

Photocatalytic Reductive Synthesis of α -Functionalised Amines and Ethers



A thesis submitted in partial fulfilment of the requirement
for the degree of Doctor of Philosophy (DPhil)

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Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from October 2017 until December 2020, under the supervision of Prof. Darren J. Dixon. I declare that the thesis has been entirely written by me, that it is the record of work carried out by me and that it has not been submitted previously for any other higher degree at this or any other university. Any work done as part of a collaboration with a research colleague has been fully acknowledged and referenced within the main text.

April 2021

Thomas Rossolini

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List of Abbreviations

AA	amino acid
AIE	α -imino ester
aq.	aqueous
ATAA	α -tertiary amino acid
BDE	bond dissociation energy
BET	back-electron transfer
BINOL	1,1'-Bi-2-naphthol
Boc	<i>tert</i> -butyloxycarbonyl
Bn	benzyl
BNAH	1-benzyl-1,4-dihydronicotinamide
CB-1	cannabinoid 1
conc.	concentration
CF₃	trifluoromethyl
CHD	cyclohexadiene
CV	cyclic voltammetry
d	doublet

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	dicyanobenzene
DFT	density functional theory
DHA	dehydroalanine
DHP	1,4-dihydropyridine
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylamino-pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPPN	1,3-diphenylpropanediamine
dr	diastereomeric ratio
EDA	electron donor-acceptor
ET	electron transfer
EtOAc	ethyl acetate
E_{red}	reduction potential
EWG	electron-withdrawing group
F-AA	fluorinated amino acid
FC	flash column chromatography
g	gram(s)
h	hour(s)
HAT	hydrogen atom transfer

HE	Hantzsch ester
HOMO	highest occupied molecular orbital
HP	Hantzsch pyridine
Hz	Hertz
ISC	intersystem crossing
<i>J</i>	coupling constant (NMR) in Hz
L.A	Lewis acid
LED	light-emitting diode
LUMO	lowest unoccupied molecular orbital
M	molar
m.p.	melting point
<i>m/z</i>	mass over charge ratio
mg	milligram(s)
MLCT	metal to ligand charge transfer
mol	mol
NHPI	<i>N</i> -hydroxyphthalimide
ncAA	non-canonical amino acid
[ox]	oxidant
PC	photocatalyst
PC*	photoexcited PC

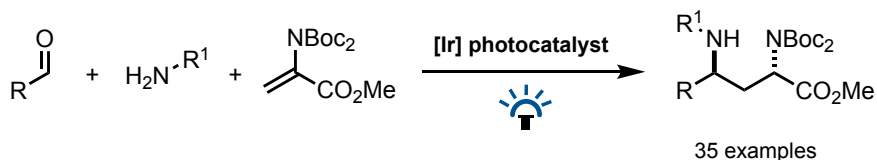
PCET	proton-coupled electron transfer
PET	photoinduced electron transfer
PFP	<i>p</i> -fluorophenyl
PG	protecting group
Phe	phenylalanine
Pin	pinacol
PMP	<i>p</i> -methoxyphenyl
POMs	polyoxometalates
ppm	parts per million
PTH	phenothiazine
q	quartet
Q	quencher
RAE	redox-active ester
RCA	radical conjugate addition
[red]	reductant
RHAT	reverse hydrogen atom transfer
RM	redox mediator
RP	radical precursor
RPC	radical-polar crossover
s	singlet; strong
sat.	saturated
SCE	saturated calomel electrode

SEO	single-electron oxidation
SER	single-electron reduction
SET	single-electron transfer
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMB	1,3,5-trimethoxybenzene
TMSCl	chlorotrimethylsilane
TMSCN	trimethylsilyl cyanide
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tfm	trifluoromethyl
UAA	unnatural amino acid
UV	ultraviolet
V	volts
ValCbz	carbobenzyloxy-L-valin
vdW	van der Waals
δ	chemical shift in ppm
$\tilde{\nu}$	wavenumber(s)
$^{\circ}$	degree
μL	microliter(s)

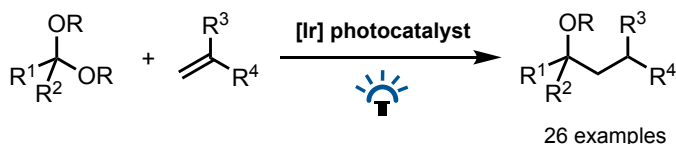
Abstract

Chapter 1 introduces fundamental notions of photocatalysis as well as its evolution into modern photoredox catalysis with seminal contributions of the past decade.

Chapter 2 describes the development of a photocatalytic three-component one-pot umpolung methodology for the diastereoselective synthesis of 1,3-diamines based on the *in situ* formation of nucleophilic α -amino radicals species. The method provides access to a broad range of 1,3-diamine products with a wide variety of functionalities and demonstrates its application as an entry point to bioactive molecules.



Chapter 3 details the design and application of a reductive synthetic methodology for the construction of challenging α -tertiary dialkyl ether compounds from readily accessible starting materials. The coupling approach pivots on a novel photocatalytic single-electron reduction of oxocarbenium ion intermediates.



Chapter 4 illustrates our efforts towards the development of a photocatalyst-free approach for the synthesis of biologically relevant α -trifluoromethyl- α -amino acid derivatives. Visible light-mediated homolytic cleavage of substituted radical precursors (RPs) is used to generate open-shell alkyl species which are believed to engage in radical addition reactions.



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Chapter 1

Introduction

1.1 Introduction to Photocatalysis

In 1912, pioneering chemist Giacomo Ciamician envisioned the use of solar radiation for industrial purposes as an alternative to non-renewable energy sources, raising awareness of environmental issues.^[1] Synthetic organic chemists have long aspired to synthesise complex organic molecules by converting solar energy into chemical potential. Despite the broad utility of photochemistry in organic synthesis,^[2–4] Ciamician’s grand vision has been considerably constrained by several challenges observed in the application of photochemical synthesis. Most simple organic molecules reach electronically excited states upon irradiation with ultraviolet (UV) light – which comprises less than 5% of the solar spectrum – however, absorption of high-energy UV photons often results in non-selective outcomes and undesired decomposition. Consequently, these limiting factors, along with the requirement for specialised UV photoreactors, negatively contributed to the development of photochemistry and photocatalysis as a general toolbox for organic chemists.^[5] The dramatic revival of photocatalysis among synthetic chemists in recent times is attributable to the recognition that visible light absorbing catalysts – photocatalysts – are capable of inducing previously unattainable reaction pathways.^[5,6] Upon excitation, the most common mechanisms by which photocatalysts can induce synthetically valuable reactions

include energy transfer, atom transfer, and photoinduced electron transfer (PET).^[7,8]

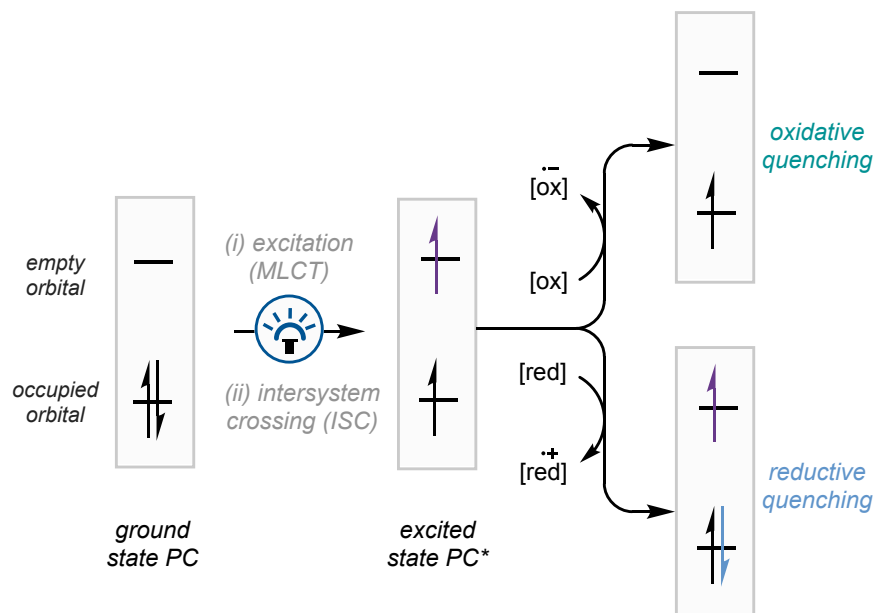
1.2 Photoredox Catalysis

The renaissance in photocatalysis by the synthetic community is linked to the ability of photoexcited molecules – organic or transition metal complexes – to partake in PET upon visible light irradiation, a process more recently referred to as photoredox catalysis.^[7] Interactions between electronically excited photocatalysts and organic (or organometallic) substrates can result in single-electron transfer (SET) events, generating reactive open-shell intermediates for subsequent transformations. Consequently, SET processes grant access to highly reactive radicals under mild reaction conditions and activate chemical entities which would be "switched-off" in the absence of visible light.^[9]

1.2.1 Mechanistic Considerations

Absorption of a photon in the visible region by a photocatalyst (PC) triggers the formation of an electronically excited state (PC*), via the promotion of an electron from an occupied orbital to an empty one, followed by intersystem crossing (ISC) to generate a long-lived triplet state species. For metal-based PCs, photoinduced excitation of an electron occurs from the metal-centred HOMO to the ligand-centred LUMO, a transition termed metal to ligand charge transfer (MLCT). Since decay to the singlet ground state is spin-forbidden, this sufficiently long-lived triplet state can engage in bimolecular single-electron transfer (SET) reactions (Scheme 1).^[10,11] As an exemplified charge-separated electron-hole pair, the photoexcited PC* species is capable of performing reductive and oxidative chemistry by donating or accepting an electron, respectively.^[7] In addition, a remarkable feature of PC*s is that they possess better oxidizing and reducing properties than their ground state species.^[11] The majority of photoredox reactions proceed via two distinct quenching modes depending on the reaction conditions: oxidative or reductive quenching cycle (Scheme 2). In an oxidative quenching cycle, the photoexcited PC* is

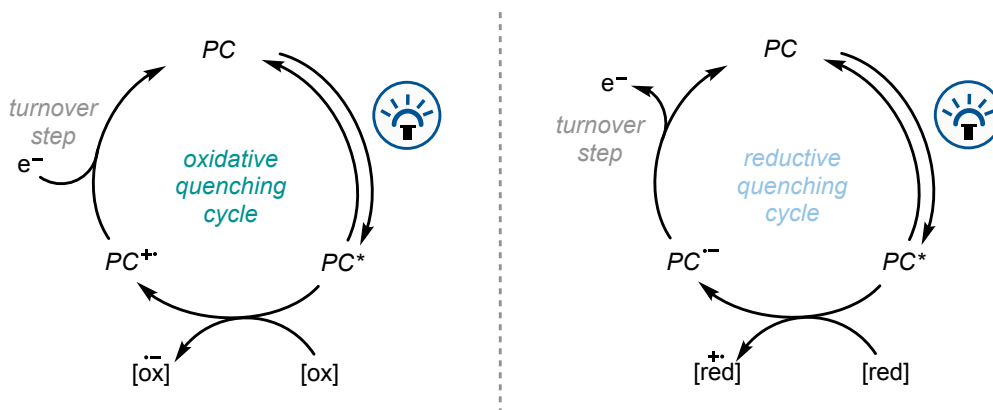
quenched by donating the high energy electron to a suitable oxidant [ox] present in the mixture; whereas in a reductive cycle PC* is quenched by gaining an electron from a suitable reductant [red], thereby pairing the electron in the lower orbital (Scheme 1 and 2).



Scheme 1. Simplified representation for the formation and reactivity of excited photoredox catalysts.

Consequently, reduction of the oxidised photocatalyst ($PC^{\bullet+}$) in the oxidative cycle and oxidation of the reduced $PC^{\bullet-}$ in the reductive cycle has to take place in order to ensure catalyst turnover (Scheme 2).^[12] Stern-Volmer (or fluorescence quenching) experiments can be conducted to determine which species – substrate, reaction intermediate or external reagent – is responsible for PC* quenching, and in turn which quenching cycle is operative under certain reaction conditions.^[11]

Despite the simplified mechanistic representation of photocatalytic reactions involving an idealised redox cycle where one photon is converted to exactly one molecule of product, certain photoredox-catalysed transformations can involve chain mechanisms, where intermediates have the ability to donate or accept electrons initiating a chain propagation.^[12] Yoon and Riedle have developed facile methods to determine if chain electron transfer is operative in photoredox catal-



Scheme 2. Model catalytic quenching modes of a photoredox catalyst: oxidative and reductive cycles.

ysis. This evaluation is based on quantum yield (Φ) measurements, whereby values of Φ above 1 imply that not only PET cycles are involved.^[13,14] Regardless of the operative mechanistic pathway, for most photoredox catalytic transformations there are three different reaction types with respect to overall redox outcome: net oxidative, net reductive, and redox neutral.^[12]

1.2.2 Thermodynamic and Kinetic Parameters of Photoredox Catalysts

In contrast to former strategies based on direct substrate photoexcitation, selective excitation of PCs upon visible light irradiation – wavelengths at which most common organic molecules do not absorb photons – substantially reduce unproductive side reactions.^[9] Moreover, access to radical ion intermediates through SET in photoredox catalysis results in novel reactivity patterns which, in some cases, were not contemplated in previously-established chemistries. This unique and targeted reactivity is provided by employing chromophores as photocatalysts (PCs).^[9,11] Despite exhibiting some common structural features – *e.g.* highly conjugated systems that enable interaction with light – the remarkably varied properties among PCs provide opportunities for the development of novel synthetic methodologies. Firstly, the broad range of redox potentials reflects the diversity of available redox behaviours and unprecedented forms of reactivity depending on reaction conditions (Figure 1). In fact, opportune choice of the PC is crucial as

reduction potentials (different from ground to excited state) can govern the mechanistic outcome of the reaction.^[7] Standard reduction potentials (E_{red}) – generally reported in the direction from oxidised to reduced species against a reference electrode – quantify the potential associated with an electrochemical half reaction (Figure 1).^[11] A general approximation for reduction potentials of PC* can be derived from established cyclic voltammetry (CV) and spectroscopic data. Although other parameters – *e.g.* solvent, temperature, concentration, and pH – alter E_{red} calculations, these thermodynamic values remain an effective tool towards reaction design.^[10] Additionally, the reactivity of metal-based PCs can be modulated by virtue of ligand design as well as manipulation of oxidation states and electronic excitation.^[9] As a general trend, E_{red} values can be tuned by modulating the ligand such that reducing electron density of the metal center will result in a stronger oxidative power of the PC, whereas more electron rich ligands will make the corresponding PC a stronger reductant.^[10]

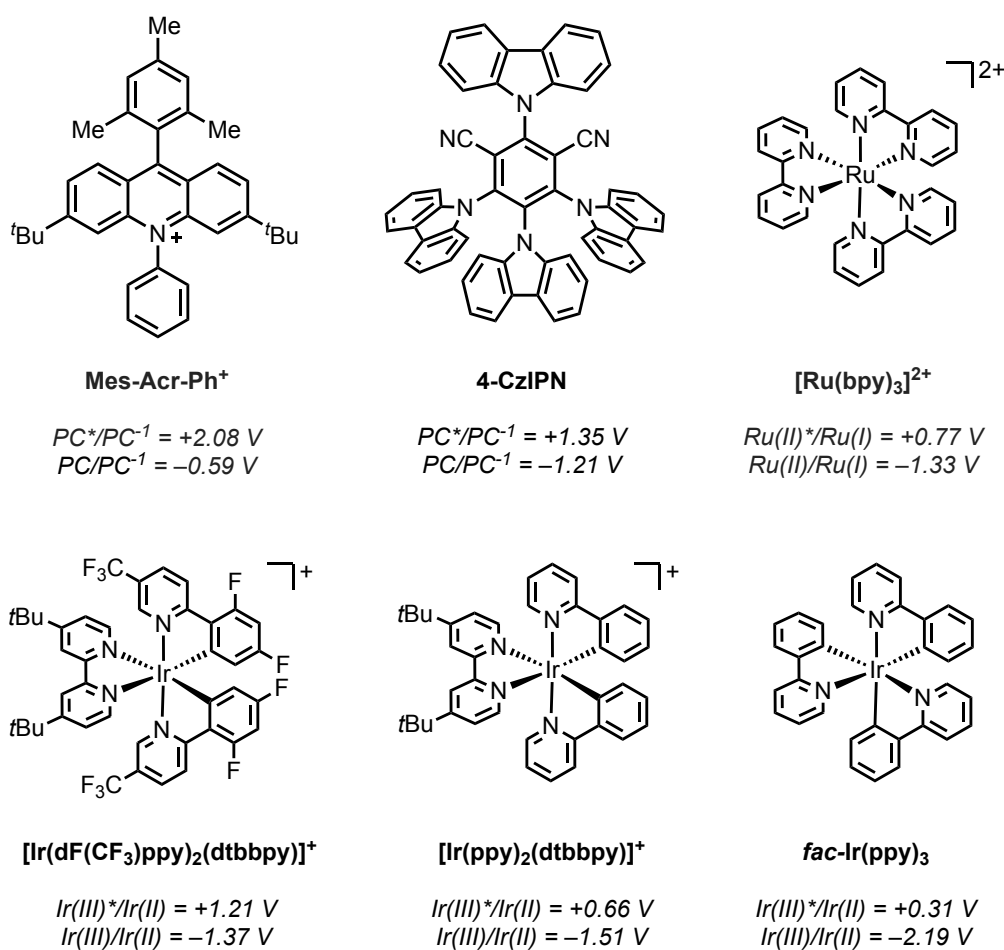


Figure 1. Chemical structures and redox potentials of common photocatalysts. Reduction potentials are reported in volts (V) versus the saturated calomel electrode (SCE).^[15,16]

While the catalyst's design is critical to achieve favorable thermodynamics (ΔG°) by modulating redox parameters, these values alone are insufficient for a successful reaction system.^[10] Contrary to closed-shell catalysis, slow steps in catalytic radical chemistry are not tolerated due to the short lifetimes of high-energy intermediates.^[17] As a consequence, while in photoredox catalysis photons can provide the activation energy to surmount activation barriers in endergonic steps, also appropriate kinetics in subsequent exergonic (or moderate endergonic) processes are indispensable to ensure desired product formation.^[10,17] For example, upon photoexcitation of a PC, an outer-sphere electron transfer (ET) process must occur to quench PC*^{*}; although this

PET might be exergonic, inefficient rates of ET (k_{ET}) between involved species can inhibit an overall successful reaction (Figure 2).^[7,10] Unfavorable kinetics of this type can be mitigated using redox mediators (RM), which increase reaction rates by mediating PET processes among reactive intermediates ($^*PC^n$ and [sub], Figure 2). Employment of a RM can also be beneficial in the case of an undesired back-electron transfer (BET) event, which regenerates the parent ground state PC and its quencher (Q) before the corresponding associated complex can escape the solvent cage to give the desired redox products ($k_{BET} > k_{DISS}$, Figure 2). Furthermore, more favorable kinetics using RM can be exploited to positively modulate endergonic PET.^[7]

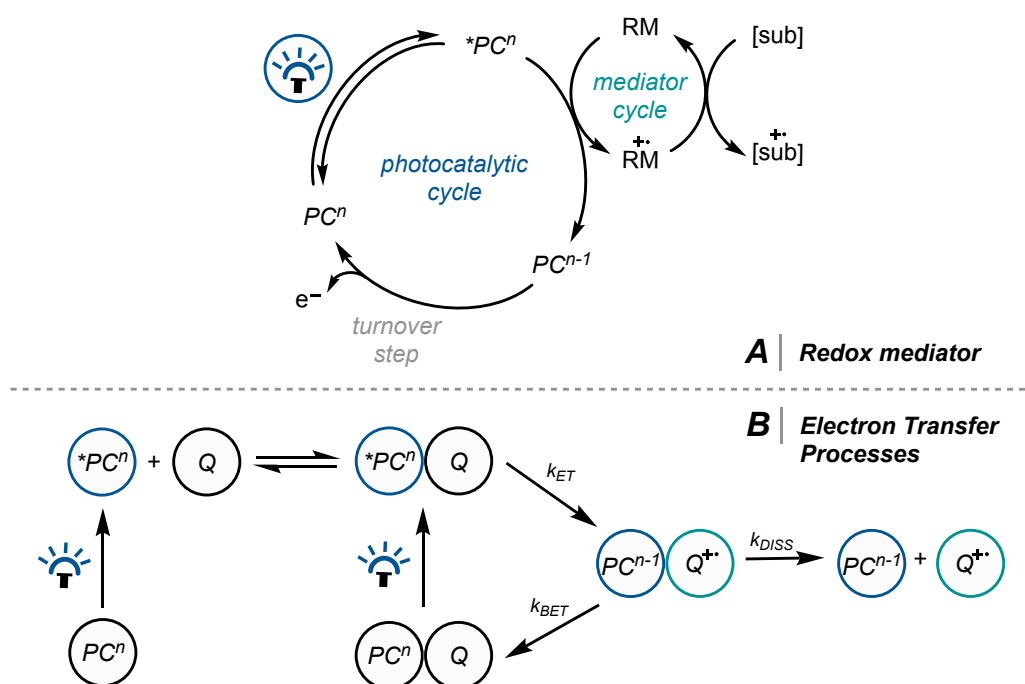
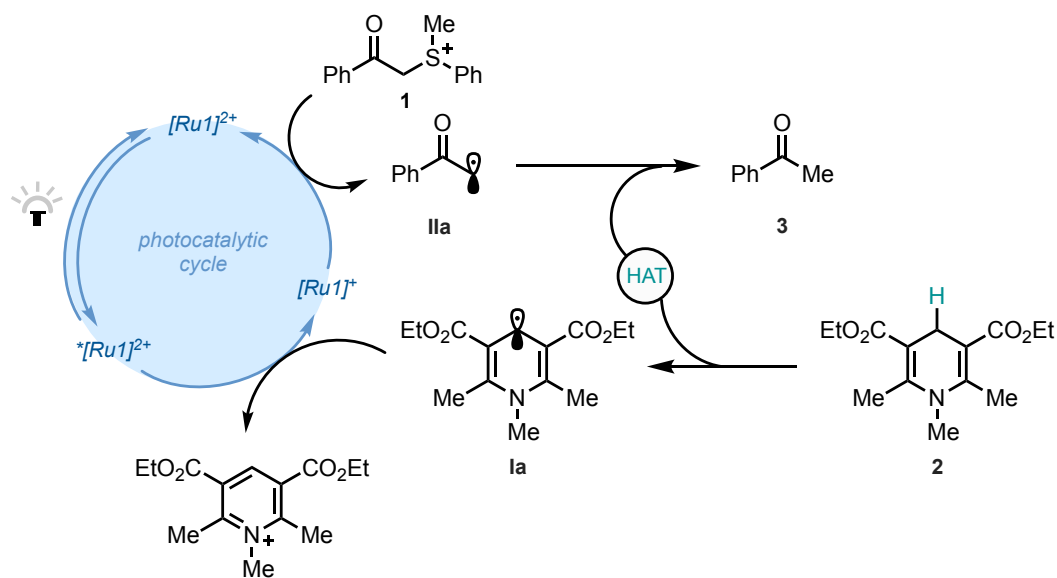
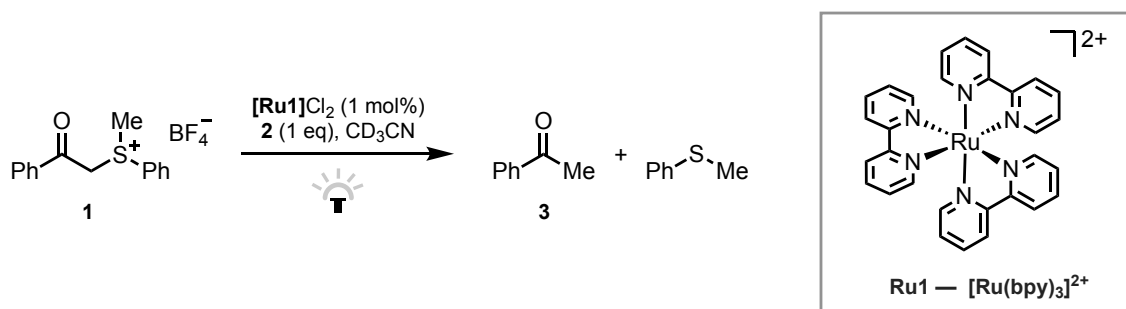


Figure 2. **A:** Representative example of a mediated electron transfer for an hypothetical kinetically slow direct redox transformation between a photocatalyst (PC) and a substrate (sub). **B:** Simplified illustration of the events and related ET processes involved in a reductive quenching cycle.

1.3 Forerunners to Photoredox Catalysis

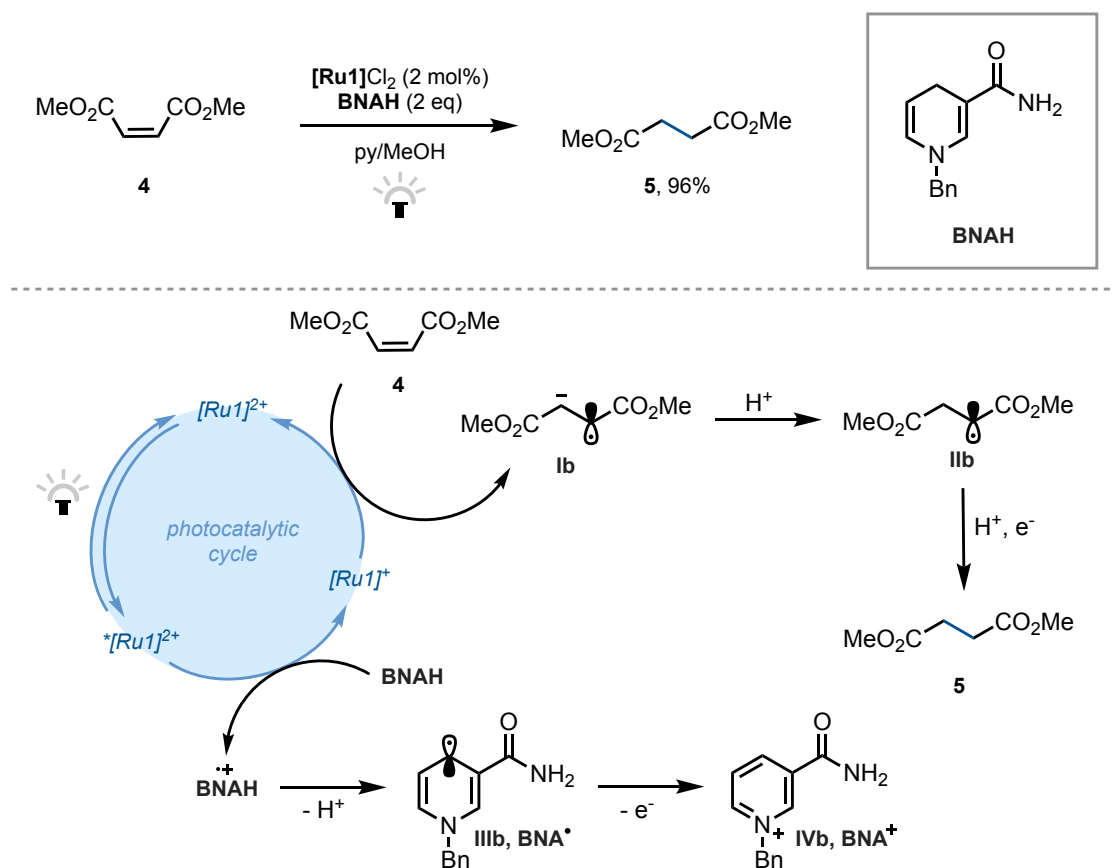
Over 40 years ago, a first contribution reported by Kellogg and co-workers demonstrated the applicability of photoredox catalysis in organic synthesis. The transition metal-based photocatalyst **Ru1** was employed in the reduction of phenacylsulfonium salt **1** using *N*-Me Hantzsch Ester **2** as stoichiometric reductant (Scheme 3).^[18] Stern-Volmer studies have shown that neither starting material **1** nor 1,4-dihydropyridine derivative **2** were responsible for PC quenching.^[11]



Scheme 3. Photocatalysed reductive desulfuration of phenacylsulfonium salt **1**.

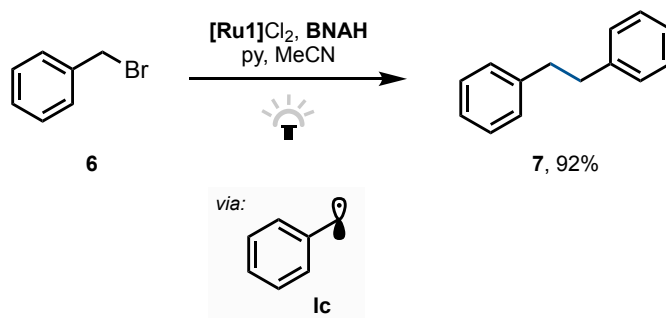
Consequently, this reductive desulfuration is proposed to involve PC quenching by radical intermediate **1a** after hydrogen atom transfer (HAT) from **2**. Reductive quenching of $^*\text{Ru1}^{2+}$ by

dihydropyridyl radical **Ia** ($E_{red} = -0.60$ V vs. SCE) affords a **Ru1**⁺ species capable of reducing sulfonium salt **1** to generate α -carbonyl radical **IIa** which undergoes the aforementioned HAT process to deliver ketone **3** (Scheme 3). Following catalytic generation of key intermediate **Ia**, photoexcitation of **2** with subsequent SET to **1** is suggested as a plausible alternative pathway for its initial formation.^[11] The vast majority of subsequent reports exploited the benefit of this catalytic system for net reductive transformations.^[8] In 1981, Pac incorporated a similar photocatalytic strategy with 1-benzyl-1,4-dihydronicotinamide (BNAH) for the reduction of electron-deficient olefins.^[19] For example, in the presence of a catalytic amount of **Ru1** under visible light irradiation, BNAH acts as an electron-donor for the reduction of dimethyl maleate **4** to dimethyl succinate **5** (Scheme 4).



Scheme 4. Illustration of reduction of electron-deficient olefins reported by Pac and co-workers.

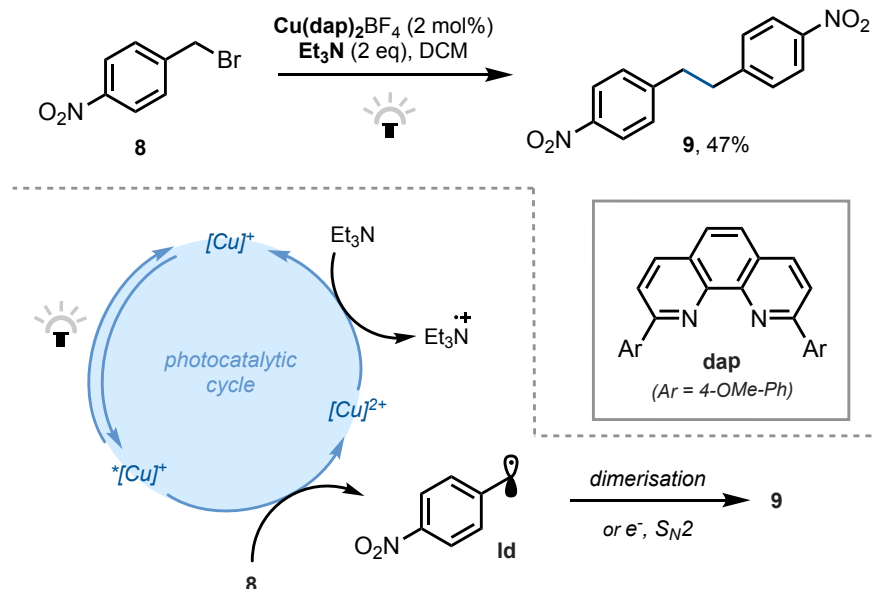
Mechanistically, upon absorption of visible light, the photoexcited species $^*\text{Ru1}^{2+}$ undergoes a SET event with BNAH ($E_{red} = +0.76$ V vs. SCE) to give radical cation $\text{BNAH}^{\bullet+}$ and Ru1^+ . Single-electron reduction (SER) of **4** by Ru1^+ closes the photocatalytic cycle along with generation of radical anion **Ib**. Radical intermediate **IIb**, formed upon protonation of **Ib**, undergoes an additional SER followed by reprotonation to afford saturated product **5**. This proposed second SER event could be performed by Ru1^+ – through another photocatalytic cycle – or by dihydropyridyl radical **IIIb** ($\text{BNA}^\bullet$, $E_{red} = -0.94$ V vs. SCE), which is ultimately oxidised to pyridinium **IVb** (BNA^+ , Scheme 4).^[11] The mechanistic analogy showcased by Pac and co-workers^[19–23] between two-electron donors BNAH and the biologically relevant 1,4-dihydronicotinamide adenine dinucleotide (NADH) inspired other groups to adopt similar **Ru1**–dihydropyridine-like structures as preferred photocatalytic systems for net reductive transformations. In 1984, Tanaka achieved reductive dimerisation of benzyl bromide employing **Ru1** and BNAH.^[24] It was shown that the reaction proceeds via benzyl radical **Ic** after SER of benzyl bromide (**6**). This radical intermediate may form bibenzyl **7** upon radical-radical recombination or via $\text{S}_{\text{N}}2$ displacement of **6** by a benzyl carbanion intermediate generated after a second SER process (Scheme 5).



Scheme 5. Photocatalytic reductive dimerisation of benzyl bromide **6** via benzyl radical **Ic**.

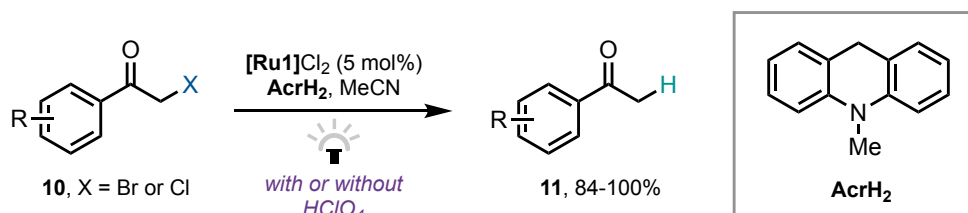
A similar termination pathway was proposed by Kern and Sauvage for the dimerisation of substituted benzyl bromides with a Cu(I)-based photocatalyst.^[25] In this visible light-mediated reductive transformation, the highly reducing photoexcited $^*\text{Cu}^+$ species ($E_{red} = -1.43$ V vs.

