Screening of Chiral Diels-Alder Catalysts by Mass Spectrometric Monitoring of the Retro Reaction

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Für Hanno und meine Eltern

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Finally, thanks to Hanno for all his patient and constant support.

Contents

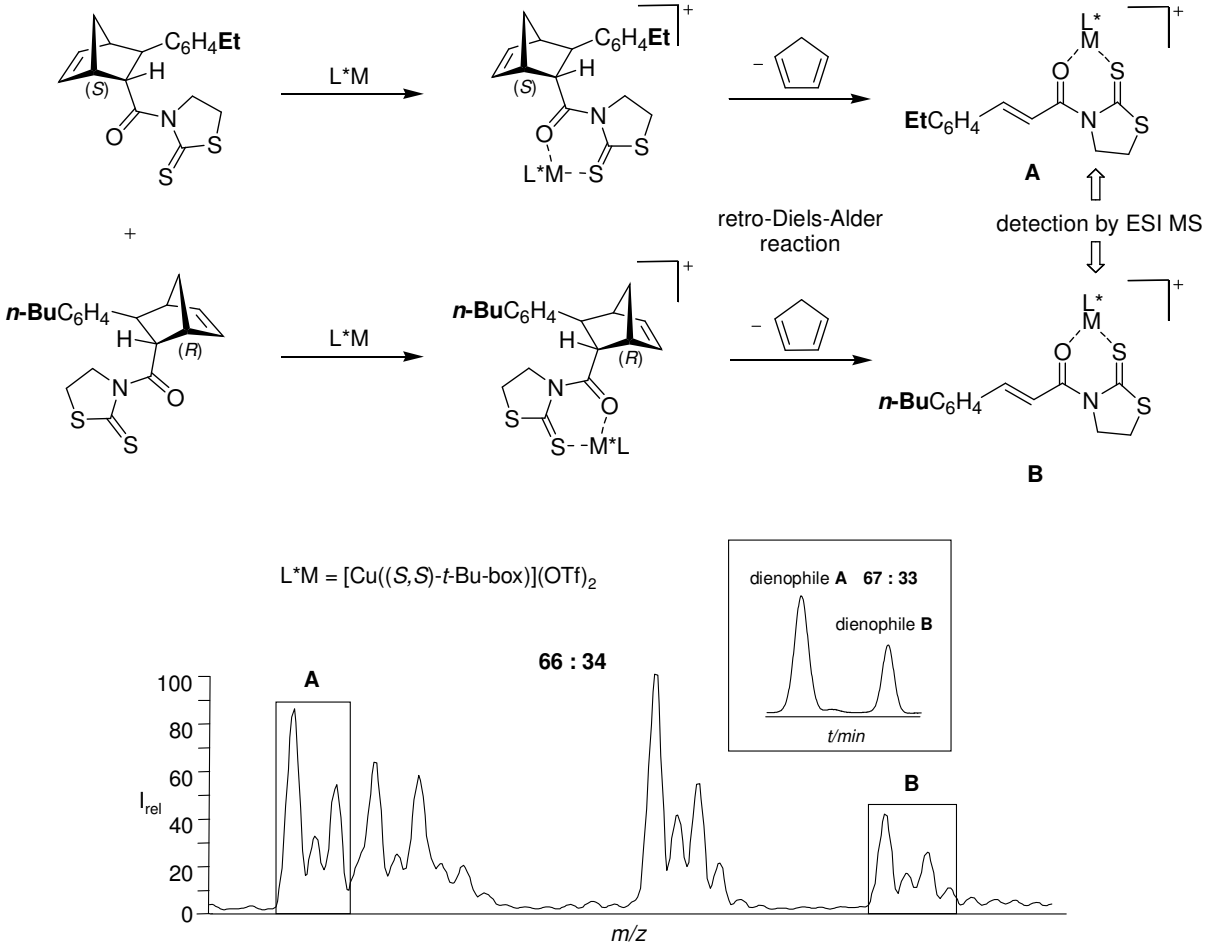
List of Abbreviations

Å	Ångström (10^{-10}m)
Ar	aryl
BINOL	2,2'-dihydroxy-1,1'-binaphthyl
Bn	benzyl
Bz	benzoyl
box	bis(oxazoline)
br	broad
Bu	butyl
c	concentration
Cat.	catalyst
CID	collision induced dissociation
Conv.	conversion
COSY	correlation spectroscopy (NMR)
DA	Diels-Alder
DABCO	1,4-diazabicyclo[2.2.2]octane
δ	chemical shift
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
EDG	electron donating group
ee	enantiomeric excess
er	enantiomeric ratio
EWG	electron withdrawing group
EI	electron impact
eq.	equivalent
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
FTIR	Fourier transform infra-red
GC	gas chromatography
h	hour
HOMO	highest occupied molecular orbital
HMBC	heteronuclear multiple bond correlation (NMR)
HMQC	heteronuclear multiple quantum coherence (NMR)
HPLC	high performance liquid chromatography
Hz	Hertz
i	iso
$\mathbf{I_{rel}}$	relative intensity
J	coupling constant
L*	chiral ligand
LA	Lewis acid
LUMO	lowest unoccupied molecular orbital
M	molar (mol/L)
Me	methyl
m.p.	melting point
MS	mass spectrometry
m/z	mass-to-charge ratio
Np	naphthyl
n.d.	not detected
NMR	nuclear magnet resonance
ob.	observed
P	product
Pr	propyl
Ph	phenyl
ppm	parts per million
rac	racemic
$\mathbf{R_f}$	retention factor
r.t.	room temperature
S	substrate
t	*tert*
TADDOL	tetraaryl-1,3-dioxolane-4,5-dimethanol
TES	triethylsilyl
TFA	trifluoromethane sulfonic acid
Tf	trifluoromethane sulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol	tolyl
t_R	retention time
TS	transition state
***p*-TsOH**	*p*-toluenesulfonic acid
$\tilde{\nu}$	wave number (IR)

Summary

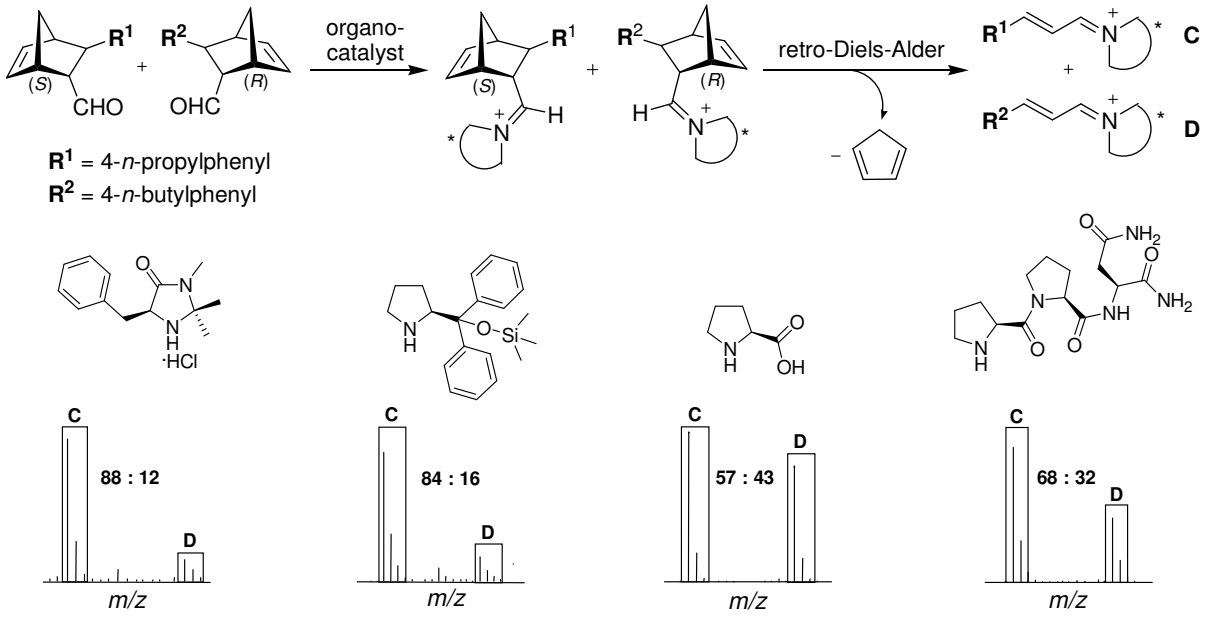
A rapid screening procedure for the identification of chiral Diels-Alder catalysts by ESI MS was developed. Screening of the retro reaction made it possible to indirectly determine the catalyst's enantioselectivity for the forward, product-forming reaction.

We were able to monitor positively charged catalytic intermediates for the retro-Diels-Alder reaction. Use of mass-labelled quasienantiomers allowed the intermediates **A** and **B** to be distinguished by mass spectrometry. The ratio of the mass peaks of **A** and **B** reflected the catalyst's intrinsic enantioselectivity. It was crucial to evaluate the influence of the mass labels on the reactivity of the two quasienantiomers. Sufficiently strong binding between the substrates and the metal catalyst was necessary to allow detection.

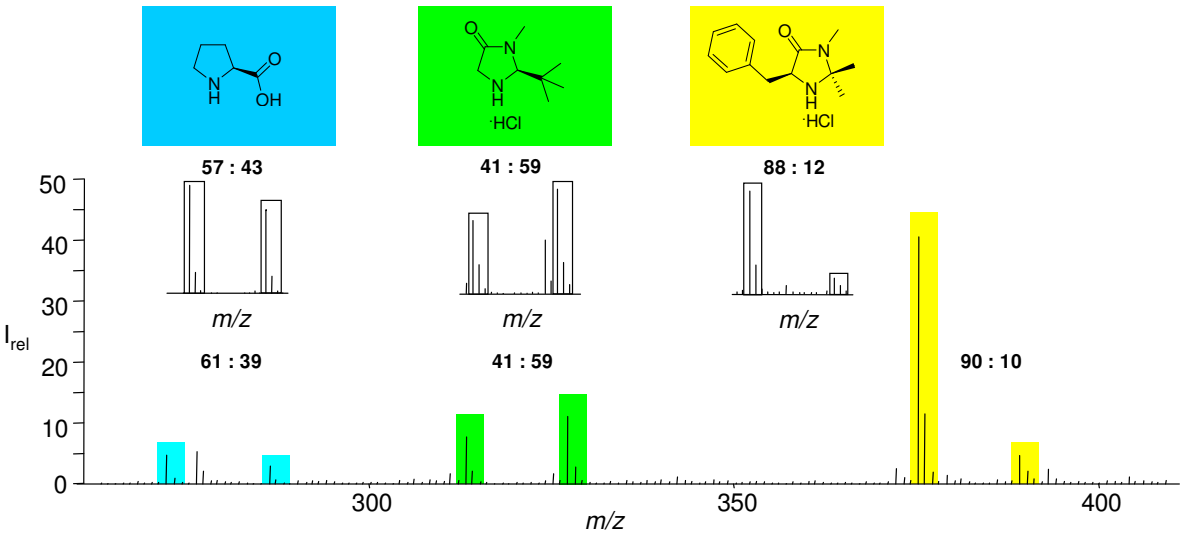


The method was used for the screening of bis(oxazoline), phosphinooxazoline and bis(imine) ligands in the copper-catalysed retro-Diels-Alder reaction to identify highly selective ligands. The selectivities were confirmed by product analysis (HPLC). In accordance to the principle of microscopic reversibility the ratios observed for the retro-Diels-Alder reaction correlated with those obtained for the preparative forward-Diels-Alder reaction.

The method was extended to organocatalytic retro-Diels-Alder reactions. Monitoring mass-labelled iminium ions **C** and **D** allowed direct determination of the catalyst's intrinsic enantioselectivity. This versatile method allowed not only rapid screening of imidazolidinone and proline-based organocatalysts but also of oligopeptide-catalysts. The results obtained by ESI MS were confirmed by preparative reactions.



After establishing a reliable protocol for the screening of organocatalysts, the procedure was successfully applied to multi-catalyst screening. The catalytic intermediates originate from different organocatalysts with different masses allowing facile assignment of the catalytic intermediates. After optimising the conditions, multi-catalyst screening showed excellent correlation with the single catalyst screening.



Chapter 1

Introduction

1 Introduction

The importance of asymmetric catalysis for the synthesis of enantiomerically enriched compounds has been highlighted by awarding SHARPLESS, NOYORI and KNOWLES the 2001 Nobel Prize in Chemistry.[1-3]

The discovery of new, highly efficient chiral catalysts is often costly and time-consuming. In recent years, many high-throughput screening methods have been developed for a variety of catalysed transformations.[4-8] Analysis is usually product-based, which has potential pitfalls as the enantioselectivity of a reaction is often lower than the catalyst's intrinsic selectivity. MARKERT and PFALTZ developed a screening method for determining the intrinsic enantioselectivity of a catalyst using ESI MS. This method was used to rapidly evaluate enantioselective catalysts for the palladium-catalysed kinetic resolution of allylic esters.[9] This work was based on an ESI MS screening method by CHEN, which allowed identification of the most effective catalyst in a palladium-catalysed polymerisation (Section 1.1.5).[10, 11]

1.1 Electrospray Ionisation Mass Spectrometry

1.1.1 Historical Perspective and Development

Electrospray ionisation (ESI) allows the transfer of low-volatile and decomposable organic compounds "gently" from solution into the gas-phase, enabling analysis of large fragile biomolecules and organometallic complexes.[12, 13] ESI is not an ionisation technique in the sense that neutral species become charged. Instead ions from solution are transferred to the gas-phase by nebulisation.[14]

The electrospray process was developed more than 80 years ago for applications ranging from painting to printing. In the late 1960's DOLE realised that electrospraying of a polymer solution into an evaporation chamber resulted in production of intact gaseous macroions.[15] This pioneering work by DOLE led FENN and co-workers, 15 years later, to considerably improve the method by coupling an ESI source with a quadrupole mass analyser.[16, 17] In contrast to classical techniques ions were transferred to the gas-phase without fragmentation and therefore allowed analysis of the intact molecules.[16] Before the implementation of ESI MS biomolecules could not accurately be analysed as their molecular weight exceeded

the mass range of most mass analysers. FENN discovered that under electrospray conditions large, non-volatile biomolecules such as proteins ("molecular elephants", FENN[18]) became multiple charged ions leading to mass-to-charge ratios below $m/z \leq 2000$.[12] Application of a deconvolution algorithm made analysis of molecules with up to 100 000 kDa possible.[18]

FENN was awarded the 2002 Nobel Prize in Chemistry for his contributions along with TANAKA, who introduced MALDI (matrix assisted laser desorption ionisation), another "soft" ionisation technique in mass spectrometry.[18, 19]

ESI MS is not limited to the analysis of large biomolecules. This method can also be used for the analysis of non-covalent and non-volatile organometallic complexes, usually not amenable to standard ionisation techniques.[20-22] Recently, ESI MS has become a powerful tool in probing the reaction mechanism of transition metal- and organocatalysed reactions (see Sections 1.1.3 and 1.1.4). As the ions are transferred directly from solution to the gas-phase, this technique is ideal to monitor short-lived reaction intermediates.

1.1.2 Electrospray Ionisation Process

In ESI MS a dilute solution of an analyte is pumped through a capillary at continuous flow. A high voltage (2-5 kV) is applied to the capillary. The resulting electric field gradient between the capillary and the counter electrode leads to the formation of the so-called "TAYLOR cone"[23] of the emerging liquid. If the imposed field is high enough, the protruding liquid is dispersed in a fine spray of charged droplets towards the counter electrode. An excess of anions or cations, depending on the applied field, accumulates on the surface of the droplets resulting in a conical spray of charged species due to COULOMB repulsion.[24] Evaporation of the solvent molecules by a counter-flow of an inert gas leads to accumulation of charge density in the droplets up to the point where the magnitude of the charge is sufficient to overcome the surface tension holding the droplet together, termed the "RAYLEIGH limit".[25] The droplet then fragments into smaller daughter ions, referred to as "COULOMB explosion" (Figure 1.1).

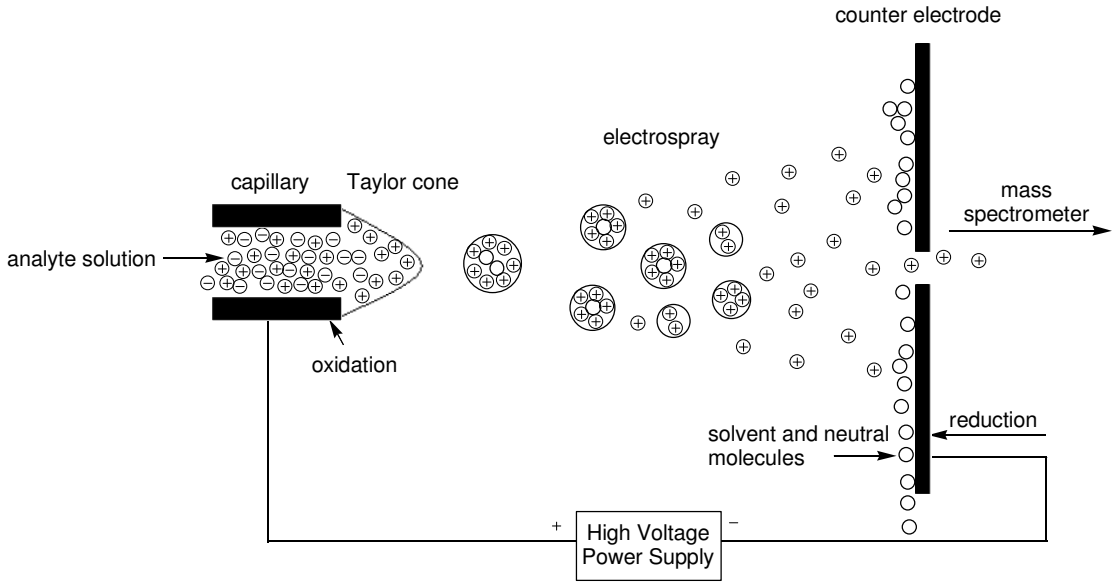


Figure 1.1: *Schematic representation of the electrospray ionisation process.*

Generation of bare, gaseous analyte ions has been proposed to occur by two possible pathways (Figure 1.2): 1) Continuous COULOMB explosions and evaporation of solvent molecules eventually result in the formation of droplets containing only a single ion. This is called the "charged residue model (CRM)" and was first proposed by DOLE.[15] 2) Two meteorologists, IRIBANE and THOMSON, suggested that before the droplets become small enough to contain only one analyte ion, the field strength of the droplet surface becomes strong enough to "evaporate" a surface ion from the droplet into the gas-phase. This is referred to as "ion evaporation model (IEM)".[26] The relative importance of the CRM and IEM remains a topic of discussion as both proposed models have yet to be confirmed by experimentation.

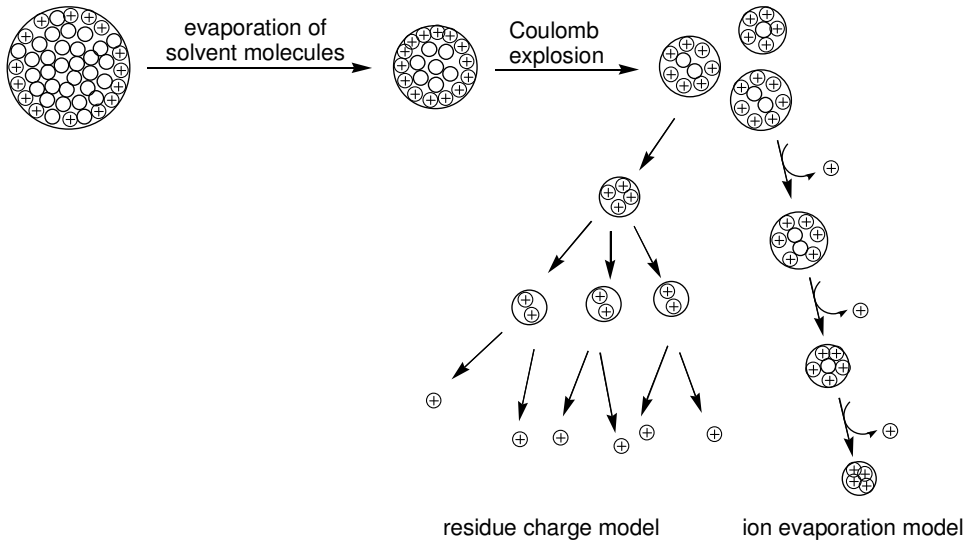


Figure 1.2: *After solvent evaporation Coulomb explosion leads to fragmentation of the droplets. The two proposed models for the transfer of single ions from the liquid to the gas-phase are shown.*

The continuous flow of charged ions from the capillary to the counter electrode leads to an accumulation of ions of the opposite charge, which must be charged balanced for the electrospray process continually to operate. KEBARLE and co-workers have described the ES ion source as "an electrolytic cell of a somewhat special kind".[27, 28] Electrochemical reactions are therefore likely to occur during the electrospray process and can have an influence on the analyte solution. This is of special importance when examining organometallic complexes as the oxidation state of the metals can be affected.[29]

1.1.3 Detection of Organometallic Reaction Intermediates by ESI MS

When using ESI MS the analyte has to be injected into the mass spectrometer as a liquid. This allows direct investigation of reaction products and/or reaction intermediates. To allow detection of intermediates the species must be charged and have a sufficiently long lifetime. The relatively gentle transfer of ions from the liquid to the gas-phase ensures a close relation between the gas-phase ion and solution species.[30]

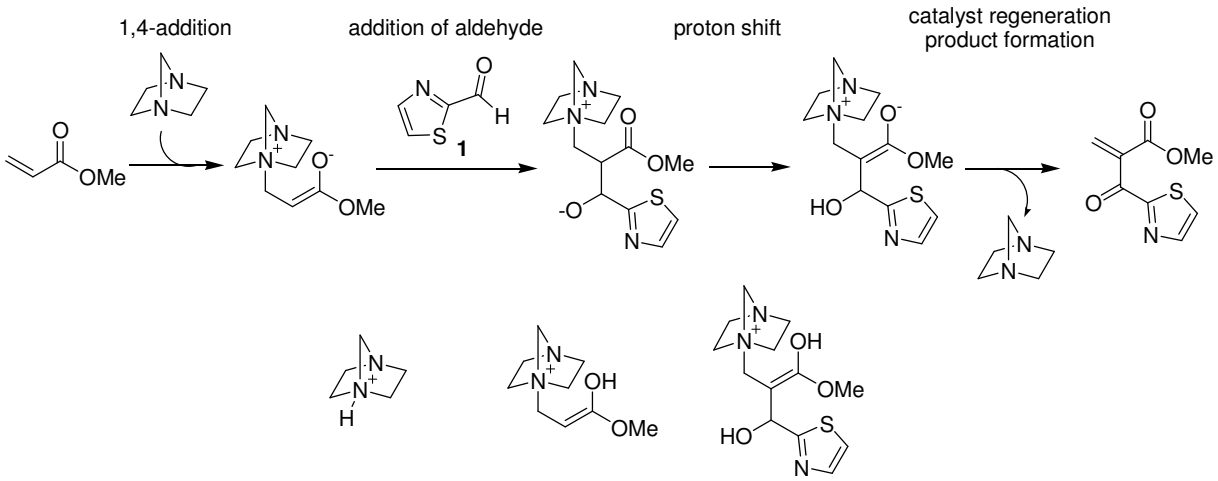
Early ESI MS investigations of ionic reaction intermediates were conducted for phosphine-mediated Wittig, Mitsunobu and Staudinger reactions.[31] Ionic intermediates were detected and used to confirm the proposed mechanisms. The disappearance and appearance of ionic species further allowed the reaction progress to be studied.

As ionic reaction intermediates are often involved in homogeneous transition metal catalysed reactions, ESI MS has become the technique of choice for mechanistic investigations and high-throughput screenings of such reactions.[30] WILSON and WU reported one of the first investigations involving the detection of nickel(I)-derived complexes in Raney-nickel catalysed C-C-coupling reactions.[32] Since then ESI MS has been widely applied in the study of palladium-catalysed transformations such as the Heck reaction, [33] the Suzuki-reaction,[34] the Stille-reaction,[35] oxidative coupling of arene- and arylboronic acids,[36, 37] polymerisation of ethane[10, 11] and the allylic substitution reaction.[9] Furthermore its broad applicability has been demonstrated by investigating different transition metal catalysed processes such as C-H activation reactions with iridium(III)[38, 39] and platinum(II),[40] catalytic hydrogenation reactions with rhodium[41, 42] and ruthenium complexes,[43, 44] olefin metathesis,[45, 46] catalytic oxidative epoxidation,[47, 48] aldehyde olefination with high-valent rhenium compounds,[49] Ziegler-Natta polymerisation using an alkylzirconocene catalyst[50, 51] and the cobalt-mediated Pauson-Khand reaction.[52]

The variety of transition metal complexes and reaction types analysed by ESI MS demonstrates the enormous potential of this fast analytical method. The fact that also catalysed reactions can be successfully studied highlights that even low-concentration species can be selectively monitored by this technique. As CHEN has studied many transition metal catalysed processes with ESI MS and developed more sophisticated instruments, he can certainly be regarded as the pioneer in this area of research.[30]

1.1.4 ESI MS as Tool for Detection of Reaction Intermediates in Organocatalysis

The first study of an organocatalytic reaction by ESI MS was reported by EBERLIN and co-workers.[53] The 1,4-diazabicyclo[2.2.2]octane (DABCO) catalysed Baylis-Hillman reaction was investigated to detect and structurally characterise the reaction intermediates. Although neutral species were expected from the proposed catalytic cycle (Scheme 1.1), these species were assumed to be in equilibrium with their protonated forms in methanolic solution. The reaction was monitored by directly pumping the reaction mixture into the ESI MS source. Reaction intermediates were observed with collision-induced dissociation (CID) measurements, which provided strong evidence for the proposed mechanism.[54, 55]

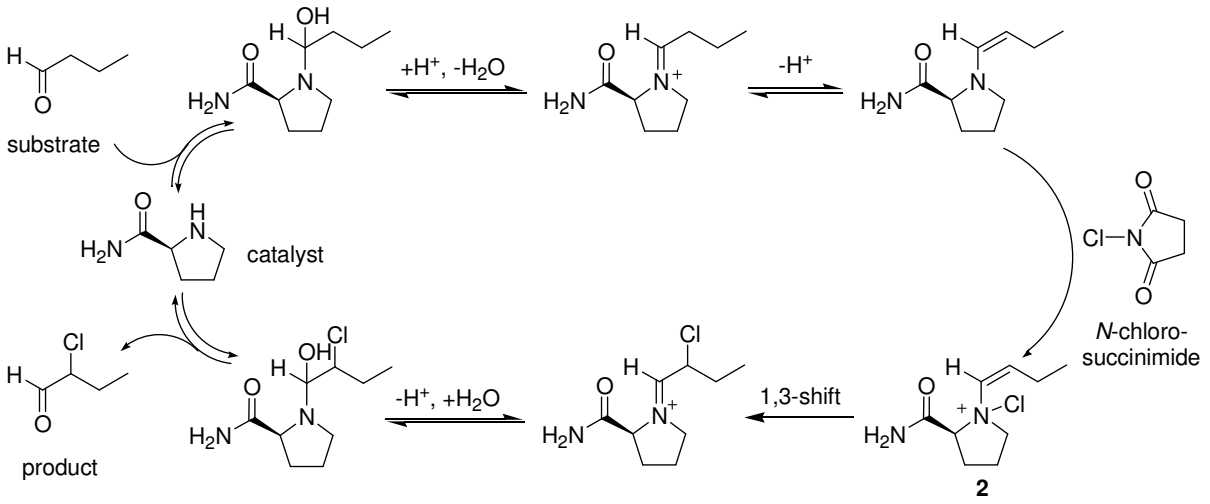


Scheme 1.1: *Catalytic cycle for the Baylis-Hillman reaction using methyl acrylate and aldehyde **1** with DABCO and observed intermediates by ESI MS.*

METZGER and co-workers recently reported an ESI MS study on the proline-catalysed aldol reaction. They characterised all proposed reaction intermediates and also followed the reaction progress over time.[56] A more sophisticated application of the technique is their recently developed "dual ESI MS".[57] By spraying the substrate and reagent solution independently in the reaction chamber, dual ESI MS allows observation of reaction intermediates after a few milliseconds. Using this technique, METZGER and co-workers were

able to clarify whether the organocatalysed α-halogenation of aldehydes proceeded via N-chlorination or direct C-chlorination of the enamine intermediate (Scheme 1.2). After reaction time of milliseconds, fragment ions resulting from CID measurements were unambiguously identified for intermediate **2**, providing evidence for the mechanism to proceed via N-chlorination.

ESI MS has also led to the confirmation of the mechanism in the conjugate *umpolung* reaction.[58]



Scheme 1.2: *Proposed mechanism of the L-prolineamide-catalysed α-chlorination of butanal. By performing CID experiments intermediate* **2** *was identified to be relevant in the catalytic cycle.*

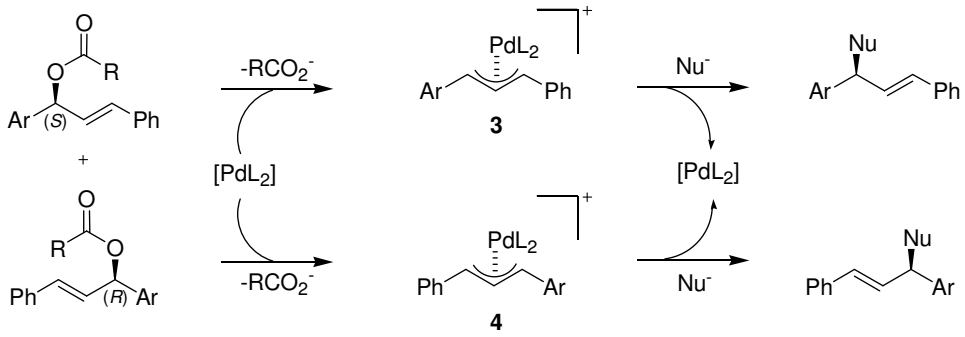
Intermediates in organocatalysis are generally charged (for example iminium ions) or are easily transformed into charged species by protic solvents (such as methanol or water), which makes them amenable to ESI MS detection. In this growing area of research useful methods are needed to aid reaction development and mechanistic understanding. As ESI MS is a very fast and practical technique with instruments available at most research institutes, it can be a very important tool for the investigation of organocatalytic reactions.

1.1.5 ESI MS Screening

HINDERLING and CHEN demonstrated an elegant application of ESI MS for the rapid screening of homogeneous polymerisation catalysts.[10] ESI MS analysis of a mixture of eight simultaneously synthesised Brookhart-type palladium(II)-olefin polymerisation catalysts and ethylene showed a complex mass spectrum. Multiple, overlapping series of oligo- and polymeric ions corresponded to each catalyst with between zero and one hundred ethylene units added. As the most effective catalyst carries the longest polymer chain, ions of the

highest molecular masses were selected and subjected to CID measurments. They underwent β-hydride elimination of the hydrocarbon chain producing ions corresponding to the most effective catalyst.

Based on that work, MARKERT and PFALTZ developed a screening method for the intrinsic enantioselectivity of chiral catalysts.[9] By examining charged catalyst-reactant complexes by ESI MS they were able to rapidly identify highly selective ligands in the palladium-catalysed kinetic resolution of allylic esters. The first step in the catalytic cycle for the kinetic resolution reaction gives palladium-allyl complexes **3** and **4**. As nucleophilic attack of these species is rate limiting, the cationic intermediates **3** and **4** exist in sufficient concentration to be detected by ESI MS (Scheme 1.3).



Scheme 1.3: *Kinetic resolution of allylic esters.*

Intermediates **3** and **4** are enantiomers and therefore cannot be distinguished by mass spectrometry. By introducing mass labels at the *para* aryl-position, which is sufficiently far removed from the reactive centre, the molecules become distinguishable by mass spectrometry (Figure 1.3). If an equimolar mixture of these "quasienantiomers" was treated with an achiral palladium catalyst, the catalytic intermediates **5** and **6** were detected with a 50:50 ratio as expected (Figure 1.3, catalyst **7**). If an equimolar mixture of quasienantiomers was subjected to a chiral catalyst, a higher reactivity for one of the quasienantiomers would be expected. This was the case when performing the experiment with the palladium-catalyst derived from ligand **8** (Figure 1.3). Using these screening conditions the most selective ligand to date was identified, illustrating the potential of this method.

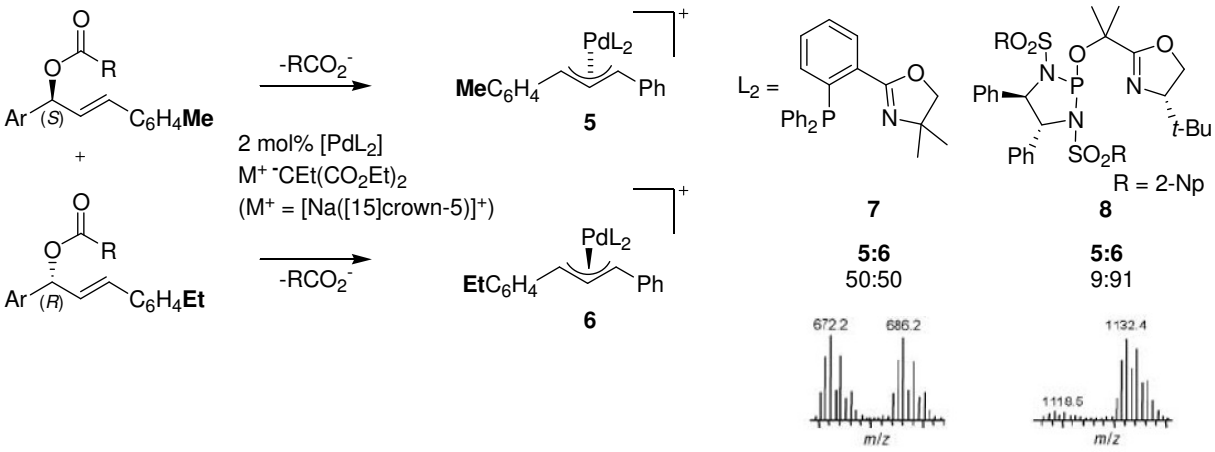


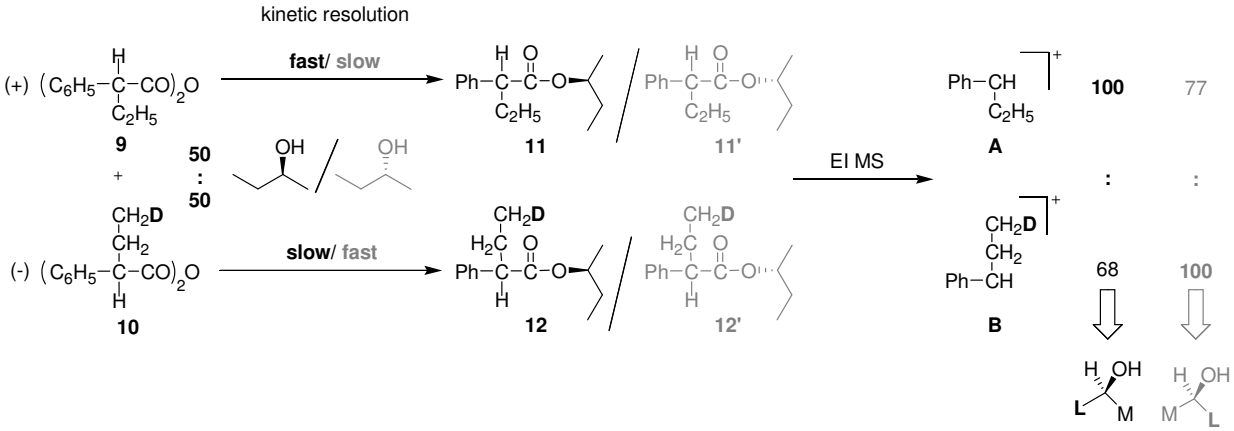
Figure 1.3: *ESI MS screening of palladium-catalysts for the kinetic resolution.*

MARKERT and PFALTZ also demonstrated that reliable selectivity data from catalyst mixtures can be obtained by analysing the corresponding reactant-catalyst complexes.[9] If the catalysts have different molecular weights, the resulting intermediates can be easily distinguished by mass spectrometry.

1.2 Mass Labels and Quasienantiomers in Mass Spectrometry

Enantio- or diastereomeric compounds cannot be distinguished by mass spectrometry as they have the same mass. By introducing mass labels, HOREAU and NOUAILLE elegantly solved this problem.[59]

They were interested in the determination of the absolute configuration of secondary alcohols by mass spectrometry. An equimolar mixture of enantiomeric anhydrides **9** and **10** was used to acylate an enantiomerically pure secondary alcohol of unknown configuration (Scheme 1.4). The anhydrides **9** and **10** differed in configuration and mass. Kinetic resolution gave diastereoisomeric esters **11** and **12** (**11'** and **12'** respectively) which had a mass difference of $\Delta\, m/z = 1$ and were therefore distinguishable by mass spectrometry. After subjecting this mixture to electron impact ionisation mass spectrometry (EI MS), the relative mass peak intensities of fragments **A** and **B** were compared. Based on the identification of the more abundant fragment, the absolute configuration of the secondary alcohol was assigned.



Scheme 1.4: *Using the mass labelling strategy by Horeau the configuration of secondary alcohols was determined.*

Almost 10 years later SUIZDAK, FINN and co-workers reported an extension of HOREAU's procedure to determine the enantiomeric excess of secondary alcohols by kinetic resolution.[60] Furthermore the mass labelling strategy for mass spectrometry has been used for the identification of enantioselective catalysts either by detection of mass-labelled products[61] or mass-labelled catalytic intermediates (Section 1.1.5)[9].

The application of mass-labelled enantiomers has been discussed in a recent review by ZHANG and CURRAN.[62]

1.3 The Diels-Alder Reaction

1.3.1 General Aspects

Since the discovery by DIELS and ALDER more than 80 years ago,[63, 64] the Diels-Alder reaction has established itself as a standard method for the formation of six-membered rings. The Nobel Prize was awarded for its discovery in 1950. Its powerful synthetic value has been demonstrated in the broad application for natural product synthesis, especially with regard to asymmetric variants.[65]

The Diels-Alder reaction proceeds via a suprafacial [π4s+π2s] cycloaddition of a diene and a dienophile (Figure 1.4). The driving force of this reaction is the formation of two new σ-bonds accompanied by the loss of two π-bonds. Both experimental data and theoretical calculations indicate that the reaction occurs via a concerted mechanism rather than a stepwise process involving diradical intermediates.[66-68]

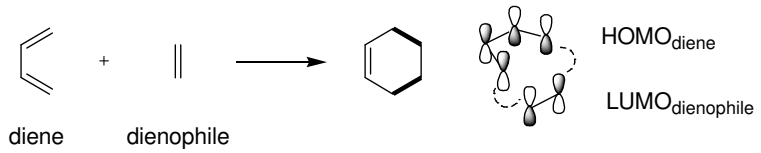


Figure 1.4: *Overlap of the frontier orbitals leads to the formation of two new σ-bonds in the Diels-Alder reaction (exemplified for the reaction between butadiene as diene and ethylene as dienophile). The dashed lines show the orbital overlap which can occur as the reaction proceeds.*

Several factors influence the diastereoselectivity of Diels-Alder reactions: reaction of two cyclopentadiene molecules produces the *endo* adduct faster than the *exo* adduct, although the latter is thermodynamically more stable. Additional frontier orbital interactions stabilise the *endo* transition state (Figure 1.5). These secondary orbital interactions lower the energy of the *endo* transition state relative to that of the *exo* transition state.[69-71] The *endo* adduct is therefore preferentially obtained under kinetically controlled reaction conditions (*endo* rule). The *endo* rule also applies to acrylates and related dienophiles. In this case the *endo* selectivity can be further increased by Lewis acid catalysis, lower reaction temperatures and the application of pressure.

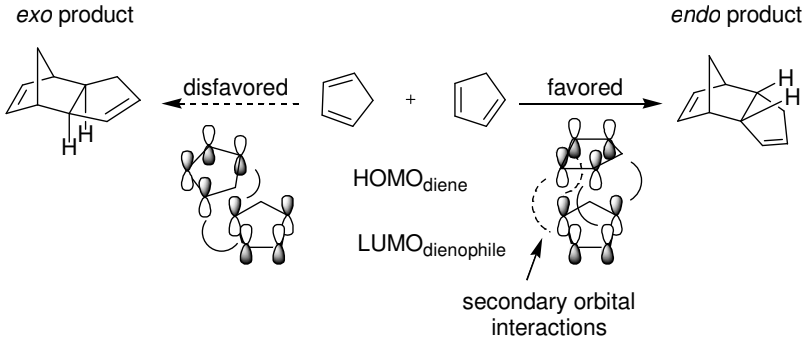
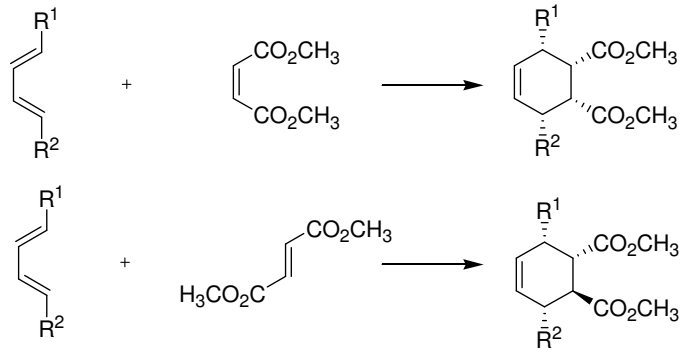


Figure 1.5: *The endo product is produced faster for the Diels-Alder reaction of cyclopentadiene which can be explained by secondary orbital interactions (dashed lines show the additional bonding in the endo transition state).*

Another aspect of diastereoselectivity in Diels-Alder reactions is the correlation of the relative configuration of the diene and dienophile part in the product with the geometries of the diene and dienophile (Scheme 1.5).



Scheme 1.5: *Diastereoselectivity in Diels-Alder reactions.*

By examining the frontier orbital interactions, predictions regarding relative reaction rates and regioselectivity can be made. A dienophile with an electron withdrawing group (EWG) has a lower energy LUMO compared to an unsubstituted diene (Figure 1.6, **a** and **b**). Therefore the energy gap between the HOMO of the diene and the LUMO of the dienophile becomes smaller leading to rate acceleration.*[71-73] This situation is usually termed "Diels-Alder reaction with normal electron demand". An electron donating group (EDG) in the dienophile can also lead to a rate acceleration. In this case the high-energy HOMO of the dienophile interacts with the LUMO of the diene. This is generally referred to as "Diels-Alder reaction with reverse electron demand" (Figure 1.6, **c**).[71]

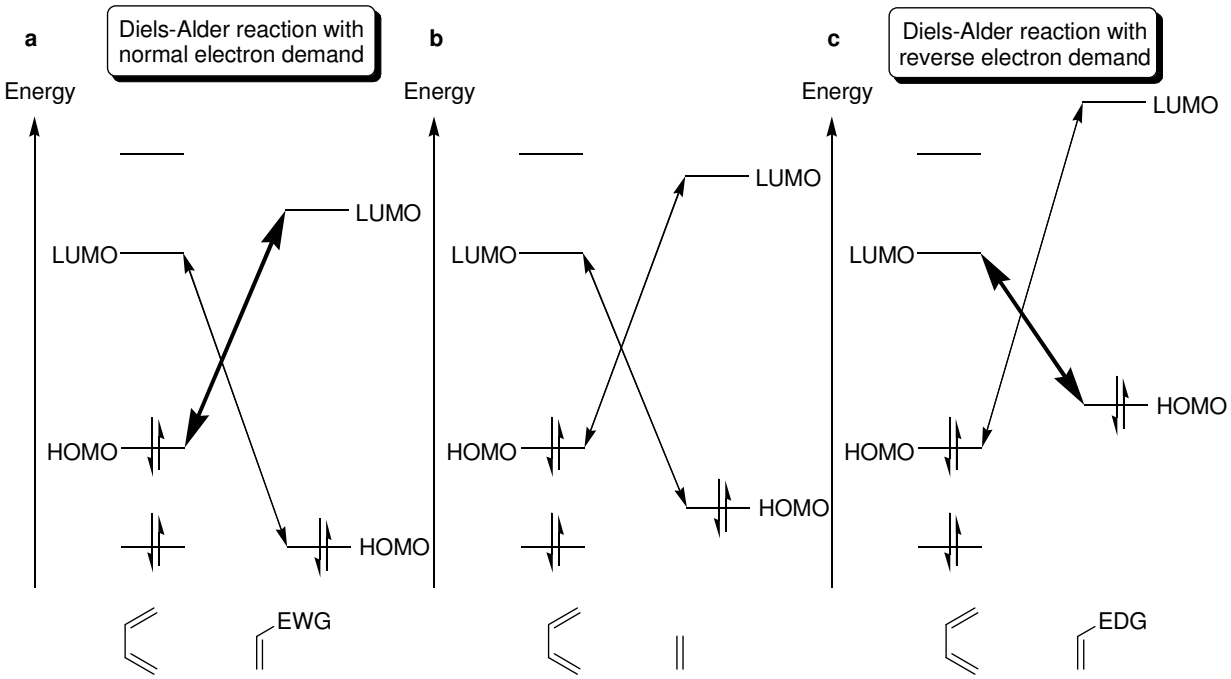


Figure 1.6: *Frontier orbital interactions for the Diels-Alder reaction.*

The large-large/small-small interactions between the frontier orbitals coefficients of the diene and dienophile determine the regioselectivity in the cycloaddition product.[71, 74]

The benefit of Lewis acid catalysis, leading to increased rates, higher *endo* diastereoselectivity and improved regioselectivity, can be explained by the influence of the Lewis acid on the LUMO of the dienophile.[71] Using a Lewis acid catalyst (LA) the HOMO and the LUMO of the dienophile are lowered compared to an uncatalysed reaction (Figure 1.7, **a** reaction between acrolein and butadiene). This results in a smaller energy gap between the HOMO of the diene and the LUMO of the dienophile and rate acceleration is

* A smaller value for E_{LUMO}-E_{HOMO} leads to an increase in rate as the overall energy ΔE is lowered according to the equation for estimating the chemical reactivity by KLOPMAN[72] and SALEM.[73]

observed. Lewis acid coordination also leads to a greater polarisation of the C=C double bond resulting in a higher regioselectivity (Figure 1.7, **b**). Finally, a larger LUMO coefficient on the carbonyl carbon enables better secondary orbital interactions increasing the *endo* selectivity (Figure 1.7, **c**).

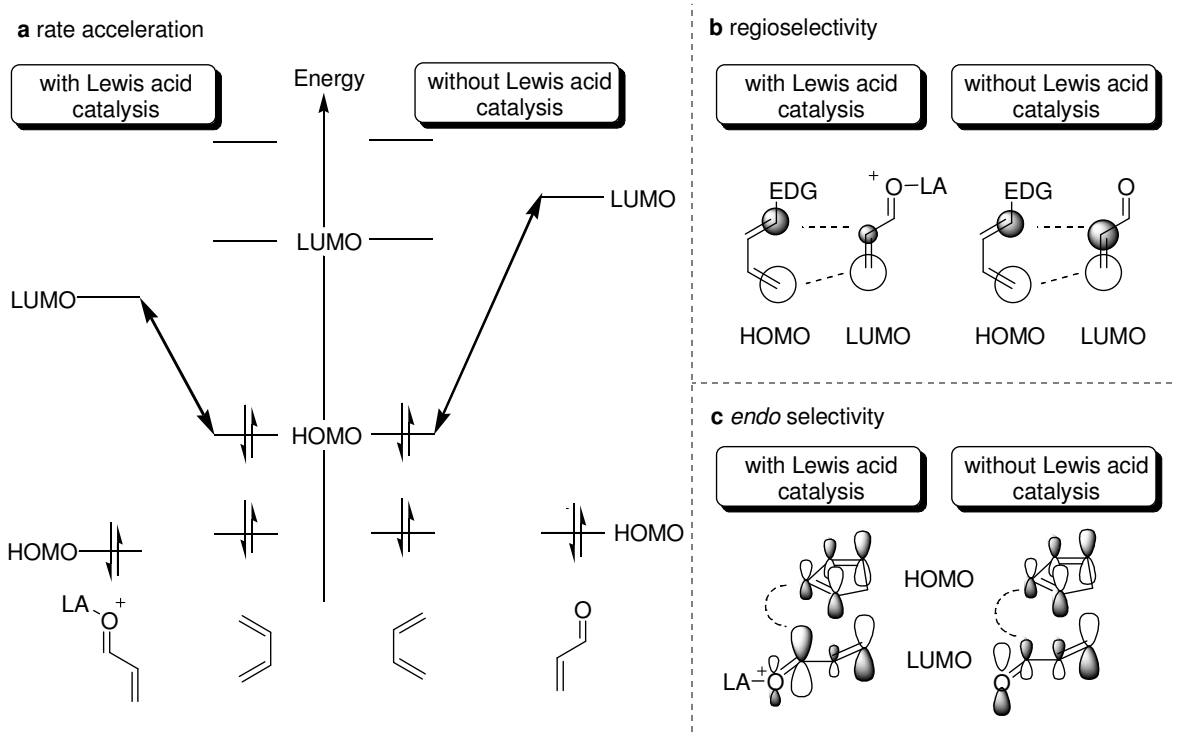


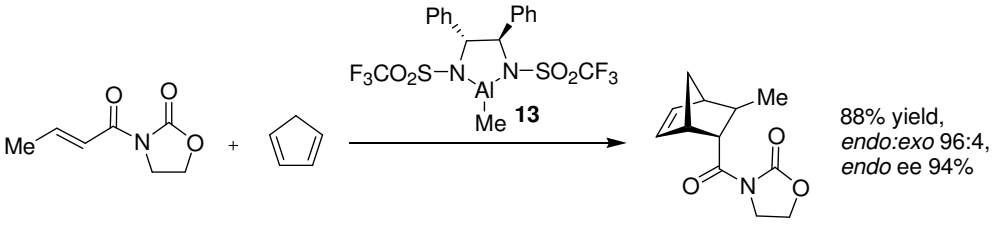
Figure 1.7: *Lewis acid catalysis: (**a**) rate acceleration (**b**) regioselectivity (**c**) endo selectivity.*

1.3.2 Lewis Acid Catalysis in Asymmetric Diels-Alder Reactions

Asymmetric variants of the Diels-Alder reaction were extensively developed starting in the 1980's.[75-77] Lewis acid catalysts have been shown to induce high enantio- and diastereoselectivities.[75] By forcing the reactants through a transition state that is distinctly lower than the competing diastereomeric transition states, a high level of stereoselectivity can be reached. A highly organised transition state is crucial and can be controlled by the following factors: a) one-point versus two-point binding in the catalyst-dienophile complex, b) metal ion coordination geometry and c) *s-cis* versus *s-trans* dienophile conformation.

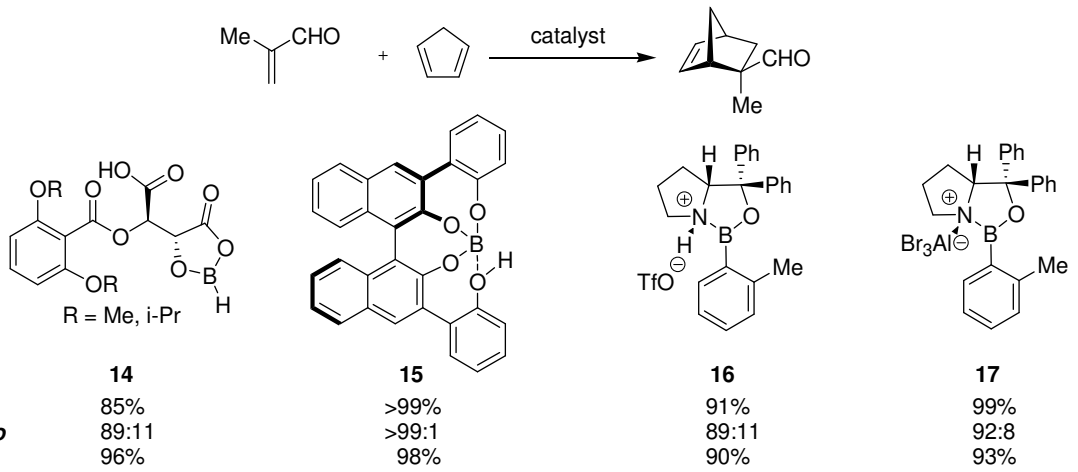
Among the first highly enantioselective catalysts for the Diels-Alder reaction were aluminium- and boron-Lewis acid complexes **13** and **14** (Scheme 1.6 and 1.7). COREY introduced the C_2-symmetric aluminium-stilbenediamine system **13**, which gave high enantiomeric excess for the reaction of cyclopentadiene with crotonyl imide (Scheme 1.6).[78] Although a two-point binding mode is generally expected for these dienophiles, X-ray

structures of the dimeric catalyst and ^{1}H NMR studies indicated a one-point binding model through the *s-trans* dienophile conformation.[79] The bistriflamide ligand can be recovered almost quantitatively.



Scheme 1.6: *Aluminium-stilbenediamine catalyst **13** for the enantioselective Diels-Alder reaction.*

At the same time YAMAMOTO and co-workers reported the *in situ* formation of (acyloxy)borane (CAB) complex **14**, which was highly selective in Diels-Alder reactions between cyclopentadiene and a number of aldehyde-based dienophiles.[80, 81] More recently, YAMAMOTO and co-workers introduced a Brønsted acid-assisted chiral Lewis acid (BLA) catalyst **15**, which was assumed to provide additional stabilisation of the transition state through intramolecular hydrogen bonding.[82] This catalyst gave excellent selectivities for the reaction between α-substituted aldehydes and cyclopentadiene. With catalyst **15** the Diels-Alder reaction with acetylenic aldehydes as dienophiles was accomplished with high enantioselectivity.[83] COREY's triflic acid activated chiral oxazaborolidine **16** is one of the more recent contributions to the field of enantioselective Diels-Alder catalysts.[84] This very reactive catalyst induces high enantio- and diastereoselectivities for aldehyde- and ester-based dienophiles. A variation of catalyst **16**, the chiral oxazaborolidine-aluminium bromide complex **17**, showed even higher reactivity and enantioselectivity.[85] The chiral oxazaborolidines can be easily recovered and synthesised on a large scale.



	14	**15**	**16**	**17**
yield	85%	>99%	91%	99%
exo:endo	89:11	>99:1	89:11	92:8
***exo* ee**	96%	98%	90%	93%

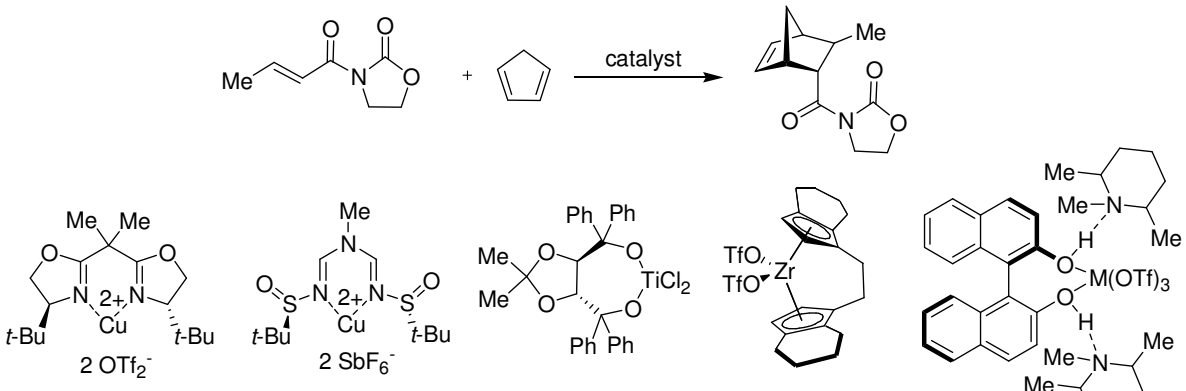
Scheme 1.7: *Catalysts for the enantioselective Diels-Alder reaction for one-point binding substrates.*[*]

[*] For catalysts **16** and **17** illustrated in Scheme 1.7 absolute configurations have been matched to the absolute configuration of the Diels-Alder adduct.

A variety of catalysts have been used in Diels-Alder reactions with 2-oxazolidinone-based dienophiles such as crotonyl imide (Scheme 1.8). Especially bis(oxazoline) ligands have been demonstrated to give high enantioselectivities in Diels-Alder reactions with these dienophiles. COREY reported the application of magnesium(II)- and iron(III)bis(oxazoline) complexes.[86, 87] EVANS found that copper(II)bis(oxazoline) complex **18** was an even more versatile and effective catalyst.[88-92] Interestingly, magnesium and iron complexes gave the enantiomeric cycloadducts compared to those from the copper-catalysed reactions. This can be rationalised by the individual metal geometries for the dienophile-catalyst complexes.[91]

The copper(II)bis(sulfinyl)imidoamidine catalyst **19** by ELLMAN and co-workers also showed very high diastereoselectivities and enantioselectivities for several 2-oxazolidinone-derived dienophiles.[93] After 6 minutes at -78 °C, the Diels-Alder adduct of acrylate imide and cyclopentadiene was obtained in 96% yield with an *endo:exo* selectivity of 99:1 and an *endo* ee of 98%. Moderate to excellent enantioselectivities have been obtained using titanium-TADDOL complex **20**. Its application was extensively studied by NARASAKA[94, 95] and others.[96-98] COLLINS used chiral zirconocene complex **21** to give the cycloadduct of crotonyl imide and cyclopentadiene in very good enantio- and diastereoselectivity showing high reactivity even at -78 °C.[99-101]

A chiral scandium(III) catalyst, prepared from (*R*)-BINOL, $Sc(OTf)_3$ and an achiral tertiary amine, was reported by KOBAYASHI.[102] A unique coordination structure indicated that axial chirality of the (*R*)-BINOL was extended to the tertiary amine leading to the proposed structure of **22a**. An octahedral scandium(III)-dienophile complex was assumed to be generated by two-point binding of the dienophile. A turnover in selectivity was observed when using the related ytterbium catalyst **22b**: addition of an achiral dicarbonyl-compound resulted in inversed stereoselectivity presumably resulting from specific coordination modes of ytterbium(III).[103]



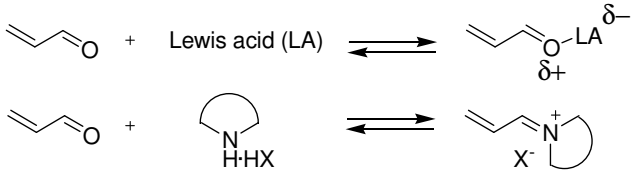
	18	**19**	**20**	**21**	
yield	85%	76%	87%	84%	**a** 84% **b** 77%
endo:exo	96:4	98:2	92:8	94:6	**a** 86:14 **b** 89:11
***endo* ee**	97%	97%	91%	95%	**a** 96% **b** 95%

Scheme 1.8: *Catalysts for the enantioselective Diels-Alder reaction for two-point binding substrates.*[*]

1.3.3 Organocatalysed Diels-Alder Reactions

The interest in metal-free enantioselective organocatalysis has increased enormously in the last 10 years.[104] The majority of organocatalysts are amines that typically form reactive intermediates such as iminium ions and enamines.[105, 106]

In 2000 the MACMILLAN group introduced a new secondary amine-based organocatalyst for a range of transformations which were formally the domain of Lewis acid catalysis.[107, 108] The formation of iminium ion intermediates led to sufficiently activated species due to LUMO-lowering, which resembles Lewis acid catalysis (Scheme 1.9).



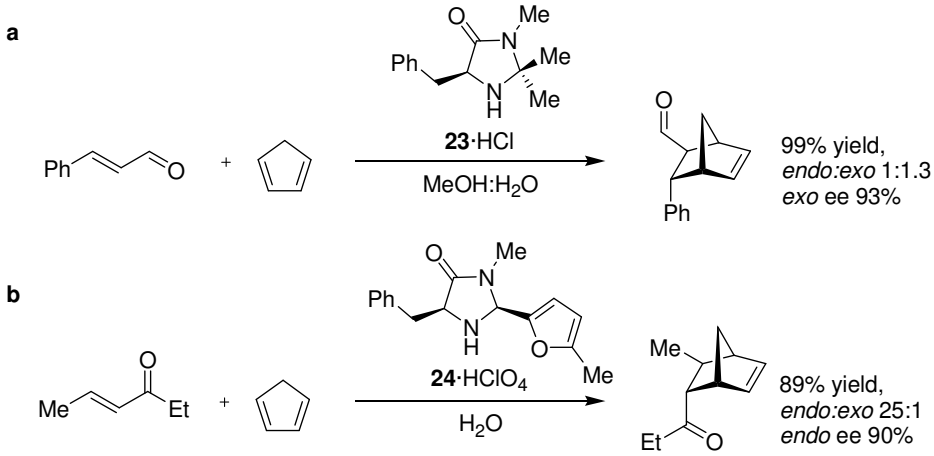
Scheme 1.9: *Iminium ion activation through LUMO-lowering.*

The first highly enantioselective Diels-Alder reaction was performed using 5 mol% of imidazolidinone catalyst **23**·HCl (Scheme 1.10, **a**).[107] Steric constraints were used in the catalyst design to induce high stereocontrol in the iminium ion intermediate. The imidazolidinone-catalysed Diels-Alder reaction has been studied extensively to achieve

[*] For catalyst **21** illustrated in Scheme 1.8 absolute configuration has been matched to the absolute configuration of the Diels-Alder adduct.

catalyst recovery: for example immobilisation on solid support [109] and fluorous variants which allowed recovery by fluorous-solid phase extractions[110] were reported.

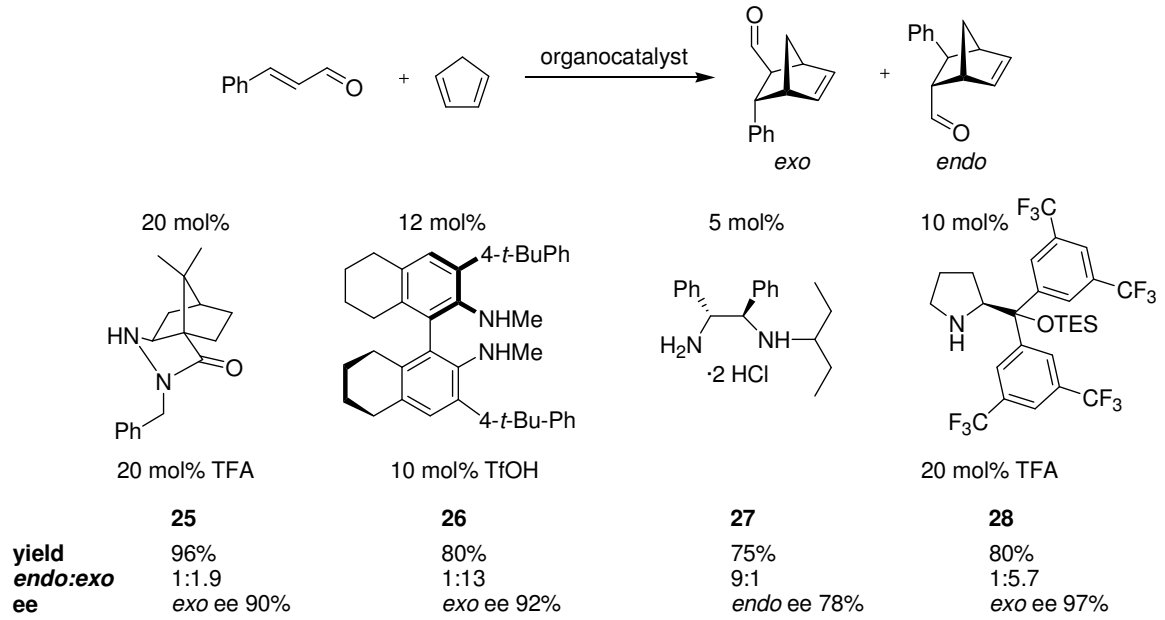
MACMILLAN also used imidazolidinone catalyst **24**·$HClO_4$ to achieve high asymmetric induction in the Diels-Alder reaction between simple, acyclic enones, considered challenging substrates, and cyclopentadiene (Scheme 1.10, **b**).[111] An advantage of the imidazolidinone catalysts is the commercial availability.



Scheme 1.10: (***a***) *The first highly enantioselective organocatalytic Diels-Alder reaction with α,β-unsaturated aldehydes.* (***b***) *The first enantioselective Diels-Alder reaction with simple enones.*

A number of other organocatalysts have been used successfully in Diels-Alder reactions (Scheme 1.11). LEMAY and OGILVIE demonstrated that cyclic hydrazide catalyst **25**, readily synthesised from camphorsulfonic acid, catalyses the Diels-Alder reaction in water with high yields, moderate diastereo- and good enantioselectivities.[112] The novel binaphthyl-based diamine catalyst **26** showed unprecedented high *exo* selectivity as well as moderate to good enantioselectivities.[113, 114] The only example for high *endo* selectivities in an organocatalysed Diels-Alder reactions was reported by HA and co-workers, using *N*-alkylated bisammonium catalyst **27**.[115]

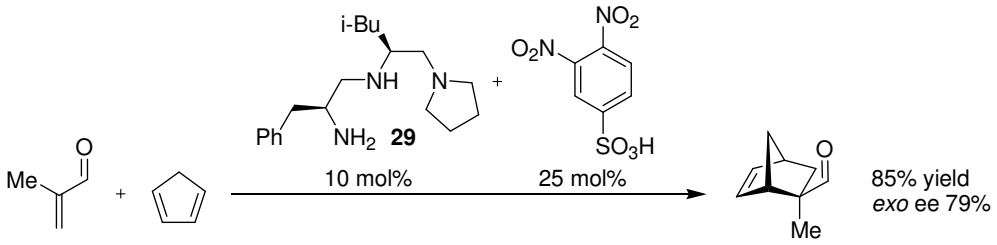
HAYASHI reported the application of diarylprolinol silyl ether **28** combined with an acid to achieve good *exo* selectivities and enantioselectivities (generally above 94%).[116] Even alkyl- and heteroaryl-substituted acroleins were successfully converted with high enantioselectivities to the corresponding cycloadduct.



	25	**26**	**27**	**28**
yield	96%	80%	75%	80%
endo:exo	1:1.9	1:13	9:1	1:5.7
ee	*exo* ee 90%	*exo* ee 92%	*endo* ee 78%	*exo* ee 97%

Scheme 1.11: *Enantioselective Diels-Alder reactions with α,β-unsaturated aldehydes.*[*]

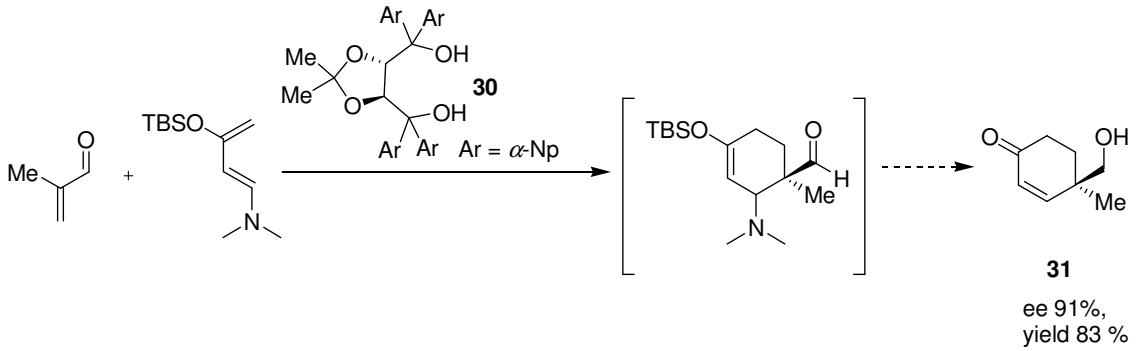
ISHIHARA and NAKANO accomplished the first enantioselective organocatalysed Diels-Alder reaction using α-substituted acroleins as dienophiles (Scheme 1.12).[117] In contrast to secondary amine imidazolidinone catalysts, which were almost inactive towards these substrates in cyclopropanation reactions,[118] the primary amine moiety of the phenylalanine-derived organocatalyst **29** activated α-substituted acroleins sufficiently, presumably through aldimine formation.



Scheme 1.12: *The first enantioselective organocatalysed Diels-Alder reaction with α-substituted acroleins.*

An alternative to secondary amines are catalysts which induce asymmetric induction through hydrogen bonding. RAWAL and co-workers introduced the TADDOL-organocatalysed Diels-Alder reaction, which produced good enantioselectivities and yields with α-substituted acroleins. The cycloadducts were isolated as the corresponding cyclohexanone **31** (Scheme 1.13).[119]

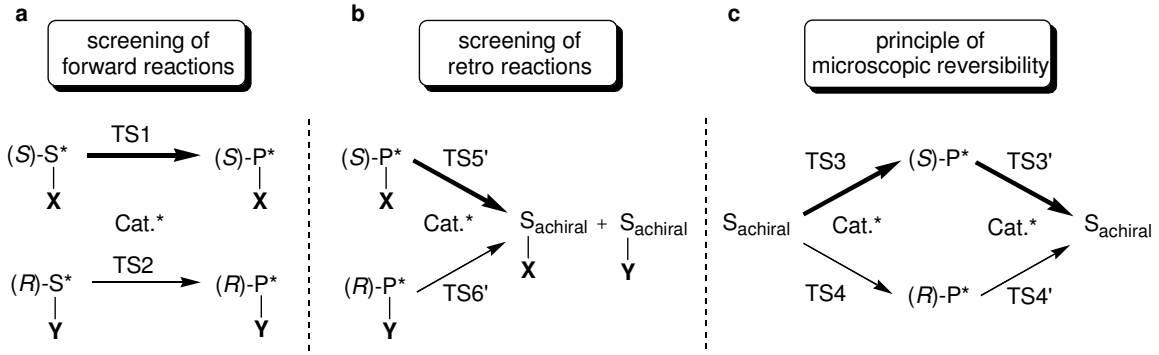
[*] For catalyst **25** illustrated in Scheme 1.11 absolute configuration has been matched to the absolute configuration of the Diels-Alder adducts.



Scheme 1.13: *Hydrogen bonding-promoted organocatalytic Diels-Alder reaction.*

1.4 Concept of Retro Reactions in ESI MS Screening

A method for the identification of enantioselective chiral catalysts for the kinetic resolution based on ESI MS was developed in our group (Section 1.1.5).[9] Accordingly, the chiral catalyst undergoes complexation with the chiral quasienantiomeric substrates. The ratio of the resulting mass-labelled reaction intermediates is analysed to determine the catalyst's inherent enantioselectivity (Scheme 1.14, **a**). This screening approach is only feasible when two quasienantiomeric substrates carrying the stereochemical information are used. However, for reactions, which lead from prochiral substrates to two enantiomeric products, this method cannot be applied. Therefore a new screening strategy was devised: by simply screening the retro reaction using chiral quasienantiomeric products as substrates, the application of the ESI MS screening method became possible (Scheme 1.14, **b**). In accordance to the principle of microscopic reversibility the retro reaction should proceed with the same selectivity as the forward reaction (Scheme 1.14, **c**). Screening of the retro reaction offers therefore the possibility to indirectly determine the catalyst's selectivity of the forward, product-forming reaction.

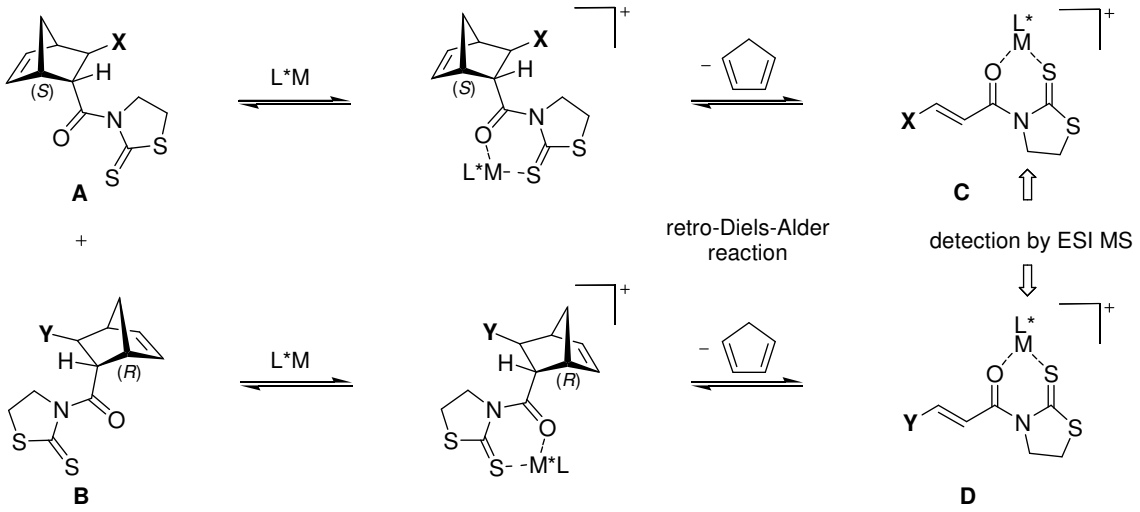


Scheme 1.14: *General scheme describing (**a**) the mass spectrometric approach for a screening method for forward reactions using chiral mass-labelled quasienantiomeric substrates (S)-S*$_{-X}$ and (R)-S*$_{-Y,}$ (**b**) for screening of retro reactions using chiral quasienantiomeric products (S)-P*$_{-X}$ and (R)-P*$_{-Y}$ leading to achiral mass-labelled substrates $S_{achiral\text{-}X}$ and $S_{achiral\text{-}Y}$. (**c**) By the principle of microscopic reversibility with TS3=TS3' and TS4=TS4' selectivities obtained for the retro reaction should be applicable to the forward reaction.*

1.5 Objectives

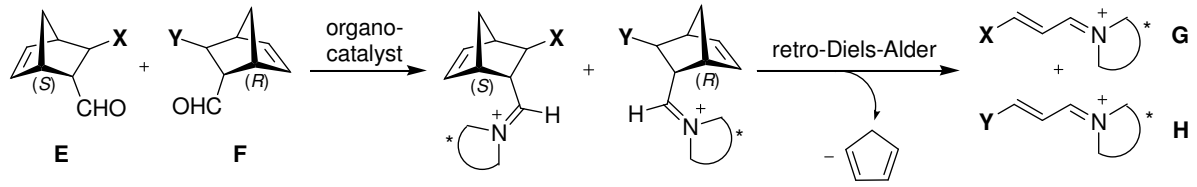
The aim of this thesis was the development of an ESI MS based screening method for enantioselective Diels-Alder catalysts. The highly enantioselective and well established bis(oxazoline)copper(II)-catalysed Diels-Alder reaction was chosen for the development of this screening method.

