“The Development of a Modular Photo Flow Reactor Setup and its Application to Photooxygenations”

Dissertation

zur Erlangung des Doktorgrades der Naturwissenschaften
Dr. rer. nat.
an der Fakultät für Chemie und Pharmazie
der Universität Regensburg

vorgelegt von

Josef Schachtner

aus Wolnzach

Regensburg 2016

The experimental part of this work was carried out between January 2013 and February 2016 at the University of Regensburg, Institute of Organic Chemistry under the supervision of Prof. Dr. Axel Jacobi von Wangelin.

The thesis was submitted: February 8th, 2016
Date of the defense: March 8th, 2016

Board of examiners:
Prof. Dr. Siavosh Mahboobi (chairman)
Prof. Dr. Axel Jacobi von Wangelin (1st referee)
Prof. Dr. Olga García Mancheño (2nd referee)
Prof. Dr. Frank-Michael Matysik (examiner)

Table of contents:

Chapter 1:

- Introduction -

1. Introduction

1.1. Light and photochemistry

In present times, our lives are strongly influenced by and extremely dependent on the products and materials provided by the chemical industry. The chemical industry produces drugs, synthetic materials, fine chemicals and petrochemicals. Especially the petrochemicals are essential for our standard of living. The overall energy consumption in Germany in 2010 – 2014 was around $1.3 \cdot 10^{19}$ J per year. About 79 % of this energy was produced by burning fossil fuels. Only 12 % was generated by renewable energy sources. In the sector of manufacturing industry and mining, the chemical industry in Germany is responsible for about 24 % of the energy consumption and therefore for 7 % of the consumed energy in total (Figure 1.1).[1,2] The extreme dependency of the chemical industry on fossil fuels, the increasing prices of oil and gas and new synthetic opportunities are the major motivating forces for creating new syntheses, based on renewable energy.

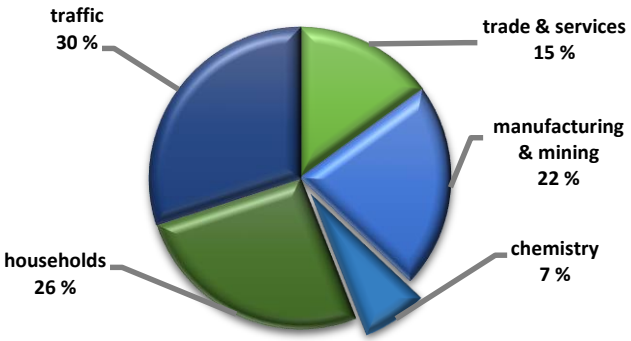


Figure 1.1: Primary energy consumption in Germany 2014[2]

The use of light as a direct energy source for suitable reactions seems to be a logical step. The idea of using solar energy for chemical reactions is not new and it was certainly not invented by humans. For billions of years, bacteria, plants and other organisms have used solar energy to produce organic molecules like sugar. More precisely all the "energy containing" macromolecules on our planet have been produced by living cells using solar energy from the sun.[3] This process called photosynthesis is the most famous example of photochemistry.

By the time, the first scientists tried to use the energy of light to perform controlled and goal oriented chemical reactions, the 20th century had already begun. One of the first

chemists dealing with photochemistry was Giacomo Ciamician from the University of Bologna. The Italian was fully convinced of the advantages and the glorious future of photochemistry. Already in 1912 he wrote an article in SCIENCE with the title: "THE PHOTOCHEMISTRY OF THE FUTURE" predicting civilizations based on photochemistry and solar energy:[4]

> *"Where vegetation is rich, photochemistry may be left to the plants… On arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over plains and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry. And if in a distant future the supply of coal becomes completely exhausted, civilization will not be checked for that, for life and civilization will continue as long as sun shines! If our black and nervous civilization, based on coal, shall be followed by a quieter civilization based on the utilization of solar energy, that will not be harmful to progress and to human happiness."*

Nowadays, about one century after Ciamician´s prognoses, we already have several profitable light-induced industrial chemical processes. All these processes are based on the irradiation of a molecule (A) with light to get a molecule in an electrically excited state (A^*). Depending on the nature of A^* and the reaction conditions several reaction pathways are possible (Figure 1.2):[5]

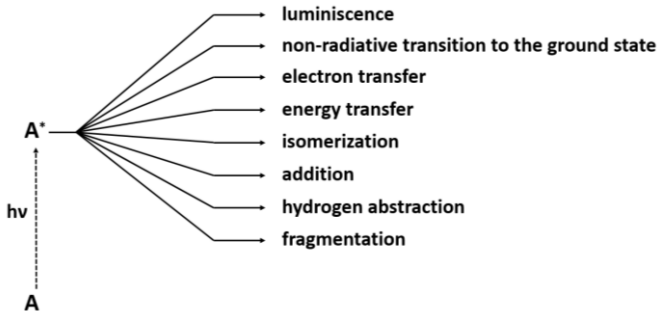


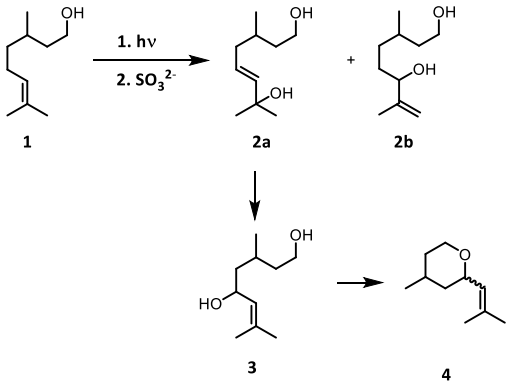
Figure 1.2: Excited state reaction paths.[6]

Some of these pathways are used in different industrial applications like optical bleaching of textiles and paper (luminescence).[6] The biggest field of industrially used photochemical processes deals with electron transfer reactions and light induced radical chain reactions. At this point chlorination, sulfochlorination, sulfoxidation, and

nitrosation have to be mentioned as well as photo-polymerisation reactions.[6] Another electron transfer process which is losing importance with the increasing number of digital cameras is classical photography that provided fundamental ideas for numerous modern applications of electron transfer, like photoconductors or reprography.[5]

Due to its great conformity to the main topic of this work, one industrial process performed by *Firmenich*, will be highlighted below.[5] The photosynthesis of Rose Oxide (**4**) starting from citronellol (**1**) *via* a photooxygenation reaction is a visible light-induced energy transfer reaction (Scheme 1.1).[5,7]

The fragrance Rose Oxide is currently mainly produced using this reaction pathway. The first step is a photocatalytic Schenck ene reaction in the presence of molecular oxygen and a sensitizer which delivers two hydroperoxides. These are reduced by sulfite or bisulfite to obtain the two alcohols **2a** and **2b** quantitatively in a ratio of 2/1. Allylic rearrangement of **2a** under acidic conditions and subsequent dehydration of **3** yields the desired product **4**.[5]



Scheme 1.1: Synthesis of Rose Oxide starting from citronellol

A major difference between this and many other industrial photochemical reactions is the wavelength of the light that is used. In most of the previously mentioned reactions, the transformed molecule itself is excited by irradiation with highly energetic UV-light, whereas lower energetic visible light is used in this example. As a second interesting aspect: the photooxygenation of **1** is a photocatalytic reaction and the oxidized reagent is not excited directly. Instead, a sensitizer molecule (a chromophore) is excited by irradiation with visible light and the energy of the excited state is transferred to one of the reactants. The opportunity to use visible light, low in energy, makes photocatalysis an interesting field of research. Although the lower energy input avoids undesired side reactions, there are numerous chemical and technical challenges especially for the

execution of industrial photooxygenations. Regarding aspects of efficiency, productivity and GREEN CHEMISTRY one has to optimize light sources, light input, oxygen distribution and minimize side reactions and photodegradation of sensitizers.[5]

1.2. Green Chemistry

In the recent past, the chemical industry has increasingly focused on the sustainability of chemical processes.

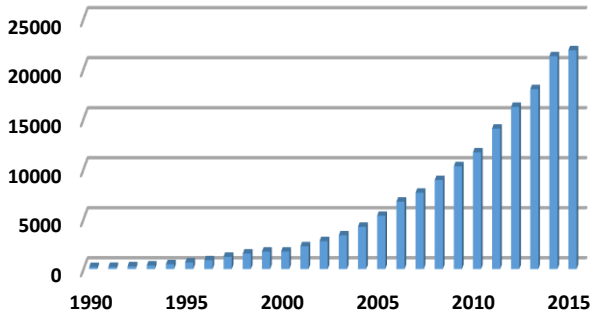


Figure 1.3: Number of cited publications about "GREEN CHEMISTRY & light" from 1990 to 2015; web of science 2016/01/14

The increasing relevance of environmental protection, the higher costs for fossil fuels and waste disposal, but also the growing importance of public awareness forced the chemical industry to explore new paths. Consequently, the 12 PRINCIPLES OF GREEN CHEMISTRY developed by PAUL ANASTAS and JOHN WARNER, have grown to be ever more important. The central idea behind all these aspects is to "design" ideal syntheses.[8,9]

*"**Prevention:** It is better to prevent waste than to treat or clean up waste after it has been created. **Atom Economy**: Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product. **Less Hazardous Chemical Syntheses:** Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment. **Designing Safer Chemicals:** Chemical products should be designed to affect their desired function while minimizing their toxicity. **Safer Solvents and Auxiliaries:** The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used. **Design for Energy Efficiency:** Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure. **Use of Renewable Feedstocks:** A raw material or feedstock should be renewable rather than depleting whenever technically*

and economically practicable. ***Reduce Derivatives:*** *Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.* ***Catalysis****: Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.* ***Design for Degradation:*** *Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.* ***Real-time analysis for Pollution Prevention:*** *Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.* ***Inherently Safer Chemistry for Accident Prevention:*** *Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires."*

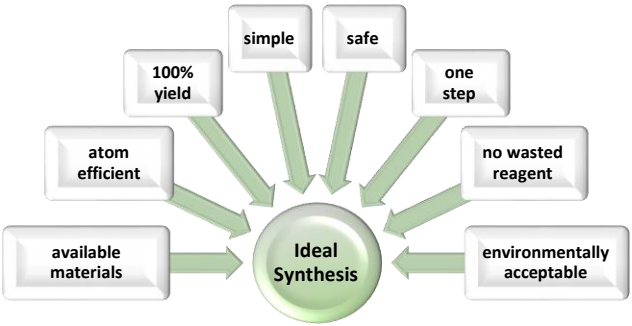


Figure 1.4: The ideal synthesis with respect to GREEN CHEMISTRY[9]

In Figure 1.4 all characteristics of an ideal synthesis, designed with regard to the main principles of GREEN CHEMISTRY are shown.[10] With respect to these principles a photocatalytic oxidation reaction, using sunlight as an energy source and molecular oxygen as an oxidation agent, would represent an almost ideal synthesis.

1.3. Singlet oxygen chemistry

On our planet we are surrounded by air, sunlight and light absorbing materials. In principle these are all components needed for the execution of singlet oxygen reactions.[11]

More closely, dioxygen is one of the most abundant elements on our planet. With about 32 % on earth, 46 % in the earth crust, about 86 % in our oceans and still 23 % of molecular oxygen in air, it is even the most abundant one in regard to the mass fractions (Figure 1.5)

Oxygen in its ground state is colourless, odorless, non-toxic, necessary for human life and available in almost infinite quantities.[13] To this effect oxygen seems to be the perfect reagent for chemical oxidation reactions, but the ground state ($^3O_2$ or $^3\Sigma_g^-$) of the oxygen molecule is a stable di-radical with two unpaired electrons in two different degenerated orbitals (Figure 1.6). This very special electronic structure is reflected in its properties and behavior.[11] The triplet state molecule (T_0) does not react or reacts, according to the spin conservation rule, only in a radical and often very unselective manner with most organic substrates.[14,15]

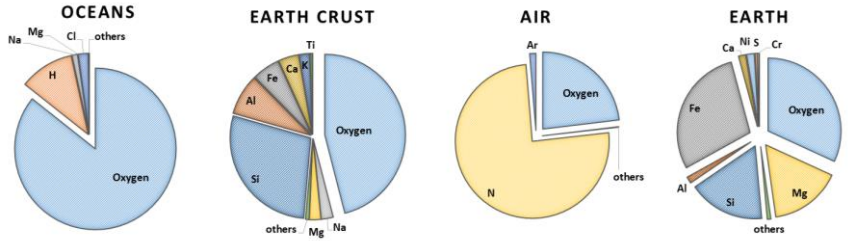


Figure 1.5: Mass fractions of elements on earth.[12]

1.3.1. Activation of Oxygen

As the triplet oxygen ground state is, with few exceptions, not usable for selective chemical transformations with organic substrates, oxygen has to be activated toward an excited reactive oxygen species. If one does not want to generate the reactive singlet oxygen chemically by thermal decomposition of peroxides, the triplet oxygen has to be excited by energy input.[11] Of greatest interest for chemical synthesis, photobiological and therapeutic applications is the first excited electronic state of molecular oxygen ($^1\Delta_g$) that can be generated by irradiation with He/Ne lasers, photolysis of ozone, microwaves or photosensitization of triplet oxygen.[16,17] Although the second excited state ($^1\Sigma_g^+$) of molecular oxygen can be generated by photosensitization it is not usable for chemical reactions due to its short lifetime of at most $2 \cdot 10^{-7}$ s in perhalogenated solvents. Responsible for these short lifetimes is the spin-allowed and fast transition of the highly energetic $^1\Sigma_g^+$ state to lower energetic $^1\Delta_g$ O_2.[18–20] The energy difference between the ground state ($^3\Sigma_g^-$) and the two mentioned excited states is 0.94 eV for $^1O_2$ ($^1\Delta_g$) with two paired electrons in one Π^*-orbital and 1.63 eV for $^1O_2$ ($^1\Sigma_g^+$) with two antiparallel electrons in two different degenerated Π^*-orbitals (Figure 1.6).[14]

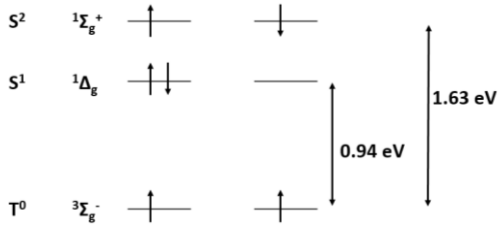


Figure 1.6: Electron configuration of the three lowest electric states of molecular oxygen

The much longer lifetime (up to ms) of the $^1O_2$ ($^1\Delta_g$) results from its spin forbidden radiative decay directly back to the ground state ($^3\Sigma_g^-$). Nevertheless, a deactivation of the metastable $^1\Delta_g$ state can be observed, after generation of singlet oxygen, by detecting infrared radiation at a wavelength of about 1270 nm (Figure 1.7).[16,20,21]

The most common way to generate singlet oxygen in organic synthesis is the photosensitization with visible light. The major advantage of this method is its wide applicability. The majority of organic molecules are colourless and do not absorb visible light which excludes their direct photonic activation. Suitable photosensitizers have to have two key properties: They absorb light of a suitable wavelength and they transfer the excited state energy to the ground state oxygen. Usually the first step in this process, the absorption of visible light, creates an excited singlet state of the sensitizer ($^1S^*$). Through a spin reversal also called intersystem crossing (ISC), an excited sensitizer triplet state ($^3S^*$), lower in energy, can be generated. By collision with an $^3O_2$ molecule energy is transferred to generate excited $^1O_2$ and to regenerate the sensitizer in its ground state (Figure 1.7).[14,15]

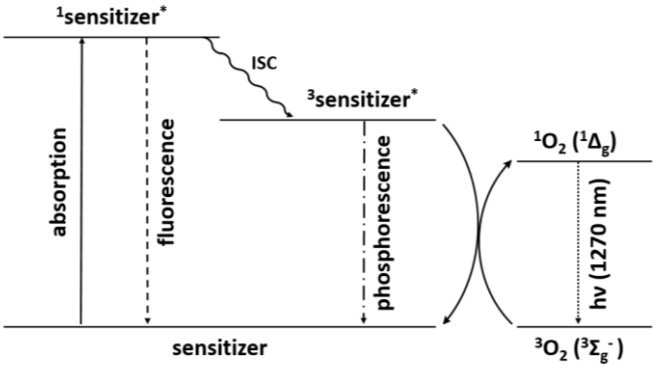


Figure 1.7: JABLONSKI diagram for the photocatalytic excitation of molecular oxygen

The singlet oxygen generated by photosensitization can be used for various oxidation reactions such as classical oxidations to form oxides or peroxides,[11] polymer degradations[22] or solar water disinfection[23]. To realize reactions in solution-phase systems one has to choose the right solvent for this type of reaction. An ideal solvent should have the following properties: good solubility of substrate, sensitizer and oxygen as well as a long lifetime of the singlet oxygen. The lifetime of singlet oxygen ($^1\Delta_g$) is extremely dependent on the chosen medium, the substrate and even the sensitizer.[19,24] In every solution-phase reaction the chemical reactions of singlet oxygen has to compete kinetically with the physical deactivation of $^1\Delta_g$ to $^3\Sigma_g^-$ by collision with (1) a substrate molecule, (2) a solvent molecule or (3) another dissolved molecule in the system.[11] In Table 1.1 the solubility of oxygen and lifetime of the first electronically excited state ($^1\Delta_g$) are shown for different conventional solvents. With its very high lifetime of $^1O_2$ ($2.8 \cdot 10^{-2}$ s) and high solubility of oxygen ($12.0 \cdot 10^{-4}$ mol%), tetrachloro-methane (CCl_4) would be the perfect solvent for reactions with singlet oxygen. However, the high toxicity and environmental impact restricts its use, ensuing the requirements of GREEN CHEMISTRY. Reasonable alternatives are frequently used alcohols or acetonitrile with moderate values for solubility ($6.2 \cdot 10^{-4}$ mol%) and $^1O_2$ lifetime ($7.7 \cdot 10^{-5}$ s).[25–27] Depending on the polarity of the used reagent and sensitizer also benzene or THF are suitable alternatives.

Table 1.1: Solubility[25,27] of oxygen and lifetime[24] of the $^1O_2$ ($^1\Delta_g$) in different solvents

Solvent	Solubility of O_2 X [$10^{-4} \cdot$ mol%]	Lifetime $^1O_2$ τ [s]
MeCN	6.2	$7.7 \cdot 10^{-5}$
MeOH	4.3	$9.0 \cdot 10^{-6}$
C_6H_6	8.0	$3.1 \cdot 10^{-5}$
CCl_4	12.0	$2.8 \cdot 10^{-2}$
THF	8.0	$2.3 \cdot 10^{-5}$
H_2O	0.25	$4.2 \cdot 10^{-6}$

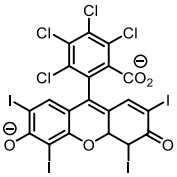
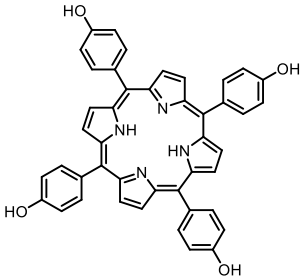
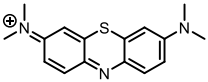
1.3.2. Sensitizer properties

As already mentioned, photosensitizers for singlet oxygen reactions are chromophores absorbing energy in the range of visible light and transferring this energy to an $^3O_2$ molecule. In principle, there are two different types of photooxygenation reactions that have to be distinguished.[20,28]

In a Type I reaction, there is a direct H atom abstraction or electron transfer between the excited photosensitizer and the substrate molecule forming radicals or radical ions.

Consequently, these initially formed radical species react with $^3O_2$ ($^3\Sigma_g^-$) to build the oxygenated product or to produce radical superoxide anions ($^1O_2^{\cdot-}$).[11]
In a Type II reaction, the excited photosensitizer directly transfers the energy to $^3O_2$ ($^3\Sigma_g^-$) creating either $^1O_2$ ($^1\Delta_g$) or radical superoxide anions ($^1O_2^{\cdot-}$) which can react with the present substrate to form the oxygenation product.[26] To summarize, one can say that the excited state sensitizer is either quenched by the substrate (Type I) or by oxygen (Type II).[11]
As we want to have as selective reactions as possible, the chosen photosensitizer should have a very high quantum yield for the formation of singlet oxygen and low quantum yields for the formation of radical superoxide anions or energy transfer to the substrate molecule. Also the quantum yield for the ISC from the $^1S^*$ to the $^3S^*$-state should preferably be high. The direct relaxation from the $^3S^*$ to the singlet ground state is spin-forbidden. This leads to a relatively long living excited triplet state and a higher collision probability with an oxygen molecule.[29]

Table 1.2: Quantum yields for the photosensitized activation of oxygen,[30] absorption maxima,[31] and triplet state energies[20,32] of selected sensitizers.

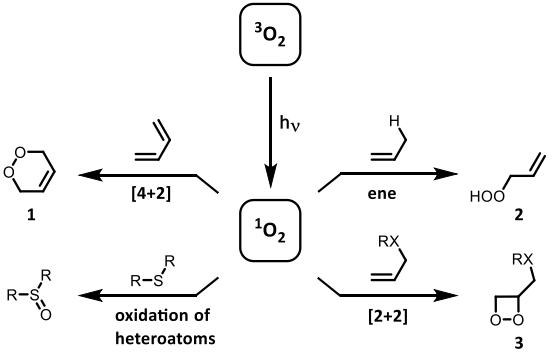
		
Rose Bengal	**THTPP**	**Methylene Blue**
λ_{max} = 548 nm	λ_{max} = 422 nm[31]	λ_{max} = 665 nm
E_λ = 2.26 eV	E_λ = 2.94 eV	E_λ = 1.87 eV
Φ ($^1O_2$) = 0.69 (MeCN)	Φ ($^1O_2$) = 0.58 (EtOH)	Φ ($^1O_2$) = 0.52 (MeCN)
Φ ($^1O_2$) = 0.80 (MeOH)	Φ ($^1O_2$) = 0.56 (MeOH)	Φ ($^1O_2$) = 0.51 (MeOH)
E_T = 1.82 eV[20]	E_T = 1.47 eV(TPP)[20]	E_T = 1.39 eV[20]

In Table 1.2, the sensitizers mainly used in this work are listed. Rose bengal (RB), (5,10,15,20-tetrakis(4-hydroxyphenyl)-21*H*,23*H*-porphine) (THTPP) and methylene blue (MB) are sufficiently polar to dissolve in acetonitrile (mostly used for oxidation of polar

substrates) and have good quantum yields for the generation of $^1O_2$. The values of Φ ($^1O_2$) in different solvents show a second aspect of solvent dependency of $^1O_2$-reactions. The absorption maxima of all these sensitizers are in the range of visible light.[31] The photon energy related to the light absorbed ranges from 1.87 eV to 2.94 eV and is therefore sufficient to generate the excited sensitizer and consequently $^1O_2$.
There is one further characteristic common to all $^1O_2$ photosensitizers. The energy difference (E_T) between the $^3S^*$ and the ground state of the chromophore has to be higher than the ΔE between T_0 and S_1 of the oxygen molecule. For the used sensitizers RB, MB and THTPP all E_T-values are >1.3 eV (Table 1.2).[20,32]

1.3.3. Reaction types of $^1O_2$

The first excited state of oxygen has an 0.94 eV higher oxidation potential than the $^3\Sigma_g^-$ oxygen. Therefore, $^1O_2$ is able to oxidize electron rich substances like sulfides[33], amines[34] or highly substituted olefins. With olefins having a higher redox potential than $^1O_2$, no electron transfer will occur. In this case, different chemical reactions can take place. Mainly three different $^1O_2$ reactions of olefins or dienes (chemical quenching) and the oxidation of heteroatoms are distinguished (Scheme 1.2).[20]



Scheme 1.2: Reaction types of singlet oxygen

The most common $^1O_2$ reactions beside heteroatom oxidation are (Scheme 1.2):
- [4+2]-cycloaddition: oxidation of 1,3-dienes to endoperoxides (**1**)[35]
- allylic oxidation of olefins via double bond migration to give allylic hydroperoxides (**2**) (Schenck ene reaction)[35]
- [2+2]-cycloaddition: formation of 1,2-dioxetanes (**3**), oxidizing electron rich alkenes.[36]

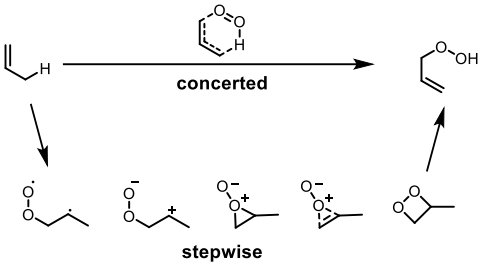
1.3.4. Mechanism and selectivity of Schenck ene reactions

The aspects of selectivity and the reaction mechanism of the Schenck ene reaction will be discussed below. Günther Otto Schenck was a pioneer of radiation chemistry. In the 1940s Schenck already postulated the concept of photosensitized oxygenations and he performed singlet oxygen reactions using sunlight and spinach leaves to oxidize *α*-terpinene in his garden (Figure 1.8).[37]

Figure 1.8: Schenck next to his photo oxidation pilot plant in his garden.[37]

The Schenck ene reaction was developed in the same period. Even though Schenck presented a mechanistic theory some 70 years ago, including an oxidizing intermediate which he called *sens*$^{rad}O_2$, the mechanism of Schenck ene reactions has hardly been discussed, up to present times.[37]

Beside a concerted mechanism, several stepwise mechanisms involving different intermediates are said to be possible. For a long time a concerted mechanism passing a six-membered ring transition state was the favored pathway. New experimental and computational investigations brought up different stepwise mechanisms passing either a biradical, an open zwitterion/dipolar, a perepoxide, an epiplex or a dioxetane intermediate. All these reaction pathways lead to the final formation of an allylic hydroperoxide (Scheme 1.3).[38]



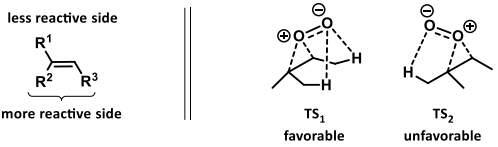
Scheme 1.3: Proposed mechanisms of Schenck ene reactions[38]

As a matter of fact, there is no single mechanism of all Schenck ene reactions. Depending on the reactant and also on the solvent polarity one or another mechanism is more probable. For example perepoxide formation seems to be the most reasonable pathway for simple olefins, whereas correlations between zwitterionic and perepoxide intermediates are possible for electron-rich olefins like enamines[39], enol ethers[40] or α-ester-functionalized olefins.[41][38]

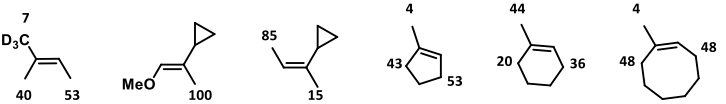
A major problem of Schenck ene reactions is the often low regio- and stereoselectivity which gives a crude mixture of hardly separable isomers. Some selectivity rules and tendencies will be presented shortly below and some selected literature examples will be shown. All the following selectivity rules show only priorities concerning the proton-abstraction and no quantitative formation of a single product. Base of all explanations regarding the observed selectivities is the assumption of a perepoxide intermediate and the abstraction of an allylic proton perpendicular to the plane of the double bond. In all the following examples the percentage of proton abstraction in different positions is noted.

***cis* effect:**

In trisubstituted cyclic or acyclic alkenes and enol ethers the proton is preferably abstracted from the more substituted site of the double bond. This effect can be explained by a better stabilization of the transition state TS_1 (Scheme 1.4) with interaction of two allylic hydrogen atoms with the incoming singlet oxygen.



Scheme 1.4: *Cis*-selectivity and possible transition states[38]

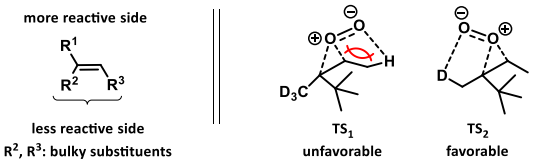


Scheme 1.5: Examples of *cis*-selectivity[38,42]

An exception is the selectivity of the proton abstraction in cyclohexenes. This effect is based on the ground state conformation of cyclohexenes and will be discussed in more detail in Chapters 3 and 5.2.

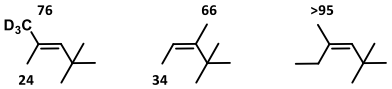
***anti cis* effect:**

A so-called *anti cis* effect, a hydrogen abstraction from the less substituted site of the double bond, can be observed in oxygenations of trisubstituted alkenes with one bulky substituent. This effect is mainly based on the steric demands of bulky substituents and the repulsion of the incoming $^1O_2$ molecule in TS_1 (Scheme 1.6).[38]



Scheme 1.6: *Anti cis*-selectivity and possible transition states[38]

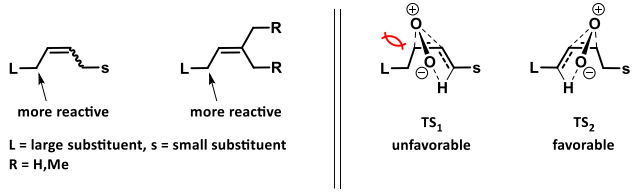
The examples in Scheme 1.7 show that this effect is not very pronounced. Product ratios of two to one or three to one can be achieved. Better selectivities are only attainable using different substituents like methyl competing with ethyl substituents.[38]



Scheme 1.7: Examples of *anti cis*-selectivity[38]

large group non-bonding effect:

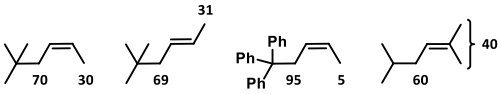
Another mainly sterically driven selectivity aspect in oxygen ene reactions with non-symmetrical *cis*- and *trans*-alkyl-substituted alkenes, is the "large group non-bonding" effect. Oxidation of alkenes with one large substituent (**L**) and one small substituent (**s**) show that the reactivity of the proton next to **L** is higher than the reactivity of the proton next to **s** (Scheme 1.8).



Scheme 1.8: Large group non-bonding effect and possible transition states[38]

A look at the transition states TS_1 and TS_2 (Scheme 1.8) shows the repulsion between the large substituent L and the incoming singlet oxygen and explains the favored product formation *via* TS_2. Examples in Scheme 1.9 demonstrate that the strength of this

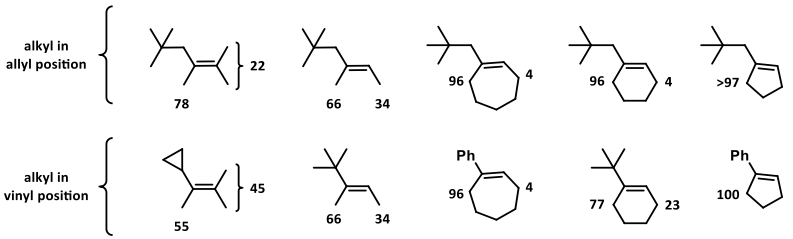
selectivity effect is strongly dependent on the relation between the crowdedness of the two substituents. Alkenes with one small and one very bulky substituent deliver very good selectivities, whereas alkenes with two substituents comparable with respect to their steric demands, give only small excess of one product.



Scheme 1.9: Examples of selectivities from the large group non-bonding effect[38]

***gem* effect:**

The so-called *gem* effect (*geminal* selectivity) describes a selectivity very similar to the "large group non-bonding" effect, looking at tri- or tetra-substituted olefins. All the compared olefins carry a large alkyl- or aryl substituent and a methyl- or methylene group at the same carbon atom. Examples in Scheme 1.10 show that this effect can be observed for bulky substituents in allyl- as well as in vinyl-position with moderate to excellent selectivities. In all cases, the proton-abstraction at the substituent geminal to the large substituent is preferred.[38] Remarkable, in regard to the results of this work (Chapter 3) and the known reactivity of substituted cyclohexenes[42] is the excellent selectivity oxidizing cyclohexene with a *tert*-butyl group in allylic position.

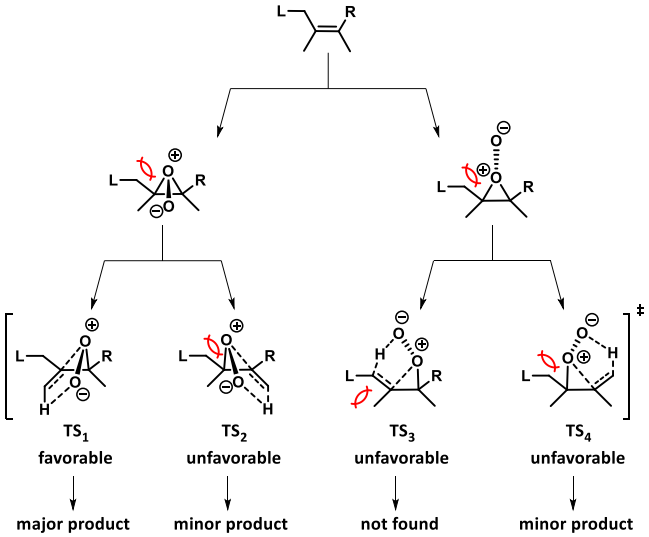


Scheme 1.10: Examples of *gem*-selectivity[38]

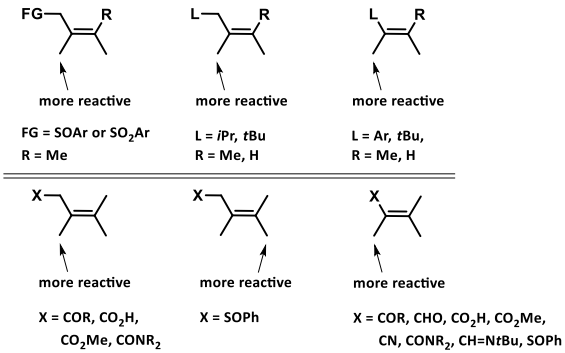
As shown in Scheme 1.11 the selectivity, considering this substitution pattern, is also a result of steric demand of the bulky substituent and repulsion of the incoming singlet oxygen in three of the four possible transition states. In certain studies other aspects like the lower rotational barrier of the *geminal* methyl group are also mentioned as a reason for the observed selectivity.

The *gem* selectivity can also be observed in oxidation reactions of other tri- and tetra-substituted olefins like shown in Scheme 1.12. A variety of different electron-withdrawing and electron-donating functional groups (COR, CO_2R, CN, SO_xR, SiR_3, SnR_3, $OSiR_3$ etc.) show equal selectivity. An exception are sulfinyl-groups in *β*-position. The

inverse selectivity in this special case is a result of the repulsion of the negatively polarized oxygen of the S-O bond and the negatively polarized oxygen of the incoming $^1O_2$ during the transition state.[38,43]



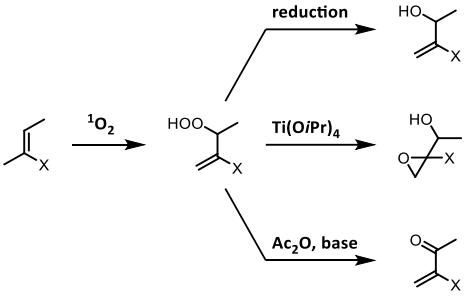
Scheme 1.11: *Gem*-selectivity and possible transition states[38]



Scheme 1.12: *Gem*-directing substituents[38]

1.3.5. Allyl hydroperoxides as synthetic building blocks

The allyl hydroperoxides produced by Schenck ene reactions turned out to be potent building blocks. Also due to their low stability, the peroxides are often converted to allylic alcohols *in situ* by reduction with PPh_3, SMe_2, Na_2SO_3 or other reducing agents. Furthermore, epoxyalcohols are accessible *via* conversion with Ti^{IV}-complexes, quite similar to the classical Sharpless epoxidation. Ketones can be synthesized *via* an esterification-, elimination reaction using acetic anhydride and pyridine.[43]

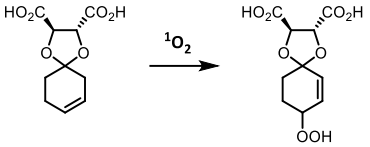


Scheme 1.13: Preparative applications of allyl hydroperoxides[43]

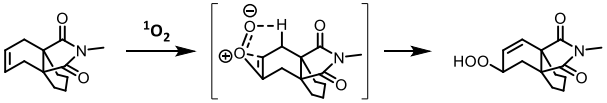
1.3.6. Schenck ene reactions of cyclohexene systems

The selectivity rules for Schenck ene reactions show that the product formation is mainly influenced by the substitution pattern and the conformation of the starting material. One can say that in these reactions the more easily available H atom is abstracted preferentially. Presuming a perepoxide intermediate, abstraction of the allylic H atom requires a perpendicular orientation to the plane of the double bond. In open-chain olefins, at least one allylic H atom can always be assumed to reach such reactive geometry. Accordingly the limited rotation and vibration in cyclic or polycyclic olefins can either reduce the reactivity or generate selectivity because of the decreased number of (potentially) perpendicular protons. Especially in cyclohexenes the reactivity is reduced, due to its ground state conformation. This effect is enhanced by big substituents or the annulation of a second ring, as the barrier for a conformation change or a ring inversion is increasing.[44] Only few examples of Schenck ene reactions with cyclohexenes are shown in literature with partially excellent regio- and stereoselectivities.

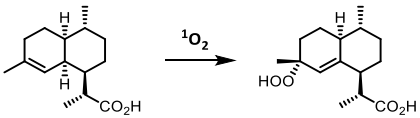
Schemes 1.14-1.16 show some known Schenck ene reactions with different cyclohexene starting materials. All examples show excellent regioselectivity. Additionally the propillane oxidation performed by GINSBURG et al., as well as the key step of the artemisinine synthesis of SEEBERGER et al., show very good stereoselectivities.



Scheme 1.14: Auxiliary controlled singlet-oxygen ene reactions of cyclohexenes: $CHCl_3$, TPP, hv, -30 °C, 2-4 d[45]



Scheme 1.15: $^1O_2$-ene reaction of olefinic propellanes: MeCN, RB, hv, RT, 4.5 h[46]



Scheme 1.16: Key step in the synthesis of the anti-malaria drug artemisinine: flow reactor, DCM. TPP, hv, RT 2 min.[47]

It is striking that these three reactions vary extremely in the required reaction times. Although we are comparing three photooxygenations of cyclohexenes, the reaction times range from 2 min to 2-4 d. This extreme difference in reaction times shows the enormous impact of the experimental setup on the required reaction time of photocatalytic singlet oxygen reactions. Apart the reactivity of the used substrate, the reaction rates in photooxygenations are dependent on several parameters (e.g. efficiency of irradiation, mixing of gaseous and liquid phase, etc.)

Therefore SEEBERGER et al. used a continuous flow reactor for their photooxygenations and achieved the shortest reaction times by far in this comparison.

1.4. Flow reactors

Effective irradiation is important for photocatalytic reactions. Constant and efficient mixing is essential for gas-liquid reactions. In photooxygenation reactions with molecular oxygen, both are needed, effective irradiation as well as effective mixing of the gaseous and liquid phase.
On that score, different flow reactor systems were developed. The high surface-to-volume ratios, the excellent mass-transfer coefficients and irradiation properties of microreactors are the major advantages of flow reactors over batch reactors. Some flow reactors suitable for gas-liquid light-induced reactions will be briefly presented below. A more precise overview of this topic will be given in Chapter 4.

1.4.1. Reactor types for gas-liquid photochemistry

Tube reactors:[48]

Tube reactors, mostly a FEP tube wrapped around a light source, are the simplest way to build a flow reactor. They are inexpensive and very flexible. Compared to other reactor types, like microchannel or thin film reactors, the surface to volume ratio is smaller and the mixing and irradiation is less efficient, but the wide-ranging application and the low costs for building such a system make it very interesting. The mass transfer as well as the irradiation in tube reactors is still far better than in classical batch synthesis. The reaction times can be reduced by orders of magnitude and selectivity can be increased by excellent thermal control and precise adjustment of reaction conditions.[47]

Microchannel reactors:[49]

These reactors are based on µm-scale channels on glass- or polymer-chips. Microchannel reactor chips are commercially available or can be produced, for example, by using laser lithography. These chips can be very simple systems with only one channel connected to a gas and a liquid inlet, but they can also have a multitude of parallel or crossing channels to realize very efficient mixing. In general these reactors are very useful devices for gas-liquid photoreactions. The mass transfer is very fast due to the high surface to volume ratio and the irradiation is extremely efficient. Additionally the material can be selected according to the intended chemistry and irradiation wavelength used. Drawbacks of the system are the complexity of the production of microchannel reactor chips, the consequently high price and the limitation to fast reactions due to the small scale of the reactor chips.

Falling film reactors:[50]

In falling film or thin film reactors, the substrate solution runs down an inclined plane or parallel channels in such a plane. Gravitational force is used to generate very thin films of liquid. The gas streams in the opposite direction. The reactors allow very effective gas-liquid contacting, full irradiation of the substrate solution, high concentrations and well defined reaction times. The dimensions of irradiated falling film reactors are usually very small, to achieve the most effective irradiation. This limits these reactors concerning the reaction times, to fast reactions. DINGERDISSEN et al. for example could realize reaction times in a range of 5 – 10 seconds. The irradiated channels they used have a length of 50 mm, a depth of 50 µm and a width of 150 µm.

Tube-in-tube reactors:[51]

This reactor type is based on two concentric capillaries. The substrate, dissolved in a liquid phase, flows through the inner, gas-permeable capillary, the pressurized gas in the outer capillary permeates through the walls of the inner one. These reactors are very versatile in their application. A broad range of gases (CO, CO_2, H_2, O_2, C_2H_4, NH_3) can be used. The reactor dimensions can be varied easily by variation of the length of the tubing. The major drawback of this reactor type is the high price of the gas permeable Teflon® AF tubing and the challenging technical structure of the needed connectors. However tube-in-tube reactors are suitable for gas liquid reactions, they are not used for gas-liquid photoreactions until now.

1.5. References

[1] a) Statistisches Bundesamt Wiesbaden, *Umweltnutzung und Wirtschaft*, **2012**, *part 2: Energie* (article number: 5850007127006); b) Statistisches Bundesamt Wiesbaden, *Umweltnutzung und Wirtschaft*, **2015**, *part 2: Energie* (article number: 5850007157006)

[2] AG Energiebilanz, Verband der Chemischen Industrie e.V, **2015**, status: October 26th 2015

[3] K. Giller, *Agric. Syst.* **1996**, *51*, 126.

[4] G. Ciamician, *Science* **1912**, *36*, 385–394.

[5] M. Fischer, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 16–26.

[6] M. Pape, *Pure Appl. Chem.* **1975**, *41*.

[7] M. Oelgemöller, C. Jung, J. Ortner, J. Mattay, E. Zimmermann, *Green Chem.* **2005**, *7*, 35.

[8] P. Anastas, N. Eghbali, *Chem.Soc. Rev.* **2010**, *39*, 301–312.

[9] P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686–694.

[10] J. H. Clark, *Green Chem.* **1999**, *1*, 1–8.

[11] P. R. Ogilby, *Chem.Soc. Rev.* **2010**, *39*, 3181–3209.

[12] a) C. Allègre, G. Manhès, É. Lewin, *Earth Planet. Sci. Lett.* **2001**, *185*, 49–69; b) A. Cameron, *Space Sci. Rev.* **1973**, *15*.

[13] C. S. Quinsey, *J. Chem. Educ.* **2003**, *80*, 1124.

[14] B. F. Minaev, H. Ågren, *Faraday Trans.* **1997**, *93*, 2231–2239.

[15] K. Krukiewicz, *Chemik* **2011**, *11*, 1190–1192.

[16] F. Wilkinson, *J. Phys. Chem. Ref. Data* **1981**, 809–999.

[17] M. N. Alberti, M. Orfanopoulos, *Chem. Eur. J.* **2010**, *16*, 9414–9421.

[18] N. V. Shinkarenko, V. B. Aleskovskii, *Russ. Chem. Rev.* **1981**, *50*, 220–231.

[19] C. Schweitzer, R. Schmidt, *Chem. Rev.* **2003**, *103*, 1685–1757.

[20] M. DeRosa, *Coord. Chem. Rev.* **2002**, *233–234*, 351–371.

[21] A. Bromberg, C. S. Foote, *J. Phys. Chem.* **1989**, *93*, 3968–3969.

[22] J. F. Rabek, B. Ranby, *Polym. Eng. Sci.* **1975**, *15*, 40–43.

[23] L. Villén, F. Manjón, D. García-Fresnadillo, G. Orellana, *Appl. Catal. B: Environ.* **2006**, *69*, 1–9.

[24] Francis Wilkinson, *J. Phys. Chem. Ref. Data* **1993**, 664–1021.

[25] S. Horstmann, A. Grybat, R. Kato, *J. Chem. Thermodyn.* **2004**, *36*, 1015–1018.

[26] Francis Wilkinson, *J. Phys. Chem. Ref. Data* **1983**, 162–178.

[27] R. Battino, T. R. Rettich, T. Tominaga, *J. Phys. Chem. Ref. Data* **1983**, *12*, 163.

[28] C. S. Foote, *Photochem Photobiol* **1991**, *54*, 659.

[29] C. S. Foote, S. Wexler, *J. Am. Chem. Soc.* **1964**, *86*, 3880–3881.

[30] F. Wilkinson, W. P. Helman, A. B. Ross, *J. Phys. Chem. Ref. Data* **1993**, *22*, 113–262.

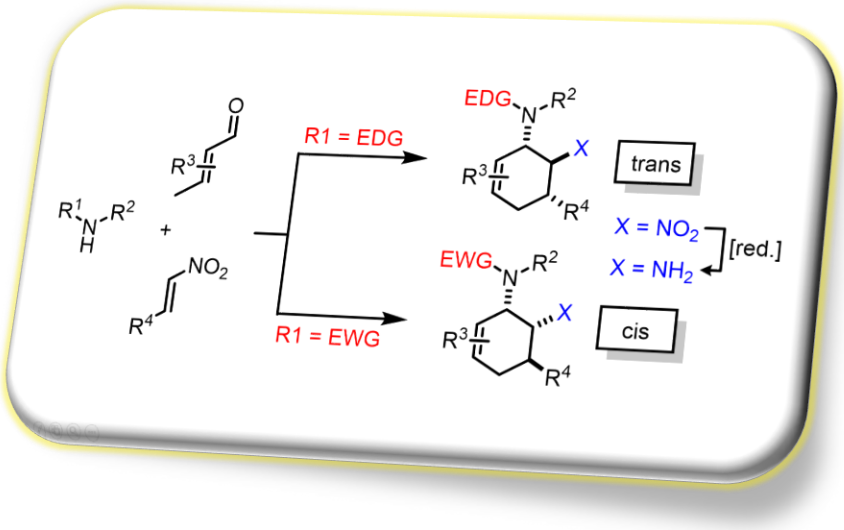
[31] A. Mazzaglia, L. M. Scolaro, R. Darcy, R. Donohue, B. J. Ravoo, *J. Incl. Phenom. Macrocycl. Chem.* **2002**, *44*, 127–132.

[32] Z. Katona, A. Grofcsik, P. Baranyai, I. Bitter, G. Grabner, M. Kubinyi, T. Vidóczy, *J. Mol. Struct.* **1998**, *450*, 41–45.

[33] A. Talla, B. Driessen, N. J. W. Straathof, L.-G. Milroy, L. Brunsveld, V. Hessel, T. Noël, *Adv. Synth. Catal.* **2015**, *357*, 2180–2186.
[34] D. B. Ushakov, K. Gilmore, D. Kopetzki, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 557–561.
[35] G. O. Schenck, *Naturwissenschaften* **1948**, *35*, 28–29.
[36] S. Mazur, C. S. Foote, *J. Am. Chem. Soc.* **1970**, *92*, 3225–3226.
[37] K. Schaffner, *Angew. Chem. Int. Ed.* **2003**, *42*, 2932–2933.
[38] M. Alberti, M. Orfanopoulos, *Synlett* **2010**, *2010*, 999–1026.
[39] I. Saito, S. Matsugo, T. Matsuura, *J. Am. Chem. Soc.* **1979**, *101*, 7332–7338.
[40] E. W. H. Asveld, R. M. Kellogg, *J. Am. Chem. Soc.* **1980**, *102*, 3644–3646.
[41] S. L. Wilson, G. B. Schuster, *J. Am. Chem. Soc.* **1983**, *105*, 679–681.
[42] K. H. Schulte-Elte, V. Rautenstrauch, *J. Am. Chem. Soc.* **1980**, *102*, 1738–1740.
[43] M. Prein, W. Adam, *Angew. Chem.* **1996**, *108*, 519–538.
[44] F. R. Jensen, C. H. Bushweller, *J. Am. Chem. Soc.* **1969**, *91*, 5774–5782.
[45] W. Fudickar, K. Vorndran, T. Linker, *Tetrahedron* **2006**, *62*, 10639–10646.
[46] I. Landheer, D. Ginsburg, *Tetrahedron* **1981**, *37*, 143–150.
[47] F. Lévesque, P. H. Seeberger, *Angew. Chem.* **2012**, *124*, 1738–1741.
[48] a) F. Lévesque, P. H. Seeberger, *Org. Lett.* **2011**, *13*, 5008–5011; b) J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052.
[49] a) M. J. Nieves-Remacha, A. A. Kulkarni, K. F. Jensen, *Ind. Eng. Chem. Res.* **2013**, *52*, 8996–9010; b) R. C. R. Wootton, R. Fortt, A. J. de Mello, *Org. Process Res. Dev.* **2002**, *6*, 187–189; c) G. Chen, J. Yue, Q. Yuan, *Chin. J. Chem. Eng.* **2008**, *16*, 663–669.
[50] a) J.-N. Tourvieille, F. Bornette, R. Philippe, Q. Vandenberghe, C. d. Bellefon, *Chem. Eng. J.* **2013**, *227*, 182–190; b) K. Jähnisch, U. Dingerdissen, *Chem. Eng. Technol.* **2005**, *28*, 426–427.
[51] a) M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349–362; b) F. Mastronardi, B. Gutmann, C. O. Kappe, *Org. Lett.* **2013**, *15*, 5590–5593; c) C. Y. Park, Y. J. Kim, H. J. Lim, J. H. Park, M. J. Kim, S. W. Seo, C. P. Park, *RSC Adv.* **2015**, *5*, 4233–4237.

Chapter 2:

- Modular Synthesis of Cyclic *cis*- and *trans*-1,2-Diamine Derivatives -



2. Modular Synthesis of Cyclic *cis*- and *trans*-1,2-Diamine Derivatives

This chapter was published:

A. K. Weber, J. Schachtner, R. Fichtler, T. M. Leermann, J. M. Neudörfl, A. Jacobi von Wangelin, *Org. Biomol. Chem.* **2014,** *12*, 5267 – 5277; DOI: 10.1039/b000000x

Schemes, figures and text may differ from published version.

Author contributions:

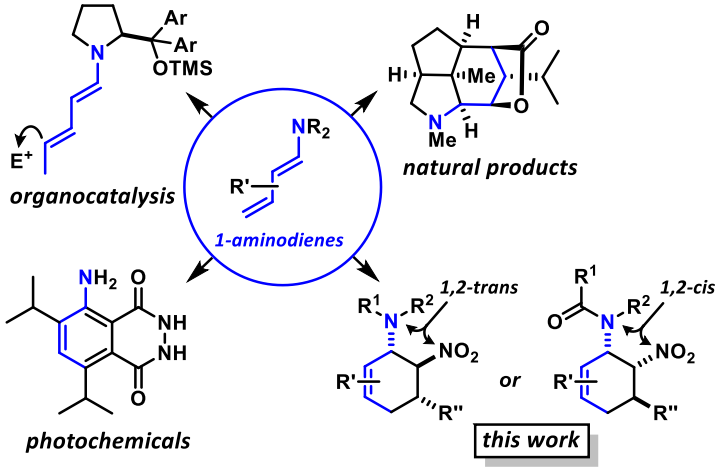
Anna Weber did three-component reactions, experiments with enantiopure starting materials and elimination reactions. Josef Schachtner did three-component reactions and reductions with Zn/HCl. Robert Fichtler did three-component reactions and oxidations with MnO_2.

Abstract

Structurally diverse carbocycles with two vicinal nitrogen-substituents were prepared in expedient three-component reactions from simple amines, aldehydes, and nitroalkenes. *Trans*,*trans*-6-nitrocyclohex-2-enyl amines were obtained in a one-pot domino reaction involving condensation, tautomerisation, conjugate addition, and nitro-Mannich cyclisation. Upon employment of less nucleophilic carboxamides, a concerted Diels-Alder cycloaddition mechanism operated to give the corresponding *cis*,*trans*-nitrocyclohexenyl amides. Both types of substituted carbocycles offer ample opportunities for chemical manipulations at the core and periphery. Ring oxidation with MnO_2 affords substituted nitroarenes. Reduction with Zn/HCl provides access to various *trans*- and *cis*-diaminocyclohexenes, respectively, in a straight-forward manner. With enantiopure secondary amines, a two-step synthesis of chiral nitrocyclohexa-dienes was developed (82 – 94 % *ee*).

2.1. Introduction

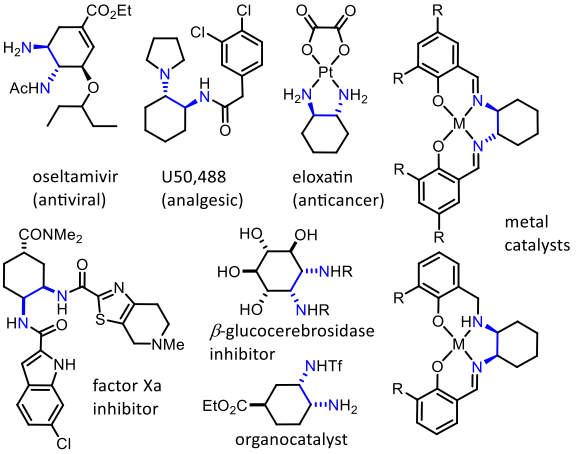
Functionalised cyclohexanes are one of the most prevalent molecular architectures in nature and synthesis. Today, a plethora of synthetic procedures is available to provide access to various saturation states and peripheral substitution patterns. The majority of syntheses involve functionalisation of already cyclic precursors whereas *de-novo*-syntheses of functionalised cyclohexanes from two or more acyclic starting materials exhibit much higher modularity and provide access to a large chemical space.[1] The most prominent examples of such intermolecular cyclisation reactions include cyclo-additions[2] and many variants of sequential condensation-addition reactions with carbonyl compounds.[3] Heteroatom(X)-substituted cyclohexanes are arguably the most interesting structures for active pharmaceutical ingredients and fine chemical building blocks due to the distinct stereoelectronic properties and chemical reactivities of polar C-X bonds and the available lone pairs at X.[4] Aminodienes were widely used in method developments, syntheses of pharmaceutically active molecules, natural products and materials (Scheme 2.1).[5]



Scheme 2.1: 1-Amino-1,3-butadienes in organic synthesis.

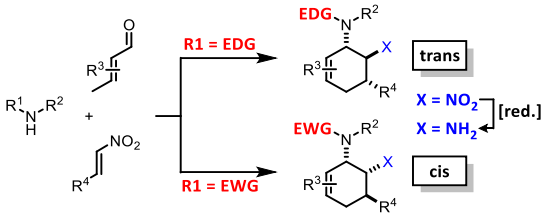
Aminodienes can be easily prepared from condensations of unsaturated carbonyl compounds and amines and exhibit high reactivity in normal-electron demand cycloadditions and nucleophilic additions due to their high-lying HOMO (highest occupied molecular orbital).[6] Further *N*-based substituents can be incorporated into the product structure by employment of α-electrophilic nitrogen compounds. Nitroolefins are a readily available class of vinylogous nitrogenous electrophiles with

widespread applications in Michael-type additions and cycloadditions.[7] We envisoned a domino process involving initial condensation of unsaturated aldehydes with amines followed by selective cyclisation of the resultant 1-amino-1,3-dienes with nitroolefins.[8] Such strategy would provide an expedient access to highly functionalised cyclohexenes containing two chemically orthogonal *N*-based substituents in vicinal positions (NR_2, NO_2). 1,2-Diaminocyclohexane motifs constitute important building blocks of pharmacologically active molecules, fine chemicals and catalysts (Scheme 2.2).[9]



Scheme 2.2: Applications of *trans*-(top) and *cis*-1,2-diaminocyclohexanes.

The electronic nature of the intermediate aminodienes can be easily tuned by the introduction of various *N*-substituents. It has been demonstrated that highly nucleophilic aminodienes bearing electron-donating (EDG) alkyl substituents engage in rapid Michael-type additions to electrophiles.[10] However, a change of mechanism can be effected by electron-withdrawing (EWG) *N*-substituents. 1-*N*-Acyl-amino-1,3-butadienes undergo concerted [4+2]-cycloadditions with electron-deficient dienophiles.[6] Here, we report the viability of controlling the reaction mechanism and stereoselectivity by the employment of secondary amines (R^1 = EDG) or less nucleophilic acylamines (R^1 = EWG) in three-component cyclisations with *α,β*-unsaturated aldehydes and nitroalkenes to give *trans*- or *cis*-1,2-diaminocyclohexenes (Scheme 2.3).



Scheme 2.3: The stereoselectivity switch: amines vs. *N*-acyl amines.

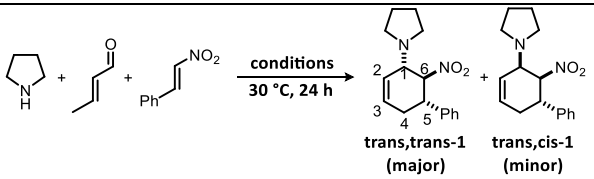
2.2. Results and Discussion

Synthesis of trans-nitrocyclohexenyl amines

As an extension of earlier work on functionalised aminocyclo-hexenes,[8] we optimised reaction conditions for the three-component cyclisation of secondary amines, α,β-unsaturated aldehydes and nitroalkenes. We chose pyrrolidine, croton-aldehyde and β-nitrostyrene as model substrates (Table 2.1). High selectivities were observed in toluene as solvent and upon slow addition of a slight excess of the aldehyde.[10]

Rapid aldehyde addition resulted in oligomer formation. The three-component cycloadduct 1-(6-nitro-5-phenylcyclohex-2-enyl)pyrrolidine (**1**) was obtained with high thermodynamic stereocontrol (*trans*,*trans* / *cis*,*trans* = 19 / 1). The minor diastereomer exhibited a *cis*-relation of the amino and nitro groups. The preferential formation of the *all-trans* stereoisomer and the observation of an identical outcome from reactions with (*Z*)-β-nitrostyrene suggest the operation of a stepwise mechanism (Scheme 2.4).[10]

Table 2.1: Selected optimisation experiments.[a]

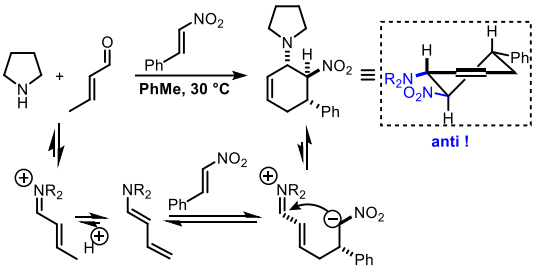


Entry	Conditions	Yield[b] [%]
1	CH_3CN	27 (40)[c]
2	CH_2Cl_2	58
3	DMF	72
4	PhMe	76

5	PhMe, 2 equiv. aldehyde	68
6	PhMe, 2 equiv. amine	29
7	PhMe, slow addition (~ 2 h) of 1.2 equiv. aldehyde	90 (19/1)[d,e]
8	As entry 7, but with pyrrolidine/benzoic acid (1/1)	64 (18/1)[d]

[a] Optimised conditions: Pyrrolidine (2 mmol), β-nitrostyrene (2 mmol), PhMe (3 mL), slow addition of crotonaldehyde (2.4 mmol in 1 mL PhMe) over 2 h, 30 °C, 20 h. [b] GC yields vs. internal hexadecane. [c] 60 °C. [d] diastereomeric ratio (*d.r.*). [e] 83 % isolated yield.

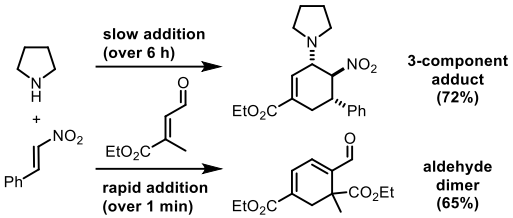
Initial condensation between the amine and aldehyde gives rise to the formation of an equilibrating mixture of imine, enamine and aminal derivatives, of which the aminodiene undergoes reversible conjugate addition to the nitroolefin.[11] Subsequent nitro-Mannich ring-closure affords the thermodynamic product containing three vicinal equatorial substituents.[12]



Scheme 2.4: Nitro-Mannich mechanism with secondary amines.

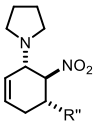
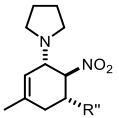
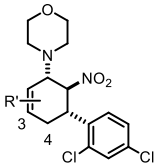
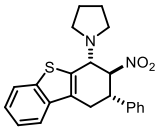
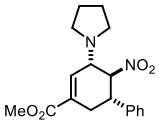
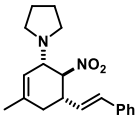
We extended the reaction conditions to various other amines, aldehydes and nitroolefins (Table 2.2).[13] The *trans*,*trans*-isomers were preferentially formed in diastereomeric ratios of >10/1.[10] Diastereomeric ratios (*d.r.*) were assigned based on high-resolution ^{1}H-NMR spectra. The *trans*-configurations of the vicinal amino/nitro and nitro/aryl groups, respectively, at the cyclohexene result in dihedral angles of 170° – 180° and $^3J_{HH}$ coupling constants of 10 – 12 Hz. Employment of morpholine gave lower *d.r.* values (**13**, **14**). Products with substituents in the 2-position formed rather slowly (**15**, **18**, **19**), possibly due to steric congestion with the amine substituent in the planar aminodiene species. Similarly, crotonaldehydes bearing γ-substituents reacted very slow due to steric inhibition of the Michael-type attack onto β-nitrostyrenes (**14**, **19**). The latter trend allowed selective conversion of citral to the 3-alkyl cycloadduct *via* the terminal aminodiene isomer (**20**, kinetic control). Cyclisation with diallylamine proceeded highly effective to give **21** which allows facile access to the free amine. Highly

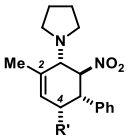
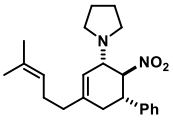
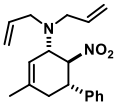
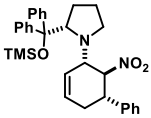
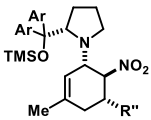
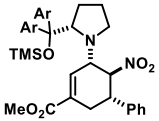
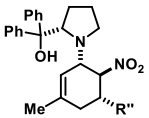
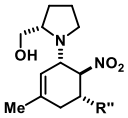
electrophilic methyl 2-methyl-4-oxobut-2-enoate dimerised upon rapid aldehyde addition (Scheme 2.5).[14]



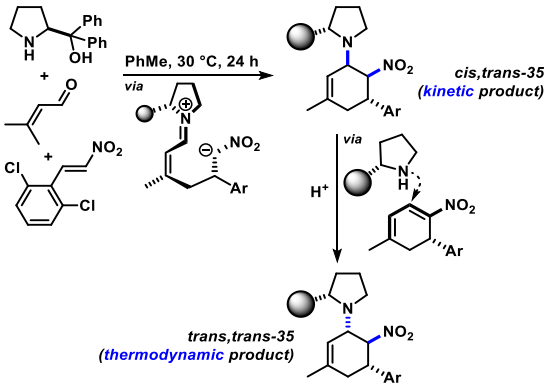
Scheme 2.5: Rate of aldehyde addition governs selectivity.

Table 2.2: Three-component synthesis of *trans*,*trans*-nitrocyclohexenyl amines.[a]

Major Isomer	Substituents		*d.r.*	Yield [%] [b]
	R'' = Ph	**1**	19:1	83
	2,3-$(MeO)_2$-C_6H_3	**2**	15:1	69
	3,4-(OCH_2O)-C_6H_3	**3**	34:1	59
	2,6-Cl_2-C_6H_3	**4**	30:1 [c]	66
	R'' = Ph	**5**	28:1	94
	2,3-$(MeO)_2$-C_6H_3	**6**	14:1	62
	3,4-(OCH_2O)-C_6H_3	**7**	34:1	78
	2-F-C_6H_4	**8**	18:1	91
	2,4-Cl_2-C_6H_3	**9**	15:1	90
	2-NO_2-C_6H_4	**10**	5:1	90
	2,6-Cl_2-C_6H_3	**11**	10:1 [c]	91
	2-furyl	**12**	12:1	90
	R' = 3-Me	**13**	13:1	70
	R' = 4-Me	**14**	7:2:1 [d]	53
		**15**	2:1	38
		**16**	6:1	72
		**17**	50:1	90

	R' = H	**18**	3:1 [d]	16
	Me	**19**	28:6:1 [d]	39
		**20**	6:1	82 [e]
		**21**	35:1	93
		**22**	10:1	46
	R'' = Ph	**23** [f]	28:1:1	86
	2,4-Cl_2-C_6H_3	**24** [f]	19:1	82
	3,4-(OCH_2O)-C_6H_3	**25** [f]	27:1	75
	2-furyl	**26** [f]	11:1	69
	2-NO_2-C_6H_4	**27** [f]	2:1	74
	2-F-C_6H_4	**28**	11:1	96
		**29** [f]	15:1	68
	R'' = Ph	**30**	40:1	82
	2,4-Cl_2-C_6H_3	**31**	6:1	82
	R'' = Ph	**32**	14:9:1	63
	2-F-C_6H_4	**33**	1.5:1	69
	2,4-Cl_2-C_6H_3	**34**	4:3:1	62

[a] Amine (4 mmol), aldehyde (1.2 equiv.) and nitroalkene in PhMe were stirred for 20 h at 30 °C; [b] Isolated yields of isomer mixtures; [c] after treatment with SiO_2 or wet $CDCl_3$; [d] major diastereomer shown, other isomers not assigned; [e] from citral; [f] Ar = 3,5-bis(trifluoromethyl)phenyl.



Scheme 2.6: Kinetic *cis,trans*-**35** and thermodynamic *trans,trans*-**35**.

The three contiguous stereocenters evolve under thermo-dynamic control. We have employed prolinol derivatives (**22** – **34**) among which bulky diarylprolinols exhibited the most effective facial discrimination of the intermediate iminium ion. Consistently, the *trans*,*trans*-isomers were formed preferentially. Crystal structure analysis confirmed the absolute and relative configuration of **24** (Figure 2.1). However, bulky 1-nitro-2-(2',6'-dichlorophenyl)ethylene preferentially gave *cis*,*trans*-**35** (*cis*,*trans*:*trans*, *trans* = 5:1). Slow epimerisation at C-1 occurred during work-up (SiO_2) or in the presence of acid (wet $CDCl_3$, HCl) to give the thermodynamic *trans*,*trans*-**35** (*cis*,*trans*:*trans*,*trans* ~1:1) possibly *via* elimination of the axial amine group (Scheme 2.6, Figure 2.2).[13]

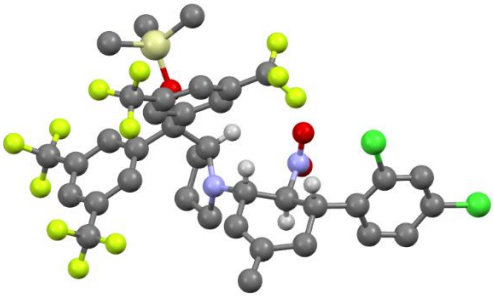


Figure 2.1: Crystal structure of *trans*,*trans*-**24**.

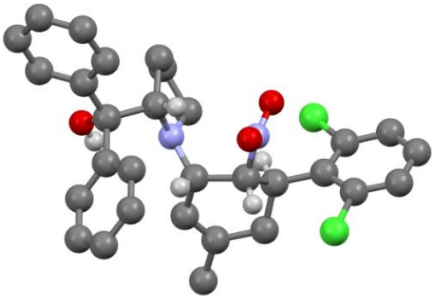
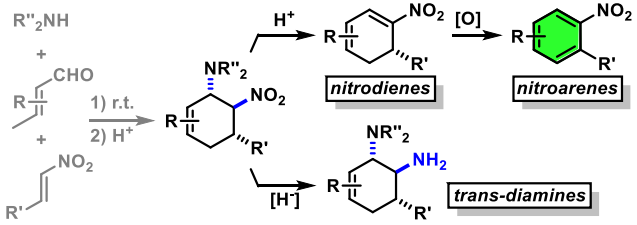


Figure 2.2: Crystal structure of the kinetic product *cis*,*trans*-**35**.

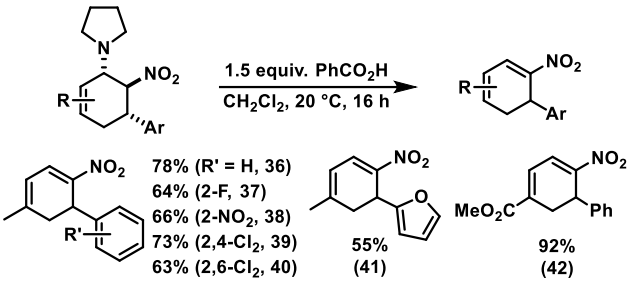
Reactions of *trans*-nitrocyclohexenyl amines

We have studied various structural manipulations at the core and periphery of the synthesised cycloadducts. Eliminations, oxidations, and reductions were realised to give access to diene, arene and diamine derivatives (Scheme 2.7).



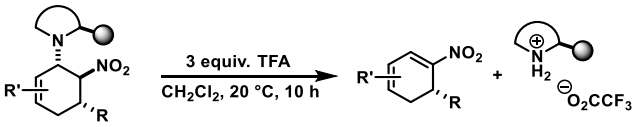
Scheme 2.7: Core and peripheral reactions to dienes, arenes and diamines.

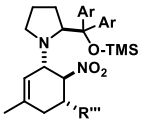
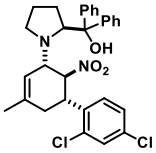
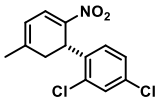
Oxidation of nitrocyclohexenyl amines with manganese dioxide (MnO_2) resulted in unselective decomposition involving dehydrogenation and amine or nitrite elimination.[15] Similarly, various Nef conditions (base (NaH/*n*-BuLi), then acid (HCl); $TiCl_3$; $KMnO_4$)[16] afforded complex mixtures. In no case was the desired ketone detected (GC-MS, IR). The solid cycloadducts appeared to be stable toward air and water; their solutions in dichloromethane or toluene withstood exposure to weak acids and bases. The equatorial amino group inhibits base-mediated elimination (E1cb pathway). However, benzoic acid effected slow elimination of pyrrolidine to nitro-cyclohexadienes (Scheme 2.8). Stronger acids (HCl, TFA) allowed elimination of prolinols to give the nitrocyclo-hexadienes **36**, **37**, **39** and **41** in good enantiomeric purity (82 – 94 % *ee*, Table 2.3).[13] Amine/acid-co-catalyzed reactions of aldehydes and nitroalkenes gave low selectivities.[13,17]



Scheme 2.8: Acid-mediated elimination of pyrrolidine.

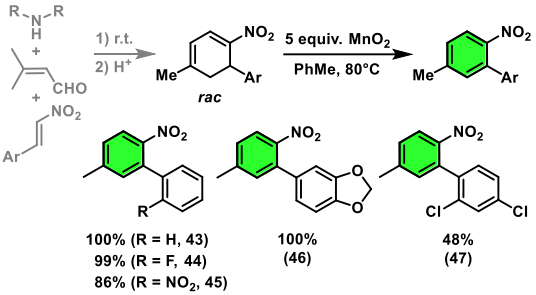
Table 2.3: Acid-mediated elimination of chiral prolinols.



Cyclohexenyl amine	Cyclohexadiene		*ee* [%] [a]	Yield [%] [b]
	R''' = Ph	**36** [c]	94	54
	2-F-C_6H_4	**37** [c]	85	29
	2,4-Cl_2-C_6H_3	**39** [c]	93	60
	2-furyl	**41** [c]	82	29
		**39**	92	55

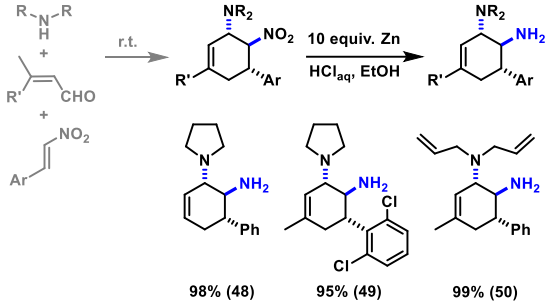
[a] Enantiomeric excess (*ee*) determined by chiral HPLC; [b] isolated yields; [c] Ar = 3,5-bis(trifluoromethyl)phenyl.

The nitrocyclohexadienes were prone to oxidation under aerobic conditions but could be stored under nitrogen at 0 °C for days. However, selective dehydrogenation would render a straight-forward access to substituted nitroarenes. Several methods for the aromatisation of carbocycles were reported (Pt, Pd, Ni catalysts, elemental sulfur or selenium, quinones, oxygen, MnO_2, SeO_2 etc.).[18] We obtained good yields of 2-aryl nitrobenzenes with 5 equiv. MnO_2 at 80 °C (Scheme 2.9). This strategy allows the three-step synthesis of 2-nitrobiaryls.



Scheme 2.9: Three-step synthesis of 2-nitrobiaryls.

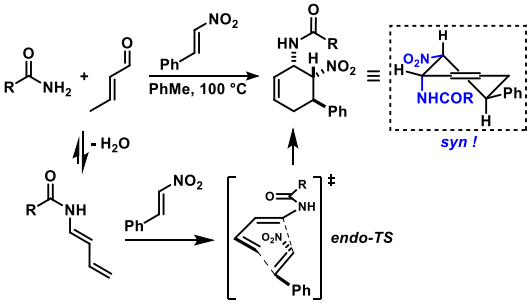
The reduction of a nitro function to a primary amine is an especially useful manipulation.[19] Application of such selective manipulation of one substituent of our three-component cycloadducts renders an expedient access to carbocyclic 1,2-*trans*-diamines (Scheme 2.10). The overall two-step sequence thus involves stereoselective three-component cyclisation with nitroolefins followed by reduction of the nitro substituents in with Zn/HCl in ethanol. The nitrocyclohexenyl amines **1**, **11** and **21** were cleanly converted to the corresponding diamine derivatives **48** – **50** in excellent yields with complete retention of stereochemistry.[13]



Scheme 2.10: Two-step synthesis of *trans*-1,2-diaminocyclohexenes.

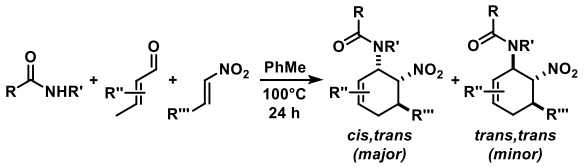
The stereoselectivity switch: Synthesis of *cis*-nitrocyclohex-enyl amides

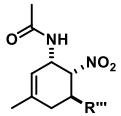
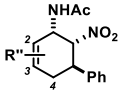
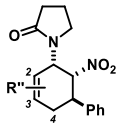
The nature of the *N*-substituents controls all three elemental steps in the Michael/Mannich-type mechanism with amines. The nucleophilicity of the amine directly affects the rate of condensation with the α,β-unsaturated aldehyde and the nucleophilic reactivity of the aminodiene intermediate at the terminal δ-position (Scheme 2.4). Stereoelectronics also govern the formation of the 1-amino-2-nitroethylene moiety *via* a formal nitro-Mannich reaction. It is therefore obvious that fine-tuning of the *N*-substituents directly effects the cyclisation mechanism. Literature reports on Diels-Alder mechanisms of cyclisations of 1-*N*-acylaminodienes with electron-deficient olefins are in full accord with this notion.[5,6] The significantly lower nucleophilicity of carboxamides (vs. amines) favours an orbital-controlled, more or less concerted, cycloaddition pathway (over a stepwise charge-controlled Michael-Mannich pathway). In order to provide a stereo-chemical complement of the three-component synthesis of *trans*-nitrocyclohexenyl amines, we have replaced the secondary amines with simple carboxamides. Indeed, formation of the *cis*-nitrocyclohexenyl amides was observed in high diastereoselectivities (Scheme 2.11). The major product results from an *endo*-selective [4+2]-cycloaddition and bears the carboxamide in axial position. Despite the presence of an axial hydrogen atom at the C*H*-NO_2 moiety, the low propensity of carboxamide to act as leaving group under the reaction conditions prevents E2-type elimination (cf. Scheme 2.6). Table 2.4 shows a selection of cycloadducts prepared from three-component reactions of carboxamides, unsaturated aldehydes and nitrostyrenes.[13] The initial amide/aldehyde condensation required elevated temperature (100 °C). The *trans*,*trans*-*N*-acyl-6-nitrocyclohex-2-enyl amines were formed as minor stereoisomers.



Scheme 2.11: *Endo*-selective Diels-Alder mechanism with carboxamides.

Table 2.4: Three-component synthesis of *cis*-nitrocyclohexenyl amides. [a]



Major Isomer	Substituents		*d.r.*	Yield [%]
	R''' = Ph	**51**	18:1	66
	2,6-Cl_2-C_6H_3	**52**	50:1	67
	2,4-Cl_2-C_6H_3	**53**	28:1	57
	2-F-C_6H_4	**54**	15:1	44
	R'' = H	**55**	8:1	75
	4-Me	**56**	50:1	39
	2,4-Me_2	**57**	40:1	74
	R''' = H	**58**	26:1	56
	3-Me	**59**	32:1	79
	2,4-Me_2	**60**	13:1	18

[a] Amide, aldehyde, β-nitrostyrene (each 3 mmol) in PhMe, 100 °C, 24 h.

The relative configurations were assigned based on the $^3J_{HH}$ coupling constants from ^{1}H-NMR spectra. Crystal structure analyses of *cis*,*trans*-**51** and *trans*,*trans*-**51** confirmed the relative configurations of the substituents (Figure 2.3).

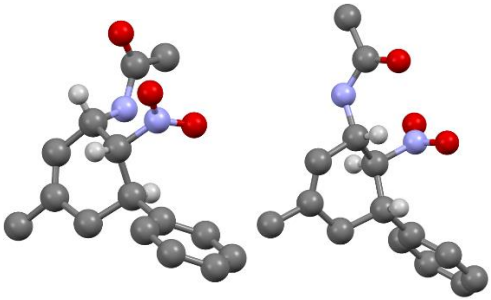
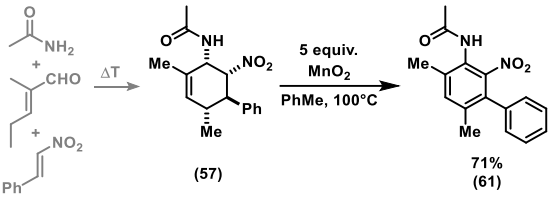


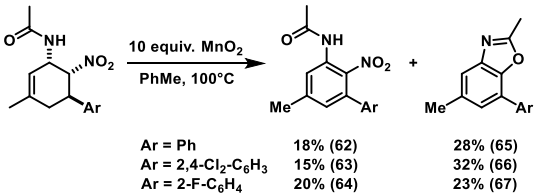
Figure 2.3: Crystal structures of *cis*,*trans*-**51** (left) and *trans*,*trans*-**51** (right).

Reactions of *cis*-nitrocyclohexenyl amides

Similar post-synthesis modifications as for the amine series were evaluated with the synthesised *cis*-nitrocyclohexenyl amides. We were delighted to observe that direct oxidation of **57** with MnO_2 proceeded with good selectivity (Scheme 2.12).[15] However, the related C3-substituted cyclohexenyl amines **51**, **53** and **54** exhibited poor dehydrogenation selectivity. Competing NO_2-elimination was observed which resulted in mixtures of nitro-acetanilides (**62** – **64**) and benzoxazoles (**65** – **67**, Scheme 2.13).[20]

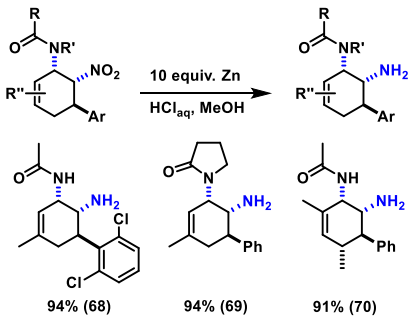


Scheme 2.12: Two-step synthesis of substituted 2-nitro acetanilide.



Scheme 2.13: Oxidative formation of acetanilides and benzoxazoles.

We have also applied the Zn/HCl reduction protocol to the cycloaddition products.[19b] Clean reduction of the nitro substituents gave the corresponding *cis*-diamines in excellent yields with retention of stereochemistry (Scheme 2.14). The overall synthetic strategy allows the straight-forward preparation of carbocyclic 1,2-diamine derivatives with high *cis*-stereocontrol in a modular manner starting from simple amide, aldehyde, and nitroethylene precursors.



Scheme 2.14: Synthesis of *cis*-1,2-diaminocyclohexenes.