SCE) is capable of reducing 4-nitrobenzyl bromide **8** ($E_{red} = -1.1$ V vs. SCE) to afford an analogous benzyl radical intermediate **Id** as previously proposed by Tanaka. Triethylamine ($E_{red} = +1.0$ V vs. SCE) donates an electron to the oxidised Cu^{2+} species to regenerate the photocatalyst (Scheme 6).^[11]



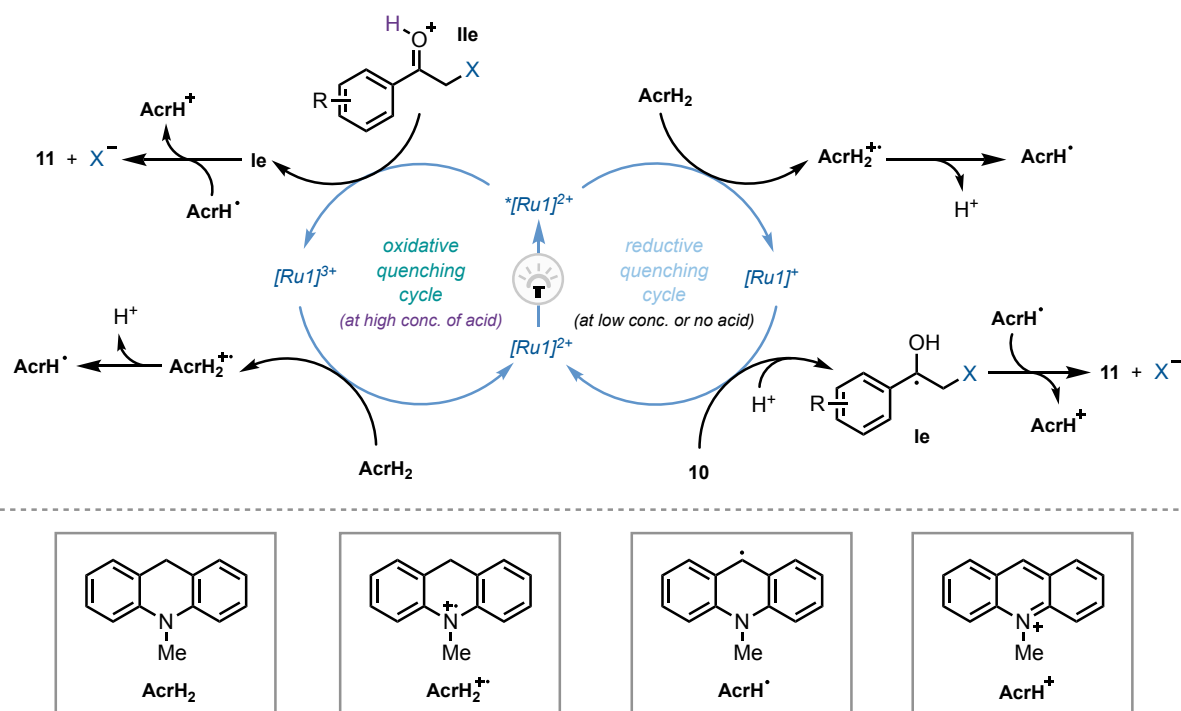
Scheme 6. Cu-based photocatalytic procedure for the formation of bibenzyl **9**.

In the context of reductive dehalogenation, Fukuzumi and co-workers accomplished the visible light mediated reduction of phenacyl halide derivatives (**10**) with 9,10-dihydro-10-methylacridine (AcrH_2) as stoichiometric reductant (Scheme 7).^[26] This pioneering example also revealed the influence of acid on the quenching mode of $^*\text{Ru1}^{2+}$.^[6,26]



Scheme 7. Reductive dehalogenation of phenacyl halides by Fukuzumi and co-workers.

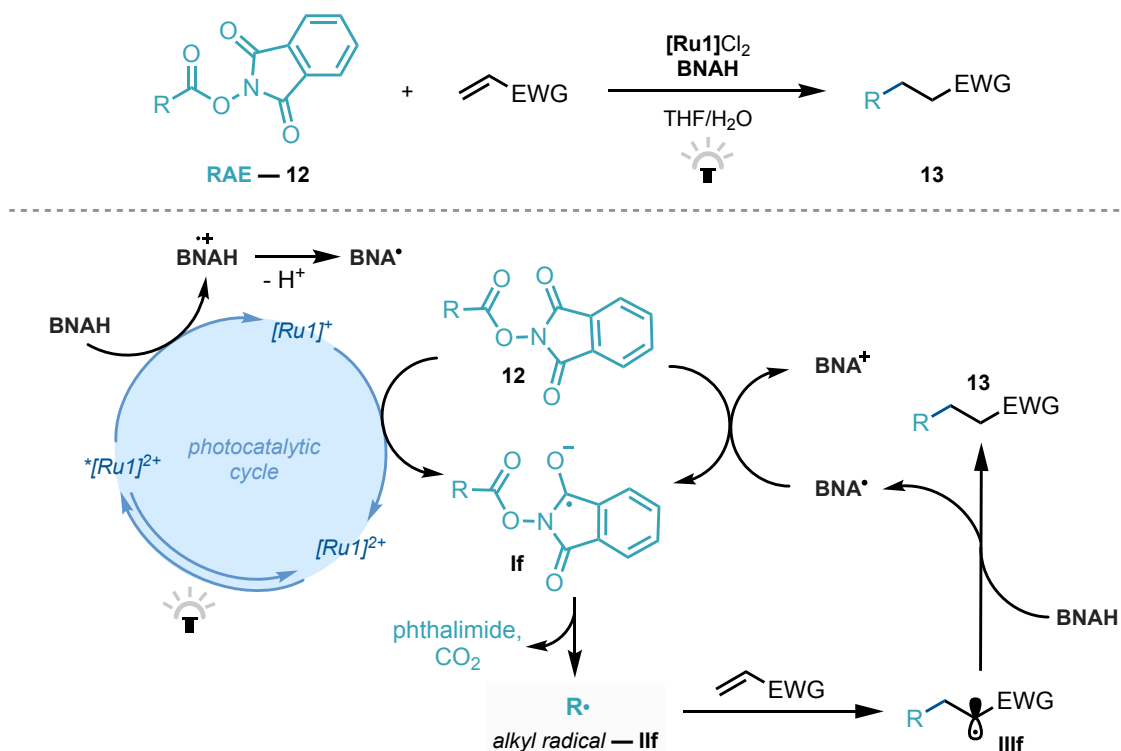
From a mechanistic standpoint, this transformation proceeds via a reductive quenching cycle in the absence of perchloric acid (HClO_4). Analogous to previously mentioned mechanisms, the photoexcited $^*\text{Ru1}^{2+}$ is reduced by acridine AcrH_2 to generate Ru1^+ along with $\text{AcrH}_2^{+\bullet}$ (Scheme 8 – reductive quenching cycle). Phenacyl bromides (**10**, $\text{X} = \text{Br}$) may be reduced by Ru1^+ , delivering ketyl radical **Ie** as well as regenerating the ground state PC. Intermediate **Ie** is converted to acetophenone **11** by concomitant oxidation of $\text{AcrH}^\bullet$ – formed upon deprotonation of $\text{AcrH}_2^{+\bullet}$ – to acridinium AcrH^+ (Scheme 8). The authors reported that reduction of phenacyl chlorides (**10**, $\text{X} = \text{Cl}$) was unsuccessful without HClO_4 .^[26] Moreover, addition of HClO_4 improved the efficiency of reductive debromination.^[11] Further studies suggest an alternative pathway centralised on oxidative quenching of $^*\text{Ru1}^{2+}$ at high concentration of HClO_4 (Scheme 8 – oxidative quenching cycle). In this situation, decreased reductive power of protonated AcrH_2 as well as protonation of phenacyl halide (**IIe**) favor initiation by oxidation of $^*\text{Ru1}^{2+}$ towards Ru1^{3+} with concurrent generation of radical species **Ie**, which ultimately delivers the same acetophenone product **11** (Scheme 8).^[6,26]



Scheme 8. Influence of Brønsted acid concentration (conc.) on the mechanism of the reductive dehalogenation of phenacyl halide derivatives **10**.

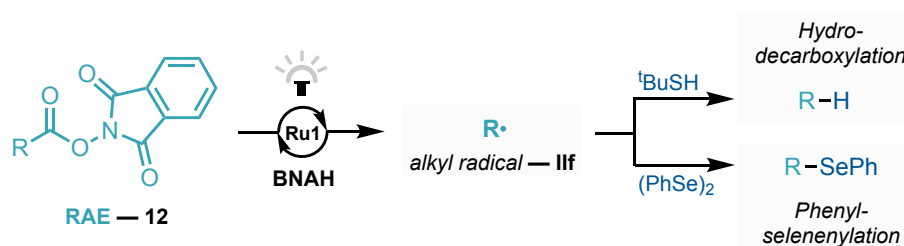
These outcomes validate the use of acids (Brønsted and Lewis acids) as cocatalysts in photoredox catalysis to unleash new reactivities by – for example – the modulation of redox properties.^[7] Another fundamental early contribution in the field of photocatalytic net reductive transformations was reported by Okada and Oda in 1991, where they demonstrated the use of *N*-(acyloxy)phthalimides as masking groups for alkyl radicals.^[27] Employing **Ru1**²⁺ and BNAH as a sacrificial electron-donor under visible light irradiation, the authors achieved fragmentation of redox-active esters (RAE) for the generation of carbon-centred radicals. SET from **Ru1**⁺ to RAE **12** results in radical anion **If**, which, after protonation, undergoes decarboxylation to give phthalimide, carbon dioxide, and key alkyl radical **IIIf**. This C-centred radical was shown to engage in conjugate addition reactions with electron-deficient alkenes to generate radical adduct **IIIf**. Working from deuterium-labelling studies, Okada and Oda proposed that hydrogen atom abstraction from BNAH gives 1,4-addition product **13** and BNA•, which would be capable of

reducing **12**, thereby initiating a radical chain process (Scheme 9).



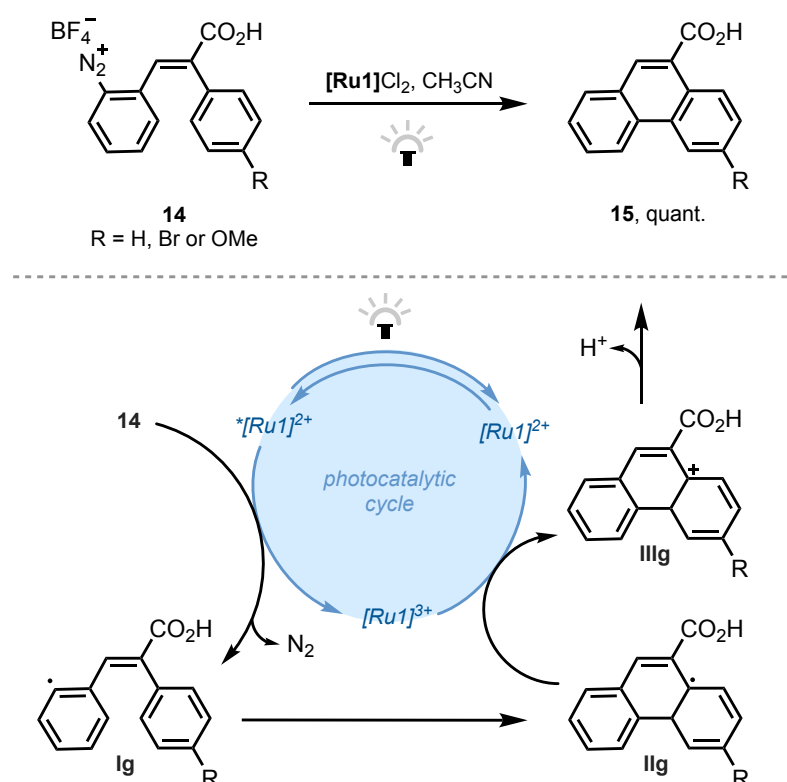
Scheme 9. Radical conjugate addition of alkyl radicals **II f** to electron-poor olefins by Okada and Oda. EWG = electron-withdrawing group.

Subsequent contributions highlighted the use of this visible light-mediated photocatalytic reductive fragmentation strategy for the formation of C–H and C–Se bonds upon reaction of alkyl radical **II f** with *tert*-butylthiol (*t*BuSH) or diphenyl diselenide (PhSeSePh), respectively (Scheme 10).^[28,29]



Scheme 10. Hydrodecarboxylation and phenylselenenylation procedures via photocatalytic reductive decarboxylation of *N*-(acyloxy)phthalimide **12**.

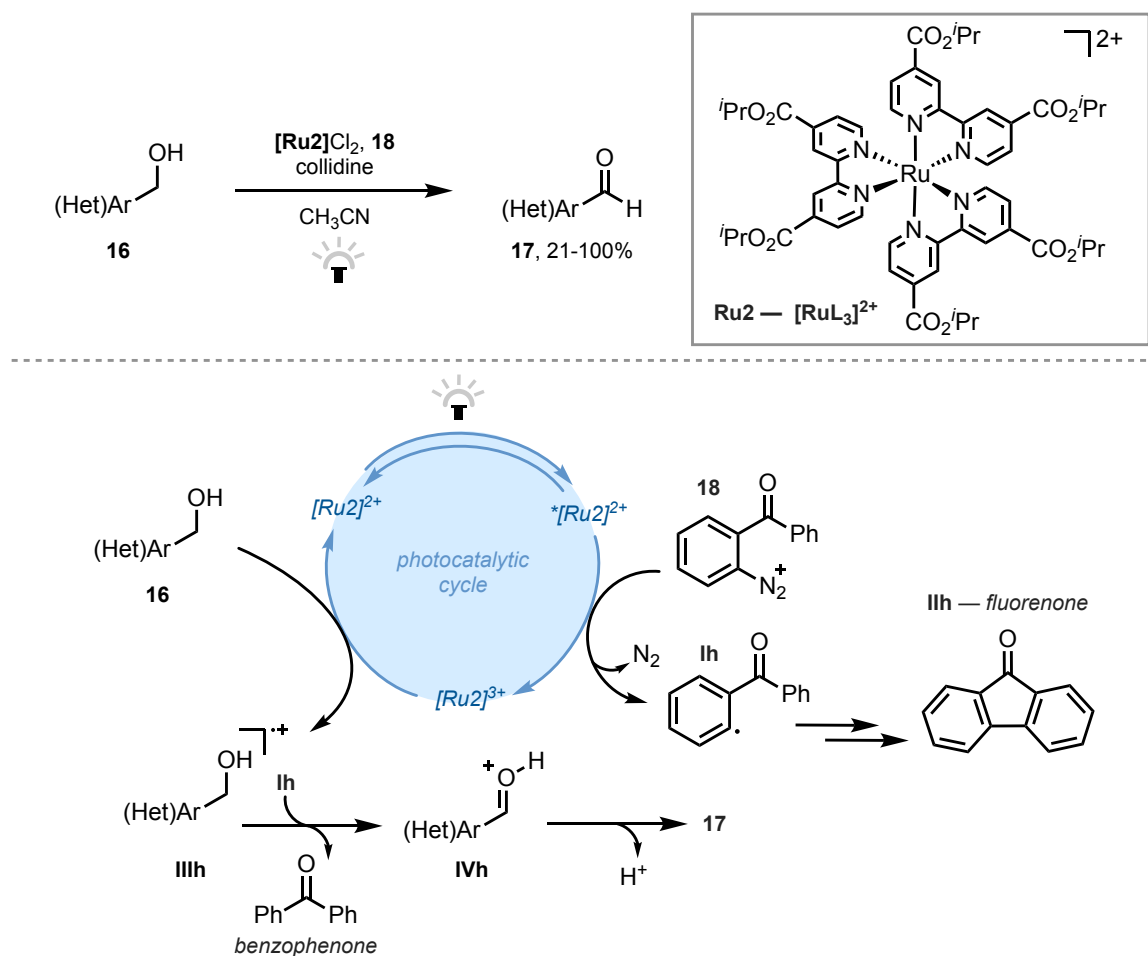
In 1984, Deronzier disclosed the first visible light-mediated photocatalytic redox-neutral transformation by converting aryldiazonium salts (**14**) to the corresponding phenanthrene products (**15**). In contrast to direct photolysis, quantitative yields were obtained in this Pschorr reaction using catalytic amounts of **Ru1**²⁺ (Scheme 11).^[30]



Scheme 11. Photoredox-catalysed Pschorr reaction to phenanthrene derivatives **15**.

Undesired trapping of a transient aryl cation intermediate by acetonitrile resulted in the formation of acetamide derivatives in the direct photolysis protocol. In contrast, reduction of **14** (for $R = \text{H}$, $E_{\text{red}} = -0.1 \text{ V vs. SCE}$)^[6] by photoexcited ***Ru1**²⁺ gives rise to aryl radical **Ig**, which undergoes intramolecular radical arylation to provide radical intermediate **IIg**. Oxidation of the latter regenerates **Ru1**²⁺ with concomitant formation of carbocation **IIIg**, which upon proton loss to restore aromaticity gives phenanthrene product **15** (Scheme 11).^[30] Inspired by this investigation, and other studies,^[31] Cano-Yelo and Deronzier reported the first net-oxidative pho-

photocatalytic reaction shortly thereafter. The authors achieved oxidation of benzylic alcohols (**16**) to the corresponding aldehydes (**17**), employing catalytic amounts of a ruthenium-based photocatalyst (**Ru2²⁺**) and aryldiazonium **18** as a sacrificial oxidant (Scheme 12).^[32] Analogously to previous considerations, this transformation is believed to initiate via oxidative quenching of ***Ru2²⁺** generating aryl radical **Ih**. Formation of fluorenone **IIh** via the aforementioned Pschorr reaction supports this intermediate. Subsequently, SET between oxidant **Ru2³⁺** and benzylic alcohol **16** is proposed to take place, providing radical cation **IIIh** and re-establishing the ground state **Ru2²⁺** species. The formation of benzophenone as an additional byproduct suggests hydrogen atom abstraction involving **Ih** and **IIIh**. Finally, resulting intermediate **IVh** is converted to aldehyde **17** under basic conditions (Scheme 12).^[6,11]

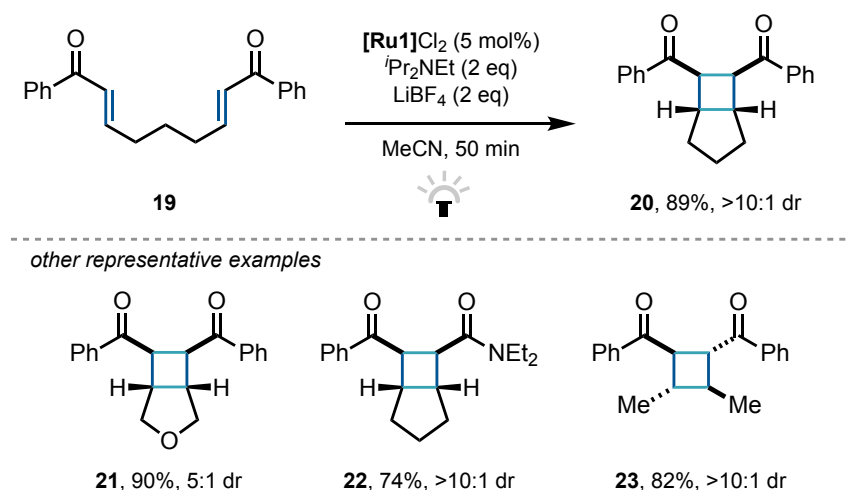


Scheme 12. Photocatalytic oxidation of benzylic alcohols **16** to aldehydes **17** by Cano-Yelo and Deronzier.

1.4 Founding Examples of Modern Photoredox Catalysis

Despite the extensive development of transition-metal-based photocatalysts over the past 50 years for synthetic inorganic applications and the aforementioned series of seminal reports demonstrating the potential benefits of this mode of catalysis in organic synthesis, it was only in the late 2000s that photoredox catalysis found widespread adoption within the organic synthetic community.^[9] Three concurrent reports helped to renew interest in this catalytic platform, contributing to the full recognition of this method towards synthetic reaction development.^[11] In 2008, Yoon and co-workers disclosed a **Ru1**-mediated [2+2] cycloaddition reaction under

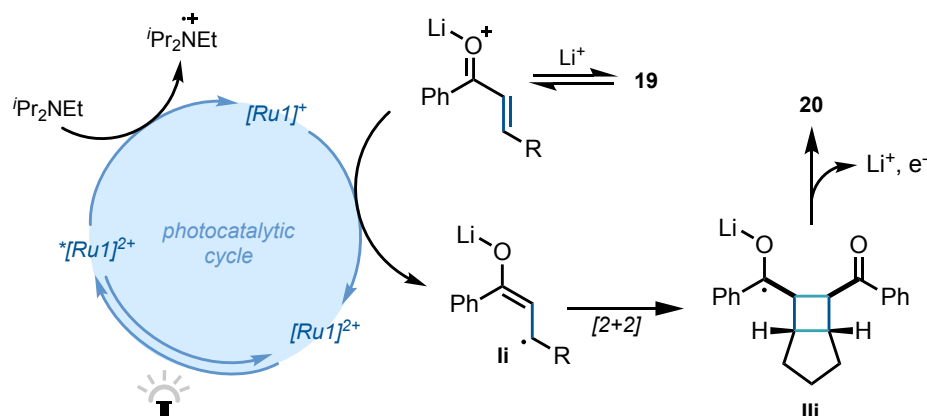
visible light irradiation. Encouraged by previous studies reporting the initiation of certain cycloadditions via one-electron reduction,^[33–37] the authors investigated conversion of enone **19** into [2+2] cycloadduct **20** using a photoreductant to mediate the initial SER event. Efficient cyclisation of **19** employing Hünig’s base (*i*Pr₂NEt) and LiBF₄ as essential additives afforded **20** in high yield and high diastereoselectivity (Scheme 13).^[38] The efficiency of this transformation was demonstrated with a series of structurally diverse enones, giving access to cycloadducts with varied tethering groups, cyclobutane-containing unsymmetrical adducts, and racemic products from intermolecular dimerisation of untethered enones (**21**, **22** and **23**). Noteworthy, in the absence of at least one aryl enone, aliphatic enones and enoates were not tolerated in this cyclisation procedure. The authors attributed the lack of desired reactivity to inaccessible reduction potentials of these functionalities.^[38]



Scheme 13. Illustration of the photocatalysed [2+2] cycloaddition reaction by Yoon and co-workers.

In fact, desired reactivity is proposed upon generation of lithium-bound radical anion **II**. This intermediate is formed via reduction of enone **19** by **Ru1**⁺, generated after reductive quenching of ***Ru1**²⁺ by *i*Pr₂NEt (Scheme 14). Essential substrate activation by LiBF₄ towards SER suggests that coordination to the enone functional group is crucial for the modulation of certain reaction parameters – likely more favorable reduction potentials upon Lewis acid activation.^[7]

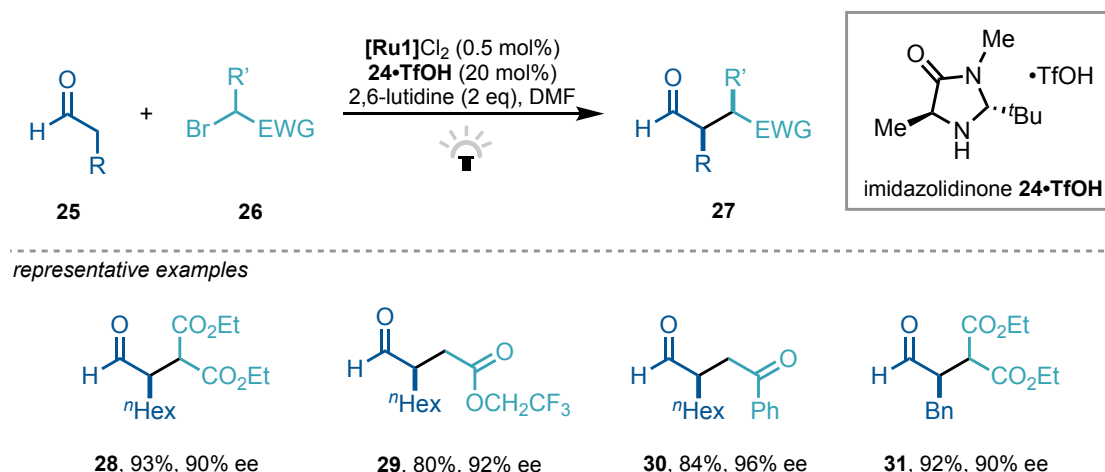
Intermediate **II** undergoes [2+2] cycloaddition with the pendant Michael acceptor to form ketyl radical **III**, which is then oxidised to give adduct **20** (Scheme 14).



Scheme 14. Proposed mechanism for Yoon's photocatalytic [2+2] cycloaddition.

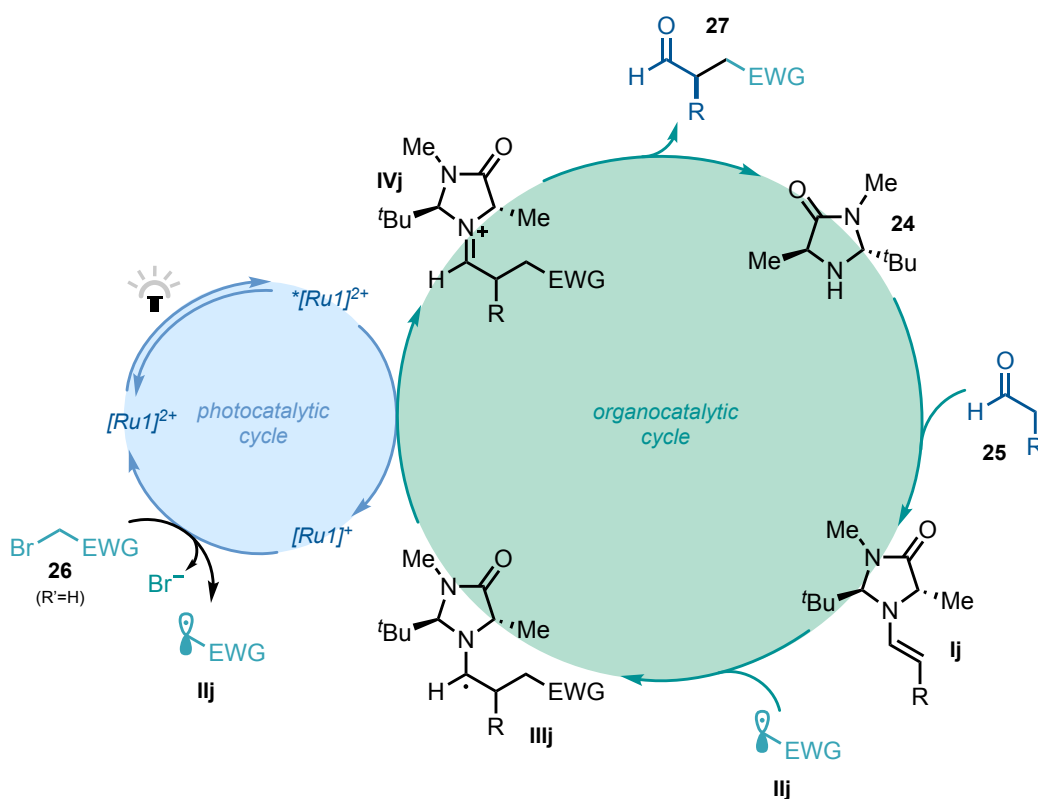
Inspired by this contribution, a wide range of cycloaddition reactions under photocatalytic conditions have been reported.^[11,39] Moreover, recognition of the potential beneficial impacts by using Lewis acids in photocatalytic strategies has uncovered a wide range of methods pivoting on their influence as cocatalysts.^[7]

A nearly simultaneous seminal report by MacMillan and Nicewicz detailed the use of an elegant dual photoredox organocatalytic approach to overcome the challenging asymmetric α -alkylation of aldehydes. This methodology pivots on the photocatalytic generation of electron-deficient radicals that engage in addition reactions in the presence of electron-rich enamines. Building on extensive research towards enantioselective organocatalytic α -functionalisation reactions,^[40] the authors achieved enantioinduction with an imidazolidinone chiral catalyst **24**. Employing a dual catalyst system composed of **24** and **Ru1**, direct coupling of aldehyde **25** with electron-poor alkyl bromide **26** provided enantioenriched α -alkylated aldehyde **27** in good to excellent yield (Scheme 15).^[41] This approach was amenable to a series of α -bromocarbonyls such as malonate **28**, ester **29**, and ketone **30**. Different β -substitution patterns were also tolerated for the aldehyde moiety, including for example benzyl aldehyde **31** (Scheme 15).



Scheme 15. Asymmetric α -alkylation of aldehydes by MacMillan and Nicewicz.

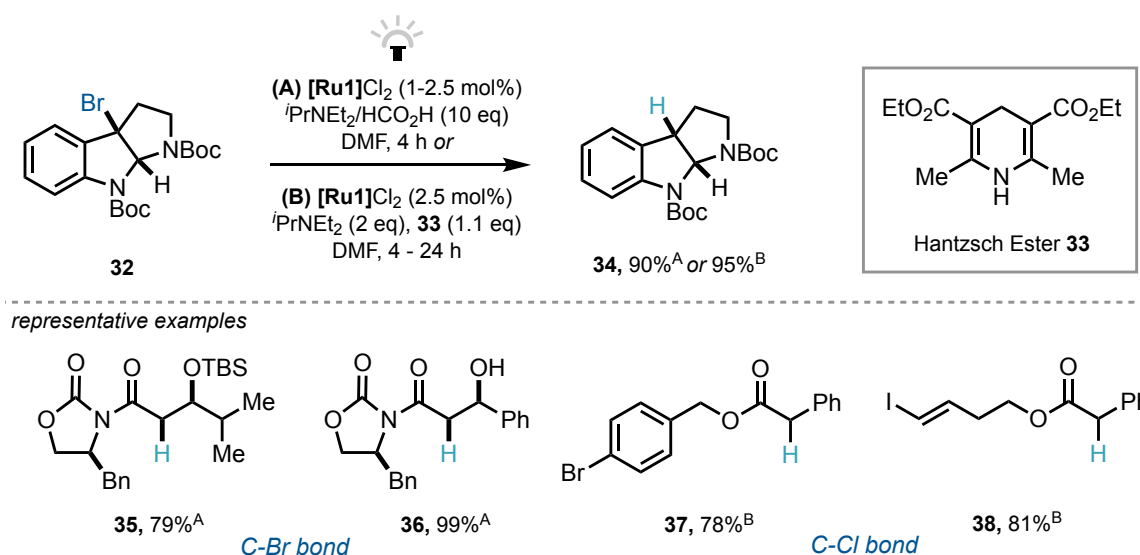
The organocatalytic cycle is initiated by condensation of aldehyde **25** with imidazolidinone **24** to provide chiral enamine **Ij** (Scheme 16). It was anticipated on the basis of density functional theory (DFT) calculations that this enamine intermediate would ensure enantiofacial discrimination from the *Si* face.^[41] Subsequent enantioselective radical addition of enamine **Ij** to the electrophilic alkyl radical **IIj** – produced via a concurrent photoredox pathway by SER of alkyl bromide **26** by **Ru1**⁺ along with regeneration of ground-state **Ru1**²⁺ – would forge the new C–C bond, furnishing α -amino radical **IIIj**. At this point, supported by luminescence quenching studies, the authors propose convergence of the catalytic cycles, whereby the photoexcited ***Ru1**²⁺ species participates as an oxidant in the SET event to give iminium **IVj** and **Ru1**⁺. Finally, hydrolysis of the iminium intermediate would deliver the desired enantioenriched α -alkylated aldehyde **27** with concomitant regeneration of the organocatalyst (Scheme 16).^[41] In analogy to this report, Zeitler and co-workers later demonstrated the efficiency of this visible light-mediated asymmetric α -alkylation methodology under purely organocatalytic conditions with a metal-free photocatalyst.^[42] Furthermore, this approach was extended by MacMillan and co-workers for the synthesis of enantioenriched α -benzyl, α -trifluoromethyl, and α -perfluoroalkyl aldehydes.^[43,44]



Scheme 16. Proposed merged photoredox organocatalysis mechanism towards enantioenriched α -alkylated aldehyde **27**.

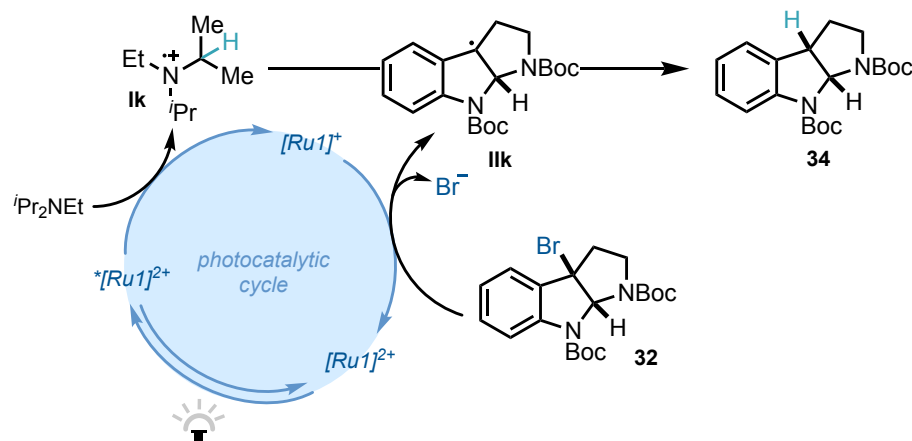
Shortly after, a third contribution by Stephenson and co-workers also aided the renaissance of photoredox catalysis. In 2009, inspired by initial studies on phenacyl halides by Fukuzumi (Scheme 7),^[26] the Stephenson group disclosed a general photocatalytic **Ru1**-mediated reductive dehalogenation procedure for activated alkyl halides.^[45] A bromine atom, as well as chlorine atom, in the α -position to carbonyl or in a benzylic position – as in substrate **32** – could be selectively reduced employing stoichiometric amounts of $i\text{Pr}_2\text{NEt}$ with formic acid or commercially available Hantzsch ester **33**. Avoiding the use of toxic or hazardous reagents, this photocatalytic transformation illustrates the benefits of mild reaction conditions with efficient dehalogenation in the presence of protecting groups (**34–35**) and free hydroxyls (**36**, Scheme 17). In addition, chemoselective reduction of alkyl C–Br and C–Cl bonds over aryl as well as vinyl halides was observed under these conditions (**37–38**, Scheme 17). Mechanistically, this alternative tin-free

procedure is proposed to proceed via single-electron oxidation (SEO) of $i\text{Pr}_2\text{NEt}$ by the photoexcited $^*\text{Ru1}^{2+}$ species, generating aminium radical cation **Ik** and Ru1^{1+} . Subsequent SET to cleave the carbon-halogen bond in **32** would deliver alkyl radical intermediate **IIk** with concomitant regeneration of Ru1^{2+} . Supported by deuterium-labelling studies highlighting $i\text{Pr}_2\text{NEt}$ as major hydrogen source towards reduced product **34**, the authors suggested hydrogen atom abstraction from **Ik** as the preferred pathway to quench intermediate **IIk** (Scheme 18). Despite the estimated bond dissociation energy of $\alpha\text{-C-H}$ bonds after SEO of amine components favouring this path,^[46] the formic acid and Hantzsch ester in the reaction mixture could also compete as hydrogen atom sources.^[45]



Scheme 17. Photocatalytic reductive dehalogenation protocol by Stephenson and co-workers.

