinduction was investigated briefly. Running the reaction at −78 °C using ligand **11** and TMSD as nucleophile a significant increase in *er* of the isolated product to 76:24 was observed, as expected, compared to running the reaction at room temperature (entry 5). Due to reduced reactivity at low temperature, prolongation of the reaction time was necessary to achieve sufficient conversion. When ligand **11** was used in combination with bulky MDPSD at −78 °C, the *er* of the desired product could even be increased to 85:15 at a slightly reduced yield of 62% (entry 6). Moreover, scandium salts with different counterions were investigated in combination with ligand **11** at room temperature. While $Sc(hfac)_3$ led to inferior results regarding the observed *er*

of the product, the use of $Sc(NTf_2)_3$ resulted in complete loss of catalytic activity (entries 7 and 8).

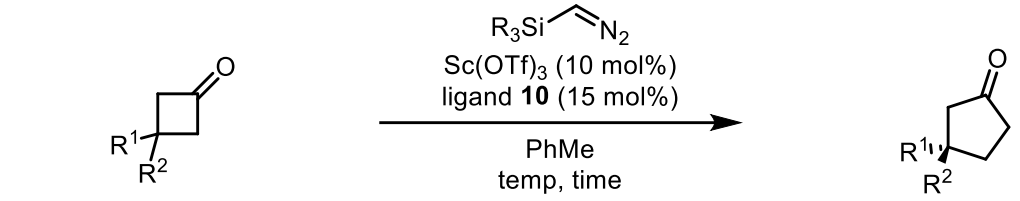
Table 5: Continued optimisation of reaction condition.

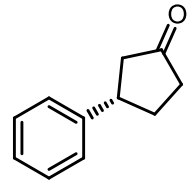


Entry	X	Ligand	Silyl diazomethane	Changes from standard	Yield	*er*
1	OTf	**8**	TMSD		76%	63:37
2	OTf	**8**	DMPSD		81%	63:37
3	OTf	**8**	MDPSD		89%	65:35
4	OTf	**11**	MDPSD		94%	70:30
5	OTf	**11**	TMSD	−78 °C, 24 h	87%	76:24
6	OTf	**11**	MDPSD	−78 °C, 24 h	62%	85:15
7	hfac	**11**	MDPSD		87%	60:40
8	NTf_2	**11**	TMSD		-	-

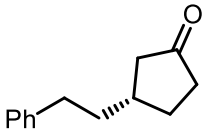
Reactions run on 0.1 mmol scale in dry solvent (0.1 M) under inert atmosphere using 10 mol% catalyst, 15 mol% ligand and 1.3 eq. silyl diazomethane. *er* determined *via* HPLC using chiral stationary phases.

Having found conditions able to at least facilitate the desired transformation with moderate *er*, it was then sought to briefly explore the substrate scope of the method (Scheme 21). It became apparent that some substrates behaved quite differently from model substrate **1** in terms of yield and selectivity. In order to still be able to compare the observed yields and enantioselectivities, the reaction conditions were adapted where the optimised condition (protocol **A**) led to insufficient reactivity. Employing either TMSD instead of MDPSD (protocol **B**) or running the reaction at room temperature instead of at −78 °C (protocol **C**) yields in an acceptable range were obtained, albeit often at the cost of lower enantioselectivity.

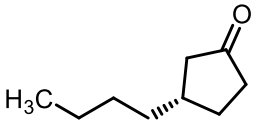




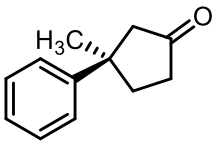
35
A: 62%, *er* 85:15
B: 87%, *er* 76:24
C: 94%, *er* 70:30



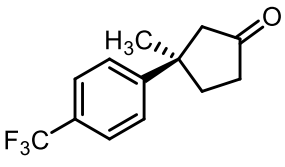
51
A: 40%, *er* 88:12
B: 80%, *er* 83:17



52
A: 29%, *er* 82:18
B: 71%, *er* 82:18

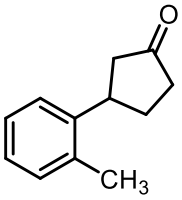


55
A: (**4%**), *er* –:–
B: 63%, *er* 63:37
C: 86%, *er* 53:47



56

B: 29%, *er* 59:41

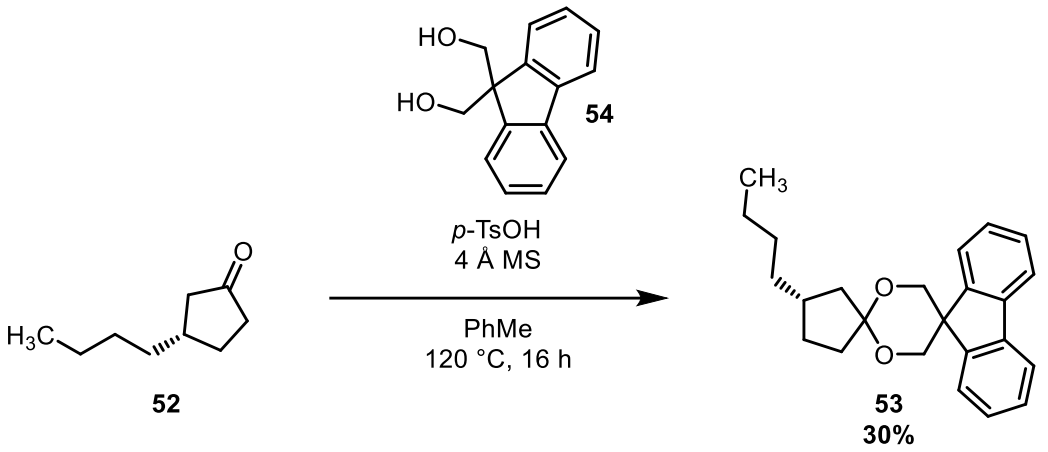


57
A: (**0%**), *er* –:–
B: 34%, *er* 49:51
C: 57%, *er* 49:51

Scheme 21: Explored substrate scope for the asymmetric ring expansion of prochiral CBone with silyl diazomethanes. Reactions were run at 0.1 mmol scale using 10 mol% catalyst, 15 mol% ligand and 1.3 eq. diazomethane in dry toluene (0.1 M). NMR yields are given in brackets and were determined *via* ^{1}H NMR analysis of the crude reaction mixture using mesitylene as internal standard. *er* determined by HPLC using chiral stationary phases (see chapter 5 for specific conditions). Absolute configuration assigned according to literature where possible (see chapter 5).

Firstly, 3-alkyl substitution was investigated. 3-Phenethylen substituted CBone **5** furnished the respective CPone **51** in moderate yield of 40% but in higher *er* of 88:12, compared to the model substrate, when using protocol **A**. In order to achieve a higher yield, protocol **B** was tested as well, affording CPone **51** in 80% yield and slightly decrease *er* of 83:17. For 3-*n*-butyl CBone (**6**) the corresponding CPone **52** was obtained in moderate *er* of 82:18 but low yield of 29% under the optimised conditions. Using protocol **B**, a significantly increased yield of 71% and, interestingly, identical *er* was afforded for this substrate. As CPone **52** itself is hardly UV/Vis-active the determination of the *er* was not possible directly by the means of chiral HPLC-UV/Vis spectroscopy. Thus, CPone **52** was derivatised to its (9*H*-fluorene-9,9-diyl)dimethanol ketal **53** to achieve a detectable analyte. Diol **54** was therefore

prepared from fluorene and paraformaldehyde and subsequently condensed to CPone **52** under acidic conditions yielding ketal **53** (Scheme 22).



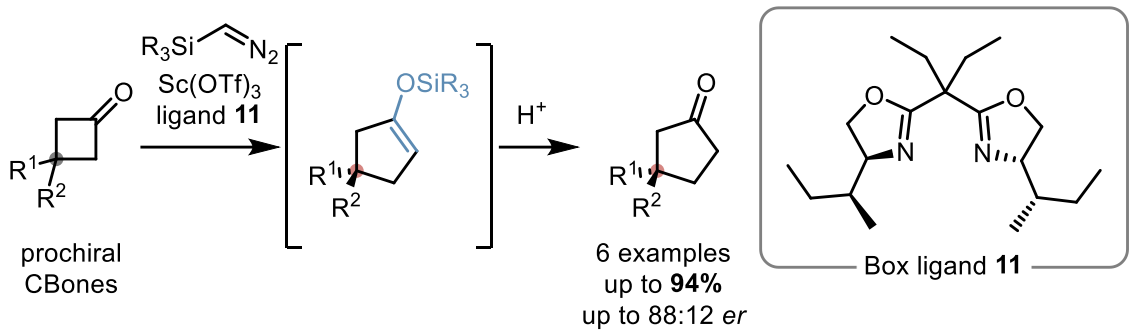
Scheme 22: Derivatisation of CPone **52** to its (9*H*-fluorene-9,9-diyl)dimethanol ketal **53** for the purpose of determination of the *er via* HPLC-UV/Vis spectroscopy.

Furthermore, the sterically more crowded 3,3-disubstituted CBone **2** was examined as a substrate. Low conversion was observed in this case using standard protocol **A**. Running the reaction according to protocol **B** furnished CPone **55** in a moderate 63% yield and 63:37 *er*, while employing protocol **C** resulted in a good yield of 86% at the expanse of obtaining almost racemic product. Weaker enantiofacial discrimination was observed for this example bearing an all-carbon quaternary stereocentre, which can be attributed to the lesser difference in steric size of the substituents at the prochiral centre compared to substrate **1**. Moreover, the influence of electron-withdrawing CF_3-substitution in *para*-position of the phenyl ring was investigated. Employing CBone **3** as substrate according to protocol **B** the respective quaternary CPone **56** was afforded in noticeably decreased yield of 29%, but with insignificant change in *er* compared to CPone **55**. Additionally, the impact of an *ortho*-substitution on the phenyl ring was to be elucidated. The respective 3-*ortho*-tolyl substituted substrate **4** showed poor results. Significantly slower reaction rates were observed for all protocols compared to most of the other tested substates resulting in a highest observed yield for CPone **57** of 57% using protocol **C**. Product **57** was isolated solely as racemic mixture no matter the protocol used. A possible explanation for these results might be the additional steric bulk of the *ortho*-methyl group in rather close proximity to the other substituent in 3-position of the CBone, in this case a hydrogen atom, complicating the enantiofacial discrimination.

2.4 Summary and outlook

Over the course of this project, a novel method for the asymmetric one-carbon ring expansion of prochiral 3-substituted CBones with silyl diazomethanes as C1-building blocks was developed. Initially, scandium triflate was identified as a potent *Lewis* acid able to catalyse the desired transformation of model substrate CBone **1** towards CPone **35** efficiently. A first proof-of-concept then demonstrated the possibility of enantioinduction using a Box ligand on the scandium(III) cation affording the desired product in a low *er* of 60:40. Successive optimisation of the reaction conditions and a ligand screening showed the initially chosen toluene to be an optimal reaction solvent as well as Box ligands being the most promising ligand motif to achieve higher enantioinduction. Therefore, the employed ligand was further evolved and after several synthesised and investigated ligands it could be concluded that a *gem*-dialkyl substitution on methylene spacer is of major importance for sufficient enantioinduction. Further, it was found that steric bulk of substituents R^1 in 4-position of the oxazolines is needed to facilitate enantiofacial discrimination. However, the *tert*-butyl substituted derivative **9** performed inferior compared to *sec*-butyl substituted ligand **10** indicating broadness of the substituent in 4-position being more important than overall steric bulk in close proximity to the metal centre. Ultimately, the best performing ligand was found in Box ligand **11**, which was able to furnish CPone **35** in 67:33 *er* in the model reaction. Further tuning of the used nucleophile towards bulkier MDPSD and lowering of the reaction temperature to −78 °C led to significant improvements in terms of enantioinduction affording the desired product in 62% yield and an *er* of 85:15.

While exploring the substrate scope of the reaction, major differences in reactivity and conversion were observed, thus it became necessary to adapt the reaction conditions for several substrates. Employing three protocols, a brief substrate scope with yields up to 94% and 88:12 *er* was presented including alkyl substituted and quaternary substrates (Scheme 23).



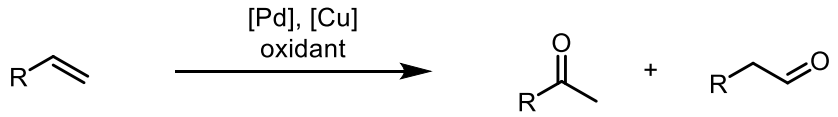
Scheme 23: Novel developed method for the asymmetric one-carbon ring expansion of prochiral CBones using a Sc(III)-Box-complex and silyl diazomethanes.

It is anticipated that further improvement of the achieved *er* is possible when carefully continued evolution of the used ligand is conducted. In the course of this work no further efforts were undertaken due to high synthetical effort for the synthesis of more complex ligands without a deeper understanding of the induction mode in action. Computational studies could be very helpful to gain such understanding and for a potential modelling of an ideal ligand facilitating highest amount of enantioinduction. With an even more potent ligand at hand, the observed limitations in the substrate scope could most likely be overcome, as high enantioselectivities could possibly be achieved even at higher temperatures and or using more reactive TMSD instead of MDPSD.

3 Asymmetric desymmetrisation of methylenecyclobutanes *via Wacker* oxidation

3.1 Introduction

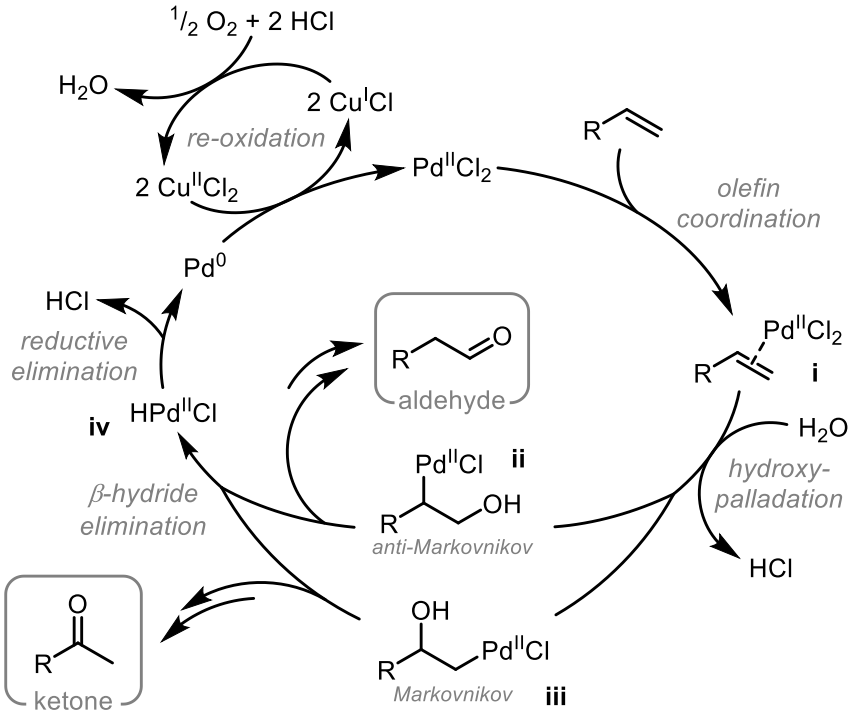
In the late 1950s a catalytic process was developed by *Wacker-Chemie* in collaboration with *Farbenwerke-Hoechst* transforming ethylene into acetaldehyde – a process with enormous industrial importance.[96,97] Traditionally using palladium(II) chloride as catalyst, this process is nowadays known as *Wacker*- or more precisely as *Wacker-Tsuji* oxidation and resembles an indispensable method for the conversion of alkenes into carbonyls. Reoxidation of the palladium catalyst is usually mediated by copper(II) chloride using atmospheric oxygen as terminal oxidant in *N,N*-dimethyl formamide (DMF)-water mixtures as solvent. The reaction on monosubstituted alkenes is typically ketone-selective due to a favoured *Markovnikov* addition of water (Scheme 24).[96,98,99] However, various conditions have since been developed able to control ketone vs. aldehyde selectivity either way (*vide infra*).



Scheme 24: General reaction scheme for the *Wacker-Tsuji* oxidation of a monosubstituted alkene.

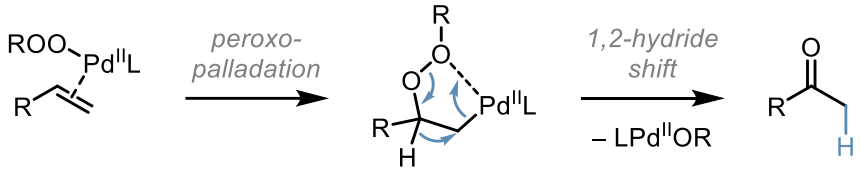
Mechanistically, the catalytic cycle of the *Wacker-Tsuji* oxidation starts with the coordination of the olefin by palladium(II) forming a η^2-Pd-olefin complex **i** followed by hydroxypalladation (Scheme 25). Two different organo-palladium species can result depending on either *Markovnikov* (**ii**) or *anti-Markovnikov* hydroxypalladation (**iii**) taking place. Subsequent β-hydride elimination of these either furnishes a ketone or the corresponding aldehyde as product. Although the formation of the carbonyl products is often described as keto-enol tautomerisation of the intermediately formed vinyl alcohols, deuterium labelling experiments, at least in the case of ethylene as a substrate, revealed that a reversed re-insertion of the palladium hydride species **iv** and subsequent β-hydride elimination from the hydroxy group or, alternatively, elimination of $Pd^{(0)}$ and H^+ is more likely to occur.[100,101] In the former case, the so formed palladium hydride species than reductively eliminates hydrogen chloride yielding palladium(0), which is re-oxidised to palladium(II) by copper(II)

chloride closing the catalytic cycle. In a co-catalytic cycle, copper(I) chloride is aerobically oxidised in the presence of HCl, reforming copper(II) chloride.[99,101,102,103]



Scheme 25: Exemplified catalytic cycle of the traditional *Wacker-Tsuji* oxidation.

Another alternative pathway for the formation of ketone products from the intermediate organopalladium species was found for *Wacker-Tsuji* oxidations using peroxides as terminal oxidants. In this case a 1,2-hydride shift from a peroxo-palladacycle was suggested, which was supported by isotope labelling experiments. This further neglects the need for a reoxidation of palladium(0), as an alkoxy palladium(II) species is eliminated during this step (Scheme 26).[104–106]

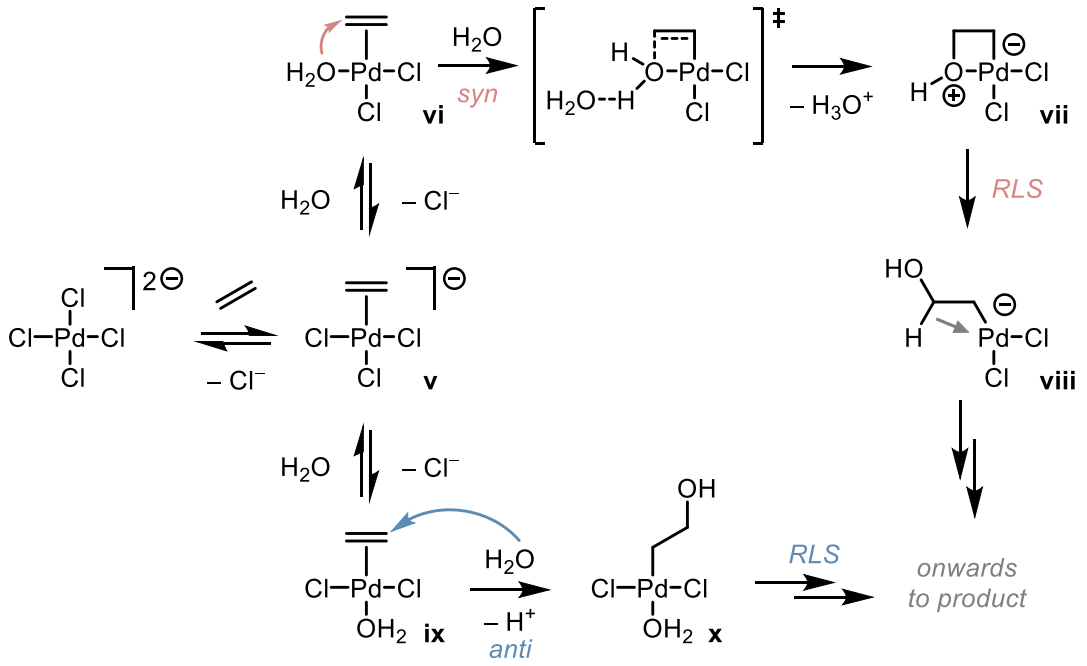


Scheme 26: Formation of ketone products *via* 1,2-hydride shift in *Wacker-Tsuji* oxidations using peroxides as terminal oxidants.

The mechanism of the hydroxypalladation in the traditional *Wacker-Tsuji* oxidation was controversially discussed in the past. Intense mechanistic studies were conducted trying to elucidate the pathway in action, which is still subject of research. Substantially, *syn*- and *anti*-hydroxypalladation can be distinguished. Further, it is under discussion which of both is preferred under certain conditions and which exact mechanistic pathway is valid. Unanimously, the *Wacker* oxidation is considered

to be quite sensitive to the applied reaction conditions, especially in terms of the concentrations of Cl^- and $CuCl_2$. It is understood that low concentration of Cl^- and $CuCl_2$, as used in the canonical *Wacker* process, advantages *syn*-hydroxypalladation. In contrast, higher chloride concentrations inhibit *syn*-hydroxypalladation and thus favour *anti*-hydroxypalladation. The role of copper is not considered in many mechanistic studies, as it is assumed to mainly facilitate the re-oxidation of Pd^0.[101,102,106] However, the isolation of a bimetallic Pd/Cu complex by *Murahashi* and co-workers, catalytically active for the aqueous aerobic oxidation of decene, calls this assumption into question.[107]

From the literature precedent, the pathway for the *syn*-hydroxypalladation considered most plausible starts from $[PdCl_4]^{2-}$, the resting state of the canonical *Wacker* process, with the coordination of the alkene under dissociation of a chloride ligand forming η^2-complex **v**. Subsequent ligand exchange of a second chloride with water furnishes a corresponding *cis*-complex **vi**. Water assisted deprotonation is then the only energetically viable explanation for the *syn*-migratory insertion resulting in a zwitterionic cyclic intermediate **vii**. As a rate-limiting-step (RLS), dissociation of the Pd-O bond supported by the formation of an agostic interaction with the neighbouring hydrogen generates complex **viii** readily undergoing subsequent β-hydride elimination (Scheme 27, top route). Regarding *anti*-hydroxypalladation, η^2-complex **v** ligand exchange with water generates *trans*-complex **ix**, as a result of the *trans*-effect of C=C-ligands. Subsequent equilibrium *anti*-addition of external water and deprotonation results in complex **x**. This intermediate then proceeds further, including a rate-limiting-step, ultimately undergoing β-hydride elimination, albeit the exact pathway needs further research (Scheme 27, bottom route).[101,102,108–111] Recent theoretical studies further suggest that the *anti*-hydroxypalladation is energetically favoured over the *syn*-approach, which includes very high energy transition states.[101,108–111]



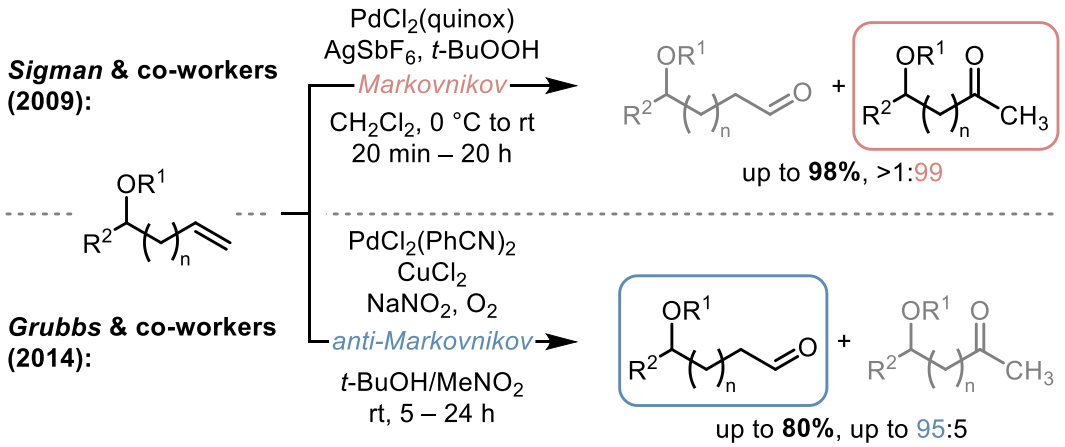
Scheme 27: Mechanistic pathways for *syn*- and *anti*-hydroxypalladation during canonical *Wacker* process considered most plausible in recent literature.

3.1.1 Selective *Wacker* oxidation of substituted alkenes

As mentioned above, extensive research was performed on the search for appropriate reaction conditions for the *Wacker* oxidation of substituted alkenes allowing for *Markovnikov* and *anti-Markovnikov* selectivity. Several protocols selectively generating either the corresponding ketone[105,112,113–115] or aldehyde[114–118,119,120,121] were published to date of which selected examples are discussed in the following:

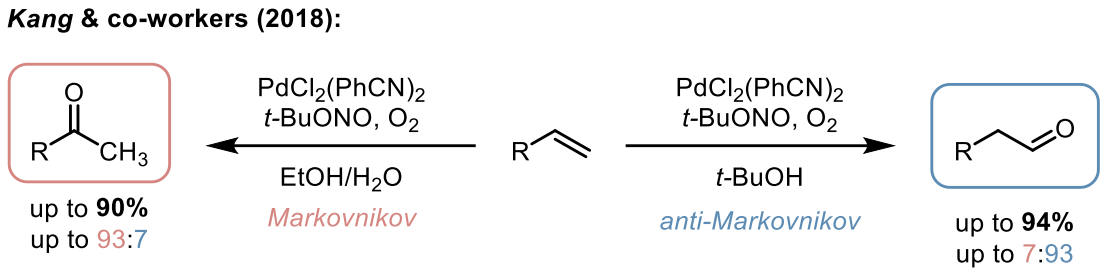
Early results for the aldehyde selective oxidation of simple alkenes was reported by *Feringa* in 1986 using a palladium(II)-nitro complex. It was postulated that the observed selectivity originates from the oxygen being transferred *via* the nitro-ligand and a intermediately formed corresponding cycloadduct.[116] Based on *Feringa's* work, a few years later *Wenzel* was able to oxidise allyl acetate using simple $PdCl_2(MeCN)_2$ as a catalyst in *tert*-butanol as solvent with high aldehyde selectivity. In this case the origin of selectivity was attributed to sterically hindered *tert*-butanol acting as nucleophile attacking the less hindered carbon of the respective olefin coordinated by the palladium catalyst.[117] Later, *Feringa* and co-workers extended their work towards the aldehyde selective oxidation of allylic amines. By employing a phthalimide protection group for amino function of the substrates, full substrate control was achieved most likely resulting from a coordination of the phthalimide to the catalyst.[118]

Sigman and co-workers did intensive research on ketone selective protocols leading to the publication of a broadly applicable, copper-free method using a palladium catalyst bearing a quinolinyl oxazoline (quinox) ligand and *tert*-butyl hydroperoxide as an oxidant in 2009 (Scheme 28, top).[113] Following mechanist investigations supported the hypothesis of efficient blocking of secondary substrate coordination by the ligand as the origin for high ketone selectivity as well as 'push-pull' electronical properties of the employed ligand being a necessity for efficient catalysis.[114] In contrast, *Grubbs* and co-workers focused on the development of aldehyde selective protocols resulting in the report of an *anti-Markovnikov* selective oxidation of functionalised alkenes mediated by sodium nitrite under oxygen atmosphere in 2014 (Scheme 28, bottom).[121] In a previous work the authors found the employed nitrite being the source of oxygen by ^{18}O-labelling experiments and suggested a metal-mediated delivery of a NO_2 radical to the alkene being responsible for high *anti-Markovnikov* selectivity.[120]



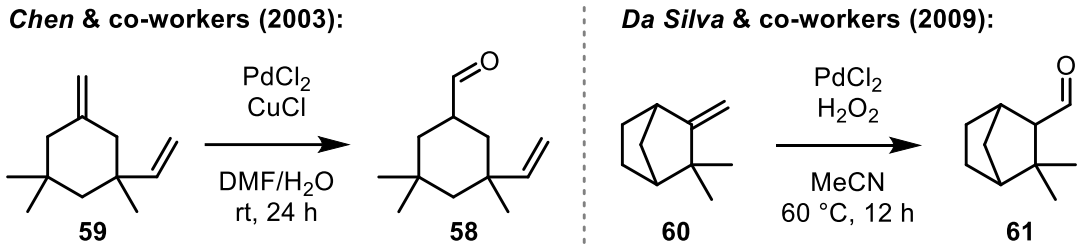
Scheme 28: Complementary work by *Sigman* and co-workers and *Grubbs* and co-workers enabling ketone and aldehyde selective *Wacker-Tsuji* oxidation of challenging functionalized alkenes, respectively.

Besides these catalyst-controlled protocols, *Kang* and co-workers more recently reported the solvent-controlled selective *Wacker-Tsuji* oxidation of functionalised alkenes. Using *tert*-butyl nitrite as a redox cocatalyst under oxygen atmosphere the authors were able to control ketone vs. aldehyde selectivity solely by the choice of solvent, wet ethanol and *tert*-butanol, respectively, under otherwise identical conditions. The authors explain the observed selectivity by the favoured *anti-Markovnikov* addition of sterically hindered *tert*-butanol, analogous to *Wenzel's* earlier findings, while smaller ethanol favours the innate *Markovnikov* addition (Scheme 29).[115]



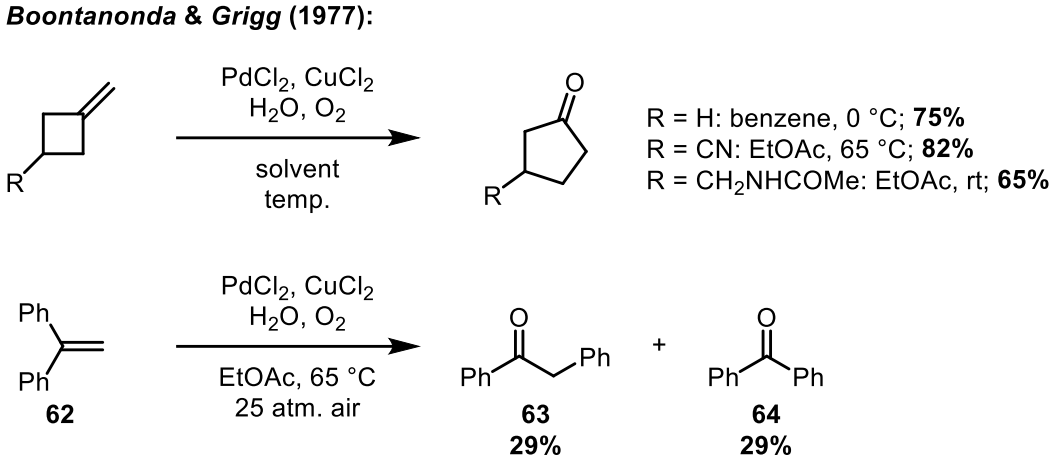
Scheme 29: Switchable ketone or aldehyde selective *Wacker-Tsuji* oxidation of functionalised alkenes by *Kang* and co-workers.

In contrast to the mono-substituted terminal alkenes, the *Wacker-Tsuji* oxidation of 1,1-disubstituted terminal alkenes is way less explored. In some rare cases the formation of the corresponding aldehyde was reported. *Chen* and co-workers observed the formation of the respective aldehyde **58** when submitting substituted methylenecyclohexane **59** to *Wacker-Tsuji* conditions,[122] while *Da Silva* and co-workers reported the oxidation of camphene (**60**) towards the corresponding aldehyde **61** (Scheme 30).[123]



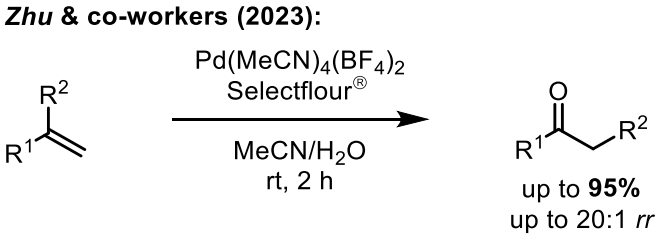
Scheme 30: Examples of oxidation of 1,1-disubstituted terminal alkenes towards the respective aldehyde product.

Classical *Wacker-Tsuji* oxidation of 1,1-disubstituted terminal alkenes towards the respective ketone is not accessible due to the lack of a hydrogen-atom in β-position preventing a β-hydrogen elimination. However, a 1,2-carbon shift would furnish a rearranged ketone as the product of such transformation, which was observed by *Boontanonda* and *Grigg* in 1977 for strained MCBs. The authors reported the formation of the corresponding CPones for three examples under classical *Wacker* conditions. A similar behaviour was observed for 1,1-diphenylethylene (**62**) as substrate yielding benzyl phenyl ketone (**63**) although this was found in a mixture with benzophenone (**64**) presumable arising from oxidative cleavage of the olefin (Scheme 31).[124] Further results supporting the feasibility of such rearrangement were presented by the oxidations of MCBs with stoichiometric amounts of Tl^{III}-nitrate or Pd^{II}-nitrite by *Ledlie* and *Likholobov*, respectively.[125]



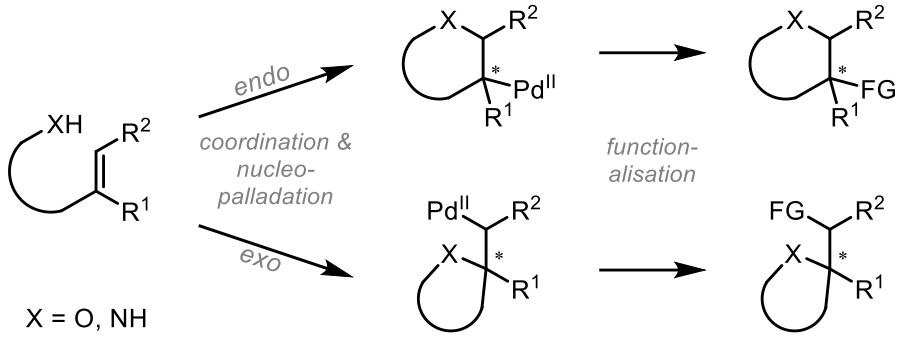
Scheme 31: *Wacker-Tsuji* oxidation of 1,1-disubstituted terminal alkenes reported by *Boontanonda* and *Grigg*.

Very recently after the herein described method for the *Wacker* oxidation of prochiral MCBs (*vide infra*, *cf.* chapter 3.1.2) was published, *Zhu* and co-workers reported a protocol for the ketone-selective palladium-catalysed oxidative rearrangement of 1,1-disubstituted terminal alkenes. Moderate to good yields were observed for numerous acyclic as well as cyclic 1,1-disubstited terminal alkenes. The authors further suggested a dyotropic rearrangement in a Pd^{II}/Pd^{IV}-cycle to enable the formation of ketones (Scheme 32).[126]



Scheme 32: Oxidative rearrangement of 1,1-disubstituted terminal alkenes by *Zhu* and co-workers.

In contrast to classical *Wacker-Tsuji* oxidation, 1,1-disubstituted olefins readily undergo *Wacker* cyclisation reactions under various conditions. During these intramolecular oxidative cyclisations with pendant hydroxy or amino groups usually a new stereocentre is formed in 1-position opening the possibility for enantioselective transformations (Scheme 33). To date a number of highly enantioselective *Wacker* cyclisation protocols were reported, which will not be further discussed here.[127]

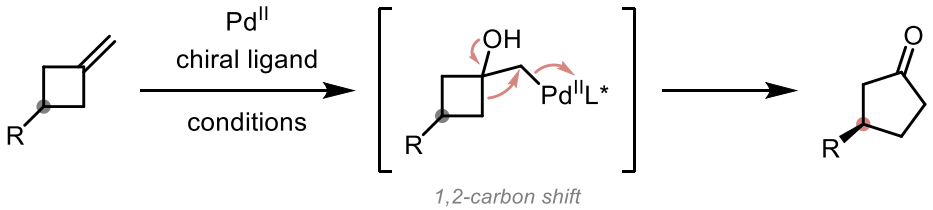


Scheme 33: Exemplified pathway of *Wacker* cyclisations of substituted alkenes giving rise to functionalised heterocycles.

In addition to terminal alkenes, the *Wacker-Tsuji* oxidation of internal alkenes has been studied as well, leading to a number of efficient synthetic protocols published to date.[128] Due to limited relevance to this work those are not discussed in further detail herein.

3.1.2 Motivation and aim

The ketone selective *Wacker-Tsuji* oxidation of 1,1-disubstituted olefins was highly limited as outlined above and respective enantioselective transformations were solely known for *Wacker* cyclisations. Based on the pioneering results of *Boontanonda* and *Grigg*, prochiral MCBs were anticipated as ideal substrates to facilitate a formal 1,2-carbon shift within their *Wacker* oxidation which would provide access to the rearranged ketone products. In collaboration with [redacted] it was sought to develop a synthetically applicable protocol for the *Wacker* oxidation of MCBs.
The fact of desymmetrisation occurring upon this envisioned transformation using prochiral MCBs further prompted to endeavour the design of respective enantioselective conditions (Scheme 34). In the following, the results of these enterprises shall be discussed.

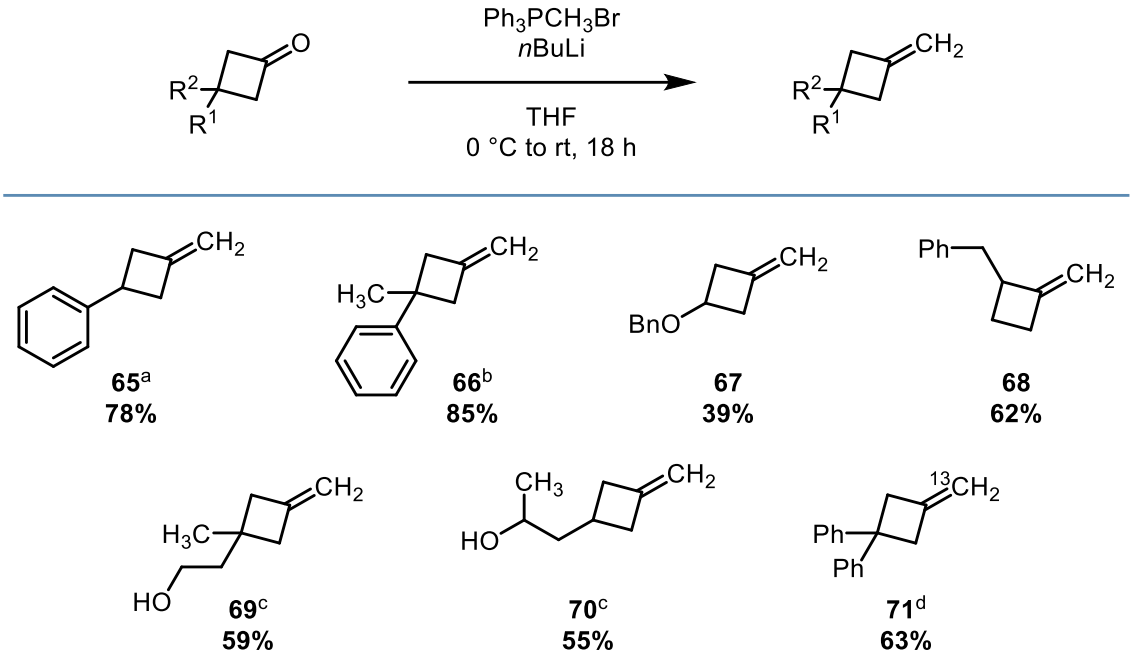


Scheme 34: Reaction scheme for desired enantioselective desymmetrisation of prochiral MCBs *via Wacker-Tsuji* oxidation.

3.2 Synthesis of starting materials

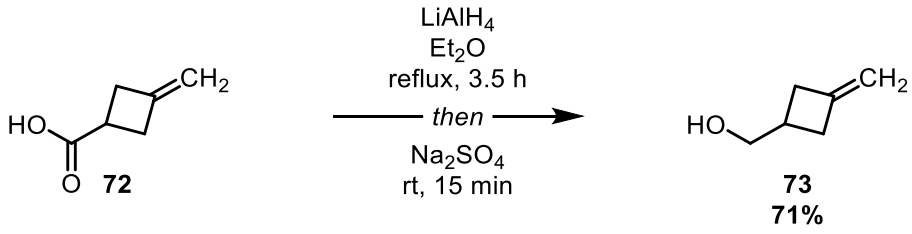
3.2.1 Synthesis of methylenecyclobutanes and other substrates

Over the course of this project several MCBs were synthesised for the subsequent use in the development of the described method as well as for the exploration of its substrate scope and the stereochemical analysis of the established method.
MCBs are easily accessible via *Wittig*-olefination of corresponding CBones (*cf.* chapter 1.3.1 & 2.2.1) using methylenetriphenyl phosphorane.
Employing standard *Wittig* conditions, MCBs **65** – **71** were synthesised using a methyltriphenyl phosphonium salt and *n*-BuLi in moderate to good yields (Scheme 35).



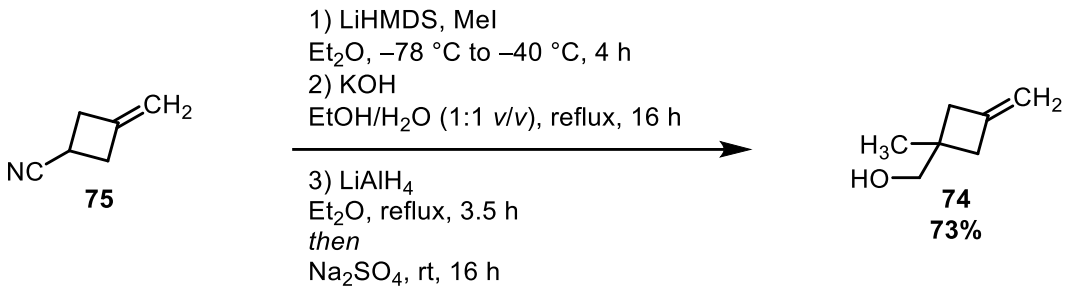
Scheme 35: MCBs synthesised for this project *via Wittig*-olefination of corresponding CBones. [a] Synthesis performed with 3 d reaction time instead of 18 h. [b] Synthesis performed with 4 d reaction time instead of 18 h. [c] The respective ethyl carbonate protected CBone was used for *Wittig*-olefination and subsequently deprotected using K_2CO_3 in MeOH; Yields given over the two steps. [d] Synthesis performed using $Ph_3P^{13}CH_3I$ instead of Ph_3PCH_3Br.

Furthermore, commercially available 3-methylenecyclobutanecarboxylic acid (**72**) was transferred to MCB **73** following a procedure of *Cowling* and *Goodby* (Scheme 36).[129]



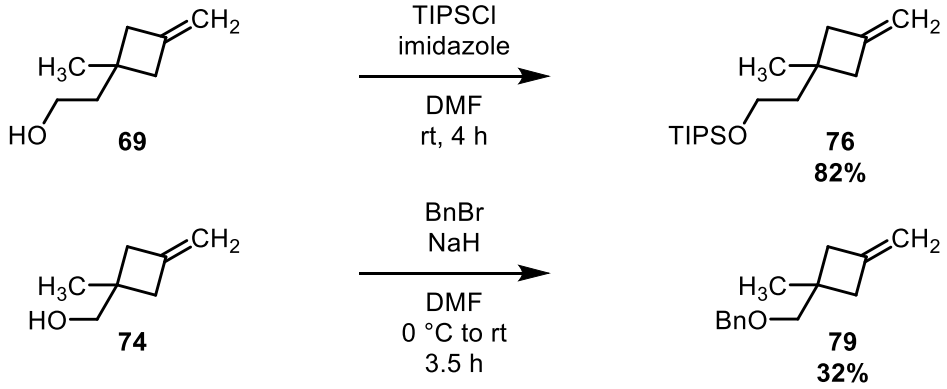
Scheme 36: Reaction scheme for the synthesis of MCB **73** *via* reduction of acid **72.**

The MCB **74** was synthesised in analogy to procedures by *Pfizer Inc.*[130] and *Cowling* and *Goodby*[129] starting from commercially available 3-methylenecyclobutane-1-carbonitrile (**75**) *via* methylation in 3-position followed by hydrolysis of the nitrile and subsequent reduction of the carboxylic acid to the alcohol (Scheme 37).



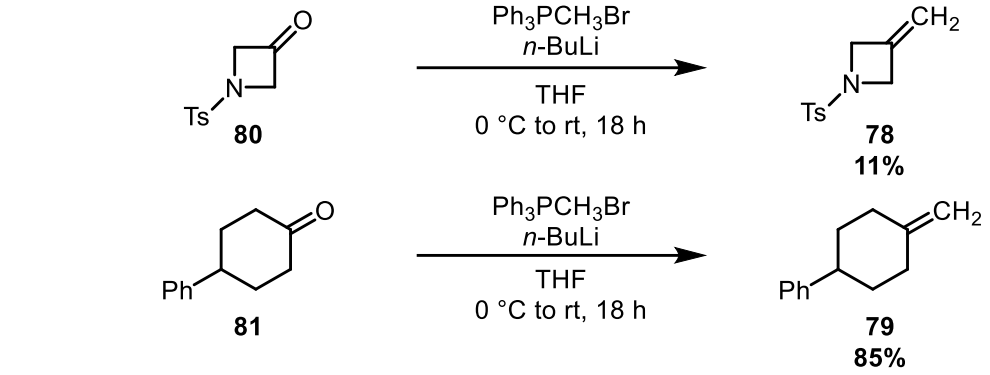
Scheme 37: Reaction scheme for the synthesis of MCB **74** starting from nitrile **75** in a three step sequence**.**

Additionally, MCBs **76** and **77** were synthesised by protection of previously obtained MCBs. Triisoproylsilyl protection of MCB **69** afforded MCB **76** in good yield of 82%, while benzyl protection of MCB **74** led to the isolation of MCB **77** in a low yield (Scheme 38).



Scheme 38: Reaction schemes for the synthesis of TIPS-protected MCB **76** and benzyl protected MCB **77.**

Besides those MCBs, heterocyclic tosyl methyleneazetidine **78** and methylenecyclohexane **79** were synthesised to be subsequently used to elucidate the scope of the method described below. Methyleneazetidine **78** was obtained in a low yield of 11% *via* standard *Wittig*-olefination of azetidinone **80**. In contrast, methylenecyclohexane **79** was afforded in a good yield of 85% using cyclohexanone **81** as a starting material (Scheme 39).

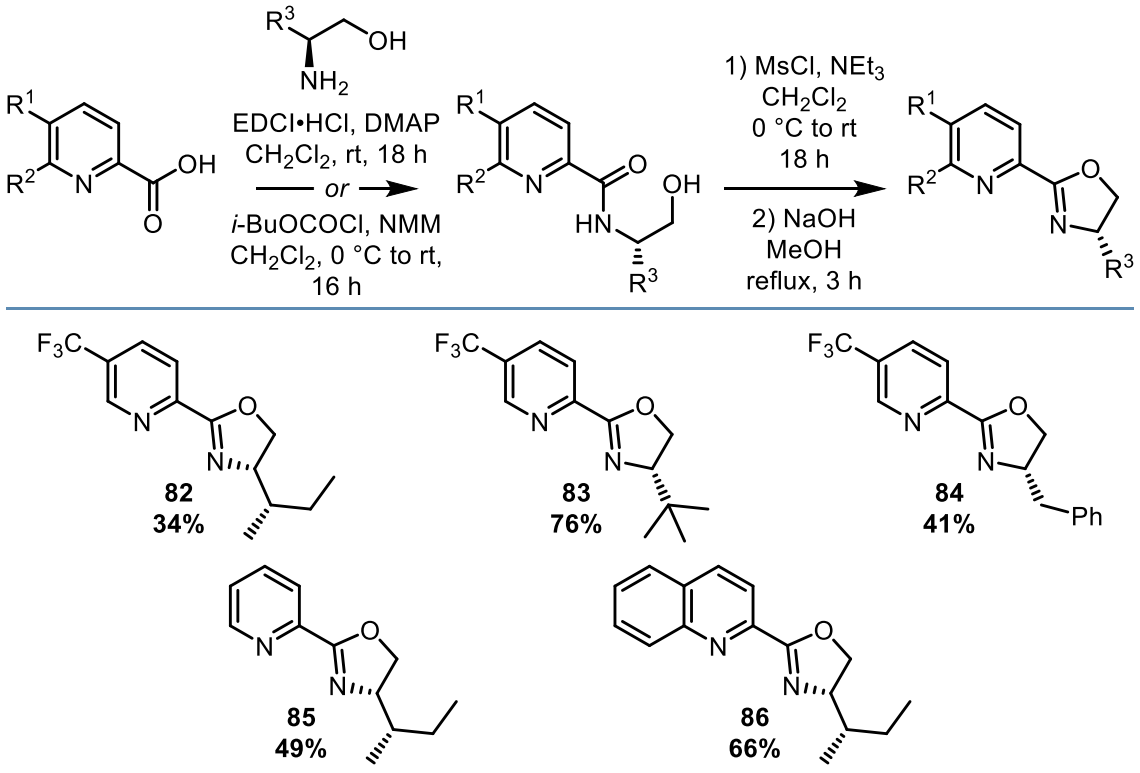


Scheme 39: Reaction schemes for the synthesis of methyleneazetidine **78** and methylenecyclohexane **79.**

3.2.2 Synthesis of ligands

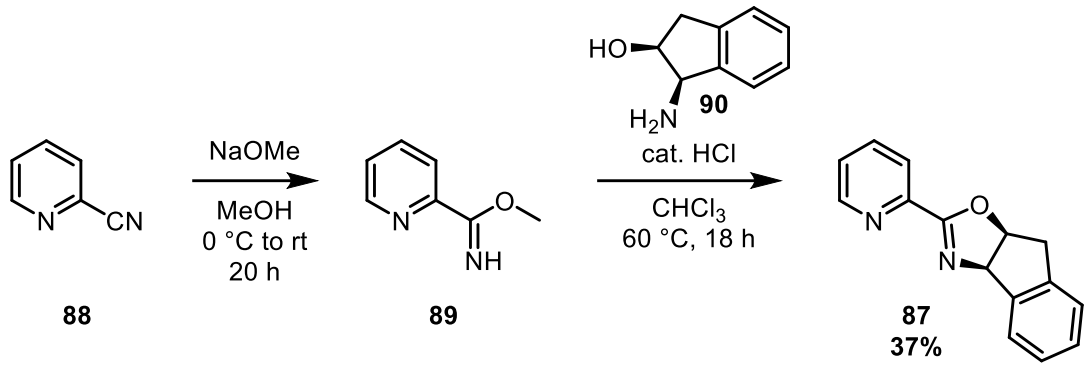
During the screening for an appropriate ligand for the method described below (*cf.* chapter 3.4) several ligands were synthesised, with the majority being pyridine-oxazoline (PyOx) ligands. For the synthesis of PyOx ligands similar methods are applied to those already discussed in chapter 2.1.2.

PyOx ligands **82** – **85** and quinox ligand **86** were synthesised *via* amide coupling of the respective picolinic or quinolinic acid with the corresponding amino alcohol. The obtained hydroxy amides were then mesylated and cyclised under basic conditions affording the desired ligands in moderate to good overall yields.



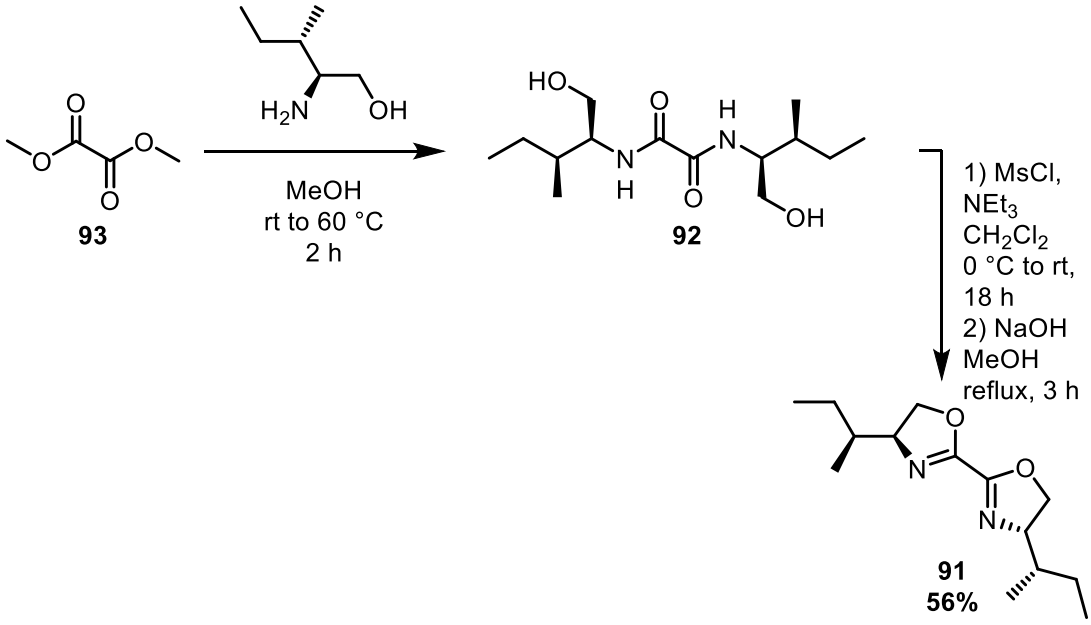
Scheme 40: PyOx and quinox ligands synthesised in this work *via* amide coupling a picolinic or quinolinic acid with an amino alcohol and subsequent activation-cyclisation of the obtained hydroxy amide affording the desired ligand. Yields given over the three steps.

The indanyl substituted PyOx **87** was synthesised in analogy to a procedure of *Malkov et al*.[131] starting form picolinonitrile (**88**), which is transformed to carboxylimidate **89**. In a second step the desired ligand was then afforded by *Brønsted* acid catalysed condensation with aminoindanol **90** in a moderate yield (Scheme 41).



Scheme 41: Reaction scheme for the synthesis of PyOx ligand **87** starting from picolinonitrile (**88**).

Additionally, BiOx ligand **91** was synthesised adapting a procedure by *Sunkur et al*.[132] for the synthesis of bisoxalamide **92**, which was then cyclised to the desired ligand employing the preciously established 2-step protocol in an overall moderate yield (Scheme 42).



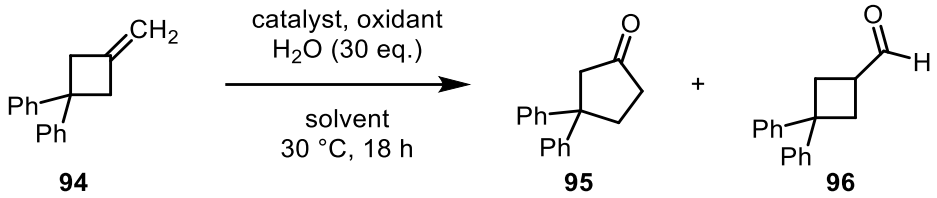
Scheme 42: Reaction scheme for the synthesis of BiOx ligand **91** starting from dimethyl oxalate (**93**).