2.3. Conclusions

We have applied an operationally simple one-pot protocol to the synthesis of multi-substituted carbocycles upon three-component reaction of amines, aldehydes, and nitroalkenes. The synthesis is highly modular, operates under practical reaction conditions with cheap starting materials (20 – 100 °C, toluene as solvent), and tolerates ester, ether, chloro, fluoro, thioether, and carbamate substituents. Upon wide variations of the starting materials, the synthesis allows the access to diverse cycloadducts in combinatorial fashion. The electronic properties of the employed amine component dictate the reaction mechanism and product stereochemistry. Reactions with secondary amines proceed *via* reversible Michael/nitro-Mannich reactions[12] to give *trans*,*trans*-6-nitrocyclohex-2-enyl amines. The less nucleophilic carbox-amides trigger a Diels-Alder-type mechanism toward *N*-acyl *cis*,*trans*-6-nitrocyclo-hex-2-enyl amines.[6] Reduction with Zn/HCl afforded the corresponding 1,2-diamine derivatives. The tri-, tetra-, and penta-substituted carbocycles constitute derivatives of *cis*- and *trans*-1,2-diaminocyclo-hexanes which are key building blocks of various natural products, fine chemicals, drugs and catalysts.[9] In the presence of enantiopure prolinols, one enantiomerically pure set of diastereomers was formed.[21] Acid-mediated amine eliminations resulted in the formation of chiral cyclohexadienes. Oxidative aromatisations proceeded with MnO_2 to give 2-nitrobiaryls. It is important to note that the presence of two chemically orthogonal *N*-based substituents (NHR, NO_2) allows various selective manipulations of the general structure. Likewise, the electronic polarisation (push-pull substitution) is of high relevance to photoactive materials.

2.4. Experimental Section

General

Unless otherwise noted, all synthesised cycloadducts are racemic mixtures of one diastereomer. For reasons of clarity, only one enantiomer is depicted in the schemes. For atom numbering used in the spectroscopic data assignment, see chemical structures in Schemes and Tables above. All chemicals were purchased from commercial suppliers and used without further purification unless otherwise noted. Solvents were dried and distilled before use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 600 (600.20 and 150.94 MHz), a Bruker DRX 500 (500.13 and 125.77 MHz) and a Bruker Avance 300 (300.13 and 75.48 MHz) at 298 K. Chemical shifts (□ in ppm) are referenced to tetramethylsilane (TMS). Abbreviations for ^{1}H-NMR data: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), q* (apparent quartet), m* (apparent multiplet). Peaks were assigned based on H,H-COSY, H,C-HMQC, and H,C-HMBC. IR-ATR spectroscopy was performed on a Perkin-Elmer 100 Paragon FT-IR. ESI-MS were measured with a Finnigan MAT 900S and an Agilent LC/MSD VL G1956A, respectively. EI-MS were measured with a Finnigan Incos 50 Galaxy and a Finnigan MAT 95, respectively (ionisation 70 eV). Exact masses (HR-MS) were determined by peak matching method. GC-MS analyses were performed on a 6890N Agilent system with 5975 MS detector on an HP-5MS column (30 m × 0.25 mm i.d. × 0.25 µm film thickness) with 5 % phenylmethyl siloxane from Macherey-Nagel. H_2 was the mobile phase. Standard method 50-300M: 50 °C (2 min hold), +25 °C/min → 300 °C (5 min hold). Determination of enantiomeric excesses (*ee*) were performed on a HP6890 GC-FID with chiral BGB 176 column (30 m, 0.25 mm i.d., 0.25 µm film thickness). Helium was the mobile phase. Standard method: 50 °C (2 min hold), 3 °C/min→150 °C, 1 °C/min→180 °C. Chiral HPLC spectra were recorded on a Merck Hitachi HPLC with D-6000 interface, L-4000A UV-detector, L-6200A intelligent pump, and a Merck differential refractometer RI-71. Mixtures of *n*- hexane and 2-propanol were used as mobile phase. Crystal structure data were collected on a Nonius Kappa CCD diffractometer using monochromated Mo-Kα radiation, structures refined by shelxs97 and shelxl97 (Table 2.5).[22]

General procedures (selected examples)[13]

Three-component cyclisation with secondary amines:

A 50 mL test tube was charged with the *sec*-amine (4 mmol), the nitroalkene (4 mmol) in toluene (10 mL). The mixture was stirred at 30 °C and the aldehyde (4.8

mmol) was slowly added over 2 h. After another 18 h, the solvent and other volatile compounds were removed in oil pump vacuum. The crude product was purified by SiO_2 flash column chromatography (ethyl acetate (ea)/cyclohexane (ch)) or crystallised from solution (for details see below).

1-(5-(2,4-Dichlorophenyl)-3-methyl-6-nitrocyclohex-2-enyl) pyrrolidine (**9**): TLC (ch/ea 5/1): R_f 0.25. Yield: 90 %; *d.r.* (*trans*,*trans*/*cis*,*trans*) 15/1. Mp. 137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (s, 1H), 7.21 (m, 2H), 5.50 (s, 1H), 4.95 (t, 10.7 Hz, 1H), 4.26 (d, 8.1 Hz, 1H), 4.21–4.11 (m, 1H), 3.14–2.90 (m, 1H), 2.81 (d, 6.5 Hz, 3H), 2.75–2.61 (m, 2H), 1.84–1.69 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.3 (2C), 135.6, 129.8, 129.0, 128.2, 127.7, 118.8, 89.2, 61.3, 47.6 (2C), 40.3, 38.0, 24.7 (2C), 24.1. FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2963 (m), 2912 (m), 2847 (m), 1668 (w), 1551 (s), 1474 (s), 1437 (w), 1368 (m), 1326 (w), 1277 (w), 1172 (w), 1125 (w), 1103 (m), 1046 (w), 910 (w), 865 (m), 823 (s), 764 (w), 744 (m), 732 (m). LR-MS (EI, 70 eV): m/z 354, 308, 272, 256, 152, 137, 122. HR-MS (ESI): calcd. $[M+H]^+$ 355.0974, found 355.0977.

N,*N*-Diallyl-3-methyl-6-nitro-5-phenylcyclohex-2-enyl-1-amine (**21**): TLC (ch/ea 5/1): R_f 0.3. Yield: 93 %; *d.r.* (*trans*,*trans*/*cis*,*trans*) 35/1. Pale yellow solid. Mp. 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–6.97 (m, 5H), 5.83–5.74 (m, 1H), 5.74–5.66 (m, 1H), 5.43 (s, 1H), 5.19 (m, 1H), 5.13 (s, 2H), 5.10 (s, 1H), 4.86 (dd, 11.8, 9.8 Hz, 1H), 4.25–4.13 (m, 1H), 3.45 (ddd, 11.8, 9.4, 7.7 Hz, 1H), 3.33–3.28 (m, 1H), 3.28–3.22 (m, 1H), 3.04 (d, 7.7 Hz, 1H), 2.99 (d, 7.7 Hz, 1H), 2.32 (d, 7.7 Hz, 2H), 1.74 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.4, 131.3, 130.8, 94.9, 66.2, 64.4, 56.8, 48.8, 41.9, 26.2. FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2968, 2920, 2831, 2806, 1643, 1548, 1495, 1418, 1373, 1315, 1261, 1176, 1109, 1086, 996, 936, 913, 860, 816, 763, 698, 655, 621, 596, 541, 460, 438. HR-MS (EI): calcd. $[M]^+$ 312.1838, found 312.1843.

1-[5-(2,4-Dichlorophenyl)-3-methyl-6-nitrocyclohex-2-enyl]-2-(*S*)-[di-(3,5-bis(trifluoromethyl)phenyl) (trimethylsilyloxy)-methyl]pyrrolidine (**24**): TLC (ch/ea 20/1): R_f 0.4. Yield: 82 %; *d.r.* (*trans*,*trans*/*cis*,*trans*) 19/1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (s, 4H), 7.87 (s, 2H), 7.40 (s, 1H), 7.19 (d, 13.9 Hz, 2H), 5.17 (s, 1H), 5.09 (s, 1H), 4.60 (s, 1H), 4.10 (d, 8.9 Hz, 1H), 3.49 (s, 1H), 2.83 (dd, 16.2, 8.5 Hz, 1H), 2.45–2.25 (m, 2H), 2.08–1.82 (m, 3H), 1.69 (s, 3H), 1.65-1.55 (m, 1H), 0.25-0.10 (m, 1H), -0.15 (d, 3.1 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.1, 143.7, 135.7, 135.2, 135.0, 133.8, 131.4, 131.2, 131.0, 130.8, 130.1, 129.5, 128.7, 127.7, 127.2, 125.0, 123.8, 122.0, 121.4, 117.8, 84.8, 83.7, 67.5, 62.3, 40.0, 37.4, 29.1, 23.3, 22.3, 1.5. FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3094 (w), 2956 (m), 2917 (m), 2855 (w), 1676 (w), 1620 (w), 1588 (w), 1547 (s), 1474 (s), 1446 (w), 1368 (s), 1337 (m), 1316 (m), 1275 (s), 1170 (s), 1125 (s), 1047 (m), 1014 (w), 983 (w), 934 (m), 905 (s), 870 (s), 840 (s), 761 (m), 753 (m), 709 (s), 681 (s). LR-MS (EI, 70 eV): m/z 881, 875, 873, 871. HR-MS (ESI): $[M+H]^+$ calcd. 881.1596, found 881.1592.

Acid-mediated elimination to give nitrocyclohexadienes:

A 10 mL flask was charged with the aminocyclohexene (1 mmol) in dichloromethane (4 mL). Then, trifluoroacetic acid (3 mmol) was added (or 2 mmol benzoic acid in case of small amine substituents). After 10-16 h at room temperature, all volatiles were removed in vacuum and the crude product subjected to SiO_2 flash chromatography (ethyl acetate/ cyclohexane).
2,4-Dichloro-1-(5-methyl-2-nitrocyclohexa-2,4-dienyl)-benzene (**39**): from **24** (with TFA): TLC (ch/ea 12/1): R_f = 0.25. Yield: 60 %; 93 % *e.e.* (HPLC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 6.3 Hz, 1H), 7.44 (d, 2.3 Hz, 1H), 7.11 (d, 8.4 Hz, 1H), 6.99 (d, 8.4 Hz, 1H), 5.97 (d, 7.2 Hz, 1H), 4.81 (d, 11.1 Hz, 1H), 3.05 (dd, 18.5, 11.3 Hz, 1H), 2.46 (d, 18.0 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 145.0, 135.8, 133.5, 133.5, 131.9, 130.1, 128.0, 127.3, 117.3, 37.2, 33.4, 23.9. FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3067 (w), 2870 (w), 2666 (w), 2544 (w), 1688 (s), 1602 (m), 1583 (s), 1558 (w), 1503 (s), 1466 (m), 1450 (w), 1426 8m), 1316 (s), 1289 (m), 1269 (w), 1103 (w), 1085 (w), 1050 (w), 1025 (w), 938 (w), 866 (w), 841 (m), 812 (m), 711 (s), 663 (m). LR-MS (EI, 70 eV): m/z 283, 266, 148, 236, 216, 202, 183, 165. HR-MS (EI, 70 eV): calcd. 283.0167, found 283.018.

MnO_2-mediated oxidation to nitrobiaryls:

The nitrocyclohexadiene (1 mmol, 1 equiv.), MnO_2 (85 %, 5 equiv.) and toluene (5 mL) were combined in a reaction tube. The tube was sealed with a septum and the reaction stirred at 80 °C. After 6 h, the solvent and other volatile compounds were removed by oil pump vacuum. Silica gel flash chromatography (ethyl acetate/cyclohexane) gave the aromatic product in analytically pure form.
2,4-Dichloro-5'-methyl-2'-nitrobiphenyl (**47**): TLC (ch/ea 10/1): R_f 0.2. Yield: 48 %. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, 8.4 Hz, 1H), 7.46 (s, 1H), 7.40–7.30 (m, 2H), 7.19 (d, 8.0 Hz, 1H), 7.11 (s, 1H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.1, 144.6, 136.2, 134.5, 133.6, 133.4, 132.7, 131.0, 130.5, 130.0, 129.8, 129.2, 128.2, 127.5, 127.3, 124.8, 115.8, 21.4. FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2922 (w), 1609 (w), 1586 (m), 1519 (s), 1466 (m), 1377 (w), 1342 (s), 1100 (m), 1066 (w), 1025 (w), 888 (w), 866 (w), 837 (s), 790 (s), 759 (m), 688 (w). LR-MS (EI, 70 eV): m/z 248, 246 $[M-Cl]^+$, 216, 165, 154, 127, 97, 81, 69, 57, 55.

Zn/HCl-mediated reduction of cyclohexenyl amines:[19b]

The 6-nitrocyclohexenyl amine (0.4 mmol, 1.0 equiv.) was dissolved in ethanol (3.0 mL) and aqueous HCl (6 N, 2.2 mL) was added. Zinc powder (262 mg, 4.0 mmol, 10 equiv.) was added in small portions and the reaction mixture was stirred for 2 h at

room temperature. After addition of saturated aqueous $NaHCO_3$ (20 mL), the solution was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried Na_2SO_4) and concentrated under reduced pressure to give the diamine in >95 % purity and yield.

N^2,*N*^{2}-Diallyl-3-methyl-5-phenylcyclohex-2-ene-1,2-diamine (**50**): Yield: 99 %. Mp. 100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.24 (m, 5H), 6.27–6.07 (m, 2H), 5.64–5.40 (m, 1H), 5.32–5.20 (m, 4H), 3.73 (d, 10.5 Hz, 1H), 3.58–3.51 (m, 2H), 3.47–3.24 (m, 3H), 3.13–2.98 (m, 2H), 2.46–2.14 (m, 2H), 1.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.8, 139.6, 129.7, 128.1, 121.9, 116.1, 77.4, 54.5, 38.6, 23.3. FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2912, 1600, 1454, 1150, 1098, 1065, 998, 965, 814, 760, 701, 645, 604, 574, 526, 461. HR-MS (EI): calcd. $[M]^+$ 282.2096; found 282.20976.

Three-component cyclisation with carboxamides:

A 50 mL pressure tube was charged with the carboxamide, unsaturated aldehyde, and nitroalkene (each 3 mmol) and toluene (20 mL) and heated to 100 °C in an oil bath. After 16 h, the volatile components were removed by vacuum distillation. The viscous residue was treated with cold diethylether (15 mL) upon which a white precipitate formed. The solids were collected and dried in vacuum.

N-3-Methyl-(6-nitro-5-phenylcyclohex-2-enyl) acetamide (**51**): TLC (ch/ea 1/3): R_f 0.3. Yield: 66 %; *d.r.* (*cis*,*trans*/*trans*,*trans*) 18/1. Mp. 205°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.09 (m, 5H), 5.93 (d, 9.0 Hz, 1H), 5.47 (d, 3.3 Hz, 1H), 5.34–5.21 (m, 1H), 5.13 (dd, 11.1, 4.9 Hz, 1H), 3.53 (td, 10.3, 6.1 Hz, 1H), 2.45 (dd, 18.4, 6.0 Hz, 1H), 2.24 (dd, 18.5, 10.0 Hz, 1H), 1.98 (s, 3H), 1.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 140.0, 138.1, 129.0 (2C), 127.6, 127.1 (2C), 118.8, 88.0, 45.6, 39.9, 37.6, 23.1, 22.8. FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3271 (w), 3030 (w), 2970 (w), 2912 (w), 1732 (w), 1654 (s), 1549 (s), 1455 (w), 1438 (w), 1369 (m), 1281 (w), 1246 (w), 1055 (w), 1029 (w), 975 (w), 832 (w), 802 (w), 785 (w), 758 (m), 699 (m). LR-MS (EI, 70 eV): m/z 274 $[M]^+$, 227 $[M\text{-}NO_2]^+$. HR-MS (ESI): calcd. $[M+Na]^+$ 297.1215, found 297.121.

N-(2,4-Dimethyl-6-nitro-5-phenylcyclohex-2-enyl) acetamide (**57**): TLC (ch/ea 1/1): R_f 0.2. Yield: 74 %; *d.r.* (*cis*,*trans*/*trans*,*trans*) 40/1. Mp 203 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.19 (m, 5H), 5.64 (d, 1H, 9.6 Hz), 5.52 (s, 1H), 5.26 (m, 1H), 5.22 (dd, 1H, 12.3/4.9 Hz), 2.81 (dd, 1H, 12.3/10.3 Hz), 2.36 (m, 1H), 2.02 (s, 3H), 1.80 (s, 3H), 0.91 (d, 3H, 6.9 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$): δ 170.3, 138.9, 131.5, 130.3, 128.9, 128.0, 127.7 (5C), 89.0, 49.3, 46.7, 38.1, 23.2, 20.6, 19.5. IR (ATR): $\tilde{\nu}$ [cm^{-1}] 3271 (w), 2970 (w), 1733 (m), 1653 (s), 1550 (s), 1454 (m), 1371 (s), 1241 (s), 1042 (m), 913 (w), 725 (m). LR-MS (ESI, MeOH/CH_2Cl_2): m/z 289 $[M+H]^+$, 242 $[M\text{-}NO_2]^+$, 200, 183, 157. HR-MS (ESI): calcd. $[M+H]^+$ 289.1552, found 289.154.

MnO_2-mediated oxidation to nitroanilides:

As above, but 10 equiv. MnO_2 were used and reactions heated to 100 °C for 12 h. *N*-(4,6-Dimethyl-2-nitrobiphen-3-yl) acetamide (**61**): TLC (ch/ea 1/1): R_f 0.6. Yield: 71 %. ^{1}H NMR (500 MHz, MeOH-d_4): δ 7.46-7.35 (m, 5H), 7.08 (s, 1H), 2.54 (s, 3H), 2.52 and 2.27 (2s, 6H), NH resonance obscured. ^{13}C NMR (125 MHz, APT, MeOH-d_4): δ 165.1, 150.5, 138.9, 136.4, 133.5, 131.0, 129.4, 128.7, 128.6, 128.5, 123.7, 19.8, 16.3, 14.1. IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2920 (m), 2860 (w), 1720 (w), 1607 (m), 1486 (m), 1441 (m), 1383 (m), 1250 (m), 1223 (s), 1061 (s), 926 (m), 759 (s), 700 (s). LR-MS (ESI, MeOH): m/z 238 $[M\text{-}NO_2]^+$, 223 $[M\text{-}NO_2\text{-}Me]^+$, 213, 186, 137, 129, 105.

Table 2.5: Crystal structure data for compounds **24**, **35**, *syn*-**51**, *trans*-**51**.

compound	**24**	**35**	***syn*-51**	***trans*-51**
CCDC number	973119	973120	973121	973122
formula	$C_{37}H_{34}Cl_2F_{12}N_2O_3Si$	$C_{30}H_{30}Cl_2N_2O_3$	$C_{15}H_{18}N_2O_3$	$C_{15}H_{18}N_2O_3$
formula mass	881.65	537.46	274.31	274.31
crystal system	orthorhombic	orthorhombic	monoclinic	monoclinic
a/Å	10.8393(5)	8.9169(13)	19.3984(10)	19.0719(12)
b/Å	16.7856(3)	17.351(3)	9.6352(5)	5.2738(3)
c/Å	42.689(2)	17.602(3)	16.2688(9)	27.2994(14)
α/°	90.00	90.00	90.00	90.00
β/°	90.00	90.00	108.737(2)	90.632(4)°
γ/°	90.00	90.00	90.00	90.00
unit cell vol./Å^3	7767.0(5)	2723.2(8)	2879.6(3)	2745.6(3)
temperature/K	100(2)	100(2)	100(2)	100(2)
space group	C2221	P212121	P21/c	C2/c
formula units/cell, Z	8	4	8	8
reflections measured	13598	12769	13657	7864
independent refl.	6278	5633	5758	3000
R_{int}	0.0651	0.0783	0.0667	0.0540
R_1 ($I > 2\sigma(I)$)	0.0658	0.0630	0.1537	0.0540
$wR(F^2)$ ($I > 2\sigma(I)$)	0.1413	0.1281	0.0713	0.1300
R_1 (all data)	0.1379	0.1520	0.1482	0.0948
$wR(F^2)$ (all data)	0.1657	0.1519	0.1851	0.1456

Zn/HCl-mediated reduction of cyclohexenyl amides:[19b]

As above, but methanol was used instead of ethanol. *N*-(6-Amino-2,4-dimethyl-5-phenylcyclohex-2-enyl) acetamide (**70**): Yield: 72 %. Mp. 67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.21 (m, 5H), 5.59 (s, 1H, 9.4 Hz, NH), 5.48 (s, 1H), 4.60 (q*, 1H, 4.69 Hz), 3.36 (dd, 1H, 11.5/4.7 Hz), 2.34 (m, 1H), 2.15 (br m, 3H), 2.10 (s, 3H), 1.76 (s, 3H), 0.81 (d, 3H, 6.8 Hz). ^{13}C NMR (75 MHz, APT, $CDCl_3$): δ 171.4 (CO), 141.4, 131.7, 131.5, 128.8, 128.7, 127.0, 54.2, 51.4 (2C), 38.2, 23.7, 21.0, 19.8. IR (ATR): ṽ [cm^{-1}] 3256 (w), 3027, (w), 2963 (w), 1643 (s), 1536 (s), 1493 (m), 1452 (m), 1370 (m), 1285 (w), 1092 (w), 1092 (w), 1036 (w), 907 (m), 755 (s), 727 (s), 700 (s). LR-MS (EI, 70 eV): m/z 258 $[M]^+$, 199 $[M\text{-}AcNH]^+$, 184, 167, 139, 119, 108. HR-MS (ESI): calcd. $[M+Na]^+$ 281.1624, found 281.162.

2.5. Acknowledgements

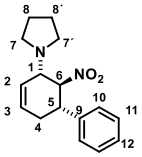
This work was financed by the 7th European framework program (Cataflu.Or).

2.6. Supporting Information

Three-component cyclisation with secondary amines:

A 50 mL test tube was charged with the *sec*-amine (4 mmol), the nitroalkene (4 mmol) in toluene (10 mL). The mixture was stirred at 30 °C and the aldehyde (4.8 mmol) was slowly added over 2 h. After another 18 h, the solvent and other volatile compounds were removed in oil pump vacuum. The crude product was purified by SiO_2 flash column chromatography (ethyl acetate/cyclohexane) or crystallised from solution (for details see below).

1-(6-Nitro-5-phenylcyclohex-2-enyl)pyrrolidine (1)



$C_{16}H_{20}N_2O_2$; 272.34 g/mol

Yield: 83 %, (*dr trans,trans / cis,trans* = 19/1)

TLC: R_f (cyclohexane/EA = 4/1) = 0.41

m.p.: 123.8 °C

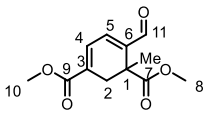
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.21 – 7.33 (m, 5H, Ph), 5.91 – 5.97 (m, 1H, H3), 5.77 – 5.81 (1H, H2), 4.93 (dd, 11.5 Hz, 10.1 Hz, 1H, H6), 4.28 (m 1H, H1), 3.43 (s, 1H, H5), 2.80 (m, 2H, H7), 2.68 (m, 2H, H7´), 2.38 – 2.52 (m, 2H, H4), 1.75 (s, 4H, H8, H8´)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 152.9 (2C, Ph), 129.3 (C3), 124.6 (Ph), 124.3 (C2), 121.5 (Ph), 116.0 (Ph), 89.5 (C6), 61.4 (C1), 61.0 (OMe), 55.76 (OMe), 47.8 (C7, C7´), 33.2 (C4), 24.2 (C8, C8´)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] 2964 (m), 2836 (m), 1688 (w), 1584 (m), 1550 (s) (NO_2), 1477 (s), 1370 (m), 1264 (s), 1127 (w), 1087 (s), 1004 (s), 786 (s), 747 (s)

LR-MS: (EI, 70 eV):332 $[M]^+$, 286 $[M\text{-}NO_2]^+$, 255 $[M\text{-}OMe]^+$, 216, 200, 169, 148, 134, 123

Dimethyl 6-formyl-1-methylcyclohexa-3,5-diene-1,3-dicarboxylate



$C_{12}H_{14}O_5$; 238.23 g/mol

Yield: 65 %

TLC: R_f (cyclohexane/EA = 6/1) = 0.2

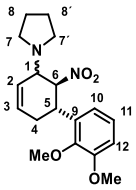
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 9.52 (s, 1H, H11), 7.21 (dd, *J* = 8.2 Hz, 5.3 Hz, 1H, H4), 7.02 – 6.80 (m, 1H, H5), 3.82 (s, 3H, H8), 3.74 – 3.62 (m, 3H, H10), 2.87 (dt, *J* = 39.6 Hz, 10.5 Hz, 2H, H2), 1.27 (s, 3H, Me)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 191.1 (C11), 175.7 (C7), 165.8 (C9), 144.7 (C6), 139.4 (C4), 133.2 (C3), 129.3 (C5), 61.5 (2C, C8, C10), 43.3 (C1), 34.8 (C2), 20.3 (Me)

FT-IR (ATR): ṽ [cm^{-1}] = 2977 (w), 1707 (s), 1678 (s), 1556 (m), 1454 (w), 1374 (m), 1275 (s), 1241 (s), 1140 (m), 1100 (s), 1069 (s), 1069 (s), 1019 (m), 859 (m), 737 (m), 701 (m)

LR-MS: (EI, 70 eV): 239 $[MH]^+$, 223 $[M\text{-}Me]^+$, 179, 164, 133, 107, 91

1-(5-(2,3-Dimethoxyphenyl)-6-nitrocyclohex-2-enyl)pyrrolidine (2)



$C_{18}H_{24}N_2O_4$, 332.39 g/mol

Yield: 69 %, (*dr trans,trans / cis,trans* = 15/1)

TLC: R_f (cyclohexane/EA = 4/1) = 0.46

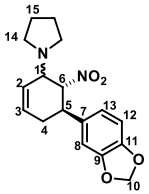
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.97 – 7.16 (m, 2H, Ph), 5.88 – 5.94 (m, 1H, H3), 5.74 – 5.78 (m, 1H, H2), 5.04 – 5.11 (1H, H6), 4.25 – 4.28 (m, 1H, H1), 3.86 – 3.90 (m, 4H, OMe, H5), 3.87 (s, 3H, OMe), 2.80 – 2.83 (m, 2H, H7), 2.65 – 2.70 (m, 2H, H7), 2.2 – 2.45 (m, 2H, H4), 1.73 – 1.77 (m, 4H, H8)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 152.9 (2C, Ph), 129.3 (C3), 124.6 (Ph), 124.3 (C2), 121.5 (Ph), 116.0 (Ph), 89.5 (C6), 61.4 (C1), 61.0 (OMe), 55.76 (OMe), 47.8 (C7, C7´), 33.2 (C4), 24.2 (C8, C8´)

FT-IR (ATR): ṽ [cm^{-1}] 2964 (m), 2836 (m), 1688 (w), 1584 (m), 1550 (s) (NO_2), 1477 (s), 1370 (m), 1264 (s), 1127 (w), 1087 (s), 1004 (s), 786 (s), 747 (s)

LR-MS: (EI, 70 eV): 332 $[M]^+$, 286 $[M\text{-}NO_2]^+$, 255 $[M\text{-}OMe]^+$, 216, 200, 169, 148, 134, 123

1-(5-(Benzene-1,3-dioxol-6-yl)-6-nitrocyclohex-2-enyl)pyrrolidine (3)



$C_{17}H_{20}N_2O_4$, 316.35 g/mol

Yield: 59 %, (*dr trans,trans / cis,trans* = 34/1)

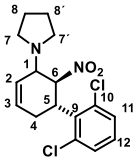
TLC: R_f (cyclohexane/EA = 10/1) = 0.38

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.65 – 6.74 (m, 3H, H8, H12, H13), 5.93 (s, 3H, H10, H3), 5.76 – 5.81 (m, 1H, H2), 4.77 – 4.68 (m, 1H, H6), 4.21 – 4.30 (m, 1H, H1), 3.29 – 3.40 (m, 1H, H5), 2.60 – 2.86 (m, 4H, H14), 2.30 – 2.51 (m, 2H, H4), 1.75 – 1.76 (m, 4H, H15)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 146.9 (C2), 112.7 (C1), 53.1 (C6), 47.9 (C3), 25.3 (C5), 25.2 (C-4)

FT-IR (ATR) : ṽ [cm^{-1}] = 2905 (m), 2820 (w), 1608 (w), 1550 (s), 1503 (m), 1486 (m), 1442 (m), 1369 (m), 1245 (s), 1201 (m), 1122 (m), 1105 (m), 1036 (s), 931 (m), 856 (w), 809 (m), 756 (m)

1-(5-(2,6-Dichlorophenyl)-6-nitrocyclohex-2-enyl)pyrrolidine (4)



$C_{16}H_{18}Cl_2N_2O_2$; 341.23 g/mol

Yield: 66 %, (*dr trans,trans / cis,trans* = 30/1) after storage in wet $CDCl_3$

TLC: R_f (cyclohexane/EA = 4/1) = 0.51

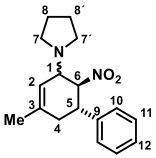
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.27 – 7.39 (m, 2H, H11, H11´), 7.10 (t, 1H, H12), 5.91 – 5.97 (m, 1H, H3), 5.76 – 5.84 (2H, H3), 4.50 – 4.60 (m, 1H, H5), 4.23 – 4.28 (m, 1H, H1), 2.89 – 3.01 (m, 1H, H4), 2.77 – 2.84 (m, 2H, H7´), 2.64 – 2.71 (m, 2H, H7), 2.30 – 2.41 (m, 1H, H4), 1.73 – 1.77 (m, 4H, H8)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 137.0 (C9), 134.9 (C10), 133.2 (C10), 130.4 (C3), 129.3 (C11), 129.2 (C11), 128.4 (C12), 124.4 (C2), 85.9 (C6), 61.0 (C1), 47.8 (C7, C7´), 41.3 (C5), 29.8 (C4), 24.3 (C8, C8´)

FT-IR (ATR): ṽ [cm^{-1}] = 2962 (m), 2819 (m), 1733 (m), 1643 (m), 1546 (s) (ν NO_2), 1434 (s), 1368 (m), 1240 (m), 1034 (m), 767 (m)

LR-MS: (EI, 70 eV): 340, 296 $[M\text{-}NO_2]^+$, 258 $[M\text{-}Cl]^+$, 224 $[M\text{-}Cl]^+$, 186, 152, 134, 123

1-(3-Methyl-6-nitro-5-phenylcyclohex-2-enyl)pyrrolidine (5)



$C_{17}H_{22}N_2O_2$, 286.37 g/mol

Yield: 94 %, (*dr trans,trans / cis,trans* = 28/1)

TLC: R_f (cyclohexane/EA = 4/1) = 0.42

m.p.: 126 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.21 – 7.33 (m, 5H, Ph), 5.47 (s, 1H, H2), 4.85 (dd, *J* = 11.7 Hz, 9.9 Hz, 1H, H6), 4.20 – 4.24 (m, 1H, H1), 3.40 – 3.50 (m, 1H, H5), 2.74 – 2.81 (m, 2H, H7), 2.64 – 2.69 (m, 2H, H7), 2.36 (s, 1H, H4), 2.33 (s, 1H, H4), 1.77 (s, 4H, H8, H8´, Me)

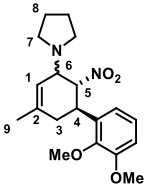
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 139.4 (C9), 136.7 (C3), 128.9 (C10), 127.5 (C11), 118.6 (C2), 91.2 (C6), 61.4 (C1), 47.8 (C7), 45.6 (C5), 38.9 (C4), 24.2 (C8), 22.8 (CMe)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2958 (m), 2901 (m), 1551 (s), 1493 (m), 1452 (m), 1369 (m), 1024 (w), 764 (m), 699 (m), 609 (m)

LR-MS: (EI, 70 eV): 286 $[M]^+$, 239 $[M\text{-}NO_2]^+$, 224 $[M\text{-}Me]^+$, 155, 137, 122

HR-MS (ESI): $[MH]^+$ = 287.1752; calculated: 287.1754

***N*-(5-(2,3-Dimethoxyphenyl)-3-methyl-6-nitrocyclohex-2-enyl)pyrrolidine (6)**



$C_{19}H_{26}N_2O_4$, 346.4207 g/mol

Yield: 62 %, (*dr trans,trans / cis,trans* = 14:1)

TLC: R_f (cyclohexane/EA = 4/1) = 0.45

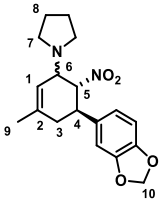
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.17 (d, 2H, Ar), 7.01 (t, 1H, Ar), 5.45 (s, 1H, H1), 5.03 (t, *J* = 10.2 Hz, 1H, H5), 4.22 (d, *J* = 9.7 Hz, 1H, H6), 3.95 – 3.84 (m 1H, H4, 3.88 (s, 3H, OMe), 3.84 (s, 3H, OMe), 2.80 (d, *J* = 8.2 Hz, 2H, H7), 2.68 (d, *J* = 6.0 Hz, 2H, H7), 1.83 – 1.61 (m, 7H, H8, Me)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 152.8, 137.0, 129.0, 128.2, 125.3, 124.2, 118.2 (C1), 89.6 (C5), 61.4 (OMe), 61.0 (OMe), 55.6 (C6), 47.6 (2C, C7), 24.1 (2C, C8), 22.7 (CMe)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3024 (w), 2964 (m), 2960 (m), 2836 (m), 1727 (w), 1688 (m), 1629 (w), 1584 (m), 1550 (s), 1513 (w), 1477 (s), 1428 (m), 1385 (w), 1341 (w), 1288 (m), 1264 (s), 1219 (m), 1168 (w), 1127 (w), 1087 (s), 1036 (w), 1004 (s), 966 (w), 925 (w), 800 (m), 786 (m), 747 (s), 697 (m), 632 (m)

LR-MS: (EI, 70 eV): 346 $[M]^+$, 315, 299, 269, 226, 137, 122

1-(5-(Benzo[*d*][1,3]dioxol-6-yl)-3-methyl-6-nitrocyclohex-2-enyl)pyrrolidine (7)



$C_{18}H_{22}N_2O_4$, 330.3783 g/mol

Yield: 78 %, (*dr trans,trans / cis,trans* = 34/1)

TLC: R_f (cyclohexane/EA = 10/1) = 0.36

m.p.: 122 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.68 (m, 3H, Ar), 5.92 (s, 2H, H10), 5.45 (s, 1H, H1), 4.76 (dd, *J* = 11.7 Hz, 9.9 Hz, 1H, H5), 4.18 (d, *J* = 9.8 Hz, 1H, H6), 3.37 (dt, *J* = 11.8 Hz, 8.6 Hz, 1H, H4), 2.82 – 2.69 (m, 2H, H7), 2.70 – 2.58 (m, 2H, H7), 2.30 (d, *J* = 8.5 Hz, 1H, H3), 1.74 (d, *J* = 3.4 Hz, 7H; H8, H9)

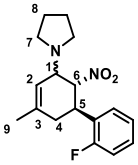
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 147.9 (Ar), 147.1 (Ar), 136.7 (Ar), 133.0 (C2), 120.9 (Ar), 118.4 (C1), 108.5 (Ar), 107.6 (Ar), 101.1 (C10), 91.4 (C5), 61.3 (C6), 47.7 (C7), 45.3 (C4), 38.8 (C3), 24.1 (C8), 22.7 (CMe)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2965 (m), 2905 (m), 2820 (w), 1608 (w), 1550 (s), 1503 (m), 1486 (m), 1442 (m), 1369 (m), 1245 (s), 1201 (m), 1122 (m), 1105 (m), 1036 (s), 931 (m), 856 (w), 809 (m), 756 (m)

LR-MS: (EI, 70 eV): 330, 284, 268, 213, 183, 155, 137, 122, 91

HR-MS (ESI): $[MH]^+$ = 331.1654; calculated; 331.1652

_N_-(5-(2-Fluorophenyl)-3-methyl-6-nitrocyclohex-2-enyl)pyrrolidine (8)



$C_{17}H_{21}FN_2O_2$, 304.3592 g/mol

Yield: 91 %, (*dr trans,trans / cis,trans* = 18/1)

TLC: R_f (cyclohexane/EA = 5/1) = 0.36

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.21 (t, 2H, Ar), 7.13 – 6.96 (m, 2H, Ar), 5.47 (s, 1H, H2), 4.99 (t, *J* = 10.7 Hz, 1H, H6), 4.16 (d, *J* = 8.1 Hz, 2H H1, H5), 2.79 (dt, *J* = 13.0 Hz, 6.3 Hz, 2H, H7), 2.72 – 2.56 (m, 3H, H7, H4), 2.34 – 2.18 (m, 1H, H4), 1.84 – 1.67 (m, 7H, H8, H9)

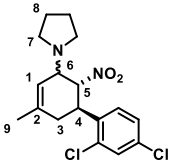
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 162.6 (CF), 136.5 (C3), 129.4 (Ar), 129.3 (Ar), 124.6 (Ar), 118.5 (C2), 116.2 (Ar), 115.9 (Ar), 89.1 (C6), 61.1 (C1), 47.7 (2C, C7), 37.0 (C4), 24.1 (2C, C8), 22.7 (C9)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2963 (s), 2909 (s), 2873 (s), 2813 (s), 1917 (w), 1668 (m), 1635 (m), 1614 (m), 1584 (m), 1552 (s), 1520 (m), 1491 (s), 1454 (s), 1376 (s), 1340 (m), 1279 (m), 1229 (s), 1196 (m), 1179 (m), 1101 (m), 1034 (m), 962 (w), 838 (m), 821 (m), 758 (s)

LR-MS: (EI, 70 eV): 304 $[M]^+$, 258 $[M\text{-}NO_2]^+$, 242, 88, 173, 152, 138, 109, 94, 70

HR-MS (ESI): $[MH]^+$ = 304.1590; calculated: 304.1587

1-(5-(2,4-Dichlorophenyl)-3-methyl-6-nitrocyclohex-2-enyl)pyrrolidine (9)



$C_{17}H_{20}Cl_2N_2O_2$, 355.25 g/mol

Yield: 90 %, (*dr trans,trans / cis,trans* = 15/1)

TLC: R_f (cyclohexane/EA = 5/1) = 0.29

m.p.: 137 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.39 – 7,18 (m, 3H, Ar), 5.50 (s, 1H, H1), 4.95 (t, *J* = 10.7 Hz, 1H, H5), 4.27 – 4.18 (m, *2*H, H6 + H4), 3.14 – 2.90 (m, 1H, H3), 2.81 (d, *J* = 6.5 Hz, 3H, H3, H7), 2.75 – 2.61 (m, 2H, H7), 1.84 – 1.69 (m, 7H, H8, H9)

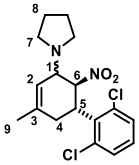
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 136.3 (2C, Ar), 135.6 (C2), 129.8 (Ar), 129.0 (Ar), 128.2 (Ar), 127.7 (Ar), 118.8 (C1), 89.2 (C5), 61.3 (C6), 47.6 (2C, C7), 40.3 (C4), 38.0 (C3), 24.7 (2C, C8), 24.1 (C9)

FT-IR (ATR): ṽ [cm^{-1}] = 2963 (m), 2912 (m), 2847 (m), 1668 (w), 1551 (s), 1474 (s), 1437 (w), 1368 (m), 1326 (w), 1277 (w), 1172 (w), 1125 (w), 1103 (m), 1046 (w), 910 (w), 865 (m), 823 (s), 764 (w), 744 (m), 732 (m)

LR-MS: (EI, 70 eV): 354, 308, 272, 256, 152, 137, 122

HR-MS (ESI): $[MH]^+$ = 355.0977; calculated: 355.0974

1-(5-(2,6-Dichlorophenyl)-3-methyl-6-nitrocyclohex-2-enyl)pyrrolidine (10)



$C_{17}H_{20}Cl_2N_2O_2$, 355.25 g/mol

Yield 91 %, (*dr trans,trans / cis,trans* = 20:1) after storage in wet $CDCl_3$

TLC: R_f (cyclohexane/EA = 12/1) = 0.5

m.p.: 138 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.32 – 7.26 (m, 2H, Ar), 7.13 – 7.08 (m, 1H, Ar), 5.95 (dd, *J* = 12.6 Hz, 5.9 Hz, 1H, H6), 5.61 – 5.54 (m, 1H, H2), 4.77 (td, *J* = 12.0 Hz, 6.3 Hz, 1H, H5), 4.18 (t, *J* = 5.5 Hz, 1H, H1), 2.88 – 2.76 (m, 1H, H4), 2.76 – 2.66 (m, 2H, H7), 2.75 – 2.64 (m, 2H, H7), 2.20 – 2.07 (m, 1H, H4), 1.83 (s, 3H, H9), 1.75 – 1.67 (m, 4H, H8)

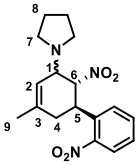
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 136.2 (Ar), 136.9 (Ar), 134.2 (Ar), 133.2 (C3), 130.3 (Ar), 129.1 (Ar), 129.2 (Ar), 118.4 (C2), 86.9 (C6), 61.1 (C1), 47.7 (C7, C7´), 41.3 (C5), 33.3 (C4), 24.1 (C8, C8´), 22.9 (C9)

FT-IR (ATR): ṽ [cm^{-1}] = 2963 (m), 1550 (s), 1435 (s), 1367 (m), 1238 (w), 1171 (m), 1081 (w), 1055 (w), 820 (w), 767 (s), 729 (w)

LR-MS: (EI, 70 eV): 355 $[M]^+$, 339, 307, 272, 238, 159, 137, 122, 94, 70

HR-MS: (EI, 70 eV) $[M]^+$ = 354.0900; calculated: 354.0901

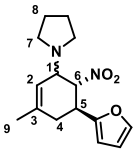
1-(3-Methyl-6-nitro-5-(2-nitrophenyl)cyclohex-2-enyl)pyrrolidine (11)



$C_{17}H_{21}N_3O_4$, 331.36 g/mol

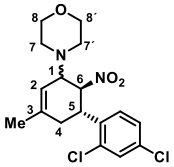
Yield: 90 %, (*dr trans,trans / cis,trans* = 5/1)
TLC: R_f (cyclohexane/EA = 5/1) = 0.17
m.p.: 108 °C
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.78 (d, 1H, Ar), 7.65 – 7.49 (m, 1H, Ar), 7.38 (s, 1H, Ar), 7.17 (d, 1H, Ar), 5.47 (s, 1H, H2), 4.99 (t, *J* = 10.7 Hz, 1H, H6), 4.16 (m, 2H, H1 + H5), 2.86 – 2.73 (m, 2H, H7a), 2.72 – 2.57 (m, 3H, H7b + H4a), 2.25 (d, *J* = 15.1 Hz, 1H, H4b), 1.81 – 1.69 (m, 7H, H8 + H9)
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 136.4, 133.7, 133.1, 129.03, 128.3, 128.2, 125.3, 124.8, 118.7, 89.5, 61.4, 47.6, 24.1, 22.6.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2965 (m), 2909 (m), 2873 (w), 1666 (m), 1606 (w), 1551 (s), 1524 (s), 1484 (w), 1444 (m), 1350 (s), 1304 (w), 1304 (w), 1236 (w), 1160 (w), 1122 (w), 1014 (w), 957 (w), 855 (m), 819 (w), 784 (m), 759 (m), 746 (m), 707 (w)
LR-MS: (EI, 70 eV): 331, 285, 267, 250, 196, 180, 152, 137, 122
HR-MS (ESI): $[MH]^+$ = 332.1606; calculated: 332.1604

1-(5-(Furan-2-yl)-3-methyl-6-nitrocyclohex-2-enyl)pyrrolidine (12)



$C_{15}H_{20}N_2O_3$, 276.33 g/mol
Yield: 90 %, (*dr trans,trans / cis,trans* =12/1)
TLC: R_f (cyclohexane/EA = 12/1) = 0.5
m.p.: 108 °C
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.33 (d, 1H, Ar), 6.28 – 6.26 (m, 1H, Ar), 6.13 (d, 1H, Ar), 5.45 (s, 1H, H2), 4.81 (dd, *J* = 9.9 Hz, 11.5 Hz, 1H, H6), 4.22 – 4.18 (m, 1H, H1), 3.67 – 3.57 (m, 1H, H5), 2.79 – 2.72 (m, 2H, H7), 2.67 – 2.61 (m, 2H, H7), 2.52 – 2.48 (m, 1H, H4), 2.38 – 2.32 (m, 1H, H4), 1.76 (s, 3H, H9), 1.74 – 1.71 (m, 4H, H8)
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 152.2 (CAr), 142.3 (CAr), 136.1 (C3), 118.3 (C2), 110.3 (CAr), 107.0 (CAr), 89.7 (C6), 60.7 (C1), 47.6 (2C, C7), 38.8 (C5), 35.1 (C4), 24.7 (2C, C8), 24.1 (C9)
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2964 (m), 2904 (m), 2874 (w), 2813 (w), 1552 (s), 1503 (w), 1438 (w), 1368 (m), 1322 (m), 1243 (w), 1174 (w), 1147 (m), 1075 (w), 1011 (m), 925 (w), 883 (m), 820 (m), 736 (s)
LR-MS: (EI, 70 eV): 276, 229, 214, 200, 159, 148, 137, 122

4-(5-(2,4-Dichlorophenyl)-3-methyl-6-nitrocyclohex-2-enyl)morpholine (13)



$C_{17}H_{20}Cl_2N_2O_3$, 371.25 g/mol

Yield: NMR: 85 %, (*dr trans,trans / cis,trans* =10/1); isolated: 70 %, (*dr trans,trans / cis,trans* =13/1)

TLC: R_f (cyclohexane/EA = 7/1) = 0.2

m.p.: 137 – 138 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.38 (s, 1H, Ar), 7.29 – 7.15 (m, 2H, Ar), 5.52 (s, 1H, H2), 4.97 (t, *J* = 10.8 Hz, 1H, H6), 4.17 (d, *J* = 5.2 Hz, 1H, H5), 4.01 (d, *J* = 8.2 Hz, 1H, H1), 3.73 – 3.58 (m, 4H, H8, H8'), 2.83 – 2.71 (m, 2H, H7'), 2.62 – 2.48 (m, 2H, H7), 2.39 (d, *J* = 18.1 Hz, 1H, H4), 2.17 – 1.96 (m, 1H, H4), 1.75 (s, 3H, Me)

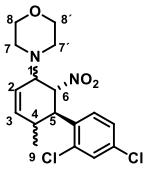
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 136.5 (2C, Ar), 130.0 (Ar), 127.8 (2C, Ar), 118.3 (C2), 87.1 (C6), 67.3 (2C, C8), 65.9 (C1), 48.7 (2C, C7), 40.0 (C5), 37.8 (C4), 22.6 (CMe)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2962 (m), 2901 (m), 2852 (m), 1663 (w), 1588 (w), 1550 (s), 1475 (s), 1449 (m), 1372 (m), 1314 (m), 1289 (w), 1235 (m), 1173 (w), 1114 (s), 1067 (w), 1046 (w), 1003 (s), 911 (m), 862 (m), 824 (m), 761 (w), 732 (s), 654 (w)

LR-MS: (EI, 70 eV): 370, 323, 288, 225, 157, 153, 138

HR-MS (ESI): $[MH]^+$ = 371.0927; calculated: 371.0923

4-(5-(2,4-Dichlorophenyl)-4-methyl-6-nitrocyclohex-2-enyl)morpholine (14)



$C_{17}H_{20}Cl_2N_2O_3$, 371.2583 g/mol

Yield (*dr*): NMR: 72 %; isolated: 53 % (7/2/1)

TLC: R_f (cyclohexane/EA = 7/1) = 0.2

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 1.8 Hz, 1H, Ar), 7.23 – 7.19 (m, 2H, Ar), 5.96 (ddd, *J* = 10.1 Hz, 4.9 Hz, 2.5 Hz, 1H, H3), 5.74 (d, *J* = 10.1 Hz, 1H,

H2), 5.15 (dd, *J* = 12.3 Hz, 9.7 Hz, 1H, H6), 4.23 (dd, *J* = 12.4 Hz, 5.4 Hz, 1H, H5), 4.01 (dd, *J* = 9.6 Hz, 1.6 Hz, 1H, H1), 3.74 – 3.63 (m, 4H, H8), 2.85 – 2.68 (m, 2H, H7'), 2.56 (dt, *J* = 10.4 Hz, 6.3 Hz, 3H, H7), 2.51-2.40 (m, 1H, H5), 0.74 (d, *J* = 7.2 Hz, 3H, H9)

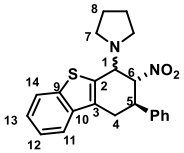
^{13}C NMR: ($CDCl_3$) δ = 135.1 (Ar), 134.9 (Ar), 133.8 (Ar), 133.4 (Ar), 130.0 (Ar), 129.1 (Ar), 126.9 (C3), 121.9 (C2), 83.0 (C6), 67.3 (2C, C8), 66.8 (C1), 48.8 (2C, C7), 43.4 (C5), 33.3 (C4), 16.5 (C9)

FT-IR (ATR): ṽ [cm^{-1}] = 2959 (s), 2860 (s), 2716 (w), 1722 (m), 1681 (m), 1629 (w), 1586 (m), 1552 (s), 1507 (m), 1473 (s), 1370 (s), 1253 (s), 1193 (m), 1114 (s), 1046 (m), 1002 (s), 913 (s), 813 (s), 784 (s), 731 (s), 682 (m), 658 (s)

LR-MS: (EI, 70 eV): 371 $[MH]^+$, 324, 271, 237, 211, 153

HR-MS (ESI): $[MH]^+$ = 371.0926; calculated: 371.0923

1-(3-Nitro-2-phenyl-1,2,3,4-tetrahydrodibenzo[*b*,*d*]thiophen-4-yl)pyrrolidine (15)



$C_{22}H_{22}N_2O_2S$, 378.4873 g/mol

Yield: 38 %, (*dr trans,trans / cis,trans* =2/1)

TLC: R_f (cyclohexane/EA = 6/1) = 0.5

m.p.: >157 °C (decomp.)

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.86 – 7.78 (m, 2H, H11, H14), 7.45-7.28 (m, 7H, H12, H13, Ph), 5.33 (dd, *J* = 9.9 Hz, 8.3 Hz, 1H, H6), 5.22 (d, *J* = 9.4 Hz, 1H, H1), 3.77 (td, *J* = 11.6 Hz, 5.4 Hz, 1H, H5), 3.41 – 3.12 (m, 2H, H4), 3.01 (dd, *J* = 15.9 Hz, 8.6 Hz, 2H, H7), 2.84 (dd, *J* = 14.0 Hz, 11.2 Hz, 2H, H7), 1.92 – 1.75 (m, *J* = 13.5 Hz, 4H, H8)

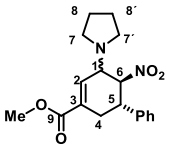
^{13}C NMR: (75 MHz, $CDCl_3$) δ = (mixture of two diastereomers) 140.3, 139.9, 138.6, 137.2, 135.6, 132.1, 130.0, 129.0, 128.1, 127.6, 124.7, 124.4, 124.3, 122.6, 122.5, 122.2, 121.1, 90.5, 90.1, 77.5, 77.0, 76.6, 61.6, 47.7, 46.3, 39.8, 32.0, 31.6, 29.7, 24.6

FT-IR (ATR): ṽ [cm^{-1}] = 3058 (w), 2920 (m), 1551 (s), 1460 (w), 1436 (w), 1372 (w), 1316 (w), 1277 (m), 1243 (m), 1136 (m), 1045 (w), 842 (w), 753 (s), 728 (s), 699 (s)

LR-MS: (EI, 70 eV): 379, 362, 347, 333, 278. 262, 229

HR-MS: (EI, 70 eV): $[M]^+$ = 378.140; calculated: 378.1402

Methyl-6-nitro-5-(pyrrolidin-1-yl)-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-carboxylate (16)



$C_{18}H_{22}N_2O_4$, 330.38 g/mol

Yield: 72 %, (*dr trans,trans / cis,trans* =6/1)

TLC: R_f (cyclohexane/EA = 6/1) = 0.28

m.p.: 100 °C (decomp.)

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.27 – 7.42 (m, 5H, Ph), 7.02 (s, 1H, H2), 4.90 (dd, 10.1 Hz, 11.7 Hz, H6), 4.35 – 4.40 (m, 1H, H1), 3.76 (s, 3H, Me), 3.39 – 3.48 (m, 1H, H5), 2.83 – 2.93 (m, 3H, H7, H4), 2.52 – 2.68 (m, 3H, H7´, H4), 1.75 – 1.80 (m, 4H, H8, H8´)

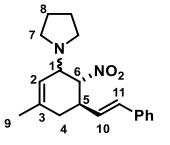
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 166.0 (C9), 138.3 (Ph), 135.9 (C2), 132.1 (C3), 129.7 (Ph), 129.0 (Ph), 127.5 (Ph), 90.2 (C6), 61.5 (C1), 52.2 (Me), 48.2 (C7, C7´), 45.2 (C5), 33.1 (C4), 24.1 (C8, C8´)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2915 (m), 1715 (s), 1554 (s), 1435 (m), 1368 (m), 1234 (s), 759 (m), 699 (s)

LR-MS: (EI, 70 eV): 330, 314, 283, 181

HR-MS: (EI, 70 eV): $[M]^+$ = 330.158; calculated: 330.1579

1-(3-Methyl-6-nitro-5-styrylcyclohex-2-enyl)pyrrolidine (17)



$C_{19}H_{24}N_2O_2$, 312.40 g/mol

Yield: 90 %, (*dr trans,trans / cis,trans* =50/1)

TLC: R_f (cyclohexane/EA =10/1) = 0.21

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.37 – 7.20 (m, 5H, Ph), 6.49 (d, *J* = 15.7 Hz, 1H, H11), 6.01 (dd, *J* = 15.7 Hz, 8.9 Hz, 1H, H10), 5.44 (s, 1H, H2), 4.55 (dd, *J* = 11.4 Hz, 10.1 Hz, 1H, H6), 4.23 – 4.12 (m, 1H, H1), 3.05 (ddd, *J* = 20.0 Hz, 11.1 Hz, 6.1 Hz, 1H, H5), 2.75 (dd, *J* = 10.8 Hz, 4.1 Hz, 2H, H7), 2.69 – 2.59 (m, 2H, H7), 2.45-2.36 (m, 1H, H4), 2.34 – 2.20 (m, 1H, H4), 1.84 – 1.66 (m, 7H, H8, H9)

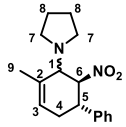
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 136.5 (Ph), 136.1 (C1), 133.2 (C11), 128.5 (2C, Ph), 127.8 (Ph), 127.1 (Ph), 126.9 (Ph), 126.5 (C10), 118.4 (C2), 90.9 (C6), 60.3 (C1), 47.7 (2C, C7), 43.1 (C5), 36.4 (C4), 24.1 (2C, C8), 22.8 (C9)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3023 (w), 2962 (m), 2869 (m), 1663 (m), 1592 (w), 1549 (s), 1492 (m), 1447 (m), 1375 (m), 1300 (m), 1174 (w), 1119 (w), 1068 (w), 1028 (w), 964 (m), 909 (m), 740 (s), 721 (s), 697 (s)

LR-MS: (EI, 70 eV): 265 $[M\text{-}NO_2]^+$, 165, 137, 122, 91, 77

HR-MS (ESI): $[MH]^+$ = 313.1912; calculated: 313.1910

1-(2-Methyl-6-nitro-5-phenylcyclohex-2-enyl)pyrrolidine (18)



$C_{17}H_{22}N_2O_2$, 286.3688 g/mol, yellow oil

Yield: 16 %, (*dr trans,trans / cis,trans* =3/1)

TLC: R_f (cyclohexane/EA =5/1) = 0.38

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.38 – 7.19 (m, 5H, Ph), 5.62 (s, 1H, H3), 5.09 (dd, *J* = 11.8 Hz, 9.3 Hz, 1H, H6), 4.33 (d, *J* = 9.7 Hz, 1H, H1), 3.48 – 3.30 (m, 1H, H5), 2.94 (dt, *J* = 12.8 Hz, 6.5 Hz, 3H, H4, H7), 2.74 (dd, *J* = 10.2 Hz, 5.0 Hz, 2H, H7), 2.41 – 2.28 (m, 1H, H4), 1.77 (d, *J* = 6.5 Hz, 7H, H8, H9)

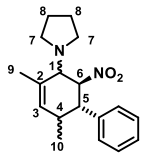
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 139.4 (Ph), 135.7 (C2), 129.4, 128.8 (2C, Ph), 127.6 (Ph), 127.4 (2C, Ph), 123.7 (C3), 90.2 (C6), 63.0 (C1), 47.5 (2C, C7), 46.1 (C5), 32.9 (C4), 24.8 (2C, C8), 20.9 (C9)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3017 (m), 2916 (s), 2730 (w), 1697 (m), 1678 (m), 1632 (s), 1546 (s), 1448 (s), 1340 (s), 1276 (s), 1259 (s), 1201 (m), 1136 (m), 1075 (m), 1029 (w), 965 (s), 844 (m), 827 (m), 726 (s), 699 (s), 648 (m)

LR-MS (ESI): 287.1 $[MH]^+$, 238, 170, 144

HR-MS (ESI): $[MH]^+$ = 287.1755; calculated: 287.1754

1-(2,4-Dimethyl-6-nitro-5-phenylcyclohex-2-enyl)pyrrolidine (19)



$C_{18}H_{24}N_2O_2$, 300.39 g/mol, yellow oil

Yield (*dr*): 39 % (28/6/1)

TLC: R_f (cyclohexane/EA =12/1) = 0.5

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.38 – 7.16 (m, 5H, Ar), 5.69 (d, *J* = 5.2 Hz, 1H, H3), 5.42 (dd, *J* = 12.5 Hz, 9.0 Hz, H6), 4.29 (d, *J* = 8.9 Hz, 1H, H1), 3.66 (dd, *J* = 12.6 Hz, 5.2 Hz, 1H, H5), 2.96 (m, 2H, H7), 2.78 (m, 2H, H7), 2.45-2.39 (m, 1H, H4), 1.79 (dd, *J* = 13.6 Hz, 8.7 Hz, 4H, H8), 1.75 (s, 3H, H9), 0.80 (d, *J* = 7.1 Hz, 3H, H10)

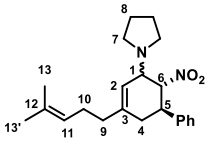
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 138.1 (Ph), 133.7 (C2), 130.7 (2C, Ph), 128.3 (2C, Ph), 128.2 (C3), 84.4 (C6), 63.9 (C1), 48.5 (C5), 47.4 (2C, C7), 36.2 (C4), 25.3 (2C, C8), 20.9 (C9), 16.1 (C10)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3107 (m), 2960 (s), 2870 (s), 1602 (w), 1547 (s), 1494 (m), 1453 (s), 1370 (s), 1309 (m), 1253 (m), 1148 (s), 1090 (m), 1063 (w), 1030 (m), 1002 (w), 820 (m), 752 (s), 737 (m), 699 (s)

LR-MS: (EI, 70 eV): 300, 253, 151, 136, 122, 91

HR-MS: (EI, 70 eV): $[M]^+$ = 300.184; calculated: 300.1837

1-(3-(4-Methylpent-3-enyl)-6-nitro-5-phenylcyclohex-2-enyl)pyrrolidine (20)



$C_{22}H_{30}N_2O_2$, 354.48 g/mol

Yield: 82 %, (*dr trans,trans / cis,trans* =6/1)

TLC: R_f (cyclohexane/EA =5/1) = 0.36

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.43 – 7.15 (m, 5H, Ph), 5.48 (s, 1H, H2), 5.08 (d, *J* = 6.5 Hz, 1H, H11), 4.87 (dd, *J* = 11.7 Hz, 10.0 Hz, 1H, H6), 4.26 (d, *J* = 8.7 Hz, 1H, H1), 3.45 (dt, *J* = 11.8 Hz, 8.6 Hz, 1H, H5), 2.80 (d, *J* = 6.6 Hz, 2H, H7), 2.75 – 2.65 (m, 2H, H7), 2.59 (dd, *J* = 12.8 Hz, 5.3 Hz, 1H, H4), 2.41 – 2.35 (m, 1H, H4), 2.15 (m, 2H, H10), 1.84 – 1.75 (m, 2H, H9), 1.76 (s, 4H, H8), 1.71 (s, 3H, H13), 1.64 (s, 3H, H13')

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 140.2 (Ph), 139.3 (C3), 132.1 (C12), 128.8 (2C, Ph), 127.7 (Ph), 127.4 (2C, Ph), 123.6 (C11), 118.1 (C2), 91.2 (C6), 61.3 (C1), 47.7 (2C, C7), 45.6 (C5), 37.3 (C9), 36.7 (C10), 26.1 (C4), 25.7 (C13), 24.1 (2C, C8), 17.8 (C13')

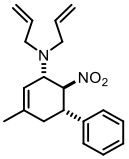
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3017 (w), 2962 (m), 2910 (m), 1669 (w), 1552 (s), 1494 (w), 1454 (w), 1374 (m), 1325 (w), 1245 (w), 1170 (w), 1122 (w), 1028 (w), 834 (w), 763 (m), 698 (s)

LR-MS (ESI): 355 $[MH]^+$, 264, 211, 169, 136

HR-MS (ESI): $[MH]^+$ = 355.2382; calculated: 355.2380

***N,N*-diallyl-5-methyl-2-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-amine (21):**

Work-up: crude reaction mixture was concentrated to dryness and residue washed with cold pentane/ethyl acetate (25/1, 10 mL).



$C_{19}H_{24}N_2O_2$, 312.41 g/mol

Yield: 83 %, (*dr trans,trans / cis,trans* =35/1)

Condition: beige crystals

m.p.: 128 – 129 °C

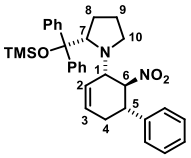
^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.43 – 6.97 (m, 5H), 5.83 – 5.74 (m, 1H), 5.74 – 5.66 (m, 1H), 5.43 (s, 1H), 5.19 (d, *J* = 1.1 Hz, 1H), 5.13 (s, 2H), 5.10 (s, 1H), 4.86 (dd, *J* = 11.8, 9.8 Hz, 1H), 4.25 – 4.13 (m, 1H), 3.45 (ddd, *J* = 11.8, 9.4, 7.7 Hz, 1H), 3.33 – 3.28 (m, 1H), 3.28 – 3.22 (m, 1H), 3.04 (d, *J* = 7.7 Hz, 1H), 2.99 (d, *J* = 7.7 Hz, 1H), 2.32 (d, *J* = 7.7 Hz, 2H), 1.74 (s, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 132.4, 131.3, 130.8, 94.9, 66.2, 64.4, 56.8, 48.8, 41.9, 26.2.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2968, 2920, 2831, 2806, 1643, 1548, 1495, 1418, 1373, 1315, 1261, 1176, 1109, 1086, 996, 936, 13, 860, 816, 763, 698, 655, 621, 596, 541, 460, 438

HR-MS: (EI, 70 eV): $[M]^+$ = 312.1843; calculated: 312.1838

2-(diphenyl((trimethylsilyl)oxy)methyl)-1-(-2-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)pyrrolidine (22)



$C_{33}H_{40}N_2O_3Si$, 540.7678 g/mol

Yield: 46 % (by NMR), (*dr trans,trans / cis,trans* =10/1)

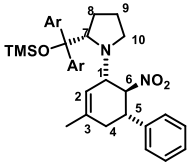
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.13 – 7.32 (m, 15H, Ph), 5.71 – 5.76 (m, 1H, H3), 5.62 – 5.66 (m, 1H, H2), 5.09 (t, 10.6 Hz, 1H, H6), 4.85 (sbr, 1H, H1), 4.06 (dd, 2.3 Hz, 8.9 Hz, 1H, H7), 3.35 – 3.44 (m, 1H, H5), 2.77 – 2.81

(m, 1H, H10), 2.30 – 2.43 (m, 3H, H-4, H10), 1.65 – 1.91 (m, 2H, H8), 1.25 – 1.37 (m, 1H, H9), 0.37 – 0.47 (m, 1H, H9)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 143.6 (Ph), 143.4 (Ph), 139.5 (Ph), 131.3 (C3), 129.9 (Ph), 129.8 (Ph), 128.8 (Ph), 127.7 (Ph), 127.5 (Ph), 127.4, (Ph), 126.9 (Ph), 126.4 (Ph), 125.4, 86.9 (C6), 85.1 (C11), 67.9 (C7), 62.8 (C1), 45.4 (C5), 33.6 (C4), 29.5 (C9), 23.8 (C8), 1.9 (3C, TMS)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3084 (w), 3057 (w), 3028 (w), 2966 (m), 2909 (m), 2866 (m), 1950 (w), 1881 (w), 1733 (s), 1632 (w), 1580 (m), 1547 (s), 1520 (w), 1493 (s), 1447 (s), 1370 (s), 1341 (m), 1324 (s), 1242 (m), 1185 (m), 1081 (m), 1030 (m), 1014 (w), 983 (w), 837 (w), 825 (w), 764 (s), 746 (s), 699 (s)

(*S*)-2-(-(di-(3',5'-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-1-(5-methyl-2-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)pyrrolidine (23)



$C_{37}H_{36}F_{12}N_2O_3Si$, 812.75 g/mol

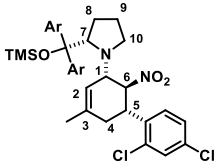
Yield: 86 %, (*dr trans,trans / cis,trans* =28/1/1)

TLC: R_f (cyclohexane/EA =20/1) = 0.41

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.96 (d, 4H, Ar), 7.91 (s, 2H, Ar), 7.37 – 7.17 (m, 5H, Ph), 5.19 (s, 1H, H2), 5.05 (t, *J* = 10.0 Hz, 1H, H6), 4.55 (s, 1H, H7), 4.17 – 4.07 (m, 1H, H1), 3.39 (dd, *J* = 20.0 Hz, 8.6 Hz, 1H, H5), 2.82 (dd, *J* = 16.4 Hz, 8.7 Hz, 1H, H4), 2.40 – 2.25 (m, 3H, H4, H10), 2.03 – 1.84 (m, 1H, H8/9), 1.70 (s, 3H, HMe), 1.69 – 1.56 (m, 1H, H8/9), 1.47 – 1.35 (m, 1H, H8/9), 0.28 – 0.16 (m, 1H, H8/9), -0.13 (s, 9H, TMS)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = (mixture of two diastereomers) 147.9 (Ar), 147.1 (Ar), 145.2 (Ar), 143.8 (Ar), 132.0 (Ar/Ph), 129.6 (Ar/Ph), 129.3 (Ar/Ph), 129.0 (Ar/Ph), 128.9 (Ar/Ph), 128.2 (Ar/Ph), 128.0 (Ar/Ph), 127.4 (Ar/Ph), 127.0 (Ph), 125.3 (Ph), 125.0 (C2), 124.7, 121.9 (C3), 87.0 (C6), 47.1 (C4), 46.8 (C5), 31.8 (C8), 29.7 (C10), 29.3 (C9), 23.7 (CMe), 1.5 (TMS)

(*S*)-2-(di-(3',5'-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-1-(-2',4'-dichloro-5-methyl-2-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)pyrrolidine (24)



$C_{37}H_{34}Cl_2F_{12}N_2O_3Si$, 881.65 g/mol

Ar = 3,5-$(CF_3)_2C_6H_3$

Yield: 82 %, (*dr trans,trans / cis,trans* =19/1)

TLC: R_f (cyclohexane/EA = 20/1) = 0.43

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.94 (s, 4H), 7.87 (s, 2H), 7.40 (s, 1H), 7.19 (d, 2H), 5.17 (s, 1H, H2), 5.09 (s, 1H, H6), 4.60 (s, 1H, H7), 4.10 (d, *J* = 8.9 Hz, 1H, H1), 3.49 (s, 1H, H5), 2.83 (dd, *J* = 16.2 Hz, 8.5 Hz, 1H, H4), 2.45 – 2.25 (m, 2H, H4,H7), 2.08 – 1.82 (m, 3H), 1.69 (s, 3H, Me), 1,65 – 1,55 (m, 1H) 0,25 – 0,10 (m, 1H), -0.15 (d, *J* = 3.1 Hz, 9H, TMS)

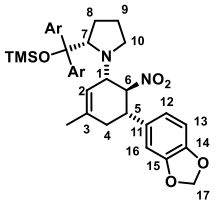
^{13}C NMR: (75 MHz, $CDCl_3$) δ = (mixture of two diastereomers) 145.1, 143.7, 135.7,135.2, 135.0, 133.8, 131.4, 131.2, 131.0, 130.8, 130.1, 129.5, 128.7, 127.7, 127.2, 125.0, 123.8, 121.9, 121.4, 117.8, 84.8, 83.7, 67.5, 62.3, 39.9, 37.4, 29.1, 23.3, 22.3, 1.5

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3094 (w), 2956 (m), 2917 (m), 2855 (w), 1676 (w), 1620 (w), 1588 (w), 1547 (s), 1474 (s), 1446 (w), 1368 (s), 1337 (m), 1316 (m), 1275 (s), 1170 (s), 1125 (s), 1047 (m), 1014 (w), 983 (w), 934 (m), 905 (s), 870 (s), 840 (s), 761 (m), 753 (m), 709 (s), 681 (s)

LR-MS: (EI, 70 eV): 881, 875, 873, 871

HR-MS (ESI): $[MH]^+$ = 881.1592; calculated: 881.1596

(*S*)-1-(5-(Benzo[*d*][1,3]dioxol-5-yl)-3-methyl-6-nitrocyclohex-2-en-1-yl)-2-(di-(3',5'-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)pyrrolidine (25)



$C_{38}H_{36}F_{12}N_2O_5Si$, 856.7692 g/mol

Ar = 3,5-$(CF_3)_2C_6H_3$

Yield: 75 %, (*dr trans,trans / cis,trans* =27/1)

TLC: R_f (cyclohexane/EA = 20/1) = 0.25

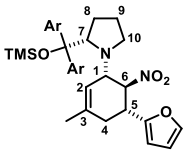
^{1}H NMR: (600 MHz, $CDCl_3$) δ = 7.93 (d, 4H, Ar), 7.88 (s, 2H, Ar), 6.73 (d, 1H, H12), 6.65 – 6.63 (m, 2H, H13, H16), 5.14 (s, 1H, H2), 4.91 (s, 1H, H5), 5.51 (br, 1H, H7), 4.10 – 4.07 (m, 1H, H1), 3.27 (dd, *J* = 17.1 Hz, 10.7 Hz, 1H, H5), 2.76 (dd, *J* = 16.4 Hz, 8.9 Hz, 1H, H4), 2.29 (dd, *J* = 16.7 Hz, 9.7 Hz, 1H, H4), 2.22 (t, *J* = 8.4 Hz, 2H, H10), 1.96 – 1.87 (m, 1H, H9/H8), 1.68 (s, 3H, HMe), 1.61 (s, 1H, H9/H8), 1.40 (dt, *J* = 11.8 Hz, 8.3 Hz, 1H, H9/H8), 0.15 (dd, *J* = 9.2 Hz, 4.9 Hz, 1H, H9/H8), -0.16 (s, 9H, TMS)

^{13}C NMR: (151 MHz, $CDCl_3$) δ = 147.9 (Ar), 147.1 (Ar), 145.2 (Ar), 143.8 (Ar), 135.9, 132.4, 131.0, 129.6 (Ar), 129.5 (Ar), 126.0 (C3), 124.2 (C14), 122.4 (C15), 121.9 (C12), 120.9 (C2), 108.6 (C13), 107.5 (C16), 101.1 (C17), 87.0 (C6), 67.6 (C1), 46,4 (C4), 45.1 (C5), 38.2 (C10), 29.1 (C8), 23.4 (C9), 22.5 (CMe), 1.5 (TMS)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2956 (w), 2837 (w), 1738 (w), 1674 (w), 1545 (s), 1478 (s), 1432 (w), 1369 (s), 1337 (m), 1316, 1275 (s), 1169 (s), 1133 (s), 1086 (s), 1053 (m), 1004 (m), 933 (m), 905 (s), 872 (m), 841 (s), 786 (m), 764 (m), 748 (m), 709 (s), 681 (s)

LR-MS (ESI): 857 $[MH]^+$, 598, 409, 305

(*S*)-2-(-(di-(3',5'-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-1-(5-(furan-2-yl)-3-methyl-6-nitrocyclohex-2-en-1-yl)pyrrolidine (26)



$C_{35}H_{34}F_{12}N_2O_4Si$, 802.7218 g/mol

Ar = 3,5 $(CF_3)_2C_6H_3$

Yield: 69 %, (*dr trans,trans / cis,trans* =11/1)

TLC: R_f (cyclohexane/EA = 20/1) = 0.35

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.11 – 7.99 (m, 6H, Ar), 7.32 (s, 1H), 6.40 (dd, *J* = 3.2 Hz, 1.9 Hz, 1H), 6.25 (d, *J* = 2.3 Hz, 1H), 5.26 (s, 1H, H2), 5.09 (s, 1H, H6), 4.65 (s, 1H, H7), 4.26 (dd, *J* = 9.2, 2.2 Hz, 1H, H1), 3.67 (td, *J* = 11.4 Hz, 5.7 Hz, 1H, H5), 2.86 (dd, *J* = 16.3 Hz, 8.9 Hz, 1H, H4), 2.62 – 2.49 (m, 1H, H4), 2.47 – 2.27 (m, 2H, H10), 2.19 – 1.97 (m, 1H H8/H9), 1.84 (s, 3H, HMe), 1.78 – 1.60 (m, 1H, H8/H9), 1.64 – 1.43 (m, 1H, H8/H9), 0.45 – 0.26 (m, 1H, H8/H9), -0.07 (s, 9H, TMS)

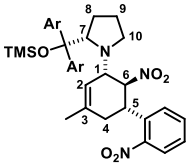
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 151.7, 142.3, 135.5, 129.5, 125.3, 125.1, 121.9, 110.3, 107.4, 85.7, 83.8, 67.7, 62.0, 38.7, 34.4, 29.2, 23.5, 22.5, 1.5 (TMS)

FT-IR (ATR): ṽ [cm^{-1}] = 2971 (m), 2913 (w), 2866 (w), 1806 (w), 1716 (w), 1680 (w), 1620 (w), 1550 (s), 1506 (w), 1466 (w), 1226 (w), 1368 (s), 1317 (w), 1275 (s), 1170 (s), 1127 (s), 1093 (s), 1011 (m), 904 (s), 871 (m), 841 (s), 753 (m), 733 (m), 709 (s), 681 (s)

LR-MS (ESI): 803 $[MH]^+$, 598, 413, 159

HR-MS (ESI): $[M+Na]^+$ = 825.1988 ; calculated: 825.1988

(*S*)-2-(Di-(3',5'-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-1-(5-methyl-2,2'-dinitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)pyrrolidine (27)



$C_{37}H_{35}F_{12}N_3O_5Si$, 857.7572 g/mol

Ar = 3,5 $(CF_3)_2C_6H_3$

Yield: 74 %, (*dr trans,trans / cis,trans* =2/1)

TLC: R_f (cyclohexane/EA = 20/1) = 0.25

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.00 – 7.79 (m, 6H, Ar), 7.57 (s, 2H), 7.40 (t, *J* = 7.1 Hz, 2H), 5.19 (s, 1H, H2), 5.17 – 4.97 (m, 1H, H6), 4.73 – 4.47 (m, 1H, H7), 4.11 (s, 1H, H1), 4.06 (d, *J* = 8.3 Hz, 1H), 2.83 (d, *J* = 7.3 Hz, 1H, H4), 2.59 (s, 1H, H4/H10), 2.36 (s, 1H, H4/H10), 2.18 (s, 1H, H8/H9), 2.00 – 1.86 (m, 1H, H8/H9), 1.72 (s, 3H, HMe), 1.61 (d, *J* = 5.2 Hz, 1H, H8/H9), 0.21 (d, *J* = 67.2 Hz, 1H, H8/H9), -0.18 (s, 9H, TMS)

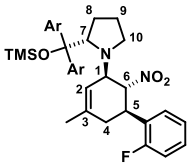
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 150.4, 145.0, 135.9, 133.1, 131.0, 129.5, 128.4, 125.9, 125.0, 124.1, 122.3, 121.9, 120.5, 67.5, 29.1, 26.9, 23.3, 22.3, 1.5

FT-IR (ATR): ṽ [cm^{-1}] = 2969 (w), 1620 (w), 1547 (m), 1530 (m), 1448 (w), 1369 (m), 1317 (w), 1276 (s), 1172 (s), 1133 (s), 1014 (w), 905 (s), 872 (m), 856 (m), 842 (s), 814 (w), 762 (w), 746 (w), 709 (s), 681 (s)

LR-MS (ESI): 858 $[MH]^+$, 526

HR-MS (ESI): $[M+Na]^+$ = 880.2048; calculated: 880.2046

(*S*)-2-(Di-(3',5'-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-1-(2'-fluoro-5-methyl-2-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)pyrrolidine (28)



$C_{37}H_{35}F_{13}N_2O_3Si$, 830.7501 g/mol

Ar = 3,5 $(CF_3)_2C_6H_3$

Yield: 96 %, (*dr trans,trans / cis,trans* = 11/1)

TLC: R_f (cyclohexane/EA = 20/1) = 0.43

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 18.8 Hz, 6H), 7.21 – 6.95 (m, 4H), 5.21 (t, *J* = 10.0 Hz, 1H H6), 5.16 (s, 1H, H2), 4.51 (s, 1H, H7), 4.14 (dd, *J* = 9.2, 2.0 Hz, 1H, H1), 3.58 (s, 1H, H5), 2.80 (dd, *J* = 16.3 Hz, 8.9 Hz, 1H, H4), 2.49 – 2.19 (m, 2H, H4, H10), 1.97 – 1.82 (m, 1H, H10), 1.69 (s, 3H, HMe), 1.58 (s, 3H, H8/H9), 0.13 (d, *J* = 12.7 Hz, 1H, H8/H9), -0.16 (s, 9H, TMS)

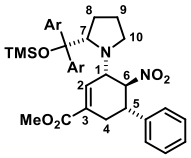
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 169.2, 145.1, 143.8, 135.9, 130.4, 129.5, 128.7, 125.1, 124.6, 123.4, 121.8, 121.4, 117.8, 116.3, 116.0, 84.9, 67.6, 62.1, 60.4, 36.2, 29.1, 23.4, 22.4, 21.0, 14.2, 1.5 (TMS)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3090 (w), 2967 (w), 2912 (w), 2358 (w), 1620 (w), 1548 (s), 1492 (m), 1454 (m), 1369 (s), 1342 (m), 1316 (w), 1276 (s), 1171 (s), 1132 (s), 906 (s), 871 (m), 842 (s), 758 (s), 709 (s), 681 (s)

LR-MS (ESI): 831 $[MH]^+$, 526, 187

HR-MS (ESI): $[MH]^+$ = 831.2289; calculated: 831.2282

Methyl-(5((*S*)-2-(di-(3',5'-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)-methyl)-pyrrolidin-1-yl)-6-nitro-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-carboxylate (29)



$C_{38}H_{36}F_{12}N_2O_5Si$, 856.7692 g/mol

Ar = 3,5 $(CF_3)_2C_6H_3$

Yield: 68 %, (*dr trans,trans / cis,trans* =15/1)

TLC: R_f (cyclohexane/EA = 20/1) = 0.37

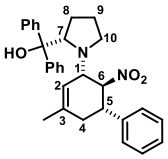
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.95 (d, 2H, Ar), 7.88 (s, 4H, Ar), 7.41 – 7.28 (m, 3H), 7.20 (d, 2H), 6.71 (s, 1H, H2), 5.12 (t, 1H, H6), 4.89 (s, 1H, H7), 4.12 (dd, *J* = 9.4 Hz, 2.1 Hz, 1H, H1), 3.77 (d, *J* = 4.8 Hz, 3H, HMe), 3.37 (td, *J* = 11.6, 5.3 Hz, 1H), 2.83 (dt, *J* = 15.9 Hz, 7.2 Hz, 1H, H4/H10), 2.56 – 2.39 (m, 1H, H4/H10), 2.38 – 2.25 (m, 1H, H4/H10), 1.96 (dd, *J* = 15.8 Hz, 7.2 Hz, 1H, H8/H9), 1.69 – 1.45 (m, 3H, H8/H9), 0.28 (d, *J* = 8.2 Hz, 1H, H8/H9), -0.15 (d, *J* = 3.0 Hz, 9H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 165.7, 144.8, 143.9, 139.6, 137.7, 131.6, 131.4, 131.1, 129.4, 129.0, 128.2, 127.4, 125.0, 124.9, 122.0, 121.3, 117.7, 85.7, 84.1, 67.7, 62.2, 52.0, 45.1, 32.3, 26.9, 23.55, 1.5

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3100 (w), 3040 (w), 2966 (w), 2918 (w), 2846 (w), 1712 (m), 1555 (s), 1370 (m), 1343 (m), 1275 (s), 1236 (m), 1172 (s), 1132 (s), 906 (m), 842 (m), 764 (m), 700 (m), 681 (s)

LR-MS (ESI): 857 $[MH]^+$, 839, 598, 526, 486, 311, 234

***N*-(5-Phenyl-3-methyl-6-nitrocyclohex-2-enyl)-2-diphenyl(pyrrolidin-2-yl)methanol (30)**



$C_{30}H_{32}N_2O_3$, 468.5867 g/mol

Yield: 82 %, (*dr trans,trans / cis,trans* =40/1)

TLC: R_f (cyclohexane/EA = 20/1) = 0.28

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.69 – 7.67 (m, 2H), 7.53 – 7.52 (m, 2H), 7.35 (t, 2H), 7.28 – 7.19 (m, 6H), 7.16 – 7.14 (m, 1H), 6.98 (d, 2H), 5.19 (s, 1H, H2), 4.44 (s, 1H, H6), 4.34 – 4.26 (m, 1H, H7), 4.20 (s, 1H), 3.67 (s, 1H, H1), 3.15 – 3.03 (m, 2H, H5/H4), 2.99 (dt, *J* = 14.9 Hz, 7.6 Hz, 1H, H4/H5), 2.06 (dd, *J* = 17.7 Hz, 5.2 Hz, 1H, H8/H9/H10), 1.97 (d, *J* = 12.2 Hz, 1H, H8/H9/H10), 1.90 – 1.81 (m, 1H, H8/H9/H10), 1.80 – 1.73 (m, 1H, H8/H9/H10), 1.70 (s, 3H, HMe), 1.69 – 1.61 (m, 1H, H8/H9/H10)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 152.9, 145.3, 140.9, 136.3, 131.0, 129.5, 125.1, 124.2, 123.2, 121.8, 121.4, 121.2, 85.0, 83.6, 67.6, 60.8, 55.6, 29.2, 23.4, 22.4

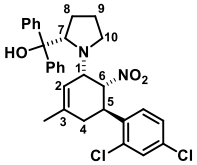
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3412 (w), 1084 (w), 3057 (w), 3028 (w), 2966 (m), 2909 (m), 2866 (m), 1950 (w), 1881 (w), 1733 (s), 1632 (w), 1595 (m), 1544 (s), 1518 (w), 1493 (s), 1447 (s), 1370 (s), 1341 (m), 1316 (s), 1242 (m),

1178 (m), 1081 (m), 1030 (m), 1014 (w), 983 (w), 837 (w), 825 (w), 764 (s), 746 (s), 697 (s)

LR-MS (ESI): 469 $[MH]^+$, 236, 169

HR-MS (ESI): $[M+Na]^+$ = 491.2304; calculated: 491.2305

***N*-(5-(2,4-Dichlorophenyl-3-methyl-6-nitrocyclohex-2-enyl)-2-diphenyl-(pyrrolidin-2-yl)methanol (31)**



$C_{30}H_{30}Cl_2N_2O_3$, 537.4768 g/mol

Yield: 82 %, (*dr trans,trans / cis,trans* =6/1)

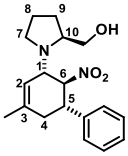
TLC: R_f (cyclohexane/EA = 20/1) = 0.29

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.68 (d, 1H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.37 (t, 2H), 7.32 – 7.26 (m, 2H), 7.27 – 7.19 (m, 2H), 7.19 – 7.08 (m, 1H), 5.65 (dd, *J* = 12.9 Hz, 5.7 Hz, 1H), 5.07 (s, 1H), 4.92 (td, *J* = 12.2 Hz, 6.3 Hz, 1H), 4.34 (d, *J* = 8.3 Hz, 1H), 4.22 – 4.12 (m, 1H), 4.03 (s, 1H), 3.63 (d, *J* = 15.2 Hz, 1H), 3.25 (s, 1H), 2.63 – 2.54 (m, 1H), 2.23 – 2.13 (m, 1H), 1.95 – 1.81 (m, 1H), 1.77 – 1.67 (m, 3H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = (mixture of two diastereomers) 147.8, 146.3, 137.2, 135.7, 134.8, 133.8, 130.4, 129.0, 128.8, 128.4, 128.2, 128.1, 128.0, 126.5, 126.2, 125.8, 125.6, 125.6, 125.5, 121.8, 86.3, 78.6, 65.8, 54.0, 48.7, 37.3, 32.6, 30.5, 26.9, 24.9, 22.9

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3408 (w), 2971 (w), 1587 (m), 1546 (s), 1521 (s), 1468 (m), 1447 (s), 1372 (m), 1372 (m), 1343 (s), 1316 (w), 1276 (w), 1173 (m), 1100 (s), 1063 (m), 1030 (w), 886 (w), 866 (m), 837 (m), 790 (m), 747 (s), 702 (s)

1-(5-(Phenyl-3-methyl-6-nitrocyclohex-2-enyl)pyrrolidin-2-yl)methanol (32)



$C_{18}H_{24}N_2O_3$, 316.3948 g/mol

Yield (*dr*): 63 % (14/9/1)

TLC: R_f (cyclohexane/EA = 20/1) = 0.28

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.43 – 6.96 (m, 5H), 6.21 – 6.19 (m, 1H), 5.34 (s, 1H), 4.98 (dd, *J* = 11.8 Hz, 9.8 Hz, 1H), 4.15 – 4.05 (m, 1H), 3.44 (ddt, *J* = 9.0 Hz, 7.0 Hz, 4.2 Hz, 3H), 3.10 – 2.98 (m, 2H), 1.80 – 1.67 (m, 7H)

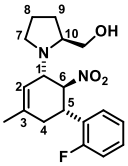
^{13}C NMR: (75 MHz, $CDCl_3$) δ = (mixture of two diastereomers) 139.1, 137.7, 137.4, 129.1, 128.9, 128.6, 128.3, 127.8, 127.8, 127.4, 125.3, 119.8, 118.6, 92.0, 91.8, 65.6, 63.5, 63.3, 61.4, 60.7, 59.1, 53.6, 46.2, 45.4, 45.3, 38.9, 38.4, 29.4, 28.1, 24.7, 24.6, 22.8, 22.7, 21.5

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3278 (w), 2959 (m), 2869 (m), 2359 (w), 2339 (w), 1646 (w), 1601 (w), 1550 (s), 1520 (m), 1444 (w), 1393 (w), 1345 (w), 1246 (m), 1140 (m), 1044 (m), 828 (w), 765 (m), 753 (w), 699 (s)

LR-MS (ESI): 378, 317 $[MH]^+$, 169

HR-MS (ESI): $[MH]^+$ = 317.186; calculated: 317.186

1-(5-(2-Fluorophenyl)-3-methyl-6-nitrocyclohex-2-enyl)pyrrolidin-2-yl)methanol (33)



$C_{18}H_{23}FN_2O_3$, 334.3852 g/mol

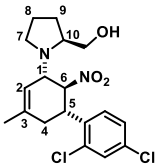
Yield: 69 %, (*dr trans,trans / cis,trans* = 1.5/1)

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.19 (m, 4H), 5.41 (s, 1H, H2), 5.30 – 5.15 (m, 1H, H6), 4.24 (d, *J* = 21.1 Hz, 3H), 3.86 – 3.69 (m, 1H), 3.55 (d, *J* = 7.3 Hz, 1H), 3.43 – 3.34 (m, 1H), 3.14 – 3.05 (m, 2H), 2.84 (m, 2H), 2.5 – 2.3 (m, 1H), 1.85 (m, 7H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = (mixture of two diastereomers) 162.5, 159.3, 137.9, 137.6, 137.2, 131.6, 129.5, 129.4, 129.3, 129.1, 128.3, 125.9, 125.7, 125.3, 124.7, 122.8, 119.9, 118.6, 116.3, 116.0, 115.3, 90.0, 89.9, 65.6, 63.3, 63.2, 62.8, 61.4, 60.6, 60.5, 59.0, 53.4, 46.2, 45.7, 37.2, 36.7, 29.5, 28.1, 26.9, 25.1, 24.7, 24.6, 22.7, 22.7, 21.5

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3296 (w), 2967 (m), 2869 (m), 1646 (m), 1585 (m), 1521 (s), 1487 (s), 1445 (s) 1348 (m), 1214 (s), 1102 (m), 1042 (m), 836 (m), 810 (m), 755 (s)

1-(5-(2,4-Dichlorophenyl)-3-methyl-6-nitrocyclohex-2-enyl)pyrrolidin-2-yl)methanol (34)



$C_{18}H_{22}Cl_2N_2O_3$, 385.2849 g/mol

Yield (*dr*): 62 % (4/3/1)

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.46 – 6.97 (m, 3H), 5.79 (t, *J* = 10.9 Hz, 1H, H6), 5.45 (s, 1H, H2), 4.73 – 4.50 (m, 1H), 4.13 (d, 1H), 3.63 – 3.24 (m, 3H), 3.27 – 2.69 (m, 4H, H), 2.34 – 2.06 (m, 1H), 1.81 (sbr, 7H)

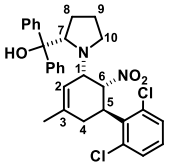
^{13}C NMR: (75 MHz, $CDCl_3$) δ =(mixture of two diastereomers) 137.3, 136.9, 136.8, 134.7, 133.0, 131.7, 130.4, 129.3, 129.2, 129.0, 128.2, 125.3, 120.1, 118.7, 86.9, 86.8, 65.6, 63.2, 63.0, 61.3, 60.3, 59.0, 53.4, 46.3, 41.1, 33.2, 32.6, 29.6, 28.1, 24.7, 24.5, 22.8, 22.7, 21.5

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3398 (w), 2936 (m), 2910 (m), 2869 (m), 1645 (w), 1578 (w), 1549 (s), 1435 8m), 1368 (m), 1309 (w), 1277 (w), 1241 (w), 1204 (w), 1173 (w), 1082 (w), 1041 (m), 918 (w), 821 (w), 780 (m), 767 (m), 729 (w)

HR-MS: (EI 70 eV): $[M]^+$ = 385.108; calculated: 385.1076

***N*-(5-(2,6-Dichlorophenyl-3-methyl-6-nitrocyclohex-2-enyl)-2-diphenyl-(pyrrolidin-2yl)methanol (35)**

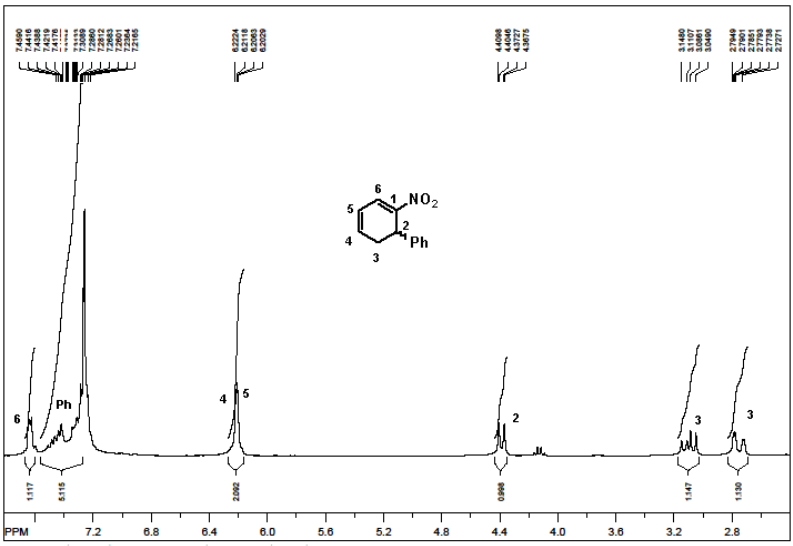
2,6-Dichloro-*trans*-*β*-nitrostyrene (108 mg, 0.5 mmol), (*S*)-diphenylprolinol (125 mg, 0.5 mmol), and 3-methyl-2-butenal (73 µL, 0.75 mmol) were dissolved in toluene (2 mL). The reaction mixture was stirred for 20 h at room temperature. The solvent was removed under reduced pressure. The diastereomeric ratio was determined by ^{1}H-NMR of the crude product. Column chromatography afforded a mixture of four isomers (237 mg, 0.44 mmol, 88 %, 30/6/1.6/1). The identities, relative and absolute configurations of the two major isomers (*cis,trans*/*trans ,trans* = 5/1) were established by crystal structure analysis.