In order to overcome the requirement of activated halides, Stephenson and co-workers later extended the concept of reductive dehalogenation towards unactivated substrates – alkyl, alkenyl and aryl iodides – employing a highly reducing iridium-based photocatalyst.^[47] Furthermore, recognising the potential of photocatalytic radical generation from C–X bonds, the Stephenson group adopted this protocol for C–C bond forming reactions via intramolecular trapping of alkyl free-radicals.^[48–50]

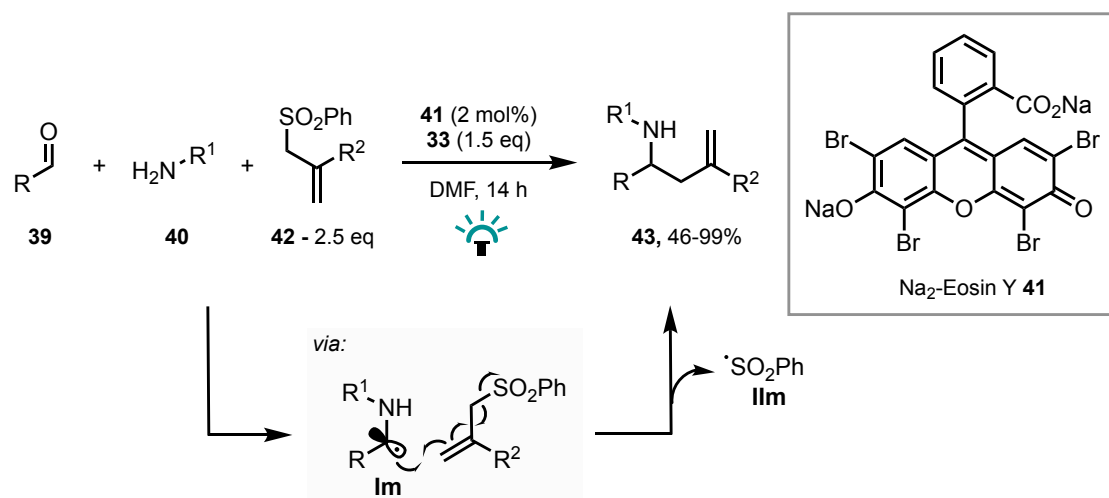


Scheme 18. Proposed major mechanistic pathway for the photocatalytic reductive dehalogenation of α -activated alkyl bromides and chlorides.

Altogether, these three independent contributions prompted extensive research into visible light photoredox catalysis,^[38,41,45] which resulted in a rapid growth of publications in this area as well as the consideration of this activation platform as a novel practical approach in organic synthesis.^[9,11]

1.5 Previous Work within the Dixon Group and DPhil Aims

The identification of modern photoredox catalysis as a novel synthetic strategy in organic chemistry fuelled a remarkable development of the field over the past decade, aiming at accessing new reactivity *via* non-traditional routes.^[7,11,51–53] In this context, at the time when this work started, the Dixon group developed an efficient photocatalytic three-component reaction for the generation of allyl amines.^[54] This synthetic protocol involved *in situ* generation of an imine functionality – from aldehyde **39** and aniline **40** – followed by SER under green light irradiation by photoorganocatalyst Na₂-Eosin Y (**41**) and Hantzsch ester **33** as terminal reductant to give open-shell radical intermediate **Im**. The latter is capable of engaging in radical addition to allyl sulfone **42** with subsequent elimination of benzene sulfinyl radical **IIIm** affording desired α -branched amine **43** (Scheme 19).^[54,55]



Scheme 19. Photocatalytic reductive formation of allyl amines by Dixon *et al.* via proposed α -amino radical intermediate **Im**.

Given the unique approach demonstrated by photoredox catalysis, we envisaged the use of this class of catalysis to uncover novel powerful methodologies for the generation of previously challenging or inaccessible carbon–carbon and carbon–heteroatom bond-forming reactions. Building on the aforementioned report (Scheme 19), the core aim of this work was to expand the synthetic toolbox of visible light-mediated umpolung chemistry towards new reaction discovery.

Initially, we sought to further examine photocatalytic imine umpolung chemistry with novel radical coupling partners to access synthetically relevant amine containing compounds. To this end, employing dehydroalanine (DHA) derivatives as acceptor moieties led to the construction of valuable 1,3-diamine products. These results are presented in Chapter 2. Furthermore, investigations on umpolung reactivity of underexplored functional groups unveiled new approaches to access complex α -tertiary ethers. Research towards the design and successful implementation of these unprecedented synthetic methodologies is described in Chapter 3 of this work. Finally, we planned to study visible light-mediated reactions for the synthesis of biologically relevant building blocks. Chapter 4 is dedicated to the development of a photocatalyst-free method for the generation of fluorine-containing unnatural α -amino acids.

Chapter 2

Photocatalytic Umpolung Synthesis of 1,3-Diamines

2.1 Chapter Overview

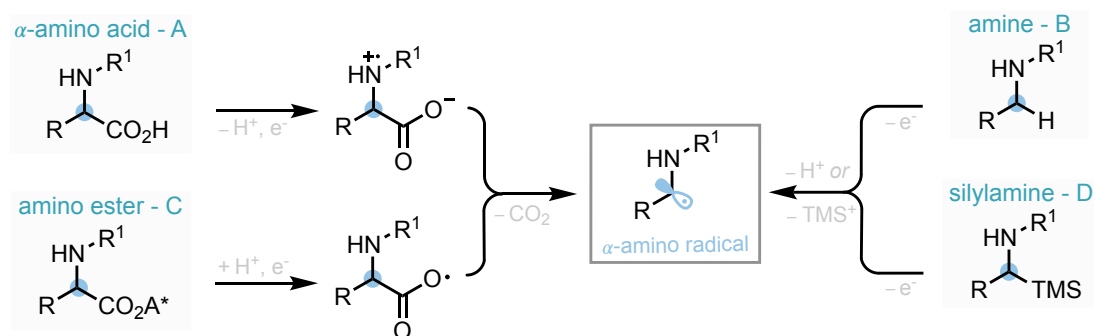
This chapter highlights key photo- and electrochemical concepts which lay the foundations for the synthetic methodology discussed. Based on these mechanistic considerations, this chapter describes the identification of a new electrophilic coupling partner and its application towards the development of an efficient photocatalytic protocol for the synthesis of unsymmetrical 1,3-diamines. The scope of this one-pot three-component reaction was broad with respect to both the aldehyde and the aniline moiety, including heterocyclic compounds as well as aliphatic aldehydes. Extension to β -amino alcohols and derivatization to biologically relevant γ -lactams were performed to demonstrate the potential applicability of this methodology in medicinal chemistry research programmes.

2.2 Introduction

Amine-containing organic compounds are among the most important chemical architectures as they find a remarkable range of applications from pharmaceutical and agrochemical research to material chemistry. The unique reactivities and characteristics of nitrogen incorporating compounds render amines pivotal building blocks in the chemical industry, justifying the ever-increasing demand of new synthetic methods towards access and manipulation of this motif.^[56,57] Accordingly, intensive research efforts in contemporary organic synthetic approaches – ranging from C–H functionalisation to electrochemistry – have focused on the development of novel methodologies for the construction of amine-derived functionalities. In this context, the advent of modern photoredox catalysis (see Section 1.4) established the use of α -amino radicals as an additional innovative strategy for amine synthesis.^[16]

2.2.1 Synthetic Approaches for the Generation of α -Amino Radicals

Traditional methods to access α -amino radicals relying on stoichiometric amounts of either oxidant or reductant have now progressed into the catalytic domain with recent advancements in photoredox catalysis. Well-established transformations include single-electron oxidation (SEO) of amino acid carboxylates (A) with subsequent decarboxylation, SEO of amine substrates followed by deprotonation (B), single-electron reduction (SER) of redox-active amino esters with release of CO₂ (C), and desilylation of α -silylamines following single-electron oxidation (D, Scheme 20).^[16,58]



Scheme 20. Synthetic one-electron pathways for the formation of α -amino radicals. A* = activating group to form redox-active ester (RAE).

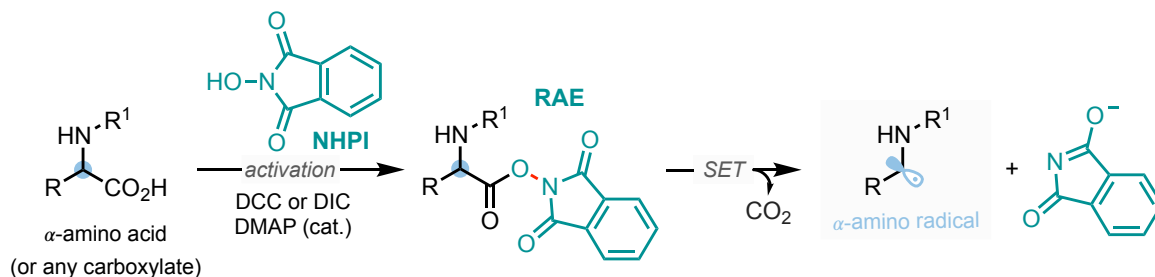
Single-Electron Oxidation of α -Amino Acids

Inspired by Nature, synthetic chemists have long recognized the value of decarboxylative transformations as a means to create chemical complexity or to remove undesired carboxyl moieties. Methodologies relying on carboxylates for the generation of new carbon–carbon and carbon–heteroatom bonds are highly desirable considering the abundance of this functionality.^[59] In this context, visible light photoredox catalysis has emerged as an attractive and powerful technique to access non-traditional sites of reactivity from common feedstock chemicals such as carboxylic acids.^[60] On this basis, the broad availability of α -amino acids provides an avenue to α -amino radical intermediates (Scheme 20), which can participate in a plethora of synthetic transformations from inexpensive starting materials.^[59]

Single-Electron Reduction of Redox Active Amino Esters

An additional major approach towards decarboxylative α -amino radical generation involves the formation of redox-active esters (RAE). Despite the requirement of an extra activation step, this reductive strategy is especially attractive when the parent carboxylate has a high and therefore not readily accessible oxidation potential.^[61] Furthermore, RAE are advantageous radical precursors for their ease of preparation from commercially available sources and benchtop stability. Widely used activating agents include *N*-hydroxyphthalimide (NHPI) derivatives which

are converted to RAE by carbodiimide-mediated coupling with carboxylic acids. Initial mesolytic cleavage of the N–O bond upon single-electron reduction (SER) by a photocatalyst or reducing metal^[63,64] triggers a cascade of events that liberates CO₂ to provide a carbon-centred radical (Scheme 21).^[62]

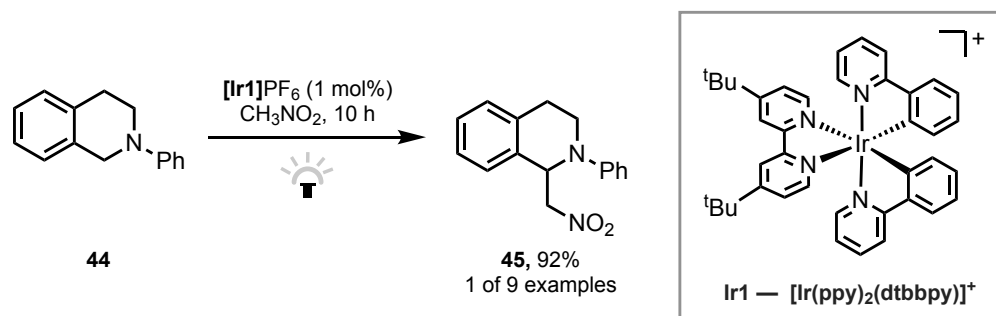


Scheme 21. Simplified illustration of a general α-amino acid activation for the synthesis of RAE and subsequent SET event to *N*-acyloxypthalimide to provide a nucleophilic carbon-centred radical.

Since the seminal work by Okada and Oda (see Chapter 1.3, Scheme 9), the utility of RAE as masked precursors of (tertiary) carbon radicals has found widespread application in photoredox catalysis, from an attractive method to forge C–C bonds to an alternative disconnection approach in total synthesis.^[62,65] Moreover, elegant recent works by Phipps and Fu showcased the value of RAE in photocatalytic asymmetric radical addition reactions.^[66,67]

Single-Electron Oxidation of Amines

The challenge of C–H functionalization adjacent to a nitrogen atom has been a long-standing target for synthetic chemists due to the wealth of bioactive compounds incorporating structural complexity around this heteroatom motif.^[68] In this regard, the landmark work by Stephenson and co-workers paved the way towards photocatalytic α-C–H amine functionalization. The authors developed an efficient aza-Henry reaction upon oxidation of tetrahydroisoquinoline **44** under photocatalytic conditions. From a mechanistic viewpoint, they proposed single-electron oxidation (SEO) of tertiary amine **44** – mediated by **Ir1** – to give a radical cation intermediate, which upon hydrogen atom abstraction would generate an iminium ion that is trapped in a nucleophilic fashion by nitromethane to afford product **45** (Scheme 22).^[69]



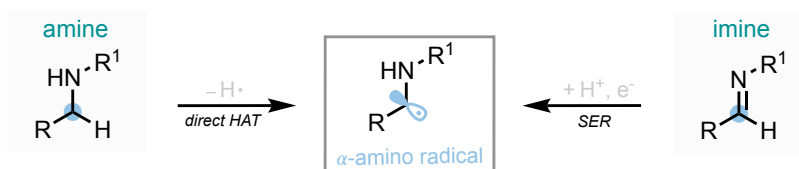
Scheme 22. Photocatalytic oxidative Aza-Henry reaction by Stephenson and co-workers.

This work demonstrated the utility of tertiary amines for direct C–H functionalization under photocatalytic conditions, prompting their use from low-cost reductive photocatalyst’s quenchers to substrates for new reaction discovery as well as valuable intermediates for the construction of molecular complexity in natural product synthesis. Selective and controlled photooxidation of amines grant access to a series of synthetically useful reactive intermediates, including α -amino radicals (Scheme 20).^[70,71] Single-electron oxidation of electron rich nitrogen-containing compounds – such as triethylamine – generates radical cation **In**, whose subsequent deprotonation event to an α -amino radical is greatly facilitated by acidification of the α -C–H and its significantly decreased bond dissociation energy (BDE). Precise SEO of the parent amine is essential for desired reactivity as the resulting radical cation intermediate is more readily oxidized to give iminium ion **IIIn** (Scheme 23).^[58,70]

Scheme 23. Fate of the amine component upon single-electron oxidation (SEO) – schematic representation with triethylamine.

2.2.2 Emerging Techniques for the Manipulation of α -Amino Radicals

In most recent literature reports, hydrogen atom transfer (HAT) and single-electron reduction (SER) of imine derivatives have been emerging as new techniques for the generation of α -amino radicals (Scheme 24).^[16]

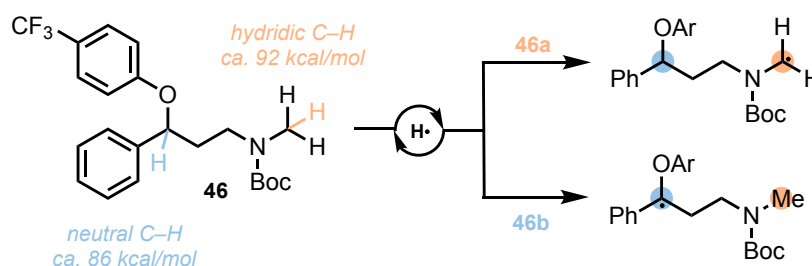


Scheme 24. Schematic representation of emerging techniques for the manipulation of α -amino radicals: direct HAT from amine components and reduction of imine substrates.

Hydrogen Atom Transfer of Amines

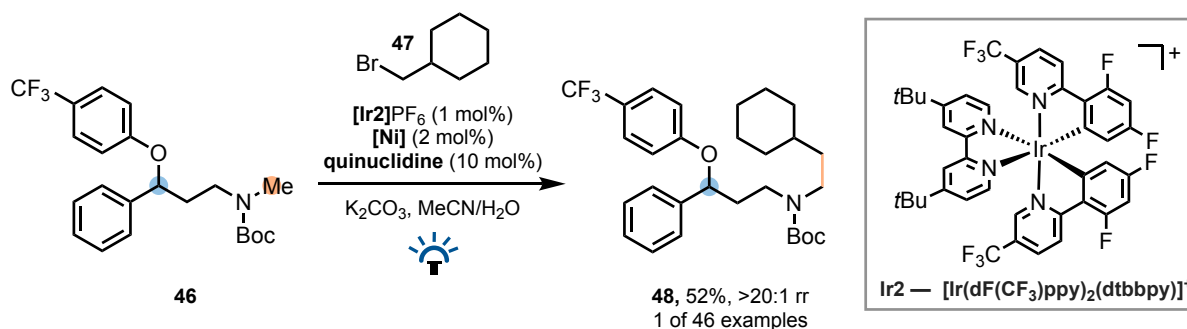
Hydrogen Atom Transfer (HAT) is a fundamental mechanistic step in organic synthesis defined as the simultaneous migration of an electron and a proton between two substrates.^[72,73] Despite its long-recognized capability to generate radical intermediates, application of this process for C–C bond formation is affected by regioselectivity issues, a prevailing limitation of common sp^3 C–H functionalization strategies as a result of the ubiquity of this chemical bond. Nevertheless, the direct functionalization of carbon-hydrogen bonds remains an ideal coupling linchpin towards molecular construction, prompting the progress of this approach in organic synthesis.^[72,74,75] In this context, advances in photocatalysis in recent years have also led to developments in visible light-mediated HAT catalysis, providing the opportunity to accomplish high levels of selectivity in (aliphatic) C–H bonds without the installation of additional directing groups.^[72,73] Furthermore, methodologies combining photoredox and HAT catalysis demonstrated the benefits of polarity matching, whereby hydrogen abstraction is favored for strong hydridic C–H bonds, thus overcoming thermodynamic driving forces and enabling, for example, selective α -C–H activation of amines even in the presence of weaker C–H bonds.^[72,74] One such case was elucidated by MacMillan and co-workers in a triple catalytic C–H activation approach for the selective

alkylation of *N*-Boc protected Prozac **46**. According to polarity-matched HAT, single-site alkylation of **46** was expected *via* intermediate **46a** despite the presence of a more favored HAT event leading to **46b** (Scheme 25).



Scheme 25. Bond dissociation energies (BDE) of sp^3 C–H bonds in **46** and corresponding intermediates following HAT.

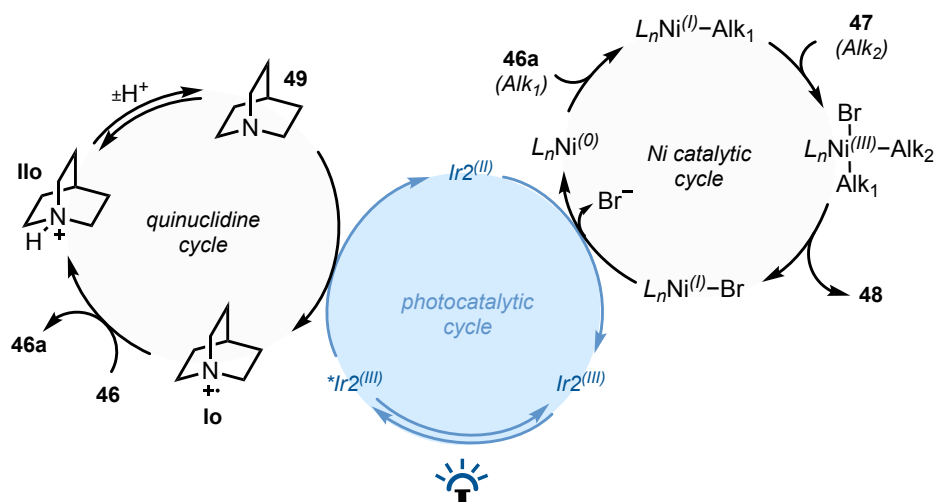
As a result, the authors reported C–H functionalization of **46** with alkyl bromide **47** to exclusively access alkylated product **48** (Scheme 26).^[74]



Scheme 26. Single-site HAT-metallophotoredox-mediated C–H alkylation by MacMillan *et al.* [Ni] = $\text{NiBr}_2 \bullet (\text{dOMebpy})$, dOMebpy = 4,4'-dimethoxy-2,2'-bipyridyl.

Observed regioselectivity via **46a** arises from the matching of electronic polarity between the C–H bond and the HAT catalyst. In fact, under photocatalytic conditions, quinuclidine **49** is proposed to undergo SET delivering reductant **Ir2(II)** and quinuclidine radical cation **Io**. The electrophilic nature of the latter is believed to be responsible for selectively abstracting the more hydridic C–H bond in **46** to give protonated quinuclidine **IIo** with concomitant formation of key radical intermediate **46a**, which is intercepted by a Ni(0) species and ultimately converted

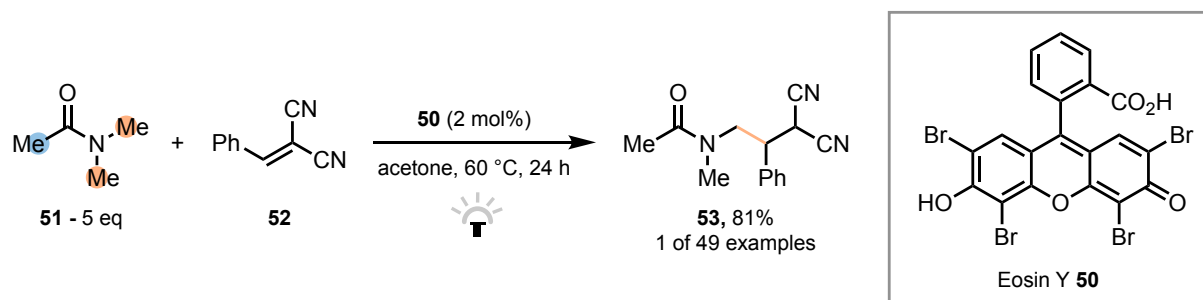
to the desired C–H alkylated product **48** (Scheme 27).^[74]



Scheme 27. Proposed triple catalytic cycle dictating selective sp^3 C–H alkylation.

The above-mentioned example illustrates the adoption of HAT in a photocatalytic method; more specifically of an indirect approach, in which an additive (stoichiometric or catalytic) is the species responsible for the generation of a thermal hydrogen abstractor upon activation by the excited PC (**49** in Scheme 27).^[73] Alternatively, a strategy involving the intrinsic reactivity of certain photocatalysts can be exploited in a more direct approach, whereby the *PC itself is able to activate a substrate by selectively abstracting a hydrogen atom. In recent years, the limited number of available PCs capable to perform the straightforward activation of C–H bonds upon excitation resulted in an expansion of indirect strategies. Nonetheless, in addition to efforts aimed at expanding this class of photocatalysts, recent trends showcased the value of direct methodologies for the activation of substrates without the limitations of redox potentials by employing aromatic ketones, polyoxometalates (POMs) and uranyl cations, among others.^[73]

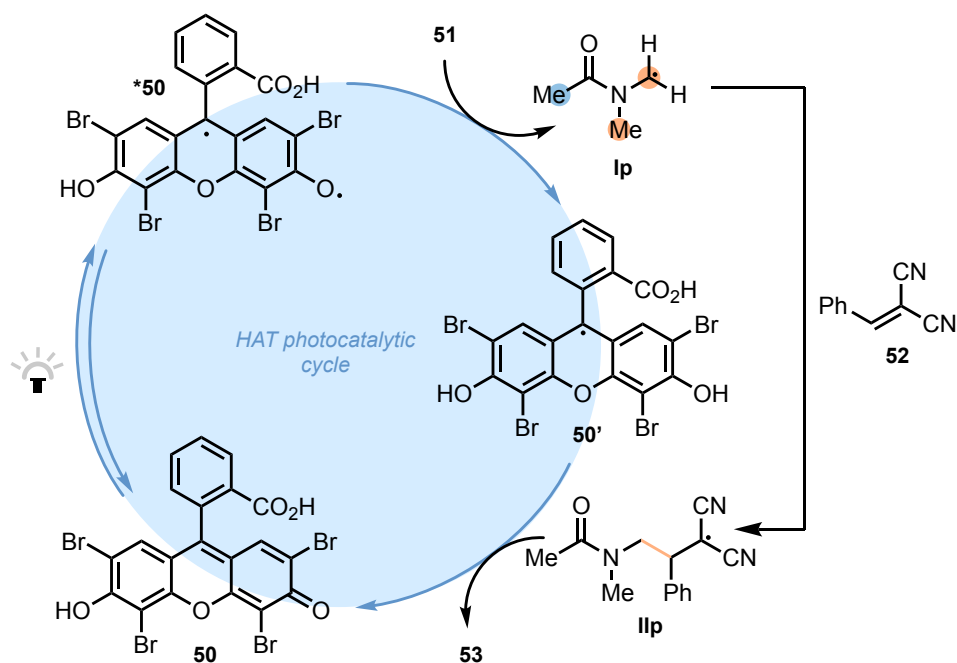
In 2018, Wu *et al.* displayed the use of Eosin Y **50**, a common photo-organocatalyst for SET reactions, also as an effective direct HAT catalyst for C–H activation. Selective hydrogen abstraction from C–H partners under irradiation with white LEDs, such as amide **51**, ensured radical addition to electron-deficient coupling partner **52** affording product **53** in 81% yield (Scheme 28).^[76]



Scheme 28. Selective functionalization of C–H bonds with Eosin Y as direct HAT photocatalyst.

It is proposed that upon visible light absorption, the triplet state of the excited xanthene dye (***50**) can participate in an HAT event to generate carbon-centred radical **Ip**. Subsequently, intermediate **Ip** is trapped by olefin **52** producing adduct **IIP**. Reverse hydrogen atom transfer (RHAT) between carbon radical **II** and eosin Y–H (**50'**) – or a reversible HAT process involving the solvent – would close the catalytic cycle regenerating ground state Eosin Y along with the formation of the alkylated product **53** (Scheme 29).^[76]

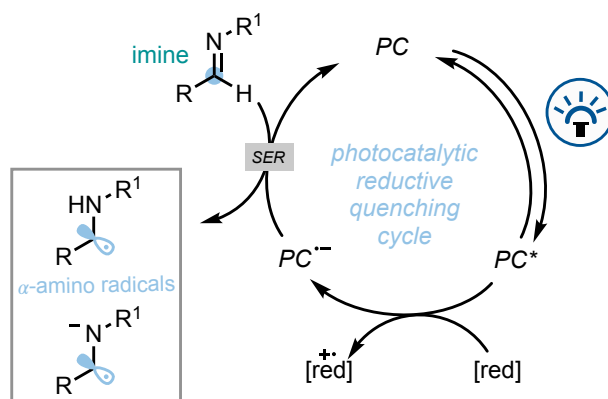
The synergy between photocatalysis and hydrogen atom transfer (HAT) offers unique opportunities to efficiently activate C–H bonds, broadening the synthetic toolbox of organic chemists towards late-stage functionalization by complementing existing cross-coupling strategies as well as contributing to new reaction discovery.^[72–75]



Scheme 29. Proposed mechanism for Eosin Y-mediated C–H functionalization by Wu and co-workers.

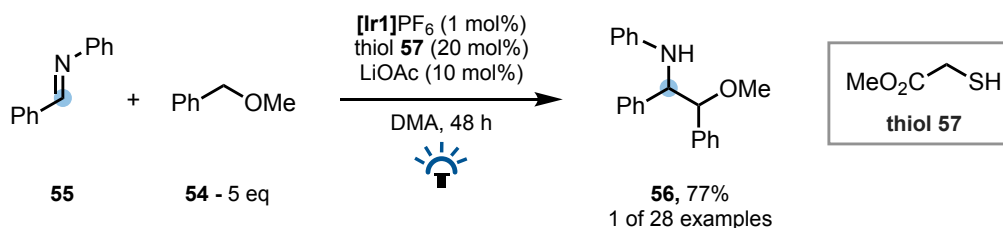
Single-Electron Reduction of Imine Derivatives

Reduction of imine derivatives has been known since 1990, when Imamoto and co-workers reported the synthesis of 1,2-diamines using stoichiometric amounts of samarium diiodide (SmI_2).^[77] In agreement with the single-electron reduction (SER) of carbonyl compounds, imine reduction was mostly achieved employing stoichiometric amounts of lanthanide-based reductants.^[16] The advent of photoredox catalysis offered the possibility to access similar synthons in the catalytic domain (Scheme 30). However, despite the renewed interest in photoredox catalysis since 2008 (see Section 1.4),^[38,41,45] the first photocatalytic method was disclosed in 2014 by MacMillan and co-workers.^[78]



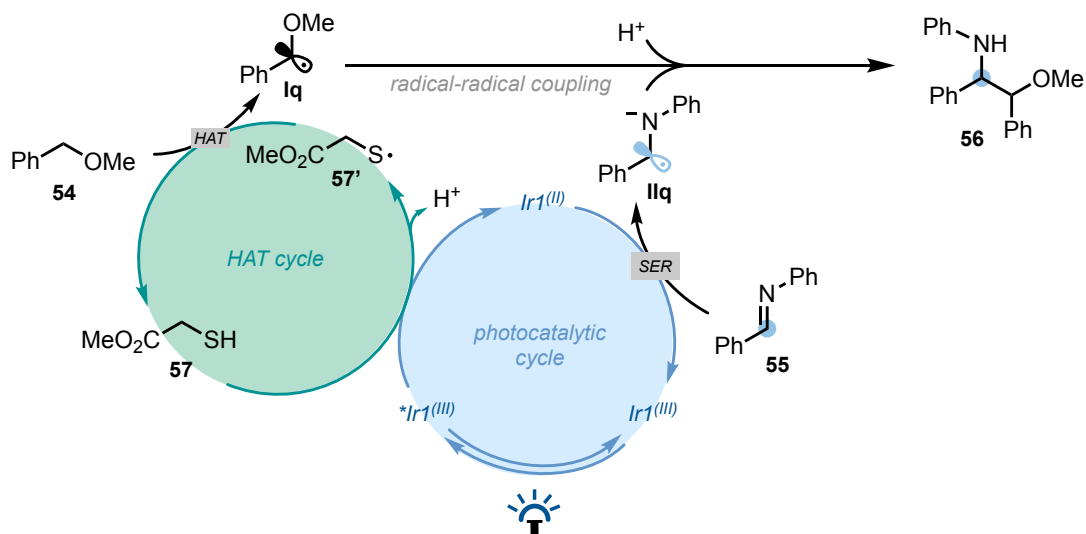
Scheme 30. Model photocatalytic mechanism for the SER of imines to access valuable α -amino radical intermediates. PC = photocatalyst, [red] = reductant.

The authors accomplished the direct photocatalytic coupling of benzylic ether **54** with *N*-arylimine **55** to afford β -amino ether **56** in a single step (Scheme 31).



Scheme 31. Photoredox-mediated C–H functionalization concept towards β -amino ethers developed by the MacMillan group.

This redox-neutral protocol relies on a radical-radical coupling event, whereby the key radical intermediates are generated via combination of a photoredox-organocatalysis C–H functionalization mechanism. Photoexcited ***Ir1(III)** is quenched by thiol co-catalyst **57** – facilitated by LiOAc – forming **Ir1(II)** and thyl radical **57'** upon loss of a proton. A HAT event is proposed to take place between the latter and substrate **54** (α -C–H BDE = 85.8 kcal/mol), completing the organocatalytic cycle and generating benzylic radical **Iq**. Single-electron reduction (SER) of *N*-arylimine **55** by **Ir1(II)** closes the photocatalytic cycle along with the formation of α -amino radical anion **IIq**, which is involved in the radical-radical recombination step to forge the desired C–C bond in β -amino ether **56** (Scheme 32).^[78]



Scheme 32. Proposed dual catalytic cycle for the heterocoupling of benzyl ethers and imines.

From a mechanistic point of view, the mismatched reduction potentials between **Ir1(II)** ($E_{1/2}^{III/II} = -1.51$ V vs. SCE) and *N*-arylimine **55** ($E_{1/2}^{red} = -1.98$ V vs. SCE) suggests that a SET event from the catalyst to the neutral imine would not be thermodynamically feasible (Scheme 32). Even if not formally discussed, certain interactions under these reaction conditions assist the occurrence of such phenomenon which would be otherwise energetically unfavorable.^[16,78] Indeed, despite several redox potentials falling out of range, reduction of iminyl – and carbonyl – species can be promoted by acid-base interactions, which function as activators lowering the energy barrier of SET processes.^[16,51] As previously showcased by Yoon for Lewis acids (Scheme 13),^[38] also the coordination/protonation of functional groups by Brønsted acid species can have a dramatic effect on their reactivity by increasing reduction potentials (become less negative in the case of imine substrates).^[16,79] Inspired by biological redox processes, Knowles and co-workers pioneered and implemented the widespread use of Brønsted acids in photocatalytic methodologies for the generation of open-shell reactive intermediates.^[7] This type of activation strategy comprising the concurrent exchange of a proton and an electron in a single concerted step is known as proton-coupled electron transfer (PCET). In contrast to HAT processes (see

Section 2.2.2), in PCET events the electron and proton can migrate to two different products or come from two independent donor moieties.^[80,81] Furthermore, the degree of protonation of basic functional groups – such as imines – could determine the choice of photocatalyst for the corresponding single-electron reduction.^[16] As an illustration, neutral ammonia-derived ketimine **58** could be considered electrochemically robust due to its high reduction potential ($E_{1/2}^{red} = -2.43$ V vs. SCE). Additionally, while **59** still possess a reduction potential ($E_{1/2}^{red} = -1.91$ V vs. SCE) which falls out of range of most common photocatalysts (see Figure 1), the introduction of an electron-withdrawing group on the nitrogen atom would give an imine derivative that is more readily reduced to the corresponding α -amino radical anion (**60**, $E_{1/2}^{red} = -1.45$ V vs. SCE). The effect of PCET on basic functional groups becomes more evident when considering the protonation of ketimine **58**, whereby its derivative **61** becomes 'electrochemically activated' with a remarkable increase (less negative) in reduction potential ($E_{1/2}^{red} = -1.10$ V vs. SCE, Figure 3).^[16]

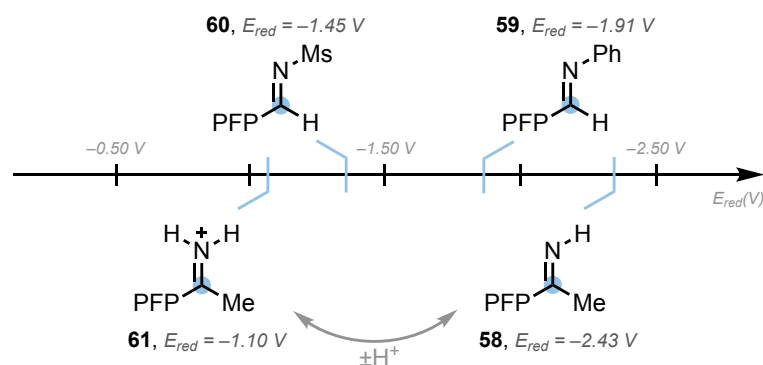


Figure 3. Illustration of PCET concept with redox potentials of selected imine substrates. Reduction potentials (E_{red}) are given in volts (V) versus the saturated calomel electrode (SCE). PFP = *p*-fluorophenyl.