3.3 Scope and stereochemical analysis for the racemic method

The optimisation of the reaction condition for the racemic *Wacker-Tsuji* oxidation of prochiral MCBs was carried out by [redacted] and is therefore only summarised and described briefly in the following.[37,133]

Using 3,3-diphenyl MCB (**94**) as a model substrate the reaction parameters were subsequently varied (Table 6). As a starting point traditional *Wacker-Tsuji* conditions proved ineffective for the desired transformation (entry 1). Switching the solvent to *t*-BuOH afforded a mixture of both possible products, ketone **95** and aldehyde **96**, in a small but detectable yield (entry 2), indicating insufficient re-oxidation of the catalyst. Other oxidants like benzoquinone (BQ) or *tert*-butyl hydroperoxide were therefore investigated but did not result in any improvement (entries 3 and 4, respectively). However, when using palladium nitrite complex $PdCl(MeCN)_2(NO_2)$ as catalyst, successful re-oxidation mediated by $CuCl_2$ under aerobic atmosphere was achieved affording the products in 88% yield and high ketone selectivity (entry 5). The solvent was found to have a crucial effect on the ketone to aldehyde selectivity, in line with the findings of *Kang* and co-workers.[115] Using *i*-PrOH instead of *t*-BuOH led to improved ketone selectivity at the cost of reduced a yield (entry 6). Further improvement of the ketone selectivity was achieved using EtOH affording solely the desired CPone **95** although in even lower yield (entry 7). This limitation was overcome by changing the catalyst back to $PdCl_2(MeCN)_2$ in combination with *tert*-butyl nitrite as oxidant in EtOH as solvent affording CPone **95** in 95% yield with complete ketone selectivity (entry 8). Attempts to employ only catalytic amount of *tert*-butyl nitrite under oxygen atmosphere revealed that *tert*-butyl nitrite is needed as the terminal oxidant (entry 9). Furthermore, water was found to be necessary for sufficient turn-over (entry 10) and chloride required as counter-ion to palladium (entry 11). Ultimately, it was shown that the catalyst loading could be reduced to 5 mol% and the reaction time cut to 3 h without any drawbacks (entry 12).

Table 6: Summarised reaction optimisation for the racemic *Wacker-Tsuji* oxidation of prochiral MCBs.



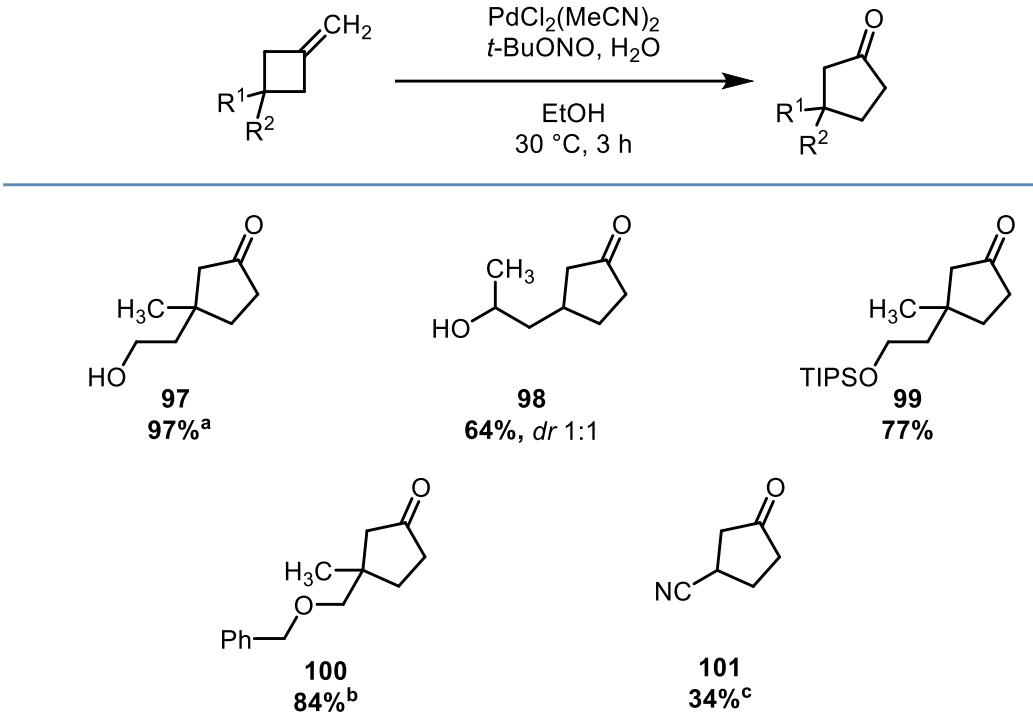
94 **95** **96**

Entry	Catalyst	Oxidant (eq.)	Solvent	NMR-Yield	95:96
1	$PdCl_2$	$CuCl_2$ (0.4), O_2	DMF/H_2O	<1%	-
2	$PdCl_2(MeCN)_2$	$CuCl_2$ (0.4)[a]	*t*-BuOH	13%	81:19
3	$PdCl_2(MeCN)_2$	BQ (1.0)	*t*-BuOH	<1%	-
4	$PdCl_2(MeCN)_2$	*t*-BuOOH (1.0)	*t*-BuOH	11%	n.d.
5	$PdCl(MeCN)_2(NO_2)$	$CuCl_2$ (0.4)[a]	*t*-BuOH	88%	88:12
6	$PdCl(MeCN)_2(NO_2)$	$CuCl_2$ (0.4)[a]	*i*-PrOH	44%	91:9
7	$PdCl(MeCN)_2(NO_2)$	$CuCl_2$ (0.4)[a]	EtOH	18%	>99:1
8	$PdCl_2(MeCN)_2$	*t*-BuONO (1.0)	EtOH	95%	>99:1
9	$PdCl_2(MeCN)_2$	*t*-BuONO (0.2), O_2	EtOH	19%	>99:1
10[b]	$PdCl_2(MeCN)_2$	*t*-BuONO (1.0)	EtOH	36%	>99:1
11	$Pd(OAc)_2$	*t*-BuONO (1.0)	EtOH	<1%	-
12[c]	$PdCl_2(MeCN)_2$	*t*-BuONO (1.0)	EtOH	95%	>99:1

Reactions run on 0.1 mmol scale in 1 mL of solvent (0.1 M) using 10 mol% catalyst. NMR yields and ratio of products 95 and 96 determined from the crude reaction mixture via ^1H NMR using mesitylene as internal standard. Reactions performed by [redacted] [a] Atmospheric oxygen was used as the terminal oxidant. [b] The reaction was run under Ar atmosphere without the addition of water. [c] Reaction was run for 3 h with 5 mol% catalyst.

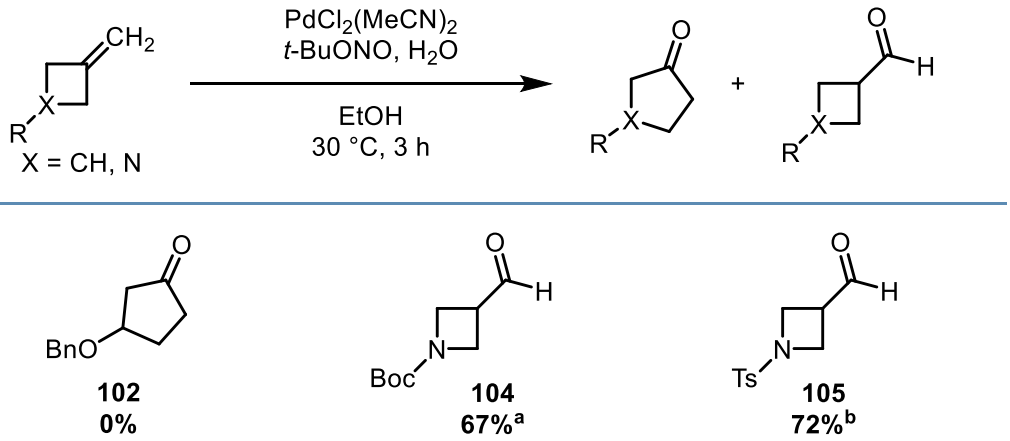
With the optimized conditions established by [redacted] the substrate scope of the developed transformation was investigated. [redacted] tested several substrates including diversely substituted aryl as well as spiro and alkyl derivatives.[37,133] Besides those, especially derivatives containing functional groups were of interest (Scheme 43). The quaternary CPone **97** bearing a primary hydroxy group was obtained in excellent yield of 97% although appearing as a mixture with its hemiketal isomer in a 66:34 ketone:hemiketal ratio. Secondary alcohols were tolerated as well providing CPone **98** in a mediocre yield. Interestingly, the respective product bearing two stereocentres was obtained in a diastereomeric ratio (*dr*) of 1:1. A direct involvement of the tethered hydroxy group is thus unlikely, as an impact on the *dr* would be expected in that case. Substrates bearing protected hydroxy functions were also compatible with the developed conditions. The triisoproylsilyl protected CPone **99** was afforded in 77% yield while benzyl protected CPone **100** was isolated in a good yield of 84%. It is worth mentioning that benzylic oxidation did not occur to a noticeable amount under the oxidative reaction conditions. Additionally, the cyano-substituted CPone **101** was obtained in moderate yield of 34%.

The lower yield can be attributed to the possibility of HCN elimination and a high volatility of the product. Further it is noteworthy that in this case a small amount of 4% of the respective aldehyde product was detected by ^{1}H NMR analysis of the crude reaction mixture.



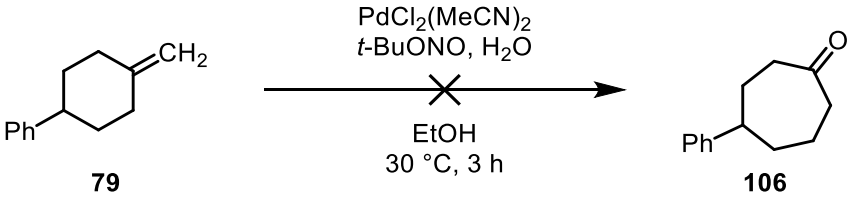
Scheme 43: Successful examples of the substrate scope investigated. Reactions run on 0.3 mmol scale in 3 mL of solvent (0.1 M) using 5 mol% catalyst, 1.00 eq. *t*-BuONO and 30.0 eq. water. [a] Isolated as 66:34 ketone:hemiketal mixture. [b] The reaction was run at 0.18 mmol scale. [c] Minor amounts of the corresponding aldehyde product were observed.

During the elucidation of the substrate scope some limitations of the developed methods were found as well. 3-Benzyloxy MCB (**67**) proved not to be a viable substrate to the reaction as the desired product **102** could not be obtained. Most likely MCB **67** is not stable under the reaction conditions and decomposes. The tolerance of heterocyclic substrates was of interest as well. The methyleneazetidines **103** and **78** were therefore submitted to the optimised reaction conditions. Interestingly, no ring expanded pyrrolidinones were found, but solely the corresponding aldehyde products **104** and **105** as mixtures with their respective diethyl acetals (Scheme 44). A possible explanation might be a directing property of the azetidine nitrogen favouring *anti-Markovnikov* hydroxypalladation.



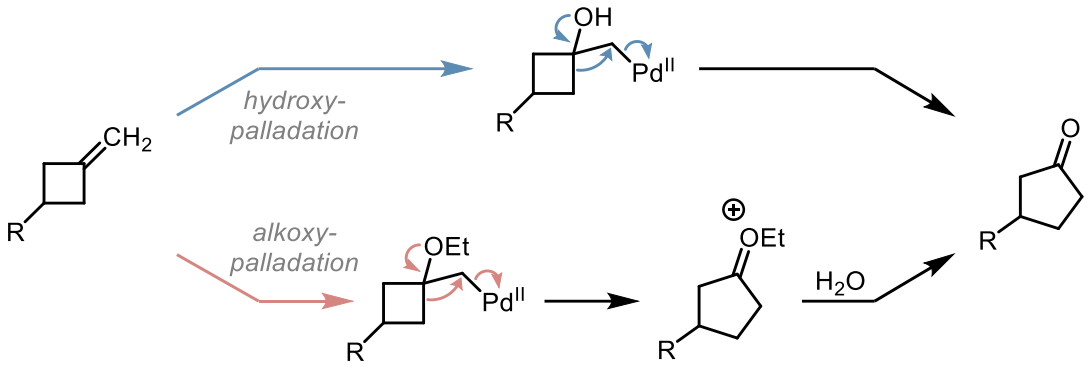
Scheme 44: Limitations found for the substrate scope of the developed method. Reactions run on 0.3 mmol scale in 3 mL of solvent (0.1 M) using 5 mol% catalyst, 1.00 eq. *t*-BuONO and 30.0 eq. water. [a] Obtained as mixture with its diethyl acetal (34:66 aldehyde:acetal). [b] Obtained as mixture with its diethyl acetal (72:28 aldehyde:acetal).

Furthermore, methylenecyclohexane **79** was investigated as a substrate as well to probe if larger cycloalkanes also undergo oxidative ring expansion under the developed reaction conditions. No reaction was observed in this case and only unconsumed starting material was isolated, indicating the release of strain energy to be an important driving force for the desired transformation under the optimised conditions (Scheme 45).



Scheme 45: Unsuccessful attempt of the *Wacker-Tsuji* oxidation of methylenecyclohexane **79** towards cycloheptanone **106**.

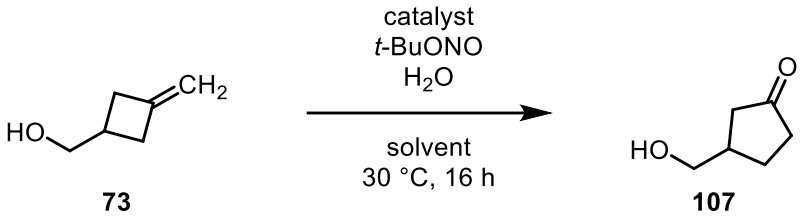
Having studied the substrate scope, attention was further drawn towards a deeper understanding of the active reaction pathway and the stereochemical analysis of the reaction. It was endeavoured to investigate the favouring of alcoholic solvents, as found by [redacted] during the optimisation of the reaction conditions.[37,133] It was assumed that the solvent might be involved in an alkoxy-palladation step resulting in the formation of an oxonium intermediate rather than direct hydroxypalladation with the water present in the reaction mixture (Scheme 46).



Scheme 46: Hypothesised pathway *via* alkoxy-palladation of the alkene with the solvent (EtOH) as a possible explanation for the high dependency on alcoholic solvents.

Therefore, a study using hydroxy MCB **73** in different solvents was performed to probe, if the tethered hydroxy group would facilitate the reaction in non-alcoholic solvents (Table 7). The respective CPone **107** was detected in all tested solvents in good to excellent yields *via* ^{1}H NMR analysis. While ethanol, not surprisingly, performed best (entry 1), high yields were obtained even for chlorinated solvents (entries 2 – 4). [redacted] had found that dichloromethane and chloroform were no viable solvents for reaction using model substrate **94** under variation of different reaction parameters during the optimisation of the reaction conditions.[133] It was further found that the addition of water is still required for sufficient product formation in this case (compare entries 6 and 7).

Table 7: Solvent study performed with hydroxy MCB **73**.



73 **107**

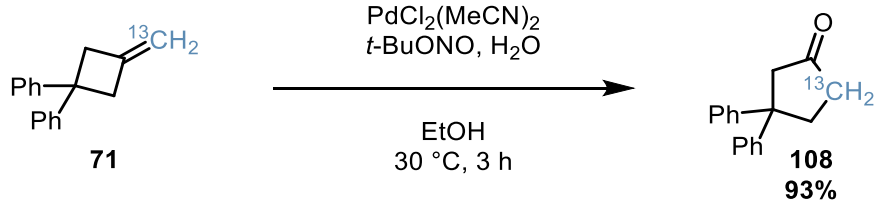
Entry	Solvent	Amount H_2O	NMR yield
1[a]	EtOH	30 eq.	99%
2[a]	$CDCl_3$	30 eq.	72%
3[b,c]	$CHCl_3$	30 eq.	92%
4[a,c]	CH_2Cl_2	30 eq.	93%
5[a]	Acetone	30 eq.	81%
6[a]	THF	30 eq.	75%
7[a]	THF	-	18%

Reactions run on 0.1 mmol scale in 1 mL of solvent (0.1 M) using 10 mol% catalyst, 1.00 eq. *t*-BuONO and the given amount of water. NMR yields determined *via* ^{1}H NMR using mesitylene as internal standard. [a] $PdCl_2(PhCN)_2$ was used. [b] $PdCl_2(MeCN)_2$ was used. [c] Reaction time 3 h instead of 16 h. The product appeared as mixture with its corresponding hemiketal form.

Although the active pathway might change in different solvents, these results indicate that the presence of hydroxy functions is beneficial to the reaction and that the

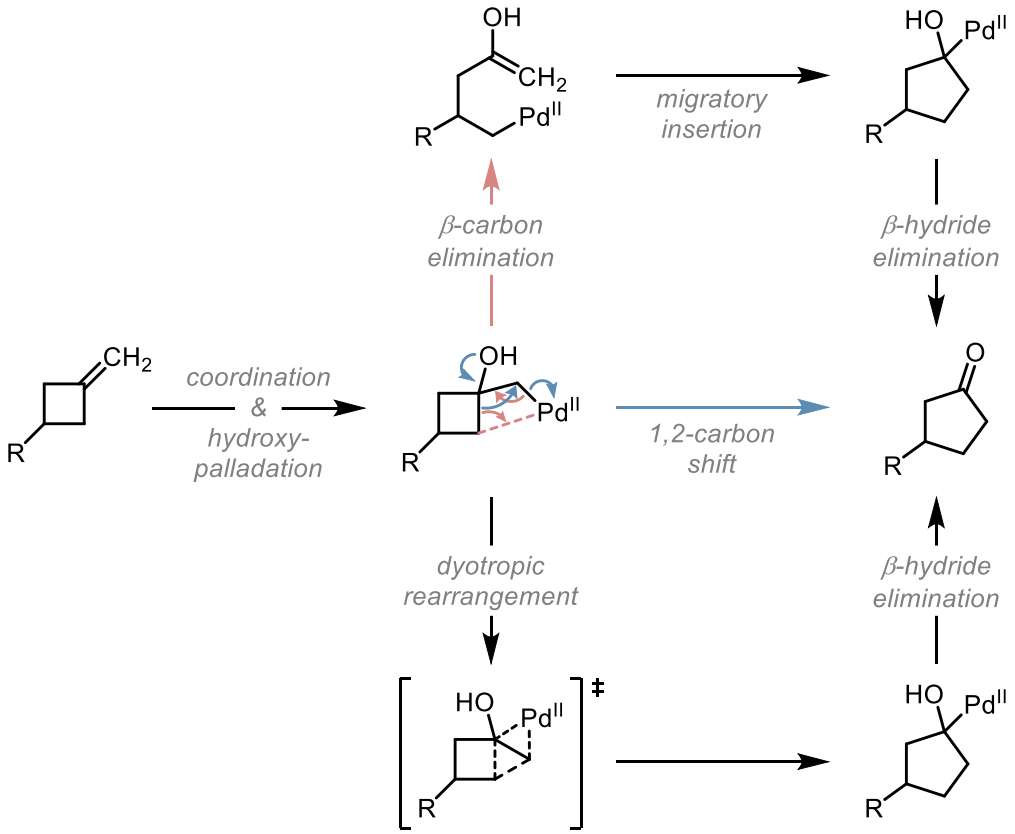
assumed alkoxy-palladation is in principle feasible, which could ultimately explain ethanol being the most potent solvent for the developed method. Nevertheless, this does not resemble a proof for such alkoxyl-palladation as product formation could just as well result from classical direct hydroxypalladation with the water present. Hydrogen bonding with the tethered hydroxy group or the alcoholic solvent might in that case be a crucial factor explaining the need for the presence of hydroxy functions in the reaction mixture to achieve sufficient product formation.

Additionally, further endeavours were undertaken to substantiate the assumed reaction pathway. ^{18}O-labeling experiments by [redacted] suggest that the oxygen atom contained in the product most likely stems from the added water under the optimised conditions.[37,133] In order to gain further insight into where the methylene carbon is eventually found in the product, terminally ^{13}C-labeled MCB **71** was submitted to the optimised reaction conditions. The α-^{13}C-labeled CPone **108** was isolated as the sole product (Scheme 47).



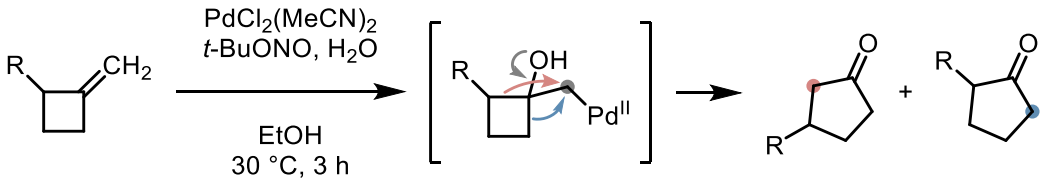
Scheme 47: Reaction scheme for the performed ^{13}C-labeling experiment on MCB **71** resulting in exclusive formation of α-^{13}C-labeled CPone **108**.

Although not conclusive proof, this result is consistent with the hypothesised 1,2-carbon shift leading to ring expansion. Alternatively, β-carbon elimination followed by re-insertion and subsequent β-hydride elimination cannot be ruled out. Another plausible pathway is a dyotropic rearrangement of the carbon-palladium(II) and the corresponding carbon-carbon bond occurring after olefin coordination and hydroxypalladation. Subsequent β-hydride elimination would also result in the formation of the product in that case (Scheme 48).



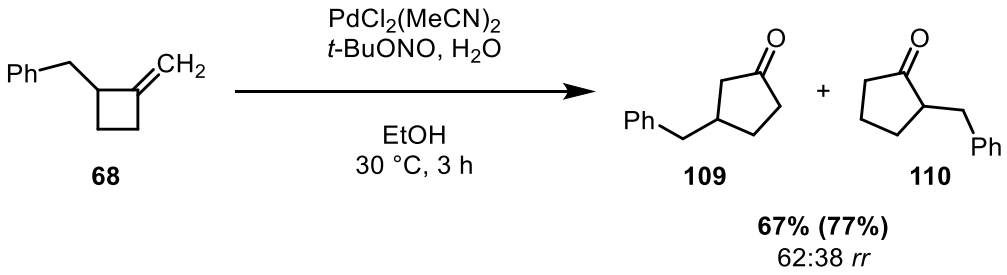
Scheme 48: Plausible mechanistic pathways consistent with the experimental findings.

It was further of interest whether the migration of one bond over the other might be favoured in the case of non-identical substitution on the two carbon atoms under consideration. The use of non-prochiral MCBs bearing different substituents in the 2- and 4-position could therefore result in the formation of two different products (Scheme 49).



Scheme 49: Possibility of the formation of two different ketone products depending on the migrating bond in the case of non-prochiral MCBs.

As a mechanistical probe, 2-benzyl MCB (**68**) was submitted to the optimised conditions. A regioisomeric ratio (*rr*) of 62:38 in favour of the β-substituted product **109** over the α-substituted **110** was found *via* ^{1}H NMR analysis of the crude reaction mixture (Scheme 50). A slightly faster 1,2-migration of the higher substituted bond, in this case the more electron-rich bond, is suggested by these findings.



Scheme 50: Mechanistical probe towards the migration tendency of the higher vs. lower substituted carbon atom. NMR-Yield determined *via* ^{1}H NMR analysis of the crude reaction mixture using mesithylene as internal standard (given in brackets).

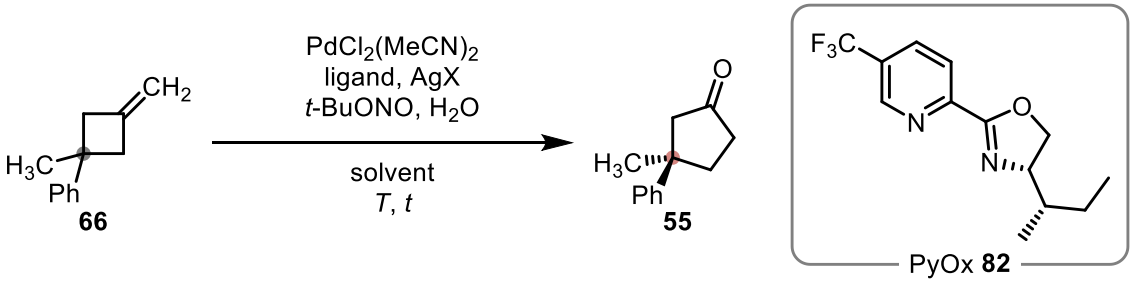
3.4 Development of asymmetric conditions and ligand evolution

The use of prochiral MCBs as substrates for the previously developed ketone-selective *Wacker-Tsuji* oxidation results in their desymmetrisation, thus the formation of a stereogenic element, in this case a new stereocentre in 3-position of the formed CPones. Based on the racemic conditions it was sought to achieve an enantioselective variant through reoptimisation using a chiral ligand on the palladium catalyst. (Table 8, *vide infra*).

It was quickly realised that catalytic activity was lost completely when a $PdCl_2$-PyOx complex was utilised as catalyst under otherwise unchanged conditions optimised for the racemic reaction using MCB **66** as a model substrate (entry 1). Thus, it was attempted to restore the catalytic activity by reoptimisation of the reaction conditions using PyOx ligand **82** as a model ligand. An increase of the reaction temperature to 78 °C to compensate for the less active catalyst was not successful (entry 2). It was anticipated, that replacing the two acetonitrile ligands with a less labile bidentate PyOx ligand renders the palladium centre less electropositive impeding the migratory insertion into the alkene. Additionally, the availability of free coordination sites is reduced in such complex. Either a chloride ligand, which is less labile compared to MeCN, or one of the two coordinating moieties of the PyOx ligand, which is kinetically disfavoured, would have to dissociate to form a quaternary planar palladium-alkene complex. Therefore, replacement of one of the chloride ligands with a weakly coordination anion, such as the perchlorate anion, was envisioned advantageous. This was accomplished by addition of silver perchlorate after the formation of the palladium-PyOx complex resulting in the precipitation of silver chloride. The so formed $PdCl(ClO_4)$(PyOx **82**) was found to be catalytically active affording desired CPone **55** in a moderate yield. Further, the anticipated enantioinduction by utilisation of a chiral ligand proved feasible as the product was isolated in an *er* of 62:38 (entry 3). It was then set on to improve this initial success. The usage of 20 mol% of silver perchlorate instead of 10 mol% showed only minor improvements on the isolated yield as well as the measured *er* (entry 4). Employing hexafluoro antimonate as weakly coordinating anion instead of perchlorate at an extended rection time of 18 h led to a slight increase in yield while leaving the enantioselectivity untouched, but at the same time required for higher operational effort due to the necessity of $AgSbF_6$ being stored under inert atmosphere in a glovebox

(entry 5). Returning to $PdCl(ClO_4)$(PyOx **82**) as the catalyst at an extended reaction of 18 h afforded desired product **55** in an increased yield of 80% and an *er* of 63:37 (entry 6). Subsequent control experiments without the addition of a palladium species and a ligand as well as at a lower temperature revealed that the added silver is not a catalytically active species and that the elevated reaction temperature of 78 °C is required for sufficient reactivity (entries 7 and 8, respectively). Additionally, several other solvents were elucidated. The use of chloroform, acetone, methyl *tert*-butyl ether (MTBE) as well as hexafluoroisopropanol (HFIP) resulted in complete loss of product formation (entries 9 – 12). The latter observation might be attributed, besides their different solvating properties, to the requirement of running the reaction at a low temperature due to their lower boiling point compared to ethanol. Besides EtOH, among all tested solvent, only the use of *t*-BuOH was feasible, however showing inferior results compared to ethanol (entry 13).

Table 8: Optimisation of reaction conditions for the asymmetric oxidative ring-expansion of methylenecyclobutanes.



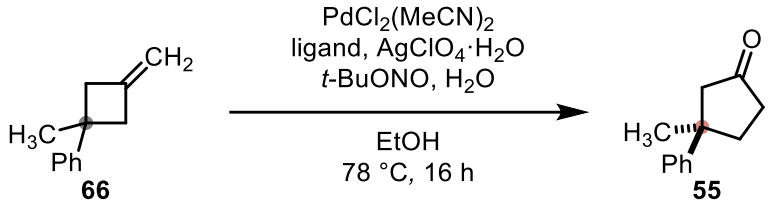
Entry	Ligand	AgX [mol%]	*T* [°C]	Solvent	*t* [h]	NMR-Yield	Yield	*er*
1	PyOx **82**	-	30	EtOH[b]	4	-	-	-
2	PyOx **82**	-	78	EtOH[b]	4	-	-	-
3	PyOx **82**	$AgClO_4$ [10]	78	EtOH[b]	4	66%	57%	62:38
4	PyOx **82**	$AgClO_4$ [20]	78	EtOH[b]	4	74%	63%	63:37
5	PyOx **82**	$AgSbF_6$ [15]	78	EtOH[b]	18	76%	69%	63:37
6	PyOx **82**	$AgClO_4$ [11]	78	EtOH[b]	18	83%	80%	63:37
7[a]	-	$AgClO_4$ [15]	78	EtOH[b]	4	-	-	-
8	PyOx **82**	$AgClO_4$ [15]	30	EtOH[b]	4	-	-	-
9	PyOx **82**	$AgClO_4$ [11]	60	$CHCl_3$	18	-	-	-
10	PyOx **82**	$AgClO_4$ [11]	60	Acetone	18	-	-	-
11	PyOx **82**	$AgClO_4$ [11]	60	MTBE	18	-	-	-
12	PyOx **82**	$AgClO_4$ [11]	60	HFIP	18	-	-	-
13	PyOx **82**	$AgClO_4$ [11]	78	*t*-BuOH	18	40%	37%	60:40

Reactions were run on 0.20 mmol scale in 2 mL solvent (0.1 M) using 10 mol% catalyst, 11 mol% ligand, 1.00 eq. *t*-BuONO and 30.0 eq. water. NMR yields determined from the crude reaction mixture *via* ^{1}H NMR using mesitylene as internal standard. *er* determined *via* HPLC using a chiral stationary phase. [a] Reaction performed without addition of catalyst and ligand. [b] Dried over activated 3 Å molecular sieves.

Having found appropriate reaction conditions enabling the asymmetric *Wacker-Tsuji* oxidation of prochiral MCBs utilising a chiral ligand on the palladium catalyst,

studies of the ligand used were conducted (Table 9). It was anticipated that steric variation of the substituent in 4-position of the respective oxazoline moiety could improve the enantioinduction, as PyOx **82** already showed the capability of enantiofacial discrimination affording the desired product in a low *er* of 63:37 (entry 1). Therefore, *tert*-butyl substituted PyOx **83** was tested surprisingly resulting in isolation of CPone **55** in a slightly reduced *er* of 60:40 (entry 2). Benzyl substituted PyOx **84** was investigated as well showing almost identical results (entry 3). The impact of the electron withdrawing group on the pyridine moiety was further of interest. Hence, ligands **85** and **87** not bearing such substitution were tested. While the enantioselectivity was found unchanged a noticeable drop in yield was observed, which can be attributed to a more electron rich catalyst complex less effectively undergoing olefin coordination and insertion (entries 4 and 5). Several other ligand motifs were tested as well, as no significant improvements on the enantioinduction were found varying the substituent in 4-position of the oxazoline moiety of the PyOx motif were found. Usage of the closely related quinox ligand **86** led to results comparable to those of the corresponding PyOx ligand (entry 6). Furthermore, Box ligands **13** and **8** were tested showing significantly reduced yield and *er* (entries 7 and 8). DBFox **43** showed a reduced yield as well and afforded the product as racemic mixture (entry 9). Moreover, the employment of BoxAx **44** resulted in a moderate yield and insignificant enantioinduction (entry 10). The results observed for *Trost*-ligand **32**, BiOx **91** and (+)-sparteine (**48**) were similar. CPone **55** was isolated in only moderate yield and racemic or *quasi*-racemic *er* in all cases (entries 11 – 13). Additionally, even though not capable of inducing enantioselectivity, SPhos (**111**) and *rac*-BINAP (**112**) were tested to elucidate if phosphine ligands are tolerated and if chiral phosphine ligands might be worth investigating. In both cases no product formation was observed indicating that phosphine ligands inhibit catalytic activity (entries 14 and 15).

Table 9: Results of the performed ligand screening for the asymmetric *Wacker-Tsuji* oxidation of prochiral MCBs. The structures of the respective ligands are given in Figure 18 and Figure 19.



Entry	Ligand	NMR Yield[a]	Yield	*er*
1	**82**	83%	80%	63:37
2	**83**	86%	75%	60:40
3	**84**	80%	80%	62:38
4	**85**	73%	n.d.	63:37
5	**87**	60%	48%	62:38
6	**86**	n.d.	77%	61:39
7	**13**	26%	n.d.	56:44
8	**8**	30%	29%	54:46
9	**43**	n.d.	37%	50:50
10	**44**	40%	n.d.	53:47
11	**32**	n.d.	52%	50:50
12	**91**	55%	55%	52:48
13	**48**	47%	37%	50:50
14	**111**	<1%	-	-
15	**112**	<1%	-	-

Reactions were run on 0.20 mmol scale in 2 mL solvent (0.1 M) using 10 mol% catalyst, 11 mol% ligand, 11 mol% $AgClO_4 \cdot H_2O$, 1.00 eq. *t*-BuONO and 30.0 eq. water. NMR yields determined *via* ^1H NMR analysis using mesitylene as internal standard. *er* determined *via* HPLC using a chiral stationary phase.

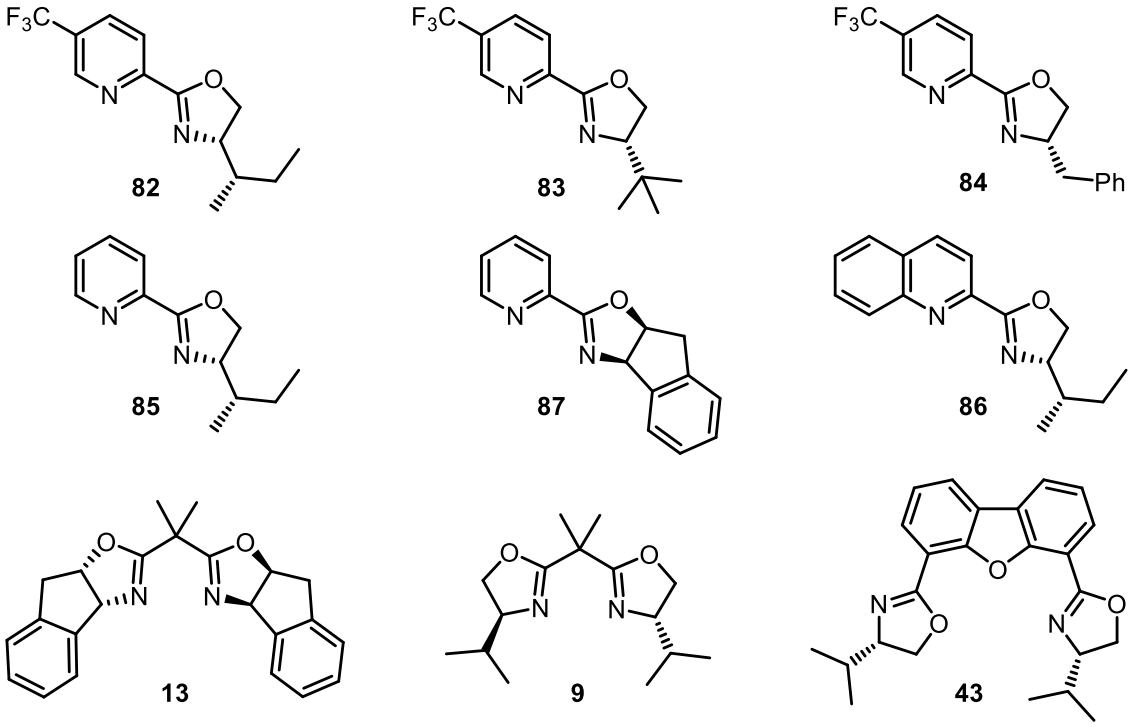


Figure 18: Structures of the ligands elucidated for the asymmetric *Wacker-Tsuji* oxidation of prochiral MCBs (part 1).

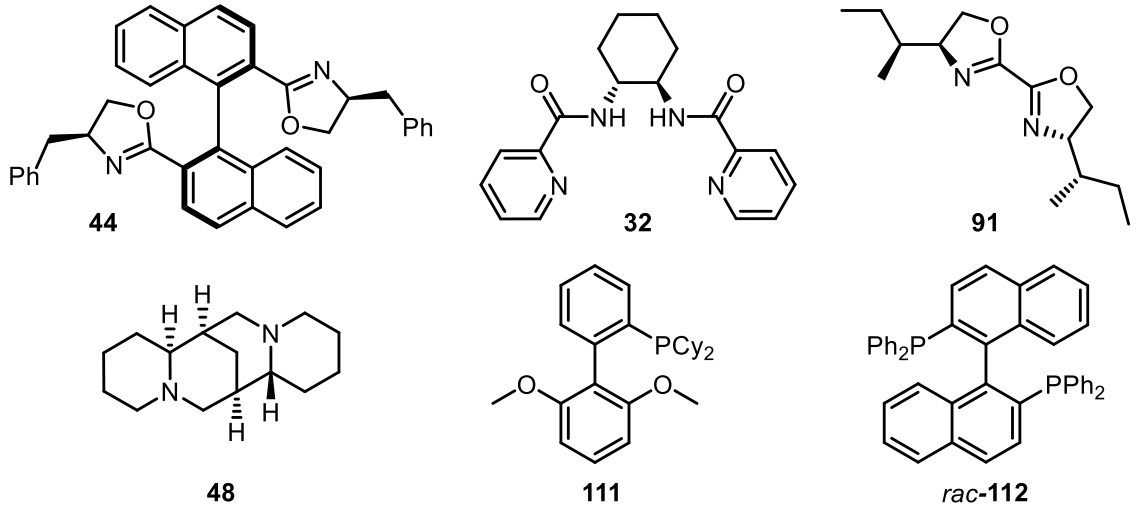
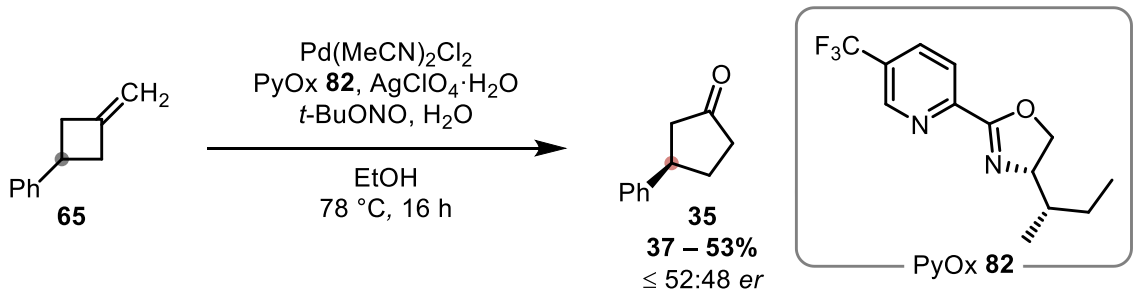


Figure 19: Structures of the ligands elucidated for the asymmetric *Wacker-Tsuji* oxidation of prochiral MCBs (part 2).

As outlined above, achieving high enantioselectivity in the *Wacker-Tsuji* oxidation of prochiral MCBs proved challenging. The best result obtained over the course of this work was an *er* of 63:37 using PyOx ligand **82**, which demonstrates the feasibility of the desired enantioinduction and thereby resembles, to the best of one's knowledge, the first example of an enantioselective *Wacker-Tsuji* oxidation. Nevertheless, this result leaves room for further improvements.

The chosen model substrate, bearing a quaternary centre, might be an especially challenging substrate for the desired transformation. It was therefore anticipated that use of 3-phenyl MCB (**65**) under the established conditions should result in an improved *er* of the respective product **35** compared to the results obtained when employing quaternary MCB **66**, as enantiofacial discrimination should be facilitated for two more differently large substituents. Surprisingly, CPone **35** was obtained in an almost racemic *er* of 52:48 and a low yield of 37%. Reproduction of this experiment led to comparably low *er* but higher yield of 53% indicating weak reproducibility for this substrate (Scheme 51). Further research is needed to understand the nature of this unexpected result.

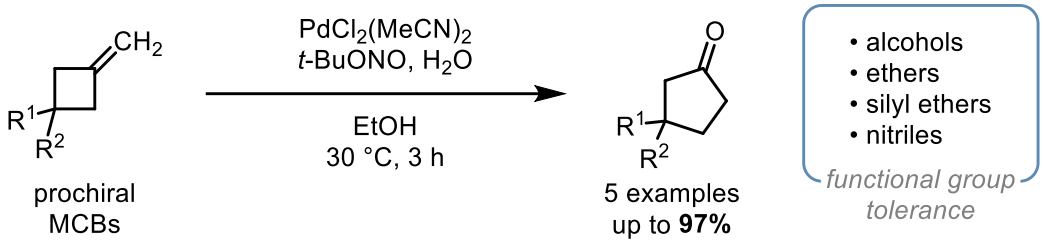


Scheme 51: The use of MCB **65** under the optimised conditions led to weakly reproduceable results and poor enantioinduction.

Further endeavours on the improvement of the enantioselectivity of the *Wacker-Tsuji* oxidation of prochiral MCBs were later undertaken by [redacted] in the course of his master's thesis. He found substitution in 6-position of the pyridine moiety of a respective PyOx ligand to be beneficial for the enantioinduction of the desired transformation, although at the cost of reduced yields.[134]

3.5 Summary and outlook

Based on the optimised reaction conditions for the ketone-selective *Wacker-Tsuji* oxidation of prochiral MCBs developed by [redacted] over the course of this project the substrate scope regarding functionalised derivates was investigated. Different functional groups were tolerated well, including free alcohols, ethers, silyl ether and nitriles (Scheme 52). It was further shown that the reaction is limited to MCBs as substrates as methyleneazetidines as well as methylenecyclohexanes did not result in the formation of the desired ring expanded ketone products.

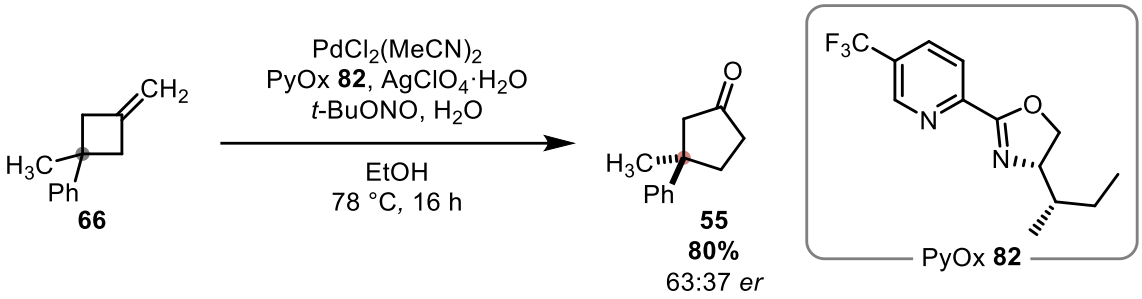


Scheme 52: The exploration of the substrate scope for functionalised derivatives of the *Wacker-Tsuji* oxidation of prochiral MCBs revealed high functional group tolerance.

Additionally, a brief mechanistic and stereochemical analysis of the developed reaction was conducted. Continued studies of the reaction solvent using hydroxy MCB **73** as substrate suggest the alcoholic solvent to be at least indirectly involved in reaction pathway. The hypothesised 1,2-carbon shift was supported by ^{13}C-labeling experiments showing the terminal methylene carbon ending up in the α-position of the desired product. However, a stepwise pathway *via* β-carbon elimination as well as *via* dyotropic rearrangement cannot be ruled out so far. Using a 2-substituted MCB as mechanistical probe a slightly larger migration aptitude for higher substituted carbon atom was further observed.

Furthermore, re-optimisation of the reaction conditions enabled the use of a chiral ligand, thus achieving the first example of an enantioselective *Wacker-Tsuji* oxidation. The exchange of one of the chloride ligands on the used palladium catalyst with a weakly coordinating anion such as perchloride in combination with a higher

reaction temperature proved to be crucial. A brief screening for an appropriate ligand revealed the challenging character of this endeavour and the PyOx motif to be most promising one. The best result was achieved using PyOx **82** leading to formation of the desired CPone **55** in 80% yield and 63:37 *er* (Scheme 53).



Scheme 53: Proof-of-concept for the asymmetric *Wacker-Tsuji* oxidation of prochiral MCB **66** towards enantioenriched CPone **55** using a chiral PyOx ligand.

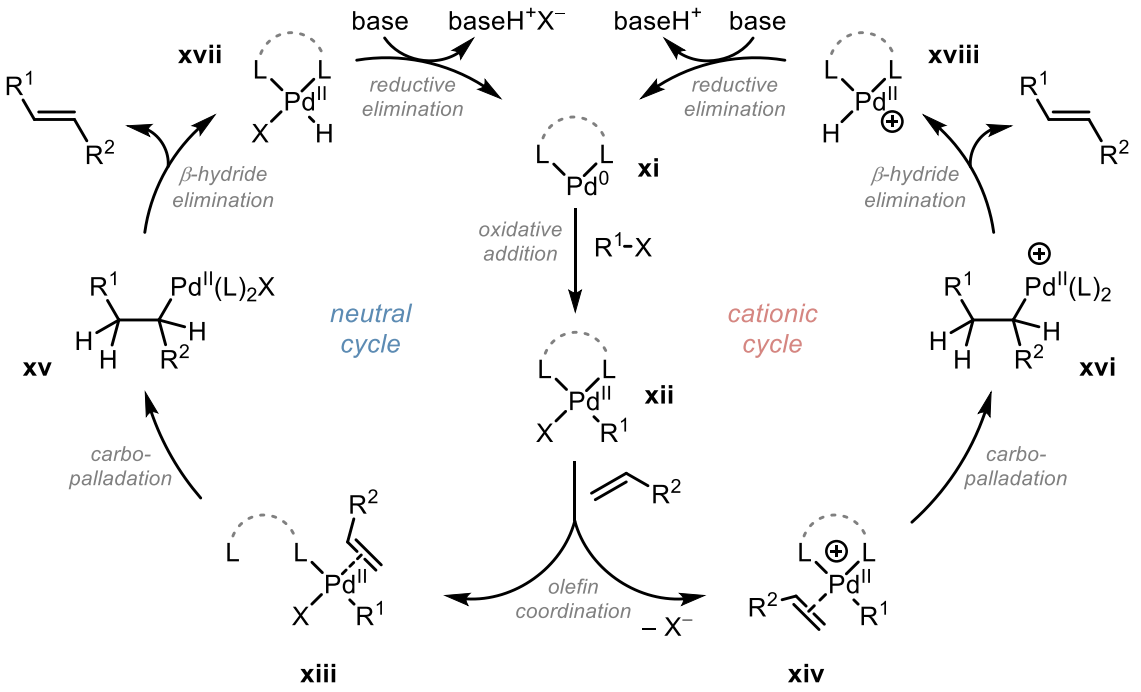
It is envisioned that the enantioselectivity of the reaction can be further optimised by continued evolution of the used ligand. Preliminary results by [redacted] have already shown slight improvements of the enantioinduction when employing a PyOx ligand bearing a sterically demanding group on the 6-position of the pyridine moiety.[134] Further studies towards improved ligands are currently underway. Further, identification of a more potent catalyst for the reaction allowing for lower reaction temperature could significantly enhance the desired enantioselectivity. Therefore, continued studies on palladium catalysts bearing weakly coordinating ligands with respect to the reaction temperature are anticipated useful.

4 Asymmetric desymmetrisation of methylenecyclobutanes *via Heck* reaction

4.1 Introduction

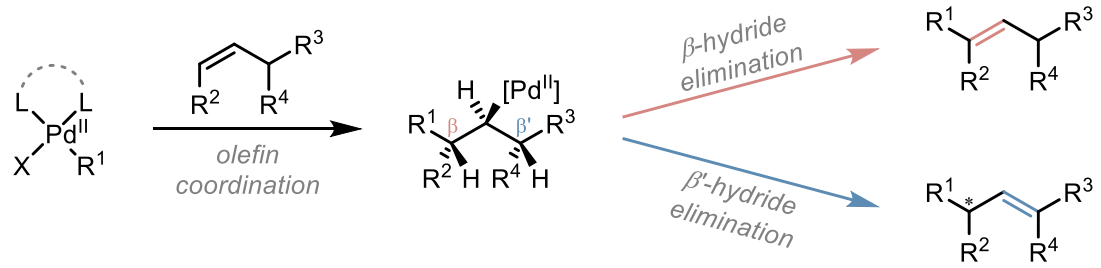
In the early 1970s *Mizoroki* and *Heck* independently discovered the palladium catalysed coupling of alkenes with aryl or alkenyl halides in the presence of base.[135] The reaction nowadays referred to as *Heck* reaction or more precise *Mizoroki-Heck* reaction received great attention and was intensely studied over the past decades resulting in the awarding of the Nobel price to *Heck* in 2010 along with *Negishi* and *Suzuki*.[136,137,138]

Regarding the mechanism, two catalytic cycles are accepted in literature (Scheme 54). The catalytic cycle generally starts with an oxidative addition of the respective halide or *pseudo*-halide to palladium(0) (**xi**), usually generated *in-situ* from a palladium(II) source. From here on, a neutral and a cationic pathway can be differentiated depending on the reaction conditions. As a next step the alkene is coordinated to palladium. Upon olefin coordination either an L-type ligand (Scheme 54, left) or an X-type ligand must dissociate from the palladium complex (Scheme 54, right) to yield a square planar palladium complex,. In the first case a neutral π-complex **xviii** is formed, in the latter, a cationic π-complex **xiv**. The use of aryl or alkenyl triflates or the presence of halide scavengers, such as Ag^+, favour a cationic pathway, while the presence of an excess of halide usually favours a neutral route. After formation of the π-complex, carbopalladation of the double bond takes place yielding a σ-alkylpalladium complex (**xv** and **xvi**, respectively) in either linear or branched fashion. Subsequently, σ-bond rotation establishes the *syn*-conformation required for the following β-hydride elimination releasing the desired product. Base-mediated reductive elimination of HX from the resulting palladium-hydride species (**xvii** and **xviii**, respectively) then closes the catalytic cycle.



Scheme 54: Exemplified neutral and cationic catalytic cycle for the *Mizoroki-Heck* reaction. Carbopalladation towards the branched product was omitted for clarity.

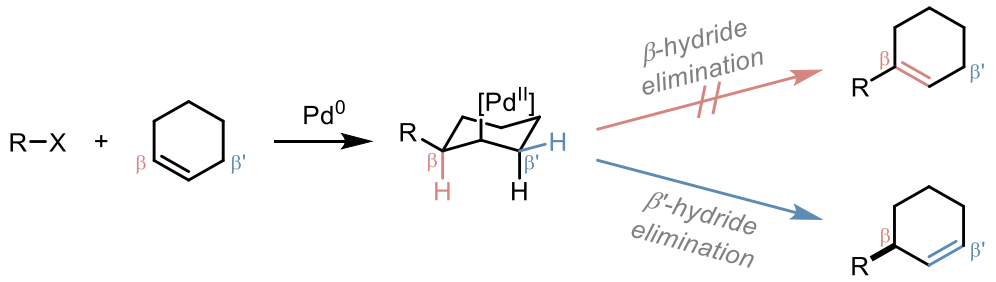
An interesting aspect of *Mizoroki-Heck* reactions, which was studied especially in recent years, is the possibility of respective enantioselective variants. The *Mizoroki-Heck* reaction traditionally yields achiral products as the sp^3 centre formed in the carbopalladation step is subsequently converted back to a sp^2 centre *via* β-hydride elimination. However, if an additional β'-hydrogen atom is present, conservation of the formed sp^3 centre is possible, providing the opportunity for the formation of a stereocentre. In this case, regioselectivity between β- and β'-hydride elimination becomes relevant. Since both carbopalladation as well as β-hydride elimination, are *syn*-processes, rotation about the C–C σ-bond is necessary for a β-hydride elimination to occur. The preferential β'-hydride elimination over the other one is crucial for an asymmetric *Mizoroki-Heck* reaction (Scheme 55).



Scheme 55: The presence of a β'-hydrogen atom provides the possibility of conservation of the sp^3 centre formed during carbopalladation *via* β'-hydride elimination.

Especially for endocyclic alkenes this scenario is easily controlled, as the required σ-bond rotation in not feasible for steric reasons. Hence, β'-hydride elimination is

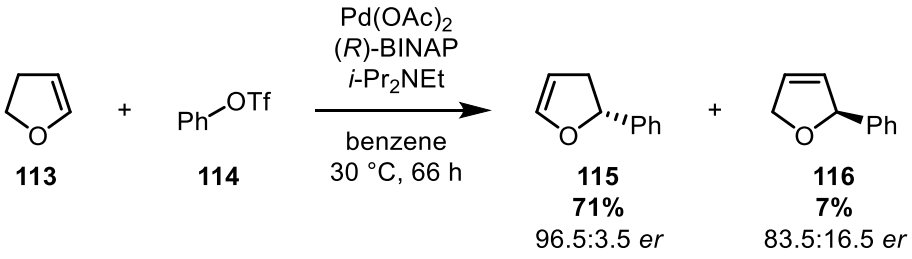
the only viable pathway in that case, which is why many enantioselective *Mizoroki-Heck* reactions published rely on endocyclic alkenes as substrates.[139–141]



Scheme 56: *Mizoroki-Heck* reactions on endocyclic alkenes result in β'-hydride elimination as rotation about the C–C σ-bond is not possible.

Intramolecular asymmetric *Mizoroki-Heck* reactions have the advantage that the alkene regiochemistry is more easily controlled. Due to limited relevance, those will not be discussed in further detail herein. In contrast, intermolecular reactions are often challenging regarding alkene regiochemistry. An early example for an asymmetric *Mizoroki-Heck* reaction was presented by *Hayashi* and co-workers in 1991. Using $Pd(OAc)_2$ as a catalyst and BINAP as chiral P,P-ligand, the authors described the *Mizoroki-Heck* reaction of 2,3-dihydrofuran (**113**) with phenyl triflate (**114**) giving 2-phenyl-2,3-dihydrofuran (**115**) in 71% yield and 96.5:3.5 *er*. Interestingly, 2-phenyl-2,5-dihydrofuran (**116**) was observed as a by-product in opposite configuration and lower *er* (Scheme 57).[142] It is suggested that one of the two diastereomeric complexes formed after carbopalladation has a preferred structure for further olefin insertion and β-hydride elimination. This yields the isomerised major product, while the other diastereomer readily releases the minor product already after the first β-hydride elimination.[140,142,143]

***Hayashi* and co-workers (1991):**

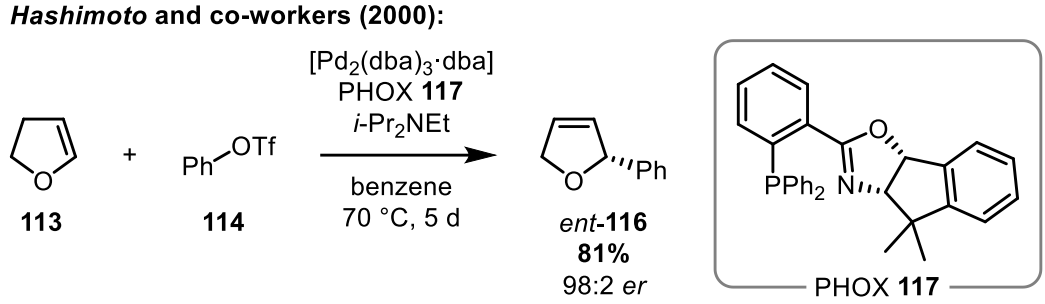


113 **114** **115** **116**
115 **71%** 96.5:3.5 *er*
116 **7%** 83.5:16.5 *er*

Scheme 57: Enantioselective *Mizoroki-Heck* arylation of 2,3-dihydrofuran by *Hayashi* and co-workers.