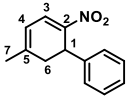
	$C_{30}H_{30}Cl_2N_2O_3$, 537.4768 g/mol
Yield (*dr*):	88 % (30/6/1.6/1)
TLC:	R_f (cyclohexane/EA = 20/1) = 0.26
^{1}H NMR:	(300 MHz, $CDCl_3$) δ = 7.68 (d, 2H), 7.52 (d, 2H), 7.37 (t, 2H), 7.31 – 7.25 (m, 3H), 7.24 – 7.19 (m, 3H), 7.18 – 7.08 (m, 3H), 5.65 (dd, *J* = 12.9 Hz, 5.7 Hz, 1H, H6), 5.07 (s, 1H, H2), 4.92 (d, *J* = 6.1 Hz, 1H), 4.34 (d, *J* = 8.3 Hz, 1H), 4.18 (s, 1H), 4.03 (s, 1H), 3.63 (d, *J* = 15.2 Hz, 1H), 3.25 (s, 1H), 2.58 (s, 1H H8/H9/H10,), 2.16 (dd, *J* = 17.6 Hz, 5.6 Hz, 1H, H8/H9/H10), 1.87 (dd, *J* = 15.4 Hz, 6.1 Hz, 1H, H8/H9/H10), 1.73 (s, 3H, HMe), 1.69 (m, 3H, H8/H9/H10)
^{13}C NMR:	(75 MHz, $CDCl_3$) δ = (mixture of diastereomers) 147.8, 146.3, 137.2, 135.7, 134.8, 133.8, 130.4, 129.0, 128.8, 128.4 (2C), 128.1 (2C), 126.5, 126.2, 125.6, 125.5 (2C), 121.8, 86.3, 78.6, 65.8, 54.0, 48.7, 37.3, 32.6, 30.5, 26.9, 24.9, 22.9
FT-IR (ATR):	$\tilde{\nu}$ [cm^{-1}] = 3408 (w), 3056 (w), 3027 (w), 2970 (m), 2910 (m), 2865 (m), 2359 (w), 1947 (w), 1734 (w), 1671 (w), 1595 (w), 1578 (w), 1545 (s), 1489 (m), 1446 (s), 1436 (s), 1371 (s), 1315 (m), 1277 (m), 1260 (w), 1199 (w), 1175 (m), 1148 (m), 1115 (s), 1082 (s), 1049 (m), 1031 (m), 993 (w), 954 (w), 919 (w), 894 (w), 842 (w), 807 (w), 779 (s), 766 (s), 745 (s), 721 (w), 704 (s), 656 (m)

Acid-mediated elimination to give nitrocyclohexadienes:

A 10 mL flask was charged with the aminocyclohexene (1 mmol) in dichloromethane (4 mL). Then, benzoic acid (1.5 mmol, for elimination of pyrrolidine) or trifluoroacetic acid (3 mmol, for elimination of bulky prolinols) was added. After 10 – 16 h at room temperature, all volatiles were removed in vacuum and the crude product subjected to SiO_2 flash chromatography (ethyl acetate/ cyclohexane).



1-Methyl-4-nitro-5-phenyl-1,3-cyclohexadiene (36)



$C_{13}H_{13}NO_2$, 215.24 g/mol

Yield: 78 %

TLC: R_f (cyclohexane/EA = 10/1) = 0.34

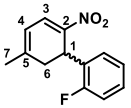
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.63 (d, 1H, H3), 7.36 – 7.19 (m, 5H, Ph), 6.04 – 5.93 (m, 1H, H4), 4.38 (d, *J* = 10.5 Hz, 1H, H1), 3.11 (dd, *J* = 18.3 Hz, 10.9 Hz, 1H, H6), 2.63 – 2.50 (m, 1H, H6), 1.89 (s, 3H, H7)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 147.1 (C2), 141.1 (C5), 139.6 (CPh), 132.1 (C3), 130.3, 128.8 (2C, CPh), 127.3 (CPh), 126.7 (2C, CPh), 117.3 (C4), 39.1 (C6), 37.2 (C1), 23.8 (C7)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927 (s), 2855 (m), 1735 (m), 1550 (s), 1528 (s), 1454 (m), 1345 (m), 1259 (m), 1045 (m), 819 (s) 706 (s)

LR-MS: (EI, 70 eV): 215 $[M]^+$, 198, 183, 168, 154, 141, 128, 115, 102, 91, 77, 65, 51, 39

1-Methyl-4-nitro-5-(2-fluorophenyl)-1,3-cyclohexadiene (37)



$C_{13}H_{12}FNO_2$, 233.23 g/mol

Yield: 64 %

TLC: R_f (cyclohexane/EA = 10/1) = 0.31

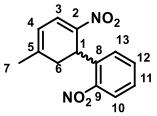
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.70 (d, 1H, H3), 7.13 – 6.96 (m, 4H, HAr), 5.96 (dd, *J* = 5.4 Hz, 1.8 Hz, 1H, H4), 4.76 (d, *J* = 10.2 Hz, 1H, H1), 3.05 (dd, *J* = 18.4 Hz, 11.0 Hz, 1H, H6), 2.62 – 2.51 (m, 1H, H6), 1.84 (s, 3H, H7)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 147.3 (C2), 144.1 (C5), 131.5 (C3), 129.4 (Ar), 128.9 (Ar), 127.4 (Ar), 124.4 (Ar), 117.2 (C4), 115.8 (Ar), 38.0 (C6), 30.2 (C1), 23.8 (C7)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3062 (w), 2929 (w), 2904 (w), 2866 (w), 1611 (w), 1585 (s), 1501 (s), 1486 (s), 1455 (m), 1440 (m), 1419 (m), 1378 (w), 1363 (w), 1316 (s), 1270 (m), 1231 (s), 1199 (w), 1178 (w), 1095 (s), 1084 (s), 1035 (m), 988 (w), 954 (w), 842 (m), 818 (m), 757 (s), 734 (m), 719 (w)

LR-MS: (EI, 70 eV): 233 $[M]^+$, 216, 186 $[M\text{-}NO_2]^+$

1-Methyl-4-nitro-5-(2-nitrophenyl)-1,3-cyclohexadiene (38)



$C_{13}H_{12}N_2O_4$, 260.24 g/mol

Yield: 66 %

TLC: R_f (cyclohexane/EA = 10/1) = 0.18

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.95 (m, 1H, H10), 7.72 (d, 1H, H12), 7.36 (ddd, *J* = 19.1 Hz, 7.8 Hz, 1.4 Hz, 3H, H11, H13, H3), 6.03 – 5.94 (m, 1H, H4), 5.01 (dd, *J* = 12.1 Hz, 2.0 Hz, 1H, H1), 3.33 – 3.12 (m, 1H, H6), 2.66 (dd, *J* = 19.1 Hz, 2.1 Hz, 1H, H6), 1.86 (s, 3H, H7)

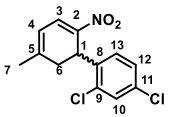
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 147.8 (C2), 145.2 (C9), 135.6 (C5), 133.8 (C8), 133.4 (C12, 128.2 (C3), 128.1 (C11), 125.4 (C10), 117.0 (C4), 38.3 (C6), 32.3 (C1), 23.8 (C7)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3069 (m), 1848 (m), 1684 (s), 1601 (m), 1584 (s), 1521 (s), 1501 (s), 1452 (s), 1423 (s), 1345 (s), 1314 (s), 1291 (s), 1211 (w), 1185 (w), 1127 (w), 1087 (w), 1072 (w), 1072 (m), 934 (m), 856 (m), 834 (m), 810 (w), 784 (m), 749 (m), 706 (s), 684 (m), 668 (s)

LR-MS (ESI): 283 $[M+Na]^+$, 262, 259, 253

HR-MS (ESI): $[M+Na]^+$ = 283.0689; calculated: 283.0689

2,4-Dichloro-1-(5-methyl-2-nitrocyclohexa-2,4-dienyl)benzene (39)



$C_{13}H_{11}Cl_2NO_2$, 284.14 g/mol

Yield: 73 %

TLC: R_f (cyclohexane/EA = 12/1) = 0.23

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 6.3 Hz, 1H, H3), 7.44 (d, *J* = 2.1 Hz, 1H, H10), 7.11 (d, 1H, H12), 6.99 (d, 1H, H13), 5.97 (d, *J* = 7.2 Hz, 1H, H4), 4.81 (d, *J* = 11.1 Hz, 1H, H1), 3.05 (dd, *J* = 18.5 Hz, 11.3 Hz, 1H, H6), 2.46 (d, *J* = 20.0 Hz, 1H, H6), 1.83 (s, 3H, H7)

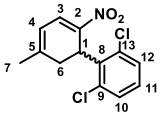
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 147.4 (C2), 144.9 (C5), 135.8 (C8), 133.5 (C9), 133.5 (C11), 131.9 (C3), 130.2 (C10), 128.0 (C12), 127.3 (C13), 117.3 (C4), 37.2 (C6), 33.4 (C1), 23.9 (C7)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}]= 3067 (w), 2870 (w), 2666 (w), 2544 (w), 1688 (s), 1602 (m), 1583 (s), 1558 (w), 1503 (s), 1466 (m), 1450 (w), 1426 8m), 1316 (s), 1289 (m), 1269 (w), 1103 (w), 1085 (w), 1050 (w), 1025 (w), 938 (w), 866 (w), 841 (m), 812 (m), 711 (s), 663 (m)

LR-MS: (EI, 70 eV): 283, 266, 148, 236, 216, 202, 183, 165

HR-MS: (EI, 70 eV): $[M]^+$ = 283.018; calculated: 283.0167

1,3-Dichloro-2-(5-methyl-2-nitrocyclohexa-2,4-dienyl)benzene (40)



$C_{13}H_{11}Cl_2NO_2$, 284.13 g/mol

Yield: 63 %

TLC: R_f (cyclohexane/EA = 10/1) = 0.32

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.38 – 7.21 (m, 3H, H3, H10, H12), 7.10 (t, 1H, H11), 5.88 (d, *J* = 6.2 Hz, 1H, H4), 5.32 (t, *J* = 13.7 Hz, 1H, H1), 2.76 (d, *J* = 13.6 Hz, 2H, H6), 1.92 (s, 3H, H7)

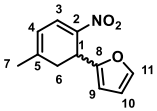
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 147.1 (C2), 145.9 (C5), 138.4 (C8), 134.0 (2C, C9, C13), 129.3 (C11), 128.4 (C10), 128.0 (C12), 117.0 (C4), 37.0 (C1), 36.1 (C6), 23.4 (C7)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3373 (w), 2920 (w), 2840 (w), 1686 (w), 1556 (s), 1509 (s), 1426 (s), 1319 (m), 1280 (m), 1253 (w), 1183 (m), 813 (w), 785 (s), 713 (m)

LR-MS: (EI, 70 eV): 283 $[M]^+$, 253, 238, 216, 180, 165, 128, 77, 62, 39

HR-MS: (EI, 70 eV): $[M]^+$ = 283.018; calculated: 283.0167

2-(5-Methyl-2-nitrocyclohexa-2,4-dienyl)furan (41)



$C_{11}H_{11}NO_3$, 205.20 g/mol

Yield: 55 %

TLC: R_f (cyclohexane/EA = 10/1) = 0.31

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 6.3 Hz, 1H, H3), 7.30 (d, *J* = 1.2 Hz, 1H, H11), 6.25 (dd, *J* = 3.1 Hz, 1.9 Hz, 1H, H10), 6.01 (d, *J* = 3.2 Hz, 1H, H9), 5.96 – 5.87 (m, 1H, H4), 4.52 (d, *J* = 9.4 Hz, 1H, H1), 2.88 (dd, *J* = 18.3 Hz, 9.5 Hz, 1H, H6), 2.71 (dd, *J* = 18.1 Hz, 1.5 Hz, 1H, H6), 1.94 (s, 3H, H7)

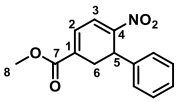
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 153.0 (C8), 147.7 (C2, C5), 141.9 (C11), 130.8 (C3), 117.1 (C4), 110.2 (C10), 105.7 (C9), 35.5 (C6), 31.4 (C1), 23.8 (C7)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3116 (w), 3053 (w), 2930 (w), 2871 (w), 1652 (w), 1583 (s), 1496 (s), 1438 (m), 1420 (m), 1377 (w), 1364 (w), 1315 (s), 1278 (s), 1232 (w), 1172 (m), 1137 (s), 1085 (m), 1072 (m), 1011 (m), 989 (w), 927 (w), 898 (w), 883 (w), 832 (s), 746 (s), 736 (s), 704 (w), 681 (w)

LR-MS: (EI, 70 eV): 205, 190, 175, 160, 144, 122, 91

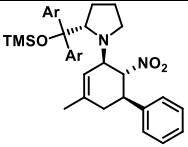
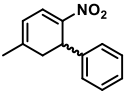
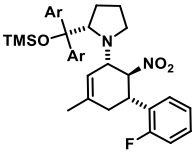
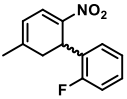
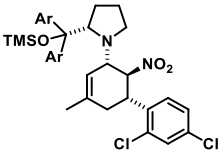
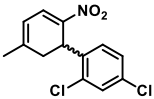
HPLC: (Diacel Chiralpak AS-H); (1 mL/min, *n*-Hex/*i*-PrOH = 90/10, 254 nm: t_R = 7.43 min and 10.25 min

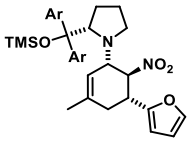
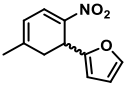
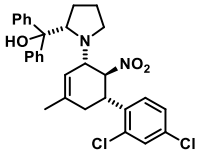
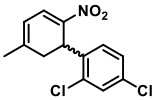
Methyl 4-nitro-5-phenylcyclohexa-1,3-diene-1-carboxylate (42)



	$C_{14}H_{13}NO_4$, 259.25 g/mol
Yield:	92 %
TLC:	R_f (cyclohexane/EA = 10/1) = 0.18
^{1}H NMR:	(300 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 6.3 Hz, 1H, H3), 7.32 – 7.16 (m, 6H, Ph, H2), 3.75 (s, 3H, H8), 3.33 – 3.12 (m, 2H, H6)
^{13}C NMR:	(75 MHz, $CDCl_3$) δ = 179.8 (C7), 147.3 (C4), 139.2 (C1), 129.0 (2C, Ph), 127.8 (C3), 127.2 (C2), 126.6 (2C, Ph), 52.4 (C8), 36.9 (C5), 32.6 (C6)
FT-IR (ATR):	$\tilde{\nu}$ [cm^{-1}] = 3069 (w), 2950 (w), 2845 (w), 2674 (w), 2603 (w), 2559 (w), 1683 (s), 1601 (w), 1582 (w), 1514 (m), 1452 (m), 1423 (m), 1325 (s), 1290 (s), 1263 (s), 1185 (w), 1098 (w), 1072 (w), 934 (m), 810 (w), 706 (s), 684 (w), 668 (m)
LR-MS:	(EI, 70 eV): 259 $[M]^+$, 227, 212, 196, 181, 167, 153, 141, 128, 115, 91, 77, 59
HR-MS:	(EI, 70 eV): $[M]^+$ = 259.085; calculated: 259.0844

Table 2.6: Eliminations of chiral amines. The given yields are isolated yields. The enantiomeric excess (ee) was determined by chiral GC-FID (a) or HPLC (b).

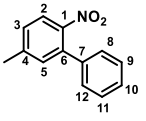
Entry	Starting material	Acid, Reaction time	product	Yield (*ee*)
1	 23 d.r. 28/1/1	TFA, 4 equiv 48h	 36	54 % (*94* %)[a]
2	 28 d.r. 11/1	TFA, 3 equiv 48h	 **37**	29 % (*85* %)[a]
3	 24 d.r. 19/1	TFA, 5 equiv. 48h	 **39**	60 % (*93* %)[a]

4	 26 d.r. 11/1	TFA, 7 equiv. 48h	 **41**	29 % (*82* %)[b]
5	 31 *dr* 11/1	TFA, 5 equiv 48h	 **39**	55 % (*92* %)[a]

MnO_2-mediated oxidation to nitrobiaryls:

The nitrocyclohexadiene (1 mmol, 1 equiv.), MnO_2 (85 %, 5 equiv.) and toluene (5 mL) were combined in a reaction tube. The tube was sealed with a septum and the reaction stirred at 80 °C. After 6 h, the solvent and other volatile compounds were removed by oil pump vacuum. Silica gel flash chromatography (ethyl acetate/cyclohexane) gave the aromatic product in analytically pure form.

5-Methyl-2-nitro-biphenyl (43)



$C_{13}H_{11}NO_2$, 213.2319 g/mol

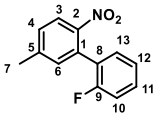
Yield: 99 %

TLC: R_f (cyclohexane/EA = 10/1) = 0.23

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 8.2 Hz, 1H, H2), 7.51 – 7.39 (m, 2H, H3, H4), 7.36 – 7.22 (m, 5H, Ph), 2.47 (s, 3H, Me)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 147.2 (C6), 143.5 (C4), 137.9 (C1), 136.7 (C7), 132.7 (C4), 128.8 bis 127.9 (6C, Ph), 124.5 (C2), 21.5 (Me)

2'-Fluoro-5-methyl-2-nitrobiphenyl (44)



$C_{13}H_{10}FNO_2$ 231.22 g/mol

Yield: 99 %

TLC: R_f (cyclohexane/EA = 20/1) = 0.24

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.3 Hz, 1H, H3), 7.47 – 7.31 (m, 3H), 7.30 – 7.22 (m, 2H), 7.17 – 7.09 (t, 1H, H12), 2.50 (s, 3H, H7)

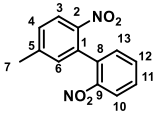
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 160.9 (C9), 146.7 (C2), 144.2 (C5), 133.1 (C6), 130.7 (C1), 130.1 (C8), 130.0 (C4), 129.4 (C11), 124.7 (C13), 124.5 (C3), 124.5 (C12), 115.3 (C10), 21.4 (C7)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3064 (w), 2922 (w), 2853 (w), 1602 (w), 1586 (w), 1518 (s), 1445 (m), 1347 (s), 1280 (w), 1247 (w), 1215 (m), 1150 (w), 1111 (w), 1024 (w), 890 (w), 836 (s), 802 (m), 755 (s), 696 (w)

LR-MS: (EI, 70 eV): 231 $[M]^+$, 203, 186, 183, 170, 133, 99, 75, 63

HR-MS: (EI, 70 eV): $[M]^+$ = 231.070; calculated: 231.0695

5-Methyl-2,2'-dinitrobiphenyl (45)



$C_{13}H_{10}N_2O_4$, 258.22 g/mol

Yield: 86 % (by ^{1}H-NMR)

TLC: R_f (cyclohexane/EA = 10/1) = 0.28

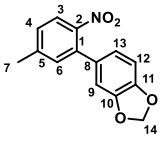
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.23 (d, 1H, H10), 8.16 (d, 1H, H3), 7.68 (d, 1H, H13), 7.58 (t, 1H, H12), 7.39 (d, 1H, H11), 7.34 – 7.28 (m, 1H, H4), 7.08 (d, 1H, H6), 2.48 (s, 3H, H7)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 144.8, 134.6, 134.3, 133.3, 131.3, 130.9, 129.6, 128.9, 125.0, 124.7, 21.4 (C7)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3058 (w), 2921 (w), 2853 (w), 1604 (m), 1586 (m), 1571 (m), 1529 (s), 1343 (s), 1310 (w), 1107 (w), 1034 (w), 970 (w), 889 (w), 852 (w), 839 (m), 786 (m), 749 (m), 698 (m), 668 (m), 620 (w)

LR-MS: (EI, 70 eV): 213 $[M\text{-}NO_2]^+$, 181, 152, 128, 115, 89, 77, 63

5-(5-Methyl-2-nitrophenyl)benzo[*d*][1,3]dioxole (46)



$C_{14}H_{11}NO_4$, 257.24 g/mol

Yield: 100 %

TLC: R_f (cyclohexane/EA = 10/1) = 0.2

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.75 (d, 1H, H3), 7.37 – 7.14 (m, 2H, H4, H6), 6.97 – 6.69 (m, 3H, H9, H12, H13), 6.01 (s, 2H, H14), 2.45 (s, 3H, H7)

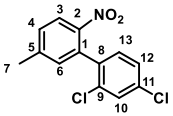
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 147.8 (C11), 147.1 (C10), 145.0 (C2), 143.2 (C5), 140.4 (C1), 132.5 (C8), 131.4 (C6), 128.5 (C4), 124.3 (C3), 121.5 (C13), 108.5 (2C, C9, C12), 101.3 (C14), 21.4 (C7)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2920 (m), 1582 (w), 1520 (s), 1476 (s), 1442 (m), 1347 (m), 1229 (s), 1108 (w), 1038 (s), 935 (w), 857 (w), 823 (m), 758 (w), 643 (w)

LR-MS: (EI, 70 eV): 257 $[M]^+$, 152, 142, 115, 89, 77, 63

HR-MS: (EI, 70 eV): $[M]^+$ = 257.069; calculated: 257.0688

2,4-Dichloro-5'-methyl-2'-nitrobiphenyl (47)



$C_{13}H_9Cl_2NO_2$, 282.1221 g/mol

Yield: 48 %

TLC: R_f (cyclohexane/EA = 10/1) = 0.2

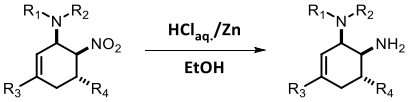
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.05 (d, 1H, H3), 7.46 (s, 1H, H6), 7.40 – 7.30 (m, 2H, H13, H10), 7.19 (d, 1H, H4), 7.11 (s, 1H, H12), 2.48 (s, 3H, H7)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 146.1 (C2), 144.6, 136.2, 134.5, 133.5, 133.4, 132.7, 131.0, 130.5, 130.0, 129.8, 129.2, 128.2, 127.5, 127.3, 124.8, 115.8, 21.4 (C7)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2922 (w), 1609 (w), 1586 (m), 1519 (s), 1466 (m), 1377 (w), 1342 (s), 1100 (m), 1066 (w), 1025 (w), 888 (w), 866 (w), 837 (s), 790 (s), 759 (m), 688 (w)

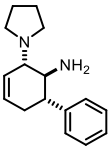
LR-MS: (EI, 70 eV): 248/246 $[M\text{-}Cl]^+$, 216, 165, 154, 127, 97, 81, 69, 57, 55

Zn/HCl-mediated reduction of cyclohexenyl amines:



The 6-nitrocyclohexenyl amine (0.4 mmol, 1.0 equiv.) was dissolved in ethanol (3.0 mL) and aqueous HCl (6 N, 2.2 mL) was added. Zinc powder (262 mg, 4.0 mmol, 10 equiv.) was added in small portions and the reaction mixture was stirred for 2 h at room temperature. After addition of saturated aqueous $NaHCO_3$ (20 mL), the solution was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried Na_2SO_4) and concentrated under reduced pressure to give the diamine in >95 % purity and yield.

3-(Pyrrolidin-1-yl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-amine (48)



$C_{16}H_{22}N_2$, 242,37g/mol

Yield: 98 %

Condition: pale yellow solid

m.p.: 263 °C decomp.

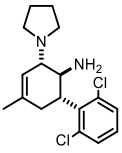
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.44 – 7.31 (m, 2H), 7.31 – 7.15 (m, 3H), 6.12 – 6.06 (m, 1H), 5.75 – 5.67 (m 1H), 3.77 – 3.63 (m, 1H), 3.24 – 2.86 (m, 6H), 2.65 (s, 2H), 2.47 – 2.28 (m, 2H), 2.13 – 1.76 (m, 4H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 139.8, 133.3, 129.6, 128.1, 128.0, 120.1, 64.0, 55.6, 47.5, 34.0, 23.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3342, 3028, 2966, 1579, 1496, 1455, 1205, 1092, 1016, 937, 892, 769, 748, 701, 645, 596, 566, 531, 510, 469

HR-MS: (EI, 70 eV): $[MH]^+$ = 243.1856; calculated: 243,1856

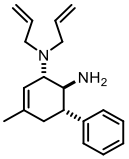
2',6'-Dichloro-5-methyl-3-(pyrrolidin-1-yl)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-amine (49)



$C_{17}H_{22}Cl_2N_2$, 325,28 g/mol

Yield: 95 %
Condition: colourless solid
m.p.: 250 °C decomp.
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.41 (dd, 1.4 Hz, 1H), 7.34 (dd, 1.4 Hz, 1H), 7.21 (t, 1H), 5.40 (s, 1H), 4.08 – 3.83 (m, 1H), 3.64 – 3.49 (m, 1H), 3.26 – 3.20 (m, 1H), 3.00 – 2.77 (m, 2H), 2.75 – 2.61 (m, 2H), 2.23 – 2.13 (m, 2H), 2.03 – 1.89 (m, 4H), 1.81 (s, 1H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 141.0, 137.3, 134.5, 133.4, 131.0, 129.9, 129.6, 114.6, 63.7, 52.8, 51.7, 46.5, 44.3, 33.6, 23.4, 23.3.
FT-IR (ATR): ṽ [cm^{-1}] = 2968, 2883, 1580, 1560, 1435, 1071, 1028, 999, 916, 869, 779, 765, 730, 689, 651, 615, 580, 521, 471, 458, 446
HR-MS: (EI, 70 eV): $[M]^+$ = 324.1108; $[MH]^+$ = 325,1238; calculated: 325.1233

***N*^{3},*N*^{3}-Diallyl-5-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2,3-diamine (50)**

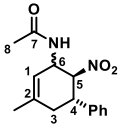


$C_{19}H_{26}N_2$, 282,43 g/mol
Yield: 99 %
Condition: pale yellow solid
m.p.: 99 – 100 °C
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.39 – 7.24 (m, 5H), 6.27 – 6.07 (m, 2H), 5.64 – 5.40 (m, 1H), 5.32 – 5.20 (m, 4H), 3.73 (d, *J* = 10.5 Hz, 1H), 3.58 – 3.51 (m, *2*H), 3.47 – 3.24 (m, 3H), 3.13 – 2.98 (m, 2H), 2.46 – 2.14 (m, 2H), 1.77 (s, 3H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 139.8, 139.6, 129.7, 128.1, 121.9, 116.1, 77.4, 54.5, 38.6, 23.3.
FT-IR (ATR): ṽ [cm^{-1}] = 2912, 1600, 1454, 1150, 1098, 1065, 998, 965, 814, 760, 701, 645, 604, 574, 526, 461
HR-MS: (EI, 70 eV): $[M]^+$ = 282.20976; calculated: 282.2096

Three-component cyclisation with carboxamides:

A 50 mL pressure tube was charged with the carboxamide, unsaturated aldehyde, and nitroalkene (each 3 mmol) and toluene (20 mL) and heated to 100 °C in an oil bath. After 16 h, the volatile components were removed by vacuum distillation. The viscous residue was treated with cold diethylether (15 mL) upon which a white precipitate formed. The solids were collected and dried in vacuum.

***N*-3-Methyl-(6-nitro-5-phenylcyclohex-2-enyl)acetamide (51)**



$C_{15}H_{18}N_2O_3$, 274.315 g/mol

Yield: 66 %, (*dr trans,trans / cis,trans* = 18/1)

m.p.: 205 °C

TLC: R_f (cyclohexane/EA = 1/3) = 0.27

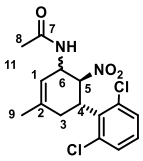
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.41 – 7.09 (m, 5H, Ph), 5.93 (d, 1H, NH), 5.47 (d, *J* = 3.3 Hz, 1H, H1), 5.34 – 5.21 (m, 1H, H6), 5.13 (dd, *J* = 11.1 Hz, 4.9 Hz, 1H, H5), 3.53 (td, *J* = 10.3 Hz, 6.1 Hz, 1H, H4), 2.45 (dd, *J* = 18.4 Hz, 6.0 Hz, 1H, H3), 2.24 (dd, *J* = 18.5 Hz, 10.0 Hz, 1H, H3), 1.98 (s, 3H, H8), 1.77 (s, 3H, Me)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 169.7 (C7), 139.9 (C2), 138.1 (Ph), 129.0, (2C, Ph), 127.6 (Ph), 127.1 (2C, Ph), 118.8 (C1), 88.0 (C5), 45.6 (C6), 39.9 (C4), 37.6 (C3), 23.1 (C8), 22.8 (Me)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3271 (w), 3030 (w), 2970 (w), 2912 (w), 1732 (w), 1654 (s), 1549 (s), 1455 (w), 1438 (w), 1369 (m), 1281 (w), 1246 (w), 1055 (w), 1029 (w), 975 (w), 832 (w), 802 (w), 785 (w), 758 (m), 699 (m)

LR-MS: (EI, 70 eV): 274 $[M]^+$, 227 $[M\text{-}NO_2]^+$

***N*-(5-(2,6-Dichlorophenyl)-3-methyl-6-nitrocyclohex-2-enyl)acetamide (52)**



$C_{15}H_{16}Cl_2N_2O_3$, 343.20 g/mol

Yield: 67 %, (*dr trans,trans / cis,trans* = 50/1)

m.p.: 230 °C (decomp.)

TLC: R_f (cyclohexane/EA = 1/3) = 0.36

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.37 (d, 1H, Ar), 7.25 (d, 1H, Ar), 7.14 (t, 1H, Ar), 6.05 (dd, J = 12.6 Hz, 4.8 Hz, 1H, H5), 5.63 (d, J = 8.9 Hz, 1H, NH), 5.55 (d, J = 4.8 Hz, 1H, H1), 5.46 – 5.34 (m, 1H, H6), 4.47 (td, J = 12.1 Hz, 6.1 Hz, 1H, H4), 2.81 (dd, J = 18.0 Hz, 11.7 Hz, 1H, H3), 2.29 (dd, J = 18.0 Hz, 6.0 Hz, 1H, H3), 2.02 (s, 3H, H8), 1.80 (s, 3H, H9)

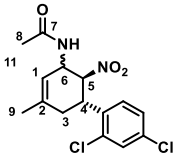
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 169.7 (C7), 138.7 (C2), 137.1 (Ar), 133.9 (Ar), 133.7 (Ar), 130.4 (Ar), 129.1 (Ar), 118.8 (C1), 85.0 (C5), 46.4 (C6), 36.3 (C4), 32.8 (C3), 23.2 (C8), 22.8 (C9)

FT-IR (ATR): ṽ [cm-1] = 3264 (m_{br}), 3044 (w), 2972 (w), 2912 (w), 1731 (w), 1656 (s), 1578 (m), 1549 (s), 1436 (s), 1370 (s), 1338 (m), 1284 (m), 1176 (w), 1123 (w), 1100 (w), 1083 (w), 1056 (w), 962 (w), 922 (w), 806 (w), 779 (s), 766 (s), 735 (m)

LR-MS (ESI): 365 $[M+Na]^+$, 318 $[M+Na\text{-}NO_2]^+$, 237, 136

HR-MS (ESI): $[M+Na]^+$ = 365.0432; calculated: 365.0432

***N*-(5-(2,4-Dichlorophenyl)-3-methyl-6-nitrocyclohex-2-enyl)acetamide (53)**



$C_{15}H_{16}Cl_2N_2O_3$, 343.20 g/mol

Yield: 57 %, (*dr trans,trans / cis,trans* = 28/1)

m.p.: 145 – 148 °C

TLC: R_f (cyclohexane/EA = 1/3) = 0.27

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.34 (dd, 1.9 Hz, 1H, Ar), 7.23 (dd, 2.0 Hz, 1H, Ar), 7.13 (d, 1H, Ar), 5.80 (d, *J* = 8.9 Hz, 1H, NH), 5.47 (s, 1H, H1), 5.24 (s, 1H, H6), 5.16 (dd, *J* = 10.1 Hz, 4.8 Hz, 1H, H5), 4.06 (ddd, *J* = 15.8 Hz, 8.2 Hz, 5.5 Hz, 1H, H4), 2.51 (dd, *J* = 18.4 Hz, 6.0 Hz, 1H, H3), 2.17 – 2.07 (m, 1H, H3), 2.02 (s, 3H, H8), 1.76 (d, *J* = 9.6 Hz, 3H, HMe)

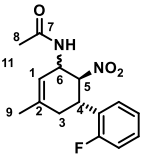
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 176.4 (C7), 138.5 (C2), 136.0 (Ar), 134.6 (Ar), 134.3 (Ar), 130.7, (Ar), 130.1 (Ar), 128.0 (Ar), 119.2 (C1), 86.0 (C5), 45.4 (C6), 36.2 (C4), 35.4 (C3), 23.2 (C8), 22.7 (C9)

FT-IR (ATR): ṽ [cm^{-1}] = 3453 (m), 3271 (m), 3037 (w), 2907 (w), 1658 (s9, 1587 (w), 1550 (s), 1476 (m), 1372 (m), 1285 (m), 1105 (m), 1061 (w9, 1047 (w9, 975 (w), 866 (w), 840 (m), 785 8w), 767 (m)

LR-MS (ESI): 365 $[M+Na]^+$, 318, 237, 136

HR-MS (ESI): $[MH]^+$ = 343.0614; calculated: 343.0610

***N*-(5-(4-Fluorophenyl)-3-methyl-6-nitrocyclohex-2-enyl)acetamide (54)**



$C_{15}H_{17}FN_2O_3$, 292.3055 g/mol

Yield: 44 %, (*dr trans,trans / cis,trans* = 15/1)

m.p.: 140 °C

TLC: R_f (cyclohexane/EA = 1/3) = 0.25

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.28 – 6.96 (m, 4H), 5.74 (d, *J* = 8.8 Hz, 1H, NH), 5.50 (d, *J* = 3.0 Hz, 1H, H1), 5.29 (dd, *J* = 9.2 Hz, 5.1 Hz, 1H, H6), 5.23 (dd, *J* = 10.9 Hz, 4.9 Hz, 1H, H5), 3.83 (td, *J* = 10.3 Hz, 6.1 Hz, 1H, H4), 2.47 (dd, *J* = 18.3 Hz, 5.9 Hz, 1H, H3), 2.29 (dd, *J* = 18.2 HZ, 9.9 Hz, 1H, H3), 2.00 (s, 3H, H8), 1.78 (s, 3H, H9)

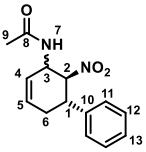
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 169.6 (C7), 138.3 (C2), 129.4 (Ar), 128.5 (Ar), 126.8 (Ar), 124.9 (Ar), 119.0 (C1), 116.5 (Ar), 116.0 (Ar), 86.5 (C5), 45.6 (C6), 35.9 (C4), 34.0 (C3), 23.3 (C8), 22.6 (C9)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3269 (w), 3032 (w), 2965 (w), 2910 (w), 1732 (w), 1654 (s), 1551 (s), 1459 (w), 1438 (w), 1372 (m), 1285 (w), 1247 (w), 1059 (w), 1029 (w), 975 (w), 828 (w), 802 (w), 785 (w), 758 (m), 697 (m)

LR-MS: (EI, 70 eV): 292 $[M]^+$, 246, 231

HR-MS (ESI): $[MH]^+$ = 343.0614; calculated: 343.0610

***N*-(6-Nitro-5-phenylcyclohex-2-enyl)acetamide (55)**



$C_{14}H_{16}N_2O_3$, 260.29 g/mol

Yield: 75 %, (*dr trans,trans / cis,trans* = 8:1)

m.p.: 66 °C (mixture of two diastereomers)

TLC: R_f (EA) = 0.48

^{1}H NMR: (300 MHz, $CDCl_3$) major diastereomer, δ = 7.14 (m, 5 H, H-Arom.), 5.91 (d, 1 H, ^3J = 9.70 Hz, H-7), 5.67 (m, 2 H, H-4, H-5), 5.15 (m, 1 H, H-3), 5.05 (dd, 1 H, ^3J = 10.31/4.89 Hz, H-2), 3.40 (m, 1 H, H-1), 2.51 (dt, 1 H,

^2J = 18.88 Hz, ^3J = 4.89 Hz, H-6), 2.28 (dd, 1 H, ^2J = 18.88 Hz, ^3J = 8.24 Hz, H-6'), 1.98 (s, 3 H, H-9)

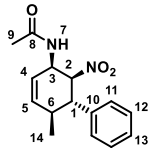
^{13}C NMR: (75 MHz, $CDCl_3$) major diastereomer, δ = 169.7 (C-8), 139.8 (C-10), 129,7, 129.2, 129.0, 127.9, 127.6, 127.2, 124.7 (C-4, C-5, C-11, C-11', C-12, C-12', C-13), 88.2 (C-2), 45.2 (C-3), 40.5 (C-1), 32.3 (C-6), 23.3 (C-9)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3273 (w), 3033 (w), 1650 (s), 1547 (s), 1370 (m), 1276 (m), 1113 (w), 906 (m), 699 (s)

GC/MS: (50-300M), R_t: 9.834 min, m/z = 260 $[M]^+$, 213 $[M\text{-}NO_2]^+$, 194, 172 $[M\text{-}CH_3CO\text{-}NO_2]^+$, 155 $[M\text{-}CH_3CONH\text{-}NO_2]^+$, 129, 115, 91, 77

HR-MS (ESI): $[M+Na]^+$ = 283.1051; calculated: 283.1053

***N*-(4-Methyl-6-nitro-5-phenylcyclohex-2-enyl)acetamide (56)**



$C_{15}H_{18}N_2O_3$, 274.32 g/mol

Yield: 39 %, (*dr cis,trans / trans,trans* = > 50/1)

m.p.: 72 °C

TLC: R_f (EA) = 0.47

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.26 – 7.19 (m, 5 H, Ar), 5.82 (m, 1 H, H-7), 5.76 (2dd, 2 H, ^3J = 5.14/2.32 Hz, H-4, H-5), 5.36 (m, 1 H, H-3), 5.16 (dd, 1 H, ^3J = 12.43/5.14 Hz, H-2), 2.87 (dd, 1 H, ^3J = 12.43/10.28 Hz, H-1), 2.41 (m, 1 H, H-6), 2.01 (s, 3 H, H-9), 0.93 (d, 3 H, ^3J = 7.13 Hz, H-14)

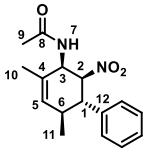
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 169.9 (C-8), 138.8 (C-10), 136.5 (C-5), 128.9, 128.8, 128.1, 128.0, 127.8 (C-11, C-11', C-12, C-12', C-13), 122.8 (C-4), 88.6 (C-2), 47.0 (C-3), 45.6 (C-1), 38.3 (C-6), 23.3 (C-9), 19.1 (C-14)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3280 (w), 2960 (w), 1653 (s), 1550 (s), 1450 (m), 1370 (m), 1280 (w), 1113 (w), 913 (w), 701 (m)

LR-MS (ESI): 297 $[M+Na]^+$, 275, 234

HR-MS (ESI): $[M+Na]^+$ = 297.121; calculated: 297.1215

_N_-(2,4-Dimethyl-6-nitro-5-phenylcyclohex-2-enyl)acetamide (57)



$C_{16}H_{20}N_2O_3$, 288.34 g/mol

Yield: 74 %, (*dr cis,trans / trans,trans* > 40:1)

m.p.: 203 °C

TLC: R_f (cyclohexane/EA = 1/1) = 0.21

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.26 – 7.19 (m, 5 H, Ar), 5.64 (d, 1 H, ^3J = 9.60 Hz, H-7), 5.52 (s, 1 H, H-5), 5.26 (m, 1 H, H-3), 5.22 (dd, 1 H, ^3J = 12.32/4.86 Hz, H-2), 2.81 (dd, 1 H, ^3J = 12.32/10.31 Hz, H-1), 2.36 (m, 1 H, H-6), 2.02 (s, 3 H, H-9), 1.80 (s, 3 H, H-10), 0.91 (d, 3 H, ^3J = 6.90 Hz, H-11)

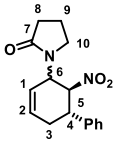
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 170.3 (C-8), 138.9 (C-12), 131.5 (C-5), 130.3 (C-4), 128.9, 128.0, 127.7 (5 C, Ar), 89.0 (C-2), 49.3 (C-3), 46.7 (C-1), 38.1 (C-6), 23.2 (C-9), 20.6 (C-10), 19.5 (C-11)

FT-IR (ATR): ṽ [cm^{-1}] = 3271 (w), 2970 (w), 1733 (m), 1653 (s), 1550 (s), 1454 (m), 1371 (s), 1241 (s), 1042 (m), 913 (w), 725 (m)

LR-MS (ESI): 289 $[MH]^+$, 242 $[M\text{-}NO_2]^+$, 200, 183, 157

HR-MS (ESI): $[MH]^+$ = 289.154; calculated: 289.1552

1-(6-Nitro-5-phenylcyclohex-2-enyl)pyrrolidin-2-one (58)



$C_{16}H_{18}N_2O_3$, 286.326 g/mol

Yield: 56 %, (*dr cis,trans / trans,trans* = 26/1)

m.p.: 187 °C

TLC: R_f (cyclohexane/EA = 1/3) = 0.22

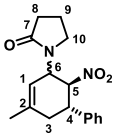
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.27 (dt, 5H, Ph), 6.15 (dd, *J* = 9.6 Hz, 5.2 Hz, 1H, H2), 5.60 (d, *J* = 9.8 Hz, 1H, H1), 5.54 (d, *J* = 5.5 Hz, 1H, H6), 5.22 (dd, *J* = 12.6 Hz, 5.9 Hz, 1H, H5), 3.72 (dd, *J* = 15.6 Hz, 7.9 Hz, 1H, H10), 3.52 (dq, *J* = 8.7 Hz, 5.6 Hz, 2H, H5, H10), 2.61 (dd, *J* = 14.7 Hz, 9.4 Hz, 1H, H3), 2.50 – 2.24 (m, 3H, H3, H8), 2.17 – 1.88 (m, 2H, H9)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 175.6 (C7), 139.9 (Ph), 131.6 (C1), 129.0 (2C, Ph), 127.7 (Ph), 127.2 (2C, Ph), 122.6 (C2), 89.0 (C5), 47.2 (C6), 45.9 (C10), 40.5 (C4), 33.5 (C3), 30.7 (C8), 18.8 (C9)

FT-IR (ATR): ṽ [cm^{-1}] = 2977 (w), 2888 (w), 2358 (w), 2339 (w), 1687 (s), 1548 (s), 1493 (w), 1455 (w), 1412 (s), 1283 (m), 1266 (m), 1189 (w), 1160 (w), 1030 (w), 762 (m), 746 (m), 701 (m)

LR-MS: (EI, 70 eV): 240 $[M\text{-}NO_2]^+$, 155, 137, 155, 86

1-(3-Methyl-6-nitro-5-phenylcyclohex-2-enyl)pyrrolidin-2-one (59)



$C_{17}H_{20}N_2O_3$, 300.35 g/mol

Yield: 79 %, (*dr cis,trans / trans,trans* = 32/1)

m.p.: 155 – 156 °C

TLC: R_f (cyclohexane/EA = 1/3) = 0.27

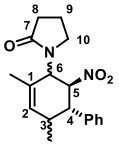
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.40 – 7.15 (m, 5H, Ph), 5.49 (d, *J* = 5.0 Hz, 1H, H6), 5.32 (d, *J* = 3.7 Hz, 1H, H1), 5.19 (dd, *J* = 12.6 Hz, 6.0 Hz, 1H, H5), 3.78 – 3.65 (m, 1H, H10), 3.63 – 3.43 (m, 2H, H4, H10), 2.37 (ddd, *J* = 20.1 Hz, 16.9 Hz, 8.6 Hz, 4H, H3, H7), 2.10 – 1.88 (m, 2H, H8), 1.81 (s, 3H, Me)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 175.6 (C7), 140.0 (C2), 140.0 (Ph), 128.9 (2C, Ph), 127.6 (Ph), 127.3 (Ph), 127.1 (2C, Ph), 116.9 (C1), 88.9 (C5), 47.6 (C6), 45.9 (C8), 40.9 (C4), 38.3 (C10), 30.8 (C3), 23.0 (Me), 18.8 (C9)

FT-IR (ATR): ṽ [cm^{-1}] = 2969 (w), 2910 (w), 1728 (w), 1688 (s), 1548 (s), 1493 (w), 1455 (m), 1413 (m), 1370 (w), 1284 (m), 1265 (m), 1194 (w), 1153 (w), 1080 (w), 878 (w), 845 (w), 785 (w), 760 (m), 700 (m)

HR-MS: (EI, 70 eV): $[M]^+$ = 300.147; calculated: 300.1474

***N*-(5-(2,4-Dichlorophenyl)-3-methyl-6-nitrocyclohex-2-enyl)acetamide (60)**



$C_{18}H_{22}N_2O_3$, 314.38 g/mol

Yield: 18 %, (*dr cis,trans / trans,trans* = 13/1), stereochemistry at C3 not determined

m.p.: 155 – 156 °C

TLC: R_f (cyclohexane/EA = 1/3) = 0.29

^{1}H NMR: (300 MHz, $CDCl_3$) δ = (major isomer) 7.40 – 7.11 (m, 6H), 5.71 (s, 1H, H2), 5.33 (d, *J* = 5.4 Hz, 1H, H6), 5.21 (dd, *J* = 12.9, 5.8 Hz, 1H, H5), 3.72 (dt, *J* = 25.7, 12.9 Hz, 1H, H10), 3.48 (s, 2H, H10, H4), 3.33 (td, *J* = 8.7, 4.2 Hz, 1H), 3.05 – 2.93 (m, 1H), 2.56 – 2.31 (m, 3H), 1.48 (s, 3H, HMe), 0.94 (s, 3H, Me).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 176.2, 138.8, 137.6, 133.2, 128.7, 128.6, 127.9, 127.7, 127.4, 89.6, 83.0, 60.4, 50.8, 48.0, 45.5, 37.5, 36.1, 30.9, 30.7, 20.4, 19.1, 14.2.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3059 (w), 3029 (w), 2962 (m), 2929 (m), 1730 (w), 1689 (s), 1549 (s), 1494 (m), 1453 (m), 1411 (s), 1370 (m), 1281 (s), 1266 (s), 1195 (w), 1032 (w), 866(w), 840 (w),766 (m),756 (m), 723 (m), 701 (s)

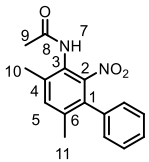
LR-MS: (EI, 70 eV): 314, 268, 252, 183, 167

HR-MS: (EI, 70 eV): $[M]^+$ = 314.163; calculated: 314.1630

MnO_2-mediated oxidation to nitrobiaryls:

The amidonitrocyclohexene (1 mmol, 1 equiv.), MnO_2 (85 %, 5 equiv.) and toluene (5 mL) were combined in a reaction tube. The tube was sealed with a septum and the reaction stirred at 80 °C. After 6 h, the solvent and other volatile compounds were removed by oil pump vacuum. Silica gel flash chromatography (ethyl acetate/cyclohexane) gave the aromatic product in analytically pure form.

***N*-(4,6-Dimethyl-2-nitrobiphenyl-3-yl)acetamide (61)**



$C_{16}H_{16}N_2O_3$, 284,3150 g/mol

Yield: 71 %

Conditions: yellow solid

TLC: R_f (cyclohexane/EA = 1/1) = 0.56

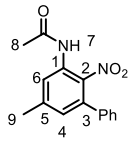
^{1}H NMR: (500 MHz, MeOD) δ = 7.46 – 7.35 (m, 5 H, Ar), 7.08 (s, 1 H, H-5), 2.54 (s, 3 H, H 9), 2.52 and 2.27 (2s, 6 H, H-10, H-11), H-7 obscured

^{13}C NMR: (125 MHz, MeOD) δ = 165.1 (C-8), 150.5 (C-2), 138.9, 136.4 and 133.5 (3 C_q), 131.0 and 129.4 (C-H_{Arom}), 128.7 (C_q), 128.6 and 128.5 (C-H_{Arom}), 123.7 (C_q), 19.8 (C-9), 16.3 and 14.1 (C-10, C-11)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2920 (m), 2860 (w), 1720 (w), 1607 (m), 1486 (m), 1441 (m), 1383 (m), 1250 (m), 1223 (s), 1061 (s), 926 (m), 759 (s), 700 (s)

LR-MS (ESI): 238 $[M\text{-}NO_2]^+$, 223 $[M\text{-}NO_2\text{-}CH_3]^+$, 213, 186, 137, 129, 105

***N*-(5-Methyl-2-nitrobiphenyl-3-yl)acetamide (62)**



$C_{15}H_{14}N_2O_3$, 270.2833 g/mol

Yield: 18 %

TLC: R_f (cyclohexane/EA = 2.5/1) = 0.18

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.48 (d, *J* = 19.9 Hz, 1H), 8.12 (s, 1H), 7.50 – 7.39 (m, 4H), 7.37 – 7.28 (m, 3H), 6.99 (s, 1H), 2.46 (s, 3H, H8), 2.23 (s, 3H, H9)

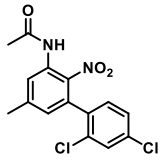
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 168.7 (CO), 143.2 (C2), 137.5, 137.0, 130.7, 128.7, 128.4 (2C, CPh), 127.8 (Ph), 127.6 (2C, Ph), 122.9, 27.0 (C8), 21.8 (C9)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3267 (m), 3056 (m), 2922 (m), 2852 (w), 1733 (m), 1674 (s), 1596 (s), 1576 (m), 1527 (s), 1498 (s), 1447 (s), 1423 (s), 1363 (s), 1254 (s), 1181 (w), 1144 (w), 1075 (w), 1040 (m), 1023 (m), 1000 (w), 858 (m), 834 (s), 776 (m), 764 (s), 698 (s), 611 (m)

LR-MS: (EI, 70 eV): 270, 224, 199, 183, 152, 91, 43

HR-MS (ESI): $[M+Na]^+$ = 293.0898; calculated: 293.0896

***N*-(2',4'-Dichloro-5-methyl-2-nitrobiphenyl-3-yl)acetamide (63)**



$C_{15}H_{12}Cl_2N_2O_3$, 339.17 g/mol

Yield: 15 %

TLC: R_f (cyclohexane/EA = 2/1) = 0.24

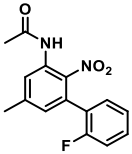
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.94 (s, 1H), 8.21 (s, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.12 (s, 1H), 6.77 (s, 1H), 2.38 (s, 3H), 2.17 (s, 3H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 163.5 (CO), 144.2, 139.5, 135.5, 134.2, 133.9, 133.4, 130.9, 129.4, 127.8, 127.5, 123.7, 27.2, 22.0

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3310 (w_{br}), 2955 (w), 2914 (w), 1700 (s), 1592 (m), 1527 (m), 1483 (s), 1367 (m), 1259 (s), 1099 (s), 1051 (m), 1021 (m), 905 (w), 861 (m), 798 (s), 729 (m)

LR-MS: (EI, 70 eV): 339 $[M]^+$, 303, 261, 231, 198, 152, 91, 43

***N*-(2'-Fluoro-5-methyl-2-nitrobiphenyl-3-yl)acetamide (64)**



$C_{15}H_{13}FN_2O_3$, 288.27 g/mol

Yield: 20 %

TLC: R_f (cyclohexane/EA = 2.5/1) = 0.19

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.91 (s, 1H), 8.24 (s, 1H), 7.39 (m, 3H), 6.98 (s, 1H), 2.47 (s, 3H), 2.25 (s, 3H)

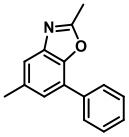
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 168.8, 143.9, 136.4, 131.8, 131.7, 131.3, 130.3, 130.2, 128.2, 124.6, 123.5, 115.7, 115.4, 25.0, 21.8

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3329 (m), 3058 (m), 2976 (w), 2914 (w), 1673 (s), 1592 (s), 1492 (s), 1364 (s), 1218 (s), 1096 (m), 1031 (m), 910 (m), 839 (m), 797 (w), 759 (s)

LR-MS: (EI, 70 eV): 288 $[M]^+$, 242 $[M\text{-}NO_2]^+$, 217, 198, 170, 152, 133

HR-MS: (EI, 70 eV): $[M]^+$ = 288.089; calculated: 288.0910

2,5-Dimethyl-7-phenylbenzo[*d*]oxazole (65)



$C_{15}H_{13}NO$, 223.26 g/mol

Yield: 28 %

TLC: R_f (cyclohexane/EA = 2.5/1) = 0.25

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.88 – 7.81 (m, 1H), 7.52 (t, 1H), 7.43 (s, 1H), 7.43 – 7.37 (m, 1H), 7.32 (s, 1H), 2.67 (s, 3H), 2.53 (s, 3H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 164.2, 146.7, 142.3, 135.9, 134.5, 128.7 (2C), 128.2 (2C), 127.9, 124.7, 124.1, 118.5, 21.8, 14.7

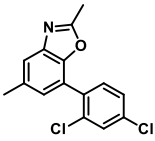
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 30058 (w), 3017 (w), 2920 (m), 2860 (w), 1694 (m), 1581 (s), 1477 (m), 1377 (m), 1317 (m), 1261 (s), 1185 (s), 1119 (w), 1072 (w),

1032 (w), 985 (m), 924 (s), 885 (m), 850 (s), 829 (m), 771 (s), 753 (s), 694 (s), 664 (m), 642 (m)

LR-MS: (EI, 70 eV): 223, 96, 168, 152, 115, 91

HR-MS: (EI, 70 eV): $[M]^+$ = 223.098; calculated: 223.0997

2,5-Dimethyl-7-(2,4-dichlorophenyl)benzo[*d*]oxazole (66)



$C_{15}H_{11}Cl_2NO$, 292.15 g/mol

Yield: 32 %

TLC: R_f (cyclohexane/EA = 2.5/1) = 0.41

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.55 (d, *J* = 1.4 Hz, 1H), 7.47 (s, 1H), 7.36 (d, *J* = 1.9 Hz, 2H), 7.08 (s, 1H), 2.60 (s, 3H), 2.50 (s, 3H)

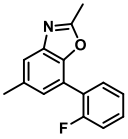
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 164.3, 146.8, 141.8, 134.6, 134.2, 133.9, 133.6, 132.4, 129.8, 127.1, 126.6, 120.9, 119.5, 21.5, 14.6

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3064 (w), 2921 (m), 2860 (w), 1724 (w), 1676 (m), 1579 (s), 1548 (m), 1465 (s), 1373 (m), 1306 (m), 1263 (m), 1189 (s), 1136 (w), 1103 (s), 1057 (s), 985 (m), 893 (s), 856 (s), 820 (s), 782 (s), 731 (m), 665 (m)

LR-MS: (EI, 70 eV): 291 $[M]^+$, 256, 223, 196, 181, 152, 128, 91

HR-MS: (EI, 70 eV): $[M]^+$ = 291.021; calculated: 291.0217

2,5-Dimethyl-7-(2-fluorophenyl)benzo[*d*]oxazole (67)



$C_{15}H_{12}FNO$, 241.26 g/mol

Yield: 23 %

TLC: R_f (cyclohexane/EA = 2/1) = 0.27

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.58 (td, *J* = 7.5, 1.7 Hz, 1H), 7.45 (s, 1H), 7.44 – 7.35 (m, 1H), 7.29 – 7.26 (m, 1H), 7.20 (m, 2H), 2.62 (s, 3H), 2.50 (s, 3H)

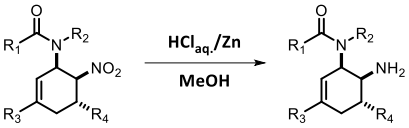
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 164.2, 146.4, 134.0, 131.3, 129.8, 129.7, 126.5, 124.2, 119.1, 116.2, 115.9, 21.5, 14.8

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3051 (w), 2922 (w), 2860 (w), 1690 (m), 1612 (m), 1580 (s), 1448 (s), 1398 (m), 1186 (s), 1098 (m), 1034 (m), 923 (m), 895 (m), 852 (m), 835 (m), 801 (s), 756 (s), 665 (m), 633 (m)

LR-MS: (EI, 70 eV): 241 $[M]^+$, 222, 199, 170, 152, 120, 85

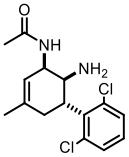
HR-MS: (EI, 70 eV): $[M]^+$ = 241.091; calculated: 241.0903

Zn/HCl-mediated reduction of amidonitrocyclohexenes:



The nitro compound (0.4 mmol, 1.0 equiv.) was dissolved in MeOH (3.0 ml) and $HCl_{aq.}$ (6 N, 2.2 ml) was added. Zinc powder (262 mg, 4.0 mmol, 10 equiv.) was added in small portions and the reaction mixture was stirred for 2 h at room temperature. After addition of saturated aqueous $NaHCO_3$ (20 ml) the solution was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to get the amide in quantitative yield.

***N*-(2-Amino-2',6'-dichloro-5-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)acetamide (68):**



$C_{15}H_{18}Cl_2N_2O$, 313.22 g/mol

Yield: 94 %

Condition: pale yellow solid

m.p.: 161 – 163 °C

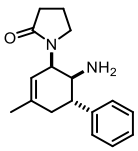
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.34 (dd, 2H), 7.21 – 7.07 (m, 1H), 6.45 (d, *J* = 7.4 Hz, 1H), 5.42 (d, *J* = 5.3 Hz, 1H), 4.94 (s, 1H), 4.46 (dd, *J* = 12.2, 4.3 Hz, 1H), 3.96 (td, *J* = 11.8, 5.9 Hz, 1H), 2.75 (m, *J* = 18.1, 11.6 Hz, 1H), 2.16 – 2.08 (m, 4H), 1.75 (s, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 140.6, 137.9, 134.7, 133.4, 130.9, 129.6, 118.5, 52.2, 39.9, 34.1, 24.2, 23.1.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3309, 3224, 1661, 1606, 1521, 1434, 1373, 1313, 1266, 1178, 1149, 1086, 1031, 917, 764, 733, 699, 583, 534, 417

HR-MS: (EI, 70 eV): $[MH]^+$ = 313.0872; calculated: 313.0869

1-(2-Amino-5-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)pyrrolidin-2-one (69):



$C_{17}H_{22}N_2O$, 270,38 g/mol

Yield: 94 %

Condition: colourless solid

m.p.: 257 °C decomp.

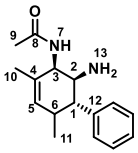
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.43 – 7.17 (m, 5H), 5.35 (d, *J* = 5.2 Hz, 1H), 5.04 (s, 1H), 3.78 – 3.54 (m, 2H), 3.47 (dd, *J* = 12.1, 4.5 Hz, 1H), 3.05 – 2.68 (m, 2H), 2.46 – 2.17 (m, 4H), 2.01 – 1.86 (m, 1H), 1.78 (s, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 181.7, 141.5, 140.2, 129.5, 128.3, 127.8, 116.9, 56.6, 51.9, 49.6, 43.9, 38.9, 32.3, 23.2, 18.1.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3302, 3205, 3137, 2971, 2913, 1659, 1606, 1492, 1443, 1416, 1291, 1198, 1144, 1082, 1056, 805, 760, 702, 650, 571, 451

HR-MS: (EI, 70 eV): $[MH]^+$ = 271.1805; calculated: 271,1805

***N*-(2-Amino-4,6-dimethyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)acetamide (70):**



$C_{16}H_{22}N_2O$, 258.36 g/mol

Yield: 91 %

m.p.: 67 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.33 bis 7.21 (m, 5 H, Ar), 5.59 (s, 1 H, ^3J = 9.39 Hz, H-7), 5.48 (s, br, 1 H, H-5), 4.60 (q*, 1 H, ^3J = 4.69 Hz, H-3), 3.36 (dd, 1 H, ^3J = 11.51/4.69 Hz, H-2), 2.34 (m, 1 H, H-6), 2.15 (m, 3 H, H-1, H-13), 2.10 (s, 3 H, H-10), 1.76 (s, 3 H, H-10), 0.81 (d, 3 H, ^3J = 6.81 Hz, H-11)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 171.4 (C-8), 141.4 (C-12), 131.7 (C-5), 131.5 (C-4), 128.8, 128.7, 127.0 (5 Ar), 54.2 (C-2), 51.4 (C-1 und C-3), 38.2 (C-6), 23.7 (C-9), 21.0 (C-10), 19.8 (C-11)

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3256 (w), 3027, (w), 2963 (w), 1643 (s), 1536 (s), 1493 (m), 1452 (m), 1370 (m), 1285 (w), 1092 (w), 1092 (w), 1036 (w), 907 (m), 755 (s), 727 (s), 700 (s)

GC/MS: (50-300M), R_t: 9.578 min, m/z = 258 $[M]^+$, 199 $[M\text{-}CH_3CONH]^+$, 184 $[M\text{-}CH_3CONH\text{-}CH_3]^+$, 184$[M\text{-}CH_3CONH\text{-}CH_3\text{-}NH_2]^+$, 167, 139, 119, 108

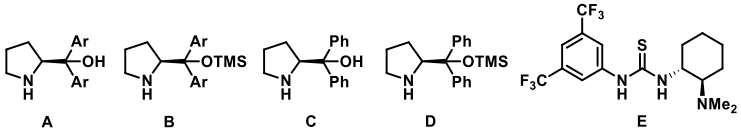
HR-MS (ESI): $[M+Na]^+$ = 281.162; calculated: 281.1624

Amine/acid co-catalyzed reactions

General procedure for amine-catalyzed syntheses of 1-Methyl-4-nitro-5-phenyl-1,3-cyclohexadienes:

Under an argon atmosphere, the nitrostyrene (1.0 equiv.), catalyst (20 mol%) and additive were dissolved in abs. solvent. Over a periode of 30 min 3-methyl-2-butenal (1.5 equiv.) was added. After the end of the reaction the solvent was removed under reduced pressure and the yield was determined by ^{1}H-NMR using hexamethyldisiloxane as internal standard.
The enantiomeric excess was detemined by chiral GC-FID.
Study about amine-catalyzed reactions of 3-Methyl-2-butenal and Nitrostyrene. Yields were determined by ^{1}H-NMR using hexamethyldisiloxane as internal standard.

The enantiomeric excess was detemined by chiral GC-FID.