This type of photochemical activation revolutionized the formation and manipulation of α -amino radicals, contributing to the impressive application of this synthon into novel synthetic methodologies. As a consequence of its rapid development, imine-derived α -amino radical chemistry was extended beyond the radical-radical coupling reactivity exploited by MacMillan's seminal

report (Scheme 31),^[78] encompassing the generation of α -amino radicals from iminium ions as well as the implementation of enantioselective variants.^[16]

2.2.3 Importance and Synthetic Precedents of 1,3-Diamines

Among nitrogen-containing compounds, molecules incorporating amines represent one of the most valuable and widely used classes (see Section 2.2).^[56] More specifically, the 1,3-diamine motif is ubiquitous in many complex molecules, from natural products to pharmaceutical agents. In fact, these moieties have also been used as key building blocks in synthetic organic chemistry for the generation of bioactive molecules like alkaloid **62** and protease inhibitor **63** (Figure 4). Moreover, 1,3-diamines find widespread application in asymmetric synthesis as chiral ligands and auxiliaries for organo- as well as transition-metal catalysis.^[82] For instance, bis-tertiary diamines **64** and (–)-sparteine **65** can play a crucial role as chiral external ligands in combination with organometallic reagents for the enantioselective deprotonation of sp^3 -carbons (Figure 4).^[83] Additionally, the introduction of 1,3-diamine ligands can have a major impact in the catalytic activity of certain transition-metal catalysts, such as chiral ligand **66** in Ru-based asymmetric hydrogenation chemistry (Figure 4).^[84]

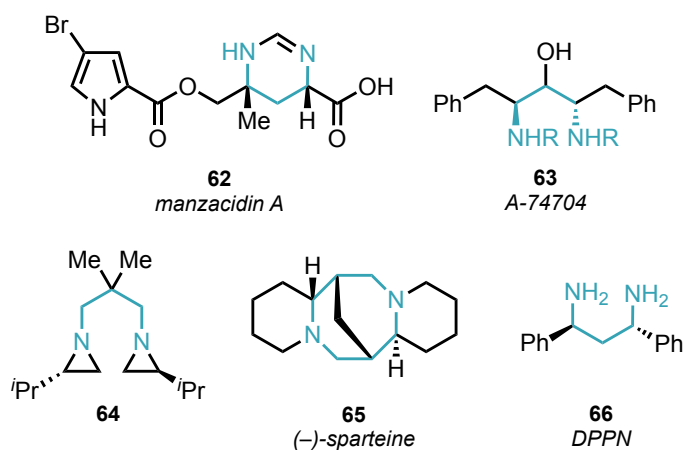


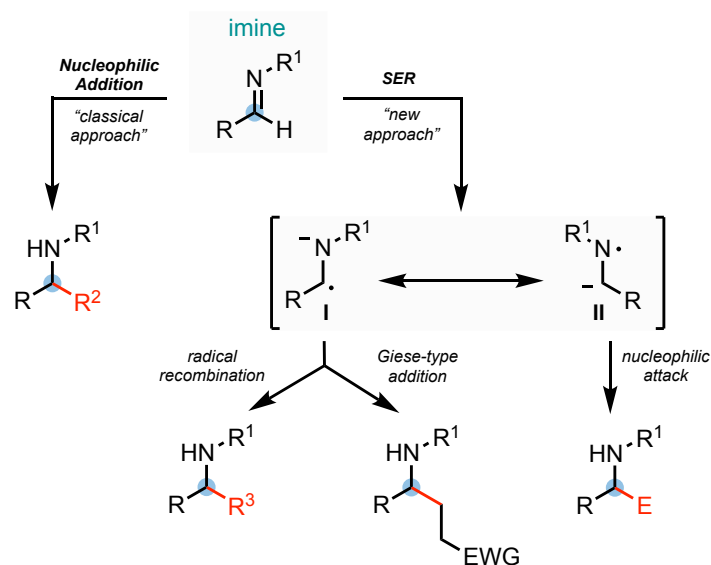
Figure 4. Examples of 1,3-diamine structural motif occurring in bioactive compounds and chiral ligands. R = ValCbz, DPPN = 1,3-diphenylpropanediamine.

Notwithstanding the importance of this scaffold, only a limited number of methods has been reported for the direct construction of this motif.^[85,86] *De facto*, the vast majority of synthetic methodologies rely on indirect approaches *via* the formation of a 1,3-diamine framework which requires subsequent transformations to obtain the desired moiety. Several procedures are based on Mannich-like reactions or nucleophilic α -*N*-substituted carbanions followed by reduction of common functionalities such as imines, nitriles, and nitro groups.^[82,85] Other protocols adopt C–N bond-forming reactions^[87] as well as cycloadditions for simultaneous C–C and C–N bond formation^[88] with consequent linker or N–N bond cleavage to afford the desired 1,3-diamine scaffold. Despite much effort towards the synthesis of this relevant structural element, existing methodologies are largely non-atom economical and suffer several limitations due the employment of stoichiometric quantities of potential harmful reagents. Consequently, a novel catalytic approach for the direct construction of 1,3-diamines would be generally attractive and of high synthetic value.^[82]

2.3 Reaction Development

When considering the synthesis of nitrogen-containing compounds, one of the most straightforward ways is through the functionalisation of imine components.^[82] In fact, the innate electrophilicity of these building blocks can be exploited as an efficient method for the generation of amines in a multitude of addition reactions.^[57] In recent years, multiple research programmes in the context of visible light photoredox catalysis for *in situ* generation of free radical intermediates have significantly contributed to the development of this classical approach by broadening the spectrum and versatility of radical-based additions to imine acceptors. Furthermore, the revival of the field disclosed the use of imine reduction under photocatalytic conditions (see Section 2.2.2) as a novel methodology for the functionalisation of this moiety towards valuable amine compounds.^[89] The photocatalytic single-electron reduction (SER) of imine derivatives has extended the reactivity of this functional group due to the generation of a putative nucleophilic

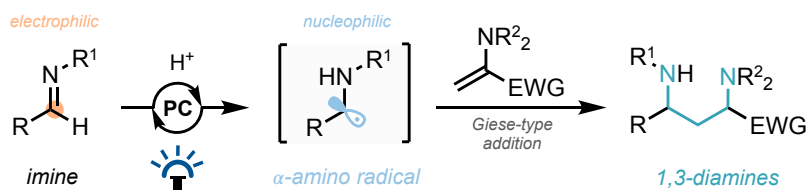
α -amino radical (**I**).^[90] Access to this intermediate unleashes a plethora of new transformations via radical-radical coupling, Giese-type radical addition with non-traditional coupling partners, and reactivity in a polar fashion via nucleophilic attack of conventional electrophiles through the *N*-centred radical resonant form **II** (Scheme 33).^[89]



Scheme 33. Imine functionalisation strategies: classical approach via – radical – addition reactions (*left*) and novel approach via photocatalytic single-electron reduction (*right*).

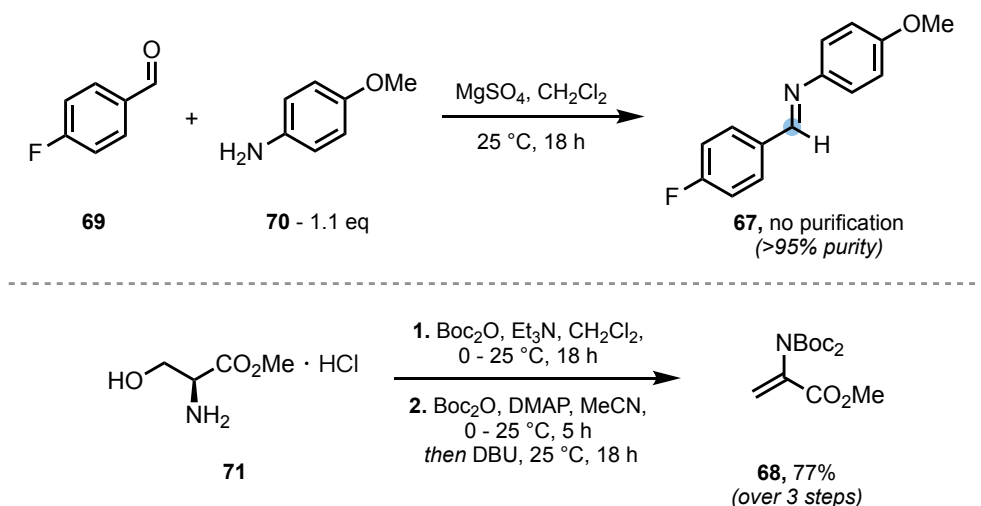
2.3.1 Proof of Concept

Following the unlocking of new reactivity with the aforementioned photocatalytic umpolung approach, a series of important developments have been made in recent years in the field of reductive imine coupling.^[16] Building on the putative nucleophilic character of *in situ* generated α -amino radicals, pioneering achievements established efficient trapping of these intermediates with a broad range of electrophilic species for the generation of valuable amine-containing products.^[54,55,91,92] In this context, we aimed to explore novel electron-deficient coupling partners to access the synthetically relevant 1,3-diamine motif (see Section 2.2.3) in a direct and stereoselective fashion (Scheme 34).^[90]



Scheme 34. Concept of novel photocatalytic imine functionalisation platform towards the direct synthesis of 1,3-diamines. PC = photocatalyst, EWG = electron-withdrawing group.

Given previous successful examples in radical conjugate addition (RCA) reactions, we decided to investigate the role of dehydroalanine (DHA) derivatives as preferred Michael acceptors for the construction of unsymmetric 1,3-diamines.^[93] Therefore, further inspired by encouraging precedents within the Dixon group,^[54,94] preliminary studies towards reaction discovery were conducted with fluorine-tagged imine **67** and bis-*N*-Boc DHA derivative **68**. These selected model substrates were easily prepared by condensing 4-fluorobenzaldehyde **69** with *p*-anisidine **70** and in three steps from commercially available *L*-serine methyl ester hydrochloride **71**, respectively (Scheme 35).^[90]

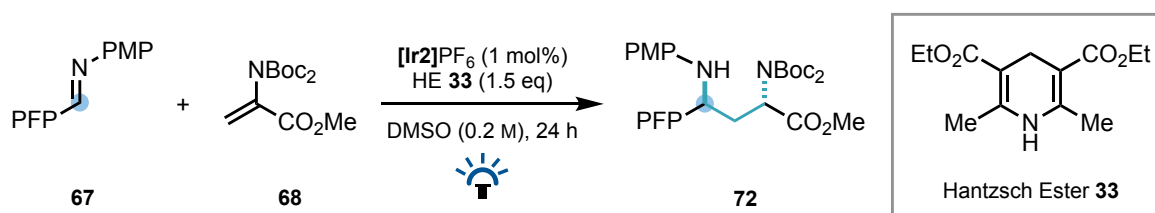


Scheme 35. Synthesis of model substrates **67** and **68**. Preformed imine **67** was used as crude.

In line with previous reaction conditions,^[94] reactivity between preformed imine **67** and alkene **68** upon irradiation with a blue light-emitting diode (LED) in dimethyl sulfoxide (DMSO)

with photocatalyst $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]^+$ (**Ir2**) and commercial Hantzsch ester (HE) **33** as stoichiometric reductant was examined. The desired 1,3-diamine product **72** was obtained in 47% yield and 1.5:1 diastereomeric ratio (dr) employing 1 equivalent of the DHA coupling partner (Table 1, entry 1). After increasing the yield of the transformation to 79% isolated yield with 2 equivalents of **68** (entry 2), control experiments were carried out to establish complete loss of reactivity in the absence of photocatalyst or light (entries 3 and 4).^[90]

Table 1. Reaction discovery and proof of principle of photocatalytic-based 1,3-diamine synthesis.



entry	PC	68	72 (%) ^[a]	dr
1	$[\text{Ir}2]\text{PF}_6$	1 eq	47	1.5:1
2	$[\text{Ir}2]\text{PF}_6$	2 eq	79	1.5:1
3	—	2 eq	0	—
4 ^[b]	$[\text{Ir}2]\text{PF}_6$	2 eq	0	—

[a] Isolated yield. [b] No blue LED light irradiation and/or no Hantzsch Ester **33**.

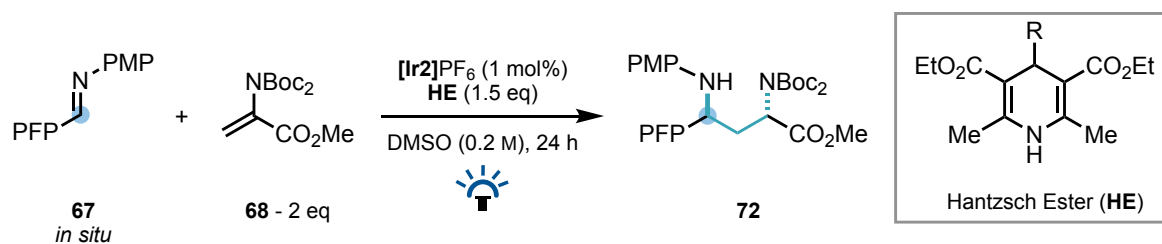
PFP = *p*-fluorophenyl, PMP = *p*-methoxyphenyl.

2.3.2 Reaction Optimisation

Importantly, product **72** was isolated in 93% yield as a 1.4:1 mixture of diastereoisomers with *in situ* imine formation (Table 2, entry 1). In order to suppress the formation of over-reduced imine experienced in previous experiments,^[94] we focussed our attention on the nature of the stoichiometric reductant. While other commonly employed reductive quenchers – *e.g.* triethy-

amine or *N,N*-diisopropylethylamine – were not effective, the use of substituted Hantzsch esters (HE) resulted in some benefits in this transformation (Table 2).¹ Alkyl substituents such as cyclohexyl **73** and isopropyl **74** led to lower reaction conversion with similar diastereomeric ratio (entries 2 and 3). Notably, addition of these alkyl groups *via* HE radical decomposition was not observed under these reaction conditions.^[95] Pleasingly, introduction of an sp²-substituted carbon as a phenyl group in *para*-position (**75**) provided product **72** in 96% yield with an increased dr of 2:1 (Table 2, entry 4). Modification of the aromatic ring with electron-donating or electron-withdrawing groups (**76** and **77**) afforded the desired product with lower efficiency and diastereoselectivity (entries 5 and 6).

Table 2. Optimisation of reaction conditions: role of the Hantzsch ester.

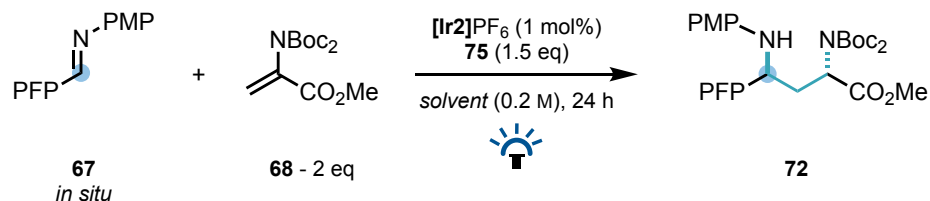


entry	Hantzsch ester	72 (%) ^[a]	dr
1	33 (R = H)	93 ^[b]	1.4:1
2	73 (R = cyclohexyl)	15	1.5:1
3	74 (R = isopropyl)	9	1.3:1
4	75 (R = phenyl)	96	2:1
5	76 (R = <i>p</i> -methoxyphenyl)	89	1.9:1
6	77 (R = <i>p</i> -trifluoromethylphenyl)	78	1.8:1

[a] ¹⁹F{¹H} NMR yield determined by direct conversion between **67** and **72**. [b] Isolated yield.

¹compounds **73**, **74**, **75**, **76** and **77** were previously synthesised by Dr. J. A. Leitch and have been included for completeness.

As further optimisation experiments conducted with various photocatalysts did not improve the reaction outcome, additional studies varying solvent conditions were endeavoured to increase the diastereomeric ratio.^[90] Following confirmation of optimal reaction concentration, a solvent screen with alternative polar aprotic solvents such as *N,N*-dimethylformamide (DMF) and tetrahydrofuran (THF) revealed the superior performance of DMSO (Table 3, entries 1 and 2). However, alcohol-based solvents such as methanol (MeOH) and ethanol (EtOH) were found to be beneficial in terms of diastereoselectivity, albeit negatively affecting reaction yields (entries 3 and 4). Consequently, we switched to a binary solvent system for further optimisation (Table 3, entries 5–9). Increasing the amount of DMSO within the solvent mixture led to full conversion without substantial alteration in diastereoselectivity (entries 5 and 6). Despite this, a further increment to a 1:1 EtOH/DMSO solvent mixture was detrimental for the reaction outcome with a decreased diastereomeric ratio (entry 7). This trend in reactivity was also validated for a binary solvent system employing MeOH instead of EtOH (entries 8 and 9). Finally, a mixture of MeOH/DMSO (3:2) resulted in full conversion while imparting good diastereoselectivity, affording 1,3-diamine **72** in 99% isolated yield and 4:1 dr on a 0.2 mmol scale (entry 9).^[90]

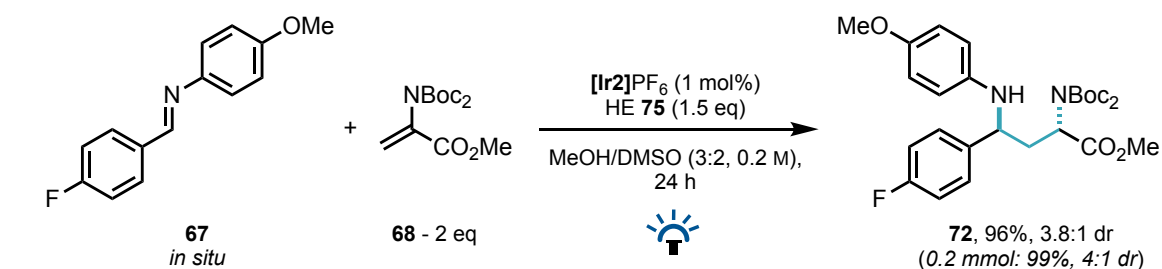
Table 3. Optimisation of reaction conditions: role of solvent mixture.

entry	solvent (ratio)	72 (%) ^[a]	dr
1	DMF	54	1.3:1
2	THF	trace	—
3	MeOH	16	3:1
4	EtOH	32	3.6:1
5	EtOH/DMSO (4:1)	76	3.2:1
6	EtOH/DMSO (3:2)	100	3.2:1
7	EtOH/DMSO (1:1)	100	2.8:1
8	MeOH/DMSO (3:2)	69	4.1:1
9	MeOH/DMSO (3:2)	100 (99)^[b]	4:1

[a] ¹⁹F{¹H} NMR yield determined by direct conversion between **67** and **72**. [b] Isolated yield.

2.3.3 Scale-Up and Determination of Major Diastereoisomer

In order to test the relevance of this transformation for potential downstream applications, we examined the methodology on a 1 mmol scale. The reaction proceeded well with comparable results to the 0.2 mmol scale, affording compound **72** as a 3.8:1 (*anti:syn*) separable mixture of diastereoisomers with a total isolated yield of 96%. Single-crystal X-ray diffraction studies certified the relative stereochemical configuration of the major diastereomeric product as *anti* (Scheme 36).^[90]



Scheme 36. Scale-up of photocatalytic umpolung synthesis of 1,3-diamine **72** on 1 mmol scale and single-crystal X-ray structure of the corresponding major diastereoisomer (*anti-72*).

2.4 Probing the Scope of the 1,3-Diamine Reaction

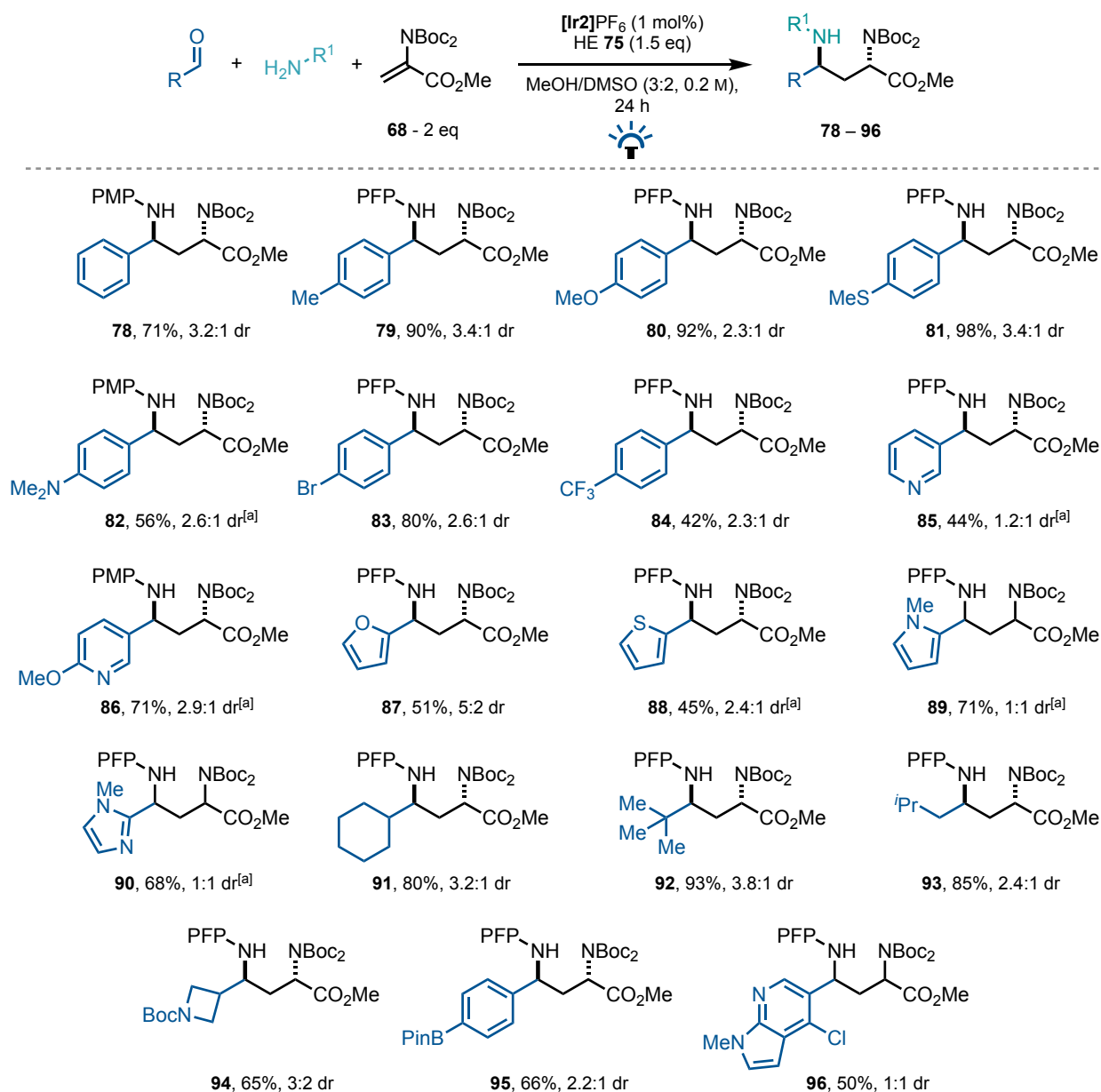
With optimal conditions established, we sought to probe the scope of this photocatalytic umpolung coupling with respect to both the aldehyde and amine moieties.

2.4.1 Scope with Respect to the Aldehyde Component

Initially, modifications of the *para*-position of the arylaldehyde to examine potential electronic effects on the *in situ* generated α -amino radicals were investigated (Scheme 37). The absence of substituents on the arene ring afforded the desired product in good yield and diastereomeric ratio (**78**, 71%, 3.2:1 dr). Substitution with electron-donating groups was widely tolerated with excellent results (**79**, **80** and **81**), despite a reduction in reactivity with the dimethylamine substituent in *para*-position which required longer reaction time (**82**, 56%, 2.6:1 dr). While no significant detriment to yield was observed in the presence of an halogen atom such as bromine

affording compound **83** in 80% isolated yield and 2.6:1 dr, lower efficiency was encountered with the introduction of a strongly electron-withdrawing CF₃ group (**84**). Superior performance with electron-donating substituents was further corroborated by outcomes gathered with pyridyl aldehydes, where better results – higher yield and diastereoselectivity – were observed with the more electron rich aromatic ring (Scheme 37, **85** and **86**). This trend in reactivity tentatively substantiates the proposed nucleophilic character of the *in situ* generated α -amino radical intermediate.^[90] In this regard, a recent publication by the Dixon and Duarte group further supports the nucleophilicity of these transient radical species with DFT calculations, although suggesting that the alteration of electronic properties on the aromatic ring via different substituents should not impact significantly the outcome of the reductive coupling reaction.^[96] Beyond pyridyl rings, heterocyclic aromatic compounds such as furan, thiophene, pyrrole, and imidazole were well tolerated in this transformation (**87–90**).

Considering the favorable implementation of substrates bearing challenging functionalities, we sought to investigate the substrate scope of this photocatalytic transformation with previously underexplored aliphatic carboxaldehyde starting materials.^[90] Therefore cyclic (**91**), α -branched (**92**) as well as linear (**93**) aliphatic substrates were successfully incorporated with good to excellent yield and good diastereoselectivity. A more elaborate *N*-containing aliphatic example provided *N*-Boc-protected azetidine **94** in one-step with 65% yield and 3:2 dr. Compatibility under these reaction conditions with a substrate bearing a boronic acid-derived functional group (**95**) illustrates the possibility to combine this photochemical methodology with subsequent transition metal cross-coupling transformations. Additionally, in order to further showcase potential applications in medicinal chemistry programmes, a pyrrolo[2,3-*b*]pyridine-decorated aldimine was converted to the corresponding 1,3-diamine product **96** in 50% yield as a 1:1 mixture of diastereoisomers (Scheme 37).^[90]

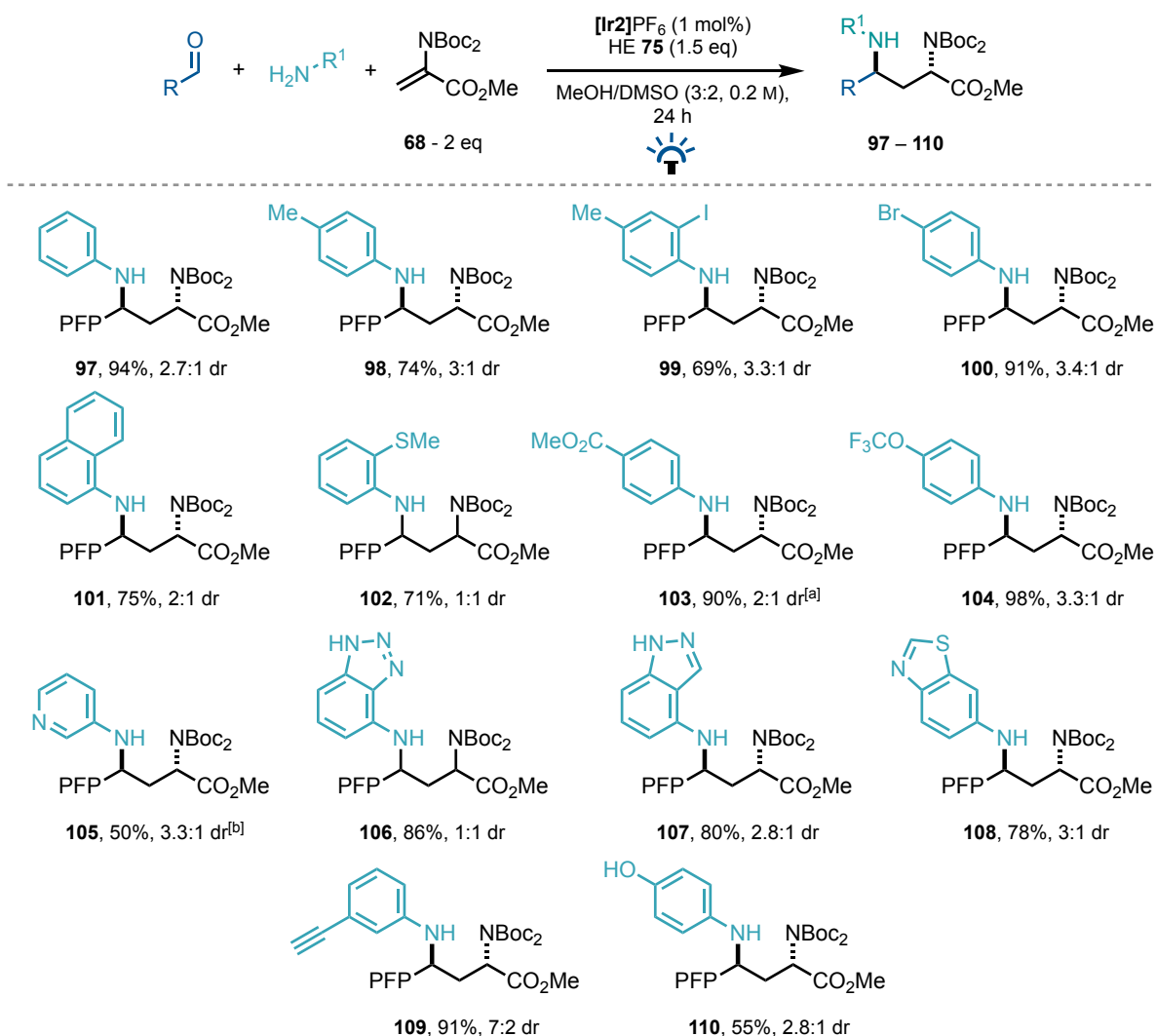


Scheme 37. Aldehyde scope of the three-component direct synthesis of unsymmetrical 1,3-diamines. Combined isolated yields given for major and minor diastereoisomers; major diastereomeric product assigned by analogy to **72** (see Scheme 36). PFP = *p*-fluorophenyl, PMP = *p*-methoxyphenyl, Pin = pinacol. ^[a]Reaction time = 48 h.

2.4.2 Scope with Respect to the Aniline Component

Subsequently, we turned our attention to expand the scope of this three-component reaction with respect to the aniline component adopting *p*-fluorobenzaldehyde **69** as model substrate. Removal

of the *p*-methoxyphenyl (PMP) group on the aniline moiety gave compound **97** in excellent yield and good diastereomeric ratio (Scheme 38). Similarly, *p*-toluidine was well-tolerated affording the corresponding diamine product **98** in 74% isolated yield and 3:1 dr. Decoration of the amine component with halogens was shown to be amenable with good to excellent yields (Scheme 38, **99** and **100**). Additionally, extended aromatic compounds such as naphthyl derivative **101** was isolated in 75% yield as a 2:1 mixture of diastereoisomers. When investigating substitution of the aryl moiety with more electron-releasing or electron-withdrawing functional groups, functionalized products were obtained in good to excellent yields (**102**, **103** and **104**), although thioether-substituted compound **102** gave a 1:1 diastereomeric ratio. Pleasingly, a good range of heterocyclic aniline derivatives were also found to be compatible with this chemistry (Scheme 38, **105–108**). While the efficiency diminished for pyridyl-substituted aldimine and longer reaction times were required (**105**), unprotected benzotriazole, indazole as well as benzothiazole derived imines were shown to be competent substrates affording product structures in high yield (**106**, **107** and **108**). Notably, introduction of a pendant alkyne on the aniline moiety resulted in successful conjugate addition to 1,3-diamine **109** with excellent yield and good dr without any undesired downstream cascade reaction byproducts. Finally, 4-aminophenol functionality was tolerated for *in situ* imine generation delivering product **110** with synthetically useful yield and good diastereoselectivity (Scheme 38).^[90]

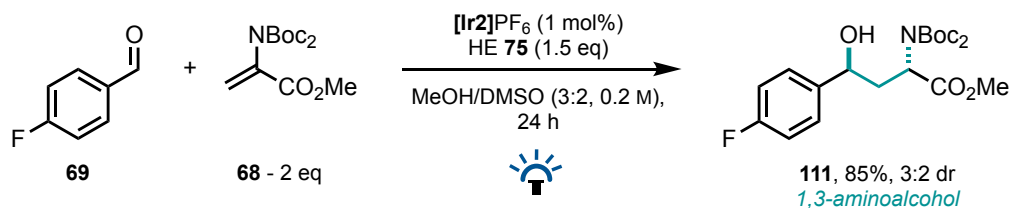


Scheme 38. Aniline scope of the three-component direct synthesis of unsymmetrical 1,3-diamines. Combined isolated yields given for major and minor diastereoisomers; major diastereomeric product assigned by analogy to **72** (see Scheme 36). PFP = *p*-fluorophenyl. ^[a]Imine was preformed, ^[b]Reaction time = 48 h.

Unfortunately, secondary aldimines bearing an aliphatic chain or a carbamate functionality on the amine component were not found to be viable substrates in this three-component methodology, most likely also due to inefficient imine formation under these reaction conditions.

2.5 Synthetic Utility and Derivatisation of 1,3-Diamines

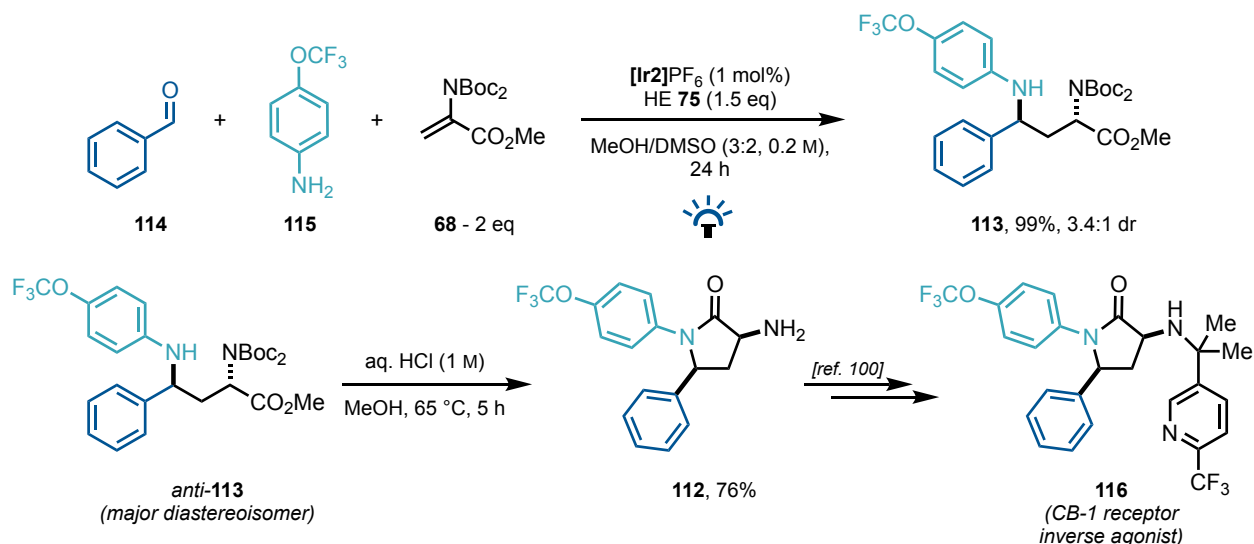
Encouraged by the pivotal role played by β -amino alcohols in asymmetric organic synthesis – both as auxiliaries and chiral ligands – as well as for their relevance in bioactive natural products and pharmaceuticals, we envisaged to extend the versatility of our newly developed methodology towards the direct synthesis of analogous 1,3-aminoalcohol compounds.^[97,98] Given the previously disclosed reactivity of ketyl radicals in photoredox catalysis^[51] and the efficiency demonstrated by our protocol, we decided to test the formation of this transient species under optimized reaction conditions omitting the aniline component. Accordingly, aldehyde **69** and an excess of alkene **68** were subjected to blue light irradiation in the presence of **Ir2** and reductant **75**. Despite the moderate diastereoselectivity, β -amino alcohol **111** was isolated in excellent yield, demonstrating the potential of this protocol as an alternative method towards the targeting of this abundant structural motif (Scheme 39).^[90]



Scheme 39. Extension of the methodology for the photocatalytic umpolung synthesis of β -amino alcohols.

