Development of Novel Synthetic Methodologies towards α-and δ-Amino Acid Derivatives using Visible Light-Induced Photoredox Catalysis

Dissertation

For the attainment of the degree

Dr. rer. nat.

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Kay Merkens

born

21.11.1993 in Langenfeld (Rhld.), Germany

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Parts of the work have already been published:

- Synthesis of Unnatural alpha-Amino Acid Derivatives via Light-mediated Radical Decarboxylative Processes, K. Merkens,[#] F.J. Aguilar Troyano,[#] J. Djossou, A. Gómez-Suárez, *Adv. Synth. Catal.* **2020**, *362*, 2354 – 2359. ([#] These authors contributed equally)
  (Highlighted in *Synfacts*[1]; highlighted in *Organic Process Research & Development* [2])

- Synthesis of γ-Oxo-α-amino Acids via Radical Acylation with Carboxylic Acids, K. Merkens,[#] F.J. Aguilar Troyano,[#] K. Anwar, A. Gómez-Suárez, *J. Org. Chem.* **2021**, *12*, 8448 – 8456. ([#] These authors contributed equally)
  (Highlighted in *Synfacts*[3]; highlighted in *Organic Process Research & Development*[4])

- Accessing α-amino ketyl radicals from β-amino alcohols via chemoselective hydrogen atom transfer catalysis, K. Merkens, N. Sanosa, I. Funes-Ardoiz, A. Gómez-Suárez, *ACS Catal.* **2022**, *12*, 13186 – 13192.

Further publications of the author:

- Selectfluor® Radical Dication ($TEDA2^{+\cdot}$) – A Versatile Species in Modern Synthetic Organic Chemistry, F.J. Aguilar Troyano,[#] K. Merkens,[#] A. Gómez-Suárez, *Asian J. Org. Chem.* **2020**, *9*, 992 – 1007. ([#] These authors contributed equally)

- Radical-Based Synthesis and Modification of Amino Acids, F.J. Aguilar Troyano,[#] K. Merkens,[#] K. Anwar, A. Gómez-Suárez, *Angew. Chem. Int. Ed.* **2021**, *60*, 1098 – 1115. ([#] These authors contributed equally)
  (German version: *Angew. Chem.* **2021**, *133*, 1112 – 1130)

- Radical Deoxyfunctionalisation Strategies, K. Anwar,[#] K. Merkens,[#] F. J. Aguilar Troyano,[#] A. Gómez-Suárez, *Eur. J. Org. Chem.* **2022**, DOI:10.1002/ejoc.202200330. ([#] These authors contributed equally)

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Dedicated to my family

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I. General Introduction

I.1 – Amino Acids

Amino acids (AAs) are of eminent importance for life. This key structural motif is considered to be among the first organic substances on Earth and it is hypothesized to have made a decisive contribution to the origin of life as we know it.[5,6] Though structurally simple, it is their defined structure that makes it possible to build complex molecules such as proteins and enzymes. Almost all biological processes are in some way linked to amino acids, that is why they are sometimes referred to as the "molecules of life".[7] In the early 1800s, Vauquelin and Robiquet isolated the first amino acid from asparagus and thus named it asparagine.[8] It took until 1935 for all canonical α-amino acids – amino acids found in the genetic code – to be isolated and characterized.[9] Twenty-one so-called proteinogenic α-amino acids (20 canonical α-AAs and selenocysteine, which is present in all eukaryotic life) are sufficient to create the multitude of different proteins and enzymes that are eminently important for life (Figure 1). Interestingly, nature has produced exclusively the L-enantiomer of these amino acids – a fact that puzzles scientists to this day.[10]

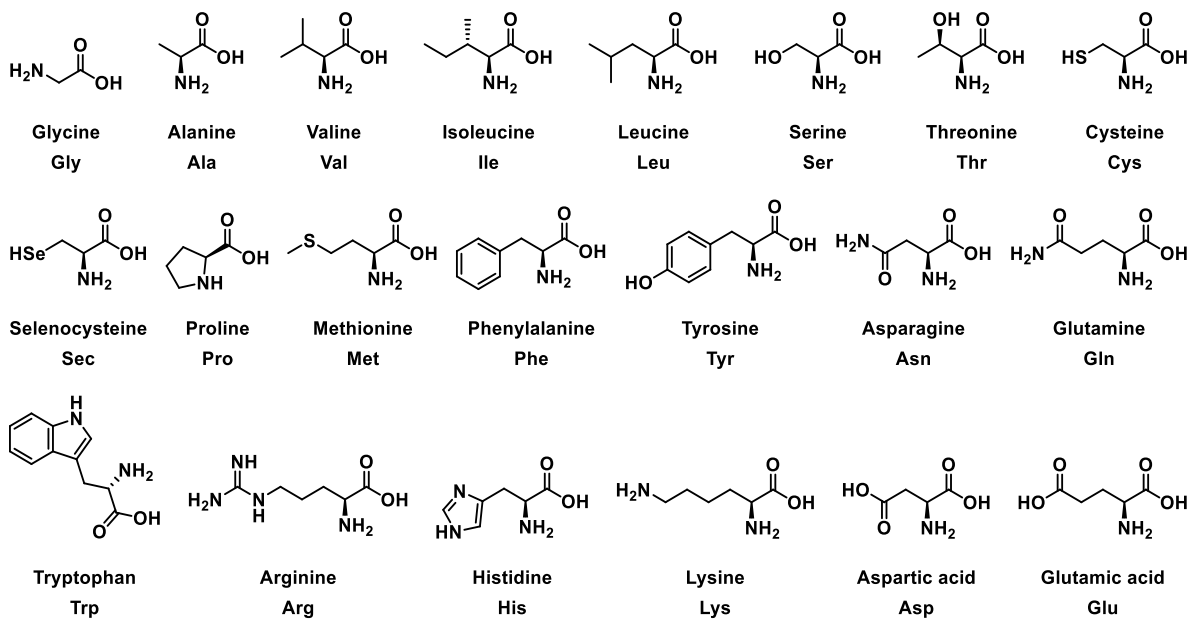


Figure 1. 21 proteinogenic α-amino acids.

In addition to these proteinogenic amino acids, there are other naturally occurring amino acids that do not function directly as building blocks in human life but are, nevertheless, of great importance. Moreover, β-,γ- and δ-amino acids have also been developed by nature for various applications. To date, over 800 naturally occurring non-proteinogenic amino acids, plus even more synthetic amino acids, are known.[11] Besides their significance in biological systems, their highly functionalized nature also makes amino acids an important class of substances with applications across many fields. For example, they are used as building blocks in synthetic

organic chemistry, as ligands in transition-metal catalysis,[12] as chiral synthons in the synthesis of biologically active molecules and peptidomimetics,[13–16] and in biochemistry and material sciences.[17,18]

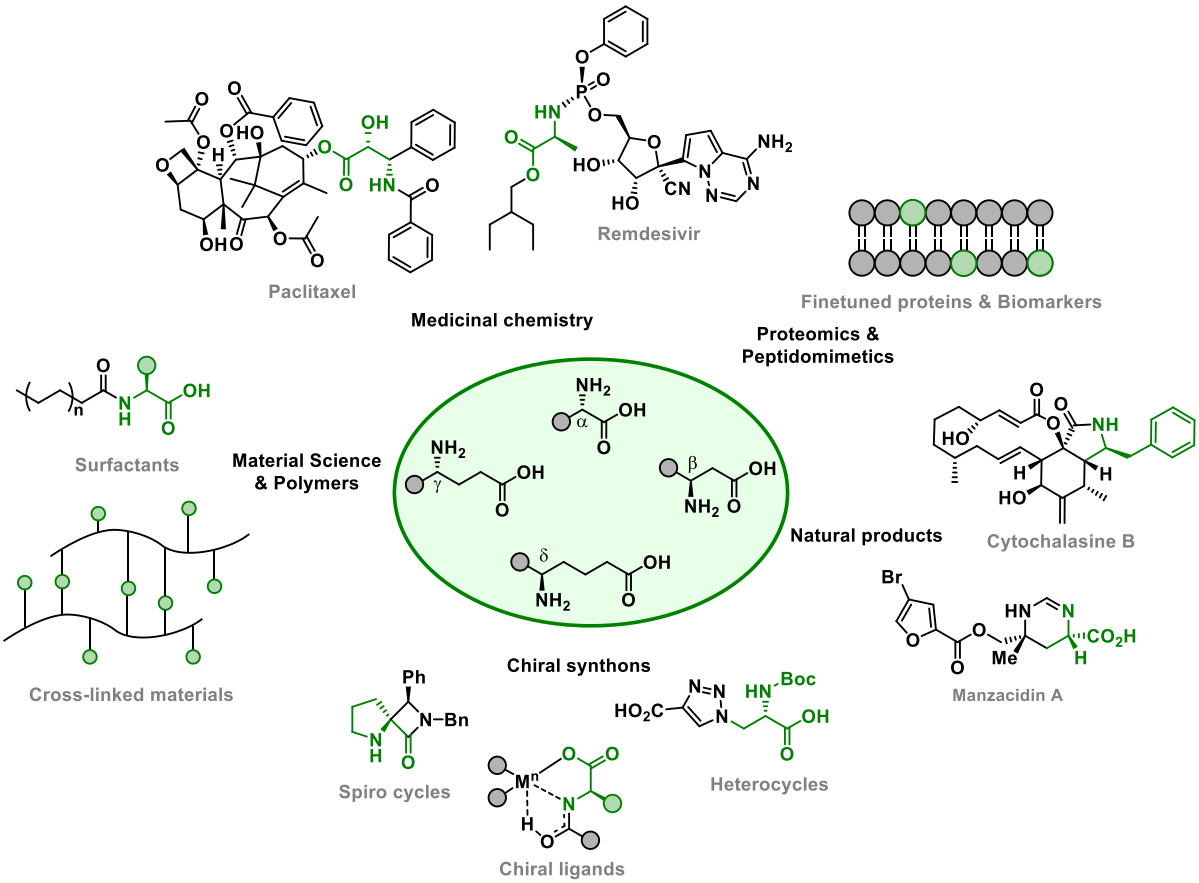


Figure 2. Applications of α,β,γ-and δ-amino acids.

For the further advancement of these fields, it is important to produce new non-naturally occurring amino acids – so-called unnatural amino acids (UAAs). By synthesizing artificial amino acids, it is, for example, possible to finetune certain properties of a peptide in which the UAA is incorporated in. For example, peptidic drug candidates are gaining more attention in pharmaceuticals,[19] attributed to their high target selectivity and effectiveness. This results in a lower risk of undesirable interactions with other drugs, as well as a lower toxicity than it would be the case when using "classical" small molecules as pharmaceuticals.[20] Notwithstanding, peptides generally lack physiological stability and membrane permeability,[16,19] which limits their use as pharmaceuticals. The use of peptidomimetics – compounds handcrafted to mimic certain properties of the parent peptide – can tackle these limitations, as they usually possess an enhanced metabolic stability as well as high selectivity and affinity compared to the parent peptide (Figure 3).

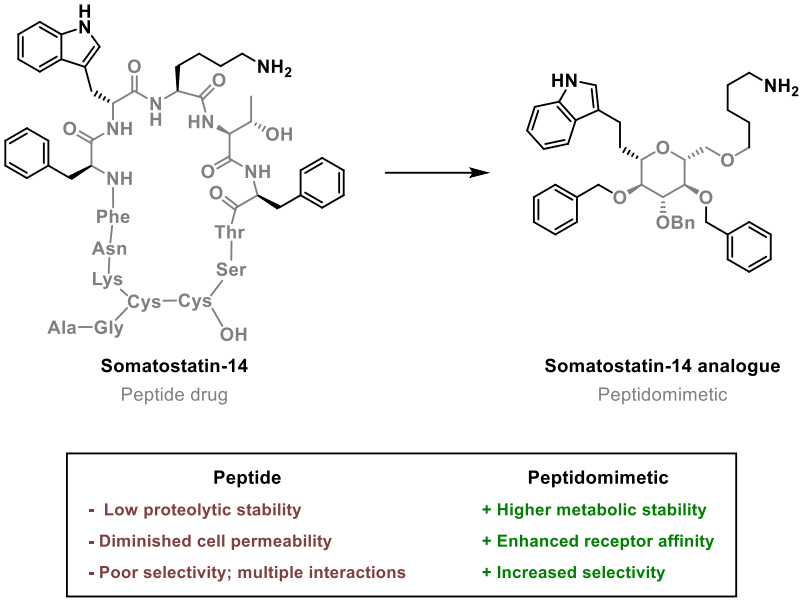


Figure 3. Advantages of peptidomimetics vs. peptides.[21]

As a general concept in peptidomimetics, the structure of the parent peptide is modified by introduction or deletion of structural elements being not important for the biological activity. If a certain side chain of a natural amino acid needs to be replaced, this can be achieved via the specific incorporation of an UAA bearing a side chain mimicking the structure of the lead compound (Figure 4).

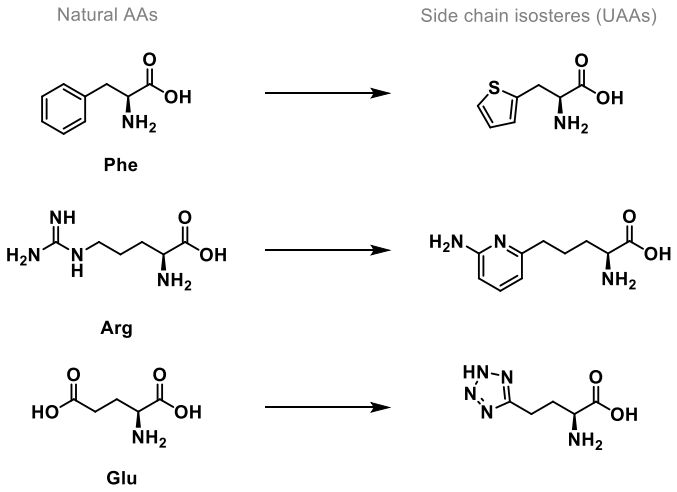


Figure 4. UAAs as side chain isosteres for natural amino acids.[21]

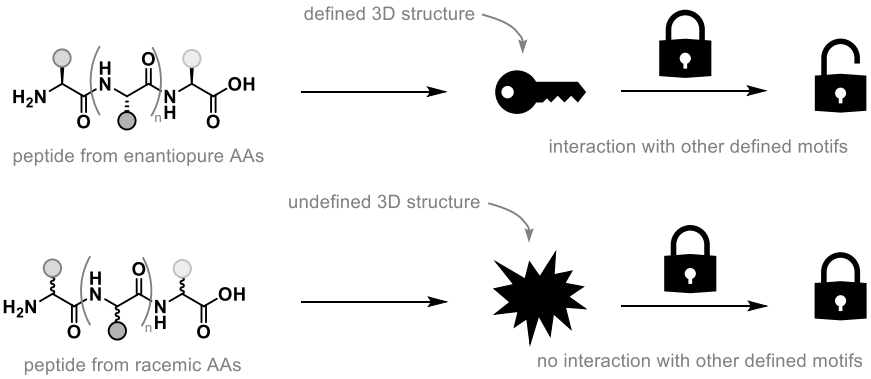
The introduction of an UAA with, for example, an additional functional group in the side chain can improve the pharmacokinetic properties (e.g., solubility, cell membrane permeability and stability) of the peptide without losing target selectivity and efficiency.[22] Therefore, to finetune the peptides pharmacokinetic properties via UAA-insertion, it is important to have access to UAA scaffolds in a straightforward manner. The same rationale applies to other fields, for example, as mentioned above, amino acids can also be employed as ligands in transition metal

catalysis or serve as chiral building blocks for asymmetric organocatalysis.[23,24] The sole use of naturally occurring amino acids would ultimately limit the number of catalysts that can be produced. Therefore, the introduction of tailor-made UAAs may open new possibilities to further improve catalytic systems in terms of stability, selectivity and reactivity.

Beside their side chain, amino- and carboxylic acid functionality, naturally occurring AAs offer another important property: chirality. As mentioned above, nature produces only the L-enantiomers of the 21 proteinogenic α-AAs.[10] It is precisely this property of chirality that makes the formation of complex, three-dimensional structures (such as proteins and enzymes) possible in the first place. Through various, non-covalent interactions between the individual chiral amino acids, an originally linear chain of AAs eventually forms a single, well-defined supramolecular conformation – a process that is known as molecular self-assembly.[25]

The precisely defined three-dimensional structure of, for example, an enzyme is – according to the so-called lock-and-key principle – the basis for physiological processes to run extremely selectively and effectively, and thus also the basis of life as we know it (Figure 5).[26]

The molecular self-assembly of racemic amino acids, on the other hand, would form numerous different, non-defined supramolecular conformations. This is because both enantiomers of an amino acid can be incorporated into a peptidic chain with equal probability, thus leading to different interactions and ultimately causing varying three-dimensional structures.



enantiopure AAs	vs.	racemic AAs
defined stereocenters		undefined stereocenters
⇓		⇓
defined intramolecular interactions		undefined intramolecular interactions
⇓		⇓
defined 3D-structure		undefined 3D-structure
⇓		⇓
defined biological activity		no or diminished biological activity

Figure 5. Peptides from enantiopure AAs build up defined 3D-structures.

Due to the importance of enantiopure UAAs across a wide range of scientific fields, numerous synthetic strategies employing traditional 2-e$^-$ disconnection logic, mostly relying on enzymatic or transition metal-catalyzed processes,[27–34] have been developed to access them (Figure 6).

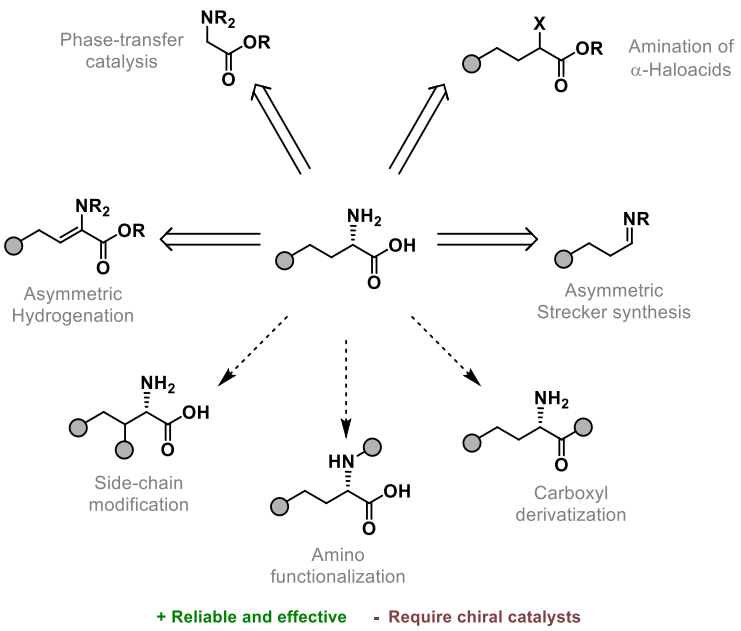


Figure 6. Classical 2-e⁻ approaches for de novo synthesis or derivatizations of amino acids.

Despite being reliable and effective, these methodologies usually require the use of chiral ligands or catalysts to generate the key α-amino stereocenter. Since the preparation and optimization of chiral ligands/catalysts is often a highly time- and resource-consuming enterprise, the development of novel methodologies to build – or derivatize – amino acids, bypassing the need for asymmetric catalysis, is of the upmost importance. As an alternative to the well-studied 2-e⁻ pathways, synthetic strategies employing radical chemistry and 1-e⁻ disconnection logic to access UAAs have experienced a boost in recent decades.[35]

I.2 – Radical Chemistry

Radical chemistry is not a new concept: first publications using open-shell species date back to the 19th century.[36] Compared to classical reactions, radical reactions offer several key advantages: in general, they can be performed under mild conditions, and tolerate a variety of common protecting and functional groups. In addition, radicals are usually very reactive intermediates that – once generated – can initiate a chemical reaction very quickly.[37] Moreover, due to their nature, radical reactions generate new radical intermediates, thus enabling the use of radical chemistry for sequential or chain reactions.[37] Of particular importance was the use of *C*-centered radicals as they grant straightforward access to C–C bond formation. This in turn allowed building complex structures from relatively simple starting materials.[38]

Arguably, the key aspect of radical chemistry is that it often allows transformations not feasible under classical 2-e⁻ pathways. For example, radical reactions in which a *C*–centered radical adds to an alkene is mostly kinetically controlled,[39] thus allowing the synthesis of

thermodynamically non-preferred products.[40] This can be illustrated by the radical cyclization of 1-bromohex-5-ene (**1**) using $Bu_3Sn–H$ (Figure 7).[40] An explanation for the generation of *C*-centered radicals from haloalkanes using $Bu_3Sn–H$ is given in (Figure 8).
Hex-3-enyl radical (**2**) can react via multiple pathways:

Pathway A: hydrogen atom transfer (HAT) with another molecule of $Bu_3Sn–H$ to afford product **3** (a process dependent on the concentration of $Bu_3Sn–H$).
Pathway B: 6-endo-trig cyclization to form product **4**.
Pathway C: 5-exo-trig cyclization to form product **5**.

Pathway B should be favored under thermodynamic control, since it generates the more stable secondary radical intermediate **6**, leading to product **4**.[40] However, it was found that compound **5** is the main product of the reaction, thus implying that the main pathway in operation is C. This can be rationalized by two major findings:

1) The 5-exo-trig cyclization is faster than the 6-endo-trig cyclization ($k_{1,5} \approx 50 \times k_{1,6}$ at 65 °C).[41]
2) The ring closing step is not reversible – thus favoring the reaction of primary radical intermediate **7** with $Bu_3Sn–H$ to deliver the targeted product.[42]

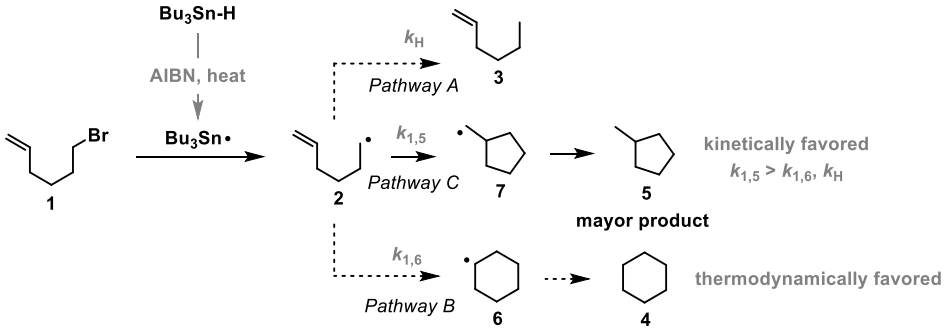


*Figure 7. Radical cyclization of 1-bromohex-5-ene (**1**).*

Another key feature of radical chemistry is that it enables access to sterically congested compounds that are not accessible – or very difficult to access – via "classical" routes.[43] One reason for this enhanced reactivity is the lack of counterions or aggregation spheres – due to the lack of solvation – when compared to ionic intermediates, making radical chemistry especially interesting for the synthesis or derivatization of sterically hindered bonds including quaternary or neopentyl centers.[43] Finally, radical reactions are typically chemo-, regio- and stereoselective.[40,44,45]
Despite the advantages offered by radical chemistry over classical transformations, it played initially only a subordinate role. This may be due to the, at the time, limited numbers of methods

available to generate radical species. Over the second half of the 20th century, numerous approaches to generate *C*-centered radicals were conceived; for example, the homolytic cleavage of labile C–X bonds, with X being mostly Br or I.

In a seminal work by Kuivila in 1963, alkanes were synthesized by the radical reduction of alkyl halides in combination with *in situ* formation of $Bu_3Sn–H$ from $Bu_3Sn–Cl$.[46] This approach is based on the homolytic cleavage of two labile bonds (Sn–H and R–X) and the corresponding formation of two more stable bonds (Sn–X and R–H) as shown in Figure 8.[47] The Bu_3Sn radical is formed via either direct thermolysis of Sn–H or thermal homolysis of azabisisobutyronitrile (AIBN) which acts as radical initiator, abstracting the hydrogen atom of Sn–H.

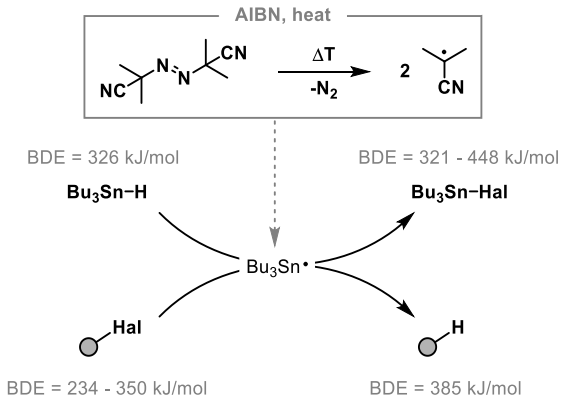


Figure 8. Use of tin hydrides to generate C-centered radicals from alkyl halogenids.

Later, alkyl radicals, generated by the use of tin hydrides, were also used for C–C bond forming reactions as for example the addition to electron-poor alkenes – a reaction that was later known as Giese reaction.[48,49]

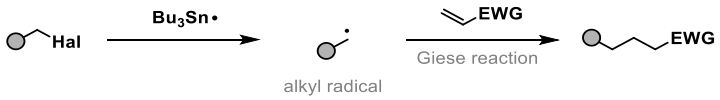


Figure 9. Giese reaction of alkyl radicals generated by the use tin hydrides and alkyl halides.

To expand the versatility of radical chemistry, alternative radical precursors were sought after. In this regard, alkyl alcohols – themselves not reactive enough to undergo direct C-O cleavage to access *C*-centered radicals – were converted into the corresponding xanthates. In the Barton-McCombie reaction, those xanthates were intensively used and proved to be a suitable alternative to alkyl halides as radical precursors.[50,51]

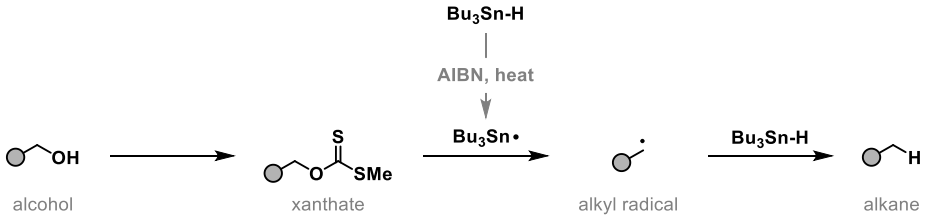


Figure 10. Barton-McCombie deoxygenation of alcohol-derived xanthates.

Unfortunately, organotin compounds are in general highly toxic[52] and thus the design of alternative tin-free methodologies became an important topic of research. Numerous approaches were developed, including the use of $(TMS)_3Si–H$, thiols, organoboranes or metal-based reagents (Ti^{III}, Sm^{II} and Mn^{II}).[53–58] In the 1980s, Barton and co-workers published their work on generating alkyl radicals from thiohydroxamate esters (so-called Barton esters).[59] Carboxylic acids were converted into redox active esters (RAEs) bearing a labile O–N bond, which can fragment upon heating, or via photolysis, to form acyloxy radicals. These, in turn, undergo decarboxylation ultimately delivering a *C*-centered alkyl radical (Figure 11).

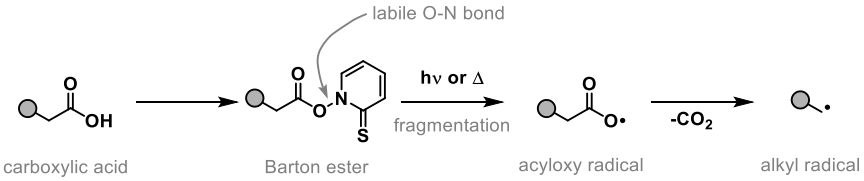


Figure 11. Formation of alkyl radicals via fragmentation of Barton esters.

Inspired by Barton's seminal work, alternative RAEs capable of undergoing fragmentation (e.g., via photolysis) were developed, including *N*-hydroxyphthalimide (NHPI) esters and benzophenone oxime esters (Figure 12).[60]

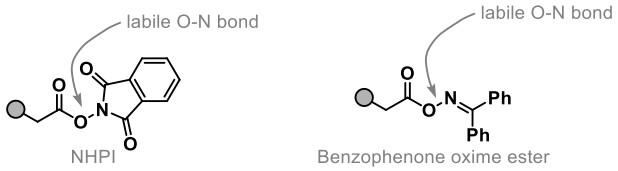
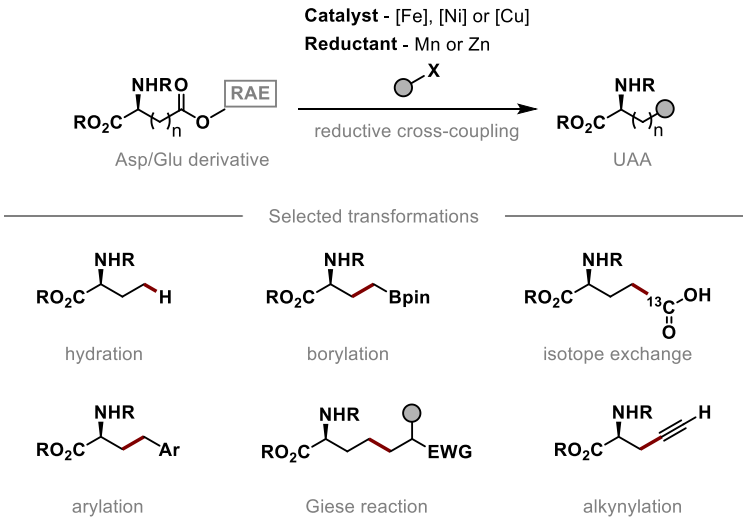


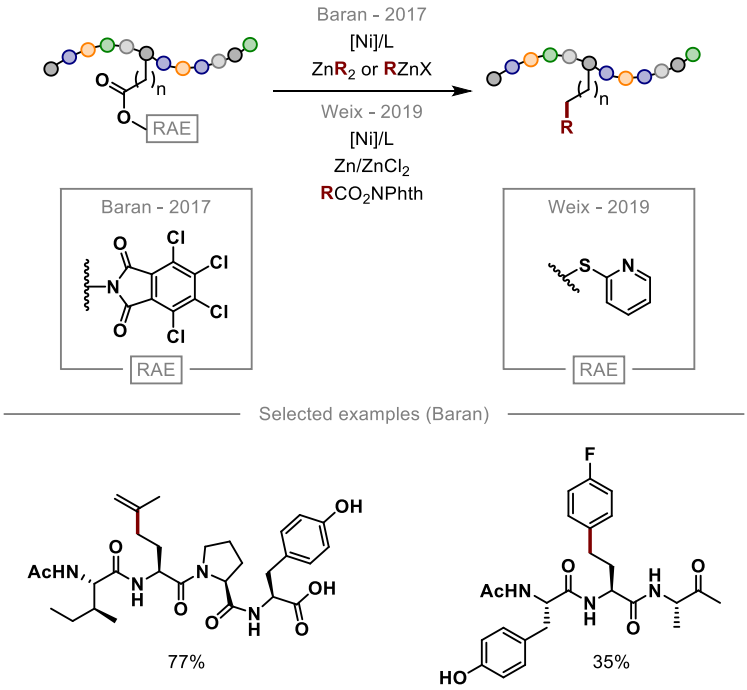
Figure 12. Alternative RAEs capable of undergoing decarboxylation.

This general approach of activating a carboxylic acid by transforming it into a RAE was also applied to the decarboxylative derivatization of amino acids like e.g., Asp or Glu in the presence of a transition metal catalyst and a reductant. Numerous derivatizations were performed including isotope exchange by introducing ^{13}C-labelled CO_2 or Giese reactions with an α,β-unsaturated acceptor molecule (Scheme 2).[35]



Scheme 1. Amino acid derivatizations using RAEs.

In addition to this, selective peptide modifications were performed by transforming Asp- or Glu-residues into RAE-derivatives and subsequently cross-couple them under reductive conditions (Scheme 2).[35]



Scheme 2. Reductive modification of Asp/Glu residues in peptide chains.

Besides being a tin-free alternative, the inherent photolability of RAEs allow for a photochemical fragmentation to deliver C-centered radicals under mild conditions.

I.3 – Photochemistry

Light-irradiation as energy source to drive a chemical reaction is attractive, since photons are considered as " traceless reagents"[61] which do not form by-products, thus leaving the reaction "without a trace". Moreover, the use of light (especially sun light) as an energy source is quite appealing when thinking about sustainable and green chemistry.[62]

However, "classical" photochemical transformations rely on the use of low-, medium- or high-pressure mercury lamps as radiation sources. Beside the significant toxicity of mercury,[63] these lamps usually possess short lifetimes (500–2000 h) that require periodic costly replacements, are fragile, and operate at very high temperatures (600–900 °C) demanding additional cooling devices.[64,65] Furthermore, mercury lamps emit polychromatic light, which further contributes to selectivity issues, as it can lead to the simultaneous activation of several functional groups.[66] To solve this problem, most of the emitted light has to be filtered out, leading to a low energy efficiency.[64]

A key development on the field of photochemistry was the replacement of mercury lamps by light-emitting diodes (LEDs). This brought several advantages, including longer life-times and a higher energy efficiency.[67,68] In addition to this, LEDs possess a narrow, nearly monochromatic emission spectrum, leading to a better control over the irradiation energy, thus allowing for the selective excitation of a given molecule.[66]

To illustrate the wavelength-dependence of photochemical processes, Figure 13 shows how the use of quinoline *N*-oxides (**8**) under mercury lamp irradiation leads to a set of nine different products **9-17**,[69,70] due to the broad UV-light emission spectra and the harsh conditions associated with it. In a recent report, Levin and co-workers presented a C2-selective net carbon deletion of quinolines to access indoles via ring contraction of quinoline *N*-oxides (**8**).[71] To overcome the aforementioned problem of the complex mixture of products obtained when **8** is irradiated using mercury lamps, the authors showed that the same reaction leads to much cleaner results when a UV light emitting LED is used instead of a mercury lamp, furnishing **18** as mayor product in very high yields. Benzoxazepine **18** was then successfully transformed into the corresponding indole using an acidolysis-deacylation sequence. In their manuscript, the authors stated that when a broad-banded mercury lamp was used as irradiation source – the complex product mixture is arising from so-called secondary photo-processes causing the intermediary formed products to undergo further rearrangements.

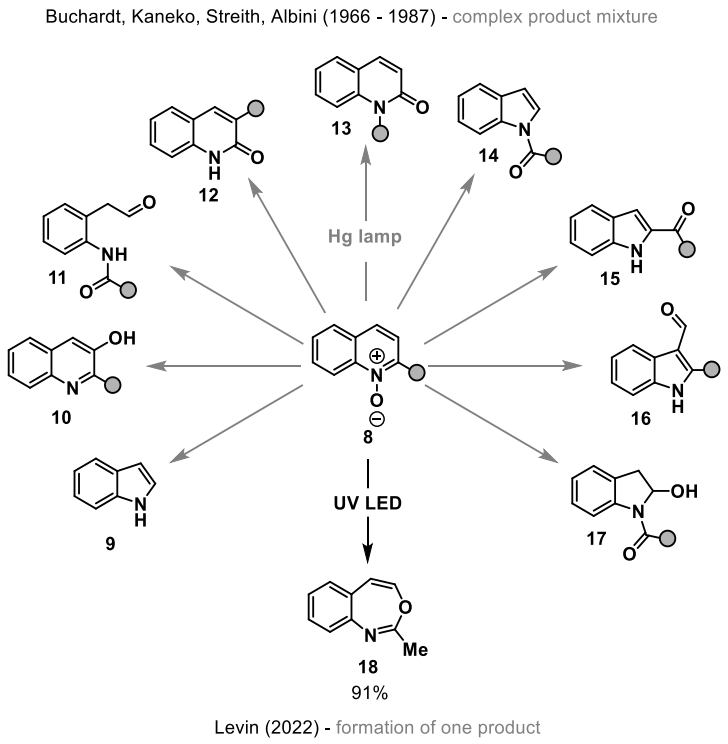


Figure 13. Quinoline N-oxide rearrangements under "classical" mercury lamp irradiation vs UV-LED irradiation.

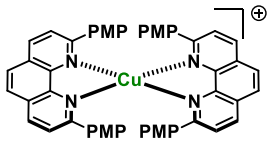
Despite those advancements, in most cases, highly energetic UV-light is required to drive photochemical reactions[47] – a fact that can be problematic when applying photochemistry to

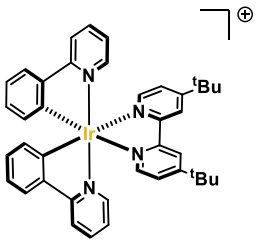
complex molecules: the more energy put into a system the more likely undesired side-reactions take place.

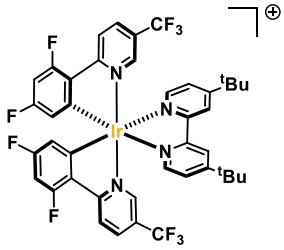
To overcome this issue, molecules with the ability to harvest the significantly lower energy of visible-light were developed.[72–74] These species – known as photocatalysts (PC) and photosensitizers – use the harvested light-energy to drive a chemical reaction that would not take place when the reactant was irradiated with visible-light. This approach enabled an elegant workaround of the problems associated with direct UV-induced photochemistry, allowing modern photochemistry to be broadly applicable and highly predictable.

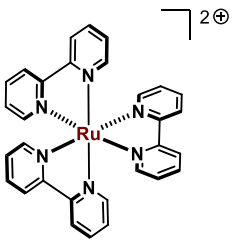
Some of the most important photosensitizers/-catalysts known to date and their photophysical properties are listed in Figure 14.[72,75–78]

Transitionmetal-Photocatalysts



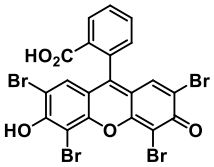


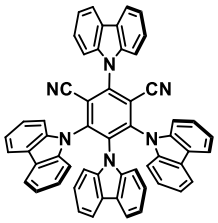


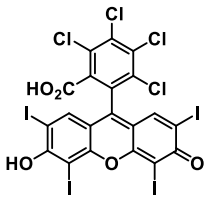


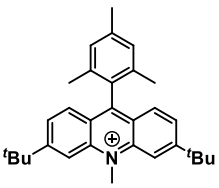
	$[Cu(dap)_2]^+$	$[Ir(ppy)_2(dtbbpy)]^+$	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]^+$ = IrF	$[Ru(bpy)_3]_2^{2+}$
$E(P^+/P)$	+ 0.62 V	+ 1.21 V	+ 1.69 V	+ 1.29 V
$E(P/P^-)$		- 1.51 V	- 1.37 V	- 1.33 V
$E(P^+/P^*)$	- 1.43 V	- 0.96 V	- 0.89 V	- 0.81 V
$E(P^*/P^-)$		+ 0.66 V	+ 1.21 V	+ 0.77 V
λ_{abs}	437 nm	384 nm	380 nm	452 nm

Organo-Photocatalysts





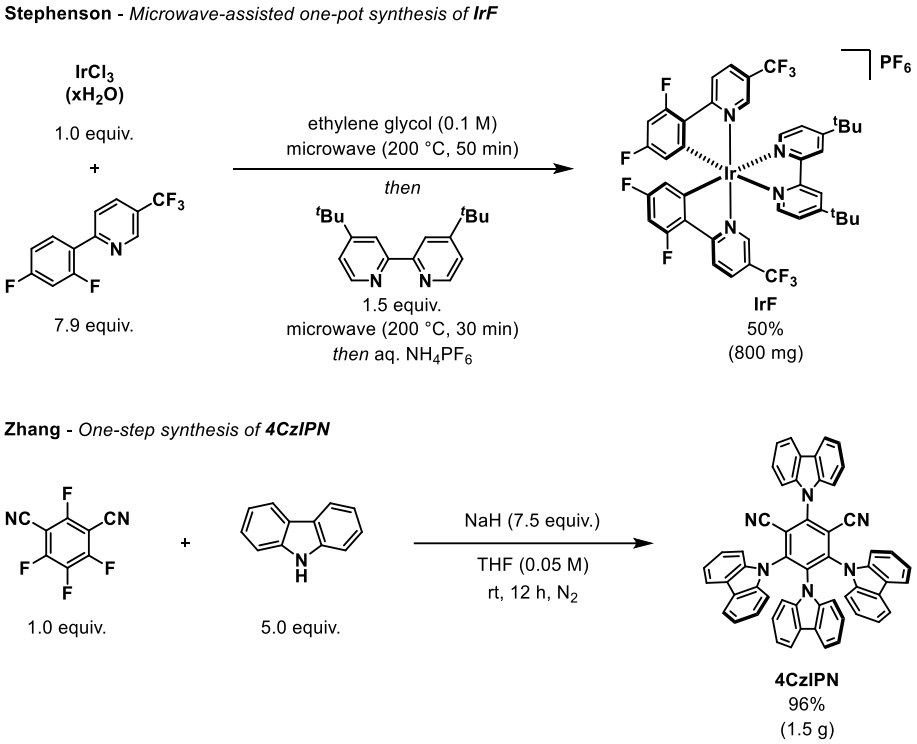




	Eosin Y	4CzIPN	Rose Bengal	Mes-Acr-Me$^+$
$E(P^+/P)$	+ 0.76 V	+ 1.49 V	+ 0.84 V	
$E(P/P^-)$	- 1.08 V	- 1.24 V	- 0.99 V	- 0.49 V
$E(P^+/P^*)$	- 1.15 V	- 1.18 V	- 0.96 V	
$E(P^*/P^-)$	+ 0.83 V	+ 1.43 V	+ 0.81 V	+ 1.45 V
λ_{abs}	520 nm	435 nm	549 nm	425 nm

Figure 14. Some of the most important photocatalysts used in modern photoredox-chemistry.

In this thesis, most photoreactions were carried out using **IrF** or **4CzIPN,** which can be readily prepared according to literature procedures (Scheme 3).[79,80] **IrF** can be made from $IrCl_3$ via a microwave-assisted one-pot protocol, whereas **4CzIPN** can be prepared via a nucleophilic aromatic substitution using 2,4,5,6-tetrafluoroisophthalonitrile as starting material.



*Scheme 3. Straightforward syntheses of **IrF** and **4CzIPN**.*

The development of both photosensitizers and photocatalysts made it possible to apply photochemistry to substrates which would not interact with irradiated light or would do so only inadequately, thus preventing their use in photochemical transformations.

Photosensitization and photocatalysis are two very similar principles, which can ultimately be distinguished by the type of elementary steps that take place during the photoreaction (Figure 16).[81] A photosensitizer absorbs photons and thus is excited. In this excited state, the photosensitizer can release its energy to the substrate to trigger a chemical reaction. This energy transfer can generally be divided into two categories: Förster energy transfer and Dexter energy transfer (Figure 15). Energy transfer between an excited state photosensitizer (D*) and an acceptor molecule can occur via two pathways:

A) The Dexter energy transfer (DET) is a concerted transfer of two e^-.[82] An e^- from the π^* orbital of the photosensitizer is transferred into the acceptors lowest-unoccupied molecular orbital (LUMO), whereas an e^- from the acceptors highest-occupied molecular orbital (HOMO) is relocated into the photosensitizers t_{2g} orbital. Overall, the excited state photosensitizer donates its energy in a double-electron transfer mechanism to a ground state substrate, delivering the ground state photosensitizer and the excited state acceptor. This energy transfer occurs through physical contact.[83]

B) Alternatively, energy transfer can pursue through space (1 – 8 nm), according to the Förster resonance energy transfer (FRET).[84] In here, the e^- from the π^* relaxes back into the

t_{2g}, by donating its energy via vibrational motion to the acceptor, in which one e^- is excited from the HOMO into the LUMO.

Both energy transfers take place with conservation of the total spin of the donor-acceptor pair.

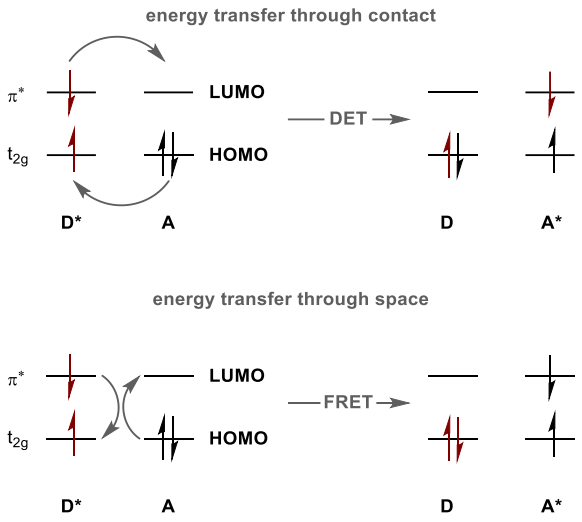


Figure 15. Non-radiative singlet-singlet energy transfers by DET and FRET.

In general, it can be said that photosensitization involves energy transfers, while photocatalysts do not transfer their energy upon excitation to the substrate but use it to initiate electron transfers (Figure 16). If the oxidation state of the photocatalyst changes during the catalytic cycle (e.g., in the case of electron transfers), this is referred to as photoredox catalysis.

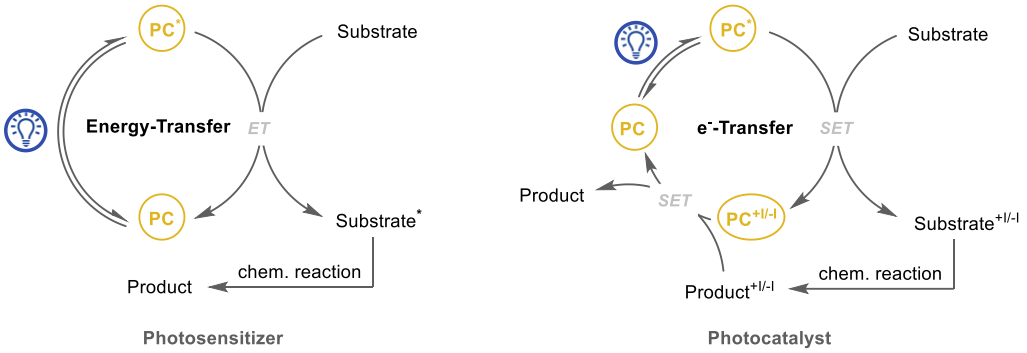


Figure 16. Elementary steps taking place during photosensitization and photocatalysis.

The various relaxation pathways of an excited state photocatalyst can be depicted in a so-called Jabłoński diagram (Figure 17).[85] Upon absorption of light of a suitable wavelength, a photocatalyst is excited from a singlet ground state (S_0) to a very short-living singlet excited state (S_1). From this activated state, the excess energy can be released again via radiative or non-radiative transitions. Radiative deactivation of S_1 to S_0 is known as fluorescence, while radiation-less transition from S_1 to S_0 is called internal conversion (IC), in which the excess energy is released as heat. Alternatively, the electron in the singlet excited state S_1 can reverse its spin, furnishing the long-living triplet excited state (T_1). This transition is named intersystem

crossing (ISC). Again, the excess energy of T_1 can be released via radiation (phosphorescence) or radiationless (ISC). If T_1 is sufficiently long-living, it can interact with another molecule in terms of a photoredox reaction or photosensitization (intermolecular quenching).

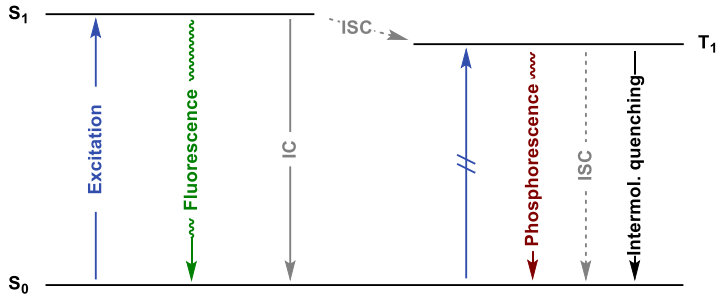


Figure 17. Schematic Jabłoński diagram for relaxation pathways of a photocatalyst.

Classically, transition metal complexes based on iridium or ruthenium are used as photocatalysts. Ligands carrying an extended π-system can capture the energy of the light and cause charge separation in the complex. Here, the choice of ligands or the introduction of additional electron-donating or -withdrawing functional groups can be used to finetune the redox potential of the complex by increasing or decreasing the electron density, and thus tailor it to the desired reactions. The difference in redox potentials of ground and excited state photocatalysts can be rationalized by their molecular orbital diagram (MO-diagram), as shown for $[Ru(bpy)_3]_2^{2+}$ (bpy = bipyridine) in Figure 18.

According to the ligand field theory, the 6d-e^- of Ru^{2+} provide an octahedral, low-spin, configuration in which all t_{2g} molecular orbitals are doubly occupied.[86] Irradiation with blue LED excites a single e^- from its singlet ground state (S_0) into the LUMO of a bpy-ligand (π*), a process that is called metal to ligand charge transfer (MLCT).[72] According to quantum mechanical selection rules, the excited e^- contains the same spin as on the ground state, furnishing the singlet excited state (S_1). Intersystem crossing, a process in which the spin of the excited e^- is switched, delivers the so-called triplet excited state (T_1), bearing two spin-unpaired e^-. The S_1 state is very short-lived ($\tau \sim 100 - 300 \times 10^{-15}$ sec), whereas T_1 is a long-living state ($\tau \sim 1 \times 10^{-6}$ sec).[87,88] This long-lived triplet excited state is of eminent importance, as the photocatalyst needs time to interact with a substrate to drive a chemical reaction.

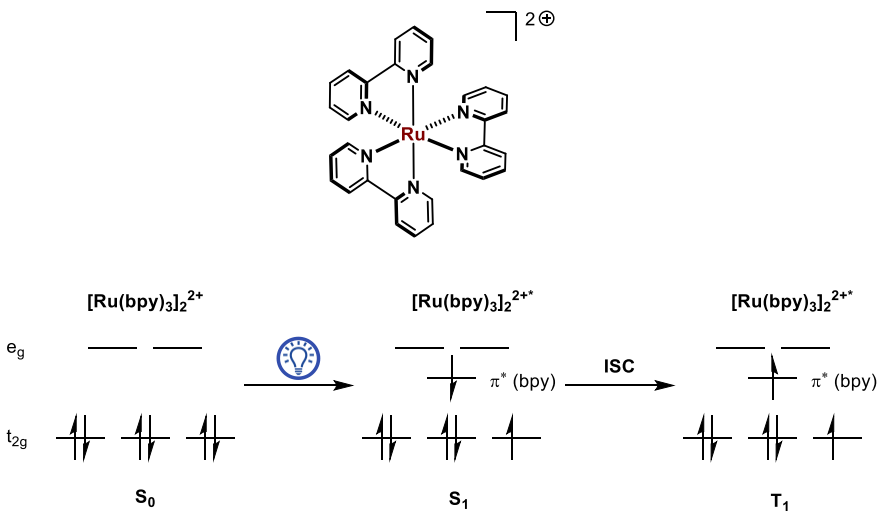


Figure 18. MO diagram of $[Ru(bpy)_3]_2^{2+}$ in ground and excited state.

In its excited state, photocatalysts such as $Ru(bpy)_3^{2+*}$ are both more reducing and more oxidizing than in their ground state. This phenomenon can be rationalized as follows: in its excited state, $Ru(bpy)_3^{2+*}$ possesses an electron in the π^* orbital that can be readily donated due to its enhanced energy level – in this case, the photocatalyst acts as a reductant. Furthermore, in its excited state, $Ru(bpy)_3^{2+*}$ contains an e^--hole in its t_{2g} orbitals, making it more prone to receive an additional e^-, thus acting as oxidant. The redox potentials of the excited state photocatalyst can be finetuned by the choice and substitution pattern of ligands. In general, increasing the electron density of the ligands results in higher reduction potentials of the complex.[89] In addition to transition-metal based complexes, organic dyes can also be used as photocatalysts. Similar to transition metal catalysts, the choice of functional groups, as well as the size of the π-system, plays a major role in the photophysical properties of the catalyst.[78]

I.4 – Applications of Photochemistry for Amino Acid and Peptide Syntheses

No matter in which way the harvested light energy is passed onto the substrates to drive the targeted chemical reaction, the development of photocatalysts and photosensitizers, in combination with the development of powerful LEDs with very distinct emissions, has further stimulated the research field of photoredox catalysis. These light-induced radical pathways represent a good alternative to the classical methodologies using 2-e^- disconnections, thus adding new, straightforward and elegant approaches to the synthetic toolbox of today's chemists. Much of progress has been made in the past decades, and numerous approaches and synthetic precursors have been developed to generate alkyl radicals, including halides, xanthates, redox-active esters, Katritzky salts, B-, S- and Si-based precursors, dihydropyridines (DHP) and many more (Figure 19).[90–94]

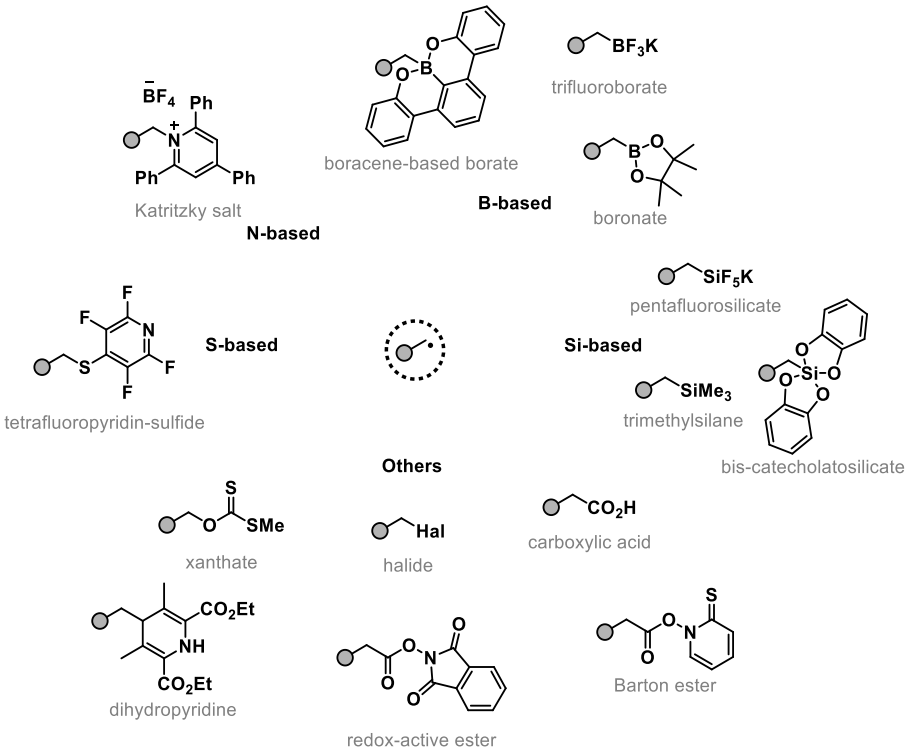
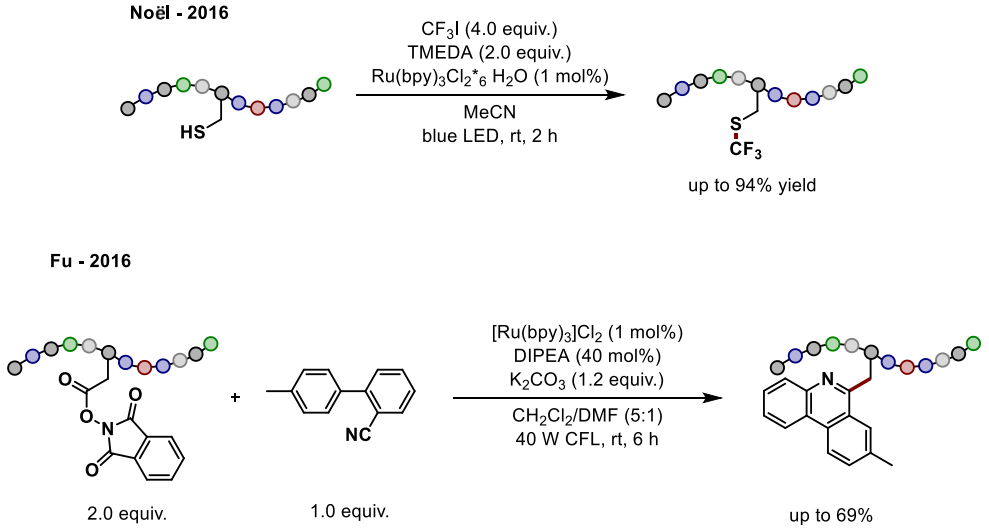


Figure 19. Precursors to generate alkyl radicals.

Some of these approaches were also used in the synthesis of UAAs and the selective derivatization of peptides (Scheme 4). For example, in 2016, Noël and co-workers presented a method to selectively trifluoromethylate Cys-residues in peptides using visible-light photoredox chemistry.[95] In addition to that, several methodologies were developed to decarboxylatively functionalize peptidic side-chains, preactivated as redox-active esters.[96,97] The Fu group reported in 2016 a visible-light mediated method to functionalize amino acids or peptides with *N*-heterocycles.[98] These methodologies do not exclusively apply to peptides and can also be used for the derivatization of amino acids.



Scheme 4. Photochemical derivatization of peptidic side chains.

While radical chemical synthesis and derivatization of unnatural amino acids, peptides and proteins are increasingly used and developed, the stereoselective or stereoretentive synthesis of amino acids remains underdeveloped: for example, α-amino acids are mostly used as radical precursors to access α-amino radicals via decarboxylative processes, which destroys the precious α-amino stereocenter.[99] The development of novel transformations granting access to enantiopure UAAs in a straightforward manner is highly desirable. Visible-light photoredox catalysis offers many opportunities and has already enriched the today's chemist toolbox. Still, methodologies towards enantiocontrolled synthesis of UAAs are underdeveloped.

I.5 – Aim of the Thesis

Aim of this thesis is to broaden the synthetic spectrum for the preparation of UAAs via photoredox-mediated radical pathways, and thus novel synthetic approaches will be investigated. Special attention is hereby paid to the stereoselective or stereoretentive synthesis of UAAs since the α-amino stereocenter is of paramount importance for their subsequent application.

First, new methodologies for the synthesis of α-amino acids will be developed, since these scaffolds represent the most abundant and exploited class of amino acids and are of eminent importance for various scientific fields.[12–14,17,18]

The second part of this thesis deals with the synthesis of the so far rather underdeveloped γ-oxo-δ-amino acids – a substance class often present in biologically active molecules and possessing a multitude of possible applications.[100–114]

Finally, the developed methodologies will be tested towards their utility in a more complex context and thus will be applied to the total syntheses of biologically active compounds.

II. Synthesis of (γ-Oxo-)α-Amino Acids

II.I. (γ-Oxo-)α-Amino Acids via Decarboxylative Giese-type Reactions

II.I.1 – Introduction

In general, the strategies to access α-AAs using radical chemistry can be divided into two main approaches:

1) *de novo* synthesis

2) side chain modification

De Novo Synthesis of α-AAs

The radical-based *de novo* synthesis of α-amino acids can be classified in three main retrosynthetic approaches (Figure 20): a) *C*-centered radical addition to imines, b) α-carbonyl C(sp^3)–H amination, and c) α-amino carboxylation with CO_2.

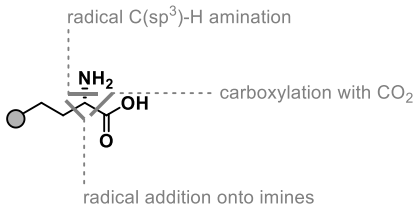
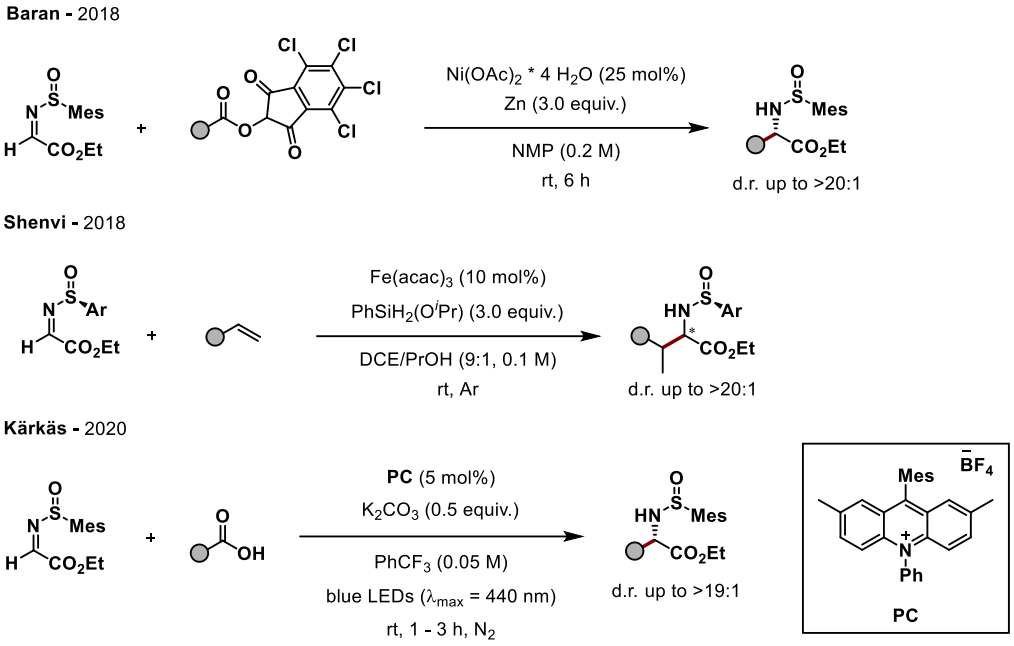


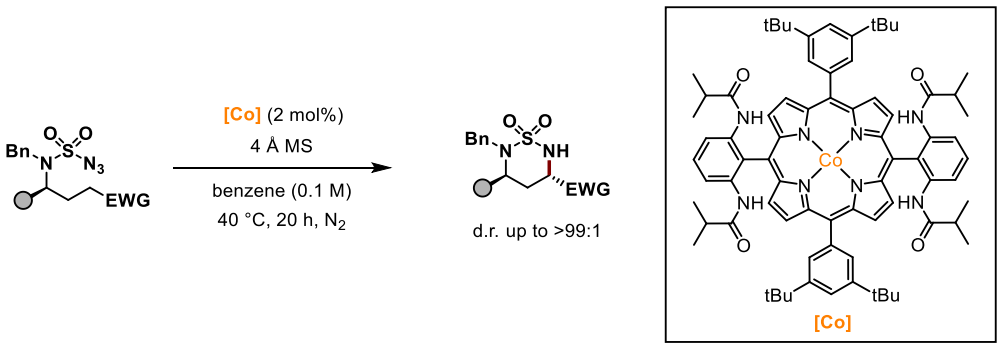
Figure 20. Retrosynthetic approaches towards α-AAs via de novo synthesis.

a) *C*-Centered radical addition to imines: the main approach towards synthesizing α-AAs consists of the installation of a side chain onto an imine. This radical addition onto imines is widely applicable, as various radical precursors can be used to generate a radical that gets intercepted by the imine. Recently, several reports using imines as radical acceptors for the synthesis of UAAs were published.[115–120] However, without the use of chiral catalyst or ligands, these approaches lack stereocontrol, delivering the UAAs mostly as their racemic versions. This issue was tackled by Baran and co-workers, who conducted the radical addition onto a chiral sulfinimine in the presence of a Ni-catalyst.[121] The groups of Shenvi and Kärkäs also used chiral sulfinimines as radical acceptors to furnish novel α-amino acids in a stereo-defined manner (Scheme 5).[122,123]



Scheme 5. Synthesis of UAAs via radical addition onto chiral sulfinimines.

b) α-Carbonyl C(sp^3)–H amination: another retrosynthetic approach is based on the radical amination of C(sp^3)-H bonds. Zhang and co-workers reported an intramolecular approach to produce cyclic α-amino acids by using a Co-porphyrin complex as catalyst.[124] The diastereocontrol obtained in this reaction is based on the use of enantiopure starting materials.



Scheme 6. Synthesis of UAAs via intramolecular radical amination.

c) α-Amino carboxylation with CO_2: methodologies towards α-amino acid synthesis relying on the introduction of the carboxylic acid functionality onto amine-systems are also documented. Here, α-amino radicals were generated and coupled with CO_2 as C_1-building block. Several published approaches generated the required α-amino radical by reducing imines with (super)stoichiometric reductants e.g., Mn, Mg or SmI_2.[125–127]

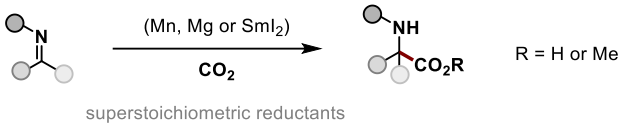
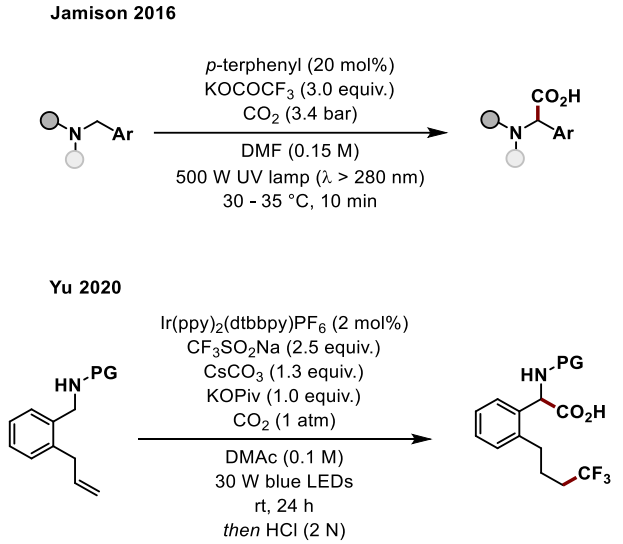


Figure 21. Coupling of CO_2 with imine-derived α-amino radicals in the present of stoichiometric reductants.

Additionally, the groups of Jamison and Yu developed more benign methodologies circumventing the need for (super)stoichiometric reductants by using photoredox-catalysis.[128–130] This allowed for an expansion of the reaction scope beyond the use of imines as radical precursors, enabling the α-amino C–H carboxylation of benzylic amines.[131,132] While these approaches have good atom economy and provide an elegant way to synthesize unnatural α-amino acids, they still lack stereocontrol over the resulting α-amino stereocenter.



Scheme 7. Coupling of CO_2 with α-amino radicals accessed via photoredox catalysis.

Side-chain modification of α-AAs

Another strategy to access unnatural α-amino acids is the modification of the side chain of already existing α-amino acids (Figure 22). Numerous approaches have been developed following this approach,[35] however, they are mostly restricted to a few naturally occurring α-AAs, such as asparagine (Asp), glutamine (Glu), dehydroalanine (Dha), leucine (Leu), phenylalanine (Phe), tryptophane (Trp) and vinyl-glycine (vinyl-Gly).

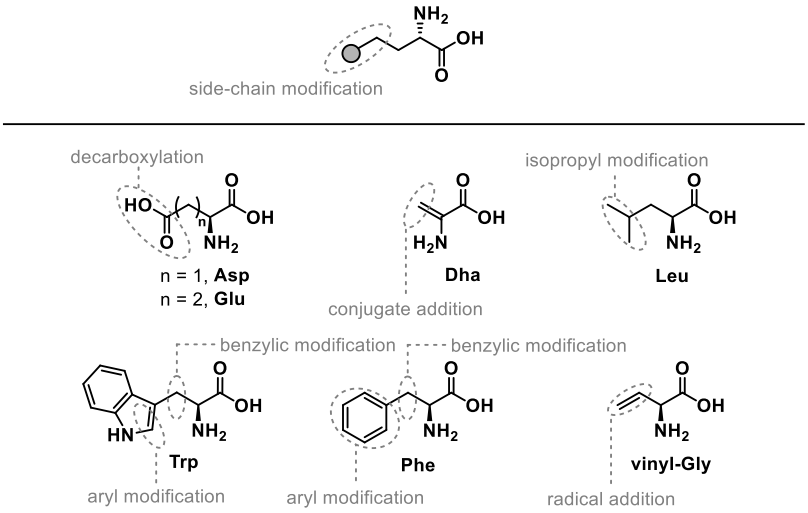


Figure 22. Accessing unnatural α-amino acids via selective side chain modification.

Among these methods, side chain modifications of dehydroalanine (Dha) show great potential, since it is an α,β-unsaturated system (Michael system), which is a good acceptor for nucleophilic radicals. However, the main disadvantage of this approach is that radical additions onto dehydroalanine result in the formation of racemic mixtures. This issue can be tackled by transforming the planar Dha into a chiral analogue (**19**) by introducing a chiral auxiliary. This would enable the realization of a stereocontrolled conjugate radical addition, furnishing enantioenriched α-AAs **20** (Figure 23).

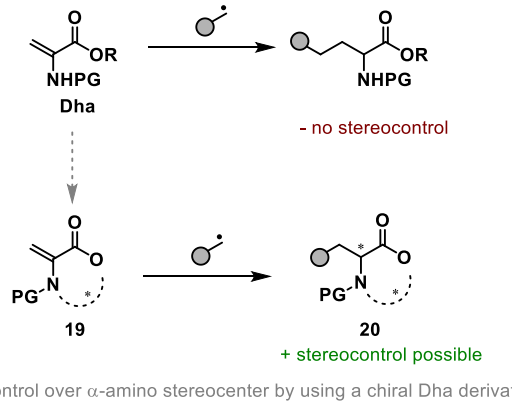
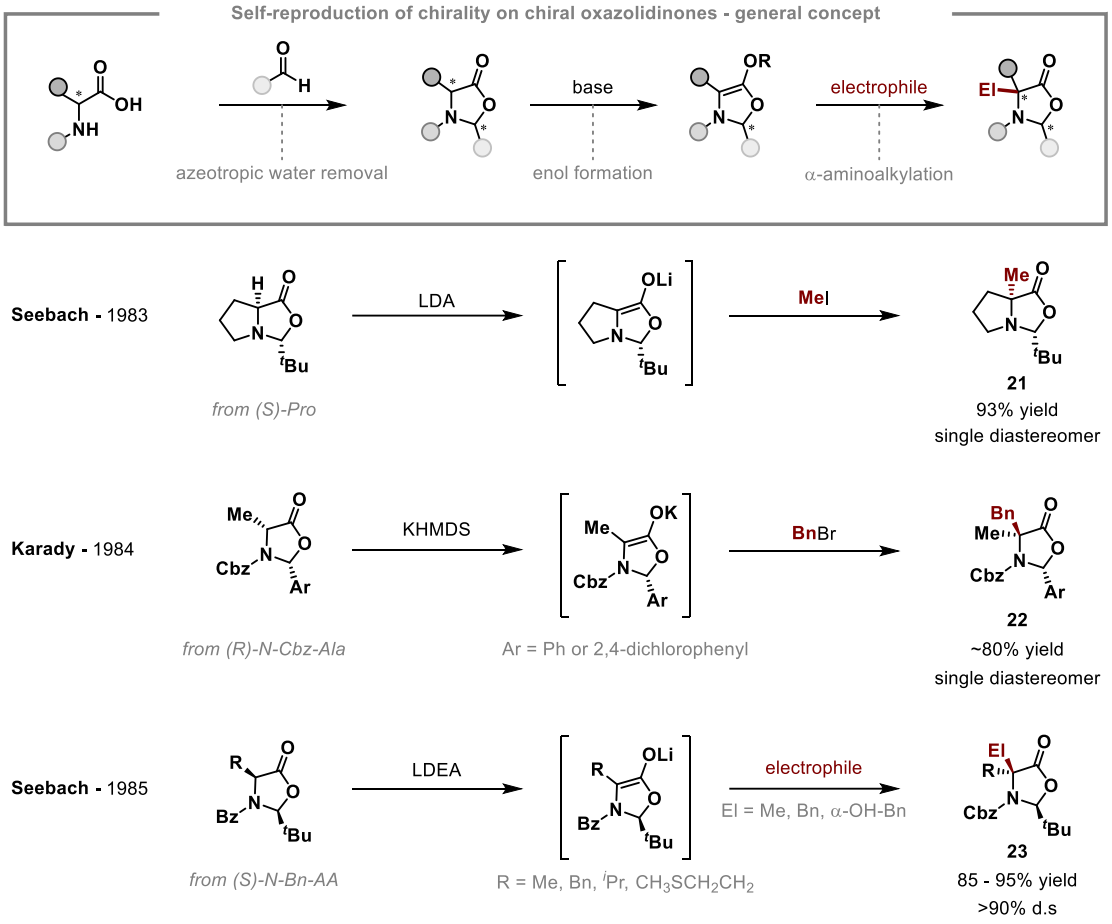


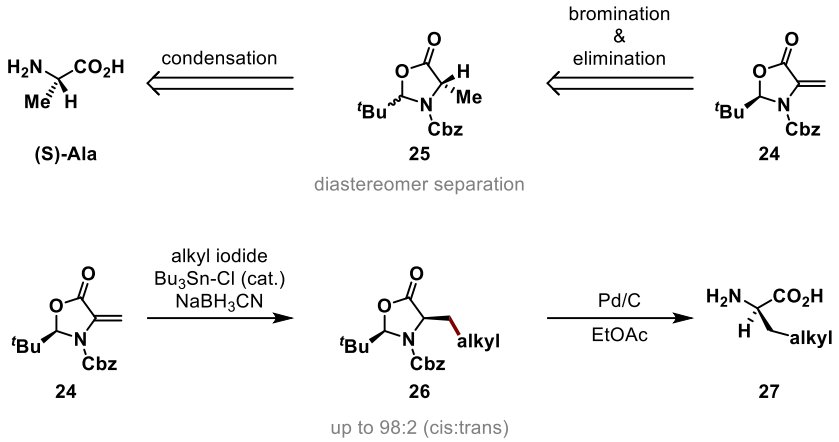
Figure 23. Dha-containing chiral auxiliaries serving as acceptors for stereocontrolled conjugate radical additions.

The idea of transforming acyclic amino acids into cyclic, and thus rigid, scaffolds – such as oxazolidinones – is known for quite a long time.[133] In the 1980s, the groups of Seebach and Karady converted several amino acids such as proline, alanine, phenylalanine, valine and methionine into the corresponding chiral oxazolidinones, and used them in alkylation reactions proceeding via self-reproduction of chirality to access enantioenriched quaternary α-amino acid derivatives **21**–**23** (Scheme 8).[134,135]. The isolated compounds were successfully deprotected afterwards to afford the corresponding α-substituted amino acids in good yields and excellent enantiomeric purities.



Scheme 8. α-Aminoalkylation of oxazolidinone-derived enolates under self-reproduction of chirality.