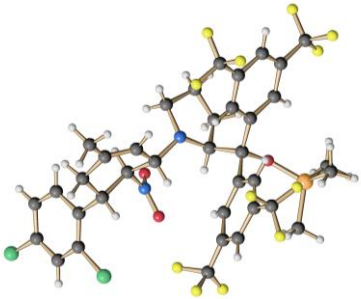


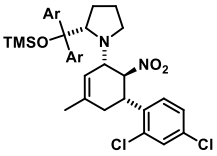
Entry	Solvent	Amine	Additive (mol%)	Temp., rxn. time	Yield (ee) [%]
1	MeCN	Pyrrolidine	$PhCO_2H$ (20)	40 °C, 48 h	12
2	MeCN	Pyrrolidine	$PhCO_2H$ (20)	40 °C, 5 d	28
3	MeCN	*L*-Proline	$PhCO_2H$ (20)	40 °C, 48 h	3 (9)
4	MeCN	C	$PhCO_2H$ (20)	40 °C, 48 h	10 (42)
5	MeCN	C	*o*-NO_2-$PhCO_2H$ (20)	40 °C, 48 h	18 (45)
6	MeCN	C	*o*-NO_2-$PhCO_2H$ (20)	40 °C, 5 d	30 (45)
7	MeOH	C	*o*-NO_2-$PhCO_2H$ (20)	40 °C, 15 h, then RT, 4 d	37 (44)

8	**MeOH**	**C**	***o*-NO_2-$PhCO_2H$ (20)**	**RT, 5 d**	**23 (62)**
9	PhMe	C	*o*-NO_2-$PhCO_2H$ (20)	110 °C, 90 h	28 (47)
10	PhMe	B	*o*-NO_2-$PhCO_2H$ (20)	110 °C, 90 h	22 (18)
11	**PhMe**	**C**	***o*-NO_2-$PhCO_2H$ (20)**	**80 °C, 3 d**	**40 (61)**
12	PhMe	B	*o*-NO_2-$PhCO_2H$ (20)	80 °C, 3 d	37 (13)
13	**PhMe, dry, degassed**	**C**	***o*-NO_2-$PhCO_2H$ (20)**	**80 °C, 4 d**	**26 (61)**
14	PhMe	C	*o*-NO_2-$PhCO_2H$ (20)	50 °C, 3 d	12 (61)
15	PhMe	A	*o*-NO_2-$PhCO_2H$ (20)	50 °C, 3 d	16 (21)
16	PhMe	B	*o*-NO_2-$PhCO_2H$ (20)	50 °C, 3 d	12 (13)
17	PhMe	D	Pyrrolidine (20)	50 °C, 3 d	6 (11)
18	MeOH	C	*o*-NO_2-$PhCO_2H$ (20)	50 °C, 3 d	12 (45)
19	MeOH	A	*o*-NO_2-$PhCO_2H$ (20)	50 °C, 3 d	12 (53)
20	MeOH	B	*o*-NO_2-$PhCO_2H$ (20)	50 °C, 3 d	12 (41)
21	MeOH	E	Pyrrolidine (20)	50 °C, 3 d	6 (11)
22	DCM	C	*o*-NO_2-$PhCO_2H$ (40)	40 °C, 70 h	29 (42)
23	DCM	B	*o*-NO_2-$PhCO_2H$ (40)	40 °C, 70 h	<5 (11)
24	**DCM**	**D**	***o*-NO_2-$PhCO_2H$ (40)**	**40 °C, 70 h**	**25 (57)**
25	DCM	A	*o*-NO_2-$PhCO_2H$ (40)	40 °C, 70 h	15

X-ray crystallography data:

24

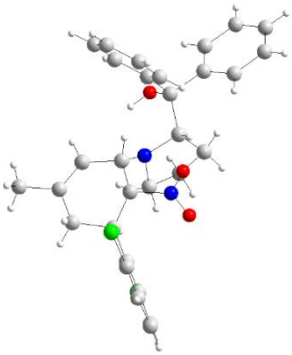


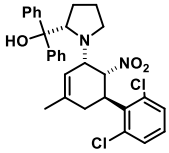


Ar = 3,5 $(CF_3)_2C_6H_3$

Empirical formula	$C_{37}\ H_{34}\ Cl_2\ F_{12}\ N_2\ O_3\ Si$
Formula weight	881.65
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, C2221
Unit cell dimensions	a = 10.8393(5) A α = 90°
	b = 16.7856(3) A β = 90°
	c = 42.689(2) A γ = 90°
Volume	7767.0(5) A^3
Z, Calculated density	8, 1.508 Mg/m^3
Absorption coefficient	0.295 mm^{-1}
F(000)	3600
Crystal size	3 x .2 x .2 mm
Theta range for data collection	1.91 to 26.91°
Limiting indices	-11<=h<=12, -19<=k<=19, -53<=l<=49
Reflections collected / unique	13598 / 6278 [R(int) = 0.0651]
Reflection observed [I>2σ(I)]	3450
Completeness to theta = 26.91	79.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6278 / 0 / 518
Goodness-of-fit on F^2	0.967
Final R indices [I>2σ(I)]	R1 = 0.0658, wR2 = 0.1413
R indices (all data)	R1 = 0.1379, wR2 = 0.1657
Absolute structure parameter	-0.13(12)
Largest diff. peak and hole	0.847 and -0.588 $e.A^{-3}$

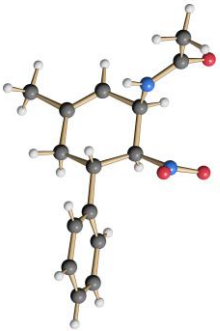
cis,trans-35

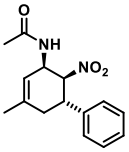




Empirical formula	$C_{30}\,H_{30}\,Cl_2\,N_2\,O_3$
Formula weight	537.46
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P212121
Unit cell dimensions	a = 8.9169(13) A α = 90°
	b = 17.351(3) A β = 90°
	c = 17.602(3) A γ= 90°
Volume	2723.2(8) A^3
Z, Calculated density	4, 1.311 Mg/m^3
Absorption coefficient	0.273 mm^{-1}
F(000)	1128
Crystal size	2 x .2 x .2 mm
Theta range for data collection	1.65 to 27.00°.
Limiting indices	-11<=h<=11, -22<=k<=22, -22<=l<=20
Reflections collected / unique	12769 / 5633 [R(int) = 0.0783]
Reflection observed [I>2σ(I)]	2904
Completeness to theta = 27.00	98.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5633 / 0 / 339
Goodness-of-fit on F^2	1.028
Final R indices [I>2σ(I)]	R1 = 0.0630, wR2 = 0.1281
R indices (all data)	R1 = 0.1520, wR2 = 0.1519
Absolute structure parameter	0.02(9)
Largest diff. peak and hole	0.240 and -0.248 $e.A^{-3}$

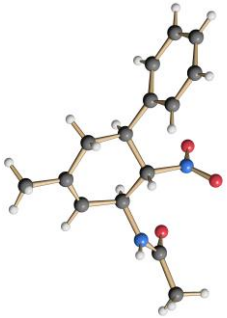
cis,trans-51

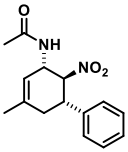




Empirical formula	C_{15} H_{18} N_2 O_3
Molmasse	274.31
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P21/c
Unit cell dimensions	a = 19.3984(10) A α = 90°
	b = 9.6352(5) A β = 108.737(2) °.
	c = 16.2688(9) A γ = 90°
Volume	2879.6(3) A^3
Z, Calculated density	8, 1.265 Mg/m^3
Absorption coefficient	0.089 mm^{-1}
F(000)	1168
Crystal size	3 x .06 x .02 mm
Theta range for data collection	1.11 to 27.00°
Limiting indices	21<=h<=24, -7<=k<=12, -20<=l<=20
Reflections collected / unique	13657 / 5758 [R(int) = 0.0684]
Reflection observed	[I>2σ(I)] 2893
Completeness to theta = 27.00	91.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5758 / 0 / 365
Goodness-of-fit on F^2	0.980
Final R indices [I>2σ(I)]	R1 = 0.0667, wR2 = 0.1537
R indices (all data)	R1 = 0.1482, wR2 = 0.1851
Largest diff. peak and hole	0.226 and -0.299 $e.A^{-3}$

trans,trans-51

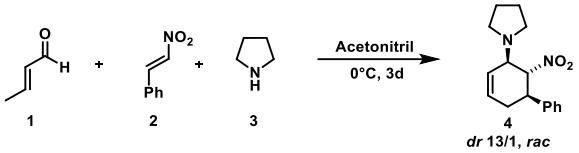


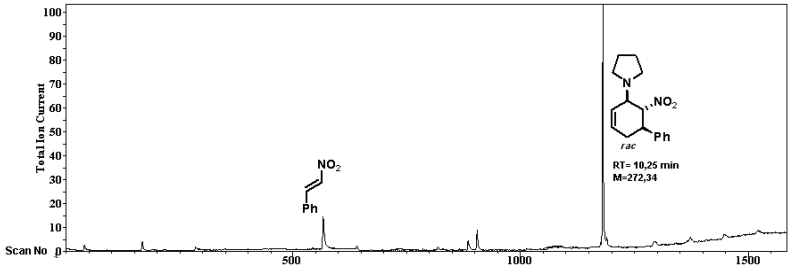


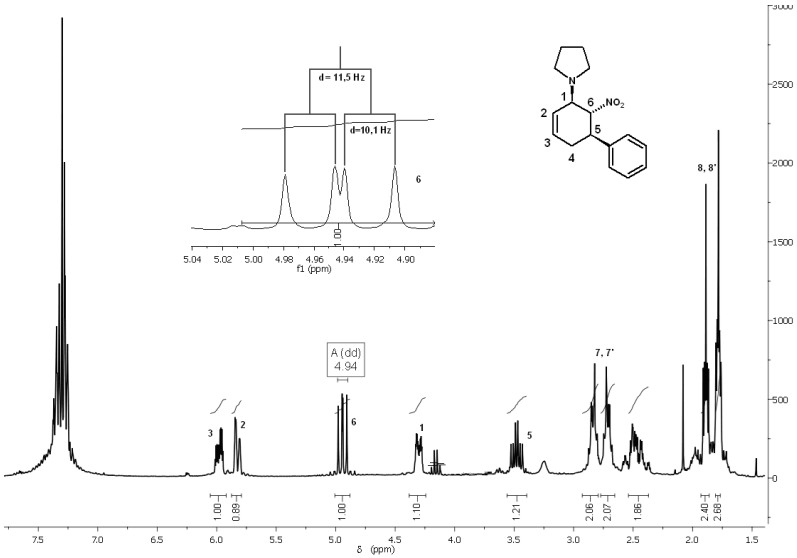
Empirical formula	$C_{15}\ H_{18}\ N_2\ O_3$
Formula weight	274.31
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 19.0719(12) Å α= 90°
	b = 5.2738(3) Å β = 90.632(4)°
	c = 27.2994(14) Å γ = 90°
Volume	2745.6(3) A^3
Z, Calculated density	8, 1.327 Mg/m^3
Absorption coefficient	0.093 mm^{-1}
F(000)	1168
Crystal size	15 x .07 x .03 mm
Theta range for data collection	1.49 to 27.00°
Limiting indices	-24<=h<=24, -6<=k<=6, -34<=l<=34
Reflections collected / unique	7864 / 3000 [R(int) = 0.0540]
Reflection observed [I>2σ(I)]	1938
Completeness to theta = 27.00	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3000 / 0 / 187
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0540, wR2 = 0.1300
R indices (all data)	R1 = 0.0948, wR2 = 0.1456
Largest diff. peak and hole	0.419 and -0.234 $e.A^{-3}$

Selected Spectra:

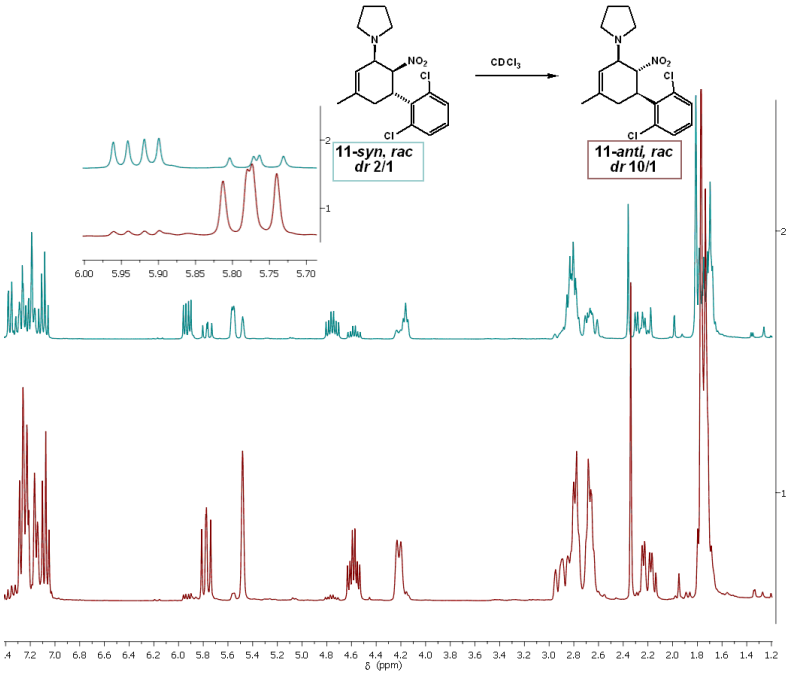
1:



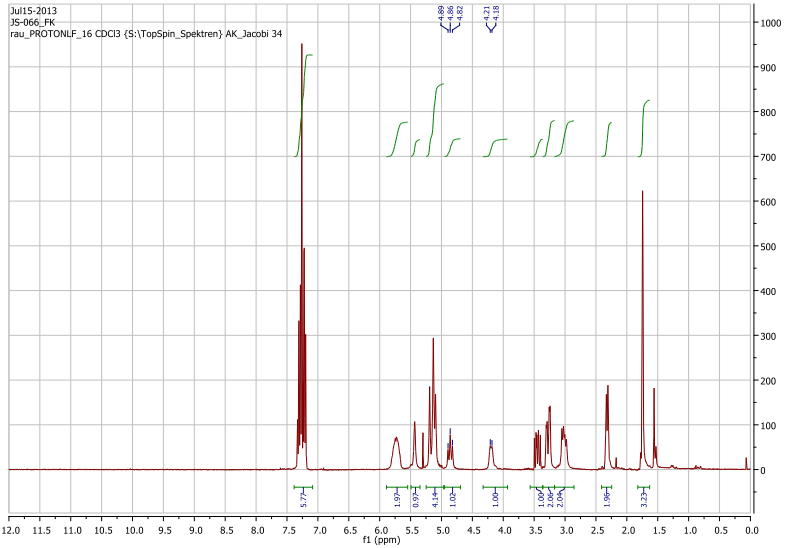


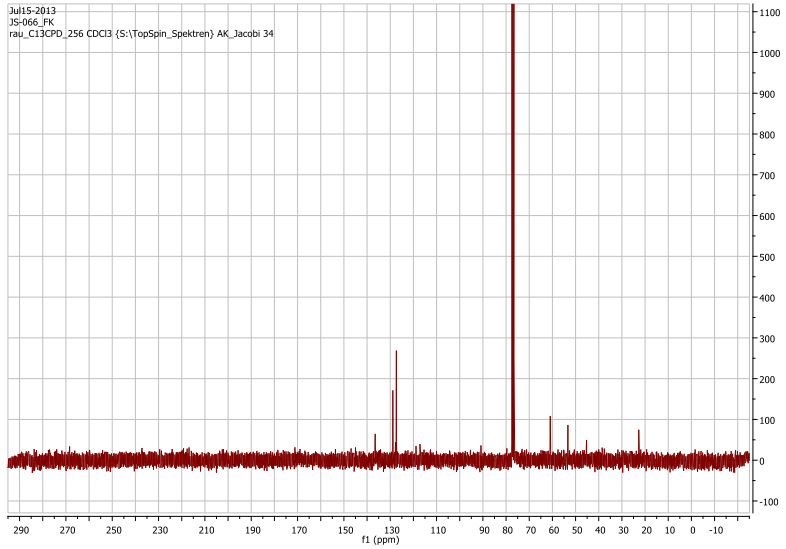


10:



21:


Jul15-2013
JS-066_FK
rau_PROTONLF_16 CDCl3 {S:\TopSpin_Spektren} AK_Jacobi 34
4.89
4.88
4.82
4.21
4.18
f1 (ppm)


Jul15-2013
JS-066_FK
rau_C13CPD_256 CDCl3 {S:\TopSpin_Spektren} AK_Jacobi 34
f1 (ppm)

22:

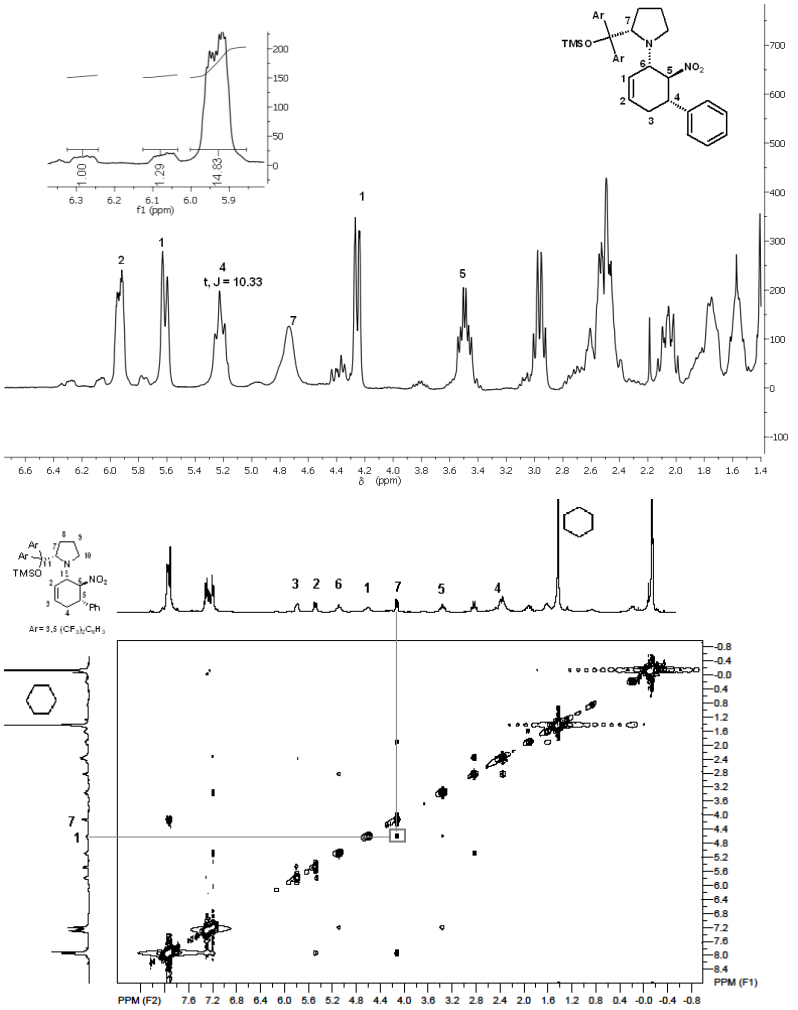


Abbildung 1: ^{1}H-NOESY-Spektrum von. Die Kopplung zwischen H_7 und H_1 ist das Zeichen einer räumlichen Nähe.

2.7. References:

[1] (a) M. J. Palframan and A. F. Parsons in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, Vol. 48; H. Hiemstra, ed.; Thieme, Stuttgart, 2009, 647-693; (b) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115-136.

[2] (a) *Cycloaddition Reactions in Organic Synthesis*; S. Kobayashi, K. A. Jorgensen, eds.; Wiley-VCH, Weinheim, 2002; (b) K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. Vassilikogiannakis, *Angew. Chem. Int. Ed.*, 2002, **41**, 1668-1698; (c) W. Oppolzer in *Comprehensive Organic Synthesis*, Vol. 5; B. M. Trost, I. Fleming, eds.; Pergamon, Oxford, 1991, 315-399.

[3] C. Thebtaranonth and Y. Thebtaranonth, *Cyclization Reactions*, CRC Press, Boca Raton, 1994.

[4] Selected examples: (a) S. Danishefsky, *Acc. Chem. Res.*, 1981, **14**, 400-406; (b) V. K. Das, *Synlett*, 2011, 430-431 (c) M. C. Aversa, A. Barattuci, P. Bonaccorsi, P. Giannetto and D. N. Jones, *J. Org. Chem.*, 1997, **62**, 4376-4384; (d) S. A. Kozmin and V. H. Rawal, *J. Am. Chem. Soc.*, 1999, **121**, 9562-9573; (a) R. C. Cookson, M. C. Cramp and P. J. Parsons, *Chem. Commun*., 1980, 197-198; (b) J. Becher, H. C. Nielsen, J. P. Jacobsen, O. Simonsen and H. Clausen, *J. Org. Chem*., 1988, **53**, 1862-1871; (c) C. J. Suckling, M. C. Tedford, L. M. Bence. J. I. Irvine and W. H. Stimson, *Bioorg. Med. Chem. Lett*., 1992, **2**, 49-52.

[5] (a) Dienamine catalysis: D. B. Ramachary and Y. V. Reddy, *Eur. J. Org. Chem.*, 2012, 865-887; (b) Somatostatin analogues: M. Sukopp, R. Schwab, L. Marinelli, E. Biron, M. Heller, E. Varkondi, A. Pap, E. Novellino, G. Keri and H. Kessler, *J. Med. Chem*., 2005, **48**, 2916-2926; (c) photoactive luminols: H. Neumann, S. Klaus, M. Klawonn, D. Strübing, S. Hübner, D. Gördes, A. Jacobi von Wangelin, M. Lalk and M. Beller, *Z. Naturforsch*., 2004, **59b**, 431-438; (d) Aza-Corollosporins: H. Neumann, D. Strübing, M. Lalk, S. Klaus, S. Hübner, A. Spannenberg, U. Lindequist and M. Beller, *Org. Biomol. Chem.*, 2006, **4**, 1365-1375; (e) Gephyrotoxin: L. E. Overman, D. Lesuisse and M. Hashimoto, *J. Am. Chem. Soc.*, 1983, **105**, 5373-5379; (f) Dendrobine: S. F. Martin and W. Li, *J. Org. Chem.*, 1991, **56**, 642-650; (g) Aspidosperma alkaloids: S. A. Kozmin, T. Iwama, Y. Huang and V. H. Rawal, *J. Am. Chem. Soc.*, 2002, **124**, 4628-4641; (h) azasteroidal building blocks: A. Jacobi von Wangelin, H. Neumann, D. Gördes, S. Hübner, C. Wendler, S. Klaus, D. Strübing, A. Spannenberg, H. Jiao, L. El Firdoussi, K. Thurow, N. Stoll and M. Beller, *Synthesis*, 2005, 2029-2038; (i) automated phthalate synthesis: A. Jacobi von Wangelin, H. Neumann, D. Gördes, S. Klaus, H. Jiao, A. Spannenberg, T. Krüger, C. Wendler, K. Thurow, N. Stoll and M. Beller, *Chem. Eur. J.*, 2003, **9**, 2273-2281.

[6] (a) Review: D. Enders and O. Meyer, *Liebigs Ann.*, 1996, 1023-1035. Selected examples: (b) W. Oppolzer, *Angew. Chem. Int. Ed.*, 1977, **16**, 10-24; (c) W. Oppolzer, L. Bieber and E. Francotte, *Tetrahedron Lett.*, 1979, **16**, 981-984; (d) W. Oppolzer, L. Bieber and E. Francotte, *Tetrahedron Lett.*, 1979, **16**, 4537-4540; (e) L. E. Overman, G. F. Taylor, C. B. Petty and P. J. Jessup, *J. Org. Chem.*, 1978, **43**, 2164-2167; (f) L. E. Overman, L. A. Clizbe, R. L. Freerks and C. K. Marlowe, *J. Am. Chem. Soc.*, 1981, **103**, 2807-2815; (g) L. E. Overman, R. L. Freerks, C. B. Petty, L. A. Clizbe, R. K. Ono, G. F. Taylor and P. J. Jessup, *J. Am. Chem. Soc.*, 1981, **103**, 2816-2822; (h) C. A. Zezza and M. B. Smith, *J. Org. Chem.*, 1988, **53**, 1161-1167; (i) M. B. Smith, *Org. Prep. Proced. Int.*, 1990, **22**, 315-335; (j) R. Sustmann, M. Rogge, U. Nüchter and H. Bandmann, *Chem. Ber.*, 1992, **125**, 1647-1656; (k) A. R. Katritzky, A. V. Ignatchenko and H. Lang, *J. Org. Chem.*, 1995, **60**, 4002-4005; (l) D. A. Alonso, E. Alonso, C. Najera and M. Yus, *Synlett*, 1997, 491-492; (m) J. Barluenga, F. Aznar, C. Ribas and C. Valdés, *J. Org. Chem.*, 1997, **62**, 6746-6753; (n) J. M. Janey, T. Iwama, S. A. Kozmin and V. H. Rawal, *J. Org. Chem.*, 2000, **65**, 9059-9068; (o) A. N. Thadani, A. R. Stankovic and V. H. Rawal, *Proc. Natl. Acad. Sci. U.S.A.*, 2004, **101**, 5846-5850; (p) M. R. Tremblay, T. J. Dickerson and K. D. Janda, *Adv. Synth. Catal.*, 2001, **343**, 577-585; (q) S. Hübner, H. Neumann, A. Jacobi von Wangelin, S. Klaus, D. Strübing, H. Klein and M. Beller, *Synthesis*, 2005, 2084-2089; *ibid.* 2270; (r) A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 2458-2459; (s) N. Momiyama, T. Konno, Y. Furiya, T. Iwamoto and M. Terada, *J. Am. Chem. Soc.*, 2011, **133**, 19294-19297.

[7] (a) A. G. M. Barrett and G. G. Graboski, *Chem. Rev.*, 1986, **86**, 751-762; (b) N. Ono, H. Miyake, A. Kamimura and A. Kaji, *Perkin Trans. 1*, 1987, 1929-1935; (c) R. Ballini, R. Castagnani and M. Petrini, *J. Org. Chem.*, 1992, **57**, 2160-2162; (d) C. Jubert and P. Knochel, *J. Org. Chem.*, 1992, **57**, 5431-5438.

[8] For related condensation-Diels-Alder reaction sequences, see: (a) H. Neumann, A. Jacobi von Wangelin, D. Gördes, A. Spannenberg and M. Beller, *J. Am. Chem. Soc.*, 2001, **123**, 8398-8399; (b) A. Jacobi von Wangelin, H. Neumann, D. Gördes, A. Spannenberg and M. Beller, *Org. Lett.*, 2001, **3**, 2895-2898; (c) H. Neumann, A. Jacobi von Wangelin, D. Gördes, A. Spannenberg, W. Baumann and M. Beller, *Tetrahedron*, 2002, **58**, 2381-2387; (d) S. Klaus, S. Hübner, H. Neumann, D. Strübing, A. Jacobi von Wangelin, D. Gördes and M. Beller, *Adv. Synth. Catal.*, 2004, **346**, 970-978; (e) D. Strübing, A. Jacobi von Wangelin, H. Neumann, D. Gördes, S. Hübner, S. Klaus, A. Spannenberg and M. Beller, *Eur. J. Org. Chem.*, 2005, 107-113

[9] (a) Review: D. Lucet, T. Le Gall and C. Mioskowski, *Angew. Chem. Int. Ed.*, 1998, **37**, 2580-2627. Selected applications of *trans*-1,2-cyclohexane diamines: (b) B.

M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395-422; (c) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97-102; (d) M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 4901-4902; (e) Y. Zhu, J. P. Malerich and V. H. Rawal, *Angew. Chem. Int. Ed.*, 2010, **49**, 153-156; (f) R. Wu, X. Chang, A. Lu, Y. Wang, G. Wu, H. Song, Z. Zhou and C. Tang, *Chem. Commun.*, 2011, **47**, 5034-5036; (g) S. Luo, H. Xu, J. Li, L. Zhang and J.-P. Cheng, *J. Am. Chem. Soc.*, 2007, **129**, 3074-3075. Selected applications of *cis*-1,2-cyclohexane diamines: (h) A. Berkessel, T. Günther, Q. Wang and J.-M. Neudörfl, *Angew. Chem. Int. Ed.*, 2013, **52**, 8467-8471; (i) S. A. Moteki, J. Han, S. Arimitsu, M. Akakura, K. Nakayama and K. Maruoka, *Angew. Chem. Int. Ed.*, 2012, **51**, 1187-1190; (j) O. Kitagawa, K. Yotsumoto, M. Kohriyama, Y. Dobashi and T. Taguchi, *Org. Lett.*, 2004, **6**, 3605-3607; (k) L. T. Vassilev, B. T. Vu, B. Graves, D. Carvajal, F. Podlaski, Z. Filipovic, N. Kong, U. Kammlott, C. Lukacs, C. Klein, N. Fotouhi and E. A. Liu, *Science*, 2004, **303**, 844-848; (l) A. Hirabayashi, H. Mukaiyama, H. Kobayashi, H. Shiohara, S. Nakayama, M. Ozawa, K. Miyazawa, K. Misawa, H. Ohnota and M. Isaji, *Bioorg. Med. Chem.*, 2008, **16**, 7347-7357; (m) K. Yoshikawa, S. Kobayashi, Y. Nakamoto, N. Haginoya, S. Komoriya, T. Yoshino, T. Nagata, A. Mochizuki, K. Watanabe, M. Suzuki, H. Kanno and T. Ohta, *Bioorg. Med. Chem.*, 2009, **17**, 8206-8220; (n) K. Caron, V. Lachapelle and J. W. Keillor, *Org. Biomol. Chem.*, 2011, **9**, 185-197; (o) T. Govindaraju, R. G. Gonnade, M. M. Bhadbhade, V. A. Kumar and K. N. Ganesh, *Org. Lett.*, 2003, **5**, 3013-3016; (p) A. Trapero and A. Llebaria, *ACS Med. Chem. Lett.*, 2011, **2**, 614-619.

[10] (a) K. Patora-Komisarska, M. Benohoud, H. Ishikawa, D. Seebach and Y. Hayashi, *Helv. Chim. Acta*, 2011, **94**, 719-745; (b) B. Potthoff and E. Breitmeier, *Chem. Ber.*, 1987, **120**, 255-257; (c) G. Bobowski, B. West and D. Omecinsky, *J. Heterocycl. Chem.*, 1992, **29**, 33-49; (d) J. Barluenga, F. Aznar and M. Fernández, *Tetrahedron Lett.*, 1995, **36**, 6551-6554; (e) K. Bogdanowicz-Szwed and A. Budzowski, *Monatsh. Chem.*, 2001, **132**, 947-957; (f) H. Sunden, R. Rios, Y. Xu, L. Eriksson and A. Cordova, *Adv. Synth. Catal.*, 2007, **349**, 2549-2555; (g) B. Han, Y.-C. Xiao, Z.-Q. He and Y.-C. Chen, *Org. Lett.*, 2009, **11**, 4660-4663.

[11] (a) For similar equilibria with *N*-acylamines, see: D. Gördes, A. Jacobi von Wangelin, S. Klaus, H. Neumann, D. Strübing, S. Hübner, H. Jiao, W. Baumann, and M. Beller, *Org. Biomol. Chem.*, 2004, **2**, 845-851; (b) A. Jacobi von Wangelin, H. Neumann, D. Gördes, S. Klaus, D. Strübing, M. Beller, *Chem. Eur. J.*, 2003, **9**, 4286-4294.

[12] A. Noble and J. C. Anderson, *Chem. Rev.* 2013, **113**, 2887-2939.

[13] For further preparative and spectroscopic details, see the Supporting Information.

[14] (a) B.-C. Hong, M.-F. Wu, H.-C. Tseng, G.-F. Huang, C.-F. Su and J.-H. Liao, *J. Org. Chem.*, 2007, **72**, 8459-8471; (b) P. Kotame, B.-C. Hong and J.-H. Liao, *Tetrahedron Lett.*, 2009, **50**, 704-707.

[15] Sequential cycloaddition and oxidation reactions: (a) S. Mekidechea and L. Désaubry, *Tetrahedron Lett*., 2008, **49**, 5268-5270; (b) J. T. Vessels, S. Z. Janicki and P. A. Petillo, *Org. Lett*., 2000, **2**, 73-76; (c) G. Hilt and K. I. Smolko, *Angew. Chem. Int. Ed.*, 2003, **42**, 2795-2797; (d) G. Hilt and M. Danz, *Synthesis*, 2008, **14**, 2257-2263; (e) G. Hilt, S. Lüers and K. I. Smolko, *Org. Lett*., 2005, **7**, 251-253; (f) H. Neumann, A. Jacobi von Wangelin, S. Klaus, D. Strübing, D. Gördes and M. Beller, *Angew. Chem. Int. Ed.*, 2003, **42**, 4503; (g) R. Fichtler, J.-M. Neudörfl and A. Jacobi von Wangelin, *Org. Biomol. Chem*., 2011, **9**, 7224-7236.

[16] (a) R. Ballini and M. Petrini, *Tetrahedron*, 2004, **60**, 1017-1047; (b) W. E. Noland, *Chem. Rev.*, 1955, **55**, 137-155.

[17] The best enantioselectivities of amine/acid co-catalyzed sequential cyclisation/elimination reactions were obtained with (*S*)-diphenyl-prolinol (or the TMS-ether thereof) and 2-nitrobenzoic acid (each 20 mol%): up to 40 % yield and 62 % *ee* of nitrocyclohexadiene **36**.

[18] Oxidative aromatisation of cyclohexadienes: (a) T. Moriuchi, K. Kikushima, T. Kajikawa and T. Hirao, *Tetrahedron Lett*., 2009, **50**, 7385-7387; (b) H. Tanaka, T. Ikeno and T. Yamada, *Synlett*, 2003, 576-578; (c) N. Nakamichi, H. Kawabata and M. Hayashi*, J. Org. Chem*., 2003, **68**, 8272-8273; (d) C. A. Busacca and Y. Dong, *Synth. Commun*., 2000, **30**, 501-509; (e) J. Cossy, D. Belotti, *Org. Lett*., 2002, **4**, 2557-2559; (f) M. Hayashi, K. Yamada and S. Nakayama, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1501-1503; (g) J. C. Leffingwell and H. J. Bluhm, *J. Chem. Soc., Chem. Commun.* 1969, **1**, 1151-1152; (h) for more examples, see also: J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, 1992, pp 1162.

[19] (a) H. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, 2001, Ch. 6.3, pp170; (b) M. R. Michaelides, Y. Hong, S. DiDomenico, Jr., E. K. Bayburt, K. E. Asin, D. R. Britton, C. W. Lin and K. Shiosaki, *J. Med. Chem.*, 1997, **40**, 1585-1599.

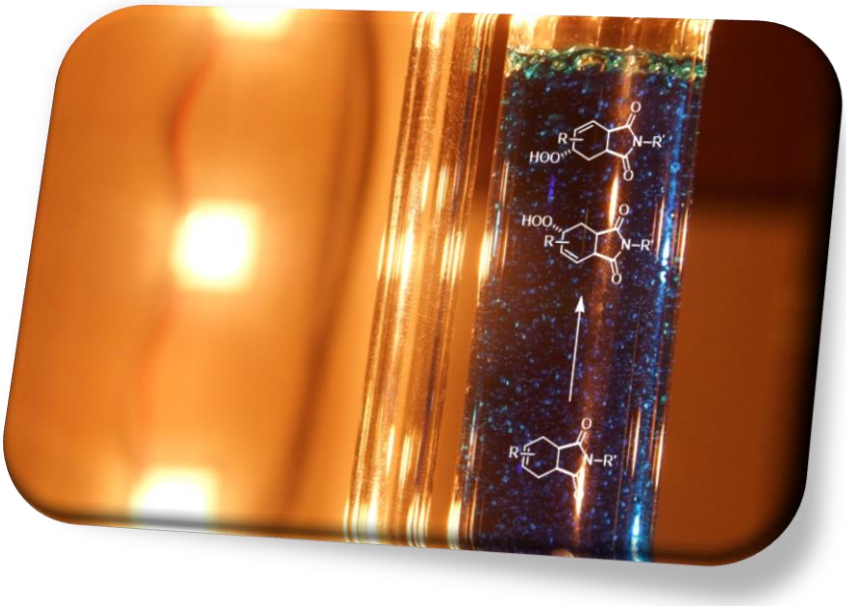
[20] (a) R. Ballini and G. Bosica, *Tetrahedron*, 1995, **51**, 4213-4222; (b) M. V. Gil, E. Roman and J. A. Serrano, *Tetrahedron Lett.*, 2001, **42**, 4625-4628.

[21] For an enantioselective synthesis of related aminocyclohexenes, see: D. Strübing, H. Neumann, S. Klaus, A. Jacobi von Wangelin, D. Gördes, M. Beller, P. Braiuca, C. Ebert, L. Gardossi and U. Kragl, *Tetrahedron*, 2004, **60**, 683.

[22] G. M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112-122.

Chapter 3:

- Stereoselective Photooxidation of Cyclohexenes -



3. Stereoselective Photooxidation of Cyclohexenes: The Imperative of Conformational Control

This chapter is planned to be published:

Josef Schachtner,[1] Michal Majek,[1] Robert Fichtler,[1] Raul Perez-Ruiz,[1] Johannes Regensburger,[2] Marcus Wegmann,[3] Wolfgang Bäumler,[2] Thorsten Bach,[3] and Axel Jacobi von Wangelin[1,*]

[1] Institute of Organic Chemistry, University of Regensburg, Universitaetsstr. 31, 93040 Regensburg. Germany

[2] University Hospital Regensburg, Clinic of Dermatology, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany

[3] Chair of Organic Chemistry I, Technical University of Munich, Lichtenbergstr. 4, 85747 Garching, Germany

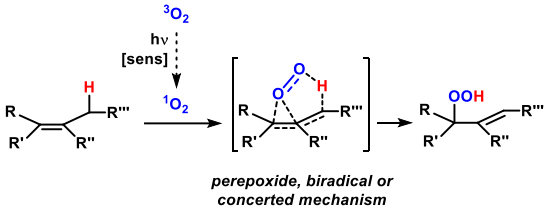
The following chapter comprised of sections of the manuscript which is in preparation. Schemes, figures and text will differ from published version.

Author contributions:

Josef Schachtner and Robert Fichtler did three-component reactions to prepair starting materials. Josef Schachtner did photooxygenations. Michal Majek did DFT calculations. Johannes Regensburger measured singlet oxygen lifetimes and Marcus Wegmann did separations of enantiomers by chiral HPLC.

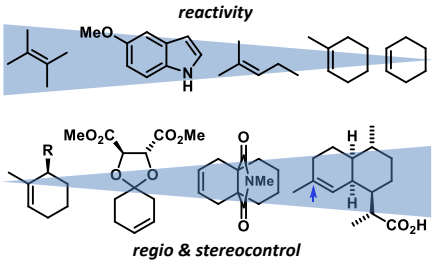
3.1. Introduction

The combination of two of the most abundant resources on the surface of our planet, visible light and atmospheric oxygen, are pivotal to various biological (lipid peroxidation, indirect DNA damage, mineralization of biomass) and artificial processes (photodynamic therapy, polymer degradation, waste treatment). However, applications to the synthesis of complex organic molecules have remained scarce due to the generally low selectivity of reactive oxygen species which can be generated under such conditions (e.g. $^{\cdot}OH$, $^1O_2$, H_2O_2). The seminal discovery of allylic oxygenations of alkenes by Schenck in 1953 provided a versatile method of functionalization of simple unbiased starting materials.[1–3] Over the past decades, the Schenck ene reaction (or singlet oxygen ene reaction) has been developed to great maturity with numerous synthetic applications.[3,4] Intensive mechanistic studies have led to a deeper understanding of the underlying photophysical and chemical elemental steps which involve the photo-sensitized formation of singlet oxygen $^1O_2$ and its (concerted or stepwise) insertion into allylic C-H bonds (Scheme 3.1).[2]



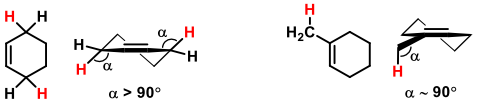
Scheme 3.1: The Schenck ene reaction.

A general intrinsic problem of the Schenck ene reaction is the low regioselectivity and stereoselectivity with many substrates despite the observation of various stereoelectronic neighbouring group effects.[2] Cyclohexenes – one of the most easily accessible and highly versatile class of alkene building blocks – exhibit especially poor reactivity in Schenck ene reactions.[5] Furthermore, only very few cases of good regio/stereocontrol were reported for cyclohexenes with special substitution patterns or rigid skeletal frameworks (Scheme 3.2).[6–9] Here, we report a rationalization of structure-reactivity relationships of a diverse set of cyclohexenes based on conformational analysis. This led to a significant expansion of the scope of photooxygenations by the employment of stereoelectronically tailored yet easily accessible cyclohexenes to give *trans*-amidoalcohol derivatives of great synthetic utility.



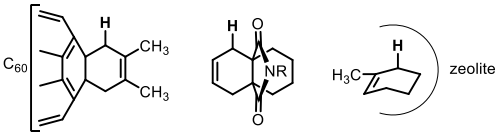
Scheme 3.2: Schenck ene reactivity of alkenes (top)[6]; selected examples of cyclohexene reactions (bottom).[7–10]

Several cyclohexenes are inert under Schenck ene conditions in the presence of singlet oxygen. The low reactivity of cyclohexene derivatives void of double bond substituents was already observed very early. On the other hand, 1-methylcyclohexenes readily react *via* exocyclic H atom abstraction from the methyl group. This is most likely a direct consequence of the ring strain and the hindered rotation of the endocyclic C-H moiety which prevents the population of a reactive conformation with nearly orthogonal C=C/C-H bonds.[11] Such structural reorganization is easily realized by the exocyclic methyl substituent (Scheme 3.3).



Scheme 3.3: Comparison of geometries of the hydrogens abstracted by $^1O_2$ in the Schenck ene reaction.

The only reported cases of *endo*-selective photooxygenations of cyclohexenes (i.e. at the ring position (*endo*) rather than alkyl substituent (*exo*)) involved substrates in the boat-conformation. Such steric bias was mostly produced by a *cis*-ring annulation which forces the reactive allylic H atoms in orthogonal arrangement with the alkene plane. Examples include the Schenck ene reactions of fullerene-anellated cyclohexenes,[12] constrained *cis*-decalines,[8] or 1-methyl-cyclohexene in zeolite confinement[13] (Scheme 3.4).



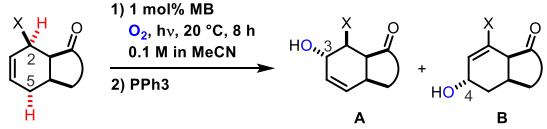
Scheme 3.4: Literature known *endo*-reactive cyclohexenes with boat-like ground state conformations.

3.2. Results and Discussion

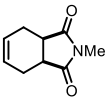
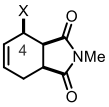
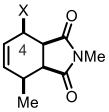
Oxygenation of *cis*-anellated cyclohexenes

Based on the assumption that conformational control of the endocyclic CH bonds will be decisive for the reactivity of cyclohexenes in Schenck ene oxygenations, we have performed a combined conformational and experimental analysis of a diverse series of cycloalkenes. Consistent with earlier reports, simple cyclohexene derivatives without alkyl substitution of the double bond exhibited only very low reactivity. Under standard conditions, we could not observe considerable conversion of *N*-(cyclohex-2-en-1-yl)acetamide, diethyl cyclohex-4-ene-1,2-*cis*-dicarboxylate, and ethyl *cis*-2-acetamido-cyclohex-3-ene-1-carboxylate, respectively. We then turned our attention to the synthesis of *cis*-anellated cyclohexenes which appeared to be a privileged substrate class for Schenck ene reactions due to the accessibility of reactive conformations (*vide supra*). Such substrates can be easily prepared from Diels-Alder reactions of various combinations of dienes and cyclic dienophiles.[14] We prepared a selection of various *cis*-anellated cyclohexene derivatives by *endo*-Diels-Alder reactions and evaluated their activity in Schenck ene photooxygenations with 1 mol% methylene blue as sensitizer in acetonitrile solution at room temperature (Table 3.1). Indeed, comparatively rapid conversions were observed for all substrates of this study; however, the unsubstituted cyclohexene derivatives gave unidentifiable mixtures of several polymeric and isomeric products (entries 1 – 3). Interestingly, 4-substituted tetrahydroisoindole-1,3-diones exhibited high reactivity and diastereoselectivity (entries 4 – 11). Highly regioselective and stereoselective photooxygenations were observed with the corresponding 4-amido derivatives (entries 7 – 9). As amides are known, to deactivate singlet oxygen physically, amido- instead of free amino-moieties were introduced.

Table 3.1: Photooxidation of *cis*-anellated cyclohexenes. [a]



	Substrate	R	A / B	Yield (Conv.) [b]
1			polymer formation	n.d.

2			mixture of regio/stereo isomers	96
3			mixture of stereo isomers	82
4		CO_2Et	3.5 / 1	69 (75) [c]
5		OAc	1 / 2	11 (15)
6		$NHCO_2Et$	1 / 1	87 [d]
7		NHAc	**>25 / 1**	74 [d]
8		**NMeAc**	**>25 / 1**	79 (90) [d]
9		NHAc	>25 / 1	66 [c]
10		CH_2OH	1 / 1.7	99
11		C(O)*t*Bu	1 / 1.5	57 [d]

[a] General procedure: 1 mmol cyclohexene, 1 mol% methylene blue, 10 mL MeCN, r.t., 8 h, then 1.25 mmol PPh_3, MeCN, r.t., 1 h; [b] isolated yields [%], conversion [%] in parentheses if not >95%; [c] 72 h ; [d] 48 h.

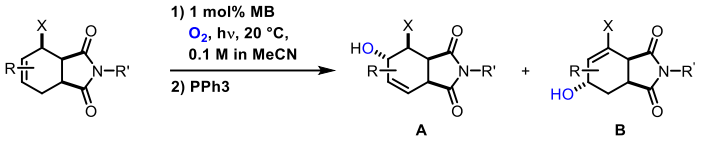
Oxygenation of 4-substituted *cis*-anellated cyclohexenes

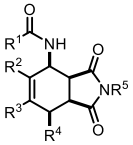
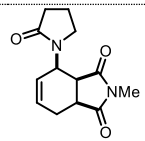
We then successfully extended this concept to a diverse family of anellated amidocyclohexenes (Table 3.2). Variations of the substituents R^3 and R^4 did not result in a decrease of the regioselectivity (entries 2 – 6). Phenyl-, and linear alkyl-substituents could be introduced, without any impact on the selectivity and even a connection of the two positions by a C_2H_4-bridge (entry 10) was tolerated. The introduction of substituents R^2 allowed the synthesis of tertiary alcohol derivatives. However, with increasing size of R^2, formation of the 1,3-bifunctional regioisomer became favourable (entries 7 – 9). This change in regioselectivity can be explained by the growing influence of the so-called *gem*-effect with increasing bulkiness of the substituent.[2]

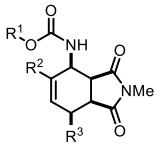
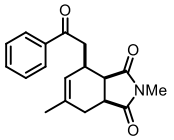
For the vast majority of carbamates (entries 15 – 19), the 1,2-bifunctional regioisomer was favourable, with a varying excess of the major isomer, depending on the substitution pattern.

The reaction times to achieve full conversion varied from 48 h – > 72 h for 4-substituted cyclohexenes. Modifications of the amide moiety resulted in a decrease of reactivity (entries 12, 14 and Table 3.1, entry 8), whereas the regioselectivity was not effected. Moderate to good yields could be achieved for the major part of the substrates, despite the strong polarity of the products and the therefore difficult separation of methylene blue and triphenylphosphine oxide.

Table 3.2: Substrate scope and regioselectivity of photooxygenations[a]



	Substrate	Substituents	A/B	yield (conv.)[b]
1		R^1 = R^2 = Me, R^3 = R^4 = H, R^5 = Me	>25 / 1	68
2		R^1 = Me, R^2 = H, R^3 = Me, R^4 = H, R^5 = Me	>25 / 1	76
3		R^1 = R^2 = Me, R^3 = H, R^4 = R^5 = Me	>25 / 1	76
4		R^1 = Me, R^2 = R^3 = H, R^4 = C_2H_5, R^5 = Me	>25 / 1	51
5		R^1 = Me, R^2 = R^3 = H, R^4 = *n*-C_6H_{13}, R^5 = Me	>25 / 1	61
6		R^1 = Me, R^2 = H, R^3 = Ph, R^4 = H, R^5 = Me	>25 / 1	82 (90)
7		R^1 = Me, R^2 = *n*-C_4H_9, R^3 = H, R^4 = *n*-C_4H_9, R^5 = Me	1.1 / 1	65
8		R^1 = Me, R^2 = Ph, R^3 = H, R^4 = *i*-Pr, R^5 = Me	1 / 1.3	70
9		R^1 = Me, R^2 = *i*-Pr, R^3 = H, R^4 = *i*-Pr, R^5 = Me	1 / >25	67 (80)
10		R^1 = Me, R^2 = H, R^3-R^4 = -$(CH_2)_4$-, R^5 = Me	>25 / 1	65
11		R^1 = Me, R^2 = R^3 = R^4 = R^5 = H	>25 / 1	42 [c]
12		R^1 = Ph, R^2 = R^3 = R^4 = H, R^5 = Me	>25 / 1	23 (55)
13		R^1 = Me, R^2 = R^3 = R^4 = H, R^5 = Ph	>25 / 1	65
14			>25 / 1	25 (55)

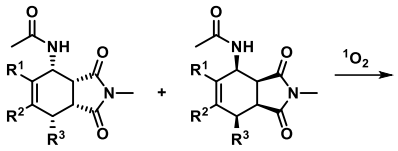
15		$R^1 = R^2 = R^3 = Me$	5 / 1	76
16		$R^1 = Et$, $R^2 = R^3 = Me$	6 / 1	83
17		$R^1 = Bn$, $R^2 = R^3 = Me$	5 / 1	81
18		$R^1 = Me$, $R^2 = R^3 = H$	>25 / 1	62
19		$R^1 = Bn$, $R^2 = R^3 = H$	>25 / 1	45
20			2 / 1	75

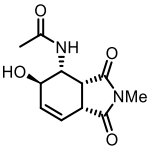
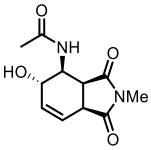
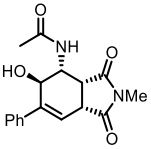
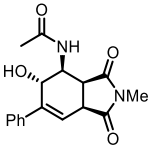
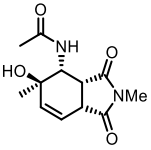
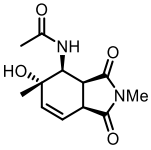
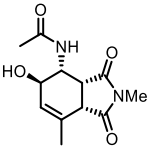
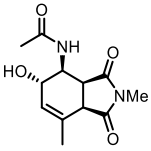
[a] General procedure: 1 mmol cyclohexene, 1 mol% methylene blue, 10 mL MeCN, r.t., 8 h, then 1.25 mmol PPh_3, MeCN, r.t., 1 h; [b] isolated yields [%], conversion [%] in parentheses if not >95%; [c] 72 h ; [d] 48 h.

Oxygenation of separated enantiomers

For a series of 4-amido substituted cyclohexenes, the enantiomers were separated by preparative chiral HPLC and each enantiomer was oxidized separately. The fact that each enatiomerically pure starting material delivered only one oxidation product with an enantiomeric excess of > 99 %, points out the excellent stereoselectivity of the photooxygenation of the presented *cis*-anellated cyclohexenes.

Table 3.3: Photo-oxidations of enantiopure cyclohexenes. [a]



	Product 1 *e.e.* [b]	Product 2 *e.e.* [b]
1	 > 99	 > 99
2	 > 99	 > 99
3	 > 99	 > 99
4	 > 99	 > 99

[a] General procedure: 40 mg of racemic cyclohexene, 1 mM methylene blue, MeCN (2 mL), 10 °C, then 55 mg PPh_3, MeCN, r.t., 1 h. Isolated yields of each enantiomer 55 – 90 %. [b] enantiomeric excess (*e.e.*) in % determined by chiral HPLC.

3.3. DFT calculations

A conformational analysis of the compounds studied in this work revealed that mostly two stable conformers were possible: *endo*- and *exo*-structures (Figure 3.1). The *exo*-conformers led to formation of the all-*syn* oxygenation products, while the *endo*-conformers gave the *anti*-products.

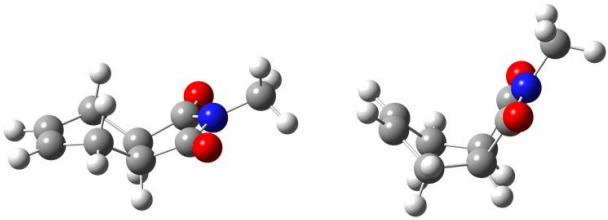
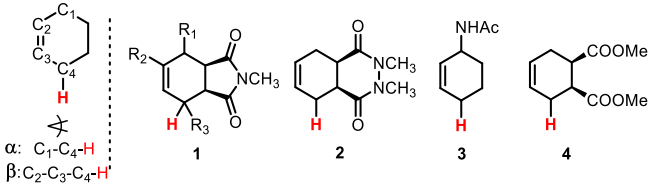


Figure 3.1: *Exo*- and *endo*-conformers for compound **1a**.

The results of the conformational analysis of selected compounds are summarized below (Table 3.4). In full accord with previous observations, the conformer geometry is key to a high *endo*-reactivity. All compounds which reacted in Schenck ene reaction under our conditions, fulfilled two criteria which rendered the allylic C-H bond susceptible to the attack by $^1O_2$: the angle α is smaller than 91° and the dihedral angle β is larger than 80°. On the other hand, all the unreactive compounds exhibit values beyond these ranges (α > 112° and β > 106°). This simple model allows predictions to be made concerning the reactivity of cyclohexene systems under standard reaction conditions. The only substrate that did not follow this rule is the *exo* conformer of **1b**. We suspect this inconsistency to be of kinetic origin. An elucidation would require a more detailed computational study. Compounds **1a** and **1b** were subjected to series of DFT calculations (Scheme 3.5).

Table 3.4: Structure-reactivity relationship based on conformational analysis.



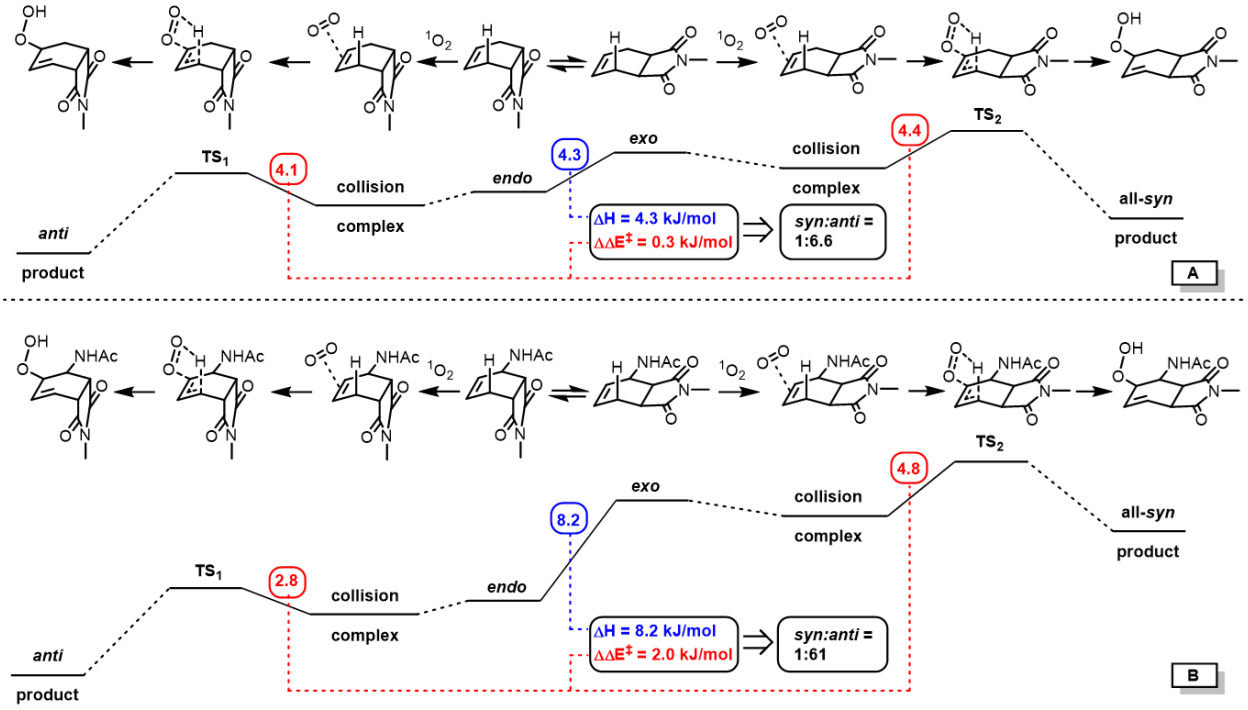
Substrate	R	Conformer	α	β	Reactivity [a]
1a	$R^1=R^2=R^3=H$	*exo*	88.8	76.9	+
		endo	91.0	79.4	+

1b	R^1=NHAc, R^2=R^3=H	*exo*	90.1	78.6	-
		endo	88.8	77.1	+
1c	R^1=NHAc, R^2=R^3=Me	*exo*	149.1	155.3	-
		endo	78.1	64.7	
1d	R^1=$NHCO_2Me$, R^2=R^3=H	*exo*	112.2	117.6	-
		endo	88.7	76.8	
2	-	- [b]	118.7	112.6	-
3	-	- [b]	113.7	107.0	-
4	-	- [b]	113.6	106.6	-

[a] a plus sign (+) denotes conversion and product formation of > 20% under standard conditions; [b] only one stable conformer found; critical angles α and β, are defined in the scheme. The positions of H abstraction by *endo*-attack of $^1O_2$ are highlighted.

For the DFT model, the following mechanism was used: both of the rapidly equilibrating conformers can undergo barrierless collision with singlet oxygen, leading to collision complex. This is then transformed to the peroxide product *via* a perepoxide-like transition state.[15] The ratio of *syn*/*anti*-products is affected by the equilibrium between conformers and the activation barriers of H abstraction. The predicted *syn*:*anti* ratios of **1a** and **1b** were 1:6.6 and 1:61, respectively.

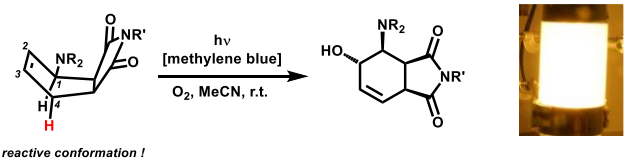
The obtained values correlate well with experimental data (6.6 *vs.* 5 for **1a** and 61 *vs.* >25 for **1b**). Moreover, we can explain the apparent inertness of the *exo*-conformer of **1b** – equilibrium is on the side of *endo*-conformer, and while the activation barrier for the hydrogen abstraction from the *exo*-conformer is relatively low, reaction is mainly controlled by the rapid equilibration of conformers, which ensures that only traces of *syn*-product are formed from **1b**. The activation energies of H abstraction are lower than 5 kJ/mol for the reactive cyclohexenes. In contrast, we have estimated the activation barriers of the Schenck ene reactions of **3** and **2** to be 16 kJ/mol and 12 kJ/mol, respectively. Cyclohexenes **2**, **3**, and **4** show a chair-like ground state conformation. The lack of geometric pre-ordering for the H abstraction in this case, as predicted by the simple geometrical model, leads to significantly increased activation barriers. Here, $^1O_2$ deactivation pathways are more rapid than the Schenck ene reaction so that no conversion of cyclohexenes was observed.



Scheme 3.5: Reaction profile of photooxygenation of **1a** (part A) and **1b** (part B). Energies are given in kJ/mol.

3.4. Conclusion

A combined experimental and theoretical structure-reactivity study of a diverse set of cyclohexenes in photooxygenations was performed. Simple bicyclic Diels-Alder adducts have been shown to undergo highly regioselective and stereoselective Schenck ene oxygenations with singlet oxygen to give versatile *trans*-amidoalcohol derivatives. Conformational analyses document the critical role of boat-like ground state conformations with an optimal value of the C_1-C_4-H angle $\alpha < 91°$ and the dihedral C_2-C_3-C_4-H angle $\beta > 80°$. In summary, it can be ascertained that the boat-conformation is the key for the reactivity and the *endo*-conformation is responsible for the stereoselectivity of *cis*-anellated cyclohexenes.



3.5. Experimental Section

General

Chemicals and Solvents

If not indicated, commercial reagents were used without purification.

Analytical thin-layer chromatography

TLC was performed using aluminium plates with silica gel and fluorescent indicator (Merck, $60F_{254}$). Thin layer chromatography plates were visualized by exposure to UV light and/or by immersion in an aqueous staining solution of $KMnO_4$ or in an ethanolic solution of molybdophosphoric acid.

Column chromatography

Flash column chromatography with silica gel 60 Å (220-240 mesh) from *Acros*. Pentane, hexanes or mixtures thereof with ethyl acetate were used as eluents.

Gas chromatography with mass-selective detector

Agilent 6890N Network GC-System, mass detector 5975 MS. Column: BPX5 (30 m x 0.25 mm x 0.25, from *SGE*, carrier gas: H_2.
Standard heating procedure: 50 °C (2 min), 25 °C/min --> 300 °C (5 min).

Gas chromatography with FID

Agilent 7820A GC-Systems. Column: HP 5 19091J 413 (30 m x 0.32 mm x 0.25 µm) from *Agilent*, carrier gas: N_2. GC-FID was used for catalyst screening (Calibration with internal standard *n*-pentadecane and analytically pure samples).

NMR

^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on *Bruker* Avance 300 (300 MHz ^{1}H; 75 MHz ^{13}C) and *Bruker* Avance 400 (400 MHz ^{1}H, 101 MHz ^{13}C) spectrometers. Chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hertz (Hz). Following abbreviations are used for spin multiplicities:
s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, ddt = doublet of doublet of triplet. For yield determinations, *n*-pentadecane was used as internal standard.

IR spectroscopy

Infrared spectra were recorded on a *Varian* Scimitar 1000 FT-IR equipped with a ATR unit or on an *Agilent* Cary 630 FTIR equipped with a ATR unit. Wavenumbers are indicated in cm^{-1}. Intensive absorption bands are indicated with „s“ (strong), medium bands with „m“ (medium), and weak bands with „w“ (weak).

High resolution mass spectrometry (HRMS)

The spectra were recorded by the Central Analytics Lab at the Department of Chemistry, University of Regensburg, on a MAT SSQ 710 A from *Finnigan*.

Chiral HPLC (semi preparative):

Racemic substances were separated by a semi preparative HPLC system P680HPLC (pump), Daicel Chiralpak AS-H, 20 × 250 mm (column), UVD170S (detector). Mixtures of hexane with isopropanol were used as eluents with a flow rate of 15 mL/min. The exact eluents are described for each compound.

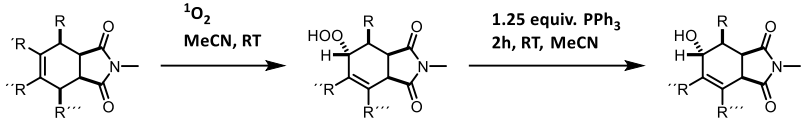
Chiral HPLC (analytical):

Enantiomeric excesses (ee) were controlled by chiral HPLC using *Dionex* Ultimate 3000, LPG3400SD (pump), WPS3000(RS) (auto sampler), TCC3x00(RS) (column ofen) und DAD3000 (detector). Mixtures of hexane with isopropanol were used as eluents with a flow rate of 1 mL/min. The exact eluents and columns are described for each compound.

Specific Rotation:
Rotation angles (specific rotation TC) were measured by an *Anton Paar* polarimeter MCP 500 in DCM at 20.0 °C.

3.6. Supporting Information

Photooxidation reactions (GP-3.1):



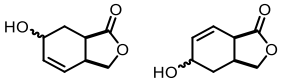
Cyclohexene (1.0 mmol, 1.0 equiv.) was diluted in 10 mL of a solution of Methylene blue (2×10^{-4} M) in Acetonitrile. Pure oxygene was bubbled through the solution while irradiating with white LEDs (6 × *Cree* MK-R, warm white, 700 mA) for 24 to 72 h. The reaction mixture was transfered to a round bottom flask. Triphenylphosphine (327.5 mg, 1.25 mmol, 1.25 equiv.) was added and the solution was stirred for 2 h at RT. The solvent was removed under reduced pressure and the crude product was purified by column chromatography.
The exact eluents and yields are described for each compound.

Components for photo oxidation in batch: Peristaltic pump (*Heidolph* Pumpdrive 5001), O_2 (*Linde 4.6, 200 bar)*, LEDs (6 × *Cree Xlamp* MK-R, warm white), syringe pump (*Landgraf Laborsysteme* LA120)

Oxidation products:

Oxidation reactions according to GP-3.1

6-Hydroxy-3a,6,7,7a-tetrahydroisobenzofuran-1(3*H*)-one and 5-Hydroxy-3a,4,5,7a-tetrahydroisobenzofuran-1(3*H*)-one



$C_8H_{10}O_3$, 154.17 g/mol

6-Hydroxy-3a,6,7,7a-tetrahydroisobenzofuran-1(3*H*)-one and 5-Hydroxy-3a,4,5, 7a-tetrahydroisobenzofuran-1(3*H*)-one were synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (100 % --> 97 % DCM).

Yield: 96 %

TLC: R_f (DCM/MeOH = 95/5) = 0.27

Condition: colourless amorphous solid (mixture of different regio- and stereoisomers)

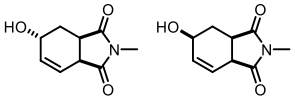
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.16 – 5.77 (m, 3H), 5.77 – 5.53 (m, 1H), 4.52 – 4.18 (m, 4H), 4.18 – 3.96 (m, 2H), 3.17 – 3.03 (m, 2H), 3.03 – 2.72 (m, 2H), 2.57 – 2.34 (m, 1H), 2.23 – 2.07 (m, 1H), 1.94 – 1.84 (m, 3H), 1.84 – 1.61 (m, 1H), 1.51 (td, *J* = 12.5, 9.7 Hz, 1H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 179.6, 178.5, 176.3, 135.2, 134.7, 133.1, 132.5, 132.2, 132.1, 131.5, 128.8, 128.7, 126.9, 126.6, 123.9, 121.8, 71.8, 71.4, 71.3, 70.5, 65.4, 63.1, 62.7, 61.9, 40.2, 40.0, 37.6, 36.7, 36.6, 36.0, 35.1, 34.2, 33.4, 31.7, 29.8, 29.3, 28.9

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3399, 2915, 1752, 1677, 1480, 1438, 1379, 1305, 1204, 1174, 1036, 1010, 977, 861, 779, 723, 678

HR-MS (ESI): $[MH]^+$ = 155.0702; calculated: 155.0703

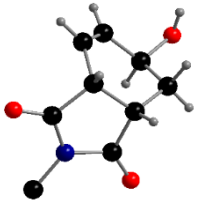
5-Hydroxy-2-methyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione



$C_9H_{11}NO_3$, 181.0739 g/mol

5-Hydroxy-2-methyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione was synthesized according to GP-3.1 (reaction time = 8 h) and purified by column chromatography using a mixture of PE and EA (33 % --> 66 % EA).

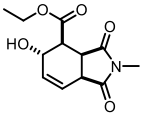
Yield: 82 % (ratio 8/1); (crude product ratio = 5/1)
Condition: pale yellow amorphous solid
TLC: R_f = 0.31 (PE/EA = 1/2)
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.12 (ddd, *J* = 9.9, 4.0, 2.2 Hz, 0.13H), 6.07 – 5.95 (m, 1.12H), 5.89 (ddd, *J* = 10.1, 4.2, 1.8 Hz, 1H), 4.37 – 4.31 (m, 0.12H), 4.22 – 4.07 (m, 1H), 3.53 – 3.40 (m, 1.12H), 3.21 (dt, *J* = 8.0, 5.7 Hz, 1H), 3.12 – 3.00 (m, 0.14H), 2.98 (s, 0.33H), 2.96 (s, 3H), 2.44 (dt, *J* = 13.1, 4.9 Hz, 1H), 1.76 (ddd, *J* = 13.1, 9.0, 6.1 Hz, 1.18H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 178.7, 176.6, 134.9, 122.8, 62.5, 40.9, 36.8, 29.9, 25.0.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3429, 2945, 1766, 1670, 1435, 1383, 1338, 1282, 1129, 1062, 1006, 828, 716
HR-MS (ESI): $[MH]^+$ = 182.0810 ; calculated: 182.0817
X-ray:



major product	
Chemical formula	$C_9H_{11}NO_3$
Formula weight	181.19
Temperature / K	297.6(3)
Wavelength / Å	1.54184
Crystal system, space group	monoclinic, $P2_1/c$
a / Å	11.9439(10)
b / Å	7.1381(4)
c / Å	20.4307(15)
α / °	90
β / °	90.180(8)
γ / °	90
V / Å^3	1741.8(2)
ρ_{calcd} / g·cm^{-3}	1.382
F(000)	768
Crystal size / mm	0.43 × 0.40 × 0.31
Z	8
Max. and min. transmission	0.977, 0.967
μ / mm^{-1}	0.873
θ range / °	4.328 – 73.807

	–14≤*h*≤14
Index ranges	–8≤*k*≤7
	–25≤*l*≤25
Total / unique reflections	10917 / 3441
Data / restraints / parameters	3441 / 2 / 254
R_{int}	0.0235
R_1, wR_2 [I≥2σ(I)]	0.0500, 0.1394
R_1, wR_2 (all data)	0.0579, 0.1465
Goodness-of-fit *S* on F^2	1.058
Largest diff. peak and hole / eÅ^{-3}	0.334, –0.179
Absolute structure parameter	–

Ethyl-5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindole-4-carboxylate



$C_{12}H_{15}NO_5$, 253.2540 g/mol

Ethyl-5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindole-4-carboxylate was synthesized according to GP-3.1 (reaction time = 72 h) and purified by column chromatography using a mixture of DCM and MeOH (99 % --> 97 % DCM)

Yield: 54 %

Condition: pale yellow solid

m.p.: 105 – 110 °C

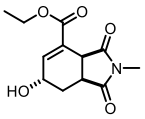
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 5.96 (dt, *J* = 10.1, 1.8 Hz, 1H), 5.81 (ddd, *J* = 10.1, 3.9, 2.4 Hz, 1H), 4.44 (ddd, *J* = 9.7, 4.2, 2.3 Hz, 1H), 4.40 – 4.22 (m, 2H), 3.74 (dd, *J* = 7.9, 5.2 Hz, 1H), 3.68 – 3.55 (m, 1H), 2.95 (s, 3H), 2.64 (dd, *J* = 9.7, 5.2 Hz, 1H), 1.43 – 1.25 (m, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 176.5, 176.0, 172.4, 133.9, 122.4, 63.6, 61.8, 45.4, 43.0, 39.6, 25.1, 14.2.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3442 (w), 2977 (w), 1782 (w), 1694 (s), 1434 (m), 1384 (m), 1319 (m), 1280 (m), 1253 (m), 1192 (s), 1092 (m), 1018 (m), 976 (w), 924 (w), 877 (w), 812 (w), 722 (m), 699 (w), 583 (m)

HR-MS (ESI): $[MH]^+$ = 254.1025 ; calculated: 254.1028

Ethyl-6-hydroxy-2-methyl-1,3-dioxo-2,3,3a,6,7,7a-hexahydro-1*H*-isoindole-4-carboxylate



$C_{12}H_{15}NO_5$, 253.2540 g/mol

Ethyl-6-hydroxy-2-methyl-1,3-dioxo-2,3,3a,6,7,7a-hexahydro-1*H*-isoindole-4-carboxylate was synthesized according to GP-3.1 (reaction time = 72 h) and purified by column chromatography using a mixture of DCM and MeOH (99 % --> 97 % DCM)

Yield: 15 %

Condition: pale yellow solid

m.p.: 121 °C decomp.

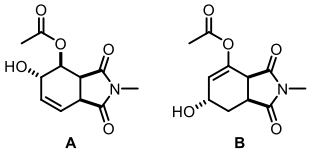
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.12 – 6.99 (m, 1H), 4.43 – 4.23 (m, 2H), 4.23 – 4.06 (m, 2H), 3.37 – 3.19 (m, 1H), 2.95 (s, 3H), 2.64 – 2.50 (m, 1H), 1.76 – 1.55 (m, 1H), 1.41 – 1.27 (m, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 178.6, 175.2, 173.5, 165.6, 144.8, 132.3, 128.7, 126.7, 63.6, 61.7, 39.6, 36.9, 30.8, 25.3, 14.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3463 (w), 2982 (w), 2941 (w), 1777 (w), 1669 (s), 1435 (m), 1383 (m), 1282 (m), 1244 (s), 1106 (m), 1039 (m), 1004 (m), 735 (w), 625 (w), 592 (w), 542 (w), 496 (w)

HR-MS (ESI): $[MH]^+$ = 254.1024 ; calculated: 254.1028

5-Hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl acetate and 6-Hydroxy-2-methyl-1,3-dioxo-2,3,3a,6,7,7a-hexahydro-1*H*-isoindol-4-yl acetate



A B

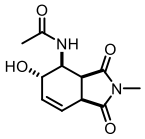
$C_{11}H_{13}NO_5$, 239.23 g/mol

5-Hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl acetate (A) and 6-Hydroxy-2-methyl-1,3-dioxo-2,3,3a,6,7,7a-hexahydro-1*H*-isoindol-4-yl acetate (B) were synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (45 % --> 70 % EA)

Yield: 11 % (A + B, ratio A/B = 1/1); conversion: 15 %

Condition: colourless amorphous solid
TLC: R_f = 0.09 (PE/EA = 2/1)
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.16 (dd, *J* = 10.5, 3.7 Hz, 1H), 5.99 (ddd, *J* = 10.0, 4.3, 2.5 Hz, 1H), 5.82 – 5.66 (m, 2H), 5.17 (t, *J* = 5.2 Hz, 1H), 4.47 – 4.22 (m, 3H), 3.81 – 3.68 (m, 2H), 3.63 (dd, *J* = 8.4, 5.0 Hz, 1H), 3.57 – 3.47 (m, 1H), 3.43 – 3.23 (m, 2H), 2.98 (s, 3H), 2.97 (s, 6H), 2.55 – 2.33 (m, 2H), 1.82 (ddd, *J* = 13.4, 8.7, 6.1 Hz, 3H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 177.9, 142.6, 132.2, 128.6, 124.6, 122.2, 70.8, 62.96, 41.6, 40.9, 37.7, 29.8, 25.3, 21.2.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3466, 2938, 1752, 1677, 1439, 1375, 1282, 1207, 1088, 1036, 1003, 935, 880, 805, 782, 749, 723
HR-MS (ESI): $[MH]^+$ = 240.0869; calculated: 240.0866

***N*-(5-Hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

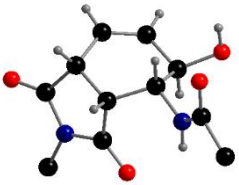


$C_{11}H_{14}N_2O_4$, 238.2430 g/mol

N-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (99 % --> 97 % DCM)

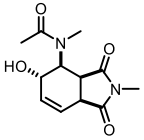
Yield: 74 %
Condition: pale yellow solid
m.p.: 168 °C
TLC: R_f (EA) = 0.14
^{1}H NMR: (400 MHz, DMSO) δ = 7.61 (d, *J* = 8.8 Hz, 1H), 5.92 – 5.83 (m, 1H), 5.83 – 5.70 (m, 1H), 5.20 (s, 1H), 4.15 – 4.01 (m, 1H), 3.92 – 3.72 (m, 1H), 3.62 – 3.52 (m, 1H), 3.45 (dd, *J* = 8.1, 5.9 Hz, 1H), 2.77 (s, 3H), 1.82 (s, 3H).
^{13}C NMR: (101 MHz, DMSO) δ = 177.0, 176.2, 169.1, 132.5, 123.3, 64.1, 49.1, 41.5,24.3, 22.6.
HR-MS (ESI): $[MH]^+$ = 239.1025 ; calculated: 239,1026
Chirale HPLC: Daicel Chiralpak, AS-H, 250x4.6; hexane/isopropanol = 50/50, 1 mL/min, ret. time enantiomere 1: 9.40 min (50 %), ret. time enantiomere 2: 24.94 min (50 %), detection wavelength: 210 nm

X-ray:



Chemical formula	$C_{11}H_{14}N_2O_4$
Formula weight	238.24
Temperature / K	123.00(10)
Wavelength / Å	1.54184
Crystal system, space group	orthorhombic, *Pbca*
a / Å	11.8941(4)
b / Å	6.8794(2)
c / Å	27.1903(9)
α / °	90
β / °	90
γ / °	90
V / Å^3	2224.83(12)
ρ_{calcd} / g·cm^{-3}	1.423
F(000)	1008
Crystal size / mm	0.12 × 0.07 × 0.02
Z	8
Max. and min. transmission	0.998, 0.992
μ / mm^{-1}	0.921
θ range / °	4.940 – 73.337
Index ranges	–14≤*h*≤10 –8≤*k*≤8 –33≤*l*≤29
Total / unique reflections	6710 / 2202
Data / restraints / parameters	2202 / 0 / 161
R_{int}	0.0272
R_1, wR_2 [I≥2σ(I)]	0.0389, 0.0898
R_1, wR_2 (all data)	0.0544, 0.0981
Goodness-of-fit *S* on F^2	1.065
Largest diff. peak and hole / eÅ^{-3}	0.216, –0.192
Absolute structure parameter	–

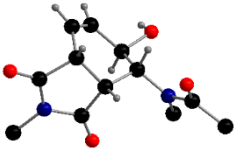
_N_-(5-Hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)-_N_-methylacetamide



$C_{12}H_{16}N_2O_4$, 252.27 g/mol

_N_-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)-_N_-methyl-acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (100 % --> 96 % DCM)

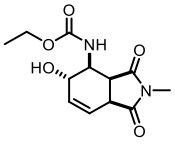
Yield:	79 %
Condition:	colourless crystalline solid
m.p.:	115 – 120 °C
^{1}H NMR:	(300 MHz, $CDCl_3$) δ = 6.02 – 5.92 (m, 1H), 5.74 (ddd, _J_ = 10.0, 3.6, 2.0 Hz, 1H), 4.41 (dd, _J_ = 11.0, 5.1 Hz, 1H), 4.36 – 4.27 (m, 1H), 3.70 – 3.62 (m, 1H), 3.51 (dd, _J_ = 7.6, 5.1 Hz, 1H), 3.24 (s, 3H), 2.91 (s, 3H), 2.15 (s, 3H).
^{13}C NMR:	(75 MHz, $CDCl_3$) δ = 176.8, 176.0, 172.9, 135.3, 122.6, 63.6, 55.8, 44.5, 41.0, 33.2, 25.0, 22.9.
FT-IR (ATR):	$\tilde{\nu}$ [cm^{-1}] = 3440, 2933, 1770, 1692, 1618, 1432, 1375, 1282, 1219, 1077, 1107, 1036, 977, 924, 861, 805, 768 701
HR-MS (ESI):	$[MH]^+$ = 253.1182 ; calculated: 253.1188
X-ray:	



Chemical formula	$C_{12}H_{16}N_2O_4$
Formula weight	252.27
Temperature / K	123.00(10)
Wavelength / Å	1.54184
Crystal system, space group	monoclinic, $P2_1/n$
_a_ / Å	6.4789(2)
_b_ / Å	29.8623(7)
_c_ / Å	6.9850(2)
α / °	90
β / °	115.182(4)
γ / °	90
V / Å^3	1222.98(7)
ρ_{calcd} / g·cm^{-3}	1.370
_F_(000)	536

Crystal size / mm	0.34 × 0.30 × 0.23
Z	4
Max. and min. transmission	0.964, 0.948
μ / mm^{-1}	0.867
θ range / °	5.927 – 73.282
Index ranges	$-6 \leq h \leq 7$ $-31 \leq k \leq 36$ $-8 \leq l \leq 8$
Total / unique reflections	6709 / 2364
Data / restraints / parameters	2364 / 0 / 168
R_{int}	0.0115
R_1, wR_2 [I≥2σ(I)]	0.0402, 0.1035
R_1, wR_2 (all data)	0.0423, 0.1049
Goodness-of-fit S on F^2	1.039
Largest diff. peak and hole / $eÅ^{-3}$	0.596, –0.235
Absolute structure parameter	–

Ethyl-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate



$C_{12}H_{16}N_2O_5$, 268.2690 g/mol

Ethyl-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (50 % --> 60 % EA)

Yield: 45 %

Condition: colourless crystalline solid

TLC: R_F (PE/EA = 1/2) = 0.51

m.p.: 111 – 115 °C

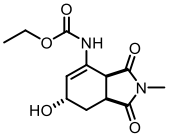
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 5.96 (dt, *J* = 10.1, 1.8 Hz, 1H), 5.81 (ddd, *J* = 10.1, 4.0, 2.4 Hz, 1H), 4.44 (ddd, *J* = 9.7, 4.2, 2.3 Hz, 1H), 4.39 – 4.14 (m, 2H), 3.73 (dd, *J* = 7.9, 5.2 Hz, 1H), 3.62 (dtd, *J* = 6.2, 4.2, 2.2 Hz, 1H), 2.93 (s, 3H), 2.70 – 2.57 (m, 1H), 1.33 (td, *J* = 7.1, 0.5 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 176.5, 176.0, 172.4, 133.9, 122.4, 63.6, 61.8, 45.4, 42.9, 39.6, 25.1, 14.2.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3515 (m), 3039 (w), 2978 (w), 2932 (w), 2858 (w), 1776 (w), 1722 (s), 1689 (s), 1440 (m), 1384 (m), 1309 (m), 1277 (m), 1198 (s), 1094 (s), 1071 (m), 1015 (s), 921 (m), 872 (m), 812 (m), 694 (m), 661 (m), 578 (s), 533 (m), 475 (w)

HR-MS (ESI): $[MH\text{-}CH_3]^+$ = 254.1046; calculated: 254.0897

Ethyl-(6-hydroxy-2-methyl-1,3-dioxo-2,3,3a,6,7,7a-hexahydro-1*H*-isoindol-4-yl)carbamate



$C_{12}H_{16}N_2O_5$, 268.2690 g/mol

Ethyl-(6-hydroxy-2-methyl-1,3-dioxo-2,3,3a,6,7,7a-hexahydro-1*H*-isoindol-4-yl)carbamate was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (50 % --> 60 % EA)

Yield: 42 %

Condition: colourless amorphous solid

TLC: R_F (PE/EA 1/2) = 0.42

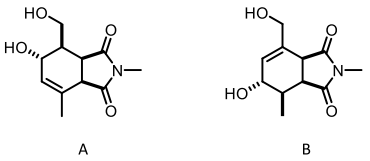
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.15 – 6.96 (m, 1H), 4.40 – 4.24 (m, 2H), 4.24 – 4.09 (m, 2H), 3.44 – 3.16 (m, 1H), 2.95 (d, *J* = 8.1 Hz, 3H), 2.69 – 2.46 (m, 1H), 1.73 – 1.54 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 178.6, 175.2, 165.5, 144.7, 126.8, 63.7, 61.7, 53.6, 39.6, 36.9, 30.9, 25.3, 14.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3446 (w), 1980 (w), 2943 (w), 1777 (w), 1686 (s), 1436 (m) 1383 (m), 1282 (m), 1246 (m), 1106 (m), 1040 (w), 1005 (m), 734 (w), 626 (w), 592 (w), 541 (w) 494 (w)

HR-MS (ESI): $[MH\text{-}CH_3]^+$ = 254.1024; calculated: 254.0897

5-Hydroxy-4-(hydroxymethyl)-2,7-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and 5-hydroxy-7-(hydroxymethyl)-2,4-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione



A B

$C_{11}H_{15}NO_4$, 225.2440 g/mol

5-hydroxy-4-(hydroxymethyl)-2,7-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (A) and 5-hydroxy-7-(hydroxymethyl)-2,4-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (B) were synthesized according to GP-3.1 (reaction time = 8 h) and purified by column chromatography using a mixture of DCM and MeOH (97 % DCM)

Yield: 99 % (ratio 1/1.7)

Condition: colourless amorphous solid

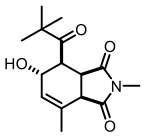
^{1}H NMR: (300 MHz, $CDCl_3$) (A) δ = 5.69 (dd, *J* = 2.9, 1.4 Hz, 1H), 4.32 – 4.03 (m, 3H), 3.40 (d, *J* = 7.6 Hz, 1H), 3.33 – 3.15 (m, 1H), 2.96 (s, 3H), 1.97 – 1.93 (m, 3H), 1.88 (dt, *J* = 15.0, 5.0 Hz, 1H).

^{13}C NMR: (75 MHz, $CDCl_3$) (A) δ = 178.9, 175.6, 131.3, 129.5, 65.3, 62.5, 47.2, 43.2, 42.5, 25.2, 21.2.

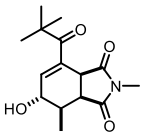
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3353 (m), 2950 (w), 2919 (w), 2890 (w), 1768 (w), 1694 (s), 1432 (m), 1386 (m), 1282 (m), 1231 (w), 1150 (w), 1115 (m), 1048 (m), 1024 (m), 955 (w), 906 (w), 794 (w), 771 (w), 727 (w), 677 (w), 597 (w), 540 (w), 480 (m)

HR-MS (ESI): $[MH]^+$ = 226.1073 ; calculated: 226.1079

5-Hydroxy-2,7-dimethyl-4-pivaloyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and 5-Hydroxy-2,4-dimethyl-7-pivaloyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione



A



B

$C_{15}H_{21}NO_4$, 279.34 g/mol

5-Hydroxy-2,7-dimethyl-4-pivaloyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (A) and 5-Hydroxy-2,4-dimethyl-7-pivaloyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (B) were synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (100 % --> 97 % DCM).

Yield: 51 % (ratio A/B = 1/1.5)

Condition: pale yellow solid

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.43 (dd, *J* = 4.1, 2.0 Hz, 1H, B), 5.70 (dt, *J* = 2.8, 1.5 Hz, 1H, A),4.45 – 4.32 (m, 1H), 4.20 (d, *J* = 8.3 Hz, 2H), 4.16 – 4.02 (m, 2H), 3.64 (dd, *J* = 8.6, 6.4 Hz, 1H), 3.42 (d, *J* = 8.6 Hz, 1H), 3.33 (dd, *J* = 8.3, 5.8 Hz, 2H), 3.16 (dt, *J* = 13.2, 8.3 Hz, 1H), 2.93 (d, *J* = 4.4 Hz,

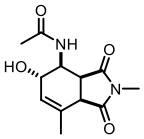
9H), 2.28 – 2.13 (m, 3H), 2.05 (t, *J* = 5.3 Hz, 5H), 1.28 (d, *J* = 6.8 Hz, 17H), 1.24 (d, *J* = 6.1 Hz, 12H), 1.06 (t, *J* = 5.8 Hz, 6H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 209.2, 177.7, 176.1, 175.4, 134.8, 132.4, 130.6, 127.8, 68.0, 64.0, 49.6, 45.5, 44.1, 41.5, 40.2, 39.6, 35.5, 28.2, 27.0, 24.9, 24.6, 21.9, 13.6

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3493, 2967, 2930, 1771, 1674, 1476, 1439, 1387, 1316, 1282, 1219, 1156, 1100, 1014, 969, 936, 790, 742, 690,

HR-MS (ESI): $[MH]^+$ = 280.1548; calculated: 280.1543

_N_-(5-Hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide



$C_{12}H_{16}N_2O_4$, 252.27 g/mol

N-(5-hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (100 % --> 97 % DCM).