The catalysts' enantioselectivity was investigated by screening the retro reaction, because the chiral Diels-Alder products carry the stereochemical information necessary for the chiral catalyst to discriminate between the enantiomers. Mass-labelled enantiomeric Diels-Alder adducts **A** and **B** ("quasienantiomers") were used as substrates to give the charged catalytic intermediates **C** and **D**, which should be detectable and distinguishable by ESI MS (Scheme 1.15). The mass peak ratio of **C** and **D** should directly reflect the intrinsic enantioselectivity of the chiral catalyst. In accordance to the principle of microscopic reversibility the screening results obtained for the retro reaction should be readily applicable to the forward reaction.



Scheme 1.15: *General concept for screening chiral Diels-Alder catalysts.* ***X*** *and* ***Y*** *represent the mass labels.*

Extension of this concept to organocatalysed retro-Diels-Alder reactions was anticipated. When using secondary amine organocatalysts the catalytic intermediates correspond to charged iminium ions and should be readily detectable by ESI MS (Scheme 1.16).



Scheme 1.16: *General concept for screening chiral Diels-Alder organocatalysts.* ***X*** *and* ***Y*** *represent the mass labels.*

Simultaneous screening of several catalysts in the same reaction mixture could significantly accelerate the screening process. For this reason a screening protocol for organocatalyst mixtures was developed.

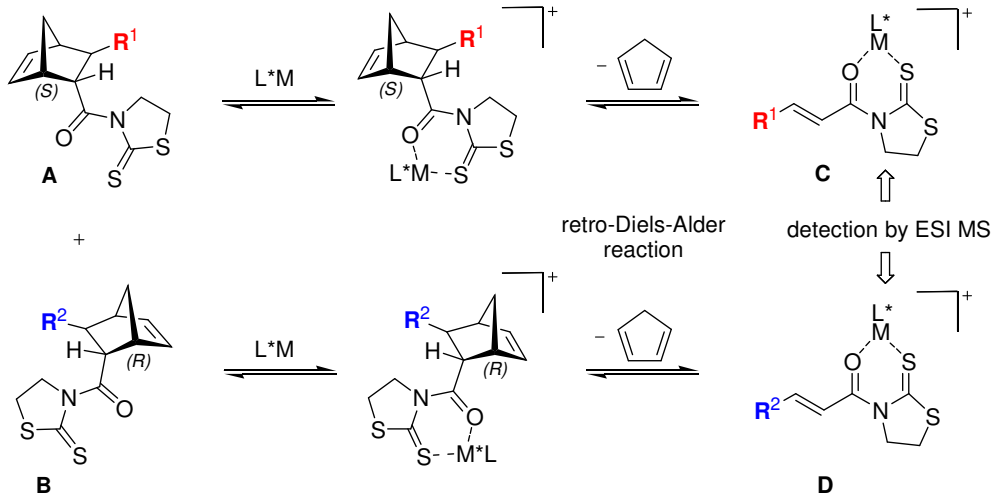
Chapter 2

ESI MS Screening of Chiral Copper(II)-Catalysts

2 ESI MS Screening of Chiral Copper(II)-Catalysts

2.1 Introduction

We were interested in developing an ESI MS screening method for the identification of highly selective chiral catalyst in the retro-Diels-Alder reaction (Scheme 2.1). By the principle of microscopic reversibility the information gained in the retro reaction should be directly applicable to the corresponding forward reaction. The Diels-Alder reaction is a powerful transformation for the construction of complex molecules with up to four stereocenters. Identification of highly enantioselective catalysts will further increase its value for synthetic applications.[76, 77]



Scheme 2.1: *Retro-Diels-Alder reaction using quasienantiomeric Diels-Alder adducts. R^1 and R^2 represent the mass labels.*

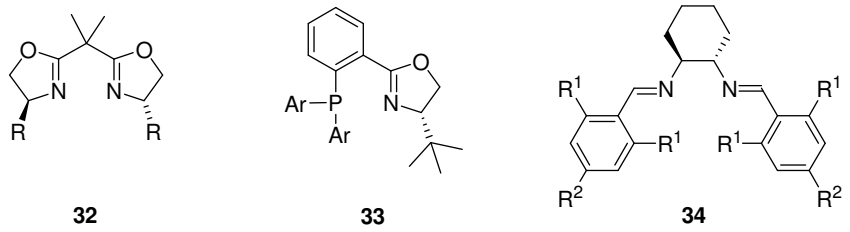
The *endo* Diels-Alder adducts **A** and **B** have different mass labels represented by R^1 and R^2 (Scheme 2.1). The mass-labelled *endo* Diels-Alder adducts **A** and **B** undergo complexation with the chiral catalyst L*M. The resulting charged adduct-catalyst complexes can be detected by ESI MS along with dienophile-catalyst complexes of interest **C** and **D**, which are generated by loss of cyclopentadiene. The different masses of **C** and **D** enable the complexes to be distinguished by mass spectrometry. The ratio of **C** and **D** reflects the ability of the chiral catalyst to enantiodiscriminate and gives a direct measure of the enantiomeric ratio. As the dienophiles are achiral, they cannot be distinguished by a chiral catalyst. It is therefore necessary to examine the retro-Diels-Alder reaction instead of the forward Diels-Alder reaction, because the Diels-Alder adducts **A** and **B** contain the stereochemical information.

2.2 Synthesis of Quasienantiomeric Diels-Alder Adducts and Chiral Ligands

The synthetic requirements for the quasienantiomeric Diels-Alder adducts were: both quasienantiomers should be enantiomerically pure and either the *endo* or the *exo* diastereoisomer must be used. In that way equal conditions regarding each quasienantiomer are ensured leading to reliable screening results.

These requirements were fulfilled by using bis(oxazoline)(box)copper(II) complexes for the synthesis of the quasienantiomers. These complexes achieve very high asymmetric induction in the Diels-Alder reaction and offer a broad substrate scope both for the dienes and dienophiles.[88, 91, 92, 120, 121] C_2-symmetric bis(oxazoline) ligands **32** have been developed independently by several research groups (Figure 2.1).[87, 122-124] Since their first successful applications in asymmetric copper-catalysed cyclopropanations,[122-124] aziridination[123] and Diels-Alder reactions[87] bis(oxazolines) have been employed in an impressive number of metal-catalysed transformations.[92, 125]

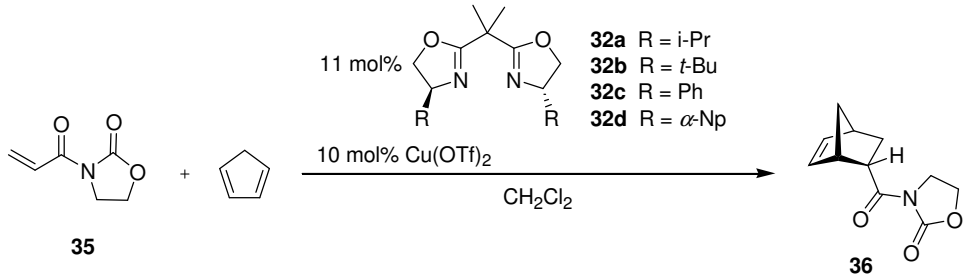
Prominent ligands used in the copper(II)-catalysed enantioselective Diels-Alder reaction apart from bis(oxazolines) **32**[91] are phosphinooxazolines **33**[126] and bis(imines) **34**[89] (Figure 2.1).



32 **33** **34**

Figure 2.1: *Prominent ligands applied in the copper(II)-catalysed enantioselective Diels-Alder reaction.*

EVANS and co-workers screened several bis(oxazoline) ligands for the copper(II)-catalysed Diels-Alder reaction of acrylate imide **35** and cyclopentadiene (Scheme 2.2). The best ligand in terms of diastereoselectivity and enantioselectivity turned out to be the *t*-Bu-box ligand **32b** (*endo:exo* 98:2, *endo* ee >98%), followed by the i-Pr-box **32a**, α-Naphthyl-box **32d** and the Ph-box **32c**.[91]

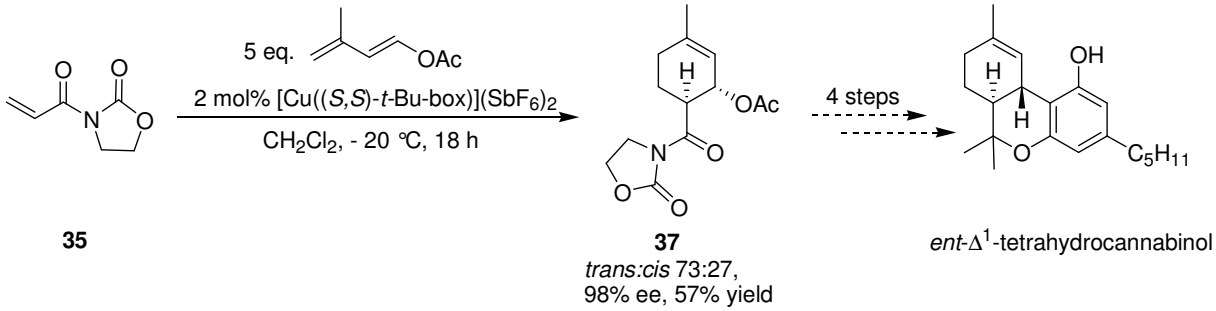


35 **36**

Scheme 2.2: *Enantioselective Diels-Alder reaction with acrylate imide **35** and cyclopentadiene.*

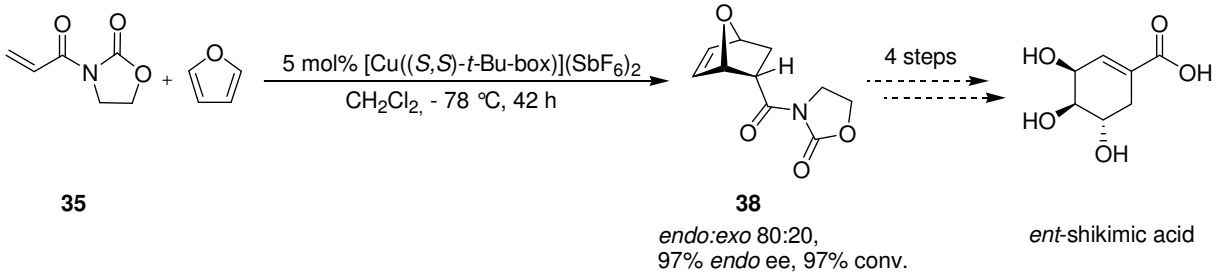
The scope of the enantioselective Diels-Alder reaction was tested by using different dienes and dienophiles. Alkyl-substituted dienes, such as cyclohexadiene or 1-phenylbutadiene, and heteroatom-substituted dienes were also shown to undergo the Diels-Alder reaction with high enantioselectivities.[121]

The cycloaddition of 1-acetoxybutadiene with acrylate imide **35** as dienophile constitutes the first step of the synthesis of *ent*-Δ^1-tetrahydrocannabinol, demonstrating the synthetic value of bis(oxazoline)copper(II) systems for highly enantioselective synthesis (Scheme 2.3).[121]



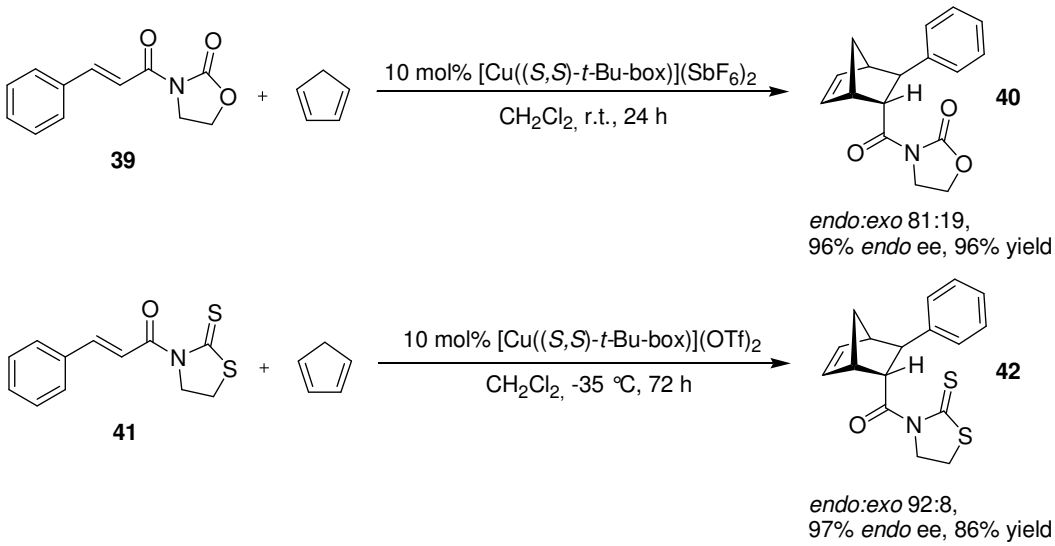
Scheme 2.3: *Enantioselective Diels-Alder reaction with heteroatom-substituted dienes.*

Although furan is generally considered a poor diene in Diels-Alder reactions[127, 128] EVANS and co-workers successfully catalysed the Diels-Alder reaction of acrylate imide **35** and furan using [Cu((*S,S*)-*t*-Bu-box)]$(SbF_6)_2$ with excellent enantioselectivity (Scheme 2.4). Cycloadduct **38** was converted to *ent*-shikimic acid in four steps and a 37% overall yield from acrylate imide **35**.[129]



Scheme 2.4: *Using furan as diene in the enantioselective Diels-Alder reaction.*

To further enhance the substrate scope 2-oxazolidinone and 2-thiazolidinone-derived dienophiles were used in the Diels-Alder reaction.[91] Very high diastereoselectivities and enantioselectivities were obtained for these substrates (Scheme 2.5).



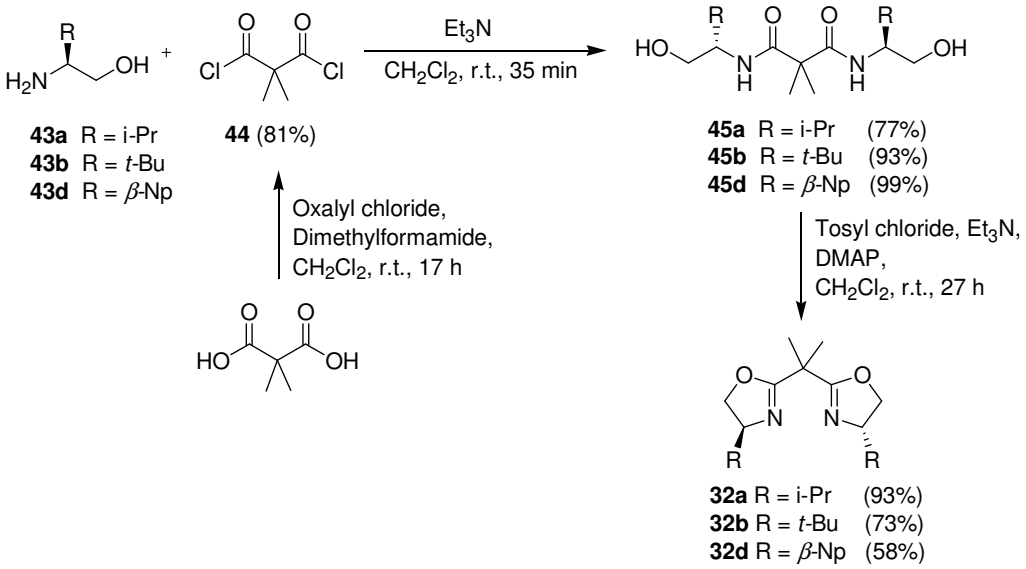
Scheme 2.5: *Enantioselective Diels-Alder reaction with ß-substituted dienophiles.*[91]

HELMCHEN and co-workers reported the application of phosphinooxazoline ligands **33** in the copper(II)-catalysed enantioselective Diels-Alder reaction.[126] Originally these non-symmetrical P,N-ligands were developed for the enantioselective palladium-catalysed allylic substitution reaction,[130, 131] but they were also applied in other metal-catalysed transformations such as palladium-catalysed Heck-reactions,[132] silver-catalysed 1,3-dipolar cycloaddition[133] and iridium-catalysed asymmetric hydrogenation.[134, 135] Enantioselectivity in the copper(II)-catalysed Diels-Alder reaction depends strongly on the steric requirements of the P-aryl groups. Increasing the steric demands from phenyl- to α-Naphthyl-phosphine led to an increase in observed enantiomeric excess.[126] Generally enantioselectivities were lower (up to 97% *endo* ee) than those obtained with bis(oxazoline)copper(II) complexes.[91]

Bis(imine) ligands **34**, initially derived from salen (*N,N'*-bis(salicylideneaminoethane)), have been successfully used for the enantioselective copper(II)-catalysed Diels-Alder reaction of *ß*-substituted dienophiles and cyclopentadiene.[89] JACOBSEN showed their first application in the highly enantioselective copper(I)-catalysed asymmetric aziridination of alkenes.[136] Bis(imines) represent a very attractive ligand class, because they are easily prepared from commercially available starting material and can be readily tuned for specific electronic and steric demands.[137, 138] EVANS and co-workers found that in the copper(II)-catalysed Diels-Alder reaction bis(imine) ligands **34** gave significantly lower diastereo- and enantioselectivities for the 2-oxazolidinone-derived dienophiles and cyclopentadiene (up to 94% *endo* ee) than the bis(oxazoline)copper(II) complexes.[89] In the case of the sulphur-derived dienophiles the diastereoselectivities were similar to those obtained for the bis(oxazoline)copper(II) complexes, but enantioselectivities were significantly lower.[89]

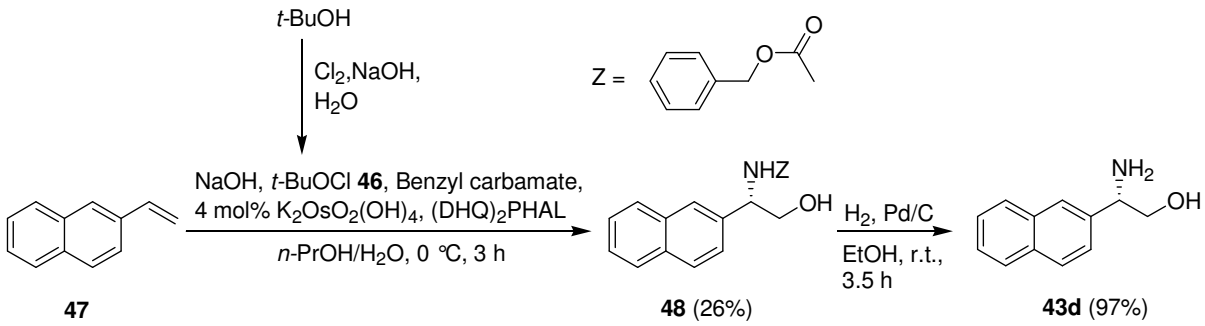
2.2.1 Bis(oxazoline) Ligand Synthesis

All chiral bis(oxazoline) ligands were synthesised according to a procedure previously reported by EVANS and co-workers.[139] Using this method four bis(oxazolines) were obtained in three steps in moderate to excellent yields (Scheme 2.6).



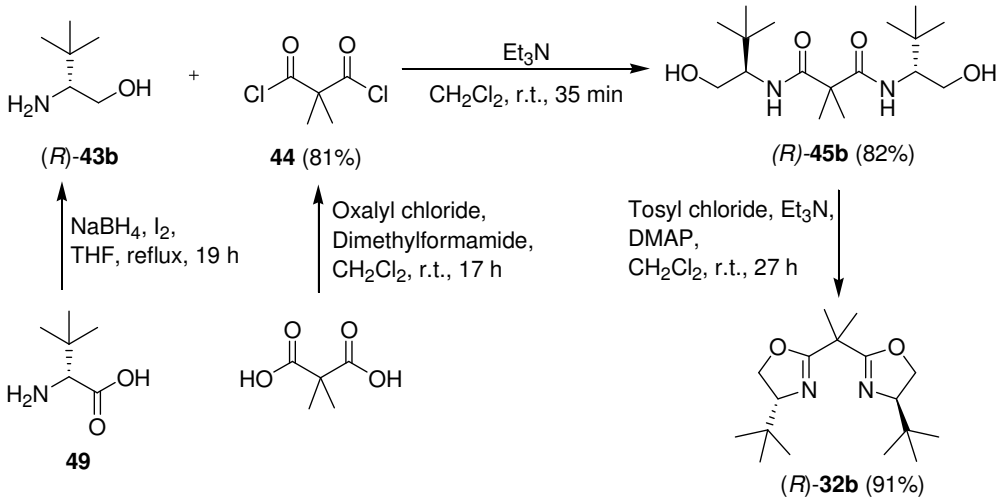
Scheme 2.6: *Synthesis of bis(oxazoline) ligands **32a**, **32b** and **32d**.*

Amino alcohols **43a** and **43b** were commercially available. Amino alcohol **43d** was prepared by asymmetric aminohydroxylation (Scheme 2.7). By the method of SHARPLESS benzyl *N*-chlorocarbamate BnOCONCl was generated *in situ* from freshly prepared *t*-BuOCl **46** and benzyl carbamate. Benzyl *N*-chlorocarbamate and 2-vinylnaphthalene **47** then underwent an osmium-catalysed asymmetric aminohydroxylation to give protected amino alcohol **48**.[140] Cleavage of the protecting group using standard conditions gave the enantiopure amino alcohol **43d** in excellent yields.[141]



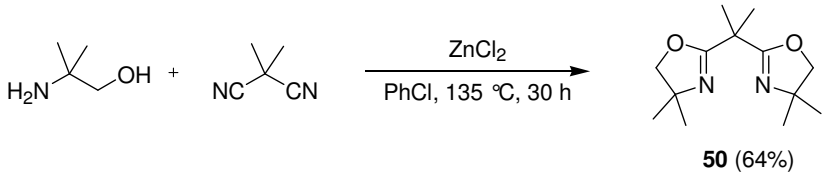
Scheme 2.7: *Synthesis of amino alcohol **43d**, precursor for the (S,S)-β-Np-box ligand **32d**.*

ESI MS control experiments required (*R,R*)-*t*-Bu-box ligand (*R*)-**32b**. (*R*)-*t*-Leucine **49** was converted to (*R*)-*t*-leucinol (*R*)-**43b**, acetylated and ring-closed to give (*R,R*)-*t*-Bu-box ligand (*R*)-**32b** in excellent yield (Scheme 2.8).



Scheme 2.8: *Synthesis of (R,R)-t-Bu-box ligand (R)-**32b**.*

Achiral bis(oxazoline) ligand **50** was synthesised by a one step synthesis using a procedure reported by LEE *et al.* (Scheme 2.9).[142]

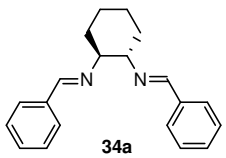


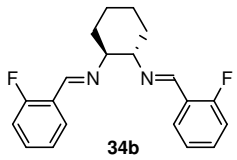
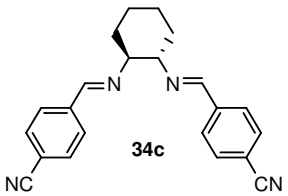
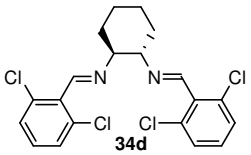
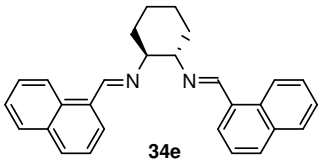
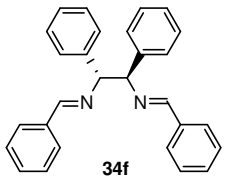
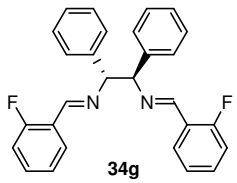
Scheme 2.9: *Synthesis of achiral bis(oxazoline) ligand **50**.*

2.2.2 Bis(imine) Ligand Synthesis

Two general methods for the preparation of bis(imine) ligands have been reported. [89, 137, 138] Bis(imines) **34a**-**g** were synthesised by condensation of the corresponding aromatic aldehyde and (1*S*,2*S*)-(+)-diaminocyclohexane or (1*R*,2*R*)-(+)-1,2-diphenylethaneamine (Table 2.1).

Table 2.1: *Synthesis of several bis(imine) ligands.*

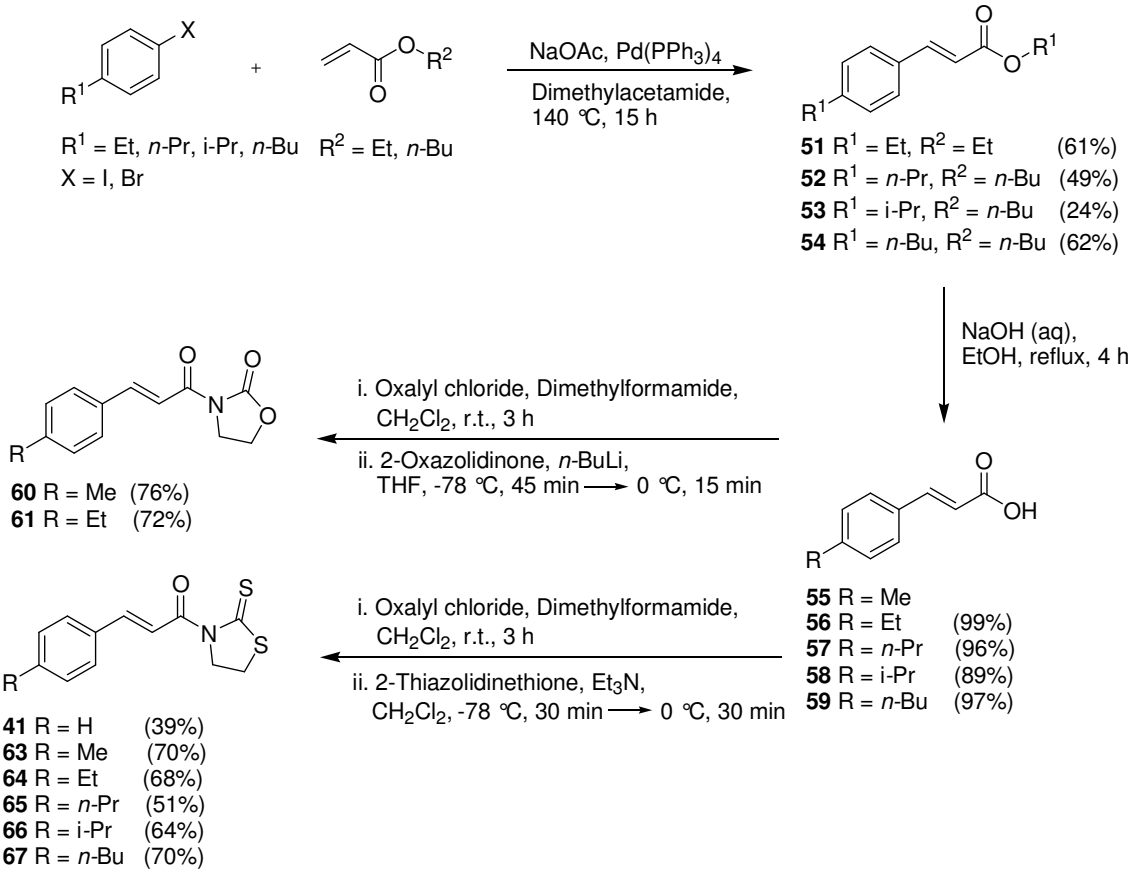
Entry	Ligand	Conditions	Yield (%)
1	 **34a**	MeOH, 30 min	41

Entry	Ligand	Conditions	Yield (%)
2	 **34b**	MeOH, 30 min	19
3	 **34c**	MeOH, 30 min	37
4	 **34d**	MeOH, 10 min	100
5	 **34e**	EtOH, 60 min	16
6	 **34f**	EtOH, 60 min	81
7	 **34g**	EtOH, 60 min	64

2.2.3 Synthesis of Dienophiles

For the synthesis of the quasienantiomers aryl-substituted α,β-unsaturated dienophiles were used to introduce the mass label. Mass labels in the aryl *para*-position were assumed to be sufficiently removed from the reactive site of the molecule such that they would not influence the selectivity or reactivity of the retro-Diels-Alder reaction.[9]

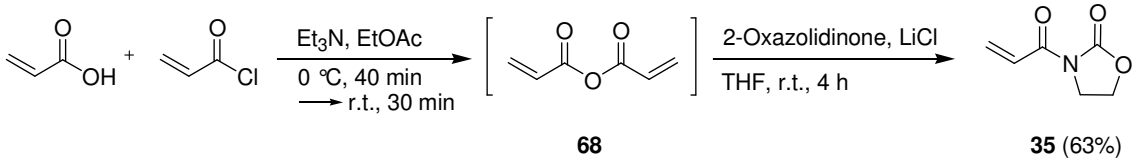
The synthesis of the 2-oxazolidinone- and 2-thiazolidinethione-derived dienophiles was accomplished in three steps: a Heck reaction, followed by saponification and introduction of the 2-oxazolidinone or the 2-thiazolidinethione moiety (Scheme 2.10).



Scheme 2.10: *Dienophile synthesis.*

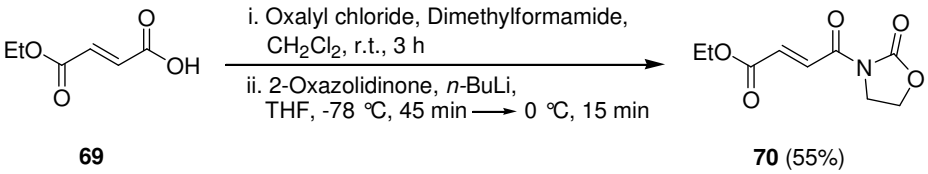
The acrylates **51**-**54** were synthesised according to the procedure of SCHULTZ with moderate yields.[143] Saponification was accomplished in near quantitative yield by heating acrylates **51**-**54** at reflux for 4 hours with aqueous sodium hydroxide solution in ethanol. By the method of EVANS, carboxylic acids **55**-**59** were converted to the 2-oxazolidinone-derived dienophiles **60** and **61** by addition of oxalyl chloride and 2-oxazolidinone.[144] After purification, the colourless crystalline products displayed excellent shelf life for at least 3 years at room temperature. 2-Thiazolidinethione-derived dienophiles **41** and **63**-**67** were prepared as described for the 2-oxazolidinone-derived dienophiles but Et_3N and 2-thiazolidinethione were used in place of *n*-BuLi and 2-oxazolidinone.

By a modified procedure of HO and MATHRE acrylate imide **35** was synthesised from *in situ* prepared anhydride **68** and 2-oxazolidinone (Scheme 2.11).[145]



Scheme 2.11: *Acrylate imide **35** synthesis.*

Fumarate-derived dienophile **70** was prepared using a one pot procedure from fumaric acid monoethyl ester **69** (Scheme 2.12).[91]



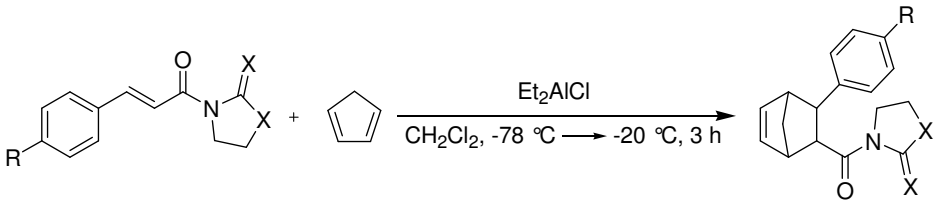
Scheme 2.12: *Synthesis of fumarate-derived dienophile **70**.*

2.2.4 Synthesis of Diels-Alder Adducts

For ESI MS screening experiments enantiopure as well as racemic Diels-Alder adducts were needed. These were synthesised in two ways: asymmetric Diels-Alder adducts were obtained by using either [Cu(*t*-Bu-box)](OTf)$_2$ or [Cu(*t*-Bu-box)](SbF$_6$)$_2$,[91] diethylaluminium chloride was used for obtaining racemic Diels-Alder adducts.[144]

The cycloaddition of 2-oxazolidinone-derived dienophiles **60** and **61** or 2-thiazolidinone-derived dienophiles **41** and **63**-**67** and cyclopentadiene using diethylaluminium chloride gave racemic Diels-Alder adducts *rac*-**71**-**76** with very high diastereoselectivities and excellent conversions (Table 2.2). The diastereoselectivities of the sulphur-derived dienophiles were generally lower than for the 2-oxazolidinone-derived dienophiles (Table 2.2, entry 1 and 4). Diastereoisomers were separated by flash column chromatography.

Table 2.2: *Synthesis of racemic Diels-Alder adducts.*



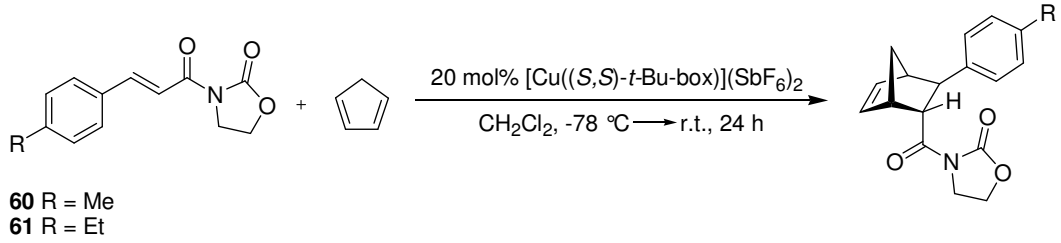
Entry	DA Adduct	*Endo:Exo*[a]	Conversion (%)[a] (Yield (%)[b])
1	*rac*-**71** R = H, X = O	96:4	100 (84)
2	*rac*-**72** R = Me, X = O	97:3	100 (79)

Entry	DA Adduct	*Endo:Exo*[a]	Conversion (%)[a] (Yield (%)[b])
3	*rac*-**73** R = Et, X = O	96:4	85 (58)
4	*rac*-**74** R = H, X = S	92:8	100 (63)
5	*rac*-**75** R = Me, X = S	93:7	96 (75)
6	*rac*-**76** R = Et, X = S	91:9	100 (74)

a Determined by ^{1}H NMR of the crude product; *b* Pure *endo* Diels-Alder adduct was obtained.

Enantioenriched Diels-Alder adducts (*S*)-**77** and (*S*)-**78** were synthesised from 2-oxazolidinone-derived dienophiles **60** or **61** and cyclopentadiene using 20 mol% of [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ (Table 2.3).[91] Traces of water were found to severely diminish the catalyst activity. The colour of the catalyst mixture gave reliable evidence of the presence of a catalyst-water adduct: a blue reaction mixture indicated a catalyst-water adduct, a green reaction mixture indicated the absence of water.

Table 2.3: *Synthesis of 2-oxazolidinone-derived Diels-Alder adducts (S)-77 and (S)-78.*



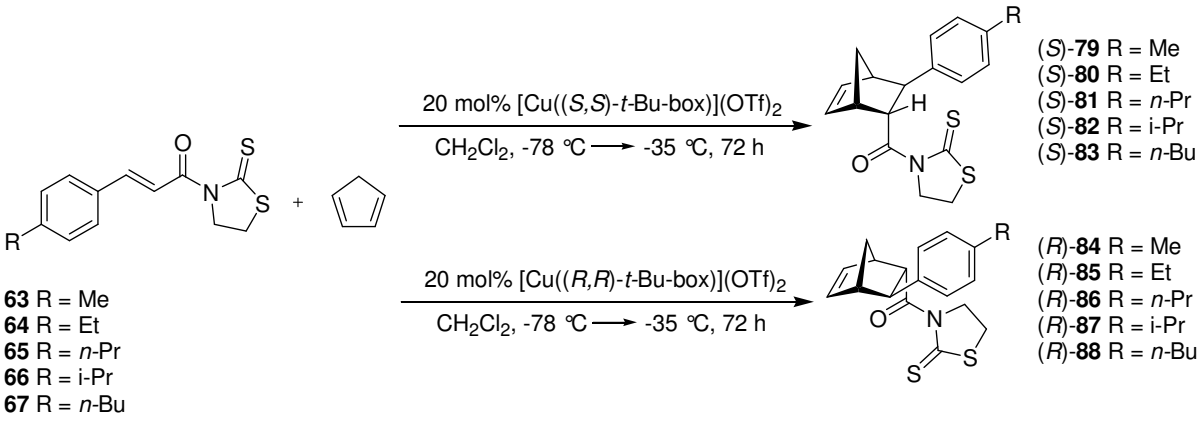
60 R = Me
61 R = Et

Entry	DA Adduct	*Endo:Exo*[a]	*Endo* ee (%)[b] (*Exo* ee (%))	Conversion (%)[a] (Yield (%)[c])
1	(*S*)-**77**	75:25	95 (86)	100 (59)
2	(*S*)-**78**	67:33	89	56 (40)

a Determined by ^{1}H NMR of the crude product; *b* Determined by chiral HPLC; *c* Pure *endo* Diels-Alder adduct was obtained.

[Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ was used for the synthesis of sulphur-containing Diels-Alder adducts (*S*)-**79**-**83** and their enantiomeric analogues (*R*)-**84**-**88** were synthesised using the [Cu((*R,R*)-*t*-Bu-box)](OTf)$_2$ catalyst (Table 2.4).[121] Conversions were in all cases near quantitative. Independent of the aryl-substituent diastereoselectivities and enantioselectivities were similar for all products. The fact that the Diels-Alder adducts were obtained as yellow needles (except for (*S*)-**79** and (*R*)-**84**) greatly facilitated their handling.

Table 2.4: *Synthesis of 2-thiazolidinethione-derived Diels-Alder adducts.*



Entry	DA Adduct	*Endo:Exo*[a]	*Endo* ee (%)[b]	*Endo* ee (%) after Recrystallisation	Conversion (%)[a] (Yield (%)[c])
1	(*S*)-**79**	97:3	95	-	99 (79)
2	(*R*)-**84**	97:3	94	-	>99 (87)
3	(*S*)-**80**	97:3	93	>99	>99 (87)
4	(*R*)-**85**	97:3	94	99	>99 (74)
5	(*S*)-**81**	97:3	94	99	100 (67)
6	(*R*)-**86**	97:3	94	>99	99 (71)
7	(*S*)-**82**	97:3	93	>99	100 (79)
8	(*R*)-**87**	97:3	94	>99	100 (87)
9	(*S*)-**83**	96:4	93	>99	100 (74)
10	(*R*)-**88**	97:3	93	99	100 (66)

a Determined by ^{1}H NMR of the crude product; *b* Determined by chiral HPLC; *c* Pure *endo* Diels-Alder adduct was obtained.

X-ray analysis of (*R*)-**86** confirmed the assumed configuration (Figure 2.2).

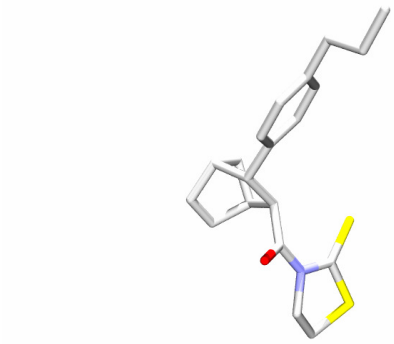
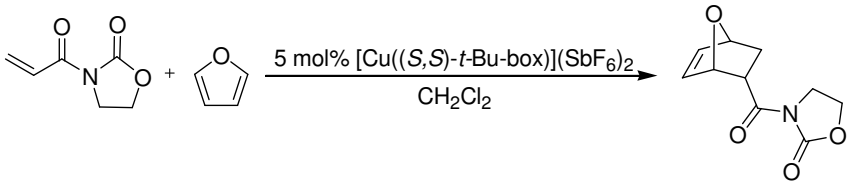


Figure 2.2: *Crystal structure of Diels-Alder adduct* (*R*)-***86***.

Furan-derived Diels-Alder adduct **38** was synthesised according to the procedure by EVANS.[121] It was not possible to obtain the enantiopure product when using acrylate imide **35**, furan and 5 mol% of catalyst. Even after recrystallisation the *endo* Diels-Alder adduct was only obtained with an enantiomeric excess of 77% (Table 2.5). The combination of higher temperatures and longer reaction times resulted in a reversed *endo:exo* ratio with the *exo* diastereoisomer predominantly formed (Table 2.5, entry 1 and 3). Shortening of the reaction times (Table 2.5, entry 2) and lowering the temperatures (Table 2.5, entry 4) resulted in the *endo* diastereoisomer becoming more favoured. EVANS reported that at higher temperatures the cycloaddition reaction presumably was in a rapid equilibrium favouring the formation of the racemic *exo* Diels-Alder products.[129]

Table 2.5: *Asymmetric Diels-Alder reaction with furan as diene.*



35 **38**

Entry	Conditions	*Endo:Exo*[a]	Conversion (%)[a]
1	RT, 22 h	22:78	17
2	-20 °C, 2.5 h	65:35 (*endo* ee 77%)[b]	86
3	-20 °C, 24 h	45:55	83
4	-78 °C, 42 h	82:18	9

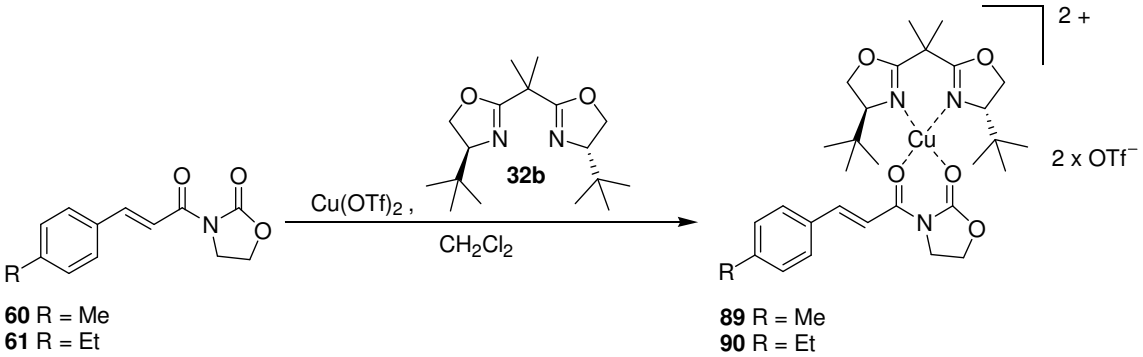
a Determined by ^{1}H NMR of the crude product; *b* Determined by chiral HPLC.

2.3 Development of Screening Method

To examine catalyst-reactant complexes the most important prerequisite is their detection by ESI MS. Therefore complexes must be charged or converted into charged species and they must have a sufficiently long lifetime to be detected by ESI MS. To evaluate which model system fulfilled the criteria, preliminary studies examining the reaction intermediates for the forward Diels-Alder reaction were conducted.

2.3.1 2-Oxazolidinone-Derived Quasienantiomers

To test if 2-oxazolidinone-derived species were suitable for ESI MS screening, an equimolar mixture of either dienophile **60** or **61** and [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ in dichloromethane was stirred at room temperature (Scheme 2.13). Aliquots of the reaction mixtures were taken at intervals (15 minutes to 24 hours) and analysed by ESI MS. Under these conditions no dienophile-catalyst complexes were detected (Figure 2.3). The only mass peaks detected at *m/z* 295, 313 and 651 were related to the *t*-Bu-box ligand **32b**. These findings were confirmed by examination of the catalyst solution showing the same mass peaks.



Scheme 2.13: *Anticipated formation of dienophile-catalyst complex **89** or **90**.*

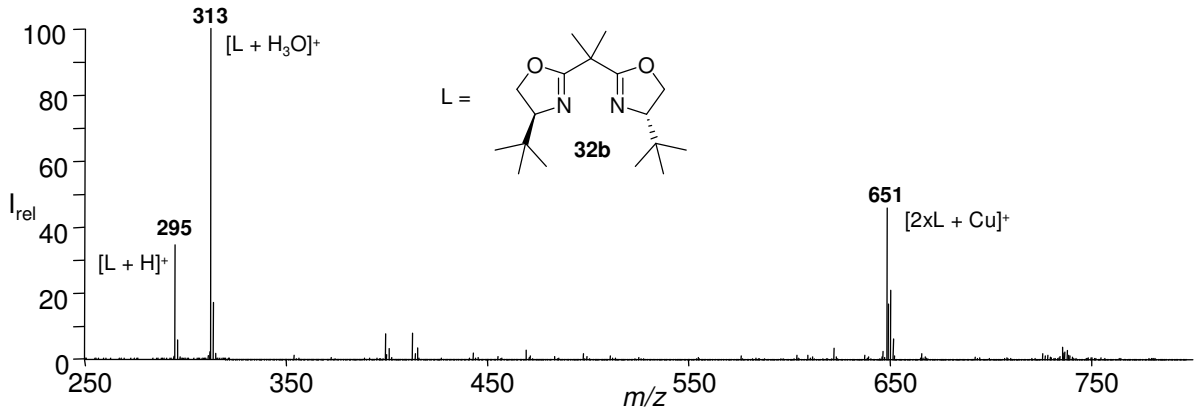
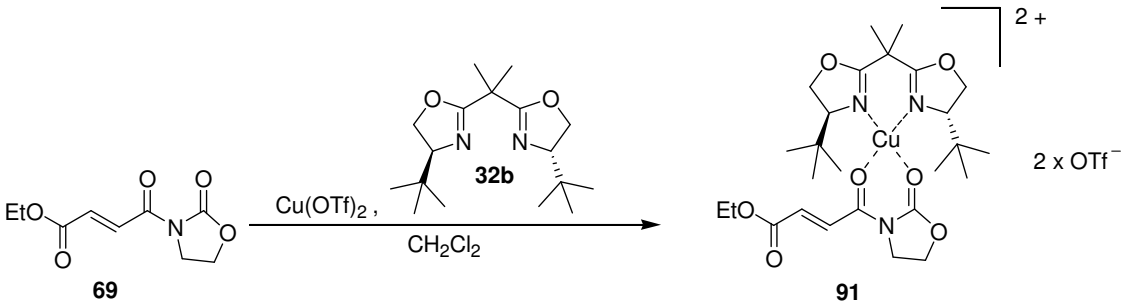


Figure 2.3: *ESI MS spectrum of dienophile **60** and [Cu((S,S)-t-Bu-box)](OTf)$_2$.*

Neither variation of the solvent (acetone, acetonitrile, methanol or methanol-water) and temperature (-78 °C to 40 °C) nor the use of a different fumarate-derived dienophile **69** resulted in detectable dienophile-catalyst complexes **89**, **90** or **91** (Scheme 2.14).

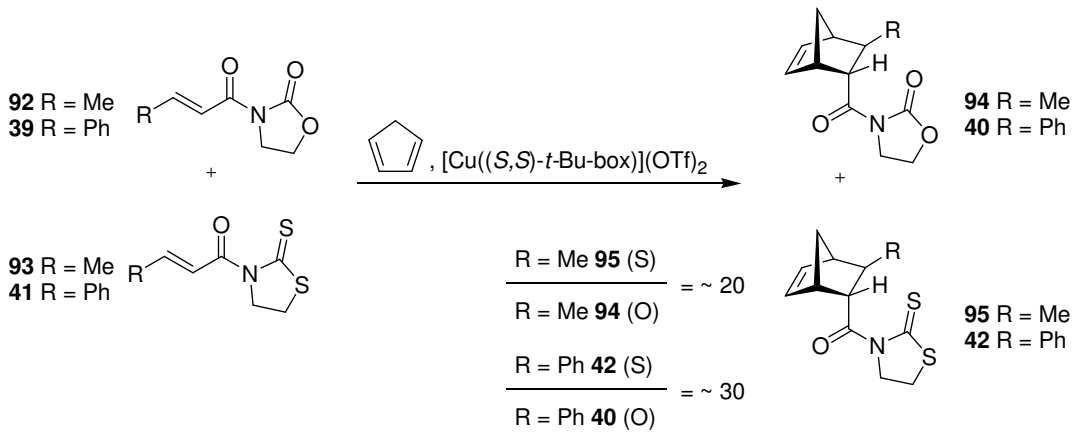


Scheme 2.14: *Anticipated formation of dienophile-catalyst complex **91**.*

Mass peak *m/z* 651, corresponding to the singly charged {Cu[(*S,S*)-*t*-Bu-box]$_2$} complex, was observed in all spectra implying that the dienophile-catalyst complex was presumably not stable under ESI MS conditions. We thought that this problem arose because the non-covalent interactions of the dienophile and the copper(II)-catalyst were not sufficiently strong for the complex to survive the ESI MS nebulisation process.

2.3.2 2-Thiazolidinethione-Derived Quasienantiomers

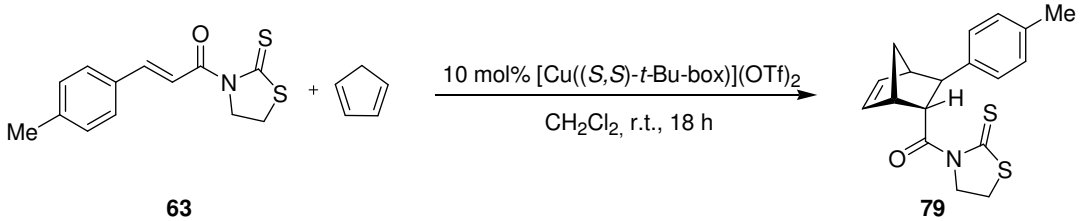
As 2-oxazolidinone-derived dienophiles were unsuitable for detection by ESI MS, dienophiles with stronger binding affinity to copper(II) had to be found. EVANS and co-workers reported that 2-thiazolidinethione-derived dienophiles showed enhanced reactivity in the asymmetric Diels-Alder reaction relative to their 2-oxazolidinone-derived counterparts.[91] To qualify these observations they performed a direct competition experiment between the 2-oxazolidinone- and the 2-thiazolidinone-derived dienophile showing that **93** and **41** were more reactive than their corresponding 2-oxazolidinone analogues **92** and **39** (Scheme 2.15). These findings can be rationalised by an inherent increase in dienophilicity and/or a greater affinity of 2-thiazolidinonethione-derived dienophiles for the catalyst relative to their 2-oxazolidinone counterparts.[91] Assuming the latter to be true, the dienophile-catalyst complexes should be more stable and therefore amenable to detection by ESI MS.



Scheme 2.15: *Direct competition experiment between 2-oxazolidinone- and 2-thiazolidinone-derived dienophiles.*[91]

Using 2-thiazolidinethione-derived dienophile **63** and cyclopentadiene with 10 mol% of [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ the Diels-Alder reaction was performed (Scheme 2.16). After stirring for 18 hours at room temperature an aliquot of the reaction mixture was analysed by ESI MS. The spectrum showed the desired dienophile-catalyst complex **96** at *m/z* 620 and the Diels-Alder adduct-catalyst complex **97** at *m/z* 686, as well as the already familiar mass peaks at *m/z* 295, 313, 357, 375 and 651 (Figure 2.4). The corresponding Et-dienophile-catalyst complexes **98** (*m/z* 634) and the Diels-Alder adduct-catalyst complex **99** (*m/z* 700) were detected in a separate experiment (Figure 2.5).

Copper-containing complexes were easily identified by their characteristic isotope pattern. Interestingly only copper(I)-complexes were observed although Cu(II)(OTf)$_2$ was used to generate the catalyst. Similar observations have been reported previously[146-148] and explained by electrochemical reactions occurring at the capillary which can affect the oxidation state of the metal species. Electrochemical processes during the electrospray process are therefore responsible for Cu^{2+} appearing as Cu^{1+} in the mass spectrum.



63 **79**

Scheme 2.16: *The Diels-Alder reaction using dienophile **63**.*

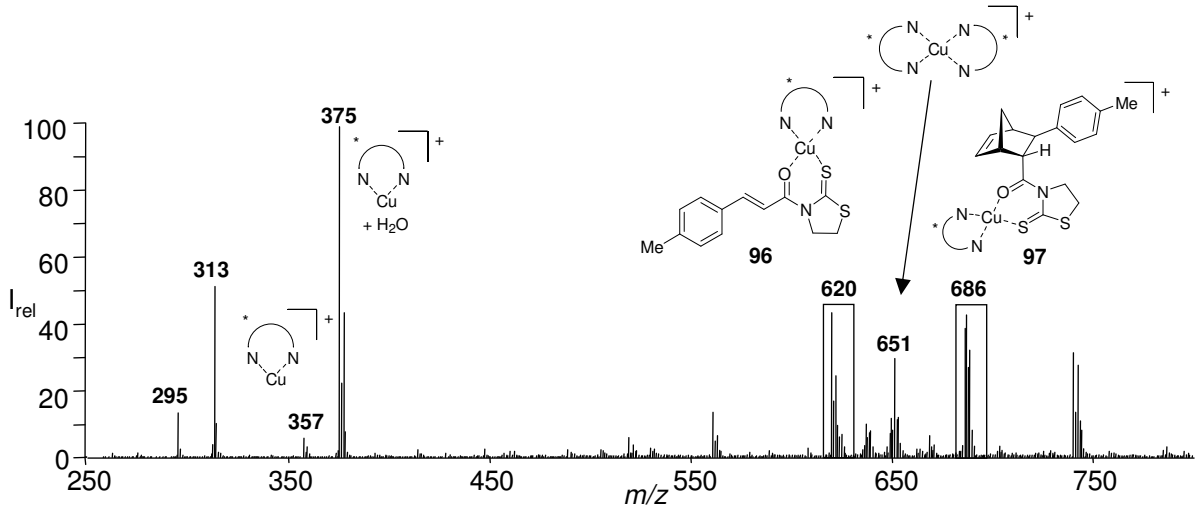


Figure 2.4: *ESI MS spectrum of the Diels-Alder reaction using dienophile **63**.*

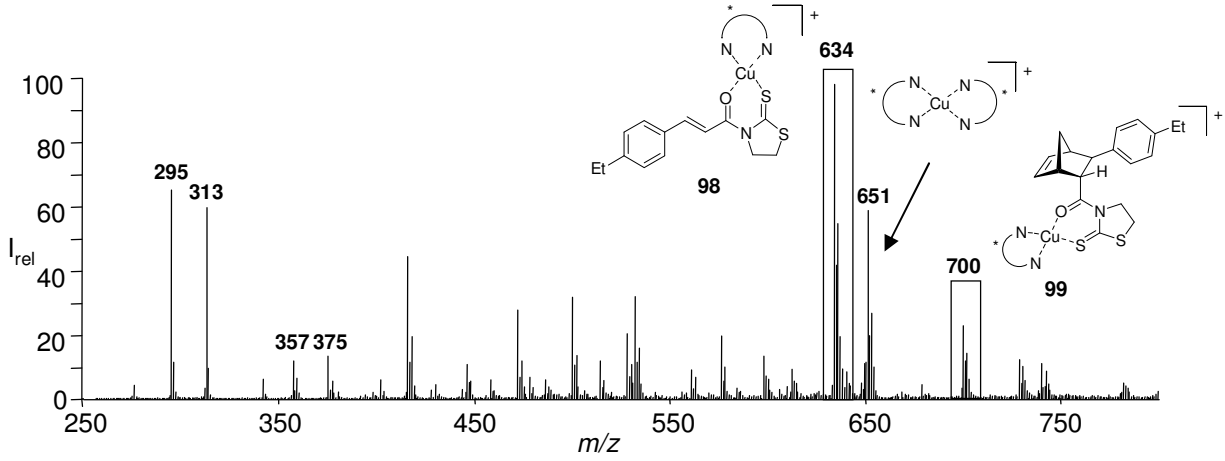
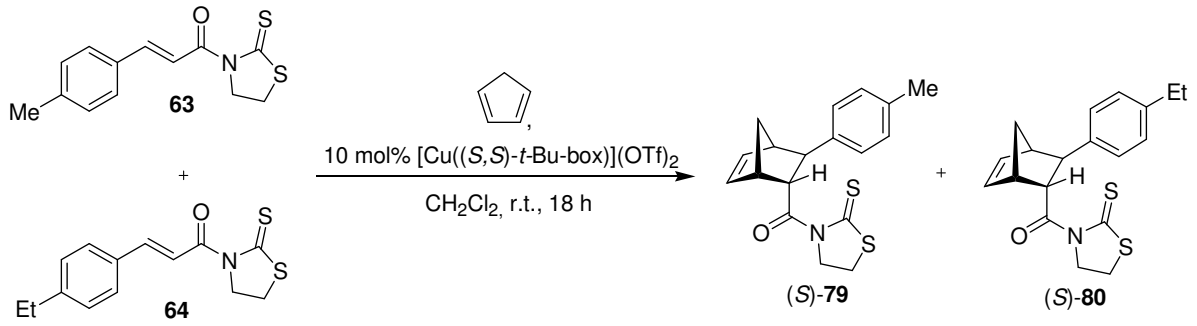


Figure 2.5: *ESI MS spectrum of the Diels-Alder reaction using dienophile **64**.*

To evaluate if the mass-labelled substrates can be detected together in the same reaction mixture by ESI MS, the Diels-Alder reaction was performed using an equimolar mixture of dienophiles **63** and **64** with [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ (Scheme 2.17). The reaction mixture was stirred for 18 hours at room temperature. An aliquot of the reaction mixture was analysed by ESI MS showing the dienophile-catalyst complexes **96** and **98** along with the Diels-Alder adduct-catalyst complexes **97** and **99** (Figure 2.6). The mass peak intensities of dienophile complexes **96** and **98** gave a 50:50 ratio representing the initial ratio. The observed ratio for the Diels-Alder adduct complexes was 53:47 suggesting a slightly higher reactivity of the Me-labelled dienophile **63**. The results showed that it was possible to detect reaction intermediates of the Diels-Alder reaction with a mass difference of Δ *m/z* = 14 conveniently by ESI MS.



Scheme 2.17: *Competition experiment between Me- and Et-labelled dienophile **63** and **64**.*

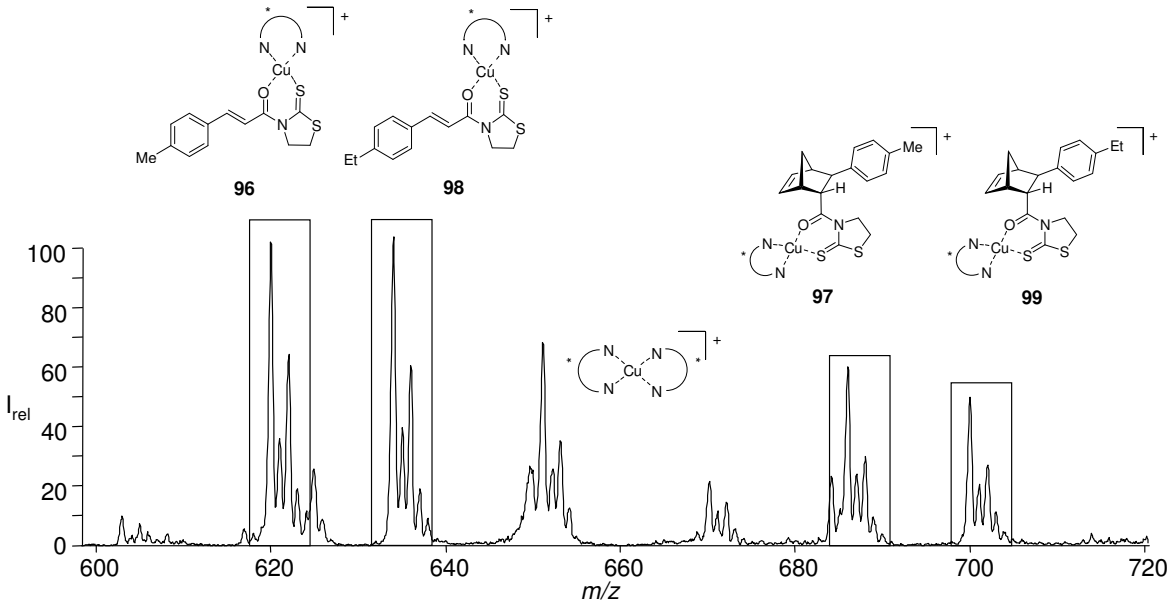


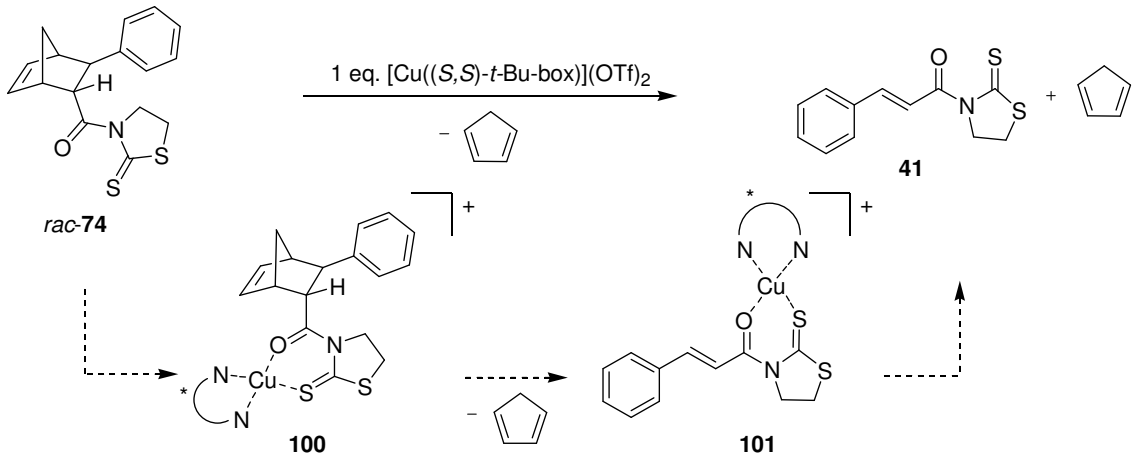
Figure 2.6: *ESI MS spectrum of the retro-Diels-Alder reaction depicted in Scheme 2.17.*

2.3.3 Evaluation of Retro-Diels-Alder Reaction Conditions

Having found substrates suitable for monitoring reaction intermediates in the forward Diels-Alder reaction, conditions for the retro reaction were investigated. Preliminary studies used one equivalent of [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ as this led to higher conversion and better detection of intermediates. Elevated temperatures were necessary for the reaction to proceed, but care was taken to prevent the uncatalysed retro-Diels-Alder reaction (see Section 2.6).

Retro-Diels-Alder reactions were performed using racemic Diels-Alder adduct *rac*-**74** and [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$. After stirring for the indicated times and temperatures, aliquots of the reaction mixture were analysed by ESI MS (Table 2.6). Reaction temperatures at 80 °C or 100 °C gave sufficient conversion to the dienophiles. Reaction times were even shortened to one hour. Microwave irradiation was also used, but gave poor results (Table 2.6, entry 7). ^{1}H NMR of the reaction mixtures confirmed the conversion observed by ESI MS.

Table 2.6: *Screening reaction conditions for the retro-Diels-Alder reaction.*



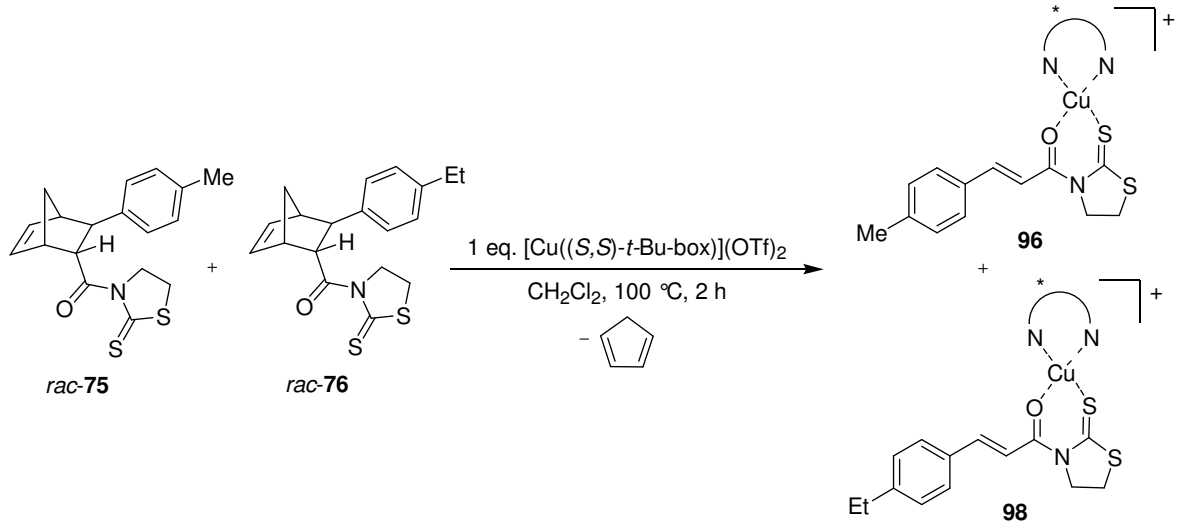
Entry	Conditions	Heating Source	DA Adduct *rac*-72 : Dienophile 62[a]	DA Adduct Complex 100 : Dienophile Complex 101[b]
1	48 h, r.t.	oil bath	98:2	97:3
2	18 h, 40 °C	oil bath	97:3	94:6
3	18 h, 50 °C	oil bath	94:6	90:10
4	1 h, 60 °C	oil bath	95:5	95:5
5	2 h, 80 °C	oil bath	86:14	82:18
6[c]	2 h, 100 °C	oil bath	75:25	81:19
7	1.5 h, 70 °C	microwave	97:3	96:4

a Ratio determined by ^{1}H NMR; *b* Ratio determined by ESI MS; *c* 1:1 mixture of *rac*-**75** and *rac*-**76** as starting material.

2.3.4 Retro-Diels-Alder Reaction under Non-Catalytic Conditions

Having found conditions for the retro-Diels-Alder reaction experiments were conducted with mass-labelled racemic Diels-Alder adducts *rac*-**75** and *rac*-**76** to test if the relevant intermediates could be detected (Scheme 2.18). The Diels-Alder adducts were structurally identical except for the mass label in aryl *para*-position. Therefore they should show the same reactivity towards the catalyst resulting in the same mass peak intensities for Me- and Et-labelled substrates. The dienophile-catalyst complexes **96** and **98** along with the Diels-Alder adduct complexes **97** and **99** were detected by ESI MS (Figure 2.7). The ratio for the dienophile complexes showed a 51:49 ratio which was very close to the expected 50:50 ratio. The slight deviation can be attributed either to weighing errors or to a higher reactivity

of the Me-labelled substrate. Investigations concerning this point will be discussed later (see Secion 2.3.5).



Scheme 2.18: *The retro-Diels-Alder reaction using rac-**75** and rac-**76**.*

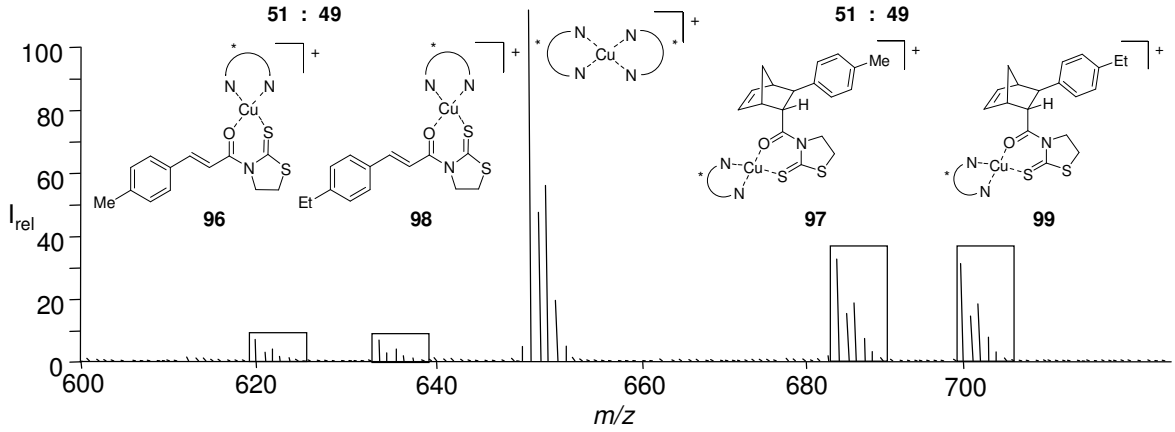
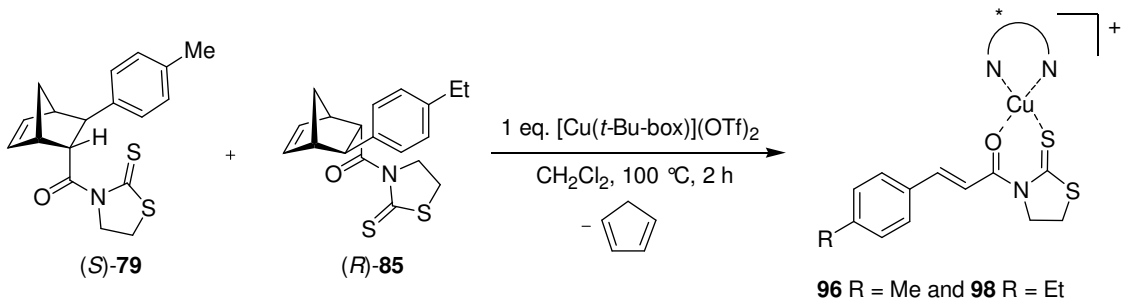


Figure 2.7: *ESI MS spectrum for the reaction depicted in Scheme 2.18.*

If the racemic Diels-Alder adducts were substituted by an equimolar mixture of mass-labelled quasienantiomers (*S*)-**79** and (*R*)-**85** (Scheme 2.19), mass peak intensities for the dienophile complexes **96** and **98** should reflect the catalyst's enantioselectivity. As seen in Figure 2.8, quasienantiomer (*S*)-**79** was converted faster to the corresponding dienophile **63** by the chiral catalyst than quasienantiomer (*R*)-**85**. By analysing the mass peak intensities of the dienophile-catalyst complexes **96** and **98** a ratio of 73:27 was observed.