Since then, the arylation of 2,3-dihydrofuran was used by many other as a benchmark to test reaction conditions and new ligands for enantioselective *Mizoroki-Heck* reactions. Besides widely used P,P-ligands with the prime-example of BINAP and its derivatives, in recent years P,N-ligands, such as phosphinooxazolines (PHOX),

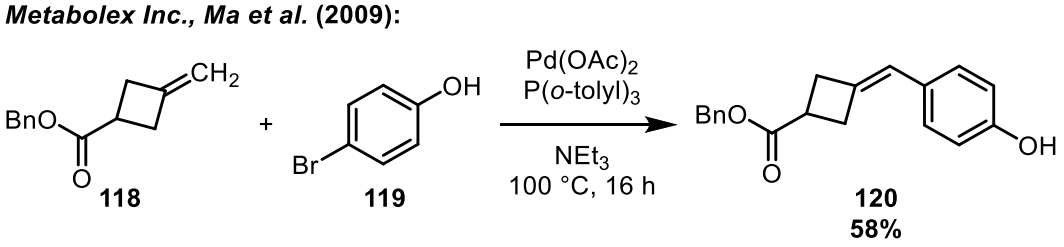
gained significant attention in this field. The latter oftentimes perform superior in terms of enantioselectivity but especially regarding regioselectivity. It is suggested that the higher regiocontrol is due to a more rapid dissociation of the catalyst complex from the alkene product.[139–141] For example, *Hashimoto* and co-workers employed PHOX ligand **117** under similar conditions to those initially used by *Hayashi* and co-workers and obtained dihydrofuran *ent*-**116** in higher yield and improved *er* while the formation of any isomerised products was completely suppressed (Scheme 58).[144]



Scheme 58: *Hashimoto's* enantioselective *Mizoroki-Heck* arylation of 2,3-dihydrofuran using PHOX ligand **117.**

4.1.1 *Mizoroki-Heck* reactions using methylenecyclobutanes as substrates

In contrast to acyclic and endocyclic alkenes, exocyclic alkenes have not received much attention in the context of *Mizoroki-Heck* reactions. Besides some rare examples in literature,[145] *Mizoroki-Heck* reactions on exocyclic alkenes were employed in several patents usually as a part of late-stage functionalisation of a target drug agent.[146] The use of MCBs in particular is poorly studied with only a handful of reports published to date.[147] In the context of the development of new drug agents for the treatment of diabetes, *Metabolex Inc.* published a patent containing the *Mizoroki-Heck* arylation of benzyloxycarbonyl MCB **118** with 4-bromophenol (**119**). The authors obtained the desired trisubstituted alkene **120** in 58% yield using palladium(II) acetate in combination with tri-*ortho*-tolyl phosphine as ligand in triethyl amine (Scheme 59).



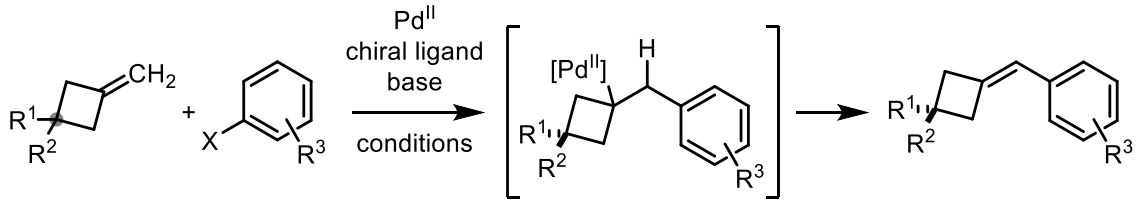
Scheme 59: *Mizoroki-Heck* arylation of MCB **118** by *Ma et al.*

If prochiral MCBs are used for such a transformation, the respective products possess the interesting property of axial chirality resulting from a stereogenic axis running through the bond axis of the alkene moiety (*cf.* chapter 1.3.2, Figure 9). Thus, such *Mizoroki-Heck* reaction forms enantiomers without the need for conservation of the intermediately formed sp^3-centre. Although the enantioselective *Mizoroki-Heck* reaction on prochiral MCBs is considered interesting, to the best of one's knowledge, no study investigating such endeavour was reported to date.

4.1.2 Motivation and aim

Due to the absence of a general method for the *Mizoroki-Heck* reaction on MCBs it was sought to develop such synthetic protocol. The initial focus of the project was a respective arylation of MCBs.

It was envisioned that enantioselective desymmetrisation would become feasible when employing prochiral MCBs as the corresponding products then possess axial chirality. Those were anticipated to be valuable targets for further research on their properties and applications due their appearance in the context of medicinal chemistry. Therefore, prochiral MCBs were chosen as substrates for the initial optimisation of reaction conditions. After identification of potent reaction conditions for the racemic variant, it was envisioned to adapt these for the use of a chiral ligand to enable enantioinduction (Scheme 60).



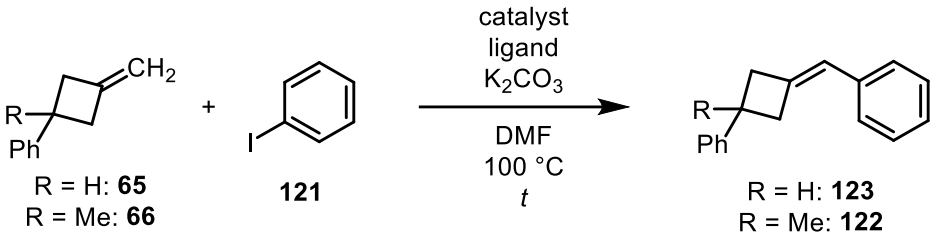
Scheme 60: Reaction scheme for the envisioned enantioselective *Mizoroki-Heck* arylation of prochiral MCBs.

4.2 Optimisation of reaction conditions

For the initial optimisation of reaction conditions for the desired transformation, the two MCBs **65** and **66** were employed as model substrates. It was intended to develop a protocol tolerating both tertiary and quaternary substrates well. Therefore, two respective model substrates were used during the optimisation. Especially less bulky 3-phenyl MCB **65** proved to be a challenging substrate in previous studies on the asymmetric *Wacker-Tsuji* oxidation of MCBs (*cf.* chapter 3.4) under conditions optimised for MCB **66**.

Iodobenzene (**121**) was used as the aryl component under classical *Mizoroki-Heck* conditions as a starting point. MCB **66** was transferred to the desired alkene **122** in a moderate yield of 43% using palladium(II) acetate in combination with triphenyl phosphine as ligand and potassium carbonate as base in DMF (Table 10, entry 1). After this initial result, the reaction parameters were successively investigated. The impact of the electronic character of the used monodentate phosphine ligand was elucidated at first (Table 10). Using MCB **65** as a substrate in combination with triphenyl phosphine resulted in formation of alkene **123** in 34% yield (entry 2). Thus, MCB **65** performed slightly weaker than quaternary MCB **66**, although one must keep in mind that the reaction scale was reduced as well. Next, triphenyl phosphite was employed as ligand in combination with MCB **66**. No difference in performance compared to PPh_3 was observed (entry 3). The use of more electron rich cyclohexyldiphenyl phosphine led to an increased yield of 54% of desired product **122** (entry 4). Further increasing the electron richness of the ligand using tricyclohexyl phosphine with MCB **65** as substrate led again to a noticeably increased yield of 62% (entry 5). Furthermore, tri-*tert*-butyl phosphine was to be tested. For reasons of operational simplicity, the commercial available bis(tri-*tert*-butylphosphine)-palladium(0) complex was used in this case. Interestingly, inferior results were observed (entry 6). The use of *Buchwald*-ligand *t*-BuXPhos in combination with substrate **66** did not lead to any improvement as well as the use of *Buchwald* precatalyst SPhos-Pd-G3 (entries 7 and 8, respectively). A control experiment further showed that alkene **123** was formed even without ligand addition although in lower yield compared to when utilising electron rich phosphines (entry 9).

Table 10: Optimisation of reaction conditions – Screening of monodentate phosphine ligands.

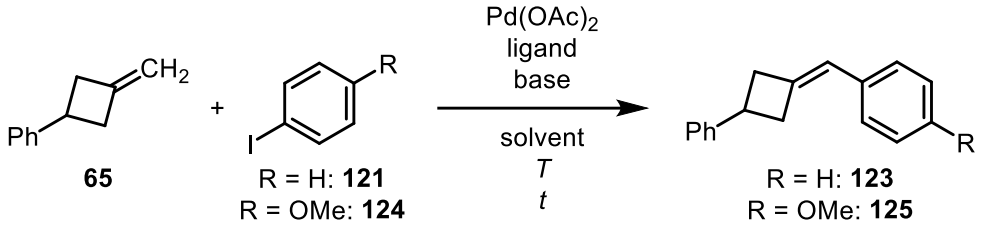


Entry	MCB	Cat.	Ligand	*t* [h]	NMR-Yield	Yield
1[a]	**66**	$Pd(OAc)_2$	PPh_3	16	n.d.	43%
2	**65**	$Pd(OAc)_2$	PPh_3	16	34%	n.d.
3	**66**	$Pd(OAc)_2$	$P(OPh)_3$	18	43%	n.d.
4	**66**	$Pd(OAc)_2$	$PCyPh_2$	18	54%	n.d.
5[b]	**65**	$Pd(OAc)_2$	PCy_3	18	62%	n.d.
6[b]	**65**	$Pd(P(t\text{-}Bu)_3)_2$		18	32%	n.d.
7	**66**	$Pd(OAc)_2$	*t*-BuXPhos	18	51%	n.d.
8[b]	**66**	*Buchwald's* SPhos-Pd-G3		18	39%	n.d.
9[b]	**62**	$Pd(OAc)_2$	-	18	48%	n.d.

Reactions were run on 0.20 mmol scale in 2 mL solvent (0.1 M) using 1.00 eq. PhI, 1.10 eq. MCB, 10 mol% catalyst, 20 mol% ligand, 2.00 eq. K_2CO_3. NMR yields determined from the crude reaction mixture *via* ^1H NMR using mesitylene as internal standard. [a] Reaction run on 0.50 mmol scale. [b] Reaction run on 0.10 mmol scale.

The influence of the reaction solvent and the used base was investigated simultaneously (Table 11). The solvents DMF, 1,4-dioxane and acetonitrile were tested while using MCB **65** as substrate, PPh_3 as ligand and K_2CO_3 as base. The use of DMF resulted in the formation of alkene **123** in 34% yield (entry 1). The other two both showed inferior results (entries 2 and 3, respectively). Furthermore, DMA was tested in combination with cyclohexyldiphenyl phosphine as ligand resulting in a yield of 52% of desired product **123** (entry 4). Compared to the respective result using the same ligand in DMF with MCB **66** as substrate (Table 10, entry 4), no significant difference between the use of DMA or DMF was observed. The use of amine base diisopropylethylamine (DIPEA) in toluene as solvent was not an appropriate choice for the desired transformation, completely suppressing the reaction (entry 5). As it was found that highly unpolar alkene **123** was practically inseparable from by-products by the means of silica column chromatography, the aryl halide substrate was changed. More polar 4-iodoanisole (**124**) was used in order to facilitate separability. A respective control experiment showed a slightly reduced yield of 53% of alkene **125** compared to using iodobenzene (**121**) under the at that point best conditions (entry 6). The use of triethylamine in DMF as solvent seemed to inhibit the reaction (entry 7, *cf.* Table 12 entry 4). The combination of caesium carbonate as base in methanol was tested as well without any improvement (entry 8).

Table 11: Optimisation of reaction conditions – Screening of solvent and base.

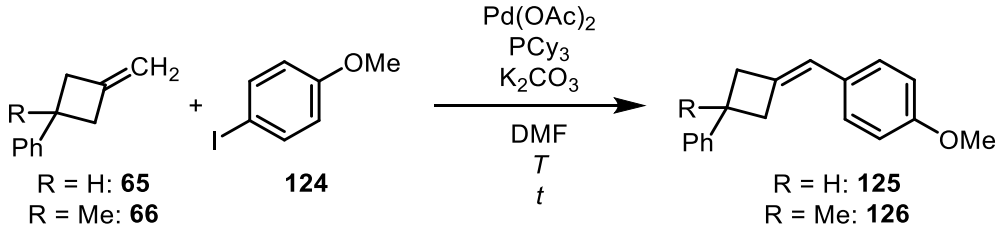


Entry	ArI	Ligand	Base	Solvent	*T* [°C]	*t* [h]	NMR-Yield
1	**121**	PPh_3	K_2CO_3	DMF	100	16	34%
2	**121**	PPh_3	K_2CO_3	1,4-dioxane	100	18	19%
3	**121**	PPh_3	K_2CO_3	MeCN	80	18	14%
4[a]	**121**	$PCyPh_2$	K_2CO_3	DMA	100	18	52%
5	**121**	PCy_3	DIPEA	PhMe	100	18	<2%
6	**124**	PCy_3	K_2CO_3	DMF	100	18	53%
7	**124**	PCy_3	NEt_3	DMF	80	3	9%
8[a]	**124**	PCy_3	Cs_2CO_3	MeOH	80	6	11%

Reactions were run on 0.20 mmol scale in 2 mL solvent (0.1 M) using 1.00 eq. ArI, 1.10 eq. MCB, 10 mol% catalyst, 20 mol% ligand, 2.00 eq. base. NMR yields determined from the crude reaction mixture *via* ^{1}H NMR using mesitylene as internal standard. [a] Reaction run on 0.10 mmol scale.

Since the observed yield seemed to be limited to moderate values, the impact of the reaction temperature and time was of interest (Table 12). It became apparent that reaction time could be reduced significantly without a loss in yield (entries 1 and 2, *cf.* Table 11, entry 6). This indicates a rather fast reaction, reaching a plateau in terms of the product formed after a short time. Lowering of the reaction temperature to 80 °C was tolerated with no loss in performance after a reaction time of 18 h (entry 3). Running the reaction at 80 °C for only one hour resulted in a slightly reduced yield of 47% (entry 4). Based on these results, it was hypothesised that the employed MCBs might degrade over time under the used reaction conditions. Therefore, MCB **65** was submitted to the reaction conditions without addition of an aryl halide for 18 h at 100 °C as well as 80 °C reaction temperature. No significant degradation was observed by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as internal standard in both cases. Only 53% of the substrate were detected in the case of the higher temperature, though. A rather high volatility of MCB **65** might, however, distort this value. At a reaction temperature of 80 °C, still 78% of the substrate was detected. Additionally, further reduction of the reaction temperature to 60 °C or room temperature led to a reduced yield for alkenes **125** and **126** and complete suppression of the reaction, respectively (entries 5 – 7).

Table 12: Optimisation of reaction conditions – Screening of reaction temperature and time.



Entry	MCB	*T* [°C]	*t* [h]	NMR-Yield
1	**66**	100	1	33%
2	**65**	100	1	55%
3	**65**	80	18	54%
4	**65**	80	1	47%
5	**66**	60	18	9%
6	**65**	60	18	20%
7	**66**	rt	18	<2%

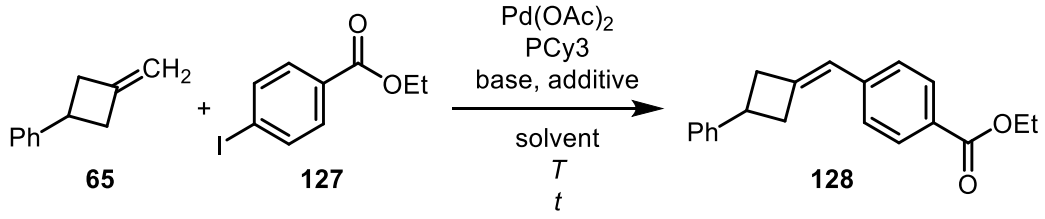
Reactions were run on 0.10 mmol scale in 1 mL solvent (0.1 M) using 1.00 eq. ArI, 1.10 eq. MCB, 10 mol% $Pd(OAc)_2$, 20 mol% PCy_3, 2.00 eq. K_2CO_3. NMR yields determined from the crude reaction mixture *via* ^1H NMR using mesitylene as internal standard.

In order to achieve higher yields, it was elucidated, if the addition of a quaternary ammonium salt would facilitate the desired reaction (Table 13). Tetraalkyl ammonium halides are known to have beneficial effects on *Mizoroki-Heck* reactions in many cases, due to their ability to act as a solid-liquid or liquid-liquid phase transfer agent as well as to stabilise underligated Pd^0 species.[137,138] It was further chosen to use ethyl 4-iodobenzoate (**127**) as aryl halide component for the continued optimisation to ease oxidative addition. Thus, tetrabutylammonium bromide (TBAB) was added under otherwise unchanged conditions leading to the formation of alkene **128** in 58% yield (entry 1). Even at a lower reaction temperature the addition of TBAB did not result in significant improvement (entry 2).

The addition of silver(I) salts acting as halogen scavengers usually results in precipitation of the respective silver halide. By removing the halide ligand from the palladium, the cationic pathway is forced (*cf.* chapter 4.1). Furthermore, many *Mizoroki-Heck* reactions are accelerated in the presence of silver(I) salts.[137,138] Therefore, the influence of silver(I) salts on the reaction outcome was investigated. Running the reaction using silver carbonate as base in acetonitrile at 80 °C resulted in the formation of alkene **128** in 55% yield (entry 3). Reduction of the reaction temperature to 40 °C led to an increased yield of 76% (entry 4). Further, it was possible to run the reaction even at room temperature without notable loss in yield (entry 5). The use of silver acetate as well as silver phosphate led to inferior results (entries 6 and

7). Moreover, it was tried to separate the source of Ag^+ from the employed base by the addition of silver(I) perchlorate hydrate while using potassium phosphate or carbonate as the base. Significantly reduced yields were obtained in both cases (entries 8 and 9, respectively).

Table 13: Optimisation of reaction conditions – Impact of TBAB and silver(I) salts.

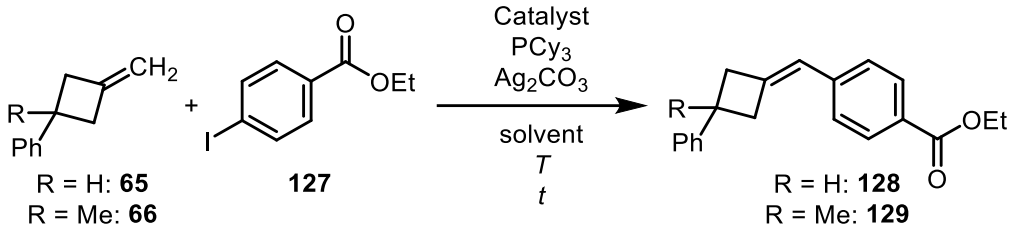


Entry	Base	Additive (eq.)	Solvent	*T* [°C]	*t* [h]	NMR-Yield
1	K_2CO_3	TBAB (1.00)	DMF	80	16	58%
2	K_2CO_3	TBAB (1.00)	DMF	40	16	23%
3	Ag_2CO_3	-	MeCN	80	16	55%
4	Ag_2CO_3	-	MeCN	40	16	76%
5	Ag_2CO_3	-	MeCN	rt	16	75%
6	Ag(OAc)	-	MeCN	rt	16	57%
7	Ag_3PO_4	-	MeCN	rt	16	47%
8	K_3PO_4	$AgOCl_4 \cdot H_2O$ (2.00)	MeCN	rt	18	23%
9	K_2CO_3	$AgOCl_4 \cdot H_2O$ (2.00)	MeCN	rt	16	17%

Reactions were run on 0.10 mmol scale in 1 mL solvent (0.1 M) using 1.00 eq. ArI, 1.00 eq. MCB, 10 mol% $Pd(OAc)_2$, 30 mol% PCy_3, 2.00 eq. base, 1.00 eq additive. NMR yields determined from the crude reaction mixture *via* ^1H NMR using mesitylene as internal standard.

Having found silver carbonate to be the base of choice for the *Mizoroki-Heck* reaction of MCB **65** with ethyl 4-iodobenzoate (**127**), the used catalyst and solvent were revalidate (Table 14). Changing the source of palladium to either $PdCl_2(MeCN)_2$ or $Pd_2(dba)_3$ was tolerated but led to inferior yields (entries 1 and 2, respectively). Switching the solvent to methanol or toluene under otherwise unchanged conditions resulted in formation of alkene **128** in 35% and 22%, respectively (entries 3 and 4, respectively). Interestingly, the presence of two equivalents of an amine base under the so far optimal condition was tolerated – in contrast to previous findings – but not beneficial for the reaction outcome (entry 5, *cf.* Table 11, entries 5 and 7). MCB **66** was tested as a substrate using the optimised conditions as well. The respective alkene **129** was detected in 40% yield, thus is found to be less reactive than MCB **65** under these conditions (entry 6). Increase of the reaction temperature to 60 °C led to a slight improvement of 48% yield (entry 7). Prolongation of the reaction time to 72 h resulted in the formation of alkene **129** in a moderate yield of 60% (entry 8).

Table 14: Continued optimisation of reaction conditions.

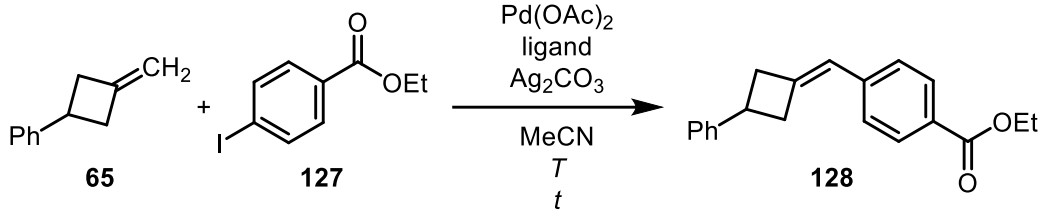


Entry	MCB	Cat.	Solvent	*T* [°C]	*t* [h]	NMR-Yield
1	**65**	$PdCl_2(MeCN)_2$	MeCN	rt	19	44%
2	**65**	$Pd_2(dba)_3$	MeCN	rt	16	33%
3	**65**	$Pd(OAc)_2$	MeOH	rt	19	35%
4	**65**	$Pd(OAc)_2$	PhMe	rt	19	22%
5[a]	**65**	$Pd(OAc)_2$	MeCN	rt	16	65%
6	**66**	$Pd(OAc)_2$	MeCN	rt	18	40%
7	**66**	$Pd(OAc)_2$	MeCN	60	18	48%
8[b]	**66**	$Pd(OAc)_2$	MeCN	60	72	60%

Reactions were run on 0.10 mmol scale in 1 mL solvent (0.1 M) using 1.00 eq. ArI, 1.00 eq. MCB, 10 mol% catalyst, 30 mol% ligand, 2.00 eq. base. NMR yields determined from the crude reaction mixture *via* ^{1}H NMR using mesitylene as internal standard. [a] Additionally, 2.00 eq. of DIPEA were added. [b] Reaction run on 0.20 mmol scale.

The need for an electron rich phosphine ligand and the tolerance of bidentate phosphine ligands in combination with the use of silver carbonate was further elucidated (Table 15). Lowering the electron richness of the phosphine from PCy_3 to PPh_3 resulted in the loss of reactivity (entry 1). Increase of the reaction temperature to 40 °C did not solve that problem, indicating that the use of an electron rich phosphine ligand is still crucial to obtain high reactivity (entry 2). Furthermore, bidentate phosphine ligands were tested briefly. The use of 1,2-bis(diphenylphosphino)ethane (dppe) at 40 °C did not lead to any product formation, which was not very surprising in the light of the previous findings (entry 3). Using 1,4-bis(diphenylphosphino)butane (dppb) at 60 °C, the desired product **128** was found in 14% yield (entry 4). These findings indicate that bidentate phosphines might as well be tolerated though the electronic properties remain essential for sufficient conversion.

Table 15: Continued optimisation of reaction conditions – Bidentate phosphines.

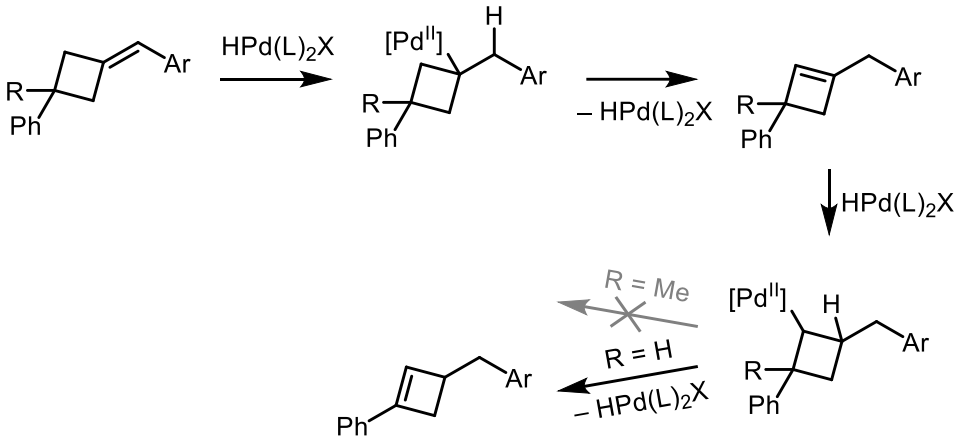


Entry	Cat.	Ligand	*T* [°C]	*t* [h]	NMR-Yield
1	$Pd(OAc)_2$	PPh_3	rt	16	<2%
2	$Pd(OAc)_2$	PPh_3	40	16	4%
3[a]	$Pd(OAc)_2$	dppe	40	16	2%
4[a]	$Pd(OAc)_2$	dppb	60	16	14%

Reactions were run on 0.10 mmol scale in 1 mL solvent (0.1 M) using 1.00 eq. ArI, 1.00 eq. MCB, 10 mol% $Pd(OAc)_2$, 30 mol% ligand, 2.00 eq. Ag_2CO_3. NMR yields determined from the crude reaction mixture *via* ^{1}H NMR using mesitylene as internal standard. [a] 15 mol% ligand were used instead of 30 mol%.

With optimised conditions at hand giving reasonable yields of the desired products in racemic fashion, it was endeavoured to introduce a chiral surrounding. It was anticipated that using a chiral ligand on palladium would enable enantioselective desymmetrisation (Table 16). A first attempt was made by employing (*R*)-BINAP as ligand resulting in complete suppression of the reaction (entry 1). In the light of previous results this can be attributed to inappropriate electronic properties of the phosphine. Alternatively, isopropyl substituted PHOX **130** was tested giving the same result (entry 2; Figure 20, *vide infra*). Raising the reaction temperature to 60 °C did not result in any improvement in this case (entry 3). It was anticipated that the PyOx might be a potent ligand motif due to their unique electronic push-pull properties. By employing PyOx **82** the desired product was formed in a low yield of 15% (entry 4). Due to the limited success using bidentate chiral ligands, chiral, monodentate ligands were of interest as well. Phoshoramidite **131** was therefore synthesised according to a procedure by *Smith et al.*[148] and subsequently tested. It appeared that at a reaction temperature of 60 °C the desired alkene **128** was formed in 47% yield (entry 5; Figure 20, *vide infra*). Though, significant amounts of by-products were observed by ^{1}H NMR analysis. Attempts to separate and characterise these by the means of silica column chromatography failed. However, representative peaks in the ^{1}H NMR spectrum suggest these to be isomers of the desired alkene probably resulting from poor regioselectivity of the migratory insertion or from isomerisation of the product *via* re-insertion of the olefin in the palladium-hydride species (Scheme 61). (*R*)-BINAP was tested again at a higher reaction temperature of 60 °C. The desired product **128** was formed in 52% yield (entry 6). In this case, the same

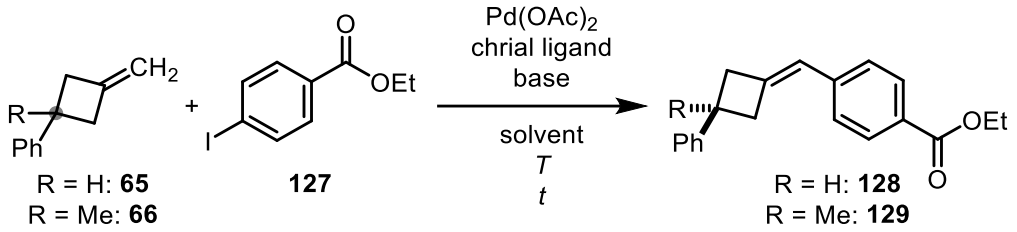
by-products as with ligand **131** were observed, albeit in a lesser amount. The isolation of the desired product was though impeded by these, which is why no *er* was determined. MCB **66** was used as substrate although less reactive to circumvent this issue. Under prolongation of the reaction time to 65 h a moderate yield of 68% of alkene **129** was isolated (entry 7). Formation of by-products was only observed in traces, which supports the hypothesis of the by-products being isomers of the desired alkenes formed by re-insertion of the alkene. Such isomerisation process could lead to two different cyclobutene by-products by two successive olefin insertions and β-hydride eliminations, if the MCBs is bearing a hydrogen in 3-position (Scheme 61). For MCBs with a quaternary centre in 3-position the second isomerisation is impossible, due to the missing hydrogen atom. Furthermore, the additional steric bulk in 3-position might already impede the first re-insertion as a result of steric repulsion with the large palladium complex.



Scheme 61: Plausible pathway for the formation of the hypothesised cyclobutene by-products.

Interestingly, BINAP proved ineffective for enantioinduction, as alkene **129** was obtained in a racemic mixture (entry 7). The use of monodentate phosphoramidite **131** using MCB **66** as substrate under prolonged reaction time led to a similar yield of 64%, but again provided alkene **129** as racemic mixture (entry 8). Moreover, *tert*-butyl substituted Box **9** was tested, but no enantioselectivity was achieved (entry 9). Changing from the optimised conditions back to using potassium carbonate as base in DMF at 80 °C the usage of PHOX ligand **130** was enabled. The desired alkene **129** was afforded in 49% yield as a racemic mixture (entry 10).

Table 16: Attempts towards the optimisation of chiral conditions of the *Mizoroki-Heck* arylation of MCBs.



Entry	MCB	Ligand	Base	Solvent	*T* [°C]	*t* [h]	NMR-Yield	Yield	*er*
1	**65**	(*R*)-**112**	Ag_2CO_3	MeCN	rt	18	<2%	-	-
2	**65**	PHOX **130**	Ag_2CO_3	MeCN	rt	18	<2%	-	-
3	**65**	PHOX **130**	Ag_2CO_3	MeCN	60	18	<2%	-	-
4[c]	**65**	PyOx **82**	Ag_2CO_3	MeCN	60	18	15%	n.d.	n.d.
5	**65**	**131**	Ag_2CO_3	MeCN	60	18	47%	n.d.	n.d.
6[a]	**65**	(*R*)-**112**	Ag_2CO_3	MeCN	60	20	52%	n.d.	n.d.
7[b,c]	**66**	(*R*)-**112**	Ag_2CO_3	MeCN	60	65	n.d.	68%	50:50
8[b,d]	**66**	**131**	Ag_2CO_3	MeCN	60	65	n.d.	64%	50:50
9[b,c]	**66**	Box **9**	Ag_2CO_3	MeCN	60	40	n.d.	54%	50:50
10[b,c]	**66**	PHOX **130**	K_2CO_3	DMF	80	40	n.d.	49%	50:50

Reactions were run on 0.10 mmol scale in 1 mL solvent (0.1 M) using 1.00 eq. ArI, 1.00 eq. MCB, 10 mol% $Pd(OAc)_2$, 20 mol% ligand, 2.00 eq. base. NMR yields determined from the crude reaction mixture *via* ^1H NMR using mesitylene as internal standard. [a] Reaction run on 0.30 mmol scale. [b] Reaction run on 0.20 mmol scale. [c] 15 mol% ligand used instead of 20 mol%. [d] 30 mol% ligand used instead of 20 mol%.

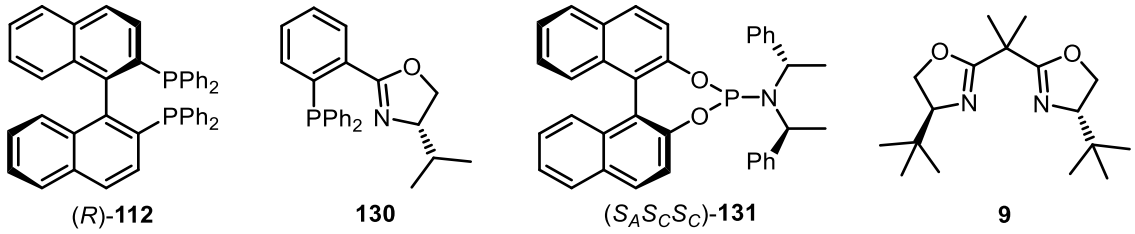


Figure 20: Structure of the ligands elucidated for the asymmetric *Mizoroki-Heck* arylation of prochiral MCBs in this study.

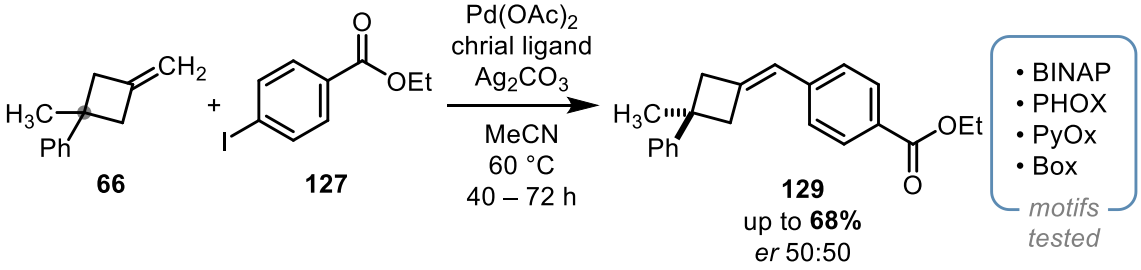
As the above discussed results indicate, the asymmetric *Mizoroki-Heck* arylation of prochiral MCBs resembles a challenging endeavour. Ligands commonly employed in asymmetric *Mizoroki-Heck* reactions like BINAP or PHOX ligands proved ineffective and no enantioinduction was achieved so far. Further optimisation of the reaction conditions and research on a potent ligand is needed to enable the desired transformation in enantioselective fashion.

4.3 Summary and outlook

Over the course of this project, it was sought to develop reaction conditions for the enantioselective *Mizoroki-Heck* arylation of prochiral MCBs. Initially, reaction conditions for the racemic reaction were optimised. The feasibility of the endeavour was successfully demonstrated by the coupling of MCB **66** with iodobenzene (**121**). Running the reaction in DMF using palladium(II) acetate, triphenyl phosphine and potassium carbonate, alkene **122** was isolated in 43% yield. Subsequently, the reaction parameters were successively investigated. Both 3-phenyl substituted MCB **65** and 3-methyl-3-phenyl substituted MCB **66** were used as model substrates. For the coupling with iodobenzene (**121**) as model aryl halide, it was found that electron rich phosphine ligands are beneficial for the reaction outcome. Tricyclohexyl phosphine proved to be most effective facilitating the formation of alkene **123** in 62% yield. A brief screening of different combinations of solvent and base did not reveal any improvements. Furthermore, using 4-iodoanisole (**124**) as model aryl halide, it was found that the reaction temperature can be reduced from 100 °C to 80 °C. Since the obtained yields were only moderate, additives known to facilitate *Mizoroki-Heck* reaction in many cases, such as quaternary ammonium salts or silver(I) salts, were elucidated employing ethyl 4-iodobenzoate (**127**) as model aryl halide. The addition of one equivalent of TBAB to the reaction led to no improvement. In contrast, the use of silver carbonate as the base in acetonitrile resulted in significantly increased yields at lower reaction temperatures. The respective alkene **128** was formed in 75% yield even at room temperature. This improvement is attributed to the presence of Ag^+-ions forcing a cationic pathway. Continued optimisation revealed that silver carbonate is the best source of silver(I) as well as that palladium acetate is the best catalyst.

Having optimised conditions for the racemic reaction, it was then attempted to use chiral ligands to enable an enantioselective transformation. It became apparent that ligands commonly used for asymmetric *Mizoroki-Heck* reactions like BINAP or PHOX were supressing the reaction under the optimised conditions. Conversion towards the desired alkene products was achieved by raising the reaction temperature to 60 °C. Inseparable by-products were encountered when using MCB **65** as a substrate. It is hypothesised that these result from isomerisation of the desired alkene **128** by re-insertion of the olefin and subsequent β-hydride elimination. This issue

was circumvented using MCB **66** as substrate. The respective alkene **129** was isolated in moderate yields of up to 68% depending on the respective ligand and reaction time. However, of the ligands investigated non was able to induce any enantioselectivity (Scheme 62).



Scheme 62: Attempt on the enantioselective *Mizoroki-Heck* arylation of prochiral MCBs.

To achieve the desired enantioinduction further research is needed. The synthesis and investigation of more electron rich derivatives of the tested ligands motifs might be useful to facilitate the reaction at lower temperatures. For example, BINAP or PHOX derivatives bearing cyclohexyl substituents instead of phenyl groups, are promising in this regard. It is further assumed that a more confined chiral pocket is needed to achieve enantioinduction. Therefore, ligands occupying more space around the active centre, such as BINAP derivatives bearing bulky substituents in 3,3'-position, may be worth investigating. Additionally, the use of aryl triflates instead of aryl iodides could be investigated. Aryl triflates are generally assumed to react *via* the cationic pathway in *Mizoroki-Heck* reactions, due to the rather weak Pd–OTf bond. This could supersede the need for the addition of a silver(I) salt and thereby open up more possibilities for further optimisation of the reaction conditions.

5 Experimental part

5.1 General Information

Nuclear magnetic resonance (NMR) spectra were recorded by the analytical departments of the Organisch-Chemisches Institut at the Westfälische Wilhelms-Universität and of the Department Chemie at Johannes Gutenberg-Universität Mainz. Following spectrometers were used: An Avance II 400 (Bruker), a DD2 500 (Agilent), a DD2 600 (Agilent), an Avance III HD 300 (Bruker), an Avance III HD 400 (Bruker). Spectra were recorded at 26 °C (unless otherwise noted). Chemical shifts are reported in ppm with the solvent resonance as the internal standard (^{1}H NMR $CHCl_3$: δ = 7.26 ppm, C_6HD_5: δ = 7.16 ppm, $(CHD_2)(CD_3)SO$: δ = 2.50 ppm; ^{13}C NMR $CDCl_3$: δ = 77.16 ppm, C_6D_6: δ = 128.06 ppm, $(CD_3)_2SO$: δ = 39.5 ppm). Chemical shifts of ^{19}F NMR are referenced to internal or external standards according to *Togni* and coworkers.[149] The data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet or combinations of these), coupling constants (Hz) and integration. Apparent multiplicity, which occurs as a result of accidental equality of coupling constants to magnetically non-equivalent protons, is marked as *app*.

Infrared (IR) spectra were obtained on a Perkin-Elmer 100 FT-IR spectrometer or on a Jasco FT/IR-4100 and are reported in wavenumbers (cm^{-1}). Bands are characterized as broad (br), strong (s), medium (m), and weak (w).

Melting points (M.P.) were measured on a Büchi B-545 and are reported uncorrected.

High Resolution Mass Spectrometry (HRMS) was performed by the analytical departments of the Organisch-Chemisches Institut at the Westfälische Wilhelms-Universität and of the Department Chemie at Johannes Gutenberg-Universität Mainz. Spectra were recorded on a Bruker Daltonics MicroTof, on a Thermo-Fisher Scientific Orbitrap LTQ XL or an Agilent G6545AQ-ToF. Signals are reported as mass to charge ratio *m/z*. GC-MS data was acquired using an Agilent 7890A Gas Chromatograph and an Agilent 5975 or 5975 VL MSD Inert Mass Selective Detector (EI) and is reported as *m/z* (relative intensity).

Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm wavelength (sodium D-line) using a standard 10 cm cell (1 mL). Specific rotations,

$[\alpha]_D^T$, are reported in degree mL/(g·dm) at the specific temperature. Concentrations (*c*) are given in grams per 100 mL of the specific solvent.

Analytical high-performance liquid chromatography (HPLC) measurements were performed on an Agilent 1100, an Agilent 1260 Infinity II or a Knauer system (Knauer HPLC Pump Smartline 1000 with degassing unit, Knauer Autosampler Smartline 3950, Knauer UV-detector Smartline 2550, Knauer RI-detector Smartline 2300). Separation was performed using Lux® i-Cellulose-5 (4.6 x 250 nm x 5 µm, Phenomenex Ltd.), Lux® Cellulose-1 (4.6 x 250 nm x 5 µm, Phenomenex Ltd.), Lux® Amylose-1 (4.6 x 250 nm x 5 µm, Phenomenex Ltd.), Lux® i-Amylose-3 (4.6 x 250 nm x 5 µm, Phenomenex Ltd.), Reprosil Chiral-AMS (4.6 x 250 nm x 5 µm, Dr Maisch GmBH.) or Chiralpak® IF-3 (4.6 x 250 nm x 5 µm, Daicel Chiral Technologies).

Purification was performed either *via* standard column chromatography (FC) techniques using 60 M silica gel (0.04 – 0.063 mm, MACHEREY-NAGEL), 40-63 µm silica gel (VWR chemicals) or Geduran® Si 60 (0.04 – 0.063 mm, Millipore) or on an automated flash chromatography (AFC) system *Biotage Isolera One* utilizing *Biotage Sfär Silica D-Duo* 60 µm columns (5 g, 25 g, 100 g). Glass silica gel plates 60 F254 (Merck) were used for thin layer chromatography (TLC) using UV light (254/366 nm), $KMnO_4$ (1.5 g $KMnO_4$, 5 g $NaHCO_3$ and 5 mL NaOH 10% in 200 mL H_2O), CAM (0.5 g $Ce(NH_4)_2(NO_3)_6$ and 24.0 g of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 28 mL H_2SO_4 in 200 mL H_2O) and PMA (10 g $H_3[P(Mo_3O_{10})_4]{\cdot}xH_2O$ in 100 mL EtOH) stain for detection.

Chemicals were purchased from *Alfa Aesar*, *Acros Organics*, *Fisher Scientific*, *Sigma Aldrich*, *BLDpharm*, *FluoroChem*, *Carbolution* or *ABCR* and used as received. Scandium triflate was dried at 200 °C over P_2O_5 prior to use and stored in a glovebox. All work-up and purification procedures were carried out with pre-distilled technical grade solvents. Dry solvents were either dried with standard techniques or collected from a *MBraun MB SPS-800* (CH_2Cl_2, Et_2O, THF). A positive argon pressure was used to pass the solvents through the following columns:

CH_2Cl_2: 2 × MB-KOL-A

Et_2O: 1 × MB-KOL-A and 1 × MB-KOL MT2-250

THF: 2 × MB-KOL MT2-150 °C

All reactions involving air or moisture sensitive reagents were carried out in oven- (125 °C) and flame-dried glassware under argon or nitrogen atmosphere using

standard *Schlenk* techniques. Reactions requiring heating were conducted using aluminium blocks as heating source.

Documentation of the experimental work was done partly using the electronic lab notebook (ELN) *Chemotion*. A respective sample number is indicated in the corresponding entries. Otherwise, the documentation was carried out using conventional lab notebooks in paper form.

5.2 Asymmetric desymmetrisation of prochiral cyclobutanones *via* ring expansion

5.2.1 Synthesis of cyclobutanones

5.2.1.1 General procedures

General Procedure A: [2+2] Cycloaddition of keteniminium salt

Following a modified procedure by *Chernykh et al.*,[28] a Schlenk tube was charged with DMA (1.20 eq.) in 1,2-dichloroethane (0.5 M). The reaction solution was kept at room temperature in a water bath. Tf_2O (2.00 eq.) was added dropwise and the reaction mixture was stirred at room temperature for 10 min. A solution of the corresponding alkene (1.00 eq.) and 2,6-lutidine (2.00 eq.) in 1,2-dichloroethane (2.0 M) was added dropwise to the reaction mixture, which was stirred at 90 °C for 8 h. The reaction was allowed to cool to room temperature and water (20 mL) was added. The reaction mixture was stirred at 90 °C for 16 h. The mixture was allowed to cool to room temperature and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was isolated *via* FC with the conditions given in the corresponding entry.

General Procedure B: [2+2] Cycloaddition of dichloroketene

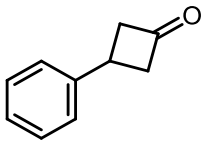
Following a modified procedure by *Malkov et al.*,[24] a Schlenk flask was charged with Zn dust (6.00 eq.) and freshly distilled Et_2O (0.14 M with respect to the alkene). The corresponding alkene (1.00 eq.) was added to the suspension. The suspension was kept at room temperature in a water bath while a solution of TCAC (2.50 eq.) and $POCl_3$ (1.10 eq.) in freshly distilled Et_2O (0.5 M with respect to the trichloroacetyl

chloride) was added. The water bath was removed and the suspension was stirred at 40 °C for 8 h. After complete conversion, the suspension was allowed to cool down to room temperature and filtered through a pad of Celite® and washed with CH_2Cl_2. The solvents were removed under reduced pressure and the residue was taken up in CH_2Cl_2. The organic layer was washed with water (3×) and with an sat. aq. $NaHCO_3$ sol. (3×). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude reaction mixture was used without further purification.

To a round flask the crude reaction mixture of the first reaction step and glacial acetic acid (0.1 M with respect to the alkene) were added. The solution was kept at 20 °C in a water bath and Zn dust (4.00 eq.) was slowly added. The suspension was heated to 80 °C and stirred for 16 h. The mixture was allowed to cool down to room temperature, filtered through a pad of Celite® and washed with CH_2Cl_2. The solvent was removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (50 mL) and the organic layer was washed with an sat. aq. $NaHCO_3$ sol. (3×) and water (3×). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was obtained *via* FC with the conditions given in the corresponding entry.

5.2.1.2 Syntheses

3-Phenylcyclobutanone [1]



Following general procedure **A** using styrene (5.75 mL, 50.0 mmol, 1.00 eq.), dimethylacetamide (5.58 mL, 60.0 mmol, 1.20 eq.), Tf_2O (16.8 mL, 100 mmol, 2.00 eq.) and 2,6-lutidine (11.6 mL, 100 mmol, 2.00 eq.), the desired product was obtained *via* AFC (CyHex:EtOAc; 100:0 → 95:5) followed by distillation (Kugelrohr, bulb-to-bulb, 0.25 mbar, 75 – 100 °C) as colourless oil (5.67 g, 38.8 mmol, 78%).

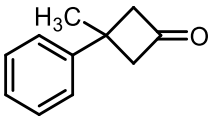
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 – 7.23 (m, 5H), 3.77 – 3.61 (m, 1H), 3.57 – 3.40 (m, 2H), 3.32 – 3.19 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 207.0, 143.7, 128.8, 126.8, 126.6, 54.9, 28.6.

Spectroscopic data was in agreement with that previously reported.[150]

Chemotion ELN sample number: MTN-5-30-A.

3-Methyl-3-phenylcyclobutanone [2]



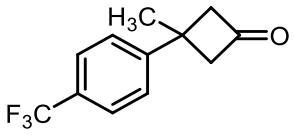
Following general procedure **A** using α-methylstyrene (3.25 mL, 25.0 mmol, 1.00 eq.), dimethylacetamide (2.79 mL, 30.0 mmol, 1.20 eq.), Tf_2O (8.41 mL, 50.0 mmol, 2.00 eq.) and 2,6-lutidine (5.83 mL, 50.0 mmol, 2.00 eq.), the desired product was obtained *via* AFC (CyHex:EtOAc; 100:0 → 80:20) as colourless oil (3.56 g, 22.3 mmol, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 – 7.35 (m, 2H), 7.34 – 7.30 (m, 2H), 7.29 – 7.22 (m, 1H), 3.60 – 3.38 (m, 2H), 3.21 – 3.02 (m, 2H), 1.61 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.9, 148.4, 128.7, 126.4, 125.8, 59.4, 34.1, 31.2.

Spectroscopic data was in agreement with that previously reported.[151]

3-Methyl-3-(4-(trifluoromethyl)phenyl)cyclobutanone [3]



Following general procedure **A** using 1-(prop-1-en-2-yl)-4-(trifluoromethyl)benzene (931 mg, 5.00 mmol, 1.00 eq.), dimethylacetamide (560 µL, 6.00 mmol, 1.20 eq.), Tf_2O (1.68 mL, 10.0 mmol, 2.00 eq.) and 2,6-lutidine (1.17 mL, 10.0 mmol, 2.00 eq.), the desired product was obtained *via* FC (pentane:Et_2O; 90:10) as colourless oil (621 mg, 2.72 mmol, 54%).

IR (neat): $\tilde{\nu}$ = 2962 (br), 2925 (br), 2871 (br), 1785 (s), 1619 (w), 1451 (w), 1411 (w), 1389 (w), 1325 (s), 1300 (m), 1163 (m), 1108 (s), 1086 (s), 1064 (s), 1015 (m), 955 (w), 875 (w), 840 (m), 718 (w), 672 (w).

^{1}H NMR (599 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.0 Hz, 2H, CH_{arom}), 7.43 (d, J = 8.0 Hz, 2H, CH_{arom}), 3.51 – 3.44 (m, 2H, CH_2), 3.20 – 3.13 (m, 2H, CH_2), 1.63 (s, 3H, CH_3).

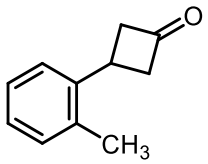
^{13}C NMR (151 MHz, $CDCl_3$): δ = 205.5 (C_q), 152.3 (C_q), 128.9 (q, J = 32.5 Hz, C_q), 126.3 (2×CH$_{arom}$), 125.8 (q, J = 3.7 Hz, 2×CH$_{arom}$), 124.3 (q, J = 271.91 Hz, CF$_3$), 59.3 (2×CH$_2$), 34.3 (C_q), 31.0 (CH$_3$).

^{19}F NMR (377 MHz, $CDCl_3$): δ = −62.46.

HRMS (EI): Calculated for $C_{12}H_{11}F_3O^+$ $[M]^+$: 228.0756, found: 228.0760.

Synthesis performed by [redacted]

3-(2-Methylphenyl)cyclobutanone [4]



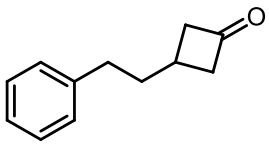
Following general procedure **A** using 2-methylstyrene (2.18 mL, 17.0 mmol, 1.00 eq.), dimethylacetamide (1.90 mL, 20.4 mmol, 1.20 eq.), Tf_2O (5.72 mL, 34.0 mmol, 2.00 eq.) and 2,6-lutidine (3.96 mL, 34.0 mmol, 2.00 eq.), the desired product was obtained *via* FC (pentane:EtOAc; 95:5) as colourless oil (1.87 g, 11.7 mmol, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 – 7.08 (m, 4H), 3.69 (*app.* p, $J \approx 8.3$ Hz, 1H), 3.44 – 3.27 (m, 2H), 3.26 – 3.09 (m, 2H), 2.25 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.8, 140.8, 136.5, 130.6, 126.9, 126.4, 124.6, 53.1, 26.2, 20.1.

Spectroscopic data was in agreement with that previously reported.[152] Synthesis performed by [redacted]

3-Phenethylcyclobutanone [5]



Following modified general procedure **B** using 4-phenyl-1-butene (150 µL, 1.00 mmol, 1.00 eq.), zinc dust (392 mg, 6.00 mmol, 6.00 eq.) and trichloroacetyl chloride (280 µL, 2.50 mmol, 2.50 eq.) in the first step[4] and zinc dust (654 mg, 10.0 mmol, 10.0 eq.) in the second step[5], the desired product was obtained *via* FC (pentane:EtOAc; 95:5 → 90:10) as a colourless oil (108 mg, 0.620 mmol, 62%).

IR (neat): $\tilde{\nu}$ = 3567 (w), 3064 (w), 3026 (w), 2933 (w), 2850 (w), 2364 (w), 2342 (w), 1781 (s), 1604 (w), 1496 (w), 1455 (w), 1386 (w), 1102 (w), 1075 (w), 913 (w), 746 (m), 699 (s), 641 (m), 631 (m), 615 (s), 597 (s), 585 (m).

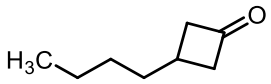
[4] [2+2] Cycloaddition performed at rt for 3 h without the addition of $POCl_3$.
[5] Reduction performed at 80 °C for 4 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.27 (m, 2H, CH_{arom}), 7.25 – 7.13 (m, 3H, CH_{arom}), 3.20 – 3.08 (m, 2H, CH_2), 2.76 – 2.62 (m, 4H, CH_2), 2.38 (ttt, J = 8.7, 7.5, 6.2 Hz, 1H, CH), 1.96 – 1.88 (m, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 208.3 (C_q), 141.5 (C_q), 128.6 (2×CH$_{arom}$), 128.5 (2×CH$_{arom}$), 126.1 (CH$_{arom}$), 52.6 (2×CH$_2$), 38.1 (CH$_2$), 34.7 (CH$_2$), 23.5 (CH$_3$).

HRMS (ESI): Calculated for $C_{12}H_{15}O^+$ $[M+H]^+$: 175.1118, found: 175.1117.

3-Butylcyclobutanone [6]



Following general procedure **B** using 1-hexene (1.24 mL, 10.0 mmol, 1.00 eq.), zinc dust (3.92 g, 60.0 mmol, 6.00 eq.) and trichloroacetyl chloride (2.79 mL, 25.0 mmol, 2.50 eq.) in the first step and zinc dust (2.62 g, 40.0 mmol, 4.00 eq.) in the second step, the desired product was obtained *via* FC (pentane:Et_2O; 95:5) as a colourless oil (471 mg, 3.70 mmol, 37%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.22 – 3.07 (m, 2H), 2.72 – 2.60 (m, 2H), 2.42 – 2.28 (m, 1H), 1.58 *(app.* q, $J \approx$ 7.6 Hz, 2H), 1.41 – 1.24 (m, 4H), 0.92 (t, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 209.0, 52.7, 36.2, 30.6, 24.0, 22.6, 14.2.