Yield: 65 %

Condition: pale yellow solid

m.p.: 140 °C

TLC: R_f (EA) = 0.15

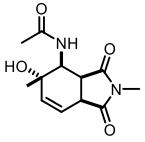
^{1}H NMR: (400 MHz, DMSO) δ = 7.61 (dd, *J* = 23.1, 7.6 Hz, 1H), 5.54 (dt, *J* = 2.8, 1.5 Hz, 1H), 5.05 (d, *J* = 5.7 Hz, 1H), 3.93 (td, *J* = 8.3, 5.1 Hz, 1H), 3.86 – 3.68 (m, 1H), 3.49 – 3.38 (m, 2H), 3.32 (s, 3H), 2.78 (s, 3H), 1.84 (s, 3H).

^{13}C NMR: (101 MHz, DMSO) δ = 177.1, 175.5, 169.2, 130.0, 128.5, 64.6, 50.1, 45.2, 24.2, 22.7, 21.1.

HR-MS (ESI): $[MH]^+$ = 253.1182 ; calculated: 253.1183

Chiral HPLC: Daicel Chiralpak, AS-H, 250x4.6; hexane/isopropanol = 60/40, 1 mL/min, ret. time enantiomere 1: 10.84 min (51 %), ret. time enantiomere 2: 19.26 min (49 %), detection wavelength: 210 nm

_N_-(5-hydroxy-2,5-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide

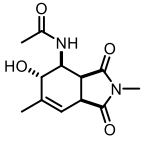


$C_{12}H_{16}N_2O_4$, 252.2700 g/mol

_N_-(5-hydroxy-2,5-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (100 % --> 97 % DCM).

Yield: 67 %
Condition: pale yellow solid
TLC: R_f (EA) = 0.14
m.p.: 168 – 180 °C
^{1}H NMR: (400 MHz, DMSO) δ = 7.26 (d, _J_ = 10.1 Hz, 1H), 5.92 (dd, _J_ = 9.8, 2.5 Hz, 1H), 5.81 – 5.64 (m, 1H), 4.48 – 4.35 (m, 1H), 3.65 – 3.43 (m, 2H), 2.77 (s, 3H), 1.74 (s, 3H), 1.07 (s, 3H).
^{13}C NMR: (101 MHz, DMSO) δ = 177.1, 176.1, 169.3, 67.4, 25.5, 24.3, 22.4, 22.4.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3423, 3295, 1696, 1626, 1558, 1434, 1381, 1285, 1232, 1082, 1028, 667, 551
HR-MS (ESI): $[MH]^+$ = 253.1182 ; calculated: 253.1188
Chiral HPLC: Daicel Chiralcel, OJ-H, 250x4.6; hexane/isopropanol = 70/30, 1 mL/min, ret. time enantiomere 1: 9.68 min (50 %), ret. time enantiomere 2: 13.68 min (50 %), detection wavelength: 210 nm

_N_-(5-Hydroxy-2,6-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide



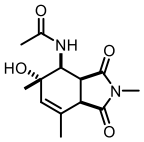
$C_{12}H_{16}N_2O_4$, 252.2700 g/mol

_N_-(5-hydroxy-2,6-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (100 % --> 97 % DCM).

Yield: 76 %

Condition: pale yellow solid
m.p.: 146 °C
TLC: R_f (EA) = 0.13
^{1}H NMR: (400 MHz, MeOD) δ = 5.73 – 5.58 (m, 1H), 4.48 – 4.35 (m, 1H), 3.83 (d, *J* = 7.0 Hz, 1 H), 3.64 – 3.50 (m, 1H), 3.46 (dd, *J* = 8.2, 5.7 Hz, 1H), 2.89 (s, 3H), 1.95 (s, 3H), 1.84 (s, 3H).
^{13}C NMR: (101 MHz, MeOD) δ = 179.1, 178.5, 173.3, 140.3, 119.2, 69.6, 50.9, 43.0, 41.1, 24.8, 22.6, 20.8
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3301 (m), 2920 (w), 1775 (w), 1700 (s), 1645 (s), 1547 (m), 1432 (m), 1378 (m), 1264 (m), 1114 (m), 1070 (s), 1024 (m), 970 (w), 931 (w), 876 (w), 771 (m), 662 (m), 596 (m), 557 (m), 499 (m)
HR-MS (ESI): $[MH]^+$ = 253.1183 ; calculated: 253.1183

***N*-(5-Hydroxy-2,5,7-trimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)-acetamide**

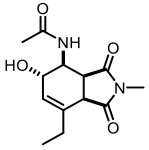


$C_{13}H_{18}N_2O_4$, 266.30 g/mol

N-(5-hydroxy-2,5,7-trimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (100 % --> 97 % DCM)

Yield: 76 %
Condition: pale yellow solid
m.p.: 161 °C decomp.
TLC: R_f (EA) = 0.18
^{1}H NMR: (400 MHz, DMSO) δ = 7.24 (d, J = 9.9 Hz, 1H), 5.40 (s, 1H), 4.87 (s, 1H), 4.33 (dd, J = 9.8, 5.6 Hz, 1H), 3.51 – 3.35 (m, 2H), 2.77 (s, 3H), 1.96 (s, 3H), 1.76 (s, 3H), 1.04 (s, 3H).
^{13}C NMR: (101 MHz, DMSO) δ = 177.2, 175.5, 169.3, 68.0, 51.2, 42.5, 40.8, 25.4, 24.2, 22.5, 21.7.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3435 (m), 3361 (m), 2903 (w), 1773 (w), 1690 (s), 1669 (s), 1521 (m), 1427 (m), 1379 (m), 1284 (m), 1263 (m), 1216 (w), 1167 (w), 1126 (s), 1093 (m), 1072 (m), 1042 (w), 928 (m), 675 (m), 598 (s), 532 (s)
HR-MS (ESI): $[MH]^+$ = 267.1340 ; calculated: 267.1345

_N_-(7-Ethyl-5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)-acetamide

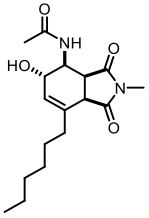


$C_{13}H_{18}N_2O_4$, 266.30 g/mol

_N_-(7-ethyl-5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of MeOH and EA (100 % --> 93 % EA).

Yield: 51 %
Condition: pale yellow solid
TLC: R_f (EA) = 0.15
m.p.: 124 – 134 °C
^{1}H NMR: (300 MHz, MeOD) δ = 5.65 – 5.51 (m, 1H), 4.08 – 3.84 (m, 2H), 3.60 (d, _J_ = 7.9 Hz, 1H), 3.52 – 3.39 (m, 1H), 2.88 (s, 3H), 2.52 – 2.18 (m, 2H), 2.03 (s, 3H), 1.10 (t, _J_ = 7.4 Hz, 3H).
^{13}C NMR: (75 MHz, MeOD) δ = 179.2, 177.2, 173.6, 137.5, 128.1, 67.1, 52.5, 46.4, 41.8, 27.8, 24.9, 22.9, 12.3.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3310, 2974, 2926, 2896, 1771, 1700, 1648, 1539, 1431, 1375, 1282, 1167, 1115, 1033, 1003, 921, 850, 809, 775, 738
HR-MS (ESI): $[MH]^+$ = 267.1345; calculated: 267.1339

_N_-(7-Hexyl-5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)-acetamide



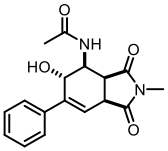
$C_{17}H_{26}N_2O_4$, 322.41 g/mol

_N_-(7-hexyl-5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of MeOH and EA (100 % --> 93 % EA).

Yield: 61 %

Condition: colourless crystalline solid (contains 0.05 equiv. $OPPh_3$)
TLC: R_f (EA) = 0.22
^{1}H NMR: (300 MHz, MeOD) δ = 7.76 – 7.43 (m, 1H), 5.70 – 5.49 (m, 1H), 4.06 – 3.84 (m, 2H), 3.60 (d, *J* = 7.9 Hz, 1H), 3.44 (dd, *J* = 7.8, 5.3 Hz, 1H), 2.89 (s, 3H), 2.52 – 2.31 (m, 1H), 2.31 – 2.15 (m, 1H), 2.03 (d, *J* = 7.3 Hz, 3H), 1.58 (dd, *J* = 16.9, 12.5 Hz, 1H), 1.34 (s, 8H), 0.92 (t, *J* = 6.6 Hz, 3H).
^{13}C NMR: (75 MHz, MeOD) δ = 177.2, 136.1, 129.2, 67.0, 52.5, 46.2, 41.8, 34.9, 32.9, 30.1, 28.5, 24.9, 23.7, 22.9, 14.5.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3396, 2930, 2859, 1771, 1666, 1539, 1435, 1383, 1287, 1226, 1167, 1103, 1059, 1025, 902, 850, 816, 682
HR-MS (ESI): $[MH]^+$ = 323.1967; calculated: 323.1965

***N*-(5-Hydroxy-2-methyl-1,3-dioxo-6-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**



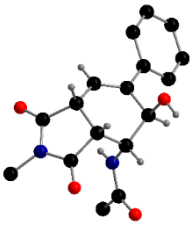
$C_{17}H_{18}N_2O_4$, 314.34 g/mol

N-(5-hydroxy-2-methyl-1,3-dioxo-6-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of EA and MeOH (100 % --> 90 % EA). The fraction containing product and $OPPh_3$ was purified again by column chromatography using a mixture of DCM and MeOH (99 % --> 90 % DCM).

Yield: 82 %
Condition: colourless crystalline solid
m.p.: 103 – 108 °C
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.41 – 7.28 (m, 5H), 7.18 (d, *J* = 8.3 Hz, 1H), 5.99 (dd, *J* = 3.8, 1.2 Hz, 1H), 4.72 – 4.49 (m, 2H), 3.74 (ddd, *J* = 7.9, 3.8, 1.9 Hz, 1H), 3.38 (dd, *J* = 7.9, 5.3 Hz, 1H), 2.97 (s, 3H), 2.08 (s, 3H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 178.1, 175.8, 172.1, 144.2, 137.6, 128.5, 128.3, 127.1, 119.7, 68.7, 50.6, 43.3, 40.4, 25.2, 23.5.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3343, 3056, 1774, 1692, 1525, 1431, 1375, 1282, 1156, 1129, 1038, 1014, 913, 883, 808, 764, 723, 697
HR-MS: (EI, 70 eV): $[MH]^+$ = 315.1343 ; calculated: 315.1345

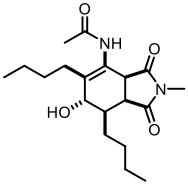
Chiral HPLC: Daicel Chiralcel, OJ-H, 250x4.6; hexane/isopropanol = 50/50, 1 mL/min, ret. time enantiomere 1: 6.95 min (51 %), ret. time enantiomere 2: 13.43 min (49 %), detection wavelength: 210 nm

X-ray:



Compd.	$C_{17}H_{18}N_2O_4 \times ½\ Et_2O$
Chemical formula	$C_{19}H_{23}N_2O_{4.5}$
Formula weight	351.39
Temperature / K	123.01(10)
Wavelength / Å	1.54184
Crystal system, space group	triclinic, *P*–1
a / Å	8.9302(4)
b / Å	9.4292(4)
c / Å	11.6411(5)
α / °	70.068(4)
β / °	82.994(3)
γ / °	75.223(4)
V / Å^3	890.38(7)
ρ_{calcd} / g·cm^{-3}	1.311
F(000)	374
Crystal size / mm	0.26 × 0.19 × 0.11
Z	2
Max. and min. transmission	0.981, 0.961
μ / mm^{-1}	0.772
θ range / °	5.126 – 73.494
Index ranges	–10≤*h*≤11 –11≤*k*≤11 –11≤*l*≤14
Total / unique reflections	9910 / 3472
Data / restraints / parameters	3472 / 0 / 263
R_{int}	0.0184
R_1, wR_2 [I≥2σ(I)]	0.0381, 0.0997
R_1, wR_2 (all data)	0.0434, 0.1041
Goodness-of-fit *S* on F^2	1.035
Largest diff. peak and hole / eÅ^{-3}	0.266, –0.224
Absolute structure parameter	–

***N*-(5,7-Dibutyl-6-hydroxy-2-methyl-1,3-dioxo-2,3,3a,6,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

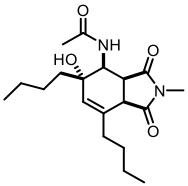


$C_{19}H_{30}N_2O_4$, 350.46 g/mol

N-(5,7-dibutyl-6-hydroxy-2-methyl-1,3-dioxo-2,3,3a,6,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (66 % --> 100 % EA).

Yield:	31 %
Condition:	pale yellow amorphous solid
TLC:	R_f (EA) = 0.22
^{1}H NMR:	(300 MHz, $CDCl_3$) δ = 8.73 (s, 1H), 6.18 (d, *J* = 6.8 Hz, 1H), 3.52 (d, *J* = 13.7 Hz, 1H), 3.04 (s, 3H), 2.72 – 2.58 (m, 1H), 2.35 – 2.24 (m, 1H), 2.24 – 2.13 (m, 4H), 1.46 – 1.30 (m, 4H), 1.30 – 1.08 (m, 8H), 0.91 – 0.78 (m, 6H).
^{13}C NMR:	(75 MHz, $CDCl_3$) δ = 137.4, 134.7, 44.0, 32.6, 32.0, 31.7, 29.4, 27.2, 24.5, 23.0, 22.4, 14.1.
FT-IR (ATR):	$\tilde{\nu}$ [cm^{-1}] = 3310, 2960, 2863, 1774, 1692, 1510, 1431, 1379, 1279, 1156, 1088, 1040, 999, 865, 775, 723, 697, 664
HR-MS (ESI):	$[MH]^+$ = 351.2284; calculated: 351.2278

***N*-(5,7-Dibutyl-5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

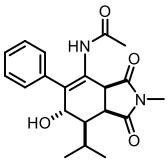


$C_{19}H_{30}N_2O_4$, 350.46 g/mol

N-(5,7-dibutyl-5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (66 % --> 100 % EA).

Yield: 34 %
Condition: pale yellow amorphous solid
TLC: R_f (EA) = 0.48
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 5.78 – 5.64 (m, 1H), 4.46 – 4.31 (m, *J* = 9.8 Hz, 1H), 3.49 (d, *J* = 8.7 Hz, 1H), 3.26 – 3.11 (m, 1H), 2.98 (s, 3H), 2.40 – 2.23 (m, 2H), 2.13 (s, 3H), 1.65 – 1.48 (m, 3H), 1.48 – 1.29 (m, 4H), 1.29 – 1.07 (m, 3H), 0.92 (t, *J* = 15.5 Hz, 3H), 0.87 – 0.76 (m, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 175.0, 73.7, 43.9, 39.3, 37.4, 34.0, 29.5, 25.4, 25.2, 23.5, 23.5, 22.5, 14.1, 14.0.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3373, 2956, 2870, 1774, 1692, 1521, 1432, 1379, 1334, 1282, 1156, 1126, 1029, 936, 902, 854, 779, 727, 690
HR-MS (ESI): $[MH]^+$ = 351.2280; calculated: 351.2278

_N_-(6-Hydroxy-7-isopropyl-2-methyl-1,3-dioxo-5-phenyl-2,3,3a,6,7,7a-hexahydro-1_H_-isoindol-4-yl)acetamide



$C_{20}H_{24}N_2O_4$, 356.42 g/mol

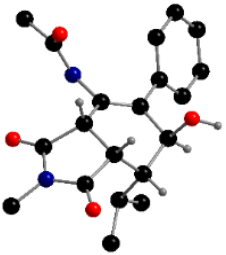
N-(6-hydroxy-7-isopropyl-2-methyl-1,3-dioxo-5-phenyl-2,3,3a,6,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (66 % --> 100 % EA).

Yield: 40 %
Condition: colourless crystalline solid
TLC: R_f (EA) = 0.34
m.p.: 184 – 186 °C
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.85 (s, 1H), 7.43 – 7.16 (m, 5H), 6.36 (d, *J* = 6.9 Hz, 1H), 3.81 (d, *J* = 8.7 Hz, 1H), 3.09 (s, 3H), 2.94 (ddd, *J* = 8.8, 6.9, 5.2 Hz, 1H), 2.26 – 2.04 (m, 1H), 1.89 (s, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 175.3, 169.0, 167.9, 140.0, 139.5, 138.6, 134.9, 128.3, 127.5, 126.5, 108.5, 42.9, 38.4, 29.3, 24.6, 23.9, 21.4, 19.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3280, 2974, 2885, 1771, 1696, 1640, 1521, 1428, 1368, 1279, 1178, 1129, 1036, 1010, 977, 913, 831, 764, 700

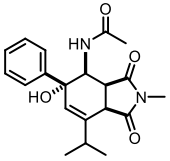
HR-MS (ESI): $[MH]^+$ = 357.1813; calculated: 357.1809

X-ray:



Chemical formula	$C_{20}H_{24}N_2O_4$
Formula weight	356.41
Temperature / K	123.00(10)
Wavelength / Å	1.54184
Crystal system, space group	monoclinic, $P2_1/n$
a / Å	8.2886(2)
b / Å	14.9305(3)
c / Å	14.7536(3)
α / °	90
β / °	99.555(2)
γ / °	90
V / Å^3	1800.47(7)
ρ_{calcd} / g·cm^{-3}	1.315
F(000)	760
Crystal size / mm	0.11 × 0.11 × 0.07
Z	4
Max. and min. transmission	0.989, 0.984
μ / mm^{-1}	0.750
θ range / °	4.243 – 73.468
Index ranges	$-10 \le h \le 7$ $-15 \le k \le 18$ $-15 \le l \le 18$
Total / unique reflections	10220 / 3515
Data / restraints / parameters	3515 / 0 / 245
R_{int}	0.0215
R_1, wR_2 [I≥2σ(I)]	0.0333, 0.0800
R_1, wR_2 (all data)	0.0401, 0.0843
Goodness-of-fit S on F^2	1.030
Largest diff. peak and hole / eÅ^{-3}	0.220, –0.177
Absolute structure parameter	–

***N*-(5-Hydroxy-7-isopropyl-2-methyl-1,3-dioxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

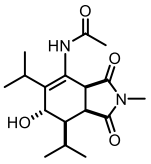


$C_{20}H_{24}N_2O_4$, 356.42 g/mol

N-(5-hydroxy-7-isopropyl-2-methyl-1,3-dioxo-5-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (66 % --> 100 % EA).

Yield: 30 %
Condition: colourless crystalline solid
TLC: R_f (EA) = 0.52
m.p.: 153 – 158 °C
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 17.0 Hz, 1H), 7.34 – 7.20 (m, 3H), 7.20 – 7.10 (m, 2H), 5.84 (s, 1H), 4.71 – 4.55 (m, 1H), 3.72 (d, *J* = 9.0 Hz, 1H), 3.14 – 3.01 (m, 2H), 2.65 (s, 3H), 2.17 (s, 3H), 1.29 – 1.17 (m, 6H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 177.5, 175.2, 173.1, 139.4, 139.3, 128.9, 128.5, 127.9, 127.6, 76.0, 55.2, 43.4, 38.8, 31.0, 24.9, 23.4, 22.5, 20.9.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3396, 3366, 2971, 2285, 2166, 1737, 1677, 1636, 1517, 1435, 1379, 1334, 1286, 1200, 1129, 1092, 1066, 1033, 954, 932, 872, 790, 708
HR-MS (ESI): $[MH]^+$ = 357.1810; calculated: 357.1809

***N*-(6-Hydroxy-5,7-diisopropyl-2-methyl-1,3-dioxo-2,3,3a,6,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**



$C_{17}H_{26}N_2O_4$, 322.41 g/mol

N-(6-hydroxy-5,7-diisopropyl-2-methyl-1,3-dioxo-2,3,3a,6,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of EA and MeOH (100 % --> 97 % EA).

Yield: 67 %

Condition: colourless crystalline solid

TLC: R_f (EA) = 0.13

m.p.: 146 – 150 °C

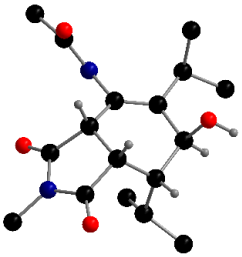
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 8.75 (s, 1H), 6.05 (d, *J* = 6.9 Hz, 1H), 3.61 (d, *J* = 8.8 Hz, 1H), 3.04 (s, 3H), 2.82 – 2.54 (m, 2H), 2.15 (d, *J* = 12.9 Hz, 3H), 2.06 – 1.92 (m, 1H), 1.75 (s, 2H), 1.18 (dd, *J* = 20.3, 13.1 Hz, 3H), 0.90 (dd, *J* = 26.3, 6.9 Hz, 6H), 0.69 (dd, *J* = 11.6, 6.9 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 175.5, 169.8, 145.6, 141.6, 128.0, 108.9, 43.4, 38.2, 29.2, 29.1, 24.8, 24.5, 24.3, 21.3, 20.5, 19.1.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3452, 3276, 2967, 2914, 2878, 1767, 1689, 1651, 1513, 1469, 1379, 1275, 1193, 1066, 1018, 962, 857, 760, 726, 686

HR-MS (ESI): $[MH]^+$ = 323.1967; calculated: 323.1965

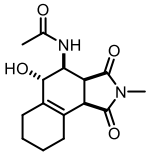
X-ray:



Chemical formula	$C_{17}H_{26}N_2O_4$
Formula weight	322.40
Temperature / K	123.01(10)
Wavelength / Å	1.54184
Crystal system, space group	orthorhombic, *Pbca*
a / Å	9.56060(10)
b / Å	18.8246(2)
c / Å	19.1845(2)
α / °	90
β / °	90
γ / °	90
V / Å^3	3452.72(6)
ρ_{calcd} / g·cm^{-3}	1.240
F(000)	1392
Crystal size / mm	0.36 × 0.30 × 0.20
Z	8
Max. and min. transmission	1.000, 0.715
μ / mm^{-1}	0.720
θ range / °	4.610 – 73.427
Index ranges	$-11 \le h \le 11$ $-23 \le k \le 23$ $-23 \le l \le 23$
Total / unique reflections	191122 / 3461
Data / restraints / parameters	3461 / 0 / 219
R_{int}	0.0471

R_1, wR_2 [I≥2σ(I)]	0.0369, 0.0914
R_1, wR_2 (all data)	0.0384, 0.0927
Goodness-of-fit S on F^2	1.068
Largest diff. peak and hole / eÅ^{-3}	0.250, 0.201
Absolute structure parameter	–

_N_-(5-Hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,6,7,8,9,9b-decahydro-1_H_-benzo[_e_]isoindol-4-yl)acetamide

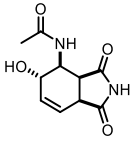


$C_{15}H_{20}N_2O_4$, 292.3400 g/mol

N-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,6,7,8,9,9b-decahydro-1*H*-benzo[*e*]isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of MeOH and EA (100 % --> 95 % EA).

Yield:	65 %
Condition:	colourless crystalline solid (contains 0.07 equiv. $OPPh_3$)
TLC:	R_f (EA) = 0.16
^{1}H NMR:	(400 MHz, DMSO) δ = 7.37 (d, *J* = 9.0 Hz, 1H), 4.21 (ddd, *J* = 8.9, 5.5, 2.6 Hz, 1H), 3.49 (d, *J* = 5.5 Hz, 1H), 3.39 – 3.29 (m, 2H), 2.74 (s, 3H), 2.72 – 2.65 (m, 1H), 2.30 – 2.13 (m, 1H), 2.02 – 1.80 (m, 2H), 1.77 (s, 3H), 1.67 – 1.48 (m, 4H).
^{13}C NMR:	(101 MHz, $CDCl_3$) δ = 177.1, 176.0, 169.1, 132.5, 131.5, 131.4, 128.78, 128.7, 125.0, 68.3, 48.8. 43.7, 27.7, 27.3, 24.1, 22.6, 22.1, 22.
FT-IR (ATR):	$\tilde{\nu}$ [cm^{-1}] = 3325, 2915, 2870, 1770, 1700, 1644, 1543, 1461, 1431, 1397, 1286, 1185, 1156, 1096, 1014, 968, 910, 842, 790, 757, 723, 667
HR-MS (ESI):	$[MH]^+$ = 293.1502; calculated: 293.1496

_N_-(5-Hydroxy-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide



$C_{10}H_{12}N_2O_4$, 224.22 g/mol

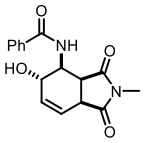
N-(5-hydroxy-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 72 h) using a mixture of MeCN and MeOH (25 % of MeOH) as solvent. The crude product was purified by column chromatography using a mixture of MeOH and EA (95 % EA).

Yield: 42 %
Condition: pale yellow solid
TLC: R_f (DCM/MeOH = 90/10) = 0.21
m.p.: 178 – 186 °C
^{1}H NMR: (300 MHz, MeOD) δ = 5.99 – 5.87 (m, 1H), 5.82 (dt, *J* = 10.1, 2.7 Hz, 1H), 4.26 – 4.09 (m, 1H), 4.09 – 3.98 (m, 1H), 3.64 – 3.11 (m, 2H + MeOH), 2.10 – 1.96 (m, 3H).
^{13}C NMR: (75 MHz, MeOD) δ = 180.2, 178.8, 173.5, 140.7, 134.6, 132.5, 124.5, 66.8, 51.6, 42.7, 22.9.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3407, 3131, 2967, 2758, 1778, 1707, 1648, 1607, 1513, 1439, 1359, 1260, 1230, 1185, 1111, 1047, 932, 854, 816, 742
HR-MS (ESI): $[MH]^+$ = 225.0869; calculated: 225.0870
X-ray:

Chemical formula	$C_{10}H_{12}N_2O_4$
Formula weight	224.22
Temperature / K	123.02(10)
Wavelength / Å	1.54184
Crystal system, space group	monoclinic, $P2_1/c$
a / Å	17.1587(2)
b / Å	8.67980(10)
c / Å	13.87950(10)
α / °	90
β / °	93.1030(10)
γ / °	90
V / Å^3	2064.10(4)
ρ_{calcd} / g·cm^{-3}	1.443
F(000)	944
Crystal size / mm	0.16 × 0.14 × 0.13
Z	8
Max. and min. transmission	1.000, 0.835
μ / mm^{-1}	0.957
θ range / °	5.163 – 73.621
Index ranges	–21≤*h*≤21

	–10≤*k*≤10
	–17≤*l*≤17
Total / unique reflections	32359 / 4134
Data / restraints / parameters	4134 / 0 / 309
R_{int}	0.0220
R_1, wR_2 [I≥2σ(I)]	0.0351, 0.0931
R_1, wR_2 (all data)	0.0371, 0.0948
Goodness-of-fit *S* on F^2	1.031
Largest diff. peak and hole / eÅ^{-3}	0.330, –0.205
Absolute structure parameter	–

_N_-(5-Hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)benzamide



$C_{16}H_{16}N_2O_4$, 300.31 g/mol

N-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)benzamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (99 % --> 95 % DCM)

Yield: 23 %

Condition: pale yellow solid (contains 0.85 equiv. $OPPh_3$)

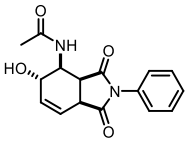
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.86 – 7.38 (m, 17.5 H, $CH_{aromat.}$ + $OPPh_3$), 5.96 (dt, *J* = 10.0, 1.8 Hz, 1H), 5.75 (ddd, *J* = 10.0, 4.0, 2.3 Hz, 1H), 4.40 (dd, *J* = 9.8, 5.8 Hz, 1H), 4.09 (ddd, *J* = 9.8, 4.1, 2.1 Hz, 1H), 3.66 (ddt, *J* = 8.5, 4.3, 2.2 Hz, 1H), 3.43 – 3.29 (m, 1H), 2.95 (s, 3 H)

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 178.6, 175.9, 135.0, 133.4, 132.3, 132.3, 132.2, 132.2, 132.0, 129.2, 128.8, 128.7, 128.6, 128.4, 127.5, 127.2, 121.5, 67.8, 51.2, 50.0, 49.8, 49.5, 49.2, 48.9, 43.7, 40.6, 25.0.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3377, 3060, 2915, 2978, 1774, 1677, 1651, 1580, 1536, 1491, 1439, 1379, 1345, 1282, 1226, 1156, 1118, 1059, 1021, 928, 854, 808, 749, 716

HR-MS (ESI): $[MH]^+$ = 301.1184; calculated: 301.1183

_N_-(5-Hydroxy-1,3-dioxo-2-phenyl-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide



$C_{16}H_{16}N_2O_4$, 300.31 g/mol

_N_-(5-hydroxy-1,3-dioxo-2-phenyl-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of EA and MeOH (100 % --> 97 % EA).

Yield: 65 %

Condition: colourless crystalline solid

TLC: R_f (EA) = 0.29

m.p.: 184 °C

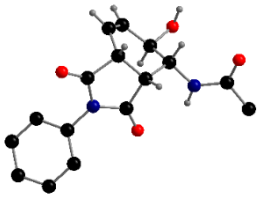
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.52 – 7.07 (m, 5H), 5.99 (ddd, _J_ = 12.7, 7.0, 3.1 Hz, 1H), 5.83 (dt, _J_ = 9.5, 3.0 Hz, 1H), 4.80 (ddq, _J_ = 8.8, 5.7, 2.8 Hz, 1H), 3.53 – 3.12 (m, 2H), 2.98 – 2.60 (m, 1H), 2.38 – 2.21 (m, 1H), 2.07 (s, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 177.4, 176.6, 174.8, 167.4, 135.3, 134.2, 131.1, 129.4, 129.1, 126.3, 121.7, 67.2, 50.6, 49.9, 49.7, 49.5, 49.3, 49.1, 44.1, 40.9, 23.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3429, 3392, 1774, 1699, 1651, 1536, 1495, 1372, 1286, 1230, 1185, 1118, 917, 857, 801, 749, 690,

HR-MS (ESI): $[MH]^+$ = 301.1187 ; calculated: 301.1188

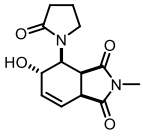
X-ray:



Chemical formula	$C_{16}H_{16}N_2O_4$
Formula weight	300.31
Temperature / K	123.01(10)
Wavelength / Å	1.54184
Crystal system, space group	monoclinic, $P2_1/c$
_a_ / Å	16.0117(3)
_b_ / Å	12.5922(2)
_c_ / Å	7.04910(10)
α / °	90
β / °	95.023(2)
γ / °	90

V / Å^3	1415.80(4)
ρ_{calcd} / g·cm^{-3}	1.409
F(000)	632
Crystal size / mm	0.20 × 0.10 × 0.02
Z	4
Max. and min. transmission	1.000, 0.864
μ / mm^{-1}	0.851
θ range / °	4.474 – 73.354
Index ranges	–19≤*h*≤19 –15≤*k*≤14 –8≤*l*≤8
Total / unique reflections	11627 / 2813
Data / restraints / parameters	2813 / 0 / 206
R_{int}	0.0220
R_1, wR_2 [I≥2σ(I)]	0.0312, 0.0784
R_1, wR_2 (all data)	0.0363, 0.0822
Goodness-of-fit *S* on *F*^{2}	1.043
Largest diff. peak and hole / eÅ^{-3}	0.283, –0.203
Absolute structure parameter	–

5-Hydroxy-2-methyl-4-(2-oxopyrrolidin-1-yl)-3a,4,5,7a-tetrahydro-1H-isoindole-1,3(2H)-dione



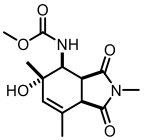
$C_{13}H_{16}N_2O_4$, 264.28 g/mol

5-Hydroxy-2-methyl-4-(2-oxopyrrolidin-1-yl)-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (95 % --> 93 % DCM)

Yield: 25 %
Condition: pale yellow solid
m.p.: 130 °C
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 5.95 (dt, *J* = 10.0, 1.9 Hz, 1H), 5.76 (ddd, *J* = 10.0, 3.5, 2.2 Hz, 1H), 4.43 – 4.26 (m, 1H), 4.04 (ddd, *J* = 13.8, 9.4, 5.2 Hz, 2H), 3.75 – 3.59 (m, 2H), 3.56 – 3.46 (m, 1H), 3.41 (t, *J* = 6.9 Hz, 1H), 2.91 (s, 3H), 2.42 (d, *J* = 7.7 Hz, 2H), 2.21 – 1.94 (m, 2H).

HR-MS: (EI, 70 eV): $[MH]^+$ = 265.1183 ; calculated: 265.1188

Methyl-(5-hydroxy-2,5,7-trimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

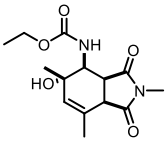


$C_{13}H_{18}N_2O_5$, 282.30 g/mol

Methyl-(5-hydroxy-2,5,7-trimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (60 % --> 80 % EA).

Yield: 81 %
Condition: colourless amorphous solid (contains 0.5 equiv. $OPPh_3$)
TLC: R_F (PE/EA = 1/2) = 0.30
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 5.67 (s, 1H), 4.25 – 4.03 (m, 1H), 3.73 (s, 3H), 3.48 – 3.32 (m, 1H), 3.26 (t, *J* = 7.6 Hz, 1H), 2.97 (s, 3H), 1.97 (s, 3H), 1.24 (dd, *J* = 14.7, 7.6 Hz, 1H), 1.05 (s, 3H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 174.6, 170.2, 133.1, 132.1, 132.0, 128.6, 18.4, 55.30, 52.7, 39.9, 25.0, 23.5, 21.4
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3407, 2974, 1685, 1528, 1439, 1379, 1342, 1290, 1231, 1185, 1118, 1070, 1044, 928, 850, 775, 697
HR-MS (ESI): $[MH\text{-}H_2O]^+$ = 265.1187; calculated: 265.1183

Ethyl-(5-hydroxy-2,5,7-trimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1H-isoindol-4-yl)carbamate



$C_{14}H_{20}N_2O_5$, 296.32 g/mol

Ethyl-(5-hydroxy-2,5,7-trimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (60 % --> 85 % EA).

Yield: 83 %
Condition: pale yellow amorphous solid
TLC: R_f (PE/EA = 1/2) = 0.41

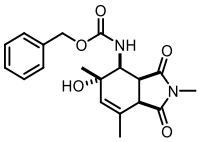
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 5.67 (s, 1H), 4.22 – 4.01 (m, 3H), 3.41 (d, *J* = 8.6 Hz, 1H), 3.31 – 3.20 (m, 1H), 2.97 (s, 3H), 1.97 (s, 3H), 1.37 – 1.17 (m, 4H), 1.05 (s, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 178.3, 174.8, 133.9, 71.4, 61.8, 55.4, 45.8, 40.1, 25.1, 23.7, 21.6, 14.7.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3403, 2982, 1774, 1685, 1513, 1435, 1379, 1331, 1282, 1230, 1163, 1096, 1066, 928, 850, 775, 670

HR-MS (ESI): $[MH]^+$ = 297.1443 ; calculated: 297.1445

Benzyl-(5-hydroxy-2,5,7-trimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1H-isoindol-4-yl)carbamate



$C_{19}H_{22}N_2O_5$, 358.39 g/mol

Benzyl-(5-hydroxy-2,5,7-trimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (60 % --> 80 % EA).

Yield: 76 %

Condition: pale yellow amorphous solid

TLC: R_f (PE/EA = 1/2) = 0.48

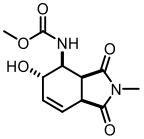
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.43 – 7.30 (m, 5H), 5.67 (s, 1H), 5.15 (q, *J* = 12.2 Hz, 2H), 4.20 (dd, *J* = 8.8, 6.9 Hz, 1H), 3.41 (d, *J* = 8.3 Hz, 1H), 3.26 (t, *J* = 7.3 Hz, 1H), 2.97 (s, 3H), 1.98 (s, 3H), 1.06 (s, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 174.7, 136.2, 128.4, 128.5, 128.4, 67.6, 60.3, 55.6, 45.5, 40.0, 25.1, 23.8, 21.6, 14.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3403, 3034, 1774, 1685, 1513, 1435, 1379, 1331, 1282, 1226, 1163, 1100, 1066, 1043, 969, 828, 742, 697

HR-MS (ESI): $[MH]^+$ = 359.1604; calculated: 359.1601

Methyl-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

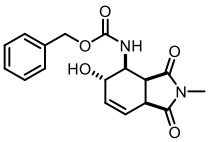


$C_{11}H_{14}N_2O_5$, 254.24 g/mol

Methyl-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (60 % --> 80 % EA).

Yield:	45 %
Condition:	pale yellow amorphous solid (contains 1.4 equiv. $OPPh_3$)
TLC:	R_f (PE/EA = 1/2) = 0.19
^{1}H NMR:	(300 MHz, $CDCl_3$) δ = 6.49 (s, 1H), 5.93 (dd, *J* = 10.0, 1.7 Hz, 1H), 5.84 – 5.64 (m, 1H), 4.18 – 3.82 (m, 2H), 3.74 – 3.64 (m, 3H), 3.64 – 3.54 (m, 1H), 3.39 – 3.25 (m, 1H), 2.93 (d, *J* = 3.0 Hz, 3H).
^{13}C NMR:	(75 MHz, $CDCl_3$) δ = 178.0, 176.0, 134.4, 133.1, 131.7, 121.9, 67.93, 52.8, 52.65, 44.0, 40.9, 24.8.
FT-IR (ATR):	$\tilde{\nu}$ [cm^{-1}] = 3329, 1774, 1700, 1543, 1435, 1379, 1282, 1185, 1118, 1085, 1018, 910, 861, 753,719
HR-MS (ESI):	$[MH]^+$ = 255.0979; calculated: 255.0975

Benzyl-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate



$C_{17}H_{18}N_2O_5$, 330.34 g/mol

Benzyl-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (66 % EA).

Yield:	62 %
Condition:	pale yellow solid
TLC:	R_f (PE/EA = 1/2) = 0.40
m.p.:	136 – 143 °C

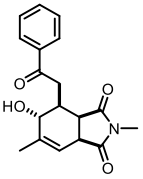
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.43 – 7.27 (m, 5H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.10 – 5.85 (m, 1H), 5.76 (ddd, *J* = 10.0, 4.0, 1.8 Hz, 1H), 5.22 – 5.03 (m, 2H), 4.19 – 3.80 (m, 2H), 3.70 – 3.48 (m, 1H), 3.25 (dd, *J* = 26.5, 13.3 Hz, 1H), 2.94 (s, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 178.0, 175.7, 157.7, 136.1, 134.4, 128.7, 128.5, 128.4, 121.8, 68.4, 67.5, 52.8, 44.0, 40.8, 25.1.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3366, 2948, 2907, 1778, 1670, 1543, 1431, 1379, 1282, 1226, 1162, 1088, 1018, 917, 865, 809, 783

HR-MS: (EI, 70 eV): $[MH]^+$ = 331.1293 ; calculated: 331.1288

5-Hydroxy-2,6-dimethyl-4-(2-oxo-2-phenylethyl)-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (A)



$C_{18}H_{19}NO_4$, 313.35 g/mol

5-Hydroxy-2,6-dimethyl-4-(2-oxo-2-phenylethyl)-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (33 % --> 75 % EA).

Yield: 75 % (A + B; ratio A/B = 2/1)

Condition: pale yellow amorphous solid

TLC: R_f (PE/EA = 2/1) = 0.24 (A)

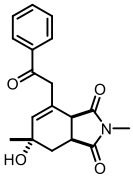
^{1}H NMR: (400 MHz, $CDCl_3$) (A) δ = 8.04 – 7.87 (m, 2H), 7.64 – 7.51 (m, 1H), 7.51 – 7.34 (m, 2H), 5.78 (s, 1H), 4.62 (d, *J* = 17.5 Hz, 1H), 3.75 (d, *J* = 13.6 Hz, 1H), 3.65 (d, *J* = 8.1 Hz, 1H), 3.48 – 3.32 (m, 1H), 2.95 (s, 3H), 2.20 (dd, *J* = 13.4, 6.4 Hz, 1H), 1.75 (dd, *J* = 13.4, 9.9 Hz, 1H).

^{13}C NMR: (101 MHz, $CDCl_3$) (A) δ = 198.5, 179.4, 176.5, 171.3, 136.8, 136.6, 133.6, 128.9, 128.4, 128.1, 66.9, 60.5, 44.1, 42.2, 37.7, 37.5, 29.2, 24.3, 21.2, 14.3.

FT-IR (ATR): (A): $\tilde{\nu}$ [cm^{-1}] = 3437, 2915, 1771, 1692, 1431, 1379, 1275, 1077, 1003, 932, 872, 850, 749, 686

HR-MS (ESI): (A): $[MH]^+$ = 314.1392; calculated: 314.1387

5-Hydroxy-2,5-dimethyl-7-(2-oxo-2-phenylethyl)-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (B)



$C_{18}H_{19}NO_4$, 313.35 g/mol

5-Hydroxy-2,5-dimethyl-7-(2-oxo-2-phenylethyl)-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (33 % --> 75 % EA).

Yield:	75 % (A + B; ratio A/B = 2/1)
TLC:	R_f (PE/EA = 2/1) = 0.10 (B)
^{1}H NMR:	(400 MHz, $CDCl_3$) (B) δ = 8.16 – 7.94 (m, 2H), 7.64 – 7.53 (m, 1H), 7.53 – 7.41 (m, 2H), 5.57 (dd, *J* = 15.6, 14.0 Hz, 1H), 4.02 – 3.85 (m, 2H), 3.66 –3.47 (m, 2H), 3.47 – 3.35 (m, 1H), 2.91 (s, 3H), 2.66 (ddt, *J* = 10.4, 7.6, 5.4 Hz, 1H), 1.86 (d, *J* = 16.0 Hz, 4H).
^{13}C NMR:	(101 MHz, $CDCl_3$) δ = 200.5, 178.3, 177.1, 141.8, 137.0, 133.5, 128.8, 128.3, 118.1, 69.9, 43.4, 40.7, 38.5, 36.9, 24.7, 19.6.
FT-IR (ATR):	(B): $\tilde{\nu}$ [cm^{-1}] = 3448, 2971, 1774, 1685, 1431, 1379, 1282, 1215, 1167, 1133, 1103, 1059, 1006, 969, 913, 828, 783, 757, 690
HR-MS (ESI)	(B): $[MH]^+$ = 314.1389; calculated: 314.1387

Photooxidation reactions of enantiopure substrates (GP-3.2):

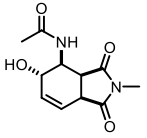
Enantiopure cyclohexene (40 mg) was dissolved in 2 mL of a solution of Methylene blue (1×10^{-3} M) in Acetonitrile.
The oxidation was performed in a continuous flow microreactor system using the following parameters: R_t = 15.5 min, T = 10 °C.
The substrate solution was collected in a round bottom flask and PPh_3 (55 mg) was added. The solution was stirred for 2 h at room temperature. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using a *Buechi* Sepacore X50 and a 12 g 40 µm silica column.
The exact eluents and yields are described for each compound.

Components of the photo-oxidation flow system:

HPLC-pump (*Bischoff* Dosierpumpe 2250), O_2 (*Linde* 4.6, 200 bar), mass flow controller (*Brooks* SLA 5850), T-fitting (*IDEX,* P-632), FEP-capillary (*IDEX*, 1520XL), LEDs (24 × *Cree Xlamp* MK-R, warm white, 700 mA), back-pressure regulator (*IDEX*, P-763, 100 psi), temperature control (*Huber*, TC45E)

Oxidation reactions according to GP-3.2

***N*-(5-Hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide (-)**



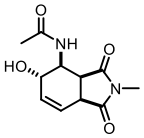
$C_{11}H_{14}N_2O_4$, 238.2430 g/mol

N-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide (-) was synthesized according to GP-3.2 and purified by column chromatography using a mixture of EA and MeOH (100 % --> 95 % EA)

Yield:	51 %
Condition:	pale yellow solid
TLC:	R_f (EA) = 0.14
^{1}H NMR:	(400 MHz, MeOD) δ = 5.92 (tt, *J* = 6.7, 3.4 Hz, 1H), 5.87 – 5.79 (m, 1H), 4.20 (dd, *J* = 8.8, 5.7 Hz, 1H), 4.03 – 3.94 (m, 1H), 3.68 – 3.60 (m, 1H), 3.52 – 3.41 (m, 1H), 2.89 (s, 3H), 2.05 – 1.98 (s, 3H).
Specific Rot.:	TC (calc.): -280°

Chiral HPLC: Daicel Chiralpak, AS-H, 250x4.6; hexane/isopropanol = 50/50, 1 mL/min, ret. time enantiomere 1: 9.53 min (100 %), detection wavelength: 210 nm

***N*-(5-Hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide (+)**

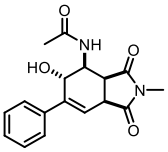


$C_{11}H_{14}N_2O_4$, 238.2430 g/mol

N-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide (+) was synthesized according to GP-3.2 and purified by column chromatography using a mixture of EA and MeOH (100 % --> 95 % EA)

Yield: 52 %
Condition: pale yellow solid
TLC: R_f (EA) = 0.14
^{1}H NMR: (400 MHz, MeOD) δ = 5.97 – 5.88 (m, 1H), 5.88 – 5.78 (m, 1H), 4.20 (dd, *J* = 8.8, 5.7 Hz, 1H), 4.06 – 3.95 (m, 1H), 3.68 – 3.57 (m, 1H), 3.53 – 3.43 (m, 1H), 2.92 – 2.88 (m, 3H), 2.02 (d, *J* = 3.5 Hz, 3H).
Specific Rot.: TC (calc.): +285°
Chiral HPLC: Daicel Chiralpak, AS-H, 250x4.6; hexane/isopropanol = 50/50, 1 mL/min, ret. time enantiomere 1: 25.42 min (100 %), detection wavelength: 210 nm

***N*-(5-Hydroxy-2-methyl-1,3-dioxo-6-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide (-)**



$C_{17}H_{18}N_2O_4$, 314.34 g/mol

N-(5-hydroxy-2-methyl-1,3-dioxo-6-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide (-) was synthesized according to GP-3.2 and purified by column chromatography using a mixture of EA and MeOH (100 % --> 96 % EA)

Yield: 88 %

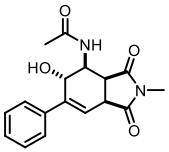
Condition: colourless crystalline solid

^{1}H NMR: (400 MHz, MeOD) δ = 7.53 – 7.23 (m, 5H), 6.44 (d, *J* = 4.6 Hz, 1H), 4.96 – 4.85 (m, 1H), 4.46 (d, *J* = 4.3 Hz, 1H), 3.67 (t, *J* = 6.7 Hz, 1H), 2.95 (s, 3H), 1.84 (s, 3H).

Specific Rot.: TC (calc.): -29°

Chiral HPLC: Daicel Chiralcel, OJ-H, 250x4.6; hexane/isopropanol = 50/50, 1 mL/min, ret. time enantiomere 1: 13.29 min (100 %), detection wavelength: 210 nm

_N_-(5-Hydroxy-2-methyl-1,3-dioxo-6-phenyl-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide (+)



$C_{17}H_{18}N_2O_4$, 314.34 g/mol

N-(5-hydroxy-2-methyl-1,3-dioxo-6-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide (+) was synthesized according to GP-3.2 and purified by column chromatography using a mixture of EA and MeOH (100 % --> 96 % EA)

Yield: 90 %

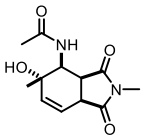
Condition: colourless crystalline solid

^{1}H NMR: (400 MHz, MeOD) δ = 7.58 – 7.22 (m, 5H), 6.44 (d, *J* = 4.6 Hz, 1H), 4.93 – 4.85 (m, 1H), 4.45 (d, *J* = 4.3 Hz, 1H), 3.67 (t, *J* = 6.7 Hz, 1H), 2.96 (s, 3H), 1.84 (s, 3H).

Specific Rot.: TC (calc.): +30°

Chiral HPLC: Daicel Chiralcel, OJ-H, 250x4.6; hexane/isopropanol = 50/50, 1 mL/min, ret. time enantiomere 1: 6.95 min (100 %), detection wavelength: 210 nm

_N_-(5-Hydroxy-2,5-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide (-)

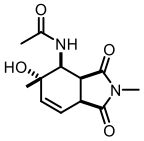


$C_{12}H_{16}N_2O_4$, 252.2700 g/mol

N-(5-hydroxy-2,5-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide (-) was synthesized according to GP-3.2 and purified by column chromatography using a mixture of EA and MeOH (100 % --> 95 % EA)

Yield: 72 %
Condition: pale yellow solid
TLC: R_f (EA) = 0.14
^{1}H NMR: (400 MHz, MeOD) δ = 6.05 (dd, *J* = 9.8, 3.2 Hz, 1H), 5.85 (dd, *J* = 10.0, 2.6 Hz, 1H), 4.59 (dd, *J* = 30.8, 5.7 Hz, 1H), 3.68 – 3.50 (m, 2H), 2.92 (s, 3H), 1.89 (d, *J* = 17.0 Hz, 3H), 1.22 (s, 3H).
Specific Rot.: TC (calc.): -156°
Chiral HPLC: Daicel Chiralcel, OJ-H, 250x4.6; hexane/isopropanol = 70/30, 1 mL/min, ret. time enantiomere 1: 9.84 min (100 %), detection wavelength: 210 nm

_N_-(5-Hydroxy-2,5-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide (+)

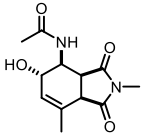


$C_{12}H_{16}N_2O_4$, 252.2700 g/mol

N-(5-hydroxy-2,5-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide (+) was synthesized according to GP-3.2 and purified by column chromatography using a mixture of EA and MeOH (100 % --> 95 % EA)

Yield: 69 %
Condition: pale yellow solid
TLC: R_f (EA) = 0.14
^{1}H NMR: (400 MHz, MeOD) δ = 6.03 (dt, *J* = 33.5, 16.8 Hz, 1H), 5.84 (dd, *J* = 10.0, 2.5 Hz, 1H), 4.62 (d, *J* = 5.6 Hz, 1H), 3.63 – 3.49 (m, 2H), 2.91 (s, 3H), 1.98 – 1.84 (m, 3H), 1.22 (d, *J* = 8.9 Hz, 3H).
Specific Rot.: TC (calc.): +173°
Chiral HPLC: Daicel Chiralcel, OJ-H, 250x4.6; hexane/isopropanol = 70/30, 1 mL/min, ret. time enantiomere 1: 13.78 min (100 %), detection wavelength: 210 nm

_N_-(5-Hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide (-)

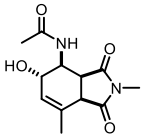


$C_{12}H_{16}N_2O_4$, 252.27 g/mol

_N_-(5-hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide (-) was synthesized according to GP-3.2 and purified by column chromatography using a mixture of EA and MeOH (100 % --> 95 % EA)

Yield: 52 %
Condition: pale yellow solid
TLC: R_f (EA) = 0.15
^{1}H NMR: (400 MHz, MeOD) δ = 5.69 – 5.56 (m, 1H), 4.15 – 4.02 (m, 1H), 3.98 – 3.84 (m, 1H), 3.51 (d, _J_ = 7.9 Hz, 1H), 3.45 (dd, _J_ = 7.9, 5.5 Hz, 1H), 2.90 (d, _J_ = 7.4 Hz, 3H), 2.03 (s, 3H), 1.96 (dd, _J_ = 2.7, 1.4 Hz, 3H).
Specific Rot.: TC (calc.): -256°
Chiral HPLC: Daicel Chiralcel, AS-H, 250x4.6; hexane/isopropanol = 60/40, 1 mL/min, ret. time enantiomere 1: 10.70 min (100 %), detection wavelength: 210 nm

_N_-(5-Hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide (+)



$C_{12}H_{16}N_2O_4$, 252.27 g/mol

_N_-(5-hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1_H_-isoindol-4-yl)acetamide (+) was synthesized according to GP-3.2 and purified by column chromatography using a mixture of EA and MeOH (100 % --> 95 % EA)

Yield: 55 %
Condition: pale yellow solid
TLC: R_f (EA) = 0.15
^{1}H NMR: (400 MHz, MeOD) δ = 5.61 (dd, _J_ = 3.4, 1.6 Hz, 1H), 4.07 (dd, _J_ = 9.3, 5.5 Hz, 1H), 3.93 (ddd, _J_ = 9.2, 3.8, 1.9 Hz, 1H), 3.55 – 3.48 (m, 1H),

3.45 (dd, *J* = 7.8, 5.5 Hz, 1H), 2.90 (d, *J* = 7.4 Hz, 3H), 2.03 (s, 3H), 1.96 (dd, *J* = 2.6, 1.4 Hz, 3H).

Specific Rot.: TC (calc.): +253°

Chiral HPLC: Daicel Chiralcel, AS-H, 250x4.6; hexane/isopropanol = 60/40, 1 mL/min, ret. time enantiomere 1: 18.81 min (100 %), detection wavelength: 210 nm

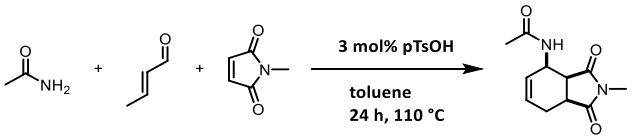
Preparation of Starting Materials

General procedure (GP-3.3) for AAD-MCR (for *α,β*-unsaturated aldehydes):

A pressure tube was charged with amide (1.0 equiv.), aldehyde (1.0 equiv.), the dienophile (1.0 equiv.), *p*-toluene sulfonic acid monohydrate (3 mol%), and toluene. The tube was sealed and the reaction stirred at 110 °C oil bath temperature. After 24 h, the solvent and other volatile compounds were removed by oil pump vacuum. The crude product was purified by SiO_2 flash column chromatography using PE/EA in different ratios as an eluent.
The exact amount, eluents and yields are described for each compound.

Example for GP-3.3

***N*-Methyl-1,2,3,6-tetrahydo-3-acetamidyl-phthalic imide**



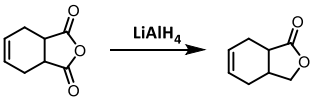
A pressure tube was charged with aceticamide (15 mmol, 890 mg, 1.0 equiv.), aldehyde (15 mmol, 1.05 g, 1.0 equiv.), the dienophile (15 mmol, 1.67 g, 1.0 equiv.), *p*-toluene sulfonic acid monohydrate (3 mol%), and toluene (35 mL). The tube was sealed and the reaction stirred at 110 °C oil bath temperature. After 24 h, the solvent and other volatile compounds were removed by oil pump vacuum. The crude product was purified by SiO_2 flash column chromatography using PE/EA (1/4 --> 0/1) as an eluent.
Product (1.8 g, 54 %) was isolated as slightly yellow crystals.

General procedure (GP-3.4) for AAD-MCR (for saturated aldehydes):

A pressure tube was charged with amide (1.0 equiv.), aldehyde (2.0 equiv.), the dienophile (1.0 equiv.), acetic anhydride (1.0 equiv.), *p*-toluene sulfonic acid monohydrate (3 mol%), and toluene. The tube was sealed and the reaction stirred at 110 °C oil bath temperature. After 24 h, the solvent and other volatile compounds were removed by oil pump vacuum. The crude product was purified by SiO_2 flash column chromatography using PE/EA in different ratios as an eluent.
The exact amount, eluents and yields are described for each compound.

Syntheses of starting materials

3a,4,7,7a-Tetrahydroisobenzofuran-1(3*H*)-one



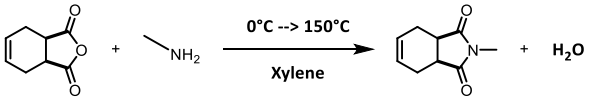
TLC: R_f = 0.29 (PE/EA = 1/2)

^{1}H NMR: ($CDCl_3$, 300 MHz) δ = 5.61 (t, *J* = 1.5 Hz, 2H), 3.73 (dd, *J* = 11.0, 6.5 Hz, 1H), 3.60 (dd, *J* = 11.2, 3.1 Hz, 1H), 2.20 – 1.95 (m, 6H).

LR-MS: (EI, 70 eV): 138 $[M]^+$

according to: J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, **1967**, *32*, 3919

***N*-Methyl-1,2,3,6-tetrahydophthalic imide**



cis-1,2,3,6-tetrahydrophthalic anhydride (7.5 g, 49 mmol, 1.0 equiv.) was suspended in xylene (27 mL) and cooled to 0 °C. Methylamine (2 M in THF, 27 mL, 54 mmol, 1.1 equiv.) was added at 0 °C. The reaction mixture was allowed to warm to RT and stirred at RT for 2 h.

Subsequently the suspension was stirred for 4 h at 150 °C using a water separator. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using PE/EA (2/1) as eluent.

Product (5.7 g, 70 %) was isolated as colourless crystals.

TLC: R_f = 0.42 (PE/EA = 2/1)

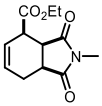
^{1}H-NMR: ($CDCl_3$, 400 MHz): δ = 5.92-5.85 (m, 2H, CH-1,2), 3.12-3.05 (m, 2H, CH-4,6), 2.96 (s, 3H, CH-5), 2.64-2.58 (m, 2H, CH-3), 2.27-2.19 (m, 2H, CH-7).

LR-MS: (EI, 70 eV): 165 $[M]^+$

Ethyl-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindole-4-carboxylate

Ethylpentadienoate (4.9 mmol, 1.1 eqiv.) and N-Methylmaleimide (4.45 mmol, 1.0 equiv.) were diluted in toluene (5 mL) and stirred for 18 h at 110 °C.

The solvent and all volatile compounds were removed and the crude product was washed with PE.



$C_{12}H_{15}NO_4$, 237.26 g/mol

Yield: 85 %

Condition: colourless crystalline solid

m.p.: 83 °C

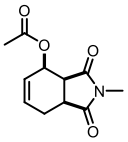
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.26 (ddd, *J* = 9.2, 4.5, 1.8 Hz, 1H), 6.07 – 5.93 (m, 1H), 4.23 (hd, *J* = 10.8, 7.1 Hz, 2H), 3.57 – 3.42 (m, 1H), 3.36 –3.30 (m, 1H), 3.15 (td, *J* = 8.8, 4.0 Hz, 1H), 2.94 (s, 3H), 2.69 – 2.56 (m, 1H), 2.35 – 2.24 (m, 1H), 1.36 – 1.23 (m, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 179.6, 177.8, 170.8, 128.9, 126.5, 61.4, 42.0, 40.2, 38.7, 25.0, 24.1, 14.2.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2979 (w), 1780 (w), 1724 (m), 1692 (s), 1438 (m), 1385 (w), 1324 (m), 1204 (m), 1130 (w), 1080 (w), 1054 (w), 1032 (w), 992 (w), 867 (w), 716 (s), 586 (w), 562 (w), 524 (w)

HR-MS (ESI): $[MH]^+$ = 238.1078; calculated: 238.1074

2-Methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl acetate



$C_{11}H_{13}NO_4$, 223.23 g/mol

TLC: R_f = 0.30 (PE/EA = 2/1)

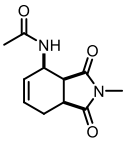
^{1}H-NMR: (300 MHz, $CDCl_3$): δ = 6.06 – 6.01 (m, 2H), 5.46 – 5.35 (m, 1H), 3.47 (dd, *J* = 9.4, 4.8 Hz, 1H), 3.16 – 3.03 (m, 1H), 2.97 (s, 3H), 2.72 – 2.61 (m, 1H), 2.47 – 2.30 (m, 1H), 2.06 (s, 3H).

LR-MS: (EI, 70 eV): 181 $[MH\text{-}C_2H_3O]^+$

According to: *Chem. Eur. J.*, **2005**, *11*, 4210 – 4218

***N*-(2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

The product was synthesized according to GP-3.3, using 15 mmol of starting material. The crude product was purified by column chromatography using PE / EA = 1 / 4 as an eluent.



$C_{11}H_{14}N_2O_3$, 222.24 g/mol

Yield: 54 %

TLC: R_f = 0.15 (PE/EA = 1/4)

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.4 Hz, 1H), 5.86 (ddt, *J* = 10.2, 7.2, 3.1 Hz, 1H), 5.72 (dt, *J* = 9.5, 3.1 Hz, 1H), 4.79 – 4.58 (m, 1H), 3.34 – 3.07 (m, 2H), 2.94 (s, 3H), 2.71 (ddt, *J* = 15.4, 7.2, 0.9 Hz, 1H), 2.37 – 2.13 (m, 1H), 2.08 (s, 3H).

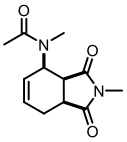
LR-MS: (EI, 70 eV): 180 $[MH\text{-}C_2H_3O]^+$

Chiral HPLC: *racemic mixture:*
Daicel Chiralcel, AS-H, 250x4.6; hexane/isopropanol = 60/40, 1 mL/min, ret. time enantiomere 1: 11.01 min (50 %), ret. time enantiomere 2: 31.93 min (50 %), detection wavelength: 210 nm
after separation:
ret. time enantiomere 1: 11.19 min (100 %)
ret. time enantiomere 2: 32.81 min (100 %)

According to: *Tetrahedron*, **2006**, *62*, 10962 – 10967

_N_-methyl-N-(2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1_H_-isoindol-4-yl)acetamide

Product was synthesized according to GP-3.3 using 8 mmol of starting material and purified by column chromatography using PE/EA = 1/1 --> EA



$C_{12}H_{16}N_2O_3$, 236.27 g/mol

Yield: 66 %

Condition: pale yellow crystalline solid

m.p.: 110 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.02 – 5.85 (m, 2H), 5.28 – 5.05 (m, 1H), 3.58 (t, *J* = 8.5 Hz, 1H), 3.14 (t, *J* = 8.3 Hz, 1H), 2.95 (d, *J* = 2.0 Hz, 3H), 2.92 (d, *J* = 2.1 Hz, 3H), 2.80 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.23 – 2.10 (m, 4H).

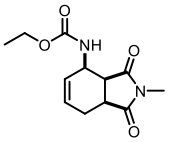
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 179.5, 177.4, 171.8, 128.5, 127.1, 50.9, 41.6, 39.0, 34.6, 25.1, 23.3, 22.5.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3049, 2974, 2933, 1767, 1692, 1633, 1476, 1408, 1386, 1286, 1239, 1118, 1081, 1051, 998, 920, 890, 760, 719

HR-MS (ESI): $[MH]^+$ = 237.1234; calculated: 237.1234

Ethyl (2-Methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

Ethylbutadienylcarbamate (353 mg, 2.5 mmol, 1.1 eqiv.), and *N*-methylmaleimide (253 mg, 2.27 mmol, 1.0 equiv.) were diluted toluene (2.5 mL). A crumb of *p*-TsOH was added and the solution was stirred for 20 h at 110 °C. The solvent and all volatile compounds were removed and the crude product was purified by column chromatography using PE/EA = 1/1 --> 1/2.



$C_{12}H_{16}N_2O_4$, 252.27 g/mol

Yield: 90 %

Condition: colourless crystalline solid

TLC: R_f (PE/EA = 2/1) = 0.47

m.p.: 83 – 85 °C

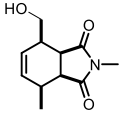
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.27 (ddd, *J* = 9.4, 4.6, 2.2 Hz, 1H), 6.10 – 5.92 (m, 1H), 4.32 – 4.17 (m, 2H), 3.52 (dd, *J* = 9.5, 6.4 Hz, 1H), 3.37 – 3.32 (m, 1H), 3.22 – 3.06 (m, 1H), 2.94 (s, 3H), 2.71 – 2.57 (m, 1H), 2.43 – 2.22 (m, 1H), 1.34 – 1.24 (t, *J* = 7.1, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 179.5, 177.8, 170.8, 128.9, 126.5, 61.4, 42.0, 40.2, 38.7, 25.0, 24.0, 14.2

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2982, 2862, 1782, 1722, 1685, 1439, 1387, 1323, 1282, 1200, 1129, 1081, 1051, 992, 891, 812, 716

HR-MS (ESI): $[MH]^+$ = 253.1182 ; calculated: 253.1183

4-(Hydroxymethyl)-2,7-dimethyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione



$C_{11}H_{15}NO_3$, 209.25 g/mol

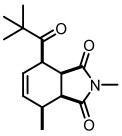
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 5.82 – 5.70 (m, 1H), 5.66 (dt, *J* = 9.1, 3.0 Hz, 1H), 4.02 (dd, *J* = 11.8, 5.7 Hz, 1H), 3.92 (dd, *J* = 11.8, 9.3 Hz, 1H), 3.35 (t, *J* = 7.8 Hz, 1H), 3.11 – 3.02 (m, 1H), 2.91 (s, 3H), 2.62 – 2.50 (m, 1H), 2.49 – 2.37 (m, 1H), 1.47 (dd, *J* = 7.4, 0.9 Hz, 3H).

LR-MS: (EI, 70 eV): 210 $[MH]^+$

According to: *Tetrahedron*, **1987**, *21*, 5019 – 5030

2,4-Dimethyl-7-pivaloyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

2,2-Dimethylocta-4,6-dien-3-one (1.53 g, 10 mmol, 1.0 equiv.) and *N*-methylmaleimide (1.1 g, 10 mmol, 1.0 equiv.) were diluted in toluene (20 mL) and stirred for 3 d at 60 °C. The solvent and all volatile compounds were removed and the crude product was purified by column chromatography using a mixture of PE and EA (20 % --> 33 % EA).



$C_{15}H_{21}NO_3$, 263.34 g/mol

Yield: 40 %

Condition: colourless crystalline solid

TLC: R_f (PE/EA = 2/1) = 0.46

m.p.: 110 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 5.99-5.91 (m, 2 H), 3.91-3.86 (m, 1 H), 3.43 (dd, ^3J = 9.4, 8.1, 1 H), 3.11 (dd, ^3J = 9.4, 7.2, 1H), 2.93 (s, 3 H), 2.68-2.59 (m, 1 H), 1.37 (d, 3 H), 1.26 (s, 9 H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 213.2, 177.8, 177.4, 135.7, 134.3, 131.8, 125.0, 45.0, 43.5, 43.0, 42.6, 41.3, 30.6, 29.9, 28.5, 26.9, 24.8, 16.4

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2967(w), 1766(w), 1694(s), 1477(m), 1433(s), 1378(m), 1281(s), 1080(s), 1003(s), 962(m), 718(s).

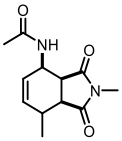
HR-MS (ESI): $[MH]^+$ = 264.1601; calculated: 264.1594

LR-MS: (EI, 70 eV): 262 $[M-H]^+$

According to: *Angew. Chem.*, **2012***, 124,* 4401 – 4404

***N*-(2,7-Dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)acetamide**

Product was synthesized according to GP-3.3 using 7.5 mmol of starting material and purified by column chromatography using PE/EA = 1/1 --> EA



$C_{12}H_{16}N_2O_3$, 236.27 g/mol

Yield: 54 %

TLC: R_f = 0.30 (EA)

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 8.1 Hz, 1H), 5.75 – 5.57 (m, 2H), 4.78 – 4.63 (m, 1H), 3.18 (dt, *J* = 9.1, 4.6 Hz, 1H), 3.15 – 3.00 (m, 1H), 2.92 (s, 3H), 2.59 – 2.43 (m, 1H), 2.08 (s, 3H), 1.41 (d, *J* = 7.4 Hz, 4H).

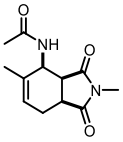
LR-MS: (EI, 70 eV): 236 $[M]^+$

Chiral HPLC: *racemic mixture:*
Daicel Chiralcel, AS-H, 250x4.6; hexane/isopropanol = 50/50, 1 mL/min, ret. time enantiomere 1: 6.72 min (51 %), ret. time enantiomere 2: 13.92 min (49 %), detection wavelength: 210 nm
after separation:
ret. time enantiomere 1: 6.66 min (100 %)
ret. time enantiomere 2: 14.04 min (100 %)

According to: *Tetrahedron*, **2006**, *62*, 10962–10967

***N*-(2,5-Dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)acetamide**

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using EA as an eluent.



$C_{12}H_{16}N_2O_3$, 236.27 g/mol

Yield: 56 %

TLC: R_f = 0.29 (EA)

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 9.3 Hz, 1H), 5.65 – 5.50 (m, 1H), 4.84 – 4.65 (m, 1H), 3.14 (dd, *J* = 7.7, 5.6 Hz, 2H), 2.94 (s, 3H), 2.61 (dd, *J* = 15.5, 7.4 Hz, 1H), 2.27 – 2.14 (m, 1H), 2.11 (s, 3H), 1.65 (s, 3H).

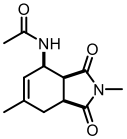
LR-MS: (EI, 70 eV): 236 $[M]^+$

Chiral HPLC: *racemic mixture:*
Daicel Chiralcel, AS-H, 250x4.6; hexane/isopropanol = 50/50, 1 mL/min, ret. time enantiomere 1: 7.34 min (50 %), ret. time enantiomere 2: 23.57 min (50 %), detection wavelength: 210 nm
after separation:
ret. time enantiomere 1: 7.58 min (100 %)
ret. time enantiomere 2: 24.29 min (100 %)

According to: *Tetrahedron*, **2006**, *62*, 10962–10967

***N*-(2,6-Dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using EA as an eluent.



$C_{12}H_{16}N_2O_3$, 236.27 g/mol

Yield: 62 %

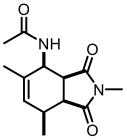
TLC: R_f = 0.29 (EA)

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 11.0 Hz, 1H), 5.36 (s, 1H), 4.71 – 4.55 (m, 1H), 3.24 – 3.09 (m, 2H), 2.94 (s, 3H), 2.54 (d, *J* = 15.3 Hz, 1H), 2.33 – 2.18 (m, 1H), 2.05 (s, 3H), 1.71 (s, 3H).

LR-MS: (EI, 70 eV): 236 $[M]^+$

According to: *Tetrahedron*, **2006**, *62*, 10962 – 10967

***N*-(2,5,7-Trimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**



$C_{13}H_{18}N_2O_3$, 250.30 g/mol

TLC: R_f = 0.33 (EA)

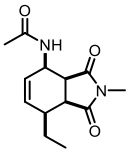
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 22.5 Hz, 1H), 5.43 – 5.30 (m, 1H), 4.83 – 4.58 (m, 1H), 3.15 – 3.08 (m, 1H), 3.05 – 2.98 (m, 1H), 2.90 (s, 3H), 2.57 – 2.41 (m, 1H), 2.09 (s, 3H), 1.67 – 1.58 (m, 3H), 1.34 (d, *J* = 7.3 Hz, 3H).

LR-MS: (EI, 70 eV): 250 $[M]^+$

According to: *Tetrahedron*, **2006**, *62*, 10962 – 10967

***N*-(7-Ethyl-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (45 % --> 100 % EA) as an eluent.



$C_{13}H_{18}N_2O_3$, 250.30 g/mol

Yield: 30 %

Condition: pale yellow crystalline solid

TLC: R_f (PE/EA = 1/2) = 0.23

m.p.: 103 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.34 (d, *J* = 8.5 Hz, 1H), 5.72 – 5.65 (m, 2H), 4.68 (dd, *J* = 8.5, 4.7 Hz, 1H), 3.16 (dd, *J* = 8.9, 5.8 Hz, 2H), 2.90 (s, 3H), 2.37 – 2.10 (m, 1H), 2.07 (s, 3H), 2.01 – 1.84 (m, 1H), 1.83 – 1.65 (m, 1H), 1.05 (t, *J* = 7.3 Hz, 2H).

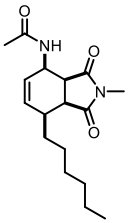
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 179.2, 176.8, 170.1, 133.1, 132.2, 132.0, 131.4, 45.9, 43.92, 43.6, 42.9, 42.2, 38.4, 38.2, 28.0, 25.2, 24.9, 24.1, 23.6, 12.8, 12.7.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3306, 2967, 2933, 2878, 1774, 1692, 1651, 1535, 1431, 1372, 1282, 1192, 1159, 1100, 1033, 995, 883, 794, 690

HR-MS (ESI): $[MH]^+$ = 251.1393; calculated: 251.1390

***N*-(7-Hexyl-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (33 % --> 100 % EA) as an eluent.



$C_{17}H_{26}N_2O_3$, 306.41 g/mol

Yield: 45 %

Condition: pale yellow crystalline solid

TLC: R_f (PE/EA = 1/2) = 0.31

m.p.: 111 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.36 (t, *J* = 9.7 Hz, 1H), 5.76 – 5.58 (m, 2H), 4.76 – 4.59 (m, 1H), 3.23 – 3.06 (m, 2H), 2.91 (s, 3H), 2.37 – 2.20 (m, 1H), 2.08

(s, 3H), 1.95 – 1.83 (m, 1H), 1.76 – 1.58 (m, 1H), 1.51 – 1.21 (m, 10H), 0.97 – 0.82 (m, 3H).

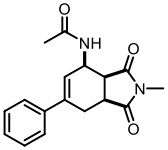
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 179.2, 176.9, 170.1, 133.4, 132.4, 46.0, 43.6, 42.4, 36.4, 31.9, 31.0, 29.3, 28.2, 24.9, 23.6, 22.8, 14.2.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3254, 3082, 2926, 2855, 1771, 1685, 1640, 1566, 1431, 1375, 1282, 1185, 1156, 1111, 1081, 992, 906, 978, 831, 708

HR-MS (ESI): $[MH]^+$ = 307.2022; calculated: 307.2016

***N*-(2-Methyl-1,3-dioxo-6-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (50 % --> 75 % EA) as an eluent.



$C_{17}H_{18}N_2O_3$, 298.34 g/mol

Yield: 52 %

Condition: colourless crystalline solid

TLC: R_f (PE/EA = 1/1) = 0.11

m.p.: 166 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 5.92-5.88 (m, 1 H), 4.90-4.82 (m, 1 H), 3.38-3.21 (m, 3 H), 2.91 (s, 3 H), 2.60-2.49 (m, 1 H), 2.12 (s, 3 H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 179.2, 179.0, 170.1, 139.6, 139.1, 128.7, 128.1, 127.4, 125.8, 46.7, 42.7, 39.5, 27.7, 25.2, 23.6

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3320(s), 3073(w), 2963(w), 1775(w), 1695(s), 1645(s), 1540(s), 1427(s), 1383(m), 1281(s), 1109(s), 1081(m), 1002(s), 761(s), 697(s), 601(s), 562(s)

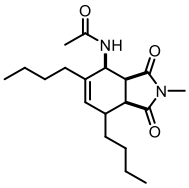
HR-MS (ESI): $[MH]^+$ = 299.1396; calculated: 299.1390

LR-MS: (EI, 70 eV): R_t = 12.244 min, m/z = 298 $[M]^+$, 255 $[M\text{-}CO\text{-}CH_3]^+$

Chiral HPLC: *racemic mixture:*
Daicel Chiralcel, AS-H, 250x4.6; hexane/isopropanol = 50/50, 1 mL/min, ret. time enantiomere 1: 8.18 min (51 %), ret. time enantiomere 2: 19.75 min (49 %), detection wavelength: 210 nm
after separation:
ret. time enantiomere 1: 8.39 min (100 %)
ret. time enantiomere 2: 21.29 min (100 %)

_N_-(5,7-Dibutyl-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1_H_-isoindol-4-yl)acetamide

Product was synthesized according to GP-3.4 using 10 mmol of starting material and purified by column chromatography using a mixture of PE and EA (50 % --> 100 % EA) as an eluent.



$C_{19}H_{30}N_2O_3$, 334.46 g/mol

Yield: 35 %

Condition: pale yellow amorphous solid

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 9.2 Hz, 1H), 5.32 (dd, *J* = 3.6, 2.6 Hz, 1H), 4.76 (d, *J* = 9.2 Hz, 1H), 3.15 – 3.05 (m, 2H), 2.88 (s, 3H), 2.27 (dt, *J* = 30.2, 13.9 Hz, 1H), 2.11 (s, 3H), 1.94 – 1.79 (m, 3H), 1.73 – 1.55 (m, 1H), 1.50 – 1.29 (m, 4H), 1.29 – 1.15 (m, 4H), 0.96 – 0.89 (m, 3H), 0.86 (td, *J* = 7.5, 3.6 Hz, 3H).

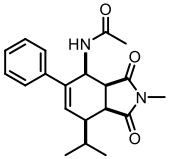
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 179.7, 177.1, 170.2, 141.4, 125.7, 48.3, 44.4, 42.8, 36.3, 31.1, 30.9, 30.4, 29.8, 24.7, 23.5, 22.7, 22.3, 14.1, 13.9

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3392, 2956, 2863, 1770, 1689, 1513, 1435, 1388, 1286, 1126, 1038, 1006, 850, 767, 731

HR-MS (ESI): $[MH]^+$ = 335.2334 ; calculated: 335.2329

_N_-(7-Isopropyl-2-methyl-1,3-dioxo-5-phenyl-2,3,3a,4,7,7a-hexahydro-1_H_-isoindol-4-yl)acetamide

Product was synthesized according to GP-3.3 using 12 mmol of starting material and purified by column chromatography using a mixture of PE and EA (50 % --> 70 % EA) as an eluent.



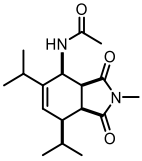
$C_{20}H_{24}N_2O_3$, 340.42 g/mol

Yield: 50 %

Condition: pale yellow crystalline solid
TLC: R_f (PE/EA = 1/2) = 0.45
m.p.: 138 – 152 °C
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.35 – 7.14 (m, 2H), 7.08 – 6.90 (m, 3H), 5.83 – 5.69 (m, 1H), 5.09 (t, *J* = 6.3 Hz, 1H), 3.43 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.27 (dd, *J* = 8.5, 5.9 Hz, 1H), 2.96 (s, 3H), 2.32 – 2.11 (m, 1H), 2.11 – 1.96 (m, 1H), 1.92 (s, 3H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 179.2, 176.9, 170.1, 142.8, 137.9, 129.9, 128.3, 128.1, 127.7, 47.9, 44.8, 41.4, 28.4, 24.9, 23.4, 22.3, 21.3
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3377, 2945, 2870, 1767, 1695, 1670, 1513, 1476, 1431, 1372, 1327, 1286, 1193, 1115, 1081, 1040, 1010, 798, 760, 697
HR-MS (ESI): $[MH]^+$ = 341.1866; calculated: 341.1860

N-(5,7-Diisopropyl-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide

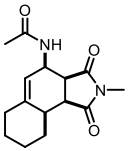
Product was synthesized according to GP-3.4 using 10 mmol of starting material and purified by column chromatography using a mixture of PE and EA (33 % --> 80 % EA) as an eluent.



$C_{17}H_{26}N_2O_3$, 306.41 g/mol
Yield: 15 %
Condition: pale yellow solid
m.p.: 122 – 130 °C
TLC: R_f (PE/EA = 1/2) = 0.21
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.34 (d, *J* = 9.3 Hz, 1H), 5.47 (t, *J* = 2.9 Hz, 1H), 4.87 – 4.67 (m, 1H), 3.29 (dd, *J* = 8.6, 5.8 Hz, 1H), 3.10 (dd, *J* = 8.5, 6.2 Hz, 1H), 2.87 (s, 3H), 2.31 – 2.15 (m, 2H), 2.13 (s, 3H), 1.88 – 1.77 (m, 1H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 179.7, 177.3, 170.3, 147.1, 123.0, 48.5, 44.6, 44.0, 41.2, 28.5, 24.7, 23.7, 22.6, 22.3, 22.1, 21.2.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3399, 2960, 2870, 1767, 1677, 1513, 1435, 1383, 1327, 1286, 1211, 1185, 1122, 1085, 1047, 1006, 824, 753, 716, 678
HR-MS (ESI): $[MH]^+$ = 307.2019; calculated: 307.2016

***N*-(2-Methyl-1,3-dioxo-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-benzo[e]isoindol-4-yl)acetamide**

Product was synthesized according to GP-3.3 using 3.95 mmol of starting material and purified by column chromatography using a mixture of PE and EA (66 % --> 100 % EA) as an eluent.



$C_{15}H_{20}N_2O_3$, 276.34 g/mol

Yield: 65 %

Condition: colourless crystalline solid

TLC: R_f (EA) = 0.20

m.p.: 162 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 8.6 Hz, 1H), 5.33 (d, *J* = 21.4 Hz, 1H), 4.69 (dd, *J* = 5.4, 3.3 Hz, 1H), 3.24 – 3.06 (m, 2H), 2.92 (s, 3H), 2.41 – 2.29 (m, 1H), 2.19 – 2.02 (m, 5H), 1.90 – 1.75 (m, 3H), 1.54(dt, *J* = 13.4, 6.2 Hz, 2H), 1.46 – 1.27 (m, 1H).

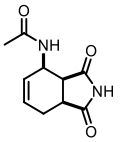
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 179.4, 177.3, 170.1, 142.1, 122.8, 45.3, 43.2, 43.2, 36.3, 29.2, 24.8, 24.5, 23.7, 22.2, 21.6.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3373, 2937, 2866, 2837, 1767, 1670, 1528, 1431, 1372, 1338, 1290, 1148, 1111, 1033, 984, 947, 850, 813, 723

HR-MS (ESI): $[MH]^+$ = 277.1552; calculated: 277.1547

***N*-(1,3-Dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

Product was synthesized according to GP-3.3 using 10 mmol of starting material and purified by column chromatography using a mixture of DCM and MeOH (DCM/MeOH = 96/4) as an eluent.