Scheme 2.19: *The retro-Diels-Alder reaction using quasienantiomers (S)-**79** and (R)-**85**.*

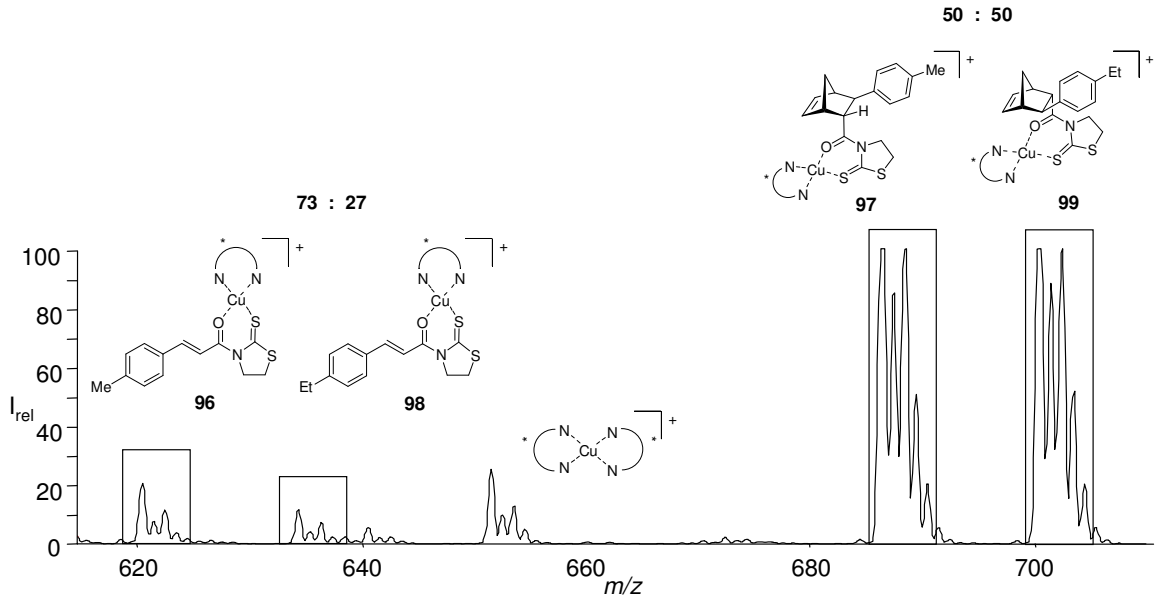


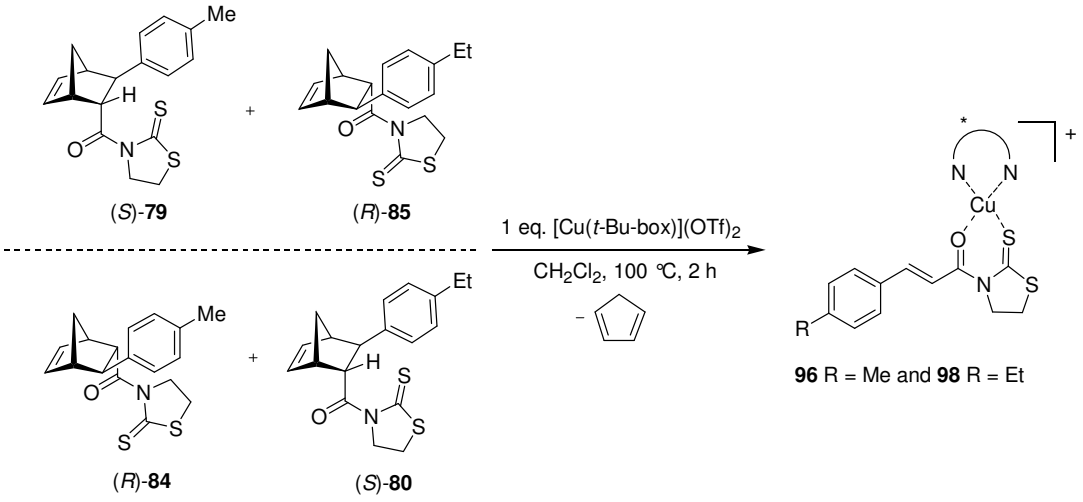
Figure 2.8: *ESI MS spectrum of the retro-Diels-Alder reaction depicted in Scheme 2.19.*

For verification of the results by ESI MS the retro-Diels-Alder reaction was conducted with the (*R,R*)-catalyst. The inversely labelled quasienantiomers (*R*)-**84** and (*S*)-**80** were also reacted with both [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ and [Cu((*R,R*)-*t*-Bu-box)](OTf)$_2$. If the method using these quasienantiomers was valid, reaction of both quasiracemates with the (*S,S*)-catalyst should lead to exact the inverse dienophile complex ratios (for example 70:30 vs. 30:70). If the reaction was conducted using the same quasiracemate with either the (*S,S*)-catalyst or the (*R,R*)-catalyst again exact inverse dienophile complex ratios should be detected.

The general trend showed that the (*S,S*)-catalyst was always more reactive towards the (*S*)-Diels-Alder adducts to undergo the retro-Diels-Alder reaction and to subsequently give the corresponding dienophiles (Table 2.7, entry 1 and 3, Figure 2.9). Vice versa the (*R,R*)-catalyst preferentially converted the (*R*)-Diels-Alder adducts to the corresponding dienophiles (Table 2.7, entry 2 and 4, Figure 2.9). Interestingly, using the same quasiracemate with either the (*S,S*)- or the (*R,R*)-catalyst led to the expected inverse ratio, but different

values (Table 2.7, entry 1/2 or 3/4; see also Section 2.3.5). For the Diels-Alder adduct complexes roughly the initial 50:50 ratio with slightly more of the less favoured Diels-Alder adduct was observed. This finding might be an indication for the conversion of the reaction. A substantial amount of the faster reacting Diels-Alder adduct had already been converted to the dienophile, therefore more of the less reactive Diels-Alder adduct remained in the reaction mixture.

Table 2.7: *Control experiments using Me- and Et-labelled quasienantiomers in the retro-Diels-Alder reaction.*



Entry	Quasienantiomers	Cat.	Dienophile Complex 96 : 98[a]	DA Adduct Complex Me : Et[a]
1	(*S*)-**79**/(*R*)-**85**	*S,S*	73:27	44:56
2	(*S*)-**79**/(*R*)-**85**	*R,R*	38:62	50:50
3	(*R*)-**84**/(*S*)-**80**	*S,S*	37:63	52:48
4	(*R*)-**84**/(*S*)-**80**	*R,R*	74:26	43:57

a Ratio determined by ESI MS.

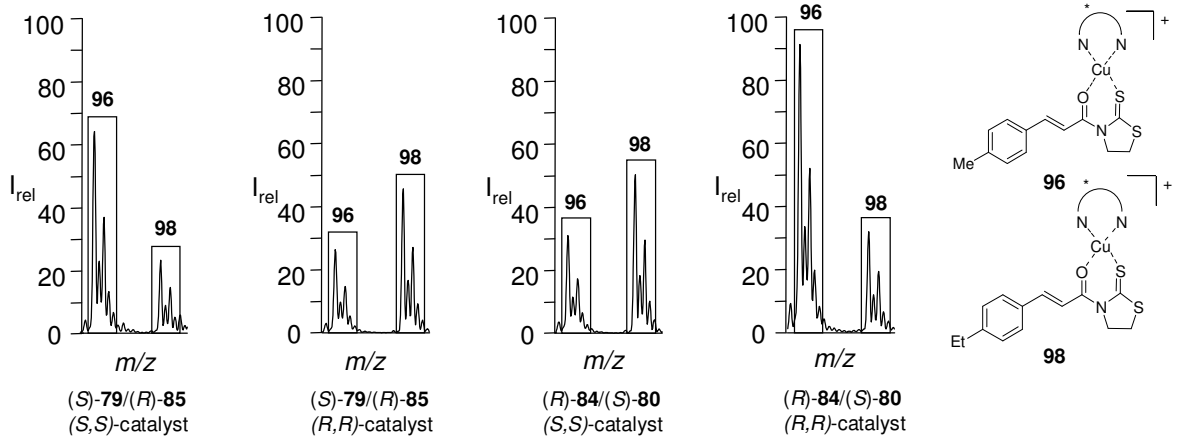


Figure 2.9: *ESI MS spectra of the control experiments using Me- and Et-labelled quasienantiomers.*

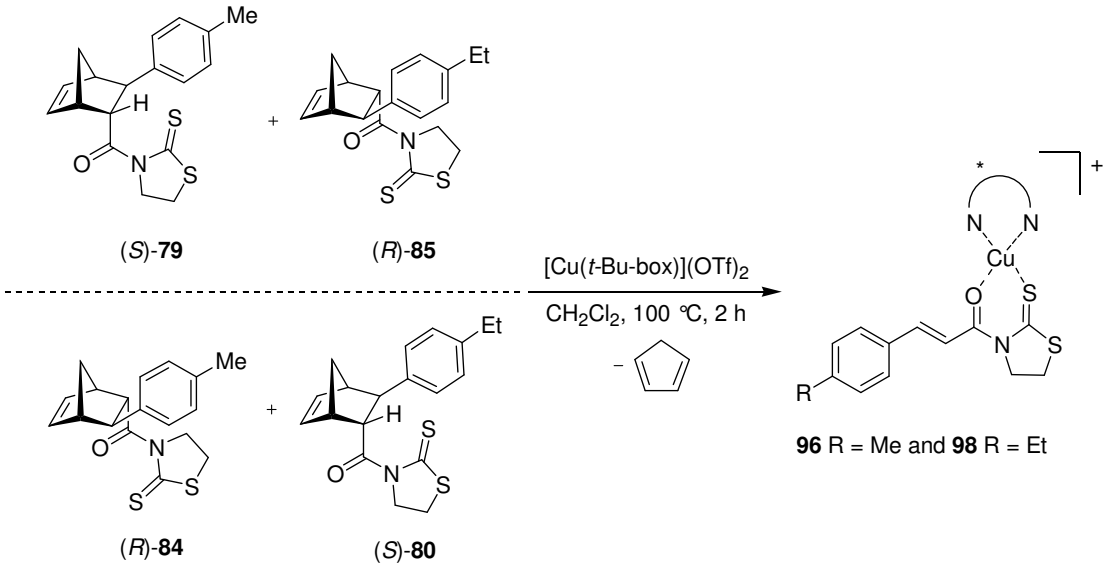
2.3.5 Retro-Diels-Alder Reaction under Catalytic Conditions

To test if this method also enabled us to monitor reaction intermediates under catalytic conditions the retro-Diels-Alder reaction was performed with 20 mol% of catalyst. High catalyst loading of 20 mol% was necessary to obtain good ESI MS detection and intensity of the mass peaks. In addition a protocol for analysing the dienophile ratio directly from the reaction mixture by HPLC was developed, so the ESI MS results were confirmed by a second analytical method.

For verification of the method control experiments using both quasiracemates (*S*)-**79** and (*R*)-**85** or (*R*)-**84** and (*S*)-**80** with both catalysts, [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ or [Cu((*R,R*)-*t*-Bu-box)](OTf)$_2$, were conducted. Using either (*S*)-**79** and (*R*)-**85** or (*R*)-**84** and (*S*)-**80** as quasienantiomers with the (*S,S*)-catalyst should led to the exact inverse ratio for the dienophile complexes. The same results are expected when using the same quasiracemate with either the (*S,S*)- or the (*R,R*)-catalyst. For comparison the results using stoichiometric amounts of catalyst were included in Table 2.8 (see Section 2.3.4, Table 2.7).

It became immediately evident that the expected inverse ratios using the same catalyst but opposite quasiracemates were not obtained (Table 2.8, entry 2/6 or 4/8). The same was observed for using the same quasiracemate, but opposite catalysts (Table 2.8, entry 2/4 or 6/8). As two experiments showed the expected enantioselectivities (Table 2.8, entry 2 and 8), the outcome of the reactions can only be explained by a higher reactivity of the chiral catalyst for the Me-Diels-Alder adduct independent of its configuration. This effect was smaller using stoichiometric amounts of catalyst and became more pronounced under catalytic conditions (Table 2.8). HPLC analysis of the reaction mixtures supported the ESI MS results.

Table 2.8: *Results of the retro-Diels-Alder reaction under non-catalytic and catalytic conditions.*

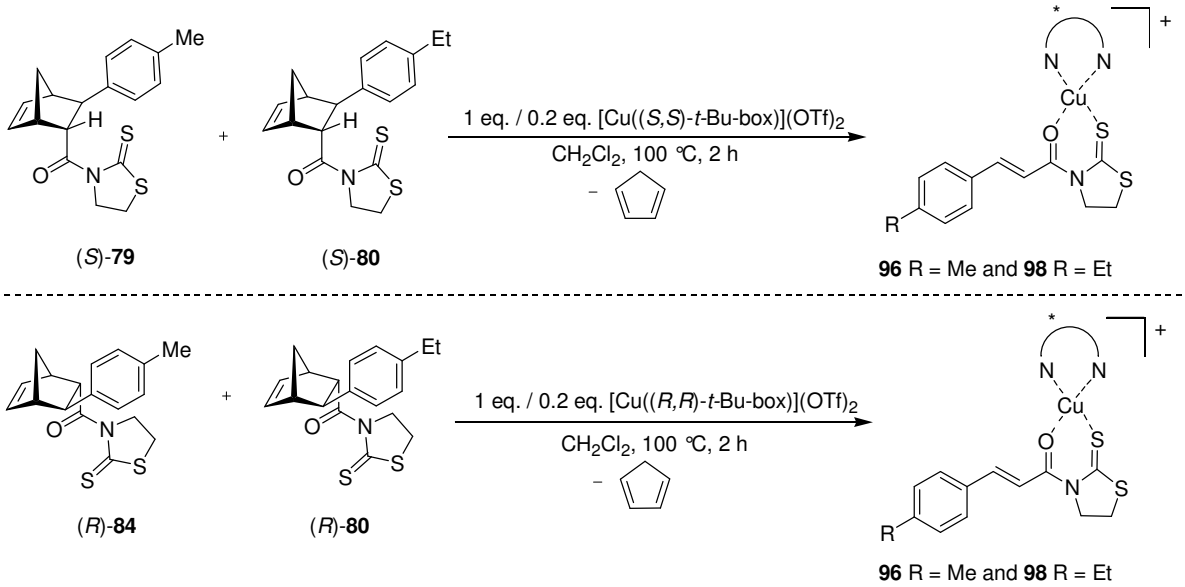


Entry	Cat.	Catalyst Loading	Quasi-enantiomers	Dienophile Complex 96 : 98[a]	Dienophile 63 : 64[b]	DA Adduct Complexes Me : Et[a]
1	*S,S*	1.0 eq.	(*S*)-**79**/(*R*)-**85**	73:27	-	44:56
2	*S,S*	0.2 eq.	(*S*)-**79**/(*R*)-**85**	68:32	66:34	50:50
3	*R,R*	1.0 eq.	(*S*)-**79**/(*R*)-**85**	38:62	23:77	52:48
4	*R,R*	0.2 eq.	(*S*)-**79**/(*R*)-**85**	50:50	43:57	50:50
5	*S,S*	1.0 eq.	(*R*)-**84**/(*S*)-**80**	37:63	21:79	52:48
6[c]	*S,S*	0.2 eq.	(*R*)-**84**/(*S*)-**80**	49:51	37:63	51:49
7	*R,R*	1.0 eq.	(*R*)-**84**/(*S*)-**80**	74:26	65:35	43:57
8[c]	*R,R*	0.2 eq.	(*R*)-**84**/(*S*)-**80**	71:29	61:39	50:50

a Dienophile and Diels-Alder adduct complex ratio determined by ESI MS; *b* Dienophile ratio determined by HPLC; *c* Reaction time 1 hour.

To further investigate the catalyst's selectivity direct competition experiments between equimolar mixtures of either (*S*)-**79** and (*S*)-**80** or (*R*)-**84** and (*R*)-**85** were conducted (Table 2.9). Taking Me- and Et-Diels-Alder adducts of the same configuration eliminated any stereochemical influence. If the catalyst was unaffected by the mass labels, a 50:50 mixture of dienophile complexes **96** and **98** would be expected.

Table 2.9: *Direct competition experiment between Me- and Et-labelled Diels-Alder adducts.*

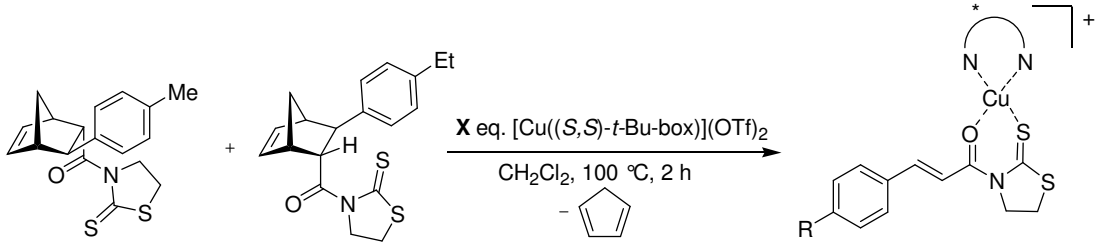


Entry	Cat.	Catalyst Loading	Quasi-enantiomers	Dienophile Complex 96 : 98[a]	DA Adduct Complexes Me : Et[a]
1	*S,S*	1.0 eq.	(*S*)-**79**/(*S*)-**80**	54:46	50:50
2	*R,R*	1.0 eq.	(*R*)-**84**/(*R*)-**85**	56:44	51:49
3	*S,S*	0.2 eq.	(*S*)-**79**/(*S*)-**80**	64:36	50:50
4[c]	*R,R*	0.2 eq.	(*R*)-**84**/(*R*)-**85**	65:35	50:50

a Dienophile and Diels-Alder adduct complex ratio determined by ESI MS.

The direct competition experiments confirmed that the catalyst is more reactive towards the Me-substituted substrates (Table 2.9). It also showed clearly that the effect was more pronounced under catalytic conditions. This was confirmed in another experiment by varying the amount of [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ in the retro-Diels-Alder reaction of (*R*)-**84** and (*S*)-**80** (Table 2.10). The ratios were monitored by ESI MS and HPLC. Using 1 - 0.6 equivalents of (*S,S*)-catalyst the expected dienophile ratio was observed. When the catalyst loading was below 0.6 equivalents the catalyst gradually distinguished less between the quasienantiomers. The initial complexation with the Diels-Alder adducts was not affected by the mass labels, generally a 50:50 ratio was observed, indicating that a difference in activation energy for the Me- and Et-substituted substrates undergoing the retro reaction must play a role.

Table 2.10: *Varying the amount of catalyst in the retro-Diels-Alder reaction.*



(*R*)-**84** (*S*)-**80** **96** R = Me and **98** R = Et

Entry	Eq. Catalyst	Dienophile Complex 96 : 98[a]	Dienophile 63 : 64[b]
1	1.0	37:63	21:79
2	0.8	36:64	27:73
3	0.6	33:67	25:75
4	0.4	42:58	26:74
5	0.2	49:51	37:63

a Dienophile and Diels-Alder adduct complex ratio determined by ESI MS; *b* Dienophile ratio determined by HPLC.

To explain the catalyst's preference for Me-labelled substrates steric and electronic factors were considered. As the mass labels were well removed from the reactive site, electronic factors must be responsible for the difference. Hammett substitution constants, σ, calculated from ionisation constants of benzoic acids,[149] quantify the effects that electron-donating or electron-withdrawing groups have on the transition state or intermediates during the course of a reaction.[150] Steric interactions are excluded by considering *meta*- and *para*-substituents only. Hammett constants can be further refined by factoring the electronic effect into a resonance component R and non-resonance "field" component F, leading to the following equation

$$\sigma = f\mathrm{F} + r\mathrm{R} + h$$

where *f, r* and *h* are entirely independent of the substituent.[151, 152] F and R are also known as Swain-Lupton constants.[150] As these constants can be useful tools to derive quantitative structure-activity relationships (QSAR)[153] they were used to explain electronic influences in the mass-labelled retro-Diels-Alder substrates. Comparing the Hammett substitution constants σ_P for methyl- and ethyl-substituents the electronic difference is very small, but significant (Table 2.11). The more refined resonance constants R show a larger difference (Table 2.11, -0.18 vs. -0.15) implying that the methyl substituent is slightly more electron-donating than the ethyl substituent.[152] Although the differences for R are small and values fluctuate depending on the parameters used,[150, 154] a preference for the more electron rich substrate by the catalyst is a possible explanation for the higher reactivity of the Me-labelled substrate. Why this preference is more pronounced under catalytic conditions remains unclear.

Table 2.11: *Hammett substitution constants and modified Swain-Lupton constants.*[150]

Entry	Substituent	σ_P	F	R
1	Me	-0.17	0.01	-0.18
2	Et	-0.15	0.00	-0.15
3	*n*-Pr	-0.15	0.04	-0.19
4	i-Pr	-0.13	0.01	-0.14
5	*n*-Bu	-0.16	-0.01	-0.15

To find suitable quasienantiomers in which the mass labels would not influence the reactivity of the catalyst several substituted Diels-Alder adducts were synthesised (Figure 2.10). They were tested in a direct competition experiment using 20 mol% of catalyst and Diels-Alder

adducts with the same configuration but different substituents (Table 2.12). If the catalyst was not influenced by the mass labels 50:50 dienophile complex ratios were expected. We found that Et- and *n*-Bu-substituted Diels-Alder adducts did not influence the catalyst reactivity therefore being suitable quasienantiomers. In other tested pairs such as Et/i-Pr and *n*-Pr/*n*-Bu the mass label had an influence on the catalyst's reactivity (Table 2.12, entry 3/4 and 5/6). A further advantage of the Et- and *n*-Bu quasienantiomers was that the reaction mixture could be directly analysed by HPLC to determine the Et- to *n*-Bu-dienophile ratio.

Steric effects did not influence the catalyst's reactivity because the results were independent of the substituent size (Table 2.12, compare entry 1 and 3). The results are consistent with the σ_P and R values listed in Table 2.11 with very similar σ_P and R values for ethyl- and *n*-butyl-substituents.

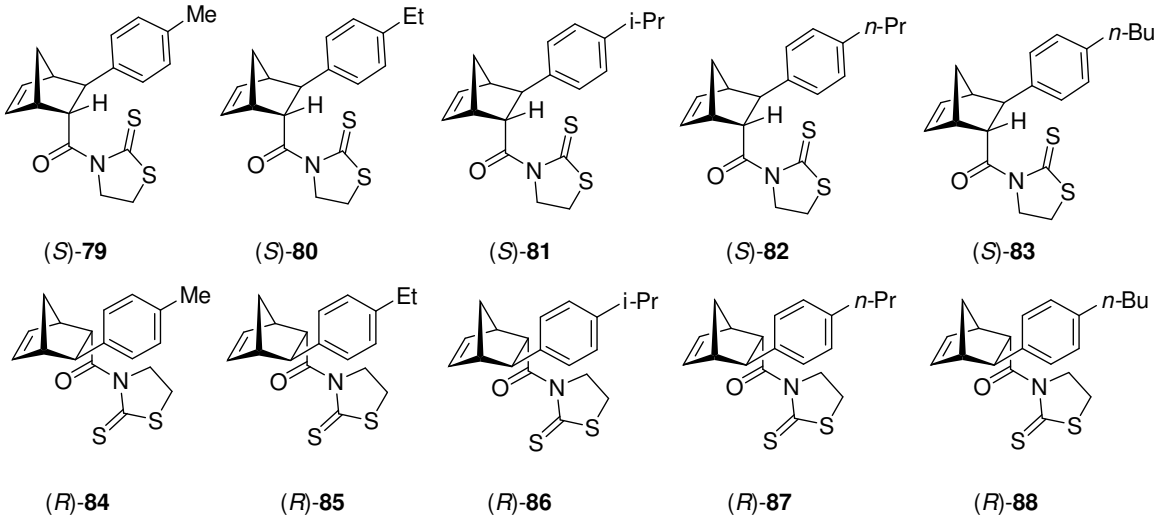
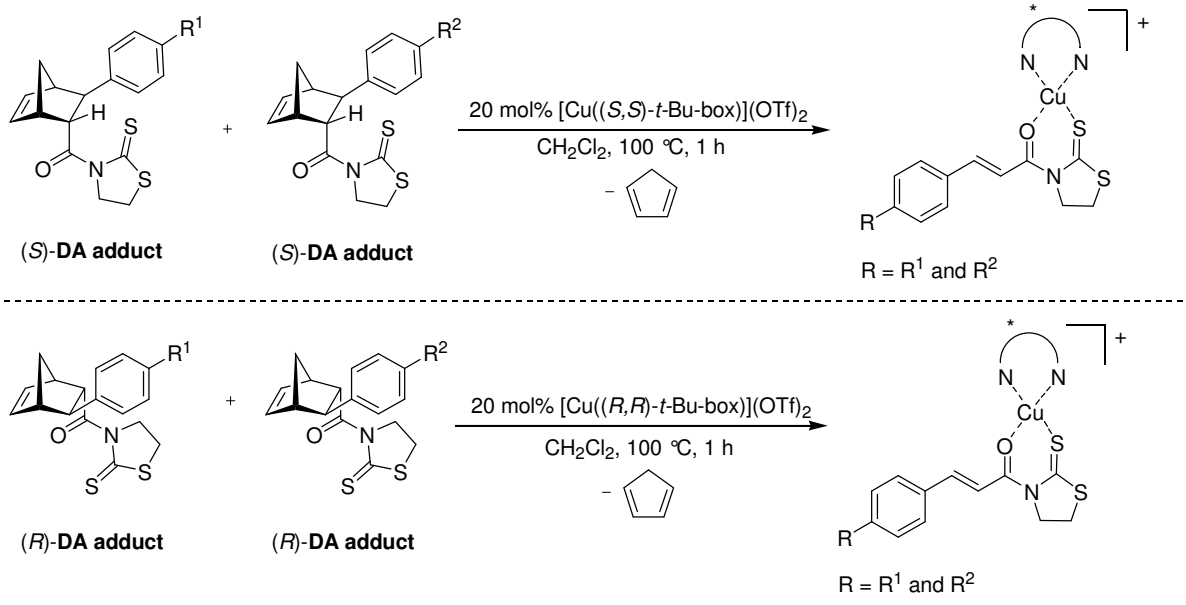


Figure 2.10: *Several differently substituted Diels-Alder adducts.*

Table 2.12: *Direct competition experiment between several Diels-Alder adducts.*



Entry	Cat.	Quasienantiomers (R^1 : R^2)	Dienophile Complex R^1 : R^2 [a]	DA Adduct Complex R^1 : R^2 [a]
1	*S,S*	(*S*)-**79**/(*S*)-**80**	64:36	50:50
2	*R,R*	(*R*)-**84**/(*R*)-**85**	65:35	50:50
3	*S,S*	(*S*)-**80**/(*S*)-**81**	47:53	50:50
4	*R,R*	(*R*)-**85**/(*R*)-**86**	47:53	50:50
5	*S,S*	(*S*)-**82**/(*S*)-**83**	54:46	50:50
6	*R,R*	(*R*)-**87**/(*R*)-**88**	54:46	50:50
7	*S,S*	(*S*)-**80**/(*S*)-**83**	50:50	49:51
8	*R,R*	(*R*)-**85**/(*R*)-**88**	51:49	49:51

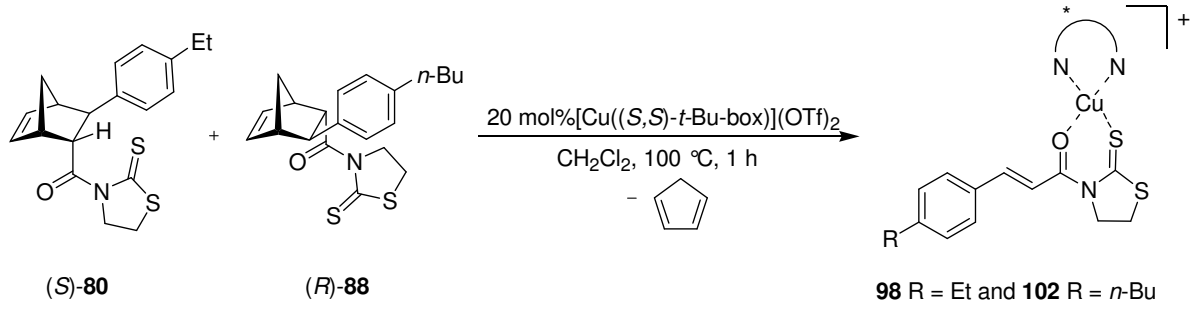
a Dienophile and Diels-Alder adduct complex ratios determined by ESI MS.

2.3.6 Direct Analysis of Catalytic Intermediates in the Retro-Diels-Alder Reaction: General Screening Protocol

The general screening protocol for the retro-Diels-Alder reaction used an equimolar mixture of Et- and *n*-Bu-Diels-Alder adducts and 20 mol% of copper(II)-catalyst in dichloromethane. For ESI MS analysis aliquots of the reaction mixture were taken, diluted to 10^{-5} M and analysed by ESI MS. The ratios for the dienophile and Diels-Alder adduct complexes were determined by integration of the mass peaks (see Section 5.5.1 for details). For verification HPLC analysis of the dienophiles **64** and **67** in the reaction mixture was performed.

Application of the general screening protocol was demonstrated by conducting the retro-Diels-Alder reaction with (*S*)-**80** and (*R*)-**88** using [Cu((*S*)-*t*-Bu-box)](OTf)$_2$ (Scheme 2.20). The ESI MS spectrum in Figure 2.11 showed a ratio of 68:32 for the Et- to *n*-Bu-dienophile complexes **98** and **102**. For the Et- to *n*-Bu-Diels-Alder adduct complexes **99** and **103** a ratio of 49:51 was obtained.

This experiment demonstrated that it is possible to directly monitor reaction intermediates of the retro-Diels-Alder reaction under catalytic conditions. Analysis of the dienophile complex mass peaks gives a direct measure of the catalysts' enantioslectivity.



(*S*)-**80** (*R*)-**88** **98** R = Et and **102** R = *n*-Bu

Scheme 2.20: *The retro-Diels-Alder reaction using (S)-**80** and (R)-**88** as quasienantiomers.*

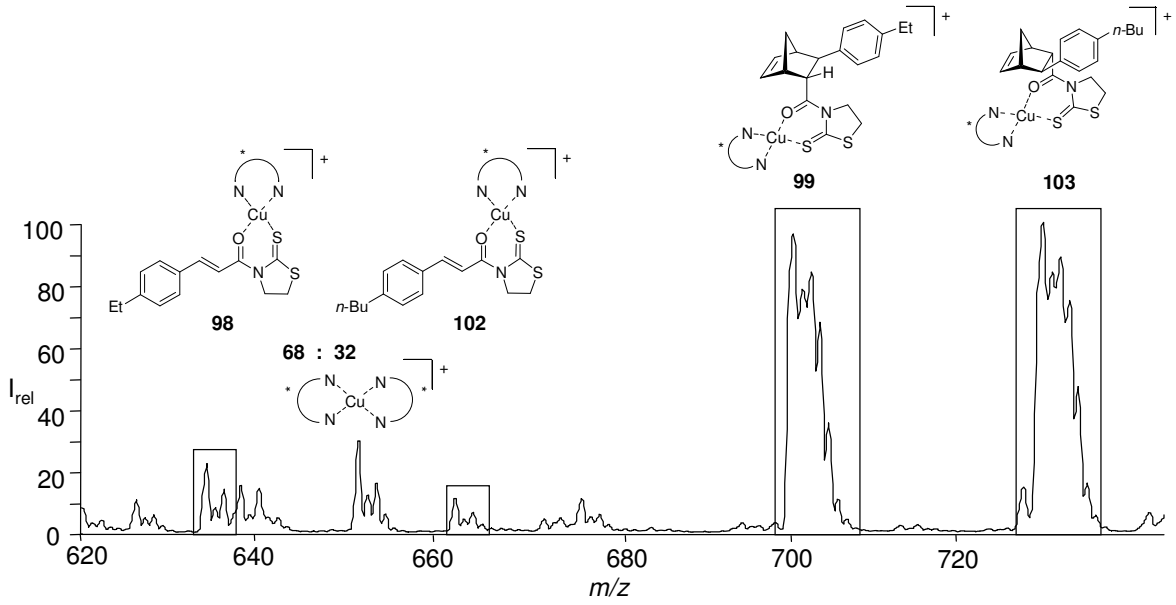
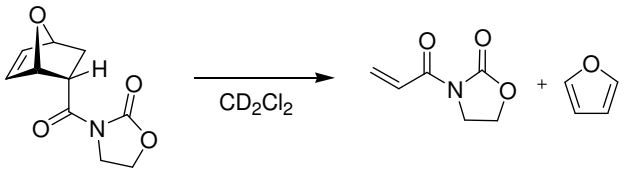


Figure 2.11: *ESI MS spectrum for the retro-Diels-Alder reaction depicted in Scheme 2.20.*

2.3.7 Furan-Based Quasienantiomers

In principle the driving force for the retro-Diels-Alder reaction with furan-containing Diels-Alder adducts should be greater than that for cyclopentadiene-derived adducts.[129] Unfortunately the synthesis of the 2-thiazolidinethione-derived Diels-Alder adduct incorporating furan was not successful. Also the retro-Diels-Alder reaction of **38** already took place at low temperatures without addition of catalyst: after storing Diels-Alder adduct **38** for 5 days at 4 °C in deuterated dichloromethane, 20% of dienophile **35** was observed by ^{1}H NMR (Scheme 2.21). For this reason and synthetic difficulties screening of furan-derived quasienantiomers was not explored further.



Scheme 2.21: *Retro-Diels-Alder reaction with furan-derived Diels-Alder adduct **38**.*

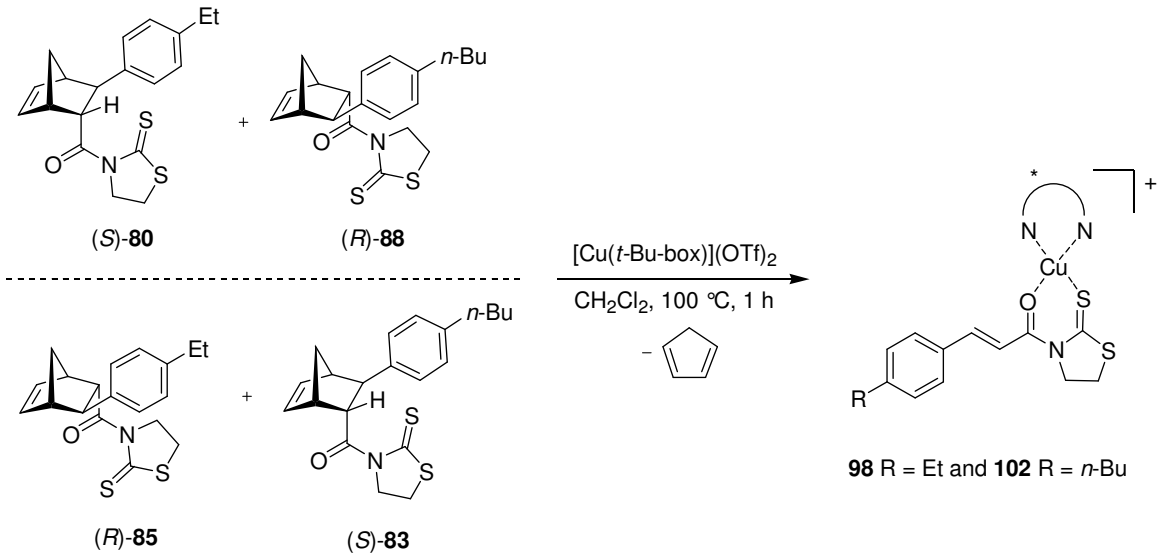
2.4 Control Experiments

2.4.1 Reversed Ligand Configuration and Inversely Labelled Quasienantiomers

To test the validity of our method control experiments using both quasiracemates, (*S*)-**80** and (*R*)-**88** or (*R*)-**85** and (*S*)-**83**, with both catalysts, [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ and [Cu((*R,R*)-*t*-Bu-box)](OTf)$_2$, were conducted. As described earlier, retro-Diels-Alder reaction with each of the quasiracemates with the (*S,S*)-catalyst should produce the exact inverse dienophile-catalyst complex ratio (for example 70:30 vs. 30:70). The same is expected for the control experiments using the (*R,R*)-catalyst.

Reaction of each quasiracemate with the (*S,S*)-catalyst produced the expected inverse ratios for the dienophile-catalyst complexes **98** and **102** (Table 2.13, entry 1 and 2, Figure 2.12). The same was detected when the ligand configuration was inverted (Table 2.13, entry 1/3 and entry 2/4, Figure 2.13). The mass peak at *m/z* 651 representing the [Cu(*t*-Bu-box)$_2$]$^+$ complex was present in all spectra. The HPLC results for the dienophiles **64** and **67** correlated perfectly with the results obtained by ESI MS (Table 2.13). The results of the control experiments were in excellent agreement and this method was therefore applied to screen for highly enantioselective catalysts for the retro-Diels-Alder reaction.

Table 2.13: *Control experiments with both quasiracemates.*



Entry	Cat.	Quasi-enantiomers	Dienophile Complex 98 : 102[a]	Dienophile 64 : 67[b]	DA Adduct Complex Et : *n*-Bu[a]
1	*S,S*	(*S*)-**80**/(*R*)-**88**	68:32	69:31	49:51
2	*S,S*	(*R*)-**85**/(*S*)-**83**	32:68	29:71	49:51
3	*R,R*	(*S*)-**80**/(*R*)-**88**	31:69	32:68	50:50
4	*R,R*	(*R*)-**85**/(*S*)-**83**	69:31	69:31	48:52

a Dienophile and Diels-Alder adduct complex ratio determined by ESI MS; *b* Dienophile ratio determined by HPLC.

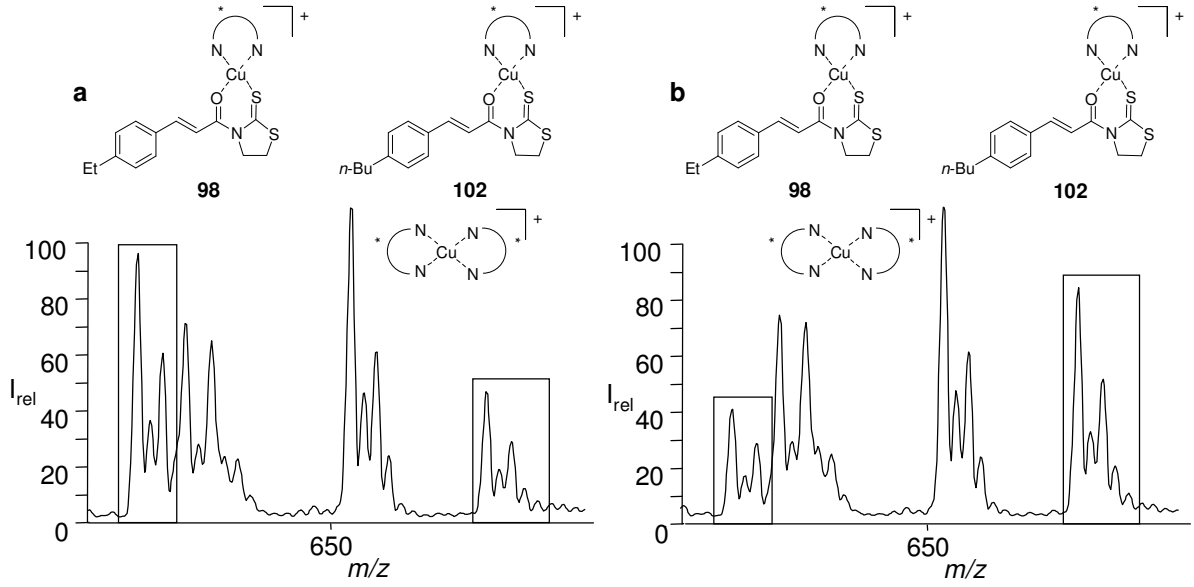


Figure 2.12: *ESI MS spectra for control experiments with (**a**) (S)-**80** and (R)-**88** and (**b**) (R)-**85** and (S)-**83** with [Cu((S,S)-t-Bu-box)](OTf)$_2$.*

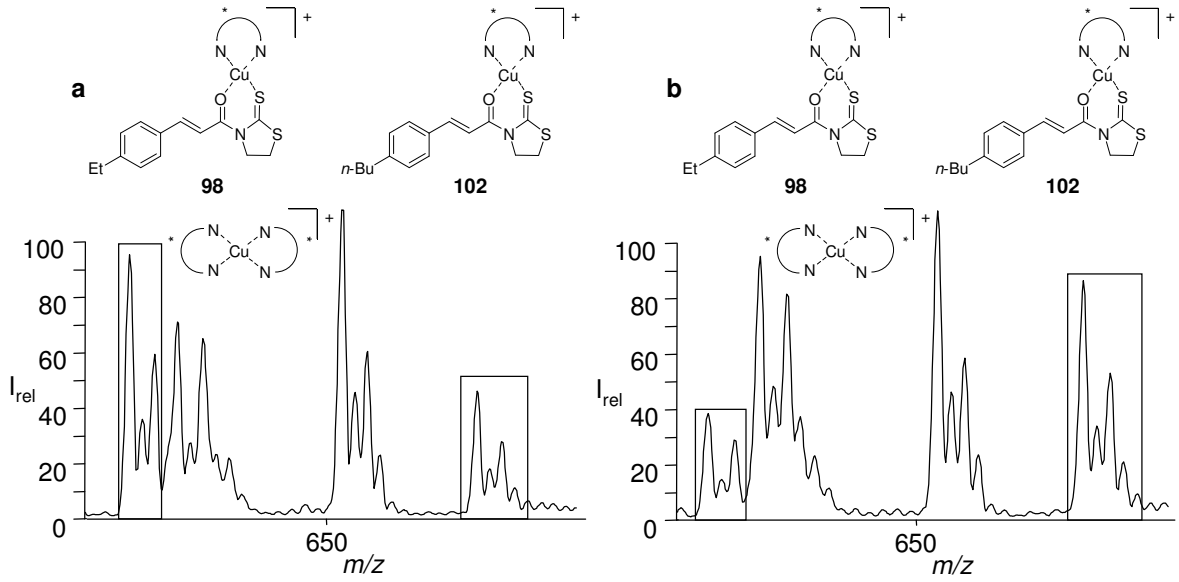
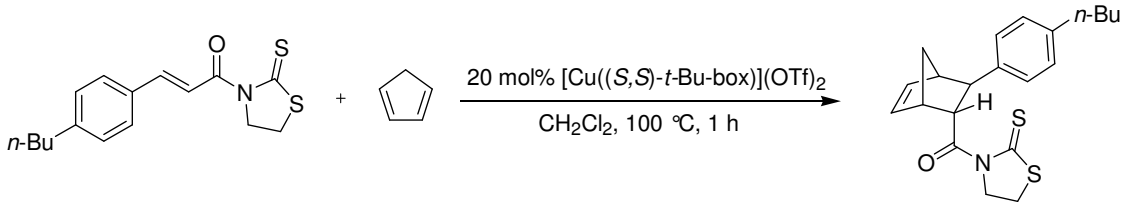


Figure 2.13: *ESI MS spectra for control experiments with (S)-**80** and (R)-**88** using (**a**) [Cu((S,S)-t-Bu-box)](OTf)$_2$ and (**b**) [Cu((R,R)-t-Bu-box)](OTf)$_2$.*

2.4.2 Comparison with the Results from the Preparative Forward Diels-Alder Reaction

In accordance to the principle of microscopic reversibility we expected the results obtained by ESI MS to be in good agreement with the preparative forward Diels-Alder reaction. *n*-Bu-dienophile **67** and cyclopentadiene were subjected to Diels-Alder reaction using 20 mol% of [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ (Scheme 2.22). Only the concentration of the starting material was changed compared to that of the retro reaction (0.01 M vs. 0.02 M) due to practical considerations. HPLC analysis was not possible when the reaction mixture was too dilute, because conversion was too small. An enantiomeric ratio of 64:36 was observed which correlated very well with the ESI MS results (ESI MS ratio 68:32).



Scheme 2.22: *The preparative forward Diels-Alder reaction.*

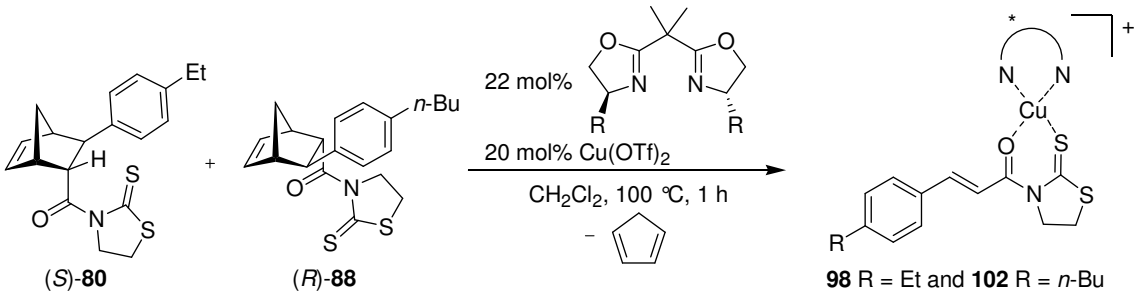
2.5 Ligand Screening

2.5.1 ESI MS Screening Using Bis(oxazoline) Ligands

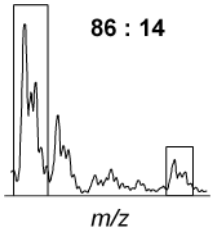
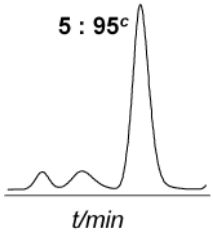
Having established a reliable ESI MS screening method a series of copper(II)-catalysts were tested for their ability to enantiodiscriminate (Table 2.14). The choice of ligands was inspired by the work of EVANS, who tested several bis(oxazoline)copper(II)-catalysts for the Diels-Alder reaction with acrylate imide **35** and cyclopentadiene (see Section 2.2).[91]

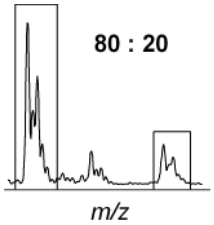
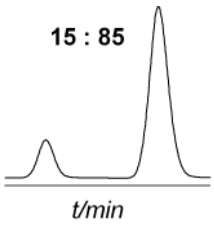
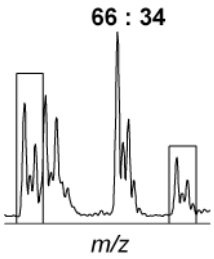
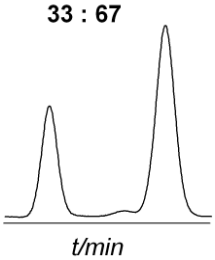
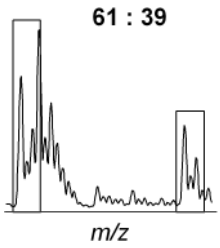
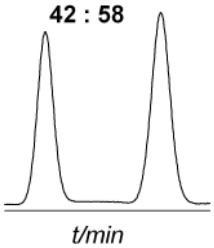
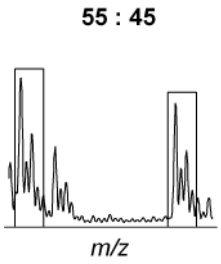
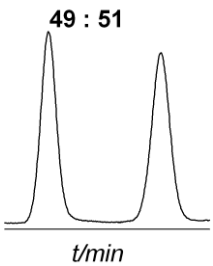
The highest enantioselectivities in the retro-Diels-Alder reaction using (*S*)-**80** and (*R*)-**88** as quasienantiomers were observed for the *β*-Naphthyl-box-derived catalyst, followed by the Ph-box-, *t*-Bu-box-, i-Pr-box- and finally the Bn-box-derived catalysts (Table 2.14). The results were confirmed by direct analysis of the reaction mixture by HPLC (Table 2.14) and by performing the preparative forward reactions (discussed in the next section). Additional peaks in the mass spectra resulted from the protonated ligand and adducts of the protonated ligand with water. Singly charged copper-box complexes were also observed along with the corresponding copper-box water adducts.

Table 2.14: *Screening results using five different bis(oxazoline) ligands.*



(*S*)-**80** (*R*)-**88** **98** R = Et and **102** R = *n*-Bu

Entry	R	Dienophile Complex 98 : 102[a]	Dienophile 67 : 64[b]
1	*β*-Np (**32d**)		

Entry	R	Dienophile Complex 98 : 102[a]	Dienophile 67 : 64[b]
2	Ph (**32c**)		
3	*t*-Bu (**32b**)		
4	i-Pr (**32a**)		
5	Bn (**32e**)		

a Dienophile and Diels-Alder adduct complex ratio determined by ESI MS; *b* Dienophile ratio determined by HPLC; *c* The additional middle peak represents the ligand.

Our results indicated an unexpected order of relative catalyst enantiodiscrimination, *β*-Np>Ph>*t*-Bu>i-Pr>Bn, which deviated from EVANS' previous observations *t*-Bu>i-Pr>*α*-Np>Ph.[91] This could be due to different dienophiles and different reaction conditions (discussed in the next section).

The reproducibility of our results was confirmed by repetition of the experiments giving nearly identical results (Table 2.15).

Table 2.15: *Reproduction of the screening results of Table 2.14.*

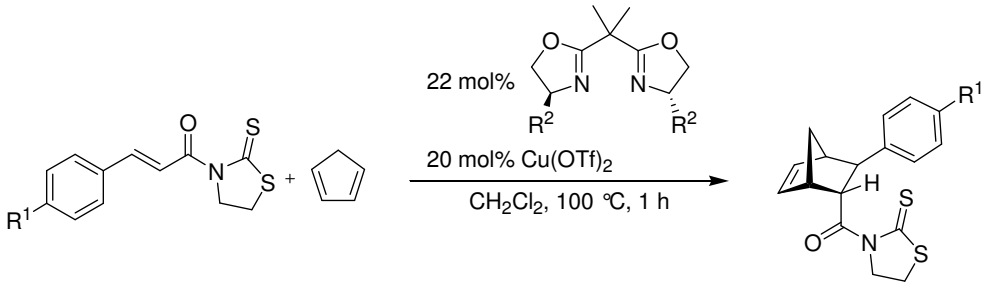
Entry	R	Dienophile Complex 98 : 102[a]	Dienophile 64 : 67[b]	DA Adduct Complex Et : *n*-Bu[a]
1	*β*-Np (**32d**)	86:14	90:10	39:61
2	Ph (**32c**)	83:17	84:16	47:53
3	*t*-Bu (**32b**)	64:36	66:34	50:50
4	i-Pr (**32a**)	65:35	60:40	50:50

a Dienophile and Diels-Alder adduct complex ratio determined by ESI MS; *b* Dienophile ratio determined by HPLC.

2.5.2 Comparison with the Results from the Preparative Forward Diels-Alder Reaction

The copper(II)-catalysed Diels-Alder reaction of dienophile **64** and dienophile **67** using bis(oxazoline) ligands **32a-e** proceeded with similar selectivities and trend as the retro reaction (Table 2.16). The *β*-Naphthyl-substituted catalyst gave the highest enantiomeric excess, the Bn-substituted catalyst the lowest. The mass labels only had a minor influence on the *endo* enantiomeric excess, generally it was 2% lower for dienophile **64**. The diastereoselectivity for all catalysts was found to be good to excellent, especially considering the high temperature. Conversions were only moderate, possibly due to dimerisation of cyclopentadiene and decomposition of starting material. A very good correlation of ESI MS and the forward reaction was found (Figure 2.14).

Table 2.16: *Results for the forward Diels-Alder reaction at 100 °C.*



64 R^1 = Et
67 R^1 = *n*-Bu

(*S*)-**80** R^1 = Et
(*S*)-**83** R^1 = *n*-Bu

Entry	Dienophile R^1	R^2	*Endo:Exo*[a]	*Endo* ee (%)[b]	Conv. (%)[a]
1	*n*-Bu (Et)	*β*-Np (**32d**)	99:1 (93:7)	76 (74)	40 (49)
2	*n*-Bu (Et)	Ph (**32c**)	96:4 (84:16)	72 (70)	76 (23)

Entry	Dienophile R^1	R^2	*Endo:Exo*[a]	*Endo* ee (%)[b]	Conv. (%)[a]
3	*n*-Bu (Et)	*t*-Bu (**32b**)	86:14 (95:5)	28 (n.d.)	31 (51)
4	*n*-Bu (Et)	i-Pr (**32a**)	85:15 (86:14)	12 (10)	72 (29)
5	*n*-Bu	Bn (**32e**)	85:15	4	11

a Determined by ^{1}H NMR of the crude product; *b* Determined by chiral HPLC.

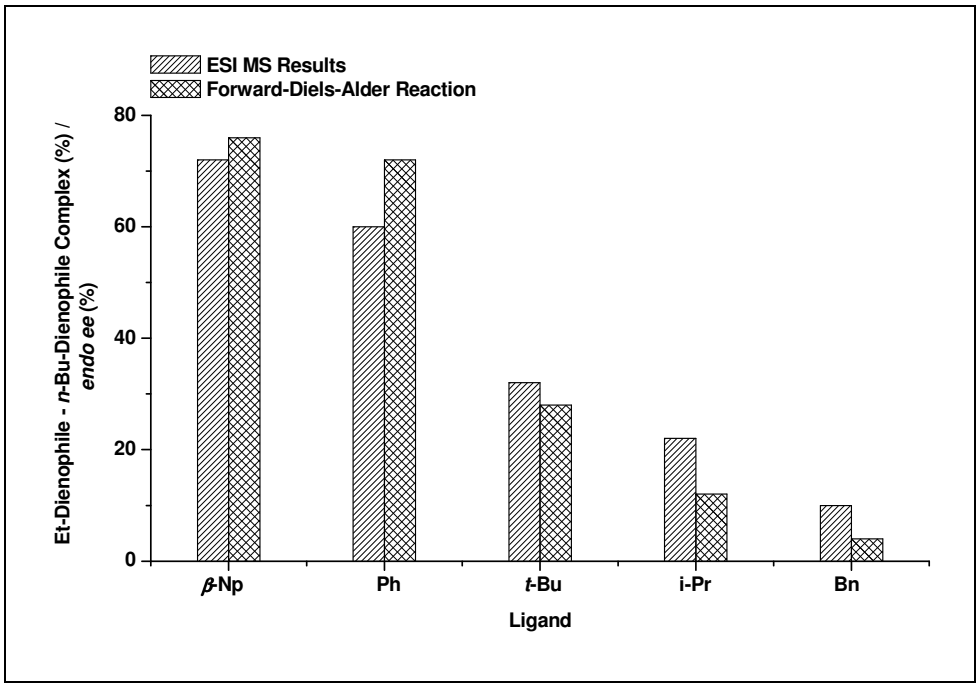
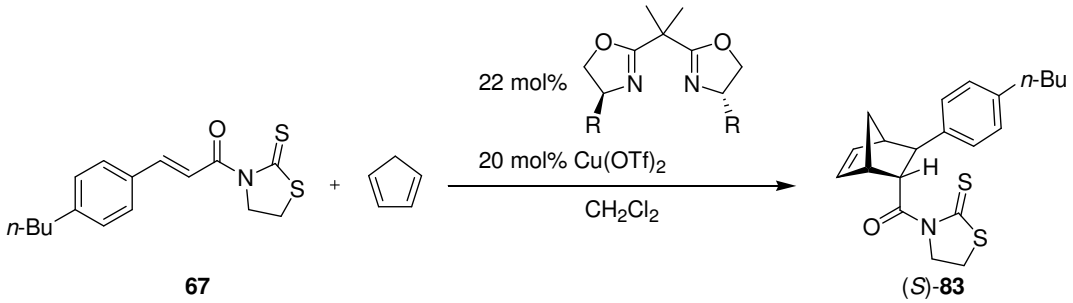


Figure 2.14: *Comparison between ESI MS results and forward reactions.*

Due to the unexpected order of relative catalyst enantiodiscrimination, *β*-Np>Ph>*t*-Bu>i-Pr>Bn, which deviated from EVANS' previous findings, *t*-Bu>i-Pr>*α*-Np>Ph, and due to the fact that EVANS' reactions were performed at lower temperatures,[91] Diels-Alder reactions were conducted under similar conditions to those described by Evans (Table 2.17, entry 1-5). The *β*-Naphthyl-box-derived catalyst again gave the best enantiomeric excess (97%) for the *β*-substituted dienophile **67** at -35 °C. Interestingly the order of the catalyst enantiodiscrimination changed to *β*-Np>*t*-Bu>Ph>i-Pr>Bn, the *t*-Bu-box-derived catalyst showing higher selectivities than the Ph-substituted catalyst (Table 2.17, entry 2 and 3). At room temperature the order was the same as that at 100 °C (Table 2.17, entry 6-10). At both temperatures diastereoselectivities were good to excellent. At -35 °C conversions fluctuated strongly, indicating that the most selective ligands also gave the most active catalysts (Table 2.17, entry 1 and 3). At room temperature conversions were good.

Table 2.17: *The forward Diels-Alder reaction usingt different reaction conditions.*



Entry	R	Conditions	*Endo:Exo*[a]	*Endo* ee (%)[b]	Conv. (%)[a]
1	*β*-Np (**32d**)	-35 °C, 48 h	>99:1	97	100
2	Ph (**32c**)	-35 °C, 48 h	>99:1	89	19
3	*t*-Bu (**32b**)	-35 °C, 48 h	>99:1	95	100
4	i-Pr (**32a**)	-35 °C, 48 h	>99:1	23	6
5	Bn (**32e**)	-35 °C, 48 h	n.d.	17	<1
6	*β*-Np (**32d**)	r.t., 20 h	99:1	92	93
7	Ph (**32c**)	r.t., 20 h	98:2	80	100
8	*t*-Bu (**32b**)	r.t., 20 h	88:12	74	65
9	i-Pr (**32a**)	r.t., 20 h	93:7	15	100
10	Bn (**32e**)	r.t., 20 h	95:5	14	68

a Determined by ^{1}H NMR of the crude product; *b* Determined by chiral HPLC.

The enantiomeric excess for all preparative reactions is summarised in Figure 2.15 in comparison with the ESI MS results. It is evident that under all conditions the *β*-Naphthyl-substituted catalyst gave the highest enantiomeric excess declining in the following order Ph>*t*-Bu>i-Pr>Bn with one exception at -35 °C where the *t*-Bu-derived catalyst performed better than the Ph-derived catalyst. The trend predicted by ESI MS was confirmed by the forward preparative reactions.

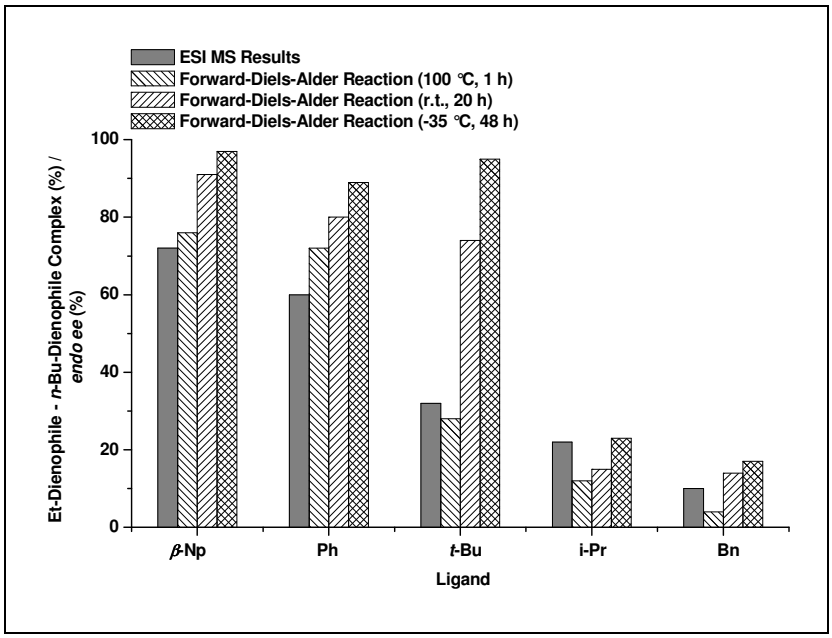
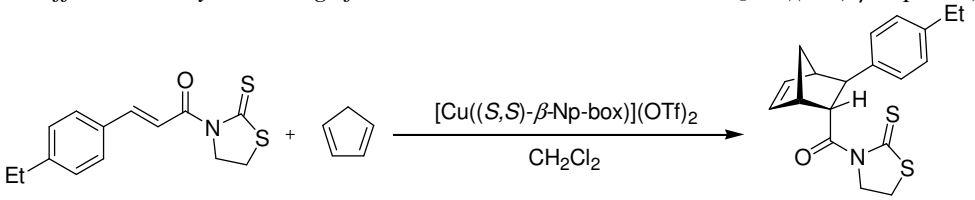


Figure 2.15: *Summary of the forward Diels-Alder results in comparison with ESI MS results.*

As the *β*-Naphthyl-substituted catalyst showed excellent enantioselectivities the Diels-Alder reaction was performed with lower catalyst loading (Table 2.18). The reactions were carried out at -35 °C and stirred for 48 hours in dichloromethane. The enantiomeric excess was very high up to 1 mol% catalyst loading and only the *endo* diastereoisomer was observed by ^{1}H NMR (Table 2.18). However, conversions decreased with lower catalyst loading. When using the unsubstituted dienophile **41** with 10 mol% of catalyst the enantiomeric excess (97%) and diastereoselectivity (*endo:exo* >99:1) were very high, but conversion was low (22%). The enantioselectivity was equal to that reported by EVANS using the *t*-Bu-box catalyst and unsubstituted dienophile **41** (*endo* ee 97%, *endo:exo* 92:8, 86% yield).[91] The low conversion compared to EVANS results can presumably be attributed to the lower dienophile concentration in our case (0.1 M vs. 1.0 M).

Table 2.18: *Different catalyst loadings for the Diels-Alder reaction with [Cu((S,S)-β-Np-box)](OTf)$_2$.*



64 (*S*)-**80**

Entry	Cat. Loading (mol%)	*Endo:Exo*[a]	*Endo* ee (%)[b]	Conv. (%)[a]
1	20	>99:1	97	>99
2	10	>99:1	97	40

Entry	Cat. Loading (mol%)	*Endo:Exo*[a]	*Endo* ee (%)[b]	Conv. (%)[a]
3	5	>99:1	96	55
4	1	>99:1	96	8
5	0.5	n.d.	89	<1

a Determined by ^{1}H NMR of the crude product; *b* Determined by chiral HPLC.

In summary, the *β*-Naphthyl-box catalyst gave equal results to the *t*-Bu-box catalyst with unsubstituted dienophile **41** but enhanced enantioselectivity for the substituted Et- and *n*-Bu-dienophiles **64** and **67**. However, the *t*-Bu-box-derived catalyst is more readily synthesised from commercially available starting material in contrast to the *β*-Naphthyl-box catalyst and will therefore remain the ligand of choice for this transformation.

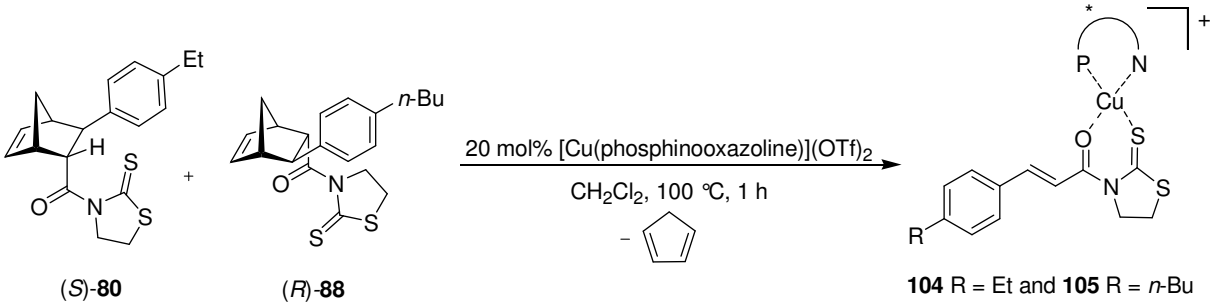
2.5.3 ESI MS Screening Using Phosphinooxazoline Ligands

To demonstrate the versatility of this screening method we tested several phosphinooxazolines as a different ligand class.

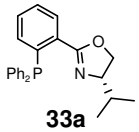
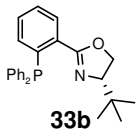
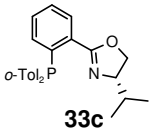
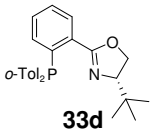
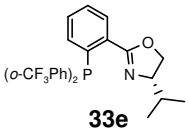
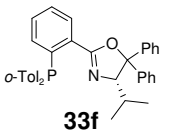
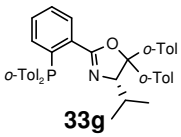
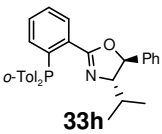
The general procedure for the retro-Diels-Alder reaction was applied (Section 2.3.6) using quasienantiomers (*S*)-**80** and (*R*)-**88**. Phosphinooxazoline ligands **33a-h**, readily available in our group, showed very low enantioselectivity (Table 2.19). Phenyl-substituted ligand **33b** showed a preference for the opposite enantiomer than its *o*-tolyl-substituted analogue **33c** (Table 2.19, entry 1 and 3). The C5-substituted ligands **33f** and **33g** with *o*-tolyl groups at the P-atom exhibited a similar selectivity than their phenyl-substituted counterparts **33a** and **33b** (Table 2.19, entry 6/7 and entry 1/2) indicating that the influence of the C5 aryl-substitution overruled the influence of the P-aryl groups. Diels-Alder adduct complex ratios were usually around 50:50 as observed in the screening with bis(oxazoline) ligands (Section 2.5.1).

Except for entries 2, 3 and 4 in Table 2.19 ESI MS results correlated well with HPLC analytics of the reaction mixtures.

Table 2.19: *Screening of phosphinooxazoline ligands in the retro-Diels-Alder reaction.*



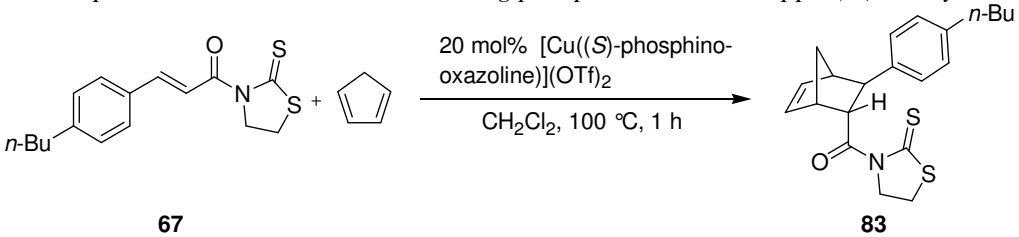
(*S*)-**80** (*R*)-**88** **104** R = Et and **105** R = *n*-Bu

Entry	Ligand	Dienophile Complex **104 : 105**[a]	Dienophile **64 : 67**[b]	DA Adduct Complex **Et : *n*-Bu**[a]
1	 **33a**	55:45	52:48	50:50
2	 **33b**	60:40	68:32	52:48
3	 **33c**	40:60	33:67	53:47
4	 **33d**	51:49	42:58	51:49
5	 **33e**	53:47	50:50	51:49
6	 **33f**	55:45	55:45	57:43
7	 **33g**	57:43	53:47	53:47
8	 **33h**	49:51	48:52	53:47

a Dienophile and Diels-Alder adduct complex ratio determined by ESI MS; *b* Dienophile ratio determined by HPLC.

To verify the ESI MS results preparative forward Diels-Alder reactions were performed according to the same conditions as described in Section 2.4.2. With a few exceptions (Table 2.20, entry 4 and 5) the enantiomeric excess obtained by ESI MS was higher than that observed for the preparative reaction. This is presumably due to monitoring the intrinsic enantioselectivity of the catalysts by ESI MS, which is not disturbed by uncatalysed side reactions or catalytically active impurities. As observed by ESI MS the preparative results confirmed **33b** and **33c** as most selective phosphinooxazoline ligands. However, a clear trend cannot be reproduced by the preparative reaction. Comparison of both data sets made clear that phosphinooxazolinecopper(II)-catalysts are not very enantioselective in the Diels-Alder reaction. Diastereoselectivities were moderate when compared to the those obtained with bis(oxazoline) ligands[91] and conversions were low.

Table 2.20: *Preparative Diels-Alder reaction using phosphinooxazolinecopper(II)-catalysts.*



67 **83**

Entry	Cat.	*Endo:Exo*[a]	*Endo* ee (%)[b]	ESI MS "ee" (%)[c]	Conv. (%)[a]
1	**33a**	85:15	rac.	10 (*S*)	28
2	**33b**	80:20	8 (*S*)	20 (*S*)	12
3	**33c**	n.d.	8 (*R*)	20 (*R*)	<1
4	**33d**	84:16	6 (*S*)	2 (*S*)	25
5	**33e**	72:28	6 (*S*)	6 (*S*)	13
6	**33f**	80:20	rac.	10 (*S*)	21
7	**33g**	n.d.	4 (*S*)	14 (*S*)	13

a Determined by ^{1}H NMR of the crude product; *b* Determined by chiral HPLC; *c* Et-dienophile-*n*-Bu-dienophile complex.

2.5.4 ESI MS Screening Using Bis(imine) Ligands

The screening of bis(imine) ligands in the copper(II)-catalysed retro-Diels-Alder reaction was motivated by their facile and diverse synthesis which readily allowed building a library.

Several bis(imine) ligands were synthesised from either (1*S*,2*S*)-(+)-1,2-diaminocyclohexane or (1*R*,2*R*)-(+)-1,2-diphenylethaneamine (Figure 2.16).

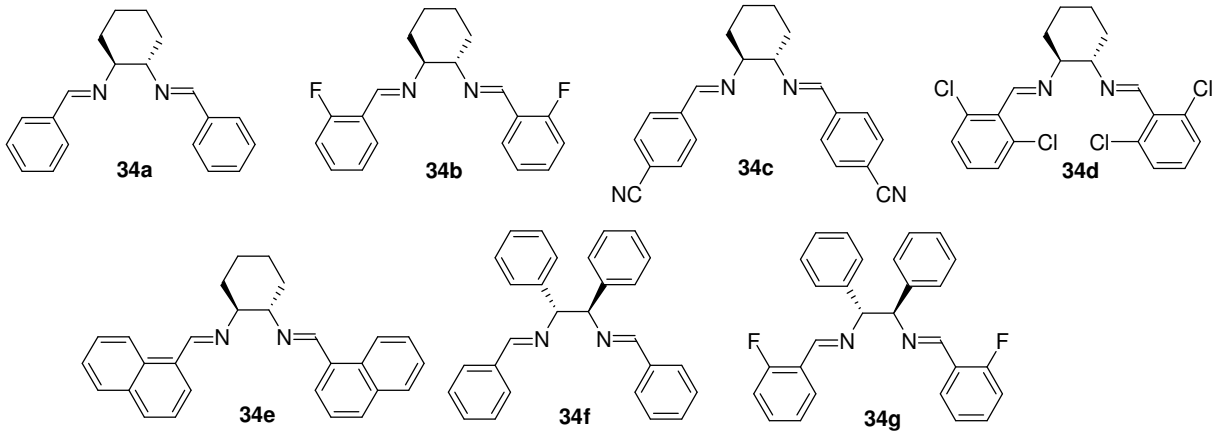
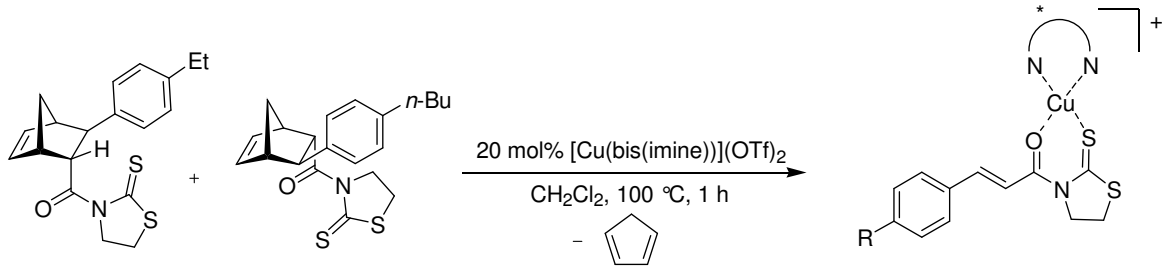


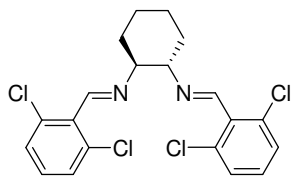
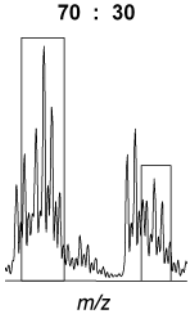
Figure 2.16: *Bis(imine) ligands used in the copper(II)-catalysed retro-Diels-Alder reaction.*

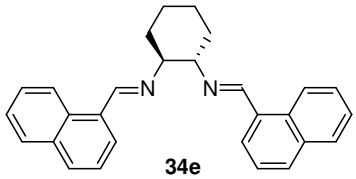
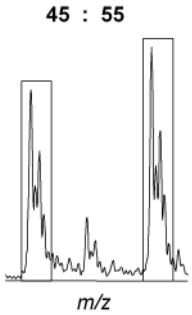
Only for ligands **34d** and **34e** dienophile-catalyst complexes were observed in the retro-Diels-Alder reaction using (*S*)-**80** and (*R*)-**88** as quasienantiomers (Table 2.21). Ligand **34d** produced a high enantiomeric ratio which was expected from previous results by EVANS.[89] The isotope pattern was complicated by the presence of chloride in the complex. The *α*-Naphthyl-substituted ligand **34e** showed almost no enantioselectivity. The results correlated with the HPLC analytics of the reaction mixture.

Table 2.21: *Screening of bis(imine)copper(II)-catalysed retro-Diels-Alder reaction.*



(*S*)-**80** (*R*)-**88** **106** R = Et and **107** R = *n*-Bu

Entry	Ligand	Dienophile Complex **106 : 107**[a]	Dienophile **64 : 67**[b]
1			74:26

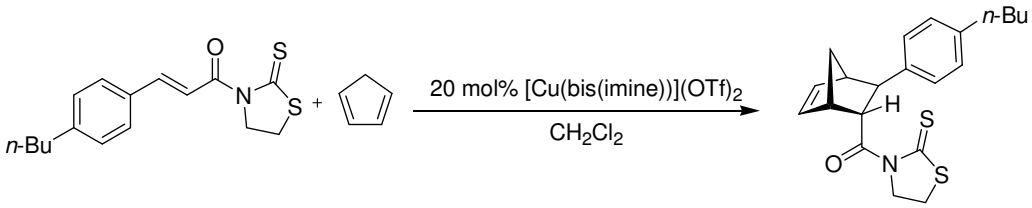
Entry	Ligand	Dienophile Complex 106 : 107[a]	Dienophile 64 : 67[b]
2	 34e		47:53

a Determined by ESI MS; *b* Determined by HPLC.