Additionally, following the identification of a key intermediate in a variety of cannabinoid 1 (CB-1) receptor inverse agonists for the treatment of obesity, γ -lactam **112** was targeted in order to further substantiate the synthetic application of this method in drug discovery programmes.^[99] To this end, diamine product **113** was synthesised in 99% yield as a 3.4:1 separable mixture of diastereoisomers from commercially available benzaldehyde **114** and trifluoromethoxyaniline **115** according to the established photocatalytic umpolung methodology.^[90] One-step Boc-deprotection followed by cyclisation of major isomer **113** under acidic conditions afforded desired α -amino- γ -lactam *syn*-**112** in 76% isolated yield. Functionalisation of this species with various

substituted ketone moieties would grant access in a two-steps process to a series of drug candidates such as **116**,^[100] which has been shown to display highly selective antagonistic activity in the low micromolar range for CB-1 receptors (Scheme 40).^[101]

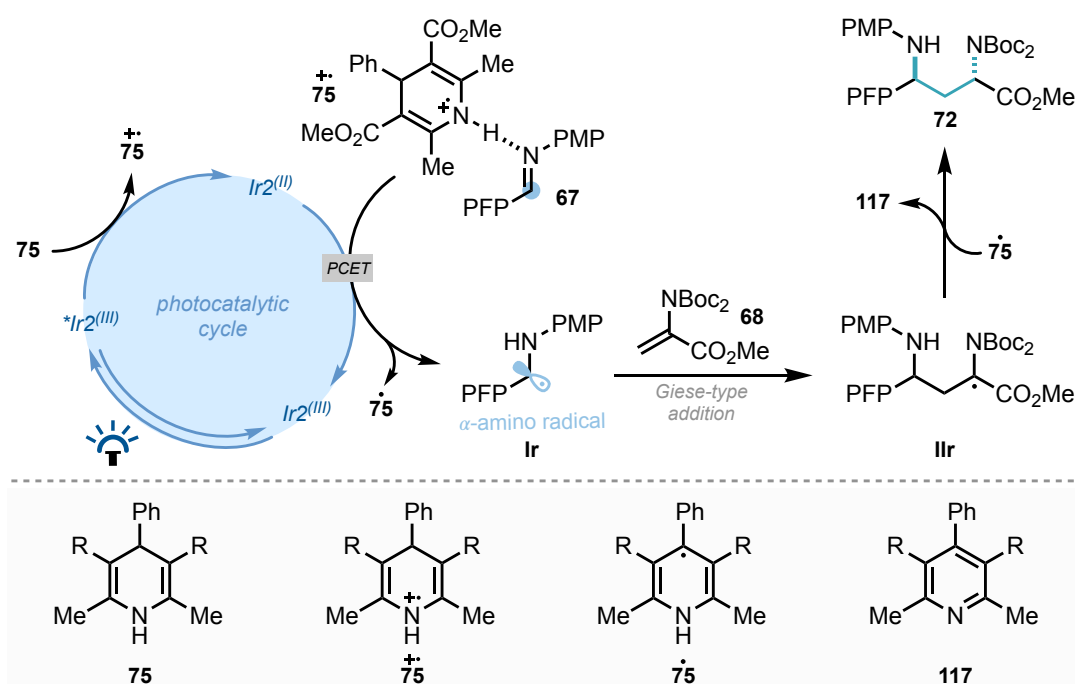


Scheme 40. Derivatisation and application towards the synthesis of bioactive compounds.

2.6 Mechanistic Considerations

From a mechanistic viewpoint, we propose that Hantzsch ester **75** is able to quench the photoexcited ***Ir2(III)** catalyst to form a reducing **Ir2(II)** species ($E^0_{1/2} = -1.37 \text{ V}$ vs SCE in CH_3CN)^[90] and the corresponding radical cation **75⁺•** (Scheme 41). In line with previous investigations, the partially oxidised state would allow the participation of the latter in a proton-coupled electron transfer (PCET) process as proton donor (see Section 2.2.2), thus favoring the reduction of the otherwise electrochemically robust *in situ* generated *N*-arylimine **67** ($E^0_{1/2} \simeq -1.90 \text{ V}$ vs SCE in CH_3CN)^[90,102] by the iridium species to generate the key nucleophilic α -amino radical **Ir** along with intermediate **75⁺•**.^[54,55,91,94] A subsequent exergonic Giese-type addition reaction is proposed to take place such that α -amino radical **Ir** would intercept the electron-deficient DHA coupling partner **68** delivering radical adduct intermediate **IIr** (Scheme 41). Despite the

absence of supplementary studies substantiating the origin of stereocontrol, we speculate that the ultimate relative diastereomeric spatial configuration is controlled in the final protonation step.^[96] In fact, radical termination leading to observed *anti*-1,3-diamine **72** is proposed to proceed through an additional reduction/anion reprotonation sequence of adduct **IIr** operated by **75**[•] – generating Hantzsch pyridine (HP) **117** – as in other DHA-derived photocatalytic radical addition precedents (Scheme 41).^[93,103]



Scheme 41. Proposed mechanism for the photocatalytic umpolung synthesis of 1,3-diamines under reductive conditions. PFP = *p*-fluorophenyl, PMP = *p*-methoxyphenyl, R = CO₂Me.

2.7 Conclusion

In conclusion, we have successfully developed the first efficient visible light-mediated photocatalytic diastereoselective umpolung method for the construction of valuable 1,3-diamine motifs. Exploiting a key nucleophilic addition of *in situ* generated α -amino radicals to a protected dehydroalanine derivative, this one-pot three-component protocol gives access to a series of 1,3-diamines efficiently and in moderate to good diastereoselectivity under mild reaction conditions. The incorporation of a substituted Hantzsch ester as stoichiometric reductant along with a binary solvent system were necessary to synthesize the model compound in almost quantitative yield and 4:1 diastereomeric ratio. A wide range of functionalities with respect to both the aldehyde and the aniline moiety was shown to be tolerated, illustrating potential application in downstream transformations. Remarkable efficiency was demonstrated with *N*-containing heterocycles as well as aldimines derived from aliphatic carboxaldehydes. Furthermore, extension of the methodology for the construction of related β -amino alcohols and derivatisation towards the synthesis of biologically active compounds via α -amino- γ -lactams showcase the promising utility of this mild umpolung transformation as a synthetic platform for the generation of molecular complexity. In this context, given the relevance of this structural motif in various fields, incorporation of this concept towards enantioenriched products could be carried out in the future by employing a Karady-Beckwith-type alkene as coupling partner (Figure 5).

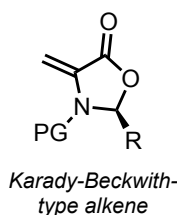


Figure 5. Karady-Beckwith-type alkene for diastereoselective radical conjugate addition. PG = protecting group.

Chapter 3

Photocatalytic Reductive α -Tertiary Ether Formation

3.1 Chapter Overview

This chapter describes the considerations behind the development of novel photoredox-based methodologies towards the synthesis of ether architectures. Pivoting on *in situ* generated α -alkoxy radicals under reductive conditions, good reactivity with a variety of readily accessible ketals and acceptor olefins is reported for the formation of a broad range of unsymmetrical ethers with an adjacent quaternary center. Mechanistic investigations along with computational calculations have also been performed to support the proposed reaction mechanism via single-electron transfer (SET) reduction of oxocarbenium ions. Building on these findings, an alternative photocatalytic strategy towards the construction of challenging all-alkyl substituted α -tertiary ethers is briefly described.

3.2 Introduction

3.2.1 Ether-containing Compounds and Their Traditional Synthesis

Ethers are prevalent structural motifs within bioactive compounds – from natural products to active pharmaceutical agents – and their preparation is considered a fundamental transformation for practicing organic chemists (Figure 6).^[104,105] More specifically, sterically demanding ethers comprising a $C(sp^3)-O-C(sp^3)$ fragment are extensively sought after structural units in medicinal chemistry, as the hindered substitution around the oxygen bond hampers undesired metabolic degradation pathways.^[106,107]

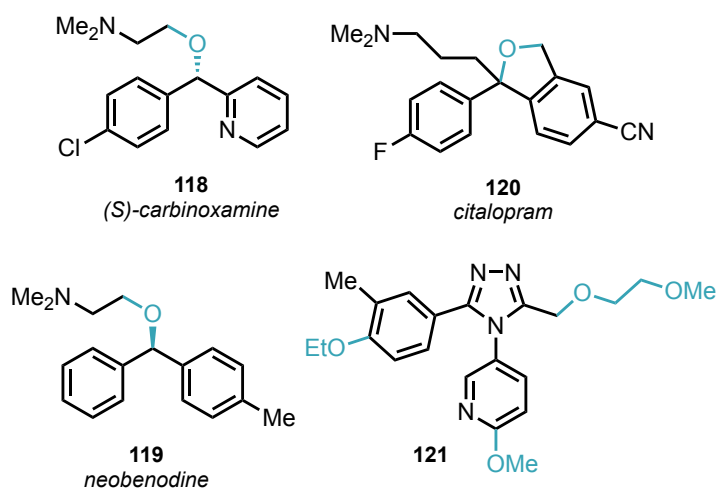


Figure 6. Examples of ether-containing bioactive compounds: structurally related antihistamine **118** and anticholinergic drug **119**, antidepressant **120**, and oxytocin antagonist **121**.^[108,109]

Despite the value and numerous applications of these functional groups, the considerable difficulties encountered when accessing ethers via traditional methods still make them an underexplored area of chemical space.^[107] Historically, the first methodology employed to construct C–O bonds is the Williamson ether synthesis, an S_N2 -type nucleophilic substitution first reported in 1851.^[110] The establishment of this method as state of the art for C–O bond formation resulted in the underdevelopment of alternative methodologies over the last 170 years, limiting the number of available approaches towards the construction of ether functionalities to a few con-

ventional protocols. Disappointingly, very low efficiency, or no reaction, is generally observed by employing Williamson ether synthesis or the alternative Mitsunobu reaction for the generation of hindered ethers due to the intrinsic steric demands of the S_N2 mechanism.^[107,111] In addition, complementary S_N1 -based protocols also tend to fail owing to harsh or strong acidic conditions required for the carbocation pathway, drastically limiting functional group tolerance.^[106,112] Regarding carbocation intermediates, a fourth traditional strategy based on electrolytic oxidation of carboxylic acids is known for the synthesis of ether compounds, namely the Hofer-Moest reaction.^[113] Despite circumventing acidic conditions, this class remained widely unexploited mainly due to solvent-quantities required for the alcoholic moiety along with practical issues related to the adoption of electrosynthetic methods by synthetic organic chemists (Figure 7).^[107]

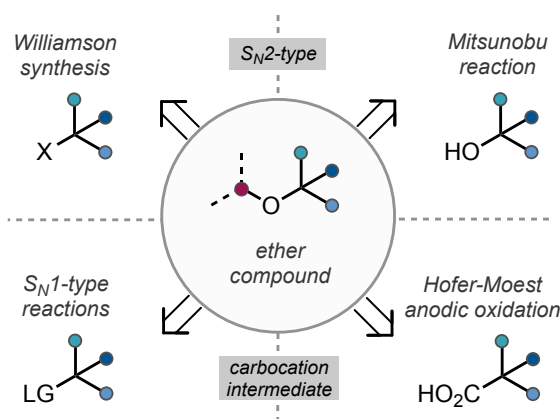


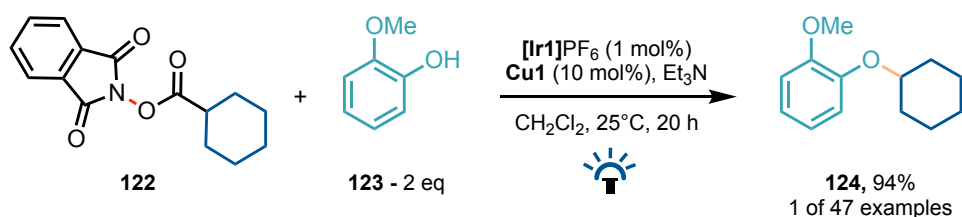
Figure 7. Summary of traditional approaches for the construction of ether functionalities.

Notwithstanding the synthetic utility of these broadly adopted methodologies for the construction of simple ether architectures, the above-mentioned approaches based on the formation of the $C(sp^3)$ -O bond are far from general for more complex and hindered ethers.^[105]

3.2.2 Contemporary Methodologies towards Ether Formation

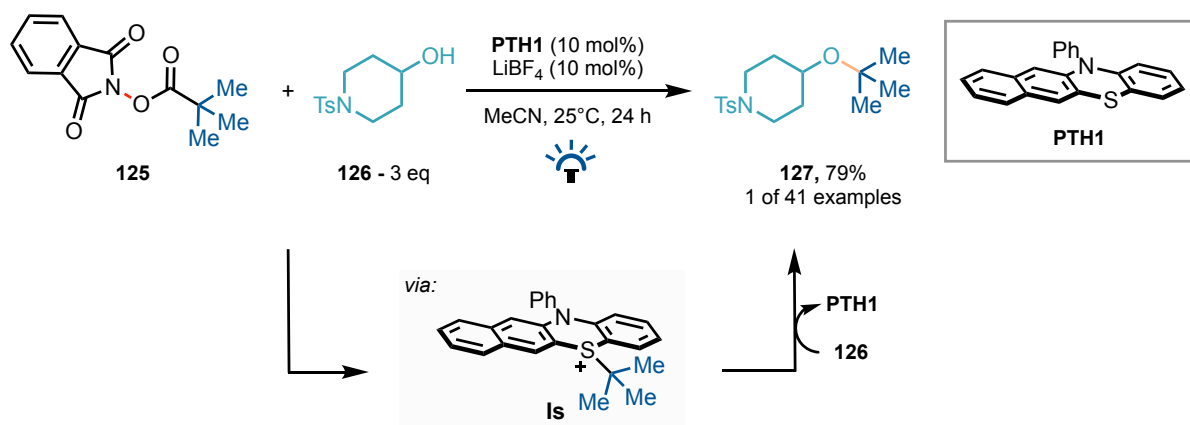
In spite of significant improvements of the traditional C-O bond-forming approach,^[112,114,115] several developments towards ether construction in recent times have focussed on C-C bond-

forming disconnection strategies.^[105] Advances in contemporary methodologies ranging from C–H functionalisation^[116] to photoredox catalysis have contributed considerably to expand the available synthetic toolbox, offering valuable and alternative opportunities to access ether components. However, the use of bespoke reagents^[111,117] or limitations set by the intrinsic reactivity of involved coupling partners^[118] prevent their employment in a broad synthetic sense, especially for the generation of increasingly attractive structural motifs such as congested dialkyl ethers.^[105,119] With the goal to bypass innate disadvantages associated with traditional two-electron based protocols (see Section 3.2.1), catalytic transition-metal methodologies via radical intermediates have become an interesting concept towards the formation of alkyl-substituted C(sp³)-heteroatom bonds, extending the breadth of nucleophilic substitution reactions and providing asymmetric control.^[120,121] However, various challenges remain in accessing all-alkyl structural units owing to generally high basic conditions, slow oxidative addition with alkyl coupling partners, and consequent undesired β -hydride elimination favored with these moieties.^[106] In the context of radical-based pathways, efforts within the field of photoredox catalysis have offered additional unique approaches trying to overcome these limitations.^[78,122,123] For example, in 2018 Hu and co-workers reported an elaborate catalytic system for the construction of alkyl aryl ethers merging photoredox and transition metal catalysis – a concept called metallophotoredox catalysis.^[9,124] This procedure is based on a decarboxylative C–O coupling between redox-active ester (RAE, see Section 2.2.1) **122** and phenol **123** to provide alkyl aryl ether product **124** with a combination of iridium-based photocatalyst **Ir1** and (CuOTf)₂·C₆H₆ (**Cu1**) under blue-light irradiation (Scheme 42).^[125]



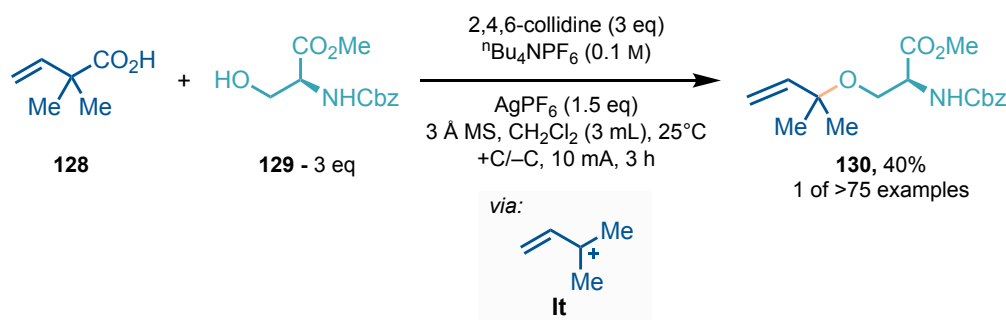
Scheme 42. Metallophotoredox-based protocol by Hu *et al.* for the synthesis of alkyl aryl ether compounds. **Cu1** = (CuOTf)₂·C₆H₆.

More recently, Ohmiya and Nagao reported an elegant synthetic procedure to target dialkyl ether structures exploiting an organophotoredox-catalyzed reductive radical-polar crossover (RPC) reaction.^[106] Under visible light irradiation with phenothiazine (PTH) as organophotocatalyst, a reactive carbocation intermediate is generated from sulfonium salt **Is** following a decarboxylative single-electron transfer (SET) event from alkyl-RAE **125**, which would be intercepted by alcohol nucleophile **126** in a substitution reaction to generate desired C(sp³)-O product **127** (Scheme 43). Mild reaction conditions allowed the extension of this decarboxylative coupling procedure to various heteroatom nucleophiles, including the construction of C(sp³)-rich scaffolds with amides and thiols.^[106]



Scheme 43. Organophotoredox-catalyzed C(sp³)-O bond-forming methodology involving an RPC process. by Nagao and Ohmiya.

Similarly, a recent report by Baran and co-workers highlighted the use of electrochemical means to access related reactive carbocation intermediates for the generation of sterically hindered ethers from readily available carboxylic acids.^[107] Building on Hofer-Moest procedures within a synthetic context,^[113,126] electrogenerated carbocation **It** is proposed to be formed via decarboxylation of aliphatic carboxylic acid **128** and subsequently trapped by alcohol nucleophile **129** to provide ether **130** in a single step – compared to previous methods which necessitated over three days for 7 steps and an overall yield of 37% (Scheme 44). In fact, mechanistic studies suggests the formation of reactive intermediate **It** following oxidation of the corresponding carboxylate at the anode. The mild reaction conditions to generate such carbocations allowed the addition of various nucleophiles – including fluorides and amides – for the formation of numerous congested functionalised architectures, overcoming substantial challenges associated with traditional approaches.^[107]

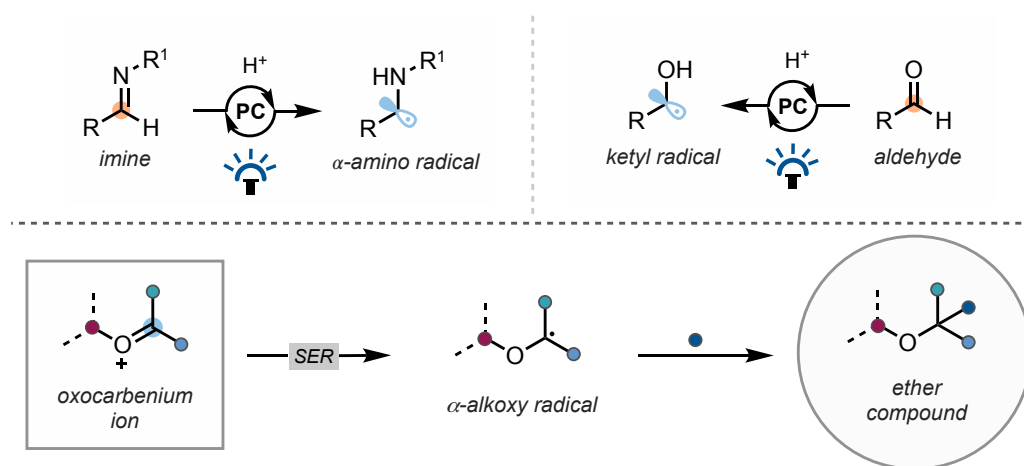


Scheme 44. Hindered alkyl ether synthesis via electrochemical decarboxylation by Baran *et al.*

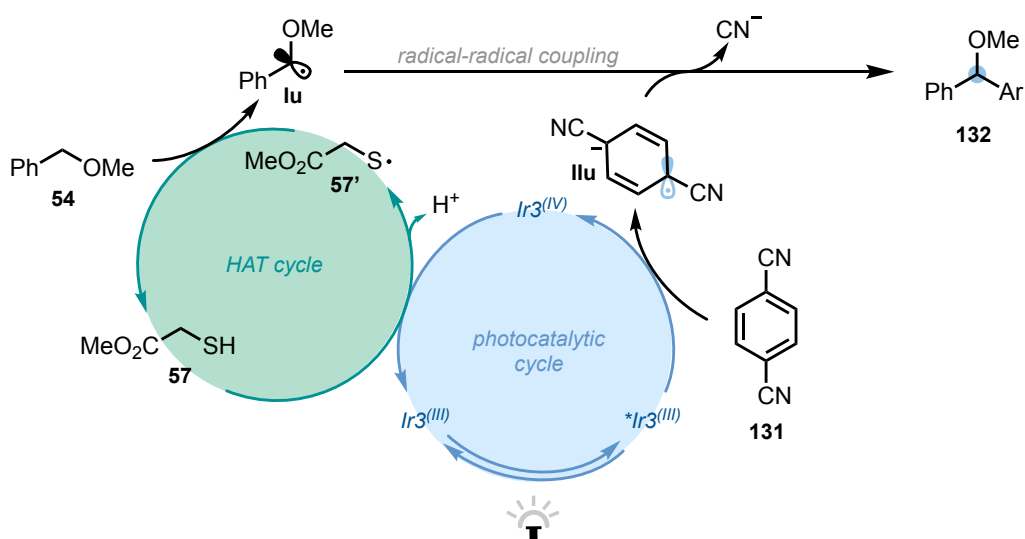
Contemporaneously to this electrogenerated method, we planned to develop a complementary route aiming at accessing all-alkyl substituted α -tertiary ethers. Given the significant constraints imposed by S_N2 and other traditional carbocation-derived settings, we envisaged that an alternative mild photocatalytic approach would provide an additional synthetic benefit for the generation of this valuable motif in complex contexts.

3.3 Proof of Principle

In light of our previous work concerning single-electron reduction (SER) of *in situ* generated imine derivatives (Chapter 2), we sought to expand this concept towards SER of carbocation intermediates for the direct generation of α -alkoxy radicals, which would grant an entry to functionalised ethers via Giese-type radical conjugate addition (RCA) chemistry. Despite extensive research in the field of metal-based HAT establishing its synthetic utility for the construction of a broad range of chemical space,^[127] access to α -alkoxy radical species via this redox process was unsuccessful to implement the methodology towards the synthesis of α -tertiary dialkyl ethers.^[119,128] To this end, the development of a novel C–C bond-forming disconnection approach based on SER of *in situ* generated oxocarbenium ions was studied. Considering the emergence of visible light-induced photocatalysis as an effective method for the formation of ketyl radicals from carbonyl compounds,^[51,129] and our experience with single-electron transfer (SET) processes for the generation of α -amino radicals, we reasoned that a similar photocatalytic umpolung method could be applied to oxocarbenium ions for the direct generation of closely related reactive open-shell species (Scheme 45).

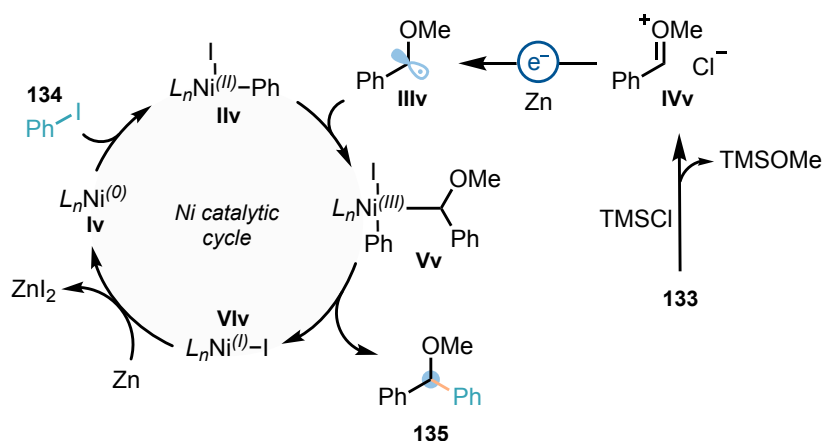
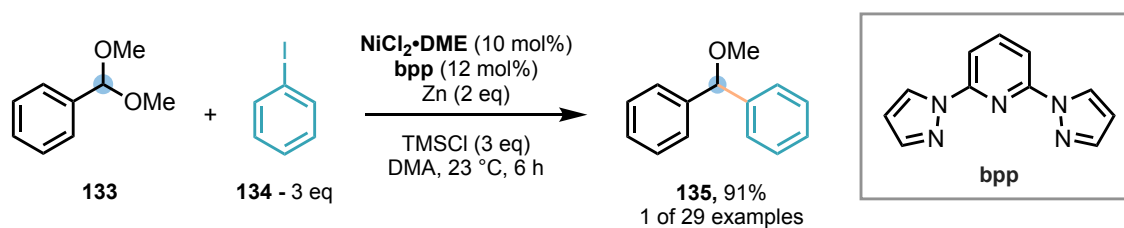


Scheme 45. Established reverse-polarity photocatalytic procedures and proposed novel C–C bond approach via α -alkoxy radical species towards ether compounds. PC = photocatalyst.



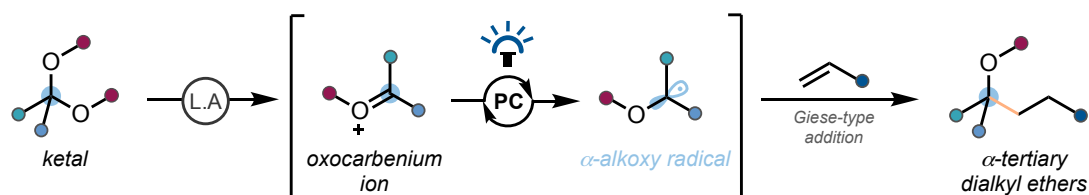
Scheme 47. Proposed reaction mechanism for the synthesis of ether **132** from 1,4-DCB (**131**) and **54**.

In 2015, the Doyle group developed a powerful nickel-catalysed cross-coupling process to access analogous benzhydryl ethers.^[130] This reductive protocol exploits the generation of an α -oxy radical via an alternative mechanism from acetal **133**. The carbon-centred radical species is involved in a Ni-based catalytic cycle with aryl iodide **134** to deliver diaryl ether **135** in excellent yield (Scheme 48). The catalytic cycle is initiated by oxidative addition of Ni^0 (**Iv**) into iodobenzene **134** resulting in a Ni^{II} species (**IIv**) which is proposed to capture organic radical **IIIv**. Regarding the formation of alkoxy radical **IIIv**, the authors exploited the activation of acetal **133** with a Lewis acid – such as chlorotrimethylsilane (TMSCl) – to a transient oxocarbenium ion (**IVv**) followed by reduction in the presence of stoichiometric amounts of Zn developed by Hatano.^[131] The interception of radical **IIIv** furnishes Ni^{III} intermediate **Vv** which is believed to then undergo reductive elimination to give desired product **135** along with a Ni^I species (**VIv**). Finally, the catalytic cycle is closed via reduction of the latter in order to regenerate Ni^0 **Iv** (Scheme 48).^[130] Notably, Wang and co-workers adopted the same strategy for the synthesis of *gem*-difluoroalkenes containing ether compounds.^[132]



Scheme 48. Nickel-catalysed cross-coupling for benzhydryl ether synthesis by Doyle and co-workers.

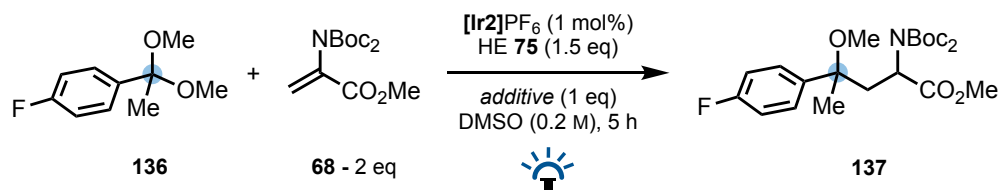
Notwithstanding the significant advances in the field of C–C bond-forming ether syntheses brought by these methodologies, a general strategy to construct α -tertiary all-alkyl ethers remains out of reach. Consequently, we envisaged to develop a novel and mild approach leveraging on the generation of α -alkoxy radical under photocatalytic conditions. To this end, a visible light-mediated SER of oxocarbenium ions following ketal activation as a complementary access to α -alkoxy radical species which could engage in RCA was investigated.^[105] Building on the above mentioned procedures with acetals, we considered Lewis acid (L.A) activation of readily available ketal starting materials to partake in radical addition chemistry with electrophilic alkene coupling partners to provide desired dialkyl ether architectures in one step (Scheme 49).



Scheme 49. Novel photocatalytic concept towards the direct synthesis of α -tertiary dialkyl ethers. L.A = Lewis acid, PC = photocatalyst.

According to our previously employed reductive conditions,^[90] preliminary studies of this proposed transformation were conducted with dimethyl ketal substrate **136**, 2 equivalents of dehydroalanine **68** as coupling partner, and HE **75** under blue LED light irradiation in DMSO with **Ir2** as photocatalyst (Table 4). Disappointingly, and contrary to prior reports,^[130–132] TMSCl was found to be ineffective for the construction of desired ether **137** (Table 4, entry 1). Evaluation of Lewis acidic boron-based complexes for ketal functionalization afforded product **137** in negligible yield (entries 2 and 3). To our delight, when 1 equivalent of trimethylsilyl trifluoromethanesulfonate (TMSOTf) was used as additive, moderate reactivity was observed (56%, entry 4).

Table 4. Proof of concept for the photocatalytic reductive synthesis of α -tertiary dialkyl ethers.



entry	additive	137 (%) ^[a]
1	TMSCl	trace
2	$\text{BF}_3 \bullet \text{OEt}_2$	trace
3	$\text{BF}_3 \bullet \text{THF}$	0
4	TMSOTf	56

[a] ^1H NMR yield determined by integration against 1,3,5-trimethoxybenzene (TMB) as internal standard.

Ir2 = $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]^+$.

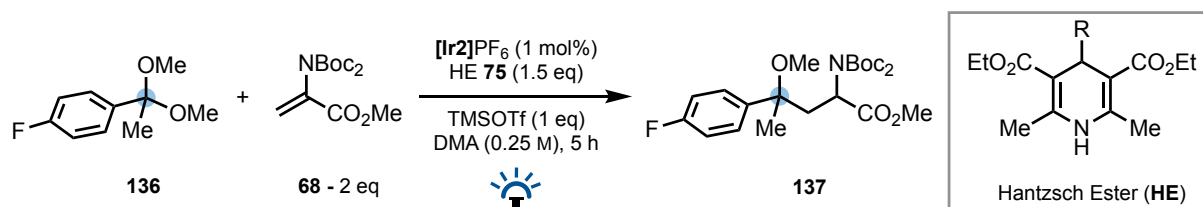
3.4 Optimisation Studies

3.4.1 Reaction Optimisation with DHA as Coupling Partner

Following the identification of TMSOTf as preferred Lewis acid, we focussed our attention on various reaction parameters to improve the performance of this photocatalytic system. Initial reaction optimisation studies with **68** as acceptor olefin assessed the importance of solvent selection and concentration on reaction efficiency. In fact, switching to *N,N*-dimethylacetamide (DMA) with a higher substrate concentration resulted in a significant enhancement, providing tertiary methyl ether **137** in an optimal 78% NMR yield (Table 5, entries 1 and 2). Comparable yields were observed by employing different photocatalysts such as organic **4-CzIPN** or **Ir4** (entries 3 and 4). Considering our previous investigations, we also examined the role of a series of Hantzsch esters (HE) on the reaction outcome (entries 5-8), with HE **75** (R = phenyl) proving

to be the most suitable stoichiometric reductant in this transformation.²

Table 5. Investigation of reaction parameters with DHA as coupling partner.



entry	deviations from above	137 (%) ^[a]
1	none	78 (66) ^[b]
2	0.2 M in DMA	65
3	4-CzIPN instead of [Ir2]PF₆	71
4	[Ir4]PF₆ instead of [Ir2]PF₆	75
5	74 (R = isopropyl) instead of 75	10
6	76 (R = <i>p</i> -methoxyphenyl) instead of 75	66
7	138 (R = methyl) instead of 75	46
8	139 (R = methyl benzoate) instead of 75	71

[a] ¹H NMR yield determined by integration against 1,3,5-trimethoxybenzene (TMB) as internal standard.

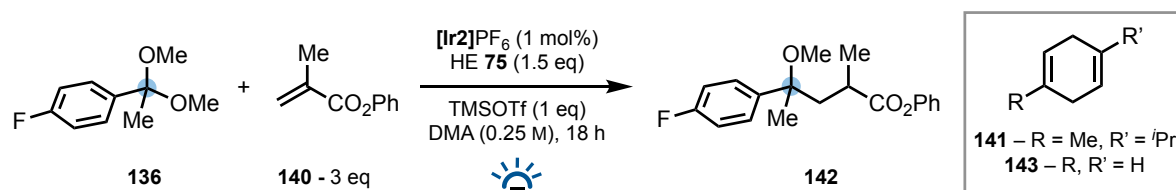
[b] Isolated yield. **Ir4** = [Ir(dFppy)₂(dtbbpy)]⁺.

²compounds **138** and **139** were previously synthesised by Dr. J. A. Leitch and have been included for completeness.

3.4.2 Reaction Optimisation with Acrylate-Type Coupling Partners

Observations made during the reaction scope with non-dehydroalanine acceptor moieties led us to consider a different termination pathway contrasting the proposed radical reduction/reprotonation mechanism for DHA.^[90] Recognizing hydrogen atom transfer (HAT) as suggested primary termination event for acrylate-type coupling partners,^[103] alternative reagents in order to assist this radical termination behaviour following RCA were examined with ketal **136** and olefin **140** as model substrates (Table 6).^[105] Consistent with mechanistic studies by Jui and co-workers,^[103] a substantial improvement with regard to reaction yield was observed by increasing the amount of phenyl-substituted HE **75** within the reaction mixture (entries 1 and 2); however, commercial Hantzsch ester **33** was not viable in this reductive process (entry 3). As thiol-derived HAT catalysts were not tolerated in this transformation, we turned our attention towards alternative H-atom donors.^[103,133] Initially, H-atom abstraction from γ -terpinene **141** was examined,^[134] providing ether adduct **142** with comparable yield (68%, entry 4). Fortunately, increasing the amount of 1,4-cyclohexadiene (1,4-CHD, **143**) as HAT additive afforded the desired product with an improved 74% isolated yield (entries 5 and 6);^[135] thus supporting a preferred termination pathway via hydrogen atom transfer with acrylate acceptors.^[103]

Table 6. Investigation of reaction parameters with acrylate **140** as coupling partner.



entry	deviations from above	142 (%) ^[a]
1	none	57
2	2 eq of HE 75	67
3	2 eq of HE 33	trace
4	2 eq of 75 and 1.5 eq of 141	68
5	2 eq of 75 and 1.2 eq of 143	69
6	2 eq of 75 and 1.5 eq of 143	78 (74) ^[b]

[a] ¹H NMR yield determined by integration against 1,3,5-trimethoxybenzene (TMB) as internal standard.

