Synthesis of Potential Pharmaceuticals and Diagnostic Markers for Liver and Pancreas Diseases through Photoredox Catalysis and Organic Chemistry

Dissertation

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Rostock, den 14.10.2020

…….

Firas El-Hage

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Abstract

Organic molecules accomplish different crucial functions in nature, pharmaceuticals, and technology. Organic synthesis, as such, represent a key tool to access and realise a broad array of transformations, ranging from simple- to highly complex and selective molecular modifications. In times where sustainable and green chemistry is gaining importance day by day, the development of highly efficient catalytic methodologies constitutes one of the main aims of the organic chemistry research and pharmaceutical industry.

Protein misfolding and Endoplasmic-reticulum-associated protein degradation play an important role in the pathogenesis of different diseases. Among a wide variety of related disorders, hereditary liver and pancreas diseases like the *Wilson*'s disease and acute pancreatitis consist two diseases for which no causal treatment is available. During this thesis, the synthesis of potential biologically active molecules for targeting different pharmacological relevant targets is adressed by the mean of classical organic chemistry and photoredox catalysis to develop new possible therapeutic approaches for the beforementioned diseases.

The first chapter during this thesis describes a brief introduction to photochemistry and the former employments of pyrimidopteridine *N*-oxide derivatives in photochemical transformations. Different substituted pyrimidopteridine *N*-oxide derivatives and their deoxygenated analogs are highlighted. Also, corresponding electro- and photochemical data were investigated.

The second chapter describes a photo-mediated photoredox decarboxylative methodology for the C–C coupling of different non-activated carboxylic acids to electron-deficient alkenes using pyrimidopteridine *N*-oxides as photocatalysts. This metal-free protocol comprises the use of catalytic amounts of base and low photocatalyst loading to achieve a regioselective decarboxylative coupling. The optimization of reaction conditions as well as the scope of both carboxylic acids and electron-deficient alkenes is described. Furthermore, mechanistic investigations and derivatization reactions of synthesized scaffolds are presented.

In the third chapter, a photomediated hydroamination reaction of different stilbene derivatives with primary unprotected amines is highlighted. Different primary amines were employed and tested for their suitability in this photocatalytic protocol using

pyrimidopteridine *N*-oxides as photocatalysts. In addition, kinetic experiments were conducted to reveal the operational mechanism of this reaction.

Next, during the fourth chapter, the total synthesis of two literature known turn-on copper chemosensors, indispensable for the evaluation of possible medicinally relevant compounds in live-cell cultures, and two glitazone derivatives, which could demonstrate beneficial effects during the *Wilson*'s disease, are revised and newly evaluated. In addition, the quantification of cellular copper levels is demonstrated in HepG2 cell cultures.

In the last part, the total synthesis of ZD-0892, a literature known peptidyl trifluoromethyl ketone possesing a high elastase inhibition effect, is described. A safer and easier way to access synthetically demanding ZD-0892, which includes multiple stereogenic centers, is presented.

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List of Abbreviations

[M]	molecular ion peak	EI	electron ionization
Ac	acetyl	ESI	electrospray ionization
AcOH	Acetic acid	Et	Ethyl
Ad	adamantyl	EWG	electron-withdrawing group
AIBN	azobisisobutylnitrile		
Alk	alkyl	equiv.	equivalent
aq.	aqueous	EI-MS	electron ionization mass spectroscopy
Ar	aryl		
ATPase	adenosylpyrophosphatase	eV	electron volt
BDE	bond dissociation energy	FRET	Förster resonance energy transfer
Bn	benzyl		
BODIPY	boron-dipyrrromethene	g	gram
Boc	*tert*- butyloxycarbonyl	GC	gas chromatography
Bu	*n*-butyl	H	hours
t-Bu	*tert*-butyl	H_2O	water
calcd.	calculated	HEK	human embryonic kidney
Cat.	catalytic	Hex	*n*-hexyl
Cbz	benzyloxy carbonyl	HFIP	Hexafluoroisopropanol
CT	charge transfer	HOMO	highest occupied molecular orbital
CV	cyclic voltammetry		
DCM	Dichloromethane	HPLC	high-performance liquid chromatography
DG	directing group		
DMA	*N*,*N*-dimethylacetamide	HRMS	high resolution mass spectroscopy
DMF	dimethylformamid		
DMSO	dimethylsulfoxid	HSAB	Hard and soft acids and bases
DPV	differential pulse voltammetry		
d.r.	diastereomeric ratio	Hz	Hertz
Ed.	Editor	ICT	Intramolecular charge transfer
ee	enantiomeric excess		
EDG	electron-donating group	IR	infrared spectroscopy
e.g.	for example	isol.	isolated
JAK	Janus kinase	*i*Pr	isopropyl

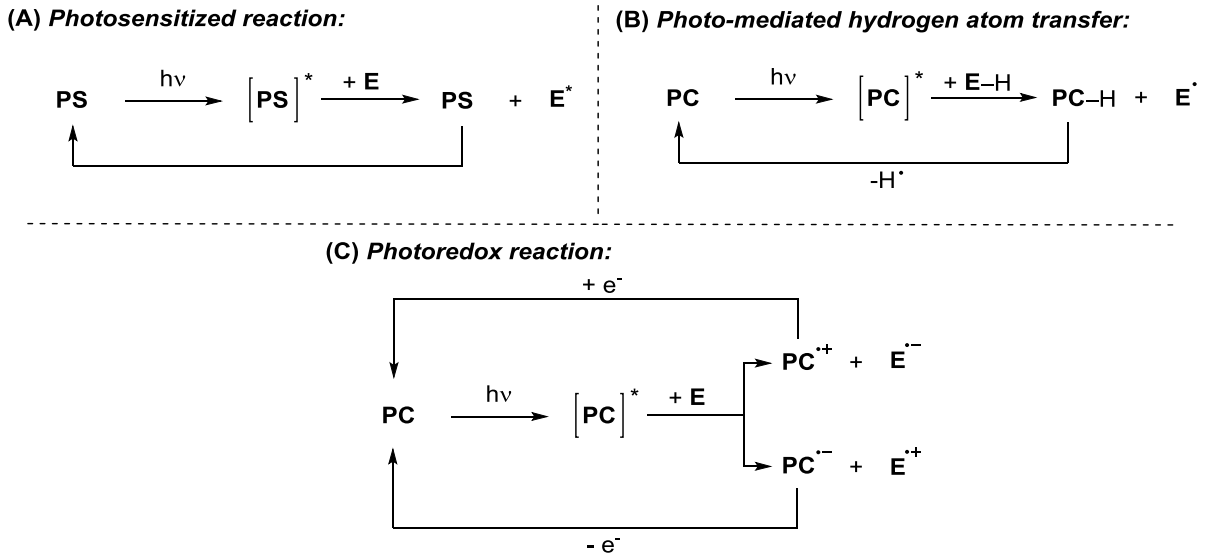
J	coupling constant
L	ligand
m	*meta*
m	multiplet
M	metal
Me	methyl
MeCN	acetonitrile
MeO	methoxy
MeOH	methanol
Mes	mesityl
m.p.	melting point
m/*z*	mass-to-charge ratio
min.	minute
ml	milliliter
mmol	millimol
MS	mass spectrometry
NMR	nuclear magnetic resonance spectroscopy
nm	nanometer
NOESY	nuclear Overhauser effect
O	*ortho*
OBF	one-bound-flip
OAc	acetate
OEt	ethoxy
PET	photoinduced electron transfer
PhMe	toluene
p	*para*
Ph	phenyl
ppm	parts per million
PPAR	peroxisome-proliferator-activated receptor
*i*PrOH	isopropyl alcohol
PCET	proton coupled electron transfer
R	rest
RSE	radical stabilization energy
r.t.	room temperature
sat.	saturated
SCE	saturated calomel electrode
SET	Single electron transfer
solv	Solved
SOMO	Single occupied molecular orbital
t	time
T	temperature
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TRIP	2,4,6-tri-*iso*-propylbenzenthiol
TLC	thin layer chromatography
TM	transition metal
TMS	trimethylsilyl
UPS	ubiquitin-proteasome-system
UV	Ultraviolet
X	halide
δ	chemical shift

1 Photochemistry and Photocatalysis

1.1 Introduction

During the past decades, the development and application of photochemistry and photoredox catalysis have gained tremendous attention in the chemical community, especially in the field of synthetic organic chemistry.[1-3] Many scientists, ranging from pharmaceutical to materials sciences, are rapidly adopting the use of photochemistry and photocatalysis as a powerful tool to achieve unique chemical reactivity and produce scaffolds inaccessible by classical approaches.[4, 5] The ability to conduct complex, thus highly selective, chemical transformations under very mild reaction conditions is especially intriguing for potential industrial applications.

First, it is essential to distinguish between frequently used terms in chemical reactions involving the use of light. Photochemistry, as such, describes the use of energy derived from absorbed photons to promote a chemical transformation.[6] This can be achieved by either direct excitation of the reactants or, in case of non-absorbing reactants, by the addition of a photocatalyst (**PC**) or photosensitizer (**PS**).[7, 8] Photocatalysts and photosensitizers are able to absorb the energy of light and interact with a reactant (**E**) *via* different mechanisms and provoke a chemical transformation (Scheme 1.1).



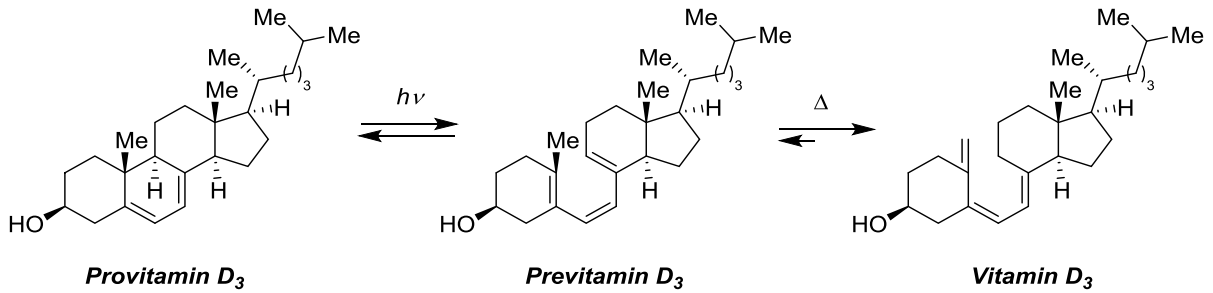
Scheme 1.1 General scheme of a (A) photosensitized-, (B) photo-mediated hydrogen atom transfer- and (C) photoredox reaction; PC = photocatalyst and PS = photosensitizer.

In this context, a photosensitization process involves, most frequently, an energy transfer (EnT) from the excited photosensitizer to the reactant (Scheme 1.1, entry A).[7] In contrast, a photocatalyzed reaction includes an electron- (ET) or hydrogen atom transfer (HAT) between a reactant and a photocatalyst in its excited-state (Scheme 1.1, entries B and C).[7] In general, these mechanisms allow the formation of different activated intermediates susceptible to chemical modifications.

In the first attempts to harness light energy for chemical reactions, the usage of solar light as the most abundant energy source to catalyze a chemical reaction has been initially reported by *Hermann Trommsdorff* and pioneered by *Giacomo Ciamician* in the early 1900s.[9, 10] The utilization of solar light as an inexhaustible renewable energy source paved the way to a new era in chemistry, establishing an environmentally sustainable key pillar in chemistry.[11, 12] Nonetheless, the wide wavelength range of solar light (300-1400 nm), along with generated heat and fluctuations in solar radiation impedes the selectivity, the scope of excitable organic molecules and the reproducibility of photochemical reactions.

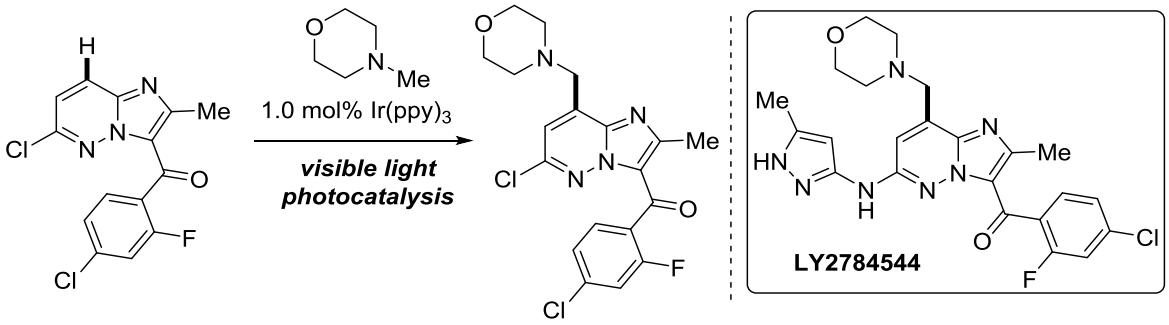
As a result, the joint venture of developments in chemistry and the field of light technology has led to the employment of custom designed and more suitable photocatalysts along with modern light sources such as LEDs (light-emitting diodes). Hence, leading to a notable enhancement in the selectivity and effectiveness of photocatalytic reactions.[13]

An prominent example of an industrially used photochemical process is the synthesis of vitamin D_3 starting from provitamin D_3 (Scheme 1.2).[14, 15] The depicted synthesis includes a light-induced isomerization step from provitamin D_3 to previtamin D_3 *via* a photo-mediated conrotary 6π-ring-opening.



Scheme 1.2 Industrial synthesis of Vitamin D_3.[14]

Also, photoredox catalysis has been applied in industry. For instance, the synthesis of LY2784544, a selective JAK2-V617F inhibitor, was accessible through an iridium-photocatalyzed α-arylation of an amine precursor (Scheme 1.3).[16]

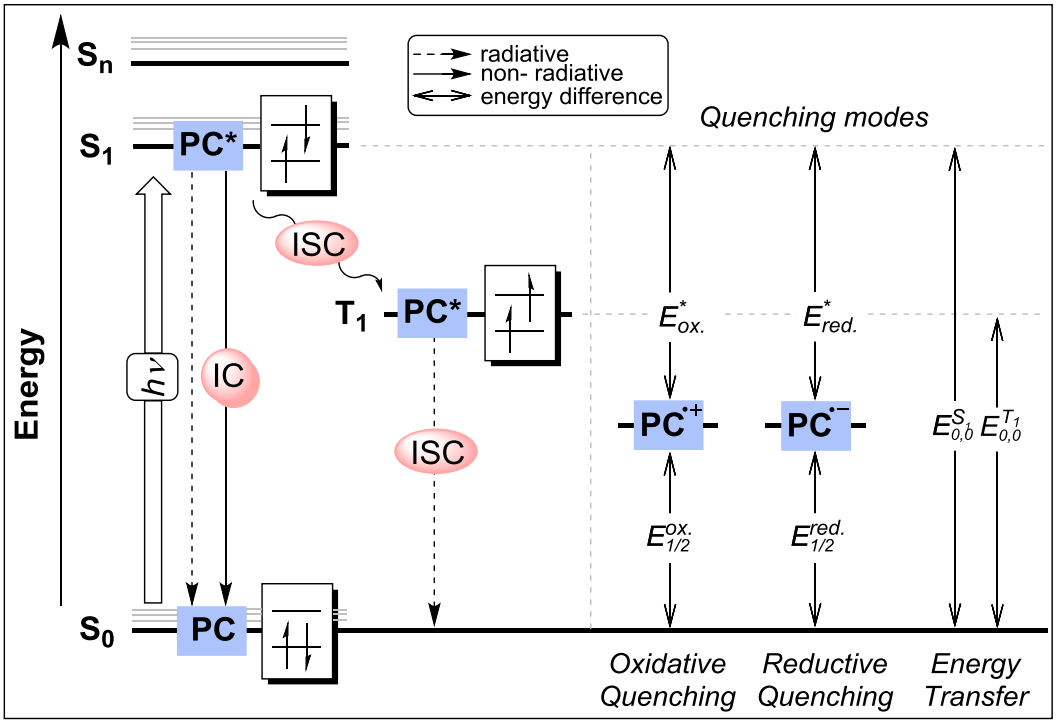


Scheme 1.3 Iridium-photocatalyzed α-arylation step during the synthesis of a precursor of LY2784544.[16]

1.2 Photophysical and electrochemical processes of photocatalysts

For the sake of clarity and simplicity and since photosensitization and photoredox events might not be clearly distinguishable in relevant protocols, photoredox catalysts and photosensitizers are refered to as photocatalysts (**PC**).

First, during a photocatalytic reaction, a photocatalyst **PC** is excited from its singlet ground state ($\mathbf{S_0}$) into an energetically higher singlet excited state by the absorption of a photon ($\mathbf{h\nu}$) of a specific energy (Scheme 1.4). Thus, a variety of singlet excited states with different vibrational energies (S_n) are achieved. According to *Kasha*'s rule, all higher energetic excited states S_n relax back to the lowest energy level of the first excited state ($\mathbf{S_1}$).[17] The first electronic transition from $\mathbf{S_0}$ to $\mathbf{S_1}$ leads to two semi occupied molecular orbitals (**SOMO**). Accordingly, the lack of one electron in the former highest occupied molecular orbital (**HOMO**) in its excited state, refered to as the electron hole, increases its electron affinity and therefore its oxidizing ability. Likewise, owing to the energetically higher laying electron during the excited state of the photocatalyst **PC***, donation to an acceptor molecule is more favorable in contrast to the ground state $\mathbf{S_0}$. Thus, an increase in the reducing capability of the excited state catalyst **PC*** is evident. In case **PC*** is considered as an isolated molecule, two relaxation scenarios from $\mathbf{S_1}$ back to $\mathbf{S_0}$ are possible; either a radiative pathway *via* emission of light (fluorescence) or a non-radiative pathway refered to as internal conversion (**IC**) in form of heat (thermal decay). Additionally, a spin-forbidden intersystem crossing (**ISC**) from $\mathbf{S_1}$ to an energetically lower laying triplet excited state ($\mathbf{T_1}$) is possible. From $\mathbf{T_1}$, a relaxation to $\mathbf{S_0}$ is possible *via* a radiationless IC or a second ISC, also referred to as phosphorescence. It is worth to mention that ISC-events are spin-forbidden and therefore slower by a factor of 10^6 compared to the radiative relaxation from S_1 to S_0 (fluorescence).[18] This is evident through a large difference in magnitude between the lifetime of fluorescence (τ_f = 2-20 ns) and phosphorescence (τ_p up to milliseconds).



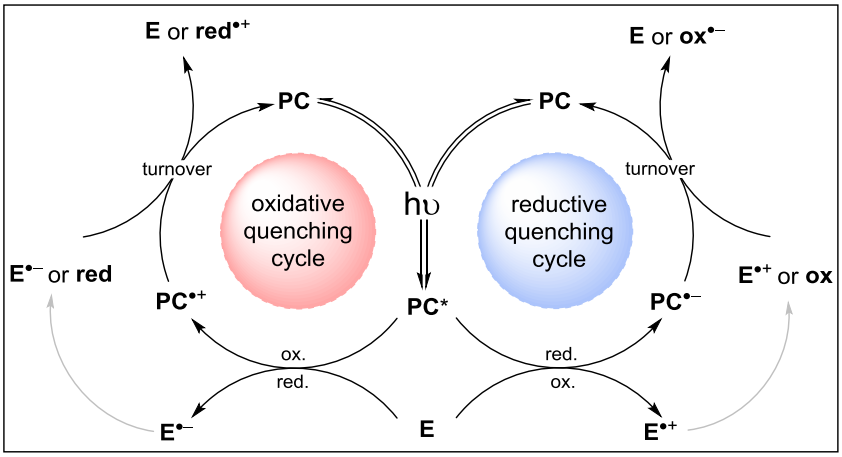
Scheme 1.4 Photophysical and electrochemical processes of photocatalysts.

During a photocatalytic reaction, a substrate (**E**) can interact with a photocatalyst in the excited state **PC*** *via* three different reaction modes. Depending on the nature of the photocatalyst, a redox process involving single electron transfer (**SET**), an atom-transfer (**AT**) or an energy transfer (**EnT**) is prevalent.[19]

Electron transfer photocatalysis, also called photoredox catalysis, makes use of the enhanced redox activity of the excited-state photocatalyst **PC*** and the ability to participate in single electron transfer events.[18] Notably, photoinduced electron transfer (PET) occurs likely from the strong oxidizing and reducing S_1 excited state.

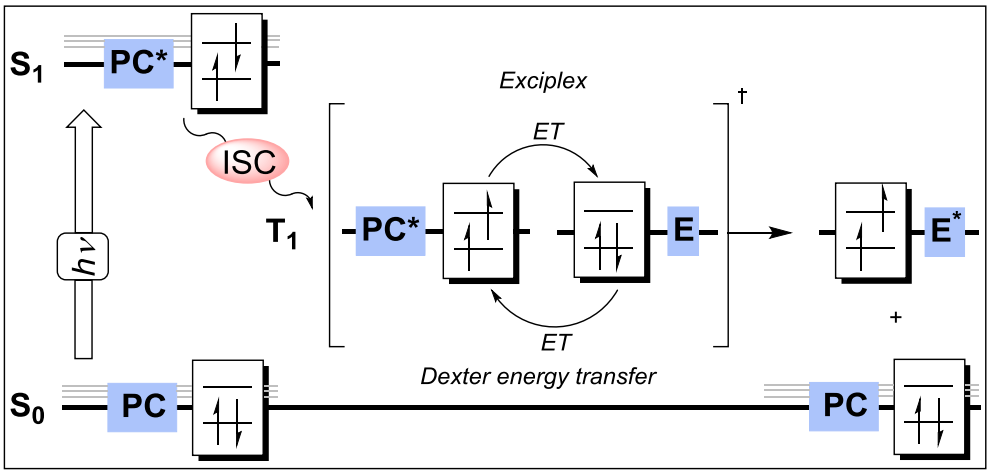
During a photoredox catalyzed event, the single electron transfer can occur through either an oxidative or reductive quenching of the excited state photocatalyst **PC*** (Scheme 1.5). In the course of an oxidative quenching cycle, the excited state photocatalyst **PC*** is oxidized by a substrate **E** in a SET fashion. The transfer of one electron from **PC*** to **E** furnishes the radical anion ($\mathbf{E}^{\bullet-}$) and the oxidized form of the ground state photocatalyst ($\mathbf{PC}^{\bullet+}$). Subsequently, the highly reactive radical intermediate $\mathbf{E}^{\bullet-}$ can undergo the desired chemical transformation. The catalytic turn-over of the formed oxidized ground state photocatalyst $\mathbf{PC}^{\bullet+}$ is accomplished by an electron transfer from an intermediate of substrate **E** or a sacrificial electron donor (**red**). This event closes the catalytical cycle providing the product and regenerating the photocatalyst in its ground state **PC**. In case of a reductive quenching cycle, the excited state photocatalyst **PC*** is reduced by a substrate **E** to form the radical

cation ($E^{\bullet+}$) and the reduced form of the photocatalyst ($PC^{\bullet-}$). The turnover of the reduced photocatalyst $PC^{\bullet-}$ is accomplished in a similar fashion to the oxidative quenching cycle by an electron transfer from an intermediate of substrate **E** or a sacrificial electron acceptor (**ox**), affording hereby an efficient turn-over of the photocatalyst.[18]



Scheme 1.5 Oxidative and reductive quenching cycles of a photoredox catalyst.

On the other hand, energy transfer **EnT** photocatalysts act by transferring energy from their excited state form **PC*** to the respective acceptor substrate **E** (Scheme 1.6).[20] In this case, a bimolecular quenching process in form of energy transfer **EnT** is rational from the triplet excited state T_1 owing to the longevity of T_1 of the photocatalyst ($\tau_T > 100$ ns). After the formation of an encounter complex between PC^* and acceptor **E** in solution, a double electron transfer within the formed exciplex, also referred to as Dexter energy transfer, takes place.[20, 21] This event excites acceptor **E** to a higher energy state (**E***).[22] Diffusion out of the solvent complex releases excited **E*** and ground-state photocatalyst **PC**.

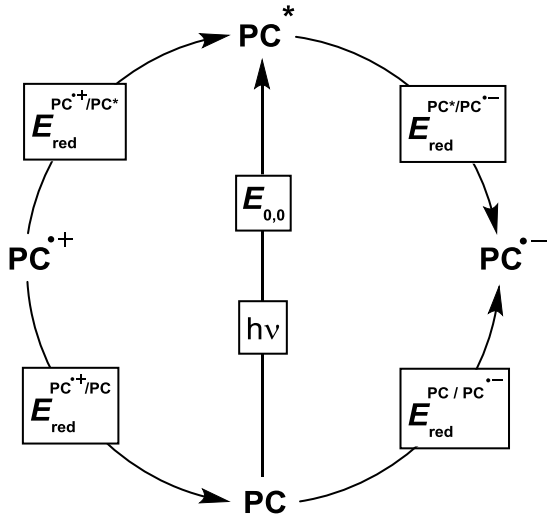


Scheme 1.6 General scheme of a photocatalyzed reaction *via* energy transfer.

1.3 Feasibility of photo-induced electron transfer processes

In order to achieve the desired reactivity in a photocatalytic reaction, the photophysical and electrochemical properties of both photocatalyst and reactants must be chosen carefully.[18] First, a suitable light source is determined by comparing the emission spectrum of the considered light source and the absorption spectrum of the photocatalyst. An overlap of both spectra is essential to ensure an excitation of the photocatalyst **PC**. As for the photoredox ability of potential photocatalysts, the electrochemical data of both photocatalyst excited- and ground state as well as of reactant **E** are considered.

The feasibility of photo-catalyzed transformations depends on the electrochemical potentials of the involved reactants. The reduction potential of the excited state photocatalyst **PC*** can be calculated using two methods. The first method relies on the comparison of excited-state electron transfer rates to molecules with known ground-state redox potentials.[23] The second method, being the most utilized, is an estimation of the redox potentials of **PC*** using the equations (Scheme 1.7, Eq. 2 in case of oxidation of **PC***, Eq. 3 in case of reduction of **PC*)** derived from the general equation of the Gibbs energy of photoinduced electron transfer (Scheme 1.7, Eq. 1) after the omission of the electrostatic work term ω.[18, 24]



Gibbs Energy of photoinduced electron transfer:

$$\Delta G_{PET} = -F\,[E_{ox}(D^{\bullet+}/D) - E_{red}(A/A^{\bullet-})] - \omega - E_{0,0} \quad \text{(Eq. 1)}^{\dagger}$$

E_{ox}^{*} = oxidation potential of **PC***:

$$E_{ox}^{*} = E_{ox}(PC^{\bullet+}/PC^{*}) = E_{ox}(PC^{\bullet+}/PC) - E_{0,0} \quad \text{(Eq. 2)}$$

E_{red}^{*} = reduction potential of **PC***:

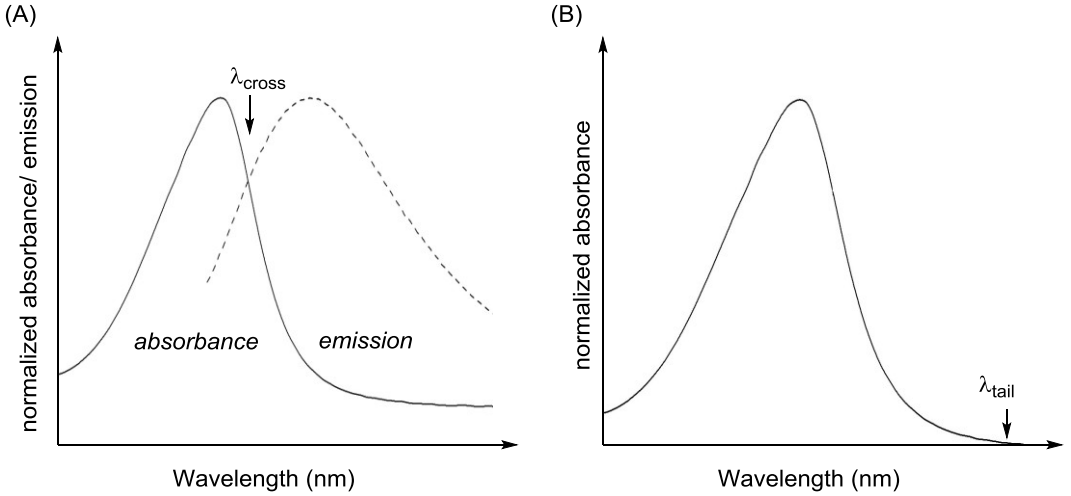
$$E_{red}^{*} = E_{red}(PC^{*}/PC^{\bullet-}) = E_{red}(PC/PC^{\bullet-}) - E_{0,0} \quad \text{(Eq. 3)}$$

† A= electron acceptor, D= electron donor

Scheme 1.7 Electrochemical processes and redox potential equations of a photoredox catalyst.

The excited state energy ($E_{0,0}$) of the photocatalyst **PC**, which is needed for the calculation of the corresponding redox potentials, can be approximated spectroscopically (Scheme 1.8). An estimation of $E_{0,0}$ is possible by identifying the photon energy of the wavelength at the crossing point between the absorption and emission spectra of a given species (Scheme 1.8,

entry A), which is a good approximation of the energy difference between the lowest vibrational level of ground state S_0 and the excited state S_n or T_n. In addition, in case of absence of the UV-vis spectra electronic transitions, $E_{0,0}$ can be determined by considering the long wavelength from the tail of the corresponding absorption spectrum (Scheme 1.8, entry B).[25] Excited state energy $E_{0,0}$ values in eV can be obtained readily by employing the equation for photon energy (Scheme 1.8, Eq. 1). Furthermore, ground state redox potentials of the employed photocatalyst **PC**, essential for the calculation of the redox potentials of the excited state species, are accessible by cyclic voltammetry measurements.[26]

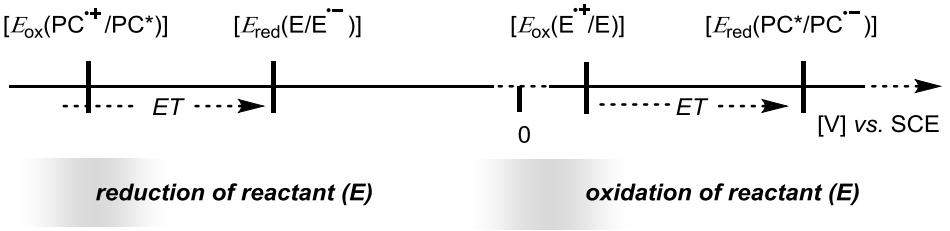


$$E_{0,0}\,(PC^{*}/PC) = h\nu = hc / \lambda \qquad \text{(Eq. 1)}$$

Scheme 1.8 Spectroscopical determination and calculation of the excited state energy ($E_{0,0}$).

Having the electrochemical potentials of ground- and excited state **PC** in hand in addition to the corresponding redox values of a reactant **E**, the thermodynamic feasibility of a light-driven reaction can be assessed.

In case the oxidation of a reactant **E** is desired during a photocatalytic reaction, the reduction potential ($\boldsymbol{E^{*}_{red}}$) of the excited-state photocatalyst **PC*** must be more positive compared to the oxidation potential ($\boldsymbol{E_{ox}}$) of reactant **E** ($\boldsymbol{E^{*}_{red} > E_{ox}}$) (Scheme 1.9, right side). Likewise, if the reduction of reactant **E** is to be feasible, the excited state oxidation potential ($\boldsymbol{E^{*}_{ox}}$) of photocatalyst **PC*** must be greater negative than the reduction potential ($\boldsymbol{E_{red}}$) of reactant **E** ($\boldsymbol{E^{*}_{ox} < E_{red}}$) to ensure an efficient electron transfer (Scheme 1.9, left side).

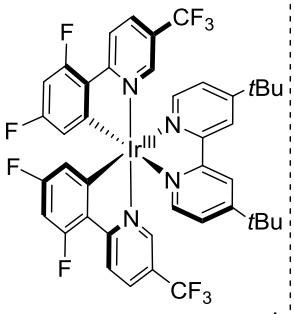


Scheme 1.9 Thermodynamic feasibility of electron transfer during a photocatalytic reaction.

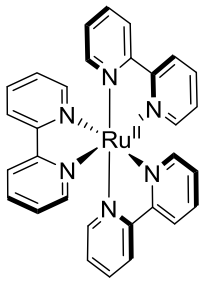
1.4 Pyrimidopteridine *N*-oxides as photoredox catalysts

During the last century, a significant number of organic dyes and transition metal complexes, with various electrochemical properties, were developed and used as powerful redox- and energy transfer photocatalysts (Scheme 1.10).[27-30] Notable examples of transition metal photocatalysts include polypyridyl iridium, ruthenium and copper complexes.[31, 32] As for organo- photocatalysts, acridinium-, xanthene- and benzophenone-based photocatalysts represent some of the most famous and well-investigated examples in the field of visible-light photocatalysis.[18, 27, 33]

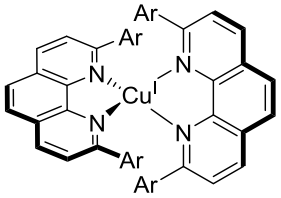
■ *Transition-Metal Photocatalysts:*



Ir[dF(CF$_3$)ppy]$_2$(dtbbbpy)$^+$
$E_{1/2}$ (PC*/PC$^{\bullet-}$) = +1.21 V
$E_{1/2}$ (PC$^{\bullet-}$/PC) = -1.37 V

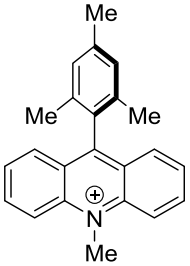


Ru(bpy)$_3^{2+}$
$E_{1/2}$ (PC*/PC$^{\bullet-}$) = +0.77 V
$E_{1/2}$ (PC$^{\bullet-}$/PC) = -1.33 V

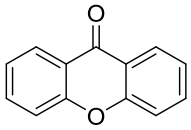


Cu(dap)$_2^+$
$E_{1/2}$ (PC$^+$/PC) = +0.62 V
$E_{1/2}$ (PC$^+$/PC*) = -1.43 V

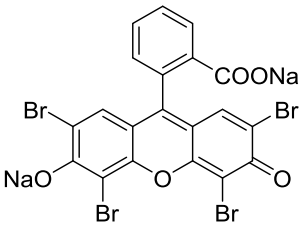
■ *Organo-Photocatalysts:*



Mes-Acr-Me$^+$
$E_{1/2}$ (PC*/PC$^{\bullet-}$) = +2.08 V
$E_{1/2}$ (PC$^{\bullet-}$/PC) = -0.57 V



Xanthone
$E_{1/2}$ (PC*/PC$^{\bullet-}$) = +1.76 V
$E_{1/2}$ (PC$^{\bullet-}$/PC) = -1.65 V



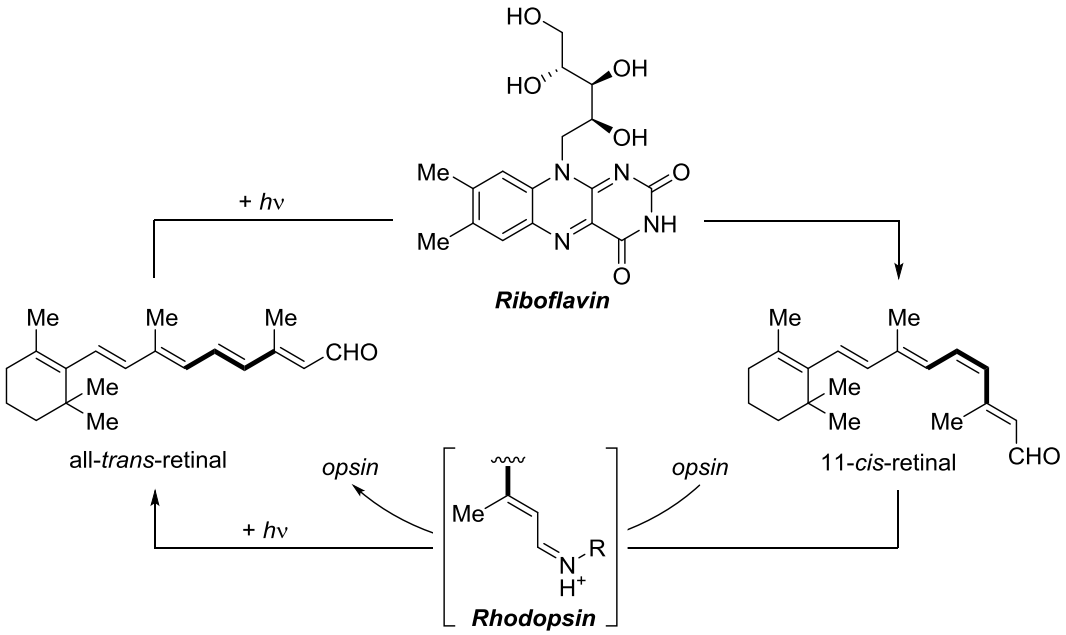
Eosin Y
$E_{1/2}$ (PC*/PC$^{\bullet-}$) = +0.83 V
$E_{1/2}$ (PC$^{\bullet-}$/PC) = -1.13 V

Scheme 1.10 Examples of transition-metal-based and organo-photocatalysts and their redox potentials.[18, 31]

These tailored photocatalysts cover a wide range of redox potentials that facilitate photomediated electron transfer (PET) processes in addition to energy- and atom transfer

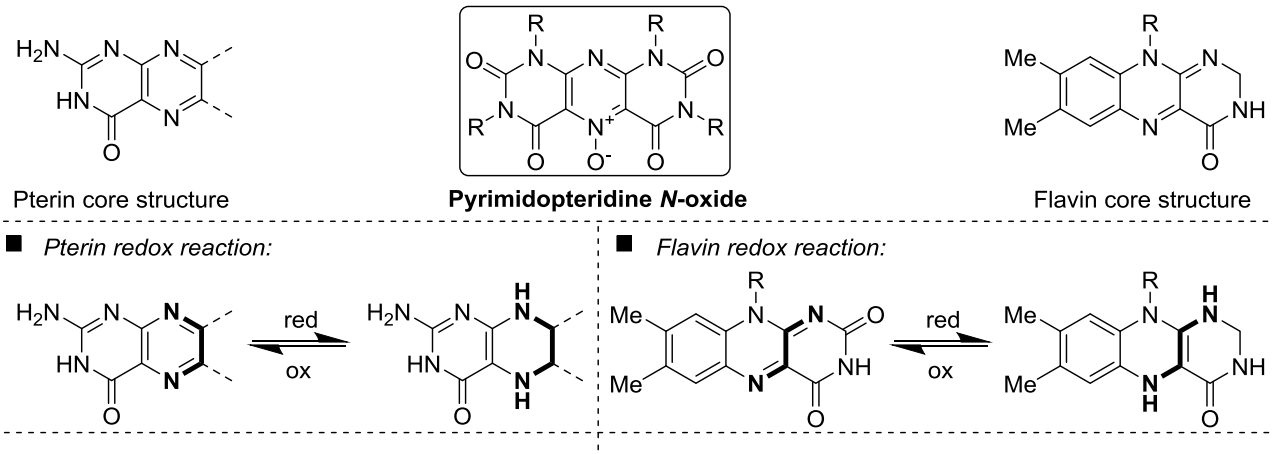
during a photomediated transformation.[18] For example, Eosin y (Scheme 1.10) with an excited state oxidation potential of $E^*_{ox} = -1.15$ V *vs.* SCE in MeOH is a potent reducing photocatalyst with an average oxidation potential.[18] On the other hand, 9-mesityl-10-methylacridinium (Mes-Acr-Me$^+$) (Scheme 1.10) possesses a high oxidizing ability in its excited state ($E^*_{red} = +2.08$ V *vs.* SCE in MeCN) and is therefore a good oxidant during PET events. In addition, photocatalysts like tris(bipyridine)ruthenium (II) Ru(bpy)$_3^{2+}$ are able to engage in energy transfer- as well as PET events.

Beside previously mentioned synthesized photocatalysts, natural analogs exhibit also outstanding chemical reactivities as photocatalysts. Among prominent examples, riboflavin also know as vitamin B_2, acts as a photocatalyst during the contra-thermodynamic (*E*→*Z*) isomerization of retinal, a polyene chromophore indispensable for the mammalian visual cycle (Scheme 1.11).[34, 35]



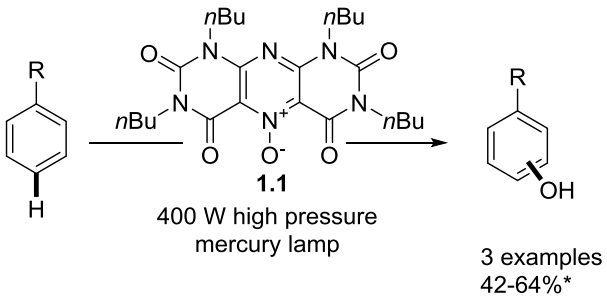
Scheme 1.11 Mammalian visual cycle *via* (*E*→*Z*) isomerization of retinal with riboflavin.

In the early 1970s, *Maki et al.* primarily reported the synthesis of *n*-butyl pyrimidopteridine *N*-oxide (**1.1**).[36] Pyrimidopteridine *N*-oxides (PPTNO) are heterocyclic molecules that are structurally related to pterins and flavins, two heterocycles known as cofactors in cytochrome-P450-enzymes and to participate in redox reactions (Scheme 1.12).[26, 37, 38]



Scheme 1.12 PPTNO structural similarity to flavin and pterin core structures and corresponding redox activity.

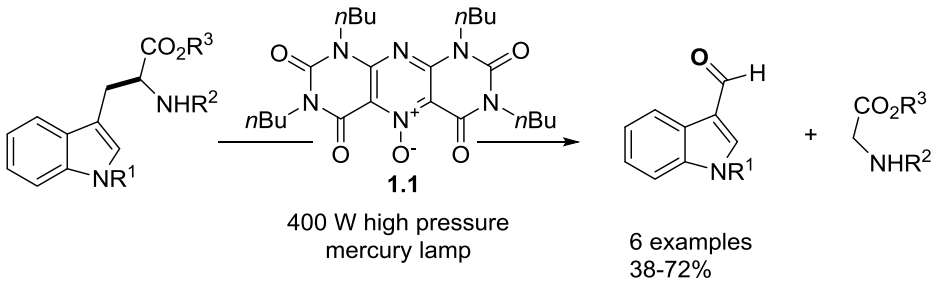
Later, *Maki* and co-workers described the synthetic application of *n*-butyl pyrimidopteridine *N*-oxide (**1.1**) as a stoichiometric photochemical reagent in a variety of oxidative transformations. The photochemical hydroxylation of a large excess of benzene derivatives was accessible *via* an oxygen atom transfer from **1.1** (Scheme 1.13).[28, 29]



* Yields are calculated based on the amount of consumed **1.1**

Scheme 1.13 Photochemical hydroxylation of benzene derivatives using *N*-oxide derivative 1.1.[28]

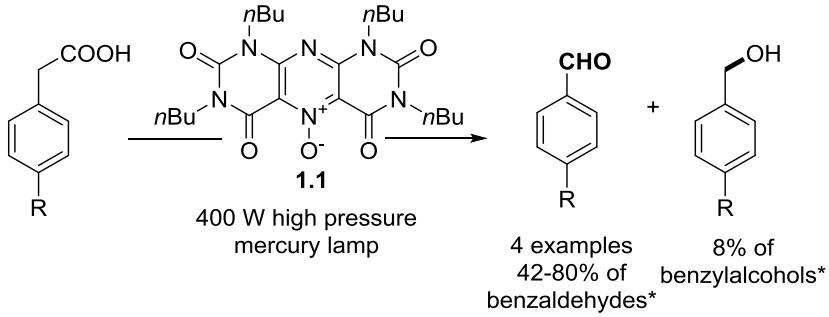
In addition, photolysis of tryptophan-derivatives in the presence of stoichiometric amounts of **1.1** and catalytic amounts of acid resulted in an oxidative C–C bond cleavage of tryptophan derivatives, generating 3-indolcarboxaldehydes and the corresponding glycine-derivatives (Scheme 1.14).[39]



Scheme 1.14 Photocatalytic C–C bond cleavage of tryptophan derivatives using *N*-oxide derivative 1.1.[40]

In later reports, *Maki et al*. reported an oxidative decarboxylation protocol of phenyl acetic acid derivatives in the presence of stoichiometric amounts of n-butyl substituted **1.1**.

This methodology allowed the generation of benzaldehyde derivatives under UV-/visible-light *via* a singlet-excited state (Scheme 1.15).[40, 41]



* Yields are calculated based on the amount of consumed **1.1**

Scheme 1.15 Photocatalytic oxidative decarboxylation of phenylacetic acid derivatives using (1.1).[41]

Yet, since the early reports of *Maki et al.*, no additional analysis of pyrimidopteridine *N*-oxide derivatives regarding their photoredox activity and applicability as photoredox catalysts was conducted.

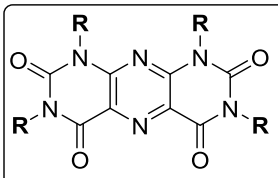
Lately, differently substituted pyrimidopteridine *N*-oxide derivatives (**1.1-1.4)** and their deoxygenated analogs (**1.5-1.8**) were synthesized and characterized by the *Pospech* group.[38] The corresponding photo- and electrochemical data are showcased in Table 1.1. The absorption maximum of the synthesized derivatives lies within the range of $\lambda_{max}^{abs} =$ 359-371 nm, rendering them suitable to UV-A/visible-light excitation. No significant difference in the excited state redox potentials of the synthesized *N*-oxide derivatives (**1.1**-**1.4**) was observed. Also, the effect of different substitution on the excited state redox potentials of the deoxygenated derivatives (**1.1a**-**1.4a**) is minimal, accounting up to a difference of 0.04 V for the excited state reduction potentials and 0.58 V for the excited state oxidation potentials. Calculated excited state reduction potentials of pyrimidopteridine *N*-oxide derivatives vary between ($E_{red}^{*} = +2.30–(+2.33)$ V *vs.* SCE in MeCN), which implies a strong oxidative ability capable of substracting an electron from a wide range of organic molecules.[26] Furthermore, the low lying ground state reduction potential of newly synthesized photocatalysts ($E_{1/2}^{red} = –0.91–(–0.95)$ V *vs.* SCE in MeCN) enables a smooth and facile turnover of the reduced photocatalyst. In the following two chapters, the suitability of pyrimidopteridine *N*-oxides and their deoxygenated analogs as photoredox catalysts was examined.

Table 1.1 Photophysical and electrochemical data of PPTNO derivatives (1.1-1.4) and the corresponding deoxygenated analogues (1.1a-1.4a).

PPTNO:

R = Bu (**1.1**)
Pr (**1.2**)
Me (**1.3**)
Ph (**1.4**)

Pyrimidopteridine *N*-oxide (PPTNO)



Pyrimidopteridine (PPT)

PPT:

R = Bu (**1.1a**)
Pr (**1.2a**)
Me (**1.3a**)
Ph (**1.4a**)

Compound	λ_{max}^{abs}	Excited state energy	Ground state redox potential		Excited state redox potential	
	[nm]	$E_{0,0}^{S1}$ [eV][a]	$E_{1/2}^{red}$ [V][b]	$E_{1/2}^{ox}$ [V][b]	E_{red}^{*} [V][c]	E_{ox}^{*} [V][d]
1.1	371	+3.25	−0.92	+2.47	+2.33	−0.78
1.1a	363	+3.31	−1.59	+1.82	+1.72	−1.49
1.2	370	+3.25	−0.95	+2.42	+2.30	−0.83
1.2a	363	+3.31	−1.59	+1.80	+1.72	−1.51
1.3	368	+3.24	−0.91	+2.42	+2.33	−0.82
1.3a	361	+3.31	−1.58	+1.82	+1.73	−1.49
1.4	366	+3.25	−0.93	+2.33	+2.32	−0.92
1.4a	359	+3.30	−1.54	+1.87	+1.76	−1.43

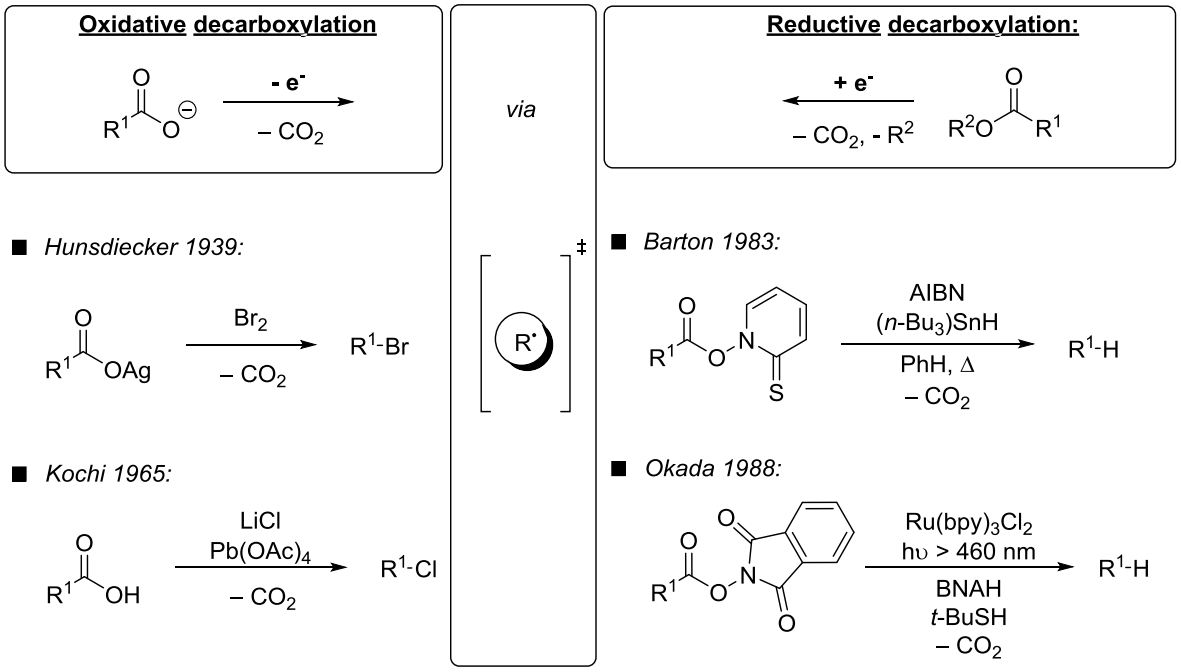
[a]values corresponding to the energy at the intersection of the excitation and emission spectra. [b]Potentials were measured using cyclicvoltammetry (CV) and differential pulse voltammetry (DPV) relative to Fc^+/Fc; deoxygenated compounds (1.1a-1.4a) were measured by Tobias Täufer; referenced to SCE by adding 0.42 V to the value relative to Fc^+/Fc.[26] [c] Calculated by $E_{red}^{*} = E_{0,0}^{S1} + E_{1/2}^{red}$. [d] Calculated by $E_{ox}^{*} = E_{1/2}^{ox} - E_{0,0}^{S1}$.

2 Pyrimidopteridine *N*-oxide photo-mediated decarboxylative Giese-type addition

2.1 Introduction

Carboxylic acids and their derivatives have long served as a multifaceted feedstock to construct valuable carbon frameworks.[42] Advantages like low cost, wide availability and noticeable bench stability turned them into ideal substrates.[43, 44] The carboxyl group, as such, can be used as a regioselective traceless leaving group *via* extrusion of carbon dioxide (CO_2) which readily evaporates from the reaction mixture. The radical nature of this transformation allows the construction of a multitude of carbon–carbon or carbon–heteroatom bonds.[45] Nevertheless, the decarboxylation of carboxylic acids requires often rather harsh and forcing conditions (e.g. high temperatures, high-energy UV light, stoichiometric amounts of oxidants and/or strong acids/bases) which impedes late stage functionalization of labile carboxylic acid frameworks and limits its use.[46]

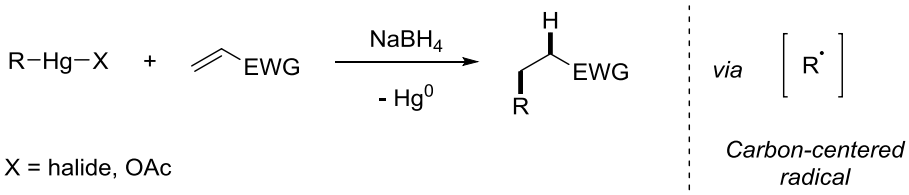
Initial decarboxylation reactions were reported by *Hunsdiecker* and *Kochi* furnishing haloalkanes from alkane carboxylic acids (Scheme 2.1).[47, 48] Carboxylate silver salts or strong oxidizing agents like lead(IV) acetate in addition to a halide source were essential to promote the oxidative radical decarboxylation. Later on, *Barton et al.* disclosed a novel reductive decarboxylation methodology through the activation of the carboxylic acid moiety from thiohydroxamate esters.[48] Heating the esters in the presence of azobisisobutyronitrile (AIBN) as a radical initiator and tributyltin hydride (*n*-Bu_3SnH) as a hydrogen-atom donor afforded the protodecarboxylated product. Successive efforts from *Hasebe* and *Tsuchiya* led to a photomediated variant of the reductive decarboxylation by employing oxime esters as activated carboxylic acids.[49] A similar strategy adopted by *Okada et al.* unveiled a robust visible-light mediated reductive decarboxylation of *N*-acyloxy phthalimides (NHPI-esters), which tolerates aqueous solvents in contrast to prior methods.[50, 51] NHPI-esters, regarded as redox-active-esters (RAE) capable of engaging in single electron transfer reactions and accepting an electron, can serve as a radical precursor to furnish the corresponding radicals.



Scheme 2.1. Evolution of oxidative and reductive decarboxylation methods over time.[47-51]

Since the middle of the last century, tremendous development has been made in the field of decarboxylative coupling. Especially, transition-metal catalyzed methodologies using palladium and copper reagents, were intensively reported.[45, 52, 53] Yet, given the progress of visible-light induced photochemical transformations in the last years and the efforts to depict more environmentally-friendly methodologies, photocatalytic decarboxylation variants emerged as a key pathway to forge new C–C and C–heteroatom bonds.[54] For example, differently hybridized C–C frameworks are accessible, using a broad range of radical acceptors such as alkyne-, aryl-, alkenyl- and alkyl substructures.[55-58]

Within this framework, one possibility to generate $C(sp^3)$–$C(sp^3)$ bonds is the trapping of a nucleophilic neutral carbon centered radicals with electron-deficient olefins, also referred to as *Giese*-type reaction.[59, 60] The seminal report described by *B. Giese* discloses the formation of alkyl carbon-centered radicals by a radical chain reaction of alkyl mercury salts and sodiumborohydride ($NaBH_4$), followed by a subsequent 1,4-addition to an electron-deficient unsaturated alkene (Scheme 2.2). A hydrogen atom transfer to the formed radical intermediate gave access to the alkylated products.[61]



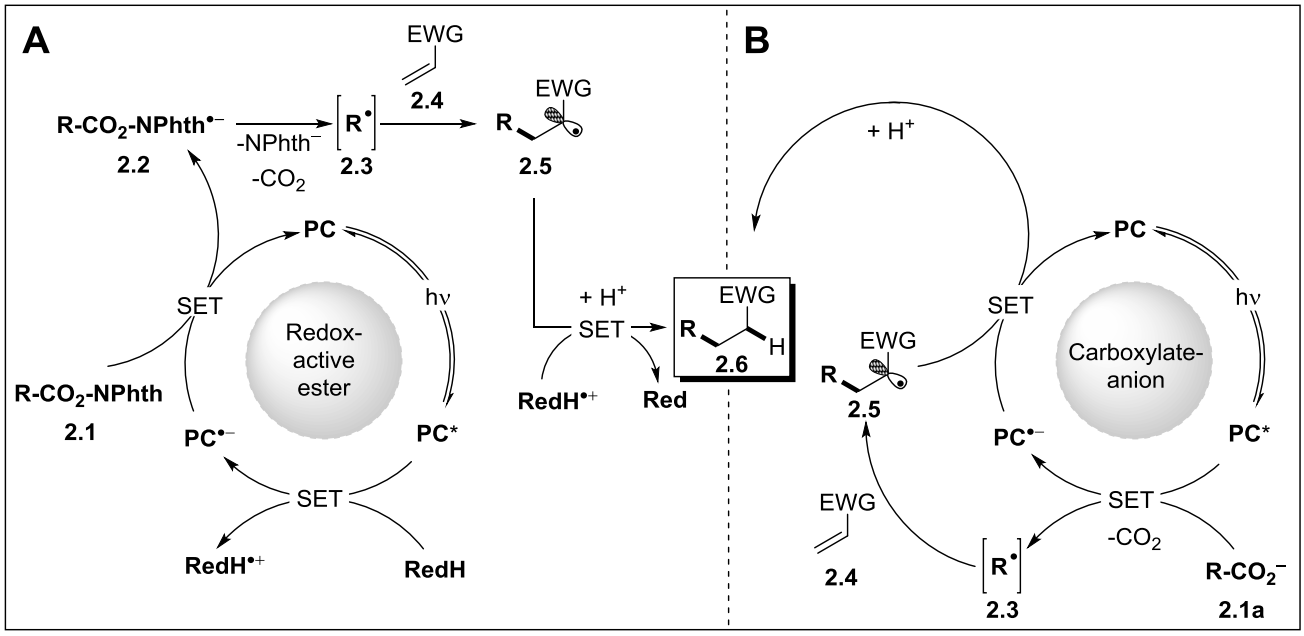
Scheme 2.2. General scheme of the initial work of *B. Giese*.[60, 61]

A photocatalyzed decarboxylative variant of the *Giese*-addition to olefins starting from carboxylic acids would eliminate the initial usage of stoichiometric heavy metal salts and provide a reaction conducted under mild conditions. Accordingly, this alternative would offer a more environmentally benign option for the alkylation of olefins using alkyl carboxylic acids. In order to generate carbon-centered radicals by a photocatalyzed decarboxylation means, two conceivable approaches are possible.

Carboxylic acids, as such, possess high oxidation potentials ($E_{ox} \approx +2.0$ V *vs.* SCE in MeCN) and are therefore challenging to oxidize.[26] Hence, an activation of the carboxyl moiety is essential to render the decarboxylation thermodynamically feasible. One way to activate the carboxylic acid is *via* a base-promoted deprotonation to the corresponding carboxylate, which decreases its oxidation potential (e.g. Boc-Pro-O$^-$; $E_{ox} = +0.95$ V *vs.* SCE in MeCN) and facilitates electron transfer.[26, 62] Another method of activation is by the formation of redox-active esters (RAE), resulting in a more positive reduction potential (Boc-Pro-O-NPhth; $E_{red} = -1.20$ V *vs.* SCE in MeCN); ergo, a higher tendency to gain an electron and engage in an oxidative quenching of the photocatalyst. The choice of activation mode depends strongly on the reaction conditions and the electrochemical properties of utilized photocatalysts.

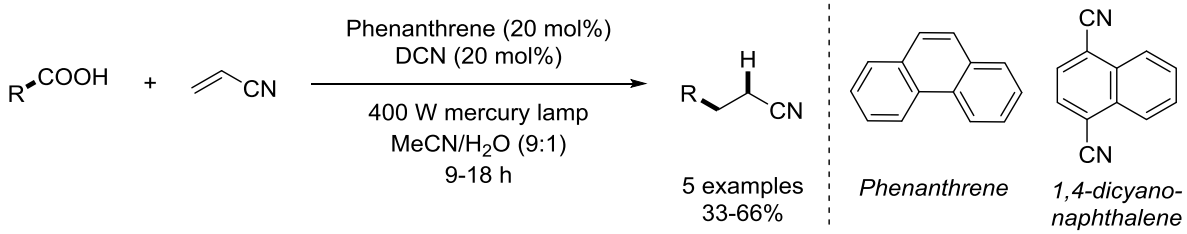
Therefore, two different reaction mechanisms are possible (Scheme 2.3). The first mechanism requires a preactivation of the carboxylic acid moiety as a RAE (Scheme 2.3, entry A). First, the irradiation of a photoredox catalyst **PC** using an appropriate light source ($h\nu$) generates the excited state photocatalyst **PC***. An added sacrificial electron donor additive (**RedH)** quenches the excited photocatalyst **PC*** in a SET fashion. Hereby, the reduced form of the photocatalyst **PC**$^{\bullet-}$ and the oxidized form of (**RedH**) are formed. Next, the photocatalyst **PC** is regenerated from the reduced form **PC**$^{\bullet-}$ by an SET to the *N*-hydroxyphthalimide-ester **2.1**. Subsequently, cleavage of the N–O bond of radical anion **2.2** followed by a rapid decarboxylation leads to the formation of carbon dioxide, phthalimidyl anion and the corresponding carbon-centered radical **2.3**. The nucleophilic neutral radical **2.3** attacks the electron-deficient olefin **2.4** generating radical intermediate **2.5** which, upon hydrogen atom abstraction from radical cation **RedH**$^{\bullet+}$, furnishes desired alkylated product **2.6**. On the other hand, the second mechanism (Scheme 2.3, entry B) proceeds directly from the carboxylate form **2.1a** of the corresponding carboxylic acid without the need for a preactivation as a RAE. The addition of a base to shift the equilibrium

to the side of the conjugate base of the corresponding carboxylic acid, in this case the carboxylate, is beneficial. Upon the generation of excited state photocatalyst **PC*** from **PC**, a direct SET from carboxylate **2.1a** to the excited photocatalyst **PC*** takes place. Quick decarboxylation of the generated carboxylate radical cation furnishes carbon-centered radical intermediate **2.3** and the reduced form of the photocatalyst $\mathbf{PC^{\bullet -}}$. Following nucleophilic attack of radical intermediate **2.3** towards olefin **2.4** provides intermediary radical species **2.5**. Next, quenching of the radical intermediate **2.5** by an SET from the reduced photocatalyst $\mathbf{PC^{-\bullet}}$ and subsequent protonation delivers product **2.6**.



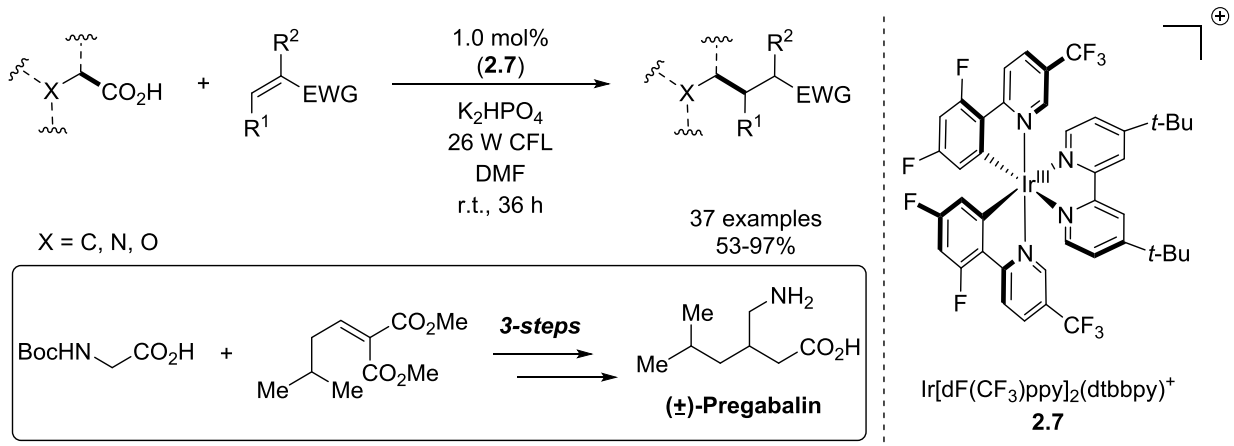
Scheme 2.3. General mechanism of (A) redox-active ester- and (B) base-promoted photocatalyzed decarboxylative *Giese*-addition to electron-deficient olefins.

Seminal reports of a metal-free photocatalyzed decarboxylative radical addition to an electron-deficient alkene was first reported by *Yoshimi et. al* (Scheme 2.4).[63] Catalytic amounts of phenanthrene and 1,4-dicyanonaphthalene as an electron-acceptor were sufficient to induce the formation of alkyl radicals *via* PET and subsequent decarboxylation when irradiated with a 400 W high-energy mercury lamp.



Scheme 2.4 Photocatalytic decarboxylative addition of alkyl radical to an electron-deficient olefin.[63]

After a while, a transition-metal photocatalyzed decarboxylative *Giese*-type reaction was described by *MacMillan* and co-workers in 2014 (Scheme 2.5).[64]

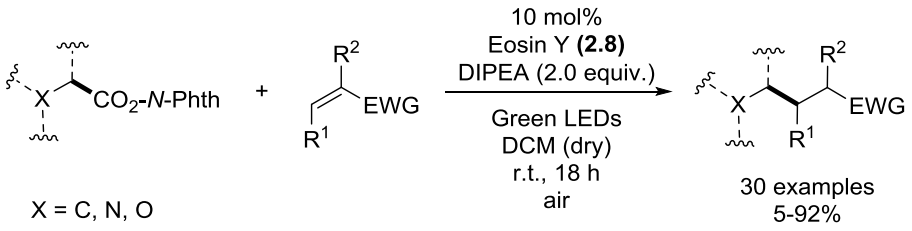


Scheme 2.5 Iridium photocatalyzed decarboxylative *Giese*-type reaction and further application in the synthesis of Pregabalin.[64]

An iridium photoredox catalyst, in this case $Ir[dF(CF_3)ppy]_2(dtbbpy)^+$ (**2.7**) ($E_{1/2}^{*III/II} = +1.21$ V *vs.* SCE in MeCN) proved to be suitable for the decarboxylation and subsequent addition of a wide variety of acyclic and cyclic alkyl- and α–heteroatom carboxylic acids to different Michael-acceptors.

A racemic synthesis of pregabalin, an anticonvulsant drug, was demonstrated through a three-step synthesis starting from *N*–Boc protected glycine and an electron-deficient Michael-acceptor (Scheme 2.5).

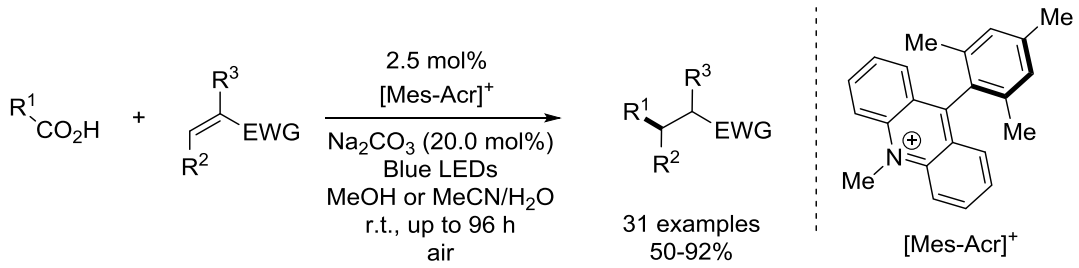
Two years later, *König* and *Schwarz* reported a metal-free, photocatalytic reductive decarboxylative protocol for the alkylation of preactivated carboxylic acids (Scheme 2.6).[65] This transformation was accessible using Eosin Y (**2.8**) (E^*(Eosin Y^*/Eosin $Y^{\cdot-}$) = +0.83 V *vs.* SCE in MeCN:H_2O 1:1) as a photoredox catalyst. An activation of the carboxyl moiety as a redox-active ester as well as the presence of super-stoichiometric amounts of a sacrificial reductant were indispensable for the reaction to take place.



Scheme 2.6 Metal-free, photocatalytic decarboxylative alkylation of pre-activated carboxylic acids.[65]

Also, *Gonzalez-Gomez* and co-worker showcased in 2017 a metal-free oxidative photocatalytic methodology using $[Mes\text{-}Acr]^+$ as a photocatalyst (Scheme 2.7).[66] The alkylation of electron-deficient alkenes was possible while using non-activated carboxylic

acids and catalytic base amounts. Yet, two different reaction systems were employed for the screening of electron-deficient alkenes and carboxylic acids. Solvent variation as well as different reactant loadings and prolonged reaction times (up to 96 hours), along with repeated addition of both photocatalyst and base limit the applicability of this protocol.

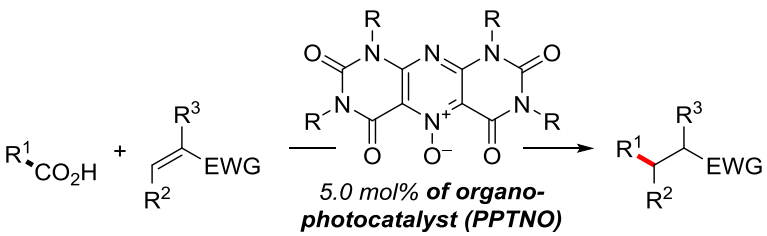


Scheme 2.7 Metal-free, oxidative, visible-light mediated decarboxylative *Giese*-type reaction.[66]

2.2 Objectives

The formation of new C–C bonds plays a pivotal role in organic chemistry. Especially, decarboxylative transformations present a versatile methodology for the construction of complex organic motifs.

Inspired by the precedent work of our group, we surmised that pyrimidopteridine *N*-oxide derivatives **1.1-1.4** and their deoxygenated analogues **1.1a-1.4a** would operate efficiently in a photocatalytic decarboxylative *Giese*-type addition to electron-deficient alkenes. This protocol would offer an atom-economical and inexpensive methodology for the alkylation of different electron-deficient olefins using widely abundant carboxylic acids (Scheme 2.8). Advantages like the high atom economy of this transformation, translated by the lack of stoichiometric waste products, as well as the metal-free nature would offer a more environmentally friendly method as compared to previous reports. In addition, the synthetic applicability is probed by using pharmaceutical- and complex natural product-derived carboxylic acids as substrates. Furthermore, attempts to lower the loading of needed base are envisioned.

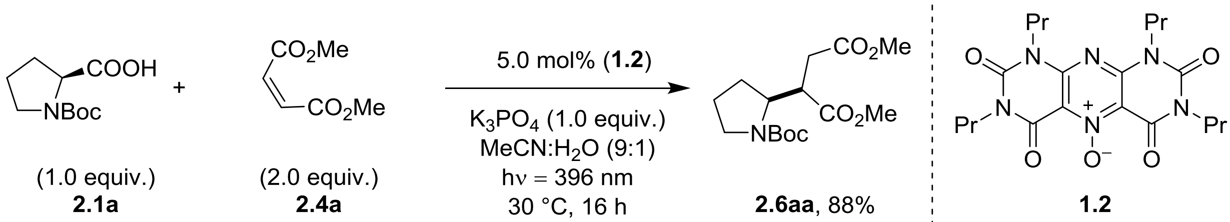


Scheme 2.8 General scheme of the pyrimidopteridine *N*-oxide- photocatalyzed decarboxylative *Giese*-addition.

2.3 Results and discussion

2.3.1 Optimization of the reaction conditions

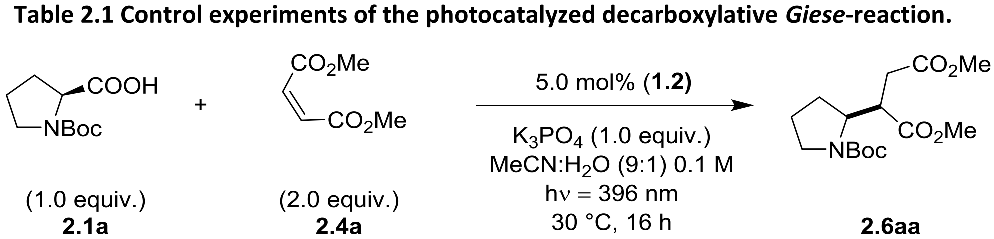
To evaluate pyrimidopteridine *N*-oxides **1.1-1.4** and their deoxygenated analogues **1.1a-1.4a** as photoredox catalysts in the decarboxylative *Giese*-type reaction, control experiments were carried out using a model reaction (Scheme 2.9). This reaction consisted of boc-*L*-proline (**2.1a**) as the carboxylic acid component, dimethyl maleate (**2.4a**) as the electron-deficient alkene and equimolar amounts of tripotassium phosphate. Catalytic amounts (5.0 mol%) of *n*-propyl derivative **1.2** was used as a photocatalyst. The reaction was conducted in a 9:1 mixture of MeCN:H_2O and irradiated with UV-light (396 nm) for 16 hours.



Scheme 2.9 Model reaction of the PPTNO photoredox catalyzed decarboxylative *Giese* reaction.

The desired product **2.6aa** was obtained in a very good yield of 88% with no modification of standard conditions (Table 2.1, entry 1). To varify the photocatalytic nature of this reaction, various alterations from standard conditions were applied (Table 2.1). In the absence of photocatalyst **1.2** or UV-light, no product formation was observed (Table 2.1, entries 2 and 3). Furthermore, the removal of the base from the reaction mixture yielded only 10% of product **2.6aa** (Table 2.1, entry 4). This is attributed to the slightly shifted acid-base equilibrium towards the corresponding carboxylate form due to the basicity of the catalyst **1.2**.

Table 2.1 Control experiments of the photocatalyzed decarboxylative *Giese*-reaction.

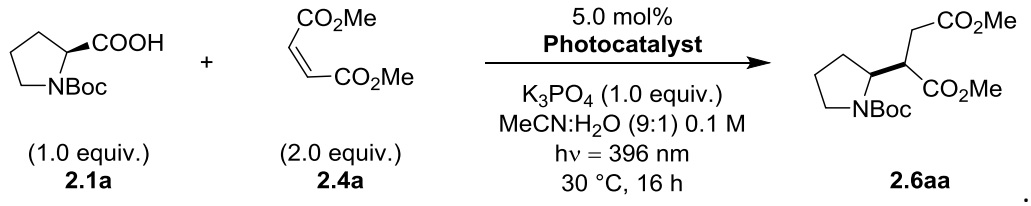


Entry	Alteration from standard conditions	Yield[a,b]
1	none	96% (88%)
2	without photocatalyst (**1.2**)	n.d.
3	In the dark/ without light	n.d.
4	without base	10%

[a] Yields were determined by GC using biphenyl as internal standard. Yields in parentheses represent isolated yields. [b]

Next, optimization of the reaction conditions was conducted by modification of solvent, photocatalyst and catalyst loading. Also, different bases and the amount of base as well as the molarity of the reaction were examined. First, differently substituted pyrimidopteridine *N*-oxides **1.1-1.4** and their deoxygenated analogues **1.1a-1.4a** were screened employing standard reaction conditions (Table 2.2). Propyl- and butyl-substituted PPTNO derivatives (**1.1** and **1.2**) furnished the product **2.6aa** in very good yields up to 88% isolated yield (Table 2.2, entry 1 and 3). Methyl- and phenyl-PPTNO's (**1.3** and **1.4**) delivered the desired product **2.6aa** in moderate yields of 49% and 38%, respectively (Table 2.2, entries 5 and 7). Despite similar electrochemical properties of **1.3** and **1.4** in comparison to other PPTNO-derivatives (**1.1** and **1.2**), low solubility of **1.3** and **1.4** in addition to the susceptibility of phenyl derivative **1.4** to decompose could be responsible for the diminished yields of desired product **2.6aa**. The utilization of deoxygenated PPT-derivatives **1.1a**-**1.4a** furnished consistently a yield improvement of up to 7% in comparison to the *N*-oxide analogues **1.1-1.4** (Table 2.2; entries 2,4,6 and 8). The deoxygenated *n*-propyl PPTN **1.1a** provided product **2.6aa** in quantitative GC- as well as isolated yield (Table 2.2, entry 2). This indicates most likely that the *N*-oxide derivatives **1.1-1.4** operate as pre-catalysts, revealing their catalytical activity shortly after deoxygenation.

Table 2.2 Photocatalyst screening of PPTNO (1.1-1.4) and PPT derivatives (1.1a-1.4a).



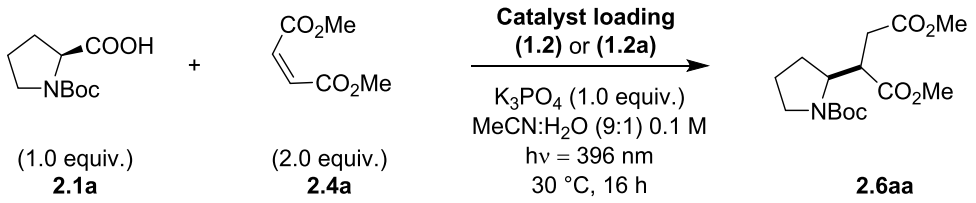
(1.0 equiv.) **2.1a** (2.0 equiv.) **2.4a** **2.6aa**

Entry	Photocatalyst	Yield[a,b]
1	PrPPTNO (**1.2**)	96% (88%)
2	PrPPTN (**1.2a**)	>99% (>99%)
3	BuPPTNO (**1.1**)	96% (87%)
4	BuPPTN (**1.1a**)	98% (91%)
5	MePPTNO (**1.3**)	49%
6	MePPTN (**1.3a**)	56%
7	PhPPTNO (**1.4**)	38%
8	PhPPTN (**1.4a**)	43%

[a] Yields were determined by GC using biphenyl as internal standard. [b] Yields in parentheses represent isolated yields.

Next, the results of different catalyst loadings of the *n*-propyl photocatalyst **1.2** and the corresponding deoxygenated analogue **1.2a** were explored (Table 2.3).

Table 2.3 Catalyst-loading screening of *n*-propyl PPTNO (1.2) and *n*-propyl PPTN (1.2a).



(1.0 equiv.) **2.1a** | (2.0 equiv.) **2.4a** | **2.6aa**

Entry	Photocatalyst	Catalyst loading	Yield[a]
1	PrPPTNO (**1.2**)	5.0 mol%	96%
2	PrPPTN (**1.2a**)	5.0 mol%	>99%
3	PrPPTNO (**1.2**)	2.5 mol%	58%
4	PrPPTN (**1.2a**)	2.5 mol%	72%
5	PrPPTNO (**1.2**)	1.0 mol%	41%
6	PrPPTN (**1.2a**)	1.0 mol%	41%
7	PrPPTNO (**1.2**)	0.5 mol%	18%
8	PrPPTN (**1.2a**)	0.5 mol%	28%

[a] Yields were determined by GC using biphenyl as internal standard.

