A New Methodology for Copper(II)-Catalyzed Enantioselective Photoinduced Electron Transfer-Mediated Radical Cyclizations

DISSERTATION

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My dear Nina
and
My Parents
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1 Abstract

The aim of this work was to develop a methodology for catalytic and potentially enantioselective photoreactions and especially cyclizations. In general, cyclizations triggered by photoinduced electron transfer (PET) of suitably functionalized acyclic polyalkene terpenoids, which mimic non-oxidative biosynthetic transformations, are shown to be a powerful method for the single step synthesis of mono- and mainly all-trans-fused polycyclic compounds. Majorly these target molecules are of relevance in view of their biological activity. However, the method lacks access to the targets in a catalytic way including enantioselectivity. A combination of these two actual demands would be of great value for synthetic applications.

The previous strategies toward enantioselective PET-initiated transformations are based on introducing a chiral auxiliary into the substrate to be cyclized. The advantage of this approach is that it usually provides a good to excellent enantioselectivity, but the main disadvantages are the impossibility to use the chiral part in a catalytic amount together with the necessity to remove the chiral auxiliary after reaction.

The utility of PET-induced cyclizations would therefore be greatly increased if it will be possible to use a chiral medium in catalytic amounts. The most promising approach toward catalytic enantioselective photochemical transformations of this sort is the use of chiral organometallic complexes as catalysts, which are able to influence the geometry and reactivity of the substrates serving the attempted purpose.

In the beginning of this work the methodology for photoinduced electron transfer (PET)-initiated cyclizations, catalyzed by organometallic chiral Lewis acids, was developed and the following parameters adjusted: Design of a chiral metal-ligand catalyst and evaluation of the proper PET-reaction conditions (electron donor/acceptor couple, solvent, wavelength of irradiation and light stability of the reaction components).
As ligands, bisoxazolines (BOX) having C₂-symmetry, were chosen. Due to this symmetry the coordination sites of the BOX ligands are homotopic rendering less uncertainty with respect to the nature of catalyst-substrate complexation.

\[
\begin{align*}
\text{BOX} & \quad \text{PyBOX} \\
R = \text{t-Bu, Ph} & \quad R_1 = \text{Ph, Et}
\end{align*}
\]

The cationic electron acceptor N-methylacridinium hexafluorophosphate (NMA⁺PF₆⁻) is employed together with biphenyl (BP) as electron acceptor couple. A cationic acceptor is utilized here in order to be able to work in an apolar solvent, which will not interfere with complexation of the substrate and catalyst.

\[
\begin{align*}
\text{NMA} & \quad \text{BP}
\end{align*}
\]

In accordance with Irving-Williams stability & kinetic order for M(II):

\[
\text{Mn} < \text{Fe} < \text{Co} < \text{Ni} < \text{Cu} > \text{Zn},
\]

Cu(II) forms the most stable ligand-metal complexes and, in an apparent paradox, the exchange rate of Cu•(H₂O)₆ is greater than those of other first row divalent transition metal ions. This effect is consistent with labilization of axial ligands through Jahn-Teller distortion, which provides enhanced stability for ligands in equatorial position while weakening the two axial coordination sites.

\[
\begin{align*}
\text{Cu} & \quad \text{Jahn-Teller distortion} & \quad \text{Cu} \\
\text{Cu} & \quad \text{L} & \quad \text{L}
\end{align*}
\]

\[
\begin{align*}
\text{Cu} & \quad \text{L} \\
\text{Cu} & \quad \text{L}
\end{align*}
\]

= stronger coordinating site; \quad = weaker coordinating site

In case of three-coordinating PyBOX ligands, which usually coordinate in equatorial position, Jahn-Teller distortion should enable a better stability of the
chiral metal-ligand complex (catalyst) and at the same time enhance the exchange rate of the substrate with the catalyst. By this reason the Cu(II) ion together with the C2-symmetric Ph-PyBOX ligand 41 was found to be the best molecular arrangement for catalysis in PET-initiated cyclizations.

The Cu(II)/Ph-PyBOX complex shows absorption up to 350 nm. To avoid photochemical excitation of the catalyst, the use of a G.W.V.-glass filter is necessary (less than 10% transmission at 366 nm).

By this way we overcame the main problem of previous investigations, where the reactive complex was unstable under irradiation conditions not using a filter system.

Thus, conditions were found which enable strong complexation of the chiral ligand to the metal center. On the other hand weak complexation of substrate-catalyst can be achieved, being a necessary condition for catalysis.

Then the newly developed methodology was probed in different applications aiming at catalytic and asymmetric PET-triggered cyclizations.

Compound 68, containing an oxazolidinone template, was applied as a substrate. Oxazolidinones are among the most widely used templates for the evaluation of enantioselective transformations so far in the ground state.

Irradiation of 68 at 400 nm in CH₂Cl₂ in the presence of NMA⁺PF₆⁻/BP as electron acceptor couple leads to very poor conversion of starting material and no formation of cyclic products was found, even after longer reaction times. However, when the same reaction was conducted in presence of one equivalent of complex 56, the cyclic product 74 resulted in 28% yield.
Lowering of the chiral complex loading to 0.3 equivalent leads to slight decrease in yield (28% → 26%) only, showing the catalytic nature of the complex 56 in this reaction.

Furthermore, it was shown for the first time that PET-initiated cyclizations can be performed catalytically and enantioselectively. It was found that the enantioselectivity for the formation of the \textit{trans}-74 shows no dependence of the substrate-chiral Lewis acid (\textit{R})-56 proportion (~9% e.e.). However, the enantioselectivity of formation of \textit{cis}-74 is dependent on the substrate-catalyst proportion and the catalyst configuration giving 17.1% e.e. with 1 equiv. of (\textit{R})-56 (see Table below).

\textbf{Enantioselectivity of cyclizations 68→74 in presence of complex 56}

<table>
<thead>
<tr>
<th>Catalyst loading</th>
<th>Configuration of 56</th>
<th>\textit{trans}-74 enantiomeric ratio (e.e.)</th>
<th>\textit{cis}-74 enantiomeric ratio (e.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 equiv.</td>
<td>(S)</td>
<td>1 : 1.070</td>
<td>1 : 1.183 (8.4%)</td>
</tr>
<tr>
<td>0.3 equiv.</td>
<td>(S)</td>
<td>1 : 1.043</td>
<td>1 : 1.111 (5.3%)</td>
</tr>
<tr>
<td>0.3 equiv.</td>
<td>(R)</td>
<td>1 : 1.205 (9.3%)</td>
<td>1 : 1.002</td>
</tr>
<tr>
<td>1.0 equiv.</td>
<td>(R)</td>
<td>1 : 1.193 (8.8%)</td>
<td>(17.1%) 1.413 : 1</td>
</tr>
</tbody>
</table>
Moreover, it was shown that the enantioselectivity depends on the orientation of the radical-accepting double bond relative to the metal center of the catalyst, i.e. giving enantioselectivity for $68 \rightarrow 74$ and no selectivity for $78a-b \rightarrow 80a-b$.

To check the applicability of the newly developed methodology to other templates, the $\beta$-ketoesters $78a$ and $78b$, which should provide sufficient complexation capacity to the metal center of the catalyst with the two available carbonyls, were cyclized.

Adopting these conditions, PET-induced cyclization of substrate $78a$ leads to the formation of a six-membered ring ($\rightarrow 80a$) in 28% yield. Moreover, when the methylated compound $78b$ was taken as substrate, the corresponding cyclic product was formed in 44% yield.

Application of 1 equivalent of $92$, instead of $56$, leads to lower yields (12-13%) of $80a$ and $80b$.

To examine the catalytic nature of reaction, the cyclizations of $78a$ and $78b$ with 0.1 equivalent of the catalyst were performed.

For example, the cyclizations of $78a$ and $78b$ proceeded with comparable yields in presence of 1 and 0.1 equivalents of $92$. In examples where the reaction was catalyzed by $56$, lower product yields were obtained (see table below).
<table>
<thead>
<tr>
<th></th>
<th>1 equivalent of 56</th>
<th></th>
<th>0.1 equivalent of 56</th>
<th></th>
<th>0.1 equivalent of 92</th>
<th></th>
<th>0.1 equivalent of 92</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yield (%)</td>
<td>conv. (%)</td>
<td>time (day)</td>
<td>yield (%)</td>
<td>conv. (%)</td>
<td>time (day)</td>
<td>yield (%)</td>
</tr>
<tr>
<td>$R^1 = \text{Me}$</td>
<td>44</td>
<td>91</td>
<td>1</td>
<td>12</td>
<td>49</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>$R^1 = \text{H}$</td>
<td>28</td>
<td>98</td>
<td>4</td>
<td>16</td>
<td>73</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

However, no relevant induction was determined so far for $\text{78} \rightarrow \text{80}$, based on chromatographic evaluation demonstrating dependence of enantioselectivity on the template type.

A potential mechanism of the cyclizations is also discussed in this work. Possible improvements of the methodology to reach higher enantioselectivity in this type of reactions are proposed.
2 Introduction

2.1 Theoretical aspects of photochemical electron transfer (PET) in view of radical cyclizations

In the last decades electron transfer photochemistry became a leading method in modern photochemistry.

The oxidative photo-induced electron transfer (PET)\(^1\) is a handy and versatile method for the conversion of acyclic polyalkene terpenoids into cyclic and polycyclic products with high stereo- and regioselectivity.\(^2,3\)

According to a simplified molecular orbital picture, electron transfer can formally be described in terms of electron motion between occupied and unoccupied orbitals of sensitizer and quencher (Diagram 1).

Diagram 1: Energetics of electron transfer when the sensitizer is the electron acceptor (left side), and the sensitizer is the electron donor (right side). IP – ionisation potential of donor, EA – electron affinity of acceptor

[Diagram showing electron transfer processes with energy levels]

The possibility of electron transfer between an electronically exited sensitizer and a quencher is dictated by the overall change in free energy \(\Delta G\). The major requirement is exothermicity (\(\Delta G < 0\)).
The role of free energy in electron transfer can be examined in terms of simplified molecular orbital diagram (Diagram 1). The unoccupied orbital of the acceptor receives an electron from an occupied orbital of the donor in an exothermic process. Thus the absorption of light reduces the ionisation potential of donor ($IP_D$) and electron affinity of acceptor ($EA_A$).

For electron transfer between two ground state species, the standard free energy change in the gas phase is:

$$\Delta G = IP_D - EA_A$$

$IP_D$ and $EA_A$ are normally estimated from the energies of the highest occupied molecular orbital and lowest unoccupied molecular orbital of donor and acceptor, respectively.

If the acceptor is excited:

$$EA_A^{\cdot} = EA_A + EA^*$$

$$\Delta G = IP_D - EA_A^\cdot - EA^*$$

If the donor is excited:

$$IP_D^{\cdot} = IP_D - ED^*$$

$$\Delta G = IP_D - EA_A - ED^*$$

To obtain a more detailed picture of the overall free energy changes, one must account for the Coulombic interactions and solvent stabilization effects of the charge transfer intermediates.

In solution, formation of an ion pair is accompanied by two interactions:

- the formation of two charged species in close proximity which results in a Coulombic interaction ($C$)
- the solvation of the ion pair ($Esolv$).

These effects can be included into the above-mentioned equations to obtain:

$$\Delta G = IP_D - EA_A - E_A^* - Esolv - C \quad \text{for excitation of acceptor}$$

$$\Delta G = IP_D - EA_A - ED^* - Esolv - C \quad \text{for excitation of donor}$$

If a solvent-separated ion pair dissociates into free ions so that they are sufficiently separated from their Coulombic fields or if the solvent has a large dielectric constant, the Coulombic energy can be neglected. For example, in acetonitrile ($\varepsilon_s = 37$) Coulombic energy is less than 1.3 kcal/mol (0.06 eV) at
separation distances ~7 Å) in contrast to a value of ~ 0.3 eV in low-polarity solvents where $\varepsilon_s = 4$ (CHCl₃).

The nature of the medium can have an important influence on the rate of electron transfer processes which lead to generation or disappearance of polar species. Upon photochemical excitation of a “collision complex” (when the reactant partners are in contact) an exciplex (EXC) is formed. If the transfer of an electron occurs during the lifetime of the exciplex a “contact ion pair” (CIP) forms immediately.

The critical step is stabilisation of the contact ion pair by separation to a “solvent-separated” ion pair (SSIP) giving then rise to the formation of free ions (FI). By this reason the majority of photosensitized electron transfer processes have been investigated in polar, good solvating solvents, such as acetonitrile, which can critically minimize back electron transfer (BET).

\[
\begin{align*}
A + D & \xrightarrow{\text{Excitation}} (A^\circ D^+)^s \\
& \xrightarrow{\text{ET}} (A^-D^+^\circ) \\
& \xrightarrow{\text{BET}} (A_s^-D_s^+^\circ) \\
& \xrightarrow{\text{SSIP}} A_s^- + D_s^+ \\
& \xrightarrow{\text{FI}}
\end{align*}
\]

Back electron transfer is a universal feature of the overall process, which decreases the efficiency of product formation by competing with separation of the radical ions. Even when reactions are fast enough to occur, their efficiencies are usually low due to competition with back electron transfer. The back electron transfer was found to be strongly dependent on exothermicity. The higher the reaction exothermicity is, the faster occurs the back electron transfer. According to this reason, the use of a strong electron donor with a strong electron acceptor is inefficient due to fast back electron transfer.

The use of electron co-acceptors (e.g. phenanthrene or 1,1'-biphenyl (BP)) can positively influence the reaction course and efficiency. They act as a catalyst offering additional charge delocalization among the respective acceptor pair which helps to slow down the BET process and gives usually rise to higher quantum yields of free ion-radical formation and hence to increased product yields shorting also noticeably the reaction time.
The role of the co-acceptor (CA) as a catalyst can be described by the following reactions:

\[
A^* + CA \rightarrow A^* - + CA^{*+} \\
CA^{*+} + D \rightarrow CA + D^{*+}
\]

Initially, electron transfer from CA to the electronically excited acceptor (A*) forms a radical anion (A\(^{-}\)) and the radical cation of the co-acceptor (CA\(^{*+}\)). Subsequent electron transfer from the donor (D) to CA\(^{*+}\) regenerates CA. Recently, the methodology for the PET-initiated cyclization in solvents of low polarity was developed by Demuth and co-workers.\(^6\) This methodology involves the use of the cationic acceptor N-methylquinolinium hexafluorophosphate (NMQ\(\cdot\)PF\(_6\)) together with biphenyl as electron acceptor couple. This acceptor couple has been proven effective for cyclizations of acyclic terpenoids in low-polarity solvents, such as in a dichloromethane/methanol (4:1) mixture. In this case, electron transfer to the excited state of the cationic acceptor from a neutral donor results in the formation of a neutral radical / radical cation pair in which there is no Coulombic barrier to separation.

2.2 PET-initiated cyclizations of polyalkene terpenoids into cyclic products

PET-initiated cyclizations of acyclic polyalkene terpenoids are shown to be a powerful method for the single step synthesis of mono- and mainly all-trans-fused polycyclic compounds.\(^2,3,7,8\) It is widely accepted that such reactions proceed through radical-type intermediates. This methodology based on the highly regioselective creation of a radical cation at the \(\omega\)-alkene site of the starting acyclic polyalkene.

According to a recent investigation toward the mechanism of PET-induced cyclizations, the initially formed cation radical can be efficiently intercepted by the protic nucleophile (e.g. water, methanol, ethanol, isopropanol) present in the
reaction mixture. The nucleophile adds highly stereoselectively in anti-Markovnikov manner to the ω-alkene of the polyalkene substrate. The proposed mechanism for such transformations is described in Scheme 1.

The electron transfer from the electron co-acceptor (CA) to the excited electron-acceptor (A) leads to the formation of an $A^+$/CA$^+$ pair (equation 1). Subsequently, regioselective single-electron transfer from the ω-alkene site of the starting acyclic polyalkene 1 to CA$^+$ affords radical cation 2, which is highly regioselectively trapped in anti-Markovnikov manner by the protic nucleophile (e.g. water, methanol). The resulting neutral radical undergoes cyclization to form the cyclic radical 3 (case [a]) or radical 4 (case [b]). The reduction of the final tertiary radical center by $A^+$ leads to the corresponding anion, followed by proton addition, resulting in the cyclic products 5 (case [a]) or 6 (case [b]), respectively.

**Scheme 1:** PET-initiated cyclizations of acyclic polyalkenes in protic nucleophile-containing media

PET

1) $A^+ + CA \rightarrow A^- + CA^+$

2)

$\text{A} = \text{acceptor}$

$\text{CA} = \text{co-acceptor}$
In early experiments such type of transformations were performed best in the presence of benzene-1,4-dicarbonitrile together with phenanthrene as an electron acceptor couple and in micellar media\textsuperscript{7}, since in homogeneous solution \textit{cis/trans}-isomerization at the \textit{\alpha}-alkene site predominated. Later investigations have demonstrated that these cyclizations proceed also in homogeneous media upon proper choice of reaction conditions. Best results were achieved when 2,3,5,6-tetramethylbenzene-1,4-dicarbonitrile in combination with BP as the electron-acceptor couple under 300nm irradiation in MeCN / H\textsubscript{2}O 4:1 or MeCN / MeOH 4:1 was used. 15-30\% product yields were achieved under these conditions (Scheme 1, case [a]).\textsuperscript{8}

In case of PET-initiated cyclizations of polyalkene derivatives containing strong electron-withdrawing functional groups (e.g. -CN, -COOR), at the \textit{\alpha}-alkene, the cyclization leads exclusively to products containing a five-membered ring in higher yields (55-65\%, Scheme 1, case [b]).\textsuperscript{2,8,11}

The reason for increased yields and a different product pattern in case [a] in comparison with [b] is explained by enhanced stabilization of the malonodinitrile radical intermediate resulting from 5-\textit{exo} cyclization as compared with radical intermediates which would result from 6-\textit{endo} closure.

The examples of Gassman\textsuperscript{12} (Scheme 2, 7 → 8+9) and Roth\textsuperscript{13} (Scheme 2, 10 → 11) represent the applicability of intramolecular functionalities as a nucleophile. In both examples the products of \textit{anti-Markovnikov} addition of the nucleophile are predominant.
**Scheme 2:** Examples of intramolecular *anti*-Markovnikov addition

\[
\begin{align*}
\text{TMDCB} / \text{BP} & \quad \text{CH}_3\text{CN} / \text{H}_2\text{O} \\
7 & \xrightarrow{300 \text{ nm}} 8 + 9 \\
7 & \xrightarrow{\text{PET}} 10 \rightarrow 11
\end{align*}
\]

\[\text{TMDCB} = 2,3,5,6\text{-tetramethylbenzene-1,4-dicarbonitrile}\]

In solvents of low polarity and in the absence of a protic nucleophile the formation of elimination products predominate (Scheme 3, 13+14 case [a]). However, in polar solvents, such as acetonitrile, mainly the bicyclic tetrahydrofuran 15 is formed besides the elimination product 13 being a minor component (Scheme 3, case [b]).

**Scheme 3:** PET-initiated cyclizations in the absence of a protic nucleophile

\[
\begin{align*}
\text{PET} & \quad \text{CH}_2\text{Cl}_2 \\
12 & \xrightarrow{\text{PET}} 13 + 14 + 15 \\
\text{Conversion 43 \%} & \quad \text{Conversion 35 \%} \\
\text{[a]} & \quad \text{[b]}
\end{align*}
\]
The examples of PET-initiated radical cyclization involving radical addition to an aromatic ring were achieved in the group of Demuth (Scheme 4).¹⁵ The conditions for these PET-initiated transformations were adopted from earlier work in this field. The reactions were performed in CH₃CN/H₂O (4:1) solutions in the presence of 1,4-dicyanotetramethylbenzene (DCTMB) and BP as electron-acceptor couple.

**Scheme 4:** PET-initiated radical cyclization involving radical addition to an aromatic ring

Mechanistically, the reactions in Scheme 4 are assumed to follow the reaction scheme proposed for non-aromatic acyclic polyterpenoids (Scheme 1) initiated by formation of a radical cation at the ω-alkene (16 → 17) prior to cyclization, but with a different termination step. The termination of such cyclizations probably involves electron transfer from 18 to the oxidizing species (DCTMB or BP⁺⁺), followed by loss of a proton (Scheme 5, [a]). Another possible termination pathway is a loss of hydrogen radical from 18 to give the aromatic product 19 (Scheme 5, [b]).
**Scheme 5**: Proposed reaction mechanism for cyclizations of aromatic acyclic terpenoids

![Scheme 5](image)

2.3 Enantioselective PET-initiated cyclizations of polyalkene terpenoids with a chiral auxiliary

The importance of single-enantiomer synthesis cannot be overstated. In 1999, 33% of all dosage form drug sales were single-enantiomer formulations; this had risen to 40% in 2001. In addition, 80% of new drugs entering development are enantiomerically pure. It is not surprising therefore, that the design of reagents for achieving high enantioselectivities during free-radical transformations continues to be one of the main fields of interest of many organic chemists. Enantioselective PET-initiated transformations are not well explored under this light. The previous strategies toward enantioselectivity in such transformations are based on introducing a chiral auxiliary into the substrate.

One of the best examples of this approach is the synthesis of an enantiomerically pure (ee > 99%) steroid polycycle by biomimetic cascade cyclization performed by Heinemann.\(^\text{16}\) In this PET-induced cyclization the formation of eight stereocenters in one step was achieved and, most notably, out of 254 possible stereoisomers only 2 were obtained in 10-12% yield (Scheme 6).\(^\text{16}\)
Scheme 6: Highly diastereoselective PET-initiated cyclization of a terpenoid polyalkene

The advantage of the approach employing a chiral auxiliary is that it usually provides a good to excellent enantioselectivity, but the main disadvantages are the impossibility to use the chiral part in a catalytic amount together with the necessity to remove the chiral auxiliary after reaction (except in the case when the chiral auxiliary is part of the target structure as in the example in Scheme 6).

The utility of PET-triggered cyclizations would therefore be greatly increased if it will be possible to use a mediator of chirality in catalytic amounts.

Enantioselectivity in photochemical transformations can principally be achieved by the following ways:

a) chiral nucleophile or environment (solvent)
b) chiral auxiliary attached to the substrate
c) complexation of chiral agent by hydrogen bonding
d) chiral complexes, e.g. metal salts, which promote the reaction.

Whereas in cases a) and b) catalysis is not possible due to stoichiometry, in case c) catalysis is theoretically possible but practically one or even more equivalents of the chiral agent are required to achieve good enantioselectivity.

The most promising approach toward catalytic enantioselective photochemical transformations of this sort is the use of chiral organometallic complexes as
catalysts (case d)), which are able to influence the geometry and reactivity of the substrates serving the attempted purpose.\textsuperscript{17}

2.4 Theoretical aspects of enantioselective radical transformations

In enantioselective radical transformations, selection will require $\pi$-facial discrimination in which the enantiotopic radical or radical trap faces are made diastereotopic by virtue of a chiral reagent or a chiral complexing agent.