This concept was further developed by Beckwith and co-workers, by using a dehydroalanine-derived oxazolidinone system **24** for diastereoselective radical additions.[136,137] The synthesis of **24** can be performed by a condensation reaction of (S)-Ala to a diastereomeric mixture of oxazolidinones (**25**). Separation of this mixture followed by a bromination-elimination sequence of the (R)-isomer affords Dha derivative **24**. This was used as radical acceptor in a radical addition reaction using alkyl iodides in the presence of catalytic amounts of *n*Bu_3Sn–H and $NaBH_3CN$. The resulting α-amino alkylated species **26** was formed in a trans-cis ratio of up to 98:2, which can be deprotected using palladium on charcoal (Pd/C) to afford (R)-configured UAA **27** as a single enantiomer (Scheme 9).



Scheme 9. Dehydroalanine-derived oxazolidinone system as used by Beckwith an co-workers in 1995.[137]

The observed diastereoselectivity during the radical conjugate addition is determined by the sterically demanding *tert*-butyl group shielding one face of the intermediary formed α-amino radical. As a consequence, addition of a H-atom occurs from the down side, leading to the preferred formation of the *syn* product with the observed diastereoselectivity (Figure 24).

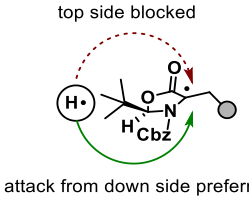
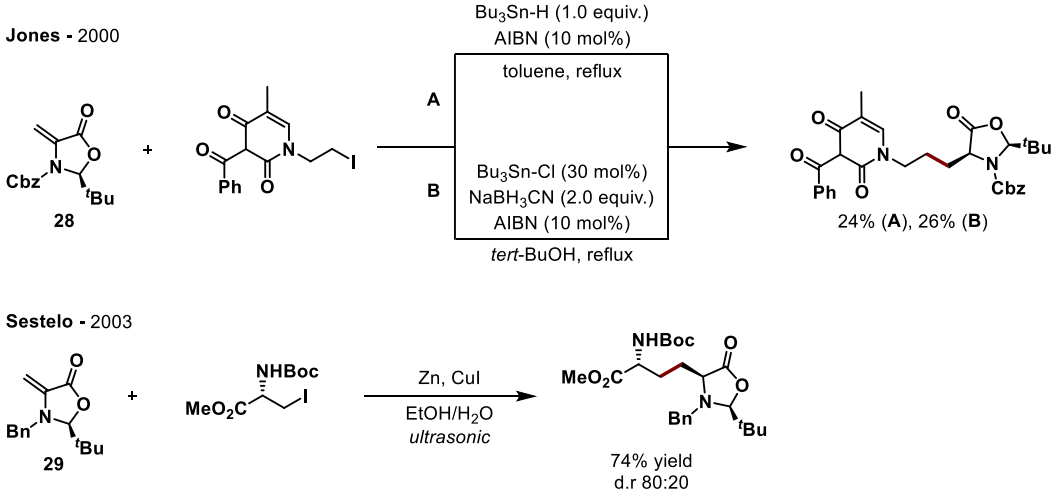


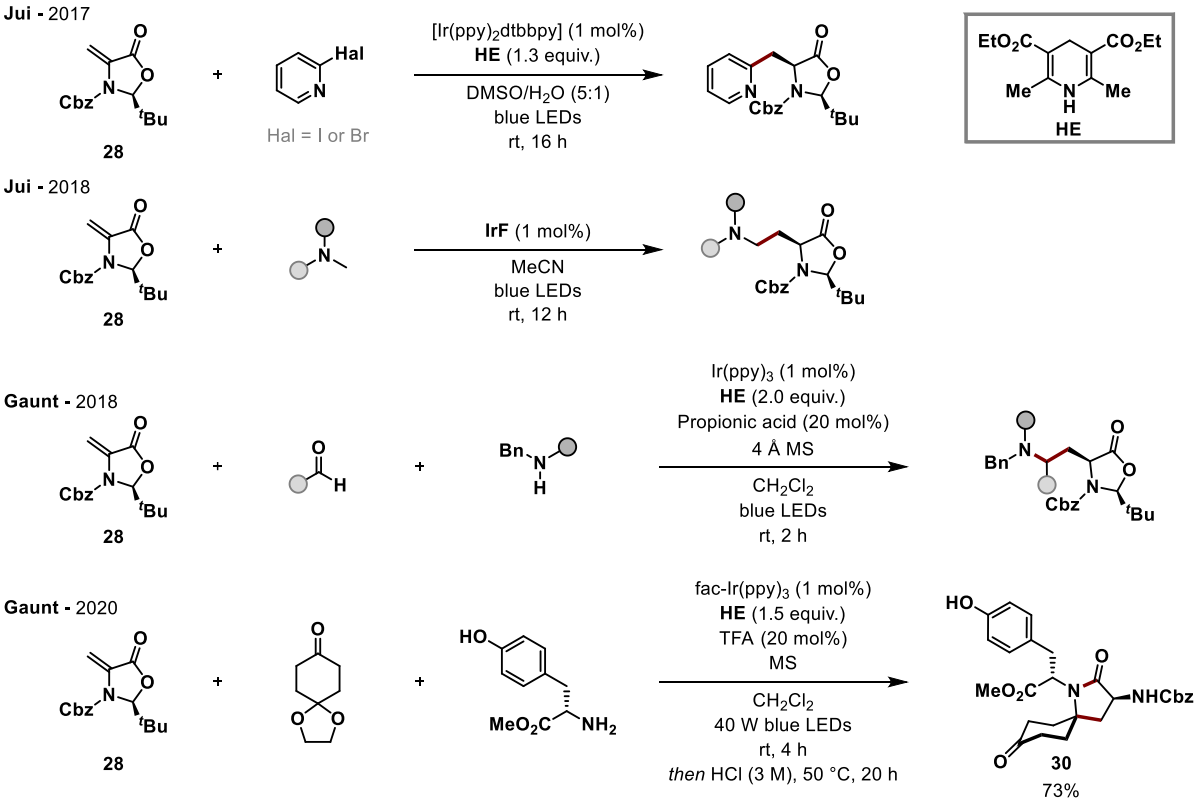
Figure 24. Preferred formation of syn products as a consequence of a tert-butyl group shielding one side of the intermediate.

Following Beckwith's seminal report, several methodologies were developed using **24**'s analogues, such as so-called Beckwith-Karady alkene **28** or **29** as radical acceptor. For example, the groups of Jones and Sestelo used these chiral oxazolidinones to access pyrimidinyl or purinyl containing amino acids or other unnatural amino acid scaffolds (Scheme 10).[138,139]



*Scheme 10. Use of chiral oxazolidinones **28** and **29** as radical acceptor.*

Although highly efficient, these methodologies used either AIBN/Bu_3Sn–H or superstoichiometric amounts of Zn and CuI as radical initiators. Therefore, with the advent of photoredox catalysis, more elegant and benign ways of generating radical species for conjugate additions onto **28** were designed (Scheme 11).[140–143]. In 2017, Jui and co-workers reported the reduction of halogenated species such as alkyl bromides, allyl bromides or bromopyridines by an excited Ir-based photocatalyst to access *C*-centered radicals that can be subsequently added to **28**. A year later, the same group showed that tertiary amines can be oxidized to the corresponding α-amino radicals – by single electron transfer (SET) with a suitable photocatalyst – and that these species can participate in conjugate additions to **28** to access novel UAAs. The same year, Gaunt and co-workers reported a similar strategy, but this time accessing α-amino radicals from *in situ* generated iminium ions. These species were generated by condensation of either an aldehyde with a secondary amine – or a ketone with a primary amine– and subsequent reduction by a Ir-based photocatalyst to achieve an α-amino radical that can undergo Giese-type addition onto **28**. In 2020, this general concept was expanded to the synthesis of spirolactam **30**, a chiral intermediate that was used for the total syntheses of two polycyclic alkaloids.



*Scheme 11. Conjugate addition onto **28** using photoredox catalysis.*

Even though these methodologies enable the synthesis of libraries of UAAs, they are limited by the choice of radical precursors. Therefore, the design and development of novel methodologies using readily available and abundant radical precursors, such as carboxylic acids, would be highly desirable.

II.I.2 – Project Goal

Inspired by previous works concerning conjugated radical addition to the Beckwith-Karady alkene **28**, the use of (α-keto-)-carboxylic acids as radical precursors should be investigated. In the presence of a base, decarboxylation of the used (α-keto)-carboxylic acid should take place under strongly oxidizing photoredox conditions. The radicals thus obtained can react with **28** in a Giese-type reaction to form the corresponding acylated or alkylated product. The sterically shielded side of **28** should generate the coupled products with high diastereoselectivities. Hydrolysis of the oxazolidinone core after coupling with various (α-keto)-carboxylic acids gives access to unnatural α-amino acids. This project was performed in collaboration with Francisco José Aguilar Troyano and Jonas Djossou.

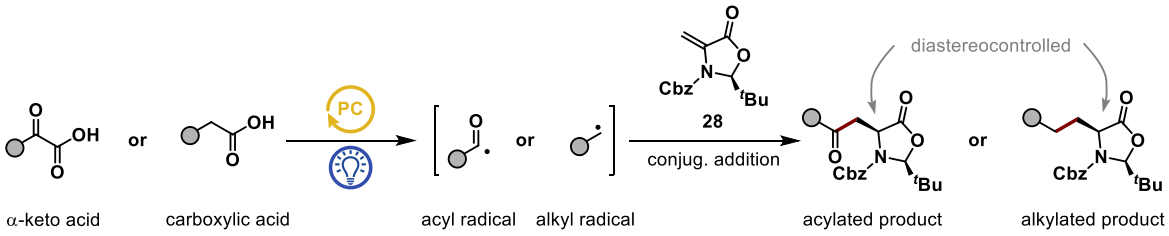
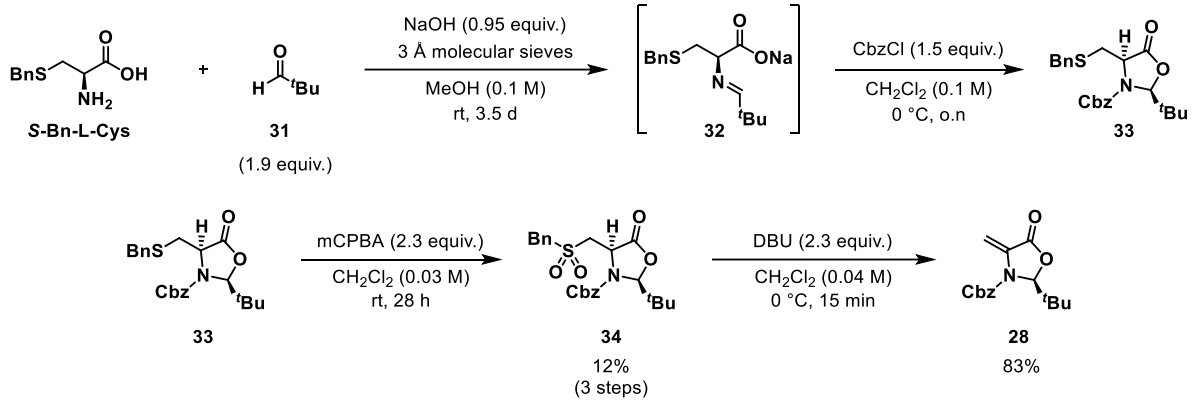


Figure 25. Concept for diastereoselective synthesis of α-amino acid derivatives via decarboxylation.

II.I.3 – Optimization Studies

The project was started by the synthesis of Beckwith-Karady alkene **28** in multi-gram scale starting from cheap and abundant *S*-Bn-L-cysteine. In a first step, treatment of *S*-Bn-L-cysteine with NaOH in dry MeOH in the presence of 3 Å molecular sieves afforded the corresponding Na-salt, to which an excess of pivaldehyde **31** was added. Stirring for 3 days at room temperature let to the formation of imine **32**. Analysis of the crude reaction mixture by ^{1}H NMR analysis revealed no full consumption of *S*-Bn-L-cysteine. The crude reaction mixture was filtered and dried before next reaction was performed. Next, crude **32** was redissolved in dry CH_2Cl_2 and CbzCl was added. After two days of stirring at room temperature, purification via flash chromatography afforded **33**. **33** was not isolated in high purity, but it was successfully separated from its diastereomer. Oxidation of **33** using an excess of *m*CPBA in CH_2Cl_2 with subsequent purification via flash chromatography furnished sulfone **34** in 12% yield over 3 steps. The diminished yield can be explained by an incomplete imine formation: most likely, the used molecular sieves were not activated enough so that the *in situ* formed H_2O hydrolyzed the imine resulting in an overall ratio of ~ 0.7:1 (*S*-Bn-L-cysteine vs. **32**), as determined by ^{1}H NMR analysis. Basic elimination of **34** to yield Beckwith-Karady alkene **28** worked smoothly and was done after roughly 15 min deploying 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2. Another flash chromatography afforded **28** in very good yields (83%). Later, the condensation reaction was repeated by a colleague implementing a Dean-Stark separator to trap the formed H_2O, which resulted in better yields of up to 43% of **34** over 3 steps.

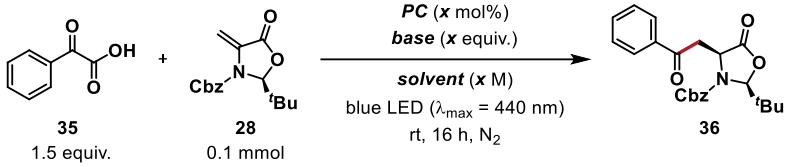


*Scheme 12. Synthesis of Beckwith-Karady alkene **28** starting from S-Bn-L-cysteine.*

With **28** in hand, optimization studies were performed by a colleague. First, the acylation protocol was optimized using phenylglyoxylic acid (**35**) as standard substrate (Table 1). Initial conditions using 2.0 equiv. of $CsCO_3$ in DMF (0.2 M) failed to give **36**, but changing the base to K_2HPO_4 or 2,6-lutidine resulted in formation of the desired product in 83% and 80% yields (Entries 1–3, Table 1). After screening various solvents (Entries 4–7, Table 1) it was found that the use of 2.0 equiv. of 2,6-lutidine in 1,4-dioxane (0.2 M) was optimal for the desired acylation (Entry 8, Table 1). Furthermore, it was found that **4CzIPN** (*$E_{1/2}$ = +1.21 V vs SCE)[144] – a

readily available organophotocatalyst – can successfully substitute **IrF** (*$E_{1/2}$ = +1.43 V vs SCE)[76] as photocatalyst in the targeted transformation, albeit at higher catalyst loading (Entry 9, Table 1). When the reaction was performed in the absence of light, no trace of **36** was formed (Entry 10, Table 1). Interestingly, the reaction yielded 20% of **36** when performed in the absence of a photocatalyst (Entry 11, Table 1). This might be explained by a possible formation of an electron donor-acceptor (EDA) complex between **35** and 2,6-lutidine.[145–148]

Table 1. Acylation protocol optimization.

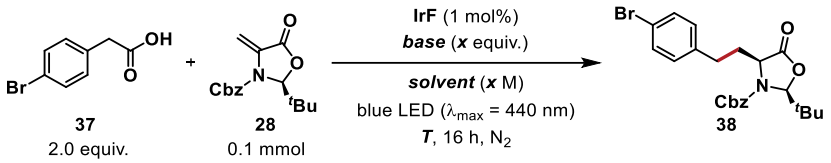


Entry	PC (mol%)	Base (equiv.)	Solvent (M)	28 left (%)	36 (%)
1	IrF (1)	Cs_2CO_3 (2.0)	DMF (0.2)	29	0
2	IrF (1)	K_2HPO_4 (2.0)	DMF (0.2)	0	83
3	IrF (1)	2,6-Lutidine (2.0)	DMF (0.2)	0	80
4	IrF (1)	2,6-Lutidine (2.0)	DMSO (0.2)	0	80
5	IrF (1)	2,6-Lutidine (2.0)	Acetone (0.2)	0	0
6	IrF (1)	2,6-Lutidine (2.0)	DCE (0.2)	22	76
7	IrF (1)	2,6-Lutidine (2.0)	EtOAc (0.2)	6	63
8	IrF (1)	2,6-Lutidine (2.0)	1,4-Dioxane (0.2)	4	86 (78)[b]
9	4CzIPN (5)	2,6-Lutidine (2.0)	1,4-Dioxane (0.2)	0	83
10[a]	IrF (1)	2,6-Lutidine (2.0)	1,4-Dioxane (0.1)	96	0
11	-----	2,6-Lutidine (2.0)	1,4-Dioxane (0.2)	25	20

[a]: no light; [b]: isolated yield in 0.5 mmol scale. Yields were determined by GC-FID analysis (IS: methyl laureate).

When applying these optimized conditions onto alkylation reactions using benzylic carboxylic acids, diminished yields were observed (Entry 1, Table 2). Therefore, further optimizations for benzylation reactions using 4-bromophenylacetic acid (**37**) as standard substrate were performed. It was found that changing the base to K_2HPO_4 resulted in formation of **38** in 75% yield (Entry 2, Table 2). Increasing the reaction temperature to 42 °C – by turning off the fan during irradiation – resulted in another increasement in reaction yield to 91% (Entry 3, Table 3). Running the reaction in other solvents, such as acetone, DMSO or DMF resulted in diminished formation of **38** (Entries 4–6, Table 2), but when performing the reaction in 1,4-dioxane at a lower concentration (0.1 M), nearly quantitative yields for the formation of **38** were obtained (Entry 8, Table 2).

Table 2. Benzylation protocol optimization.

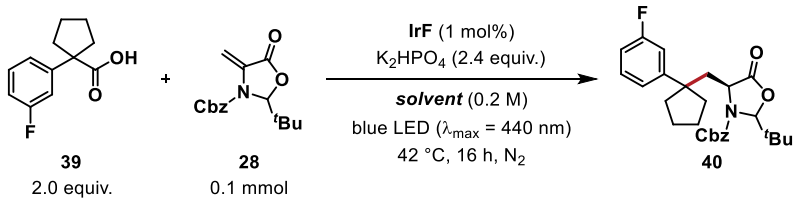


Entry	Base (equiv.)	Solvent (M)	T (°C)	28 left (%)	38 (%)
1[a]	2,6-Lutidine (2.0)	1,4-Dioxane (0.2)	rt	71	11
2	K_2HPO_4 (2.4)	1,4-Dioxane (0.2)	rt	20	75
3	K_2HPO_4 (2.4)	1,4-Dioxane (0.2)	42	1	91
4	K_2HPO_4 (2.4)	Acetone (0.2)	42	58	17
5	K_2HPO_4 (2.4)	DMSO (0.2)	42	9	75
6[b]	K_2HPO_4 (2.4)	DMF (0.2)	42	20	42
7	K_2HPO_4 (2.4)	DMF (0.1)	42	0	75
8	K_2HPO_4 (2.4)	1,4-Dioxane (0.1)	42	1	97

[a]: 1.5 equiv. of **37**, 13 h irradiation; [b]: 1.0 equiv. of **37**. Yields were determined by GC-FID analysis (IS: methyl laureate).

However, solubility issues for alkylation reactions with α-quaternary carboxylic acids, such as **39**, in 1,4-dioxane were observed, leading to diminished yields (Entry 1, Table 3). A small solvent screening revealed that both DMSO and DMF are suitable solvents for the targeted transformation (Entries 2 & 3, Table 3). Even though DMF resulted in a slightly higher conversion of **28** to **40**, toxicity considerations led to the selection of DMSO as optimal solvent.

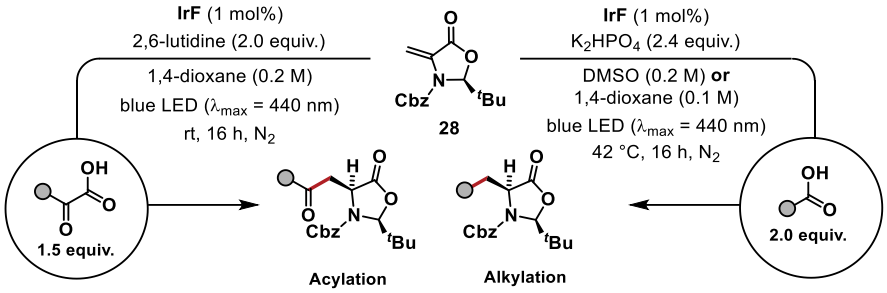
Table 3. Alkylation protocol optimization.



Entry	Solvent	Conversion of 28 (%)
1[a]	1,4-Dioxane	19
2[b]	DMSO	92
3	DMF	96
4	1,4-Dioxane + DMF	72

[a]: 2 mol% **IrF**, [b]: 40% isolated yield of **40** in 0.5 mmol scale. Yields were determined by GC-FID analysis (IS: methyl laureate).

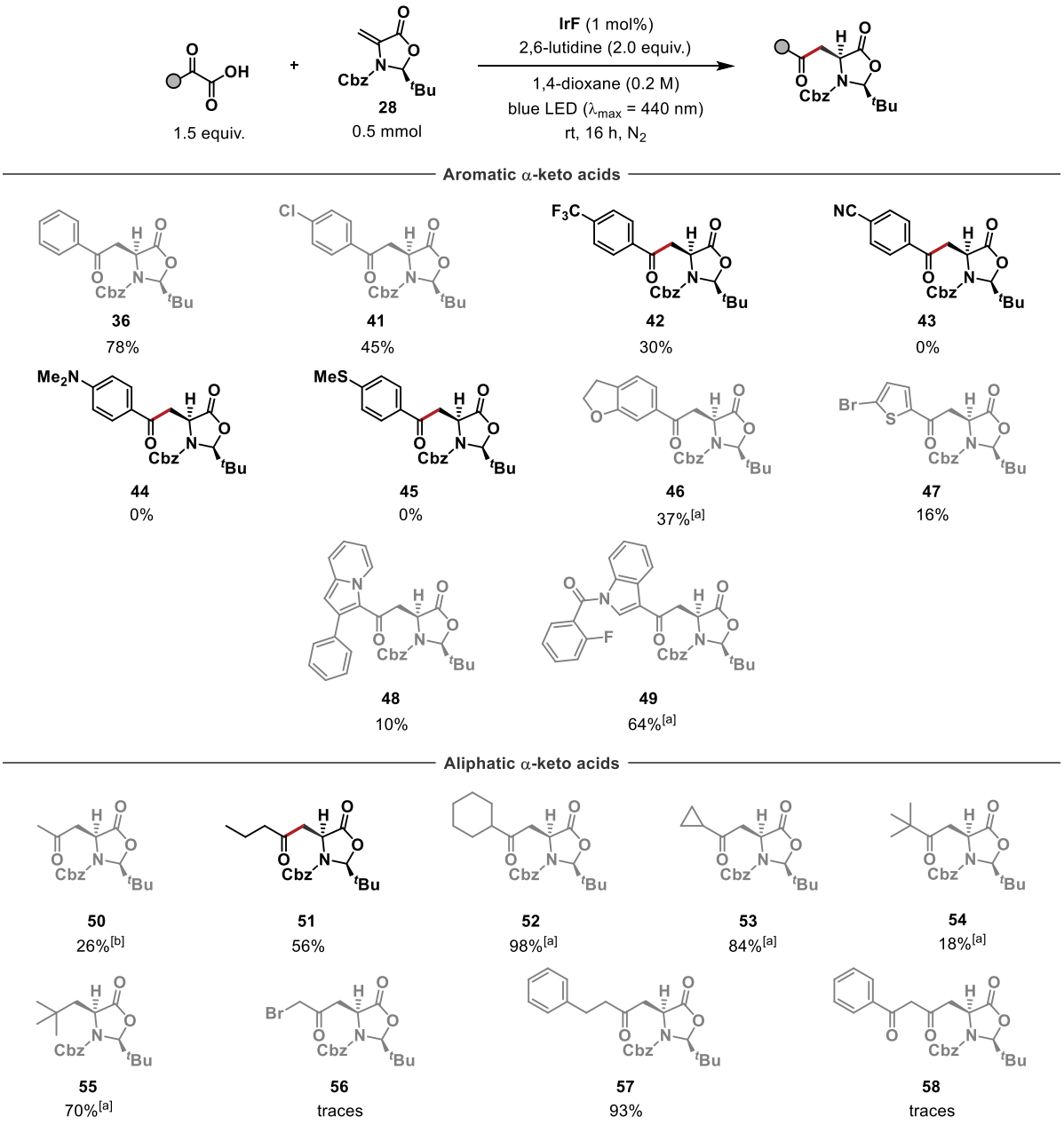
The three sets of optimized conditions are summarized in Scheme 13.



*Scheme 13. Optimized reaction conditions for acylation and alkylation of **28**.*

II.I.4 – Scope and Limitations

To explore the scope and limitations of both acylation and alkylation reactions, several unnatural amino acid derivatives bearing diverse functional groups were synthesized. To give a proper overview of the applicability of the reaction, all synthesized products are listed in the following schemes, including those that were performed by colleagues (depicted in grey). The investigations were started using α-keto acids in the developed acylation protocol (Scheme 14). Starting with benzylic α-keto acids, phenylglyoxylic acid **35** furnished the acylated product **36** in 78% yield. In general, the crude products were analyzed by ^{1}H NMR to determine the diastereoselectivity of the reaction. If not stated otherwise, the found diastereomeric ratio (d.r.) was >20:1. A NOESY experiment performed by a colleague using **36** proved formation of the *syn* product. When adding electron-withdrawing groups such as *p*-Cl (**41**) or *p*-CF_3 (**42**) to the phenyl ring of phenylglyoxylic acid, the yield for the acylation reaction dropped to 45% and 30%. Furthermore, *p*-CN (**43**), *p*-NMe_2 (**44**) and *p*-SMe (**45**) could not be obtained. While dihydrobenzofuran derivative **46** was furnished in moderate 37% yield, thiophene- (**47**) and indolizine- (**48**) derived α-keto acids gave only 16% and 10% of the desired product. Delightfully, indole-derived product **49** was obtained in 64% yield. Next, the scope of aliphatic α-keto acids was investigated. It was found that while 2-oxopropanoic acid gave product **50** in a diminished 26% yield, 2-oxo-pentanoic acid afforded the targeted product **51** in good yield (56%). Pleasingly, cyclohexyl- and cyclopropyl-containing products (**52** and **53**, respectively) were obtained in excellent yields, 98% and 84% respectively. When using trimethylpyruvic acid as starting material, **54** was isolated only in 18% yield, while the corresponding decarbonylated product **55** was formed in a remarkable 70% yield. The latter product is preferentially formed due to the tendency of tertiary acyl radicals to undergo fast decarbonylation due to the high stabilization of the resulting tertiary radical species.[149] The use of bromopyruvic acid resulted in trace formation of the desired product **56**. While 2-oxo-4-phenylbutanoic acid gave **57** in excellent 93% yield, using 2,4-dioxo-4-phenylbutanoic acid resulted in trace formation of **58**. Overall, it was found that aliphatic α-keto acids underwent the targeted transformation in higher yields than their aromatic counterparts.



Scheme 14. α-Keto acid scope and limitations.

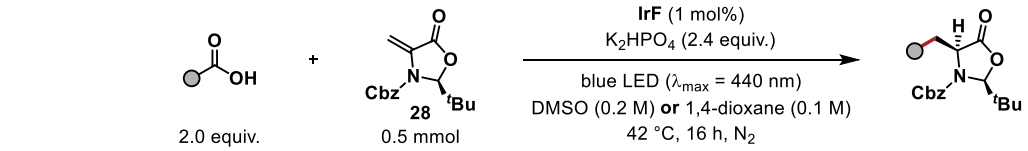
[a]: 2.5 equiv. acid, 3.3 equiv. 2,6-lutidine; [b]: 10.0 equiv. acid. Unless stated otherwise, the product was obtained with d.r. >20:1, according to ^{1}H NMR investigations of the crude reaction mixture.

Next, the scope and limitations of the alkylation protocol were investigated (Scheme 15). Starting with primary carboxylic acids, it was found that phenylacetic acid derivatives containing *p*-Br (**38**), *p*-F (**59**), *p*-OMe (**60**), *o*-I (**61**) or *m*-OMe (**62**) substituents all furnished the targeted alkylated products in 40–90% yield. Delightfully, chloropyridine-containing product **63** could be isolated in good yields (78%). However, other (hetero)aromatic compounds, such as pyrazine- or 2-pyridine- derived carboxylic acids, as well as 2-(naphthalen-1-yl) acetic acid did not afford the desired benzylated products **64**, **65** and **66**. Furthermore, 3-phenylpropanoic acid – which generates an unstabilized primary radical – failed to afford product **67**, while the

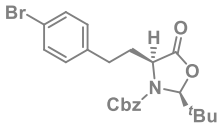
use of Cbz-protected glycine – which generates a highly stabilized α-amino radical – gave product **68** in good 78% yield.

Next, the use of secondary carboxylic acids as radical precursors was investigated. Pleasingly, cyclobutyl- (**69**) and azetidyl- (**70**) containing products were formed in excellent yields (80% and 93%, respectively). Furthermore, products **71** and **72**, bearing a terminal alkene and a cyclopropyl ring, afforded the targeted products even though in diminished yields of 25% and 20%. *N*-Boc protected piperidine derivative **73** was obtained in an excellent 95% yield. Proline-derived product **74** was obtained in good 80% yield with a d.r. of 1:1, while some diastereocontrol was observed when using methoxyphenyl acetic acid (**75** was isolated in 76% yield with a d.r. of 1.5:1). Delightfully, the use of *N*-Boc protected phenylglycine furnished **76** in 78% yield with a good d.r. of 5:1.

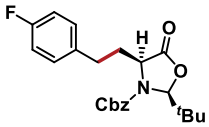
Finally, a variety of tertiary carboxylic acids were tested. Interestingly, **55** was isolated in moderate 48% yield when using *tert*-butylcarboxylic acid, while the use of trimethylpyruvic acid in the acylation protocol afforded **55** in a remarkable 70% as the decarbonylated by-product. Cyclopropyl-containing product **77** was formed only in traces, while cyclobutyl- and cyclopentyl-containing products **78**, **79** and **40** were obtained in 40–73% yield. In addition, benzylated products **80** and **81**, bearing an *N*-Boc protected piperidine and a tetrahydropyran motif, could be isolated in 87% and 72% yield. Propellane-derived product **82** was isolated in 45% yield, while adamantol-derived **83** was prepared in 73% yield. However, compound **84** could not be obtained; this might be attributed to steric effects of both the cyclohexyl- and phenyl rings.



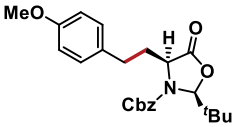
Primary acids



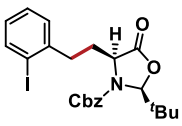
38
81%[a]



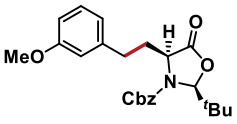
59
66%[b]



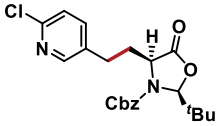
60
90%[b]



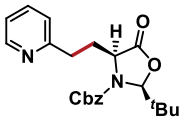
61
40%[b]



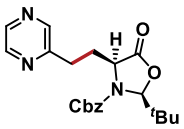
62
59%[b]



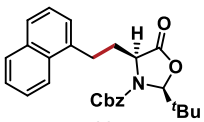
63
78%[a]



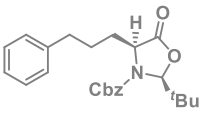
64
0%



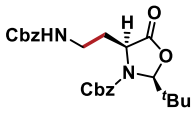
65
0%



66
0%

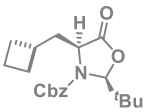


67
0%

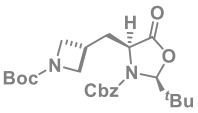


68
78%[a]

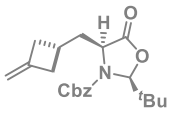
Secondary acids



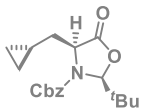
69
80%[b]



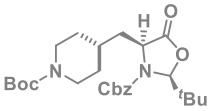
70
93%[b]



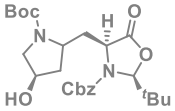
71
25%[b]



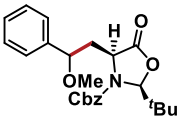
72
20%[b]



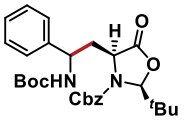
73
95%[b]



74
80%[b] (1:1 d.r.)

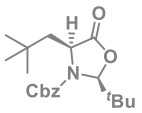


75
76%[a] (1.5:1 d.r.)

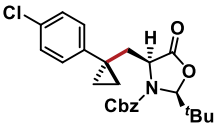


76
78%[a] (5:1 d.r.)

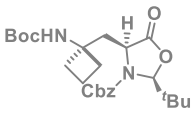
Tertiary acids



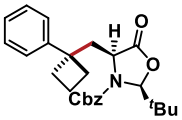
55
48%[b]



77
traces



78
65%[b]



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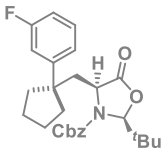

40
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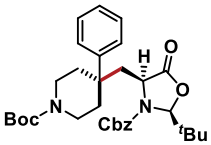

80
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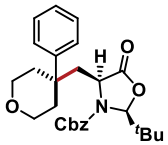

81
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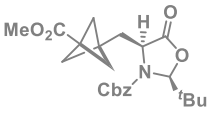

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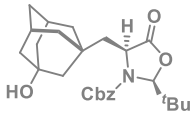

83
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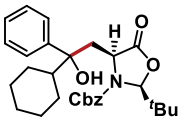


84
0%

Scheme 15. Carboxylic acid scope and limitations.

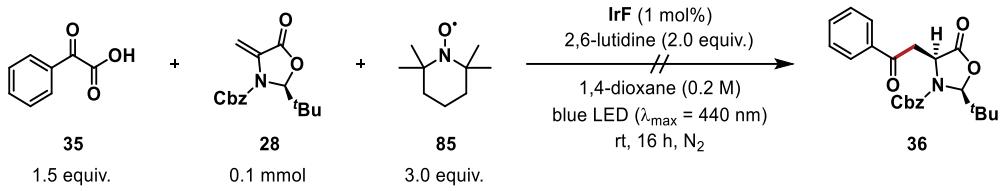
[a]: DMSO (0.2 M); [b]: 1,4-dioxane (0.1 M). Unless stated otherwise, the product was obtained with d.r. >20:1, according to ^{1}H NMR investigations of the crude reaction mixture.

II.I.5 – Mechanistic Studies

To shed some light on the underlying mechanism of the developed reactions several experiments, including a radical trapping experiment and quantum yield determination, were performed.

Radical trapping experiment

To determine whether a radical mechanism is in operation, a colleague performed a standard reaction in the presence of an excess of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) **85** as radical scavenger (Scheme 16). Formation of **36** was suppressed under these conditions, suggesting that the reaction proceeds through a radical pathway.



Scheme 16. Radical trap experiment with TEMPO as radical scavenger.

Next, the quantum yield of the reaction was determined. This was done to check whether a radical chain is in progress or not. If the quantum yield is >1, this means that, per absorbed photon, more than one molecule of product is formed and, therefore a radical chain pathway is likely in operation. To determine the quantum yield of a certain reaction, first the photon flux of the used LED (λ_{max} = 440 nm) had to be determined.

Photon flux determination

According to a procedure reported by Yoon,[150] standard ferrioxalate actinometry[151–153] was employed to determine the photon flux of the used LED. Therefore, two solutions were prepared and stored in the dark:

> **Solution A** – *0.15 M ferrioxalate solution*: potassium ferrioxalate trihydrate (730 mg, 1.49 mmol) was dissolved in 10 mL of a 0.05 M H_2SO_4 solution.
>
> **Solution B –** *0.0056 M 1,10-phenanthroline solution*: 1,10-phenanthroline (25 mg, 0.14 mmol) and sodium acetate (5.6 g, 68.27 mmol) were dissolved in 25 mL of a 0.5 M H_2SO_4 solution.

The photon flux of the LED (λ_{max} = 440 nm) was determined by irradiating solution **A** (1.0 mL, 0.15 mmol ferrioxalate) for 120 seconds. After irradiation, solution **B** (175 µL, 0.98 µmol phenanthroline) was added to the irradiated sample and stirred in the dark for 1 h. This was done to make sure that the phenanthroline fully coordinated the ferrous ions. Afterwards, the

absorption of this solution was measured at 510 nm. Simultaneously, a non-irradiated sample was prepared as described above and its absorption at 510 nm was measured.
The amount of formed Fe^{2+} was calculated using Equation 1:

Eq. 1 $$\text{mol } Fe^{2+} = \frac{V \bullet \Delta A(510\text{ nm})}{l \bullet \varepsilon}$$

V is the total volume of the sample after addition of the phenanthroline solution (V = 0.001175 L), l is the pathlength of the cuvette (1.0 cm), ε is the molar absorptivity of the ferrioxalate actinometer at 510 nm (ε = 11,1 L $mol^{-1}cm^{-1}$)[153] and ΔA is the difference in absorbance of the irradiated and non-irradiated sample at 510 nm (ΔA = 1.36205). This led to an amount of formed Fe^{2+} = 1.44 x 10^{-7} mmol. Using Equation 2, the fraction of absorbed light by the ferrioxalate actinometer f was calculated. The absorption spectrum of the ferrioxalate solution gave a value of > 3 at 440 nm, thus leading to f being > 0.999.

Eq. 2 $$f = 1 - 10^{-A(440\,nm)}$$

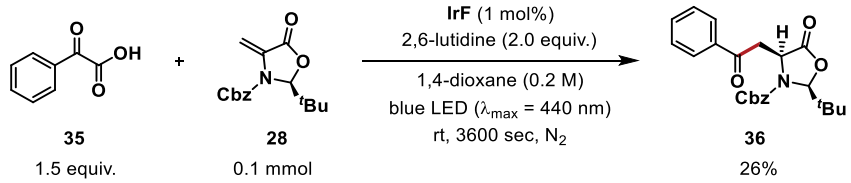
Finally, the photon flux of the used LED (λ_{max} = 440 nm) was calculated using Equation 3, with Φ being the quantum yield for the ferrioxalate actinometer (Φ = 1.01, λ_{ex} = 437 nm)[151], *t* being the irradiation time (120 s) and f being the calculated amount of light absorbed by the ferrioxalate actinometer (f > 0.999).

Eq. 3 $$\text{Photon flux} = \frac{\text{mol } Fe^{2+}}{\Phi \bullet t \bullet f}$$

As an average of three experiments, the photon flux was calculated to be 1.1917 x 10^{-9} einsteins s^{-1} for the used LED (λ_{max} = 440 nm).

Quantum yield acylation protocol

To determine the quantum yield for the acylation protocol, the standard reaction mixture was irradiated for 3600 sec (Scheme 17). Afterwards, the reaction was diluted with 1 mL EtOAc, methyl laureate (24.6 µL, 0.1 mmol, 1.0 equiv.) added as internal standard, and the reaction outcome was checked via GC-FID analysis. Product **36** was formed in 26% yield (2.6 x 10^{-5} mol). This reaction was performed by a colleague.



Scheme 17. Reaction performed for quantum yield determination of acylation protocol.

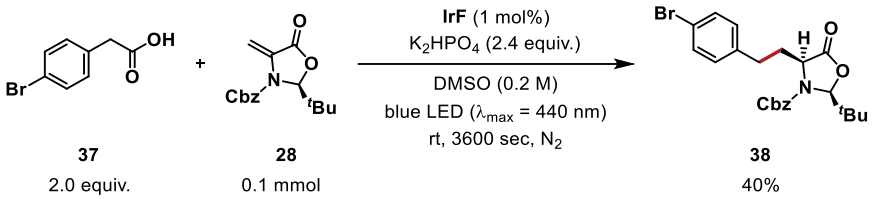
The quantum yield (Φ) of the reaction was determined according to Equation 4.

Eq. 4 $$\Phi = \frac{\text{mol of product formed}}{\text{Photon flux} \bullet t \bullet \text{f}}$$

The photon flux is 1.1917 x 10^{-9} einsteins s^{-1} (determined via ferrioxalate actinometry as described above), *t* is the irradiation time (3600 s) and f is the fraction of light being absorbed by the reaction mixture using Equation 2. According to experiments performed by a colleague, the absorbance value for the reaction mixture was found to be 4.18468 at 437 nm, so that f was calculated to be >0.999. The quantum yield (Φ) of the reaction was thus calculated to be 6.06

Quantum yield alkylation protocol

The same procedure was employed to determine the quantum yield of the alkylation protocol. A reaction under the standard conditions was irradiated for 3600 sec, and afterwards analyzed by GC-FID using methyl laureate as internal standard (Scheme 18). Product **38** was formed in 40% yield (4.0 x 10^{-5} mol). With this data the quantum yield (Φ) of the reaction was calculated to be 9.32. This reaction was performed by a colleague.



Scheme 18. Reaction performed for quantum yield determination of alkylation protocol.

Plausible mechanistic proposal

With the above information in hand, a plausible reaction mechanism was proposed (Figure 26). The excited state photocatalyst (***Ir^{III}**) oxidizes the deprotonated version of carboxylic acid **86** via SET (*$E_{1/2}$ = +1.21 V vs SCE)[144]. The resulting acyloxy radical undergoes decarboxylation, furnishing alkyl radical **87** (when using α-keto acids, an acyl radical intermediate is formed). Radical **87** readily adds to Beckwith-Karady alkene **28** leading to formation of α-amino radical **88**. SET from the reduced photocatalyst (**Ir^{II}**) ($E_{1/2}$ = -1.37 V vs

SCE)[144] to **89** regenerates the ground state photocatalyst (**Ir^{III}**), while forming an α-amino carbanion, which gets readily protonated to furnish the targeted alkylated product **90**. This mechanistic proposal is in accordance with previously described mechanisms, in which α,β-unsaturated acceptors get alkylated under photoredox conditions.[154]

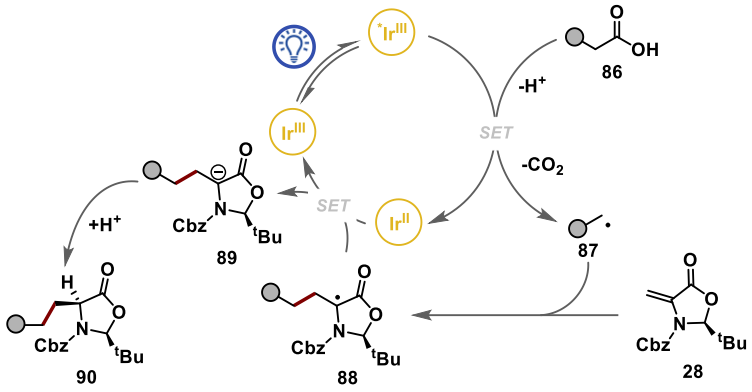
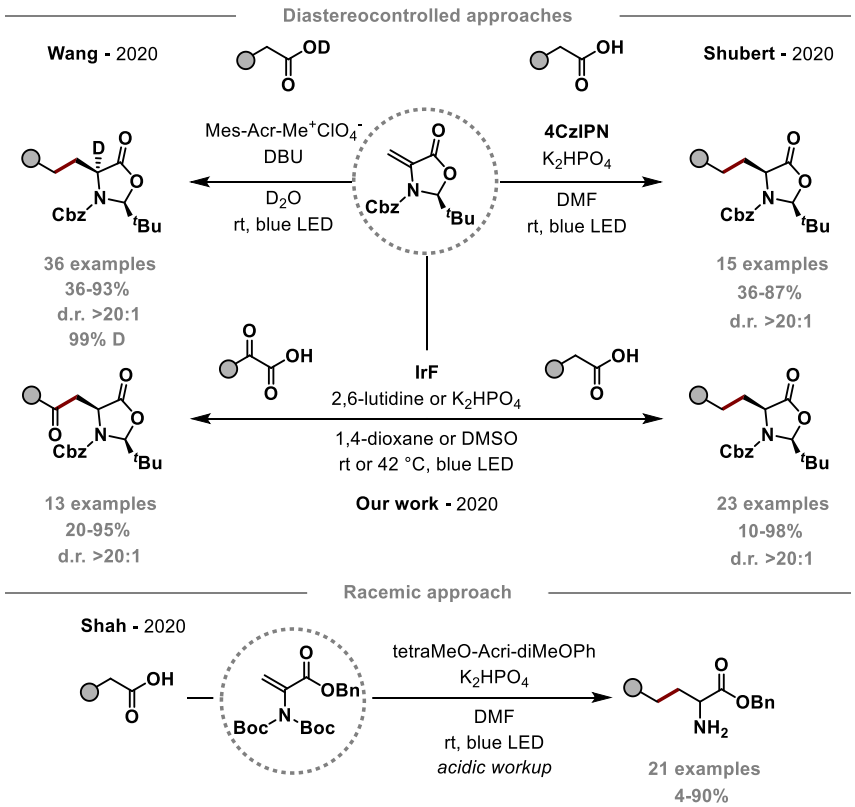


Figure 26. Proposed mechanism.

While working on this project, similar decarboxylative methodologies for the synthesis of UAAs were independently reported by the groups of Wang, Schubert and Shah (Scheme 19).[155–157] The latter two work at Merck & Co., thus highlighting the interest for novel methods for the synthesis of UAAs in the life science industry.



Scheme 19. Similar scientific reports towards synthesis of UAAs reported simultaneously.

II.I.6 – Project Summary

Overall, an effective and operationally simple method for the synthesis of enantioenriched unnatural α-amino acids was successfully developed. The approach is based on the generation of alkyl and acyl radicals via light-induced decarboxylation of (α-keto) carboxylic acids. Giese-type conjugated addition to chiral acceptor **28** allowed the isolation of *syn* addition products with very high diastereoselectivities (>20:1). The results of this collaborative project were successfully published in *Advanced Synthesis and Catalysis* and highlighted by both academic and industrial scientists in *Synfacts* and *Organic Process Research & Development*, respectively.[1,2,158]

II.II. γ-Oxo-α-Amino Acids via Phosphoranyl Radicals

II.II.1 – Introduction

γ-Oxo-α-amino acid derivatives possess several vectors for derivatizations or further modifications, thus allowing to expand the accessible chemical space for exploration (Figure 27).

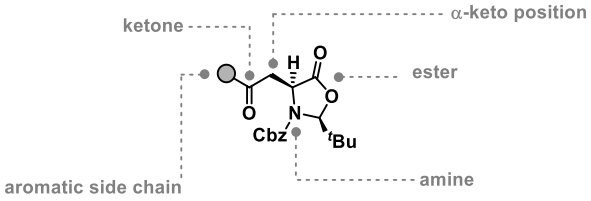


Figure 27. Possible derivatization vectors of γ-oxo-α-amino acid derivatives.

In the previous section, a decarboxylative methodology to access γ-oxo-α-amino acid derivatives using visible light-mediated photoredox catalysis was presented. However, the acylation protocol faces some limitations. The use of electron-deficient α-keto acids delivered the targeted γ-oxo-α-amino acid derivatives in diminished yields. Additionally, α-keto acids are not readily available, and often require harsh and hazardous reaction conditions to be synthesized (Figure 28).[159]

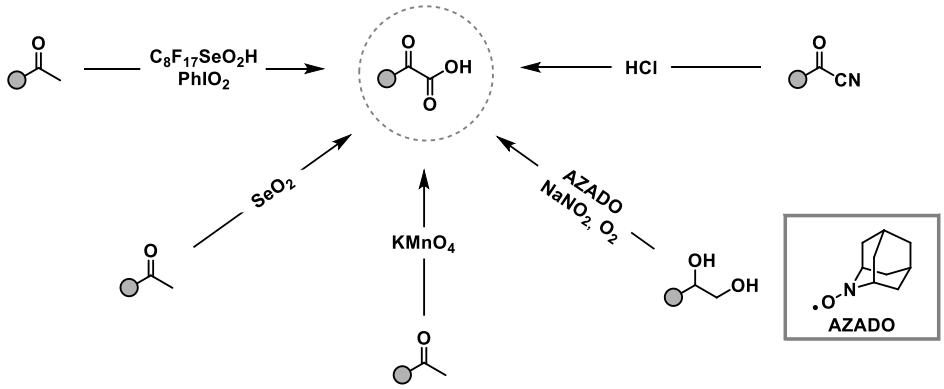
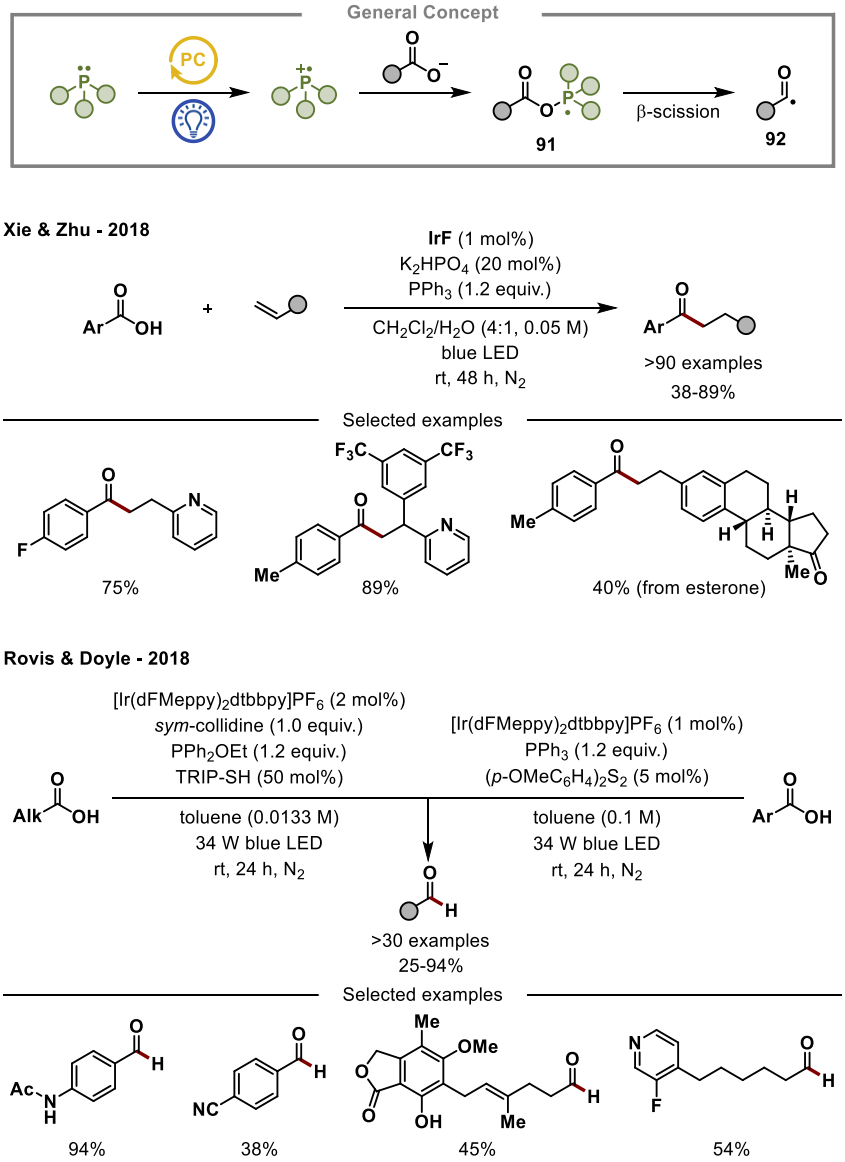


Figure 28. Synthesis of α-keto acids.

To overcome these limitations, new methods were sought to replace α-keto acids with more readily available acyl radical precursors to access γ-oxo-α-amino acids. In addition to α-keto acids, several species can serve as acyl radical precursors, e.g., aldehydes, anhydrides, acyl thioesters, acyl chlorides, acyl silanes, and carboxylic acids.[160] The latter are the best match for the desired criteria: cheap and readily available radical precursor. However, as shown in the previous section, under "classical" photoredox conditions, carboxylic acids undergo decarboxylation to the corresponding alkyl radical species

An elegant method to circumvent this reactivity, enabling access to acyl radicals from carboxylic acids, was independently described in 2018 by Xie & Zhu, and Rovis & Doyle (Scheme 20).[161,162] The key to this reactivity switch is the use of a suitable phosphine that can be oxidized by the excited photocatalyst. This generates a phosphine radical cation, which – due to the inherent oxophilicity of phosphorous – reacts with a carboxylate to form a phosphoranyl radical intermediate (**91**). β-Scission from the latter results in the formation of the thermodynamically favored phosphine oxide by-product and the targeted acyl radical **92**.



Scheme 20. Acyl radical formation via phosphoranyl radical intermediates by Xie & Zhu, and Rovis & Doyle.

Inspired by this seminal work, it was questioned whether it would be possible to exploit this strategy to access γ-oxo-α-amino acids using carboxylic acids as acyl radical precursors.

II.II.2 – Project Goal

Development of an alternative route to access γ-oxo-α-amino acid derivatives relying on the use of carboxylic acids as acyl radical precursors. As stablished in **section II.I.5**, once formed, these acyl radicals should undergo Giese-type addition onto the Beckwith-Karady alkene **28**, enabling the synthesis of a wide range of UAA derivatives from readily available radical precursors. This project was performed in collaboration with Francisco José Aguilar Troyano and Khadijah Anwar.

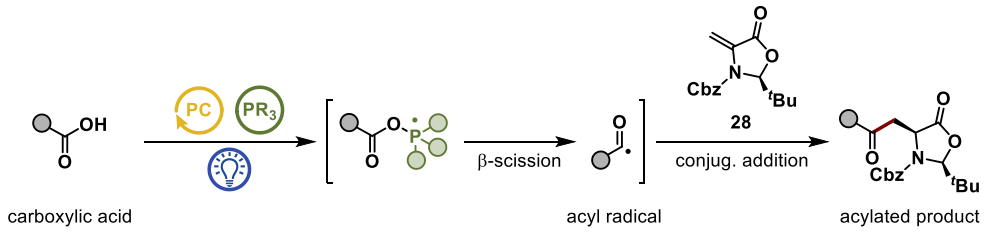
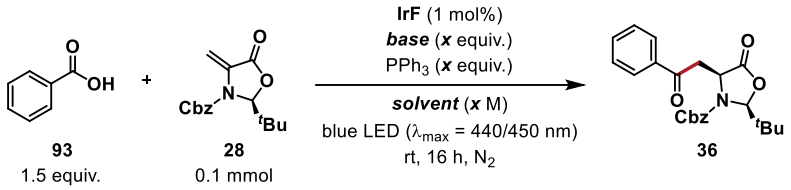


Figure 29. Concept for diastereoselective synthesis of acylated α-amino acid derivatives.

II.II.3 – Optimization Studies

Optimization studies to find the best conditions to access γ-oxo-α-amino acids using carboxylic acids as readily available starting materials were carried out by a colleague. Starting with benzoic acid (**93**) as radical precursor, the use of 2.0 equiv. 2,6-lutidine, 2.0 equiv. PPh_3 in 0.2 M 1,4-dioxane resulted in formation of **36** in quantitative yields (Entry 1, Table 4). It was found, that changing the solvent to DMF (Entry 2, Table 4) or reducing the amount of PPh_3 and 2,6-lutidine to 1.5 equiv. each (Entry 3, Table 4) gave lower yields of **36**. Running the reaction with reduced amounts of base (1.5 equiv. 2,6-lutidine) and PPh_3 (1.5 equiv.) in 0.1 M MeCN gave **36** in quantitative yields (Entry 5, Table 4), identifying a second set of optimal conditions for the targeted transformation. The use of inorganic bases ($CsCO_3$, K_2HPO_4 or KH_2PO_4) yielded **36** in only low to medium quantities (Entries 6–8, Table 4).

*Table 4. Optimization studies for the acylation of **28** with benzoic acid (**93**).*

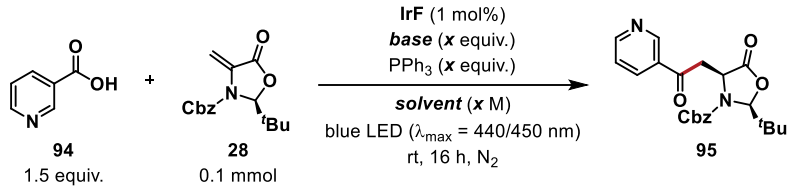


Entry	Base (equiv.)	PPh_3 (equiv.)	Solvent (M)	28 left (%)	36 (%)
1	2,6-Lutidine (2.0)	2.0	1,4-Dioxane (0.2)	0	Quant.
2	2,6-Lutidine (2.0)	2.0	DMF (0.2)	10	78
3	2,6-Lutidine (1.5)	1.5	1,4-Dioxane (0.2)	5	95
4	2,6-Lutidine (1.5)	1.5	1,4-Dioxane (0.1)	7	84
5	2,6-Lutidine (1.5)	1.5	MeCN (0.1)	0	Quant.
6	Cs_2CO_3 (2.0)	1.8	1,4-Dioxane (0.2)	60	35
7	K_2HPO_4 (2.0)	1.8	1,4-Dioxane (0.2)	21	70
8	KH_2PO_4 (2.0)	1.8	1,4-Dioxane (0.2)	76	10

Yields were determined by GC-FID analysis (IS: methyl laureate).

However, when these conditions were applied to a heteroaromatic carboxylic acid – such as nicotinic acid (**94**) – it was found that the targeted product **95** was only formed in diminished yields (Entries 1 & 2, Table 5). Changing the amounts of base and PPh_3 to 1.5 equiv. while running the reaction in 0.1 M 1,4-dioxane resulted in even more diminished yields of **95** (Entry 3, Table 5). Furthermore, using DMF (0.2 M) as solvent did not furnish **95** in satisfactory yields (Entry 4, Table 5). It was found that the use of *sym*-collidine as base gave **95** in moderate 46% yield (Entry 5, Table 5). The optimal conditions for the acylation of **28** using nicotinic acid were found to be 2.0 equiv. *sym*-collidine and 1.8 equiv. PPh_3 in 0.2 M 1,4-dioxane under 24 h of blue LED irradiation, forming **95** in acceptable 56% yield (Entry 6, Table 5).

*Table 5. Optimization studies for the acylation of **95** with nicotinic acid (**94**).*



Entry	Base (equiv.)	PPh_3 (equiv.)	Solvent (M)	28 left (%) left	95 (%)
1	2,6-Lutidine (2.0)	2.0	1,4-Dioxane (0.2)	40	41
2	2,6-Lutidine (1.5)	1.5	MeCN (0.1)	21	55
3	2,6-Lutidine (1.5)	1.5	1,4-Dioxane (0.1)	86	24
4	2,6-Lutidine (2.0)	2.0	DMF (0.2)	16	39
5	*sym*-Collidine (1.5)	1.5	1,4-Dioxane (0.1)	29	46
6[a]	*sym*-Collidine (2.0)	1.8	1,4-Dioxane (0.2)	20	56

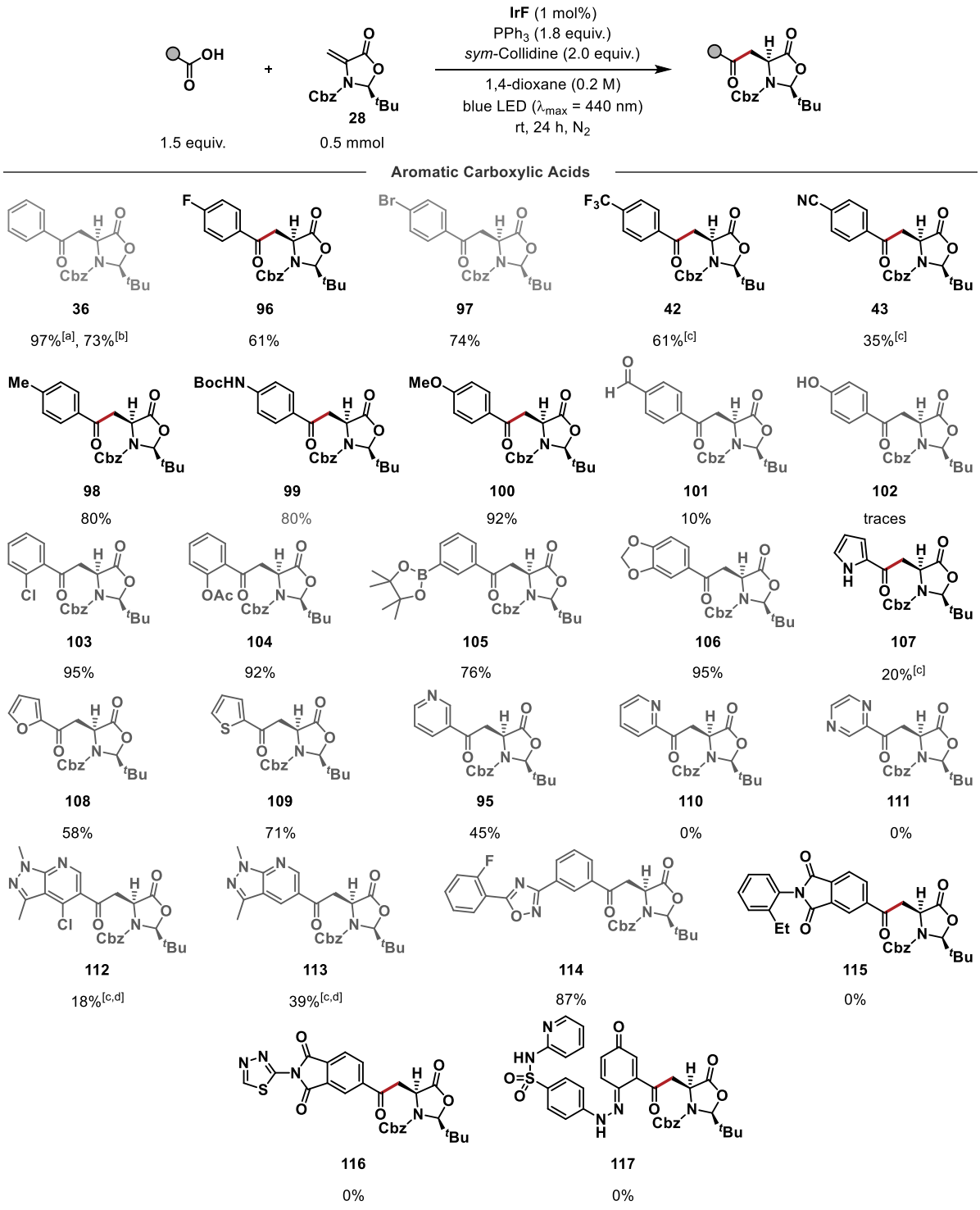
[a]: 24 h irradiation. Yields were determined by GC-FID analysis (IS: methyl laureate).

II.II.4 – Scope and Limitations

With the optimized reaction conditions in hand, the scope and limitations of this deoxygenative acylation protocol were investigated (Scheme 21 and Scheme 22). To give a proper overview of the applicability of the reaction, all synthesized products are listed in the following schemes, including those that were performed by colleagues (depicted in grey).

Initially, aromatic carboxylic acids were used as reactants. It was possible to upscale the methodology to 5.0 mmol when using benzoic acid, to receive **36** in 95% (1.9 g) and 73% (1.4 g) yield. This was even more impressive as the photocatalyst loading was successfully reduced to 0.5 mol% and 0.25 mol%, respectively. According to this, the turn-over-number (TON) of the photocatalyst was determined to be 288 under the given conditions. In addition, benzoic acid derivatives containing electron-withdrawing substituents, such as *p*-F (**96**), *p*-Br (**97**), *p*-CF_3 (**42**) and *p*-CN (**43**) afforded the targeted products in 35–74% yield. This is especially interesting since compound **42** was formed in diminished yields (30%) and compound **43** was not obtained at all using the decarboxylative approach presented in **section II.I.4**, thus highlighting the advantages of this novel methodology. More electron-rich benzoic acid derived products *p*-Me (**98**), *p*-NHBoc (**99**) and *p*-OMe (**100**) were isolated in good to excellent yields (80–92%). While aldehyde **101** was obtained in poor 10% yield, free alcohol **102** was only formed in traces. Next, *o*- and *m*-substituted benzoic acid derivatives were also tested. Ortho-substituents, such as a chloride (**103**) or an Ac-protected alcohol (**104**), as well as a *m*-boronic ester (**105**) were well tolerated (76–95% yield). Furthermore, 1,3-benzodioxole-containing **106** was isolated in an excellent 95% yield.

Next, heteroaromatic carboxylic acids were investigated. Unprotected pyrrole-, furan- and thiophene-containing products **107**–**109** were obtained in moderate to good yields (20–71%). Interestingly, while nicotinic acid gave the corresponding product **95** in a reasonable 45% yield, other *N*-containing heteroaromatic carboxylic acids, such as picolinic and pyrazinoic acids, failed to furnish the targeted products **110** and **111**. To determine the applicability of the methodology onto more complex systems, several aromatic carboxylic acids bearing multiple functional groups were investigated. Surprisingly, when using 4-chloro-1,3-dimethylpyrazolo[3,4-b]-pyridine-5-carboxylic acid, a mixture of the desired product **112** (18% yield) and the dechlorinated product **113** (39% yield) was obtained. Oxadiazole-containing product **114** was isolated in a remarkable 87% yield, whereas phthalimides and sulfasalazine-derived benzoic acids did not afford the targeted products **115**–**117**.

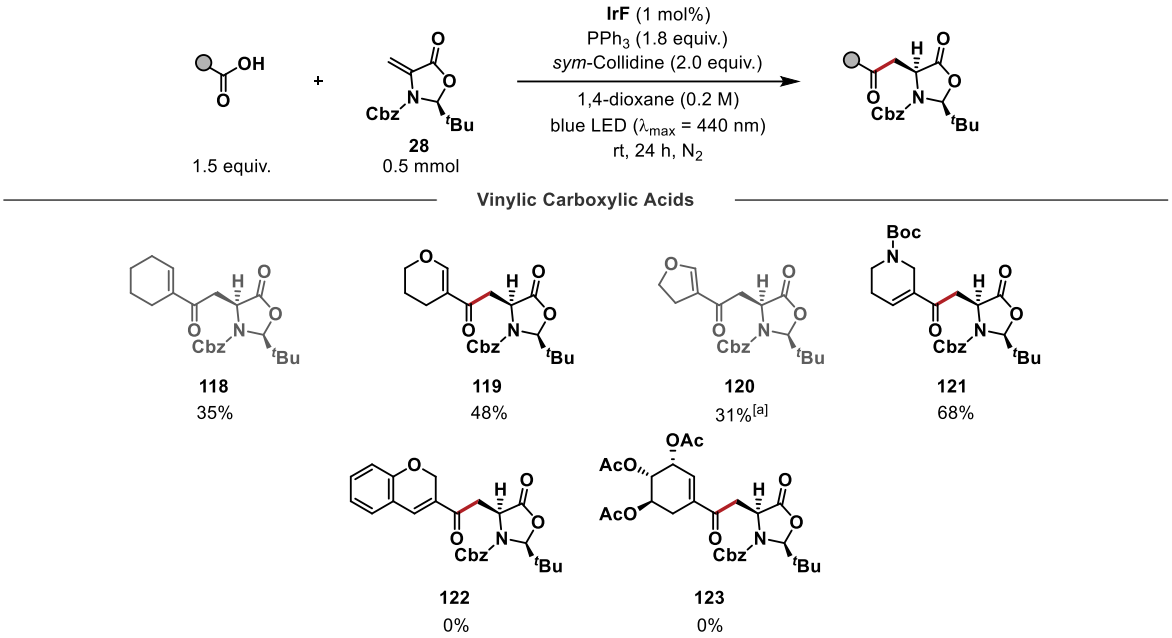


Scheme 21. Scope & limitations of acylation protocol using aromatic carboxylic acids.

[a]: **IrF** (0.5 mol%), 5.0 mmol scale; [b]: **IrF** (0.25 mol%), 5.0 mmol scale, 72 h; [c]: 48 h; [d]: DMF (0.2 M). Unless otherwise stated, the product was obtained with d.r. >20:1, according to ^{1}H NMR investigations of the crude.

Next, vinylic carboxylic acids were investigated as acyl radical precursors (Scheme 22). This is of particular interest, as – to the best of our knowledge – no direct use of vinylic carboxylic acids as acyl radical precursors has been reported before. It was found that cyclohexene-, dihydropyran-, dihydrofuran- and tetrahydropyridine-motifs were well tolerated, given the

desired products **118**–**121**, in 31-68% yield. Surprisingly, chromene-containing product **122** and protected Shikimic acid derived product **123** could not be obtained.



Scheme 22. Scope & limitations of acylation protocol using vinylic carboxylic acids.

[a]: 48 h. Unless otherwise stated, the product was obtained with d.r. >20:1, according to 1H NMR investigations of the crude.

Overall, the presented methodology is broadly applicable throughout a variety of (hetero)aromatic carboxylic acids and can also be used with vinylic carboxylic acids. This protocol shows some improvements for the synthesis of γ-oxo-α-amino acids over the previously described decarboxylative methodology whereas it results in higher yields for electron-poor systems.

II.II.5 – Mechanism

Based on previously described light-mediated acylation reactions using phosphine reagents, [161–166] a plausible reaction mechanism was proposed (Figure 30). The excited state photocatalyst (***Ir^{III}**) (*$E_{1/2}$ = +1.21 V vs SCE)[144] gets reductively quenched by PPh_3 (**124**) ($E_{1/2}$ = +0.98 V vs SCE)[167] via a SET. The generated triphenylphosphine radical cation **125** adds to the carboxylic acid **126**, forming phosphoranyl radical **127**. Subsequent β-scission of **127** generates acyl radical **128** and phosphine oxide **129** as by-product. Giese-type addition of **128** to **28** delivers α-amino radical intermediate **130**, which reacts with the reduced photocatalyst (**Ir^{II}**) ($E_{1/2}$ = -1.37 V vs SCE)[144] via SET and, upon protonation, affords product **131** while closing the photoredox-catalytic cycle.

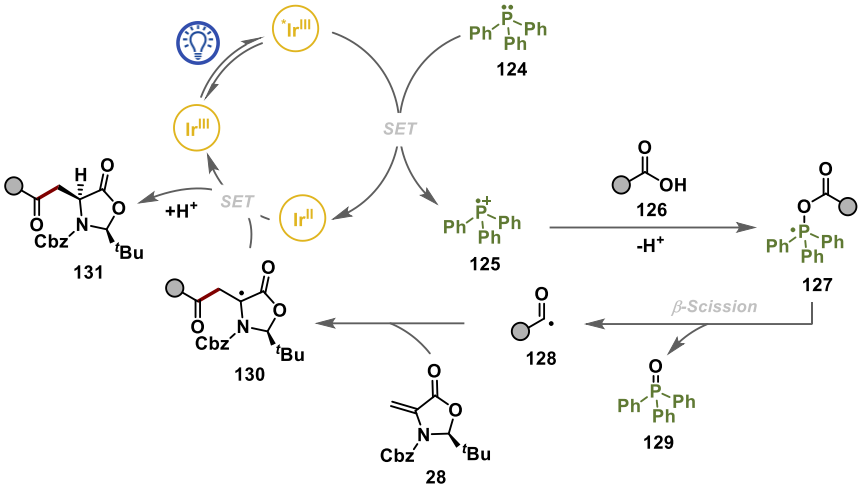


Figure 30. Proposed mechanism.

Calculation of the reaction's quantum yield (Φ = 13.57) indicated a significant contribution of a radical chain pathway (see **section VI.III.1** for further details). It was hypothesized that the organic base, *sym*-collidine, might play a role in this radical chain. Therefore, a colleague carried out the standard reaction using inorganic bases (K_2HPO_4, KH_2PO_4 or Cs_2CO_3), which resulted in diminished yields of **36**. Furthermore, even when catalytic amounts of *sym*-collidine (20 mol%) were used, the reaction yielded 79% of **36** after only 3 h (Φ = 6.8). These observations suggest that *sym*-collidine plays a crucial role as a radical chain carrier in the reaction. Therefore, an alternative radical chain pathway was proposed (Figure 31). Instead of being reduced by the Ir^{II}-photocatalyst, α-amino radical **130** can undergo a proton-coupled electron transfer (PCET) with the protonated *sym*-collidine **132**, furnishing the targeted product **131** and *sym*-collidine radical cation **133**. The latter oxidizes ($E_{1/2}$ ≥ +2 V vs SCE)[168] triphenylphosphine **124** to the corresponding radical cation **125** which will interact with carboxylate **134** being formed by deprotonation of carboxylic acid **126** by *sym*-collidine (**135**). During optimization studies, it was found that irradiation of the reaction mixture is mandatory for the reaction to take place. Therefore, this alternative pathway is believed to be in operation at the same time as the photocatalytic pathway.

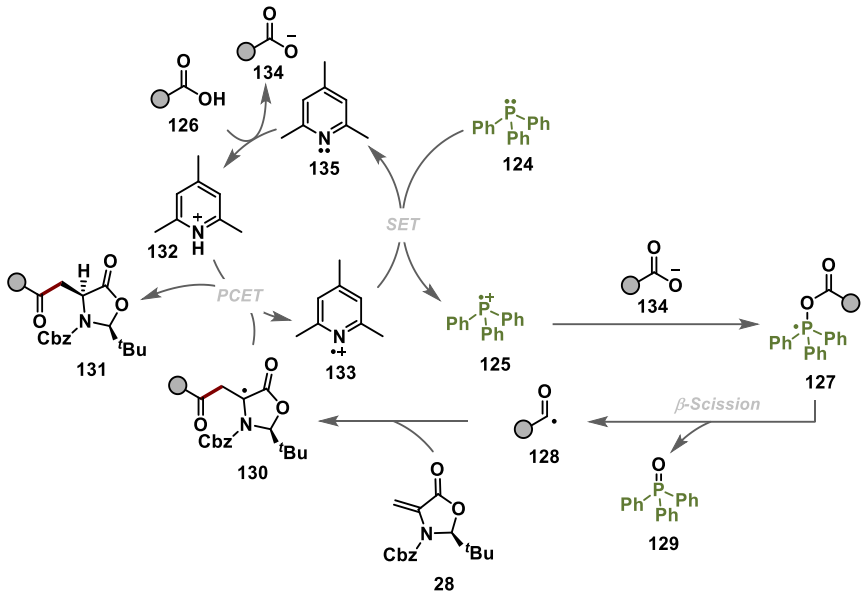


Figure 31. Alternative mechanism explaining the quantum yield.

II.II.6 – Derivatization Reactions

γ-Oxo-α-amino acids are versatile species possessing a variety of potential vectors for further functionalizations (Figure 32). **Section II.II.6** summarizes the studies performed to derivatize the products obtained in **section II.II.4**.