Spectroscopic data was in agreement with that previously reported.[153] Synthesis performed by [redacted]

5.2.2 Synthesis of diazomethanes

PDMSD and DPMSD were prepared according to a literature procedure of *Kim et al.*[56] The diazomethanes were stored as solution in dry PhMe over 4 Å MS at –32 °C and titrated prior to use according to a procedure of Kingsbury and co-workers.[154]

5.2.3 Synthesis of ligands

Following ligands were either commercially available or prepared according to literature procedures:

36 (CAS [132098-59-0]), **37** (CAS [141362-77-8]), **38** (Synthesis performed by [redacted]),[52] **40** (CAS [133463-88-4]), **41** (CAS [131864-67-0]), **42** (CAS [147409-41-4]), **43**,[155] **44** (CAS [180857-90-3]), **45**,[57] **46** (CAS [135616-36-3]), **47** (CAS [18531-94-7]), **48** (CAS [492-08-0]) **49.**[67]

The benzyl protected aminoalcohol **132** used for the synthesis of ligand **50** was prepared according to a literature procedure by [redacted].[156]

5.2.3.1 General procedures

General procedure C: Bis(hydroxy)amide formation

Following a modified procedure by *Evans et al.*,[77] a flame dried Schlenk tube was charged with the corresponding aminoalcohol (2.00 eq.) and dry CH_2Cl_2 (0.8 M with respect to the aminoalcohol). The mixture was cooled to 0 °C and dry NEt_3 (5.00 eq.) was added. Then, a solution of the corresponding acid chloride (1.00 eq.) in dry CH_2Cl_2 (1.25 M) was added dropwise over 15 min. It was stirred at 0 °C for 30 min., before the reaction mixture was warmed to rt and stirred for 16 h. It was diluted with CH_2Cl_2 until all formed solids dissolved. It was washed with 1 M aq. HCl (1×). The aq. layer was extracted with CH_2Cl_2 (1×) and the combined org. phases were washed with sat. aq. $NaHCO_3$ sol. (1×). The aq. layer was extracted with CH_2Cl_2 (1×) and the combined org. phases were washed with sat. aq. NaCl sol. (1×), dried over $MgSO_4$ filtered and concentrated *in vacuo*. The product was obtained *via* recrystallisation with the conditions given in the corresponding entry or was used without further purification.

General procedure D: Synthesis of bis(oxazoline)-ligands

Following a modified procedure by *Bandini et al.*,[157] the corresponding bis(hydroxy)amide (1.00 eq.) was suspended in dry CH_2Cl_2 (0.1 M with respect to the amide) in an oven dried Schlenk tube. The mixture was cooled to 0 °C and dry NEt_3 (5.0 eq.) was added. Then, mesyl chloride (2.50 eq.) was added dropwise. After complete addition the reaction mixture was stirred for 15 min at 0 °C before it was gradually warmed to rt and stirred for additional 16 h. Water was added and the phases were separated. The aq. layer was extracted with CH_2Cl_2 (4×). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The residue was taken up in MeOH (0.1 M with respect to the amide). Sodium hydroxide (3.00 eq.) was added and the mixture was heated to reflux for 3 h. After cooling to rt the mixture was concentrated and water was added. It was extracted with CH_2Cl_2 (3×). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

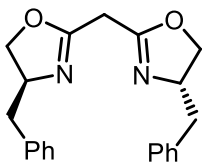
The product was obtained *via* FC, recrystallisation or distillation with the conditions given in the corresponding entry.

General procedure E: Alternative synthesis of bis(oxazoline)-ligands

In an oven dried Schlenk tube dimethyl malononitrile (1.00 eq.) was dissolved in dry PhMe (0.8 M with respect to the nitrile) and $Zn(OTf)_2$ (2.00 eq.) was added. The corresponding aminoalcohol (2.00 eq.) was added and the mixture was heated to 130 °C for 3 d. After cooling to rt, it was washed with sat. aq. $NaHCO_3$-sol. (1×) and sat. aq. NaCl sol. (1×). The org. phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was obtained *via* FC, recrystallisation or distillation with the conditions given in the corresponding entry.

5.2.3.2 Syntheses

Bis((*S*)-4-benzyl-4,5-dihydrooxazol-2-yl)methane [7]



(*S*)-Phenylglycinol (1.66 g, 11.0 mmol, 2.20 eq.) and malonic acid (520 mg, 5.00 mmol, 1.00 eq.) were dissolved in CH_2Cl_2 (20 mL). Then, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (2.11 g, 11.0 mmol, 2.20 eq.) and DMAP (122 mg, 1.00 mmol, 0.20 eq.) were added and it was stirred at rt for 6 h. Then, 1 M aq. HCl (20 mL) was added. The phases were separated and the aq. layer extracted with CH_2Cl_2 (3×15 mL). The combined org. phases were washed with 1 M aq. NaOH (2×10 mL) and sat. aq. NaCl sol. (10 mL). The org. layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. N^1,N^3-Bis((*S*)-1-hydroxy-3-phenylpropan-2-yl)malonamide was obtained *via* recrystallisation from hot EtOAc as colourless solid (689 mg, 1.86 mmol, 37%).

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 7.93 (d, J = 8.3 Hz, 2H), 7.31 – 7.20 (m, 4H), 7.24 – 7.11 (m, 6H), 4.80 (t, J = 5.4 Hz, 2H), 3.88 (m, 2H), 3.40 – 3.23 (m, 4H), 2.97 (s, 2H), 2.80 (dd, J = 13.6, 6.1 Hz, 2H), 2.62 (dd, J = 13.6, 7.7 Hz, 2H).

Following general procedure **D** using N^1,N^3-bis((*S*)-1-hydroxy-3-phenylpropan-2-yl)malonamide (370 mg, 1.00 mmol, 1.00 eq.), dry NEt_3 (700 µL, 5.00 mmol,

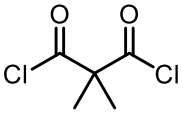
5.00 eq.), mesyl chloride (190 µL, 2.50 mmol, 2.50 eq.) and NaOH (133 mg, 3.00 mmol, 3.00 eq.), the desired product was obtained *via* FC (CH_2Cl_2:MeOH; 95:5) as a yellow oil (201 mg, 0.601 mmol, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.26 (m, 4H), 7.25 – 7.14 (m, 6H), 4.52 – 4.37 (m, 2H), 4.24 (dd, *J* = 9.4, 8.5 Hz, 2H), 4.02 (dd, *J* = 8.5, 7.2 Hz, 2H), 3.37 – 3.28 (m, 2H), 3.11 (dd, *J* = 13.8, 5.4 Hz, 2H), 2.68 (dd, *J* = 13.8, 8.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8, 137.9, 129.3, 128.6, 126.6, 71.8, 67.0, 41.5.

Spectroscopic data was in agreement with that previously reported.[157]

2,2-Dimethylmalonyl dichloride



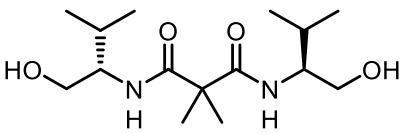
Following a modified procedure by *Breising et al.*,[158] dimethylmalonic acid (1.00 g, 7.57 mmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (10 mL) under Ar-atmosphere. Then, DMF (60 µL, 0.76 mmol, 0.10 eq.) was added and the mixture was cooled to 0 °C. Oxalyl chloride (1.95 mL, 22.7 mmol, 3.00 eq.) was added *via* syringe pump over 20 min. After complete addition the reaction mixture was gradually warmed to rt and stirred for 16 h. The solvent was removed *in vacuo*. Distillation of the residue (Kugelrohr, 80 mbar, 77 – 85 °C) afforded the desired product as pale-yellow oil (1.16 g, 6.87 mmol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.1, 69.2, 23.3.

Spectroscopic data was in agreement with that previously reported.[158]

N^1,*N*^{3}-Bis((*S*)-1-hydroxy-3-methylbutan-2-yl)-2,2-dimethylmalonamide [133]



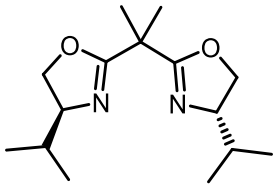
Following general procedure **C** using L-valinol (586 mg, 5.00 mmol, 2.00 eq.), dry NEt_3 (1.73 mL, 12.5 mmol, 5.00 eq.) and 2,2-dimethylmalonyl dichloride (423 mg, 2.50 mmol, 1.00 eq.), the desired product was obtained as a colourless solid (620 mg, 2.05 mmol, 82%) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (d, *J* = 8.8 Hz, 2H), 3.86 – 3.68 (m, 4H), 3.52 (dd, *J* = 11.4, 7.2 Hz, 2H), 2.62 (br s, 2H), 1.80 (hept, *J* = 6.7 Hz, 2H), 1.49 (s, 6H), 0.98 – 0.72 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 63.5, 57.3, 50.3, 29.3, 23.9, 19.8, 18.9.

Spectroscopic data was in agreement with that previously reported.[79]

(4*S*,4'*S*)-2,2'-(Propane-2,2-diyl)bis(4-isopropyl-4,5-dihydrooxazole) [8]



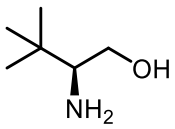
Following general procedure **D** using bis(hydroxy)amide **133** (212 mg, 0.701 mmol, 1.00 eq.), dry NEt_3 (490 µL, 3.50 mmol, 5.00 eq.), mesyl chloride (140 µL, 1.75 mmol, 2.50 eq.) and NaOH (84.0 mg, 2.10 mmol, 3.00 eq.), the desired product was obtained *via* distillation (Kugelrohr, 1 mbar, 160 °C) as a colourless oil (173 mg, 0.650 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20 (td, *J* = 7.7, 1.2 Hz, 2H), 4.03 – 3.93 (m, 4H), 1.85 – 1.75 (m, 2H), 1.51 (s, 6H), 0.91 (d, *J* = 6.8 Hz, 6H), 0.85 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 71.6, 70.0, 38.7, 32.3, 24.6, 18.7, 17.5.

Spectroscopic data was in agreement with that previously reported.[68]

(*S*)-*tert*-Leucinol



According to a procedure by *McKennon et al.*,[159] *tert*-leucine (4.00 g, 30.5 mmol, 1.00 eq.) and $NaBH_4$ (2.77 g, 73.2 mmol, 2.40 eq.) were suspended in dry THF (80 mL). The mixture was cooled to 0 °C and a solution of iodine (7.74 g, 30.5 mmol, 1.00 eq.) in dry THF (30 mL) is added dropwise over 30 min. After complete addition, it was heated to reflux for 18 h. The reaction mixture was allowed to cool to rt and MeOH (20 mL) was added forming a clear solution. It was stirred for further 30 min before the solvent was removed *in vacuo*. The resulting white paste was dissolved in 20% aq. KOH solution (70 mL) and it was stirred for four hours. Thereafter, it was extracted with CH_2Cl_2 (3×50 mL). The combined org. layers were dried over

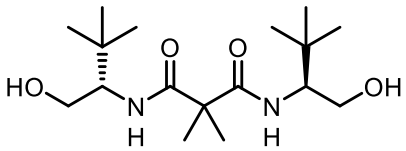
Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified *via* distillation (Kugelrohr, 0.6 mbar, 65 – 85 °C). The product was obtained as a colourless solid (2.96 g, 25.2 mmol, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.70 (dd, J = 10.2, 3.9 Hz, 1H), 3.20 (t, J = 10.2 Hz, 1H), 2.51 (dd, J = 10.2, 3.9 Hz, 1H), 1.90 (s, 3H), 0.89 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 62.4, 61.8, 33.2, 26.4.

Spectroscopic data was in agreement with that previously reported.[160]

N^1,*N*^{3}-Bis((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)-2,2-dimethylmalonamide [134]



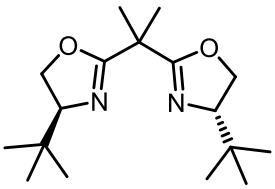
Following general procedure **C** using (*S*)-*tert*-leucinol (560 mg, 4.78 mmol, 2.00 eq.), dry NEt_3 (1.66 mL, 12.0 mmol, 5.00 eq.) and 2,2-dimethylmalonyl dichloride (404 mg, 2.39 mmol, 1.00 eq.), the desired product was obtained as a colourless solid (649 mg, 1.97 mmol, 82%) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.43 (d, J = 9.6 Hz, 2H), 3.93 – 3.80 (m, 4H), 3.51 – 3.29 (m, 2H), 1.51 (s, 6H), 0.93 (s, 18H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.0, 62.5, 59.7, 50.4, 33.6, 26.9, 23.9.

Spectroscopic data was in agreement with that previously reported.[77]

(4*S*,4'*S*)-2,2'-(Propane-2,2-diyl)bis(4-(*tert*-butyl)-4,5-dihydrooxazole) [9]



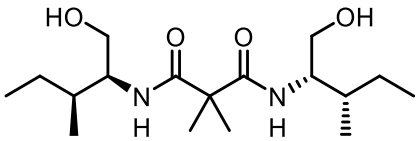
Following general procedure **D** using bis(hydroxy)amide **134** (628 mg, 1.90 mmol, 1.00 eq.), dry NEt_3 (1.32 mL, 9.50 mmol, 5.00 eq.), mesyl chloride (370 µL, 4.75 mmol, 2.50 eq.) and NaOH (228 mg, 5.70 mmol, 3.00 eq.), the desired product was obtained as a pale-yellow oil (491 mg, 1.67 mmol, 88%). No further purification was required.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21 – 3.98 (m, 4H), 3.83 (dd, J = 10.0, 6.9 Hz, 2H), 1.50 (s, 6H), 0.86 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 75.4, 69.1, 38.7, 34.0, 25.7, 24.5.

Spectroscopic data was in agreement with that previously reported.[77,160]

N^1,*N*^{3}-Bis((2*S*,3*S*)-1-hydroxy-3-methylpentan-2-yl)-2,2-dimethylmalonamide [135]



Following general procedure **C** using L-isoleucinol (1.17 g, 10.0 mmol, 2.00 eq.), dry NEt_3 (3.47 mL, 25.0 mmol, 5.00 eq.) and 2,2-dimethylmalonyl dichloride (845 mg, 5.00 mmol, 1.00 eq.), the desired product was obtained as a colourless solid (1.32 g, 4.00 mmol, 80%) and used without further purification.

M.P.: 89 – 90 °C.

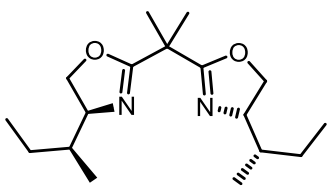
IR (neat): $\tilde{\nu}$ = 3325 (m), 2967 (m), 2938 (m), 2880 (m), 2360 (m), 2335 (m), 1643 (s), 1523 (s), 1464 (m), 1386 (m), 1284 (w), 1193 (w), 1074 (m), 1024 (w), 984 (w), 895 (w), 755 (s), 668 (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.50 (d, J = 9.0 Hz, 2H, N*H*), 3.89 – 3.78 (m, 2H, C*H*), 3.72 (dd, J = 11.6, 3.4 Hz, 4H, 2×CH_2, 2×O*H*), 3.50 (dd, J = 11.4, 7.3 Hz, 2H, CH_2), 1.63 – 1.52 (m, 2H, C*H*), 1.49 – 1.41 (m, 2H, CH_2), 1.46 (s, 6H, CH_3), 1.18 – 1.05 (m, 2H, CH_2), 0.90 (d, J = 6.9 Hz, 6H, CH_3), 0.87 (t, J = 7.5 Hz, 6H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.6 (2×C_q), 63.4 (2×*C*H$_2$), 56.0 (2×*C*H), 50.3 (C_q), 35.7 (2×*C*H), 25.6 (2×*C*H$_2$), 23.8 (2×*C*H$_3$), 15.7 (2×*C*H$_3$), 11.2 (2×*C*H$_3$).

HRMS (ESI): Calculated for $C_{17}H_{34}N_2O_4Na^+$ [M+Na]$^+$: 353.2411, found: 353.2407.

(4*S*,4'*S*)-2,2'-(Propane-2,2-diyl)bis(4-((*S*)-*sec*-butyl)-4,5-dihydrooxazole) [10]

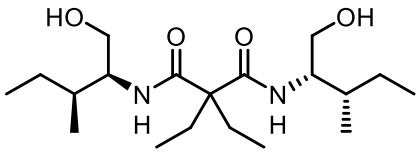


Following general procedure **D** using bis(hydroxy)amide **135** (661 mg, 2.00 mmol, 1.00 eq.), dry NEt_3 (1.39 mL, 10.0 mmol, 5.00 eq.), mesyl chloride (0.39 mL, 5.00 mmol, 2.50 eq.) and NaOH (240 mg, 6.00 mmol, 3.00 eq.), the desired product

was obtained as a pale-yellow oil (555 mg, 1.88 mmol, 94%). No further purification was required.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21 – 4.14 (m, 2H), 4.14 – 4.06 (m, 2H), 4.03 – 3.96 (m, 2H), 1.73 – 1.62 (m, 2H), 1.51 (s, 6H), 1.49 – 1.34 (m, 2H), 1.23 – 1.07 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 6H), 0.78 (d, *J* = 6.8 Hz, 6H).
Spectroscopic data was in agreement with that previously reported.[161]

N^1,*N*^{3}-Bis((2*S*,3*S*)-1-hydroxy-3-methylpentan-2-yl)-2,2-diethylmalonamide [136]



Following a modified procedure by *Breising et al.*,[158] diethylmalonic acid (801 mg, 5.00 mmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (7 mL) under Ar-atmosphere. Then, DMF (40 µL, 0.50 mmol, 0.10 eq.) was added and the mixture was cooled to 0 °C. Oxalyl chloride (1.29 mL, 15.0 mmol, 3.00 eq.) was added *via* syringe pump over 20 min. After complete addition the reaction mixture was gradually warmed to rt and stirred for 16 h. The solvent was removed *in vacuo*. Distillation of the residue (Kugelrohr, 60 mbar, 110 °C) afforded diethylmalonyl dichloride as colourless oil (791 mg, 4.02 mmol, 80%), which was used in the next step.

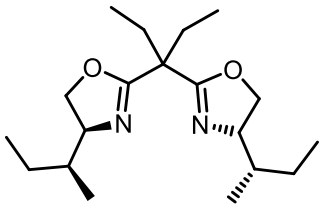
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (q, *J* = 7.6 Hz, 2H), 0.91 (t, *J* = 7.6 Hz, 3H).

Following general procedure **C** using L-isoleucinol (938 mg, 8.00 mmol, 2.00 eq.), dry NEt_3 (2.77 mL, 20.0 mmol, 5.00 eq.) and 2,2-diethylmalonyl dichloride (788 mg, 4.00 mmol, 1.00 eq.), the desired product was obtained as a colourless solid (1.38 g, 3.84 mmol, 96%) and used without further purification.

M.P.: 128 – 129 °C.
IR (neat): $\tilde{\nu}$ = 3350 (w), 2968 (w), 2880 (w), 2360 (w), 1654 (w), 1522 (w), 1461 (w), 1385 (w), 1216 (m), 1075 (w), 1049 (w), 753 (s), 667 (w), 624 (w).
^{1}H NMR (599 MHz, $CDCl_3$): δ = 6.84 (d, *J* = 8.6 Hz, 2H, N*H*), 3.87 (qd, *J* = 7.3, 3.1 Hz, 2H, C*H*), 3.78 – 3.69 (m, 2H, CH_2), 3.59 – 3.53 (m, 2H, CH_2), 3.39 (br s, 2H, O*H*), 2.03 – 1.83 (m, 4H, CH_2), 1.68 – 1.55 (m, 2H, C*H*), 1.55 – 1.41 (m, 2H, CH_2), 1.21 – 1.08 (m, 2H, CH_2), 0.92 (d, *J* = 6.8 Hz, 6H, CH_3), 0.89 (t, *J* = 7.4 Hz, 6H, CH_3), 0.86 (t, *J* = 7.5 Hz, 6H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.9 (2×C_q), 63.8 (2×CH_2), 58.6 (C_q), 56.1 (2×CH), 35.6 (2×CH), 27.5 (2×CH_2), 25.6 (2×CH_2), 15.8 (2×CH_3), 11.2 (2×CH_3), 8.9 (2×CH_3).
HRMS (ESI): Calculated for $C_{19}H_{38}N_2O_4Na^+$ $[M+Na]^+$: 381.2724, found: 381.2418.

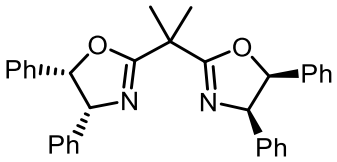
(4*S*,4'*S*)-2,2'-(Pentane-3,3-diyl)bis(4-((*S*)-*sec*-butyl)-4,5-dihydrooxazole) [11]



Following general procedure **D** using bis(hydroxy)amide **136** (1.36 g, 3.80 mmol, 1.00 eq.), dry NEt_3 (2.65 mL, 19.0 mmol, 5.00 eq.), mesyl chloride (0.74 mL, 9.50 mmol, 2.50 eq.) and NaOH (456 mg, 11.4 mmol, 3.00 eq.), the desired product was obtained as a pale-yellow oil (1.15 g, 3.56 mmol, 94%). No further purification was required.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.19 – 4.06 (m, 4H), 3.97 – 3.90 (m, 2H), 2.08 – 1.88 (m, 4H), 1.74 – 1.60 (m, 2H), 1.50 – 1.36 (m, 2H), 1.25 – 1.08 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 6H), 0.87 – 0.76 (m, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.3, 70.4, 69.0, 46.7, 38.7, 26.4, 25.2, 14.1, 11.9, 8.4.
Spectroscopic data was in agreement with that previously reported.[162]

(4*R*,4'*R*,5*S*,5'*S*)-2,2'-(Propane-2,2-diyl)bis(4,5-diphenyl-4,5-dihydrooxazole) [12]



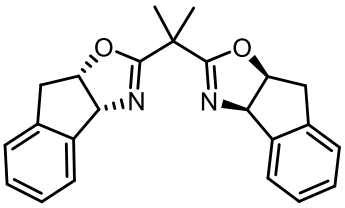
Following general procedure **E** using dimethyl malononitrile (**16**, 90 mg, 0.96 mmol, 1.00 eq.), $Zn(OTf)_2$ (694 mg, 1.91 mmol, 2.00 eq.) and (1*S*,2*R*)-2-amino-1,2-diphenylethan-1-ol (407 mg, 1.91 mmol, 2.00 eq.), the desired product was obtained *via* FC (pentane:acetone; 80:20) as a yellow solid (212 mg, 0.436 mmol, 46%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02 (s, 10H), 6.96 (s, 10H), 5.97 (d, *J* = 10.1 Hz, 2H), 5.60 (d, *J* = 10.1 Hz, 2H), 1.93 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 137.6, 136.3, 128.0, 127.7, 127.5, 127.0, 126.7, 86.4, 73.9, 39.7, 24.9.

Spectroscopic data was in agreement with that previously reported.[163]

(3a*R*,3a'*R*,8a*S*,8a'*S*)-2,2'-(Propane-2,2-diyl)bis(3a,8a-dihydro-8*H*-indeno[1,2-d]-oxazole) [13]



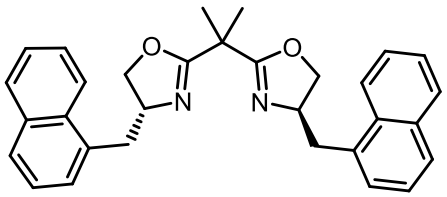
Following general procedure **E** using dimethyl malononitrile (**16**, 47 mg, 0.50 mmol, 1.00 eq.), $Zn(OTf)_2$ (364 mg, 1.00 mmol, 2.00 eq.) and (1*R*,2*S*)-1-amino-2,3-dihydro-1H-inden-2-ol (**90**, 149 mg, 1.00 mmol, 2.00 eq.), the desired product was obtained *via* recrystallisation from hot EtOH as an off-white solid (115 mg, 0.320 mmol, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 – 7.46 (m, 2H), 7.32 – 7.18 (m, 6H), 5.54 – 5.49 (m, 2H), 5.34 – 5.20 (m, 2H), 3.30 (dd, *J* = 17.9, 7.1 Hz, 2H), 3.05 – 2.85 (m, 2H), 1.42 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.3, 142.0, 139.9, 128.5, 127.5, 125.8, 125.2, 83.3, 76.6, 39.8, 38.6, 24.0.

Spectroscopic data was in agreement with that previously reported.[164]

(4*R*,4'*R*)-2,2'-(Propane-2,2-diyl)bis(4-(naphthalen-1-ylmethyl)-4,5-dihydrooxa-zole) [14]



According to a procedure by *Slattery et at.*,[165] $LiAlH_4$ (380 mg, 10.0 mmol, 5.00 eq.) was suspended in dry THF (40 mL) and cooled to 0 °C. (*R*)-3-(1-Naphthyl)-alanine (431 mg, 2.00 mmol, 1.00 eq.) was added in small portions. After complete addition, the mixture was stirred at 0 °C for 1 h and afterwards heated to 66 °C for 16 h. After cooling to rt, water (0.5 mL) was added dropwise followed by aq. NaOH (10%, 0.5 mL) and additional water (1.5 mL). The mixture was stirred until a white

suspension was observed. The mixture was filtered, the precipitate collected and heated to reflux in THF for 1 h. It was filtered again and the combined filtrates were concentrated. The residue was taken up in CH_2Cl_2 (40 mL) and washed with sat. aq. NaCl sol. (40 mL). The aq. layer was extracted with CH_2Cl_2 (30 mL) and the combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. (*R*)-2-Amino-3-(naphthalen-1-yl)propan-1-ol was obtained as brown solid (388 mg, 1.93 mmol, 96%) and used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 – 7.99 (m, 1H), 7.90 – 7.84 (m, 1H), 7.75 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.46 – 7.39 (m, 1H), 7.34 (dd, *J* = 7.0, 1.3 Hz, 1H), 3.71 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.49 (dd, *J* = 10.6, 6.5 Hz, 1H), 3.38 – 3.25 (m, 2H), 3.03 – 2.89 (m, 1H), 1.93 (br s, 3H).

Following general procedure **E** using dimethyl malononitrile (**16**, 86 mg, 0.91 mmol, 1.00 eq.), $Zn(OTf)_2$ (661 mg, 1.82 mmol, 2.00 eq.) and (*R*)-2-Amino-3-(naphthalen-1-yl)propan-1-ol (367 mg, 1.82 mmol, 2.00 eq.), the desired product was obtained *via* FC (CH_2Cl_2:MeOH; 97:3 and Et_2O:pentane; 80:20 → 100:0) as a brown resin (283 mg, 0.612 mmol, 67%).

IR (neat): $\tilde{\nu}$ = 3003 (w), 2360 (w), 2336 (w), 1653 (m), 1510 (w), 1396 (w), 1357 (w), 1259 (w), 1216 (w), 1148 (w), 1119 (w), 973 (w), 930 (w), 749 (s), 667 (w).

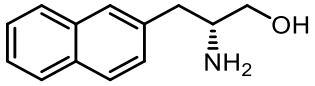
^{1}H NMR (599 MHz, $CDCl_3$): δ = 8.17 – 8.13 (m, 2H, CH_{arom}), 7.85 (dd, *J* = 8.0, 1.6 Hz, 2H, CH_{arom}), 7.75 (d, *J* = 8.2 Hz, 2H, CH_{arom}), 7.52 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 2H, CH_{arom}), 7.49 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 2H, CH_{arom}), 7.40 (dd, *J* = 8.2, 7.0 Hz, 2H, CH_{arom}), 7.34 – 7.31 (m, 2H, CH_{arom}), 4.61 (dtd, *J* = 9.4, 7.9, 4.6 Hz, 2H, C*H*), 4.12 – 4.08 (m, 4H, CH_2), 3.69 (dd, *J* = 14.1, 4.7 Hz, 2H, CH_2), 2.96 (dd, *J* = 14.1, 9.4 Hz, 2H, CH_2), 1.51 (s, 6H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 169.7 (2×C_q), 134.1 (2×C_q), 134.0 (2×C_q), 132.3 (2×C_q), 128.9 (2×CH$_{arom}$), 127.6 (2×CH$_{arom}$), 127.3 (2×CH$_{arom}$), 126.1 (2×CH$_{arom}$), 125.8 (2×CH$_{arom}$), 125.5 (2×CH$_{arom}$), 124.2 (2×CH$_{arom}$), 72.4 (2×CH$_2$), 66.4 (2×CH$_2$), 38.8 (2×CH$_2$), 38.8 (C_q), 24.4 (2×CH$_3$).

HRMS (ESI): Calculated for $C_{17}H_{28}N_2O_2Na^+$ $[M+Na]^+$: 485.2120, found: 485.2192.

Optical rotation: $[\alpha]_D^{25}$ = +19.8 (*c* = 1.00, $CHCl_3$).

(*R*)-2-Amino-3-(naphthalen-2-yl)propan-1-ol [137]



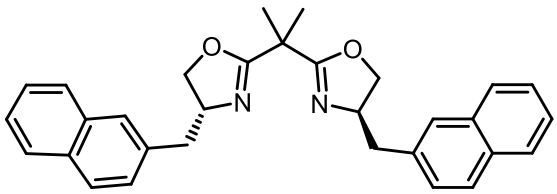
According to a procedure by *Slattery et at.*,[165] $LiAlH_4$ (380 mg, 10.0 mmol, 5.00 eq.) was suspended in dry THF (40 mL) and cooled to 0 °C. (*R*)-3-(2-Naphthyl)-alanine (431 mg, 2.00 mmol, 1.00 eq.) was added in small portions. After complete addition, the mixture was stirred at 0 °C for 1 h and afterwards heated to 66 °C for 16 h. After cooling to rt, water (0.5 mL) was added dropwise followed by aq. NaOH (10%, 0.5 mL) and additional water (1.5 mL). The mixture was stirred until a white suspension was observed. The mixture was filtered, the precipitate collected and heated to reflux in THF for 1 h. It was filtered again and the combined filtrates were concentrated. The residue was taken up in CH_2Cl_2 (40 mL) and washed with sat. aq. NaCl sol. (40 mL). The aq. layer was extracted with CH_2Cl_2 (30 mL) and the combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained as an off-white solid (402 mg, 2.00 mmol, 99%) and used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 – 7.73 (m, 3H), 7.68 – 7.59 (m, 1H), 7.53 – 7.39 (m, 2H), 7.32 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.68 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.44 (dd, *J* = 10.6, 7.1 Hz, 1H), 3.30 – 3.18 (m, 1H), 2.96 (dd, *J* = 13.5, 5.3 Hz, 1H), 2.71 (dd, *J* = 13.5, 8.6 Hz, 1H), 2.00 (br s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.8, 133.6, 132.4, 128.5, 127.9, 127.8, 127.6, 127.6, 126.3, 125.7, 65.9, 54.3, 40.6.

Spectroscopic data was in agreement with that previously reported.[165]

(4*R*,4'*R*)-2,2'-(Propane-2,2-diyl)bis(4-(naphthalen-2-ylmethyl)-4,5-dihydrooxazole) [15]



Following general procedure **E** using dimethyl malononitrile (**16**, 94 mg, 1.00 mmol, 1.00 eq.), $Zn(OTf)_2$ (727 mg, 2.00 mmol, 2.00 eq.) and aminoalcohol **137** (403 mg, 2.00 mmol, 2.00 eq.), the desired product was obtained *via* FC (pentane:EtOAc;

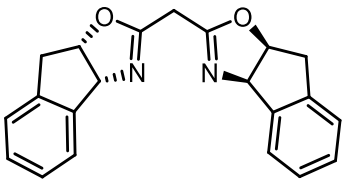
50:50 → 0:100) and crystallisation from $CHCl_3$/MeOH as a white solid (289 mg, 0.625 mmol, 63%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 – 7.70 (m, 6H), 7.62 (d, *J* = 1.8 Hz, 2H), 7.52 – 7.39 (m, 4H), 7.33 (dd, *J* = 8.4, 1.7 Hz, 2H), 4.60 – 4.41 (m, 2H), 4.13 (dd, *J* = 9.3, 8.5 Hz, 2H), 4.00 (dd, *J* = 8.5, 7.0 Hz, 2H), 3.24 (dd, *J* = 13.7, 4.7 Hz, 2H), 2.83 (dd, *J* = 13.7, 8.4 Hz, 2H), 1.47 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 135.3, 133.6, 132.3, 128.1, 128.0, 128.0, 127.7, 127.6, 126.2, 125.6, 72.1, 67.0, 41.5, 38.7, 24.3.

Spectroscopic data was in agreement with that previously reported.[165]

Bis((3a*R*,8a*S*)-3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazol-2-yl)methane [*ent*-17]



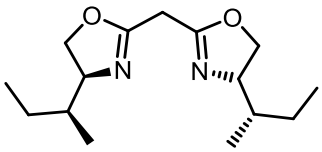
According to a procedure by *Synder et at.*,[87] diethyl malonimidate dihydrochloride (578 mg, 2.50 mmol, 1.00 eq.) and (1*R*,2*S*)-1-amino-2,3-dihydro-1H-inden-2-ol (**90**, 783 mg, 5.52 mmol, 2.10 eq.) were dissolved in CH_2Cl_2 (25 mL) and stirred at 40 °C for 18 h. Then, the mixture was poured into water (50 mL) and it was extracted with CH_2Cl_2 (4×10 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained *via* recrystallisation from hot *i*-PrOH as white needles (478 mg, 1.45 mmol, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 – 7.43 (m, 2H), 7.28 – 7.22 (m, 6H), 5.57 (d, *J* = 7.9 Hz, 2H), 5.34 (ddd, *J* = 8.2, 7.0, 1.8 Hz, 2H), 3.39 (dd, *J* = 18.0, 7.0 Hz, 2H), 3.26 (d, *J* = 1.0 Hz, 2H), 3.16 (dd, *J* = 18.0, 1.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.1, 141.7, 139.8, 128.6, 127.6, 125.6, 125.4, 83.7, 76.7, 39.8, 28.8.

Spectroscopic data was in agreement with that previously reported.[87]

Bis((*S*)-4-((*S*)-*sec*-butyl)-4,5-dihydrooxazol-2-yl)methane [18]



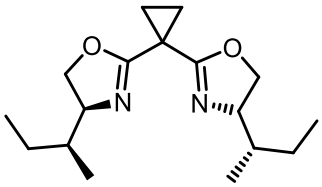
According to a procedure by *Synder et at.*,[87] diethyl malonimidate dihydrochloride (1.16 g, 5.00 mmol, 1.00 eq.) and L-isoleucinol (1.33 g, 10.5 mmol, 2.10 eq.) were dissolved in CH_2Cl_2 (50 mL) and stirred at 40 °C for 24 h. Then, the mixture was poured into water (100 mL) and it was extracted with CH_2Cl_2 (4×25 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained *via* FC (CH_2Cl_2:MeOH; 95:5) as a yellow oil (622 mg, 2.24 mmol, 47%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30 – 4.16 (m, 2H), 4.10 – 3.95 (m, 4H), 3.33 (s, 2H), 1.68 – 1.42 (m, 4H), 1.23 – 1.10 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 6H), 0.81 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.6, 70.8, 70.1, 38.9, 28.5, 26.0, 14.2, 11.4.

Spectroscopic data was in agreement with that previously reported.[69]

(4*S*,4'*S*)-2,2'-(Cyclopropane-1,1-diyl)bis(4-((*S*)-*sec*-butyl)-4,5-dihydrooxazole) [19]



Following a modified procedure by *Hofstra et al.*,[85] sodium hydride (174 mg, 4.34 mmol, 3.00 eq., 60% on mineral oil) was suspended in dry THF (6 mL) in a flame dried Schlenk tube and cooled to 0 °C. Bis(oxazoline) **18** (385 mg, 1.45 mmol, 1.00 eq.) dissolved in dry THF (5 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min before it was allowed to warm to rt. Then, dibromoethane (190 µL, 2.17 mmol, 1.50 eq.) was added slowly and the reaction mixture was heated to 50 °C for 16 h. After cooling to rt water was added. The phases were separated and the aq. layer was extracted with CH_2Cl_2 (3×10 mL). the combined org. phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The desired product was obtained *via* FC (Et_2O:CH_2Cl_2:MeOH; 88:10:2) as a pale-yellow resin (88 mg, 0.30 mmol, 21%).

IR (neat): $\tilde{\nu}$ = 3342 (w), 2967 (m), 2929 (w), 2877 (w), 1709 (w), 1659 (s), 1556 (m), 1463 (w), 1382 (w), 1260 (w), 1216 (w), 1120 (m), 1035 (w), 980 (w), 850 (w), 802 (w), 753 (s), 666 (w), 646 (w), 625 (w), 616 (w), 594 (w), 584 (w).

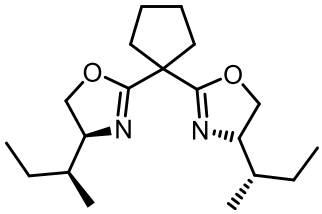
^{1}H NMR (599 MHz, $CDCl_3$): δ = 4.25 – 4.15 (m, 2H, CH_2), 4.06 – 3.97 (m, 4H, 2×CH_2, 2×CH), 1.65 – 1.54 (m, 2H, CH), 1.51 – 1.44 (m, 2H, CH_2), 1.44 – 1.41 (m, 2H, CH_2), 1.36 – 1.30 (m, 2H, CH_2), 1.18 – 1.09 (m, 2H, CH_2), 0.89 (t, J = 7.4 Hz, 6H, CH_3), 0.78 (d, J = 6.8 Hz, 6H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 165.5 (2×C_q), 70.4 (2×CH), 69.9 (2×CH$_2$), 38.9 (2×CH), 26.1 (2×CH$_2$), 18.4 (C_q), 15.4 (2×CH$_2$), 14.1 (2×CH$_3$), 11.8 (2×CH$_3$).

HRMS (ESI): Calculated for $C_{17}H_{28}N_2O_2Na^+$ $[M+Na]^+$: 315.2043, found: 315.2029.

Optical Rotaion: $[\alpha]_D^{25}$ = −80.8 (c = 1.00, $CHCl_3$).

(4*S*,4'*S*)-2,2'-(Cyclopentane-1,1-diyl)bis(4-((*S*)-*sec*-butyl)-4,5-dihydrooxazole) [20]



Following a modified procedure by *Barnes et al.*,[86] bis(oxazoline) **18** (266 mg, 1.00 mmol, 1.00 eq.) was dissolved in dry THF (5 mL) in a flame dried Schlenk tube and placed in a cold water bath. Dibromobutane (240 µL, 2.05 mmol, 2.05 eq.) was added followed by dropwise addition of LiHMDS (1.02 mL, 1.02 mmol, 1.02 eq., 1.0 M in PhMe). The mixture was stirred for 1 h remaining the temperature below 25 °C. Then, a second portion of LiHMDS (1.70 mL, 1.70 mmol, 1.70 eq., 1.0 M in PhMe) was added dropwise over 30 min *via* syringe pump. The reaction mixture was then stirred at rt for 16 h. Sat. aq. NH_4Cl-sol. (5 mL) was added. The phases were separated and the aq. layer was extracted with EtOAc (3×20 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained as a yellow oil (234 mg, 0.730 mmol, 73%). No further purification was required.

IR (neat): $\tilde{\nu}$ = 3399 (w), 2962 (s), 2876 (m), 2358 (w), 2340 (w), 2328 (w), 1736 (w), 1656 (s), 1523 (m), 1463 (m), 1380 (w), 1357 (w), 1248 (m), 1155 (m), 1060 (w), 1003 (m), 964 (m), 907 (w), 761 (w), 747 (w).

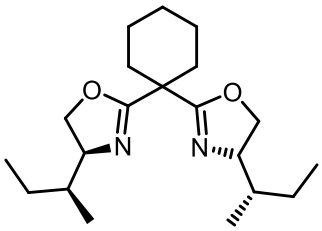
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.18 (dd, *J* = 9.7, 8.0 Hz, 2H, CH_2), 4.08 (ddd, *J* = 9.7, 7.2, 5.1 Hz, 2H, C*H*), 3.98 (dd, *J* = 8.0, 7.2 Hz, 2H, CH_2), 2.38 – 2.28 (m, 2H, CH_2), 2.21 – 2.09 (m, 2H, CH_2), 1.79 – 1.69 (m, 4H, CH_2), 1.69 – 1.58 (m, 2H, C*H*), 1.48 – 1.36 (m, 2H, CH_2), 1.20 – 1.10 (m, 2H, CH_2), 0.90 (t, *J* = 7.5 Hz, 6H, CH_3), 0.78 (d, *J* = 6.8 Hz, 6H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.2 (2×C_q), 70.2 (2×*C*H), 69.6 (2×*C*H_2), 49.2 (C_q), 38.7 (2×*C*H), 35.6 (2×*C*H_2), 26.2 (2×*C*H_2), 25.1 (2×*C*H_2), 13.9 (2×*C*H_3), 11.9 (2×*C*H_3).

HRMS (ESI): Calculated for $C_{17}H_{28}N_2O_2Na^+$ $[M+Na]^+$: 343.2356, found: 343.2352.

Optical rotation: $[\alpha]_D^{25}$ = −64.9 (*c* = 1.00, $CHCl_3$).

(4*S*,4'*S*)-2,2'-(Cyclohexane-1,1-diyl)bis(4-((*S*)-*sec*-butyl)-4,5-dihydrooxazole) [21]



Following a modified procedure by *Barnes et al.*,[86] bis(oxazoline) **18** (175 mg, 0.655 mmol, 1.00 eq.) was dissolved in dry THF (3.3 mL) in a flame dried Schlenk tube and placed in a cold water bath. Dibromopentane (180 µL, 1.34 mmol, 2.05 eq.) was added followed by dropwise addition of LiHMDS (0.67 mL, 0.67 mmol, 1.02 eq., 1.0 M in PhMe). The mixture was stirred for 1 h remaining the temperature below 25 °C. Then, a second portion of LiHMDS (1.09 mL, 1.09 mmol, 1.70 eq., 1.0 M in PhMe) was added dropwise over 30 min *via* syringe pump. The reaction mixture was then stirred at rt for 16 h. Sat. aq. NH_4Cl-sol. (5 mL) was added. The phases were separated and the aq. layer was extracted with EtOAc (3×15 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained *via* FC (pentane:Et_2O; 50:50) as a yellow oil (165 mg, 0.493 mmol, 75%).

IR (neat): $\tilde{\nu}$ = 3400 (m), 2957 (s), 2928 (s), 2878 (m), 1739 (w), 1655 (s), 1518 (m), 1463 (m), 1379 (w), 1348 (w), 1228 (m), 1211 (m), 1128 (m), 1057 (m), 1047 (m), 1034 (m), 1013 (w), 1002 (w), 979 (s), 955 (w), 941 (w), 906 (w), 894 (w).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.18 – 4.07 (m, 4H, 2×CH_2, 2×C*H*), 3.99 – 3.93 (m, 2H, CH_2), 2.12 – 2.04 (m, 2H, CH_2), 2.01 – 1.93 (m, 2H, CH_2), 1.72 – 1.65 (m, 2H, C*H*), 1.65 –

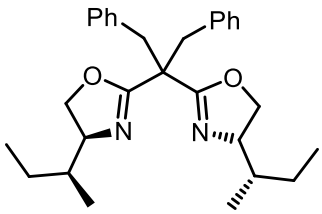
1.57 (m, 2H, CH_2), 1.56 – 1.47 (m, 2H, CH_2), 1.47 – 1.37 (m, 4H, CH_2), 1.21 – 1.09 (m, 2H, CH_2), 0.91 (t, J = 7.4 Hz, 6H, CH_3), 0.80 (d, J = 6.8 Hz, 6H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.6 (2×C_q), 70.4 (2×CH), 69.0 (2×CH$_2$), 43.3 (C_q), 38.7 (2×CH), 32.8 (2×CH$_2$), 26.3 (2×CH$_2$), 25.6 (CH$_2$), 22.8 (2×CH$_2$), 14.0 (2×CH$_3$), 11.9 (2×CH$_3$).

HRMS (ESI): Calculated for $C_{17}H_{28}N_2O_2Na^+$ $[M+Na]^+$: 357.2513, found: 357.2509.

Optical rotation: $[\alpha]_D^{25}$ = −61.5 (c = 1.00, $CHCl_3$).

(4*S*,4'*S*)-2,2'-(1,3-Diphenylpropane-2,2-diyl)bis(4-((*S*)-*sec*-butyl)-4,5-dihydro-oxazole) [22]



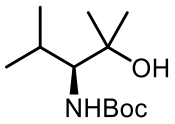
Following a modified procedure by *Barnes et al.*,[86] bis(oxazoline) **18** (133 mg, 0.500 mmol, 1.00 eq.) was dissolved in dry THF (2.5 mL) in a flame dried Schlenk tube and placed in a cold water bath. Benzyl bromide (120 µL, 1.03 mmol, 2.05 eq.) was added followed by dropwise addition of LiHMDS (0.51 mL, 0.51 mmol, 1.02 eq., 1.0 M in PhMe). The mixture was stirred for 1 h remaining the temperature below 25 °C. Then, a second portion of LiHMDS (0.83 mL, 0.83 mmol, 1.70 eq., 1.0 M in PhMe) was added dropwise over 30 min *via* syringe pump. The reaction mixture was then stirred at rt for 16 h. Sat. aq. NH_4Cl-sol. (5 mL) was added. The phases were separated and the aq. layer was extracted with EtOAc (3×10 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained *via* FC (pentane:Et_2O; 100:0 → 0:100) as a yellow oil (196 mg, 0.438 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 – 7.18 (m, 10H), 4.21 – 4.09 (m, 2H), 4.07 – 3.95 (m, 2H), 3.95 – 3.85 (m, 2H), 3.39 (d, J = 14.1 Hz, 2H), 3.24 (d, J = 14.2 Hz, 2H), 1.61 – 1.49 (m, 2H), 1.49 – 1.38 (m, 2H), 1.18 – 1.03 (m, 2H), 0.88 (t, J = 7.4 Hz, 6H), 0.74 (d, J = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.2, 137.1, 130.6, 128.1, 126.7, 70.7, 69.4, 48.3, 39.2, 38.9, 26.4, 14.3, 11.8.

Spectroscopic data was in agreement with that previously reported.[84]

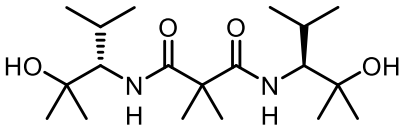
tert-Butyl (*S*)-(2-hydroxy-2,4-dimethylpentan-3-yl)carbamate [138]



Following a procedure by *Xu et al.*,[166] Boc-L-valine methyl ester (**24**, 1.40 g, 6.06 mmol, 1.00 eq.) was dissolved in dry THF (20 mL) in an oven dried Schlenk tube. It was cooled to −10 °C and methyl magnesium bromide solution (8.08 mL, 24.2 mmol, 3.00 eq., 3.0 M in Et_2O) was added dropwise. The mixture was gradually warmed to rt and stirred for 2 d. Then, sat. aq. $NaHCO_3$-sol. (10 mL) was added. The phases were separated and the aq. layer was extracted CH_2Cl_2 (3×10 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained *via* AFC (CyHex:EtOAc; 90:10 → 70:30) as a colourless solid (1.15 g, 4.98 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.81 (d, *J* = 10.3 Hz, 1H), 3.44 – 3.33 (m, 1H), 2.10 (pd, *J* = 6.8, 2.6 Hz, 1H), 1.45 (s, 9H), 1.26 (s, 3H), 1.23 (s, 3H), 0.97 – 0.88 (m, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.1, 79.2, 74.0, 61.9, 29.2, 28.6, 28.3, 27.2, 22.4, 17.0.
Spectroscopic data was in agreement with that previously reported.[166]

N^1,N^3-Bis((*S*)-2-hydroxy-2,4-dimethylpentan-3-yl)-2,2-dimethylmalonamide [26]



Following a procedure by *Xu et al.*,[166] amino alcohol **138** (544 mg, 2.35 mmol, 1.00 eq.) was dissolved in MeOH (10 mL) and cooled to 0 °C. Then, conc. aq. HCl (1.18 mL, 14.1 mmol, 6.00 eq.) dissolved in MeOH (5 mL) was added dropwise. The mixture was warmed to rt and stirred for 16 h before a second portion of conc. aq. HCl (1.18 mL, 14.1 mmol, 6.00 eq.) dissolved in MeOH (5 mL) was added. It was stirred for additional 20 h. Then, it was cooled to 0 °C and NaOH (1.14 g, 28.2 mmol, 12.0 eq.) was added. After 15 min of stirring the formed precipitate was filtered off and the filter cake was washed with CH_2Cl_2. The filtrate was dried over $MgSO_4$, filtered and concentrated *in vacuo*. (*S*)-3-amino-2,4-dimethylpentan-2-ol (**25**) was

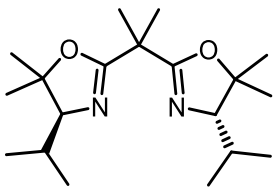
obtained *via* distillation (Kugelrohr, 45 mbar, 90 – 98 °C) as a colourless oil (252 mg, 1.92 mmol, 82%) and used in the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (d, *J* = 2.9 Hz, 1H), 1.93 (heptd, *J* = 6.9, 2.9 Hz, 1H), 1.20 (s, 3H), 1.12 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

Following general procedure **C** using amino alcohol **25** (252 mg, 1.92 mmol, 2.00 eq.), dry NEt_3 (0.66 mL, 4.75 mmol, 5.00 eq.) and 2,2-dimethylmalonyl dichloride (161 mg, 0.95 mmol, 1.00 eq.), the desired product was obtained as an off-white solid (242 mg, 0.68 mmol, 71%) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (d, *J* = 9.8 Hz, 2H), 3.77 (dd, *J* = 9.8, 2.6 Hz, 2H), 2.13 (heptd, *J* = 6.8, 2.6 Hz, 2H), 1.56 (s, 6H), 1.24 (s, 6H), 1.18 (s, 6H), 0.93 (d, *J* = 6.8 Hz, 6H), 0.91 (d, *J* = 6.8 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.6, 74.0, 60.8, 50.1, 29.4, 28.3, 26.7, 24.6, 22.6, 17.0.
Spectroscopic data was in agreement with that previously reported.[167]

(4*S*,4'*S*)-2,2'-(Propane-2,2-diyl)bis(4-isopropyl-5,5-dimethyl-4,5-dihydroxazole) [23]

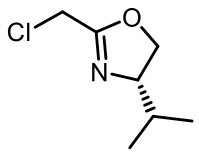


According to a procedure by *Bennett et al.*,[167] an oven dried Schlenk tube was charged with 4 Å molecular sieves. Bis(hydroxy)amide **26** (81 mg, 0.23 mmol, 1.00 eq.) and dry CH_2Cl_2 (2 mL) were added followed by methanesulphonic acid (60 µL, 0.92 mmol, 4.00 eq.). Then, the mixture was heated to 40 °C for 3 h. After cooling to rt, sat. aq. $NaHCO_3$ sol. (2 mL) was added and the phases were separated. The aq. layer was extracted with CH_2Cl_2 (3×5 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained *via* FC (CH_2Cl_2:MeOH; 90:10) as a pale-yellow oil (52 mg, 0.16 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.30 (d, *J* = 6.6 Hz, 2H), 1.83 – 1.70 (m, 2H), 1.45 (d, *J* = 2.7 Hz, 6H), 1.33 (s, 6H), 1.28 (s, 6H), 0.98 (dd, *J* = 6.6, 1.2 Hz, 12H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.4, 86.3, 79.2, 38.6, 29.2, 29.1, 23.8, 21.4, 21.1, 19.5.

Spectroscopic data was in agreement with that previously reported.[167]

(*S*)-2-(Chloromethyl)-4-isopropyl-4,5-dihydrooxazole [31]



A solution of chloroacetonitrile (4.17 mL, 66.0 mmol, 1.00 eq.) and EtOH (4.24 mL, 72.6 mmol, 1.10 eq.) in dry Et_2O (10 mL) was cooled to −10 °C. Then, $HCl_{(g)}$ was bubbled through the solution until a white precipitation was observed. The suspension was degassed with argon before the solids were collected *via* filtration and washed with cold Et_2O, affording ethyl 2-chloroacetimidate hydrochloride as a white solid. Additional crops of the product were obtained from precipitation of the mother liquor in the cold (7.16 g, 45.3 mmol, 69% in total).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.37 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H).

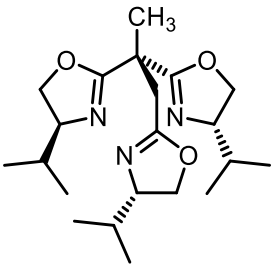
According to a procedure by *Ye et at.*,[88] ethyl 2-chloroacetimidate hydrochloride (869 mg, 5.50 mmol, 1.10 eq.) was suspended in dry CH_2Cl_2 (15 mL) and L-valinol (516 mg, 5.00 mmol, 1.00 eq.) was added. The mixture was cooled to 0 °C and NEt_3 (0.76 mL, 5.5 mmol, 1.10 eq.) was added. The reaction mixture was gradually warmed to rt and stirred for 16 h. The solvent was removed *in vacuo* and the residue was extracted with EtOAc (3×20 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained *via* FC (pentane:EtOAc; 80:20) as a colourless oil (432 mg, 2.68 mmol, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.35 (dd, J = 9.7, 8.4 Hz, 1H), 4.11 (s, 2H), 4.10 – 4.01 (m, 1H), 4.01 – 3.92 (m, 1H), 1.84 – 1.70 (m, J = 6.7 Hz, 1H), 0.97 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5, 72.5, 71.3, 36.5, 32.5, 18.8, 18.2.

Spectroscopic data was in agreement with that previously reported.[88]

(4*S*,4'*S*,4''*S*)-2,2',2''-(Propane-1,2,2-triyl)tris(4-isopropyl-4,5-dihydrooxazole) [27]



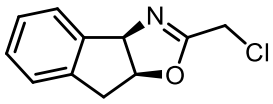
According to a procedure by *Synder et at.*,[87] diethyl malonimidate dihydrochloride (578 mg, 2.50 mmol, 1.00 eq.) and L-valinol (774 mg, 7.50 mmol, 3.00 eq.) were dissolved in CH_2Cl_2 (25 mL) and stirred at 40 °C for 18 h. Then, the mixture was poured into water (50 mL) and it was extracted with CH_2Cl_2 (4×10 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)methane was obtained *via* distillation (Kugelrohr, 2 mbar, 160 °C) as a colourless oil (278 mg, 1.17 mmol, 47%) and used in the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.26 (dd, J = 9.4, 8.0 Hz, 2H), 4.02 – 3.96 (m, 2H), 3.96 – 3.89 (m, 2H), 3.37 – 3.31 (m, 2H), 1.82 – 1.68 (m, J = 6.7 Hz, 2H), 0.94 (d, J = 6.8 Hz, 6H), 0.86 (d, J = 6.8 Hz, 6H).
Spectroscopic data was in agreement with that previously reported.[69]

According to a procedure by *Rendina et at.*,[51] the bis(oxazoline) (278 mg, 1.17 mmol, 1.00 eq.) obtained in the first step was added to a suspension of sodium hydride (49.0 mg, 1.23 mmol, 1.05 eq.) in dry THF (5 mL). The mixture was heated to 50 °C for 30 min then allowed to cool to rt. Methyl iodide (70.0 µL, 1.17 mmol, 1.00 eq.) dissolved in dry THF (1 mL) was added dropwise. It was stirred for 30 min before a second portion of sodium hydride (49.0 mg, 1.23 mmol, 1.05 eq.) was added. The mixture was stirred for another 30 min. Then, oxazoline **31** (226 mg, 1.40 mmol, 1.20 eq.) was added and it was stirred for 18 h. The reaction mixture was poured in sat. aq. $NaHCO_3$-sol. (10 mL), the phases were separated and the aq. layer was extracted with CH_2Cl_2 (3×10 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained *via* FC (pentane:EtOAc:MeOH; 50:50:0 → 0:95:5) as a colourless oil (317 mg, 0.839 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.26 – 4.08 (m, 3H), 4.05 – 3.78 (m, 6H), 3.11 – 3.02 (m, 1H), 2.98 – 2.88 (m, 1H), 1.86 – 1.66 (m, 3H), 1.59 (s, 3H), 1.02 – 0.74 (m, 18H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.1, 163.8, 72.3, 72.1, 71.7, 70.5, 70.1, 69.9, 41.0, 35.1, 32.7, 32.5, 32.3, 21.4, 19.0, 19.0, 18.7, 18.3, 18.2, 18.0, 17.5.
Spectroscopic data was in agreement with that previously reported.[168]

(3a*R*,8a*S*)-2-(Chloromethyl)-3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole [139]



A solution of chloroacetonitrile (4.17 mL, 66.0 mmol, 1.00 eq.) and EtOH (4.24 mL, 72.6 mmol, 1.10 eq.) in dry Et_2O (10 mL) was cooled to −10 °C. Then, $HCl_{(g)}$ was bubbled through the solution until a white precipitation was observed. The suspension was degassed with argon before the solids were collected *via* filtration and washed with cold Et_2O, affording ethyl 2-chloroacetimidate hydrochloride as a white solid. Additional crops of the product were obtained from precipitation of the mother liquor in the cold (7.16 g, 45.3 mmol, 69% in total).