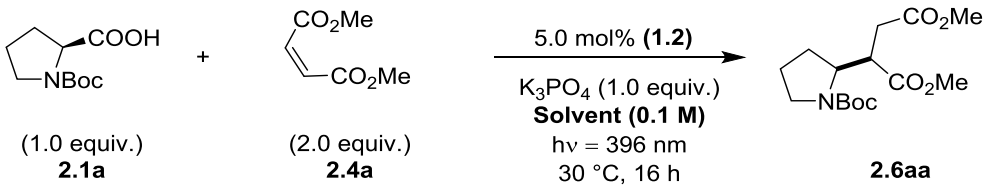
Unfortunately, lowering the catalyst loading of **1.2** and **1.2a** below 5.0 mol% led to a decline in product formation (Table 2.3, entries 3-8) in comparison to a 5.0 mol% loading of **1.2** and **1.2a** (Table 2.3, entries 1 and 2). Furthermore, deoxygenated *n*-propyl analog **1.2a** delivered in most cases a better yield than the corresponding *N*-oxide derivatives, in exception of the reaction with 1.0 mol% catalyst loading of **1.2** and **1.2a** (Table 2.3, entries 5 and 6).

Subsequently, different polar protic- and aprotic solvents were screened using photocatalyst **1.2** (Table 2.4). Moderate to good yields of product **2.6aa** (40-73%) were obtained using polar aprotic solvents like MeCN, DCM, acetone, THF or DCE (Table 2.4, entries 3-6). A low Coulombic barrier for charge separation of the radical ion pair intermediates in MeCN compared to other polar aprotic solvents allows an effective diffusive separation.[67] In this context, productive competition to back electron transfer, results in efficient product formation.[67]

A superior yield of 96% GC-yield of **2.6aa** was obtained when a 9:1 ratio of MeCN:H_2O was used (Table 2.4, entry 1). The enhanced solubility of the generated carboxylate salts in a MeCN:H_2O mixture over pure MeCN could explain the improved yield. Nonetheless, further increase of amount of H_2O with respect to acetonitrile impaired the product formation (Table 2.4, entry 2) indicating a delicate balance between the solubility of organic components **2.1a**, **2.4a** and photocatalyst **1.2** as well as the inorganic base.

On the other hand, running the reaction in polar protic solvents (e.g. iPrOH, H_2O, HFIP or DMSO) attenuated the generation of **2.6aa** (Table 2.4, entries 7-11). Strongly diminished yields of product **2.6aa** could be attributed to competing side reactions of the formed neutral radicals with the protic solvent. Hydrogen atom abstraction and/or enhanced solvating and stabilizing properties of radical intermediates by the solvation shell could negatively influence the reactivity of intermediate radicals.[68]

Table 2.4 Solvent screening of the PPTNO-catalyzed decarboxylative *Giese*-addition.

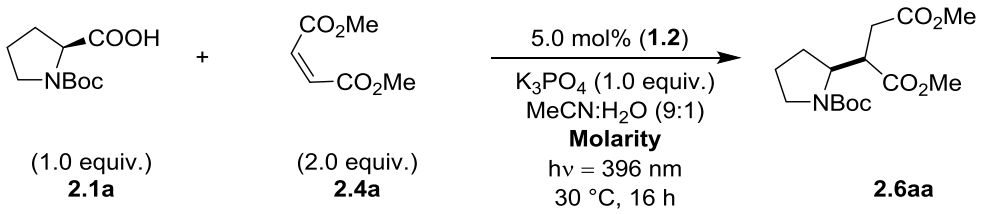


Entry	Solvent	Yield[a]
1	MeCN:H_2O (9:1)	96% (88%)
2	MeCN:H_2O (7:3)	73%
3	MeCN	73%
4	DCM	61%
5	Acetone	58%
6	DCE	40%
7	iPrOH	17%
8	THF	12%
9	H_2O	8%
10	HFIP	8%
11	DMSO	1%

[a] Yields were determined by GC using biphenyl as internal standard. Yields in parentheses represent isolated yields.

Following, the effect of the molarity was investigated (Table 2.5). The highest yield of 96% GC- and 88% isolated yield of **2.6aa** was obtained when running the reaction in a molar concentration of 0.1 M with respect to the used carboxylic acid (Table 2.5, entry 2). Increasing the reaction concentration would automatically lead to a gain in the absorbance (extinction) of the reaction solution at a given wavelength.[69] Thus, the employed light will be more strongly absorbed as compared to lower concentrations. An increase in the molarity up to 0.2 M resulted in a decrease in the yield of **2.6aa** to 50% (Table 2.5, entries 3 and 4). On the other hand, reducing the molar concentration down to 0.05 M resulted in a lower impact on the yield of **2.6aa** (Table 2.5, entry 1). A lower concentration of the radical scavenger, in this case the electron-deficient alkene **2.4a**, could be the reason for the slightly declined yield.

Table 2.5 Molarity effect on the decarboxylative *Giese*-type addition.



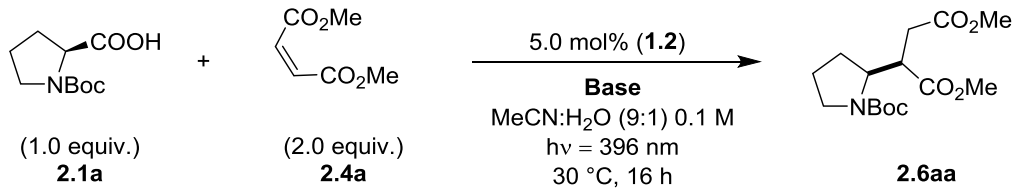
Entry	Molarity	Yield[a]
1	0.05 M	83%
2	0.10 M	96%
3	0.15 M	69%
4	0.20 M	50%

[a] Yields were determined by GC using biphenyl as internal standard.

In the next step, a variety of organic- and inorganic bases were tested (Table 2.6). Equimolar amounts of inorganic bases including phosphates and carbonates (Table 2.6, entries 1-9) delivered **2.6aa** in good to very good isolated yields, accounting up to 88% after 16 hours. The yield fluctuation of **2.6aa** between tested inorganic bases could have its origin in the different solubility and basicity of the tested bases in acetonitrile. The use of tertiary- (Table 2.6, entries 10 and 11) and aromatic amines (Table 2.6, entry 12) as organic bases decreased the yield of **2.6aa**. The high oxidation ability of the deoxygenated *n*-propyl pyrimidopteridine photocatalyst **1.2a** in the excited-state ($E^*_{red} = +1.72$ V *vs.* SCE in MeCN) favors one-electron oxidation of tertiary amines like triethylamine (TEA) ($E^{red}_{1/2}$ (TEA) $= +1.0$ V

vs. SCE). Hence, intermediary formed ammonium radical cations could impede the course of the reaction. Satisfyingly, reducing the amount of base from equimolar to a catalytical amount of 20 mol% of tripotassium phosphate did not impair the yield of **2.6aa** (87% isolated yield) (Table 2.6, entry 13).

Table 2.6 Base screening of the photomediated decarboxylative *Giese*-addition.



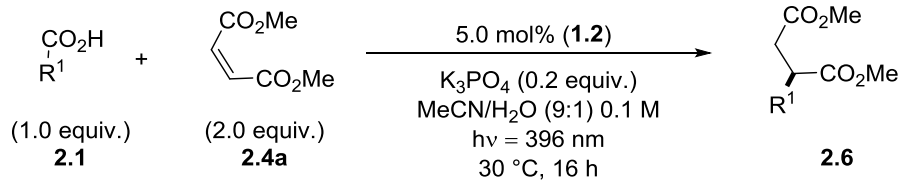
Entry	Base	Equivalents of base	Yield[a]
1	K_3PO_4	1.0	88%
2	K_2HPO_4	1.0	64%
3	K_2CO_3	1.0	72%
4	Cs_2CO_3	1.0	88%
5	Na_2CO_3	1.0	83%
6	$NaHCO_3$	1.0	86%
7	NaOH	1.0	71%
8	CsF	1.0	85%
9	NaOAc	1.0	63%
10	NEt_3	1.0	28%
11	DIPEA	1.0	34%
12	pyridine	1.0	35%
13	K_3PO_4	0.2	87%

[a] Isolated yields.

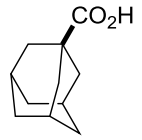
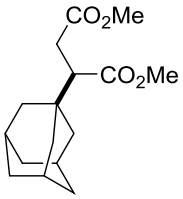
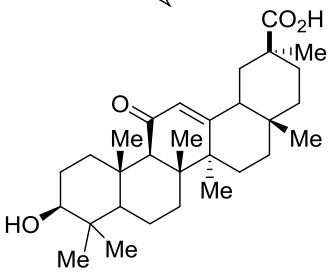
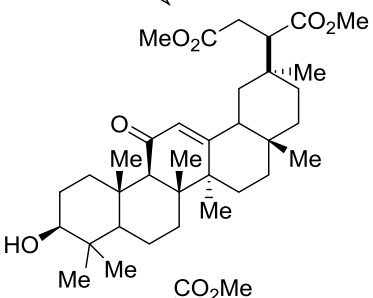
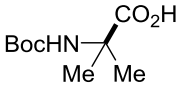
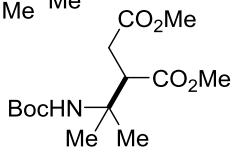
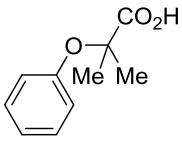
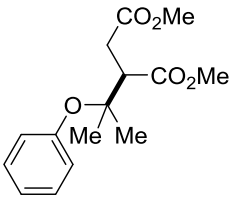
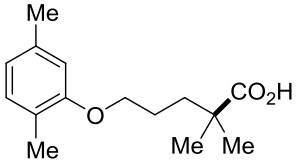
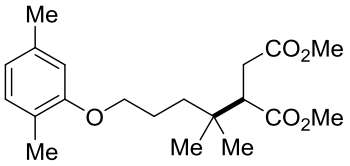
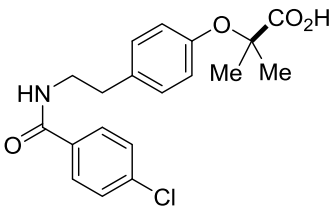
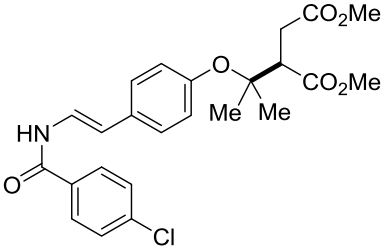
2.3.2 Scope of the carboxylic acids in the decarboxylative Giese-type addition

Based on the optimized conditions for the decarboxylative *Giese*-addition, the reaction scope was explored with a range of different carboxylic acids and electron-deficient alkenes. The screening of carboxylic acids was conducted using dimethyl maleate (**2.4a**) (Table 2.7) and diethyl ethylidenemalonate (**2.4b**) (Table 2.8) as 1,2- and 1,1'-disubstituted electron-deficient alkenes, respectively. Tertiary hydrocarbon carboxylic acids delivered corresponding alkylated products in good to excellent yields (Table 2.7, entry 1 and Table 2.8, entries 1-4). Substrates with unprotected hydroxy- and α,β- unsaturated carbonyl moieties, such as in the case of the triterpenoid carboxylic acid enoxolone **2.1c** (Table 2.7, entry 2) and the adamantane carboxylic acid derivative bearing a free hydroxy group **2.1k** (Table 2.8, entry 5), were well tolerated under the reaction conditions. Tertiary carboxylic acids bearing α- and β-heteroatom like in the case of **2.1d** (Table 2.7, entry 3) and **2.1l** (Table 2.8, entry 6) resulted in lower yields of 45% and 29% of alkylated products, respectively. Hydrolysis of the acetale subunit in **2.6lb** could be responsible for the declined yield when using carboxylic acid precursor **2.1l** in an aqueous solvent mixture. Also, destabilization of the generated carbon-centered radical by the inductive effect of the electronegative oxygen in the β-position may impair the yield of **2.6lb**.[70] Substrates **2.1e** and **2.1f** (Table 2.7, entries 4 and 5) bearing a phenol ether substructure exhibit an antioxidative effect due to the enhanced resonance stabilization of the phenoxy radical (RSE $= -121$ kJ/mol) and could act as an electron scavenger during the reaction.[71, 72] As a result, an interruption of the catalytic cycle could explain the lower yield of **2.6ea** and **2.6fa**.

Table 2.7 Photocatalyzed decarboxylative *Giese*-addition of tertiary carboxylic acid derivatives to dimethyl maleate (2.4a).

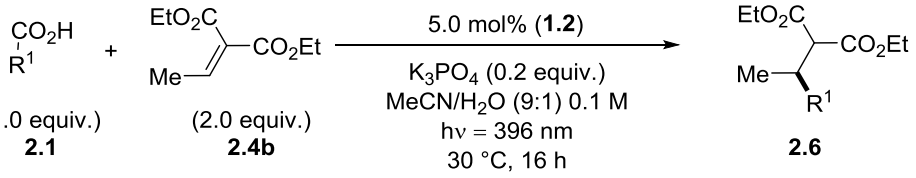


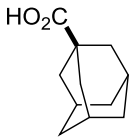
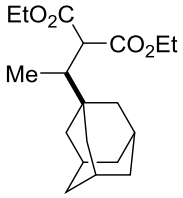
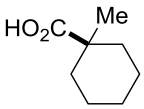
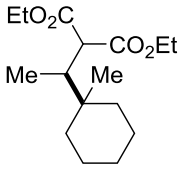
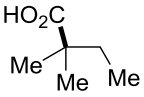
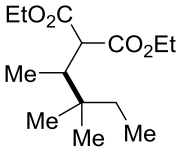
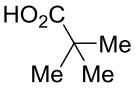
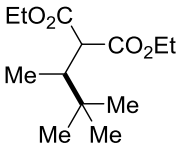
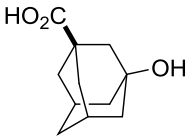
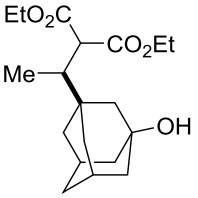
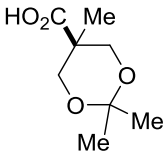
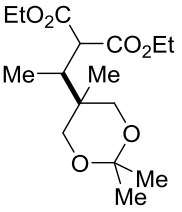
(1.0 equiv.) **2.1** (2.0 equiv.) **2.4a** **2.6**

Entry	Substrate		Product		Yield (%)[a]
1		**2.1b**		**2.6ba**	82%
2		**2.1c**		**2.6ca**	78%[b]
3		**2.1d**		**2.6da**	45%
4		**2.1e**		**2.6ea**	26%
5		**2.1f**		**2.6fa**	17%[b]
6		**2.1g**		**2.6ga**	31%[b]

Reaction conditions: scale: 0.5 mM, 2.0 equiv. of alkene **2.4a** were added to a 0.1 M MeCN:H_2O solution (9:1) of 1.0 equiv. of carboxylic acid **2.1**, 5.0 mol% of PrPPTNO **1.2** and K_3PO_4 (0.2 equiv.) under Ar. The reaction mixture was irradiated for 16 h under UV-light. [a]isolated yields are shown.[b]48 h instead of 16 h.

Table 2.8 Photocatalyzed decarboxylative *Giese*-addition of tertiary carboxylic acids to diethyl ethylidenemalonate (2.4b).

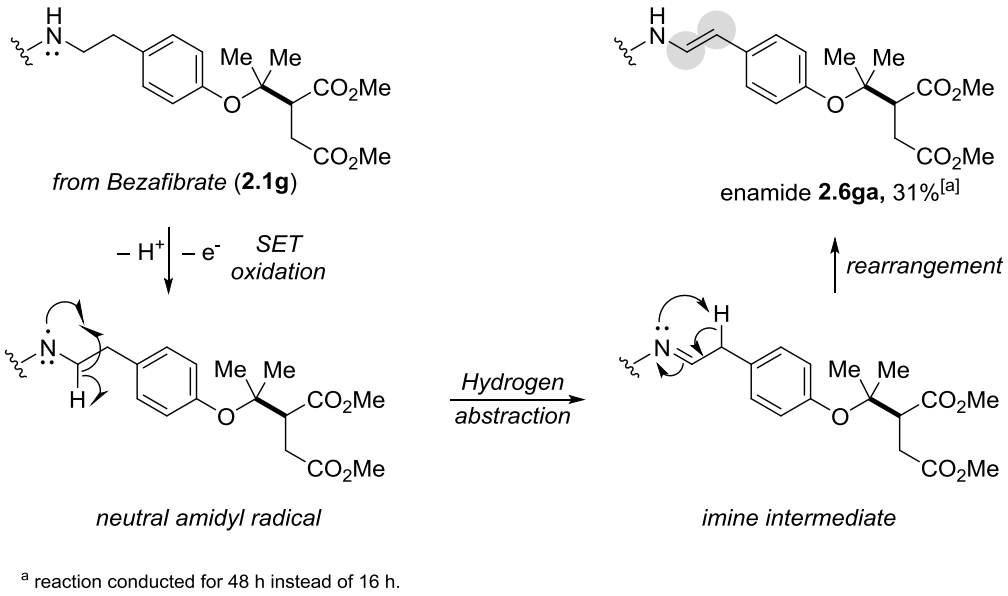


Entry	Substrate		Product		Yield (%)[a]
1		**2.1b**		**2.6bb**	92%
2		**2.1h**		**2.6hb**	87%
3		**2.1i**		**2.6ib**	78%
4		**2.1j**		**2.6jb**	66%
5		**2.1k**		**2.6kb**	84%
6		**2.1l**		**2.6lb**	29%

Reaction conditions: scale: 0.5 mM, 2.0 equiv. of alkene **2.4b** were added to a 0.1 M MeCN:H_2O solution (9:1) of 1.0 equiv. of carboxylic acid **2.1**, 5.0 mol% of PrPPTNO **1.2** and K_3PO_4 (0.2 equiv.) under Ar. The reaction mixture was irradiated for 16 h under UV-light. [a]isolated yields are shown.

The decarboxylative coupling of pharmaceutical bezafibrate **2.1g** resulted in a concomitant dehydration yielding the enamide **2.6ga** (Table 2.7, entry 6). This side-reaction putatively proceeds through an SET induced oxidation of the amid moiety in the desired product (Scheme 2.10). The deprotonation of formed amid radical cation could lead to the

generation of a neutral amidyl radical species. A fast abstraction of an adjacent hydrogen atom and a subsequent rearrangement would generate the enamide **2.6ga** with an extended π-system.



[a] reaction conducted for 48 h instead of 16 h.

Scheme 2.10 Possible mechanism for the photomediated formation of unsatured product (2.6ga).

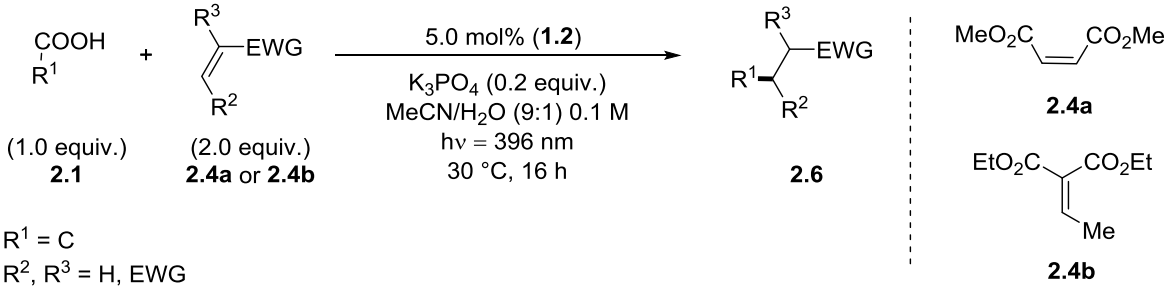
The structure of alkylated product **2.6ba**, generated from the reaction of adamantane carboxylic acid (**2.1b**) with dimethyl maleate (**2.4a**) was confirmed by X-ray analysis (Figure 2.1).

Figure 2.1 X-ray crystal structure of alkylated compound (2.6ba) in the solid state. Displacement ellipsoids correspond to 30% probability.

Secondary carboxylic acids furnished products **2.6ma**-**2.6vb** in isolated yields up to 75% (Table 2.9, entries 1-10). Dipeptide derivative **2.6ma** consisting of *L*-proline and amide protected *L*-valine was tolerated and obtained in a good yield of 75% (Table 2.9, entry 1). Furthermore, *N*-protected secondary amino acids delivered desired products **2.6na** and **2.6qb** in moderate to good yields of 68% and 45%, respectively (Table 2.9, entries 2 and 5). Significant interaction of the molecular orbital containing the unpaired electron of the

neutral C-centered radical with the lone-pair of the adjacent α–heteroatom could explain the better yield of generated product **2.6pb** (Table 2.9, entry 4).

Table 2.9 Scope of secondary carboxylic acids in photocatalyzed decarboxylative *Giese*-addition.



(1.0 equiv.) **2.1**

(2.0 equiv.) **2.4a** or **2.4b**

2.6

R^1 = C

R^2, R^3 = H, EWG

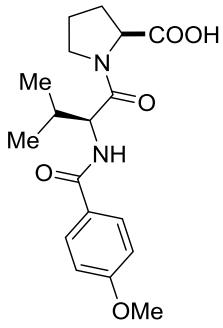
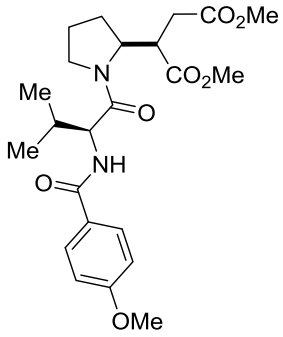
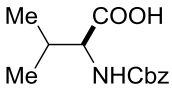
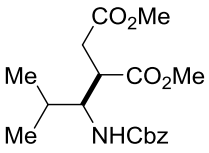
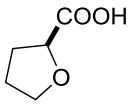
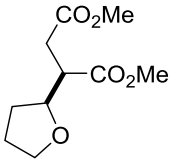
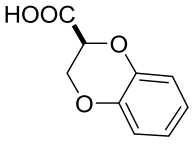
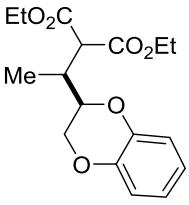
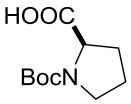
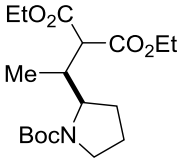
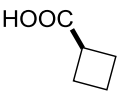
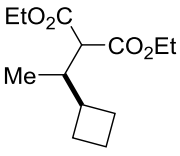
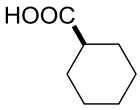
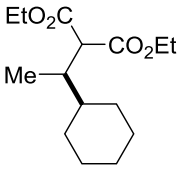
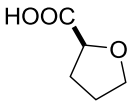
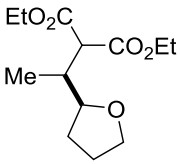
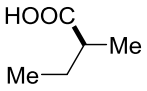
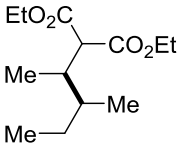
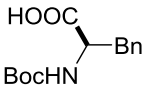
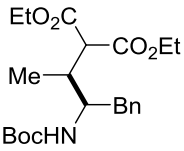
Entry	Substrate	Product		Yield (%)
1			**2.6ma**	75%[b]
2			**2.6na**	68%[a]
3			**2.6oa**	52%[c,d]
4			**2.6pb**	70%
5			**2.6qb**	45%
6			**2.6rb**	35%

Table 2.9 (continued) Scope of secondary carboxylic acids in photocatalyzed decarboxylative *Giese*-addition.

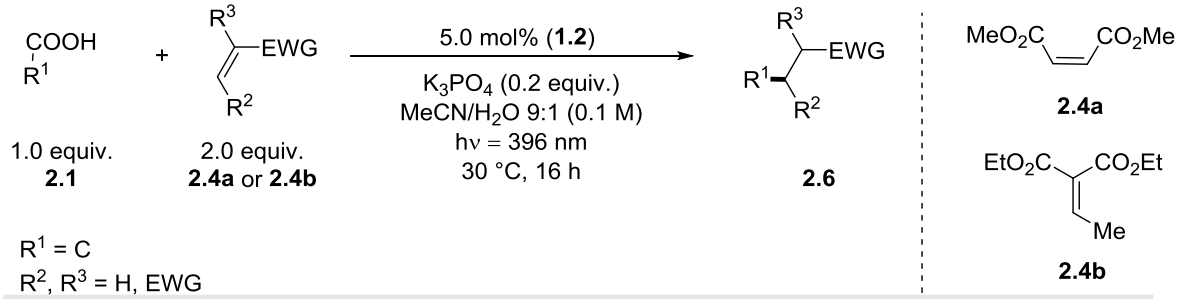
7			**2.6sb**	37%[c,d]
8			**2.6tb**	34%[c,d]
9			**2.6ub**	29%
10			**2.6vb**	30%

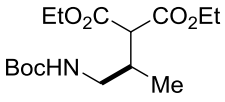
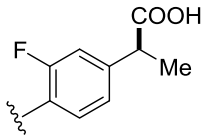
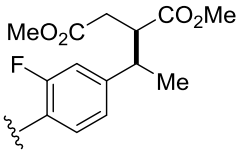
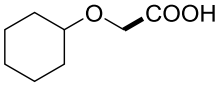
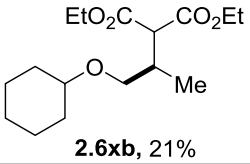
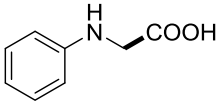
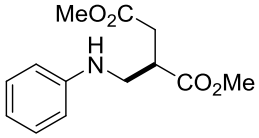
Reaction conditions: 2.0 equiv. of alkene **2.4a** or **2.4b** were added to a 0.1 M MeCN:H_2O solution (9:1) of 1.0 equiv. of carboxylic acid **2.1**, 5.0 mol% of PrPPTNO **1.2** and K_3PO_4 (0.2 equiv.) under Ar. The reaction mixture was irradiated for 16 h under UV-light. [a] reaction was performed with 1.0 equiv. base. [b] reaction was performed on a 0.15 mmol scale. [c] 2.0 equiv. acid, 1.0 equiv. alkene, 0.4 equiv. base were used. [d] 24 h instead of 16 h.

On the other hand, the decarboxylative *Giese*-addition of cyclic and acyclic secondary hydrocarbon carboxylic acids yielded the desired alkylated products **2.6rb**, **2.6sb**, and **2.6ub** in rather lower yields (Table 2.9, entries 6,7, and 9). Also, a lower yield of product **2.6vb** was obtained, most likely due to enhanced benzylic radical stabilization (Table 2.9, entry 10). In the case of **2.1t**, a difficult decarboxylation was observed, yielding the desired product **2.6tb** in 34% isolated yield after 24 hours (Table 2.9, entry 8).

In contrast, the decarboxylation of primary carboxylic acids was more challenging in comparison to secondary and tertiary counterparts (Table 2.10). The strong C(sp^3)–CO_2H bond of primary carboxylic acids (e.g. acetic acid, BDE = 93.1 kcal/mol)[73] accentuates the extrusion of carbon dioxide. In addition, the stability of C-centered radicals is known to decrease with decreasing number of substituents on the carbon-center (radical stability = 3 °> 2 °> 1 °).[72] Hence, products **2.6wb** and **2.6xb** derived from *N*-Boc-glycine and 2-(cyclohexyloxy)acetic acid were obtained in low yields of 18% and 21%, respectively (Table 2.10, entries 1 and 2). Also, the conversion of the pharmaceutically relevant, benzylic secondary carboxylic acid flurbiprofen (**2.1y**) did not yield any decarboxylative C–C coupling product (Table 2.10, entry 3).

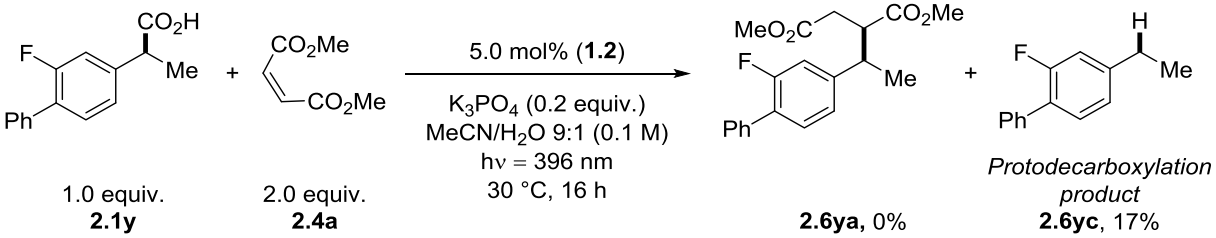
Table 2.10 Scope and limitations of primary carboxylic acids in photocatalyzed decarboxylative *Giese*-addition.



Entry	Substrate	Product, yield (%)	Entry	Substrate	Product, yield (%)
(1)		 **2.6wb,** 18%	(3)		 **2.6ya,** 0%
(2)		 **2.6xb,** 21%	(4)		 **2.6za,** <5%

Reaction conditions: 2.0 equiv. of alkene **2.4a** or **2.4b** were added to a 0.1 M MeCN:H_2O solution (9:1) of 1.0 equiv. of carboxylic acid **2.1**, 5.0 mol% of PrPPTNO **1.2** and K_3PO_4 (0.2 equiv.) under Ar. The reaction mixture was irradiated for 16 h under UV-light

Both insufficient decarboxylation, which was evident in the course of the reaction, as well as the formation of reductive decarboxylation product **2.6yc**, impeded the formation of the desired product **2.6ya** (Scheme 2.11). Thus, protodecarboxylation product **2.6yc** was isolated in a yield of 17% after 16 hours. Also, rapid decomposition of *N*-phenyl substituted primary amino acid **2.1z** was evident. In this case, the formation of desired product **2.6za** was almost completely supressed (Table 2.10, entry 4).

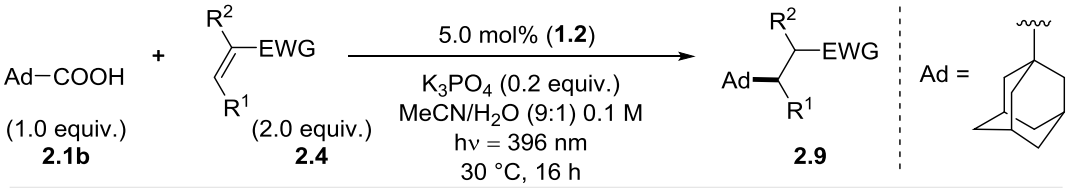


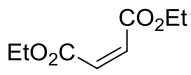
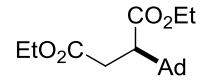
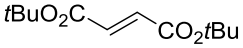
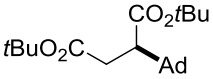
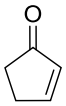
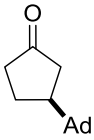
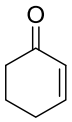
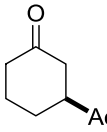
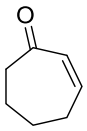
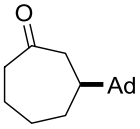
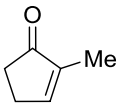
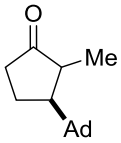
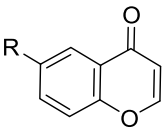
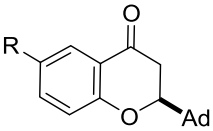
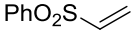
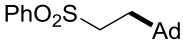
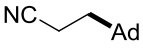
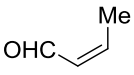
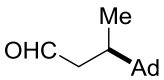
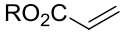
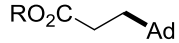
Scheme 2.11 Reductive decarboxylation of benzylic carboxylic acid derivative flurbiprofen (2.1y).

2.3.3 Scope of electron-deficient olefins in the decarboxylative *Giese*-type addition

Subsequently, the scope of electron-deficient alkenes was investigated. Monosubstituted- in addition to 1,1'- and 1,2- disubstituted olefins bearing strongly electron-withdrawing groups, commonly esters, nitriles, as well as carbonyl- and sulfonyl group-containing alkenes were tested (Table 2.11). The reaction of diethyl ethylidenmalonate (**2.4b**) and carboxylic acid **2.1b** delivered alkylated product **2.6bb** in a excellent yield of 92%. Also, diethyl maleate (**2.4c**) as well as dimethyl maleate (**2.4a**) participated efficiently in this transformation, generating products **2.9c** (Table 2.11, entry 1) and **2.6ba** (Table 2.7, entry 1) in very good yields of 83% and 82%, respectively. Conversely, *trans*-alkene di-*tert*-butyl fumarate (**2.4d**) delivered product **2.9d** in a moderate yield of 53% (Table 2.11, entry 2). Hence, the superiority of *cis*-isomeres of olefins over *trans*-analogs became evident. Possible enhanced quenching of the excited-state photocatalyst **1.2a*** in the presence of (*E*)-alkene isomers as compared to (*Z*)-analogues might be evident. Cyclic alkylated ketones **2.9e** and **2.9f** were also obtained from their corresponding α,β-unsaturated precursors **2.4e** and **2.4f** in very good yields of 89% and 81%, respectively (Table 2.11, entries 3 and 4). Yet, the expansion of the cyclic precursors to a seven-membered ring **2.4g** impaired the yield of **2.9g** (Table 2.11, entry 5). The lack of ideal bond angle as well as considerable ring strain putatively reduces the stability of the corresponding radical intermediate, leading to a competing ring opening.[70] Also, the introduction of an α-methyl group in **2.4h** furnished product **2.9h** in a moderate yield of 57% (Table 2.11, entry 6). Next, we investigated the efficiency of differently substituted chromone derivatives (**2.4i**-**2.4l)**. Desired products **2.9i**-**2.9l** were obtained in yields varying between 29-55% (Table 2.11, entries 7-10). A visible trend in yield was observed depending on the electronegativity of the halogen substituent at the 4-position of chromones. **2.4j** furnished product **2.9j** in a diminished yield of 29% with fluorine being the substituent with the highest electronegativity[74], whereas bromo derivative **2.4l** gave access to **2.9l** in a moderate yield of 55%. Phenyl vinyl sulfone **2.4m** proved to be compatible with the reaction conditions. Corresponding product **2.9m** was obtained in a synthetically useful yield of 69% (Table 2.11, entry 11). Diverse acrylates as well as acyclic α,β-unsaturated aldehyde (**2.4n**-**2.4r**) delivered the corresponding alkylated products **2.9n**-**2.9r** in rather lower yields (26-40%) (Table 2.11, entries 12-16). Radical polymerization of acrylate monomeres is feasible under the employed reaction conditions. Thus, the concentration of available acrylate in solution would be considerably decreased.

Table 2.11 Scope of electron-deficient alkenes (2.4) in the photocatalytic *Giese*-addition.

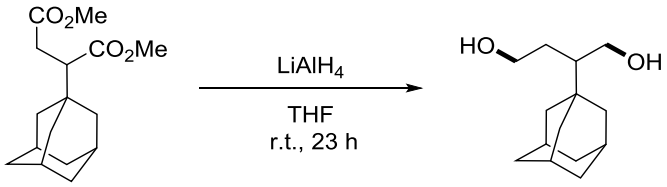


Entry	Substrate		Product		Yield (%)[a]
1		**2.4c**		**2.9c**	83%
2		**2.4d**		**2.9d**	53%
3		**2.4e**		**2.9e**	89%
4		**2.4f**		**2.9f**	81%
5		**2.4g**		**2.9g**	19%
6		**2.4h**		**2.9h**	57%
7		R = H **2.4i**		**2.9i**	39%
8		F **2.4j**		**2.9j**	29%
9		Cl **2.4k**		**2.9k**	44%
10		Br **2.4l**		**2.9l**	55%
11		**2.4m**		**2.9m**	69%
12		**2.4n**		**2.9n**	40%
13		**2.4o**		**2.9o**	32%
14		R = Et **2.4p**		**2.9p**	28%[b]
15		Bn **2.4q**		**2.9q**	27%
16		Ph **2.4r**		**2.9r**	26%

Reaction conditions: scale: 0.5 mM, 2.0 equiv. of olefin **2.4** were added to MeCN:H_2O (9:1) solution containing 1.0 equiv. of 1-adamantanecarboxylic acid (**2.1b**), 20 mol% of K_3PO_4 and 5.0 mol% of PrPPTNO **1.2** under Ar. The reaction mixture was irradiated for 16 h under UV-light. [a]isolated yields are shown. [b] reaction was performed with 1.0 equiv. K_2CO_3.

2.3.4 Derivatization of synthesized products and scale-up

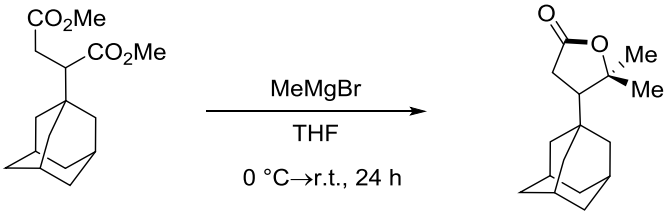
To demonstrate the synthetic utility of products formed from the photo-mediated decarboxylative coupling, different derivatization reactions were conducted. Synthesized 1,2-diester **2.6ba** was readily reduced with lithium aluminium hydride in THF to the corresponding diole **2.10** in 93% yield after 23 hours (Scheme 2.12).



2.6ba **2.10**, 93%

Scheme 2.12 Reduction of 1,2-diester (2.6ba) to the corresponding primary diole (2.10) with $LiAlH_4$.

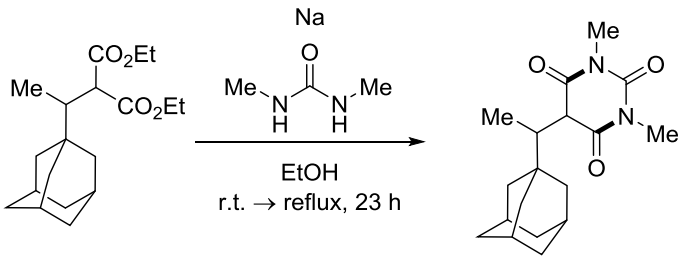
Moreover, a concerted alkylation and lactonization of **2.6ba** with methyl magnesium bromide in THF furnished the 5,5'-disubstituted lactone **2.11** in a very good yield of 87% after 24 hours (Scheme 2.13).



2.6ba **2.11,** 87%

Scheme 2.13 Concerted dialkylation and lactonization of 1,2-diester (2.6ba) with methyl magnesium bromide.

Also, tri-substituted barbiturate **2.12**, a class of compounds with high pharmaceutical value, was directly obtained from 1,1'- diester **2.6bb** and *N,N'*-dimethyl urea under reflux conditions in EtOH *via* a dual alkoxid-base-promoted amidation (Scheme 2.14).[75]

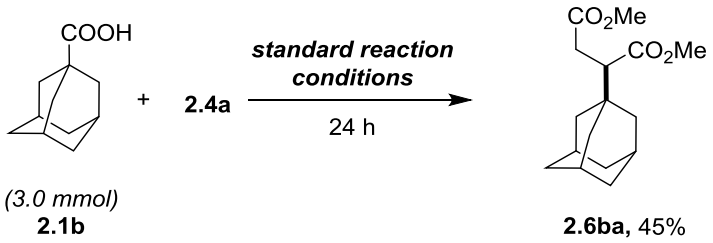


2.6bb **2.12**, 33%

Scheme 2.14 Base-promoted direct synthesis of barbiturate derivative (2.12) from 1,1'-diester (2.6bb).[75]

In addition, a six-fold scale up of the photo-mediated coupling using 1-adamantanecarboxylic acid (**2.1b**) and dimethyl maleate (**2.4a**) was performed. The

corresponding alkylated product **2.6ba** was obtained in 45% isolated yield after irradiation for 24 hours (Scheme 2.15).

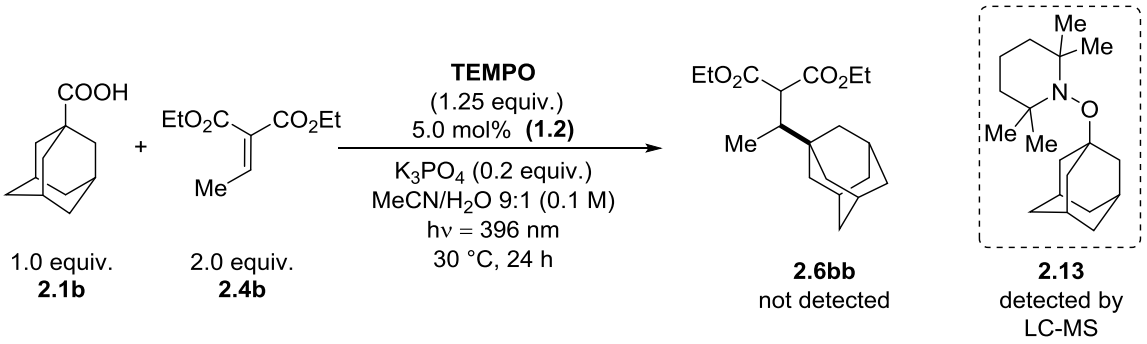


Scheme 2.15 Scale-up of the photo-mediated decarboxylative coupling of (2.1b) and dimethyl maleate (2.4a).

The decline in the yield of **2.6h** from 92% in a small-scale reaction (Table 2.7, entry 1) to 45% is probably attributed to the change of the reaction vessel. The big scale reaction was conducted in a round bottom Schlenk flask (FengTecEx® F53 250 mL schlenk flask) rather than a microwave reaction vessel (Biotage® 5 mL microwave reaction vessels). Both reaction vessels possess different diameters at the widest point. According to the *Beer-Lambert* law, the penetration of electromagnetic waves is known to decrease with increasing path length through a given medium.[76] Thus, enhanced excitation of the photocatalyst molecules closer to the surface of the reaction vessel in contrast to molecules located in the center of the reaction solution is conceivable. A possible route to solve this hurdle is by applying flow techniques, which possess a more efficient surface-to-volume ratio.

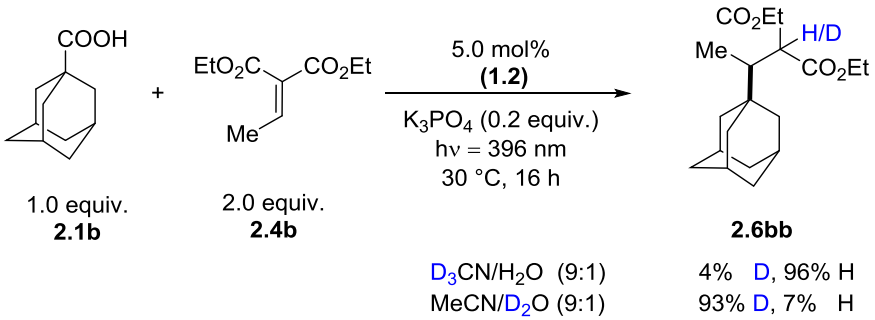
2.3.5 Mechanistic considerations

To gain a better insight into the reaction, multiple mechanistic experiments targeting the key steps of the pyrimidopteridine-*N*-oxide photocatalyzed decarboxylative *Giese*-type addition were conducted. First, quenching of the reaction of carboxylic acid **2.1b** and electron-deficient alkene **2.4b** with 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) was investigated (Scheme 2.16). The formation of the corresponding product **2.6bb** was completely inhibited. Furthermore, the radical adduct **2.13** consisting of decarboxylated **2.1b** and TEMPO was detected by LC-MS, confirming a decarboxylative radical mechanism operational during the course of the reaction (see experimental section of chapter 2 for further details).



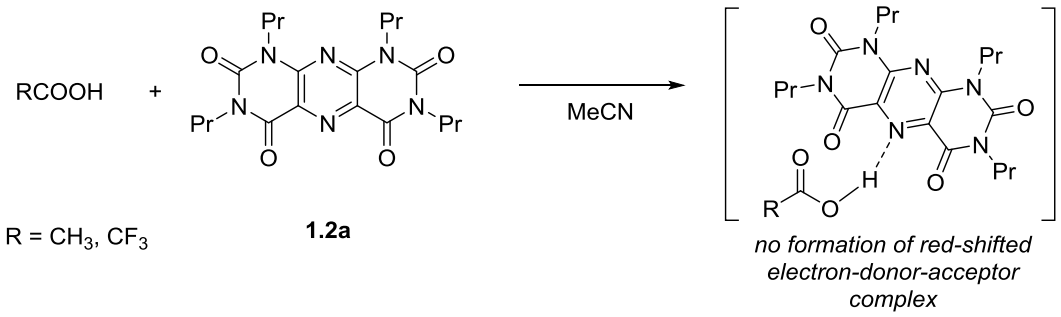
Scheme 2.16 TEMPO radical quenching experiment of the reaction of (2.1b) with (2.4b).

Subsequently, deuterium incorporation experiments were evaluated (Scheme 2.17). The reaction of carboxylic acid **2.1b** with **2.4b** was conducted in two different deuterated solvent mixtures. The usage of a MeCN:D_2O (9:1) mixture revealed a high deuterium content (93% D) in the corresponding product **2.6bb**, whereas the utilization of a D_3CN:H_2O (9:1) mixture furnished the desired product **2.6bb** with a minimal deuterium incorporation (4% D) (see experimental section to chapter 2 for further details and spectra). Hence, this indicates that the protonation step of the anionic form of product **2.6bb** happens solely from H_2O with no hydrogen atom transfer from MeCN.



Scheme 2.17 Deuterium incorporation experiments.

Since the overlap of the absorption spectrum of PrPPTN (**1.2b**) and the emission spectrum of the used lamp is minimal, the formation of a possible red-shifted electron-donor-acceptor (EDA) complex between the carboxylic acids and the deoxygenated propyl derivative photocatalyst PrPPTN (**1.2b**) was probed (Scheme 2.18). Therefore, stoichiometric excess amounts (20, 50, 100, and 500 equivalents) of acetic acid and strong acidic trifluoro acetic acid were added to a solution of PrPPTN (**1.2a**) in MeCN.



Scheme 2.18 Possible formation of EDA-complex between carboxylic acids and deoxygenated PrPPTN (1.2a).

The UV-absorption of the corresponding solutions was measured and compared (Figure 2.2).

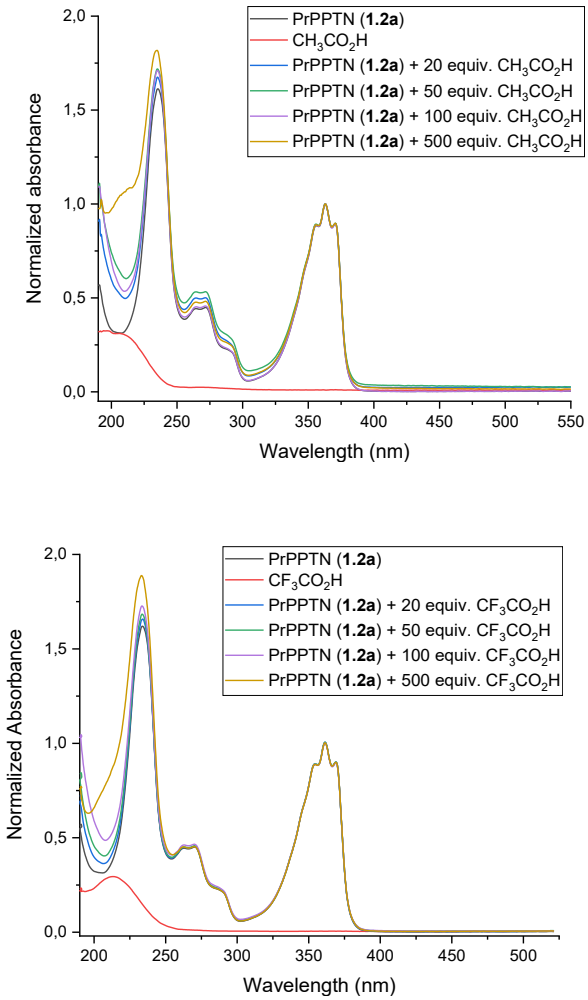
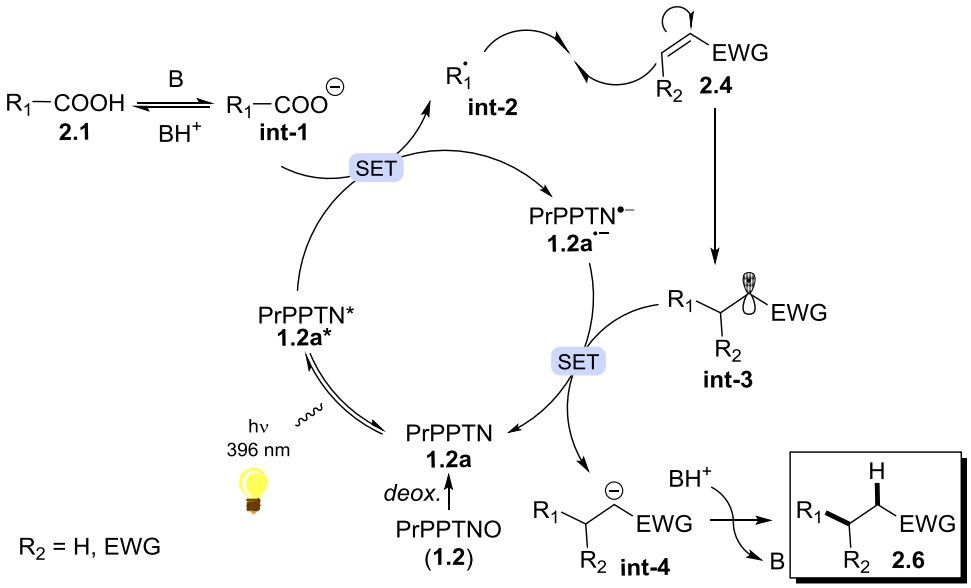


Figure 2.2 UV-absorption spectra of PrPPTN (1.2a) after addition of excess amounts of acetic acid (top) and trifluoroacetic acid (bottom).

No bathochromic shift of spectral band position, which can result from the formation of an EDA complex, was observed. Furthermore, the formation of a colored solution from a colorless PrPPTN (**1.2a**) solution, typical for EDA-complexes, was absent.

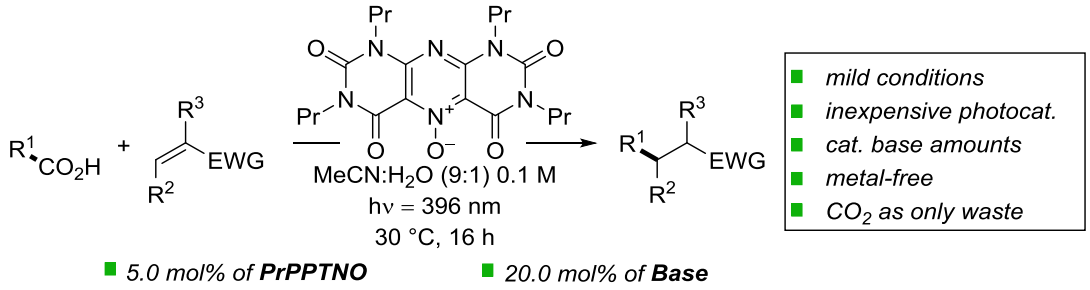
Based on the conducted control experiments and the preceding work of our group, a plausible reaction mechanism is proposed in (Scheme 2.19). Propyl pyrimidopteridine *N*-oxide (**1.2**) most likely acts as a pre-catalyst. Rapid deoxygenation during the initial reaction time delivers the active form of the photocatalyst **1.2a**. The deoxygenation of **1.2** occurs most likely *via* the generation of hydroxyl radical upon photolysis.[77] The photoexcitation of **1.2a** gives access to the highly oxidative excited-state photocatalyst **1.2a*** (E^*_{red} (**1.2a**)= +1.72 V *vs*. SCE in MeCN).[38] Single-electron oxidation of the carboxylate form **int-1** (e.g. Boc-Pro-O$^-$, ($E^{\mathrm{red}}_{1/2}$ = +0.95 V *vs.* SCE in MeCN)[64], generated after deprotonation of **2.1**, provides radical intermediate **int-2** after CO_2 extrusion. Subsequent addition of neutral radical intermediate **int-2** across an electron-deficient olefin **2.4** furnishes α-acyl radical intermediate **int-3** (potential of alkyl radicals are in the range of $E^{\mathrm{red}}_{1/2}$ = –0.6 - (–0.8) V *vs.* SCE in MeCN).[78] The turnover of the reduced form of the photocatalyst **1.2a**$^{\bullet-}$ ($E^{\mathrm{red}}_{1/2}$ = –1.59 V *vs.* SCE in MeCN) is feasible through an single-electron transfer from **1.2a**$^{\bullet-}$ to **int-3**, thus regenerating the ground-state photocatalyst **1.2a**. Eventually, protonation of the anionic form of the product **int-3** regenerates the base and delivers the desired product **2.6**.



Scheme 2.19 Proposed mechanism for the PPTNO photocatalyzed decarboxylative *Giese*-type reaction.

2.4 Conclusion

In conclusion, a metal-free oxidative variant of a photocatalytic decarboxylative *Giese*-type addition to electron-deficient olefins was developed using pyrimdopteridine *N*-oxides and their deoxygenated analogues as organo-photocatalysts (Scheme 2.20). A variety of primary, secondary, and tertiary carboxylic acids including amino acids and natural products as well as various electron-deficient olefins were suitable for this transformation. Also, the utilization of catalytic amounts of base proved to deliver comparable yields. In addition, good functional group tolerance, including halides, unprotected alcohols and α,β-unsaturated ketone moieties were showcased. Mechanistic experiments confirmed the presence of a C-centered radical as a key intermediate. Furthermore, derivatization reactions of the synthesized products and a scale-up reaction were demonstrated.

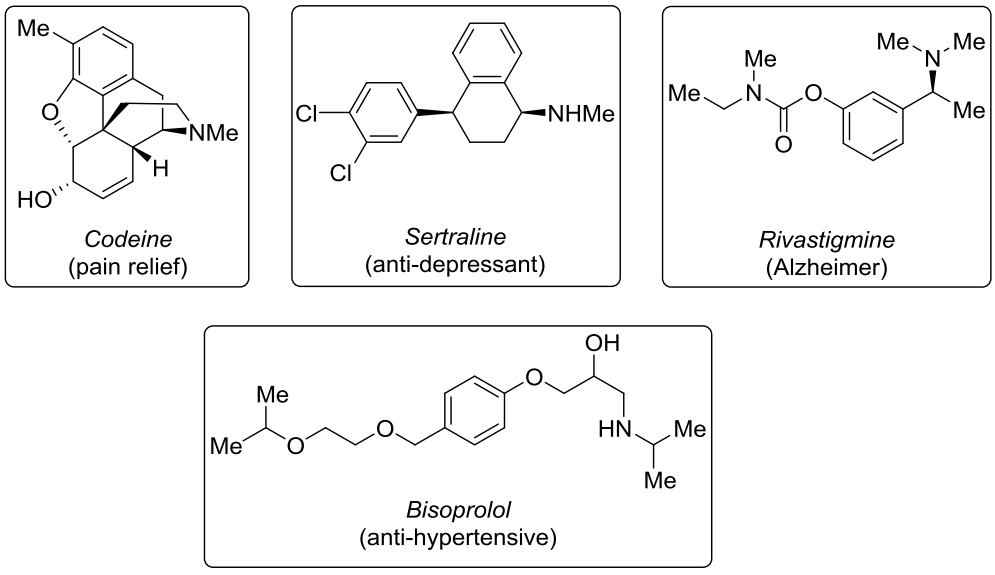


Scheme 2.20 PrPPTNO (1.2) photocatalyzed decarboxylative *Giese*-type reaction.

3 Pyrimidopteridine *N*-oxide photo-mediated hydroamination of unactivated stilbenes

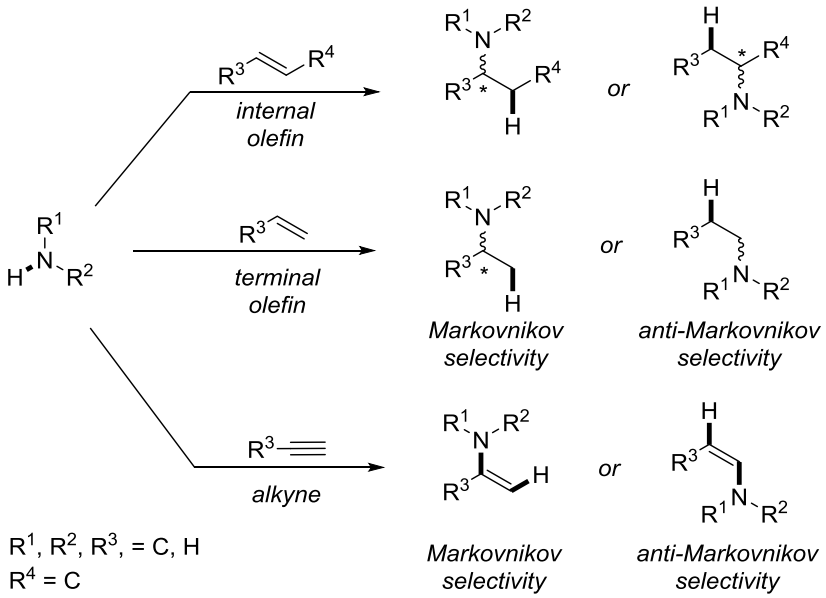
3.1 Introduction

Alkyl amines are a substantial class of chemical compounds that are widely encountered in synthetic pharmaceuticals and natural products.[79-81] Some of the advantages present in broad classes of nitrogen-containing drugs (Scheme 3.1) such as the improvement of biological potency, bioavailability and physicochemical properties render them highly attractive for the chemical as well as pharmaceutical research.[82-84] As such, methods for the catalytic synthesis of differently hybridized C–N bonds are of particular interest and subject of intensive investigation.[85] Among numerous available methodologies, the hydroamination of C–C multiple bonds holds great potential in terms of atom economy in addition to the high abundance and availability of amines and alkene precursors.[86]



Scheme 3.1 Nitrogen-containing pharmaceuticals.

The hydroamination reaction of C(sp^2)–C(sp^2) and C(sp)–C(sp) hybridized bonds describes the addition of primary or secondary N–H amines to internal/terminal olefins or alkynes, with cleavage of the N–H bond and formation of a new C–N and C–H bond (Scheme 3.2). Despite the seemingly simplicity of this transformation, thermodynamic-, kinetic-, and selectivity issues need to be overcome to establish a practicable and synthetically useful reaction.



Scheme 3.2 General scheme of the intermolecular hydroamination of internal/terminal olefins and alkynes.

The addition of an amine to an unsaturated C–C multiple bond is kinetically challenging.[87] The high electron density of the amine moiety and the electron-rich olefin result in a strong electrostatic repulsion between the amine lone-pair and the olefins π-bond. Consequently, a high activation barrier needs to be surmounted to achieve this transformation. Also, due to the negative entropy of this reaction, a shift in the equilibrium toward the starting materials is conceivable if high temperatures are used to overcome the high activation barrier.[88] Thus, this kinetic hurdle suggests the use of a catalyst to activate the C–C multiple bond or the amine moiety in order to assure a positive reaction outcome. Other significant hurdles of hydroamination reactions of alkenes are chemo-, regio-, and stereoselectivity (Figure 3.1). Notably, the control of a regioselective addition across olefins possesing alike or bulky substituents on both sides of the unsaturated bond is critical and non-trivial. For example, the addition of amines to terminal olefins can furnish two regioisomers, Markovnikov and *anti*-Markovnikov products. Furthermore, the control of stereoselectivity is crucial to achieve an asymmetric product formation. This is strongly driven by steric properties of both reaction partners and the employed catalyst, favoring a nucleophilic attack of the amines from the Re or Si face of the C–C multiple bond.

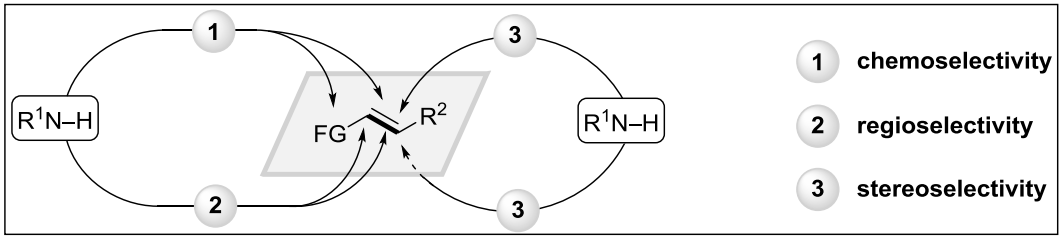
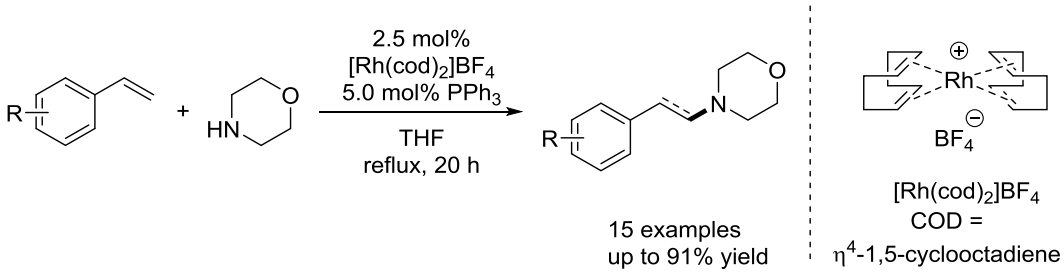


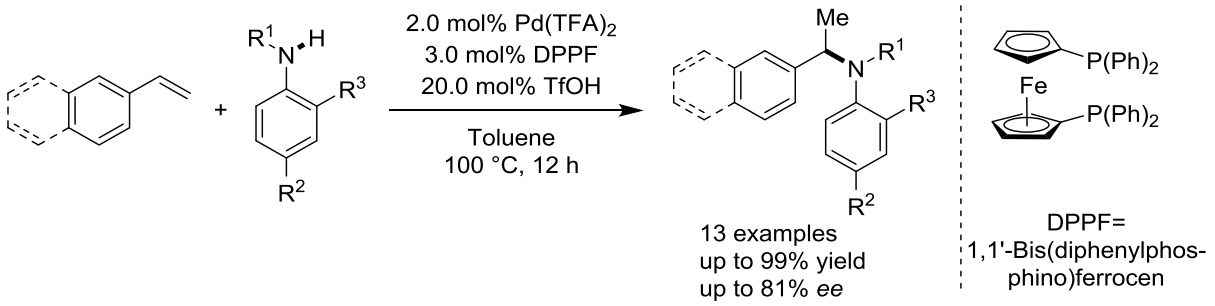
Figure 3.1 Selectivity aspects of the hydroamination reaction of unsaturated bonds.

Pursuing the search for a convenient catalyst for the addition reaction of N–H nucleophiles to C–C multiple bonds, early transition metal catalysts such as zirconium and lanthanum have been found to promote this transformation through the activation of the N–H bond *via* coordination to the metal center.[89, 90] Nevertheless, drawbacks of early transition metals catalysts such as the high oxophilicity and consequent diminished tolerance of oxygen containing functional groups in addition to air and moisture sensitivity complicates the handling of those catalysts and limits their use.[91] Later on, late transition metals like rhodium, iridium, palladium and ruthenium were found to be more suitable for the hydroamination reaction, showing enhanced tolerance of functional groups.[86] The mechanism of late transition-metal catalyzed hydroamination reaction proceeds *via* the activation of the C–C multiple bond, resulting in an enhanced regio- and stereoselectivity.[92-94] For instance, *Beller et al.* reported the first *anti*-Markovnikov hydroamination of styrene derivatives employing an *in situ* generated cationic COD-Rh complex with a phosphine ligand (Scheme 3.3).[92]



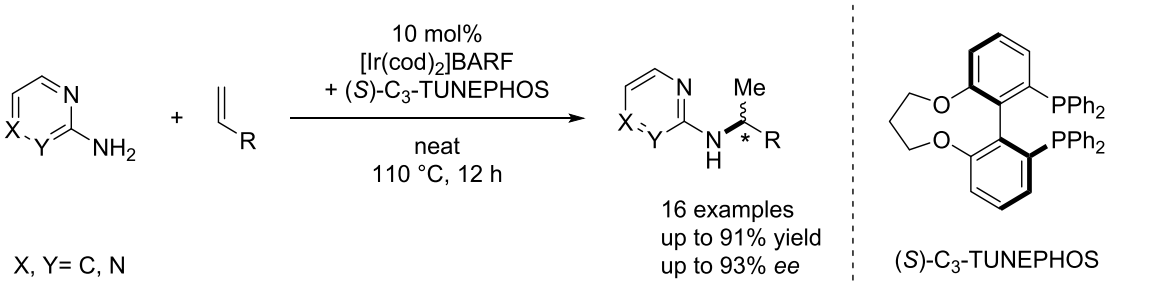
Scheme 3.3 *anti*-Markovnikov selective hydroamination of styrenes with cationic COD-Rh complex.[92]

The activation of C–C unsaturated bonds was also possible *via* palladium catalysis. In a seminal report of *Hartwig* and co-workers, the hydroamination of vinylarenes with anilines was accessible through the catalysis of phosphine-ligated palladium triflates (Scheme 3.4).[95, 96] Mechanistic investigations of this intermolecular hydroamination protocol revealed that it proceeded *via* the generation of a η^3-phenethyl palladium complex, formed upon insertion of an olefin into a palladium-hydride species.



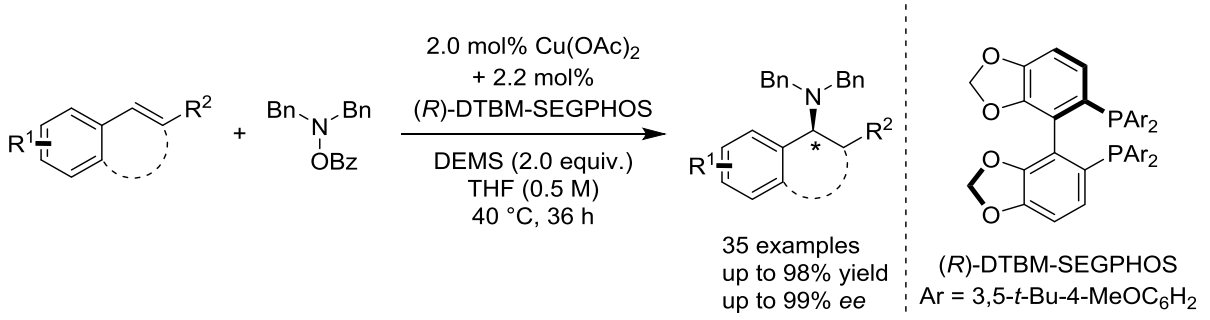
Scheme 3.4 Palladium-catalyzed intermolecular hydroamination of vinylarenes using arylamines.[95, 96]

At a later date, a cationic Ir(I)-C_3-TUNEPHOS complex was used by *Shibata et al.* to catalyze a solvent-free asymmetric intermolecular hydroamination of styrene derivatives with different heteroaromatic amines (Scheme 3.).[93] This methodology furnished Markovnikov products with defined regio- and good to high enantioselectivities, reaching up to 93% *ee*.



Scheme 3.5 Iridium-catalyzed intermolecular enantio- and regioselective hydroamination of alkenes.[93]

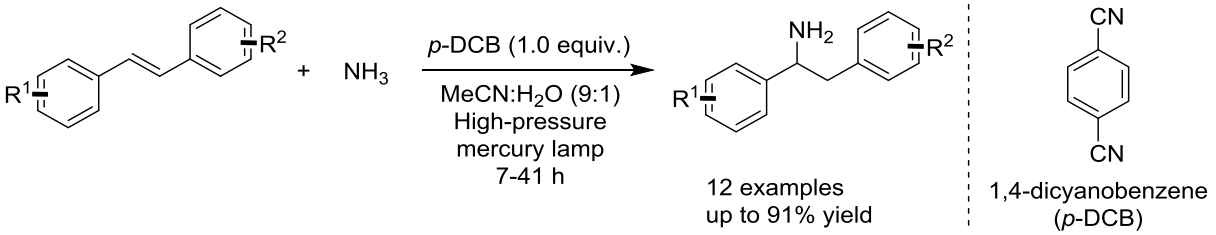
In 2013, *Buchwald* and co-workers disclosed an enantio- and regioselective copper-hydride catalyzed hydroamination of monosubstituted styrenes (Scheme 3.6).[97] This transformation was achieved using an electrophilic amine source as well as a chiral phosphine ligand to generate chiral tertiary amines with high enantiomeric excess.



Scheme 3.6 Asymmetric regioselective copper-hydride catalyzed hydroamination reaction of styrenes.[97]

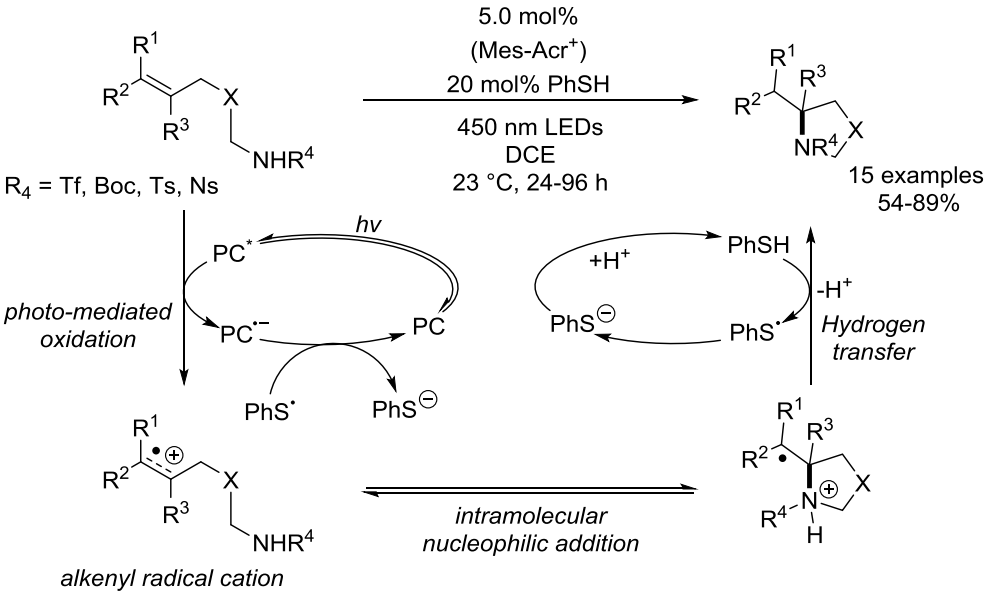
In addition to the mentioned methodologies, photomediated approaches for the regioselective hydrofunctionalization of C–C multiple bonds, especially olefins, were described. In the early 1990s, Yasuda and co-workers reported a photomediated hydroamination protocol of differently substituted stilbenes utilizing ammonia and stoichiometric amounts of 1,4-dicyanobenzene (*p*-DCB) (Scheme 3.7).[98] Upon direct excitation of stilbenes utilizing a high-energetic mercury lamp, a SET towards *p*-DCB enabled

the formation of a radical cation intermediate. Subsequent nucleophilic addition of ammonia across the radical cation intermediate, followed by a reduction and protonation, gave access to the aminated product.



Scheme 3.7 Photoamination of stilbene derivatives using ammonia.[98]

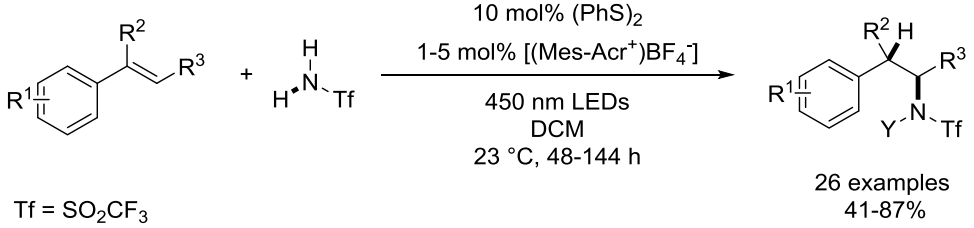
Later, a seminal report by *Nicewicz et al.* described an intramolecular *anti*-Markovnikov selective hydroamidation of electron-rich alkenes utilizing *N*-protected electron-deficient amides (Scheme 3.8).[99] This transformation was realized using *Fukuzumi*'s photocatalyst (Mes-Acr$^+$) and thiophenol (PhSH) as a hydrogen-atom donor. Later mechanistic studies validated the proposed catalytic cycle which commences with an oxidative electron transfer from the electron-rich alkene to the excited-state photocatalyst. Next, the addition of the amine component to the generated alkenyl radical cation intermediate, followed by a subsequent hydrogen-atom transfer from thiophenol furnished the desired hydroamidation product. The formed thiyl radical reoxidized the reduced form of the photocatalyst, ensuring an efficient turn-over and regeneration of the photocatalyst.[100]



Scheme 3.8 Photochemical intramolecular *anti*-Markovnikov hydroamidation of unsaturated amines.[99, 100]

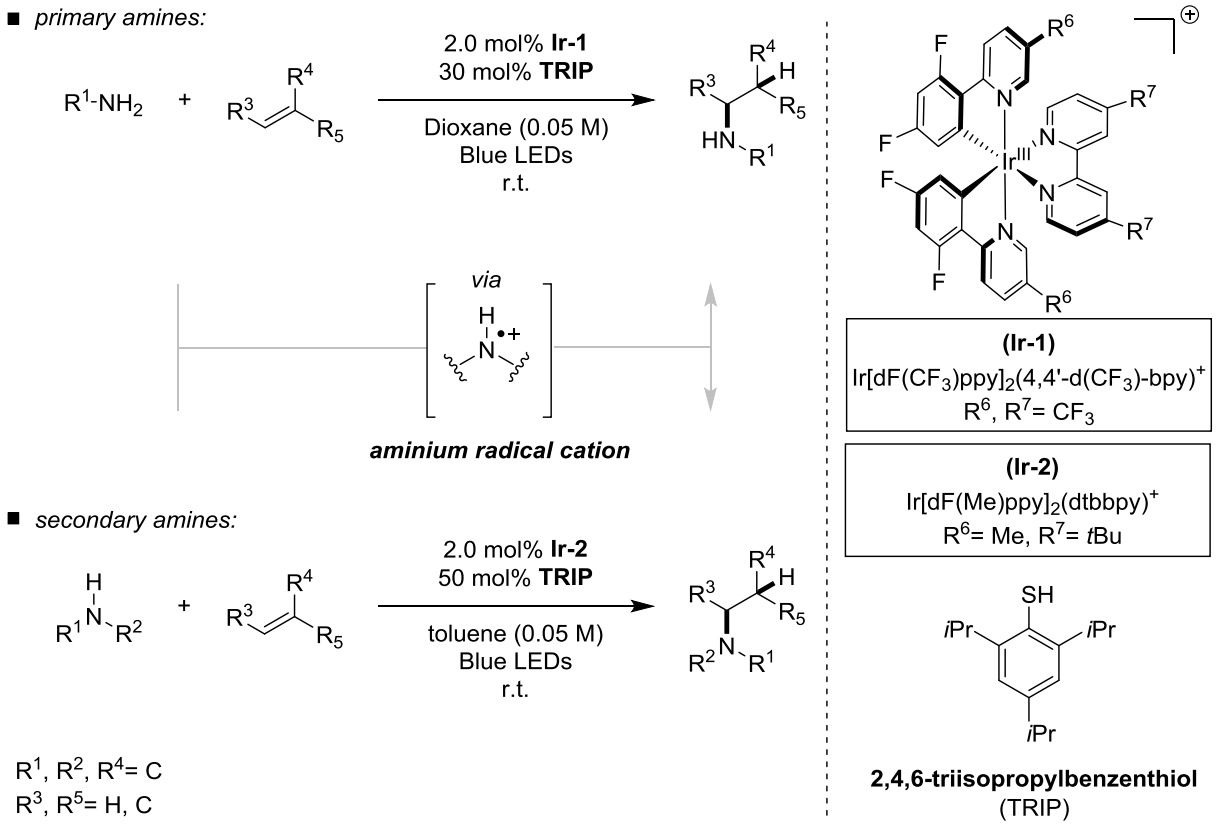
The preceeding protocol for the photochemical intramolecular hydroamidation of unsaturated alkenes was extended to an intermolecular variant (Scheme 3.9). This expanded

protocol allowed the hydroamidation of α- and β-substituted styrenes as well as aliphatic alkenes.[101] The addition of triflylamides and heterocyclic amine nucleophiles provided access to medicinally relevant motifs, including phenethylamines. In the course of the reaction, a reduction of the amount of catalytic hydrogen-atom donor was achieved by replacing thiophenol with phenyl disulfide [$(PhS)_2$], maintaining hereby the good reaction outcome. Yet, this methodology was limited to electron-poor amines given the high oxidation susceptibility of electron-rich amines, which could lead to undesirable side reactions and competetive quenching of the excited photocatalyst.