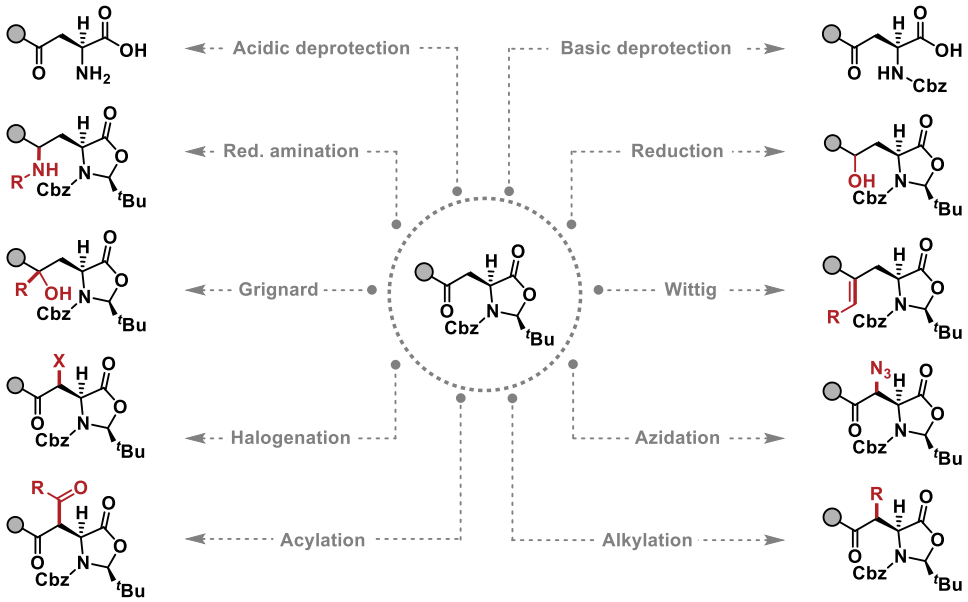
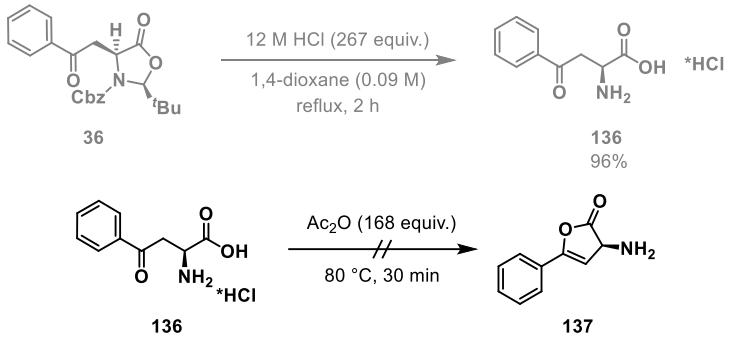


Figure 32. Potential functionalizations of γ-oxo-α-amino acid derivatives.

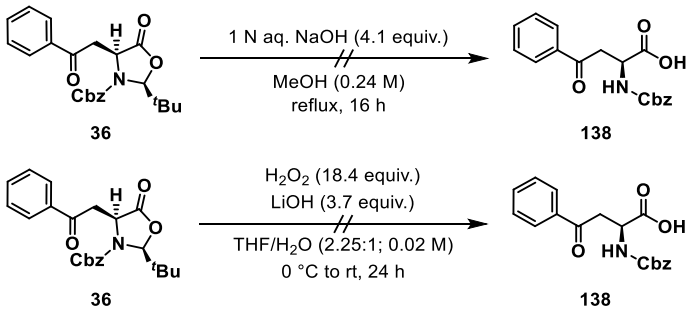
Deprotections

The first derivatization attempts focused on accessing the UAAs by opening the oxazolidinone core either via acidic or basic conditions. A colleague showed that acidic deprotection of oxazolidinone **36** using 12 M HCl in 1,4-dioxane under reflux conditions afforded free amino acid **136** as the corresponding HCl-salt in nearly quantitative yield (depicted in grey). With this in mind, further derivatizations of **136** were explored. Initially, cyclization of γ-keto-α-amino acid **136** to the corresponding unsaturated furanone using acetic anhydride was tested.[169] Unfortunately, neither the targeted product **137**, nor other by-products could be isolated (Scheme 23).



*Scheme 23. Attempt to access furanone **137**.*

Next, two sets of basic deprotection conditions were tested to access Cbz-protected amino acids (Scheme 24). Firstly, a saponification protocol using NaOH failed to afford Cbz-protected amino acid **138**.[170] Secondly, saponification of the oxazolidinone core of **36** using H_2O_2 and LiOH was attempted.[171] Unfortunately, analysis of the crude reaction mixture showed mainly remaining starting material.

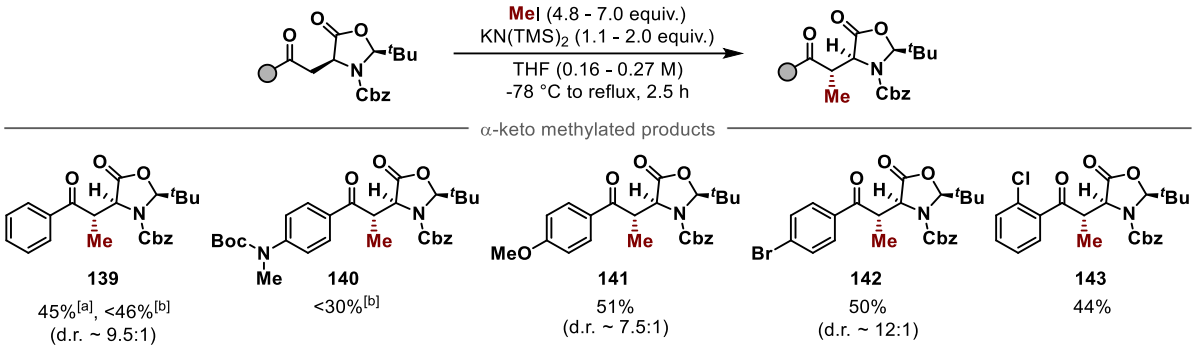


Scheme 24. Basic deprotection attempts.

Alkylations

Next, alkylation reactions were performed (Scheme 25). Ketone **36** could be successfully methylated in the α-carbonyl position to give product **139** in 45% yield. Analysis of this reaction repeated in a smaller scale suggested a d.r. ~ 9.5:1 for the preferred diastereomer. Additional

methylation reactions using various γ-oxo-α-amino oxazolidinones were performed. In an attempt to increase the yield of the reaction, more equivalents of iodomethane were used. However, this showed no further improvements on the yield of **139** (<46% vs 45%). The methylated species **140**–**143** were all obtained in low to moderate yields (<30–51%). The diastereomeric ratios (d.r.) were calculated (whenever possible) from the crude reaction mixtures by ^{1}H NMR analysis and determined to be between 7.5:1 and 12:1.



Scheme 25. Synthesized α-keto methylated products.

[a]: 1.6 equiv. MeI, -78 °C to rt, o.n.; [b]: contains significant amounts of solvent.

Unfortunately, it was not possible to determine the stereochemistry of the newly formed C–C bond through NOESY-NMR analysis of **139.** However, analysis of the 3D-structure (created with *PerkinElmer Chem3D*®, structure depicted according to MM2 Minimization) suggested that methylation occurs in the anti-position with respect to the sterically demanding *tert*-butyl group to form product **139** with the shown configuration as preferred isomer. In its enol form (**144**) both, the *tert*-butyl and the Cbz-group shield one side of the molecule so that attack of the nucleophile will occur preferentially from the backside as depicted in Figure 33. The used MM2 Minimization calculates the lowest steric energy of a molecule, which is the optimal combination of two forces: steric repulsion of all atoms/groups result in an occupation of the largest possible distance to each other, but, this optimal distance usually goes along with the energetically unfavored stretching or bending of certain bonds.[172] However, it must be mentioned that the sole consideration of steric effects neglects other energetic factors, such as polar and entropic effects.

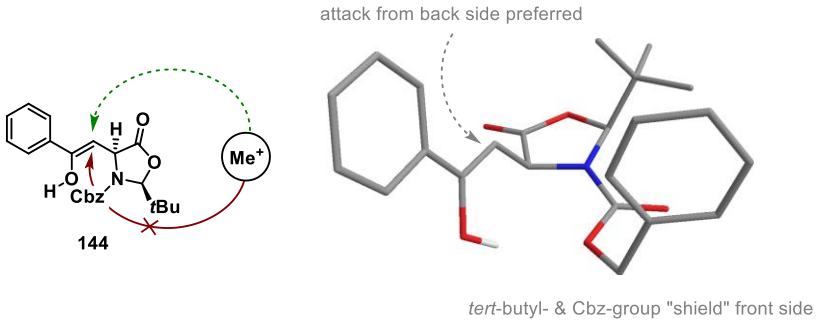
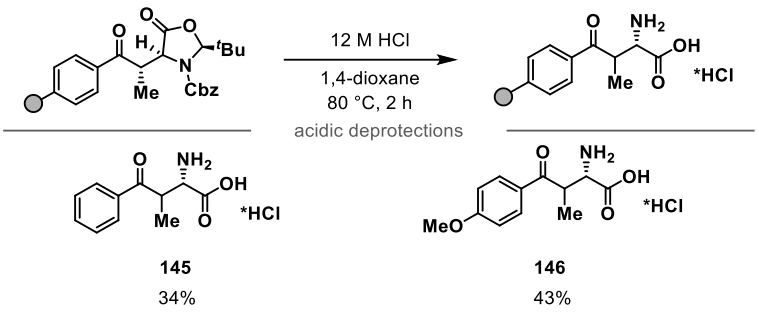


Figure 33. Plausible explanation for the observed diastereoselectivity.

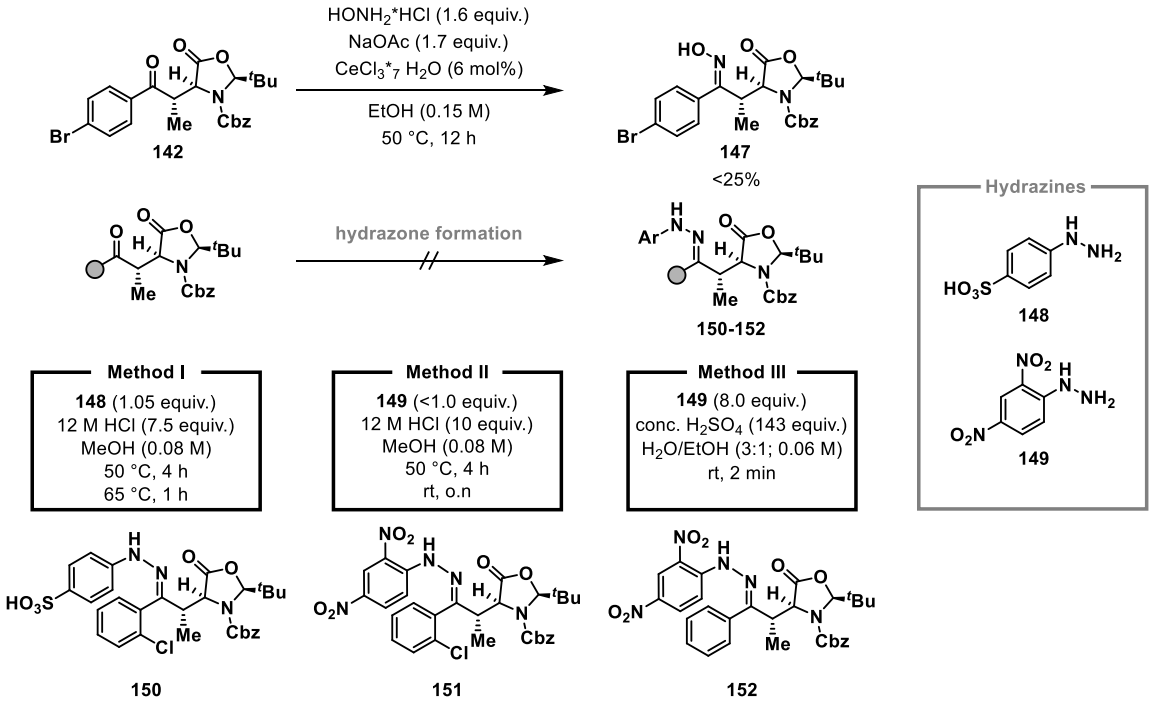
To try to fully elucidate the stereochemistry of the newly formed C–C bonds, a couple of follow-up reactions with the methylated species were performed with the aim of obtaining a representative crystal structure.

Starting with **139** and **141**, acidic deprotections using 12 M HCl were performed. Unfortunately, the corresponding products **145** and **146** were both isolated as racemic mixtures (Scheme 26).



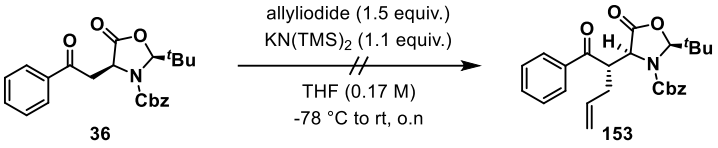
Scheme 26. Acidic deprotections of α-methylated compounds.

Next, reactions to transform the benzylic ketone into the corresponding hydrazone were carried out (Scheme 27). **142** could be converted into **147** in <25% yield by using $HONH_2$*HCl in the presence of $CeCl_3$ and NaOAc – conditions that were inspired by a literature procedure using methoxyamine to form the corresponding hydrazone.[173] The obtained product possessed a significant amount of cyHex residues, but was found to be unstable: it started decomposing while drying it properly to carry out full analytics. Therefore, other hydrazines (**148** & **149**) were tested to try to generate the corresponding hydrazones **150**–**152**. However, all trials remained unsuccessful.



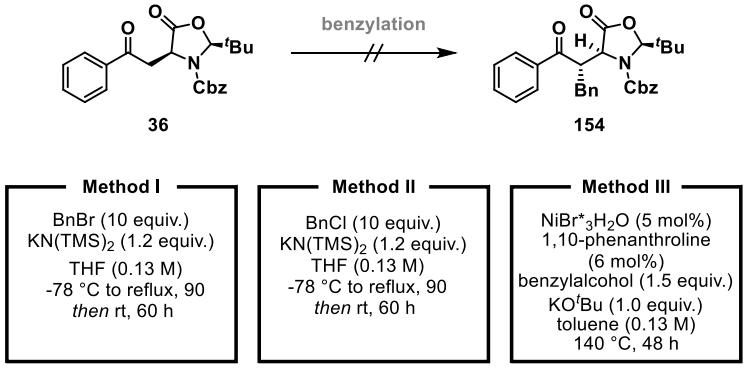
Scheme 27. Trials to access hydrazones from α-methylated compounds.

As a result of the success of the above methylation reactions, this approach was tested using other haloalkanes. (Scheme 28). Treatment of **36** with $KN(TMS)_2$ as base and subsequent addition of allyl iodide resulted in a complex mixture from which the targeted product **153** could not be isolated.



*Scheme 28. Trials towards α-keto allylation of **36**.*

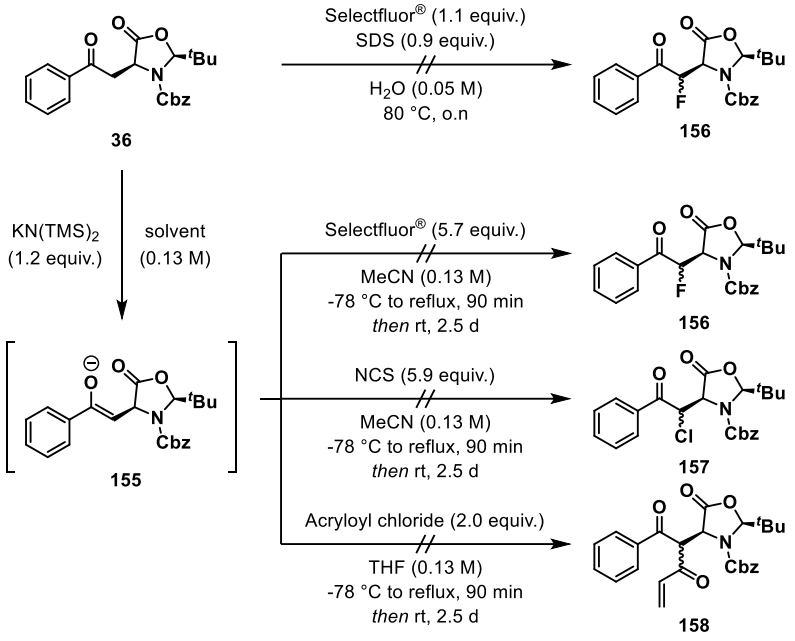
Next, benzylation of the α-carbonyl position using benzyl chloride or benzyl bromide was attempted. However, both reactions did not give the desired product **154**. Therefore, a Ni-catalyzed α-keto benzylation reaction was tested.[174] Unfortunately, although after 2 days full consumption of starting material **36** was observed, NMR analysis of the crude reaction mixture did not show product formation.



*Scheme 29. Benzylation attempts to access **154**.*

Further α-carbonyl functionalizations

Next, further α-carbonyl functionalizations, such as halogenations, acylations and alkylations were explored (Scheme 30). Adapting conditions for α-fluorinations of ketones,[175] **36** was treated with Selectfluor® in the presence of sodium dodecyl sulfate (SDS) in H_2O. After stirring to 80 °C overnight, ^1H and ^{19}F NMR analysis of the crude reaction mixture showed only unreacted **36**. Based on this result, it was questioned whether it is necessary to form the enolate **155** prior to functionalization of **36** with suitable electrophiles. Therefore, **36** was first treated with $KN(TMS)_2$ forming **155** *in situ* before adding Selectfluor® to try to access fluorinated compound **156**. However, once again, just starting material was observed. To see if the reaction would work using a different halogenation source, the reaction was repeated using *N*-chlorosuccinimide (NCS). Unfortunately, chlorinated species **157** could not be obtained. Furthermore, enolate **155** was treated with acryloyl chloride to give acylated product **158**. However, the reaction remained unsuccessful.

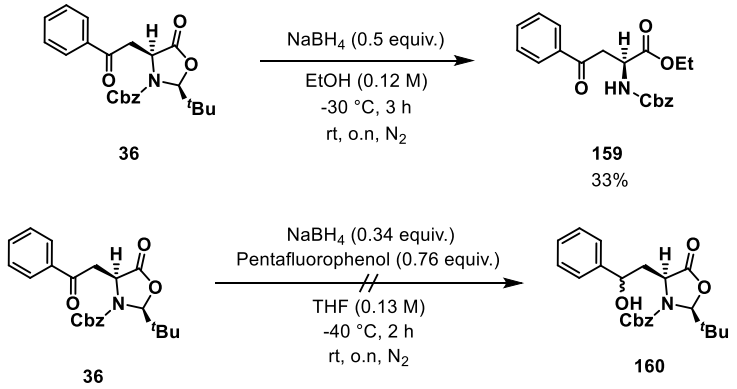


Scheme 30. Halogenation and acylation trials.

Reductions

Next, it was tested if the ketone of **36** can be reduced in the presence of the oxazolidinone core. If successful, it was hypothesized that the sterically demanding oxazolidinone core might help with the diastereoselectivity of the reduction.

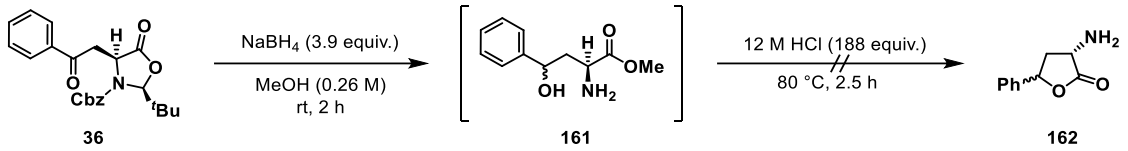
It was found that when reducing **36** with $NaBH_4$ in EtOH, not the ketone but the oxazolidinone core was reduced, furnishing *N*-Cbz protected amino ester **159** in 33% yield. To access alcohol **160**, the reaction was repeated in the presence of pentafluorophenol in THF – conditions that have been reported to selectively reduce ketones in the presence of oxazolidinones.[176] However, no reaction was observed (Scheme 31).



*Scheme 31. Reduction trials on **36**.*

Based on these results, it was hypothesized that reducing **36** with larger equivalents of $NaBH_4$ in a more concentrated MeOH solution might lead to reduction of both the oxazolidinone core and the benzylic ketone, affording methyl ester species **161**. However, raw analysis of **161**

gave no clear evidence, whether the reduction did work or not. The signals that might belong to the desired product partially overlapped with some unknown compound. However, since both, Cbz- and *tert*-butyl-group of **36** could not be seen in the crude NMR, it was decided to perform an easy-to-do follow-up reaction to help analyze the reaction outcome. Therefore, the reaction mixture was treated with 12 M HCl to form amino lactone **162**. Both reactions (reduction and acidic cyclization) were adapted from the literature.[177] Unfortunately, the targeted amino lactone **162** could not be obtained.



*Scheme 32. Trial to access amino lactone **162**.*

Overall, all trials to selectively reduce the ketone of **36** remained unsuccessful. The solely successful reductive transformation was achieved when reducing the oxazolidinone core of **36** using $NaBH_4$ and EtOH to give **159** in 33% yield.

In general, the follow-up functionalization of the obtained γ-oxo-α-amino acid derivatives proved to be quite difficult. Either the oxazolidinone core prevents functionalization reaction by its bulky character shielding most of the substrate, or the oxazolidinone core reacted faster than the targeted position. However, a couple of derivatizations were successfully performed, including α-carbonyl methylations.

II.II.7 – Project Summary

In summary, a deoxygenative strategy for the preparation of γ-oxo-α-amino acid derivatives was developed. The straightforward method is based on the generation of acyl radicals starting from carboxylic acids. Key to the reaction is the addition of PPh_3, which is readily oxidized by the excited photocatalyst, generating a phosphine radical cation which gets trapped by the carboxylate species. The resulting phosphoranyl radical undergoes facile β-scission, giving access to the corresponding acyl radical. Giese-type radical addition to the Beckwith-Karady alkene **28** then affords the corresponding γ-oxo-α-amino acid in good to excellent yields, and with excellent diastereoselectivities. Various derivatizations and functionalizations of the obtained products gave access to additional unnatural α-amino acid derivatives. The results of this collaborative project were published in 2021 in *The Journal of Organic Chemistry* and were highlighted by both academic and industrial scientists in *Synfacts* and *Organic Process Research & Development*, respectively.[3,4,178]

III. Synthesis of γ-Oxo-δ-Amino Acids

III.1. – Introduction

Unnatural amino acids (UAAs) are of eminent importance throughout numerous scientific areas. Arguably, α- and β-amino acids are the predominantly investigated examples for this class of substances. However, in recent years, also higher analogues, namely γ- and δ-amino acids, have gained increased attention in the scientific community. While research towards γ-amino acids is mostly focused on the development of γ-aminobutyric acid (GABA) derivatives, δ-amino acids – and especially γ-oxo-δ-amino acids – are versatile species with applications in the synthesis of peptide nucleic acid (PNA) structures or porphyrins used in photodynamic therapies. In addition, they can also be employed as synthons in natural product or pharmaceutical syntheses, and as well as building blocks for peptide drugs or peptidomimetics (Figure 34).[100–114]

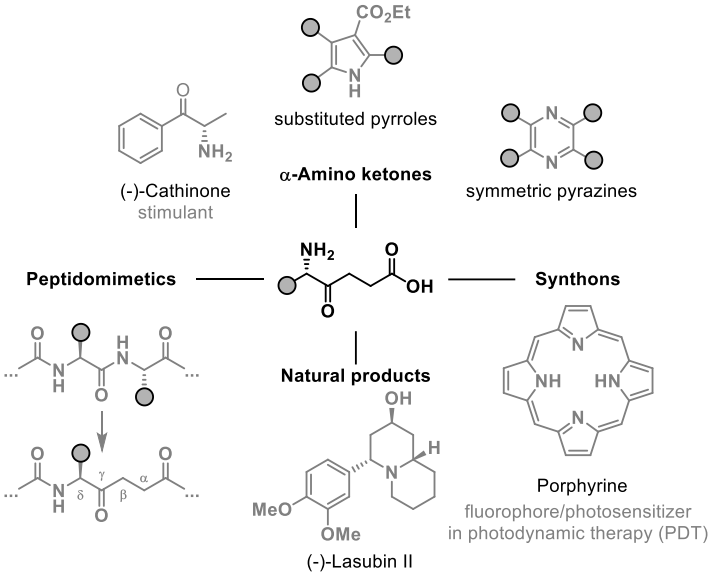


Figure 34. Possible applications of γ-oxo-δ-amino acids.

It is due to the lack of straightforward methodologies to access these scaffolds that limit their application. "Classical" 2-e⁻-approaches towards these building blocks require the use of chiral catalysts or chiral auxiliaries – the development of which can be time- and resource-consuming – and usually involve several steps.

Radical chemistry, especially visible-light mediated photoredox catalysis, offers new possibilities to accomplish challenging transformations in a rapid and clean fashion.[90,91,179] The controlled generation of open-shell species opens up new routes to access so far underdeveloped chemical space under extremely mild conditions.

Following a 1-e⁻-disconnection approach, two possible strategies to access γ-oxo-δ-amino acids were identified (Figure 35):

Pathway a): Giese-type conjugate addition of an α-amino acyl radical onto an α,β-unsaturated acceptor.

Pathway b): Giese-type conjugate addition of an α-amino ketyl radical onto an α,β-unsaturated acceptor.

Pathway a) was ruled out by the fact that (especially α-heteroatom-stabilized) acyl radicals are prone to undergo rapid decarbonylation.[180,181] Even when performing the reaction under a CO-atmosphere, the decarbonylation-carbonylation equilibrium[182] of the α-amino acyl radical would obliterate the α-amino stereocenter.

Pathway b) was selected as strategy of choice to access the desired γ-oxo-δ-amino acid scaffolds. However, α-amino ketyl radicals are typically generated via single electron reduction (approx. -2 V vs. SCE) of carbonyl species (e.g., aldehydes or ketones), requiring superstoichiometric amounts of strong reductants.[183] This in turn limits the application to molecules bearing functional groups being sensitive towards reductions.

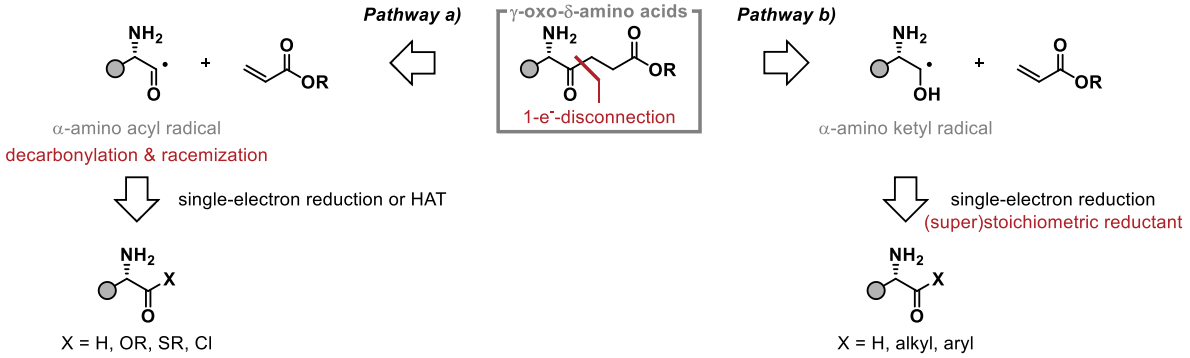
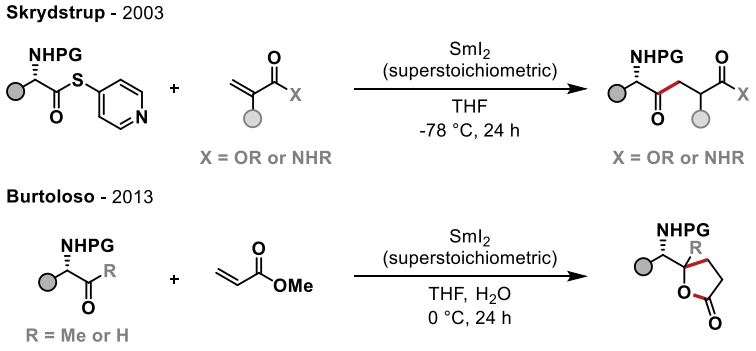


Figure 35. Radical disconnection approach reveals two possible pathways to access γ-oxo-δ-amino acids.

As state-of-the-art concepts to generate α-amino ketyl radicals, the groups of Skrydstrup and Burtoloso developed strategies using SmI_2 to reduce α-amino thioesters and α-amino ketones or aldehydes, respectively (Scheme 33).[184–186]



Scheme 33. Generation of α-amino ketyl radicals via single-electron reduction using superstoichiometric SmI_2.

Encouraged by the lack of mild and efficient strategies to access α-amino ketyl radicals, a novel methodology grating access to these versatile intermediates was sought after. It was hypothesized that a selective α-oxo hydrogen atom abstraction of β-amino alcohols would furnish the desired α-amino ketyl intermediate which, when being intercepted by a suitable acceptor (e.g., an acrylate) would deliver γ-oxo-δ-amino esters (Figure 36). Main challenge for this straightforward approach is the selective hydrogen atom abstraction in the presence of bonds with similar polarity and strength (BDE: ~94-96 kcal/mol for α-oxo C_{sp}^3–H vs. ~91 kcal/mol for α-amino C_{sp}^3–H).[187,188]

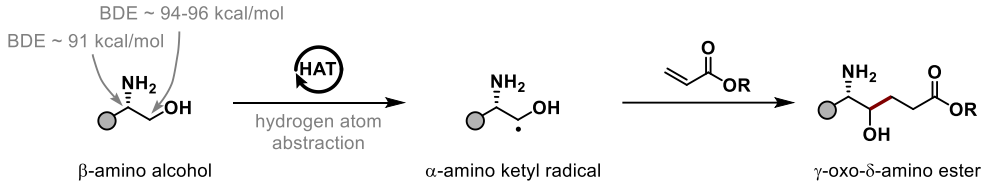
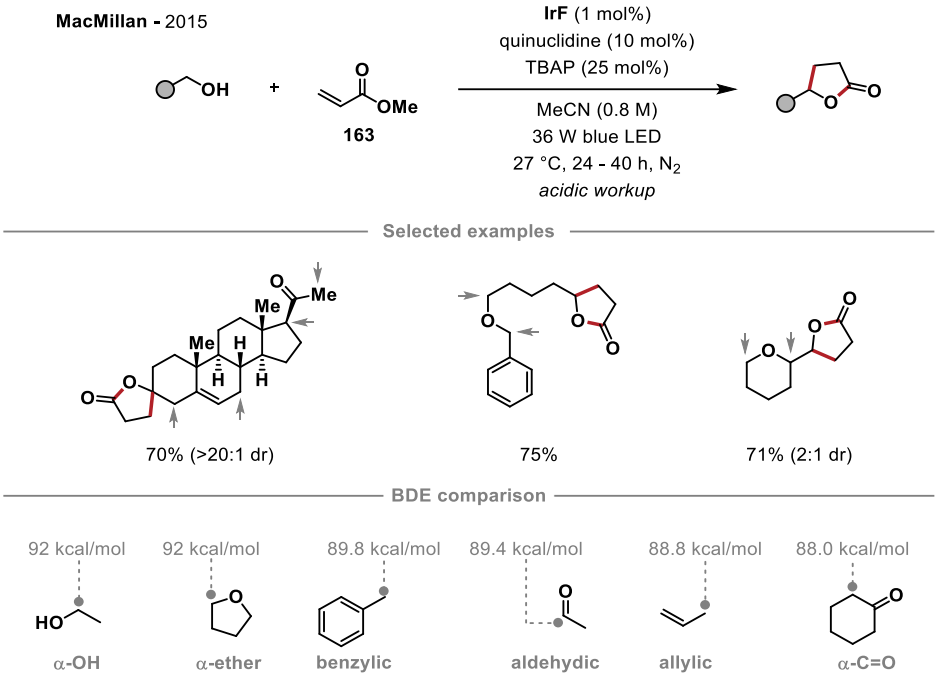


Figure 36. Novel approach to access α-amino ketyl radicals via selective HAT catalysis.

In recent years, the principle of polarity-reversal catalysis[189] has been used to selectively activate both α-oxo C_{sp}^3–H[190–202] and α-amino C_{sp}^3–H[203–208] bonds by combination of photoredox and HAT catalysis.

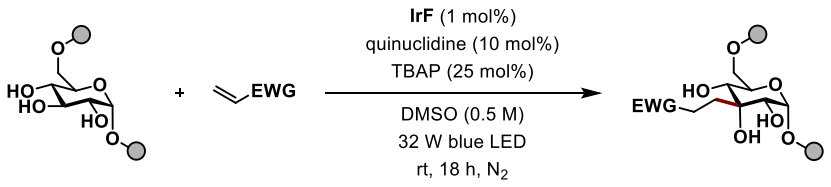
For example, MacMillan and co-workers reported 2015 a methodology for the selective α-hydroxy C–H functionalization of primary and secondary alcohols with methylacrylate (**163**) in the presence of weaker C–H bonds (Scheme 34; weaker C–H bonds are highlighted with a grey arrow).[190]

This was accomplished by addition of a hydrogen-bond acceptor catalyst, tetrabutylammonium phosphate (TBAP). According to the authors, the interaction of the hydroxy group with TBAP leads to strengthen the n-s* delocalization of the oxygen lone pair, increasing the hydridic character of the α-hydroxy hydrogen. Quinuclidine, upon single-electron oxidation acts as HAT catalyst, abstracting this hydridic hydrogen and generating a stabilized ketyl-radical that can be further functionalized.



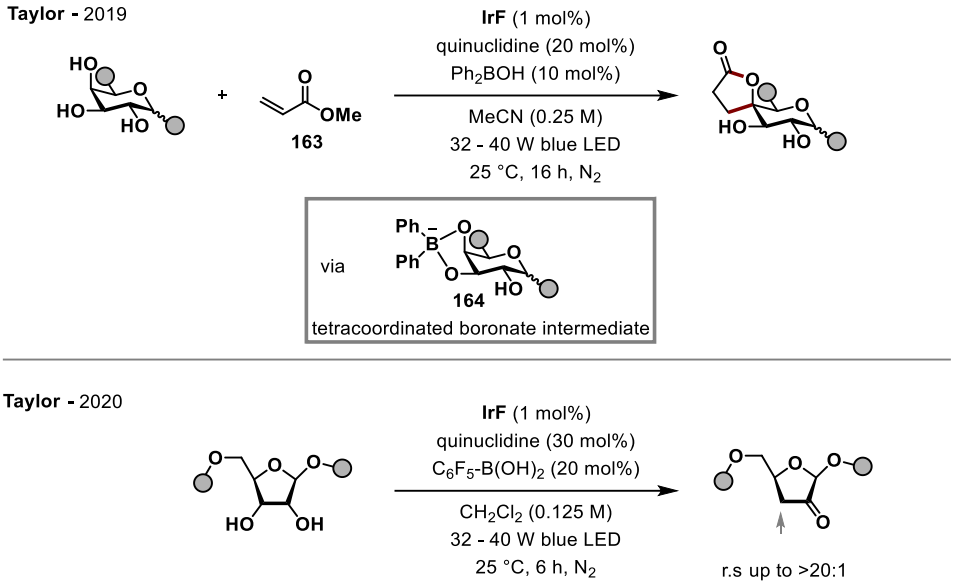
Scheme 34. Selective α-hydroxy functionalization by MacMillan and co-workers.

In 2017, Witte & Minnaard exploited MacMillan's methodology for the stereoselective α-hydroxy-functionalization of saccharides (Scheme 35).[209]



Scheme 35. Selective α-hydroxy functionalizations in saccharides by Witte & Minnaard.

Another catalytic system for the selective α-hydroxy-functionalization of saccharides was developed by Taylor and co-workers (Scheme 36).[197,198] Instead of using TBAP as hydrogen-bond acceptor catalyst, boron-derived additives were used as Lewis acid (LA) catalysts. The formation of a tetracoordinated boronate intermediate **164** allowed both, selective hydrogen abstraction at the α-OH position in the presence of bonds with similar BDEs, and control over the regioselectivity of the reaction, as the tetracoordinated boronate intermediate only forms from 1,2-diols in *cis*-configuration.



Scheme 36. Selective α-hydroxy functionalizations in saccharides by Taylor.

This general approach of selectively functionalizing α-oxo positions in the presence of weaker C–H bonds has great potential for application. However, research has so far mostly been focused on the selective functionalization of (poly)alcohols, especially saccharides. Furthermore, a selective use of this approach in molecules containing both classes of C_{sp}^3–H bonds (α-NH and α-OH) remained scarce and was – to the best of our knowledge – never reported for molecules in which these bonds are alpha to each other.

Extending this concept to other classes of compounds should allow a range of novel transformations, thus granting access to new chemical space. Especially the use of β-amino alcohols would open a straightforward approach to access γ-oxo-δ-amino acid derivatives.

It was hypothesized that a suitable catalyst (e.g., a B-based Lewis acid as used by Taylor *et al.*), would interact with both, the amino- and the alcohol functionality of the β-amino alcohol, thus forming a cyclic and therefore rigid intermediate. By starting with a chiral β-amino alcohol it is expected that this cyclic intermediate would provide a diastereomerically enriched γ-oxo-δ-amino ester.

Due to alkoxide-Lewis acid bonding, the BDE of the α-oxo-hydrogen should decrease due to enhanced n–σ* (C–H) delocalization,[191] allowing the selective hydrogen abstraction by a suitable HAT catalyst. Additionally, the polarity difference between the α-amino and α-oxo C_{sp}^3–H bond might be further increased by installing an electron-withdrawing protecting group on the amine.

The selective generation of α-amino ketyl radicals without destroying the neighboring stereocenter, and their subsequent functionalization (e.g., via Giese-type addition onto α,β-unsaturated carboxylic acid derivatives) would open several new and straightforward routes to access amino acid motifs stereoretentively without the necessity of a chiral catalyst.

III.2. – Project Goal

Development of a chemoselective hydrogen atom transfer reaction to access α-amino ketyl radicals from β-amino alcohols, and their exploitation to access γ-oxo-δ-amino esters. The main challenge of the proposed transformation is the selective generation of the targeted α-amino ketyl radical in the presence of an adjacent α-amino hydrogen with a similar polarity and BDE. In addition, it should be investigated if the use of a suitable Lewis acid catalyst would allow control over the diastereoselectivity of the reaction.

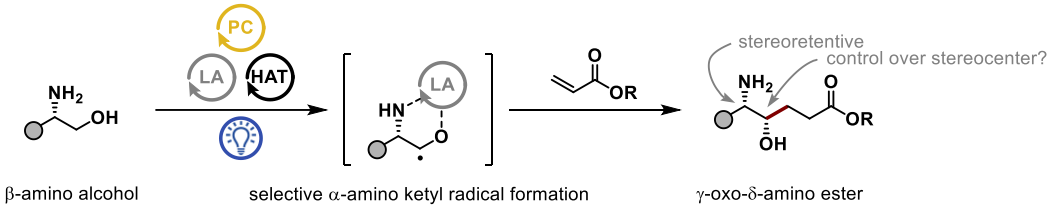


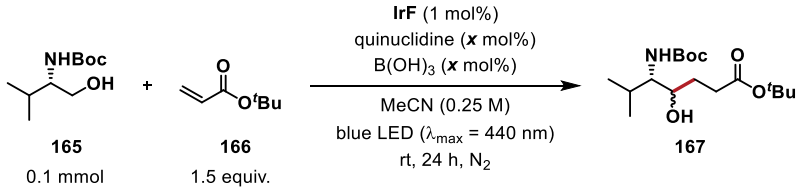
Figure 37. Concept for diastereoselective synthesis of γ-oxo-δ-amino esters.

III.3. – Optimization Studies

Inspired by conditions priorly used for hydrogen atom abstraction on α-hydroxy C_{sp}^3-H bonds (see e.g., selective α-hydroxy functionalizations of saccharides by Taylor *et al.*[197]), the optimization was started by using **IrF** as photocatalyst and quinuclidine as HAT catalyst in MeCN. $B(OH)_3$ as simplest example for a B-based Lewis acid was selected as activator, and *N*-Boc-valinol (**165**) was used as standard amino alcohol. *tert*-Butyl acrylate (**166**) was chosen as radical acceptor due to – compared to other acrylates (e.g., methyl acrylate) – its enhanced stability against intramolecular cyclization of the formed secondary alcohol nucleophilically attacking the ester group.

First, the optimal ratio of quinuclidine as the HAT catalyst and $B(OH)_3$ as additive was investigated (Table 6). It was found that 10 mol% quinuclidine and 20 mol% $B(OH)_3$ resulted in the best consumption of **165** (Entry 2, Table 6). Increasing the amount of quinuclidine relative to $B(OH)_3$ resulted in diminished consumptions (Entries 3–8, Table 6), while increasing the amount of $B(OH)_3$ relative to the quinuclidine still gave high consumption of starting material, but only trace amounts of the targeted product **167** (Entries 12–15, Table 6).

Table 6. Quinuclidine/additive ratio screening.



165 0.1 mmol + **166** 1.5 equiv. → **167**

Entry	Quinuclidine (mol%)	Additive (mol%)	165 consumption (%)	d.r.[a]
1	5	$B(OH)_3$ 20	0	-----
2	10	$B(OH)_3$ 20	93[b]	2.0 / 1
3	20	$B(OH)_3$ 20	70	1.9 / 1
4	40	$B(OH)_3$ 20	69	2.2 / 1
5	50	$B(OH)_3$ 20	51	2.1 / 1
6	60	$B(OH)_3$ 20	49	2.1 / 1
7	80	$B(OH)_3$ 20	69	1.7 / 1
8	100	$B(OH)_3$ 20	70	1.4 / 1
9	10	none	61	1.4 / 1
10	10	$B(OH)_3$ 5	89	1.6 / 1
11	10	$B(OH)_3$ 10	100	1.5 / 1
12	10	$B(OH)_3$ 40	100[c]	1.8 / 1
13	10	$B(OH)_3$ 60	64[c]	-----
14	10	$B(OH)_3$ 80	73[c]	-----
15	10	$B(OH)_3$ 100	100[c]	-----

[a]: calculated by GC-FID; [b]: average of three runs; [c]: only traces of **167** were observed.

Although this initial screening showed good reactivity towards amino alcohol consumption, the observed diastereoselectivity was relatively low. With this in mind, it was decided that oxidation of the secondary alcohol to the corresponding ketone would increase the applicability of the methodology by providing a single product. Therefore, a one-pot, two-step protocol was developed to transform β-amino alcohols to their corresponding γ-oxo-δ-amino esters (Figure 38).

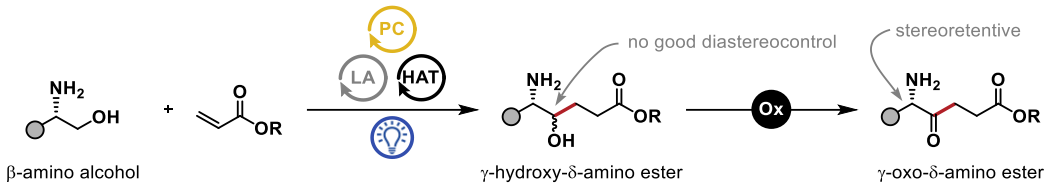
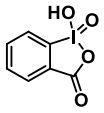


Figure 38. Concept to access γ-oxo-δ-amino derivatives.

To achieve this one-pot transformation, it was decided to use a mild and selective oxidant for the oxidation of secondary alcohols: 2-iodoxybenzoic acid (IBX, **168**, Figure 39). IBX can be readily synthesized from 2-iodobenzoic acid, a cheap and abundant starting material which is easy and safe to handle.



IBX

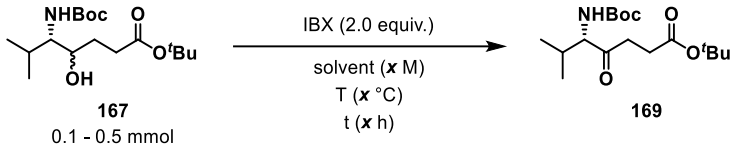
(168)

Figure 39. 2-Iodoxybenzoic acid (IBX).

It should be noted, however, that IBX has been reported to be explosive on impact or heating to high temperatures.[210] Nevertheless, no hazards were observed throughout synthesis, storage and handling of IBX when working at temperatures between 20 °C and 90 °C, which is in accordance with previously reported observations.[211]

A reaction screening for the oxidation step to access γ-oxo-δ-amino ester **169** showed, that full consumption of **167** was obtained when using IBX in DMSO at room temperature (Entry 1, Table 7), conditions previously reported by Kirsch and co-workers for the oxidation of secondary alcohols.[212] Exchanging DMSO by EtOAc, and increasing the reaction temperature to 85 °C[211] showed full consumption of the alcohol after only 3 h (Entry 2, Table 7). Since the photoreaction proceeds only in MeCN, EtOAc was exchanged by the latter. Delightfully, this protocol also afforded full consumption of **167** in 3 h (Entry 3, Table 7). With these final conditions, no solvent exchange is necessary after the photoreaction, since the oxidation step can be carried out by simply adding IBX to the reaction mixture and increasing the temperature for 3 h.

Table 7. Oxidation protocols.

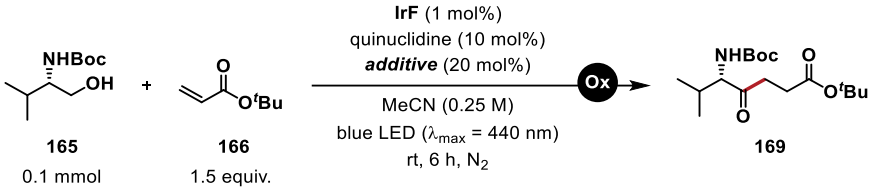


Entry	Solvent (M)	T (°C)	t (h)	167 Consumed (%)	Protocol name
1	DMSO (0.1 M)	rt	14	>99	**Ox-A**
2	EtOAc (0.1 M)	85	3	>99	**Ox-B**
3	MeCN (0.25 – 0.0125 M)	85	3	>99	**Ox-C**

With the optimized conditions for the oxidation step in hand, further screenings were carried out to optimize the photoreaction step. A summary of selected findings from these studies screenings is shown in the following section.

Initially, several additives were tested as cocatalyst, including previously reported additives for selective α-hydroxy H-atom abstraction, such as TBAP and Ph_2BOH (Table 8). It was found that $PhB(OH)_2$ was the best additive, providing **169** in 63%, as determined by GC-FID.

Table 8. Additive screening.

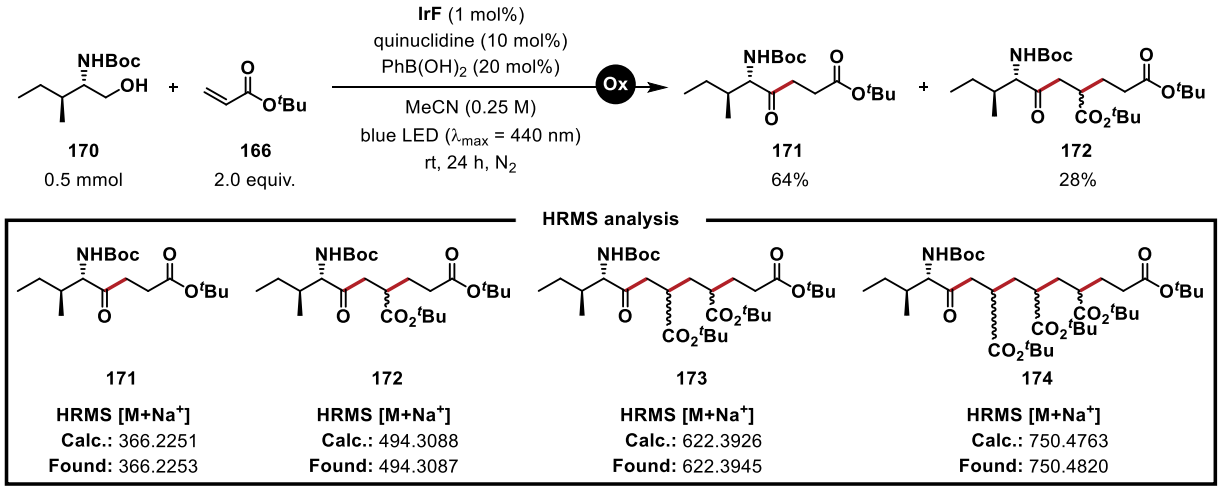


Entry	Additive	Yield 169 (%)[a]
1	Ph_2BOH	15
2	TBAP	25
3	$B(OH)_3$	53
4	$PhB(OH)_2$	63

[a]: determined by GC-FID. Oxidations were performed according to **Ox-A** (2.0 equiv. IBX, DMSO, rt, 14 h).

Unfortunately, when the reaction was scaled-up to obtain an isolated yield, **169** was not received in good purity due to the co-elution of unknown by-products. Different workup methods and flash chromatography procedures were tried to isolate **169** in a clean fashion. However, all trials were unsuccessful. Therefore, it was decided that it was of paramount importance to identify the by-products, so that their formation could be avoided and the targeted γ-oxo-δ-amino esters could be isolated in high purity. The use of *N*-Boc-protected isoleucinol (**170**) as starting material, followed by a careful separation using an automated flash purification system, enabled the isolation of product **171** and a clean fraction of the unknown by-products. High resolution mass spectrometry (HRMS) analysis revealed that the

isolated by-products were a mixture of oligomerized compounds **172**–**174**, with dimer **172** as the main component (Scheme 37).



Scheme 37. Identification of formed by-product(s).

Oxidation was performed according to **Ox-B** (2.0 equiv. IBX, EtOAc, 85 °C, 3 h).

A plausible explanation for the formation of these by-products is given in Figure 40. Addition of α-amino ketyl radical **175** to *tert*-butyl acrylate (**166**) results in the formation of α-carbonyl radical intermediate **176**. The latter can subsequently react via two pathways:

> ***Pathway a)***: reaction via SET with the excited state photocatalyst to yield **177**.
> ***Pathway b)***: radical addition onto another molecule of **166**, affording α-carbonyl radical **178**. The latter can then react with the photocatalyst, forming by-product **179**, or undergo another radical addition to an acrylate, affording even more complex oligomers.

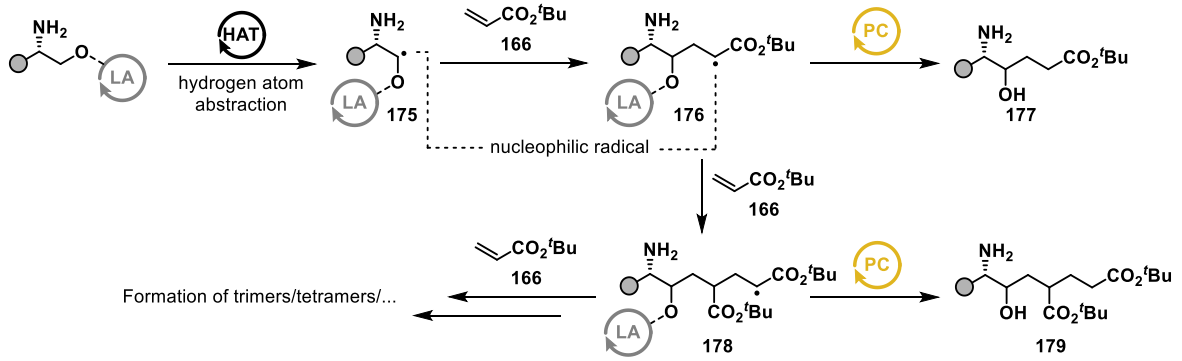


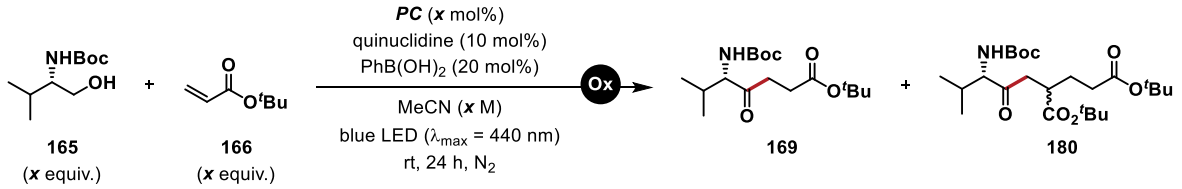
Figure 40. Possible explanation for oligomerization reaction.

Once the by-products were identified, another screening was performed focusing on finding new conditions minimizing their formation (Table 9). The driving hypotheses were that decreasing the acrylate concentration would reduce the chances for oligomerization reactions,

while increasing the photocatalyst loading would increase the rate of product formation through ***pathway a)***, thus leading to a better product distribution.

It was found that **IrF** could be replaced by **4CzIPN** without significantly affecting the yield of the reaction (Entries 1 & 2, Table 9). Therefore, it was decided to use the less costly organophotocatalyst rather than the precious metal containing **IrF**. Gratifyingly, increasing the catalyst loading from 1 to 5 mol% resulted in higher yields and, most importantly, higher product/by-product ratios (Entries 3 & 4, Table 9), which is in accordance with the hypothesis for the formation of **180**. Diluting the reaction concentration from 0.25 M to 0.025 M resulted in a further increase in yield up to 86% (Entries 5–7, Table 9). Inversion of the amino alcohol/acrylate ratios maintained the yield of **169**, while increasing the product/by-product ratio to 85.4:1 (Entries 8–12, Table 9). Scale-up and purification of the reaction using the conditions from Entry 12 afforded **169** in 80% yield and high purity. In addition, the screening also showed that it is possible to carry out the reaction using a slight excess of the amino alcohol (1.1 equiv.), albeit using longer reaction times (66 h), and isolate **169** in 84% yield and high purity (Entry 9, Table 9).

Table 9. Photocatalyst & Concentration screening.



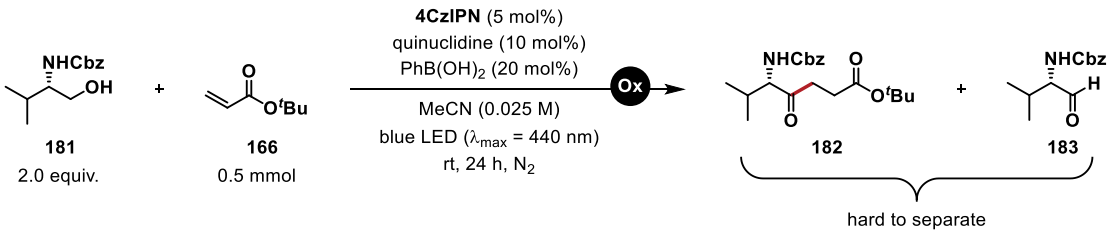
165 (***x*** equiv.) + **166** (***x*** equiv.) → **169** + **180**

Entry	Ratio 165/166	PC (mol%)	MeCN (M)	Ratio 169/180	169 Yield (%)[a]
1	1 / 2	IrF (1)	0.25	5.4 / 1	68
2	1 / 2	4CzIPN (1)	0.25	4.8 / 1	64
3	1 / 2	4CzIPN (2)	0.25	7.8 / 1	82
4	1 / 2	4CzIPN (5)	0.25	16.4 / 1	76
5	1 / 2	4CzIPN (5)	0.1	12.5 / 1	84
6	1 / 2	4CzIPN (5)	0.05	11.4 / 1	85
7	1 / 2	4CzIPN (5)	0.025	12.9 / 1	86[b]
8	1 / 1.1	4CzIPN (5)	0.025	46.5 / 1	82
9	1.1 / 1	4CzIPN (5)	0.025	62.3 / 1	87 (84%)[c][d]
10	1.25 / 1	4CzIPN (5)	0.025	82 / 1	90 (54%)[c]
11	1.5 / 1	4CzIPN (5)	0.025	65.3 / 1	87
12	2 / 1	4CzIPN (5)	0.025	85.4 / 1	86 (80%)[c]

[a]: determined by GC-FID, 0.1 mmol scale; [b]: average of three runs; [c]: isolated yields in 0.5 mmol scale; [d]: reaction run for 66 h. All oxidations were performed according to **Ox-C** (2.0 equiv. IBX, MeCN, 85 °C, 3 h).

III.4. – Scope and Limitations

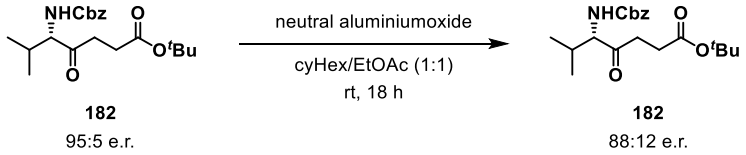
When starting to investigate the scope of the reaction the use of *N*-Cbz-valinol (**181**) led to an inseparable mixture of the desired product **182** and *N*-Cbz-valinal **183** – which is formed in significant amounts due to the excess of amino alcohol used in the reaction. (Scheme 38).



Scheme 38. Production of α-amino aldehyde coproducts led to separation issues.

Even though an intensive search for suitable solvent systems was undertaken, no good separation via flash chromatography was achieved. Pleasingly, changing the stationary phase from silica to neutral aluminiumoxide resulted in very good separation between **182** and **183**. However, analysis of the isolated products showed partial racemization.

To prove this, an experiment was performed (Scheme 39): stirring **182** in a 1:1 mixture of EtOAc/cyHex in the presence of neutral aluminiumoxide resulted in racemization (95:5 e.r. before, 88:12 e.r. afterwards).

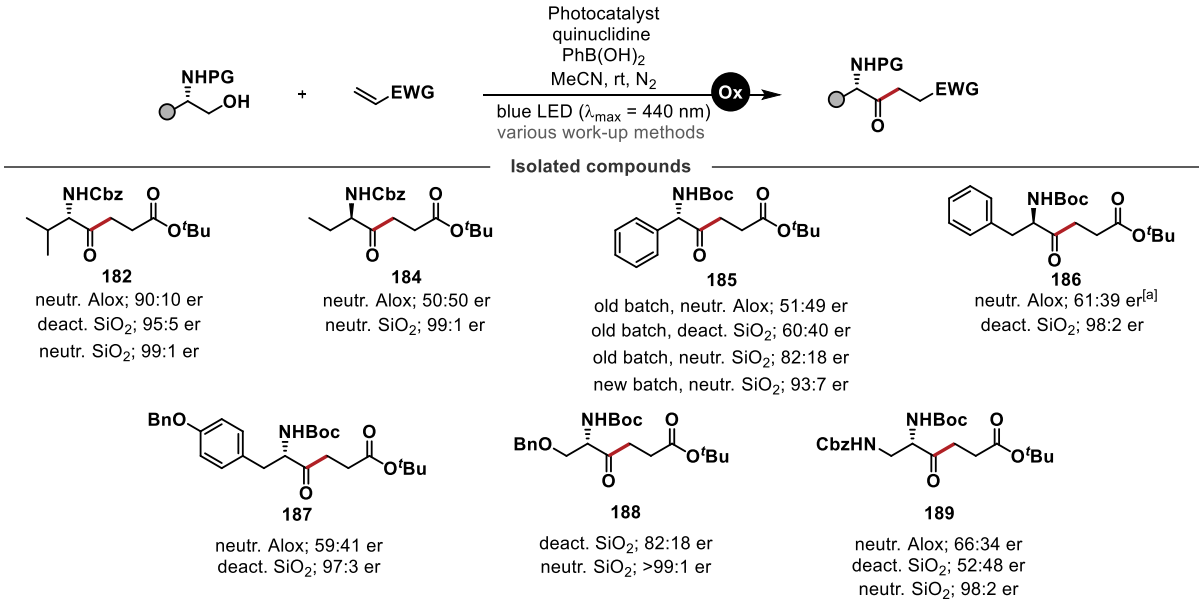


*Scheme 39. Experiment to prove racemization of **182** on neutral aluminiumoxide.*

The use of silica as stationary phase resulted in stereoretention of the isolated products, but gave no good separation from the aldehyde by-product. It was hypothesized that changing the polarity of the used silica by passing a 1% Et_3N solution in cyHex through it, would result in a better separation between product and aldehyde by-product. Prior to its use in flash column chromatography, the Et_3N solution was washed off using pure cyHex. Gratifyingly, the so-prepared silica showed sufficiently good separation between **182** and **183** while preserving the stereochemical information (95:5 e.r.).

To prove that the reaction proceeds under full stereoretention, and to explore the influence of the used stationary phase during flash chromatography on the enantiomeric purity of the isolated products, some representative scope examples bearing aliphatic, aromatic, and hetero-atom containing sidechains were synthesized and their enantiomeric purity was determined using a chiral HPLC (Scheme 40). See **section VI.IV.3** for experimental details.

Aliphatic compounds **182** and **184** were obtained with excellent e.r. of 99:1 when being purified on silica. While purification of **184** over neutral Alox resulted in full racemization, **182** did only partially racemize (e.r. 90:10). Phenylglycinol-derived product **185** gave an e.r. of 82:18 when purified on neutral SiO_2, which would be in accordance with previous reports, in which *N*-Boc-phenylglycinal racemized during purification over SiO_2 and under basic conditions.[213,214] This can be rationalized by enhanced acidity of the α-amino proton due to the carbonyl-and aryl-functionality. However, the statement of Badía *et al.*, not observing any racemization of *N*-Boc-phenylglycinal during reaction or purification left the question why there was now a problem of racemization here.[211] Therefore, the used starting material was analyzed, revealing an already racemized phenylglycinol (88:12 e.r.) has been used. To prove that **185** did not racemize during the reaction or workup the reaction was repeated with a new, enantiomerically pure batch of phenylglycinol and purified on neutral SiO_2 to give the corresponding product **185** with a very good e.r. (93:7). In addition to that phenylalaninol- and tyrosinol-derivatives **186** and **187** were isolated over deactivated SiO_2 with excellent enantiomeric ratios: 98:2 and 97:3, respectively. Finally, products **188** and **189** – both bearing a heteroatom in the α-amino position of the side chain – were obtained with full stereoretention (e.r. >99:1 and 98:2).

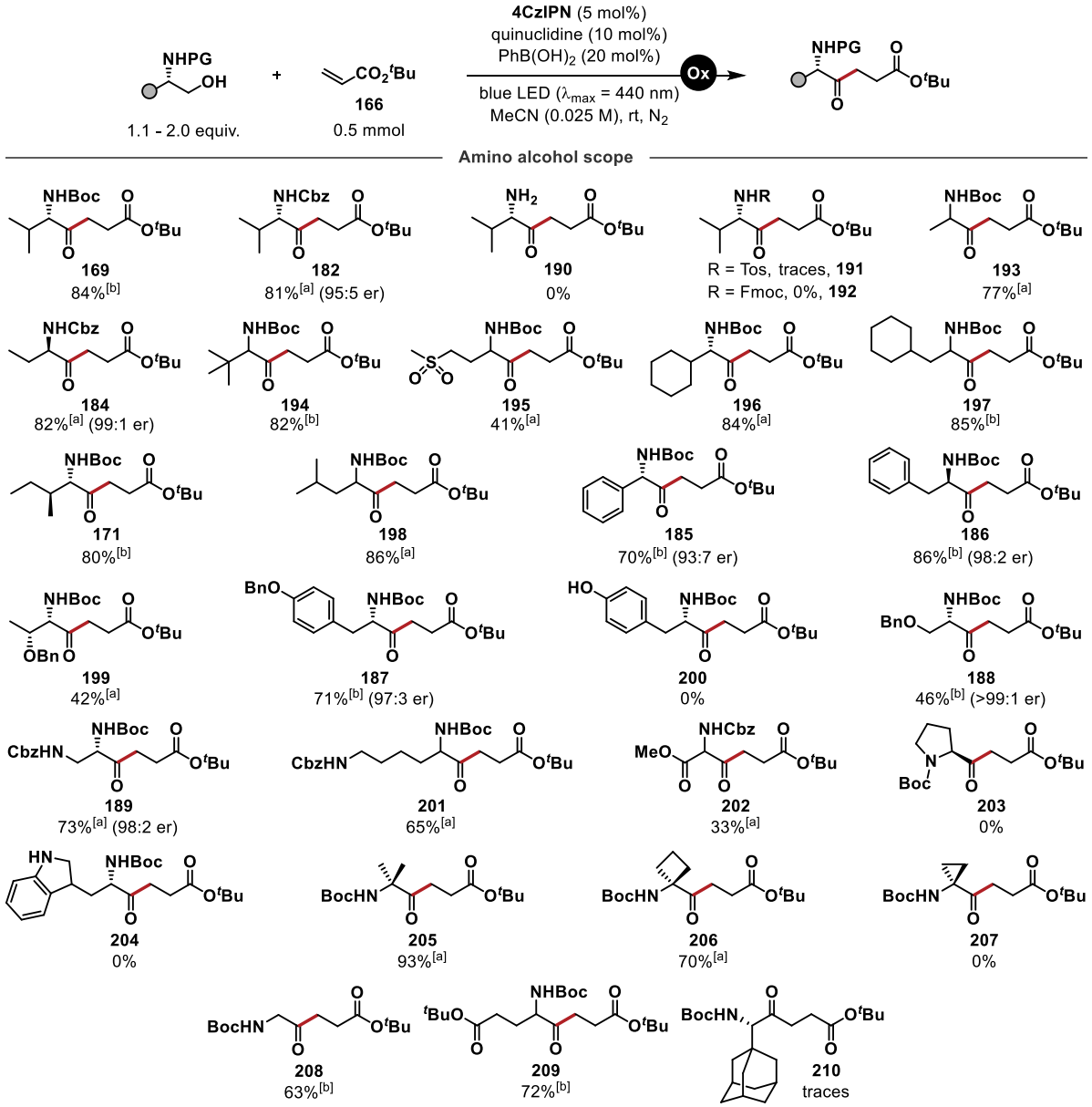


Scheme 40. Enantiomeric ratios of isolated compounds.

[a]: (S)-enantiomer was used.

With the optimized conditions in hand, the scope and limitations of the methodology were explored (Scheme 41). Initially, the use of valinol derivatives bearing different *N*-protecting groups was investigated. *N*-Boc- and *N*-Cbz-valinol furnished the corresponding γ-oxo-δ-amino acids **169** and **182** in very good yields of 81–84%. Furthermore, unprotected, *N*-Tos- and *N*-Fmoc-protected valinol failed to produce the targeted products **190**–**192**. The latter might be

explained due to the presence of quinuclidine: the Fmoc-protecting group is labile in the presence of primary, secondary and tertiary amines.[215] Knowing which *N*-protecting groups were tolerated, several readily available amino alcohols exposed to the reaction conditions. Products with aliphatic side chains derived from alaninol (**193**), 2-aminobutanol (**184**), *tert*-butylglycinol (**194**), methioninol (**195**), cyclohexylglycinol (**196**), cyclohexylalaninol (**197**), *iso*-leucinol (**171**) and leucinol (**198**) were furnished in moderate to very good yields (41–86%). Products obtained from aromatic amino alcohols as phenylglycinol (**185**), phenylalaninol (**186**) and the *O*-Bz-protected reactants threoninol (**199**), tyrosinol (**187**) and serinol (**188**) were isolated in 42–86% yield. Interestingly, the reaction using *N*-Boc-tyrosinol did not afford product **200**. In addition, double *N*-protected lysinol, and its two methylene groups shorter homologue, afforded the corresponding γ-oxo-δ-amino acid derivatives **189** and **201** in good yields (65–73%). *N*-Boc-serine methyl ester afforded **202** in moderate yield (33%), while *N*-Boc-prolinol and *N*-Boc-tryptophanol were unsuccessful (**203** and **204**). Furthermore, 2,2-dimethylglycinol-derived and cyclobutyl-containing amino esters **205** and **206** were isolated in good to excellent yields (70–93%), whereas the cyclopropyl-containing derivative **207** could not be obtained. This might be due to ring opening side-reactions known for α-cyclopropyl radicals, leading to complex mixtures.[216] The use of *N*-Boc-glycinol resulted in 63% of **208**, while *N*-Boc-glutanol γ-*tert*-butyl ester afforded **209** in 72% yield, and adamantane-derived product **210** was only obtained in traces.

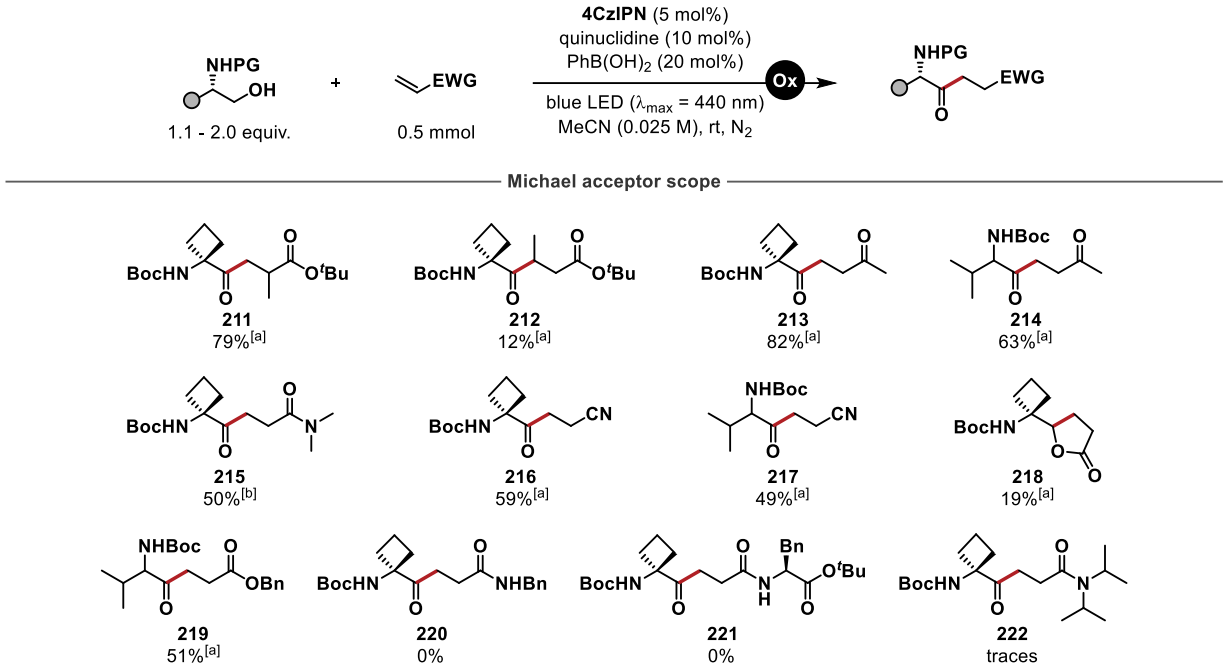


Scheme 41. Amino alcohol scope.

[a]: amino alcohol (2.0 equiv.), irradiated for 24 h; [b]: amino alcohol (1.1 equiv.), irradiated for 66 h. Oxidations were performed according to **Ox-C** (2.0 equiv. IBX, MeCN, 85 °C, 3 h).

Next, the α,β-unsaturated acceptor scope was investigated (Scheme 42). To this end, (1-*N*-Boc-aminocyclobutyl)-methanol and *N*-Boc-valinol were reacted with several Michael acceptors under the standard reaction conditions. It was found that while *tert*-butylmethacrylate afforded **211** in very good yield (79%), *tert*-butylcrotonate provided **212** in only 12% yield. This diminished yield was attributed to the higher sterical hindrance at the site of radical addition. Methyl vinyl ketone, *N*,*N*-dimethylacrylamide, and acrylonitrile all gave the corresponding products **213**–**217** in 49–82% yield. Lactone **218** was obtained in only 19% yield when using methylacrylate as radical acceptor. Unfortunately, while Bn-ester **219** was formed in 51% yield,

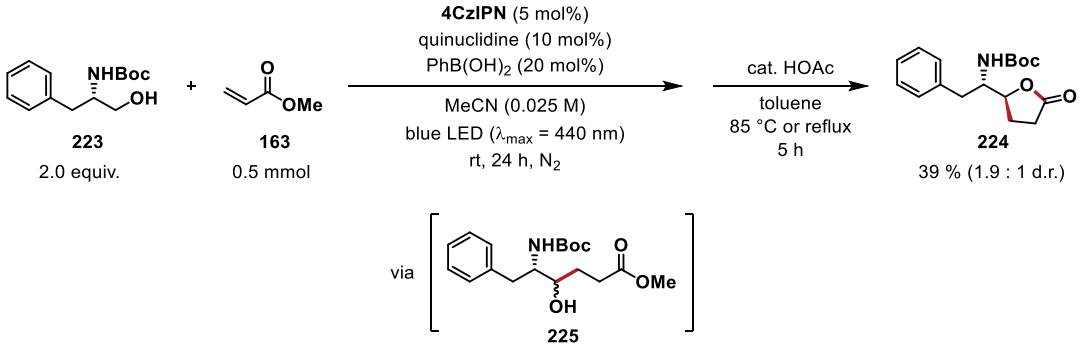
Bn-amide **220** could not be isolated. Moreover, the synthesis of dipeptide **221** and diisopropylamide **222** both remained unsuccessful.



Scheme 42. Michael acceptor scope.

[a]: amino alcohol (2.0 equiv.), irradiated for 24 h; [b]: amino alcohol (1.1 equiv.), irradiated for 66 h. Oxidations were performed according to **Ox-C** (2.0 equiv. IBX, MeCN, 85 °C, 3 h).

Overall, the developed one-pot, two-step protocol to synthesize γ-oxo-δ-amino acid derivatives proved to be highly applicable to numerous, readily available β-amino alcohols and α,β-unsaturated acceptors. Most importantly, it was demonstrated that the methodology is stereoretentive, as shown by measuring the enantiomeric excess of products **182**, **184–189**.
To further demonstrate the synthetic utility of the methodology, *N*-Boc-phenylalaninol (**223**) was coupled with methylacrylate (**163**) to give lactone **224** in 39% yield, and a d.r. of 1.9:1 (Scheme 43). The reaction proceeds via alcohol **225** which, upon acidic treatment cyclizes to give **224**. The latter scaffold has been shown to be a key intermediate in the synthesis of several biologically active agents, such as peptidomimetic γ-secretase inhibitors,[217] and ritonavir,[105] a protease inhibitor to treat HIV.[218] Classical approaches required several steps to access building block **224**, whereas the in here presented methodology allows formation of **224** in one single step starting from readily available and abundant β-amino alcohol **223**.



*Scheme 43. Reaction of N-Boc-phenylalaninol with methylacrylate affords lactone **224**.*

III.5. – Derivatizations

γ-Oxo-δ-amino esters present several vectors for further functionalization (Figure 41). Therefore, some derivatization approaches were undertaken.

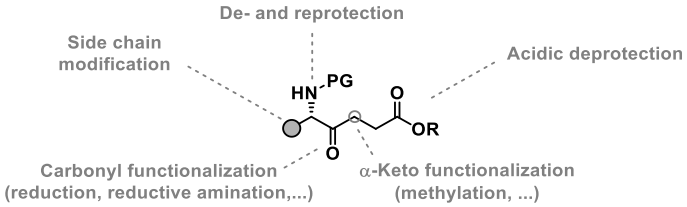
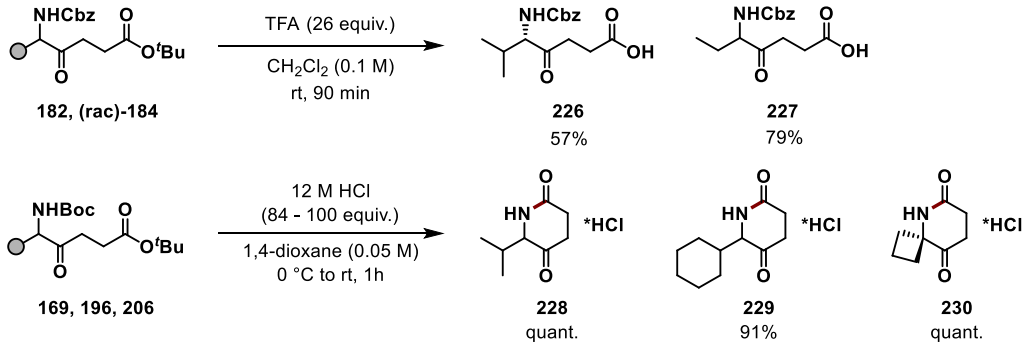


Figure 41. Possible functionalization vectors of γ-oxo-δ-amino esters.