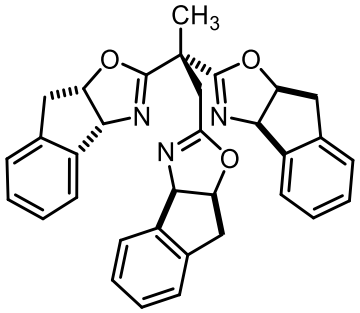
^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.37 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H).

According to a procedure by *Ye et al.*,[88] ethyl 2-chloroacetimidate hydrochloride (869 mg, 5.50 mmol, 1.10 eq.) was suspended in dry CH_2Cl_2 (20 mL) and (1*R*,2*S*)-1-amino-2,3-dihydro-1H-inden-2-ol (746 mg, 5.00 mmol, 1.00 eq.) was added. The mixture was cooled to 0 °C and NEt_3 (0.76 mL, 5.5 mmol, 1.10 eq.) was added. The reaction mixture was gradually warmed to rt and stirred for 16 h. The solvent was removed *in vacuo* and the residue was extracted with EtOAc (3×20 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained *via* FC (pentane:EtOAc:MeOH; 79:19:2) as a colourless oil (720 mg, 3.47 mmol, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 – 7.45 (m, 1H), 7.34 – 7.23 (m, 3H), 5.61 (dd, J = 8.0, 0.9 Hz, 1H), 5.50 – 5.42 (m, 1H), 4.10 (dd, J = 13.0, 0.8 Hz, 1H), 4.04 (dd, J = 13.0, 0.7 Hz, 1H), 3.46 (ddd, J = 18.1, 7.0, 0.9 Hz, 1H), 3.29 (dd, J = 18.1, 1.6 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0, 141.0, 140.0, 128.8, 127.6, 125.5, 125.4, 84.4, 76.7, 39.6, 36.5.

Spectroscopic data was in agreement with that previously reported.[88]

(3a*R*,3a'*R*,3a''*R*,8a*S*,8a'*S*,8a''*S*)-2,2',2''-(Propane-1,2,2-triyl)tris(3a,8a-dihydro-8*H*-indeno[1,2-d]oxazole) [28]



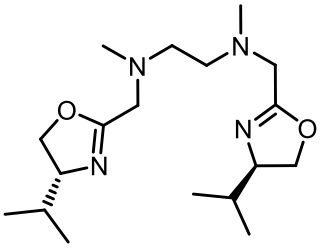
According to a procedure by *Rendina et at.*,[51] the bis(oxazoline) **17** (278 mg, 1.17 mmol, 1.00 eq.) was added to a suspension of sodium hydride (49.0 mg, 1.23 mmol, 1.05 eq.) in dry THF (5 mL). The mixture was heated to 50 °C for 30 min then allowed to cool to rt. Methyl iodide (70.0 µL, 1.17 mmol, 1.00 eq.) dissolved in dry THF (1 mL) was added dropwise. It was stirred for 30 min before a second portion of sodium hydride (49.0 mg, 1.23 mmol, 1.05 eq.) was added. The mixture was stirred for another 30 min. Then, oxazoline **139** (226 mg, 1.40 mmol, 1.20 eq.) was added and it was stirred for 18 h. The reaction mixture was poured in sat. aq. $NaHCO_3$-sol. (10 mL), the phases were separated and the aq. layer was extracted with CH_2Cl_2 (3×10 mL). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was obtained *via* FC (EtOAc:MeOH; 90:10 → 85:15) and crystallisation from $CHCl_3$/MeOH as a colourless solid (389 mg, 0.755 mmol, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 6.9 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.36 – 7.31 (m, 1H), 7.30 – 7.13 (m, 9H), 5.57 (d, *J* = 8.0 Hz, 1H), 5.49 (d, *J* = 7.9 Hz, 1H), 5.32 – 5.24 (m, 1H), 5.19 (d, *J* = 8.0 Hz, 1H), 5.14 (ddd, *J* = 8.3, 7.0, 1.8 Hz, 1H), 4.11 – 4.04 (m, 1H), 3.31 (ddd, *J* = 17.0, 9.5, 7.1 Hz, 2H), 3.13 – 2.74 (m, 6H), 1.45 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.6, 167.2, 164.2, 142.1, 142.0, 141.7, 140.5, 139.7, 139.7, 128.5, 128.3, 127.4, 127.4, 127.3, 125.7, 125.7, 125.4, 125.2, 125.1, 83.5, 83.5, 82.6, 76.6, 76.5, 76.1, 40.8, 39.9, 39.8, 39.6, 34.9, 21.1.

Spectroscopic data was in agreement with that previously reported.[169]

N^1-(((*R*)-4-Isopropyl-4,5-dihydrooxazol-2-yl)methyl)-N^2-(((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)methyl)-N^1,N^2-dimethylethane-1,2-diamine [29]



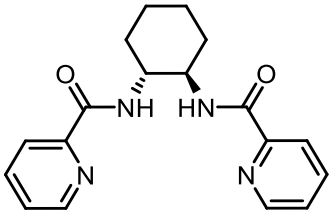
According to a procedure by *Guillemot et at.*,[89] oxazoline **31** (647 mg, 4.00 mmol, 2.00 eq.) was dissolved in dry MeCN (5 mL) in an oven dried Schlenk tube. *N*,*N*'-dimethylethylendiamine (**30**, 200 µL, 2.00 mmol, 1.00 eq.) and K_2CO_3 (1.22 g, 8.80 mmol, 4.40 eq.) were added and the mixture was heated to 82 °C for 3 h. After cooling to rt, the solids were filtered off and the filtrate was concentrated *in vacuo*. The desired product was obtained *via* distillation (Kugelrohr, 0.15 mbar, 160 °C) as a pale-yellow resin (396 mg, 1.17 mmol, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 – 4.19 (m, 2H), 3.99 – 3.84 (m, 4H), 3.31 – 3.25 (m, 4H), 2.62 (s, 4H), 2.33 (s, 6H), 1.81 – 1.62 (m, 2H), 0.94 (d, *J* = 6.8 Hz, 6H), 0.87 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.5, 72.2, 70.1, 54.9, 54.4, 42.9, 32.3, 18.9, 18.3.

Spectroscopic data was in agreement with that previously reported.[89]

N,*N*'-((1*R*,2*R*)-Cyclohexane-1,2-diyl)dipicolinamide [32]

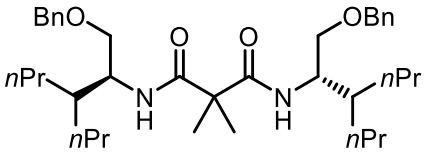


(1*R*,2*R*)-1,2-diaminocyclohexane (**33**, 571 mg, 5.00 mmol, 1.00 eq.) and 2-picolinic acid (**34**, 1.54 g, 12.5 mmol, 2.50 eq.) were dissolved in CH_2Cl_2 (25 mL). Then, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (2.88 g, 15.0 mmol, 3.00 eq.) and DMAP (122 mg, 1.00 mmol, 0.20 eq.) were added and it was stirred at rt for 32 h. Then, 1 M aq. HCl (20 mL) was added. The phases were separated and the aq. layer extracted with CH_2Cl_2 (3×15 mL). The combined org. phases were washed with 1 M aq. NaOH (2×10 mL) and sat. aq. NaCl sol. (10 mL). The org. layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired product was

obtained *via* recrystallisation from hot EtOH as colourless needles (825 mg, 2.54 mmol, 51%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (ddd, J = 4.8, 1.7, 0.9 Hz, 2H), 8.33 – 8.15 (m, 2H), 8.03 (dt, J = 7.8, 1.1 Hz, 2H), 7.70 (td, J = 7.7, 1.7 Hz, 2H), 7.36 – 7.26 (m, 2H), 4.14 – 3.98 (m, 2H), 2.27 – 2.09 (m, 2H), 1.92 – 1.67 (m, 2H), 1.54 – 1.31 (m, 4H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 149.8, 148.2, 137.1, 126.0, 122.1, 53.3, 32.7, 24.9.
Spectroscopic data was in agreement with that previously reported.[170]

N^1,N^3-Bis((*S*)-1-(benzyloxy)-3-propylhexan-2-yl)-2,2-dimethylmalonamide [140]



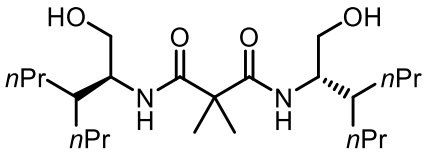
Following general procedure **C** using benzyl protected aminoalcohol **132** (75 mg, 0.30 mmol, 2.00 eq.), dry NEt_3 (0.10 mL, 0.80 mmol, 5.00 eq.) and 2,2-dimethylmalonyl dichloride (25 mg, 0.15 mmol, 1.00 eq.), the desired product was obtained *via* filtration through silica plug with CH_2Cl_2 as a pale-yellow resin (80 mg, 0.13 mmol, 87%) and used without further purification.

IR (neat): $\tilde{\nu}$ = 3341 (m), 2959 (s), 2929 (s), 2871 (s), 2241 (w), 1743 (w), 1671 (s), 1509 (s), 1456 (s), 1363 (w), 1257 (w), 1101 (s), 910 (m), 735 (s), 697 (s).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.22 (m, 10H, CH_{arom}), 6.76 (d, J = 9.1 Hz, 2H, NH), 4.45 (d, J = 1.3 Hz, 4H, OCH_2), 4.14 (dq, J = 9.2, 5.3 Hz, 2H, NCH), 3.45 (dd, J = 9.7, 5.1 Hz, 2H, OCH_2), 3.37 (dd, J = 9.8, 5.1 Hz, 2H, OCH_2), 1.69 – 1.57 (m, 2H, CH), 1.44 (s, 6H, CH_3), 1.41 – 1.04 (m, 20H, CH_2)[6], 0.86 (td, J = 7.1, 4.4 Hz, 13H, CH_3)[7].
^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.57 (2×C_q), 138.32 (2×C_q), 128.50 (4×CH$_{arom}$), 127.75 (4×CH$_{arom}$), 73.10 (2×CH$_2$), 70.01 (2×CH$_2$), 50.86 (2×CH), 49.62 (C_q), 38.30 (2×CH), 32.77 (2×CH$_2$), 31.93 (2×CH$_2$), 24.44 (2×CH$_3$), 20.35 (2×CH$_2$), 20.12 (2×CH$_2$), 14.56 (2×CH$_3$).
HRMS (ESI): Calculated for $C_{37}H_{58}N_2O_4Na^+$ [M+Na]$^+$: 617.4289, found: 617.4282.

[6] The increased number of hydrogen signals of 20 instead of 16 hydrogen signals is due to signal overlap as a result of insufficient resolution.
[7] The increased number of hydrogen signals of 13 instead of 12 hydrogen signals is due to signal overlap as a result of insufficient resolution.

Synthesis performed by [redacted].[94]

N^1,N^3-Bis((*S*)-1-hydroxy-3-propylhexan-2-yl)-2,2-dimethylmalonamide [141]



Following a procedure by *Poremba et al.*,[156] palladium (5% on carbon, 62 mg) was suspended in EtOAc (1 mL) under N_2-atmosphere. Then, bisbenzyloxy amide **140** (80 mg, 0,13 mmol, 1,00 eq.) dissolved in MeOH/EtOAc (1:1, *v*/*v*, 4 mL) was added. It was purged with H_2 and stirred at rt for 5 h under H_2-atmosphere (H_2-balloon). It was filtered through celite® and the filter cake washed with EtOAc (20 mL). The filtrate was concentrated *in vacuo* affording the desired product as a colourless solid (55 mg, 0.13 mmol, quant.).

M.P.: 98 – 103 °C.

IR (neat): $\tilde{\nu}$ = 3340 (m), 2958 (s), 2927 (s), 2873 (m), 2244 (w), 1735 (w), 1640 (s), 1544 (m), 1458 (m), 1379 (w), 1260 (w), 1034 (m), 907 (s), 817 (w), 732 (s), 670 (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.39 (d, *J* = 8.8 Hz, 2H, N*H*), 4.10 – 3.96 (m, 2H, NC*H*), 3.70 (dd, *J* = 11.5, 3.4 Hz, 2H, OCH_2), 3.52 (dd, *J* = 11.5, 7.8 Hz, 2H, OCH_2), 1.58 – 1.50 (m, 2H, CH_2), 1.47 (s, 6H, CH_3), 1.27 (tdd, *J* = 16.3, 8.7, 4.9 Hz, 21H, CH_2)[8], 0.88 (t, *J* = 6.8 Hz, 14H, CH_3)[9].

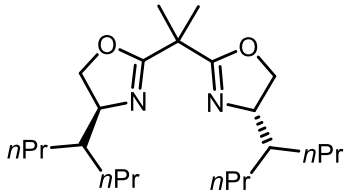
^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.67 (2×C_q), 64.26 (2×CH$_2$), 54.09 (2×CH), 50.15 (C_q), 38.55 (2×CH), 32.81 (2×CH$_2$), 32.20 (2×CH$_2$), 23.73 (2×CH$_3$), 20.20 (2×CH$_2$), 20.07 (2×CH$_2$), 14.50 (4×CH$_3$).

HRMS (ESI): Calculated for $C_{23}H_{46}N_2O_4Na^+$ [M+Na]$^+$: 437.3350, found: 437.3345.

Synthesis performed by [redacted].[94]

[8] The increased number of hydrogen signals of 21 instead of 16 hydrogen signals is due to signal overlap as a result of insufficient resolution.
[9] The increased number of hydrogen signals of 14 instead of 12 hydrogen signals is due to signal overlap as a result of insufficient resolution.

(4*S*,4'*S*)-2,2'-(Propane-2,2-diyl)bis(4-(heptan-4-yl)-4,5-dihydrooxazole) [50]



Following general procedure **D** using bis(hydroxy)amide **141** (55 mg, 0.13 mmol, 1.00 eq.), dry NEt_3 (90 µL, 0.70 mmol, 5.00 eq.), mesyl chloride (250 µL, 3.30 mmol, 2.50 eq.) and NaOH (100 mg, 2.50 mmol, 19.0 eq.), the desired product was obtained *via* AFC (CyHex:EtOAc; 90:10 → 80:20) as an orange resin (22 mg, 58 µmol, 46%).

IR (neat): $\tilde{\nu}$ = 2959 (s), 2929 (s), 2871 (s), 2241 (w), 1743 (w), 1662 (s), 1466 (m), 1386 (w), 1248 (w), 1119 (w), 982 (m), 908 (w), 740 (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.29 – 4.05 (m, 4H, C*H*/CH_2), 4.05 – 3.95 (m, 2H, CH_2), 1.67 – 1.55 (m, 2H, C*H*), 1.51 (s, 6H, CH_3), 1.40 – 0.98 (m, 21H, CH_2)[8], 0.89 (td, *J* = 7.0, 3.5 Hz, 14H, CH_3)[9].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.79 (2×C_q), 70.04 (2×*C*H), 68.70 (2×*C*H_2), 41.52 (2×*C*H), 38.71 (C_q), 33.14 (2×*C*H_2), 31.58 (2×*C*H_2), 24.60 (2×*C*H_3), 20.72 (2×*C*H_2), 20.55 (2×*C*H_2), 14.65 (4×*C*H_3).

HRMS (ESI): Calculated for $C_{23}H_{43}N_2O_2^+$ [M+H]$^+$: 379.3319, found: 379.3317.

Synthesis performed by [redacted].[94]

5.2.4 Synthesis of cyclopentanones

5.2.4.1 Substrate scope

General procedures F: Asymmetric one-carbon ring-expansion of prochiral cyclobutanones

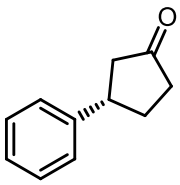
Protocol A: In an flame-dried tube, $Sc(OTf)_3$ (0.10 eq.) and the ligand (0.15 eq.) were suspended in dry PhMe (0.1 M) under argon-atmosphere and it was stirred for 15 min at rt. The corresponding cyclobutanone (1.00 eq.) was added and it was stirred for additional 15 min at rt. Then, it was cooled to −78 °C, DMPSD (1.30 eq.) was added and the mixture was stirred at −78 °C for 24 h. Thereafter, an excess amount of trifluoroacetic acid (TFA) (6.50 eq.) dissolved in CH_2Cl_2 (2 mL) was added. After additional 10 min at −78 °C it was allowed to warm to rt and the solvent

was removed *in vacuo*. The desired product was obtained *via* FC with the conditions given in the corresponding entry.

Protocol B: In an flame-dried tube, $Sc(OTf)_3$ (0.10 eq.) and the ligand (0.15 eq.) were suspended in dry PhMe (0.1 M) under argon-atmosphere and it was stirred for 15 min at rt. The corresponding cyclobutanone (1.00 eq.) was added and it was stirred for additional 15 min at rt. Then, it was cooled to −78 °C. TMSD (1.30 eq.) was added and the mixture was stirred at −78 °C for 24 h. Thereafter, an excess amount of TFA (6.50 eq.) dissolved in CH_2Cl_2 (2 mL) was added. After additional 10 min at −78 °C it was allowed to warm to rt and the solvent was removed *in vacuo.* The crude residue was purified *via* FC with the conditions given in the corresponding entry.

Protocol C: In an flame-dried tube, $Sc(OTf)_3$ (0.10 eq.) and the ligand (0.15 eq.) were suspended in dry PhMe (0.1 M) under Argon-atmosphere and it was stirred for 15 min at rt. The corresponding cyclobutanone (1.00 eq.) was added and it was stirred for additional 15 min at rt. Then, DPMSD (1.30 eq.) was added and the mixture was stirred at rt for 16 h. Thereafter, an excess amount of TFA (6.50 eq.) was added and the solvent was removed *in vacuo*. The desired product was obtained *via* FC with the conditions given in the corresponding entry.

(−)-3-Phenylcyclopentanone [(−)-35]



According to general procedure **F-A**, using CBone **1** (14.6 mg, 0.10 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.), ligand **11** (4.8 mg, 15 µmol, 0.15 eq.) and DPMSD (0.14 mL, 0.13 mmol, 0.9 M in PhMe, 1.30 eq.), the product was obtained *via* FC (CH_2Cl_2) as a colourless oil (10.0 mg, 62.4 µmol, 62%).

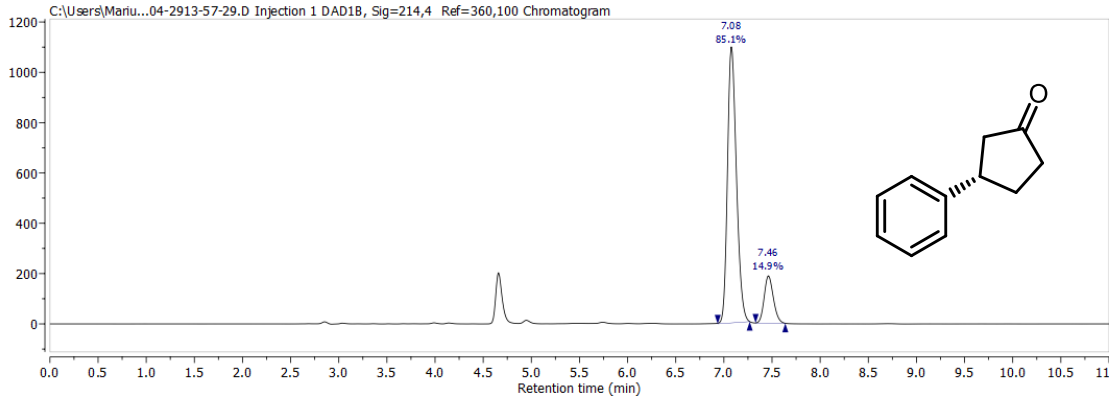
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.31 (m, 2H), 7.30 – 7.22 (m, 3H), 3.49 – 3.37 (m, 1H), 2.68 (dd, *J* = 18.0, 7.3, 1H), 2.54 – 2.40 (m, 2H), 2.40 – 2.25 (m, 2H), 2.09 – 1.92 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 218.5, 143.2, 128.8, 126.9, 126.9, 45.9, 42.4, 39.0, 31.3.

Optical rotation: $[\alpha]_D^{25}$ = −43.4° (*c* = 1.0, $CHCl_3$) for an enantiomerically enriched sample of 85:15 *er*; the major enantiomer is (*S*)-configured, assigned in analogy to literature ($[\alpha]_D$ = −92° (*c* = 0.82 , $CHCl_3$), 98.5:1.5 *er* in favour of the (*S*)-enantiomer).[171] The enantiomeric purity was established by HPLC analysis using a chiral column (Chiralpak® IF3 column, 40 °C, 1 mL/min, 90:10 hexane:ethanol, 214 nm, t_R(major) = 7.0 min, t_R(minor) = 7.3 min).

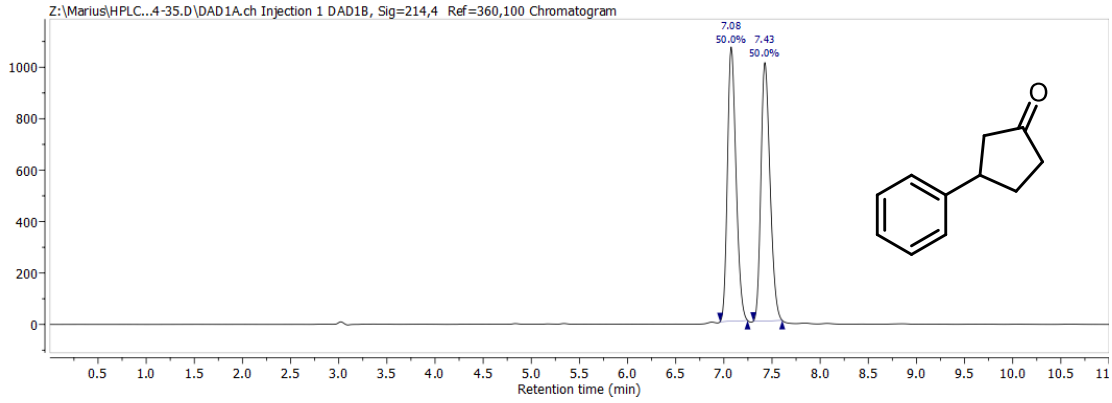
Spectroscopic data was in agreement with that previously reported.[171]

Chemotion ELN sample number: MTN-4-80-A.



Retention Time	Area	Area %
7.078	70672.915	85.10
7.463	12378.226	14.90

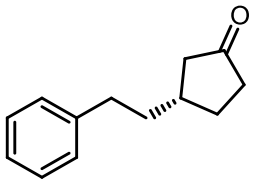
Figure 21: HPLC chromatogram for (−)-3-Phenylcyclopentanone [(−)-**35**].



Retention Time	Area	Area %
7.076	66302.853	50.03
7.426	66227.619	49.97

Figure 22: HPLC chromatogram for *rac*-3-Phenylcyclopentanone [*rac*-**35**].

(−)-3-Phenethylcyclopentanone [(−)-51]



According to general procedure **F-A**, using CBone **5** (17.4 mg, 0.10 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.), ligand **11** (4.8 mg, 15 µmol, 0.15 eq.) and DPMSD (0.14 mL, 0.13 mmol, 0.9 M in PhMe, 1.30 eq.), the product was obtained *via* FC (pentane:EtOAc; 95:5) as a colourless oil (7.5 mg, 40 µmol, 40%).

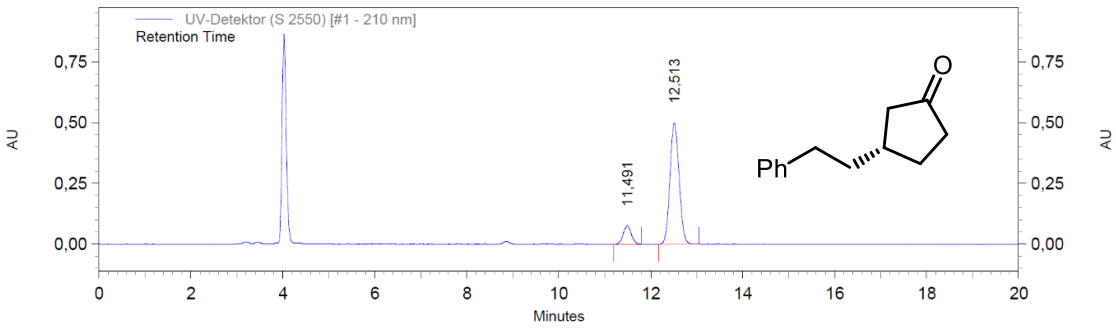
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 – 7.27 (m, 2H), 7.20 (m, 3H), 2.67 (t, *J* = 7.8, 2H), 2.47 – 2.38 (m, 1H), 2.37 – 2.26 (m, 1H), 2.24 – 2.09 (m, 3H), 1.89 – 1.73 (m, 3H), 1.63 – 1.50 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 219.6, 141.9, 128.5, 128.3, 126.0, 45.2, 38.6, 37.4, 36.6, 34.2, 29.5.

Optical rotation: $[\alpha]_D^{25}$ = −58.0° (*c* = 0.5, $CHCl_3$) for an enantiomerically enriched sample of 88:12 *er*; the major enantiomer is (*S*)-configured, assigned in analogy to literature ($[\alpha]_D^{22.4}$ = +67° (*c* = 0.57, $CHCl_3$), 97.5:2.5 in favour of the (*R*)-enantiomer).[172] The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Cellulose 5 column, rt, 1 mL/min, 90:10 hexane:*i*-PrOH, 210 nm, t_R(minor) = 11.2 min, t_R(major) = 12.0 min).

Spectroscopic data was in agreement with that previously reported.[173]

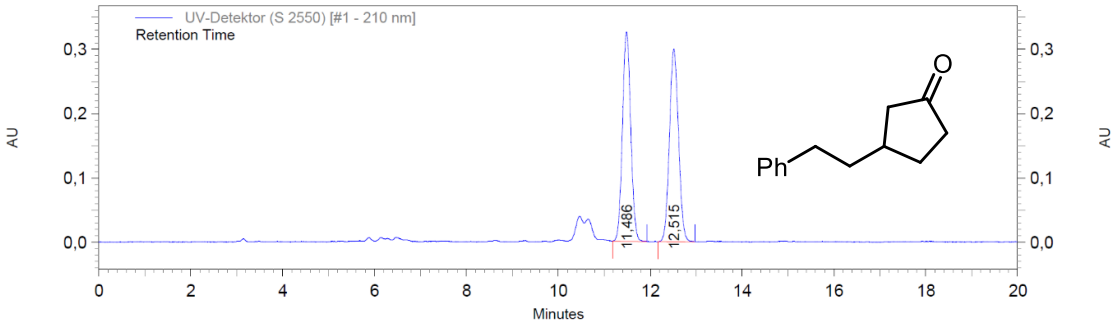
Chemotion ELN sample number: MTN-4-100-A.



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
11,491	935916	11,97
12,513	6882966	88,03

Figure 23: HPLC chromatogram for (−)-3-Phenethylcyclopentanone [(−)-**51**].

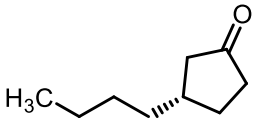


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
11,486	4084702	49,85
12,515	4108519	50,15

Figure 24: HPLC chromatogram for *rac*-3-Phenethylcyclopentanone [*rac*-**51**].

(−)-3-Butylcyclopentanone [(−)-52]



According to general procedure **F-B**, using CBone **6** (12.6 mg, 0.10 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.), ligand **11** (4.8 mg, 15 µmol, 0.15 eq.) and TMSD (0.22 mL, 0.13 mmol, 0.6 M in hex, 1.32 eq.), the product was obtained *via* FC (pentane:Et_2O; 95:5) as a colourless oil (10.0 mg, 71.3 µmol, 71%). *Note:* The product is fairly volatile.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 – 2.23 (m, 2H), 2.22 – 2.03 (m, 3H), 1.85 – 1.71 (m, 1H), 1.58 – 1.23 (m, 7H), 0.95 – 0.84 (m, 3H).

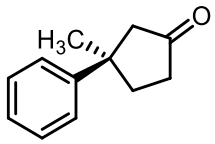
^{13}C NMR (75 MHz, $CDCl_3$): δ = 220.3, 45.5, 38.7, 37.3, 35.5, 30.2, 29.7, 22.9, 14.2.

Optical rotation: $[\alpha]_D^{25}$ = −66.2° (*c* = 0.5, $CHCl_3$) for an enantiomerically enriched sample of 82:18 *er*; the major enantiomer is (*S*)-configured, assigned in analogy to literature ($[\alpha]_D^{25}$ = −157° (*c* = 1.14, $CHCl_3$), 98.5:1.5 *er* in favour of the (*S*)-enantiomer).[174] For determination of the *er* cyclopentanone **2c** was converted into its (9*H*-fluorene-9,9-diyl)dimethanol ketal (*cf.* chapter 5.2.4.3). The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® Amylose 1 column, rt, 1 mL/min, 99.5:0.5 hexane:*i*-PrOH, 254 nm, t_R(major) = 13.1 min, t_R(minor) = 19.8 min).

Spectroscopic data was in agreement with that previously reported.[175,176]

Chemotion ELN sample number: MTN-4-104-A.

(+)-3-Methyl-3-phenylcyclopentanone [(+)-55]



According to general procedure **F-B**, using CBone **2** (16.0 mg, 0.10 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.), ligand **11** (4.8 mg, 15 µmol, 0.15 eq.) and TMSD (0.22 mL, 0.13 mmol, 0.6 M in hex, 1.32 eq.), the product was obtained *via* FC (pentane:EtOAc; 95:5) as a colourless oil (11.0 mg, 63.1 µmol, 63%).

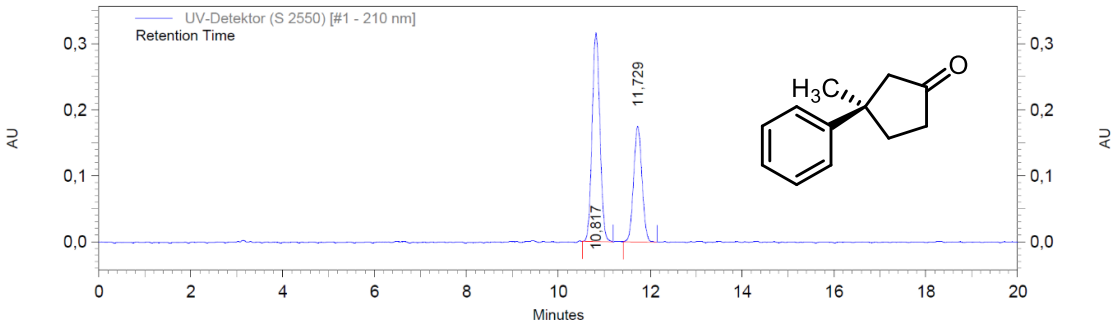
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.27 (m, 4H), 7.27 – 7.21 (m, 1H), 2.66 (d, *J* = 17.6, 1H), 2.48 (d, *J* = 17.6, 1H), 2.45 – 2.34 (m, 2H), 2.34 – 2.21 (m, 2H), 1.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 218.8, 148.6, 128.7, 126.5, 125.6, 52.4, 44.0, 36.9, 35.9, 29.6.

Optical rotation: $[\alpha]_D^{25}$ = +3.8° (*c* = 0.5, $CHCl_3$) for an enantiomerically enriched sample of 63:37 *er*; the major enantiomer is (*R*)-configured, assigned in analogy to literature ($[\alpha]_D$ = +23.0° (*c* = 0.85, $CHCl_3$), 99.5:0.5 *er* in favour of the (*R*)-enantiomer).[177] The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Cellulose 5 column, rt, 1 mL/min, 95:5 hexane:*i*-PrOH, 210 nm, t_R(major) = 10.8 min, t_R(minor) = 11.7 min).

Spectroscopic data was in agreement with that previously reported.[177,178]

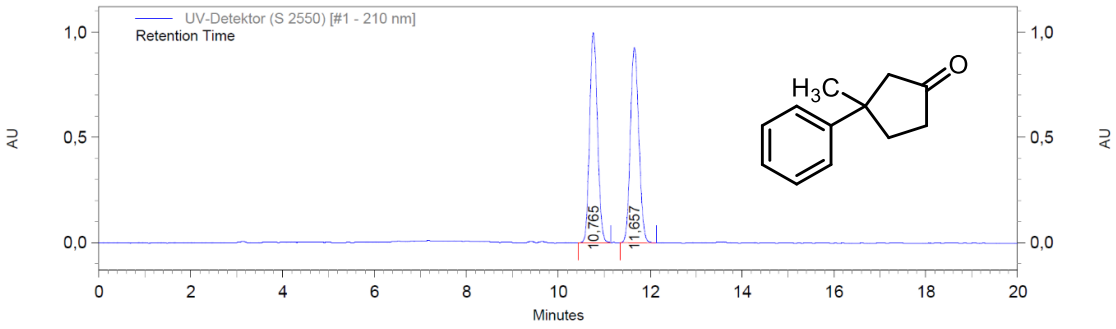
Chemotion ELN sample number: MTN-4-95-A.



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
10,817	3724644	62,67
11,729	2218816	37,33

Figure 25: HPLC chromatogram for (+)-3-Methyl-3-phenylcyclopentanone [(+)-**55**].

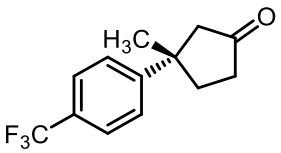


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
10,765	11834750	49,85
11,657	11907863	50,15

Figure 26: HPLC chromatogram for *rac*-3-Methyl-3-phenylcyclopentanone [*rac*-**55**].

(−)-3-Methyl-3-[4-(trifluoromethyl)phenyl]cyclopentanone [(−)-56]



According to general procedure **F-B**, using CBone **3** (22.8 mg, 0.10 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.), ligand **11** (4.8 mg, 15 µmol, 0.15 eq.) and TMSD (0.22 mL, 0.13 mmol, 0.6 M in hex, 1.32 eq.), the product was obtained *via* FC (pentane:EtOAc; 95:5 → 90:10) as a colourless oil (7.0 mg, 29 µmol, 29%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (*app.* d, *J* = 8.2 Hz, 2H, CH_{arom}), 7.40 (*app.* d, *J* = 8.2 Hz, 2H, CH_{arom}), 2.64 (d, *J* = 17.5 Hz, 1H, CH_2), 2.51 (dt, *J* = 17.7, 1.3 Hz, 1H, CH_2), 2.52 – 2.34 (m, 2H, CH_2), 2.35 – 2.25 (m, 2H, CH_2), 1.40 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 217.6 (C_q), 152.5 (C_q), 128.7 (q, *J* = 32.6 Hz, C_q), 125.9 (2×CH$_{arom}$), 125.6 (q, *J* = 3.9 Hz, 2×CH$_{arom}$), 124.13 (q, *J* = 272.0 Hz, CF$_3$), 51.9 (CH$_2$), 44.0 (C_q), 36.6 (CH$_2$), 35.6 (CH$_2$), 29.3 (CH$_3$).

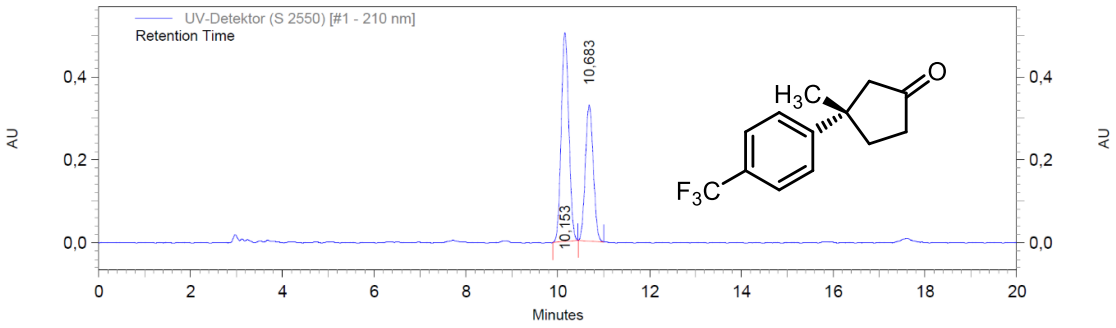
^{19}F NMR (377 MHz, $CDCl_3$): δ = −63.6.

IR (neat): $\tilde{\nu}$ = 2965 (w), 2350 (w), 1744 (s), 1620 (w), 1410 (m), 1329 (s), 1164 (s), 1121 (s), 1082 (m), 1067 (m), 1015 (m), 842 (m), 745 (w), 668 (m), 634 (s), 623 (s), 611 (m), 593 (m).

HRMS (APCI, CH_3COONH_4): Calculated for $C_{13}H_{14}F_3O^+$ $[M+H]^+$: 243.0991, found 243.0985.

Optical rotation: $[\alpha]_D^{25}$ = −0.4° (*c* = 0.5, $CHCl_3$) for an enantiomerically enriched sample of 59:41 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Cellulose 5 column, rt, 1 mL/min, 95:5 hexane:*i*-PrOH, 210 nm, t_R(major) = 10.3 min, t_R(minor) = 10.8 min).

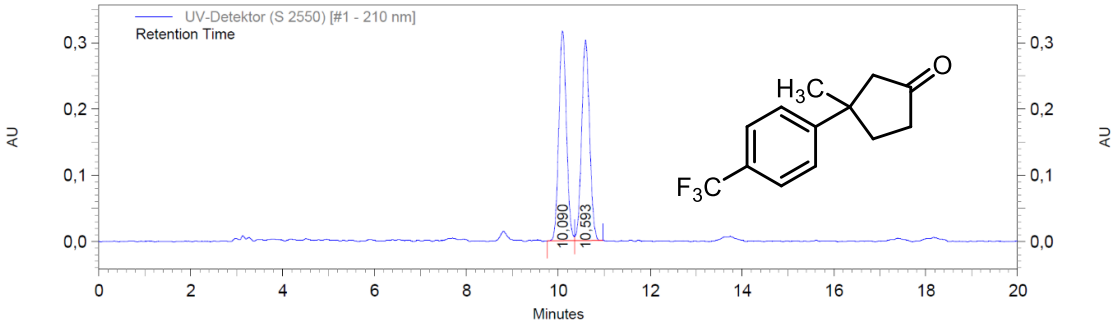
Chemotion ELN sample number: MTN-4-110-A.



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
10,153	5765152	59,33
10,683	3951986	40,67

Figure 27: HPLC chromatogram for (−)-3-Methyl-3-[4-(trifluoromethyl)phenyl]cyclopentanone [(−)-**56**].

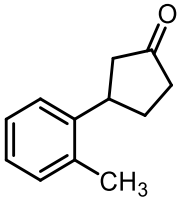


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
10,090	3647426	49,90
10,593	3662364	50,10

Figure 28: HPLC chromatogram for *rac*-3-Methyl-3-[4-(trifluoromethyl)phenyl]cyclopentanone [*rac*-**56**].

3-(2-Methylphenyl)cyclopentanone [57]



According to general procedure **F-C**, using CBone **4** (16.0 mg, 0.10 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.), ligand **11** (4.8 mg, 15 µmol, 0.15 eq.) and DPMSD (0.14 mL, 0.13 mmol, 0.9 M in PhMe, 1.30 eq.), the product was obtained *via* FC (pentane:EtOAc; 95:5) as a colourless oil (10.0 mg, 57.4 µmol, 57%).

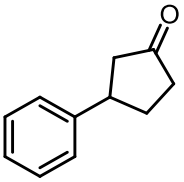
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 – 7.12 (m, 4H), 3.70 – 3.54 (m, 1H), 2.68 – 2.58 (m, 1H), 2.56 – 2.40 (m, 1H), 2.38 (s, 3H), 2.38 – 2.21 (m, 3H), 2.08 – 1.93 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 218.9, 141.1, 136.1, 130.8, 126.7, 126.6, 124.9, 45.5, 38.7, 38.5, 30.2, 19.8.
An enantiomeric ratio of 49:51 was established by HPLC analysis using a chiral column (Lux® i-Amylose 3 column, rt, 1 mL/min, 98:2 hexane:*i*-PrOH, 210 nm, t_{R1} = 11.9 min, t_{R2} = 12.4 min).
Spectroscopic data was in agreement with that previously reported.[179]
Chemotion ELN sample number: MTN-4-99-A.

5.2.4.2 Preparation of racemic material

General procedure G: Scandium catalysed ring expansion

In an flame-dried tube, $Sc(OTf)_3$ (0.10 eq.) was suspended in dry PhMe (0.1 M) under Argon-atmosphere. The corresponding cyclobutanone (1.00 eq.) was added and it was stirred for 15 min at rt. Then, TMSD (0.6 M in hex, 1.30 eq.) was added and the mixture was stirred at rt for 16 h. Thereafter, an excess amount of TFA (6.50 eq.) was added and the solvent was removed *in vacuo*. The desired product was obtained *via* FC with the conditions given in the corresponding entry.

rac-3-Phenylcyclopentanone [*rac*-35]



According to general procedure **G**, using CBone **1** (14.6 mg, 0.100 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.) and TMSD (0.22 mL, 0.13 mmol, 0.6 M in hex, 1.32 eq.), the product was obtained *via* FC (CH_2Cl_2) as a colourless oil (12.0 mg, 74.9 µmol, 75%).

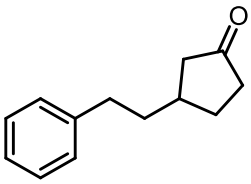
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 – 7.33 (m, 2H), 7.33 – 7.24 (m, 3H), 3.54 – 3.37 (m, 1H), 2.79 – 2.62 (m, 1H), 2.58 – 2.22 (m, 4H), 2.13 – 1.94 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 218.1, 143.0, 128.7, 126.7, 126.7, 46.0, 42.5, 39.1, 31.5.

Spectroscopic data was in agreement with that previously reported.[171]

Chemotion ELN sample number: MTN-4-75-A.

rac-3-Phenethylcyclopentanone [*rac*-51]



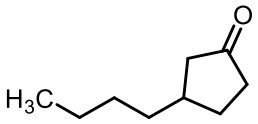
According to general procedure **G**, using CBone **5** (17.4 mg, 0.100 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.) and TMSD (0.22 mL, 0.13 mmol, 0.6 M in hex, 1.32 eq.), the product was obtained *via* FC (CH_2Cl_2) as a colourless oil (15.7 mg, 83.4 µmol, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 – 7.27 (m, 2H), 7.20 (m, 3H), 2.67 (t, J = 7.8, 2H), 2.47 – 2.38 (m, 1H), 2.37 – 2.26 (m, 1H), 2.24 – 2.09 (m, 3H), 1.89 – 1.73 (m, 3H), 1.63 – 1.50 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 219.6, 141.9, 128.5, 128.3, 126.0, 45.2, 38.6, 37.4, 36.6, 34.2, 29.5.

Spectroscopic data was in agreement with that previously reported.[173]

rac-3-Butylcyclopentanone [*rac*-52]



According to general procedure **G**, using CBone **6** (12.6 mg, 0.100 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.) and TMSD (0.22 mL, 0.13 mmol, 0.6 M in hex, 1.32 eq.), the product was obtained *via* FC (CH_2Cl_2) as a colourless oil (10.0 mg, 71.3 µmol, 71%).

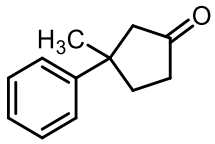
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 – 2.23 (m, 2H), 2.23 – 2.04 (m, 3H), 1.87 – 1.69 (m, 1H), 1.58 – 1.16 (m, 7H), 0.96 – 0.78 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 220.3, 45.5, 38.7, 37.3, 35.5, 30.2, 29.7, 22.9, 14.2.

Spectroscopic data was in agreement with that previously reported.[175,176]

Chemotion ELN sample number: MTN-4-82-A.

rac-3-Methyl-3-phenylcyclopentanone [*rac*-55]



According to general procedure **G**, using CBone **2** (16.0 mg, 0.100 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.) and TMSD (0.22 mL, 0.13 mmol, 0.6 M in hex, 1.32 eq.), the product was obtained *via* FC (pentane:EtOAc; 95:5) as a colourless oil (12.0 mg, 68.9 µmol, 69%).

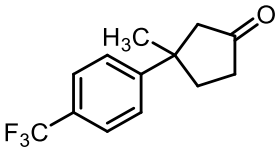
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 – 7.27 (m, 4H), 7.27 – 7.21 (m, 1H), 2.66 (d, *J* = 17.6, 1H), 2.48 (d, *J* = 17.6, 1H), 2.45 – 2.34 (m, 2H), 2.34 – 2.22 (m, 2H), 1.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 218.7, 148.6, 128.7, 126.5, 125.6, 52.4, 44.0, 36.9, 35.9, 29.5.

Spectroscopic data was in agreement with that previously reported.[177,178]

Chemotion ELN sample number: MTN-4-92-A.

rac-3-Methyl-3-[4-(trifluoromethyl)phenyl]cyclopentanone [*rac*-56]



According to general procedure **G**, using CBone **3** (22.8 mg, 0.100 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.) and TMSD (0.22 mL, 0.13 mmol, 0.6 M in hex, 1.32 eq.), the product was obtained *via* FC (pentane:EtOAc; 95:5) as a yellow oil (16.0 mg, 66.1 µmol, 66%).

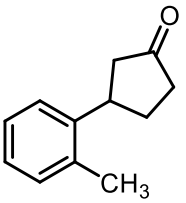
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (*app.* d, *J* = 8.2 Hz, 2H), 7.40 (*app.* d, *J* = 8.2 Hz, 2H), 2.64 (d, *J* = 17.5 Hz, 1H), 2.51 (dt, *J* = 17.7, 1.3 Hz, 1H), 2.52 – 2.34 (m, 2H), 2.35 – 2.25 (m, 2H), 1.40 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 217.6, 152.5, 128.7 (q, *J* = 32.6 Hz), 125.9, 125.6 (q, *J* = 3.9 Hz), 124.13 (q, *J* = 272.0 Hz), 51.9, 44.0, 36.6, 35.6, 29.3.

Spectroscopic data was in agreement with that previously obtained (*vide supra*).

Chemotion ELN sample number: MTN-4-107-A.

rac-3-(2-Methylphenyl)cyclopentanone [*rac*-57]



According to general procedure **G**, using CBone **4** (16.0 mg, 0.100 mmol, 1.00 eq.), $Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.10 eq.) and TMSD (0.22 mL, 0.13 mmol, 0.6 M in hex, 1.32 eq.), the product was obtained *via* FC (CH_2Cl_2) as a colourless oil (11.0 mg, 63.1 µmol, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 – 7.12 (m, 4H), 3.68 – 3.55 (m, 1H), 2.69 – 2.59 (m, 1H), 2.55 – 2.40 (m, 1H), 2.40 (s, 3H), 2.37 – 2.22 (m, 3H), 2.06 – 1.95 (m, 1H).

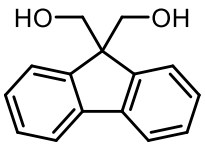
^{13}C NMR (101 MHz, $CDCl_3$): δ = 218.9, 141.1, 136.1, 130.8, 126.7, 126.5, 124.9, 45.5, 38.7, 38.5, 30.2, 19.8.

Spectroscopic data was in agreement with that previously reported.[179]

Chemotion ELN sample number: MTN-4-93-A.

5.2.4.3 Derivatisation of non-UV/vis-active β-substituted cyclopentanones for the determination of their *er*

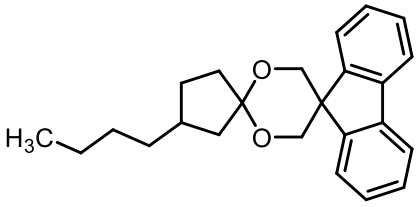
[9-(Hydroxymethyl)-9-fluorenyl]methanol [54]



Paraformaldehyde (249 mg, 8.30 mmol, 2.77 eq.) and sodium ethoxide (53 mg, 0.78 mmol, 0.26 eq.) were suspended in a mixture of DMSO (1.5 mL), ethanol (0.5 mL) and toluene (1 mL). The mixture was cooled to 0 °C and a solution of fluorene (499 mg, 3.00 mmol, 1.00 eq.) in DMSO (1.5 mL) was added. It was stirred at 0 °C for 30 min before it was gradually warmed to rt and stirred for additional 16 h. Then, it was acidified to pH ≈ 1 by addition of conc. aq. HCl (10 drops) and diluted with water (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic fractions were washed successively with water (2×5 mL) and Brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was obtained *via* recrystallisation (from EtOH, then from PhMe) as colourless solid (281 mg, 1.24 mmol, 41%).

^{1}H NMR (400 MHz, DMSO): δ = 7.82 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.4 Hz, 2H), 7.44 – 7.24 (m, 4H), 4.87 (t, J = 5.3 Hz, 2H), 3.71 (d, J = 5.3 Hz, 4H).
^{13}C NMR (101 MHz, DMSO): δ = 147.6, 140.4, 127.2, 126.6, 125.2, 119.8, 63.8, 57.5.
Spectroscopic data was in agreement with that previously reported.[180]
Chemotion ELN sample number: MTN-4-78-A.

rac-3-Butyldispiro[cyclopentane-1,2'-[1,3]dioxane-5',9''-fluorene] [*rac*-53]



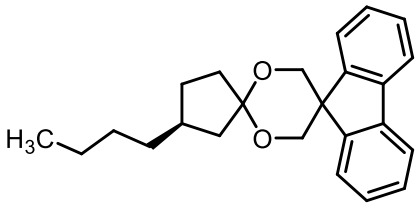
In a tube containing activated 4 Å molecular sieves, CPone *rac*-**52** (10.0 mg, 71.3 µmol, 1.00 eq.), diol **54** (45.3 mg, 20.0 µmol, 2.80 eq.) and *p*-toluenesulphonic acid monohydrate (1.9 mg, 10 µmol, 0.14 eq.) were suspended in dry PhMe (1 mL). The mixture was stirred at 120 °C for 16 h. After cooling to rt, it was poured into

water and diluted with Et_2O (5 mL). The org. layer was washed with water and sat. aq. NaCl sol., dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was taken up in CH_2Cl_2 and filtered through a silica plug which was eluted with CH_2Cl_2. The product was obtained *via* FC (pentane:EtOAc; 97:3) as a colourless solid (10.0 mg, 28.7 µmol, 40%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 – 7.70 (m, 4H), 7.41 (td, *J* = 7.5, 1.3 Hz, 2H), 7.34 (tt, *J* = 7.4, 1.2 Hz, 2H), 3.99 (d, *J* = 3.7, 4H), 2.55 (dd, *J* = 13.1, 7.4, 1H), 2.43 – 2.27 (m, 1H), 2.23 – 2.02 (m, 2H), 2.02 – 1.90 (m, 1H), 1.67 (dd, *J* = 13.1, 10.0, 1H), 1.53 – 1.28 (m, 7H), 0.98 – 0.87 (m, 3H).

Chemotion ELN sample number: MTN-4-86-A.

3-Butyldispiro[cyclopentane-1,2'-[1,3]dioxane-5',9''-fluorene] [53]

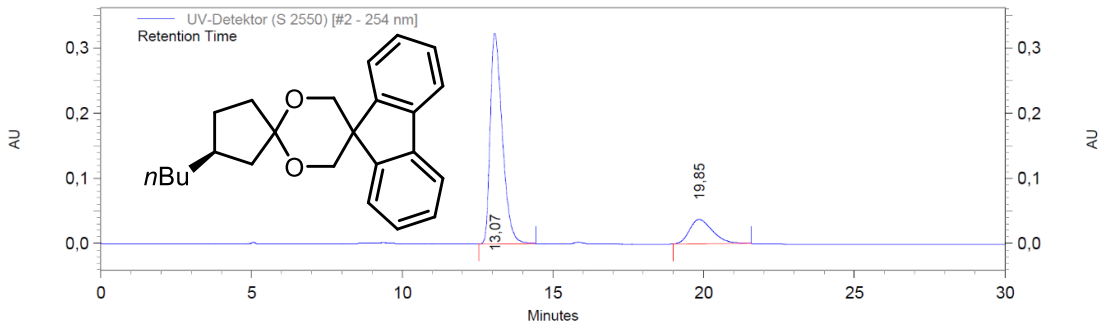


In a tube containing activated 4 Å molecular sieves, CPone **52** (4.0 mg, 29 µmol, 1.00 eq.), diol **54** (13 mg, 57 µmol, 2.00 eq.) and *p*-toluenesulphonic acid monohydrate (1.0 mg, 5.2 µmol, 0.18 eq.) were suspended in dry PhMe (1 mL). The mixture was stirred at 120 °C for 16 h. After cooling to rt, it was poured into water and diluted with Et_2O (5 mL). The org. layer was washed with water and sat. aq. NaCl sol., dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was taken up in CH_2Cl_2 and filtered through a silica plug which was eluted with CH_2Cl_2. The product was obtained *via* FC (pentane:EtOAc; 97:3) as a colourless solid (3.0 mg, 8.6 µmol, 30%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 – 7.72 (m, 4H), 7.41 (td, *J* = 7.3, 1.2 Hz, 2H), 7.33 (tt, *J* = 7.4, 1.3 Hz, 2H), 3.98 (d, *J* = 5.2 Hz, 4H), 2.55 (dd, *J* = 13.1, 7.5 Hz, 1H), 2.39 – 2.27 (m, 1H), 2.21 – 2.06 (m, 2H), 2.00 – 1.91 (m, 1H), 1.66 (dd, *J* = 13.1, 10.1 Hz, 1H), 1.49 – 1.28 (m, 7H), 0.99 – 0.82 (m, 3H).

The enantiomeric purity of 82:18 *er* was established by HPLC analysis using a chiral column (Lux® Amylose 1 column, rt, 1 mL/min, 99.5:0.5 hexane:*i*-PrOH, 254 nm, t_R(major) = 13.1 min, t_R(minor) = 19.8 min).