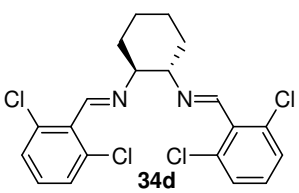
Results from the preparative forward Diels-Alder reaction further confirmed the 2,6-dichlorosubstituted ligand **34d** as highly diastereoselective and enantioselective (Table 2.22). Ligand **34e** showed excellent diastereoselectivities but, as expected from the ESI MS screenings, hardly any enantioselectivity. For both ligands diastereoselectivities and conversion increased with lower reaction temperatures.

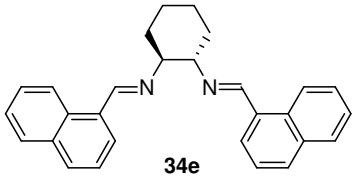
Unfortunately synthesis of several ligands in one pot and subsequent screening of this mixture in the copper(II)-catalysed retro-Diels-Alder reaction could not be accomplished because for some bis(imine) ligands no catalytic intermediates were detected by ESI MS.

Table 2.22: *Bis(imine)copper(II)-catalysed forward Diels-Alder reaction.*



67 (*S*)-**83**

Entry	Ligand	Conditions	*Endo:Exo*[a]	*Endo* ee (%)[b]	Conv. (%)[a]
1	 34d	100 °C, 1 h	87:13	28	55
2		r.t., 20 h	89:11	73	97
3		-20 °C, 48 h	99:1	87	95

Entry	Ligand	Conditions	*Endo:Exo*[a]	*Endo* ee (%)[b]	Conv. (%)[a]
4	 **34e**	100 °C, 1 h	84:16	-2	36
5		r.t., 20 h	95:5	4	51
6		-20 °C, 48 h	>99:1	14	78

a Determined by ^{1}H NMR of the crude product; *b* Determined by chiral HPLC.

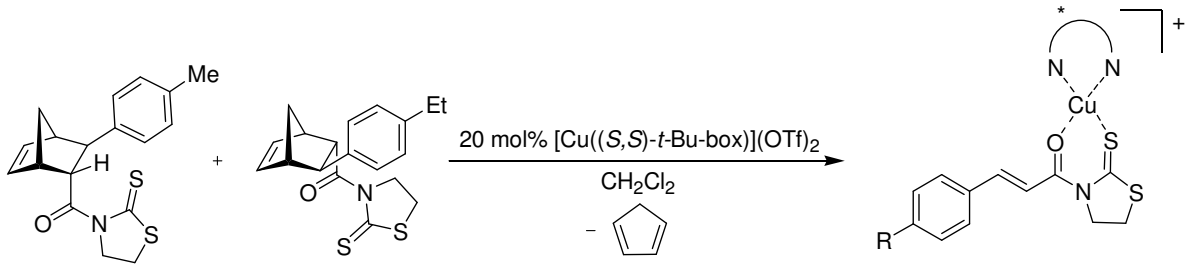
2.6 Studies on the Retro-Diels-Alder Reaction

2.6.1 Influence of Temperature and Reaction Time on the Retro-Diels-Alder Reaction

Elevated temperature was crucial to achieve retro reaction but could also lead to non-catalytic decomposition of the Diels-Alder adducts. If the uncatalysed retro reaction occurs to any extent the observed ratio of dienophile complexes does not correspond to the intrinsic enantioselectivity of the catalyst. To investigate this we subjected the retro-Diels-Alder reaction to different temperatures and analysed the reaction mixtures by ESI MS. A decline of dienophile complex ratios towards a 50:50 ratio would indicate occurrence of an uncatalysed retro reaction. Although Me- and Et-substituted Diels-Alder adducts were used in these experiments, the conclusions should be applicable to the reactions with Et- and *n*-Bu-quasienantiomers.

The experiments were performed using the general screening procedure at different temperatures. At 160 °C the dienophile complex ratio remained constant for 2 minutes (Table 2.23, entry 1-3). After 10 minutes ESI MS analysis revealed a nearly racemic mixture (adjusting for the catalyst's preference for the Me-Diels-Alder adduct) indicating that the uncatalysed retro reaction was dominating (Table 2.23, entry 4). A similar result was observed at 200 °C (Table 2.23, entry 5-7).

Table 2.23: *Influence of reaction conditions on the retro-Diels-Alder reaction.*



(*S*)-**79** (*R*)-**85** **96** R = Me and **98** R = Et

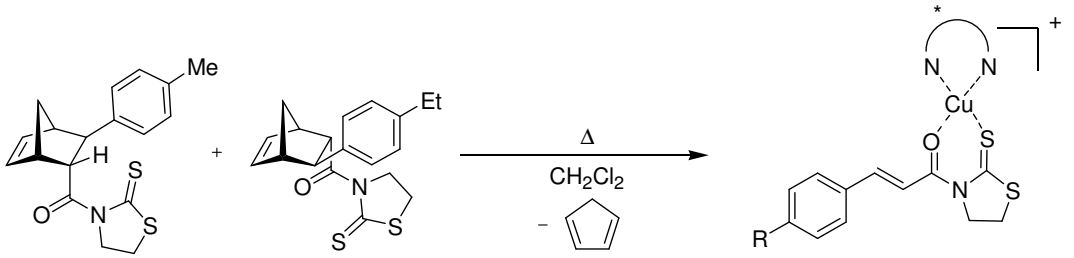
Entry	Conditions	Dienophile Complex 96 : 98[a]	Dienophile 63 : 64[b]
1	160 °C, 30 s	72:28	-
2	160 °C, 2 min	73:27	-
3	160 °C, 10 min	57:43	52:48
4	160 °C, 1 h	52:48	51:49
5	200 °C, 10 s	69:31	-
6	200 °C, 40 s	70:30	-
7	200 °C, 5 min	54:46	50:50

a Dienophile and Diels-Alder adduct complex ratio determined by ESI MS; *b* Dienophile ratio determined by HPLC.

To confirm that the uncatalysed retro reaction was the reason for the decline in selectivity the retro-Diels-Alder reaction was carried out in the absence of catalyst. If the uncatalysed retro reaction took place, dienophile would be observed. After terminating the reaction after the indicated times, possibly present dienophiles underwent complexation with a copper(II)-catalyst. The complexation reactions were performed to render dienophiles present in solution amenable to ESI MS detection.

As seen in Table 2.24 the uncatalysed retro-Diels-Alder reaction only occurred above 110 °C. Stirring for 1 minute at 160 °C gave a relatively small amount of dienophile, which seemed to contradict earlier observations (compare Table 2.23, entry 1 and 2). No influence of the uncatalysed retro reaction had been detected after 1 minute at 160 °C. The proportion of uncatalysed retro reaction was probably small compared to the catalysed process therefore the dienophile complex ratio had not been yet affected. The findings in Table 2.24 proved that the retro-Diels-Alder reaction does not occur below 110 °C and therefore selectivities of reactions carried out below that temperature should not be affected.

Table 2.24: *Uncatalysed retro-Diels-Alder reaction at elevated temperatures.*



(*S*)-**79** (*R*)-**85** **96** R = Me and **98** R = Et

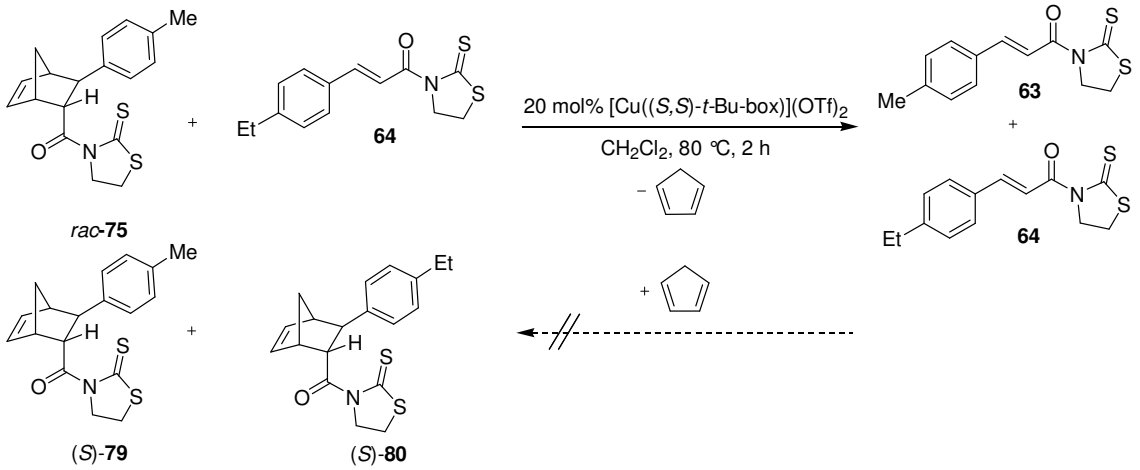
Entry	Conditions	Amount of Dienophile Complexes 96 and 98[a,b]
1	80 °C, 15 min	-
2	80 °C, 2 h	-
3	100 °C, 15 min	-
4	100 °C, 2 h	-
5	110 °C, 15 min	-
6	110 °C, 2 h	-
7	120 °C, 15 min	-
8	120 °C, 2 h	4%[c]
9	160 °C, 1 min	10%[c]
10	160 °C, 2 h	37%[c]

a Amount of dienophiles compared to the amount of DA adducts determined by ESI MS; *b* Achiral [Cu(dimethyl-box)](OTf)$_2$ or chiral [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ was added after the reaction and stirred for 20 minutes at room temperature; *c* Conversion calculated from the integration of both Diels-Alder adduct complex mass peaks versus the integration of both dienophile complex mass peaks.

2.6.2 Reversibility of the Retro-Diels-Alder Reaction under Standard Reaction Conditions

For evaluation concerning the reversibility of the retro-Diels-Alder reaction and thus possible inaccuracies for selectivity measurements, an equimolar mixture of Me-Diels-Alder adduct *rac*-**75** and Et-dienophile **64** was added to [Cu((*S,S*)-*t*-Bu-box)](OTf)$_2$ (Scheme 2.23). If the retro-Diels-Alder reaction was reversible under the applied conditions, the product of the Diels-Alder reaction between the Et-dienophile **64** and the liberated cyclopentadiene should be detected by ESI MS. Of course the generated Me-dienophile **63** can also undergo the Diels-Alder reaction with cyclopentadiene, but it cannot be detected separately, because Me-Diels-Alder adduct *rac*-**75** is already present.

After stirring for 30 minutes at room temperature ESI MS analysis showed the expected complexes for the Me-Diels-Alder adduct **97** and the Et-dienophile **98** (Figure 2.17, **a**). After subjecting the reaction mixture to standard retro-Diels-Alder reaction conditions the reaction mixture was again analysed by ESI MS (Figure 2.17, **b**). If the reaction was reversible under the applied conditions, formation of the Et-Diels-Alder adduct (*S*)-**80** was expected. Analysis of the ESI MS spectrum showed the Me-Diels-Alder adduct complex **97**, the Me-dienophile complex **96** (product of the retro-Diels-Alder reaction) and the Et-dienophile complex **98**. The absence of the Et-Diels-Alder adduct complex **99** in the ESI MS spectrum indicated that the reaction was not reversible under these conditions. Either the concentration of the liberated diene was too small to sufficiently undergo the Diels-Alder reaction or the liberated cyclopentadiene dimerised immediately under the applied conditions. Even if the reaction was reversible the amount was negligible and would not affect the dienophile ratios.



Scheme 2.23: *Investigating the reversibility of the retro-Diels-Alder reaction.*

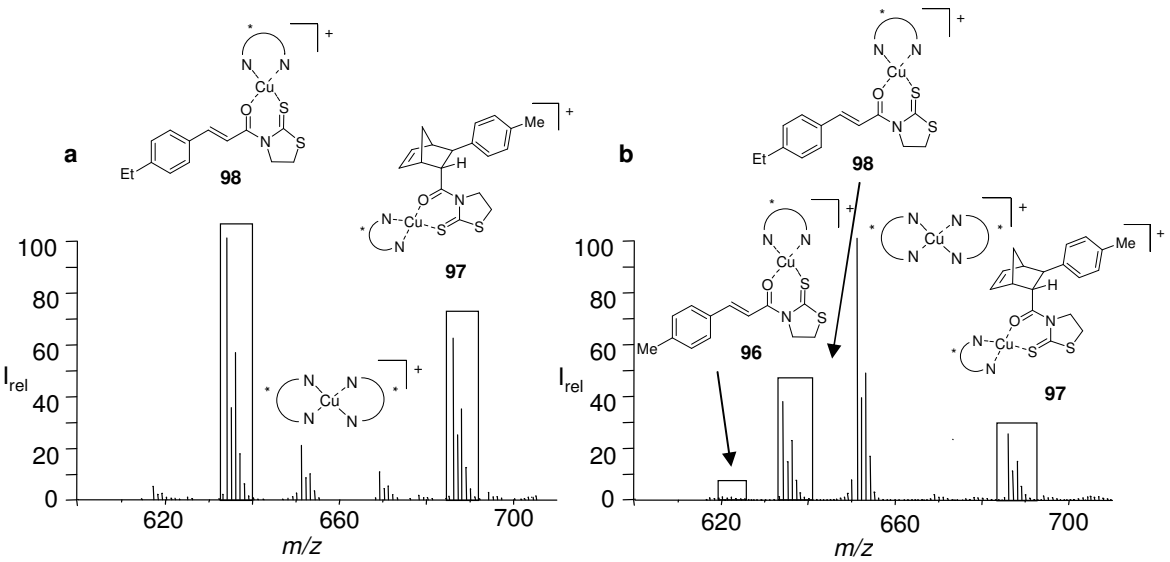


Figure 2.17: *ESI MS spectra for the reaction depicted in Scheme 2.23 (**a**) before and (**b**) after subjecting to standard reaction conditions.*

2.7 Conclusion and Outlook

The objectives of this work were to develop a screening method for the identification of chiral catalysts in the retro-Diels-Alder reaction based on electrospray ionisation mass spectrometry (ESI MS). We have shown that it is possible to selectively monitor the relevant catalyst-reactant intermediates by ESI MS and use the results to identify highly enantioselective catalysts. Sufficiently strong binding between the substrates and the metal catalyst is necessary to allow detection. It was crucial to evaluate the influence of the mass labels that distinguish the complexes by ESI MS.

By using mass-labelled quasienantiomers this method was shown to give a direct measure of the intrinsic enantioselectivity of a chiral catalyst. As the intrinsic selectivity is measured, unselective background reactions, catalytically active impurities and ligand dissociation do not alter the results in contrast to product analysis. A general screening protocol was developed allowing rapid screening limited only by the reaction time. Several control experiments confirmed the validity of this screening technique.

The applicability of this method was demonstrated with five bis(oxazoline) ligands in copper(II)-catalysed retro-Diels-Alder reactions. This led to the identification of highly selective ligands. A separate analytical method (HPLC) confirmed the selectivities obtained by ESI MS. Preparative forward Diels-Alder reactions further confirmed the results in accordance to the principle of microscopic reversibility. The versatility of this method was shown by screening different ligand classes such as phosphinooxazolines and bis(imines).

After successful establishment of an ESI MS screening method for catalyst-reactant complexes of organometallic species this concept was extended to organocatalytic reactions.

Chapter 3

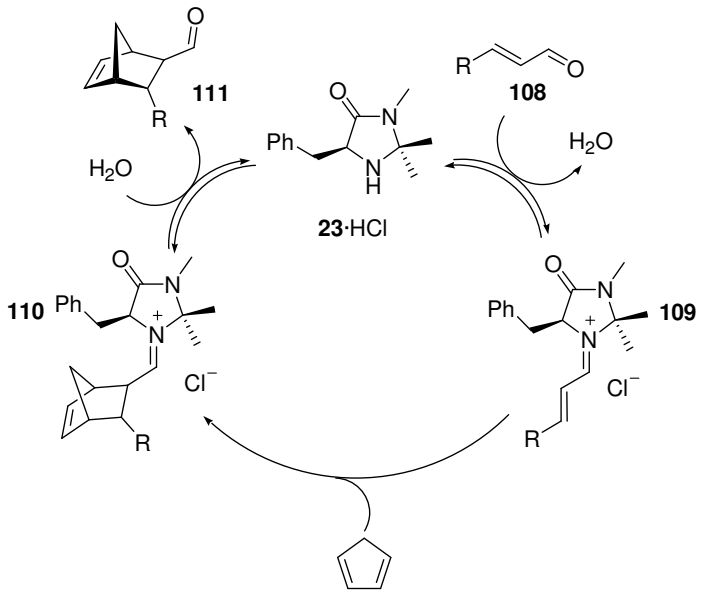
ESI MS Screening of Organocatalysed Retro-Diels-Alder Reactions

3 ESI MS Screening of Organocatalysed Retro-Diels-Alder Reactions

3.1 Introduction

Our ESI MS screening method was originally developed for the copper(II)-catalysed retro-Diels-Alder reaction and was later extended to metal-free organocatalytic reactions.

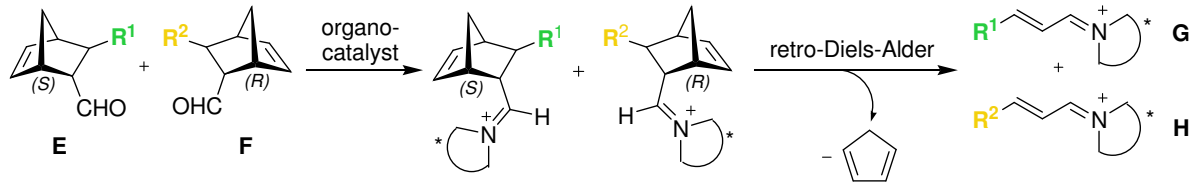
The first highly enantioselective organocatalytic Diels-Alder reaction was reported by MACMILLAN and co-workers in 2000.[107] *α,β*-Unsaturated aldehyde **108** and chiral imidazolidinone catalyst **23**·HCl formed iminium ion species **109**, which was sufficiently activated due to LUMO-lowering to undergo cycloaddition. Accordingly, Diels-Alder reaction with cyclopentadiene involved the intermediacy of iminium ion species **110**. Hydrolysis produced Diels-Alder adduct **111** and the regenerated imidazolidinone catalyst **23**·HCl (Scheme 3.1). Iminium ion intermediates, which are the relevant reaction intermediates in this catalytic cycle, are easily detectable by ESI MS.[57]



Scheme 3.1: *Organocatalysed Diels-Alder reaction with an α,β-unsaturated aldehyde **118** and cyclopentadiene.*

In order to identify highly enantioselective organocatalysts for the retro-Diels-Alder reaction, we envisioned a general screening protocol for secondary amine organocatalysts, including imidazolidinone-derived catalyst **23**·HCl. As demonstrated for the copper(II)-catalysed retro-Diels-Alder reaction the screening was conducted by monitoring catalytic intermediates by ESI MS. Therefore *endo* Diels-Alder adducts **E** and **F,** representing the mass-labelled

quasienantiomers, underwent iminium ion formation with a chiral organocatalyst (Scheme 3.2). The resulting charged Diels-Alder adduct iminium ion species can be detected by ESI MS along with the dienophile iminium ions of interest **G** and **H**. The different masses of **G** and **H** enable the iminium ions to be distinguished by mass spectrometry. The ratio of **G** and **H** reflects the catalyst ability for enantiodiscrimination and gives a direct measure of the enantiomeric ratio. By the principle of microscopic reversibility the information obtained for the retro-Diels-Alder reaction should be directly applicable to the corresponding forward-Diels-Alder reaction.

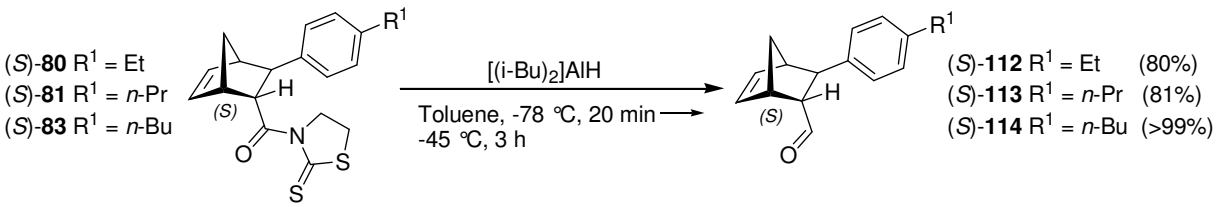


Scheme 3.2: *Iminium ion intermediates for the retro-Diels-Alder reaction with secondary amine organocatalysts. R^1 and R^2 represent the mass labels.*

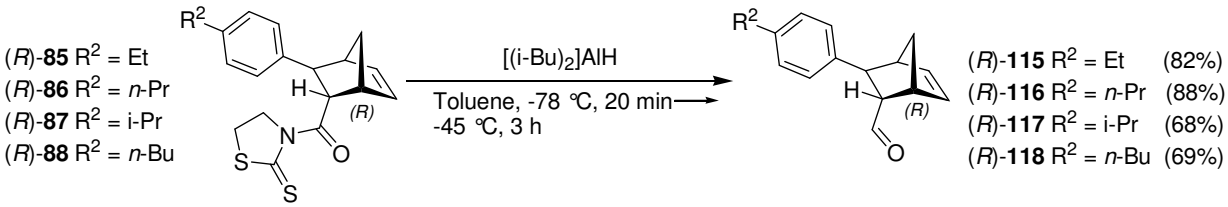
3.2 Synthesis of Quasienantiomeric Diels-Alder Adducts

The quasienantiomers should be: a) enantiopure or highly enantioenriched (both to the same degree) and b) consisting of the same, single diastereoisomer. The mass labels must also be sufficiently removed from the reaction centre such that they do not influence the catalyst reactivity. The quasienantiomers were structurally related to those used for the screening of copper(II)-catalysed retro-Diels-Alder reactions.

Diels-Alder adducts for the organocatalysed retro-Diels-Alder reaction were obtained by reduction of the previously used Diels-Alder adducts (*S*)-**80**, (*S*)-**81** and (*S*)-**83** and (*R*)-**85**-**88**. The enantio- and diastereopure *endo* Diels-Alder adducts (*S*)-**112**, (*S*)-**113** and (*S*)-**114** and (*R*)-**115**-**118** were readily obtained following a reduction procedure by IZAWA and MUKAIYAMA (Schemes 3.3 and 3.4).[155, 156] Good to excellent yields were obtained when the reaction was performed in 0.2 mmol scale or less.

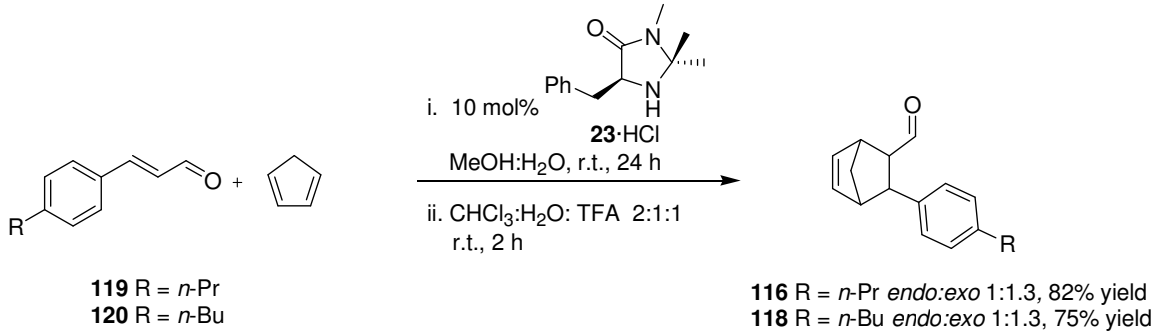


Scheme 3.3: *Synthesis of (S)-Diels-Alder adducts for the organocatalytic retro-Diels-Alder reaction.*



Scheme 3.4: *Synthesis of (R)-Diels-Alder adducts for the organocatalytic retro-Diels-Alder reaction.*

An alternative route to obtain mass-labelled Diels-Alder adducts was the direct synthesis from the aldehydes **119** and **120** and cyclopentadiene with imidazolidinone catalyst **23**·HCl (Scheme 3.5). This strategy was abandoned because the diastereoisomers of adducts **116** and **118** could not be separated. Initially the organocatalysed Diels-Alder reaction gave the dimethyl diacetal which was hydrolysed to give the corresponding aldehyde.

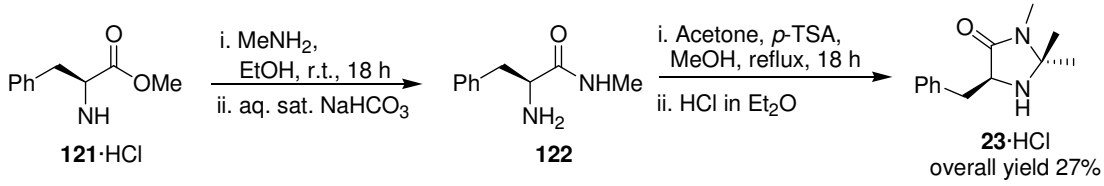


Scheme 3.5: *Diels-Alder reactions using aldehydes **119** and **120** as starting material.*

3.3 Development of Screening Method

3.3.1 Preliminary Experiments

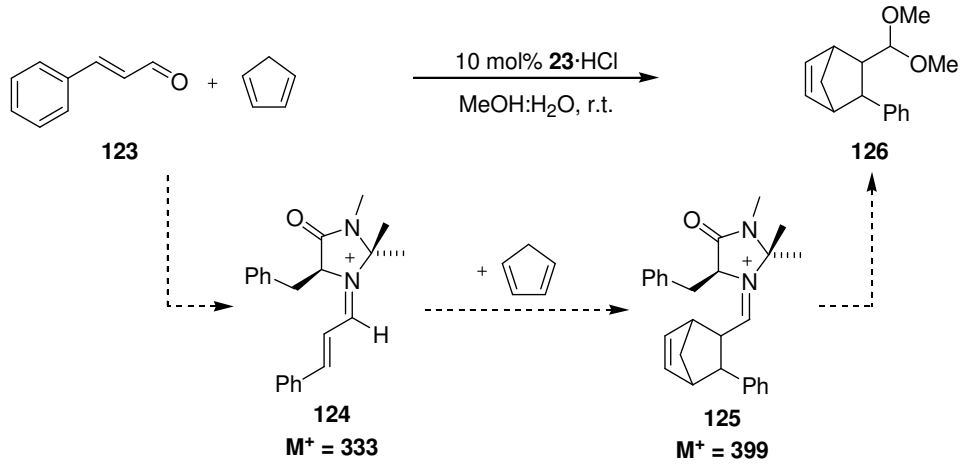
To develop the screening conditions, the Diels-Alder reaction of cinnamaldehyde and cyclopentadiene using imidazolidinone catalyst **23**·HCl was investigated. Both enantiomers of imidazolidinone catalyst **23**·HCl were commercially available or were synthesised in a one pot procedure from (*S*)- or (*R*)-phenylalanine methyl ester **121**·HCl (Scheme 3.6).[107]



Scheme 3.6: *Synthesis of imidazolidinone catalyst **23**·HCl.*[107]

The forward-Diels-Alder reaction was conducted as depicted in Scheme 3.7. Analysis by ESI MS showed the best iminium ion detection when the reaction mixture was diluted in

either methanol or acetonitrile. After 10 minutes of stirring at room temperature, the iminium ion species **124** at *m/z* 333 was observed (Figure 3.1, **a**). The most prominent mass peak at *m/z* 241 represented catalyst **23** plus sodium cation. The mass peak at *m/z* 219 was identified as the protonated catalyst **23**. After 6 hours a new peak at *m/z* 267 was detected which was assigned to the dimethyl diacetal sodium adduct (Figure 3.1, **b**). Iminium ion intermediate **125** at *m/z* 399 was not observed under these conditions. For confirmation dimethyl diacetal adduct **126** was dissolved in methanol and analysed by ESI MS showing an intense peak at *m/z* 267.



Scheme 3.7: *The iminium ion intermediates in the organocatalysed Diels-Alder reaction with imidazolidinone **23**·HCl as catalyst.*

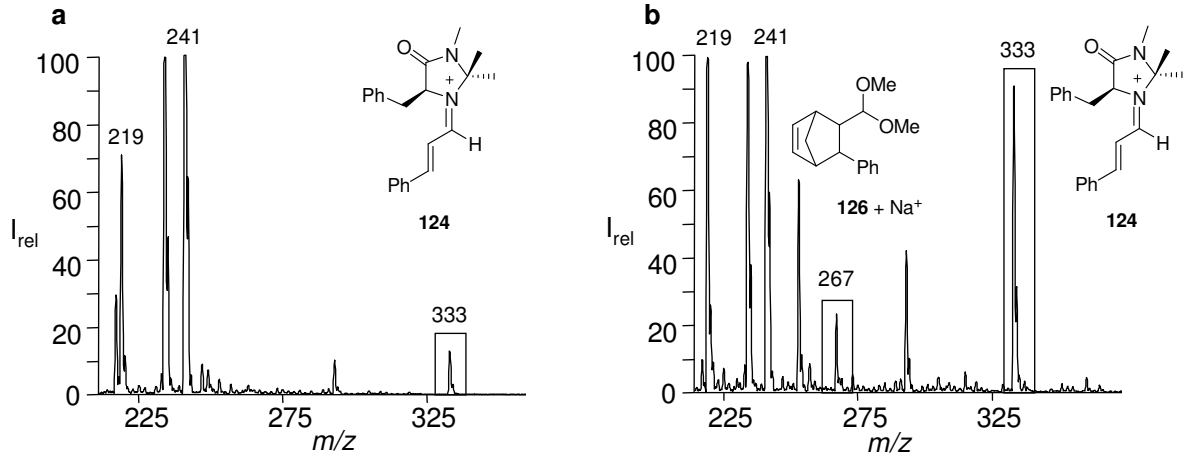
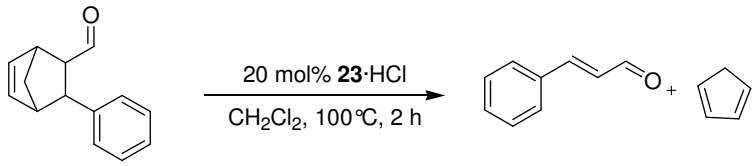


Figure 3.1: *ESI MS spectra of the Diels-Alder reaction with catalyst **23**·HCl (**a**) after 10 min and (**b**) after 6 hours.*

Retro-Diels-Alder reaction was not achieved by heating Diels-Alder adduct **127** in methanol at 100 °C for 24 hours. As retro-Diels-Alder reactions had worked well in dichloromethane for the copper(II)-catalysed reactions, organocatalytic retro-Diels-Alder reactions were performed using 20 mol% imidazolidinone catalyst in that solvent at 100 °C (Scheme 3.8).

After 2 hours iminium ion species **124** and **125** along with catalyst-derived mass peaks (*m/z* 219 and 241) were observed in the ESI MS spectrum (Figure 3.2). Because no methanol was present the dimethyl diacetal adduct **126** was not detected. Addition of water to the reaction mixture resulted in low peak intensities of the iminium ion intermediates. Retro-Diels-Alder reaction also proceeded at room temperature. These conditions were milder and closely resembled those for the originally developed Diels-Alder reaction by MACMILLAN and co-workers (room temperature, 8 hours).[107]



Scheme 3.8: *The organocatalysed retro-Diels-Alder reaction in dichloromethane.*

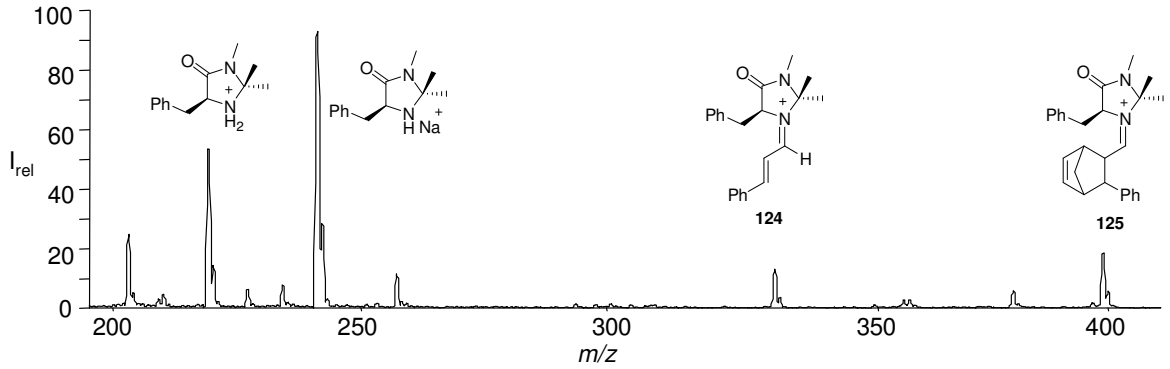


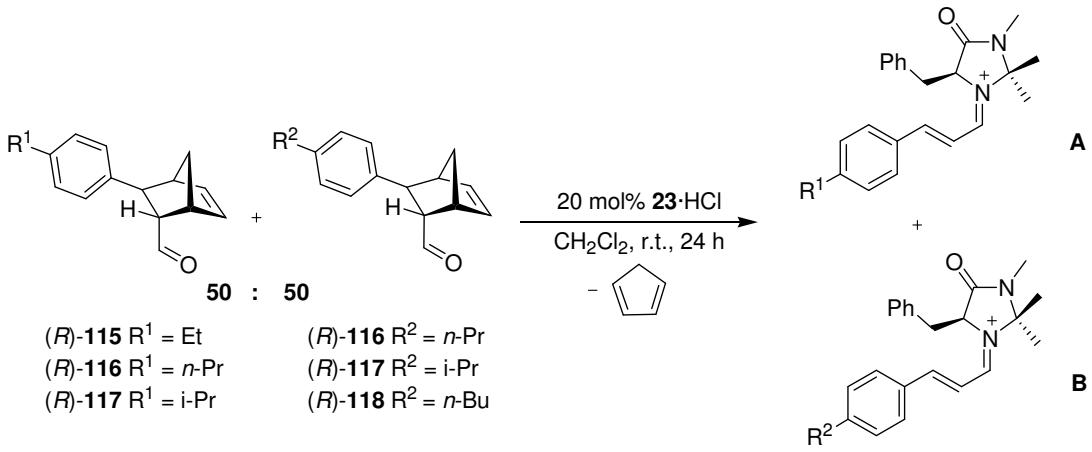
Figure 3.2: *ESI MS spectrum of the retro-Diels-Alder reaction as depicted in Scheme 3.8.*

3.3.2 Evaluation of Appropriate Quasienantiomers

To determine suitable quasienantiomers, combinations of differently substituted Diels-Alder adducts were tested in a direct competition experiment (Table 3.1). Equimolar mixtures of (*R*)-Diels-Alder adducts, for example (*R*)-**115** and (*R*)-**116**, underwent the retro-Diels-Alder reaction with imidazolidinone catalyst **23**·HCl. Taking only the (*R*)-Diels-Alder adducts eliminated the stereochemical influence and the reaction could be analysed with regard to the mass labels. If the catalyst was unaffected by the mass substituents, a 50:50 ratio for the dienophile iminium ions **A** and **B** was expected. Out of all tested combinations (*R*)-**116** and (*R*)-**118** showed the least difference towards the catalyst (Table 3.1, entry 5) and were therefore chosen to be used as quasienantiomers in the following screening reactions. A near 50:50 ratio of the Diels-Alder adduct iminium ions indicated also no influence of the mass

labels for the initial iminium ion formation. The results are not entirely consistent with the Hammett substitution constants σ_P and R values (see Section 2.3.5, Table 2.11). Although Hammett substitution constants σ_P give similar values for substituents in entry 1, 3 and 5 (Table 3.1), the more refined R values are electronically more similar for substituents in entry 2, 3 and 4 than in entry 1 and 5.

Table 3.1: *Direct competition experiment for determination of suitable quasienantiomers.*



(*R*)-**115** R^1 = Et (*R*)-**116** R^2 = *n*-Pr
(*R*)-**116** R^1 = *n*-Pr (*R*)-**117** R^2 = i-Pr
(*R*)-**117** R^1 = i-Pr (*R*)-**118** R^2 = *n*-Bu

Entry	Quasienantiomers R^1 : R^2	Dienophile Iminium Ions A : B[a]	DA Adduct Iminium Ions R^1 : R^2 [a]
1	(*R*)-**115**/(*R*)-**116**	43:57	n.d.
2	(*R*)-**115**/(*R*)-**117**	63:37	59:41
3	(*R*)-**115**/(*R*)-**118**	47:53	n.d.
4	(*R*)-**117**/(*R*)-**118**	36:64	40:60
5	(*R*)-**116**/(*R*)-**118**	48:52	51:49

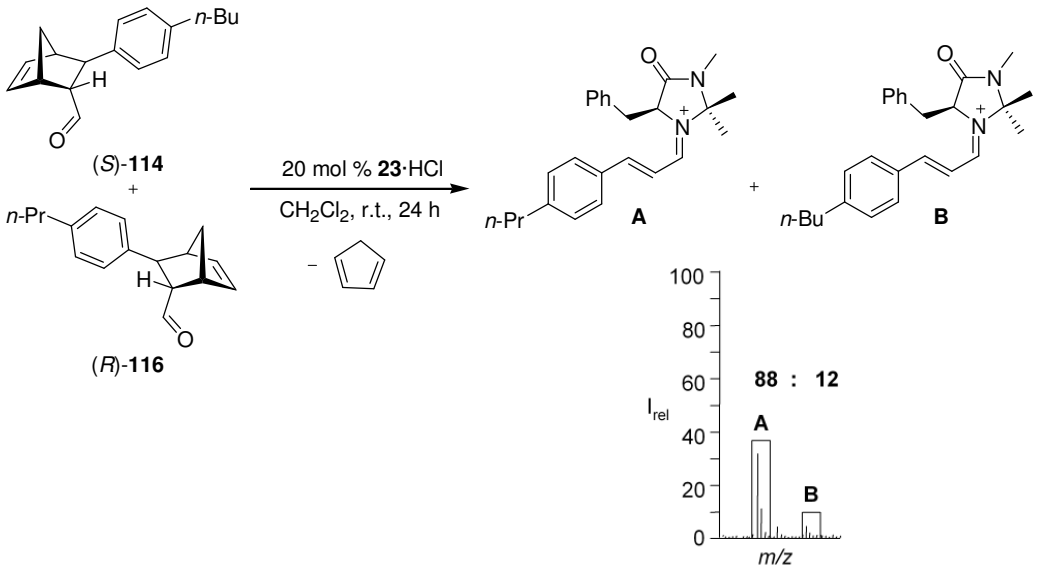
a Ratio determined by ESI MS.

3.3.3 Direct Monitoring of Iminium Ion Intermediates in the retro-Diels-Alder Reaction using Imidazolidinone and Proline-Based Catalysts: General Screening Protocol

The retro-Diels-Alder reaction was conducted under inert atmosphere and anhydrous solvents to ensure reproducible reaction conditions. Typical conditions were 20 mol% of organocatalyst and performing the reactions at room temperature. An aliquot of the reaction mixture was diluted in acetonitrile and injected directly into the mass spectrometer. The ratios for the dienophile iminium ions were determined by integration (see Section 5.5.1 for details).

It was important to keep the same mass range (Δ *m/z* = 300) throughout all experiments for comparable data.

Using quasienantiomers (*S*)-**114** and (*R*)-**116** a 88:12 ratio of dienophile iminium ions **A** and **B** was observed (Scheme 3.9). As expected the (*S*)-catalyst was more reactive towards the (*R*)-Diels-Alder adduct which is in agreement with the results reported in the literature.[107]



Scheme 3.9: *The organocatalysed retro-Diels-Alder reaction.*

3.4 Control Experiments

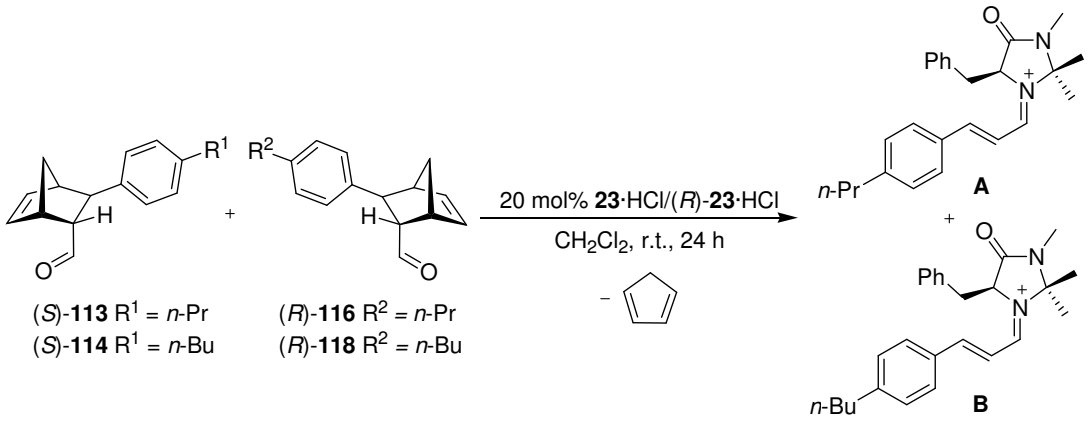
3.4.1 Reversed Ligand Configuration and Inversely Labelled Quasienantiomers

Control experiments were performed to prove the validity of this method. Four experiments involving both quasiracemates, (*S*)-**114** and (*R*)-**116** and (*R*)-**118** and (*S*)-**113**, with either the (*S*)- or the (*R*)-imidazolidinone catalyst **23**·HCl or (*R*)-**23**·HCl were conducted. If the method is valid reaction of the same quasiracemate either with the (*S*)- or the (*R*)-catalyst should give exactly the inverse ratios for the dienophiles (for example 88:12 vs. 12:88). Comparing the results of both quasiracemates with the same catalyst should also show the exact inverted ratio. If the dienophile ratios do not match, this implies that the mass labels of the quasienantiomers affect the stereoselectivity of the catalyst.

All experiments showed the expected matching ratios validating our method (Table 3.2, Figure 3.3). Diels-Alder adduct iminium ion ratios were very similar to those obtained for the

dienophile adducts (except for entry 4) suggesting that iminium ion formation was already determined by the configuration of the Diels-Alder adducts.

Table 3.2: *Control experiments with both quasiracemates and inversely configurated catalysts.*



Entry	Cat.	Quasienantiomers $R^1 : R^2$	Dienophile Iminium Ions A : B[a]	DA Adduct Iminium Ions $R^1 : R^2$ [a]
1	*S*	(*S*)-**113**/(*R*)-**118**	12:88	10:90
2	*S*	(*R*)-**116**/(*S*)-**114**	88:12	92:8
3	*R*	(*S*)-**113**/(*R*)-**118**	88:12	86:14
4	*R*	(*R*)-**116**/(*S*)-**114**	15:85	30:70

a Dienophile and Diels-Alder adduct iminium ion ratios determined by ESI MS.

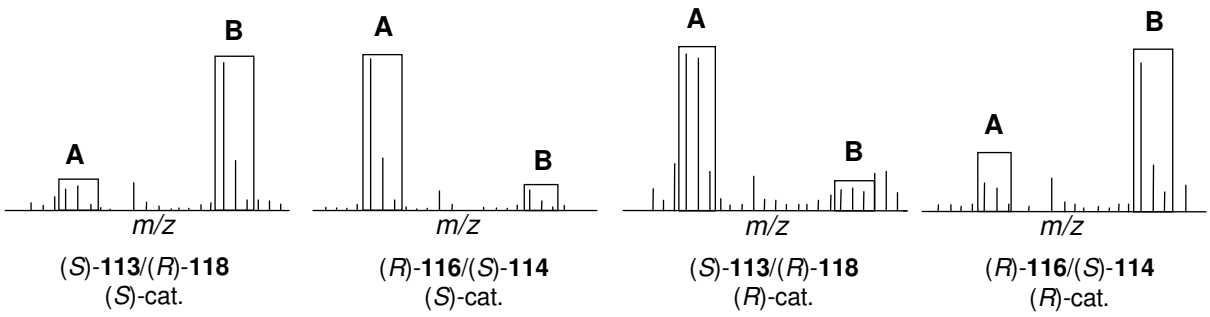


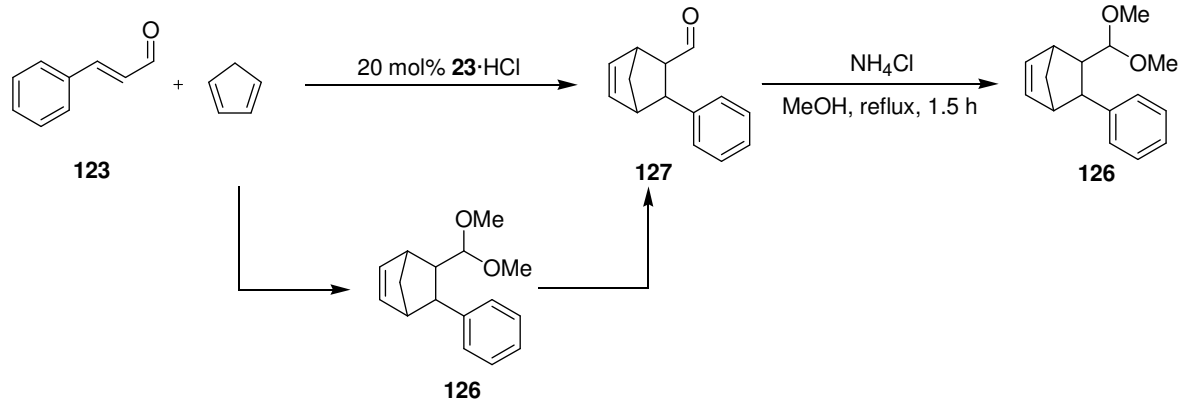
Figure 3.3: *ESI MS spectra of the control experiments.*

3.4.2 Comparison with Preparative Experiments

In accordance to the principle of microscopic reversibility we expected the stereoselectivity of the forward-Diels-Alder reaction to be in good agreement with that of the retro-Diels-Alder reaction. At similar conditions as the retro reaction, the obtained enantiomeric excess for the Diels-Alder reaction was in excellent agreement with the ESI MS results (Table 3.3, entry 1,

75% ee; compare Table 3.2, ESI MS 76% ee). The Diels-Alder adduct **127** was converted to the dimethyl diacetal **126**[157] for additional GC analysis confirming the results for the Diels-Alder adduct **127**. Conversions in dichloromethane were low whereas good to excellent conversions were obtained in methanol:water as solvent. Presumably catalyst regeneration in anhydrous dichloromethane was not possible resulting in low conversion. Concentration of the dienophile was lower in dichloromethane because retro-Diels-Alder reaction conditions were simulated. This also could have had an effect on conversion. A remarkably high enantiomeric excess was observed when stirring the reaction for 10 minutes at 50 °C.

Table 3.3: *Preparative Diels-Alder reactions with cinnamaldehyde **123** and cyclopentadiene.*



Entry	Conditions	Conv. (%)[a]	*Endo:Exo*[a]	*Endo* ee (%)[b]	*Exo* ee (%)[b]
1[c]	CH_2Cl_2, r.t., 24 h	5	1 : 3.2	75 (74)[d]	84 (83)[d]
2[e, f, g]	MeOH:H_2O 95:5, r.t., 24 h	99	1 : 1.4	90	92
3[c]	CH_2Cl_2, 50 °C, 10 min	6	1 : 1.5	82	86

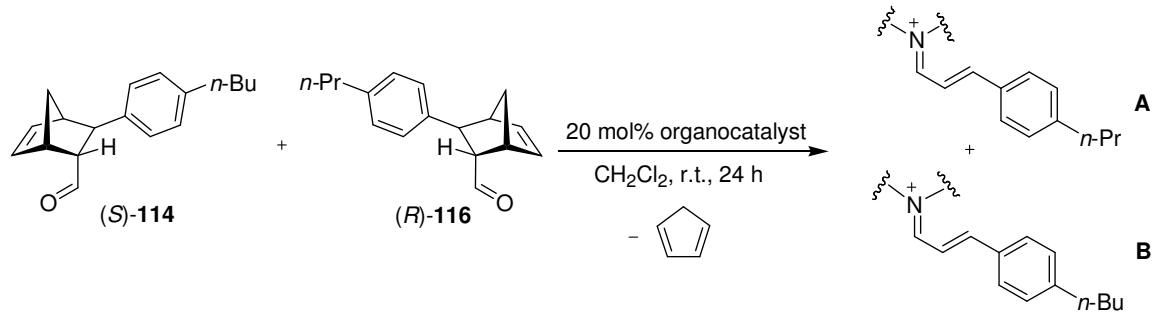
a Determined by ^{1}H NMR of the crude product; *b* Determined by chiral GC; *c* 0.1 M; *d* The corresponding dimethyl diacetal **126** was analysed; *e* 1.0 M; *f* The dimethyl diacetal **126** was treated with $CHCl_3$:TFA:water 2:1:1 for 2 hours at r.t. to give the aldehyde; *g* 5 mol% of catalyst was used.

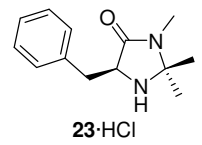
3.5 ESI MS Screening of Imidazolidinone and Proline-based Organocatalysts

3.5.1 ESI MS Screening Results

Applying the general screening protocol, a series of readily available organocatalyst were screened in the retro-Diels-Alder reaction (Table 3.4).

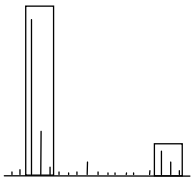
Table 3.4: *Screening results for a series of organocatalysts.*





23·HCl

88 : 12



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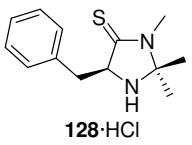
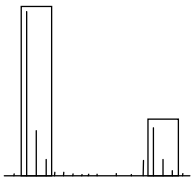


128·HCl

83 : 17



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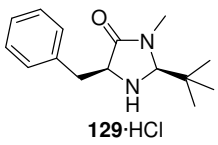
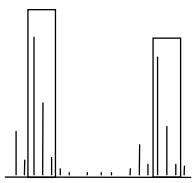


129·HCl

54 : 46



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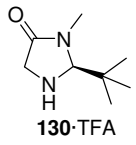
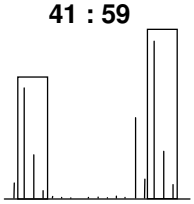


130·TFA

41 : 59



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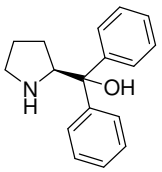
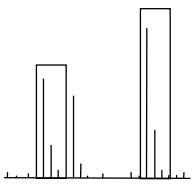


131

40 : 60



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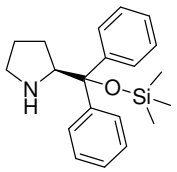
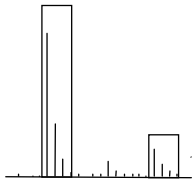


132

84 : 16



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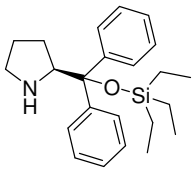
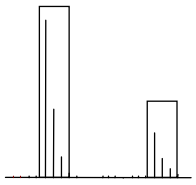


133

78 : 22



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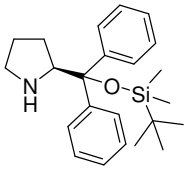
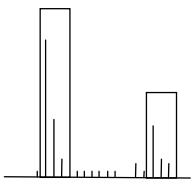


134

73 : 27



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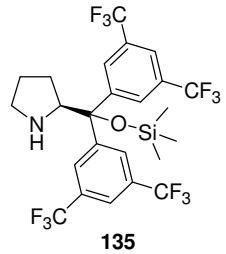
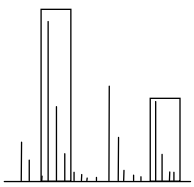


135

67 : 33



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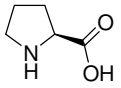
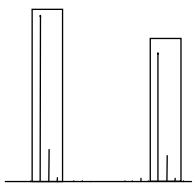


136

57 : 43



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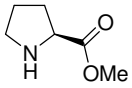
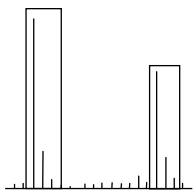


137·HCl

59 : 41



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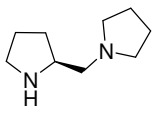
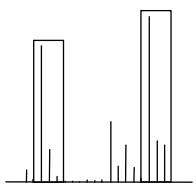


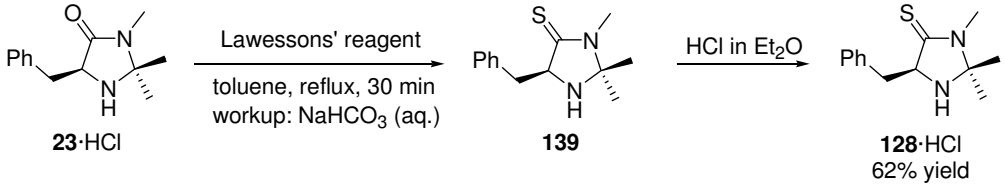
138

45 : 55



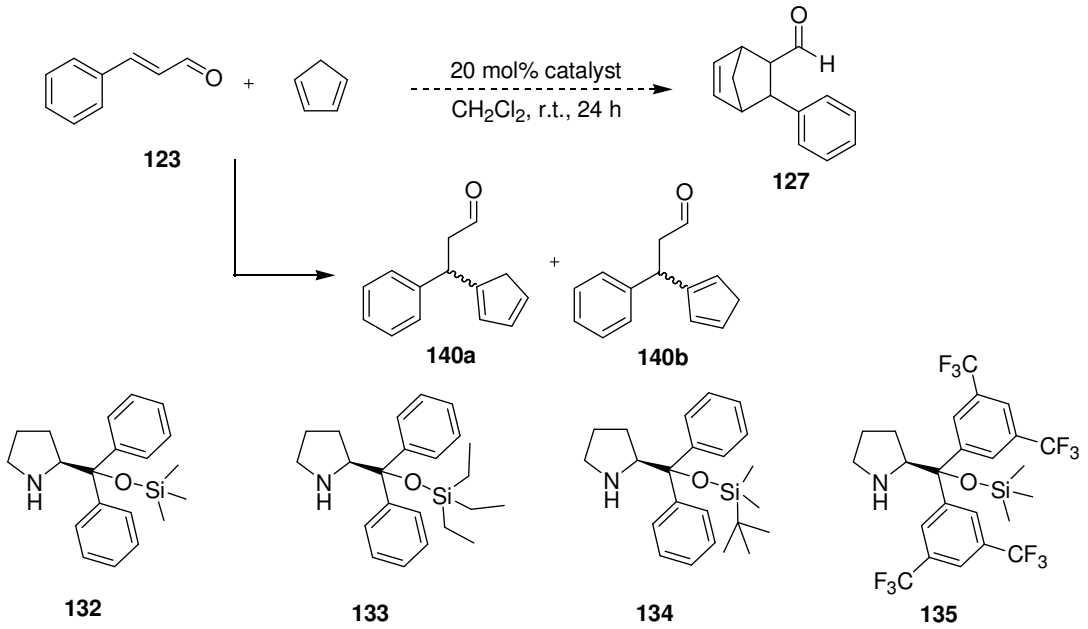
m/z

The highest enantioselectivity was observed for the imidazolidinone catalyst **23**·HCl.[107] The sulphur-substituted catalyst **128**·HCl showed good enantioselectivity. Synthesis of **128**·HCl was achieved using Lawessons' reagent to introduce the sulphur (Scheme 3.10). The crude product was converted to the free secondary amine **139** for purification by column chromatography. Addition of HCl to a solution of **139** gave the secondary amine salt **128**·HCl. The preparative forward-Diels-Alder reaction in methanol:water using 20 mol% of **128**·HCl proceeded with 92% conversion, an endo*:exo* selectivity of 1:1.5, an *endo* enantiomeric excess of 86% and an *exo* enantiomeric excess of 85%. As the results were comparable to those of imidazolidinone catalyst **23**·HCl (compare Table 3.3, entry 2) exchange of oxygen by sulphur had only a minimal influence on the enantioselectivity.



Scheme 3.10: *Synthesis of sulphur-containing catalyst **128**·HCl.*

Diarylprolinol silyl-derived catalysts **132**-**135**[158, 159] showed promising enantioselectivities. However, the forward-Diels-Alder reactions with cinnamaldehyde and cyclopentadiene using 20 mol% of the corresponding diarylprolinol silyl ether gave less than 1% conversion to the Diels-Alder adduct in all cases (Scheme 3.11). Instead formation of the ene-products **140a** and **140b** was observed in some cases (catalyst **132** 7% conversion, catalyst **133** and **134** 5%, catalyst **135** no conversion). An enantioselective ene-reaction using the same starting material and the same catalysts in methanol was reported by HAYASHI and co-workers previously.[160] Higher yields (83-91%) than in dichloromethane were obtained presumably because hydrolysis and regeneration of the catalyst were facilitated in methanol. They reported that using **134**·HCl in methanol:water gave the Diels-Alder adduct **127** in 12% yield without ene product formation. These results suggested that the course of the reaction can change dramatically under acid conditions. In a recent publication, HAYASHI and co-workers reported that in the presence of an acid catalyst the Diels-Alder reaction becomes the major pathway affording the *exo* isomer with high diastereo- and excellent enantioselectivities.[116]



Scheme 3.11: *Diarylprolinol silyl ethers **132-135** as catalysts for the reaction between cinnamaldehyde **123** and cyclopentadiene.*

To summarise diarylprolinol silyl-derived catalysts **132**-**135** showed promising enantioselectivities in ESI MS, but almost no reactivity when applied in the Diels-Alder reaction. As catalyst reactivity is an important aspect, we investigated if relative reactivity can be correctly predicted by ESI MS. From the ESI MS spectra the catalyst's reactivity was deduced by comparing the mass peak intensities of the dienophile iminium ions to those of the Diels-Alder adducts. Three catalysts showing high (catalyst **136**), medium (catalyst **23**·HCl) and low (catalyst **132**) dienophile to adduct iminium ion ratios in the retro-Diels-Alder reaction were compared to the forward reaction with cinnamaldehyde and cyclopentadiene. The Diels-Alder reaction was conducted in methanol:water with 5 mol% catalyst loading at room temperature and terminated after 6 hours. The most reactive catalyst turned out to be imidazolidinone catalyst **23**·HCl, followed by proline **136** and diarylprolinol silyl ether **132** (Table 3.5). These were different from the ESI MS results, for which proline **136** seemed to be the most efficient catalyst. However, a correlation for the measured reactivities of the retro reaction by ESI MS and the preparative forward reaction cannot be expected because different solvents (dichloromethane/ methanol) were used.

Table 3.5: *Comparison of the reactivity in the retro-Diels-Alder reaction by ESI MS and in the preparative forward-Diels-Alder reaction.*

Entry	Cat.	Dienophile vs. DA Adduct Iminium Ions (ESI-MS)[a]	Conv. DA Reaction (%)[b]
1	**136**	97:3	11
2	**23**·HCl	67:33	77
3	**132**	6:94	3

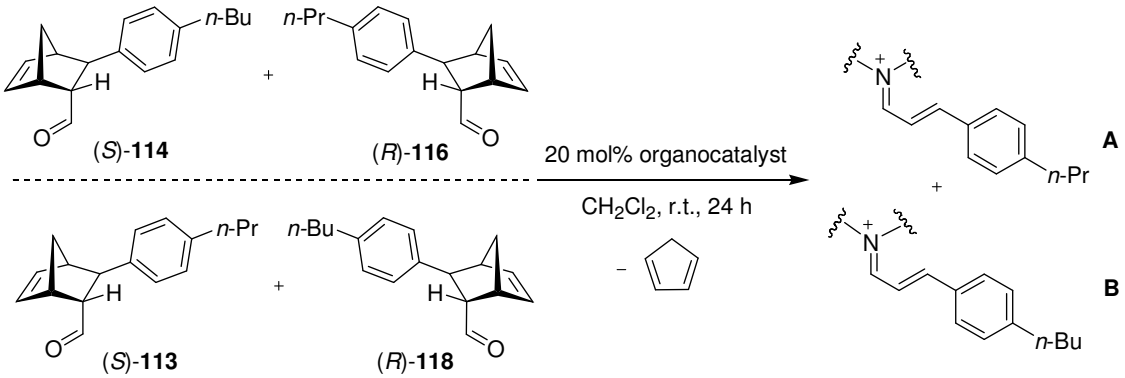
a Ratio determined by ESI MS by comparing the amount of dienophile iminium ions to DA adduct iminium ions; *b* Conversion determined by ^{1}H NMR.

With this ESI MS screening method iminium ion intermediates of organocatalysts can be monitored to give information about the catalysts' enantioselectivity. In principle, the method is broadly applicable as long as charged iminium ion intermediates are formed. In some cases organocatalysts form iminium ions, but give zwitterionic species during the electron ionisation process which cannot be detected by ESI MS.

3.5.2 Control Experiments with Inversely Labelled Quasienantiomers

The screening results were confirmed by conducting control experiments with the inversely labelled quasienantiomers. When those were used, exact inversion of the dienophile iminium ion ratios was expected. Comparison of both data sets showed that the dienophile ratios matched perfectly in most cases (Table 3.6).

Table 3.6: *Confirmation of screening results with opposite quasienantiomers.*



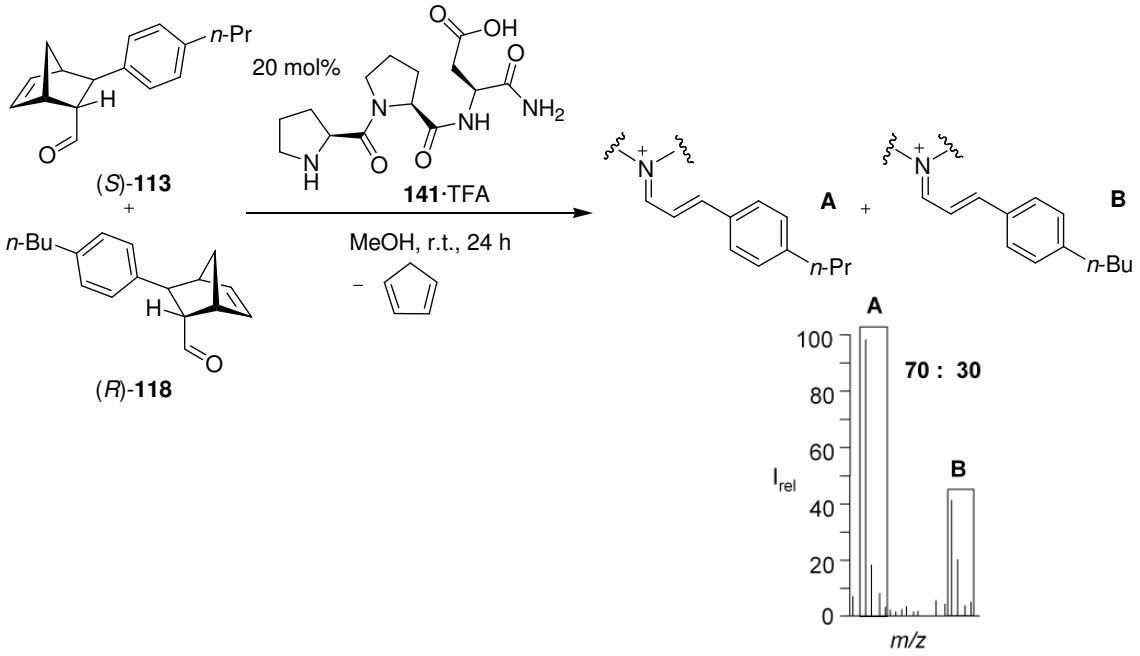
Entry	Cat.	(*R*)-116/(*S*)-114 Dienophile Iminium Ion A : B	DA Adduct Iminium Ion *n*-Pr : *n*-Bu	(*S*)-113/(*R*)-118 Dienophile Iminium Ion A : B	DA Adduct Iminium Ion *n*-Pr : *n*-Bu
1	**23**·HCl	88:12	92:8	12:88	10:90
2	**128**·HCl	83:17	46:54	19:81	28:72
3	**129**·HCl	54:46	22:78	43:57	74:26
4	**130**·TFA	41:59	30:70	60:40	65:35
5	**131**	40:60	27:73	60:40	78:22
6	**132**	84:16	70:30	20:80	29:71
7	**133**	78:22	63:37	23:77	33:67
8	**134**	73:27	55:45	19:81	28:72
9	**135**	67:33	21:79	28:72	76:24
10	**136**	57:43	63:37	43:57	27:73
11	**137**·HCl	59:41	63:37	40:60	22:78
12	**138**	45:55	44:56	55:45	51:49

3.6 ESI MS Screening of Peptide-Catalysts

Small oligopeptides present an interesting class of potential catalysts since they are not as complex as enzymes and antibodies, but offer many sites for functional and structural modifications.[106, 161] Using peptides in metal-free asymmetric catalysis is a newly developing field,[162-171] we therefore became interested in screening enantioselective peptides for the retro-Diels-Alder reaction in collaboration with the group of H. WENNEMERS. Peptides contain secondary amines which can undergo iminium ion formation with aldehydes rendering them amenable to screening conditions similar to those applied for the imidazolidinone and proline-based organocatalysts.

3.6.1 General Screening Protocol

To ensure reproducible results, the retro-Diels-Alder reaction was conducted under inert atmosphere and with anhydrous solvents. *Endo* *n*-Pr- and *n*-Bu-labelled quasienantiomers with 20 mol% of peptide-catalyst in methanol were used. These are typical conditions for organocatalysis. Peptides were used as TFA salts. An aliquot of the reaction mixture was diluted in methanol and injected directly in the mass spectrometer. The ratios for the dienophile iminium ions were determined by integration. A representative reaction using quasienantiomers (*S*)-**113** and (*R*)-**128** is shown in Scheme 3.12. The dienophile iminium ion ratio was 70:30, which confirmed that the retro-Diels-Alder reaction was actually catalysed by the peptide.



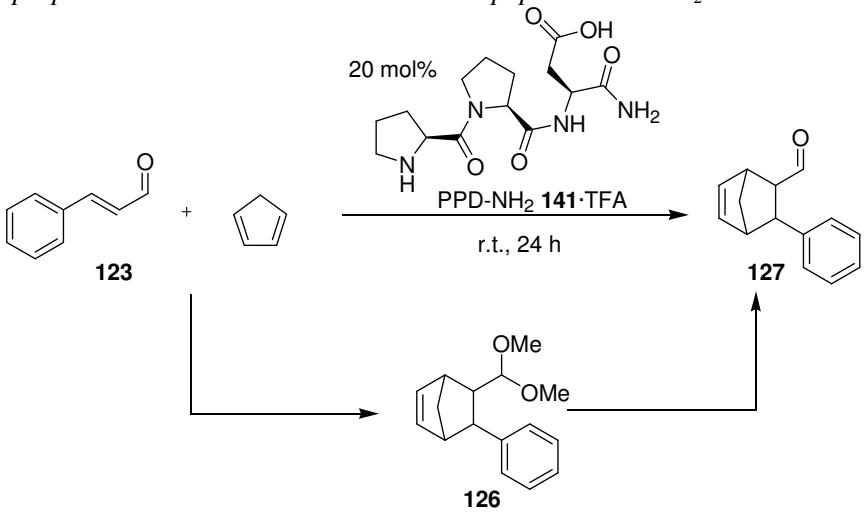
Scheme 3.12: *The peptide-catalysed retro-Diels-Alder reaction.*

3.6.2 Comparison with the Forward-Diels-Alder Reaction

For confirmation of the results by ESI MS and to investigate the activity of the peptide-catalyst, the Diels-Alder reaction was conducted in methanol under similar conditions to that of the retro-Diels-Alder reaction (Table 3.7). Additionally, the reaction was conducted in dimethylformamide and dichloromethane to evaluate the potential of the peptide-catalysts. When methanol was used as solvent, dimethyl diacetal **126** was obtained and hydrolysed to give **127**.

The *endo* enantiomeric excess obtained for the forward reactions in methanol and methanol:water was very similar (Table 3.7, entry 1 and 2) and correlated excellently with the results obtained by ESI MS (Scheme 3.12, ESI MS 40% ee). Addition of water led to better conversion presumably because regeneration of the catalyst was facilitated by hydrolysis (Table 3.7, entry 1).[107] The reaction in dimethylformamide (not dried) gave lower *endo* enantiomeric excess and moderate conversion. Very low conversion was observed for the reaction in dichloromethane with 5 % of water probably due to the low solubility of the peptide salt in that solvent. As enantioselectivities were promising, a screening consisting of several peptide-catalysts was conducted.

Table 3.7: *The preparative Diels-Alder reaction with tripeptide PPD-NH$_2$* ***141***·*TFA.*[a]



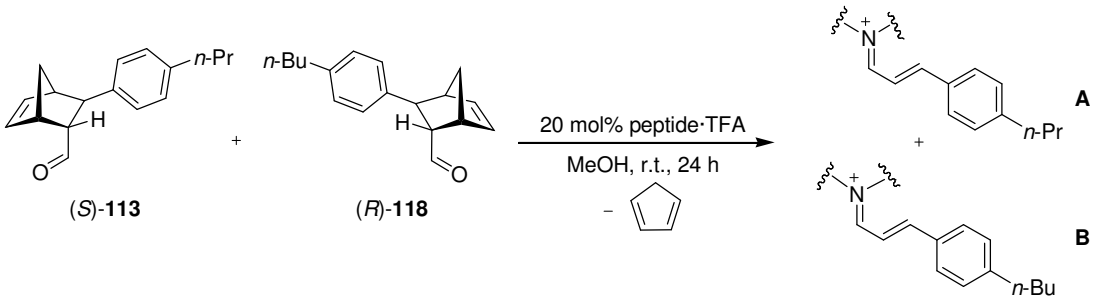
Entry	Solvent	*Endo:Exo*[b]	*Endo* ee (%)[c]	*Exo* ee (%)[c]	Conv. (%)[b]
1[d]	MeOH:H_2O 95:5	1:2.3	41	39	83
2[e]	MeOH	1:2.2 (1:2.2)[d]	41 (40)[d]	32 (30)[d]	27
3	Dimethylformamide	1:2.2	35	30	56
4	CH_2Cl_2:H_2O 95:5	1:2.3	n.d.	n.d.	4

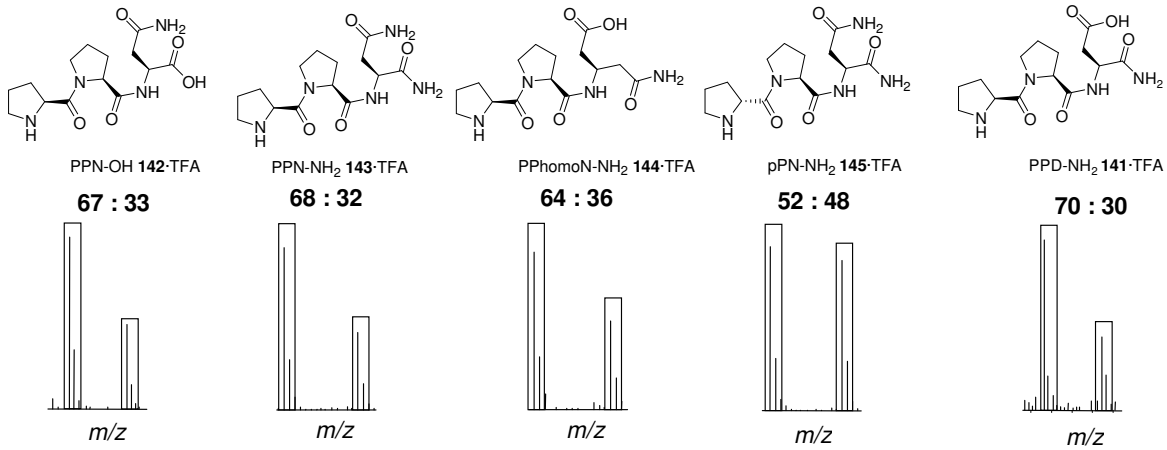
a All reactions were 1.0 M regarding dienophile **123**; *b* Determined by ^{1}H NMR of the crude product; *c* Determined by chiral GC; *d* The dimethyl diacetal **126** was analysed; *e* The dimethyl diacetal **126** was treated with $CHCl_3$:TFA:water 2:1:1 for 2 hours at r.t. to give **127**.