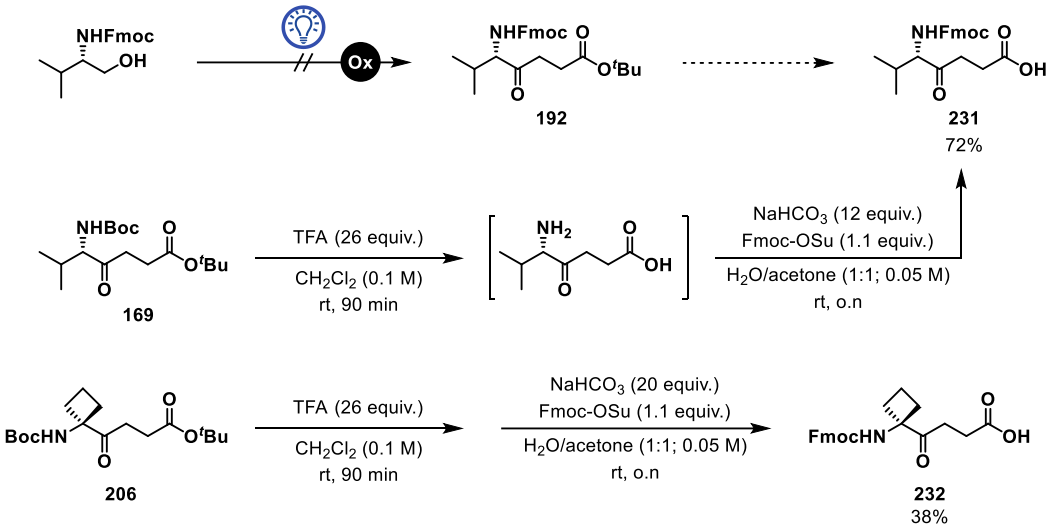
Acidic deprotection

First, selective deprotection of the *tert*-butyl ester was tested (Scheme 44). Treating **182** and **184** with TFA in CH_2Cl_2 at room temperature for 90 min afforded the corresponding acids **226** and **227** in 57% and 79% yield, respectively. It was hypothesized that if stronger acidic conditions were used with γ-oxo-δ-amino esters bearing more labile *N*-Boc-protecting groups, deprotection of both the carbamate and ester group followed by an intramolecular cyclization could take place. Treatment of **169** with 12 M HCl afforded piperidine derivative **228** in quantitative yield. In addition, cyclohexyl derived γ-oxo-δ-amino ester **196** afforded the corresponding product **229** in 91% yield, while the use of **206** as starting material afforded spirocyclic product **230** in quantitative yields.



Scheme 44. Performed acidic deprotections.

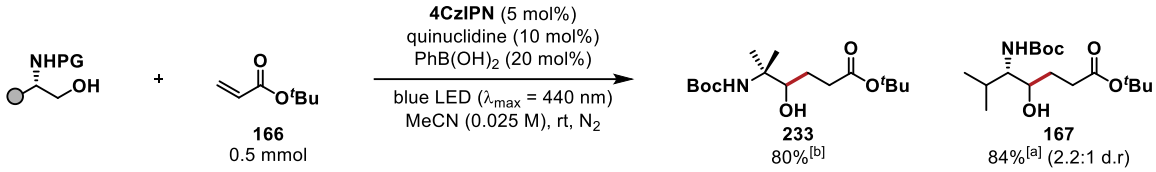
To use the accessible γ-oxo-δ-amino esters in solid-phase peptide synthesis, it would be convenient to have an Fmoc-protected amine. Since Fmoc-protected β-amino alcohols did not provide the targeted product during the investigation of the reaction scope, a deprotection/protection sequence was performed to access Fmoc-protected γ-oxo-δ-amino acids **231** and **232** in 72% and 38% yield, respectively (Scheme 45).



Scheme 45. Performed de- and Fmoc-reprotections.

Reduction

During investigating the scope of the reaction, it was tried to isolate the secondary alcohol formed after the photoreaction step (Scheme 46). While **233** and **167** were obtained in very good yields (80–84%), **167** was formed as a mixture of diastereoisomers with a poor d.r. of 2.2:1, as analysis of the crude reaction mixture by GC-FID revealed.

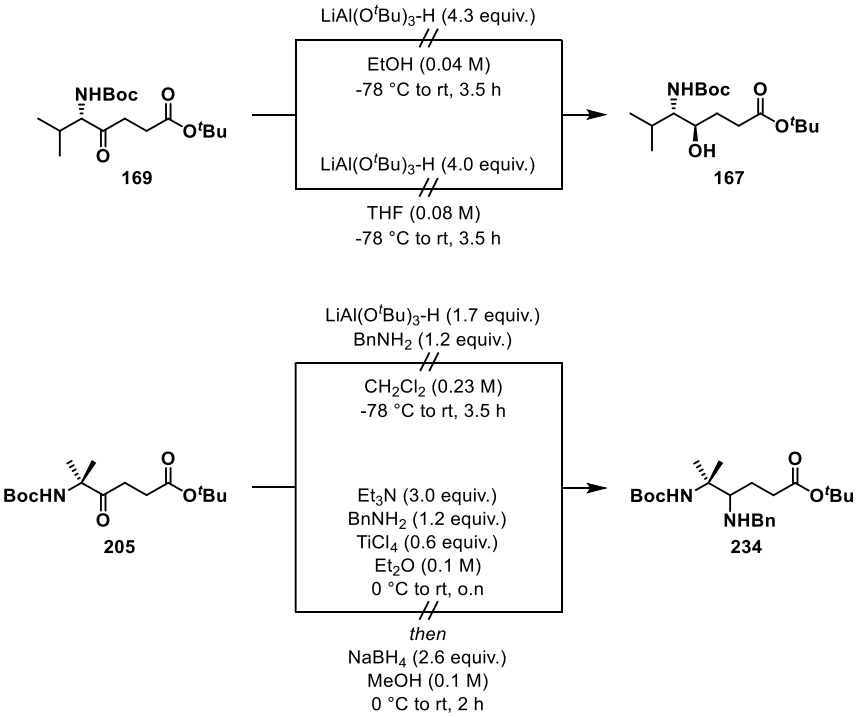


Scheme 46. Synthesized γ-hydroxy-δ-amino esters.

[a]: amino alcohol (2.0 equiv.), irradiated for 24 h; [b]: amino alcohol (1.1 equiv.), irradiated for 66 h.

To receive γ-hydroxy-δ-amino esters in higher diastereomeric ratios, some trials for selective reduction were performed (Scheme 47). According to literature, reduction of γ-keto-δ-amino esters using LiAl(O^{t}Bu)$_3$-H should afford the corresponding secondary alcohol with good stereochemical control.[219] However, even running the reaction with a fresh batch of LiAl(O^{t}Bu)$_3$H did not afford **167**.

Furthermore, trials towards reductive aminations on **205** were performed. In addition to the "classical" approach of *in situ* reduction of an imine formed by condensation between the ketone and an amine, a $TiCl_4$-mediated approach was tested as well – conditions that were inspired by a literature protocol to reductively aminate benzylic ketones.[220] However, all attempts failed to give the desired product **234**.



Scheme 47. Performed reductions and reductive aminations.

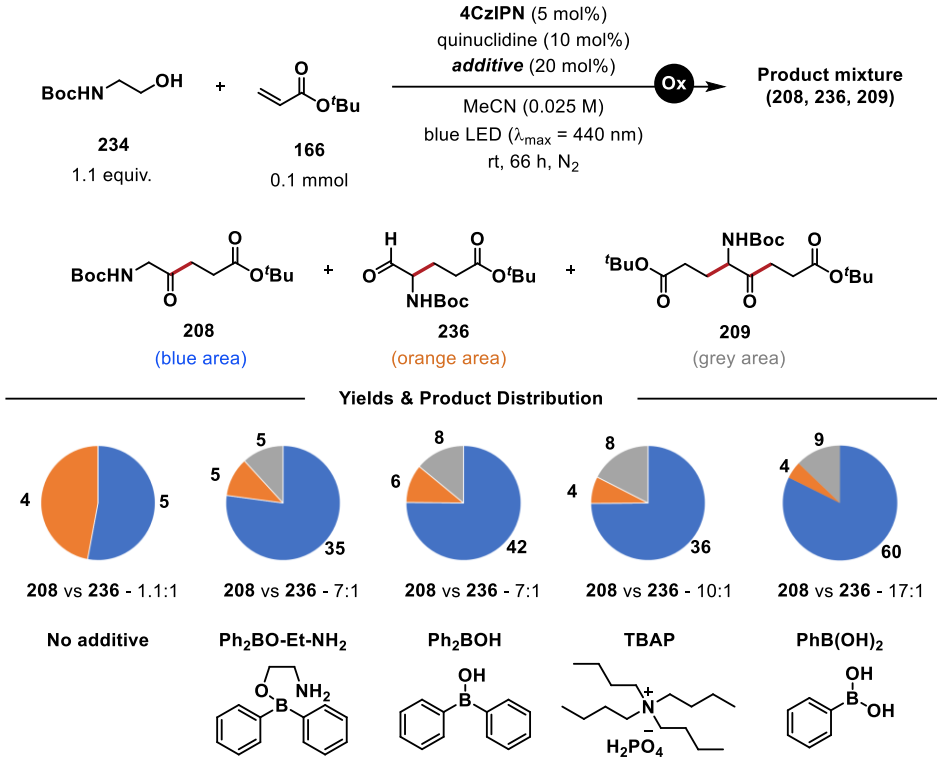
III.6. – Further Studies

After studying the scope and limitations of the methodology, as well as the derivatization of the obtained products, the selectivity in the HAT step, as well as the robustness of the reaction was investigated.

Selectivity studies

The key step of the reaction is the chemoselective α-hydroxy hydrogen abstraction of the β-amino alcohol. Since amino alcohols possess two C–H bonds with similar bond dissociation energies (BDEs) of ~91–93 kcal/mol (α-amino position) and ~94–96 kcal/mol (α-oxo position),[221] it was investigated how the use of different additives affects the hydrogen abstraction at the α-oxo over the α-amino position. To minimize the influence of steric effects, the study was carried out using *N*-Boc-protected glycinol **235** (Scheme 48).

As expected, when running the reaction without additive, nearly no selectivity between the α-amino and α-oxo position is achieved and the yield for the targeted α-oxo-product **208** is extremely low (5%). Using $Ph_2BO–Et–NH_2$ or Ph_2BOH – additives previously used by Taylor and co-workers for α-oxo-functionalizations[197,222] – the yield for **208** was increased to 35% and 42%, respectively. More importantly, the **208** vs **236** selectivity increased to 7:1. The use of TBAP, the catalyst reported by MacMillan and co-workers for selective α-hydroxy HAT,[190] yielded the targeted product **208** in 39% and a 10:1 **208** vs **236** ratio. Pleasingly, $PhB(OH)_2$ increased the yield of the reaction by a factor of 12 – compared to the reaction without additive – furnishing **208** in 60% yield, while affording an excellent **208** vs **236** selectivity, (17:1). Overall, all tested additives proved to successfully increase the selectivity of the reaction towards the desired α-oxo-product, which is in accordance with the rational of a Lewis acid increasing the hydricity of the α-oxo position. $PhB(OH)_2$ gave the best results in terms of yield and selectivity, which is in good agreement with aforementioned screenings already proving $PhB(OH)_2$ to be the superior additive for the targeted transformation.



Scheme 48. Product distribution of selectivity screenings.

Oxidations were performed according to **Ox-C** (2.0 equiv. IBX, MeCN, 85 °C, 3 h).

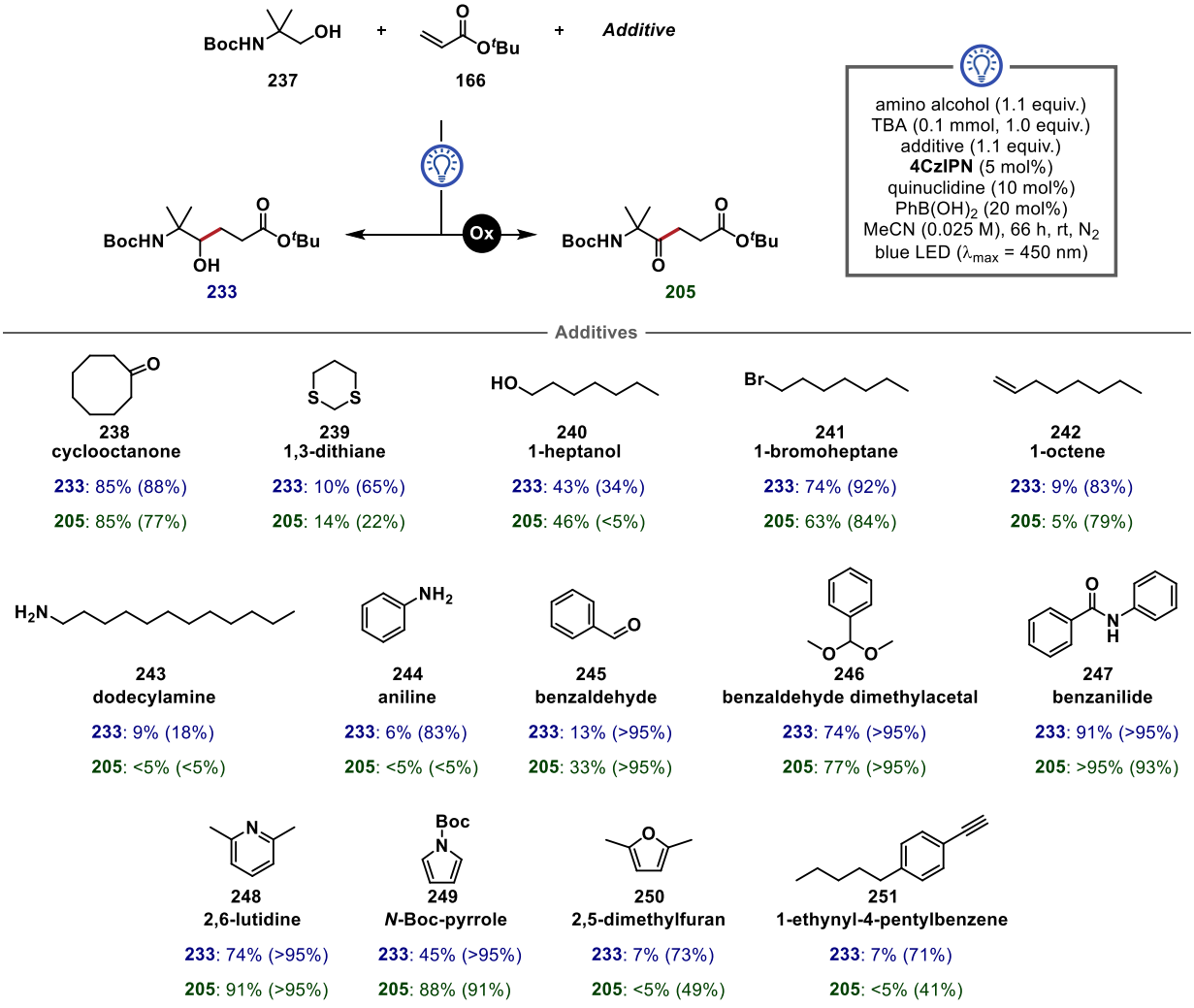
Functional group tolerance screening

In the previous decade, the pioneering work of Glorius and co-workers established the use of robustness screenings in which developed reactions were tested towards their utility outside their optimized conditions (e.g., in the presence of certain functional groups) or whether certain structural motifs remain intact under the given reaction conditions.[223–226] As stated by the authors, it is this lack of information about tolerance to non-idealized conditions that hinders the application of novel reactions to other scientific problems, as this knowledge must be developed over time and is often difficult to find as it is spread over multiple scientific reports.[227] This problem can be addressed by a simple and rapid robustness screening of a novel synthetic method, with the results being shared along with the scope and limitations of the reaction. Therefore, to assess the robustness of the method developed here in this thesis – and thus the potential applicability to other scientific challenges – a functional group tolerance screening was conducted.

To do so, two sets of reactions, one with and one without oxidation step, were performed. In each reaction, *N*-Boc-2-amino-2-methylpropanol (**237**) was reacted under the standard reaction conditions with *tert*-butylacrylate (**166**) in the presence of an equimolar amount of an additive. After the reaction, an aliquot was analyzed via GC-FID. The amount of additive left was determined via one-point calibration. The results of these tests are summarized in Scheme 49, with the yields in parenthesis showing the amount of additive left after the reaction.

The tests showed that the standard reaction in the presence of functional groups such as ketones (cyclooctanone, **238**), acetal-protected aldehydes (benzaldehyde dimethylacetal, **246**), amides (benzanilide, **247**) and heteroaromatic systems (2,6-lutidine, **248** and *N*-Boc-pyrrole, **249**) continued to give satisfactory yields. While unprotected primary alcohols (1-heptanol, **240**), primary haloalkanes (1-bromoheptane, **241**) and unprotected aldehydes (benzaldehyde, **245**) caused a significant decrease in the yield of **205**, functional groups such as *S*-containing alkanes (1,3-dithiane, **239**), terminal alkenes (1-octene, **242**), unprotected aliphatic and aromatic amines (dodecylamine, **243** and aniline, **244**), as well as 2,5-dimethylfuran (**250**) and terminal alkynes (1-ethynyl-4-pentylbenzene, **251**) led to an almost complete suppression of the targeted reaction.

Overall, it was found that the IBX oxidation step influences the functional group preservation but has no detrimental effect on the product yield. The observed discrepancy in the obtained yields of **233** and **205** when using benzaldehyde (**245**), 2,6-lutidine (**248**) and *N*-Boc-pyrrole (**249**) as additives remains elusive at this point.



Scheme 49. Functional group tolerance screening.

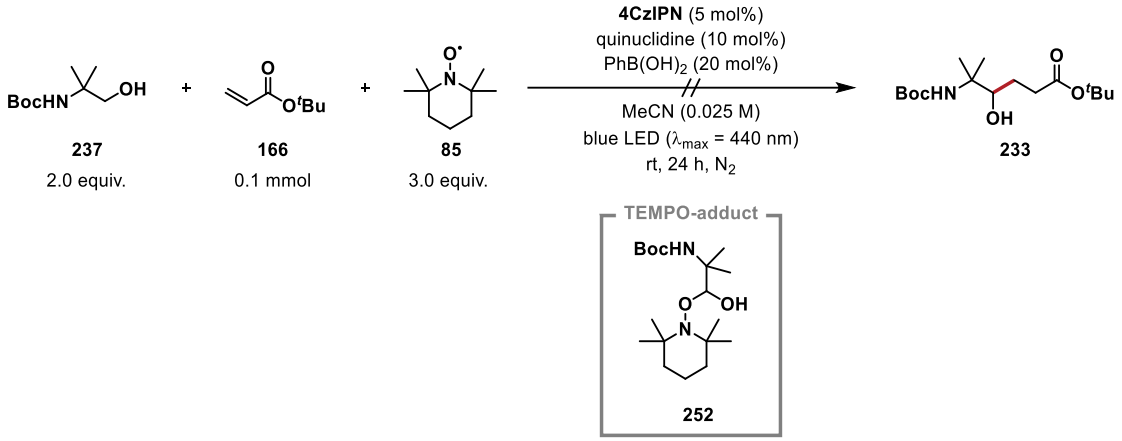
Oxidations were performed according to **Ox-C** (2.0 equiv. IBX, MeCN, 85 °C, 3 h).

III.7. – Mechanistic Studies

Mechanistic investigations were carried out to shed some light onto the reaction pathway (see **section VI.IV.I** for experimental details).

Radical trapping experiment

To determine whether a radical mechanism is in operation, a standard reaction was performed in the presence of an excess of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, **85**) as radical scavenger. The reaction was performed twice. In both cases, no traces of **233** were formed, supporting that the reaction proceeds through a radical pathway that gets suppressed by TEMPO (Scheme 50). Unfortunately, the expected TEMPO-adduct **252** could not be detected via MS analysis, most likely due to its instability.



Scheme 50. Radical trap experiment with TEMPO as radical scavenger.

Stern-Volmer Quenching experiments

Next, Stern-Volmer quenching experiments were performed to investigate which compound of the reaction mixture quenches the excited state photocatalyst during the reaction. To do so, a **4CzIPN** stock solution was prepared and its emission spectrum was recorded in the presence of varying amounts of each reactant. When mixed with a quencher, the recorded fluorescence of the excited state photocatalyst is lower the higher the quencher concentration is. If the emission spectrum is independent of the amount of added reactant, the reactant is not capable of interacting with the excited state photocatalyst. By performing the Stern-Volmer quenching experiments it is possible to elucidate with which reactant the excited **4CzIPN** interacts with, thus helping to propose a suitable reaction mechanism. All measurements were performed in dry and degassed MeCN and under N_2-atmosphere. This was necessary to prevent undesired fluorescence quenching of the excited state photocatalyst by triplet oxygen.[228,229]

The Stern-Volmer quenching experiments revealed, that only quinuclidine is capable of quenching the excited state photocatalyst, while $PhB(OH)_2$, *tert*-butylacrylate, and the amino alcohol do not affect the fluorescence intensity of the photocatalyst (Figure 42 to Figure 46). This is in accordance with the expected behavior of the highly oxidizing **4CzIPN** in its excited state ($^*E_{1/2}$ = +1.43 V vs SCE),[76] if mixed with quinuclidine ($E_{1/2}$ = +1.1 V vs SCE).[230]

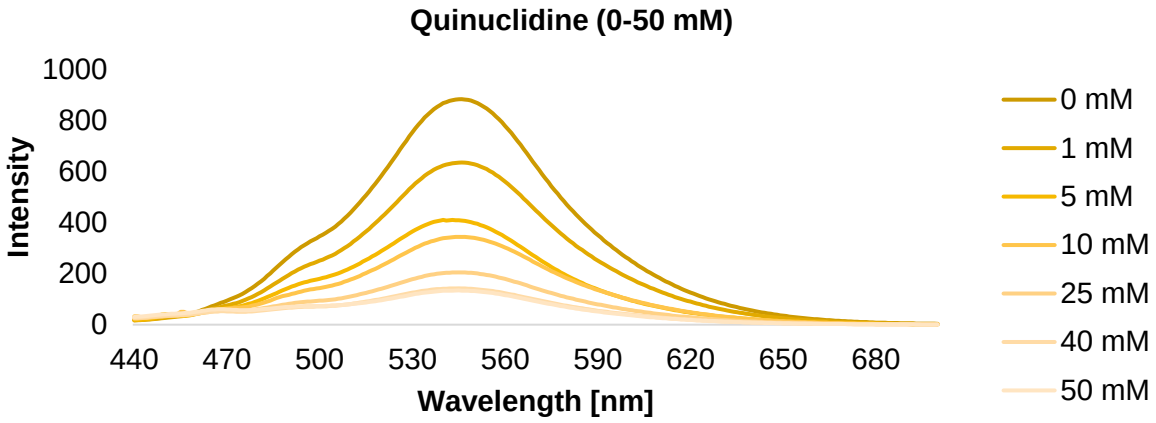


*Figure 42. Fluorescence of **4CzIPN** in the presence of different quinuclidine concentrations.*

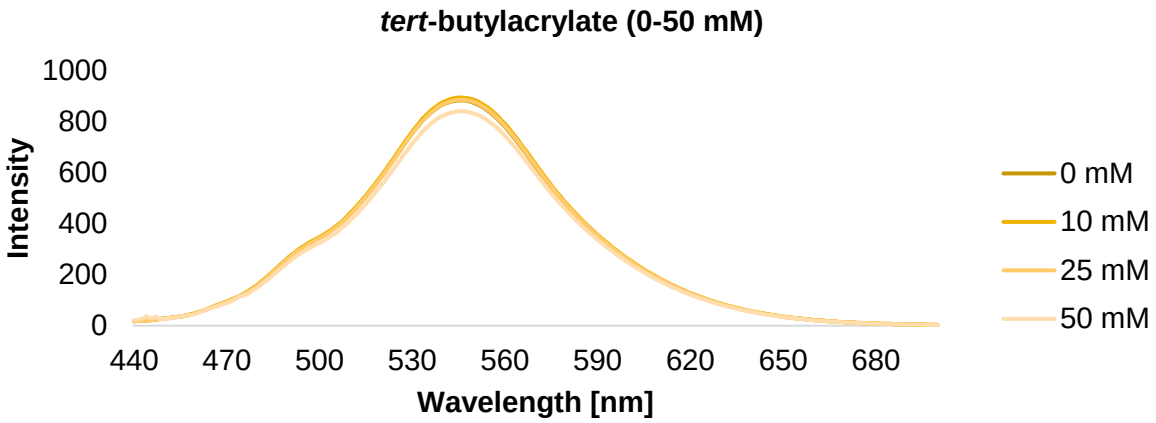


*Figure 43. Fluorescence of **4CzIPN** in the presence of different tert*-butylacrylate *concentrations.*

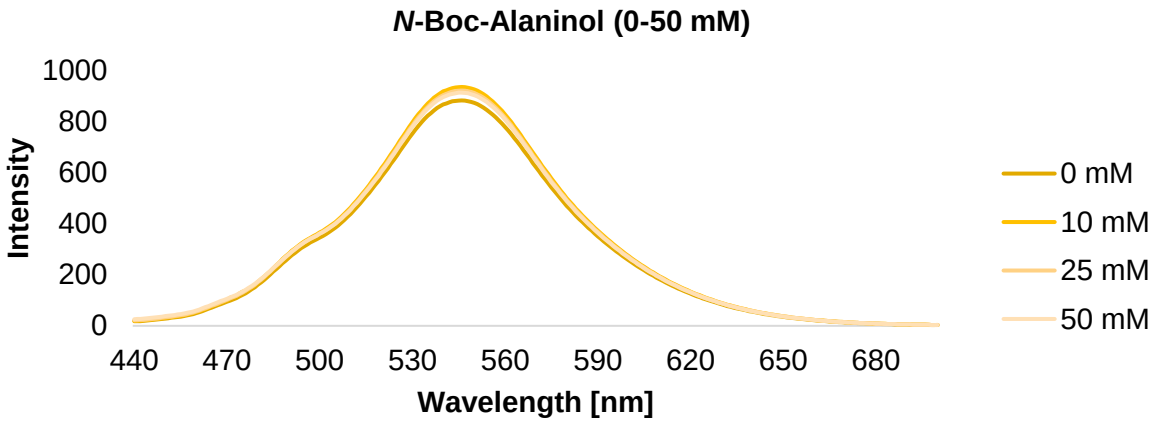


*Figure 44. Fluorescence of **4CzIPN** in the presence of different N-Boc-Alaninol concentrations.*

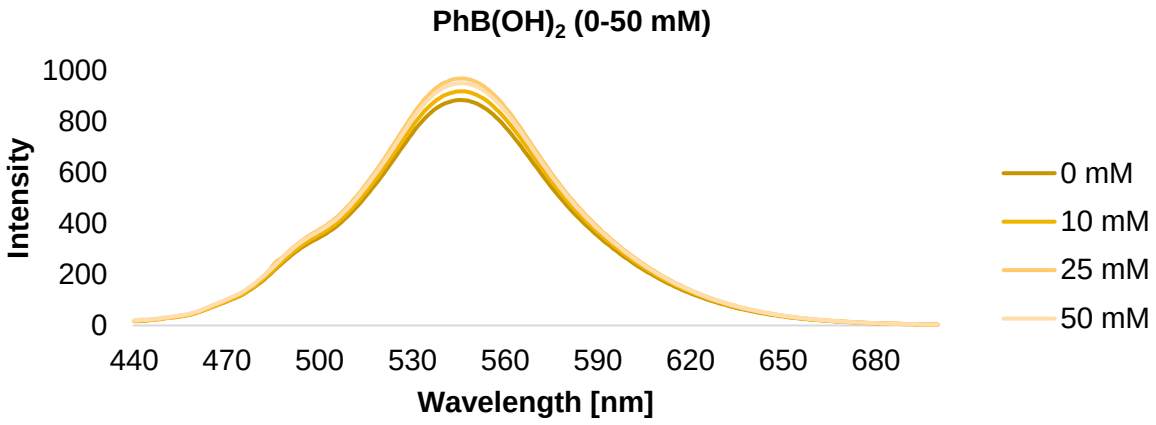


*Figure 45. Fluorescence of **4CzIPN** in the presence of different $PhB(OH)_2$ concentrations.*

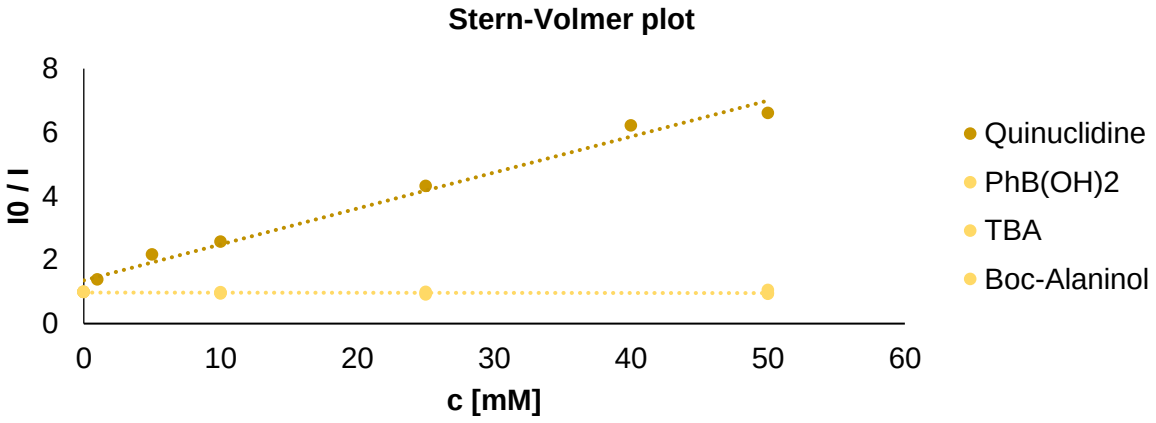


*Figure 46. Stern-Volmer plot of fluorescence quenching of **4CzIPN** with different possible quenchers.*

To rule out that reaction intermediates – generated by the interaction of quinuclidine with other reaction components – displayed a higher quenching of the excited state **4CzIPN** than quinuclidine alone, a colleague performed a couple of experiments mixing quinuclidine with $PhB(OH)_2$ and *N*-Boc-alaninol (Figure 47 to Figure 50).

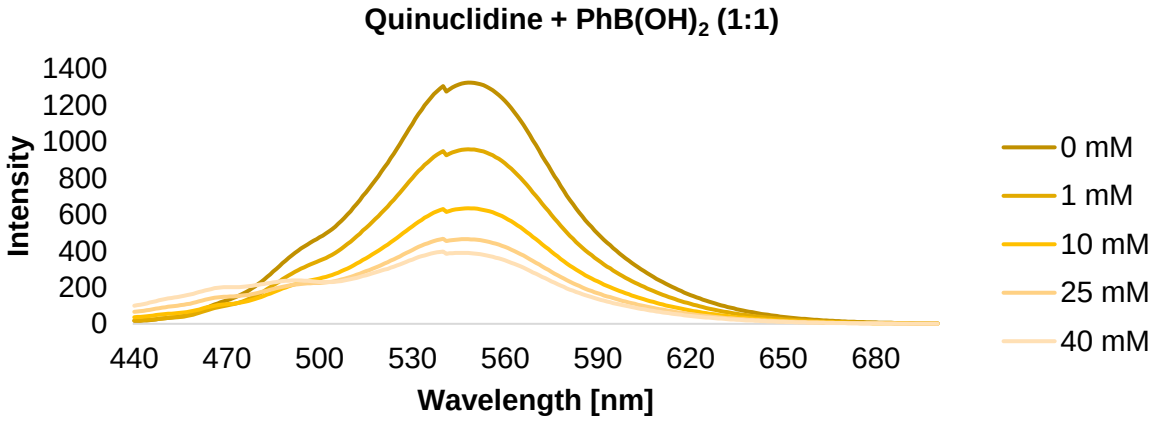


*Figure 47. Fluorescence of **4CzIPN** in the presence of quinuclidine + $PhB(OH)_2$ (1:1) at various concentrations.*

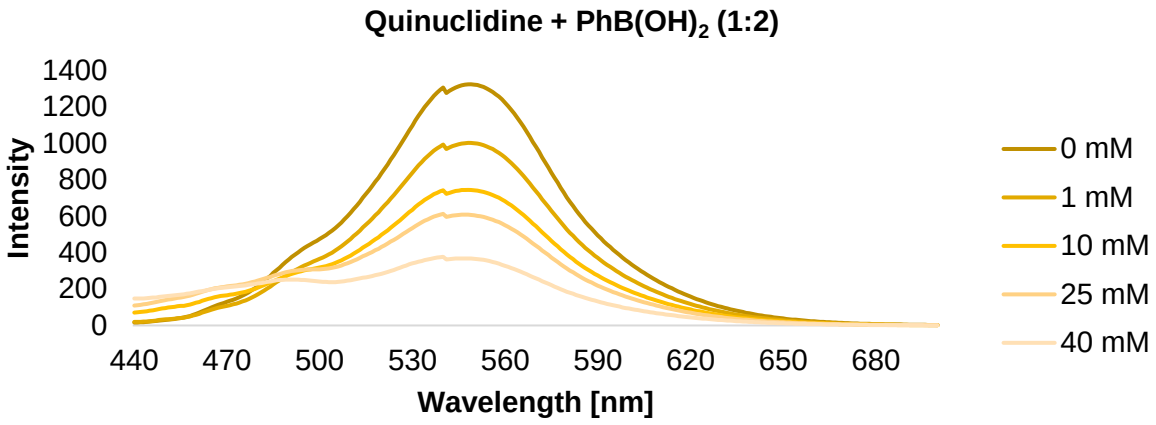


*Figure 48. Fluorescence of **4CzIPN** in the presence of quinuclidine + PhB(OH)₂ (1:2) at various concentrations.*

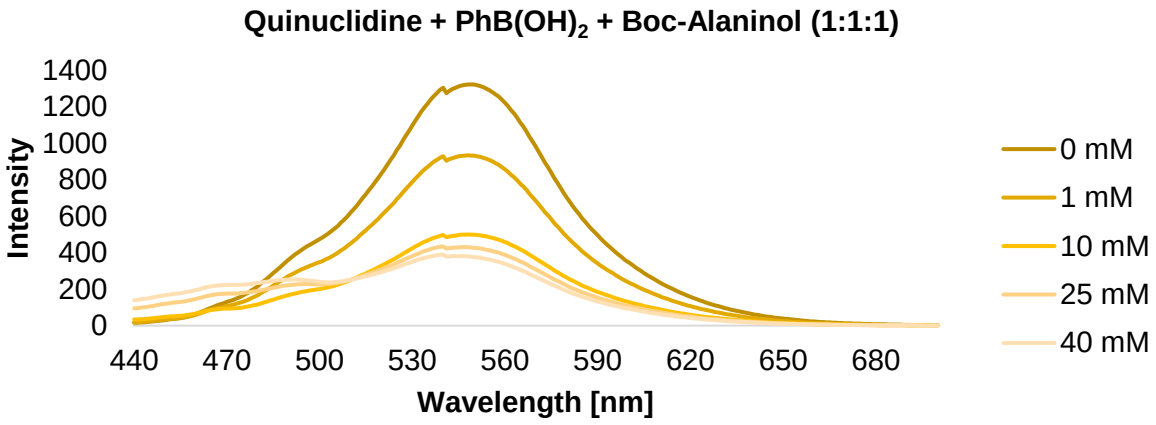


*Figure 49. Fluorescence of **4CzIPN** in the presence of quinuclidine + PhB(OH)₂ + Boc-Alaninol (1:1:1) at various concentrations.*

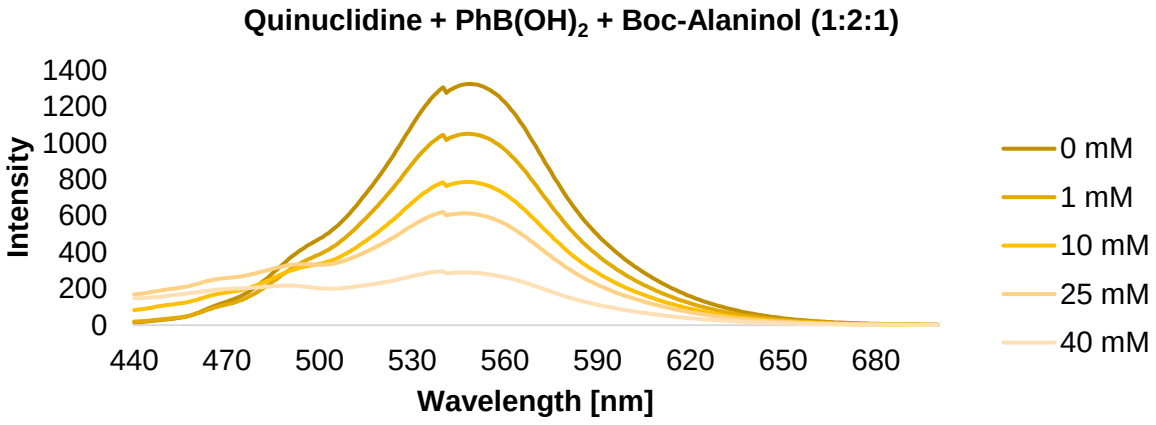


*Figure 50. Fluorescence of **4CzIPN** in the presence of quinuclidine + PhB(OH)₂ + Boc-Alaninol (1:2:1) at various concentrations.*

A comparison of the quenching abilities of these mixtures revealed that quinuclidine is the most efficient quencher of the excited state **4CzIPN** (Figure 51).

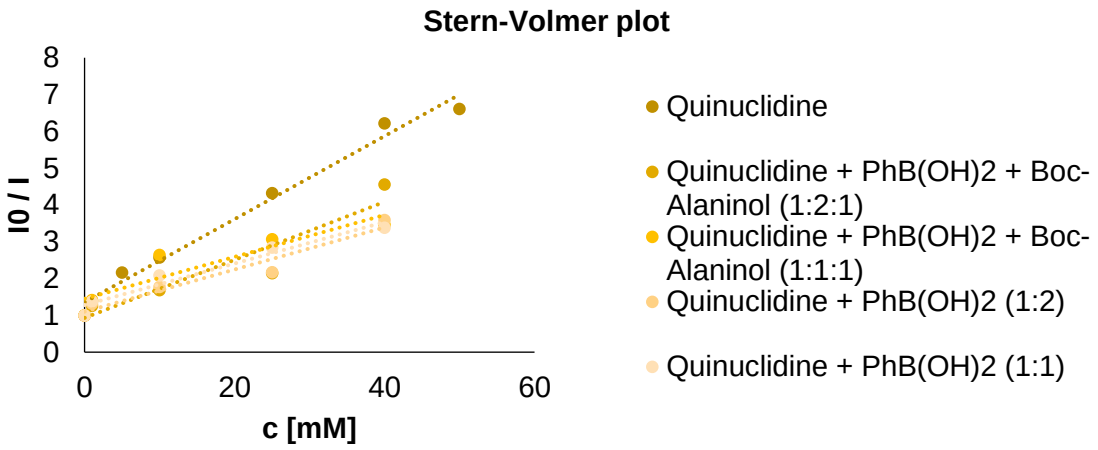


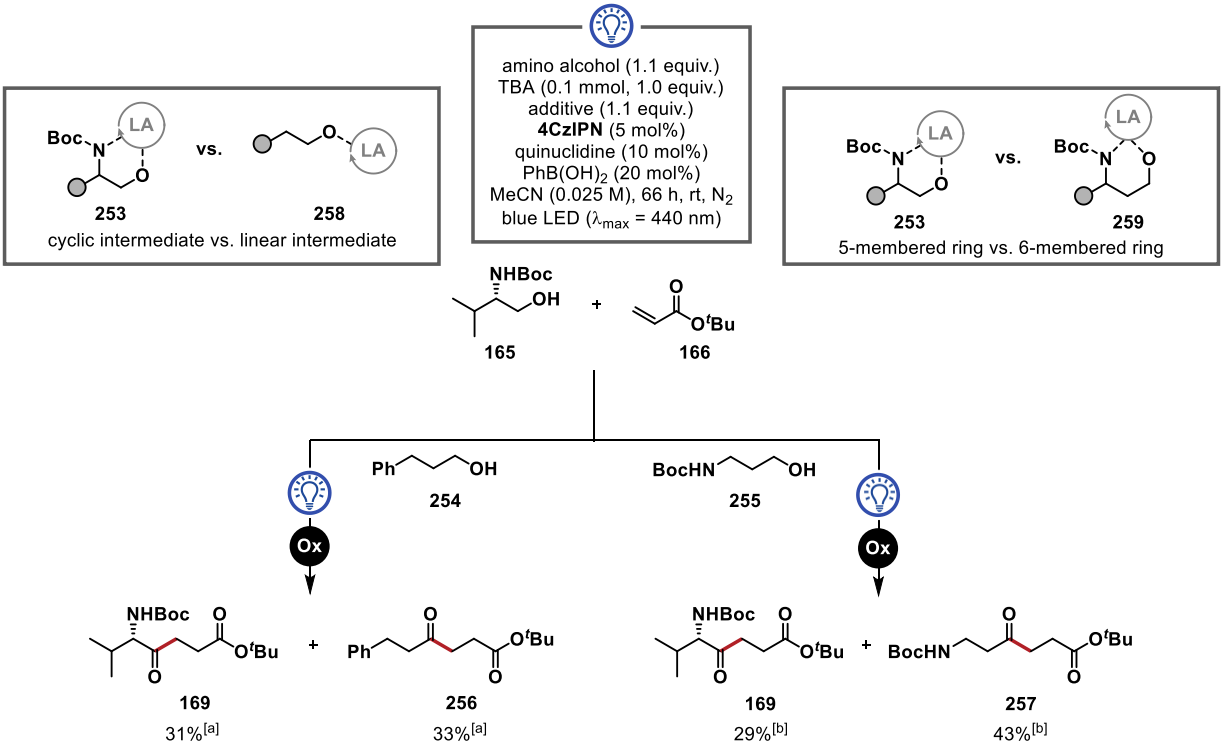
*Figure 51. Stern-Volmer plot of fluorescence quenching of **4CzIPN** with quinuclidine and quinuclidine-containing mixtures.*

Quantum Yield Determination

Next, the quantum yield of the reaction was determined. As described earlier, this was done to check whether a radical chain is in progress or not. If the quantum yield is >1, this means that per absorbed photon, more than one product molecule is formed and that a radical chain pathway is likely in operation. The reaction quantum yield (Φ) was calculated to be 18.54, indicating a radical chain pathway is involved (see **section VI.IV.1** for experimental details).

Competition experiments

Next, a couple of competition experiments were performed. To elucidate how the $PhB(OH)_2$ drives the reaction, a standard reaction using *N*-Boc-protected valinol and *tert*-butylacrylate in the presence of two different additives was performed. To test the initial rational that a Lewis acid like $PhB(OH)_2$ will form a five-membered intermediate **253** with the B-atom being bond to both, the alcohol- and the amino-functionality, a primary alcohol (3-phenylpropan-1-ol, **254**) and a 1,3-amino alcohol (*N*-Boc protected propanol, **255**) were selected as additives. If the reaction proceeds via adduct **253**, the reaction in the presence of the additives should afford product **169** in high yields with possible by-products **256** and **257** being only formed in traces. This rational is since the possible intermediate **253** cannot be formed with the alcohol **254** or 1,3-amino alcohol **255**, as they would form intermediates **258** or **259** instead. The results of these competition experiments are presented below (Scheme 51). The given yields are the average of two (with **254** as additive) and three experiments (with **255** as additive). It was found that no selectivity for formation of **169** in the presence of a primary alcohol **254** or an 1,3-amino alcohol **255** was achieved. Based on these results, a cyclic intermediate **253** is not or not preferentially formed during the reaction, indicating formation of a linear boronate adduct.



Scheme 51. Competition experiments.

[a]: average of two experiments; [b]: average of three experiments. Oxidations were performed according to **Ox-C** (2.0 equiv. IBX, MeCN, 85 °C, 3 h).

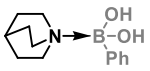
NMR studies

To further elucidate the role of the boronic acid in the mechanism, a couple of stoichiometric NMR experiments were undertaken (Figure 54 & Figure 55). First, 0.05 M stock solutions of Cbz-valinol, quinuclidine and $PhB(OH)_2$ in MeCN-d_3 were prepared and treated with freshly activated 3 Å MS. From these stock solutions, the following reagent mixtures were prepared and analyzed via ^{1}H- or ^{11}B-NMR spectroscopy.

Cbz-Valinol + quinuclidine (1:1): the ^{1}H-NMR spectrum showed deprotonation of the alcoholic proton of Cbz-valinol, as seen by the disappearing proton (marked blue).

Cbz-Valinol + $PhB(OH)_2$: neither the ^{1}H-NMR spectrum, nor the ^{11}B-NMR spectrum showed any signal shifts compared to the two reagents measured alone.

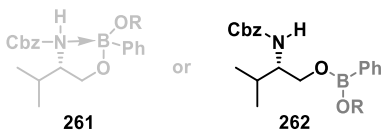
Quinuclidine + $PhB(OH)_2$: the ^{11}B-NMR spectrum revealed a shift from 28.9 ppm ($PhB(OH)_2$ alone) to 20.0 ppm (when mixed with quinuclidine). This was explained by a coordination of quinuclidine, acting as Lewis base, to $PhB(OH)_2$, acting as Lewis acid, to form adduct **260**.



260

*Figure 52. Lewis acid-base adduct **260**.*

Cbz-Valinol + quinuclidine + $PhB(OH)_2$ (1:1:2): the ^{11}B-NMR showed a shift to 4.0 ppm, which is consistent with the formation of a boronate complex. The ^{1}H-NMR spectrum revealed that the alcoholic proton is deprotonated, while the amino-proton does neither disappear, nor shift. This can be explained by the formation of boronate complex **261**, in which a very weak dative bonding between the lone pair of the amine with the B-atom is present or by formation of **262** in which the B-atom is covalently bond to the alcohol but does not interact with the amine at all. The latter is in better agreement with the results from the competition experiments as described above. The absence of a covalent bond between the amine and the B-atom prevents the boronate to form a cyclic and, therefore, rigid structure – this might explain the low diastereoselectivities of ~2:1 that were observed during the optimization studies.



261 **262**

*Figure 53. Cyclic boronate complex **261** and linear boronate complex **262**.*

Cbz-Valinol + quinuclidine + $PhB(OH)_2$ (1:1:1): the ^{11}B-NMR spectrum showed only a shifted signal at 20.0 ppm (which is in accordance with the previous findings explaining formation of adduct **260**) with a very low intensity. The signal at 4.0 ppm (boronate complex **262**) was not observed at all. This was reasoned by the preferred formation of **260** over **262**. This is in accordance with the observations made during the optimization studies in which an excess of $PhB(OH)_2$, with respect to the used quinuclidine, is mandatory for the reaction to proceed.

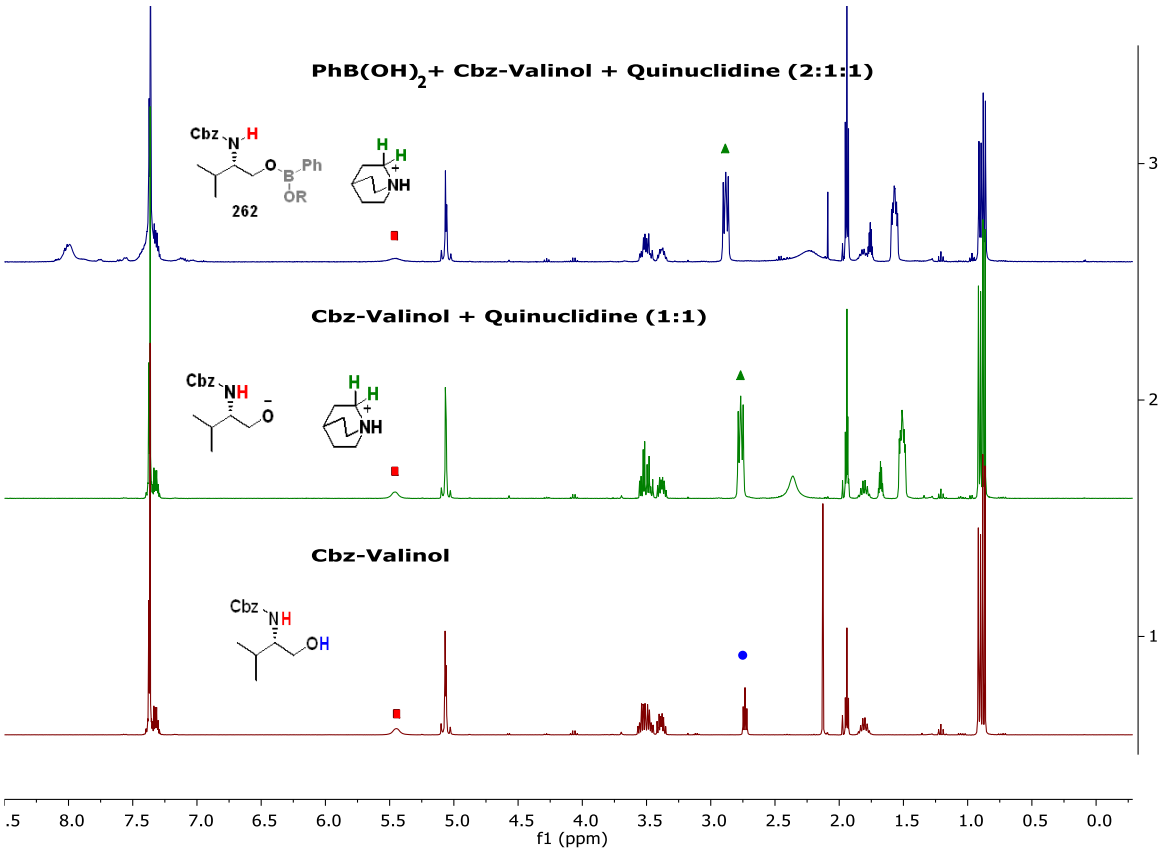


Figure 54. ^1H-NMR mechanistic investigations.

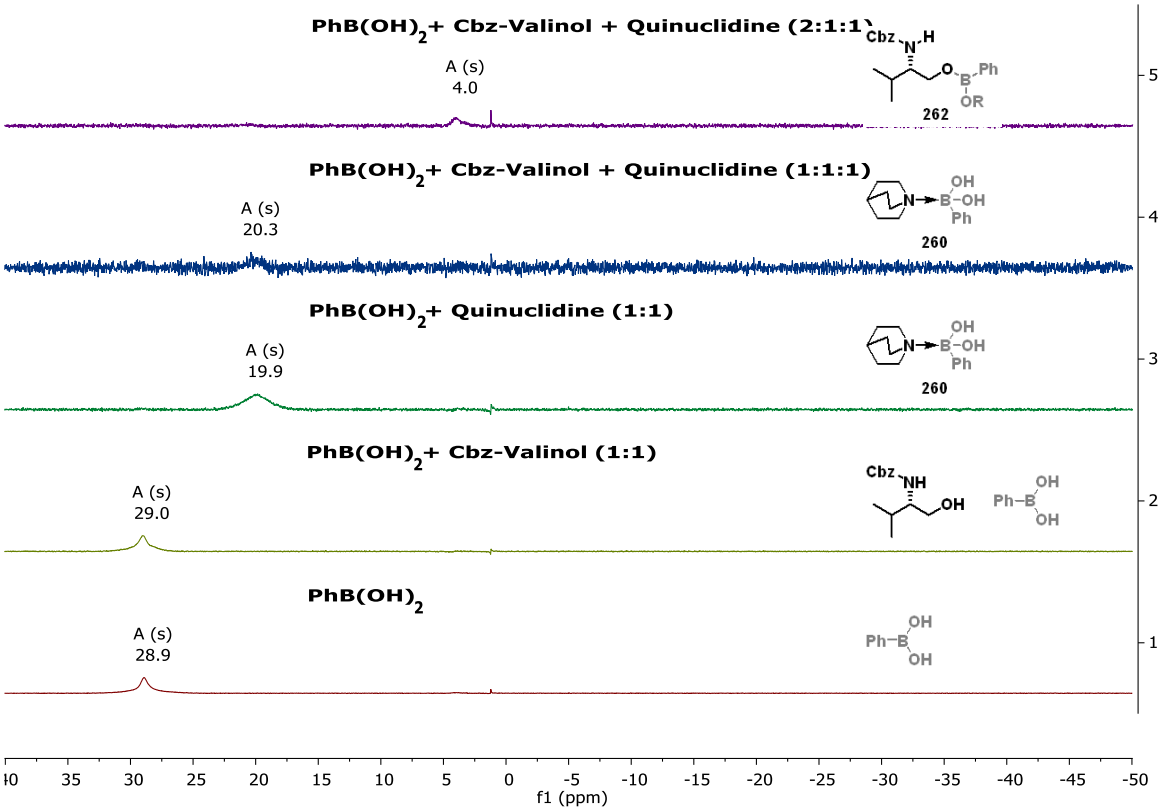


Figure 55. ^{11}B-NMR mechanistic investigations.

Mechanism

Combining the findings of the mechanistic studies, the following reaction pathway was proposed (Figure 56). Excitation of ground state photocatalyst **4CzIPN** under blue LED irradiation (λ_{max} = 440 nm) gives highly oxidizing species ***PC** (*$E_{1/2}$ = +1.43 V vs SCE)[76]. Reductive quenching by quinuclidine (**263**) ($E_{1/2}$ = +1.1 V vs SCE)[230] results in radical cation **264** and the reduced **4CzIPN** (**$^{-}$PC)**. At the same time, *N*-protected β-amino alcohol **265** reacts with phenylboronic acid in the presence of quinuclidine as a base (Lewis acid-base adduct **260**) and forms boronate **266**. The increased α-hydroxy-hydricity of **266** allows electrophilic quinuclidine radical cation **264** to abstract a hydrogen atom, forming ketyl radical **267** and quinuclidinium **268**. Giese-type conjugate addition of **267** to *tert*-butylacrylate **166** affords α-carbonyl radical **269**, which gets hydrolyzed in the presence of quinuclidine and water to yield intermediate **270**, while closing the boronic acid catalytic cycle. Single electron reduction of **270** ($E_{1/2}$ = –0.60 V vs SCE)[231] by the reduced **4CzIPN** (**$^{-}$PC)** ($E_{1/2}$ = –1.24 V vs SCE)[76] with subsequent protonation by quinuclidinium **268** yields coupled product **271**, while closing both remaining catalytic cycles. The quantum yield (Φ) for this transformation was determined to be 18.54, indicating a significant contribution of a radical chain pathway. An alternative pathway involving hydrogen atom transfer from quinuclidinium **268** to intermediate **270**, forming **271** and regenerating radical cation **264** as chain carrier, is proposed.

The subsequent oxidation of **271** to the corresponding ketone using hypervalent iodine species IBX will occur as described in the literature.[232,233]

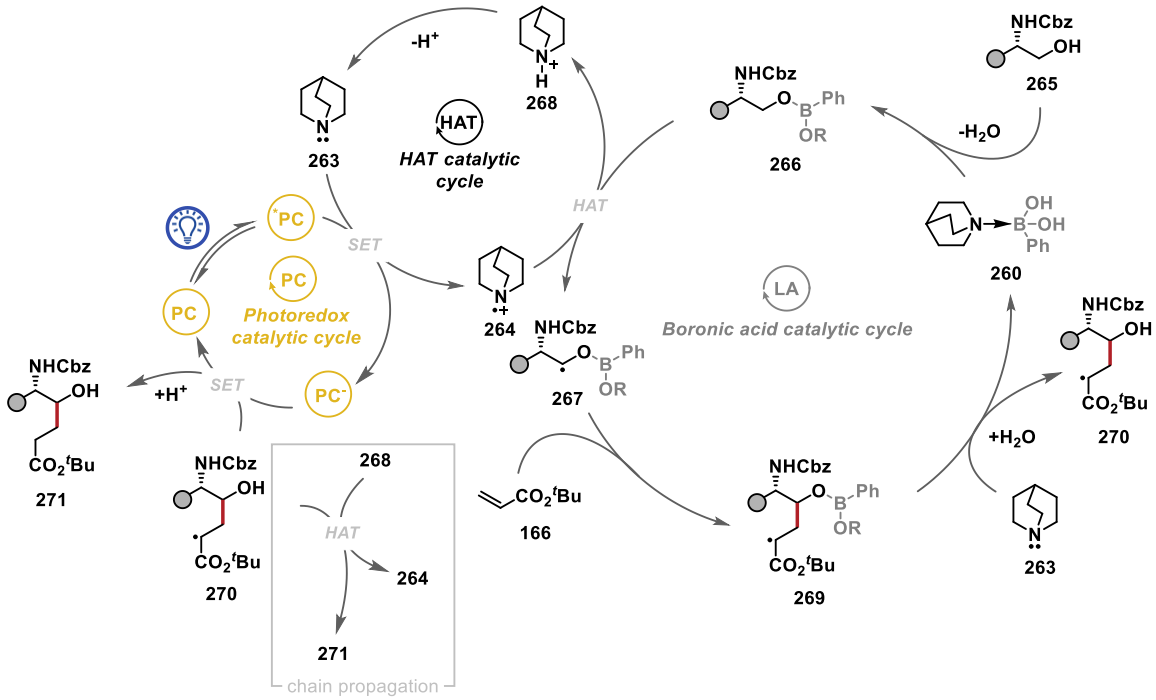


Figure 56. Proposed triple-catalytic mechanism for synthesis of γ-oxo-δ-amino esters.

III.8. – Project Summary

In summary, an effective, one-pot, two-step method for the stereoretentive synthesis of γ-oxo-δ-amino esters was developed. This approach is based on the generation of an α-amino ketyl radical, which is accessible by selective photoredox-mediated hydrogen atom transfer by means of polarity-reversal catalysis.[189] Starting from readily available β-amino alcohols, activation of the α-oxo-C–H bond using a suitable Lewis acid catalyst enabled the selective abstraction of the α-oxo hydrogen in the presence of C–H bonds of similar strength (e.g., α-amino C–H), by stereoelectronic effects. Coupling of α-amino ketyl radicals with conjugated olefins as radical acceptors produced the targeted γ-hydroxy-δ-amino acid derivatives, which were oxidized in a second step by a hypervalent iodine-species. The used triple-catalytic protocol furnished a variety of novel, unnatural δ-amino acid derivatives in good to very good yields with up to complete stereoretention of the α-amino stereo center. In addition, the products obtained could be further functionalized in a variety of ways, e.g., granting access to Fmoc-protected δ-amino acid derivatives that can be applied to solid-phase peptide synthesis. The results of this project were successfully published in *ACS Catalysis*.[234]

IV. Total Synthetic Application of the Developed Methodologies

The focus of this thesis was the design and development of novel synthetic methodologies to access (γ-oxo-)α-amino acid and γ-oxo-δ-amino acid derivatives in a stereodefined manner using radical chemistry. However, to investigate whether these methods could also be applied in the synthesis of more complex molecules, they were used to design novel synthetic routes towards manzacidin A/C and aliskiren.

IV.I. Total Synthesis of Manzacidin A/C

IV.I.1. – Introduction

Manzacidin A-C (Figure 57) are naturally occurring bromopyrrole alkaloids. They were first isolated by Kobayashi and co-workers from an Okinawan sponge *Hymeniacidon* sp. in 1991.[235] Investigations of their biological activity showed several possible applications: in addition to their antifungal activity,[236] bromopyrrol alkaloids in general are known for their pharmacological activities as serotonin antagonists or α-adrenoceptor blockers.[237]

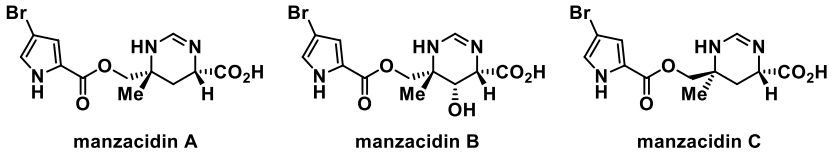


Figure 57. Manzacidin A-C.

Due to their interesting properties, several total syntheses towards one or more members of the manzacidin family have been developed.[238,239]

In 2000, Ohfune and co-workers reported the first total synthesis for mancadin A and C (Figure 58).[240] (S)-Allylglycinol was transformed into chiral auxiliary **272**. Key step of their approach was the use of an asymmetric Strecker reaction to access **273**, followed by *N*-oxidation and acidic hydrolysis furnishing tetrahydropyrimidine scaffold **(R)-274**. The latter was subsequently coupled with a bromopyrrole building block to afford manzacidin A. Manzacidin C could obtained *via* a similar approach using the other diastereomer of **272**.

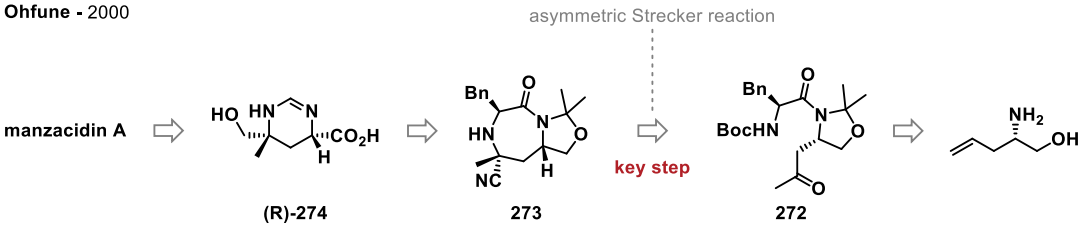


Figure 58. First total synthesis of manzacidin A by Ohfune and co-workers.

Since then, several racemic and asymmetric total syntheses have been published.[237,241–248] A selection of the most representative strategies towards both manzacidin A and C are described in Figure 59 and Figure 60.

Manzacidin A: In 2002, Du Bois and co-workers reported the synthesis of manzacidin A and C using the stereospecific Rh-catalyzed C–H amination of sulfamate **275** to **276** as key step.[237] In 2006, Maruoka designed an asymmetric 1,3-dipolar cycloaddition using a chiral titanium Lewis acid catalyst as key step to access building block **277** as intermediate for the total synthesis of manzacidin A.[242] Finally, in 2015 Inoue and co-workers reported a radical approach to access manzacidin A and it's C4-epimer in a 1:1-mixture using a decarbonylative radical coupling of an α-aminoacyl telluride **278** as key step.[245]

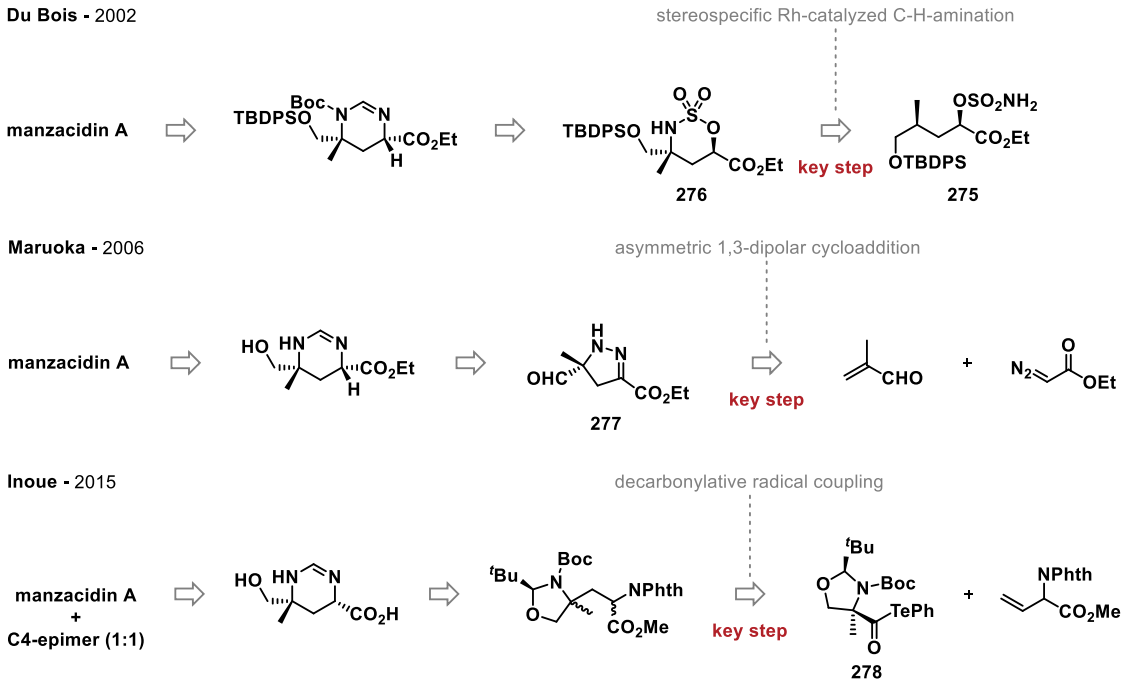


Figure 59. Selected total synthetic approaches towards manzacidin A.

Manzacidin C: Lanter and co-workers reported in 2005 an asymmetric aza-Mannich reaction between chiral sulfinimine **279** and imine **280** as key step towards the synthesis of manzacidin C.[241] In 2007, Deng designed another strategy to access manzacidin C using an organocatalyzed asymmetric tandem conjugate addition-protonation sequence as key step to access intermediate **281**.[243] Finally, Renata recently reported a chemoenzymatic, 5-step formal synthesis of manzacidin C starting from L-Leu.[247] The key step is a photoazidation reaction followed by an enzymatic δ-hydroxylation to generate enantiopure alcohol **282**. The latter was transformed into lactone **(S)-283**, a known precursor to manzacidin C.

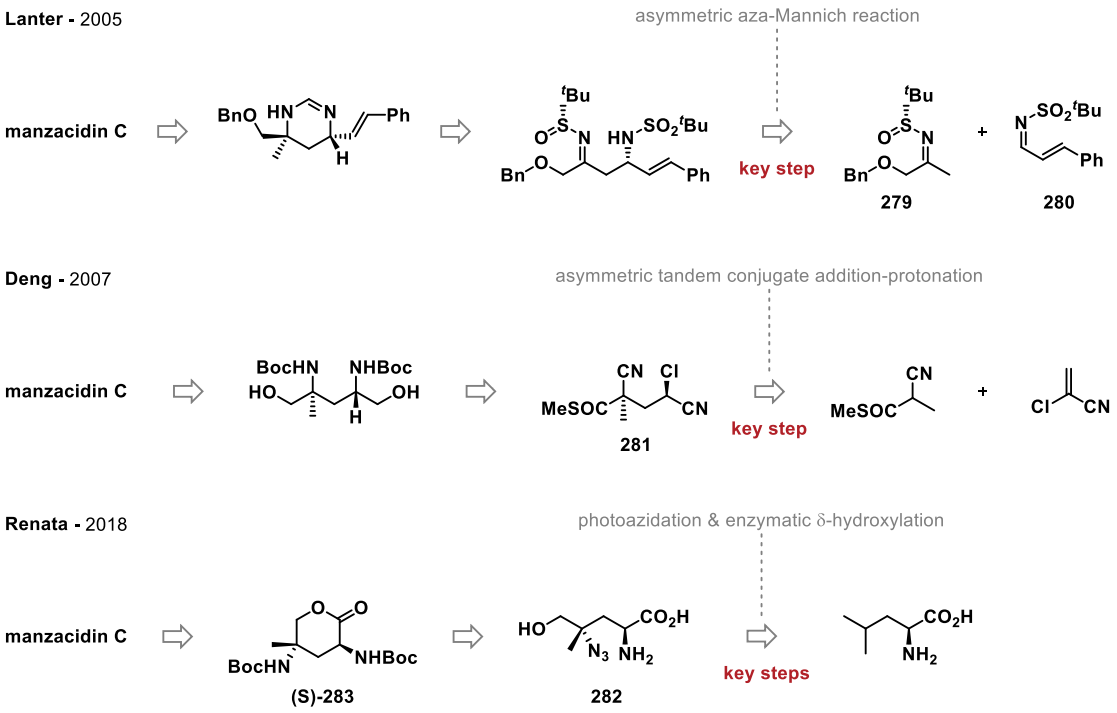


Figure 60. Selected total synthetic approaches towards manzacidin C.

Due to the number of reported strategies for the synthesis of manzacidin A/C, and the wealth of characterization data available for both molecules, as well as synthetic intermediates, they were selected as target molecules to test the applicability of the methodology developed in **section II.I** for the synthesis of complex molecules. Moreover, the synthetic route presented here would allow a novel general access to the unusual 1,4,5,6-tetrahydropyrimidine core, which in turn would be interesting for the total synthesis of other natural products or biologically active molecules exhibiting this structural motif as for example lanesoic acid (Figure 61).[249]

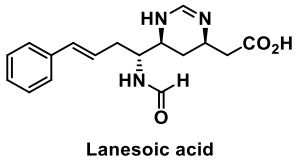


Figure 61. Lanesoic acid.

To this end, a retrosynthetic analysis of manzacidin A and C inspired by the radical approach developed by Inoue and co-workers[245] is shown in Figure 62. The tetrahydropyrimidine core of manzacidin A/C (**274**) could be constructed from a corresponding 1,3-diamino compound **284**. The latter can be prepared via a ring opening/deprotection of bicyclic intermediate **285**, which can be generated using the developed decarboxylative Giese-type reaction between oxazolidine **286** and Beckwith-Karady alkene **28**. Finally, **286** can be readily accessed from D-serine, while the Beckwith-Karady alkene **28** can be prepared from cysteine. Moreover, it was hypothesized that the steric hindrance of the *tert*-butyl group of **286** in combination with the Beckwith-Karady alkene, will help to achieve high levels of diastereocontrol at both α-amino stereocenters.

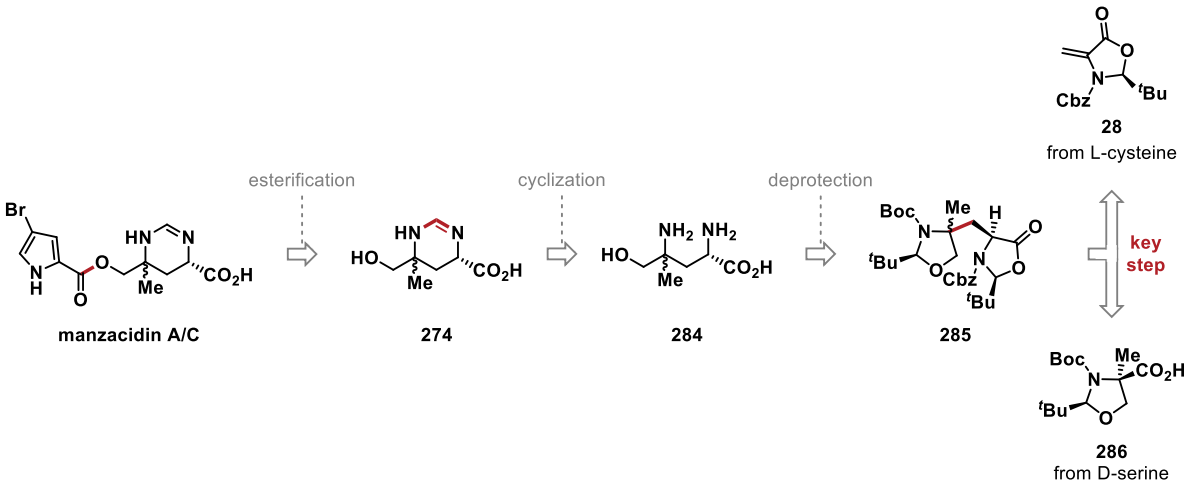
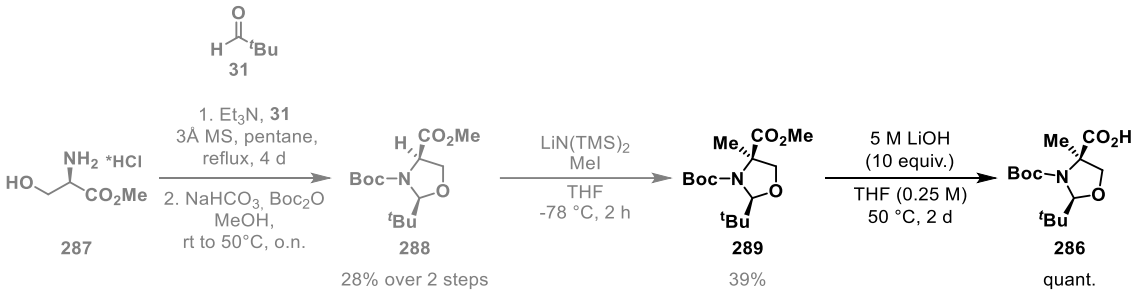


Figure 62. Retrosynthetic analysis of manzacidin A/C.

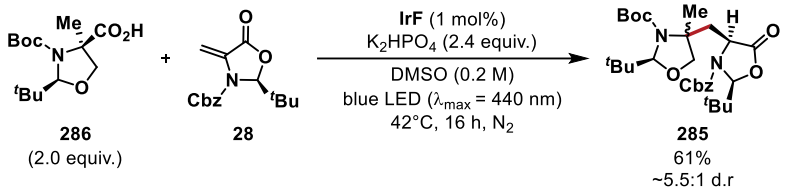
IV.I.2. – Results and Discussion

The first step of the synthesis was the preparation of building block **286** (Scheme 52) Starting from D-serine methyl ester (**287**), a condensation with pivaldehyde **31** and subsequent cyclization and Boc-protection of the intermediary imine afforded oxazolidine **288** in 28% over 2 steps. Methylation of **288** with iodomethane in presence of $LiN(TMS)_2$ afforded methyl ester **289** in 39% yield. Subsequent saponification of **289** with LiOH afforded **286** in quantitative yield. Reactions performed by a colleague are depicted in grey.



*Scheme 52. Synthesis of building block **286**.*

With the oxazolidine building block in hands, the key step of the synthesis, the light-mediated decarboxylative Giese-type reaction, was performed using the standard conditions presented in **section II.I** (Scheme 53). Delightfully, while analysis of the crude by ^{1}H NMR revealed formation of the targeted product as a ~5.5:1 diastereomeric mixture, purification by flash column chromatography afforded **285** in 61% yield with excellent diastereomeric purity (d.r. >20:1).