Enantioselection in free radical reactions can be distinguished as being complex-controlled or reagent-controlled. Complex-controlled transformations involve an achiral substrate being coordinated to a chiral reagent ($A^*$) before reaction.

\[ \text{Substrate} + A^* \xrightarrow{B} \text{Substrate} - A^* \]

\[ \text{Substrate} - A^* \rightarrow [\text{Substrate} - B-A^*]^\# \rightarrow \text{Product} - A^* \]

\[ \text{Product} - A^* \xrightarrow{} \text{Product} + A^* \]

In this complex, an enantiotopic face of a radical or radical trap becomes diastereotopic and selectivity is achieved when one of the diastereomeric transition states is favoured.

The control of stereochemistry in free radical reactions has been significantly advanced in recent years and today there is a good understanding of factors that are important in determining the configuration of stereogenic centers formed in diastereoselective and enantiostereoselective free radical additions.\textsuperscript{18}

General demands for enantioselective radical conjugate addition are the following:

- The reactivity of the substrate-chiral complex must exceed that of the free substrate so that nonselective reactions of the uncomplexed substrate do
not interfere. The best case is if reaction is impossible or inefficient without activation of the chiral complex

- The orientation of the complexing chiral group must be fixed in the complex relative to the reactive center
- For the use of catalytic amounts of chiral Lewis acids, labile complexation of the substrate is essential for the turnover
- The chiral group must shield the alkene faces diastereotopically upon complexation.

In some cases rotamer control can play a crucial role in the successful execution of complex-controlled radical transformations, e.g. in enantioselective conjugate radical addition. For example, for oxazolidinone templates the orientation about the N-C(O) bond and the C(O)-C bond must be controlled. The stereogenic center present in a chiral catalyst must be fixed relative to the reacting center in the substrate.

Two-point binding to the metal center controls the conformation about the N-C(O) bond by coordinating both carbonyls (see drawing below), and the conformation about C(O)-C is fixed as s-cis. A one-point binding model is not fixed relatively to the metal and the reactive center is ambiguous.

\[ ML^* - \text{chiral complex} \]
2.5 Enantioselective radical transformations promoted by chiral complexes

Organic free radicals have historically been regarded as intermediates poorly suited for selective reactions because of their high reactivity. In the past 30 years it has become apparent that radicals can react in chemo- and regioselective manner. Furthermore in the past decade, steroselective transformations of free radicals have been achieved. During this time, a variety of useful synthetic strategies have been developed for radical-based C-C bond formations. On the other hand, enantioselective transformations of organic radicals remain uncommon.

Early strategies of enantioselective radical transformations are based on successful strategies utilized for other reaction types, and in most of them enantioselectivity was achieved by introducing chiral auxiliaries in the substrates.

In the last decade a number of enantioselective radical transformations such as atom transfer including cyclizations, reductive alkylations, fragmentations, tandem addition-trapping reactions, promoted by chiral complexes were accomplished, but the most significant progress was achieved in enantioselective conjugate addition (Michael addition).

2.6 Enantioselective radical transformations promoted by complexes with $C_2$-symmetric ligands

$C_2$-symmetric BINOL, BINAP, TADDOL and BOX ligands (see structures below) belong to the most popular and frequently used chiral ligands. Due to $C_2$-symmetry the coordination site of them are homotopic that makes less uncertainty in the nature of catalyst-substrate complexation.
A first example of the enantioselective intramolecular conjugate radical addition, promoted by a chiral complex, was reported by Nishida et al., using a BINOL-based chiral aluminum complex 22 (Scheme 7). Formation of a vinylic radical followed by a 5-exo or 6-exo (for n = 1 or 2, respectively) cyclization controlled by the chiral complex provides enantiofacial selection. Four equivalents of the complex 22 are required in these reactions for obtaining maximum selectivity. Employment of one equivalent of the chiral complex 22 reduces the ee’s to 2% for 5-exo and 12% for 6-exo cyclization, respectively.

Scheme 7: Enantioselective intramolecular radical cyclization promoted by chiral complex 22

The requirement to use at least stoichiometric amounts of chiral catalyst in order to obtain higher enantioselectivity originates from nonselective reaction of free
substrate which competes effectively with the reaction in complex being responsible for enantioselective induction.

Porter and co-workers have shown that BOX-based chiral catalysts, which were employed before for cycloadditions and carbanion reactions, work successfully for free radicals. They have reported that zinc ion used in conjunction with chiral bidentate ligands, promotes free radical addition to a suitably substituted acrylamide. These addition reactions occur with good to excellent enantioselectivity (34-90%, Scheme 8).

**Scheme 8:** Tandem addition-trapping reaction promoted by the BOX-based chiral complexes 25a, b

![Scheme 8](attachment:image.png)

The enantioselectivity in these reactions critically depends on the chiral ligand, the solvent, metal center, and the radical undergoing the addition reaction. The best results were achieved when the ligand 25a was applied in combination with zinc triflate in substrate:metal:ligand ratios 1:2:2. The best solvent for this reaction is a pentane/CH$_2$Cl$_2$ (40:60) mixture.
The first example of enantioselective conjugate radical addition to β-positions with substoichiometric amount of chiral agent was achieved in collaboration of the Sibi and Porter groups in 1996. This work is a continuation of previously described work in which addition of an alkyl radical to 26 in the presence of the chiral complex 28 results in the product 27 with good chemical yields and high enantioselectivities (Scheme 9). The best enantioselectivity was achieved with Mg(II) and Zn(II) ions (Table 1).

**Scheme 9:** Enantioselective conjugate radical addition to the β-position catalysed by the chiral BOX-based complexes 28 a-c

![Scheme 9 Diagram](image)

Table 1: Addition of R₂I to a functionalized acrylamide 26

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ligand (L⁺)</th>
<th>Lewis acid (M)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26a</td>
<td>28a (S,S)</td>
<td>MgBr₂</td>
<td>92</td>
<td>77 (R)</td>
</tr>
<tr>
<td>2</td>
<td>26a</td>
<td>28b (S,S)</td>
<td>MgI₂</td>
<td>88</td>
<td>82 (R)</td>
</tr>
<tr>
<td>3</td>
<td>26a</td>
<td>28c (S,S)</td>
<td>Zn(OTf)₂</td>
<td>88</td>
<td>61 (S)</td>
</tr>
<tr>
<td>4</td>
<td>26b</td>
<td>28c (R,R)</td>
<td>Zn(OTf)₂</td>
<td>90</td>
<td>82 (R)</td>
</tr>
<tr>
<td>5</td>
<td>26b</td>
<td>28a (S,S)</td>
<td>MgBr₂</td>
<td>78</td>
<td>82 (R)</td>
</tr>
</tbody>
</table>

It is interesting that the use of ligands of identical absolute configuration 28a and 28b (both S,S) yields product of R-configuration but when ligand 28c of identical S,S configuration is used the product of S-configuration forms.
The catalytic nature of this reaction was also examined using the best ligand-Lewis-acid combination (28b-MgI₂). With 0.5 equivalent of catalyst loading, the formation of products occurs with an ee being comparable with results obtained with stoichiometric amounts of catalyst (79%). Further lowering of the catalyst loading to 0.2 equivalent results in only a small decrease of enantioselectivity (67%). Even with 0.05 equivalent of catalyst loading notable enantioselectivity was obtained (40%).

Iserloh, Curran and Kanemasa explored the use of the DBFOX/Ph ligand 29 for the same reaction. This ligand had previously proven to be effective in Diels-Alder reactions and nitrone cycloadditions. Evaluation of various transition-metal Lewis acids showed that only Mg(ClO₄)₂ provides good reactivity (100% yield) and enantioselectivity (75% ee).

The possible reason for a lower enantioselectivity in reactions catalyzed by DBFOX-based complexes in comparison with BOX-based ones is that the tridentate DBFOX ligand increases the electron density at the metal center and makes it a weaker Lewis acid. This leads to the non-selective background reaction (non-metal-complex-catalyzed) and hence to a lower enantioselectivity.

Murakata et al. examined the role of additives in chiral complex-mediated radical conjugate addition (Scheme 10).
Scheme 10: Chiral complex-promoted enantioselective conjugate radical addition in presence of achiral additives

With stoichiometric loading of chiral complex 32 very low enantioselectivity was achieved. When 33a or 33b were added, there was a marked increase in ee’s (Table 2, entries 2 and 3). This increase was more pronounced when 4,4-diphenyl-substituted oxazolidinone 30b was used as the template with 33b as the additive (Table 2, entries 4 and 5). In an effort to understand the origin of this additive effect the N-methylated compound 33c was prepared and tested. The fact that there was no change in selectivity compared to that found in the experiment without any additives suggests that the additives 33a and 33b are coordinating to zinc through the NH group. By low-temperature NMR experiments it was shown that the substrate could displace the additive 33c but not 33a. The reaction was also carried out with substoichiometric loading of chiral Lewis acid without significant loss in selectivity (entries 9 and 10).
Table 2: Addition of R-I to a functionalized acrylamide 30

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>ML* (eq)</th>
<th>Additive</th>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31a</td>
<td>1.0</td>
<td>-</td>
<td>t-Bu</td>
<td>88</td>
<td>9(S)</td>
</tr>
<tr>
<td>2</td>
<td>31a</td>
<td>1.0</td>
<td>33a</td>
<td>t-Bu</td>
<td>86</td>
<td>41(S)</td>
</tr>
<tr>
<td>3</td>
<td>31a</td>
<td>1.0</td>
<td>33b</td>
<td>t-Bu</td>
<td>78</td>
<td>52(S)</td>
</tr>
<tr>
<td>4</td>
<td>31b</td>
<td>1.0</td>
<td>-</td>
<td>t-Bu</td>
<td>80</td>
<td>3(S)</td>
</tr>
<tr>
<td>5</td>
<td>31b</td>
<td>1.0</td>
<td>33b</td>
<td>t-Bu</td>
<td>96</td>
<td>88(R)</td>
</tr>
<tr>
<td>6</td>
<td>31b</td>
<td>1.0</td>
<td>-</td>
<td>i-Pr</td>
<td>72</td>
<td>32(S)</td>
</tr>
<tr>
<td>7</td>
<td>31b</td>
<td>1.0</td>
<td>33b</td>
<td>i-Pr</td>
<td>86</td>
<td>82(R)</td>
</tr>
<tr>
<td>8</td>
<td>31b</td>
<td>1.0</td>
<td>33c</td>
<td>i-Pr</td>
<td>98</td>
<td>29(S)</td>
</tr>
<tr>
<td>9</td>
<td>31b</td>
<td>0.25</td>
<td>33b</td>
<td>i-Pr</td>
<td>92</td>
<td>80(R)</td>
</tr>
<tr>
<td>10</td>
<td>31b</td>
<td>0.25</td>
<td>33b</td>
<td>t-Bu</td>
<td>72</td>
<td>83(R)</td>
</tr>
</tbody>
</table>

Sibi et al. have shown that the templates used in these reactions have a significant impact on outcome, reactivity and selectivity. Changing of the oxazolidinone template to 3,5-dimethyl pyrazole resulted in a reversal of stereochemistry when using the same chiral complex.\(^{35}\)

**Scheme 11**: The impact on stereochemistry in complex-promoted conjugate addition depending on the template used

Much efforts have been made to obtain information about the structure of the intermediate in the [M(BOX)]\(^{2+}\) catalyzed reactions.
Several X-ray structures of complexes containing water, halides, substrates and substrate-like compounds, coordinating to the [Cu(BOX)]^{2+} catalyst support a distorted square-planar intermediate structure for reactions, catalyzed by these complexes.

In contrast to Cu^{2+} the complexes of Zn^{2+} or Mg^{2+} are usually tetrahedrally arranged. Such a difference in geometries opens the possibility to find a metal-chiral ligand pair which would be most efficient for the control of stereogenic centers during our planned transformations.

D. A. Evans, PM3 calculation, Karl-Ziegler-Seminar 2003

3 Results and discussion

3.1 General concept for catalytic PET-initiated cyclizations

The design of complex catalyzed enantioselective reactions includes a number of parameters: the nature of metal center, the nature of chiral ligand, and the nature of solvent.

Due to the several reaction partners present in the reaction mixture (including donor/acceptor couple and metal-containing complexes) and the possibility of these being unstable under PET irradiation conditions for successful execution of such reactions, parameters such as a suitable electron donor/acceptor couple, the wavelength of irradiation and light stability of the reaction components should be adjusted.

The compatibility of these parameters is most important and offers the opportunity for optimisation of the reaction conditions and efficiency.

Another essential component of such catalytic enantioselective transformations is the substrate itself in view of binding and complexation properties as well as sufficient stability under the given conditions.

3.1.1 Choice of the solvent and considerations on the acceptor

The choice of solvent is extremely important for catalysis. Our demands can be summarized as follows:

- **Non-complexing solvent**  
  (to avoid passivation of catalyst by complexation of solvent to the metal)

- **Strong complexation of metal to the chiral ligand**  
  (to avoid reaction of the substrate in a complex not containing the chiral ligand)

- **Weak complexation of metal to substrate**  
  (is essential for turnover)
• **PET in the solvent of choice should be efficient.**

The majority of “photosensitized” electron transfer processes have been investigated in polar solvents, such as acetonitrile and water, being excellent coordinating media. The use of polar solvents serves the necessity to stabilize the initially formed charged species upon PET, i.e. donor radical cations and acceptor radical anions.

For processes, catalyzed by organometallic complexes, the presence of a nucleophile that can passivate the chiral catalyst by complexation to the metal, is unacceptable.

The majority of non- or badly-complexing solvents are usually solvents of low polarity.

Recently, a methodology for PET-initiated reactions in solvents of low polarity, i.e. in a dichloromethane/methanol mixture (4:1), was developed in our group.\(^3\) This procedure involves the use of a cationic acceptor, N-methylquinolinium hexafluorophosphate (NMQ\(_{\text{PF}_6}\)), together with biphenyl, as electron acceptor couple. In this case, electron transfer from a neutral donor to the excited state of the cationic acceptor results in the formation of a neutral radical / radical cation pair in which there is no Coulombic barrier to separation. Using this methodology, a number of acyclic polyterpenoids were cyclized successfully and with good yields.

These experiments have demonstrated the applicability of cationic acceptors in PET-initiated transformations of a broader choice of substrates.

Moreover, it was shown that when the cationic-type acceptor N-methylacridinium hexafluorophosphate (NMA\(_{\text{PF}_6}\)) was used together with bipyridine (BP), the quantum yields of separated radical cations of BP are higher than those with 2,6,9,10–tetracyanoanthracene (TCA) in all of the investigated solvents (Table 3).

Furthermore, the yields of separated radical cations of BP obtained by using NMA\(_{\text{PF}_6}\) are higher in solvents of low polarity, reaching a value of ca. 0.9 in dichloromethane.
Table 3: Quantum yields of formation of BP radical cation in different solvents

<table>
<thead>
<tr>
<th>Solvent (ε)</th>
<th>Biphenyl (TCA)</th>
<th>Biphenyl (NMA(\text{PF}_6))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile (35.9)</td>
<td>0.18</td>
<td>0.33</td>
</tr>
<tr>
<td>Butyronitrile (24.3)</td>
<td>0.17</td>
<td>0.39</td>
</tr>
<tr>
<td>o-Dichlorobenzene (9.93)</td>
<td>0.08</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Dichloromethane (8.93)</strong></td>
<td><strong>0.06</strong></td>
<td><strong>0.89</strong></td>
</tr>
<tr>
<td>Tetrahydrofuran (7.58)</td>
<td>0.02</td>
<td>0.43</td>
</tr>
<tr>
<td>Fluorobenzene (5.42)</td>
<td>0.01</td>
<td>0.52</td>
</tr>
<tr>
<td>Chloroform (4.81)</td>
<td>0.01</td>
<td>0.71</td>
</tr>
<tr>
<td>Benzene (2.27)</td>
<td></td>
<td>0.34</td>
</tr>
</tbody>
</table>

These considerations strongly suggest that the use of a cationic-type of acceptor in solvents of low polarity, such as dichloromethane, would be most favorable for the planned photochemical transformations in this work. The use of solvents of lower polarity than dichloromethane would be problematic due to the low solubility of the cationic acceptors and chiral complexes.

3.1.2 Choice of the metal and counter ion

The choice of the metal is crucial for successful catalytic transformations, since it should influence the electronic structure of the substrate so that the reactivity of complexed material must exceed that of the free substrate. Moreover, in complex-controlled enantioselective transformations the metal provides the basic geometry of the reactive complex and can influence the stereoselectivity of the catalytic process importantly. In accordance with Irving-Williams stability & kinetic order for complexes formed by bivalent ions of the first transition series:

\[\text{Mn} < \text{Fe} < \text{Co} < \text{Ni} < \text{Cu} > \text{Zn}\]
Cu(II) forms the most stable ligand-metal complexes and, in an apparent paradox, the exchange rate of Cu•(H₂O)₆ is greater than those of other first row divalent transition metal ions. This effect is caused mainly by two fundamental factors: Jahn-Teller distortion and the Pauling electrononeutrality principle. Both factors provide enhanced stability for ligands in equatorial positions while weakening the two axial coordination sites.

**Scheme 12**: Geometry and strength of complexation in Cu(II) complexes

This unique ability of Cu(II) gives an opportunity to provide enhanced stability of up to two two-coordinating ligands (chiral ligand and substrate) in equatorial position while the two axial sites are occupied by counter ions (Scheme 12, I). In case of three-coordinating chiral ligands, Jahn-Teller distortion should enable a better stability of the chiral metal-ligand complex (catalyst). At the same time only one equatorial site remains free for coordination and the substrate should occupy equatorial-axial sites that enhance its exchange rate with the catalyst, which is essential for turnover (Scheme 12, II).

More than 80% of the Cu(II) complexes compiled in the Cambridge crystallographic database are square planar, octahedrally and square pyramidal.
Formally, all three types are octahedral but in square planar complexes the distance between Cu(II) and the ligands in axial sites is so long and the interaction so weak that they cannot influence interactions with the metal center noticeably and can therefore be omitted for simplification. The same argumentation is valid for one of ligands in axial position in square pyramidal complexes.

The copper(II) ion is a typical transition metal ion in respect to the formation of coordination complexes, but less typical in its reluctance to adopt a regular stereochemistry. The 3d⁹ outer electron configuration of the copper(II) ion lacks cubic symmetry, and hence adopts distorted forms of the basic stereochemistry.⁴⁰

These considerations work generally in concepts to provide well-defined complexes that display excellent properties as catalysts.

The counterion can also influence the stereoselectivity of the reaction substantially.³¹ The application of counterions with considerable nucleophilicity (e.g. Cl⁻ or Br⁻) is undesirable in PET-initiated cyclizations of polyalkene terpenoids due to their possible addition to intermediately formed radical cations.⁴¹ For this reason utilization of large counterions (e.g. ClO₄⁻, SbF₆⁻, OTf⁻) is desirable.

In accordance with these aspects, commercially available Cu(OTf)₂ can be used favorably as Lewis acid for the complex preparation.

### 3.1.3 Choice of the ligands

Chiral ligands play a crucial role in catalytic enantioselective transformations. In the beginning of enantioselective catalysis with transition metal compounds chiral
mono-coordinating ligands were in the focus of interest. Soon thereafter, chiral two-coordinating ligands took over.\textsuperscript{42} Chiral three-coordinating ligands have so far not been used extensively in enantioselective catalysis but recently started to attract attention of many research groups.\textsuperscript{43}

Among a wide variety of ligands, $C_2$-symmetrical chiral ligands are the most promising ones for asymmetric catalysis. Due to $C_2$-symmetry, the coordination sites are homotopic hence giving rise to less uncertainty with respect to the nature of catalyst-substrate complexation.

Chiral bis(oxazoline) derivatives (e.g. BOX and PyBOX) belong to the most popular $C_2$-symmetrical ligands and have recently been employed for a variety of metal-complex-catalyzed asymmetric reactions. The Lewis basicity of the nitrogen donor atoms and the conformationally rigid framework of the chelate represent important structural features of this type of ligand (see structures below).

Another advantage of this type of ligand is that they can be synthesized from readily available diacid derivatives and amino alcohols.

3.1.3.1 Synthesis of chiral ligands

As chiral ligands the C-2 symmetrical BOX-based two-coordinating ligands \textsuperscript{39}, \textsuperscript{40} and the three-coordinating ligand \textsuperscript{41} were selected.
The ligands 39 and 40 were synthesized by following literature methods and both enantiomers of the chiral ligand 41 were obtained from \((R)\)-2-amino-2-phenylethanol or \((S)\)-2-Amino-2-phenylethanol in three steps using improved combination of literature methods (method\(^{45}\) for step [a] and method\(^{46}\) for steps [b] and [c], Scheme 13).

**Scheme 13: Synthesis of chiral ligand 41**

The main advantages of this procedure are an improved and comparably high overall yield (65%), and a handy synthesis in which practically no purification of intermediate products is needed.
3.1.4 Choice of an achiral template, i.e. oxazolidinone, and design of the substrate

The choice of achiral templates for chiral Lewis acid-mediated enantioselective reactions is very important. It is integral part of the substrate-Lewis acid complex, which must efficiently provide face shielding. Two-point-binding templates enable to avoid rotation around the metal-ligand bonds hence providing a much better stereochemical organization around the metal center. The concept that a high level of stereocontrol might be possible if similar substrates are activated in the same manner, which had previously served successfully for ground state transformations, was chosen as a basis for the present work.

In accordance with these earlier findings concerning enantioselective conjugate additions in the ground state, oxazolidinone (see picture) was used here as a template, being most effective in conjunction with Cu(II)-BOX chiral complexes.\textsuperscript{27d,47} Moreover, this template was used before effectively also in combination with Mg(II)-BOX and Zn(II)-BOX chiral complexes\textsuperscript{30,27a-b,27d} in the ground state. We anticipated the potential suitability of this combination also for our purposes. The success of the oxazolidinone template in providing high enantioselectivity in ground state reactions can be attributed to the availability of two donor sites for chelation and the possibility to form relatively rigid complexes.