Scheme 3.9 Photochemical intermolecular *anti*-Markovnikov hydroamidation of olefins.[101]

Knowles and co-workers described a mechanistically orthogonal iridium photocatalyzed hydroamination protocol of unactivated electron-rich olefins using primary and secondary alkyl amines (Scheme 3.10).[102, 103] In contrast to the beforementioned methodology by *Nicewicz* and co-workers comprising the oxidation of unsaturated alkenes, an oxidation of the amine moiety by an SET from alkyl amines to the excited-state photocatalyst enabled the generation of an electrophilic key aminium radical cation intermediate. Thus, an nucleophilic attack from electron-rich olefins towards the aminium radical cation, followed by a hydrogen-atom transfer (HAT), selectively furnished secondary and tertiary amine *anti*-Markovnikov products. The ability of 2,4,6-triisopropylbenzenthiol (TRIP) to reduce α-amino radical intermediates resulting from tertiary amine oxidation is probably responsible for the protective effect.[102] In this context, the impact of possible further oxidation of the formed tertiary alkyl amines is likely prevented by the added (TRIP) co-catalyst. In recent years, numerous research groups have taken advantage of the reactivity of aminium radical cations for diverse transformations.[104, 105]

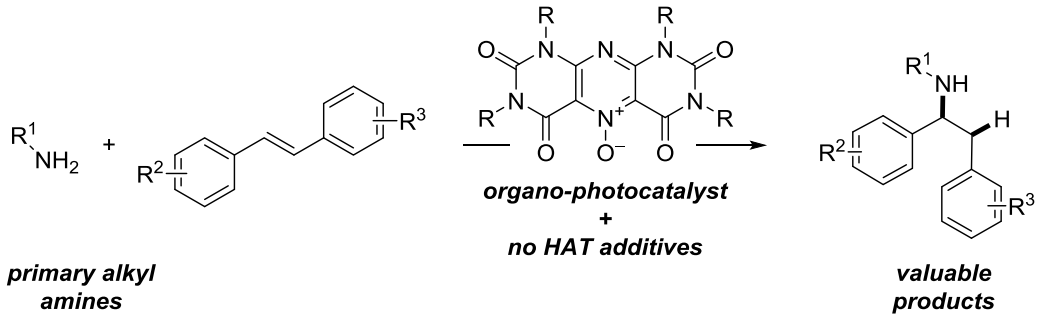


Scheme 3.10 Photoredox catalyzed hydroamination of unactivated olefins *via* aminium radical cation intermediate.[102, 103]

3.2 Objectives

The hydroamination reaction of unsaturated bonds present a key tool to access alkylated amines, known for their pharmaceutical importance and essential as fine chemicals. In addition to well-established transition-metal catalyzed hydroamination protocols, photomediated variants present a complementary tool to access high-value alkylated amines. Nevertheless, numerous photocatalytic methodologies suffer from the need of additional hydrogen-atom transfer reagents to ensure an efficient turnover of the photocatalyst. Also, restrictions regarding the electrochemical properties of used reactants limit the scope of previously mentionend methodologies to electron-poor amines.

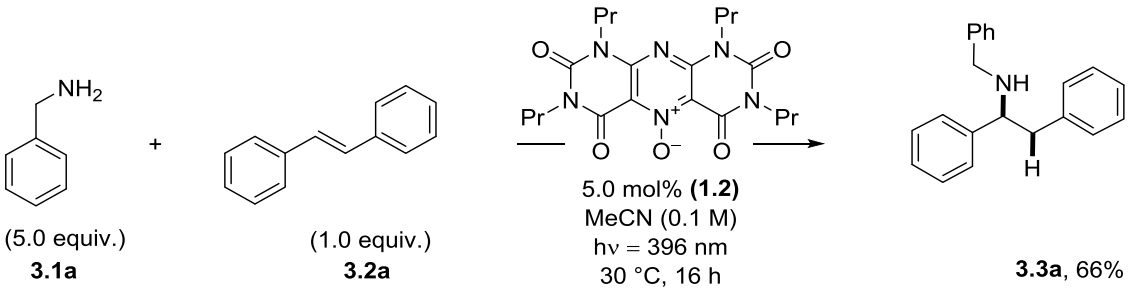
This project was outlined to investigate the photocatalytic hydroamination of various stilbene derivatives using primary alkyl amines. Encouraged by the results in our group, we investigated the efficiency of pyrimidopteridine *N*-oxides as photocatalysts in this transformation (Scheme 3.11).



Scheme 3.11 Pyrimidopteridine *N*-oxides photo-mediated hydroamination of stilbenes using primary alkyl amines.

3.3 Results and discussion

Recently, our group investigated the photoredox catalyzed hydroamination of differently substituted stilbenes using primary alkyl amines. This transformation was possible using catalytic amounts of *n*-propyl pyrimidopteridine-*N*-oxide (**1.2**) as a photocatalyst (Scheme 3.12). The optimization of the reaction conditions revealed that a 5.0 mol% catalyst loading of *n*-propyl-pyrimidopteridine-*N*-oxide (**1.2**) in acetonitrile (0.1 M) as well as a five-fold excess of primary benzylamine (**3.1a**) with respect to (*E*)-stilbene (**3.2a**) generated the best yield of the hydroamination product (**3.3a**) after 16 hours of irradiation.



Scheme 3.12 Optimized conditions for the metal-free PrPPTNO (1.2) photocatalyzed hydroamination of electron-deficient stilbenes (3.2) with primary alkyl amines (3.1).

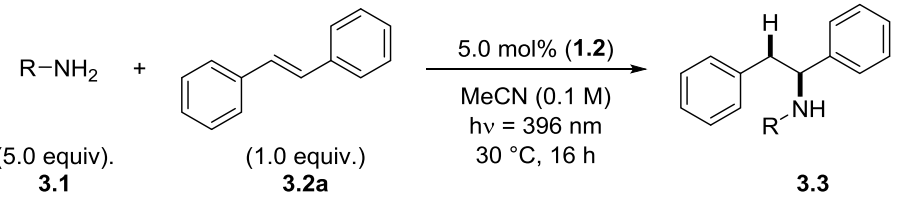
In order to evaluate the applicability of this protocol, differently substituted stilbenes **3.2** and primary alkyl amines **3.1** were investigated (Tables 3.1 and 3.2).

3.3.1 Scope of alkyl amines in the photo-mediated hydroamination reaction

The scope of primary alkyl amines **3.1** was examined in the hydroamination reaction using (*E*)-stilbene (**3.2a**) as an olefin (Table 3.1). Benzylamine (**3.2a**) delivered the corresponding product **3.3a** in a synthetically useful yield of 66% (Table 3.1, entry 1). Notably, generated product **3.3a** could deliver potential biologically active phenethylamine derivative upon deprotection of the benzylic group. Aliphatic amines like *n*-butylamine (**3.1b**) and

cyclohexylamine (**3.1c**) participated in the hydroamination reaction, generating corresponding products **3.3b** and **3.3c** in a comparable moderate yield of 50% (Table 3.1, entries 2 and 3). Also, sillyl protected amino alcohol **3.1d** was well tolerated under reaction conditions, furnishing product **3.3d** (Table 3.1, entry 4). Remarkably, unsaturated allyl amine **3.1e** delivered the corresponding product **3.3e** in only 34% yield (Table 3.1, entry 5). Possible 5-*exo*-trig cyclic adduct of the radical intermediate of **3.1e** was not detected during the reaction. Fortunately, no C–C bond formation was observed between benzylic carbon of benzylamine (**3.1a)** and stilbene **3.2a**, disfavoring the intermediacy of a carbon-centered radical resulting from a benzylic C–H abstraction upon amine oxidation.

Table 3.1 Scope of primary amines (3.1) with (*E*)-stilbene (3.2a) in the photocatalytic hydroamination reaction.



(5.0 equiv). **3.1** (1.0 equiv.) **3.2a** **3.3**

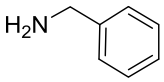
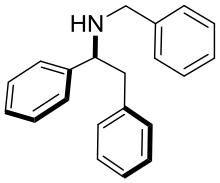
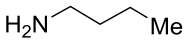
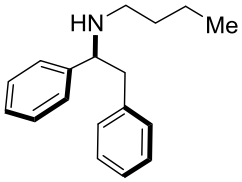
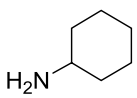
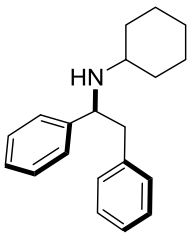
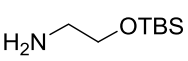
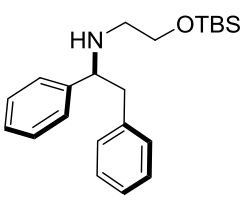
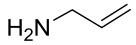
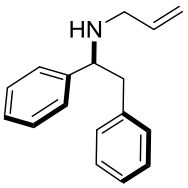
Entry	Substrate		Product		Yield (%)[a]
1		**3.1a**		**3.3a**	66%
2		**3.1b**		**3.3b**	50%
3		**3.1c**		**3.3c**	50%
4		**3.1d**		**3.3d**	40%

Table 3.1 (continued) Scope of primary amines (3.1) with (*E*)-stilbene (3.2a) in the photocatalytic hydroamination reaction.

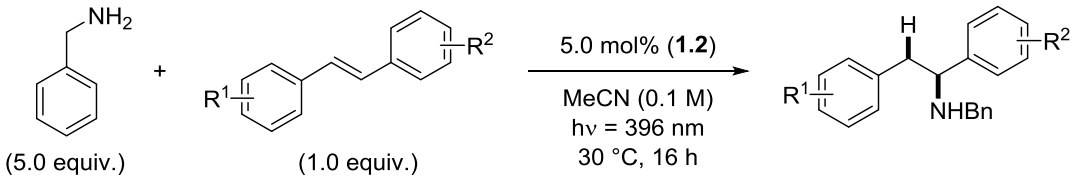
5		**3.1e**		**3.3e**	34%

Reaction conditions: 5.0 equiv. of amine **3.1** were added to a 0.1 M MeCN solution of 1.0 equiv. of (*E*)-stilbene (**3.2a**) and 5.0 mol% of PrPPTNO **1.2** under Ar. The reaction mixture was irradiated for 16 h under UV-light. [a] isolated yields are shown.

3.3.2 Scope of stilbene-derivatives in the photo-mediated hydroamination reaction

Next, the scope of differently substituted stilbene derivatives **3.2** in the hydroamination reaction with benzylamine (**3.1a**) was explored (Table 3.2). Methyl-substituted stilbene **3.2b** generated product **3.3f** (Table 3.2, entry 1) in a comparable yield to non-polarized (*E*)-stilbene (**3.2a**) (Table 3.1, entry 1). Stilbene derivatives bearing electron-withdrawing substituents delivered corresponding products **3.3g**, **3.3h** and **3.3i** in rather lower yields (Table 3.2, entries 2-4). Also, electron-rich arene produced product **3.3k** in a comparatively low yield of 20% after 24 hours (Table 3.2, entry 5).

Table 3.2 Scope of (*E*)-stilbenes (3.2) with benzylamine (3.1a) during the photocatalytic hydroamination.



(5.0 equiv.) **3.1a** (1.0 equiv.) **3.2** **3.3**

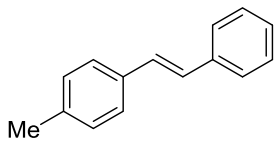
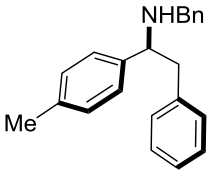
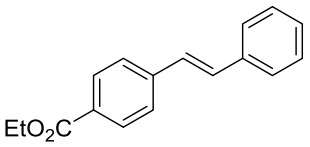
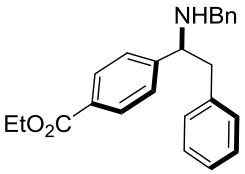
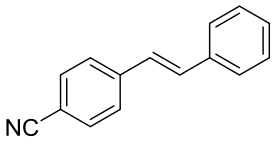
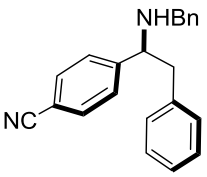
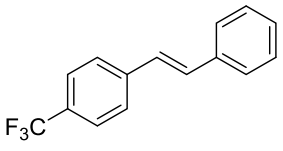
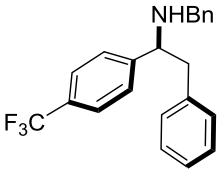
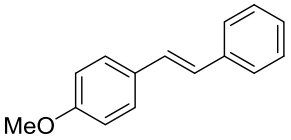
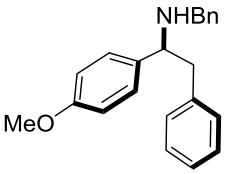
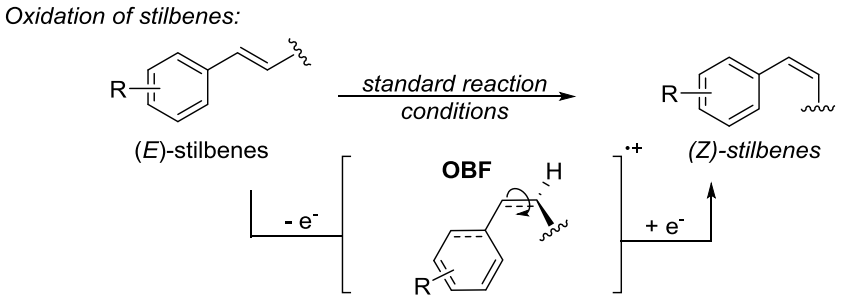
Entry	Substrate		Product		Yield (%)[a], *(d.r.)*
1		**3.2b**		**3.3f**	67%, (63:37)
2		**3.2c**		**3.3g**	40%, (66:34)
3		**3.2d**		**3.3h**	37%, (73:27)

Tabelle 3.2 (continued) Scope of (*E*)-stilbenes (3.2) with benzylamine (3.1a) during the photocatalytic hydroamination.

4		**3.2e**		**3.3i**	32%, (68:32)
5		**3.2f**		**3.3k**	20%[b], (93:7)

Reaction conditions: 5.0 equiv. of benzylamine (**3.1a**) were added to a 0.1 M MeCN solution of 1.0 equiv. of stilbene **3.2** and 5.0 mol% of PrPPTNO **1.2** under Ar. The reaction mixture was irradiated for 16 h under UV-light. [a] isolated yields are shown. [b] 24 h instead of 16 h.

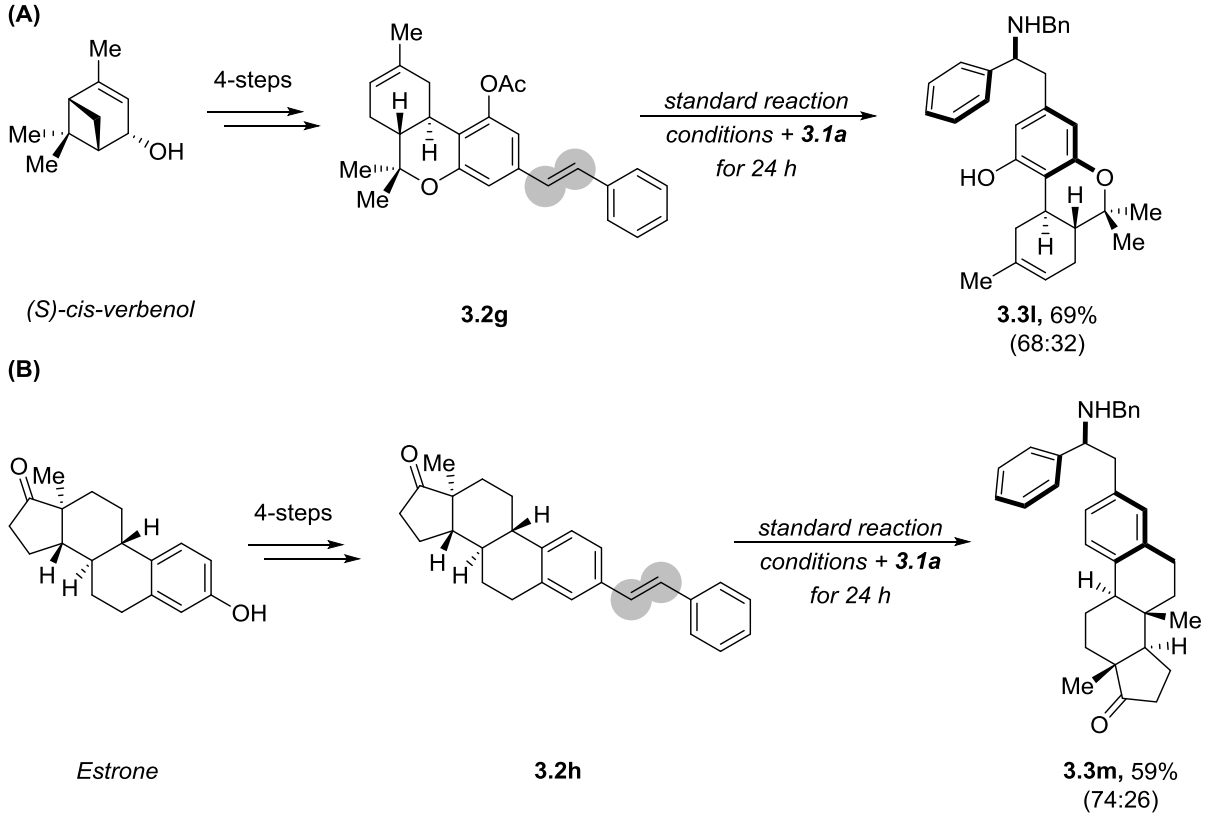
The diminished yields in the case of highly polarized stilbenes could be attributed to the concomitant isomerization reaction of stilbene derivatives (Table 3.2, entries 2-5). For example, the oxidation of the electron-rich arene **3.2f** ($E_{1/2}^{ox}$ (**3.2f**) = +0.79 V *vs.* Ag/AgNO$_3$)[98] by the excited-state photocatalyst **1.2a*** (*E**[PrPPTN*/PrPPTN$^{\bullet-}$] = +1.72 V *vs.* SCE in MeCN) is conceivable under reaction conditions.[106] Thus, a subsequent One-Bond-Flip (OBF) about the ethylene double bond during the radical cation transition state would furnish a mixture of (*E*)- and (*Z*)-stilbenes (Scheme 3.13). Furthermore, an increased amount of homocoupling product of benzylamine (**3.1a**) was observed in the case of **3.2c**, **3.2d** and **3.2e**. Accordingly, this suggest a reaction mechanism comprising also amine oxidation. Hence, simultaneous oxidation of amines as well as stilbenes during the reaction could be considered.



Scheme 3.13 Photomediated oxidation and subsequent isomerization of stilbenes during the hydroamination reaction.

Moreover, challenging stilbene derivatives bearing biologically active moieties were investigated (Scheme 3.14). Stilbene derivative **3.2g**, possessing a tetrahydrocannabinol subunit, was generated over four steps from (*S*)-cis-verbenol according to a literature

procedure.[107] **3.2g** delivered with benzylamine (**3.1a**) the hydroamination product **3.3l** in 69% isolated yield after 24 hours (Scheme 3.14, entry A). Remarkably, the acetyl-protecting group in **3.2g** was cleaved during the hydroamination reaction. In addition, stilbene **3.2h** derived from steroid estrone participated well in the reaction with benzylamine (**3.1a**) (Scheme 3.14, entry B). Corresponding product **3.3m** was obtained in a moderate yield of 59% after 24 hours.

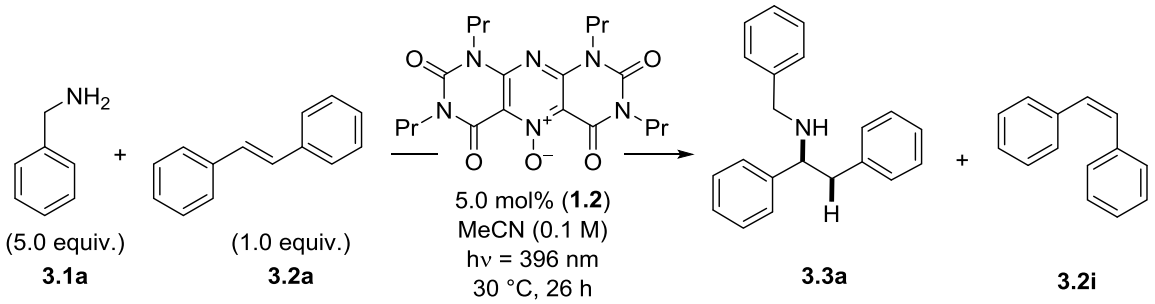


Scheme 3.14 Hydroamination of (A) THC-stilbene derivative (3.2g) ; (B) Estrone-stilbene derivative (3.2h).

3.3.3 Mechanistic considerations

In the course of the photocatalytic hydroamination reaction of (*E*)-stilbene (**3.2a**) and (*Z*)-stilbene (**3.2i**) with benzylamine (**3.1a**), we noticed that product **3.3a** was formed in a good GC-yield of 72% after 26 hours when using (*E*)-stilbene (**3.2a**) (Figure 3.2), whereas the GC-yield of **3.3a** was diminished to 35% after 26 hours when employing (*Z*)-stilbene (**3.2i**) in the reaction (Figure 3.3). Furthermore, increasing the polarity of the used stilbene, as in the case of ester derivative **3.2c**, showed a deteriorating effect on the product yield of **3.3g** (48%, 26 hours) (Figure 3.4). To evaluate the effect of stilbene geometry and polarity on the rate of product formation, kinetic profiles of the corresponding reactants and products were obtained (Figures 3.2, 3.3, and 3.4).

First, the hydroamination reaction of (*E*)-stilbene (**3.2a**) with benzylamine (**3.1a**) was examined (Figure 3.2). The corresponding product **3.3a** was formed with an initial rate of $1.62 \cdot 10^{-6}$ M·s^{-1} reaching a yield of 72% after 26 hours. In addition, minimal (*E*→*Z)* isomerization of **3.2a** to **3.2i** was detected in the presence of benzylamine (**3.1a**), furnishing (*Z*)-stilbene (**3.2i**) in only 6% after 26 hours (initial rate of formation of **3.2i** is $1.06 \cdot 10^{-7}$ M·s^{-1}). The total of yields of **3.3a**, **3.2a** and **3.2i** acccount for 99% at any specific time, indicating a low yield of side products (<1%).



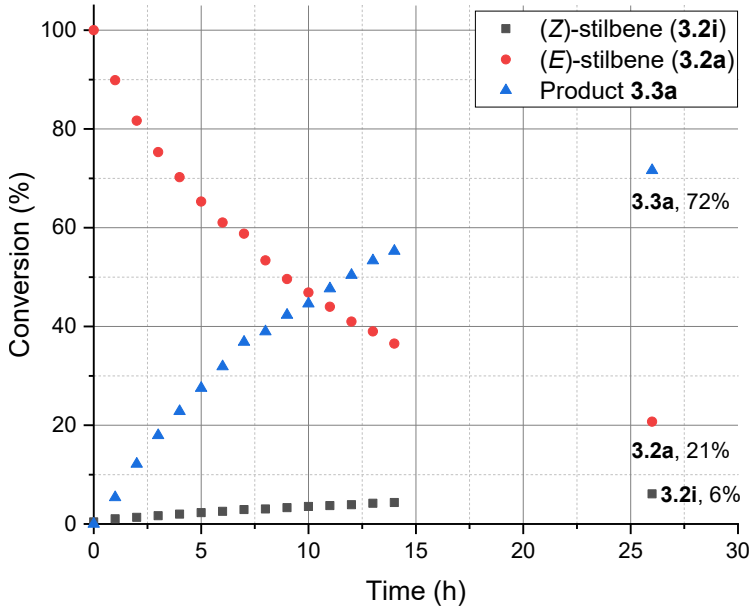
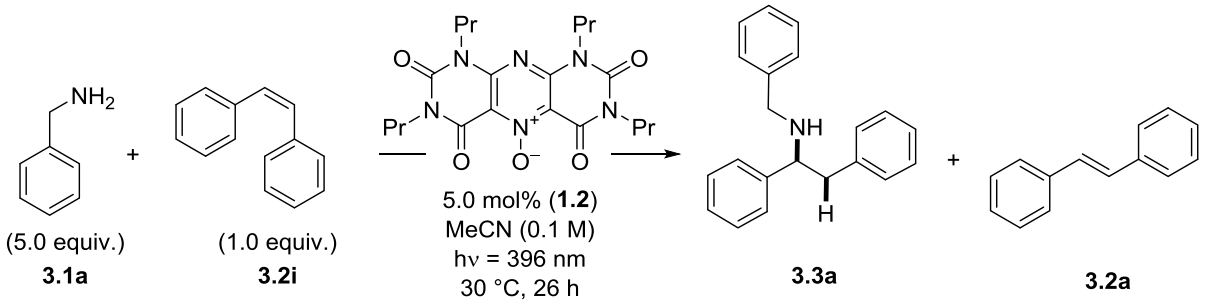


Figure 3.2 Course of formation of (3.3a) from (*E*)-stilbene (3.2a).

On the other hand, in case of the reaction of (*Z*)-stilbene (**3.2i**) with benzylamine (**3.1a**), the hydroamination product **3.3a** was formed with an initial rate of $4.45 \cdot 10^{-7}$ M·s^{-1} and reached a yield of 35% after 26 hours (Figure 3.3). The total of yields of **3.3a**, **3.2a** and **3.2i** acccount for 94% at any specific time, indicating a higher yield of side products (≈ 4%) when using (*Z*)-stilbene (**3.2i**). Similar to the reaction with (*E*)-stilbene (**3.2a**) (Figure 3.2), (*Z*→*E*) isomerization of **3.2i** to **3.2a** provided (*E*)-stilbene (**3.2a**) in 5% GC-yield after 26 hours.

The product formation of **3.3a** is 3.6 times faster from (*E*)-stilbene (**3.2a**) in comparison to (*Z*)-stilbene (**3.2i**). Yet, the grade of isomerization reactions is comparable in both cases accounting to 5-6% after 26 hours.



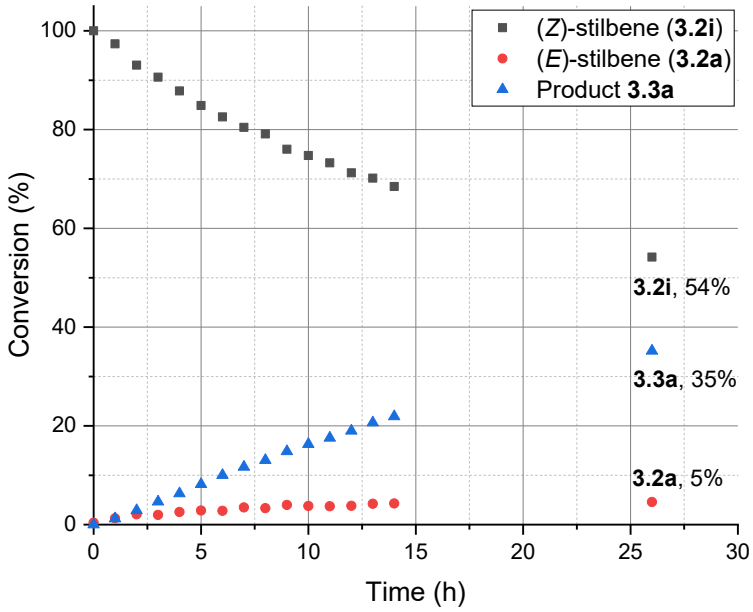
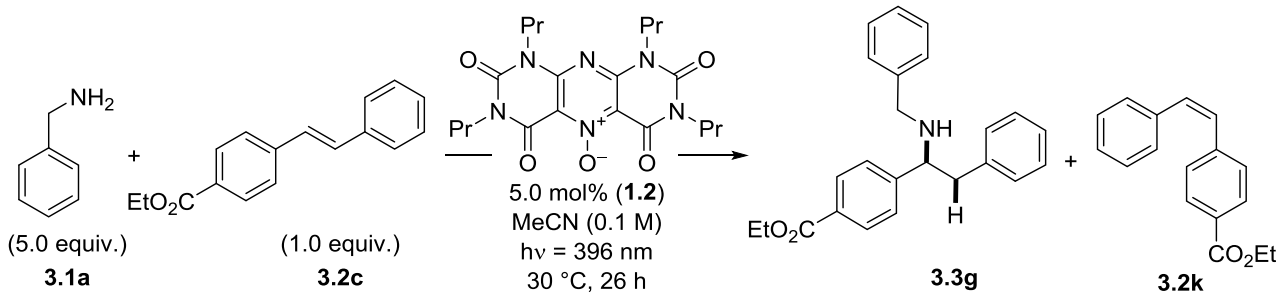


Figure 3.3 Course of formation of (3.3a) from (*Z*)-stilbene (3.2i).

Next, the effect of polarized (*E*)-stilbene ethylester (**3.3g**) in the hydroamination reaction with benzylamine (**3.1a**) was investigated (Figure 3.4). The initial rate of formation of the corresponding product **3.3g** ($1.93 \cdot 10^{-7}$ $M \cdot s^{-1}$) is two times higher as compared to the unpolarized (*E*)-stilbene (**3.2a**) ($1.62 \cdot 10^{-6}$ $M \cdot s^{-1}$). The amount of formed (*Z*)-isomer of stilbene ethylester **3.2k** reached 9% after 26 hours. Thus, the isomerization of the polarized stilbene **3.3g (**$1.93 \cdot 10^{-7}$ $M \cdot s^{-1}$) is 1.5 times faster as compared to the unpolarized stilbene **3.2a** ($1.06 \cdot 10^{-7}$ $M \cdot s^{-1}$). The induction of nonbonding interactions in polarized (*E*)-stilbene ethylester (**3.2c**) results in a reduced conjugation and bond-order of the ethylene group.[108, 109] Thus, a decrease in rotational barrier around the C–C double bond in **3.2c** is evident. This translates through an enhanced susceptibility of **3.2c** for (*E*→*Z*) isomerization.



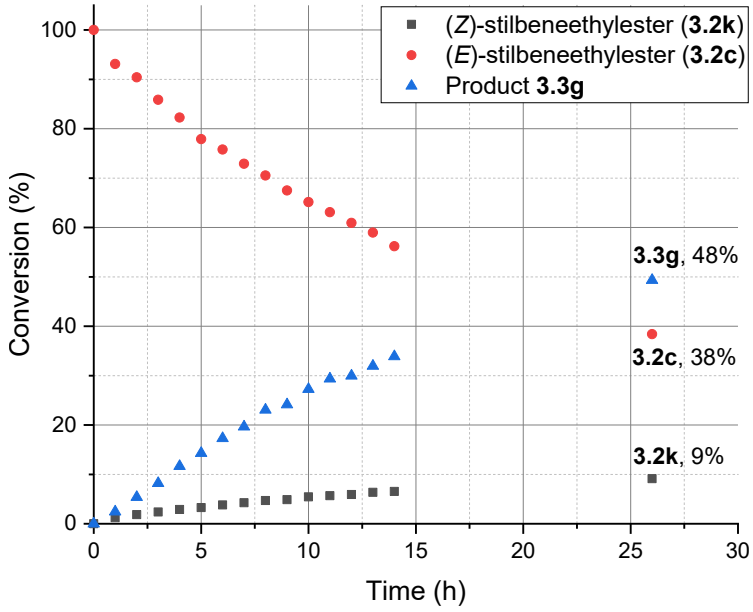
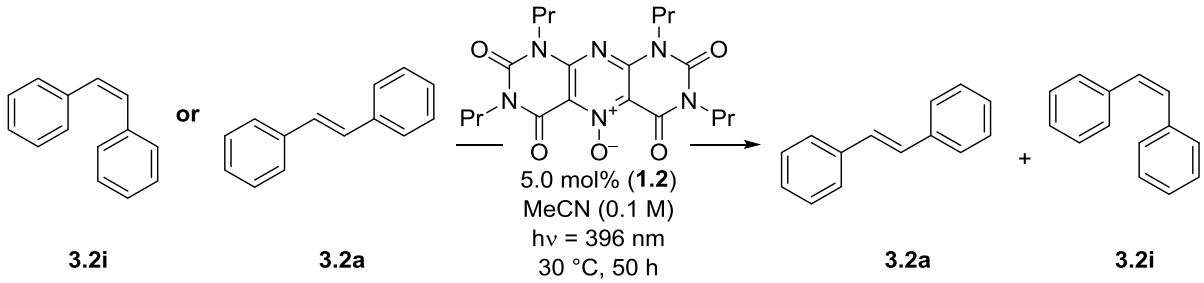
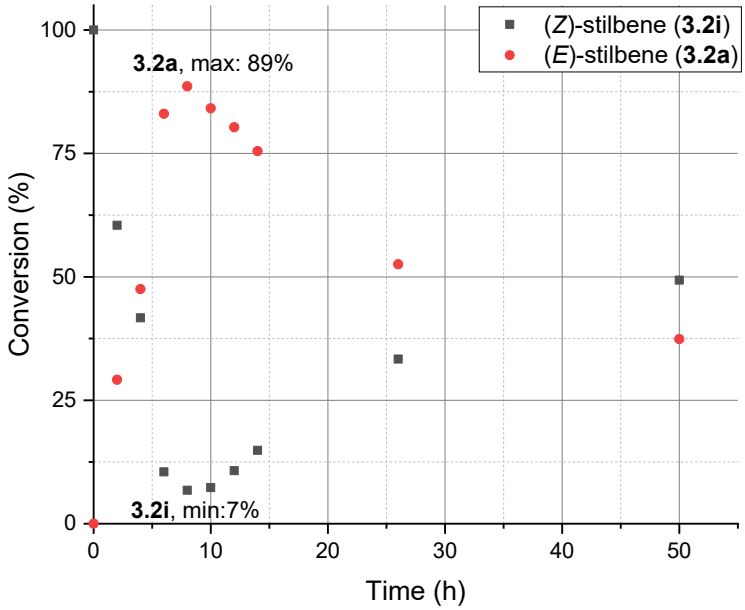


Figure 3.4 Course of formation of (3.3g) from (*E*)-stilbene ethylester (3.2c).

In the absence of benzylamine (**3.1**), different isomerization patterns of both stilbene isomers **3.2a** and **3.2i** became obvious under standard reaction conditions (Figure 3.5). When starting with (*Z*)-stilbene (**3.2i**), thermodynamic (*Z*→*E*) isomerization from **3.2i** to **3.2a** occurred during the first 8 hours of the reaction furnishing a maximum of 89% of (*E*)-isomer **3.2a** (Figure 3.5, top). Subsequently, a slower conversion back to (*Z*)-stilbene (**3.2i**) was evident (49% of **3.2i** after 50 hours). This oscillating behaviour of photoisomerization is atypical.[110] On the other hand, conducting the reaction with the *trans*-isomer (*E*)-stilbene (**3.2a**) resulted in a considerably slower and constant contra-thermodynamic (*E*→*Z*) isomerization (Figure 3.5, bottom), accounting up to 25% of (*Z*)-isomere **3.2i** after 50 hours. No photostationary states were achieved in both reactions during the investigated reaction time of 50 hours. The shape of both (*Z*)- and (*E*)-stilbene concentration-time curves are almost symmetrical to each other, suggesting that none of the used reactants were consumed considerably during the photoisomerization reactions.





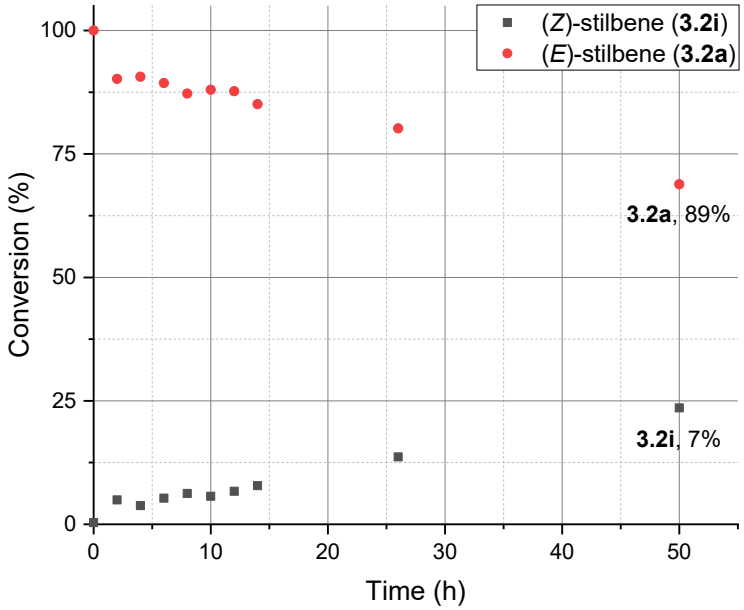


Figure 3.5 PrPPTNO (1.2) photo-mediated isomerization reaction of (*E*)-stilbene (3.2a) (top); (*Z*)-stilbene (3.2i) (bottom).

To confirm the photocatalytic nature of the investigated hydroamination protocol, an On-Off experiment was conducted (Figure 3.6). The reaction of benzylamine (**3.1a**) with stilbene **3.2a** under standard reaction conditions was irradiated for two hours, then the light source was switched off for two consecutive hours. This process was repeated alternately for 12 hours. Samples were taken every two hours and analyzed by calibrated GC. No hydroamination product **3.3a** was formed during the off phases. Thus, a radical propagation mechanism leading to product formation can be excluded.

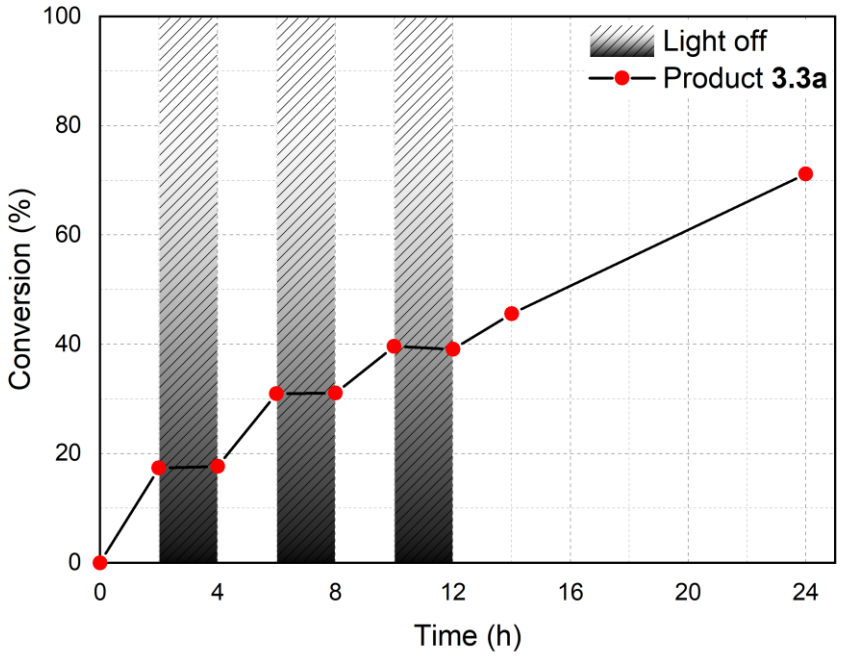
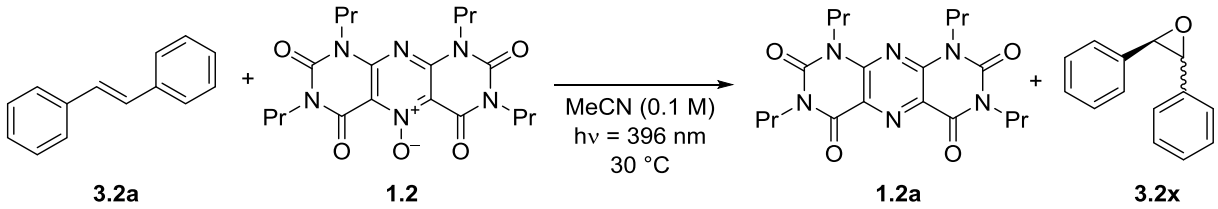


Figure 3.6 Course of PrPPTNO (1.2) photo-mediated formation of (3.3a) during the On-Off experiment.

Additionally, Stern-Volmer quenching experiments conducted with *Richy Hauptmann* revealed that both reaction partners, (*E*)-stilbene (**3.2a**) (K_{sv} = 40.0 M^{-1}) and benzylamine (**3.1a**) (K_{sv} = 27.8 M^{-1}), are able to quench the fluorescence of the excited-state form of the deoxygenated photocatalyst **1.2a***. Accordingly, three reaction mechanisms are feasible from the singlet excited state S_1 of **1.2a***.

All mechanistic proposals for the photo-mediated hydroamination of stilbenes with primary amines commence with a light-promoted deoxygenation of the *N*-oxide photocatalyst **1.2**. The oxygen atom is transferred to stilbene **3.2** to form stilbeneoxide **3.2x** as verified by GC and GC-MS (Scheme 3.15).



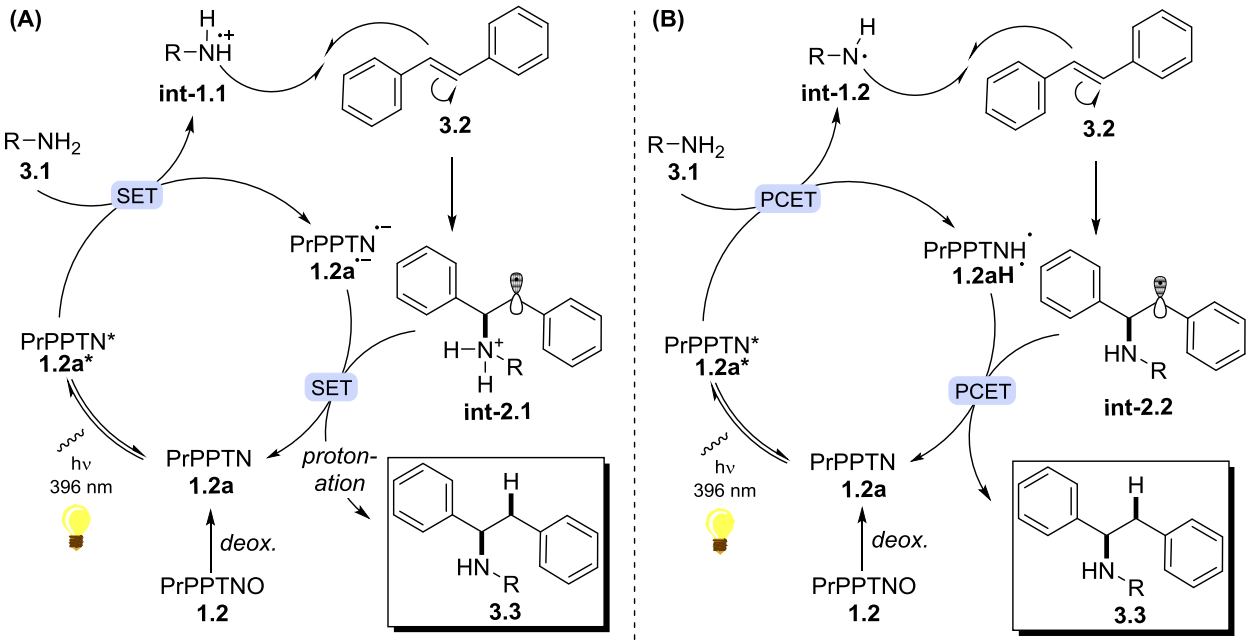
3.2a **1.2** **1.2a** **3.2x**

Scheme 3.15 Photo-mediated deoxygenation of the propyl pyrimidopteridine *N*-oxide (1.2).

Upon irradiation, the deoxygenated heterocycle **1.2a** is promoted to its excited state **1.2a*.** In the first two scenarios, the amine (e.g. benzylamine (**3.1a**), $E_{1/2}^{ox}$ [**3.1a**$^{\bullet+}$/**3.1a**] = +1.29 V *vs.* SCE in MeCN) is oxidized by the excited state photocatalyst **1.2a*** (E^*[**1.2a***/**1.2a**$^{\bullet-}$] = +1.72 V *vs.* SCE in MeCN) to yield the corresponding aminium radical cation **int-1.1** (Scheme 3.16).

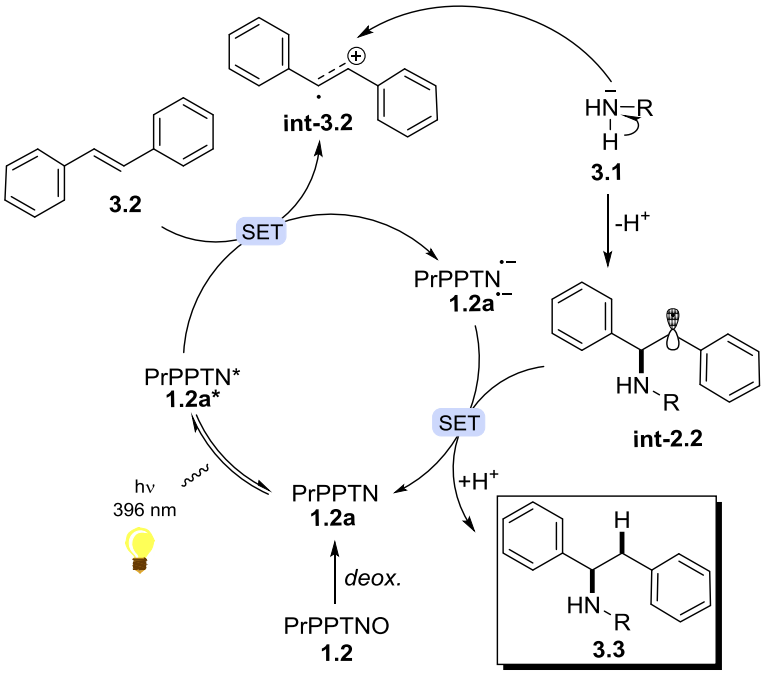
The generated aminium radical cation **int-1.1** can either participate directly in the hydroamination reaction of stilbenes **3.2** in an electrophilic manner (Scheme 3.16, entry A). The resulting radical intermediate **int-2.1** is then reduced to the corresponding anion by SET from the reduced photocatalyst **1.2a**$^{\bullet-}$ ($E_{1/2}^{red}$ [**1.2a**$^{\bullet-}$/**1.2a**] = −1.58 V *vs.* SCE in MeCN) which regenerates the ground state catalyst. The desired product **3.3** can be formed from the benzylic carbanion intermediate *via* an intramolecular 1,3-proton shift or more likely through deprotonation of excess amine **3.1**.

In another plausible mechanism involving nitrogen centered radicals, the formed aminium radical cation can be deprotonated by the reduced form of the photocatalyst **1.2a**$^{\bullet-}$ through a proton coupled electron transfer (PCET), which allows the formation of a neutral aminyl radical **int-1.2** and the protonated form of the radical photocatalyst **1.2aH**$^{\bullet}$ (Scheme 3.16, entry B). Subsequent addition of the the neutral aminyl radical **int-1.2** across the unsaturated stilbene **3.2**, followed by a fast hydrogen-atom transfer from **1.2aH**$^{\bullet}$ to radical intermediate **int-2.2** in a second PCET step gives access to the desired hydroamination product **3.3**, simultaneously restoring the active form of the photocatalyst **1.2a**.



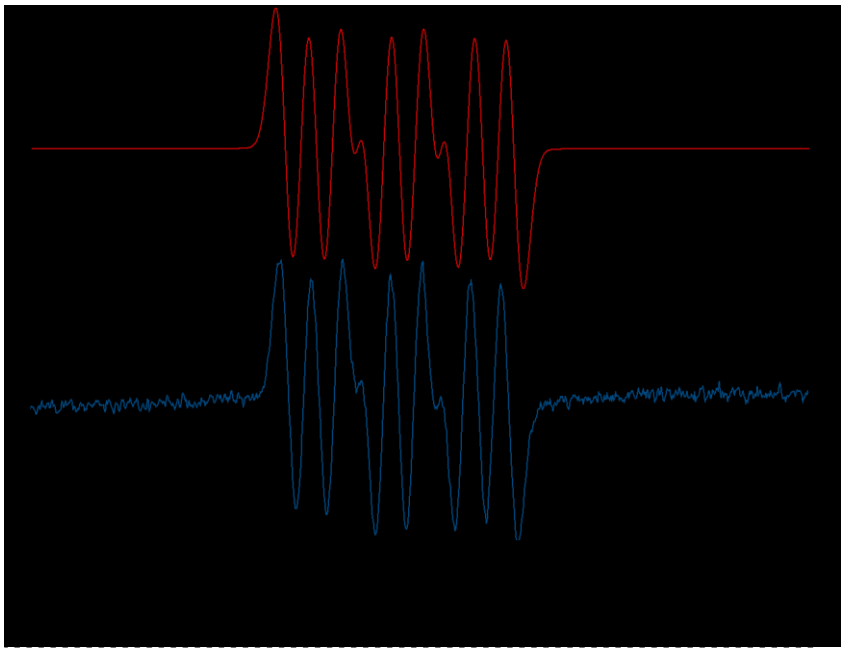
Scheme 3.16 Proposed mechanism for the photocatalytic hydroamination *via* oxidation of amines; (A) involving aminium radical cation (int-1.1) ; (B) involving neutral aminyl radical (int-1.2).

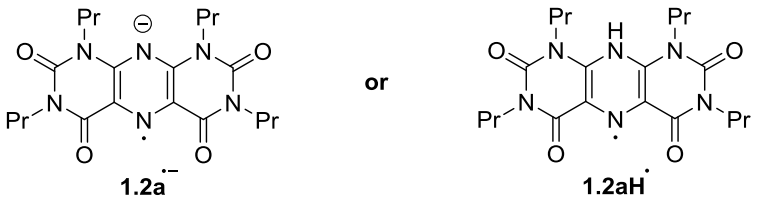
Alternatively, the strong reduction potential of the excited-state photocatalyst **1.2a** allows also the oxidation of stilbenes ($E_{1/2}^{ox} \geq +1.50$ V vs. SCE in MeCN), generating radical cation intermediate **int-3.2** (Scheme 3.17). Next, nucleophilic attack of the amine of **3.1** towards **int-3.2** and subsequent deprotonation furnishes the neutral benzylic radical **int-2.2**. The reduction of radical intermediate **int-2.2** by an SET from the reduced form of the ground-state photocatalyst **1.2a**$^{\bullet-}$ ensures the turnover of the photocatalyst. Finally, protonation of the anionic form of **int-2.2** gives access to the desired product **3.3**.



Scheme 3.17 Proposed mechanism of the photocatalytic hydroamination *via* oxidation of stilbenes.

In cooperation with *Richy Hauptmann* and *Dr. Jabor Rabeah*, electron paramagnetic resonance (EPR) spectroscopy of two irradiated solutions of 1) benzylamine (**3.1a**) and the deoxygenated photocatalyst **1.2a** and 2) (*E*)-stilbene (**3.2**) and photocatalyst **1.2a** were conducted. Indeed, a reduced radical form of the photocatalyst (**1.2a**$^{\bullet-}$ or **1.2aH**$^{\bullet}$) was detected in the first solution, indicating an electron transfer from benzylamine (**3.1a**) to the excited-state photocatalyst **1.2a*** (Figure 3.7). Yet, further analysis of the hyperfine splitting (HFS) of the radical EPR-spectrum were indecisive whether a deprotonation of aminium radical cation **int-1.1** took place or a solely electron-transfer from benzylamine (**3.1a**) occurred. An additional small coupling constant of a hydrogen nucleus (A_H > 0.4 G) does not induce notable changes to the simulated EPR spectrum.





1.2a$^{\bullet-}$ *radical anion form*

1.2aH$^{\bullet}$ *protonated neutral radical form*

Figure 3.7 EPR spectrum of an irradiated solution 1 containing benzylamine (3.1a) and PrPPT (1.2a); the orange line is a simulated spectrum considering a hyperfine splitting from two nonequivalent N (blue line, A_{N1} = 8.25 G and A_{N2} = 3.25 G)

Contrarily, the irradiated solution of stilbene (**3.2**) and deoxygenated photocatalyst **1.2a** remained EPR-silent. By combining the two facts that stilbene-isomerization was operational under reaction conditions and the absence of a radical detection, it quickly becomes obvious that the photoisomerization of stilbenes proceeds *via* an energy transfer from the singlet

excited-state of **1.2a***. Thus, the photo-mediated hydroamination of stilbenes proceeds most likely *via* an amine oxidation pathway as depicted in Scheme 3.16.

3.4 Conclusion

In conclusion, a metal-free photocatalyzed hydroamination reaction of stilbenes by using primary alkyl amines and tetrapropyl pyrimidopteridine-*N*-oxide as a photocatalyst have been developed. A wide range of primary amines comprising linear and branched examples as well as functionalized amines were tolerated under the reaction conditions. Also, numerous stilbene derivatives, including natural product derived components were competent coupling partners. Thus, valuable hydroamination products were obtained without the need of any sacrificial additives, especially hydrogen-atom transfer reagents.

Conducted mechanistic experiments validated the photocatalytic nature of this methodology and the involvement of radical electron transfer events. Yet, different possible reaction mechanisms became evident while analyzing the reaction and the products. The oxidation of primary amines as well as used stilbenes is both thermodynamically feasible. Yet, the analysis of EPR experiments favors the amine oxidation pathway. The deprotonation of the aminium radical cation, generated in the case of amine oxidation, could not be unambigiously disclosed. For the moment, a clear statement about the operating mechanisms and the involvement of a neutral aminyl species is difficult to make. Thus, further mechanistic studies are necessary.

4 Fluorescence-based Bioimaging and novel therapeutic approaches for the *Wilson*'s disease

4.1 Introduction

Copper (Cu) is an essential, ubiquitous, trace metal found in all living organisms. It occupies diverse roles in living cell physiology as a catalytic cofactor of various enzymes involved in electron transfer reactions, free radical scavenger, and mitochondrial processes.[111] Copper, is a redox-active metal that exists in both Cu(II) and Cu(I) states in living organisms.[112] Yet, the presence of copper as Cu(I)-ions within cells is more favored due to the reductive intracellular environment.[113]

A delicate and precise balance between intake (influx) and elimination (efflux) of cellular copper prevails and maintains a steady copper homeostasis.[112] In case of perturbance of this balance, pathological conditions and cytotoxicity are described. An excess of free circulating copper is associated with the formation of highly reactive oxygen species (ROS), resulting in oxidative stress and cell damage.[114] Oxidation of proteins, lipid peroxidation, and subsequent injury and degradation of cell components are often the result of excessive copper levels.[115]

The *Wilson*'s disease is an inherited autosomal recessive genetic disorder of the human copper metabolism resulting in accumulation of pathological copper levels.[116] This disorder is mainly caused by mutations of the ATP7B gene, which codes for a P-Type copper transporting ATPase (Wilson disease protein) in the *trans*-Golgi network.[116] Consequently, misfolded and residual/nonfunctional ATP7B proteins, especially in the liver and brain, are responsible for abnormal copper levels leading to a variety of neurological and psychiatric symptoms.[117]

Among numerous cell mechanisms to avert protein misfolding, molecular chaperones in addition to the ubiquitin-proteasome system (UPS) adopt a critical function. They comprise a family of proteins responsible of protein synthesis regulation, folding into their corresponding native fold, unfolding in case of disrupted elements and degradation.[118, 119] Molecular chaperones are proteins which are able to bind and stabilize mis- or unfolded proteins, facilitating the correct folding of non-native conformations.[119] Also, in case of a

defect misfolded protein, a series of ubiquitylation enzymes are activated. These enzymes are responsible for the ligation of multiple ubiquitin units adjacent to the misfolded unit. Ubiquitin is a regulatory protein found ubiquitously in the organism, marking defective proteins for degradation *via* the proteasome.[120]

It has been reported that multiple mutations of ATP7B in *Wilson*'s disease show enhanced interactions with enzymes responsible for protein ubiquitination and proteosomal degradation.[121] Thus, premature breakdown of ubiquitinated, misfolded proteins, regardless of the fact that these proteins can effect partial activity and residual functionality, is anticipated.

Given the importance of these mechanisms in relation to the longevity of cells and restoration of function, substantial interest in therapeutic intervention evoked.[122, 123]

Currently, symptomatic therapies are only capable of reducing the abnormal concentration of free circulating copper in human body.[124] These therapies consist of zinc supplementation as well as copper chelation using triethylentetramine and *D*-penicillamine (Figure 4.1).[125] Despite the importance of current therapies, causal treatment approaches directly addressing the misfolded ATP7B protein and restoration of function are not available.[126]

- *Copper Chelating Agents:*

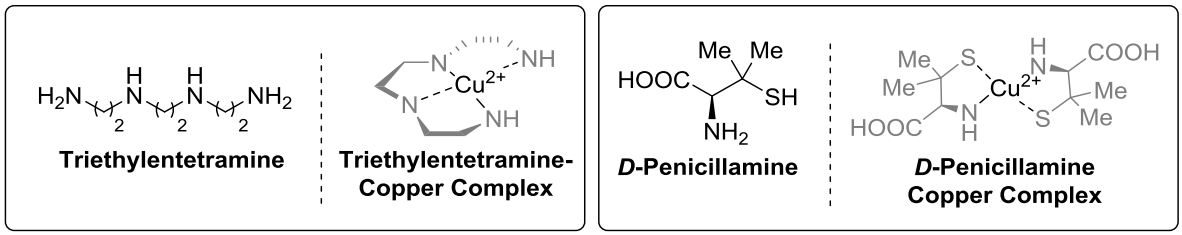


Figure 4.1 Copper chelating compounds for treating *Wilson*'s disease and the corresponding copper complex structures.

Thiazolidinediones, also referred to as glitazones, are a class of heterocyclic-, biologically active molecules (Figure 4.2).[127] They act by activating the peroxisome proliferator-activated receptors (PPAR) that constitute a group of nuclear receptors. Especially, the subfamily PPAR gamma (PPAR-γ) is activated by glitazones.[128] Furthermore, dual activation of both PPAR gamma and alpha subunits is feasible by novel representatives like lobeglitazone (Figure 4.2, right). Upon activation, the receptor-agonist complex in addition to the retinoid receptors are capable of modulating the transcription of multiple genes.[129] The group of *Marfella et al.* reported that rosiglitazone (Figure 4.2, left), one of the early

representatives of the glitazone family, is able to interrupt the ubiquitin proteasome pathway.[130] Also, *Lukas et al.* revealed an inhibiting effect of rosiglitazone on the ubiquitination of α-galactosidase A enzyme in the course of *Fabry*'s disease.[131]

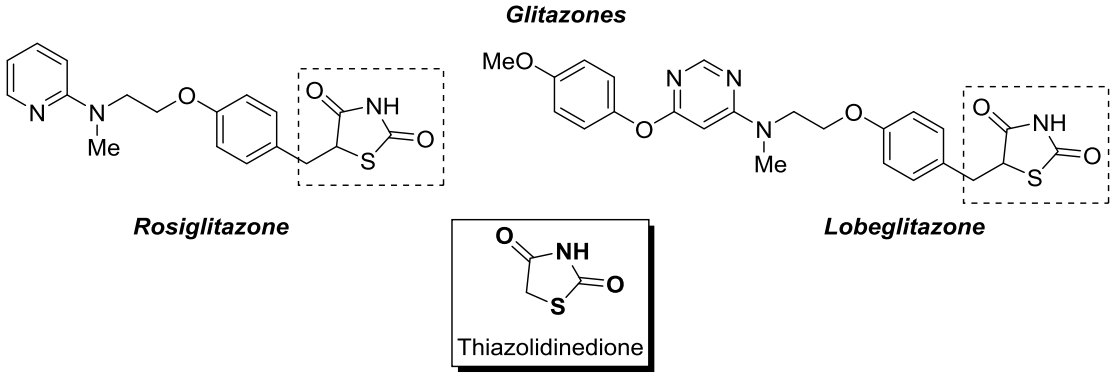


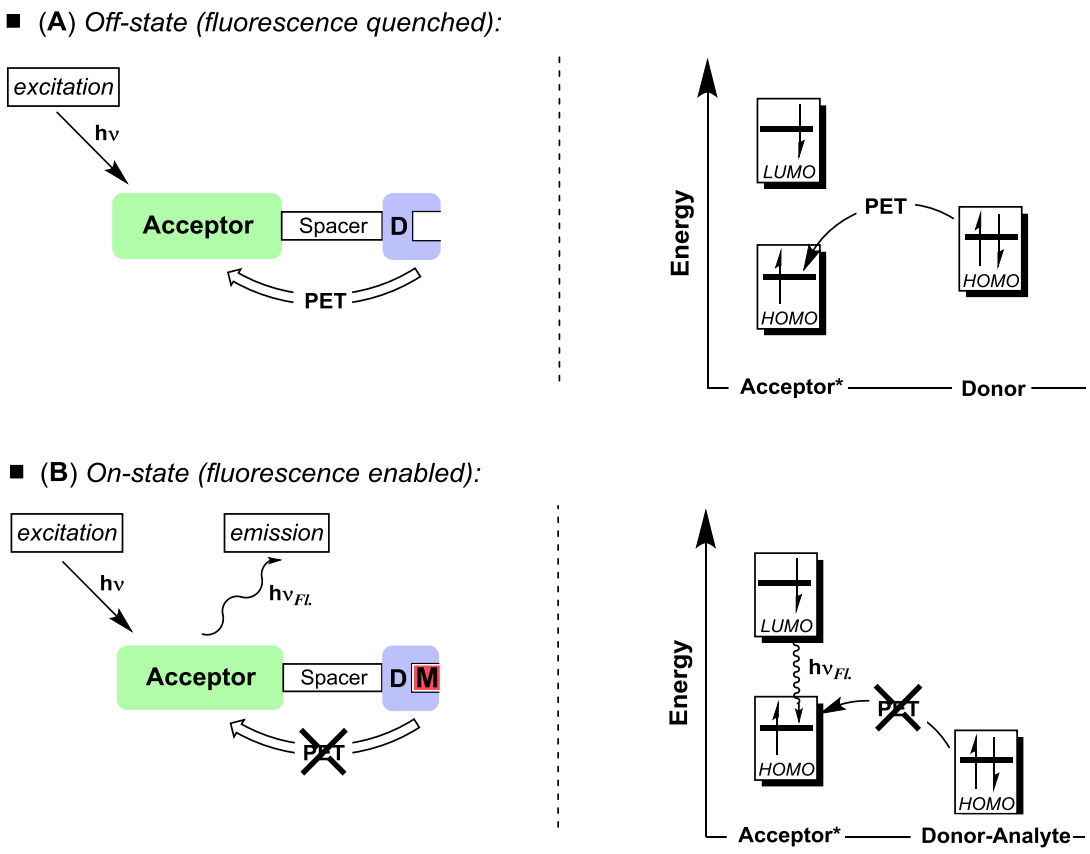
Figure 4.2 Molecular structure of two thiazolidinedione representatives: Rosiglitazone (left) and Lobeglitazone (right).

In addition to the targeted and precise treatment of a disease, a correct and accurate diagnosis is a crucial prerequisite for a target-oriented therapy.[132] Among several methodologies, fluorescence-based bioimaging represents a reliable technique for unequivocal diagnosis and non-invasive *in cellulo* monitoring of different components in living cells, especially trace metal ions.[133] This is achieved by using selective fluorescent proteins or small molecular dyes.[134] The large Stokes shift of fluorescent probes, manifested by a significant difference between absorption- and emission wavelengths with minimal interference, renders this method selective and sensitive as well as quantifiable for trace metal ion analysis.[135] Beside the intramolecular charge transfer (ICT) and the Förster resonance energy transfer (FRET), one of the most common adapted mechanisms for fluorescence biosensing is the suppression of photoinduced electron transfer (PET) in fluorescent molecules upon interaction with a specific analyte.[136]

Fluorescent molecular probes consist for the most instances of two main substructures, an excitable fluorophore part (acceptor, A) and an electron-rich analyte recognition ionophore (donor, D) connected through a spacer (Scheme 4.1).[133] Upon irradiation with a suitable light source, an excitation of the fluorophore part (A) takes place as one electron of the HOMO of (A) is excited to the corresponding energetically higher lying LUMO. A relaxation of the electron of the fluorophore in the excited state back to the corresponding HOMO in form of fluorescence is hindered and alternatively quenched by a PET from the donor (D) moiety. The quenched state is referred to as the "off-state" of a fluorescent probe

(Scheme 4.1, entry A). This form of quenching is thermodynamically favorable since the energy level of the HOMO of (D) lies in between the HOMO and LUMO of (A).

In case of interaction of the donor part (D) with a specific metal (M) in form of e.g. coordination, the HOMO energy level of (D) is reduced to a lower energetic level in comparison to the HOMO of the acceptor (A) (Scheme 4.1, entry B). Thus, a PET quenching from (D) to the HOMO of excited (A) is thermodynamically unfavorable. The resulting inhibition leads to a re-establishment of the fluorescence of (A). The latter state is referred to as the "on-state" of the fluorescent probe. Thus, the restored fluorescence of the metal-bound chemosensor can be detected and quantified using fluorescence microscopy.



Scheme 4.1 General scheme of the mode of action of fluorescent probes and the corresponding energy diagrams in off and on states.

In course of the *Wilson*'s disease, the selective detection and quantification of labile copper(I) levels are indispensable. This is particularly challenging due to the parallel presence of copper in different oxidation states and other cellular divalent metal ions like iron, zinc and magnesium.[137] This hurdle is overcome by using a polythioether-rich scaffold as an analyte binding domain, commonly bis(2-((2-(ethylthio)ethyl)-thio)ethyl)amine (BETA) (Figure 4.3). The high selectivity of Cu(I) for polythioether substructures could be explained by the principles of hard and soft bases and acids (HSAB) described by *Pearson*.[138] Cu(I)-

ions, as a soft Lewis-acid, are likely to react and form a more stable complex with a soft Lewis-base, in this case sulfur atoms of the polythioether moiety.[139] Hence, increased interactions of complexed Cu(I)-ions with the nitrogen of BETA leads to a more vigorous impact on the acceptors moiety (A) in its excited-state. This scaffold has been adopted in various rhodol-based (CPF1) and BODIPY-based (RCS1, CS1 and CS3) Cu(I)-chemosensors (Figure 4.3) and is used for copper concentration evaluation in a wide range of living cell cultures.[140, 141]

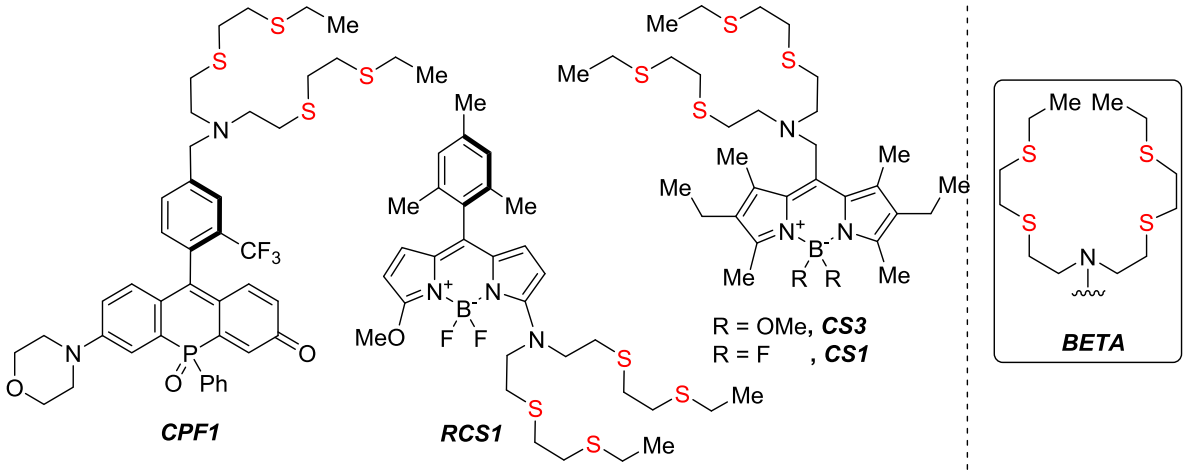


Figure 4.3 Molecular structures of Cu(I)-chemosensors with common polythioether (BETA) acceptor moiety.

4.2 Objectives

The *Wilson*'s disease is an autosomal genetic disorder manifested in defective and misfolded ATP7B protein, which plays an important role in copper trafficking in human body. As a result, excessive harmful amounts of copper accumulate in human body, leading to organ failure and even, in severe cases, to death. To establish a valid therapeutic concept, diagnosis as well as *in vitro* cell tests of potential compounds are crucial. Based on former reports for the synthesis and application of fluorescent probes for the detection and quantification of cellular copper levels, we envisioned to employ two copper-chemosensors, CS3 and CPF1, to determine the copper levels in cells with defective ATP7B proteins. Therefore, we revised and optimized the synthesis of CS3, CPF1 and its corresponding control molecule Ctrl-CPF1.

Also, assumed from previously noticed effects of two glitazone derivatives on the mechanism of protein degradation in cells, we surmise that affected cells showing mutations in the ATP7B-gene would benefit from a treatment with glitazones. A possible pharmacological interference in the degradation of misfolded, yet partially functional, ATP7B

protein could lead to a partial restoration of function. Therefore, we synthesized and revised the synthesis of two glitazone derivatives, rosiglitazone and lobeglitazone.

4.3 Results and discussion

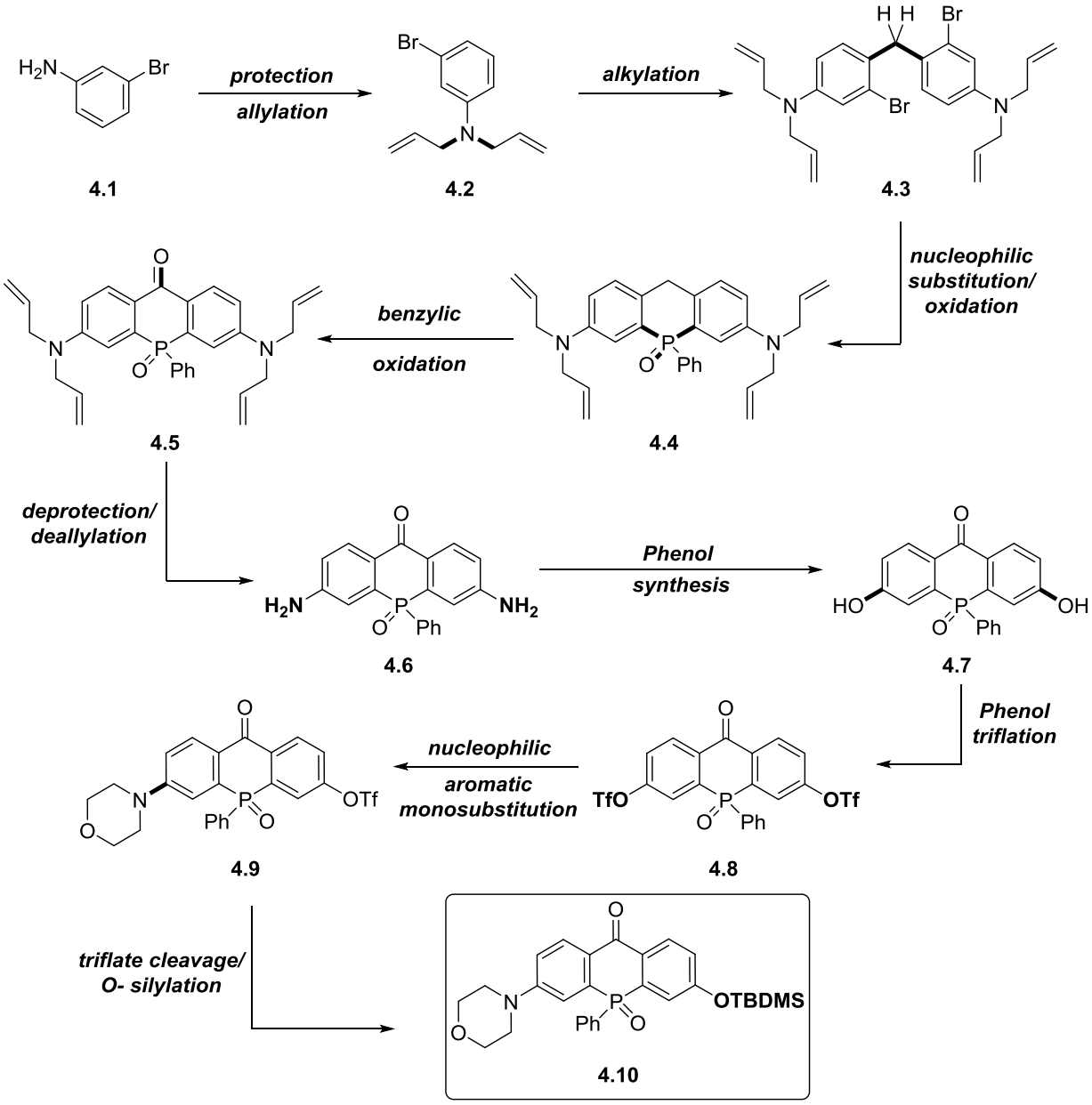
4.3.1 Fluorescence-based bioimaging of labile cellular copper levels

The synthesis of BODIPY-based (CS3) as well as the Rhodol-based (CPF1) Chemosensors and its corresponding control molecule (Ctrl-CPF1) were conducted and optimized taking into account the initial synthetic reports.[140, 142-144]

4.3.1.1 Synthesis of copper Chemosensor CPF1 and the corresponding control molecule ctrl-CPF1

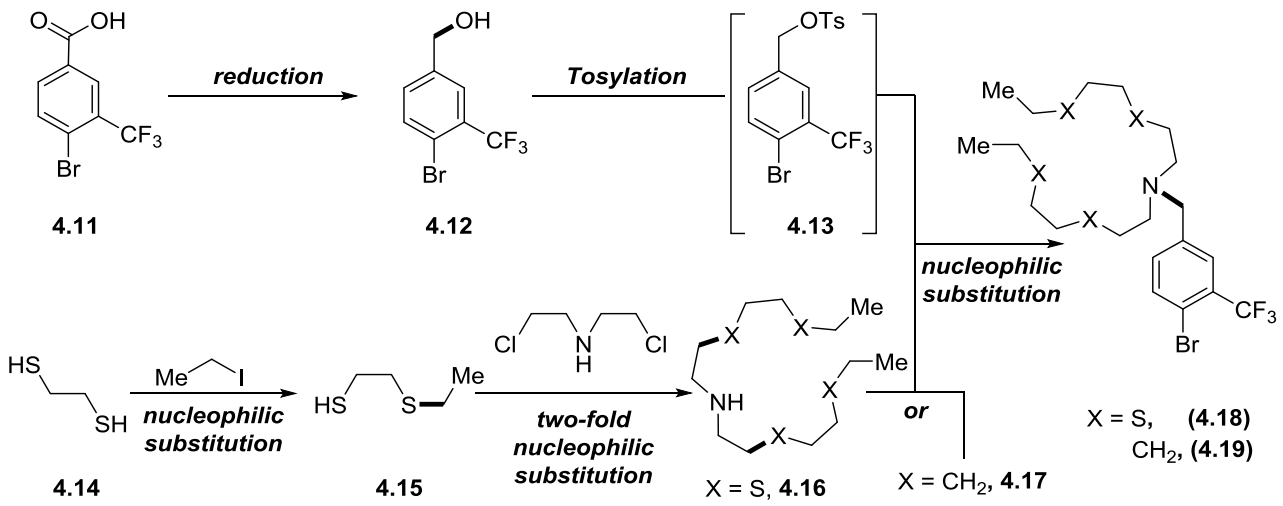
First, we targeted the synthesis of CPF1 **4.20** and the corresponding control molecule Ctrl-CPF1 **4.21**. The synthetic approach to access the fluorescent molecule **4.20** consists of the synthesis of two molecular fragments, the rhodol-based chromophore **4.10** (Scheme 4.2) and the electron-rich amino polythioether moiety **4.18** (Scheme 4.3). Both fragments are combined in the last step to furnish the desired chemosensor **4.20** and control molecule **4.21** (Scheme 4.4).

The synthesis of the chromophore Rhodol-based part **4.10** was accessible over 9 steps starting from 3-Bromoaniline (**4.1**) (Scheme 4.2).[142] First, diallylation of the aniline **4.1** provided **4.2**. Next, two diallylated bromo anilines **4.2** were merged *via* a methylene bridge using formaldehyde to afford arene **4.3**.[142] Subsequent cyclization with dichlorophenylphosphine and following oxidation provided acridophosphine **4.4**.[142] The oxidation of the benzylic methylene of **4.4** followed by a palladium-catalyzed deprotection of the allyl moieties in **4.5** furnished bisaniline derivative **4.6**.[142] To access the phenolic form **4.7**, hydrolysis of the intermediate diazonium salt generated from **4.6** was conducted. Then, a triflation of the phenolic groups in **4.7** installed a better leaving group, which paved the way for the monosubstitution of **4.8** with morpholine affording compound **4.9**. Subsequent basic cleavage of the sulfone in **4.9** and protection of the intermediate phenol as a silylether provided the desired chromophore **4.10**.