*Scheme 53. Key conjugate Giese-type addition of **286** to **28**.*

Unfortunately, 2D NMR investigation (NOESY) did not help to determine the absolute configuration of the isolated product **285**. A hypothesis as to which of the two possible products is formed is shown in (Figure 63). The 3D analysis (created with *PerkinElmer Chem3D*®; structures depicted according to MM2 Minimization) suggests that radical **290** (formed via decarboxylation of **286**) is not trigonal planar but in a slightly curved shape. Based on this, a conjugated addition of **290** to **28** should preferentially afford product **(S)-285**. However, an analysis of the two possible products shows that – as calculated by the program – the (R)-enantiomer possesses the lower steric energy (36.9 vs 39.0 kcal/mol). As mentioned before, the lowest steric energy of a molecule is the optimal combination of steric repulsion of all atoms/groups resulting in the largest possible distance to each other and the energetically disfavored stretching or bending going along with the steric repulsion.[172]

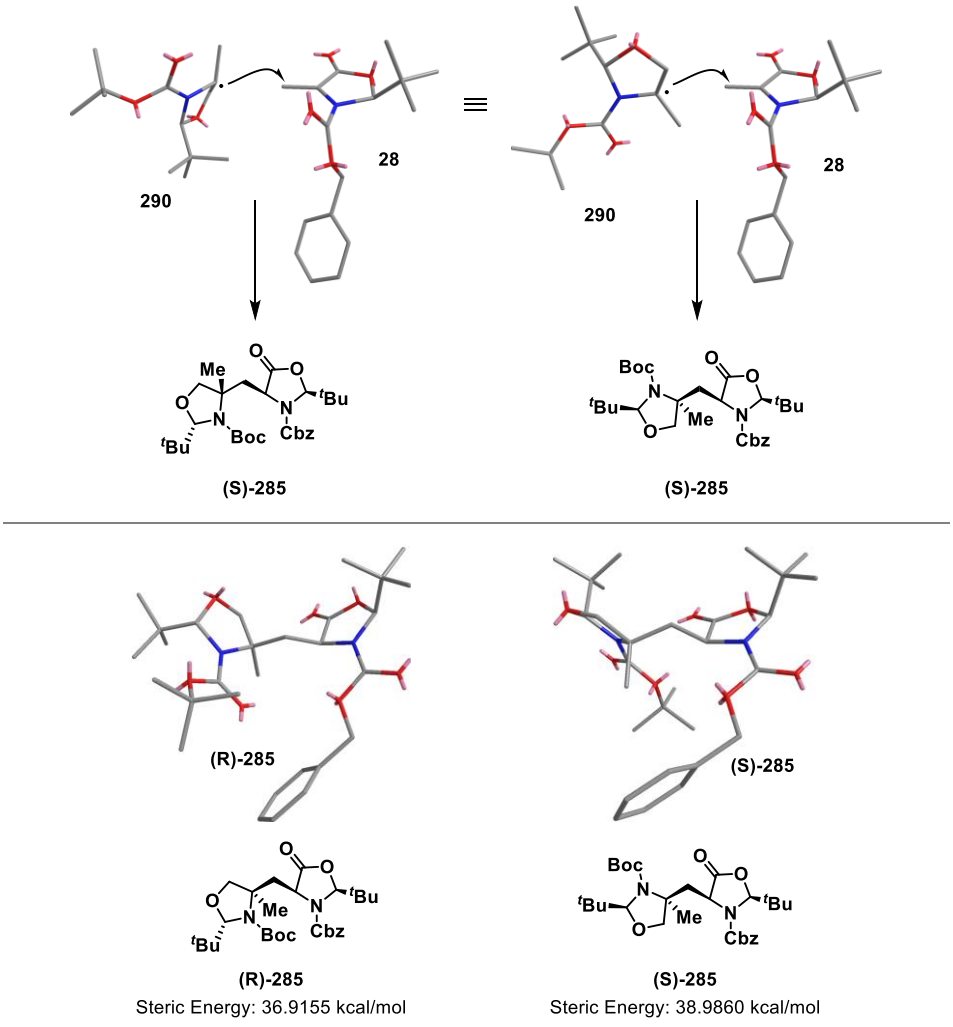


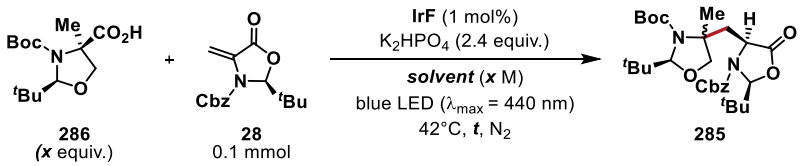
*Figure 63. 3D analysis of the conjugate Giese-type addition of **290** to **28**.*

Either way, the absolute configuration of **285** is not of paramount importance for the planned synthesis, since both possible products **(S)-285** and **(R)-285** would lead to either manzacidin C or manzacidin A.

Although the key step of the reaction proceeded smoothly under the standard reaction conditions, it still required 2 equiv. of **286** to work. Therefore, an optimization screening was performed with the aim to reduce the amount of carboxylic acid **286** needed for the reaction to proceed (Table 10).

Reactions using the optimal alkylation conditions found in **section II.I.3** confirmed 1,4-dioxane (yield of **285** >95%) as the solvent of choice for the targeted transformation (Entries 1 & 2, Table 10). Gratifyingly, reducing the excess of **286** to 1.1 equiv. still afforded **285** after 16 h in excellent yield (91%). This could be further increased to >95% yield of **285** by running the reaction for 72 h (Entry 4, Table 10).

*Table 10. Optimization studies performed on conjugate addition of **286** to **28**.*



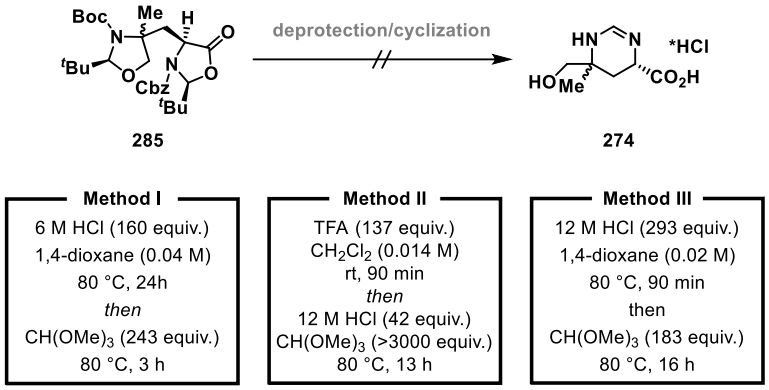
Entry	286 / 28	Solvent	t (h)	Yield (%)[a]	d.r.[b]
1	2 / 1	1,4-dioxane (0.1M)	16	>95	5.7
2	2 / 1	DMSO (0.2 M)	16	79	1.2
3	1.1 / 1	1,4-dioxane (0.1M)	16	91	1.8
4	1.1 / 1	1,4-dioxane (0.1M)	72	>95	5.0

[a]: combined yield of **(S)-285** & **(R)-285** calculated by ^{1}H NMR (IS: trichloroethylene); [b]: calculated by ^{1}H NMR.

With **285** in hand, the next step of the synthesis was explored: deprotection of **285** and subsequent cyclization to tetrahydropyrimidine **274** (Scheme 54).

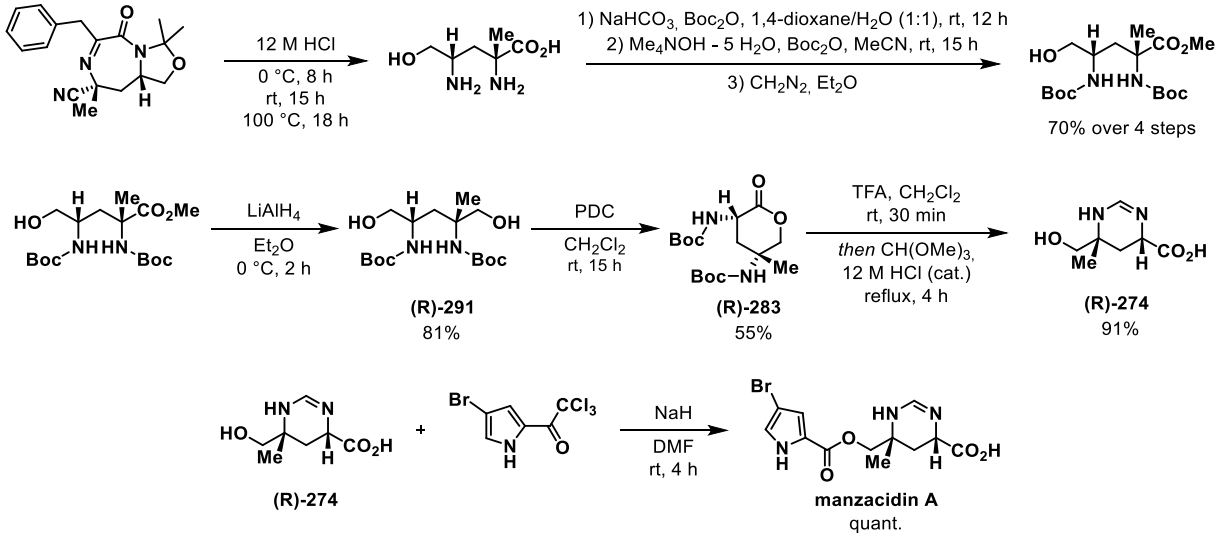
Acidic deprotection of **285** using 6 M HCl was performed for 24 h and the outcome was subsequently treated with trimethyl orthoformate. The formed product was not clearly identified but the presence of a *tert*-butyl group suggested only partial deprotection of the starting material. Also, when partially deprotecting **285** with TFA in CH_2Cl_2 and subsequently treating it with trimethyl orthoformate in the presence of concentrated HCl – a slightly modified protocol than used in a former total synthesis by Ohfune for cyclizing a different building block[240] – **274** was not obtained. Instead, NMR analysis suggested again formation of partially deprotected starting material. To obtain full deprotection of the intermediary product, slightly harsher conditions were tried: **285** was dissolved 1,4-dioxane, then 12 M HCl was added and the reaction was stirred to 80 °C for 90 min. ^{1}H NMR analysis of the crude suggested full

deprotection since no trace of the Cbz-group or any of the *tert*-butyl groups could be observed. Therefore, the same reaction was repeated and subsequently treated with trimethyl orthoformate, in the presence of conc. HCl to form the targeted product **274**. Unfortunately, the reaction outcome looked the same as the deprotected intermediate, indicating **274** was not formed.



*Scheme 54. Trials to access **274** via an acidic deprotection/cyclization sequence of **285**.*

Following up especially the latest result of the deprotection/cyclization trials, it was questioned whether the one-pot two-step strategy of directly cyclizing **285** to the tetrahydropyrimidine **274** is actually possible: Ohfune and co-workers installed in their total synthesis of manzacidin A the targeted tetrahydropyrimidine scaffold **(R)-274** by treating a δ-lactone **(R)-283** – generated from **(R)-291** – with trimethyl orthoformate (Scheme 55).[240]



Scheme 55. Endgame total synthesis of manzacidin A by Ohfune and co-workers.

This strategy should be compatible with our route: deprotection and subsequent Boc-protection of **285** would afford intermediate **292**. Reduction of **292** affords diol **291**, from which the synthesis could proceed through the pathway described by Ohfune and co-workers (Figure 64).

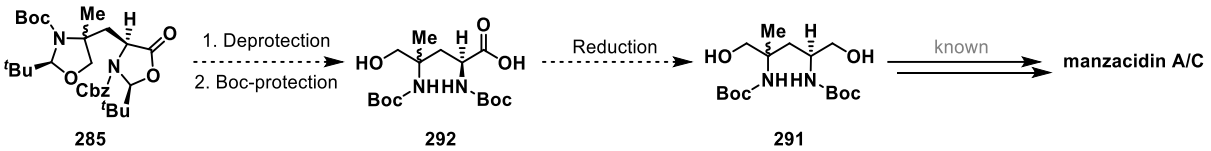
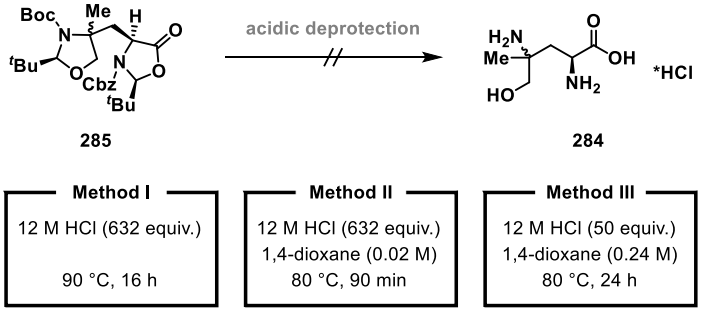


Figure 64. Possible approach to finish the total synthesis.

Following the new strategy, the acidic deprotection of **285** to the free amino acid **284** was tried. The previous trials to access **274** via an acidic deprotection/cyclization sequence showed the necessity for strong acidic conditions to achieve full deprotection of **285**. However, dissolving **285** in concentrated HCl and stirring the reaction to 90 °C for 16 h resulted in formation of a non-identifiable product. Thus, it was assumed that **285** decomposed under these conditions. To prevent this, the reaction was repeated with the same amount of 12 M HCl in 1,4-dioxane, stirring for 90 min at 80 °C, and using a smaller amount of 12 M HCl in 1,4-dioxane, stirring at 80 °C for 24 h. In both cases, ^{1}H NMR analysis of the crude showed full deprotection. However, the obtained products did neither match the expectations for **284**, nor could be identified.



*Scheme 56. Trials to access **284** via acidic deprotection of **285**.*

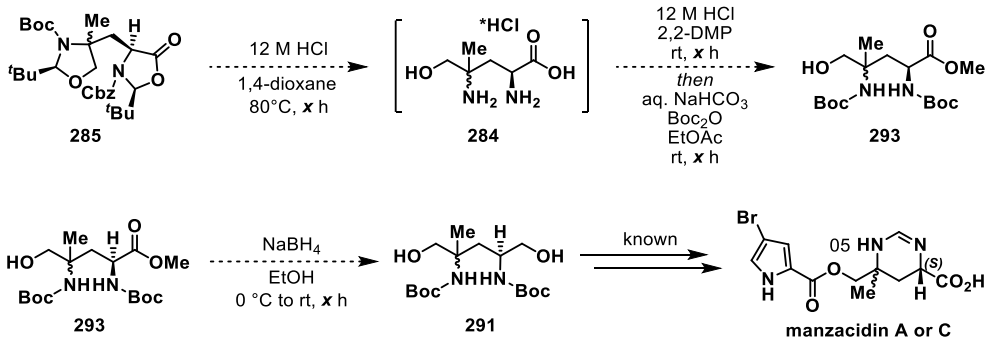
The total synthesis was not continued at this point, as all attempts to access free acid **284** via acidic deprotection of **285** failed.

IV.I.3. – Summary & Outlook

Even though the targeted total synthesis could not be completed, the key step of the designed route was successfully realized to afford intermediate **285** in good yield (61%) and high levels of diastereomeric purity (d.r. >20:1), proving the applicability of the decarboxylative methodology developed in **section II.I** to more complex targets. The completion of the total synthesis requires further tests to access the other key intermediate, **291**.

One possibility would be to perform a deprotection/protection sequence of **285** to obtain double N-Boc-protected ester **293**. Reduction using $NaBH_4$ in EtOH should afford **291** (Scheme 57). A similar three-step protocol was successfully used to access *N*-Boc-protected β-amino

alcohols from unprotected α-amino acids (e.g., see syntheses of *tert*-butyl (1-(hydroxymethyl)-cyclobutyl)carbamate or **(rac)-181** in **section VI.IV.2** for experimental details). With **291** in hand, the total synthesis of manzacidin A/C can be achieved following Ohfune's strategy.



Scheme 57. Suggested continuation to finish the total synthesis.

In addition, it should be investigated whether the use of L-serine methyl ester, instead of D-serine methyl ester, affords the corresponding diastereomer of **285** after the Giese-type reaction. If successful, this would enable the targeted synthesis of manzacidin A or C by simply choosing the proper enantiomer of serine as starting material.

IV.II. Total Synthesis of Aliskiren

IV.II.1. – Introduction

Aliskiren is a non-peptidic, pharmacologically active compound that can be used primarily for hypertension,[250,251] one of the main causes of strokes and infarcts (Figure 65).[252] One reason for hypertension is the conversion of the protein angiotensinogen to angiotensin I and further to angiotensin II by the protease renin, an enzyme secreted by the kidneys.[253,254] A possible approach to treat hypertension is to prevent this degradation with the use of renin inhibitors. Aliskiren was specifically designed for this purpose by scientists at Novartis using molecular modeling,[255] and was approved by the US Food and Drug Administration (FDA) under the brand name Tekturna® (or Rasilez®) as renin inhibitor in 2007.[256]

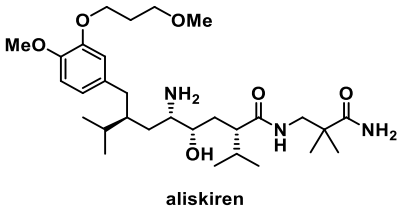


Figure 65. Aliskiren, a renin inhibitor.

To date, there have been numerous successful total syntheses using different retrosynthetic approaches. In 2000, the groups of Maibaum and Sandham both reported a total synthesis of aliskiren relying on the Grignard addition of an *in situ* generated Grignard species – derived from **294** – and either chiral lactone **295** or chiral spirocycle **296**.[257,258] Coupled product **297** was transformed into azide **298** which, after lactone opening and azide reduction, afforded aliskiren (Figure 66).

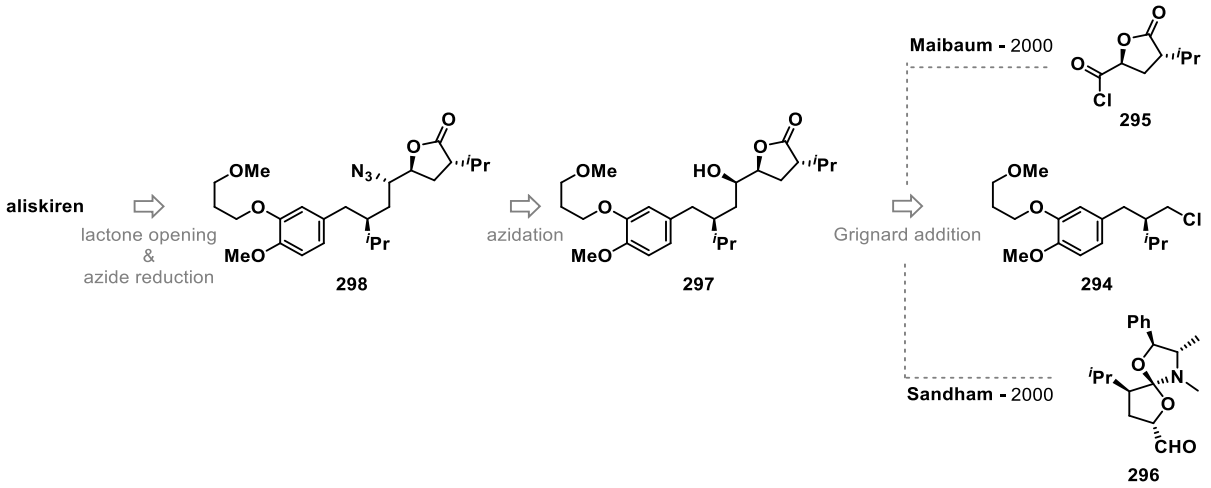


Figure 66. Selected total synthetic approaches towards aliskiren.

A couple of years later, Skrydstrup and co-workers used a slightly different approach.[253] **299** was coupled with bis-lactim **300** and then further functionalized to yield 4-pyridylthioester **301**. A SmI_2-promoted coupling of a **301**-derived acyl radical with methylacrylate **163** with subsequent functionalization ultimately furnished lactone **302,** which was subjected to a lactone opening to give aliskiren (Figure 67).

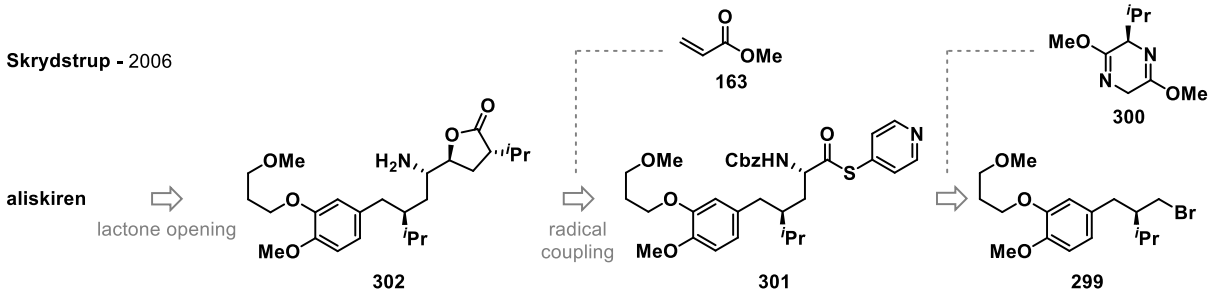


Figure 67. Radical approach towards total synthesis of aliskiren.

A summary of the early retrosynthetic approaches was published by Skrydstrup in 2006 (Figure 68).[253] In addition to these syntheses, further successful approaches were published by numerous groups, including Ma,[259],Hanessian,[260],Andersson[261] and Rasparini & Taddei.[262]

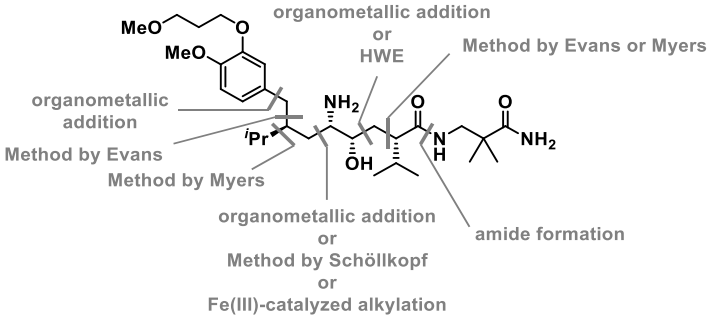


Figure 68. Summary of some early approaches towards aliskiren as presented by Skrydstrup and co-workers.

Due to the number of reported strategies for the synthesis of aliskiren, and the wealth of characterization data available for synthetic intermediates, it was selected as a target to test the applicability of the methodologies developed in **section II.I** and **section III** for the synthesis of complex **molecules** (Figure 69).

The two key steps of the synthesis are:

1st key step: Giese-type conjugate addition of acid **303** – readily accessed from isovanillin – onto Beckwith-Karady alkene **28** to afford intermediate **(S)-304**.

2nd key step: HAT mediated α-hydroxy-functionalization of β-amino alcohol **(S)-305** – generated by a deprotection/reduction sequence of **(S)-304** – with Michael acceptor **306**.

A global deprotection would give aliskiren via a novel, innovative route using two photoredox-mediated key-steps.

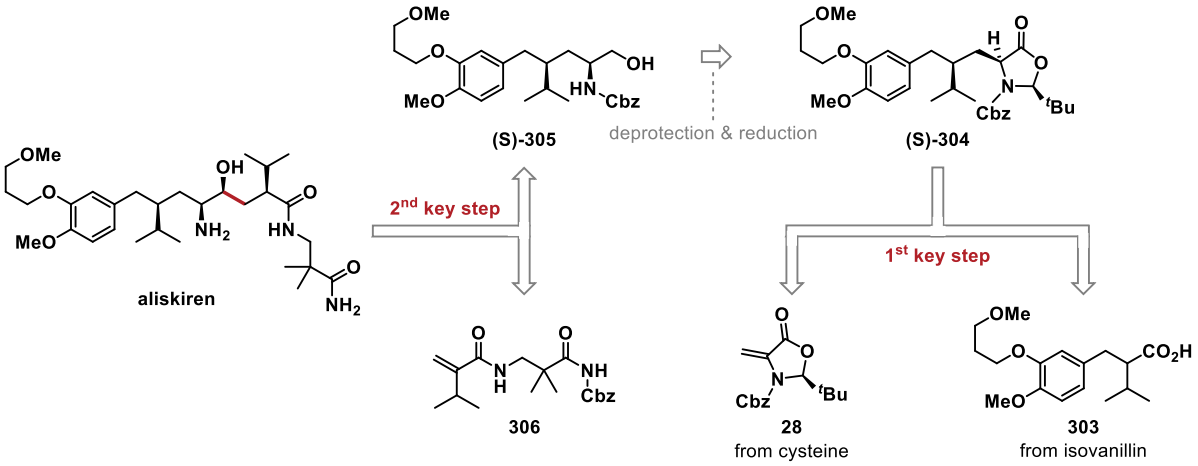
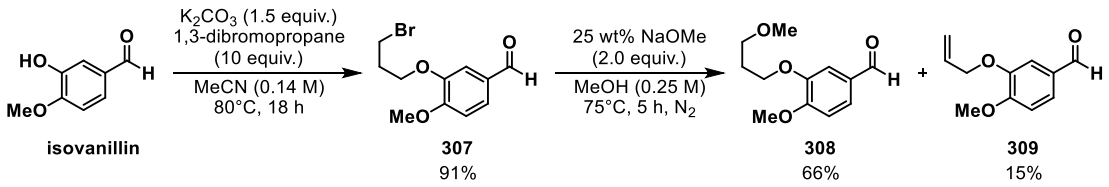


Figure 69. Retrosynthetic analysis of aliskiren.

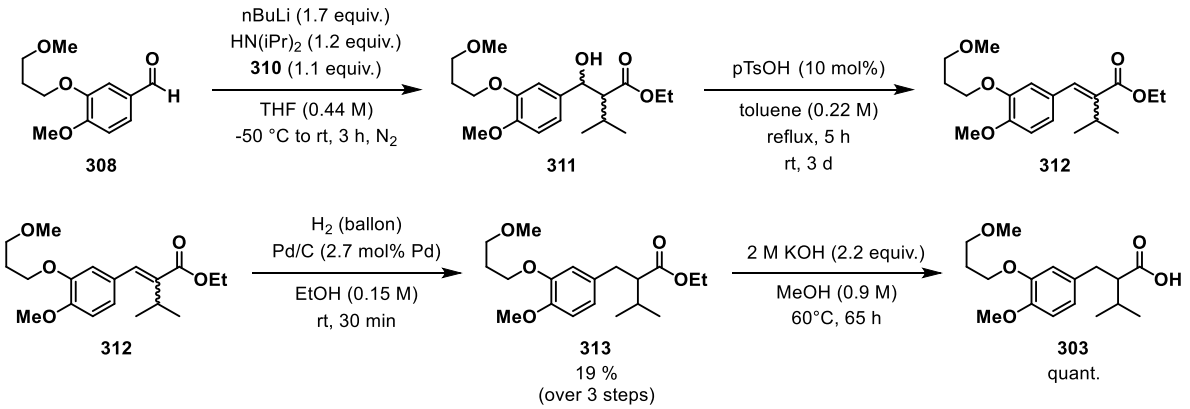
IV.II.2. – Results and Discussion

The first step of the synthesis of aliskiren was the generation of carboxylic acid **303** from isovanillin. Nucleophilic substitution of isovanillin with 1,3-dibromopropane and K_2CO_3 readily afforded aldehyde **307** in 91% yield.[261] Subsequent nucleophilic substitution using NaOMe afforded **308** in 66% yield, with 15% formation of alkene **309** as elimination by-product.[263]



*Scheme 58. Nucleophilic substitution using isovanillin and 1,3-dibromopropane leads to formation of **307**.*

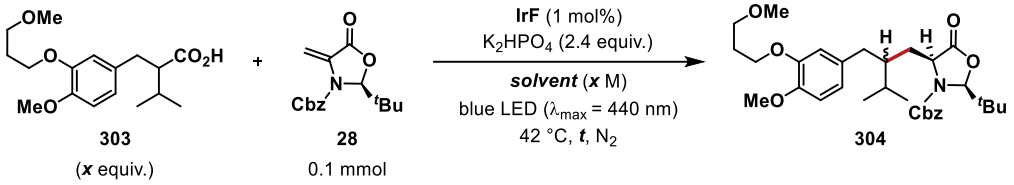
Next, aldehyde **308** was converted to ester **313** in a three-step synthetic sequence.[264,265] For this purpose, an aldol reaction was first carried out between aldehyde **308** and ethyl isovalerate (**310**). H_2O was then eliminated from the product mixture of **311** with the aid of *p*TsOH to give the α,β-unsaturated ester **312**. Finally, hydrogenation over Pd/C yielded the reduced ester **313** in 19% over 3 steps, which was saponified using aqueous KOH solution in MeOH at elevated temperature to afford the targeted acid **303** in quantitative yields.



*Scheme 59. Synthesis of **303** from aldehyde **308**.*

Having successfully produced carboxylic acid **303**, the first key step was performed; the Giese-type addition onto Beckwith-Karady alkene **28**. Firstly, to not waste precious amounts of **303**, a couple of test reactions were performed to check if the optimized conditions found in **section IV.I.2** (Table 10) for the key step of the synthesis of manzacidin A/C can be used (Table 11). Indeed, it was found that the amount of **303** can be reduced to 1.1 equiv. without affecting the yield, resulting in nearly quantitative results when irradiated for 72 h (Entries 1 & 2, Table 11). The use of DMSO resulted in lower yields (Entry 3, Table 11), showing 1,4-dioxane to be the superior solvent for the targeted transformation. Combined tests afforded **304** in 73% isolated yield (average of 6 test reactions) as a ~1.5:1 diastereomeric mixture. Attempts to separate both diastereomers via manual flash chromatography failed. Nevertheless, it was decided to continue with the synthesis plan as the diastereomeric mixture can also be separated at a later stage.

*Table 11. Optimization studies performed on conjugate addition of **303** to **28**.*

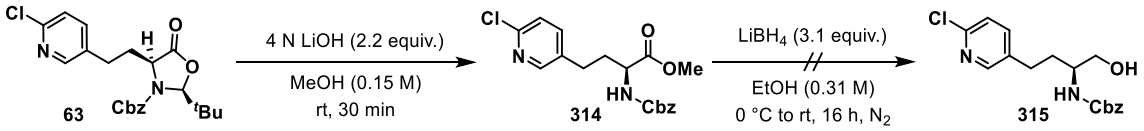


Entry	303 / 28	Solvent	t (h)	304 (%)[a]
1	2 / 1	1,4-dioxane (0.1 M)	72	93
2	1.1 / 1	1,4-dioxane (0.1 M)	72	>95
3	1.1 / 1	DMSO (0.2 M)	72	83

[a]: combined yield of **304** calculated by NMR (IS: trichloroethylene).

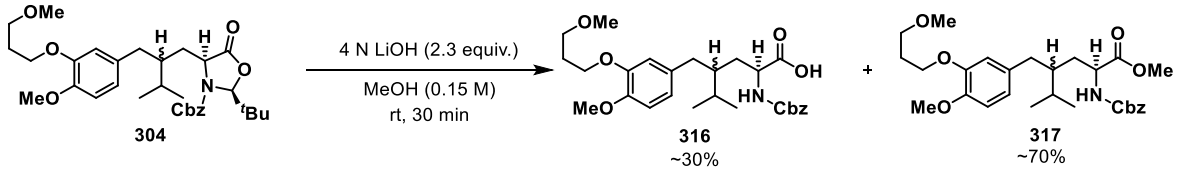
Next, the deprotection of the oxazolidinone core was explored. Acidic deprotection of **304** with 12 M HCl would also cleave the Cbz-protecting group of the amine, which is needed for the subsequent reactions. Therefore, an alternative deprotection method was sought. Patent literature showed that it is possible to saponify a substituted oxazolidinone core and

subsequently reduce formed methyl ester to the primary alcohol.[266] To not waste precious oxazolidinone **304**, the reported conditions were tested on **63** first (Scheme 60). Gratifyingly, the deprotected product **314** could be detected by ^{1}H NMR. However, a subsequent reduction failed to give alcohol **315**, which might be attributed to the use of an old batch of $LiBH_4$.



*Scheme 60. Test reaction to saponify and subsequently reduce oxazolidinone **63**.*

Nevertheless, since the test reaction showed the possibility of saponifying the oxazolidinone core under basic conditions, it was decided to apply these conditions directly on **304** (Scheme 61). The reaction yielded two products: carboxylic acid **316** and ester **317**. The generation of both products was supported by HRMS analysis. Formation of ester **317** can be explained due to conducting the reaction in MeOH. However, both isolated compounds were not obtained in pure fashion, containing by-products and the corresponding diastereomer. Accordingly, no exact yield was determined. A rough calculation suggested a yield of ~30% (**316**) and ~70% (**317**).



*Scheme 61. Basic deprotection of the oxazolidinone core of **304**.*

IV.II.3. – Summary & Outlook

Unfortunately, the total synthesis of aliskiren could not be continued at this point. Anyway, the first key step of the designed route was successfully realized to afford intermediate **304** in good yield (73%, combined yield from 6 test reactions) as a mixture of two diastereomers (d.r. ~1.5:1). To complete the total synthesis the basic saponification of **304** needs to be repeated to receive **316** and **317** in a pure fashion. It is advised to try the separation of the diastereomeric mixture of **304** prior to the deprotection by using a preparative HPLC. When in hand, **316** and **317** can be reduced, both affording the same product: alcohol **305** (Figure 70).

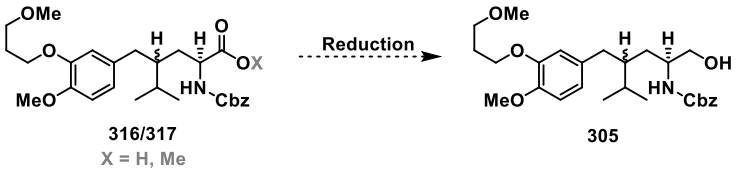
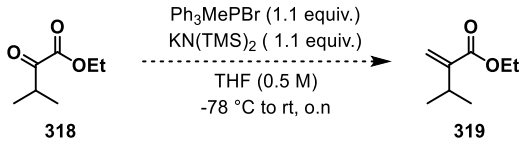


*Figure 70. Reduction of **316** and **317** leads to alcohol **305**.*

Once this is achieved, there are two main routes to finish the synthesis. Both routes require building block **319**, which can be prepared from readily available α-keto ester **318** (Scheme 62).[267]



*Scheme 62. Synthesis of building block **319** according to literature.*

With building block **319** in hand, the total synthesis of aliskiren can proceed as follows:

Route 1: building block **319** is used to synthesize acrylamide **306**. With the latter in hand the second key step of the synthesis, the photoredox-mediated α-hydroxy-functionalization of amino alcohol **(S)-305** with **306**, can be explored. It is expected that after the oxidation step with IBX, a diastereomeric mixture of ketones **320** will be obtained. This mixture must be separated at this point so that the epimer which has the correct (S)-configuration with respect to the isopropyl side chain is isolated. Stereoselective reduction of the ketone to the secondary alcohol with the desired configuration followed by a global Cbz-deprotection (e.g., with $Pd/C/H_2$)[253] would yield aliskiren.

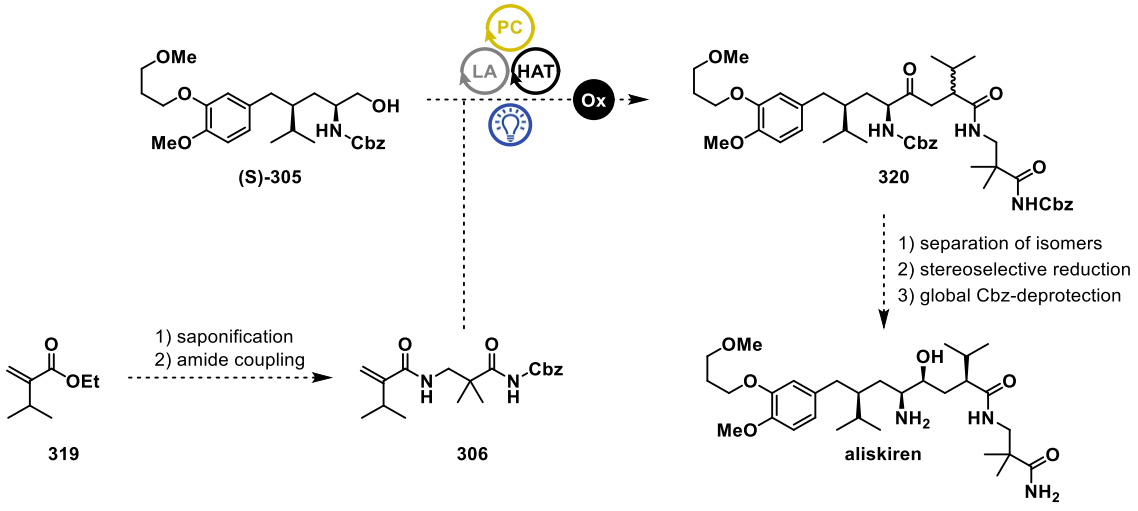


Figure 71. Possible follow-up route 1 to finish the total synthesis of aliskiren.

Experience has shown that the use of a secondary amide as an acceptor in the photoredox-mediated coupling with amino alcohols resulted in diminished yields. To overcome this possible limitation, an alternative route to proceed with the total synthesis of aliskiren is proposed:

Route 2: building block **319** is directly coupled with amino alcohol **(S)-305**, and the product mixture is oxidized with IBX. As mentioned above, the product mixture **321** must be separated so that further work can be carried out with the (S)-isomer with respect to the isopropyl side chain. The ketone can then be stereoselectively converted into the corresponding secondary alcohol **322** by using a suitable reducing agent. Saponification, followed by subsequent amide formation, subsequent amide formation, and global deprotection would provide aliskiren. Alternatively, the stereoselective reduction can be performed after installing the amide group.

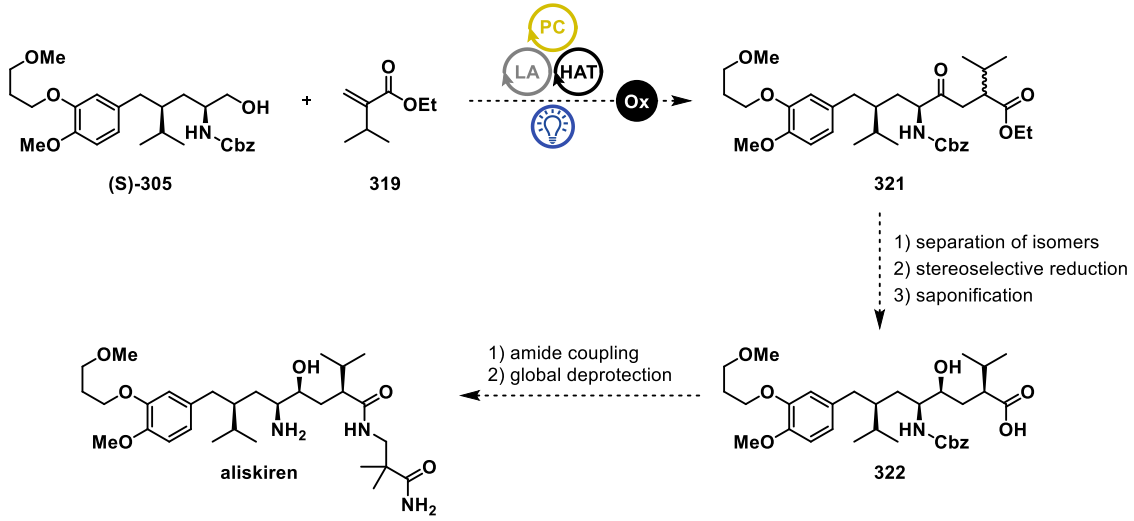


Figure 72. Possible follow-up route 2 to finish the total synthesis of aliskiren.

V. Conclusions

Synthesis of (γ-oxo-)α-amino acids via decarboxylative Giese-type reactions

In the first part of this thesis, a joint project together with Francisco José Aguilar Troyano and Jonas Djossou was focused on the synthesis of enantiomerically enriched α-amino acid derivatives. The developed approach is based on a Giese-type conjugate addition of alkyl and acyl radicals – *in situ* generated from readily available (α-keto)-carboxylic acids via photoredox-mediated decarboxylation – onto the so-called Beckwith-Karady alkene, a chiral Dha motif. A total number of 36 scope examples were obtained in synthetically useful yields (10–98%) and with excellent diastereomeric purities (d.r.>20:1). In 2020, the results of this collaborative project were successfully published in *Advanced Synthesis and Catalysis* and highlighted by both academic and industrial scientists in *Synfacts* and *Organic Process Research & Development*, respectively.[1,2,158] The relevance of the presented methodology was particularly demonstrated by the fact that three other similar approaches were published at the same time.[155–157] Furthermore, two of these publications were developed in the context of an industrial project, which in turn demonstrates the industrial interest in straightforward and operationally-simple protocols to access α-amino acid derivatives.

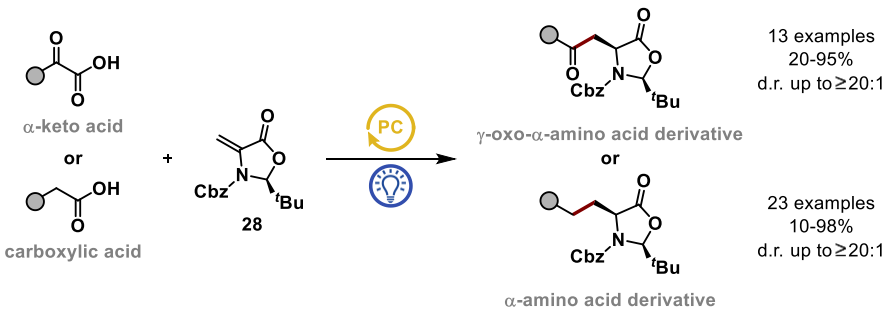


Figure 73. Project summary for the synthesis of α-amino acid derivatives via decarboxylative conjugate addition.

Synthesis of γ-oxo-α-amino acids via phosphoranyl radicals

Especially γ-oxo-α-amino acid derivatives were identified to possess several additional functionalization vectors that would allow the synthesis of even more complex UAAs. However, synthesis via the developed decarboxylative strategy faced some limitations as e.g., the lack of general abundance of α-keto acids and the reduced reactivity when applying the methodology to electron-poor systems.

Therefore, in another joint project together with Francisco José Aguilar Troyano and Khadijah Anwar an alternative approach to access γ-oxo-α-amino acid derivatives was developed. As a result, a deoxygenative strategy to generate acyl radicals from abundant carboxylic acids using photoredox-mediated generation of phosphoranyl radicals was developed. The phosphoranyl radical gets trapped by the carboxylate and undergoes β-scission, delivering the targeted acyl

radical. This in turn reacts with the Beckwith-Karady alkene, ultimately forming a γ-oxo-α-amino acid derivative.

Again, 24 examples (10–97% yield) with excellent diastereomeric purities (d.r. >20:1) proved the broad applicability of the developed methodology and represent a very good alternative to the decarboxylative synthesis of γ-oxo-α-amino acid derivatives, allowing the synthesis of this interesting substance class starting from abundant starting materials in an operationally-simple manner. In addition to that, the protocol is applicable to vinylic carboxylic acids which is – to the best of our knowledge – the first time that these motifs were employed as acyl radical precursors. Furthermore, some derivatization reactions were performed to showcase the possibility of further expanding the accessible chemical space. The results of this collaborative project were published in 2021 in *The Journal of Organic Chemistry* and were again highlighted by both academic and industrial scientists in *Synfacts* and *Organic Process Research & Development*, respectively.[3,4,178]

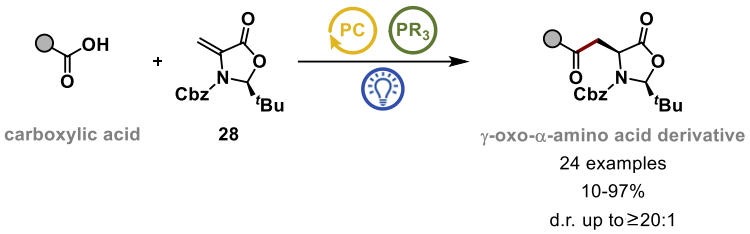


Figure 74. Project summary for the synthesis of γ-oxo-α-amino acid derivatives via phosphoranyl radicals.

Synthesis of γ-oxo-δ-amino acids

The second part of this thesis was focused on the synthesis of γ-oxo-δ-amino esters, a substance class often present in biologically active molecules. Based on a 1-e$^-$-disconnection approach, γ-oxo-δ-amino esters should be accessible via α-amino ketyl radicals, generated from readily available β-amino alcohols using hydrogen atom abstraction. However, β-amino alcohols possess bonds of similar polarity and strength (α-NH and α-OH). Therefore, a chemoselective functionalization approach of β-amino alcohols was developed. The presented triple-catalytic methodology is based on the combination of photoredox and HAT catalysis in which a boron-based catalyst ensures the chemoselective α-hydroxy hydrogen atom abstraction. The generated α-amino ketyl radicals were subsequently intercepted by electron-demanding alkenes (e.g., acrylate) and oxidized by a hypervalent iodine species afterwards, ultimately forming γ-oxo-δ-amino esters. The developed methodology furnished a variety of novel, unnatural δ-amino acid derivatives in good to very good yields (34 examples, 12–93% yield) and with up to complete stereoretention (e.r. up to >99:1) of the α-amino stereo center. In addition, the products obtained could be further functionalized in a variety of ways, e.g.,

granting access to Fmoc-protected δ-amino acid derivatives that can be applied to solid-phase peptide synthesis. To the best of our knowledge, the approach of chemoselective α-hydroxy C_{sp}^3–H abstraction on β-amino alcohols has not been reported before. It is expected that this novel concept and its way of stereoretentively accessing α-amino ketyl radicals will find application in further scientific contexts soon.

The results of this project were successfully published this year in *ACS Catalysis*.[234]

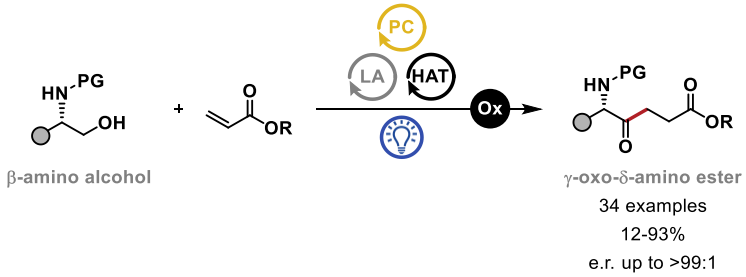


Figure 75. Project summary for the synthesis of γ-oxo-δ-amino esters.

Total syntheses of manzacidin A/C & aliskiren

To prove the applicability of the developed methodologies, approaches towards two novel total syntheses of bromoalkaloid manzacidin A/C and renin inhibitor aliskiren were undertaken. For both total syntheses, retrosynthetic analysis revealed the possible application of the decarboxylative Giese-type reaction developed for the diastereocontrolled synthesis of unnatural α-AAs. Additionally, for the total synthesis of aliskiren the use of a HAT-catalyzed α-oxo-functionalization as developed for the stereoretentive synthesis of unnatural δ-AAs was identified as a possible key step.

Even though both syntheses were not completed, the key decarboxylative Giese-type reaction was successfully implemented in both total synthetic approaches, thus confirming its applicability to more complex systems.

Conclusions

Aim of this thesis was the development of novel, photoredox-mediated strategies to access enantiopure UAAs. These goals were achieved. Two novel, operationally-simple approaches for the synthesis of enantiomerically-pure (γ-oxo)-α-amino acid derivatives were developed, one of which was proven to be applicable in two different total synthetic approaches. Furthermore, with the development of a chemoselective hydrogen atom abstraction of β-amino alcohols, a new possibility for the preparation of α-amino ketyl radicals for the stereoretentive synthesis of γ-oxo-δ-amino esters was presented. This approach, as a new state-of-the-art concept to access α-amino ketyl radicals under photoredox conditions, is expected to inspire further research projects making use of this versatile intermediate.

VI. Experimental Section

VI.I. Used Materials and Equipment

Solvents & Reagents

Prior using, dry solvents such as CH_2Cl_2, MeCN, THF and Et_2O were purified by the solvent purification system MB-SPS 800 from *MBraun GmbH*, stored over molecular sieves and transferred under N_2 atmosphere. Other dry solvents were purchased commercially and used without further workup. Cyclohexane and ethyl acetate used for flash column chromatographic purposes were distilled before use. Commercially purchased reactants were used without further workup. Self-made compounds were checked for purity prior using.

Reaction set up

Reactions sensitive to oxygen or moisture were carried out under nitrogen atmosphere. Heating of the reaction solutions was performed using an oil bath filled with paraffin oil. Here, temperature control was ensured by a contact thermometer. For reactions that required cooling, appropriate cooling baths were prepared in suitable plastic or Dewar vessels or the cryostat FT902 from *Julabo* GmbH was used. For example, ice and ice-NaCl baths were used for temperatures from 0 °C to -15 °C, while a mixture of acetone and dry ice was used for temperatures down to -78 °C. The temperature was controlled by using a cooling thermometer. Photoreactions were performed in suitable air-tight vials (4–20 mL). Blue LEDs (32 W, λ_{max} = 440 nm and λ_{max} = 450 nm) were used in combination with an EvoluChem™ PhotoRedOx box. The reaction temperature could be adjusted to 27 °C (integrated fan on) or 42 °C (fan off).

Analytics

Thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60, F_{254} or ALUGRAM® ALOX N / UV_{254}). The plates were evaluated under UV light (254 nm) or by staining with basic KMnO4, ninhydrin, cer ammonium molybdate (CAM) or *p*-anisaldehyde solutions followed by heating.

For flash column chromatographic purification silica gel (40 - 60 µm) or neutral alumina (Brockmann Grade I, 58 Å) was used. For some special reactions, the silica gel was deactivated in advance. For this purpose, the silica gel was first conditioned with a 1% Et_3N solution in cyclohexane and then the excess Et_3N was washed off with pure cyclohexane. If not otherwise stated, cyclohexane and ethyl acetate were used as eluent system.

NMR spectroscopic spectra were recorded using a *Bruker Avance III 600* and a *Bruker Avance 400*. ^{1}H NMR spectra were measured at 400 MHz or 600 MHz and ^{13}C NMR spectra at 101 MHz or 151 MHz, while ^{19}F NMR spectra were recorded at 376 MHz, and ^{11}B NMR spectra at 128 MHz.

The chemical shifts are given in ppm, relative to the solvent signal, whereas coupling constants *J* are reported in Hz. The multiplicities found are abbreviated according to the standard notation. If not otherwise stated, the measurements were performed at 300 K.

For high-resolution mass spectroscopy (HRMS), a *Bruker micrOTOF* with ESI ionization (positive) was used

IR spectrometry was performed on a *Bruker ALPHA* using attenuated total reflexion (ATR). Analysis of the measured spectra was performed by using the software *OPUS 7.5*. The found peaks were classified according to their relative strength as weak (w), medium (m) and strong (s).

For chiral compounds, a *P8000-T* polarimeter from *A. Krüss Optronic GmbH* was used for the determination of the optical rotation at 20 °C. Here, the samples were dissolved beforehand in the given solvents and concentrations (c = g / 100 mL)

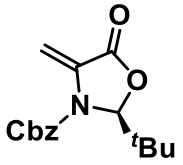
Enantiomeric excess was determined by using a HPLC system from *Agilent Technologies* (*1260 Infinity II*). To do so, chiral prepacked columns (CHIRALPAK IA and CHIRALCEL OJ-H) from *Daicel Chemical Industries Ltd.* were used.

UV/Vis absorption spectrometry was conducted using a *Mettler Toledo UV5* and the Stern-Volmer experiments were performed using a *JASCO FP 8300* spectrofluorometer.

VI.II (γ-Oxo-)α-Amino Acids via Decarboxylative Giese-type Reactions

VI.II.1 – Syntheses and Characterizations of Starting Materials

Benzyl (S)-2-(*tert*-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (28)



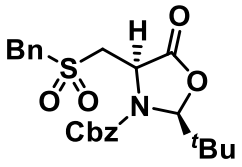
$C_{16}H_{19}NO_4$
289,33 g/mol

Following a slightly modified literature procedure,[142] **34** (2.55 g, 5.7 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (150 mL, 0.04 M) and cooled down in an ice-bath. Dropwise via a syringe, added DBU (2 mL, 13.4 mmol, 2.3 equiv.) over a period of 5 min. After 15 min, TLC analysis revealed full consumption of the starting material. While still stirring in an ice-bath, added 80 mL of a satd. NH_4Cl-solution and let stir for additional 20 min. The organic layer was then separated and the aqueous layer was washed with CH_2Cl_2, before the combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography afforded the product as a colorless oil in 83% yield (1.37 g, 4.7 mmol). The analytical data are in agreement with those previously reported.[268]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.36 (m, 5H), 5.72 (d, *J* = 1.0 Hz, 1H), 5.68 (s, 1H), 5.67 (s, 1H), 5.26 (d, *J* = 1.9 Hz, 2H), 0.93 (s, 9H).

R_f (cyHex/EtOAc, 5:1) = 0.48 [UV]

Benzyl (2S,4R)-4-((benzylsulfonyl)methyl)-2-(*tert*-butyl)-5-oxo-oxazolidine-3-carboxylate (34)



$C_{23}H_{27}NO_6S$
445,53 g/mol

Following a slightly modified literature procedure,[142] a 1 l three-necked-flask was charged with *S*-benzyl-*L*-cysteine (10.1 g, 47.8 mmol, 1.0 equiv.) and sodium hydroxide (1.8 g, 45.0 mmol, 0.94 equiv.). The flask was then shortly evacuated and backfilled with N_2. This was repeated three times. Then, 600 mL dry MeOH was added and the suspension was stirred for 30 min at

room temperature to receive a clear, nearly colorless solution. To this solution, added 50 g preactivated 3 Å molecular sieves, followed by pivaldehyde (10.0 mL, 91.7 mmol, 1.9 equiv.). The reaction was stirred at room temperature for 4 days. ^{1}H NMR analysis of the crude suggested a 1.4:1 ratio of product vs. starting material. The reaction mixture was filtered through Celite® and the yellow filtrate was concentrated in vacuum. The resulting beige-yellow solid was redissolved in 470 mL dry CH_2Cl_2 and cooled down to 0 °C, using a cryostat. Under a N_2-atmosphere, CbzCl (10.0 mL, 71.5 mmol, 1.5 equiv.) was added over a period of 5 min, before letting stir the reaction mixture at 0 °C for 18 h and additional 24 h at room temperature. To the reaction mixture, added 250 mL 1 M NaOH solution and separated the organic layer. The aqueous layer was washed with CH_2Cl_2 (3 x 50 mL), before the combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography afforded the intermediate oxazolidinone **33** (~5.2 g, R_f (cyHex/EtOAc, 2:1) = 0.67 [p-Anisaldehyde]) as a mixture of diastereomers, which was directly used for the next reaction step.

The crude mixture of **33** was dissolved in 400 mL CH_2Cl_2 to give a clear, light-yellow solution. To this, added mCPBA (≥ 77%, 5.05 g, 29.3 mmol, ~2.3 equiv.) and let stir the reaction mixture for 28 h at room temperature. Then, added 300 mL 1 M NaOH solution and separated the organic layer. The aqueous layer was washed with CH_2Cl_2, before the combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography afforded the product as a highly-viscous, white oil in 12% yield (2.55 g, 5.7 mmol, containing cyHex) over 3 steps. The analytical data are in agreement with those previously reported.[142]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 – 7.32 (m, 10H), 5.62 (s, 1H), 5.28 (d, *J* = 12.1, 1H), 5.21 (d, *J* = 11.9, 1H), 5.08 (dd, *J* = 8.1, 4.1, 1H), 4.66 (d, *J* = 14.1, 1H), 4.42 (d, *J* = 14.1, 1H), 3.44 (dd, *J* = 15.3, 8.0, 1H), 3.15 (ddd, *J* = 15.3, 4.1, 1.5, 1H), 0.89 (s, 9H).

R_f (cyHex/EtOAc, 5:1) = 0.16 [UV]

VI.II.2 – Syntheses and Characterizations of Products

General procedure I (GP-I) – *Acylation protocol*

Into an 8 mL Biotage® microwave reaction vial added the corresponding acid (0.75 mmol, 1.5 equiv.), Beckwith-Karady alkene **28** (145 mg, 0.5 mmol, 1.0 equiv.), **IrF** (5.5 mg, 5 µmol, 1 mol%) and a magnetic stir bar before sealing it with a septum cap. The reaction vial was then evacuated and backfilled with N_2 for 1 min each. This was repeated three times. Afterwards, 2,6-lutidine (115 µL, 1.0 mmol, 2.0 equiv.) and dry and degassed 1,4-dioxane (2.5 mL, 0.2 M) were added to the reaction mixture, which was then sparged with N_2 for 2-5 min. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 440 nm) at room temperature for 16 h. After the irradiation was done, the reaction mixture was combined with a mixture of H_2O and a saturated brine solution (ca. 15 mL) before extracting the organic phase with EtOAc (ca. 3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. Purification via flash column chromatography over silica gel afforded the desired product.

General procedure II (GP-II) – *Alkylation protocol*

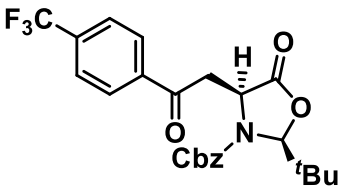
Into an 8 mL Biotage® microwave reaction vial added the corresponding acid (1.0 mmol, 2.0 equiv.), Beckwith-Karady alkene **28** (145 mg, 0.5 mmol, 1.0 equiv.), **IrF** (5.5 mg, 5 µmol, 1 mol%), K_2HPO_4 (209 mg, 1.2 mmol, 2.4 equiv.) and a magnetic stir bar before sealing it with a septum cap. The reaction vial was then evacuated and backfilled with N_2 for 1 min each. This was repeated three times. Afterwards, dry and degassed 1,4-dioxane (5.0 mL, 0.1 M) was added to the reaction mixture, which was then sparged with N_2 for 2-5 min. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 440 nm) at 42 °C for 16 h. After the irradiation was done, the reaction mixture was combined with a mixture of H_2O and a saturated brine solution (ca. 15 mL) before extracting the organic phase with EtOAc (ca. 3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. Purification via flash column chromatography over silica gel afforded the desired product.

General procedure III (GP-III) – *Alkylation protocol*

Into an 8 mL Biotage® microwave reaction vial added the corresponding acid (1.0 mmol, 2.0 equiv.), Beckwith-Karady alkene **28** (145 mg, 0.5 mmol, 1.0 equiv.), **IrF** (5.5 mg, 5 µmol, 1 mol%), K_2HPO_4 (209 mg, 1.2 mmol, 2.4 equiv.) and a magnetic stir bar before sealing it with a septum cap. The reaction vial was then evacuated and backfilled with N_2 for 1 min each. This was repeated three times. Afterwards, dry and degassed DMSO (2.5 mL, 0.2 M) was added to the reaction mixture, which was then sparged with N_2 for 2-5 min. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 440 nm) at 42 °C for 16 h. After the irradiation was done, the reaction mixture was combined with a mixture of H_2O and a saturated brine

solution (ca. 15 mL) before extracting the organic phase with EtOAc (ca. 3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. Purification via flash column chromatography over silica gel afforded the desired product.

Benzyl (2S,4S)-2-(*tert*-butyl)-5-oxo-4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-oxazolidine-3-carboxylate (42)



$C_{24}H_{24}F_3NO_5$
463,45 g/mol

Synthesized following **GP-I** using 2-oxo-2-(4-(trifluoromethyl)phenyl)acetic acid (164 mg, 0.75 mmol, 1.5 equiv.). Purification via flash chromatography afforded the product as a yellow oil in 30% yield (70 mg, 0.15 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.32 – 7.27 (m, 3H), 7.24 – 7.19 (m, 2H), 5.63 (s, 1H), 5.18 (dd, *J* = 6.8, 5.2 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 5.03 (d, *J* = 12.0 Hz, 1H), 3.54 (dd, *J* = 16.3, 6.9 Hz, 1H), 3.39 (dd, *J* = 16.2, 5.2 Hz, 1H), 1.02 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 194.1, 171.9, 155.6, 139.1 (q, $J_{C\text{-}F}$ = 1 Hz), 135.1, 134.9 (q, $J_{C\text{-}F}$ = 33 Hz), 128.8, 128.8, 128.7, 128.6, 126.0 (q, $J_{C\text{-}F}$ = 4 Hz), 123.6 (q, $J_{C\text{-}F}$ = 273 Hz), 96.5, 68.6, 53.9, 42.2, 37.6, 24.9.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -63.21.

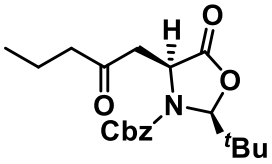
HRMS (ESI): [m/z] calculated for $C_{24}H_{24}F_3NNaO_5^+$ ([M+Na]$^+$): 486.1499; Found: 486.1497.

IR: ṽ [cm^{-1}] = 2975 (w), 1792 (s), 1721 (s), 1696 (m), 1482 (w), 1456 (w), 1394 (m), 1323 (s), 1291 (s), 1235 (m), 1168 (s), 1125 (s), 1066 (s), 1042 (s), 1014 (s), 994 (m), 911 (m), 849 (m), 823 (m), 731 (s), 697 (s), 650 (w), 599 (m), 509 (m), 454 (w)

R_f (cyHex/EtOAc, 5:1) = 0.45 [Ninhydrin]

$[\alpha]_D^{20}$ = + 24.6 (ρ = 1.03, CH_2Cl_2)

Benzyl (2S,4S)-2-(*tert*-butyl)-5-oxo-4-(2-oxopentyl)oxazolidine-3-carboxylate (51)



$C_{20}H_{27}NO_5$
361,44 g/mol

Synthesized following **GP-I** using 2-oxopentanoic acid (90 mg, 0.78 mmol, 1.6 equiv.). Purification via flash chromatography afforded the product as a yellow oil in 56% yield (101 mg, 0.28 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.31 (m, 5H), 5.58 (s, 1H), 5.14 (s, 2H), 5.06 (dd, *J* = 7.6, 4.4 Hz, 1H), 2.94 (dd, *J* = 16.5, 7.6 Hz, 1H), 2.81 (dd, *J* = 16.5, 4.4 Hz, 1H), 2.47 – 2.30 (m, 2H), 1.58 (h, *J* = 7.4 Hz, 2H), 0.96 (s, 9H), 0.89 (t, *J* = 7.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 205.3, 172.3, 155.6, 135.3, 128.8, 128.8, 128.6, 96.3, 68.5, 53.3, 45.5, 45.3, 37.5, 24.8, 17.2, 13.7.

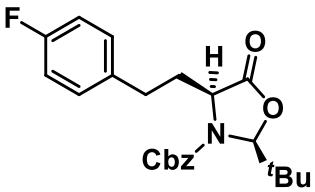
HRMS (ESI): [m/z] calculated for $C_{20}H_{27}NNaO_5^+$ ([M+Na]$^+$): 384.1781; Found: 384.1778.

IR: ṽ [cm^{-1}] = 2965 (m), 2876 (w), 1792 (s), 1715 (s), 1481 (w), 1457 (w), 1393 (s), 1345 (s), 1287 (s), 1233 (m), 1197 (s), 1175 (s), 1123 (s), 1080 (m), 1035 (s), 1015 (s), 972 (s), 780 (m), 737 (m), 697 (s), 631 (w), 580 (w), 506 (m), 454 (m), 436 (m).

R_f (cyHex/EtOAc, 5:1) = 0.34 [Ninhydrin]

$[\alpha]_D^{20}$ = + 19.6 (ρ = 0.97, CH_2Cl_2)

(2S,4S)-Benzyl-2-(*tert*-butyl)-4-(4-fluorophenethyl)-5-oxooxazolidine-3-carboxylate (59)



$C_{23}H_{26}FNO_4$
399,46 g/mol

Synthesized following **GP-II** using 4-fluorophenylacetic acid (154 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography afforded the product as a yellow oil in 66% yield (134 mg, 0.34 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.35 (m, 3H), 7.33 – 7.28 (m, 2H), 7.15 – 7.09 (m, 2H), 6.96 – 6.89 (m, 2H), 5.55 (s, 1H), 5.14 (s, 2H), 4.26 (dd, *J* = 8.7, 6.0 Hz, 1H), 2.94 (ddd, *J* = 14.8, 9.9, 5.3 Hz, 1H), 2.84 (ddd, *J* = 14.1, 9.3, 7.6 Hz, 1H), 2.26 – 2.08 (m, 2H), 0.97 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 172.5, 161.6 (d, J_{C-F} = 244 Hz), 156.0, 136.3 (d, J_{C-F} = 3 Hz), 135.4, 130.0 (d, J_{C-F} = 8 Hz), 128.9, 128.8, 128.6, 115.4 (d, J_{C-F} = 21 Hz), 96.4, 68.5, 56.4, 37.2, 34.9, 31.5, 25.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -117.08.

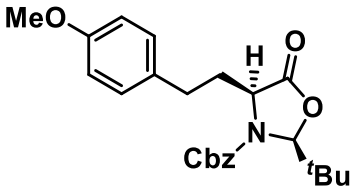
HRMS (ESI): [m/z] calculated for $C_{23}H_{26}FNNaO_4^+$ ($[M+Na]^+$): 422.1738; Found: 422.1745.

IR: ṽ [cm^{-1}] = 2963 (w), 2873 (w), 1788 (s), 1716 (s), 1602 (w), 1509 (s), 1481 (m), 1454 (m), 1391 (s), 1329 (s), 1292 (s), 1221 (s), 1197 (s), 1159 (s), 1119 (m), 1042 (s), 1011 (s), 971 (s), 834 (m), 750 (s), 697 (s), 581 (w), 506 (m), 482 (m).

R_f (cyHex/EtOAc, 5:1) = 0.36 [UV]

$[\alpha]_D^{20}$ = + 37.8 (ρ = 1.05, CH_2Cl_2)

(2S,4S)-Benzyl-2-(*tert*-butyl)-4-(4-methoxyphenethyl)-5-oxooxazolidine-3-carboxylate (60)



$C_{24}H_{29}NO_5$
411,50 g/mol

Synthesized following **GP-II** using 2-(4-methoxyphenyl)acetic acid (167 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography afforded the product as a yellow oil in 91% yield (186 mg, 0.45 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.34 (m, 3H), 7.32 – 7.28 (m, 2H), 7.12 – 7.07 (m, 2H), 6.83 – 6.77 (m, 2H), 5.55 (s, 1H), 5.14 (s, 2H), 4.28 (dd, *J* = 8.6, 6.1 Hz, 1H), 3.78 (s, 3H), 2.91 (ddd, *J* = 14.9, 10.0, 5.3 Hz, 1H), 2.81 (ddd, *J* = 14.0, 9.5, 7.4 Hz, 1H), 2.25 – 2.07 (m, 2H), 0.97 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 172.7, 158.2, 156.1, 135.5, 132.7, 129.6, 128.8, 128.8, 128.6, 114.0, 96.4, 68.4, 56.5, 55.4, 37.2, 35.2, 31.5, 25.1.

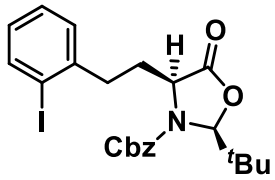
HRMS (ESI): [m/z] calculated for $C_{24}H_{29}NNaO_5^+$ ($[M+Na]^+$): 434.1938; Found: 434.1938.

IR: ṽ [cm^{-1}] = 2960 (w), 1788 (s), 1715 (s), 1611 (w), 1512 (s), 1455 (m), 1391 (m), 1328 (s), 1296 (s), 1243 (s), 1229 (s), 1197 (s), 1174 (s), 1119 (m), 1034 (s), 971 (s), 890 (w), 834 (m), 747 (m), 697 (s), 636 (w), 581 (w), 555 (w), 510 (m), 454 (w).

R_f (cyHex/EtOAc, 5:1) = 0.33 [UV]

$[\alpha]_D^{20}$ = + 63.5 (ρ = 1.07, CH_2Cl_2)

(2S,4S)-Benzyl-2-(*tert*-butyl)-4-(2-iodophenethyl)-5-oxooxazolidine-3-carboxylate (61)



$C_{23}H_{26}INO_4$
507,37 g/mol

Synthesized following **GP-II** using 2-(2-iodophenyl)acetic acid (262 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography afforded the product as a colorless oil in 40% yield (102 mg, 0.20 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.77 (m, 1H), 7.38 – 7.30 (m, 5H), 7.28 – 7.21 (m, 2H), 6.89 (ddd, *J* = 7.9, 6.6, 2.4 Hz, 1H), 5.58 (s, 1H), 5.16 (q, *J* = 12.0 Hz, 2H), 4.34 (t, *J* = 7.4 Hz, 1H), 3.10 (ddd, *J* = 13.8, 9.9, 6.2 Hz, 1H), 2.96 (ddd, *J* = 13.7, 9.9, 7.2 Hz, 1H), 2.21 – 2.11 (m, 2H), 0.99 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.5, 156.1, 143.5, 139.8, 135.5, 129.8, 128.9, 128.8, 128.7, 128.6, 128.3, 100.4, 96.6, 68.5, 56.6, 37.6, 37.2, 33.6, 25.1.

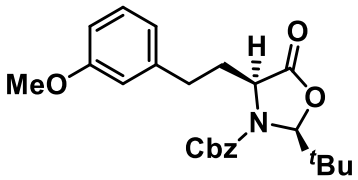
HRMS (ESI): [m/z] calculated for $C_{23}H_{26}INNaO_4^+$ ([M+Na]$^+$): 530.0799; Found: 530.0793.

IR: ṽ [cm^{-1}] = 2963 (w), 2873 (w), 1787 (s), 1715 (s), 1465 (m), 1390 (m), 1327 (s), 1290 (s), 1226 (s), 1196 (s), 1168 (m), 1114 (m), 1042 (s), 1005 (s), 970 (s), 749 (s), 696 (s), 645 (m), 581 (w), 507 (m), 446 (m).

R_f (cyHex/EtOAc, 5:1) = 0.43 [UV]

$[\alpha]_D^{20}$ = + 35.9 (ρ = 0.98, CH_2Cl_2)

(2S,4S)-Benzyl-2-(*tert*-butyl)-4-(3-methoxyphenethyl)-5-oxooxazolidine-3-carboxylate (62)



$C_{24}H_{29}NO_5$
411,50 g/mol

Synthesized following **GP-II** using 2-(3-methoxyphenyl)acetic acid (166 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography afforded the product as a yellow oil in 59% yield (121 mg, 0.29 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 – 7.34 (m, 3H), 7.33 – 7.29 (m, 2H), 7.19 (td, *J* = 7.5, 1.0 Hz, 1H), 6.80 – 6.73 (m, 3H), 5.55 (s, 1H), 5.15 (s, 2H), 4.33 – 4.28 (m, 1H), 3.79 (s, 3H), 2.96

(ddd, *J* = 15.0, 10.4, 5.1 Hz, 1H), 2.84 (ddd, *J* = 13.9, 10.0, 7.1 Hz, 1H), 2.23 (dddd, *J* = 13.7, 10.1, 8.6, 5.1 Hz, 1H), 2.16 (dddd, *J* = 13.4, 10.4, 7.1, 6.1 Hz, 1H), 0.97 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 172.6, 159.9, 156.0, 142.4, 135.5, 129.6, 128.8, 128.8, 128.6, 121.0, 114.5, 111.7, 96.4, 68.4, 56.6, 55.3, 37.1, 34.9, 32.5, 25.1.

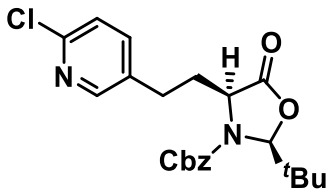
HRMS (ESI): [m/z] calculated for $C_{24}H_{29}NNaO_5^+$ ($[M+Na]^+$): 434.1938; Found: 434.1940.

IR: ṽ [cm^{-1}] = 2961 (w), 2873 (w), 1788 (s), 1715 (s), 1600 (m), 1585 (m), 1484 (m), 1454 (m), 1391 (s), 1327 (s), 1291 (s), 1259 (s), 1227 (s), 1197 (s), 1165 (s), 1155 (s), 1120 (m), 1041 (s), 1011 (s), 971 (s), 872 (m), 781 (m), 737 (m), 696 (s), 579 (m), 505 (m), 452 (m).

R_f (cyHex/EtOAc, 5:1) = 0.27 [$KMnO_4$]

$[\alpha]_D^{20}$ = + 45.6 (ρ = 1.01, CH_2Cl_2)

(2S,4S)-Benzyl-2-(*tert*-butyl)-4-(2-(6-chloropyridin-3-yl)ethyl)-5-oxooxazolidine-3-carboxylate (63)



$C_{22}H_{25}ClN_2O_4$
416,90 g/mol

Synthesized following **GP-III** using 2-(6-chloropyridin-3-yl)acetic acid (172 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography afforded the product as a yellowish, highly-viscous oil in 78% yield (163 mg, 0.39 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 2.5 Hz, 1H), 7.45 – 7.29 (m, 6H), 7.18 (d, *J* = 8.2 Hz, 1H), 5.56 (s, 1H), 5.14 (d, *J* = 2.3 Hz, 2H), 4.23 (dd, *J* = 8.5, 6.0 Hz, 1H), 2.95 (ddd, *J* = 15.0, 9.9, 5.4 Hz, 1H), 2.85 (ddd, *J* = 14.3, 9.4, 7.4 Hz, 1H), 2.26 – 2.06 (m, 2H), 0.96 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 172.3, 155.9, 149.8, 149.7, 138.9, 135.2, 134.8, 129.0, 128.9, 128.7, 124.1, 96.5, 68.7, 56.3, 37.2, 34.2, 28.8, 25.0.

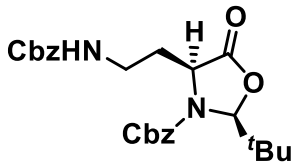
HRMS (ESI): [m/z] calculated for $C_{22}H_{25}ClN_2NaO_4^+$ ($[M+Na]^+$): 439.1395; Found: 439.1404.

IR: ṽ [cm^{-1}] = 2962 (w), 2873 (w), 1787 (s), 1716 (s), 1586 (w), 1565 (w), 1457 (s), 1389 (s), 1369 (m), 1327 (s), 1285 (s), 1228 (s), 1197 (s), 1173 (m), 1106 (s), 1043 (s), 970 (m), 913 (m), 890 (w), 838 (w), 820 (w), 785 (w), 733 (s), 697 (s), 632 (w), 581 (w), 529 (w), 506 (w), 455 (w), 413 (w).