By application of the oxazolidinone template with the inner double bond in e.g. 44 and 45 (Scheme 14) being in conjugation with a carbonyl, will constitute an effective electron trap by deconjugation of the intermediate radical in 46 on the way to 47. This should increase the reactivity of the complexed vs. the free substrate.
3.2 Synthesis of \emph{trans}-3-(3,7-dimethyl-octa-2,6-dienoyl)-oxazolidin-2-one (44)

According to the discussion before, substrate 44 was chosen for further cyclization attempts. The synthesis of it is shown in Scheme 15. We started from commercially available 6-methyl-hept-5-en-2-one (48). The Horner-Wadsworth-Emmons reaction of 48 with the sodium enolate of triethyl phosphonoacetate resulted in a \emph{cis}:\emph{trans}-isomeric mixture (1:3.5) of ethyl geranate (the \emph{trans}-isomer is depicted in the scheme as 49) in 89% yield. Effective separation of the isomers was achieved by column chromatography. \emph{Trans}-ethyl geranate (49) was then hydrolyzed to the corresponding acid 50 and converted to the acid chloride, which was reacted with N-lithium oxazolidin-2-one to give 44 in about 40% yield.
**Scheme 15:** Synthesis of 3-(3,7-dimethyl-octa-2,6-dienoyl)-oxazolidin-2-one

\[
\begin{align*}
\text{48} & \quad \xrightarrow{1.3 \text{ equiv. } \text{(EtO)}_2\text{P(O)CH}_2\text{C(O)OEt}} \quad \xrightarrow{1.3 \text{ equiv. NaH}} \quad \text{THF (dry), } 0^\circ\text{C} \\
\text{49} \quad (89\%) & \quad \xrightarrow{\text{reflux}} \quad \text{NaOH (1N)} \quad \text{MeOH} \\
\text{44} \quad (40\%) & \quad \xrightarrow{1) \text{ClC(O)C(O)Cl / benzene}} \quad 2) \text{ Oxazolidin-2-one, BuLi / THF} \quad -78^\circ\text{C} \\
\text{50} \quad (90\%) & \quad \xrightarrow{\text{NaOH (1N)}} \quad \text{MeOH}
\end{align*}
\]

It should be noticed that the main side product in the last step is chlorinated compound 51. The amount of formation of this compound is largely dependent on the origin of the oxalyl dichloride.\(^{[a]}\)

3.3 Complexation of Cu(OTf)\(_2\) to BOX-based ligands

For realization of catalysis in enantioselective radical transformations a number of demands are important (see Chapter 2.4). According to this demands a strong complexation of the chiral ligand to the metal center is necessary to avoid reaction out of complex and weak complexation of substrate to the metal is essential for turnover.

For the detection of complexation UV spectroscopy was chosen. It is assumed that complexation should lead to changes in absorption. Furthermore, the absorption spectrum of the reactive complex is important for determination of the

\(^{[a]}\) Oxalyl dichloride ordered from Aldrich gave higher yields of target product 44 and lower percentages of chlorinated side product 51 than in reactions run with the reagent ordered from Fluka.
irradiation wavelength in order to avoid direct excitation of the complex, which can lead to its decomposition. As it was discussed in the Chapters 3.1.3, C-2 symmetrical BOX-based two-coordinating chiral ligands 39 and 40, and the three-coordinating ligand 41 were selected for complexation.

Complexation of 39 to 
\(\text{Cu(OTf)}_2\)

The ligand 39 has a weak absorption with the maximum at 229 nm (\(\varepsilon = 120 \text{ dm}^3\text{mol}^{-1}\text{cm}^{-1}, \text{C=N}\)) (Figure 1).

The complexation to \(\text{Cu(OTf)}_2\) leads to big changes in the absorption spectrum. The formed complex has a very broad absorption up to 400 nm with a maximum at 230 nm and a local maximum at 338 nm.

The exact extinction coefficient of the formed complex in dichloromethane was not calculated due to relatively bad complexation of the ligand to \(\text{Cu(OTf)}_2\) (some amount of the salt was insoluble even after 1 day).
**Complexation of 40 to Cu(OTf)$_2$**

The ligand 40 has a weak absorption peak with the maximum at 227 nm ($\varepsilon = 800$ dm$^3$mol$^{-1}$cm$^{-1}$, C=N) and to peaks at 266 nm ($\varepsilon = 2140$ dm$^3$mol$^{-1}$cm$^{-1}$) and at 273 nm ($\varepsilon = 2160$ dm$^3$mol$^{-1}$cm$^{-1}$) attributable to the aromatic substituents (Figure 2).

The formed complex absorbs up to 370 nm with a maximum at 229 nm ($\varepsilon = 4310$ dm$^3$mol$^{-1}$cm$^{-1}$) and local maxima of the aromatic substituents at 264 nm ($\varepsilon = 2710$ dm$^3$mol$^{-1}$cm$^{-1}$) and at 271 nm ($\varepsilon = 2370$ dm$^3$mol$^{-1}$cm$^{-1}$), respectively.

**Complexation of 41 to Cu(OTf)$_2$**

The best complexation was achieved with the three-coordinating PyBOX ligand (41). In contrast to the two-coordinating ligand 39 all Cu(OTf)$_2$ was dissolved in dichloromethane and this much faster than in the case of ligand 40.

The free ligand 41 has due to
the availability of two C=N groups being conjugated with a pyridine ring and in the presence of aromatic substituents a broad absorption spectrum with two maxima at 243 ($\varepsilon = 11862 \text{ dm}^3\text{mol}^{-1}\text{cm}^{-1}$) and 284 nm ($\varepsilon = 11272 \text{ dm}^3\text{mol}^{-1}\text{cm}^{-1}$) (Figure 3). The formed complex shows absorption up to 350 nm with a maximum at 232 nm ($\varepsilon = 13050 \text{ dm}^3\text{mol}^{-1}\text{cm}^{-1}$).

For all three ligands is a broad absorption band with a maximum at 229-232 nm characteristic.

It should be mentioned that addition of the substrate 44 to the chiral complexes does not lead to significant changes in the absorption spectrum; the observed spectrum is a combination of the spectra of the chiral complexes with the spectrum of 44.

These results suggest that the complexation of the chiral ligand to the metal is rather strong and on the other hand the complexation of the substrate to the metal is quite weak which meets overall the requirements for catalysis in enantioselective radical transformations as indicated earlier.

3.4 Choice of the acceptor in accordance to the irradiation wavelength

As it was demonstrated in the previous chapter the chiral complexes show absorbance up to 350 nm in case of the three-coordinating ligand 41, and up to 400 nm in case of the two-coordinating ligand 39. In view of these results, irradiation of the reaction mixture should be conducted at 400 nm or even at longer wavelengths to avoid direct excitation of the complexes. In this case the use of the cationic acceptor N-methylquinolinium hexafluorophosphate (NMQ•PF$_6$), which was
shown to be effective for PET-initiated cyclizations in solvents of low polarity\textsuperscript{3}, is not possible due to the absence of absorption at 400 nm or at longer wavelengths.

To find another effective cationic acceptor for PET-initiated cyclizations three compounds, which have absorption at 400 nm, were selected.

2,4,6-Tris-(4-methoxy-phenyl)-pyranylium tetrafluoroborate (52):

This acceptor has a strong absorption in the area from 360 nm up to 520 nm with a maximum at 425 nm ($\varepsilon = 54500$ dm$^3$mol$^{-1}$cm$^{-1}$) (Figure 5). The calculated oxidation potential $E_{\text{ox}}^{\text{calc}} = 1.98$ V vs NHE\textsuperscript{48} is high enough for oxidation of BP with its oxidation potential BP/BP$^{\ast\ast}$ of about 1.6 V\textsuperscript{[a]}.

2,4,6-Triphenyl-pyranylium tetrafluoroborate (53):

The acceptor 53 has a broad absorption spectrum with two maxima at 369 nm ($\varepsilon = 37600$ dm$^3$mol$^{-1}$cm$^{-1}$) and at 414 nm ($\varepsilon = 26140$ dm$^3$mol$^{-1}$cm$^{-1}$) (Figure 4).

\textsuperscript{[a]} Calculated by Weller equation: $\Delta G = E_{1/2}^{\text{ox}}(D) - E_{1/2}^{\text{red}}(A) - \Delta E_{\text{excit.}} + \Delta E_{\text{coul}}$

$E_{\text{ox}}^{\text{calc}} = E_{\text{red}}(A) + \Delta E_{\text{excit.}} \rightarrow \Delta G = E_{1/2}^{\text{ox}}(D) - E_{\text{ox}}^{\text{calc}}$

In PET reactions with cationic acceptors there is no Coulombic interaction between electron donor and neutral acceptor as well as between the species formed after electron transfer; $\Delta E_{\text{coul}}$ can be omitted.
The main difference between structurally similar 52 and 53 is the oxidation potential, which is much higher for 53 ($E^{\text{ox}}_{\text{calcd.}} = 2.5$ V vs NHE$^{48,49}$). Such a high potential normally leads to higher yields in case of monocyclizations, but in apparent paradox, to lower yields in case of polycyclizations.$^{50}$

*N-methylacridinium hexafluorophosphate (54):*

The cationic acceptor 54 has a strong absorption from 325 to 375 nm with its maximum at 360 nm ($\varepsilon = 24500$ dm$^3$mol$^{-1}$cm$^{-1}$), but unfortunately the absorption in the range of 400 nm, being interesting for us, is comparably low ($\varepsilon = 3700$ dm$^3$mol$^{-1}$cm$^{-1}$ at 402 nm, $\varepsilon = 4000$ dm$^3$mol$^{-1}$cm$^{-1}$ at 422 nm). The main advantage of this
acceptor is its structural similarity with NMQ•PF₆, which was shown to be effective as electron acceptor for PET-initiated cyclizations in low-polarity solvents.³

These compounds (52, 53 and 54) were tested as electron acceptors together with biphenyl in dichloromethane/methanol (10:1) mixture for the cyclization of the oxazolidinone-containing compound 44 (Scheme 16).

**Scheme 16: PET-initiated cyclization of 44 to 55**

<table>
<thead>
<tr>
<th>Electron acceptor (EA)</th>
<th>52</th>
<th>53</th>
<th>54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield (%)</td>
<td>0</td>
<td>29</td>
<td>38</td>
</tr>
<tr>
<td>Conversion (%)</td>
<td>0</td>
<td>65</td>
<td>72</td>
</tr>
</tbody>
</table>

The best yield of cyclic product and conversion of starting material were achieved when N-methylacridinium hexafluorophosphate (NMA•PF₆, 54) was used as electron acceptor. In view of these results, compound 54 was chosen as cationic acceptor for further PET-initiated cyclizations.
3.5 Stability examination of reaction components and adjustment of reaction conditions

The stability of the reaction components, especially of the chiral complex, during the reaction is one of the most important factors in view of the intended catalysis. In photochemical reactions the most probable reason of compound instability is the direct excitation during irradiation, which can lead to decomposition. That is why the accurate choice of irradiation wavelengths is essential for photochemical transformations.

3.5.1 Chiral complex stability during the irradiation at different wavelengths

In catalytic reactions the stability of the chiral complex, which is intended to be used in substoichiometric amounts, is one of the most important factors. Due to the absorption at longer wavelengths the chiral complex can be excited by direct irradiation that can lead either to rapid back electron transfer (BAT) or to complex decomposition.

For our experiments the most promising pair Cu(II)/Ph-PyBOX (56) and the complex Cu(II)/t-BuBOX (57), having the absorption at the longest wavelengths among the ligands of choice, were selected.

The stability of the complexes under irradiation at different wavelengths was examined by UV spectroscopy.
The instability of these complexes under irradiation at 300 and 350 nm (*Rayonet*, \(\lambda_{\text{max}}\)) was not surprising in view of their significant absorptions in this range (see Figure 7).

However, both complexes 56 and 57 were found to be unstable under irradiation even at 400 nm (Figure 8).

The reason of such “strange” decomposition is the broad emission spectrum of the *Rayonet* lamps used (Figure 9).

To intercept emission in the wavelength region in which the chiral complex absorbs, the use of a light filter is essential. A large variety of glass and chemical filters is available commercially and their characteristics can be found in manufacturers’ catalogues or on web-pages.\(^{51}\)

The light filters, which can be used for our purpose, can be divided into two groups:
• chemical filters
• glass filters

Many chemical filters have been described in the literature. The main disadvantage of this sort of filters is that they are relatively unstable and can be used for a limited period of time only. Moreover, many of such filters should be prepared in advance and need some period of time to reach a constant transmission value of light in the selected wavelengths region.

For that reason glass filters, which can be used over unlimited periods of time and are always “ready for utilization”, were found to be optimal for our photochemical purposes.

Utilization of a G.W.V. filter (Schott glass, Mainz), which has no or negligible light transmission at wavelengths shorter than 366 nm (Figure 10) must enhance the stability of complex 56 significantly.

In contrast to the decomposition after 2 days of irradiation, found earlier (Figure 8), this complex is stable even after 4 days of irradiation when a G.W.V. filter is applied (Figure11).
In case of complex 57 the utilisation of a G.W.V. filter gave positive results as well. After 3 days of irradiation using this filter, only a minor part of the complex was decomposed (Figure 12).

3.5.2 Temperature stability of the chiral complex

The temperature stability of the chiral complex is also an important factor. To check the temperature stability of the complex, as well as of the free ligand, samples were heated to 40 °C for four days in dichloromethane. Both, ligand and complex are stable under this condition that gives the opportunity to perform photoreactions in a wide temperature range (Figures 13, 14).
Note, the increase of absorption in both figures is caused by evaporation of the solvent, but the shape of the spectra and the absorption ratios at different wavelengths remain constant.

3.5.3 Stability of the electron acceptor during irradiation

It was found that the most unstable component of such reactions is the electron acceptor. The main part of the acceptor was decomposed after one day of irradiation either with or without G.W.V.-light filter (Figure 15). This fact is in paradox with results received in Chapter 3.4 where for 72% of starting material conversion 39 hours were needed. The reason of this paradox is as follows. The absorption spectra were measured for very dilute solutions (10^-4-10^-5 mol/l) in which all of N-
methylacridinium hexafluorophosphate (NMA•PF$_6$) is soluble. In the reaction however, the concentration of electron acceptor is much higher and not all of the acceptor is dissolved under this condition. After decomposition of some of the NMA•PF$_6$ a next portion dissolves that makes the concentration of acceptor in the reaction mixture more or less constant.

3.6 Cyclizations of trans-3-(3,7-dimethyl-octa-2,6-dienoyl)-oxazolidin-2-one (44) in presence of BOX-based chiral complexes

After the conditions were determined, a number of attempts to perform cyclizations stereoselectively were undertaken.

For that reason the PET-initiated cyclizations of the substrate 44 in the presence of either chiral complex 56 or 57 were conducted (Scheme 17).

**Scheme 17:** PET-initiated cyclization of 44 to 55 in presence of chiral complexes

Attempts to determine the enantiomeric ratio for the cyclized compound 55 by chiral GC were unsuccessful and it was therefore hydrolyzed to the corresponding acid 58. However, even for the acid separation of the peaks was not complete, but their shape is symmetrical and hence allows integration.
Due to the incomplete separation of the enatiomers’ GC signals it is impossible to determine an exact enantiomeric ratio, but it can be concluded that no significant induction was achieved.

Possible reasons for the failure in achievement of enantioselectivity:

- **Temperature:**
  The majority of the previously described successful enantioselective conjugate radical additions in the ground state were carried out at $-78^\circ$C and it was shown that temperature can influence the stereoselectivity of the reaction importantly.\(^5\)

- **Presence of a nucleophile:**
  Although the amount of the nucleophile used in our reactions with chiral complexes was decreased significantly, in comparison with the previous PET-induced reactions done in our laboratory,\(^3\) it possibly can still inactivate the complex.

- **Reactivity of the substrate:**
  The substrate \(^{44}\) can be cyclized even without activation by a chiral complex and possibly such activation is not so important to render cyclizations out of the complex negligible.

- **Complex geometry:**
  Selective face shielding, as required for enantioselectivity, is provided by the chiral catalyst and optimization of the chiral ligand together with the metal center should be a feasible way to enhance selectivity.

  However, the design and optimization of ligands is often time consuming.

To check the temperature influence, the reaction \(^{44}\rightarrow^{55}\) (in presence of \(^{56}\) or \(^{57}\)) was performed at $-40^\circ$C, but no significant changes in enantiomeric ratios were observed.
3.7. Attempts to perform the PET-initiated cyclizations in absence of a good complexing nucleophile

As it was mentioned in the previous chapter one of the possible reasons of failure in achievement of enantioselectivity (44→55) is likely the presence of a good complexing nucleophile in the reaction medium.

As a consequence we have tried two ways to perform the PET-initiated cyclizations without a good complexing nucleophile:

- **Reactions with a nucleophile being a weak complexer:**
  Hydride ion would be excellent for this purpose since it a very bad complexer and hence, cannot inactivate the chiral complex by complexation to the metal. The advantage of this method is the possibility to use the substrate which was already applied for cyclizations in the presence of methanol since the reaction mechanism in both cases should be comparable (see Chapter 3.7.1).

- **Cyclizations in the absence of a nucleophile:**
  In this case the initially formed radical cation intermediate should undergoes elimination ([b], see Scheme below) instead of nucleophile addition ([a]) to form a neutral allylic radical which could undergo radical cyclizations (see Chapter 3.7.2).
3.7.1 Hydride ion as a weakly complexing nucleophile-attempted PET-initiated cyclization in presence of 1,4-dihydropyridine

1,4-Dihydropyridine derivatives have been widely used as models of NAD(P) to mimic reduction processes. There are a number of examples in literature where 1,4-dihydropyridine derivatives were used as a source of hydrogen ion.\textsuperscript{54} Moreover, the use of hydride ion as a nucleophile in polycyclizations gives the possibility to mimic non-oxidative enzymatic cyclizations of e.g. squalene to hopanoid-like polycyclic terpenoids, which were never mimicked before.

The mechanistic proposal is presented in Scheme 18. Excitation of the cationic electron acceptor, N-methylacridinium hexafluorophosphate (NMA$^+$), leads to oxidation of biphenyl (BP). The so-formed cation radical of biphenyl (BP$^{++}$) oxidizes the $\omega$-alkene site of the polyalkene 44 to a radical cation (59). This radical cation could then be trapped in \textit{anti-Markovnikov} fashion by hydride ion from 1,4-dihydropyridine (60), which is oxidized to a protonated pyridine derivative (61). The neutral radical (62) could undergo radical cyclization yielding the intermediate 63. Termination of the entire process could be achieved by reduction of the final radical center to the parent anion (64), followed by protonation. By this mechanistic proposal 1,4-dihydropyridine would be involved twofold, first as a source of hydride ion ([a]) and secondly as a source of a proton ([b]).
The commercially available 1,4-dihydropyridine 66 was chosen for the intended purpose. Initially the absorption properties of 66 were checked. This compound shows a significant absorption with its maximum at 231 nm ($\varepsilon = 14780\ \text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$) including a shoulder at approximately 250 nm and a broad absorption peak with the maximum at 337 nm ($\varepsilon = 7260\ \text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$) (Figure 16).
Next we have examined the stability of the substrate/1,4-dihydropyridine mixture in the dark since the substrate 44, having a reactive C=C bond in conjugation with the acceptor group, could react with 66 without activation.\textsuperscript{54b}

The solution of the substrate 44 and 1,4-dihydropyridine 66 in dichloromethane is stable even after 20 days in the dark which meets our requirements.

However, due to the availability of the absorption at wavelengths longer than 366 nm the stability examination of 66 under the irradiation conditions (400 nm, G.W.V. filter, CH\textsubscript{2}Cl\textsubscript{2}) is essential.

To mimic the reaction conditions and to check the risk of side reactions under these conditions (reduction of the C=C bond being in conjugation with the electron withdrawing C(O)-N group) 1,4-dihydropyridine 66 was irradiated in the presence of one equivalent of substrate 44.

Unfortunately, compound 66 is not stable under these conditions and after one day of irradiation it was nearly decomposed (Figure 17).

To intercept emission at the wavelengths shorter than 380 nm a liquid filter (75 g of NaNO\textsubscript{2} in 100 ml H\textsubscript{2}O) was utilized. It was found that under these conditions 1,4-dihydropyridine...
66 is more stable but still after 3 days of irradiation only a small part of starting 1,4-dihydropyridine was left (Figure 18). Due to these facts the time of reaction has to be no longer than 2-3 days. However, irradiation of the starting material 44 in the presence of 5 equivalents of 1,4-dihydropyridine 66 with byphenyl and NMA•PF₆ as electron acceptor couple (Scheme 19) leads to very poor conversion of starting material and no cyclic product formation, even after longer reaction times (3 days), was detected. The isolation of the corresponding pyridine from the reaction mixture suggests that 1,4-dihydropyridine 66 undergoes disproportionation, possibly much faster than photocyclization, rendering the formation of the expected target product 65 inefficient.

Scheme 19: Irradiation of 44 in presence of 1,4-dihydropyridine 66
At this point of the work we have to conclude that in spite of the potential advantages and application possibilities of this method it will not be possible to make it easily applicable.

3.7.2 PET-initiated cyclizations in the absence of a nucleophile - elimination instead of nucleophile addition

3.7.2.1 Design of the substrate for cyclizations in the absence of a nucleophile

As it was discussed in Chapter 3.7, in PET-initiated cyclizations in the absence of a nucleophile the intermediately formed radical cation should undergo elimination instead of nucleophile addition to form a neutral allylic radical which could trigger radical cyclizations (see Scheme on page 50). The possibility of such sort of reaction was demonstrated by H. Roth$^{14}$ and Y. Makhynya.$^{55}$ In both cases elimination of the proton occurs from the methyl group and isopropylene-substituted five-membered rings were formed. For such a reaction type that is intended to be catalytic and possibly enantioselective, structurally adequate substrates have to be designed.

It was decided to leave the oxazolidinone template in conjugation to one C=C bond serving as an electron trap which could likely increase the reactivity of the complexed as compared to the free substrate. However, the chain length between the two C=C bonds (the terminal and the conjugated one) must be increased to favor cyclization at all and to circumvent the anfavorite formation of a four-membered ring (Scheme 20, [a]).
Scheme 20: Consideration of the substrate to be cyclized in the absence of a nucleophile

For that reason 68, which can be readily synthesized from commercially available compounds (see next Chapter 3.8.2), was chosen as potential substrate for the intended cyclization. This compound has two carbons more than 44 in the chain between the C=C bonds and in view of previously described reactions (H. Roth, Y. Makhynya) should offer the opportunity to form upon cyclization the isopropylene-substituted six-membered ring intermediate 68a (Scheme 20, [b]).

3.7.2.2 Synthesis of trans-3-(5,5,9-trimethyl-deca-2,8-dienoyl)-oxazolidin-2-one (68)

As discussed in the previous chapter, the compound 68 was chosen as substrate for further cyclizations, the synthesis of which is shown in Scheme 21.

Methylation of commercially available cis/trans citral (69) by the earlier prepared organocuprate reagent affords the compound 70 in 70-75% yield. The following Horner-Wadsworth-Emmons reaction with 70 and the in advance prepared enolate of triethyl phosphonoacetate resulted in 71 as the trans-isomer in 93% yield, which was then hydrolyzed to the corresponding acid 72 and converted to the parent acid chloride before reaction with N-lithium oxazolidin-2-one to give 68 in 40% yield.
Scheme 21: Synthesis of trans-3-(5,5,9-trimethyl-deca-2,8-dienoyl)-oxazolidin-2-one (68)

It should be noticed that similarly as in the preparation of 44, the main side-product in the last step is the chlorinated compound 73. The amount of its formation is again found to be extremely dependent on the origin of oxalyl dichloride used for this preparation (see Chapter 3.2).