$C_{10}H_{12}N_2O_3$, 208.22 g/mol

Yield: 53 %

TLC: R_f = 0.35 (DCM/MeOH = 95/5)

^{1}H NMR: (300 MHz, DMSO-d_6) δ = 11.20 (s, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 6.08 – 5.84 (m, 1H), 5.84 – 5.60 (m, 1H), 4.46 – 4.22 (m, 1H), 3.30 (d, *J* = 7.2 Hz,

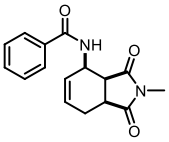
1H), 3.14 (t, *J* = 8.3 Hz, 1H), 2.48 – 2.38 (m, 1H), 2.20 – 2.04 (m, 1H), 1.88 (s, 3H).

LR-MS: (EI, 70 eV): 209 $[MH]^+$

According to: *Tetrahedron*, **2006**, *62*, 10962 – 10967

***N*-(2-Methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)benzamide**

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (33 % --> 66 % EA) as an eluent.



$C_{16}H_{16}N_2O_3$, 284.32 g/mol

Yield: 30 %

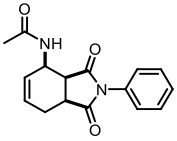
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.96 – 7.87 (m, 2H), 7.87 – 7.79 (m, 3H), 5.97 – 5.87 (m, 1H), 5.87 – 5.79 (m, 1H), 5.01 – 4.87 (m, 1H), 3.39 – 3.29 (m, 1H), 3.29 – 3.15 (m, 1H), 2.99 (s, 3H), 2.81 – 2.69 (m, 1H), 2.39 – 2.18 (m, 1H).

LR-MS: (EI, 70 eV): 284 $[M]^+$

According to: *Tetrahedron*, **2006**, *62*, 10962 – 10967

***N*-(1,3-Dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

Product was synthesized according to GP-3.3 using 10 mmol of starting material and purified by column chromatography using a mixture of PE and EA (50 % --> 100 % EA) as an eluent.



$C_{16}H_{16}N_2O_3$, 284.32 g/mol

Yield: 65 %

Condition: pale yellow crystalline solid

m.p.: 135 – 145 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.57 – 7.34 (m, 3H), 7.23 – 7.15 (m, 2H), 5.99 (tt, *J* = 7.1, 3.1 Hz, 1H), 5.84 (dt, *J* = 9.5, 3.0 Hz, 1H), 4.81 (qd, *J* = 5.6, 2.6 Hz,

1H), 3.38 (qd, *J* = 9.2, 3.7 Hz, 2H), 2.83 (dd, *J* = 15.5, 7.2 Hz, 1H), 2.40 – 2.25 (m, 1H), 2.08 (s, 3H).

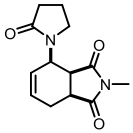
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 178.5, 170.2, 133.1, 131.5, 129.4, 129.2, 127.7, 126.5, 45.6, 42.7, 39.0, 24.6, 23.6.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3276, 3079, 2930, 1703, 1651, 1550, 1495, 1372, 1286, 1185, 1137, 1081, 984, 943, 880, 790, 760, 719

HR-MS (ESI): $[MH]^+$ = 285.1238 ; calculated: 285.1234

2-Methyl-4-(2-oxopyrrolidin-1-yl)-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (33 % --> 66 % EA) as an eluent.



$C_{13}H_{16}N_2O_3$, 248.28 g/mol

Yield: 22 %

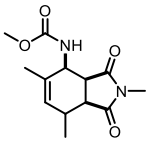
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.13 – 5.85 (m, 2H), 4.73 (d, *J* = 7.3 Hz, 1H), 3.67 – 3.44 (m, 3H), 3.24 – 3.09 (m, 1H), 2.92 (s, 3H), 2.82 – 2.72 (m, 1H), 2.55 – 2.38 (m, 2H), 2.25 – 1.93 (m, 4H).

LR-MS: (EI, 70 eV): 248 $[M]^+$

According to: *Tetrahedron*, **2006**, *62*, 10962 – 10967

Methyl-(2,5,7-trimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)carbamate

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (33 % EA) as an eluent.



$C_{13}H_{18}N_2O_4$, 266.30 g/mol

Yield: 70 %

Condition: colourless crystalline solid

TLC: R_f (PE/EA = 2/1) = 0.36

m.p.: 114 – 116 °C

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 6.54 (d, *J* = 9.6 Hz, 1H), 5.33 (s, 1H), 4.50 – 4.36 (m, 1H), 3.71 (s, 3H), 3.15 (dd, *J* = 8.6, 5.4 Hz, 1H), 3.10 – 2.96 (m,1H), 2.89 (s, 3H), 2.48 (s, 1H), 1.66 (d, *J* = 1.0 Hz, 3H), 1.34(d, *J* = 7.3 Hz, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 179.2, 177.0, 157.1, 138.3, 127.1, 52.5, 50.1, 44.9, 44.4, 30.7, 24.8, 18.5, 16.7.

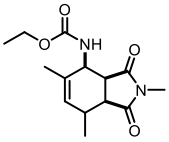
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3403, 2967, 2937, 1767, 1718, 1685, 1517, 1435, 1383, 1327, 1293, 1238, 1193, 1144, 1092, 1062, 962, 924, 842, 783

HR-MS (ESI): $[MH]^+$ = 267.1343; calculated: 267.1340

LR-MS: (EI, 70 eV): 266.3$[M]^+$

Ethyl-(2,5,7-trimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (33 % EA) as an eluent.



$C_{14}H_{20}N_2O_4$, 280.32 g/mol

Yield: 62 %

Condition: colourless crystalline solid

TLC: R_f (PE/EA = 2/1) = 0.4

m.p.: 52 – 58 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.51 (d, *J* = 9.6 Hz, 1H), 5.33 (d, *J* = 0.7 Hz, 1H), 4.56 – 4.32 (m, 1H), 4.22 – 4.05 (m, 2H), 3.16 (dd, *J* = 8.6, 5.4 Hz, 1H), 3.08 – 2.95 (m, 1H), 2.90 (s, 3H), 2.55 – 2.38 (m, 1H), 1.68 – 1.59 (m, 3H), 1.35 (d, *J* = 7.3 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 179.3, 177.1, 156.7, 138.4, 127.0, 61.3, 50.0, 44.9, 44.4, 30.7, 24.9, 18.5, 16.9, 14.8.

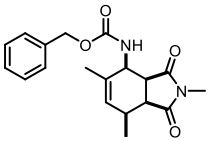
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3418, 2982, 2937, 1767, 1689, 1510, 1431, 1375, 1327, 1279, 1230, 1170, 1122, 1092, 1062, 835, 783

HR-MS (ESI): $[MH]^+$ = 281.1500; calculated: 281.1496

LR-MS: (EI, 70 eV): 280 $[M]^+$

Benzyl-(2,5,7-trimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (33 % EA) as an eluent.



$C_{19}H_{22}N_2O_4$, 342.40 g/mol

Yield: 67 %

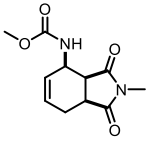
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.46 – 7.28 (m, 5H), 6.71 – 6.56 (m, 1H), 5.37 (s, 1H), 5.17 (d, *J* = 6.1 Hz, 2H), 4.52 – 4.37 (m, 1H), 3.25 – 3.08 (m, 1H), 3.08 – 2.96 (m, 1H), 2.89 (s, 3H), 2.57 – 2.35 (m, 1H), 1.68 – 1.59 (m, 3H), 1.35 (d, *J* = 7.3 Hz, 3H).

LR-MS: (EI, 70 eV): 207 $[M\text{-}C_8H_7O_2]^+$

According to: *Org. Biomol. Chem.*, **2011**, *9*, 7224 – 7236

Methyl-(2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (66 % EA) as an eluent.



$C_{11}H_{14}N_2O_4$, 238.24 g/mol

Yield: 58 %

Condition: colourless amorphous solid

TLC: R_f (PE/EA = 1/2) = 0.60

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 6.42 (d, *J* = 8.6 Hz, 1H), 5.87 – 5.81 (m, 1H), 5.77 (dt, *J* = 9.5, 2.7 Hz, 1H), 4.43 (s, 1H), 3.71 (s, 3H), 3.23 (dt, *J* = 13.6, 6.9 Hz, 1H), 3.16 (dd, *J* = 15.2, 6.7 Hz, 1H), 2.92 (s, 3H), 2.76 – 2.61 (m, 1H), 2.28 – 2.12 (m, 1H).

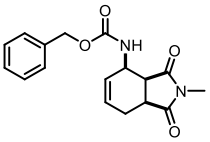
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 179.5, 178.9, 156.9, 133.2, 127.3, 52.4, 52.4, 47.3, 43.0, 38.9, 25.1, 24.2

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3343, 2952, 1774, 1685, 1532, 1431, 1380, 1356, 1282, 1252, 1189, 1126, 1103, 1058, 999, 883, 783, 731, 675

HR-MS (ESI): $[MH]^+$ = 239.1027 ; calculated: 239.1026

Benzyl-(2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

Product was synthesized according to GP-3.3 using 10 mmol of starting material and purified by column chromatography using a mixture of PE and EA (25 % --> 66 % EA) as an eluent.



$C_{17}H_{18}N_2O_4$, 314.34 g/mol

Yield: 45 %

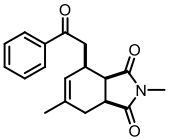
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.44 – 7.17 (m, 5H), 6.54 (d, *J* = 9.2 Hz, 1H), 5.91 – 5.65 (m, 2H), 5.18 – 4.91 (m, 2H), 4.56 – 4.22 (m, 1H), 3.36 – 2.97 (m, 2H), 2.86 (s, 3H), 2.68 (ddd, *J* = 22.2, 13.5, 7.4 Hz, 1H), 2.22 – 2.04 (m, 1H).

LR-MS: (EI, 70 eV): 223 $[M\text{-}C_7H_7]^+$

According to: *Org. Biomol. Chem.*, **2011**, *9*, 7224 – 7236

2,6-Dimethyl-4-(2-oxo-2-phenylethyl)-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

Product was synthesized according to *Angew. Chem. 2012, 124, 4401 – 4404* and purified by column chromatography using a mixture of PE and EA (20 % EA) as an eluent.



$C_{18}H_{19}NO_3$, 297.35 g/mol

Yield: 20 %

Condition: pale yellow amorphous solid

TLC: R_f (PE/EA = 2/1) = 0.45

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.08 – 8.01 (m, 2H), 7.63 – 7.44 (m, 3H), 5.32 (s, 1H), 3.85 (dd, *J* = 18.3, 8.1 Hz, 1H), 3.29 (ddd, *J* = 18.3, 10.1, 5.4 Hz, 2H), 3.16 (ddd, *J* = 10.5, 6.0, 2.4 Hz, 1H), 3.08 – 2.95 (m, 1H), 2.90 (s, 3H), 2.63 – 2.54 (m, 1H), 2.36 – 2.22 (m, 1H), 1.76 – 1.68 (m, 3H).

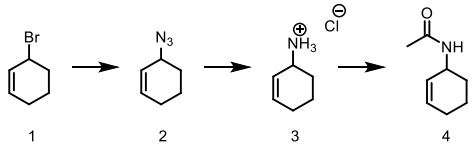
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 199.3, 180.0, 178.9, 137.2, 137.2, 133.3, 128.7, 128.2, 125.2, 42.2, 40.6, 40.1, 31.5, 29.4, 24.9, 23.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2945, 1771, 1685, 1435, 1379, 1328, 1282, 1208, 1137, 1111, 1006, 835, 783, 753, 693

HR-MS (ESI): $[MH]^+$ = 298.1443; calculated: 298.1438

Unreactive substrates

***N*-(Cyclohex-2-en-1-yl)acetamide**

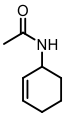


3-Bromocyclohex-1-ene (3.0 g, 18.6 mmol, 1.0 equiv.) was dissolved in CCl_4 (30 mL) and sodium azide (4.0 g, 61.8 mmol, 3.3 equiv.) dissolved in water (30 mL) was added at room temperature. The mixture was stirred for 48 h at room temperature. The phases were separated and the aqueous phase was extracted with DCM (2 × 50 mL) and EA (50 mL). Combined organic phases were dried over Na_2SO_4, the drying agent was filtered off and the solvent was removed under reduced pressure.

The crude product (**2**) was dissolved in dry THF (12 mL) and PPh_3 (8.8 g, 33.5 mmol, 1.8 equiv.) was added. The solution was stirred for 2 h at room temperature before $NaOH_{aq.}$ (1 N, 40 mL) was added. The aqueous phase was extracted with EA (3 × 50 mL). Combined organic phases were washed with 1 M $HCl_{aq.}$ (30 mL) and dried over Na_2SO_4, the drying agent was filtered off and the solvent was removed under reduced pressure to get 2.5 g of pale yellow solid (**3**) in a quantitative yield.

The crude product (**3**) (500 mg, 3.7 mmol, 1.0 equiv.) was suspended in DCM (50 mL) and NEt_3 (1.56 mL, 11.2 mmol, 3.0 equiv.) was added. When the precipitate was completely dissolved DMAP (46 mg, 0.37 mmol, 0.1 equiv.) and acetyl chloride (0.29 mL, 4.1 mmol, 1.1 equiv.) were added and the mixture was stirred for 3 h at RT. The solution was washed with brine (50 mL), phases were separated, the organic phase was dried over Na_2SO_4, the drying agent was filtered off and the solvent was removed under reduced pressure.

The crude product was purified by column chromatography using a mixture of Pentan and EA (66 % --> 100 % EA). Product **4** was isolated as a crystalline colourless solid (417 mg, 80 %)



$C_8H_{13}NO$, 139.20 g/mol

Yield: 80 %

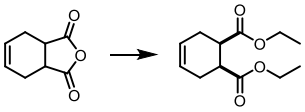
Condition: colourless crystalline solid

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 5.93 – 5.77 (m, 1H), 5.63 – 5.49 (m, 1H), 4.55 – 4.38 (m, 1H), 2.07 – 1.95 (m, 5H), 1.95 – 1.81 (m, 1H), 1.70 – 1.57 (m, 2H), 1.57 – 1.41 (m, 1H).

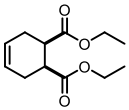
LR-MS: (EI, 70 eV): 139 $[M]^+$, 111, 97, 79, 69

Synthesis according to: *Green Chem.*, **2015**, *17*, 1408 – 1413

Diethyl cyclohex-4-ene-1,2-dicarboxylate



Tetrahydrophthalic anhydride (1.52 g, 10 mmol, 1.0 equiv.) was suspended in EtOH (40 mL) and H_2SO_4 conc. (2 mL) was added. The solution was stirred at 80 °C for 2 h. After cooling down to RT a saturated aqueous solution of $NaHCO_3$ (50 mL) was added and the aqueous phase was extracted with DCM (2 × 50 mL) and with EA (50 mL). Combined organic phases were dried over Na_2SO_4, the drying agent was filtered off and the solvent was removed under reduced pressure to get product as a colourless liquid (2.05 g, 92 %)



$C_{12}H_{18}O_4$, 226.27 g/mol

Yield: 92 %

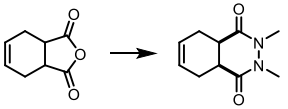
Condition: colourless crystalline solid

^{1}H NMR: (400 MHz, MeOD) δ = 5.75 – 5.56 (m, 2H), 4.25 – 4.01 (m, 4H), 3.10 – 3.03 (m, 2H), 2.60 – 2.42 (m, 2H), 2.41 – 2.23 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 6H).

LR-MS: (EI, 70 eV): 226 $[M]^+$, 181, 152, 136, 107, 79

Synthesis according to: *Tetrahedron*, **2011**, *67*, 501 – 504

2,3-Dimethyl-2,3,4a,5,8,8a-hexahydrophthalazine-1,4-dione

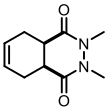


N,*N*´-Dimethylhydrazine dihydrochloride (1.9 g, 14.5 mmol, 1.1 equiv.) and the anhydride (2.0 g, 13.1 mmol, 1.0 equiv.) were dissolved in acetic acid (100 mL) and stirred at 135 °C over night. After cooling down to RT, H_2O (100 mL) was added and the

aqueous phase was extracted with DCM (4 × 50 mL). Combined organic phases were dried over Na_2SO_4, the drying agent was filtered off and the solvent was removed under reduced pressure.

The crude product was purified by column chromatography using a mixture of pentane and EA (75 % EA)

Product was isolated as a crystalline colourless solid (1.32 g, 52 %)



	$C_{10}H_{14}N_2O_2$, 194.23 g/mol
Yield:	52 %
Condition:	colourless crystalline solid
^{1}H NMR:	(300 MHz, $CDCl_3$) δ = 5.67 (t, *J* = 1.4 Hz, 2H), 3.25 (s, 6H), 2.97 – 2.81 (m, 1H),2.45 – 2.04 (m, 4H).
^{13}C NMR:	(75 MHz, $CDCl_3$) δ = 170.4, 124.5, 37.1, 32.8, 22.8
HR-MS (ESI):	$[MH]^+$ = 195.1131; calculated: 195.1128
LR-MS:	(EI, 70 eV): 194 $[M]^+$, 165, 136, 107, 79, 59

Synthesis according to: *J. Med. Chem.*, **2011***, 54,* 312 – 319

DFT calculations

Quantum chemical calculations were performed using Gaussian G09 software package.[1] Geometries of substrate molecules were optimized using B3LYP/6-311+g(d,p) method *in vacuo*. Frequency calculations were performed on the minima in order to ascertain the type of stationary point as well as to obtain zero-point vibrational energies. Thermodynamic properties were calculated at 298 Kelvin. Transition state geometries were optimized using the same method, verifying each time that only one imaginary vibrational frequency is present in the transition state. Geometries of singlet oxygen-starting material complexes as well as the geometries of products were obtained by geometry optimization in the direction of the displacement vector of the vibration with imaginary frequency. Expected relative product distribution was calculated taking both the conformer equilibration as well as the relative reactivity of the conformers in the reaction into account. Rapid equilibration assures that the relative ratio of conformers remains constant over the course of reaction and the conformer ratio can be obtained from relative conformer energies by Arrhenius-like relationship:

$$K = e^{-\frac{\Delta E}{RT}}$$

where ΔE is the energy difference between conformers, R is the universal gas constant, and T is the thermodynamic temperature. Relative reactivity of the conformers can be obtain by similar relationship:

$$k = e^{-\frac{\Delta\Delta E^{\ddagger}}{RT}}$$

where the $\Delta\Delta E^{\ddagger}$ is the energy difference between the activation energies of the reaction for the two corresponding conformers. Expected ratio of products was then calculated as follows:

$$R = Kk$$

1: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J., J. A. ; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; E. Brothers; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.;Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision A.1*, Gaussian, Inc.,: Wallingford, CT, 2009.

3.7. Additional oxidation reactions according to GP-3.1

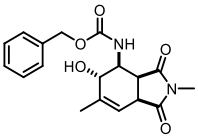
3.7.1. Statement concerning additional oxidation products

Within the scope of photooxidation of anellated cyclohexenes, presented in this chapter, several further substrates were oxidized. As these substrates deliver no new information concerning selectivity and reactivity, and due to their similarity to already listed compounds, they will not be published. For the sake of completeness, these compounds and the corresponding oxidation products, are listed below.

3.7.2. Oxidation products: Reaction procedures and analytical data

Benzyl-(5-hydroxy-2,6-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

Benzyl-(5-hydroxy-2,6-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carba-mate was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (33 % --> 80 % EA)



$C_{18}H_{20}N_2O_5$, 344.37 g/mol

Yield: 45 %

Condition: pale yellow solid

m.p.: 135 – 140 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.44 – 7.28 (m, 5H), 6.52 (d, *J* = 9.2 Hz, 1H), 5.49 – 5.46 (m,1H), 5.15 (s, 2H), 4.13 – 4.06 (m, 1H), 3.94 (d, *J* = 9.5 Hz, 1H), 3.63 – 3.49 (m, 1H), 3.25 (dd, *J* = 7.9, 5.5 Hz, 1H), 2.93 (s, 3H), 1.85 – 1.82 (m, 3H), 0.97 – 0.79 (m, 1H).

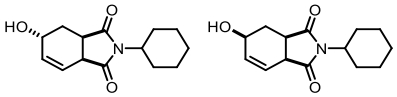
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 176.4, 136.2, 128.7, 128.5, 128.4, 116.6, 70.7, 67.50, 52.7, 43.4, 40.9, 25.0, 19.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3429, 3299, 2933, 1774, 1685, 1543, 1515, 1431, 1379, 1327, 1275, 1226, 1159, 1081, 924, 880, 772, 693

HR-MS (ESI): $[MH]^+$ = 345.1450; calculated: 345.1445

2-Cyclohexyl-5-hydroxy-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

2-Cyclohexyl-5-hydroxy-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione was synthesized according to GP-3.1 (reaction time = 19 h) and purified by column chromatography using a mixture of PE and EA (33 % EA)



A B

$C_{14}H_{19}NO_3$, 249.3100 g/mol

Yield: 93% (ratio 5/1)

Condition: pale yellow solid

m.p.: 93 – 99 °C

^{1}H NMR: (400 MHz, DMSO) δ = 5.89 (dt, *J* = 10.0, 1.8 Hz, 1H, A), 5.77 (ddd, *J* = 10.0, 4.0, 1.6 Hz, 1H, B), 5.66 (ddd, *J* = 10.0, 4.5, 2.0 Hz, 1H, A), 5.09 (d, *J* = 5.1 Hz, 1H, A), 4.94 (d, *J* = 4.6 Hz, 1H, B), 3.85 – 3.71 (m, 2H A+B), 3.45 – 3.37 (m, 1H, A+B), 3.19 (ddd, *J* = 8.0, 5.8, 4.6 Hz, 1H, A), 3.06 – 2.97 (m, 1H, B), 2.16 (dt, *J* = 12.4, 4.5 Hz, 1H, A), 2.04 – 1.88 (m, 2H, A+B), 1.74 (d, *J* = 13.0 Hz, 2H, A+B), 1.59 (d, *J* = 12.6 Hz, 1H, A+B), 1.46 (ddd, *J* = 12.9, 9.3, 6.0 Hz, 3H, A+B), 1.31 – 1.15 (m, 2H, A+B), 1.16 – 1.00 (m, 1H, A+B).

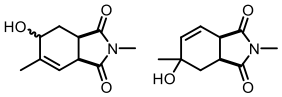
^{13}C NMR: (101 MHz, DMSO) δ = 178.91, 176.73, 136.27, 135.64, 121.88, 121.52, 62.77,61.05, 50.51, 36.34, 36.11, 32.32, 30.02, 28.43, 28.23, 25.27, 25.23, 24.78.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3444 (w), 2936 (w), 2853 (w), 1767 (w), 1682 (s), 1437 (w), 1380 (m), 1257 (m), 1187 (m), 1145 (w), 1076 (w), 949 (w), 895 (w), 822 (w), 716 (w), 631 (w), 557 (w)

HR-MS (ESI): $[MH]^+$ = 250.1441 ; calculated: 250.1443

5-Hydroxy-2,6-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and 5-Hydroxy-2,5-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

5-Hydroxy-2,6-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and 5-Hydroxy-2,5-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione were synthesized according to GP-3.1 (reaction time = 24 h) and purified by column chromatography using a mixture of DCM and MeOH (97 % DCM).



A B

$C_{10}H_{13}NO_3$, 195.090 g/mol

Yield: 93 % (ratio 1/4)

Condition: colourless amorphous solid

TLC: R_f (DCM/MeOH = 95/5) = 0.29

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.03 – 5.92 (m, 2H, B), 5.72 – 5.53 (m, 1H, A), 4.10 – 3.97 (m, 1H, A), 3.44 (dt, *J* = 7.6, 3.8 Hz, 1H, A+B), 3.35 – 3.22 (m, 1H, B), 3.23 – 3.12 (m, 1H, A), 2.98 (s, 3H, B), 2.96 (s, 3H, A) 2.21 – 2.08 (m, 1H, B), 2.05 – 1.88 (m, 1H, A), 1.86 – 1.82 (m, 1H, B), 1.79 (s, 3H, A), 1.75 (d, *J* = 4.1 Hz, 1H, A), 1.30 (s, 3H, B).

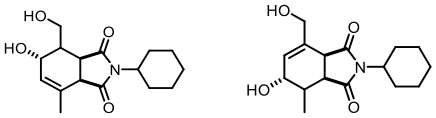
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 179.5, 176.6, 140.8, 136.9, 122.5, 117.5, 66.6, 65.8, 41.5, 40.5, 37.1, 36.7, 36.3, 31.1, 29.7, 25.1, 25.0, 20.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3421 (w), 2973 (w), 1771 (w), 1689 (s), 1431 (m), 1381 (m), 1332 (m), 1277 (m), 1162 (w), 1117 (w), 1079 (w), 1056 (w), 985 (w), 916 (w), 822 (w), 750 (w), 710 (w), 619 (m), 542 (m), 480 (w)

HR-MS (ESI): $[MH]^+$ = 196.0968 ; calculated: 196.0974

2-Cyclohexyl-5-hydroxy-4-(hydroxymethyl)-7-methyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and 2-Cyclohexyl-5-hydroxy-7-(hydroxymethyl)-4-methyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

2-Cyclohexyl-5-hydroxy-4-(hydroxymethyl)-7-methyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and 2-Cyclohexyl-5-hydroxy-7-(hydroxymethyl)-4-methyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione were synthesized according to GP-3.1 (reaction time = 24 h) and purified by column chromatography using a mixture of DCM and MeOH (95 % DCM).



A B

$C_{16}H_{23}NO_4$, 293.36 g/mol

Yield: 89 % (A+B), product contains 1.18 equiv. $OPPh_3$

Condition: colourless crystalline solid

TLC: R_f (DCM/MeOH = 95/5) = 0.19 (A)

R_f (DCM/MeOH = 95/5) = 0.09 (B)

^{1}H NMR: (400 MHz, $CDCl_3$) (A): δ = 5.68 (d, *J* = 1.5 Hz, 1H), 4.26 – 4.07 (m, 3H), 4.00 – 3.80 (m, 1H), 3.29 (d, *J* = 7.7 Hz, 1H), 3.25 – 3.09 (m, 1H), 2.96 (s, 3H), 2.17 – 1.97 (m, 2H), 1.87 – 1.73 (m, 3H), 1.63 (dd, *J* = 20.7, 9.9 Hz, 1H), 1.58 – 1.44 (m, 2H), 1.36 – 1.07 (m, 3H).

^{1}H NMR: (300 MHz, $CDCl_3$) (B): δ = 5.96 (d, *J* = 2.4 Hz, 1H), 4.51 – 4.21 (m, 2H), 4.20 – 3.80 (m, 2H), 3.48 (dd, *J* = 8.2, 1.2 Hz, 1H), 3.27 (dt, *J* = 34.7, 17.4 Hz, 1H), 2.38 – 2.17 (m, 4H), 2.17 – 1.94 (m, 2H), 1.94 – 1.73 (m, 2H), 1.73 – 1.45 (m, 3H), 1.45 – 1.09 (m, 3H), 0.95 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) (B): δ = 178.3, 177.5, 135.1, 127.2, 68.2, 65.2, 52.1, 41.7, 40.2, 35.9, 29.0, 28.7, 25.9, 25.1, 13.7.

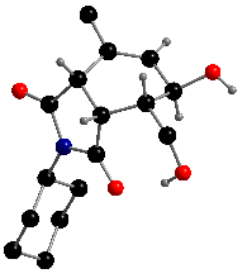
FT-IR (ATR) (A): $\tilde{\nu}$ [cm^{-1}] = 3248 (w), 2939 (w), 2863 (w), 1761 (w), 1679 (s), 1439 (w), 1404 (m), 1371 (m), 1254 (w), 1189 (s), 1148 (m), 1121 (m), 1059 (m), 967 (w), 928 (w), 756 (w), 720 (s), 696 (s), 536 (s), 505 (m)

FT-IR (ATR) (B): $\tilde{\nu}$ [cm^{-1}] = 3235 (w), 2924 (w), 2856 (w), 1772 (w), 1687 (s), 1456 (w), 1373 (m), 1359 (m), 1259 (w), 1182 (m), 1142 (m), 1006 (s), 914 (w), 801 (m), 772 (w), 673 (w), 631 (w), 611 (w), 577 (w), 544 (m), 416 (m)

HR-MS (ESI): (A):$[MH]^+$ = 294.1700; calculated: 294.1700

HR-MS (ESI): (B):$[MH]^+$ = 294.1704; calculated: 294.1700

X-ray: (A)

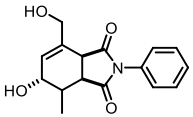


Chemical formula	C16H23NO4
Formula weight	293.35
Temperature / K	123.00(10)
Wavelength / Å	1.54184
Crystal system, space group	monoclinic, *P*21
a / Å	7.7853(2)
b / Å	6.6118(2)
c / Å	14.5803(4)
α / °	90
β / °	101.909(3)
γ / °	90
V / Å3	734.36(4)
ρcalcd / g·cm–3	1.327
F(000)	316
Crystal size / mm	0.24 × 0.14 × 0.06
Z	2
Max. and min. transmission	1.000, 0.807
μ / mm–1	0.774
θ range / °	5.808 – 73.506
Index ranges	–9≤*h*≤6 –7≤*k*≤8

	–15≤*l*≤18
Total / unique reflections	3289 / 2111
Data / restraints / parameters	2111 / 1 / 197
*R*int	0.0234
*R*1, *wR*2 [I≥2σ(I)]	0.0340, 0.0899
*R*1, *wR*2 (all data)	0.0355, 0.0918
Goodness-of-fit *S* on *F*2	1.094
Largest diff. peak and hole / eÅ–3	0.223, –0.195
Absolute structure parameter	0.3(2)

5-Hydroxy-7-(hydroxymethyl)-4-methyl-2-phenyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

5-Hydroxy-7-(hydroxymethyl)-4-methyl-2-phenyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione was synthesized according to GP-3.1 (reaction time = 24 h) and purified by column chromatography using a mixture of DCM and MeOH (95 % DCM).



$C_{16}H_{17}NO_4$, 287.32 g/mol

Yield: 45 %

Condition: colourless crystalline solid (product contains 0.75 equiv. $OPPh_3$)

TLC: R_f (DCM/MeOH = 95/5) = 0.08

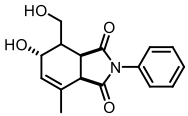
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.53 – 7.36 (m, 3H), 7.28 – 7.21 (m, 2H), 6.05 (d, *J* = 2.1 Hz, 1H), 4.52 – 4.31 (m, 2H), 4.08 (t, *J* = 4.8 Hz, 1H), 3.76 (d, *J* =7.4 Hz, 1H), 3.53 (dt, *J* = 16.5, 8.2 Hz, 1H), 2.42 – 2.27 (m, 1H), 1.12 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 177.4, 176.3, 134.8, 129.4, 129.1, 127.6, 126.5, 77.6, 77.2, 76.7, 68.2, 64.9, 41.9, 40.9, 36.1, 13.9.

HR-MS (ESI): $[MH]^+$ = 288.1232; calculated: 288.1230

5-Hydroxy-4-(hydroxymethyl)-7-methyl-2-phenyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

5-Hydroxy-4-(hydroxymethyl)-7-methyl-2-phenyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione was synthesized according to GP-3.1 (reaction time = 24 h) and purified by column chromatography using a mixture of DCM and MeOH (95 % DCM).



$C_{16}H_{17}NO_4$, 287.32 g/mol

Yield: 29 %

Condition: colourless crystalline solid (product contains 0.75 equiv.$OPPh_3$)

TLC: R_f (DCM/MeOH = 95/5) = 0.18

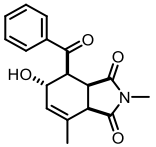
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.82 – 7.13 (m, 40H, $CH_{aromat.}$ + $OPPh_3$), 5.78 (d, *J* = 1.5 Hz, 1H), 4.41 – 4.22 (m, 2H), 4.22 – 4.01 (m, 1H), 3.52 (d, *J* = 7.7 Hz, 1H), 3.49 – 3.32 (m, 1H), 2.05 – 1.86 (m, 4H).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3365 (w),2895 (w), 1771 (w), 1699 (s), 1598 (w), 1498 (m), 1381 (s), 1188 (s), 1155 (s), 1027 (m), 1005 (m), 902 (w), 840 (w), 791 (w), 692 (s), 748 (s), 599 (w)

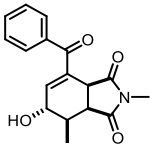
HR-MS (ESI): $[MH]^+$ = 288.1227; calculated: 288.1230

4-Benzoyl-5-hydroxy-2,7-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and 7-Benzoyl-5-hydroxy-2,4-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

4-Benzoyl-5-hydroxy-2,7-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and 7-Benzoyl-5-hydroxy-2,4-dimethyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione were synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (100 % --> 97 % DCM).



A



B

$C_{17}H_{17}NO_4$, 299.33 g/mol

Yield: 30 % (A + B, ratio A/B = 1/1.1)

Condition: pale yellow solid

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.96 – 7.36 (m, 10H, A + B), 6.48 (dd, *J* = 3.4, 1.5 Hz, 1H, B), 5.76 (d, *J* = 1.5 Hz, 1H, A), 4.60 (dd, *J* = 9.0, 2.0 Hz, 1H),4.48 (d, *J* = 8.3 Hz, 1H), 4.22 – 4.14 (m, 1H), 3.69 (dd, *J* = 8.2, 5.5 Hz, 1H), 3.52 (d, *J* = 8.3 Hz, 1H), 3.40 (dt, *J* = 8.4, 6.2 Hz, 2H), 2.98 (s, 3H), 2.87 (s, 3H), 2.04 (d, *J* = 4.7 Hz, 3H, A), 1.24 (dd, *J* = 7.1, 3.1 Hz, 3H, B).

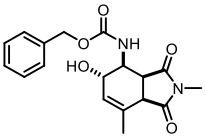
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 201.4, 195.4, 177.7, 176.1, 175.3, 175.0, 140.8, 137.1, 136.8, 135.0, 133.2, 133.1, 129.8, 129.1, 128.6, 128.1, 68.5, 63.8, 49.9, 46.3, 41.0, 40.8, 40.6, 36.4, 25.0, 24.9, 21.5, 14.0

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3556, 2922, 1774, 1692, 1599, 1435, 1383, 1323, 1286, 1215, 1111, 1021, 973, 909, 854, 775, 723, 701, 667

HR-MS (ESI): $[MH]^+$ = 300.1231; calculated: 300.1230

Benzyl-(5-hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

Benzyl-(5-hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (60 % --> 80 % EA).



$C_{18}H_{20}N_2O_5$, 344.37 g/mol

Yield: 50 %

Condition: pale yellow solid

TLC: R_f (PE/EA = 1/2) = 0.57

m.p.: 124 – 132 °C

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.45 – 7.28 (m, 5H), 6.61 (d, *J* = 7.5 Hz, 1H), 5.64 (d, *J* = 1.4 Hz, 1H), 5.22 – 5.10 (m, 2H), 4.02 – 3.86 (m, 2H), 3.45 (t, *J* = 9.8 Hz, 1H), 3.25 (dd, *J* = 7.9, 5.3 Hz, 1H), 2.95 (s, 3H), 1.95 (s, 3H).

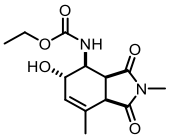
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 178.1, 174.9, 136.2, 129.8, 128.7, 128.4, 128.3, 68.3, 67.5, 53.3, 47.4, 41.0, 25.1, 21.1.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3534, 3436, 3362, 2952, 1774, 1677, 1524, 1435, 1383, 1342, 1286, 1252, 1223, 1156, 1111, 1021, 924, 835, 772, 697

HR-MS (ESI): $[MH]^+$ = 345.1450; calculated: 345.1445

Ethyl-(5-hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

Ethyl-(5-hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carba-mate was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (60 % --> 80 % EA).



$C_{13}H_{18}N_2O_5$, 282.30 g/mol

Yield: 45 %

Condition: pale yellow solid

TLC: R_f (PE/EA = 1/2) = 0.47

m.p.: 127 – 134 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.51 (d, *J* = 8.5 Hz, 1H), 5.64 (dd, *J* = 2.9, 1.4 Hz, 1H), 4.23 – 4.04 (m, 2H), 4.03 – 3.82 (m, 2H), 3.45 (d, *J* = 7.9 Hz, 1H), 3.26 (dd, *J* = 7.9, 5.3 Hz, 1H), 2.95 (s, 3H), 1.95 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

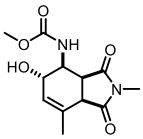
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 178.3, 175.0, 163.6, 157.1, 129.7, 68.5, 61.7, 53.1, 47.4, 41.0, 25.1, 21.1, 14.7.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3530, 3414, 2978, 2915, 1771, 1730, 1677, 1525, 1439, 1387, 1316, 1252, 1223, 1163, 1107, 1051, 928, 898, 839, 794,

HR-MS (ESI): $[MH]^+$ = 283.1294; calculated: 283.1288

Methyl-(5-hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

Methyl-(5-hydroxy-2,7-dimethyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)carbamate was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of PE and EA (60 % --> 80 % EA).



$C_{12}H_{16}N_2O_5$, 268.27 g/mol

Yield: 44 %

Condition: pale yellow solid

TLC: R_f (PE/EA = 1/2) = 0.34

m.p.: 117 °C

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 6.53 (d, *J* = 8.0 Hz, 1H), 5.64 (dd, *J* = 2.9, 1.4 Hz, 1H), 4.00 – 3.82 (m, 2H), 3.72 (s, 3H), 3.45 (d, *J* = 7.9 Hz, 1H), 3.25 (dd, *J* = 7.9, 5.3 Hz, 1H), 2.95 (s, 3H), 1.95 (s, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 178.1, 175.0, 129.6, 68.4, 53.2, 52.8, 47.4, 41.0, 25.1, 21.1.

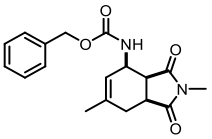
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3526, 3437, 2960, 2851, 1774, 1722, 1677, 1517, 1439, 1387, 1334, 1286, 1222, 1111, 1051, 916, 842, 793, 705, 671

HR-MS (ESI): $[MH]^+$ = 269.1134; calculated: 269.1132

3.7.3. Starting materials: reaction procedures and analytical data

Benzyl-(2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)carbamate[18]

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (33 % EA) as an eluent.

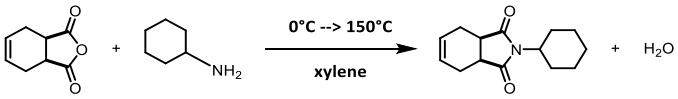


$C_{18}H_{20}N_2O4$, 328.37 g/mol

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.48 – 7.31 (m, 5H), 6.46 (d, *J* = 8.9 Hz, 1H), 5.38 (s, 1H), 5.21 – 5.04 (m, 2H), 4.51 – 4.30 (m, 1H), 3.31 – 3.06 (m, 2H), 2.91 (s, 3H), 2.54 (d, *J* = 15.3 Hz, 1H), 2.32 – 2.14 (m, 1H), 1.88 – 1.52 (m, 5H).

LR-MS: (EI, 70 eV): 328, 193, 91

***N*-Cyclohexyl-1,2,3,6-tetrahydophthalic imide**



cis-1,2,3,6-Tetrahydrophthalic anhydride (18.25 g, 120 mmol, 1.0 equiv.) was suspended in xylene (60 mL) and cooled to 0°C. Cyclohexylamine (13.0 g, 15.2 mL, 132 mmol, 1.1 equiv.) was added dropwise at 0°C. The reaction mixture was allowed to warm to RT and stirred at RT for 1 h.

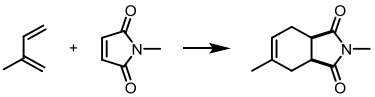
Subsequently the suspension was stirred for 6 h at 150 °C using a *Dean-Stark apparatus*. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using PE/EA (25 % EA) as an eluent. Product (21 g, 76 %) was isolated as colourless crystals.

$C_{14}H_{19}NO_2$, 233.31 g/mol

^{1}H NMR: (300 MHz, DMSO) δ = 5.98 – 5.75 (m, 2H), 3.91 (tt, *J* = 12.3, 3.9 Hz, 1H), 3.09 – 2.91 (m, 2H), 2.69 – 2.46 (m, 2H), 2.29 – 1.99 (m, 4H), 1.86 – 1.70 (m, 2H), 1.69 – 1.57 (m, 1H), 1.56 – 1.42 (m, 2H), 1.42 – 1.07 (m, 3H).

HR-MS (ESI): $[MH]^+$ = 234.1488; calculated: 234.1489

2,5-Dimethyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione



Isoprene (45 mmol, 3.07 g, 3.0 equiv.) and *N*-methylmaleimide (15 mmol, 1.67 g, 1.0 equiv.) were dissolved in toluene (15 mL) and stirred for 20 h at 110 °C. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using PE/EA (25 % EA) as an eluent.

$C_{10}H_{13}NO_2$, 179.22 g/mol

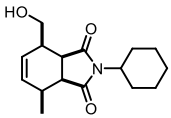
TLC: R_f (PE/EA = 3/1) = 0.23

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 5.59 – 5.41 (m, 1H), 3.16 – 2.97 (m, 2H), 2.93 (s, 3H), 2.59 – 2.38 (m, 2H), 2.30 – 2.06 (m, 2H), 1.79 – 1.56 (m, 3H).

LR-MS: (EI, 70 eV): 179, 151, 112, 79

2-Cyclohexyl-4-(hydroxymethyl)-7-methyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

2,4-Hexadien-1-ol (540 mg, 5.5 mmol, 1.1 eqiv.) and *N*-cyclohexylmaleinimide (896 mg, 5.0 mmol, 1.0 equiv.) were diluted toluene (5 mL) and stirred for 20 h at 110 °C. The solvent and all volatile compounds were removed and the crude product was washed with PE.



$C_{16}H_{23}NO_3$, 277.36 g/mol

Yield: 65 %

Condition: pale yellow solid

m.p.: 109 – 111 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 5.75 (dt, *J* = 9.2, 3.1 Hz, 1H), 5.64 (dt, *J* = 9.2, 3.1 Hz, 1H), 4.00 (dd, *J* = 11.9, 5.6 Hz, 1H), 3.95 – 3.79 (m, 2H), 3.34 – 3.18

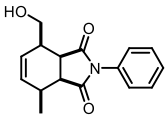
(m, 1H), 2.98 (dd, *J* = 8.6, 6.4 Hz, 1H), 2.60 – 2.50 (m, 1H), 2.46 – 2.35 (m, 2H), 2.07 (q, *J* = 12.2 Hz, 2H), 1.79 (d, *J* = 12.7 Hz, 2H), 1.65 – 1.59 (m, 1H), 1.50 – 1.42 (m, 5H), 1.36 –1.07 (m, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 179.5, 177.8, 135.3, 128.2, 63.1, 52.0, 44.7, 42.7, 38.3, 31.4, 29.0, 28.9, 26.0, 25.2, 17.0.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3478, 2941, 2855, 1756, 1674, 1461, 1379, 1342, 1275, 1189, 1137, 1088, 1059, 984, 895, 816, 716

HR-MS (ESI): $[MH]^+$ = 278.1751 ; calculated: 278.1751

4-(Hydroxymethyl)-7-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione[16]



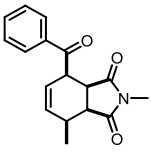
$C_{16}H_{17}NO_3$, 271.32 g/mol

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.53 – 7.29 (m, 3H), 7.21 – 6.98 (m, 2H), 5.87 (dt, *J* = 9.2, 3.2 Hz, 1H), 5.76 (dt, *J* = 9.2, 3.1 Hz, 1H), 4.12 – 3.87 (m, 2H), 3.54 (dd, *J* = 8.7, 7.2 Hz, 1H), 3.30 – 3.10 (m, 1H), 2.74 – 2.62 (m, 1H), 2.62 – 2.46 (m, 1H), 1.53 (d, *J* = 7.4 Hz, 3H).

LR-MS: (EI, 70 eV): 271, 254, 194, 77

4-Benzoyl-2,7-dimethyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

1-Phenylhexa-2,4-dien-1-one (1.16 g, 6.8 mmol, 1.0 eqiv.) and *N*-Methylmalein-imide (0.75 g, 6.8 mmol, 1.0 equiv.) were diluted in toluene (14 mL) and stirred for 20 h at 110 °C. The solvent and all volatile compounds were removed and the crude product was purified by column chromatography using a mixture of PE and EA (20 % --> 33 % EA).



$C_{17}H_{17}NO_3$, 283.33 g/mol

Yield: 16 %

Condition: colourless solid

TLC: R_f (PE/EA = 2/1) = 0.42

m.p.: 146 °C

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.77-7.72 (m, 2 H), 7.60-7.52 (m, 2 H), 7.48-7.41 (m, 3 H), 6.57-6.53 (m, 1 H), 4.40 (dd, ^{3}J = 8.4, 1.3, 1 H), 3.2 (dd, ^{3}J = 8.4, 1 H), 2.99 (s, 3 H), 2.15 (dqd, ^{3}J = 4.5, 1.3, 1 H), 1.10 (d, ^{3}J = 7.0, 3 H).

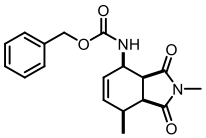
^{13}C NMR: (101 MHz, $CDCl_3$) δ = 140.3, 137.3, 134.1, 132.7, 129.8, 128.5, 43.5, 40.6, 31.1, 28.7, 24.7, 16.6

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2964(w), 2933(w), 2879(w), 1695(s), 1674(s), 1431(s), 1379(m), 1285(s), 1226(m), 1099(m), 1004(m), 960(m), 787(m),722(s), 689(s), 666(s)

HR-MS (ESI): $[MH]^+$ = 284.1284; calculated: 284.1281

Benzyl-(2,7-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)carbamate[18]

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (25 % --> 35 % EA) as an eluent.



$C_{18}H_{20}N_2O_4$, 328.37 g/mol

Yield: 14 %

Condition: pale yellow amorphous solid

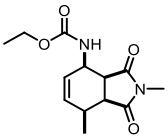
TLC: R_f (PE/EA = 2/1) = 0.38

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.47 – 7.25 (m, 11H), 6.61 (d, *J* = 9.2 Hz, 1H), 5.82 – 5.69 (m, 5H), 5.64 (dt, *J* = 9.3, 3.1 Hz, 1H), 5.15 (d, *J* = 1.0 Hz, 2H), 3.22 (dd, *J* = 8.6, 6.1 Hz, 1H), 3.14 – 2.98 (m, 1H), 2.90 (s, 3H), 2.87 (d, *J* = 3.3 Hz, 1H), 2.56 – 2.35 (m, 1H), 1.41 (d, *J* = 7.4 Hz, 3H).

LR-MS: (EI, 70 eV): 328, 193, 91

Ethyl-(2,7-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (25 % --> 35 % EA) as an eluent.



$C_{13}H_{18}N_2O_4$, 266.30 g/mol

Yield: 15 %

Condition: pale yellow amorphous solid

TLC: R_f (PE/EA = 2/1) = 0.48

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.46 (d, *J* = 8.9 Hz, 1H), 5.77 – 5.67 (m, 1H), 5.63 (dt, *J* = 9.3, 3.1 Hz, 1H), 4.48 – 4.38 (m, 1H), 4.18 – 4.08 (m, 2H), 3.22 (dd, *J* = 8.6, 6.0 Hz, 1H), 3.10 – 3.01 (m, 1H), 2.91 (s, 3H), 2.54 – 2.37 (m, 1H), 1.47 – 1.36 (m, 3H), 1.30 – 1.23 (m, 3H).

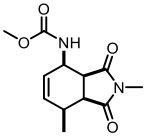
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 133.9, 132.4, 61.3, 47.6, 44.2, 43.8, 30.7, 24.9, 16.8, 14.7.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3396, 2974, 1771, 1685, 1513, 1435, 1379, 1331, 1286, 1238, 1170, 1092, 1059, 969, 865, 820, 779, 708, 678

HR-MS (ESI): $[MH]^+$ = 267.1343; calculated: 267.1339

Methyl-(2,7-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)carbamate

Product was synthesized according to GP-3.3 using 15 mmol of starting material and purified by column chromatography using a mixture of PE and EA (25 % --> 35 % EA) as an eluent.



$C_{12}H_{16}N_2O_4$, 252.27 g/mol

Yield: 13 %

Condition: pale yellow amorphous solid

TLC: R_f (PE/EA = 2/1) = 0.27

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.50 (d, *J* = 9.1 Hz, 1H), 5.75 (dt, *J* = 9.3, 2.7 Hz, 1H), 5.63 (dt, *J* = 9.3, 3.0 Hz, 1H), 4.43 (s, 1H), 3.71 (s, 3H), 3.21 (dd, *J* =

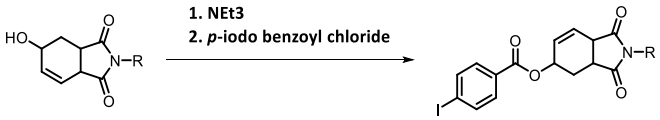
8.6, 6.1 Hz, 1H), 3.05 (dd, *J* = 4.4, 5.9 Hz, 1H), 2.91 (s, 3H), 2.53 – 2.46 (m, 1H), 1.41 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 133.9, 132.3, 60.4, 52.5, 47.8, 44.1, 43.8, 30.7, 24.9, 21.2, 16.8, 14.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3310, 2960, 2844, 1767, 1681, 1551, 1435, 1383, 1346, 1286, 1193, 1159, 1081, 1044, 980, 943, 876, 828, 783, 708

HR-MS (ESI): $[MH]^+$ = 253.1186; calculated: 253.1183

3.8. Stereochemistry of 2-Cyclohexyl-5-hydroxy-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and 2-methyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

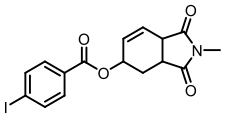


As the stereochemistry of 2-cyclohexyl-5-hydroxy-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione and 2-methyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione could not be determined conclusively by NMR spectroscopy the free hydroxyl groups were esterified using *p*-iodo benzoylchloride. By means of the bulky substituent the diastereoisomers could be separated and the stereochemistry of the major product was identified.

For both compounds the product with the diastereomeric groups oriented *anti* to each other could be identified as major product.

2-Methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1H-isoindol-5-yl 4-iodobenzoate

p-Iodo benzoylchloride (839 mg, 3.15 mmol, 1.05 equiv.) was dissolved in dry THF (7.5 mL) and cooled to 0 °C. NEt_3 (440 µL, 3.15 mmol, 1.05 equiv.) and 2-methyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (543 mg, 3 mmol. 1.0 equiv.) were added. The reaction mixture was stirred for 2 h at 0 °C and over night at room temperature. EA (50 mL) was added and the organic phase was washed with 1 M $HCl_{aq.}$ (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and saturated aqueous NaCl (20 mL). The organic phase was dried over Na_2SO_4, the drying agent was filtered off. The solvent was removed under reduced pressure. The crude product was purified by column chromatography using a mixture of PE and EA (5 % --> 25 % EA) as an eluent.



$C_{16}H_{14}INO_4$, 411.20 g/mol

Yield: 45 %

Condition: colourless crystalline solid

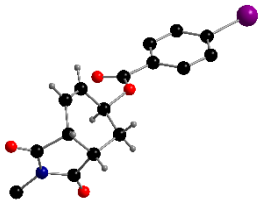
^{1}H NMR: (300 MHz, CDCl3) δ = 7.85 – 7.78 (m, 2H), 7.76 – 7.68 (m, 2H), 6.18 – 6.05 (m, 2H), 5.44 – 5.35 (m, 1H), 3.59 – 3.51 (m, 1H), 3.33 – 3.23 (m, 1H), 3.01 (s, 3H), 2.39 (ddd, *J* = 13.3, 6.6, 4.7 Hz, 1H), 2.21 – 2.09 (m, 1H).

^{13}C NMR: (75 MHz, CDCl3) δ = 178.2, 176.2, 165.4, 137.9, 131.2, 130.3, 129.4, 125.2, 101.2, 65.7, 40.9, 36.3, 26.9, 25.2.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3302 (m), 2937 (m), 2855 (m), 1767 (w), 1689 (s), 1584 (m), 1480 (m), 1446 (m), 1372 (s), 1264 (s), 1178 (s), 1144 (m), 1100 (s), 1001 (s), 842 (s), 753 (s)

HR-MS (ESI): $[MH]^+$ = 412.0041; calculated: 412.0040

X-ray:

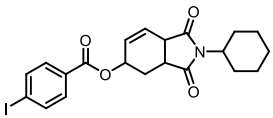


Chemical formula	$C_{16}H_{14}INO_4$
Formula weight	411.18
Temperature / K	123(2)
Wavelength / Å	1.54184
Crystal system, space group	monoclinic, $P2_1/c$
a / Å	6.1030(3)
b / Å	25.2827(10)
c / Å	10.3340(5)
α / °	90
β / °	105.647(4)
γ / °	90
V / Å^3	1535.45(13)
ρ_{calcd} / g·cm^{-3}	1.779
F(000)	808
Crystal size / mm	0.26 × 0.08 × 0.04
Z	4
Max. and min. transmission	0.963, 0.819
μ / mm^{-1}	16.552
θ range / °	4.776–73.703
Index ranges	$-6 \le h \le 7$
	$-31 \le k \le 31$
	$-12 \le l \le 10$

Total / unique reflections	16650 / 3056
Data / restraints / parameters	3056 / 0 / 200
R_{int}	0.0406
R_1, wR_2 [I≥2σ(I)]	0.0221, 0.0494
R_1, wR_2 (all data)	0.0284, 0.0518
Goodness-of-fit S on F^2	1.042
Largest diff. peak and hole / eÅ^{-3}	0.327, –0.499
Absolute structure parameter	–

2-Cyclohexyl-5-hydroxy-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

p-Iodo benzoylchloride (559 mg, 2.10 mmol, 1.05 equiv.) was dissolved in dry THF (7.5 mL) and cooled to 0 °C. NEt_3 (293 µL, 2.10 mmol, 1.05 equiv.) and 2-cyclohexyl-5-hydroxy-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (498 mg, 2 mmol. 1.0 equiv.) were added. The reaction mixture was stirred for 2 h at 0 °C and over night at room temperature. EA (50 mL) was added and the organic phase was washed with 1 M $HCl_{aq.}$ (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and saturated aqueous NaCl (20 mL). The organic phase was dried over Na_2SO_4, the drying agent was filtered off. The solvent was removed under reduced pressure. The crude product was purified by column chromatography using a mixture of PE and EA (5 % --> 25 % EA) as an eluent.



$C_{21}H_{22}INO_4$, 479.31 g/mol

Yield: 40 %

Condition: pale yellow crystalline solid

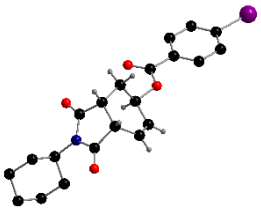
^{1}H NMR: (400 MHz, CDCl3) δ = 7.87 – 7.75 (m, 2H), 7.75 – 7.65 (m, 2H), 6.10 (qdd, *J* = 10.1, 3.5, 1.6 Hz, 2H), 5.43 – 5.32 (m, 1H), 3.94 (tt, *J* = 12.4, 3.9 Hz, 1H), 3.45 (ddt, *J* = 8.2, 3.5, 1.8 Hz, 1H), 3.20 (dt, *J* = 8.3, 6.5 Hz, 1H), 2.32 (ddd, *J* = 13.5, 6.9, 4.7 Hz, 1H), 2.18 – 2.04 (m, 3H), 1.82 (dd, *J* = 13.3, 4.0 Hz, 2H), 1.69 – 1.51 (m, 4H), 1.34 – 1.17 (m, 2H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 178.2, 176.2, 165.4, 137.9, 131.2, 130.0, 129.5, 125.6, 101.2, 65.6, 52.0, 40.8, 36.0, 28.9, 28.9, 27.1, 25.9, 25.1.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2945 (w), 1771 (w), 1692 (s), 1588 (m), 1431 (m), 1379 (m), 1338 (m), 1271 (s), 1170 (m), 1115 (s), 1006 (s), 931 (m), 887 (m), 820 (m), 749 (s), 663 (m)

HR-MS (ESI): $[MH]^+$ = 480.0665; calculated: 480.0666

X-ray:



Chemical formula	$C_{21}H_{22}INO_4$
Formula weight	479.29
Temperature / K	293(2)
Wavelength / Å	1.54184
Crystal system, space group	monoclinic, $P2_1$
a / Å	10.7388(3)
b / Å	5.9400(2)
c / Å	16.1392(3)
α / °	90
β / °	98.538(2)
γ / °	90
V / Å^3	1018.09(5)
ρ_{calcd} / g·cm^{-3}	1.563
F(000)	480
Crystal size / mm	0.47 × 0.10 × 0.04
Z	2
Max. and min. transmission	0.778, 0.215
μ / mm^{-1}	12.571
θ range / °	4.163 – 73.557
Index ranges	$-13 \le h \le 13$ $-7 \le k \le 7$ $-17 \le l \le 20$
Total / unique reflections	11539 / 4027
Data / restraints / parameters	4027 / 1 / 245
R_{int}	0.0335
R_1, wR_2 [I≥2σ(I)]	0.0323, 0.0769
R_1, wR_2 (all data)	0.0388, 0.0816
Goodness-of-fit *S* on F^2	1.078
Largest diff. peak and hole / eÅ^{-3}	0.455, –0.616
Absolute structure parameter	–0.013(4)

3.9. Acknowledgment

This work was supported by the Graduate School “Photocatalysis” (GRK 1626) of the German Science Foundation (DFG). M.M. thanks the GRK 1626 for a doctoral fellowship. R.P.R. is a Marie Curie postdoctoral fellow of the European Union.

3.10. References

[1] P. Esser, B. Pohlmann, H.-D. Scharf, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2009–2023.

[2] M. Alberti, M. Orfanopoulos, *Synlett*, **2010**, *2010*, 999–1026.

[3] M. Prein, W. Adam, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 477–494.

[4] M. Fischer, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 16–26.

[5] K. R. Kopecky, H. J. Reich, *Can. J. Chem.* **1965**, *43*, 2265–2270.

[6] Frimer A.A.: *Singlet Oxygen Volume I, Physical-Chemical Aspects*, CRC Press, **1985**

[7] W. Fudickar, K. Vorndran, T. Linker, *Tetrahedron*, **2006**, *62*, 10639–10646.

[8] D. G. Iman Landheer, *Tetrahedron Lett.* **1981**, 143–150.

[9] F. Lévesque, P. H. Seeberger, *Angew. Chem. Int. Ed. Engl*. **2012**, *51*, 1706–1709.

[10] A. G. Griesbeck, M. Cho, *Org. Lett.* **2007**, *9*, 611–613.

[11] K. H. Schulte-Elte, V. Rautenstrauch, *J. Am. Chem. Soc.* **1980**, *102*, 1738–1740.

[12] Y.-Z. An, A. L. Viado, M.-J. Arce, Y. Rubin, *J. Org. Chem.* **1995**, *60*, 8330–8331.

[13] X. Li, V. Ramamurthy, *J. Am. Chem. Soc.* **1996**, *118*, 10666–10667.

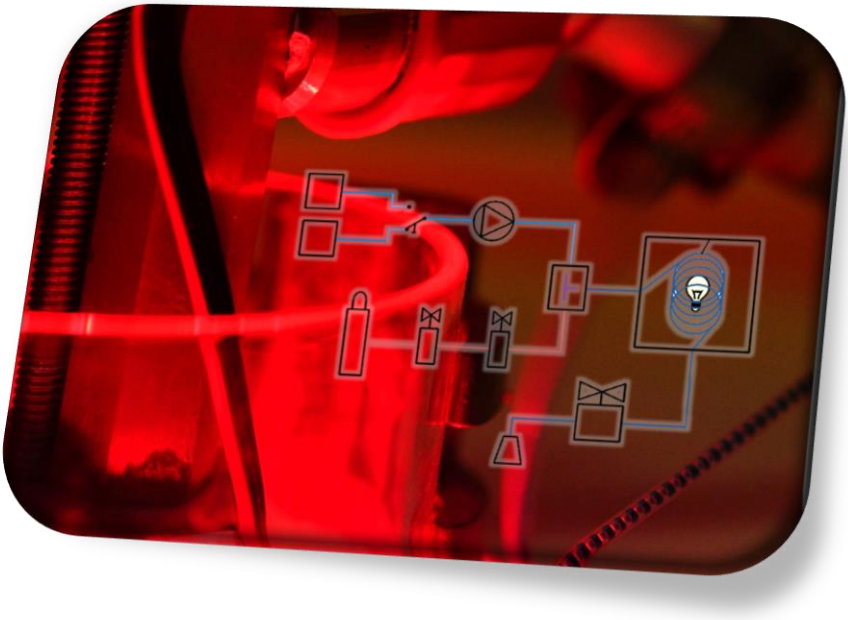
[14] a) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. E. Vassilikogiannakis, *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1668–1698; b) X.-F. Xiong, Q. Zhou, J. Gu, L. Dong, T.-Y. Liu, Y.-C. Chen, *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 4401–4404; c) S. Hübner, D. Michalik, H. Jiao, H. Neumann, S. Klaus, D. Strübing, A. Spannenberg, M. Beller, *Chem. Asian J.* **2007**, *2*, 734–746; d) R. Fichtler, J.-M. Neudörfl, A. Jacobi von Wangelin, *Org. Biomol. Chem.* **2011**, *9*, 7224–7236.

[15] M. Stratakis, M. Orfanopoulos, *Tetrahedron*, **2000**, *56*, 1595–1615.

[16] R. J. Vijn, H. Hiemstra, J. J. Kok, M. Knotter, W. N. Speckamp, *Tetrahedron*, **1987**, *21*, 5019 – 5030

Chapter 4:

- Flow Reactor Setup -



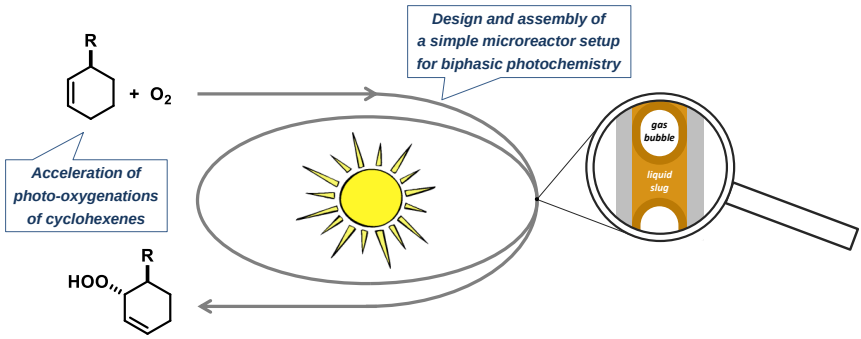
4. A Flow Reactor Setup for Photochemistry of Biphasic Gas/Liquid Reactions

This chapter is submitted to Beilstein Journal of Organic Chemistry (Feb. 2016):

Josef Schachtner and Axel Jacobi von Wangelin
Schemes, figures and text may differ from published version.

Abstract

A home-built microreactor system for light-mediated gas/liquid reactions was assembled from simple commercial components and successfully applied to photooxygenation of hydrocarbons. This paper describes in full detail the nature and function of the required building elements, the assembly of parts, and the tuning and interdependencies of the most important reactor and reaction parameters. The microreactor set-up was applied to visible light-induced biphasic reactions at gas/liquid interphases which is exemplified by the use of air and a liquid phase containing the sensitizer and the hydrocarbon substrate in an organic solvent (Schenck ene reaction). Major emphasis was laid on the realization of a constant gas/liquid slug flow and the effective illumination by an appropriate light source. The optimized set of conditions enabled the shortening of reaction times by more than 99 % with equal chemoselectivities. The modular home-made flow reactor can serve as a prototype model for the continuous operation of various other reactions at light/liquid/gas interfaces in student, research, and industrial laboratories.



4.1. Introduction

The recent developments of microreactor technologies have significantly impacted the art of organic synthesis and manufacture.[1,2] The efficiency of chemical reactions can be greatly enhanced over common batch processes and new approaches to the optimization of established reaction protocols and the execution of hitherto unfeasible processes can be enabled due to the inherent properties of micro/flow reactors: high mass-transfer rates[3,4], spatial separation of reagent additions and mixing, high reagent dispersion, high energy efficiency, improved irradiation[4–6], ease of upscaling, low hazard potential and multi-dimensional parameter control.[2,4,6,7] The high energy efficiency, low hazard potential, and precise control of reaction parameters have also prompted several adoptions of microflow techniques in technical manufactures of fine chemicals, polymers[8] and pharmaceutical intermediates.[9,10] Important applications include among others the technical processes towards artemisinine[9], ibuprofen[11] and efaproxiral.[12]

Over the past decade, various reactor types and technical specifications have been developed to address the intricate challenges of many chemical reactions including the handling of hazardous[13,14,15] or explosive[16,17] reagents and organometallics[14,18], special concentration and temperature gradients[8,14,19], slow addition protocols[9], multiphasic reactions, precise control over short residence times, addition of gaseous reagents[15], high-pressure conditions[17] and cascade conversions without intermediate work-up operations.[10,20,21] Prominent examples include the use of micro-channel reactors for reactions with diazomethane or organometallic, solid-phase[21–23], and hazardous reagents or to avoid side reactions like over-oxidation[24]; thin film, falling film[25], micro-channel[26–28] and tube-in-tube reactors[29,30] for reactions between gaseous and liquid components.

For many applications, the versatility of reagent addition and mixing methods and the high dispersion of reagents are probably the most important advantages of flow reactors over batch reactors. The vast majority of applications of microflow setups involve reagents in the same aggregation state (homogeneous, mostly liquid phase) where the addition and mixing events can be spatially and temporally separated but the latter still occurs spontaneously in a single-phase system.[2,4,31] An especially complex problem beyond the scope of most microreactor setups are heterogeneous reactions[21–23,32] between three dispersed entities such as a liquid phase, a gas phase, and an electromagnetic radiation field where an effective interaction of three quasi mobile phases of different physical states is required for high selectivities. Such scenarios are highly relevant for photochemical reactions with reactive gases (e.g. air, O_2, O_3, H_2, Cl_2,

acetylene, NO_x, CO, CO_2 etc.) but obviously bear several challenges with regard to the precise control of the addition and mixing of 1) the liquid phase containing the organic substrates, the photo-active component (catalyst, sensitizer), the solvent, and possibly additives; 2) the gas phase containing the gaseous reagents; and 3) the light (Figure 4.1).

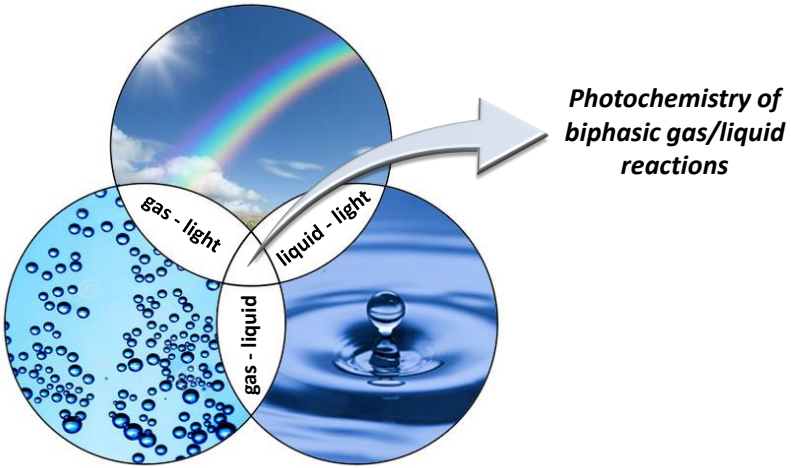
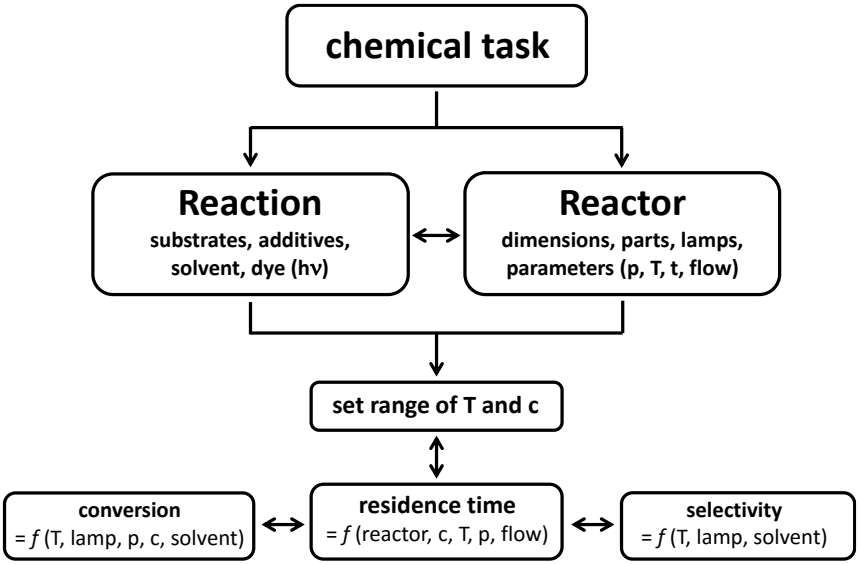


Figure 4.1: The challenge of effectively mixing the three dispersed entities gas, liquid, and light for photochemical applications.

Only very few microreactor setups for such "quasi tri-phasic" processes have been reported.[33,34] Most of these systems are thin film/falling film[25,35], microchannel[26–28,36], or simple tube reactors[29,37–39]. The reactor reported herein differs from most of the known systems in some key characteristics. Small-dimensioned thin film/falling film and microchannel reactors allow residence times in the seconds-to-few-minutes range, which holds great potential for rapid conversions but is unsuitable for significantly slower rates of many common organic reactions. Additionally, the gas-permeable tubes for tube-in-tube reactors ant the photo-lithographically etched[40] microchannel plates are highly sensitive and expensive parts which limit their use by the average organic lab chemist. For comparison, the home-built reactor detailed in this report reliably operates at much longer residence times (0.2 – 20 min) and uses cheap yet robust FEP (fluorinated ethylene propylene) tubings as transparent reactor material. While film/falling film and microchannel reactors display excellent mass-transfer and irradiation properties in several cases, [41] our reactor shows higher versatility and tunability at a much lower price. In the following, we detail the technical specifications, step-by-step assembly, and lab-scale operation of an affordable, robust, and modular home-made flow reactor which shows great promise for general applications to photochemical reactions at

gas/liquid interphases. Special attention has been paid to an especially simple reactor set-up which is based on cheap and available materials and parts, which can be assembled and operated with minimal technological expertise by students and researchers, yet is applicable to a wide range of reaction types. All parts of the modular reactor can be easily exchanged (capillaries, light source, pumps, mixer, valves etc.) and the reagents widely varied up to 2 mL/min liquid reagents and 50 bar inlet pressure. The overall price of the whole system is below 10,000 €.



Scheme 4.1: Mutual interdependencies of critical reaction and reactor parameters.

The wide variation of all three reaction components (liquid, gas, light) with regard to their nature (type of substrates, solvents, additives, gases, wavelength of light) and concentration (chemicals in solution, partial pressure of gas, light intensity) was a prime objective of this work. Furthermore, the technical parameters of the reaction and the reactor should be varied (temperature, pressure, flow rate, residence time, size and type of tubing and reaction chamber etc.). It is important to realize that most of these parameters cannot be varied individually but are mutually dependent on each other (e.g. choice of chromophore vs. wavelength of light vs. type of (transparent) reactor walls; concentration of reagents vs. residence time for complete conversion vs. length of reactor vs. flow rate; etc.).[2] The awareness of such multi-dimensional interdependencies is a prerequisite for the expedient optimization of a given chemical

task by proper choice of the general reactor setup and wide variations of the critical reaction and reactor parameters (Scheme 4.1).

The general addition/mixing problem of heterogeneous reactions of gaseous and liquid components is further complicated by the presence of an electromagnetic radiation field (e.g. visible light) as another dispersed component. An efficient interaction of all three "reagents" will require careful adjustment of the light source, the wall material, the penetration length, the solution absorbance and other parameters. Until today, such protocols under flow conditions are most advanced with photosensitized oxidations. Prominent examples include the photo-oxidations of citronellol[27,37], indanes[36], monoterpenes[29], furans[37], furfurals[39], thiols[38] and amines[42] and the syntheses of ascaridol[26] and artemisinine.[9] Related microreactor setups were applied to biphasic gas-liquid mixtures in the photo-chlorination of alkylbenzenes[43] and [2+2]-cycloadditions with ethylene.[44]

The benefit of microreaction technologies applied to photochemical processes is especially evident from a consideration of the extent of light attenuation when passing through condensed matter. The molar attenuation coefficients of common organic photosensitizers are in the range of 20,000 – 500,000 $M^{-1} \cdot cm^{-1}$ (Table 4.1) which significantly limits the penetration depth of visible light into standard batch reactions at 10^{-4} – 10^{-2} M concentrations of the dye so that large volumes of the reaction remain in the dark.[4,45]

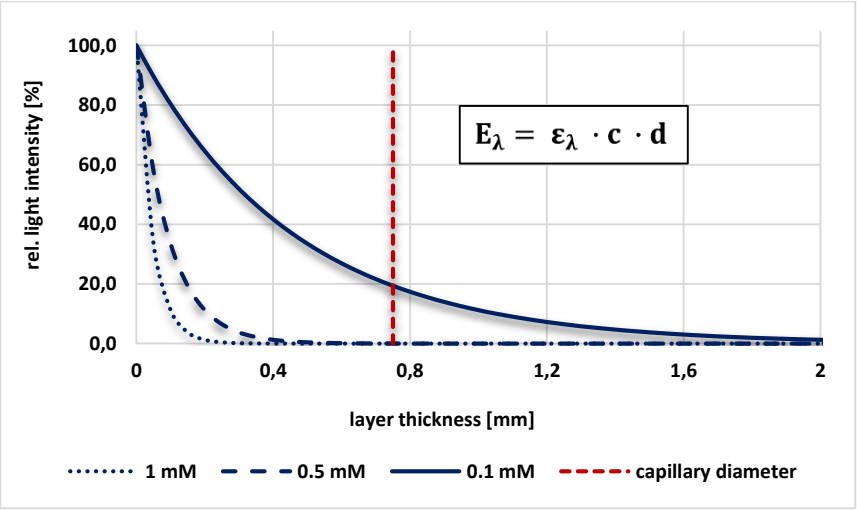
It is important to note that the magnitude of attenuation coefficients of the employed chromophores is a key difference between the recently emerging field of photocatalysis (with dyes of $\varepsilon > 10{,}000\ M^{-1} \cdot cm^{-1}$) and the traditional photochemistry (involving mostly UV irradiation of colourless organic molecules of $\varepsilon < 1{,}000\ M^{-1} \cdot cm^{-1}$).[51]

Table 4.1. Attenuation coefficients of common photosensitizers.

Sensitizer	**Molar attenuation coefficient [$M^{-1} \cdot cm^{-1}$]**
rose Bengal (RB)	37,600[46]
methylene blue (MB)	95,000[47]
meso-tetraphenyl porphyrin (TPP)	470,000[48]
disodium fluorescein	70,000[49]
$[Ru(bpy)_3]Cl_2$	27,000[50]

(bpy = 2,2'-bipyridine)

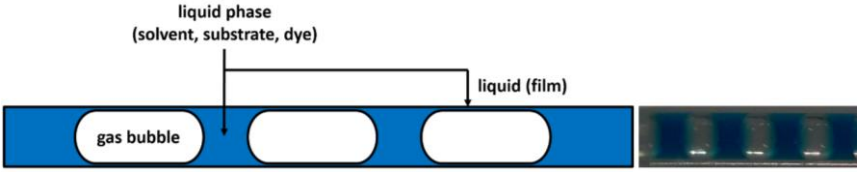
The much lower absorption coefficients of the majority of organic molecules which are directly irradiated by UV light in photochemical processes (e.g. *N*-alkyl maleimides, ε = ~700 $M^{-1} \cdot cm^{-1}$)[52] lead to more efficient light penetration in batch reactions and therefore show only a limited benefit of using flow reactors for such purposes. On the other hand, a 1 mM solution of methylene blue exhibits total absorption (>99.9 %) at 0.32 mm penetration depths (Scheme 4.2).[53,54] The high surface-to-volume ratio of microreactors therefore increases the relative pathway of light through the solution, speeds up the rate of reactions, and minimizes competing side reactions.[6,45,55,56]



Scheme 4.2: Total absorption of methylene blue solutions as consequence of the Beer-Lambert law.[53]

Total light absorption of dye solutions with high attenuation coefficients can be prevented by low-diameter reactor dimensions and flow conditions that favour the formation of thin films along the reactor walls. With gas-liquid two-phase flows, several flow regimes can form which mostly depend on the configuration of the inlets, the gravity, the size of the tube, the fluid properties, and the flow rate. A steady and highly dispersed two-phase flow is present in the so-called slug flow (Scheme 4.3). The resultant thin film around the gas bubbles and along the reactor walls allows large portions of the substrate solution to be efficiently irradiated while being at the same time in contact with the gas phase.

This leads to strongly enhanced mass transfer coefficients compared to traditional stirred tanks.[41] Depending on the flow rates of gas and liquid phases, their ratio, the solvent viscosity and the reactor dimensions, different flow pattern can be obtained. The so-called slug flow leads to very efficient irradiation but also other spatial distributions (plug flow, bubbly flow, annular flow or isolated gas and liquid segments) can occur under certain conditions.[57]

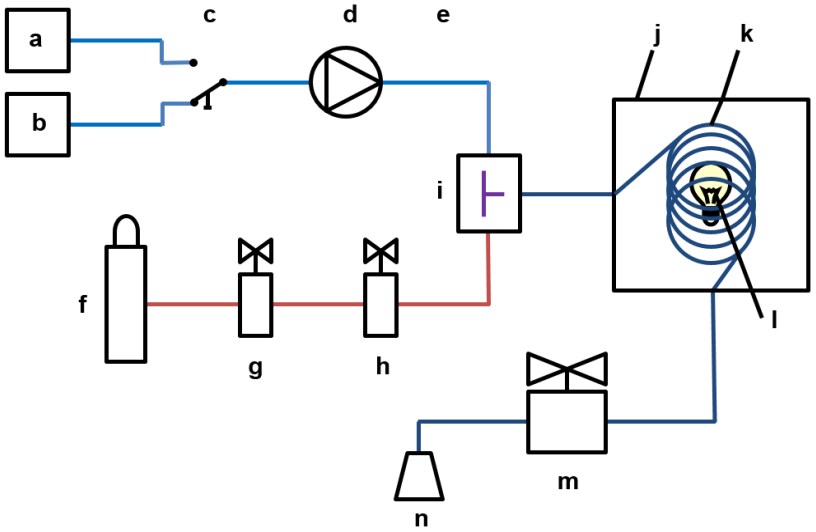


Scheme 4.3: Slug flow conditions of two-phase gas-liquid mixtures. Photograph of a slug flow of a solution of methylene blue (1.0 mM) and a cyclohexene (0.1 M) and oxygen at 30 bar and 1.5 mL/min flow rate in an FEP tubing reactor (0.75 mm inner diameter).

4.2. Microreactor Parts and Setup

When studying the numerous literature reports of applications of flow reactors to organic synthesis it became obvious that there are no simple and quick technical solutions to such endeavours available to John Doe lab chemists who have no close collaboration with engineering specialists or do not wish to purchase sophisticated high-end devices for > 10,000 Euros.

We therefore decided to develop our own home-made flow reactor for photooxidations of organic molecules but also envisaged its general applicability to other challenging processes with the ternary "reagent" combinations liquid/gas/light. With the objective of constructing a robust and versatile flow reactor, we set out to explore and test commercially available parts.

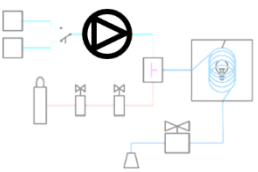


Scheme 4.4: Blueprint of the home-built microflow photoreactor; Schematic illustration of the reactor setup with a) solvent reservoir, b) substrate solution, c) T valve, d) HPLC pump (*Bischoff* dosage pump 2250), e) capillary (for back-pressure build-up), f) oxygen supply (Linde 4.6, 200 bar), g) pressure reducing valve *(GO* regulator, *TeamTrade*, PR1-1I11ACW-111), h) mass flow controller (*Brooks* SLA 5850), i) T mixer (*IDEX*, P-727 or P-632), j) thermostat bath, k) FEP capillary, l) LED light source (24 × *Cree Xlamp* MK-R, warm white, 700 mA), m) back-pressure regulator (*IDEX*, P-763, 100 psi), n) collecting vessel

Major emphasis was placed on maximum flexibility with regard to reaction parameters (reagents, concentrations, temperature, reaction/residence time) and technical

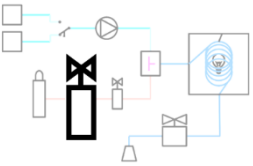
parameters (light sources, flow rates, pressure, reactor type, size and length). The continuous operation with reproducible results would require the use of components that ensure strictly constant gas and liquid flow rates, mixing properties, irradiation over the period of operation. In the following, we wish to provide a hands-on manual for the design and set-up of a flow reactor for photochemical reactions at gas/liquid interfaces in any standard student or research laboratory. The requirements, specifications, and pitfalls of the most critical technical components will be discussed from the perspective of a non-expert user (Scheme 4.4).