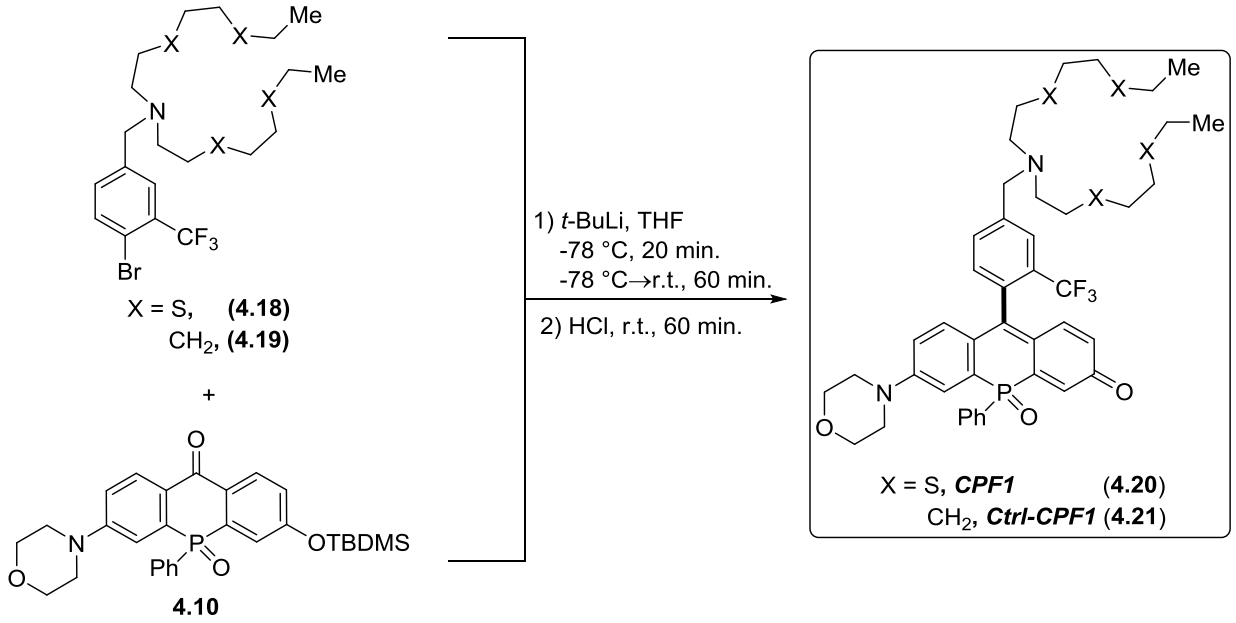
Scheme 4.2 9-Step synthesis of rhodol-based chromophore (4.10) starting from 3-Bromo aniline (4.1).[142]

On the other hand, thioether-rich receptor **4.18** was accessed over 4 steps (Scheme 4.3). The spacer moiety was synthesized starting with the reduction of 4-bromo-3-(trifluoromethyl)benzoic acid (**4.11**) to furnish the corresponding benzylic alcohol **4.12**. Subsequent tosylation of **4.12** allows the installation of a better leaving group in intermediate **4.13**. On the other hand, the mono alkylation of 1,2-ethandithiol (**4.14**) and successive dialkylation of the formed monoalkyl thioether **4.15** furnished the amino polythioether scaffold **4.16**. Nucleophilic substitution of the *in situ* tosylated intermediate **4.13** with amine **4.16** provided the bridged amino polythioether **4.18**. In contrast, the synthesis of the control molecule scaffold **4.19** is achieved by replacing amino polythioether **4.16** with the corresponding dioctyl amine (**4.17**) in the nucleophilic substitution of **4.13**.



Scheme 4.3 Synthesis of (4.18) and (4.19) starting from benzoic acid derivative (4.11).

The last step of the synthesis of **4.20** and the corresponding control molecule **4.21** consists of the coupling of **4.10** and, **4.18** for CPF1 or **4.19** for Ctrl-CPF1, mediated by a lithium-halogen exchange and a subsequent acid-catalyzed dehydration (Scheme 4.4).

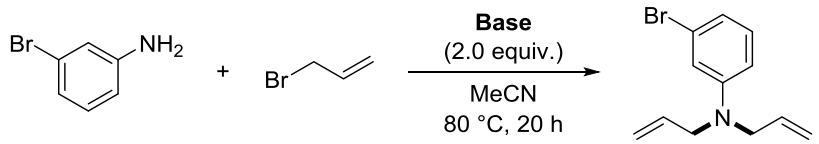


Scheme 4.4 Coupling of amino polythioether (4.18) or alkyl amine (4.19) with chromophore (4.10).[142]

First, we tested the effect of different bases on the nucleophilic bisallylation reaction of aniline **4.1** (Table 4.1) with allyl bromide (**4.1a**). Cs_2CO_3 furnished the highest yield of the desired product **4.2** (Table 4.1, entry 1), whereas sodium- and potassium carbonates provided **4.2** in slightly diminished yields (Table 4.1, entries 2-3). This can be attributed to the fact that cesium-ions, which could behave as a Lewis acid by coordination to the amine moiety, increase the acidity of adjacent N–H. This facilitates the deprotonation of the amine

by the carbonate base and, thus, increases the nucleophilicity of the corresponding anion.[145, 146]

Table 4.1. Base screening in the nucleophilic bisallylation of aniline (4.1).



4.1 **4.1a** **4.2**

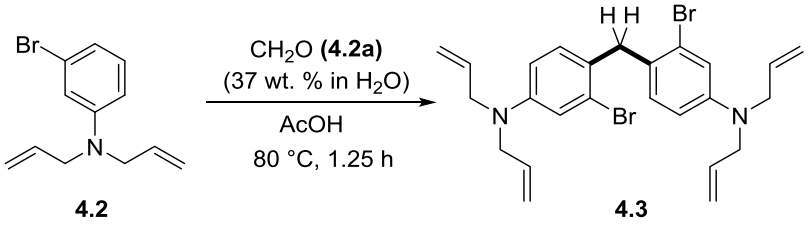
Entry	Base	Yield[a]
1	Cs_2CO_3	94%
2	Na_2CO_3	90%
3	K_2CO_3	92%
4	NaOH	72%
5	NEt_3	29%

[a] Isolated yields are shown.

Organic amine bases proved to be inadequate for this nucleophilic susbtitution reaction due to the competetive formation of quartenary ammonium salts, leading to a detetrioration in the yield of **4.2** (Table 4.1, entry 5). Also, due to the strong hygroscopy while handling Cs_2CO_3, especially in multigram-scales, K_2CO_3 is likely more suitable for this reaction. Thus, slightly higher yields of **4.2** compared to the literature yield of 84% were achieved (Table 4.1, entry 3).[147]

In the next step, the feasibility of bridging two molecules of **4.2** with formaldehyde (**4.2a**) in different acidic solvents mixture was explored (Table 4.2). The use of formaldehyde as a stock solution (37 wt. % in H_2O) in acetic acid as a solvent delivered product **4.3** in 85% yield (Table 4.2, entry 1).[147] No desired product was formed when a 0.1 M aq. HCl solution was used as a solvent (Table 4.2, entry 2). The elimination of water, critical for the formation of **4.3**, is likely favored when using the more glacial acetic acid. Thus, an equilibrium shift to the product side is expected. Additionally, the effect of using paraformaldehyde as a polymer in acetic acid was tested (Table 4.2, entry 3). A slight deterioration in the yield of **4.3** was observed due to diminished solubility of the polymeric form of formadelhyde.

Table 4.2 Optimization of the synthesis of diallylated bisaniline (4.3).



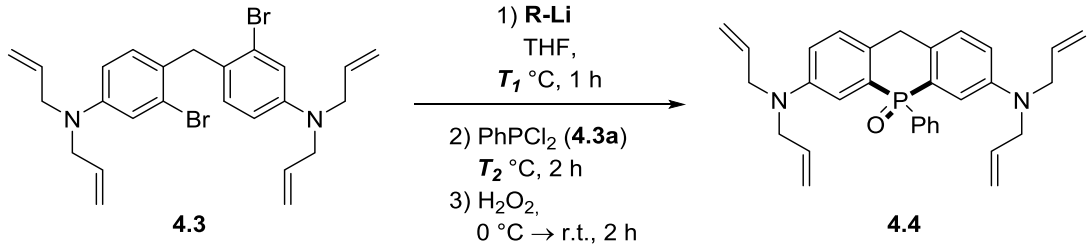
4.2 **4.3**

Entry	Alteration from std. conditions	Yield[a]
1	none	85%
2	aq. HCl (0.1 M) instead of AcOH	0%
3	Paraformaldehyde (**4.2a**) in AcOH instead of CH_2O stock solution	72%

[a] Isolated yields are shown.

Notably, the cyclization- and oxidation step of **4.3** to acridophosphine **4.4** was described by *Yamaguchi* with a rather low yield of 28%.[148] Indeed, trials to reproduce the reaction led to an initial yield of 15% of **4.4** (Table 4.3, entry 1). A noticeable improvement in the amount of generated **4.4** was achieved through substitution of *sec*-butyllithium with the more basic *tert*-butyllithium and the incremental increase of the reaction temperature (Table 4.3, entries 2-4). Especially, the increase in temperature after the addition of dichlorophenylphosphine (**4.3a**) had a noticeable beneficial influence on the outcome of the reaction (Table 4.3, entry 3).

Table 4.3 Optimization of the synthesis of acridoposphine (4.4).

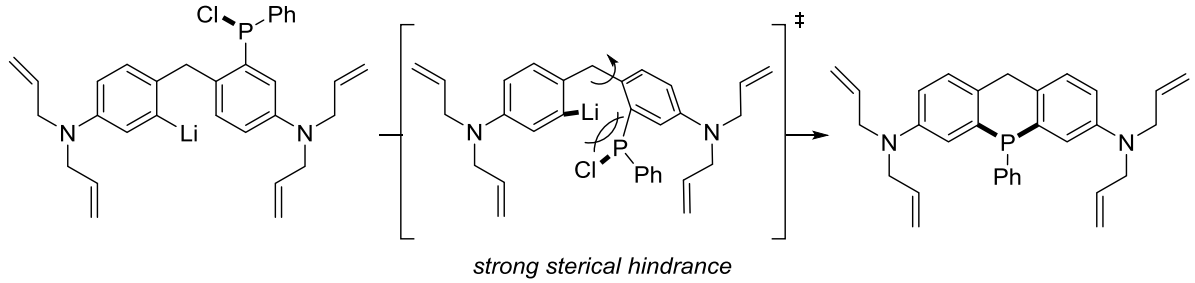


4.3 **4.4**

Entry	R-Li[a]	T_1	T_2	Yield[b]
1[148]	*s*-BuLi	−78 °C	−78 °C	15%
2	*t*-BuLi	−78 °C	−78 °C	17%
3	*t*-BuLi	−78 °C	−78→0 °C	55%
4	*t*-BuLi	−78→0 °C	−78→reflux	61%

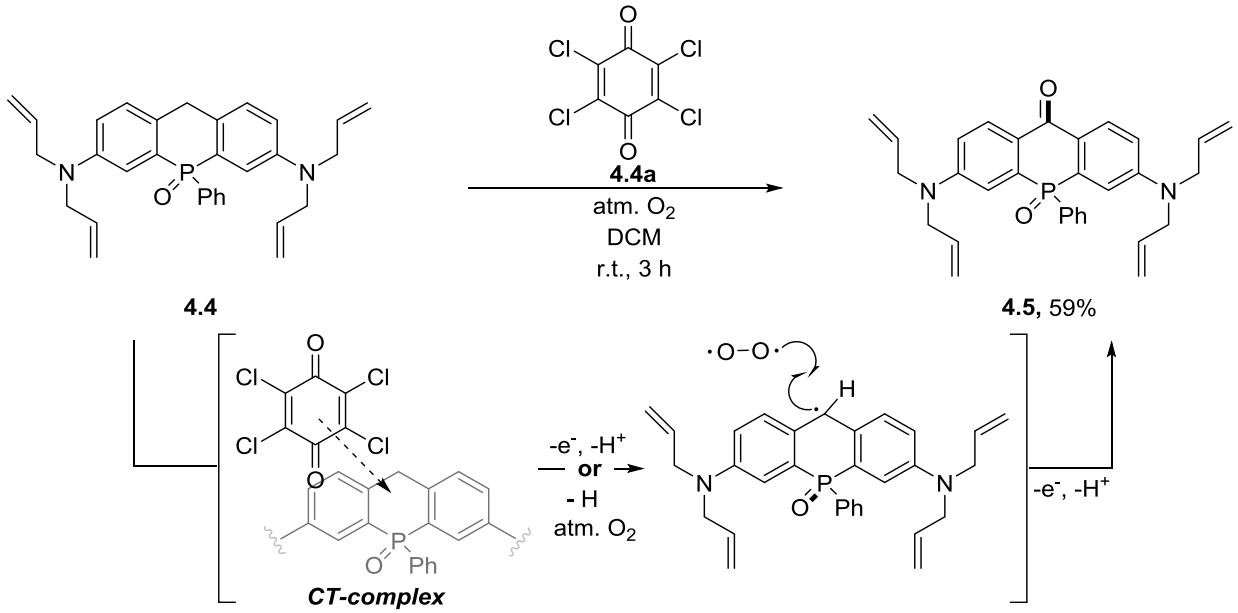
[a] *s*-BuLi: 2.1 equiv.; *t*-BuLi: 2.5 equiv. [b] Isolated yields are shown.

The sterical hindrance of the second nucleophilic attack of the lithiated arene towards the monochlorinated phosphine moiety is likely overcome when increasing the temperature of the reaction to reflux (Scheme 4.5).



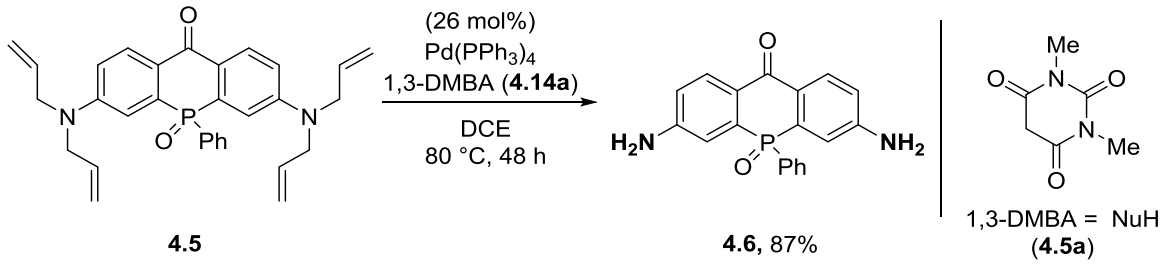
Scheme 4.5 Sterical hindrance of the second nucleophilic substitution in the synthesis of (4.4).

Subsequent benzylic oxidation of the methylene bridge was conducted using the procedure described by *Yamaguchi* and co-workers.[148] The tetrachlorinated quinone derivative *p*-chloranil (**4.4a**), possesing a high reduction potential, served as a sufficient redox-active agent to generate oxidized acridophosphine **4.5** (Scheme 4.6) in a reaction under atmospheric oxygen pressure. After the formation of a charge-transfer (CT) complex between **4.4** and **4.4a**, the mechanism of oxidation is thought to proceed over two possible pathways: a one-electron oxidation followed by a deprotonation or a hydride abstraction from quinone **4.4a**.[149] As distinct from the procedure of *Yamaguchi* and coworkers, **4.13** was isolated in moderate yields and completely characterized.



Scheme 4.6 Synthesis of (4.5) under atm. oxygen using *p*-chloranil (4.4a) as an oxidation reagent.[148]

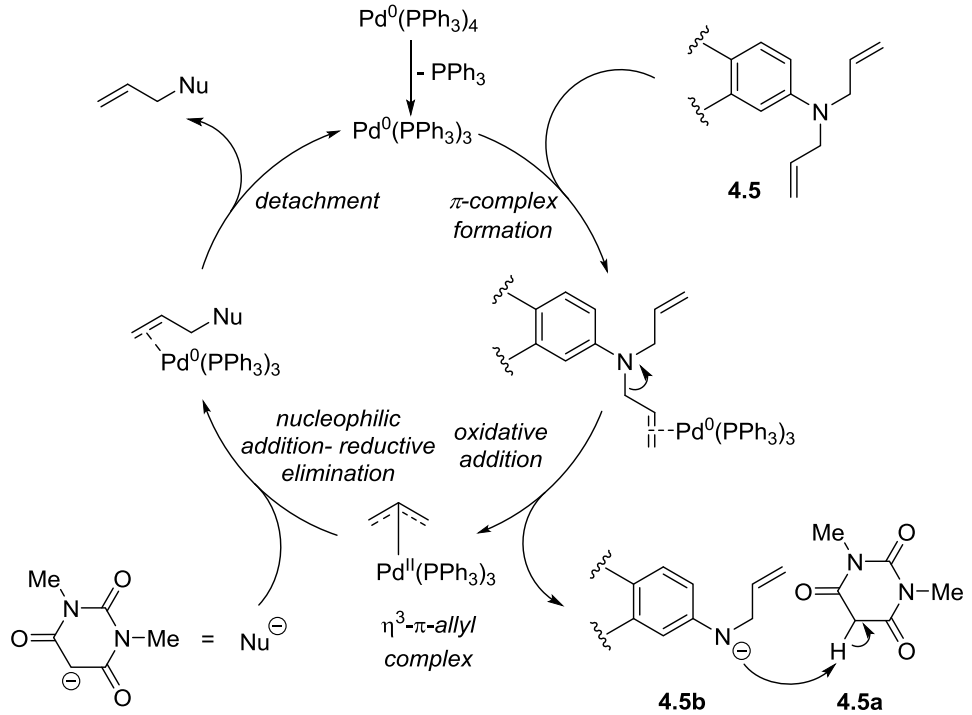
Subsequently, the deprotection of the *N,N'* bis-allyl protected aniline moieties in **4.5** was achieved by employing a palladium catalyzed *Tsuji-Trost*-allylation (Scheme 4.7).[148, 150]



Scheme 4.7 Palladium catalyzed de-allylation of *N,N'*-diallyl phosphoacridone (4.5) using sacrificial allyl scavenger 1,3-dimethylbarbituric acid (4.5a).

The corresponding mechanism is depicted in Scheme 4.8, below. The reaction mechanism commences with the formation of a π-complex through the coordination of the allyl moiety in **4.5** to a zerovalent palladium (Scheme 4.8). Then, an oxidative addition and expulsion of the anion form of mono-allylated species **4.5b** gives access to the η^3-π-allyl-palladium complex. Afterwards, anion **4.5b** deprotonates the C–H acidic sacrificial nucleophile 1,3 dimethylbarbituric acid (**4.5a**), which acts as an allyl group scavenger.

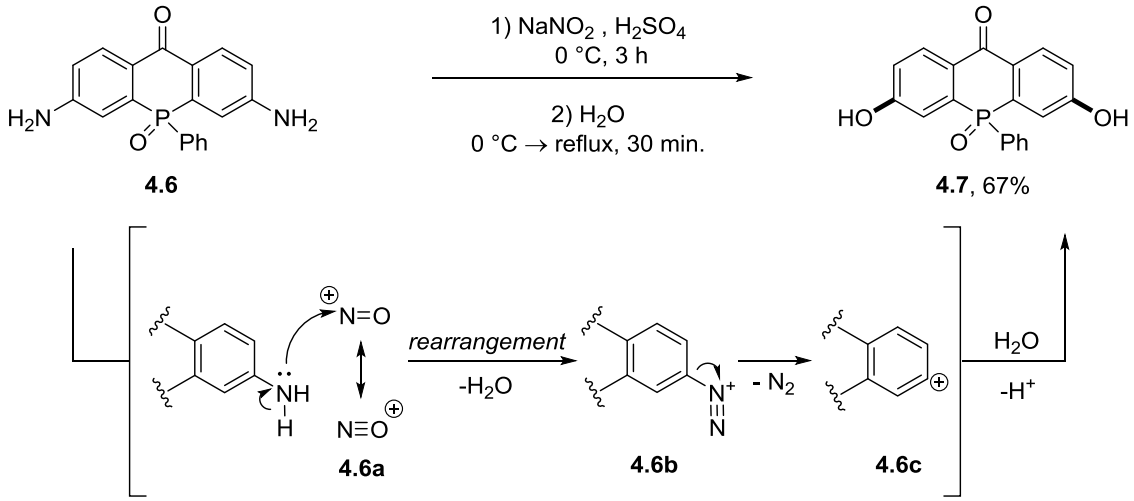
Mechanism of de-allylation:



Scheme 4.8 Plausible mechanism of the palladium catalyzed deprotection of *N,N'*-diallyl aniline (4.14).[150]

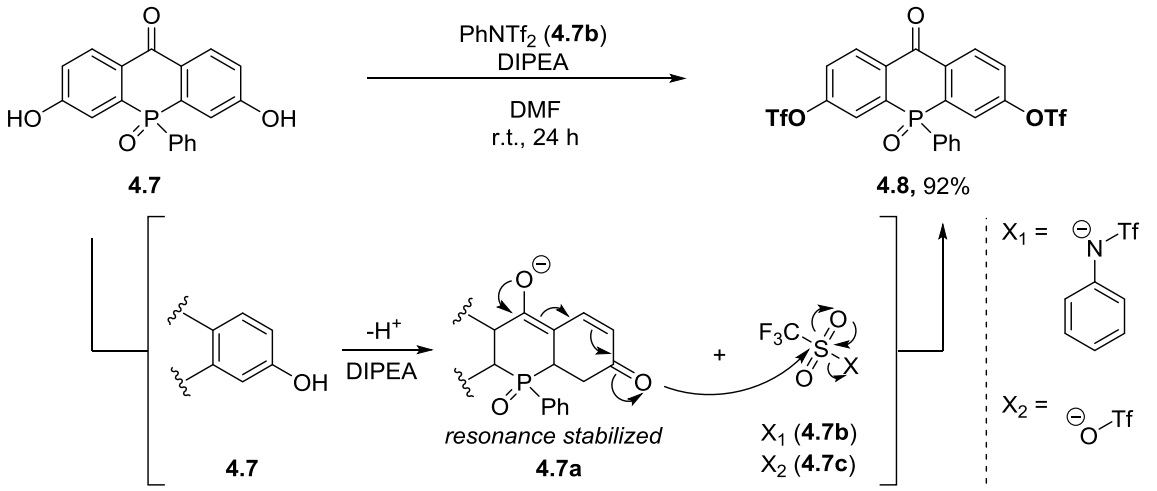
The strong nucleophilic character of the deprotonated form of **4.5a** allows a smooth addition to the formed η^3-π-allyl-palladium complex. Reductive elimination regenerates the catalyst and closes the catalytic cycle. Thus, a total of four deallylation cycles are required to generate the desired 3,7-diamino-5-phenyl-10H-acridophosphin-10-one 5-oxide (**4.6**) in a very good yield of 87%.

The synthesis of phenol derivative **4.7** from aniline precursor **4.6** proceeded with a similar yield to the one reported by *Yamaguchi* and co-workers (64%) (Scheme 4.9).[148] A nucleophilic attack of the aniline moiety in **4.6** towards the *in situ* formed nitrosonium **4.6a**, generated from sodium nitrite under strong acidic conditions, gives access to the diazonium-intermediate **4.6b** after a rearrangement. The elimination of gaseous nitrogen provides access to the aryl-cation intermediate **4.6c**, prone to nucleophilic attack from H_2O, which furnishes the desired phenol acridophosphine **4.7** in a good synthetical yield of 67%.



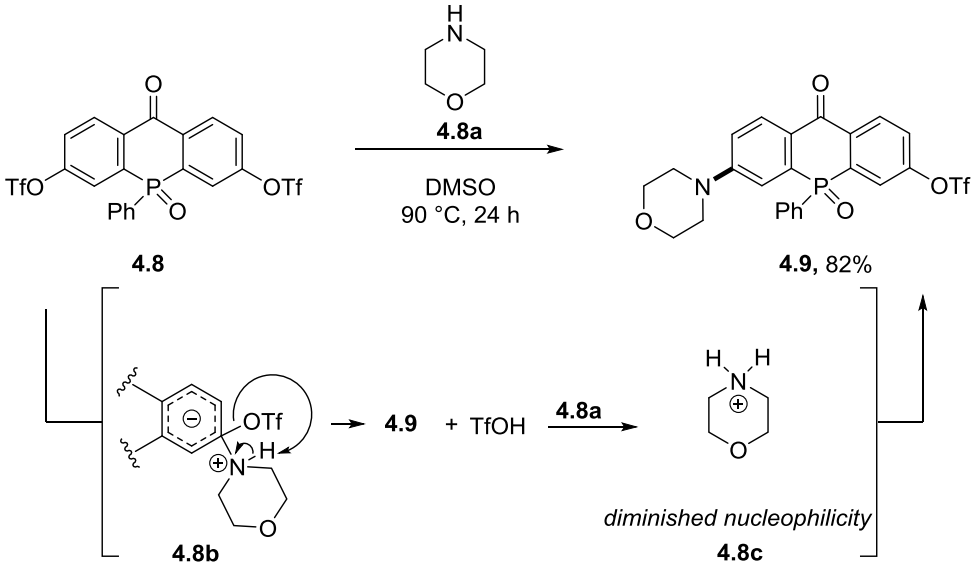
Scheme 4.9 Synthesis of phenol derivative (4.7) from aniline (4.6).

Next, to render phenol **4.7** susceptible to a nucleophilic substitution at the *ipso*-position, the installation of a good leaving group is essential. This is accomplished by a *Hünig*-base promoted triflation of **4.7** using phenyl triflimide (**4.7b**) (Scheme 4.10). The corresponding product **4.8** was obtained in a very good yield of 92%.[142] Attempts to replace phenyl triflimide (**4.7b**) with triflate anhydride (**4.7c**) did not lead to any product formation. The diminished nucleophilicity of intermediate phenolate **4.7a**, due to the enhanced mesomeric effect, could reveal the reason why **4.7a** only reacted with the more electrophilic phenyl triflimide (**4.7b**). Also, the mesomeric stabilization of the negative charge in the leaving group of **4.7b** to the adjacent phenyl ring raises the electrophilicity of **4.7b**. Hence, less nucleophilic **4.7a** would likely engage in an improved manner with **4.7b**.



Scheme 4.10 Triflation of bisphenol (4.7) using phenyl triflimide (4.7b).

Afterwards, a nucleophilic monosubstitution of **4.8** using morpholine (**4.8a**) in DMSO was carried out (Scheme 4.11).

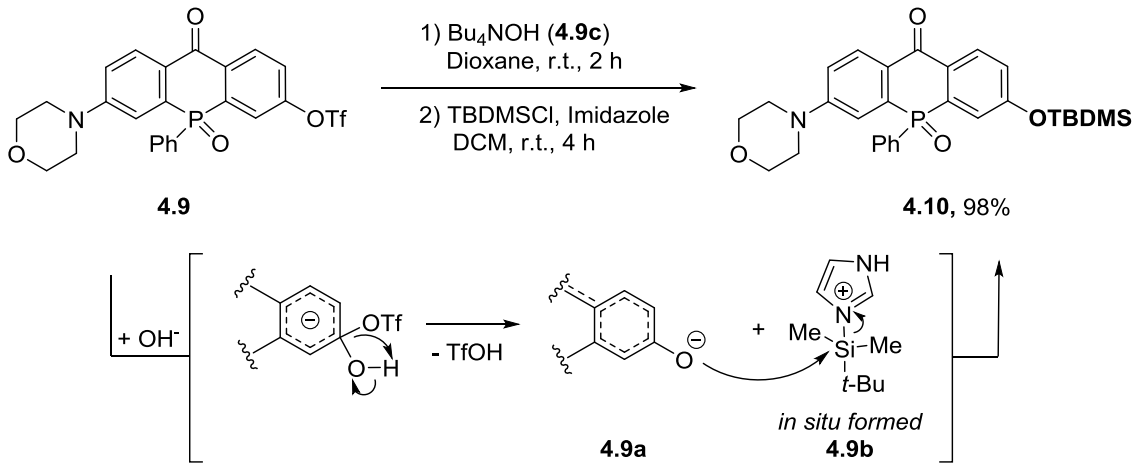


Scheme 4.11 Nucleophilic aromatic monosubstitution of (4.8) with morpholine (4.8a).

Chang and co-workers described the use of one equivalent of nucleophilic **4.8a**, which yielded monosubtituted product **4.9** in a rather lower yield of 49%.[142] Upon nucleophilic attack of the secondary amine **4.8a** towards **4.8**, rearomatisation and subsequent protonation of the elimination product in intermediate **4.8b** leads to the formation of desired product **4.9**. In course of the reaction, triflic acid is formed as a by-product. Protonation of secondary amine **4.8a** by the generated triflic acid would immensely diminish the nucleophilicity in **4.8c** and explain the lower yield of **4.9**. Hence, we presumed an improvement in the formation of **4.9** when using an excess of two equivalents of **4.8a**.

Indeed, monosubstituted product **4.9** was obtained in a very good yield of 82% with two equivalents of **4.8a** after 24 hours.

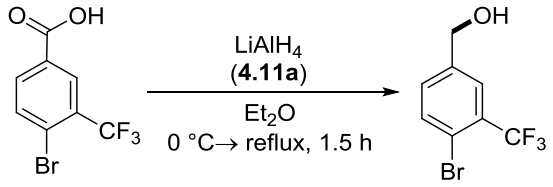
The last step to access chromophore **4.10** proceeded smoothly using a similar procedure described by *Chang* and co-workers.[142] Nucleophilic aromatic substitution of **4.9** using tetrabutylammonium hydroxide (**4.9c**) as a strong base furnished intermediate phenolate **4.9a** (Scheme 4.12). Intermediate **4.9a** was then protected as a TBDMS-ether **4.10**, which is less prone to hydrolysis under following reaction conditions. The silylation step was accessible by employing *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole.[151] The *in situ* formed silyl-imidazolium cation **4.9b** participated efficiently in the reaction with **4.9a**. In contrast to the procedure described by *Chang* and co-workers, A yield improvement to almost quantitative yield of the desired product **4.10** was accomplished when tetrabutylammonium hydroxide (**4.9c**) was used instead of the less soluble tetraethylammonium hydroxide (Et_4NOH).[142]



Scheme 4.12 Nucleophilic aromatic substitution and silyl protection of triflate derivative (4.9).

Next, the synthesis of the electron-rich receptor scaffold **4.18** was accomplished in a 4-step synthesis starting from commercially available 4-bromo-3-(trifluoromethyl)benzoic acid (**4.11**) and 1,2-ethanedithiol (**4.14**) (Tables 4.4 and 4.5). First, the benzylic alcohol derivative **4.12** was obtained by the reduction of the corresponding benzoic acid **4.11** with lithium aluminium hydride (**4.11a**) (Table 4.4). The reduction of precursor **4.11** was accomplished by employing modified reaction conditions compared to the described procedure by *Dodani* and co-workers (Table 4.4, entry 2).[143] The use of Et_2O as a solvent under reflux conditions were indispensable for a good reaction outcome (Table 4.4, entries 1 and 3). Thus, **4.12** was obtained in a very good yield of 90%.

Table 4.4 Optimization of the reaction conditions for the reduction of benzoic acid derivative (4.11).

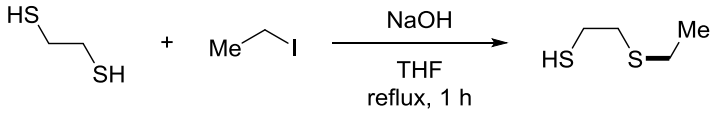


4.11 **4.12,** 90%

Entry	Alteration from std. conditions	Yield[a]
1	none	90%
2	THF instead of Et_2O, room temperature[143]	21%
3	room temperature instead of reflux	53%

[a] Isolated yields are shown.

Moreover, following the modified procedures described by *Kimura et al.*, amino polythioether **4.16** was furnished over two steps.[152] 2-(Ethylthio)ethane-1-thiol (**4.15**) was obtained in the first step *via* a base-promoted nucleophilic substitution of ethyl iodide (**4.14a**) and 1,2-ethanedithiol (**4.14**) (Scheme 4.13).[152] Undesired over-alkylation of desired product **4.15** in course of the reaction and difficulties in purification led to a noticeable decrease in the yield of **4.15**. Thus, multiple distillations were required to obtain pure **4.15**.

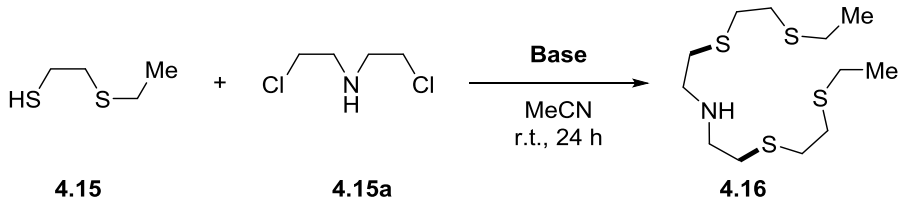


4.14 **4.14a** **4.15,** 62%

Scheme 4.13 Base-promoted monoalkylation of 1,2-ethanedithiol (4.14) with ethyliodide (4.14a).

Afterwards, a two-fold nucleophilic substitution of bis(2-chloroethyl)amine (**4.15a**) with **4.15** afforded the desired electron-rich receptor moiety **4.16** (Table 4.5). The performance of different bases during the reaction was investigated and evaluated. Alkoxide bases (Table 4.5, entries 1 and 2) as well as sodium carbonate (Table 4.5, entry 3) failed to generate the desired product **4.16**, whereas sodium hydroxide and cesium carbonate delivered **4.16** in very good yields reaching 88% (Table 4.5, entries 4 and 5). Cesium as a bulky counter ion (ionic radius of Cs^+ = 167 pm)[153] to the deprotonated form of **4.15** is known to be more reactive in aprotic polar solvents.[154] Enhanced nucleophilicity and dissociation of generated salt in MeCN explains most likely the improved yield of desired **4.16**.[146, 154]

Table 4.5 Base screening for the dual nucleophilic substitution reaction of thiol derivative (4.15) and (4.15a).

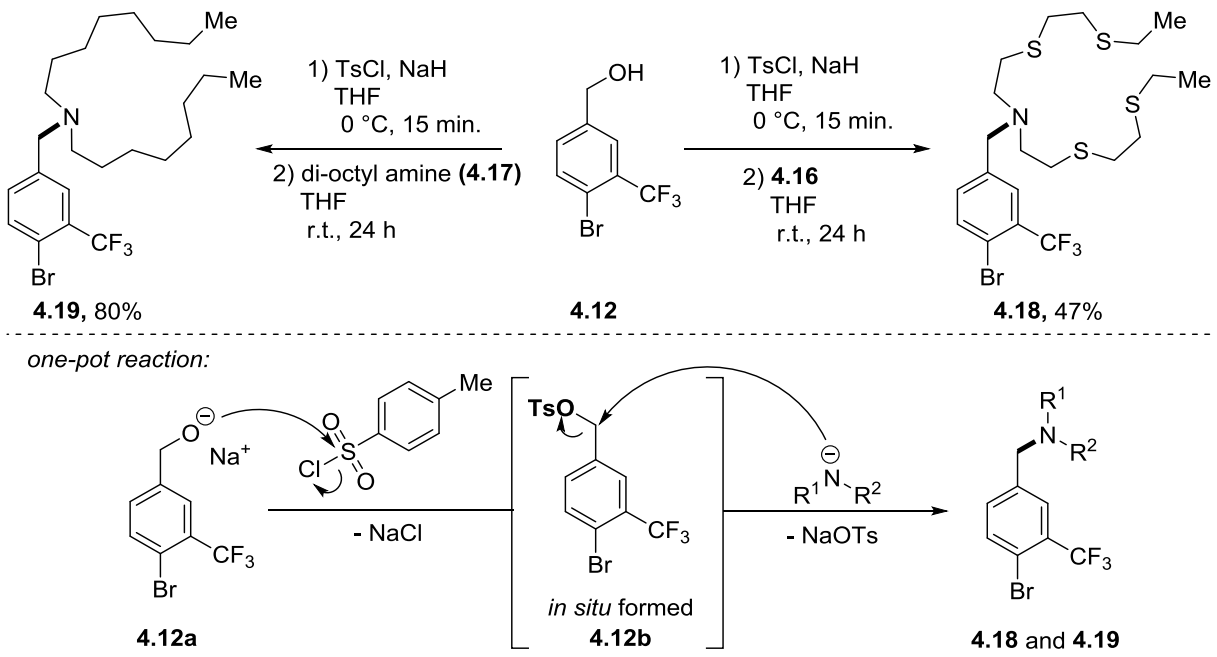


4.15 **4.15a** **4.16**

Entry	Base	Yield[a]
1	NaOMe	0%
2	NaOEt	0%
3	Na_2CO_3	0%
4	NaOH	77%
5	Cs_2CO_3	88%

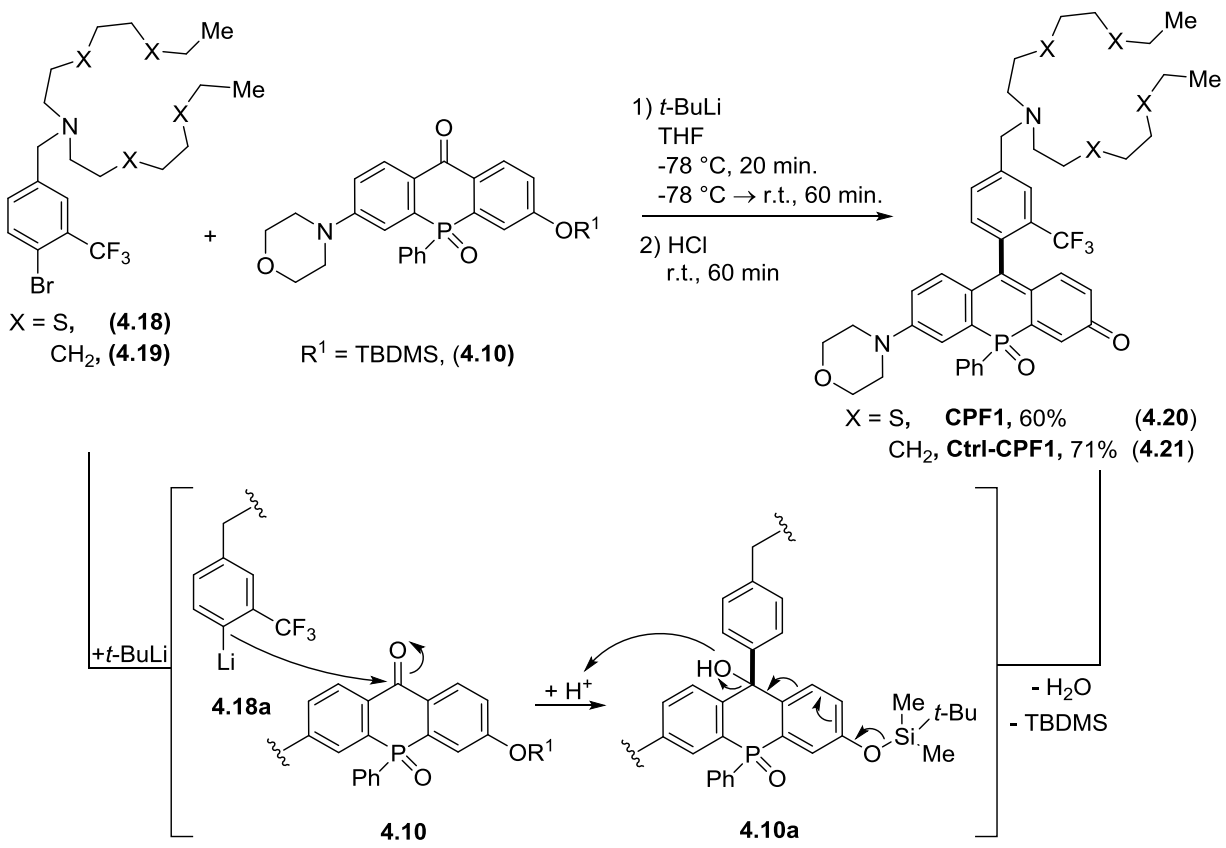
[a] Isolated yields are shown.

Then, receptor fragment **4.16** as well as dioctyl amine (**4.17**) were merged with the pre-synthesized bridging scaffold **4.12** (Scheme 4.14). A procedure reported by *Dodani et al.* relied on the chlorination of benzylic alcohol **4.12** and a subsequent nucleophilic substitution with amines **4.16** and **4.17** in two consecutive reactions.[143] We presumed that a one-pot *in situ* tosylation of benzylic alcohol **4.12**, followed by the nucleophilic base-promoted substitution with amines **4.16** and **4.17** would furnish desired products **4.18** and **4.19** without the need for an intermediate purification and isolation (Scheme 4.14). Indeed, benzylic substitution of the *in situ* formed tosylate **4.12b** afforded desired products **4.18** and **4.19** in yields of 47% and 80%, respectively. The use of two equivalents of sodium hydride as a base proved to be sufficient for the deprotonation of benzylic alcohol **4.12** and the amine scaffolds **4.16** and **4.17**.



Scheme 4.14 Synthesis of receptor- (4.18) and control molecule scaffold (4.19) from benzylic alcohol derivative (4.12).

In the last step, the desired copper sensor CPF1 **4.20** and the corresponding control molecule Ctrl-CPF1 **4.21** were obtained by the coupling of the synthesized acridophosphine chromophore **4.10** with the electron-rich receptor fragment **4.18** and alkyl amine **4.19**, respectively (Scheme 4.15). Multiple trials to reproduce the procedure described by *Chang et al.* failed.[142] The published procedure consisted of a halogen-metal exchange of **4.18** or **4.19** with *tert*-butyllithium (*t*-BuLi) to generate intermediate **4.18a** with a highly polarized aryl-carbon-lithium bond. The nucleophilic attack of aryl carbanion from **4.18a** to the ketone moiety of chromophore **4.10** gives access to the tertiary alcohol **4.10a**. Subsequent acid-catalyzed protonation of the tertiary alcohol and dehydration of **4.10a** as well as the elimination of the silyl protecting group leads to restoration of the conjugated π-system and furnishes desired copper chemosensor CFP1 **4.20** and its corresponding control molecule Ctrl-CPF1 **4.21**. No product was formed following the procedure described by *Chang* and co-workers. We presumed that the order of addition during the reaction could be responsible for the lack of formation of **4.20** and **4.21**. Indeed, adding lithiated aryl component **4.18a** to a solution of **4.10** in THF, otherwise than stated by *Chang et al.*, and subsequent raise of the reaction mixtures temperature from −78 °C to room temperature revealed an almost 1.5-2 fold raise in the yields of **4.20** and **4.21**. Desired control molecule **4.21** and chemosensor CPF1 **4.20** were obtained in good isolated yields of 71% and 61%, respectively.

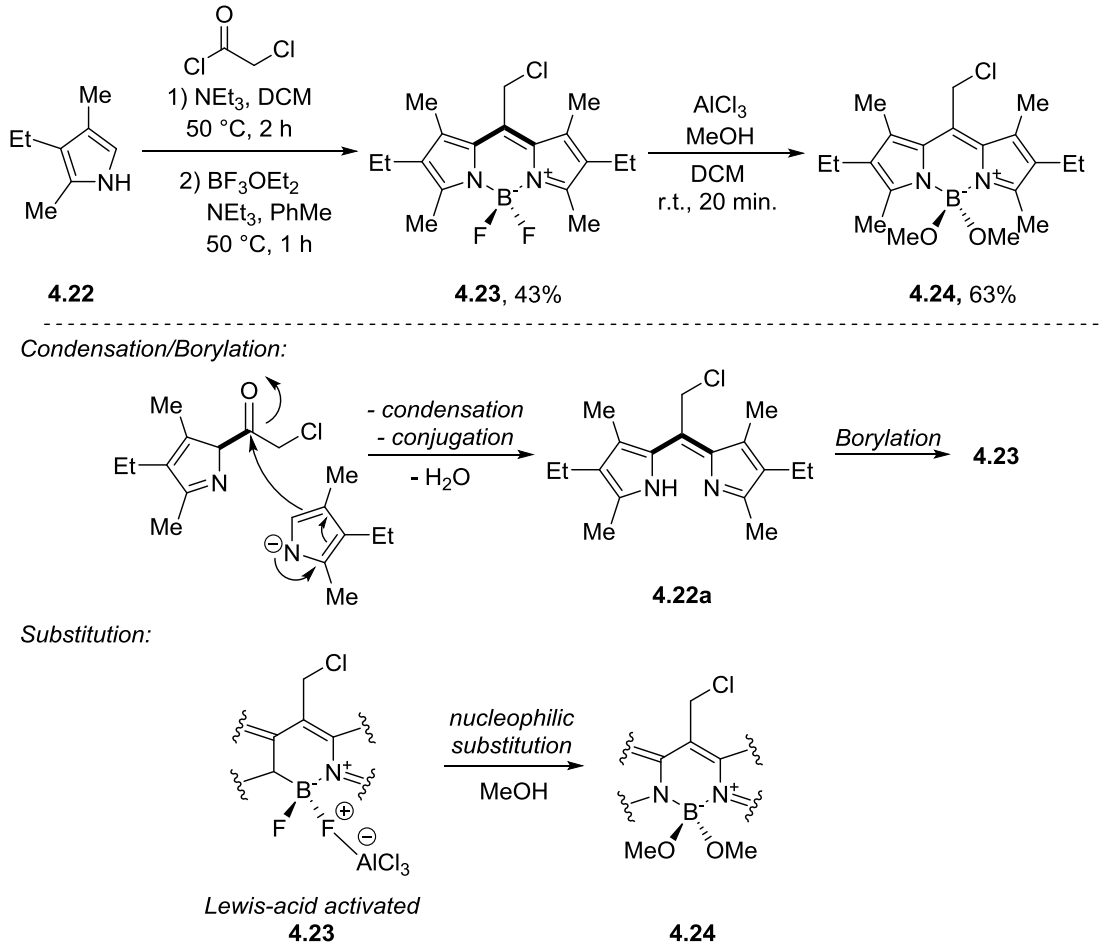


Scheme 4.15 Synthesis of copper-sensor (CPF1, 4.20) and control molecule (Ctrl-CPF1, 4.21) by coupling of (4.10) and (4.18) or (4.19) and subsequent dehydration/restoration of conjugation.

4.3.1.2 Synthesis of copper chemosensor CS3

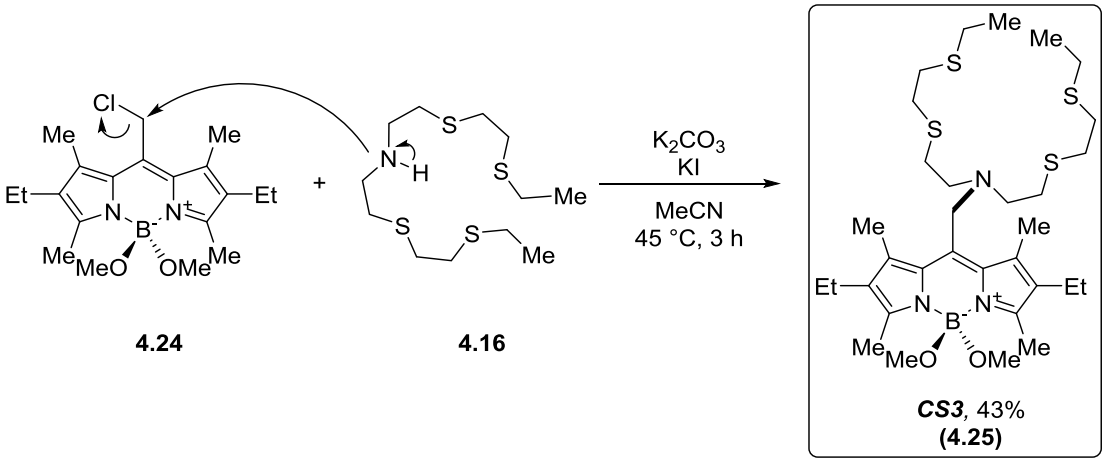
The Boron-dipyrromethene (BODIPY)-based copper sensor CS3 **4.25** was synthesized in a similar fashion to chemosensor CPF1 **4.20**, following the synthesis described by *Dodani* and co-workers (Scheme 4.16 and 4.17).[144] The corresponding chromophore BODIPY-scaffold **4.24** was obtained over two steps starting from pyrrole derivative 3-ethyl-2,4-dimethyl-1*H*-pyrrole (**4.22**). First, a base-promoted nucleophilic disubstitution of chloroacetyl chloride by two equivalents of pyrrole **4.22** followed by a condensation yielded conjugated chlorodipyrrole **4.22a**. A difluoroborylation using the Lewis-acid-base-adduct boron trifluoride diethyl etherate provided intermediate **4.23** in a rather low yield of 43%.[144] During the reaction, a variety of side reactions were evident. In addition, challenging purification led to diminished yields of **4.23**. Nevertheless, synthetically useful amounts could be obtained. The substitution of the fluorine moieties in **4.23** with methoxy groups was accomplished *via* a Lewis-acid catalyzed substitution.[144] The sonication of a pre-

activated mixture of **4.23** with aluminium trichloride, followed by the addition of methanol afforded the dimethoxylated diazaborinine derivative **4.24** in a moderate yield of 63%.



Scheme 4.16 Two step synthesis of BODIPY scaffold (4.24) from pyrrole derivative (4.22).

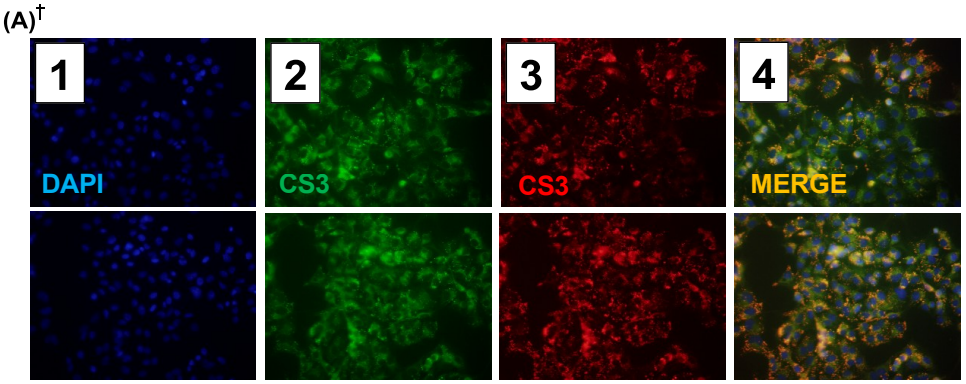
Finally, the copper chemosensor CS3 (**4.25**) was obtained through a base-promoted nucleophilic substitution of the pre-synthesized amino polythioether **4.16** and the chlorinated precursor chromophore **4.24** (Scheme 4.17) in a moderate yield of 43%.[144]



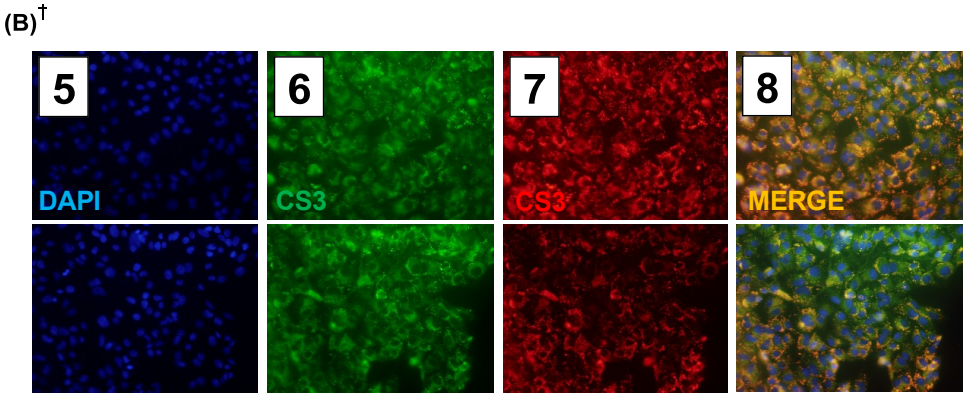
Scheme 4.17 Synthesis of CS3 (4.25) by nucleophilic substitution of BODIPY scaffold (4.24) with (4.16).

4.3.1.3 Evaluation and application of chemosensors CS3, CPF1, and ctrl-CPF1 in HepG2 cells

In cooperation with the group of *Dr. Jan Lukas* at the Albrecht Kossel institute, CS3 Copper sensor **4.25** was applied to cell cultures containing HepG2 cells, a human liver cancer cell line. From two tested wildtyp cell cultures ($ATP7B^{+/+}$), one was treated with a 500 µM solution of $CuSO_4$ and incubated for two hours (Figure 4.4, entry B). The control sample was measured in the absence of $CuSO_4$ addition (Figure 4.4, entry A). The increase in copper(I)-concentrations in the investigated cells upon exposure to a copper-rich medium is evident by an augmentation of fluorescence through different filters (Figure 4.4, entry B).



DAPI (4',6-Diamidin-2-phenylindol), HepG2 (WT), incubated with 200µM of BCS for 24 h.
(two pictures from the same sample)



DAPI (4',6-Diamidin-2-phenylindol), HepG2 (WT), incubated with 200µM of BCS for 24 h and with **500 µM of $CuSO_4$ for 2 h.**
(two pictures from the same sample)

† Fluorescence Microscope Keyence BZ8000-K, Lens: 20x PlanApo Fluor, Filters: DAPI (1/6s) (1,5), GFP (Exc. 470+/-20nm; Em 535+/-25nm) (exposure 1/5s) (2,6), TxRed (Exc. 560+/-20nm; Em 630+/-30nm) (exposure 1/1.8s) (3,7); Exposure time calibrated using DMSO-only staining (background fluorescence), scale bar 100µm.

Figure 4.4 CS3 copper sensor in HepG2 cells (A) without and (B) after incubation with a 500 µM $CuSO_4$ solution.

Next, the application of CS3 **4.25** in the quantification of copper levels in ATP7B deficient HepG2 cells ($ATP7B^{-/-}$) in comparison to the corresponding wildtyp cells ($ATP7B^{+/+}$) was

examined (Figure 4.5). Increased basal copper levels in cells with deficient ATP7B proteins were evident after staining with CS3 **4.25** in comparison to wildtyp cells (Figure 4.5, A and B). In the same context, both cell cultures were treated with a 200 µM solution of $CuSO_4$ for 24 hours. The treatment resulted in an augmentation of copper levels in wildtyp cells in comparison to basal levels in untreated cells, implementing a functional copper trafficking from extra- to intracellular compartiments.

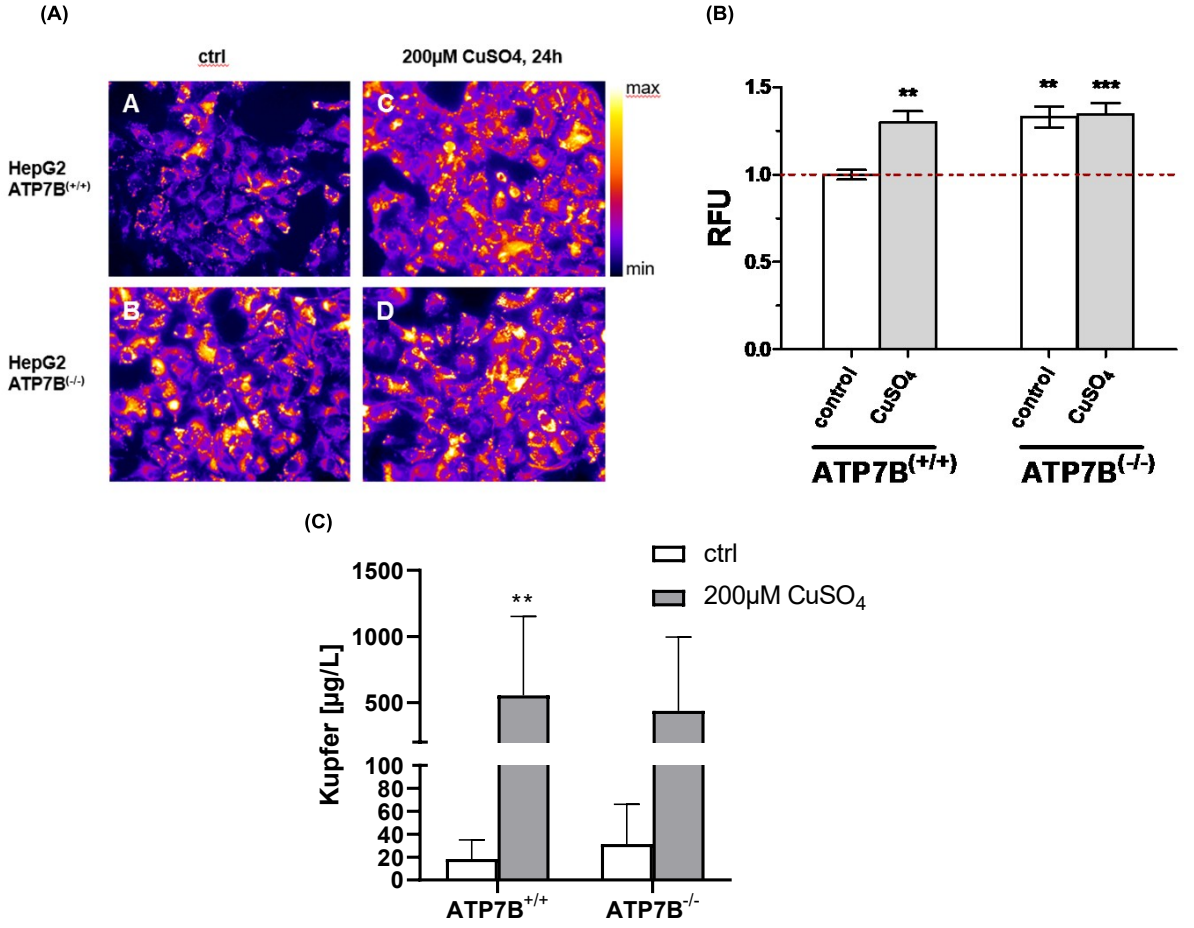
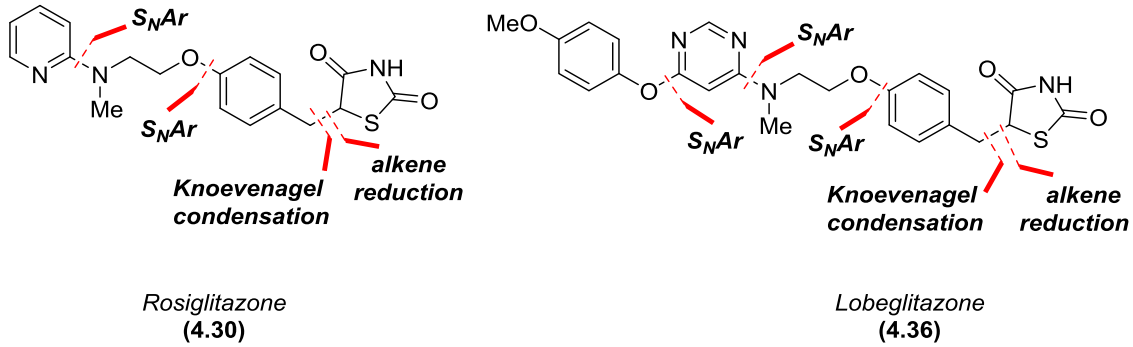


Figure 4.5 (A) staining of ($ATP7B^{+/+}$) and ($ATP7B^{-/-}$) HepG2 cells with CS3. (B) quantification of fluorescence signal generated from (A), (C) quantification of intracellular copper levels by atomic absorption spectroscopy.

Remarkably, no significant difference was noticed in copper levels of ATP7B deficient cells post to treatment compared to basal levels. Thus, CS3 **4.25** proved initial functionality in copper concentration evaluation in wildtyp- and ATP7B deficient HepG2 cells. In addition, intracellular copper levels were measured by atomic absorption spectroscopy (AAS) (Figure 4.5, C). In the same context, the employment of CPF1 copper sensor **4.20** and ctrl-CPF1 **4.21** in HepG2 cell cultures is still a subject of current research in the group of *Dr. Jan Lukas* at the Albrecht Kossel Institute in Rostock.

4.3.2 Glitazones as a novel therapeutic approach for the treatment of *Wilson*'s disease

Rosiglitazone **4.30** and lobeglitazone **4.36**, two representatives of the thiazolidinedione family, were obtained in a four- and five-step total synthesis, respectively, following reported procedures in literature (Figure 4.6).[155-159]



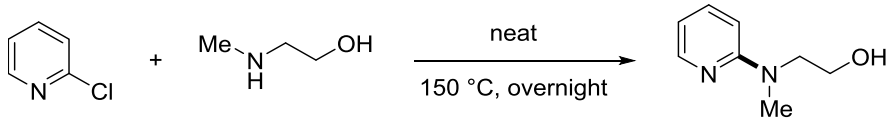
Rosiglitazone **(4.30)**

Lobeglitazone **(4.36)**

Figure 4.6 Multiple step synthesis of rosiglitazone (4.30) and lobeglitazone (4.36).

4.3.2.1 Synthesis of rosiglitazone

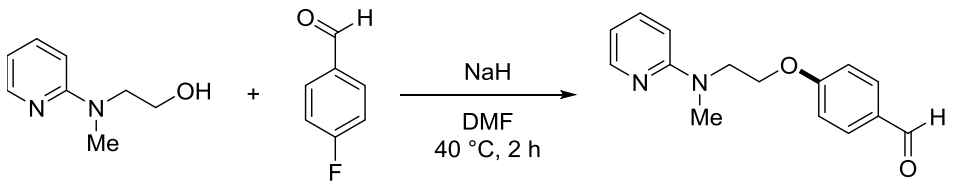
The first step in the synthesis of rosiglitazone **4.30** comprised a nucleophilic aromatic substitution of 2-chloropyridine (**4.26**) in neat 2-(methylamino)ethanol (**4.26a**) at 150 °C (Scheme 4.18).[155] Thus, desired product **4.27** was obtained in an excellent yield of 93%.



4.26 **4.26a** **4.27**, 93%

Scheme 4.18 Nucleophilic aromatic substitution of 2-chloropyridine (4.26) using amine (4.26a).

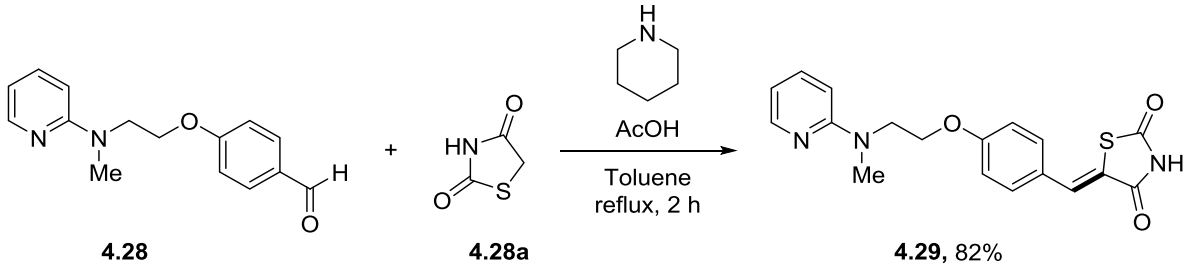
Next, 2-(methyl(pyridin-2-yl)amino)ethan-1-ol (**4.27**) was reacted with 4-fluorobenzaldehyde (**4.27a**) in a second nucleophilic aromatic substitution after deprotonation with sodium hydride in DMF at 40 °C (Scheme 4.19).[156] The *O*-arylation product **4.28** was obtained in a moderate yield of 57%. The diminished yield of **4.28** is probably associated with a competetive base-catalyzed *Cannizzaro* reaction of non-enolizable carbonyl educt **4.27a**, resulting in a disproportionation of the aldehyde.[160]



4.27 **4.27a** **4.28**, 57%

Scheme 4.19 Nucleophilic aromatic substitution of benzaldehyde derivative (4.27a) with primary alcohol (4.27).

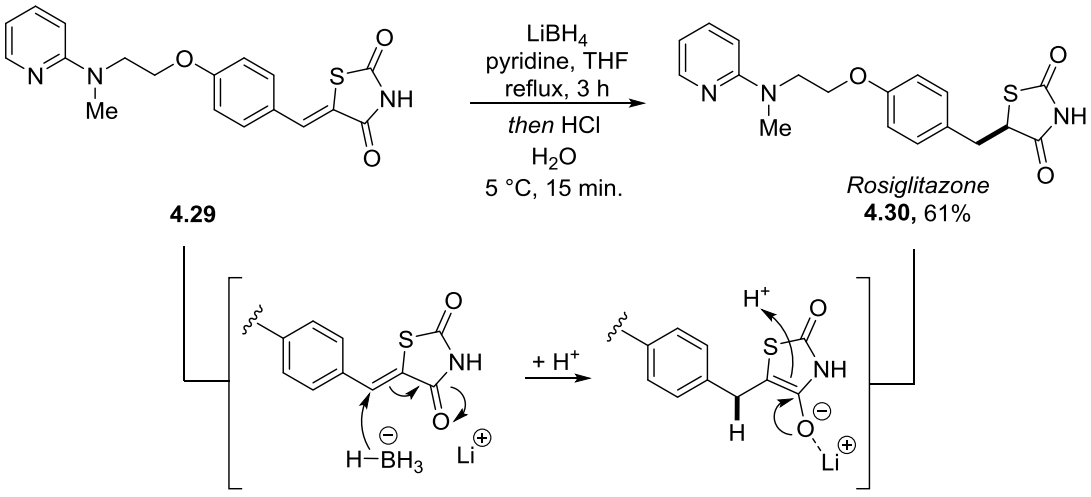
Afterwards, a Knoevenagel condensation of 2,4-thiazolidinedione (**4.28a**) and **4.28** in the presence of piperidine and acetic acid in toluene afforded α,β-unsaturated carbonyl compound **4.29** in a good yield of 82% (Scheme 4.20).[156] Piperidine served as a base for the deprotonation of C–H-acidic thiazolidinedione **4.28a** (pK_a = 6.24)[161]. Upon nucleophilic attack of deprotonated **4.28a** towards the carbonyl moiety in **4.28**, subsequent protonation and elimination of water generates desired unsaturated precursor **4.29**.



4.28 **4.28a** **4.29,** 82%

Scheme 4.20 Knoevenagel condensation of benzaldehyde derivative (4.28) with thiazolidinedione (4.28a).

With precursor **4.29** in hand, the unsaturated alkene moiety was reduced *via* a hydride transfer from lithium borohydride ($LiBH_4$) in a mixture of pyridine and THF under reflux for 2 hours (Scheme 4.21).[157] Recrystallization of the precipitated solid during the reaction afforded the desired rosiglitazone **4.30** in a moderate yield of 61%.



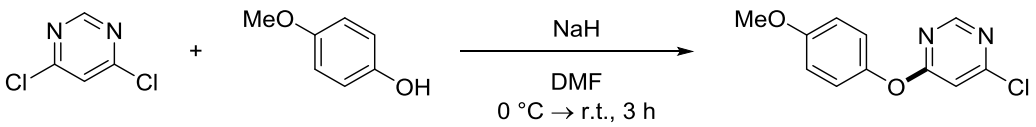
4.29 *Rosiglitazone* **4.30,** 61%

Scheme 4.21 Reduction of α,β-unsaturated carbonyl precursor (4.29) to rosiglitazone (4.30) using $LiBH_4$.

4.3.2.2 Synthesis of lobeglitazone

In the same context, lobeglitazone **4.36** was synthesized over five-steps starting from 4,6-dichloropyrimidine (**4.31**) (Scheme 4.22). In the first step, a nucleophilic aromatic monosubstitution of **4.31** was conducted with 4-methoxyphenol (**4.31a**) after deprotonation using sodium hydride in DMF.[158] The fast addition of **4.31** to the reaction mixture was crucial. The slow addition of pyrimidine **4.31** at room temperature resulted in a

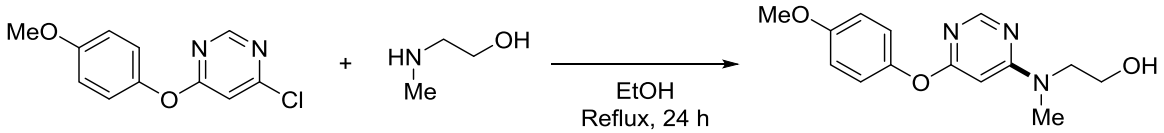
disubstitution of **4.31**. By adding **4.31** at once under vigorous stirring to deprotonated **4.31a** at 0 °C, an excellent yield of 96% of monosubstituted pyrimidine **4.32** was achieved.



4.31 **4.31a** **4.32,** 96%

Scheme 4.22 Base-promoted monosubstitution of 4,6-dichloropyrimidine (4.31) with (4.31a).

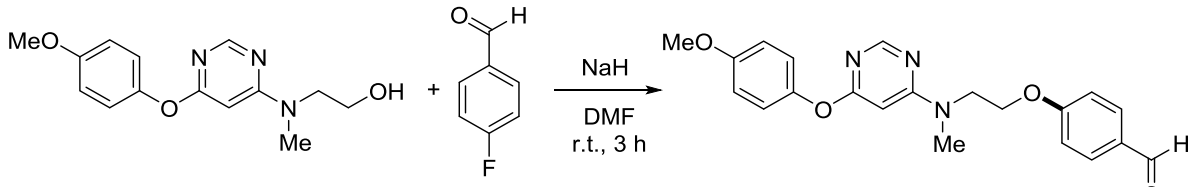
In a similar procedure to the synthesis of rosiglitazone **4.30**, a second nucleophilic aromatic substitution of **4.32** with **4.26a** under reflux afforded substituted *N*-methylaminoalcohol **4.33** in a quantitative yield after 24 hours (Scheme 4.23).[158]



4.32 **4.26a** **4.33,** quant.

Scheme 4.23 Nucleophilic aromatic substitution of substituted pyrimidine (4.32) with aminoalcohol (4.26a).

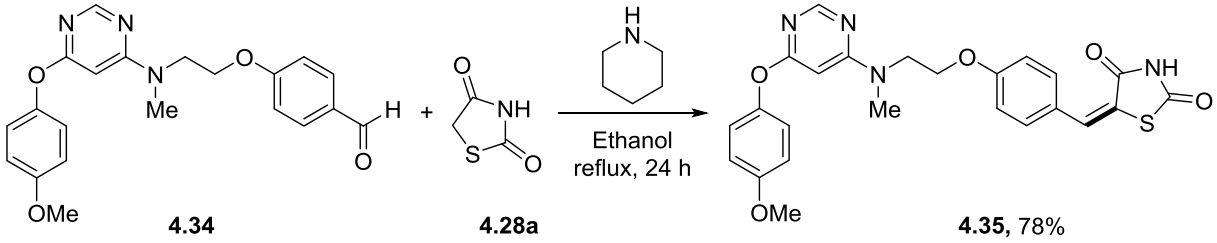
With *N*-substituted aminoalcohol **4.33** in hand, a base-promoted nucleophilic aromatic substitution of 4-fluorobenzaldehyde (**4.27a**) using sodium hydride in DMF was conducted.[158] The desired benzaldehyde derivative **4.34** was obtained in a good yield of 85% after 3 hours (Scheme 4.24). In contrast to the similar step in the synthesis of Rosiglitazone **4.30**, running the reaction at room temperature instead of 40 °C (Scheme 4.19) had a positive effect on the yield of the desired product.



4.33 **4.27a** **4.34,** 85%

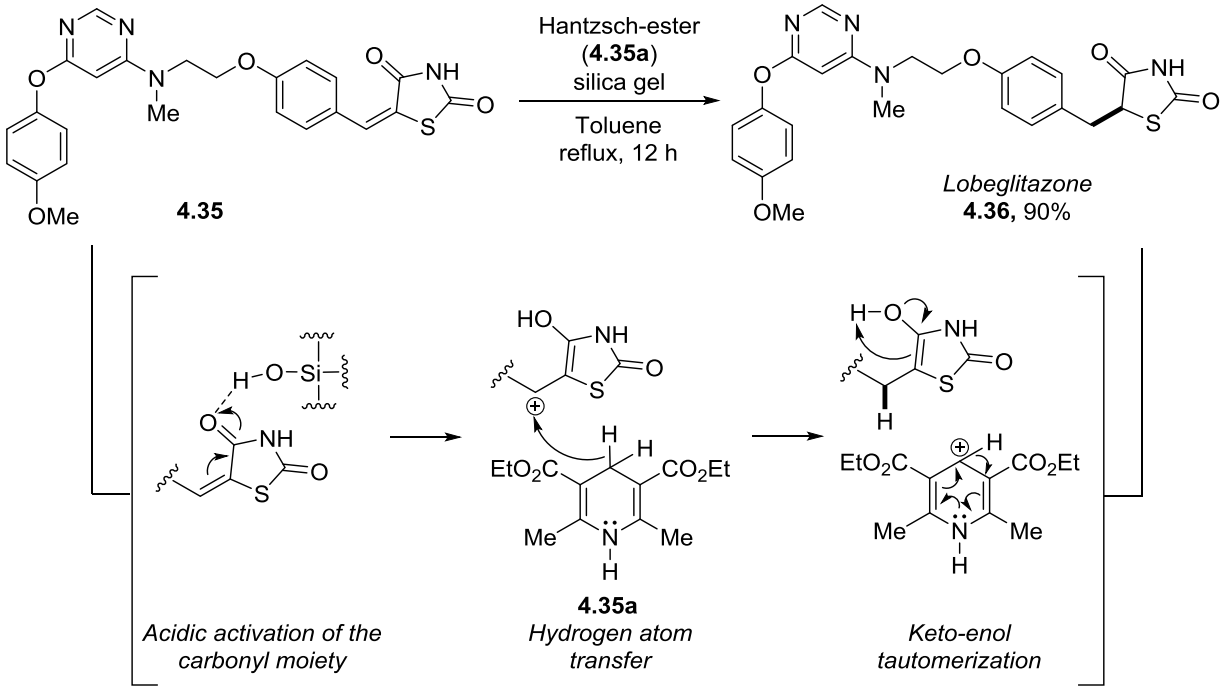
Scheme 4.24 Nucleophilic aromatic substitution of 4-fluorobenzaldehyde (4.27a) with *N*-substituted aminoalcohol 4.33.

Next, the lobeglitazone precursor **4.35** was obtained by a Knoevenagel condensation of 2,4-thiazolidinedione (**4.28a**) and benzaldehyde derivative **4.34** in a refluxing mixture of piperidine and anhydrous ethanol for 24 hours (Scheme 4.25). The corresponding product **4.35** was isolated in 78% yield.



Scheme 4.25 Knoevenagel condensation of benzaldehyde derivative (4.34) with thiazolidinedione 4.28a.

The last step to access lobeglitazone **4.36** from precursor **4.35** consisted of the reduction of the α,β-unsaturated carbonyl bond in **4.35**. Literature procedures reported for the reduction of **4.35** suffered from diminished yields when employing palladium-catalyzed hydrogenation protocols.[158] Thus, a chemoselective procedure described by *Nakamura* and co-workers using diethyl-1,4-dihydro-2,6-dimethyl-3,5-pyridindicarboxylate (**4.35a**), also referred to as Hantzsch-ester, in the presence of silica gel in refluxing toluene was adopted (Scheme 4.26).[159, 162] A hydrogen atom transfer from the Hantzsch ester (**4.35a**) after acidic activation of the carbonyl moiety of thiazolidinedione **4.35** with silica, followed by a keto-enol tautomerization, generated the desired lobeglitazone **4.36** in a very good yield of 90%.



Scheme 4.26 Selective reduction of α,β-unsaturated carbonyl precursor (4.35) using Hantzsch ester (4.35a) and silica.

In cooperation with *Dr. Jan Lukas*, *in vitro* cell tests investigating the effect of rosiglitazone **4.30** and lobeglitazone **4.36** on the extent of ubiquitination in modified HEK 297T cells are pending and still subject of current research.

4.4 Conclusion

In summary, rhodol-based copper sensor CPF1 and the corresponding control molecule ctrl-CPF1 were successfully obtained over a 14-step total synthesis. The optimization of intermediate reactions based on early reports mentioned in literature as well as new approaches led to a noticeable improvement in yield. In addition, characterization of newly isolated intermediates was achieved. In contrast, BODIPY-based copper sensor CS3 was obtained based on literature procedures and successfully employed in the quantification of copper levels in HepG2 containing cell cultures. Yet, CPF1 and Ctrl-CPF-1 have not been tested *in vitro* and are subject of ongoing research.

In Addition, two glitazone representatives were synthesized. Rosiglitazone was accessed over a four-step synthesis, whereas lobeglitazone was obtained using a five-step procedure. Different conditions for similar steps were compared and assessed. *In vitro* cell tests of both potential compounds are still pending and currently being addressed in the group of *Dr. Jan Lukas* in the translational neurodegeneration section at the Albrecht Kossel institute in Rostock.

5 Peptidyl Trifluoromethylketone-based elastase inhibitors in acute pancreatitis

5.1 Introduction

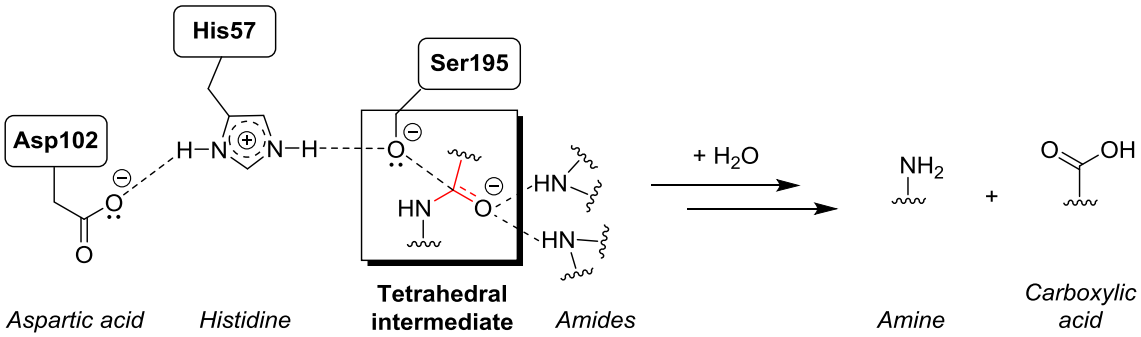
Protein misfolding and Endoplasmic Reticulum (ER)-stress play a pivotal role in human disease pathogenesis.[163, 164] Prevalent examples like *Wilson*'s disease, acute pancreatitis and *Alzheimer*'s disease are thought to have their origins in misfolded, aggregated and accumulated defective proteins.[118, 122, 165] The presence of distinctive amounts of misfolded proteins in ER induces protective intracellular signaling pathways including the unfolded protein response (UPR), as well as the ER-associated degradation (ERAD).[166] Those responses consist of a group of translational and transcriptional occurrences in order to restore the ER functionality and homeostasis.[165] Yet, if high levels of misfolded proteins are present and ER stress persists, a terminal UPR pathway is initiated that leads to apoptosis induction (programmed cell death) and subsequent loss of functionality of affected cells.