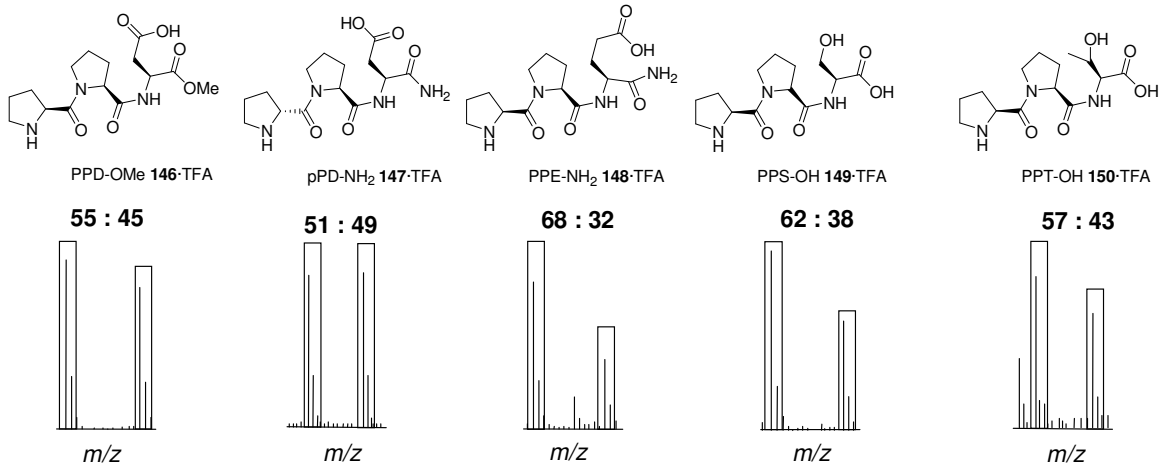
3.6.3 ESI MS Screening Results

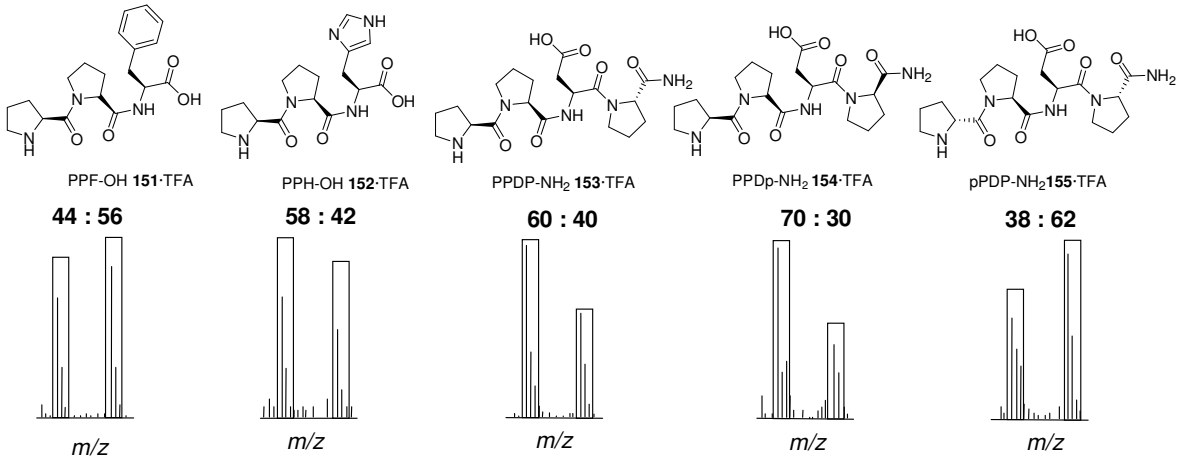
Applying the general screening protocol several small oligopeptide were subjected to screening (Table 3.8). Common mass peaks in all spectra next to the iminium ion intermediates of interest were the protonated peptide, the sodium adduct along with $[(peptide)_2H]^+$ complex and its corresponding sodium adduct.

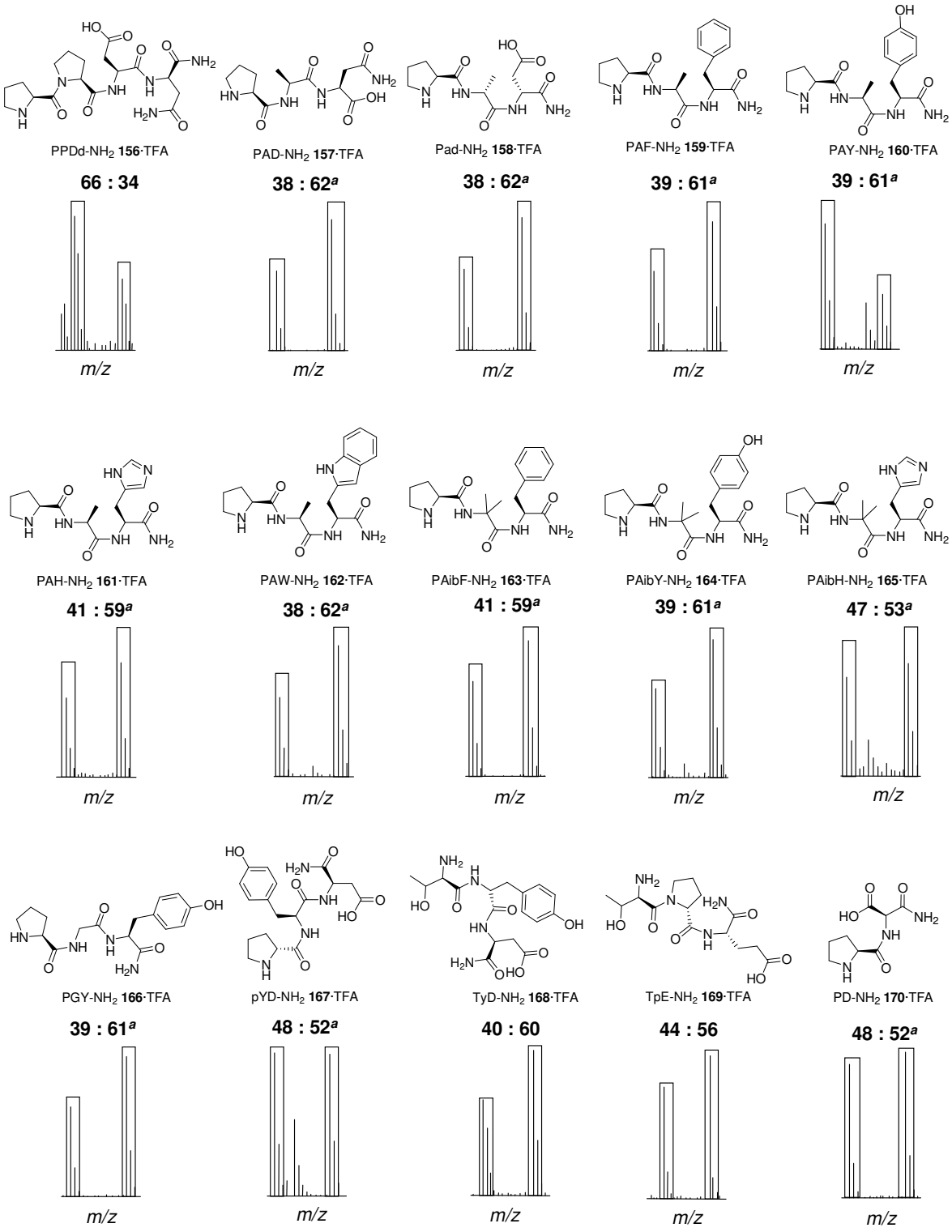
Table 3.8: *ESI MS screening results of a series of peptides.*











a Inversely labelled quasienantiomers were used.

PPD-NH_2 **141**·TFA gave the highest enantiomeric excess of 40%. Peptides containing the proline-proline motif generally gave enantiomeric excesses between 24-40% and the proline-alanine motif produced 25% enantiomeric excess. All peptide-catalysts favoured the (*S*)-enantiomer with one exception (PPF-OH **151**·TFA). The stereochemistry of the first amino acid determined the overall stereoselectivity of the peptide-catalysts

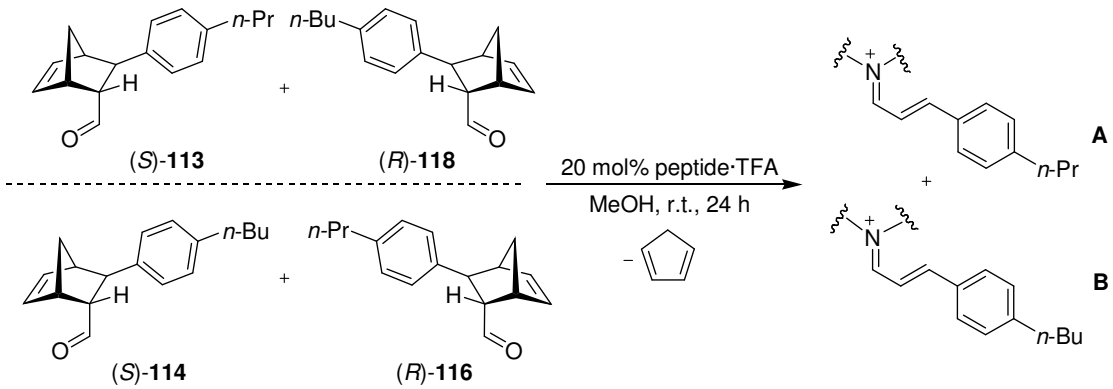
(PPDP-NH_2 **153**·TFA and pPDP-NH_2 **155**·TFA) and remained quantitatively unchanged by the second, third or fourth amino acid (PAD-NH_2 **157**·TFA and Pad-NH_2 **158**·TFA). Peptides starting with a non-cyclic amino acid such as threonine showed low enantioselectivities (TyD-NH_2 **168**·TFA).

Peptides as catalysts showed an improvement in enantioselectivity compared to proline (Section 3.5.1, ratio 57:43). Modification of the amino acid chain did not significantly influence stereoselectivity. In all cases, MACMILLAN's imidazolidinone catalyst **23**·HCl was found to give better enantioselectivities than the tested peptides.[107]

3.6.4 Control Experiments with Inversely Labelled Quasienantiomers

The screening results were confirmed by conducting a screening with the inversely labelled quasienantiomers (*R*)-**114** and (*S*)-**116**, for which we expected to observe inverted ratios compared to those with (*S*)-**113** and (*R*)-**118**. As seen in Table 3.9 dienophile ratios for both quasiracemates correlated well, demonstrating once more the applicability of this ESI MS screening method. The Diels-Alder adduct iminium ions either showed a near 50:50 mixture or more of the non-favoured Diels-Alder adduct, which might reflect the distribution of the remaining Diels-Alder adducts in solution.

Table 3.9: *Confirmation of screening results with inversely labelled quasienantiomers.*



Entry	Cat.	(*S*)-113/(*R*)-118 Dienophile Iminium Ions A : B	DA Adduct Iminium Ions *n*-Pr : *n*-Bu	(*R*)-116/(*S*)-114 Dienophile Iminium Ions A : B	DA Adduct Iminium Ions *n*-Pr : *n*-Bu
1	**141**·TFA	70:30	57:43	36:64	62:38
2	**142**·TFA	67:33	40:60	32:68	54:46

Entry	Cat.	(*S*)-113/(*R*)-118 Dienophile Iminium Ions A : B	DA Adduct Iminium Ions *n*-Pr : *n*-Bu	(*R*)-116/(*S*)-114 Dienophile Iminium Ions A : B	DA Adduct Iminium Ions *n*-Pr : *n*-Bu
3	**147**·TFA	45:55	27:73	55:45	25:75
4	**150**·TFA	57:43	38:62	36:64	58:42
5	**151**·TFA	44:56	45:55	54:46	69:31
6	**152**·TFA	58:42	44:56	40:60	57:43
7	**153**·TFA	60:40	57:43	36:64	61:39
8	**155**·TFA	38:62	19:81	61:39	-
9	**156**·TFA	66:34	48:52	36:64	-
10	**168**·TFA	40:60	51:49	54:46	54:46
11	**169**·TFA	44:56	47:53	56:44	50:50

3.7 Conclusion and Outlook

Our ESI MS screening method was extended to organocatalytic retro-Diels-Alder reactions. After testing the influence of the mass labels and establishing a reliable screening protocol, we successfully demonstrated that monitoring of iminium ion species in the retro-Diels-Alder reaction is a valuable tool to gain information about the catalysts' enantioselectivity. The application of this method in a screening with imidazolidinone and proline-based ligands confirmed that MACMILLAN's imidazolidinone **23**·HCl was a highly enantioselective catalyst for the retro-Diels-Alder reaction. Control experiments and the results of preparative forward-Diels-Alder reactions validated our method.

The versatility of this method was demonstrated by conducting a screening of 30 peptides to evaluate their potential as enantioselective catalyst in the retro-Diels-Alder reaction. It was found that peptides can function as catalysts in the retro-Diels-Alder reaction with moderate enantioselectivities.

So far it was not possible to determine a catalyst's activity by this ESI MS screening method. An extension of this method including this aspect would greatly increase the usefulness of this technique. Also diastereoselectivity still remains a problem in organocatalysed Diels-Alder

reactions. An additional screening set-up concerning this issue would therefore be desirable. By using a mixture of mass-labelled enantiopure *endo* and *exo* Diels-Alder adducts this could be accomplished.

This screening method, enabling the rapid identification of highly selective organocatalysts, is not limited to the Diels-Alder reaction. This methodology should be readily applicable to other organocatalysed transformations. Work on extending this concept to Michael reactions is currently carried out in our group.

Chapter 4

ESI MS Screening of Organocatalyst Mixtures

4 ESI MS Screening of Organocatalyst Mixtures

4.1 Objectives

After establishing a reliable protocol for the screening of single organocatalysts, we wanted to test if this method was amenable to screening mixtures of organocatalysts in a one pot procedure for the retro-Diels-Alder reaction.

Previously HINDERLING and CHEN demonstrated that olefin polymerisation reactions, catalysed simultaneously by eight different palladium-catalysts, can be analysed by ESI MS to identify the most active catalyst.[10] ELLMAN and co-workers used multi-substrate screening to discover new substrates for C-H activation reactions. Subsequent selective product labelling allowed analysis by ESI MS.[172] MARKERT and PFALTZ showed that it was possible to obtain reliable selectivity data from catalyst mixtures by ESI MS screening of quasienantiomers. By detection of the catalytic intermediates by ESI MS the intrinsic enantioselectivity of each individual catalyst was determined for the palladium-catalysed allylic substitution reaction.[9] This was the first and to date only example of multi-catalyst screening by ESI MS to evaluate enantioselectivity. There was no restriction to the number of catalysts screened in one mixture as long as the mass peaks did not overlap. Using the quasienantiomer strategy, catalysts did not need further labelling as the intermediates were easily distinguished by their inherent mass differences.

Multi-catalyst screenings greatly accelerate the trial and error process for (organo)catalyst development making it interesting for high-throughput applications. With conventional product analysis it is not possible to screen for enantioselectivity in multi-catalyst mixtures. This encouraged us to pursue the development of an ESI MS screening method to simultaneously screen several organocatalysts in one reaction mixture.

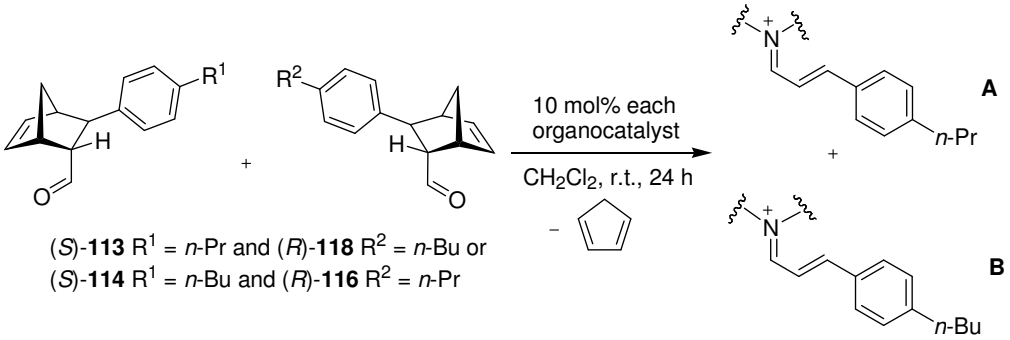
4.2 Development of a Screening Method for Mixtures of Imidazolidinone and Proline-Based Organocatalysts

4.2.1 Preliminary Studies

In order to successfully screen mixtures of organocatalysts, the masses of the tested catalysts must be theoretically different by at least Δ *m/z* = 1 to avoid mass peak overlap. The catalysts should also show similar mass peak intensities for the reactive intermediates, otherwise the least-intense mass peaks become too small. The mass range should be held constant (for example Δ *m/z* 500) for comparable results.

Preliminary experiments were conducted using imidazolidinone catalyst **23**·HCl, which showed excellent enantioselectivities in the screening of single catalysts (Section 3.5.1, ratio 12:88), and imidazolidinone catalyst **130**·TFA, which showed moderate enantio- and opposite stereoselectivity (Section 3.5.1, ratio 60:40). To demonstrate the compatibility with a different catalyst type proline **136** (Section 3.5.1, ratio 43:57) was used as well. Mass peak intensities for all three ligands were good to excellent making them amenable to testing.

The starting point was to use two catalysts in one reaction mixture with either (*S*)-**113** and (*R*)-**118** or (*S*)-**114** and (*R*)-**116** as quasienantiomers (Scheme 4.1). Standard reaction conditions developed for single catalyst screening were applied (Section 3.3.3).



Scheme 4.1: *Multi-catalyst screening in one reaction mixture for the retro-Diels-Alder reaction.*

Using proline **136** and imidazolidinone **130**·TFA in the retro-Diels-Alder reaction, ESI MS spectra showed the expected ratios (Figure 4.1, **a**). It is remarkable that catalysts with opposite stereoselectivity can be successfully tested in one reaction mixture. When screening proline **136** and imidazolidinone **23**·HCl the correct ratio was detected for proline **136**, but for **23**·HCl lower enantioselectivity than for the single screening was observed (Figure 4.1, **b**). The outcome for testing imidazolidinones **23**·HCl and **130**·TFA was similar: the expected

ratio was detected for **130**·TFA whereas the ratio for **23**·HCl was lower than anticipated (Figure 4.1, **c**).

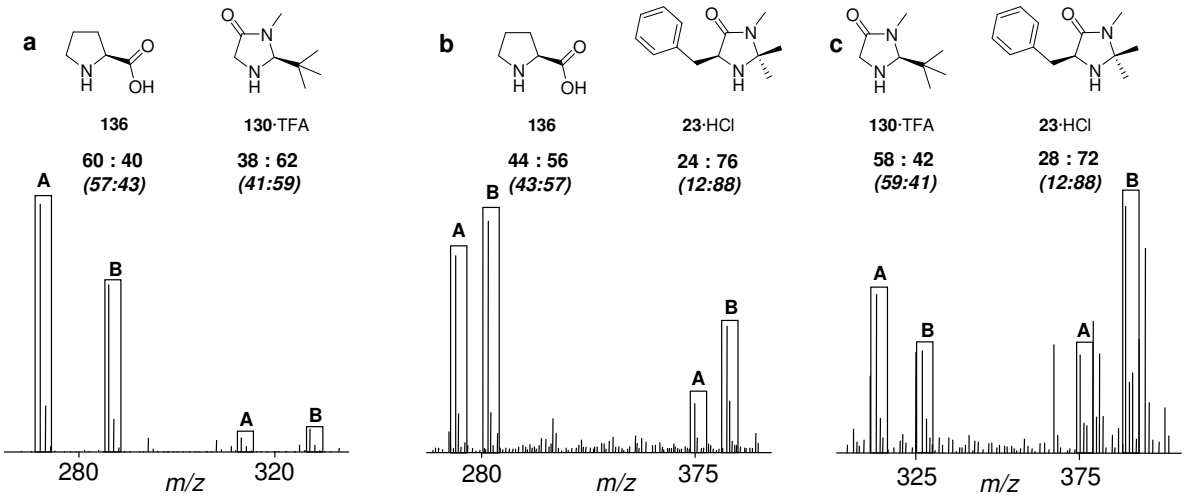


Figure 4.1: *ESI MS spectra for screening of two organocatalysts in one reaction mixture: (**a**) and (**c**) using (S)-**114** and (R)-**116** and (**b**) (S)-**113** and (R)-**118** as quasienantiomers. The reaction conditions are depicted in Scheme 4.1. The ratios of the single catalyst screening are given in brackets.*

Upon addition of proline **136** to imidazolidinones **23**·HCl and **130**·TFA the most selective imidazolidinone catalyst **23**·HCl was easily identified, followed by imidazolidinone catalyst **130**·TFA and proline **136** (Figure 4.2). The ratios for the latter two were in accordance to those for the single catalyst screening. Although **23**·HCl was clearly the most selective catalyst in this mixture, its ratio remained lower compared to that of the single screening (29:71 vs. 12:88).

The spectrum showed hardly any contamination, which allowed correct analysis of the less-intense mass peaks. Prominent additional mass peaks resulted from the Diels-Alder adduct iminium ion intermediates, the protonated catalysts and their sodium ion adducts.

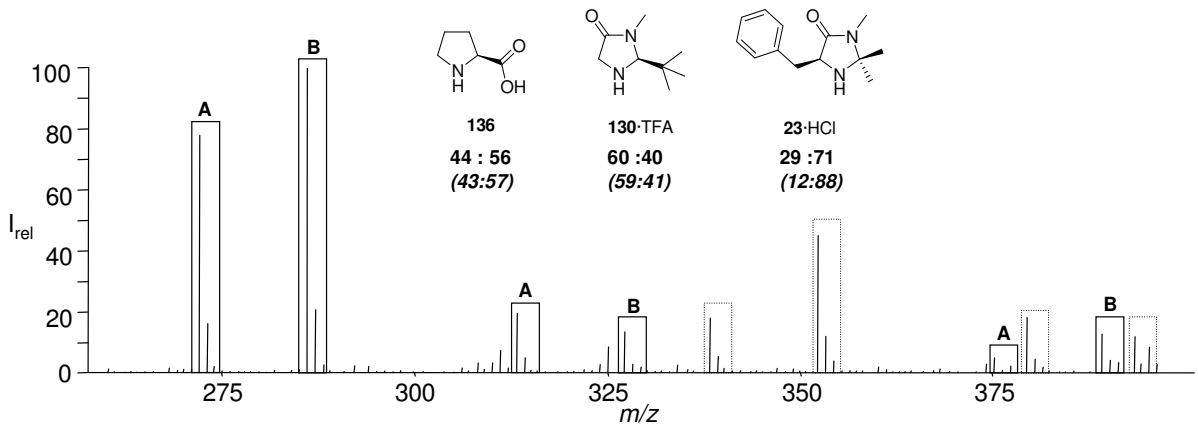


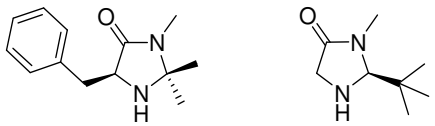
Figure 4.2: *ESI MS screening using three organocatalysts. The reaction conditions are depicted in Scheme 4.1. The dashed boxes frame the mass peaks of the Diels-Alder adduct iminium ion intermediates for **136** and **130**·TFA. The ratios of the single catalyst screening are given in brackets.*

As acids influence diastereo- and enantioselectivity of Diels-Alder reactions,[116, 160] mixing of trifluoroacetate and chloride counter-ions could be responsible for the drop in enantioselectivity for **23**·HCl.

Several more combinations of organocatalysts were tested including diarylprolinol silyl ether derived catalysts **132**-**135**, which generally gave low mass peak intensities and selectivities deviated from those in the single catalyst screening. Therefore mixtures containing these organocatalysts were not investigated further.

4.2.2 Influence of Counter-Ions in Catalyst Mixtures

To investigate the counter-ion influence on the retro-Diels-Alder reaction, two catalysts were tested in combination with chloride and trifluoroacetate.



23·HCl
23·TFA

130·HC
130·TFA

Figure 4.3: *Imidazolidinone catalysts **23** and **130** with chloride and trifluoroacetate as counter-ions.*

Single screening of **23**·HCl and **23**·TFA gave similar ratios, demonstrating that counter-ion influence on enantioselectivity was minimal (Figure 4.4, **a** and **b**). However, mixing catalysts with different counter-ions produced lower ratios than those in the single catalyst screening (Figure 4.4, **c**). Subsequent use of a mixture of catalyst **23** and **130** both with the same counter-ion (chloride or trifluoroacetate) resulted in the expected ratio for **130**, but again in a lower ratio for **23**.

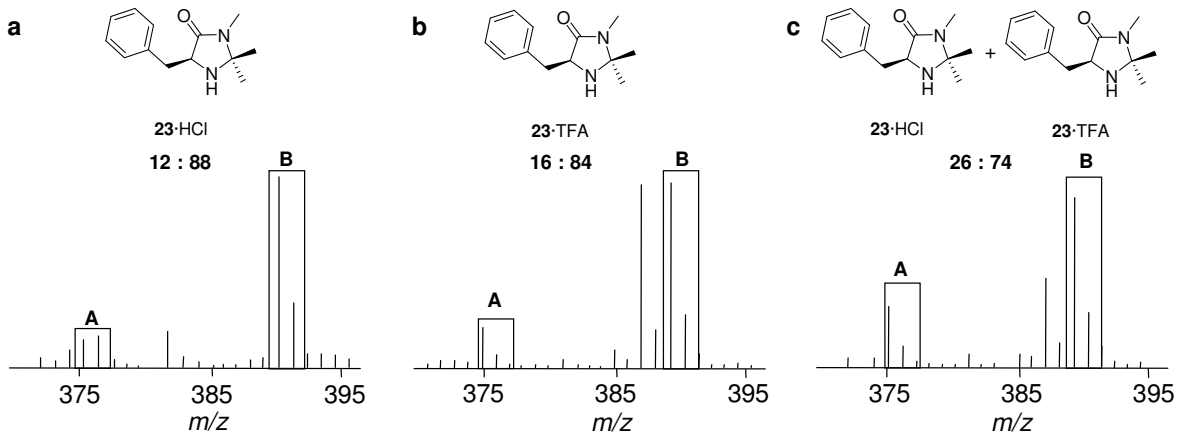


Figure 4.4: *ESI MS spectra for (**a**) single screening of **23**·HCl and (**b**) **23**·TFA and (**c**) screening of a mixture of **23**·HCl and **23**·TFA. Reactions were conducted at room temperature for 24 hours using 20 mol% of catalyst for the single screening and 10 mol% of each catalyst for the mixture.*

Testing structurally closely related catalysts **23**·HCl and **128**·HCl in the same reaction mixture also gave ratios which were lower than those of the single catalyst screening (Figure 4.5, **a**). Addition of proline **136** to imidazolidinones **23**·HCl and **128**·HCl resulted in further lowering of the ratios for **23**·HCl and **128**·HCl. The observed ratio for the proline-derived intermediates was in accordance to that of the single catalyst screening (Figure 4.5, **b**).

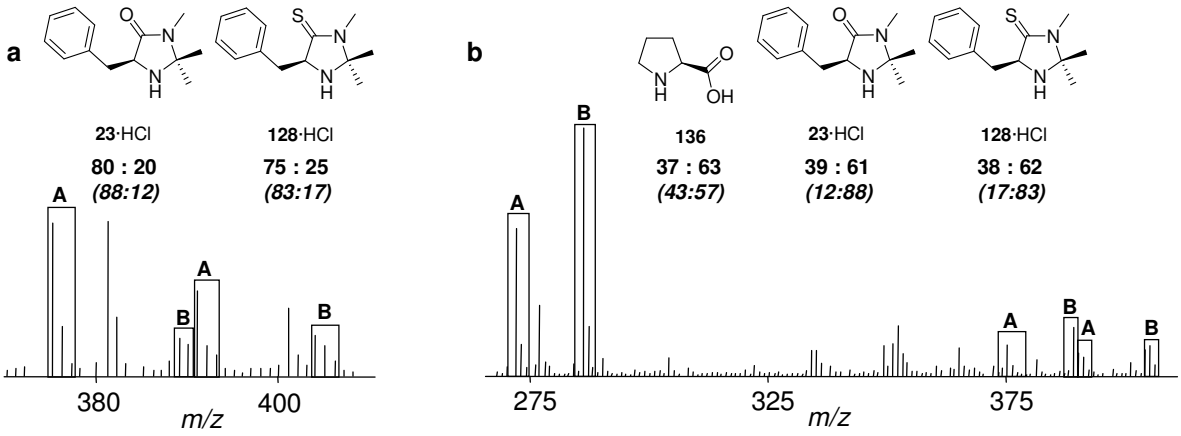


Figure 4.5: *ESI MS spectra for (**a**) screening catalysts **23**·HCl and **128**·HCl using (S)-**114** and (R)-**116** as quasienantiomers and (**b**) screening of three organocatalysts in one reaction mixture using (S)-**113** and (R)-**118** as quasienantiomers. The reaction conditions are depicted in Scheme 4.1. The ratios of the single catalyst screening are given in brackets.*

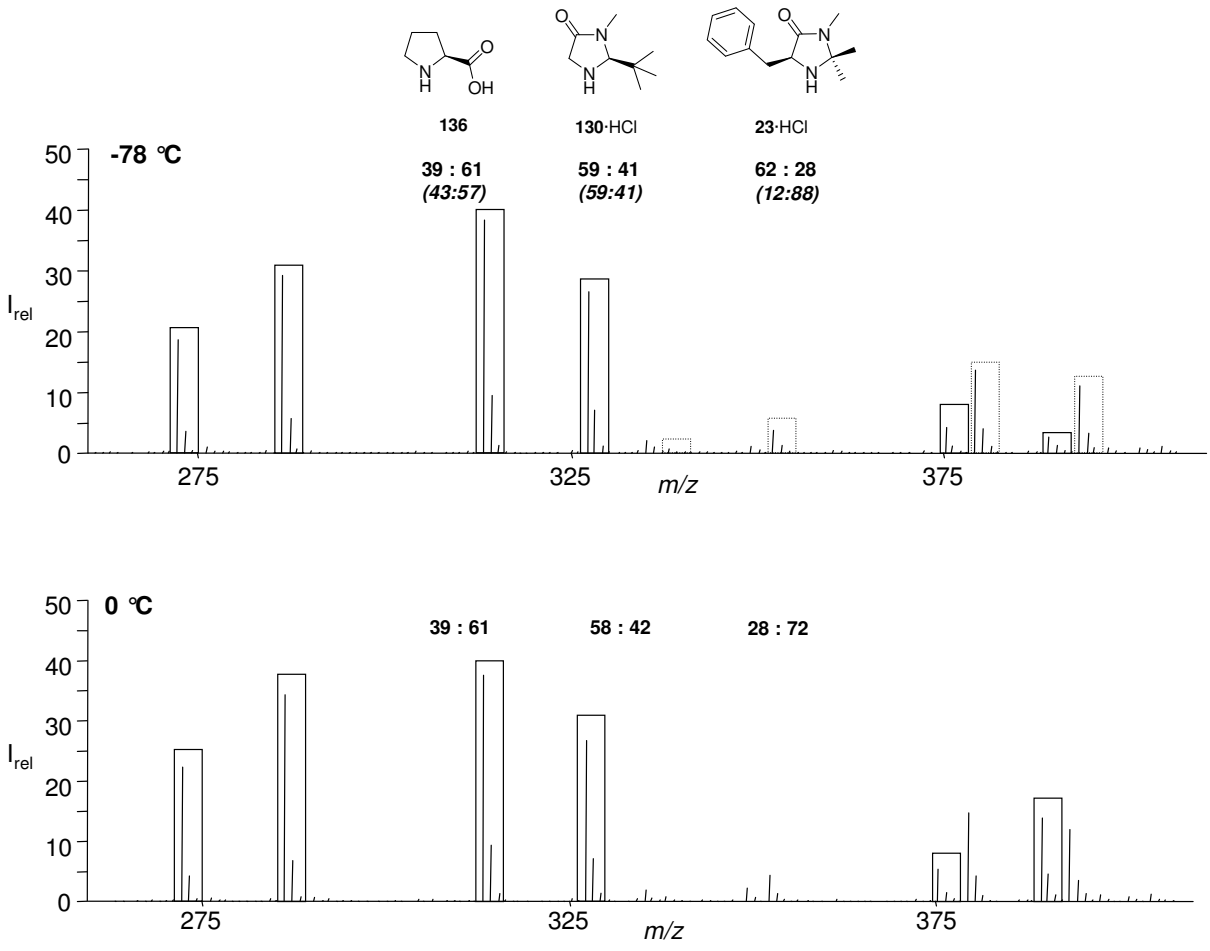
In general, the effect of the counter-ions was ambiguous. Nonetheless catalysts with the same counter-ions were used in the following experiments to exclude any possible influence of different counter-ions. The presence of proline **136** seemed to have a major influence on the reaction mixture, possibly induced by the presence of its free carboxylic acid. Therefore proline **136** was substituted in some cases by proline methyl ester **137**·HCl.

4.2.3 Optimisation of the Reaction Conditions

Several factors such as catalyst loading, temperature and reaction time were evaluated for catalyst mixtures as the reaction conditions applied for the single catalyst screening did not give optimal results.

Screening of four different catalyst loadings (1, 5, 10 and 20 mol%) with catalyst **23**·HCl, **130**·HCl and **136** showed best results when 20 mol% of each catalyst were used. Therefore the following experiments were conducted with that amount of each catalyst.

Reaction temperatures were varied from -78 °C to 50 °C (Figure 4.6). Quasienantiomers (*S*)-**113** and (*R*)-**118** were used and the reaction time was 24 hours. To our surprise the best ratio for catalyst **23**·HCl was detected at 50 °C. It was remarkable that at elevated temperatures the catalyst displayed a higher enantioselectivity than at lower temperatures. At -78 °C an inverse ratio was detected for catalyst **23**·HCl, which was even more pronounced when shortening the reaction time to 2 hours (ratio 83:17). The selectivities of proline **136** were independent of the reaction temperature whereas enantioselectivity for catalyst **130**·HCl constantly declined going from -78 °C to 50 °C.



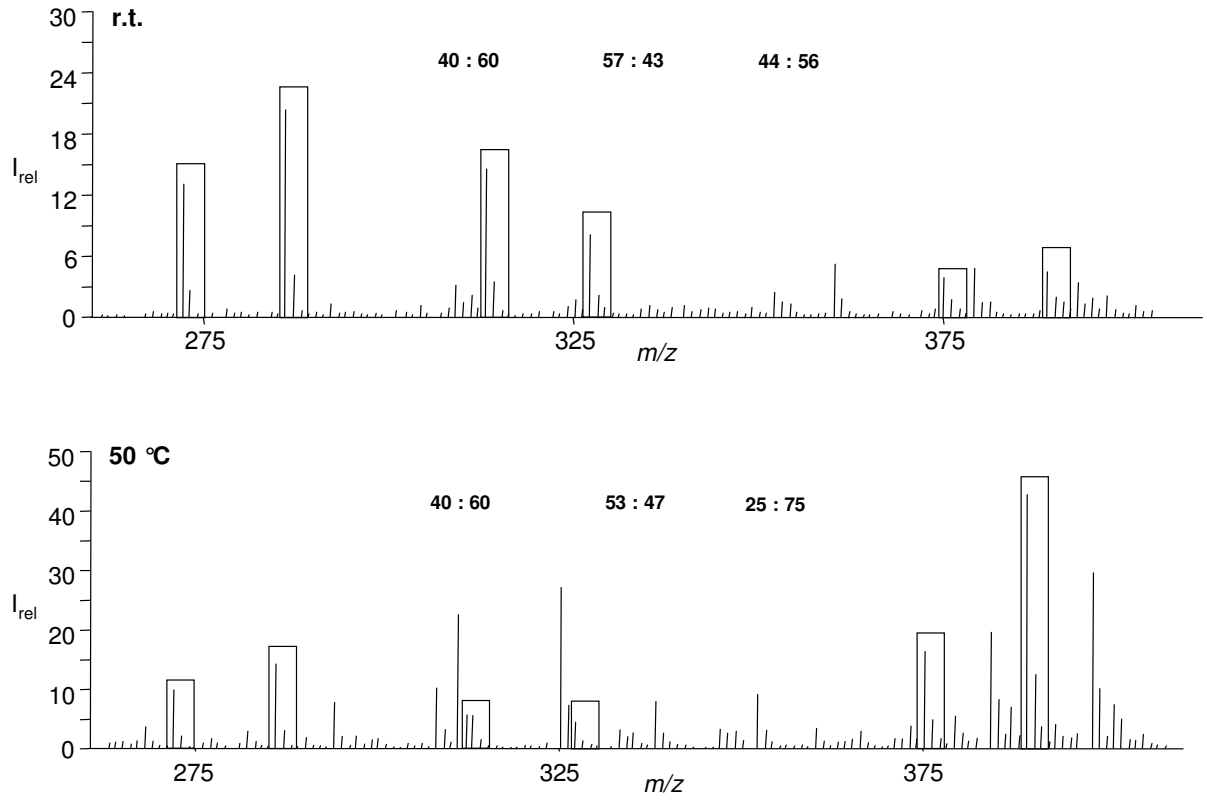


Figure 4.6: *ESI MS spectra for temperature screening using **136**, **130**·HCl and **23**·HCl. The reactions were conducted at the indicated temperatures for 24 hours using 20 mol% of each catalyst. The dashed boxes in the top spectrum frame the Diels-Alder adduct iminium ion intermediates of catalyst **136** and **130**·HCl. The ratios of the single catalyst screening are given in brackets.*[*]

The temperature screening was repeated with proline methyl ester **137**·HCl to eliminate the effect of the carboxylic acid side chain of proline **136**. The reaction time was shortened to 8 hours as a decline of the ratio for catalyst **23**·HCl was observed after that time at room temperature (2 h, ratio 36:64; 8 h, ratio 35:65; 130 h, ratio 46:54; 48 h, ratio 46:54).

As observed previously, catalyst **23**·HCl showed enhanced enantioselectivity at 50 °C (ratio 15:85) compared to that at -78 °C (ratio 47:53) (Figure 4.7). The ratio obtained at 50 °C corresponded to that of the single catalyst screening. For proline methyl ester **137**·HCl ratios were largely unaffected by temperature, whereas the ratio for catalyst **130**·HCl declined going from -78 °C to 50 °C from 59:41 to nearly racemic.

[*] Relative mass peak intensities are given with regard to the most-intense mass peak in the spectrum, generally the [**23**+H]$^+$ or [**23**+Na]$^+$ mass peak.

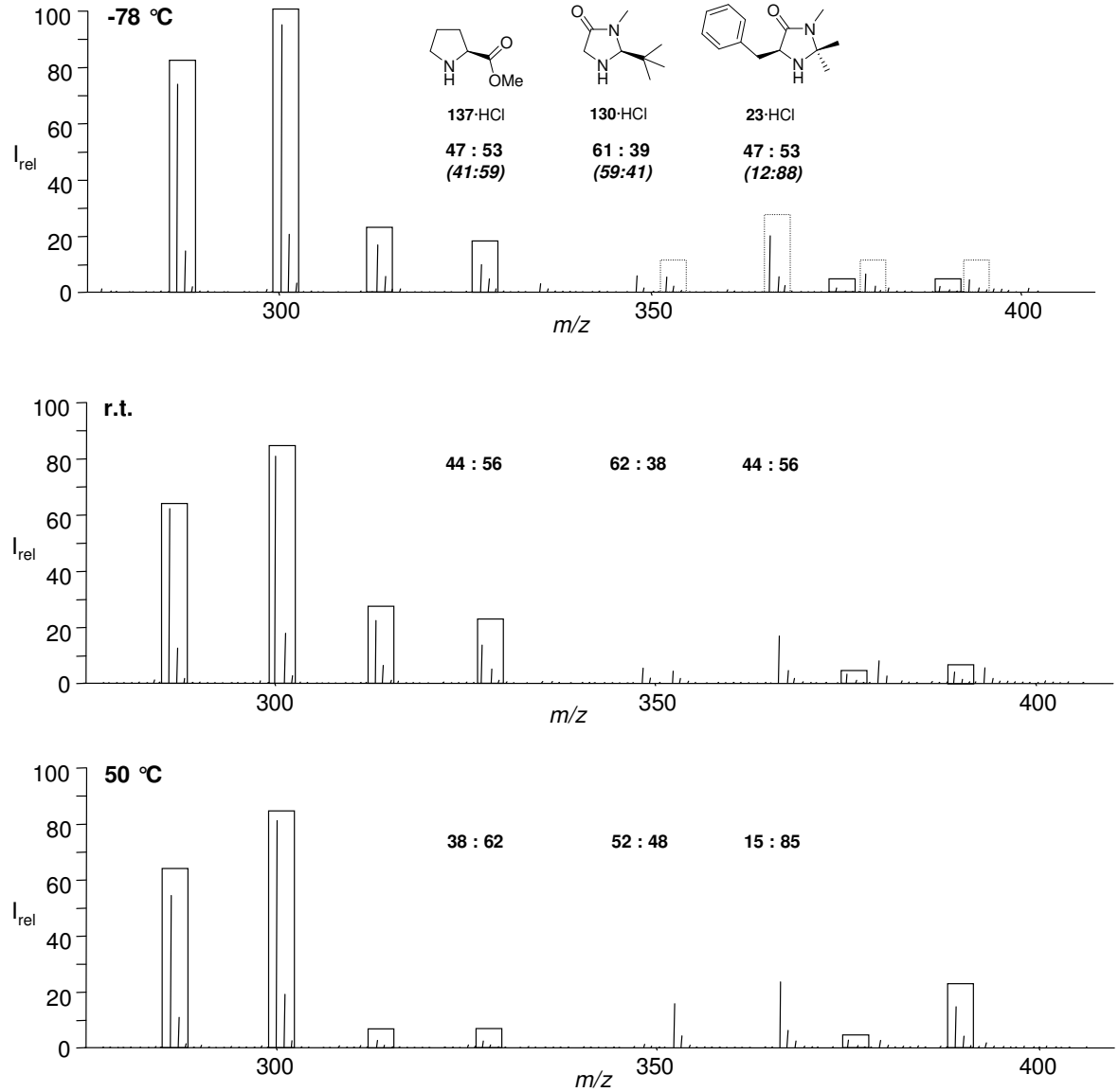


Figure 4.7: *ESI MS spectra for the temperature screening using proline methyl ester **137**·HCl, **130**·HCl and **23**·HCl. The reactions were conducted at the indicated temperatures for 8 hours using 20 mol% of each catalyst. The ratios of the single catalyst screening are given in brackets.*

Further shortening of the reaction time to 60 minutes produced perfect correlation with the single screening for all three catalysts. Catalyst **23**·HCl performed with the expected high enantioselectivity. For **137**·HCl and **130**·HCl similar enantioselectivities with inverse stereoselectivity were observed (Figure 4.8). Shortening of the reaction time to 30 minutes gave very similar results, although the ratio of **23**·HCl was slightly lower compared to that for 60 minutes.

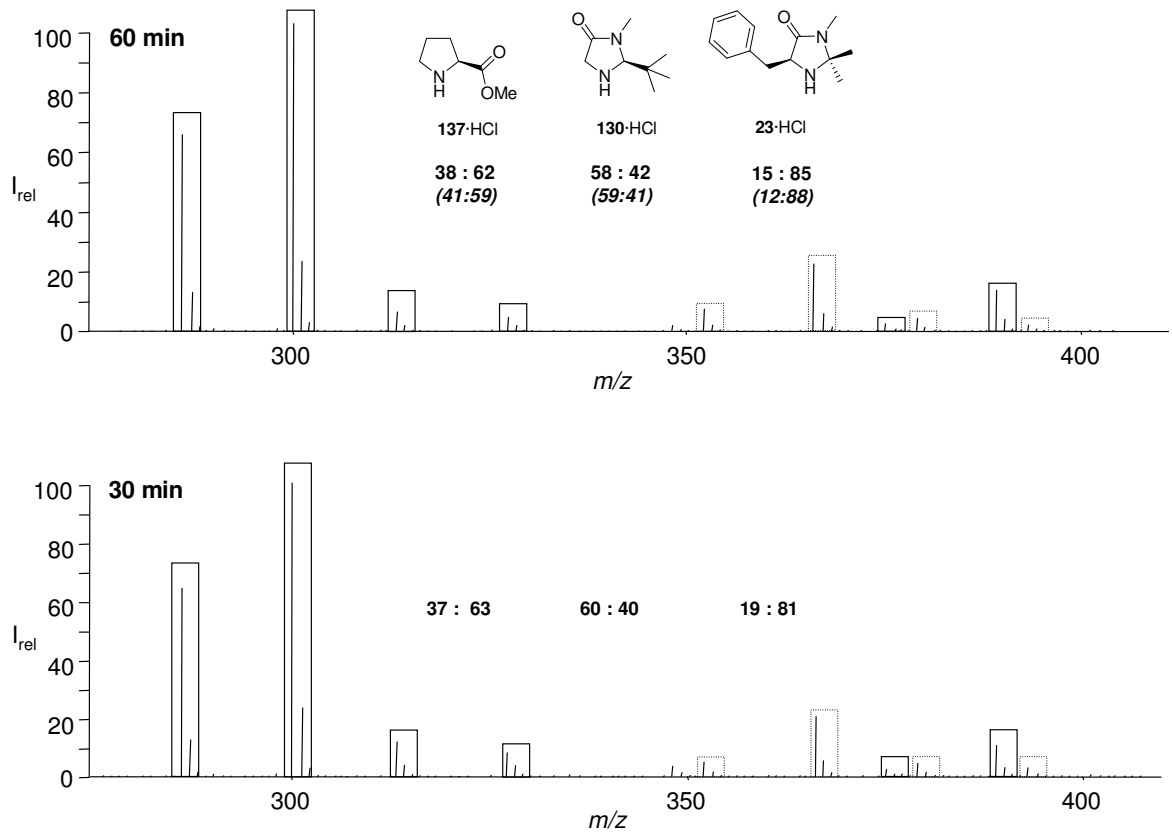


Figure 4.8: *ESI MS spectra for reaction times of 30 and 60 minutes. The reactions were conducted at 50 °C for the indicated times using 20 mol% of each catalyst. The dashed boxes frame the Diels-Alder adduct iminium ion intermediates for* ***137***·*HCl and* ***130***·*HCl. The ratios of the single catalyst screening are given in brackets.*

The screening for enantioselectivity of three organocatalysts in one reaction mixture was accomplished by using 20 mol% of each catalyst, shortening the reaction time from 24 hours to 1 hour and performing the reaction at 50 °C instead of at room temperature. During the course of investigation for optimal screening conditions, an increase of enantioselectivity with increasing temperature was observed for catalyst **23**·HCl.

Similar temperature effects such as the enhancement and/or inversion of enantiomeric excess with increasing temperature in asymmetric processes have been reported before (for example for the reduction with chiral 1,4-dihydronicotinamides,[173] the desymmetrisation with chiral tin-compounds,[174] the addition of diethyl zinc to aldehydes[175] and the cobalt-catalysed homo Diels-Alder reaction[176]). In some cases the Eyring equation*[177-179] was applied to

* Evaluation of temperature dependence for stereoselectivity in terms of differential activation enthalpy and entropy can be calculated from the Eyring equation[177-179] $\ln(k_S/k_R)=-(\Delta\Delta H^{\ddagger}_{S-R}/RT)+(\Delta\Delta S^{\ddagger}_{S-R}/R)$ derived from $\ln(k_S/k_R)=-\Delta\Delta G^{\ddagger}_{S-R}/RT$ with $\Delta G^{\ddagger}=\Delta H^{\ddagger}-T\Delta S^{\ddagger}$, in which k_S and k_R are the overall rate constants leading to the two enantiomers and $\Delta\Delta H^{\ddagger}_{S-R}=\Delta\Delta H^{\ddagger}_{S}-\Delta\Delta H^{\ddagger}_{R}$ and $\Delta\Delta S^{\ddagger}_{S-R}=\Delta\Delta S^{\ddagger}_{S}-\Delta\Delta S^{\ddagger}_{R}$ represent the differential activation enthalpy and entropy. $\Delta\Delta G^{\ddagger}_{S-R}$ is the difference in free activation energy for the (*S*)- and the (*R*)-enantiomers. $\Delta\Delta H^{\ddagger}_{S-R}$ and $\Delta\Delta S^{\ddagger}_{S-R}$ can be calculated by plotting $\ln(k_S/k_R)$ values, derived from $\ln(k_S/k_R)=\ln[(100+\%ee)/(100-\%ee)]$, as a function of the reciprocal temperature.

calculate the differential activation parameters $\Delta\Delta H^{\ddagger}_{S\text{-}R}$ and $\Delta\Delta S^{\ddagger}_{S\text{-}R}$.[173, 174] Comparatively large values for $\Delta\Delta S^{\ddagger}_{S\text{-}R}$ were obtained for these calculations, indicating that the entropy term contributes to the differential free activation energy $\Delta\Delta G^{\ddagger}_{S\text{-}R}$ more than usual.[173, 174] Therefore the entropy term accounts for the unique temperature dependence.[173, 174] The relatively large $\Delta\Delta S^{\ddagger}_{S\text{-}R}$-values were assumed to originate from large activation volume variations caused for example by the broad movement sphere of an benzylic group.[173]

This rationale can be applied to our experimental findings, where an increase in enantioselectivity with increasing temperature was exclusively observed for the benzyl-group containing imidazolidinone catalyst **23** and not for imidazolidinone catalyst **130** and proline **136** or proline methyl ester **137**·HCl, respectively. An alternative explanation for the unusual temperature behaviour could be that a different reaction pathway operates at lower temperatures.

4.2.4 ESI MS Screening Results

Subjecting the initially used catalyst mixture including imidazolidinone **23**·HCl and **130**·HCl and proline **136** to optimised reaction conditions (50 °C, 1 hour, 20 mol% of each catalyst) gave results which were in perfect agreement with previous data from single catalyst screening (Figure 4.9). Imidazolidinone **23**·HCl was correctly identified as the most selective ligand in this mixture, whereas proline **136** and imidazolidinone **130**·HCl showed essentially the same stereoselectivity values but opposite sense of chiral induction.

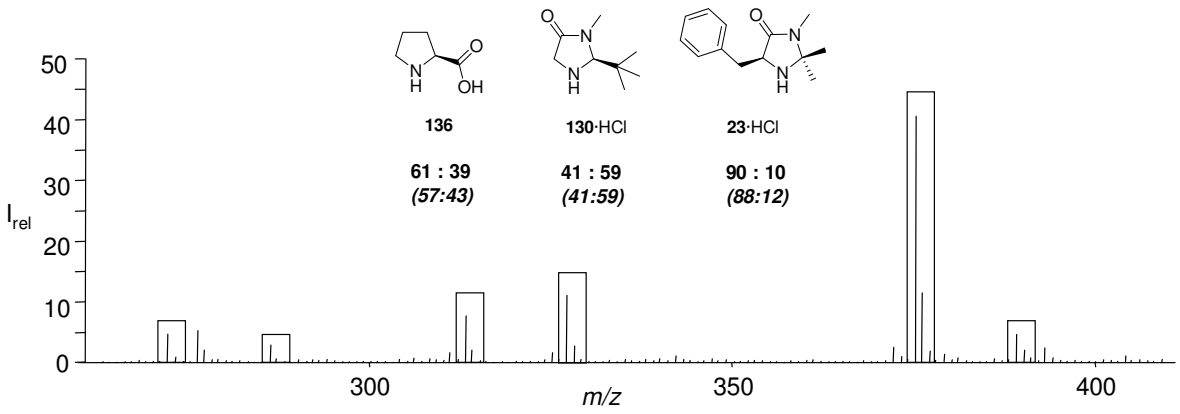
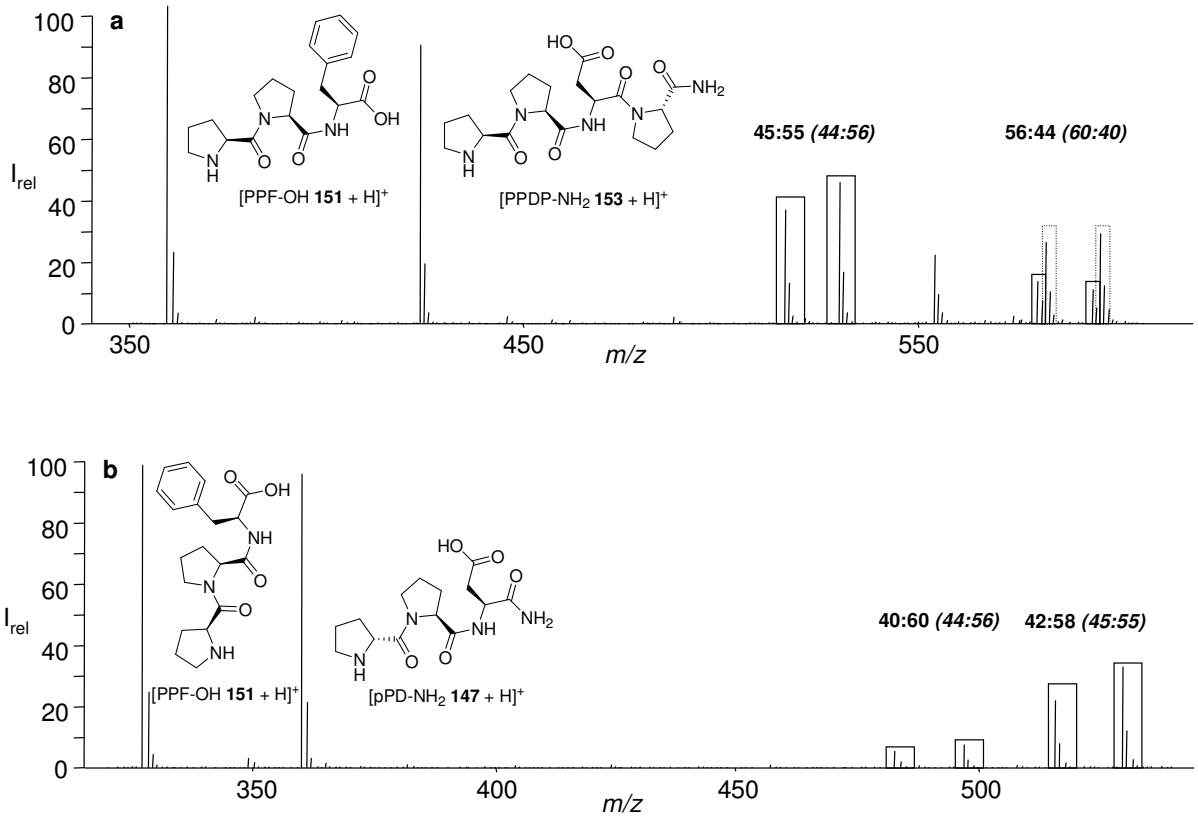


Figure 4.9: *Screening of three organocatalysts in the same reaction mixture using quasienantiomers (S)-**114** and (R)-**116**. The reaction was conducted at 50 °C for 1 hour using 20 mol% of each catalyst. The ratios of the single catalyst screening are given in brackets.*

4.3 Screening of Peptide-Catalyst Mixtures

4.3.1 Preliminary Studies

Preliminary studies for screening peptide-catalyst mixtures in the retro-Diels-Alder reaction were conducted with two peptide-catalysts (10 mol% each) using (*S*)-**113** and (*R*)-**118** as quasienantiomers (Figure 4.10). The mass peak intensities were sufficiently intense, showing the dienophile and Diels-Alder adduct iminium ion intermediates as well as the protonated peptides. The selectivities for both peptide-catalysts were in accordance to those for the single screening, even when catalysts with opposite selectivities were screened (Figure 4.10, **a**). Catalysts with a mass difference of only Δ *m/z* = 5 were comfortably analysed next to each other (Figure 4.10, **c**). In one case even enhanced selectivity compared to the single screening was observed for both catalysts (Figure 4.10, **b**). Although selectivities did not match exactly with those of the single catalyst screening in some cases, the more selective catalyst was always clearly identified (Figure 4.10, for example in **d**, catalyst PPDp-NH_2 **154**·TFA).



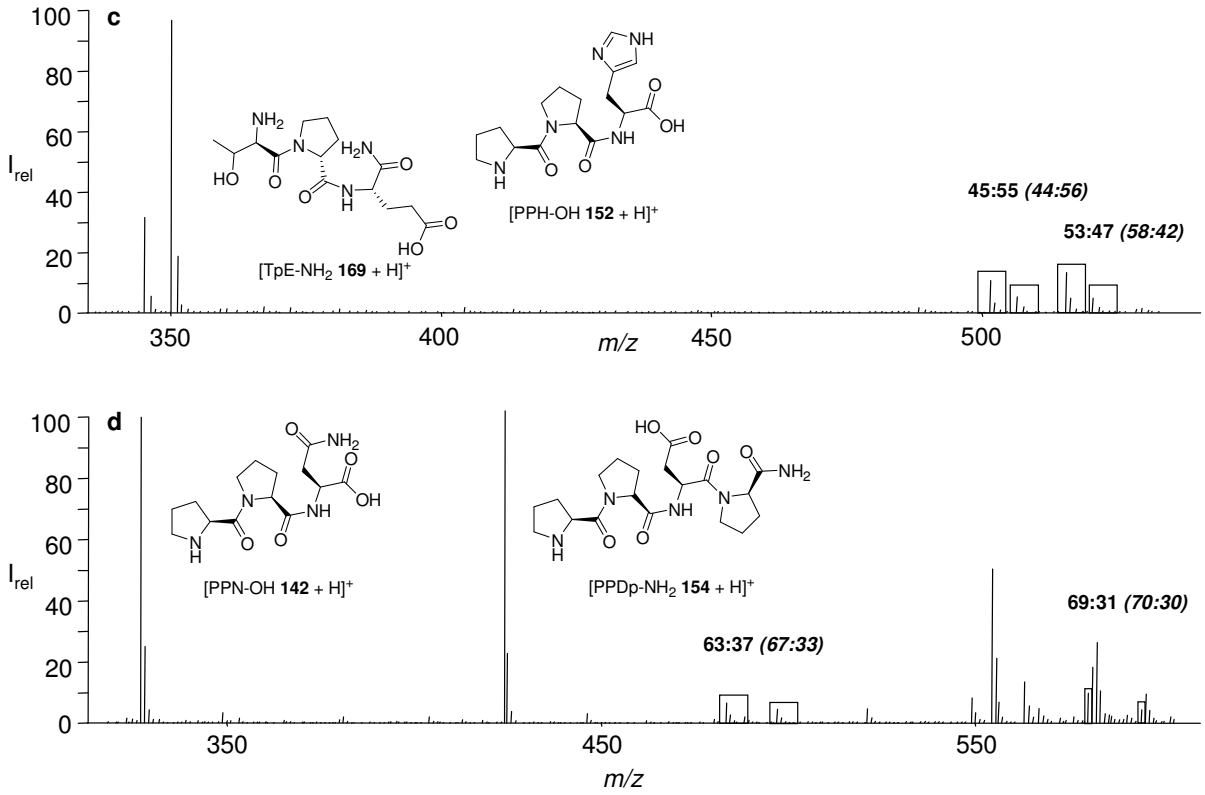


Figure 4.10: *ESI MS spectra for the screenings with two peptide-catalysts in one reaction mixture using 10 mol% of each catalyst. The reactions were conducted at room temperature for 24 hours. The dashed boxes frame the Diels-Alder adduct iminium ion intermediates if present in the spectrum. The ratios of the single catalyst screening are given in brackets.*

4.3.2 ESI MS Screening Results

Applying the general screening conditions (20 mol% of each catalyst, r.t., 24 h) to mixtures of three peptide-catalysts did not give the ratios expected from the single screening. Interestingly the observed ratios were generally better than in the single screening.

Subsequently, the optimised conditions developed previously for the imidazolidinone and proline-based catalysts were applied (20 mol% of each catalyst, 50 °C, 1 h) using (*S*)-**113** and (*R*)-**118** as quasienantiomers. The correlation between the selectivities of the catalysts in the mixtures compared to those in the single catalyst screening was very good (Figure 4.11). Although selectivities were very similar for all peptide-catalysts, the trend for the most selective catalyst in a mixture was clearly identified (Figure 4.11, **a** PPDp-NH_2 **154**·TFA>PPD-OMe **146**·TFA>pPN-NH_2 **144**·TFA). As observed before, peptide-catalysts with opposite stereoselectivity can be monitored in the same reaction mixture (Figure 4.11, **b**).

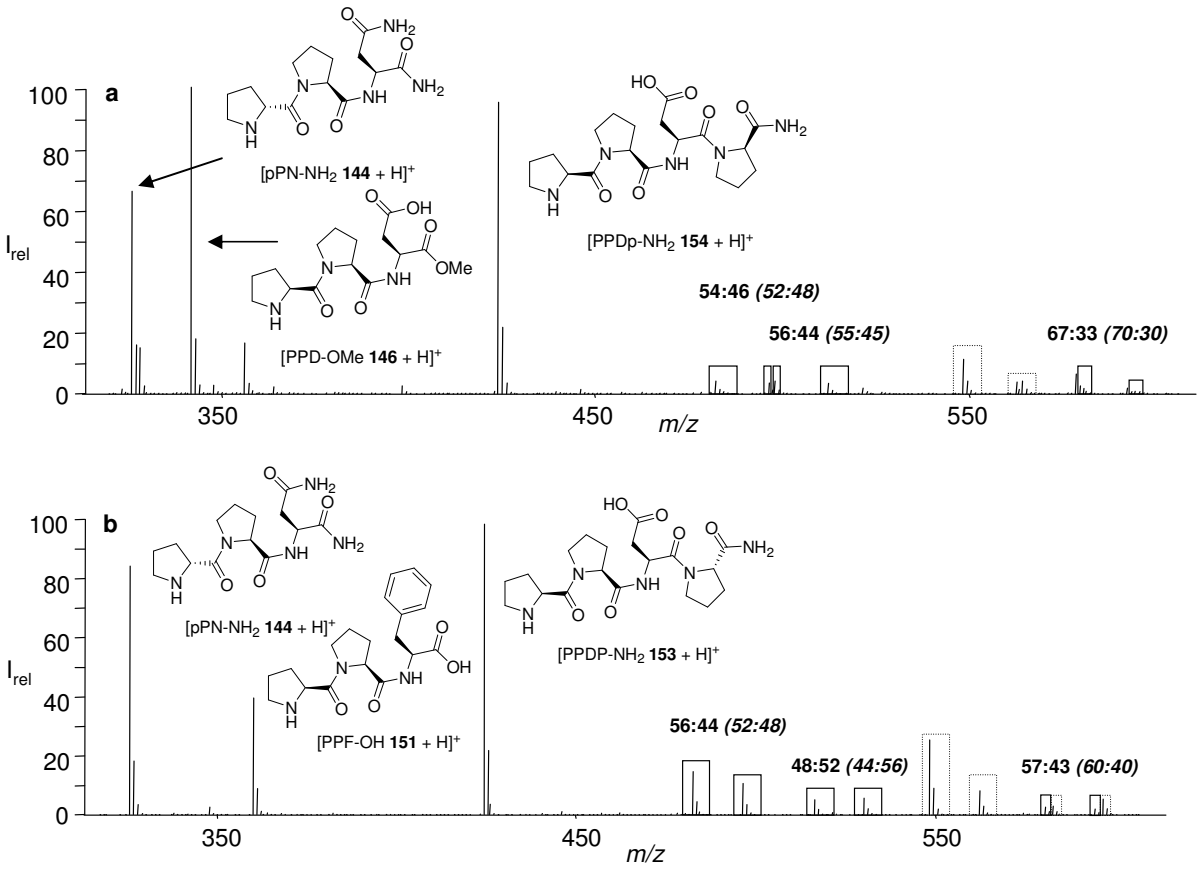


Figure 4.11: *ESI MS spectra for the screening of three peptide-catalysts in the same reaction mixture using optimised reaction conditions. The dashed boxes frame the Diels-Alder adduct iminium ion intermediates if present in the spectrum. The ratios of the single catalyst screening are given in brackets.*

Simultaneous screening of imidazolidinone and proline-based organocatalysts with peptide-catalysts was not possible because different retro-Diels-Alder conditions were mandatory: peptide-catalysed reactions were conducted in methanol whereas imidazolidinone and proline-based organocatalysis was performed in dichloromethane.

4.4 Conclusion and Outlook

Based on the previously developed screening method, a procedure for screening simultaneously up to three organocatalysts in one reaction mixture was developed.

This method allowed to distinguish catalytic intermediates originating from different organocatalysts due to their inherently different masses. Therefore mass peaks were easily assigned and subsequent analysis gave the intrinsic enantioselectivities of the individual catalysts. It was possible to observe a clear trend to identify the most selective catalyst in a mixture. After optimising the reaction conditions, the results of the multi-catalyst screenings

were in perfect agreement with those for the single screening. We also showed that the optimised conditions were successfully applied for the simultaneous screening of up to three peptide-catalysts.

During the development of the screening conditions, an unusual temperature-enantioselectivity relationship was discovered for imidazolidinone catalyst **23**·HCl. Further studies will be necessary to elucidate the origin of these temperature effects.

Chapter 5

Experimental

5 Experimental

5.1 Analytical Methods

NMR-Spectroscopy: NMR spectra were measured either on a Bruker Advance 400 (400 MHz) or a Bruker Advance DRX 500 (500 MHz) NMR spectrometer, equipped with BBO broadband probe heads. The chemical shift, δ value, is given in ppm. The chemical shift δ values were corrected to the following references: 7.26 ppm (^{1}H NMR) and 77.0 ppm (^{13}C NMR) for $CHCl_3$, 5.32 ppm (^{1}H NMR) and 54.0 ppm (^{13}C NMR) for CH_2Cl_2, 3.35 ppm and 4.78 ppm (^{1}H NMR) and 49.3 ppm (^{13}C NMR) for CH_3OH, 7.16 ppm (^{1}H NMR) and 128.06 (^{13}C NMR) for C_6H_6 and 2.50 ppm (^{1}H NMR) and 39.5 ppm (^{13}C NMR) for $(CH_3)_2SO$. The assignment of ^{1}H- and ^{13}C-signals was partly made by 2D-NMR, namely COSY, HMQC and HMBC. ^{13}C NMR spectra were recorded ^{1}H-decoupled. Multiplets were assigned with s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), m (multiplet). The index br stands for broad.

Mass Spectrometry (MS): Mass spectra were measured by DR. H. NADIG (Department of Chemistry, University of Basel) on a VG70-250 (electron ionisation (EI)) mass spectrometer or on MAR 312 (fast atom bombardment (FAB)) mass spectrometer. FAB was performed with 3-nitrobenzyl alcohol (NBA) as matrix. ESI MS spectra were measured on a Finnigan MAT LCQ and on a Varian 1200L Triple Quad MS/MS. The signals are given in mass-to-charge ratio (*m*/*z*). The fragment and intensities are given in brackets. All values are rounded to the nearest whole number.

Infra-red Spectroscopy (IR): Infra-red spectra were measured on a Perkin Elmer 1600 series FTIR spectrometer. Solid samples were measured as KBr discs, liquid samples were measured between NaCl plates. Absorption bands are given in wave numbers $\tilde{\nu}$ [cm^{-1}]. The peak intensity is assigned with s (strong), m (medium) and w (weak). The index br stands for broad.

Melting Point (m.p.): Melting points were measured on a Büchi 535 melting point apparatus. The values are not corrected.

Optical Rotation ($[\alpha]_D^{20}$): $[\alpha]_D^{20}$-Values were measured on a Perkin Elmer Polarimeter 341 in a cuvette (1 = 1 dm) at 20 °C. Concentration, c, is given in g/100 mL.

Thin Layer Chromatography (TLC): TLC plates were obtained from *Macherey-Nagel* (Polygram® SIL/UV_{254}, 0.2 mm silica with fluorescence indicator, 40 × 80 mm; Polygram® ALOX N/UV_{254}, 0.2 mm alox with fluorescence indicator, 40 × 80 mm). UV light (254 nm, 366 nm), basic permanganate solution [3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% (w/w) aqueous NaOH and water (300 mL)] and cerammoniummolybdate solution [2 g $Ce(SO_4)_2 \cdot H_2O$, 48 g $(NH_4)_6MoO_{24} \cdot H_2O$ in 1000 mL 10% aqueous (w/w) H_2SO_4] were used to aid visualisation.

Gas Chromatography (GC): Gas chromatographs were measured on Carlo Erba HRGC Mega2 Series 800 (HRGS Mega 2). For chiral separations *ß*- and *γ*-cyclodextrine columns (30 m × 0.25 mm × 0.25 µm) were used.

High Performance Liquid Chromatography (HPLC): HPLC analyses were measured on *Shimadzu* systems with SLC-10A System Controller, CTO-10AC column oven, LC10-AD pump system, DGU-14A degasser and SPD-M10A Diode Array- or UV-vis detector. Chiral columns used included Chiracel OD-H, OB-H, OJ, AS, AD-H and Chiralpak AD (4.6 × 250 mm) as well as Chiracel OD and AD (20 × 300 mm) from *Diacel Chemical Industries Ltd*.

Elemental Analysis (EA): Elemental analyses were measured by MR. W. KIRSCH (Department of Chemistry, University of Basel) on a Leco CHN-900 (C-, H-, N-detection) and Leco RO-478 (O-detection) analysers. The data are indicated in mass percent.

Chemicals: Commercially available starting material were purchased from *Acros*, *Aldrich*, *Alfa Aesar*, *Fluka* or *Lancaster* and *Strem Chemicals*.

5.2 Working Techniques

Sensitive Compounds: Syntheses of air- and moisture-sensitive compounds were carried out under an inert atmosphere in a glove box (MBRAUN labmaster 130, N_2) and using standard Schlenk techniques (Ar).

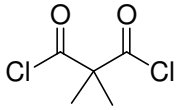
Solvents: Dichloromethane, diethyl ether, pentane, tetrahydrofuran and toluene were dried and degassed by distillation from an adequate drying agent under a nitrogen atmosphere.[180] Other solvents were purchased dry from *Fluk*a or *Aldrich* in septum sealed bottles and kept under an inert atmosphere over molecular sieves. If necessary, solvents were degassed by three freeze-pump-thaw cycles.

Column Chromatography: Silica gel was obtained from *Merck* (silica gel 60, 0.040-0.063 mm) and aluminium oxide from *Fluka* (Buchs; basic, 0.040-0.063 mm, Brockmann activity I). Flash column chromatography was performed under 0.1-0.8 bar (N_2 pressure), solvents were technical grade and were purified prior to use by distillation.

5.3 Synthesis of Quasienantiomeric Diels-Alder Adducts and Chiral Ligands for the Copper(II)-Catalysed Retro-Diels-Alder Reaction

5.3.1 Bis(oxazoline) Ligand Synthesis

2,2-Dimethylmalonyl dichloride (44)[139]



N,N-Dimethylformamide was added (0.33 mL) to dimethylmalonic acid (5 g, 37.8 mmol) in dichloromethane (57 mL). After cooling to 0 °C oxalyl chloride (9.60 mL, 114 mmol) was added dropwise during 30 minutes. After stirring for 17 hours at room temperature, evaporation of the solvent under reduced pressure gave a yellow oil with orange droplets. The mixture was distilled immediately under argon (180 °C, 5×10^{-1} mbar) to give 2,2-dimethylmalonyl dichloride **44** (5.20 g, 81%) as a colourless transparent liquid.

$C_5H_6Cl_2O_2$ (169.01):

^{1}H NMR (400.1 MHz, $CDCl_3$): δ= 1.68 (s, 6 H, CH_3).

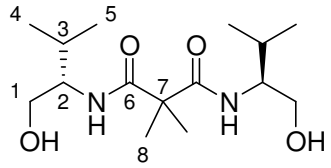
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ= 23.1 (CH_3), 69.1 (C), 172.0 (C).

IR (NaCl): $\tilde{\nu}$ = 3000w, 1794s, 1464m, 980m, 913m, 845m, 722m.

EA calcd (%) for $C_5H_6Cl_2O_2$: C, 35.53; H, 3.58. Found: C, 35.65; H, 3.66.

The spectroscopic data are in agreement with that previously reported in the literature.[139]

(*S*)-*N,N'*-Bis[1-(hydroxymethyl)-2-methylpropyl]-2,2-dimethyl-malonamide (45a)



General Method I: Triethylamine (6.87 mL, 48.5 mmol) was added dropwise to L-valinol (2.00 g, 19.4 mmol) in dichloromethane (23 mL) at 0 °C. Then a solution of 2,2-dimethylmalonyl dichloride **44** (1.64 g, 9.70 mmol) in dichloromethane (8 mL) was added via cannula during 5 minutes. A white precipitate formed and the suspension was stirred for 35 minutes at room temperature. Dichloromethane (60 mL) was added, dissolving most of the white solid. The reaction mixture was washed with 1 N HCl (15 mL) and the aqueous layer was extracted with dichloromethane (8 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was extracted with dichloromethane (8 mL). The combined organic extracts were washed with brine (15 mL) and the aqueous layer was extracted with dichloromethane (8 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a colourless solid. The crude product was recrystallised (ethyl acetate) to give diamide **45a** (2.26 g, 77%) as colourless crystals.

$C_{15}H_{30}N_2O_4$ (302.41):

m.p. 90-91 °C (ethyl acetate).

^{1}H NMR 400.1 MHz, $CDCl_3$): δ = 0.90 (d, ^3J = 6.6 Hz, 6 H, CHCH_3), 0.93 (d, ^3J = 6.6 Hz, 6 H, CHCH_3), 1.48 (s, 6 H, CCH_3), 1.77-1.83 (m, 2 H, C*H*CH$_3$), 3.35 (br s, 2 H, O*H*), 3.50 (m, 2 H, NHC*H*), 3.69-3.79 (m, 4 H, CH_2), 6.50 (br d, ^3J = 9.1 Hz, 2 H, N*H*).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 18.8 (CH_3, 4/5), 19.6 (CH_3, 4/5), 23.7 (CH_3, 8), 29.1 (CH, 3), 50.2 (C, 7), 57.2 (CH, 2), 63.6 (CH_2, 1), 174.5 (C, 6).

IR (KBr): $\tilde{\nu}$ = 3327s, 2964s, 1644s, 1546s, 1455s, 1390m, 1287m, 1187m, 1073m, 1027s.