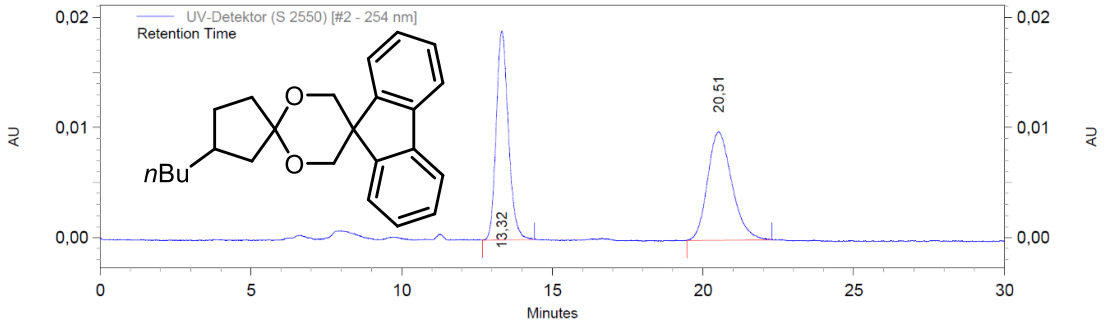
Chemotion ELN sample number: MTN-4-105-A, MTN-4-143-A.



UV-Detektor (S 2550) [#2 - 254 nm] Results

Retention Time	Area	Area %
13,072	8948684	81,88
19,854	1980187	18,12

Figure 29: HPLC chromatogram for 3-Butyldispiro[cyclopentane-1,2'-[1,3]dioxane-5',9''-fluorene] [**53**].



UV-Detektor (S 2550) [#2 - 254 nm] Results

Retention Time	Area	Area %
13,321	533269	49,14
20,514	551884	50,86

Figure 30: HPLC chromatogram for *rac*-3-Butyldispiro[cyclopentane-1,2'-[1,3]dioxane-5',9''-fluorene] [*rac*-**53**].

5.3 Asymmetric desymmetrisation of methylenecyclobutanes *via Wacker* oxidation

5.3.1 Synthesis of cyclobuntanones

5.3.1.1 General procedures

General procedure H: [2+2] cycloaddition of dichloroketene under ultrasonication

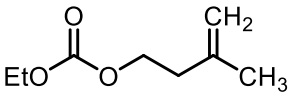
Following a modified procedure by *Du et al.*,[25] a flame dried three neck flask equipped with condenser and dripping funnel und N_2-atmosphere was charged with

Zn/Cu-Couple (2.00 eq.), the corresponding alkene (1.00 eq.) and dry Et_2O (0.2 M with respect to the alkene). The mixture was placed in an ultrasonic bath and a solution of trichloroacetyl chloride (1.50 eq.) in dry Et_2O (0.6 M) was added dropwise over 1 h under sonication. The temperature of the ultrasonic bath was maintained between 15 – 20 °C by addition of ice. After complete addition, the mixture was sonicated under these conditions for at least two additional hours or until TLC showed no further conversion. Then, water is added and the reaction mixture was filtered through a plug of Celite® which was washed with Et_2O. The filtrate was washed with water, sat. aq. $NaHCO_3$ sol. and sat. aq. NaCl sol. The combined org. layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was used without further purification.

The crude product of the first step was dissolved in glacial acetic acid (1.2 M) and added to a stirred suspension of zinc dust (6.40 eq. with respect to the alkene from the first step, –100 mesh) in glacial acetic acid (0.4 mL per gram Zn). The mixture was heated to reflux for 4 h before it was allowed to cool to rt. Then, water is added and the reaction mixture was filtered through a plug of Celite® which was washed with Et_2O. The phases of the filtrate were separated and the aq. layer was extracted with Et_2O (2×). The combined org. layers were washed with water, sat. aq. $NaHCO_3$ sol. and sat. aq. NaCl sol. The org. phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The product was obtained by flash column chromatography with the conditions given in the corresponding entry.

5.3.1.2 Syntheses

Ethyl (3-methylbut-3-en-1-yl) carbonate [142]



Following a procedure by *Horn and Kazmaier*,[181] 3-methylbut-3-en-1-ol (1.51 mL, 15.0 mmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 °C. Pyridine (1.82 mL, 22.5 mmol, 1.50 eq.) was added followed by dropwise addition of ethyl chloroformate (1.71 mL, 18.0 mmol, 1.20 eq.). The mixture was gradually warmed to rt and stirred for 3 d. Then, Et_2O (10 mL) was added and it was washed with 1 M aq. HCl (2×50 mL). The aq. layer was extracted with Et_2O (20 mL). The combined org. layers were washed with sat. aq. NaCl sol. (50 mL), dried over Na_2SO_4,

filtered and concentrated *in vacuo* affording the desired product as colourless oil (2.05 g, 12.9 mmol, 86%).

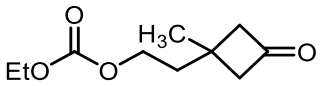
IR (neat): $\tilde{\nu}$ = 2988 (w), 2938 (w), 2917 (w), 2353 (w), 2341 (w), 1746 (s), 1651 (w), 1457 (w), 1382 (w), 1256 (s), 1090 (w), 1025 (w), 952 (w), 894 (w), 849 (w), 793 (w), 733 (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 – 4.70 (m, 2H, CH_2), 4.23 (t, J = 6.9 Hz, 2H, CH_2), 4.18 (q, J = 7.1 Hz, 2H, CH_2), 2.42 – 2.34 (m, 2H, CH_2), 1.76 (t, J = 1.2 Hz, 3H, CH_3), 1.30 (t, J = 7.1 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.3 (C_q), 141.3 (C_q), 112.7 (CH$_2$), 66.0 (CH$_2$), 64.0 (CH$_2$), 36.8 (CH$_2$), 22.6 (CH$_3$), 14.4 (CH$_3$).

HRMS (APCI, CH_3COONH_4): Calculated for $C_8H_{15}O_3^+$ $[M+H]^+$: 159.1012, found: 159.1016.

Ethyl (2-(1-methyl-3-oxocyclobutyl)ethyl) carbonate [143]



Following general procedure **H** using alkene **142** (2.00 g, 12.7 mmol, 1.00 eq.), Zn/Cu couple (1.65 g, 25.3 mmol, 2.00 eq.) and TCAC (2.14 mL, 19.0 mmol, 1.50 eq.) in the first step and zinc dust (5.30 g, 81.1 mmol, 6.40 eq.) and acetic acid (10 mL) in the second step, the desired product was obtained *via* AFC (CyHex:EtOAc; 95:5 → 80:20) as colourless oil (745 mg, 3.72 mmol, 29%).

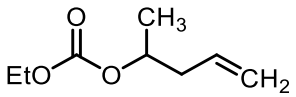
IR (neat): $\tilde{\nu}$ = 2970 (w), 2917 (w), 2877 (w), 2241 (w), 1784 (s), 1742 (s), 1459 (w), 1403 (w), 1386 (w), 1368 (m), 1252 (s), 1188 (w), 1144 (w), 1085 (w), 1005 (m), 879 (w), 792 (w), 733 (w), 644 (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.24 (t, J = 6.9 Hz, 2H, OCH_2), 4.18 (q, J = 7.1 Hz, 2H, OCH_2), 2.99 – 2.87 (m, 2H, CH_2), 2.83 – 2.71 (m, 2H, CH_2), 2.02 (t, J = 6.9 Hz, 2H, CH_2), 1.34 (s, 3H, CH_3), 1.29 (t, J = 7.1 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 207.4 (C_q), 155.2 (C_q), 65.3 (OCH$_2$), 64.2 (OCH$_2$), 58.8 (2×CH$_2$), 39.5 (CH$_2$), 27.7 (C_q), 25.6 (CH$_3$), 14.4 (CH$_3$).

HRMS (ESI): Calculated for $C_{10}H_{16}O_4Na^+$ $[M+Na]^+$: 223.0941, found: 223.0943.

Ethyl pent-4-en-2-yl carbonate [144]



Following a procedure by *Horn and Kazmaier*,[181] 4-penten-2-ol (2.06 mL, 20.0 mmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 °C. Pyridine (2.42 mL, 30.0 mmol, 1.50 eq.) was added followed by dropwise addition of ethyl chloroformate (2.29 mL, 24.0 mmol, 1.20 eq.). The mixture was gradually warmed to rt and stirred for 18 h. Then, Et_2O (10 mL) was added and it was washed with 1 M aq. HCl (2×25 mL). The aq. layer was extracted with Et_2O (20 mL). The combined org. layers were washed with sat. aq. NaCl sol. (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* affording the desired product as colourless oil (3.03 g, 19.1 mmol, 96%).

IR (neat): $\tilde{\nu}$ = 2982 (w), 2931 (w), 1743 (s), 1642 (w), 1461 (w), 1373 (m), 1261 (s), 1133 (w), 1055 (w), 1011 (m), 919 (w), 878 (w), 772 (m), 759 (w), 738 (m).

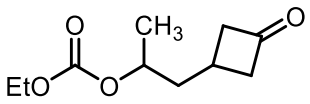
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 – 5.70 (m, 1H, C*H*), 5.16 – 5.05 (m, 2H, CH_2), 4.87 – 4.72 (m, 1H, OC*H*), 4.22 – 4.11 (m, 2H, OCH_2), 2.47 – 2.36 (m, 1H, CH_2), 2.36 – 2.25 (m, 1H, CH_2), 1.33 – 1.24 (m, 6H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.8 (C_q), 133.4 (*C*H), 118.2 (*C*H_2), 74.2 (O*C*H), 63.8 (*C*H_2), 40.4 (*C*H_2), 19.6 (*C*H_3), 14.4 (*C*H_3).

HRMS (APCI, CH_3COONH_4): Calculated for $C_8H_{14}O_3^+$ $[M+H]^+$: 159.1016, found: 159.1013.

Chemotion ELN sample number: MTN-4-33-A.

Ethyl (1-(3-oxocyclobutyl)propan-2-yl) carbonate [145]



Following general procedure **H** using alkene **144** (3.13 g, 15.8 mmol, 1.00 eq.), Zn/Cu couple (4.07 g, 31.5 mmol, 2.00 eq.) and TCAC (4.30 g, 2.64 mL, 23.6 mmol, 1.50 eq.) in the first step and zinc dust (6.80 g, 104 mmol, 6.59 eq.) and acetic acid (15 mL) in the second step, the desired product was obtained *via* AFC (CH_2Cl_2:MeOH; 100:0 → 99:1) as colourless oil (220 mg, 1.10 mmol, 7%).

IR (neat): $\tilde{\nu}$ = 2980 (w), 2942 (w), 2346 (w), 1785 (s), 1738 (s), 1461 (w), 1374 (m), 1346 (w), 1257 (s), 1173 (w), 1140 (w), 1103 (m), 1053 (w), 1009 (m), 924 (w), 862 (w), 819 (w), 792 (m), 672 (w), 640 (m), 618 (m), 607 (m).

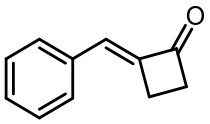
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79 (dqd, J = 8.0, 6.3, 4.7 Hz, 1H, OC*H*), 4.18 (q, J = 7.1 Hz, 2H, OCH_2), 3.26 – 3.08 (m, 2H, CH_2), 2.84 – 2.69 (m, 2H, CH_2), 2.49 (dtt, J = 15.3, 8.5, 6.7 Hz, 1H, C*H*), 2.03 – 1.93 (m, 1H, CH_2), 1.85 – 1.74 (m, 1H, CH_2), 1.36 – 1.31 (d, J = 6.3, 3H, CHCH_3), 1.30 (t, J = 7.1 Hz, 3H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 207.5 (C_q), 154.9 (C_q), 74.1 (O*C*H), 64.0 (O*C*H_2), 53.0 (*C*H_2), 52.8 (*C*H_2), 42.3 (*C*H_2), 20.8 (*C*H), 20.3 (CH_2*C*H_3), 14.4 (CH*C*H_3).

HRMS (ESI): Calculated for $C_{10}H_{17}O_4^+$ $[M+H]^+$: 201.1121, found 201.1119.

Chemotion ELN sample number: MTN-4-34-A & MTN-4-35-A.

2-Benzylidenecyclobutan-1-one [146]



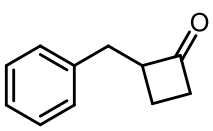
An oven dried Schlenk tube was charged with $Ca(OH)_2$ (111 mg, 1.50 mmol, 0.10 eq.). Then, a solution of benzaldehyde (1.52 mL, 15.0 mmol, 1.00 eq.) and cyclobutanone (3.35 mL, 45.0 mmol, 3.00 eq.) in EtOH (45 mL) was added under N_2-atmosphere. It was stirred at 80 °C for 24 h. The solvent was removed under reduced pressure. The desired product was obtained *via* AFC (CyHex:EtOAc; 95:5) as colourless oil (1.15 g, 7.25 mmol, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 – 7.49 (m, 2H), 7.45 – 7.38 (m, 3H), 7.04 (t, J = 2.8 Hz, 1H), 3.21 – 3.11 (m, 2H), 3.06 – 2.96 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.8, 146.3, 134.7, 130.2, 130.2, 129.1, 126.6, 45.9, 23.7.

Spectroscopic data was in agreement with that previously reported.[182]

2-Benzylcyclobutan-1-one [147]



A flask was charged with Pd/C (5% *w*/*w*, 345 mg, 0.162 mmol, 2.35 mol%) and purged with N_2. Cyclobutanone **146** (1.09 g, 6.90 mmol, 1.00 eq.) was dissolved in

dry THF/EtOH (4:1) and added to the flask *via* syringe. Then, the reaction mixture was purged with H_2 for ~15 min using a H_2-balloon. Thereafter, the mixture was stirred for 6 h at rt under H_2-atmosphere. The mixture was filtered through Celite® with EtOAc and concentrated *in vacuo*. The crude residue was purified *via* AFC (CyHex:EtOAc; 98:2 → 92:8). The product was obtained as colourless oil (613 mg, 3.83 mmol, 55%).

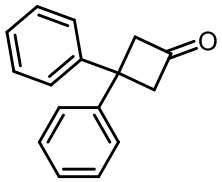
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 3.67 – 3.54 (m, 1H), 3.10 – 2.99 (m, 2H), 2.92 – 2.76 (m, 2H), 2.23 – 2.11 (m, 1H), 1.82 – 1.69 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.1, 139.0, 128.9, 128.6, 126.4, 61.3, 44.6, 35.3, 16.7.

Spectroscopic data was in agreement with that previously reported.[183]

Chemotion ELN sample number: MTN-4-63-A.

3,3-Diphenylcyclobutan-1-one [148]



Following general procedure **A** using ethene-1,1-diyldibenzene (2.16 g, 12.0 mmol, 1.00 eq.), dimethylacetamide (1.34 mL, 14.4 mmol, 1.20 eq.), Tf_2O (4.04 mL, 24.0 mmol, 2.00 eq.) and 2,6-lutidine (2.80 mL, 24.0 mmol, 2.00 eq.), the desired product was obtained *via* FC (pentane:Et_2O, 95:5) as an off-white solid (1.48 g, 6.65 mmol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.23 (m, 8H), 7.22 – 7.14 (m, 2H), 3.77 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.7, 147.3, 128.8, 126.8, 126.6, 60.6, 42.1.

Spectroscopic data was in agreement with that previously reported.[184] Synthesis performed by [redacted].

5.3.2 Synthesis of methylenecyclobutanes

MCB **72** (CAS [15760-36-8]) and MCB **75** (CAS [15760-35-7]) were commercially available.

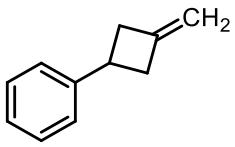
5.3.2.1 General procedures

General procedure I: Wittig olefination

In an oven dried Schlenk tube methyl(triphenyl)phosphonium bromide (1.35 eq.) was suspended in dry THF (0.1 M with respect to the substrate) and it was cooled to 0 °C. A solution of *n*-butyl lithium (1.30 eq., 2.5 M in hexanes) was added dropwise. After complete addition the mixture was allowed to warm to rt and stirred for 30 min. It was cooled to 0 °C and the respective cyclobutanone (1.00 eq.) was added dropwise and the mixture was stirred at rt for 18 h. Water (half amount of THF) was added, the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3×). The combined org. layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual triphenylphosphine oxide was removed *via* filtration through a short silica plug with CH_2Cl_2. The product was isolated by flash column chromatography with the conditions given in the corresponding entry.

5.3.2.2 Syntheses

(3-Methylenecyclobutyl)benzene [65]



Following general procedure **I**[10] using cyclobutanone **1** (5.67 g, 38.8 mmol, 1.00 eq.), methyl(triphenyl)phosphonium bromide (18.7 g, 52.4 mmol, 1.35 eq.) and *n*-BuLi (20.2 mL, 50.4 mmol, 2.5 M in hexanes, 1.30 eq.), the desired product was obtained *via* FC (pentane) as colourless oil (4.43 g, 30.3 mmol, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 – 7.30 (m, 4H), 7.30 – 7.22 (m, 1H), 4.90 (ddd, J = 4.7, 2.5, 1.3 Hz, 2H), 3.60 (*app* p, $J \approx$ 8.4 Hz, 1H), 3.25 – 3.10 (m, 2H), 2.99 – 2.84 (m, 2H).

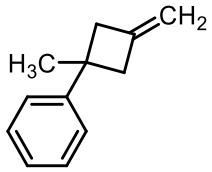
^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.2, 145.8, 128.5, 126.6, 126.1, 105.8, 39.9, 35.0.

Spectroscopic data was in agreement with that previously reported.[35]

Chemotion ELN sample number: MTN-5-33-A.

[10] Synthesis performed with 4 d reaction time instead of 18 h.

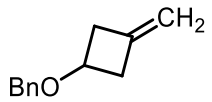
(1-Methyl-3-methylenecyclobutyl)benzene [66]



Following general procedure **I**[11] using cyclobutanone **2** (450 mg, 2.81 mmol, 1.00 eq.), methyl(triphenyl)phosphonium bromide (1.36 g, 3.79 mmol, 1.35 eq.) and *n*-BuLi (1.46 mL, 3.65 mmol, 2.5 M in hexanes, 1.30 eq.), the desired product was obtained *via* FC (pentane) as colourless oil (380 mg, 2.40 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 – 7.28 (m, 2H), 7.26 – 7.16 (m, 3H), 4.89 (ddt, *J* = 4.1, 2.7, 1.3 Hz, 2H), 3.15 – 3.03 (m, 2H), 2.78 – 2.69 (m, 2H), 1.48 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.9, 144.9, 128.4, 125.6, 125.3, 107.2, 44.9, 38.7, 30.5.
Spectroscopic data was in agreement with that previously reported.[37]
Chemotion ELN sample number: MTN-5-19-A.

(3-Methylenecyclobutyl)oxymethylbenzene [67]

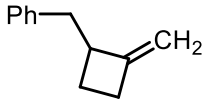


Following general procedure **I** using 3-benzoxycyclobutanone (529 mg, 3.00 mmol, 1.00 eq.), methyl(triphenyl)phosphonium bromide (1.45 g, 4.05 mmol, 1.35 eq.) and *n*-BuLi (1.56 mL, 3.90 mmol, 2.5 M in hexanes, 1.30 eq.), the desired product was obtained *via* FC (pentane:Et_2O; 95:5) followed by distillation (Kugelrohr, 0.7 mbar, 75 – 80 °C) as a colourless oil (202 mg, 1.16 mmol, 38%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.27 (m, 5H), 4.85 (tt, *J* = 2.8, 2.0 Hz, 2H), 4.45 (s, 2H), 4.11 (p, *J* = 6.6 Hz, 1H), 2.96 – 2.83 (m, 2H), 2.83 – 2.67 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.25, 138.20, 128.55, 128.04, 127.83, 107.13, 70.62, 68.99, 40.41.
Spectroscopic data was in agreement with that previously reported.[185]
Chemotion ELN sample number: MTN-5-38-A.

[11] Synthesis performed with 4 d reaction time instead of 18 h.

(2-Methylidenecyclobutyl)methylbenzene [68]



Following general procedure **I** using cyclobutanone **147** (128 mg, 0.800 mmol, 1.00 eq.), methyl(triphenyl)phosphonium bromide (372 mg, 1.04 mmol, 1.35 eq.) and *n*-BuLi (1.56 mL, 3.90 mmol, 2.5 M in hexanes, 1.30 eq.), the desired product was obtained *via* FC (pentane) as a colourless oil (78 mg, 0.49 mmol, 62%).

IR (neat): $\tilde{\nu}$ = 3484 (br), 3068 (w), 3025 (w), 2979 (w), 2921 (w), 2375 (w), 1673 (w), 1602 (w), 1496 (w), 1454 (w), 1158 (w), 1090 (w), 1031 (w), 905 (w), 874 (m), 806 (w), 740 (m), 697 (s), 650 (m), 635 (m), 618 (s), 602 (s), 588 (s).

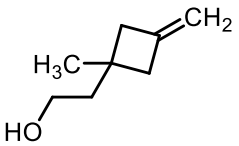
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.24 (m, 2H, CH_{arom}), 7.24 – 7.15 (m, 3H, CH_{arom}), 4.73 (dq, *J* = 7.7, 2.4 Hz, 2H, CH_2), 3.24 (tdd, *J* = 11.6, 5.8, 2.7 Hz, 1H, C*H*), 2.95 (dd, *J* = 14.0, 6.1 Hz, 1H, CH_2), 2.74 (dd, *J* = 14.0, 9.1 Hz, 1H, CH_2), 2.70 – 2.52 (m, 2H, CH_2), 2.07 (dtd, *J* = 10.8, 9.0, 5.0 Hz, 1H, CH_2), 1.72 (dddd, *J* = 10.9, 9.3, 8.2, 7.3 Hz, 1H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.4 (C_q), 140.7 (C_q), 128.9 (2×CH$_{arom}$), 128.4 (2×CH$_{arom}$), 126.0 (CH$_{arom}$), 103.9 (CH$_2$), 45.5 (CH), 40.5 (CH$_2$), 29.1 (CH$_2$), 24.0 (CH$_2$).

HRMS (APCI, CH_3COONH_4): Calculated for $C_{12}H_{15}^+$ $[M+H]^+$: 159.1168, found 159.1165.

Chemotion ELN sample number: MTN-4-54-A.

2-(1-Methyl-3-methylenecyclobutyl)ethan-1-ol [69]



Following general procedure **I** using cyclobutanone **143** (719 mg, 3.59 mmol, 1.00 eq.), methyl(triphenyl)phosphonium bromide (1.73 g, 4.85 mmol, 1.35 eq.) and *n*-BuLi (1.87 mL, 4.67 mmol, 2.5 M in hexanes, 1.30 eq.), ethyl (2-(1-methyl-3-methylenecyclo-butyl)ethyl) carbonate was obtained after filtration through a silica plug (CyHex:EtOAc; 95:5).

The crude carbonate was dissolved in MeOH (10 mL) and K_2CO_3 (78 mg, 0.56 mmol, 0.16 eq.) was added. The mixture was stirred at rt for 18 h. It was acidified to pH = 1 with 1 M aq. HCl and extracted with CH_2Cl_2 (4×15 mL). The combined org. phases

were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The desired product was obtained after filtration through a plug of silica with CH_2Cl_2 as colourless oil (267 mg, 2.11 mmol, 59%).

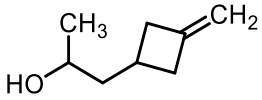
IR (neat): $\tilde{\nu}$ = 3395 (br), 2954 (s), 2362 (m), 2342 (m), 2238 (w), 1746 (w), 1678 (m), 1461 (m), 1377 (m), 1332 (w), 1274 (w), 1147 (w), 1050 (s), 1015 (m), 908 (m), 876 (s), 814 (w), 728 (m), 645 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79 (p, J = 2.4 Hz, 2H, CH_2), 3.73 – 3.64 (m, 2H, CH_2), 2.57 – 2.47 (m, 2H, CH_2), 2.41 – 2.29 (m, 2H, CH_2), 1.80 – 1.73 (m, 2H, CH_2), 1.15 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.5 (C_q), 107.2 (CH_2), 60.4 (CH_2), 44.1 (2×CH_2), 44.1 (CH_2), 32.8 (C_q), 25.9 (CH_3).

HRMS (APCI, CH_3COONH_4): Calculated for $C_8H_{15}O^+$ $[M+H]^+$: 127.1118, found: 127.1114.

1-(3-Methylenecyclobutyl)propan-2-ol [70]



Following general procedure **I** using cyclobutanone **145** (202 mg, 1.01 mmol, 1.00 eq.), methyl(triphenyl)phosphonium bromide (487 mg, 1.36 mmol, 1.35 eq.) and *n*-BuLi (525 µL, 1.31 mmol, 2.5 M in hexanes, 1.30 eq.), ethyl (1-(3-methylenecyclobutyl)propan-2-yl) carbonate was obtained as a colourless oil (171 mg, 0.86 mmol, 85%) which was used without further purification.

The crude carbonate (171 mg, 0.86 mmol, 1.00 eq.) was dissolved in methanol (5 mL) and potassium carbonate (30 mg, 0.22 mmol, 0.25 eq.) was added. The mixture was stirred at rt for 4 h. Then, 1 M aq. HCl (2 mL) and water (5 mL) were added and it was extracted with CH_2Cl_2 (4×5 mL). The comb. org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was obtained as colourless oil (71 mg, 0.56 mmol, 65%) and used without further purification.

IR (neat): $\tilde{\nu}$ = 3389 (br), 2965 (s), 2913 (s), 1783 (w), 1732 (w), 1676 (m), 1461 (m), 1417 (m), 1375 (m), 1269 (m), 1135 (m), 1057 (m), 1003 (m), 939 (m), 873 (s), 833 (w), 705 (s), 672 (s), 661 (s), 638 (s), 626 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.72 (p, J = 2.3 Hz, 2H, CH_2), 3.77 (dqd, J = 7.4, 6.2, 5.2 Hz, 1H, CH), 2.87 – 2.71 (m, 2H, CH_2), 2.46 – 2.27 (m, 3H, CH/CH_2), 1.68 (ddd,

J = 13.8, 7.4, 6.5 Hz, 1H, C*H*$_2$), 1.57 (ddd, *J* = 13.7, 7.7, 5.2 Hz, 1H, C*H*$_2$), 1.50 (s, 1H, O*H*), 1.18 (d, *J* = 6.2 Hz, 3H, C*H*$_3$).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 147.4 (C_q), 105.6 (CH$_2$), 67.1 (CH), 46.1 (CH$_2$), 38.1 (CH$_2$), 38.0 (CH$_2$), 27.3 (CH), 23.8 (CH$_3$).

HRMS (ESI): Calculated for $C_8H_{15}O^+$ [M+H]$^+$: 127.1118, found 127.1117.

Chemotion ELN sample number: MTN-4-36-A & MTN-4-37-A.

(3-Methylenecyclobutyl)methanol [73]

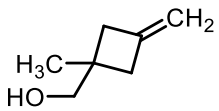
In analogy to a procedure of *Cowling and Goodby*,[129] $LiAlH_4$ (285 mg, 7.50 mmol, 1.50 eq.) was added to a solution of acid **72** (561 mg, 5.00 mmol, 1.00 eq.) in dry Et_2O (10 mL) in a single portion. It was heated to reflux for 3.5 h. Thereafter, it was cooled to <10 °C and sat. aq. Na_2SO_4 (10 mL) was added. It was stirred for additional 15 min before the resulting precipitate was filtered off and washed with Et_2O (20 mL). The filtrate was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The desired product was obtained *via* filtration through a plug of silica with Et_2O as a colourless oil (350 mg, 3.56 mmol, 71%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 4.78 (p, *J* = 2.4 Hz, 2H), 3.67 (d, *J* = 6.7 Hz, 2H), 2.87 – 2.68 (m, 1H), 2.58 – 2.35 (m, 3H), 1.46 (s, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 146.7, 106.7, 67.0, 34.4, 31.9.

Spectroscopic data was in agreement with that previously reported.[186]

(1-Methyl-3-methylenecyclobutyl)methanol [74]



In analogy to a procedure by *Pfizer Inc.*,[130] MCB **75** (0.51 mL, 5.0 mmol, 1.00 eq.) was dissolved in dry Et_2O (3.5 mL) and cooled to −78 °C. Then, lithium bis(trimethylsilyl) amide solution (1 M in THF, 5.50 mL, 5.50 mmol, 1.10 eq.) was added dropwise and it was stirred for 1 h at −78 °C. Thereafter, methyl iodide (0.37 mL, 6.00 mmol, 1.20 eq.) was added and the mixture was gradually warmed to −40 °C under stirring for 3 h. Subsequently, sat. aq. NH_4Cl sol. (5 mL) was added. The phases were separated and the aq. layer was extracted with Et_2O (3×15 mL). The combined

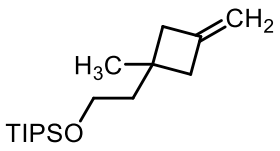
org. phases were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was filtered through a plug of silica with Et_2O, concentrated and used in the next step without further purification.

The crude carbonitrile was dissolved in a mixture of EtOH/H_2O (6 mL, 1:1 *v*/*v*) and potassium hydroxide (701 mg, 12.5 mmol, 2.50 eq.) was added. The mixture was heated to reflux for 16 h. Then, it was cooled to <10 °C and acidified to pH <1 by addition of conc. aq. HCl. The phases were separated and the aq. layer was extracted with EtOAc (3×10 mL). The combined org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. 1-methyl-3-methylenecyclobutane-1-carboxylic acid was obtained as colourless oil and used in the next step without further purification.

In analogy to a procedure of *Cowling and Goodby*,[129] $LiAlH_4$ (303 mg, 7.99 mmol, 2.00 eq.) was added to a solution of the acid (504 mg, 4.00 mmol, 1.00 eq.) in dry Et_2O (60 mL) in a single portion. It was heated to reflux for 3.5 h. Thereafter, it was cooled to <10 °C and sat. aq. Na_2SO_4 (10 mL) was added. It was stirred for additional 16 h before the resulting precipitate was filtered off and washed with Et_2O (20 mL). The filtrate was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The desired product was obtained *via* filtration through a plug of silica with Et_2O as mixture with Et_2O (460 mg, 90% *w*/*w*, 3.67 mmol, 73%) and was used as is in the ring expansion. *Note:* The product is fairly volatile.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.82 (p, *J* = 2.4 Hz, 2H), 3.53 (s, 2H), 2.61 – 2.46 (m, 2H), 2.40 – 2.28 (m, 2H), 1.52 – 1.42 (m, 1H), 1.20 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.6, 107.7, 70.6, 40.3, 35.7, 29.8, 23.5.
Spectroscopic data was in agreement with that previously reported.[130]

Triisopropyl(2-(1-methyl-3-methylenecyclobutyl)ethoxy)silane [76]



A tube was charged with MCB **69** (100 mg, 0.73 mmol, 1.00 eq.) and DMF (2 mL). Imidazole (124 mg, 1.82 mmol, 2.50 eq.) was added and the tube was set under N_2-atmosphere. Then, chloro(triisopropyl)silane (0.22 mL, 1.03 mmol, 1.41 eq.) was added *via* syringe and the mixture was stirred at rt for 4 h. The progress of the reaction was observed *via* TLC control (pentane:EtOAc; 50:50). It was diluted with

CH_2Cl_2 (3 mL) and the org. phase was washed with sat. aq. LiCl sol. (4×5 mL). The comb. org. layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 and filtered through a short silica plug, which was eluted with CH_2Cl_2, to afford the product as colourless oil (168 mg, 0.60 mmol, 82%).

IR (neat): $\tilde{\nu}$ = 2942 (s), 2868 (s), 2360 (w), 1739 (m), 1678 (m), 1466 (m), 1383 (w), 1292 (w), 1245 (m), 1204 (w), 1098 (s), 1071 (m), 997 (m), 949 (w), 878 (s), 781 (m), 758 (w), 740 (s), 680 (s).

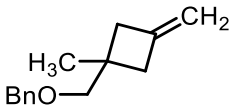
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (p, J = 2.4 Hz, 2H, CH_2), 3.73 (t, J = 7.1 Hz, 2H, OCH_2), 2.58 – 2.49 (m, 2H, CH_2), 2.38 – 2.26 (m, 2H, CH_2), 1.75 (t, J = 7.1 Hz, 2H, CH_2), 1.15 (s, 3H, CH_3), 1.08 – 1.04 (m, 21H, CH/CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.2 (C_q), 106.9 (CH_2), 60.8 (OCH_2), 44.3 (2×CH_2), 44.2 (CH_2), 32.9 (C_q), 25.8 (CH_3), 18.2 (6×CH_3), 12.1 (3×CH).

HRMS (ESI): Calculated for $C_{17}H_{35}OSi^+$ $[M+H]^+$: 283.2452, found 283.2446.

Chemotion ELN sample number: MTN-4-30-A.

(((1-Methyl-3-methylenecyclobutyl)methoxy)methyl)benzene [77]



In an oven dried Schlenk tube sodium hydride (29 mg, 0.72 mmol, 1.10 eq.) was suspended in *N*,*N*-dimethylformamide (5 mL) and cooled to 0 °C. Then, MCB **74** (73 mg, 0.65 mmol, 1.00 eq.) dissolved in *N*,*N*-dimethylformamide (2 mL) was added dropwise. After stirring at 0 °C for approx. 5 min the mixture was allowed to warm to rt and stirred for additional 30 min. It was cooled again to 0 °C and benzyl bromide (0.09 mL, 0.72 mmol, 1.10 eq.) was added. The mixture was allowed to warm to rt and stirred for 3 h. The progress of the reaction was observed *via* TLC control (CH_2Cl_2:MeOH; 98:2). Then, sat. aq. NH_4Cl sol. (2 mL) was added and it was diluted with water (10 mL). It was extracted with dichloromethane (4×10 mL). The comb. org. layers were washed with sat. aq. NaCl sol. (10 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue, still containing larger amounts of DMF, was taken up in Et_2O (10 mL) and washed with aq. LiCl sol. (3×15 mL). The org. phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The desired product was obtained *via* AFC

(pentane:EtOAc; 100:0 → 95:5) as mixture with Bn_2O (58 mg, 72% *w*/*w*, 0.21 mmol, 32%) and was used as is in the ring expansion.

IR (neat): $\tilde{\nu}$ = 2952 (m), 2913 (m), 2855 (w), 2332 (w), 1676 (w), 1497 (w), 1454 (w), 1358 (w), 1162 (w), 1095 (m), 1028 (w), 908 (w), 876 (m), 811 (w), 739 (s), 697 (s), 649 (m), 634 (m), 619 (s), 609 (s), 590 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.26 (m, 7H, CH_{arom})[12], 4.80 (p, *J* = 2.4 Hz, 2H, CH_2), 4.57 (s, Bn_2O), 4.56 (s, 2H, OCH_2), 3.35 (s, 2H, OCH_2), 2.65 – 2.55 (m, 2H, CH_2), 2.37 – 2.28 (m, 2H, CH_2), 1.22 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.3 (C_q), 139.0 (C_q), 138.4 (Bn_2O), 128.6 (Bn_2O), 128.5 (2×CH$_{arom}$), 128.0 (Bn_2O), 127.8 (Bn_2O), 127.6 (2×CH$_{arom}$), 127.6 (CH$_{arom}$), 107.4 (CH$_2$), 77.9 (CH$_2$), 73.4 (CH$_2$), 72.3 (Bn_2O), 41.0 (2×CH$_2$), 34.8 (C_q), 24.1 (CH$_3$)

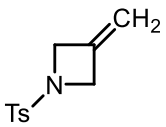
HRMS (APCI, CH_3COONH_4): Calculated for $C_{14}H_{19}O^+$ $[M+H]^+$: 203.1430, found 203.1430.

Chemotion ELN sample number: MTN-4-50-A.

5.3.3 Synthesis of other substrates

Methyleneazetidine **103** (CAS [934664-41-2]) was commercially available.

3-Methylene-1-tosylazetidine [78]



Following general procedure **I** using azetidinone **80** (225 mg, 1.00 mmol, 1.00 eq.), methyl(triphenyl)phosphonium bromide (482 mg, 1.35 mmol, 1.35 eq.) and *n*-BuLi (520 µL, 1.30 mmol, 2.5 M in hexanes, 1.30 eq.), the desired product was obtained *via* FC (CH_2Cl_2) as a colourless oil (25 mg, 0.11 mmol, 11%).

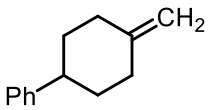
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 – 7.69 (m, 2H), 7.41 – 7.32 (m, 2H), 4.91 (p, *J* = 2.5 Hz, 2H), 4.37 (t, *J* = 2.5 Hz, 4H), 2.45 (s, 3H).

Spectroscopic data was in agreement with that previously reported.[187]

Chemotion ELN sample number: MTN-4-43-A.

[12] The increased integral in the aromatic region is caused by overlap with the signals of residual Bn_2O.

(4-Methylenecyclohexyl)benzene [79]



Following general procedure **I** using 4-phenyl cyclohexanone (871 mg, 5.00 mmol, 1.00 eq.), methyl(triphenyl)phosphonium bromide (2.41 g, 6.75 mmol, 1.35 eq.) and *n*-BuLi (2.60 mL, 6.50 mmol, 2.5 M in hexanes, 1.30 eq.), the desired product was obtained *via* FC (pentane) as a colourless oil (733 mg, 4.23 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.27 (m, 2H), 7.24 – 7.15 (m, 3H), 4.69 (t, *J* = 1.7 Hz, 2H), 2.68 (tt, *J* = 12.2, 3.5 Hz, 1H), 2.49 – 2.37 (m, 2H), 2.27 – 2.10 (m, 2H), 2.06 – 1.93 (m, 2H), 1.65 – 1.47 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.0, 147.0, 128.5, 127.0, 126.1, 107.5, 44.3, 35.7, 35.3.

Spectroscopic data was in agreement with that previously reported.[188]

Chemotion ELN sample number: MTN-5-28-A.

5.3.4 Synthesis of ligands

5.3.4.1 General procedures

General Procedure J: Amide coupling using EDCI/DMAP

Following a modified procedure of *Lutjen et al.*,[189] a flask was charged with the corresponding acid (1.00 eq.), the corresponding aminoalcohol (1.00 eq.), EDCI hydrochloride (1.10 eq.) and DMAP (0.10 eq.). Then, CH_2Cl_2 (0.25 M with respect to the acid) was added and the mixture was stirred at rt for 18 h. Water was added and the phases were separated. The aq. layer was extracted with CH_2Cl_2 (1×). The combined org. phases were washed with sat. aq. $NaHCO_3$ sol. (1×). The aq. layer was extracted with CH_2Cl_2 (1×). The combined org. phases were washed with sat. aq. NaCl sol. (1×), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The product was obtained by AFC with the conditions given in the corresponding entry.

General Procedure K: Amide coupling using NMM/*i*-BuOCOCl

Following a procedure of *Werner et al.*,[190] an oven dried Schlenk tube was charged with the corresponding acid (1.00 eq.) and dry CH_2Cl_2 (0.2 M with respect to the

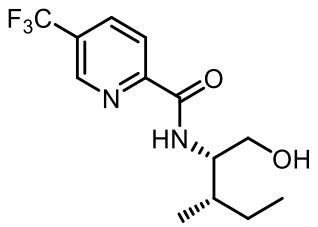
acid). *N*-Methyl morpholine (1.15 eq.) was added and it was cooled to 0 °C. Then, *i*-butyl chloroformate (1.20 eq.) was added dropwise. The mixture was stirred for 20 min before the corresponding aminoalcohol (1.20 eq.) was added as a solution in dry CH_2Cl_2 (1.0 M with respect to the aminoalcohol). The reaction mixture was gradually warmed to rt and stirred for 18 h. Water was added and the phases were separated. The aq. layer was extracted with CH_2Cl_2 (1×). The combined org. phases were washed with water (1×) and sat. aq. NaCl sol. (1×), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The product was obtained by AFC with the conditions given in the corresponding entry.

General Procedure L: Synthesis of PyOx-Ligands

In an oven dried Schlenk tube the corresponding amide (1.00 eq.) was suspended in dry CH_2Cl_2 (0.1 M with respect to the amide). The mixture was cooled to 0 °C and dry NEt_3 (2.50 eq.) was added. Then, mesyl chloride (1.25 eq.) was added dropwise. After complete addition the reaction mixture was stirred for 15 min at 0 °C before it was gradually warmed to rt and stirred for additional 16 h. Water was added and the phases were separated. The aq. layer was extracted with CH_2Cl_2 (4×). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The residue was taken up in MeOH (0.1 M with respect to the amide). Sodium hydroxide (3.00 eq.) was added and the mixture was heated to reflux for 3 h. After cooling to rt the mixture was concentrated and water was added. It was extracted with CH_2Cl_2 (3×). The combined org. phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was obtained by AFC with the conditions given in the corresponding entry.

5.3.4.2 Syntheses

N-((2*S*,3*S*)-1-Hydroxy-3-methylpentan-2-yl)-5-(trifluoromethyl)picolinamide [149]



Following general procedure **J** using 5-(trifluoromethyl)picolinic acid (573 mg, 3.00 mmol, 1.00 eq.), (*S*)-isoleucinol (352 mg, 3.00 mmol, 1.00 eq.), EDCI hydrochloride (633 mg, 3.30 mmol, 1.10 eq.) and DMAP (36.7 mg, 0.30 mmol, 0.1 eq.), the desired product was obtained *via* AFC (CyHex:EtOAc; 80:20 → 20:80) as a pale yellow oil (480 mg, 1.65 mmol, 55%).

IR (neat): $\tilde{\nu}$ = 3394 (br), 2968 (w), 2927 (w), 2877 (w), 2332 (w), 2241 (w), 1669 (m), 1578 (w), 1528 (s), 1465 (w), 1386 (w), 1326 (s), 1167 (s), 1134 (s), 1076 (s), 1018 (m), 906 (w), 869 (m), 797 (w), 781 (w), 702 (w), 640 (m).

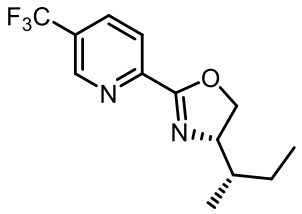
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, J = 2.2 Hz, 1H, CH_{arom}), 8.30 (d, J = 8.2 Hz, 1H, CH_{arom}), 8.21 (d, J = 8.8 Hz, 1H, NH), 8.08 (dd, J = 8.4, 2.2 Hz, 1H, CH_{arom}), 4.06 – 3.96 (m, 1H, CH), 3.89 – 3.75 (m, 2H, CH_2), 2.86 (s, 1H, OH), 1.87 – 1.74 (m, 1H, CH), 1.64 – 1.50 (m, 1H, CH_2), 1.30 – 1.15 (m, 1H, CH_2), 1.00 (d, J = 6.8 Hz, 3H, CH_3), 0.93 (t, J = 7.4 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.7 (C_q), 152.7 (C_q), 145.3 (d, J = 4.0 Hz, CH$_{arom}$), 135.0 (q, J = 3.5 Hz, CH$_{arom}$), 129.0 (q, J = 33.3 Hz, C_q), 123.25 (q, J = 272.5 Hz, CF$_3$), 122.3 (CH$_{arom}$), 63.8 (CH$_2$), 56.7 (CH), 35.9 (CH), 25.6 (CH$_2$), 15.8 (CH$_3$), 11.5 (CH$_3$).

^{19}F NMR (282 MHz, $CDCl_3$) δ = – 62.45 (s, 3F, CF_3).

HRMS (ESI): Calculated for $C_{13}H_{18}F_3N_2O_2^+$ $[M+H]^+$: 291.1315, Found: 291.1314.

(*S*)-4-((*S*)-sec-Butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole [82]



Following general procedure **L** using picolinamide **149** (431 mg, 1.49 mmol, 1.00 eq.), mesyl chloride (0.14 mL, 1.86 mmol, 1.25 eq.), dry NEt_3 (0.52 mL, 3.71 mmol, 2.50 eq.) and NaOH (178 mg, 4.46 mmol, 3.00 eq.), the desired product was obtained *via* AFC (CyHex:EtOAc; 80:20 → 60:40) as a colourless solid (831 mg, 3.05 mmol, 62%).

M.P.: 94 – 95 °C.

IR (neat): $\tilde{\nu}$ = 3469 (br), 3042 (w), 2968 (w), 2927 (w), 2882 (w), 2325 (w), 2245 (w), 1746 (w), 1637 (m), 1604 (w), 1577 (w), 1494 (w), 1462 (w), 1402 (m), 1332 (s), 1282 (w), 1248 (w), 1165 (s), 1122 (s), 1097 (s), 1077 (m), 1055 (w), 1015 (m), 962 (m), 943 (w), 909 (m), 872 (m), 730 (m), 711 (m), 677 (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (dt, J = 2.4, 0.9 Hz, 1H, CH_{arom}), 8.17 (dt, J = 8.2, 0.8 Hz, 1H, CH_{arom}), 8.00 (ddd, J = 8.2, 2.3, 0.8 Hz, 1H, CH_{arom}), 4.56 – 4.47 (m, 1H, CH_2), 4.37 – 4.27 (m, 1H, CH_2), 4.27 – 4.19 (m, 1H, CH_2), 1.80 – 1.69 (m, 1H, CH), 1.69 – 1.57 (m, 1H, CH_2), 1.31 – 1.18 (m, 1H, CH_2), 0.94 (t, J = 7.4 Hz, 3H, CH_3), 0.87 (d, J = 6.8 Hz, 3H, CH_3).

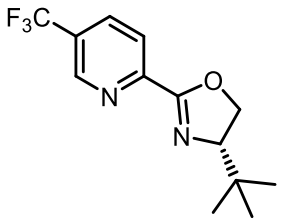
^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.6 (C_q), 150.1 (q, J = 1.6 Hz, C_q), 146.7 (q, J = 4.0 Hz, CH$_{arom}$), 134.0 (q, J = 3.5 Hz, CH$_{arom}$), 128.1 (q, J = 33.3 Hz, C_q), 123.7 (CH$_{arom}$), 123.3 (q, J = 272.7 Hz, CF$_3$), 71.8 (CH), 70.7 (CH$_2$), 39.1 (CH), 26.2 (CH$_2$), 14.5 (CH$_3$), 11.6 (CH$_3$).

^{19}F NMR (282 MHz, $CDCl_3$) δ = −62.50 (s, 3F, CF_3).

HRMS (ESI): Calculated for $C_{13}H_{16}F_3N_2O^+$ $[M+H]^+$: 273.1209, Found: 273.1211.

Optical Rotation: $[\alpha]_D^{25}$ = −55.7 (c = 1.00, $CHCl_3$).

(*S*)-4-(*tert*-Butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole [83]



Following general procedure **K** using 5-(trifluoromethyl)picolinic acid (764 mg, 4.00 mmol, 1.00 eq.), L-*tert*-leucinol (563 mg, 4.80 mmol, 1.20 eq.), *N*-methyl morpholine (0.49 mL, 4.40 mmol, 1.10 eq.) and isobutyl chloroformate (0.56 mL, 4.80 mmol, 1.2 eq.), the resulting residue was filtered through a silica plug with CyHex:EtOAc – 40:60 and used without further purification.

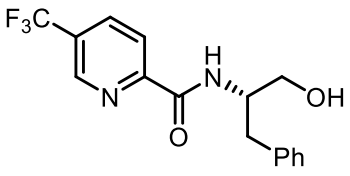
Following general procedure **L** using the crude picolinamide, mesyl chloride (0.39 mL, 5.00 mmol, 1.25 eq.), dry NEt_3 (1.39 mL, 10.0 mmol, 2.50 eq.) and NaOH (480 mg, 12.0 mmol, 3.00 eq.), the desired product was obtained *via* AFC (CyHex:EtOAc; 80:20 → 55:45) as a colourless solid (831 mg, 3.05 mmol, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.95 (dt, *J* = 2.4, 0.9 Hz, 1H), 8.24 (dt, *J* = 8.2, 0.8 Hz, 1H), 8.02 (ddd, *J* = 8.3, 2.3, 0.7 Hz, 1H), 4.49 (dd, *J* = 10.3, 8.8 Hz, 1H), 4.35 (t, *J* = 8.6 Hz, 1H), 4.16 (dd, *J* = 10.3, 8.4 Hz, 1H), 0.98 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.6, 150.1 (q, *J* = 1.6 Hz), 146.7 (q, *J* = 4.0 Hz), 134.0 (t, *J* = 3.5 Hz), 128.1 (q, *J* = 33.3 Hz), 123.8, 123.3 (q, *J* = 272.7 Hz), 76.8, 69.7, 34.1, 26.0.

Spectroscopic data was in agreement with that previously reported.[190]

(*S*)-*N*-(1-Hydroxy-3-phenylpropan-2-yl)-5-(trifluoromethyl)picolinamide [150]



Following general procedure **J** using 5-(trifluoromethyl)picolinic acid (764 mg, 4.00 mmol, 1.00 eq.), (*S*)-2-amino-3-phenylpropan-1-ol (605 mg, 4.00 mmol, 1.00 eq.), EDCI hydrochloride (844 mg, 4.40 mmol, 1.10 eq.) and DMAP (48.9 mg, 0.40 mmol, 0.1 eq.), the desired product was obtained *via* AFC (CyHex:EtOAc; 80:20 → 20:80) as a colourless solid (732 mg, 2.26 mmol, 56%).

M.P.: 112.5 – 113.5 °C.

IR (neat): $\tilde{\nu}$ = 3372 (br), 3043 (br), 2353 (w), 1674 (w), 1524 (w), 1328 (m), 1266 (m), 1169 (w), 1140 (m), 1076 (w), 1018 (w), 869 (w), 781 (w), 735 (s), 704 (m), 651 (w), 631 (w), 621 (m).

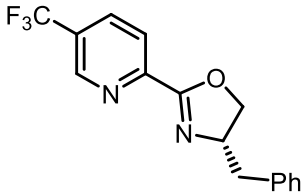
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.78 (dt, J = 2.3, 0.8 Hz, 1H, CH_{arom}), 8.34 – 8.22 (m, 2H, NH/CH_{arom}), 8.07 (dd, J = 8.2, 2.2 Hz, 1H, CH_{arom}), 7.35 – 7.18 (m, 5H, CH_{arom}), 4.44 – 4.33 (m, 1H, CH), 3.81 (dd, J = 11.1, 3.8 Hz, 1H, CH_2), 3.73 (dd, J = 11.1, 5.2 Hz, 1H, CH_2), 3.10 – 2.96 (m, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.3 (C_q), 152.6 (q, J = 1.7 Hz, C_q), 145.3 (q, J = 3.9 Hz, CH$_{arom}$), 137.6 (C_q), 134.9 (q, J = 3.5 Hz, CH$_{arom}$), 129.4 (2×CH$_{arom}$), 129.0 (d, J = 33.3 Hz), 128.8 (2×CH$_{arom}$), 126.9 (CH$_{arom}$), 123.2 (d, J = 273.0 Hz, CF$_3$), 122.3 (CH$_{arom}$), 64.1 (CH$_2$), 53.3 (CH), 37.3 (CH$_2$).

^{19}F NMR (282 MHz, $CDCl_3$) δ = −62.45 (s, 3F, CF_3).

HRMS (ESI): Calculated for $C_{16}H_{15}F_3N_2O_2Na^+$ [M+Na]$^+$: 347.0978, Found: 347.0969.

(S)-4-benzyl-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole [84]



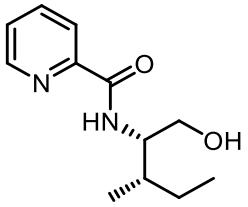
Following general procedure **L** using picolinamide **150** (708 mg, 2.19 mmol, 1.00 eq.), mesyl chloride (0.21 mL, 2.73 mmol, 1.25 eq.), dry NEt$_3$ (0.76 mL, 5.46 mmol, 2.50 eq.) and NaOH (262 mg, 6.56 mmol, 3.00 eq.), the desired product was obtained *via* AFC (CyHex:EtOAc; 80:20 → 55:45) as a colourless solid (488 mg, 1.59 mmol, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.96 (dq, J = 2.4, 0.8 Hz, 1H), 8.18 (dt, J = 8.3, 0.8 Hz, 1H), 8.05 – 7.99 (m, 1H), 7.36 – 7.27 (m, 2H), 7.27 – 7.21 (m, 3H), 4.78 – 4.64 (m, 1H), 4.49 (dd, J = 9.5, 8.6 Hz, 1H), 4.26 (dd, J = 8.6, 7.8 Hz, 1H), 3.29 (dd, J = 13.8, 5.2 Hz, 1H), 2.79 (dd, J = 13.8, 8.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.3, 150.0 (q, J = 1.6 Hz), 146.8 (q, J = 4.0 Hz), 137.6, 134.1 (q, J = 3.6 Hz), 129.4, 128.8, 128.2 (q, J = 33.3 Hz), 126.8, 123.8, 123.2 (q, J = 272.5 Hz), 72.9, 68.4, 41.6.

Spectroscopic data was in agreement with that previously reported.[191]

N-((2*S*,3*S*)-1-Hydroxy-3-methylpentan-2-yl)picolinamide [151]



Following general procedure **J** using picolinic acid (315 mg, 2.56 mmol, 1.00 eq.), (*S*)-isoleucinol (300 mg, 2.56 mmol, 1.00 eq.), EDCI hydrochloride (540 mg, 2.82 mmol, 1.10 eq.) and DMAP (31.3 mg, 0.26 mmol, 0.1 eq.), the desired product was obtained *via* AFC (CyHex:EtOAc; 80:20 → 20:80) as a colourless oil (332 mg, 1.49 mmol, 58%).

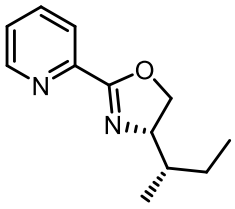
IR (neat): $\tilde{\nu}$ = 3388 (br), 2961 (m), 2928 (m), 2877 (w), 2325 (w), 2259 (w), 2241 (w), 1661 (s), 1592 (w), 1570 (m), 1529 (s), 1465 (m), 1435 (w), 1380 (w), 1346 (w), 1291 (w), 1242 (w), 1161 (w), 1071 (w), 1043 (w), 998 (w), 985 (w), 907 (w), 822 (w), 749 (m), 693 (m), 652 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H, CH_{arom}), 8.27 (d, J = 8.4 Hz, 1H, NH), 8.18 (dt, J = 7.8, 1.1 Hz, 1H, CH_{arom}), 7.85 (td, J = 7.7, 1.7 Hz, 1H, CH_{arom}), 7.43 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H, CH_{arom}), 4.05 – 3.94 (m, 1H, CH), 3.88 – 3.74 (m, 2H, CH_2), 2.70 (s, 1H, OH), 1.89 – 1.74 (m, 1H, CH), 1.64 – 1.49 (m, 1H, CH_2), 1.33 – 1.17 (m, 1H, CH_2), 1.01 (d, J = 6.8 Hz, 3H, CH_3), 0.93 (t, J = 7.4 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.2 (C_q), 149.7 (C_q), 148.1 (CH$_{arom}$), 137.7 (CH$_{arom}$), 126.4 (CH$_{arom}$), 122.6 (CH$_{arom}$), 64.2 (CH$_2$), 56.8 (CH), 36.0 (CH), 25.7 (CH$_2$), 15.8 (CH$_3$), 11.6 (CH$_3$).