3.7.2.3 Enantioselective cyclization of trans-3-(5,5,9-trimethyl-deca-2,8-dienoyl)-oxazolidin-2-one (68) catalyzed by the chiral Cu(II) / Ph-PyBOX complex 56

Irradiation of substrate 68 at 400 nm with a G.W.V. filter in CH₂Cl₂ in the presence of NMA·BP as electron acceptor couple leads to very poor conversion of starting material and to no formation of cyclic product even after longer reaction times.
Finally, our efforts were rewarded, when the same reaction was conducted in presence of one equivalent of chiral complex 56 to give the cyclic product 74 in 28% yield. All other reaction parameters were left unchanged.

The formation of compound 74 containing a five-membered ring, instead of the expected six-membered ring (Scheme 20, [b]), indicates kinetic control of product formation.

The proposed reaction mechanism is presented in Scheme 22. Excitation of the cationic electron acceptor N-methylacridinium hexafluorophosphate (NMA+) leads to oxidation of biphenyl (BP). The so-formed cation radical of biphenyl (BP+) oxidizes the ω-alkene site of the substrate 68 to give a radical cation (75) which undergoes elimination to form the allylic radical 76. This neutral allylic radical 76 initiates then radical cyclization yielding the cyclic intermediate 77. Termination of this process is most likely achieved by reduction of the final radical center in 77 to the corresponding anion, followed by protonation and ligand exchange to afford 74.

**Scheme 22:** Proposed mechanism of PET-initiated cyclization of 68→74 promoted by the Cu(II) / Ph-PyBOX complex (56)
Moreover, reduction of the chiral complex loading to 0.3 equivalent leads to a slight decrease in yield (28→26%) only, demonstrating the catalytic nature of complex 56 in this reaction.

Furthermore, this cyclizations show enantioselective nature under applied conditions. It was found that the enantioselectivity for the formation of the trans-74 shows no dependence of the substrate-chiral Lewis acid (R)-56 proportion (~9% e.e.). However, the enantioselectivity of formation of cis-74 is dependent on the substrate-catalyst proportion and the catalyst configuration (see Table 4).

Table 4: Enantioselectivity of cyclizations 68→74 in presence of the chiral complex 56

<table>
<thead>
<tr>
<th>Catalyst loading</th>
<th>Configuration of 56</th>
<th>trans-74 enantiomeric ratio (e.e.)</th>
<th>cis-74 enantiomeric ratio (e.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 equiv. (S)</td>
<td>1 : 1.070</td>
<td>1 : 1.183 (8.4%)</td>
<td></td>
</tr>
<tr>
<td>0.3 equiv. (S)</td>
<td>1 : 1.043</td>
<td>1 : 1.111 (5.3%)</td>
<td></td>
</tr>
<tr>
<td>0.3 equiv. (R)</td>
<td>1 : 1.205 (9.3%)</td>
<td>1 : 1.002</td>
<td></td>
</tr>
<tr>
<td>1.0 equiv. (R)</td>
<td>1 : 1.193 (8.8%) (17.1%) 1.413 : 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.8 The β-ketoesters group as template

In the previous Chapter 3.7.2.3 a new type of the PET-initiated radical cyclizations, catalyzed by the Cu(II)-based complex 56 was achieved with encouraging enantioselectivity.

The most probable reason of incomplete enantioselectivity is inefficient shielding of the alkene faces by chiral group which can be improved by optimisation of complex geometry.

[a] Separation of the peaks for cis-74 was not complete, but due to their symmetrical shape the integration is possible.
The complex geometry could principally be changed by the following ways [a]:

- Changing of the metal center and counter ion
- Utilization of other types of ligands
- Substrate containing another achiral template.

The first and second options are very promising and can be performed best in combination with computational methods. However, these options will experimentally be very time consuming.

The third option, i.e., the utilization of another template in addition to changes in the complex geometry gives an opportunity to check the applicability of the newly developed methodology to other types of substrates. The β-ketoesters 78a, 78b and 78c, which should provide sufficient complexation capacity to the metal center of the catalyst with the two available carbonyls where probed as substrates having β-ketoester unit as template. These should exhibit a different orientation (as compared to 68) of the radical-accepting group relative to the metal center. This should give the opportunity to change the reactive center geometry by still using the same chiral complex as in examples with the oxazolidinone template used before.

Along this line of thinking the substrates 78a-c were prepared and subjected to the previously elaborated reaction conditions.

It should be mentioned that enolization of β-ketoesters in solvents of low polarity (e.g. dichloromethane) is inefficient and normally the use of strong bases is necessary to shift the equilibrium to the enol-form. That is why comparably weak π-type of complexation between the substrate and the chiral complex is expected being essential for the intended catalysis.

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[a] For the more detailed discussion about possible improvements of the complex geometry, see Chapter 5 (Outlook).
Moreover, in case of successful cyclizations the role of the keto carbonyl as the radical acceptor for such reactions could be demonstrated. The methylated β-ketoesters 78b and 78c have been prepared for two reasons: To show the influence of the substituents on the reaction efficiency and to examine the influence of bulky substituents in α-position to the carbonyl on the stereoselectivity in the planned cyclizations. Due to the different number of carbons in the chain between two double bonds in the substrate 78, as compared to 68, the formation of another cyclic system is expected (Scheme 23).

**Scheme 23:** Proposed cyclization pathways for the substrates 78

![Scheme 23 Diagram]

Usually, due to the stereoelectronic requirements, formation of a 5-membered ring via 5-exo ring closure takes place much faster than formation of a 6-membered ring, especially for 6-exo closures. But in this case (Scheme 23, [a]) the steric hindrance, caused by two methyl substituents, could slow down the cyclization speed leading to the 5-membered system that could exceptionally result in preferential formation of the six-membered ring (Scheme 23, [b]).
3.8.1 Synthesis of β-ketoesters 78a, 78b and 78c

The β-ketoester 78a was obtained in two ways (Scheme 24). A first way involves alkylation of dimethyl carbonate by commercially available 6-methyl-hept-5-en-2-one (48) using sodium hydride in THF. By this way the target product 78a was synthesized in about 73% yield.

A second method involves the γ-alkylation of methylacetoacetate (AcAc) by prenyl bromide. For this synthesis either two equivalents of lithium diisopropylamid (LDA) or an excess of two differently strong bases (NaH and BuLi) was used. This way is synthetically more complicated and usually provides lower yields (about 40-45%) as compared to the first approach.

The alkylation of 78a by one equivalent of methyl iodide in the presence of potassium carbonate and at reflux in methanol leads to the formation of monoalkylated β-ketoester 78b in about 80% yield. If 78a is alkylated by 2.2 equivalents of methyl iodide at room temperature in the presence of sodium methoxide, a mixture of 78b (22%) and 78c (55%) was obtained and separated effectively by column chromatography.
Scheme 24: Synthesis of β-ketoesters 78a, 78b and 78c

3.8.2 Cyclizations of β-ketoesters 78a and 78b catalyzed by Cu(II) / Ph-PyBOX

Even a longer irradiation time of 78a at 400 nm in dichloromethane in the presence of NMA$^+$PF$_6$/$\text{BP}$ as electron acceptor couple leads to very poor conversion of starting material without formation of cyclic products. However, when the same reaction was conducted in the presence of one equivalent of complex 56, the cyclic product 80a resulted in 28% yield (Scheme 25).
Scheme 25: Cyclizations of 78a and 78b in presence of the complex 56

Furthermore, when 78b is cyclized under the same conditions in presence of 56, the yield of cyclic products is increased to 44% with complete conversion of starting material in a much shorter reaction time (Scheme 25, 78b → 80b). So far we cannot find a sound explanation for this effect.

The proposed reaction mechanism is presented in Scheme 26. The electronically excited cationic electron acceptor N-methylacridinium hexafluorophosphate (NMA+) oxidizes biphenyl (BP) resulting in the formation of a cation radical of biphenyl (BP+●), which oxidizes the alkene site of the substrate 78 to a radical cation (81). This radical cation undergoes elimination to form an allylic radical (82). This step differs from the elimination step in the cyclizations of the oxazolidinone-containing substrate 68 (Scheme 22), where elimination of a proton occurs not from the methyl group as in the present case (81 → 82) but from a chain CH2 group (75 → 76).

The so-formed neutral allylic radical 82 undergoes subsequently radical cyclization to the cyclic radical intermediate 83. Termination of the whole process is likely achieved by reduction of the final radical center to the corresponding anion, followed by protonation and ligand exchange in analogy to the mechanistic sequence discussed in chapter 3.7.2.3.
Scheme 26: Proposed mechanism of PET-initiated cyclizations of 78a and 78b promoted by the Cu(II)/Ph-PyBOX complex 56

Lowering of the chiral complex loading to 0.1 equivalent leads to significant decrease in yield (28→16% for 78a→80a; 44→12% for 78b→80b), but still demonstrating the catalytic nature of complex 56 in this reaction.

In contrast to the cyclization of 68→74 (Scheme 22, p. 58), the cyclizations 78a→80a and 78b→80b show no stereoselectivity. The most probable reason for no relevant stereoselectivity in these reactions is that the changes in orientation of the reactive double bond relative to the metal resulted to worse shielding of it by the chiral ligand.

3.8.3 Irradiation of 78c in presence of complex 56

In contrast to 78a and 78b, the dimethylated analog 78c does not form cyclic products under the given conditions. The irradiation of 78c in dichloromethane in the presence of NMA*PF6/BP and 0.3 equiv. of the complex 56 leads to the
formation of the oxidation product 84 in 49% yield at 57% conversion of starting material (Scheme 27).

**Scheme 27:** Photochemical formation of 84 from 78c in the presence of 56

Most probably the cyclic product 85 does not form due to the neopentylic nature of the radical accepting keto group which is shielded by geminal methyls effectively.

The proposed mechanism leading to the oxidation product 84 is presented in Scheme 28.
Scheme 28: The photochemical Cu(II)-mediated oxidation of 78c

The initiation of this reaction is analogous to that described in Scheme 26 and for the simplification is omitted. The formed by PET radical-cation 86 undergoes elimination to form an allylic radical intermediate 87. The keto group is effectively shielded by geminal methyls and hence the radical cyclization being similar to 82→83 does not occur. The radical center in 87 is probably oxidized by Cu(II) to the corresponding cationic intermediate 88 which undergoes elimination to form the highly conjugated compound 84.

The ability of the Cu$^{2+}$-salts to oxidize radicals was discovered by Heiba and Dessau,$^{57}$ then it was extensively used for the Mn(III)-acetate-induced radical cyclizations, where Cu(II)-acetate plays the role of a mild co-oxidant.$^{58}$ Moreover, in the last years the first examples of Cu(II)-mediated photochemical cyclizations were achieved in our group.$^{55}$

It should be mentioned that oxidation of radicals by Cu(II) ions coordinated to a bulky and good coordinating ligand, such as Ph-PyBOX, is not efficient and usually no products of oxidation can be isolated after Cu(II)/Ph-PyBOX-promoted reactions (e.g. 68→74 (p. 58) or 78a,b→80a,b). It is most probable that in case of 78c the lifetime of the radical greatly increases, due to the impossibility of the cyclization, so that oxidation becomes favorable.
3.9 Examination of the precipitation formed during the complex preparation

It should be noticed that during the preparation of the chiral catalyst 56, after all Cu(OTf)$_2$ was dissolved, some precipitation was observed. The formed dark-blue crystals were collected and dried in vacuum.

It was assumed initially that this material is a Cu$^{2+}$(Ph-PyBOX)$_2$ complex. To check this possibility, two equivalents of Ph-PyBOX were mixed with one equivalent of Cu(OTf)$_2$. The absorption spectrum of this mixture turned out to be very similar to the absorption spectrum of the precipitate that validates assumption (Figure 19).

The formation of badly soluble Cu(Ph-PyBOX)$_2$ in dichloromethane reduces the concentration of catalytically active mono-substituted complex 56 that should decrease the cyclization efficiency. On the other hand, due to the Jahn-Teller distortion the complexation of the second ligand should be much weaker as compared to the first one that should provide significant exchange with the substrate leading to the reactive complex.
3.10 Synthesis of Et-PyBOX and its complexation to Cu(OTf)$_2$

With the aim to reduce the catalyst cost the ligand Et-PyBOX (89) being a much cheaper modification of the so far successfully utilized Ph-PyBOX 41 was synthesized. The synthesis of 89 is analogous to the synthesis of 41 (see Chapter 3.1.3.1), but for the preparation of this ligand the much cheaper (R)-(-)-2-amino-1-butanol was utilized as a chiral precursor (Scheme 29).

Scheme 29: Synthesis of the chiral ligand 89

Similarly as 41, the ligand 89 exhibits a broad absorption spectrum consistent with the availability of two C=N groups being conjugated with a pyridine ring. The formed complex with Cu(OTf)$_2$ shows absorption up to 340 nm (Figure 20). The complexes of Ph-PyBOX and Et-PyBOX show similar absorption spectra (Figure 21) but PhPyBOX has due to the availability of aromatic substituents a shoulder at about 310 nm and absorbs up to longer wavelengths.
Figure 21: Absorption of PyBOX complexes in CH$_2$Cl$_2$, c=10$^{-5}$ mol/l

Figure 20: Complexation of Et-PyBOX to Cu(OTf)$_2$ in CH$_2$Cl$_2$, c=5*10$^{-5}$
3.10.1 Cyclizations of β-ketoesters 78a and 78b catalyzed by Cu(II) / Et-PyBOX (85)

Irradiation of substrate 78a at 400 nm with a G.W.V. filter in CH₂Cl₂ in the presence of NMA+PF₆/BP as electron acceptor couple and one equivalent of the chiral complex 85 leads to the cyclic product 80a in 13% yield. When the same conditions are applied to 78b the cyclic product 80b results in 12% yield.

Scheme 28: Cyclization of 78a,b in presence of the complex 92

These product yields are lower than in case of the application of the chiral complex 56 (80a: 28%→13%; 80b: 44%→12%) but due to the much lower cost of the ligand 89 (see Chapter 3.10) its application could be still reasonable in some cases.

Lowering of the chiral complex loading to 0.1 equivalent leads to comparable product formation yields (80a: 13%→9%; 80b: 12%→15%) which documents the catalytic nature of 92 in these reactions.
4 Summary

In this work the following results have been achieved:

- **A general methodology for PET-initiated catalytic cyclizations was successfully developed.**

  This methodology includes a number of more general parameters for catalytic PET-reactions probed in this work. These include the nature of the metal center, the nature of the chiral ligand and the solvent, as well as parameters consistent with the photochemical initiation of the performed reactions (donor/acceptor couple and irradiation wavelength). All these parameters were successfully adjusted.

  Moreover, the conditions being essential for the catalysis such as strong complexation of the chiral ligand and weak complexation of the substrate to the metal were worked out.

- **The stability problem of the reactive Cu(II) complexes (catalysts) was solved by adjustment of the reaction conditions.**

  To master this problem the absorption spectra of the metal-chiral ligand complexes were analyzed and their stability under irradiation at different wavelengths was examined. It was found that the utilization of a G.W.V. filter, which has no or negligible transmission at wavelengths shorter than 366 nm, enhances the stability of the chiral complexes during irradiation significantly.

- **Application of the new methodology of catalysis for two types of reactions.**

  The applicability of the methodology was shown for reactions of an allylic radical in conjugate addition and with a carbonyl.
• **First example of an enantioselective PET-triggered radical cyclization catalyzed by a chiral metal complex.**

It was shown for the first time that PET-initiated cyclizations can be performed catalytically and enantioselectively (see Chapter 3.7.2.3, p. 57). It was found that the enantioselectivity for the formation of the *trans*-74 shows no dependence of the substrate-chiral Lewis acid (*R*)-56 proportion (~ 9% e.e.). However, the enantioselectivity of formation of *cis*-74 is dependent on the substrate-catalyst proportion and the catalyst configuration (see Table below).

<table>
<thead>
<tr>
<th>Catalyst loading</th>
<th>Configuration of 56</th>
<th><em>trans</em>-74 enantiomeric ratio (e.e.)</th>
<th><em>cis</em>-74 enantiomeric ratio (e.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 equiv.</td>
<td>(S)</td>
<td>1 : 1.070</td>
<td>1 : 1.183 (8.4%)</td>
</tr>
<tr>
<td>0.3 equiv.</td>
<td>(S)</td>
<td>1 : 1.043</td>
<td>1 : 1.111 (5.3%)</td>
</tr>
<tr>
<td>0.3 equiv.</td>
<td>(R)</td>
<td>1 : 1.205 (9.3%)</td>
<td></td>
</tr>
<tr>
<td>1.0 equiv.</td>
<td>(R)</td>
<td>1 : 1.193 (8.8%)</td>
<td>1.413 : 1</td>
</tr>
</tbody>
</table>

Moreover, it was shown that the enantioselectivity depends on the orientation of the radical-accepting double bond relative to the metal center of the catalyst, i.e. giving enantioselectivity for 68→74 and no selectivity for 78a-b→80a-b (see Chapter 3.8.2).
5 Outlook

In order to increase the enantioselectivity in the reactions probed in this work, the factors which are responsible for the asymmetric induction have to be analyzed.

General demands for enantioselective radical cyclizations are as follows:

<table>
<thead>
<tr>
<th>Demand</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The reactivity of the substrate-chiral Lewis acid complex must exceed that of the free substrate</td>
<td><strong>Is achieved in this work</strong></td>
</tr>
<tr>
<td>2. The orientation of the complexing chiral group must be fixed in the complex relative to the reactive center</td>
<td></td>
</tr>
<tr>
<td>3. For the use of catalytic amounts of chiral Lewis acids, labile complexation of substrate is essential for the turnover</td>
<td><strong>Should be improved in the future</strong></td>
</tr>
<tr>
<td>4. The chiral group must shield the alkene faces efficiently and diastereotopically upon complex formation</td>
<td></td>
</tr>
</tbody>
</table>

The major demand that should be improved concerns the complex geometry and nature of the shielding groups.
There are a number of ways in which a reorganization of the complex geometry is possible:

- **Application of a substrate containing another achiral template** (partially probed in this work, see Chapter 3.8)

    As it was mentioned in Chapter 3.8 the utilization of alternative achiral templates, than the ones used in this work, can change the geometry of the reactive complex significantly. The presently used templates (e.g. the
oxazolidinone [a] form a six-membered chelate with the chiral Lewis acid. The utilization of alternative achiral templates that would form five-membered chelates (such as in [b]) with the chiral complex could change the position of the reactive double bond relative to the metal center.

- **Change of the metal center from Cu(II) to another transition metal**

  By this way it is possible to change the complex geometry, for example, from the typical Cu(II)-distorted planar to a tetrahedral configuration, which is typical for Zn(II) or Mg(II).

  Moreover, a Sc(III)-ligand complex might be more active as Lewis acid catalyst than Cu(II) analogues by virtue of a higher formal positive charge.

  Utilization of Sn(II) which has opposite orientation of “strong” and “weak” coordination sites gives an opportunity to change orientation of a substrate in complex.

- **Variation of counter ions**

  In all experiments done in this work a triflate ion was utilized as counter ion in the chiral complex. It is known that for reactions, catalyzed by such types of Lewis acids, the counter ion plays a crucial role for enantioselectivity.  

\[ \text{M} = \text{Zn}^{2+}, \text{Mg}^{2+} \]
By examination of different combinations of metal-counter ion pairs in combination with computation methods it should be possible to find the metal-counter ion pair corresponding best to the chosen substrates.

- **Changes in the chiral ligands**

This work shows that PET-initiated radical cyclizations can be performed catalytically with encouraging enantioselectivity (8-17% e.e.) when the Cu(II)/Ph-PyBOX chiral complex is used as catalyst. Possibly the Ph substituent cannot provide enough shielding of the stereogenic centers. Using computational methods it should be possible to find the group, ideally fitting the control of stereogenic centers in the transition stage.

Utilization of other types of C2-symmetrical ligands should change the geometry of the complex. Moreover, the utilization of tartaric acid derivatives, such as the chiral ligand 93, should be envisaged which would lower the cost of the catalyst.59

- **Control of rotamers**

As it was described in Chapter 2.3 rotamer control plays a crucial role in the successful execution of complex-controlled enantioselective conjugate radical addition, especially for the oxazolidinone template, which is part of the substrate 68. Two-point binding of the substrate to the metal should help to avoid rotation around the C(O)-N double bond (such as in the anti-rotamer) but still allowing rotation around C(O)-C (s-cis/s-trans) rendering the complex geometry ambiguous (see Scheme below).
This problem can be overcome by the use of a template having geminal methyl groups in $\alpha$-position to the nitrogen, which would not allow the template to adopt an $s$-trans configuration due to steric constrains.$^{60}$
6 Experimental section

I would like to thank the following co-workers of the Max Planck Institute for Bioinorganic Chemistry and the Max Planck Institute for Coal Research (Mülheim an der Ruhr) for their help and services: Mrs. K. Sand, Mr. J. Bitter (NMR spectrometry); Mrs. G. Schmitz, Mrs. U. Westhoff and Mrs. M. Trinoga (GC and HPLC analysis); Mr. W. Schmoeller and Mr. W. Joppek (MS spectrometry). I am also very appreciate to all the members of the administration, library staff and technical staff of the Max Planck Institute for Bioinorganic Chemistry, whose assistance has made the realization of this work much easier.

6.1 Instruments, methods and materials

Infrared spectra (IR):
Recorded on Brucker IFS 66 (FT-IR-Spectrometer) or a Perkin-Elmer 1600 spectrometer using thin film deposition on KBr-pressed plates. Peak values are given in wavenumbers (cm\(^{-1}\)). The symbols s (strong), m (medium) and w (weak) characterize the relative band intensities.

Ultraviolet absorption spectra (UV):
Recorded on Cary 17 or Bruins Omega-10 spectrometers. \(\lambda_{\text{max}}\) values are given in nm; \(\varepsilon\) values in units of mol\(^{-1}\)dm\(^3\)cm\(^{-1}\) are given in parentheses.

Mass spectra (MS):
Recorded on a Finnigan MAT 311A or MAT 95 (HRMS) instrument at 70 eV ionisation energy. Data are presented in m/z values. When required, molecular ion peaks were ascertained by chemical ionisation (CI), electron ionisation (EI) or fast atom bombardment (FAB) techniques.
Nuclear Magnetic Resonance spectra (NMR):
Recorded in *Fourier* Transform mode on the following *Brucker* instruments: A DRX-500 (500 MHz for $^1$H, 125.8 MHz for $^{13}$C), an AM-400 (400 MHz for $^1$H, 100.6 MHz for $^{13}$C), or an ARX-250 (250 MHz for $^1$H, 62.9 MHz for $^{13}$C) with dilute solutions in deuteriochloroform (CDCl$_3$) at 300 K unless stated otherwise. Chemical shift values are given in $\delta$ units (parts per million, ppm) with the solvent resonance as the internal standard (CDCl$_3$: $\delta$ = 7.26 (1H NMR), $\delta$ = 77.00 (13C NMR)). All coupling constants, $J$, are reported in Hz. The multiplicity of a signal is denoted by one of the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). NOE: abbreviations: s (strong), m (medium) and w (weak).