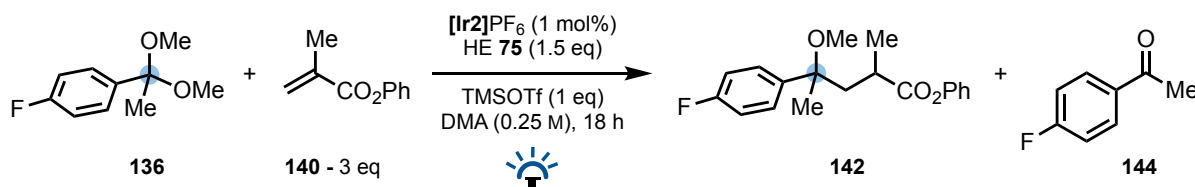
[b] Isolated yield.

3.4.3 Control Experiments

Contemporaneously to initial feasibility studies with additional H-atom abstractors, control experiments were also conducted in the case of acrylate-type coupling partners (Table 7, entry 1). In the absence of TMSOTf, no conversion of starting material **136** was observed, supporting the essential role of the Lewis acid for ketal activation (entry 2). Desired reactivity towards carbon-carbon coupled product **142** was also not achieved without stoichiometric reductant **75** in the reaction mixture, although providing 72% of 4'-fluoroacetophenone **144** following ketal deprotection with TMSOTf (entry 3). Moreover, similar profiles were obtained excluding photocatalyst or light from reaction conditions (entries 4 and 5). Altogether, these results substantiate our proposed working hypothesis, whereby upon ketal activation an oxocarbenium ion intermediate is reduced *in situ* via SET under photocatalytic conditions delivering a putative

nucleophilic α -alkoxy radical responsible for RCA (see Scheme 49).

Table 7. Control experiments for the photocatalytic Lewis acid-promoted dialkyl ether synthesis.



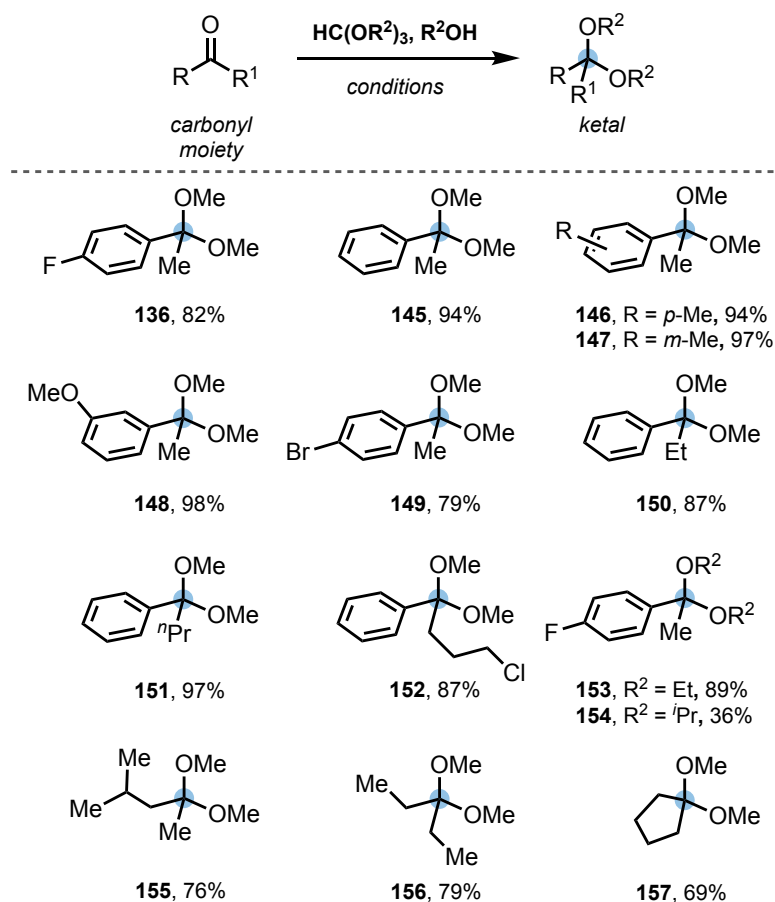
entry	deviations from above	142 (%)	144 (%) ^[a]	unreacted 136 (%) ^[a]
1	none	57 ^[b]	0	0
2	no TMSOTf	—	—	100
3	no Hantzsch ester 75	0	72	0
4	no $[\text{Ir}2]\text{PF}_6$	0	88	2
5	no blue LED irradiation	0	87	4

[a] NMR yield based on conversion between **136** and known products. [b] NMR yield based on 1,3,5-trimethoxybenzene (TMB) as internal standard.

3.5 Probing the Scope of the α -Tertiary Dialkyl Ether Reaction

3.5.1 Synthesis of a Range of Ketal Substrates

With optimal reaction conditions in hand, we looked to assess the scope of this photocatalytic C–C bond-forming reductive coupling protocol. To this end, a range of substrates were synthesised in order to investigate the limitations of this process with respect to the ketal moiety. The ketals examined in this transformation were prepared from the parent ketones with the corresponding orthoformate reagent ($\text{HC}(\text{OR}^2)_3$) and alcohol (R^2OH) as solvent in yields ranging from 36% to 98% (Scheme 50).



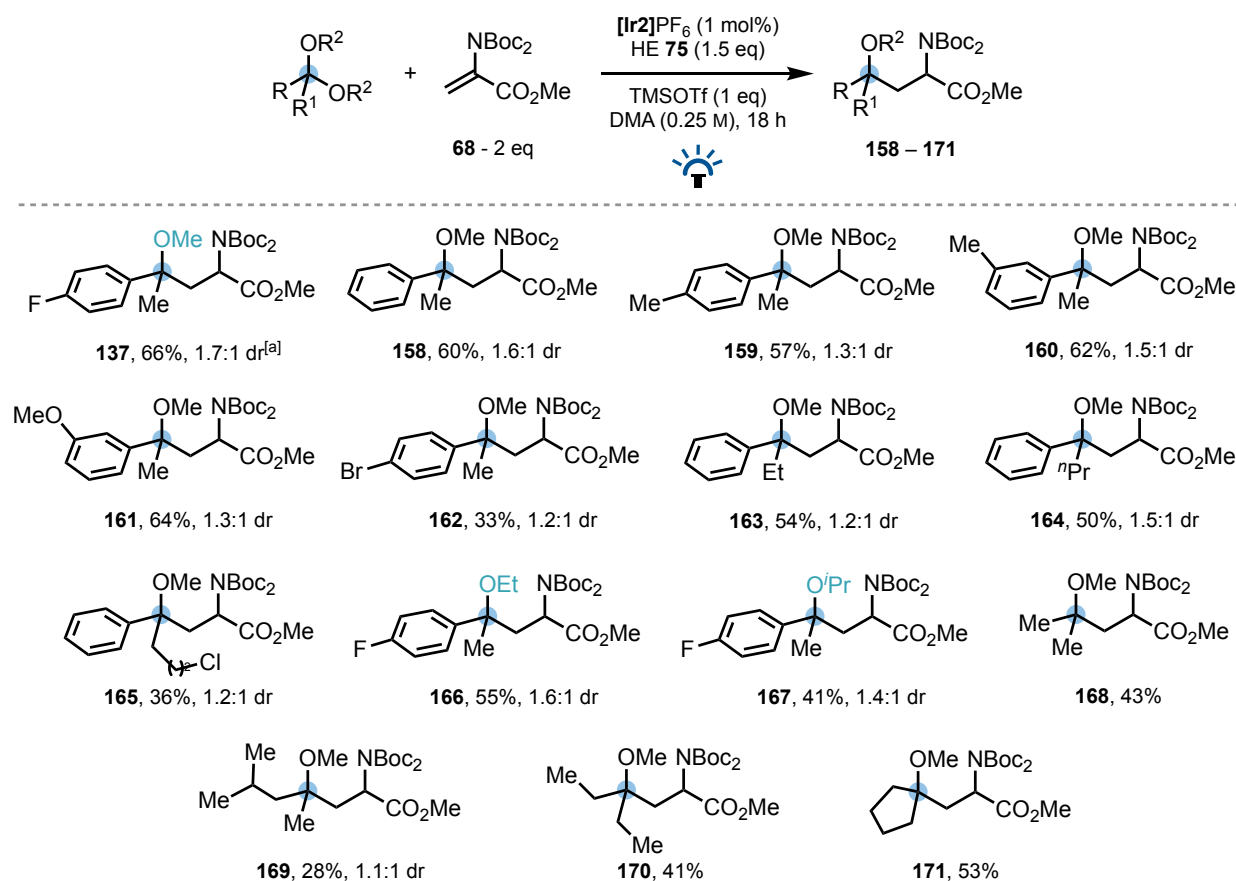
Scheme 50. One-step synthesis of ketals from corresponding ketones.

Considering 4'-fluoroacetophenone-derived ketal **136** as our model substrate, we synthesised a series of ketals with various substitutions on the arene moiety (**145–149**) as well as more hindered substituents at the carbonyl position (**150–152**). Furthermore, variations at the oxygen position were introduced (**153** and **154**) along with the synthesis of all-alkyl ketal substrates (**155–157**).³

³compounds **145–152** and **155–157** were synthesised by B. Ferko, visiting PhD Student and have been included for completeness.

3.5.2 Scope with Respect to the Ketal Component

With optimised reaction conditions established (see Table 5), the scope of the method with respect to the ketal component was studied using dehydroalanine **68** as model coupling partner (Scheme 51).



Scheme 51. Ketal scope of the photocatalytic reductive synthesis of α -tertiary ethers. Combined isolated yields given for major and minor diastereoisomers. ^[a]Reaction time = 5 h.

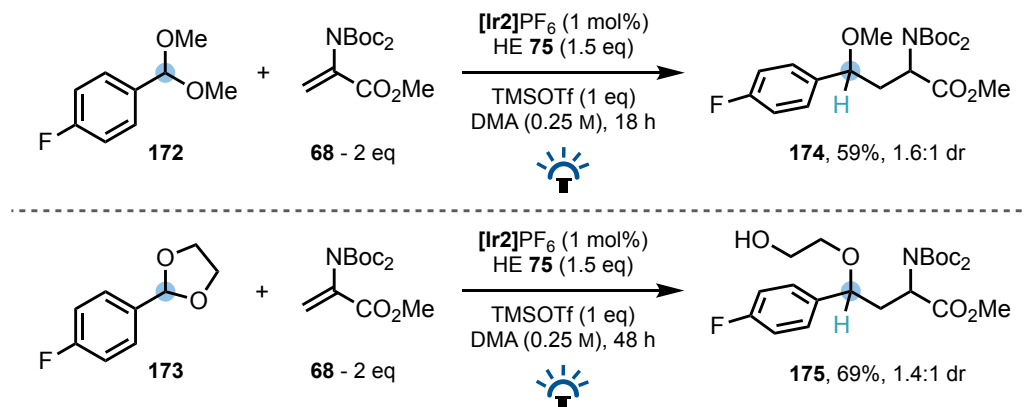
Following optimisation studies which led to the formation of ether adduct **137** in an optimal 66% isolated yield and 1.7:1 dr, substitution around the aromatic ring was initially examined (Scheme 51, **158–162**).⁴ Notably, while the reaction proceeded well with electron-donating functional groups (**159–161**), suppressed reaction efficiency was observed with an electron-withdrawing

⁴although the model substrate showed full conversion after 5 h, reactions for the scope were run overnight to ensure consistency for all starting materials.

group in the *para* position (**162**, 33% yield). More electron-withdrawing substituents – such as the nitro functional group – were not effective in forging the desired C–C bond, supporting the putative nucleophilic character of the *in situ* generated α -alkoxy radical.^[90,96] Despite a small decrease in reactivity consistent with increasing steric demand, efficient reaction outcomes were also obtained with ketals bearing larger alkyl substituents (54% and 50% yield for compounds **163** and **164**, respectively). Pleasingly, ketal **152** with an extended halogen-containing side chain delivered coupled product **165** in 36% and 1.2:1 diastereomeric ratio. Moreover, more sterically hindered ketals **153** and **154** were successfully converted to the corresponding ether adducts **166** and **167** in moderate to good yields (55% and 41%, respectively), improving significant limitations reported by the Doyle group with acyclic acetals.^[130] On the other hand, heterocycle-containing derivatives were not effective under our reaction conditions.^[105] In an attempt to develop a general approach for the construction of α -tertiary all-alkyl ethers, we considered to test ketals of aliphatic ketones as starting materials. At first, commercially available 2,2-dimethoxypropane was subjected to reaction conditions affording methyl ether **168** in 43% yield. Following this promising result, the substrate scope was extended to the aforementioned aliphatic-derived ketals (Scheme 50, **155–157**). While β -branched substrate **155** underwent the reaction to give all-alkyl ether **169** in synthetically useful yield, ketals of α -branched ketones were not reactive under these conditions. However, dimethoxypentane and dimethoxycyclopentane (**156** and **157**) were found to be more competent starting materials for radical generation, affording compounds **170** and **171** after conjugate addition in moderate to good yields (41% and 53%, respectively).⁵ In order to expand the generality of this photocatalytic reductive process, acyclic and cyclic acetals (**172** and **173**) were synthesised and subjected to optimal reaction conditions (Scheme 52). Pleasingly, both substrates underwent the desired radical conjugate addition process furnishing ether adducts **174** and **175** in good yields. Notably, the ethoxy alcohol tether present in compound **175** could serve as a handle to access more elaborate architectures, highlighting the possibility to exploit this method to generate molecular complexity.

⁵compounds **158–165** and **168–171** were synthesised by B. Ferko, visiting PhD Student and have been included for completeness.

Moreover, successful inclusion of acetal substrates showcases the complementarity with previous reports.^[130,132]



Scheme 52. Performance evaluation of acetal substrates for the synthesis of dialkyl ethers. Combined isolated yields given for major and minor diastereoisomers.

3.5.3 Scope with Respect to the Alkene Component

Next, we focussed on the scope of this transformation with respect to the alkene component employing a range of relevant acceptor moieties commonly investigated in photoredox catalysis (Figure 8).⁶

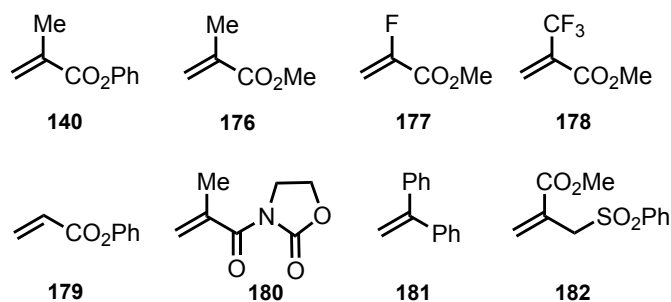
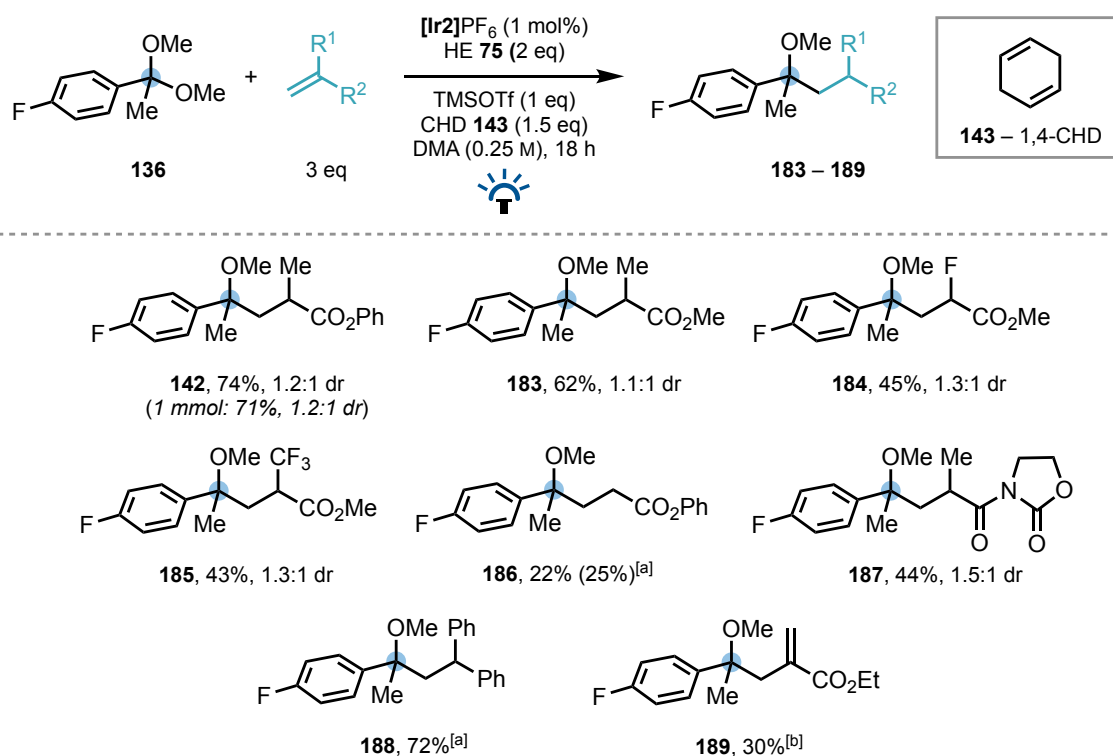


Figure 8. Series of acceptor olefins investigated as non-dehydroalanine coupling partners.

Based on the modified reaction conditions developed for acrylate **140** (see Table 6) and employing ketal **136** as model substrate, we aimed to validate good reaction efficiency with these

⁶similarly to acrylate **140**, coupling partners **176–179** and **181** are commercially available; **180** and **182** were previously synthesised by K. Yamazaki, PhD Student and Dr. J. A. Leitch, respectively.

diversified coupling partners. Initially, the performance of this reaction with phenyl methacrylate **140** on a 1 mmol scale was examined, affording carbon-carbon coupled product **142** with similar reaction efficacy (Scheme 53). Next, we sought to examine the influence of substitution on the acrylate moiety against reaction outcome (**183–187**). While variation at the ester functionality with a methyl group (**176**) gave tertiary methyl adduct **183** in good yield and comparable diastereomeric ratio, changes at the α -position of the acrylate component were found to be a crucial factor, reflecting significantly on reaction efficiency. Incorporation of electron-withdrawing substituents such as fluorine-containing acrylates **177** and **178** resulted in a distinct decrease in reactivity, although providing valuable fluorinated ethers in synthetically useful yields (Scheme 53, **184** and **185**).⁷



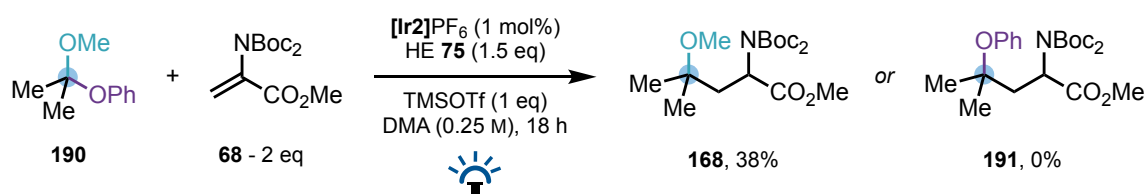
Scheme 53. Reaction scope with respect to the olefin coupling partner. Combined isolated yields given for major and minor diastereoisomers. ^[a]10 eq of coupling partner, ^[b]Reaction performed without 1,4-CHD.

⁷no *gem*-difluoroalkene product was observed under these conditions. ^[132,136]

Contrarily, unsubstituted phenyl acrylate **179** delivered the corresponding adduct **186** in very low yield, even with 10 equivalents of the coupling partner (22% and 25% yield, respectively). Additionally, using acceptor **180** restored reactivity to a moderate level, affording oxazolidinone-derived adduct **187** in 44% yield and 1.5:1 dr. These results illustrate the pivotal role of α -substituents, whereby their mutual electronic properties could directly affect the result of the coupling reaction by a putative key stabilizing captodative effect.^[105] A large excess of electron neutral diphenylethylene (Figure 8, **181**) underwent the anticipated RCA reaction furnishing the corresponding ether adduct in high yield (Scheme 53, **188**). Finally, in spite of a diverse and unique mechanism associated with this type of radical acceptors (see Scheme 19), sulfone derivative **182** was subjected to the reaction conditions to give allyl ether **189** in 30% yield.^[54,55]

3.6 Mechanistic Investigations

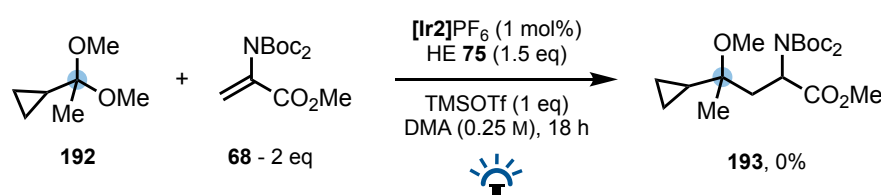
Following the validation of TMSOTf as essential additive towards desired reactivity (see Table 7), the performance of mixed ketal **190** was evaluated to examine the role of the alkoxide functionality and legitimize the proposed activation pathway previously described.^[131] Interestingly, formation of phenyl ether **191** was not observed under our reaction conditions, with exclusive isolation of methyl derivative **168** in 38% yield in analogy to the outcome obtained with dimethoxypropane as starting material (Scheme 54).⁸



Scheme 54. Performance evaluation of mixed ketal substrate **190** investigating the role of the alkoxide functionality.

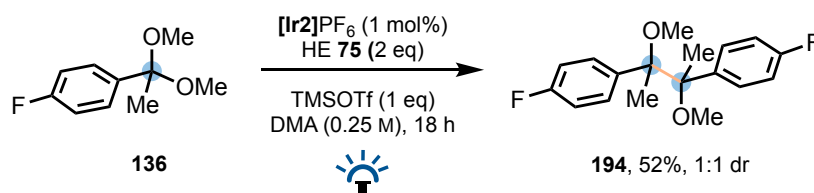
⁸compound **168** was achieved in 43% yield starting from commercially available dimethoxypropane (see Scheme 51)

Regarding the alkoxide functionality, the superior leaving group ability of the phenoxy group compared to the methoxy group would explain the result of this evaluation experiment and support the existence of an oxocarbenium ion intermediate in this transformation. With the goal to substantiate the subsequent single-electron reduction – and thus the *in situ* formation of a key α -alkoxy radical species – we decided to verify the involvement of a radical mechanism with a ring-opening radical-clock experiment; therefore, cyclopropyl ketal **192** was subjected to reaction conditions (Scheme 55).



Scheme 55. Radical-clock experiment with cyclopropyl-derived ketal **192**.

Unfortunately, the attempted experiment failed to provide evidence for the proposed radical pathway as neither coupled product **193** following direct radical conjugate addition nor any adducts attributed to cyclopropane ring-opening could be identified after examination of the resulting complex reaction mixture. Consequently, inspired by the photoredox-catalysed dimerization of aldehydes and ketones via generation of ketyl radical species,^[137] we envisaged the direct photoreduction of a ketal substrate in the absence of an acceptor partner in order to probe our hypothesis. Accordingly, subjection of compound **136** to reaction conditions without further optimisation afforded predicted dimerized aryl methyl ether **194** in 52% isolated yield as a 1:1 mixture of diastereomers (Scheme 56).

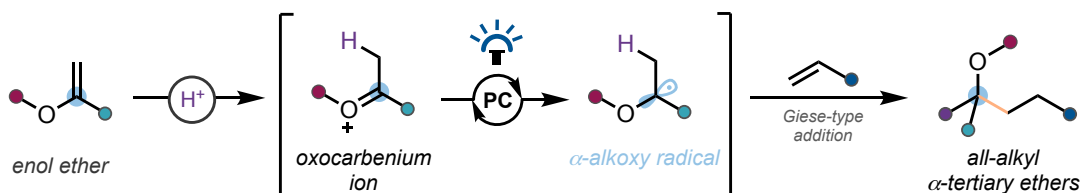


Scheme 56. Photoredox-catalysed reductive coupling of ketal **136**.

In addition to provide a new approach towards the formation of ether pinacol adducts, the obtained result strengthens the assumption of an α -alkoxy radical intermediate via SET as the subsequent radical pinacol-type dimerization to access product **194** would not be achieved through a classic two-electron process. On the basis of these outcomes, two distinct scenarios were considered to propose a plausible reaction mechanism. Regardless of the termination pathway attributed to the structure of the coupling partner, two potential photocatalytic cycles could be foreseen to account for *in situ* generation of the key α -alkoxy radical and the obtained coupled products (Scheme 57 and 58).^[105] In line with our previous study,^[90] we could imagine the **Ir2(II)** species ($E_{1/2}$ (III/II) = -1.37 V vs SCE in CH_3CN), generated via SET from Hantzsch ester reductant **75**, to be capable of reducing oxocarbenium ion intermediate **Iw** ($E_{red}^0 = -0.61$ V vs SCE in CH_3CN calculated for **Iw** derived from ketal **136**) to form the corresponding nucleophilic α -alkoxy radical species **IIw** involved in RCA with an appropriate alkene acceptor (Scheme 57).⁹

⁹reduction and oxidation potentials for Hantzsch ester intermediates and oxocarbenium ion **Iw** were calculated by T. Rogova, PhD Student; reduction potentials for **[Ir2]** species are reported from the literature^[11].

ketals in combination with a range of olefinic coupling partners demonstrates the synthetic utility of this methodology for the construction of congested ether architectures, successful extension to acetal components showcases its complementarity with previous methods. Notwithstanding substantial limitations with respect to heterocyclic-containing compounds as well as reduced efficiency observed with ketals of aliphatic ketones, we consider that the SET reduction of oxocarbenium ions under photocatalytic conditions unlocked in this protocol could open up new avenues in the context of future reaction development. In this regard, considering the initial aim to develop a general strategy for the generation of all-alkyl substituted α -tertiary ethers, we conceptualised that β -protonation of enol ethers and subsequent photoredox-catalysed SER of resulting oxonium intermediates could be leveraged to establish an entry to such broadly inaccessible relevant ether building blocks (Scheme 60).¹¹ Pleasingly, this newly discovered reductive functionalisation strategy was successfully exploited for the synthesis of a wide range of C(sp³)-rich complex ether products, including compatibility with heterocyclic derivatives and dipeptide-derived dehydroalanine analogues.^[119]



Scheme 60. Designed α -functionalisation of enol ethers as a complementary synthetic approach towards α -tertiary dialkyl ethers.

¹¹Design and proof of concept were the fruits of my efforts, while exploration of the majority of the scope was conducted by Dr. J. A. Leitch

Chapter 4

Visible Light-Mediated Synthesis of Fluorinated α -Amino Acid Derivatives

4.1 Chapter Overview

This chapter describes initial investigations towards the design and development of a metal-free radical-based approach for the synthesis of fluorinated amino acids (F-AAs). Mechanistic considerations of previously documented methodologies are firstly discussed to identify prior limitations that prompted research in this field as well as to highlight factors distinguishing this newly developed transformation. Preliminary studies with various radical sources determined higher reaction efficiency with Hantzsch ester radical precursors even in the absence of an exogenous photoredox catalyst. Furthermore, with the intention to develop a stereoselective method, the opportunity was taken to design and explore different strategies for the synthesis of enantioenriched unnatural amino acids (UAAs).

4.2 Introduction

4.2.1 Beyond Proteinogenic Amino Acids

Amino acids (AAs) are widely recognized as one of the most essential classes among natural products for their central role played in both biological and chemical sciences. Besides serving as fundamental building blocks for the construction of peptides and proteins, they are also considered highly versatile elements in synthetic and medicinal chemistry as readily available reagents employed as chiral auxiliaries, ligands, catalysts, or drug precursors in a myriad of useful transformations.^[93,138] The 20 proteinogenic α -AAs constituting essential biomolecules contain, in addition to the α -amino and carboxylate groups, side chains conferring unique characteristics depending on their polar, aromatic, or aliphatic nature. In particular, the signature side chains of canonical amino acids have a crucial role providing interactions to stabilize the three-dimensional peptide or protein conformation, for the recognition and binding of other molecules as well as for their contribution in catalytic processes on enzymes' surface.^[139] The widespread utilization of amino acids across various fields is reflected in an increasing demand for unnatural amino acids (UAAs) exhibiting properties beyond those of proteomic AAs, thus further diversifying and improving the application of these important building blocks.^[140] In fact, nature itself exploits modification of canonical amino acids to modulate their physicochemical properties and impart a precise conformational motif in the final oligopeptide structure. Accordingly, numerous strategies have also been developed by synthetic chemists over the years to access non-canonical amino acids (ncAAs) via *de novo* synthesis or more direct approaches relying on the modification of naturally occurring AAs.^[140,141] The vast majority of well-established AA synthetic methodologies relies on polar disconnection strategies with classic approaches comprising asymmetric Strecker-type reactions, derivatization of glycine and imino ester derivatives with chiral catalysts or auxiliaries, and enantioselective hydrogenation of dehydroamino acids (Figure 9).^[142]

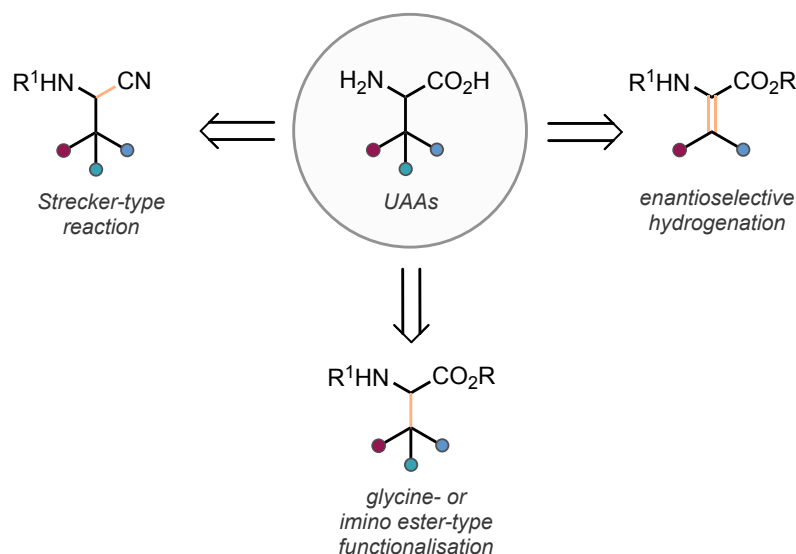


Figure 9. Traditional two-electron approaches towards the synthesis of unnatural α -AAs.

Among UAAs, α,α -disubstituted α -AAs are viewed as a vital subclass for their unique properties emerging from the fully substituted carbon center. As essential motifs of biologically active compounds with improved bioactivity and stability compared to the parent monosubstituted α -amino acids, the conformational rigidity resulting from the quaternary center can be exploited to design specific small molecule interactions as well as to induce defined spatial arrangements. In line with previously mentioned traditional transformations aiming at developing new ways for UAAs, the most frequently employed synthetic methods established over the years to afford α -tertiary amino acids (ATAAs) are also based on two-electron mechanisms that often require additional steps to install essential reactive functionalities or the use of toxic and sensitive reagents which limit the scope and practicality of these protocols.^[143,144] These challenges have thus prompted research into alternative platforms to overcome these limitations as well as to rapidly access a broader range of valuable UAAs.^[140,142]

4.2.2 Relevance of Fluorine Incorporation into Amino Acids

In the context of non-canonical AAs (ncAAs), fluorine-containing amino acids (F-AAs) have recently gained significant interest due to their improved physicochemical properties and bio-

logical activities.^[145,146] As a matter of fact, despite organofluorine compounds represent the least abundant class of all naturally occurring organic halides, the remarkable effects of selective fluorine introduction into organic compounds resulted in a rapid progress of the field, with an increase of around 5% of fluorinated small molecule drugs in the pharmaceutical market over the last decade.^[147–149] Notwithstanding the similar van der Waals (vdW) radius size of the fluorine and hydrogen atoms (1.47 Å vs. 1.2 Å, respectively)^[150], the frequently sought-after H to F exchange encountered in medicinal chemistry can dramatically alter the nature and behaviour of the newly generated compound owing to their drastically different stereoelectronic characteristics. Fluorine is the most electronegative atom in the periodic table and its unique electron-withdrawing property can profoundly affect pK_a values (of neighbouring groups), influencing in turn various parameters such as solubility, lipophilicity, and ADME properties (absorption, distribution, metabolism, and excretion) of the corresponding fluorine-substituted compounds. Fluorine introduction can also provide an enhancement in terms of binding efficiency, with attractive electrostatic interactions resulting in overall improved affinities.^[147,151,152] At the same time, even detrimental replacements with regard to favorable binding interactions can be exploited to gain insightful informations. One such example is the C–OH bond substitution with C–F which has emerged as an important tool to study the role of H-bonding interactions in certain structures due to the ineffective nature of C–F-derived hydrogen bonds.^[152,153] Furthermore, the polarization of the C–F bond is responsible for conformational preferences observed in hydrocarbons.^[147,151,152] A medically relevant example of geometrical changes imparted by F substitution is represented by the incorporation of a trifluoromethyl (CF₃) group in α -position to an amine. In addition to the increased amide character associated with multiple α -fluoride substitutions and similar dipole moments, the bond angle of the CF₃ group with respect to the nitrogen atom is comparable to the 120° angle of a carbonyl group within a peptide bond. For these reasons, despite similar volume sizes of the trifluoromethyl and ethyl groups,^[147] the α -CF₃ amine motif is considered an important bioisostere of the amide functionality with protease-resistant characteristics (Figure 10).^[154]

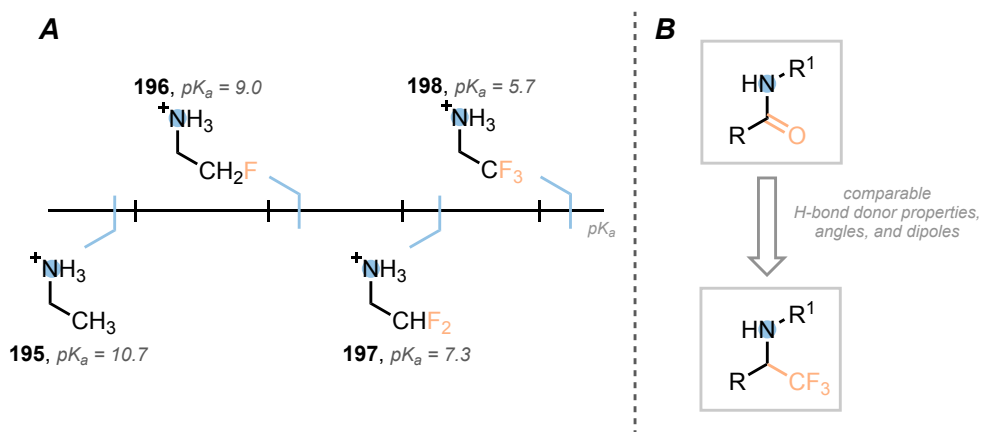
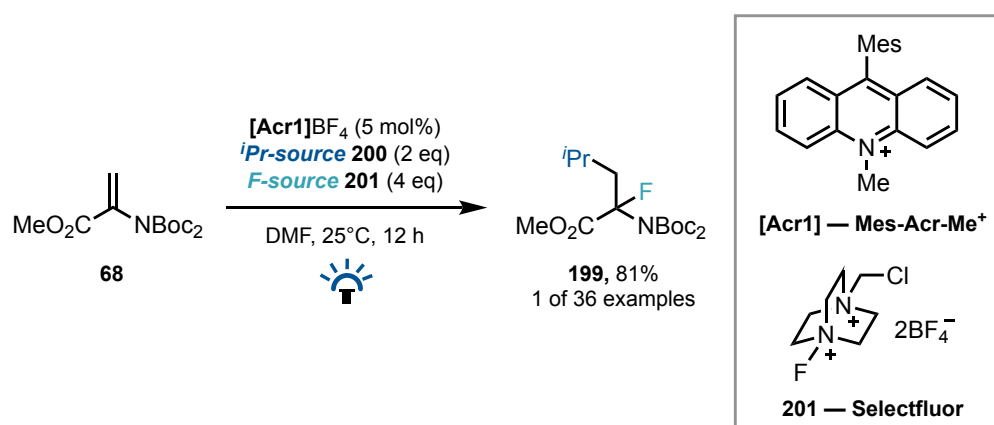


Figure 10. A: Variation of pK_a values of α -fluorinated ammonium ions (195–198). B: Amide surrogate behaviour of α -CF₃ amine moieties.