R_f (cyHex/EtOAc, 5:1) = 0.11 [$KMnO_4$]

$[\alpha]_D^{20}$ = + 33.8 (ρ = 0.99, CH_2Cl_2)

Benzyl (2S,4S)-4-(2-(((benzyloxy)carbonyl)amino)ethyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (68)



$C_{25}H_{30}N_2O_6$
454,52 g/mol

Synthesized following **GP-III** using ((benzyloxy)carbonyl)glycine (210 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography afforded the product as a light-yellow oil in 78% yield (178 mg, 0.39 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.29 (m, 10H), 5.57 (s, 1H), 5.17 (d, *J* = 1.3 Hz, 2H), 5.14 – 5.04 (m, 2H), 4.39 (dd, *J* = 8.9, 5.8 Hz, 1H), 3.65 – 3.52 (m, 1H), 3.26 – 3.16 (m, 1H), 2.20 – 2.10 (m, 1H), 2.03 – 1.93 (m, 1H), 0.94 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.5, 156.5, 156.5, 136.8, 135.0, 129.0, 129.0, 128.8, 128.7, 128.6, 128.3, 128.2, 127.8, 127.1, 96.8, 69.0, 66.8, 55.6, 38.0, 37.0, 33.3, 25.1.

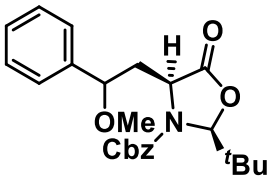
HRMS (ESI): [m/z] calculated for $C_{25}H_{30}N_2NaO_6^+$ ([M+Na]$^+$): 477.1996; Found: 477.2018.

IR: ṽ [cm^{-1}] = 3417 (w), 3365 (w), 2971 (w), 1788 (s), 1703 (s), 1512 (m), 1454 (m), 1393 (m), 1327 (s), 1291 (s), 1228 (s), 1191 (s), 1126 (m), 1084 (m), 1035 (s), 1006 (s), 970 (m), 912 (m), 775 (m), 736 (s), 696 (s), 580 (m), 504 (m), 453 (m).

R_f (cyHex/EtOAc, 5:1) = 0.21 [Ninhydrin]

$[\alpha]_D^{20}$ = *No exact measurement possible*

(2S,4S)-Benzyl-2-(*tert*-butyl)-4-((S)-2-methoxy-2-phenylethyl)-5-oxooxazolidine-3-carboxylate (75)



$C_{24}H_{29}NO_5$
411,50 g/mol

Synthesized following **GP-III** using (S)-2-methoxy-2-phenylacetic acid (166 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography afforded the product as a 1.5:1 diastereomeric mixture – based on calculation from the ^{1}H NMR spectrum of the crude reaction mixture – and was isolated as a slightly yellowish, highly viscous oil in 76% yield (157 mg, 0.38 mmol).

^{1}H NMR (400 MHz, $CDCl_3$, *mayor isomer*): δ 7.49 – 7.26 (m, 10 H), 5.54 (s, 1H), 5.09 (s, 2H), 4.51 (dd, *J* = 7.9, 6.7 Hz, 1H), 4.32 (q, *J* = 5.3, 3.9 Hz, 1H), 3.12 (s, 3H), 2.47 – 2.40 (m, 1H), 2.12 (dt, *J* = 13.8, 6.4 Hz, 1H), 0.95 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, *mayor isomer*): δ 172.8, 156.1, 140.8, 135.5, 128.8, 128.7, 128.7, 128.2, 128.0, 127.2, 96.6, 79.8, 68.4, 56.4, 54.6, 41.7, 37.2, 25.1.

R_f (cyHex/EtOAc, 5:1, *mayor isomer*) = 0.53 [$KMnO_4$]

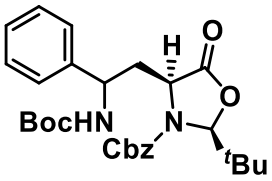
^{1}H NMR (400 MHz, $CDCl_3$, *minor isomer*): δ 7.49 – 7.26 (m, 10 H), 5.57 (s, 1H), 5.29 – 5.19 (m, 2H), 4.82 (dd, *J* = 10.2, 4.2 Hz, 1H), 4.70 (dd, *J* = 10.9, 3.0 Hz, 1H), 3.21 (s, 3H), 2.41 – 2.33 (m, 1H), 2.04 (ddd, *J* = 13.6, 10.2, 3.1 Hz, 1H), 0.94 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, *minor isomer*): δ 172.9, 155.9, 141.6, 135.7, 128.8, 128.7, 128.7, 128.5, 128.2, 126.8, 96.3, 79.4, 68.1, 56.7, 54.2, 41.9, 37.2, 25.0.

R_f (cyHex/EtOAc, 5:1, *minor isomer*) = 0.44 [$KMnO_4$]

HRMS (ESI): [m/z] calculated for $C_{24}H_{29}NNaO_5^+$ ([M+Na]$^+$): 434.1938; Found: 434.1937.

(2S,4S)-Benzyl-4-((S)-2-((*tert*-butoxycarbonyl)amino)-2-phenylethyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (76)



$C_{28}H_{36}N_2O_6$
496,60 g/mol

Synthesized following **GP-III** using (S)-2-((*tert*-butoxycarbonyl)amino)-2-phenylacetic acid (251 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography afforded the product as a 5:1 diastereomeric mixture – based on calculation from the ^{1}H NMR spectrum of the crude reaction mixture – and was isolated as a white, crystalline solid in 78% yield (193 mg, 0.39 mmol).

^{1}H NMR (400 MHz, DMSO-d_6, 354 K, *mayor isomer*): δ 7.45 – 7.15 (m, 10H), 6.94 (d, *J* = 8.1 Hz, 1H), 5.48 (s, 1H), 5.11 – 5.02 (m, 2H), 4.88 (q, *J* = 7.8 Hz, 1H), 4.24 (dd, *J* = 8.5, 5.5 Hz, 1H), 2.30 – 2.14 (m, 2H), 1.33 (s, 9H), 0.89 (s, 9H).

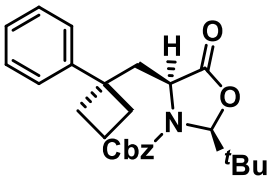
^{1}H NMR (400 MHz, DMSO-d_6, 354 K, *minor isomer*): δ 7.45 – 7.15 (m, 10H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.52 (s, 1H), 5.22 – 5.13 (m, 2H), 5.02 – 4.94 (m, 1H), 4.38 (dd, *J* = 7.5, 5.5 Hz, 1H), 2.30 – 2.14 (m, 2H), 1.35 (s, 9H), 0.89 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6, 353 K, *both isomers*): δ 171.7, 155.1, 154.4, 154.3, 142.4, 142.3, 135.5, 127.8, 127.8, 127.7, 127.6, 127.5, 127.4, 127.4, 127.2, 126.5, 126.4, 126.3, 126.2, 126.1, 95.2, 77.4, 66.9, 66.8, 54.3, 54.1, 51.6, 35.9, 27.8, 27.7, 24.2.

HRMS (ESI): [m/z] calculated for $C_{28}H_{36}N_2NaO_6^+$ ([M+Na]$^+$): 519.2466; Found: 519.2487.

R_f (cyHex/EtOAc, 5:1) = 0.26 [$KMnO_4$]

(2S,4S)-2-(*tert*-Butyl)-benzyl-5-oxo-4-((1-phenylcyclobutyl)methyl)oxazolidine-3-carboxylate (79)



$C_{26}H_{31}NO_4$
421,54 g/mol

Synthesized following **GP-III** using 1-phenylcyclobutane-1-carboxylic acid (175 mg, 0.99 mmol, 2.0 equiv.). Purification via flash chromatography afforded the product as a yellow oil in 73% yield (155 mg, 0.37 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.33 (m, 3H), 7.29 – 7.26 (m, 4H), 7.20 – 7.15 (m, 3H), 5.42 (s, 1H), 4.94 (d, *J* = 3.4 Hz, 2H), 4.03 (dd, *J* = 9.2, 4.1 Hz, 1H), 2.59 – 2.48 (m, 2H), 2.48 – 2.34 (m, 2H), 2.33 – 2.21 (m, 2H), 2.03 – 1.90 (m, 1H), 1.87 – 1.76 (m, 1H), 0.95 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.6, 155.9, 148.0, 135.7, 128.7, 128.6, 128.2, 126.6, 125.9, 96.2, 68.0, 54.8, 46.1, 45.7, 37.1, 35.7, 32.6, 25.1, 16.1.

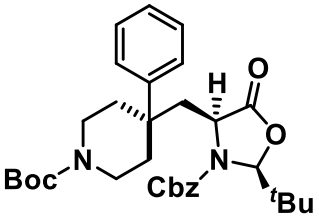
HRMS (ESI): [m/z] calculated for $C_{26}H_{31}NNaO_4^+$ ([M+Na]$^+$): 444.2145; Found: 444.2157.

IR: ṽ [cm^{-1}] = 2960 (w), 2873 (w), 1791 (s), 1715 (s), 1481 (w), 1445 (w), 1390 (m), 1350 (m), 1309 (s), 1273 (m), 1226 (s), 1194 (s), 1117 (m), 1045 (m), 1032 (m), 1012 (m), 969 (m), 915 (m), 876 (w), 764 (m), 747 (m), 698 (s), 630 (w), 594 (w), 582 (w), 557 (m), 506 (m), 451 (w).

R_f (cyHex/EtOAc, 5:1) = 0.61 [UV]

$[\alpha]_D^{20}$ = + 9.9 (ρ = 1.03, CH_2Cl_2)

(2S,4S)-Benzyl-4-((1-(*tert*-butoxycarbonyl)-4-phenylpiperidin-4-yl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (80)



$C_{32}H_{42}N_2O_6$
550,70 g/mol

Synthesized following **GP-III** using 1-(*tert*-butoxycarbonyl)-4-phenylpiperidine-4-carboxylic acid (305 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography afforded the product as a yellow oil in 87% yield (241 mg, 0.44 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.35 (m, 3H), 7.33 – 7.30 (m, 4H), 7.25 – 7.19 (m, 3H), 5.42 (s, 1H), 4.94 (s, 2H), 4.13 – 4.08 (m, 1H), 3.71 (d, *J* = 12.4 Hz, 2H), 3.07 – 2.94 (m, 1H), 2.88 (ddd, *J* = 13.6, 10.7, 2.8 Hz, 1H), 2.46 (d, *J* = 14.2 Hz, 1H), 2.26 – 2.17 (m, 2H), 2.04 – 1.98 (m, 1H), 1.86 (ddd, *J* = 14.5, 10.8, 4.0 Hz, 1H), 1.76 (ddd, *J* = 14.3, 10.8, 3.9 Hz, 1H), 1.43 (s, 9H), 0.90 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.8, 155.8, 155.0, 142.5, 135.6, 128.8, 128.8, 128.7, 128.7, 127.6, 126.6, 96.2, 79.4, 68.2, 54.0, 48.3, 40.1, 37.0, 36.9, 34.4, 28.6, 25.1.

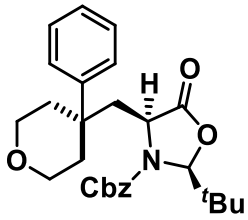
HRMS (ESI): [m/z] calculated for $C_{32}H_{42}N_2NaO_6^+$ ([M+Na]$^+$): 573.2935; Found: 573.2934.

IR: $\tilde{\nu}$ [cm^{-1}] = 2972 (w), 2935 (w), 2872 (w), 2251 (w), 1791 (m), 1717 (m), 1686 (s), 1451 (m), 1424 (m), 1391 (m), 1316 (m), 1279 (m), 1247 (m), 1230 (m), 1163 (s), 1117 (s), 1081 (m), 1041 (m), 969 (m), 911 (m), 871 (m), 823 (w), 767 (m), 730 (s), 699 (s), 646 (m), 611 (w), 538 (m), 507 (w), 458 (w).

R_f (cyHex/EtOAc, 5:1) = 0.24 [$KMnO_4$]

$[\alpha]_D^{20}$ = + 17.9 (ρ = 1.02, CH_2Cl_2)

(2S,4S)-Benzyl-2-(*tert*-butyl)-5-oxo-4-((4-phenyltetrahydro-2*H*-pyran-4-yl)methyl)-oxazolidine-3-carboxylate (81)



$C_{27}H_{33}NO_5$
451,56 g/mol

Synthesized following **GP-III** using 4-phenyltetrahydro-2*H*-pyran-4-carboxylic acid (205 mg, 0.99 mmol, 2.0 equiv.). Purification via flash chromatography afforded the product as a yellow oil in 73% yield (165 mg, 0.37 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.34 (m, 3H), 7.34 – 7.30 (m, 4H), 7.25 – 7.19 (m, 3H), 5.43 (s, 1H), 4.95 (d, *J* = 1.4 Hz, 2H), 4.15 – 4.07 (m, 1H), 3.78 – 3.67 (m, 2H), 3.54 (ddd, *J* = 12.1, 10.0, 2.5 Hz, 1H), 3.42 (ddd, *J* = 12.0, 9.9, 2.5 Hz, 1H), 2.42 (ddt, *J* = 14.3, 4.7, 2.5 Hz, 1H), 2.30 (dd, *J* = 14.4, 8.9 Hz, 1H), 2.16 (ddt, *J* = 13.9, 4.9, 2.5 Hz, 1H), 2.09 – 1.99 (m, 2H), 1.91 (ddd, *J* = 13.9, 9.9, 3.8 Hz, 1H), 0.92 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 172.8, 155.8, 143.3, 135.6, 128.8, 128.7, 128.7, 127.6, 126.6, 96.2, 68.2, 64.4, 64.3, 54.0, 48.3, 39.5, 37.9, 37.0, 35.4, 25.1.

HRMS (ESI): [m/z] calculated for $C_{27}H_{33}NNaO_5^+$ ([M+Na]$^+$): 474.2251; Found: 474.2263.

IR: $\tilde{\nu}$ [cm^{-1}] = 2957 (w), 2858 (w), 1790 (s), 1714 (s), 1497 (w), 1481 (w), 1448 (m), 1391 (m), 1348 (m), 1314 (s), 1279 (m), 1226 (m), 1194 (s), 1106 (m), 1038 (s), 1019 (m), 974 (m), 911 (m), 873 (m), 730 (s), 698 (s), 647 (w), 621 (w), 554 (m), 506 (m), 456 (w).

R_f (cyHex/EtOAc, 5:1) = 0.19 [$KMnO_4$]

$[\alpha]_D^{20}$ = + 18.2 (ρ = 0.95, CH_2Cl_2)

VI.III γ-Oxo-α-Amino Acids via Phosphoranyl Radicals

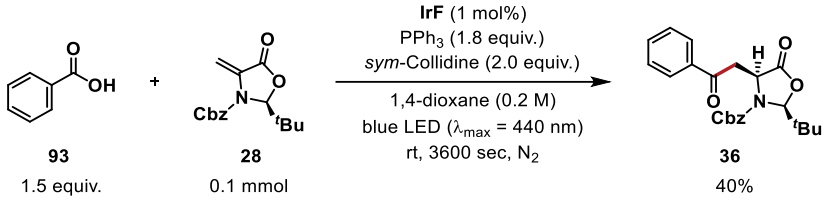
VI.III.1 – Mechanistic Investigations

Photon flux determination

To check whether the photon flux of the LED (λ_{max} = 440 nm) has changed since the last measurement, it was determined using ferrioxalate actinometry. A detailed description of the procedure can be found in **section II.I.5**. As an average of three measurements a photon flux of 8.24081 x 10^{-10} einsteins s^{-1} was determined. This is in good agreement with the previously determined photon flux of 1.1917 x 10^{-9} einsteins s^{-1}.

Quantum yield determination

To determine the quantum yield, a reaction under the standard conditions was performed (Scheme 63) using the same lamp as used for the photon flux determination. The sample was irradiated for 3600 sec. Afterwards, the reaction was diluted with 1 mL EtOAc, then methyl laureate (24.6 µL, 0.1 mmol, 1.0 equiv.) was added as internal standard and the reaction outcome was checked via GC-FID analysis. Product **36** was formed in 40% yield (4.0 x 10^{-5} mol). This reaction was performed by a colleague.



Scheme 63. Reaction performed for quantum yield determination.

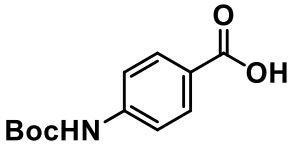
According to Equation 4, the quantum yield (Φ) of the reaction was determined.

Eq. 4 $$\Phi = \frac{\text{mol of product formed}}{\text{Photon flux} \bullet t \bullet \text{f}}$$

The photon flux is 8.24081 x 10^{-10} einsteins s^{-1} (determined via ferrioxalate actinometry as described above), t is the irradiation time (3600 s) and f is the fraction of light being absorbed by the reaction mixture using Equation 2 (see **section II.I.5**). According to experiments performed by a colleague, the absorbance value for the reaction mixture was found to be 2.19444 at 437 nm, so that f was calculated to be 0.9936. The quantum yield (Φ) of the reaction was thus calculated to be 13.57.

VI.III.2 – Synthesis and Characterization of Starting Materials

4-((*tert*-Butoxycarbonyl)amino)benzoic acid



$C_{12}H_{15}NO_4$
237,26 g/mol

Following a slightly modified literature procedure,[269] 4-Aminobenzoic acid (1.35 g, 9.84 mmol, 1.0 equiv.) was dissolved in a mixture of 1,4-dioxane/H_2O (2:1, 36 mL, 0.27 M). Added Boc_2O (3.36 g, 15.40 mmol, 1.6 equiv.) and, after stirring for 5 min, Et_3N (2 mL, 14.43 mmol, 1.5 equiv.). Under a N_2-atmosphere let stir at room temperature for 24 h. Then, the reaction mixture was concentrated in vacuum to give a nearly colorless oil, which was treated dropwise with 3 M HCl (18 mL). A white precipitate was formed, which was filtered and washed with H_2O (150 mL). After drying in vacuum, the product was isolated as a white powder in 90% yield (2.09 g, 8.81 mmol).

The analytical data are in agreement with those previously reported.[269]

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.56 (s, 1H), 9.69 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 1.48 (s, 9H).

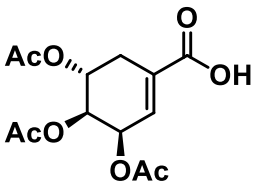
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 167.0, 152.5, 143.7, 130.3, 123.9, 117.2, 79.6, 28.0.

HRMS (ESI): [m/z] calculated for $C_{12}H_{15}NNaO_4^+$ ([M+Na]$^+$): 260.0893; Found: 260.0894.

IR: ṽ [cm^{-1}] = 3368 (w), 2979 (w), 2870 (w), 2820 (w), 2667 (w), 2538 (w), 1706 (s), 1678 (s), 1609 (m), 1589 (m), 1524 (m), 1505 (s), 1421 (m), 1410 (m), 1390 (m), 1369 (m), 1312 (m), 1286 (m), 1233 (s), 1159 (s), 1130 (m), 1054 (m), 1016 (m), 940 (m), 906 (w), 856 (m), 841 (m), 800 (w), 773 (m), 760 (m), 693 (w), 642 (m), 611 (m), 548 (m), 506 (m).

R_f (cyHex/EtOAc, 1:1) = 0.31 [$KMnO_4$]

(3R,4S,5R)-3,4,5-Triacetoxycyclohex-1-ene-1-carboxylic acid



$C_{13}H_{16}O_8$
300,26 g/mol

According to a literature procedure,[270] (3R,4S,5R)-3,4,5-trihydroxycyclohex-1-ene-1-carboxylic acid (820 mg, 4.7 mmol, 1.0 equiv.) was treated with pyridine (12 mL, 148.7 mmol,

31.6 equiv.) and Ac_2O (6 mL, 84.1 mmol, 17.9 equiv.) under a N_2-atmosphere. Let stir at room temperature for 24 h. The reaction mixture was concentrated in vacuum. Here, toluene (2 mL) was added to help with removing pyridine residues. To the orange residue added EtOAc (100 mL). Washed with 1 M HCl (2 x 50 mL) and brine (50 mL), then dried org. layer over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography afforded the product as a colorless, foamy oil in 71% yield (1.01 g, 3.36 mmol, containing ~12% EtOAc).

The analytical data are in agreement with those previously reported.[270]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 – 6.84 (m, 1H), 5.77 – 5.73 (m, 1H), 5.32 – 5.25 (m, 2H), 2.89 (ddt, *J* = 19.1, 4.8, 1.9 Hz, 1H), 2.47 – 2.39 (m, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 170.1, 169.9, 169.9, 169.9, 135.0, 130.6, 67.5, 66.7, 66.0, 28.0, 20.9, 20.7, 20.7.

HRMS (ESI): [m/z] calculated for $C_{13}H_{16}NaO_8^+$ ($[M+Na]^+$): 323.0737; Found: 323.0741.

IR: ṽ [cm^{-1}] = 2942 (w), 1725 (s), 1700 (s), 1657 (m), 1429 (w), 1369 (m), 1212 (s), 1146 (m), 1107 (m), 1073 (m), 1034 (s), 938 (m), 910 (m), 835 (m), 778 (w), 739 (m), 645 (m), 624 (m), 601 (m), 522 (w), 446 (m), 413 (m).

R_f (EtOAc) = 0.18 [$KMnO_4$]

VI.III.3 – Synthesis and Characterization of Products

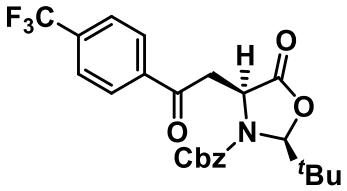
General procedure IV (GP-IV)

Into an 8 mL Biotage® microwave reaction vial added the corresponding acid (0.75 mmol, 1.5 equiv.), Beckwith-Karady alkene **28** (145 mg, 0.50 mmol, 1.0 equiv.), PPh_3 (235 mg, 0.90 mmol, 1.8 equiv.), **IrF** (5.5 mg, 5 µmol, 1 mol%) and a magnetic stir bar before sealing it with a septum cap. The reaction vial was then evacuated and backfilled with N_2 for 1 min each. This was repeated three times. Afterwards, *sym*-collidine (132 µL, 1.00 mmol, 2.0 equiv.) and dry and degassed 1,4-dioxane (2.5 mL, 0.2 M) were added to the reaction mixture, which was then sparged with N_2 for 2-5 min. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 440 nm or 32 W, λ_{max} = 450 nm) at room temperature for 24 h. After the irradiation was done, the reaction mixture was concentrated in vacuum. Purification via flash column chromatography over silica gel afforded the desired product.

General procedure V (GP-V)

Into an 8 mL Biotage® microwave reaction vial added the corresponding acid (0.75 mmol, 1.5 equiv.), Beckwith-Karady alkene **28** (145 mg, 0.50 mmol, 1.0 equiv.), PPh_3 (235 mg, 0.90 mmol, 1.8 equiv.), **IrF** (5.5 mg, 5 µmol, 1 mol%) and a magnetic stir bar before sealing it with a septum cap. The reaction vial was then evacuated and backfilled with N_2 for 1 min each. This was repeated three times. Afterwards, *sym*-collidine (132 µL, 1.00 mmol, 2.0 equiv.) and dry and degassed DMF (2.5 mL, 0.2 M) were added to the reaction mixture, which was then sparged with N_2 for 2-5 min. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 440 nm or 32 W, λ_{max} = 450 nm) at room temperature for 24 h. After the irradiation was done, the reaction mixture was concentrated in vacuum. Purification via flash column chromatography over silica gel afforded the desired product.

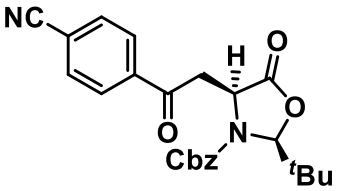
Benzyl (2S,4S)-2-(*tert*-butyl)-5-oxo-4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl) oxazolidine-3-carboxylate (42)



$C_{24}H_{24}F_3NO_5$
463,45 g/mol

Synthesized following **GP-IV** using 4-(trifluoromethyl)benzoic acid (142 mg, 0.75 mmol, 1.5 equiv.) with 48 h of irradiation. Purification via flash chromatography afforded the product as a yellow oil in 61% yield (141 mg, 0.30 mmol). The analytical data are in agreement with those reported in **section VI.II.2**.

Benzyl (2S,4S)-2-(*tert*-butyl)-4-(2-(4-cyanophenyl)-2-oxoethyl)-5-oxooxazolidine-3-carboxylate (43)



$C_{24}H_{24}N_2O_5$
420,47 g/mol

Synthesized following **GP-IV** using 4-cyanobenzoic acid (111 mg, 0.75 mmol, 1.5 equiv.) with 48 h of irradiation. Purification via flash chromatography afforded the product as an off-white solid in 35% yield (73 mg, 0.17 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.29 (m, 3H), 7.25 – 7.21 (m, 2H), 5.62 (s, 1H), 5.16 (dd, *J* = 7.0, 5.1 Hz, 1H), 5.10 (d, *J* = 11.9 Hz, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 3.53 (dd, *J* = 16.2, 7.0 Hz, 1H), 3.37 (dd, *J* = 16.2, 5.1 Hz, 1H), 1.01 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 193.8, 171.8, 155.6, 139.3, 135.0, 132.7, 128.9, 128.8, 128.7, 128.6, 117.9, 116.9, 96.5, 68.6, 53.8, 42.1, 37.6, 24.9.

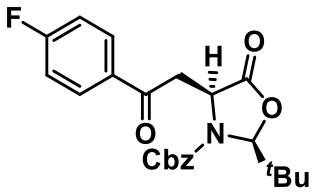
HRMS (ESI): [m/z] calculated for $C_{24}H_{24}N_2NaO_5^+$ ([M+Na]$^+$): 443.1577; Found: 443.1580.

IR: ṽ [cm-1] = 2964 (w), 2875 (w), 2230 (w), 1790 (s), 1719 (s), 1695 (s), 1607 (w), 1567 (w), 1498 (w), 1481 (m), 1455 (m), 1394 (s), 1336 (s), 1289 (s), 1269 (s), 1233 (s), 1198 (s), 1174 (s), 1119 (s), 1069 (m), 1041 (s), 1016 (s), 996 (s), 890 (m), 844 (m) , 821 (m), 782 (m), 749 (s), 697 (s), 636 (m), 567 (m), 545 (m), 532 (m), 505 (m), 455 (m).

R_f (cyclohexane/EtOAc, 4:1) = 0.30 [$KMnO_4$]

$[\alpha]_D^{20}$ = + 38.7 (ρ = 0.99, CH_2Cl_2)

Benzyl (2S,4S)-2-(*tert*-butyl)-4-(2-(4-fluorophenyl)-2-oxoethyl)-5-oxooxazolidine-3-carboxylate (96)



$C_{23}H_{24}FNO_5$
413,45 g/mol

Synthesized following **GP-IV** using 4-fluorobenzoic acid (105 mg, 0.75 mmol, 1.5 equiv.). Purification via flash chromatography afforded the product as a yellowish oil in 61% yield (127 mg, 0.31 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.89 (m, 2H), 7.33 – 7.28 (m, 3H), 7.25 – 7.21 (m, 2H), 7.14 – 7.07 (m, 2H), 5.62 (s, 1H), 5.21 (dd, *J* = 7.0, 5.0 Hz, 1H), 5.11 (d, *J* = 12.1 Hz, 1H), 5.03 (d, *J* = 12.1 Hz, 1H), 3.51 (dd, *J* = 16.3, 7.0 Hz, 1H), 3.34 (dd, *J* = 16.2, 5.0 Hz, 1H), 1.01 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 193.3, 172.1, 166.1 (d, $J_{C\text{-}F}$ = 256 Hz), 155.6, 135.2, 132.8 (d, $J_{C\text{-}F}$ = 3 Hz), 131.0 (d, $J_{C\text{-}F}$ = 9 Hz), 128.8, 128.7, 128.5, 116.0 (d, $J_{C\text{-}F}$ = 22 Hz), 96.4, 68.5, 53.8, 41.9, 37.6, 24.9.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -104.42.

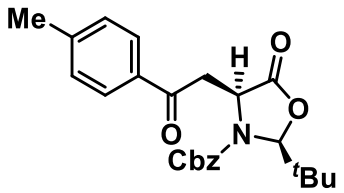
HRMS (ESI): [m/z] calculated for $C_{23}H_{24}FNNaO_5^+$ ([M+Na]$^+$): 436.1531; Found: 436.1535.

IR: ṽ [cm-1] = 3067 (w), 3035 (w), 2969 (w), 2913 (w), 2875 (w), 1791 (s), 1719 (s), 1687 (s), 1596 (s), 1507 (w), 1481 (w), 1456 (w), 1392 (m), 1345 (s), 1289 (s), 1230 (s), 1199 (s), 1178 (s), 1156 (s), 1122 (m), 1069 (m), 1042 (s), 1018 (m), 993 (m), 911 (w), 891 (w), 842 (m), 822 (m), 786 (w), 732 (m), 697 (m), 637 (w), 593 (m), 561 (w), 531 (w), 510 (w), 456 (w), 419 (w).

R_f (cyclohexane/EtOAc, 4:1) = 0.43 [$KMnO_4$]

$[\alpha]_D^{20}$ = + 29.5 (ρ = 1.02, CH_2Cl_2)

Benzyl (2S,4S)-2-(*tert*-butyl)-5-oxo-4-(2-oxo-2-(p-tolyl)ethyl)oxazolidine-3-carboxylate (98)



$C_{24}H_{27}NO_5$
409,48 g/mol

Synthesized following **GP-IV** using 4-methylbenzoic acid (103 mg, 0.76 mmol, 1.5 equiv.). Purification via flash chromatography afforded the product as a yellow oil in 80% yield (165 mg, 0.40 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83 – 7.79 (m, 2H), 7.30 – 7.27 (m, 3H), 7.26 – 7.23 (m, 2H), 7.23 – 7.20 (m, 2H), 5.61 (s, 1H), 5.23 (dd, *J* = 6.9, 5.0 Hz, 1H), 5.11 (d, *J* = 12.1 Hz, 1H), 4.99 (d, *J* = 12.1 Hz, 1H), 3.53 (dd, *J* = 16.2, 6.9 Hz, 1H), 3.35 (dd, *J* = 16.2, 5.1 Hz, 1H), 2.42 (s, 3H), 1.01 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 194.4, 172.2, 155.7, 144.5, 135.3, 134.0, 129.6, 128.7, 128.6, 128.5, 128.4, 96.4, 68.3, 53.8, 41.9, 37.6, 24.9, 21.8.

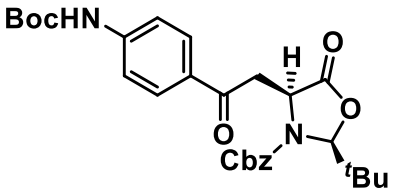
HRMS (ESI): [m/z] calculated for $C_{24}H_{27}NNaO_5^+$ ([M+Na]$^+$): 432.1781; Found: 432.1789.

IR: ṽ [cm-1] = 3063 (w), 3034 (w), 2966 (w), 2875 (w), 1792 (s), 1719 (s), 1682 (s), 1606 (m), 1573 (m), 1480 (w), 1453 (m), 1393 (s), 1344 (s), 1289 (s), 1235 (s), 1174 (s), 1120 (s), 1068 (m), 1041 (s), 1018 (s), 984 (s), 890 (m), 840 (m), 807 (m), 745 (s), 697 (s), 635 (w), 592 (m), 560 (m), 531 (m), 506 (m), 455 (m).

R_f (cyclohexane/EtOAc, 4:1) = 0.45 [p-Anisaldehyde]

$[\alpha]_D^{20}$ = + 43.6 (ρ = 1.03, CH_2Cl_2)

Benzyl (2S,4S)-4-(2-(4-((*tert*-butoxycarbonyl)amino)phenyl)-2-oxoethyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (99)



$C_{28}H_{34}N_2O_7$
510,59 g/mol

Synthesized following **GP-IV** using 4-((*tert*-butoxycarbonyl)amino)benzoic acid (178 mg, 0.75 mmol, 1.5 equiv.). Purification via flash chromatography afforded the product as a fine yellowish powder in 80% yield (203 mg, 0.40 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.27 (m, 3H), 7.24 – 7.20 (m, 2H), 6.81 (d, *J* = 4.6 Hz, 1H), 5.60 (s, 1H), 5.23 (dd, *J* = 6.9, 5.0 Hz, 1H), 5.10 (d, *J* = 12.1 Hz, 1H), 4.99 (d, *J* z= 12.1 Hz, 1H), 3.49 (dd, *J* = 16.2, 7.0 Hz, 1H), 3.33 (dd, *J* = 16.2, 5.0 Hz, 1H), 1.53 (s, 9H), 1.01 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 193.4, 172.2, 155.7, 152.2, 143.4, 135.3, 131.0, 129.8, 128.7, 128.6, 128.5, 117.7, 96.3, 81.5, 68.3, 53.8, 41.7, 37.6, 28.4, 24.9.

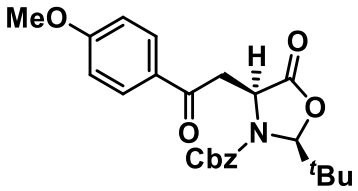
HRMS (ESI): [m/z] calculated for $C_{28}H_{34}N_2NaO_7^+$ ([M+Na]$^+$): 533.2258; Found: 533.2265.

IR: ṽ [cm-1] = 3338 (w), 2972 (w), 2930 (w), 2875 (w), 2852 (w), 1792 (m), 1718 (m), 1679 (m), 1588 (m), 1525 (m), 1502 (m), 1481 (w), 1454 (w), 1393 (m), 1366 (m), 1344 (m), 1312 (m), 1290 (m), 1229 (s), 1149 (s), 1122 (m), 1045 (m), 990 (m), 900 (w), 838 (m), 822 (m), 769 (m), 747 (m), 696 (m), 626 (m), 593 (w), 576 (w), 540 (m), 510 (m), 458 (m).

R_f (cyclohexane/EtOAc, 4:1) = 0.29 [p-Anisaldehyde]

$[\alpha]_D^{20}$ = + 35.6 (ρ = 1.02, CH_2Cl_2)

Benzyl (2S,4S)-2-(*tert*-butyl)-4-(2-(4-methoxyphenyl)-2-oxoethyl)-5-oxooxazolidine-3-carboxylate (100)



$C_{24}H_{27}NO_6$
425,48 g/mol

Synthesized following **GP-IV** using 4-methoxybenzoic acid (114 mg, 0.75 mmol, 1.5 equiv.). Purification via flash chromatography afforded the product as a yellow oil in 92% yield (195 mg, 0.46 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 – 7.87 (m, 2H), 7.31 – 7.27 (m, 3H), 7.25 – 7.21 (m, 2H), 6.94 – 6.89 (m, 2H), 5.61 (s, 1H), 5.23 (dd, *J* = 7.0, 5.0 Hz, 1H), 5.11 (d, *J* = 12.1 Hz, 1H), 5.00 (d, *J* = 12.1 Hz, 1H), 3.88 (s, 3H), 3.50 (dd, *J* = 16.1, 7.0 Hz, 1H), 3.33 (dd, *J* = 16.1, 5.0 Hz, 1H), 1.01 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 193.3, 172.2, 163.9, 155.7, 135.3, 130.6, 129.5, 128.7, 128.6, 128.5, 114.0, 96.4, 68.3, 55.7, 53.9, 41.7, 37.6, 24.9.

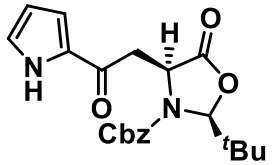
HRMS (ESI): [m/z] calculated for $C_{24}H_{27}NNaO_6^+$ ([M+Na]$^+$): 448.1731; Found: 448.1734.

IR: ṽ [cm-1] = 2964 (w), 2914 (w), 2874 (w), 2842 (w), 1792 (s), 1718 (s), 1677 (m), 1599 (s), 1575 (m), 1511 (m), 1481 (w), 1457 (m), 1393 (m), 1345 (s), 1291 (s), 1258 (s), 1238 (s), 1217 (s), 1200 (m), 1168 (s), 1118 (m), 1067 (m), 1040 (s), 1027 (s), 989 (s), 889 (m), 840 (m), 824 (m), 783 (m), 738 (m), 697 (s), 633 (m), 596 (m), 563 (m), 531 (m), 505 (m), 454 (m).

R_f (cyclohexane/EtOAc, 4:1) = 0.31 [p-Anisaldehyde]

$[\alpha]_D^{20}$ = + 41.1 (ρ = 0.99, CH_2Cl_2)

Benzyl (2S,4S)-2-(*tert*-butyl)-5-oxo-4-(2-oxo-2-(1*H*-pyrrol-2-yl)ethyl)oxazolidine-3-carboxylate (107)



$C_{21}H_{24}N_2O_5$
384,43 g/mol

Synthesized following **GP-IV** using 1*H*-pyrrole-2-carboxylic acid (84 mg, 0.75 mmol, 1.5 equiv.) with 48 h of irradiation. Purification via flash chromatography afforded the product as a dark yellow oil in 20% yield (39 mg, 0.10 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.42 (s, 1H), 7.33 – 7.28 (m, 3H), 7.25 – 7.21 (m, 2H), 7.00 (td, *J* = 2.7, 1.2 Hz, 1H), 6.87 (ddd, *J* = 3.8, 2.4, 1.3 Hz, 1H), 6.26 (dt, *J* = 3.9, 2.5 Hz, 1H), 5.61 (s, 1H), 5.13 (t, *J* = 6.3 Hz, 1H), 5.09 (d, *J* = 12.1 Hz, 1H), 5.02 (d, *J* = 12.1 Hz, 1H), 3.33 (dd, *J* = 15.3, 6.6 Hz, 1H), 3.20 (dd, *J* = 15.3, 5.9 Hz, 1H), 1.01 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 184.7, 172.0, 155.7, 135.3, 131.5, 128.7, 128.6, 128.5, 125.5, 116.7, 111.0, 96.5, 68.4, 54.4, 41.3, 37.5, 24.9.

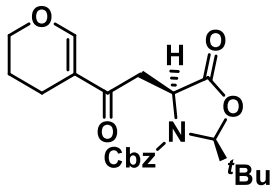
HRMS (ESI): [m/z] calculated for $C_{21}H_{24}N_2NaO_5^+$ ([M+Na]$^+$): 407.1577; Found: 407.1587.

IR: ṽ [cm-1] = 3290(w), 2968 (w), 2875 (w), 2254 (w), 1790 (m), 1715 (s), 1640 (m), 1547 (w), 1481 (w), 1397 (s), 1345 (m), 1334 (m), 1292 (s), 1231 (m), 1179 (m), 1109 (s), 1067 (m), 1041 (s), 1017 (m), 979 (m), 909 (m), 727 (s), 697 (s), 648 (w), 602 (w), 582 (w), 512 (w), 455 (w).

R_f (cyclohexane/EtOAc, 4:1) = 0.19 [p-Anisaldehyde]

$[\alpha]_D^{20}$ = + 32.9 (ρ = 1.00, CH_2Cl_2)

Benzyl (2S,4S)-2-(*tert*-butyl)-4-(2-(3,4-dihydro-2*H*-pyran-5-yl)-2-oxoethyl)-5-oxooxazolidine-3-carboxylate (119)



$C_{22}H_{27}NO_6$
401,46 g/mol

Synthesized following **GP-IV** using 3,4-dihydro-2*H*-pyran-5-carboxylic acid (96 mg, 0.75 mmol, 1.5 equiv.). Purification via flash chromatography afforded the product as a yellow oil in 48% yield (39 mg, 0.24 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.38 – 7.30 (m, 5H), 5.58 (s, 1H), 5.18 – 5.12 (m, 3H), 4.05 (t, *J* = 5.4 Hz, 2H), 3.08 (dd, *J* = 15.7, 7.4 Hz, 1H), 2.94 (dd, *J* = 15.7, 4.8 Hz, 1H), 2.29 – 2.20 (m, 2H), 1.87 – 1.78 (m, 2H), 0.98 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 192.8, 172.3, 157.1, 155.8, 135.5, 128.8, 128.6, 128.4, 116.9, 96.2, 68.3, 67.3, 53.9, 40.0, 37.5, 24.9, 21.1, 18.5.

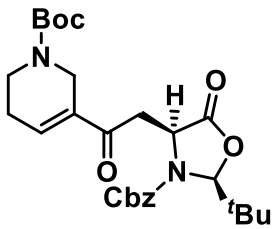
HRMS (ESI): [m/z] calculated for $C_{22}H_{27}NNaO_6^+$ ([M+Na]$^+$): 424.1731; Found: 424.1739.

IR: ṽ [cm-1] = 3065 (w), 3034 (w), 2961 (w), 2879 (w), 1791 (s), 1717 (s), 1656 (m), 1617 (s), 1481 (w), 1465 (w), 1450 (w), 1393 (m), 1345 (m), 1329 (s), 1289 (s), 1267 (m), 1230 (s), 1171 (s), 1122 (m), 1086 (m), 1041 (s), 1005 (s), 985 (s), 963 (m), 930 (m), 908 (m), 852 (m), 779 (m), 736 (m), 697 (s), 676 (m), 637 (w), 581 (w), 557 (w), 531 (w), 508 (m), 449 (m).

R_f (cyclohexane/EtOAc, 4:1) = 0.26 [p-Anisaldehyde]

$[\alpha]_D^{20}$ = + 39.2 (ρ = 1.04, CH_2Cl_2)

Benzyl (2S,4S)-4-(2-(1-(*tert*-butoxycarbonyl)-1,2,5,6-tetrahydropyridin-3-yl)-2-oxoethyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (121)

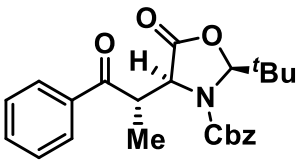


$C_{27}H_{36}N_2O_7$
500,59 g/mol

Synthesized following **GP-IV** using 1-(*tert*-butoxycarbonyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid (171 mg, 0.75 mmol, 1.5 equiv. Purification via flash chromatography afforded the product as an off-white solid in 68% yield (170 mg, 0.34 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.29 (m, 5H), 6.89 (t, *J* = 4.2 Hz, 1H), 5.57 (s, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 5.09 (d, *J* = 12.1 Hz, 1H), 5.08 (dd, *J* = 7.2, 5.0 Hz, 1H), 3.45 (s, 2H), 3.23 (dd, *J* = 16.0, 7.2 Hz, 1H), 3.07 – 2.99 (m, 1H), 2.34 – 2.29 (m, 2H), 1.46 (s, 9H), 0.97 (s, 9H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 193.6, 172.1, 155.6, 154.9, 138.8, 137.0, 135.3, 128.8, 128.7, 128.5, 96.3, 80.2, 68.4, 53.7, 42.3, 40.3, 38.6, 37.5, 28.5, 25.9, 24.8.
HRMS (ESI): [m/z] calculated for $C_{27}H_{36}N_2NaO_7^+$ ([M+Na]$^+$): 523.2415; Found: 523.2410.
IR: ṽ [cm-1] = 2972 (w), 2935 (w), 2874 (w), 1792 (m), 1720 (m), 1693 (s), 1673 (s), 1621 (w), 1479 (m), 1455 (m), 1391 (m), 1365 (m), 1342 (m), 1285 (s), 1234 (s), 1159 (s), 1111 (s), 1068 (m), 1040 (s), 985 (m), 890 (w), 865 (m), 826 (w), 766 (m), 743 (m), 697 (m), 637 (w), 593 (w), 582 (w), 508 (m), 455 (m).
R_f (cyclohexane/EtOAc, 4:1) = 0.20 [$KMnO_4$]
$[\alpha]_D^{20}$ = + 37.1 (ρ = 1.00, CH_2Cl_2)

Benzyl (2S,4S)-2-(*tert*-butyl)-5-oxo-4-(1-oxo-1-phenylpropan-2-yl)oxazolidine-3-carboxylate (139)



$C_{24}H_{27}NO_5$
409,48 g/mol

36 (303 mg, 0.77 mmol, 1.0 equiv.) was dissolved in dry THF (4 mL, 0.19 M). Cooled down bright yellow solution to -55 °C. After 10 min, slowly added 0.5 M $KN(TMS)_2$ in toluene (1.7 mL, 0.85 mmol, 1.1 equiv.) dropwise. Let stir to -70 °C for 30 min before iodomethane (75 µL, 1.20 mmol, 1.6 equiv.) was added dropwise. Continued stirring at -70 °C to rt until the next morning. The next day, reaction was cooled down to -60 °C again and quenched via addition of satd. $NaHCO_3$ solution (5 mL) and satd. NH_4Cl solution (1 mL). Concentrated in vacuum, then extracted residue with EtOAc (3 x 25 mL). Combined org. layers were washed with H_2O, satd. $NaHCO_3$ solution and brine (20 mL each). Dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography afforded the product as a yellow, milky oil 45% yield (140 mg, 0.34 mmol).
Later, ^{1}H NMR analysis of the crude reaction mixture of a smaller scale repetition of this experiment using the same reaction conditions, revealed formation of the product as a ~9.5:1 diastereomeric mixture.
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 – 7.87 (m, 2H), 7.60 – 7.55 (m, 1H), 7.50 – 7.44 (m, 2H), 7.43 – 7.33 (m, 5H), 5.67 (s, 1H), 5.32 (d, J = 10.6 Hz, 1H), 5.24 (d, J = 4.8 Hz, 2H), 3.80 (dq, J = 10.6, 7.3 Hz, 1H), 1.32 (d, J = 7.3 Hz, 3H), 1.03 (s, 9H).

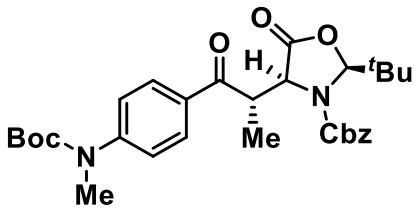
$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 200.0, 172.1, 157.0, 136.3, 135.3, 133.5, 128.9, 128.9, 128.8, 128.6, 128.4, 97.1, 68.8, 58.8, 43.6, 36.9, 25.1, 16.0.

HRMS (ESI): [m/z] calculated for $C_{20}H_{27}NNaO_5^+$ ($[M+Na]^+$): 432.1781; Found: 432.1780.

IR: ṽ [cm^{-1}] = 2974 (m), 2880 (w), 1786 (s), 1716 (s), 1683 (s), 1595 (w), 1481 (m), 1451 (m), 1390 (m), 1324 (s), 1289 (s), 1251 (s), 1191 (s), 1108 (m), 1044 (s), 968 (s), 910 (m), 875 (m), 788 (m), 731 (s), 697 (s), 647 (m), 628 (m), 595 (m), 582 (m), 541 (m), 504 (m).

R_f (cyHex/EtOAc, 5:1) = 0.34 [CAM]

Benzyl (2S,4S)-4-((S)-1-(4-((*tert*-butoxycarbonyl)(methyl)amino)phenyl)-1-oxopropan-2-yl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (140)



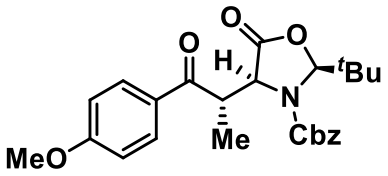
$C_{30}H_{38}N_2O_7$
538,64 g/mol

99 (127 mg, 0.25 mmol, 1.0 equiv.) was dissolved in dry THF (1.6 mL, 0.16 M). Cooled down intensively yellow solution to -78 °C. After 5 min, slowly added $KN(TMS)_2$ (1 mL, 0.50 mmol, 2.0 equiv.). Let stir in cooling bath for 30 min before iodomethane (80 µL, 1.29 mmol, 5.2 equiv.) was added all at once. Continued stirring at -78 °C to rt until the next morning. The next day, reaction was cooled down to -78 °C again and quenched via addition of satd. $NaHCO_3$ solution and satd. K_2CO_3 solution (0.5 mL each). Concentrated in vacuum, then extracted residue with EtOAc (3 x 5 mL). Combined org. layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography the product with minor impurities of its diastereomer as a yellow oil in <37% combined yield (49 mg, 91 µmol, EtOAc residues).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 – 7.84 (m, 2H), 7.40 – 7.34 (m, 7H), 5.66 (s, 1H), 5.30 (d, *J* = 10.6 Hz, 1H), 5.23 (d, *J* = 4.6 Hz, 2H), 3.76 (dq, *J* = 10.7, 7.3 Hz, 1H), 3.30 (s, 3H), 1.48 (s, 9H), 1.31 (d, *J* = 7.3 Hz, 3H), 1.03 (s, 9H).

R_f (cyHex/EtOAc, 5:1) = 0.15 [CAM]

Benzyl (2S,4S)-2-(*tert*-butyl)-4-((S)-1-(4-methoxyphenyl)-1-oxopropan-2-yl)-5-oxooxazolidine-3-carboxylate (141)



$C_{25}H_{29}NO_6$
439,51 g/mol

100 (235 mg, 0.55 mmol, 1.0 equiv.) was dissolved in dry THF (2.5 mL, 0.22 M). Cooled down yellow solution to -78 °C. After 10 min, slowly added 1 M $KN(TMS)_2$ in 2-Me-THF (0.75 mL, 0.75 mmol, 1.4 equiv.). Let stir in cooling bath for 5 min before iodomethane (200 µL, 3.21 mmol, 5.8 equiv.) was added all at once. After stirring at -78 °C for 15 min, the reaction mixture was stirred at room temperature for another 15 min, before it was stirred to 65 °C for 2 h. Afterwards, added satd. NH_4Cl solution (3 mL) and let stir at room temperature for 1 h, before the mixture was extracted with EtOAc (3 x 20 mL). Combined org. layers were washed with H_2O and brine (10 mL each), dried over Na_2SO_4 and concentrated in vacuum. ^{1}H NMR analysis of the crude reaction mixture revealed formation of the product as a ~7.5:1 diastereomeric mixture. Purification via flash chromatography afforded a mixture of both diastereomeric products as a yellowish foam in 51% combined yield (125 mg, 0.28 mmol).

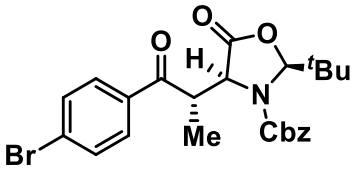
^{1}H NMR (400 MHz, $CDCl_3$, *mayor isomer*): δ 7.92 – 7.86 (m, 2H), 7.43 – 7.33 (m, 5H), 6.96 – 6.91 (m, 2H), 5.66 (s, 1H), 5.30 (d, *J* = 10.6 Hz, 1H), 5.23 (d, *J* = 2.4 Hz, 2H), 3.86 (s, 3H), 3.80 – 3.72 (m, 1H), 1.31 (d, *J* = 7.3 Hz, 3H), 1.03 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, *mayor isomer*): δ 198.3, 172.1, 163.9, 156.9, 135.3, 130.7, 129.2, 128.8, 128.7, 128.5, 114.1, 97.0, 68.7, 58.8, 55.6, 43.2, 36.9, 25.0, 16.1.

HRMS (ESI): [m/z] calculated for $C_{25}H_{29}NNaO_6^+$ ([M+Na]$^+$): 462.1887; Found: 462.1884.

R_f (cyHex/EtOAc, 5:1) = 0.26 [p-Anisaldehyde]

Benzyl (2S,4S)-4-((S)-1-(4-bromophenyl)-1-oxopropan-2-yl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (142)



$C_{24}H_{26}BrNO_5$
488,38 g/mol

97 (318 mg, 0.67 mmol, 1.0 equiv.) was dissolved in dry THF (2.5 mL, 0.27 M). Cooled down yellow solution to -78 °C. After 10 min, slowly added 1 M $KN(TMS)_2$ in 2-Me-THF (0.75 mL,

0.75 mmol, 1.1 equiv.). Let stir in cooling bath for 5 min before iodomethane (200 µL, 3.21 mmol, 4.8 equiv.) was added all at once. After stirring at -78 °C for 15 min, the reaction mixture was stirred at room temperature for another 15 min, before it was stirred to 65 °C for 2 h. Afterwards, added satd. NH_4Cl solution (3 mL) and let stir at room temperature for 1 h, before the mixture was extracted with EtOAc (3 x 20 mL). Combined org. layers were washed with H_2O and brine (10 mL each), dried over Na_2SO_4 and concentrated in vacuum. ^1H NMR analysis of the crude reaction mixture revealed formation of the product as a ~12:1 diastereomeric mixture. Purification via flash chromatography afforded the product with little impurities of its diastereomer as a yellow oil in 50% combined yield (162 mg, 0.33 mmol).

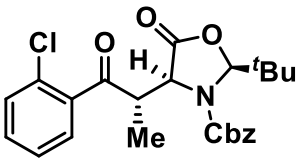
^{1}H NMR (600 MHz, $CDCl_3$, *mayor isomer*): δ 7.77 – 7.74 (m, 2H), 7.63 – 7.60 (m, 2H), 7.41 – 7.35 (m, 5H), 5.66 (s, 1H), 5.27 (d, J = 10.6 Hz, 1H), 5.23 (d, J = 4.2 Hz, 2H), 3.72 (dq, J = 10.7, 7.2 Hz, 1H), 1.30 (d, J = 7.3 Hz, 3H), 1.02 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, *mayor isomer*): δ 199.1, 172.1, 156.9, 135.2, 135.1, 132.3, 129.9, 128.9, 128.8, 128.8, 128.6, 97.2, 68.9, 58.8, 43.6, 36.9, 25.0, 15.9.

HRMS (ESI): [m/z] calculated for $C_{24}H_{26}BrNNaO_5^+$ ([M+Na]$^+$): 510.0887; Found: 510.0888.

R_f (cyHex/EtOAc, 5:1) = 0.40 [p-Anisaldehyde]

Benzyl (2S,4S)-2-(*tert*-butyl)-4-((S)-1-(2-chlorophenyl)-1-oxopropan-2-yl)-5-oxooxazolidine-3-carboxylate (143)



$C_{24}H_{26}ClNO_5$
443,92 g/mol

103 (280 mg, 0.65 mmol, 1.0 equiv.) was dissolved in dry THF (2.5 mL, 0.26 M). Cooled down yellow solution to -78 °C. After 10 min, slowly added 1 M $KN(TMS)_2$ in 2-Me-THF (0.75 mL, 0.75 mmol, 1.2 equiv.). Let stir in cooling bath for 5 min before iodomethane (200 µL, 3.21 mmol, 4.9 equiv.) was added all at once. After stirring at -78 °C for 15 min, the reaction mixture was stirred at room temperature for another 15 min, before it was stirred to 65 °C for 2 h. Afterwards, added satd. NH_4Cl solution (3 mL) and let stir at room temperature for 1 h, before the mixture was extracted with EtOAc (3 x 20 mL). Combined org. layers were washed with H_2O and brine (10 mL each), dried over Na_2SO_4 and concentrated in vacuum. ^1H NMR analysis of the crude reaction mixture revealed formation of the product as a ~12:1 diastereomeric mixture. Purification via flash chromatography afforded a mixture of both diastereomeric products as a yellow oil in 44% combined yield (126 mg, 0.28 mmol).

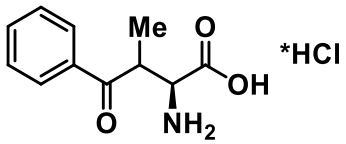
^{1}H NMR (600 MHz, $CDCl_3$, *mayor isomer*): δ 7.54 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.41 – 7.40 (m, 3H), 7.36 – 7.31 (m, 5H), 5.66 (s, 1H), 5.27 – 5.12 (m, 3H), 3.68 (dq, *J* = 10.7, 7.3 Hz, 1H), 1.31 (d, *J* = 7.3 Hz, 3H), 0.98 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, *mayor isomer*): δ 202.0, 172.0, 156.8, 138.6, 135.3, 132.2, 131.4, 130.7, 130.0, 128.8, 128.8, 128.6, 127.0, 97.1, 68.8, 58.4, 48.0, 36.9, 25.0, 14.9.

HRMS (ESI): [m/z] calculated for $C_{24}H_{26}ClNNaO_5^+$ ([M+Na]$^+$): 466.1392; Found: 466.1397.

R_f (cyHex/EtOAc, 5:1) = 0.37 [p-Anisaldehyde]

(2S)-2-Amino-3-methyl-4-oxo-4-phenylbutanoic acid hydrochloride (145)



$C_{11}H_{14}ClNO_3$
243,69 g/mol

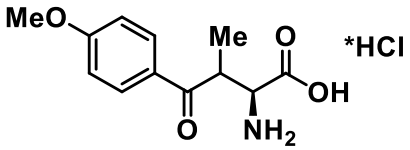
139 (45 mg, 0.11 mmol, 1.0 equiv.) was dissolved in dry 1,4-dioxane (0.25 mL, 0.44 M). Added 12 M HCl (1 mL, 12.00 mmol, 109 equiv.) and let stir to 80 °C in a closed vial for 2 h. The reaction mixture was concentrated in vacuum, before residue was washed with Et_2O. Drying again in vacuum afforded the product in a ~1:1 mixture of diastereomers as a beige-white solid in 34% combined yield (9 mg, 37 µmol).

^{1}H NMR (600 MHz, D_2O, *first isomer*): δ 8.08 – 8.00 (m, 2H), 7.77 (t, *J* = 7.4 Hz, 1H), 7.63 (dt, *J* = 8.8, 4.5 Hz, 2H), 4.42 – 4.31 (m, 2H), 1.37 (d, *J* = 7.6 Hz, 3H).

^{1}H NMR (600 MHz, D_2O, *second isomer*): δ 8.08 – 8.00 (m, 2H), 7.77 (t, *J* = 7.4 Hz, 1H), 7.63 (dt, *J* = 8.8, 4.5 Hz, 2H), 4.52 – 4.46 (m, 2H), 1.46 (d, *J* = 7.6 Hz, 3H).

HRMS (ESI): [m/z] calculated for $C_{11}H_{14}NO_3^+$ ([M+H]$^+$): 208.0968; Found: 208.0972.

(2S)-2-Amino-4-(4-methoxyphenyl)-3-methyl-4-oxobutanoic acid hydrochloride (146)

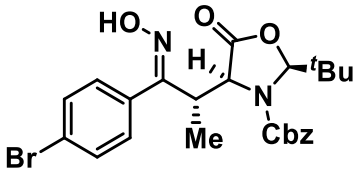


$C_{12}H_{16}ClNO_4$
273,71 g/mol

141 (105 mg, 0.24 mmol, 1.0 equiv.) was dissolved in dry 1,4-dioxane (0.25 mL, 0.96 M). Added 12 M HCl (1 mL, 12.00 mmol, 50 equiv.) and let stir to 80 °C in a closed vial for 2 h. The reaction mixture was concentrated in vacuum, before residue was washed with Et_2O. Drying again in vacuum afforded the product in a ~1:1 mixture of diastereomers as a slightly greenish solid in 43% combined yield (28 mg, 0.10 mmol).

^{1}H NMR (600 MHz, D_2O, *first isomer*): δ 8.04 – 7.99 (m, 2H), 7.14 – 7.08 (m, 2H), 4.35 – 4.28 (m, 2H), 3.92 (s, 3H), 1.35 (d, *J* = 7.5 Hz, 3H).
^{1}H NMR (600 MHz, D_2O, *second isomer*): δ 8.04 – 7.99 (m, 2H), 7.14 – 7.08 (m, 2H), 4.46 – 4.39 (m, 2H), 3.92 (s, 3H), 1.44 (d, *J* = 7.5 Hz, 3H).
HRMS (ESI): [m/z] calculated for $C_{12}H_{15}NNaO_4^+$ ([M+Na]$^+$): 260.0893; Found: 260.0894

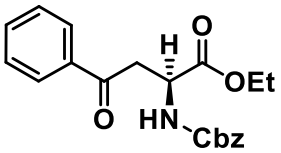
Benzyl (2S,4S)-4-((S,Z)-1-(4-bromophenyl)-1-(hydroxyimino)propan-2-yl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (147)



$C_{24}H_{27}BrN_2O_5$
503,39 g/mol

Inspired by a literature protocol using methoxyamine,[173] dissolved **142** (71 mg, 0.15 mmol, 1.0 equiv.) in dry EtOH (1 mL, 0.15 M). Added this solution to a mixture of hydroxylamine hydrochloride (16.2 mg, 0.23 mmol, 1.6 equiv.), NaOAc (20.1 mg, 0.25 mmol, 1.7 equiv.) and $CeCl_3$ heptahydrate (3.4 mg, 9 µmol, 6 mol%). Let stir under ambient atmosphere to 50 °C for 12 h. Purification via flash chromatography afforded the product as a slightly yellowish oil in <25% yield (18 mg, 0.10 mmol, cyHex residues). The product was found to be unstable and started decomposing after ^{1}H NMR analysis.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 – 7.48 (m, 2H), 7.39 – 7.34 (m, 3H), 7.27 – 7.23 (m, 4H), 5.58 (s, 1H), 5.13 (d, *J* = 1.5 Hz, 2H), 4.77 (d, *J* = 11.4 Hz, 1H), 3.00 (dq, *J* = 11.5, 7.2 Hz, 1H), 1.32 (d, *J* = 7.3 Hz, 3H), 0.97 (s, 9H).

Ethyl (S)-2-(((benzyloxy)carbonyl)amino)-4-oxo-4-phenylbutanoate (159)



$C_{20}H_{21}NO_5$
355,39 g/mol

Under a N_2-atmosphere, dissolved **36** (97.7 mg, 0.25 mmol, 1.0 equiv.) in EtOH (1 mL, 0.25 M) and cooled down to -10 to - 15 °C using an ice-NaCl cooling bath. After 10 min, slowly added $NaBH_4$ (4.8 mg, 0.13 mmol, 0.5 equiv.), dissolved in EtOH (1 mL, 0.13 M). Let stir at room temperature overnight. The next day, cooled down reaction mixture in an ice-bath, added 1 M HCl (5 mL) and diluted mixture with H_2O (20 mL). After extraction with EtOAc (3 x 20 mL),

combined org. layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography afforded the product as a yellow oil in 33% yield (29 mg, 82 µmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.88 (m, 2H), 7.62 – 7.55 (m, 1H), 7.47 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.36 – 7.32 (m, 5H), 5.90 (d, *J* = 8.7 Hz, 1H), 5.15 – 5.07 (m, 2H), 4.74 (dt, *J* = 8.5, 4.2 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.76 (dd, *J* = 18.1, 4.3 Hz, 1H), 3.55 (dd, *J* = 18.1, 4.2 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 197.5, 171.0, 156.1, 136.2, 136.1, 133.6, 128.7, 128.5, 128.1, 128.1, 128.0, 67.0, 61.7, 50.2, 40.8, 14.0.

HRMS (ESI): [m/z] calculated for $C_{20}H_{21}NNaO_5^+$ ($[M+Na]^+$): 378.1312; Found: 378.1322.

IR: ṽ [cm^{-1}] = 3347 (w), 3063 (w), 3033 (w), 2980 (w), 2936 (w), 1786 (w), 1715 (s), 1683 (s), 1597 (w), 1582 (w), 1502 (s), 1450 (m), 1400 (w), 1367 (m), 1334 (m), 1286 (m), 1249 (m), 1210 (s), 1027 (s), 1000 (m), 988 (m), 939 (w), 861 (w), 751 (m), 691 (s), 638 (w), 616 (w), 595 (w), 574 (w), 558 (w), 500 (w), 458 (w).

R_f (cyHex/EtOAc, 4:1) = 0.23 [p-Anisaldehyde]

$[\alpha]_D^{20}$ = + 15.2 (ρ = 0.98, CH_2Cl_2)

VI.IV γ-Oxo-δ-Amino Esters via α-Amino Ketyl Radicals

VI.IV.1 – Selectivity Studies and Mechanistic Investigations

In the following, experimental details of the performed studies to determine the reactions selectivity or robustness, and the investigations undertaken to propose a suitable mechanism are given.

Selectivity studies

For the selectivity screening as presented in Scheme 48 a set of five independent reactions were performed.

A 4 ml vial was charged with a stir bar and an activator (0.02 mmol, 20 mol%). The reaction vial was then sealed with a septum cap, and evacuated and backfilled with N_2 for 1 min each. This was repeated three times.

To the activators, added a 2 mL dry and degassed MeCN solution containing *N*-Boc-glycinol **235** (17.7 mg, 0.11 mmol, 1.1 equiv.), **4CzIPN** (3.9 mg, 5 µmol, 5 mol%) and quinuclidine (1.1 mg, 0.01 mmol, 10 mol%). Afterwards, **166** in MeCN (0.05 M, 2 mL, 0.1 mmol, 1.0 equiv.) was added and the vial was sealed with parafilm. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 440 nm) at room temperature for 66 h. Afterwards, the vial cap was removed, IBX (112 mg, 0.4 mmol, 3.6 equiv.) was added and the vial was resealed. The reaction mixture heated in an oil bath at 85 °C for 3 h, then allowed to cool to room temperature. Afterwards, methyl laureate (24.6 µL, 0.1 mmol, 1.0 equiv.) was added as internal standard, and an aliquot of the reaction mixture was analyzed by GC-FID to determine the product distribution of **208**, **209** and **236**.

Functional group tolerance screening

For the functional group tolerance screening (Scheme 49) 2 sets of 14 independent reactions with varying additives were performed: 1 set for the photoreaction step, and 1 set for the photoreaction step with subsequent IBX oxidation.

A 4 ml vial was charged with a stir bar and – if solid – with an additive (0.11 mmol, 1.1 equiv.). The reaction vial was then sealed with a septum cap, and evacuated and backfilled with N_2 for 1 min each. This was repeated three times. If liquid, additives were added (0.11 mmol, 1.1 equiv.) to the vial with the stir bar after evacuation and backfilling with N_2.

To the additives, added a 2 mL dry and degassed MeCN solution containing *N*-Boc-2-amino-2-methylpropanol **237** (20.8 mg, 0.11 mmol, 1.1 equiv.), **4CzIPN** (3.9 mg, 5 µmol, 5 mol%), quinuclidine (1.1 mg, 0.01 mmol, 10 mol%) and $PhB(OH)_2$ (2.4 mg, 0.02 mmol, 20 mol%).

Afterwards, **166** in MeCN (0.05 M, 2 mL, 0.1 mmol, 1.0 equiv.) was added and the vial was sealed with parafilm. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 450 nm) at room temperature for 66 h.
Upon completion, added methyl laureate (24.6 µL, 0.1 mmol, 1.0 equiv.) as internal standard to the first set of reactions. To determine the yields of **233** in the photochemical step, an aliquot of the reaction mixture was taken and analyzed by GC-FID.
The second set of reaction mixtures was oxidized after the photoreaction. Therefore, the vial cap was removed, IBX (61.6 mg, 0.22 mmol, 2.0 equiv.) was added and the vial was resealed. The reaction mixture heated in an oil bath at 85 °C for 3 h, then allowed to cool to room temperature. Afterwards, methyl laureate (24.6 µL, 0.1 mmol, 1.0 equiv.) was added as internal standard, and an aliquot of the reaction mixture was analyzed by GC-FID to determine the yields of **205**.

Radical trapping experiment

For the radical trapping experiment presented in Scheme 50 a standard reaction in the presence of an excess of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as radical scavenger was performed.
A 4 ml vial, charged with a stir bar, was sealed with a septum cap, and evacuated and backfilled with N_2 for 1 min each. This was repeated three times. Added a 2 mL dry and degassed MeCN solution containing *N*-Boc-2-amino-2-methylpropanol **237** (37.8 mg, 0.2 mmol, 2.0 equiv.), **4CzIPN** (4.0 mg, 5 µmol, 5 mol%), quinuclidine (1.1 mg, 0.01 mmol, 10 mol%), $PhB(OH)_2$ (2.4 mg, 0.02 mmol, 20 mol%) and TEMPO (46.8 mg, 0.3 mmol, 3.0 equiv.). Afterwards, **166** in MeCN (0.05 M, 2 mL, 0.1 mmol, 1.0 equiv.) was added and the vial was sealed with parafilm. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 440 nm) at room temperature for 24 h. Then, methyl laureate (24.6 µL, 0.1 mmol, 1.0 equiv.) was added as internal standard, and an aliquot of the reaction mixture was analyzed by GC-FID to determine the yield of **233**.

Competition experiments

For the competition experiment as presented in Scheme 51 two sets of independent reactions were performed: 1 set containing 3-phenylpropan-1-ol **254**, and 1 set containing *N*-Boc-3-aminopropan-1-ol **255** as additive.
A 4 ml vial, charged with a stir bar, was sealed with a septum cap, and evacuated and backfilled with N_2 for 1 min each. This was repeated three times. Added a 2 mL dry and degassed MeCN solution containing *N*-Boc-valinol **165** (22.4 mg, 0.11 mmol, 1.1 equiv.), **4CzIPN** (3.9 mg, 5 µmol, 5 mol%), quinuclidine (1.1 mg, 0.01 mmol, 10 mol%), $PhB(OH)_2$ (2.4 mg, 0.02 mmol, 20 mol%), and the additive (0.11 mmol, 1.1 equiv.). Afterwards, **166** in MeCN (0.05 M, 2 mL, 0.1

mmol, 1.0 equiv.) was added and the vial was sealed with parafilm. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 440 nm) at room temperature for 66 h. Afterwards, the vial cap was removed, IBX (61.6 mg, 0.22 mmol, 2.0 equiv.) was added and the vial was resealed. The reaction mixture heated in an oil bath at 85 °C for 3 h, then allowed to cool to room temperature. Then, methyl laureate (24.6 µL, 0.1 mmol, 1.0 equiv.) was added as internal standard, and an aliquot of the reaction mixture was analyzed by GC-FID to determine the yields of **169** and **256** or **257**.

UV/Vis absorption spectra

Optimization studies revealed that light and photocatalyst both are needed for the reaction to take place. Nevertheless, UV/Vis spectra of the reaction mixture with and without **4CzIPN** with the same concentration used in the reaction (0.025 M) in the presence of air, using MeCN as solvent, were recorded (Figure 76). Later, those measurements were repeated by Khadijah Anwar using more diluted concentrations (0.01 M and 0.005 M).

The UV/Vis spectra showed that the reaction mixture without **4CzIPN** exclusively absorbs UV-light. In the presence of **4CzIPN**, the light absorption ranges into the visible-light spectrum up to approx. 460 nm. These results confirm that the presence of **4CzIPN** is mandatory for the reaction mixture to absorb the light energy under the standard reaction conditions.

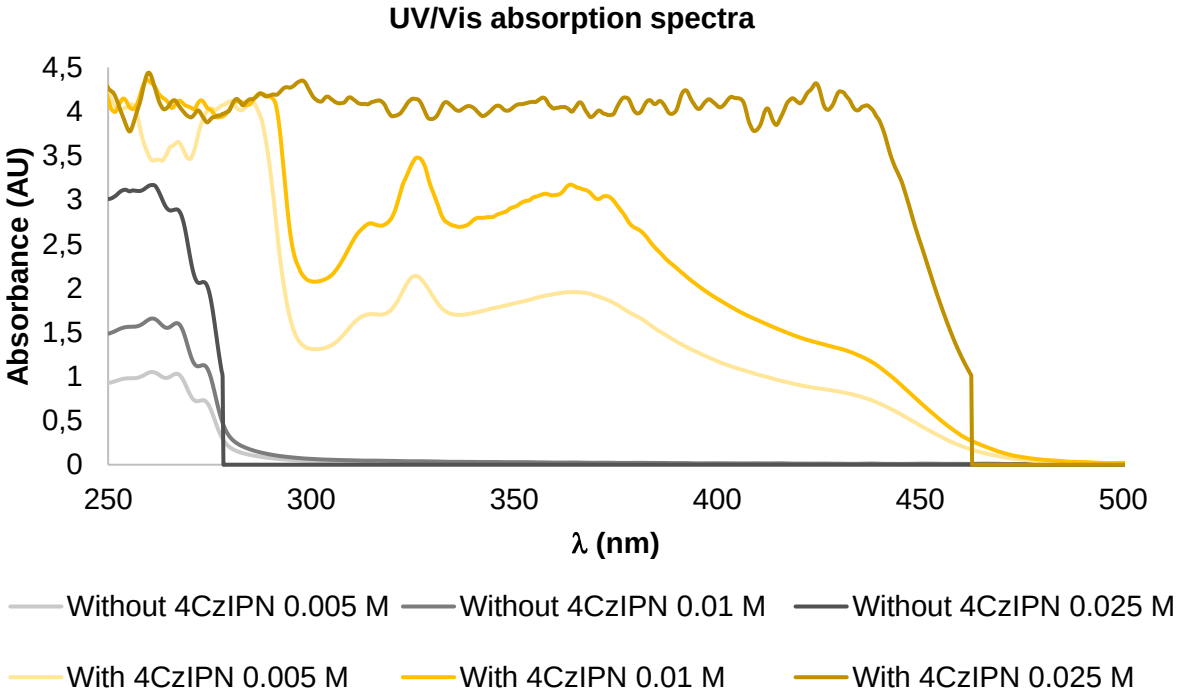


*Figure 76. UV/Vis absorption spectra of reaction mixture with and without **4CzIPN** in various concentrations.*

Stern-Volmer quenching experiments

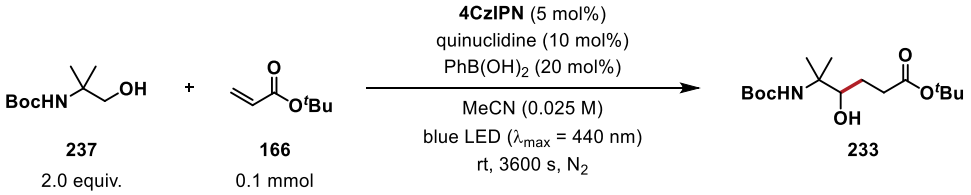
For the Stern-Volmer quenching experiments presented in Figure 42 to Figure 46 four individual quenching studies using stock solutions of quinuclidine, $PhB(OH)_2$, **166** and *N*-Boc-alaninol were performed. A stock solution of **4CzIPN** (20 µM) in dry and degassed MeCN was prepared and stored under N_2. Into a 1 cm quartz cuvette added 100 µL of the 20 µM **4CzIPN** stock solution and varying amounts of reactant. The total volume was filled up to 1 mL using dry and degassed MeCN. Under N_2 atmosphere, the quartz cuvette was sealed with a cap and parafilm, and the emission spectrum was measured. Therefore, the solutions were excited at λ = 410 nm and the obtained fluorescence intensities at λ = 546 nm used for analysis.

Photon flux determination

The photon flux of the used LED (λ_{max} = 440 nm) had to be determined. Since the same LED was used for this reaction as in beforementioned projects, the previously determined photon flux of 8.24081 x 10^{-10} einsteins s^{-1} could be used. A detailed description of its calculation can be found in **section II.I.5.**

Quantum yield determination

To determine the quantum yield, a reaction under the standard conditions was performed (Scheme 64) using the same lamp as used for the photon flux determination. The sample was irradiated for 3600 sec. Afterwards, methyl laureate (24.6 µL, 0.1 mmol, 1.0 equiv.) was added as internal standard and the reaction outcome was checked via GC-FID analysis. As an average of three experiments, the product **233** was formed in 55% yield (5.5 x 10^{-5} mol).