Acute pancreatitis (AP) is one of the most common gastrointestinal inflammatory disorders.[167] Damaged pancreatic acinar cells are believed to trigger inflammatory responses that can lead to a severe disorder form and successive high mortality. The most common cause of AP are duct obstruction by gallstones and alcohol misuse.[168] As a result, digestive zymogens are thought to be subject of premature activation, leading to an intracellular autodigestion as well as subsequent pancreatic cell damage.[169] This event is often followed by the recruitment and stimulation of different inflammatory cells, especially neutrophile granulocytes.[170]

Among affected enzymes during AP, both pancreatic- and neutrophil elastases are considered to play a crucial function in activating and influencing disease severity.[170, 171] In this context, the selective inhibition of both enzymes could provide an opportunity for causal treatment of AP. Elastase enzymes belong to the class of proteases. This proteolytic enzyme group catalyzes the breakdown of proteins peptide bonds into smaller peptide units or amino acids *via* hydrolysis.[172] Proteases, as such, can be grouped as serine-, aspartic-, cysteine-, glutamic-, asparagine-, threonine-, or metallo-proteases depending on the catalytic mechanism and involved amino acids at the active site of the enzyme.[173]

Serine proteases, to which the group of elastase enzymes belong, bear a catalytic triad at the enzyme's active site responsible of peptide bond hydrolysis.[174] This triad consists of three amino acids with different tasks; aspartic acid, histidine and serine, respectively (Scheme 5.1).

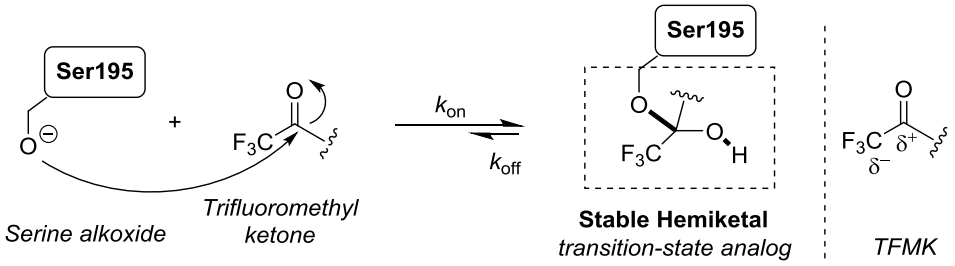
Initially, aspartic acid forms a hydrogen bond with the histidine amine residue and stabilizes its positive charge by polarization, thus ensuring proper orientation of the imidazole part towards serine. Next, the imidazole moiety of histidine deprotonates and polarizes serine, the nucleophilic member of the triad, thereby enhancing the oxygen's nucleophilicity. Subsequently, a nucleophilic attack of the generated alkoxide towards the positively polarized carbon of the peptide carbonyl group leads to the formation of a tetrahedral intermediate. The formed intermediate is stabilized by dipole-charge interactions in the oxyanion-hole, consisting of two backbone amide NH's groups of serine and glycine. Successive protonation and release of the amine part of the peptide bond followed by a hydrolysis of the covalent-acyl-enzyme intermediate *via* a second tetrahedral intermediate furnishes the corresponding carboxylic acid and regenerates the enzyme.



Scheme 5.1 Mechanism of peptide bond cleavage *via* hydrolysis by serine proteases.

The inhibition of proteases could be realized by employing transition-state analogs inhibitors. These inhibitors resemble the tetrahedral intermediate in structure, preserving the hydrogen bonding properties at the enzyme's active site. First trials to inhibit a protease by employing transition-state analogues were depicted by *Abeles* and co-workers.[175] Replacing the amide bond of the peptide by a non-hydrolizable bioisostere, for example a trifluoromethylketone (TFMK), afforded a selective and reversible inhibition of chymotrypsin. The introduction of a strong electron withdrawing group adjacent to the ketone's carbonyl moeity, especially a trifluoromethyl group (CF_3), leads to remarkable amplification of its reactivity. Hence, the enhanced positive charge at the carbonyl carbon makes it more susceptible to nucleophilic attacks.[176] Also, TFMK are able to form stable

hydrates with improved water solubility. Thus, a stable, yet reversible, hemiketal formation of trifluoromethylketone moieties with deprotonated serine alkoxide is reasonable at the enzyme's active site (Scheme 5.2).[177]

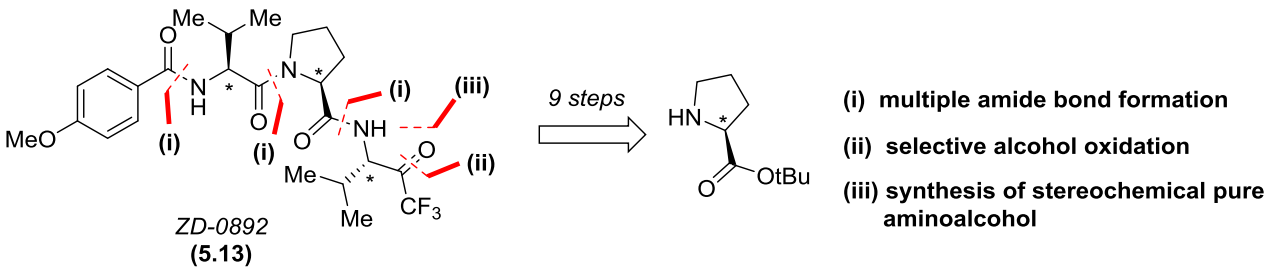


Scheme 5.2 Reversible inhibition of a serine protease by trifluoromethylketones (TFMK).

In 1997, peptidyl trifluoromethylketone ZD-0892 **5.13** bearing an *N*-methoxy benzamide group was reported by *Veale* and co-workers as a potent inhibitor of neutrophile-elastase (PMN-elastase) (Scheme 5.3).[178] The distinct inhibition capacity of ZD-0892 **5.13** in addition to its oral availability makes it a potential pharmaceutical candidate for the causal treatment of acute pancreatitis.

5.2 Objectives

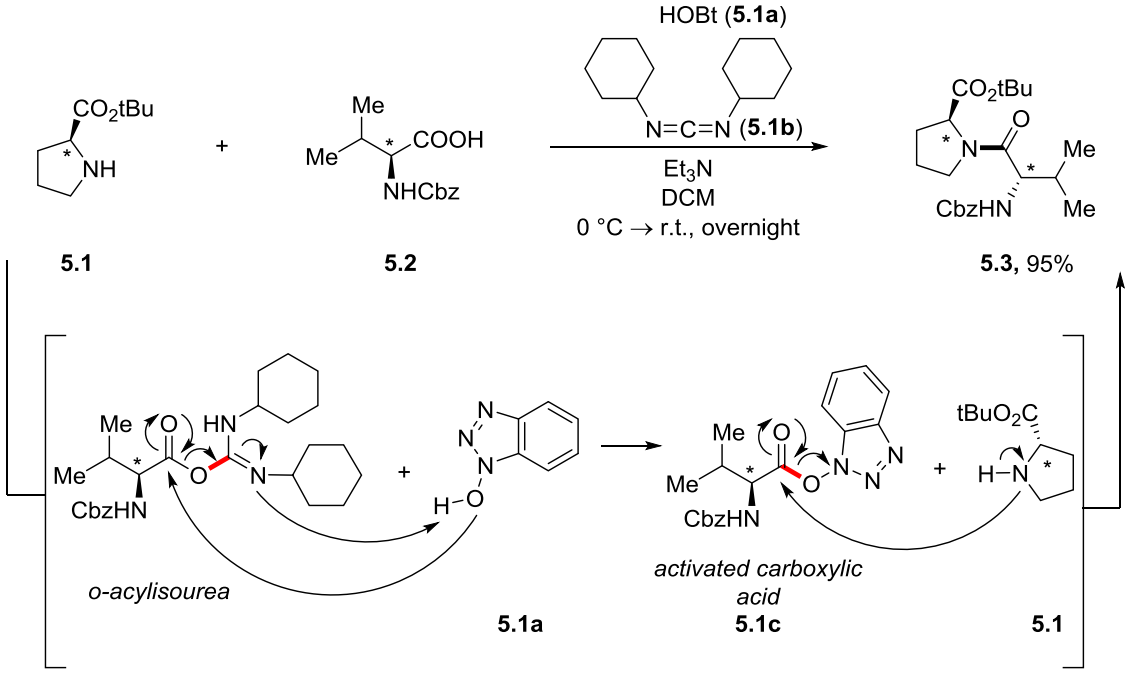
The reported stereoselective synthesis of ZD-0892 **5.13**, a potent peptidyltrifluoromethylketone-based elastase inhibitor, containing three chiral centers, is challenging (Scheme 5.3). Early synthetical reports require demanding fractional crystallization and handling sensitive and hazardous intermediates.[179] The Optimization of the total synthesis of ZD-0892 based on reports from *Veale et al.* and different approaches to access essential intermediates was conducted. A safer and easier total-synthesis protocol of ZD-0892 was envisioned with the aim to test **5.13** *in vitro* in acute pancreatitis cell-models.



Scheme 5.3 Retrosynthetic analysis of neutrophile-elastase inhibitor ZD-0892 (5.13) and challenging bond formations and transformations.

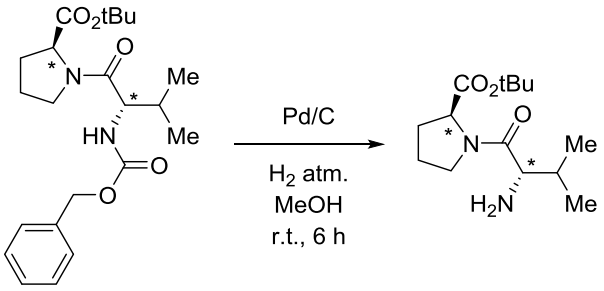
5.3 Results and discussion

First, we started with the synthesis of the peptide core **5.3** of ZD-0892 by a carbodiimide **5.1b** and 1-hydroxybenzotriazole (HOBt) (**5.1a**) mediated amide bond formation using the *tert*-butyl ester of *L*-proline (**5.1**) and Cbz-protected amino acid *L*-valine (**5.2**) as coupling partners (Scheme 5.4). Initially, the formation of *O*-acylisourea adduct of free carboxylic acid **5.2** and *N,N'*-dicyclohexylcarbodiimide (DCC) (**5.1b**) takes place.[180] The subsequent addition of HOBt **5.1a**, a good leaving group, is essential to activate the formed *O*-acylisourea and prevent a transposition of the *O*-acyl group to the adjacent *N*-atom.[180] Next, a nucleophilic attack of the amine lone-pair of **5.1** towards the carbonyl moiety of the activated carboxylic acid ester **5.1c** followed by the cleavage of the HOBt subunit generates the desired dipeptide **5.3** with intact stereochemical centers in an excellent isolated yield of 95%.



Scheme 5.4 Carbodiimide (5.1b) and HOBt (5.1a) mediated peptide-bond formation between α-amino acids (5.1) and (5.2).

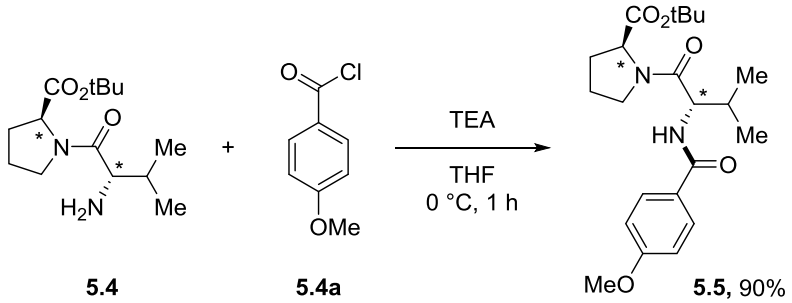
Following, deprotection of the Cbz-amino protecting group in dipeptide **5.3** was realized in methanol using palladium on carbon and atmospheric hydrogen pressure (Scheme 5.5). The desired free-amine **5.4** was obtained in an excellent yield of 96% after six hours.



5.3 **5.4,** 96%

Scheme 5.5 Deprotection of *N*-protected dipeptide (5.3) using palladium on carbon and atmospheric hydrogen pressure.

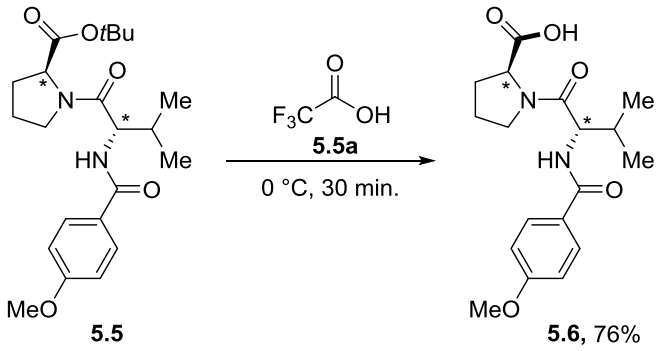
With the dipeptide **5.4** bearing a free amine moiety in hand, we continued with the *N*-protection of the free amine in **5.4** using *p*-anisoyl chloride (**5.4a**) and stoichiometric amounts of triethylamine as a base in THF (Scheme 5.6). The nucleophilic substitution of the benzoyl chloride **5.4a** by the free amine of **5.4** resulted in the formation of the desired benzamide **5.5** and hydrochloric acid as a byproduct. The amine base serves as an acid scavenger upon formation of ammonium chloride salts. Due to the diminished solubility of ammonium chloride salts in THF, a shift of the reaction equilibrium towards the product side translates in an excellent yield of **5.5**, accounting up to 90% after one hour.



5.4 **5.4a** **5.5,** 90%

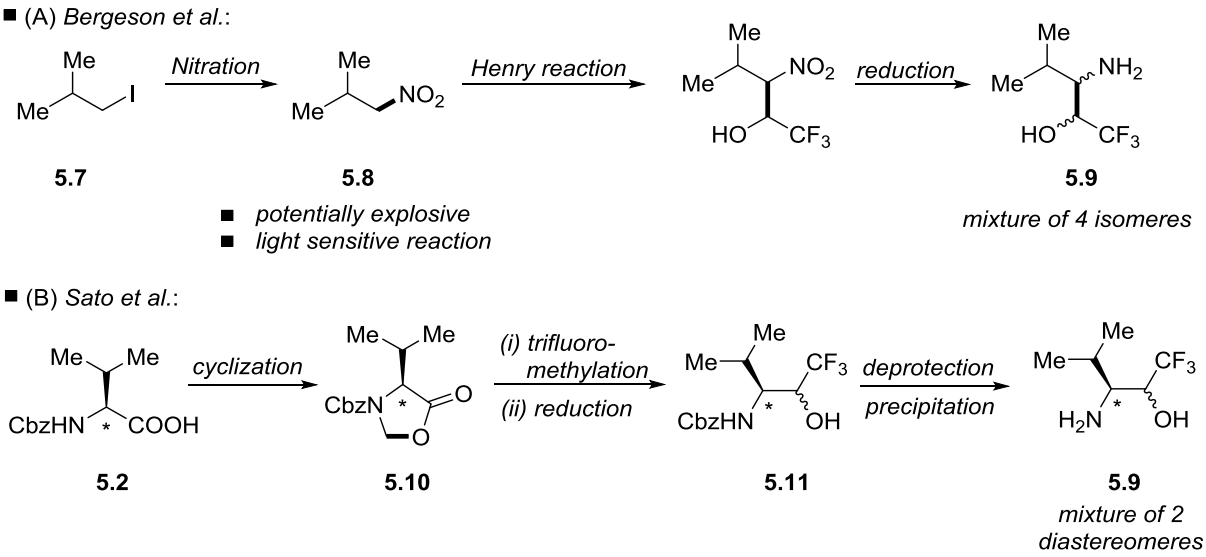
Scheme 5.6 Base-promoted benzamide formation using didpeptide (5.4) and *p*-anisoyl chloride (5.4a).

The cleavage of the *tert*-butyl ester of **5.5** on a gram-scale was readily achieved by the treatment of ester **5.5** with trifluoroacetic acid (**5.5a**) for 30 minutes (Scheme 5.7). The strong acidic trifluoroacetic acid (**5.5a**) enables the protonation of the carbonyl moiety of ester **5.5** followed by a cleavage of the corresponding free carboxylic acid **5.6** and the extrusion of a *tert*-butyl cation.



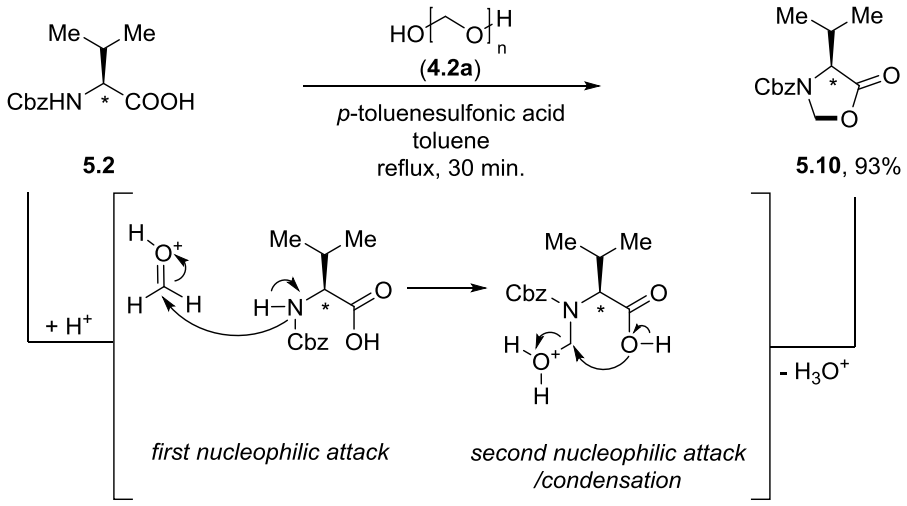
Scheme 5.7 Cleavage of *tert*-butyl ester in dipeptide (5.5) using trifluoroacetic acid (5.5a).

Next, we focused on the synthesis of the aminoalcohol (3*S*)-3-amino-1,1,1-trifluoro-4-methylpentan-2-ol (**5.9**) (Scheme 5.8). In a patented procedure by *Bergeson* and co-workers, **5.9** was obtained as a *threo* mixture over a 3-step synthesis starting from 1-iodo-2-methylpropane (**5.7**).[181] Due to safety concerns and light sensitivity of nitro containing intermediate **5.8** as well as significant difficulty to obtain stereochemical pure **5.9** out of the corresponding mixture of isomers following the method of *Bergeson et al.*, we presumed that the patented methodology described by *Sato* and coworkers would ensure a safer and easier protocol to access **5.9** as a mixture of only 2 diastereomers.[181, 182]



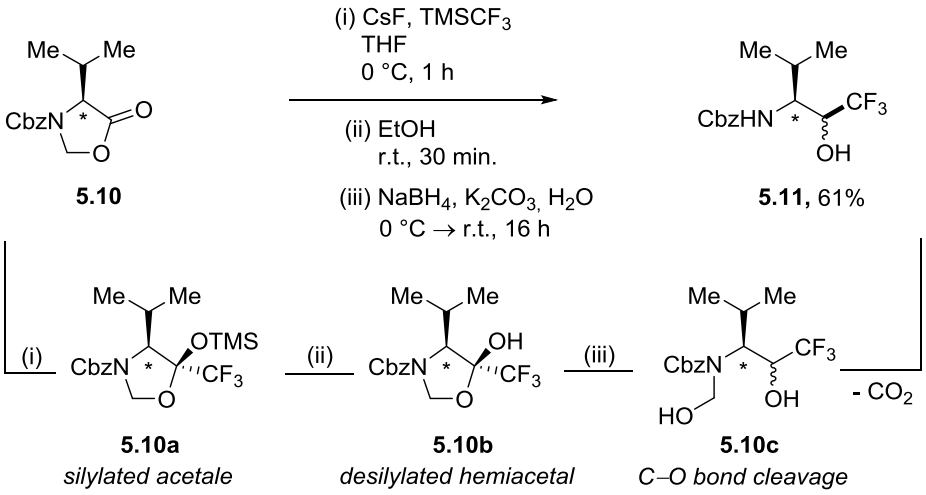
Scheme 5.8 Patented methods for the synthesis of (5.9) by (A) Bergeson *et al.* and (B) Sato *et.al.*.[181, 182]

Optical pure oxazolidinone **5.10** was obtained starting from Cbz-*L*-valine (**5.2**) *via* introduction of a methylene bridge using paraformaldehyde (**4.2a**) under acidic conditions (Scheme 5.9). Decomposition of paraformaldehyde to formaldehyde under acidic conditions using *p*-toluenesulfonic acid paved the way for two consecutive nucleophilic attacks from both amine lone-pair of **5.2** and oxygen lone-paire of the carboxylic acid moiety in **5.2**. Subsequent elimination of water upon protonation generate optical pure **5.10** in an excellent yield of 93%.



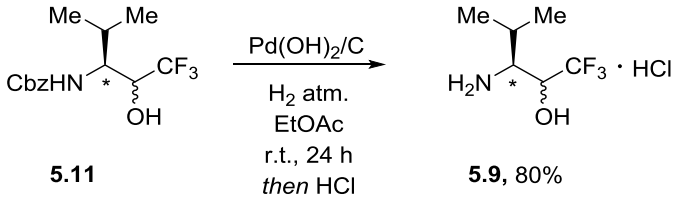
Scheme 5.9 Synthesis of cyclic (5.10) *via* methylene bridge formation from amino acid (5.2) and paraformaldehyde (4.2a) under acidic conditions.

Afterwards, adopting the procedure described by *Sato et al.*, a one-pot multistep reaction including a trifluoromethylation-, reductive C–O bond cleavage-, and an elimination step of **5.10** was conducted (Scheme 5.10).[182] First, a nucleophilic trifluoromethyl anion was generated *in situ* by employing trifluoromethyl trimethylsilane ($TMSCF_3$), also known as *Ruppert-Prakash* reagent, with catalytic amounts of cesium fluoride (CsF) in THF at 0 °C for one hour. Subsequently, the highly reactive trifluoromethyl anion attacks the carbonyl group of the lactone moiety in **5.10** generating an intermediate alkoxide anion. The latter alkoxide anion is quickly silylated by the *in situ* formed trimethyl silane cation, furnishing acetale intermediate **5.10a**. Next, cleavage of the trimethyl silane group was accomplished by the addition of ethanol as a protic solvent which yielded hemiacetal **5.10b**. The addition of reducing sodiumborohydride ($NaBH_4$) to the reaction promoted the reductive C–O bond cleavage in **5.10b**, giving access to **5.10c**. Subsequent base-promoted elimination of carbon dioxide from **5.10c** furnishes desired benzyl ((3*S*)-1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)carbamate (**5.11**) in a good synthetic yield of 61%. The existence of (**5.11**) as a mixture of two diastereomers does not affect the optical purity outcome of end-product ZD-0892 (**5.13**), since the last step in the total synthesis of **5.13** consists of the oxidation of the secondary alcohol moiety in **5.9**.



Scheme 5.10 One-pot synthesis of protected trifluoromethyl amino alcohol (5.11) from cyclic (5.10).[182]

Following, deprotection of benzyl ((3*S*)-1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)carbamate (**5.11**) was enabled by a similar procedure to the reaction of **5.3** to **5.4** (Scheme 5.5) using palladium(II) hydroxide on carbon and atmospheric hydrogen pressure for 24 hours (Scheme 5.11). Upon precipitation with hydrochloric acid, diastereomeric 3-amino-1,1,1-trifluoro-4-methylpentan-2-ol (**5.9**) was obtained in a good yield of 80% as a hydrochloride.



Scheme 5.11 Palladium-catalyzed cleavage of the Cbz amine protecting group in amino alcohol (5.11).

Upon deprotonation and crystallization, the structure of the (2*R*,3*S*) diastereomeric free amine form of product **5.9** was confirmed by X-ray analysis (Figure 5.1). It is worth mentioning, that this method offers an easier way to access diastereomeric amino alcohol **5.9** without the need for multiple crystallization and addition of enantiopure additives.[178]

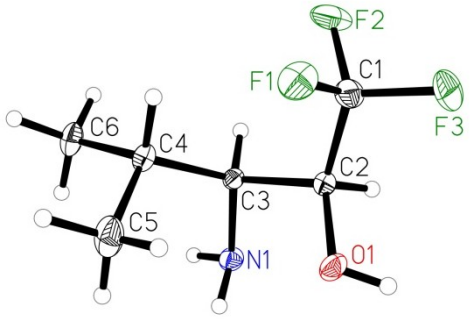
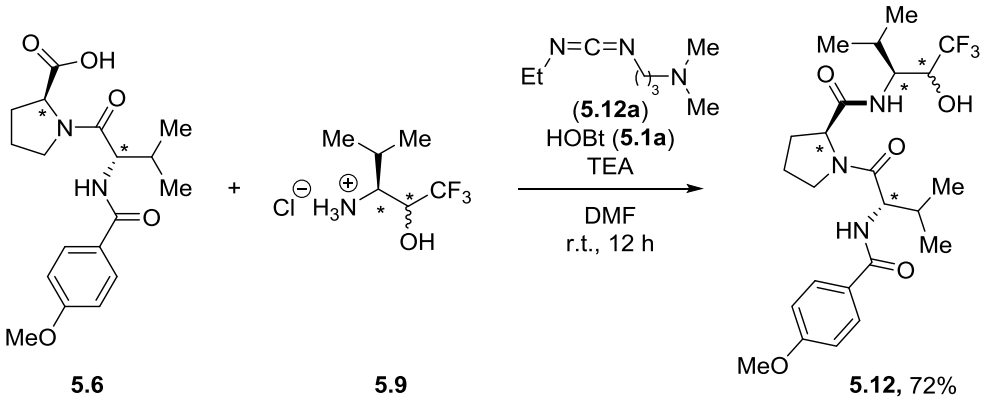


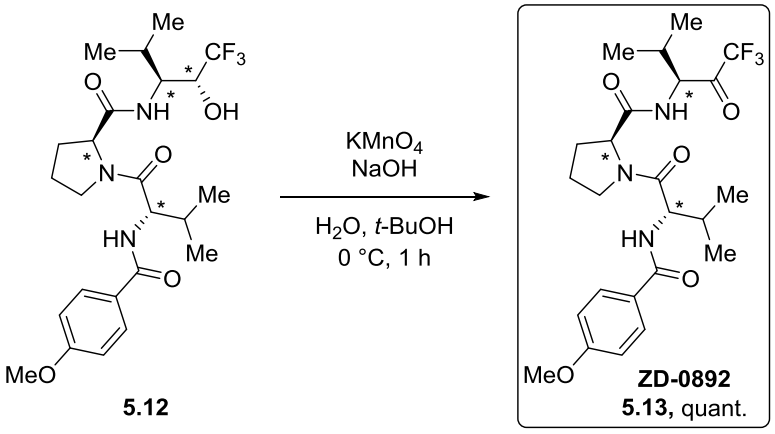
Figure 5.1 Molecular structure of the base form of (5.9). Displacement ellipsoids correspond to 30% probability.

Afterwards, the coupling of dipeptide **5.6**, containing a free carboxylic acid, with diastereomeric aminoalcohol salt **5.9** generated the precursor alcohol **5.12** (Scheme 5.12).[178] The amide bond formation was conducted in a similar procedure to the reaction of α-amino acids **5.1** and **5.2** to **5.3** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (**5.12a**), 1-hydroxybenzotriazole (**5.1a**) and triethylamine as a base in DMF for 12 hours. The desired peptidyl trifluoromethylalcohol **5.12** was obtained as a crystalline product in a good yield of 72%.



Scheme 5.12 Coupling of peptidyl carboxylic acid (5.6) with (*2R,3S*)-3-amino-1,1,1-trifluoro-4-methylpentan-2-ol (5.9).[178]

The last step consisted of a selective oxidation of the secondary alcohol contained in precursor **5.12** to the corresponding desired ketone ZD-0892 **5.13** using potassium permanganate in aqueous basic conditions (Scheme 5.13).[178] Thus, the desired elastase-inhibitor ZD-0892 **5.13** was obtained in quantitative yield after one hour at 0 °C.



Scheme 5.13 Oxidation of secondary alcohol precursor (5.12) to the corresponding peptidyl-trifluoromethylketone ZD-0892 (5.13) using potassium permanganate.[178]

The application of ZD-0892 **5.13** in acute pancreatitis cell models is still a subject of ongoing research in the Group of *Dr. Matthias Sendler* at the university medical center of Greifwald.

5.4 Conclusion

In conclusion, an advanced stereoselective synthesis of the peptidyl trifluoromethylketone ZD-0892 was accomplished over an optimized 9 step synthesis. A reevaluation of published synthetical protocols allowed the establishment of a safer and easier way to access stereodemanding intermediates. The *in vitro* test results regarding the dual inhibition of both pancreatic- as well as neutrophil elastase in acinus cells using ZD-0892, which are being conducted by the group of *Dr. Matthias Sendler* in the clinic and polyclinic for internal medicine A at the university medical center of Greifswald, are still a subject of ongoing research. ZD-0892 could potentially offer a causal treatment of acute pancreatitis.

6 Summary and Outlook

This thesis summarizes initial approaches to access pharmaceutically relevant motifs for the individualized therapies of hereditary liver and pancreas diseases. Beside the use of different well-established organic chemistry related methods to access literature-known compounds, the development of new highly sustainable protocols for the catalytic functionalization of organic scaffolds is described.

An efficient photoredox catalytic decarboxylative methodology to forge new C–C bonds was described. The photocatalytic decarboxylative *Giese*-type addition of corresponding carboxylic acids to electron-deficient alkenes was accomplished using pyrimidopteridine *N*-oxides as photocatalysts. Moreover, the use of catalytic amounts of base and the metal-free nature of this protocol offers an environmentally-benign method.

Also, the photocatalytic hydroamination of different stilbene derivatives using primary unprotected amines was showcased. This transformation was accessible using pyrimidopteridine *N*-oxides as photocatalysts in an additive-free setup. Different primary unprotected amines proved to be competing coupling partners, giving access to α-phenyl phenethylamine derivatives, known for their biological activity.

Moreover, two glitazone derivatives, rosiglitazone and lobeglitazone, as well as two different copper chemosensors, CS3 and, CPF1 in addition to the corresponding control molecule ctrl-CPF1, were synthesized. Literature reports addressing the total-synthesis of latter compounds were re-evaluated. Also, optimization of the reactions during different steps of the total-synthesis of CS3, CPF1 and ctrl-CPF1 was achieved. The use of a copper chemosensor CS3 for the quantification of labile copper pools in HepG2 cell cultures was demonstrated. In the same context, the total-synthesis of a potent peptidyl trifluoromethyl ketone elastase-inhibitor ZD-0892 was revised and optimized. The combination of different literature known methodologies allowed the establishment of a safer and easier way to access ZD-0892.

The wide variety of synthesized potential bioactive compounds are still under investigation and subject of ongoing research within the interdisciplinary research cluster of the project. Successfully tested compounds could provide a platform for the treatment of hereditary liver and pancreas diseases.

7 Experimental section

7.1 General remarks

All reactions involving moisture- or air-sensitive reactants or products were performed under an atmosphere of dry argon using standard Schlenk techniques and predried glassware. Syringes for handling of dry solvents or liquid reactants were flushed with dry argon prior to use. All chemicals, unless otherwise indicated, were obtained from commercial sources. The synthesis of the starting materials, if not purchased, was carried out by literature methods.

Solvents

All solvents for reactions containing moisture-sensitive reactants were purchased from SIGMA-ALDRICH and ACROS ORGANICS or dried by the usual methods and stored under inert atmosphere (argon) according to following standard procedures. Water was degassed by bubbling Argon through the solution over 30 minutes and ultrasonication.

Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F plates (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Unless otherwise noted, plates were visualized under ultraviolet light (254 nm) and developed by treatment with the $KMnO_4$ solution.

Chromatographic purification of products was accomplished by flash column chromatography on Fluka silica gel, grade 60 (0.063-0.200 mm, 70–230 mesh). Solvents used for column chromatography were distilled prior of use.

Analytical Data

Analytical data of substances that are known in literature (marked by corresponding references) were compared with those described in the literature.

Infrared Spectroscopy

Infrared spectra were recorded using a Nicolet 550 FT-IR spectrometer with ATR sampling technique. Liquid probes were measured as film, solid probes were measured neat. Absorption is given in wavenumbers (cm^{-1}). Signal characterization: w = weak, m = medium, s = strong.

Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV 300 (300 MHz), Bruker AV 400 (400 MHz), and Fourier 300 (300 MHz). For characterization of the observed signal multiplicities the following abbreviations were applied: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Unless otherwise mentioned, all NMR spectra were collected in $CDCl_3$ solution. Chemical shifts are reported as *δ*-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively. Coupling constants are indicated as *J* with residual peaks of $CHCl_3$ at δ = 7.24 ppm, DMSO at δ = 2.49 ppm, CH_2Cl_2 at δ = 5.32 ppm, CHD_2OD at δ = 3.35 ppm. Coupling constants *J* are reported in Hertz (Hz). Residual carbon peaks are as following: $CHCl_3$ at δ = 77.23 ppm, DMSO at δ = 39.51 ppm, CH_2Cl_2 at δ = 54.00 ppm, CHD_2OD at δ = 49.15 ppm. 2D NMR techniques (NOESY, COSY, HMBC, HSQC) were performed confirming the structures of the synthesized molecules. The spectra were measured with a standard number of scans.

Mass spectroscopy

Mass spectra were measured on FINNIGAN MAT 95 (200 eV, EI-MS) or LCQ (70 eV, ESI-MS). The ratio of mass to charge are indicated, intensities relative to the base peak (I = 100) are written in parentheses. High resolution mass spectras (HRMS) were recorded on BRUKER APEX IV (7 T, Transform Ion Cyclotron Resonance (FTICR) mass spectrometer).

Melting Points

Melting points were measured using a BÜCHI melting point apparatus. Reported values are uncorrected.

Crystallographic data

Crystallographic data were collected on a BRUKER KAPPA APEX II DUO diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares procedures on F^2 with the SHELXTL software package (Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112.). XP (BRUKER AXS) was used for graphical representation. Displacement ellipsoids are drawn at the 30% probability level.

Photoreactions

Reactions were performed under Schlenk conditions using a 5 ml reaction vial from Biotage® equipped with a NS 14.5 rubber septum. The reaction mixture was then irradiated with 2 UV-lamps ONFURO IP66 (30 W) (λ_{max} = 396 nm) for the indicated time with a distance

of 5.7 cm to the nearest- and 10.4 cm to the distant lamp and quenched afterwards upon exposure to air.

7.2 General procedures

General procedure A: Pyrimidopteridine *N*-oxide photo-mediated decarboxylative Giese-type addition

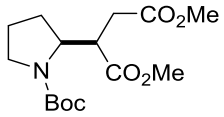
Unless otherwise mentioned, reactions were performed under Schlenk conditions using a 5 ml reaction vial equipped with a NS 14.5 rubber septum. To this vial was added the appropriate carboxylic acid **2.1** (0.50 mmol, 1.0 equiv.), photocatalyst PrPPTNO **1.2** (5.0 mol%) and K_3PO_4 (20.0 mol%). Next, the vial was evacuated and purged with argon for 3 times. The corresponding olefin **2.4** (1.0 mmol, 2.0 equiv.) was then added to the flask under argon. Afterwards, acetonitrile (4.5 ml) and degased water (0.5 ml) were added and the reaction mixture was stirred for 2 minutes in the dark. The reaction mixture was then irradiated for the indicated time and quenched afterwards upon exposure to air and bubbling air through the solution using a pipette. The reaction temperature was monitored in an adjacent microwave vial filled with paraffin oil and equipped with a thermal sensor. The reaction mixture was concentrated under reduced pressure and the crude mixture was purified by column chromatography.

General procedure B: Pyrimidopteridine *N*-oxide photo-mediated hydroamination of unactivated stilbenes

Reactions were performed under Schlenk conditions using a 5 ml reaction vial equipped with a NS 14.5 rubber septum. The vial containing the corresponding stilbene **3.2** (0.50 mmol, 1.0 equiv.) and photocatalyst PrPPTNO **1.2** (5.0 mol%) was evacuated for 5 minutes and purged with argon. Acetonitrile (2.5 ml) was added and the corresponding amine **3.1** (2.50 mmol, 5.0 equiv.) was added to the stirring solution. The reaction vial was rinsed with acetonitrile (2.5 ml). Next, the reaction mixture was irradiated at 396 nm for 16-24 h. The reaction temperature was monitored in an adjacent microwave vial filled with paraffin oil and equipped with a thermal sensor. A constant temperature of 30 °C was measured due to heat emission of the LED. No extra heating or cooling was applied. After the indicated time, the reaction was quenched upon exposure to air and bubbling air through the solution using a pipette. The reaction was concentrated under reduced pressure and the crude product was purified by column chromatography.

7.2.1 Experimental section to Chapter 2

Synthesis of dimethyl 2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)succinate (2.6aa).



2.6aa

Compound **2.6aa** was prepared following general procedure **A**. Dimethyl maleate **2.4a** (144 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane: acetone = 40:1 → 20:1) yielded the title compound **2.6aa** (140 mg, 0.4 mmol, 88%) as a yellow oil. Analytical data are stated for a mixture of two diastereomers (dr: 1:1).

$\mathbf{R_f}$ = 0.20 (*n*-pentane:acetone = 10:1, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.28 – 3.86 (m, 1H), 3.72 – 3.65 (s, 3H), 3.64 (s, 3H), 3.62–3.06 (m, 3H), 2.73 (m, 1H), 2.55 – 2.22 (m, 1H), 1.97 – 1.61 (m, 4H), 1.45 (s, 9H).

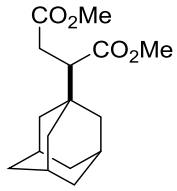
^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.8, 173.4, 172.6, 58.5, 57.6, 52.1, 51.9, 47.3, 44.5, 44.1, 33.8, 28.5, 27.9, 23.6, 22.9.

MS (EI) *m*/*z* relative Intensity: 315 (0.1) [M], 154 (15), 128 (19), 114 (57), 70 (100), 57 (57), 41 (19).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{15}H_{25}NO_6$ $[M]^+$ 338.1676, found 338.1678.

IR (ATR, neat, cm^{-1}): 2974 (w), 2955 (w), 2885 (w), 1733 (s), 1689 (s), 1557 (w), 1478 (w), 1436 (m), 1388 (s), 1366 (s), 1314 (m), 1255 (m), 1157 (s), 1116 (s), 1009 (m), 942 (w), 913 (m), 873 (m), 846 (m), 772 (m), 675 (w), 544 (w), 509 (w), 462 (w).

Synthesis of dimethyl 2-((3r,5r,7r)-adamantan-1-yl)succinate (2.6ba)



2.6ba

Compound **2.6ba** was prepared following general procedure **A**. Dimethyl maleate **2.4a** (144 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 15:1) yielded the title compound **2.6ba** (115 mg, 0.41 mmol, 82%) as a colorless solid. The analytic data is in correspondence with those reported in literature.[183]

m.p. = 51 °C

$\mathbf{R_f}$ = 0.58 (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.64 (s, 3H), 3.60 (s, 3H), 2.70 (m, 1H), 2.45 (m, 2H), 1.96 (m, 3H), 1.61 (q, J = 12.2 Hz, 9H), 1.42 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.3, 173.4, 52.3, 51.8, 51.3, 40,0, 36.8, 34.4, 31.0, 28.5.

MS (EI) *m*/*z* (relative intensity): 280 (1), 248 (13), 145 (7), 135 (100), 107 (6), 93 (12), 79 (14).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{16}H_{24}O_4$ [M^+] 280.1669, found 280.1664.

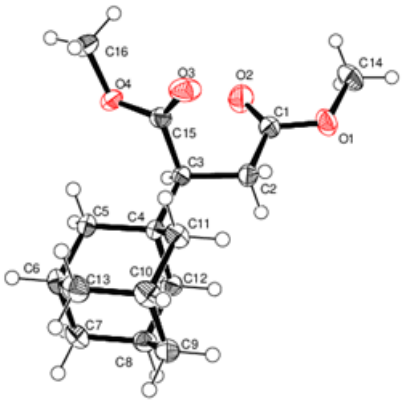
IR (ATR, neat, cm^{-1}): 2900 (s), 2847 (m), 1725 (s), 1438 (s), 1413 (w), 1366 (m), 1340 (m), 1304 (m), 1285 (w), 1229 (s), 1208 (s), 1194 (s), 1161 (s), 1119 (m), 1097 (m), 1081 (w), 1011 (w), 987 (m), 964 (m), 887 (w), 845 (m), 819 (w), 798 (w), 773 (w), 720 (w), 681 (w), 590 (w), 525 (w), 454 (w).

Big scale synthesis of dimethyl 2-((3r,5r,7r)-adamantan-1-yl)succinate (2.6ba)

To a 100 ml flame dried Schlenk flask equipped with a stir bar was added 1-adamantanecarboxylic acid **2.1b** (541 mg, 3.0 mmol, 1.0 equiv.), *n*-propyl PPTNO **1.2** (65 mg, 0.150 mmol, 0.05 equiv.) and K_3PO_4 (127 mg, 0.600 mmol, 0.2 equiv.). The flask was evacuated and flushed with argon for 3 times. Afterwards, dimethyl maleate **2.4a** (865 mg, 6.0 mmol, 2.0 equiv.) was added, followed by dry MeCN (27 ml) and degassed water (3 ml) under argon. The reaction mixture was allowed to stir in the dark for 2 minutes, then it was irradiated for 24 hours. The reaction was quenched by bubbling air through the reaction mixture using a pipette. Drying the mixture under vacuum afforded an oil which was purified by column chromatography (*n*-pentane:EtOAc = 15:1) and the title compound **2.6ba** (375 mg, 1.34 mmol, 45%) was obtained as a colorless solid.

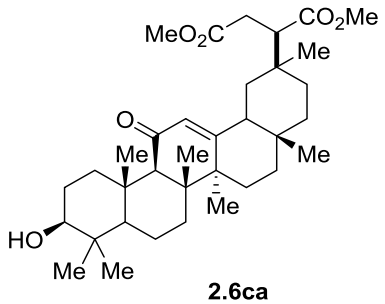
Crystallographic Data of dimethyl 2-((3r,5r,7r)-adamantan-1-yl)succinate (2.6ba)

Data were collected on a Bruker Kappa APEX II Duo diffractometer using Mo-Ka radiation. The structures were solved by direct methods (SHELXS-97: Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112.) and refined by full-matrix least-squares procedures on F^2 (SHELXL-2014 and SHELXL-2018, resp.: Sheldrick, G. M. *Acta Cryst.* **2015**, *C71*, 3.). XP (Bruker axs) was used for graphical representations.



chemical formula	$C_{16}H_{24}O_4$	
formula weight	280.35	
crystal system	monoclinic	
unit cell dimensions		
	a = 9.3426(9) Å	α = 90 °
	b = 21.642(2) Å	β = 1473.5(2) °
	c = 7.3217(7) Å	γ = 150(2) °
space group	$P2_1/c$	
Z	4	
μ [mm^{-1}]	0.09	
density [g/cm^3]	1.264	
no. of reflections measured	27916	
no. of independent reflections	3562 (R_{int} = 0.028)	
no. of observed reflections ($I > 2\sigma(I)$)	2926	
no. of parameters	183	
R_1 ($I>2\sigma(I)$)	0.041	
wR_2 (all data)	0.116	
Goodness of fit on F^2	1.03	
largest diff. peak and hole [e/Å^3]	0.36 and -0.18	

Synthesis of dimethyl 2-((4a*R*,6a*S*,6b*R*,10*S*,12a*S*,12b*R*)-10-hydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicen-2-yl)succinate (2.6ca)



2.6ca

Compound **2.6ca** was prepared following general procedure **A** for 48 h. 18β-Glycyrrhetinic acid (enoxolone) **2.1j** (235 mg, 0.5 mmol, 1.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 10:1 → 5:2) yielded the title compound **2.6ca** (223 mg, 0.391 mmol, 78%) as a colorless thick oil. (mixture of diastereomers)

R_f = 0.2 (*n*-pentane:EtOAc = 5:2, UV, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.55 (m, 1H), 3.65 (m, 6H), 3.21 (dd, J = 10.5, 5.8 Hz, 1H), 2.76 (m, 2H), 2.58 (m, 1H), 2.46 (ddd, J = 16.4, 7.1, 2.8 Hz, 1H), 2.31 (d, J = 7.3 Hz, 1H), 2.11 (m, 1H), 1.90 (m, 3H), 1.60 (m, 5H), 1.38 (m, 10H), 1.15 (m, 8H), 0.96 (m, 9H), 0.81 (d, J = 16.2 Hz, 6H).

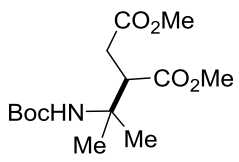
^{13}C NMR (75 MHz, $CDCl_3$) δ = 200.4, 200.2, 174.4, 174.3, 173.2, 173.1, 169.7, 169.5, 128.6, 128.5, 78.8, 61.9, 61.9, 55.0, 53.3, 53.2, 52.0, 51.7, 51.6, 46.9, 45.6, 43.4, 41.8, 40.5, 39.2, 37.2, 36.1, 35.7, 32.8, 32.4, 32.4, 31.8, 31.8, 31.2, 30.1, 28.7, 28.6, 28.2, 27.4, 26.4, 26.3, 23.6, 23.5, 18.8, 18.5, 18.5, 17.6, 16.5, 16.4, 15.7.

MS (EI) *m/z* (relative intensity): 570 (56) [M], 539 (7), 403 (100), 362 (84), 339 (18), 302 (12), 235 (15), 217 (15), 193 (16), 188 (11), 175 (71), 161 (10), 135 (46), 121 (17), 95 (19).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{35}H_{55}O_6$ $[M+H]^+$ 571.3998, found 571.4002.

IR (ATR, neat, cm^{-1}): 3433 (w, br.), 2946 (w), 2926 (w), 2865 (w), 1730 (w), 1655 (w), 1436 (w), 1195 (w), 1162 (w), 1037 (w), 729 (w).

Synthesis of dimethyl 2-(2-((tert-butoxycarbonyl)amino)propan-2-yl)succinate (2.6da)



2.6da

Compound **2.6da** was prepared following general procedure **A**. α-(Boc-amino)isobutyric acid **2.1d** (102 mg, 0.5 mmol, 1.0 equiv.) and dimethyl maleate **2.4a** (144 mg, 1.0 mmol, 2.0 equiv.) were used. Purification by column chromatography (*n*-pentane:EtOAc = 9:1) yielded the title compound **2.6da** (69 mg, 0.222 mmol, 45%) as a colorless oil. The product mixture gives multiple sets of NMR signals, owing to the presence of rotamers around the amide.

$\mathbf{R_f}$ = 0.47 (*n*-pentane:EtOAc = 9:2, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.72 (br. s, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 3.41 (m, 1H), 2.61 (m, 2H), 1.42 (m, 9H), 1.32 (s, 3H), 1.26 (s, 3H).

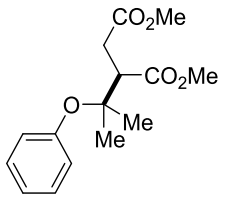
^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.2, 172.5, 154.4, 154.4, 79.4, 79.4, 79.3, 53.5, 53.4, 52.0, 52.0, 51.8, 48.8, 48.8, 32.7, 28.5, 28.3, 25.6, 25.3, 17.5.

MS (EI) *m*/*z* (relative intensity): 230 (4), 216 (6), 198 (5), 172 (7), 155 (21), 128 (19), 114 (21), 102 (57), 96 (7), 84 (10), 69 (6), 57 (100).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{14}H_{25}NO_6Na$ $[M+Na]^+$ 326.1579, found 326.1575.

IR (ATR, neat, cm^{-1}): 3379 (w), 2977 (w), 2953 (w), 1714 (m), 1510 (m), 1439 (m), 1366 (m), 1243 (m), 1160 (s), 1074 (m), 1021 (w).

Synthesis of dimethyl 2-(2-phenoxypropan-2-yl)succinate (2.6ea)



2.6ea

Compound **2.6ea** was prepared following general procedure **A**. Dimethyl maleate **2.4a** (144 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 9:1) yielded the title compound **2.6ea** (37 mg, 0.132 mmol, 26%) as a colorless oil.

$\mathbf{R_f}$ = 0.45 (*n*-pentane:EtOAc = 9:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31 (m, 2H), 7.19 (m, 1H), 6.88 (m, 2H), 4.24 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.71 (m, 1H), 3.29 (dd, *J* = 17.5, 11.0 Hz, 1H), 1.55 (s, 3H), 1.26 (s, 3H).

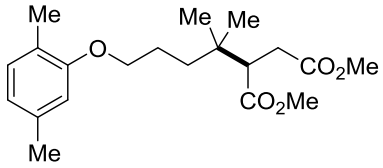
^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.7, 172.4, 152.5, 129.0, 127.6, 120.9, 118.0, 117.4, 108.5, 75.0, 52.6, 52.3, 50.8, 42.8, 28.6, 20.9.

MS (EI) *m*/*z* (relative intensity): 280 (6), 249(4), 220 (14), 188 (16), 166 (23), 161 (17), 145 (25), 134 (100), 127 (15), 119 (10), 106 (46), 95 (39), 83 (21), 77 (44).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{15}H_{21}O_5$ $[M+H]^+$ 281.1389, found 281.1393.

IR (ATR, neat, cm^{-1}): 2986 (w), 2955 (w), 1729 (s), 1583 (w), 1436 (w), 1333 (w), 1254 (m), 1162 (m), 1114 (m), 1018 (w), 943 (w), 765 (m).

Synthesis of dimethyl 2-(5-(2,5-dimethylphenoxy)-2-methylpentan-2-yl)succinate (2.6fa)



2.6fa

Compound **2.6fa** was prepared following general procedure **A** for 48 h. Dimethyl maleate **2.4a** (144 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 10:1) yielded the title compound **2.6fa** (30 mg, 0.085 mmol, 17%) as a colorless oil.

$\mathbf{R_f}$ = 0.42 (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.00 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 6.61 (s, 1H), 3.91 (m, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 2.82 (m, 2H), 2.48 (m, 1H), 2.31 (s, 3H), 2.17 (s, 3H), 1.82 (m, 2H), 1.45 (m, 2H), 0.97 (d, J = 2.0 Hz, 6H).

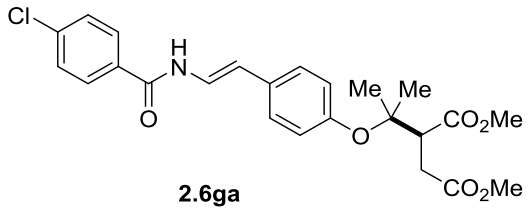
^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.8, 173.3, 157.1, 136.6, 130.4, 123.7, 120.8, 112.1, 68.2, 51.9, 51.6, 49.5, 37.3, 35.1, 32.4, 25.2, 25.0, 24.1, 21.5, 15.9.

MS (EI) *m*/*z* (relative intensity): 350 (37) [M], 229 (100), 197 (10), 179 (11), 169 (15), 165 (57), 137 (35), 122 (80), 109 (24), 95 (18), 83 (51).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{20}H_{31}O_5$ $[M+H]^+$ 351.2171, found 351.2171.

IR (ATR, neat, cm^{-1}): 2951 (w), 2873 (w), 1732 (s), 1614 (w), 1509 (w), 1261 (m), 1191 (w), 1156 (s), 1129 (m), 1008 (w), 504 (w).

Synthesis of dimethyl (*E*)-2-(2-(4-(2-(4-chlorobenzamido)vinyl)phenoxy)propan-2-yl)succinate (2.6ga)



2.6ga

Compound **2.6ga** was prepared following general procedure **A** for 48 h. 2-(4-(2-(4-chlorobenzamido)ethyl)phenoxy)-2-methylpropanoic acid (Bezafibrate) **2.1g** (181 mg, 0.5 mmol, 1.0 equiv.) was used. Purification by column chromatography (*n*-pentane:acetone = 10:1) yielded the title compound **2.6ga** (72 mg, 0.157 mmol, 31%) as a white solid.

m.p.= 172−173 °C

R_f = 0.17 (*n*-pentane: acetone = 20:3, UV, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.63 (m, 2H), 7.36 (m, 2H), 7.08 (m, 1H), 7.02 (m, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.26 (t, J = 5.5 Hz, 1H), 4.17 (d, J = 11.8 Hz, 1H), 3.71 (m, 7H), 3.53 (m, 1H), 3.24 (d, J = 11.7 Hz, 1H), 2.81 (m, 2H), 1.50 (s, 3H), 1.22 (s, 3H).

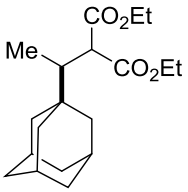
^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.8, 172.3, 166.5, 151.3, 137.7, 133.0, 131.2, 129.4, 128.9, 128.4, 127.9, 118.3, 117.6, 75.0, 52.6, 52.4, 50.8, 42.7, 41.4, 35.0, 28.5, 21.0.

MS (EI) *m*/*z* (relative intensity): 459 (3) [M], 400 (9), 304 (100), 272 (37), 244 (64), 229 (52), 199 (24), 171 (22), 159 (10), 139 (45), 128 8), 111 (16).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{24}H_{26}O_6NCl$ $[M+H]^+$ 460.1527, found 460.1521.

IR (ATR, neat, cm^{-1}): 3233 (w), 3083 (w), 2952 (w), 1731 (m), 1630 (w), 1303 (w), 1193 (m), 847 (w), 737 (w).

Synthesis of diethyl 2-(1-((3r,5r,7r)-adamantan-1-yl)ethyl)malonate (2.6bb)



2.6bb

Compound **2.6bb** was prepared following general procedure **A**. Diethyl ethylidenmalonate **2.4b** (186 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound **2.6bb** (148 mg, 0.460 mmol, 92%) as a colorless oil. The analytic data is in correspondence with those reported in literature.[183]

R_f = 0.60 (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.14 (m, 4H), 3.53 (d, J = 5.2 Hz, 1H), 2.03 (qd, J = 7.3, 5.5 Hz, 1H), 1.93 (s, 3H), 1.54 (m, 12H), 1.23 (m, 6H), 0.94 (d, J = 7.3 Hz, 3H).

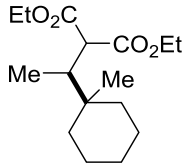
^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.4, 169.8, 61.4, 60.9, 51.9, 43.1, 39.4, 37.1, 35.3, 28.7, 14.1,14.1, 10.4.

MS (EI) *m/z* (relative intensity): 276 (11), 208 (11), 187 (11), 163 (12), 135 (100), 115 (5), 107 (12), 93 (20), 79 (21), 69 (8).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{19}H_{30}O_4$ $[M+Na]^+$ 345.2041, found 345.2033.

IR (ATR, neat, cm^{-1}): 2980 (w), 2901 (m), 2848 (w), 1752 (m), 1728 (m), 1448 (w), 1218 (m), 1138 (m), 1031 (m). 864 (w).

Synthesis of diethyl 2-(1-(1-methylcyclohexyl)ethyl)malonate (2.6hb)



2.6hb

Compound **2.6hb** was prepared following general procedure **A**. 1-Methyl-1 cyclohexanecarboxylic acid **2.1h** (71 mg, 0.5 mmol, 1.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 100:2) yielded the title compound **2.6hb** (123 mg, 0.432 mmol, 87%) as a colorless oil. The analytic data is in correspondence with those reported in literature.[184]

$\mathbf{R_f}$ = 0.67 (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.12 (m, 4H), 3.52 (d, J = 4.7 Hz, 1H), 2.29 (qd, J = 7.2, 4.7 Hz, 1H), 1.31 (m, 17H), 0.96 (d, J = 7.2 Hz, 3H), 0.78 (s, J = 5.8 Hz, 3H).

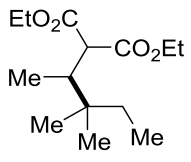
^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.4, 169.8, 61.4, 60.9, 52.3, 42.0, 36.3, 35.9, 35.9, 26.3, 22.0, 21.9, 19.4, 14.1, 11.0.

MS (EI) *m/z* (relative intensity): 285 (1), 239 (13), 188 (48), 173 (9), 142 (100), 125 (20), 115 (87), 109 (6), 97 (71), 87 (27), 81 (25), 69 (53).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{13}H_{28}O_4Na$ $[M+Na]^+$ 307.1885, found 307.1886.

IR (ATR, neat, cm^{-1}): 2979 (w), 2926 (w), 2851 (w), 1729 (s), 1462 (w), 1389 (w), 1296 (m), 1216 (m), 1143 (m), 1059 (m), 1029 (w), 864 (w).

Synthesis of diethyl 2-(3,3-dimethylpentan-2-yl)malonate (2.6ib)



2.6ib

Compound **2.6ib** was prepared following general procedure **A**. 2,2-Dimethylbutyric acid **2.1i** (58 mg, 0.5 mmol, 1.0 equiv.) was used. Purification by column chromatography

(*n*-pentane:EtOAc = 100:2) yielded the title compound **2.6ib** (104 mg, 0.403 mmol, 78%) as a colorless oil.

$\mathbf{R_f}$ = 0.38 (*n*-pentane:EtOAc = 20:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.15 (m, 4H), 3.49 (d, J = 4.9 Hz, 1H), 2.31 (qd, J = 7.2, 4.9 Hz, 1H), 1.26 (m, 8H), 0.97 (d, J = 7.2 Hz, 3H), 0.80 (m, 9H).

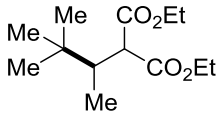
^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.3, 169.8, 61.4, 61.0, 52.9, 40.4, 36.0, 32.9, 24.2, 24.1, 14.1, 11.7, 8.2.

MS (EI) *m*/*z* (relative intensity): 229 (25), 213 (27), 188 (35), 173 (9), 169 (8), 155 (46), 142 (88), 127 (11), 115 (100), 99 (26), 87 (31), 71 (26).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{14}H_{26}O_4Na$ $[M+Na]^+$ 281.1728, found 281.1729.

IR (ATR, neat, cm^{-1}): 2968 (w), 2881 (w), 1752 (w), 1729 (m), 1464 (w), 1369 (w), 1284 (m), 1143 (m), 1029 (m), 864 (w).

Synthesis of diethyl 2-(3,3-dimethylbutan-2-yl)malonate (2.6jb)



2.6jb

Compound **2.6jb** was prepared following general procedure **A**. Diethyl ethylidenmalonate **2.4b** (186 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 40:1) yielded the title compound **2.6jb** (80 mg, 0.327 mmol, 66%) as colorless oil. The analytic data is in correspondence with those reported in literature.[185]

$\mathbf{R_f}$ = 0.74 (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.14 (qd, J = 7.1, 3.1 Hz, 4H), 3.48 (d, J = 5.4 Hz, 1H), 2.20 (m, 1H), 1.22 (ddd, J = 7.1, 5.8, 3.2 Hz, 6H), 0.97 (d, J = 7.2 Hz, 3H), 0.86 (s, 9H).

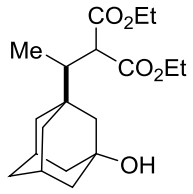
^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.3, 169.6, 61.4, 61.0, 53.4, 42.7, 33.7, 27.6, 14.1, 14.1, 12.1.

MS (EI) *m*/*z* (relative intensity): 245 (1) [M], 229 (9), 199 (28), 188 (26), 173 (7), 155 (39), 142 (72), 127 (12), 115 (100), 109 (13), 99 (24), 87 (41), 69 (45).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{13}H_{25}O_4$ $[M+H]^+$ 245.1753, found 245.1753.

IR (ATR, neat, cm^{-1}): 2967 (w), 2907 (w), 1729 (s), 1466 (w), 1368 (m), 1296 (m), 1239 (m), 1144 (m), 1030 (m), 865 (w), 775 (w).

Synthesis of diethyl 2-(1-((1r,3s,5*R*,7*S*)-3-hydroxyadamantan-1-yl)ethyl)malonate (2.6kb)



2.6kb

Compound **2.6kb** was prepared following general procedure **A**. 3-Hydroxyadamantane-1-carboxylic acid **2.1k** (98 mg, 0.5 mmol, 1.0 equiv.) was used. Purification by column chromatography (DCM:MeOH = 100:1) yielded the title compound **2.6kb** (142 mg, 0.420 mmol, 84%) as a colorless oil. The analytic data is in correspondence with those reported in literature.[185]

$\mathbf{R_f} = 0.31$ (DCM:MeOH = 100:2, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 4.13$ (m, 4H), 3.49 (d, $J = 5.1$ Hz, 1H), 2.09 (m, 3H), 1.86 (m, 1H), 1.57 (m, 4H), 1.36 (m, 8H), 1.21 (td, $J = 7.1$, 4.5 Hz, 6H), 0.94 (d, $J = 7.3$ Hz, 3H).

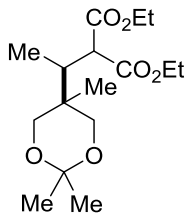
^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 170.1$, 169.5, 68.9, 61.4, 61.0, 52.0, 47.3, 44.7, 44.6, 42.9, 39.2, 38.2, 37.9, 35.5, 30.6, 30.5, 14.1, 14.0, 10.7.

MS (EI) *m*/*z* (relative intensity): 338 (1) [M], 292 (18), 206 (42), 188 (86), 179 (27), 161 (18), 151 (72), 142 (100), 133 (16), 121 (10), 115 (69), 109 (13), 107 (27), 95 (58), 93 (59).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{19}H_{30}O_5Na$ $[M+Na]^+$ 361.1990, found 361.1990.

IR (ATR, neat, cm^{-1}): 3399 (w, br.), 2980 (w), 2906 (w), 2852 (w), 1726 (m), 1448 (w), 1297 (w), 1210 (m), 1138 (m), 1027 (m), 939 (w).

Synthesis of diethyl 2-(1-(2,2,5-trimethyl-1,3-dioxan-5-yl)ethyl)malonate (2.6lb)



2.6lb

Compound **2.6lb** was prepared following general procedure A. 2,2,5-trimethyl-1,3-dioxane-5-carboxylic acid **2.1l** (87 mg, 0.5 mmol, 1.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound **2.6lb** (46 mg, 0.145 mmol, 29%) as a colorless oil.

$\mathbf{R_f} = 0.31$ (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.17 (m, 4H), 3.74 (dd, *J* = 21.1, 11.5 Hz, 2H), 3.58 (d, *J* = 5.0 Hz, 1H), 3.46 (ddd, *J* = 11.8, 6.0, 1.1 Hz, 2H), 2.56 (qd, *J* = 7.2, 5.1 Hz, 1H), 1.38 (d, *J* = 3.7 Hz, 6H), 1.26 (td, *J* = 7.1, 3.5 Hz, 6H), 1.01 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 3H).

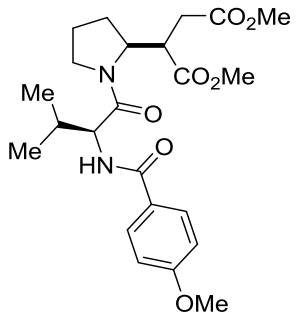
^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.7, 169.3, 98.1, 68.7, 68.0, 61.7, 61.2, 52.3, 36.5, 35.5, 24.5, 23.2, 16.4, 14.1, 11.1.

MS (EI) *m*/*z* (relative intensity): 301 (90), 271 (5), 231 (12), 213 (33), 185 (14), 167 (19), 161 (24), 155 (100), 136 (18), 127 (18), 109 (18), 99 (11), 69 (21).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{16}H_{28}O_6Na$ $[M+Na]^+$ 339.1783, found 339.1789.

IR (ATR, neat, cm^{-1}): 2984 (w), 2940 (w), 2874 (w), 1728 (s), 1461 (w), 1371 (m), 1202 (m), 1148 (m), 1085 (m), 1028 (m), 831 (m).

Synthesis of dimethyl-2-(1-((4-methoxybenzoyl)-*L*-valyl)pyrrolidin-2-yl)succinate (2.6ma)



2.6ma

Compound **2.6ma** was prepared following general procedure **A** on a 0.2 mmol scale. (4-methoxybenzoyl)-*L*-valylproline **2.1m** (52 mg, 0.15 mmol, 1.0 equiv.), dimethyl maleate **2.4a** (45 mg, 0.3 mmol, 2.0 equiv.), PrPPTNO **1.2** (3 mg, 0.01 mmol, 0.05 equiv.) and K_3PO_4 (32 mg, 0.2 mmol, 1.0 equiv.) were used in 2 ml of MeCN:H_2O (9:1). Purification by column chromatography (*n*-pentane:EtOAc = 2:1) yielded the title compound **2.6ma** (51 mg, 0.114 mmol, 75%) as a light yellow oil. Analytical data are stated for a mixture of two diastereomers (dr 1:1).

$\mathbf{R_f}$ = 0.17 (*n*-pentane: acetone = 1:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.77 (dd, *J* = 8.8, 6.8 Hz, 4H), 6.85 (m, 6H), 4.79 (m, 2H), 4.34 (m, 2H), 3.82 (d, *J* = 3.2 Hz, 6H), 3.67 (d, *J* = 4.0 Hz, 3H), 3.65 (s, 3H), 3.60 (s, 3H), 3.57 (s, 3H), 3.52 (d, *J* = 4.4 Hz, 3H), 2.41 (m, 8H), 1.89 (m, 8H), 0.99 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.3, 173.0, 172.2, 172.1, 172.0, 171.9, 171.8, 171.4, 171.1, 171.1, 166.8, 166.8, 166.6, 162.3, 128.9, 126.5, 126.4, 126.3, 113.8, 113.7, 113.7, 77.5, 77.1, 76.6, 58.8, 58.3, 58.0, 57.7, 56.3, 56.2, 55.9, 55.9, 55.4, 52.1, 52.1, 52.1, 52.0, 52.0, 51.8, 51.7, 48.1, 47.6, 47.2, 43.3, 42.7, 42.6, 42.3, 42.0, 33.7, 33.4, 31.8, 31.6, 31.5, 31.3, 31.1,

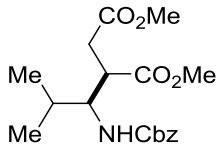
31.0, 29.7, 27.3, 27.1, 27.0, 26.4, 25.0, 24.5, 24.3, 24.2, 23.7, 19.8, 19.8, 19.7, 19.6, 18.0, 18.0, 17.4, 17.3, 17.3, 17.2.

LCMS (ESI, *m/z*): 471.2 $[M+Na]^+$

HRMS (ESI-TOF, *m/z*): calcd. for $C_{23}H_{32}N_2O_7$ [M] 448.2215, found 448.2216.

IR (ATR, neat, cm^{-1}): 3323 (w), 2957 w), 1732 (s), 1623 (s), 1606 (s), 1576 (w), 1536 (w), 1500 (m), 1433 (s), 1308 (m), 1251 (s), 1170 (s), 1121 (m), 1027 (m), 896 (w), 845 (m), 767 (m), 732 (w), 606 (m), 563 (m), 523 (m).

Synthesis of dimethyl 2-(1-(((benzyloxy)carbonyl)amino)-2-methylpropyl)succinate (2.6na)



2.6na

Compound **2.6na** was prepared following general procedure **A**. Dimethyl maleate **2.4a** (144 mg, 1.0 mmol, 2.0 equiv.) and K_3PO_4 (80 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by column chromatography (*n*-pentane: acetone = 20:1) yielded the title compound **2.6na** (120 mg, 0.34 mmol, 68%) as a light-yellow oil. Analytical data are stated for a mixture of two diastereomers (dr 1:1).

$\mathbf{R_f} = 0.28$ (*n*-pentane: acetone = 20:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 (m, 5H), 5.28 (m, 1H), 5.10 (m, 2H), 3.67 (d, J = 6.6 Hz, 5H), 3.55 (m, 1H), 3.21 (m, 1H), 2.66 (m, 2H), 1.64 (m, 1H), 0.94 (m, 6H).

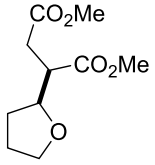
^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.1, 172.0, 156.7, 136.6, 128.8, 128.6, 128.6, 128.1, 128.0, 127.9, 66.8, 58.1, 52.0, 52.0, 42.4, 34.9, 32.0, 19.9, 19.4.

MS (EI) *m/z* (relative intensity): 308 (6), 204 (23), 114 (6), 91 (100), 79 (4), 65 (6), 55 (6).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{18}H_{25}NO_6$ $[M^+]$ 351.1676, found 351.1671.

IR (ATR, neat, cm^{-1}): 3350 (w), 2957 (w), 1719 (s), 1587 (w), 1527 (m), 1455 (w), 1436 (m), 1409 (w), 1390 (w), 1343 (m), 1232 (s), 1168 (s), 1116 (m), 1093 (m), 1027 (m), 999 (m), 912 (w), 889 (w), 844 (w), 772 (w), 739(m), 697 (s), 597 (w), 523 (w), 457 (w).

Synthesis of dimethyl 2-(tetrahydrofuran-2-yl)succinate (2.6oa)



2.6oa

Compound **2.6oa** was prepared following general procedure **A** for 24 h. Tetrahydro-2-furoic acid **2.1o** (216 mg, 1.0 mmol, 2.0 equiv.) , dimethyl maleate **2.4a** (144 mg, 0.5 mmol, 1.0 equiv.) and K_3PO_4 (32 mg, 0.2 mmol, 0.4 equiv.) were used. Purification by column chromatography (*n*-pentane:EtOAc = 3:1) yielded the title compound **2.6oa** (57 mg, 0.26 mmol, 52%) as colorless oil (mixture of diastereomers: 1:1). Diastereomers **2.6oa-1** and **2.6oa-2** were then separated by column chromatography (*n*-pentane:EtOAc = 3:1). The analytical data is in correspondence with those reported in literature.[186]

2.6oa-1

R_f = 0.59 (*n*-pentane:EtOAc = 3:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.00 (dd, *J* = 14.1, 6.8 Hz, 1H), 3.76 (m, 5H), 3.67 (s, 3H), 2.82 (m, 3H), 1.92 (m, 3H), 1.71 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.5, 172.8, 78.8, 68.2, 52.2, 51.9, 46.8, 33.3, 29.8, 25.7.

MS (EI) *m*/*z* (relative intensity): 185 (3), 153 (3), 143 (15), 111 (11), 87 (3), 71 (100), 59 (13).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{10}H_{16}O_5Na$ $[M+Na]^+$ 239.0895, found 239.0899.

IR (ATR, neat, cm^{-1}): 2953 (w), 2874 (w), 1731 (s), 1436 (m), 1358 (m), 1260 (m), 1195 (m), 1159 (s), 1063 (m), 1030 (m), 922 (w), 890 (w), 849 (m).

2.6oa-2

R_f = 0.35 (n-pentane:EtOAc = 3:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.05 (m, 1H), 3.85 (m, 1H), 3.73 (m, 4H), 3.67 (s, 3H), 3.08 (m, 1H), 2.76 (m, 1H), 2.47 (dd, *J* = 16.6, 4.5 Hz, 1H), 1.90 (m, 3H), 1.63 (m, 1H).

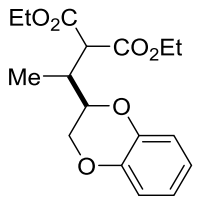
^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.4, 172.4, 79.0, 68.6, 52.2, 52.0, 46.2, 32.6, 28.8, 25.8.

MS (EI) *m*/*z* (relative intensity): 185 (4), 153 (2), 143 (14), 111 (10), 87 (2), 71 (100), 59 (13).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{10}H_{16}O_5Na$ $[M+Na]^+$ 239.0895, found 239.0894.

IR (ATR, neat, cm^{-1}): 2953 (w), 2874 (w), 1731 (s), 1436 (m), 1361 (w), 1260 (m), 1194 (m), 1160 (s), 1065 (m), 1004 (m), 925 (w), 890 (w), 849 (w).

Synthesis of diethyl 2-(1-(2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)ethyl)malonate (2.6pb)



2.6pb

Compound **2.6pb** was prepared following general procedure **A**. 1,4-Benzodioxane-6-carboxylic acid **2.1p** (90 mg, 0.5 mmol, 1.0 eq.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 100:2) yielded the title compound **2.6pb** (112 mg, 0.347 mmol, 70%) as a colorless oil (mixture of diastereomers 1:1). The analytical data is in correspondence with those reported in literature.[66]

$\mathbf{R_f}$ = 0.31 (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.83 (m, 4H), 4.23 (m, 6H), 4.01 (m, 1H), 3.75 (dd, *J* = 51.8, 7.1 Hz, 1H), 2.57 (m, 1H), 1.27 (m, 6H), 1.12 (dd, *J* = 19.9, 7.0 Hz, 3H).

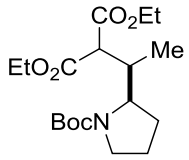
^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.0, 168.5, 168.4, 168.3, 143.7, 143.4, 143.3, 143.0, 121.6, 121.5, 121.4, 117.3, 117.1, 117.1, 74.6, 73.7, 66.4, 66.2, 61.7, 61.6, 61.5, 61.3, 54.4, 52.2, 34.6, 34.4, 14.2, 14.2, 14.2, 14.1, 13.1, 11.9.

MS (EI) *m/z* (relative intensity): 322 (34) [M], 277 (17), 231 (10), 162 (100), 147 (19), 139 (16), 135 (48), 121 (28), 111 (13), 95 (7), 69 (11).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{17}H_{22}O_6Na$ $[M+Na]^+$ 345.1313, found 345.1314.

IR (ATR, neat, cm^{-1}): 2981 (w), 2938 (w), 1727 (m), 1594 (w), 1493 (m), 1369 (w), 1265 (m), 1252 (m), 1175 (w), 1029 (m), 859 (w).

Synthesis of diethyl 2-(1-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)ethyl)malonate (2.6qb)



2.6qb

Compound **2.6qb** was prepared following general procedure **A**. Diethyl ethylidenmalonate **2.4b** (186 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 20:1 → 20:3) yielded the title compound **2.6qb** (80 mg, 0.225 mmol, 45%) as translucent oil. The products give multiple sets of NMR signals, owing to the presence of rotamers around the amide. Analytical data states for the diastereomeric mixture (1:1). The analytic data is in correspondence with those reported in literature.[183]

$\mathbf{R_f}$ = 0.23 (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.14 (m, 4H), 3.84 (m, 1H), 3.38 (m, 2H), 3.06 (m, 1H), 2.58 (m, 1H), 1.81 (m, 4H), 1.46 (d, *J* = 23.9 Hz, 9H), 1.24 (m, 6H), 0.89 (d, *J* = 6.6 Hz, 3H).

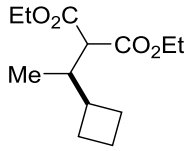
^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.0, 168.4, 155.3, 154.9, 79.8, 79.2, 61.3, 61.2, 60.6, 60.4, 55.6, 54.8, 54.1, 47.2, 46.9, 37.1, 36.9, 29.3, 28.5, 28.5, 28.3, 28.2, 23.6, 23.4, 14.2, 14.1, 13.8, 13.6.

MS (EI) *m/z* (relative intensity): 301 (13), 255 (16), 227 (4), 187 (65), 181 (8), 160 (19), 141 (100), 133 (12), 115 (15), 113 (21), 99 (8), 87 (13), 69 (32).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{18}H_{31}NO_6Na$ $[M+Na]^+$ 380.2043, found 380.2060.

IR (ATR, neat, cm^{-1}): 2975 (w), 2936 (w), 1751 (w), 1729 (m), 1689 (m), 1455 (w), 1381 (m), 1365 (m), 1161 (m), 1105 (m), 1030 (m), 916 (w), 861 (w), 773 (w).

Synthesis of diethyl 2-(1-cyclobutylethyl)malonate (2.6rb)



2.6rb

Compound **2.6rb** was prepared following general procedure **A**. Cyclobutane carboxylic acid **2.1r** (50 mg, 0.5 mmol, 1.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 100:2) yielded the title compound **2.6rb** (43 mg, 0.177 mmol, 35%) as a colorless oil. The analytical data is in correspondence with those reported in literature.[64]

R_f = 0.45 (*n*-pentane:EtOAc = 20:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.15 (qt, *J* = 13.7, 6.8 Hz, 4H), 3.20 (d, *J* = 6.3 Hz, 1H), 2.19 (m, 2H), 1.93 (m, 2H), 1.71 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 6H), 0.90 (d, *J* = 6.5 Hz, 3H).

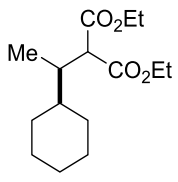
^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.4, 168.8, 61.3, 61.1, 55.1, 40.2, 40.1, 27.4, 27.2, 17.6, 14.2, 14.2, 14.1.

MS (EI) *m/z* (relative intensity): 227 (27), 199 (10), 197 (41), 169 (48), 160 (100), 150 (22), 141 (92), 133 (38), 122 (22), 115 (57), 105 (9), 95 (34), 87 (25), 83 (21), 69 (30).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{13}H_{22}O_4Na$ $[M+Na]^+$ 265.1415, found 265.1418.

IR (ATR, neat, cm^{-1}): 2974 (w), 2938 (w), 1729 (s) 1463 (w), 1369 (w), 1242 (m), 1174 (m), 1148 (m), 1031 (m), 862 (w).