Solution pump



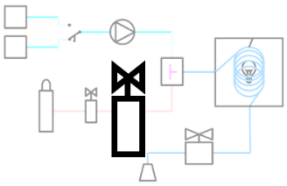
Standard syringe pumps generate significant pulsation so that HPLC compact pumps are much better suited for the continuous generation of a steady slug flow. However, HPLC pumps are in direct contact with the reaction medium and thus can experience degradation with reactive reagents/solvents. Special attention should be directed at the homogeneity of the liquid phase in case of limited solubility, biphasic systems etc which might require the addition of a co-solvent, prior filtration of the solution phase, or the installation of an upstream filter. It is important to consider, that most HPLC pumps only provide accurate and steady solution pumping when operating against a significantly high back-pressure from the column chromatography unit. Therefore, a very thin capillary (l = 6 m, internal d = 0.13 mm) was placed between the pump and the reactor. This capillary generates significant back-pressures at low flow rates (16 bar/32 bar in acetonitrile and 27 bar/54 bar in methanol at 0.5/1.0 mL · min^{-1}, respectively) and ensures a pulsation-free operation of the pump.
(Pump: Bischoff dosage pump 2250; capillary: Bischoff PEEK capillary 1021903PK)

Pressure reducing valve & manometer



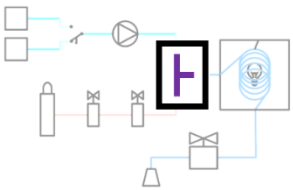
As with the pumps, the pressure reducing valve has to ensure a constant pressure regime during the whole span of the reaction time. Upon careful consideration and multiple tests, we have opted for a *GO* regulator (*TeamTrade*, PR1-1I11ACW-111), prepared for oxygen usage, which covers the targeted flow rates (0 – 25 mL · min^{-1}) and pressure range (0 – 52 bar outlet pressure). An erratic operation of the pressure reducing valve causes pressure spikes which prohibits a steady volume stream through the mass flow controller.

Mass flow controller



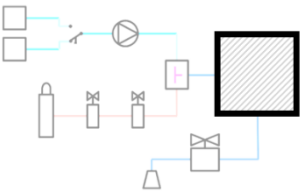
The mass flow controller fulfills an identical role as its liquid phase complement, the pulsation-free pump. The precise control of the mass flow of the gaseous reagents (here oxygen) ensures a constant gas stream which directly correlate with the built-up of a constant slug flow, a reproducible and constant productivity (conversion per time interval) and thereby allows the continuous operation of the flow reactor. Unlike the so-called gas flow meters, mass flow controllers are active devices that constantly measure and adjust the current volume stream to the target value. It is especially important that the mass flow controller is sufficiently pressure-resistent for the specific gases and pressure range used and precisely calibrated. As aforementioned for the HPLC pumps, thin capillary reactors can build up large back-pressures. The initial upstream entry pressure should be set rather high in order to accommodate the significant pressure gradient over the capillary length.

T mixer



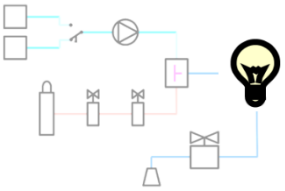
There are numerous types of mixers for various purposes. However, simple T-valves are suitable for most applications. A low dead volume and a high pressure resistance are key characteristics of T mixers. However, careful optimizations of the internal size, shape, and dead volume of the T-mixer directly affects the local concentrations of the reagents and thus can have dramatic effects on reaction rates and selectivities. Furthermore, specific properties of the reagents and solvents (viscosity, surface tension, gas solubility) will be critical to the dispersion and slug flow formation.

Temperature control



The microreactor system is equipped with a dual water cooling. The LED rod has an interior active water cooling. The reaction tubing is immersed in a water bath which is controlled by an external thermostat. This setup avoids that the light has to pass through the cooling media as in double-walled reaction vessels (absorption).

Light source



Energy-saving light bulbs and light emitting diodes (LEDs) of different wavelengths (red, green, blue, white) were used for irradiation of the reactions. The light source was placed in the center of the reactor to achieve optimal irradiation.[58] Key characteristics are the emission spectrum and the light intensity. A perfect match of the light emission maximum and the dye's absorption maximum is desirable. It should also be considered that potential excitation of other reagents could trigger competitive reaction mechanisms and pathways.

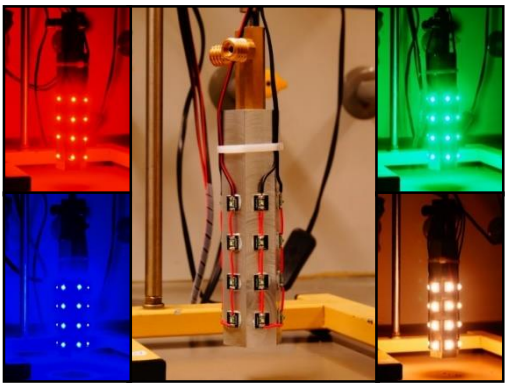


Figure 4.2: Red (λ_{max} = 633 nm), blue (λ_{max} = 448 nm), green (λ_{max} = 520 nm) and white (λ_{max} = 620 nm) LEDs mounted on a water cooled aluminium cooling element;

The LEDs were mounted on an aluminium rod which is water-cooled from the interior to prevent (over-)heating of the LEDs and the reaction (Figure 4.2). White light was also obtained from a commercial energy-saving light bulb (Osram Dulux Superstar).
LEDs exhibit high light power (~ *110 lm/W*) at low energy consumption in comparison with other powerful light sources such as mercury lamps (~ *50 lm/W*). The availability of various LED types with different wavelengths and narrow emission spectra obviates the need for filters and allows high quantum yields by the correct matching of lamp emission and chromophore absorption bands. The absence of UV emission bands in the used red and warm white LEDs enhances the selectivity of many organic reactions by suppression of unwanted UV-mediated degradation processes.

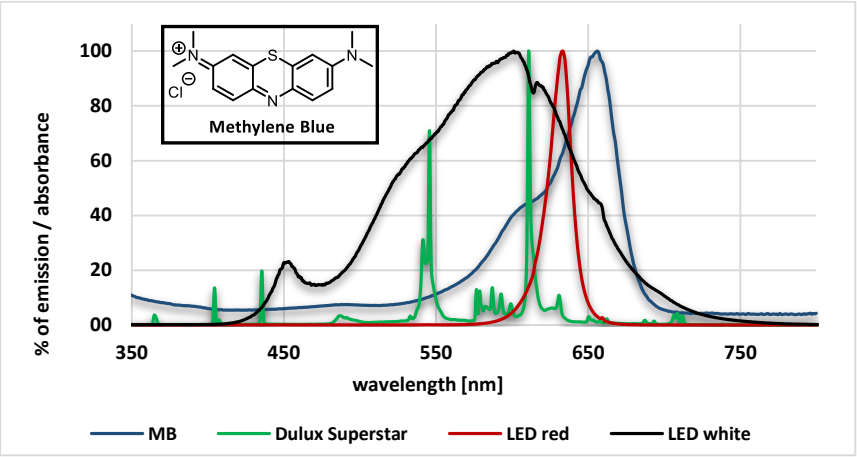


Figure 4.3: Overlap of absorption spectrum of methylene blue (blue) and emission spectra of different sight sources; red LED (red), white LED (black) and Dulux Superstar (green)

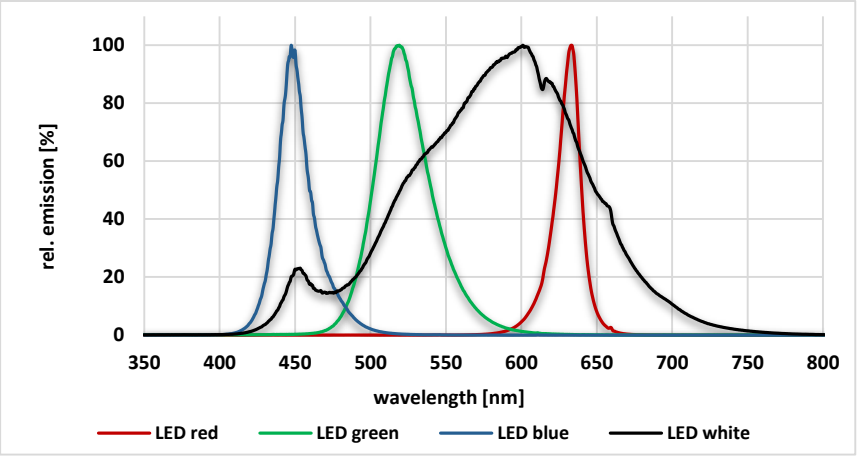
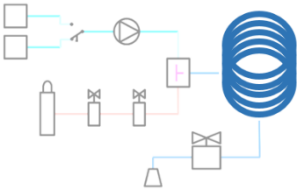


Figure 4.4: Emission spectra of different LEDs; red (λ_{max} = 633 nm), blue (λ_{max} = 448 nm), green (λ_{max} = 520 nm) and white (λ_{max} = 620 nm).

Capillary tubing:



The formation of a steady slug flow can be best achieved in a long tubular reactor and leads to very efficient irradiation. Mixing of liquid phase and gas phase occurs upstream in a T mixer while the tubular reactor should provide a high surface area for maximum exposure to the light source. For reaction times in the range of 10 s to 20 min, commercial fluorinated ethylene-propylene (FEP)-capillaries with an internal diameter of less than *2 mm* (here 0.75 mm) were used and coiled around a glass cylinder containing the light source. It is important to note that the tubing diameter can significantly influence the formation of the slug flow, the magnitude of light absorption and the back-pressure build-up. The latter again is dependent on the tubing length and the speification of the back-pressure regulator. The choice of an FEP coil around the lamp allows maximal versatility with regard to the type of light source, the wall material, the size and length of the tubing and thus allows multidimensional tuning of some of the most important reactor parameters. The length of the tubing coil directly determines the residence time in the reactor. The FEP tubing does not exhibit a significant absorption in the visible spectrum.[9,37,59] Furthermore, the reaction temperature can be easily set and controlled by immersion of the reactor coil into a thermostat bath. This set-up is advantageous as the cooling liquid does not absorb any of the incident light before it penetrates the reactor and the outer cooling counters the heat generated by the central lamp.

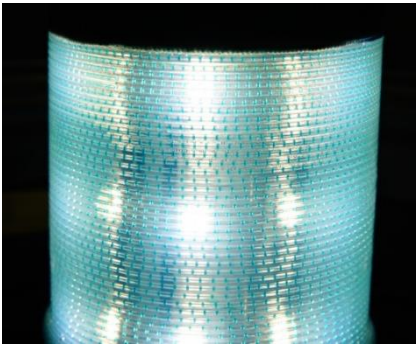
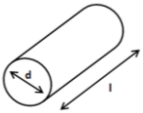


Figure 4.5: Photograph of the operating flow reactor, irradiated with white LEDs, filled with a solution of methylene blue (1.0 mM) and a cyclohexene (0.1 M) and oxygen at 30 bar and 1.0 mL/min flow rate in an FEP tubing reactor (0.75 mm inner diameter).

FEP-capillaries for HPLC applications are available in various internal and external diameters. The optimal tubing gauge of photoreactors allows irradiation of the whole reactor width, which is determined by the Lambert-Beer law. The light intensity within the reactor is dependent on the concentration and absorption coefficient of the absorbing materials (reactor walls, dye etc.).

Generally, the used capillaries should be of high quality to resist up to the required pressures (~35 bar for a 30 m tube, with a ID = 0.75 mm) without significant expansion of the inner size, which would cause variable internal pressures and perturb the slug flow.

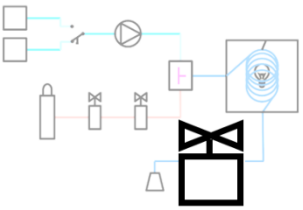
The back-pressure generated by the capillary tubing is dependent on the length and gauge of the capillary and the flow rate of the solution. If the dynamic viscosity of the solution is known, the pressure gradient can be calculated from the Hagen-Poiseuille equation.



$$\Delta p \sim l \times \frac{1}{d^4}$$

Figure 4.6: Schematic illustration of a reactor tube (length l, inner diameter d) and pressure gradient Δp according to the Hagen-Poiseuille law.

Back-pressure regulator

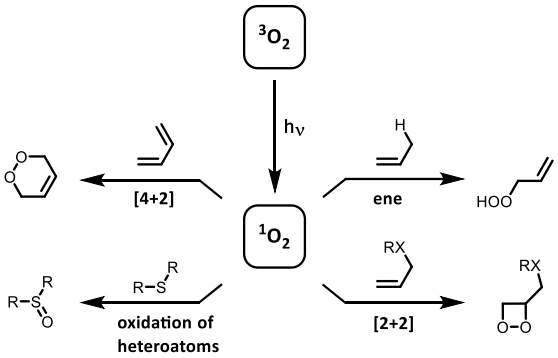


This device fulfills many roles: It controls the pressure at the downstream end of the reactor which should be greater than the ambient pressure in order to avoid both, the increasing expansion of the gas bubbles and the exceeding increase of the flow rate over the length of the reactor. A sufficiently high back-pressure secures a constant flow throughout the length of the tubing. This set back-pressure has to be higher than the pressure drop within the capillary which is especially high in long and thin capillaries. The back-pressure regulator also controls the solubility of the gas in the liquid phase which is pressure-dependent according to Henry's law.[60]

Figure 4.7: Home-made flow reactor and peripheral devices for photochemical reactions at light/liquid/gas interfaces.

4.3. Reaction parameters of a model photooxygenation

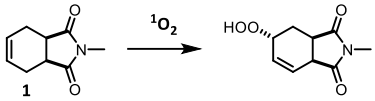
The often poor selectivities of reactions with molecular oxygen (being a triplet biradical in its ground state)[61–65] have prompted applications of microflow reactors to selective oxidations of various organic molecules (Scheme 4.5).[9,29,34,45,55,56] The application of microreactors to photo-oxidations, however, is still on an infant stage with only a handful of recent reports.[9,26,27,29,36–39,42] From a conceptual point of view, the combination of two of the most abundant „reagents" on the surface of our planet, oxygen and visible light, with a safe, scalable, and efficient reactor technology for chemical reactions constitutes an approach to oxidation chemistry of utmost sustainability. The most prominent examples include the oxidation of citronellol[37], the synthesis of artemisinine[9] and various fine chemicals like ascaridol[66]. All these reports take advantage of the facile generation of singlet oxygen $^1O_2$ from the triplet ground state by a photosensitization process of a ternary liquid/gas/light system and therefore are especially suited for the evaluation of microflow photoreactors.[61–65]



Scheme 4.5: Reaction types of organic molecules with singlet oxygen

We applied the home-made photo-flow reactor to the visible light mediated oxygenation of a cyclohexene derivative (i.e. Schenck ene reaction with singlet oxygen)[67] and evaluated the critical reaction and reactor parameters. Following an optimized Schenck ene reaction procedure, *N*-methyl-1,2,3,6-tetrahydrophthalimide was reacted with molecular oxygen in the presence of methylene blue as sensitizer (Scheme 4.6). The choice of solvent is crucial as it determines the solubility of the organic substrate, the dye, oxygen as well as its lifetime in the singlet state ($^1O_2$).[68] The properties and nature of the dye obviously guide the choice of solvent and light source. All reactions were

performed under irradiation with an energy-saving light bulb (Osram Dulux Superstar) against a back-pressure of 2.4 bar while one parameter was varied in each experiment.



Scheme 4.6: Photooxygenation of *N*-methyl-1,2,3,6-tetrahydro phthalimide.

It is especially important to note that reactions of non-activated substrates which require long residence times and low flow rates can lead to strong interdependencies of several reaction parameters which are often negligible at high flow rates.[37] While higher substrate concentrations showed only slightly higher conversions, a significant increase of residence time at constant flow rates was observed (Table 4.2).

Table 4.2: Conversion vs. substrate concentration

Substrate [mol · L^{-1}]	Residence time [min]	Conversion [%]	Productivity [µmol · min^{-1}]
0.01	5.00	75	1.9
0.05	5.50	70	8.8
0.10	6.25	75	18.8
0.20	6.75	80 (87[a])	40.0
0.30	8.00	90	67.5
0.40	7.70	84	84.0
0.50	10.5	89 (95[a])	111.3

Reactions at constant flow rates in acetonitrile at 10 °C; 1 mM methylene blue, 2.4 bar back-pressure, Osram Dulux Superstar. Conversions were determined by quantitative GC-FID vs. internal 1-dodecanitrile. [a] Conversion at identical residence time and 0.01 M substrate solution.

This can be attributed to the increased O_2 consumption at higher substrate concentrations and the resultant reduction of gas volume and flow rate over the capillary length. At identical residence times, the conversion of **1** could only be slightly improved with lower concentrations (after 6.75 min: 80 % with 0.20 M, 87 % with 0.01 M). This results in an overall dramatic increase of reaction productivity at higher substrate concentrations. In order to minimize the effect of substrate concentration on the flow rates, the internal reactor pressure must be increased which leads to higher O_2 density, lower relative O_2 consumptions, and shorter residence times. Later experiments with an

inlet pressure of 35 bar show only insignificantly longer residence times for higher substrate concentrations.

A similar effect on the residence time was observed by variation of the reaction temperature. Gas phase expansion at higher temperature leads to shorter reaction times while maximal conversion and productivity were achieved at room temperature. A more direct dependency of the conversion resulted from variations of the concentration of the sensitizer methylene blue, without affecting the residence time. At >0.5 mmol · L^{-1}, a plateau was reached (at very high dye concentrations, >2.0 mmol · L^{-1}, $^1O_2$ quenching leads to lower conversions).[37,69]

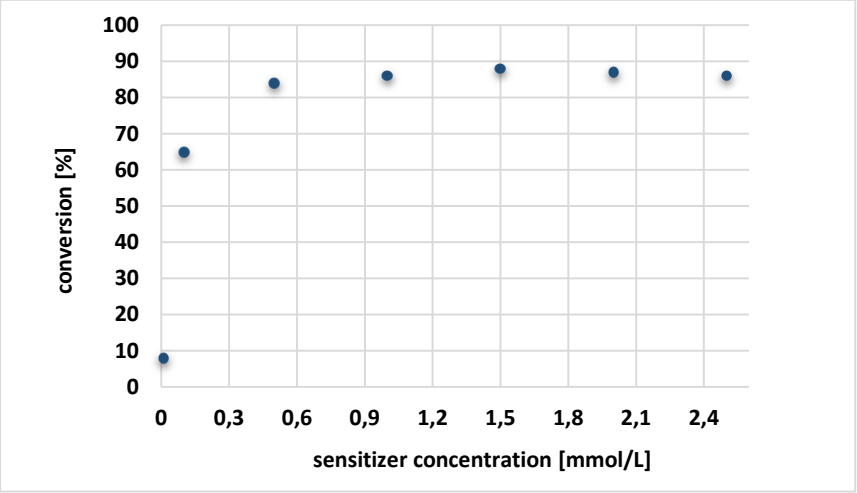


Figure 4.8: Conversion vs. sensitizer concentration. Reactions at constant flow rates in acetonitrile at 10 °C; 0.01 M **1**, 2.4 bar, Osram Dulux Superstar.

Variations of the used light source regarding power and wavelength show the importance of the conformance of absorption spectrum of the sensitizer and the emission spectrum of the light source.
Table 4.3 illustrates the influence of the irradiation wavelength and the intensity on the conversion at different residence times.

Table 4.3: Residence time and conversion with different light sources.

Light source	Residence time [min]	Conversion [%]
Energy-saving lamp (white)	6.25	75
LED (white)	1.50	87
LED (white)	3.50	> 99
LED (red)	3.50	80
LED (red)	6.25	92
LED (red)	8.00	> 99

The reactions were performed in acetonitrile at 10 °C with concentrations of 0.1 M **1** and 1 mM methylene blue (MB) and a back-pressure of 2.4 bar (inlet pressure 10 bar). The conversions of the photo-oxidation were determined by quantitative GC/FID vs. internal dodecanenitrile.

A direct relation between residence time and conversion is illustrated in Figure 4.9. Quantitative conversions were reached after min. 13.5 min; shorter residence led to lower conversion. The flow reactor assured full conversion after several minutes for which the batch reactions required 8 h. Furthermore, the residence time can generally be modulated by the length of the reactor tubing and the flow rates of solution and gas phases.

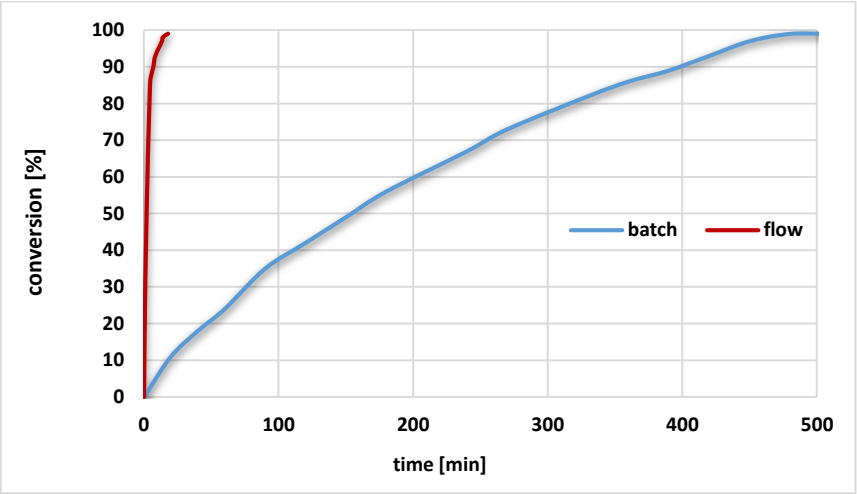
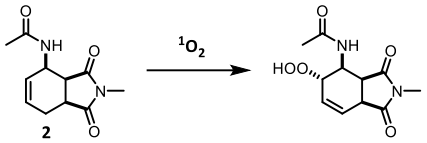


Figure 4.9: Reaction progress at different residence times in flow and batch reactions. Flow: reactions at different flow rates in MeCN at 10 °C; 0.01 M **1**, 1 mM methylene blue, 2.4 bar, Osram Dulux Superstar. Batch: 0.05 M **1**, 0.1 mM methylene blue in MeCN at r.t., irradiation by six Cree Power LED, warm white.

A comparison of the utilized light power of identical LEDs which is required for complete conversion of 1 mmol substrate in batch and flow documents that the six LEDs of the batch reactions have consumed 0.56 kWh electricity within 8 h. This equals the power of the 24 LEDs of the flow reactor after 2 h operation which converts 9 mmol of substrate (0.062 kWh · $mmol^{-1}$). An even more pronounced advantage of the flow reactor becomes evident when using less reactive starting materials (Scheme 4.7). The amidocyclohexene derivative **2** was quantitatively converted after 48 h in batch mode and consumed 3.37 kWh · $mmol^{-1}$ which in flow mode would suffice for continuous conversion of 36 mmol substrate over 12 h at 0.5 mL · min^{-1} flow rate (0.09 kWh · $mmol^{-1}$).



Scheme 4.7: Oxidation of *N*-methyl-1,2,3,6-tetrahydro-3-acetamido phthalimide.

4.4. Conclusion

The basic technological and practical aspects of a home-made microreactor setup for applications to photochemical processes with gas/liquid mixtures have been described in full detail. Special care should be taken with the design of the key components (pumps, tubing, pressure valves) and the key parameters (tube diameter, tube length, back-pressure, flow rate) and with their mutual interdependencies. We have presented a thorough analysis of critical parts and conditions of a general microflow reactor setup for photochemical reactions and an exemplary application to oxidations with gaseous oxygen as the stoichiometric oxidant. The application range of such modular home-built reactor is 0.04-0.5 mmol/min substrate throughput, 0.4-2.5 mL/min liquid phase flow rates, -40 to 60 °C, 5-40 bar oxygen pressure. The device can be easily assembled within one day from commercial parts at an overall price of less than 1000 € for the microreactor, less than 5000 € for the peripheral pump and mass flow controller, and less than 500 € for each light source coil. The application of this microreactor system to the visible light-driven photooxygenation of cyclohexene derivatives documented the superiority over a standard batch process in terms of productivity. Depending on the solubility of the substrates up to 30 mmol/h could be oxidized.

We believe that this report provides a stepping stone for researchers, teachers, and students around the world who wish to enter the field of microreactor technology for organic reactions at a reasonable price and effort. This detailed report on the theoretical, technical, and chemical aspects of a non-expert application of a home-built microreactor to a standard chemical reaction is specifically intended to stimulate multiple reproduction.

4.5. Experimental Part

General

Chemicals and Solvents
If not indicated, commercial reagents were used without purification.

Analytical thin-layer chromatography
TLC was performed using aluminium plates with silica gel and fluorescent indicator (Merck, $60F_{254}$). Thin layer chromatography plates were visualized by exposure to UV light and/or by immersion in an aqueous staining solution of $KMnO_4$ or in an ethanolic solution of molybdophosphoric acid.

Column chromatography
Flash column chromatography with silica gel 60 Å (220-240 mesh) from *Acros*. Pentane, hexanes or mixtures thereof with ethyl acetate were used as eluents.

Gas chromatography with mass-selective detector
Agilent 6890N Network GC-System, mass detector 5975 MS. Column: BPX5 (30 m x 0.25 mm x 0.25, from *SGE*, carrier gas: H_2.
Standard heating procedure: 50 °C (2 min), 25 °C/min -> 300 °C (5 min).

Gas chromatography with FID
Agilent 7820A GC-Systems. Column: HP 5 19091J 413 (30 m x 0.32 mm x 0.25 µm) from *Agilent*, carrier gas: N_2. GC-FID was used for catalyst screening (Calibration with internal standard *n*-pentadecane and analytically pure samples).

NMR
^1H and ^{13}C nuclear magnetic resonance spectra were recorded on *Bruker* Avance 300 (300 MHz ^1H; 75 MHz ^{13}C) and *Bruker* Avance 400 (400 MHz ^1H, 101 MHz ^{13}C) spectrometers. Chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hertz (Hz). Following abbreviations are used for spin multiplicities:
s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, ddt = doublet of doublet of triplet. For yield determinations, *n*-pentadecane was used as internal standard.

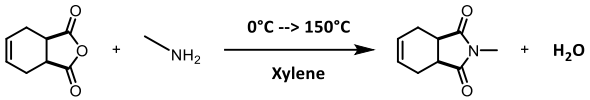
IR spectroscopy
Infrared spectra were recorded on a *Varian* Scimitar 1000 FT-IR equipped with a ATR unit or on an *Agilent* Cary 630 FTIR equipped with a ATR unit. Wavenumbers are indicated in cm^{-1}. Intensive absorption bands are indicated with „s“ (strong), medium bands with „m“ (medium), and weak bands with „w“ (weak).

High resolution mass spectrometry (HRMS)

The spectra were recorded by the Central Analytics Lab at the Department of Chemistry, University of Regensburg, on a MAT SSQ 710 A from *Finnigan*.

Preparation of Starting Materials

***N*-Methyl-1,2,3,6-tetrahydophthalic imide**



cis-1,2,3,6-tetrahydrophthalic anhydride (7.5 g, 49 mmol, 1.0 equiv.) was suspended in xylene (27 mL) and cooled to 0 °C. Methylamine (2 M in THF, 27 mL, 54 mmol, 1.1 equiv.) was added at 0 °C. The reaction mixture was allowed to warm to RT and stirred at RT for 2 h.

Subsequently the suspension was stirred for 4 h at 150 °C using a water separator. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using PE/EA (2/1) as eluent.

Product (5.7 g, 70 %) was isolated as colourless crystals.

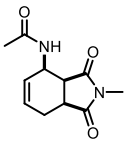
TLC: R_f = 0.42 (PE/EA = 2/1)

^{1}H-NMR: ($CDCl_3$, 400 MHz): δ = 5.92-5.85 (m, 2H, CH-1,2), 3.12-3.05 (m, 2H, CH-4,6), 2.96 (s, 3H, CH-5), 2.64-2.58 (m, 2H, CH-3), 2.27-2.19 (m, 2H, CH-7).

LR-MS: (EI, 70 eV): 165 $[M]^+$

***N*-(2-Methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**

The product was synthesized according to GP-3.3, using 15 mmol of starting material. The crude product was purified by column chromatography using PE / EA = 1 / 4 as an eluent.



$C_{11}H_{14}N_2O_3$, 222.24 g/mol

Yield: 54 %

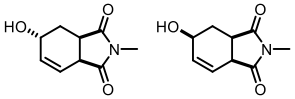
TLC: R_f = 0.15 (PE/EA = 1/4)

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.4 Hz, 1H), 5.86 (ddt, *J* = 10.2, 7.2, 3.1 Hz, 1H), 5.72 (dt, *J* = 9.5, 3.1 Hz, 1H), 4.79 – 4.58 (m, 1H), 3.34 – 3.07 (m, 2H), 2.94 (s, 3H), 2.71 (ddt, *J* = 15.4, 7.2, 0.9 Hz, 1H), 2.37 – 2.13 (m, 1H), 2.08 (s, 3H).

LR-MS: (EI, 70 eV): 180 $[MH\text{-}C_2H_3O]^+$

Preparation of Oxidation Products

5-Hydroxy-2-methyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione



$C_9H_{11}NO_3$, 181.0739 g/mol

5-Hydroxy-2-methyl-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione was synthesized according to GP-3.1 (reaction time = 8 h) and purified by column chromatography using a mixture of PE and EA (33 % --> 66 % EA).

Yield: 82 % (ratio 8/1); (crude product ratio = 5/1)

Condition: pale yellow amorphous solid

TLC: R_f = 0.31 (PE/EA = 1/2)

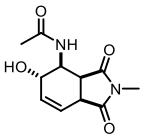
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.12 (ddd, *J* = 9.9, 4.0, 2.2 Hz, 0.13H), 6.07 – 5.95 (m, 1.12H), 5.89 (ddd, *J* = 10.1, 4.2, 1.8 Hz, 1H), 4.37 – 4.31 (m, 0.12H), 4.22 – 4.07 (m, 1H), 3.53 – 3.40 (m, 1.12H), 3.21 (dt, *J* = 8.0, 5.7 Hz, 1H), 3.12 – 3.00 (m, 0.14H), 2.98 (s, 0.33H), 2.96 (s, 3H), 2.44 (dt, *J* = 13.1, 4.9 Hz, 1H), 1.76 (ddd, *J* = 13.1, 9.0, 6.1 Hz, 1.18H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 178.7, 176.6, 134.9, 122.8, 62.5, 40.9, 36.8, 29.9, 25.0.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3429, 2945, 1766, 1670, 1435, 1383, 1338, 1282, 1129, 1062, 1006, 828, 716

HR-MS (ESI): $[MH]^+$ = 182.0810 ; calculated: 182.0817

***N*-(5-Hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide**



$C_{11}H_{14}N_2O_4$, 238.2430 g/mol

N-(5-hydroxy-2-methyl-1,3-dioxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-yl)acetamide was synthesized according to GP-3.1 (reaction time = 48 h) and purified by column chromatography using a mixture of DCM and MeOH (99 % --> 97 % DCM)

Yield:	74 %
Condition:	pale yellow solid
m.p.:	168 °C
TLC:	R_f (EA) = 0.14
^{1}H NMR:	(400 MHz, DMSO) δ = 7.61 (d, *J* = 8.8 Hz, 1H), 5.92 – 5.83 (m, 1H), 5.83 – 5.70 (m, 1H), 5.20 (s, 1H), 4.15 – 4.01 (m, 1H), 3.92 – 3.72 (m, 1H), 3.62 – 3.52 (m, 1H), 3.45 (dd, *J* = 8.1, 5.9 Hz, 1H), 2.77 (s, 3H), 1.82 (s, 3H).
^{13}C NMR:	(101 MHz, DMSO) δ = 177.0, 176.2, 169.1, 132.5, 123.3, 64.1, 49.1, 41.5,24.3, 22.6.
HR-MS (ESI):	$[MH]^+$ = 239.1025 ; calculated: 239,1026

4.6. Acknowledgements

We gratefully acknowledge financial and intellectual support from the Graduate School on Chemical Photocatalysis of the German Science Foundation (DFG, GRK 1626). We thank the group of Prof. Peter H. Seeberger (Max Planck Institute of Colloids and Interfaces) for stimulating discussions.

4.7. References

[1] a) J.-I. Yoshida, *Basics of flow microreactor synthesis*, Springer, Tokyo, **2015**; b) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors*. *New technology for modern chemistry*, Wiley-VCH, Weinheim, **2004**; c) W. Reschetilowski, *Microreactors in preparative chemistry*. *Practical aspects in bioprocessing, nanotechnology, catalysis and more*, Wiley-VCH, Weinheim, **2013**; d) V. Hessel, H. Löwe, S. Hardt, *Chemical micro process engineering*. *Fundamentals, modelling and reactions*, Wiley-VCH, Weinheim, **2004**; e) C. Wiles, P. Watts, *Micro Reaction Technology in Organic Synthesis*, CRC Press, Hoboken, **2011**; f) C. Wiles, P. Watts, *Green Chem.* **2012**, *14*, 38–54; g) P. T. Baraldi, V. Hessel, *Green Process Synth.* **2012**, *1*, 149–167.

[2] K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem. Int*. *Ed*. **2004**, *43*, 406–446.

[3] a) M. N. Kashid, A. Renken, L. Kiwi-Minsker, *Chem. Eng. Sci.* **2011**, *66*, 3876–3897; b) Y. Zhao, G. Chen, Q. Yuan, *AIChE J.* **2007**, *53*, 3042–3053; c) J. H. Xu, J. Tan, S. W. Li, G. S. Luo, *Chem. Eng. J.* **2008**, *141*, 242–249.

[4] Y. Su, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Eur. J.* **2014**, *20*, 10562–10589.

[5] H. Lu, M. A. Schmidt, K. F. Jensen, *Lab on a chip* **2001**, *1*, 22–28.

[6] B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry, K. I. Booker-Milburn, *J. Org. Chem.* **2005**, *70*, 7558–7564.

[7] H. Pennemann, P. Watts, S. J. Haswell, V. Hessel, H. Löwe, *Org. Process Res. Dev.* **2004**, *8*, 422–439.

[8] T. Iwasaki, N. Kawano, J.-I. Yoshida, *Org. Process Res. Dev.* **2006**, *10*, 1126–1131.

[9] F. Lévesque, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2012**, *51*, 1706–1709.

[10] D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675–680.

[11] A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. T. McQuade, *Angew. Chem. Int. Ed.* **2009**, *48*, 8547–8550.

[12] a) A. Sugimoto, Y. Sumino, M. Takagi, T. Fukuyama, I. Ryu, *Tetrahedron Lett.* **2006**, *47*, 6197–6200; b) Z. Qian, I. Baxendale, S. Ley, *Synlett*, **2010**, 505–508; c) R. J. Bogaert-Alvarez, P. Demena, G. Kodersha, R. E. Polomski, N. Soundararajan, S. S. Y. Wang, *Org. Process Res. Dev.* **2001**, *5*, 636–645.

[13] a) P. Löb, H. Löwe, V. Hessel, *J. Fluorine Chem.* **2004**, *125*, 1677–1694; b) T. Kawaguchi, H. Miyata, K. Ataka, K. Mae, J.-i. Yoshida, *Angew. Chem. Int. Ed.* **2005**, *44*, 2413–2416; c) L. Ducry, D. M. Roberge, *Angew. Chem. Int. Ed*. **2005**, *44*, 7972–7975.

[14] X. Zhang, S. Stefanick, F. J. Villani, *Org. Process Res. Dev.* **2004**, *8*, 455–460.

[15] N. de Mas, A. Günther, M. A. Schmidt, K. F. Jensen, *Ind. Eng. Chem. Res.* **2003**, *42*, 698–710.

[16] a) L. J. Martin, A. L. Marzinzik, S. V. Ley, I. R. Baxendale, *Org. Lett.* **2011**, *13*, 320–323; b) R. Fortt, R. C. R. Wootton, A. J. de Mello, *Org. Process Res. Dev.* **2003**, *7*,

762–768; c) K. Mikami, M. Islam, M. Yamanaka, Y. Itoh, M. Shinoda, K. Kudo, *Tetrahedron Lett.* **2004**, *45*, 3681–3683.

[17] A. Leclerc, M. Alamé, D. Schweich, P. Pouteau, C. Delattre, C. de Bellefon, *Lab on a chip*, **2008**, *8*, 814–817.

[18] A. Nagaki, Y. Uesugi, Y. Tomida, J.-I. Yoshida, *Beilstein J. Org. Chem.* **2011**, *7*, 1064–1069.

[19] M. Fernandez-Suarez, S. Y. Wong, B. H. Warrington, *Lab on a chip*, **2002**, *2*, 170–174.

[20] a) T. Schwalbe, D. Kadzimirsz, G. Jas, *QSAR Comb. Sci.* **2005**, *24*, 758–768; b) X. Liu, K. F. Jensen, *Green Chem.* **2013**, *15*, 1538; c) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17–57.

[21] I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby, G. K. Tranmer, *Chem. Commun.* **2006**, 2566–2568.

[22] N. Nikbin, P. Watts, *Org. Process Res. Dev.* **2004**, *8*, 942–944.

[23] A. J. Sandee, D. G. I. Petra, J. N. H. Reek, P. C. J. Kamer, van Leeuwen, Piet W. N. M., *Chem. Eur. J.* **2001**, *7*, 1202–1208.

[24] S. L. Bourne, S. V. Ley, *Adv. Synth. Catal.* **2013**, *355*, 1905–1910.

[25] K. Jähnisch, U. Dingerdissen, *Chem. Eng. Technol.* **2005**, *28*, 426–427.

[26] R. C. R. Wootton, R. Fortt, A. J. de Mello, *Org. Process Res. Dev.* **2002**, *6*, 187–189.

[27] S. Meyer, D. Tietze, S. Rau, B. Schäfer, G. Kreisel, *J. Photochem. Photobiol. A*, **2007**, *186*, 248–253.

[28] T. Carofiglio, P. Donnola, M. Maggini, M. Rossetto, E. Rossi, *Adv. Synth. Catal.* **2008**, *350*, 2815–2822.

[29] C. Y. Park, Y. J. Kim, H. J. Lim, J. H. Park, M. J. Kim, S. W. Seo, C. P. Park, *RSC Adv.* **2015**, *5*, 4233–4237.

[30] a) M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349–362; b) B. Tomaszewski, A. Schmid, K. Buehler, *Org. Process Res. Dev.* **2014**, *18*, 1516–1526.

[31] a) P. Watts, C. Wiles, *J. Chem. Res.* **2012**, *36*, 181–193; b) F. Darvas, V. Hessel, G. Dorman (eds.), *Flow Chemistry*, de Gruyter, Berlin, **2014**.

[32] a) K. Kaizuka, K.-Y. Lee, H. Miyamura, S. Kobayashi, *J. Flow Chem.* **2012**, *2*, 1–4; b) G. N. Doku, W. Verboom, D. N. Reinhoudt, A. van den Berg, *Tetrahedron*, **2005**, *61*, 2733–2742; c) C. G. Frost, L. Mutton, *Green Chem.* **2010**, *12*, 1687-1703; d) Y. Su, Y. Zhao, G. Chen, Q. Yuan, *Chem. Eng. Sci.* **2010**, *65*, 3947–3956.

[33] G. Chen, J. Yue, Q. Yuan, *Chin. J. Chem. Eng.* **2008**, *16*, 663–669.

[34] H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noël, *Chem. Soc. Rev.* **2015**, *45*, 83–117.

[35] J.-N. Tourvieille, F. Bornette, R. Philippe, Q. Vandenberghe, C. de Bellefon, *Chem. Eng. J.* **2013**, *227*, 182–190.

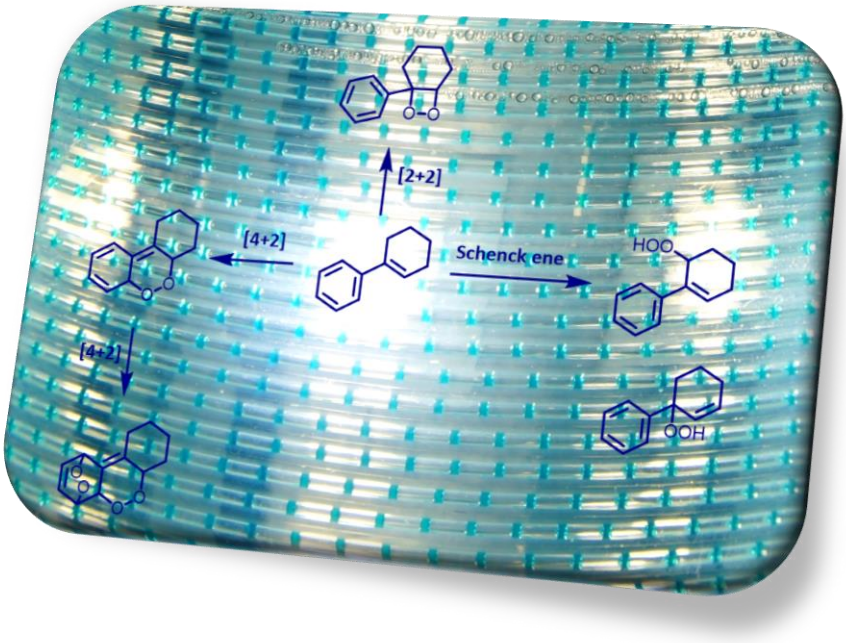
[36] Y. Nagasawa, K. Tanba, N. Tada, E. Yamaguchi, A. Itoh, *Synlett* **2015**, *26*, 412–415.

[37] F. Lévesque, P. H. Seeberger, *Org. Lett.* **2011**, *13*, 5008–5011.
[38] A. Talla, B. Driessen, N. J. W. Straathof, L.-G. Milroy, L. Brunsveld, V. Hessel, T. Noël, *Adv. Synth. Catal.* **2015**, *357*, 2180–2186.
[39] T. S. A. Heugebaert, C. V. Stevens, C. O. Kappe, *ChemSusChem* **2015**, *8*, 1648–1651.
[40] A. Hibara, S. Iwayama, S. Matsuoka, M. Ueno, Y. Kikutani, M. Tokeshi, T. Kitamori, *Anal. Chem.* **2005**, *77*, 943–947.
[41] M. J. Nieves-Remacha, A. A. Kulkarni, K. F. Jensen, *Ind. Eng. Chem. Res.* **2013**, *52*, 8996–9010.
[42] D. B. Ushakov, K. Gilmore, D. Kopetzki, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2014**, *53*, 557–561.
[43] H. Ehrich, D. Linke, K. Morgenschweis, M. Baerns, K. Jähnisch, *Chimia* **2002**, *56*, 647–653.
[44] K. Terao, Y. Nishiyama, H. Tanimoto, T. Morimoto, M. Oelgemöller, *J. Flow Chem.* **2012**, *2*, 73–76.
[45] J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052.
[46] C. Lambert, T. Sarna, T. G. Truscott, *Faraday Trans.* **1990**, *86*, 3879–3882.
[47] J. Cenens, R. A. Schoonheydt, *Clays Clay Miner.* **1988**, *36*, 214–224
[48] J. B. Kim, J. J. Leonard, F. R. Longo, *J. Am. Chem. Soc.* **1972**, *94*, 3986–3992.
[49] M. C. Mota, P. Carvalho, J. Ramalho, E. Leite, *Int Ophthalmol.* **1991**, *15*, 321–326.
[50] K. Kalyanasundaram, *Coord. Chem. Rev.* **1982**, *46*, 159–244.
[51] L. D. Elliott, J. P. Knowles, P. J. Koovits, K. G. Maskill, M. J. Ralph, G. Lejeune, L. J. Edwards, R. I. Robinson, I. R. Clemens, B. Cox, D. D. Pascoe, G. Koch, M. Eberle, M. B. Berry, K. I. Booker-Milburn, *Chem. Eur. J.* **2014**, *20*, 15226–15232.
[52] C. E. Hoyle, S. C. Clark, S. Jonsson, M. Shimose, *Polymer* **1997**, *38*, 5695–5697.
[53] W. G. Zijlstra, A. Buursma, O. W. von Assendelft, *Visible and near infrared absorption spectra of human and animal haemoglobin*. *Determination and application*, VSP, Utrecht, Boston, **2000**.
[54] M. D. Milošević, M. M. Logar, A. V. Poharc-Logar, N. L. Jakšić, *Int. J. Spectrosc.* **2013**, *2013*, 1–6.
[55] E. E. Coyle, M. Oelgemöller, *Photochem. Photobiol. Sci.* **2008**, *7*, 1313–1322.
[56] K. Ulbrich, P. Kreitmeier, O. Reiser, *Synlett* **2010**, 2037–2040.
[57] a) A. Yavorskyy, O. Shvydkiv, C. Limburg, K. Nolan, Y. M. C. Delauré, M. Oelgemöller, *Green Chem.* **2012**, *14*, 888–892; b) A. Günther, S. A. Khan, M. Thalmann, F. Trachsel, K. F. Jensen, *Lab on a chip*, **2004**, *4*, 278–286.
[58] M. Fischer, *Angew. Chem. Int. Edit. Engl.* **1978**, *17*, 16–26.
[59] A. Galante, O. L. Galante, L. L. Campos, *Nucl. Instrum. Methods Phys. Res. A*, **2010**, *619*, 177–180.

[60] a) W. J. Moore, D. O. Hummel, G. Trafara, *Physikalische Chemie*, de Gruyter, Berlin, **1986**; b) M. Görgényi, J. Dewulf, H. van Langenhove, *Chemosphere* **2002**, *48*, 757–762.
[61] P. R. Ogilby, *Chem. Soc. Rev.* **2010**, *39*, 3181–3209.
[62] H. Mimoun, *Ang. Chem.* **1982**, *94*, 750–766.
[63] G. Ohloff, *Pure Appl. Chem.* **1975**, *43*, 481–502.
[64] D. R. Kearns, *Chem. Rev.* **1971**, *71*, 395–427.
[65] H. Mimoun, *Angew. Chem. Int. Ed.* **1982**, *21*, 734–750.
[66] P. Esser, B. Pohlmann, H.-D. Scharf, *Angew. Chem. Int*. *Ed*. **1994**, *33*, 2009–2023.
[67] a) M. Alberti, M. Orfanopoulos, *Synlett*, **2010**, 999–1026; b) M. Prein, W. Adam, *Angew. Chem. Int. Ed.* **1996**, *35*, 477–494.
[68] a) F. Wilkinson, *J. Phys. Chem. Ref. Data* **1983**, 162–178; b) F. Wilkinson, *J. Phys. Chem. Ref. Dat*. **1981**, 809–999.
[69] K. Gollnick, A. G. Griesbeck, *Tetrahedron* **1984**, *40*, 3235–3250.

Chapter 5:

- Oxidation of Phenylcyclohexenes -



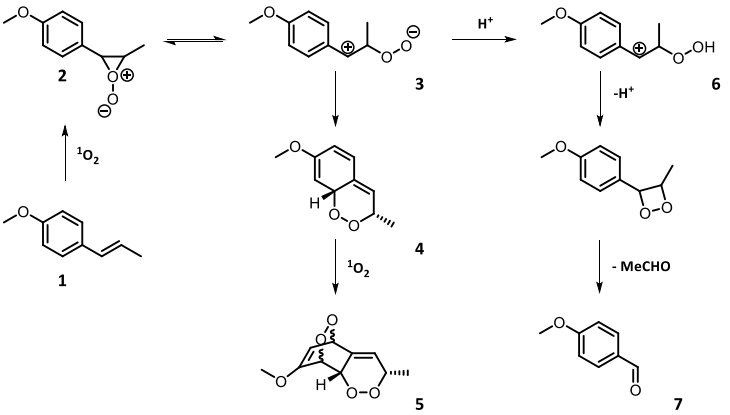
5. Oxidation of 1-Phenylcyclohex-1-enes

5.1. Introduction

Photooxygenations can be performed in several different solvents. Most frequently used are alcohols, chloroform or acetonitrile, but also aromatic solvents (e.g. benzene or toluene)[1,2] can be used. The aromatic system of benzene is not attacked by the singlet oxygen.

In contrast, in very special cases, other aromatic systems like naphthalenes,[3] 9-vinylphenanthrenes,[4] stilbenes,[5] indenes,[6] and selected styrenes[1] could be oxidized by the use of singlet oxygen. It is striking that most of these systems have an aromatic double bond in conjugation with an extranuclear unsaturation.[4] This styrene-like motive represents a diene, active enough to undergo a [4+2]-cycloaddition with $^1O_2$. Substrates, carrying an additional methyl- or methylene-group at the non-aromatic double bond can react in yet another reaction pathway, giving Schenck ene products, by abstraction of one allylic proton, while keeping the aromatic system untouched.[1,4]

One very interesting example is the photooxygenation of *trans*-propenylanisol (**1**) performed in different solvents, by FOOTE et al. using TPP, and a xenon lamp. Depending on the solvent used, different products could be obtained. The proposed mechanism shows an equilibrium between a perepoxide intermediate (**2**) and an open-chain zwitterionic intermediate (**3**) with a positive charge, stabilized by the aromatic system.



Scheme 5.1: Proposed mechanism of the photooxygenation of *trans*-propenylanisol[1]

Depending on the solvent this intermediate can either be protonated (in protic solvents, e.g. MeOH) to form a cationic hydroperoxide (**6**), further reacting to anisaldehyde (**7**), or undergo a nucleophilic attack on the aromatic ring (in aprotic solvents, e.g. benzene) to form a first endoperoxide (**4**) followed by a [4+2]-cycloaddition to form a second endoperoxide (**5**) (Scheme 5.1).[1]

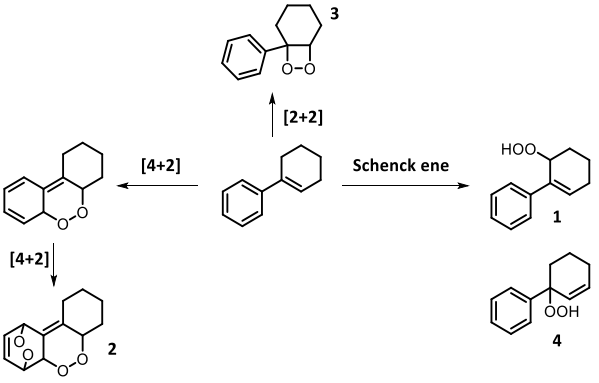
FOOTE et al. proved their mechanism by adding acid to aprotic solvents during the oxidation. Depending on the amount of acid, the formation of endoperoxide could be reduced or completely inhibited.
Most of the studies dealing with photooxygenations of styrene-like compounds were performed under low temperature conditions.[2,6]. Especially the 1,4-cycloaddition product mostly could not be isolated, due to its thermal instability.

5.2. Results and Discussion

To further investigate the photooxygenation of cyclohexenes described in Chapter 3, and considering the results of FOOTE, MATSUMOTO and others, we decided to try reactions of 1-phenylcyclohexenes with singlet oxygen. All photooxygenation experiments were executed in a flow reactor system, described in Chapter 4.

Photooxygenation of phenylcyclohexenes

As a test substrate, commercially available 1-phenylcyclohexene (**PCH**) was chosen for investigations of reaction and reactor parameters. Acetonitrile was used as a solvent, and methylene blue as photosensitizer. Theoretically, oxidation of 1-phenylcyclohexene with $^1O_2$ can proceed *via* three different oxidation mechanisms: Schenck ene reaction, [4+2]- and [2+2]-cycloaddition.(Scheme 5.2).
Surprisingly, the Schenck ene product (**1**) was, the major product in our first attempts. Regarding the results of Chapter 3 (photooxidation of cyclohexenes) and the inertness of unsubstituted cyclohexene in $^1O_2$ reactions, this result is a first indication of a different reaction mechanism. As a second reaction product, the endoperoxide (**2**) was obtained. Dioxetane (**3**), as well as the second possible Schenck ene product (**4**) could not be detected (Scheme 5.2).



Scheme 5.2: Possible reaction pathways for the photooxygenation of phenylcyclohexene.

Due to the first results and the mechanistic proposal of FOOTE et al., a mechanism passing a zwitterionic open-chain intermediate was assumed (Scheme 5.3). According to the photooxygenation of *trans*-propenylanisol, this would mean that a solvent change to a more protic solvent (e.g. methanol) should result in a different ratio of Schenck ene to cycloaddition product.

Ratios of product **1** to product **2**, listed in Table 5.1 show a decreasing percentage of [4+2]-cycloaddition product in protic solvents like methanol. This is in accordance with the proposed mechanism of FOOTE et al. although the effect is not as dramatic as observed in the oxidation of *trans*-propenylanisol. The very high ratio of **1** to **2** in methanol decreases for higher conversions (5.0 at full conversion) and is most likely the result of a too small amount of product **2** (below the calibration range).

Table 5.1: Solvent dependency of the product formation[a]

solvent	conversion [%]	ratio 1 to 2
MeCN	67	2.4
MeOH	25	14.0
EtOH	30	4.0
*i*Propanol	22	7.3
CH_2Cl_2	53	3.4
$CHCl_3$	51	2.5
Aceton	42	5.0

[a] Standard conditions: 1 min irradiation in the flow reactor, c(MB) = 1 mM, c(PCH) = 0.1 M, conversion and product quantities determined by analytical HPLC using *m*-xylene as internal standard

As a second proof of the assumed mechanism, arylcyclohexenes bearing different electron donating or electron withdrawing substituents in the *para*-position to the cyclohexene moiety were synthesized, and oxidized under identical conditions. Depending on the electronical behavior of the substituent, the stabilization of the positive charge of the zwitterionic intermediate in *para*-position should vary. In addition, the reaction rate and the ratio of Schenck ene and [4+2]-cycloaddition product should be influenced. All these statements presuppose the formation of the zwitterionic intermediate being the rate-determining step.[7]
All substituted arylcyclohexenes were synthesized *via* a three step procedure: formation of Grignard reagent from *para*-substituted bromobenzenes, its addition to cyclohexanone, finally followed by an elimination of water. A list of *p*-substituents and the corresponding Hammett constants σ_p is shown in Table 5.2.

Table 5.2: *p*-Substituents and the corresponding Hammett constants σ_p[8]

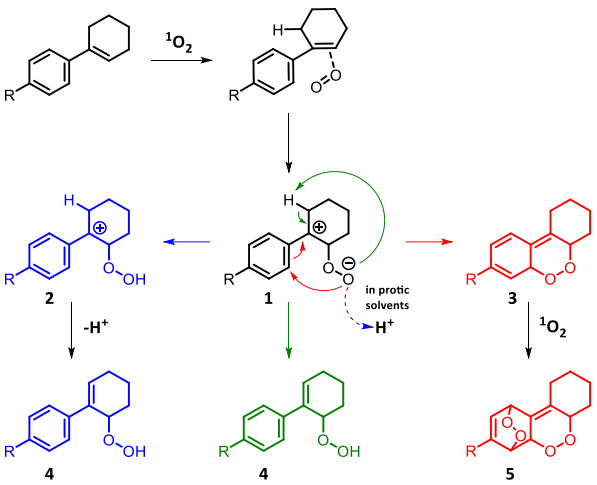
***p*-substituent**	**σ_p**	**Conversion [%]**	**product ratio[a]**
-CF_3	0.54	16	6.4
-OCF_3	0.35	34	4.8
-F	0.06	47	2.5
-Ph	-0.01	48	2.3
-H	0.00	57	2.2
-Me	-0.17	61	2.2
-*t*Bu	-0.20	65	2.1
-OMe	-0.27	72	2.7

[a] Product ratio: ratio of Schenck ene product to [4+2]-cycloaddition product; Conversions were determined after 50 s irradiation in the flow reactor with red LEDs, c(MB) = 1 mM, c(substrate) = 0.1 M, conversion determined by analytical GC/FID using dodecanitrile as an internal standard, product ratios determined by NMR of the crude mixture.

para-Substituted phenylcyclohexenes with σ_p values in a range of -0.27 to 0.54 were oxidized. For every substrate, the conversion and the ratio of Schenck ene product to [4+2]-cycloadddition product was determined.

The reaction rate for the photooxygenation of arylcyclohexenes shows an undisputable dependency with the electronical character of the *para*-substituent (Figure 5.1). The stronger the electron donating character of the substituent, the faster the reaction proceeds. Highest conversions with 72 % of material converted within 50 s could be achieved using *p*-methoxy substituted phenylcyclohexene (σ_p = -0.27), whereas *p*-trifluoromethyl substituted phenylcyclohexene (σ_p = 0.54) delivered only 16 % conversion under identical conditions. This dependency provides us with two new hints: first it indicates the existence of a zwitterionic intermediate and the stabilisation of its positive charge by the aromatic system. Second, it shows that the formation of this intermediate has to be the rate-determining step in these photooxygenation reactions. The experimental results and conclusions were supported by DFT calculations. According to these, the positive charge of the zwitterionic intermediate of *p*-methoxy substituted phenylcyclohexene is stabilized by -8.0 kJ/mol, whereas the zwitterionic intermediate of *p*-trifluoromethyl substituted phenylcyclohexene is destabilized by 5.4 kJ/mol compared to unsubstituted phenylcyclohexene.

Under the conditions of this investigation, unsubstituted cyclohexene shows a conversion of only 24 %. Therefore, the deactivated 4-trifluoro-methoxy-1-phenylcyclohexene is still more reactive than unsubstituted cyclohexene.



Scheme 5.3: Proposed mechanism for photooxygenation of 1-arylcyclohexenes

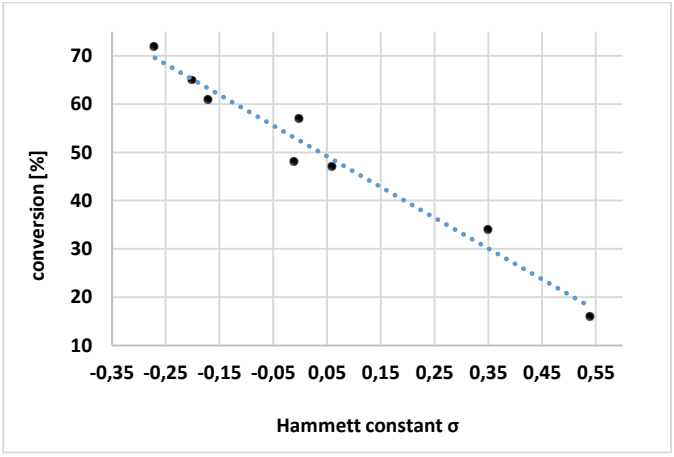


Figure 5.1: Conversion of phenylcyclohexenes with different *para*-substituents. Conversions were determined after 50 s irradiation in the flow reactor with red LEDs, c(MB) = 1 mM, c(substrate) = 0.1 M, conversion determined by analytical GC/FID using dodecanitrile as an internal standard;

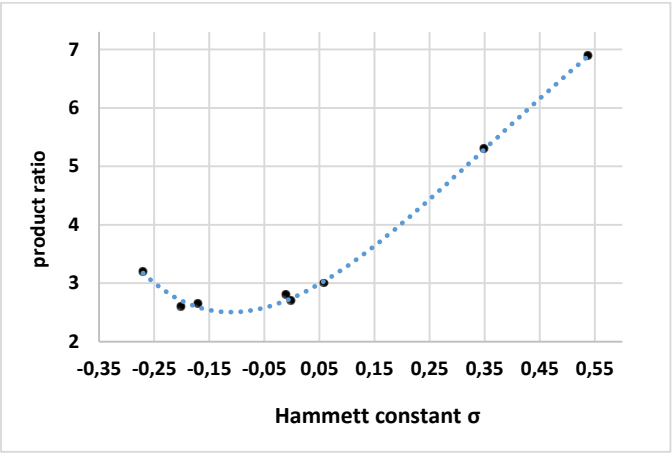
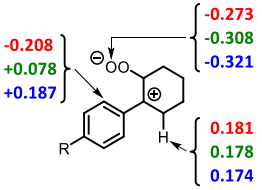


Figure 5.2: Ratio of Schenck ene product to [4+2]-cycloadddition product for phenylcyclohexenes with different *para*-substituents, determined after 50 s irradiation in the flow reactor with red LEDs, c(MB) = 1 mM, c(substrate) = 0.1 M. Product ratios were determined by NMR of the crude mixture.

Besides the reaction rate, the ratio of Schenck ene and the [4+2]-cycloaddition product varies depending on the *p*-substituent of the arylcyclohexene. As shown in Figure 5.2, the amount of the Schenck ene product increases for EWG´s as well as for *p*-methoxy substituted phenylcyclohexene and reaches its minimum for weak electron-donating substituents like methyl or *tert*-butyl. This ascent at both sides indicated a change in mechanism. With regard to the experimental results and supported by DFT calculations the mechanism shown in Scheme 5.3 was proposed.



Scheme 5.4: Charge on the 2-position of the aromatic ring, on the terminal oxygen of the peroxy anion, and on the H atom next to the positive charge (according to DFT calculations for *p*-OMe (blue), *p*-CF_3 (red) and 1-phenylcyclohexene (green))

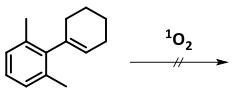
Depending on the *p*-substituent different conditions have to be distinguished:

- ***p*-OMe:** Due to the strong stabilization (-50 kJ/mol) of the cationic intermediate (**2**), compared to 1-phenylcyclohexene, the peroxy anion of intermediate **1** is easily protonated. The lower nucleophilicity of the hydroperoxide compared to the peroxy

anion excludes the nucleophilic attack on the arene and results in a higher fraction of Schenck ene product, by abstraction of the acidic proton next to the positive charge.

- ***p*-CF_3:** In cases of strongly electron withdrawing funtionalization the protonation of the peroxy anion in the zwitterionic intermediate (**1**) is disfavoured, as the cationic intermediate (**2**) is destabilized (40 kJ/mol). The higher fraction of Schenck ene product results from the higher acidity of the allylic proton and the direct reaction of intermediate **1** to hydroperoxide **4**. Additionally, partially negative charge is developed by induction at the *o*-position (to the cyclohexenyl) which inhibits the nucleophilic attack of the peroxy anion (Scheme 5.4).
- ***p*-H:** For unsubstituted phenylcyclohexene and arylcyclohexenes bearing weak electron donating substituents different reaction pathways are possible. Due to the moderate acidity of the allylic proton, the partially positive charge at the *o*-position, and the stabilization of the cationic intermediate (**2**), the zwitterionic intermediate (**1**) can either react directly to the hydroperoxide (**4**), form the cationic intermediate (**2**) or the endoperoxide (**3**) by nucleophilic attack at the *o*-position. This results in a lower selectivity in these cases.

Another hint on the correctness of the proposed mechanism and the importance of the stabilization of the zwitterionic intermediate by the aromatic system, gives the photooxygenation of 1-(2,6-dimethylphenyl)-cyclohexene (Scheme 5.5).



Scheme 5.5: Photooxygenation of 1-(2,6-dimethylphenyl)-cyclohexene

Under the standard conditions used for oxidations during the Hammett study, 1-(2,6-dimethylphenyl)-cyclohexene does not react at all. DFT calculations showed the cyclohexene double bond twisted out of the plane of the aromatic system in the ground state. Therefore, the empty p-orbital is not perpendicular to the aromatic plane and the positive charge of the zwitterionic intermediate can´t be stabilized by the arene.

Influence of the ring size

In addition to the various phenylcyclohexenes, 1-phenylcyclopentene and 1-phenylcycloheptene were used for photooxygenations. In contrast to cyclohexene, the cyclopentene and cycloheptene delivered higher conversions and better selectivities under identical conditions. After 50 s in the flow reactor, 1-phenylcyclopentene and 1-phenylcycloheptene were converted quantitatively and Schenck ene product could be

detected exclusively, whereas 1-phenylcyclohexene delivered two products and only 57 % conversion (Figure 5.3).

Generally cyclohexenes show small reaction rates in photooxygenation reactions.[9] In Schenck ene reactions of 1-methyl substituted cyclopentene, cycloheptene and cyclohexene the poor endo-selectivity of 1-methylcyclohexene is remarkable and is not consistent with the commonly assumed *cis*-selectivity in $^1O_2$-ene reactions.[10] Unlike the ground states of cycloheptene and –pentene, the ground state conformation of cyclohexene seems to be disadvantageous for Schenck ene reactions. The far better *endo*-selectivity of 1-methylcycloheptene and 1-methylcyclopentene gives a hint on the better suitability of five- and seven-membered olefins for Schenck ene reactions, thanks to their geometry in ground state[10]

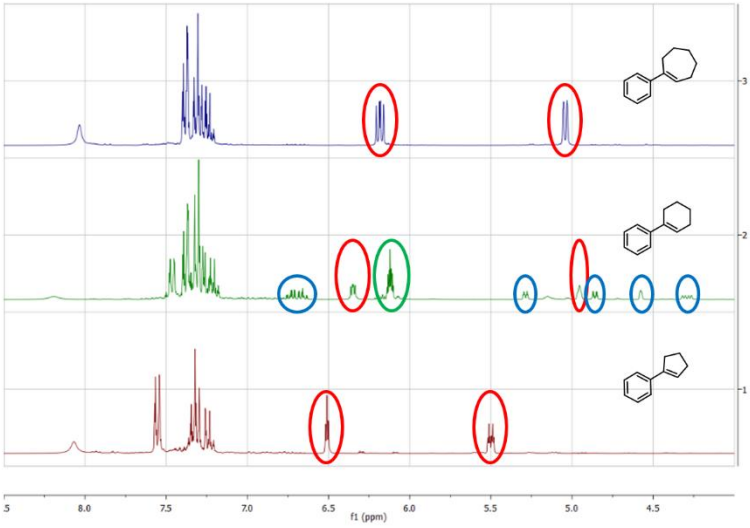


Figure 5.3: Crude NMR of the photooxygenation of 1-phenylcyclohexene, 1-phenylcyclopentene and 1-phenylcycloheptene with signals of statring material (green), [4+2]-cycloaddition product (blue) and Schenck ene product (red); t = 50 s, red LEDs, c(substrate) = 0.1 M, c(MB) = 1 mM, T = 0°C, p = 36 --> 7 bar,

Oxidation and isolation of different styrene-like substrates

In addition to the investigations into the reaction rate and selectivity in photooxygenation reactions of 1-phenyl substituted cyclic olefins, different substrates were oxidized quantitatively and the products were isolated and characterized if possible. As already mentioned, the required reaction times to achieve complete conversion varied, exchanging the *para*-substituent on the arene. Besides the *para*-

substituted 1-arene-cyclohexenes, *ortho*- and *meta*-methoxy phenylcyclohexene as well as some examples bearing substituents on the cyclohexene ring were oxidized. For *ortho*- and *meta*-methoxy phenylcyclohexene exclusively the Schenck ene product could be isolated, although for *meta*-methoxy phenylcyclohexene the [4+2]-cycloaddition product was identifiable in the NMR of the crude reaction mixture. Overall, several products identified by NMR spectroscopy could not be isolated or substantial losses of mass were observed. Although quantitative conversions were achieved, isolated yields did not exceed 70 %. Due to the thermal instability (O–O bond generally has a low dissociation energy) and the tendency to decomposition under basic conditions the quantitative isolation of endo- and hydroperoxides has proved to be difficult.[11]
In some single cases, diastereomeric oxidation products could be determined or even separated. The Schenck ene product of the 1-(4-*tert*-butylphenyl)-cyclohexene oxidation showed different diastereo-isomers as well as the double [4+2]-cycloaddition product of 1,4,4a,6a,7,8-hexahydro-1,4-epidioxybenzo[*c*]-naphtho[1,2-*e*][1,2]dioxine. In the second case, due to the nonexistent H atom in the allylic position, no Schenck ene product can be formed. Two different endoperoxides were the only isolated oxidation products.
The oxidation products of 1-phenylcyclohexene were used for further reactions. The hydroperoxide could be reduced to the alcohol using PPh_3, the endoperoxide could be converted to 6,7,8,9-tetrahydrodibenzofuran-1-ol by the use of base or thiourea.
Individual substituted phenylcyclohexenes could not be oxidized using singlet oxygen. For example, NMe_2 and SMe substituents resulted in complete inertness of the substrate towards $^1O_2$. The capacity of amines and thiols to completely inhibit the oxidation with singlet oxygen could also be observed in studies about functional group tolerance. Considering the documented potential for physical deactivation of singlet oxygen by amines[12] and thiols,[13] these results can be explained.

Reactor productivity and performance

Several reactor parameters were varied to determine ideal conditions for the photooxygenation of 1-aryl-substituted cyclohexenes in the flow reactor. 1-phenylcyclohexene was used as a test substrate.
Using an inlet pressure of 36 bar, a back-pressure regulator of 7 bar, red LEDs (24 × *Cree* XP-E 2, red) and acetonitrile at 0 °C, excellent results with regard to productivity and energy efficiency were achieved without exhausting the pressure resistance of the reactor. Catalyst loading could be reduced to 0.05 mol% at the minimum.
Comparing batch and flow reactions, the production capacity of the flow system clearly stands out. The energy saving potential is immense and the productivity in flow surpasses the batch systems by orders of magnitude. Based on required catalyst loadings and high productivities, turn over frequencies of up to 14,000 h^{-1} are feasible. Although the batch reaction has not been optimized with respect to all reaction parameters, the energy saving of up to 99.99 % (comparing the best results of both systems) is

outstanding and shows the great potential of flow reactors in photo-catalyzed gas-liquid reactions.

Table 5.3: Productivity and power consumption of photooxygenations in batch and flow

reactor type	concentration [mmol/L]	LED	time[a]	power consumption [W/mmol]	productivity [mmol/h]
batch	0.1	white	8 h	786	0.25
batch	1.0	white	> 48 h	468	< 0.42
flow	0.1	white	1.0 min	21.8	9.0
flow	0.1	red	4.3 min	9.60	4.5
flow	1.0	red	8.5 min	1.44	30.0

[a] time = required time to achieve complete coversion

5.3. Conclusion

Various 1-arylcyclohexenes, 1-phenylcyclopentene, and 1-phenylcycloheptene could be synthesized, in moderate to excellent yields, according a two-step procedure starting from commercially available bromoarenes and cyclic ketons.

Based on a Hammett study, the observed selectivities, and reactivities, and supported by DFT calculations, we assumed a reaction mechanism passing an open-chain zwitterion as the key intermediate and its formation as the rate determining step of the reaction. Also supported by DFT calculations, different ratios of Schenck ene and [4+2]-cycloaddition product in the case of different electron withdrawing or electron donating substituents, could be explained by a change in the reaction mechanism. Furthermore, the shift of the product ratio towards the Schenck ene product when using protic solvents supports the proposed mechanism.

The oxidation products of numerous arylcyclohexenes were characterized, and isolated in moderate yields. In contrast to numerous examples found in the literature, hydro- and endoperoxides could be isolated and stored without decomposition. The photoxygenation protocol shows tolerance towards various functional groups such as alkyl, aryl, halide, methoxy, trifluoromethyl or trifluoromethoxy substituents.

5.4. General procedures and analytical data

General procedures:

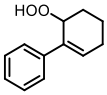
Oxidation of 1-arylcyclohexenes, -heptene and -pentene (GP-5.1):

As described in Chapter 4, the substrates were oxidized using the continuous flow system: (12.5 m, 5.7 mL), red LEDs (24 × *Cree* XP-E 2), 0 °C, pressure of 36 bar to 7 bar (inlet/BPR). After the oxidation, the solvent was removed under reduced pressure and the crude product was purified by column chromatography using a mixture of petroleum ether and ethyl acetate as an eluent. The used concentrations, retention times, solvents, exact eluents and yields are described for each compound.

2-Hydroperoxy-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.1 M / 1 mM	retention time:	5 min 30 s
eluent:	PE / EA (5 % --> 25 % EA)	solvent:	MeCN
quantity	2.5 mmol		



$C_{12}H_{14}O_2$, 190.24 g/mol

Yield: 42 %

Condition: pale yellow liquid

TLC: R_f (PE/EA = 4/1) = 0.58

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.83 (s, 1H), 7.52 – 7.22 (m, 5H), 6.35 (dd, *J* = 4.9, 3.1 Hz, 1H), 5.06 – 4.89 (m, 1H), 2.50 – 2.38 (m, 1H), 2.31 (dtd, *J* = 19.1, 5.5, 3.3 Hz, 1H), 2.25 – 2.07 (m, 1H), 1.83 (qdt, *J* = 10.3, 5.9, 3.0 Hz, 1H), 1.75 – 1.58 (m, 2H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 140.6, 134.0, 133.2, 128.6, 128.5, 127.2, 126.4, 125.9, 79.4, 26.5, 26.3, 16.9

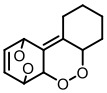
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3384 (b), 2937 (m), 2870 (w), 2829 (w), 1640 (w), 1599 (w), 1495 (w), 1446 (m), 1357 (m), 1267 (w), 1156 (w), 1066 (m), 1003 (w), 958 (m), 757 (s), 693 (s)

HR-MS (ESI): $[MH]^+$ = 191.1070; calculated: 191.1067

1,4,4a,6a,7,8,9,10-Octahydro-1,4-epidioxydibenzo[*c*,*e*][1,2]dioxine

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.1 M / 1 mM	retention time:	5 min 30 s
eluent:	PE / EA (5 % --> 25 % EA)	solvent:	MeCN
quantity	2.5 mmol		



$C_{12}H_{14}O_4$, 222.24 g/mol

Yield: 24 %

Condition: colourless crystalline solid

TLC: R_f (PE/EA = 4/1) = 0.38

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 6.81 – 6.58 (m, 2H), 5.37 – 5.13 (m, 1H), 4.95 – 4.76 (m, 1H), 4.65 – 4.52 (m, 1H), 4.29 (dd, *J* = 11.3, 5.3 Hz, 1H), 2.86 – 2.68 (m, 1H), 2.20 – 1.66 (m, 5H), 1.57 – 1.42 (m, 2H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 137.9, 132.3, 130.0, 118.6, 81.2, 78.1, 74.8, 69.0, 34.2, 29.0, 27.2, 24.8.

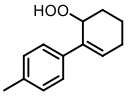
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2945 (m), 1692 (w), 1640 (w), 1443 (m), 1334 (m), 1297 (w), 1241 (w), 1185 (m), 1102 (w), 1070 (m), 749 (s), 719 (s), 880 (s)

HR-MS (ESI): $[MH]^+$ = 223.0960; calculated: 223.0965

2-Hydroperoxy-4'-methyl-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min 15 s
eluent:	PE / EA = 9 / 1	solvent:	MeCN
quantity	5.0 mmol		



$C_{13}H_{16}O_2$, 204.27 g/mol

Yield: 35 %

Condition: pale yellow liquid

TLC: R_f (PE/EA = 6.5/1) = 0.48

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.93 (s, 1H), 7.42 – 7.30 (m, 2H), 7.19 – 7.07 (m, 2H), 6.31 (dd, *J* = 4.8, 3.1 Hz, 1H), 5.01 – 4.87 (m, 1H), 2.50 – 2.38 (m, 1H), 2.34 (s, 3H), 2.30 – 2.15 (m, 1H), 1.90 – 1.73 (m, 2H), 1.72 – 1.63 (m, 2H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 137.7, 136.9, 133.7, 132.4, 129.2, 125.8, 79.4, 26.4, 26.2, 21.2, 16.9.

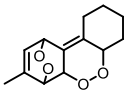
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3399 (b), 2933 (m), 2863 (w), 1707 (w), 1640 (w), 1513 (m), 1439 (m), 1353 (m), 1260 (w), 1185 (w), 1156 (w), 1111 (w), 1066 (m), 1036 (w), 958 (m), 880 (w), 805 (s), 749 (m), 719 (w)

HR-MS (ESI): $[MH]^+$ = 205.1226; calculated: 205.1223

3-Methyl-1,4,4a,6a,7,8,9,10-octahydro-1,4-epidioxydibenzo[*c,e*][1,2]dioxine

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min 15 s
eluent:	PE / EA = 9 / 1	solvent:	MeCN
quantity	5.0 mmol		



$C_{13}H_{16}O_4$, 236.27 g/mol

Yield: 19 %

Condition: colourless crystalline solid

TLC: R_f (PE/EA = 6.5/1) = 0.36

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.36 – 6.31 (m, 1H), 5.23 (dd, *J* = 6.0, 1.2 Hz, 1H), 4.67 – 4.62 (m, 1H), 4.59 – 4.55 (m, 1H), 4.28 (dd, *J* = 11.1, 5.3 Hz, 1H), 2.88 – 2.70 (m, 1H), 2.18 – 2.08 (m, 1H), 2.02 (d, *J* = 1.8 Hz, 3H), 1.96 – 1.72 (m, 4H), 1.55 – 1.39 (m, 2H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 140.1, 136.7, 125.0, 119.9, 81.2, 79.1, 78.0, 69.4, 34.2, 28.9, 27.2, 24.8, 18.9.

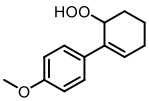
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2937 (m), 2855 (m), 1700 (w), 1651 (w), 1439 (s), 1346 (m), 1252 (m), 1208 (m), 1126 (m), 1070 (m), 1040 (m), 980 (m), 939 (m), 895 (s), 861 (s), 813 (m), 719 (s), 682 (s)

HR-MS (ESI): $[MH]^+$ = 237.1123; calculated: 237.1121

2-Hydroperoxy-4'-methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min 15 s
eluent:	PE / EA = 8 / 1 --> 5 / 1	solvent:	MeCN
quantity	2.5 mmol		



$C_{13}H_{16}O_3$, 220.27 g/mol

Yield: 42 %

Condition: pale yellow liquid

TLC: R_f (PE/EA = 6.5/1) = 0.24

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 8.04 – 7.91 (m, 1H), 7.44 – 7.32 (m, 2H), 6.93 – 6.79 (m, 2H), 6.26 (dd, *J* = 4.9, 3.2 Hz, 1H), 4.99 – 4.86 (m, 1H), 3.80 (s, 3H), 2.52 – 2.37 (m, 1H), 2.30 – 2.14 (m, 1H), 1.89 – 1.72 (m, 2H), 1.72 – 1.60 (m, 2H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 158.9, 133.2, 131.7, 127.0, 113.9, 79.5, 60.6, 55.4, 26.4, 26.2, 16.9.

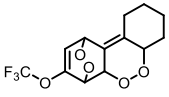
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3410 (m), 2926 (m), 2866 (m), 1640 (w), 1603 (m), 1510 (s), 1446 (m), 1357 (m), 1282 (s), 1241 (s), 1185 (s), 1092 (m), 1066 (m), 1021 (s), 962 (s), 883 (m), 850 (m), 805 (s)

HR-MS (ESI): $[MH]^+$ = 221.1170; calculated: 221.1172

3-(Trifluoromethoxy)-1,4,4a,6a,7,8,9,10-octahydro-1,4-epidioxydibenzo[c,e]-[1,2]dioxine

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min
eluent:	PE / EA = 8 / 1 --> 5 / 1	solvent:	MeCN
quantity	2.5 mmol		



$C_{13}H_{13}F_3O_5$, 306.24 g/mol

Yield: 15 % (20 % of starting material recovered)

Condition: pale yellow liquid

TLC: R_f (PE/EA = 6.5/1) = 0.44

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.15 (dp, *J* = 6.6, 2.2 Hz, 1H), 5.49 (d, *J* = 6.7 Hz, 1H), 4.87 (dt, *J* = 2.2, 0.9 Hz, 1H), 4.78 (dt, *J* = 2.5, 1.3 Hz, 1H), 4.37 –

4.21 (m, 1H), 2.77 (dq, *J* = 13.2, 2.2 Hz, 1H), 2.21 – 2.09 (m, 1H), 2.04 – 1.80 (m, 4H), 1.63 – 1.41 (m, 2H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 138.2, 118.3, 110.5, 81.1, 78.0, 75.9, 70.1, 34.1, 29.0, 27.1, 24.7.