Scheme 64. Reaction performed for quantum yield determination.

The quantum yield (Φ) of the reaction was thus calculated using Equation 4.

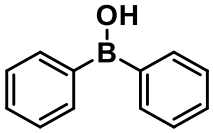
Eq. 4 $$\Phi = \frac{\text{mol of product formed}}{\text{Photon flux} \bullet t \bullet f}$$

The photon flux is 8.24081 x 10^{-10} einsteins s^{-1}, t is the irradiation time (3600 s) and f is the fraction of light being absorbed by the reaction mixture using Equation 2 (see **section II.I.5**). The absorbance value for the reaction mixture was found to be 4.07037 at 437 nm (Figure 76), so that f was calculated to be >0.999.

The reaction quantum yield (Φ) was calculated to be 18.54, indicating a radical chain pathway is involved.

VI.IV.2 – Synthesis and Characterization of Starting Materials

Diphenylborinic acid



$C_{12}H_{11}BO$
182,03 g/mol

According to a literature protocol,[271] 2-((Diphenylboraneyl)oxy)ethan-1-amine (0.20 g, 0.89 mmol, 1.0 equiv.) was suspended in acetone/MeOH (1:1, 1 mL, 0.9 M). Added 1 M HCl (1 mL, 1.00 mmol, 1.1 equiv.) and let stir reaction at room temperature for 2 h. Diluted reaction mixture by addition of Et_2O (1 mL), then washed with H_2O (1 mL) and extracted the aq. layer with Et_2O (3 x 1 mL). Combined org. layers were dried over Na_2SO_4 and concentrated in vacuum to afford the product as an off-white solid in 78% yield (127 mg, 0.70 mmol).

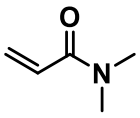
It is suggested to prepare the titled product freshly before usage, as it is prone to undergo oxidative fragmentation into phenol and phenylboronic acid.[272]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.87 (m, 1H), 7.84 – 7.79 (m, 3H), 7.56 – 7.50 (m, 2H), 7.49 – 7.39 (m, 4H), 5.82 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.0, 134.8, 131.2, 128.1.

^{11}B NMR (128 MHz, $CDCl_3$) δ -5.00.

N,*N*-Dimethylacrylamide



C_5H_9NO
99,13 g/mol

Inspired by a literature report for the synthesis of acrylamides,[273] dimethylamine (2 M in THF, 5 mL, 10.00 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (18 mL). Added Et_3N (3.6 mL, 25.97 mmol, 2.6 equiv.) and cooled down in ice-bath. After stirring for 5 min, slowly added acryloyl chloride (0.8 mL, 9.81 mmol, 1.0 equiv.). The reaction was stirred in the cooling bath, which was allowed to warm up to room temperature, for several days. Added H_2O (10 mL) to quench unreacted acryloyl chloride. Let stir at room temperature for 15 min, before the reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL). Combined org. layers were dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography afforded the product as a yellow

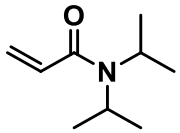
oil in 23% yield (0.22 g, 2.23 mmol). The product was found to be volatile and evaporated when drying in vacuum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dd, *J* = 16.8, 10.5 Hz, 1H), 6.21 (dd, *J* = 16.8, 2.1 Hz, 1H), 5.59 (dd, *J* = 10.5, 2.1 Hz, 1H), 2.97 (s, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.6, 127.7, 127.4, 37.1, 35.8.

R_f (EtOAc) = 0.20 [$KMnO_4$]

***N*,*N*-Diisopropylacrylamide**



$C_9H_{17}NO$
155,24 g/mol

Inspired by a literature report for the synthesis of acrylamides,[273] diisopropylamine (1.0 mL, 7.12 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (20 mL, 0.36 M). Added Et_3N (2.8 mL, 20.20 mmol, 2.8 equiv.) and cooled down in ice-bath. Carefully added acryloyl chloride (0.6 mL, 7.36 mmol, 1.0 equiv.). The reaction was stirred in the cooling bath, which was allowed to warm up to room temperature, for several days. Added H_2O (10 mL) to quench unreacted acryloyl chloride. Let stir at room temperature for 1 h, then the reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL). Combined org. layers were dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography afforded the product as a yellow oil in 43% yield (0.475 g, 3.06 mmol).

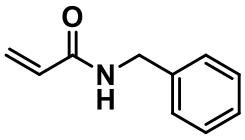
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (dd, *J* = 16.8, 10.6 Hz, 1H), 6.13 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.52 (dd, *J* = 10.6, 2.0 Hz, 1H), 3.97 (br, 1H), 3.73 (br, 1H), 1.31 (br, 6H), 1.23 (br, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.3, 130.9, 125.6, 48.2, 45.8, 21.4, 20.7.

HRMS (ESI): [m/z] calculated for $C_9H_{17}NNaO^+$ ([M+Na]$^+$): 178.1202; Found: 178.1206.

R_f (cyHex/EtOAc, 1:1) = 0.50 [$KMnO_4$]

***N*-Benzylacrylamide**



$C_{10}H_{11}NO$
161,20 g/mol

Inspired by a literature report for the synthesis of acrylamides,[273] benzylamine (1.1 mL, 10.06 mmol, 1.1 equiv.) was dissolved in dry CH_2Cl_2 (50 mL, 0.2 M). Added Et_3N (3.5 mL, 25.25 mmol, 2.7 equiv.) and cooled down in ice-bath. After stirring for 10 min, slowly added acryloyl chloride (0.75 mL, 9.20 mmol, 1.0 equiv.) over a period of 10 min. The reaction was stirred in

the cooling bath, which was allowed to warm up to room temperature, for several days. Added H_2O (10 mL) to quench unreacted acryloyl chloride. The reaction mixture was extracted with CH_2Cl_2 (2 x 20 mL). Combined org. layers were concentrated in vacuum. Purification via flash chromatography afforded the product as a pale-yellow solid in 74% yield (1.10 g, 6.82 mmol). The analytical data are in agreement with those previously reported.[274]

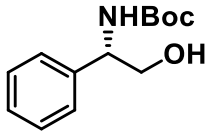
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 5H), 6.31 (dd, *J* = 17.0, 1.5 Hz, 1H), 6.12 (dd, *J* = 17.0, 10.3 Hz, 1H), 6.00 (s, 1H), 5.65 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.51 (d, *J* = 5.8 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.5, 138.2, 130.8, 128.9, 128.0, 127.7, 126.8, 43.8.

HRMS (ESI): [m/z] calculated for $C_{10}H_{11}NNaO^+$ ([M+Na]$^+$): 184.0733; Found: 184.0733.

R_f (cyHex/EtOAc, 1:1) = 0.46 [$KMnO_4$]

tert-Butyl (S)-(2-hydroxy-1-phenylethyl)carbamate



$C_{13}H_{19}NO_3$
237,30 g/mol

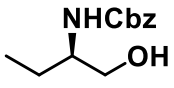
L-Phenylglycinol (1.49 g, 10.9 mmol, 1.0 equiv.) and NaOH (0.60 g, 15.0 mmol, 1.4 equiv.) were dissolved in H_2O (10 mL, 1.09 M). To this solution, added Boc_2O (2.56 g, 11.7 mmol, 1.1 equiv.) dissolved in 1,4-dioxane (10 mL). The reaction was stirred at room temperature for several days. Added some EtOAc, then extracted with CH_2Cl_2 (2 x 50 mL), before drying over Na_2SO_4 and concentrating in vacuum. Purification via flash chromatography afforded the product as a white powder in 26% yield (0.68 g, 2.87 mmol).

The analytical data are in agreement with those previously reported.[275]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 7.31 – 7.28 (m, 3H), 5.20 (s, 1H), 4.78 (s, 1H), 3.85 (d, *J* = 4.4 Hz, 2H), 2.21 (br, 1H), 1.44 (s, 9H).

R_f (cyHex/EtOAc, 2:1) = 0.24 [Ninhydrin]

Benzyl (R)-(1-hydroxybutan-2-yl)carbamate



$C_{12}H_{17}NO_3$
223,27 g/mol

(R)-2-Aminobutan-1-ol (4.75 mL, 50.1 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (100 mL). Added Et_3N (14 mL, 101.0 mmol, 2.0 equiv.) and cooled down in an ice-bath. After 5 min, added CbzCl (7.3 mL, 52.2 mmol, 1.0 equiv.) over a period of 15 min. Continued stirring in the ice-bath for 5 min, then let stir at room temperature overnight. The next day, the reaction

mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1 M HCl (3 x 50 mL). Aq. layers were washed with CH_2Cl_2, then combined org. layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography afforded the product as a white, crystalline solid in 20% yield (2.26 g, 10.12 mmol).

The analytical data are in agreement with those previously reported.[276]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 5.09 (s, 2H), 4.99 (s, 1H), 3.71 – 3.50 (m, 3H), 2.45 (s, 1H), 1.57 (dp, *J* = 13.7, 7.4 Hz, 1H), 1.45 (dp, *J* = 14.8, 7.5 Hz, 1H), 0.94 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.0, 136.5, 128.6, 128.2, 128.2, 67.0, 65.1, 54.9, 24.5, 10.6.

***tert*-Butyl (1-(hydroxymethyl)cyclobutyl)carbamate**

$C_{10}H_{19}NO_3$
201,27 g/mol

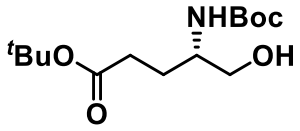
1-Aminocyclobutane-1-carboxylic acid hydrochloride (10.0 g, 66.0 mmol, 1.0 equiv.) was suspended in 2,2-dimethoxypropane (200 mL). Added 12 M HCl (20 mL, 240.0 mmol, 3.6 equiv.) and let stir at room temperature overnight. The next day, received a black solution. Slowly added $NaHCO_3$ (30 g, 357.0 mmol, 5.4 equiv.) dissolved in H_2O (330 mL). Afterwards, added Boc_2O (14.54 g, 66.6 mmol, 1.0 equiv.), dissolved in EtOAc (180 mL), and let stir at room temperature for 60 h. The reaction mixture was extracted with EtOAc and the combined org. layers were dried over Na_2SO_4 and concentrated in vacuum. The residue was redissolved in EtOH/H_2O (16:1, 640 mL, 0.1 M) to receive a brown solution. While stirring in an ice-bath, slowly added $NaBH_4$ (7.5 g, 198.3 mmol, 3.0 equiv.) to receive a yellow solution. The reaction was stirred in the cooling bath, which was allowed to warm up to room temperature, for 72 h. The reaction was cooled down in an ice-bath and quenched by adjusting the pH to 1 via careful addition of 1 M to 12 M HCl. After concentration in vacuum, a first attempt to purify the product via flash chromatography failed. The obtained, impure product was dissolved in $CHCl_3$ (150 mL) and washed with 1 M HCl and 1 M NaOH (100 mL each). Combined org. layers were dried over Na2SO4 and concentrated in vacuum. Another purification via flash chromatography afforded the product as a light-brown solid in 48% yield (6.35 g, 31.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (s, 1H), 3.75 (s, 2H), 2.11 (dddd, *J* = 22.1, 13.5, 8.6, 5.9 Hz, 4H), 1.99 – 1.87 (m, 1H), 1.79 (dp, *J* = 11.7, 8.8 Hz, 1H), 1.44 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.0, 80.1, 68.3, 57.3, 30.7, 28.5, 14.6.

R_f (cyHex/EtOAc, 2:1) = 0.18 [Ninhydrin]

tert-Butyl (S)-4-((_tert_-butoxycarbonyl)amino)-5-hydroxypentanoate



$C_{14}H_{27}NO_5$
289,37 g/mol

According to a literature procedure,[277] (S)-5-(*tert*-Butoxy)-2-((*tert*-butoxycarbonyl)-amino)-5-oxopentanoic acid (2.17 g, 7.14 mmol, 1.0 equiv.) was dissolved in THF (50 mL, 0.14 M) and cooled down to -18 °C using an ice-NaCl bath. While stirring at this temperature, slowly added Et_3N (1 mL, 7.21 mmol, 1.0 equiv.) and, afterwards, ethyl chloroformate (0.7 mL, 7.35 mmol, 1.0 equiv.) over a period of 1 min. Let stir between -10 and -20 °C for 40 min, then filtered reaction mixture and washed colorless solid with 2 x 10 mL THF. Over a period of 45 min, the filtrate was added dropwise to a mixture of $NaBH_4$ (0.75 g, 19.80 mmol, 2.8 equiv.) in H_2O (10 mL, 2 M) while stirring in an ice-bath. Continued stirring at this temperature for 3 h, then allowed reaction mixture to warm up to room temperature and stirred for additional 3 days. Ice water (20 mL) and, slowly, 1 M HCl (20 mL) were added, and the reaction mixture was extracted with EtOAc (3 x 50 mL). The combined org. layers were washed with 10% citric acid (50 mL), satd. $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL). After drying over Na_2SO_4, purification via flash chromatography afforded the product as a colorless solid in 86% yield (1.78 g, 6.15 mmol).

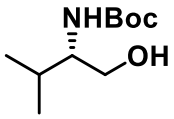
The analytical data are in agreement with those previously reported.[277]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (s, 1H), 3.67 – 3.50 (m, 3H), 2.31 (dt, *J* = 7.1, 3.5 Hz, 2H), 1.83 (dtd, *J* = 14.4, 7.2, 5.6 Hz, 1H), 1.74 (dq, *J* = 8.2, 6.9 Hz, 1H), 1.44 (s, 9H), 1.43 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.4, 156.4, 81.0, 79.8, 65.4, 52.8, 32.2, 28.5, 28.2, 26.1.

R_f (cyHex/EtOAc, 1:1) = 0.32 [Ninhydrin]

(S)-_N_-Boc-valinol (165)

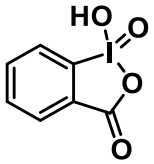


$C_{10}H_{21}NO_3$
203,28 g/mol

L-Valinol (2.14 g, 20.7 mmol, 1.0 equiv.) and NaOH (1.38 g, 34.5 mmol, 1.7 equiv.) were dissolved in H_2O (30 mL, 0.69 M). To this clear solution, added Boc_2O (5.60 g, 25.7 mmol, 1.2 equiv.) dissolved in 1,4-dioxane (30 mL). The reaction was stirred at room temperature for 60 h. Received a colorless solution with white precipitate. Added some H_2O to redissolve precipitate, then extracted with EtOAc (3 x 100 mL) and washed combined org. layers with

brine, before drying over Na_2SO_4 and concentrating in vacuum. Purification via flash chromatography afforded the product as a colorless oil in 84% yield (3.54 g, 17.4 mmol).
The analytical data are in agreement with those previously reported.[278]
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (s, 1H), 3.69 (dd, *J* = 11.1, 3.8 Hz, 1H), 3.60 (dd, *J* = 11.1, 6.4 Hz, 1H), 3.42 (s, 1H), 1.83 (h, *J* = 6.8 Hz, 1H), 1.44 (s, 9H), 0.94 (d, *J* = 8.2 Hz, 3H), 0.94 (d, *J* = 8.2 Hz, 3H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.0, 79.6, 64.2, 58.2, 29.5, 28.5, 19.6, 18.6.
R_f (cyHex/EtOAc, 1:1) = 0.28 [Ninhydrin]

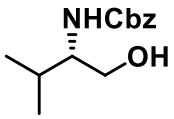
1-Hydroxy-1-oxo-1λ^5-benzo[d][1,2]iodaoxol-3(1*H*)-one, IBX (168)



$C_7H_5IO_4$
280,02 g/mol

Following a slightly modified literature procedure,[210] Oxone® (110.0 g, 357.9 mmol, 5.2 equiv.) was dissolved in H_2O (600 mL, 0.11 M). Added 2-iodobenzoic acid (17.0 g, 68.5 mmol, 1.0 equiv.), then heated up suspension to 70 °C for 3 h. A white precipitate was formed. After cooling down to room temperature, the reaction mixture was cooled in an ice-bath and filtered through a glass frit. The filtrate was treated with $Na_2S_2O_4$ to quench its oxidizing character before disposal. The filtered, white solid was washed with H_2O (300 mL) and acetone (100 mL). Drying in vacuum overnight afforded the product as a fine, white powder in 76% yield (14.64 g, 52.3 mmol).
The analytical data are in agreement with those previously reported.[279]
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.15 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.04 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.00 (ddd, *J* = 8.3, 7.3, 1.4 Hz, 1H), 7.84 (td, *J* = 7.4, 1.1 Hz, 1H).
^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 167.4, 146.5, 133.3, 132.9, 131.4, 130.1, 125.0.

(S)-*N*-Cbz-valinol (181)



$C_{13}H_{19}NO_3$
237,30 g/mol

L-Valinol (2.03 g, 19.7 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (30 mL, 0.66 M). To this solution, added NaOH (1.46 g, 36.5 mmol, 1.9 equiv.) dissolved in 30 mL H_2O, then added

CbzCl (3.5 mL, 24.6 mmol, 1.2 equiv.). The reaction was stirred at room temperature overnight. The next day, reaction mixture was extracted with EtOAc (3 x 100 mL) and the combined org. layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography afforded the product as a white solid in 42% yield (1.98 g, 8.3 mmol).

(rac)-181: (rac)-Valine (0.76 g, 6.5 mmol, 1.0 equiv.) was suspended in 2,2-dimethoxypropane (20 mL). Added 12 M HCl (2 mL, 24.0 mmol, 3.7 equiv.) and let stir at room temperature overnight. The next day, received a black solution. Slowly added $NaHCO_3$ (5.0 g, 59.5 mmol, 9.2 equiv.) which dissolved in H_2O (75 mL). Afterwards, added CbzCl (1 mL, 7.0 mmol, 1.1 equiv.) and let stir at room temperature for 60 h. The reaction mixture was extracted with EtOAc (2 x 50 mL) and the combined org. layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuum. The residual yellow oil was dissolved in dry THF (10 mL) and slowly added to an ice-cold suspension of $LiAlH_4$ (272 mg, 7.2 mmol, 1.1 equiv.) in dry THF (10 mL). After 5 min, the cooling bath was removed and the reaction was stirred at room temperature for 4 h. The reaction was cooled in an ice-bath and quenched by the slow addition of H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (2 x 30 mL). To receive a better phase separation, a bit of satd. K-Na-tartrate solution was added. Combined org. layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated in vacuum.

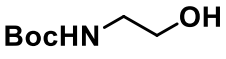
Purification via flash chromatography afforded the product as a yellowish oil in 51% yield (0.78 g, 3.3 mmol).

The analytical data are in agreement with those previously reported.[280]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 5H), 5.13 (s, 2H), 4.93 (d, *J* = 8.9 Hz, 1H), 3.77 – 3.62 (m, 2H), 3.53 (dtd, *J* = 10.1, 6.3, 3.8 Hz, 1H), 2.02 (s, 1H), 1.88 (dt, *J* = 13.5, 6.8 Hz, 1H), 0.98 (d, *J* = 10.7 Hz, 3H), 0.96 (d, *J* = 10.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 136.5, 128.7, 128.3, 128.3, 67.1, 64.1, 58.8, 29.4, 19.6, 18.6.

***tert*-Butyl (2-hydroxyethyl)carbamate (235)**



$C_7H_{15}NO_3$
161,20 g/mol

2-Aminoethan-1-ol (0.6 mL, 10.0 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (20 mL, 0.5 M). While stirring in an ice-bath, added Boc_2O (2.2 g, 10.1 mmol, 1.0 equiv.), dissolved in CH_2Cl_2 (13 mL). The reaction was stirred in the cooling bath, which was allowed to warm up to room temperature, overnight. The next day, added satd. $NaHCO_3$ solution (40 mL) and, after stirring for another 2 h, added H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 60 mL) and the combined org. layers were dried over Na_2SO_4 and concentrated in vacuum.

Purification via flash chromatography afforded the product as a colorless oil in 97% yield (1.57 g, 9.7 mmol).

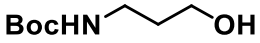
The analytical data are in agreement with those previously reported.[281]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (dd, *J* = 5.6, 4.7 Hz, 2H), 3.25 (dd, *J* = 5.6, 4.7 Hz, 2H), 1.42 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.8, 79.6, 62.3, 43.2, 28.3.

R_f (cyHex/EtOAc, 2:1) = 0.07 [Ninhydrin]

***tert*-Butyl (3-hydroxypropyl)carbamate (255)**



$C_8H_{17}NO_3$
175,23 g/mol

3-Aminopropan-1-ol (0.75 mL, 9.8 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (10 mL, 0.98 M). While stirring in an ice-bath, added Boc_2O (2.18 g, 10.0 mmol, 1.0 equiv.), dissolved in CH_2Cl_2 (20 mL). After 5 min, the cooling bath was removed and the reaction was stirred at room temperature overnight. The next day, added satd. $NaHCO_3$ solution (40 mL) and, after stirring for another 15 min, added H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 60 mL) and the combined org. layers were dried over Na_2SO_4 and concentrated in vacuum.

Purification via flash chromatography afforded the product as a colorless oil in 89% yield (1.52 g, 8.7 mmol).

The analytical data are in agreement with those previously reported.[282]

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.91 (s, 1H), 3.63 (t, *J* = 5.8 Hz, 2H), 3.24 (d, *J* = 6.4 Hz, 2H), 1.69 – 1.58 (m, 2H), 1.41 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.2, 79.6, 59.4, 37.1, 32.9, 28.5.

VI.IV.3 – Synthesis and Characterization of Products

General procedure VI (GP-VI)

Into a 10–20 mL Biotage® microwave reaction vial added amino alcohol (1.0 mmol, 2.0 equiv.), **4CzIPN** (19.7 mg, 25 µmol, 5 mol%), quinuclidine (5.6 mg, 50 µmol, 10 mol%), $PhB(OH)_2$ (12.2 mg, 0.1 mmol, 20 mol%) and a magnetic stirring bar before sealing it with a septum cap. The reaction vial was then evacuated and backfilled with N_2 for 1 min each. This was repeated three times. Then, dry and degassed MeCN (10 mL) was added and the reaction mixture was stirred for 5 min to receive a clear solution. Afterwards, added a 0.05 M solution of the corresponding Michael acceptor in dry and degassed MeCN (10 mL, 0.5 mmol, 1.0 equiv.) and sealed the vial cap with parafilm. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 440 nm) at room temperature for 24 h. After the irradiation was done, the vial cap was removed and IBX (560 mg, 2.0 mmol, 2.0 equiv.) was added. The resealed reaction mixture was heated in an oil bath at 85 °C for 3 h. After cooling down to room temperature, the reaction mixture was concentrated in vacuum.

Achiral products were purified via flash column chromatography on neutral aluminiumoxide. To do so, the concentrated reaction mixture was suspended in CH_2Cl_2 and loaded on the column. First, washed with 200 mL of CH_2Cl_2 (to remove **4CzIPN**), then started purifying the product using cyclohexane/EtOAc as eluent system.

Chiral products were isolated via flash chromatography on silica or deactivated silica. To obtain the deactivated silica, silica was conditioned with 200 mL of 1% Et_3N solution in cyclohexane. Then, the excess Et_3N was washed down with another 100 mL of cyclohexane. A suspension of the raw product in CH_2Cl_2 was loaded to the column, and the product purified using cyclohexane/EtOAc as eluent system.

The isolated products were concentrated in high vacuum overnight.

General procedure VII (GP-VII)

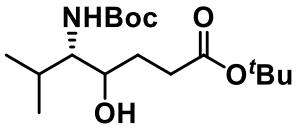
Into a 10–20 mL Biotage® microwave reaction vial added amino alcohol (0.55 mmol, 1.1 equiv.), **4CzIPN** (19.7 mg, 25 µmol, 5 mol%), quinuclidine (5.6 mg, 50 µmol, 10 mol%), $PhB(OH)_2$ (12.2 mg, 0.1 mmol, 20 mol%) and a magnetic stirring bar before sealing it with a septum cap. The reaction vial was then evacuated and backfilled with N_2 for 1 min each. This was repeated three times. Then, dry and degassed MeCN (10 mL) was added and the reaction mixture was stirred for 5 min to receive a clear solution. Afterwards, added a 0.05 M solution of the corresponding Michael acceptor in dry and degassed MeCN (10 mL, 0.5 mmol, 1.0 equiv.) and sealed the vial cap with parafilm. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 440 nm) at room temperature for 66 h. After the irradiation was done, the vial cap was removed and IBX (308 mg, 1.1 mmol, 2.0 equiv.) was added. The resealed

reaction mixture was heated in an oil bath at 85 °C for 3 h. After cooling down to room temperature, the reaction mixture was concentrated in vacuum.
Achiral products were purified via flash column chromatography on neutral aluminiumoxide. To do so, the concentrated reaction mixture was suspended in CH_2Cl_2 and loaded on the column. First, washed with 200 mL of CH_2Cl_2 (to remove **4CzIPN**), then started purifying the product using cyclohexane/EtOAc as eluent system.
Chiral products were isolated via flash chromatography on silica or deactivated silica. To obtain the deactivated silica, silica was conditioned with 200 mL of 1% Et_3N solution in cyclohexane. Then, the excess Et_3N was washed down with another 100 mL of cyclohexane. A suspension of the raw product in CH_2Cl_2 was loaded to the column, and the product purified using cyclohexane/EtOAc as eluent system.
The isolated products were concentrated in high vacuum overnight.

General procedure VIII (GP-VIII)

Into a 10–20 mL Biotage® microwave reaction vial added amino alcohol (0.50 mmol, 2.0 equiv.), **4CzIPN** (19.7 mg, 25 µmol, 10 mol%), quinuclidine (5.6 mg, 50 µmol, 20 mol%), $PhB(OH)_2$ (12.2 mg, 0.1 mmol, 40 mol%) and a magnetic stirring bar before sealing it with a septum cap. The reaction vial was then evacuated and backfilled with N_2 for 1 min each. This was repeated three times. Then, dry and degassed MeCN (10 mL) was added and the reaction mixture was stirred for 5 min to receive a clear solution. Afterwards, added a 0.025 M solution of the corresponding Michael acceptor in dry and degassed MeCN (10 mL, 0.25 mmol, 1.0 equiv.) and sealed the vial cap with parafilm. The reaction mixture was stirred under blue LED irradiation (32 W, λ_{max} = 440 nm) at room temperature for 24 h. After the irradiation was done, the vial cap was removed and IBX (560 mg, 2.0 mmol, 2.0 equiv.) was added. The resealed reaction mixture was heated in an oil bath at 85 °C for 3 h. After cooling down to room temperature, the reaction mixture was concentrated in vacuum.
Achiral products were purified via flash column chromatography on neutral aluminiumoxide. To do so, the concentrated reaction mixture was suspended in CH_2Cl_2 and loaded on the column. First, washed with 200 mL of CH_2Cl_2 (to remove **4CzIPN**), then started purifying the product using cyclohexane/EtOAc as eluent system.
Chiral products were isolated via flash chromatography on silica or deactivated silica. To obtain the deactivated silica, silica was conditioned with 200 mL of 1% Et_3N solution in cyclohexane. Then, the excess Et_3N was washed down with another 100 mL of cyclohexane. A suspension of the raw product in CH_2Cl_2 was loaded to the column, and the product purified using cyclohexane/EtOAc as eluent system.
The isolated products were concentrated in high vacuum overnight.

***tert*-Butyl (5S)-5-((*tert*-butoxycarbonyl)amino)-4-hydroxy-6-methylheptanoate (167)**



$C_{17}H_{33}NO_5$
331,45 g/mol

Synthesized following **GP-VI** using (S)-Boc-valinol (203.2 mg, 1.00 mmol, 2.0 equiv.). After the irradiation step, the d.r. was checked via GC-FID analysis (d.r. ~2.2 : 1) and then worked up. Purification via flash chromatography using SiO_2 afforded the product in a ~3:1 mixture of diastereomers as a yellow oil in 84% combined yield (138 mg, 0.42 mmol).

^{1}H NMR (600 MHz, $CDCl_3$, *mayor isomer*): δ 4.81 (d, *J* = 10.0 Hz, 1H), 3.84 – 3.75 (m, 1H), 3.17 – 3.12 (m, 1H), 2.92 (d, *J* = 4.7 Hz, 1H), 2.40 (ddt, *J* = 30.5, 16.4, 7.7 Hz, 2H), 1.88 (dh, *J* = 21.0, 6.8 Hz, 1H), 1.81 – 1.68 (m, 2H), 1.44 (s, 18H), 0.97 – 0.90 (m, 6H).

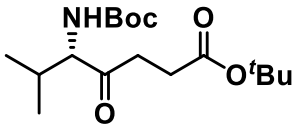
^{1}H NMR (600 MHz, $CDCl_3$, *minor isomer*): δ 4.45 (d, *J* = 9.5 Hz, 1H), 3.65 – 3.59 (m, 1H), 3.47 (dt, *J* = 11.3, 6.0 Hz, 1H), 2.40 (ddt, *J* = 30.5, 16.4, 7.7 Hz, 2H), 1.88 (dh, *J* = 21.0, 6.8 Hz, 1H), 1.81 – 1.68 (m, 2H), 1.61 (dq, *J* = 9.5, 7.1 Hz, 1H), 1.44 (s, 18H), 0.97 – 0.90 (m, 6H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, *both isomers*) δ 174.2, 156.8, 80.9, 79.2, 77.4, 77.2, 76.9, 71.1, 60.6, 60.5, 32.7, 32.2, 30.3, 30.2, 28.6, 28.5, 28.3, 28.2, 27.1, 20.4, 20.0, 19.3.

HRMS (ESI): [m/z] calculated for $C_{17}H_{33}NNaO_5^+$ ([M+Na]$^+$): 354.2251; Found: 354.2248.

R_f (cyHex/EtOAc, 4:1) = 0.18 [Ninhydrin]

***tert*-Butyl (S)-5-((*tert*-butoxycarbonyl)amino)-6-methyl-4-oxoheptanoate (169)**



$C_{17}H_{31}NO_5$
329,44 g/mol

Synthesized following **GP-VI** using (S)-Boc-valinol (202.7 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a slightly yellowish oil in 80% yield (132 mg, 0.40 mmol).

Synthesized following **GP-VII** using (S)-Boc-valinol (111.6 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 78% yield (129 mg, 0.39 mmol).

Synthesized following **GP-VII** using (S)-Boc-valinol (111.8 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a yellow oil in 84% yield (139 mg, 0.42 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.10 (d, *J* = 8.7 Hz, 1H), 4.27 (dd, *J* = 8.7, 4.2 Hz, 1H), 2.83 (dt, *J* = 18.2, 6.8 Hz, 1H), 2.69 (dt, *J* = 18.3, 6.3 Hz, 1H), 2.60 – 2.40 (m, 2H), 2.25 – 2.18 (m, 1H), 1.43 (d, *J* = 2.1 Hz, 18H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 208.1, 171.8, 156.1, 80.8, 79.8, 64.1, 35.8, 30.4, 29.2, 28.5, 28.2, 20.0, 16.8.

HRMS (ESI): [m/z] calculated for $C_{17}H_{31}NNaO_5^+$ ([M+Na]$^+$): 352.2094; Found: 352.2093.

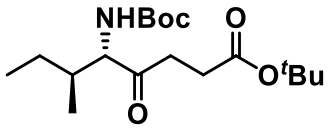
IR: ṽ [cm^{-1}] = 3363 (w), 2971 (m), 2932 (m), 2877 (m), 2637 (w), 1705 (s), 1496 (s), 1460 (m), 1391 (m), 1365 (s), 1309 (m), 1238 (s), 1152 (s), 1081 (m), 1040 (m), 1014 (m), 958 (w), 924 (w), 875 (m), 848 (m), 780 (w), 754 (w), 733 (w), 622 (w), 575 (w), 539 (w), 462 (w), 430 (w).

R_f (cyHex/EtOAc, 4:1) = 0.39 [Ninhydrin]

$[\alpha]_D^{20}$ = + 19.4° (ρ = 1.01, CH_2Cl_2) (purified on neutral aluminiumoxide)

$[\alpha]_D^{20}$ = + 26.1° (ρ = 1.01, CH_2Cl_2) (purified on deactivated SiO_2)

***tert*-Butyl (5S,6S)-5-((*tert*-butoxycarbonyl)amino)-6-methyl-4-oxooctanoate (171)**



$C_{18}H_{33}NO_5$
343,46 g/mol

Synthesized following **GP-VI** using (2S,3S)-Boc-isoleucinol (217.6 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as an orange oil in 56% yield (97 mg, 0.28 mmol).

Synthesized following **GP-VII** using (2S,3S)-Boc-isoleucinol (119.7 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a slightly yellowish oil in 80% yield (137 mg, 0.40 mmol).

Synthesized using following conditions: (2S,3S)-Boc-isoleucinol (108.9 mg, 0.50 mmol, 1.0 equiv.), **IrF** (5.8 mg, 5 µmol, 1 mol%), quinuclidine (5.5 mg, 0.05 mmol, 10 mol%), $PhB(OH)_2$ (11.9 mg, 0.10 mmol, 20 mol%) and *tert*-butylacrylate (150 µL, 1.03 mmol, 2.1 equiv.) in dry and degassed MeCN (2 mL, c = 0.25 M). The reaction was irradiated at rt for 24 h using blue LED (32W, λ_{max} = 440 nm). For the oxidation step, redissolved photoreaction outcome in EtOAc (5 mL, c = 0.1 M), added IBX (280 mg, 1.00 mmol, 2.0 equiv.) and let stir to 85 °C for 3 h. Purification via automatic flash chromatography using neutral SiO_2 afforded the product as a yellowish oil in 64% yield (110 mg, 0.32 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.08 (d, *J* = 8.8 Hz, 1H), 4.28 (dd, *J* = 8.8, 4.5 Hz, 1H), 2.81 (dt, *J* = 18.4, 6.9 Hz, 1H), 2.72 (dt, *J* = 18.3, 6.4 Hz, 1H), 2.50 (qt, *J* = 17.1, 6.6 Hz, 2H), 1.94 (dt,

J = 13.2, 6.0 Hz, 1H), 1.43 (s, 18H), 1.34 – 1.27 (m, 1H), 1.07 (ddd, *J* = 13.1, 9.5, 6.7 Hz, 1H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 208.4, 171.9, 156.0, 80.8, 79.8, 64.0, 37.1, 36.1, 29.2, 28.5, 28.2, 24.3, 16.2, 11.8.

HRMS (ESI): [m/z] calculated for $C_{18}H_{33}NNaO_5^+$ ($[M+Na]^+$): 366.2251; Found: 366.2252.

IR: ṽ [cm^{-1}] = 3362 (w), 2971 (w), 2933 (w), 2878 (w), 1705 (s), 1495 (m), 1457 (w), 1390 (m), 1365 (s), 1242 (m), 1152 (s), 1078 (m), 1044 (m), 1010 (m), 955 (w), 920 (w), 873 (w), 848 (m), 778 (w), 753 (w), 735 (w), 462 (w), 431 (w).

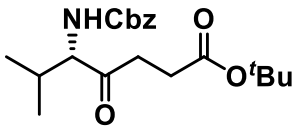
R_f (cyHex/EtOAc, 4:1) = 0.44 [Ninhydrin]

$[\alpha]_D^{20}$ = + 15.2° (ρ = 0.99, CH_2Cl_2) (purified on neutral aluminiumoxide)

$[\alpha]_D^{20}$ = + 22.4° (ρ = 1.01, CH_2Cl_2) (purified on deactivated SiO_2)

$[\alpha]_D^{20}$ = + 22.6° (ρ = 1.01, CH_2Cl_2) (purified on neutral SiO_2)

***tert*-Butyl (S)-5-(((benzyloxy)carbonyl)amino)-6-methyl-4-oxoheptanoate (182)**



$C_{20}H_{29}NO_5$
363,45 g/mol

Synthesized following **GP-VI** using (S)-Cbz-valinol (237.6 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a dark-yellow oil in 69% yield (126 mg, 0.35 mmol).

Synthesized following **GP-VI** using (S)-Cbz-valinol (237.6 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a slightly yellowish oil in 81% yield (148 mg, 0.41 mmol).

Synthesized using following conditions: (S)-Cbz-valinol (119.0 mg, 0.50 mmol, 1.0 equiv.), **IrF** (5.5 mg, 5 mmol, 1 mol%), quinuclidine (5.7 mg, 0.05 mmol, 10 mol%), $PhB(OH)_2$ (12.1 mg, 0.10 mmol, 20 mol%) and *tert*-butylacrylate (150 µL, 1.03 mmol, 2.1 equiv.) in dry and degassed MeCN (2 mL, c = 0.25 M). The reaction was irradiated at rt for 24 h using blue LED (32W, λ_{max} = 440 nm). For the oxidation step, redissolved photoreaction outcome in EtOAc (5 mL, c = 0.1 M), added IBX (286 mg, 1.02 mmol, 2.0 equiv.) and let stir to 85 °C for 3 h. Purification via automatic flash chromatography using neutral SiO_2 afforded the product as a colorless oil in 45% yield (81 mg, 0.22 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 5H), 5.38 (d, *J* = 8.8 Hz, 1H), 5.10 (s, 2H), 4.37 (dd, *J* = 8.7, 4.1 Hz, 1H), 2.84 (dt, *J* = 18.3, 6.8 Hz, 1H), 2.69 (dt, *J* = 18.3, 6.3 Hz, 1H), 2.60 –

2.42 (m, 2H), 2.31 – 2.20 (m, 1H), 1.42 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 207.6, 171.8, 156.6, 136.5, 128.7, 128.3, 128.2, 80.9, 67.1, 64.5, 35.7, 30.4, 29.1, 28.2, 20.0, 16.7.

HRMS (ESI): [m/z] calculated for $C_{20}H_{29}NNaO_5^+$ ($[M+Na]^+$): 386.1938; Found: 386.1944.

IR: ṽ [cm^{-1}] = 3338 (w), 3065 (w), 3034 (w), 2968 (w), 2932 (w), 2876 (w), 1705 (s), 1503 (m), 1455 (m), 1392 (m), 1366 (m), 1308 (m), 1229 (s), 1151 (s), 1096 (m), 1078 (m), 1025 (m), 1008 (m), 981 (m), 915 (m), 887 (m), 846 (m), 775 (m), 750 (m), 740 (m), 697 (s), 592 (m), 577 (m), 496 (m), 457 (m).

R_f (cyHex/EtOAc, 4:1) = 0.34 [Ninhydrin]

$[\alpha]_D^{20}$ = + 23.4° (ρ = 1.00, CH_2Cl_2) (purified on neutral aluminiumoxide)

$[\alpha]_D^{20}$ = + 25.4° (ρ = 0.99, CH_2Cl_2) (purified on deactivated SiO_2)

$[\alpha]_D^{20}$ = + 28.4° (ρ = 0.98, CH_2Cl_2) (purified on neutral SiO_2)

Chiral HPLC (CHIRALPAK IA, Heptane / Ethanol 95:5, 0.8 ml/min, 25 min, 220 nm, 254 nm):

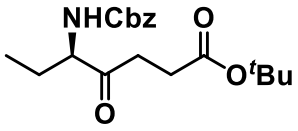
Retention times: 11.1 min ((S)-Enantiomer); 13.1 – 13.4 min ((R)-Enantiomer)

99:1 e.r. (purification on SiO_2)

95:5 e.r. (purification on deactivated SiO_2)

90:10 e.r. (purification on neutral Aluminiumoxide)

***tert*-Butyl (R)-5-(((benzyloxy)carbonyl)amino)-4-oxoheptanoate (184)**



$C_{19}H_{27}NO_5$
349,43 g/mol

Synthesized following **GP-VIII** using (R)-Cbz-2-amino butanol (111.7 mg, 0.50 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 77% yield (67 mg, 0.19 mmol).

Synthesized following **GP-VI** using (R)-Cbz-2-amino butanol (112 mg, 0.50 mmol, 1.0 equiv.). Purification via flash chromatography using neutral SiO_2 afforded the product as an orange oil in 82% yield (143 mg, 0.41 mmol).

(rac)-275: Synthesized following **GP-VI** using Cbz-2-amino butanol (112 mg, 0.50 mmol, 1.0 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a yellow oil in 84% yield (147 mg, 0.42 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.29 (m, 5H), 5.50 (d, *J* = 7.5 Hz, 1H), 5.10 (s, 2H), 4.40 (td, *J* = 7.0, 4.8 Hz, 1H), 2.81 (dt, *J* = 18.2, 6.7 Hz, 1H), 2.70 (dt, *J* = 18.2, 6.4 Hz, 1H), 2.58 –

2.46 (m, 2H), 2.01 (dqd, *J* = 14.8, 7.5, 5.1 Hz, 1H), 1.67 (dt, *J* = 14.4, 7.2 Hz, 1H), 1.42 (s, 9H), 0.89 (t, *J* = 7.4 Hz, 3H).

$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 207.4, 171.8, 156.1, 136.5, 128.7, 128.3, 128.2, 80.9, 67.0, 60.8, 34.7, 29.1, 28.2, 24.9, 9.2.

HRMS (ESI): [m/z] calculated for $C_{19}H_{27}NNaO_5^+$ ([M+Na]$^+$): 372.1781; Found: 372.1780.

IR: ṽ [cm^{-1}] = 3336 (w), 2974 (w), 2935 (w), 2880 (w), 1705 (s), 1517 (m), 1502 (m), 1455 (m), 1392 (w), 1366 (m), 1334 (m), 1229 (s), 1150 (s), 1077 (m), 1052 (m), 1028 (m), 976 (m), 915 (w), 878 (w), 846 (m), 776 (w), 738 (m), 697 (s), 577 (m), 496 (m).

R_f (cyHex/EtOAc, 4:1) = 0.23 [Ninhydrin]

$[\alpha]_D^{20}$ = + 1.8° (ρ = 1.01, CH_2Cl_2) (purified on neutral aluminiumoxide)

$[\alpha]_D^{20}$ = - 26.0° (ρ = 0.98, CH_2Cl_2) (purified on neutral SiO_2)

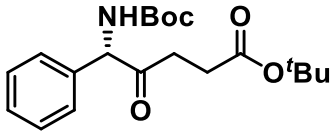
Chiral HPLC (CHIRALPAK IA, Heptane / Ethanol 93:7, 0.8 ml/min, 20 min, 220 nm, 254 nm):

Retention times: 13.4 – 13.5 min ((S)-Enantiomer); 14.2 – 14.3 min ((R)-Enantiomer)

50:50 e.r. (purification on neutral aluminiumoxide)

1:99 e.r. (purification on neutral SiO_2)

***tert*-Butyl (S)-5-((*tert*-butoxycarbonyl)amino)-4-oxo-5-phenylpentanoate (185)**



$C_{20}H_{29}NO_5$
363,45 g/mol

Synthesized following **GP-VII** using (S)-Boc-phenylglycine (130.0 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using neutral SiO_2 afforded the product as a yellow oil in 70% yield (128 mg, 0.35 mmol).

^1H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 5H), 5.87 (s, 1H), 5.31 (d, *J* = 6.3 Hz, 1H), 2.72 (dt, *J* = 18.9, 7.8 Hz, 1H), 2.51 (dt, *J* = 12.9, 7.8 Hz, 2H), 2.35 (dt, *J* = 16.5, 6.7 Hz, 1H), 1.39 (s, 18H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 204.6, 171.5, 155.0, 137.2, 129.3, 128.6, 128.0, 80.9, 80.0, 64.4, 34.8, 29.4, 28.4, 28.1.

HRMS (ESI): [m/z] calculated for $C_{20}H_{29}NNaO_5^+$ ([M+Na]$^+$): 386.1938; Found: 386.1941.

IR: ṽ [cm^{-1}] = 3425 (w), 2977 (w), 2930 (w), 1707 (s), 1486 m), 1456 (m), 1392 (w), 1365 (s), 1331 (m), 1245 (m), 1151 (s), 1097 (m), 1078 (m), 1055 (m), 1026 (m), 1011 (m), 955 (w), 876 (w), 847 (m), 753 (m), 700 (s), 617 (m), 576 (m), 512 (m), 462 (m).

R_f (cyHex/EtOAc, 4:1) = 0.38 [Ninhydrin]

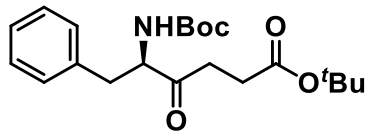
$[\alpha]_D^{20}$ = + 161.6° (ρ = 0.98, CH_2Cl_2) (purified on neutral SiO_2)

Chiral HPLC (CHIRALCEL OJ, Heptane / Ethanol 99.6:0.4, 0.8 ml/min, 40 min, 220 nm, 254 nm):

Retention times: 26.1 – 27.7 min ((S)-Enantiomer); 30.1 – 31.8 min ((R)-Enantiomer)

93:7 e.r. (purification on neutral SiO_2)

***tert*-Butyl (R)-5-((*tert*-butoxycarbonyl)amino)-4-oxo-6-phenylhexanoate (186)**



$C_{21}H_{31}NO_5$
377,48 g/mol

Synthesized following **GP-VI** using (S)-phenylalaninol (251.6 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a deep-yellow solid in 76% yield (143 mg, 0.38 mmol).

Synthesized following **GP-VII** using (R)-phenylalaninol (138.5 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as an off-white solid in 86% yield (163 mg, 0.43 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.0, 6.6 Hz, 2H), 7.25 – 7.21 (m, 1H), 7.18 – 7.15 (m, 2H), 5.07 (d, *J* = 7.7 Hz, 1H), 4.54 (q, *J* = 7.0 Hz, 1H), 3.13 (dd, *J* = 14.1, 6.3 Hz, 1H), 2.95 (dd, *J* = 14.0, 6.9 Hz, 1H), 2.72 – 2.67 (m, 2H), 2.48 (t, *J* = 6.6 Hz, 2H), 1.43 (s, 9H), 1.40 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 207.7, 171.8, 155.4, 136.5, 129.4, 128.7, 127.1, 80.8, 80.0, 60.3, 37.7, 35.4, 29.2, 28.4, 28.2.

HRMS (ESI): [m/z] calculated for $C_{21}H_{31}NNaO_5^+$ ([M+Na]$^+$): 400.2094; Found: 400.2089.

IR: ṽ [cm^{-1}] = 3333 (w), 2979 (w), 2936 (w), 1722 (s), 1679(s), 1604 (w), 1526 (m), 1496 (w), 1454 (w), 1393 (w), 1365 (m), 1320 (m), 1251 (m), 1227 (m), 1151 (s), 1109 (m), 1080 (w), 1051 (m), 1023 (m), 1003 (w), 938 (w), 888 (w), 849 (w), 787 (w), 756 (w), 739 (m), 699 (m), 662 (m), 571 (w), 541 (w), 493 (w), 467 (w), 428 (w).

R_f (cyHex/EtOAc, 4:1) = 0.39 [Ninhydrin]

$[\alpha]_D^{20}$ = + 6.6° (ρ = 1.00, CH_2Cl_2) (purified on neutral aluminiumoxide; (S)-enantiomer was used)

$[\alpha]_D^{20}$ = - 19.4° (ρ = 1.01, CH_2Cl_2) (purified on deactivated SiO_2; (R)-enantiomer was used)

Chiral HPLC (CHIRALPAK IA, Heptane / Ethanol 99.5:0.5, 1.0 ml/min, 45 min, 220 nm, 254 nm):

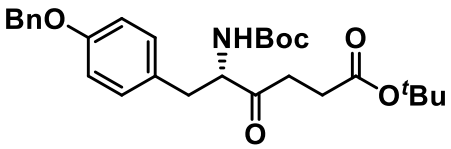
Retention times: 34.4 – 35.2 min ((R)-Enantiomer); 40.5 – 41.3 min ((S)-Enantiomer)

99:1 e.r. (no workup, crude, (R)-enantiomer was used)

98:2 e.r. (purification on deactivated SiO_2; (R)-enantiomer was used)

39:61 e.r. (purification on neutral aluminiumoxide; (S)-enantiomer was used)

***tert*-Butyl (S)-6-(4-(benzyloxy)phenyl)-5-((*tert*-butoxycarbonyl)amino)-4-oxohexanoate (187)**



$C_{28}H_{37}NO_6$
483,61 g/mol

Synthesized following **GP-VI** using Boc-Tyr(Bzl)-ol (357.5 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 55% yield (133 mg, 0.28 mmol).

Synthesized following **GP-VII** using Boc-Tyr(Bzl)-ol (197.6 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a yellow oil in 71% yield (171 mg, 0.35 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 – 7.41 (m, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.34 – 7.30 (m, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.07 (d, *J* = 7.4 Hz, 1H), 5.03 (s, 2H), 4.50 (q, *J* = 6.8 Hz, 1H), 3.07 (dd, *J* = 14.2, 6.3 Hz, 1H), 2.91 (dd, *J* = 14.1, 6.6 Hz, 1H), 2.70 (t, *J* = 6.6 Hz, 2H), 2.48 (t, *J* = 6.6 Hz, 2H), 1.43 (s, 9H), 1.40 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 207.8, 171.9, 158.0, 155.4, 137.2, 130.5, 128.7, 128.6, 128.1, 127.6, 115.1, 80.8, 80.0, 70.2, 60.4, 36.8, 35.4, 29.2, 28.5, 28.2.

HRMS (ESI): [m/z] calculated for $C_{28}H_{37}NNaO_6^+$ ([M+Na]$^+$): 506.2513; Found: 506.2522.

IR: ṽ [cm^{-1}] = 3427 (w), 3360 (w), 2976 (w), 2930 (w), 2870 (w), 1705 (s), 1611 (w), 1583 (w), 1510 (s), 1497 (m), 1454 (m), 1391 (m), 1365 (s), 1313(m), 1297 (m), 1239 (s), 1152 (s), 1039 (m), 1017 (m), 915 (m), 845 (m), 821 (m), 780 (m), 737 (m), 696 (m), 610 (m), 531 (m), 511 (m).

R_f (cyHex/EtOAc, 4:1) = 0.34 [Ninhydrin]

$[\alpha]_D^{20}$ = + 5.3° (ρ = 0.98, CH_2Cl_2) (purified on neutral Aluminiumoxide)

$[\alpha]_D^{20}$ = + 24.3° (ρ = 1.00, CH_2Cl_2) (purified on deactivated SiO_2)

Chiral HPLC (CHIRALPAK IA, Heptane / Ethanol 98.5:1.5, 0.8 ml/min, 60 min, 220 nm, 254 nm):

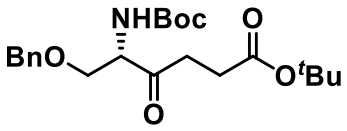
Retention times: 40.2 – 40.5 min ((R)-Enantiomer); 47.4 – 48.6 min ((S)-Enantiomer)

<1:99 e.r. (no workup, crude)

3:97 e.r. (purification on deactivated SiO_2)

41:59 e.r. (purification on neutral Aluminiumoxide)

***tert*-Butyl (S)-6-(benzyloxy)-5-((*tert*-butoxycarbonyl)amino)-4-oxohexanoate (188)**



$C_{22}H_{33}NO_6$
407,51 g/mol

Synthesized following **GP-VI** using (R)-Boc-Serinol(Bzl) (281.4 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a yellow oil in 89% yield (181 mg, 0.44 mmol).

Synthesized following **GP-VII** using (R)-Boc-Serinol(Bzl (154.5 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using neutral SiO_2 afforded the product as a yellow oil in 46% yield (93 mg, 0.23 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.26 (m, 5H), 5.51 (d, *J* = 7.6 Hz, 1H), 4.50 (q, *J* = 12.1 Hz, 2H), 4.40 (dt, *J* = 7.7, 3.9 Hz, 1H), 3.90 (dd, *J* = 9.8, 3.6 Hz, 1H), 3.69 (dd, *J* = 9.8, 4.2 Hz, 1H), 2.78 (td, *J* = 6.7, 1.6 Hz, 2H), 2.54 (dt, *J* = 17.1, 6.8 Hz, 1H), 2.48 (dt, *J* = 17.1, 6.6 Hz, 1H), 1.44 (s, 9H), 1.43 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 206.3, 171.8, 155.6, 137.6, 128.6, 128.0, 127.9, 80.8, 80.1, 73.6, 69.8, 60.00, 34.9, 29.2, 28.5, 28.2.

HRMS (ESI): [m/z] calculated for $C_{22}H_{33}NNaO_6^+$ ([M+Na]$^+$): 430.2200; Found: 430.2201.

IR: ṽ [cm^{-1}] = 3431 (w), 3359 (w), 2977 (w), 2931 (w), 2870 (w), 1708 (s), 1494 (m), 1454 (m), 1392 (m), 1365 (s), 1246 (m), 1151 (s), 1102 (s), 1069 (m), 1027 (m), 1002 (m), 954 (m), 917 (m), 865 (m), 846 (m), 780 (m), 748 (m), 698 (m), 595 (w), 462 (w).

R_f (cyHex/EtOAc, 4:1) = 0.35 [Ninhydrin]

$[\alpha]_D^{20}$ = +14.9° (ρ = 1.00, CH_2Cl_2) (purified on deactivated SiO_2)

$[\alpha]_D^{20}$ = +24.2° (ρ = 1.01, CH_2Cl_2) (purified on neutral SiO_2)

Chiral HPLC (CHIRALPAK IA, Heptane / Ethanol 99:1, 1.0 ml/min, 35 min, 220 nm, 254 nm):

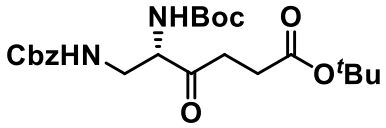
Retention times: 20.8 – 21.0 min ((S)-Enantiomer); 24.0 – 24.2 min ((R)-Enantiomer)

>99:1 e.r. (no workup, crude)

82:18 e.r. (purification on deactivated SiO_2)

>99:1 e.r. (purification on neutral SiO_2)

***tert*-Butyl (S)-6-(((benzyloxy)carbonyl)amino)-5-((*tert*-butoxycarbonyl)amino)-4-oxohexanoate (189)**



$C_{23}H_{34}N_2O_7$
450,53 g/mol

Synthesized following **GP-VI** using benzyl *tert*-butyl (3-hydroxypropane-1,2-diyl)(S)-dicarbamate (324.3, mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a dark-yellow oil in 86% yield (193 mg, 0.43 mmol).

Synthesized following **GP-VII** using benzyl *tert*-butyl (3-hydroxypropane-1,2-diyl)(S)-dicarbamate (178.0 mg, 0.55 mmol,1.1 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a yellowish oil in 77% yield (173 mg, 0.38 mmol).

Synthesized following **GP-VI** using benzyl *tert*-butyl (3-hydroxypropane-1,2-diyl)(S)-dicarbamate (324.3 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral SiO_2 afforded the product as a yellow oil in 73% yield (165 mg, 0.37 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 – 7.29 (m, 5H), 5.67 (s, 1H), 5.48 (s, 1H), 5.09 (d, *J* = 3.1 Hz, 2H), 4.35 (d, *J* = 5.7 Hz, 1H), 3.78 – 3.72 (m, 1H), 3.61 (d, *J* = 14.9 Hz, 1H), 2.84 (t, *J* = 11.9 Hz, 1H), 2.69 (dt, *J* = 18.2, 6.1 Hz, 1H), 2.63 – 2.51 (m, 2H), 1.43 (s, 9H), 1.42 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 206.7, 172.4, 157.2, 155.7, 136.5, 128.6, 128.2, 128.0, 81.2, 80.2, 67.0, 60.5, 42.3, 34.5, 29.2, 28.4, 28.2.

HRMS (ESI): [m/z] calculated for $C_{23}H_{34}N_2NaO_7^+$ ([M+Na]$^+$): 473.2258; Found: 473.2255.

IR: ṽ [cm^{-1}] = 3347 (w), 2977 (w), 2932 (w), 1703 (s), 1511 (m), 1454 (m), 1391 (m), 1366 (s), 1244 (s), 1150 (s), 1067 (m), 1009 (m), 912 (m), 846 (m), 777 (m), 750 (m), 735 (m), 697 (m), 604 (m), 575 (m), 460 (m).

R_f (cyHex/EtOAc, 4:1) = 0.24 [Ninhydrin]

$[\alpha]_D^{20}$ = + 1.4° (ρ = 0.99, CH_2Cl_2) (purified on neutral aluminiumoxide)

$[\alpha]_D^{20}$ = + 0.3° (ρ = 1.00, CH_2Cl_2) (purified on deactivated SiO_2)

$[\alpha]_D^{20}$ = + 2.7° (ρ = 1.00, CH_2Cl_2) (purified on SiO_2)

Chiral HPLC (CHIRALPAK IA, Heptane / Ethanol 90:10, 1.0 ml/min, 35 min, 220 nm, 254 nm):

Retention times: 21.8 – 22.7 min ((S)-Enantiomer); 25.1 – 25.9 min ((R)-Enantiomer)

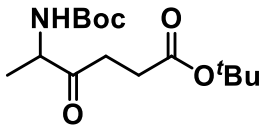
98:2 e.r. (no workup, crude)

52:48 e.r. (purification on deactivated SiO_2)

66:34 e.r. (purification on neutral aluminiumoxide)

98:2 e.r. (purification on neutral SiO_2)

***tert*-Butyl 5-((*tert*-butoxycarbonyl)amino)-4-oxohexanoate (193)**



$C_{15}H_{27}NO_5$
301,38 g/mol

Synthesized following **GP-VIII** using (S)-alaninol (87.6 mg, 0.50 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a deep yellow oil in 77% yield (58 mg, 0.19 mmol).

Synthesized following **GP-VI** using (S)-alaninol (175.2 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a deep yellow oil in 77% yield (116 mg, 0.39 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (s, 1H), 4.37 – 4.25 (m, 1H), 2.80 (dd, *J* = 16.4, 8.7 Hz, 1H), 2.69 (dt, *J* = 18.1, 6.4 Hz, 1H), 2.60 – 2.46 (m, 2H), 1.43 (d, *J* = 3.5 Hz, 18H), 1.35 (d, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 208.2, 171.8, 155.3, 80.9, 79.8, 55.2, 34.0, 29.2, 28.5, 28.2, 18.0.

HRMS (ESI): [m/z] calculated for $C_{15}H_{27}NNaO_5^+$ ($[M+Na]^+$): 324.1781; Found: 324.1783.

IR: ṽ [cm^{-1}] = 3364 (w), 2978 (w), 2933 (w), 1707 (s), 1498 (m), 1453 (w), 1391 (w), 1366 (s), 1289 (w), 1245 (m), 1152 (s), 1063 (m), 1002 (w), 847 (m), 782 (w), 753 (w).

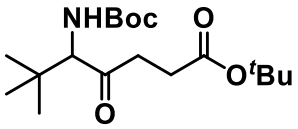
R_f (cyHex/EtOAc, 4:1) = 0.27 [Ninhydrin]

$[\alpha]_D^{20}$ = - 0.8° (ρ = 1.00, CH_2Cl_2) (purified on neutral aluminiumoxide)

$[\alpha]_D^{20}$ = +7.0° (ρ = 0.98, CH_2Cl_2) (purified on deactivated SiO_2)

Lit.: $[\alpha]_D^{20}$ = +13.3° (ρ = 2.0, $CHCl_3$)[283]

***tert*-Butyl 5-((*tert*-butoxycarbonyl)amino)-6,6-dimethyl-4-oxoheptanoate (194)**



$C_{18}H_{33}NO_5$
343,46 g/mol

Synthesized following **GP-VI** using *tert*-butyl (S)-(1-hydroxy-3,3-dimethylbutan-2-yl)carbamate (206.1 mg, 0.95 mmol, 1.9 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a dark-yellow oil in 48% yield (82 mg, 0.24 mmol).

Synthesized following **GP-VII** using *tert*-butyl (S)-(1-hydroxy-3,3-dimethylbutan-2-yl)carbamate (119.4 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a slightly yellowish oil in 82% yield (140 mg, 0.41 mmol). The sample contains 8% of *tert*-leucinal as impurity.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.11 (d, *J* = 9.4 Hz, 1H), 4.14 (d, *J* = 9.3 Hz, 1H), 2.90 (dt, *J* = 18.7, 6.9 Hz, 1H), 2.79 (dt, *J* = 18.7, 6.3 Hz, 1H), 2.53 – 2.40 (m, 2H), 1.42 (s, 9H), 1.42 (s, 9H), 0.98 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 209.4, 171.9, 155.8, 80.7, 79.9, 65.8, 39.3, 34.7, 29.2, 28.5, 28.2, 26.8.

HRMS (ESI): [m/z] calculated for $C_{18}H_{33}NNaO_5^+$ ([M+Na]$^+$): 366.2251; Found: 366.2253.

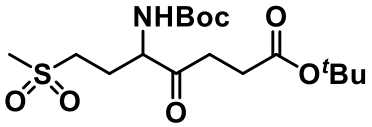
IR: ṽ [cm^{-1}] = 3441 (w), 3372 (w), 2973 (w), 2934 (w), 2874 (w), 1703 (s), 1496 (m), 1457 (m), 1392 (m), 1365 (s), 1241 (s), 1151 (s), 1093 (m), 1059 (m), 1003 (m), 953 (w), 909 (w), 882 (m), 848 (m), 780 (m), 755 (m), 698 (m), 574 (m), 462 (m), 432 (m).

R_f (cyHex/EtOAc, 4:1) = 0.56 [Ninhydrin

$[\alpha]_D^{20}$ = + 6.1° (ρ = 1.00, CH_2Cl_2) (purified on neutral aluminiumoxide)

$[\alpha]_D^{20}$ = +3.9° (ρ = 1.02, CH_2Cl_2) (purified on deactivated SiO_2)

***tert*-Butyl 5-((*tert*-butoxycarbonyl)amino)-7-(methylsulfonyl)-4-oxoheptanoate (195)**



$C_{17}H_{31}NO_7S$
393,50 g/mol

Synthesized following **GP-VI** using Boc-methioninol (235.5, mg, 1.00 mmol, 2.0 equiv.). After the IBX oxidation, the reaction mixture was concentrated in vacuum, then suspended in CH_2Cl_2 (25 mL) and filtered. Filtrate was treated with mCPBA (~75%, 575 mg, 2.52 mmol, 2.5 equiv.) and stirred at room temperature for 3 days. The reaction mixture was washed with 1 M NaOH solution (3 x 30 mL), then the organic layer was dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography using neutral SiO_2 afforded the product as a yellow oil in 41% yield (80 mg, 0.20 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.47 – 5.42 (m, 1H), 4.45 (q, *J* = 6.6 Hz, 1H), 3.12 (ddd, *J* = 16.0, 10.7, 5.2 Hz, 1H), 3.03 (ddd, *J* = 14.3, 10.8, 5.1 Hz, 1H), 2.92 (s, 3H), 2.80 (ddd, *J* = 16.8, 8.2, 5.1 Hz, 1H), 2.69 (ddd, *J* = 18.1, 7.2, 4.7 Hz, 1H), 2.60 (ddd, *J* = 17.4, 8.1, 4.7 Hz, 1H), 2.54 – 2.50 (m, 1H), 2.50 – 2.43 (m, 1H), 2.18 – 2.07 (m, 1H), 1.43 (s, 9H), 1.41 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 206.7, 171.9, 155.6, 81.1, 80.6, 57.8, 50.8, 40.8, 34.3, 29.2, 28.4, 28.2, 24.7.

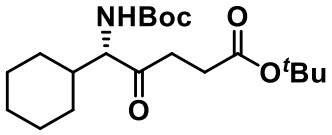
HRMS (ESI): [m/z] calculated for $C_{17}H_{31}NNaO_7S^+$ ([M+Na]$^+$): 416.1713; Found: 416.1714.

IR: ṽ [cm^{-1}] = 3354 (w), 2978 (w), 2932 (w), 1703 (s), 1512 (m), 1499 (m), 1454 (w), 1392 (m), 1366 (m), 1296 (s), 1246 (s), 1147 (s), 1130 (s), 1047 (m), 1023 (m), 999 (m), 966 (m), 931 (w), 920 (w), 863 (w), 846 (m), 766 (m), 754 (m), 733 (m), 699 (w), 660 (w), 648 (w), 619 (w), 582 (w), 546 (w), 511 (m), 496 (m), 472 (m).

R_f (cyHex/EtOAc, 1:1) = 0.18 [Ninhydrin]

$[\alpha]_D^{20}$ = + 0.1 (ρ = 0.98, CH_2Cl_2)

***tert*-Butyl (S)-5-((*tert*-butoxycarbonyl)amino)-5-cyclohexyl-4-oxopentanoate (196)**



$C_{20}H_{35}NO_5$
369,50 g/mol

Synthesized following **GP-VIII** using Boc-*L*-cyclohexylglycinol (121.7 mg, 0.50 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 78% yield (72 mg, 0.20 mmol).

Synthesized following **GP-VI** using Boc-*L*-cyclohexylglycinol (243.3 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a slightly yellowish oil in 84% yield (155 mg, 0.42 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.11 (d, *J* = 8.8 Hz, 1H), 4.25 (dd, *J* = 8.7, 4.5 Hz, 1H), 2.82 (dt, *J* = 18.3, 6.9 Hz, 1H), 2.71 (dt, *J* = 18.3, 6.5 Hz, 1H), 2.56 – 2.43 (m, 2H), 1.84 (ddt, *J* = 14.4, 7.5, 2.6 Hz, 1H), 1.79 – 1.68 (m, 3H), 1.64 (ddt, *J* = 12.3, 3.5, 1.8 Hz, 1H), 1.44 (s, 9H), 1.43 (s, 9H), 1.33 – 1.05 (m, 5H), 0.97 (qd, *J* = 12.5, 3.6 Hz, 1H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 208.3, 171.8, 156.0, 80.8, 79.8, 63.9, 40.3, 36.0, 30.4, 29.2, 28.5, 28.2, 27.3, 26.4, 26.2, 26.1.

HRMS (ESI): [m/z] calculated for $C_{20}H_{35}NNaO_5^+$ ([M+Na]$^+$): 392.2407; Found: 392.2411.

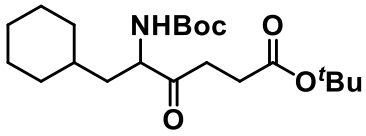
IR: ṽ [cm^{-1}] = 3363 (w), 2977 (w), 2927 (m), 2854 (w), 1704 (s), 1495 (m), 1452 (w), 1391 (w), 1365 (s), 1295 (m), 1244 (m), 1151 (s), 1059 (m), 1012 (w), 958 (w), 920 (w), 902 (w), 880 (w), 847 (w), 779 (w), 753 (w), 733 (w).

R_f (cyHex/EtOAc, 4:1) = 0.44 [Ninhydrin]

$[\alpha]_D^{20}$ = + 17.7° (ρ = 1.00, CH_2Cl_2) (purified on neutral aluminiumoxide)

$[\alpha]_D^{20}$ = + 32.4° (ρ = 0.98, CH_2Cl_2) (purified on deactivated SiO_2)

***tert*-Butyl 5-((*tert*-butoxycarbonyl)amino)-6-cyclohexyl-4-oxohexanoate (197)**



$C_{21}H_{37}NO_5$
383,53 g/mol

Synthesized following **GP-VI** using (S)-Boc-cyclohexylalaninol (257.6 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 67% yield (128 mg, 0.33 mmol).

Synthesized following **GP-VII** using (S)-Boc-cyclohexylalaninol (140.5 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a light-yellow oil in 85% yield (163 mg, 0.43 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 (d, *J* = 8.2 Hz, 1H), 4.33 (s, 1H), 2.76 (tdt, *J* = 18.3, 12.7, 6.7 Hz, 2H), 2.58 – 2.43 (m, 2H), 1.87 (d, *J* = 12.9 Hz, 1H), 1.73 – 1.60 (m, 5H), 1.43 (s, 9H), 1.42 (s, 9H), 1.34 – 1.12 (m, 5H), 1.00 – 0.82 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 208.9, 171.9, 155.7, 80.7, 79.9, 57.3, 39.3, 34.7, 34.3, 34.2, 32.6, 29.2, 28.5, 28.2, 26.5, 26.4, 26.2.

HRMS (ESI): [m/z] calculated for $C_{21}H_{37}NNaO_5^+$ ([M+Na]$^+$): 406.2564; Found: 406.2565.

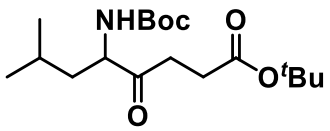
IR: ṽ [cm^{-1}] = 3363 (w), 2977 (w), 2924 (m), 2851 (w), 1707 (s), 1504 (m), 1450 (m), 1391 (m), 1365 (s), 1317 (w), 1275 (m), 1246 (m), 1152 (s), 1046 (m), 1018 (m), 958 (w), 915 (w), 847 (m), 779 (w), 751 (m), 733 (m), 647 (w), 462 (w), 432 (w).

R_f (cyHex/EtOAc, 4:1) = 0.48 [Ninhydrin]

$[\alpha]_D^{20}$ = + 1.3° (ρ = 1.00, CH_2Cl_2) (purified on neutral aluminiumoxide)

$[\alpha]_D^{20}$ = + 4.8° (ρ = 1.00, CH_2Cl_2) (purified on deactivated SiO_2)

***tert*-Butyl 5-((*tert*-butoxycarbonyl)amino)-7-methyl-4-oxooctanoate (198)**



$C_{18}H_{33}NO_5$
343,46 g/mol

Synthesized following **GP-VI** using (S)-Boc-Leucinol (217.3 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 65% yield (112 mg, 0.33 mmol).

Synthesized following **GP-VI** using (S)-Boc-Leucinol (217.3 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a yellow oil in 86% yield (147 mg, 0.43 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.97 (d, *J* = 8.3 Hz, 1H), 4.29 (d, *J* = 10.3 Hz, 1H), 2.77 (qt, *J* = 18.3, 6.7 Hz, 2H), 2.50 (q, *J* = 6.6 Hz, 2H), 1.71 (ddtdd, *J* = 13.0, 8.5, 6.5, 4.8, 2.3 Hz, 1H), 1.63 – 1.54 (m, 1H), 1.42 (s, 9H), 1.42 (s, 9H), 1.39 – 1.30 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 208.8, 171.9, 155.7, 80.7, 79.9, 57.9, 40.8, 34.7, 29.2, 28.5, 28.2, 25.0, 23.4, 21.9.

HRMS (ESI): [m/z] calculated for $C_{18}H_{33}NNaO_5^+$ ([M+Na]$^+$): 366.2251; Found: 366.2253.

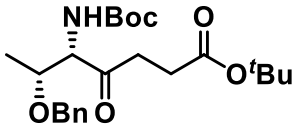
IR: ṽ [cm^{-1}] = 3361 (w), 2961 (w), 2933 (w), 2872 (w), 1707 (s), 1509 (m), 1471 (w), 1454 (w), 1391 (m), 1366 (s), 1330 (w), 1249 (m), 1153(s), 1046 (m), 1019 (m), 955 (w), 919 (w), 874 (w), 847 (m), 780 (w), 752 (w), 734 (w), 589 (w), 462 (w), 431 (w).

R_f (cyHex/EtOAc, 4:1) = 0.35 [Ninhydrin]

$[\alpha]_D^{20}$ = - 1.5° (ρ = 1.01, CH_2Cl_2) (purified on neutral aluminiumoxide)

$[\alpha]_D^{20}$ = - 1.4° (ρ = 0.99, CH_2Cl_2) (purified on deactivated SiO_2)

***tert*-Butyl (5S,6R)-6-(benzyloxy)-5-((*tert*-butoxycarbonyl)amino)-4-oxoheptanoate (199)**



$C_{23}H_{35}NO_6$
421,53 g/mol

Synthesized following **GP-VI** using (2R,3R)-Boc-threoninol(Bzl) (295.2 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a yellow oil in 42% yield (88 mg, 0.21 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 – 7.31 (m, 2H), 7.29 – 7.26 (m, 3H), 5.43 (d, *J* = 8.5 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.29 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.13 (qd, *J* = 6.4, 2.6 Hz, 1H), 2.78 (qq, *J* = 18.6, 6.5 Hz, 2H), 2.53 – 2.41 (m, 2H), 1.45 (s, 9H), 1.43 (s, 9H), 1.21 (d, *J* = 6.3 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 207.4, 171.9, 156.1, 138.1, 128.5, 128.0, 127.9, 80.6, 80.0, 74.4, 71.2, 63.8, 35.6, 29.1, 28.5, 28.2, 16.3.

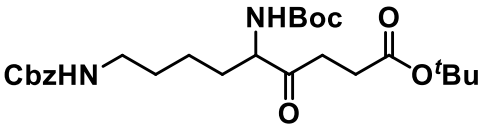
HRMS (ESI): [m/z] calculated for $C_{23}H_{35}NNaO_6^+$ ([M+Na]$^+$): 444.2357; Found: 444.2360.

IR: ṽ [cm^{-1}] = 3434 (w), 2977 (w), 2931 (w); 2872 (w), 1710 (s), 1493 (m), 1455 (m), 1391 (m), 1365 (s), 1313 (m), 1245 (m), 1152 (s), 1087 (s), 1068 (s), 1028 (m), 999 (m), 872 (m), 847 (m), 780 (m), 747 (m), 698 (s), 598 (m), 461 (m), 433 (m).

R_f (cyHex/EtOAc, 4:1) = 0.36 [Ninhydrin]

$[\alpha]_D^{20}$ = + 11.4° (ρ = 0.98, CH_2Cl_2) (purification on deactivated SiO_2)

***tert*-Butyl 9-(((benzyloxy)carbonyl)amino)-5-((*tert*-butoxycarbonyl)amino)-4-oxononanoate (201)**



$C_{26}H_{40}N_2O_7$
492,61 g/mol

Synthesized following **GP-VI** using Boc-Lysinol(Z) (369.9, mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a yellow oil in 65% yield (161 mg, 0.33 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (d, *J* = 4.4 Hz, 4H), 7.31 – 7.28 (m, 1H), 5.25 (dd, *J* = 9.4, 5.2 Hz, 1H), 5.08 (s, 2H), 4.98 (s, 1H), 4.30 (td, *J* = 7.7, 4.6 Hz, 1H), 3.18 (t, *J* = 6.4 Hz, 2H), 2.84 – 2.75 (m, 1H), 2.67 (dt, *J* = 18.3, 6.2 Hz, 1H), 2.55 (ddd, *J* = 17.3, 7.8, 5.5 Hz, 1H), 2.47 (dt, *J* = 17.3, 6.3 Hz, 1H), 1.85 (qd, *J* = 15.9, 6.2 Hz, 1H), 1.61 – 1.53 (m, 2H), 1.53 – 1.46 (m, 2H), 1.42 (s, 9H), 1.40 (s, 9H), 1.32 (dt, *J* = 10.4, 6.4 Hz, 1H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 207.9, 171.9, 156.6, 155.7, 136.8, 128.6, 128.3, 128.2, 80.9, 79.9, 66.7, 59.1, 40.6, 34.6, 31.3, 29.6, 29.0, 28.5, 28.2, 22.1.