HRMS (ESI): Calculated for $C_{12}H_{18}N_2O_2Na^+$ $[M+Na]^+$: 245.1260, Found: 245.1257.

(*S*)-4-((*S*)-*sec*-Butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole [85]



Following general procedure **L** using picolinamide **151** (327 mg, 1.47 mmol, 1.00 eq.), mesyl chloride (0.14 mL, 1.84 mmol, 1.25 eq.), dry NEt_3 (0.51 mL, 3.68 mmol, 2.50 eq.) and NaOH (176 mg, 4.41 mmol, 3.00 eq.), the desired product

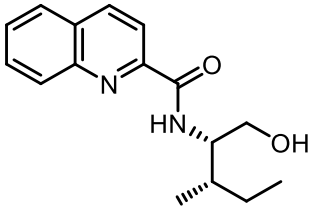
was obtained *via* AFC (CyHex:EtOAc; 60:40 → 0:100) as a yellow oil (254 mg, 1.24 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.05 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.76 (td, *J* = 7.8, 1.8 Hz, 1H), 7.37 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 4.55 – 4.44 (m, 1H), 4.34 – 4.17 (m, 2H), 1.83 – 1.57 (m, 2H), 1.33 – 1.15 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.2, 149.7, 148.1, 137.7, 126.4, 122.6, 64.2, 56.8, 36.0, 25.7, 15.8, 11.6.

Spectroscopic data was in agreement with that previously reported.[81]

N-((2*S*,3*S*)-1-Hydroxy-3-methylpentan-2-yl)quinoline-2-carboxamide [152]



Following general procedure **K** using 2-quinaldic acid (693 mg, 4.00 mmol, 1.00 eq.), L-isoleucinol (563 mg, 4.80 mmol, 1.20 eq.), *N*-methyl morpholine (0.49 mL, 4.40 mmol, 1.10 eq.) and isobutyl chloroformate (0.56 mL, 4.80 mmol, 1.2 eq.), the desired product was obtained *via* AFC (CyHex:EtOAc; 80:20 → 20:80) as a colourless resin (1.07 g, 3.91 mmol, 98%).

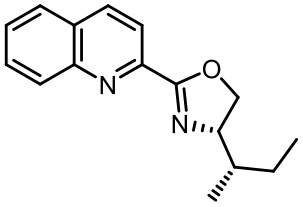
IR (neat): $\tilde{\nu}$ = 3378 (br), 2960 (m), 2931 (m), 2880 (m), 2364 (w), 2249 (w), 1739 (w), 1661 (s), 1616 (w), 1566 (m), 1529 (s), 1501 (s), 1461 (m), 1428 (m), 1381 (m), 1342 (w), 1210 (w), 1146 (m), 1072 (m), 913 (m), 879 (m), 847 (m), 774 (s), 736 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 8.6 Hz, 1H, N*H*), 8.26 (s, 2H, CH_{arom}), 8.12 (dd, *J* = 8.5, 1.1 Hz, 1H, CH_{arom}), 7.84 (ddd, *J* = 8.2, 1.5, 0.6 Hz, 1H, CH_{arom}), 7.75 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, CH_{arom}), 7.60 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, CH_{arom}), 4.12 – 3.99 (m, 1H, C*H*), 3.94 – 3.80 (m, 2H, CH_2), 1.96 – 1.81 (m, 1H, C*H*), 1.70 – 1.56 (m, 1H, CH_2), 1.35 – 1.22 (m, 1H, CH_2), 1.04 (d, *J* = 6.8 Hz, 3H, CH_3), 0.95 (t, *J* = 7.4 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.3 (C_q), 149.6 (C_q), 146.4 (C_q), 137.8 (*C*H), 130.3 (*C*H), 129.8 (*C*H), 129.4 (C_q), 128.1 (*C*H), 127.8 (*C*H), 119.0 (*C*H), 64.1 (*C*H_2), 56.8 (*C*H), 36.0 (*C*H), 25.7 (*C*H_2), 15.8 (*C*H_3), 11.5 (*C*H_3).

HRMS (ESI): Calculated for $C_{16}H_{20}N_2O_2Na^+$ $[M+Na]^+$: 295,1417, Found: 295.1413.

(*S*)-4-((*S*)-*sec*-Butyl)-2-(quinolin-2-yl)-4,5-dihydrooxazole [86]



Following general procedure **L** using quinolinamide **152** (1.07 g, 3.91 mmol, 1.00 eq.), mesyl chloride (0.38 mL, 4.89 mmol, 1.25 eq.), dry NEt_3 (1.36 mL, 9.79 mmol, 2.50 eq.) and NaOH (470 mg, 11.7 mmol, 3.00 eq.), the desired product was obtained *via* AFC (CyHex:EtOAc; 80:20 → 20:80) as a pale yellow resin (668 mg, 2.63 mmol, 67%).

IR (neat): $\tilde{\nu}$ = 3395 (w), 2965 (m), 2935 (w), 2877 (m), 2375 (w), 2332 (w), 2234 (w), 1956 (w), 1674 (w), 1642 (m), 1596 (w), 1562 (w), 1504 (m), 1464 (m), 1368 (m), 1210 (w), 1123 (m), 1085 (s), 969 (m), 920 (m), 840 (s), 764 (s), 730 (m), 626 (m), 615 (s), 604 (m), 586 (s).

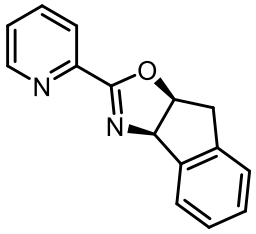
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 – 8.22 (m, 1H, CH_{arom}), 8.18 (s, 2H, CH_{arom}), 7.83 – 7.78 (m, 1H, CH_{arom}), 7.72 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H, CH_{arom}), 7.56 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H, CH_{arom}), 4.54 (td, J = 7.5, 0.9 Hz, 1H, CH_2), 4.37 – 4.23 (m, 2H, CH/CH_2), 1.83 – 1.71 (m, 1H, CH), 1.70 – 1.56 (m, 1H, CH_2), 1.32 – 1.20 (m, 1H, CH_2), 0.95 (t, J = 7.4 Hz, 3H, CH_3), 0.88 (d, J = 6.8 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.8 (C_q), 147.6 (C_q), 147.0 (C_q), 136.7 (CH$_{arom}$), 130.4 (CH$_{arom}$), 130.0 (CH$_{arom}$), 128.8 (C_q), 127.9 (CH$_{arom}$), 127.6 (CH$_{arom}$), 120.9 (CH$_{arom}$), 71.6 (CH), 70.5 (CH$_2$), 39.1 (CH), 26.3 (CH$_2$), 14.5 (CH$_3$), 11.7 (CH$_3$).

HRMS (ESI): Calculated for $C_{16}H_{19}N_2O^+$ $[M+H]^+$: 255.1492, Found: 255.1495.

Optical Rotation: $[\alpha]_D^{25}$ = −85.4 (c = 1.00, $CHCl_3$).

(3a*R*,8a*S*)-2-(Pyridin-2-yl)-3a,8a-dihydro-8*H*-indeno[1,2-d]oxazole [87]



Following a procedure of *Kočovský*,[131] picolinonitrile (1.04 g, 10.0 mmol, 1.00 eq.) was dissolved in MeOH (10 mL) and cooled to 0 °C. Then, NaOMe (54.0 mg, 1.00 mmol, 0.10 eq.) was added in a single portion and it was stirred at 0 °C for 30 min. It was gradually warmed to rt and stirred for 20 h. Acetic acid (1 mL) was added and the solvent was removed *in vacuo*. The resulting residue was taken up in CH_2Cl_2 (10 mL) and washed with water (2×20 mL) and sat. aq. NaCl sol. (2×20 mL). The org. layer was dried over $MgSO_4$, filtered and solvent was removed *in vacuo*.

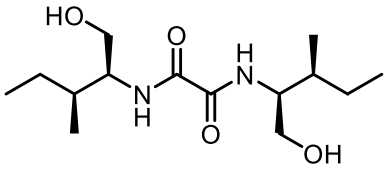
The crude carboxyimidate was dissolved in $CHCl_3$ (3 mL) and (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (789 mg, 5.29 mmol, 1.00 eq.) and catalytic amounts of conc. aq. HCl (2 drops) were added. The mixture was heated to 60 °C for 18 h. It was allowed to cool to rt and the solvent was removed *in vacuo*. The desired product was obtained *via* AFC (CH_2Cl_2:MeOH; 99:1 → 97:3) as an off-white solid (467 mg, 1.98 mmol, 37%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.10 – 8.03 (m, 1H), 7.74 (td, *J* = 7.8, 1.8 Hz, 1H), 7.66 – 7.56 (m, 1H), 7.36 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.30 – 7.26 (m, 3H), 5.82 (dd, *J* = 7.9, 0.8 Hz, 1H), 5.60 (ddd, *J* = 8.2, 6.2, 2.3 Hz, 1H), 3.59 – 3.43 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.3, 149.8, 146.9, 141.6, 139.9, 136.6, 128.7, 127.6, 125.8, 125.6, 125.4, 124.2, 84.1, 77.2, 39.8.

Spectroscopic data was in agreement with that previously reported.[192]

N^1,*N*^{2}-Bis((2*S*,3*S*)-1-hydroxy-3-methylpentan-2-yl)oxalamide [92]

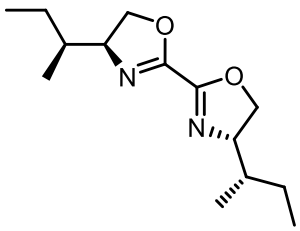


Following a procedure of *Sunkur et al.*,[132] dimethyl oxalate (354 mg, 3.00 mmol, 1.00 eq.) was dissolved in MeOH (6 mL) and a solution of L-isoleucinol (703 mg,

6 mmol, 2.00 eq.) in MeOH (12 mL) was added over 5 min. The mixture was stirred for 45 min at rt and 30 min at 60 °C. While cooling to rt a colourless precipitation appeared. The solids were collected and washed with Et_2O affording the bisoxalamide as a colourless solid (580 mg, 2.01 mmol, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 9.3 Hz, 2H), 3.91 – 3.75 (m, 4H), 3.69 (dd, *J* = 12.0, 7.4 Hz, 2H), 1.74 – 1.66 (m, 2H), 1.61 – 1.47 (m, 2H), 1.29 – 1.10 (m, 2H), 0.98 (d, *J* = 6.8 Hz, 6H), 0.93 (t, *J* = 7.4 Hz, 6H).
Spectroscopic data was in agreement with that previously reported.[132]

(4*S*,4'*S*)-4,4'-Di((*S*)-sec-butyl)-4,4',5,5'-tetrahydro-2,2'-bioxazole [91]



Following general procedure **L** using oxalamide **92** (576 mg, 2.00 mmol, 1.00 eq.), mesyl chloride (0.39 mL, 4.99 mmol, 2.5 eq.), dry NEt_3 (1.58 mL, 9.99 mmol, 5.00 eq.) and NaOH (240 mg, 5.99 mmol, 3.00 eq.), the desired product was obtained *via* AFC (CH_2Cl_2:MeOH; 99:1 → 97:3) as a pale yellow solid (424 mg, 1.68 mmol, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.42 (dd, *J* = 9.5, 7.9 Hz, 2H), 4.21 (td, *J* = 9.1, 6.2 Hz, 2H), 4.13 (dd, *J* = 9.0, 7.9 Hz, 2H), 1.77 – 1.56 (m, 4H), 1.28 – 1.14 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 6H), 0.86 (d, *J* = 6.8 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.6, 71.9, 70.8, 38.8, 26.1, 14.6, 11.5.
Spectroscopic data was in agreement with that previously reported.[193]

5.3.5 Substrate scope

5.3.5.1 General procedures

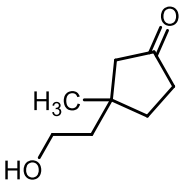
General procedure M: Oxidative ring expansion

A tube was charged with $PdCl_2(MeCN)_2$ (3.9 mg, 0.015 mmol, 0.05 eq.) and EtOH (3.00 ml, 0.1 M with respect to the MCB). H_2O (162 mg, 162 µL, 30.0 mmol, 30.0 eq.) was added before the methylenecyclobutane and *t*-BuONO (90% purity, 34.4 mg,

40 µL, 0.30 mmol, 1.00 eq.) were added *via* micro-syringe. The reaction mixture was stirred for 3 h at 30 °C. The crude mixture was concentrated *in vacuo*. The NMR-yield was determined *via* ^{1}H NMR analysis of the crude reaction mixture using mesitylene (14 µL, 0.10 mmol) as internal standard. The product was obtained *via* FC with the conditions given in the corresponding entry.

5.3.5.2 Syntheses

3-(2-Hydroxyethyl)-3-methylcyclopentan-1-one [97]



Following general procedure **M** using MCB **69** (40 mg, 0.29 mmol, 1.00 eq.), the desired product was obtained *via* FC (CH_2Cl_2:MeOH; 95:5) as a mixture with its hemiketal[13] (colourless oil, 40 mg, 0.28 mmol, 97%).

IR (neat): $\tilde{\nu}$ = 3451 (br), 2952 (m), 2359 (w), 1737 (s), 1461 (w), 1405 (m), 1378 (w), 1324 (w), 1248 (w), 1168 (m), 1125 (m), 1064 (m), 1028 (m), 993 (w), 924 (w), 876 (w), 774 (w), 736 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 – 3.68 (m, 2H, CH_2), 2.32 – 2.24 (m, 2H, CH_2), 2.21 – 2.10 (m, 1H, CH_2), 2.10 – 2.00 (m, 1H, CH_2), 1.91 – 1.74 (m, 2H, CH_2), 1.71 (t, *J* = 7.2 Hz, 2H, CH_2), 1.07 (s, 3H, CH_3).

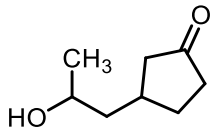
^{13}C NMR (101 MHz, $CDCl_3$): δ = 219.9 (C_q), 59.7 (CH_2), 52.5 (CH_2), 44.0 (CH_2), 38.4 (C_q), 36.5 (CH_2), 35.7 (CH_2), 25.2 (CH_3).

HRMS (ESI): Calculated for $C_8H_{15}O_2^+$ $[M+H]^+$: 143.1067, found 143.1070.

Chemotion ELN sample number: MTN-4-24-A/B, MTN-4-44-A/B.

[13] 66:34 ketone:hemiketal according to ^{1}H NMR.

3-(2-Hydroxypropyl)cyclopentan-1-one [98]



Following general procedure **M** using MCB **70** (38 mg, 0.30 mmol, 1.00 eq.), the desired product was obtained *via* FC (CH_2Cl_2:MeOH; 99:1) as colourless oil (mixture of diastereomers, *dr* = 50:50 according to ^{13}C NMR; 27 mg, 0.19 mmol, 64%).

IR (neat): $\tilde{\nu}$ = 3505 (br), 2963 (m), 2917 (m), 2335 (w), 1736 (s), 1461 (w), 1405 (m), 1371 (w), 1309 (w), 1277 (w), 1237 (w), 1160 (m), 1056 (w), 1017 (w), 981 (w), 938 (w), 869 (w), 840 (w), 650 (m), 637 (m), 617 (m), 609 (s), 603 (s), 593 (m), 585 (m).

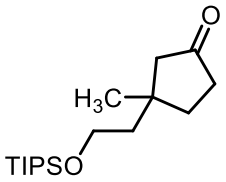
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 – 3.77 (m, 1H, C*H*), 2.48 – 2.23 (m, 3H, CH_2/C*H*), 2.23 – 2.06 (m, 2H, CH_2), 1.88 – 1.70 (m, 2H, CH_2/O*H*), 1.70 – 1.56 (m, 1H, CH_2), 1.56 – 1.42 (m, 2H, CH_2), 1.21 (d, *J* = 6.2 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 219.93 (C_q), 219.81 (C_q), 66.73 (*C*H), 66.46 (*C*H), 45.68 (*C*H_2), 45.16 (*C*H_2), 45.13 (*C*H_2), 45.06 (*C*H_2), 38.65 (*C*H_2), 38.50 (*C*H_2), 34.22 (*C*H), 34.12 (*C*H), 30.09 (*C*H_2), 29.64 (*C*H_2), 24.40 (*C*H_3), 24.30 (*C*H_3).

HRMS (ESI): Calculated for $C_8H_{15}O_2^+$ $[M+H]^+$: 143.1067, found 143.1067.

Chemotion ELN sample number: MTN-4-25-A.

3-Methyl-3-(2-((triisopropylsilyl)oxy)ethyl)cyclopentan-1-one [99]



Following general procedure **M** using MCB **76** (85 mg, 0.30 mmol, 1.00 eq.), the desired product was obtained *via* FC (CH_2Cl_2) as a colourless oil (69 mg, 0.23 mmol, 77%).[14]

IR (neat): $\tilde{\nu}$ = 3492 (br), 2944 (s), 2868 (s), 2245 (w), 1744 (s), 1463 (m), 1403 (w), 1382 (w), 1255 (w), 1165 (m), 1098 (s), 1013 (m), 997 (m), 912 (m), 882 (s), 811 (m), 746 (m), 677 (s), 641 (s), 607 (s).

[14] Deprotection was partly observed, resulting in minor impurities with TIPSOH.

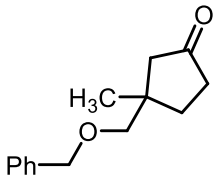
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 – 3.79 (m, 1H, CH_2), 3.79 – 3.73 (m, 1H, CH_2), 2.32 – 2.25 (m, 2H, CH_2), 2.24 – 2.12 (m, 1H, CH_2), 2.12 – 2.02 (m, 1H, CH_2), 1.95 – 1.85 (m, 1H, CH_2), 1.82 – 1.74 (m, 1H, CH_2), 1.69 (t, J = 6.7 Hz, 2H, CH_2), 1.08 (s, 3H, CH_2), 1.07 – 1.03 (m, 21H, CH/CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 220.31 (C_q), 60.42 (OCH$_2$), 52.85 (CH$_2$), 44.31 (CH$_2$), 38.63 (C_q), 36.69 (CH$_2$), 35.95 (CH$_2$), 25.29 (CH$_3$), 18.19 (6×CH$_3$), 17.84 (TIPSOH), 12.41 (TIPSOH), 12.05 (3×CH).

HRMS (ESI): Calculated for $C_{17}H_{34}O_2SiNa^+$ [M+Na]$^+$: 321.2220, found 321.2218.

Chemotion ELN sample number: MTN-4-32-A.

3-((Benzyloxy)methyl)-3-methylcyclopentan-1-one [100]



Following general procedure **M** using MCB **77** (51 mg, 0.18 mmol, 1.00 eq.), $PdCl_2(MeCN)_2$ (2.3 mg, 9.0 µmol, 0.05 eq.), *t*-BuONO (90% purity, 24 µL, 0.18 mmol, 1.00 eq.) and H_2O (100 µL, 5.42 mmol, 30.0 eq.) the desired product was obtained *via* FC (CH_2Cl_2) as a colourless oil (33 mg, 0.15 mmol, 84%).

IR (neat): $\tilde{\nu}$ = 2960 (w), 2875 (m), 2329 (w), 1739 (s), 1497 (w), 1454 (m), 1404 (w), 1363 (w), 1258 (w), 1205 (w), 1173 (w), 1099 (s), 1032 (w), 912 (w), 873 (w), 740 (m), 698 (s), 615 (s), 586 (s).

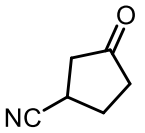
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.26 (m, 5H, CH_{arom}), 4.52 (s, 2H, CH_2), 3.34 – 3.27 (m, 2H, CH_2), 2.41 – 2.22 (m, 3H, CH_2), 2.10 – 1.94 (m, 2H, CH_2), 1.78 – 1.66 (m, 1H, CH_2), 1.11 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 219.8 (C_q), 138.5 (C_q), 128.5 (2×CH$_{arom}$), 127.7 (CH$_{arom}$), 127.5 (2×CH$_{arom}$), 77.9 (CH$_2$), 73.4 (CH$_2$), 49.4 (CH$_2$), 40.7 (C_q), 37.4 (CH$_2$), 32.7 (CH$_2$), 24.2 (CH$_3$).

HRMS (ESI): Calculated for $C_{14}H_{19}O_2^+$ [M+H]$^+$: 219.1380, found 219.1375.

Chemotion ELN sample number: MTN-4-59-A.

3-Oxocyclopentane-1-carbonitrile [101]



Following general procedure **M** using MCB **75** (27.9 mg, 0.30 mmol, 1.00 eq.), the desired product was obtained *via* FC (CH_2Cl_2) as a colourless oil (11.0 mg, 0.101 mmol, 34%). *Note:* The product is fairly volatile.

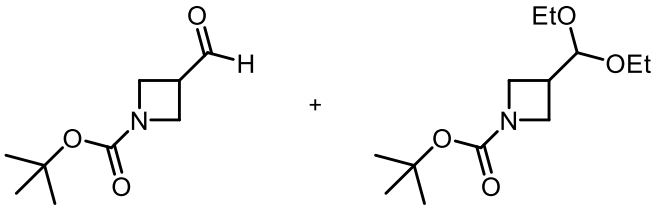
^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.22 – 3.15 (m, 1H), 2.64 – 2.58 (m, 1H), 2.54 – 2.40 (m, 3H), 2.32 – 2.22 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 212.8, 120.9, 41.5, 36.8, 27.5, 25.7.

Spectroscopic data was in agreement with that previously reported.[194]

Chemotion ELN sample number: MTN-4-119-A.

tert-Butyl 3-formylazetidine-1-carboxylate [104], *tert*-butyl 3-(diethoxymethyl)azetidine-1-carboxylate [153]



Following general procedure **M** using MCB **103** (50.8 mg, 300 µmol, 1.00 eq.), the product was obtained *via* AFC (CyHex:EtOAc; 95:5 → 40:60) as a colourless oil (13 mg, 70 µmol, 23%). As a by-product its respective diethyl acetal was isolated (34 mg, 0.13 mmol, 44%).

Aldehyde [104]:

IR (neat): $\tilde{\nu}$ = 3391 (br), 2979 (m), 2931 (w), 2895 (w), 2375 (w), 2350 (w), 1699 (s), 1483 (m), 1393 (s), 1367 (s), 1252 (m), 1149 (s), 1071 (m), 1006 (w), 917 (w), 855 (w), 772 (m), 729 (w), 704 (w), 671 (w), 641 (m), 616 (m), 607 (s), 597 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (d, J = 2.1 Hz, 1H, C*H*O), 4.16 – 4.03 (m, 4H, CH_2), 3.42 – 3.28 (m, 1H, C*H*), 1.43 (s, 9H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.2 (C_q), 156.3 (C_q), 80.3 (*C*H), 49.0 (2×*C*H_2), 38.9 (*C*H), 28.5 (3×*C*H_3).

HRMS (APCI, CH_3COONH_4): Calculated for $C_{10}H_{18}NO_6^-$ [M+H_2O+HCOO]$^-$: 248.1140, found 248.1141.

Acetal [153]:

IR (neat): $\tilde{\nu}$ = 2978 (m), 2888 (m), 1705 (s), 1475 (w), 1454 (m), 1391 (s), 1371 (s), 1252 (m), 1158 (s), 1136 (s), 1119 (s), 1065 (s), 999 (w), 866 (w), 772 (m), 671 (w), 649 (m), 639 (m), 629 (m), 614 (m), 599 (s).

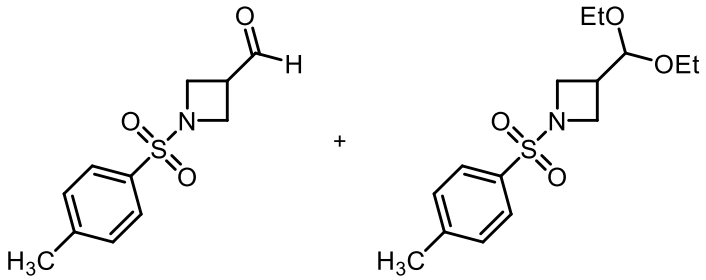
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.64 (d, J = 7.3 Hz, 1H, OC*H*), 3.94 (t, J = 8.6 Hz, 2H, CH_2), 3.78 – 3.69 (m, 2H, CH_2), 3.64 (dq, J = 9.4, 7.1 Hz, 2H, OCH_2), 3.53 (dq, J = 9.3, 7.0 Hz, 2H, OCH_2), 2.77 (tdt, J = 8.4, 7.3, 5.4 Hz, 1H, C*H*), 1.43 (d, J = 1.6 Hz, 9H, CHCH_3), 1.19 (t, J = 7.1 Hz, 6H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.5 (C_q), 104.1 (*C*H), 79.5 (C_q), 62.1 (2×*C*H_2), 50.9 (2×*C*H_2), 31.8 (*C*H), 28.5 (3×*C*H_3), 15.5 (2×*C*H_3).

HRMS (ESI): Calculated for $C_{13}H_{26}NO_4^+$ $[M+H]^+$: 260.1856, found 260.1856.

Chemotion ELN sample number: MTN-4-39-B/C.

tert-Butyl 3-formylazetidine-1-carboxylate [105], 3-(diethoxymethyl)-1-tosylazetidine [154]



Following general procedure **M** using MCB **78** (25 mg, 0.11 mmol, 1.00 eq.), $PdCl_2(MeCN)_2$ (1.5 mg, 5.6 µmol, 0.05 eq.), water (61 µL, 3.4 mmol, 30.0 eq.) and *t*-BuONO (90% purity, 13 mg, 15 µL, 0.11 mmol, 1.00 eq.), the product was obtained *via* FC (CH_2Cl_2:MeOH; 99:1) as a yellow oil (14 mg, 59 µmol, 52%). As a by-product its respective diethyl acetal was isolated (7.0 mg, 22 µmol, 20%).

Aldehyde [105]:

IR (neat): $\tilde{\nu}$ = 3505 (br), 2917 (w), 2332 (w), 2252 (w), 1723 (m), 1597 (w), 1454 (w), 1400 (w), 1341 (m), 1306 (w), 1158 (s), 1087 (m), 914 (w), 816 (m), 733 (m), 710 (m), 673 (s), 636 (m), 618 (s), 605 (s), 586 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (d, J = 1.8 Hz, 1H, C*H*O), 7.77 – 7.68 (m, 2H, CH_{arom}), 7.44 – 7.31 (m, 2H, CH_{arom}), 4.00 – 3.90 (m, 4H, CH_2), 3.26 – 3.18 (m, 1H, C*H*), 2.46 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.6 (C_q), 144.7 (C_q), 131.2 (C_q), 130.1 (2×CH$_{arom}$), 128.5 (2×CH$_{arom}$), 50.3 (2×CH$_2$), 38.2 (CH), 21.8 (CH$_3$).

HRMS (ESI): Calculated for $C_{11}H_{14}NO_3S^+$ [M+H]$^+$: 240.0689, found 240.0686.

Acetal [154]:

IR (neat): $\tilde{\nu}$ = 3506 (w), 2980 (w), 2888 (w), 2332 (w), 1725 (w), 1598 (w), 1454 (w), 1341 (m), 1157 (s), 1090 (m), 1056 (m), 916 (w), 817 (m), 745 (w), 712 (w), 674 (s), 635 (m), 617 (s), 602 (s).

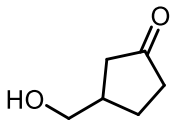
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 – 7.71 (m, 2H, CH_{arom}), 7.38 – 7.35 (m, 2H, CH_{arom}), 4.34 (d, J = 6.7 Hz, 1H, OCH), 3.79 (t, J = 8.3 Hz, 2H, CH_2), 3.61 (dd, J = 8.2, 6.2 Hz, 2H, CH_2), 3.51 (dq, J = 9.4, 7.1 Hz, 2H, CH_2), 3.38 (dq, J = 9.3, 7.0 Hz, 2H, CH_2), 2.66 (tq, J = 8.4, 6.3 Hz, 1H, CH), 2.45 (s, 3H, CH_3), 1.08 (t, J = 7.0 Hz, 6H, CH$_2$CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.1 (C_q), 131.6 (C_q), 129.8 (2×CH$_{arom}$), 128.6 (2×CH$_{arom}$), 102.9 (CH), 62.3 (2×CH$_2$), 52.2 (2×CH$_2$), 31.5 (CH), 21.7 (CH$_3$), 15.3 (2×CH$_3$).

HRMS (ESI): Calculated for $C_{15}H_{24}NO_4S^+$ [M+H]$^+$: 314.1421, found 314.1421.

Chemotion ELN sample number: MTN-4-47-B/C.

3-(Hydroxymethyl)cyclopentan-1-one [107]

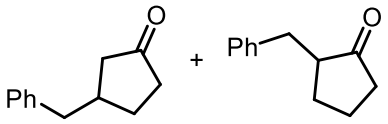


A tube was charged with $PdCl_2(PhCN)_2$ (3.8 mg, 0.010 mmol, 0.10 eq.) and CH_2Cl_2 (1 ml). Then, water (54 mg, 54 µL, 3.00 mmol, 30.0 eq.) was added *via* micro-syringe followed by MCB **73** (9.8 mg, 0.10 mmol, 1.00 eq.) and *t*-BuONO (90% purity, 11.5 mg, 13 µL, 0.10 mmol, 1.00 eq.). The reaction mixture was stirred for 16 h at rt. The crude mixture was concentrated *in vacuo*. The NMR-yield (93%) was determined *via* ^{1}H NMR analysis of the crude reaction mixture using mesitylene (14 µL, 0.10 mmol) as internal standard. The product was obtained *via* AFC (CyHex:EtOAc; 80:20 → 0:100) as a mixture with its hemiketal form (6.0 mg, 53 µmol, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69 (d, J = 6.0 Hz, 2H), 2.59 – 2.27 (m, 3H), 2.26 – 2.09 (m, 2H), 2.07 – 1.95 (m, 1H), 1.82 – 1.68 (m, 1H), 1.66 (s, 1H).

Spectroscopic data was in agreement with that previously reported.[195]

3-Benzylcyclopentan-1-one [109], 2-benzylcyclopentan-1-one [110]



Following general procedure **M** using MCB **68** (57 mg, 0.30 mmol, 1.00 eq.), two products were obtained *via* FC (CH_2Cl_2) as pale-yellow oils: 3-benzylcyclopentan-1-one (**109,** 16 mg, 92 µmol, 31%) and 2-benzylcyclopentan-1-one (**110,** 19 mg, 0.11 mmol, 36%).[15]

Major regioisomer [109]:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.27 (m, 2H), 7.25 – 7.14 (m, 3H), 2.79 – 2.69 (m, 2H), 2.55 – 2.41 (m, 1H), 2.39 – 2.24 (m, 2H), 2.20 – 2.05 (m, 2H), 1.96 – 1.87 (m, 1H), 1.70 – 1.56 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 219.4, 140.1, 128.9, 128.6, 126.4, 45.1, 41.6, 39.0, 38.5, 29.2.

Spectroscopic data was in agreement with that previously reported.[196]

Minor regioisomer [110]:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 – 7.25 (m, 2H), 7.23 – 7.15 (m, 3H), 3.15 (dd, *J* = 13.8, 4.1 Hz, 1H), 2.54 (dd, *J* = 13.8, 9.5 Hz, 1H), 2.41 – 2.29 (m, 2H), 2.19 – 2.03 (m, 2H), 2.02 – 1.89 (m, 1H), 1.81 – 1.66 (m, 1H), 1.62 – 1.50 (m, 1H).

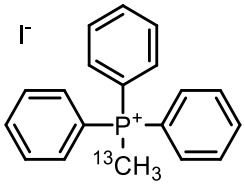
^{13}C NMR (101 MHz, $CDCl_3$): δ = 220.4, 140.1, 129.0, 128.6, 126.3, 51.2, 38.4, 35.7, 29.3, 20.7.

Spectroscopic data was in agreement with that previously reported.[197]

Chemotion ELN sample number: MTN-4-67-A/B.

5.3.6 ^{13}C-Labeling experiments

Methyl-^{13}C-triphenylphosphonium iodide



Triphenylphosphine (1.84 g, 7.00 mmol, 1.00 eq.) was suspended in dry PhMe (15 mL) and Iodo(^{13}C)methane (1.00 g, 437 µL, 7.00 mmol, 1.00 eq.) was added.

[15] Regioselectivitiy: 62:38 – **109**:**110** according to ^{1}H NMR analysis of the crude reaction mixture.

Colorless precipitation occurred quickly after addition of the iodomethane. The mixture was stirred for 17 h at rt. The solids were collected, washed with hexane and dried under vacuum, affording the product as colourless solid (2.62 g, 6.47 mmol, 92%).

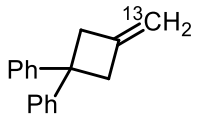
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (ddt, *J*=8.8, 6.4, 1.7, 3H), 7.75 – 7.71 (m, 3H), 7.71 – 7.63 (m, 9H), 3.40 – 2.87 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.3 (d, *J* = 3.2 Hz, 3C), 133.4 (d, *J* = 10.8 Hz, 6C), 130.6 (d, *J* = 13.0 Hz, 6C), 119.0 (d, *J* = 89.2 Hz, 3C), 11.7 (d, *J* = 57.1 Hz).

Spectroscopic data was in agreement with that previously reported.[198]

Chemotion ELN sample number: MTN-4-117-A.

1-(^{13}C)Methylen-3,3-diphenylcyclobutan [71]



Following general procedure **A** using cyclobutanone **148** (121 mg, 544 µmol, 1.00 eq.), methyl-^{13}C-triphenylphosphonium iodide (298 mg, 735 µmol, 1.35 eq.) and *n*-BuLi (283 µL, 708 µmol, 2.5 M in hexanes, 1.30 eq.), the desired product was obtained *via* FC (pentane) as colourless oil (78 mg, 0.49 mmol, 62%).

IR (neat): $\tilde{\nu}$ = 3060 (w), 2917 (w), 1945 (w), 1876 (w), 1804 (w), 1743 (w), 1656 (w), 1595 (w), 1493 (m), 1446 (w), 1411 (w), 1313 (w), 1023 (w), 866 (m), 757 (m), 699 (s), 663 (m), 652 (m), 633 (m), 623 (m), 609 (m), 589 (s).

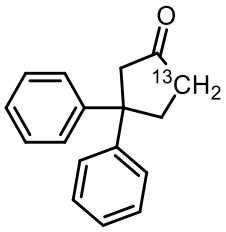
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.26 (m, 8H, CH_{arom}), 7.22 – 7.13 (m, 2H, CH_{arom}), 5.08 (dp, J_{C-H} = 156.8 Hz, *J* = 2.4 Hz, 1H, ^{13}CH_2), 3.45 (dt, *J* = 3.4, 2.4 Hz, 4H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.2 (2×C_q), 144.4 (C_q), 143.6 (C_q), 128.4 (4×CH$_{arom}$), 126.6 (4×CH$_{arom}$), 125.9 (2×CH$_{arom}$), 106.8 (CH$_2$), 46.2 (2×CH$_2$).

HRMS (APCI, CH_3COONH_4): Calculated for $C_{16}{}^{13}CH_{17}^+$ $[M+H]^+$: 222.1358, found: 222.1352.

Chemotion ELN sample number: MTN-4-123-A.

3,3-Diphenylcyclopentan-1-one-5-^{13}C [108]



Following general procedure **M** using MCB **71** (22.1 mg, 0.10 mmol, 1.00 eq.), $PdCl_2(MeCN)_2$ (1.3 mg, 5.0 µmol, 0.05 eq.), *t*-BuONO (90% purity, 13.3 µL, 0.10 mmol, 1.00 eq.) and H_2O (54 µL, 3.00 mmol, 30.0 eq.) the desired product was obtained *via* FC (pentane:EtOAc; 95:5) as pale-yellow resin (22 mg, 93 µmol, 93%).

IR (neat): $\tilde{\nu}$ = 3058 (w), 2919 (w), 2363 (m), 2341 (m), 1596 (w), 1494 (m), 1446 (w), 1401 (w), 1252 (w), 1146 (m), 1034 (w), 771 (m), 755 (m), 697 (s), 653 (m), 623 (m), 596 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.29 (m, 8H, CH_{arom}), 7.29 – 7.22 (m, 2H, CH_{arom}), 3.07 (s, 2H, CH_2), 2.79 (td, J = 7.5, 3.3 Hz, 2H, CH_2), 2.33 (dt, J_{C-H} = 131.4 Hz, J = 7.6 Hz, 2H, ^{13}CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 217.5 (d, J = 36.7 Hz, C_q), 146.7 (2×C_q), 128.7 (4×CH$_{arom}$), 126.8 (4×CH$_{arom}$), 126.6 (2×CH$_{arom}$), 52.0 (d, J = 14.7 Hz, CH$_2$), 51.2 (d, J = 147.8 Hz, C_q), 36.7 (CH$_2$), 35.5 (d, J = 35.1 Hz, CH$_2$).

HRMS (ESI): Calculated for $C_{16}{}^{13}CH_{16}ONa^+$ [M+Na]$^+$: 260.1127, found 260.1127.

Chemotion ELN sample number: MTN-4-128-A.

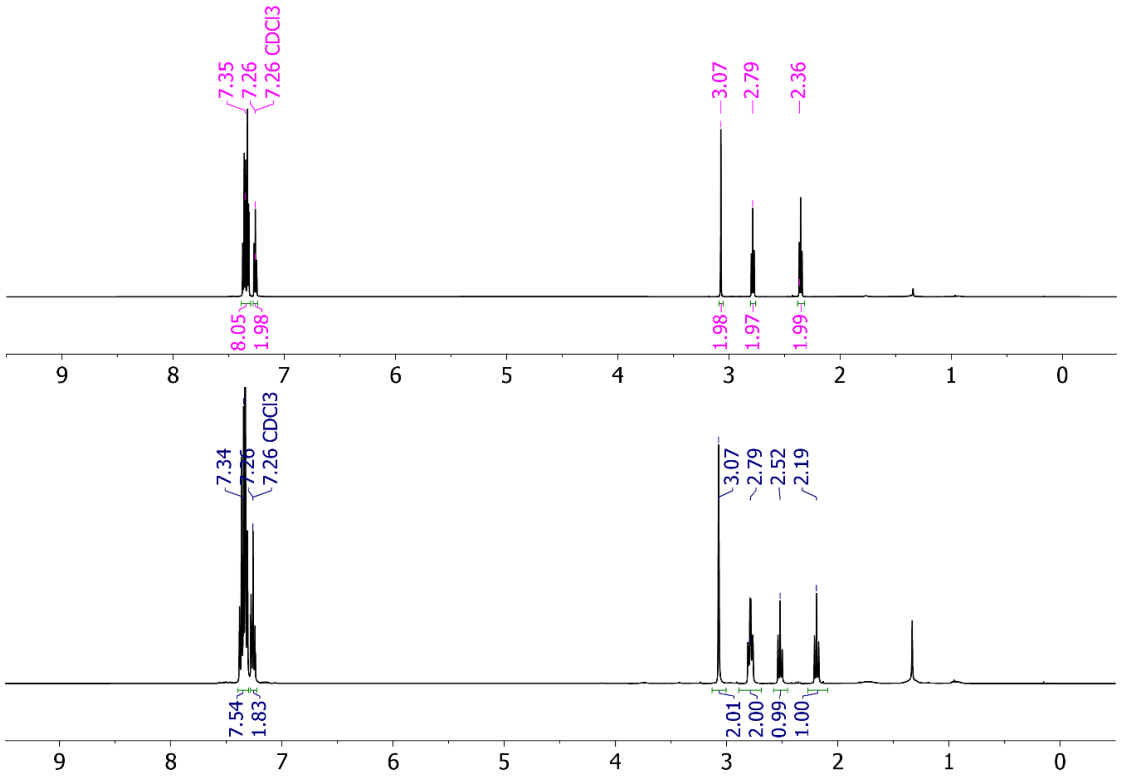


Figure 31: Comparison of the ^{1}H NMR spectra of [**95**] (top) and [**108**] (bottom).

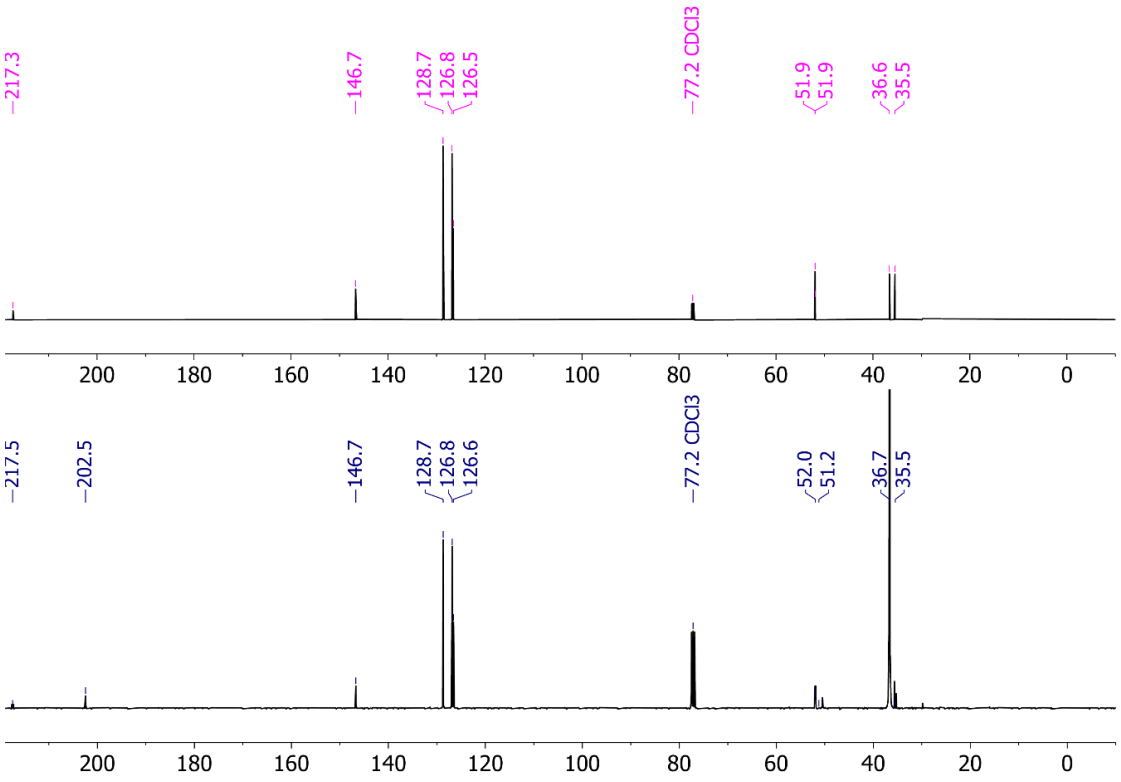
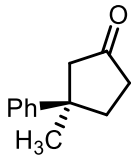


Figure 32: Comparison of the ^{13}C NMR spectra of [**95**] (top) and [**108**] (bottom).[16]

[16] The peak at 202.5 ppm in the bottom spectrum is probably caused by residually formed ^{13}C-labeled aldehyde.

5.3.7 Asymmetric examples

(+)-3-Methyl-3-phenylcyclopentan-1-one [(+)-55]



A tube was charged with $PdCl_2(MeCN)_2$ (5.2 mg, 0.020 mmol, 0.10 eq.) and ligand **82**(6.0 mg, 0.022 mmol, 0.11 eq.). Then, CH_2Cl_2 (3 mL) was added and the mixture was heated to reflux until a clear solution had formed (about 5 min.). The solvent was removed *in vacuo* and the residue dried under vacuum. Dry EtOH (2 mL) was added and the suspension was heated to 60 °C. Silver perchlorate hydrate (5.0 mg, 0.022 mmol, 0.11 eq.) was added. Water (0.11 mL, 6.0 mmol, 30.0 eq.), MCB **66** (32 mg, 0.20 mmol, 1.00 eq.) and *t*-BuONO (90% purity, 27 µL, 0.20 mmol, 1.00 eq.) were added successively. The tube was sealed and heated to 78 °C under stirring for 18 h. After cooling to rt the mixture was filtered through a whatman glas fibre filter and the solvent was removed *in vacuo*. The desired product was obtained *via* FC (hexane:Et_2O; 100:0 → 90:10) as a colourless oil (28 mg, 0.16 mmol, 80%).

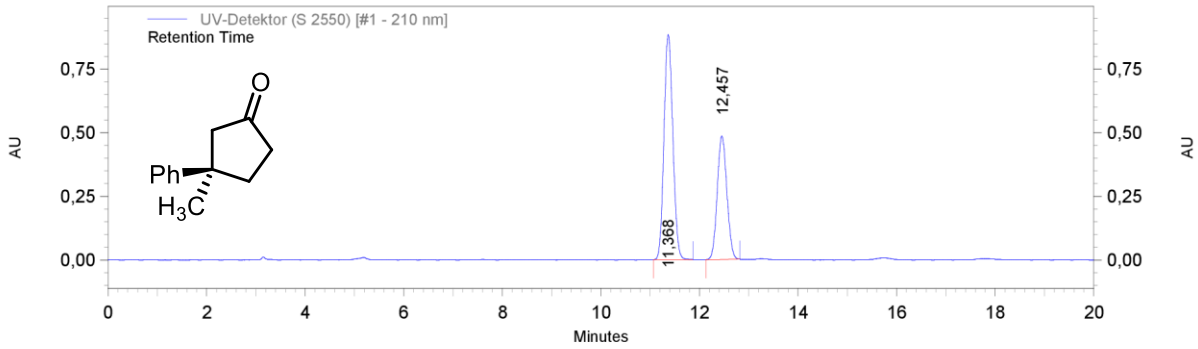
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.41 – 7.35 (m, 2H), 7.33 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 2.68 (d, *J* = 17.6 Hz, 1H), 2.51 (d, *J* = 17.6 Hz, 1H), 2.48 – 2.27 (m, 4H), 1.41 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 218.8, 148.6, 128.7, 126.4, 125.5, 52.3, 43.9, 36.8, 35.8, 29.5.

Optical Rotation: $[\alpha]_D^{25}$ = +5.2 (*c* = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 63:37 *er*, the major enantiomer is (*R*)-configured, assigned in analogy to literature ($[\alpha]_D$ = +23.0° (*c* = 0.85, $CHCl_3$), 99.5:0.5 *er* in favor of the (*R*)-enantiomer).[177] The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Cellulose-5 column, 22 °C, 1 mL/min, 95:5 hexane: *i*-PrOH, 210 nm, t_R(major) = 11.4 min, t_R(minor) = 12.5 min).

Spectroscopic data was in agreement with that previously reported.[177,178]

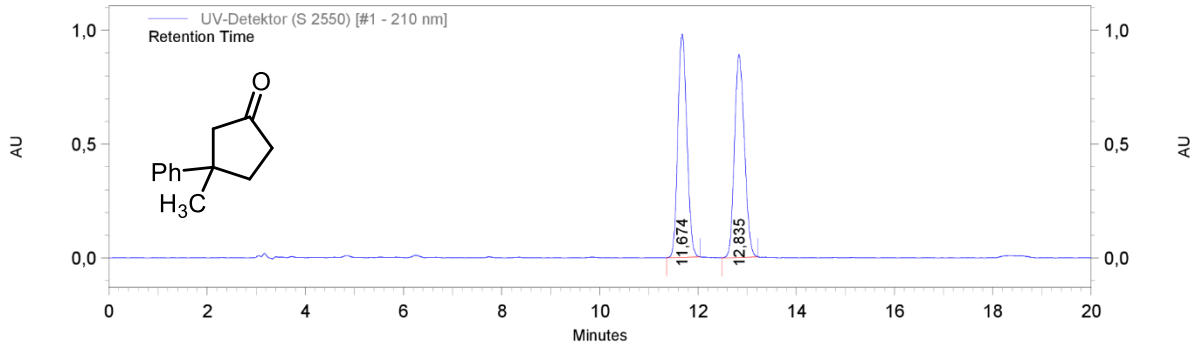
Chemotion ELN sample number: MTN-4-68-A.



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
11,368	11048499	62,60
12,457	6600172	37,40

Figure 33: HPLC chromatogram for (+)-3-methyl-3-phenylcyclopentanone [(+)-**55**].

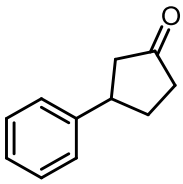


UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
11,674	12558275	49,91
12,835	12601237	50,09

Figure 34: HPLC chromatogram for *rac*-3-Methyl-3-phenylcyclopentanone [*rac*-**55**].

3-Phenylcyclopentanone [35]



A tube was charged with $PdCl_2(MeCN)_2$ (5.2 mg, 0.020 mmol, 0.10 eq.) and ligand **82**(6.0 mg, 0.022 mmol, 0.11 eq.). Then, CH_2Cl_2 (3 mL) was added and the mixture was heated to reflux until a clear solution had formed (about 5 min.). The solvent was removed *in vacuo* and the residue dried under vacuum. Dry EtOH (2 mL) was added and the suspension was heated to 60 °C. Silver perchlorate hydrate (5.0 mg, 0.022 mmol, 0.11 eq.) was added. Water (0.11 mL, 6.0 mmol, 30.0 eq.), MCB **65** (29 mg, 0.20 mmol, 1.00 eq.) and *t*-BuONO (90% purity, 27 µL, 0.20 mmol,

1.00 eq.) were added successively. The tube was sealed and heated to 78 °C under stirring for 18 h. After cooling to rt the mixture was filtered through a whatman glas fibre filter and the solvent was removed *in vacuo*. The desired product was obtained *via* FC (hexane:Et_2O; 95:5 → 90:10) as a colourless oil (17 mg, 0.11 mmol, 53%).

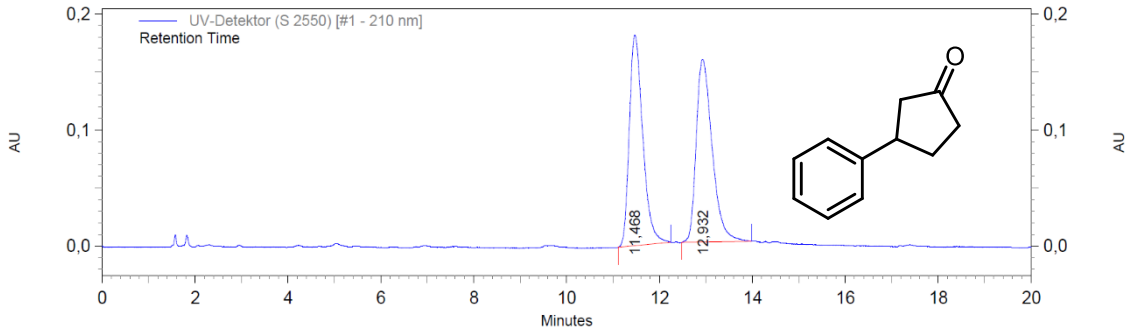
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.31 (m, 2H), 7.30 – 7.22 (m, 3H), 3.49 – 3.37 (m, 1H), 2.68 (dd, *J* = 18.0, 7.3, 1H), 2.54 – 2.40 (m, 2H), 2.40 – 2.25 (m, 2H), 2.09 – 1.92 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 218.5, 143.2, 128.8, 126.9, 126.9, 45.9, 42.4, 39.0, 31.3.

An enantiomeric ratio of 49:51 was established by HPLC analysis using a chiral column (Reprosil Chiral-AMS column, rt, 2 mL/min, 99:1 hexane:*i*-PrOH, 210 nm, t_{R1} = 9.7 min, t_{R2} = 11.5 min).

Spectroscopic data was in agreement with that previously reported.[171]

Chemotion ELN sample number: MTN-5-36-A.



UV-Detektor (S 2550) [#1 - 210 nm] Results

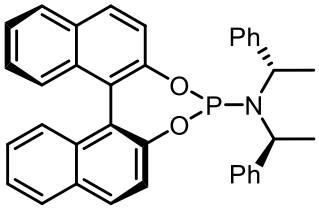
Retention Time	Area	Area %
11,468	3649202	49,29
12,932	3754465	50,71

Figure 35: HPLC chromatogram for 3-Phenylcyclopentanone [**35**].

5.4 Asymmetric desymmetrisation of methylenecyclobutanes *via Heck* reaction

5.4.1 Synthesis of ligands

(11b*S*)-*N*,*N*-Bis((*S*)-1-phenylethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine [131]



Following a procedure by *Smith et al.*,[148] a flask was charged with (*S*)-(−)-1,1'-bi(2-naphthol) (1.43 g, 5.00 mmol, 1.00 eq.) and phosphorus trichloride (4.20 mL, 48.0 mmol, 9.60 eq.). *N*-Methylpyrrolidone (4.0 mg, 40 µmol, 0.01 eq.) was added and the reaction mixture was stirred at 80 °C for 30 minutes. After cooling to rt, all volatiles were removed *in vacuo*. The resulting foamy resin was dissolved in dry Et_2O (10 mL) and all volatiles were again removed *in vacuo*. The crude product was dried under high vacuum for 24 h affording (*S*)-(1,1'-binaphthalene-2,2'-dioxy)chlorophosphine as a pinkish solid (1.75 g, 4.99 mmol, 99%), which was used without further purification.

In a flame dried schlenk tube, (*S*)-bis((*S*)-1-phenylethyl)amine hydrochloride (524 mg, 2.00 mmol, 1.00 eq.) was suspended in dry THF (6 mL) and cooled to −78 °C. Then, *n*-BuLi (1.64 mL, 4.10 mmol, 2.50 M in hexanes, 2.05 eq.) was added dropwise. The reaction mixture was stirred for 10 min at −78 °C before it was allowed to warm to rt. It was then immediately re-cooled to −78 °C and stirred for additional 20 min. Now, (*S*)-(1,1'-binaphthalene-2,2'-dioxy)chlorophosphine (772 mg, 2.20 mmol, 1.10 eq.) dissolved in dry THF (6 mL) was added dropwise. After complete addition it was stirred at −78 °C for 2 h before it was gradually warmed to rt and stirred for additional 16 h. The mixture was concentrated *in vacuo*. The desired product was obtained *via* FC (pentane:CH_2Cl_2; 80:20) as a white solid (297 mg, 550 µmol, 28%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.8 Hz, 1H), 7.96 – 7.90 (m, 1H), 7.83 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.59 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.46 – 7.40

(m, 1H), 7.40 – 7.34 (m, 3H), 7.30 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.27 – 7.20 (m, 2H), 7.20 (s, 10H), 4.44 (dq, *J* = 10.9, 7.0 Hz, 2H), 1.71 (d, J = 7.1 Hz, 6H).

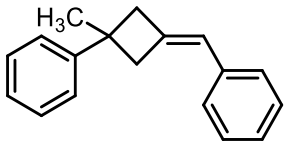
^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.6, 150.5, 149.8, 143.1, 132.9, 132.8, 131.4, 130.5, 130.4, 129.6, 128.3, 128.1, 128.1, 128.0, 127.8, 127.3, 127.2, 126.7, 126.1, 125.9, 124.8, 124.4, 124.3, 124.2, 122.6, 122.5, 122.4, 121.2, 54.6, 54.5, 23.1, 23.0.

Spectroscopic data was in agreement with that previously reported.[148]

Chemotion ELN sample number: MTN-5-77-A & MTN-5-84-A.