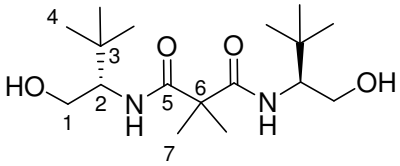
MS (FAB, NBA (subtr)), *m/z* (%): 303 ([M+H]$^+$, 100), 285 ([M-OH$_2$]$^+$, 26), 200 (18), 130 (20), 86 (35), 69 (38).

$[\alpha]_D^{20}$ = −31.8 (c = 1.02, MeOH).

EA calcd (%) for $C_{15}H_{30}N_2O_4$: C, 59.58; H, 10.00; N, 9.26; O, 21.16. Found: C, 59.60; H, 9.84; N, 9.28; O, 20.81.

The spectroscopic data are in agreement with that previously reported in the literature.[181]

(*S*)-*N,N'*-Bis[1-(hydroxymethyl)-2,2-dimethylpropyl]-2,2-dimethyl-1,3-propanediamide (45b)[139]



By **general method I** (*S*)-*t*-leucinol (4.68 g, 40.0 mmol), triethylamine (13.4 mL, 100 mmol) and 2,2-dimethylmalonyl dichloride **44** (3.38 g, 20.0 mmol) in dichloromethane (60 mL) gave the crude product. It was purified by recrystallisation (ethyl acetate) to give malonamide **45b** (6.13 g, 93%) as colourless plates.

$C_{17}H_{34}N_2O_4$ (330.46):

m.p. 159-161 °C (ethyl acetate) [lit.,[139] 163.3-163.7 °C].

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.92 (s, 18 H, C(C*H*$_3$)$_3$), 1.50 (s, 6 H, C*H*$_3$), 3.12 (br s, 2 H, O*H*), 3.42-3.47 (m, 2 H, C*H*), 3.81-3.89 (m, 4 H, C*H*$_2$), 6.45 (br d, ^3J = 9.9 Hz, 2 H, N*H*).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 23.8 (CH_3, 7), 26.8 (CH_3, 4), 33.4 (C, 3), 50.2 (C, 6), 59.6 (CH, 2), 62.3 (CH_2, 1), 174.7 (C, 5).

IR (KBr): $\tilde{\nu}$ = 3333s, 2956s, 1644s, 1533s, 1472s, 1361m, 1272m, 1183m, 1044m, 889m, 644m.

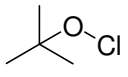
MS (FAB, NBA (subtr)), *m/z* (%): 331 ($[M+H]^+$, 100), 313 ($[M-OH_2]^+$, 22), 214 (12), 144 (16), 100 (21), 83 (22).

$[\alpha]_D^{20}$ = +2.00 (c = 1.00, MeOH) [lit.,[139] +2.5 (c = 0.75, MeOH)].

EA calcd (%) for $C_{17}H_{34}N_2O_4$: C, 61.79; H, 10.37; N, 8.48; O, 19.37. Found: C, 61.68; H, 10.25; N, 8.49; O, 19.19.

The spectroscopic data are in agreement with that previously reported in the literature.[139]

***t*-Butyl-hypochlorite (46)[182]**



A flask equipped with a gas inlet tube was charged with a solution of NaOH (16.0 g, 0.40 mol) in water (100 mL) and placed into a water bath at 15-20 °C. After all contents were cooled to this temperature, *t*-butyl alcohol (14.8 g, 0.20 mol) in water (100 mL) was added. The reaction mixture was stirred rapidly while Cl_2 was bubbled through at a constant rate for 1 hour. The upper oily layer of the yellow reaction mixture was separated and washed with

10% (w/w) aqueous Na_2CO_3 (6 × 5 mL), followed by water (4 × 15 mL). After drying ($CaCl_2$) and filtration *t*-butyl-hypochlorite **46** (14.80 g, 68%) was obtained as a yellow transparent liquid which was kept in the dark at -20 °C.

C_4H_9ClO (108.57):

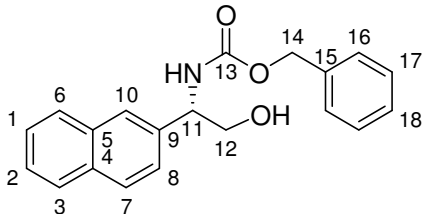
^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.17 (s, 9 H, CH_3).

IR (NaCl): $\tilde{\nu}$ = 2982s, 1462s, 1367s, 1248s, 1180s, 841s.

Density ρ = 0.96.

The spectroscopic data are in agreement with that previously reported in the literature.[182]

(*S*)-(2-Hydroxy-1-naphthalen-2-yl-ethyl)-carbamic acid benzyl ester (48)[140]



Benzyl carbamate (469 mg, 3.10 mmol) was dissolved in *n*-propanol (4 mL) with gentle heating and ultrasound. 7 mL freshly prepared aqueous NaOH (7.5 mL, 122 mg, 3.05 mmol) were added and the mixture was sonicated until all solid had dissolved. Then freshly prepared *t*-butyl-hypochlorite **46** (331 mg, 3.05 mmol) was added, followed by a solution of hydroquinine 1,4-phthalazinediyl diether [$(DHQ)_2PHAL$] ligand (40 mg, 0.05 mmol) in *n*-propanol (3.5 mmol). The reaction mixture was cooled to 0 °C and 2-vinylnaphthalene **47** (154 mg, 1 mmol) in *n*-propanol (1 mL) was added. The reaction mixture was quickly warmed to room temperature to achieve complete solvation of 2-vinylnaphthalene. A solution of $K_2OsO_2(OH)_4$ (14.7 mg, 0.04 mmol) in aqueous NaOH (0.5 mL) was added and the clear green reaction mixture was stirred at 0 °C for 3 hours. The grey slurry was filtered off, followed by a wash with cold *n*-propanol/water (1:1, 3 mL) giving a white solid. The crude product was purified by flash column chromatography (SiO_2, 1 × 4 cm, ethyl acetate/hexanes 1:1) to remove the undesired regioisomer, and recrystallisation (ethyl acetate) to give protected amino alcohol **48** (83 mg, 26%) as colourless prisms.

$C_{20}H_{19}NO_3$ (321.37):

m.p. 138-139 °C (ethyl acetate) [lit.,[140] 133-134 °C].

R_f = 0.57 (ethyl acetate/hexanes 1:1).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.83 (d, ^3J = 9.0 Hz, 1 H, O*H*), 3.93 (s, 2 H, CH_2OH), 5.00-5.15 (m, 3 H, CH_2O, C*H*), 5.68 (s, 1 H, N*H*), 7.36-7.50 (m, 8 H, H_{ar}), 7.79-7.84 (m, 4 H, H_{ar}).

^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 57.3 (CH, 11), 66.5 (CH_2, 12), 67.2 (CH_2, 14), 124.6 (C_{ar}H), 125.6 (C_{ar}H), 126.3 (C_{ar}H), 125.5 (C_{ar}H), 127.8 (C_{ar}H), 128.0 (C_{ar}H), 128.4 (C_{ar}H), 128.7 (C_{ar}H), 128.9 (C_{ar}H), 133.1 (C_{ar}), 133.4 (C_{ar}), 136.4 (C_{ar}), 136.6 (C_{ar}), 156.7 (C, 13).

IR (KBr): $\tilde{\nu}$ = 3316s, 1683s, 1545s, 1454m, 1332m, 1261s, 1060s.

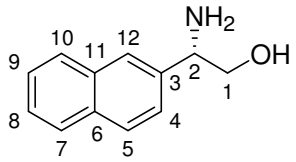
MS (FAB, NBA (subtr)), *m/z* (%): 322 ([M+H]$^+$, 30), 290 ([M-CH_3O]$^+$, 18), 243 (6), 171 (13), 91 ([C_7H_7]$^+$, 100).

$[\alpha]_D^{20}$ = +54.0 (c = 0.32, EtOH, 99% ee) [lit.,[140] +50.9 (c = 0.32, EtOH)].

EA calcd (%) for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C,74.73; H, 5.99; N, 4.41.

HPLC: Chiralcel AD, i-propanol/heptane (30:70), 0.70 mL/min, 20 °C, 220 nm, t_R = 9.5 min (major), t_R = 11.5 min (minor).

(*S*)-2-Amino-2-naphthalen-2-yl-ethanol (43d)[141]



Protected amino alcohol **48** (321 mg, 1 mmol) was dissolved in EtOH (13 mL) aided by ultrasound, then 10% Pd/C (109 mg) was added. The reaction mixture was stirred for 3.5 hours under a hydrogen-atmosphere until the completion of the reaction (checked by TLC). The catalyst was removed by filtration over celite and the solvent was removed under reduced pressure to give amino alcohol **43d** (181 mg, 97%) as an amorphous grey solid.

$C_{12}H_{13}NO$ (187.23):

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.87 (s, 3 H, O*H*, NH_2), 3.56 (dd, ^2J = 10.8 Hz, ^3J = 8.1 Hz, 1 H, C*H*H), 3.77 (dd, ^2J = 10.6 Hz, ^3J = 4.6 Hz, 1 H, C*H*H), 4.19 (dd, ^3J = 8.1 Hz, ^3J = 4.6 Hz, 1 H, C*H*), 7.44-7.50 (m, 3 H, H_{ar}), 7.80-7.84 (m, 4 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 57.8 (CH, 2), 68.3 (CH_2, 1), 125.3 (C_{ar}H), 125.3 (C_{ar}H), 126.1 (C_{ar}H), 126.5 (C_{ar}H), 127.9 (C_{ar}H), 128.1 (C_{ar}H), 128.4 (C_{ar}H), 131.4 (C_{ar}), 133.2 (C_{ar}), 133.8 (C_{ar}).

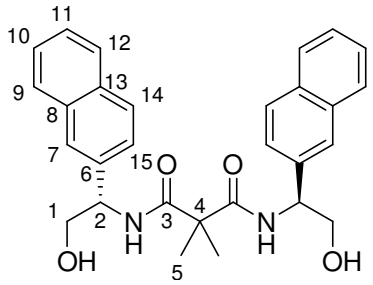
IR (KBr): $\tilde{\nu}$ = 3194bs, 2897bs, 1573s, 1504m, 1462m, 1362s, 1281s, 1061s, 953s, 900s, 823s, 747bs.

$[\alpha]_D^{20}$ = +32.0° (c = 0.20, EtOH) [lit.,[141] +33.9 (c = 1.39, $CHCl_3$)].

MS (FAB, NBA (subtr)), *m/z* (%): 341 (13), 216 (41), 188 ($[M+H]^+$, 100), 171 ($[M-NH_2]^+$, 87), 156 ($[M-CH_2OH]^+$, 88), 77 (18).

The spectroscopic data are in agreement with that previously reported in the literature.[141]

(*S*)-*N,N'*-Bis[2-hydroxy-1-naphthalen-2-yl-ethyl]-2,2-dimethyl-malonamide (45d)



Triethylamine (0.40 mL, 2.79 mmol) was added dropwise to amino alcohol **43d** (209 mg, 1.11 mmol) in dichloromethane (1.5 mL) at 0 °C Then a solution of 2,2-dimethylmalonyl dichloride **44** (94.0 mg, 0.558 mmol) in dichloromethane (0.5 mL) was added during 3 minutes. A white precipitate formed and the suspension was stirred for 20 minutes at 0 °C, followed by 70 min at room temperature. Dichloromethane (3 mL) was added to dissolve the white solid, the reaction mixture was washed with 1 N HCl (1 mL) and the aqueous layer was extracted with dichloromethane (1 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give malonamide **45d** (281 mg, >99%) as a colourless amorphous solid.

$C_{29}H_{30}N_2O_4$ (470.56):

m.p. 64-65 °C (dichloromethane) [lit.,[141] 169-170 °C].

R_f = 0.67 (ethyl acetate/MeOH 19 : 1).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.55 (s, 6 H, C*H*$_3$), 3.90 (dd, ^2J = 11.4 Hz, ^3J = 6.6 Hz, 2 H, CH*H*), 3.99 (dd, ^2J = 11.4 Hz, ^3J = 4.0 Hz, 2 H, CH*H*), 5.25 (dt, ^3J = 7.0 Hz, ^3J = 4.0 Hz, 2 H, C*H*), 2.29-7.81 (m, 14 H, H_{ar}).

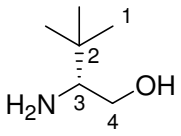
^{13}C{^{1}H} NMR (100.6 MHz, MeOH-D_4): δ = 24.6 (CH_3, 5), 51.9 (C, 4), 57.6 (CH, 2), 66.2 (CH_2, 1), 126.2 ($C_{ar}H$), 126.9 ($C_{ar}H$), 127.1 ($C_{ar}H$), 127.4 ($C_{ar}H$), 128.9 ($C_{ar}H$), 129.2 ($C_{ar}H$), 129.5 ($C_{ar}H$), 134.5 (C_{ar}, 7), 135.1 (C_{ar}, 12), 138.6 (C_{ar}, 6), 176.2 (C, 3).

IR (KBr): $\tilde{\nu}$ = 2976s, 1786s, 1690s, 1515s, 1466s, 1391s, 1334s, 1277s, 1225s, 1039s, 802m, 761m, 702s, 528s.

$[\alpha]_D^{20}$ = +79 (c = 0.18, EtOH) [lit.,[141] +85 (c = 0.20, EtOH)].

The spectroscopic data are in agreement with that previously reported in the literature.[141]

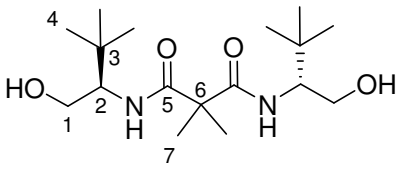
(*R*)-*t*-Leucinol ((*R*)-43b)[139]



(*R*)-*t*-Leucine **49** (500 mg, 3.81 mmol) was added in one portion to a stirred solution of $NaBH_4$ (346 mg, 9.16 mmol) in THF (10 mL). After cooling to 0 °C a solution of I_2 (967 mg, 3.81 mmol) in THF (8 mL) was added dropwise during 30 minutes. After warming the reaction mixture to room temperature, the reaction was heated at reflux for 19 hours. After cooling to room temperature the reaction mixture turned into a white suspension. MeOH (3 mL) was added carefully until all solid had dissolved. Vigorous gas evolution was observed during the addition. After removal of the solvent under reduced pressure, the white paste was stirred for 5 hours at room temperature with 20% (w/w) aqueous KOH (10 mL). The slightly green solution was extracted with dichloromethane (3 × 10 mL, 1 × 5 mL). Brine was added after the first extraction to reduce the emulsion in the aqueous layer. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow transparent oil, which solidified upon cooling to 4 °C. The product (*R*)-**43b** was used without purification in the next step.

$C_6H_{15}NO$ (117.19):
^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.90 (s, 9 H, CH_3), 2.49 (dd, ^3J = 10.1 Hz, ^2J = 3.8 Hz, 1 H, CH_2), 3.19 (t, ^3J = 10.1 Hz, 1 H, C*H*), 3.70 (dd, ^3J = 10.1 Hz, ^2J = 3.8 Hz, 1 H, CH_2).
The spectroscopic data are in agreement with that previously reported in the literature.[139]

(*R*)-*N,N'*-Bis[1-(hydroxymethyl)-2,2-dimethylpropyl]-2,2-dimethyl-1,3-propanediamide ((*R*)-45b)



By **general method I** (*R*)-*t*-leucinol (100 mg, 0.85 mmol), triethylamine (0.30 mL, 0.43 mmol) and 2,2-dimethylmalonyl dichloride **44** (72.0 mg, 0.427 mmol) in

dichloromethane (16 mL) gave the crude product. It was purified by recrystallisation (ethyl acetate) to give diamide (*R*)-**45b** (116 mg, 82%) as colourless plates.

$C_{17}H_{34}N_2O_4$ (330.46):

m.p. 158-159 °C (ethyl acetate).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.93 (s, 18 H, C*H*$_3$), 1.52 (s, 6 H, C*H*$_3$), 2.45 (br s, 2 H, O*H*), 3.45-3.48 (m, 2 H, C*H*), 3.84-3.90 (m, 4 H, C*H*$_2$), 6.40 (br d, ^3J = 9.1 Hz, 2 H, N*H*).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 23.7 (CH_3, 7), 26.8 (CH_3, 4), 33.4 (C, 3), 50.2 (C, 6), 59.6 (CH_2, 1), 62.6 (CH, 2), 174.7 (C, 5).

IR (KBr): $\tilde{\nu}$ = 3335s, 2966s, 2361s, 1648s, 1541s, 1473s, 1395m, 1368m, 1268m, 1184m, 1051m.

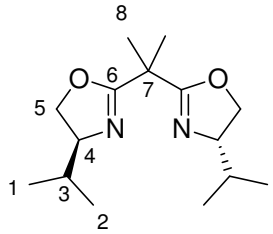
MS (FAB, NBA (subtr)), *m*/*z* (%): 331 ($[M+H]^+$, 100), 313 ($[M-OH_2]^+$, 28), 214 (15), 187 (9), 144 (21), 100 (23), 83 (27), 57 (36), 41 (33).

$[\alpha]_D^{20}$ = −2.6 (c = 0.47, MeOH).

EA calcd (%) for $C_{17}H_{34}N_2O_4$: C, 61.79; H, 10.37; N, 8.48; O, 19.37. Found: C, 61.67; H, 10.18; N, 8.48; O, 19.43.

The spectroscopic data are in agreement with that of the enantiomer previously reported in the literature.[139]

2,2-Bis{2-[4(*S*)-i-propyll-1,3-oxazolinyl]}propane (32a)



General Method II: According to a procedure by EVANS,[139] triethylamine (4.01 mL, 29.1 mmol) was added to a solution of malonamide **44** (2.00 g, 6.61 mmol) and 4-(dimethylamino)pyridine (81.0 mg, 0.61 mmol) in dichloromethane (26 mL). The flask was placed in a room temperature water bath and a solution of *p*-toluenesulfonyl chloride (2.53 g, 13.22 mmol) in dichloromethane (6 mL) was added during 10 minutes, followed by a rinse with dichloromethane (2 mL). After stirring for 27 hours at room temperature, the solution was diluted with dichloromethane (20 mL) and washed with saturated aqueous NH_4Cl (30 mL). To dissolve the solid formed in the aqueous layer water (15 mL) was added. The aqueous layer was extracted with dichloromethane (3 × 25 mL). The combined organic

extracts were washed with saturated aqueous $NaHCO_3$ (25 mL) and the aqueous layer was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting white-yellow solid was triturated with hot pentane (1 × 20 mL, 1 × 6 mL, 1 × 4 mL), followed by gravity filtration through a hot frit. After removal of the solvent, the colourless solid was recrystallised (pentane) to give ligand **32a** (1.64, 93%) as a colourless transparent oil.

$C_{15}H_{26}N_2O_2$ (266.38):

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 0.83 (d, ^3J = 6.8 Hz, 6 H, CHC*H*$_3$), 0.90 (d, ^3J = 6.8 Hz, 6 H, CHC*H*$_3$), 1.44 (s, 6 H, C*H*$_3$), 1.66-1.77 (m, 2 H, C*H*CH$_3$), 3.85-3.97 (m, 4 H, C*H*$_2$), 4.16-4.21 (m, 2 H, NC*H*).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 17.6 (CH_3, 1/2), 18.3 (CH_3, 1/2), 24.3 (CH_3, 8), 32.5 (CH, 3), 38.6 (C, 7), 70.2 (CH_2, 5), 71.8 (CH, 4), 168.5 (C, 6).

IR (NaCl): $\tilde{\nu}$ = 2960s, 1662s, 1467s, 1353m, 1248m, 1144s, 1112s, 980s, 925m.

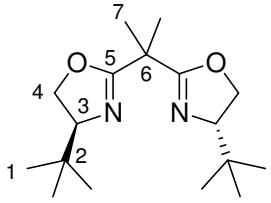
MS (FAB, NBA (subtr)), *m*/*z* (%): 267 ([M+H]$^+$, 100), 181 (15), 155 (13), 69 (21), 41 (22).

$[\alpha]_D^{20}$ = −125.6 (c = 1.09, CH_2Cl_2).

EA calcd (%) for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52; O, 12.01. Found: C, 66.87; H, 9.72; N, 10.43; O, 13.01.

The spectroscopic data are in agreement with that previously reported in the literature.[183]

2,2-Bis{2-[4(*S*)-*t*-butyl-1,3-oxazolinyl]}propane (32b)[139]



By **general method II** malonamide **45b** (3.00 g, 9.08 mmol), 4-(dimethylamino)pyridine (111 mg, 0.91 mmol), triethylamine (5.57 mL, 40.0 mmol) in dichloromethane (36 mL) and a solution of *p*-toluenesulfonyl chloride (3.47 g, 18.2 mmol) in dichloromethane (8 mL) gave ligand **32b** (1.96 g, 73%) as colourless plates.

$C_{17}H_{30}N_2O_2$ (294.43):

m.p. 86-87 °C (pentane) [lit.,[139] 88.9-89.8 °C].

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.86 (s, 18 H, C*H*$_3$), 1.50 (s, 6 H, C*H*$_3$), 3.84 (dd, ^3J = 10.0 Hz, ^3J = 7.0 Hz, 2 H, C*H*), 4.05-4.16 (m, 4 H, C*H*$_2$).

$^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 24.4 (CH_3, 7), 25.6 (CH_3, 1), 33.9 (C, 2), 38.6 (C, 6), 69.0 (CH_2, 4), 75.3 (CH, 5), 168.6 (C, 5).

IR (KBr): $\tilde{\nu}$ = 2956s, 2870m, 1660s, 1478s, 1360s, 1259s, 1146s, 1123s, 978s, 925s.

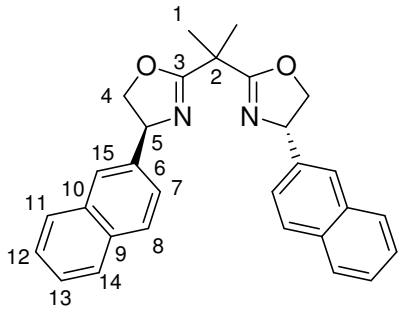
MS (FAB, NBA (subtr)), *m/z* (%): 295 ($[M+H]^+$, 100), 237 (11), 195 (11), 169 (13), 57 (31), 41 (22).

$[\alpha]_D^{20}$ = −128.20 (c = 0.61, MeOH) [lit.,[139] +113.2 (c = 1.22, dichloromethane)].

EA calcd (%) for $C_{17}H_{30}N_2O_2$: C, 69.35; H, 10.27; N, 9.51; O, 10.87. Found: C, 69.32; H, 10.13; N, 9.43; O, 10.97.

The spectroscopic data are in agreement with that previously reported in the literature.[139]

2,2-Bis{2-[4(*S*)-(2'-naphthyl)-1,3-oxazolinyl]}propane (32d)



By **general method II** malonamide **45d** (280 mg, 0.595 mmol), 4-(dimethylamino)pyridine (5.40 mg, 59.6 µmol) and triethylamine (0.34 mL, 2.62 mmol) in dichloromethane (3 mL) and a solution of *p*-toluenesulfonyl chloride (239 mg, 1.19 mmol) in dichloromethane (1 mL) gave the crude product. It was purified by flash column chromatography (SiO_2, 1 × 10 cm, ethyl acetate/hexanes 1:3 → 2:3) and treated with Et_2O (to dissolve a yellow impurity) to give ligand **32d** (151 mg, 58%) as a colourless amorphous solid.

$C_{29}H_{26}N_2O_2$ (434.53):

m.p. 170-172 °C (Et_2O) [lit.,[141] 173-174 °C].

R_f = 0.30 (ethyl acetate/hexanes 1:1).

^1H NMR (400.1 MHz, CD_2Cl_2): δ = 1.70 (s, 6 H, CH_3), 4.24 (dd, ^3J = 8.4 Hz, ^3J = 7.6 Hz, 2 H, C*H*), 4.75 (dd, ^2J = 10.1 Hz, ^3J = 8.6 Hz, 2 H, C*H*H), 5.39 (dd, ^2J = 10.1 Hz, ^3J = 7.6 Hz, 2 H, C*H*H), 7.38-7.48 (m, 6 H, H_{ar}), 7.73-7.83 (m, 8 H, H_{ar}).

$^{13}C\{^1H\}$ NMR (100.6 MHz, CD_2Cl_2): δ = 24.3 (CH_3, 1), 39.1 (C, 2), 69.8 (CH, 5), 75.3 (CH_2, 4), 124.8 ($C_{ar}H$), 125.5 ($C_{ar}H$), 125.9 ($C_{ar}H$), 126.2 ($C_{ar}H$), 127.6 ($C_{ar}H$), 127.9 ($C_{ar}H$), 128.6 ($C_{ar}H$), 132.9 (C_{ar}), 133.4 (C_{ar}), 140.2 (C_{ar}), 170.4 (C, 3).

IR (KBr): $\tilde{\nu}$ = 3352 bs, 2933s, 1714m, 1425s, 1347s, 1056s.

MS (EI, 70 eV, ca. 250 °C), *m/z* (%): 434 ([M]$^+$, 53), 307 (8), 265 (20), 239 (100), 154 (100), 69 (13), 41 (7).

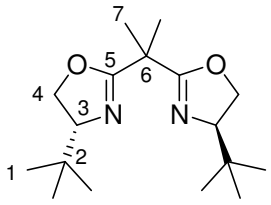
$[\alpha]_D^{20}$ = −240.0 (c = 0.22, CH_2Cl_2, >99% ee) [lit.,[141] −232.5 (c = 0.55, $CHCl_3$)].

EA calcd (%) for $C_{29}H_{26}N_2O_2$: C, 80.16; H, 6.03; N, 6.45. Found: C, 78.35; H, 6.01; N, 6.35.

HPLC: Chiralcel AD, i-propanol/heptane (20:80), 1.00 mL/min, 20 °C, 220 nm, t_R = 7.7 min (major).

The spectroscopic data are in agreement with that previously reported in the literature.[141]

2,2-Bis{2-[4(*R*)-*t*-butyl-1,3-oxazolinyl]}propane ((*R*)-32b)



By **general method II** diamide (*R*)-**45b** (260 mg, 0.787 mmol), 4-(dimethylamino)pyridine (9.60 mg, 79.0 µmol), triethylamine (0.47 mL, 3.46 mmol) in dichloromethane (3 mL) and a solution of *p*-toluenesulfonyl chloride (299 mg, 1.57 mmol) in dichloromethane (1 mL) gave (*R,R*)-*t*-Bu-box ligand (*R*)-**32b** (212 mg, 91%) as colourless plates.

$C_{17}H_{30}N_2O_2$ (294.43):

m.p. 79-81 °C (dichloromethane).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.87 (s, 18 H, CH_3), 1.52 (s, 6 H, CH_3), 3.83 (dd, ^3J = 10.1 Hz, ^3J = 6.8 Hz, 2 H, CH), 4.06-4.17 (m, 4 H, CH_2O).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 24.4 (CH_3, 7), 25.6 (CH_3, 1), 33.9 (C, 2), 69.0 (CH_2, 4), 75.3 (CH, 5), 168.6 (C, 5).

IR (KBr): $\tilde{\nu}$ = 3418s, 2958s, 1661s, 1480s, 1359m, 1299m, 1252s, 1211m, 1145s, 980s, 923s.

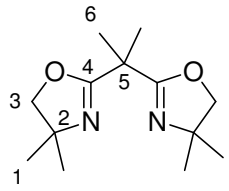
MS (FAB, NBA (subtr)), *m/z* (%): 313 ([M+H_2O]$^+$, 18), 295 ([M]$^+$, 100), 237 (12), 195 (14), 169 (17), 112 (16), 83 (14), 57 (37).

$[\alpha]_D^{20}$ = +100.0 (c = 0.25, dichloromethane).

EA calcd (%) for $C_{17}H_{30}N_2O_2$: C, 69.35; H, 10.27; N, 9.51; O, 10.87. Found: C, 69.08; H, 9.94; N, 9.31; O, 11.34.

The spectroscopic data are in agreement with that of the enantiomer previously reported in the literature.[139]

2,2-Bis[2-(4-dimethyl-1,3-oxazolinyl)]propane (50)[142]



2-Amino-2-methyl-1-propanol (3.00 mL, 31.9 mmol) was added dropwise to a solution of dimethylmalononitrile (1.00 g, 10.6 mmol) and dry $ZnCl_2$ (1.45 g, 10.6 mmol) in chlorobenzene (6 mL) which was heated at reflux. After 30 hours at this temperature and cooling to room temperature, the mixture was washed twice with 25% (w/w) aqueous NH_4OH and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed with water, the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil. A Kugelrohr distillation (10^{-1} Torr, 100 °C → 140 °C) of the crude product gave ligand **50** (1.62 g, 64%) as a colourless transparent oil which solidified at -20 °C.

$C_{13}H_{22}N_2O_2$ (238.33):

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.21 (s, 12 H, CH_3), 1.41 (s, 6 H, CH_3), 3.89 (s, 4 H, CH_2).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 24.1 (CH_3, 6), 27.9 (CH_3, 1), 38.3 (C, 5), 67.0 (C, 2), 79.3 (CH_2, 3), 167.3 (C, 4).

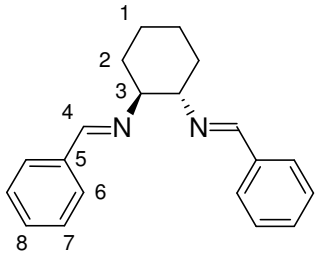
IR (NaCl): $\tilde{\nu}$ = 3436 b s, 2070s, 1659s, 1463s, 1362s, 1294s, 1250m, 1192s, 1129s, 1103s, 979s, 930s.

MS (FAB, NBA (subtr)), *m/z* (%): 239 ($[M+H]^+$, 100), 167 (34), 55 (21).

EA calcd (%) for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30; N, 11.75. Found: C, 64.90; H, 9.14; N, 11.54.

5.3.2 Bis(imine) Ligand Synthesis

(*S*,*S*)-(1,2)-*N*,*N*'-Dibenzylidene-cyclohexane-1,2-diamine (34a)



General Method III: Benzaldehyde (0.44 mL, 4.38 mmol) was added to a solution of (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (250 mg, 2.19 mmol) in refluxing MeOH (2 mL). After heating at reflux for 30 minutes, the reaction mixture was cooled to room temperature and solvent was removed under reduced pressure until a precipitate formed. The solid was filtered off and washed with cold hexanes to give bis(imine) ligand **34a** (263 mg, 41%) as colourless rhomboids.

$C_{20}H_{22}N_2$ (290.40):

m.p. 102-103 °C (hexanes).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.49 (dd, ^2J = 9.3 Hz, ^3J = 8.1 Hz, 2 H, CH_2), 1.85-1.88 (m, 6 H, CH_2), 3.41-3.43 (m, 2 H, C*H*), 7.30-7.32 (m, 6 H, H_{ar}), 7.57-7.59 (m, 4 H), 8.34 (s, 2 H, N=C*H*).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 24.5 (CH_2, 1), 33.0 (CH_2, 2), 73.8 (CH, 3), 127.9 (C_{ar}H, 7), 128.4 (C_{ar}H, 6), 129.0 (C, 5), 130.2 (C_{ar}H, 8), 161.0 (CH, 4).

IR (KBr): $\tilde{\nu}$ = 2926s, 2852s, 1642s, 1575m, 1449s, 1374s, 1290m, 1214m, 1161m, 1063m, 939m, 756s, 693s.

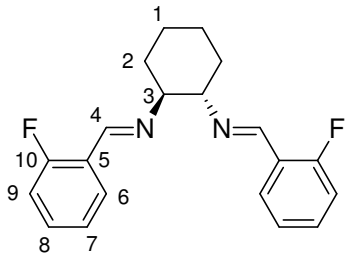
MS (FAB, NBA (subtr)), *m*/*z* (%): 291 ([M+H]$^+$, 100), 203 (10), 187 (22), 106 (34), 91 (23).

$[\alpha]_D^{20}$ = +276.4 (c = 1.00, dichloromethane).

EA calcd (%) for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.85; H, 7.77; N, 9.59.

The spectroscopic data are in agreement with that previously reported in the literature.[184]

(*S,S*)-*N,N'*-Bis-(2-fluoro-benzylidene)-cyclohexane-1,2-diamine (34b)



By **general method III** (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (250 mg, 2.19 mmol) and 1-fluoro-benzaldehyde (0.46 mL, 4.38 mmol) in MeOH (1.2 mL) gave bis(imine) ligand **34b** (133 mg, 19%) as colourless rhomboids after stored overnight at -20 °C without prior removal of solvent.

$C_{20}H_{20}F_2N_2$ (326.38):

m.p. 86-87° C (MeOH).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.48-1.53 (m, 2 H, CH_2), 1.75-1.87 (m, 6 H, CH_2), 3.38-3.43 (m, 2 H, C*H*), 6.97-7.02 (m, 2 H, H_{ar}), 7.10 (dt, ^3J = 7.3 Hz, ^4J = 0.7 Hz, 2 H, H_{ar}), 7.29-7.35 (m, 2 H, H_{ar}), 7.84 (dt, ^3J = 7.6 Hz, ^4J = 1.8 Hz, 2 H, H_{ar}), 8.48 (s, 2 H, N=C*H*).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 25.0 (CH_2, 1), 33.5 (CH_2, 2), 74.7 (CH, 3), 116.0 ($J_{C\text{-}F}$ = 21.1 Hz, C_{ar}H, 9), 124.6 ($J_{C\text{-}F}$ = 9.0 Hz, C, 5), 124.7 ($J_{C\text{-}F}$ = 3.5 Hz, C_{ar}H, 7), 128.1 ($J_{C\text{-}F}$ = 3.1 Hz, C_{ar}H, 6), 132.3 ($J_{C\text{-}F}$ = 8.4 Hz, C_{ar}H, 8), 154.2 ($J_{C\text{-}F}$ = 4.6 Hz, CH, 4), 162.6 ($J_{C\text{-}F}$ = 251 Hz, C, 10).

IR (KBr): $\tilde{\nu}$ = 2928s, 2853s, 1639s, 1577s, 1483s, 1453s, 1374s, 1274s, 1226s, 1181m, 1072s, 803m, 763s.

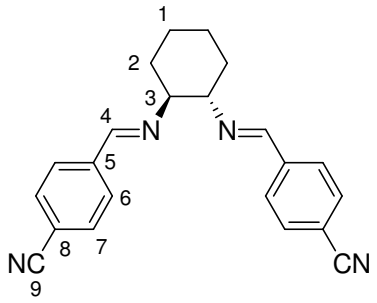
MS (FAB, NBA (subtr)), *m/z* (%): 327 ([M+H]$^+$, 100), 221 (8), 205 (21), 124 (30), 109 (16).

$[\alpha]_D^{20}$ = +238.8 (c = 1.00, dichloromethane).

EA calcd (%) for $C_{20}H_{20}F_2N_2$: C, 73.60; H, 6.18; N, 8.58. Found: C, 73.54; H, 6.16; N, 8.46.

The spectroscopic data are in agreement with that previously reported in the literature.[184]

(*S,S*)-*N,N'*-Bis-(4-cyano-benzylidene)-cyclohexane-1,2-diamine (34c)



By **general method III** (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (250 mg, 2.19 mmol) and 4-cyano-benzaldehyde (574 mg, 4.38 mmol) in MeOH (1.2 mL) gave a yellow solid after stored overnight at -20 °C without prior removal of solvent. The crude product was purified by recrystallisation (ethyl acetate/hexanes) to give bis(imine) ligand **34c** (272 mg, 37%) as colourless rhomboids.

$C_{22}H_{20}N_4$ (340.42):

m.p. 145-146 °C (ethyl acetate/hexanes).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.48-1.53 (m, 2 H, C*H*$_2$), 1.83-1.90 (m, 6 H, C*H*$_2$), 3.48 (s, 2 H, C*H*), 7.61 (d, ^3J = 8.4 Hz, 4 H, H_{ar}(7)), 7.70 (d, ^3J = 8.1 Hz, 4 H, H_{ar}(6)), 8.20 (s, 2 H, N=C*H*).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 24.2 (CH_2, 1), 32.6 (CH_2, 2), 73.9 (CH, 3), 113.7 (C, 8), 118.4 (C, 9), 128.2 ($C_{ar}H$, 7), 132.3 ($C_{ar}H$, 6), 139.9 (C, 5), 159.0 (CH, 4).

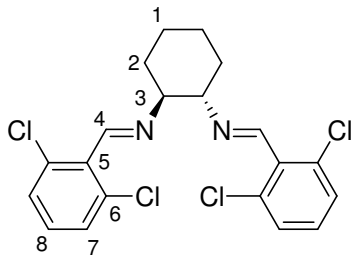
IR (KBr): $\tilde{\nu}$ = 2924s, 2847s, 2223s, 1642s, 1375s, 1079s, 940s, 832s, 555s.

MS (FAB, NBA (subtr)), *m/z* (%): 494 (9), 341 ([M+H]$^+$, 100), 228 (13), 211 (15), 131 (20).

$[\alpha]_D^{20}$ = +439.9 (c = 1.00, dichloromethane).

EA calcd (%) for $C_{22}H_{20}N_4$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.52; H, 5.92; N, 16.60.

(*S,S*)-*N,N'*-Bis(2,6-dichloro-benzylidene)-cyclohexane-1,2-diamine (34d)



By **general method III** (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (250 mg, 2.19 mmol) and 2,6-dichloro-benzaldehyde (767 mg, 4.38 mmol) in MeOH (1.2 mL) gave the crude product.

The crude product was purified by washing with cold ethyl acetate/hexanes (1:9) and recrystallisation (ethyl acetate/hexanes 4:3) to give bis(imine) ligand **34d** (940 mg, 100 %) as colourless rhomboids.

$C_{20}H_{18}Cl_4N_2$ (428.18):

m.p. 153-155° C (ethyl acetate/hexanes).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.51-1.54 (m, 2 H, CH_2), 1.85-1.88 (m, 6 H, CH_2), 3.53-3.55 (m, 2 H, C*H*), 7.19 (dd, ^3J = 8.8 Hz, ^3J = 7.1 Hz, 2 H, H_{ar}), 7.29 (d, ^3J = 8.3 Hz, 4 H, H_{ar}), 8.43 (s, 2 H, N=C*H*).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 24.8 (CH_2, 1), 33.4 (CH_2, 2), 75.6 (CH, 3), 129.2 (C_{ar}H, 7), 130.5 (C_{ar}H, 8), 133.4 (C, 6), 135.3 (C, 5), 156.5 (CH, 4).

IR (KBr): $\tilde{\nu}$ = 2928s, 2855s, 2360s, 1645s, 1580s, 1555s, 1429s, 1375s, 1191m, 1090m, 927m, 842m, 774s.

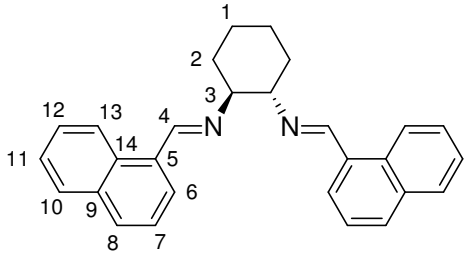
MS (FAB, NBA (subtr)), *m*/*z* (%): 429 ([M+H]$^+$, 100), 271 (17), 255 (27), 174 (65), 81 (61).

$[\alpha]_D^{20}$ = −15.4 (c = 1.00, dichloromethane).

EA calcd (%) for $C_{20}H_{18}Cl_4N_2$: C, 56.10; H, 4.24; N, 6.54. Found: C, 56.06; H, 4.22; N, 6.48.

The spectroscopic data are in agreement with that previously reported in the literature.[184]

(*S,S*)-*N,N'*-Bis-naphthalen-1-ylmethyl ene-cyclohexane-1,2-diamine (34e)



1-Naphtaldehyde (0.59 mL, 4.38 mmol) was added in small portions to a solution of (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (250 mg, 2.19 mmol) in refluxing EtOH (10 mL). After heating at reflux for 1 hour, the reaction mixture was cooled down to room temperature and water was added. A white-yellow solid precipitated, which was filtered off and recrystallised (ethyl acetate/hexanes) to give bis(imine) ligand **34e** (166 mg, 16%) as colourless rhomboids.

$C_{28}H_{26}N_2$ (390.52):

m.p. 130-131 °C (ethyl acetate/hexanes).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.57-1.63 (m, 2 H, CH_2), 1.92-2.00 (m, 6 H, CH_2), 3.57-3.59 (m, 2 H, C*H*), 7.30-7.44 (m, 6 H, H_{ar}), 7.69 (dd, ^3J = 7.3 Hz, J = 1.0 Hz, 2 H, H_{ar}), 7.79

(dd, ^3J = 8.3 Hz, J = 1.0 Hz, 4 H, H_{ar}), 8.79 (dd, ^3J = 8.6 Hz, J = 1.0 Hz, 2 H, H_{ar}), 8.82 (s, 2 H, N=C*H*).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 25.1 (CH_2, 1), 33.7 (CH_2, 2), 75.7 (CH, 3), 125.2 ($C_{ar}H$), 125.6 ($C_{ar}H$), 126.4 ($C_{ar}H$), 127.2 ($C_{ar}H$), 128.8 ($C_{ar}H$), 129.0 ($C_{ar}H$), 130.9 ($C_{ar}H$), 131.7 (C), 132.7 (C), 134.2 (C), 160.9 CH, 4).

IR (KBr): $\tilde{\nu}$ = 3039s, 2922s, 2833s, 1634s, 1444m, 1377s, 1333s, 1233s, 1085s, 1010s, 935s, 776s.

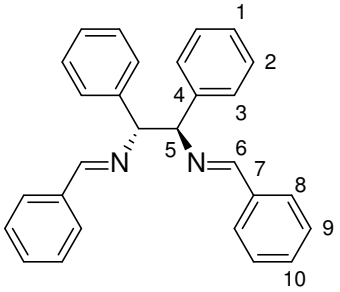
MS (FAB, NBA (subtr)), *m*/*z* (%): 391 ([M+H]$^+$, 100), 237 (27), 141 (29), 81 (12).

$[\alpha]_D^{20}$ = +226.0 (c = 1.00, dichloromethane).

EA calcd (%) for $C_{28}H_{26}N_2$: C, 86.12; H, 6.71; N, 7.17. Found: C, 86.12; H, 6.75; N, 6.97.

The spectroscopic data are in agreement with that previously reported in the literature.[184]

(*R,R*)-*N,N'*-Dibenzylidene-1,2-diphenylethane-1,2-diamine (34f)



Benzaldehyde (0.19 mL, 1.88 mmol) was added to a solution of (1*R*,2*R*)-(+)-1,2-diphenylethaneamine (200 mg, 0.94 mmol) in refluxing EtOH (4.7 mL). After heating at reflux for 1 hour, the reaction mixture was cooled down to room temperature. At this temperature a precipitate formed which was filtered and wash with cold ethyl acetate/hexanes 1:1 to give bis(imine) ligand **34f** (326 mg, 81%) as colourless prisms.

$C_{28}H_{24}N_2$ (388.50):

m.p. 160-161 °C (ethyl acetate/hexanes) [lit.,[185] 158-159 °C (racemic compound)]

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 4.76 (s, 2 H, NC*H*), 7.12-7.20 (m, 6 H, H_{ar}), 7.28-7.36 (m, 10 H, H_{ar}), 7.66-7.68 (m, 4 H, H_{ar}), 8.28 (s, 2 H, N=C*H*).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 81.7 (CH, 8), 127.5 ($C_{ar}H$), 128.4 ($C_{ar}H$), 128.6 ($C_{ar}H$), 128.9 ($C_{ar}H$), 129.0 ($C_{ar}H$), 131.0 ($C_{ar}H$), 136.9 (C, 6), 141.8 (C, 14), 162.1 (C, 7).

IR (KBr): $\tilde{\nu}$ = 3448 bs, 3026s, 2846s, 2362s, 1644s, 1489m, 1451s, 1377m, 1312m, 1216m, 1050s, 755s, 696s.

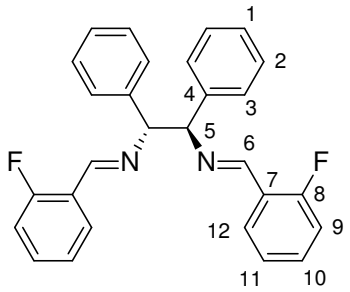
MS (FAB, NBA (subtr)), *m*/*z* (%): 389 ([M+H]$^+$, 26), 301 (13), 284 (14), 194 (100), 91 (30).

$[\alpha]_D^{20}$ = −0.30 (c = 1.10, dichloromethane)

EA calcd (%) for $C_{28}H_{24}N_2$: C, 86.56; H, 6.23; N, 7.21. Found: C, 86.26; H, 6.22; N. 7.15.

The spectroscopic data are in agreement with that previously reported for the racemic compound.[185]

(*R,R*)-*N,N'*-Bis(2-fluoro-benzylidene)1,2-diphenyl-ethane-1,2-diamine (34g)



To a solution of (1*R*,2*R*)-(+)-1,2-diphenylethaneamine (200 mg, 0.94 mmol) in refluxing EtOH (4.7 mL) was added 2-fluoro-benzaldehyde (0.20 mL, 1.88 mmol). After heating at reflux for 1 hour, the reaction mixture was cooled down to room temperature. At this temperature a precipitate formed which was filtered off and washed with cold ethyl acetate/hexanes 1:1 to give bis(imine) ligand **34g** (255 mg, 64%) as colourless prisms.

$C_{28}H_{22}F_2N_2$ (424.48):

m.p. 124-125 °C (ethyl acetate/hexanes).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 4.82 (m, 1 H, NC*H*), 5.25 (m, 1 H, NC*H*), 6.80-6.88 (m, 2 H, H_{ar}), 6.97-7.02 (m, 1 H, H_{ar}), 7.07-7.19 (m, 6 H, H_{ar}), 7.21-7.37 (m, 5 H, H_{ar}), 7.65-7.77 (m, 3 H, H_{ar}), 7.95-8.04 (m, 1 H, H_{ar}), 8.30-8.31 (m, 1 H, N=C*H*), 8.59-8.61 (m, 1 H, N=C*H*).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 72.1 ($J_{C\text{-}F}$ = 10.4 Hz, CH, 5) 115.4 ($J_{C\text{-}F}$ = 22.0 Hz, $C_{ar}H$), 116.2 ($J_{C\text{-}F}$ = 22.0 Hz, $C_{ar}H$), 124.5 ($C_{ar}H$), 124.8 ($C_{ar}H$), 128.4 ($J_{C\text{-}F}$ = 3.1 Hz, C_{ar}), 128.7 ($J_{C\text{-}F}$ = 2.7 Hz, C_{ar}), 129.2 ($C_{ar}H$), 130.8 ($C_{ar}H$), 131.2 ($J_{C\text{-}F}$ = 3.8 Hz, $C_{ar}H$), 131.3 (C_{ar}), 163.4 (CH, 6).

IR (KBr): $\tilde{\nu}$ = 3424bs, 3028s, 2848s, 1643s, 1581s, 1487s, 1381s, 1228s, 1049m, 757s, 695s.

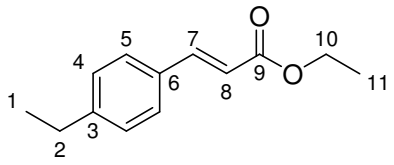
MS (FAB, NBA (subtr)), *m/z* (%): 461 (8), 443 (23), 425 ([M+1]$^+$, 19), 320 (14), 230 (61), 212 (100).

$[\alpha]_D^{20}$ = +1.7 (c = 0.94, dichloromethane).

EA calcd (%) for $C_{28}H_{22}F_2N_2$: C, 79.23; H, 5.22; N, 6.60. Found: C, 77.24; H, 5.09; N, 6.47.

5.3.3 Synthesis of Dienophiles

(*E*)-Ethyl 3-(4-ethylphenyl)-acrylate (51)



General Method IV: According to a procedure by SCHULTZ,[143] $Pd(PPh_3)_4$ (32.2 mg, 28.0 µmol) in *N,N*-dimethylacetamide (10 mL) was added to a solution of 1-ethyl-4-iodobenzene (6.00 g, 26.0 mmol), ethyl acrylate (3.15 mL, 29.0 mmol) and sodium acetate (2.87 g, 35.0 mmol) in *N,N*-dimethylacetamide (80 mL) at 140 °C. After 24 hours at this temperature, the reaction mixture was cooled to room temperature and diluted with hexanes (250 ml). The solution was washed with water (3 × 150 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 8 × 20 cm, ethyl acetate/hexanes 1:10) to give acrylate **51** (3.24 g, 61%) as a colourless oil.

$C_{13}H_{16}O_2$ (204.26):

R_f = 0.45 (ethyl acetate/pentane 1:10).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.6 Hz, 3 H, CH_3), 1.32 (t, ^3J = 7.1 Hz, 3 H, CH_3), 2.66 (q, ^3J = 7.6 Hz, 2 H, CH_2CH$_3$), 4.26 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH$_3$), 6.39 (d, $^3J_{trans}$ = 16.2 Hz, 1 H, C*H*C=O), 7.21 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.45 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.67 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, C$_6$H$_4$C*H*).

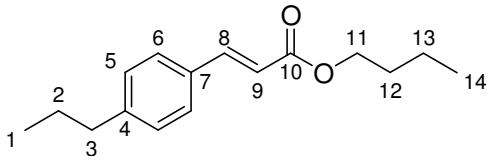
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 14.3 (CH_3, 1), 15.3 (CH_3, 11), 28.8 (CH_2, 2), 60.4 (CH_2, 10), 117.2 (CH, 8), 128.1 ($C_{ar}H$, 4), 128.4 ($C_{ar}H$, 5), 131.9 (C, 6), 144.6 (CH, 7), 146.9 (C, 3), 167.2 (C, 9).

MS (EI, 70 eV, r.t.), *m/z* (%): 204 ($[M]^+$, 75), 189 ($[M-CH_3]^+$, 11), 176 ($[M]^+$, 22), 159 ($[M-C_2H_5O]^+$, 100), 131 ($[M-C_3H_3O_2]^+$, 45), 115 (31), 91 ($[C_7H_7]^+$, 16).

IR (NaCl): $\tilde{\nu}$ = 2967s, 1724s, 1633s, 1568m, 1513s, 1456m, 1418m, 1366s, 1318s, 1262s, 1037s, 984s, 828s.

EA calcd (%) for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89; O, 15.66. Found: C, 76.16; H, 7.90; O, 15.89.

(*E*)-*n*-Butyl 3-(4-*n*-propylphenyl)-acrylate (52)



Using **general method IV** $Pd(PPh_3)_4$ (26.0 mg, 23.0 µmol) in *N,N*-dimethylacetamide (10 mL) added to 4-bromo-1-*n*-propylbenzene (3.52 mL, 22.6 mmol), *n*-butyl acrylate (3.87 mL, 27.1 mmol) and sodium acetate (2.60 g, 31.6 mmol) in *N,N*-dimethylacetamide (65 mL) gave a brown oil. The crude product was purified by flash column chromatography (SiO_2, 5 × 18 cm, ethyl acetate/hexanes 1:10) to give acrylate **52** (2.74 g, 49%) as a yellow transparent oil.

$C_{16}H_{22}O_2$ (246.34):

R_f = 0.55 (ethyl acetate/hexanes 1:3).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.95 (t, ^3J = 7.8 Hz, 3 H, C*H*$_3$), 0.97 (t, ^3J = 7.8 Hz, 3 H, C*H*$_3$), 1.39-1.49 (m, 2 H, C*H*$_2$CH$_3$), 1.60-1.73 (m, 4 H, CH$_2$C*H*$_2$CH$_2$, C*H*$_2$CH$_3$), 2.60 (t, ^3J = 7.6 Hz, 2 H, C*H*$_2$(3)CH2CH3), 4.20 (t, ^3J = 6.6 Hz, 2 H, OC*H*$_2$), 6.40 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, C*H*C=O), 7.19 (d, ^3J = 7.6 Hz, 2 H, H_{ar}), 7.44 (d, ^3J = 7.6 Hz, 2 H, H_{ar}), 7.66 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, C$_6$H$_4$C*H*).

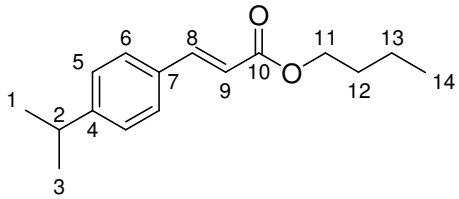
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 13.7 (CH_3), 13.8 (CH_3), 19.2 (CH_2, 13), 24.3 (CH_2, 2), 30.8 (CH_2, 12), 37.9 (CH_2, 3), 64.3 (CH_2, 11), 117.2 (CH, 9), 128.0 ($C_{ar}H$), 129.0 ($C_{ar}H$), 132.0 (C, 7), 144.6 (CH, 8), 145.4 (C, 4), 167.3 (C, 10).

MS (EI, 70 eV, r.t.), *m/z* (%): 246 ([M]$^+$, 35), 217 ([M$^-$C$_2$H$_5$]$^+$, 15), 190 ([M$^-$C$_4$H$_8$]$^+$, 100), 173 (57), 161 (67), 131 ([M$^-$C$_9$H$_7$O]$^+$, 22), 115 (33), 91 (5), 43 (9).

IR (NaCl): $\tilde{\nu}$ = 2960s, 2871s, 1713s, 1637s, 1461m, 1315m, 1272m, 1170s, 984m, 828m.

EA calcd (%) for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.00; H, 9.14.

(*E*)-*n*-Butyl 3-(4-i-propylphenyl)-acrylate (53)



Using **general method IV** $Pd(PPh_3)_4$ (24.0 mg, 20.0 µmol) in *N,N*-dimethylacetamide (5 mL) was added to 4-iodo-1-i-propyl-benzene (4.92 g, 20.0 mmol), *n*-butyl acrylate (3.42 mL,

24.0 mmol) and sodium acetate (2.30 g, 28.0 mmol) in *N,N*-dimethylacetamide (60 mL) to give the crude product as a brown oil. The crude product was purified by flash column chromatography (SiO_2, 5 × 20 cm, ethyl acetate/hexanes 1:10) to give acrylate **53** (1.18 g, 24%) as a colourless transparent oil.

$C_{16}H_{22}O_2$ (246.34):

R_f = 0.8 (ethyl acetate/hexanes 1:3).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.97 (t, ^3J = 7.8 Hz, 3 H, CH_3), 1.25 (d, ^3J = 6.8 Hz, 6 H, CHCH_3), 1.39-1.49 (m, 2 H, CH_2CH$_3$), 1.66-1.72 (m, 2 H, CH_2CH$_2$CH$_3$), 2.92 (sept, ^3J = 6.8 Hz, CHCH$_3$), 4.21 (t, ^3J = 6.6 Hz, 2 H, OCH_2), 6.40 (d, $^3J_{trans}$ = 16.2 Hz, 1 H, CHC=O), 7.24 (d, ^3J = 8.2 Hz, 2 H, H_{ar}), 7.46 (d, ^3J = 8.3 Hz, 2 H, H_{ar}), 7.66 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, C$_6$H$_4$CH).

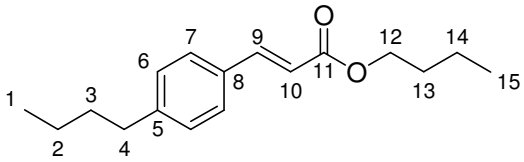
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 13.7 (CH_3, 14), 19.2 (CH_2, 13), 23.8 (CH_3, 1 or3), 23.8 (CH_3, 1 or 3), 30.8 (CH_2, 12), 34.1 (CH, 2), 64.3 (CH_2, 11), 117.2 (CH, 9), 127.0 (C_{ar}H), 128.1 (C_{ar}H), 132.1 (C, 7), 144.5 (CH, 8), 151.5 (C, 4), 167.3 (C, 10).

IR (NaCl): $\tilde{\nu}$ = 2961s, 2363s, 1712s, 1636s, 1462m, 1314m, 1271m, 1170s, 1059m, 984m, 828s.

MS (EI, 70 eV, r.t.), *m/z* (%): 246 ([M]$^+$, 56), 231 ([M$^-$CH$_3$]$^+$, 70), 190 ([M$^-$C$_4$H$_8$]$^+$, 100), 175 (82), 131 ([M$^-$C$_9$H$_7$O]$^+$, 60), 115 (12), 91 (6), 43 (11).

EA calcd (%) for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.09; H, 9.06.

(*E*)-*n*-Butyl 3-(4-*n*-butylphenyl)-acrylate (54)



Using **general method IV** $Pd(PPh_3)_4$ (41.0 mg, 35.0 µmol) in *N,N*-dimethylacetamide (10 mL) added to 4-iodo-1-*n*butyl-benzene (6.22 g, 35.0 mmol), *n*-butyl acrylate (6.00 mL, 42.0 mmol) and sodium acetate (4.02 g, 49.0 mmol) in *N,N*-dimethylacetamide (110 mL) gave a brown oil. The crude product was purified by flash column chromatography (SiO_2, 5 × 20 cm, ethyl acetate/hexanes 1:10) to give acrylate **54** (5.60 g, 62%) as a colourless transparent oil.

$C_{17}H_{24}O_2$ (260.37):

R_f = 0.77 (ethyl acetate/hexanes 1:3).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.3 Hz, 3 H, CH_3), 0.97 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.31-1.49 (m, 4 H, CH_2CH$_3$), 1.56-1.72 (m, 4 H, CH_2CH$_2$CH$_3$), 2.62 (t, ^3J = 7.6 Hz, 2 H, C_6H_4CH_2), 4.20 (t, ^3J = 6.8 Hz, 2 H, OCH_2), 6.39 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, CHC=O), 7.19 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.44 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.66 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, C_6H_4CH).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 13.7 (CH_3), 13.9 (CH_3),19.2 (CH_2, 14), 22.3 (CH_2, 2), 30.8 (CH_2, 13), 33.4 (CH_2, 3), 35.5 (CH_2, 4), 64.3 (CH_2, 12), 117.2 (CH, 10), 128 (C_{ar}H,), 128.9 (C_{ar}H,), 131.9 (C, 8), 144.6 (CH, 9), 145.6 (C, 5), 167.3 (C, 11).

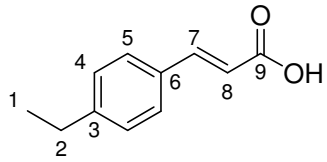
IR (NaCl): $\tilde{\nu}$ = 2958s, 1713s, 1637s, 1462m, 1315s, 1269m, 1169s, 984s, 827m.

MS (EI, 70 eV, ca. 50 °C), *m/z* (%): 260 ([M]$^+$, 34), 217 ([M$^-$C$_3$H$_7$]$^+$, 19), 204 ([M$^-$C$_4$H$_8$]$^+$, 100), 187 (46), 161 (57), 131 (18), 115 (27), 91 (4), 41 (8).

EA calcd (%) for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.41; H, 9.33.

The spectroscopic data are in agreement with that previously reported in the literature.[186]

(*E*)-3-(4-Ethylphenyl)-acrylic acid (56)



General Method V: Acrylate **51** (1.00 mg, 4.90 mmol) was dissolved in 1 M aqueous NaOH (19.6 mL, 19.6 mmol) and ethanol (40 mL) and the reaction mixture was heated at reflux for 4 hours. After cooling, the solvent was removed under reduced pressure and the remaining white slurry was completely dissolved in water. The pH-value of the solution was reduced to 1 with conc. HCl and the aqueous phase was extracted with Et_2O (5 × 80 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure to give acid **56** (0.860 g, 99%) as an amorphous colourless solid.

$C_{11}H_{12}O_2$ (176.21):

m.p. 155.5-156.5 °C (Et_2O).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.25 (t, ^3J = 7.6 Hz, 3 H, CH$_2$CH_3), 2.68 (q, ^3J = 7.6 Hz, 2 H, CH_2CH$_3$), 6.42 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, CHC=O), 7.24 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.48 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.77 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, C_6H_4CH).

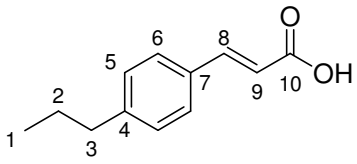
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 15.3 (CH_3, 1), 28.8 (CH_2, 2), 116.1 (CH, 8), 128.5 (C_{ar}H, 4), 128.5 (C_{ar}H, 5), 131.5 (C, 6), 147.2 (CH, 7), 147.6 (C, 3), 172.2 (C, 9).

IR (KBr): $\tilde{\nu}$ = 2958s, 1675s, 1628s, 1513m, 1426s, 1320s, 1291s, 1226s, 1180s, 942s, 822s, 687s, 546s.

MS (EI, 70 eV, r.t.), *m*/*z* (%): 176 ($[M]^+$, 97), 161 ($[M-CH_3]^+$, 100), 147 ($[M-C_2H_5]^+$, 17), 131 ($[M]^+$, 16), 115 (33), 91 ($[C_7H_7]^+$, 10).

EA calcd (%) for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; O, 18.16. Found: C, 74.81; H, 6.86; O, 18.21.

(*E*)-3-(4-*n*-Propylphenyl)-acrylic acid (57)



By **general method V** acrylate **52** (2.50 g, 10.1 mmol) was dissolved in 1 M aqueous NaOH (40.4 mL, 40.4 mmol) and ethanol (82 mL) to give acid **57** (1.84 g, 96%) as colourless prisms.

$C_{12}H_{14}O_2$ (190.24):

m.p. 168.5-169.5 °C (ethanol).

R_f = 0.32 (ethyl acetate/hexanes 1 : 3).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.95 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.65 (sext, ^3J = 7.3 Hz, 2 H, CH_2CH$_3$), 2.62 (t, ^3J = 7.3 Hz, 2 H, CH_2CH$_2$CH$_3$), 6.42 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, C*H*C=O), 7.21 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.47 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.78 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, C_6H_4C*H*), 9.94 (br s, 1 H, OH).

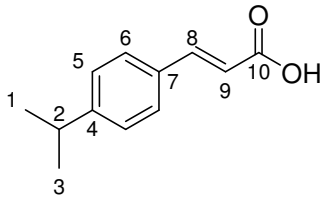
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 13.8 (CH_3, 1), 24.3 (CH_2, 2), 37.9 (CH_2, 3), 116.1 (CH, 9), 128.4 (C_{ar}H), 129.1 (C_{ar}H), 131.6 (C, 7), 146.0 (C, 4), 147.1 (CH, 8), 172.4 (C, 10).

IR (KBr): $\tilde{\nu}$ = 2960s, 2584s, 1680s, 1619s, 1511m, 1418s, 1310s, 1280s, 1215s, 941s, 810s, 686s.

MS (EI, 70 eV, ca. 50 °C), *m*/*z* (%): 190 ($[M]^+$, 42), 161 ($[M-C_2H_5]^+$, 100), 115 (28), 91 ($[C_7H_7]^+$, 6).

EA calcd (%) for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.83; H, 7.50.

(*E*)-3-(4-i-Propylphenyl)-acrylic acid (58)



By **general method V** acrylate **53** (1.18 g, 4.79 mmol) dissolved in 1 M aqueous NaOH (19.2 mL, 19.2 mmol) and ethanol (40 mL) gave acid **58** (0.813 g, 89%) as colourless crystals.

$C_{12}H_{14}O_2$ (190.24):

m.p. 152-153 °C (ethanol).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.26 (d, ^3J = 6.8 Hz, 6 H, CH_3), 2.94 (sept, ^3J = 7.1 Hz, 1 H, CHCH$_3$), 6.41 (d, $^3J_{trans}$ = 16.2 Hz, 1 H, CHC=O), 7.27 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.49 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.77 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, C$_6$H$_4$CH).

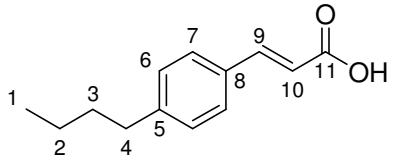
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 23.7 (CH$_3$, 1 and 3), 34.1 (CH, 2), 116.1 (CH, 9), 127.1 (C$_{ar}$H), 128.5 (C$_{ar}$H), 131.7 (C, 7), 147.1 (CH, 8), 152.2 (C, 4), 172.0 (C, 10).

IR (KBr): $\tilde{\nu}$ = 3459s, 2956s, 2586s, 1681s, 1621s, 1421s, 1312s, 1279s, 1218s, 1053m, 983m, 941s, 826s, 673s.

MS (EI, 70 eV, ca. 100 °C), *m*/*z* (%): 190 ([M]$^+$, 41), 175 ([M–CH$_3$]$^+$, 100), 129 (16), 115 (8), 91 ([C$_7$H$_7$]$^+$, 7).

EA calcd (%) for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.71; H, 7.34.

(*E*)-3-(4-*n*-Butylphenyl)-acrylic acid (59)



By **general method V** acrylate **54** (5.60 g, 21.5 mmol) dissolved in 1 M aqueous NaOH (86.2 mL, 86.2 mmol) and ethanol (180 mL) gave acid **59** (4.29 g, 97%) as a crystalline solid.

$C_{13}H_{16}O_2$ (204.26):

m.p. 137-138 °C (ethanol).

R$_f$ = 0.20 (ethyl acetate/hexanes 1:3).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.35 (sext, ^3J = 7.8 Hz, 2 H, CH_2CH$_3$), 1.57-1.65 (m, 2 H, CH_2CH$_2$CH$_3$), 2.64 (t, ^3J = 7.6 Hz, 2 H, CH_2CH$_2$CH$_2$CH$_3$),

6.41 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, C*H*C=O), 7.21 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.47 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.77 (d, $^3J_{trans}$= 15.9 Hz, 1 H, C_6H_4CH).

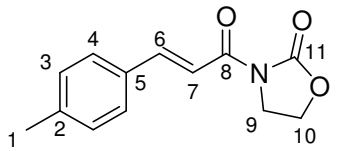
$^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (CH_3, 1), 22.3 (CH_2, 2), 33.3 (CH_2, 3), 35.6 (CH_2, 4), 116.0 (CH, 10), 128.4 ($C_{ar}H$), 129.1 ($C_{ar}H$), 131.5 (C, 8), 146.3 (C, 5), 147.1 (CH, 9), 171.9 (C, 11).

IR (KBr): $\tilde{\nu}$ = 3448s, 2926s, 2586m, 1685s, 1623s, 1511m, 1422s, 1314s, 1281m, 1222m, 939s, 810m.

MS (EI, 70 eV, ca. 100 °C), *m/z* (%): 204 ($[M]^+$, 43), 161 ($[M^-C_3H_7]^+$, 100), 115 (17).

EA calcd (%) for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.32; H, 7.88.

3-[(*E*)-3-*p*-Tolylacryloyl]-2-oxazolidinone (60)



General Method VI: According to a procedure by EVANS,[144] oxalyl chloride (0.78 mL, 9.25 mmol) and *N,N*-dimethylformamide (2 drops) were added dropwise to a suspension of 4-methylcinnamic acid (200 mg, 1.23 mmol) in dichloromethane (5 mL) at 0 °C. After stirring for 3 hours at ambient temperature, the solvent and excess oxalyl chloride were removed under reduced pressure. The 4-methylcinnamic acid chloride was obtained as a colourless amorphous solid and used immediately.

n-BuLi (1.6 M in hexane, 0.70 mL, 1.12 mmol) was added to a solution of 2-oxazolidinone (98.0 mg, 1.12 mmol) in THF (5 mL) at -78 °C. After stirring for 15 minutes at this temperature 4-methylcinnamic acid chloride (222 mg, 1.23 mmol) in THF (2 mL) was added. The yellow suspension was stirred for 30 minutes at -78 °C and 15 minutes at 0 °C. After quenching with saturated aqueous NH_4Cl, the organic layer was washed with saturated aqueous Na_2CO_3 (2 ×) and then with brine, dried (Na_2SO_4) and removal of the solvent under reduced pressure gave a yellow gum. The crude product was purified by flash column chromatography (SiO_2, 2 × 20 cm, ethyl acetate/hexanes 1:1) to give oxazolidinone **60** (197 mg, 76%) as colourless prisms.

$C_{13}H_{13}NO_3$ (213.25):

m.p. 178.5-179.5 °C.

R_f = 0.18 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 4.13 (t, ^3J = 8.0 Hz, 2 H, NCH_2), 4.45 (t, ^3J = 8.0 Hz, 2 H, OCH_2), 7.20 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.52 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.85 (s, 2 H, C*H*=C*H*).

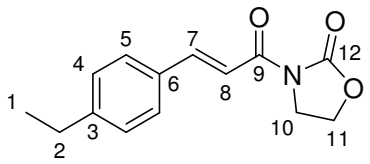
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 21.5 (CH_3, 1), 42.8 (CH_2, 9), 62.0 (CH_2, 10), 115.4 (CH, 7), 128.7 (C_{ar}H), 129.6 (C_{ar}H), 131.8 (C, 5), 141.2 (CH, 6). 146.4 (C, 2), 153.6 (C, 11), 165.5 (C, 8).

IR (KBr): $\tilde{\nu}$ = 1769s, 1674s, 1616s, 1512m, 1481m, 1392s, 1354s, 1203s, 1108m, 1038s, 818s, 757s, 690s, 498s.

MS (EI, 70 eV, ca. 100 °C), *m*/*z* (%): 213 ([M]$^+$, 28), 145 ([M-$C_3H_4NO_2$]$^+$, 100), 115 (25).

EA calcd (%) for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06; O, 20.76. Found: C, 67.66; H, 5.79; N, 6.10; O, 20.56.

3-[(*E*)-3-(4-Ethylphenyl)acryloyl]-2-oxazolidinone (61)[144]



By **general method VI** acid chloride (553 mg, 2.84 mmol), generated from acid **56**, in THF (2 mL) was added to 2-oxazolidinone (247 mg, 2.84 mmol) and *n*-BuLi (1.6 M in hexane, 1.75 mL, 2.84 mmol) in THF (8 mL) to give a yellow gum. The crude product was purified by recrystallisation (pentane/dichloromethane) to give oxazolidinone **61** (398 mg, 72%) as colourless prisms.

$C_{14}H_{15}NO_3$ (245.27):

m.p. 123-124 °C (pentane/dichloromethane).

R_f = 0.15 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.6 Hz, 3 H, CH_2CH_3), 2.67 (q, ^3J = 7.6 Hz, 2 H, CH_2CH_3), 4.13 (t, ^3J = 8.0 Hz, 2 H, NCH_2), 4.45 (t, ^3J = 8.0 Hz, 2 H, OCH_2), 7.22 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.54 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.86 (s, 2 H, C*H*=C*H*).

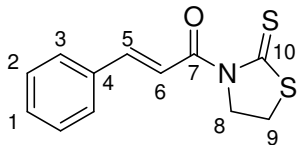
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 15.3 (CH_3, 1), 28.8 (CH_2, 2), 42.8 (CH_2, 10), 62.0 (CH_2, 11), 115.5 (CH, 8), 128.4 (C_{ar}H), 128.8 (C_{ar}H), 132.0 (C, 6), 146.4 (CH, 7), 147.6 (C, 3), 153.6 (C, 12), 165.6 (C, 9).

IR (KBr): $\tilde{\nu}$ = 2924s, 1783s, 1668s, 1615s, 1478m, 1348s, 1215s, 1117m, 1938s, 984m, 824s, 755s, 686s, 550m.

MS (EI, 70 eV, r.t.), *m*/*z* (%): 245 ([M]$^+$, 36), 159 ([M-$C_3H_4NO_2$]$^+$, 100), 131 (20), 115 (14).

EA calcd (%) for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71; O, 19.57. Found: C, 68.56; H, 6.25; N, 5.65; O, 19.57.

3-[(*E*)-3-Phenyl-2-propenoyl]-2-thiazolidinethione (41)[91]



General Method VII: Oxalyl chloride (1.15 mL, 13.5 mmol) and *N,N*-dimethylformamide (3 drops) were added dropwise to cinnamic acid (1.00 g, 6.75 mmol) in dichloromethane (25 mL) at 0 °C. After stirring for 3 hours at ambient temperature, the solvent and excess oxalyl chloride were removed under reduced pressure. The remaining off-white solid was dissolved in dichloromethane (15 mL) and cooled to -78 °C. 2-Thiazolidinethione (805 mg, 6.75 mmol) was added, followed by dropwise addition of triethylamine (0.85 mL, 7.43 mmol). The reaction mixture became bright yellow and a suspension formed. After stirring for 30 min at -78 °C and 30 min at 0 °C the transparent yellow solution was diluted with Et_2O (20 mL), washed with saturated aqueous $NaHCO_3$ (20 mL) and water (20 mL). Drying (Na_2SO_4) and removal of the solvent under reduced pressure gave a yellow oil. The crude product was purified by column chromatography (SiO_2, 4 × 12 cm, ethyl acetate/hexanes 1:4) followed by recrystallisation (dichloromethane/pentane) to give thiazolidinethione **62** (659 mg, 39%) as yellow prisms.

$C_{12}H_{11}NOS_2$ (249.35):

m.p. 81-82 °C (pentane/dichloromethane) [lit.,[91] 80-83 °C].

R_f = 0.19 (ethyl acetate/hexanes 1:4).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.38 t, ^3J = 7.3 Hz, 2 H, SCH_2), 4.60 (t, ^3J = 7.3 Hz, 2 H, NCH_2), 7.39-7.40 (m, 3 H, H_{ar}), 7.55-7.57 (m, 2 H, H_{ar}), 7.69 (d, $^3J_{trans}$ = 15.6 Hz, 1 H, C*H*C=O), 7.87 (d, $^3J_{trans}$ = 15.6 Hz, 1 H, C_6H_4C*H*).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 29.1 (CH_2, 9), 56.0 (CH_2, 8), 119.9 (CH, 6), 128.5 (C_{ar}H), 128.9 (C_{ar}H), 130.5 (C_{ar}H), 134.7 (C, 4), 144.1 (CH, 5), 167.3 (C, 7), 201.8 (C, 10).