Synthesis of diethyl 2-(1-cyclohexylethyl)malonate (2.6sb)



2.6sb

Compound **2.6sb** was prepared following general procedure **A** for 24 h. Diethyl ethylidenmalonate **2.4b** (93 mg, 0.5 mmol, 1.0 equiv.), cyclohexanecarboxylic acid **2.1s** (128 mg, 1.0 mmol, 2.0 equiv.) and K_3PO_4 (43 mg, 0.2 mmol, 0.4 equiv.) were used. Purification by column chromatography (*n*-pentane:EtOAc = 40:1) yielded the title compound **2.6sb** (50 mg, 0.185 mmol, 37%) as colorless oil. The analytical data is in correspondence with those reported in literature.[66]

$\mathbf{R_f}$ = 0.34 (*n*-pentane:EtOAc = 40:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.17 (m, 4H), 3.37 (d, *J* = 9.1 Hz, 1H), 2.32 – 2.06 (m, 1H), 1.80 – 1.51 (m, 5H), 1.38 – 1.00 (m, 12H), 0.88 (d, *J* = 7.0 Hz, 3H).

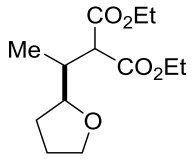
^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.4, 169.2, 61.2, 61.2, 55.9, 40.4, 38.7, 31.6, 27.5, 26.9, 26.7, 26.6, 14.2, 13.0.

MS (EI) *m/z* (relative intensity): 271 (1) [M+H], 225 (11), 187 (42), 160 (100), 141 (31), 133 (50), 115 (54), 105 (13), 88 (18), 81 (33), 69 (60).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{15}H_{26}O_4Na$ $[M+Na]^+$ 293.1728, found 293.1727.

IR (ATR, neat, cm^{-1}): 2979 (w), 2925 (m), 2853 (w), 1153 (w), 1730 (m), 1463 (w), 1448 (w), 1149 (w), 1032 (w).

Synthesis of diethyl 2-(1-(tetrahydrofuran-2-yl)ethyl)malonate (2.6tb)



2.6tb

Compound **2.6tb** was prepared following general procedure **A** for 24 h. Tetrahydro-2-furoic acid (116 mg, 1.0 mmol, 2.0 equiv.) and diethyl ethylidenmalonate **2.4b** (93 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound **2.6tb** (44 mg, 0.170 mmol, 34%) as a colorless oil (mixture of diastereomers 1:1.3). The analytical data is in correspondence with those reported in literature.[187]

$\mathbf{R_f}$ = 0.14 (*n*-pentane:EtOAc = 20:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.17 (qdd, *J* = 7.1, 2.6, 2.0 Hz, 4H), 3.75 (m, 3H), 3.59 (d, *J* = 6.4 Hz, 0.52H), 3.40 (d, *J* = 8.6 Hz, 0.43H), 2.47 (m, 0.43H), 2.27 (m, 0.56H), 1.90 (m, 3H), 1.53 (m, 1H), 1.25 (m, 6H), 0.96 (dd, *J* = 6.9, 4.0 Hz, 3H).

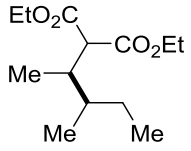
^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.4, 169.0, 168.9, 168.9, 81.4, 80.5, 68.4, 67.9, 61.3, 61.3, 61.2, 61.1, 55.1, 54.5, 39.2, 37.5, 30.1, 28.6, 26.1, 26.0, 14.2, 14.2, 14.2, 13.6, 12.4.

MS (EI) *m*/*z* (relative intensity): 257 (1) [M], 213 (17), 189 (11), 167 (16), 139 (11), 115 (7), 98 (76), 71 (100).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{13}H_{22}O_5Na$ $[M+Na]^+$ 281.1364, found 281.1369.

IR (ATR, neat, cm^{-1}): 2977 (w), 2940 (w), 2875 (w), 1728 (s), 1464 (w), 1265 (m), 1174 (m), 1153 (m), 1065 (m), 1030 (m), 863 (w).

Synthesis of diethyl 2-(3-methylpentan-2-yl)malonate (2.6ub)



2.6ub

Compound **2.6ub** was prepared following general procedure **A**. 2,2-Dimethylbutyric acid **2.1u** (51 mg, 0.5 mmol, 1.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 100:2) yielded the title compound **2.6ub** (35 mg, 0.143 mmol, 29%) as a colorless oil. The analytical data is in correspondence with those reported in literature.[185]

R_f = 0.43 (*n*-pentane:EtOAc = 20:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.17 (m, 4H), 3.33 (dd, *J* = 21.7, 9.9 Hz, 1H), 2.28 (m, 1H), 1.30 (m, 9H), 0.92 (m, 10H).

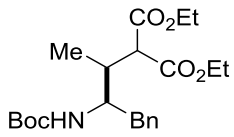
^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.4, 169.2, 169.1, 61.3, 61.2, 57.0, 56.2, 38.9, 37.0, 36.6, 36.2, 28.1, 23.8, 17.5, 14.2, 13.5, 12.6, 12.2, 12.1, 11.2.

MS (EI) *m*/*z* (relative intensity): 199 (17), 187 (10), 160 (100), 141 (14), 133 (39), 115 (41), 105 (8), 87 (24), 69 (28), 55 (10).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{13}H_{24}O_4Na$ $[M+Na]^+$ 267.1572, found 267.1570.

IR (ATR, neat, cm^{-1}): 2964 (w), 2936 (w), 1754 (m), 1730 (s), 1463 (w), 1368 (w), 1274 (w), 1191 (m), 1129 (m), 1096 (w), 1031 (m), 860 (w).

Synthesis of diethyl 2-(3-((tert-butoxycarbonyl)amino)-4-phenylbutan-2-yl)malonate (2.6vb)



2.6vb

Compound **2.6vb** was prepared following general procedure **A**. Boc-*L*-Phenylalanine **2.1v** (133 mg, 0.5 mmol, 1.0 equiv.) and diethyl ethylidenmalonate **2.4b** (186 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 8:1) yielded the title compound **2.6vb** (61 mg, 0.150 mmol, 30%) as a pale yellow oil (mixture of diastereomers). The analytical data is in correspondence with those reported in literature.[64]

R_f = 0.44 (*n*-pentane:EtOAc = 8:2, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.26 (m, 2H), 7.15 (m, 3H), 4.51 (d, *J* = 9.4 Hz, 0.39H), 4.21 (m, 5.88H), 3.77 (m, 0.53H), 3.48 (d, *J* = 6.8 Hz, 0.52H), 3.34 (m, 0.48H), 2.99 (m, 0.53H), 2.76 (d, *J* = 6.7 Hz, 0.76H), 2.62 (m, 0.54H), 2.45 (m, 1.08H), 1.28 (m, 15.88H), 1.11 (m, 1.77H), 0.92 (t, *J* = 7.2 Hz, 1.41H).

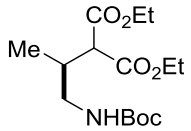
^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.6, 169.0, 168.4, 155.6, 155.3, 138.0, 129.4, 129.2, 128.5, 128.5, 126.5, 79.3, 79.1, 61.6, 61.4, 61.3, 61.2, 55.6, 55.4, 55.2, 54.3, 52.8, 39.9, 39.1, 37.2, 35.8, 28.3, 28.0, 15.1, 14.2, 14.1, 11.1.

MS (EI) *m/z* (relative intensity): 334 (2), 316 (18), 288 (4), 262 (17), 216 (100), 198 (16), 170 (32), 142 (27), 131 (16), 124 (49), 96 (17), 91 (33), 69 (10), 57 (52).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{13}H_{24}O_4Na$ $[M+Na]^+$ 430.2205, found 430.2217.

IR (ATR, neat, cm^{-1}): 2978 (w), 2936 (w), 1726 (w), 1700 (w), 1497 (w), 1455 (w), 1389 (w), 1366 (w), 1168 (w), 1028 (w), 700 (w).

Synthesis of diethyl 2-(1-((tert-butoxycarbonyl)amino)propan-2-yl)malonate (2.6wb)



2.6wb

Compound **2.6wb** was prepared following general procedure A. Boc-glycine **2.1w** (88 mg, 0.5 mmol, 1.0 equiv.) and diethyl ethylidenmalonate **2.4b** (186, 1.0 mmol, 2.0 equiv.) were used.Purification by column chromatography (*n*-pentane:EtOAc = 8:1) yielded the title compound **2.6wb** (29 mg, 0.091 mmol, 18%) as a colorless oil. The analytical data is in correspondence with those reported in literature.[64]

R_f = 0.26 (*n*-pentane:EtOAc = 8:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.72 (br. s, 1H), 4.19 (qd, *J* = 7.1, 1.3 Hz, 4H), 3.30 (d, *J* = 7.4 Hz, 1H), 3.15 (m, 2H), 2.44 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.42 (s, *J* = 6.3 Hz, 9H), 1.27 (m, 6H), 1.00 (d, *J* = 6.9 Hz, 3H).

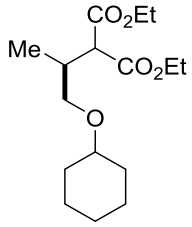
^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.9, 168.7, 156.1, 79.4, 61.6, 61.5, 55.2, 34.2, 28.5, 15.7, 14.2, 14.2.

MS (EI) *m*/*z* (relative intensity): 260 (3), 244 (13), 216 (36), 198 (19), 172 (22), 160 (34), 152 (12), 142 (28), 126 (29), 115 (32), 101 (27), 87 (23), 69 (22), 57 (100).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{15}H_{27}NO_6Na$ $[M+Na]^+$ 340.1735, found 340.1736.

IR (ATR, neat, cm^{-1}): 3399 (w), 2978 (w), 2936 (w), 1715 (m), 1513 (w), 1366 (m), 1254 (m), 1162 (s), 1114 (m), 1029 (m), 994 (w), 861 (w).

Synthesis of diethyl 2-(1-(cyclohexyloxy)propan-2-yl)malonate (2.6xb)



2.6xb

Compound **2.6xb** was prepared following general procedure **A**. 2-(cyclohexyloxy)acetic acid **2.1x** (79 mg, 0.5 mmol, 1.0 equiv.) and diethyl ethylidenmalonate **2.4b** (186, 1.0 mmol, 2.0 equiv.) were used. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound **2.6xb** (32 mg, 0.107 mmol, 21%) as a colorless oil.

R_f = 0.65 (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.17 (qd, *J* = 7.1, 1.6 Hz, 4H), 3.48 (d, *J* = 7.4 Hz, 1H), 3.37 (m, 2H), 3.16 (dt, *J* = 8.6, 4.0 Hz, 1H), 2.47 (m, 1H), 1.76 (m, 4H), 1.47 (m, 1H), 1.23 (m, 11H), 1.01 (d, *J* = 6.9 Hz, 3H).

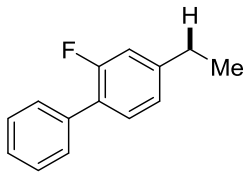
^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.2, 169.0, 77.6, 70.4, 61.2, 61.1, 54.3, 34.3, 32.1, 26.0, 24.1, 14.8, 14.2, 14.2.

MS (EI) *m*/*z* (relative intensity): 217 (3), 201 (14), 173 (100), 161 (38), 145 (35), 140 (78), 133 (16), 127 (64), 115 (38), 109 (5), 82 (61), 69 (17).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{16}H_{28}O_5Na$ $[M+Na]^+$ 323.1833, found 323.1835.

IR (ATR, neat, cm^{-1}): 2980 (w), 2932 (w), 2856 (w), 1730 (s), 1450 (w), 1367 (w), 1258 (m), 1176 (m), 1094 (s), 1029 (m), 947 (w).

Synthesis of 4-ethyl-2-fluoro-1,1'-biphenyl (2.6yc)



2.6yc

Compound **2.6yc** was prepared following general procedure **A**. 2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoic acid (flurbiprofen) **2.6y** (122 mg, 0.5 mmol, 1.0 equiv.) and Dimethyl maleate **2.4a** (172 mg, 1.0 mmol, 2.0 equiv.) were used. The reaction mixture of two vials with the same content was combined, dried under reduced pressure and purified by column chromatography (*n*-pentane:EtOAc = 50:1) which yielded the title compound **2.6yc** (33 mg, 165 µmol, 17%) as a colorless oil.

$\mathbf{R_f} = 0.70$ (*n*-pentane:EtOAc = 50:1, UV, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.64 – 7.52 (m, 2H), 7.48 – 7.41 (m, 2H), 7.40 – 7.31 (m, 2H), 7.10 – 6.71 (m, 2H), 2.95 – 2.31 (m, 2H), 1.40 – 0.85 (t, J = 7.6, 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.5, 158.2, 146.1, 146.0, 130.6, 130.6, 129.1, 129.1, 128.5, 127.5, 126.4, 126.3, 124.0, 124.0, 115.7, 115.6, 28.5, 28.5, 15.4.

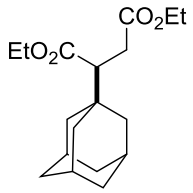
^{19}F NMR (282 MHz, $CDCl_3$) δ = –118.81 (dd, J = 11.5 Hz, 8.3 Hz).

MS (EI) *m/z* (relative intensity): 200 (50) [M], 185 (100), 165 (17), 157 (4), 133 (9), 92 (5), 63 (5).

HRMS (ESI-TOF) m/z: calcd. for $C_{14}H_{13}F_1$ $[M]^+$ 200.0996, Found 200.0996.

IR (ATR, neat, cm^{-1}): 2996 (w), 2873 (w), 1625 (w), 1483 (m), 1416 (m). 1266 (w), 1128 (w), 1011 (w), 911 (m), 763 (m), 695 (s).

Synthesis of diethyl 2-((3r,5r,7r)-adamantan-1-yl)succinate (2.9c)



2.9c

Compound **2.9c** was prepared following general procedure **A**. Diethyl maleate **2.4c** (172 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 100:3) yielded the title compound **2.9c** (128 mg, 0.415 mmol, 83%) as a colorless oil.

$\mathbf{R_f} = 0.58$ (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.12 (m, 4H), 2.72 (dd, J = 16.9, 12.2 Hz, 1H), 2.46 (dt, J = 11.7, 3.1 Hz, 2H), 1.96 (s, 3H), 1.64 (m, 9H), 1.44 (m, 3H), 1.24 (m, 6H).

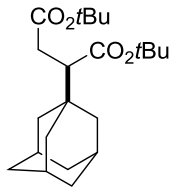
^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.9, 173.0, 60.6, 60.2, 52.4, 40.1, 36.9, 34.5, 31.4, 28.6, 14.4, 14.3.

MS (EI) *m/z* (relative intensity): 308 (1) [M], 263 (16), 235 (11), 193 (3), 173 (17), 135 (100), 119 (2), 107 (6), 93 (11), 79 (12).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{18}H_{28}O_4Na$ $[M+Na]^+$ 331.1885, found 331.1883.

IR (ATR, neat, cm^{-1}): 2980 (w), 2902 (m), 2849 (w), 1726 (s), 1447 (w), 1369 (w), 1188 (m), 1156 (s), 1028 (m).

Synthesis of di-tert-butyl 2-((3r,5r,7r)-adamantan-1-yl)succinate (2.9d)



2.9d

Compound **2.9d** was prepared following general procedure **A**. Di-*tert*-butyl fumarate **2.4d** (228 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 100:2) yielded the title compound **2.9d** (97 mg, 0.266 mmol, 53%) as a white solid.

m.p.= 64-66 °C

R_f = 0.12 (*n*-pentane:EtOAc = 100:2, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.42 (m, 3H), 1.94 (m, 3H), 1.62 (m, 9H), 1.48 (m, 3H), 1.43 (s, 9H), 1.40 (s, 9H).

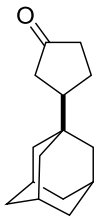
^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.9, 172.4, 80.4, 80.3, 53.4, 40.2, 37.0, 34.4, 32.6, 28.7, 28.2, 28.2.

MS (EI) *m/z* (relative intensity): 308 (1), 252 (26), 234 (10), 207 (15), 165 (2), 135 (100), 107 (3), 93 (6), 79 (6), 57 (24).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{22}H_{36}O_4Na$ $[M+Na]^+$ 387.2510, found 387.2507.

IR (ATR, neat, cm^{-1}): 2976 (w), 2903 (m), 2849 (w), 1720 (m), 1365 (m), 1247 (w), 1141 (s), 1119 (m), 849 (m).

Synthesis of 3-((3r,5r,7r)-adamantan-1-yl)cyclopentan-1-one (2.9e)



2.9e

Compound **2.9e** was prepared following general procedure A. 2-Cyclopentenon **2.4e** (82 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound **2.9e** (97 mg, 0.444 mmol, 89%) as a colorless oil. The analytical data is in correspondence with those reported in literature.[188]

R_f = 0.50 (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.28 (m, 1H), 2.11 (m, 2H), 1.93 (m, 5H), 1.81 (m, 1H), 1.70 (m, 3H), 1.61 (m, 4H), 1.49 (m, 6H).

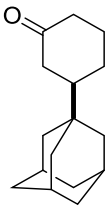
^{13}C NMR (101 MHz, $CDCl_3$) δ = 220.1, 48.9, 40.1, 39.2, 38.9, 37.3, 33.5, 28.5, 22.5.

MS (EI) *m/z* (relative intensity): 218 (6) [M], 135 (100), 105 (3), 93 (14), 79 (15), 53 (3).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{15}H_{22}O_1$ $[M]^+$ 218.1665, found 218.1672.

IR (ATR, neat, cm^{-1}): 2898 (m), 2845 (m), 1739 (s), 1449 (w), 1404 (w), 1171 (w), 1131 (w), 1099 (w), 499 (w).

Synthesis of 3-((3r,5r,7r)-adamantan-1-yl)cyclohexan-1-one (2.9f)



2.9f

Compound **2.9f** was prepared following general procedure **A**. 2-cyclohexenone **2.4f** (96 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 15:1) yielded the title compound **2.9f** (94 mg, 0.405 mmol, 81%) as a white solid. The analytical data is in correspondence with those reported in literature.[188]

R_f = 0.61 (n-pentane:EtOAc = 10:1, $KMnO_4$)

m.p. = 64–65 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.36 (m, 2H), 2.20 (m, 1H), 2.06 (m, 2H), 1.92 (m, 4H), 1.61 (m, 6H), 1.48 (m, 7H), 1.27 (m, 2H).

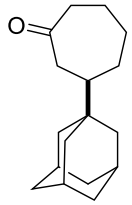
^{13}C NMR (75 MHz, $CDCl_3$) δ = 213.5, 49.8, 42.2, 41.7, 37.3, 34.6, 28.7, 25.8, 24.7.

MS (EI) *m*/*z* (relative intensity): 232 (3), 135 (100), 107 (10), 93 (19), 79 (23), 69 (4).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{16}H_{24}O$ [M^+] 232.1822, found 232.1821.

IR (ATR, neat, cm^{-1}): 2964 (s), 2843 (s), 1708 (m), 1448 (w), 1346 (w), 1316 (w), 1228 (w), 1167 (w), 1034 (w), 923 (w).

Synthesis of 3-((3r,5r,7r)-adamantan-1-yl)cycloheptan-1-one (2.9g)



2.9g

Compound **2.9g** was prepared following general procedure **A**. 2-Cyclohepten-1-one **2.4g** (110 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 97:3) yielded the title compound **2.9g** (23 mg, 0.093 mmol, 19%) as a white solid.

m.p.= 71–73 °C

$\mathbf{R_f}$ = 0.23 (*n*-pentane:EtOAc = 20:1, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.46 (m, 3H), 2.30 (dd, *J* = 14.2, 11.5 Hz, 1H), 1.98 (m, 5H), 1.89 (m, 1H), 1.57 (m, 13H), 1.27 (m, 2H), 1.01 (m, 1H).

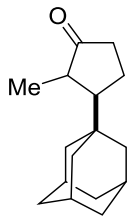
^{13}C NMR (101 MHz, $CDCl_3$) δ = 216.1, 46.5, 44.5, 43.4, 39.2, 37.3, 35.4, 29.7, 29.6, 28.8, 25.4.

MS (EI) *m*/*z* (relative intensity): 246 (11) [M], 228 (10), 135 (100), 107 (7), 93 (13), 79 (13), 67 (5), 54 (1).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{17}H_{26}O_1$ $[M]^+$ 246.1978, found 246.1984.

IR (ATR, neat, cm^{-1}): 2897 (m), 2846 (m), 1697 (m), 1446 (w), 1346 (w), 1131 (w), 1005 (w).

Synthesis of 3-((3r,5r,7r)-adamantan-1-yl)-2-methylcyclopentan-1-one (2.9h)



2.9h

Compound **2.9h** was prepared following general procedure **A**. 2-Methyl-2-cyclopenten-1-one **2.4h** (96 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography

(*n*-pentane:EtOAc = 40:1) yielded the title compound **2.9h** (66 mg, 0.284 mmol, 57%) as a colorless oil (mixture of diastereomers 1:2.3).

R_f = 0.70 (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.28 (m, 1H), 2.10 (m, 1H), 2.00 (m, 4H), 1.84 (m, 1H), 1.57 (m, 14H), 1.12 (m, 3H).

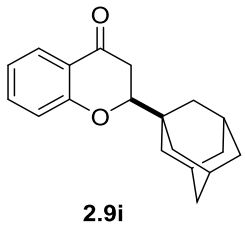
^{13}C NMR (75 MHz, $CDCl_3$) δ = 222.8, 222.6, 55.5, 52.7, 45.8, 44.1, 41.3, 40.4, 37.5, 37.4, 37.3, 37.3, 34.5, 28.7, 28.7, 20.9, 19.8, 17.7, 13.2.

MS (EI) *m*/*z* (relative intensity): 232 (9) [M], 135 (100), 119 (1), 107 (10), 93 (17), 79 (19), 67 (7), 55 (7), 41 (9).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{16}H_{24}ONa$ $[M+Na]^+$ 255.1724, found 255.1725.

IR (ATR, neat, cm^{-1}): 2963 (w), 2892 (s), 2845 (m), 1729 (s), 1445 (w), 1404 (w), 1268 (w), 1132 (w), 981 (w), 824 (w).

Synthesis of 2-((1*S*,3*s*)-adamantan-1-yl)chroman-4-one (2.9i)



2.9i

Compound **2.9i** was prepared following general procedure **A**. 4H-chromen-4-one **2.4i** (146 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 90:5) yielded the title compound **2.9i** (54 mg, 0.191 mmol, 39%) as a colorless solid. The analytical data is in correspondence with those reported in literature.[66]

m.p.= 103–105 °C

R_f = 0.26 (*n*-pentane:EtOAc = 90:3, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.85 (m, 1H), 7.45 (m, 1H), 6.97 (m, 2H), 3.90 (dd, *J* = 13.5, 3.1 Hz, 1H), 2.66 (qd, *J* = 16.5, 8.3 Hz, 2H), 2.05 (m, 3H), 1.67 (m, 12H).

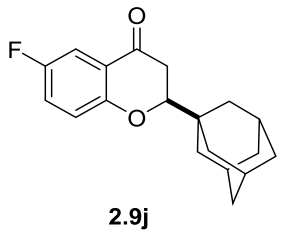
^{13}C NMR (75 MHz, $CDCl_3$) δ = 193.9, 162.4, 135.9, 127.0, 121.0, 118.0, 85.6, 37.9, 37.2, 37.2, 36.0, 28.3.

MS (EI) *m*/*z* (relative intensity): 282 (68) [M], 164 (3), 147 (49), 135 (100), 121 (13), 93 (17), 79 (16), 67 (6).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{19}H_{23}O_2$ $[M+H]^+$ 283.1698, found 283.1693.

IR (ATR, neat, cm^{-1}): 2897 (m), 2848 (m), 1689 (m), 1604 (m), 1472 (m), 1462 (m), 1306 (m), 1233 (m), 1147 (w), 753 (m).

Synthesis of 2-((1*S*,3s)-adamantan-1-yl)-6-fluorochroman-4-one (2.9j)



2.9j

Compound **2.9j** was prepared following general procedure **A**. 6-fluoro-4H-chromen-4-one **2.4j** (164 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 90:5) yielded the title compound **2.9j** (43 mg, 0.143 mmol, 29%) as a white solid.

m.p.= 120–122 °C

R$_f$ = 0.61 (*n*-pentane:EtOAc = 10:1, UV, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.49 (m, 1H), 7.17 (ddd, J = 9.0, 7.8, 3.2 Hz, 1H), 6.95 (m, 1H), 3.88 (dd, J = 12.9, 3.8 Hz, 1H), 2.65 (m, 2H), 2.06 (m, 3H), 1.68 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 193.1, 193.1, 158.7, 158.7, 158.6, 155.5, 123.6, 123.3, 121.4, 121.3, 119.7, 119.6, 112.0, 111.7, 86.0, 37.8, 37.1, 37.0, 36.0, 28.2.

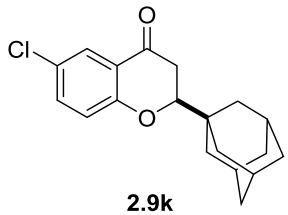
^{19}F NMR (282 MHz, $CDCl_3$) δ = –122.04, –122.06, –122.07, -122.09, –122.10, –122.11.

MS (EI) *m*/*z* (relative intensity): 300 (36) [M], 191 (1), 165 (74), 139 (15), 135 (100), 119 (3), 110 (20), 93 (28), 82 (10), 79 (40), 67 (13), 41 (19).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{19}H_{22}O_2F$ $[M+H]^+$ 301.1604, found 301.1605.

IR (ATR, neat, cm^{-1}): 2893 (m), 2851 (w), 1686 (m), 1618 (w), 1478 (m), 1450 (w), 1292 (w), 1273 (w), 1164 (w), 1001 (w), 881 (w).

Synthesis of 2-((1*S*,3s)-adamantan-1-yl)-6-chlorochroman-4-one (2.9k)



2.9k

Compound **2.9k** was prepared following general procedure **A**. 6-chloro-4H-chromen-4-one **2.4k** (181 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 90:5) yielded the title compound **2.9k** (70 mg, 0.221 mmol, 44%) as a light yellow solid.

m.p.= 152–154 °C

R$_f$ = 0.63 (*n*-pentane:EtOAc = 10:1, UV, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.81 (m, 1H), 7.39 (dd, J = 8.8, 2.7 Hz, 1H), 6.96 (m, 1H), 3.88 (dt, J = 21.8, 10.9 Hz, 1H), 2.67 (qd, J = 16.6, 8.4 Hz, 2H), 2.08 (m, 3H), 1.71 (m, 12H).

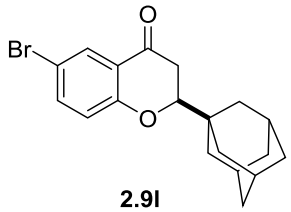
^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.7, 160.8, 135.7, 126.5, 126.2, 121.7, 119.7, 85.9, 37.8, 37.1, 36.9, 36.0, 28.2.

MS (EI) *m/z* (relative intensity): 316 (25) [M], 183 (21), 181 (65), 154 (17), 135 (100), 126 (19), 107 (13), 98 (5), 93 (27), 79 (38), 67 (14).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{19}H_{22}O_2Cl$ $[M+H]^+$ 317.1308, found 317.1303.

IR (ATR, neat, cm^{-1}): 2899 (w), 2848 (w), 1694 (w), 1602 (w), 1469 (w), 1270 (m), 1222 (w), 997 (w), 819 (w), 797 (w).

Synthesis of 2-((1S,3s)-adamantan-1-yl)-6-bromochroman-4-one (2.9l)



2.9l

Compound **2.9l** was prepared following general procedure **A**. 6-bromo-4H-chromen-4-one **2.4l** (225 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 95:5) yielded the title compound **2.9l** (100 mg, 0.277 mmol, 55%) as a white solid.

m.p.= 195–196 °C

R_f = 0.91 (*n*-pentane:EtOAc = 9:1, UV, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.93 (m, 1H), 7.50 (dd, J = 8.8, 2.6 Hz, 1H), 6.87 (m, 1H), 3.87 (dd, J = 12.9, 3.8 Hz, 1H), 2.64 (qd, J = 16.6, 8.3 Hz, 2H), 2.05 (m, 3H), 1.69 (m, 12H).

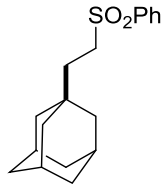
^{13}C NMR (75 MHz, $CDCl_3$) δ = 192.5, 161.2, 138.5, 129.4, 122.2, 120.1, 113.7, 85.9, 37.8, 37.1, 36.9, 36.0, 28.4, 28.2, 28.0.

MS (EI) *m/z* (relative intensity): 361 (11) [M], 281 (2), 227 (53), 2100 (10), 172 (6), 146 (2), 135 (100), 118 (8), 93 (16), 79 (20), 63 (8).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{19}H_{22}O_2Br$ $[M-H]^+$ 359.0647, found 359.0648.

IR (ATR, neat, cm^{-1}): 2898 (w), 2847 (w), 1693 (m), 1597 (w), 1465 (w), 1414 (w), 1267 (m), 1221 (w), 989 (w), 818 (m).

Synthesis of (3r,5r,7r)-1-(2-(phenylsulfonyl)ethyl)adamantane (2.9m)



2.9m

Compound **2.9m** was prepared following general procedure **A**. Phenyl vinyl sulfone **2.4m** (168 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-hexane:EtOAc = 30:1) yielded the title compound **2.9m** (105 mg, 0.345 mmol, 69%) as a colorless thick oil. The analytical data is in correspondence with those reported in literature.[66]

R_f = 0.10 (*n*-hexane:EtOAc = 97:3, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.89 (m, 2H), 7.64 (m, 1H), 7.55 (m, 2H), 3.04 (m, 2H), 1.91 (s, 3H), 1.58 (m, 6H), 1.45 (m, 2H), 1.38 (d, *J* = 2.6 Hz, 6H).

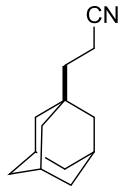
^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.3, 133.7, 129.3, 128.1, 51.3, 42.0, 36.9, 35.9, 31.9, 28.5.

MS (EI) *m*/*z* (relative intensity): 304 (1) [M], 276 (2), 239 (2), 163 (2), 135 (100), 107 (5), 93 (9), 77 (15), 67 (3).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{18}H_{25}O_2S$ $[M+H]^+$ 305.1575, found 305.1574.

IR (ATR, neat, cm^{-1}): 2898 (m), 2845 (m), 1584 (w), 1447 (m), 1322 (m), 1150 (s), 1099 (m), 995 (w) 778 (m), 730 (m), 532 (s).

Synthesis of 3-((3r,5r,7r)-adamantan-1-yl)propanenitrile (2.9n)



2.9n

Compound **2.9n** was prepared following general procedure **A**. Acrylonitrile **2.4n** (53 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 10:1) yielded the title compound **2.9n** (38 mg, 0.201 mmol, 40%) as a white solid. The analytical data is in correspondence with those reported in literature.[189]

m.p. = 43–44 °C

R_f = 0.55 (*n*-pentane:EtOAc = 10:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.26 (m, 2H), 1.97 (s, 3H), 1.62 (m, 6H), 1.47 (m, 8H).

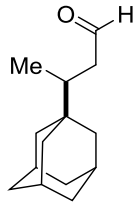
^{13}C NMR (75 MHz, $CDCl_3$) δ = 121.0, 41.7, 39.6, 36.9, 32.2, 28.5, 11.1.

MS (EI) *m/z* (relative intensity): 189 (4) [M], 135 (100), 107 (7), 93 (12), 79 (12), 67 (4).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{13}H_{20}N$ $[M+H]^+$ 190.1595, found 190.1597.

IR (ATR, neat, cm^{-1}): 2896 (m), 2846 (m), 2242 (w), 1448 (w), 1360 (w), 1345 (w), 1100 (w), 973 (w), 812 (w).

Synthesis of 3-((3r,5r,7r)-adamantan-1-yl)butanal (2.9o)



2.9o

Compound **2.9o** was prepared following general procedure **A**. Crotonaldehyde **2.4o** (70 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 100:2) yielded the title compound **2.9o** (33 mg, 0.160 mmol, 32%) as a white solid. The analytical data is in correspondence with those reported in literature.[66]

m.p. = 101−103 °C

$\mathbf{R_f}$ = 0.29 (*n*-pentane:EtOAc = 100:2, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.73 (dd, J = 3.4, 1.3 Hz, 1H), 2.57 (m, 1H), 2.02 (m, 4H), 1.65 (m, 7H), 1.48 (m, 6H), 0.86 (m, 3H).

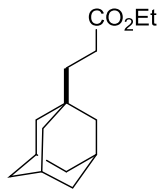
^{13}C NMR (75 MHz, $CDCl_3$) δ = 204.1, 45.7, 39.5, 37.9, 37.3, 34.4, 28.7, 14.0.

MS (EI) *m/z* (relative intensity): 188 (2), 135 (100), 107 (8), 93 (13), 91 (6), 79 (13), 67 (4), 53 (2).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{14}H_{21}O_1$ $[M-H]^+$ 205.1587, found 205.1590.

IR (ATR, neat, cm^{-1}): 2901 (m), 2885 (m), 2849 (m), 1699 (m), 1448 (w), 1352 (w), 1305 (m), 1208 (w), 967 (w).

Synthesis of ethyl 3-((3r,5r,7r)-adamantan-1-yl)propanoate (2.9p)



2.9p

Compound **2.9p** was prepared following general procedure **A**. Ethylacrylat **2.4p** (100 mg, 1.0 mmol, 2.0 equiv.) and K_2CO_3 (69 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by

column chromatography (*n*-pentane:diethylether = 200:1) yielded the title compound **2.9p** (32 mg, 0.135 mmol, 27%) as a colorless oil. The analytical data is in correspondence with those reported in literature.[190]

$\mathbf{R_f}$ = 0.61 (*n*-pentane:EtOAc = 20:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.11 (q, *J* = 7.1 Hz, 2H), 2.24 (m, 2H), 1.94 (s, 3H), 1.62 (m, 6H), 1.42 (m, 8H), 1.25 (t, *J* = 7.1 Hz, 3H).

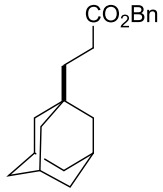
^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.9, 60.4, 42.2, 39.1, 37.2, 32.1, 28.7, 28.4, 14.4.

MS (EI) *m*/*z* (relative intensity): 236 (7) [M], 191 (9), 135 (100), 119 (1), 107 (6), 93 (11), 79 (12), 67 (4).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{15}H_{25}O_2$ $[M+H]^+$ 237.1854, found 237.1852.

IR (ATR, neat, cm^{-1}): 2949 (w), 2898 (m), 2846 (m), 1734 (m), 1450 (w), 1376 (w), 1301 (w), 1188 (m), 1150 (m), 1103 (w).

Synthesis of benzyl 3-((3r,5r,7r)-adamantan-1-yl)propanoate (2.9q)



2.9q

Compound **2.9q** was prepared following general procedure **A**. Benzylacrylat **2.4q** (162 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:toluene = 5:2) yielded the title compound **2.9q** (41 mg, 0.137 mmol, 27%) as a colorless oil. The analytical data is in correspondence with those reported in literature.[191]

$\mathbf{R_f}$ = 0.32 (*n*-pentane:toluene = 1:1, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (m, 5H), 5.11 (s, 2H), 2.32 (m, 2H), 1.95 (s, 3H), 1.63 (m, 6H), 1.45 (m, 8H).

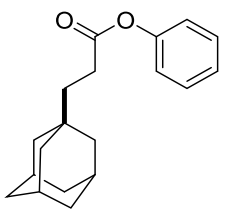
^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.7, 136.3, 128.7, 128.4, 128.3, 66.3, 42.2, 39.0, 37.2, 32.0, 28.7, 28.3.

MS (EI) *m*/*z* (relative intensity): 298 (4), 207 (66), 189 (16), 161 (6), 147 (16), 135 (74), 107 (18), 91 (100), 81 (8), 79 (35), 65 (17).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{20}H_{26}O_2Na$ $[M+Na]^+$ 321.1830, found 321.1828.

IR (ATR, neat, cm^{-1}): 2898 (m), 2845 (M), 1734 (m), 1451 (w), 1140 (m), 979 (w), 696 (m).

Synthesis of phenyl 3-((3r,5r,7r)-adamantan-1-yl)propanoate (2.9r)



2.9r

Compound **2.9r** was prepared following general procedure **A**. Phenylacrylat **2.4r** (148 mg, 1.0 mmol, 2.0 equiv.) was used. Purification by column chromatography (*n*-pentane:EtOAc = 100:2→100:5) yielded the title compound **2.9r** (37 mg, 0.130 mmol, 26%) as a white solid. The analytical data is in correspondence with those reported in literature.[192]

m.p.= 45–46 °C

$\mathbf{R_f}$ = 0.41 (*n*-pentane:EtOAc = 100:2, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (m, 2H), 7.39 (m, 1H), 7.25 (m, 2H), 2.69 (m, 2H), 2.16 (s, 3H), 1.84 (m, 6H), 1.73 (m, 8H).

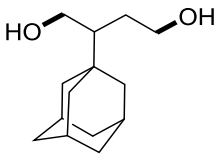
^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.3, 150.9, 129.5, 125.8, 121.7, 42.2, 39.0, 37.2, 32.2, 28.7, 28.5.

MS (EI) *m*/*z* (relative intensity): 284 (2) [M], 191 (100), 173 (18), 163 (9), 147 (5), 135 (61), 121 (3), 94 (19), 79 (19).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{19}H_{24}O_2Na$ $[M+Na]^+$ 307.1674, found 307.1675.

IR (ATR, neat, cm^{-1}): 2897 (m), 2843 (m), 1753 (m), 1591 (w), 1492 (w), 1452 (w), 1381 (w), 1195 (m), 1124 (m), 1103 (m), 930 (m).

Synthesis of 2-((3r,5r,7r)-adamantan-1-yl)butane-1,4-diol (2.10)



2.10

Compound **2.10** was prepared in a similar fashion to the procedure described in literature.[193] A solution of diester **2.6ba** (100 mg, 0.357 mmol, 1.0 equiv.) in THF (0.5 ml) was added dropwise under argon to a stirred suspension of $LiAlH_4$ (27 mg, 0.713 mmol, 2.0 equiv.) in THF (1.15 ml) at 0 °C over 5 minutes. The cooling bath was removed, and the mixture was stirred at room temperature for 24 h. Then, the reaction mixture was quenched with water (0.5 ml) and 10% aqueous NaOH (0.1 ml) at 0 °C and stirred for further

15 minutes. Afterwards, the reaction mixture was extracted with 3 x 10 ml of CH_2Cl_2 and the combined organic fractions were dried over Na_2SO_4 and filtered. The filtrate was dried under reduced pressure and purified by column chromatography (DCM:EtOAc = 1:1) to give diol **2.10** (74 mg, 0.330 mmol, 93%) as a colorless oil.

R_f = 0.36 (DCM:EtOAc = 1:2, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.82 (m, 4H), 3.53 (ddd, J = 10.5, 8.8, 4.1 Hz, 1H), 3.41 (dd, J = 10.3, 8.7 Hz, 1H), 1.88 (m, 4H), 1.60 (m, 12H), 1.40 (m, 1H), 1.15 (m, 1H).

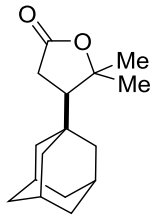
^{13}C NMR (75 MHz, $CDCl_3$) δ = 62.9, 62.8, 50.0, 34.0, 37.3, 34.9, 30.4, 28.7.

MS (EI) *m*/*z* (relative intensity): 224 (1) [M], 176 (3), 165 (4), 152 (34), 135 (100), 119 (2), 107 (9), 93 (18), 81 (5), 79 (19), 67 (7).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{14}H_{24}O_2Na$ $[M+Na]^+$ 247.1673, found 247.1677.

IR (ATR, neat, cm^{-1}): 3261 (br., w.), 2902 (w), 2844 (w), 1443 (w), 1347 (w), 1192 (w), 1103 (w), 1021 (w), 879 (w).

Synthesis of 4-((3r,5r,7r)-adamantan-1-yl)-5,5-dimethyldihydrofuran-2(3*H*)-one (2.11)



2.11

Diester **2.6ba** (100 mg, 0.357 mmol, 1.0 equiv.) was dissolved in dry THF (4.0 ml) under argon. The reaction mixture was then cooled to 0 °C and MeMgBr (3.0 M in diethylether) (490 µl, 1.46 mmol, 4.1 equiv.) was added dropwise over 5 minutes. Subsequently, the cooling bath was removed, and the mixture was stirred at room temperature for further 24 h. Then, the reaction mixture was quenched at 0 °C with a sat. ammonium chloride solution and diluted with diethylether (10 ml). The aqueous phase was extracted with diethylether (2 x 10 ml). Afterwards, combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. Purification by column chromatography (*n*-pentane:EtOAc = 100:2) afforded product **2.11** (77 mg, 0.310 mmol, 87%) as a white solid.

m.p.= 110–113 °C

R_f = 0.10 (*n*-pentane:EtOAc = 100:2, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.43 (dd, J = 12.2, 9.2 Hz, 1H), 1.91 (m, 8H), 1.67 (m, 6H), 1.48 (m, 3H), 1.41 (s, 3H), 1.32 (s, 3H).

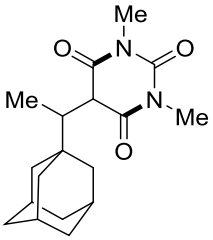
^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.4, 80.6, 50.7, 39.3, 36.9, 36.2, 33.9, 28.9, 28.4, 27.2.

MS (EI) *m*/*z* (relative intensity): 248 (5) [M], 192 (9), 147 (4), 135 (100), 105 (8), 91 (16), 79 (20), 67 (9), 55 (11).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{16}H_{25}O_2$ $[M+H]^+$ 249.1854, found 249.1847.

IR (ATR, neat, cm^{-1}): 2978 (w), 2909 (m), 2847 (w), 1747 (m), 1451 (w), 1385 (w), 1286 (w), 1197 (w), 1114 (m), 954 (m).

Synthesis of 5-(1-((3r,5r,7r)-adamantan-1-yl)ethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (2.12)



2.12

Compound **2.12** was prepared in a similar fashion to the procedure described in literature.[194] Sodium (54 mg, 2.36 mmol, 3.1 equiv.) was dissolved in absolute ethanol (1 ml) in a 25 ml flame dried flask equipped with a reflux condenser. A solution of diester **2.6bb** (245 mg, 760 µmol, 1.0 equiv.) in 1 ml of absolute ethanol was added followed by a solution of dimethyl urea (35 mg, 752 µmol, 1.0 equiv) in 0.7 ml of absolute ethanol. The reaction mixture was then refluxed for 23 h and cooled to room temperature. Afterwards, the reaction was quenched with water (2 ml) and the reaction solution was acidified by adding conc. HCl (0.3 ml). The aqueous phase was extracted with 3 x dichloromethane (15 ml) and the combined organic phases were dried over Na_2SO_4 and filtered. Afterwards, the filtrate was dried under vacuum and the crude material was purified by column chromatography (*n*-pentane:EtOAc = 15:1) which afforded desired product **2.12** (81 mg, 0.254 mmol, 33%) as a white solid.

m.p.= 195–198 °C

R_f = 0.44 (*n*-pentane:EtOAc = 5:1, UV, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.71 (d, *J* = 2.0 Hz, 1H), 3.28 (d, *J* = 5.6 Hz, 6H), 2.04 (m, 4H), 1.64 (m, 12H), 0.90 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.6, 168.9, 151.9, 50.0, 49.9, 40.1, 37.0, 36.1, 28.8, 28.8, 28.4, 11.0.

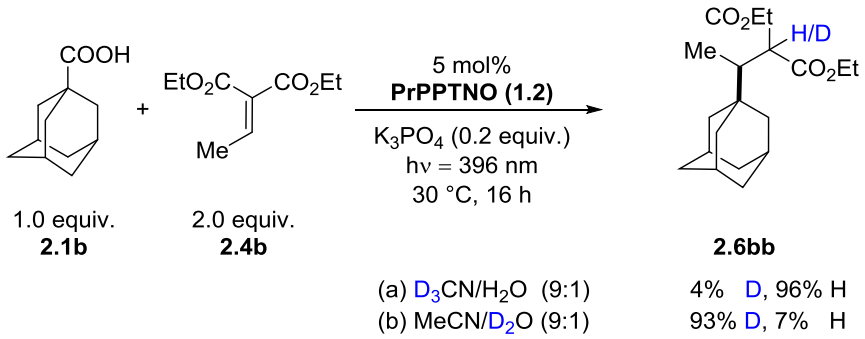
MS (EI) *m/z* (relative intensity): 318 (1) [M], 182 (6), 135 (100), 119 (1), 107 (6), 93 (10), 79 (11), 69 (4), 55 (2).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{18}H_{27}O_3N_2$ $[M+H]^+$ 319.2021, found 319.2016.

IR (ATR, neat, cm^{-1}): 2965 (w), 2896 (w), 2848 (w), 1668 (w), 1416 (w), 1368 (w), 1122 (w), 1086 (w), 755 (w).

Deuterium incorporation experiments.

Deuterium incorporation experiments (Scheme S2.1) were performed under Schlenk conditions using a 5 ml process vial equipped with a NS 14.5 rubber septum. To this vial was added 1-adamantanecarboxylic acid **2.1b** (45 mg, 0.25 mmol, 1.0 equiv.), photocatalyst **1.2** (5 mg, 125 µmol ,0.05 equiv.) and K_3PO_4 (11 mg, 0.05 mmol, 0.2 equiv.). Next, the vial was evacuated and purged with argon for 3 times. Diethyl ethylidenmalonate **2.4b** (93 mg, 0.5 mmol, 2.0 equiv.) was then added to the flask under argon. Afterwards, 5 ml of (a) D_3CN:H_2O (9:1) or (b) MeCN:D_2O (9:1) were added and the reaction mixture was stirred for 2 minutes in the dark. The reaction mixture was then irradiated for 16 h and quenched afterwards upon exposure to air and bubbling air through the solution using a pipette. The reaction was concentrated under reduced pressure and the crude product was purified by column chromatography (*n*-pentane:EtOAc = 20:1) yielding the title compound **2.6bb** as a colorless oil.



Scheme S2.1 Deuterium incorporation experiments.

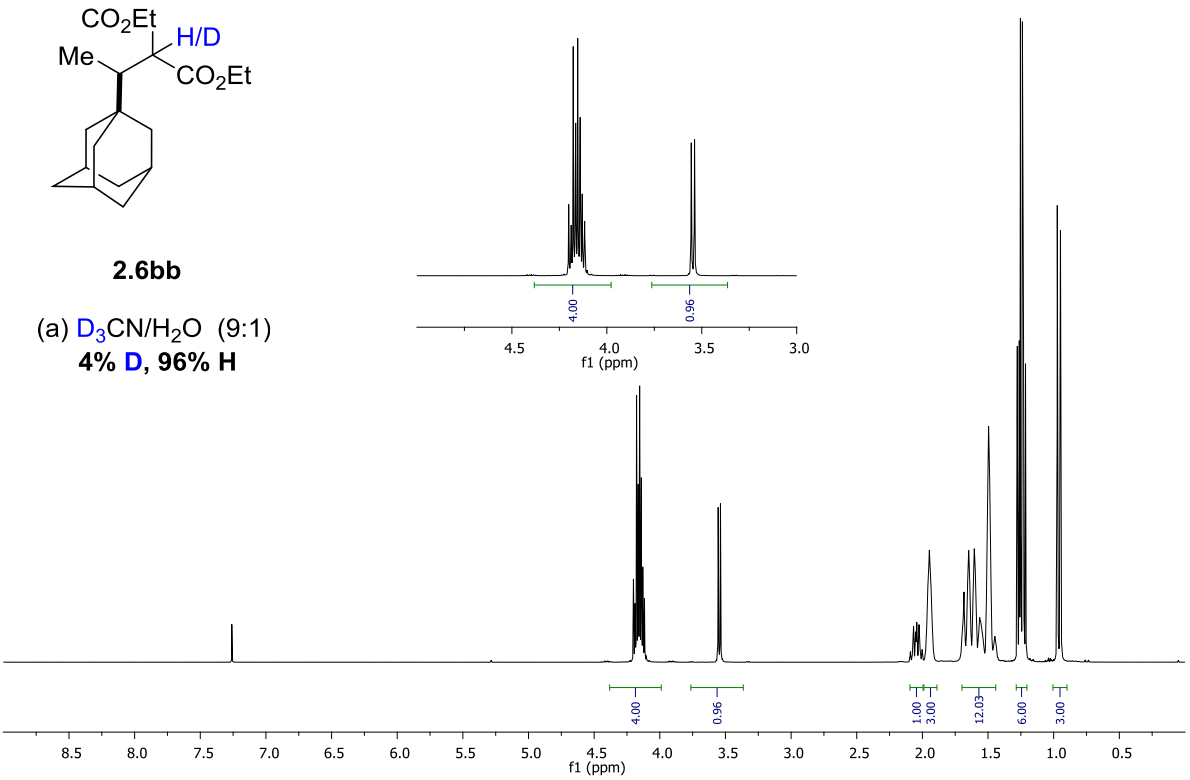


Figure S1.1 1H NMR of product 2.6bb using conditions (a).

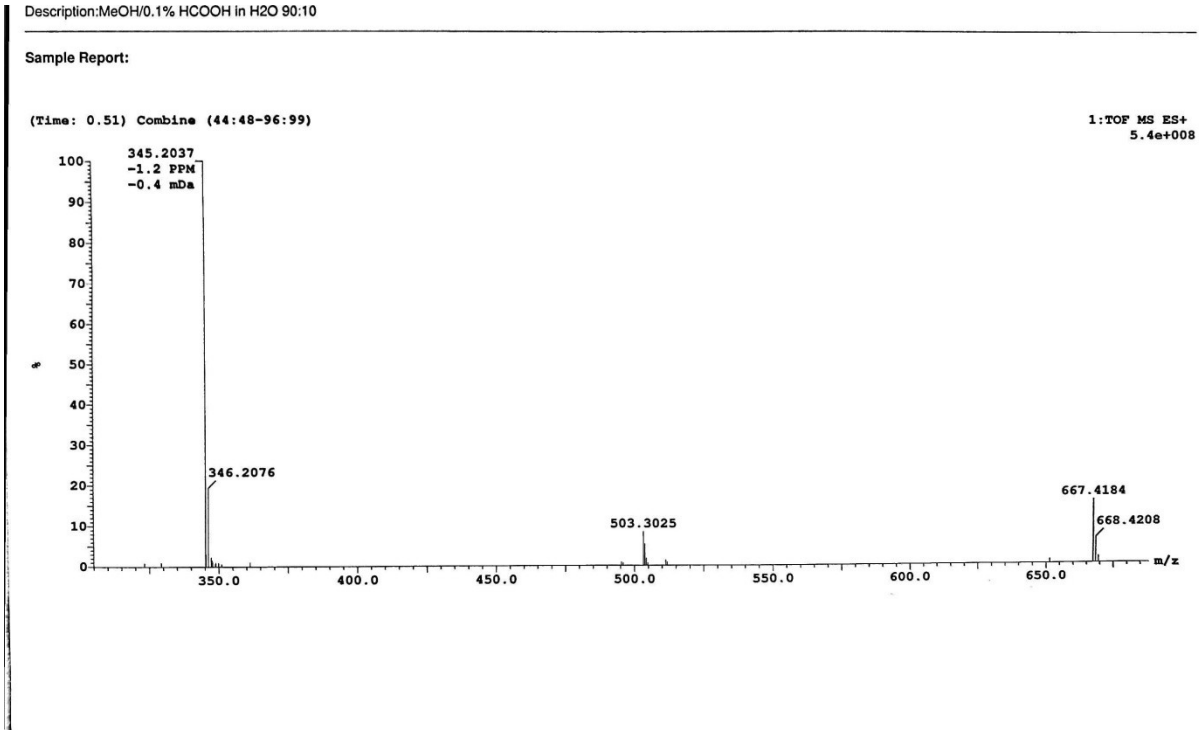


Figure S2.2 HRMS spectrum of (2.6bb) using conditions (a).

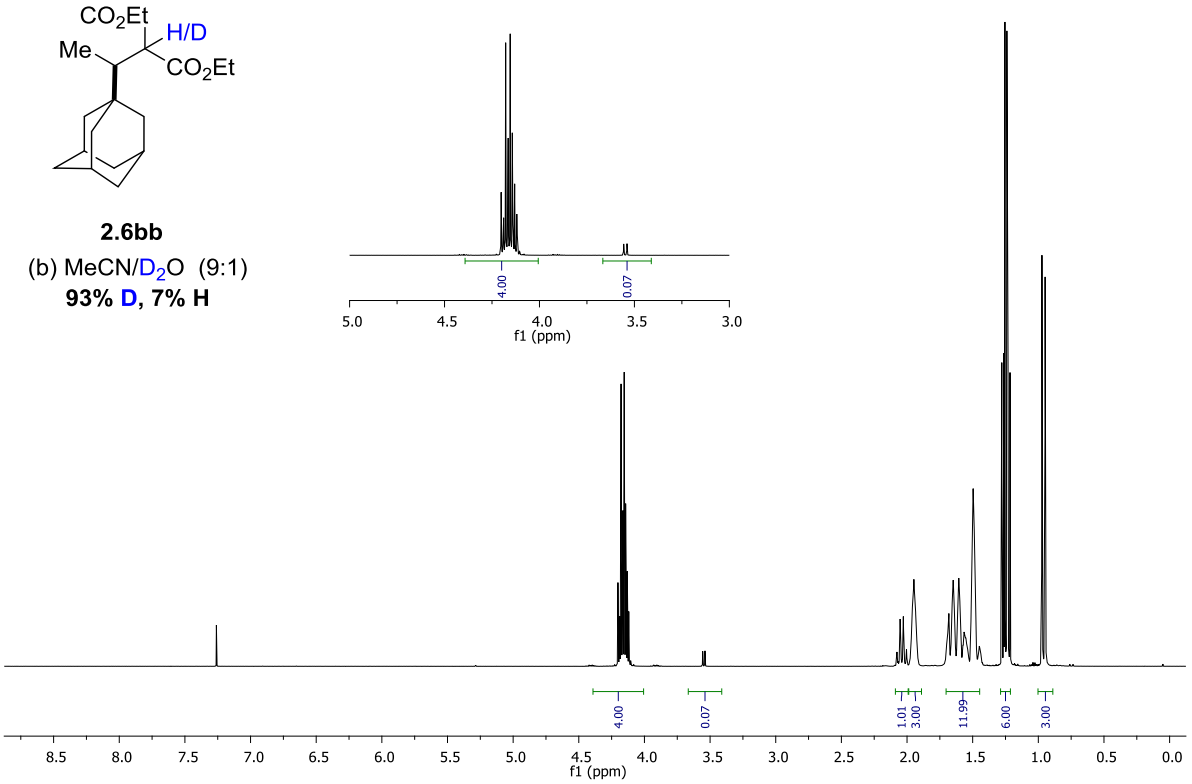


Figure S2.3 1H NMR of product 2.6bb using conditions (b).

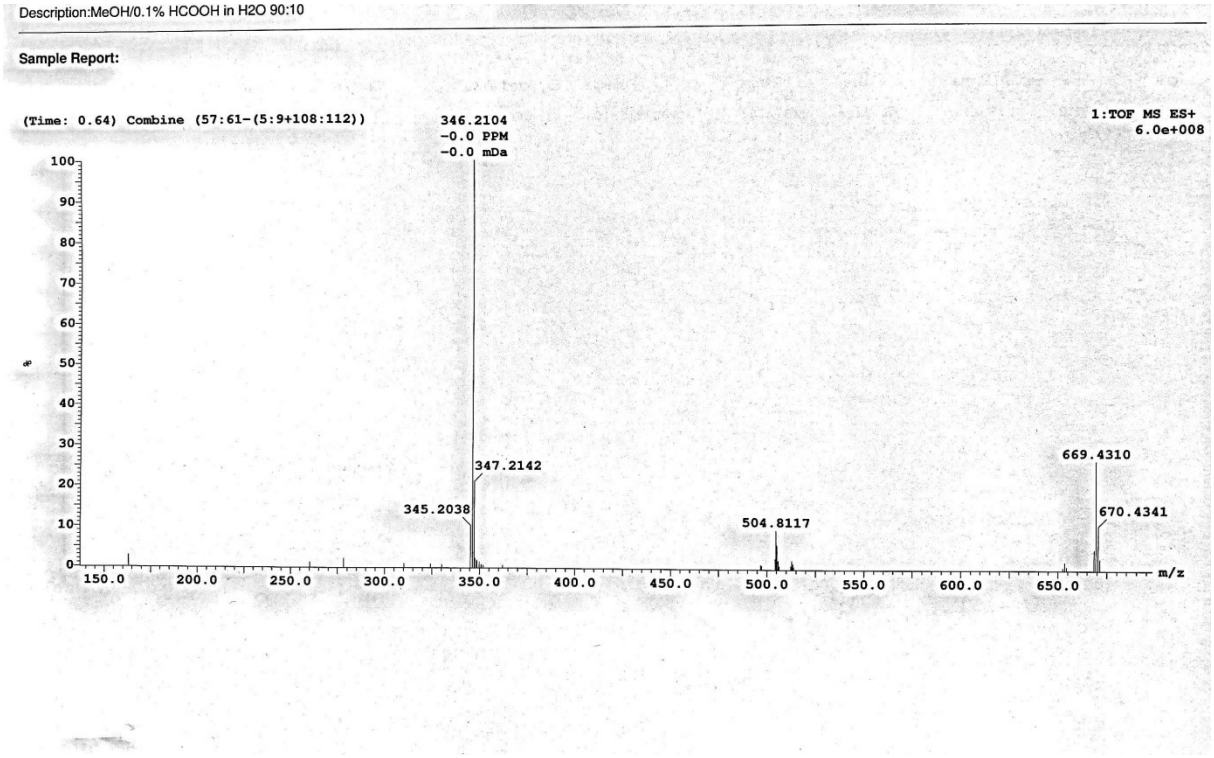
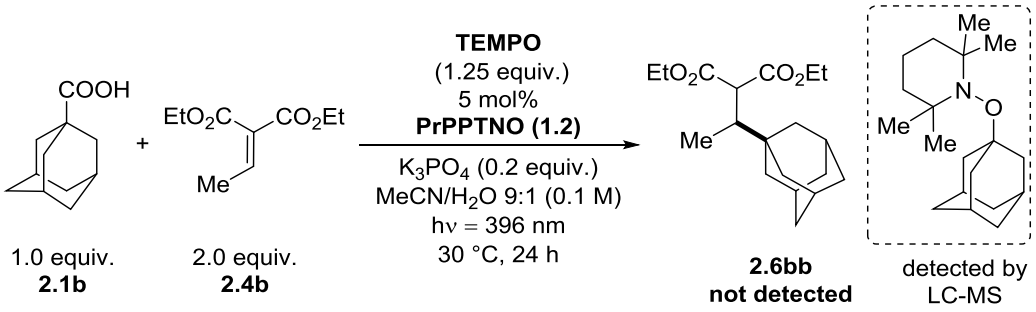


Figure S2.4 HRMS spectrum of 2.6bb using conditions (b).

TEMPO quenching experiment

TEMPO quenching experiment (Scheme S2.2) was performed under Schlenk conditions using a 5 ml process vial equipped with a NS 14.5 rubber septum. To this vial was added 1-

adamantanecarboxylic acid carboxylic acid **2.1b** (90 mg, 0.5 mmol, 1.0 equiv.), photocatalyst **1.2** (10.8 mg, 0.05 equiv.), 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (98 mg, 0.625 mmol, 1.25 equiv.) and K_3PO_4 (21 mg, 0.2 mmol, 0.2 equiv.). Next, the vial was evacuated and purged with argon for 3 times followed by the addition of Diethyl ethylidenmalonate **2.4b** (93 mg, 0.5 mmol, 2.0 equiv.) under argon. Afterwards, 4.5 ml of MeCN and 0.5 ml degassed H_2O were added and the reaction mixture was irradiated for 16 h. Subsequently, 0.5 ml sample was taken and measured by LC-MS (Figure S2.5).



Scheme S2.2 TEMPO quenching experiment.

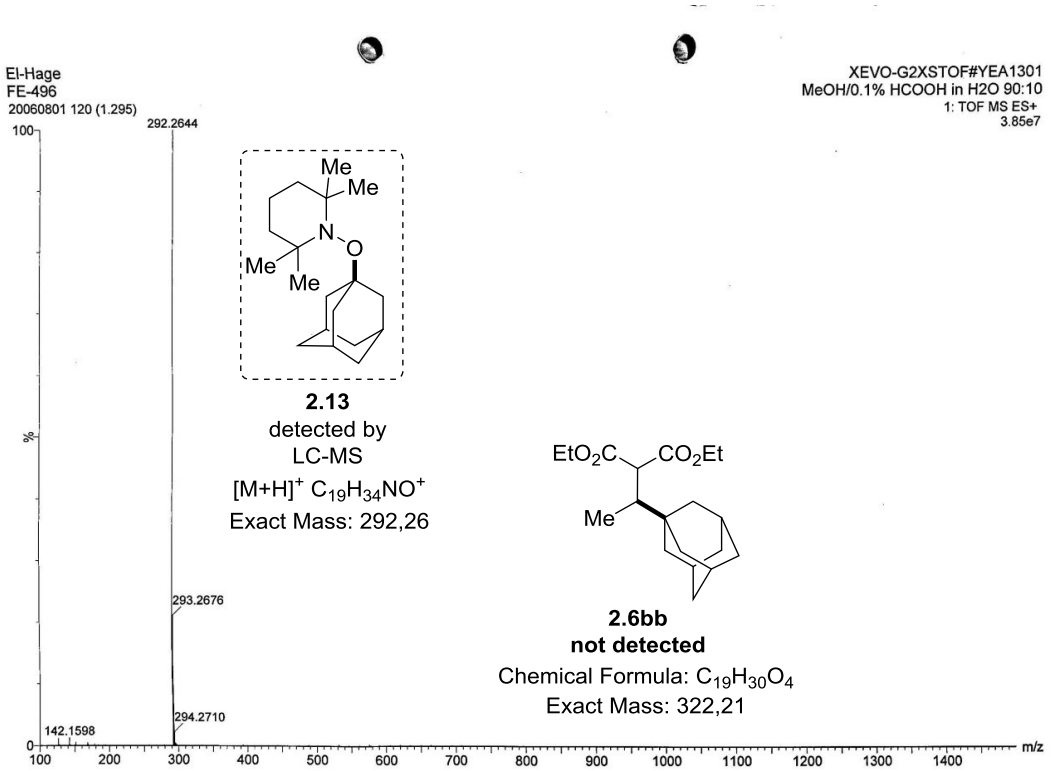


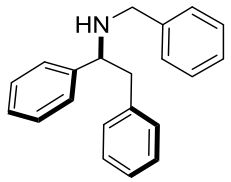
Figure 2.5 LC-MS spectrum of the TEMPO quenching experiment.

7.2.2 Experimental section to Chapter 3

This project was conducted with *Richy Hauptmann.*

The letter (a) and (b) stated after the compound numbers during the experimental section to chapter 3 (e.g. X.Xm**a** or X.Xm**b**) correspond to different possible regioisomers.

Synthesis of *N*-benzyl-1,2-diphenylethan-1-amine (3.3a)



3.3a

Compound **3.3a** was prepared following general procedure **B**. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound **3.3a** (95 mg, 0.33 mmol, 66%) as a colorless solid.

m.p. = 52–54 °C.

$\mathbf{R_f}$ = 0.3 (*n*-pentane:EtOAc = 9:1, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.19 (m, 4H), 7.19 – 7.06 (m, 7H), 7.00 (dt, *J* = 7.9, 1.4 Hz, 4H), 3.79 (dd, *J* = 8.5, 5.5 Hz, 1H), 3.56 (d, *J* = 13.5 Hz, 1H), 3.36 (d, *J* = 13.5 Hz, 1H), 2.97 – 2.70 (m, 2H), 1.64 (s, 1H).

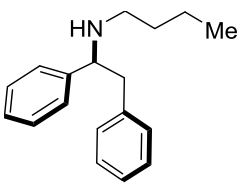
^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.8, 140.6, 138.9, 129.4, 128.5, 128.5, 128.4, 128.0, 127.5, 127.2, 126.8, 126.5, 63.7, 51.5, 45.4.

MS (EI) *m*/*z* (relative intensity): 286 (1), 197 (15), 196 (100), 91 (87).

HRMS (EI, *m*/*z*): calcd. for $C_{21}H_{22}N$ $[M+H]^+$ 288.1752, found 288.1759.

IR (ATR, neat, cm^{-1}): 2704 (w), 1952 (w), 1871 (w), 1813(w), 1601 (w), 1582 (w), 1491 (m), 1452 (m), 1398 (w), 1357 (w), 1315 (w), 1288 (w), 1269 (w), 1227 (w), 1195 (w), 1179 (w), 1162 (w), 1153 (w), 1120 (m), 1068 (m), 1028 (m), 1000 (w), 988 (w), 946 (w), 911 (w), 832 (w), 820(w), 793 (w), 758 (m), 741 (m), 728 (s), 695 (s), 635 (m), 619 (w), 579 (w), 547 (s), 506 (m), 460 (m).

Synthesis of *N*-(1,2-diphenylethyl)butan-1-amine (3.3b)



3.3b

Compound **3.3b** was prepared following general procedure **B**. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound **3.3b** (63 mg, 0.25 mmol, 50%) as a yellow oil.

R_f = 0.4 (*n*-pentane:EtOAc = 9:1, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 4.3 Hz, 4H), 7.18 – 7.08 (m, 4H), 7.07 – 7.01 (m, 2H), 3.75 (dd, *J* = 8.0, 6.0 Hz, 1H), 2.93 – 2.72 (m, 2H), 2.41 – 2.15 (m, 2H), 1.39 (s, 1H), 1.33 – 1.19 (m, 2H), 1.19 – 1.01 (m, 2H), 0.72 (t, *J* = 7.2 Hz, 3H).

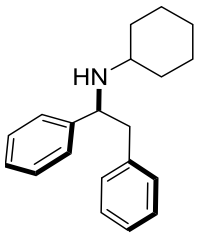
^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.1, 139.1, 129.4, 128.4, 128.4, 127.4, 127.1, 126.4, 65.0, 47.6, 45.5, 32.3, 20.4, 14.0.

MS (EI) *m/z* (relative intensity): 252 (1), 163 (12), 162 (100), 106 (17), 91 (10).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{18}H_{24}N$ $[M+H]^+$ 254.1908, found 254.1911.

IR (ATR, neat, cm^{-1}): 3062 (w), 3028 (w), 2956 (w), 2928 (w), 2869 (w), 2795 (w), 2727 (w), 2565 (w), 2461 (w), 1721 (w), 1674 (w), 1601 (w), 1585 (w), 1494 (w), 1454 (m), 1377 (w), 1314 (w), 1244 (w), 1212 (w), 1141 (w), 1127 (w), 1072 (w), 1028 (w), 1001 (w), 984 (w), 922 (w), 879 (w), 839 (w), 793 (w), 770 (w), 758 (m), 739 (m), 697 (s), 613 (w), 563 (w), 507 (w), 473 (w), 447 (w).

Synthesis of *N*-(1,2-diphenylethyl)cyclohexanamine (3.3c)



3.3c

Compound **3.3c** was prepared following general procedure **B**. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound **3.3c** (73 mg, 0.25 mmol, 50%) as yellow oil.

R_f = 0.2 (*n*-pentane:EtOAc = 9:1, $KMnO_4$).

m.p. = 53–55 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31 – 7.15 (m, 8H), 7.08 (ddt, *J* = 7.3, 1.5, 0.7 Hz, 2H), 4.02 (dd, *J* = 8.1, 6.0 Hz, 1H), 2.95 – 2.75 (m, 2H), 2.19 (tt, *J* = 10.0, 3.7 Hz, 1H), 1.82 (d, *J* = 12.4 Hz, 1H), 1.69 – 1.39 (m, 4H), 1.30 – 1.18 (m, 1H), 1.14 – 0.92 (m, 4H), 0.87 – 0.69 (m, 1H).

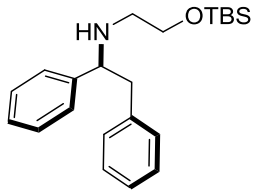
^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.7, 139.2, 129.4, 128.4, 128.3, 127.4, 126.9, 126.4, 61.3, 53.6, 45.8, 34.9, 32.8, 26.2, 25.3, 24.9.

MS (EI) *m*/*z* (relative intensity): 188 (100), 106 (67), 103 (11), 91 (50), 79 (14), 77 (13), 65 (10), 55 (15), 41 (13).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{20}H_{26}N$ $[M+H]^+$ 280.2065, found 280.2066.

IR (ATR, neat, cm^{-1}): 3083 (w), 3061 (w), 3026 (w), 2922 (m), 2850 (w), 1602 (w), 1584 (w), 1493 (w), 1451 (m), 1359 (w), 1345 (w), 1307 (w), 1259 (w), 1181 (w), 1143 (w), 1120 (w), 1070 (w), 1028 (w), 976 (w), 911 (w), 889 (w), 846 (w), 804 (w), 779 (w), 756 (m), 696 (s), 624 (w), 565 (m), 532 (m), 500 (w), 464 (w), 417 (w).

Synthesis of *N*-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1,2-diphenylethan-1-amine (3.3d)



3.3d

Compound **3.3d** was prepared following general procedure **B**. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound **3.3d** (70 mg, 0.20 mmol, 40%) as colorless solid.

$\mathbf{R_f}$ = 0.6 (*n*-pentane:EtOAc = 9:1, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.28 – 7.05 (m, 10H), 3.81 (dd, *J* = 8.3, 5.6 Hz, 1H), 3.61 – 3.47 (m, 2H), 2.97 – 2.74 (m, 2H), 2.49 – 2.33 (m, 2H), 1.96 (s, 1H), 0.74 (d, *J* = 0.7 Hz, 9H), −0.08 – −0.16 (m, 6H).

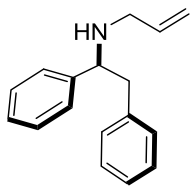
^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.0, 138.9, 129.4, 128.5, 128.4, 127.5, 127.1, 126.5, 64.7, 62.4, 49.8, 45.6, 26.0, 18.3, -5.3.

MS (EI) *m*/*z* (relative intensity): 354 (1), 265 (36), 264 (100), 248 (14), 166 (10), 165 (10), 105 (13), 103 (14), 91 (25), 73 (21).

HRMS (EI, *m*/*z*): calcd. for $C_{22}H_{32}NOSi$ [M-H] 354.2239, found 354.2248.

IR (ATR, neat, cm^{-1}): 3084 (w), 3062 (w), 3027 (w), 2952 (w), 2927 (w), 2855 (w), 1602 (w), 1494 (w), 1462 (w), 1453 (m), 1388 (w), 1360 (w), 1309 (w), 1253 (m), 1226 (w), 1085 (m), 1020 w), 1006 (w), 957 (w), 939 (w), 888 (w), 832 (s), 811 (m), 775 (s), 756 (s), 697 (s), 662 (m), 629 (w), 568 (w), 548 (w), 512 (w), 450 (w).

Synthesis of *N*-(1,2-diphenylethyl)prop-2-en-1-amine (3.3e)



3.3e

Compound **3.3e** was prepared following general procedure **B**. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound **3.3e** (40 mg, 169 µmol, 34%) as colorless oil.

R_f = 0.4 (*n*-pentane:EtOAc = 9:1, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.28 – 7.09 (m, 8H), 7.08 – 7.01 (m, 2H), 5.68 (dddd, *J* = 17.6, 9.7, 6.6, 5.3 Hz, 1H), 5.00 – 4.86 (m, 2H), 3.82 (dd, *J* = 8.0, 6.1 Hz, 1H), 3.01 (ddt, *J* = 14.3, 5.3, 1.6 Hz, 1H), 2.93 – 2.76 (m, 3H), 1.46 (s, 1H).

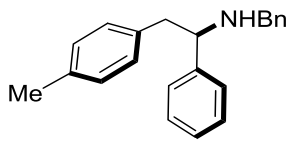
^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.7, 138.9, 136.9, 129.4, 128.5, 128.4, 127.5, 127.2, 126.5, 115.7, 64.0, 50.1, 45.3.

MS (EI) *m*/*z* (relative intensity): 236 (1), 147 (13), 146 (100), 91 (17), 41 (17).

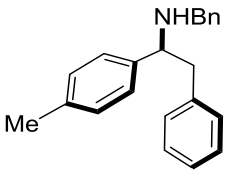
HRMS (EI, *m*/*z*): calcd. for $C_{17}H_{18}N$ [M-H] 236.1430, found 236.1434.

IR (ATR, neat, cm^{-1}): 3062 (w), 3026 (w), 2977 (w), 2918 (w), 2845 (w), 1948 (w), 1879 (w), 1808 (w), 1642 (w), 1602 (w), 1584 (w), 1494 (w), 1453 (m), 1417 (w), 1355 (w), 1328 (w), 1308 (w), 1229 (w), 1208 (w), 1180 (w), 1141 (w), 1109 (w), 1070 (w), 1028 (w), 993 (w), 914 (m), 844 (w), 794 (w), 756 (m), 742 (m), 696 (s), 625 (w), 591 (w), 562 (m), 547 (m), 503 (w), 444 (w).

Synthesis of *N*-benzyl-1-phenyl-2-(*p*-tolyl)ethan-1-amine (3.3fa) and *N*-benzyl-2-phenyl-1-(p-tolyl)ethan-1-amine (3.3fb)



3.3fa



3.3fb

Compounds **3.3fa** and **3.3fb** were prepared following general procedure **B** with a reaction time of 16 h. Purification by column chromatography (*n*-pentane:EtOAc = 10:1) yielded the title compounds as inseparable mixture (101 mg, 0.34 mmol, 67%, **3.3fa**:**3.3fb** = 61:39) as a colorless oil.

R_f = 0.3 (*n*-pentane:EtOAc = 9:1, $KMnO_4$).

^{1}H NMR (300 MHz, CD_2Cl_2) δ = 7.46 – 7.00 (m, 14H), 3.91 (ddd, *J* = 8.0, 6.0, 4.0 Hz, 1H), 3.65 (dd, *J* = 13.5, 0.8 Hz, 1H), 3.49 (dd, *J* = 13.4, 1.7 Hz, 1H), 3.03 – 2.83 (m, 2H), 2.36 (d, *J* = 12.5 Hz, 3H), 1.71 (s, 1H).

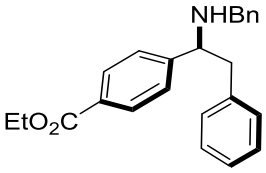
^{13}C NMR (75 MHz, CD_2Cl_2) δ = 144.6, 141.3, 141.3, 139.6, 137.0, 136.2, 129.7, 129.5, 129.4, 129.4, 128.7, 128.7, 128.6, 128.3, 127.8, 127.7, 127.4, 127.0, 126.6, 64.3, 63.9, 51.8, 51.7, 45.6, 45.2, 21.3, 21.2.

MS (EI) *m*/*z* (relative intensity): 300 (1), 210(27), 197 (12), 196 (76), 105 (11), 91 (100), 65 (11).

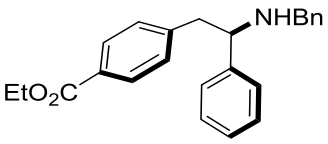
HRMS (EI, *m*/*z*): calcd. for $C_{22}H_{24}N$ $[M+H]^+$ 302.1909, found 302.1910.

IR (ATR, neat, cm^{-1}): 3025 (w), 2918 (w), 1513 (w), 1493 (w), 1452 (w), 1109 (w), 1027 (w), 732 (m), 696 (s), 547 (m).

Synthesis of ethyl -4-(1-(benzylamino)-2-phenylethyl)benzoate (3.3ga) and ethyl 4-(2-(benzylamino)-2-phenylethyl)benzoate (3.3gb)



3.3ga



3.3gb

Compounds **3.3ga** and **3.3gb** were prepared following general procedure **B** with a reaction time of 16 h. Purification by column chromatography (*n*-pentane:EtOAc = 9:1) yielded the title compounds (61 mg, 0.17 mmol, 34%, **3.3ga**:**3.3gb** = 67:33) as a colorless oil. Analytically pure samples of each regioisomere were obtained by flash chromatography (*n*-pentane:EtOAc = 9:1). When the reaction was run for 24 h, the products **3.3ga** and **3.3gb** (73 mg, 0.20 mmol, 40%, **3.3ga:3.3gb** = 66:34) were obtained as colorless oil.

3.3ga:

R_f = 0.4 (*n*-pentane:EtOAc = 5:1, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.11 – 8.01 (m, 2H), 7.51 – 7.41 (m, 2H), 7.33 – 7.20 (m, 6H), 7.17 – 7.05 (m, 4H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.99 (dd, *J* = 7.9, 6.2 Hz, 1H), 3.68 (d, *J* = 13.5 Hz, 1H), 3.49 (d, *J* = 13.5 Hz, 1H), 3.04 – 2.89 (m, 2H), 1.91 (s, 1H), 1.44 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.3, 148.8, 141.3, 138.3, 129.9, 129.6, 129.4, 128.6, 128.5, 128.1, 127.6, 127.0, 126.7, 63.1, 58.4, 50.8, 43.2, 13.5.

MS (EI) *m*/*z* (relative intensity): 358 (1), 314 (1), 268 (42), 91 (100), 65 (9).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{24}H_{26}NO_2$ $[M+H]^+$ 360.1964, found 360.1969.