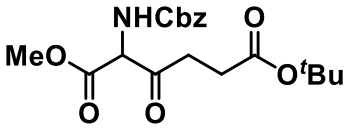
HRMS (ESI): [m/z] calculated for $C_{26}H_{40}N_2NaO_7^+$ ([M+Na]$^+$): 515.2728; Found: 515.2731.

IR: ṽ [cm^{-1}] = 3343 (w), 2976 (w), 2933 (w), 2867 (w), 1697 (s), 1517 (m), 1455 (m), 1392 (w), 1365 (m), 1309 (w), 1244 (s), 1152 (s), 1096 (m), 1055 (m), 1024 (m), 917 (w), 865 (w), 846 (w), 777 (w), 752 (m), 735 (m), 697 (m), 606 (w), 577 (w), 493 (w), 460 (w).

R_f (cyHex/EtOAc, 4:1) = 0.21 [Ninhydrin]

$[\alpha]_D^{20}$ = + 11.7° (ρ = 0.99, CH_2Cl_2) (purified on deactivated SiO_2)

6-(*tert*-Butyl) 1-methyl 2-(((benzyloxy)carbonyl)amino)-3-oxohexanedioate (202)



$C_{19}H_{25}NO_7$
379,41 g/mol

Synthesized following **GP-VI** using Cbz-L-serine-methyl ester (254.1 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using SiO_2 afforded the product as a yellow oil in 33% yield (62 mg, 0.16 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 5H), 6.00 (d, *J* = 7.1 Hz, 1H), 5.14 (d, *J* = 7.0 Hz, 1H), 5.11 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 3.00 (dt, *J* = 18.5, 6.6 Hz, 1H), 2.86 (dt, *J* = 18.5, 6.4 Hz, 1H), 2.56 (t, *J* = 6.5 Hz, 2H), 1.42 (d, *J* = 2.2 Hz, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 199.6, 171.3, 166.8, 155.6, 136.1, 128.7, 128.7, 128.5, 128.4, 128.2, 81.1, 67.5, 64.1, 53.5, 35.5, 29.3, 28.2.

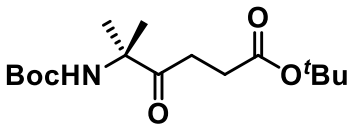
HRMS (ESI): [m/z] calculated for $C_{19}H_{25}NNaO_7^+$ ([M+Na]$^+$): 402.1523; Found: 402.1523.

IR: ṽ [cm^{-1}] = 3367 (w), 2978 (w), 2934 (w), 1715 (s), 1601 (w), 1498 (m), 1455 (w), 1438 (w), 1408 (w), 1394 (w), 1367 (m), 1340 (m), 1245 (m), 1213 (m), 1149 (s), 1086 (m), 1059 (m), 1027 (m), 974 (w), 921 (w), 845 (w), 779 (w), 751 (w), 739 (w), 698 (m), 580 (w), 472 (w), 460 (w).

R_f (cyHex/EtOAc, 4:1) = 0.16 [Ninhydrin]

$[\alpha]_D^{20}$ = + 1.7° (ρ = 0.98, CH_2Cl_2) (purified on SiO_2)

***tert*-Butyl 5-((*tert*-butoxycarbonyl)amino)-5-methyl-4-oxohexanoate (205)**



$C_{16}H_{29}NO_5$
315,41 g/mol

Synthesized following **GP-VI** using Boc-2-amino-2-methyl-1-propanol (189.4 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 93% yield (146 mg, 0.46 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.15 (s, 1H), 2.81 (t, *J* = 6.7 Hz, 2H), 2.51 (t, *J* = 6.7 Hz, 2H), 1.42 (s, 9H), 1.42 (s, 9H), 1.42 (s, 6H).

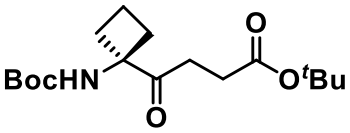
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 209.8, 172.3, 154.7, 80.5, 80.5, 60.7, 30.9, 29.6, 28.5, 28.2, 24.5.

HRMS (ESI): [m/z] calculated for $C_{16}H_{29}NNaO_5^+$ ([M+Na]$^+$): 338.1938; Found: 338.1945.

IR: ṽ [cm^{-1}] = 3362 (w), 2978 (w), 2931 (w), 1708 (s), 1508 (m), 1454 (m), 1412 (w), 1385 (m), 1365 (s), 1317 (m), 1275 (m), 1251 (s), 1151 (s), 1076 (s), 1033 (m), 980 (m), 953 (m), 905 (m), 879 (w), 846 (m), 787 (m), 752 (m), 600 (m), 485 (m), 461 (m), 431 (m).

R_f (cyHex/EtOAc, 4:1) = 0.41 [Ninhydrin]

***tert*-Butyl 4-(1-((*tert*-butoxycarbonyl)amino)cyclobutyl)-4-oxobutanoate (206)**



$C_{17}H_{29}NO_5$
327,42 g/mol

Synthesized following **GP-VI** using Boc-1-aminocyclobutylmethanol (201.4 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 70% yield (115 mg, 0.35 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38 – 5.17 (m, 1H), 2.80 – 2.71 (m, 2H), 2.64 – 2.56 (m, 2H), 2.56 – 2.45 (m, 2H), 2.14 – 2.03 (m, 1H), 2.02 – 1.86 (m, 2H), 1.84 – 1.71 (m, 1H), 1.42 (s, 9H), 1.42 (s, 9H).

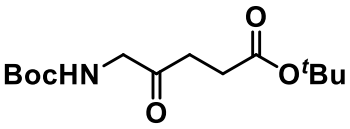
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 207.8, 172.4, 154.8, 80.5, 80.2, 63.2, 31.1, 30.8, 29.5, 28.4, 28.2, 14.4.

HRMS (ESI): [m/z] calculated for $C_{17}H_{29}NNaO_5^+$ ([M+Na]$^+$): 350.1938; Found: 350.1937.

IR: ṽ [cm^{-1}] = 3356 (w), 2977 (w), 2935 (w), 2878 (w), 1706 (s), 1502 (m), 1456 (w), 1392 (m), 1365 (s), 1327 (w), 1273 (m), 1249 (m), 1149 (s), 1090 (m), 1069 (m), 1022 (m), 1003 (m), 976 (w), 954 (w), 940 (w), 846 (m), 785 (m), 752 (m), 588 (m), 500 (w), 445 (m).

R_f (cyHex/EtOAc, 4:1) = 0.39 [Ninhydrin]

***tert*-Butyl 5-((*tert*-butoxycarbonyl)amino)-4-oxopentanoate (208)**



$C_{14}H_{25}NO_5$
287,36 g/mol

Synthesized following **GP-VI** using Boc-glycinol (161.2 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 37% yield (53 mg, 0.18 mmol).

Synthesized following **GP-VII** using Boc-glycinol (88.4 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using deactivated SiO_2 afforded the product as a yellowish oil in 63% yield (90 mg, 0.31 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (s, 1H), 4.05 (d, *J* = 4.7 Hz, 2H), 2.65 (dd, *J* = 7.6, 5.5 Hz, 2H), 2.56 (ddd, *J* = 6.9, 5.9, 1.2 Hz, 2H), 1.44 (s, 9H), 1.43 (s, 9H).

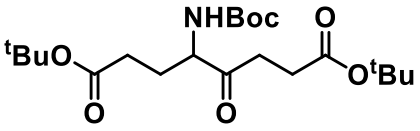
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 204.5, 171.7, 155.8, 81.1, 80.0, 50.5, 34.7, 29.2, 28.5, 28.2.

HRMS (ESI): [m/z] calculated for $C_{14}H_{25}NNaO_5^+$ ([M+Na]$^+$): 310.1625; Found: 310.1630.

IR: ṽ [cm^{-1}] = 3369 (w), 2978 (w), 2932 (w), 1708 (s), 1502 (m), 1455 (w), 1392 (m), 1365 (s), 1275 (m), 1248 (m), 1148 (s), 1098 (m), 1056 (w), 983 (w), 960 (w), 908 (w), 850 (m), 780 (w), 753 (w), 545 (w), 462 (w), 431 (w).

R_f (cyHex/EtOAc, 4:1) = 0.15 [Ninhydrin]

di-*tert*-Butyl 4-((*tert*-butoxycarbonyl)amino)-5-oxooctanedioate (209)



$C_{21}H_{37}NO_7$
415,53 g/mol

Synthesized following **GP-VII** using *tert*-butyl 4-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanoate (159.0 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow-brownish oil in 72% yield (149 mg, 0.36 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.25 (d, *J* = 7.8 Hz, 1H), 4.33 (p, *J* = 4.1 Hz, 1H), 2.84 (dt, *J* = 18.3, 6.6 Hz, 1H), 2.72 (dt, *J* = 18.3, 6.4 Hz, 1H), 2.51 (q, *J* = 6.3 Hz, 2H), 2.32 (dt, *J* = 16.3, 7.4 Hz, 1H), 2.24 (dt, *J* = 16.4, 6.8 Hz, 1H), 2.18 (dddd, *J* = 11.9, 9.1, 6.7, 4.1 Hz, 1H), 1.79 (dtd, *J* = 14.3, 7.9, 6.2 Hz, 1H), 1.43 (s, 9H), 1.42 (s, 9H), 1.42 (s, 9H).

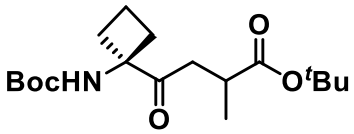
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 207.7, 172.3, 171.8, 155.6, 80.8, 80.8, 79.9, 58.9, 34.6, 31.3, 29.2, 28.5, 28.2, 28.2, 26.7.

HRMS (ESI): [m/z] calculated for $C_{21}H_{37}NNaO_7^+$ ([M+Na]$^+$): 438.2462; Found: 438.2462.

IR: ṽ [cm^{-1}] = 3366 (w), 2977 (w), 2930 (w), 1709 (s), 1582 (w), 1505 (m), 1455 (w), 1437 (w), 1391 (w), 1366 (m), 1248 (m), 1148 (s), 1058 (w), 1012 (w), 953 (w), 907 (w), 846 (w), 780 (w), 753 (w), 639 (w), 590 (w), 556 (w), 459 (w), 426 (w).

R_f (cyHex/EtOAc, 4:1) = 0.31 [Ninhydrin]

***tert*-Butyl 4-(1-((*tert*-butoxycarbonyl)amino)cyclobutyl)-2-methyl-4-oxobutanoate (211)**



$C_{18}H_{31}NO_5$
341,45 g/mol

Synthesized following **GP-VI** using *tert*-butyl (1-(hydroxymethyl)cyclobutyl)carbamate (201.6 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 79% yield (135 mg, 0.40 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.27 (s, 1H), 2.90 (s, 2H), 2.64 (s, 1H), 2.52 (dq, *J* = 12.2, 3.9 Hz, 2H), 2.16 – 2.04 (m, 1H), 2.00 – 1.90 (m, 2H), 1.89 – 1.78 (m, 1H), 1.42 (s, 18H), 1.14 (d, *J* = 6.9 Hz, 3H).

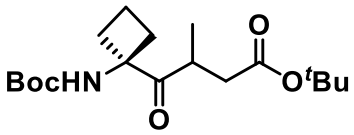
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 207.4, 175.5, 154.7, 80.2, 63.1, 39.7, 35.7, 30.9, 30.3, 28.4, 28.1, 17.3, 14.4.

HRMS (ESI): [m/z] calculated for $C_{18}H_{31}NNaO_5^+$ ([M+Na]$^+$): 364.2094; Found: 364.2089.

IR: ṽ [cm^{-1}] = 3270 (w), 3134 (w), 2971 (w), 2937 (w), 2880 (w), 1727 (m), 1705 (s), 1475 (w), 1459 (w), 1393 (m), 1355 (m), 1299 (m), 1250 (w), 1226 (m), 1194 (w), 1152 (s), 1072 (m), 1056 (w), 1018 (m), 964 (w), 905 (w), 877 (w), 852 (w), 785 (w), 775 (w), 748 (w), 707 (w), 670 (w), 645 (w), 600 (w), 553 (w), 447 (w).

R_f (cyHex/EtOAc, 4:1) = 0.38 [Ninhydrin]

tert-Butyl 4-(1-((*tert*-butoxycarbonyl)amino)cyclobutyl)-3-methyl-4-oxobutanoate (212)



$C_{18}H_{31}NO_5$
341,45 g/mol

Synthesized following **GP-VI** using *tert*-butyl (1-(hydroxymethyl)cyclobutyl)carbamate (201.8 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 12% yield (21 mg, 62 µmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.34 (s, 1H), 3.47 – 3.31 (m, 1H), 2.71 – 2.56 (m, 3H), 2.26 (dd, *J* = 16.3, 7.3 Hz, 1H), 2.12 (s, 1H), 2.01 (s, 2H), 1.89 (s, 1H), 1.46 – 1.43 (m, 6H), 1.42 (s, 9H), 1.41 (s, 3H), 1.11 (d, *J* = 6.9 Hz, 3H).

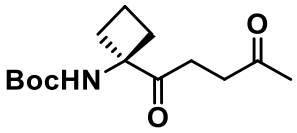
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 212.3, 171.8, 154.8, 80.7, 80.1, 63.6, 39.6, 36.3, 31.2, 30.8, 28.5, 28.2, 17.7, 15.0.

HRMS (ESI): [m/z] calculated for $C_{18}H_{31}NNaO_5^+$ ([M+Na]$^+$): 364.2094; Found: 364.2100.

IR: ṽ [cm^{-1}] = 3359 (w), 2977 (w), 2935 (w), 2879 (w), 1702 (s), 1500 (m), 1455 (m), 1392 (w), 1366 (s), 1301 (w), 1274 (m), 1251 (m), 1151 (s), 1055 (m), 1004 (m), 958 (w), 919 (w), 861 (w), 844 (w), 784 (w), 750 (w), 733 (w), 701 (w), 594 (w), 461 (w).

R_f (cyHex/EtOAc, 4:1) = 0.33 [Ninhydrin]

***tert*-Butyl (1-(4-oxopentanoyl)cyclobutyl)carbamate (213)**



$C_{14}H_{23}NO_4$
269,34 g/mol

Synthesized following **GP-VI** using Boc-1-aminocyclobutylmethanol (201.6 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as an off-white solid in 82% yield (110 mg, 0.41 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.27 (s, 1H), 2.77 (s, 4H), 2.64 (s, 2H), 2.19 (s, 3H), 2.11 – 2.04 (m, 1H), 1.95 (s, 2H), 1.88 – 1.81 (m, 1H), 1.43 (s, 9H).

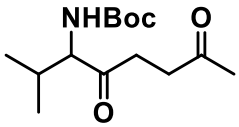
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 208.1, 207.7, 154.8, 80.2, 63.2, 37.3, 31.2, 30.8, 30.1, 30.0, 28.4, 14.4.

HRMS (ESI): [m/z] calculated for $C_{14}H_{23}NNaO_4^+$ ([M+Na]$^+$): 292.1519; Found: 292.1523.

IR: ṽ [cm^{-1}] = 3315 (m), 2977 (w), 2938 (w), 2911 (w), 1707 (s), 1677 (s), 1519 (s), 1455 (w), 1396 (m), 1380 (m), 1363 (s), 1294 (s), 1280 (m), 1253 (m), 1161 (s), 1095 (m), 1075 (m), 1039 (m), 1024 (m), 1000 (m), 975 (w), 956 (w), 921 (w), 878 (w), 862 (w), 822 (w), 793 (w), 762 (w), 711 (w), 670 (w), 618 (w), 595 (w), 533 (w), 484 (w), 463 (w), 421 (m).

R_f (cyHex/EtOAc, 2:1) = 0.37 [Ninhydrin]

***tert*-Butyl (2-methyl-4,7-dioxooctan-3-yl)carbamate (214)**



$C_{14}H_{25}NO_4$
271,36 g/mol

Synthesized following **GP-VII** using (S)-Boc-valinol (203.3 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 63% yield (85 mg, 0.31 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.08 (d, *J* = 8.8 Hz, 1H), 4.26 (dd, *J* = 8.8, 4.3 Hz, 1H), 2.89 – 2.75 (m, 2H), 2.70 – 2.61 (m, 2H), 2.27 – 2.21 (m, 1H), 2.18 (s, 3H), 1.43 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 208.3, 206.8, 155.9, 79.7, 64.0, 36.6, 34.4, 30.2, 29.9, 28.3, 19.9, 16.6.

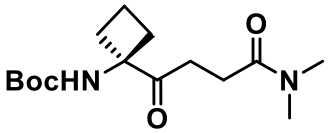
HRMS (ESI): [m/z] calculated for $C_{14}H_{25}NNaO_4^+$ ([M+Na]$^+$): 294.1676; Found: 294.1676.

IR: ṽ [cm^{-1}] = 3354 (w), 2967 (w), 2932 (w), 2876 (w), 1702 (s), 1496 (m), 1456 (m), 1391 (m), 1364 (s), 1307 (m), 1240 (m), 1162 (s), 1079 (m), 1043 (m), 1005 (m), 928 (w), 869 (m), 779 (m), 753 (m), 533 (m), 461 (m), 430 (m).

R_f (cyHex/EtOAc, 4:1) = 0.13 [Ninhydrin]

$[\alpha]_D^{20}$ = + 26.0 (ρ = 1.02, CH_2Cl_2)

***tert*-Butyl (1-(4-(dimethylamino)-4-oxobutanoyl)cyclobutyl)carbamate (215)**



$C_{15}H_{26}N_2O_4$
298,38 g/mol

Synthesized following **GP-VII** using Boc-1-aminocyclobutylmethanol (110.7 mg, 0.55 mmol, 1.1 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 50% yield (75 mg, 0.25 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.38 (s, 1H), 3.04 (s, 3H), 2.92 (s, 3H), 2.85 (t, *J* = 6.5 Hz, 2H), 2.68 (q, *J* = 6.6, 4.9 Hz, 2H), 2.64 (dt, *J* = 13.0, 5.4 Hz, 2H), 2.15 – 2.08 (m, 2H), 1.97 – 1.93 (m, 1H), 1.91 – 1.82 (m, 1H), 1.41 (d, *J* = 19.7 Hz, 9H).

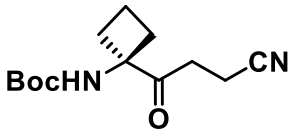
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 208.6, 171.9, 154.9, 80.0, 63.3, 37.2, 35.6, 31.2, 30.7, 28.4, 27.3, 14.4.

HRMS (ESI): [m/z] calculated for $C_{15}H_{26}N_2NaO_4^+$ ($[M+Na]^+$): 321.1785; Found: 321.1786.

IR: ṽ [cm^{-1}] = 3250 (w), 3120 (w), 2973 (w), 2950 (w), 2918 (w), 2876 (w), 1697 (s), 1648 (s), 1498 (w), 1477 (w), 1457 (w), 1415 (m), 1393 (m), 1362 (s), 1291 (m), 1255 (m), 1232 (w), 1162 (s), 1141 (m), 1071 (s), 1005 (m), 974 (w), 947 (w), 919 (w), 901 (w), 855 (w), 817 (w), 784 (m), 751 (w), 722 (w), 699 (w), 659 (w), 616 (w), 561 (w), 538 (w), 513 (w), 447 (m).

R_f (EtOAc) = 0.38 [Ninhydrin]

***tert*-Butyl (1-(3-cyanopropanoyl)cyclobutyl)carbamate (216)**



$C_{13}H_{20}N_2O_3$
252,31 g/mol

Synthesized following **GP-A** using Boc-1-aminocyclobutylmethanol (201.4 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as an orange oil in 59% yield (74 mg, 0.29 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.22 (s, 1H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.62 (t, *J* = 7.3 Hz, 2H), 2.60 – 2.56 (m, 2H), 2.04 – 1.99 (m, 2H), 1.98 – 1.93 (m, 1H), 1.92 – 1.82 (m, 1H), 1.43 (s, 9H).

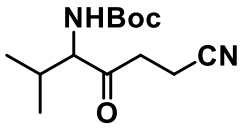
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 205.3, 154.9, 119.4, 80.9, 63.0, 32.1, 31.0, 28.4, 14.2, 12.1.

HRMS (ESI): [m/z] calculated for $C_{13}H_{20}N_2NaO_3^+$ ([M+Na]$^+$): 275.1366; Found: 275.1368.

IR: ṽ [cm^{-1}] = 3291 (w), 2975 (w), 2950 (w), 2249 (w), 1765 (w), 1711 (m), 1678 (m), 1662 (s), 1518 (s), 1455 (w), 1419 (w), 1393 (w), 1368 (m), 1358 (m), 1303 (s), 1254 (m), 1228 (w), 1162 (s), 1095 (m), 1064 (m), 1043 (m), 1023 (m), 998 (w), 979 (w), 956 (w), 922 (w), 901 (w), 862 (w), 794 (w), 766 (w), 749 (w), 734 (w), 672 (w), 634 (w), 584 (w), 525 (w), 456 (w).

R_f (cyHex/EtOAc, 2:1) = 0.37 [Ninhydrin]

***tert*-Butyl (6-cyano-2-methyl-4-oxohexan-3-yl)carbamate (217)**



$C_{13}H_{22}N_2O_3$
254,33 g/mol

Synthesized following **GP-VII** using (S)-Boc-valinol (203.3 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 49% yield (62 mg, 0.24 mmol).

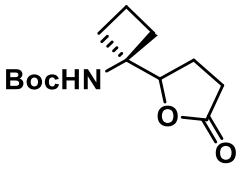
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.02 (d, *J* = 8.2 Hz, 1H), 4.19 (dd, *J* = 8.3, 4.9 Hz, 1H), 2.96 – 2.83 (m, 2H), 2.67 – 2.53 (m, 2H), 2.16 (ddd, *J* = 12.1, 8.6, 6.1 Hz, 1H), 1.44 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 206.1, 156.1, 118.9, 80.4, 77.4, 77.2, 76.9, 64.1, 36.4, 30.2, 28.4, 19.8, 17.3, 11.5.

HRMS (ESI): [m/z] calculated for $C_{13}H_{22}N_2NaO_3^+$ ([M+Na]$^+$): 277.1523; Found: 277.1522.

IR: ṽ [cm^{-1}] = 3354 (w), 2969 (w), 2933 (w), 2876 (w), 2249 (w), 1701 (s), 1500 (s), 1457 (m), 1412 (m), 1391 (m), 1366 (s), 1308 (m), 1241 (m), 1162 (s), 1101 (m), 1077 (m), 1042 (m), 1014 (m), 1001 (m), 941 (m), 874 (m), 779 (m), 752 (m), 617 (m), 558 (m), 531 (m), 462 (m).
R_f (cyHex/EtOAc, 4:1) = 0.13 [Ninhydrin]
$[\alpha]_D^{20}$ = + 3.7 (ρ = 1.01, CH_2Cl_2)

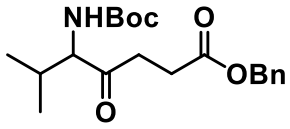
***tert*-Butyl (1-(5-oxotetrahydrofuran-2-yl)cyclobutyl)carbamate (218)**



$C_{13}H_{21}NO_4$
255,31 g/mol

Synthesized following **GP-VI** using *tert*-butyl (1-(hydroxymethyl)cyclobutyl)carbamate (201.3 mg, 1.00 mmol, 2.0 equiv.). After irradiation and concentration of the reaction mixture, the residue was redissolved in 5 mL toluene. Inspired by a literature protocol for intramolecular lactonizations,[284] conc. HOAc (18 µL, 0.315 mmol, 0.63 equiv.) was added and the reaction mixture was stirred at 85 °C for 5 h, and then at room temperature for additional 60 h. Purification via multiple flash chromatographies using SiO_2 afforded the product as colorless needles in 19% yield (24 mg, 94 µmol).
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.82 (t, *J* = 7.6 Hz, 1H), 4.73 (s, 1H), 2.59 – 2.51 (m, 2H), 2.40 – 2.32 (m, 1H), 2.27 – 2.19 (m, 3H), 2.17 – 2.09 (m, 1H), 2.07 – 1.94 (m, 2H), 1.87 – 1.78 (m, 1H), 1.42 (s, 9H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 177.3, 154.6, 82.6, 79.9, 58.0, 29.4, 29.2, 28.5, 22.9, 14.7.
IR: ṽ [cm^{-1}] = 3333 (m), 2980 (w), 2955 (w), 2928 (w), 1781 (m), 1760 (m), 1709 (w), 1682 (s), 1515 (s), 1458 (m), 1425 (w), 1411 (w), 1389 (w), 1364 (m), 1348 (w), 1287 (m), 1272 (s), 1250 (m), 1210 (m), 1160 (s), 1096 (w), 1070 (m), 1040 (s), 1029 (m), 1014 (s), 965 (m), 908 (m), 892 (m), 866 (m), 811 (w), 784 (m), 739 (w), 629 (m), 565 (w), 541 (w), 518 (w), 456 (w).
R_f (cyHex/EtOAc, 1:1) = 0.36 [Ninhydrin]

Benzyl 5-((*tert*-butoxycarbonyl)amino)-6-methyl-4-oxoheptanoate (219)



$C_{20}H_{29}NO_5$
363,45 g/mol

Synthesized following **GP-VII** using (S)-Boc-valinol (203.3 mg, 1.00 mmol, 2.0 equiv.). Purification via flash chromatography using neutral aluminiumoxide afforded the product as a yellow oil in 51% yield (93 mg, 0.26 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 5H), 5.11 (s, 2H), 5.10 – 5.05 (m, 1H), 4.27 (dd, *J* = 9.0, 4.3 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.81 – 2.66 (m, 2H), 2.61 (dt, *J* = 17.3, 6.3 Hz, 1H), 2.21 (ddd, *J* = 13.6, 9.1, 5.5 Hz, 1H), 1.43 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 207.9, 172.5, 156.1, 135.9, 128.7, 128.4, 128.4, 79.9, 77.4, 77.2, 76.9, 66.7, 64.1, 35.6, 30.4, 28.5, 27.9, 20.0, 16.8.

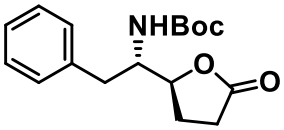
HRMS (ESI): [m/z] calculated for $C_{20}H_{29}NNaO_5^+$ ([M+Na]$^+$): 386.1938; Found: 386.1939.

IR: ṽ [cm^{-1}] = 3371 (w), 2968 (w), 2932 (w), 2876 (w), 1704 (s), 1496 (m), 1455 (m), 1390 (m), 1366 (m), 1308 (m), 1239 (m), 1159 (s), 1078 (m), 1042 (w), 1001 (m), 963 (w), 875 (m), 780 (w), 748 (m), 738 (m), 698 (m), 603 (w), 577 (m), 508 (m), 457 (m).

R_f (cyHex/EtOAc, 4:1) = 0.33 [Ninhydrin]

$[\alpha]_D^{20}$ = + 15.1 (ρ = 1.00, CH_2Cl_2)

***tert*-Butyl ((S)-1-((S)-5-oxotetrahydrofuran-2-yl)-2-phenylethyl)carbamate (224)**



$C_{17}H_{23}NO_4$
305,37 g/mol

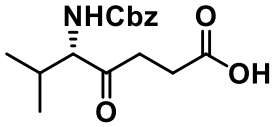
Synthesized following **GP-VI** using (S)-Boc-phenylalaninol (251.1 mg, 1.00 mmol, 2.0 equiv.). After irradiation and concentration of the reaction mixture, the residue was redissolved in 5 mL toluene. Inspired by a literature protocol for intramolecular lactonizations,[284] conc. HOAc (18 µL, 0.315 mmol, 0.63 equiv.) was added and the reaction mixture was stirred to 85 °C for 5 h. After cooling down to room temperature, the d.r. was checked via GC-FID analysis (d.r. ~1.9 : 1). Purification via flash chromatography using SiO_2 afforded the product as an off-white solid in 39% yield (60 mg, 0.20 mmol). The analytical data are in agreement with those previously reported.[285]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 2H), 7.26 – 7.20 (m, 3H), 4.63 (d, *J* = 9.9 Hz, 1H), 4.47 (td, *J* = 7.6, 1.5 Hz, 1H), 4.01 (q, *J* = 8.7 Hz, 1H), 2.95 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.88 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.58 – 2.43 (m, 2H), 2.19 – 2.07 (m, 2H), 1.39 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 177.3, 156.0, 137.3, 129.5, 128.8, 126.9, 80.1, 80.0, 54.2, 39.5, 28.8, 28.4, 24.3.

R_f (cyHex/EtOAc, 1:1) = 0.38 [Ninhydrin]

(S)-5-(((Benzyloxy)carbonyl)amino)-6-methyl-4-oxoheptanoic acid (226)



$C_{16}H_{21}NO_5$
307,35 g/mol

182 (181.7 mg, 0.50 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (5 mL, 0.1 M) and then TFA (1 mL, 13.07 mmol, 26.1 equiv.) was added all at once. The reaction mixture was stirred at room temperature for 90 min, and then concentrated in vacuum. The resulting residue was treated with H_2O (10 mL), and the aq. layer was washed with MTBE (5 x 2 mL). Purification via flash chromatography using SiO_2 afforded the product as an off-white solid in 57% yield (88 mg, 0.29 mmol).

^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 7.42 – 7.24 (m, 2H), 5.10 (s, 1H), 4.12 (d, *J* = 5.7 Hz, 0H), 2.80 (td, *J* = 6.2, 3.4 Hz, 0H), 2.53 (td, *J* = 6.5, 2.2 Hz, 1H), 2.23 (dq, *J* = 13.3, 6.7 Hz, 0H), 0.96 (d, *J* = 6.8 Hz, 1H), 0.87 (d, *J* = 6.8 Hz, 1H).

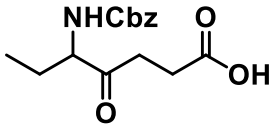
^{13}C{^{1}H} NMR (101 MHz, MeOD-*d*$_4$) δ 210.0, 176.1, 158.9, 138.3, 129.5, 129.0, 128.8, 67.7, 66.7, 49.6, 49.4, 49.2, 49.0, 48.8, 48.6, 48.4, 36.0, 30.7, 28.4, 20.1, 17.8.

HRMS (ESI): [m/z] calculated for $C_{16}H_{21}NNaO_5^+$ ($[M+Na]^+$): 330.1312; Found: 330.1312.

IR: ṽ [cm^{-1}] = 3330 (w), 3032 (w), 2966 (w), 2892 (w), 2765 (w), 2679 (w), 2654 (w), 2571 (w), 2479 (w), 1687 (s), 1528 (m), 1470 (w), 1432 (m), 1389 (m), 1343 (m), 1327 (m), 1307 (m), 1232 (s), 1183 (m), 1158 (m), 1136 (m), 1116 (m), 1076 (m), 1049 (m), 1013 (m), 970 (m), 935 (m), 912 (m), 864 (m), 836 (w), 816 (w), 759 (m), 722 (w), 695 (s), 664 (w), 641 (w), 607 (m), 568 (w), 520 (w), 489 (m), 412(w).

R_f (cyHex/EtOAc, 1:1 + 1% HOAc) = 0.19 [CAM]

5-(((Benzyloxy)carbonyl)amino)-4-oxoheptanoic acid (227)



$C_{15}H_{19}NO_5$
293,32 g/mol

(rac)-184 (36.1 mg, 0.10 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (1 mL, 0.1 M) and then TFA (0.2 mL, 2.60 mmol, 25 equiv.) was added all at once. The reaction mixture was stirred at room temperature for 60 min, followed by addition of H_2O (2 mL) and extraction with MTBE (6 x 2 mL). The combined org. layers were dried in vacuum. Purification via flash chromatography using SiO_2 afforded the product as an off-white solid in 79% yield (24 mg, 82 µmol).

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.37 – 7.28 (m, 5H), 5.09 (s, 2H), 4.11 (dd, *J* = 8.7, 4.9 Hz, 1H), 2.79 (t, *J* = 6.5 Hz, 2H), 2.53 (q, *J* = 6.1 Hz, 2H), 1.88 (dtd, *J* = 14.9, 7.4, 5.0 Hz, 1H), 1.60 (dq, *J* = 15.1, 7.7 Hz, 1H), 0.94 (t, *J* = 7.4 Hz, 3H).

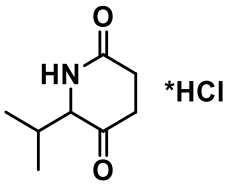
^{13}C{^{1}H} NMR (151 MHz, MeOD-d_4): δ 210.2, 176.2, 158.7, 138.3, 129.5, 129.0, 128.8, 67.7, 62.9, 35.0, 28.5, 24.8, 10.5.

HRMS (ESI): [m/z] calculated for $C_{15}H_{19}NNaO_5^+$ ([M+Na]$^+$): 316.1155; Found: 316.1161.

IR: ṽ [cm^{-1}] = 3289 (w), 2968(w), 2939 (w), 2925 (w), 2882 (w), 2737 (w), 2672 (w), 2639 (w), 2554 (w), 1714 (s), 1657 (s), 1609 (w), 1586 (w), 1500 (w), 1464 (w), 1416 (m), 1386 (w), 1354 (s), 1310 (m), 1284 (w), 1257 (m), 1220 (m), 1173 (m), 1114 (w), 1095 (w), 1071 (m), 1060 (m), 1027 (m), 1004 (w), 972 (w), 928 (m), 881 (w), 851 (w), 805 (w), 772 (m), 734 (s), 693 (m), 640 (w), 583 (w), 502 (m), 464 (m) 435 (w).

R_f (cyHex/EtOAc+HOAc, 1:1+1%) = 0.23 [Ninhydrin]

6-Isopropylpiperidine-2,5-dione hydrochloride (228)

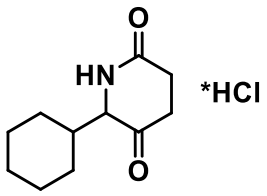


$C_8H_{14}ClNO_2$
191,66 g/mol

169 (164.6 mg, 0.50 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (5 mL, 0.1 M), then an ice-cold solution of 12 M HCl (4 mL, 48.00 mmol, 96 equiv.) in 5 mL 1,4-dioxane was added. The reaction was stirred at room temperature for 60 min, and then concentrated under vacuum. The resulting residue was treated with H_2O (10 mL), and the aq. layer was washed with MTBE (5 x 2 mL). Drying the aq. layer in vacuum afforded the product as white solid in quantitative yield (96 mg, 0.5 mmol).

^{1}H NMR (400 MHz, MeOD-d_4) δ 4.19 – 4.14 (m, 1H), 3.03 – 2.90 (m, 1H), 2.89 – 2.77 (m, 1H), 2.75 – 2.61 (m, 2H), 2.61 – 2.50 (m, 1H), 1.17 (d, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, MeOD-d_4) δ 205.8, 174.5, 65.1, 35.7, 29.8, 28.3, 19.5, 16.3.
HRMS (ESI): [m/z] calculated for $C_8H_{14}NO_2^+$ ([M+H]$^+$): 156.1019; Found: 156.1021.
IR: ṽ [cm^{-1}] = 3435 (w), 2965 (m), 2908 (m), 2878 (m), 2641 (w), 1721 (s), 1594 (w), 1514 (m), 1465 (w), 1407 (m), 1373 (m), 1328 (w), 1278 (w), 1258 (m), 1224 (s), 1188 (m), 1177 (m), 1138 (m), 1114 (w), 1087(s), 1067 (w), 1048 (w), 1014 (w), 986 (w), 969 (w), 936 (w), 916 (w), 832 (w), 802 (w), 753 (w), 700 (w), 637 (w), 588 (w), 562 (w), 529 (w), 478 (w).

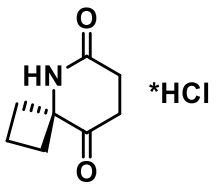
6-Cyclohexylpiperidine-2,5-dione hydrochloride (229)



$C_{11}H_{18}ClNO_2$
231,72 g/mol

196 (58 mg, 0.16 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (0.7 mL, 0.22 M) and added to an ice-cold solution of 12 M HCl (1.1 mL, 13.20 mmol, 84 equiv.) in 2 mL 1,4-dioxane. The reaction was stirred at room temperature for 60 min, and then concentrated under vacuum. The resulting residue was treated with H_2O (10 mL), and the aq. layer was washed with MTBE (5 x 2 mL). Drying the aq. layer in vacuum afforded the product as colorless needles in 90% yield (33 mg, 0.14 mmol).
^{1}H NMR (400 MHz, MeOD-d_4) δ 4.12 (d, *J* = 3.6 Hz, 1H), 3.05 – 2.89 (m, 1H), 2.88 – 2.76 (m, 1H), 2.75 – 2.59 (m, 2H), 2.17 (td, *J* = 12.2, 3.2 Hz, 1H), 1.91 – 1.69 (m, 4H), 1.56 – 1.01 (m, 6H).
HRMS (ESI): [m/z] calculated for $C_{11}H_{18}NO_2^+$ ([M+H]$^+$): 196.1332; Found: 196.1334.
IR: ṽ [cm^{-1}] = 2923 (s), 2856 (s), 2621 (w), 1718 (s), 1599 (w), 1580 (w), 1480 (s), 1451 (m), 1394 (m), 1375 (m), 1351 (m), 1280 (w), 1244 (m), 1217 (s), 1173 (m), 1154 (m), 1140 (m), 1081 (s), 1052 (m), 987 (m), 965 (m), 936 (m), 920 (w), 894 (w), 845 (w), 794 (w), 613 (w), 504 (m), 455 (m).

5-Azaspiro[3.5]nonane-6,9-dione hydrochloride (230)



$C_8H_{12}ClNO_2$
186.64 g/mol

206 (33.3 mg, 0.10 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (1 mL, 0.1 M) and then an ice-cold solution of 12 M HCl (0.83 mL, 10.00 mmol, 100 equiv.) in 1 mL 1,4-dioxane was added to the mixture. The reaction was stirred at room temperature for 60 min, and then concentrated under vacuum. The resulting residue was treated with H_2O (2 mL), and the aq. layer was washed with MTBE (6 x 2 mL). Drying the aq. layer in vacuum afforded the product as yellow needles in quantitative yield (20 mg, 0.11 mmol, contains minimal residues of solvent).

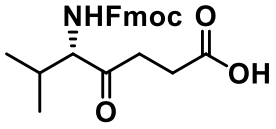
^{1}H NMR (400 MHz, MeOD-d_4): δ 3.63 (s, 1H), 3.14 (ddd, *J* = 15.5, 7.0, 4.8 Hz, 2H), 2.81 (dd, *J* = 13.5, 7.9 Hz, 2H), 2.71 (td, *J* = 7.7, 4.7 Hz, 2H), 2.45 (dt, *J* = 14.2, 9.7 Hz, 2H), 2.31 (q, *J* = 8.1 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, MeOD-d_4): δ 206.0, 174.6, 64.1, 31.8, 29.5, 28.4, 15.3.

HRMS (ESI): [m/z] calculated for $C_8H_{12}NO_2^+$ ([M+H]$^+$): 154.0863; Found: 154.0865.

IR: ṽ [cm^{-1}] = 2956 (w), 2938 (w), 2757 (w), 2252 (w), 2188 (m), 2120 (m), 1997 (w), 1953 (w), 1902 (w), 1739 (m), 1711 (s), 1503 (w), 1434 (w), 1415 (m), 1400 (m), 1372 (m), 1304 (w), 1247 (m), 1223 (s), 1189 (m), 1150 (m), 1116 (w), 1086 (s), 1024 (m), 985 (w), 972 (w), 955 (w), 932 (m), 888 (w), 847 (w); 814 (w), 792 (w), 779 (w), 731 (w), 674 (w), 656 (w), 566 (w), 548 (w), 514 (w), 463 (m), 409 (w).

(S)-5-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-6-methyl-4-oxoheptanoic acid (231)



$C_{23}H_{25}NO_5$
395,46 g/mol

169 (164.7 mg, 0.50 mmol, 1.0 equiv.) was dissolved CH_2Cl_2 (5 mL, 0.1 M), then added TFA (1.0 mL, 13.00 mmol, 26 equiv.) all at once. The rection was stirred at room temperature for 90 min, and then concentrated under vacuum. The resulting residue was redissolved in $CHCl_3$ and concentrated in vacuum again (x 3). Afterwards, the crude product was dissolved in H_2O/acetone (5 mL each), and $NaHCO_3$ (400 mg, 4.76 mmol, 9.5 equiv.) was added. The reaction mixture was stirred for 5 min, followed by addition of Fmoc-OSu (190 mg, 0.56 mmol,

1.1 equiv.) and further stirring at room temperature for 90 min. Another portion $NaHCO_3$ (100 mg, 1.19 mmol, 2.4 equiv.) was added before continued stirring at room temperature overnight. Afterwards, the acetone was removed under vacuum, and the aq. residue adjusted to pH = 1 by adding 10% HCl, followed by extraction with $CHCl_3$ (3 x 20 mL). The combined org. layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification via flash chromatography using SiO_2 afforded the product as an off-white solid in 72% yield (143 mg, 0.36 mmol).

^{1}H NMR (400 MHz, MeOD-*d*$_4$): δ 7.79 (d, *J* = 7.4 Hz, 2H), 7.71 – 7.64 (m, 2H), 7.41 – 7.35 (m, 2H), 7.31 (tdd, *J* = 7.5, 2.7, 1.2 Hz, 2H), 4.44 (qd, *J* = 10.7, 6.6 Hz, 2H), 4.22 (t, *J* = 6.4 Hz, 1H), 4.06 (d, *J* = 5.9 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.51 (t, *J* = 6.4 Hz, 2H), 2.21 (h, *J* = 6.8 Hz, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H).

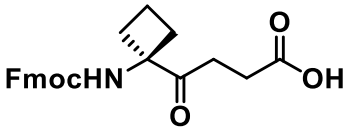
^{13}C{^{1}H} NMR (101 MHz, MeOD-*d*$_4$): δ 210.0, 176.2, 158.9, 145.3, 142.7, 128.8, 128.2, 128.1, 126.2, 126.1, 120.9, 67.7, 66.7, 35.9, 30.6, 28.5, 20.1, 17.9.

HRMS (ESI): [m/z] calculated for $C_{23}H_{25}NNaO_5^+$ ([M+Na]$^+$): 418.1625; Found: 418.1626.

IR: ṽ [cm^{-1}] = 3316 (w), 3065 (w), 3039 (w), 2958 (w), 2921 (w), 2871 (w), 1714 (s), 1686 (s), 1610 (w), 1528 (s), 1464 (w), 1449 (m), 1428 (w), 1396 (m), 1367 (w), 1344 (w), 1317 (m), 1305 (m), 1270 (m), 1253 (s), 1240 (s), 1221 (s), 1177 (m), 1153 (m), 1135 (w), 1116 (w), 1104 (w), 1076 (m), 1028 (m), 1005 (w), 980 (w), 931 (m), 849 (w), 780 (w), 757 (m), 732 (s), 646 (m), 621 (m), 584 (w), 551 (w), 536 (w), 503 (w), 422 (w).

R_f (cyHex/EtOAc+HOAc, 1:1+1%) = 0.28 [$KMnO_4$]

4-(1-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)cyclobutyl)-4-oxobutanoic acid (232)

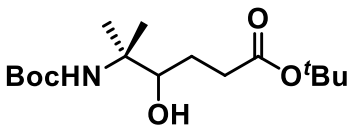


$C_{23}H_{23}NO_5$
393,44 g/mol

206 (65.5 mg, 0.20 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (2 mL, 0.1 M), then added TFA (0.4 mL, 5.20 mmol, 26 equiv.) all at once. Let stir at room temperature for 90 min, then concentrated in vacuum. Residue was redissolved in $CHCl_3$ and concentrated in vacuum again for 3 times. Afterwards, residue was taken up in H_2O/acetone (2 mL each). Added $NaHCO_3$ (336 mg, 4.0 mmol, 20.0 equiv.) in two portions. After 5 min of stirring, added Fmoc-OSu (74.2 mg, 0.22 mmol, 1.1 equiv.) and let stir at room temperature overnight. The next day, removed acetone in vacuum, adjusted aq. residue to pH = 1 by adding 6 M HCl and extracted with $CHCl_3$ (3 x 15 mL). Combined org. layers were dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography using SiO_2 afforded the product as a slightly yellowish oil in 38% yield (30 mg, 76 µmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.62 – 7.44 (m, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 5.42 (s, 1H), 4.67 – 4.45 (m, 2H), 4.25 – 4.06 (m, 1H), 2.73 – 2.58 (m, 4H), 2.39 – 2.25 (m, 1H), 2.20 – 2.06 (m, 2H), 2.02 – 1.83 (m, 2H), 1.76 – 1.62 (m, 1H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 207.2, 177.4, 155.2, 143.8, 141.6, 127.9, 127.2, 125.1, 120.2, 66.4, 63.3, 47.6, 30.8, 30.7, 27.8, 14.4.
HRMS (ESI): [m/z] calculated for $C_{23}H_{23}NNaO_5^+$ ([M+Na]$^+$): 416.1468; Found: 416.1474.
IR: ṽ [cm^{-1}] = 3248 (w), 3129 (w), 2954 (w), 2938 (w), 2903 (w), 2662 (w), 2579 (w), 1697 (s), 1520 (w), 1471 (w), 1448 (m), 1399 (m), 1353 (w), 1324 (s), 1294 (m), 1252 (m), 1207(m), 1180 (m), 1161 (m), 1105 (m), 1072 (s), 1001 (m), 969 (m), 931 (m), 893 (w), 870 (w), 835 (w), 797 (w), 779 (m), 736 (s), 724 (s), 701 (m), 685 (m), 665 (m), 620 (m), 570 (m), 507 (w), 460 (w), 423 (m).
R_f (cyHex/EtOAc+HOAc, 1:1+1%) = 0.41 [Ninhydrin]

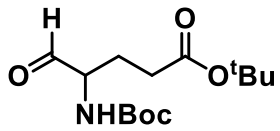
***tert*-Butyl 5-((*tert*-butoxycarbonyl)amino)-4-hydroxy-5-methylhexanoate (233)**



$C_{16}H_{31}NO_5$
317,43 g/mol

Synthesized following **GP-VII** using Boc-2-amino-2-methyl-1-propanol (103.9 mg, 0.55 mmol, 1.1 equiv.). The reaction was worked up after the irradiation step. Purification via flash chromatography using SiO_2 afforded the product as an off-white solid in 80% yield (127 mg, 0.40 mmol).
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.63 (s, 1H), 4.41 (s, 1H), 3.41 (t, *J* = 9.5 Hz, 1H), 2.52 (ddd, *J* = 16.5, 7.9, 6.1 Hz, 1H), 2.40 (dt, *J* = 16.0, 7.5 Hz, 1H), 1.87 – 1.81 (m, 1H), 1.55 (s, 1H), 1.44 (s, 9H), 1.43 (s, 9H), 1.37 (s, 3H), 1.20 (s, 3H).
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 173.8, 156.5, 80.3, 80.0, 76.9, 56.8, 32.7, 28.5, 28.3, 27.6, 25.6, 24.5.
HRMS (ESI): [m/z] calculated for $C_{16}H_{31}NNaO_5^+$ ([M+Na]$^+$): 340.2094; Found: 340.2101.
IR: ṽ [cm^{-1}] = 3266 (w), 3069 (w), 2978 (w), 2932 (w), 1729 (s), 1680 (s), 1554 (m), 1468 (w), 1454 (w), 1417 (m), 1391 (m), 1365 (s), 1287 (m), 1240 (m), 1211 (m), 1174 (s), 1146 (s), 1087 (s), 1075 (s), 1015 (w), 951 (m), 924 (w), 903 (w), 885 (w), 838 (m), 786 (w), 768 (w), 740 (w), 680 (m), 577 (w), 518 (w), 471 (w), 460 (w), 437 (w).
R_f (cyHex/EtOAc, 4:1) = 0.25 [Ninhydrin]

***tert*-Butyl 4-((*tert*-butoxycarbonyl)amino)-5-oxopentanoate (236)**



$C_{14}H_{25}NO_5$
287,36 g/mol

tert-Butyl 4-((*tert*-butoxycarbonyl)amino)-5-hydroxypentanoate (145.4 mg, 0.50 mmol, 1.0 equiv.) was dissolved in EtOAc (20 mL). Added 2-iodobenzoic acid (IBX; 280.5 mg, 1.00 mmol, 2.0 equiv.) and let stir to 85 °C for 3 h. The reaction mixture was concentrated in vacuum. Purification via flash chromatography using SiO_2 afforded the product as a colorless oil in 38% yield (54 mg, 0.19 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.57 (s, 1H), 5.22 (d, *J* = 7.2 Hz, 1H), 4.22 (q, *J* = 6.9 Hz, 1H), 2.32 (qt, *J* = 16.7, 7.1 Hz, 2H), 2.18 (dq, *J* = 13.5, 6.7 Hz, 1H), 1.84 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.43 (s, 9H), 1.43 (s, 9H).

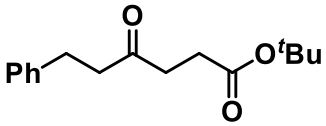
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 199.4, 172.3, 155.7, 81.1, 80.3, 59.5, 31.1, 28.4, 28.2, 24.3.

HRMS (ESI): [m/z] calculated for $C_{14}H_{25}NNaO_5^+$ ([M+Na]$^+$): 310.1625; Found: 310.1625.

IR: ṽ [cm^{-1}] = 3366 (w), 2978 (w), 2933 (w), 1708 (s), 1508 (m), 1455 (w), 1392 (w), 1366 (m), 1321 (w), 1248 (m), 1148 (s), 1056 (w), 1030 (w), 953 (w), 845 (w), 780 (w), 753 (w), 588 (w), 461 (w), 428 (w).

R_f (cyHex/EtOAc, 1:1) = 0.69 [Ninhydrin]

***tert*-Butyl 4-oxo-6-phenylhexanoate (256)**



$C_{16}H_{22}O_3$
262,35 g/mol

Synthesized using following conditions: 3-phenylpropan-1-ol (136,2 µL, 1.00 mmol, 2.0 equiv.), **IrF** (5.6 mg, 5 µmol, 1 mol%), quinuclidine (5.6 mg, 0.05 mmol, 10 mol%), tetrabutylammonium phosphate (42.5 mg, 0.125 mmol, 25 mol%) and *tert*-butylacrylate (72.8 µL, 0.50 mmol, 1.0 equiv.) in dry and degassed MeCN (0.63 mL, c = 0.8 M). The reaction was irradiated at rt for 24 h using blue LED (32W, λ_{max} = 450 nm). For the oxidation step, added IBX (308 mg, 1.10 mmol, 1.1 equiv.) and let stir to 85 °C for 3 h. Purification via multiple flash chromatographies using neutral SiO_2 and neutral aluminiumoxide afforded the product as a slightly yellowish oil in 59% yield (78 mg, 0.30 mmol).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 8.6, 6.6 Hz, 2H), 7.29 – 7.22 (m, 3H), 2.99 (t, *J* = 7.7 Hz, 2H), 2.85 (t, *J* = 7.7 Hz, 2H), 2.72 (t, *J* = 6.6 Hz, 2H), 2.57 (t, *J* = 6.6 Hz, 2H), 1.51 (s, 9H).

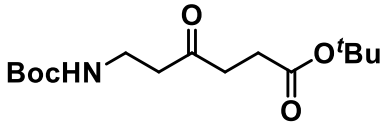
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 208.2, 172.1, 141.2, 128.6, 128.4, 126.2, 80.7, 44.4, 37.5, 29.8, 29.3, 28.2.

HRMS (ESI): [m/z] calculated for $C_{16}H_{22}NaO_3^+$ ([M+Na]$^+$): 285.1461; Found: 285.1459.

IR: ṽ [cm^{-1}] = 2977 (w), 2928 (w), 1715 (s), 1681 (m), 1626 (w), 1603 (w), 1496 (w), 1454 (w), 1409 (w), 1392 (w), 1365 (s), 1239 (m), 1151 (s), 1094 (m), 1030 (w), 993 (w), 846 (w), 749 (m), 699 (s), 556 (w), 517 (w), 488 (w), 431 (w).

R_f (cyHex/EtOAc, 4:1) = 0.45 [$KMnO_4$]

tert-Butyl 6-((*tert*-butoxycarbonyl)amino)-4-oxohexanoate (257)



$C_{15}H_{27}NO_5$
301,38 g/mol

Synthesized following **GP-VI** using *tert*-butyl (3-hydroxypropyl)carbamate (175.2 mg, 1.00 mmol, 2.0 equiv.). For the oxidation step, a 1.1-fold excess of IBX was used. Purification via multiple flash chromatographies using neutral SiO_2 and neutral aluminiumoxide afforded the product as a slightly yellowish oil in 64% yield (97 mg, 0.32 mmol).

Alternatively, synthesized using following conditions: *tert*-butyl (3-hydroxypropyl)carbamate (175.2 mg, 1.00 mmol, 2.0 equiv.), **IrF** (5.6 mg, 5 µmol, 1 mol%), quinuclidine (5.6 mg, 0.05 mmol, 10 mol%), tetrabutylammonium phosphate (42.5 mg, 0.125 mmol, 25 mol%) and *tert*-butylacrylate (72.8 µL, 0.50 mmol, 1.0 equiv.) in dry and degassed MeCN (0.63 mL, c = 0.8 M). The reaction was irradiated at rt for 24 h using blue LED (32W, λ_{max} = 450 nm). For the oxidation step, added IBX (308 mg, 1.10 mmol, 1.1 equiv.) and let stir to 85 °C for 3 h. Purification via flash chromatography using neutral aluminiumoxide afforded the product as a slightly yellowish oil in 38% yield (57 mg, 0.19 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (s, 1H), 3.34 (q, *J* = 5.9 Hz, 2H), 2.69 – 2.57 (m, 4H), 2.48 (dd, *J* = 7.5, 5.4 Hz, 2H), 1.40 (s, 9H), 1.39 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 208.7, 172.0, 156.0, 80.8, 79.3, 42.8, 37.5, 35.4, 29.3, 28.5, 28.1.

HRMS (ESI): [m/z] calculated for $C_{15}H_{27}NNaO_5^+$ ([M+Na]$^+$): 324.1781; Found: 324.1789.

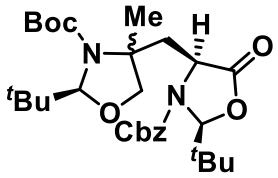
IR: ṽ [cm^{-1}] = 3391 (w), 2977 (w), 2932 (w), 1708 (s), 1505 (m), 1455 (w), 1392 (m), 1365 (s), 1270 (m), 1247 (m), 1150 (s), 1098 (m), 847 (w), 780 (w), 754 (w), 570 (w), 460 (w), 432 (w).

R_f (cyHex/EtOAc, 4:1) = 0.22 [Ninhydrin]

VI.V Total Synthesis of Manzacidin A/C

VI.V.1 – Synthesis and Characterization

Benzyl (2S,4S)-4-(((2S)-3-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidin-4-yl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (285)



$C_{29}H_{44}N_2O_7$
532,68 g/mol

Synthesized following **GP-III** using **286** (163 mg, 0.57 mmol, 2.0 equiv.). Purification via flash chromatography afforded a single diastereomer of the product as a yellow oil in 61% yield (93 mg, 0.18 mmol, contains cyHex residues).

Repetition in a smaller scale following **GP-III** using **286** (29 mg, 0.10 mmol, 2.0 equiv.) afforded the crude product as a ~5.5:1 diastereomeric mixture – based on calculation from the ^{1}H NMR spectrum of the crude reaction mixture.

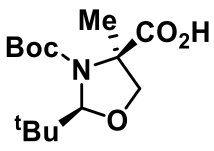
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.32 (m, 5H), 5.51 (s, 1H), 5.17 (s, 2H), 5.15 (s, 1H), 4.56 (d, *J* = 9.4 Hz, 1H), 4.47 – 4.23 (m, 1H), 3.74 (d, *J* = 9.1 Hz, 1H), 1.96 (d, *J* = 14.5 Hz, 1H), 1.55 (s, 1H), 1.47 (s, 3H), 1.45 (s, 9H), 0.97 (s, 9H), 0.94 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 172.0, 155.7, 153.9, 135.2, 128.9, 128.9, 128.9, 96.0, 68.6, 62.1, 54.1, 46.6, 39.1, 37.1, 28.5, 27.6, 27.1, 25.0. *Three signals were not detected.*

HRMS (ESI): [m/z] calculated for $C_{29}H_{44}N_2NaO_7^+$ ([M+Na]$^+$): 555.3041; Found: 555.3041.

R_f (cyHex/EtOAc, 5:1) = 0.32 [p-Anisaldehyde]

(2S,4R)-3-(*tert*-Butoxycarbonyl)-2-(*tert*-butyl)-4-methyloxazolidine-4-carboxylic acid (286)



$C_{14}H_{25}NO_5$
287,36 g/mol

A slightly modified literature procedure was used.[286] To LiOH (601 mg, 25.09 mmol, 10.1 equiv.) in H_2O (5 mL) added 3-(*tert*-butyl) 4-methyl (2S,4R)-2-(*tert*-butyl)-4-methyloxazolidine-3,4-dicarboxylate (747 mg, 2.48 mmol, 1.0 equiv.) dissolved in THF (10 mL, 0.25 M). Stirred vigorously at 50 °C for 48 h to receive an orange suspension. Adjusted pH to 4 by careful

addition of 3 M HCl. The reaction mixture was extracted with EtOAc (3 x 20 mL) and the combined org. layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated in vacuum to afford the product as a beige solid in quantitative yield (<712 mg, <2.48 mmol, contains solvent residues)

The analytical data are in agreement with those previously reported.[286]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 1H), 4.67 (d, *J* = 9.3 Hz, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 1.70 (d, *J* = 0.8 Hz, 3H), 1.52 (s, 9H), 1.26 (s, 1H), 0.93 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 157.5, 97.7, 84.6, 76.4, 66.8, 38.9, 28.2, 26.4, 21.9.

HRMS (ESI): [m/z] calculated for $C_{14}H_{25}NNaO_5^+$ ($[M+Na]^+$): 310.1625; Found: 310.1618.

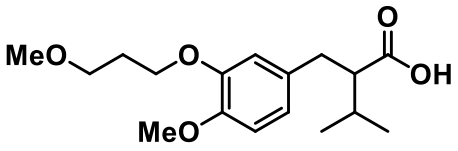
IR: ṽ [cm^{-1}] = 2954 (m), 2920 (s), 2852 (s), 1728 (s), 1649 (m), 1460 (m), 1391 (m), 1364 (s), 1346 (s), 1270 (m), 1238 (m), 1188 (m), 1165 (s), 1152 (s), 1122 (s), 1055 (s), 1033 (m), 958 (m), 940 (w), 912 (m), 880 (m), 852 (m), 798 (w), 783 (m), 722 (w), 701 (m), 611 (w), 573 (w), 539 (w), 464 (w), 417 (w).

R_f (EtOAc) = 0.50 [Ninhydrin]

VI.VI Total Synthesis of Aliskiren

VI.VI.1 – Synthesis and Characterization

2-(4-Methoxy-3-(3-methoxypropoxy)benzyl)-3-methylbutanoic acid (303)



$C_{17}H_{26}O_5$
310,39 g/mol

313 (310 mg, 0.92 mmol, 1.0 equiv.) was dissolved in MeOH (1 mL, 0.9 M). Added 2 M KOH (1 mL, 2.00 mmol, 2.2 equiv.) and let stir in a closed vial at 60 °C for 65 h. Removed MeOH in vacuum and adjusted pH to 1 by careful addition of 3 M HCl. Added NaCl to saturate aq. layer, then extracted with Et_2O (3 x 2 mL). Combined org. layers were dried over Na_2SO_4 and concentrated in vacuum to afford the product as an orange oil in quantitative yield (>286 mg, >0.92 mmol, contains EtOAc residues).

The analytical data are in agreement with those previously reported for the enantiopure product.[263]

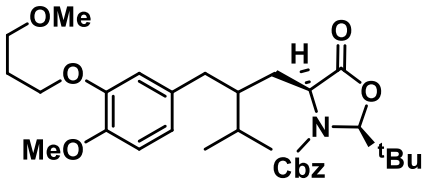
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.77 – 6.74 (m, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 3.56 (t, *J* = 6.1 Hz, 2H), 3.35 (s, 3H), 2.83 – 2.74 (m, 2H), 2.45 (dt, *J* = 9.9, 5.9 Hz, 1H), 2.09 – 2.05 (m, 2H), 1.94 (h, *J* = 6.8 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 179.9, 148.3, 148.1, 132.4, 121.2, 114.4, 112.0, 69.6, 66.1, 58.8, 56.2, 54.6, 35.2, 30.6, 29.6, 20.5, 20.1.

HRMS (ESI): [m/z] calculated for $C_{17}H_{26}NaO_5^+$ ([M+Na]$^+$): 333.1672; Found: 333.1676.

IR: ṽ [cm^{-1}] = 2959 (m), 2930 (m), 2874 (m), 2835 (w), 1729 (m), 1703 (s), 1607 (w), 1590 (w), 1513 (s), 1465 (m), 1442 (m), 1424 (m), 1390 (w), 1372 (w), 1331 (w), 1257 (s), 1232 (s), 1191 (m), 1158 (s), 1137 (s), 1117 (s), 1024 (s), 995 (m), 955 (w), 924 (w), 852 (m), 801 (m), 766 (m), 633 (w), 600 (w), 530 (w), 514 (w), 460 (w).

Benzyl (2S,4S)-2-(*tert*-butyl)-4-(2-(4-methoxy-3-(3-methoxypropoxy)benzyl)-3-methylbutyl)-5-oxooxazolidine-3-carboxylate (304)



$C_{32}H_{45}NO_7$
555,71 g/mol

The combination of 6 different test reactions (0.1 mmol scale) afforded the clean product in a ~1.5:1 mixture of diastereomers as nearly colorless oil in 73% combined yield (242 mg, 0.44 mmol).

^{1}H NMR (400 MHz, $CDCl_3$, *mayor isomer*): δ 7.42 – 7.31 (m, 5H), 6.80 – 6.59 (m, 3H), 5.50 (s, 1H), 5.23 – 5.10 (m, 2H), 4.38 – 4.29 (m, 1H), 4.14 – 4.03 (m, 2H), 3.82 (s, 3H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.34 (s, 3H), 2.61 – 2.33 (m, 2H), 2.14 – 2.03 (m, 3H), 1.90 – 1.64 (m, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.78 (d, *J* = 6.8 Hz, 3H).

^{1}H NMR (400 MHz, $CDCl_3$, *minor isomer*): δ 7.42 – 7.31 (m, 5H), 6.80 – 6.59 (m, 3H), 5.48 (s, 1H), 5.23 – 5.10 (m, 2H), 4.38 – 4.29 (m, 1H), 4.14 – 4.03 (m, 2H), 3.82 (s, 3H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.35 (s, 3H), 2.61 – 2.33 (m, 2H), 2.14 – 2.03 (m, 3H), 1.90 – 1.64 (m, 3H), 10.85 (d, *J* = 6.8 Hz, 3H), 0.82 – 0.78 (m, 3H) 0.80 (s, 9H).

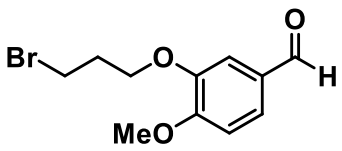
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, *mayor isomer*): δ 172.6, 156.2, 148.5, 147.8, 135.4, 133.8, 128.8, 128.8, 128.7, 121.5, 114.8, 112.0, 96.3, 69.6, 68.6, 66.3, 58.8, 56.3, 55.6, 41.3, 37.0, 36.0, 33.9, 29.8, 28.0, 25.1, 18.6.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, *minor isomer*): δ 173.0, 156.3, 148.6, 147.9, 135.5, 134.0, 128.8, 128.8, 128.7, 121.4, 114.8, 112.2, 96.4, 69.6, 68.5, 66.3, 58.8, 56.3, 55.6, 41.6, 36.8, 36.0, 34.0, 29.8, 28.3, 24.9, 18.6.

HRMS (ESI): [m/z] calculated for $C_{32}H_{45}NNaO_7^+$ ([M+Na]$^+$): 578.3088; Found: 578.3097.

R_f (cyHex/EtOAc, 4:1) = 0.22 [$KMnO_4$]

3-(3-Bromopropoxy)-4-methoxybenzaldehyde (307)



$C_{11}H_{13}BrO_3$
273,13 g/mol

Following a literature procedure,[263] isovanillin (4.22 g, 27.74 mmol, 1.0 equiv.) was suspended in MeCN (200 mL), then K_2CO_3 (5.87 g, 42.48 mmol, 1.5 equiv.) and 1,3-dibromopropane (28.1

mL, 276.98 mmol, 10.0 equiv.) were added. Let stir to 80 °C overnight. The next day, the obtained yellow suspension was filtered and the filtrate was concentrated in vacuum. Purification of the concentrated filtrate via flash chromatography afforded the product as a beige solid in 91% yield (6.90 g, 25.26 mmol).

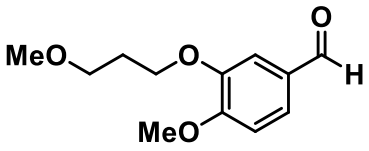
The analytical data are in agreement with those previously reported.[287]

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.47 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.43 (d, *J* = 1.9 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 4.21 (t, *J* = 5.9 Hz, 2H), 3.94 (s, 3H), 3.62 (t, *J* = 6.4 Hz, 2H), 2.39 (p, *J* = 6.2 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 190.9, 155.1, 148.9, 130.2, 127.0, 111.2, 110.9, 66.7, 56.2, 32.3, 29.9.

R_f (cyHex/EtOAc, 2:1) = 0.39 [$KMnO_4$]

4-Methoxy-3-(3-methoxypropoxy)benzaldehyde (308)



$C_{12}H_{16}O_4$
224,26 g/mol

Following a slightly modified literature procedure,[263] **307** (4.95 g, 18.1 mmol, 1.0 equiv.) was dissolved in MeOH (72 mL, 0.25 M). While stirring vigorously, added NaOMe solution (25 wt% in MeOH, 7.92 g, 36.67 mmol, 2.0 equiv.) over a period of 2 min. Let reflux at 75 °C for 20 h. The obtained, clear yellow solution was concentrated in vacuum and the residue redissolved in Et_2O (100 mL). Cooled down in an ice-bath, then washed with 4 N HCl (60 mL), H_2O (60 mL) and satd. $NaHCO_3$ (60 mL) before the org. layer was dried over Na_2SO_4 and concentrated in vacuum. Purification via flash chromatography afforded the product as a yellow oil in 66% yield (2.70 g, 12.04 mmol).

As a mayor by-product, elimination product **309** was obtained in 15% yield (0.54 g, 2.81 mmol). This is in good agreement with a literature report yielding a 4:1 ratio of **308** vs. **309** using similar conditions.[263]

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.43 – 7.39 (m, 2H), 6.94 (d, *J* = 8.1 Hz, 1H), 4.14 (t, *J* = 6.6 Hz, 2H), 3.91 (s, 3H), 3.54 (t, *J* = 6.2 Hz, 2H), 3.32 (s, 3H), 2.09 (p, *J* = 6.3 Hz, 2H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 190.9, 154.9, 149.1, 130.2, 126.6, 110.9, 110.8, 77.4, 77.2, 76.9, 69.2, 66.2, 58.7, 56.2, 29.5.

HRMS (ESI): [m/z] calculated for $C_{12}H_{16}NaO_4^+$ ([M+Na]$^+$): 247.0941; Found: 247.0944.

IR: ṽ [cm^{-1}] = 2932 (w), 2875 (w), 2838 (w), 1682 (s), 1584 (m), 1509 (s), 1461 (w), 1435 (m), 1394 (m), 1339 (w), 1263 (s), 1238 (s), 1190 (m), 1160 (m), 1119 (s), 1018 (s), 864 (w), 807 (m), 773 (w), 735 (w), 641 (m), 559 (w), 516 (w), 433 (w).

R_f (cyHex/EtOAc, 2:1) = 0.20 [p-Anisaldehyde]

Analytical data for by-product 309:

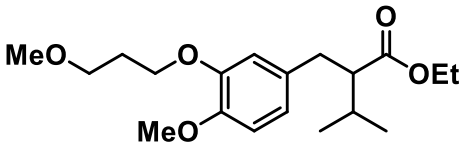
The analytical data are in agreement with those previously reported.[288]

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.45 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.39 (d, *J* = 1.9 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.08 (ddt, *J* = 17.2, 10.7, 5.4 Hz, 1H), 5.43 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.31 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.65 (d, *J* = 5.5 Hz, 2H), 3.94 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 190.9, 155.0, 148.7, 132.6, 130.2, 126.9, 118.7, 111.1, 110.8, 69.9, 56.3.

HRMS (ESI): [m/z] calculated for $C_{11}H_{13}O_3^+$ ([M+H]$^+$): 193.0859; Found: 193.0868.

Ethyl 2-(4-methoxy-3-(3-methoxypropoxy)benzyl)-3-methylbutanoate (313)



$C_{19}H_{30}O_5$
338,44 g/mol

Following a slightly modified literature procedure,[265] diisopropylamine (1.5 mL, 10.67 mmol, 1.2 equiv.) was dissolved in dry THF (7 mL) and cooled down in a cooling bath to -50 °C. Simultaneously added **308** (2.0 g, 8.92 mmol, 1.0 equiv.) dissolved in dry THF (10 mL, 0.9 M), ethyl isovalerate (1.5 mL, 9.96 mmol, 1.1 equiv.) dissolved in dry THF (3 mL) and nBuLi (2.5 M in hexane, 6 mL, 15.00 mmol, 1.7 equiv.) dropwise. Continued stirring at -50 °C for 2 h, then the cooling bath was allowed to slowly warm up to room temperature and the reaction was stirred for another 60 min. The reaction was quenched by dropwise addition of H_2O (5 mL) and let stir at room temperature overnight. The next day, adjusted pH to 1 via careful addition of 12 M HCl. The phases were separated and the aq. layer was washed with toluene (2 x 5 mL). Combined org. layers were concentrated in vacuum to give a yellow oil, which was redissolved in toluene (40 mL). pTsOH monohydrate (165 mg, 0.87 mmol, 10 mol%) was added and the reaction mixture was refluxed at 120 °C for 5 h. Formed H_2O was removed from the reaction mixture by using a Dean-Stark separator. Let stir at room temperature overnight. After standing at room temperature for another 2 days, the reaction mixture was washed with satd. $NaHCO_3$ solution (25 mL) and H_2O (25 mL). The org. layer was dried over Na_2SO_4 and concentrated in vacuum to receive a deep-orange oil. Purification via flash chromatography failed to give intermediate product in sufficiently high purity. The subsequent hydrogenation was performed according to a literature procedure.[264] To do so, all fractions containing the intermediate product were combined and dissolved in EtOH (60 mL). The clear, yellow solution was purged with N_2 for 10 min, before Pd/C (10% palladium on charcoal, 256 mg, 0.24 mmol) was added.

Using a balloon, the reaction solution was purged with H_2 for 10 min. Without purging, continued stirring under a H_2-atmosphere for another 10 min, before purging the solution again with H_2 for 10 min. The reaction mixture was filtered through Celite® and the filter was washed with EtOH. Concentration of the filtrate afforded a slightly yellowish oil. Purification via vacuum distillation (11 mbar, 200 °C oil bath) failed to give a distillate and was aborted after 150 min. The residue has turned black. The apparatus was washed with EtOH and all residues were combined. Purification via flash chromatography afforded the product as a yellow oil in 19 % yield over three steps (583 mg, 1.72 mmol).

The analytical data are in agreement with those previously reported.[264]

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.75 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.68 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.07 (td, *J* = 6.5, 1.4 Hz, 2H), 4.00 (dddd, *J* = 18.0, 10.8, 7.1, 3.7 Hz, 2H), 3.81 (s, 3H), 3.56 (t, *J* = 6.2 Hz, 2H), 3.35 (s, 3H), 2.79 – 2.75 (m, 2H), 2.41 (dt, *J* = 8.7, 6.8 Hz, 1H), 2.08 (p, *J* = 6.3 Hz, 2H), 1.91 (dp, *J* = 13.3, 6.7 Hz, 1H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 175.0, 148.4, 148.0, 132.8, 121.2, 114.3, 111.9, 69.5, 66.2, 60.0, 58.8, 56.2, 55.0, 35.6, 30.8, 29.8, 20.6, 20.3, 14.4.

HRMS (ESI): [m/z] calculated for $C_{19}H_{30}NaO_5^+$ ([M+Na]$^+$): 361.1985; Found: 361.1983.

IR: ṽ [cm^{-1}] = 2959 (m), 2932 (m), 2874 (m), 2834 (w), 1727 (s), 1652 (w), 1608 (w), 1590 (w), 1514 (s), 1464 (m), 1442 (m), 1425 (m), 1388 (m), 1373 (m), 1259 (s), 1234 (s), 1192 (m), 1156 (s), 1138 (s), 1116 (s), 1094 (s), 1025 (s), 988 (m), 919 (w), 855 (w), 803 (m), 766 (w), 734 (w), 633 (w), 601 (w), 556 (w), 516 (w), 468 (w).

R_f (cyHex/EtOAc, 4:1) = 0.27 [CAM]

VII. List of Abbreviations

2,2-DMP	2,2-Dimethoxypropane
AAs	Amino acids
AIBN	Azobisisobutyronitrile
Ala	Alanine
Arg	Arginine
Asn	Asparagine
Asp	Aspartic acid
BDE	Bond dissociation energy
bpy	Bipyridine
CyHex	Cyclohexane
Cys	Cysteine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethylene
DET	Dexter energy transfer
Dha	Dehydroalanine
DIPA	Diisopropylamine
DMP	Dess-Martin periodinane
d.r.	diastereomeric ratio
e.r.	enantiomeric ratio
FRET	Förster resonance energy transfer
GABA	γ-Aminobutyric acid
Gln	Glutamine
Glu	Glutamic acid
Gly	Glycine
HAT	Hydrogen atom transfer
His	Histidine

HOMO	Highest occupied molecular orbital
IBX	2-Iodoxybenzoic acid
IC	Internal conversion
Ile	Isoleucine
IrF	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$
ISC	Intersystem crossing
LA	Lewis acid
LED	Light-emitting diode
Leu	Leucine
LUMO	Lowest unoccupied molecular orbital
Lys	Lysine
MeI	Iodomethane
Met	Methionine
3 Å MS	3 Å Molecular sieves
MTBE	Methyl *tert*-butyl ether
NCS	*N*-Chlorosuccinimide
PC	Photocatalyst
PDC	Pyridinium dichromate
Phe	Phenylalanine
PNA	Peptide nucleic acid
Pro	Proline
RAE	Redox-active ester
SDS	Sodium dodecyl sulfate
Sec	Selenocysteine
Ser	Serine
SET	Single electron transfer
SPD	Spectral power distribution

TBAP	Tetrabutylammonium phosphate
Thr	Threonine
TRIP-SH	2,4,6-Triisopropylthiophenol
Trp	Tryptophan
Tyr	Tyrosine
UAAs	Unnatural amino acids
Val	Valine

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