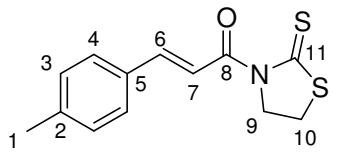
IR (KBr): $\tilde{\nu}$ = 3086w, 1675s, 1611s, 1570s, 1438s, 1371s, 1327s, 1272s, 1225s, 1168s, 1043s, 970s, 918s, 848s, 764s.

MS (EI, 70 eV, ca. 100 °C), *m*/*z* (%): 249 ([M]$^+$, 43), 131 ([C_6H_5CH=CHC=O]$^+$, 100), 103 ([C_6H_5CH=CH]$^+$, 37), 77 ([C_6H_5]$^+$,16).

EA calcd (%) for $C_{12}H_{11}NOS_2$: C, 57.80; H, 4.45; N, 5.62; O, 6.42. Found: C, 57.84; H, 4.44; N, 5.62; O, 6.32.

The spectroscopic data are consistent with that reported in the literature.[91]

3-[(*E*)-3-*p*-Tolyl-2-propenoyl]-2-thiazolidinethione (63)



By **general method VII** the acid chloride was generated from 4-methylcinnamic acid (1.00 g, 6.17 mmol), oxalyl chloride (1.04 mL, 12.3 mmol) and *N,N*-dimethylformamide (3 drops) in dichloromethane (25 mL). After dissolving the acid chloride in dichloromethane (12 mL) 2-thiazolidinethione (736 mg, 6.17 mmol) and triethylamine (0.95 mL, 6.79 mmol) were added to give a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 4 × 12 cm, ethyl acetate/hexanes 1:4) to give thiazolidinethione **63** (1.14 g, 70%) as a yellow amorphous solid.

$C_{13}H_{13}NOS_2$ (263.38):

m.p. 107.5-109.0 °C (ethyl acetate/hexanes).

R_f = 0.20 (ethyl acetate/hexanes 1:4).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 3.02 (t, ^3J = 7.6 Hz, 2 H, SCH_2), 4.59 (t, ^3J = 7.6 Hz, 2 H, NCH_2), 7.20 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.45 (d, ^3J = 7.8 Hz, 2 H, H_{ar}), 7.68 (d, $^3J_{trans}$ = 15.4 Hz, 1 H, CHC=O), 7.83 (d, $^3J_{trans}$ = 15.4 Hz, 1 H, C_6H_4CH).

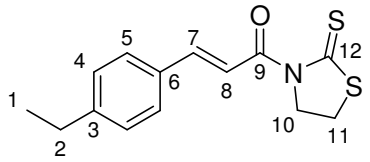
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 21.5 (CH_3, 1), 29.1 (CH_2, 10), 56.0 (CH_2, 9), 118.8 (CH, 7), 128.5 (C_{ar}H), 129.7 (C_{ar}H), 132.0 (C, 5), 141.1 (C, 2), 144.3 (CH, 6), 167.4 (C, 8), 201.7 (C, 11).

IR (KBr): $\tilde{\nu}$ = 3480w, 2289w, 1674s, 1599s, 1376m, 1323s, 1282s, 1218s, 1162s, 1057m, 802s.

MS (EI, 70 eV, 100 °C), *m*/*z* (%): 263 ([M]$^+$, 29), 145 (100), 115 (21), 91 ([C_7H_7]$^+$, 11).

EA calcd (%) for $C_{13}H_{13}NOS_2$: C, 59.29; H, 4.97; N, 5.32; O, 6.07. Found: C, 59.23; H, 4.95; N, 5.37; O, 6.08.

3-[(*E*)-3-(4-Ethylphenyl)-2-propenoyl]-2-thiazolidinethione (64)



By **general method VII** the acid chloride was generated from acid **56** (290 mg, 1.65 mmol), oxalyl chloride (0.28 mL, 3.30 mmol) and *N,N*-dimethylformamide (3 drops) in dichloromethane (7 mL). After dissolving the acid chloride in dichloromethane (4 mL) 2-thiazolidinethione (197 mg, 1.65 mmol) and triethylamine (0.25 mL, 1.82 mmol) were added to give a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 2 × 12 cm, ethyl acetate/hexanes 1:4) to give thiazolidinethione **64** (309 mg, 68%) as a yellow amorphous solid.

$C_{14}H_{15}NOS_2$ (277.41):

m.p. 65-66 °C (ethyl acetate/hexanes).

R_f = 0.27 (ethyl acetate/hexanes 1:4).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.6 Hz, 3 H, CH_3), 2.66 (q, ^3J = 7.6 Hz, 2 H, CH_2CH$_3$), 3.37 (t, ^3J = 7.6 Hz, 2 H, SCH_2), 4.59 (t, ^3J = 7.3 Hz, 2 H, NCH_2), 7.22 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.48 (d, ^3J = 7.8 Hz, 2 H, H_{ar}), 7.68 (d, $^3J_{trans}$ = 15.6 Hz, 1 H, CHC=O), 7.84 (d, $^3J_{trans}$ = 15.4 Hz, 1 H, C_6H_4CH).

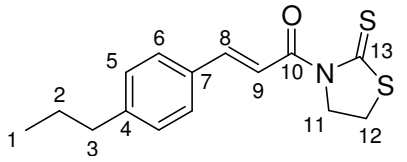
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 15.3 (CH_3, 1), 28.8 (CH_2, 2), 29.1 (CH_2, 11), 56.0 (CH_2, 10), 118.9 (CH, 8), 128.5 (C_{ar}H), 128.7 (C_{ar}H), 132.2 (C, 6), 144.3 (CH, 7), 147.4 (C, 3), 167.4 (C, 9), 201.7 (C, 12).

IR (KBr): $\tilde{\nu}$ = 2922m, 1681s, 1611s, 1374m, 1325s, 1283m, 1163s, 1049m, 819m, 676m.

MS (EI, 70 eV, 100 °C), *m*/*z* (%): 277 ([M]$^+$, 39), 159 (100), 131 (22), 115 (14), 91([C_7H_7]$^+$, 10).

EA calcd (%) for $C_{14}H_{15}NOS_2$: C, 60.62; H, 5.45; N, 5.05; O, 5.77. Found: C, 60.67; H, 5.47; N, 5.05; O, 5.90.

3-[(*E*)-3-(4-*n*-Propylphenyl)-2-propenoyl]-2-thiazolidinethione (65)



By **general method VII** the acid chloride was generated from acid **57** (1.56 g, 8.21 mmol), oxalyl chloride (1.39 mL, 16.4 mmol) and *N,N*-dimethylformamide (3 drops) in dichloromethane (27 mL). After dissolving the acid chloride in dichloromethane (20 mL), 2-thiazolidinethione (979 mg, 8.21 mmol) and triethylamine (1.26 mL, 9.03 mmol) were added to give a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 5 × 15 cm, ethyl acetate/hexanes 1:5) to give thiazolidinethione **65** (1.21 g, 51%) as yellow prisms.

$C_{15}H_{17}NOS_2$ (291.43):

m.p. 77.5-78.5 °C (dichloromethane/pentane).

$\mathbf{R_f}$ = 0.52 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 7.3 Hz, 3 H, CH_2CH_3), 1.64 (sext, ^3J = 7.3 Hz, 2 H, CH_2CH_3), 2.60 (t, ^3J = 7.3 Hz, 2 H, $CH_2CH_2CH_3$), 3.37 (t, ^3J = 7.6 Hz, 2 H, SCH_2), 4.59 (t, ^3J = 7.6Hz, 2 H, NCH_2), 7.20 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.48 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.69 (d, $^3J_{trans}$ = 15.4 Hz, 1 H, CHC=O), 7.84 (d, $^3J_{trans}$ = 15.4 Hz, 1 H, C_6H_4CH).

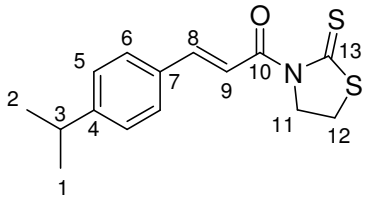
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 13.8 (CH_3, 1), 24.3 (CH_2, 2), 29.1 (CH_2, 3), 38.0 (CH_2, 12), 56.0 (CH_2, 11), 118.8 (CH, 9), 128.6 ($C_{ar}H$), 129.1 ($C_{ar}H$), 132.3 (C, 7), 144.4 (CH, 8), 145.9 (C, 4), 167.5 (C, 10), 201.7 (C, 13).

IR (KBr): $\tilde{\nu}$ = 2920s, 1682s, 1607s, 1461w, 1378s, 1326s, 1280s, 1219s, 1171s, 1056s, 682s.

MS (EI, 70 eV, 150 °C), *m*/*z* (%): 291 ($[M]^+$, 42), 173 (100), 131 (27), 115 (23), 43 ($[C_3H_7]^+$, 9).

EA calcd (%) for $C_{15}H_{17}NOS_2$: C, 61.82; H, 5.88; N, 4.81. Found: C, 61.65; H, 5.63; N, 4.82.

3-[(*E*)-3-(4-i-Propylphenyl)-2-propenoyl]-2-thiazolidinethione (66)



By **general method VII** the acid chloride was generated from acid **58** (760 mg, 4.00 mmol), oxalyl chloride (0.87 mL, 10.3 mmol) and *N,N*-dimethylformamide (3 drops) in dichloromethane (16 mL). After dissolving the acid chloride in dichloromethane (10 mL), 2-thiazolidinethione (477 mg, 4.00 mmol) and triethylamine (0.60 mL, 4.40 mmol) were added to give a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 4 × 12 cm, ethyl acetate/hexanes 1:5) to give thiazolidinethione **66** (750 mg, 64%) as yellow prisms.

$C_{15}H_{17}NOS_2$ (291.43):

m.p. 81-83 °C.

R_f = 0.63 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.24 (d, ^3J = 6.8 Hz, 6 H, CH_3), 2.93 (sept, ^3J = 6.8 Hz, 1 H, CH(CH_3)$_2$), 3.37 (t, ^3J = 7.3 Hz, 2 H, SCH_2), 4.55 (t, ^3J = 7.3 Hz, 2 H, NCH_2), 7.27 (d, ^3J = 8.6 Hz, 2 H, H_{ar}), 7.50 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 7.64 (d, $^3J_{trans}$ = 15.6 Hz, 1 H, CHC=O), 7.90 (d, $^3J_{trans}$ = 15.7 Hz, 1 H, C_6H_4CH).

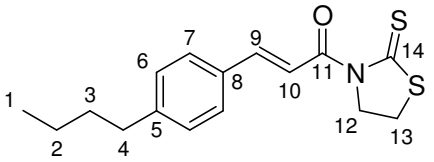
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 23.6 (CH_3, 1/2), 29.3 (CH_2, 12), 34.2 (CH, 3), 56.2 (CH_2, 11), 119.3 (CH, 9), 127.1 (C_{ar}H), 128.6 (C_{ar}H), 132.5 (C, 7), 143.6 (CH, 8), 152.1 (C, 4), 167.3 (C, 10), 202.2 (C, 13).

IR (KBr): $\tilde{\nu}$ = 3442s, 2959s, 2361s, 1682s, 1614s, 1374s, 1324s, 1284s, 1214s, 1166s, 1052s, 824s, 676s.

MS (EI, 70 eV, ca. 200 °C), *m*/*z* (%): 291 ([M]$^+$, 58), 173 (76), 131 (100), 115 (10), 43 ([C_3H_7]$^+$, 16).

EA calcd (%) for $C_{15}H_{17}NOS_2$: C, 61.82; H, 5.88; N, 4.81. Found: C, 61.62; H, 5.79; N. 4.89.

3-[(*E*)-3-(4-*n*-Butylphenyl)-2-propenoyl]-2-thiazolidinethione (67)



By **general method VII** the acid chloride was generated from acid **59** (1.22 g, 6.00 mmol), oxalyl chloride (1.27 mL, 15.0 mmol) and *N,N*-dimethylformamide (3 drops) in dichloromethane (24 mL). After dissolving the acid chloride in dichloromethane (15 mL), 2-thiazolidinethione (715 mg, 6.00 mmol) and triethylamine (0.90 mL, 6.60 mmol) were added to give a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 5 × 12 cm, ethyl acetate/hexanes 1:5) to give thiazolidinethione **67** (1.28 g, 70%) as yellow prisms.

$C_{16}H_{19}NOS_2$ (305.46):

m.p. 59.0-60.5 °C (dichloromethane/pentane).

R_f =0.70 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.6 Hz, 3 H, CH_3), 1.35 (sext, ^3J = 7.6 Hz, 2 H, CH_2CH$_3$), 1.56-1.64 (m, 2 H, CH_2CH$_2$CH$_3$), 2.63 (t, ^3J = 7.6 Hz, 2 H, CH_2CH$_2$CH$_2$CH$_3$), 3.37 (t, ^3J = 7.3 Hz, 2 H, SCH_2), 4.59 (t, ^3J = 7.3Hz, 2 H, NCH_2), 7.20 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.47 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.68 (d, $^3J_{trans}$ = 15.6 Hz, 1 H, CHC=O), 7.83 (d, $^3J_{trans}$ = 15.4 Hz, 1 H, C$_6$H$_4$CH).

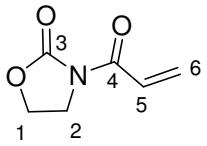
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (CH_3, 1), 22.3 (CH_2, 2), 29.1 (CH_2, 3), 33.3 (CH_2, 4), 35.6 (CH_2, 13), 56.0 (CH_2, 12), 118.8 (CH, 10), 128.6 ($C_{ar}H$), 129.0 ($C_{ar}H$), 132.2 (C, 8), 144.4 (CH, 9), 146.1 (C, 5), 167.5 (C, 11), 201.7 (C, 14).

IR (KBr): $\tilde{\nu}$ = 2943s, 1674s, 1597s, 1510m, 1461m, 1326s, 1262s, 1220s, 1151s, 1056s, 823s, 718s.

MS (EI, 70 eV, 150 °C), *m/z* (%): 305 ([M]$^+$, 39), 187 (100), 131 (25), 115 (19), 57 ([C_4H_9]$^+$, 6).

EA calcd (%) for $C_{16}H_{19}NOS_2$: C, 62.92; H, 6.27; N, 4.59. Found: C, 62.82; H, 6.27; N, 4.57.

3-(2-Propenoyl)-2-oxazolidinone (35)[91]



Triethylamine (8.75 mL, 62.5 mmol) and then dropwise acrolyl chloride (5.05 mL, 62.5 mmol) were added to a solution of acrylic acid (4.30 mL, 62.5 mmol) in ethyl acetate (300 mL) at 0 °C. After stirring for 40 minutes at 0 °C followed by 30 minutes at room temperature, the reaction mixture was filtered through a Büchner funnel and the filter cake was washed three times with ethyl acetate. The filtrate was concentrated under reduced pressure dissolved in hexanes (125 mL), then filtered and concentrated again. The anhydride was dissolved in THF (12.5 mL) and immediately used in the next step.

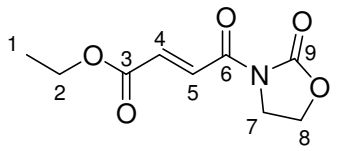
To a suspension of 2-oxazolidinone (4.35 g, 50.0 mmol) and LiCl (2.65 g, 62.5 mmol) in THF (45 mL) was slowly added triethylamine (8.75 mL, 62.5 mmol), followed by the anhydride and a 4 mL wash with THF. After stirring at room temperature for 4 hours, the solvent was removed under reduced pressure, 1 N HCl (125 mL) was added and the aqueous solution was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with 1:1 saturated aqueous $NaHCO_3$/water (160 mL), then brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give an off-white solid. The crude product was purified by flash column chromatography (SiO_2, 10 × 18 cm, ethyl acetate/hexanes 3:7) and recrystallised (pentane/dichloromethane) to give oxazolidinone **35** (4.45 g, 63%) as colourless plates.

$C_6H_7NO_3$ (141.12):
m.p. 82-83 °C (pentane/dichloromethane) [lit.,[187] 82-83 °C]
$\mathbf{R_f}$ = 0.42 (ethyl acetate/hexanes 1:1).
^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.49 (dd, $^3J_{trans}$ = 16.9 Hz, $^3J_{cis}$ = 10.4 Hz, 1 H, C*H*), 6.56 (dd, $^3J_{trans}$ = 16.9 Hz, ^2J = 1.8 Hz, 1 H, CH_{trans}), 5.90 (dd, $^3J_{cis}$ = 10.4 Hz, ^2J = 1.8 Hz, 1 H, CH_{cis}), 4.47-4.42 (m, 2 H, OCH_2), 4.11-4.07 (m, 2 H, NCH_2).
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 42.6 (CH_2, 2), 62.1 (CH_2, 1), 126.9 (CH, 5), 131.8 (CH_2, 6), 153.4 (C, 3), 165.0 (C, 4).
IR (KBr): $\tilde{\nu}$ = 3112m, 2983m, 2924m, 1779s, 1683s, 1612s, 1398s, 1317s, 1227s, 1120s, 1015s, 801s, 752s, 690s.
MS (FAB, NBA (substr)), *m/z* (%): 295 (8), 142 ([M+H]$^+$, 100), 100 ([M-C_2H_2O]$^+$, 10), 55 (31).

EA calcd (%) for $C_6H_7NO_3$: C, 51.07; H, 5.00; N, 9.93; O, 34.01. Found: C, 51.00; H, 4.96; N, 9.94; O, 34.01.

The spectroscopic data are in agreement with that previously reported in the literature.[187]

3-[(*E*)-3-(Ethoxycarbonyl)propenyl]-2-oxazolidinone (70)[91]



By **general method VI** acid chloride (406 mg, 2.50 mmol), generated from fumaric acid monoethyl ester, in THF (2 mL) was added to 2-oxazolidinone (218 mg, 2.50 mmol) and *n*-BuLi (1.6 M in hexane, 1.56 mL, 2.50 mmol) in THF (8 mL) to give the crude product. It was purified by flash column chromatography (SiO_2, 2 × 14 cm, ethyl acetate/hexanes 1:4) to give oxazolidinone **70** (292 mg, 55%) as colourless prisms.

$C_9H_{11}NO_5$ (213.19):

m.p. 60-62 °C (dichloromethane/hexanes) [lit.,[188] 62-63 °C].

R_f = 0.38 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.33 (t, ^3J = 7.1 Hz, 3 H, CH_3), 4.10 (t, ^3J = 7.9 Hz, 2 H, NCH_2), 4.27 (q, ^3J = 7.3 Hz, 2 H, CH_2CH$_3$), 4.48 (t, ^3J = 7.6 Hz, 2 H, OCH_2CH$_2$), 6.95 (d, $^3J_{trans}$ = 15.4 Hz, 1 H, CH(4)=CH), 8.14 (d, $^3J_{trans}$ = 15.4 Hz, 1 H, CH(5)=CH).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 14.1 (CH_3, 1), 42.6 (CH_2, 7), 61.4 (CH_2, 2), 62.3 (CH_2, 8), 131.7 (CH, 4), 134.5 (CH, 5), 153.0 (C, 9), 163.9 (C, 6), 164.8 (C, 3).

IR (KBr): $\tilde{\nu}$ = 2993w, 1775s, 1720m, 1680s, 1390s, 1296s, 1228w, 1178s, 1111m, 1022s, 756s, 666s.

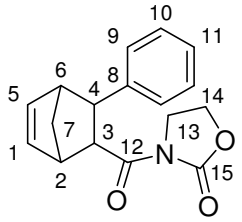
MS (EI, 70 eV, r.t.), *m*/*z* (%): 214 ([M+H]$^+$, 100), 168 ([M-C_2H_6O]$^+$, 19), 124 (27).

EA calcd (%) for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57; O, 37.52. Found: C, 50.79; H, 5.16; N, 6.52; O, 37.42.

The spectroscopic data are in agreement with that previously reported in the literature.[188]

5.3.4 Synthesis of Diels-Alder Adducts

Racemic *endo* 3-(3-Phenyl-bicyclo[2.2.1]hept-5-ene-2-carbonyl)-2-oxazolidinone (*rac*-71)[144]



General Method VIII: Diethylaluminium chloride (1 M in hexane, 1.4 mL, 1.4 mmol) was added to a solution of (*E)*-3-phenylacryloyl-2-oxazolidinone (217 mg, 1.00 mmol) in dichloromethane (16 mL) at -78 °C. Pre-cooled cyclopentadiene (0.40 mL, 4.7 mmol) was added to the bright yellow solution. The reaction was warmed up to -20 °C and stirred for 2.5 hours, during which time the colour completely faded. Dichloromethane (50 mL) was added and the mixture washed with 1 N HCl, dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate /hexanes 1:1) to give *endo* DA adduct *rac*-**71** (237 mg, 84%) as colourless prisms.

$C_{17}H_{17}NO_3$ (283.32):

m.p. 128-129 °C (ethyl acetate /hexanes).

R_f = 0.58 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.56-1.60 (m, 1 H, CHCH*H*CH), 1.96 (d, ^2J = 8.8 Hz, 1 H, CHC*H*HCH), 3.00 (m, 1H, C*H*(6)), 3.35 (dd, ^3J = 5.3 Hz, J = 1.8 Hz, 1 H, PhC*H*), 3.47 (s, 1 H, C*H*(2)), 3.93-4.06 (m, 2 H, NCH_2), 4.20 (dd, ^3J = 5.3 Hz, J = 3.3 Hz, 1 H, C*H*C=O), 4.36-4.45 (m, 2 H, OCH_2), 5.93 (dd, ^3J = 5.5 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.53 (dd, , ^3J = 5.6 Hz, J = 3.0 Hz, 1H, C*H*(5)=CH), 7.17-7.21 (m, 1 H, H_{ar}), 7.27-7.31 (m, 4 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 43.0 (CH_2, 13), 46.9 (CH, 4), 47.5 (CH, 2), 48.1 (CH_2, 7), 49.7 (CH, 6), 50.3 (CH, 3), 61.9 (CH_2, 14), 126.1 ($C_{ar}H$), 127.6 ($C_{ar}H$), 128.5 ($C_{ar}H$), 132.2 (CH, 1), 140.2 (CH, 5), 143.7 (C, 8), 153.4 (C, 15), 173.9 (C, 12).

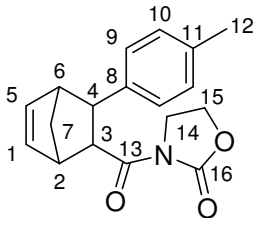
IR (KBr): $\tilde{\nu}$ = 3420br s, 2980s, 1765s, 1690s, 1485s, 1385s, 1275s, 1210s, 1105s, 1020s, 695s.

MS (FAB, NBA (subtr)), *m/z* (%): 284 ($[M+H]^+$, 33), 218 (100), 197 (23), 131($[C_6H_5CH=CH=O]^+$, 100), 77 ($[C_6H_5]^+$, 17).

EA calcd (%) for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94; O, 16.94. Found: C, 71.76; H, 6.05; N, 4.97; O, 16.84.

The spectroscopic data are consistent with that previously reported in the literature.[91]

Racemic *endo* 3-[(3-*p*-Tolylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-2-oxazolidinone (*rac*-72)



By **general method VIII** oxazolidinone **60** (231 mg, 1.00 mmol), cyclopentadiene (0.30 mL, 4.7 mmol) and diethylaluminium chloride (1.4 M in hexane, 1.4 mL, 1.4 mmol) in dichloromethane (16 mL) gave the crude product. It was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate/hexanes 1:5) to give *endo* DA adduct *rac*-**72** (235 mg, 79%, *endo:exo* 97:3, 100% conversion) as a colourless transparent oil.

$C_{18}H_{19}NO_3$ (297.34):

R_f = 0.45 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.57 (dd, ^2J = 8.6 Hz, J = 1.5 Hz, 1 H, CHCH*H*CH), 1.95 (d, ^2J = 8.6 Hz, 1 H, CHC*H*HCH), 2.31 (s, 3H, CH_3), 2.96 (s, 1H, C*H*(6)), 3.31 (d, ^3J = 4.6 Hz, 1H, PhC*H*), 3.46 (s, 1H, C*H*(2)), 3.93-4.05 (m, 2H, NCH_2), 4.19 (dd, ^3J = 5.3 Hz, J = 3.3 Hz, 1H, C*H*C=O), 4.35-4.45 (m, 2H, OCH_2), 5.92 (dd, ^3J = 5.5 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.52 (dd, ^3J = 5.5 Hz, J = 3.3 Hz, 1H, C*H*(5)=CH), 7.10 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.16 (d, ^3J = 8.1 Hz, 2 H, H_{ar}).

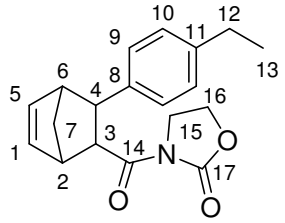
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 20.9 (CH_3, 12), 43.0 (CH_2, 14), 46.6 (CH, 4), 47.4 (CH, 2), 48.1 (CH_2, 7), 49.9 (CH, 6), 50.2 (CH, 3), 61.9 (CH_2, 15), 127.5 (C_{ar}H), 129.1 (C_{ar}H), 132.1 (CH, 1), 135.7 (C, 11), 140.2 (CH, 5), 140.6 (C, 8), 153.4 (C, 16), 174.0 (C, 13).

IR (NaCl): 2976s, 1772s, 1695s, 1511s, 1477s, 1384s, 1219s, 1112s, 1031s, 812m, 760m, 696.

MS (FAB, NBA (subtr)), *m/z* (%): 298 ([M+H]$^+$, 49), 232 ([M-C_5H_6]$^+$, 100), 211 (29), 145 (88).

EA calcd (%) for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71; O, 16.14. Found: C, 71.77; H, 6.69; N, 4.51.

Racemic *endo* 3-{[3-(*p*-Ethylphenyl)bicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-oxazolidinone (*rac*-73)



By **general method VIII** oxazolidinone **61** (123 mg, 0.50 mmol), cyclopentadiene (0.20 mL, 2.35 mmol) and diethylaluminium chloride (1.4 M in hexane, 0.7 mL, 0.7 mmol) in dichloromethane (8 mL) gave the crude product. It was purified by flash column chromatography (SiO_2, 2 × 20 cm, ethyl acetate/hexanes 1:5) to give *endo* DA adduct *rac*-**73** (91 mg, 58%, *endo:exo* 96:4, 85% conversion) as a colourless, transparent oil.

$C_{19}H_{21}NO_3$ (311.37):

R_f = 0.58 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.22 (t, ^3J = 7.6 Hz, 3 H, CH_3), 1.57 (dd, ^2J = 8.6 Hz, J = 1.5 Hz, 1 H, CHC*H*HCH), 1.96 (d, ^2J = 8.6 Hz, 1 H, CHCH*H*CH), 2.61 (q, ^3J = 7.6 Hz, 2 H, CH_2CH$_3$), 2.97 (d, ^3J = 1.2 Hz, 1H, C*H*(6)), 3.31 (d, ^3J = 4.3 Hz, 1H, PhC*H*), 3.46 (s, 1H, C*H*(2)), 3.93-4.05 (m, 2H, NCH_2), 4.20 (dd, ^3J = 5.3 Hz, J = 3.6 Hz, 1H, C*H*C=O), 4.32-4.44 (m, 2H, OCH_2), 5.92 (dd, ^3J = 5.6 Hz, J = 2.5 Hz, 1H, C*H*(1)=CH), 6.52 (dd, ^3J = 5.6 Hz, J = 3.0 Hz, 1H, C*H*(5)=CH), 7.12 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.19 (d, ^3J = 8.3 Hz, 2 H, H_{ar}).

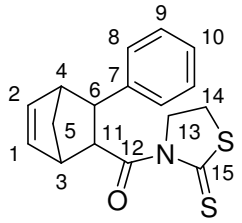
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 15.6 (CH_3, 13), 28.3 (CH_2, 12), 43.0 (CH_2, 17), 46.6 (CH, 4), 47.4 (CH, 2), 48.1 (CH_2, 7), 49.9 (CH, 6), 50.2 (CH, 3), 61.9 (CH_2, 16), 127.6 (C_{ar}H), 129.9 (C_{ar}H), 132.1 (CH, 1), 140.2 (CH, 5), 140.9 (C, 11), 142.1 (C, 8), 153.4 (C, 15), 174.0 (C, 14).

IR (NaCl): $\tilde{\nu}$ = 2968s, 1773s, 1695s, 1385s, 1221s, 1112s, 1041s, 824s, 695s.

MS (FAB, NBA (subtr)), *m/z* (%): 312 ([M+H]$^+$, 33), 246 ([M-C_5H_6]$^+$, 78), 225 (24), 159 (100).

EA calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.44; H, 6.85; N, 4.30.

Racemic *endo* [(3-Phenyl-bicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-2-thiazolidinethione (*rac*-74)



By **general method VIII** thiazolidinethione **62** (249 mg, 1.00 mmol), cyclopentadiene (0.40 mL, 4.70 mmol) and diethylaluminium chloride (1.4 M in hexane, 1.40 mL, 1.40 mmol) in dichloromethane (16 mL) were stirred for 4 hours at -20 °C to give a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate/hexanes 1:5) to give *endo* DA adduct *rac*-**74** (200 mg, 63%, *endo:exo* 92:8, 100% conversion) as yellow needles.

$C_{17}H_{17}NOS_2$ (315.45):

m.p. 139-140 °C (ethyl acetate/hexanes).

$\mathbf{R_f}$ = 0.65 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.53 (ob. dq, ^2J = 8.6 Hz, J = 1.8 Hz, 1 H, CHCH*H*CH), 1.83 (d, ^2J = 8.6 Hz, 1 H, CHC*H*HCH), 2.97 (d, J = 1.2 Hz, 1H, C*H*(4)), 3.33-3.58 (m, 3 H, PhC*H*, SCH_2), 3.58 (s, 1H, C*H*(3)), 4.47-4.58 (m, 2 H, NCH_2), 5.18 (dd, ^3J = 5.1 Hz, J = 3.3 Hz, 1H, C*H*C=O), 5.94 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.54 (dd, ^3J = 5.6 Hz, J = 3.0 Hz, 1H, C*H*(2)=CH), 7.20-7.32 (m, 5 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 28.1 (CH_2, 14), 47.5 (CH, 3), 47.6 (CH_2, 7), 48.6 (CH, 6), 50.3 (CH, 4), 51.0 (CH, 11), 56.9 (CH_2, 13), 126.2 (CH, 1), 127.7 ($C_{ar}H$), 128.5 ($C_{ar}H$), 132.2 ($C_{ar}H$), 140.3 (CH, 2), 143.6 (C, 7), 175.7 (C, 12), 201.6 (C, 15).

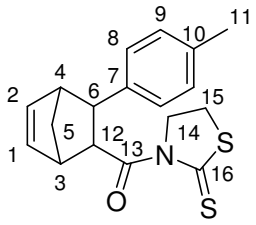
IR (KBr): $\tilde{\nu}$ = 3500br m, 3050s, 3000s, 1710s, 1515m, 1470s, 1385s, 1330m, 1290s, 1240s, 1185s, 1055s, 915m, 870m, 760m, 715s.

MS (EI, 70 eV, 150 °C), *m/z* (%): 315 ($[M]^+$, 4), 281($[M-H_2S]^+$, 5), 248 (53), 131 ($[C_6H_5CH=CH=O]^+$, 100), 103 ($[C_6H_5CH=CH]^+$, 24), 77 ($[C_6H_5]^+$, 10).

EA calcd (%) for $C_{17}H_{17}NOS_2$: C, 64.73; H, 5.43; N, 4.44; O, 5.07. Found: C, 64.58; H, 5.45; N, 4.42; O, 5.10.

The spectroscopic data are in agreement with that for the enantiopure compound previously reported in the literature.[188]

Racemic *endo* [(3-*p*-Tolylbicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-2-thiazolidinethione (*rac*-75)



By **general method VIII** thiazolidinethione **63** (263 mg, 1.00 mmol), cyclopentadiene (0.39 mL, 4.70 mmol) and diethylaluminium chloride (1.4 M in hexane, 1.40 mL, 1.40 mmol) in dichloromethane (16 mL) gave a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate/hexanes 1:4) to give *endo* DA adduct *rac*-**75** (248 mg, 75%, *endo:exo* 93:7, 96% conversion) as a yellow amorphous solid.

$C_{18}H_{19}NOS_2$ (329.48):

m.p. 81-83 °C (ethyl acetate/hexanes).

$\mathbf{R_f}$ = 0.56 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.51 (dd, ^2J = 8.6 Hz, J = 1.5 Hz, 1 H, CHCH*H*CH), 1.82 (d, ^2J = 8.8 Hz, 1 H, CHC*H*HCH), 2.31 (s, 3H, CH_3), 2.94 (s, 1 H, C*H*(4)), 3.19-3.32 (m, 3 H, PhC*H*, SCH_2), 3.57 (s, 1H, C*H*(3)), 4.46-4.57 (m, 2 H, NCH_2), 5.14-5.16 (m, 1 H, C*H*C=O), 5.93 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.53 (dd, ^3J = 5.6 Hz, J = 3.3 Hz, 1H, C*H*(2)=CH), 7.11(d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.17 (d, ^3J = 8.1 Hz, 2 H, H_{ar}).

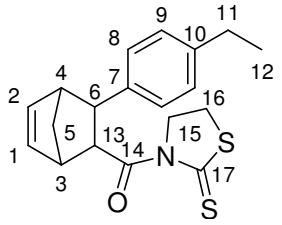
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 20.9 (CH_3, 11), 28.1 (CH_2, 15), 47.5 (CH_2, 7), 47.5 (CH, 3), 48.3 (CH, 6), 50.4 (CH, 4), 51.0 (CH, 12), 56.8 (CH_2, 14), 127.6 (C_{ar}H), 129.2 (C_{ar}H), 132.1 (CH, 1), 135.7 (C, 10), 140.3 (CH, 2), 140.5 (C, 7), 175.9 (C, 13), 201.5 (C, 16).

IR (KBr): $\tilde{\nu}$ = 3377m, 3000s, 1697s, 1573w, 1513s, 1457s, 1366s, 1328s, 1276s, 1220s, 1157s, 1049s, 900s, 863s, 812s 763s, 707s, 536s.

MS (FAB, NBA (subtr)), *m*/*z* (%): 330 ([M+H]$^+$, 22), 295 (11), 263 (20), 211 (12), 145 (100).

EA calcd (%) for $C_{18}H_{19}NOS_2$: C, 65.62; H, 5.81; N, 4.25. Found: C, 65.65; H, 5.73; N, 4.44.

Racemic *endo* 3-[(4-Ethylphenyl)bicyclo[2.2.1]hept-5-en-2-yl)carbonyl]-2-thiazolidine-thione (*rac*-76)



By **general method VIII** thiazolidinethione **64** (139 mg, 0.50 mmol), cyclopentadiene (0.20 mL, 2.35 mmol) and diethylaluminium chloride (1.4 M in hexane, 0.70 mL, 0.70 mmol) in dichloromethane (8 mL) gave a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 2 × 20 cm, ethyl acetate/hexanes 1:4) to give *endo* DA adduct *rac*-**76** (127 mg, 74%, *endo:exo* 91:9, 100% conversion) as a yellow transparent oil.

$C_{19}H_{21}NOS_2$ (343.51):

R_f =0.69 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.23 (t, ^3J = 7.6 Hz, 3 H, CH_3), 1.51 (dd, ^2J = 8.8 Hz, J = 1.5 Hz, 1 H, CHC*H*HCH), 1.83 (d, ^2J = 8.6 Hz, 1 H, CHCH*H*CH), 2.62 (q, ^3J = 7.6 Hz, 2 H, CH_2CH$_3$), 2.95 (s, 1 H, C*H*(4)), 3.18-3.32 (m, 3 H, PhC*H*, SCH_2), 3.40 (s, 1H, C*H*(3)), 4.46-4.57 (m, 2 H, NCH_2), 5.16 (dd, ^3J = 5.1 Hz, J = 3.6 Hz, 1H, C*H*C=O), 5.93 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H(1)*=CH), 6.53 (dd, ^3J = 5.6 Hz, J = 3.0 Hz, 1H, C*H*(5)=CH), 7.13 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.18 (d, ^3J = 8.3 Hz, 2 H, H_{ar}).

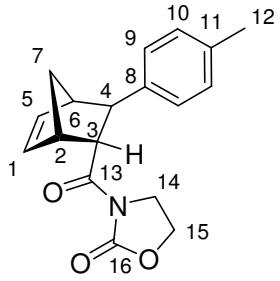
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 15.6 (CH_3, 12), 28.1 (CH_2, 11), 28.3 (CH_2, 16), 47.5 (CH, 3), 47.5 (CH_2, 5), 48.4 (CH, 6), 50.5 (CH, 4), 50.9 (CH, 13), 56.8 (CH_2, 15), 127.7 (C_{ar}H), 128.0 (C_{ar}H), 132.1 (CH, 1), 140.3 (CH, 2), 140.7 (C, 10), 142.1 (C, 7), 175.8 (C, 14), 201.5 (C, 15).

IR (NaCl): $\tilde{\nu}$ = 2967s, 2361w, 1697s, 1513s, 1458s, 1366s, 1328sm 1276s, 1220s, 1159s, 1050s, 899m, 863m, 827m, 762m, 702m, 586w, 544w.

MS (FAB, NBA(subtr)), *m/z* (%): 344 ([M+H]$^+$, 17), 277 (18), 225 (11), 159 (100).

EA calcd (%) for $C_{19}H_{21}NOS_2$: C, 66.44; H, 6.16; N, 4.08; O, 4.66. Found: C, 66.20; H, 6.16; N, 4.01; O, 4.80.

***endo* 3-{[(1*S*,2*R*,3*R*,4*R*)-3-*p*-Tolylbicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-oxazolidinone ((*S*)-77)[91]**



General Method IX: $Cu(II)Cl_2$ (13.4 mg, 0.10 mmol), (*S,S*)-*t*-Bu-box ligand **32b** (32.4 mg, 0.11 mmol) and $AgSbF_6$ (68.7 mg, 0.20 mmol) were mixed together in a glove box and the flask was wrapped in aluminium foil to protect the reaction mixture from light. After connecting the flask to a Schlenk line, dichloromethane (1 mL) was added and the blue reaction mixture was stirred for 6 hours at room temperature. The solution was filtered through a plug of celite (rinsed with dichloromethane (3 mL)) to give a clear blue solution, which was cooled to -78 °C. Oxazolidinone **60** (231 mg, 1.00 mmol) in dichloromethane (2 mL) was added and immediately after cyclopentadiene (0.83 mL, 10.0 mmol). After stirring for 24 hours at room temperature (28 °C), ethyl acetate/Et_2O 1:1 (3 mL) was added. The mixture was directly applied to a short column (SiO_2, 1.5 × 4 cm) and eluted with Et_2O (3 × 20 mL). After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate/hexanes 1:5) to give *endo* DA adduct (*S*)-**77** (174 mg, 59%, *endo* ee 95%, *exo* ee 86%, *endo:exo* 75:25, 100% conversion) as a colourless transparent oil.

$C_{18}H_{19}NO_3$ (297.35):

R_f = 0.45 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.57 (dd, ^2J = 8.6 Hz, J = 1.5 Hz, 1 H, CHCH*H*CH), 1.95 (d, ^2J = 8.6 Hz, 1 H, CHC*H*HCH), 2.31 (s, 3H, CH_3), 2.96 (d, J = 1.0 Hz, 1H, C*H*(6)), 3.31 (d, ^3J = 4.6 Hz, 1H, PhC*H*), 3.46 (s, 1H, C*H*(2)), 3.93-4.05 (m, 2H, NCH_2), 4.19 (dd, ^3J = 5.3 Hz, J = 3.3 Hz, 1H, C*H*C=O), 4.35-4.45 (m, 2H, OCH_2), 5.92 (dd, ^3J = 5.5 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.52 (dd, ^3J = 5.5 Hz, J = 3.3 Hz, 1H, C*H*(5)=CH), 7.10 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.16 (d, ^3J = 8.1 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 20.9 (CH_3, 12), 43.0 (CH_2, 14), 46.6 (CH, 4), 47.4 (CH, 2), 48.1 (CH_2, 7), 49.9 (CH, 6), 50.2 (CH, 3), 61.9 (CH_2, 15), 127.5 (C_{ar}H), 129.1 (C_{ar}H), 132.1 (CH, 1), 135.7 (C, 11), 140.2 (CH, 5), 140.6 (C, 8), 153.4 (C, 16), 174.0 (C, 13).

IR (NaCl): $\tilde{\nu}$ = 2976s, 1786s, 1690s, 1515s, 1466s, 1391s, 1334s, 1277s, 1225s, 1039s, 802m, 761m, 702s, 528s.

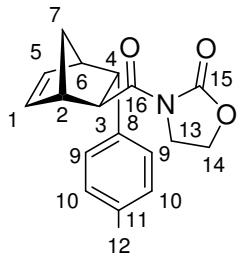
MS (FAB, NBA (subtr)), *m*/*z* (%): 298 ($[M+H]^+$, 44), 232 ($[M-C_5H_6]^+$, 100), 211 (29), 145 (100).

$[\alpha]_D^{20}$ = −136.7 (c = 0.38, dichloromethane, 95% ee).

EA calcd (%) for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71; O, 16.14. Found: C, 72.49; H, 6.44; N, 4.72; O, 16.00.

HPLC: Chiralcel AD-H, i-propanol/heptane (20:80), 0.5 mL/min, 20 °C, 210 nm, t_R = 17.0 min (minor), t_R = 23.9 min (major).

exo 3-{[(1*R*,2*S*,3*S*,4*S*)-3-*p*-Tolylbicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-oxazolidinone ((*S*)-77)



$C_{18}H_{19}NO_3$ (297.35):

R_f = 0.55 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.48 (dd, ^2J = 8.6 Hz, ^3J = 1.3 Hz, 1 H, CHCH*H*CH), 1.83 (d, ^2J = 8.4 Hz, 1 H, CHC*H*HCH), 2.29 (s, 3H, CH_3), 3.10 (s, 2H, C*H*, bridgehead), 3.69 (d, ^3J = 5.1 Hz, 1H, PhC*H*), 4.00-4.09 (m, 3H, NCH_2, C*H*C=O), 4.33-4.44 (m, 2H, OCH_2), 6.06 (dd, ^3J = 5.3 Hz, J = 2.5 Hz, 1H, C*H*(1)=CH), 6.48 (dd, ^3J = 5.6 Hz, J = 3.2 Hz, 1H, C*H*(5)=CH), 7.05 (s, 4 H, H_{ar}).

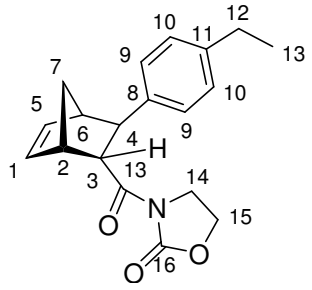
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 20.9 (CH_3, 12), 43.0 (CH_2, 14), 46.7 (CH, 4), 46.8 (CH_2, 7), 49.1 (CH, 6), 50.0 (CH, 2), 50.2 (CH,3), 61.8 (CH_2, 13), 127.9 ($C_{ar}H$), 128.7 ($C_{ar}H$), 135.7 (C, 11), 135.8 (CH, 1), 137.1 (CH, 5), 139.9 (C, 8), 153.4 (C, 15), 174.6 (C, 16).

IR (NaCl): $\tilde{\nu}$ = 2973s, 1776s, 1693s, 1514s, 1478s, 1387s, 1223m, 1116s, 1042s, 912s, 761m, 730s.

MS (FAB, NBA (subtr)), *m*/*z* (%): 298 ($[M+H]^+$, 20), 232 ($[M-C_5H_6]^+$, 68), 145 (100).

HPLC: Chiralcel AD-H, i-propanol/heptane (20:80), 0.5 mL/min, 20 °C, 210 nm, t_R = 15.5 min (minor), t_R = 20.9 min (major).

***endo* 3-{[(1*S*,2*R*,3*R*,4*R*)-3-Ethylphenylbicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-oxazolidinone ((*S*)-78)**



By **general method IX** $Cu(II)Cl_2$ (3.40 mg, 25.0 µmol), $AgSbF_6$ (17.1 mg, 50.0 µmol), (*S,S*)-*t*-Bu-box ligand **32b** (8.1 mg, 27.5 µmol), oxazolidinone **61** (61.3 mg, 0.25 mmol) and cyclopentadiene (0.21 mL, 2.50 mmol) in dichloromethane (4 mL) gave a brown oil. The crude product was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate/hexanes 1:5) to give *endo* DA adduct (*S*)-**78** (31.0 mg, 40%, *endo* ee 89%, *endo:exo* 67:33, 56% conversion) as a colourless transparent oil.

$C_{19}H_{21}NO_3$ (311.37):

R_f = 0.74 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.20 (t, ^3J = 7.6 Hz, 3 H, CH_3), 1.56 (dd, ^2J = 8.6 Hz, J = 1.8 Hz, 1 H, CHC*H*HCH), 1.92 (d, ^2J = 8.6 Hz, 1 H, CHCH*H*CH), 2.60 (q, ^3J = 7.6 Hz, 2 H, CH_2CH$_3$), 2.97 (d, ^3J = 1.5 Hz, 1H, C*H*(6)), 3.29 (d, ^3J = 4.8 Hz, 1H, PhC*H*), 3.43 (s, 1H, C*H*(2)), 3.88-3.99 (m, 2H, NCH_2), 4.12 (dd, ^3J = 5.3 Hz, J = 3.6 Hz, 1H, C*H*C=O), 4.34-4.38 (m, 2H, OCH_2), 5.91 (dd, ^3J = 5.6 Hz, J = 2.5 Hz, 1H, C*H*(1)=CH), 6.50 (dd, ^3J = 5.6 Hz, J = 3.0 Hz, 1H, C*H*(5)=CH), 7.12 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.18 (d, ^3J = 8.3 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 15.6 (CH_3, 13), 28.4 (CH_2, 12), 43.1 (CH_2, 17), 46.4 (CH, 4), 47.5 (CH, 2), 48.1 (CH_2, 7), 49.8 (CH, 6), 50.5 (CH, 3), 62.2 (CH_2, 16), 127.5 (C_{ar}H), 127.9 (C_{ar}H), 132.2 (CH, 1), 140.0 (CH, 5), 141.2 (C, 11), 142.2 (C, 8), 153.6 (C, 15), 173.7 (C, 14).

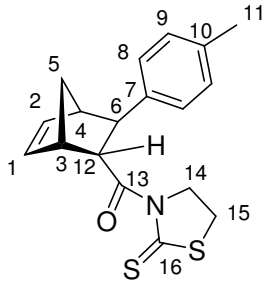
IR (NaCl): $\tilde{\nu}$ = 2967s, 1777s, 1695s, 1513m, 1477m, 1385s, 1222s, 1112s, 1028s, 976m, 824m, 759m, 694s.

MS (EI, 70 eV, ca. 100 °C), *m/z* (%): 245 ([M-C_5H_6]$^+$, 100), 159 (100), 131 (8), 115 (7), 91 (5).

$[\alpha]_D^{20}$ = −162.0 (c = 0.23, dichloromethane, 89% ee).

HPLC: Chiralcel AD-H, i-propanol/heptane (20:80), 0.5 mL/min, 20 °C, 210 nm, t_R = 31.0 min (minor), t_R = 36.9 min (major).

***endo* 3-{[(1*S*,2*R*,3*R*,4*R*)-(4-Tolyl)-bicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-thiazolidine-thione ((*S*)-79)**



General Method X: Cu(II)(OTf)$_2$ (72.0 mg, 0.20 mmol) and (*S,S*)-*t*-Bu-box ligand **32b** (65.0 mg, 0.22 mmol) were mixed together in a glove box. After connecting the flask to a Schlenk line, dichloromethane (2 mL) was added and the green reaction mixture was stirred for 2.5 hours at room temperature. The reaction mixture was cooled to -78 °C and thiazolidinethione **63** (263 mg, 1.00 mmol) in dichloromethane (2 mL) was added and immediately after cyclopentadiene (0.83 mL, 10.0 mmol). After 72 hours at –35 °C, ethyl acetate/Et_2O (1:1, 3 mL) was added and the mixture was directly applied to a short column (SiO_2, 1.5 × 4 cm) and eluted with Et_2O (3 × 20 mL). After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate/hexanes 1:5) to give *endo* DA adduct (*S*)-**79** (260 mg, 79%, *endo* ee 95%, *endo:exo* 97:3, >99% conversion) as a yellow transparent oil.

$C_{18}H_{19}NOS_2$ (329.48):

R_f = 0.66 (ethyl acetate/hexanes 1:1)

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.49 (ob. dq, ^2J = 8.6 Hz, J = 1.8 Hz, 1 H, CHCH*H*CH), 1.79 (d, ^2J = 8.8 Hz, 1 H, CHC*H*HCH), 2.29 (s, 3 H, CH_3), 2.92 (d, ^2J = 1.0 Hz, 1 H, C*H*, (4)), 3.15-3.34 (m, 3 H, PhC*H*, SCH_2), 3.52 (s, 1H, C*H*(3)), 4.45-4.49 (m, 2 H, NCH_2), 5.10 (dd, ^3J = 5.1 Hz, J = 3.3 Hz, 1 H, C*H*C=O), 5.92 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.49 (dd, ^3J = 5.6 Hz, J = 3.3 Hz, 1H, C*H*(2)=CH), 7.08 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.14 (d, ^3J = 8.3 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 20.7 (CH_3, 11), 28.3 (CH_2, 15), 47.5 (CH_2, 7), 47.5 (CH, 3), 47.7 (CH, 6), 50.2 (CH, 4), 51.5 (CH, 12), 57.1 (CH_2, 14), 127.5 ($C_{ar}H$), 129.1 ($C_{ar}H$), 132.2 (CH, 1), 135.8 (C, 10), 140.2 (CH, 2), 140.7 (C, 7), 175.6 (C, 13), 202.0 (C, 16).

IR (NaCl): $\tilde{\nu}$ = 2975s, 1698s, 1513m, 1458m, 1367m, 1328m, 1276m, 1220m, 1159m, 1049m, 900m, 863m, 812m, 762m, 706m.

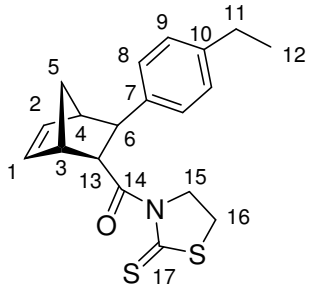
MS (FAB, NBA (subtr)), *m/z* (%): 330 ([M+H]$^+$, 19), 263 (20), 211 (9), 145 (100).

$[\alpha]_D^{20}$ = −155.5 (c = 0.50, dichloromethane, 95% ee).

EA calcd (%) for $C_{18}H_{19}NOS_2$: C, 65.62; H, 5.81; N, 4.25. Found: C, 64.89; H, 5.84; N. 4.26.

HPLC: Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm, t_R = 22.3 min (major), t_R = 59.2 min (minor).

endo 3-{[(1*S*,2*R*,3*R*,4*R*)-(4-Ethylphenyl)-bicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-thiazolidinethione ((*S*)-80)



By **general method X** Cu(II)(OTf)$_2$ (72.0 mg, 0.20 mmol), (*S,S*)-*t*-Bu-box **32b** (65.0 mg, 0.22 mmol), thiazolidinethione **64** (277 mg, 1.00 mmol) and cyclopentadiene (0.83 mL, 10.0 mmol) in dichloromethane (4 mL) gave a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate/hexanes 1:5) and recrystallisation (Et_2O/pentane) to give *endo* DA adduct (*S*)-**80** (299 mg, 87%, *endo* ee >99%, *endo:exo* 97:3, >99% conversion) as yellow needles.

$C_{19}H_{21}NOS_2$ (343.51):

m.p. 73-74 °C (Et_2O/pentane).

R_f = 0.63 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.20 (t, ^3J = 7.8 Hz, 3 H, C*H*$_3$), 1.49 (ob. dq, ^2J = 8.6 Hz, J = 1.8 Hz, 1 H, CHC*H*HCH), 1.80 (d, ^2J = 8.6 Hz, 1 H, CHCH*H*CH), 2.59 (q, ^3J = 7.6 Hz, 2 H, C*H*$_2$CH$_3$), 2.94 (d, J = 1.5 Hz, 1 H, C*H*(4)), 3.16-3.35 (m, 3 H, PhC*H*, SC*H*$_2$), 3.53 (s, 1H, C*H*(3)), 4.46-4.50 (m, 2 H, NC*H*$_2$), 5.13 (dd, ^3J = 4.6 Hz, J = 3.3 Hz, 1H, C*H*C=O), 5.93 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.50 (dd, ^3J = 5.8 Hz, J = 3.3 Hz, 1H, C*H*(2)=CH), 7.12 (d, ^3J = 8.3 Hz, 2 H, H_{ar}), 7.18 (d, ^3J = 8.3 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 15.5 (CH_3, 12), 28.3 (CH_2, 11), 28.4 (CH_2, 16), 47.5 (CH_2, 5), 47.5 (CH, 3), 47.8 (CH, 6), 50.2 (CH, 4), 51.5 (CH, 13), 57.1 (CH_2, 15), 127.6 C_{ar}H), 128.0 (C_{ar}H), 132.2 (CH, 1), 140.2 (CH, 2), 141.0 (C, 10), 142.2 (C, 7), 175.6 (C, 14), 202.0 (C, 17).

IR (KBr): $\tilde{\nu}$ = 2967s, 2872m, 1699s, 1512m, 1458m, 1367s, 1328m, 1277s, 1220m, 1160s, 1049s, 826m, 761m, 702m.

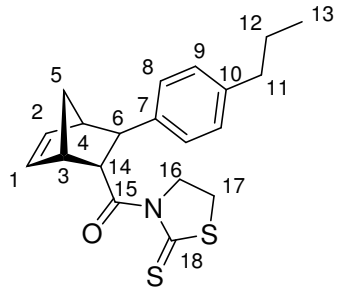
MS (FAB, NBA (subtr)), *m*/*z* (%): 344 ([M+H]$^+$, 20), 277 (20), 225 (10), 159 (100).

$[\alpha]_D^{20}$ = −157.3 (c = 0.50, dichloromethane, >99% ee).

EA calcd (%) for $C_{19}H_{21}NOS_2$: C, 66.44; H, 6.16; N, 4.08. Found: C, 66.25; H, 6.23; N, 3.89.

HPLC: Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm, t_R = 21.8 min (major), t_R = 48.2 min (minor).

endo 3-{[(1*S*,2*R*,3*R*,4*R*)-(4-*n*-Propylphenyl)-bicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-thiazolidinethione ((*S*)-81)



By **general method X** Cu(II)(OTf)$_2$ (36.0 mg, 0.10 mmol), (*S,S*)-*t*-Bu-box **32b** (32.0 mg, 0.11 mmol), thiazolidinethione **65** (146 mg, 0.50 mmol) and cyclopentadiene (0.42 mL, 5.00 mmol) in dichloromethane (2 mL) gave a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 2 × 20 cm, ethyl acetate/hexanes 1:5) and recrystallisation (Et_2O/pentane) to give *endo* DA adduct (*S*)-**81** (119 mg, 67%, *endo* ee >99%, *endo:exo* 97:3, 99% conversion) as yellow needles.

$C_{20}H_{23}NOS_2$ (357.53):

m.p. 91-92 °C (Et_2O/pentane).

R$_f$ = 0.69 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 0.93 (t, ^3J = 7.3 Hz, 3 H, C*H*$_3$), 1.49 (ob. dq, ^2J = 8.8 Hz, ^3J = 3.5 Hz, ^3J = 1.8 Hz, 1 H, CHCH*H*CH), 1.69 (sext, ^3J = 7.6 Hz, C*H*$_2$CH$_3$), 1.80 (d, ^2J = 8.6 Hz, 1 H, CHC*H*HCH), 2.54 (t, ^3J = 7.6 Hz, 2 H, C*H*$_2$CH$_2$CH$_3$), 2.94 (d, ^3J = 1.5 Hz, 1 H, C*H*(4)), 3.16-3.35 (m, 2 H, SC*H*$_2$), 3.27 (dd, ^3J = 4.8 Hz, ^3J = 1.3 Hz,, 1 H, PhC*H*), 3.54 (s, 1 H, C*H*(3)), 4.46-4.50 (m, 2 H, NC*H*$_2$), 5.13 (dd, ^3J = 5.1 Hz, J = 3.6 Hz, 1H, C*H*C=O), 5.92 (dd, ^3J = 5.5 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.51 (dd, ^3J = 5.6 Hz, J = 3.0 Hz, 1H, C*H*(2)=CH), 7.19 (d, ^3J = 8.3 Hz, 2 H, H_{ar}), 7.17 (d, ^3J = 8.1 Hz, 2 H, H_{ar}).

$^{13}C\{^1H\}$ NMR (100.6 MHz, CD_2Cl_2): δ = 13.7 (CH_3, 13), 24.7 (CH_2, 12), 28.3 (CH_2, 17), 37.5 (CH_2, 11), 47.5 (CH, 3), 47.5 (CH_2, 5), 47.8 (CH, 6), 50.3 (CH, 4), 51.4 (CH, 14), 57.1 (CH_2, 16), 127.5 ($C_{ar}H$), 128.5 ($C_{ar}H$), 132.2 (CH, 1), 140.2 (CH, 2), 140. 7 (C, 10), 141.0 (C, 7), 175.6 (C, 15), 202.0 (C, 18).

IR (KBr): $\tilde{\nu}$ = 2949s, 1711s, 1511s, 1459s, 1432s, 1364s, 1327s, 1278s, 1214s, 1155s, 1027s, 803s, 707s.

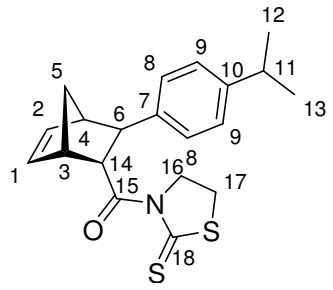
MS (FAB, NBA (subtr)), *m/z* (%): 358 ($[M+H]^+$, 15), 291 (19), 239 (11), 173 ($[291\text{-}C_9H_{10}]^+$, 100), 91 (10), 43 ($[C_3H_7]^+$, 10).

$[\alpha]_D^{20}$ = −167.6 (c = 0.50, dichloromethane, >99% ee).

EA calcd (%) for $C_{20}H_{23}NOS_2$: C, 67.19; H, 6.48; N, 3.92. Found: C, 66.94; H, 6.51; N, 3.95.

HPLC: Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm, t_R = 19.1 min (major), t_R = 39.7 min (minor).

endo 3-{[(1*S*,2*R*,3*R*,4*R*)-(4-i-Propylphenyl)-bicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-thiazolidinethione ((*S*)-82)



By **general method X** Cu(II)$(OTf)_2$ (36.0 mg, 0.10 mmol), (*S,S*)-*t*-Bu-box **32b** (32.0 mg, 0.11 mmol), thiazolidinethione **66** (146 mg, 0.50 mmol) and cyclopentadiene (0.42 mL, 5.00 mmol) in dichloromethane (2 mL) gave a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 2 × 20 cm, ethyl acetate/hexanes 1:5) and recrystallisation (Et_2O/pentane) to give *endo* DA adduct (*S*)-**82** (142 mg, 79%, *endo* ee >99%, *endo:exo* 97:3, 100% conversion) as yellow needles.

$C_{20}H_{23}NOS_2$ (357.53):

m.p. 68-70 °C (Et_2O/pentane).

R_f = 0.69 (ethyl acetate/hexanes 1:1).

^1H NMR (400.1 MHz, CD_2Cl_2): δ = 1.22 (d, ^3J = 7.1 Hz, 6 H, C*H*$_3$), 1.49 (ob. dq, ^2J = 8.8 Hz, ^3J = 1.8 Hz, 1 H, CHCH*H*CH), 1.80 (d, ^2J = 8.8 Hz, 1 H, CHC*H*HCH), 2.87 (sept, ^3J = 6.8 Hz, C*H*$(CH_3)_2$), 2.94 (d, ^3J = 1.5 Hz, 1 H, C*H*(4)), 3.17-3.35 (m, 2 H, SC*H*$_2$), 3.27 (dd, ^3J =

4.8 Hz, *J* = 1.3 Hz, 1 H, PhC*H*), 3.54 (s, 1 H, C*H*(3)), 4.46-4.50 (m, 2 H, NCH_2), 5.14 (dd, ^3J = 5.0 Hz, *J* = 3.6 Hz, 1H, C*H*C=O), 5.92 (dd, ^3J = 5.6 Hz, *J* = 2.8 Hz, 1H, C*H*(1)=CH), 6.50 (dd, ^3J = 5.6 Hz, ^3J = 3.3 Hz, 1H, C*H*(2)=CH), 7.15 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 7.19 (d, ^3J = 8.3 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2): δ = 24.3 (CH_3, 12 and 13), 28.8 (CH_2, 17), 34.2 (CH, 11), 48.0 (CH_2, 5), 48.3 (CH, 6), 48.3 (CH, 3), 50.8 (CH, 4), 51.9 (CH, 14), 57.6 (CH_2, 16), 127.0 ($C_{ar}H$), 128.1 ($C_{ar}H$), 132.7 (CH, 1), 140.7 (CH, 2), 141.6 (C, 10), 147.3 (C, 7), 176.1 (C, 15), 202.5 (C, 18).

IR (NaCl): $\tilde{\nu}$ = 2961s, 1905w, 1697s, 1512s, 1480s, 1365s, 1275s, 1219s, 1157s, 1051s, 898s, 863m, 827s, 761m, 734m, 696s.

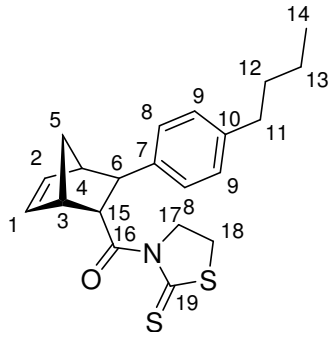
MS (EI, 70eV, ca. 150 °C), *m/z* (%): 323 ([M-H_2S]$^+$, 9), 291 (91), 263 (5), 195 (10), 173 (100), 131 (58), 115 (7), 91 (5), 43 ([C_3H_7]$^+$, 11).

$[\alpha]_D^{20}$ = −153.3 (c = 0.41, dichloromethane, >99% ee).

EA calcd (%) for $C_{20}H_{23}NOS_2$: C, 67.19; H, 6.48; N, 3.92. Found: C, 67.29; H, 6.33; N, 4.01.

HPLC: Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm, t_R = 19.9 min (major), t_R = 35.5 min (minor).

endo 3-{[(1*S*,2*R*,3*R*,4*R*)-(4-*n*-Butylphenyl)-bicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-thiazolidinethione ((*S*)-83)



By **general method X** Cu(II)$(OTf)_2$ (72.0 mg, 0.20 mmol), (*S,S*)-*t*-Bu-box **32b** (65.0 mg, 0.22 mmol), thiazolidinethione **67** (305 mg, 1.00 mmol) and cyclopentadiene (0.42 mL, 5.00 mmol) in dichloromethane (4 mL) gave a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate/hexanes 1:5) and recrystallisation (Et_2O/pentane) to give *endo* DA adduct (*S*)-**83** (274 mg, 74%, *endo* ee >99%, *endo:exo* 96:4, 100% conversion) as yellow needles.

$C_{21}H_{25}NOS_2$ (371.56):

m.p. 65-66 °C (Et_2O/pentane).

R_f = 0.69 (ethyl acetate/hexanes 1:1).

^{1}H NMR (500.1 MHz, CD_2Cl_2): δ = 0.92 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.34 (sext, ^3J = 7.3 Hz, CH_2CH$_3$), 1.48 (ob. dq, ^2J = 8.8 Hz, J = 1.8 Hz, 1 H, CHCH*H*CH), 1.54-1.60 (m, 2 H, CH_2CH$_2$CH$_3$), 1.80 (d, ^2J = 8.8 Hz, 1 H, CHC*H*HCH), 2.56 (t, ^3J = 7.8 Hz, 2 H, CH_2CH$_2$ CH$_2$CH$_3$), 2.94 (m, 1 H, C*H*(4)), 3.16-3.33 (m, 2 H, SCH_2), 3.27 (dd, ^3J = 5.5 Hz, J = 1.5 Hz, 1 H, PhC*H*), 3.53 (m, 1 H, C*H*(3)), 4.46-4.50 (m, 2 H, NCH_2), 5.13 (dd, ^3J = 5.3 Hz, J = 3.6 Hz, 1H, C*HC*=O), 5.92 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.50 (dd, ^3J = 5.6 Hz, J = 3.0 Hz, 1H, C*H*(2)=CH), 7.10 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 7.17 (d, ^3J = 7.8 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2): δ = 13.8 (CH_3, 14), 22.5 (CH_2, 13), 28.3 (CH_2, 18), 33.8 (CH_2, 12), 35.1 (CH_2, 11), 47.5 (CH, 3), 47.5 (CH_2, 5), 47.8 (CH, 6), 50.3 (CH, 4), 51.4 (CH, 15), 57.1 (CH_2, 17), 127.5 (C_{ar}H), 128.5 (C_{ar}H), 132.2 (CH, 1), 140.2 (CH, 2), 140.9 (C, 10), 140.9 (C, 7), 175.6 (C, 16), 202.0 (C, 19).

IR (KBr): $\tilde{\nu}$ = 2956s, 2361w, 1699s, 1512s, 1460s, 1367s, 1277s, 1159s, 1052s, 890s, 863s, 828s, 761s, 705s.

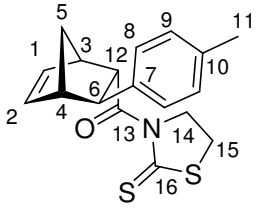
MS (EI, 70eV, ca. 150 °C), *m*/*z* (%): 337 ([M-H_2S]$^+$, 6), 305 (41), 187 (100), 131 (19), 115 (18), 91 (5), 57 ([C_4H_9]$^+$, 6).

$[\alpha]_D^{20}$ = −148.7 (c = 0.52, dichloromethane, >99% ee).

EA calcd (%) for $C_{21}H_{25}NOS_2$: C, 67.89; H, 6.78; N, 3.77. Found: C, 67.92; H, 6.79; N, 3.80.

HPLC: Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm, t_R = 19.1 min (major), t_R = 44.0 min (minor).

endo 3-{[(1*R*,2*S*,3*S*,4*S*)-(4-Tolyl)-bicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-thiazolidine-thione ((*R*)-84)



By **general method X** Cu(II)(OTf)$_2$ (72.0 mg, 0.20 mmol), (*R,R*)-*t*-Bu-box ligand (*R*)-**32b** (65.0 mg, 0.22 mmol), thiazolidinethione **63** (263 mg, 1.00 mmol) and cyclopentadiene (0.83 mL, 10.0 mmol) in dichloromethane (4 mL) gave a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate/hexanes 1:5) to give

endo DA adduct (*R*)-**84** (292 mg, 87%, *endo* ee 94%, *endo:exo* 97:3, >99% conversion) as a yellow transparent oil.

$C_{18}H_{19}NOS_2$ (329.48):

R_f = 0.61 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.49 (ob. dq, ^2J = 8.6 Hz, J = 1.8 Hz, 1 H, CHCH*H*CH), 1.79 (dd, ^2J = 8.8 Hz, J = 0.8 Hz, 1 H, CHC*H*HCH), 2.30 (s, 3 H, CH_3), 2.92 (d, ^2J = 1.0 Hz, 1 H, C*H*(4)), 3.16-3.35 (m, 3 H, PhC*H*, SCH_2), 3.52 (s, 1H, C*H*(3)), 4.46-4.50 (m, 2 H, NCH_2), 5.10 (dd, ^3J = 5.0 Hz, J = 3.3 Hz, 1 H, C*H*C=O), 5.92 (dd, ^3J = 5.8 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.50 (dd, ^3J = 5.6 Hz, ^3J = 3.3 Hz, 1H, C*H*(2)=CH), 7.08 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 7.14 (d, ^3J = 8.3 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 20.7 (CH_3, 11), 28.3 (CH_2, 15), 47.5 (CH_2, 7), 47.5 (CH, 3), 47.8 (CH, 6), 50.2 (CH, 4), 51.5 (CH, 12), 57.1 (CH_2, 14), 127.5 (C_{ar}H), 129.1 (C_{ar}H), 132.2 (CH, 1), 135.8 (C, 10), 140.2 (CH, 2), 140.7 (C, 7), 175.6 (C, 13), 202.0 (C, 16).

IR (NaCl): $\tilde{\nu}$ = 2980s, 1696s, 1513s, 1513m, 1492m, 1366m, 1329m, 1276m, 1157m, 1048s.

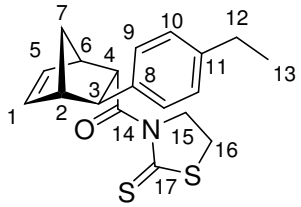
MS (FAB, NBA (subtr)), *m/z* (%): 330 ([M+H]$^+$, 21), 263 (21), 211 ([C_8H_7O]$^+$, 10), 145 (100).

$[\alpha]_D^{20}$ = +153.8 (c = 0.50, dichloromethane, 99% ee).

EA calcd (%) for $C_{18}H_{19}NOS_2$: C, 65.62; H, 5.81; N, 4.25. Found: C, 65.65; H, 5.81; N, 4.36.

HPLC: Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm, t_R = 22.5 min (minor), t_R = 58.4 min (major).

endo 3-{[(1*R*,2*S*,3*S*,4*S*)-(4-Ethylphenyl)-bicyclo[2.2.1]hept-5-en-2-yl]-carbonyl}-2-thiazolidinethione ((*R*)-85)



By **general method X** Cu(II)$(OTf)_2$ (72.0 mg, 0.20 mmol), (*R,R*)-*t*-Bu-box (*R*)-**32b** (65.0 mg, 0.22 mmol), thiazolidinethione **64** (277 mg, 1.00 mmol) and cyclopentadiene (0.83 mL, 10.0 mmol) in dichloromethane (4 mL) gave a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate/hexanes 1:5) and recrystallisation (Et_2O/pentane) to give *endo* DA adduct (*R*)-**85** (255 mg, 74%, *endo* ee >99%, *endo:exo* 97:3, >99% conversion) as yellow needles.

$C_{19}H_{21}NOS_2$ (343.51):

m.p. 68-70 °C (Et_2O/pentane).

R_f = 0.57 (ethyl acetate/ hexanes 1 : 1).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.20 (t, ^3J = 7.6 Hz, 3 H, CH_3), 1.49 (ob. dq, ^2J = 8.6 Hz, J = 1.8 Hz, 1 H, CHC*H*HCH), 1.80 (d, ^2J = 8.6 Hz, 1 H, CHCH*H*CH), 2.59 (q, ^3J = 7.6 Hz, 2 H, CH_2CH$_3$), 2.94 (d, J = 1.5 Hz, 1 H, C*H*(4)), 3.16-3.35 (m, 3 H, PhC*H*, SCH_2), 3.54 (s, 1H, C*H*(3)), 4.46-4.50 (m, 2 H, NCH_2), 5.13 (dd, ^3J = 5.0 Hz, J = 3.3 Hz, 1H, C*H*C=O), 5.93 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.51 (dd, ^3J = 5.6 Hz, ^3J = 3.0 Hz, 1H, C*H*(2)=CH), 7.12 (d, ^3J = 8.3 Hz, 2 H, H_{ar}), 7.18 (d, ^3J = 8.1 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 15.5 (CH_3, 12), 28.3 (CH_2, 11), 28.4 (CH_2, 16), 47.5 (CH_2, 5), 47.5 (CH, 3), 47.8 (CH, 6), 50.2 (CH, 4), 51.5 (CH, 13), 57.1 (CH_2, 15), 127.6 (C_{ar}H), 128.0 (C_{ar}H), 132.2 (CH, 1), 140.2 (CH, 2), 141.0 (C, 10), 142.2 (C, 7), 175.6 (C, 14), 202.0 (C, 17).

IR (KBr): $\tilde{\nu}$ = 2966s, 1696s, 1513m, 1457m, 1366m, 1276m, 1158m, 1049s.

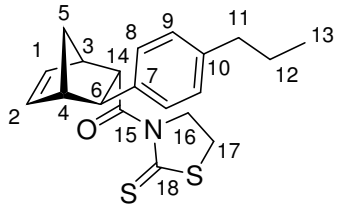
MS (FAB, NBA (subtr)), *m*/*z* (%): 344 ([M+H]$^+$, 19), 277 (20), 225 (11), 159 (100).

$[\alpha]_D^{20}$ = +150.1 (c = 0.50, dichloromethane, 99% ee).

EA calcd (%) for $C_{19}H_{21}NOS_2$: C, 66.43; H, 6.16; N, 4.08. Found: C, 66.31; H, 6.09; N, 4.17.