Following the establishment of fluorine editing as preferred substitution strategy within medicinal chemistry programmes to modulate pharmacokinetic properties of lead compounds, it became clear that replacement of canonical AAs with fluorinated analogues could also be advantageous to improve certain features of peptides and proteins. Additionally, the ever-increasing relevance of peptides as bioactive compounds in drug design further contributed to the rapid advancements observed in the context of fluorine-containing amino acids.^[145,155] Despite impressive developments have recently been made for the construction of F-AAs *via* traditional two-electron transfer chemistry, several challenges remain to be addressed regarding in particular the versatile application of these approaches to achieve general reaction efficiency towards the synthesis of various fluorine derivatives.^[156,157] Owing to the mild reaction conditions and consequent substrate generality, radical-based strategies for the formation of complex unnatural amino acids have gained substantial interest, especially in the last decade with *in situ* generation of open-shell species under photocatalytic conditions.^[140,142] Along with the contribution concerning *de novo* synthesis of (previously inaccessible) UAAs, single-electron strategies have also significantly expanded the methodologies based on direct amino acid modification through derivatisation of individual canonical and non-canonical AAs. In particular, following the free-radical-derived seminal works from Davis and Park demonstrating chemoselective

peptide-compatible C–C bond forming transformations,^[158] a plethora of photocatalytic dehydroalanine derivatisations have been exploited to access a variety of UAAs.^[139,140,159] With respect to fluorinated amino acids, Molander and co-workers developed a photoredox-catalyzed method for the generation of monofluorinated AA derivatives.^[157] Under blue light irradiation with mesityl acridinium organophotocatalyst **Acr1** ($E_{red}^* = +2.06$ V vs SCE in CH₃CN), the authors achieved the incorporation of fluorine into DHA **68** for the synthesis of α -fluoro- α -amino acid **199** employing potassium isopropyltrifluoroborate salt **200** and Selectfluor **201** in stoichiometric amounts as preferred alkyl and fluorine source, respectively (Scheme 61). In addition to the formation of valuable ncAAs with extended alkyl side chains, this protocol illustrates the synthetic utility of photoredox catalysis for the generation of challenging α -fluorinated AA compounds, thus overcoming considerable limitations imposed by two-electron approaches.^[157]



Scheme 61. Radical-based functionalisation of dehydroalanine derivatives by Molander *et al.* Mes = 1,3,5-trimethylbenzene.

4.2.3 Trifluoromethyl-Containing Unnatural Amino Acids

The importance of α -trifluoromethyl (α -Tfm) amine motifs in modulating the properties of drug candidates stimulated the exploration of CF₃-substituted AAs for their potential enhanced chemical and biological features.^[146,154] For instance, the installation of hexafluoroleucine **202**

and trifluoroisoleucine **203** into peptide resulted in reduced degradation towards a series of proteolytic enzymes (Figure 11).^[145]

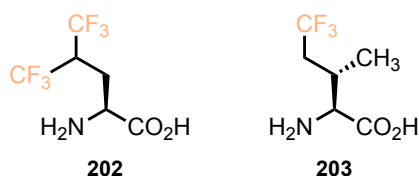


Figure 11. Examples of unnatural Tfm-AA displaying enhanced hydrolytic stability when incorporated within peptide structures.

One particular class of CF_3 -amino acids which received much attention with significant developments towards their synthesis is represented by quaternary $\alpha\text{-CF}_3\text{-}\alpha\text{-AAs}$. In line with the aforementioned traditional two-electron approaches (see Figure 9), the range of catalytic methodologies recently established for *de novo* α -fluoroalkyl- α -AA formation can be categorized into four major bond disconnection strategies: Strecker-type approaches, nucleophilic addition into α -iminoesters, electrophilic alkylation reactions with α -Tfm-aminoesters, and a few reports based on Mannich-type reactions with fluoroenolates (Figure 12).^[156]

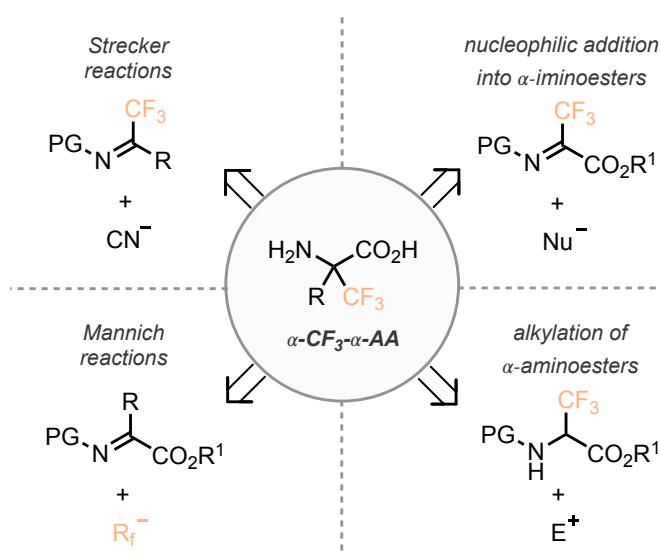
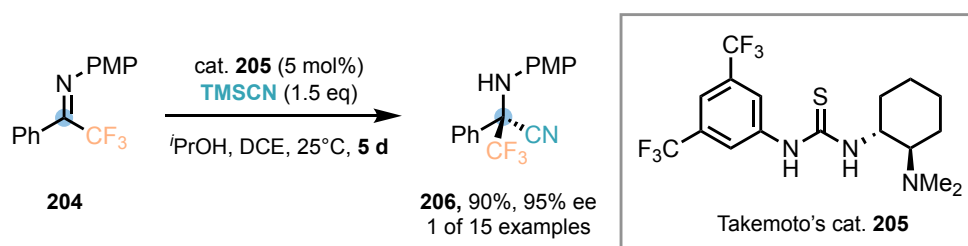


Figure 12. Common catalytic two-electron disconnection approaches to access the $\alpha\text{-CF}_3\text{-}\alpha$ -amino acid framework. PG = protecting group, R_f = fluoroalkyl group.

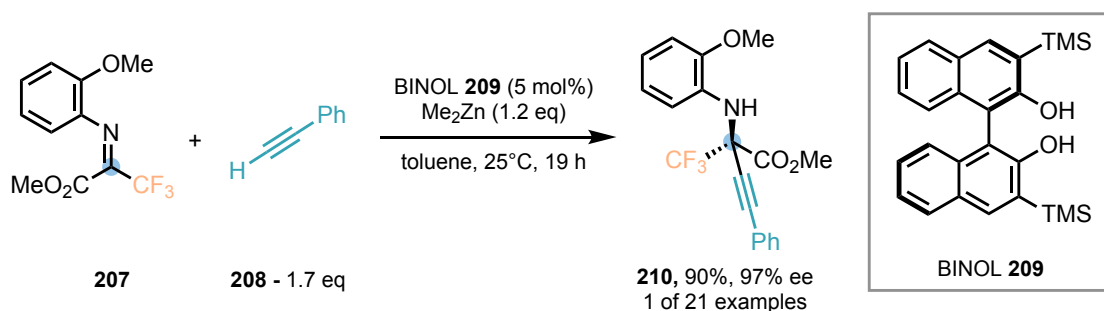
Following extensive research in the context of chiral auxiliary-based stereoselective Strecker reactions,^[154] Enders and co-workers developed the first organocatalytic enantioselective Strecker reaction towards the construction of α -quaternary- α -CF₃-AA derivatives.^[160] The authors realized the enantioselective addition of trimethylsilyl cyanide (TMSCN) to ketimine **204** with thiourea catalyst **205** affording chiral α -amino nitrile **206** with excellent yield and enantiocontrol (Scheme 62). Notwithstanding the fundamental contribution introduced by this organocatalytic protocol, the transformation requires very long reactions times (5–27 days).^[160] Accordingly, many variants have been developed over the years in order to overcome these limitations as well as to improve the general efficiency of enantioselective Strecker-derived methodologies. Despite these efforts establishing the asymmetric Strecker reaction as an attractive tool providing access to α -tertiary Tfm-UAAs, important disadvantages such as multiple-step procedures usually requiring harsh conditions for hydrolysis of the α -amino nitrile intermediates – *e.g.* compound **206**, Scheme 62 – and protecting groups (PGs) removal have to be taken into account when planning a synthetic route.^[154,156]



Scheme 62. Common catalytic two-electron disconnection approaches to access the α -CF₃- α -amino acid framework. PMP = *p*-methoxyphenyl, PG = protecting group, R_f = fluoroalkyl group.

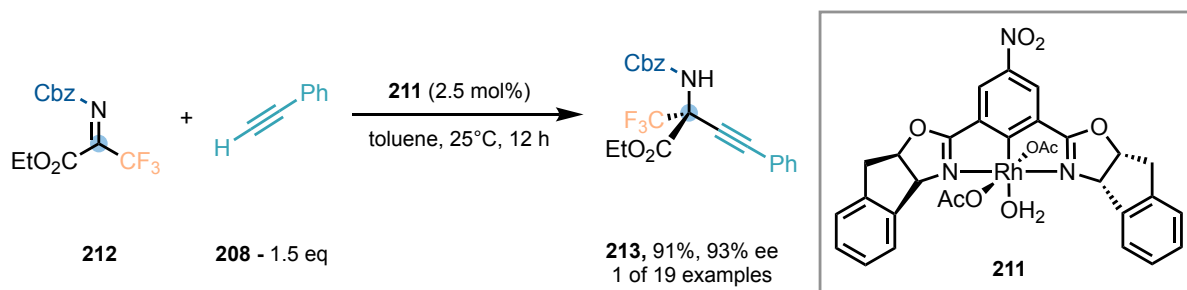
An alternative approach for the synthesis of these valuable α -tertiary amino acid (ATAA) scaffolds is built upon straightforward addition of nucleophiles to fluorinated *N*-protected α -imino esters (AIEs). In 2011, a seminal report by the Zhang group laid the foundations for the construction of tetrasubstituted α -alkynyl α -CF₃ amino esters exploiting the electrophilic nature of AIEs. Subjection of acyclic ketimino ester **207** with stoichiometric amounts of phenylacetylene **208** to a zinc/BINOL **209**-catalysed complex afforded enantioenriched amino ester **210** in 90%

yield (Scheme 63).^[161]



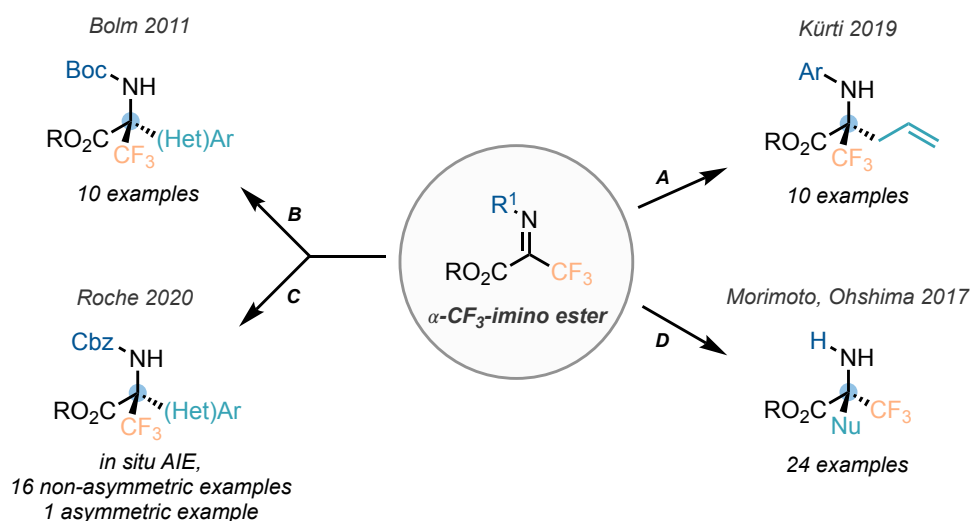
Scheme 63. Enantioselective terminal alkynes addition towards the synthesis of quaternary α -CF₃ UAAs by Zhang *et al.* BINOL = 1,1'-Bi-2-naphthol.

An alternative Rh-Phebox **211**-catalysed alkynylation approach was later reported by Mashima and Ohshima. Notably, this protocol employs benzyloxycarbonyl (Cbz) *N*-protected α -ketiminoester **212** as starting material which is removed under milder conditions from the resulting propargylamine product **213** in comparison to the *N*-aryl substituted ketimines employed by Zhang (Scheme 64).^[162]



Scheme 64. Asymmetric Rh-Phebox-catalysed alkynylation of Cbz-protected α -Tfm imino esters by Mashima and Ohshima. Cbz = benzyloxycarbonyl.

Building on these pioneering two-electron approaches, additional catalytic asymmetric protocols have been developed, mainly expanding the nature of the nucleophilic moieties.^[156] Pioneering methodologies include metal-catalysed allylation reactions (Scheme 65 A),^[163] enantioselective Friedel-Crafts-type transformations with chiral phosphoric acids (B and C),^[143,164] and organocatalysed Mannich-type addition reactions to *N*-unprotected AIEs (Scheme 65 D).^[165]



Scheme 65. Summary of recent asymmetric catalytic two-electron-based methodologies exploiting the electrophilicity of α -CF₃-imino esters. Boc = *tert*-butoxycarbonyl, Nu = enolate-derived nucleophile.

Despite promising results following this direct approach, it seems clear that while nucleophilic addition into α -iminoglycinate derivatives is well-established, only a few relevant stereoselective catalytic transformations are applicable for the generation of quaternary α -Tfm-amino esters from the parent AIEs. In particular, recognizing the absence of such method towards the formation of α -alkyl- α -CF₃-UAAs and the limitations associated with uncatalysed organometallic-based strategies, we considered to investigate this still underexplored territory employing one-electron approaches.^[143,144]

4.3 Initial Considerations and Proof of Concept

Leveraging on the growing interest of radical chemistry for unnatural amino acid synthesis especially in the context of alkyl radicals as preferred nucleophiles to forge new C–C bonds from activated imine derivatives, we considered to exploit the intrinsic electrophilicity of α -CF₃-imino esters *via* alkyl radical addition as a straightforward route to quaternary α -alkyl- α -CF₃-UAAs (Figure 13).^[89,144]

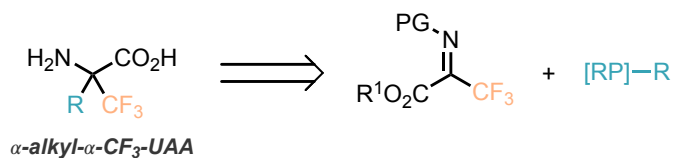
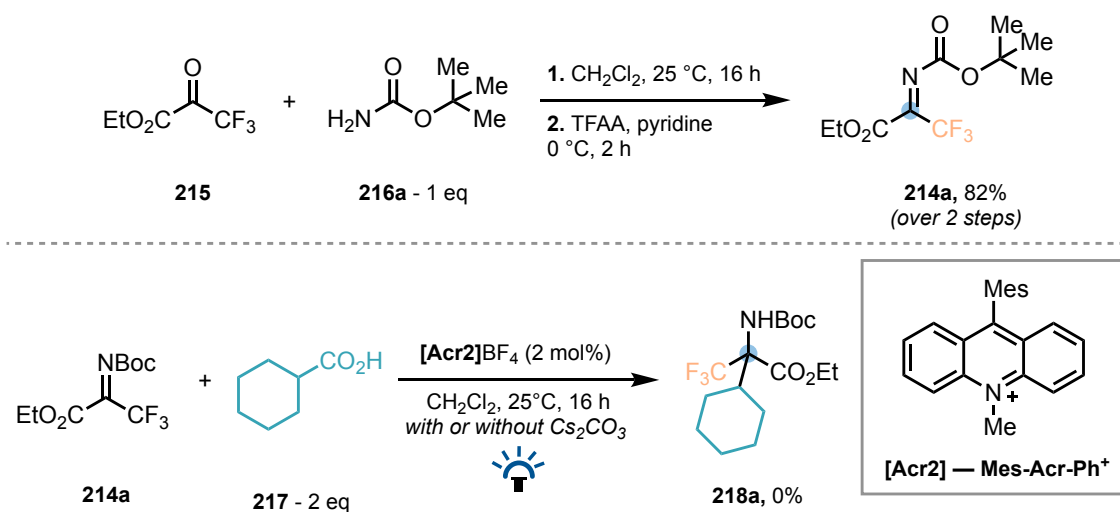


Figure 13. Proposed direct radical addition approach towards the formation of valuable fully substituted α -CF₃- α -AAs. PG = protecting group, RP = radical precursor.

While traditional one-electron strategies relied largely on toxic and harmful radical initiators, the operational simplicity associated with photoredox catalysis ensure high radical reactivity whilst preserving broad functional group tolerance under mild reaction conditions.^[142] Moreover, the renaissance of photoinduced electron transfer reactions resulted in the development of various novel alkyl radical precursors (RPs), including alkyltrifluoroborates, alkylsilicates, and alkyl 1,4-dihydropyridines (DHPs).^[166] Despite this, carboxylic acids were first examined as preferred RPs owing to their ubiquity as versatile and inexpensive alkyl radical sources. Accordingly, following the synthesis of *N*-Boc protected imino ester **214a** by condensing ethyl trifluoropyruvate **215** and carbamate **216a**,^[167] decarboxylative single-electron oxidation of carboxylic acid **217** with mesityl acridinium **Acr2** under blue light irradiation was attempted. Unfortunately, desired product formation was not observed under these reaction conditions, even upon addition of cesium carbonate (Cs₂CO₃) to promote deprotonation (Scheme 66). In fact, control experiments in the absence of base and **Acr2** or light irradiation provided almost exclusive direct addition of the corresponding carboxylate species into AIE **214a**.



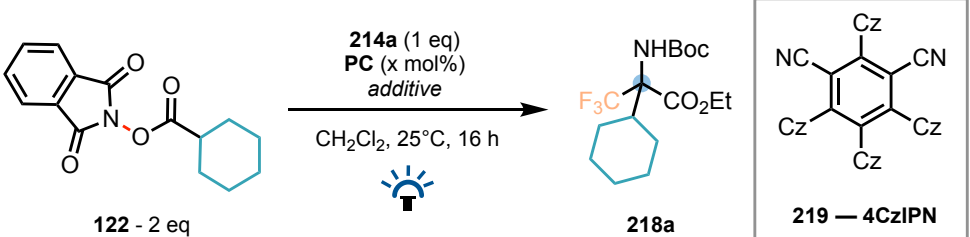
Scheme 66. Attempted visible light-mediated decarboxylative protocol towards UAA **218a**.

Next, building on a former report detailing cyclohexyl radical generation under photocatalytic conditions,^[168] redox-active ester **122** was investigated as viable radical precursor in our system (Table 8).¹² Initial examinations with organophotocatalyst **219** (4CzIPN) with previously successful reductants such as commercial Hantzsch ester (HE) **33** and diisopropylethylamine (DIPEA) were all ineffective to generate coupled product **218a**, providing a complex mixture of unknown products (Table 8, entries 1 and 2). Unfortunately, also a photocatalytic system based on [Ru(bpy)₃]²⁺ (**Ru1**) and combinations of these amine reductants did not afford the desired α -CF₃-amino ester compound (entries 3–5). In light of these unsuccessful results, possibly also due to inefficient radical generation from redox-active ester derivative **122**, our attention was directed towards the implementation of other alkyl radical precursors (RPs). To this end, we reasoned that substituted Hantzsch esters – or 1,4-dihydropyridines (DHPs) – would serve as effective radical-based alkylating reagents.^[169] Indeed, besides being widely employed as terminal reductants with comparable redox properties to amine moieties in photoredox catalysis, 4-alkyl-substituted DHPs represent preferred radical precursors due to their facile synthesis from convenient feedstock chemicals.^[95,157] Furthermore, recent advances in organic photochemical

¹²compound **122** was previously synthesised within the Dixon group and used without further purification.

research demonstrated the potential of HEs to participate in single-electron transfer (SET) events without the need for an exogenous photoredox catalyst.^[170,171]

Table 8. Investigation of RAE derivative **122** as alkyl radical precursor under photocatalytic conditions.

			
entry	PC	additive	218a (%)
1	219 (2 mol%)	HE 33 (1.5 eq)	0
2	219 (2 mol%)	DIPEA (1.3 eq)	0
3	[Ru1](PF ₆) ₂ (1 mol %)	HE 33 (1.5 eq)	0
4	[Ru1](PF ₆) ₂ (1 mol %)	DIPEA (1.3 eq)	0
5	[Ru1](PF ₆) ₂ (1 mol %)	HE 33 (1.5 eq), DIPEA (1.3 eq)	0

PC = photocatalyst, Cz = carbazole, DIPEA = *N,N*-diisopropylethylamine.

Inspired by fruitful utilization of 1,4-DHPs in previous photocatalyst-free synthetic radical-based transformations,^[172–174] we speculated that an electron-rich Hantzsch ester donor (D) and electron-poor acceptor (A) substrate – such as α -CF₃-imino ester **214a** – would associate into a photoactive electron donor–acceptor (EDA) complex. Upon visible light-absorption, the EDA complex would undergo a single-electron transfer (SET) event generating a radical ion pair. The presence of a labile bond within the radical cation DHP substrate would ensure an irreversible fragmentation to give alkyl radical R• responsible for desired coupled product formation, whilst preventing an unproductive back electron transfer (BET) event returning the ground state EDA complex (Figure 14A).^[170,171,175] An alternative mechanism not requiring an

external PC would involve individual irradiation of 1,4-DHP (D) leading to an excited form D^* , which could combine with the acceptor moiety (A) to form an excited complex $D^*(A)$ that is converted to an equivalent radical ion pair *via* SET prior to fragmentation (Figure 14B).^[95,170]

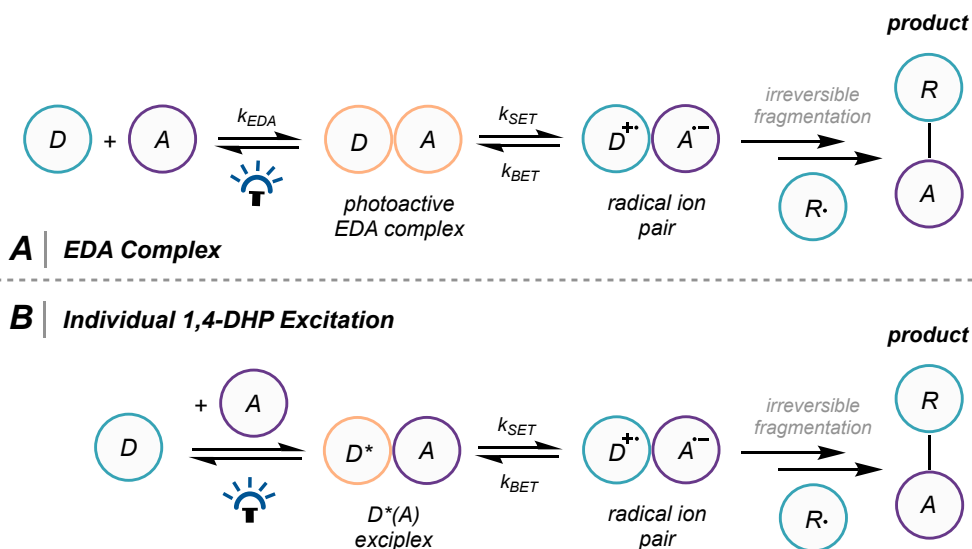
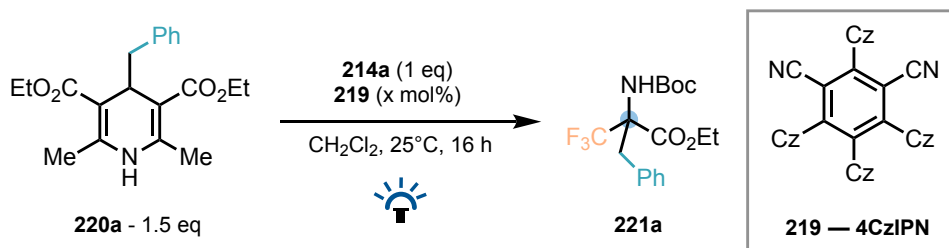


Figure 14. Simplified scenarios towards product formation involving an electron-rich donor (D, 1,4-DHP) and an electron-poor acceptor (A, α -Tfm-imino ester) component without an exogenous photocatalyst.

Along these lines, we decided to test our hypothesis with Hantzsch ester **220a** as benzyl radical precursor for the synthesis of α -Tfm phenylalanine (Phe) derivative **221a** (Table 9). Firstly, we performed the desired radical addition into imino ester **214a** with an excess of radical precursor (RP) **220a** under blue light irradiation and organophotocatalyst **219**. In agreement with a photocatalytic reductive quenching cycle, the Hantzsch ester underwent the expected homolytic cleavage to afford coupled product **221a** in 80% NMR yield (entry 1). Pleasingly, α -Tfm-Phe was also obtained without photocatalyst **219** in the reaction mixture. Despite the lower yield, this result supports the assumption of a potential visible light-induced radical-based mechanism exclusively involving interactions between electron-rich DHP **220a** and electron-poor imino ester **214a** (entry 2). Accordingly, control experiments undoubtedly confirm blue light irradiation as the sole prerequisite to product formation (entries 3 and 4).

Table 9. Proof of concept for the photocatalyst-free synthesis of α -alkyl- α -CF₃ unnatural amino acids.



entry	PC	221a (%) ^[a]
1	219 (2 mol%)	80
2	—	48
3 ^[b]	219 (2 mol%)	0
4 ^[b]	—	0

[a] ¹H NMR yield determined by integration against 1,3,5-trimethoxybenzene (TMB) as internal standard.

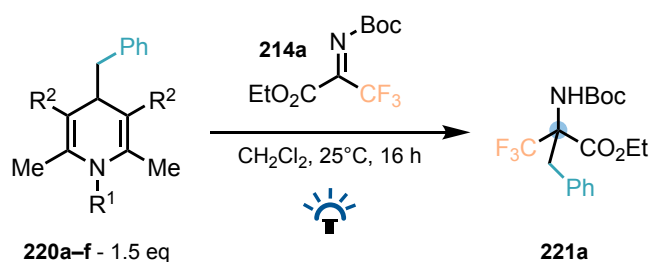
[b] No light irradiation.

4.4 Reaction Optimisation

After confirming desired C–C bond formation in the absence of a photocatalyst, we sought to improve the reaction efficiency of our visible light-mediated system. Initial reaction optimisation studies determined superior reaction outcomes with dichloromethane (CH₂Cl₂) compared to other common organic solvents employed in photoredox catalysis. Moreover, addition of molecular sieves to the reaction mixture was not beneficial under these conditions. Following an unproductive solvent screening, we decided to test the performance of various Hantzsch ester derivatives to improve benzyl-transfer efficiency.^[176,177] To this end, a series of 4-benzyl-substituted dihydropyridines were synthesised to compare reactivity towards UAA **221a** with a variety of ester groups (Table 10). Replacement of the ester moiety with a cyano group (**220b**) resulted in a substantial decrease in reactivity from 48% to 23% yield (entries 1 and 2).

Considering the increased electron-withdrawing properties of nitrile, we decided to proceed our investigation by changing the substituents of the ester functionality not to drastically alter the electronic properties of the donor substrate. DHPs **220c** and **220d** bearing a benzyl (Bn) and a *tert*-butyl (*t*Bu) ester group afforded the trifluoromethyl product with equally lower reaction efficiency (entries 3 and 4). Subsequently, less sterically hindered methyl ester **220e** was found to be the most effective Hantzsch ester in promoting benzyl transfer, affording **221a** in 55% yield (Table 10, entry 5). In contrast, *N*-methyl-substituted DHP **220f** gave the desired outcome in only 17% yield, indicating a potential substrate activation interaction involving the N–H bond of the electron-rich donor component (entry 6).

Table 10. Performance evaluation of a range of 4-benzyl-substituted DHP derivatives.

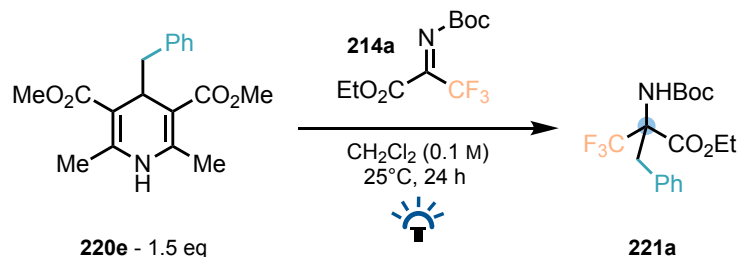


entry	DHP	R ¹	R ²	221a (%) ^[a]
1	220a	H	CO ₂ Et	48
2	220b	H	CN	23
3	220c	H	CO ₂ Bn	38
4	220d	H	CO ₂ ^t Bu	36
5	220e	H	CO ₂ Me	55
6	220f	Me	CO ₂ Me	17

[a] ¹H NMR yield determined by integration against 1,3,5-trimethoxybenzene (TMB) as internal standard.

After ascertaining methyl ester **220e** as most efficient DHP-derived benzyl radical precursor, we focused our attention on other reaction parameters to enhance reaction yield (Table 11). In this context, longer reaction times were beneficial in terms of increased conversion towards α -CF₃-Phe **221a**, although two days were necessary to obtain a very high yield (entries 1 and 2). While the increase of benzyl-substituted DHP equivalents resulted in significantly improved reaction outcomes (entries 3 and 4), improved reaction efficiency was not achieved by increasing reaction concentration (entries 5 and 6). Consequently, and given the availability of the reagents necessary to prepare **220e**, imino ester **214a** was subjected to 3 equivalents of the dihydropyridine-based benzyl radical precursor to deliver product **221a** in an optimal 93% NMR yield (Table 11, entry 7).

Table 11. Investigation of reaction parameters with DHP **220e** as preferred alkylating agent.



entry	deviations from above	221a (%) ^[a]
1	none	57
2	48 h reaction time	87
3	2 eq of 220e	64
4	2.5 eq of 220e	75
5	2 eq of 220e , 0.5 M	75
6	2.5 eq of 220e , 0.5 M	73
7	3 eq of 220e	93 (81) ^[b]

[a] ¹H NMR yield determined by integration against 1,3,5-trimethoxybenzene (TMB) as internal standard.

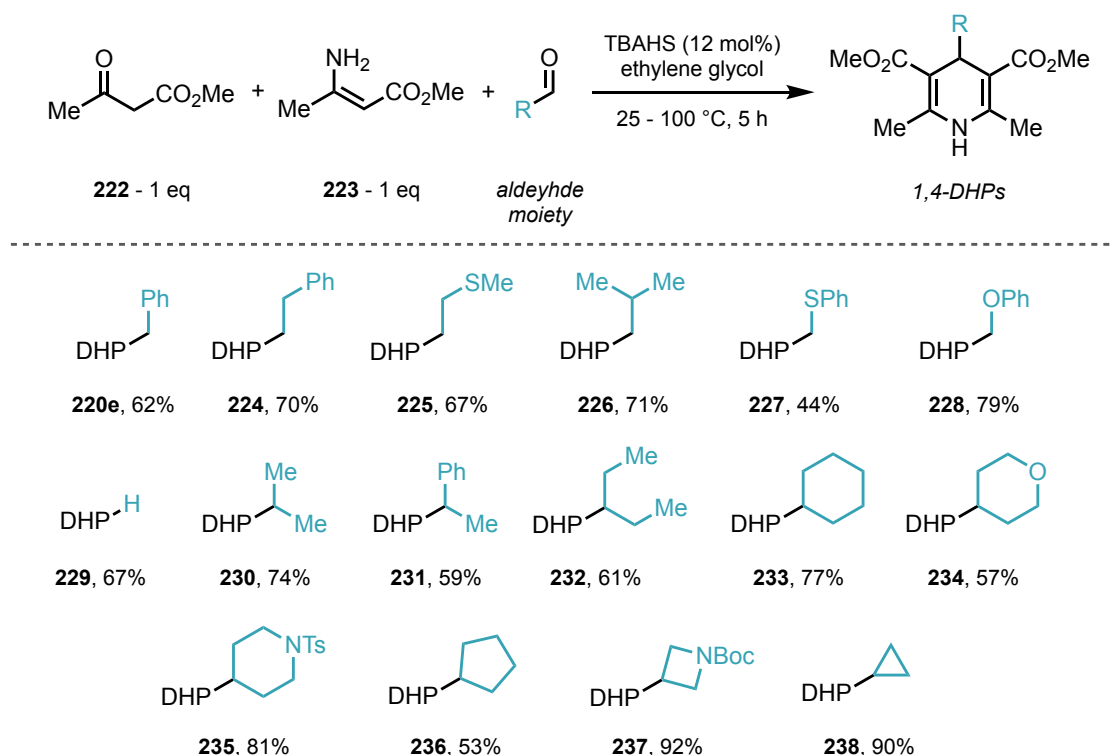
[b] Isolated yield.

4.5 Probing the Scope of Radical Addition to α -CF₃-Imino Esters

4.5.1 Scope with Respect to Non-Stereoselective Alkyl Radical Addition

With optimal reaction conditions in hand, we turned to investigate the scope and limitations of this photocatalyst-free radical transformation. In order to examine radical transfer efficiency of various alkyl groups a range of substituted Hantzsch ester derivatives were easily synthesised in one-step from commercially available methyl acetoacetate **222**, methyl 3-aminocrotonate **223**, and the corresponding aldehyde moiety with yields ranging from 44% to 92% (Scheme

67). With the aim to extend the variation on primary alkyl radicals, current DHP derivatives include substituents with an extended or branched aliphatic chain (**224–226**) as well as with heteroatoms in α -position (**227** and **228**). In addition to unsubstituted HE **229** to examine potential $\text{H}^\bullet$ radical addition, DHPs bearing secondary alkyl groups were also explored (Scheme 67, **230–238**).