IR (ATR, neat, cm^{-1}): 3084 (w), 2980 (w), 2927 (w),1712 (s), 1609 (w), 1577 (w), 1494 (w), 1453 (m), 1415 (w), 1390 (w), 1366 (w), 1307 (w), 1270 (s), 1199 (w), 1172 (m), 1099 (s), 1019 (m), 979 (w), 909 (w), 858 (w), 769 (m), 742 (m), 696 (s), 657 (w), 621 (w), 604 (w), 572 (w), 550 (m), 482 (w).

3.3gb:

$\mathbf{R_f} = 0.3$ (*n*-pentane:EtOAc = 5:1, $KMnO_4$).

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.93 – 7.86 (m, 2H), 7.38 – 7.10 (m, 12H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.93 (dd, *J* = 7.4, 6.7 Hz, 1H), 3.64 (d, *J* = 13.4 Hz, 1H), 3.49 (d, *J* = 13.4 Hz, 1H), 3.07 – 2.94 (m, 2H), 1.68 (s, 1H), 1.37 (t, *J* = 7.1 Hz, 3H).

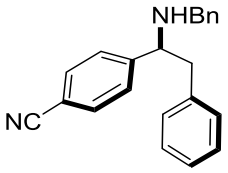
^{13}C NMR (101 MHz, CD_2Cl_2) δ = 166.7, 144.8, 143.8, 141.0, 129.9, 129.7, 129.7, 129.1, 128.7, 128.6, 128.3, 127.8, 127.6, 127.1, 64.0, 51.7, 45.5, 14.5.

MS (EI) *m*/*z* (relative intensity): 358 (1), 314 (1), 197 (11), 196 (72), 91 (100), 65 (9).

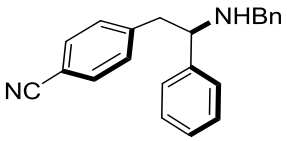
HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{24}H_{26}NO_2$ $[M+H]^+$ 360.1964, found 360.1958.

IR (ATR, neat, cm^{-1}): 3327 (w), 3061 (w), 3027 (w), 2980 (w), 2926 (w), 2850 (w), 1947 (w), 1809 (w), 1714 (s), 1610 (w), 1575 (w), 1493 (w), 1453 (m), 1415 (w), 1391 (w), 1366 (w), 1309 (w), 1274 (s), 1199 (w), 1178 (m), 1103 (s), 1022 (m), 974 (w), 912 (w), 854 (w), 762 (m), 699 (s), 651 (w), 638 (w), 612 (w), 584 (w), 553 (w), 500 (w), 462 (w), 426 (w).

Synthesis of 4-(1-(benzylamino)-2-phenylethyl)benzonitrile (3.3ha) and 4-(2-(benzylamino)-2-phenylethyl)benzonitrile (3.3hb)



3.3ha



3.3.hb

Compounds **3.3ha** and **3.3hb** were prepared following general procedure **B** with a reaction time of 16 h. Purification by column chromatography (*n*-pentane:EtOAc = 10:1) yielded the title compounds (58 mg, 0.19 mmol, 37%, **3.3ha**:**3.3hb** = 74:26) as a colorless oil. Yield of **3.3h** after 24 h (46 mg, 0.15 mmol, 29%, **3.3ha:3.3hb** = 74:26). Analytically pure samples of each regioisomere were obtained by flash chromatography (*n*-pentane:EtOAc = 20:1).

3.3ha:

$\mathbf{R_f} = 0.3$ (*n*-pentane:EtOAc = 9:1, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.36 – 7.16 (m, 7H), 7.11 (ddt, J = 14.0, 5.5, 1.7 Hz, 4H), 3.98 (dd, J = 8.2, 6.0 Hz, 1H), 3.66 (d, J = 13.5 Hz, 1H), 3.49 (d, J = 13.5 Hz, 1H), 3.00 – 2.85 (m, 2H), 1.80 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.6, 140.0, 137.8, 132.4, 129.3, 128.7, 128.5, 128.3, 127.9, 127.1, 126.9, 119.2, 111.0, 63.6, 51.6, 45.2.

MS (EI) *m/z* (relative intensity): 222 (16), 221 (82), 92 (15), 91 (100), 65 (24).

HRMS (EI, *m/z*): calcd. for $C_{22}H_{21}N_2$ $[M+H]^+$ 313.1705, found 313.1710.

IR (ATR, neat, cm^{-1}): 3326 (w), 3084 (w), 3061 (w), 3027 (w), 2919 (w), 2840 (w), 2226 (m), 1950 (w), 1808 (w), 1647 (w), 1605 (w), 1583 (w), 1494 (m), 1453 (m), 1411 (w), 1349 (w), 1301 (w), 1200 (w), 1177 (w), 1155 (w), 1103 (w), 1076 (w), 1028 (w), 1019 (w), 971 (w), 909 (w), 832 (m), 733 (s), 696 (s), 647 (w), 626 (w), 605 (w), 584 (m), 562 (s), 514 (m), 479 (m).

3.3hb:

R_f = 0.1 (*n*-pentane:EtOAc = 9:1, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, J = 8.3 Hz, 1H), 7.30 – 7.09 (m, 11H), 7.09 – 6.99 (m, 4H), 3.78 (dd, J = 7.0 Hz, 1H), 3.73 (s, 1H), 3.58 (d, J = 13.4 Hz, 1H), 3.41 (d, J = 13.3 Hz, 1H), 3.00 – 2.83 (m, 2H).

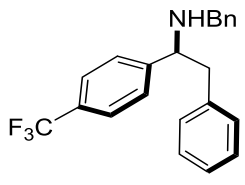
^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.6, 142.7, 140.4, 140.3, 132.1, 130.3, 128.7, 128.5, 128.5, 128.3, 128.1, 127.6, 127.4, 127.1, 119.1, 110.3, 63.4, 53.3, 51.4, 45.2.

MS (EI) *m/z* (relative intensity): 221 (1), 197 (9), 196 (59), 116 (10), 91 (100), 89 (11), 65 (13).

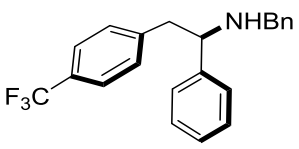
HRMS (EI, *m/z*): calcd. for $C_{22}H_{21}N_2$ $[M+H]^+$ 313.1705, found 313.1705.

IR (ATR, neat, cm^{-1}): 3084 (w), 3061 (w), 3027 (w), 2923 (w), 2850 (w), 2226 (w), 1641 (w), 1606 (w), 1493 (w), 1453 (m), 1413 (w), 1358 (w), 1331 (w), 1307 (w), 1199 (w), 1177 (w), 1155 (w), 1113 (w), 1074 (w), 1027 (w), 1002 (w), 970 (w), 912 (w), 848 (w), 823 (m), 733 (m), 697 (s), 616 (w), 587 (w), 562 (m), 547 (m), 486 (w), 462 (w), 426 (w).

Synthesis of *N*-benzyl-2-phenyl-1-(4-(trifluoromethyl)phenyl)ethan-1-amine (3.3ia) and *N*-benzyl-1-phenyl-2-(4-(trifluoromethyl)phenyl)ethan-1-amine (3.3ib)



3.3ia



3.3ib

Compounds **3.3ia** and **3.3ib** were prepared following general procedure **B**, with a reaction time of 16 h. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound (57 mg, 0.16 mmol, 32%, **3.3ia**:**3.3ib** = 68:32; after 24h: 49 mg, 0.14 mmol, 28%, **3.3ia:3.3ib** = 69:31) as colorless oil. Analytically pure samples were obtained by flash chromatography (*n*-pentane:EtOAc = 20:1).

3.3ia:

$\mathbf{R_f}$ = 0.2 (*n*-pentane:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.27 (dqt, *J* = 5.5, 3.8, 1.9 Hz, 6H), 7.18 – 7.02 (m, 4H), 3.97 (dd, *J* = 8.4, 5.7 Hz, 1H), 3.66 (d, *J* = 13.5 Hz, 1H), 3.47 (d, *J* = 13.6 Hz, 1H), 3.05 – 2.81 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.1, 140.2, 138.2, 129.4, 129.3, 128.7, 128.5, 128.0, 127.9, 127.0, 126.8, 125.5, 125.5, 63.4, 51.5, 45.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ = –62.30.

MS (EI) *m/z* (relative intensity): 354 (1), 264 (82), 91 (100), 65 (10).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{22}H_{21}NF_3$ $[M+H]^+$ 356.1626, found 356.1631.

IR (ATR, neat, cm^{-1}): 3330 (w), 3085 (w), 3063 (w), 3028 (w), 2920 (w), 2846 (w), 1948 (w), 1807 (w), 1618 (w), 1603 (w), 1585 (w), 1495 (w), 1454 (w), 1417 (w), 1322 (s), 1161 (m), 1118 (s), 1065 (s), 1029 (w), 1017 (m), 976 (w), 909 (w), 834 (m), 734 (m), 696 (s), 649 (w), 609 (m), 565 (w), 543 (m), 515 (w), 473 (w).

3.3ib:

$\mathbf{R_f}$ = 0.1 (n-pentane:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53 – 7.45 (m, 2H), 7.38 – 7.21 (m, 9H), 7.15 (dddd, *J* = 9.5, 7.6, 1.8, 1.1 Hz, 4H), 3.88 (t, *J* = 7.0 Hz, 1H), 3.67 (d, *J* = 13.4 Hz, 1H), 3.49 (d, *J* = 13.4 Hz, 1H), 2.99 (d, *J* = 7.0 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.1, 140.4, 129.8, 128.6, 128.5, 128.1, 127.5, 127.5, 127.0, 125.3, 125.3 (q, *J* = 3.8 Hz), 63.5, 51.5, 45.1.

^{19}F NMR (282 MHz, $CDCl_3$) δ = –62.30.

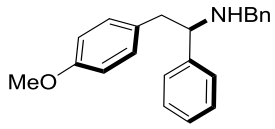
MS (EI) *m/z* (relative intensity): 354 (1), 196 (50), 91 (100), 65 (10).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{22}H_{21}NF_3$ $[M+H]^+$ 356.1626, found 356.1631.

IR (ATR, neat, cm^{-1}): 3085 (w), 3063 (w), 3028 (w), 2920 (w), 2846 (w), 1948 (w), 1807 (w), 1618 (w), 1603 (w), 1585 (w), 1495 (w), 1454 (w), 1417 (w), 1322 (s), 1161 (m), 1118 (s),

1065 (s), 1029 (w), 1017 (m), 976 (w), 909 (w), 834 (m), 734 (m), 696 (s), 649 (w), 609 (m), 565 (w), 543 (m), 515 (w), 473 (w).

Synthesis of (*R*)-*N*-benzyl-2-(4-methoxyphenyl)-1-phenylethan-1-amine (3.3k)



3.3k

Compound **3.3k** was prepared following general procedure **B** with a reaction time of 16 h. Purification by column chromatography (*n*-pentane:EtOAc = 10:1) yielded the title compounds (18 mg, 0.06 mmol, 12%, **3.3ka**:**3.3kb** = 93:7; after 24 h: 33 mg, 0.10 mmol, 20%, **3.3ka**:**3.3kb** = 93:7) as a colorless oil.

$\mathbf{R_f}$ = 0.1 (*n*-pentane:EtOAc = 10:1, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30 – 7.06 (m, 8H), 7.06 – 6.87 (m, 4H), 6.82 – 6.65 (m, 2H), 3.83 – 3.62 (m, 4H), 3.57 (d, *J* = 13.5 Hz, 1H), 3.37 (d, *J* = 13.5 Hz, 1H), 2.96 – 2.54 (m, 2H), 1.65 (s, 1H).

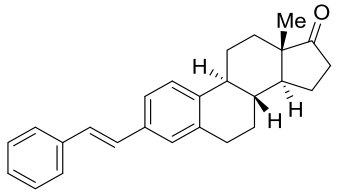
^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.1, 171.2, 159.4, 153.9, 152.3, 149.9, 144.2, 143.6, 142.7, 141.8, 141.6, 141.3, 140.8, 140.4, 140.1, 139.7, 128.1, 77.2, 75.9, 68.2, 64.8, 64.7, 58.8, 57.8.

MS (EI) *m*/*z* (relative intensity): 316 (1), 226 (5), 197 (15), 196 (100), 194 (9), 121 (6), 91 (67).

HRMS (EI, *m*/*z*): calcd. for $C_{22}H_{24}NO$ $[M+H]^+$ 318.1858, found 318.1858.

IR (ATR, neat, cm^{-1}): 3322 (w), 3083 (w), 3060 (w), 3027 (w), 3001 (w), 2931 (w), 2913 (w), 2834 (w), 1947 (w), 1885 (w), 1810 (w), 1611 (w), 1583 (w), 1510 (s), 1493 (m), 1453 (m), 1356 (w), 1300 (m), 1245 (s), 1176 (m), 1109 (m), 1073 (w), 1034 (m), 975 (w), 912 (w), 822 (m), 738 (m), 698 (s), 619 (w), 597 (w), 548 (m), 519 (w), 466 (w), 442 (w).

Synthesis of (8*R*,9*S*,13*S*,14*S*)-13-methyl-3-((*E*)-styryl)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (3.2h)



3.2h

Compound **3.2h** was synthesized using a modified literature procedure.[107] Potassium (*E*)-trifluoro(styryl)-borane[195] (167 mg, 0.80 mmol, 1.6 equiv.) and estrogen trifluoromethanesulfonate[196] (200 mg, 0.50 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 0.10 equiv.), PCy_3 (28 mg, 0.10 mmol, 0.2 equiv.) and Cs_2CO_3 (486 mg, 1.50 mmol, 3.0 equiv.)

in THF:H_2O (10:1, 10 ml) was stirred at 80 °C over night. The mixture was allowed to cool to room temperature and filtered through a plug of celite and washed with EtOAc. The filtrate was concentrated under reduced pressure and purified by column chromatography (*n*-pentane:EtOAc = 20:1). (8*R*,9*S*,13*S*,14*S*)-8,13-dimethyl-3-((*E*)-styryl)-6-9,11-16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one **3.2h** (157 mg, 0.44 mmol, 89%) was obtained as a pale yellow crystalline solid.

m.p. = 184–187 °C.

R_f = 0.3 (*n*-pentane:EtOAc = 9:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.58 – 7.48 (m, 2H), 7.43 – 7.23 (m, 6H), 7.10 (s, 2H), 3.05 – 2.89 (m, 2H), 2.63 – 2.28 (m, 3H), 2.27 – 1.93 (m, 4H), 1.79 – 1.39 (m, 6H), 0.95 (s, 3H).

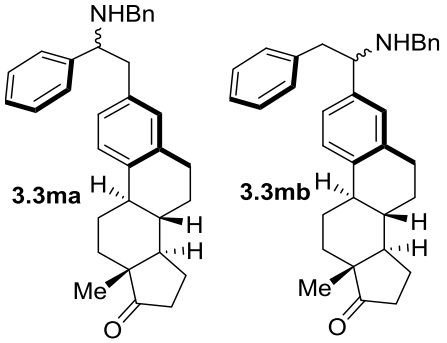
^{13}C NMR (75 MHz, $CDCl_3$) δ = 220.9, 139.5, 137.5, 136.7, 134.9, 128.7, 128.4, 128.1, 127.5, 127.1, 126.4, 125.7, 124.0, 50.5, 48.0, 44.5, 38.2, 35.9, 31.6, 29.5, 26.5, 25.7, 21.6, 13.9.

MS (EI) *m*/*z* (relative intensity): 357 (29), 356 (100), 232 (12), 229 (13), 22 (11), 215 (20), 202 (16), 178 (12), 165 (11), 153 (14), 128 (12), 115 (15), 91 (27), 77 (12), 55 (15), 41 (16).

HRMS (EI, *m*/*z*): calcd. for $C_{26}H_{28}O$ [M^+] 356.2135, found 356.2140.

IR (ATR, neat, cm^{-1}): 3447 (w), 3058 (w), 3021 (w), 2953 (w), 2927 (w), 2877 (w), 2858 (w), 2828 (w), 2312 (w), 1730 (w), 1633 (w), 1594 (w), 1574 (w), 1557 (w), 1495 (w), 1469 (w), 1448 (w), 1425 (w), 1402 (w), 1372 (w), 1338 (w), 1297 (w), 1286 (w), 1257 (w), 1192 (w), 1157 (w), 1135 (w), 1114 (w), 1082 (m), 1051 (w), 1026 (w), 1003 (m), 983 (w), 959 (s), 920 (w), 906 (m), 894 (w), 842 (w), 818 (m), 784 (m), 759 (s), 742 (s), 722 (w), 709 (m), 691 (s), 667 (w), 631 (w), 612 (w), 586 (w), 578 (m), 565 (m), 529 (m), 510 (m), 492 (w), 471 (w), 447 (w), 437 (m).

Synthesis of (8*S*,9*R*,13*R*,14*R*)-3-(2-(benzylamino)-2-phenylethyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[a]phenanthren-17-one (3.3ma) and (8*S*,9*R*,13*R*,14*R*)-3-(1-(benzylamino)-2-phenylethyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[a]phenanthren-17-one (3.3mb)



Compound **3.3m** was prepared following general procedure **B**. Purification by column chromatography (*n*-pentane:EtOAc **=** 20:1) yielded the title compound (146 mg, 0.31 mmol, 63%, **3.3ma:3.3mb =** 74:26) as colorless viscous oil. The regioisomers were separated using *n*-heptane:EtOAc = 8:1(+0.1% $NH_3 \cdot H_2O$) as eluent. The epimers were not separated.

3.3ma:

$\mathbf{R_f}$ = 0.30 (*n*-heptane:EtOAc = 2:1, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (dt, *J* = 8.1, 1.5 Hz, 2H), 7.36 (dd, *J* = 8.3, 6.6 Hz, 2H), 7.31 – 7.11 (m, 8H), 6.94 (ddd, *J* = 11.9, 7.9, 2.0 Hz, 1H), 6.87 (dd, *J* = 8.5, 1.9 Hz, 1H), 3.90 (ddd, *J* = 9.3, 4.8, 2.3 Hz, 1H), 3.67 (d, *J* = 13.7 Hz, 1H), 3.46 (dd, *J* = 13.7, 2.0 Hz, 1H), 2.99 – 2.75 (m, 4H), 2.52 (dd, *J* = 18.7, 8.6 Hz, 1H), 2.47 – 2.35 (m, 1H), 2.34 – 2.25 (m, 1H), 2.21 – 1.95 (m, 4H), 1.72 (d, *J* = 2.7 Hz, 1H), 1.70 – 1.40 (m, 7H), 0.93 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 221.1 (C_q), 144.1 (C_q), 140.7 (C_q), 138.0 (C_q), 136.6 (C_q), 136.3 (C_q), 130.0 (CH), 129.9 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 128.0 (CH), 127.5 (CH), 127.2 (CH), 126.8 (CH), 126.8 (CH), 126.7 (CH), 125.5 (CH), 63.4 (CH), 51.4 (CH_2), 50.6 (CH), 48.1 (CH_2), 44.9 (C_q), 44.4 (CH), 38.3 (CH), 36.0 (CH_2), 31.7 (CH_2), 29.5 (CH_2), 26.7 (CH_2), 25.9 (CH_2), 21.7 (CH_2), 14.0 (CH_3).

MS (EI) *m*/*z* (relative intensity): 463 (0) [M], 429 (1), 341 (2), 281 (5), 196 (100), 141 (3), 91 (75).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{33}H_{38}NO$ $[M+H]^+$ 464.2953, found 464.2952.

IR (ATR, neat, cm^{-1}): 3324 (w), 3059 (w), 3025 (w), 2918 (w), 2855 (w), 1950 (w), 1878 (w), 1736 (s), 1602 (w), 1584 (w), 1494 (m), 1452 (m), 1406 (w), 1372 (w), 1340 (w), 1258 (w), 1213 (w), 1168 (w), 1156 (w), 1113 (w), 1083 (w), 1052 (w), 1027 (w), 1007 (m), 982 (w), 965 (w), 910(w), 819 (w), 782 (w), 731 (s), 698 (s), 657 (w), 621 (w), 579 (m), 559 (w), 540 (w), 501 (w), 443 (w).

3.3mb:

$\mathbf{R_f}$ = 0.27 (*n*-heptane:EtOAc = 2:1, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.3 – 7.0 (m, 13H), 3.8 (dd, *J* = 9.4, 4.7 Hz, 1H), 3.7 (d, *J* = 13.6 Hz, 1H), 3.4 (d, *J* = 13.6 Hz, 1H), 3.1 – 2.7 (m, 5H), 2.7 – 2.4 (m, 2H), 2.4 – 2.3 (m, 1H), 2.3 – 1.9 (m, 3H), 1.8 – 1.4 (m, 7H), 0.9 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 221.1 (C_q), 141.4 (C_q), 140.7 (C_q), 139.2 (C_q), 138.7 (C_q), 136.6 (C_q), 129.4 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 128.0 (CH), 127.5 (CH), 127.2 (CH), 126.8 (CH), 126.5 (CH), 125.5 (CH), 125.5 (CH), 124.9 (CH), 63.4 (CH_2), 63.3

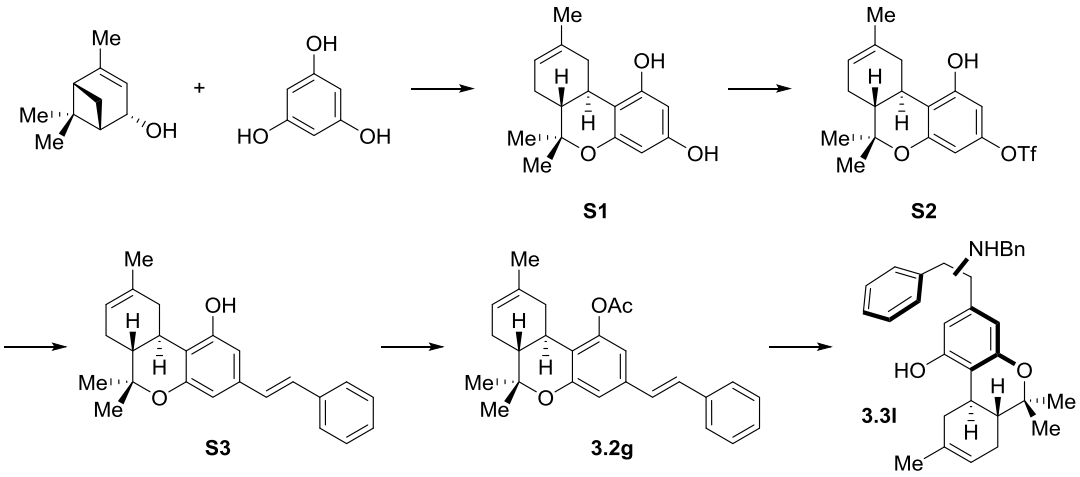
(CH_2), 63.2 (CH_2), 51.2 (C_q), 50.7 (CH_2), 48.2 (C_q), 45.4 (C_q), 44.6 (CH_2), 38.3 (CH_2), 36.0 (C_q), 31.8 (C_q), 29.6 (C_q), 25.9 (C_q), 21.8 (C_q), 14.0 (CH_2).

MS (EI) *m/z* (relative intensity): 462 (1), 373 (10), 372 (35), 128 (2), 115 (2), 91 (100).

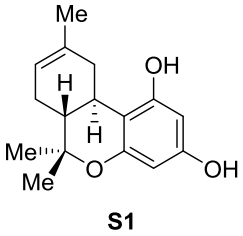
HRMS (ESI-TOF, *m/z*): calcd. for $C_{33}H_{38}NO$ $[M+H]^+$ 464.2953, found 464.2951.

IR (ATR, neat, cm^{-1}): 3330 (w), 3085 (w), 3063 (w), 3028 (w), 2920 (w), 2846 (w), 1948 (w), 1807 (w), 1618 (w), 1603 (w), 1585 (w), 1495 (w), 1454 (w), 1417 (w), 1322 (s), 1161 (m), 1118 (s), 1065 (s), 1029 (w), 1017 (m), 976 (w), 909 (w), 834 (m), 734 (m), 696 (s), 649 (w), 609 (m), 565 (w), 543 (m), 515 (w), 473 (w).

Synthesis of (6a*R*,10a*R*)-3-(2-(benzylamino)-2-phenylethyl)-6,6,9-trimethyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-yl acetate (3.2g)



Synthesis of (6a*R*,10a*R*)-6,6,9-trimethyl-6a,7,10,10*a*-tetrahydro-6*H*-benzo[c]chromene-1,3-diol (S1)



S1 was synthesized according to literature procedure.[107] (*S*)-*cis*-Verbenol (1.00 g, 6.57 mmol, 1.0 equiv.) and phloroglucinol (4.14 g, 32.8 mmol, 5.0 equiv.) were dissolved in a mixture of dry $MeNO_2$ (80 ml) and dry THF (20 ml). The solution was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (1.53 g, 6.90 mmol, 1.05 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched upon addition of a saturated aqueous solution of $NaHCO_3$ (20 ml). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 ml). The combined

organic layer was washed with brine and dried over Na_2SO_4. The crude product was concentrated under reduced pressure and purified by column chromatography (CH_2Cl_2:acetone = 20:1). The title compound **S1** (1.37 g, 5.26 mmol, 80%) was isolated as a yellow solid.

m.p. = 78–81 °C.

R_f = 0.2 (CH_2Cl_2:acetone = 20:1, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.94 (d, J = 2.4 Hz, 1H), 5.86 (d, J = 2.4 Hz, 1H), 5.43 – 5.35 (m, 1H), 3.21 – 3.08 (m, 1H), 2.63 (td, J = 11.0, 4.8 Hz, 1H), 2.10 (ddd, J = 12.4, 5.0, 2.7 Hz, 1H), 1.77 (td, J = 10.7, 4.5 Hz, 3H), 1.67 (d, J = 1.5 Hz, 3H), 1.35 (s, 3H), 1.08 (s, 3H).

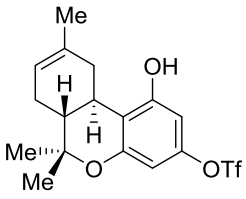
^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.2, 155.6, 154.9, 134.9, 119.3, 106.6, 97.1, 96.2, 50.9, 45.0, 36.2, 31.4, 28.0, 27.5, 23.6, 18.6.

MS (EI) m/z (relative intensity): 260 (22), 217 (13), 192 (17), 178 (11), 177 (100), 139 (20), 119 (10), 91 (17), 79 (11), 77 (16), 69 (27), 67 (12), 55 (14), 53 (14), 43 (17), 41 (26), 39 (17).

HRMS (EI, m/z): calcd. for $C_{16}H_{20}O_3$ [M^+] 260.1407, found 260.1408.

IR (ATR, neat, cm^{-1}): 3355 (w), 2974 (w), 2931 (w), 2913 (w), 2889 (w), 2843 (w), 1701 (w), 1601 (s), 1509 (w), 1444 (m), 1405 (w), 1384 (m), 1370 (m), 1302 (w), 1261 (s), 1180 (m), 1146 (s), 1127 (s), 1111 (s), 1083 (s), 1051 (m), 1032 (s), 1010 (s), 961 (w), 938 (w), 907 (m), 849 (m), 818 (s), 789 (m), 765 (w), 732 (s), 703 (m), 684 (m), 629 (m), 538 (m), 527 (m), 475 (m).

Synthesis of (6a*R*,10a*R*)-1-hydroxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-3-yl trifluoromethanesulfonate (S2)



S2

N-Phenyl-bis(trifluoromethanesulfonimide) (3.52 g, 9.85 mmol, 1.0 equiv.) and (6a*R*,10a*R*)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromene- 1,3-diol **S1** (2.56 g, 9.85 mmol, 1.0 equiv.) were dissolved in dry THF (70 ml). The mixture was cooled to 0 °C and a solution of lithium bis(trimethylsilyl)amide in THF (1.0 M, 9.85 ml, 1.0 equiv.) was added dropwise. The reaction mixture was stirred for 90 min. at 0 °C and then concentrated under reduced pressure. The product was purified by column chromatography

(*n*-pentane:EtOAc:MeOH = 100:2:0.5). The title compound **S2** (2.83 g, 7.22 mmol, 73%) was isolated as colorless oil.

$\mathbf{R_f}$ = 0.3 (*n*-pentane:EtOAc = 20:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 = (d, J = 2.5 Hz, 1H), 6.23 (d, J = 2.5 Hz, 1H), 5.44 (ddd, J = 5.0, 2.4, 1.2 Hz, 1H), 3.26 – 3.08 (m, 1H), 2.70 (td, J = 11.1, 4.8 Hz, 1H), 2.24 – 2.05 (m, 1H), 1.91 – 1.73 (m, 3H), 1.69 (d, J = 2.0 Hz, 3H), 1.39 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.0, 156.0, 148.2, 134.6, 119.40, 118.8 (q, J = 320.9 Hz), 113.9, 103.50, 100.8, 78.1, 44.6, 35.6, 31.7, 27.9, 27.4, 23.5, 18.6.

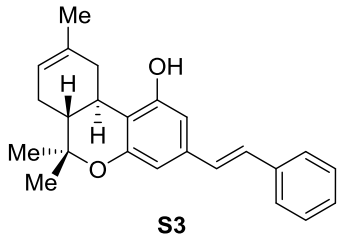
^{19}F NMR (282 MHz, $CDCl_3$) δ = –73.01.

MS (EI) m/z (relative intensity): 393 (13) [M+H], 392 (66), 377 (11), 349 (55), 324 (16), 311 (11), 310 (13), 309 (100), 216 (11), 191 (29), 176 (13), 91 (12), 69 (30).

HRMS (EI, m/z): calcd. for $C_{17}H_{19}O_5F_3S$ [M^+] 392.0900, found 392.0900.

IR (ATR, neat, cm^{-1}): 3546 (w), 3386 (w), 2977 (w), 2894 (w), 2846 (w), 1597 (m), 1498 (w), 1419 (m), 1387 (w), 1375 (w), 1334 (w), 1244 (m), 1207 (m), 1179 (m), 1137 (m), 1100 (m), 1085 (m), 1051 (w), 1035 (m), 1020 (w), 982 (s), 941 (w), 909 (w), 898 (w), 862 (m), 842 (m), 827 (m), 794 (m), 757 (w), 720 (w), 678 (w), 643 (w), 611 (m), 595 (m), 566 (w), 515 (m), 503 (m), 476 (w), 440 (w).

Synthesis of (6a*R*,10a*R*)-6,6,9-trimethyl-3-((*E*)-styryl)-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-1-ol (S3)



S3

Compound **S3** was synthesized using a modified literature procedure.[107] Potassium (*E*)-trifluoro(styryl)-borane (437 mg, 2.08 mmol, 1.6 equiv.) and (6a*R*,10a*R*)-1-hydroxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromen-3-yl trifluoromethanesulfonate (**S2**) (510 mg, 1.30 mmol, 1.0 equiv.), $Pd(OAc)_2$ (30 mg, 0.13 mmol, 0.10 equiv.), PCy_3 (73 mg, 0.26 mmol, 0.20 equiv.) and Cs_2CO_3 (1.27 g, 3.90 mmol, 3.0 equiv.) in THF:H_2O (10:1, 10 ml) was stirred at 80 °C for 22 h. The mixture was allowed to cool to room temperature and filtered through a plug of celite and washed with EtOAc. The filtrate was concentrated under reduced pressure and purified by column chromatography (*n*-pentane:EtOAc = 20:1).

(6a*R*,10a*R*)-6,6,9-trimethyl-3-((*E*)-styryl)-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol **S3** (399 mg, 1.15 mmol, 88%) was obtained as an off-white solid.

m.p. = 62–64 °C.

R_f = 0.5 (*n*-pentane:EtOAc = 9:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 – 7.44 (m, 2H), 7.41 – 7.20 (m, 3H), 7.02 (d, *J* = 16.3 Hz, 1H), 6.91 (d, *J* = 16.3 Hz, 1H), 6.63 (d, *J* = 1.7 Hz, 1H), 6.44 (d, *J* = 1.7 Hz, 1H), 5.52 – 5.34 (m, 1H), 4.93 (s, 1H), 3.31 – 3.14 (m, 1H), 2.76 (s, 1H), 1.98 – 1.78 (m, 3H), 1.72 (d, *J* = 1.7 Hz, 3H), 1.41 (s, 3H), 1.13 (s, 3H).

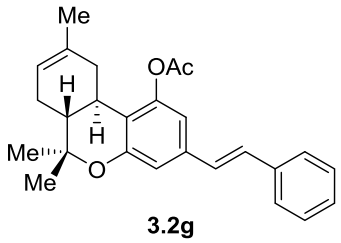
^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.4, 155.3, 137.4, 137.0, 134.8, 129.8, 128.8, 128.8, 128.2, 127.8, 127.7, 126.6, 123.9, 119.5, 113.3, 108.7, 105.7, 45.0, 36.0, 32.0, 28.0, 27.7, 23.6, 18.6.

MS (EI) m/z (relative intensity): 346 (49), 303 (13), 278 (13), 264 (19), 263 (100), 225 (20), 165 (11), 91 (15).

HRMS (EI, m/z): calcd. for $C_{24}H_{26}O_2$ [M^+] 346.1927, found 346.1930.

IR (ATR, neat, cm^{-1}): 3351 (w), 3025(w), 2971 (w), 2887 (w), 2840 (w), 1700 (w), 1614 (w), 1566 (w), 1542 (w), 1508 (w), 1496 (w), 1474 (w), 1447 (w), 1419 (w), 1383 (w), 1370 (w), 1360 (w), 1345 (w), 1325 (m), 1258 (m), 1182 (s), 1152 (m), 1128 (m), 1111 (m), 1081 (s), 1048 (w), 1031 (s), 1017 (m), 957 (s), 907 (m), 893 (m), 862 (m), 842 (m), 818 (m), 788 (m), 767 (w), 748 (s), 730 (m), 690 (s), 621 (m), 602 (m), 578 (m), 565 (m), 556 (m), 540 (m), 513 (m), 487 (m), 473 (m), 446 (m), 434 (m).

Synthesis of (6a*R*,10a*R*)-6,6,9-trimethyl-3-((*E*)-styryl)-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-yl acetate (3.2g)



3.2g

Acetic anhydride (250 µl, 2.5 mmol, 1.25 equiv.) was added dropwise to a stirring solution of **S3** (693 mg, 2.0 mmol, 1.0 equiv.), NEt_3 (350 µl, 2.50 mmol, 1.25 equiv.) and DMAP (25 mg, 0.02 mmol, 0.1 equiv.) in dichloromethane (20 ml). The reaction mixture was stirred for 3 h at ambient temperature. The crude reaction mixture was concentrated under reduced pressure and purified by column chromatography (*n*-pentane:EtOAc = 20:1). The title compound **3.2g** (639 mg, 1.65 mmol, 83%) was isolated as a colorless solid.

m.p. = 54–58 °C.

R_f = 0.3 (*n*-pentane:EtOAc = 20:1, UV).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.52 – 7.45 (m, 2H), 7.39 – 7.31 (m, 2H), 7.30 – 7.22 (m, 1H), 7.10 – 6.93 (m, 2H), 6.90 (d, *J* = 1.7 Hz, 1H), 6.76 (d, *J* = 1.8 Hz, 1H), 5.51 – 5.39 (m, 1H), 2.83 – 2.54 (m, 2H), 2.32 (s, 3H), 2.25 – 2.08 (m, 1H), 2.00 – 1.75 (m, 3H), 1.75 – 1.67 (m, 3H), 1.41 (s, 3H), 1.13 (s, 3H).

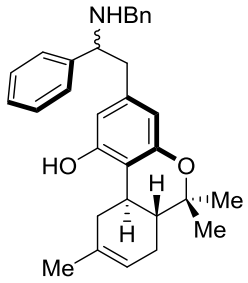
^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.9, 155.1, 150.3, 137.2, 137.1, 133.8, 129.3, 128.7, 127.7, 127.6, 126.6, 119.8, 118.5, 113.4, 112.5, 77.1, 44.6, 36.1, 32.1, 27.7, 27.4, 23.6, 21.3, 18.6.

MS (EI) *m/z* (relative intensity): 389 (29), 388 (100), 347 (10), 346 (40), 345 (14), 329 (15), 305 (30), 303 (32), 278 (22), 264 (20), 263 (100), 225 (26), 91 (12), 43 (22).

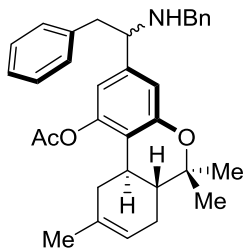
HRMS (EI, *m/z*): calcd. for $C_{26}H_{28}O_3$ [M^+] 388.2033, found 388.2032.

IR (ATR, neat, cm^{-1}): 3026 (w), 2973 (w), 2931 (w), 2891 (w), 2841 (w), 1764 (w), 1677 (w), 1617 (w), 1558 (w), 1496 (w), 1481 (w), 1447 (w), 1420 (m), 1384 (w), 1368 (m), 1338 (w), 1315 (w), 1259 (w), 1200 (s), 1179 (s), 1156 (m), 1127 (m), 1078 (m), 1033 (s), 1018 (m), 984 (w), 958 (m), 900 (m), 846 (m), 826 (w), 789 (w), 749 (m), 691 (s), 640 (w), 617 (w), 582 (w), 572 (w), 547 (w), 535 (w), 512 (w), 493 (w), 473 (w), 434 (w).

Synthesis of (6a*R*,10a*R*)-3-((*S*)-2-(benzylamino)-2-phenylethyl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-yl acetate (3.3la) and (6a*R*,10a*R*)-3-((*R*)-1-(benzylamino)-2-phenylethyl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-yl acetate (3.3lb)



3.3la



3.3lb

Compound **3.3l** was prepared following general procedure **B**. Purification by column chromatography (*n*-pentane:EtOAc = 20:1) yielded the title compound (156 mg, 0.34 mmol, 69%, **3.3la**:**3.3lb =** 68:32) as brownish viscous oil. The regioisomers were separated using *n*-heptane:*i*-PrOH = 30:1(+0.1% NEt_3) as eluent. The diastereomers were not separated.

3.3la:

d.r. **=** 60:40.

R_f = 0.53 (*n*-heptane:EtOAc) = 1:1, $KMnO_4$).

m.p. = 67–69 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (ddd, J = 7.4, 4.5, 1.8 Hz, 2H), 7.43 – 7.31 (m, 2H), 7.35 -7.26 (m, 1H), 7.26 – 7.11 (m, 3H), 7.00 (ddd, J = 17.9, 5.4, 1.7 Hz, 2H), 6.24 (d, J = 1.6 Hz, 1H, CH_{i1}), 6.20 (d, J = 1.6 Hz, 1H, CH_{i2}), 6.15 (d, J = 1.7 Hz, 1H, CH_{i1}), 6.06 (d, J = 1.7 Hz, 1H, CH_{i2}), 5.46 (d, J = 5.0 Hz, 1H), 3.86 (dd, J = 10.3, 3.8 Hz, 1H), 3.70 (dd, J = 13.7, 10.7 Hz, 1H), 3.47 – 3.33 (m, 2H), 2.91 – 2.60 (m, 3H), 2.21 – 2.11 (m, 1H), 1.96 – 1.77 (m, 2H), 1.75 (d, J = 6.1 Hz, 3H), 1.41 (d, J = 2.1 Hz, 3H), 1.34 – 1.22 (m, 1H), 1.16 (d, J = 27.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.5, 156.4, 155.6, 142.7, 142.4, 139.2, 138.9, 138.1, 137.8, 135.2, 135.1, 128.7, 128.5, 128.5, 128.3, 128.2, 128.0, 127.8, 127.6, 127.6, 127.2, 119.5, 119.3, 112.1, 112.1, 109.8, 109.0, 108.6, 76.8, 64.1, 63.1, 51.3, 50.8, 45.2, 45.0, 44.5, 44.4, 36.2, 35.9, 32.0, 31.9, 28.1, 27.8, 27.8, 23.8, 23.8, 18.8, 18.6.

MS (EI) m/z (relative intensity): 452 (1), 374 (1), 257 (1), 197 (15), 186 (88), 174 (6), 123 (3), 91 (100).

HRMS (ESI-TOF, m/z): calcd. for $C_{33}H_{38}NO_3$ $[M+H]^+$ 454.2746, found 454.2747.

IR (ATR, neat, cm^{-1}): 3273 (w), 3027 (w), 2971 (w), 2913 (w), 2841 (w), 2638 (w), 2324 (w), 1618 (w), 1578 (w), 1511 (w), 1495 (w), 1424 (m), 1382 (m), 1368 (m), 1358 (m), 1340 (m), 1280 (w), 1259 (m), 1182 (m), 1153 (w), 1129 (m), 1112 (m), 1085 (m), 1053 (w), 1035 (m), 1001 (m), 909 (m), 895 (w), 843 (m), 789 (m), 758 (m), 729 (m), 696 (s), 603 (m), 550 (w), 526 (w), 508 (w), 485 (w), 474 (w), 464 (w), 435 (w).

3.3lb:

d.r. = 54:46.

R_f = 0.44 (*n*-heptane:EtOAc) = 1:1, $KMnO_4$).

m.p. = 46–47 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.16 (m, 6H), 7.16 – 7.02 (m, 4H), 6.53 – 6.29 (m, 2H), 5.44 (d, J = 5.0 Hz, 1H), 3.71 (ddd, J = 13.7, 8.1, 3.9 Hz, 2H), 3.47 (d, J = 13.6 Hz, 1H), 3.32 – 3.21 (m, 1H), 2.95 (ddd, J = 13.1, 8.0, 4.9 Hz, 1H), 2.83 (ddd, J = 13.7, 9.2, 7.2 Hz, 1H), 2.73 (td, J = 10.7, 4.5 Hz, 1H), 2.15 (dt, J = 15.3, 8.8 Hz, 1H), 1.93 – 1.76 (m, 3H), 1.71 (s, 3H), 1.40 (d, J = 2.6 Hz, 3H), 1.28 (d, J = 15.7 Hz, 2H), 1.13 (d, J = 11.5 Hz, 3H), 1.01 – 0.79 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.8, 155.8, 155.1, 155.1, 143.3, 143.2, 140.2, 140.1, 139.0, 139.0, 135.0, 129.4, 129.4, 128.7, 128.6, 128.5, 128.4, 128.4, 128.1, 128.1, 127.2, 126.9,

126.9, 126.5, 126.5, 119.4, 112.5, 112.4, 109.6, 109.4, 106.1, 106.0, 76.8, 63.5, 63.3, 53.2, 51.5, 51.4, 45.0, 45.0, 44.8, 36.1, 36.1, 32.0, 28.1, 27.7, 23.7, 18.7, 18.6.

MS (EI) m/z (relative intensity): 362 (M-Bn, 100), 318 (1), 228 (4), 207 (4), 188 (4), 91 (83), 69 (11).

HRMS (EI, m/z): calcd. for $C_{33}H_{38}NO_3$ $[M+H]^+$ 454.2746, found 454.2747.

IR (ATR, neat, cm^{-1}): 3286 (w), 3060 (w), 3027 (w), 2970 (w), 2916 (w), 2889 (w), 2842 (w), 1619 (w), 1580 (m), 1495 (w), 1453 (m), 1426 (s), 1382 (m), 1358 (m), 1330 (m), 1263 (m), 1181 (m), 1153 (w), 1131 (w), 1112 (w), 1084 (m), 1051 (w), 1034 (m), 986 (w), 960 (w), 940 (w), 908 (m), 846 (m), 823 (m), 787 (w), 745 (m), 696 (s), 657 (m), 602 (w), 579 (m), 555 (w), 540 (w), 477 (m), 436 (w).

On-Off-Experiment

In a preheated dry Schlenk-tube, *E*-stilbene **3.2a** (90 mg, 0.5 mmol, 1.0 equiv.), PrPPTNO **1.2** (11 mg, 25 µmol, 0.05 equiv.) and biphenyl (39 mg, 0.25 mmol, 0.5 equiv.) were added under argon. The Schlenk tube was evacuated and purged with argon 3 times. Next, benzylamine (**3.1a**) (0.27 ml, 2.5 mmol, 5.0 equiv.) and dry acetonitrile (5.0 ml) were added under argon and the reaction mixture was stirred for 5 minutes at room temperature. The reaction mixture was irradiated for 2 h, then the light source was switched off for 2 consecutive hours. This process was repeated alternately for 16 h. A 0.1 ml Sample was taken every 2 hours from the reaction mixture, quenched with air and analyzed with calibrated GC. The final areas represent the average of 3 measurements per sample.

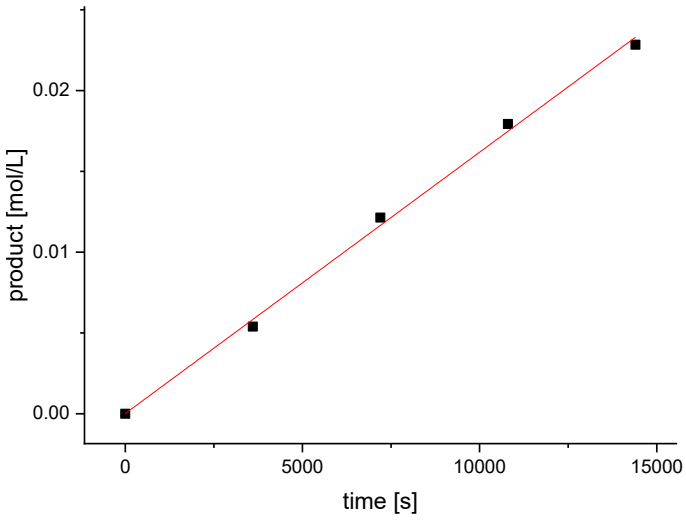
Kinetic Experiments

Kinetic experiments were performed under standard conditions on a 0.5 mmol-scale, using biphenyl as internal standard. Samples of 0.1 ml were taken in one-hour intervals under an argon atmosphere, quenched with air and analyzed by calibrated GC. Initial rates were determined within the first 4 hours at conversions below 20%.

Rate of formation of 3.3a from (*E*)-stilbene (3.2a):

Time [s]	Product **3.3a** [mol/l]
0	0
3600	0.00539
7200	0.01214
10800	0.01793
14400	0.02283

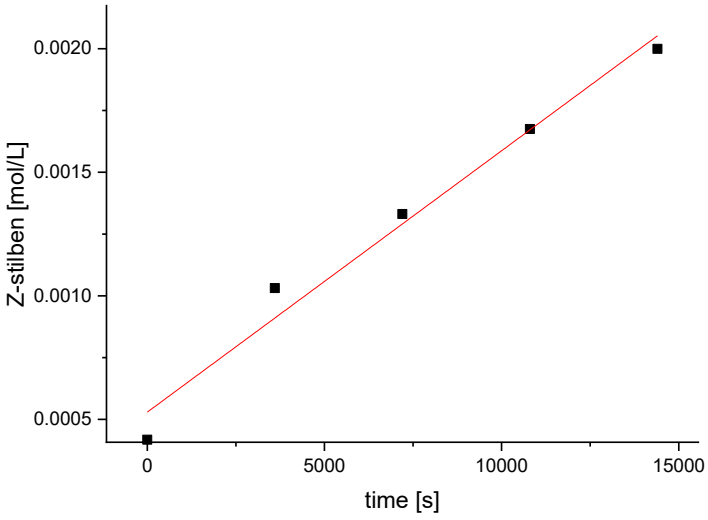
$$k_{E\rightarrow P} = 1.61698 \cdot 10^{-6}\mathrm{M} \cdot s^{-1}$$



Rate of isomerization from (*E*)-stilbene (3.2a) to (*Z*)-stilbene (3.2i):

time [s]	(*Z*)-stilbene (**3.2i**) [mol/l]
0	$4.17914E^{-4}$
3600	0.00103
7200	0.00133
10800	0.00167
14400	0.002

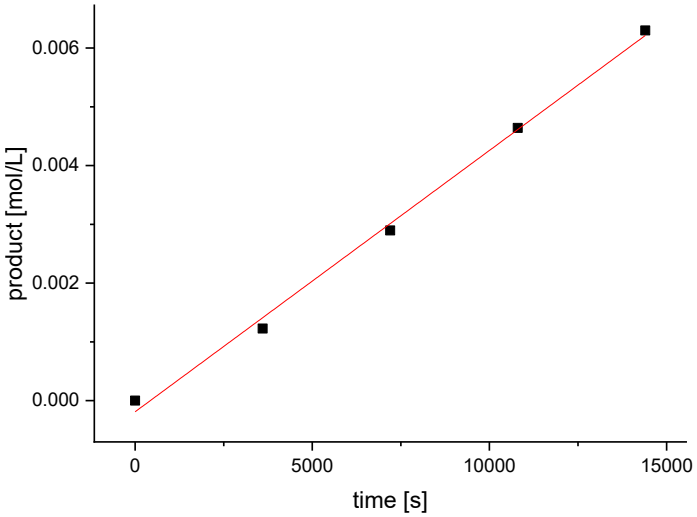
$$k_{E\rightarrow Z} = 1.05753 \cdot 10^{-7}\mathrm{M} \cdot s^{-1}$$



Rate of formation of 3.3a from (*Z*)-stilbene (3.2i):

time [s]	product **3.3a** [mol/l]
0	0
3600	0.00123
7200	0.0029
10800	0.00464
14400	0.0063

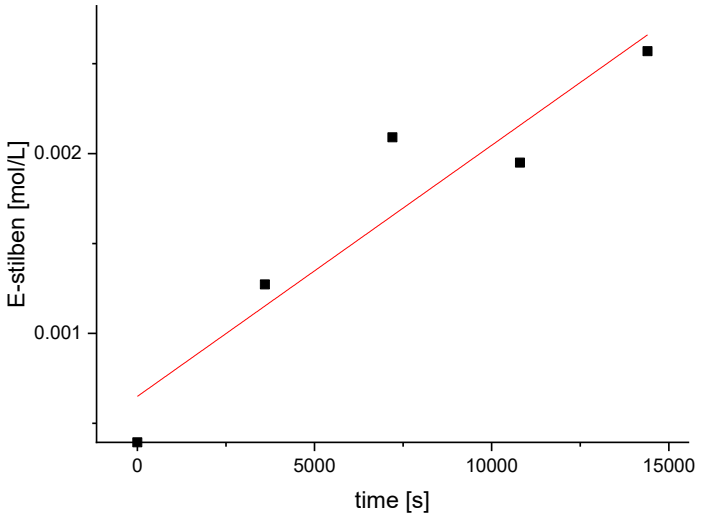
$$k_{Z\rightarrow 3.3a} = 4.44748 \cdot 10^{-7}\mathrm{M} \cdot s^{-1}$$



Rate of isomerization from (*Z*)-stilbene (3.2i) to (*E*)-stilbene (3.2a):

time [s]	(*E*)-stilbene (**3.2a**) [mol/l]
0	3.93857E-4
3600	0.00127
7200	0.00209
10800	0.00195
14400	0.00257

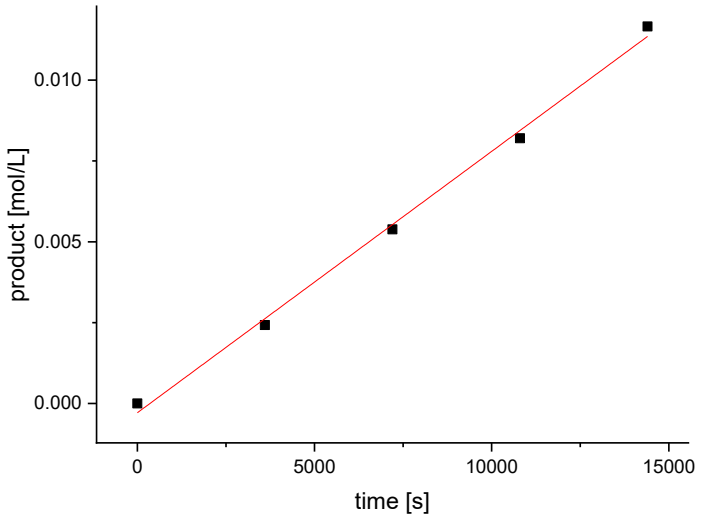
$$k_{Z\rightarrow E} = 1{,}39685 \cdot 10^{-7}\mathrm{M} \cdot s^{-1}$$



Rate of formation of 3.3g from 3.2c:

time [s]	product **3.3g** [mol/l]
0	0
3600	0.00242
7200	0.00538
10800	0.0082
14400	0.01166

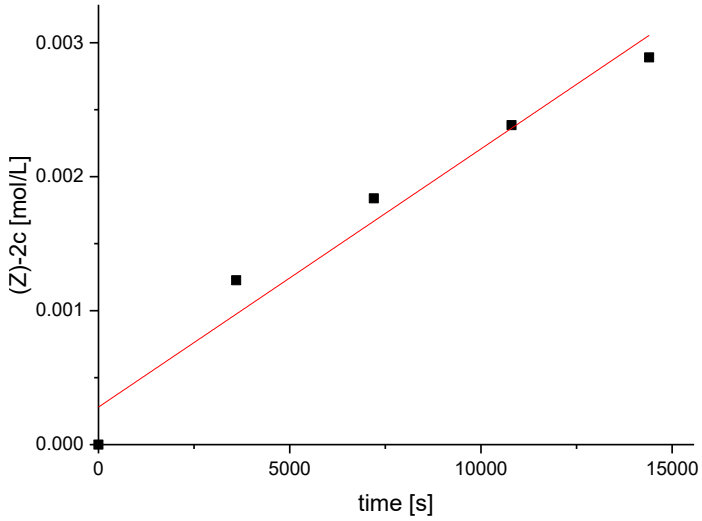
$$k_{E\rightarrow 3.3g} = 8.08077 \cdot 10^{-7}\mathrm{M} \cdot s^{-1}$$



Rate of isomerization from 3.2c to the (*Z*)-isomer of stilbeneethylester:

time [s]	(*Z*)-stilbeneethylester [mol/l]
0	0
3600	0.00123
7200	0.00184
10800	0.00238
14400	0.00289

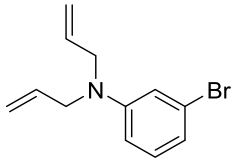
$$k_{E\rightarrow Z} = 1.92725 \cdot 10^{-7}\mathrm{M} \cdot s^{-1}$$



7.2.3 Experimental section to chapter 4

Fluorescence measurements and *in vitro* cell-tests were conducted in cooperation with the group of *Dr. Jan Lukas* from the translational neurodegeneration section of the Albrecht-Kossel institute in Rostock.

Synthesis of *N,N*-diallyl-3-bromoaniline (4.2):



4.2

4.2 was prepared following a modified literature procedure.[147] 3-bromoaniline **4.1** (98% purity, 33.0 µl, 291 µmol, 1.0 equiv.) and allyl bromide (98% purity, 80.0 µl, 901 µmol, 3.1 equiv.) were added to a suspension/homogeneous mixture of K_2CO_3 (84 mg, 610 µmol, 2.1 equiv.) in dry acetonitrile (1 ml) at room temperature. The mixture was stirred for 20 hours at 80 °C and allowed to cool to room temperature. The suspension was filtered through a pad of Celite, extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (*n*-pentane:EtOAc = 50:1) yielding the desired product **4.2** (69 mg, 274 µmol, 94%) as a colorless oil.

$\mathbf{R_f}$ = 0.71 (*n*-hexane:EtOAc = 20:1, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.04 (dd, *J* = 8.4, 7.7 Hz, 1H), 6.90 – 6.76 (m, 2H), 6.61 (ddd, *J* = 8.5, 2.5, 0.9 Hz, 1H), 5.84 (ddt, *J* = 16.7, 10.8, 4.8 Hz, 2H), 5.27 – 5.09 (m, 4H), 3.91 (dt, *J* = 4.8, 1.7 Hz, 4H).

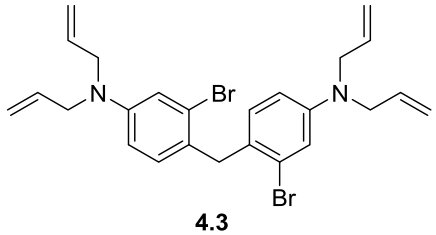
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 150.0, 133.3, 130.4, 123.4, 119.1, 116.4, 115.1, 110.9, 52.8.

MS (EI) *m/z* (relative intensity): 252 (25) [M^+], 251 (81), 224 (97), 210 (18), 184 (34), 157 (49), 145 (30), 130 (100), 82 (13), 77 (28).

HRMS (ESI-TOF, *m/z*): calculated for $C_{12}H_{14}N_1Br$ [M]$^+$: 251.0304, found: 251.0302.

IR (ATR, neat, cm^{-1}): 3081 (w), 2980 (w), 2862 (w), 1587 (s), 1487 (s), 1355 (w), 1232 (m), 981 (m), 755 (s).

Synthesis of 4,4'-methylenebis(*N,N*-diallyl-3-bromoaniline) (4.3):



4.3

Compound **4.3** was prepared following a literature procedure.[147] To a stirred solution of *N,N*-diallyl-3-bromoaniline **4.2** (52 mg, 204 µmol, 1.0 equiv.) in acetic acid (1 ml) was added a solution of formaldehyde (36% wt., 76.0 µl, 992 µmol, 5.0 equiv.) at room temperature. The mixture was heated at 80 °C for 2 hours and cooled to room temperature. Next, the reaction mixture was neutralized with a saturated solution of aqueous $NaHCO_3$ (10 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (*n*-pentane:EtOAc = 50:1) yielding the desired product **4.3** (45 mg, 87 µmol, 85%) as a light pale yellow oil.

$\mathbf{R_f}$ = 0.65 (*n*-hexane:EtOAc = 10:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.91 (d, J = 2.7 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.56 (dd, J = 8.6, 2.7 Hz, 2H), 5.83 (m, 4H), 5.17 (m, 8H), 3.97 (s, 2H), 3.88 (m, 8H).

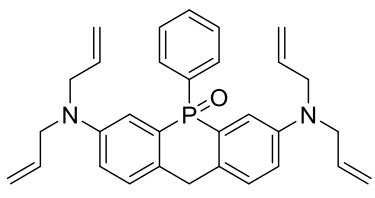
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 148.2, 133.6, 130.9, 125.7, 116.5, 116.1, 111.8, 52.9, 39.9.

MS (EI) *m*/*z* (relative intensity): 516 (100) [M^+], 435 (5), 419 (5), 273 (4), 266 (20), 245 (7), 218 (12), 198 (24), 165 (6), 109 (4).

HRMS (ESI-TOF, *m*/*z*): calculated for $C_{25}H_{28}N_2Br_2$ $[M]^+$: 514.0614, found: 514.0612.

IR (ATR, neat, cm^{-1}): 3078 (w), 2978 (w), 1602 (s), 1497 (s), 1385 (w), 1229 (m), 1019 (m), 915 (s), 803 (m).

Synthesis of 3,7-bis(diallylamino)-5-phenyl-10*H*-acridophosphine 5-oxide (4.4):



4.4

4.4 was prepared following a modified literature procedure.[148] To a stirred solution of 4,4'-methylenebis(*N,N*-diallyl-3-bromoaniline) (**4.3)** (203 mg, 394 µmol, 1.0 equiv.) in anhydrous THF (2 ml) was added a solution of *tert*-butyllithium in pentane (1.9 M, 510 µl, 969 µmol, 2.5 equiv.) dropwise at −78 °C. The mixture was stirred for further 10 min. at −78 °C and

warmed slowly to 0 °C and stirred for another 1 hour. The reaction mixture was then cooled again to −78 °C and dichlorophenylphosphine **4.4a** (97% purity, 81 µl, 581 µmol, 1.5 equiv.) was added dropwise to the reaction mixture over 1 minute. The resulting solution was warmed to room temperature and refluxed afterwards at 70 °C for 2 hours. After cooling to 0 °C, a 30% aqueous solution of hydrogen peroxide (0.3 ml) was added dropwise and the solution was further stirred at room temperature for 2 hours. The reaction mixture was then extracted using dichloromethane (3 x 15 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The formed residue was purified by column chromatography (dichloromethane:EtOAc = 6:1) yielding the desired product **4.4** (116 mg, 241 µmol, 61%) as a viscous yellow oil.

$\mathbf{R_f}$ = 0.41 (dichloromethane:EtOAc = 1:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53 – 7.40 (m, 4H), 7.39 – 7.24 (m, 3H), 7.16 (dd, *J* = 8.5, 5.9 Hz, 2H), 6.76 (dd, *J* = 8.5, 2.8 Hz, 2H), 5.93 – 5.67 (m, 4H), 5.21 – 5.05 (m, 8H), 4.05 – 3.77 (m, 9H), 3.64 (dd, *J* = 18.2, 3.6 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 147.4 (d, *J* = 12.7 Hz), 134.5 (d, *J* = 104.3 Hz), 133.5, 131.1 (d, *J* = 2.7 Hz), 130.8 (d, *J* = 10.5 Hz), 129.7 (d, *J* = 78.9 Hz), 129.0 (d, *J* = 12.4 Hz), 128.9 (d, *J* = 11.6 Hz), 128.3 (d, *J* = 12.1 Hz), 116.3, 115.6 (d, *J* = 2.6 Hz), 113.9 (d, *J* = 8.2 Hz), 52.8, 35.3 (d, *J* = 9.5 Hz).

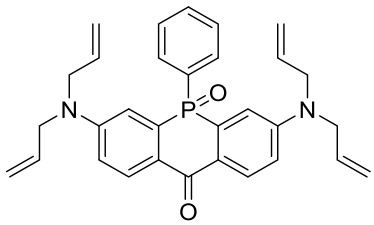
^{31}P-NMR (122 MHz, $CDCl_3$) δ = 13.86.

LCMS (ESI, *m/z*): 481 $[M+H]^+$.

HRMS (ESI-TOF, *m/z*): calculated for $C_{31}H_{34}N_2OP$ $[M+H]^+$: 481.2407, found: 481.2409.

IR (ATR, neat, cm^{-1}): 2923 (w), 1578 (s), 1387 (m), 1303 (m), 1230 (m), 1148 (m), 919 (m), 830 (m), 716 (m).

Synthesis of 3,7-bis(diallylamino)-5-phenyl-10*H*-acridophosphin-10-one 5-oxide (4.5):



4.5

Compound **4.5** was prepared following a literature procedure.[148] To a solution of 3,7-bis(diallylamino)-5-phenyl-10*H*-acridophosphine 5-oxide **4.4** (2.54 g, 5.28 mmol, 1.0 equiv.) in dichloromethane (50 ml) was added *p*-chloranil **4.4a** (3.90 g, 15.84 mmol, 3.0 equiv.) at

room temperature. The reaction mixture was stirred overnight open to air at room temperature and was then quenched with an aqueous solution of Na_2SO_3. Subsequently, the crude mixture was extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (dichloromethane:EtOAc = 7:1) yielding the desired product **4.5** (1.55 g, 3.13 mmol, 59%) as a yellow oil.

$\mathbf{R_f}$ = 0.48 (dichloromethane:EtOAc = 1:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.26 (dd, *J* = 9.0, 6.0 Hz, 2H), 7.64 – 7.50 (m, 2H), 7.41 – 7.23 (m, 3H), 7.13 (dd, *J* = 14.8, 2.7 Hz, 2H), 6.85 (dd, *J* = 9.0, 2.6 Hz, 2H), 5.77 (m, 4H), 5.29 – 4.99 (m, 8H), 3.99 (m, 8H).

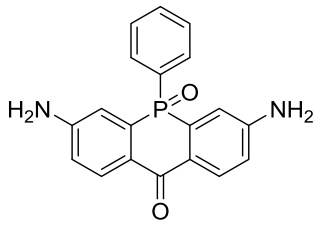
^{13}C-NMR (75 MHz, $CDCl_3$) δ = 180.2 (d, *J* = 8.7 Hz), 151.5 (d, *J* = 12.7 Hz), 134.9 (d, *J* = 106.8 Hz), 134.7 (d, *J* = 97.2 Hz), 132.2, 131.4 (d, *J* = 10.0 Hz), 130.7 (d, *J* = 10.2 Hz), 128.5 (d, *J* = 12.4 Hz), 124.9 (d, *J* = 6.7 Hz), 117.1, 115.2 (d, *J* = 2.3 Hz), 112.6 (d, *J* = 7.9 Hz), 52.7.

^{31}P-NMR (122 MHz, $CDCl_3$) δ = 6.24.

HRMS (ESI-TOF, *m/z*): calculated for $C_{31}H_{32}N_2O_2P$ $[M+H]^+$: 495.2201, found: 495.2209.

IR (ATR, neat, cm^{-1}): 3313 (m), 2927 (w), 1475 (m), 1314 (m), 1167 (m), 1097 (s), 1018 (m), 813 (m), 654 (m).

Synthesis of 3,7-diamino-5-phenyl-10*H*-acridophosphin-10-one 5-oxide (4.6):



4.6

Compound **4.6** was prepared following a literature procedure.[148] To a solution of 3,7-bis(diallylamino)-5-phenyl-10*H*-acridophosphine 5-oxide **4.5** (477 mg, 965 µmol, 1.0 equiv.) in 1,2-dichloroethane (18 ml) was added Tetrakis(triphenylphosphane)palladium (145 mg, 125 µmol, 0.13 equiv.) and 1,3-dimethylbarbituric acid (699 mg, 4.28 mmol, 4.4 equiv.) at room temperature. The reaction mixture was stirred at 80 °C for 24 hours and was then cooled down to room temperature. Subsequently, the crude mixture was filtered through Celite and the solvent was removed under reduced pressure. The resulting residue was

purified by flash column chromatography (dichloromethane:MeOH = 20:1) yielding the desired product **4.6** (281 mg, 841 µmol, 87%) as a yellow solid.

$\mathbf{R_f}$ = 0.23 (dichloromethane:methanol = 12:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, CD_3OD) δ = 8.26 (dd, *J* = 9.0, 6.0 Hz, 2H), 7.64 – 7.50 (m, 2H), 7.41 – 7.23 (m, 3H), 7.13 (dd, *J* = 14.8, 2.7 Hz, 2H), 6.85 (dd, *J* = 9.0, 2.6 Hz, 2H), 5.77 (ddt, *J* = 17.0, 9.9, 4.8 Hz, 4H), 5.29 – 4.99 (m, 8H), 3.99 (m, 8H).

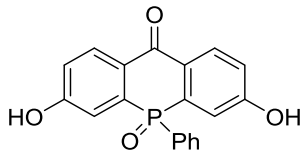
^{13}C-NMR (101 MHz, CD_3OD) δ = 181.3 (d, *J* = 8.9 Hz), 154.8 (d, *J* = 13.1 Hz), 135.1 (d, *J* = 98.0 Hz), 134.4 (d, *J* = 108.9 Hz), 133.3 (d, *J* = 2.9 Hz), 132.6 (d, *J* = 10.3 Hz), 131.6 (d, *J* = 10.6 Hz), 129.9 (d, *J* = 12.8 Hz), 125.5 (d, *J* = 7.0 Hz), 118.5 (d, *J* = 2.3 Hz), 115.2 (d, *J* = 7.3 Hz).

^{31}P-NMR (162 MHz, CD_3OD) δ = 8.78.

HRMS (ESI-TOF, *m/z*): calculated for $C_{19}H_{16}N_2O_2P$ $[M+H]^+$: 335.0949, found: 335.0949.

IR (ATR, neat, cm^{-1}): 3349 (w), 3207 (w), 1621 (w), 1580 (m), 1435 (w), 1302 (m), 1143 (m), 913 (w).

Synthesis of 3.7-Dihydroxy-5-phenylacridophosphin-10(5*H*)-on-5-oxid (4.7)



4.7

Compound **4.7** was prepared following a literature procedure.[148] To a solution of **4.6** (450 mg, 1.35 mmol, 1.0 equiv.) in 96% H_2SO_4 (17 ml) was added sodium nitrite (326 mg, 4.58 mmol, 3.4 equiv.) at 0 °C under air. after stirring for 3 hours at room temperature, the mixture was slowly poured to ice and stirred at 110 °C for 1 hour. The resulting precipitate was filtrated, washed with distilled water and dispersed in methanol. the filtrate was dried under vacuum and purified by column chromatography (dichloromethane:MeOH = 100:3 → 100:5) yielding product **4.7** (303 mg, 901 µmol, 67%) as a yellow solid.

$\mathbf{R_f}$ = 0.42 (dichloromethane:methanol = 12:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, CD_3OD) δ = 7.15 (ddd, 2H, *J* = 8.6, 2.5, 0.8 Hz), 7.21 (ddd, 2H, *J* = 14.2, 2.5, 0.4 Hz), 7.40 – 7.63 (m, 5H), 8.31 (dd, 1H, *J* = 8.6, 0.4 Hz), 8.33 (dd, 1H, *J* = 8.8, 0.3 Hz).

^{13}C-NMR (101 MHz, CD_3OD) δ = 117.6 (d, *J* = 6.8 Hz), 121.5 (d, *J* = 2.1 Hz), 129.1 (d, *J* = 6.7 Hz), 130.2 (d, *J* = 12.8 Hz), 131.7 (d, *J* = 10.7 Hz), 133.3 (d, *J* = 10.3 Hz),

133.6 (d, $J = 109.9$ Hz), 133.7 (d, $J = 2.7$ Hz), 135.6 (d, $J = 98.0$ Hz), 163.9 (d, $J = 13.8$ Hz), 181.4 (d, $J = 8.9$ Hz).

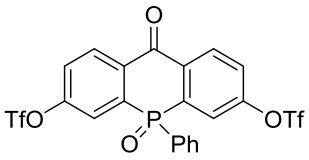
^{31}P-NMR (162 MHz, CD_3OD) $\delta = 7.3$.

LCMS (ESI, *m/z*): 337 $[M+H]^+$.

HRMS (ESI-TOF, *m/z*): calculated for $C_{19}H_{14}O_4P$ $[M+H]^+$ 337.0630, found 337.0633.

IR (ATR, neat, cm^{-1}): 3053 (br. w), 2683 (w), 2292 (w), 1586 (m), 1565 (m), 1292 (m), 1134 (m), 909 (w), 881 (w).

Synthesis of 5-oxido-10-oxo-5-phenyl-10*H*-acridophosphine-3,7-diyl bis(trifluoromethanesulfonate) (4.8)



4.8

Compound **4.8** was synthesized according to a literature procedure.[142] A solution of **4.7** (253 mg, 752 µmol, 1.0 equiv.)**,** phenyl triflimide (823 mg, 2.3 mmol, 3.0 equiv.) and DIPEA (770 µl, 4.5 mmol, 6.0 equiv.) in anhydrous DMF (5 ml) was stirred at room temperature overnight. The reaction was diluted with H_2O (15 ml) and extracted with EtOAc (3x 20 ml), dried over sodium sulfate and dried under vacuum. The resulted residue was purified by column chromatography (*n*-pentane:EtOAc = 7:1) which yielded desired product **4.8** (414 mg, 690 µmol, 92%) as a white solid.

$\mathbf{R_f} = 0.26$ (dichloromethane:methanol = 200:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.59 (m, 5H), 7.67 (ddd, 2H, $J = 8.8, 2.5, 0.6$ Hz), 7.92 (dd, 2H, $J = 13.0, 2.5$ Hz), 8.56 (ddd, 2H, $J = 8.8, 5.2, 0.4$ Hz).

^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 118.7$ (q, $J = 320$ Hz), 124.0 (d, $J = 7.4$ Hz), 126.2 (d, $J = 1.4$ Hz), 129.5 (d, $J = 13.0$ Hz), 130.8 (d, $J = 10.6$ Hz), 130.9 (d, $J = 111.2$ Hz), 132.8 (d, $J = 9.4$ Hz), 133.2 (d, $J = 2.8$ Hz), 134.9 (d, $J = 5.5$ Hz), 136.5 (d, $J = 96.1$ Hz), 153.1 (d, $J = 15.1$ Hz), 180.1 (d, $J = 8.9$ Hz).

^{31}P NMR (162 MHz, $CDCl_3$) $\delta = 2.4$.

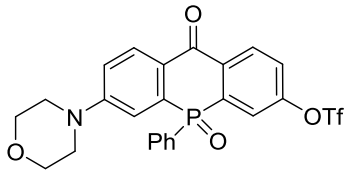
^{19}F NMR (376 MHz, $CDCl_3$) $\delta = -72.6$.

LCMS (ESI, *m/z*): 601 $[M+H]^+$.

HRMS (ESI-TOF, *m/z*): calculated for $C_{21}H_{11}F_6O_8PS_2$ $[M]^+$ 600.9615, found 600.9612.

IR (ATR, neat, cm^{-1}): 3105 (w), 2924 (w), 1672 (w), 1589 (w), 1424 (s), 1204 (s), 1134 (s), 926 (m), 804 (m), 717 (m).

Synthesis of 7-morpholino-5-oxido-10-oxo-5-phenyl-10*H*-acridophosphin-3-yl trifluoromethanesulfonate (4.9)



4.9

Compound **4.9** was synthesized according to a modified literature procedure.[142] Morpholine (10 mg, 113 µmol, 2.0 equiv.) was diluted in anhydrous DMSO (1 ml). The resulting solution was added to a mixture of **4.8** in DMSO (1 ml) at room temperature. Next, the reaction mixture was heated to 90 °C overnight and cooled afterwards to room temperature. The reaction mixture was diluted with H_2O (2 ml) and extracted with EtOAc (3 x 5 ml), dried over sodium sulfate and dried under reduced pressure. the crude residue was purified by column chromatography (dichloromethane:EtOAc = 1:1) yielding desired **4.9** (25 mg, 47 µmol, 82%) as a solid.

$\mathbf{R_f}$ = 0.34 (dichloromethane/EtOAc = 1:1, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.33 – 3.48 (m, 4H), 3.77 – 3.87 (m, 4H), 7.12 (dd, 1H, *J* = 9.1, 2.7 Hz), 7.32 (dd, 1H, *J* = 15.3, 2.8 Hz), 7.36 – 7.60 (m, 6H), 7.88 (dd, 1H, *J* = 12.7, 2.6 Hz), 8.35 (dd, 1H, *J* = 9.0, 6.0 Hz), 8.52 (ddd, 1H, *J* = 8.8, 5.2, 0.4 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 46.9, 66.4, 114.2 (d, *J* = 8.2 Hz), 117.1 (d, *J* = 2.1 Hz), 123.4 (d, *J* = 6.4 Hz), 125.4 (d, *J* = 6.9 Hz), 125.5 (d, *J* = 1.8 Hz), 129.2 (d, *J* = 12.7 Hz), 130.7 (d, *J* = 10.6 Hz), 132.0, 132.1 (d, *J* = 1.5 Hz), 132.3, 132.5 (d, *J* = 2.8 Hz), 133.5, 133.9, 135.2, 135.9 (d, *J* = 6.0 Hz), 136.2, 137.5, 153.1 (d, *J* = 121.4 Hz), 153.3 (d, *J* = 119.5 Hz), 179.7 (d, *J* = 8.3 Hz).

^{31}P NMR (122 MHz, $CDCl_3$) δ = 4.0.

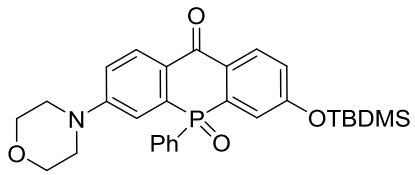
^{19}F NMR (282 MHz, $CDCl_3$) δ = –72.7.

LCMS (ESI, *m/z*): 538 $[M+H]^+$.

HRMS (ESI-TOF, *m/z*): calculated for $C_{24}H_{20}NO_6F_3PS$ $[M+H]^+$ 538.0701, found 538.0704.

IR (ATR, neat, cm^{-1}): 2962 (w), 1586 (w), 1258 (w), 1088 (m), 1021 (m), 796 (s).

Synthesis of 3-((tert-butyldimethylsilyl)oxy)-7-morpholino-5-phenyl-10*H*-acridophosphin-10-one 5-oxide (4.10)



4.10

Compound **4.10** was synthesized according to a modified literature procedure.[142] A solution of **4.9** (54 mg, 12 µmol, 1.0 equiv.) in dioxane (3 ml) was treated with a solution of tetrabutyl ammonium hydroxide (40% w/w in H_2O) (130 mg, 201 µmol, 2.0 equiv.). The reaction mixture was stirred at room temperature for 2.5 hours. the resulting mixture was then dried under reduced pressure and re-dissolved in dichloromethane (3 ml). After cooling the solution to 0 °C, imidazole (35 mg, 502 µmol, 5.0 equiv.) was added to the solution followed by TBDMSCl (77 mg, 502 µmol, 5.0 equiv.). After stirring the solution for 4 hours at room temperature, the reaction mixture was diluted with DCM (5 ml) and washed with H_2O (5 ml). The organic fractions were dried over sodium sulfate and dried under reduced pressure. the crude residue was purified by column chromatography (dichloromethane:EtOAc = 2:1) which afforded desired product **4.10** (51 mg, 99 µmol, 98%) as a white solid.

$\mathbf{R_f}$ = 0.21 (dichloromethane/EtOAc = 1:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.18 (d, 6H, J = 3.8 Hz), 0.93 (s, 9H), 3.35 (dd, 4H, J = 5.9, 3.8 Hz), 3.80 (t, 4H, J = 4.7 Hz), 7.05 – 7.11 (m, 2H), 7.27 – 7.45 (m, 5H), 7.50 – 7.62 (m, 2H), 8.29 – 8.38 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = –4.3 (d, J = 7.3 Hz), 18.3, 25.6, 47.0, 66.4, 114.3 (d, J = 7.8 Hz), 117.0 (d, J = 1.9 Hz), 121.7 (d, J = 6.3 Hz), 124.2, (d, J = 2.2 Hz), 126.4 (d, J = 6.8 Hz), 128.8 (d, J = 12.8 Hz), 129.8 (d, J = 6.3 Hz), 130.6 (d, J = 10.5 Hz), 131.6 (d, J = 10.0 Hz), 131.8 (d, J = 4.9 Hz), 131.9 (d, J = 2.7 Hz), 133.7 (d, J = 83.9 Hz), 134.7 (d, J = 8.8 Hz), 135.8 (d, J = 31.9 Hz), 153.6 (d, J = 12.4 Hz), 160.3 (d, J = 14.0 Hz), 180.6 (d, J = 9.1 Hz).