HPLC: Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm, t_R = 21.2 min (minor), t_R = 46.9 min (major).

endo 3-{[(1*R*,2*S*,3*S*,4*S*)-(4-*n*-Propylphenyl)-bicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-thiazolidinethione ((*R*)-86)



By **general method X** Cu(II)(OTf)$_2$ (36.0 mg, 0.10 mmol), (*R,R*)-*t*-Bu-box (*R*)-**32b** (32.0 mg, 0.11 mmol), thiazolidinethione **65** (146 mg, 0.50 mmol) and cyclopentadiene (0.42 mL, 5.00 mmol) in dichloromethane (2 mL) gave a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 2 × 20 cm, ethyl acetate/hexanes 1:5) and recrystallisation (Et_2O/pentane) to give *endo* DA adduct (*R*)-**86** (127 mg, 71%, *endo* ee >99%, *endo:exo* 97:3, 100% conversion) as yellow needles.

$C_{20}H_{23}NOS_2$ (357.53):

m.p. 95-96 °C (Et_2O/pentane).

R_f = 0.69 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 0.93 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.49 (ob. dq, ^2J = 8.8 Hz, ^3J = 3.5 Hz, ^3J = 1.8 Hz, 1 H, CHCH*H*CH), 1.69 (sext, ^3J = 7.6 Hz, CH_2CH$_3$), 1.80 (d, ^2J = 8.6 Hz, 1 H, CHC*H*HCH), 2.54 (t, ^3J = 7.6 Hz, 2 H, CH_2CH$_2$CH$_3$), 2.94 (d, ^3J = 1.5 Hz, 1 H, C*H*(4)), 3.16-3.35 (m, 2 H, SCH_2), 3.27 (dd, ^3J = 4.8 Hz, J = 1.3 Hz,, 1 H, PhC*H*), 3.54 (s, 1 H, C*H*(3)), 4.46-4.50 (m, 2 H, NCH_2), 5.13 (dd, ^3J = 5.1 Hz, J = 3.6 Hz, 1H, C*H*C=O), 5.92 (dd, ^3J = 5.5 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.51 (dd, ^3J = 5.6 Hz, J = 3.0 Hz, 1H, C*H*(2)=CH), 7.19 (d, ^3J = 8.3 Hz, 2 H, H_{ar}), 7.17 (d, ^3J = 8.1 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 13.7 (CH_3, 13), 24.7 (CH_2, 12), 28.3 (CH_2, 17), 37.5 (CH_2, 11), 47.5 (CH, 3), 47.5 (CH_2, 5), 47.8 (CH, 6), 50.3 (CH, 4), 51.4 (CH, 14), 57.1 (CH_2, 16), 127.5 (C_{ar}H), 128.5 (C_{ar}H), 132.2 (CH, 1), 140.2 (CH, 2), 140. 7 (C, 10), 141.0 (C, 7), 175.6 (C, 15), 202.0 (C, 18).

IR (KBr): $\tilde{\nu}$ = 2950s, 1712s, 1511m, 1459m, 1432m, 1364s, 1327s, 1278s, 1215s, 1154s, 1027s, 803s, 755s, 707s.

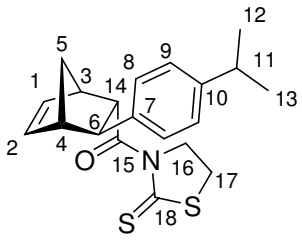
MS (FAB, NBA (subtr)), *m/z* (%): 358 ($[M+H]^+$, 40), 291 ($[M-C_5H_6]^+$, 26), 239 (24), 173 ($[291-C_9H_{10}]^+$, 100), 91 (9), 43 ($[C_3H_7]^+$, 11).

$[\alpha]_D^{20}$ = +188.9 (c = 0.49, dichloromethane, >99% ee).

EA calcd (%) for $C_{20}H_{23}NOS_2$: C, 67.19; H, 6.48; N, 3.93. Found: C, 67.00; H, 6.57; N, 3.93.

HPLC: Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm, t_R = 19.0 min (minor), t_R = 39.7 min (major).

endo 3-{[(1*R*,2S,3*S*,4*S*)-(4-i-Propylphenyl)-bicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-thiazolidinethione ((*R*)-87)



By **general method X** Cu(II)$(OTf)_2$ (36.0 mg, 0.10 mmol), (*R,R*)-*t*-Bu-box (*R*)-**32b** (32.0 mg, 0.11 mmol), thiazolidinethione **66** (146 mg, 0.50 mmol) and cyclopentadiene (0.42 mL, 5.00 mmol) in dichloromethane (2 mL) gave a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 2 × 20 cm, ethyl acetate/hexanes 1:5) and

recrystallisation (Et_2O/pentane) to give *endo* DA adduct (*R*)-**87** (156 mg, 87%, *endo* >99% ee, *endo:exo* 97:3, 100% conversion) as yellow needles.

$C_{20}H_{23}NOS_2$ (357.53):

R_f = 0.69 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.22 (d, ^3J = 7.1 Hz, 6 H, CH_3), 1.49 (ob. dq, ^2J = 8.8 Hz, ^3J = 1.8 Hz, 1 H, CHCH*H*CH), 1.80 (d, ^2J = 8.8 Hz, 1 H, CHC*H*HCH), 2.87 (sept, ^3J = 6.8 Hz, C*H*(CH_3)$_2$), 2.94 (d, ^3J = 1.5 Hz, 1 H, C*H*(4)), 3.17-3.35 (m, 2 H, SCH_2), 3.27 (dd, ^3J = 4.8 Hz, ^3J = 1.3 Hz, 1 H, PhC*H*), 3.54 (s, 1 H, C*H*(3)), 4.46-4.50 (m, 2 H, NCH_2), 5.14 (dd, ^3J = 5.0 Hz, J = 3.6 Hz, 1H, C*H*C=O), 5.92 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.50 (dd, ^3J = 5.6 Hz, J = 3.3 Hz, 1H, C*H*(2)=CH), 7.15 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 7.19 (d, ^3J = 8.3 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 23.8 (CH_3, 12/13), 28.3 (CH_2, 17), 33.7 (CH, 11), 47.5 (CH_2, 5), 47.5 (CH_2, 6), 47.8 (CH, 3), 50.3 (CH, 4), 51.4 (CH, 14), 57.1 (CH_2, 16), 126.5 ($C_{ar}H$), 127.6 ($C_{ar}H$), 132.2 (CH, 1), 140.3 (CH, 2), 141.1 (C, 7), 146.8 (C, 10), 175.6 (C, 15), 202.0 (C, 18).

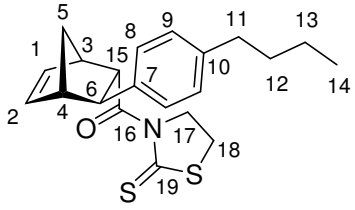
MS (EI, 70eV, ca. 150 °C), *m/z* (%): 323 ([M-H_2S]$^+$, 7), 291 (70), 263 (5), 195 (8), 173 (100), 131 (71), 115 (8), 66 (10), 43 ([C_3H_7]$^+$, 12).

$[\alpha]_D^{20}$ = +135.8 (c = 0.41, dichloromethane, >99% ee).

EA calcd (%) for $C_{20}H_{23}NOS_2$: C, 67.19; H, 6.48; N, 3.92. Found: C, 66.52; H, 6.34; N, 4.00.

HPLC: Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm, t_R = 19.8 min (minor), t_R = 35.2 min (major).

endo 3-{[(1*R*,2*S*,3*S*,4*S*)-(4-*n*-Butylphenyl)-bicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-2-thiazolidinethione ((*R*)-88)



By **general method X** Cu(II)$(OTf)_2$ (72.0 mg, 0.20 mmol), (*R,R*)-*t*-Bu-box (*R*)-**32b** (65.0 mg, 0.22 mmol), thiazolidinethione **67** (305 mg, 1.00 mmol) and cyclopentadiene (0.42 mL, 5.00 mmol) in dichloromethane (4 mL) gave a yellow oil. The crude product was purified by flash column chromatography (SiO_2, 3 × 25 cm, ethyl acetate/hexanes 1:5) and

recrystallisation (Et_2O/pentane) to give *endo* DA adduct (*R*)-**88** (245 mg, 66%, *endo* ee >99%, *endo:exo* 97:3, 100% conversion) as yellow needles.

$C_{21}H_{25}NOS_2$ (371.56):

m.p. 66-67 °C (Et_2O/pentane).

R_f = 0.69 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 0.92 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.34 (sext, ^3J = 7.3 Hz, CH_2CH$_3$), 1.48 (ob. dq, ^2J = 8.8 Hz, J = 1.8 Hz, 1 H, CHCH*H*CH), 1.54-1.60 (m, 2 H, CH_2CH$_2$CH$_3$), 1.80 (d, ^2J = 8.8 Hz, 1 H, CHC*H*HCH), 2.56 (t, ^3J = 7.8 Hz, 2 H, CH_2CH$_2$ CH$_2$CH$_3$), 2.94 (m, 1 H, C*H*(4)), 3.16-3.33 (m, 2 H, SCH_2), 3.27 (dd, ^3J = 5.5 Hz, J = 1.5 Hz, 1 H, PhC*H*), 3.53 (m, 1 H, C*H*(3)), 4.46-4.50 (m, 2 H, NCH_2), 5.13 (dd, ^3J = 5.3 Hz, J = 3.6 Hz, 1H, C*HC*=O), 5.92 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.50 (dd, ^3J = 5.6 Hz, J = 3.0 Hz, 1H, C*H*(2)=CH), 7.10 (d, ^3J = 8.4 Hz, 2 H, H_{ar}), 7.17 (d, ^3J = 7.8 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 13.8 (CH_3, 14), 22.5 (CH_2, 13), 28.3 (CH_2, 18), 33.8 (CH_2, 12), 35.1 (CH_2, 11), 47.5 (CH, 3), 47.5 (CH_2, 5), 47.8 (CH, 6), 50.3 (CH, 4), 51.4 (CH, 15), 57.1 (CH_2, 17), 127.5 (C_{ar}H), 128.5 (C_{ar}H), 132.2 (CH, 1), 140.2 (CH, 2), 140.9 (C, 10), 140.9 (C, 7), 175.6 (C, 16), 202.0 (C, 19).

IR (KBr): $\tilde{\nu}$ = 2924m, 1686s, 1511m, 1458m, 1368s, 1264s, 1170s, 1037s, 820m, 764m, 701s.

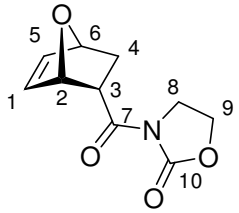
MS (EI, 70eV, ca. 150 °C), *m*/*z* (%): 337 ([M-H_2S]$^+$, 6), 305 (46), 187 (100), 131 (19), 115 (16), 66 (5), 57 ([C_4H_9]$^+$, 5).

$[\alpha]_D^{20}$ = +176.6 (c = 0.51, dichloromethane, 99% ee).

EA calcd (%) for $C_{21}H_{25}NOS_2$: C, 67.89; H, 6.78; N, 3.77. Found: C, 67.87; H, 6.70; N, 3.86.

HPLC: Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm, t_R = 19.3 min (major), t_R = 43.8 min (minor).

3-{[(1*S*,2*S*,4*S*)-7-Oxa-bicyclo[2.2.1]hept-5-en-2yl]carbonyl}-2-oxazolidinone (38)[121]



Cu(II)Cl_2 (6.70 mg, 0.05 mmol), (*S,S*)-*t*-Bu-box **32b** (16.2 mg, 55.0 µmol) and $AgSbF_6$ (34.4 mg, 0.10 mmol) were mixed together in glove box and the flask was wrapped in

aluminium foil to protect the reaction mixture from light. The flask was connected to a Schlenk line and dichloromethane (1.5 mL) was added. After stirring for 16 hours at room temperature, the catalyst mixture was filtered through a plug of celite (rinsed with dichloromethane (3 mL)) into a solution of oxazolidinone **35** (142 mg, 1.00 mmol) and furan (0.80 mL, 10.0 mmol) in dichloromethane (1.2 mL) at –78 °C. After stirring for 3 hours at -20 °C the blue reaction mixture was quenched with 25% aqueous NH_4OH (1 mL). The aqueous phase was extracted with dichloromethane (3 × 2 mL), the combined organic extracts were washed with brine and dried (Na_2SO_4). After removal of the solvent under reduced pressure an oil with white solid was obtained. The crude product was purified by flash column chromatography (SiO_2, 2 × 10 cm, ethyl acetate/hexanes 2:3) and recrystallisation (ethyl acetate/hexanes) to give DA adduct **38** (14 mg, 5%, *endo* ee 77%, *dr* 35:65, 86% conversion) as colourless crystals.

$C_{18}H_{19}NO_3$ (209.20):

m.p. 90-91 °C (ethyl acetate/hexanes) [lit.,[121] 89 °C].

R_f = 0.22 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, CD_2Cl_2): major diastereoisomer δ = 1.63 (dd, ^2J =11.4 Hz, ^3J = 4.0 Hz, 1 H, CHCH*H*CH), 2.11 (ddd, ^2J =11.4 Hz, ^3J = 9.1 Hz, ^3J = 4.8 Hz, 1 H, CHC*H*HCH), 4.02-3.86 (m, 3 H, C*H*C=O, NCH_2), 4.44-4.34 (m, 2 H, OCH_2), 5.02 (ddd, ^3J = 5.8 Hz, J = 1.5 Hz, J = 0.8 Hz, 1H, C*H*(6)), 5.26 (ddd, ^3J = 5.6 Hz, J = 1.5 Hz, J = 0.8 Hz, 1H, CH(2)), 6.16 (dd, ^3J = 5.8 Hz, ^3J = 1.5 Hz, 1H, C*H*=CH), 6.44 (dd, ^3J = 5.8 Hz, ^3J = 1.8 Hz, 1H, C*H*=CH).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): 1 diastereoisomer δ = 29.2 (CH_2, 4), 42.9 (CH, 3), 43.3 (CH_2, 8), 62.4 (CH_2, 9), 79.2 (CH , 2/6), 79.4 (CH, 2/6), 131.9 (CH, 1/5), 137.0 (CH, 1/5), 153.0 (C, 10), 171.6 (C, 7).

IR (KBr): $\tilde{\nu}$ = 3433s, 2920s, 1774s, 1690s, 1396s, 1231s, 1124s, 1049s, 866s, 755s, 700s.

MS (FAB, NBA (subtr)), *m/z* (%): 295 (5), 210 ([M+H]$^+$, 17).

[α]$_D^{20}$ = –81.5 (c = 1.00, $CHCl_3$, 77% ee) [lit.,[121] -99.1 (c = 1.00, $CHCl_3$, 97% ee)].

EA calcd (%) for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.18; H, 5.29; N, 6.59.

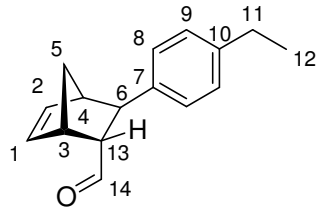
HPLC: Chiralcel OD-H, i-propanol/heptane (30:70), 0.65 mL/min, 20 °C, 210 nm, t_R = 27.3 min (major), t_R = 38.7 min (minor).

The spectroscopic data are in agreement with that previously reported in the literature.[121]

5.4 Synthesis of Diels-Alder Adducts for the Organocatalysed Retro-Diels-Alder Reaction

5.4.1 Synthesis of Diels-Alder Adducts

***endo* 3-[(1*S*,2*R*,3*R*,4*R*)-(4-Ethylphenyl)-bicyclo[2.2.1]hept-5-en-2-yl]-carbaldehyde ((*S*)-112)**



General Method XI: *Endo* DA adduct (*S*)-**80** (120 mg, 0.35 mmol) was added in one portion to a solution of di-i-butylaluminium hydride (1.7 M in toluene, 0.28 mL, 0.42 mmol) in toluene (0.4 mL) at -78 °C. An extra 0.6 mL of toluene were added to dissolve all solid. After stirring for 20 minutes at -78 °C and 3 hours at -20 °C the reaction mixture was quenched with 1 M H_2SO_4 (0.2 mL), diluted with dichloromethane (12 mL) and dried over plenty of Na_2SO_4. Removal of the solvent under reduced pressure gave a colourless oil. The crude product was purified by flash column chromatography (SiO_2, 1 × 16 cm, ethyl acetate/hexanes 1:4) to give *endo* DA adduct (*S*)-**112** (54 mg, 68%) as a colourless oil.

$C_{16}H_{18}O$ (226.31):

R_f = 0.87 (ethyl acetate/hexanes 1:4).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.20 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.58 (ob. dq, ^2J = 8.6 Hz, ^3J = 1.8 Hz, 1 H, CHCH*H*CH), 1.79 (dt, ^2J = 8.6 Hz, ^3J = 1.5 Hz, 1 H, CHC*H*HCH), 2.60 (q, ^3J = 7.6 Hz, 2 H, CH_2CH$_3$), 2.92-2.94 (m, 1 H, C*H*C(=O)H)), 2.99-3.01 (m, 1 H, PhC*H*), 3.05-3.06 (m, 1 H, C*H*(4)), 3.30-3.31 (m, 1 H, C*H*(3)), 6.16 (dd, ^3J = 5.5 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.41 (dd, ^3J = 5.6 Hz, J = 3.3 Hz, 1H, C*H*(2)=CH), 7.13-7.19 (m, 4 H, H_{ar}), 9.55 (d, ^3J = 2.5 Hz, 1 H, *H*C=O).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 15.5 (CH_3, 12), 28.9 (CH_2, 11), 45.7 (CH, 3), 46.1 (CH, 6), 47.5 (CH_2, 5), 49.4 (CH, 4), 61.3 (CH, 13), 127.9 (C_{ar}H), 128.5 (C_{ar}H), 134.2 (CH, 1), 139.7 (CH, 2), 141.5 (C, 7), 142.6 (C, 10), 204.0 (C, 14).

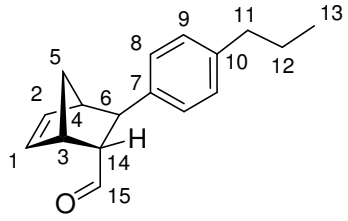
IR (NaCl): $\tilde{\nu}$ = 3057s, 2968s, 2873m, 2714m, 1719s, 1513m, 1455m, 1332m, 1067m, 826m, 718m.

MS (EI, 70eV, ca. 100 °C), *m/z* (%): 176 (35), 161 ([M-C_5H_5]$^+$, 53), 131 ([M-C_7H_{10}]$^+$, 100), 115 (20), 66 (36).

$[\alpha]_D^{20}$ = −114.0 (c = 0.20, dichloromethane).

EA calcd (%) for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.85; H, 8.20.

endo 3-[(1*S*,2*R*,3*R*,4*R*)-(4-*n*-Propylphenyl)-bicyclo[2.2.1]hept-5-ene]-2-carbaldehyde ((*S*)-113)



By **general method XI** di-i-butylaluminium hydride (1.7 M in toluene, 0.10 mL, 0.14 mmol) and *endo* DA adduct (*S*)-**82** (42.0 mg, 0.118 mmol) in toluene (0.7 mL) gave a colourless oil. The crude product was purified by flash column chromatography (SiO_2, 1 × 12 cm, ethyl acetate/hexanes 1:4) to give *endo* DA adduct (*S*)-**113** (23 mg, 81%) as a colourless oil.

$C_{17}H_{20}O$ (240.34):

R_f = 0.81 (ethyl acetate/hexanes 1:4).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.62 (m, 3 H, CH_2CH$_3$, CHCH*H*CH), 1.80 (d, ^2J = 8.8 Hz, 1 H, CHC*H*HCH), 2.56 (t, ^3J = 7.3 Hz, 2 H, CH_2CH$_2$CH$_3$), 2.97-2.99 (m, 1 H, C*H*C(=O)H), 3.05-3.06 (m, 1H, PhC*H*), 3.10 (s, 1 H, C*H*(4)), 3.31-3.32 (m, 1 H, C*H*(3)), 6.16 (dd, ^3J = 5.8 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.41 (dd, ^3J = 5.8 Hz, J = 3.3 Hz, 1H, C*H*(2)=CH), 7.11-7.18 (m, 4 H, H_{ar}), 9.58 (d, ^3J = 2.2 Hz, 1 H, C*H*=O).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (CH_3, 13), 24.6 (CH_2, 12), 37.5 (CH_2, 11), 45.1 (CH, 3), 45.4 (CH, 6), 47.1 (CH_2, 5), 48.5 (CH, 4), 60.8 (CH, 14), 127.2 (C_{ar}H), 128.6 (C_{ar}H), 133.7 (CH, 1), 139.2 (CH, 2), 140.6 (C, 7), 140.7 (C, 10), 203.7 (C, 15).

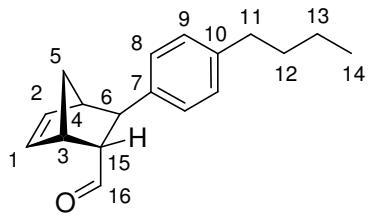
IR (NaCl): $\tilde{\nu}$ = 2963s, 2879m, 1718s.

MS (EI, 70eV, r.t.), *m/z* (%): 175 ([M-C_5H_5]$^+$, 44), 131 ([M-C_8H_{13}], 100), 117 (8), 66 (17).

$[\alpha]_D^{20}$ = −90.0 (c = 0.20, dichloromethane).

EA calcd (%) for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 85.23; H, 8.59.

***endo* 3-[(1*S*,2*R*,3*R*,4*R*)-(4-*n*-Butylphenyl)-bicyclo[2.2.1]hept-5-ene]-2-carbaldehyde ((*S*)-114)**



By **general method XI** di-i-butylaluminium hydride (1.7 M in toluene, 0.09 mL, 134 µmol) and *endo* DA adduct (*S*)-**83** (42.0 mg, 112 µmol) in toluene (0.7 mL) gave a colourless oil. The crude product was purified by flash column chromatography (SiO_2, 1 × 12 cm, ethyl acetate/hexanes 1:4) to give *endo* DA adduct (*S*)-**114** (21 mg, 74%) as a colourless oil.

$C_{18}H_{22}O$ (254.37):

R_f = 0.95 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.35 (sext, ^3J = 7.6 Hz, CH_2CH$_3$), 1.54-1.62 (m, 3 H, CH_2CH$_2$CH$_3$, CHCH*H*CH), 1.80 (d, ^3J = 8.8 Hz, 1 H, CHC*H*HCH), 2.58 (t, ^3J = 7.8 Hz, 2 H, CH_2CH$_2$CH$_2$CH$_3$), 2.97-2.95 (m, 1 H, C*H*C(=O)H), 3.04-3.05 (m, 1 H, PhC*H*), 3.09-3.10 (m, 1 H, C*H*(4)), 3.32 (s, 1 H, C*H*(3)), 6.16 (dd, ^3J = 5.8 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.41 (dd, ^3J = 5.6 Hz, J = 3.3 Hz, 1H, C*H*(2)=CH), 7.11 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.17 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 9.58 (d, ^3J = 2.2 Hz, 1 H, *H*C=O).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (CH_3, 14), 22.4 (CH_2, 13), 33.6 (CH_2, 12), 35.1 (CH_2, 11), 45.1 (CH, 3), 45.4 (CH, 6), 47.1 (CH_2, 5), 48.5 (CH, 4), 60.8 (CH, 15), 127.2 (C_{ar}H), 128.6 (C_{ar}H), 133.7 (CH, 1), 139.2 (CH, 2), 140.6 (C, 7), 140.8 (C, 10), 203.7 (C, 16).

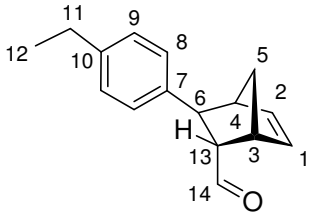
IR (NaCl): $\tilde{\nu}$ = 2959s, 2865s, 2713m, 1719s, 1513m, 1458m, 1333m, 1069m, 721s.

MS (EI, 70eV, r.t.), *m*/*z* (%): 189 ([M-C_5H_5]$^+$, 5), 131 ([M-C_9H_{14}]$^+$, 100), 117 (8), 66 (12).

[α]$_D^{20}$ = −67.2 (c = 0.50, dichloromethane).

EA calcd (%) for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.89; H, 8.73.

***endo* 3-[(1*R*,2*S*,3*S*,4*S*)-(4-Ethylphenyl)-bicyclo[2.2.1]hept-5-en-2-yl]-carbaldehyde ((*R*)-115)**



By **general method XI** di-i-butylaluminium hydride (1.7 M in toluene, 0.14 mL, 0.21 mmol) and *endo* DA adduct (*R*)-**85** (60.0 mg, 0.175 mmol) in toluene (0.6 mL) gave a colourless oil. The crude product was purified by flash column chromatography (SiO_2, 1×12 cm, ethyl acetate/hexanes 1:4) to give *endo* DA adduct (*R)*-**115** (30 mg, 76%) as a colourless oil.

$C_{16}H_{18}O$ (266.31):

R_f = 0.87 (ethyl acetate/hexanes 1:4).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.23 (t, ^3J = 7.2 Hz, 3 H, C*H*$_3$), 1.61 (dd, ^2J = 8.6 Hz, ^3J = 1.8 Hz, 1 H, CHCH*H*CH), 1.81 (d, ^2J = 8.6 Hz, 1 H, CHC*H*HCH), 2.62 (q, ^3J = 7.6 Hz, 2 H, C*H*$_2$CH$_3$), 2.97-2.98 (m, 1 H, C*H*C=O), 3.05-3.06 (m, 1 H, PhC*H*), 3.10 (s, 1 H, C*H*(4)), 3.32 (s, 1 H, C*H(*3)), 6.17 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.41 (dd, ^3J = 5.8 Hz, J = 3.3 Hz, 1H, C*H*(2)=CH), 7.14 (d, ^3J = 8.3 Hz, 2 H, H_{ar}), 7.19 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 9.59 (d, ^3J = 2.3 Hz, 1 H, C*H*=O).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 15.6 (CH_3, 12), 28.3 (CH_2, 11), 45.1 (CH, 3), 45.4 (CH, 6), 47.1 (CH_2, 5), 48.5 (CH, 4), 60.8 (CH, 13), 127.3 ($C_{ar}H$), 128.0 ($C_{ar}H$), 133.7 (CH, 1), 139.2 (CH, 2), 140.7 (C, 7), 142.6 (C, 10), 203.7 (C, 14).

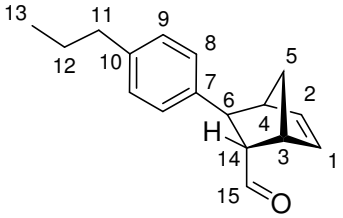
IR (NaCl): $\tilde{\nu}$ = 2966s, 1720s, 1513m, 1458m, 1244m, 1126m.

MS (EI, 70eV, r.t.), *m/z* (%): 161 ([M-C_5H_5]$^+$, 56), 131 ([M-C_7H_{10}]$^+$, 100), 66 (18).

$[\alpha]_D^{20}$ = +99.0 (c = 0.20, dichloromethane).

EA calcd (%) for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 83.71; H, 8.16.

***endo* 3-[(1*R*,2*S*,3*S*,4*S*)-(4-*n*-Propylphenyl)-bicyclo[2.2.1]hept-5-ene]-2-carbaldehyde ((*R*)-116)**



By **general method XI** di-i-butylaluminium hydride (1.7 M in toluene, 0.06 mL, 94.0 µmol) and *endo* DA adduct (*R*)-**87** (28.0 mg, 78.7 µmol) in toluene (0.4 mL) gave a colourless oil. The crude product was purified by flash column chromatography (SiO_2, 1 × 10 cm, ethyl acetate/hexanes 1:4) to give *endo* DA adduct (*R*)-**116** (16 mg, 85%) as a colourless oil.

$C_{17}H_{20}O$ (240.34):

R_f = 0.81 (ethyl acetate/hexanes 1:4).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 7.3 Hz, 3 H, C*H*$_3$), 1.60 (m, 3 H, C*H*$_2$CH$_3$, CHCH*H*CH), 1.81 (d, ^3J = 8.8 Hz, 1 H, CHC*H*HCH), 2.56 (t, ^3J = 7.3 Hz, 2 H, C*H*$_2$CH$_2$CH$_3$), 2.97-2.99 (m, 1 H, C*H*C(=O)H), 3.05 (d, ^3J = 4.0 Hz, 1 H, PhC*H*), 3.09-3.10 (m, 1 H, C*H*(4)), 3.32 (s, 1 H, C*H*(3)), 6.16 (dd, ^3J = 5.8 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.41 (dd, ^3J = 5.8 Hz, J = 3.3 Hz, 1H, C*H*(2)=CH), 7.12 (d, ^3J = 8.3 Hz, 2 H, H_{ar}), 7.17 (d, ^3J = 7.8 Hz, 2 H, H_{ar}), 9.59 (d, ^3J = 2.3 Hz, 1 H, C*H*=O).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (CH_3, 13), 24.5 (CH_2, 12), 37.5 (CH_2, 11), 45.1 (CH, 3), 45.4 (CH, 6), 47.1 (CH_2, 5), 48.5 (CH, 4), 60.8 (CH, 14), 127.2 ($C_{ar}H$), 128.6 ($C_{ar}H$), 133.7 (CH, 1), 139.2 (CH, 2), 140.6 (C, 7), 140.7 (C, 10), 203.7 (C, 15).

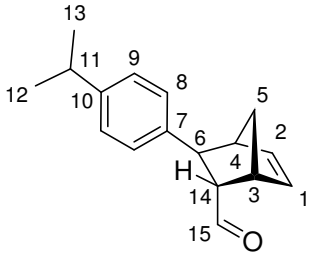
IR (NaCl): $\tilde{\nu}$ = 2962s, 2711m, 1718s, 1513s, 1332m.

MS (EI, 70eV, r.t.), *m*/*z* (%): 175 ([M-C_5H_5]$^+$, 44), 131 ([M-C_9H_{14}]$^+$, 100), 117 (8), 66 (17).

$[\alpha]_D^{20}$ = +103.0 (c = 0.20, dichloromethane).

EA calcd (%) for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.95; H, 8.57.

***endo* 3-[(1*R*,2*S*,3*S*,4*S*)-(4-i-Propylphenyl)-bicyclo[2.2.1]hept-5-ene]-2-carbaldehyde ((*R*)-117)**



By **general method XI** di-i-butylaluminium hydride (1.7 M in toluene, 0.11 mL, 0.17 mmol) and *endo* DA adduct (*R*)-**86** (50.0 mg, 0.14 mmol) in toluene (0.7 mL) gave a colourless oil. The crude product was purified by flash column chromatography (SiO_2, 1 × 12 cm, ethyl acetate/hexanes 1:4) to give *endo* DA adduct (*R*)-**117** (23 mg, 68%) as a colourless oil.

$C_{17}H_{20}O$ (240.34):

R_f = 0.87 (ethyl acetate/hexanes 1:4).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.24 (d, ^3J = 7.1 Hz, 3 H, CH_3), 1.25 (d, ^3J = 6.8 Hz, 3 H, CH_3), 1.60 (dd, ^2J = 8.6 Hz, ^3J = 1.5 Hz, 1 H, CHCH*H*CH), 1.82 (d, ^3J = 8.6 Hz, 1 H, CHC*H*HCH), 2.89 (sept, ^3J = 7.1 Hz, 1 H, C*H*CH_3), 2.97-3.00 (m, 1 H, C*H*C(=O)H), 3.05 (d, ^3J = 4.8 Hz, 1 H, PhC*H*), 3.11 (s, 1 H, C*H*(4)), 3.32 (s, 1 H, C*H*(3)), 6.17 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.41 (dd, ^3J = 5.6 Hz, J = 3.3 Hz, 1H, C*H*(2)=CH), 7.17-7.21 (m, 4 H, H_{ar}), 9.59 (d, ^3J = 2.2 Hz, 1 H, C*H*=O).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 24.0 (CH_3, 12/13), 33.6 (CH, 11), 45.1 (CH, 3), 45.4 (CH, 6), 47.1 (CH_2, 5), 48.5 (CH, 4), 60.7 (CH, 14), 126.6 ($C_{ar}H$), 127.3 ($C_{ar}H$), 133.7 (CH, 1), 140.8 (CH, 2), 140.8 (C, 7), 146.8 (C, 10), 203.7 (C, 15).

IR (NaCl): $\tilde{\nu}$ = 3058s, 2963s, 2873m, 2810m, 2713m, 1719s, 1512m, 1458m, 1332m, 1064m, 1018m, 826m, 729m.

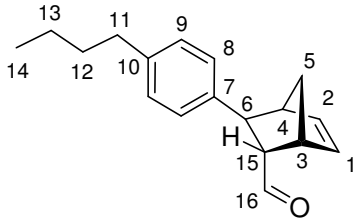
MS (EI, 70eV, r.t.), *m*/*z* (%):175 ([M-C_5H_5]$^+$, 38), 131 (100), 115 (7), 66 (10).

$[\alpha]_D^{20}$ = +97.0 (c = 0.20, dichloromethane).

EA calcd (%) for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 83.85; H, 8.51.

The spectroscopic data (^{1}H NMR, ^{13}C NMR) are in agreement with that previously reported in the literature.[112]

***endo* 3-[(1*R*,2*S*,3*S*,4*S*)-(4-*n*-Butylphenyl)-bicyclo[2.2.1]hept-5-ene]-2-carbaldehyde ((*R*)-118)**



By **general method XI** di-i-butylaluminium hydride (1.7 M in toluene, 0.07 mL, 97.0 µmol) and *endo* DA adduct (*R*)-**88** (30.0 mg, 81.0 µmol) in toluene (0.5 mL) gave a colourless oil. The crude product was purified by flash column chromatography (SiO_2, 1 × 10 cm, ethyl acetate/hexanes 1:4) to give *endo* DA adduct (*R*)-**118** (18 mg, 87%) as a colourless oil.

$C_{18}H_{22}O$ (254.37):

R_f = 0.95 (ethyl acetate/hexanes 1:1).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 0.92 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.34 (sext, ^3J = 7.6 Hz, CH_2CH$_3$), 1.53-1.61 (m, 3 H, CH_2CH$_2$CH$_3$, CHCH*H*CH), 1.79 (dt, ^3J = 8.6 Hz, ^3J = 1.5 Hz, 1 H, CHC*H*HCH), 2.57 (t, ^3J = 7.8 Hz, 2 H, CH_2CH$_2$CH$_2$CH$_3$), 2.93-2.95 (m, 1 H, C*H*C(=O)H), 3.00-3.01 (m, 1 H, PhC*H*), 3.05-3.06 (m, 1 H, C*H*(4)), 3.30-3.31 (m, 1 H, C*H*(3)), 6.16 (dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1H, C*H*(1)=CH), 6.40 (dd, ^3J = 5.6 Hz, J = 3.3 Hz, 1H, C*H*(2)=CH), 7.11-7.18 (m, 4 H, H_{ar}), 9.55 (d, ^3J = 2.2 Hz, 1 H, C*H*=O).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 14.3 (CH_3, 14), 22.9 (CH_2, 13), 34.3 (CH_2, 12), 35.6 (CH_2, 11), 45.7 (CH, 3), 46.0 (CH, 6), 47.5 (CH_2, 5), 49.4 (CH, 4), 61.3 (CH, 15), 127.8 (C_{ar}H), 129.1 (C_{ar}H), 134.2 (CH, 1), 139.7 (CH, 2), 141.4 (C, 7), 141.4 (C, 10), 204.0 (CH, 16).

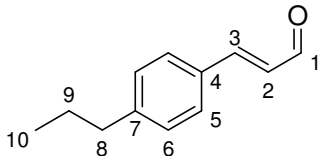
IR (NaCl): $\tilde{\nu}$ = 2960s, 2713s, 1719s, 1513s.

MS (EI, 70eV, r.t.), *m*/*z* (%): 189 ([M-C_5H_5]$^+$, 31), 131 ([M-C_9H_{14}]$^+$, 100), 117 (11), 66 (15).

$[\alpha]_D^{20}$ = +79.0 (c = 0.50, dichloromethane).

EA calcd (%) for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.89; H, 8.73.

3-(4-Propylphenyl)-propenal (119)[189]



Acroleindiethyl acetal (3.43 mL, 22.5 mmol), tetrabutylammoniumacetate (4.52 g, 15.0 mmol), K_2CO_3 (1.56 g, 11.3 mmol), KCl (0.56 g, 7.50 mmol) and palladium acetate (25.0 mg, 225 µmol) were added to a solution of 1-*n*-propyl-4-iodobenzene (1.85 mL, 7.50 mmol) in *N,N*-dimethylformamide (30 mL). After stirring for 2 hours at 90 °C and cooling to room temperature, 1 N HCl (25 mL) and Et_2O (120 mL) were added. Washing with ice water (280 mL), drying (Na_2SO_4) and concentration under reduced pressure gave a brown oil. The crude product was purified by flash column chromatography (SiO_2, 3 × 17 cm, ethyl acetate/hexanes 1:10) to give aldehyde **119** (1.05 g, 80%) as a transparent yellow oil.

$C_{12}H_{14}O$ (174.24):

R_f = 0.67 (ethyl acetate/hexanes 1:1)

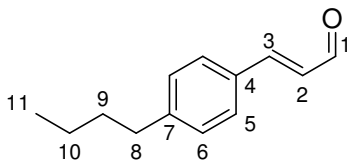
^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.95 (t, ^3J = 7.6 Hz, 3 H, CH_3), 1.65 (sext, ^3J = 7.6 Hz, 2 H, CH_2CH$_3$), 2.63 (t, ^3J = 7.6 Hz, 2 H, CH_2CH$_2$CH$_3$), 6.69 (dd, ^3J = 15.9 Hz, ^3J = 7.8 Hz, 1 H, C*H*CH=O), 7.24 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.46 (d, ^3J = 15.2 Hz, 1 H, C_6H_4C*H*), 7.48 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 9.68 (d, ^3J = 7.8 Hz, 1 H, C*H*=O).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (CH_3, 10), 24.3 (CH_2, 9), 38.0 (CH_2, 8), 127.7 (CH, 2), 128.5 (C_{ar}H, 5), 129.2 (C_{ar}H, 6), 131.5 (C, 4), 146.7 (C, 7), 153.0 (CH, 3), 193.8 (CH, 1).

IR (NaCl): $\tilde{\nu}$ = 2960s, 2868s, 2736m, 2362m, 1675s, 1618s, 1460m, 1423m, 1126s, 977s, 816s.

MS (EI, 70 eV, r.t.), *m*/*z* (%): 175 ([M+H]$^+$, 10), 131 ([C_9H_7O]$^+$,100), 117 (16), 91 ([C_7H_7]$^+$, 25).

3-(4-Butylphenyl)-propenal (120)[189]



Acroleindiethyl acetal (3.43 mL, 22.5 mmol), then tetrabutylammoniumacetate (4.52 g, 15.0 mmol), K_2CO_3 (1.56 g, 11.3 mmol), KCl (0.56 g, 7.50 mmol) and palladium acetate

(25.0 mg, 225 µmol) were added to a solution of 1-*n*-butyl-4-iodobenzene (1.33 mL, 7.50 mmol) in *N,N*-dimethylformamide (30 mL). After stirring for 2 hours at 90 °C and cooling to room temperature, 1 N HCl (30 mL) and Et_2O (120 mL) were added. Washing with ice water (280 mL), drying (Na_2SO_4) and concentration under reduced pressure gave a brown oil. The crude product was purified by flash column chromatography (SiO_2, 3 × 16 cm, ethyl acetate/hexanes 1:10) to give aldehyde **120** (1.31 g, 93%) as a yellow transparent oil.

$C_{13}H_{16}O$ (188.27):

R_f = 0.83 (ethyl acetate/hexanes 1:1).

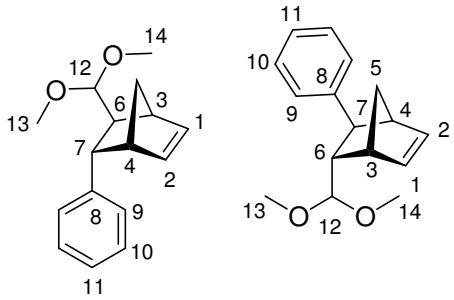
^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.3 Hz, 3 H, CH_3), 1.35 (sext, ^3J = 7.3 Hz, 2 H, CH_2CH$_3$), 1.61 (m, 2 H, CH_2CH$_2$CH$_3$), 2.65 (t, ^3J = 7.6 Hz, 2 H, CH_2CH$_2$CH$_2$CH$_3$), 6.69 (dd, ^3J = 15.6 Hz, ^3J = 7.8 Hz, 1 H, C*H*CH=O), 7.24 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 7.45 (d, ^3J = 14.7 Hz, 1 H, C$_6$H$_4$C*H*), 7.49 (d, ^3J = 8.1 Hz, 2 H, H_{ar}), 9.68 (d, ^3J = 7.6 Hz, 1 H, C*H*=O).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (CH_3, 11), 22.3 (CH_2, 10), 33.3 (CH_2, 9), 35.6 (CH_2, 8), 127.7 (CH, 2), 128.6 ($C_{ar}H$, 5), 129.2 ($C_{ar}H$, 6), 131.5 (C, 4), 146.9 (C, 7), 153.0 (CH, 3), 193.8 (CH, 1).

IR (NaCl): $\tilde{\nu}$ = 2956s, 2930s, 2862m, 1678s, 1619s, 1511m, 1461m, 1422m, 1297m, 1250m, 1125s, 975s, 815m.

MS (EI, 70 eV, r.t.), *m*/*z* (%): 188 ([M]$^+$, 7), 161 (12), 131 ([C_9H_7O]$^+$, 100), 117 (24), 91 ([C_7H_7]$^+$, 25).

***exo* 3-[(1*S*,2*S*,3*S*,4*R*)-Phenyl-bicyclo[2.2.1]hept-5-ene]-2-dimethoxymethane (126a) and *endo* 3-[(1*R*,2*S*,3*S*,4*S*)-Phenyl-bicyclo[2.2.1]hept-5-ene]-2-dimethoxymethane (126b)[107, 190]**



Cinnamaldehyde (131 µL, 1.00 mmol) was added to a solution of (5*S*)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone **23**·HCl (12.7 mg, 0.216 mmol) in MeOH/water (950 µL:50 µL). The solution was stirred for 2 minutes at room temperature before addition of cyclopentadiene (249 µL, 3.00 mmol). After stirring for 24 hours, the reaction mixture was diluted with Et_2O (20 mL), washed with water (50 mL) and then with

brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a colourless oil. The crude product was purified by flash column chromatography (SiO_2, 2 × 12 cm, ethyl acetate/hexanes 1:10) to give a mixture of *endo:exo* diacetales **126a** and **126b** (full conversion, *endo:exo* 41:59, *endo* ee 90%, *exo* ee 92%) as a colourless oil.

$C_{16}H_{20}O_2$ (244.33):

R_f = 0.37 (ethyl acetate/hexanes 1:10).

^{1}H NMR (400.1 MHz, $CDCl_3$): mixture of diastereoisomers δ = 1.50 (d, ^3J = 8.6 Hz, 2 H, C*H*), 1.69-1.79 (m, 3 H, C*H*), 2.03-2.06 (m, 1 H, C*H*), 2.40 (d, ^3J = 4.3 Hz, 1 H, C*H*), 2.53-2.57 (m, 1 H, C*H*), 2.89 (d, *J* = 13.9 Hz, 2 H, C*H*), 2.99 (d, *J* = 14.6 Hz, 2 H, C*H*), 3.09 (s, 3 H, CH_3, *exo*), 3.13 (s, 3 H, CH_3, *exo*), 3.34 (s, 3 H, CH_3, *endo*), 3.39 (s, 3 H, CH_3, *endo*), 3.95 (d, ^3J = 9.1 Hz, 1 H, C*H*$(OCH_3)_2$, *endo*), 4.37 (d, ^3J = 8.4 Hz, 1 H, C*H*$(OCH_3)_2$, *exo*), 5.94 (dd, ^3J = 5.8 Hz, *J* = 3.0 Hz, 1 H, CH=C*H*), 6.17 (dd, ^3J = 5.6 Hz, *J* = 2.8 Hz, 1 H, CH=C*H*), 6.36 (dd, ^3J = 5.6 Hz, ^3J = 3.0 Hz, 2 H, CH=C*H*), 7.14-7.39 (m, 10 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) mixture of diastereoiosmers: δ = 44.6 (CH), 45.3 (CH), 47.2 (CH_2), 47.3 (CH), 47.6 (CH_2), 47.6 (CH), 49.2 (CH), 49.2 (CH), 49.4 (CH), 49.8 (CH), 52.4 (CH_3), 52.4 (CH_3), 52.7 (CH_3), 53.5 (CH_3), 108 (CH, 12), 108.3 (CH, 12), 125.9 ($C_{ar}H$), 127.9 ($C_{ar}H$), 128.0 ($C_{ar}H$), 128.2 ($C_{ar}H$), 128.3 ($C_{ar}H$),128.4 ($C_{ar}H$), 135.2 (C, 1 or 2), 135,3 (C, 1 or 2), 137.4 (C, 1 or 2), 138.5 (C, 1 or 2), 144.3 (C, 8), 145.1 (C, 8).

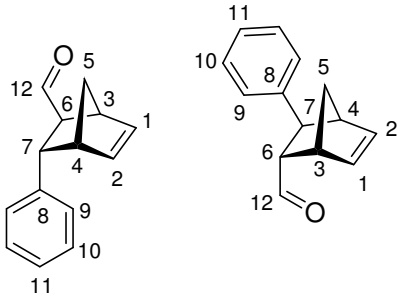
IR (KBr): $\tilde{\nu}$ = 2942s, 2829s, 1718s, 1602s, 1498s, 1458s, 1334m, 1132s, 1110s, 1060s.

$[\alpha]_D^{20}$ = +117.7 (c = 1.03, $CHCl_3$).

Chiral GC: ß-CD DetTButSil (SE54) column 60 °C → 180 °C (10 min), 1.5 °C/min, t_R = 59.1 min (*exo* minor), t_R = 61.8 (*exo* major), t_R = 62.3 min (*endo* minor), t_R = 62.7 (*endo* major).

The spectroscopic data are in agreement with that previously reported for the racemic *exo* compound.[191]

***exo* 3-[(1*S*,2*S*,3*S*,4*R*)-Phenyl-bicyclo[2.2.1]hept-5-ene]-2-carbaldehyde (127a) and *endo* 3-[[1*R*,2*S*,3*S*,4*S*]-Phenyl-bicyclo[2.2.1]hept-5-ene]-2-carbaldehyde (127b)[107, 190]**



Diacetale **126** was stirred in TFA:water:$CHCl_3$ (1:1:2, 12 mL) for 2 hours at room temperature. The reaction mixture was carefully neutralised with saturated aqueous $NaHCO_3$ (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a colourless oil. The crude product was purified by flash column chromatography (SiO_2, 2 × 12 cm, ethyl acetate/hexanes 1:10) to give a mixture of *endo:exo* DA aldehyde adducts **127a** and **127b** (full conversion, *endo:exo* 43:57, *exo* ee 89%, *endo* ee 89%) as a colourless oil.

$C_{14}H_{14}O$ (198.26):

R_f = 0.37 (ethyl acetate/hexanes 1:10).

^{1}H NMR (400.1 MHz, $CDCl_3$): mixture of diastereoisomers δ = 1.56 (ob. dq, ^3J = 8.8 Hz, J = 1.8 Hz, 1 H, CHCH*H*CH), 1.60-1.64 (m, 2 H, CHCH*H*CH), 1.80-1.83 (m, 1 H, CHCH*H*CH), 2.60 (dt, ^3J = 5.3 Hz, J = 2.0 Hz, 1 H, C*H*, *exo*), 2.97-3.00 (m, 1 H, C*H*, *endo*), 3.09-3.10 (m, 1 H, C*H*, *endo*), 3.13-3.14 (m, 1 H, C*H*, *endo*), 3.21-3.28 (m, 2 H, C*H*, *exo*), 3.33-3.34 (m, 1 H, C*H*, *endo*), 3.73 (dd, ^3J = 5.3 Hz, J = 3.6 Hz, 1 H, C*H*, *exo*), 6.07 (dd, ^3J = 5.6 Hz, J = 3.0 Hz, 1 H, CH=C*H*, *exo*), 6.17 dd, ^3J = 5.6 Hz, J = 2.8 Hz, 1 H, CH=C*H*, *endo*), 6.34 (dd, ^3J = 5.6 Hz, J = 3.8 Hz, 1 H, CH=C*H*, *exo*), 6.42 (dd, ^3J = 5.6 Hz, J = 3.3 Hz, 1 H, CH=C*H*, *endo*), 7.14-7.34 (m, 10 H, H_{ar}), 9.60 (d, ^3J = 2.3 Hz, 1 H, C*H*=O, *endo*), 9.93 (d, ^3J = 2.0 Hz, 1 H, C*H*=O, *exo*).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) mixture of diastereoiosmers: δ = 45.1 (CH, *endo*), 45.4 (CH, *exo*), 45.5 (CH, *exo*), 45.6 (CH, *endo*), 47.1 (CH_2, 5, *endo*), 47.6 (CH_2, 5, *exo*), 48.3 (CH, *endo*), 48.4 (CH, *exo*), 59.4 (CH, *exo*), 60.8 (CH, *endo*), 126.2 ($C_{ar}H$), 126.3 ($C_{ar}H$), 127.3 ($C_{ar}H$), 127.9 ($C_{ar}H$), 128.1 ($C_{ar}H$), 128.6 ($C_{ar}H$), 133.8 (CH, 1 or 2, *endo*), 136.3 (CH, 1 or 2, *exo*), 136.5 (CH, 1 or 2, *exo*), 139.2 (CH, 1 or 2, *endo*), 142.6 (C, 8, *exo*), 143.5 (C, 8, *endo*), 202.8 (C, 12, *exo*), 203.5 (C, 12, *endo*).

IR (KBr): $\tilde{\nu}$ = 3061s, 3027s, 2972s, 2874s, 2815s, 2716s, 1717s, 1601m, 1498m, 1452m, 1334m.

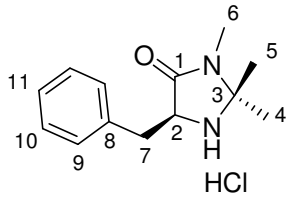
$[\alpha]_D^{20}$ = +164.9 (c = 1.08, $CHCl_3$).

Chiral GC: *β*-CD DetTButSil (SE54) column 60 °C → 180 °C (10 min), 1.5 °C/min, t_R = 58.2 min (*exo* minor), t_R = 58.5 (*endo* minor), t_R = 59.0 min (*exo* major), t_R = 59.6 (*endo* major).

The spectroscopic data are in agreement with that previously reported for the *endo* compound.[192]

5.4.2 Synthesis of Organocatalysts

(5*S*)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone hydrochloride (23·HCl)[107]



To (*S*)-phenylalanine methyl ester hydrochloride (4.80 g, 22.3 mmol) ethanolic $MeNH_2$ (8 M, 11 mL, 89.2 mmol) was added and stirred for 24 hours at room temperature. After removal of the solvent, the off-white residue was suspended in Et_2O and concentrated (4 ×). The amide hydrochloride was treated with saturated aqueous $NaHCO_3$ (20 mL) and extracted three times with dichloromethane (3 ×). The organic extracts were dried ($NaSO_4$) and the solvent was removed under reduced pressure to give a colourless oil which was dissolved in Et_2O. Upon addition of HCl solution (2 M in Et_2O) imidazolidinone **23** precipitated as colourless plates. Imidazolidinone **23**·HCl (1.04 g, 18%) was recrystallised from i-propanol.

$C_{13}H_{19}ClN_2O$ (254.12):

m.p. 144-146 °C (Et_2O).

R_f = 0.69 (dichloromethane/methanol 1:10).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, CHC*H*$_3$), 1.67 (s, 3 H, CHC*H*$_3$), 2.78 (s, 3 H, NC*H*$_3$), 3.33 (dd, ^2J = 15.1 Hz, ^3J = 5.0 Hz, 1H, CH*H*), 3.47 (dd, ^2J = 15.2 Hz, ^3J = 6.3 Hz, 1H, CH*H*), 4.40 (b s, 1H, C*H*), 7.24-7.35 (m, 3 H, H_{ar}), 7.46-7.47 (m, 3 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 24.2 (CH_3, 6), 24.6 (CH_3, 4/5), 25.1 (CH_3, 4/5), 34.4 (CH_2, 7), 57.9 (C, 3), 77.7 (CH, 2), 127.7 (CH, 11), 128.9 (C_{ar}H), 129.9 (C_{ar}H), 134.4 (C, 8), 166.0 (C, 1).

IR (KBr): $\tilde{\nu}$ = 3422s, 2915s, 2700s, 1724s, 1590s, 1428s, 1394s, 1319m, 1265m, 1161m, 1058m, 745m, 698m.

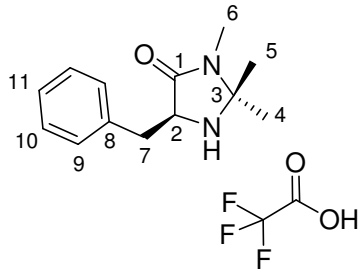
$[\alpha]_D^{20}$ = −110.6 (c = 1.00, MeOH, >99 ee).

EA calcd (%) for $C_{13}H_{19}ClN_2O$: C, 61.29; H, 7.52; N, 11.00. Found: C, 61.41; H, 7.45; N, 11.01.

HPLC (of the free secondary amine): Chiralcel OD-H, ethanol/heptane (4:96), 1.0 mL/min, 20 °C, 220 nm, t_R = 8.1 min (major), t_R = 9.2 min (minor).

The spectroscopic data are in agreement with that previously reported in the literature.[107]

(5*S*)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone trifluoroacetic acid (23·TFA)[193]



(5*S*)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone **23**·HCl[107] was dissolved in saturated aqueous $NaHCO_3$. The aqueous phase was extracted three times with dichloromethane. The organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a colourless oil, which was dissolved in Et_2O. Upon addition of trifluoroacetic acid imidazolidinone **23**·TFA precipitated as a colourless amorphous solid.

$C_{15}H_{19}F_3N_2O_3$ (332.32):

m.p. 144-145 °C (Et_2O).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.37 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 2.79 (s, 3 H, NCH_3), 3.18 (dd, ^2J = 15.2 Hz, ^3J = 7.6 Hz, 1H, CH_2), 3.18 (dd, ^2J = 15.2 Hz, ^3J = 4.8 Hz, 1H, CH_2), 4.26 (dd, ^3J = 7.3 Hz, ^3J = 5.0 Hz, 1H, CH), 7.23-7.32 (m, 5 H, H_{ar}), 7.96 (b s, 2 H, NH_2^+).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 23.0 (CH_3, 6), 24.8 (CH_3, 4/5), 25.1 (CH_3, 4/5), 30.7 (C, 3), 34.8 (CH_2, 7), 57.7 (CH, 2), 127.6 (CH, 11), 128.9 ($C_{ar}H$), 129.3 ($C_{ar}H$), 134.9 (C, 8), 167.2 (C, 1).

IR (KBr): $\tilde{\nu}$ = 2923s, 2748s, 2580s, 2480s, 1728s, 1658s, 1431s, 1396s, 1182s, 1129s, 839m, 724m, 696m.

MS (FAB, NBA (subtr)), *m*/*z* (%): 219 ([(M+H)-$C_2HF_3O_2$]$^+$, 100), 127 (25), 72 (20).

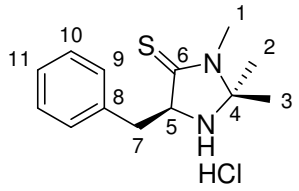
$[\alpha]_D^{20}$ = −64.7 (c = 1.00, MeOH, >99% ee).

EA calcd (%) for $C_{15}H_{19}N_2O_3$: C, 54.21; H, 5.76; N, 8.43. Found: C, 54.20; H, 5.80; N, 8.38.

HPLC (of the free secondary amine): Chiralcel OD-H, ethanol/heptane (4:96), 1.0 mL/min, 20 °C, 220 nm, t_R = 8.1 min (major), t_R = 9.2 min (minor).

The spectroscopic data are in agreement with that previously reported in the literature.[193]

(5*S*)-2,2,3-Trimethyl-5-benzyl-imidazolidine-4-thione hydrochloride (128·HCl)



Lawessons` reagent (2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane) (202 mg, 0.50 mmol) was added to a solution of (5*S*)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone **23**·HCl[107] (127 mg, 0.50 mmol) in toluene (2 mL). After heating for 30 minutes at reflux and cooling to room temperature, saturated aqueous $NaHCO_3$ was added and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to give a transparent colourless oil. The crude product was purified by flash column chromatography (SiO_2, 1 × 5 cm, ethyl acetate/hexanes 1:3) to give a transparent oil. It was dissolved in Et_2O and imidazoline-thione **128**·HCl (84 mg, 62%) precipitated upon addition of HCl (2 M in Et_2O) as a colourless amorphous solid.

$C_{13}H_{19}ClN_2S$ (270.82):

m.p. 133-134 °C (Et_2O).

R_f = 0.18 (ethyl acetate/hexanes 1:3).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 3.13 (s, 3 H, NCH_3), 3.59-3.61 (m, 1 H, CH_2), 4.76 (t, ^3J = 5.6 Hz, 1 H, C*H*), 7.25-7.34 (m, 3 H, H_{ar}), 7.52 (d, ^3J = 7.1 Hz, 2 H, H_{ar}).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 24.0 (CH_3, 2/3), 24.4 (CH_3, 2/3), 30.6 (CH_3, 1), 37.2 (CH_2, 7), 68.4 (CH, 5), 84.2 (C, 4), 127.8 ($C_{ar}H$, 11), 128.9 ($C_{ar}H$, 9), 130.0 ($C_{ar}H$, 10), 134.6 (C, 8), 192.4 (C, 6).

IR (KBr): $\tilde{\nu}$ = 2924s, 2517s, 2406s, 1498s, 1392s, 1271s, 1128s, 1055m, 1020m, 733s, 693s, 476s.

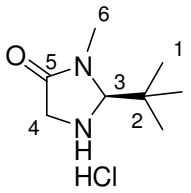
MS (EI, 70eV, ca. 100 °C), *m/z* (%): 234 ([M-HCl]$^+$, 73), 219 ([M-CH_3]$^+$, 35), 117 ([M-C_3H_8N]$^+$, 100), 160 (69), 143 (79), 128 (53), 104 (27), 91 ([C_7H_7]$^+$, 22), 58 ([C_3H_8N]$^+$, 15).

$[\alpha]_D^{20}$ = −109.0 (c = 0.30, MeOH).

EA calcd (%) for $C_{13}H_{19}ClN_2S$: C, 57.66; H, 7.07; N, 10.34. Found: C, 57.23; H, 6.92; N, 10.34.

HPLC (of the free secondary amine): Chiralcel OD-H, i-propanol/heptane (4:96), 0.5 mL/min, 20 °C, 220 nm, t_R = 19.3 min (major), t_R = 24.4 min (minor).

(*S*)-2-(*t*-Butyl)-3-methyl-4-imidazolidinone hydrochloride (130·HCl)



(*S*)-2-(*t*-Butyl)-3-methyl-4-imidazolidinone **130**·TFA[194] was dissolved in saturated aqueous $NaHCO_3$. The aqueous phase was extracted three times with dichloromethane. The organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a colourless oil which was dissolved in Et_2O. Upon addition of HCl solution (2 M in Et_2O) imidazolidinone **130**·HCl precipitated as a colourless amorphous solid.

$C_8H_{17}ClN_2O$ (192.69):

m.p. 172-173 °C (Et_2O).

^{1}H NMR (400.1 MHz, CD_2Cl_2): δ = 1.19 (s, 9 H, CH_3), 2.99 (s, 3 H, NCH_3), 3.75 (d, ^3J = 15.9 Hz, 1H, CH_2), 3.94 (d, ^3J = 15.9 Hz, 1H, CH_2), 4.61 (s, 1 H, CH).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ = 24.9 (CH_3, 1), 31.4 (CH3, 6), 36.6 (C, 2), 53.4 (CH_2, 4), 82.1 (C, 3), 190.1 (C, 5).

IR (KBr): $\tilde{\nu}$ = 2985s, 2928s, 2567s, 2463s, 2376s, 1710s, 1580s, 1776s, 1417s, 1327s, 1256s, 1123m, 1032m, 677m, 627m, 571m.

MS (FAB, NBA (subtr)), *m*/*z* (%): 310 (10), 157 ([(M+H)-HCl]$^+$, 100), 100 (19).

$[\alpha]_D^{20}$ = +55.8 (c = 1.00, MeOH).

EA calcd (%) for $C_8H_{17}ClN_2O$: C, 49.87; H, 8.89; N, 14.54; O, 8.30. Found: C, 49.93; H, 8.75; N, 14.53.

5.5 General Working Methods and Conditions for ESI MS Experiments

5.5.1 Bis(oxazoline)copper(II)-Catalysed Retro-Diels-Alder Reaction: General Method

The bis(oxazoline)copper(II)-catalysed retro-Diels-Alder reactions were conducted in 10 mL flasks equipped with a Young valve. The standard conditions were the following: Inside the glove box Cu(II)$(OTf)_2$ (1.8 mg, 5.0 µmol) and the appropriate ligand (5.5 µmol) were weighted into a flask. After connecting the flask to a Schlenk line dichloromethane (0.6 mL) was added and the reaction mixtures were stirred for 2.5 hours at room temperature. Then the quasienantiomers (*S*)-**80** and (*R*)-**88** (or (*R*)-**85** and (*S*)-**83**, respectively) (12.5 µmol each), pre-mixed in dichloromethane (0.6 mL) were added to the catalyst solution. The reaction mixture was stirred for 1 hour at 100 °C and cooled immediately in an ice bath. For ESI MS analyses aliquots of the reaction mixture were diluted to 10^{-5} M in dichloromethane, using 2 mL glass screw-thread-vials with septum and cut-out top caps. All solutions were filtered through syringe filters to eliminate any particle contaminations. The diluted solutions were directly injected in the mass spectrometer. The parameters used for the Varian 1200L Triple Quad MS/MS were: Drying Gas 100 °C, 17 psi; Capillary Voltage 38 V; Needle Voltage 4900 V; Needle Current -2 µA, Shield Voltage 600 V; Housing 49 °C, 40 psi. Every spectrum consisted of at least 25 averaged scans. Best spectra were obtained by applying 35 µL/min as flow rate, using a single syringe pump Model 11 Plus from *Harvard Apparatus*.

The selectivity of the catalyst was obtained by determination of the area-under-the-curve (integration) of the major mass peak of the isotope pattern for both dienophile complexes. Considering all four major mass peaks of the isotope pattern produced the same results. Generally, the spectra were recorded both in the centroid and profile mode.

For verification of the ESI MS results, HPLC samples were prepared by filtrating the reaction mixture through a small plug of silica gel (ethyl acetate/Et_2O 1:1, eluation with Et_2O), followed by removal of the solvent under reduced pressure. **HPLC**: Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm/259nm, t_R = 34.6 min (*n*-Bu-dienophile **67**), t_R = 40.0 min (Et-dienophile **64**). Validation curves for both dienophiles **64** and **67** were made to ensure the correlation of the dienophile ratio in the sample with the integration of the HPLC peak.

The preparative Diels-Alder reaction was done under similar conditions as the retro reaction. The standard procedure was the following: Inside the glove box Cu(II)$(OTf)_2$ (4.50 mg,

12.5 µmol) and the appropriate ligand (13.7 µmol) were weighted into a flask. After connecting the flask to a Schlenk line dichloromethane (0.3 mL) was added and the reaction mixture were stirred for 2.5 hours at room temperature. The reaction mixture was cooled to -78 °C and dienophile **67** (19.0 mg, 62.3 µmol) in dichloromethane (0.3 mL) was added and immediately after cyclopentadiene (0.05 mL, 0.623 mmol). After stirring the reaction mixture for 1 hour at 100 °C (or 20 hours at room temperature or 48 hours at -35 °C, respectively), the reaction mixture was filtered through a plug of silica gel (ethyl acetate/Et_2O 1:1). After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (SiO_2, ethyl acetate/hexanes 1:5) to give DA adduct **83**. The enantiomeric excess was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane (5:95), 0.5 mL/min, 20 °C, 210 nm, t_R = 19.1 min (major), t_R = 44.0 min (minor)).

5.5.2 Phosphinooxazolinecopper(II)-Catalysed Retro-Diels-Alder Reaction

As described in Section 5.5.1 Cu(II)$(OTf)_2$ (0.9 mg, 2.5 µmol) and ligands **33a-33h** (2.75 µmol) were stirred in dichloromethane (0.3 mL) for 2 hours at room temperature. The quasienantiomers (*S*)-**80** and (*R*)-**88** (6.25 µmol each), premixed in dichloromethane (0.3 mL), were added to the catalyst solution. The reaction mixture was stirred for 1 hour at 100 °C and cooled immediately in an ice bath. ESI MS analyses were done as described in Section 5.5.1.

The preparative, forward reaction was done according to the procedure for the bis(oxazoline)copper(II)-catalysed Diels-Alder reactions (Section 5.5.1).

5.5.3 Bis(imine)copper(II)-Catalysed Retro-Diels-Alder Reaction

As described in Section 5.5.1 Cu(II)$(OTf)_2$ (0.9 mg, 2.5 µmol) and ligands **34d** or **34e** (2.75 µmol) were stirred in dichloromethane (0.3 mL) for 5 hours at room temperature. The quasienantiomers (*S*)-**80** and (*R*)-**88** (6.25 µmol each), premixed in dichloromethane (0.3 mL), were added to the catalyst solution. The reaction mixture was stirred for 1 hour at 100 °C and cooled immediately in an ice bath. ESI MS analyses were done as described in Section 5.5.1.
The preparative, forward reaction was done according to the procedure for the bis(oxazoline)copper(II)-catalysed Diels-Alder reactions (Section 5.5.1), except that the catalyst solution was stirred for 5 hours at room temperature instead of 2 hours.

5.5.4 Organocatalysed Retro-Diels-Alder Reaction

The organocatalysed retro-Diels-Alder reaction was conducted in 2 mL glass screw-thread-vials with septum and cut-out top caps. The standard conditions were the following: The quasienantiomers (*S*)-**113** and (*R*)-**118** (or (*R*)-**116** and (*S*)-**114**, respectively)(3.12 µmol each) were dissolved in dichloromethane (150 µL) and the organocatalyst (1.25 µmol) was added. The reaction mixture was stirred for 24 hours at room temperature.

When screening mixtures of organocatalysts 10 mL flasks equipped with a Young valve were employed. The reaction mixture was stirred for 1 hour at 50 °C and immediately cooled to room temperature.

For ESI MS analyses aliquots of the reaction mixture were diluted to 10^{-4} M in acetonitrile. For ESI MS analyses of organocatalyst mixtures the reaction mixtures were diluted to 10^{-3} M in acetonitrile. All solutions were filtered through syringe filters to eliminate any particle contamination. The diluted solutions were directly injected in the mass spectrometer. The parameters used for the Varian 1200L Triple Quad MS/MS were: Drying Gas 200 °C, 18 psi; Capillary Voltage 38 V; Needle Voltage 4900 V; Needle Current 1 µA, Shield Voltage 600 V; Housing 49 °C, 40 psi. Every spectrum consisted of at least 25 averaged scans. Best spectra were obtained by applying 20 µL/min as flow rate, employing a single syringe pump Model 11 Plus from *Harvard Apparatus*.

The preparative Diels-Alder reaction was done according to a varied procedure by MACMILLAN.[107] Cinnamaldehyde **123** (136 µL, 1.08 mmol) was added to a solution of (5*S*)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone **23**·HCl (55.0 mg, 0.216 mmol) in dichloromethane (11 mL). The solution was stirred for 2 minutes before addition of cyclopentadiene (0.27 mL, 3.24 mmol). After stirring for 24 hours at room temperature, the reaction mixture was washed with water (50 mL) and then with brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product. It was purified by flash column chromatography (SiO_2, 1 × 12 cm, ethyl acetate/hexanes 1:10) to give DA adduct **126** as a colourless transparent oil. The enantiomeric excess and diastereoselectivity were determined by chiral GC (ß-CD DetTButSil (SE54) column 60 °C → 180 °C (10 min), 1.5 °C/min, t_R = 58.2 min (*exo* (*R*)), t_R = 58.5 (*endo* (*R*)), t_R = 59.0 min (*exo* (*S*)), t_R = 59.6 (*endo* (*S*)).

5.5.5 Peptide-Catalysed Retro-Diels-Alder Reaction

The peptide-catalysed retro-Diels-Alder reaction was conducted in 2 mL glass screw-thread-vials with septum and cut-out top caps. The standard conditions were the following: The quasienantiomers (*S*)-**113** and (*R*)-**118** (or (*R*)-**116** and (*S*)-**114**, respectively) (3.12 µmol each) were dissolved in MeOH (150 µL), then the peptide (1.25 µmol) was added and the reaction mixture was stirred for 24 hours at room temperature.

When screening mixtures of peptides 10 mL flasks equipped with a Young valve were employed. The reaction mixture was stirred for 1 hour at 50 °C and immediately cooled to room temperature.

For ESI MS analyses aliquots of the reaction mixture were diluted to 10^{-3}-10^{-4} M in MeOH. All solutions were filtered through syringe filters to eliminate any particle contamination. The diluted solutions were directly injected in the mass spectrometer. The parameters used for the Varian 1200L Triple Quad MS/MS were: Drying Gas 200 °C, 18 psi; Capillary Voltage 40 V; Needle Voltage 4900 V; Needle Current -1 µA, Shield Voltage 600 V; Housing 49 °C, 40 psi. Every spectrum consisted of at least 25 averaged scans. Best spectra were obtained by applying 30 µL/min as flow rate, employing a single syringe pump Model 11 Plus from *Harvard Apparatus*.

The preparative peptide-catalysed Diels-Alder reaction was done according to the following procedure: Cinnamaldehyde **123** (63.0 µL, 0.50 mmol) was added to a solution of peptide **141**·TFA (44.0 mg, 0.216 mmol) in MeOH (500 µL). The solution was stirred for 2 minutes before addition of cyclopentadiene (124 µL, 1.50 mmol). After stirring for 24 hours, the reaction mixture was diluted with Et_2O (20 mL), washed with water (20 mL) and then with brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was hydrolised by stirring in TFA:water:$CHCl_3$ (1:1:2, 12 mL) for 2 hours at room temperature. The reaction mixture was carefully neutralised with saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 1 × 10 cm, ethyl acetate/hexanes 1:10) to give DA adduct **126** as a colourless transparent oil. The enantiomeric excess and diastereoselectivity were determined by chiral GC (*ß*-CD DetTButSil (SE54) column 60 °C → 180 °C (10 min), 1.5 °C/min, t_R = 58.2 min (*exo* (*R*)), t_R = 58.5 (*endo* (*R*)), t_R = 59.0 min (*exo* (*S*)), t_R = 59.6 (*endo* (*S*)).

Chapter 6

Appendix

6 Appendix

6.1 X-Ray Crystal Structures

X-ray data analyses were carried out and crystal structures were solved by Markus Neuburger and Dr. Sylvia Schaffner at the Department of Chemistry of the University of Basel.

Single crystals for (*R*)-**86** were obtained through crystallisation by dissolving the product in Et_2O and carefully adding a layer of pentane. Data collection was performed with a Nonius KappaCCD diffractometer. Measurements were recorded at 173 K. The structure was solved with SIR92[195] and refinded with crystals.[196] CHEBYCHEV polynomial weights were used to complete the refinement. Hydrogen atoms were calculated and refined as riding atoms.[197] The absolute configuration and enantiopurity was determined by refinement of the flack parameter.[198] The refined structure was checked with checkcif.[199]

Compound	(*R*)-**86**
Molecular Formular	$C_{20}H_{23}N_1O_1S_2$
Formulat Weight	357.54
Shape	Plate
Colour	Colourless
Temperature (K)	173
Crystal Size (mm^3)	0.05×0.11×0.28
Crystal System	monoclinic
Space Group	P 1 2_1 1
a (Å)	6.1870(3)
b (Å)	9.9672(3)
c (Å)	14.8721(8)
α (°)	90
β (°)	92.571(4)
γ (°)	90
Volume ($Å^3$)	916.20(7)
Z	2
$Density_{calc.}$ (mg m^{-3})	1.296
Absorption coeff. (mm^{-1})	0.297
Radiation type (λ [Å])	MoK_α (0.71073)
F (000)	380
Completeness to Θ_{max} (%)	0.99
Reflections measured	28497
Reflections independent	4409
Reflections used	3981
Number of parameters	218
R (observed data)	0.0284
wR (all data)	0.0306
Goodness of fit on F	1.1035
Residual density (e $Å^{-3}$)	-0.16/0.22
Flack-parameter	-0.07(4)
CCDC deposition code	-

Chapter 7

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7 Bibliography

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Publications

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B. C. Sih, A. Teichert, M. O. Wolf *Chem. Mater.* **2004**, *16*, 2712-2718. *Electrodeposition of Oligothiophene-Linked Gold Nanoparticle Films*

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Eidesstattliche Erklärung

Ich erkläre, dass ich die Dissertation „Screening of Chiral Diels-Alder Catalysts by Mass Spectrometric Monitoring of the Retro Reaction“ nur mit der darin angegebene Hilfe verfasst und bei keiner anderen Universität und bei keiner anderen Fakultät der Universität Basel eingereicht habe.

Basel, 22. Oktober 2007 Antje Teichert