$^{13}$C NMR resonance assignments were aided by the use of DEPT-135 and DEPT-90 technique to determine numbers of attached hydrogens; HMQC technique for correlation between $^{13}$C and $^1$H signals; HMBC and COSY technique for structure determination.

Gas chromatographic analysis (GC):
Chromatograms were recorded on *Hewlett-Packard HP 5890* and *HP 6890* instruments equipped with a flame ionisation detector (FID) and capillary columns. Hydrogen was used as a carrier gas. Conditions are given in the following sequence: type of the column, the length of the column, starting temperature [$^\circ$C], heating rate [$^\circ$C /min], final temperature [$^\circ$C]. Unless stated otherwise, the standard chromatography runs involved an initial column temperature of 60 $^\circ$C or 80 $^\circ$C with 6 $^\circ$C or 8 $^\circ$C/min increments, an injector temperature of 230 $^\circ$C and a detector temperature of 250 $^\circ$C.

Thin layer chromatography (TLC):
Performed on *Merck* silica gel 60 F$_{254}$ precoated aluminium plates. The plates were visualized with UV light and then were thermally developed. Solution containing 30 g vanillin, 5 ml conc. H$_2$SO$_4$, and 1000 ml ethanol or 2 g KMnO$_4$, 5 g K$_2$CO$_3$ and 100 ml water was used as a development reagent.
Column chromatography:
Gravimetric columns or high pressure variant on self-packed Kronlab Sepakron-FPGC glass columns of different sizes on Merck silica gel 60 (0.063-0.20 or 0.04-0.063 mm) with pressure pumps Buechi 688 or Besta E-100 and pressure 1-10 bar were used. All solvents were distilled before use.

Irradiations:
All samples were stirred and flushed with argon prior to irradiation. Cylindrical Pyrex reaction vessels equipped with cooling finger (i-PrOH or H₂O coolant) were used. Rayonet reactors (RPR-100-System, Southern New England Ultraviolet (S.N.E.U.) company) with sixteen 300 or 350 nm ($\lambda_{\text{max}}$) lamps (S.N.E.U. company) or Rayonet reactors (RS-System, S.N.E.U. company) with four 400 nm ($\lambda_{\text{max}}$) lamps (Leuchtstoffwerk, Heidelberg) were employed.

Solvents:
Purchased from Merck, Aldrich or Fluka and used directly or purified by a standard procedures. Absolute solvents were purchased from Fluka and kept under molecular sieves. If necessary, the absolution was performed using the standard methods.⁶¹

Reagents:
The chemical name, abbreviated molecular formula (within parentheses, if appropriate), quality, purification procedure and company of purchase are listed below:
Acridin: 98%, ACROS.
(R)-(−)-2-Amino-1-butanol: 90%, Fluka.
(1R, 2S)-(−)-cis-1-Amino-2-indanol: 99%, Fluka.
(R)-2-Amino-2-phenylethanol: 98% (99% e.e.), Aldrich.
(S)-2-Amino-2-phenylethanol: 98% (99% e.e.), Aldrich.
Ammonium chloride: 99%, Merck.
Biphenyl (BP): 99%, *Fluka*.

*n*-Butyllithium (*n*-BuLi): 15% solution (ca. 1.6 M) in hexane, *Aldrich*.

Chloroform-d1 (Deuterochloroform): Deuteration > 99.5%, *Deutero GmbH*.

Citral (*cis/trans*): 95%, *Fluka*.

Cupric trifluoromethanesulfonate: 97%, *Fluka*.

Diethyl-4-ethyl-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate dimethyl carbonate: 99%, *Fluka*.

Dimethylmalononitrile: 97%, *Aldrich*.

Hydrogen peroxide, 30 wt.% solution in water, *Aldrich*.

L-tert-Leucinol: 96%, *Fluka*.

Lithium chloride: 99%, *Fluka*.


Lithium hydroxide: 98%, *Aldrich*.

Methyl acetoacetate: 99%, *Aldrich*.

3-Methyl-but-2-en-1-ol (Prenol): 98 %, *Aldrich*.

6-Methyl-hept-5-en-2-one (Prenylacetone): 98%, *Fluka*.

Methyl iodide: 99%, *Fluka*.

N-methylquinoliniumhexafluorophosphate (NMQ-PF₆): Prepared according to a literature procedure. ⁶²

Oxalyl chloride: 96%, *Fluka* or 98%, *Aldrich*.

Phosphorus tribromide (PBr₃): 99%, *Fluka*.

Potassium hexafluorophosphate (KPF₆): 99%, *Aldrich*.

2,6-Pyridinecarbonyl dichloride: 97%, *Aldrich*.

Quinolin: 97%, *Fluka*.

Sodium hydride (NaH): 55-60% by wt. dispersion in mineral oil, *Fluka*.

Sodium hydroxide (NaOH): flakes, z. A. *Merck*.

Sodium nitrite: 98%, *Fluka*.

Triethyl phosphonoacetate: 97%, *Fluka*. 
6.2 Nomenclature and general synthetic and photochemical procedures

Nomenclature: Compounds have been named according to the standard nomenclature rules (IUPAC) by means of the program AUTONOM. In some cases the numbering system was chosen differently in order to facilitate correlation with NMR signal assignments.

General synthetic procedures: A cooling bath of –20 °C to –78 °C consisted of a mixture of “dry ice” (CO₂) and acetone. Oxygen- or moisture-sensitive reactions were performed under an argon flow in either oven- or heat-gun-dried glassware equipped with a rubber septum. Air- or moisture-sensitive liquids and solutions were transferred by a syringe; solids were transferred through the funnel under a rapid argon flow. “Concentration” involved drying the combined organic layers over anhydrous Na₂SO₄, filtration and removal of the solvent(s) by rotary evaporation and/or at high vacuum (10⁻¹ - 10⁻³ torr).

6.2.1 General procedure for the PET-initiated reactions in dichloromethane / methanol (10:1) mixture

In a representative procedure, the substrate (1 equiv., about 0.001 mol), biphenyl (1 mol equiv.) and cationic electron acceptor 54 (0.41 mol equiv.) were dissolved in CH₂Cl₂/MeOH 10/1 (20 ml) and the resulting solution was stirred and degassed (argon) for 15 minutes inside the cylindrical Pyrex irradiation vessel equipped with a cooling finger (isopropanol as the coolant) prior to be placed in a Rayonet reactor. [a]

The reaction mixture was irradiated at -9 °C for 2-3 days (monitoring by TLC) and then was transferred into a round bottom flask. The reaction vessel was washed

---

[a] In experiments with G.W.V. filter the Pyrex irradiation vessel was placed in a cylindrical G.W.V. glass filter (Schott glass, Mainz) prior to be placed in a Rayonet reactor.
twice with dichloromethane and the combined organic phases were concentrated
followed by isolation of the products by column chromatography on silica gel.

6.2.2 General procedure for the PET-initiated reactions in presence of
chiral complexes

The chiral ligand (1 equiv., about 0.001 mol) was added to one equivalent of
Cu(OTf)$_2$ (about 0.001 mol) suspended in 5 ml of dry CH$_2$Cl$_2$. The resulting
mixture was stirred under argon flow inside the cylindrical Pyrex irradiation vessel
equipped with a cooling finger (isopropanol as the coolant) until all Cu(OTf)$_2$ was
dissolved (20-30 min).[a] To this mixture one equivalent of substrate in 15 ml of
dry CH$_2$Cl$_2$[b] was added and the resulting mixture was stirred for five minutes
followed by addition of biphenyl (1 mol equiv.) and cationic electron acceptor
(0.41 mol equiv.). The resulting solution was stirred and degassed (argon) for 15
minutes prior to be placed in a Rayonet reactor.[c]
The reaction mixture was irradiated at -9°C for 2-4 days (monitoring by TLC) and
then was transferred into a round-bottomed flask. The reaction vessel was
washed twice with dichloromethane and the combined organic phases were
bubbled with H$_2$S for 1-2 min in order to precipitate copper as sulphide. The
resulting suspension was degassed (argon) for 30 min. and the precipitation was
filtered off, washed twice on a filter with dichloromethane before concentration.
The solvent was evaporated followed by isolation of the products by column
chromatography on silica gel.

[a] In experiments with chiral ligand 41, after all Cu(OTf)$_2$ was dissolved, some precipitation of
bis-substituted complex was formed.
[b] In reactions performed in CH$_2$Cl$_2$:MeOH (10:1) instead of 15 ml of dichloromethane the
mixture of 2 ml of dry methanol with 13 ml of dry dichloromethane was added.
[c] In experiments with G.W.V. filter the Pyrex irradiation vessel was placed in a cylindrical
G.W.V. glass filter (Schott glass, Mainz) prior to be placed in a Rayonet reactor.
6.3 Synthesis of chiral ligands 39, 40, 41 and 89

6.3.1 Synthesis of chiral ligands 39 and 40

The ligands 39 and 40 were synthesized by following literature methods.63

6.3.2 Synthesis of chiral ligands (S)- and (R)-41 via (S)/(R)-42 and (S)/(R)-43

Both enantiomers of the chiral ligand 41 (see Scheme 13, p. 33) were obtained from (R)-2-amino-2-phenylethanol or (S)-2-amino-2-phenylethanol in three steps using an improved combination of literature methods64,46 (see discussion in Chapter 3.1.3.1).

6.3.2.1 Synthesis of bis(amid) (R)- and (S)-42

The bis(amid) 42 was synthesised from commercially available pyridine-2,6-dicarboxylic acid dichloride and two equivalents of (R)- or (S)-2-amino-2-phenylethanol by the following procedure:
To a solution of (R)- or (S)-2-Amino-2-phenylethanol (5.0 g, 36.4 mmol) in isopropylacetate (IPAC, 120 ml) at 65 0C an aqueous solution of sodium hydrogen carbonate (1.5 M, 27 ml) was added. The mixture was stirred at 65-70 0C for five minutes and then pyridine-2,6-dicarboxylic acid dichloride (3.72 g, 18.2 mmol) was added portionwise over 30 minutes. The resulting mixture was stirred at 80 0C for 2h and then allowed to reach room temperature. The organic layer was separated and the aqueous layer was extracted with 30 ml of IPAC. The combined organic layers were dried over anhydrous sodium sulfate and filtered. The evaporation of the solvent gave 6.9 g of crude 42 (purity > 90%, ~94% yield), which was used in further reactions without purification.
Pyridine-2,6-dicarboxylic acid bis-[(2-hydroxy-1-phenyl-ethyl)-amide] (42)$^[a]$: 

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{Ph} & \quad \text{HN} \\
\text{O} & \quad \text{OH}
\end{align*}
\]

$^1$H NMR (250 MHz, CDCl$_3$):

8.69 (d, 2H, $2\text{NH}$, $J$=7.5 Hz), 8.21 (d, 2H, $2\text{CH}$ (3) and (5), $J$ = 7.8 Hz), 7.89 (t, 1H, $\text{CH}$ (4), $J$ = 7.8 Hz), 7.21-7.38 (m, 10H, 10$\text{CH}_2$(2Ph)), 5.19 (td, 2H, $2\text{CH}$, $J_1$ = 4.9 Hz, $J_2$ = 7.4 Hz), 3.93 (d, 4H, $2\text{CH}_2$, $J$ = 4.9 Hz), 3.28 (br. s, 2H, $2\text{OH}$).

$^{13}$C NMR (62.9 MHz, BB, DEPT, CDCl$_3$):

163.64 (C=O), 148.57 (C=O (2) and (6)), 139.08 (C, Ph), 138.81 (CH (4)), 128.85 (CH, Ph), 127.86 (CH), 126.64 (CH, Ph), 125.09 (CH, 66.18 (CH$_2$), 55.81 (CH).

6.3.2.2 Condensation of 42 to Ph-PyBOX 41

To a solution of bis(amide) (42) (1.0 g, 2.47 mmol) in 30 ml of chloroform 1.8 ml (24.7 mmol) of SOCl$_2$ in 10 ml of chloroform were added. The resulting solution was refluxed for 2h and was then slowly poured in ice water. The organic layer was collected, washed with brine, dried over anhydrous sodium sulfate and filtered. The evaporation of the solvent gave 0.84 g of crude salt 43 (purity >90%, ~77% yield), which was used in further reactions without purification.

$^[a]$ An analytical data are represented here due to the different, as compared to the literature, deuterated solvent for NMR. Furthermore, the coupling constant have been added here.
2,6-Bis[4’-phenyloxazolin-2-yl]piridine dihydrochloride (43): \(^{[a]}\)

![Chemical structure of 2,6-Bis[4’-phenyloxazolin-2-yl]piridine dihydrochloride (43)](image)

\(1^H\) NMR (500 MHz, CDCl\(_3\)):
8.50 (d, 2H, J = 8.1 Hz), 8.36 (d, 2H, 2CH (3) and (5), J = 7.8 Hz),
8.05 (t, 1H, CH (4), J = 7.8 Hz), 7.35-7.42 (m, 8H, 8CH (Ph)), 7.32 (t,
2H, 2CH (Ph), J = 6.9 Hz), 5.55 (td, 2H, 2CH, J\(_1\) = 4.8 Hz, J\(_2\) = 8.6
Hz), 3.99 (dq, 4H, 2CH\(_2\), J\(_1\) = 4.9 Hz, J\(_2\) = 11.3 Hz).

\(13^C\) NMR (125.8 MHz, BB, DEPT, CDCl\(_3\)):
162.74 (Cq, C=N), 148.42 (Cq, (2) and (6)), 139.40 (CH (4)), 138.20
(Cq, Ph), 128.93 (CH, Ph), 128.33 (CH), 126.61 (CH, Ph), 125.45
(CH), 53.49 (CH\(_2\)), 48.51 (CH).

To a solution of crude salt 43 (0.8 g) in 50 ml of methanol a solution of NaOH in
water (8 ml, 5%) was added. The resulting mixture was stirred for 3 days at
room temperature. The excess of methanol was evaporated and the resulting
mixture was extracted with dichloromethane (2x50 ml). The extract was washed
with brine, dried over anhydrous sodium sulfate and filtered. The evaporation of
the solvent gave 0.6 g of 41 as a white solid (purity >90%, ~ 90% yield). \(^{[b]}\)

6.3.3 Synthesis of the chiral ligand (R)-89 via (R)-90 and (R)-91

\(^{[a]}\) An analytical data are represented here because in literature source this compound was
converted to the 41 without isolation and characterization.
\(^{[b]}\) An analytical data are in agreement with the literature source.\(^{66}\)
Was synthesised from $\,(R)$-(-)-2-Amino-1-butanol \,(90a)\, following the same synthetic procedure as for 41 (see Chapter 5.3.2).

\[
\begin{align*}
\text{\textbf{90}} \, &\text{(40\% yield from 90a)} \\
\end{align*}
\]

$^1\text{H} \text{ NMR} \, (400 \text{ MHz, CDCl}_3-\text{DMF}_d) :$

8.55 (d, 2H, 2NH, J = 8.7 Hz), 8.23 (d, 2H, 2CH (3) and (5), J = 8.7 Hz), 8.00 (t, 1H, CH (4), J = 7.8 Hz), 3.90-4.01 (m, 2H, 2CH (3')), 3.32-3.88 (m, 6H, 2CH$_2$ (4'), 2OH), 1.46-1.59 (m, 2H, CH$_2$ (5')), 1.61-1.73 (m, 2H, CH$_2$ (5')), 0.89 (t, 6H, 2CH$_3$ (6'), J = 7.4 Hz).

$^{13}\text{C} \text{ NMR} \, (100.6 \text{ MHz, BB, DEPT, CDCl}_3-\text{DMF}_d)$:

162.64 (Cq (1')), 148.29 (Cq (2) and (6)), 137.53 (CH (4)), 123.40 (CH (3) and (5)), 62.58 (CH$_2$ (4')), 52.39 (CH (3')), 22.86 (CH$_2$ (5')), 9.52 (CH$_3$ (6')).

\[
\begin{align*}
\text{\textbf{91}} \, &\text{(87\% yield from 90)} \\
\end{align*}
\]

$^1\text{H} \text{ NMR} \, (400 \text{ MHz, CDCl}_3):$

8.32 (d, 2H, 2CH (3) and (5), J = 7.8 Hz), 8.03 (t, 1H, CH (4), J = 7.8 Hz), 7.95 (d, 2H, J = 8.5Hz), 4.35 (dtt, 2H, 2CH (3')), J$_1$ = 3.4 Hz, J$_2$ = 7.1 Hz, J$_3$ = 10.6 Hz), 3.79 (dd, 4H, 2CH$_2$ (2'), J$_1$ = 2.3 Hz, J$_2$ = 3.4 Hz), 1.77 ( p, 4H, 2CH$_2$ (4'), J = 7.5 Hz), 1.00 (t, 6H, 2CH$_3$ (5'), J = 7.4 Hz).
\( ^{13} \text{C NMR} \) (100.6 MHz, BB, DEPT, CDCl\(_3\)):

- 162.86 (Cq (1'))
- 148.51 (Cq (2) and (6))
- 139.23 (CH (4))
- 125.10 (CH (3) and (5))
- 50.68 (CH (3'))
- 47.90 (CH\(_2\) (2'))
- 25.08 (CH\(_2\) (4'))
- 10.34 (CH\(_3\) (5'))

\( ^{1} \text{H NMR} \) (400 MHz, CDCl\(_3\)):

- 8.14 (d, 2H, 2CH (3) and (5), J = 7.8 Hz)
- 7.83 (t, 1H, CH (4) J = 7.8 Hz)
- 4.55 (dd, 2H, 2CH\(_2\) (2') J\(_1\) = 8.5 Hz, J\(_2\) = 9.3 Hz)
- 4.26 (ddd, 2H, 2CH (3'), J\(_1\) = 6.7 Hz, J\(_2\) = 9.5 Hz, J\(_3\) = 15.9 Hz)
- 4.12 (t, 2H, 2CHH (2') J = 8.2 Hz)
- 1.69-1.84 (m, 2H, CH\(_2\) (4'))
- 1.52-1.67 (m, 2H, CH\(_2\) (4'))
- 0.99 (t, 6H, 2CH\(_3\) (5'), J = 7.4 Hz)

\( ^{13} \text{C NMR} \) (100.6 MHz, BB, DEPT, CDCl\(_3\)):

- 162.26 (Cq (1'))
- 146.86 (Cq (2) and (6))
- 137.22 (CH (4))
- 125.60 (CH (3) and (5))
- 72.89 (CH\(_2\) (2'))
- 68.26 (CH (3'))
- 28.56 (CH\(_2\) (4'))
- 10.12 (CH\(_3\) (5'))

**MS** (EI) m/z (rel. int.):

- 273 (molecular peak, 7.78)
- 245 (27.79)
- 244 (100.00)
- 216 (23.39)
- 145 (11.25)
- 130 (5.82)
- 117 (11.40)
- 104 (5.34)
- 103 (8.81)
- 55 (6.56)

**HRMS:** m/z calculated for C\(_{19}\)H\(_{19}\)N\(_3\)O\(_2\):

- Theory: 273.147726
- Found: 273.147591
6.4 Synthesis of the substrate 44

6.4.1 Synthesis of 3,7-dimethyl-octa-2,6-dienoic acid ethyl ester 49a,b (trans- and cis-isomers)

The synthesis of compound 49a,b was adopted from the literature, however with a number of modifications (e.g. amount of solvent and separation of cis-/trans-isomers).

In a 500-ml three-necked flask equipped with a dropping funnel, magnetic stirring bar and thermometer was placed sodium hydride (4.1 g as a 60% dispersion in mineral oil, 103 mmol). Then 70 ml of dry THF was added and the flask was surrounded by an ice-salt mixture. Then a solution of triethyl phosphonoacetate (23.1 g, 103 mmol) in 70 ml of dry THF was added by stirring at 0 °C and the mixture was further stirred at this temperature for 30 min. After dropwise addition of a solution of 6-methyl-5-hepten-2-one (10 g, 79 mmol) in 50 ml of dry THF at 0 °C stirring of the reaction mixture was continued at this temperature for 1 h. The ice-salt bath was removed and the reaction stirred overnight before pouring it into a mixture of diethyl ether (200 ml) and saturated aqueous ammonium chloride (70 ml). The ether layer was separated and the aqueous layer was extracted with 100 ml of ether. The combined organic layer was dried over anhydrous sodium sulfate and filtered. Evaporation of the solvent gave a yellow oil containing cis-trans-ethyl geranate (1:3.5 by NMR). Column chromatography with silica gel (EtOAc / pentane = 1 / 15) afforded 10.7 g of trans-ethyl geranate (49a, 68.8% yield) and 3.1 g of cis-ethyl geranate (49b, 19.9% yield).

trans-3,7-Dimethyl-octa-2,6-dienoic acid ethyl ester (49a):

\[
\begin{align*}
49a &:
\end{align*}
\]

89
TLC  \( R_f = 0.62 \) (Et\(_2\)O / pentane = 1 / 9)

\(^1\)H NMR  (250 MHz, CDCl\(_3\)):
5.62 (s, 1H, CH\( \text{(2)} \)), 4.99-5.08 (m, 1H, CH\( \text{(6)} \)), 4.10 (q, 2H, CH\(_2\) (11), J = 7.1 Hz), 2.09-2.13 (m, 7H, CH\(_2\) (4), CH\(_2\) (5), CH\(_3\) (9)), 1.64 (s, 3H, CH\(_3\) (8) or (10)), 1.56 (s, 3H, CH\(_3\) (8) or (10)) 1.23 (t, 3H, CH\(_3\) (12) J = 7.1 Hz).