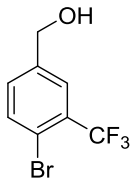
^{31}P NMR (122 MHz, $CDCl_3$) δ = 4.8.

LCMS (ESI, *m/z*): 520 $[M+H]^+$.

HRMS (ESI-TOF, *m/z*): calculated for $C_{29}H_{34}NO_4PSi$ $[M+H]^+$ 520.2073, found 520.2078.

IR (ATR, neat, cm^{-1}): 2928 (w), 1642 (w), 1581 (w), 1237 (w), 951 (w), 826 (w).

Synthesis of (4-bromo-3-(trifluoromethyl)phenyl)methanol (4.12)



4.12

Compound **4.12** was prepared following a modified literature procedure.[197] A solution of 4-bromo-3-(trifluoromethyl)benzoic acid **4.11** (2.0 g, 7.43 mmol, 1.0 equiv.) in dry diethyl ether (15 ml) was added dropwise to a suspension of $LiAlH_4$ (97% purity, 597 mg, 15.3 mmol, 2.05 equiv.) in dry diethyl ether (10 ml) at 0 °C. The reaction mixture was stirred at 48 °C for 3 hours and was allowed to cool down to room temperature. Subsequently, the reaction was quenched with water (15 ml) at 0 °C and acidified with 0.5 M aqueous HCl (10 ml). The crude mixture was extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (*n*-pentane:EtOAc = 5:1) yielding the desired product **4.12** (1.692 g, 6.39 mmol, 89%) as a sticky pale solid.

$\mathbf{R_f}$ = 0.38 (SiO_2, *n*-pentane:EtOAc = 3:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75 – 7.60 (m, 1H), 7.36 (ddq, J = 8.2, 2.0, 0.8 Hz, 1H), 4.69 (s, 1H), 2.18 (s, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 140.5, 135.1, 131.2, 130.3 (q, J = 31.2 Hz), 126.2 (q, J = 5.4 Hz), 123.0 (q, J = 273.4 Hz), 118.9 (q, J = 1.6 Hz), 64.0.

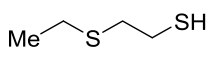
^{19}F-NMR (282 MHz, $CDCl_3$) δ = –62.7.

MS (EI) *m*/*z* (relative intensity): 254 (42) [M^+], 237 (14), 225 (8), 207 (20), 175 (21), 155 (100), 127 (72), 107 (6), 95 (7), 77 (26).

HRMS (ESI-TOF, *m*/*z*): calculated for $C_8H_6O_1Br_1F_3$ [M^+] 253.9549, found: 253.9547.

IR (ATR, neat, cm^{-1}): 3313 (m), 2927 (w), 1475 (m), 1314 (m), 1167 (m), 1097 (s), 1018 (m), 813 (m), 654 (m).

Synthesis of 2-(ethylthio)ethane-1-thiol (4.15):



4.15

Compound **4.15** was prepared following a literature procedure.[152] The mixture of dithioethyleneglycol **4.14** (22.1 ml, 250 mmol, 5.0 equiv.) and powdered sodium hydroxide

(3.0 g, 75 mmol, 1.5 equiv.) was refluxed in THF (200 ml) under inert atmosphere for 30 min. A solution of ethyl iodide (4.1 ml, 50 mmol, 1.0 equiv.) in THF (50 ml) was added dropwise over the course of 1 h and the reaction mixture was refluxed for another 1 h. The residue obtained by solvent evaporation was poured into 50% aqueous solution of NH_4Cl (40 ml) and the product was extracted with CH_2Cl_2 (3 x 30 ml). The combined organic phase was washed with brine (2 x 25 ml), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by vacuum distillation to give the title product **4.15** (3.8 g, 31 mmol, 62%) as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.23 (t, J = 7.4 Hz, 3H), 1.68 – 1.74 (m, 1H), 2.53 (q, J = 7.4 Hz, 2H), 2.65 – 2.77 (m, 4H).

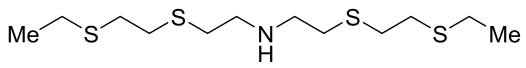
^{13}C NMR (75 MHz, $CDCl_3$) δ = 35.6, 25.7, 24.6, 14.7.

MS (EI) *m/z* (relative intensity): 122 (99) [M^+], 89 (7), 75 (100), 61 (53), 47 (43), 35 (6), 27 (17).

HRMS (EI): calcd. for $C_4H_{10}S_2$ [M]$^+$ 122.0218, found 122.0217.

IR (ATR, neat, cm^{-1}): 2965 (m), 2923 (m), 2546 (w), 1450 (m), 1426 (m), 1374 (w), 1260 (s), 1208 (s), 1139 (w), 969 (m), 697 (s).

Synthesis of bis(2-((2-(ethylthio)ethyl)thio)ethyl)amine (4.16):



4.16

Compound **4.16** was prepared following a modified literature procedure.[140] Cs_2CO_3 (150 mg, 455 µmol, 3.0 equiv.) was added to a solution of 3-thiapentan-1-thiol **4.15** (50 mg, 409 µmol, 2.7 equiv.) in MeCN (1 ml). Next, a mixture of bis(2-chloroethyl)amine hydrochloride (27 mg, 152 µmol, 1.0 equiv.) in MeCN (1ml) was dissolved at 85 °C and added dropwise to the first solution of **4.15**. The reaction mixture was allowed to stir overnight. Afterwards, the reaction mixture was filtered and dried under vacuum. the residue was then extracted with DCM (3x3ml) and water (5.0 ml), dried over sodium sulfate and dried under vacuum. Purification of the residue via column chromatography (dichloromethane:MeOH = 50:1) generated desired product **4.16** (42 mg, 134 µmol, 88%).

$\mathbf{R_f}$ = 0.22 (dichlormethane:MeOH = 40:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.22 (t, J = 7.4 Hz, 6H), 1.85 (bs, 1H), 2.53 (q, J = 7.4 Hz, 4H), 2.65 – 2.72 (m, 12H), 2.77 – 2.82 (m, 4H).

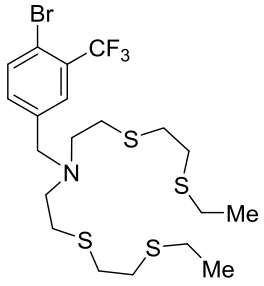
^{13}C NMR (75 MHz, $CDCl_3$) δ = 48.2, 32.4, 31.9, 31.6, 25.9, 14.7.

MS (EI) *m/z* (relative intensity): 252 (24), 178 (19), 121 (11), 89 (100), 61 (14).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{12}H_{27}NS_4$ $[M+H]^+$ 314.1104, found 314.1100.

IR (ATR, neat, cm^{-1}): 2959 (m), 2919 (s), 2821 (w), 1450 (s), 1423 (s), 1373 (w), 1259 (s), 1199 (s), 1122 (s), 1053 (w), 970 (w), 715 (s), 650 (m).

Synthesis of *N*-(4-Bromo-3-(trifluormethyl)benzyl)-2-((2-(ethylthio)ethyl)thio)-*N*-(2-((2-(ethylthio)-ethyl)thio)ethyl)ethanamin (4.18)



4.18

NaH (66 mg, 1.65 mmol, 2.1 equiv.) was added portionswise over 5 minutes to a solution of (4-bromo-3-(trifluoromethyl)phenyl)methanol (**4.12**) (201 mg, 788 µmol, 1.0 equiv.) in THF (4.5 ml) at 0 °C. The reaction mixture was allowed to stir for 15 minutes at 0 °C . Then, TsCl (157 mg, 824 µmol, 1.05 equiv.) was added and the reaction was stirred for 1.5 h at room temperature. bis(2-((2-(ethylthio)ethyl)thio)ethyl)amine (**4.16)** (545 mg, 1.74 mmol, 2.2 equiv.) was dissolved in dry THF (3 ml) and added to the first solution of **4.12**. The mixture was allowed to stir overnight at room temperature. Subsequently, the reaction mixture was extracted with EtOAc (3 x 20 ml), H_2O and brine, dried over sodium sulfate and concentrated under vacuum. Purification of the residue via column chromatography (*n*-pentane:acetone:EtOAc = 200:3:3) afforded desired product **4.18** (206 mg, 374 µmol, 47%) as a colorless oil.

$\mathbf{R_f}$ = 0.42 (*n*-pentane:acetone:EtOAc = 50:2:2, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.24 (t, 6H, J = 7.4 Hz), 2.54 (q, 4H, J = 7.4 Hz), 2.68 (s, 16H), 3.63 (s, 2H), 7.41 (d, 1H, J = 8.3 Hz), 7.64 (d, 1H, J = 8.3 Hz), 7.70 (d, 1H, J = 1.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.9, 26.2, 30.3, 31.9, 32.6, 53.9, 57.7, 118.4 (d, J = 1.6 Hz), 123.1 (d, J = 274 Hz), 127.9 (q, J = 6.2 Hz), 130.1 (d, J = 31.3 Hz), 133.1, 135.0, 139.5.

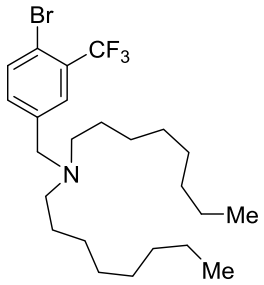
^{19}F NMR (282 MHz, $CDCl_3$) δ = –62.5.

MS (LCMS) *m*/*z* (relative intensity): 552 $[M+H]^+$.

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{20}H_{32}BrF_3NS_4$ $[M+H]^+$ 550.0553, found 550.0555.

IR (ATR, neat, cm^{-1}): 2962 (w), 2819 (w), 1451 (w), 1314 (m), 1259 (w), 1125 (s), 1022 (w), 826 (w).

Synthesis of *N*-(4-Bromo-3-(trifluormethyl)benzyl)-*N*-octyloctan-1-amin (4.19)



4.19

NaH (67 mg, 1.68 mmol, 2.15 equiv.) was added portionswise over 5 minutes to a solution of (4-bromo-3-(trifluoromethyl)phenyl)methanol (**4.12**) (199 mg, 780 µmol, 1.0 equiv.) in THF (4.5 ml) at 0 °C. The reaction mixture was allowed to stir for 15 minutes at 0 °C . Then, TsCl (160 mg, 823 µmol) was added and the reaction was stirred for 1.5 h at room temperature. di-octylamine (**4.17)** (741 µl, 2.35 mmol, 3.0 equiv.) was dissolved in dry THF (3 ml) and added to the first solution of **4.12**. The mixture was allowed to stir overnight at room temperature. Subsequently, the reaction mixture was extracted with EtOAc (3 x 20 ml), H_2O and brine, dried over sodium sulfate and dried under vacuum. Purification of the residue via column chromatography (*n*-pentane:EtOAc = 50:1) afforded desired product **4.19** (299 mg, 624 µmol, 80%) as a colorless oil.

R_f = 0.81 (*n*-pentane:EtOAc = 5:1, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.89 (dd, 6H, J = 6.5, 6.0 Hz), 1.26 (s, 20H), 1.44 (m, 4H), 2.39 (m, 4H), 3.56 (m, 2H), 7.32 – 7.44 (m, 1H), 7.45 – 7.72 (m, 2H).

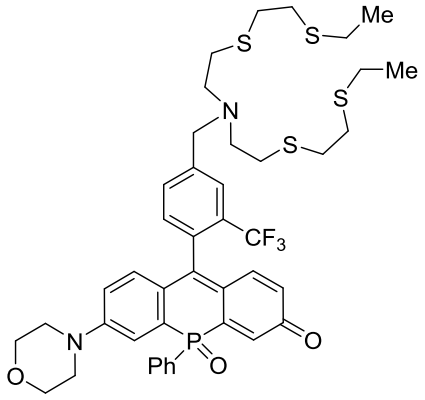
^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.2, 22.8, 27.2, 27.6, 29.5, 29.7, 32.0, 54.1, 58.0, 117.7 (d, J = 1.7 Hz), 123.6 (q, J = 3.8 Hz), 125.5 (q, J = 3.8 Hz), 128.0 (q, J = 5.5 Hz), 128.6, 133.1, 134.7, 141.0.

^{19}F NMR (282 MHz, $CDCl_3$) $\delta = -62.5$.

MS (LCMS), *m*/*z* (relative intensity): 478 $[M]^+$.

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{24}H_{40}F_3NBr$ $[M+H]^+$ 478.2296, found 478.2289.

Synthesis of 10-(4-((bis(2-((2-(ethylthio)ethyl)thio)ethyl)amino)methyl)-2-(trifluoromethyl)phenyl)-7-morpholino-5-phenyl-3*H*-acridophosphin-3-one 5-oxide (4.20)



CPF1
4.20

Compound **4.20** was synthesized according to a modified literature procedure.[142] Polythioether **4.18** (106 mg, 192 µmol, 2.0 equiv.) was dissolved in 1.2 ml of dry THF and cooled to −78 °C. A 1.9 M solution of *tert*-butyl lithium (110 µl, 202 µmol, 2.1 equiv.) was added dropwise over 5 minutes. The resulting solution was stirred over 1 hour at −78 °C and 10 minutes at room temperature. After cooling the reaction mixture back to −78 °C, a solution of phosphoacridone **4.10** (50 mg, 96 µmol, 1.0 equiv.) in 3 ml THF was added dropwise over 10 minutes and the solution was allowed to stirr for 15 minutes at −78 °C. The reaction mixture was allowed to warm to room temperature and was stirred for further 1.5 hours. A solution of 6M HCl (5 ml) was added at 0 °C to the above solution and stirred at room temperature for 1 hour. Next, the dark solution was quenched with a solution of 15% w/w sodium hydroxide and extracted with dichloromethane (3x20 ml), dried over sodium sulfate and concentrated under reduced pressure. The residue was then purified by column chromatography (dichloromethane:MeOH = 100:2) which afforded desired **4.20** (50 mg, 58 µmol, 60%) as a blue solid.

$\mathbf{R_f} = 0.3$ (dichloromethane:MeOH = 9:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, CD_2Cl_2) δ = 1.23 (t, 6H, *J* = 7.3 Hz), 2.55 (q, 4H, *J* = 7.4 Hz), 2.72 (s, 10H), 2.74 – 2.88 (m, 6H), 3.35 (br s, 4H), 3.75 (t, 4H, *J* = 4.9 Hz), 3.83 (s, 2H), 6.20 (d, 1H, *J* = 9.9 Hz), 6.63 – 6.94 (m, 3H), 7.10 (dd, 1H, *J* = 16.9, 1.1 Hz), 7.28 (d, 1H, *J* = 7.7 Hz),

7.37 – 7.58 (m, 4H), 7.64 (dd, 1H, J = 12.8, 1.5 Hz), 7.66 (d, 1H, J = 12.6 Hz), 7.77 (d, 1H, J = 7.2 Hz), 7.94 (s, 1H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ = 15.1, 26.3, 30.5, 32.2, 32.9, 47.0, 54.4, 58.1, 66.6, 116.1 (m), 117.2 (m), 125.2 (m), 126.9 (m), 128.0 (m), 129.2 (d, J = 12.2 Hz), 130.5 (d, J = 10.0 Hz), 132.2 (m), 132.5, 132.7 (q, J = 4.8 Hz), 134.0 (m), 134.4 (m), 135.4 (m), 135.7 (m), 139.7 (m), 142.2 (m), 149.1 (m), 152.1 (m), 152.3 (m), 183.9 (m).

^{31}P NMR (122 MHz, CD_2Cl_2) δ = 7.1.

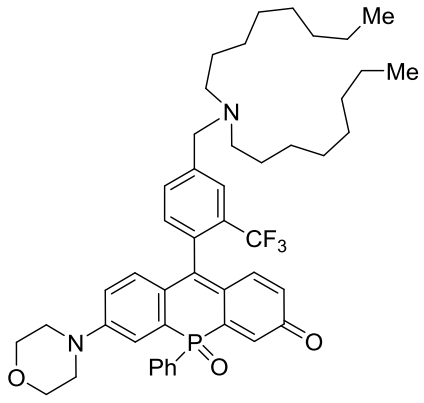
^{19}F NMR (282 MHz, CD_2Cl_2) δ = –59.3

LCMS (ESI, *m/z*): 859 $[M]^+$.

HRMS (ESI-TOF, *m/z*): calculated for $C_{43}H_{50}F_3N_2O_3PS_4$ $[M]^+$ 859.2472, found 859.2492.

IR (ATR, neat, cm^{-1}): 3055 (w), 2919 (w), 1597 (w), 1378 (w), 1235 (w), 1200 (w), 1112 (w), 857 (w), 692 (w).

Synthesis of 10-(4-((dioctylamino)methyl)-2-(trifluoromethyl)phenyl)-7-morpholino-5-phenyl-3*H*-acridophosphin-3-one 5-oxide (4.21)



Ctrl-CPF1
4.21

Compound **4.21** was synthesized according to a modified literature procedure.[142] **4.19** (92 mg, 192 µmol, 2.0 equiv.) was dissolved in 1.2 ml of dry THF and cooled to –78 °C. A 1.9 M solution of *tert*-butyl lithium (110 µl, 202 µmol, 2.1 equiv.) was added dropwise over 5 minutes to the first solution of **4.19**. The resulting solution was stirred for 1 hour at –78 °C and for further 10 minutes at room temperature. After cooling the reaction mixture back to –78 °C, a solution of phosphoacridone **4.10** (50 mg, 96 µmol, 1.0 equiv.) in 3 ml THF was added dropwise over 10 minutes and stirred for 15 minutes at –78 °C. The reaction mixture was allowed to warm to room temperature and was stirred for further 1.5 hours. Next, a solution of 6M HCl (5 ml) was added at 0 °C to the reaction mixture and was allowed to stirr at room temperature for 1 hour. the dark solution was then quenched with a solution of

15% w/w sodium hydroxide and extracted with dichloromethane (3x20 ml), dried over sodium sulfate and dconcentrated under reduced pressure. The residue was then purified by column chromatography (dichloromethane:MeOH = 100:3) which afforded desired **4.21** (54 mg, 69 µmol, 71%) as a dark blue solid.

$\mathbf{R_f}$ = 0.25 (dichloromethane:MeOH = 100:5, UV, $KMnO_4$).

^{1}H NMR (300 MHz, CD_2Cl_2) δ = 0.87 (t, 6H, *J* = 7.1 Hz), 1.29 (s, 20H), 1.50 (q, 4H, *J* = 7.1 Hz), 2.49 (t, 4H, *J* = 7.4 Hz), 3.35 (q, 4H, *J* = 5.5 Hz), 3.71 (s, 2H), 3.76 (t, 4H, *J* = 4.8 Hz), 6.18 (dd, 1H, *J* = 10.2, 1.8 Hz), 6.70 – 6.82 (m, 3H), 7.11 (dd, 1H, *J* = 17.0, 1.8 Hz), 7.25 (d, 1H, *J* = 7.8 Hz), 7.39 – 7.56 (m, 4H), 7.61 – 7.74 (m, 3H), 7.90 (s, 1H)

^{13}C NMR (75 MHz, CD_2Cl_2) δ = 14.3, 23.1, 27.6, 27.8, 29.9, 32.3, 47.1, 54.5, 58.5, 66.6, 116.0, 117.2 (d, *J* = 7.7 Hz), 123.1, 125.3 (d, *J* = 5.8 Hz), 125.8, 126.9 (q, *J* = 5.1 Hz), 127.1 (d, = 6.4 Hz), 128.0, 128.8 (d, *J* = 30.8 Hz), 129.2 (d, *J* = 12.8 Hz), 130.5 (d, *J* = 10.3 Hz), 132.2 (d, *J* = 47.3 Hz), 132.5 (d, *J* = 2.7 Hz), 132.9, 133.9, 143.7 (d, *J* = 108.3 Hz), 135.3 (d, *J* = 9.9 Hz), 135.7 (d, *J* = 2.7 Hz), 139.8 (d, *J* = 8.9 Hz), 140.5 (d, *J* = 90.5 Hz), 143.6, 149.3 (d, *J* = 7.2 Hz), 152.2 (d, *J* = 12.3 Hz), 184.0 (d, *J* = 13.0 Hz)

^{31}P NMR (122 MHz, CD_2Cl_2) δ = 10.4.

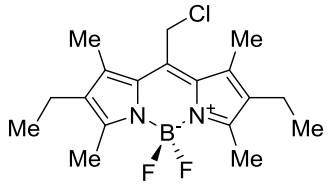
^{19}F NMR (282 MHz, CD_2Cl_2) δ = –60.1

LCMS (ESI, *m/z*): 787 $[M+H]^+$.

HRMS (ESI-TOF, *m/z*): calculated for $C_{47}H_{58}F_3N_2O_3P$ $[M+H]^+$ 787.4215, found 787.4215.

IR (ATR, neat, cm^{-1}): 2923 (w), 2851 (w), 1600 (w), 1574 (w), 1307 (w), 1280 (m), 1123 (m), 1057 (w), 891 (w).

Synthesis of 10-(chloromethyl)-2,8-diethyl-5,5-difluoro-1,3,7,9-tetramethyl-5*H*-4l4,5l4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinine (4.23):



4.23

Compound **4.23** was prepared following a literature procedure.[198] Chloroacetyl chloride (513 mg, 4.5 mmol, 1.0 equiv.) was added dropwise into a stirred solution of 3-ethyl-2,4-dimethylpyrrole **4.22** (1.15 g, 9.0 mmol, 2.0 equiv.) in argon-sparged dichloromethane (50 ml) under inert atmosphere, and the solution was stirred at 55 °C for 2 h. The mixture was dried under reduced pressure and the crude was dissolved in toluene (105 ml) and

dichloromethane (6 ml). Subsequently, triethylamine (2.96 ml, 21.0 mmol, 4.7 equiv.) was added under an inert atmosphere and the solution was stirred for 15 min. at room temperature. Next, boron trifluoride diethyl etherate (7.96 ml, 31 mmol, 6.8 equiv.) was added and the reaction mixture was stirred at 55 °C for 2 h. The solution was concentrated under reduced pressure, poured into saturated aqueous $NaHCO_3$ (25 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic phase was washed with brine (20 ml), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-pentane:acetone = 150:1 → 10:1) to give the title product **4.23** (683 mg, 1.93 mmol, 43%) as a metallic green solid.

m.p. = 185–187 °C

$\mathbf{R_f}$ = 0.30 (*n*-pentane:acetone = 20:1)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.05 (t, J = 7.6 Hz, 6H), 2.36–2.44 (m, 10H), 2.51 (s, 6H), 4.80 (s, 2H).

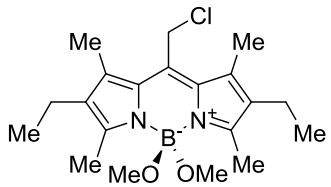
^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.9, 136.2, 134.2, 133.5, 130.9, 37.9, 17.1, 14.6, 12.6, 12.5.

MS (EI) *m*/*z* (relative intensity): 352 (72) [M^+], 337 (98), 318 (50), 303 (100), 298 (53), 287 (32), 273 (9), 267 (14), 143 (12), 134 (12).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{18}H_{24}BClF_2N_2$ $[M+H]^+$ 353.1771, found 353.1777.

IR (ATR, neat, cm^{-1}): 2965 (w), 2927 (w), 2868 (w), 1549 (s), 1473 (m), 1405 (m), 1321 (m), 1261 (m), 1186 (s), 1042 (s), 973 (s), 693 (m), 531 (s).

Synthesis of 10-(chloromethyl)-2,8-diethyl-5,5-dimethoxy-1,3,7,9-tetramethyl-5*H*-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinine (4.24):



4.24

Compound **4.24** was prepared following a literature procedure.[144] Aluminum chloride (468 mg, 3.5 mmol, 3.0 equiv.) was added to the solution of **4.23** (413 mg, 1.17 mmol. 1.0 equiv.) in dichloromethane (11.7 ml) under inert atmosphere and sonicated for 5 min. at room temperature. Next, methanol (5.85 mL) was gently added to the suspension, and the reaction mixture was stirred for another 5 min. The mixture was then diluted with ethyl acetate (50 ml), washed with water (2×20 ml) and brine (20 ml). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography

(dichloromethane:EtOAc = 2:1 → 1:1) to give the title product **4.24** (277 mg, 0.73 mmol, 63%) as a golden-green solid.

m.p. = 133-135 °C (decomposition)

$\mathbf{R_f}$ = 0.30 (dichloromethane:EtOAc = 1:2)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.05 (t, J = 7.5 Hz, 6H), 2.41 (q, J = 7.5 Hz, 4H), 2.46 (s, 6H), 2.49 (s, 6H), 2.80 (s, 6H), 4.86 (s, 2H).

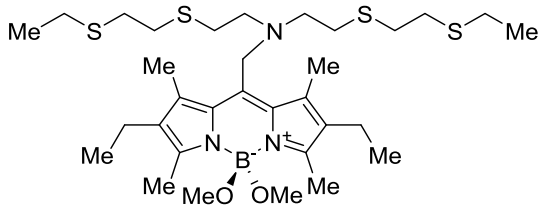
^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.2, 134.1, 134.0, 133.0, 132.3, 49.0, 38.4, 17.2, 14.8, 12.6, 12.3.

MS (EI) *m*/*z* (relative intensity): 376 (14) [M^+], 344 (71), 309 (61), 295 (61), 279 (19), 267 (20), 250 (18), 208 (20), 165 (15), 147 (17), 140 (19), 73 (16), 69 (18), 57 (24), 44 (38), 36 (81), 32 (100).

HRMS (ESI-TOF, *m*/*z*): calcd. for $C_{20}H_{30}BClN_2O_2Na$ $[M+Na]^+$ 399.1992, found 399.1987.

IR (ATR, neat, cm^{-1}): 2958 (w), 2923 (w), 2867 (w), 2809 (w), 1548 (s), 1470 (m), 1383 (m), 1317 (m), 1177 (s), 1104 (s), 949 (s), 683 (m), 644 (m), 594 (m), 524 (s).

Synthesis of *N*-((2,8-diethyl-5,5-dimethoxy-1,3,7,9-tetramethyl-5*H*-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)methyl)-2-((2-(ethylthio)ethyl)thio)-*N*-(2-((2-(ethylthio)ethyl)thio)ethyl)ethan-1-amine (4.25):



4.25

Compound **4.25** was prepared following a literature procedure.[144] The suspension of **4.24** (75 mg, 0.2 mmol, 1.0 equiv.), polythioether amine **4.16** (82 mg, 0.26 mmol, 1.3 equiv.), KI (33 mg, 0.2 mmol, 1.0 equiv.) and K_2CO_3 (55 mg, 0.4 mmol, 2.0 equiv.) in CH_3CN (2.0 ml) was stirred at 45 °C for 3 h under inert atmosphere. The mixture was concentrated under reduced pressure, the residue was dissolved in dichloromethane (50 ml) and washed with water (2×20 ml). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane:EtOAc = 3:1 → 1:1) to give the title product **4.25** (57 mg, 0.08 mmol, 43%) as a dark red oil.

$\mathbf{R_f}$ = 0.42 (dichloromethane:EtOAc = 1:3)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.04 (t, J = 7.5 Hz, 6H), 1.24 (t, J = 7.3 Hz, 6H), 2.36–2.44 (m, 10H), 2.49 (s, 6H), 2.52–2.66 (m, 16H), 2.79 (s, 6H), 2.88–2.91 (m, 4H), 4.05 (s, 2H).

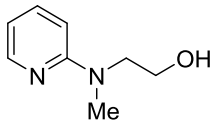
^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.8, 136.8, 135.0, 134.1, 132.8, 52.6, 49.7, 49.0, 32.3, 31.7, 30.4, 26.0, 17.3, 14.9, 14.7, 14.1, 12.3.

MS (EI) *m/z* (relative intensity): 653 (10) [M^+], 621 (14), 340 (100), 325 (26), 309 (88), 295 (30), 252 (14), 178 (17), 121 (16), 89 (97), 61 (18).

HRMS (ESI-TOF, *m/z*): calcd. for $C_{32}H_{56}BN_3O_2S_4Na$ [M+Na^+] 676.3251, found 676.3253.

IR (ATR, neat, cm^{-1}): 2956 (w), 2922 (w), 2806 (w), 1542 (s), 1473 (m), 1358 (m), 1320 (m), 1258 (m), 1173 (s), 1111 (s), 1064 (m), 1019 (m), 970 (s), 951 (s), 840 (w), 709 (m), 648 (w), 527 (m).

Synthesis of 2-(methyl(pyridin-2-yl)amino)ethan-1-ol (4.27):



4.27

Compound **4.27** was prepared following a similar literature procedure.[155] 2-(methylamino)ethanol (1.60 ml, 19.82 mmol, 3.0 equiv.) was added to a solution of 2-chlorpyridine (638 µl, 6.61 mmol, 1.0 equiv.) at r.t. and the mixture was heated and stirred at 160 °C overnight. After the reaction was completed judging TLC, water (15 ml) was added to the solution. The aqueous solution was then extracted with DCM (3x20 ml). The combined organic phase was then washed with water (20 ml), brine (20 ml), and dried over Na_2SO_4. The solvent was removed afterwards under reduced pressure. The oily residue was purified by column chromatography (*n*-pentane:EtOAc = 3:2) yielding the desired compound **4.27** (935 mg, 6.13 mmol, 93%) as a light yellowish oil.

R_f = 0.14 (*n*-pentane:EtOAc = 3:2, UV, $KMnO_4$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.03 (s, 3H), 3.62 – 3.73 (m, 2H), 3.77 – 3.86 (m, 2H), 5.36 (s, 1H), 6.44 – 6.64 (m, 2H), 7.44 (ddd, *J* = 8.6, 7.1, 2.0 Hz, 1H), 8.03 (ddd, *J* = 5.1, 2.0, 0.9 Hz, 1H).

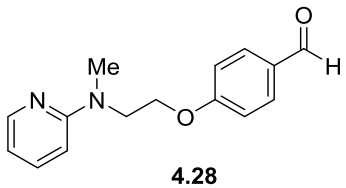
^{13}C NMR (75 MHz, $CDCl_3$) δ = 38.0, 54.4, 62.9, 106.4, 112.3, 137.9, 147.1, 159.3.

MS (EI) *m/z* (relative intensity): 152 (15) [M^+], 133 (11), 121 (100), 107 (12), 93 (10), 80 (17), 78 (54), 67 (3), 51 (25), 42 (20), 31 (54).

HRMS (ESI-TOF, *m/z*): calculated for $C_8H_{12}N_2O$ $[M]^+$ 152.09441, found: 152.09488.

IR (ATR, neat, cm^{-1}): 3289 (w), 2923 (w), 1594 (s), 1495 (s), 1421 (m), 1319 (m), 1160 (w), 1044 (m), 984 (m), 766 (s).

Synthesis of 4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzaldehyde (4.28):



4.28

Compound **4.28** was prepared following a literature procedure.[156] To a stirred solution of 2-(methyl-2-pyridinylamino)ethanol **4.27** (860 mg, 5.65 mmol, 1.0 equiv.) in dry DMF (10 ml) was added sodium hydride (60% dispersion)(249 mg, 6.22 mmol, 1.1 equiv.) portion-wise at r.t. under Argon. The mixture was the stirred at r.t. until the vigorous reaction ceased. Next, a solution of 4-Fluorobenzaldehyde (687 µl, 6.22 mmol, 1.1 equiv.) was added dropwise over 15 minutes. The reaction mixture was stirred at r.t. for further 20 hours. Afterwards, the solution was carefully quenched with water and extracted with EtOAc (3x15 ml). The combined organic phase was then washed with water (2x10 ml), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residual oil was purified by flash chromatography (dichloromethane:MeOH = 200:1) yielding the desired compound **4.28** (819 mg, 3.20 mmol, 57%) as a translucent oil.

R_f = 0.27 (dichloromethane:MeOH = 50:1, UV)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.14 (s, 3H), 4.02 (t, J = 5.6 Hz, 2H), 4.28 (t, J = 5.6 Hz, 2H), 6.52 (dt, J = 8.6, 0.9 Hz, 1H), 6.57 (ddd, J = 7.1, 5.0, 0.9 Hz, 1H), 6.94 – 7.07 (m, 2H), 7.46 (ddd, J = 8.6, 7.1, 2.0 Hz, 1H), 7.74 – 7.87 (m, 2H), 8.15 (ddd, J = 5.0, 2.0, 0.9 Hz, 1H), 9.86 (s, 1H).

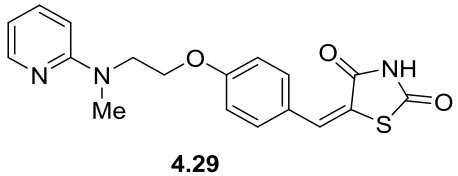
^{13}C NMR (75 MHz, $CDCl_3$) δ = 38.1, 49.4, 66.8, 105.9, 112.1, 114.9, 130.1, 132.1, 137.6, 147.9, 158.2, 164.0, 190.9.

MS (EI) *m/z* (relative intensity): 256 (12) [M^+], 151 (1), 147 (1), 135 (23), 133 (14), 121 (100), 107 (12), 92 (13), 78 (49), 65 (20), 51 (18), 39 (12).

HRMS (EI): calcd. for $C_{15}H_{16}N_2O_2$ $[M]^+$ 256.1206, found: 256.1201.

IR (ATR, neat, cm^{-1}): 2253 (w), 1692 (w), 1690 (m), 1599 (s), 1578 (w), 1562 (w), 1500 (m), 1257 (w), 1160 (w), 902 (s), 722 (s), 649 (m).

Synthesis of 5-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzylidene)thiazolidine-2,4-dione (4.29):



4.29

Compound **4.29** was prepared following a literature procedure.[156] 4-[2-(N-methyl-*N*-(2-pyridyl)amino)ethoxy]benzaldehyde (**4.28)** (619 mg, 2.42 mmol, 1.0 equiv.) was dissolved in 10 ml of toluene before adding 2,4-thiazolidinedione (320 mg, 2.73 mmol, 1.13 equiv.) at 25-30 °C. Piperidine (24 µl, 242 µmol, 0.10 equiv.) and acetic acid (14 µl, 242 µmol, 0.10 equiv.) were added afterwards to the solution. Next, the reaction mixture was then heated to reflux over 3 hours. A yellow colored solid was formed. The reaction was then cooled to 25-30 °C. The precipitated solid was filtered off, washed with methanol, and dried afterwards at 70 °C under reduced pressure to obtain the title compound **4.29** (780 mg, 2.19 mmol, 82%) as a pale yellow solid.

m.p. = 192-194 °C

$\mathbf{R_f}$ = 0.42 (*n*-pentane:EtOAc = 1:1, UV, $KMnO_4$)

^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.06 (s, 3H), 3.92 (t, J = 5.8 Hz, 2H), 4.21 (t, J = 5.9 Hz, 2H), 6.56 (m, 1H), 6.64 (d, J = 8.6, 0.9 Hz, 1H), 6.98 – 7.22 (m, 2H), 7.39 – 7.61 (m, 3H), 7.72 (s, 1H), 8.08 (ddd, J = 4.9, 2.0, 0.9 Hz, 1H), 12.50 (br. s, 1H).

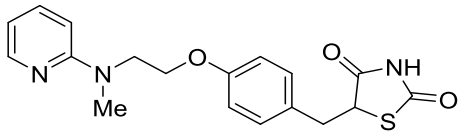
^{13}C NMR (75 MHz, DMSO-d_6) δ = 37.1, 48.3, 65.8, 105.8, 111.6, 115.3, 120.4, 125.6, 131.7, 132.1, 137.4, 147.5, 158.0, 160.2, 167.5, 168.0.

MS (EI) *m/z* (relative intensity): 355 (5) [M^+], 223 (1), 221 (19), 178 (1), 150 (47), 142 (2), 136 (18), 135 (96), 121 (100), 108 (14), 94 (10), 78 (29), 51 (5).

HRMS (ESI, *m/z*): calculated for $C_{18}H_{18}N_3O_3S$ $[M+H]^+$ 356.1063, found: 356.1065.

IR (ATR, neat, cm^{-1}): 2935 (w), 2885 (w), 2620 (w), 2432 (w), 1689 (s), 1596 (s), 1503 (m), 1427 (m), 1164 (m), 774 (m), 518 (s).

Synthesis of 5-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzyl)thiazolidine-2,4-dione (4.30):



4.30

Compound **4.30** was prepared following a modified literature procedure.[157] A 2.0 M solution of lithium borohydride in THF (930 µl, 1.86 mmol, 2.2 equiv.) was added dropwise to a stirred solution of 5-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzylidene)thiazolidine-2,4-dione (**4.29**) (301 mg, 846 µmol, 1.0 equiv.) in pyridine (515 µl, 844 µmol, 1.0 equiv.) and dry THF (566 µl) over 10 min. under vigorous stirring. After approximately half of the $LiBH_4$ had been added the effervescence ceased and a yellow solution was formed. The mixture was

heated afterwards to reflux for 2 h during which the color deepened to a wine-red solution. An orange solid precipitated after 1 h of refluxing. After cooling the mixture to r.t., it was added dropwise to a stirred solution of hydrochloric acid (406 µl) in water (2.65 ml) at 5 °C keeping the internal temperature of the solution below 20 °C. The resulting orange/white suspension was stirred below 15 °C for 15 minutes and was then heated to reflux while stirring for further 1 hour. The resulting reaction mixture was filtered hot through Celite to remove the formed brown residue and the brown mother liquor was allowed to cool to 25 °C and left overnight in the fridge. An off-white solid precipitated which was filtered under vacuum, washed with cold water, and dried in an oven at 50 °C overnight to give crude product as an off-white solid. The isolated solid was then recrystallized out of ethanol yielding the desired compound **4.30** (184 mg, 515 µmol, 61%) as a white solid.

m.p. = 152–155 °C

$\mathbf{R_f}$ = 0.48 (*n*-pentane:EtOAc = 4:1, UV, $KMnO_4$)

^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.94 – 3.15 (m, 4H), 3.29 (dd, *J* = 14.2, 4.3 Hz, 1H), 3.45 (d, *J* = 7.0 Hz, 0H), 3.89 (m, 2H), 4.10 (m, 2H), 4.85 (m, 1H), 6.56 (m, 1H), 6.63 (dt, *J* = 8.6, 0.9 Hz, 1H), 6.82 – 6.95 (m, 2H), 7.05 – 7.20 (m, 2H), 7.49 (ddd, *J* = 8.6, 7.1, 2.0 Hz, 1H), 8.08 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H), 11.98 (br. s, 1H).

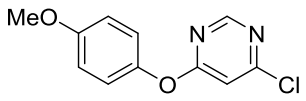
^{13}C NMR (75 MHz, DMSO-d_6) δ = 36.3, 37.0, 48.5, 53.0, 65.3, 105.7, 111.5, 114.3, 128.6, 130.4, 137.3, 147.5, 157.5, 158.0, 171.6, 175.7.

MS (EI) *m/z* (relative intensity): 357 (35) [M^+], 327 (1), 232 (1), 221 (1), 168 (1), 150 (2), 136 (11), 135 (100), 133 (18), 94 (14), 78 (48), 51 (6).

HRMS (EI): calcd. for $C_{18}H_{19}N_3O_3S$ [$M]^+$ 357.1142, found: 357.1144.

IR (ATR, neat, cm^{-1}): 2933 (w), 2577 (w), 1737 (w), 1690 (s), 1608 (m), 1554 (w), 1506 (m), 1473 (w), 1423 (m), 1244 (m), 1159 (m), 1036 (m), 993 (m).

Synthesis of 4-chloro-6-(4-methoxyphenoxy)pyrimidine (4.32):



4.32

Compound **4.32** was prepared following a modified literature procedure.[158] To a suspension of sodium hydride (60% dispersion in mineral oil) (128 mg, 3.20 mmol, 1.20 equiv.) in DMF (10 ml) under argon was added 4-Methoxyphenol (350 mg, 2.74 mmol, 1.02 equiv.) at 0 °C (caution: gas evolution) and the mixture was allowed to stir for 5 minutes. 4,6-

dichloropyrimidine (400 mg, 2.69 mmol, 1.0 equiv.) was then added to the mixture at once (the addition at once is important in order to avoid the formation of the 2,4-substituted side-product) at 0 °C and stirred at r.t. for further 2 hours. The reaction mixture was then quenched with cold water at 0 °C and extracted with EtOAc (3x15 ml). The combined organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The colorless oily residue was then purified by column chromatography (*n*-pentane:EtOAc = 10:1) yielding the title compound **4.32** (611 mg, 2.58 mmol, 96%) as a viscous oil which solidifies upon standing overnight into a white amorph solid.

m.p. = 70-72 °C

R_f = 0.10 (*n*-pentane:EtOAc = 10:1, UV, $KMnO_4$)

^{1}H NMR (300 MHz, CD_2Cl_2) δ = 3.82 (s, 3H), 6.90 (d, J = 0.9 Hz, 1H), 6.92 – 6.99 (m, 2H), 7.03 – 7.13 (m, 2H), 8.54 (d, J = 0.9 Hz, 1H).

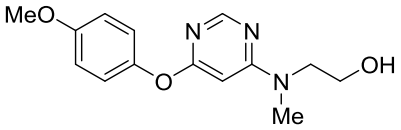
^{13}C NMR (101 MHz, CD_2Cl_2) δ = 56.1, 108.1, 115.4, 122.9, 146.0, 158.2, 159.0, 162.3, 171.3.

MS (EI) *m/z* (relative intensity): 236 (34) [M^+], 220 (1), 173 (1), 158 (1), 134 (100), 123 (5), 113 (4), 107 (14), 86 (12), 77 (9), 63 (8), 51 (7).

HRMS (EI): calcd. for $C_{11}H_9O_2N_2Cl$ $[M]^+$ 236.0347, found: 236.0348.

IR (ATR, neat, cm^{-1}): 3085 (w), 3007 (w), 2836 (w), 1613 (m), 1561 (m), 1540 (s), 1502 (s), 1317 (m), 1260 (w), 1237 (s), 1187 (s).

Synthesis of 2-((6-(4-methoxyphenoxy)pyrimidin-4-yl)(methyl)amino)ethan-1-ol (4.33):



4.33

Compound **4.33** was prepared following a literature procedure.[158] To a stirred solution of 4-chloro-6-(4-methoxyphenoxy)pyrimidine (**4.32**) (500 mg, 2.11 mmol, 1.0 equiv.) in anhydrous ethanol (12 ml) was added 2-methylaminoethanol (513 µl, 6.34 mmol, 3.0 equiv.) and the mixture was refluxed for 24 h under an argon atmosphere. The reaction mixture was then cooled to room temperature, quenched with aq. NH_4Cl solution (5 ml), and extracted with EtOAc (3x15 ml). The extracted organic layers were combined and washed with water (15 ml) and brine (15 ml), respectively, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-pentane:EtOAc = 2:3) yielding the title compound **4.33** as a colorless oil (580 mg, 2.11 mmol, quant.).

R_f = 0.12 (*n*-pentane: EtOAc = 2:3, UV, $KMnO_4$).

^{1}H NMR (300 MHz, CD_2Cl_2) δ = 3.02 (s, 3H), 3.49 (br. s, 1H), 3.69 – 3.78 (m, 4H), 3.81 (s, 3H), 5.84 (s, 1H), 6.87 – 6.97 (m, 2H), 6.97 – 7.09 (m, 2H), 8.16 (s, 1H).

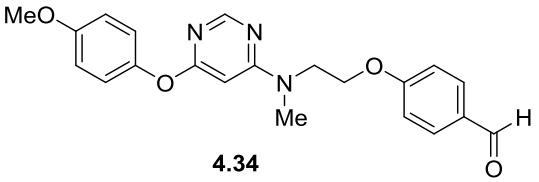
^{13}C NMR (75 MHz, CD_2Cl_2) δ = 37.4, 53.4, 56.1, 61.9, 86.1, 115.1, 123.0, 147.0, 157.5, 157.9, 165.1, 171.0.

MS (EI) *m/z* (relative intensity): 275 (11) [M^+], 244 (100), 231 (4), 216 (2), 201 (6), 134 (12), 121 (4), 107 (4), 92 (5), 81 (8), 68 (4), 44 (7).

HRMS (EI): calcd. for $C_{14}H_{17}O_3N_3$ $[M]^+$ 275.1264, found: 275.1266.

IR (ATR, neat, cm^{-1}): 3054 (w), 2987 (w), 2304 (w), 1596 (w), 1504 (w), 1264 (m), 896 (w), 731 (s), 703 (m).

Synthesis of 4-(2-((6-(4-methoxyphenoxy)pyrimidin-4-yl)(methyl)amino)ethoxy)benzaldehyde (4.34):



4.34

Compound **4.34** was prepared following a modified literature procedure.[158] To a suspension of sodium hydride (60% dispersion in mineral oil)(87 mg, 2.18 mmol, 1.9 equiv.) in anhydrous DMF (10 ml) at 0 °C was added 2-((6-(4-methoxyphenoxy)pyrimidin-4-yl)(methyl)amino)ethan-1-ol (**4.33**) (316 mg, 1.15 mmol, 1.0 equiv.) in a slow manner and the mixture was stirred at r.t. for 30 minutes. Then, 4-fluorobenzaldehyde (270 mg, 2.18 mmol, 1.9 equiv.) was added dropwise in the reaction mixture under argon atmosphere at room temperature. After stirring at the same temperature for 3 hours, the reaction mixture was quenched with aq. NH_4Cl solution (2 ml) at 0 °C. Then, cold water was added (20 ml), and the solution was extracted with EtOAc (3x20 ml). The combined organic phase was washed with water (20 ml) and brine (20 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using (*n*-pentane/EtOAc = 2:1) as eluent to yield the title compound **4.34** (371 mg, 978 µmol, 85%) as pale-yellow viscous oil.

$\mathbf{R_f}$ = 0.32 (*n*-pentane:EtOAc = 1:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, CD_2Cl_2) δ = 3.11 (s, 3H), 3.81 (s, 3H), 4.02 (t, *J* = 5.5 Hz, 2H), 4.27 (t, *J* = 5.5 Hz, 2H), 5.88 (s, 1H), 6.83 – 6.98 (d, 2H), 6.98 – 7.17 (m, 4H), 7.74 – 7.96 (m, 2H), 8.22 (s, 1H), 9.87 (s, 1H).

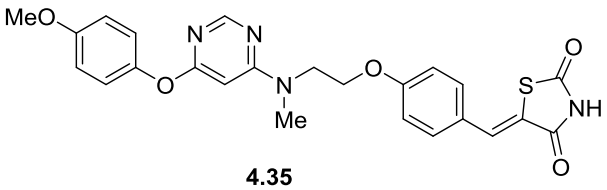
^{13}C NMR (75 MHz, CD_2Cl_2) δ = 37.8, 49.5, 56.08, 67.1, 86.1, 115.0, 115.2, 123.1, 130.7, 132.3, 147.1, 157.5, 158.0, 164.2, 164.5, 191.0.

MS (ESI): 380.20 $[M+H]^+$.

HRMS (EI): calcd. for $C_{21}H_{21}O_4N_3$ $[M]^+$ 379.1527, found: 379.1522.

IR (ATR, neat, cm^{-1}): 3046 (w), 2930 (w), 2739 (w), 1741 (m), 1687 (m), 1584 (s), 1500 (s), 1197 (s), 811 (m).

Synthesis of (*Z*)-5-(4-(2-((6-(4-methoxyphenoxy)pyrimidin-4-yl)(methyl)amino)ethoxy) benzylidene)thiazolidine-2,4-dione (4.35):



4.35

Compound **4.35** was prepared following a literature procedure.[158] A mixture of 4-(2-((6-(4-methoxyphenoxy) pyrimidin-4-yl) (methyl)amino)ethoxy)benzaldehyde (**4.34**) (325 mg, 857 µmol, 1 equiv.), 2,4-thiazolidinedione (130 mg, 1.11 mmol, 1.3 equiv.), and piperidine (111 µl, 1.11 mmol, 1.3 equiv.) in anhydrous ethanol (8 ml) was refluxed for 24 hours. The reaction mixture was then cooled to room temperature and diluted with EtOAc (20 ml). The diluted mixture was washed with water (3x20 m) and brine (20 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by column chromatography (dichloromethane:methanol = 70:1) to give the title compound **4.35** (320 mg, 668 µmol, 78%) as an off-white solid.

$\mathbf{R_f}$ = 0.27 (dichloromethane:methanol = 30:1, UV, $KMnO_4$)

^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.07 (s, 3H), 3.75 (s, 3H), 3.94 (m, 2H), 4.23 (t, J = 5.6 Hz, 2H), 6.05 (s, 1H), 6.88 – 6.99 (m, 2H), 7.01 – 7.30 (m, 4H), 7.49 – 7.58 (m, 2H), 7.73 (s, 1H), 8.17 (d, J = 0.8 Hz, 1H), 12.50 (s, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ = 36.5, 48.1, 55.4, 65.7, 85.6, 114.5, 115.3, 120.6, 122.5, 125.7, 131.6, 132.0, 146.1, 156.3, 157.2, 159.9, 163.6, 167.6, 168.0, 169.8.

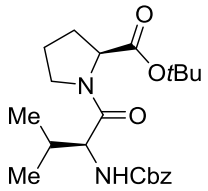
MS (EI) *m/z* (relative intensity): 478 (3) $[M^+]$, 258 (100), 244 (35), 231 (6), 221 (21), 150 (55), 135 (7), 124 (17), 109 (9), 81 (8), 77 (6), 44 (14).

HRMS (EI): calcd. for $C_{24}H_{22}O_5N_4S_1$ $[M]^+$ 478.13054, found: 478.12968.

IR (ATR, neat, cm^{-1}): 3132 (w), 3037 (w), 2935 (w), 1741 (m), 1679 (s), 1583 (s), 1226 (s), 1008 (m), 807 (m).

7.2.4 Experimental section to Chapter 5

Synthesis of tert-butyl ((benzyloxy)carbonyl)-*L*-valyl-*L*-prolinate (5.3):



5.3

Compound **5.3** was prepared following a modified literature procedure.[199] To a cold solution of *Z*-Val-OH **5.2** (2.0 g, 7.94 mmol, 1.10 equiv.) in dichloromethane (15 ml) was added HOBt.H_2O (1.11 g, 7.22 mmol, 1.0 equiv.) and the mixture was allowed to stir for 15 minutes at 0 °C. Then, *N,N'*-Dicyclohexylcarbodiimid (1.71 g, 8.31 mmol, 1.15 equiv.) was added at once at 0 °C and stirred for further 30 minutes. Pro.O-*t*-Bu.HCl **5.1** (1.5 g, 7.22 mmol, 1.0 equiv.) was then added at 0 °C followed by triethylamine (1.56 ml, 11.37 mmol, 1.57 equiv.) and the mixture was allowed to stir at r.t. overnight. The precipitated *N,N´*-dicyclohexylurea was filtered off and the filter cake was washed with dichloromethane (15 ml). Subsequently, the filtrate was washed with 10% citric acid, 4% $NaHCO_3$, and brine, respectively. The organic phase was then dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified afterwards by flash chromatography (dichloromethane:methanol = 300:1) yielding the title compound **5.3** (2.78 g, 6.87 mmol, 95%) as a viscous colorless oil.

$\mathbf{R_f}$ = 0.82 (dichloromethane:methanol = 30:2, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.94 (d, J = 6.7 Hz, 3H), 1.04 (d, J = 6.7 Hz, 3H), 1.44 (s, 9H), 1.80 – 2.27 (m, 5H), 3.52 – 3.69 (m, 1H), 3.75 (m, 1H), 4.27 – 4.45 (m, 2H), 5.07 (d, J = 2.1 Hz, 2H), 5.52 (d, J = 9.2 Hz, 1H), 7.28 – 7.40 (m, 5H).

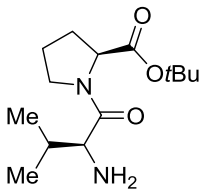
^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.4, 19.6, 25.0, 28.0, 29.2, 31.3, 47.3, 57.4, 59.8, 66.9, 81.4, 128.0, 128.1, 128.6, 136.5, 156.6, 170.6, 171.3.

MS (EI) *m/z* (relative intensity): 404 (1) [M^+], 348 (5), 331 (2), 303 (2), 261 (2), 234 (5), 206 (5), 162 (14), 114 (15), 91 (100), 70 (42), 57 (39).

HRMS (EI): calcd. for $C_{22}H_{32}N_2O_5$ $[M]^+$ 404.2306, found: 404.2314.

IR (ATR, neat, cm^{-1}): 2978 (w), 1719 (s), 1643 (s), 1508 (w), 1436 (w), 1369 (w), 1264 (m), 1222 (w), 1152 (m), 1027 (w), 731 (s), 700 (m).

Synthesis of tert-butyl *L*-valyl-*L*-prolinate (5.4):



5.4

Compound **5.4** was prepared following a literature procedure.[200] The Protected dipeptide **5.3** (1.68 g, 4.15 mmol, 1.0 equiv.) was dissolved in methanol (10 ml). Next, 10% Pd/C (177 mg, 166 µmol, 0.04 equiv.) was added and the mixture was allowed to stir under a H_2 atm. for 6 hours. Afterwards, the mixture was filtered through a pad of celite and dried under reduced pressure. The crude was purified using flash chromatography (dichloromethane:methanol = 30:2) yielding the title compound **5.4** (1.08 g, 4.0 mmol, 96%) as a colorless oil.

$\mathbf{R_f}$ = 0.14 (dichloromethane:methanol = 30:2, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.93 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.44 (s, 9H), 1.75 – 2.32 (m, 7H), 3.33 (d, J = 5.4 Hz, 1H), 3.55 – 3.62 (m, 2H), 4.35 – 4.44 (m, 1H).

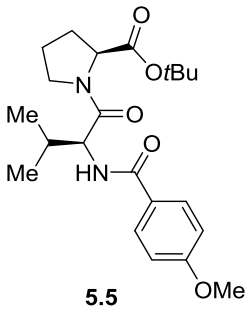
^{13}C NMR (75 MHz, $CDCl_3$) δ = 16.9, 20.1, 25.1, 28.1, 29.1, 32.0, 47.0, 58.3, 59.9, 81.3, 171.6, 173.7.

MS (GCMS) *m/z* (relative intensity): 270 (1) [M^+], 197 (2), 171 (6), 125 (4), 72 (100), 70 (41), 57 (20), 55 (16), 41 (16), 29 (6).

HRMS (EI): calcd. for $C_{14}H_{26}N_2O_3$ $[M]^+$ 270.1938, found: 270.1935.

IR (ATR, neat, cm^{-1}): 3309 (w), 2970 (w), 1736 (m), 1624 (m), 1501 (m), 1438 (m), 1250 (m), 1148 (s), 1029 (m), 842 (m), 767 (m).

Synthesis of tert-butyl (4-methoxybenzoyl)-*L*-valyl-*L*-prolinate (5.5):



5.5

Compound **5.5** was prepared following a literature procedure.[178] The *t*-Bu-dipeptide ester **5.4** (839 mg, 3.30 mmol, 1.0 equiv.) was dissolved in THF (7 ml) and the solution was cooled to 0 °C. Then, 4-methoxy benzoyl chloride (474 µl, 3.47 mmol, 1.05 equiv.) was added dropwise to the mixture followed by triethylamine (1.30 ml, 9.25 mmol, 2.8 equiv.) at 0 °C.

The mixture was allowed to stir for further 2 hours. The solvent was then removed under reduced pressure and the crude was dissolved in EtOAc (20 ml) and washed with water, aq. sat. Na_2CO_3, aq. sat. NH_4Cl, and brine, respectively. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Subsequently, the crude material was purified by flash chromatography (dichloromethane:methanol = 100:1) yielding the title compound **5.5** (1.20 g, 2.98 mmol, 90%) as a white foam.

m.p. = 47–49 °C

$\mathbf{R_f}$ = 0.14 (dichloromethane:methanol = 99:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.00 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 1.46 (s, 9H), 1.85 – 2.28 (m, 6H), 3.63 – 3.75 (m, 1H), 3.83 (s, 3H), 3.84 – 3.91 (m, 1H), 4.32 – 4.42 (m, 1H), 4.84 (dd, J = 8.8, 6.2 Hz, 1H), 6.83 – 6.93 (m, 3H), 7.71 – 7.82 (m, 2H).

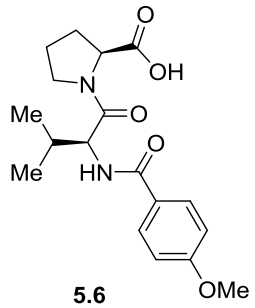
^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.9, 19.7, 25.1, 28.1, 29.3, 31.8, 47.5, 55.5, 55.7, 60.0, 81.5, 113.8, 126.6, 129.0, 162.4, 166.9, 170.9, 171.3.

MS (EI) *m/z* (relative intensity): 404 (1) [M^+], 348 (2), 234 (3), 206 (7), 162 (15), 114 (6), 91 (100), 70 (44), 65 (7), 57 (20), 41 (10).

HRMS (EI): calcd. for $C_{22}H_{32}N_2O_5$ $[M]^+$ 404.2306, found: 404.2307.

IR (ATR, neat, cm^{-1}): 2972 (w), 1734 (m), 1640 (m), 1433 (m), 1365 (m), 1149 (s), 1093 (w), 1046 (w), 850 (w), 472 (w).

Synthesis of (4-methoxybenzoyl)-*L*-valyl-*L*-proline (5.6):



5.6

Compound **5.6** was prepared following a literature procedure.[178] Tert-butyl (4-methoxybenzoyl)-*L*-valyl-*L*-prolinate **5.5** (901 mg, 2.47 mmol, 1.0 equiv.) was dissolved in trifluoroacetic acid (12 ml) at 0 °C and the solution was stirred at r.t. for further 2 hours. After completion of the reaction, trifluoroacetic acid was removed under reduced pressure and the crude mixture was dissolved in ethylacetate (20 ml) and washed with water (2x15 ml). The organic fractions were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography

(dichloromethane:methanol:acetic acid = 200:1:2) yielding the title compound **5.6** (590 mg, 1.69 mmol, 76%) as a white foam.

m.p. = 68–70 °C

$\mathbf{R_f}$ = 0.19 (dichloromethane:methanol:acetic acid = 97:3:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, DMSO-d_6) δ = 0.95 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 1.77 – 2.02 (m, 3H), 2.08 – 2.26 (m, 2H), 3.55 – 3.71 (m, 1H), 3.80 (s, 3H), 3.90 – 4.05 (m, 1H), 4.20 – 4.30 (m, 1H), 4.45 (dd, J = 9.4, 8.1 Hz, 1H), 6.93 – 7.02 (m, 2H), 7.86 – 7.97 (m, 2H), 8.34 (d, J = 8.1 Hz, 1H).

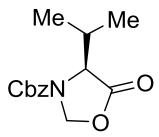
^{13}C NMR (75 MHz, DMSO-d_6) δ = 18.8, 19.2, 24.6, 28.8, 29.9, 46.9, 55.3, 56.7, 58.6, 113.4, 126.1, 129.5, 161.7, 165.8, 170.4, 173.3.

MS (EI) *m*/*z* (relative intensity): 348 (6) [M^+], 234 (7), 207 (14), 206 (74), 191 (6), 153 (5), 135 (100), 114 (3), 107 (9), 92 (15), 77 (19).

HRMS (EI): calcd. for $C_{18}H_{24}N_2O_5$ $[M]^+$ 348.1680, found: 348.1684.

IR (ATR, neat, cm^{-1}): 3305 (w), 2964 (m), 1711 (m), 1601 (s), 1503 (m), 1453 (m), 1252 (s), 1176 (s), 1027 (m), 843 (m), 767 (w), 598 (m).

Synthesis of benzyl (*S*)-4-isopropyl-5-oxooxazolidine-3-carboxylate (5.10):



5.10

Compound **5.10** was prepared following a similar literature procedure.[182] To a solution of *N*-benzyloxycarbonyl-*L*-valine **5.2** (3.0 g, 11.94 mmol, 1.0 equiv.) in toluene (20 ml) was added paraformaldehyde (477 mg, 15.88 mmol, 1.33 equiv.) and *p*-toluenesulfonic acid monohydrate (114 mg, 597 µmol, 0.05 equiv.) and the mixture was refluxed for 1 hour. Next, the reaction solution was washed successively with 5% aq. $NaHCO_3$ solution (10 ml) and brine (10 ml). The organic phase was then dried over Na_2SO_4 and the solvent was evaporated under reduced pressure yielding compound **5.10** (2.93 g, 11.13 mmol, 93%) as a colorless oil which solidifies upon standing into a colorless amorph solid.

m.p. = 54–55 °C

$\mathbf{R_f}$ = 0.65 (dichloromethane:methanol = 99:1, UV, $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.04 (dd, J = 18.6, 6.9 Hz, 6H), 2.36 (s, 1H), 4.23 (s, 1H), 5.10 – 5.24 (m, 3H), 5.59 (s, 1H), 7.31 – 7.42 (m, 5H).

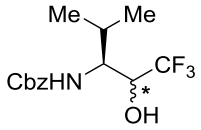
^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.9, 18.0, 31.3, 60.2, 68.1, 78.6, 128.4, 128.7, 128.8, 135.5, 153.6, 171.6.

MS (EI) *m/z* (relative intensity): 263 (3) [M^+], 221 (1), 190 (1), 107 (1), 91 (100), 86 (5), 77 (4), 65 (15), 43 (9), 39 (8).

HRMS (EI): calcd. for $C_{14}H_{17}N_1O_4$ $[M]^+$ 263.1152, found: 263.1152.

IR (ATR, neat, cm^{-1}): 2965 (w), 2936 (w), 1784 (m), 1687 (s), 1446 (m), 1422 (m), 1235 (m), 1125 (m), 1053 (s), 969 (m), 766 (m), 696 (s).

Synthesis of benzyl ((3*S*)-1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)carbamate (5.11):



5.11

Compound **5.11** was prepared following a literature procedure.[182] (4*S*)-4-isopropyl-5-oxo-1,3-oxazolidine-3-carboxylic acid benzyl ester **5.10** (2.0 g, 7.6 mmol, 1.0 equiv.) was dissolved in THF (4 ml), and thereto was added cesium fluoride (231 mg, 1.52 mmol, 0.2 equiv.) at 0 °C all at once. Trimethyl(trifluoromethyl)silane (1.36 ml, 9.12 mmol, 1.2 equiv.) was added dropwise to the reaction mixture over a period of 30 minutes. Then, the mixture was stirred at 0 °C for 1 hour. Subsequently, to the above THF solution was added methanol (7.5 ml) at 0 °C and the mixture was allowed to stir at r.t. for 30 minutes. Sodium borohydride (290 mg, 7.67 mmol, 1.0 equiv.) was added slowly at 0 °C over 5 minutes and the mixture was stirred for further 1 hour. Then, water (7.5 ml) was added slowly to the reaction solution, and further thereto was added potassium carbonate (630 mg, 4.56 mmol, 0.6 equiv.) at 0 °C. The mixture was then stirred at r.t. for 15 hours. Afterwards, the mixture solution was extracted with EtOAc (3x20 ml) and the organic phase was washed with 5% aq. HCl solution (10 ml) and brine (20 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude was purified by flash chromatography (*n*-pentane:EtOAc = 10:1 → 6:1) yielding the desired compound **5.11** (1.40 g, 4.58 mmol, 61%) as a waxy solid (mixture of diastereomers).

$\mathbf{R_f}$ = 0.33 (*n*-pentane:EtOAc = 8:2, UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.79 – 1.05 (m, 12H), 1.93 – 2.15 (m, 2H), 3.55 (t, 1H), 3.76 – 3.97 (m, 1H), 4.02 – 4.25 (m, 3H), 4.87 (d, *J* = 9.4 Hz, 1H), 5.05 – 5.20 (m, 4H), 5.33 (d, *J* = 9.2 Hz, 1H), 7.26 – 7.43 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 18.0, 19.0, 19.5, 20.2, 28.7, 30.2, 55.6, 57.4, 65.4, 67.2, 67.5, 69.2 (q, J = 30.1 Hz), 70.8 (q, J = 28.6 Hz), 124.9 (q, J = 283.3 Hz), 125.1 (q, J = 283.63 Hz), 127.2, 127.8, 128.0, 128.1, 128.3, 128.4, 128.6, 128.7, 128.7, 136.1, 136.4, 157.1, 157.6.

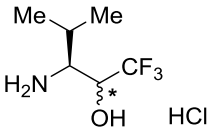
^{19}F NMR (282 MHz, $CDCl_3$) δ = –77.45 (d, J = 6.4 Hz), –74.41 (d, J = 7.0 Hz).

MS (EI) *m*/*z* (relative intensity): 305 (1) [M^+], 218 (1), 206 (2), 162 (3), 115 (2), 108 (10), 91 (100), 77 (8), 65 (16), 56 (3), 51 (7), 43 (12).

HRMS (EI): calcd. for $C_{14}H_{18}N_1O_3F_3$ $[M]^+$ 305.1233, found: 305.1235.

IR (ATR, neat, cm^{-1}): 3327 (m), 2971 (w), 1690 (s), 1540 (s), 1466 (w), 1295 (m), 1262 (s), 1145 (s), 1099 (s), 1019 (m), 694 (s).

Synthesis of (3*S*)-3-amino-1,1,1-trifluoro-4-methylpentan-2-ol hydrochloride (5.9):



5.9

Compound **5.9** was prepared following a modified literature procedure.[182] benzyl ((3*S*)-1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)carbamate (**5.11)** (3.86 g, 12.63 mmol, 1.0 equiv.) was dissolved in EtOAc (9 ml), and thereto was added palladium hydroxide (20% on carbon) (160 mg, 228 µmol, 0.02 equiv.) all at once. The mixture was stirred under an H_2 atmosphere for 24 hours. Thereafter, the catalyst was removed by filtration through a pad of Celite. The filtrate was concentrated under reduced pressure (max. of 100 mbar due to the sublimation of the free aminoalcohol). The oily residue was purified by column chromatography (*n*-pentane:EtOAc = 5:3) and concentrated under reduced pressure (max. of 100 mbar vacuum). Thereto was added 1M HCl in diethyl ether (36 ml) and the mixture was immediately concentrated under reduced pressure and dried at 40 °C yielding the title compound **5.9** (2.085 g, 10.04 mmol, 80%) as a white solid. The analytical data is stated for the free amine base form of **5.9**.

m.p. = 78–79 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.96 (qd, J = 7.7, 5.6 Hz, 1H), 2.66 – 2.53 (m, 1H), 1.84 (dt, J = 13.5, 6.8 Hz, 1H), 1.06 – 0.92 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 125.9 (q, J = 284.8 Hz), 69.2 (q, J = 28.2, 25.6 Hz), 59.4, 30.6, 20.0.

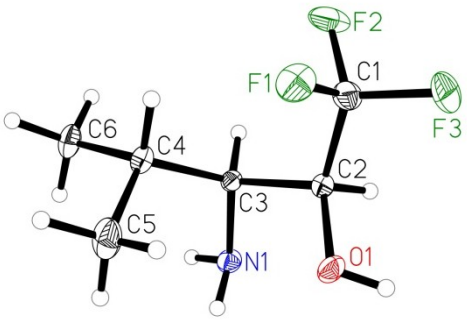
^{19}F NMR (282 MHz, $CDCl_3$) δ = –73.25 (q, J = 9.6, 8.9 Hz).

MS (EI) *m/z* (relative intensity): 171 (1) [M^+], 128 (100), 108 (2), 80 (14), 73 (4), 72 (70), 55 (24).

IR (ATR, neat, cm^{-1}): 3123 (br., w), 2962 (w), 2756 (w), 1576 (w), 1275 (m), 1153 (s), 1124 (s), 1093 (s), 934 (s), 854 (s).

Crystallographic Data of of (3*S*)-3-amino-1,1,1-trifluoro-4-methylpentan-2-ol (5.9)

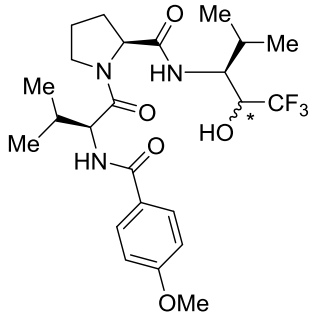
Data were collected on a Bruker Kappa APEX II Duo diffractometer using Mo-Kα radiation. The structures were solved by direct methods (SHELXS-97: Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112.) and refined by full-matrix least-squares procedures on F^2 (SHELXL-2014 and SHELXL-2018, resp.: Sheldrick, G. M. *Acta Cryst.* **2015**, *C71*, 3.). XP (Bruker axs) was used for graphical representations.



chemical formula	$C_6H_{12}F_3NO$	
formula weight	171.17	
crystal system	orthorhombic	
unit cell dimensions		
	$a = 6.3680(3)$ Å	$\alpha = 90$ °
	$b = 9.0144(5)$ Å	$\beta = 90$ °
	$c = 14.1363(8)$ Å	$\gamma = 90$ °
***V* [Å^3]**	811.48(7)	
***T* [K]**	150(2)	
space group	$P2_12_12_1$	
Z	4	
μ [mm^{-1}]	0.14	
density [g/cm^3]	1.401	
no. of reflections measured	20076	
no. of independent reflections	1967 (R_{int} = 0.020)	
no. of observed reflections (*I* > 2σ(*I*))	1920	

no. of parameters	115
R_1 ($I>2\sigma(I)$)	0.025
wR_2 (all data)	0.068
Goodness of fit on F^2	1.05
largest diff. peak and hole [e/Å^3]	0.21 and -0.19

Synthesis of (2*S*)-1-((4-methoxybenzoyl)-*L*-valyl)-*N*-((3*S*)-1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)pyrrolidine-2-carboxamide (5.12):



5.12

Compound **5.12** was prepared following a similar literature procedure.[178] (4-methoxybenzoyl)-*L*-valyl-*L*-proline (**5.6**) (81 mg, 232 µmol, 1.0 equiv.) was dissolved in DMF (4 ml), and thereto were added (3*S*)-3-amino-1,1,1-trifluoro-4-methylpentan-2-ol (**5.9**) (44 mg, 253 µmol, 1.1 equiv.) and *N*-hydroxybenzotriazole hydrate (72 mg, 471 µmol, 2.05 equiv.) all at once and the mixture was allowed to stir for 10 minutes. Thereafter, triethylamine (82 µl, 586 µmol, 2.55 equiv.) was added followed by EDCI (69 mg, 366 µmol, 1.55 equiv.) and the mixture was stirred at r.t. for 20 hours. The reaction mixture was then diluted with EtOAc (15 ml) and washed with 1N aq. HCl solution (10 ml), water (10 ml), 1N aq. NaOH (10 ml) and brine, respectively. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (dichloromethane:methanol = 99:1 → 97:3) yielding the desired compound **5.12** (84 mg, 167 µmol, 72%) as a white foam.

R_f = 0.34 (dichloromethane:methanol = 95:5, UV, $KMnO_4$).

^{1}H NMR (300 MHz, DMSO-d_6) δ = 0.81 (d, J = 6.9 Hz, 6H), 0.95 (dd, J = 11.5, 6.7 Hz, 6H), 1.62 – 2.21 (m, 6H), 3.54 – 3.67 (m, 1H), 3.80 (m, 4H), 3.86 – 4.14 (m, 2H), 4.30 (dd, J = 7.6, 5.0 Hz, 1H), 4.43 (t, J = 8.7 Hz, 1H), 6.38 (d, J = 7.5 Hz, 1H), 6.91 – 7.05 (m, 2H), 7.69 (d, J = 10.0 Hz, 1H), 7.85 – 7.95 (m, 2H), 8.30 (d, J = 8.1 Hz, 1H).

^{13}C NMR (75 MHz, DMSO-d_6) δ = 15.0, 18.8, 19.2, 19.4, 24.7, 27.5, 28.9, 30.1, 47.3, 50.9, 55.3, 56.8, 59.5, 68.3 (q, J = 27.4, 26.9 Hz), 113.3, 125.9 (q, J = 284.9 Hz) 126.1, 129.4, 161.6, 165.8, 170.1, 171.3.

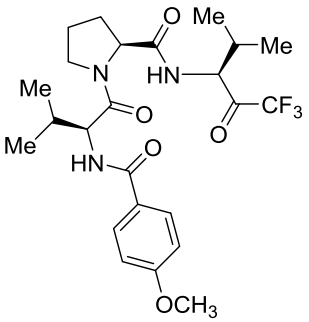
^{19}F-NMR (282 MHz, DMSO-d_6) δ = −74.2.

MS (EI) *m/z* (relative intensity): 501 (1) [M^+], 295 (1), 269 (1), 234 (21), 206 (16), 191 (1), 170 (1), 152 (1), 136 (9), 135 (100), 117 (1), 107 (4), 92 (6), 77 (9), 70 (44), 43 (5).

HRMS (EI): calcd. for $C_{24}H_{32}N_3O_5F_3$ [M-H] 499.2289, found: 499.2290.

IR (ATR, neat, cm^{-1}): 3300 (m), 2963 (m), 1622 (s), 1536 (m), 1500 (m), 1439 (m), 1307 (w), 1253 (s), 1167 (m), 1139 (s), 1099 (m), 1028 (m).

Synthesis of (*S*)-1-((4-methoxybenzoyl)-*L*-valyl)-*N*-((*S*)-1,1,1-trifluoro-4-methyl-2-oxopentan-3-yl)pyrrolidine-2-carboxamide (5.13):



5.13

Compound **5.13** was prepared following a similar literature procedure.[178] (2*S*)-1-((4-methoxybenzoyl)-*L*-valyl)-*N*-((3*S*)-1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl)pyrrolidine-2-carboxamide (**5.12**) (40 mg, 80 µmol, 1.0 equiv.) was dissolved in a mixture of *t*-BuOH (320 µl) and water (400 µl) and the solution was cooled to 0 °C. Then, 0.6 N aq. NaOH (400 µl) was added to the mixture followed by the dropwise addition of an aqueous solution of $KMnO_4$ (39 mg, 240 µmol in 614 µl of water) over 1 h at 0 °C. The reaction was complete judging TLC after 1 hour. Methanol (155 µl) was then added to the reaction mixture to quench the remaining $KMnO_4$ and the solution was stirred for further 1 hour at 0 °C. Thereafter, the solution mixture was filtered through Celite and extracted with EtOAc (3x10 ml). The organic fraction was washed with 1N aq. HCl (10 ml) and brine (10 ml) respectively and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (dichloromethane:methanol = 99:1) yielding the title compound **5.13** (40 mg, 80 µmol, quant.) as a white foam.

$\mathbf{R_f}$ = 0.26 (dichloromethane:methanol = 97:3, UV (254 nm), $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.94 – 1.02 (m, 3H), 1.06 – 1.21 (m, 9H), 1.90 – 2.05 (m, 1H), 2.06 – 2.17 (m, 1H), 2.16 – 2.32 (m, 2H), 2.33 – 2.47 (m, 2H), 3.75 – 3.87 (m, 1H), 3.94 (s, 3H), 4.03 (m, 1H), 4.75 (dd, J = 8.1, 2.9 Hz, 1H), 4.86 – 5.00 (m, 2H), 6.85 – 7.10 (m, 3H), 7.73 (d, J = 7.4 Hz, 1H), 7.78 – 8.05 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 16.8, 18.2, 19.6, 19.8, 25.2, 27.3, 29.2, 31.7, 48.1, 55.5, 56.1, 59.2, 59.8, 113.8, 115.5 (q, j = 292.91 Hz), 126.1, 129.1, 162.5, 166.9, 171.5, 172.8, 190.56 (q, J = 34.4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ = –76.41.

MS (EI): *m*/*z* (relative intensity): 499 (1) [M^+], 267 (1), 234 (12), 206 (14), 191 (1), 152 (1), 135 (100), 125 (1), 107 (4), 92 (6), 77 (9), 70 (37), 43 (7).

HRMS (EI): calcd. for $C_{24}H_{32}F_3N_3O_5$ [$M]^+$ 499.2289, found: 499.2294.

IR (ATR, neat, cm^{-1}): 3257 (br., w), 2967 (w), 1767 (w), 1694 (w), 1622 (m), 1538 (w), 1152 (m), 1026 (w), 843 (w).

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9 Curriculum Vitae

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09/10-09/12/2018	**ORCHEM 2018**, Berlin, Germany **F. El-Hage**, J. Pospech *"Development of new Pharmaceuticals for individualized Therapies of Hereditary Disorders of the Liver and Pancreas"* (Poster presentation)
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10 Publications

[1] J. M. Modenbach, F. U. Weiss, M. Gronbach, C. Oppermann, **F. El-Hage**, J. Pospech, M. M. Lerch, M. Sendler, *Pancreatology* **2018**, *18*, 24.
"An in vitro system to evaluate potential therapeutic substances for ER stress reduction during pancreatitis"

[2] J. Lukas, J. Pospech, C. Oppermann, C. Hund, K. Iwanov, S. Pantoom, J. Petters, M. Frech, S. Seemann, F.-G. Thiel, J.-M. Modenbach, R. Bolsmann, L. de Freitas Chama, F. Kraatz, **F. El-Hage**, M. Gronbach, A. Klein, R. Müller, S. Salloch, F.-U. Weiss, P. Simon, P. Wagh, A. Klemenz, E. Krüger, J. Mayerle, M. Delcea, U. Kragl, M. Beller, A. Rolfs, M. M. Lerch, M. Sendler, *Advances in Medical Sciences* **2019**, *64*, 315–323.
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"Photo-mediated Decarboxylative Giese-Type Reaction using Organic Pyrimidopteridine Photoredox Catalysts"