5.4.2 Synthesis of (cyclobutylidenemethyl)benzenes

(3-Benzylidene-1-methylcyclobutyl)benzene [122]



A tube was charged with palladium acetate (11 mg, 50 µmol, 0.10 eq.), triphenylphosphine (26 mg, 0.10 µmol, 0.20 eq.), potassium carbonate (138 mg, 1.00 mmol, 2.00 eq.) and DMF (5 mL). Then, MCB **66** (87 mg, 0.55 mmol, 1.10 eq.) and iodobenzene (102 mg, 56.0 µL, 500 µmol, 1.00 eq.) were added and it was heatet to 100 °C under stirring for 16 h. It was diluted with EtOAc and filtered through celite. The filtrate was washed with LiCl-solution (2×15 mL). The org layer was dried over $MgSO_4$ and concentrated *in vacuo*. The product was obtained *via* FC (pentane:PhMe; 100:0 → 95:5) as a colourless oil (50 mg, 0.21 mmol, 43%).

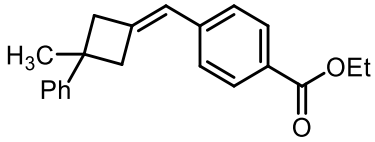
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 – 7.18 (m, 10H), 6.30 (p, *J* = 2.3 Hz, 1H), 3.47 (dt, *J* = 15.6, 3.1 Hz, 1H), 3.32 (dt, *J* = 15.2, 2.9 Hz, 1H), 3.16 – 3.09 (m, 1H), 2.94 (dtd, *J* = 15.2, 3.1, 1.8 Hz, 1H), 1.55 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.6, 138.7, 137.9, 128.4, 128.3, 127.2, 126.0, 125.6, 125.2, 122.8, 45.7, 45.6, 40.4, 30.

Spectroscopic data was in agreement with that previously reported.[199]

Chemotion ELN sample number: MTN-5-1-A.

rac-Ethyl 4-((3-methyl-3-phenylcyclobutylidene)methyl)benzoate [*rac*-129]



A tube was charged with palladium acetate (2.3 mg, 10 µmol, 0.10 eq.), tricyclohexylphosphane (5.6 mg, 20 µmol, 0.20 eq.), silver(I) carbonate (55 mg, 0.20 µmol, 2.00 eq.) and MeCN (1 mL). Then, MCB **66** (16 mg, 0.10 µmol, 1.00 eq.) and ethyl 4-iodobenzoate (16.8 µL, 100 µmol, 1.00 eq.) were added and it was stirring at 40 °C for 16 h. It was diluted with EtOAc and filtered through celite. The filtrate was washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was submitted to ^{1}H NMR analysis for yield determination. The product was obtained *via* AFC (CyHex:CH_2Cl_2:EtOAc; 70:29:1) as pale yellow oil (36 mg, 0.12 mmol, 59%).

IR (neat): $\tilde{\nu}$ = 2951 (w), 2374 (w), 2356 (w), 1712 (s), 1605 (m), 1495 (w), 1411 (w), 1367 (w), 1271 (s), 1177 (m), 1105 (s), 1019 (m), 887 (w), 781 (m), 759 (w), 733 (m), 699 (s), 671 (m), 658 (m), 628 (s), 619 (m), 610 (m), 599 (s), 587 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 – 7.97 (m, 2H, C*H*$_{arom}$), 7.39 – 7.32 (m, 2H, C*H*$_{arom}$), 7.32 – 7.26 (m, 4H, C*H*$_{arom}$), 7.24 – 7.19 (m, 1H, C*H*$_{arom}$), 6.31 (p, *J* = 2.4 Hz, 1H, C*H*), 4.38 (q, *J* = 7.1 Hz, 2H, C*H*$_2$), 3.53 – 3.38 (m, 1H, C*H*$_2$), 3.38 – 3.21 (m, 1H, C*H*$_2$), 3.21 – 3.03 (m, 1H, C*H*$_2$), 3.03 – 2.84 (m, 1H, C*H*$_2$), 1.53 (s, 3H, C*H*$_3$), 1.40 (t, *J* = 7.1 Hz, 3H, C*H*$_3$).

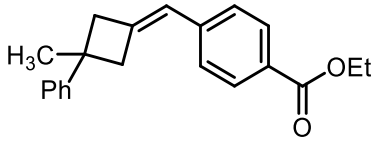
^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.7 (*C*$_q$), 150.3 (*C*$_q$), 142.5 (*C*$_q$), 142.5 (*C*$_q$), 129.9 (2×*C*H$_{arom}$), 128.5 (2×*C*H$_{arom}$), 127.8 (*C*$_q$), 127.0 (2×*C*H$_{arom}$), 125.8 (*C*H$_{arom}$), 125.3 (2×*C*H$_{arom}$), 122.5 (*C*H), 60.9 (*C*H$_2$), 46.0 (*C*H$_2$), 45.9 (*C*H$_2$), 40.5 (*C*$_q$), 31.0 (*C*H$_3$), 14.5 (*C*H$_3$).

HRMS (ESI): Calculated for $C_{21}H_{23}O_2^+$ $[M+H]^+$: 307.1693, found 307.1696.

The reaction was performed in similar fashion with other substrates (*cf.* chapter 4.2). In the case of alkenes **123**, **125**, **126** and **128**, isolation was impeded by inseparable by-products.

Chemotion ELN sample number: MTN-5-102-A.

Ethyl 4-((3-methyl-3-phenylcyclobutylidene)methyl)benzoate [129]



A tube was charged with palladium acetate (2.3 mg, 10 µmol, 0.10 eq.), (*R*)-BINAP (9.3 mg, 15 µmol, 0.15 eq.), silver(I) carbonate (55 mg, 0.20 µmol, 2.00 eq.) and MeCN (1 mL). Then, MCB **66** (16 mg, 0.10 µmol, 1.00 eq.) and ethyl 4-iodobenzoate (16.8 µL, 100 µmol, 1.00 eq.) were added and it was stirring at 60 °C for 65 h. It was diluted with EtOAc and filtered through celite. The filtrate was washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was obtained *via* AFC (CyHex:CH_2Cl_2:EtOAc; 70:29:1) as colourless oil (42 mg, 0.14 mmol, 68%).

The reaction was performed in similar fashion with other ligands (*cf.* chapter 4.2). In the case of ligand **131**, 30 mol% ligand was used instead of 15 mol%.

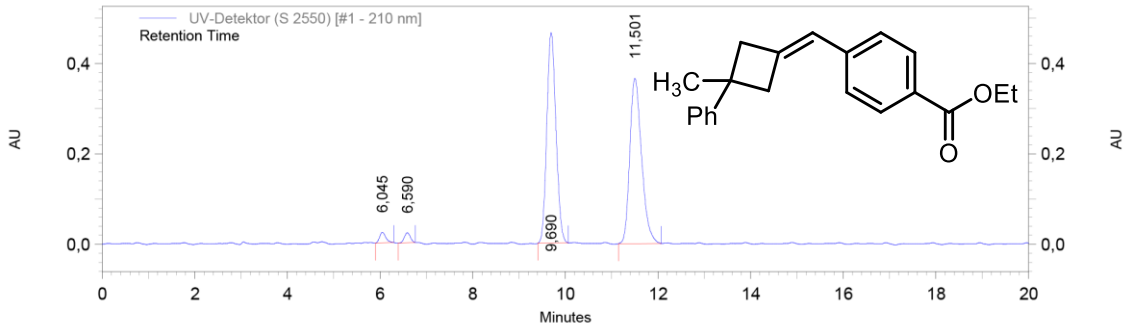
^{1}H NMR (400 MHz, $CDCl_3$): 8.08 – 7.92 (m, 2H), 7.41–7.34 (m, 2H), 7.34 – 7.29 (m, 4H), 7.27 – 7.19 (m, 1H), 6.33 (p, *J* = 2.4 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.48 (dt, *J* = 15.8, 3.1 Hz, 1H), 3.33 (dt, *J* = 15.6, 2.9 Hz, 1H), 3.14 (dq, *J* = 15.7, 2.9 Hz, 1H), 2.96 (dtd, *J* = 15.5, 3.2, 1.8 Hz, 1H), 1.54 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.7, 150.3, 142.5, 142.5, 129.9, 128.5, 127.8, 127.0, 125.8, 125.3, 122.5, 60.9, 46.0, 45.9, 40.5, 31.0, 14.5.

An enantiomeric ratio of 50:50 was established by HPLC analysis using a chiral column (Lux® Cellulose 1 column, rt, 1 mL/min, 98:2 hexane:*i*-PrOH, 210 nm, t_{R1} = 9.7 min, t_{R2} = 11.5 min).

Spectroscopic data was in agreement with that previously obtained (*vide supra*).

Chemotion ELN sample number: MTN-5-101-A.



UV-Detektor (S 2550) [#1 - 210 nm] Results

Retention Time	Area	Area %
6,045	223489	1,68
6,590	197912	1,49
9,690	6417990	48,25
11,501	6461104	48,58

Figure 36: HPLC chromatogram for Ethyl 4-((3-methyl-3-phenylcyclobutylidene)methyl)benzoate [129]. The two peaks at t_R = 6.0 min and t_R = 6.6 min can be attributed to traces of the corresponding alkene isomers (*cf.* chapter 4.2).

References

[1] a) G. Blaschke, H. P. Kraft, K. Fickentscher, F. Köhler, *Arzneim. Forsch.* **1979**, *29*; b) E. Tokunaga, T. Yamamoto, E. Ito, N. Shibata, *Sci Rep* **2018**, *8*.

[2] a) H. Stecher, K. Faber, *Synthesis* **1997**, *1997*, 1; b) S. Oudeyer, J.-F. Brière, V. Levacher, *Eur. J. Org. Chem.* **2014**, *2014*, 6103; c) C. Aranda, G. Oksdath-Mansilla, F. R. Bisogno, G. Gonzalo, *Adv. Synth. Catal.* **2020**, *362*, 1233; d) Y. Zhou, J. Ye, *Tetrahedron Lett.* **2022**, *98*, 153808.

[3] M. C. Willis, *J. Chem. Soc., Perkin Trans. 1* **1999**, *19*, 1765.

[4] A. Borissov, T. Q. Davies, S. R. Ellis, T. A. Fleming, M. S. W. Richardson, D. J. Dixon, *Chem. Soc. Rev.* **2016**, *45*, 5474.

[5] Iupac, *Compendium of Chemical Terminology, 2nd ed. (the "Gold Book")*, Blackwell Scientific Publications, Oxford, **1997**.

[6] J. Merad, M. Candy, J.-M. Pons, C. Bressy, *Synthesis* **2017**, *49*, 1938.

[7] J. Sietmann, J. M. Wahl, *Angew. Chem. Int. Ed.* **2020**, *59*, 6964.

[8] A. Sandvoß, J. M. Wahl, *Chem. Eur. J.* **2021**, *27*, 5871.

[9] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, *10*, 496.

[10] Z. G. Hajos, D. R. Parrish, DE2102623A1, **1971**.

[11] B. List, M. Turberg, *Synfacts* **2019**, *15*, 200.

[12] a) A.-S. Chapelon, D. Moraléda, R. Rodriguez, C. Ollivier, M. Santelli, *Tetrahedron* **2007**, *63*, 11511; b) H. Hagiwara, *Nat. Prod. Commun.* **2020**, *15*, 1934578X2092534.

[13] E. V. Anslyn, D. A. Dougherty, *Modern physical organic chemistry*, University Science Books, Mill Valley, California, **2006**.

[14] J. F. Liebman, A. Greenberg, *Chem. Rev.* **1976**, *76*, 311.

[15] K. B. Wiberg, *Angew. Chem. Int. Ed.* **1986**, *25*, 312.

[16] X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou, J. Zhou, *Chem. Rev.* **2016**, *116*, 7330.

[17] a) A. J. Ferreira, C. M. Beaudry, *Tetrahedron* **2017**, *73*, 965; b) B. Heasley, *Justus Liebigs Ann. Chem.* **2009**, 1477; c) A. Barrero, J. Del Quilez Moral, M. Herrador, H. Rodriguez, M. Perez Morales, *Curr. Org. Chem.* **2009**, *13*, 1164; d) A. Ghasemi Pirbalouti, S. E. Sajjadi, K. Parang, *Arch. Pharm.* **2014**, *347*, 229.

[18] W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, J. L. Thompson, *J. Am. Chem. Soc.* **1968**, *90*, 5895.

[19] R. D. Bach, O. Dmitrenko, *J. Am. Chem. Soc.* **2006**, *128*, 4598.

[20] a) D. Bellu, B. Ernst, *Angew. Chem. Int. Ed.* **1988**, *27*, 797; b) K. Tamagawa, R. L. Hilderbrandt, *J. Phys. Chem.* **1983**, *87*, 5508.

[21] a) W. T. Brady, H. G. Liddell, W. L. Vaughn, *J. Org. Chem.* **1966**, *31*, 626; b) D. A. Bak, W. T. Brady, *J. Org. Chem.* **1979**, *44*, 107.

[22] L. R. Krepski, A. Hassner, *J. Org. Chem.* **1978**, *43*, 2879.

[23] a) A. Hassner, J. L. Dillon, *J. Org. Chem.* **1983**, *48*, 3382; b) G. Mehta, H. S. P. Rao, *Synth. Commun.* **1985**, *15*, 991.

[24] A. V. Malkov, F. Friscourt, M. Bell, M. E. Swarbrick, P. Kocovský, *J. Org. Chem.* **2008**, *73*, 3996.

[25] Z. Du, M. J. Haglund, L. A. Pratt, K. L. Erickson, *J. Org. Chem.* **1998**, *63*, 8880.

[26] a) J. Marchand-Brynaert, L. Ghosez, *J. Am. Chem. Soc.* **1972**, *94*, 2870; b) J.-B. Falmagne, J. Escudero, S. Taleb-Sahraoui, L. Ghosez, *Angew. Chem.* **1981**, *93*, 926; c) I. Marko, B. Ronsmans, A. M. Hesbain-Frisque, S. Dumas, L. Ghosez, B. Ernst, H. Greuter, *J. Am. Chem. Soc.* **1985**, *107*, 2192; d) A. Sidani, J. Marchand-Brynaert, L. Ghosez, *Angew. Chem. Int. Ed.* **1974**, *13*, 267.

[27] J.-B. Falmagne, J. Escudero, S. Taleb-Sahraoui, L. Ghosez, *Angew. Chem. Int. Ed.* **1981**, *20*, 879.

[28] A. V. Chernykh, D. S. Radchenko, A. V. Chernykh, I. S. Kondratov, N. A. Tolmachova, O. P. Datsenko, M. A. Kurkunov, S. X. Zozulya, Y. P. Kheylik, K. Bartels et al., *Eur. J. Org. Chem.* **2015**, 6466.

[29] a) A. B. Charette, M. Grenon, *Can. J. Chem.* **2001**, *79*, 1694; b) M. Ramirez, W. Li, Y.-H. Lam, L. Ghosez, K. N. Houk, *J. Org. Chem.* **2020**, *85*, 2597.

[30] Q. Shen, O. V. Dorofeeva, V. S. Mastryukov, A. Almeninngen, *J. Mol. Struct.* **1991**, *246*, 237.

[31] a) H. N. Cripps, J. K. Williams, W. H. Sharkey, *J. Am. Chem. Soc.* **1958**, *80*, 751; b) H. N. Cripps, J. K. Williams, W. H. Sharkey, *J. Am. Chem. Soc.* **1959**, *81*, 2723; c) E. Gil-Av, J. Shabtai, *J. Org. Chem.* **1964**, *29*, 257; d) M. T. Crimmins, F. J. Pulido, P. Castreño, A. Barbero in *Encyclopedia of reagents for organic synthesis* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**; e) S. Niwayama, Y. Wang, K. N. Houk, *Tetrahedron Lett.* **1995**, *36*, 6201; f) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Soc. Rev.* **2010**, *39*, 783.

[32] a) B. B. Snider, D. K. Spindell, *J. Org. Chem.* **1980**, *45*, 5017; b) H. Hoffmann, Z. M. Ismail, A. Weber, *Tetrahedron Lett.* **1981**, *22*, 1953; c) B. B. Snider, E. Ron, *J. Org. Chem.* **1986**, *51*, 3643; d) M. L. Conner, Y. Xu, M. K. Brown, *J. Am. Chem.*

Soc. **2015**, *137*, 3482; e) M. L. Conner, M. K. Brown, *J. Org. Chem.* **2016**, *81*, 8050.

[33] a) S. Shirakawa, S. Liu, S. Kaneko, *Chem. - Asian J.* **2016**, *11*, 330; b) L. Gramigna, S. Duce, G. Filippini, M. Fochi, M. Franchini, L. Bernardi, *Synlett* **2011**, *2011*, 2745; c) D. Campolo, S. Gastaldi, C. Roussel, M. P. Bertrand, M. Nechab, *Chem. Soc. Rev.* **2013**, *42*, 8434.

[34] a) W. F. Bailey, E. R. Punzalan, E. W. Della, D. K. Taylor, *J. Org. Chem.* **1995**, *60*, 297; b) M. T. Hossain, J. W. Timberlake, *J. Org. Chem.* **2001**, *66*, 4409.

[35] E. W. Della, P. E. Pigou, C. H. Schiesser, D. K. Taylor, *J. Org. Chem.* **1991**, *56*, 4659.

[36] a) D. Hasselmann, *Chem. Ber.* **1974**, *107*, 3486; b) E. Vedejs, G. P. Meier, K. A. J. Snoble, *J. Am. Chem. Soc.* **1981**, *103*, 2823; c) S. P. Samuel, T. Q. Niu, K. L. Erickson, *J. Am. Chem. Soc.* **1989**, *111*, 1429; d) B. P. Branchaud, A. G. Glenn, H. C. Stiasny, *J. Org. Chem.* **1991**, *56*, 6656; e) Y. Takahashi, H. Ohaku, S. Morishima, T. Suzuki, H. Ikeda, T. Miyashi, *J. Chem. Soc., Perkin Trans. 1* **1996**, 319.

[37] J. Sietmann, M. Tenberge, J. M. Wahl, *Angew. Chem. Int. Ed.* **2023**, *62*, e202215381.

[38] a) E. Demole, E. Lederer, D. Mercier, *Helv. Chim. Acta* **1962**, *45*, 675; b) E. Demole, M. Stoll, *Helv. Chim. Acta* **1962**, *45*, 692; c) D. C. Aldridge, S. Galt, D. Giles, W. B. Turner, *J. Chem. Soc. C* **1971**, 1623; d) R. V. Stevens, N. Hrib, *Tetrahedron Lett.* **1981**, *22*, 4791; e) K. Weinges, H. Gethöffer, U. Huber-Patz, H. Rodewald, H. Irngartinger, *Justus Liebigs Ann. Chem.* **1987**, *1987*, 361; f) G. Helmchen, A. Goeke, G. Lauer, M. Urmann, J. Fries, *Angew. Chem. Int. Ed.* **1990**, *29*, 1024; g) M. Ernst, G. Helmchen, *Angew. Chem. Int. Ed.* **2002**, *41*, 4054.

[39] a) E. J. Corey, I. Vlattas, K. Harding, *J. Am. Chem. Soc.* **1969**, *91*, 535; b) R. Noyori, M. Suzuki, *Angew. Chem. Int. Ed.* **1984**, *23*, 847; c) S. Das, S. Chandrasekhar, J. S. Yadav, R. Grée, *Chem. Rev.* **2007**, *107*, 3286.

[40] a) G. Anner, K. Miescher, *Helv. Chim. Acta* **1948**, *31*, 2173; b) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, W. M. McLamore, *J. Am. Chem. Soc.* **1952**, *74*, 4223; c) N. Cohen, B. L. Banner, J. F. Blount, M. Tsai, G. Saucy, *J. Org. Chem.* **1973**, *38*, 3229; d) J. H. Hutchinson, T. Money, *Tetrahedron Lett.* **1985**, *26*, 1819; e) G. H. Posner, C. Switzer, *J. Am. Chem. Soc.* **1986**, *108*, 1239; f) D.

Soorukram, P. Knochel, *Org. Lett.* **2007**, *9*, 1021; g) Y.-Y. Yeung, R.-J. Chein, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 10346.

[41] a) M. Lopp, A. Paju, T. Kanger, T. Pehk, *Tetrahedron Lett.* **1996**, *37*, 7583; b) C. Bolm, T. Khanh Luong, G. Schlingloff, *Synlett* **1997**, 1151; c) H. Kotsuki, T. Shinohara, S. Fujioka, *Heterocycles* **2001**, *55*, 237; d) S. Xu, Z. Wang, X. Zhang, X. Zhang, K. Ding, *Angew. Chem. Int. Ed.* **2008**, *47*, 2840; e) S. Xu, Z. Wang, Y. Li, X. Zhang, H. Wang, K. Ding, *Chem. Eur. J.* **2010**, *16*, 3021; f) S. Xu, Z. Wang, X. Zhang, K. Ding, *Chin. J. Chem.* **2010**, *28*, 1731; g) K. S. Petersen, B. M. Stoltz, *Tetrahedron* **2011**, *67*, 4352; h) P. P. Poudel, K. Arimitsu, K. Yamamoto, *Chem. Commun.* **2016**, *52*, 4163; i) T. Uchida, T. Katsuki, *Tetrahedron Lett.* **2001**, *42*, 6911.

[42] L. Zhou, X. Liu, J. Ji, Y. Zhang, X. Hu, L. Lin, X. Feng, *J. Am. Chem. Soc.* **2012**, *134*, 17023.

[43] M. Tenberge, J. M. Wahl, *Synthesis* **2023**, *55*, 892.

[44] a) E. Mosettig, A. Burger, *J. Am. Chem. Soc.* **1930**, *52*, 3456; b) C. D. Gutsche, *J. Am. Chem. Soc.* **1949**, *71*, 3513; c) A. E. Greene, J. P. Depres, *J. Am. Chem. Soc.* **1979**, *101*, 4003; d) J.-P. Depres, A. E. Greene, *J. Org. Chem.* **1980**, *45*, 2036; e) I. Erden, E. M. Sorenson, *Tetrahedron Lett.* **1983**, *24*, 2731; f) S. Fukuzawa, T. Tsuchimoto, *Tetrahedron Lett.* **1995**, *36*, 5937; g) L. M. Reeder, L. S. Hegedus, *J. Org. Chem.* **1999**, *64*, 3306; h) D. C. Moebius, V. L. Rendina, J. S. Kingsbury, *Top. Curr. Chem.* **2014**, *346*, 111; i) N. R. Candeias, R. Paterna, P. M. P. Gois, *Chem. Rev.* **2016**, *116*, 2937.

[45] T. Hashimoto, K. Maruoka, *Bull. Chem. Soc. Jpn.* **2013**, *86*, 1217.

[46] K. Maruoka, A. B. Concepcion, H. Yamamoto, *Synthesis* **1994**, 1283.

[47] K. Maruoka, A. B. Concepcion, H. Yamamoto, *J. Org. Chem.* **1994**, *59*, 4725.

[48] a) T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 6614; b) T. Hashimoto, Y. Naganawa, K. Maruoka, *Chem. Commun.* **2010**, *46*, 6810.

[49] a) D. C. Moebius, J. S. Kingsbury, *J. Am. Chem. Soc.* **2009**, *131*, 878; b) A. J. Wommack, D. C. Moebius, A. L. Travis, J. S. Kingsbury, *Org. Lett.* **2009**, *11*, 3202.

[50] J. A. Dabrowski, D. C. Moebius, A. J. Wommack, A. F. Kornahrens, J. S. Kingsbury, *Org. Lett.* **2010**, *12*, 3598.

[51] V. L. Rendina, D. C. Moebius, J. S. Kingsbury, *Org. Lett.* **2011**, *13*, 2004.

[52] T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 8834.

[53] L. Gao, B. C. Kang, D. H. Ryu, *J. Am. Chem. Soc.* **2013**, *135*, 14556.

[54] B. C. Kang, S. Y. Shim, D. H. Ryu, *Org. Lett.* **2014**, *16*, 2077.

[55] B. C. Kang, D. G. Nam, G.-S. Hwang, D. H. Ryu, *Org. Lett.* **2015**, *17*, 4810.

[56] J. Y. Kim, B. C. Kang, D. H. Ryu, *Org. Lett.* **2017**, *19*, 5936.

[57] X. Li, X. Liu, Y. Fu, L. Wang, L. Zhou, X. Feng, *Chem. Eur. J.* **2008**, *14*, 4796.

[58] a) Wei Li, Xiaohua Liu, Xiaoyu Hao, Yunfei Cai, Lili Lin, Xiaoming Feng, *Angew. Chem.* **2012**, *124*, 8772; b) J. Zhang, Y. Zhang, X. Liu, J. Guo, W. Cao, L. Lin, X. Feng, *Adv. Synth. Catal.* **2014**, *356*, 3545; c) C. Yin, L. Lin, D. Zhang, J. Feng, X. Liu, X. Feng, *J. Org. Chem.* **2015**, *80*, 9691; d) D. Zhang, L. Lin, J. Yang, X. Liu, X. Feng, *Angew. Chem. Int. Ed.* **2018**, *57*, 12323; e) W. Wu, W. Cao, L. Hu, Z. Su, X. Liu, X. Feng, *Chem. Sci.* **2019**, *10*, 7003.

[59] F. Tan, M. Pu, J. He, J. Li, J. Yang, S. Dong, X. Liu, Y.-D. Wu, X. Feng, *J. Am. Chem. Soc.* **2021**.

[60] S. Dong, X. Liu, X. Feng, *Acc. Chem. Res.* **2022**.

[61] a) A. Pfaltz, *Chimia* **1990**, *44*, 202; b) A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339; c) A. Pfaltz, H. Adolfsson, K. Wärnmark, K. Aasbø, M. Klinga, A. Romerosa, *Acta Chem. Scand.* **1996**, *50*, 189.

[62] A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1.

[63] G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561.

[64] G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2011**, *111*, PR284-437.

[65] R. E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005.

[66] R. E. Lowenthal, S. Masamune, *Tetrahedron Lett.* **1991**, *32*, 7373.

[67] E. J. Corey, N. Imai, H. Y. Zhang, *J. Am. Chem. Soc.* **1991**, *113*, 728.

[68] D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726.

[69] D. Müller, G. Umbricht, B. Weber, A. Pfaltz, *Helv. Chim. Acta* **1991**, *74*, 232.

[70] R. Tokunoh, H. Tomiyama, M. Sodeoka, M. Shibasaki, *Tetrahedron Lett.* **1996**, *37*, 2449.

[71] a) D. A. Evans, S. J. Miller, T. Lectka, *J. Am. Chem. Soc.* **1993**, *115*, 6460; b) I. W. Davies, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *Tetrahedron Lett.* **1996**, *37*, 1725; c) G. Desimoni, G. Faita, P. P. Righetti, *Tetrahedron Lett.* **1996**, *37*, 3027; d) M. Johannsen, K. A. Joergensen, *J. Org. Chem.* **1995**, *60*, 5757; e) M. Johannsen, K. Anker Jørgensen, *Tetrahedron* **1996**, *52*, 7321; f) A. K. Ghosh, P. Mathivanan, J. Cappiello, K. Krishnan, *Tetrahedron:*

Asymmetry **1996**, *7*, 2165; g) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron Lett.* **1997**, *38*, 2427.

[72] A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron Lett.* **1996**, *37*, 3815.

[73] a) P. von Matt, G. C. Lloyd-Jones, A. B. E. Minidis, A. Pfaltz, L. Macko, M. Neuburger, M. Zehnder, H. Rüegger, P. S. Pregosin, *Helv. Chim. Acta* **1995**, *78*, 265; b) A. S. Gokhale, A. B. Minidis, A. Pfaltz, *Tetrahedron Lett.* **1995**, *36*, 1831; c) M. B. Andrus, A. B. Argade, X. Chen, M. G. Pamment, *Tetrahedron Lett.* **1995**, *36*, 2945.

[74] a) D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *J. Am. Chem. Soc.* **1993**, *115*, 5328; b) K. B. Hansen, N. S. Finney, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **1995**, *34*, 676.

[75] D. A. Evans, J. A. Murry, M. C. Kozlowski, *J. Am. Chem. Soc.* **1996**, *118*, 5814.

[76] a) G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2003**, *103*, 3119; b) G. Yang, W. Zhang, *Chem. Soc. Rev.* **2018**, *47*, 1783.

[77] D. A. Evans, G. S. Peterson, J. S. Johnson, D. M. Barnes, K. R. Campos, K. A. Woerpel, *J. Org. Chem.* **1998**, *63*, 4541.

[78] a) A. M. Harm, J. G. Knight, G. Stemp, *Synlett* **1996**, *1996*, 677; b) K. Alexander, S. Cook, C. L. Gibson, *Tetrahedron Lett.* **2000**, *41*, 7135; c) D. A. Evans, K. A. Woerpel, M. J. Scott, *Angew. Chem. Int. Ed.* **1992**, *31*, 430.

[79] A. Sakakura, R. Kondo, K. Ishihara, *Org. Lett.* **2005**, *7*, 1971.

[80] a) N. Ouhamou in *Encyclopedia of reagents for organic synthesis* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, p. 728; b) A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, V. Martínez-Merino, J. A. Mayoral, E. Pires, I. Villalba, *Synlett* **2005**, 2321.

[81] C. Bolm, K. Weickhardt, M. Zehnder, T. Ranff, *Chem. Ber.* **1991**, *124*, 1173.

[82] J. Hall, J.-M. Lehn, A. DeCian, J. Fischer, *Helv. Chim. Acta* **1991**, *74*, 1.

[83] a) I. W. Davies, L. Gerena, L. Castonguay, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *Chem. Commun.* **1996**, 1753; b) Denmark, Stiff, *J. Org. Chem.* **2000**, *65*, 5875.

[84] C. Yang, Z.-L. Liu, D.-T. Dai, Q. Li, W.-W. Ma, M. Zhao, Y.-H. Xu, *Org. Lett.* **2020**, *22*, 1360.

[85] J. L. Hofstra, *Org. Synth.* **2020**, *97*, 172.

[86] D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger et al., *J. Am. Chem. Soc.* **2002**, *124*, 13097.

[87] S. A. Snyder, A. M. Elsohly, F. Kontes, *Angew. Chem. Int. Ed.* **2010**, *49*, 9693.

[88] M.-C. Ye, B. Li, J. Zhou, X.-L. Sun, Y. Tang, *J. Org. Chem.* **2005**, *70*, 6108.

[89] G. Guillemot, M. Neuburger, A. Pfaltz, *Chem. Eur. J.* **2007**, *13*, 8960.

[90] a) A. G. Brook, W. W. Limburg, D. M. MacRae, S. A. Fieldhouse, *J. Am. Chem. Soc.* **1967**, *89*, 704; b) A. G. Brook, *Acc. Chem. Res.* **1974**, *7*, 77; c) W. H. Moser, *Tetrahedron* **2001**, *57*, 2065.

[91] P. R. Meehan, D. R. Aris, G. R. Willey, *Coordination Chemistry Reviews* **1999**, *181*, 121.

[92] The Cambridge Crystallographic Data Centre, *CCDC ConQuest, CSD version 5.43 (Nov 2022)*.

[93] a) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, J. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 10780; b) D. A. Evans, Z. K. Sweeney, T. Rovis, J. S. Tedrow, *J. Am. Chem. Soc.* **2001**, *123*, 12095.

[94] S. Kuhn, *Bachelor's Thesis*, Johannes Gutenberg-Universität Mainz, Mainz, **2021**.

[95] V. L. Rendina, *Dissertation*, Boston College, Boston, **2013**.

[96] R. Jira, *Angew. Chem. Int. Ed.* **2009**, *48*, 9034.

[97] a) J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttinger, H. Kojer, *Angew. Chem.* **1959**, *71*, 176; b) J. Smidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier, A. Sabel, *Angew. Chem. Int. Ed.* **1962**, *1*, 80.

[98] J. Tsuji, *Synthesis* **1984**, 369.

[99] T. V. Baiju, E. Gravel, E. Doris, I. N. Namboothiri, *Tetrahedron Lett.* **2016**, *57*, 3993.

[100] a) P. M. Henry, *J. Am. Chem. Soc.* **1964**, *86*, 3246; b) J.-E. Bäckvall, B. Åkermark, S. O. Ljunggren, *J. Chem. Soc., Chem. Commun.* **1977**, 264; c) J.-E. Bäckvall, B. Åkermark, S. O. Ljunggren, *J. Am. Chem. Soc.* **1979**, *101*, 2411.

[101] P. Kočovský, J.-E. Bäckvall, *Chem. Eur. J.* **2015**, *21*, 36.

[102] J. A. Keith, P. M. Henry, *Angew. Chem. Int. Ed.* **2009**, *48*, 9038.

[103] a) J. J. Dong, W. R. Browne, B. L. Feringa, *Angew. Chem. Int. Ed.* **2015**, *54*, 734; b) R. A. Fernandes, A. K. Jha, P. Kumar, *Catal. Sci. Technol.* **2020**, *10*, 7448.

[104] M. Roussel, H. Mimoun, *J. Org. Chem.* **1980**, *45*, 5387.

[105] C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc.* **2005**, *127*, 2796.

[106] C. N. Cornell, M. S. Sigman, *Inorg. Chem.* **2007**, *46*, 1903.

[107] T. Hosokawa, T. Nomura, S.-I. Murahashi, *J. Organomet. Chem.* **1998**, *551*, 387.

[108] J. A. Keith, R. J. Nielsen, J. Oxgaard, W. A. Goddard, *J. Am. Chem. Soc.* **2007**, *129*, 12342.

[109] A. Comas-Vives, A. Stirling, A. Lledós, G. Ujaque, *Chem. Eur. J.* **2010**, *16*, 8738.

[110] N. N. Nair, *J. Phys. Chem. B* **2011**, *115*, 2312.

[111] V. Imandi, S. Kunnikuruvan, N. N. Nair, *Chem. Eur. J.* **2013**, *19*, 4724.

[112] a) C. N. Cornell, M. S. Sigman, *Org. Lett.* **2006**, *8*, 4117; b) Y.-F. Wang, Y.-R. Gao, S. Mao, Y.-L. Zhang, D.-D. Guo, Z.-L. Yan, S.-H. Guo, Y.-Q. Wang, *Org. Lett.* **2014**, *16*, 1610; c) K. L. Walker, L. M. Dornan, R. N. Zare, R. M. Waymouth, M. J. Muldoon, *J. Am. Chem. Soc.* **2017**, *139*, 12495.

[113] B. W. Michel, A. M. Camelio, C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc.* **2009**, *131*, 6076.

[114] B. W. Michel, L. D. Steffens, M. S. Sigman, *J. Am. Chem. Soc.* **2011**, *133*, 8317.

[115] K.-F. Hu, X.-S. Ning, J.-P. Qu, Y.-B. Kang, *J. Org. Chem.* **2018**, *83*, 11327.

[116] B. L. Feringa, *J. Chem. Soc., Chem. Commun.* **1986**, 909.

[117] T. T. Wenzel, *J. Chem. Soc., Chem. Commun.* **1993**, *0*, 862.

[118] B. Weiner, A. Baeza, T. Jerphagnon, B. L. Feringa, *J. Am. Chem. Soc.* **2009**, *131*, 9473.

[119] a) P. Teo, Z. K. Wickens, G. Dong, R. H. Grubbs, *Org. Lett.* **2012**, *14*, 3237; b) Y.-Y. Jiang, Q. Zhang, H.-Z. Yu, Y. Fu, *ACS Catal.* **2015**, *5*, 1414; c) K. E. Kim, J. Li, R. H. Grubbs, B. M. Stoltz, *J. Am. Chem. Soc.* **2016**, *138*, 13179; d) X.-S. Ning, M.-M. Wang, C.-Z. Yao, X.-M. Chen, Y.-B. Kang, *Org. Lett.* **2016**, *18*, 2700.

[120] Z. K. Wickens, B. Morandi, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2013**, *52*, 11257.

[121] Z. K. Wickens, K. Skakuj, B. Morandi, R. H. Grubbs, *J. Am. Chem. Soc.* **2014**, *136*, 890.

[122] T.-L. Ho, M. H. Chang, C. Chen, *Tetrahedron Lett.* **2003**, *44*, 6955.

[123] A. A. de Oliveira, M. L. Da Silva, M. J. Da Silva, *Catal. Lett.* **2009**, *130*, 424.

[124] P. Boontanonda, R. Grigg, *J. Chem. Soc., Chem. Commun.* **1977**, 583.

[125] a) D. Farcasiu, P. V. R. Schleyer, D. B. Ledlie, *J. Org. Chem.* **1973**, *38*, 3455; b) I. Beck, E. Gusevskaya, A. Golovin, V. Likholobov, *J. Mol. Catal.* **1993**, *83*, 287; c) I. Beck, E. Gusevskaya, A. Golovin, V. Likholobov, *J. Mol. Catal.* **1993**, *83*, 301.

[126] Q. Feng, Q. Wang, J. Zhu, *Science* **2023**, *379*, 1363.

[127] a) M. F. Semmelhack, N. Zhang, *J. Org. Chem.* **1989**, *54*, 4483; b) M. F. Semmelhack, W. R. Epa, *Tetrahedron Lett.* **1993**, *34*, 7205; c) T. M. Meulemans, N. H. Kiers, B. L. Feringa, P. W. Leeuwen, *Tetrahedron Lett.* **1994**, *35*, 455; d) Y. Uozumi, K. Kato, T. Hayashi, *J. Am. Chem. Soc.* **1997**, *119*, 5063; e) Y. Uozumi, K. Kato, T. Hayashi, *J. Org. Chem.* **1998**, *63*, 5071; f) Y. Uozumi, H. Kyota, K. Kato, M. Ogasawara, T. Hayashi, *J. Org. Chem.* **1999**, *64*, 1620; g) R. M. Trend, Y. K. Ramtohul, E. M. Ferreira, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2003**, *42*, 2892; h) L. F. Tietze, K. M. Sommer, J. Zinngrebe, F. Stecker, *Angew. Chem. Int. Ed.* **2004**, *44*, 257; i) Y. J. Zhang, F. Wang, W. Zhang, *J. Org. Chem.* **2007**, *72*, 9208; j) K. Takenaka, Y. Tanigaki, M. L. Patil, C. L. Rao, S. Takizawa, T. Suzuki, H. Sasai, *Tetrahedron: Asymmetry* **2010**, *21*, 767; k) Z. Lu, S. S. Stahl, *Org. Lett.* **2012**, *14*, 1234; l) R. Zhu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2012**, *51*, 1926; m) S. Giofrè, L. Molteni, D. Nava, L. Lo Presti, E. M. Beccalli, *Angew. Chem. Int. Ed.* **2021**, *60*, 21723.

[128] a) J. Tsuji, H. Nagashima, K. Hori, *Tetrahedron Lett.* **1982**, *23*, 2679; b) T. Mitsudome, K. Mizumoto, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Angew. Chem. Int. Ed.* **2010**, *49*, 1238; c) B. Morandi, Z. K. Wickens, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2013**, *52*, 9751; d) X.-Y. Zhou, X. Chen, L.-G. Wang, *Synlett* **2016**, *27*, 2742; e) A. S. Carlson, C. Calcanas, R. M. Brunner, J. J. Topczewski, *Org. Lett.* **2018**, *20*, 1604; f) V. B. Corless, A. Holownia, H. Foy, R. Mendoza-Sanchez, S. Adachi, T. Dudding, A. K. Yudin, *Org. Lett.* **2018**, *20*, 5300; g) Q. Huang, Y.-W. Li, X.-S. Ning, G.-Q. Jiang, X.-W. Zhang, J.-P. Qu, Y.-B. Kang, *Org. Lett.* **2020**, *22*, 965.

[129] S. J. Cowling, J. W. Goodby, *Chem. Commun.* **2006**, 4107.

[130] M. F. Brown, A. E. Fenwick, M. E. Flanagan, A. Gonzales, T. A. Johnson, N. Kaila, M. J. Mitton-Fry, J. W. Strohbach, R. E. Tenbrink, J. D. Trzupek et al., US2014243312A1, **2014**.

[131] A. V. Malkov, A. J. P. S. Liddon, P. Ramírez-López, L. Bendová, D. Haigh, P. Kocovský, *Angew. Chem. Int. Ed.* **2006**, *45*, 1432.

[132] M. Sunkur, D. Baris, H. Hosgoren, M. Togrul, *J. Org. Chem.* **2008**, *73*, 2570.

[133] J. Sietmann, *Dissertation*, Westfälische Wilhelms-Universität Münster, Münster, **2023**.

[134] A. W. Walz, *Master's thesis*, Johannes Gutenberg-Universität Mainz, Mainz, **2022**.

[135] a) T. Mizoroki, K. Mori, A. Ozaki, *BCSJ* **1971**, *44*, 581; b) R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320.

[136] a) G. D. Daves, A. Hallberg, *Chem. Rev.* **1989**, *89*, 1433; b) W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2.

[137] A. de Meijere, F. E. Meyer, *Angew. Chem. Int. Ed. Engl.* **1995**, *33*, 2379.

[138] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009.

[139] M. Shibasaki, E. M. Vogl, T. Ohshima, *Adv. Synth. Catal.* **2004**, *346*, 1533.

[140] D. Mc Cartney, P. J. Guiry, *Chem. Soc. Rev.* **2011**, *40*, 5122.

[141] M. Diéguez, O. Pàmies, *Isr. J. Chem.* **2012**, *52*, 572.

[142] F. Ozawa, A. Kubo, T. Hayashi, *J. Am. Chem. Soc.* **1991**, *113*, 1417.

[143] a) J. M. Brown, J. J. Perez-Torrente, N. W. Alcock, H. J. Clase, *Organometallics* **1995**, *14*, 207; b) J. M. Brown, K. K. Hii, *Angew. Chem. Int. Ed.* **1996**, *35*, 657; c) R. J. Deeth, A. Smith, J. M. Brown, *J. Am. Chem. Soc.* **2004**, *126*, 7144.

[144] Y. Hashimoto, Y. Horie, M. Hayashi, K. Saigo, *Tetrahedron: Asymmetry* **2000**, *11*, 2205.

[145] a) R. Grigg, P. Stevenson, T. Worakun, *Tetrahedron* **1988**, *44*, 2033; b) W. Yong, P. Yi, Z. Zhuangyu, H. Hongwen, *Synthesis* **1991**, *1991*, 967; c) R. Grigg, P. Kennewell, A. Teasdale, V. Sridharan, *Tetrahedron Lett.* **1993**, *34*, 153; d) R. Azzam, W. M. de Borggraeve, F. Compernolle, G. J. Hoornaert, *Tetrahedron* **2005**, *61*, 3953; e) Y. Endo, T. Yoshimi, K. Ohta, T. Suzuki, S. Ohta, *J. Med. Chem.* **2005**, *48*, 3941; f) B. Yucel, N. Valentić, M. Noltemeyer, A. de Meijere, *Justus Liebigs Ann. Chem.* **2007**, *2007*, 4081; g) M. A. Seleem, A. M. Disouky, H. Mohammad, T. M. Abdelghany, A. S. Mancy, S. A. Bayoumi, A. Elshafeey, A. El-Morsy, M. N. Seleem, A. S. Mayhoub, *J. Med. Chem.* **2016**, *59*, 4900; h) S. Riebe, S. Jopp, P. Ehlers, E. Frank, G. Schneider, J. Wölfling, A. Villinger, P. Langer, *Tetrahedron Lett.* **2017**, *58*, 2801; i) J. de Souza-Ferrari, E. A. Silva-Júnior, J. A. Vale, L. A. de Albuquerque Simões, M. O. de Moraes-Júnior, B. B. Dantas, D. A. M. de Araújo, *Bioorg. Med. Chem. Lett.* **2021**, *52*, 128393; j) X. Huang, B.-Z. Chen, P. Li, D.-W. Ji, J. Liu, H. Zheng, S.-N. Yang, Y.-C. Hu, B. Wan, X.-P. Hu et al., *Nat. Chem.* **2022**, *14*, 1185.

[146] a) S. T. Davis, S. H. Dickerson, S. V. Frye, Harris, Philip Anthony, R. N. Hunter, III, L. F. Kuyper, K. E. Lackey, M. J. Luzzio, J. M. Veal, D. H. Walker, WO9915500A1, **1998**; b) M. J. Coghlan, J. E. Green, T. A. Grese, P. K. Jadhav, D. P. Matthews, M. I. Steinberg, K. R. Fales, M. G. Bell, WO2004052847A2, **2003**; c) J. E. Stelmach, K. G. Rosauer, E. R. Parmee, J. R. Tata, WO2006102067A1, **2006**; d) A. Khan, D. P. Medland, G. S. Bhatia, EP1749829A1, **2006**; e) H.-R. Tsou, S. Ayral-Kaloustian, G. H. Birnberg, M. B. Floyd, J. Kaplan, K. M. Kutterer, X. Liu, R. Nilakantan, M. A. Otteng, Z. Tang et al., WO2007075783A2, **2006**; f) P. K. Bhavar, S. K. V. S. Vakkalanka, S. Viswanadha, M. G. Swaroop, G. Babu, WO2015101958A2, **2015**; g) C. Puig Duran, J. Aiguade Bosch, S. Gual Roig, M. Prat Quiñones, WO2016046390A1, **2015**; h) M. S. Cushman, A. S. Mayhoub, M. Seleem, US2018319784A1, **2018**; i) J. Alcazar, M. K. Ameriks, C. B. Berry, P. Garcia-Reynaga, B. N. Laforteza, A. V. Samant, WO2022063784A1, **2021**; j) K. L. Granberg, G. Bergonzini, H. F. Bergström, S. J. Boström, H. Gradén, L. J. A. Ulander, S. Sakamaki, R. Fuchigami, Y. Niwa, M. Fujio, WO2022122773A1, **2021**.

[147] a) J. Hitce, O. Baudoin, *Adv. Synth. Catal.* **2007**, *349*, 2054; b) J. Ma, A. Novack, I. Nashashibi, P. Pham, C. J. Rabbat, J. Song, D. F. Shi, Z. Zhao, Y.-J. Choi, X. I. Chen, WO2010048207A2, **2009**; c) Y. Xiong, T. Schrader, A. Chen, J. R. Roppe, J. M. Baccei, Y. Bravo, WO2019241131A1, **2019**; d) M. M. Elsebaie, H. T. Nour El-Din, N. S. Abutaleb, A. A. Abuelkhir, H.-W. Liang, A. S. Attia, M. N. Seleem, A. S. Mayhoub, *Eur. J. Med. Chem.* **2022**, *234*, 114204; e) W. Xu, X. Cong, K. An, S.-J. Lou, Z. Li, M. Nishiura, T. Murahashi, Z. Hou, *Angew. Chem. Int. Ed.* **2022**, *61*, e202210624.

[148] C. R. Smith, D. J. Mans, T. V. RajanBabu, S. E. Denmark, S. T. Nguyen, *Org. Synth.* **2008**, *85*, 238.

[149] C. P. Rosenau, B. J. Jelier, A. D. Gossert, A. Togni, *Angew. Chem. Int. Ed.* **2018**, *57*, 9528.

[150] J. Guo, X. Xu, Q. Xing, Z. Gao, J. Gou, B. Yu, *Org. Lett.* **2018**, *20*, 7410.

[151] B. D. W. Allen, M. D. Hareram, A. C. Seastram, T. McBride, T. Wirth, D. L. Browne, L. C. Morrill, *Org. Lett.* **2019**, *21*, 9241.

[152] J. Sietmann, M. Ong, C. Mück-Lichtenfeld, C. G. Daniliuc, J. M. Wahl, *Angew. Chem. Int. Ed.* **2021**, *60*, 9719.

[153] S. Baj, R. Słupska, A. Chrobok, A. Drożdż, *J. Mol. Catal. A: Chem.* **2013**, *376*, 120.

[154] V. L. Rendina, J. S. Kingsbury, *J. Org. Chem.* **2012**, *77*, 1181.

[155] S. Kanemasa, Y. Oderaotoshi, S. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada, D. P. Curran, *J. Am. Chem. Soc.* **1998**, *120*, 3074.

[156] K. E. Poremba, N. T. Kadunce, N. Suzuki, A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2017**, *139*, 5684.

[157] M. Bandini, F. Bernardi, A. Bottoni, P. G. Cozzi, G. P. Miscione, A. Umani-Ronchi, *Eur. J. Org. Chem.* **2003**, *2003*, 2972.

[158] V. M. Breising, T. Gieshoff, A. Kehl, V. Kilian, D. Schollmeyer, S. R. Waldvogel, *Org. Lett.* **2018**, *20*, 6785.

[159] M. J. McKennon, A. I. Meyers, K. Drauz, M. Schwarm, *J. Org. Chem.* **1993**, *58*, 3568.

[160] M. Körner, M. Hiersemann, *Org. Lett.* **2007**, *9*, 4979.

[161] M. Li, A. Hawkins, D. M. Barber, P. Bultinck, W. Herrebout, D. J. Dixon, *Chem. Commun.* **2013**, *49*, 5265.

[162] S. K. Ginotra, V. K. Singh, *Org. Biomol. Chem.* **2007**, *5*, 3932.

[163] M. T. Bovino, S. R. Chemler, *Angew. Chem. Int. Ed.* **2012**, *51*, 3923.

[164] D. P. Hari, J. Waser, *J. Am. Chem. Soc.* **2017**, *139*, 8420.

[165] C. N. Slattery, S. O'Keeffe, A. R. Maguire, *Tetrahedron: Asymmetry* **2013**, *24*, 1265.

[166] S. Xu, Y. Magoon, R. R. Reinig, B. M. Schmidt, A. Ellern, A. D. Sadow, *Organometallics* **2015**, *34*, 3508.

[167] S. Bennett, S. M. Brown, G. Conole, M. Kessler, S. Rowling, E. Sinn, S. Woodward, *J. Chem. Soc., Dalton Trans.* **1995**, 367.

[168] J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030.

[169] P. Cao, C. Deng, Y.-Y. Zhou, X.-L. Sun, J.-C. Zheng, Z. Xie, Y. Tang, *Angew. Chem. Int. Ed.* **2010**, *49*, 4463.

[170] L. Bateman, S. W. Breeden, P. O'Leary, *Tetrahedron: Asymmetry* **2008**, *19*, 391.

[171] Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579.

[172] T. J. Hoffman, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 10670.

[173] R. C. Gadwood, I. M. Mallick, A. J. DeWinter, *J. Org. Chem.* **1987**, *52*, 774.

[174] Y. Moritani, D. H. Appella, V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 6797.

[175] H. Ahlbrecht, P. Weber, *Synthesis* **1992**, *1992*, 1018.

[176] K. Sammet, C. Gastl, A. Baro, S. Laschat, P. Fischer, I. Fettig, *Adv. Synth. Catal.* **2010**, *352*, 2281.

[177] C. Hawner, D. Müller, L. Gremaud, A. Felouat, S. Woodward, A. Alexakis, *Angew. Chem. Int. Ed.* **2010**, *49*, 7769.

[178] R. C. Gadwood, *J. Org. Chem.* **1983**, *48*, 2098.

[179] Y. Otomaru, K. Okamoto, R. Shintani, T. Hayashi, *J. Org. Chem.* **2005**, *70*, 2503.

[180] J. R. Finnegan, X. He, S. T. G. Street, J. D. Garcia-Hernandez, D. W. Hayward, R. L. Harniman, R. M. Richardson, G. R. Whittell, I. Manners, *J. Am. Chem. Soc.* **2018**, *140*, 17127.

[181] A. Horn, U. Kazmaier, *Org. Lett.* **2019**, *21*, 4595.

[182] Y. Zhou, C. Rao, Q. Song, *Org. Lett.* **2016**, *18*, 4000.

[183] Y. Chen, J. Du, Z. Zuo, *Chem* **2020**, *6*, 266.

[184] M. Zhang, J. Gao, J. Zhao, T. Qiu, Z. Li, Z. Guo, C. Liu, Y. Liu, *Eur. J. Org. Chem.* **2021**, *2021*, 6111.

[185] J.-Q. Huang, C.-Y. Ho, *Angew. Chem. Int. Ed.* **2020**, *59*, 5288.

[186] T. Delcaillau, P. Boehm, B. Morandi, *J. Am. Chem. Soc.* **2021**, *143*, 3723.

[187] J. A. Law, N. M. Bartfield, J. H. Frederich, *Angew. Chem. Int. Ed.* **2021**, *60*, 14360.

[188] A. Tsoukaki, E. Skolia, I. Triandafillidi, C. G. Kokotos, *Justus Liebigs Ann. Chem.* **2022**, *2022*.

[189] A. B. Lutjen, M. A. Quirk, A. M. Barbera, E. M. Kolonko, *Bioorg. Med. Chem.* **2018**, *26*, 5291.

[190] E. W. Werner, T.-S. Mei, A. J. Burckle, M. S. Sigman, *Science* **2012**, *338*, 1455.

[191] C. Zhang, C. B. Santiago, J. M. Crawford, M. S. Sigman, *J. Am. Chem. Soc.* **2015**, *137*, 15668.

[192] W. Huang, X. Wan, Q. Shen, *Angew. Chem. Int. Ed.* **2017**, *56*, 11986.

[193] H.-Y. Tu, F. Wang, L. Huo, Y. Li, S. Zhu, X. Zhao, H. Li, F.-L. Qing, L. Chu, *J. Am. Chem. Soc.* **2020**, *142*, 9604.

[194] K. Kim, S. Lee, S. H. Hong, *Org. Lett.* **2021**, *23*, 5501.

[195] J. Wang, L. Yan, G. Qian, S. Li, K. Yang, H. Liu, X. Wang, *Tetrahedron* **2007**, *63*, 1826.

[196] R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong, M. J. Gaunt, *J. Am. Chem. Soc.* **2012**, *134*, 10773.

[197] X.-J. Dai, H. Wang, C.-J. Li, *Angew. Chem. Int. Ed.* **2017**, *56*, 6302.

[198] D. C. Braddock, J. Clarke, H. S. Rzepa, *Chem. Commun.* **2013**, *49*, 11176.

[199] X. Ning, Y. Chen, F. Hu, Y. Xia, *Org. Lett.* **2021**, *23*, 8348.

Declaration

I hereby declare that this thesis was prepared independently and no sources or aids other than those expressly indicated have been used. I assure that any ideas taken over verbatim or in spirit have been clearly stated.

_____ _____

(Place, Date) (Marius Tenberge)

Curriculum Vitae

Personal data

[redacted]

Education

[redacted]

Publications

2022 – 2023

***Lewis* Acid Catalysed Asymmetric One-Carbon Ring-Expansion of Prochiral Cyclobutanones**
M. Tenberge, J. M. Wahl, *Synthesis* **2023**, *55*, 892 – 898.

Wacker Oxidation of Methylenecyclobutanes: Scope and Selectivity in an Unusual Setting
J. Sietmann,[#] M. Tenberge,[#] J. M. Wahl, *Angew. Chem. Int. Ed.* **2023**, *62*, e202215381.
[#] These authors contributed equally to this work

2019 **Photocatalytic $E \rightarrow Z$ Isomerization of β-Ionyl Derivatives**
K. Livingstone, M. Tenberge, F. Pape, C. G. Daniliuc, C. Jamieson, R. Gilmour, *Org. Lett.* **2019**, *21*, 9677 – 9680.

Poster Presentation on Scientific Conferences

[redacted]

Experience

[redacted]

Additional Education, Certificates, Awards

[redacted]