\(^{13}\)C NMR  (62.9 MHz, BB, DEPT, CDCl\(_3\)):
166.78 (Cq (1)), 159.64 (Cq (3)), 132.37 (Cq (7)), 122.94 (CH (6)), 115.55 (CH (2)), 59.35 (CH\(_2\) (11)), 40.87 (CH\(_2\) (4)), 25.99 (CH\(_2\) (5)), 25.56 (CH\(_3\) (8) or (10)), 18.69 (CH\(_3\) (9)), 17.58 (CH\(_3\) (8) or (10)), 14.25 (CH\(_3\) (12)).

cis-3,7-Dimethyl-octa-2,6-dienoic acid ethyl ester (49b):

\[
\begin{array}{c}
8 \quad 7 \\
6 \\
5 \quad 4 \quad 3 \quad 9 \\
10 \\
11 \\
12
\end{array}
\]

\(49b \text{ (cis-isomer)}\)

TLC  \( R_f = 0.70 \) (Et\(_2\)O / pentane = 1 / 9)

\(^1\)H NMR  (250 MHz, CDCl\(_3\)):
5.60 (s, 1H, CH\( \text{(2)} \)), 5.10 (tdt, 1H, CH\( \text{(6)} \)), J\(_1 = 1.4\) Hz, J\(_2 = 2.8\) Hz, J\(_3 = 7.3\) Hz), 4.08 (q, 2H, CH\(_2\) (11), J = 7.1 Hz), 2.58 (dd, 2H, CH\(_2\) (4), J\(_1 = 7.1\) Hz, J\(_2 = 8.6\) Hz), 2.11 (q, 2H, CH\(_2\) (5), J = 8.0 Hz), 1.83 (d, 3H, CH\(_3\) (9), J = 1.3 Hz), 1.63 (s, 3H, CH\(_3\) (8) or (10)), 1.57 (s, 3H, CH\(_3\) (8) or (10)), 1.21 (t, 3H, CH\(_3\) (12), J = 7.1 Hz).
**13C NMR** (62.9 MHz, BB, DEPT, CDCl₃):

166.19 (Cq (1)), 159.89 (Cq (3)), 131.96 (Cq (7)), 123.63 (CH (6)), 116.19 (CH (2)), 59.28 (CH₂ (11)), 33.36 (CH₂ (4)), 26.72 (CH₂ (5)), 25.55 (CH₃ (8) or (10)), 25.20 (CH₃ (9)), 17.49 (CH₃ (8) or (10)), 14.22 (CH₃ (12)).

6.4.2 Synthesis of trans-3,7-dimethyl-octa-2,6-dienoic acid (50)

*trans*-3,7-Dimethyl-octa-2,6-dienoic acid ethyl ester (49a) (1.82 g, 9.3 mmol) was suspended in 1N NaOH solution (50 ml), then 15 ml of methanol were added. The resulting solution was refluxed for 3 days and after cooling was extracted with diethyl ether (two times, each 50 ml) to yield some recovered starting material (220 mg). The aqueous solution was acidified and then extracted with diethyl ether (two times, each 100 ml). The combined extracts were dried over anhydrous sodium sulfate and filtered. Evaporation of the solvent resulted acid 50 (1.25 g, 90% yield) as a colorless oil.

*trans*-3,7-Dimethyl-octa-2,6-dienoic acid (50):

\[ 
\begin{array}{c}
\text{O} \\
\text{H} \\
1 \\
2 \\
3 \\
4 \\
5 \\
6 \\
7 \\
8 \\
9 \\
10 \\
11 \\
12 \\
\end{array} 
\]

trans-3,7-Dimethyl-octa-2,6-dienoic acid (50):

\[
\begin{align*}
\text{1H NMR} & \quad (400 \text{ MHz, CDCl}_3): \\
10.83 & \text{ (broad s, OH)}, 5.67 & \text{ (s, 1H, CH (2))}, 5.07 & \text{ (s, 1H, CH (6))}, 2.12-2.19 & \text{ (m, 7H, CH₃ (9), CH₂ (5) and CH₂ (4))}, 1.66 & \text{ (s, 3H, CH₃ (8) or (10))}, 1.54 & \text{ (s, 3H, CH₃ (8) or (10))}.
\end{align*}
\]
13C NMR (100.6 MHz, BB, DEPT, CDCl3):
172.37 (Cq (1)), 162.94 (Cq (3)), 132.61 (Cq (7)), 122.77 (CH (6)),
115.22 (CH (2)), 41.17 (CH2 (4)), 25.98 (CH2 (5)), 25.58 (CH3 (8) or
(10)), 19.08 (CH3 (9)), 17.62 (CH3 (8) or (10)).

6.4.3 Synthesis of 3-(3,7-dimethyl-octa-2,6-dienoyl)-oxazolidin-2-one (44)

In a 100-ml two-necked flask, equipped with a dropping funnel and magnetic
stirring bar, was placed a solution of trans-3,7-dimethyl-octa-2,6-dienoic acid (50)
(3.0 g, 18 mmol) in 20 ml of benzene. To this was added dropwise a solution of
oxalyl chloride (11.3 g, 89 mmol) in 40 ml of benzene and the resulting solution
was stirred for 3 h at 45 °C. The solvent and remaining oxalyl chloride where
removed by reduced-pressure distillation. After cooling to room temperature the
resulting carboxylic acid chloride was dissolved in 20 ml of dry THF and added
dropwise to a pre-cooled lithiated oxazolidin-2-one suspension (in a 250-ml two-
necked flask equipped with a dropping funnel and magnetic stirring bar), which
was prepared in advance by adding n-butyllithium (18 mmol) into a solution of
oxazolidin-2-one in 100 ml of dry THF at –78 °C. The resulting mixture was
stirred at –78 °C for 2 h and then at room temperature overnight. The reaction
was quenched thereafter by adding of saturated aqueous NH4Cl solution (40 ml)
and diethyl ether (100 ml). The ether layer was separated and the aqueous layer
was extracted with 50 ml of ether. The combined organic layer was dried over
anhydrous sodium sulfate and filtered. Solvent evaporation resulted the crude
product which was purified by column chromatography with silica gel (Et2O /
pentane = 1 / 1) to give 1.68 g of 44 (40% yield) and 0.7-1.1 g of chlorinated
compound 51 (see Chapter 3.2).
3-(3,7-Dimethyl-octa-2,6-dienoyl)-oxazolidin-2-one (44):

\[
\begin{align*}
\text{TLC} & \quad R_f = 0.22 \text{ (Et}_2\text{O / pentane = 1 / 1)} \\
\text{\textsuperscript{1}H NMR} & \quad (250 \text{ MHz, \textsuperscript{1}H-\textsuperscript{1}H-COSY, CDCl}_3): \quad 6.91 \text{ (dd, 1H, CH (2')), J}_1 = 1.0 \text{ Hz, J}_2 = 2.2 \text{ Hz), 5.01-5.11 (m, 1H, CH (6')), 4.36 (t, 2H, CH}_2 (5), J = 8.1 \text{ Hz), 4.02 (t, 2H, CH}_2 (4), J = 8.2 \text{ Hz), 2.12-2.24 (m, 7H, CH}_2 (4'), CH}_2 (5') \text{ and CH}_3 (9')), 1.66 (s, 3H, CH}_3 (8') \text{ or (10'))}, 1.58 (s, 3H, CH}_3 (8') \text{ or (10'))}. \\
\text{\textsuperscript{13}C NMR} & \quad (62.9 \text{ MHz, BB, DEPT, \textsuperscript{1}H-\textsuperscript{13}C-COSY, CDCl}_3): \quad 165.32 \text{ (Cq (1'))}, 162.60 \text{ (Cq (3'))}, 153.40 \text{ (Cq (2))}, 132.50 \text{ (Cq (7'))}, 122.88 \text{ (CH (6'))}, 114.87 \text{ (CH (2'))}, 61.71 \text{ (CH}_2 (5)), 42.61 \text{ (CH}_2 (4)), 41.50 \text{ (CH}_2 (4')), 26.11 \text{ (CH}_2 (5')), 25.60 \text{ (CH}_3 (8') \text{ or (10'))}, 19.96 \text{ (CH}_3 (9'))}, 17.66 \text{ (CH}_3 (8') \text{ or (10'))}. \\
\text{IR} & \quad (\text{KBr, } \nu_{\text{max}}): \quad 3530 \text{ (H}_2\text{O in KBr, s), 2921 (s), 2478 (w), 2167 (w), 1772 (s), 1675 (s), 1628 (s), 1384 (s), 1269 (s), 1107 (s), 1041 (s), 972 (m), 927 (w), 850 (s), 816 (m), 760 (s), 707 (s), 618 (m), 581 (w), 450 (w), 410 (w)}. \\
\text{MS} & \quad (\text{EI}) m/z \text{ (rel. int.):} \quad 237 \text{ (molecular peak, 12.65), 169 (30.77), 150 (28.26), 122 (9.27), 107 (9.91), 88 (13.34), 83 (13.81), 82 (100.00), 69 (78.19), 53 (11.80), 41 (55.96), 39 (14.17)}.
HRMS: \( m/z \) calculated for \( \text{C}_{13}\text{H}_{19}\text{NO}_{3} \):
Theory: 237.136494
Found: 237.136757

3-(7-Chloro-3,7-dimethyl-oct-2-enoyl)-oxazolidin-2-one (51):

\[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{N} \\
\text{O} \\
\end{array}
\]

TLC \( R_f = 0.20 \) (Et\(_2\)O / pentane = 1 / 1)

\(^1\text{H NMR}\) (250 MHz, \(^1\text{H}-^1\text{H-COSY}, \text{CDCl}_3\)):
6.92 (dd, 1H, CH (2')), J\(_1 = 1.2\) Hz, J\(_2 = 2.3\) Hz), 4.37 (dd, 2H, CH\(_2\) (5), J\(_1 = 7.4\) Hz, J\(_2 = 8.4\) Hz), 4.02 (t, 2H, CH\(_2\) (4), J = 8.1 Hz), 2.18-2.27 (m, 2H, CH\(_2\) (4')), 2.15 (d, 3H, CH\(_3\) (9'), J = 1.2 Hz), 1.66-1.75 (m, 4H, 2CH\(_2\) (6') and (5')), 1.54 (s, 6H, 2CH\(_3\) (8') and (10')).

\(^{13}\text{C NMR}\) (62.9 MHz, BB, DEPT, \(^1\text{H}-^{13}\text{C-COSY}, \text{CDCl}_3\)):
165.19 (Cq (1')), 161.87 (Cq (3')), 153.42 (Cq (2)), 115.22 (CH (2')), 70.67 (Cq (7')), 61.75 (CH\(_2\) (5)), 45.10 (CH\(_2\) (6')), 42.60 (CH\(_2\) (4')), 41.14 (CH\(_2\) (4)), 32.37 (CH\(_3\) (8') and (10')), 22.82 (CH\(_2\) (5')), 19.69 (CH\(_3\) (9')).

MS (EI) \( m/z \) (rel. int.):
273 (molecular peak, 6.36), 238 (37.92), 237 (24.02), 186 (44.83), 169 (23.40), 151 (56.52), 150 (77.32), 135 (17.49), 123 (30.38), 122 (18.66), 109 (35.95), 108 (35.13), 107 (27.84), 95 (100), 88 (32.00),
6.5 PET-initiated cyclizations of 44 in presence of cationic electron acceptors in dichloromethane/methanol (10:1) mixture

Reactions were performed according to the general synthetic procedure, described in Chapter 6.2.1 with one of the cationic electron acceptors 52[a], 53 or 54 (0.41 mol equiv.). After 39 h of irradiated at -9 °C the reaction mixture was transferred into a round bottom flask. The reaction vessel was washed twice with dichloromethane and the combined organic phases were concentrated and the residue purified by column chromatography on silica gel using pentane/ether 50/1 → 3/1 as eluant to give a mixture of diastereomeric cyclic products 55 (1:1.1)[b] and starting material 44. Yields of the cyclic products 55 and conversions of starting material 44 are summarized in the table of Scheme 16. An analytical sample of the diastereomeric mixture of the cis- and trans-products 55 was separated by HPLC.

Instrument parameters:

| Instrument: | Shimadzu |
| Column: | Nicrospher-5-100, 250/8mm (Merck) |
| Detector: | UV (210 nm) |
| Temperature: | RT |
| Eluant: | n-Hexane/Propanol-2 (0.5%) |

[a] Cationic electron acceptor 52 is almost insoluble in dichloromethane that could be a reason of no of cyclic product formation in reaction performed with this electron acceptor.

[b] Exact diastereomeric ratio was determined by GC analysis of the reaction mixture. For the instrument parameters see Chapter 5.6.
3-[2-(3-Methoxy-1,2,2-trimethyl-cyclopentyl)-acetyl]-oxazolidin-2-one (55):

**trans-55:**

![Chemical structure of trans-55](image)

**$^1$H NMR** (400 MHz, $^1$H-$^1$H-COSY, CDCl$_3$):

- 4.36 (t, 2H, CH$_2$ (5), J = 8 Hz), 4.00 (t, 2H, CH$_2$ (4), J = 8 Hz), 3.41 (dd, 1H, CH (3’’), J$_1$ = 5.2 Hz, J$_2$ = 8.0 Hz), 3.28 (s, 3H, CH$_3$ (OMe)), 3.09 (d, 1H, CH$_2$ (2’), J = 14.5 Hz), 2.73 (d, 1H, CH$_2$ (2’), J = 14.5 Hz), 1.98-2.12 (m, 1H, CH$_2$ (4’’)), 1.78-1.90 (m, 1H, CH$_2$ (5’’)), 1.53-1.69 (m, 2H, 2CH$_2$ (4’’)) and (5’’)), 1.02 (s, 3H, CH$_3$ (6’’)), 0.90 (s, 3H, CH$_3$ (7’’)), 0.88 (s, 3H, CH$_3$ (8’’)).

**$^{13}$C NMR** (100.6 MHz, BB, DEPT, $^1$H-$^{13}$C-COSY, CDCl$_3$):

- 173.08 (Cq (1’)), 153.62 (Cq (2’)), 90.21 (CH (3’’)), 61.59 (CH$_2$ (5)), 57.77 (CH$_3$ (OMe)), 47.63 (Cq (2’’)), 45.48 (Cq (1’’)), 42.72 (CH$_2$ (4)), 40.20 (CH$_2$ (2’)), 33.93 (CH$_2$ (5’’)), 27.71 (CH$_2$ (4’’)), 23.33 (CH$_3$ (7’’)) or (8’’), 20.73 (CH$_3$ (6’’)), 17.68 (CH$_3$ (7’’) or (8’’)).

**MS** (El) m/z (rel. int.):

- 269 (molecular peak, 2.50), 237 (32.08), 198 (23.83), 197 (16.19), 196 (100.00), 150 (15.01), 141 (17.95), 140 (79.29), 125 (26.64), 111 (44.43), 110 (17.05), 109 (28.52), 108 (14.24), 88 (22.83), 85 (18.01), 83 (22.51), 71 (20.57), 67 (14.59), 55 (23.87), 43 (12.34), 41 (24.56).
NOE correlation:

\[
\begin{array}{c}
\text{cis-55:}
\end{array}
\]

\[
\begin{array}{c}
\text{\textit{1H NMR} (400 MHz, \textit{1H-1H-COSY, CDCl3}):}
4.35 (t, 2H, CH}_2 (5), J = 8 \text{ Hz}), 3.99 (t, 2H, CH}_2 (4), J = 8 \text{ Hz}), 3.50 (t, 1H, CH (3’’), J = 7.5 \text{ Hz}), 3.30 (s, 3H, CH}_3 (\textit{OMe})), 3.26 (d, 1H, CHH (2’), J = 15.1 \text{ Hz}), 2.74 (d, 1H, CHH (2’), J = 15.1 \text{ Hz}), 1.90-2.10 (m, 2H, CH}_2 (4’’ and (5’’)), 1.42-1.78 (m, 2H, CH}_2 (4’’ and (5’’)), 0.91-0.97 (m, 6H, 2 CH}_3 (6’’) and ((7’’) or (8’’))), 0.84 (s, 3H, CH}_3 (7’’) or (8’’)).
\end{array}
\]

\[
\begin{array}{c}
\text{\textit{13C NMR} (100.6 MHz, BB, DEPT, \textit{1H-13C-COSY, CDCl3}):}
173.04 (Cq (1’’)), 153.56 (Cq (2’’)), 88.92 (CH (3’’)), 61.59 (CH}_2 (5’’), 57.90 (CH}_3 (\textit{OMe})), 46.82 (Cq (2’’)), 44.93 (Cq (1’’)), 42.66 (CH}_2 (4’’), 40.24 (CH}_2 (2’’)), 34.10 (CH}_2 (5’’)), 26.83 (CH}_2 (4’’)), 21.78 (CH}_3 (7’’) or (8’’)), 21.59 (CH}_3 (6’’)), 17.54 (CH}_3 (7’’) or (8’’)).
\end{array}
\]
6.6 PET-initiated cyclizations of 44 in presence of the complexes 56 and 57

The reactions were performed according to the general synthetic procedure described in Chapter 6.2.2 in presence of either one equivalent of complex 56 ((R) or (S)) or 57. A G.W.V.-glass filter was used in these reactions (see footnote [c], Chapter 6.2.2).

After three days of irradiation at $-90^\circ$C the reaction mixture was transferred into a round bottom flask. The reaction vessel was washed twice with dichloromethane and the combined organic phases were bubbled with $\text{H}_2\text{S}$ for 1-2 min. in order to precipitate copper as sulphide and remove all organic molecules from the complex. The resulting suspension was degassed (argon) for 30 min. and the precipitation was filtered off and washed twice with dichloromethane before concentration of the filtrate.

- To see the exact diastereomeric ratio the analytical sample was analyzed by GC without preliminary purification.

**Instrument parameters:**

<table>
<thead>
<tr>
<th>Instrument:</th>
<th>H.P. 6890</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column:</td>
<td>Rtx-5, 15 m, S-72</td>
</tr>
<tr>
<td>Detector:</td>
<td>FID</td>
</tr>
<tr>
<td>Temperature:</td>
<td>$S = 60-300 / 8$ p. min., $E = 240$, $D = 330$</td>
</tr>
<tr>
<td>Gas:</td>
<td>$\text{H}_2 (0.4 \text{ bar}), 1.7 \text{ ml, split 1:40}$</td>
</tr>
<tr>
<td>Sample size:</td>
<td>0.2 $\mu\text{l (3/4)}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First diastereomer (minor):</th>
<th>$t_r = 17.31 \text{ min}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second diastereomer (major):</td>
<td>$t_r = 17.44 \text{ min}$</td>
</tr>
</tbody>
</table>

In both cases when the reactions were performed in presence of complex 56 or 57, the diastereomeric ratio showed no significant changes as
compared to that obtained from the reaction performed in absence of chiral complexes.

Attempts to achieve separation of the GC signals of enantiomers 55 on chiral columns under various conditions gave no positive results.

• The main part of the crude reaction mixture was purified by column chromatography on silica gel using pentane/ether 50/1 → 3/1 as eluant to give a diastereomeric mixture of cyclic products 55 (1:1.1) which was consecutively hydrolyzed to the corresponding acid 58 by the following procedure.

To one equivalent of 55 in THF (1 ml per 10 mg of 55) and H₂O (1 ml per 30 mg of 55) was added LiOOH (prepared from LiOH (2 equiv.) and H₂O₂ (8 equiv.)). This mixture was stirred for 12 h at room temperature, then quenched by addition of a saturated N₂SO₃ solution (1 ml per 1 mmol of H₂O₂). The resulting mixture was transferred to a separatory funnel and diluted with 1N HCl (10 ml per 1mmol of LiOH), then extracted two times with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate, then filtered, and concentrated to give the desired acid 58 as a colorless oil in ~85% yield (1:1.1 diastereomeric mixture).[a]

An analytical sample was analyzed by chiral GC:

Instrument parameters:

Instrument:          H.P. 5890 II
Column:             Se-54/TBCD, 70/30, 30 m, Kobor
Detector:           FID
Temperature:        S = 80-220 / 2 p. min., E = 220, D = 320
Gas:                H₂ (0.7 bar)
Sample size:        0.1 yl (2/5)

[a] To obtain the spectra of diastereomers the sample of diastereomeric mixture of 55 was separated on HPLS (see Chapter 5.5), and than each of diastereomers was hydrolized.
**trans-58 (minor):**

| First enantiomer: | $t_r = 44.21$ min |
| Second enantiomer: | $t_r = 44.36$ min |

**cis-58 (major):**

| First enantiomer: | $t_r = 44.75$ min |
| Second enantiomer: | $t_r = 44.87$ min |

Due to the incomplete separation of the GC peaks of the enantiomers it was impossible to determine an exact enantiomeric ratio, but in both cases, when the reactions were performed in presence of complex 56 or 57, no significant asymmetric induction was achieved (see Chapter 3.6).

(3-Methoxy-1,2,2-trimethyl-cyclopentyl)-acetic acid (58):

**trans-58:**

![Chemical Structure](image)

**$^1$H NMR** *(400 MHz, CDCl$_3$):*

3.36 (dd, 1H, CH (3'), $J_1 = 5.2$ Hz, $J_2 = 8.1$ Hz), 3.28 (s, 3H, CH$_3$ (OMe)), 2.21 (s, 2H, CH$_2$ (2)), 1.79-1.91 (m, 2H, CH$_2$ (4' or 5')), 1.61-1.73 (m, 2H, CH$_2$ (4' or 5')), 1.05 (s, 3H, CH$_3$), 0.8-0.87 (m, 6H, 2CH$_3$).

**$^{13}$C NMR** *(100.6 MHz, BB, DEPT, $^1$H-13-C-COSY, CDCl$_3$):*

179.21 (Cq (1)), 90.36 (CH (3')), 57.72 (CH$_3$ (OMe)), 47.33 (Cq (2')), 44.73 (Cq (1')), 41.94 (CH$_2$ (2)), 33.93 (CH$_2$ (5')), 27.57 (CH$_2$ (4')), 23.21 (CH$_3$), 21.03 ((CH$_3$)), 17.69 ((CH$_3$)).
cis-58

$^1$H NMR (400 MHz, CDCl$_3$):
3.48 (dd, 1H, CH$_3$(3'), $J_1$ = 6.6 Hz, $J_2$ = 8.2 Hz), 3.30 (s, 3H, CH$_3$(OMe)), 2.43 (d, 1H, CHH(2), $J$ = 13.5 Hz), 2.20 (d, 1H, CHH(2), $J$ = 13.5 Hz), 1.88-2.11 (m, 2H, CH$_2$(4') or (5')), 1.45-1.62 (m, 2H, CH$_2$(4') or (5')), 0.98 (s, 3H, CH$_3$), 0.89 (s, 3H, CH$_3$), 0.81 (s, 3H, CH$_3$).

$^{13}$C NMR (100.6 MHz, BB, DEPT, CDCl$_3$):
178.82 (Cq(1)), 89.18 (CH(3')), 57.85 (CH$_3$(OMe)), 46.72 (Cq(2')), 44.14 (Cq(1')), 41.57 (CH$_2$(2)), 34.12 (CH$_2$(5')), 26.85 (CH$_2$(4')), 22.04 (CH$_3$), 21.84 (CH$_3$), 17.41 (CH$_3$).

MS (EI) m/z (rel. int.):
200 (15.09, molecular peak), 140 (36.90), 109 (14.22), 85 (23.87), 83 (25.32), 72 (58.45), 71 (100.00), 69 (13.73), 58 (12.97), 55 (19.90), 43 (13.28), 41 (25.33).