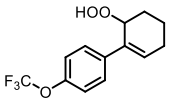
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2941 (m), 2863 (w), 1651 (m), 1510 (w), 1446 (w), 1256 ((s), 1204 (s), 1163 (s), 1040 (m), 980 (m), 921 (m), 876 (m), 846 (m), 805 (m), 697 (m)

HR-MS (ESI): $[MH]^+$ = 307.0793; calculated: 307.0788

2-Hydroperoxy-4'-(trifluoromethoxy)-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min
eluent:	PE / EA = 8 / 1 --> 5 / 1	solvent:	MeCN
quantity	2.5 mmol		



$C_{13}H_{13}F_3O_3$, 274.24 g/mol

Yield: 19 % (20 % of starting material recovered)

Condition: pale yellow liquid

TLC: R_f (PE/EA = 4/1) = 0.37

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.89 (s, 1H), 7.54 – 7.37 (m, 2H), 7.26 – 7.09 (m, 2H), 6.35 (dd, *J* = 4.9, 3.1 Hz, 1H), 4.92 (t, *J* = 3.3 Hz, 1H), 2.55 – 2.38 (m, 1H), 2.31 (dtd, *J* = 19.2, 5.2, 3.0 Hz, 1H), 2.24 – 2.06 (m, 1H), 1.94 – 1.73 (m, 1H), 1.73 – 1.59 (m, 2H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 148.4, 139.3, 134.1, 132.7, 128.0, 127.2, 121.0, 79.3, 26.3, 26.3, 16.7.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3384 (b), 2937 (w), 1510 (m), 1356 (w), 1252 (s), 1208 (s), 1156 (s), 1018 (m), 962 (m), 920 (m), 850 (m), 805 (s), 764 (w), 731 (w), 678 (m),

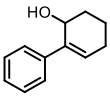
HR-MS (ESI): $[MH]^+$ = 275.0894; calculated: 275.0890

2,3,4,5-Tetrahydro-[1,1'-biphenyl]-2-ol

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min 15 s
quantity	7.5 mmol	solvent:	MeCN

After the oxidation PPh_3 (7.5 mmol, 1.97 g, 1.0 equiv.) was added and the mixture was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using a mixture of petroleum ether and ethylacetate (PE / EA = 8 / 1) as an eluent.



$C_{12}H_{14}O$, 174.24 g/mol

Yield: 41 %

Condition: colourless liquid

TLC: R_f (PE/EA = 6.5/1) = 0.33

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.55 – 7.41 (m, 2H), 7.41 – 7.30 (m, 2H), 7.30 – 7.19 (m, 1H), 6.17 (dd, *J* = 4.6, 3.4 Hz, 1H), 4.79 – 4.65 (m, 1H), 2.41 – 2.08 (m, 2H), 2.08 – 1.57 (m, 4H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 140.3, 139.1, 128.8, 128.6, 127.2, 126.1, 65.6, 31.7, 26.2, 17.4.

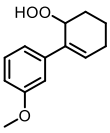
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3347 (b), 3056 (w), 3027 (w), 2933 (m), 2863 (m), 2829 (w), 1599 (w), 1495 (m), 1439 (m), 1349 (w), 1264 (w), 1237 (m), 1159 (m), 1059 (m), 969 (s), 917 (m), 876 (w), 842 (w), 816 (w), 753 (s), 693 (s)

HR-MS: (EI, 70 eV): $[M]^+$ = 174.10406; 156; 146; 141; 129; 115; 102; 96; 91; 83; 77; 63; 51; 39; 27, calculated: 174.10392

2-Hydroperoxy-3'-methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min
eluent:	PE / EA (0 % --> 15 % EA)	solvent:	MeCN
quantity	2.5 mmol		



$C_{13}H_{16}O_3$, 220.27 g/mol

Yield: 44 % (20 % of starting material recovered)

Condition: red oil

TLC: R_f (PE/EA = 6.5/1) = 0.34

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.25 (t, *J* = 7.9 Hz, 1H), 7.07 – 6.96 (m, 2H), 6.81 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 6.35 (dd, *J* = 4.9, 3.1 Hz, 1H), 4.94 (q, *J* = 2.7, 2.1 Hz, 1H), 3.82 (s, 3H), 2.50 – 2.37 (m, 1H), 2.36 – 2.07 (m, 2H), 1.91 – 1.74 (m, 1H), 1.74 – 1.59 (m, 2H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 159.8, 142.2, 133.8, 133.6, 129.5, 118.5, 112.5, 111.9, 79.5, 55.4, 26.4, 26.3, 16.8.

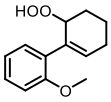
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3388 (b), 2937 (m), 2866 (w), 2833 (w), 1722 (w), 1640 (w), 1580 (m), 1487 (m), 1431 (m), 1353 (m), 1316 (m), 1282 (s), 1204 (s), 1170 (m), 1092 (w), 1044 (m), 865 (m), 813 (m), 775 (s), 742 (m)

HR-MS (ESI): $[MH]^+$ = 221.1175; calculated: 221.1172

2-Hydroperoxy-2'-methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min
eluent:	PE / EA (0 % --> 15 % EA)	solvent:	MeCN
quantity	2.5 mmol		



$C_{13}H_{16}O_3$, 220.27 g/mol

Yield: 49 % (13 % of starting material recovered)

Condition: colourless crystalline solid

TLC: R_f (PE/EA = 6.5/1) = 0.32

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.97 (s, 1H), 7.31 – 7.20 (m, 1H), 7.13 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.02 – 6.84 (m, 2H), 6.00 (ddd, *J* = 4.3, 3.3, 1.0 Hz, 1H), 5.02 – 4.84 (m, 1H), 3.83 (s, 3H), 2.37 – 2.09 (m, 3H), 1.94 – 1.80 (m, 2H), 1.75 – 1.59 (m, 1H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 156.8, 134.8, 134.4, 130.6, 128.6, 121.0, 110.9, 80.5, 60.6, 55.7, 26.9, 25.9, 18.4.

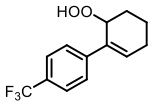
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3377 (s), 2930 (m), 2837 (m), 1595 (m), 1487 (s), 1435 (s), 1402 (s), 1293 (m), 1238 (s), 1182 (s), 1118 (s), 1070 (s), 1010 (s), 962 (s), 854 (m), 794 (s), 757 (s)

HR-MS (ESI): $[MH]^+$ = 221.1173; calculated: 221.1172

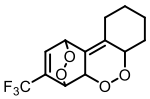
2-Hydroperoxy-4'-(trifluoromethyl)-2,3,4,5-tetrahydro-1,1'-biphenyl and 3-(trifluoromethyl)-1,4,4a,6a,7,8,9,10-octahydro-1,4-epidioxydibenzo[*c*,*e*][1,2]diox-ine

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min
eluent:	PE / EA (0 % --> 15 % EA)	solvent:	MeCN
quantity	2.5 mmol		



A



B

Yield: 56 % (17 % of starting material recovered)
mixture of A andB (ratio: 1/0.5)

Condition: colourless crystalline solid

TLC: R_f (PE/EA = 6.5/1) = 0.40

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.99 (s, 1H), 7.57 – 7.55 (m, 4H, A), 7.17 (dp, *J* = 6.1, 2.1 Hz, 0.5H, B), 6.44 (dd, *J* = 4.9, 3.1 Hz, 1H, A), 5.51 – 5.38 (m, 0.5H, B), 5.07 (q, *J* = 1.5 Hz, 0.5H, B), 4.95 (dtd, *J* = 3.2, 2.1, 1.3 Hz, 1H, A), 4.60 (dt, *J* = 2.6, 1.4 Hz, 0.5H, B), 4.37 – 4.26 (m, 0.5H, B), 2.85 – 2.70 (m, 0.5H, B), 2.53 – 2.09 (m, 4H, A+B), 1.98 – 1.45 (m, 6H, A+B).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 144.1, 140.3, 135.3, 133.0, 126.8, 126.2, 125.5, 125.4, 81.3, 79.0, 77.9, 68.7, 60.6, 41.0, 34.2, 29.1, 27.2, 26.3, 26.3, 24.7, 23.9, 21.2, 17.6, 17.4, 16.7, 14.8, 14.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3388 (b), 2941 (w), 1617 (w), 1443 (w), 1413 (w), 1323 (s), 1163 (s), 1111 (s), 1066 (s), 1018 (m), 954 (m), 921 (m), 835 (m), 753 (w)

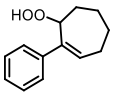
HR-MS (ESI): (A): $[MH]^+$ = 259.0942; calculated: 259.0940

HR-MS (ESI): (B): $[MH]^+$ = 291.0842; calculated: 291.0839

7-Hydroperoxy-1-phenylcyclohept-1-ene

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min
eluent:	PE / EA (0 % --> 10 % EA)	solvent:	MeCN
quantity	2.5 mmol		



$C_{13}H_{16}O_2$, 204.27 g/mol

Yield: 65 %

Condition: colourless liquid

TLC: R_f (PE/EA = 9/1) = 0.40

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.99 – 7.81 (m, 1H), 7.47 – 7.17 (m, 5H), 6.19 (dd, *J* = 7.8, 5.7 Hz, 1H), 5.06 (dd, *J* = 7.0, 1.4 Hz, 1H), 2.49 (dddd, *J* = 16.0, 10.4, 5.7, 2.3 Hz, 1H), 2.33 – 2.16 (m, 2H), 2.10 – 1.94 (m, 1H), 1.89 – 1.67 (m, 3H), 1.64 – 1.44 (m, 1H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 143.0, 142.2, 135.3, 128.3, 126.9, 126.6, 86.2, 29.6, 27.9, 26.9, 25.4, 23.9.

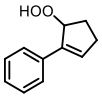
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3384 (b), 2930 (m), 2855 (w), 2599 (w), 1491 (w), 1446 (m), 1364 (w), 1264 (w), 1174 (w), 1118 (w), 1074 (m), 1033 (w), 988 (m), 932 (w), 891 (m), 842 (m), 757 (s), 697 (s)

HR-MS (ESI): $[MH]^+$ = 205.1223; calculated: 205.1223

(5-Hydroperoxycyclopent-1-en-1-yl)benzene

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min
eluent:	PE / EA (0 % --> 15 % EA)	solvent:	MeCN
quantity	2.5 mmol		



$C_{11}H_{12}O_2$, 176.22 g/mol

Yield: 43 %

Condition: colourless liquid

TLC: R_f (PE/EA = 6.5/1) = 0.40

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.71 – 7.59 (m, 1H), 7.59 – 7.48 (m, 2H), 7.40 – 7.19 (m, 3H), 6.59 – 6.47 (m, 1H), 5.53 (dt, *J* = 7.0, 2.4 Hz, 1H), 2.79 – 2.59 (m, 1H), 2.56 – 2.24 (m, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 139.3, 134.8, 134.6, 128.7, 127.6, 126.1, 90.8, 31.3, 29.2.

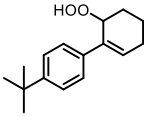
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3366 (b), 3056 (w), 2930 (w), 2848 (w), 1722 (w), 1625 (w), 1599 (w), 1495 (m), 1446 (m), 1379 (w), 1327 (m), 1249 (w), 1185 (w), 1156 (w), 1036 (m), 980 (m), 939 (m), 828 (m), 753 (s), 693 (s)

HR-MS (ESI): $[MH]^+$ = 177:0910; calculated: 177:0910

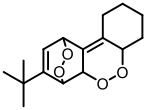
4'-(*tert*-Butyl)-2-hydroperoxy-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min
eluent:	PE / EA (0 % --> 10 % EA)	solvent:	MeCN
quantity	2.5 mmol		



A



B

$C_{16}H_{22}O_2$, 246.35 g/mol (A)
$C_{16}H_{22}O_4$, 278.35 g/mol (B)

Yield: 71 % mixture of A andB (ratio: 1.6/1)

Condition: pale yellow solid

TLC: R_f (PE/EA = 6.5/1) = 0.50

^{1}H NMR: (300 MHz, CDCl3) δ = 7.41 – 7.30 (m, 4H, A), 6.33 (dd, *J* = 4.9, 3.2 Hz, 1H, A), 6.28 (dd, *J* = 6.1, 1.9 Hz, 1H, B), 5.28 – 5.22 (m, 1H, B), 4.98 (d, *J* = 3.5 Hz, 1H, A), 4.95 – 4.91 (m, 1H, B), 4.51 (dt, *J* = 2.5, 1.3 Hz, 1H, B), 4.34 – 4.23 (m, 1H, B), 2.84 – 2.70 (m, 1H, B), 2.49 – 2.38 (m, 1H, A), 2.33 – 1.43 (m, 12H, A+B), 1.32 (s, 9H, A), 1.15 (s, 9H, B).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 152.2, 150.1, 137.6, 136.5, 133.5, 132.5, 126.1, 125.5, 120.5, 120.1, 81.2, 79.3, 78.9, 75.8, 69.5, 53.6, 34.6, 34.3, 34.2, 31.5, 28.9, 28.1, 27.8, 27.1, 26.5, 26.3, 24.8, 24.0, 16.9.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3388 (w), 2960 (m), 2870 (m), 1722 (w), 1513 (w), 1461 (w), 1364 (m), 1267 (m), 1200 (w), 1111 (w), 1066 (w), 962 (m), 921 (w), 831 (m), 705 (m)

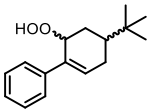
HR-MS (ESI): (A) $[MH]^+$ = 247.1698; calculated: 247.1693

HR-MS (ESI): (B) $[MH\text{-}H_2O]^+$ = 261.1488; calculated: 261.1485

4-(*tert*-Butyl)-2-hydroperoxy-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min
eluent:	PE / EA (0 % --> 10 % EA)	solvent:	MeCN
quantity	2.5 mmol		



$C_{16}H_{22}O_2$, 246.35 g/mol

Yield: 41 % (mixture of two diastereo isomers)

Condition: pale yellow liquid

TLC: R_f (PE/EA = 6.5/1) = 0.58

^{1}H NMR: (300 MHz, $CDCl_3$) δ = δ 7.58 – 7.21 (m, 13.5H, A+B), 6.40 (dd, *J* = 5.5, 2.7 Hz, 1H, A), 6.14 (dt, *J* = 5.9, 2.1 Hz, 1.7H, B), 5.20 – 5.11 (m, 1.7H, B), 5.07 – 5.01 (m, 1H, A), 2.59 – 2.49 (m, 1H, A), 2.41 – 2.19 (m, 5H, A+B), 2.08 – 1.88 (m, 4H, A+B), 1.81 – 1.65 (m, 4H, A+B), 1.61 – 1.47 (m, 4H, A+B), 0.95 (s, 9H, A), 0.94 (s, 15H, B).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 131.7, 128.6, 128.5, 127.2, 126.5, 125.8, 82.7,43.2,37.2, 32.5,29.3, 27.7, 27.5, 27.4, 27.2. (major isomere)

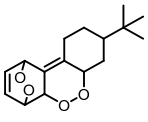
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3407 (b), 2960 (m), 2870 (w), 1648 (w), 1599 (w), 1472 (w), 1394 (w), 1364 (m), 1327 (w), 1238 (w), 1159 (w), 1096 (w), 1066 (w), 1029 (w), 988 (w), 921 (w), 824 (w), 760 (m), 697 (s)

HR-MS (ESI): $[MH]^+$ = 247.1697; calculated: 247.1693

8-(*tert*-Butyl)-1,4,4a,6a,7,8,9,10-octahydro-1,4-epidioxydibenzo[*c*,*e*][1,2]di-oxine

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min
eluent:	PE / EA (0 % --> 10 % EA)	solvent:	MeCN
quantity	2.5 mmol		



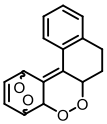
$C_{16}H_{22}O_4$, 278.35 g/mol

Yield: 18 %
Condition: pale yellow solid
TLC: R_f (PE/EA = 6.5/1) = 0.33
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 6.80 – 6.63 (m, 2H), 5.31 – 5.26 (m, 1H), 4.89 – 4.85 (m, 1H), 4.59 – 4.54 (m, 1H), 4.30 (ddd, *J* = 11.4, 5.1, 1.2 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.26 – 2.15 (m, 1H), 1.95 – 1.83 (m, 2H), 1.58 – 1.48 (m, 1H), 1.35 – 1.27 (m, 2H), 0.90 (s, 9H).
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 137.6, 132.4, 129.9, 118.4, 81.4, 78.1, 74.7, 69.0, 46.9, 35.7, 32.6, 28.2, 28.1, 27.8, 27.3.
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2952 (m), 2889 (m), 1696 (w), 1476 (w), 1364 (m), 1334 (w), 1238 (m), 1111 (w), 1070 (m), 992 (m), 965 (m), 880 (s), 746 (m), 719 (s), 686 (m)
HR-MS (ESI): $[MH]^+$ = 279.1596; calculated: 279.1591

1,4,4a,6a,7,8-Hexahydro-1,4-epidioxybenzo[*c*]naphtho[1,2-*e*][1,2]dioxine

Product was synthesized according to GP-5.1, using the following concentrations, retention time, solvent and eluents:

c(substrat/sensitizer):	0.25 M / 1 mM	retention time:	7 min
eluent:	PE / EA (0 % --> 15 % EA)	solvent:	MeCN
quantity	2.5 mmol		



$C_{16}H_{14}O_4$, 270.28 g/mol
Yield: 20 % (two diastereo isomers)
Condition: pale yellow oil
TLC: R_f (PE/EA = 6.5/1) = 0.30 (A)
R_f (PE/EA = 6.5/1) = 0.24 (B)
^{1}H NMR: (A) (300 MHz, $CDCl_3$) δ = 7.49 – 7.21 (m, 4H), 6.90 (ddd, *J* = 8.0, 6.2, 1.6 Hz, 1H), 6.72 (ddd, *J* = 8.3, 6.0, 1.4 Hz, 1H), 5.49 (dt, *J* = 6.2, 1.5 Hz, 1H), 4.99 (dd, *J* = 4.0, 1.9 Hz, 1H), 4.74 (dt, *J* = 6.0, 1.6 Hz, 1H), 2.67 – 2.51 (m, 1H), 2.36 – 2.17 (m, 2H), 2.01 – 1.87 (m, 1H), 1.62 – 1.49 (m, 1H).
^{1}H NMR: (B) (300 MHz, $CDCl_3$) δ = 7.40 – 7.01 (m, 4H), 6.95 – 6.52 (m, 2H), 5.68 (dt, *J* = 5.9, 1.6 Hz, 1H), 4.96 (dq, *J* = 6.5, 1.4 Hz, 1H), 4.74 – 4.69 (m, 1H), 4.64 (ddd, *J* = 11.6, 4.5, 1.2 Hz, 1H), 3.23 – 2.90 (m, 2H), 2.56 (dtd, *J* = 12.4, 11.2, 7.6 Hz, 1H), 2.44 – 2.29 (m, 1H).

^{13}C NMR: (A) (75 MHz, $CDCl_3$) δ = 136.2, 134.6, 133.2, 133.0, 132.1, 129.2, 128.6, 127.4, 77.4, 74.6, 74.3, 70.1, 25.4, 24.2.

^{13}C NMR: (B) (75 MHz, $CDCl_3$) δ = δ 131.9, 130.5, 129.5, 128.8, 127.8, 126.1, 78.7, 76.7, 74.2, 70.6, 30.4, 28.1.

FT-IR (ATR): (A) ṽ [cm^{-1}] = 2937 (w), 2870 (w), 1659 (w), 1625 (w), 1491 (m), 1446 (m), 1353 (m), 1245 (m), 1156 (m), 1088 (m), 917 (s), 883 (s), 783 (m), 738 (s)

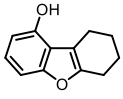
FT-IR (ATR): (B) ṽ [cm^{-1}] = 2944 (m), 2889 (m), 1696 (w), 1655 (w), 1625 (w), 1480 (w), 1450 (m), 1364 (m), 1334 (m), 1238 (m), 1152 (w), 1111 (w), 1070 (m), 1036 (m), 965 (m), 924 (m), 880 (s), 760 (m), 719 (s)

HR-MS (ESI): (A) $[MH]^+$ = 271.0968; calculated: 271.0965 (F2)

HR-MS (ESI): (B) $[MH]^+$ = 271.0966; calculated: 271.0965 (F3)

6,7,8,9-Tetrahydrodibenzo[*b*,*d*]furan-1-ol

1,4,4a,6a,7,8,9,10-octahydro-1,4-epidioxydibenzo[*c*,*e*][1,2]dioxine (100 mg, 0.45 mmol, 1.0 equiv.) was dissolved in methanol (5 mL) and thiourea (86 mg, 1.13 mmol, 2.5 equiv.) was added at RT. The reaction mixture was stirred for 4 h at RT (reaction controlled by TLC). The solvent was removed under reduced pressure and the crude product was purified by column chromatography using a mixture of petroleum ether and ethyl acetate (14 % → 20 % EA) as an eluent.



$C_{12}H_{12}O_2$, 188.23 g/mol

Yield: 28 %

Condition: colourless solid

TLC: R_f (PE/EA = 4/1) = 0.55

^{1}H NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.03 – 6.98 (m, 2H), 6.57 – 6.50 (m, 1H), 2.88 – 2.82 (m, 2H), 2.75 – 2.69 (m, 2H), 1.96 – 1.88 (m, 2H), 1.88 – 1.79 (m, 2H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 156.1, 152.6, 149.6, 123.6, 117.4, 111.7, 107.9, 104.3, 23.5, 23.0, 22.8, 22.1.

FT-IR (ATR): ṽ [cm^{-1}] = 3429 (b), 2933 (m), 2851 (m), 1640 (w), 1599 (m), 1495 (m), 1443 (s), 1402 (w), 1361 (m), 1282 (m), 1204 (m), 1122 (m), 1077 (w), 1029 (s), 954 (w), 872 (w), 824 (w), 775 (m), 731 (s), 708 (w)

LR-MS: (EI, 70 eV): 188 $[M]^+$, 160, 131, 115

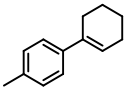
Synthesis of starting materials[14]

Unless otherwise noted, Phenylcyclohexenes, -cycloheptenes and cyclopentenes were synthesized by Grignard reaction of a cyclic ketone and the appropriate Grignard reagent followed by an elimination reaction (GP-5.2):

Mg (607 mg, 25 mmol, 1.25 equiv.) was suspended in dry THF (20 mL) under inert conditions. The bromoarene (22 mmol, 1.1 equiv.) was added at room temperature. After boiling subsided, the reaction mixture was stirred for an additional hour at room temperature. The reaction mixture was cooled to 0 °C, the cyclic ketone (20 mmol, 1.0 equiv.), dissolved in dry THF (15 mL), was added at 0 °C and the reaction mixture was stirred at 95 °C for 1 h.
The reaction mixture was cooled to 0 °C and 1 M aqueous HCl (10 mL) was added dropwise. The mixture was stirred for 30 min at room temperature and extracted with EA (50 mL). The phases were separated and the organic phase was washed with brine (50 mL). The organic phase was dried over Na_2SO_4, the drying agent was filtered off, the solvent was removed under reduced pressure.
The crude product was dissolved in toluene (100 mL) and a catalytic amount of *p*-TsOH was added. The reaction mixture was stirred over night at 140 °C using a *Dean-Stark* apparatus.
The solvent was removed under reduced pressure and the crude product was purified by column chromatography using mixtures of petroleum ether and ethyl acetate.
The exact eluents and yields as well as differing quantities are described for each compound.

4'-Methyl-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.2. Pure PE was used as an eluent for column chromatography.



$C_{13}H_{16}$, 172.27 g/mol

Yield: 94 %

Condition: colourless liquid

TLC: R_f (PE) = 0.57

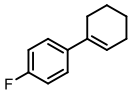
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.38 – 7.19 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.11 (tt, *J* = 3.9, 1.7 Hz, 1H), 2.48 – 2.38 (m, 2H), 2.36 (s, 3H), 2.29 – 2.15 (m, 2H), 1.88 – 1.73 (m, 2H), 1.73 – 1.59 (m, 2H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 140.0, 136.5, 136.2, 129.0, 124.9, 124.0, 27.5, 26.0, 23.2, 22.3, 21.2.

LR-MS: (EI, 70 eV): 172 $[M]^+$, 158, 142, 127, 105, 79, 51

4'-fluoro-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.2. Reaction was performed using 30 mmol of starting material. A mixture of PE and EA (0 --> 2 % EA) was used as an eluent for column chromatography.



$C_{13}H_{13}F$, 176.23 g/mol

Yield: 53 %

Condition: colourless liquid

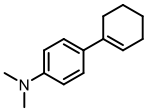
TLC: R_f (PE) = 0.72

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.37 – 7.30 (m, 2H), 7.05 – 6.92 (m, 2H), 6.06 (tt, *J* = 3.9, 1.7 Hz, 1H), 2.43 – 2.26 (m, 2H), 2.27 – 2.13 (m, 2H), 1.85 – 1.71 (m, 2H), 1.72 – 1.59 (m, 2H).

LR-MS: (EI, 70 eV): 176 $[M]^+$, 155, 133, 109, 101, 75, 51

***N*,*N*-Dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-amine**

Product was synthesized according to GP-5.2. Reaction was performed using 10 mmol of starting material. A mixture of PE and EA (0 --> 2 % EA) was used as an eluent for column chromatography.



$C_{14}H_{19}N$, 201.31 g/mol

Yield: 82 %

Condition: colourless liquid

TLC: R_f (PE) = 0.82

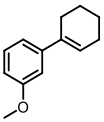
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.41 – 7.19 (m, 2H), 6.76 (ddd, *J* = 13.1, 6.8, 2.8 Hz, 2H), 6.06 – 6.00 (m, 1H), 2.96 (d, *J* = 2.8 Hz, 6H), 2.35 – 2.49 (m, 2H), 2.27 – 2.14 (m, 2H), 1.87 – 1.73 (m, 2H), 1.61 – 1.72 (m, 2H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 149.4, 136.0, 129.1, 125.6, 121.7, 116.7, 112.7, 112.6, 40.8, 40.7, 27.4, 25.9, 23.2, 22.4.

LR-MS: (EI, 70 eV): 202 $[M]^+$, 180, 157, 129, 101, 77, 51

3'-Methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.2. Reaction was performed using 10 mmol of starting material. A mixture of PE and EA (0 --> 5 % EA) was used as an eluent for column chromatography.



$C_{13}H_{16}O$, 188.27 g/mol

Yield: 91 %

Condition: colourless liquid

TLC: R_f (PE/EA = 15/1) = 0.26

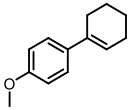
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.23 (pt, *J* = 7.9 Hz, 1H), 6.99 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 6.96 – 6.86 (m, *J* = 2.5, 1.7 Hz, 1H), 6.78 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 6.14 (tt, *J* = 3.9, 1.7 Hz, 1H), 3.84 – 3.80 (s, 3H), 2.45 – 2.36 (m, *J* = 6.3, 2.5, 2.1 Hz, 2H), 2.26 – 2.16 (m, 2H), 1.84 – 1.72 (m, *J* = 6.9, 4.8, 2.5 Hz, 2H), 1.72 – 1.60 (m, 2H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 159.6, 144.3, 136.5, 129.1, 125.1, 117.6, 111.8, 110.9, 55.2, 27.5, 25.9, 23.1, 22.2.

LR-MS: (EI, 70 eV): 188 $[M]^+$, 160, 128, 91, 65

4'-Methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.2. Reaction was performed using 10 mmol of starting material. A mixture of PE and EA (0 --> 20 % EA) was used as an eluent for column chromatography.



$C_{13}H_{16}O$, 188.27 g/mol

Yield: 81 %

Condition: colourless liquid

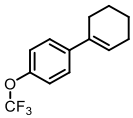
TLC: R_f (PE/EA = 15/1) = 0.98

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.35 – 7.25 (m, 2H), 6.88 – 6.82 (m, 2H), 6.08 – 5.96 (m, 1H), 3.81 (d, *J* = 3.8 Hz, 3H), 2.38 (m, 1H), 2.25 – 2.14 (m, 1H), 1.85 – 1.73 (m, 1H), 1.71 – 1.58 (m, 1H).

LR-MS: (EI, 70 eV): 188 $[M]^+$, 160, 129, 103, 80, 51

4'-(Trifluoromethoxy)-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.2. Reaction was performed using 10 mmol of starting material. A mixture of PE and EA (0 --> 20 % EA) was used as an eluent for column chromatography.



$C_{13}H_{13}F_3O$, 242.24 g/mol

Yield: 70 %

Condition: colourless liquid

TLC: R_f (PE/EA = 15/1) = 0.80

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.43 – 7.33 (m, 2H), 7.14 (ddt, *J* = 7.7, 2.1, 1.0 Hz, 2H), 6.11 (td, *J* = 4.0, 1.9 Hz, 1H), 2.43 – 2.33 (m, 2H), 2.27 – 2.15 (m, 2H), 1.84 – 1.73 (m, 2H), 1.73 – 1.61 (m, 2H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 141.4, 135.5, 126.2, 125.7, 120.7, 27.4, 25.9, 23.0, 22.0.

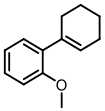
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2930 (w), 2863 (w), 2840 (w), 1510 (m), 1439 (w), 1256 (s), 1208 (s), 1156 (s), 1003 (m), 921 (m), 861 (m), 831 (m), 798 (s), 746 (w), 678 (w)

HR-MS: (EI, 70 eV): $[M]^+$ = 242.09082; calculated: 242.09130

LR-MS: (EI, 70 eV): 243 $[M]^+$, 214, 175, 141, 117, 80, 51

2'-Methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.2. Reaction was performed using 10 mmol of starting material. A mixture of PE and EA (0 --> 5 % EA) was used as an eluent for column chromatography.



$C_{13}H_{16}O$, 188.27 g/mol

Yield: 83 %

Condition: colourless liquid

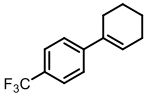
TLC: R_f (PE/EA = 15/1) = 0.90

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.33 – 7.14 (m, 2H), 7.03 – 6.88 (m, 2H), 5.85 (tt, *J* = 3.8, 1.7 Hz, 1H), 3.87 (s, 3H), 2.46 (tt, *J* = 6.2, 2.2 Hz, 2H), 2.34 – 2.21 (m, 2H), 1.90 – 1.66 (m, 4H).

LR-MS: (EI, 70 eV): 188 $[M]^+$, 160, 129, 103, 80, 51

4'-(Trifluoromethyl)-2,3,4,5-tetrahydro-1,1'-biphenyl

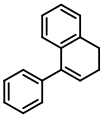
Product was synthesized according to GP-5.2. Reaction was performed using 10 mmol of starting material. A mixture of PE and EA (0 --> 20 % EA) was used as an eluent for column chromatography.



	$C_{13}H_{13}F_3$, 226.24 g/mol
Yield	78 %
Condition	colourless liquid
TLC:	R_f (PE/EA = 15/1) = 0.94
^{1}H NMR	(300 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 8.3 Hz, 2H), 7.53 – 7.43 (m, 2H), 6.24 (tt, *J* = 4.0, 1.7 Hz, 1H), 2.50 – 2.37 (m, 2H), 2.31 – 2.19 (m, 2H), 1.90 – 1.76 (m, 2H), 1.76 – 1.64 (m, 2H).
LR-MS	(EI, 70 eV): 227 $[M]^+$, 211, 185, 159, 130, 109, 80, 51

4-Phenyl-1,2-dihydronaphthalene

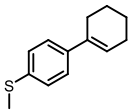
Product was synthesized according to GP-5.2. Pure PE was used as an eluent for column chromatography.



	$C_{16}H_{14}$, 206.29 g/mol
Yield:	51 %
Condition:	colourless liquid
TLC:	R_f (PE) = 0.41
^{1}H NMR:	(300 MHz, $CDCl_3$) δ = 7.43 – 7.27 (m, 5H), 7.24 – 7.05 (m, 3H), 7.01 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.09 (t, *J* = 4.7 Hz, 1H), 2.86 (t, *J* = 7.9 Hz, 2H), 2.42 (ddd, *J* = 9.1, 7.2, 4.7 Hz, 2H).
^{13}C NMR:	(75 MHz, $CDCl_3$) δ = 128.9, 128.3, 127.8, 127.7, 127.2, 126.3, 125.6, 28.4, 23.7.
HR-MS:	(EI, 70 eV): $[M]^+$ = 206.1085, 191, 165, 152, 128, 115, 101, 91, 76, 51; calculated: 206.1090
LR-MS:	(EI, 70 eV): m/z 206 $[M]^+$, 178, 165, 152, 128, 102, 78, 51

Methyl(2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-yl)sulfane

Product was synthesized according to GP-5.2. Reaction was performed using 10 mmol of starting material. A mixture of PE and EA (0 --> 15 % EA) was used as an eluent for column chromatography.



$C_{13}H_{16}S$, 204.33 g/mol

Yield: 99 %

Condition: colourless liquid

TLC: R_f (PE/EA = 15/1) = 0.90

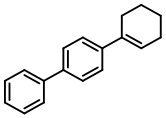
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.39 – 7.28 (m, 2H), 7.28 – 7.22 (m, 2H), 6.16 (tt, *J* = 4.2, 1.8 Hz, 1H), 2.51 (s, 3H), 2.47 – 2.38 (m, 2H), 2.30 – 2.21 (m, 2H), 1.88 – 1.77 (m, 2H), 1.77 – 1.65 (m, 2H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ = 139.7, 135.9, 128.9, 126.8, 126.7, 125.4, 125.1, 124.5, 27.3, 26.0, 23.1, 22.2, 16.2.

LR-MS: (EI, 70 eV): 205 $[M]^+$, 176, 153, 129, 102, 77, 51

2,3,4,5-Tetrahydro-1,1':4',1''-terphenyl

Product was synthesized according to GP-5.2. Reaction was performed using 10 mmol of starting material. A mixture of PE and EA (0 --> 15 % EA) was used as an eluent for column chromatography.



$C_{18}H_{18}$, 234.34 g/mol

Yield: 41 %

Condition: colourless liquid

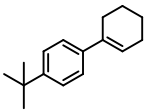
TLC: R_f (PE) = 0.51

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.65 – 7.48 (m, 5H), 7.48 – 7.39 (m, 4H), 6.22 – 6.16 (m, 1H), 2.51 – 2.40 (m, 2H), 2.30 – 2.16 (m, 1H), 1.88 – 1.74 (m, 2H), 1.74 – 1.62 (m, 2H).

LR-MS: (EI, 70 eV): 234 $[M]^+$, 205, 178

4'-(*tert*-Butyl)-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.2. Reaction was performed using 10 mmol of starting material. A mixture of PE and EA (0 --> 2 % EA) was used as an eluent for column chromatography.



$C_{16}H_{22}$, 214.35 g/mol

Yield: 82 %

Condition: colourless liquid

TLC: R_f (PE) = 0.95

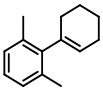
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.37 – 7.29 (m, 4H), 6.16 – 6.04 (m, 1H), 2.51 – 2.32 (m, 2H), 2.27 – 2.11 (m, 2H), 1.81 – 1.71 (m, 2H), 1.71 – 1.59 (m, 2H), 1.32 (s, 9H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 149.4, 139.8, 136.2, 128.1, 125.4, 125.3, 125.1, 124.6, 124.1, 34.4, 31.4, 27.4, 25.9, 23.1, 22.3.

LR-MS: (EI, 70 eV): 215 $[M]^+$, 198, 176, 141, 115, 91, 56

2',6'-Dimethyl-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.2. Reaction was performed using 10 mmol of starting material. A mixture of PE and EA (0 --> 2 % EA) was used as an eluent for column chromatography.



$C_{14}H_{18}$, 186.30 g/mol

Yield: 14 %

Condition: colourless liquid

TLC: R_f (PE) = 0.65

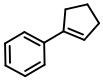
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.11 – 6.97 (m, 3H), 5.48 (tt, *J* = 3.7, 1.8 Hz, 1H), 2.29 – 2.23 (m, 6H), 2.23 – 2.13 (m, 2H), 2.13 – 2.02 (m, 2H), 1.86 – 1.66 (m, 4H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ = 143.9, 137.5, 135.5, 127.1, 126.2, 126.1, 125.3, 29.2, 25.4, 23.1, 22.3, 21.4, 19.7.

LR-MS: (EI, 70 eV): 187 $[M]^+$, 158, 129, 105, 77, 51

Cyclopent-1-en-1-ylbenzene

Product was synthesized according to a modified GP-ZV. Reaction was performed using 20 mmol of starting material. Grignard reaction was excecuted as usual. For the elimination, the crude product was dissolved in acetic acid (80 mL). The reaction mixture was stirred for 3 h at 118 °C. After cooling down to room temperature 1 M aqueous NaOH (100 mL) was added and the aqueous phase was extracted with EA (3 · 100 mL). The combined organic phases were washed with brine (75 mL). The organic phase was dried over Na_2SO_4, the drying agent was filtered off, the solvent was removed under reduced pressure. The crude product was purified by column chromatography using PE as an eluent



$C_{11}H_{12}$, 144.22 g/mol

Yield: 69 %

Condition: colourless liquid

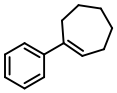
TLC: R_f (PE) = 0.66

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.48 – 7.42 (m, 2H), 7.36 – 7.27 (m, 2H), 7.25 – 7.18 (m, 1H), 6.19 (h, *J* = 2.1 Hz, 1H), 2.82 – 2.61 (m, 2H), 2.54 (tq, *J* = 7.6, 2.5 Hz, 2H), 2.15 – 1.93 (m, 2H).

LR-MS: (EI, 70 eV): 144 $[M]^+$, 129, 115, 103, 91, 77, 63, 51

1-Phenylcyclohept-1-ene

Product was synthesized according to GP-5.2. Reaction was performed using 20 mmol of starting material. PE was used as an eluent for column chromatography.



$C_{13}H_{16}$, 172.27 g/mol

Yield: 84 %

Condition: colourless liquid

TLC: R_f (PE) = 0.69

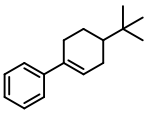
^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.42 – 7.16 (m, 5H), 6.13 (td, *J* = 6.8, 1.3 Hz, 1H), 2.75 – 2.52 (m, 2H), 2.43 – 2.25 (m, 2H), 1.94 – 1.80 (m, 2H), 1.74 – 1.50 (m, 4H).

HR-MS: (EI, 70 eV): $[M]^+$ = 172.1249, 157, 144, 129, 104, 91, 81, 65, 39; calculated: 172.1247

LR-MS: (EI, 70 eV): 172 $[M]^+$, 157, 144, 129, 115, 104, 91, 77, 63, 51

4-(*tert*-Butyl)-2,3,4,5-tetrahydro-1,1'-biphenyl

Product was synthesized according to GP-5.2. Reaction was performed using 20 mmol of starting material. PE was used as an eluent for column chromatography.



$C_{16}H_{22}$, 214.35 g/mol

Yield: 73 %

Condition: colourless liquid

TLC: R_f (PE) = 0.70

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.44 – 7.14 (m, 5H), 6.13 (ddd, *J* = 5.7, 2.7, 1.5 Hz, 1H), 2.56 – 2.33 (m, 2H), 2.33 – 2.16 (m, 1H), 2.06 – 1.86 (m, 2H), 1.43 – 1.23 (m, 2H), 0.92 (s, 9H).

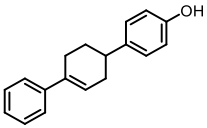
^{13}C NMR: (75 MHz, $CDCl_3$) δ = 142.4, 136.5, 128.3, 126.6, 125.1, 125.0, 43.9, 32.4, 29.0, 27.6, 27.4, 24.5.

FT-IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3027 (w), 2948 (m), 2870 (m), 1599 (w), 1495 (w), 1446 (w), 1364 (m), 1252 (w), 1170 (w), 1074 (w), 1021 (w), 980 (w), 910 (w), 839 (w), 779 (w), 749 (s), 693 (s)

HR-MS: (EI, 70 eV): $[M]^+$ = 214.17165, 195, 158, 143, 130, 115, 104, 91, 69, 57, 41, 29; calculated: 214.17160

1',2',3',6'-Tetrahydro-[1,1':4',1''-terphenyl]-4-ol

Product was synthesized according to GP-5.2. Reaction was performed using 20 mmol of starting material. A mixture of PE and EA (10 --> 25 % EA) was used as an eluent for column chromatography.



$C_{18}H_{18}O$, 250.34 g/mol

Yield: 52 %

Condition: colourless solid

TLC: R_f (PE/EA = 3/1) = 0.54

^{1}H NMR: (300 MHz, $CDCl_3$) δ = 7.45 – 7.39 (m, 2H), 7.37 – 7.29 (m, 2H), 7.27 – 7.20 (m, 1H), 7.19 – 7.11 (m, 2H), 6.83 – 6.76 (m, 2H), 6.20 (dd, *J* = 4.6, 2.4 Hz, 1H), 4.63 (s, 1H), 2.92 – 2.73 (m, 1H), 2.63 – 2.51 (m, 2H), 2.47

(ddt, *J* = 5.4, 3.5, 1.7 Hz, 1H), 2.37 – 2.20 (m, 1H), 2.15 – 2.02 (m, 1H), 1.96 – 1.76 (m, 1H).

^{13}C NMR: (75 MHz, $CDCl_3$) 139.3, 128.4, 128.1, 126.9, 125.1, 124.4, 115.3, 39.0, 34.4, 30.5, 28.1.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3392 (b), 3027 (m), 2922 (m), 2889 (m), 2833 (m), 1595 (m), 1510 (s), 1443 (m), 1375 (m), 1230 (s), 1144 (m), 1103 (m), 1014 (m), 969 (m), 913 (m), 820 (s), 734 (s), 686 (s)

HR-MS: (EI, 70 eV): $[M]^+$ = 250.1354, 129, 120, 107, 91, 77; calculated: 250.1352

LR-MS: (EI, 70 eV): 250 $[M]^+$, 133, 120, 107, 91, 77, 65, 51

5.5. References

[1] A. Greer, G. Vassilikogiannakis, K.-C. Lee, T. S. Koffas, K. Nahm, C. S. Foote, *J. Org. Chem.* **2000**, *65*, 6876–6878.

[2] C. S. Foote, S. Mazur, P. A. Burns, D. Lerdal, *J. Am. Chem. Soc.* **1973**, *95*, 586–588.

[3] a) T. Linker, F. Rebien, G. Tóth, *Chem. Commun.* **1996**, 2585; b) M. Oelgemöller, N. Healy, L. de Oliveira, C. Jung, J. Mattay, *Green Chem.* **2006**, *8*, 831–834.

[4] M. Matsumoto, S. Dobashi, K. Kondo, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 185–187.

[5] B. M. Kwon, C. S. Foote, S. I. Khan, *J. Org. Chem.* **1989**, *54*, 3378–3382.

[6] P. A. Burns, C. S. Foote, S. Mazur, *J. Org. Chem.* **1976**, *41*, 899–907.

[7] I.-H. Um, H.-J. Han, J.-A. Ahn, S. Kang, E. Buncel, *J. Org. Chem.* **2002**, *67*, 8475–8480.

[8] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.

[9] W. M. Horspool, F. Lenci, *CRC handbook of organic photochemistry and photobiology*, CRC Press, Boca Raton, **2004**.

[10] K. H. Schulte-Elte, V. Rautenstrauch, *J. Am. Chem. Soc.* **1980**, *102*, 1738–1740.

[11] a) B. Halliwell, J. M. C. Gutteridge, *Free Radical Bio. Med.* Oxford University Press, Oxford, New York, **2007**; b) P. R. Ogilby, *Chem. Soc. Rev.* **2010**, *39*, 3181–3209.

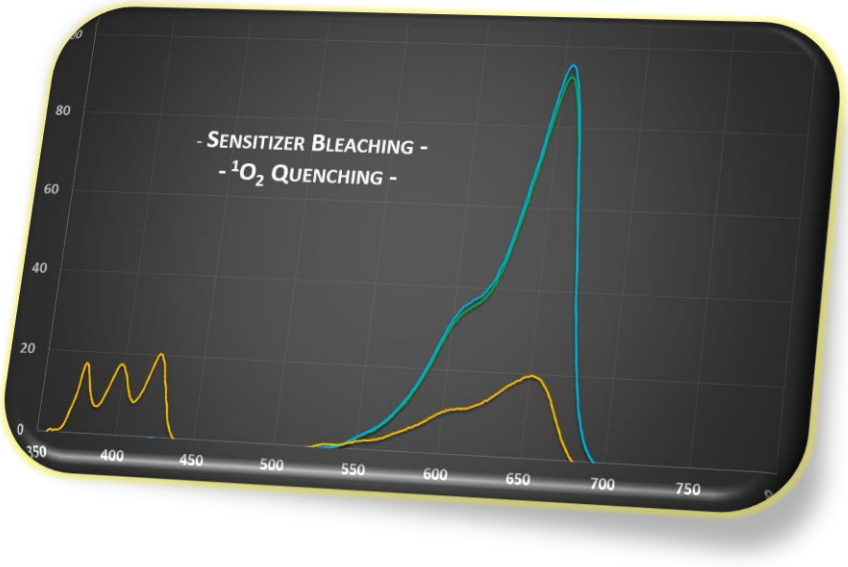
[12] R. H. Young, R. L. Martin, *J. Am. Chem. Soc.* **1972**, *94*, 5183–5185.

[13] T. P. Devasagayam, A. R. Sundquist, P. Di Mascio, S. Kaiser, H. Sies, *J. Photochem. Photobio. B: Bio.* **1991**, *9*, 105–116.

[14] G. Hu, J. Xu, P. Li, *Org. Lett.* **2014**, *16*, 6036–6039.

Chapter 6:

- Interactions and Side Reactions -



6. Interactions and side reactions in photosensitized oxidations

6.1. Sensitizer Bleaching

Frequently, and especially in the batch reactor setup, bleaching of methylene blue could be noticed in the standard reaction conditions. The deep blue solution turns green first, and subsequently yellow. It was observed that the degree of the bleaching is dependent on the oxidized substrate, its concentration and the time (Figure 6.1).
Since these were just subjective observations, some bleaching experiments with different substrates and different reaction times were performed.

Figure 6.1: Bleaching of methylene blue after 24 h with no substrate (blue), 0.1 M 1-phenylcyclohexene (green) and 1 M 1-phenylcyclohexene (yellow) in acetonitrile; irradiation with white LEDs.

The absorption spectra of methylene blue solutions (c = 1 mM) containing different substrates (c = 0.1 M) were measured at T_0, after 50 s and 100 s retention time in the flow reactor, irradiated with red LEDs. Additionally, the conversions of the different substrates were determined to get an idea of the potential correlation of product formation and sensitizer bleaching.

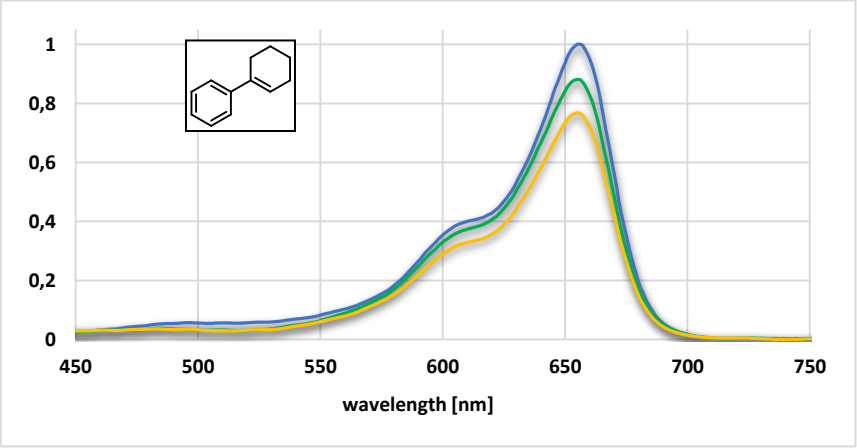


Figure 6.2: relative absorption of a methylene blue solution containing 1-phenylcyclohexene at T_0 (blue), after 50 s (green) and after 100 s (yellow) in the flow reactor;

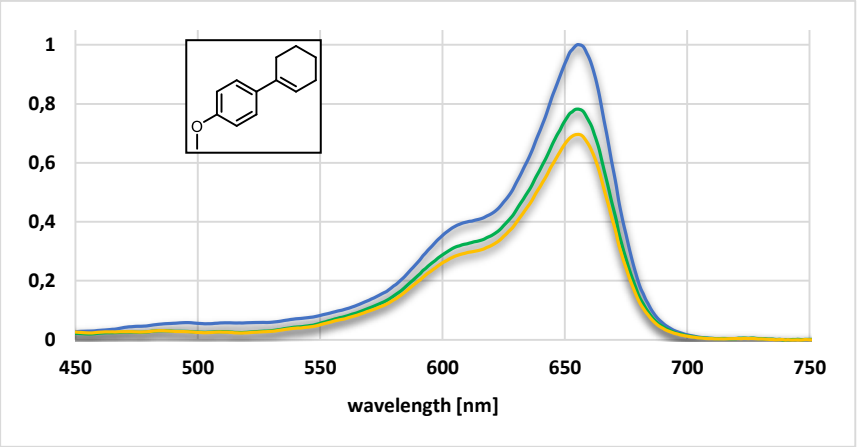


Figure 6.3: relative absorption of a methylene blue solution containing 4'-methoxy-2,3,4,5-tetrahydro-1,1'-biphenyl at T_0 (blue), after 50 s (green) and after 100 s (yellow) in the flow reactor;

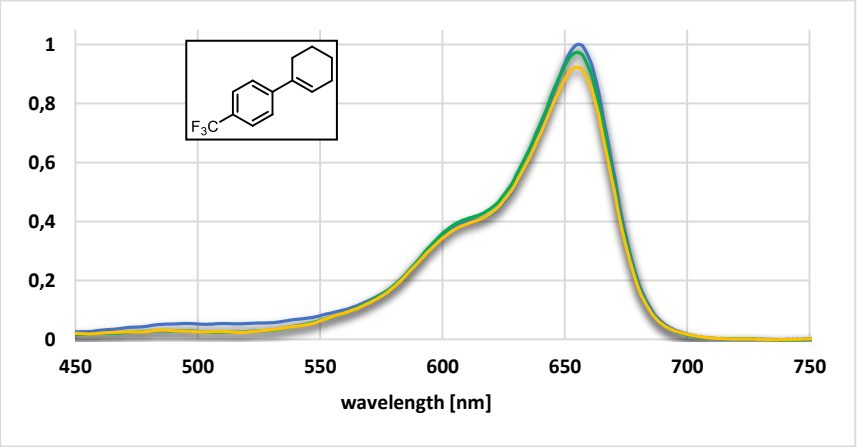
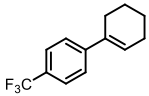
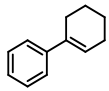
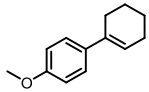


Figure6.4: relative absorption of a methylene blue solution containing 4'-(trifluoromethyl)-2,3,4,5-tetrahydro-1,1'-biphenyl at T_0 (blue), after 50 s (green) and after 100 s (yellow) in the flow reactor;

Figures 6.2, 6.3 and 6.4 show the decrease of absorption at 655 nm in dependency with the residence time for three different substrates. Taking the relative rates of the substrate conversion, it is striking that the decrease of absorption is proportional to the rate of the reaction (Table 6.1)

Table 6.1: Conversion and relative absorption of MB at 655 nm[a]

substrate	conversion 50 s	relative absorption 50 s	100 s
	16 %	97 %	92 %
	57 %	88 %	76 %
	72 %	78 %	69 %

[a] Conversion of different substrates and relative absorption of methylene blue after photooxygenation (50 s and 100 s).

As the most reactive substrate causes the biggest drop in absorption, it can be concluded that the amount of produced endo- and/or hydroperoxides is responsible for the sensitizer bleaching. To clear up the detailed influence of the different substances on the bleaching reaction, they were considered separately from each other. 100 equivalents of 1-phenylcyclohexene (**PCH**), its [4+2]-cycloaddition product (**[4+2]**), its hydroperoxide product (**HPO**) and H_2O_2 were added to identical solutions of methylene blue (c = 1 mM) in acetonitrile. The reaction mixtures were stirred without irradiation for 20 min first and irradiated with white LEDs for 10 min subsequently (Table 6.2).

Table 6.2: Relative absorption of MB at 655 nm[a]

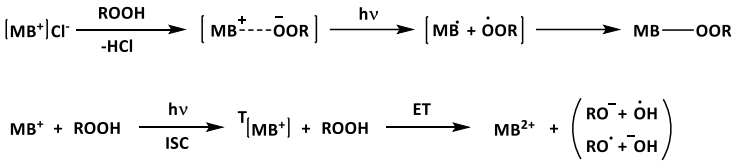
additive	relative absorption T_0	20 min	10 min irradiation
PCH	100 %	99 %	97 %
[4+2]	98 %	98 %	54 %
HPO	90 %	90 %	0 %
H_2O_2	95 %	94 %	19 %

[a] different solutions containing additives and methylene blue (1 mol%)

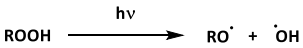
The results show the need of light for the bleaching reaction. It is also obvious that molecular oxygen is not necessary for the bleaching reaction. The hydroperoxide product, also the major product in the photooxygenation of 1-phenylcyclohexene, showed the strongest bleaching potential and seems to be largely responsible for the decomposition of the sensitizer. After 10 min of irradiation in the presence of hydroperoxide, the absorption of methylene blue at 655 nm was completely

extinguished. The requirement of irradiation suggests that the peroxides react with the activated state of the sensitizer, whereas the ground state methylene blue seems to stay untouched.

Two different pathways for the discoloration of the methylene blue are conceivable (Scheme 6.1). Electron transfer from the excited MB^+ triplet state to the peroxide as well as electron transfer from the peroxide anion to the excited triplet state of the sensitizer can occur, depending on the redox potential of the hydroperoxide, and the likelihood of the ion-pair formation.



Scheme 6.1: Possible pathways of methylene blue bleaching in the presence of hydroperoxides



Scheme 6.2: Photoinduced homolysis of hydoperoxides

But the direct photolysis of peroxides is also possible. Especially hydroperoxides tend to homolysis after irradiation (Scheme 6.2). According to WILES et al. the energy of light in range of 300 – 400 nm is sufficient for a homolytic cleavage of O-O bonds to form alkoxy and hydroxyl radicals.[1]

The degradation of methylene blue in the presence of radicals is known, and used as an indication for the appearance of hydroxyl radicals.[2]

Table 6.3: Relative absorption of RB at 558 nm[a]

additive	relative absorption		
	T_0	20 min	10 min irradiation
PCH	100 %	100 %	73 %
[4+2]	100 %	100 %	82 %
HPO	100 %	100 %	37 %
H_2O_2	100 %	100 %	80 %

[a] different solutions containing additives and Rose Bengal (1 mol%)

In contrast to methylene blue, rose bengal (RB) seems to be less vulnerable to bleaching reactions under the given reaction conditions. Especially after irradiation in the presence of endo- and hydrogene peroxide, RB keeps a moderate absorption potential (Table 6.3). This demonstrates that the degree of bleaching can be minimized,

in coordination with the expected reaction products and the available light sources, by a suitable choice of the used sensitizer.

6.2. Substrate interaction with MB and $^1O_2$

Compared to open-chain olefins, but also to other cyclohexenes, the photooxygenations of amide-substituted cyclohexenes described in Chapter 3 required extremely long reaction times, in some cases more than 72 h using a standard batch reactor. As other substrates showed shorter reaction times in the same batch setup and as the selectivity of in the photooxygenation of amide-substituted cyclohexenes was good, despite the prolonged irradiation, two conclusions can be drawn. First, there is no second reaction pathway of the amide-substituted cyclohexenes with $^1O_2$ and second, the amount of singlet oxygen produced in the setup should be sufficient for faster oxygenations.
To check the interaction of amide-substituted cyclohexenes with the sensitizer, absorption and fluorescence of methylene blue were measured in relationship to the amount of added *N*-methyl-1,2,3,6-tetrahydo-3-acetamidyl-phthalic imide (**substrate 1**). Neither the absorption, nor the fluorescence of methylene blue showed any dependency with the concentration of the substrate up to 100 equivalents of quencher.
As a final point, the possibility of a physical deactivation of $^1O_2$ should be excluded by determining the lifetime of singlet oxygen in the presence of different substrates. Therefore, the decay of the emission of $^1O_2$ at 1270 nm, was measured. As the decrease of singlet oxygen lifetime in the presence of *N*-methyl-1,2,3,6-tetrahydo-3-acetamidyl-phthalic imide was very small compared to citronellol, known to react fast with $^1O_2$, a physical quenching of the singlet, as a reason for the long reaction times, can be excluded. Only a slight effect of the substrate concentration on the lifetime of singlet oxygen could be determined. A quantifiable decrease could not be measured until the substrate concentration was 5000 times higher than the sensitizer concentration. The *Stern-Volmer*-plot in Figure 6.6 shows the different reaction rates for photooxygenations of citronellol and *N*-methyl-1,2,3,6-tetrahydo-3-acetamidyl-phthalic imide, based on the measurements of singlet oxygen lifetime.

Based on the different slopes of the graphs in Figure 6.6 and the *Stern-Volmer* equation (Figure 6.5) various information about the $^1O_2$ quenching can be calculated.

$$\frac{F_0}{F} - 1 = K_{SV} \cdot [Q] \quad \text{and} \quad K_{SV} = k_q \cdot \tau_0$$

Figure 6.5: *Stern-Volmer* equation with F_0 = intensity of emission in the absence of quencher, F = intensity of emission in the presence of quencher, K_{SV} = *Stern-Volmer* constant, [Q] = concentration of quencher, k_q = the bimolecular rate constant for the quenching and τ_0 = lifetime of $^1O_2$ without quenching

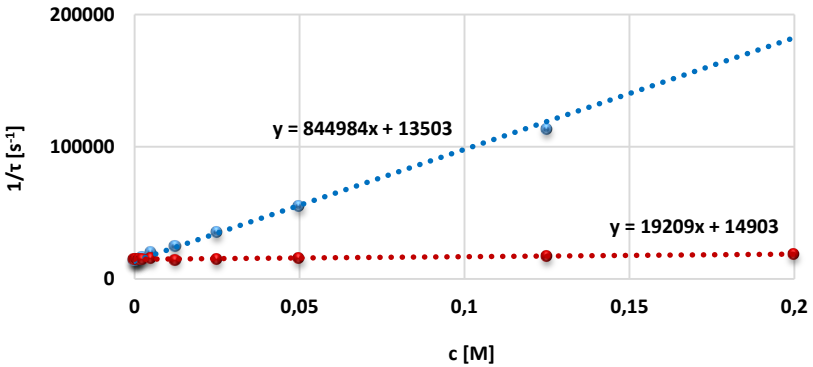


Figure 6.6: *Stern-Volmer*-plot of the chemical quenching of $^1O_2$ emission at 1270 nm, caused by citronellol (blue) and *N*-methyl-1,2,3,6-tetrahydo-3-acetamidyl-phthalic imide (red).

The average lifetime $\bar{\tau}_0$ of singlet oxygen in this experiment is 70 µs in acetonitrile. This value is in good accordance with the literature (71 µs).[3]
The rate constants for the bimolecular quenching can be calculated as, k_d (citronellol) = $8.45 \cdot 10^5$ and k_d (substrate 1) = $1.92 \cdot 10^4$. According to the chemical quenching of $^1O_2$ emission at 1270 nm the photooxygenation of citronellol should be about 44 times faster than the photooxygenation of *N*-methyl-1,2,3,6-tetrahydo-3-acetamidyl-phthalic imide. This result is in good agreement with the experimental evidence. In the batch reactor setup, citronellol could be oxidized quantitatively in about 1 h, whereas *N*-methyl-1,2,3,6-tetrahydo-3-acetamidyl-phthalic imide required a reaction time of 48 h to achieve complete conversions.

6.4. Experimental Section

Chemicals and Solvents

If not indicated, commercial reagents were used without purification.

Analytical thin-layer chromatography

TLC was performed using aluminium plates with silica gel and fluorescent indicator (Merck, $60F_{254}$). Thin layer chromatography plates were visualized by exposure to UV light and/or by immersion in an aqueous staining solution of $KMnO_4$ or in an ethanolic solution of molybdophosphoric acid.

Column chromatography

Flash column chromatography with silica gel 60 Å (220-240 mesh) from Acros. Pentane, hexanes or mixtures thereof with ethyl acetate were used as eluents.

Gas chromatography with mass-selective detector

Agilent 6890N Network GC-System, mass detector 5975 MS. Column: BPX5 (30 m x 0.25 mm x 0.25, from *SGE*, carrier gas: H_2.

Standard heating procedure: 50°C (2 min), 25°C/min -> 300°C (5 min).

Gas chromatography with FID

Agilent 7820A GC-Systems. Column: HP 5 19091J 413 (30 m x 0.32 mm x 0.25 µm) from *Agilent*, carrier gas: N_2. GC-FID was used for catalyst screening (Calibration with internal standard *n*-pentadecane and analytically pure samples).

NMR

^1H and ^{13}C nuclear magnetic resonance spectra were recorded on *Bruker* Avance 300 (300 MHz ^1H; 75 MHz ^{13}C) and *Bruker* Avance 400 (400 MHz ^1H, 101 MHz ^{13}C) spectrometers. Chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hertz (Hz). Following abbreviations are used for spin multiplicities:

s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, ddt = doublet of doublet of triplet. For yield determinations, *n*-pentadecane was used as internal standard.

IR spectroscopy

Infrared spectra were recorded on a *Agilent Varian* Scimitar 1000 FT-IR equipped with a ATR unit or on an *Agilent* Cary 630 FTIR equipped with a ATR unit. Wavenumbers are

indicated in cm^{-1}. Intensive absorption bands are indicated with „s“ (strong), medium bands with „m“ (medium), and weak bands with „w“ (weak).

High resolution mass spectrometry (HRMS)
The spectra were recorded by the Central Analytics Lab at the Department of Chemistry, University of Regensburg, on a MAT SSQ 710 A from *Finnigan*.

Analytical HPLC
Bischoff HPLC/UHPLC with a *Bischoff* Compact Pump 3350 and a *Bischoff* DAD-4L UV/VIS multiwavelength detector was used for analytical HPLC. A P*RONTOSIL* 120-5-C18-ace-EPS 5.0 µm column (150 × 4.6 mm) and a mixture of acetonitrile and water (65/35) were used (calibration with internal standard *m*-xylene and analytically pure samples).

$^1O_2$ lifetime determination[4]
Singlet oxygen lifetimes were determined by Dr. Johannes Regensburger (Universitätsklinikum Regensburg) according the following procedure:
Solutions were excited using a frequency-doubled Nd:YAG laser (PhotonEnergy, Ottensoos, Germany) with a repetition rate of 2.0 kHz (pulse duration 100 ns). The diameter of the laser spot was 8 mm on the cuvette surface (area: 1 cm · 3 cm) containing 3 ml of solution. The solution was magnetically stirred. Singlet oxygen luminescence was detected with an IR-sensitive photomultiplier (R5509-42, Hamamatsu Photonics Deutschland GmbH, Herrsching, Germany) with a rise time of about 3 ns. The luminescence signal was detected at different wavelengths from 1200 to 1350 nm at regular steps of 10 nm using a monochromator (Horiba, Yobin Yvon Inc. USA) in front of the photomultiplier. The different interference filters, placed in front of the photomultiplier entrance, show a transmission maximum at 1271 nm (LOT Oriel GmbH, Darmstadt, Germany) with a full width of half-maximum (FWHM) of 10 nm, at 1273 nm with a FWHM of 30 nm, and at 1275 nm with a FWHM of 80 nm (both Interferenzoptik Elektronik GmbH, Nabburg, Germany). The 950 nm cut-off filter was obtained from Omega Opticals, Photomed GmbH, Seefeld, Germany.

Fluorescence measurements
Fluorescence spectra were recorded on a *Agilent Varian* Cary Eclipse Fluore-scence Spectrophotometer

Absorption Spectra
UV/VIS spectra were recorded on a *Agilent Varian* Cary 50 Bio UV-Visible Spectro-photometer

Flow reactor

Photooxygenations were performed in a flow reactor setup described in chapter 4, cconsisting of: HPLC pump (*Bischoff* dosage pump 2250), oxygen supply (*Linde* 4.6, 200 bar), pressure reducing valve *(GO* regulator, *TeamTrade*, PR1-1I11ACW111),) mass flow controller (*Brooks* SLA 5850), FEP capillary, LED light source (24 × *Cree* XP-E 2, red), 700 mA), back-pressure regulator (*IDEX*, P-763, 100 psi).

6.5. References

[1] a) D. J. Carlsson, D. M. Wiles, *Macromol.* **1969**, *2*, 597–606; b) K. R. Maples, C. H. Kennedy, S. J. Jordan, R. P. Mason, *Arch. Biochem. Biophys.* **1990**, *277*, 402–409; c) J. van der Zee, D. P. Barr, R. P. Mason, *Free Radical Bio. Med* **1996**, *20*, 199–206.

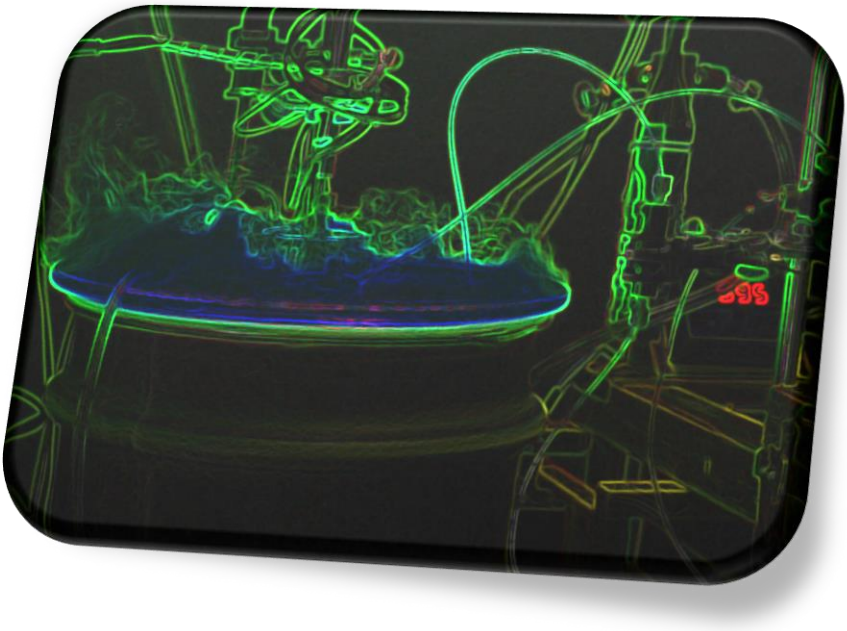
[2] a) A. Y. Satoh, J. E. Trosko, S. J. Masten, *Environ. Sci. Technol.* **2007**, *41*, 2881–2887; b) I. A. Salem, M. S. El-Maazawi, *Chemosphere* **2000**, *41*, 1173–1180; c) A. Houas, *Appl. Catal. B: Environ.* **2001**, *31*, 145–157.

[3] Francis Wilkinson, *Rate Constants for the Decay and Reactions of the Lowest Electronically Excited Singlet State of Molecular Oxygen in Solution. An Expanded and Revised Compilation.* **1994**

[4] J. Regensburger, T. Maisch, A. Felgenträger, F. Santarelli, W. Bäumler, *J. Biophoton.* **2010**, *3*, 319 – 327

Chapter 7:

- Appendix -



7.1. List of abbreviations

Ac Acetyl
AF Amorphous fluoropolymer
Ar Aryl
ATR Attenuated total reflection
BPR Back-pressure regulator
d Day
d.r. Diastereomeric ratio
DCM Dichloromethane
DFT Density functional theory
DMSO Dimethylsulfoxide
EA Ethyl acetate
EDG Electron donating group
ee Enantiomeric excess
EI Electron impact
ESI Electrospray ionization
ET Electron transfer
E_T Energy of the triplet state
Et Ethyl
eV Electronvolt
EWG Electron withdrawing group
FEP Fluorinated ethylene-propylene co-polymere
FG Functional group
FID Flame ionization
FT-IR Fourier-Transform-Infrared spectroscopy
GC Gas chromatography
GP General procedure
h Hour
HOMO Highest occupied molecular orbital
HPLC High performance liquid chromatography
HR High resolution
Hz Hertz
ID Inner Diameter
ISC Intersystem crossing
LED Light emitting diode
LR Low resolution
LUMO Lowest unoccupied molecular orbital
MB Methylene blue
Me Methyl
MeCN Acetonitrile
MeOH Metahnol
MHz Megahertz
min Minute
µm Micrometer
mmol Milli mol
MS Mass spectrometry
nm Nanometer
NMR Nuclear magnetic resonance
PE Petroleum ether
Ph Phenyl
R Alkyl rest
RB Rose Bengal
RT Room temperature
R_f Retention factor
s Second
^{t}Bu *tert*-Butyl
Teflon Fluorinated polyethylene
TFA Trifluoro acetic acid
THF Tetrahydrofurane
THTPP 5,10,15,20-tetrakis(4-hydroxyphenyl)-21*H*,23*H*-porphine
TLC Thin layer chromatography
TPP *meso*-Tetraphenylporphyrine
TS Transition state
UV Ultraviolet radiation
VIS Visible radiation
vs. Versus
X Substance amount fraction

7.2. Summary

The main topics of this thesis were the synthesis of substituted cyclohexenes using three-component reactions as well as the photooxygenation of various cyclic olefins by the use of visible light and molecular oxygen.

Structurally diverse carbocycles with two vicinal nitrogen-substituents were prepared in expedient three-component reactions from simple amines, aldehydes, and nitroalkenes. *Trans*,*trans*-6-nitrocyclohex-2-enyl amines were obtained in a one-pot domino reaction involving condensation, tautomerisation, conjugate addition, and nitro-Mannich cyclisation. Upon employment of less nucleophilic carboxamides, a concerted Diels-Alder cycloaddition mechanism operated to give the corresponding *cis*,*trans*-nitrocyclohexenyl amides.

Diverse *trans*-amidoalcohol derivatives were synthesized. Therefor, numerous *cis*-anellated cyclohexenes, mainly produced by three-component reactions or Diels-Alder reactions were oxidized in highly regioselective and stereoselective Schenck ene reactions by the use of singlet oxygen. Supported by DFT calculations and experimental data a boat-like ground state conformation and the orientation of an abstractable H atom perpendicular to the plane of the double bond could be identified to be the key to high regio- and stereoselectivity in these photooxygenations.

Investigations about the photooxygenation of different cyclohexenes indicated different operating mechanisms for the singlet oxygen reactions of *cis*-anellated and aryl substituted cyclohexenes. The key intermediate in the photooxygenation of *cis*-anellated cyclohexenes is a so-called perepoxide, whereas the oxidation of 1-phenyl cyclohexenes passes an open chain zwitterionic intermediate, stabilized by the aromatic system. A variation of the substitution pattern on the arene (electronic properties and position of the substituents) allowed the tuning of the reactivity and the chemoselectivity of aryl-substituted cyclohexenes in photooxygenations.

A flow reactor was designed and built up to realize better reaction control and to speed up photocatalytic oxygenations in gas-liquid-biphasic systems. The immense internal surface and the huge surface-to-volume ratio of the reactor result in more efficient mixing of gaseous and liquid phases and in a very effective irradiation of the reaction mixture. Therefore, the required reaction times could be reduced significantly, compared to batch reactions. High productivity, efficiency and flexibility of the system allow an easier adjustment of reaction and reactor conditions, lower catalyst wastage and power saving of more than 99 %, compared with common batch-syntheses.

7.3. Zusammenfassung

Hauptthemengebiete dieser Arbeit waren die Synthese substituierter Cyclohexene mit Hilfe von Dreikomponenten-Reaktionen sowie die Umsetzung verschiedener cyclischer Olefine in Photooxygenierungsreaktionen mit Hilfe von sichtbarem Licht und molekularem Sauerstoff.

In Dreikomponeten-Reaktionen mit einfachen Aminen oder Amiden, Aldehyden und Nitroalkenen konnten unterschiedliche Diastereoselektivitäten beobachtet werden. Während *trans*,*trans*-6-Nitrocyclohex-2-enyl-amine in einer Eintopf-Dominoreaktion bestehend aus Kondensation, Tautomerisierung, Addition und Nitro-Mannich-Cyclisierung hergestellt werden konnten, lieferten Amide in einer konzertierten Diels-Alder Cycloaddition bevorzugt *cis*,*trans*-Nitrocyclohexenyl-amide.

Diverse *trans*-Amidoalkohole wurden synthetisiert. Dafür wuden, in Drei-Komponenten- und Diels-Alder-Reaktionen, eine Reihe von *cis*-anellierten Cyclohexenen hergestellt, die in hochgradig regio- und stereoselektiven Schenck-En Reaktionen, mit Hilfe von Singulett Sauerstoff oxidiert wurden. Gestützt durch DFT-Rechnungen und experimentelle Daten konnten eine wannenförmige Konformation im Grundzustand und ein senkrecht zur Doppelbindungsebene orientieres, abstrahierbares H-Atom als Schlüssel für diese hohe Regio- und Stereoselektivität identifiert werden.

Untersuchungen zur Photooxygenierung verschiedener Cyclohexene lieferten Aufschluss über unterschiedliche Mechanismen bei der Reaktion von *cis*-anellierten beziehungsweise arylsubstituierten Cyclohexenen mit Singulett Sauerstoff. Während bei der Schenck-En Reaktion anellierter Cyclohexene ein Perepoxid als Schlüsselintermediat auftritt, verlaufen Reaktionen von 1-Phenylcyclohexenen über ein durch den Aromaten stabilisiertes, offenkettiges zwitterionisches Intermediat. Veränderungen der Substituenten am Aromaten hinsichtlich ihrer elekronischen Eigenschaften und Position, ermöglichten eine Beeinflussung der Reaktivität und Chemoselektivität von aryl-substituierten Cyclohexenen in Photooxygenierungen.

Zur besseren Reaktionskontrolle, sowie zur Beschleunigung der photokatalytischen Oxidationsreaktionen in Gas-Flüssigkeits-Mischphasen wurde ein Durchflussreaktor entworfen und gebaut. Aus der immensen inneren Oberfläche und dem großen Oberflächen zu Volumen Verhältnis des Systems ergibt sich eine effizientere Mischung von flüssiger und gasförmiger Phase und eine effektivere Bestrahlung des Reaktionsgemisches als in Batch-Reaktionen. Dadurch konnten die erforderlichen Reaktionszeiten erheblich reduziert werden. Die hohe Produktivität, Effektivität und Flexibilität des Systems ermöglichten eine einfachere Anpassung der nötigen Reaktions-

und Reaktorparameter, geringeren Katalysatorverbrauch und Energieeinsparungen von über 99 % im Vergleich zu gewöhnlichen Batch-Synthesen.

7.4. Acknowledgements

Die letzten drei Jahre waren eine sehr lehrreiche und prägende Zeit für mich, als Wissenschaftler, aber vor allem auch für mich persönlich. Deshalb möchte ich mich bei einigen Menschen bedanken, die mich in den letzten Jahren begleitet haben.

Mein Dank gilt an erster Stelle meiner Frau Christel, die mir zwei wunderbare Kinder geschenkt hat und die mich nun schon seit über zehn Jahren begleitet. Ich danke ihr für unzählige wunderbare Augenblicke, für ihre Unterstützung, für ihre Kraft und einfach dafür, dass sie da ist in all den schönen, aber auch in den schwierigen Momenten.

Auch möchte ich mich bei meinen Eltern und meiner Schwester bedanken, die mich immer unerstützt haben und dies bis heute tun. Es ist schön zu wissen, jemanden zu haben, auf den man sich zu jeder Zeit und in jeder Situation verlassen kann.

Bei Axel möchte ich mich ganz herzlich bedanken, dass er mir die Tür nach Regensburg geöffnet hat. Ich möchte mich für die angenehme Zusammenarbeit, das interessante Thema und die vielen Anregungen und Ideen bedanken, aber auch dafür, dass seine Tür immer offen steht für Fragen, egal ob wissenschaftlicher oder privater Natur. Es freut mich, dass ich nach meiner Promotion auf drei schöne Jahre zurückblicken kann.

Dafür möchte ich mich natürlich auch bei den restlichen Mitgliedern des Arbeitskreises bedanken – für ihre fachliche Hilfe, aber vor allem für Schafkopf-, Grill- und Steakabende, das ein oder andere Bierchen, rauschende Feste und dafür, dass sie den alten Mann beim Kickern immer gewinnen lassen. Allen voran denke ich hierbei an Tim Gieshoff, Michál Majek, Dominik Gärtner und Michaela Lutz, die mich die gesamte Zeit über begleitet haben und die immer da waren für Diskussionen über wissenschaftliche Fragen, aber auch für persönliche Gespräche.

Für besondere Unterstützung in wissenschaftlicher Hinsicht möchte ich mich bei Michál bedanken, bei Marcus Wegmann von der TU München, bei Dr. Johannes Regensburger vom Klinikum Regensburg und bei Dr. Kerry Gilmore vom Max-Planck-Institut in Potsdam.

Für die Erstellung des Zweitgutachtens und für die Übernahme des Amtes des Drittprüfers möchte ich mich sehr herzlich bei Frau Prof. Dr. Olga Garcia Mancheño und bei Herrn Prof. Dr. Frank-Michael Matysik bedanken.

Außerdem danke ich Herrn Prof. Dr. Siavosh Mahboobi für die Übernahme des Prüfungsvorsitzes.

Diese Liste könnte man endlos weiter führen, aber abschließend möchte ich noch bei allen bedanken, die mir die letzten drei Jahre begegnet sind, bei den vielen neuen

Freunden und Bekannten aus den Arbeitskreisen Gschwind, Wolf, Garcia, Fleischer, Reiser und König, den Praktikanten und Laboranten und bei allen helfenden Händen.
Ich hoffe, dass mir viele von euch wieder über den Weg laufen, bedanke mich für drei Jahre mit vielen neuen Freunden und wünsche euch allen viel Erfolg bei euren neuen Projekten!

Die letzten, bei denen ich mich bedanken möchte sind meine beiden Zwerge Jonas und Leni für ihre leuchtenden Augen, wenn ich nach Hause komme.

7.5. Curriculum Vitae

Personal Data:

Name:	Josef Schachtner
Birth Data:	February 13th, 1983 in Wolnzach
Nationality:	german
Marital Status:	married, 2 children

Education and professional experience:

2013 – 2016	Doctoral Thesis in Organic Chemistry, in the group of Prof. Dr. Axel Jacobi von Wangelin *"The Development of a Modular Photo Flow Reactor Setup and its Application to Photooxygenations"*
2010 – 2012	Master of Science – chemistry; Technical University Munich; organic and analytical chemistry: 1.4 Master Thesis: *„Synthese photoreaktiver ABPP-Sonden und Identifizierung ihrer Angriffsziele";* (1.3)
2007 – 2010	Bachelor of Science – chemistry; Technical University Munich: 1.9 Bachelor Thesis: *„Bestimmung der Kreuzreaktivität monoklonaler B[a]P Antikörper gegenüber den 16 EPA polyzyklischen aromatischen Kohlenwasserstoffen";* (1.0)
2005 – 2007	Research Assistant: 4SC AG in Martinsried (organic synthesis)
2003 – 2005	Apprenticeship: *Chemisch-Technischen Assistenten* (Chemie-schule Dr. Erwin Elhardt)
2002 – 2003	Military service in Mengen and Oberstimm
1993 – 2002	Secondary School, Wolnzach – graduation: Allgemeine Hochschulreife
1989 – 1993	Primary School, Wolnzach

List of publications

"A vHTS approach for the identification of b-adrenoceptor ligands", S. Tasler, R. Baumgartner, A. Aschenbrenner, A, Ammendola, K. Wolf, T. Wieber, J. Schachtner, M. Blisse, U. Quotschalla, P. Ney, *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 3399

"Thienopyrimidines as b3-adrenoceptor agonists: Hit-to-lead optimization", S. Tasler, R. Baumgartner, A. Ammendola, J. Schachtner, T. Wieber, M. Blisse, S. Rath, M. Zaja, P. Klahn, U. Quotschalla, P. Ney, *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 6108

"Modular Synthesis of Cyclic cis- *and* trans-*1,2-Diamine Derivatives"*, A. K. Weber, J. Schachtner, R. Fichtler, T. K. Leermann, J. M. Neudörfl, A. Jacobi von Wangelin, *Org. Biomol. Chem.* **2014**, *12*, 5267.

"A Flow Reactor Setup for Photochemistry of Biphasic Gas/Liquid Reactions", J. Schachtner, A. Jacobi von Wangelin, *submitted*.

"Stereoselective Photooxidation of Cyclohexenes: The Imperative of Conform-ational Control", J. Schachtner, M. Majek, R. Fichtler, R. Perez-Ruiz, J. Regensburger, M. Wegmann, W. Bäumler, T. Bach, A. Jacobi von Wangelin, *manuscript in preparation*

"Stereoselective Photooxygenations by the Schenck Ene reaction", R. Perez-Ruiz, J. Schachtner, A. Jacobi von Wangelin, *manuscript in preparation*

7.6. Eidestattliche Versicherung

I. Ich erkläre hiermit an Eides statt, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe des Literaturzitats gekennzeichnet.

II. Bei der Auswahl und Auswertung haben mir die in den jeweiligen Kapiteln aufgeführten Personen in der beschriebenen Art und Weise unentgeldlich geholfen.

III. Weitere Personen waren an der inhaltlich-materiellen Herstellung der vorliegenden Arbeit nicht beteiligt. Insbesondere habe ich hierfür nicht die entgeltliche Hilfe eines Promotionsberaters oder anderer Personen in Anspruch genommen. Niemand hat von mir weder unmittelbar noch mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen.

IV. Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

_____

Regensburg, den 08.02.2016