HRMS: m/z calculated for C$_{11}$H$_{20}$O$_{3}$:
Theory: 200.141245
Found: 200.141359
6.7 PET-initiated cyclizations of 44 in presence of 1,4-dihydropyridine 66

The substrate 44 (1 equiv., 0.2 g, 0.84 mmol), biphenyl (1 equiv.) and cationic electron acceptor 54 (0.41 equiv.) were dissolved in CH$_2$Cl$_2$ (20 ml), and then 1,4-dihydropyridine 66 (5 equiv., 1.18 g, 4.19 mmol) was added. The resulting solution was stirred and degassed (argon) for 15 minutes inside a cylindrical Pyrex irradiation vessel equipped with a cooling finger (isopropanol as the coolant, temp. –9 $^\circ$C) and subsequently was placed in a cylindrical flask containing a solution of NaNO$_2$ (chemical filter, 75 g NaNO$_2$/100 ml H$_2$O, flask diameter ~60 mm) prior to be placed in a Rayonet reactor.

The reaction mixture was irradiated at -9 $^\circ$C for 3 days and then transferred into a round bottom flask. The reaction vessel was washed twice with dichloromethane and the combined organic phases were concentrated following by isolation of the products from the residue by column chromatography on silica gel to give 0.172 g of starting material 44 and 0.324 g of the oxidized form of 1,4-dihydropyridine (66) to give the pyridine showed below.

4-Ethyl-2,6-dimethyl-pyridine-3,5-dicarboxylic acid diethyl ester:

\[
\begin{align*}
\text{H NMR} & \quad (400 \text{ MHz, CDCl}_3): \\
4.16-4.25 & \text{ (m, 4H, 2CH}_2(3')) , 2.36-2.51 & \text{ (m, 2H, CH}_2(5')) , 2.30-2.33 & \text{ (m, 6H, 2CH}_3(1')) , 1.14-1.21 & \text{ (m, 6H, 2CH}_3(4')) , 0.95-1.12 & \text{ (m, 3H, CH}_3(6')).
\end{align*}
\]
13C NMR (100.6 MHz, BB, DEPT, CDCl3):
167.98 (Cq (2’)), 154.67 (Cq (2) and (6)), 147.20 (Cq (5)), 126.74 (Cq (3) and (5)), 61.10 (CH2 (3’)), 24.34 (CH2 (5’)), 22.45 (CH3 (1’)), 14.75 (CH3 (9’)), 13.72 (CH3 (4’)).

6.8 Synthesis of substrate 68

6.8.1 Methylation of cis/trans-citral

To a suspension of 15.23 g of cuprous iodide (80 mmol) in 200 ml of diethyl ether at 0 °C under argon were added 1.67 g of MeLi (160 mmol, 1.3 M in hexane). After stirring at 0 °C for 10 min the solution was cooled to –78 °C and 11.75 g of cis/trans-citral (76 mmol) in 50 ml of ether was added dropwise. The resulting mixture was stirred at –78 °C for 20 min and at –20 °C for 4 h, then poured into ice-cold, saturated NH4Cl solution and extracted two times with ether. The combined organic extracts where dried over anhydrous sodium sulfate, filtered, concentrated and the residue purified by column chromatography on silica gel (Et2O:pentane (1:7)) to give 9.7 g of aldehyde 70 (~75% yield).

3,3,7-Trimethyl-oct-6-enal (70):

TLC $R_f = 0.43$ (hexane / ethyl acetate = 1 / 1)
$R_f = 0.55$ (pentane / diethyl ether = 5 / 1)
$^1$H NMR (400 MHz, CDCl$_3$):
9.79 (t, 1H, CH (1), J = 3.1 Hz), 5.05 (t, 1H, CH (6), J = 5.7 Hz), 2.22 (d, 2H, CH$_2$ (2), J = 3.2 Hz), 1.92 (dd, 2H, CH$_2$ (5), J$_1$ = 7.6 Hz, J$_2$ = 16.5 Hz), 1.62 (s, 3H, CH$_3$ (8) or (11)), 1.55 (s, 3H, CH$_3$ (8) or (11)), 1.30 (dd, 2H, CH$_2$ (4), J$_1$ = 4.9 Hz, J$_2$ = 12.1 Hz), 1.01 (s, 6H, 2CH$_3$ (9) and (10)).

$^{13}$C NMR (100.6 MHz, BB, DEPT, CDCl$_3$):
203.33 (CH (1)), 131.39 (Cq (7)), 124.25 (CH (6)), 54.64 (CH$_2$ (2)), 42.62 (CH$_2$ (5)), 33.40 (Cq (3)), 27.35 (2CH$_3$ (9) and (10)), 25.56 (CH$_3$ (8) or (11)), 22.64 (CH$_2$ (4)), 17.45 (CH$_3$ (8) or (11)).

6.8.2 Synthesis of trans-5,5,9-trimethyl-deca-2,8-dienoic acid ethyl ester (71)

The ethyl ester 71 was synthesized by adopting the synthetic procedure described for 48→49 in the procedure 6.4.1 from 70 without column purification. The desired product 71 was formed in 93% yield with >95% selectivity (by NMR analysis) as trans-isomer.

trans-5,5,9-Trimethyl-deca-2,8-dienoic acid ethyl ester (71):

$^1$H NMR (500 MHz, CDCl$_3$):
6.93 (td, 1H, CH (3), J$_1$ = 7.8 Hz, J$_2$ = 15.5 Hz), 5.77 (d, 1H, CH (2), J = 15.5 Hz), 5.04 (t, 1H, CH (8), J = 7.1 Hz), 4.14 (q, 2H, CH$_2$ (14), J =
7.2 Hz), 2.06 (dd, 2H, CH$_2$ (4), J$_1$ = 1.1 Hz, J$_2$ = 7.8 Hz), 1.88 (dd, 2H, CH$_2$ (7), J$_1$ = 7.6 Hz, J$_2$ = 16.6 Hz), 1.24 (t, 3H, CH$_3$ (15), J = 7.1 Hz), 1.16-1.21 (m, 2H, CH$_2$ (6)), 0.87 (s, 6H, 2CH$_3$ (11) and (12)).

$^{13}$C NMR (125.8 MHz, BB, DEPT, CDCl$_3$):

166.43 (Cq (1)), 146.54 (CH (3)), 131.10 (Cq (9)), 124.74 (CH (8) or (2)), 123.31 (CH (8) or (2)), 60.06 (CH$_2$ (14)), 44.77 (CH$_2$ (4)), 42.00 (CH$_2$ (7)), 33.82 (Cq (5)), 26.95 (CH$_3$ (11) and (12)), 25.63 (CH$_3$, (10) or (13)), 22.71(CH$_2$ (6)), 17.50 (CH$_3$ (10) or (13)), 14.23 (CH$_3$ (15)).

6.8.3 Hydrolysis of ester 71 to trans-5,5,9-trimethyl-deca-2,8-dienoic acid (72)

The acid 71 was hydrolyzed by adopting the synthetic procedure described for 49a$\rightarrow$50 in procedure 6.4.2 from 71 (was refluxed for 5 days). The desired product 72 was formed in 88% yield.

trans-5,5,9-Trimethyl-deca-2,8-dienoic acid (72):

$^1$H NMR (500 MHz, CDCl$_3$):

7.09 (td, 1H, CH (3), J$_1$ = 7.8 Hz, J$_2$ = 15.5 Hz), 5.81 (d, 1H, CH (2), J = 15.5 Hz), 5.03-5.07 (m, 1H, CH (8)), 2.12 (dd, 2H, CH$_2$ (4), J$_1$ = 7.8 Hz, J$_2$ = 1.1 Hz), 1.85-1.93 (m, 2H, CH$_2$ (7)), 1.65 (s, 3H, CH$_3$ (10) or (13)), 1.58 (s, 3H, CH$_3$ (10) or (13)), 1.18-1.24 (m, 2H, CH$_2$ (6)), 0.90 (s, 6H, 2CH$_3$ (11) and (12)).
**13C NMR** (125.8 MHz, BB, DEPT, CDCl₃):
171.97 (Cq (1)), 149.76 (CH (3)), 131.24 (Cq (9)), 124.67 (CH (2) or (8)), 122.67 (CH (2) or (8)), 44.87 (CH₂ (4)), 42.08 (CH₂ (7)), 33.94 (Cq (5)), 26.98 (CH₃, (11) and (12)), 25.65 (CH₃ (10) or (13)), 22.73 (CH₂ (6)), 17.53 (CH₃ (10) or (13)).

6.8.4 Synthesis of *trans*-3-(5,5,9-trimethyl-deca-2,8-dienoyl)-oxazolidin-2-one (68)

The oxazolidinone derivative 68 was synthesized by adopting the procedure described in 6.4.3. The reaction mixture was first purified by column chromatography with silica gel (Et₂O / pentane = 5/1) to give a mixture of 68 and chlorinated compound 73 (5.5:1, as determined by NMR analysis). This mixture was separated by a second column chromatography with silica gel (EtOAc/Et₂O/pentane = 2/5/5) to give the desired product 68 as a colorless oil in about 40% yield and chlorinated compound 73 (see Chapter 3.7.2.2).

*trans*-3-(5,5,9-Trimethyl-deca-2,8-dienoyl)-oxazolidin-2-one (68):

![Chemical Structure of 68]

**TLC**  
Rᵣ = 0.50 (ethyl acetate / diethyl ether / pentane = 5 / 5 / 2)

**1H NMR** (400 MHz, CDCl₃):
7.09–7.23 (m, 2H, 2CH (2') and (3'))), 5.04 (t, 1H, CH (8'), J = 6.9 Hz), 4.37 (dt, 2H, CH₂ (5), J₁ = 2.0 Hz, J₂ = 8.0 Hz), 4.03 (dt, 2H, CH₂ (4),
$J_1 = 2.3 \text{ Hz, } J_2 = 8.0 \text{ Hz}$), 2.16 (dd, 2H, CH$_2$ (4')), J$_1 = 2.0 \text{ Hz, } J_2 = 6.5 \text{ Hz}$), 1.90 (dd, 2H, CH$_2$ (7')), J$_1 = 7.5 \text{ Hz, } J_2 = 16.4 \text{ Hz}$), 1.63 (s, 3H, CH$_3$ (10) or (13')), 1.55 (s, 3H, CH$_3$ (10') or (13'))), 1.17-1.23 (m, 2H, CH$_2$ (6')), 0.87-0.90 (m, 6H, 2 CH$_3$ (11') and (12')).

$^{13}$C NMR (100.6 MHz, BB, DEPT, CDCl$_3$):
164.95 (Cq (1')), 153.39 (Cq (2)), 149.01 (CH (3')), 131.08 (Cq (9')), 124.69 (CH (8') or (2')), 121.83 (CH (8') or (2')), 61.94 (CH$_2$ (5)), 45.07 (CH$_2$ (4')), 42.62 (CH$_2$ (7') or (4)), 42.12 (CH$_2$ (7') or (4)), 34.00 (Cq (5')), 26.93 (2CH$_3$ (11') and (12'))), 25.59 (CH$_3$ (10') or (13')), 22.68 (CH$_2$ (6')), 17.48 (CH$_3$ (10') or (13')).

IR (KBr, $\nu_{\text{max}}$):
3533 (s), 3089 (s), 2962 (s), 2729 (w), 2599 (w), 2486 (w), 2181 (w), 1773 (s), 1683 (s), 1635 (s), 1520 (w), 1474 (m), 1384 (s), 1284 (s), 1221 (s), 1110 (s), 1073 (m), 1041 (s), 986 (m), 896 (m), 843 (m), 759 (m), 708 (m), 688 (m), 621 (m), 567 (w), 511 (w), 447 (w)

MS (EI) m/z (rel. int.):
279 (molecular peak, 10.27), 196 (13.63), 192 (21.97), 177(14.52), 155 (38.40), 150 (17.74), 123 (16.48), 109 (30.82), 88 (18.41), 81 (11.93), 69 (100.00), 68 (36.73), 55 (16.62), 41 (52.62).

HRMS: m/z calculated for C$_{16}$H$_{25}$NNaO$_3$ (M+Na):
Theory: 302.173213
Found: 302.17314
trans-3-(9-Chloro-5,5,9-trimethyl-dec-2-enoyl)-oxazolidin-2-one (73):

TLC  \( R_f = 0.48 \) (ethyl acetate / diethyl ether / pentane = 5 / 5 / 2)

\(^1H\) NMR  \((400 MHz, CDCl_3)\):
- 7.09-7.25 (m, 2H, 2CH (2') and (3'))
- 4.38 (t, 2H, CH\(_2\) (5), J = 8.0 Hz)
- 4.03 (t, 2H, CH\(_2\) (4), J = 8.0 Hz)
- 2.17 (d, 2H, CH\(_2\) (4'), J = 6.8 Hz)
- 1.61-1.69 (m, 2H, CH\(_2\) (8'))
- 1.53 (s, 6H, 2 CH\(_3\) (10') and (13'))
- 1.35-1.48 (m, 2H, CH\(_2\) (6') or (7'))
- 1.15-1.25 (m, 2H, CH\(_2\) (6') or (7'))
- 0.90 (s, 6H, 2CH\(_3\) (11') and (12'))

\(^13C\) NMR  \((100.6 MHz, BB, DEPT, CDCl_3)\):
- 164.98 (Cq (1'))
- 153.40 (Cq (2))
- 148.83 (CH (3'))
- 121.98 (CH (2'))
- 71.11 (Cq (9'))
- 61.96 (CH\(_2\) (5))
- 46.68 (CH\(_2\) (4') or (8'))
- 45.11 (CH\(_2\) (4') or (8'))
- 42.64 (CH\(_2\) (4) or (6'))
- 42.11 (CH\(_2\) (4) or (6'))
- 34.13 (Cq (5'))
- 32.40 (CH\(_3\) (10') and (13'))
- 27.03 (CH\(_3\) (11') and (12'))
- 19.62 (CH\(_2\) (7')).

HRMS:  \( m/z \) calculated for C\(_{16}\)H\(_{26}\)ClN\(_2\)O\(_3\) (M+Na):
- Theory: 338.149891
- Found: 338.14981
6.9 Enantioselective PET-initiated cyclizations of **68** \(\rightarrow 74\) in presence of the chiral complex **56**

Reactions were performed according to the general synthetic procedure described in 6.2.2 in presence of either one or 0.3 equivalents of complex **56** ((R) or (S)). A G.W.V.-glass filter was used in these reactions (see footnote [c], experiment 6.2.2).

The obtained residue was purified by column chromatography on silica gel using pentane/ether 50/1 \(\rightarrow\) 3/1 as eluant to give a diastereomeric mixture of cyclic product **74** (1:1.8)\[^{[a]}\]. The analytical sample was analyzed by GC (normal and chiral columns).

**Instrument parameters** (normal column):

<table>
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<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
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<tr>
<td>Instrument:</td>
<td><em>H.P. 6890</em></td>
</tr>
<tr>
<td>Column:</td>
<td>Rtx-5, 15 m, S-72</td>
</tr>
<tr>
<td>Detector:</td>
<td>FID</td>
</tr>
<tr>
<td>Temperature:</td>
<td>S = 60-300 / 8 p. min, E = 240, D = 330</td>
</tr>
<tr>
<td>Gas:</td>
<td>H(_2) (0.4 bar), 1.7 ml, split 1:40</td>
</tr>
<tr>
<td>Sample size:</td>
<td>0.1 yl (3/4)</td>
</tr>
</tbody>
</table>

| Diastereomer (minor):     | \(t_r = 17.01\) min                        |
| Diastereomer (major):     | \(t_r = 17.28\) min                        |

**Instrument parameters** (chiral column):

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<td><em>H.P. 6890</em></td>
</tr>
<tr>
<td>Column:</td>
<td>Rt – DEXsa, 30m, S-38</td>
</tr>
<tr>
<td>Detector:</td>
<td>FID</td>
</tr>
<tr>
<td>Temperature:</td>
<td>S = 100-220 / 2 p. min, E = 200, D = 300</td>
</tr>
</tbody>
</table>

\[^{[a]}\] Determined by HPLC analysis of crude reaction mixture.
Gas: \( H_2 \) (1.54 bar), 4 ml, split 1:20
Sample size: 0.2 yl (2/5)

First diastereomer (minor):

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<th></th>
<th>( t_r )</th>
</tr>
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<tbody>
<tr>
<td>First enantiomer</td>
<td>55.26 min</td>
</tr>
<tr>
<td>Second enantiomer</td>
<td>55.49 min</td>
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</tbody>
</table>

Second diastereomer (major):

<table>
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<th>( t_r )</th>
</tr>
</thead>
<tbody>
<tr>
<td>First enantiomer</td>
<td>56.33 min</td>
</tr>
<tr>
<td>Second enantiomer</td>
<td>56.46 min</td>
</tr>
</tbody>
</table>

The other analytical sample of the diastereomeric mixture of cyclic product 74 was separated on HPLC to give pure diastereomers which were analyzed by NMR spectroscopy and MS analysis.

Instrument parameters:

<table>
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<th>Instrument:</th>
<th>Shimadzu</th>
</tr>
</thead>
<tbody>
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<td>Column:</td>
<td>Lichrosorb-5-100, Sel 233</td>
</tr>
<tr>
<td>Detector:</td>
<td>UV (220 nm)</td>
</tr>
<tr>
<td>Temperature:</td>
<td>RT</td>
</tr>
<tr>
<td>Eluant:</td>
<td>C-hexan/propanol-2 (0.5%)</td>
</tr>
<tr>
<td>Sample size:</td>
<td>10 yl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>( t_r )</th>
</tr>
</thead>
<tbody>
<tr>
<td>First diastereomer (minor):</td>
<td>41.10 min</td>
</tr>
<tr>
<td>Second diastereomer (major):</td>
<td>43.23 min</td>
</tr>
</tbody>
</table>
3-[2-[4,4-Dimethyl-2-(2-methyl-propenyl)-cyclopentyl]-acetyl]-oxazolidin-2-one (74):

trans-74:

1H NMR (400 MHz, 1H-1H-COSY, CDCl3):
4.92 (d, 1H, CH (6''), J = 9.3 Hz), 4.35 (t, 2H, CH₂ (5), J = 8.0 Hz),
3.95 (t, 2H, CH₂ (4), J = 8 Hz), 3.00 (dd, 1H, CHH (2''), J₁ = 4.6 Hz, J₂ = 16.3 Hz),
2.76 (dd, 1H, CHH (2'), J₁ = 9.5 Hz, J₂ = 16.3 Hz), 2.48 (dt, 1H, CH (2''), J₁ = 10.5 Hz, J₂ = 18.3 Hz),
2.03-2.15 (m, 1H, CH (1'')), 1.79 (dd, 1H, CHH (5''), J₁ = 8.0 Hz, J₂ = 13.1 Hz), 1.65 (s, 3H, CH₃ (9'') or (8'')),
1.54-1.63 (m, 4H, CH₃ (9'') or (8'') and CHH (3'')), 1.06-1.19 (m, 2H, CHH (3'') and CHH (5'')),
1.01 (s, 6H, 2CH₃ (10'') and (11'')).

13C NMR (100.6 MHz, BB, DEPT, 1H-13C-COSY, CDCl₃):
173.34 (Cq (1'')), 153.48 (Cq (2'')), 132.05 (Cq (7'')), 128.35 (CH (6'')),
61.86 (CH₂ (5''), 48.52 (CH₂ (3'') or (5''))), 47.74 (CH₂ (3'') or (5'')),
44.73 (CH (1'')), 42.87 (CH (2'')), 42.51 (CH₂ (4''), 39.33 (CH₂ (2'')),
37.07 (Cq (4''), 31.49 (CH₃ (10''') or (11''))), 31.36 (CH₃ (10''') or (11'')),
25.83 (CH₃ (9'') or (8''))), 18.15 (CH₃ (9'') or (8'')).

MS (El) m/z (rel. int.):
279 (16.53, molecular peak), 192 (34.68), 151 (13.63), 150 (100.00),
149 (19.10), 136 (13.94), 135 (40.41), 109 (12.16), 88 (12.42), 67 (13.82), 55 (12.74), 41 (19.06).
**HRMS:** m/z calculated for C_{16}H_{25}NNaO_{3} (M+Na):

Theory: 302.173213
Found: 302.17302

**NOE correlation:**

cis-74:

\[ \text{\textsuperscript{1}H NMR} \ (400 \text{ MHz, } \text{\textsuperscript{1}H-\textsuperscript{1}H-COSY, CDCl}_3): \]

5.04 (d 1H, CH\textsubscript{6''}, J = 10.2 Hz), 4.35 (t, 2H, CH\textsubscript{2} \textsubscript{5}, J = 8 Hz), 3.86-4.03 (2H, CH\textsubscript{2} \textsubscript{4}), 3.14 (dd, 1H, CHH \textsubscript{2'}, J\textsubscript{1} = 7.7 Hz, J\textsubscript{2} = 16.8 Hz), 2.98-3.07 (m, 1H, CH \textsubscript{2''}), 2.73 (dt, 1H, CH \textsubscript{1''}, J\textsubscript{1} = 7.4 Hz, J\textsubscript{2} = 15.2 Hz), 2.57 (dd, 1H, CHH \textsubscript{2'}, J\textsubscript{1} = 7.2 Hz, J\textsubscript{2} = 16.8 Hz), 1.51-1.65 (m, 8H, 2CH\textsubscript{3} \textsubscript{9''} and \textsubscript{8''}, CHH \textsubscript{3''} and CHH \textsubscript{5''}), 1.21-1.28 (m, 2H, CHH \textsubscript{3'} and CHH \textsubscript{5''}), 1.04 (s, 3H, CH\textsubscript{3} \textsubscript{10''} or \textsubscript{11''}), 0.98 (s, 3H, CH\textsubscript{3} \textsubscript{10''} or \textsubscript{11''}).
\(^{13}\)C NMR (100.6 MHz, BB, DEPT, \(^1\)H\(^{13}\)C-COSY, CDCl\(_3\)):

173.51 (Cq (1')), 153.44 (Cq (2)), 131.73 (Cq (7'')), 126.85 (CH (6'')), 61.81 (CH\(_2\) (5)), 48.16 (CH\(_2\) (3'')), 47.00 (CH\(_2\) (5'')), 42.59 (CH\(_2\) (4)), 39.47 (CH (2'')), 38.13 (CH (1'')), 38.02 (Cq (4'')), 36.79 (CH\(_2\) (2'')), 30.66 (CH\(_3\) (10'') or (11'')), 29.39 (CH\(_3\) (10'') or (11'')), 25.87 (CH\(_3\) (8'') or (9'')), 17.88 (CH\(_3\) (8'') or (9'')).

NOE correlation:

6.10 Synthesis of \(\beta\)-ketoesters 78a, 78b and 78c

6.10.1 Synthesis of 7-methyl-3-oxo-oct-6-enoic acid methyl ester (78a)

The \(\beta\)-ketoester 78a was obtained best by following a literature procedure.\(^6\)\(^6\)

The residue obtained by this method residue was purified by column chromatography on silica gel using \(n\)-pentane/ether 5/1 as eluant giving pure 78a in a yield of 75%.

TLC \(R_f = 0.59\) (diethyl ether / pentane = 1 / 2)
6.10.2 Synthesis of 2,7-dimethyl-3-oxo-oct-6-enoic acid methyl ester (78b)

Compound 78b was synthesized according to a literature procedure, but 78a was taken instead of methyl acetoacetate as a starting material. The obtained residue was purified by column chromatography on silica gel using n-pentane/ether 10/3 as eluant to give 78b as a colorless oil in ~80% yield.

2,7-Dimethyl-3-oxo-oct-6-enoic acid methyl ester (78b):

\[
\begin{array}{c}
\text{TLC} \\
R_f = 0.71 \text{ (diethyl ether / pentane = 1 / 2)} \\
\end{array}
\]

\[
\begin{array}{c}
\text{\textsuperscript{1}H NMR} \quad (400 \text{ MHz}, \text{\textsuperscript{1}H-\textsuperscript{1}H-COSY, CDCl}_3): \\
4.99 \text{ (t, 1H, CH (6), J = 6.5 Hz)}, 3.67 \text{ (s, 3H, CH}_3 \text{ (OMe))}, 3.47 \text{ (q, 1H, CH (2), J = 7.1 Hz)}, 2.36-2.59 \text{ (m, 2H, CH}_2 \text{ (4))}, 2.21 \text{ (dd, 2H, CH}_2 \text{ (5) J = 7.1 Hz, J = 14.3 Hz)}, 1.61 \text{ (s, 3H, CH}_3 \text{ (7') or (8))}, 1.55 \text{ (s, 3H, CH}_3 \text{ (7') or (8))}, 1.27 \text{ (d, 3H, CH}_3 \text{ (2') J = 7.2 Hz)}. \\
\end{array}
\]

\[
\begin{array}{c}
\text{\textsuperscript{13}C NMR} \quad (100.6 \text{ MHz, BB, DEPT, \textsuperscript{1}H-\textsuperscript{13}C-COSY, CDCl}_3): \\
205.35 \text{ (Cq (3))}, 170.91 \text{ (Cq (1))}, 132.80 \text{ (Cq (7))}, 122.35 \text{ (CH (6))}, 52.65 \text{ (CH (2))}, 52.20 \text{ (CH}_3 \text{ (OMe))}, 41.28 \text{ (CH}_2 \text{ (4))}, 25.53 \text{ (CH}_3 \text{ (8) or (7'))}, 22.22 \text{ (CH}_2 \text{ (5))}, 17.50 \text{ (CH}_3 \text{ (8) or (7'))}, 12.64 \text{ (CH}_3 \text{ (2'))}. \\
\end{array}
\]
IR (KBr, $\nu_{\text{max}}$):
3466 (H$_2$O in KBr, s), 2954 (s), 1746 (s), 1716 (s), 1454 (m), 1436 (m), 1406 (w), 1377 (m), 1344 (m), 1243 (m), 1204 (s), 1177 (m), 1123 (m), 1067 (m), 992 (w), 864 (w).

MS (EI) m/z (rel. int.):
198 (molecular peak, 15.32), 130 (9.44), 115 (11.05), 111 (65.40), 110 (17.38), 95 (10.94), 88 (39.37), 83 (21.36), 82 (40.03), 69 (100.00), 67 (14.99), 59 (20.82), 56 (10.67), 55 (34.57), 53 (9.58), 43 (24.51), 41 (55.87), 39 (13.42), 29 (10.18), 27 (13.14).

HRMS: m/z calculated for C$_{11}$H$_{18}$O$_3$:
Theory: 198.125595
Found: 198.125706

6.10.3 Synthesis of 2,2,7-trimethyl-3-oxo-oct-6-enoic acid methyl ester (78c)

The β-ketoester 78c was synthesized from 78a by the following procedure. To 20 ml of dry methanol 0.37 g (16 mmol) of sodium was added portionwise under an argon flow. The resulting mixture was stirred until the gas evolution ceased and then β-ketoester 78a (1.5 g, 8 mmol) dissolved in 10 ml of methanol was added dropwise. This solution was stirred for 15 min followed by addition of methyl iodide (2.54 g, 1.12 ml, 18 mmol). The stirring was continued at room temperature overnight and then the reaction mixture poured into diethyl ether (200 ml) and saturated aqueous ammonium chloride (70 ml). The ether layer was separated and the aqueous layer was extracted with 100 ml of ether. The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. The residue thus obtained was purified by column chromatography on silica gel (pentane/diethyl ether = 10/1) to give 0.95 g of 78c (55% yield) and 0.35 g of 78b (22% yield).
2,2,7-Trimethyl-3-oxo-oct-6-enolic acid methyl ester (78c):

\[
\text{O} \quad \text{O}
\]

\[1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 7' \quad 7''
\]

TLC \[ R_f = 0.73 \text{ (diethyl ether / pentane = 1 / 2)} \]

\[\begin{align*}
\text{H NMR} & \quad (400 MHz, \text{ CDCl}_3): \\
5.00 \text{ (t, 1H, CH} & \text{ (6), J = 7.2 Hz), 3.67 \text{ (s, 3H, CH}_3 \text{ (OMe)), 2.41 \text{ (t, 2H, CH}_2 \text{ (4), J = 7.4 Hz), 2.21 \text{ (q, 2H, CH}_2 \text{ (5), J = 7.3 Hz), 1.62 \text{ (s, 3H, CH}_3 \text{ (8 or (7'))), 1.56 \text{ (s, 3H, CH}_3 \text{ (8 or (7'))}, 1.31 \text{ (s, 6H, 2CH}_3 \text{ (2') and (2'')}).}
\end{align*}\]

\[\begin{align*}
\text{C NMR} & \quad (100.6 MHz, BB, DEPT, CDCl}_3): \\
207.54 \text{ (Cq (3)), 174.15 \text{ (Cq (1)), 132.68 \text{ (Cq (7)), 122.65 \text{ (CH (6)), 55.52 \text{ (Cq (2)), 52.30 \text{ (CH}_3 \text{ (OMe)), 38.01 \text{ (CH}_2 \text{ (4)), 25.58 \text{ (CH}_3 \text{ (8 or (7'))), 22.54 \text{ (CH}_2 \text{ (5)), 21.83 \text{ (CH}_3 \text{ (2') and (2'')})), 17.52 \text{ (CH}_3 \text{ (8 or (7'))).}
\end{align*}\]

IR \[ (\text{KBr, } \nu \text{ max):} \]

3451 (H\text{O in KBr, s), 2981 (s), 2935 (s), 1746 (s), 1715 (s), 1458 (m), 1435 (m), 1385 (m), 1367 (w), 1343 (w), 1194 (m), 1070 (m), 1108 (w), 1032 (w), 985 (w), 855 (w), 845 (w), 769 (w).} \]

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MS (EI) m/z (rel. int.):
212 (molecular peak, 7.96), 111 (45.45), 102 (18.17), 83 (25.09), 69 (100.00), 55 (16.62), 41 (34.98).

HRMS: m/z calculated for C_{12}H_{20}O_{3}:
Theory: 212.141245
Found: 212.141090

6.11 PET-initiated cyclizations of β-ketoesters 78a and 78b in presence of complex 56 or 92

6.11.1 PET-initiated cyclizations of 7-methyl-3-oxo-oct-6-enoic acid methyl ester (78a) in presence of complex 56 or 92

PET-initiated cyclizations of 78a were performed according to the general synthetic procedure described in 6.2.2, in presence of either complex 56 (1.0 or 0.1 equivalents, (R) or (S)) or complex 92 (1.0 or 0.1 equivalents, (R)). A G.W.V.-glass filter was used in these reactions (see footnote [c], 6.2.2).
The obtained residue was purified by column chromatography on silica gel using pentane/ether 50/1 → 10/1 as eluant to give the cyclic product 80a. An analytical sample was analyzed by GC (normal and chiral columns).

Instrument parameters (normal column):

- Instrument: H.P. 6890
- Column: Rtx-5, 15 m, S-72
- Detector: FID
- Temperature: S = 60-300 / 8 p. min, E = 240, D = 330
- Gas: H_{2} (0.4 bar), 1.7 ml, split 1:40
- Sample size: 0.1 μl (3/4)
Cyclic product 80a  \[ t_r = 7.89 \text{ min} \]

Instrument parameters (chiral column):

<table>
<thead>
<tr>
<th>Instrument:</th>
<th>H.P. 6890</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column:</td>
<td>Rt – DEXse, 30m, S-59</td>
</tr>
<tr>
<td>Detector:</td>
<td>FID</td>
</tr>
<tr>
<td>Temperature:</td>
<td>S = 60-220 / 2 p. min, E = 200, D = 300</td>
</tr>
<tr>
<td>Gas:</td>
<td>H₂ (0.65 bar), 1.5 ml, split 1:40</td>
</tr>
<tr>
<td>Sample size:</td>
<td>0.2 yl (2/5)</td>
</tr>
</tbody>
</table>

First enantiomer:  \[ t_r = 35.18 \text{ min} \]
Second enantiomer: \[ t_r = 35.39 \text{ min} \]

Acceptable separation was achieved also on Rt – βDEXsa chiral column.

Instrument parameters (chiral column):

<table>
<thead>
<tr>
<th>Instrument:</th>
<th>H.P. 6890</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column:</td>
<td>Rt – DEXsa, 30m, S-38</td>
</tr>
<tr>
<td>Detector:</td>
<td>FID</td>
</tr>
<tr>
<td>Temperature:</td>
<td>S = 80-220 / 2 p. min, E = 200, D = 300</td>
</tr>
<tr>
<td>Gas:</td>
<td>H₂ (1.44 bar), 4 ml, split 1:40</td>
</tr>
<tr>
<td>Sample size:</td>
<td>0.2 yl (2/5)</td>
</tr>
</tbody>
</table>

First enantiomer:  \[ t_r = 25.52 \text{ min} \]
Second enantiomer: \[ t_r = 25.88 \text{ min} \]

(1-Hydroxy-3-methyl-cyclohex-3-enyl)-acetic acid methyl ester (80a):
**1H NMR** (500 MHz, 1H-1H-COSY, CDCl₃):
5.35 (dt, 1H, CH (4'), J₁ = 1.5 Hz, J₂ = 3.2 Hz), 3.68 (s, 3H, CH₃ (OMe)), 3.45 (s, OH), 2.48 (d, 2H, CH₂ (2), J = 1.4 Hz), 2.13 - 2.21 (m, 1H, CH₂ (5')), 2.03 (q, 2H, CH₂ (2'), J = 17.6Hz), 1.91-2.00 (m, 1H, CH₂ (5')), 1.67 (td, 1H, CH₂ (6'), J₁ = 6.5 Hz, J₂ = 13.0 Hz), 1.61 (s, 3H, CH₃ (7')), 1.53 (td, 1H, CH₂ (6'), J₁ = 6.5 Hz, J₂ = 13.0 Hz).

**13C NMR** (125.8 MHz, BB, DEPT, 1H-13C-COSY, CDCl₃):
173.19 (Cq (1)), 131.14 (Cq (3')), 119.90 (CH (4')), 69.46 (Cq (1')), 51.60 (CH₃ (OMe)), 43.68 (CH₂ (2)), 42.57 (CH₂ (2')), 33.00 (CH₂ (6')), 23.48 (CH₃ (7')), 22.81 (CH₂ (5')).

**IR** (KBr, ν max):
3474 (s), 2926 (s), 1734 (m), 1637 (m), 1437 (m), 1344 (w), 1202 (m), 1170 (m), 1126 (w), 1077 (w), 1006 (w), 883 (w), 810 (w).

**MS** (EI) m/z (rel. int.):
184 (molecular peak, 2.33), 166 (16.46), 116 (12.61), 111 (17.75), 110 (11.65), 106 (10.45), 95 (12.42), 93 (26.53), 91 (12.15), 74 (100), 68 (17.84), 67 (14.82), 55 (11.51), 43 (30.89), 41 (12.84).

**HRMS:** m/z calculated for C₁₀H₁₆O₃:
Theory: 184.109941
Found: 184.110163

6.11.2 PET-initiated cyclizations of 2,7-dimethyl-3-oxo-oct-6-enoic acid methyl ester (78b) in presence of complex 56 or 92

PET-initiated cyclizations of 78b were performed according to the general synthetic procedure described in 6.2.2, in presence of either complex 56 (1.0 or
0.1 equivalents, (R) or (S)) or complex 92 (1.0 or 0.1 equivalents, (R)). A G.W.V.-glass filter was used in these reactions (see footnote [c], 6.2.2).

The obtained residue was purified by column chromatography on silica gel using pentane/ether 50/1 → 10/1 as eluant to give a diastereomeric mixture of the cyclic product 80b (1:1)[a]. An analytical sample was analyzed by GC (normal and chiral columns).

**Instrument parameters** (normal column):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instrument</td>
<td><em>H.P. 6890</em></td>
</tr>
<tr>
<td>Column</td>
<td>Rtx-5, 15 m, S-72</td>
</tr>
<tr>
<td>Detector</td>
<td>FID</td>
</tr>
<tr>
<td>Temperature</td>
<td>S = 60-300 / 8 p. min, E = 240, D = 330</td>
</tr>
<tr>
<td>Gas</td>
<td>H₂ (0.4 bar), 1.7 ml, split 1:40</td>
</tr>
<tr>
<td>Sample size</td>
<td>0.1 μl (3/4)</td>
</tr>
</tbody>
</table>

| First diastereomer 80b   | tᵣ = 8.73 min                           |
| Second diastereomer 80b  | tᵣ = 8.85 min                           |

The best separation of the GC peaks of the enantiomers was achieved under following conditions:

**First diastereomer:**

**Instrument parameters** (chiral column):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instrument</td>
<td><em>H.P. 6890</em></td>
</tr>
<tr>
<td>Column</td>
<td>Rt – DEXse, 30m, S-59</td>
</tr>
<tr>
<td>Detector</td>
<td>FID</td>
</tr>
<tr>
<td>Temperature</td>
<td>S = 60-220 / 2 p. min, E = 200, D = 300</td>
</tr>
<tr>
<td>Gas</td>
<td>H₂ (0.64 bar), 1.5ml, split 1:40</td>
</tr>
<tr>
<td>Sample size</td>
<td>0.2 μl (2/4)</td>
</tr>
</tbody>
</table>

[a] Determined by HPLC analysis of the crude reaction mixture.
First enantiomer: \( t_r = 37.73 \text{ min} \)

Second enantiomer: \( t_r = 37.78 \text{ min} \)

**Second diastereomer:**

**Instrument parameters** (chiral column):

- **Instrument:** *H.P. 6890*
- **Column:** Rt – DEXsa, 30m, S-38
- **Detector:** FID
- **Temperature:** S = 60-220 / 2 p. min, E = 200, D = 300
- **Gas:** \( \text{H}_2 \) (1.44 bar), 4 ml, split 1:40
- **Sample size:** 0.4 \( \mu l \) (2/4)

First enantiomer: \( t_r = 36.74 \text{ min} \)

Second enantiomer: \( t_r = 36.94 \text{ min} \)

Another analytical sample of diastereomeric mixture of the cyclic product 80b was separated on HPLC to give pure samples of diastereomers.

**Instrument parameters:**

- **Instrument:** *Shimadzu*
- **Column:** Nucleosil-7-C18, 250x10 (Macherey-Nagel)
- **Detector:** UV (220 nm)
- **Temperature:** RT
- **Eluant:** MeOH/H2O (3/2)

2-(1-Hydroxy-3-methyl-cyclohex-3-enyl)-propionic acid methyl ester (80b):
**First diastereomer:**

**$^1$H NMR** (400 MHz, $^1$H-$^1$H-COSY, CDCl$_3$):
5.38-5.43 (m, 1H, CH (4')), 3.70 (s, 3H, CH$_3$ (OMe)), 3.07 (broad s, 1H, OH), 2.58 (q, 1H, CH (2), J = 7.2 Hz), 2.13-2.25 (m, 1H, CH$_2$), 2.08 (d, 1H, CH$_2$, J = 17.5 Hz), 1.89-2.02 (m, 2H, CH$_2$), 1.70-1.78 (m, 1H, CH$_2$), 1.63 (s, 3H, CH$_3$ (7')), 1.39-1.48 (m, 1H, CH$_2$), 1.22 (d, 3H, CH$_3$ (3), J = 7.2 Hz).

**$^{13}$C NMR** (100.6 MHz, BB, DEPT, $^1$H-$^{13}$C-COSY, CDCl$_3$):
177.15 (Cq (1)), 131.08 (Cq (3')), 120.21 (CH (4')), 70.96 (Cq (1')), 51.67 (CH$_3$ (OMe)), 46.56 (CH (2)), 42.01 (CH$_2$ (2')), 29.60 (CH$_2$ (5') or (6')), 23.61 (CH$_3$ (7')), 22.25 (CH$_2$ (5') or (6')), 11.86 (CH$_3$ (3)).

**IR** (KBr, $\nu_{\text{max}}$):
3495 (s), 2927 (m), 1718 (m), 1437 (m), 1351 (m), 1170 (m), 963 (w), 928 (w), 909 (w), 877 (w), 854 (w), 804 (w).

**MS** (EI) m/z (rel. int.):
198 (molecular peak, 4.48), 180 (17.55), 130 (14.84), 111 (23.94), 110 (15.55), 98 (10.94), 95 (10.40), 93 (28.80), 88 (100), 68 (13.03), 67 (11.65), 57 (13.56), 56 (14.92), 55 (14.99), 43 (15.22), 41 (14.77).

**HRMS**: m/z calculated for C$_{11}$H$_{19}$O$_3$ (M+H):
The reaction was performed according to the general synthetic procedure described in 6.2.2 in presence of 0.3 equiv. of complex (S)-56. A G.W.V.-glass filter was used in these reactions (see footnote [c], 6.2.2).

The obtained residue was purified by column chromatography on silica gel using pentane/ether 50/1 → 10/1 as eluant to give the oxidation product 84 (49%, at 57% conversion of 78c).

2,2,7-Trimethyl-3-oxo-octa-4,6-dienoic acid methyl ester (84):
7.61 (dd, 1H, CH (5), J₁ = 11.8 Hz, J₂ = 14.6 Hz), 6.15 (d, 1H, CH (6), J = 14.6 Hz), 5.98 (d, 1H, CH (4), J = 11.8 Hz), 3.68 (s, 3H, CH₃ (OMe)), 1.89 (s, 3H, CH₃ (8) or (7')), 1.88 (s, 3H, CH₃ (8) or (7')), 1.37 (s, 6H, 2CH₃ (2') and (2'')).

**¹³C NMR** (100.6 MHz, BB, DEPT, ¹H-¹³C-COSY, CDCl₃):
196.99 (Cq (3)), 174.58 (Cq (1)), 148.88 (Cq (7)), 140.43 (CH (5)), 124.18 (CH (4)), 121.72 (CH (6)), 54.52 (Cq (2)), 52.38 (CH₃ (OMe)), 26.69 (CH₃ (8) or (7')), 21.98 (CH₃ (2') and (2'')), 19.07 (CH₃ (8) or (7')).

**IR** (KBr, v max):
3460 (m, H₂O in KBr), 2981 (s), 2936 (s), 1739 (s), 1687 (s), 1628 (s), 1589 (s), 1466 (m), 1435 (m), 1385 (m), 1354 (m), 1278 (s), 1194 (m), 1147 (s), 1064 (s), 1008 (m), 993 (m), 877 (m), 838 (w), 795 (w), 764 (w), 740 (w), 692 (w), 588 (w), 563 (w), 537 (w), 499 (w), 458 (w).

**MS** (EI) m/z (rel. int.):
210 (11.23, molecular peak), 195 (17.32), 110 (7.44), 109 (100.00), 81 (34.46), 79 (8.05), 53 (7.89), 41 (13.19).

**HRMS**: m/z calculated for C₁₂H₁₈O₃:
Theory: 210.125596
Found: 210.125558
7 References

1 For a review on PET see: J. Mattay, Synthesis 1989, 233.


39 L. Pauling, *The Nature of The Chemical Bond*, University Press, Oxford, **1940**.
51 Schott glass filters:  
Many other supplier of glass filters can be found on:
http://www.chemindustry.com/popular/F/filter_supplier.asp


Abbreviations

The following abbreviations are used in this work:

A  acceptor
BET  back electron transfer
BINAP  2,2'-bis(diphenylphosphino)-1,1'-binaphthaene
BINOL  1,1'-binaphtalene-2,2'-diol
BOX  bisoxazoline
BP  1,1'-biphenyl
BuLi  n-butyllithium
C  coulombic interaction
CA  co-acceptor
CI  chemical ionisation
CIP  contact ion pair
COSY  correlation spectroscopy
D  Donor
DBFOX/Ph  (R,R)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline)
DCTMB  1,4-dicyano-2,3,5,6-tetramethylbenzene
de  diastereomeric excess
DME  1,2-dimethoxyethane
DMF  N,N-dimethylformamide
DMSO  dimethyl sulfoxide
EA  electron affinity
e.e.  enantiomeric excess
EI  electronic ionisation
ET  electron transfer
EXC  exciplex
FI  free ion
HOMO  highest occupied molecular orbital
HRMS  high resolution mass spectroscopy
IP  ionisation potential
IR  infrared spectroscopy
LDA  lithium diisopropylamide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>NMQ</td>
<td>N-methylquinoline</td>
</tr>
<tr>
<td>NMA</td>
<td>N-methylacridine</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser enhancement spectroscopy</td>
</tr>
<tr>
<td>PET</td>
<td>photoinduced electron transfer</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>SSIP</td>
<td>solvent-separated ion pair</td>
</tr>
<tr>
<td>TADDOL</td>
<td>(α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol)</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet spectroscopy</td>
</tr>
</tbody>
</table>
CURRICULUM VITAE

Andriy Kuklya

Name: Andriy
Surname: Kuklya
Date of birth: 28 April 1978
Place of birth: Kiev, Ukraine
Nationality: Ukrainer
Sex: Male
Civil status: Married

Education:

April 2005: Ph. D. in Chemistry, Department of Chemistry, Campus Essen, University of Duisburg-Essen, Germany.

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Ph. D. student at the Max-Planck-Institut für Bioanorganische Chemie, Mülheim/Ruhr, Germany.


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The diploma was attested with the grade “excellent” and qualified as a Chemical Engineer in Chemical Technology of Organic Compounds.

Subject of the diploma: “α-Yliden-substituted enamines of cyclic ketones in the synthesis of heterocyclic compounds”. Supervisor: Dr. A. N. Kostyuk.²

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Diploma and qualified as a bachelor in Chemical Technology and Engineering.

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1995-1996:
National Technical University of the Ukraine, Inorganic Chemistry Division, Ukraine, Kiev.

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Awards:
1995 First place in young chemist competition (Kiev, Ukraine) and participation in all-Ukrainian young chemist’s competition (Simferopol, Ukraine).
1995 Winner of the first round of Soros competition (chemistry) and participation in the final part of competition (Kiev, Ukraine).
1997 Research grant for students from Soros-foundation.