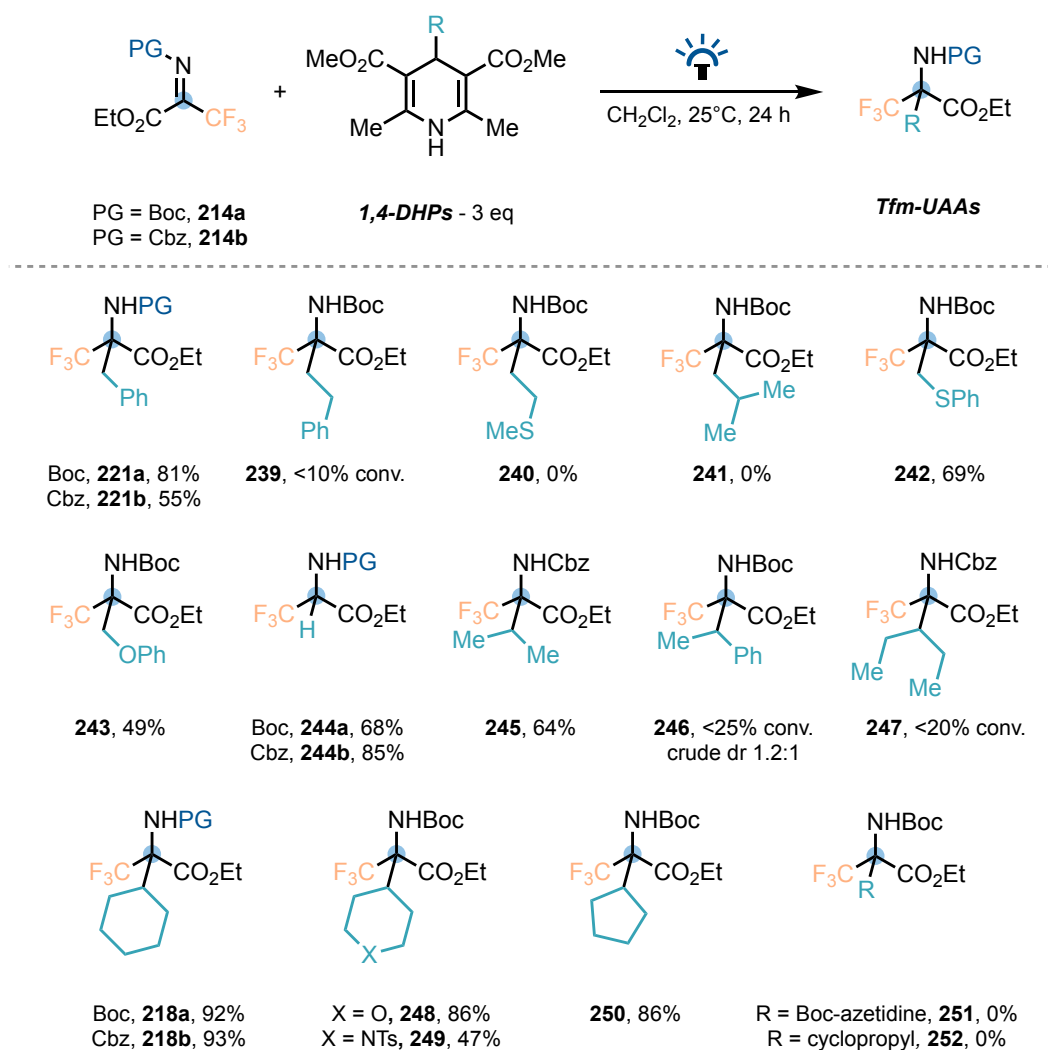
Scheme 67. Three component one-pot procedure for the synthesis of alkyl-substituted DHPs. TBAHS = tetrabutylammonium hydrogensulfate, Ts = tosyl.

To this end, acyclic-based secondary alkyl group derivatives (**230–232**) as well as cyclic DHPs containing heteroatoms (**234** and **235**) or small ring side chains (**237** and **238**) were prepared following the same three component protocol (Scheme 67).¹³

¹³compounds **228** and **234** were synthesised by J. A. P. Maitland, PhD Student and have been included for completeness.

Building on optimisation studies with α -Tfm-imino ester **214a**, the scope of this visible light-mediated procedure with respect to the DHPs as radical precursors was also investigated with *N*-Cbz imino ester **214b** (Scheme 68). In the case of model substrate **220e**, benzyl radical addition into **214b** afforded the corresponding Cbz-protected α -CF₃-UAA in moderate yield compared to the Boc-protected substrate (Scheme 68, **221a** and **221b**). Unfortunately, attempts towards addition of primary alkyl radicals other than benzyl did not provide the desired outcomes (**239–241**). Notably, DHP **224** with an extra methylene bridge to the model substrate, only provided very low conversion to product **239** without formation of any benzyl-rearranged product. In light of these results, we speculate that the stability of these *in situ* generated open-shell species is not sufficient to ensure productive addition into α -Tfm-imino esters. Contrarily, stabilized primary alkyl radicals formed next to heteroatom moieties delivered the expected coupled products in moderate to good yields (Scheme 68, **242** and **243**). Although additional experiments should be performed to exclude hydride-derived nucleophilic addition, good reactivity towards both *N*-protected CF₃ Alanine derivatives was observed when subjecting unsubstituted DHP **229** to our reaction conditions (**244a** and **244b**). Next, we sought to test the performance of DHPs in transferring secondary alkyl open-shell species into α -CF₃-imino esters. While isopropyl-derived radical from **230** granted access to α -Tfm Valine **245** in 64% yield, poor conversion was detected with more sterically demanding branched aliphatic chains (Scheme 68, **246** and **247**). On the other hand, cyclic secondary alkyl radicals were found to be particularly effective under these reaction conditions. Notably, and in contrast to our previously attempted strategies, photoinduced fragmentation of DHP **233** gave *N*-Boc and Cbz-protected cyclohexyl unnatural amino acids **218a** and **218b** in excellent yields. Incorporation of a heteroatom into the six-membered ring resulted in efficient radical addition reactions, affording heterocyclic-containing α -Tfm-AAs **248** and **249** in 86% and 47% yield, respectively. Moreover, cyclopentane substitution was tolerated forming unnatural amino acid **250** in very good yield. Unfortunately, open-shell species derived from smaller 4- and 3-membered rings were not viable under our reaction conditions, whereby cyclopropyl and *N*-Boc-azetidine radicals did not

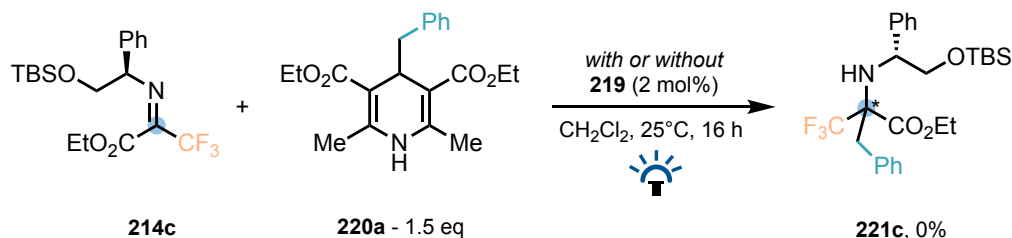
afford the corresponding unnatural AAs even in the presence of 4CzIPN **219** as photocatalyst (Scheme 68, **251** and **252**). Actually, poor conversion of the substituted DHP reagents was observed by TLC after 24 h in both cases, suggesting unfavored radical fragmentation with these substituents. Moreover, regarding cyclopropyl-DHP **238**, increased conversion to reduced product **244a** instead of the expected alkyl-substituted **252** was detected after 48 h (Scheme 68).



Scheme 68. Scope with respect to alkyl radical addition from substituted-dihydropyridine compounds.

4.5.2 Studies towards a Stereoselective Alkyl Radical Addition Approach

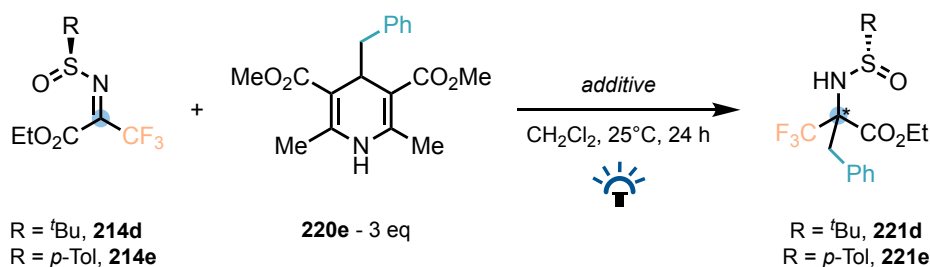
Taking into consideration the reduced Lewis basicity of *N*-protected α -imino esters **214** leading to inadequate activation by Lewis and Brønsted acid catalysts,^[143] chiral auxiliary-based approaches were favored in an attempt to develop a stereoselective alkyl radical addition protocol in parallel to the racemic scope. Initially, reactivity of phenylglycinol-based imino ester **214c** towards radical addition with stoichiometric amounts of benzyl precursor **220a** was investigated. Disappointingly, no conversion of starting material **214c** was observed under these reaction conditions (Scheme 69).



Scheme 69. Attempted benzyl radical addition into α -Tfm-imino esters bearing a phenylglycinol-derived chiral auxiliary. TBS = *tert*-butyldimethylsilyl.

Next, inspired by successful catalytic precedents in the context of diastereoselective radical alkylation to chiral sulfinyl imines, radical addition into *N*-sulfinyl α - CF_3 -imino ester **214d** and **214e** was envisaged.^[178–180] Following optimisation studies with respect to non-stereoselective radical addition, sulfinimines **214d** and **214e** were subjected to reaction conditions with **220e** as preferred radical precursor (Table 12). *tert*-Butyl-substituted *N*-sulfinyl imino ester **214d** failed to deliver radical addition product **221d**, whereby a complex crude reaction mixture was obtained instead (entry 1). Supposing a radical addition mechanism into the electrophilic carbon–nitrogen double bond, the resulting N-centred azanyl radical could undergo decomposition to generate a more stable *tert*-butyl radical along with an iminosulfanone intermediate, thus hindering desired product formation.^[180,181] Unfortunately, and in stark contrast to previous reports,^[178–180] even *para*-tolyl *N*-sulfinyl imino ester **214e** was found to be a very inefficient radical acceptor in this transformation (Table 12, entries 2 and 3).

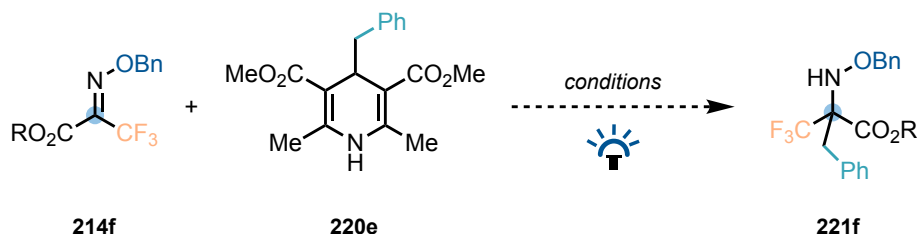
Table 12. Investigation of radical alkylation to α -CF₃-imino esters with *N*-sulfinyl-derived chiral auxiliaries.



entry	imino ester	additive	product (%)
1	214d	—	0
2	214e	—	trace
3	214e	[Ir2]PF ₆ (1 mol%)	0

^tBu = *tert*-butyl, *p*-Tol = *para*-tolyl

In light of these results, we sought to incorporate a stabilizing element within the α -Tfm-imino ester acceptor moiety in order to prevent decomposition of a putative radical intermediate following alkyl addition. To this end, we envisage the use of benzyl oxime compound **214f** as a promising radical addition approach towards unnatural α -CF₃-AA **221f** owing to the stabilizing effect furnished by the lone pair on the oxygen atom (Scheme 70). Furthermore, the ester moiety in **214f** could be exploited to introduce a chiral auxiliary for the synthesis of valuable enantioenriched α -alkyl- α -CF₃ AAs.^[182]



Scheme 70. Planned future approach towards stereoselective alkyl radical addition.

4.6 Conclusion

In conclusion, our efforts towards a novel photocatalytic approach for the formation of α -Tfm unnatural amino acids led to the identification of a photocatalyst-free methodology exploiting direct addition of *in situ* generated alkyl radical species from readily available 1,4-dihydropyridines. Despite the limitations discovered during the current scope with various alkyl substituents, we believe that with additional improvements, especially in the context of non-stabilized primary alkyl addition exploiting different strategies, the chemistry established within this project should be of interest to the synthetic community due to the ever-increasing importance of non-proteinogenic amino acids. Furthermore, promising preliminary reaction outcomes were obtained with a newly designed oxime ether-derived substrate aimed at expanding this methodology towards the construction of enantioenriched UAAs.¹⁴

4.7 Closing Remarks

Over the course of this DPhil, we were able to exploit visible light-mediated photoredox catalysis as a unique approach to generate free-radical intermediates enabling new sites of reactivity for the construction of complex organic molecules. Chapter 2 demonstrated the ability to access, under mild reaction conditions, key nucleophilic α -amino radical species which can engage in radical conjugate addition reactions with a dehydroalanine coupling partner to form valuable amine-containing products. In particular, this newly developed transformation offers a novel synthetic approach to access 1,3-diamine compounds in one-pot from commercially available starting materials. Chapter 3 described our investigation into the development of a complementary new synthetic methodology for the construction of challenging ether architectures. Inspired by our investigations on imine umpolung chemistry through photocatalytic single-electron transfer, the concept was successfully expanded to incorporate other common functional groups such as ketals and acetals to form α -tertiary dialkyl ethers *via* an unprecedented visible light-mediated

¹⁴while the design of this approach was the fruit of my efforts, J. A. P. Maitland, PhD Student performed preliminary reactions for proof of principle.

reduction of *in situ* generated oxocarbenium ions. Chapter 4 presented the efforts made with the aim to establish a novel photocatalyst-free radical approach for the generation of important α -alkyl- α -CF₃ unnatural amino acid derivatives. Initial studies determined the utility of 1,4-dihydropyridines as a means to efficiently provide alkyl radical species which can be manipulated to directly functionalise readily available α -Tfm-imino esters. In addition, considerations towards the development of a diastereoselective approach were also presented in this chapter.

Chapter 5

Experimental Part

5.1 General Experimental Details

General Techniques: Reactions were carried out under a N₂ atmosphere unless stated otherwise. Room temperature refers to 22 ± 2 °C. Inert atmosphere techniques, such as Schlenk technique, were used for the handling of air/moisture sensitive reagents. Reactions carried out at 0 °C were cooled using an ice bath, those at −10/−15 °C were cooled using a mixture of ice and NaCl, and those at −78 °C were carried out using a solid CO₂/acetone bath. Reactions carried out at high temperatures were heated using an oil bath or, preferably, using DrySyn[®] heating blocks. Reaction temperatures refer to external temperatures, for example of a heating block or oil bath, not of internal reaction temperatures unless stated otherwise.

Photoreactor Set-Up: Hepatochem EvoluChem[™] PhotoRedOx Duo, equipped with two EvoluChem[™] LED 18W lights. A cardboard cover was placed over the reactor during reactions. Capable of carrying out up to 16 reactions at one time (2, 4, or 8 mL vials).

Nomenclature: Compounds are named following IUPAC nomenclature as generated by ACD LABS or ChemDraw.

Reagents and solvents were purchased at reagent-grade from Acros Organics, Sigma-Aldrich, Fluka, TCI Chemicals, Alfa Aesar, STREM, and Fluorochem and used without further purification unless otherwise stated. Solvents for extraction or column chromatography were of technical quality. All water used was purified via a Merck Millipore reverse osmosis purification system prior to use. All reactions were performed under N₂ atmosphere if not stated otherwise. Anhydrous dimethyl sulfoxide (DMSO) and dimethylacetamide (DMA) were used as supplied (Acros Organics). Anhydrous solvents (tetrahydrofuran, toluene, dichloromethane, and diethyl ether) were dried by filtration through activated alumina (Sigma-Aldrich, 58 Å pore size, powder 150 mesh, basic) columns and stored under N₂ atmosphere prior to use. Solvents were removed under reduced pressure using Büchi Rotavapor apparatus.

Thin-layer chromatography (TLC) was performed on SiO₂-60 UV₂₅₄ coated aluminum sheets from Merck (silica gel 60 F254). Visualisation was achieved with a UV lamp at a wavelength of 254 nm, with a KMnO₄ solution, or a Vanillin stain solution.

Flash column chromatography (FC) was carried out on silica gel 60 (VWR, 40-63 µm). Solvents for extraction and chromatography were of technical quality. Solvent mixtures are individually reported in parenthesis.

Proton, Carbon, and Fluorine nuclear magnetic resonance (¹H, ¹³C, ¹⁹F, and ¹⁹F {¹H} NMR) spectra were recorded on Bruker 400 MHz (¹H NMR at 400 MHz, ¹³C NMR at 101 MHz, and ¹⁹F NMR at 377 MHz) or Bruker 500 MHz (¹H NMR at 500 MHz, ¹³C NMR at 126 MHz). Chemical shifts (δ) are given in ppm in descending order and reported as follows: multiplicity (s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (dou-

plet of triplets), and m (multiplet)), coupling constants (J) in Hz, number of equivalent nuclei by integration; suggested assignment. Additionally, peaks may be described as broad (br), or apparent (app). The residual deuterated solvent was used as internal standard (*e.g.* CDCl₃: δ_H = 7.26 ppm, δ_C = 77.16 ppm). COSY, HSQC, HMBC, and NOESY experiments were used for ¹H and ¹³C NMR signals assignment where required.

Melting points (m.p.) were determined with a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degree Celsius (°C).

Infrared (IR) spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Selected absorption bands are reported in wave numbers (cm⁻¹) with relative signal intensities described as s (strong), m (medium), or w (weak). When applicable, peak shape characterized by br (broad) or sh (shoulder).

High-resolution mass spectrometry (HR-MS) was performed by the MS service of the Chemistry Research Laboratory. Spectra were measured on a Bruker Daltonics MicroTOF spectrometer (ESI). The molecular ion (M^+) is reported in m/z units with relative signal intensities given in brackets.

X-Ray Crystallography: Single crystal X-Ray diffraction data were collected using an Enraf-Nonius KCCD diffractometer or an Oxford Diffraction SuperNova diffractometer at 150 K. Crystal structures were solved with SIR92 and refined with CRYSTALS by Dr. Heyao Shi (University of Oxford) with assistance and guidance from Dr. Amber L. Thompson and Dr. Kirsten E. Christensen (University of Oxford Chemical Crystallography department).

Synthesis of Known Compounds: The synthesis of compounds previously reported in the literature are labelled as such. References are given for experimental procedures and data.

Details for experimental procedures are provided where relevant, however ^1H and ^{13}C NMR data is only included where relevant, unless the compound is used without further purification in the next step.

5.2 Experimental Details for Chapter 2

5.2.1 General Procedure A: Preformed Imine Substrates

A solution of relevant aldehyde (1 eq) and aniline (1.1 eq) in CH_2Cl_2 (0.25 M) under N_2 atmosphere was treated with MgSO_4 (4 eq.) at $25\text{ }^\circ\text{C}$ and stirred at the same temperature for 18 h. The reaction was filtered and the filtrate was concentrated under reduced pressure. The compounds were used crude as ^1H NMR showed >95% purity.

5.2.2 General Procedure B: Reaction Optimisation

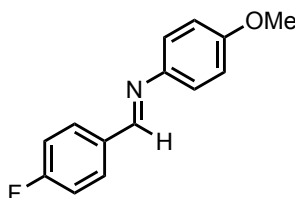
To a 1.6 mL glass vial equipped with a microstirrer, was charged relevant aldehyde (or imine) (0.2 mmol, 1 eq), relevant aniline (0.2 mmol, 1 eq), coupling partner **68** (0.4 mmol, 2 eq), relevant Hantzsch ester (0.3 mmol, 1.5 eq), photocatalyst (0.002 mmol, 1 mol%), and dissolved in reaction solvent of choice (1 mL, 0.2 M). Nitrogen was then bubbled through the stirred solution for 5 minutes. The vial was then sealed and then irradiated with blue light while stirring for 24 h. The reaction mixture was then diluted in EtOAc (20 mL), H_2O (10 mL) and brine (10 mL), the organic phase extracted and the aqueous phase re-extracted with EtOAc (2x 20 mL). The combined organic phases were dried over MgSO_4 , filtered, and concentrated under reduced pressure. An aliquot from the crude residue was dissolved in CDCl_3 to determine diastereomeric ratio (dr) and NMR yield based by direct conversion between starting material and desired product mixture.

5.2.3 General Procedure C: Synthesis of 1,3-Diamine Compounds

To a 1.6 mL glass vial equipped with a microstirrer, was charged relevant aldehyde (or imine) (0.2 mmol, 1 eq), relevant aniline (0.2 mmol, 1 eq), coupling partner **68** (0.4 mmol, 2 eq), diethyl 4- phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate HE **75** (99 mg, 0.3 mmol, 1.5 eq), and [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (**[Ir2]**PF₆, 2.24 mg, 0.002 mmol, 1 mol%). To the vial were sequentially added anhydrous DMSO (0.4 mL) and dry MeOH (0.6 mL). Nitrogen was then bubbled through the stirred solution for 5 minutes. The vial was then sealed and then irradiated with blue light while stirring for 24 h. The reaction mixture was then diluted in EtOAc (20 mL), H₂O (10 mL) and brine (10 mL), the organic phase extracted and the aqueous phase re-extracted with EtOAc (2x 20 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. Prior to purification by flash column chromatography (see individual experiments), an aliquot from the crude residue was dissolved in CDCl₃ to determine the diastereomeric ratio.

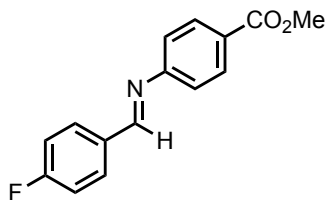
5.2.4 Synthesis of Substrates

1-(4-fluorophenyl)-*N*-(4-methoxyphenyl)methanimine (**67**)



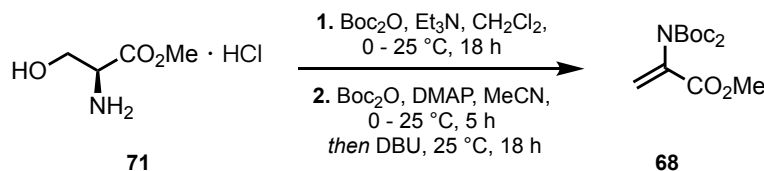
The above compound was prepared according to General Procedure **A** using 4-fluorobenzaldehyde (1.07 mL, 10 mmol) and *p*-anisidine (1.35 g, 11 mmol). Crude grey solid aldimine residue was used for the next reaction without further purification as >95% purity was confirmed via ¹H NMR. NMR Spectra and physical properties matched those from reported literature.^[183]

methyl-4-((4-fluorobenzylidene)amino)benzoate (67a)



The above compound was prepared according to General Procedure **A** using 4-fluorobenzaldehyde (1.07 mL, 10 mmol) and methyl 4-aminobenzoate (1.66 g, 11 mmol). Crude off-white solid aldimine was used without further purification as >95% purity was confirmed *via* ^1H NMR (2.11 g, 82%). ^1H NMR (400 MHz, CDCl_3): δ = 8.38 (s, 1 H), 8.11–8.03 (m, 2 H), 7.95–7.85 (m, 2 H), 7.24–7.15 (m, 4 H), 3.91 ppm (s, 3H); ^{13}F NMR (377 MHz, CDCl_3): δ = –107.06 ppm (ddd, J = 14.1, 8.5, 5.5 Hz); ^{13}C NMR (101 MHz, CDCl_3): δ = 166.9, 165.1 (d, J = 253.5 Hz), 160.2, 156.1, 131.2 (d, J = 8.8 Hz), 131.0, 120.8, 116.2 (d, J = 22.1 Hz), 113.9, 52.2 ppm.

methyl 2-(bis(*tert*-butoxycarbonyl)amino)acrylate (68)



A solution of L-serine methyl ester hydrochloride **71** (5 g, 32.1 mmol, 1 eq) in CH_2Cl_2 (33 mL) under N_2 atmosphere was treated by dropwise addition of Et_3N (9.86 mL, 70.7 mmol, 2.2 eq) and di-*tert*-butyl dicarbonate (8.1 mL, 35.4 mmol, 1.1 eq) at 0 °C. The resulting white suspension was warmed up to 25 °C and stirred for 18 h. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc, washed with 1M aq. HCl solution, aq. sat. NaHCO_3 , and brine. The organic phase was dried over MgSO_4 , filtered and concentrated to afford a colourless oil. The resulting crude **Boc-Ser-OMe** intermediate was directly used for the next

Data of ***syn-72a***:

¹H NMR (400 MHz, CDCl₃): δ = 7.36 (dd, J = 8.6, 5.4 Hz, 2 H; ArH), 7.00 (d, J = 8.7 Hz, 2 H; ArH), 6.68 (d, J = 8.9 Hz, 2 H; ArH), 6.46 (d, J = 9.0 Hz, 2 H; ArH), 4.99 (d, J = 2.1 Hz, 1 H; CHCO₂CH₃), 4.47 (dd, J = 9.0, 4.6 Hz, 1 H; CHNH), 3.72 (s, 3 H; CO₂CH₃), 3.69 (s, 3 H; OCH₃), 2.77 (ddd, J = 14.5, 7.2, 4.6 Hz, 1 H; CH₂), 2.01 (ddd, J = 14.5, 9.0, 5.2 Hz, 1 H; CH₂), 1.48 ppm (s, 18 H; (C(CH₃)₃)₂); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = -116.06 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 171.3 (CO₂CH₃), 162.03 (d, J = 244.7 Hz; C-F), 152.3 (NC=O), 152.2 (ArC), 141.6 (ArC), 139.4 (d, J = 3.1 Hz; ArC), 128.0 (d, J = 8.0 Hz; ArCH), 115.6 (d, J = 21.4 Hz; ArCH), 114.9 (ArCH), 114.7 (ArCH), 83.7 (CO₂C(CH₃)₃), 56.4 (CHNH), 56.0 (CHCO₂CH₃), 55.9 (OCH₃), 52.5 (CO₂CH₃), 40.9 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3381 (w, N-H), 2981 (m), 2932 (m), 1746 (s, NC=O), 1698 (s, OC=O), 1511 (s); **HRMS** (ESI): m/z = 533.26563 ([M+H]⁺, calcd. for C₂₈H₃₈O₇N₂F⁺: 533.26576).

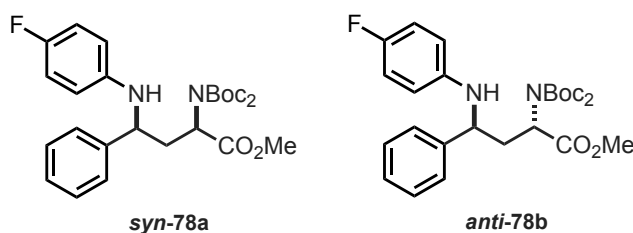
Data of ***anti-72b***:

m.p. = 147 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 7.31–7.26 (m, 2 H; ArH), 6.98 (t, J = 8.7 Hz, 2 H; ArH), 6.66 (d, J = 8.9 Hz, 2 H; ArH), 6.44 (d, J = 8.9 Hz, 2 H; ArH), 5.13 (dd, J = 7.7, 5.3 Hz, 1 H; CHCO₂CH₃), 4.36 (dd, J = 10.3, 4.0 Hz, 1 H; CHNH), 3.73 (s, 3 H; CO₂CH₃), 3.68 (s, 3 H; OCH₃), 2.65–2.54 (m, 1 H; CH₂), 2.24 (ddd, J = 14.9, 7.7, 4.1 Hz, 1 H; CH₂), 1.43 ppm (s, 18 H; (C(CH₃)₃)₂); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = -115.93 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 171.9 (CO₂CH₃), 162.02 (d, J = 244.8 Hz; C-F), 152.26 (NC=O), 152.1 (ArC), 141.1 (ArC), 139.4 (ArC), 127.9 (d, J = 8.0 Hz; ArCH), 115.7 (d, J = 21.4 Hz; ArCH), 114.9 (ArCH), 114.9 (ArCH), 83.6 (CO₂C(CH₃)₃), 56.3 (CHCO₂CH₃), 56.2 (CHNH), 55.9 (OCH₃), 52.6 (CO₂CH₃), 40.1 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3395 (w, N-H), 2980 (br), 1741 (s, NC=O), 1699 (s, OC=O), 1511 (s); **HRMS**

(ESI): $m/z = 533.26550$ ($[M+H]^+$, calcd. for $C_{28}H_{38}O_7N_2F^+$: 533.26576).

Scale up: reaction performed on a 1 mmol scale without further modifications gave **72a** (94.6 mg, 18%) as yellow oil, a mixture of **72a** and **72b** (122.9 mg, 23%) as yellow oil, and **72b** (293.39 mg, 55%) as off-white solid (**72**: 96% total isolated yield, crude dr 3.8:1).

Synthesis of compound **78**



Compound **78** was synthesised according to General Procedure **C** using benzaldehyde (0.02 mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 3.2:1. FC (SiO_2 ; pentane/acetone 95:5 to 90:10) gave **78a** (20.2 mg, 20%) as off-white solid and **78a** (51.3 mg, 51%) as off-white solid (**78**: 71% total isolated yield).

Data of ***syn*-78a**:

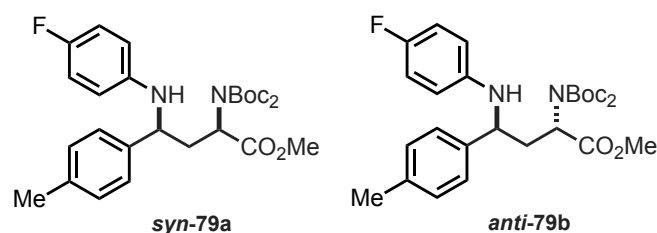
m.p. = 160 °C; ^1H NMR (400MHz, $CDCl_3$): δ = 7.41–7.35 (m, 2 H; ArH), 7.34–7.28 (m, 2 H; ArH), 7.25–7.19 (m, 1 H; ArH), 6.77 (t, J = 8.8 Hz, 2 H; ArH), 6.44 (dd, J = 9.0, 4.4 Hz, 2 H; ArH), 5.01 (dd, J = 7.3, 5.2 Hz, 1 H; CHCO₂CH₃), 4.50 (dd, J = 9.2, 4.4 Hz, 1 H; CHNH), 4.47–4.38 (m, 1 H; NH), 3.73 (s, 3 H; CO₂CH₃), 2.81 (ddd, J = 14.5, 7.3, 4.4 Hz, 1 H; CH₂), 2.04 (ddd, J = 14.5, 9.2, 5.3 Hz, 1 H; CH₂), 1.47 ppm (s, 18 H; (C(CH₃)₃)₂); ^{19}F { ^1H } NMR (377 MHz, $CDCl_3$): δ = –128.47 ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3 (CO₂CH₃), 157.0 (C–F), 152.3 (NC=O), 143.8 (ArC), 143.4 (ArC), 128.9 (ArCH), 127.3 (ArCH), 126.4 (ArCH),

115.6 (d, $J = 22.2$ Hz; ArCH), 114.3 (d, $J = 7.2$ Hz; ArCH), 83.7 (CO₂C(CH₃)₃), 56.8 (CHNH), 56.1 (CHCO₂CH₃), 52.5 (CO₂CH₃), 40.8 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3657 (w, N-H), 2980 (s), 2888 (m), 1747 (w, NC=O), 1695 (w, OC=O), 1510 (m); **HRMS** (ESI): $m/z = 503.25385$ ([M+H]⁺, calcd. for C₂₇H₃₆O₆N₂F⁺: 503.25519).

Data of **anti-78b**:

m.p. = 130 °C; ¹H NMR (400 MHz, CDCl₃): $\delta = 7.30$ (d, $J = 4.3$ Hz, 4 H; ArH), 7.25–7.19 (m, 1 H; ArH), 6.76 (t, $J = 8.8$ Hz, 2 H; ArH), 6.50–6.39 (m, 2 H; ArH), 5.15 (dd, $J = 7.7, 5.4$ Hz, 1 H; CHCO₂CH₃), 4.37 (dd, $J = 10.6, 3.8$ Hz, 2 H; CHNH), 3.74 (s, 3 H; CO₂CH₃), 2.60 (ddd, $J = 14.9, 10.5, 5.4$ Hz, 1 H; CH₂), 2.29 (ddd, $J = 14.9, 7.7, 3.8$ Hz, 1 H; CH₂), 1.42 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): $\delta = -128.38$ ppm; ¹³C NMR (101 MHz, CDCl₃): $\delta = 171.9$ (CO₂CH₃), 155.9 (d, $J = 234.5$ Hz; C-F), 152.0 (NC=O), 143.5 (ArC), 143.4 (ArC), 128.9 (ArCH), 127.4 (ArCH), 126.3 (ArCH), 115.5 (d, $J = 22.3$ Hz; ArCH), 114.4 (d, $J = 7.2$ Hz; ArCH), 83.6 (CO₂C(CH₃)₃), 56.6 (CHNH), 56.3 (CHCO₂CH₃), 52.6 (CO₂CH₃), 40.1 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3658 (w, N-H), 2980 (s), 2888 (m), 1741 (w, NC=O), 1510 (w); **HRMS** (ESI): $m/z = 503.25430$ ([M+H]⁺, calcd. for C₂₇H₃₆O₆N₂F⁺: 503.25519).

Synthesis of compound **79**



Compound **79** was synthesised according to General Procedure C using *p*-tolualdehyde (0.024

mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 3.4:1. FC (SiO₂; pentane/EtOAc 95:5 to 90:10) gave **79a** (26.5 mg, 26%) as off-white solid and **79b** (66.1 mg, 64%) as off-white solid (**79**: 90% total isolated yield).

Data of *syn*-**79a**:

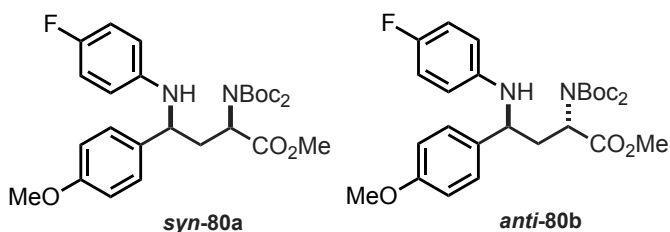
m.p. = 156 °C; ¹H NMR (400MHz, CDCl₃): δ = 7.28–7.23 (m, 2 H; ArH), 7.15–7.08 (m, 2 H; ArH), 6.77 (t, *J* = 8.8 Hz, 2 H; ArH), 6.47–6.40 (m, 2 H; ArH), 4.99 (dd, *J* = 7.1, 5.4 Hz, 1 H; CHCO₂CH₃), 4.51–4.43 (m, 1 H; CHNH), 3.72 (s, 3 H; CO₂CH₃), 2.78 (ddd, *J* = 14.5, 7.1, 4.6 Hz, 1 H; CH₂), 2.31 (s, 3 H; Ar-CH₃), 2.04 (ddd, *J* = 14.5, 9.0, 5.4 Hz, 1 H; CH₂), 1.47 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = -128.57 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 171.3 (C=O), 156.9 (C-F), 152.3 (NC=O), 143.9 (ArC), 140.3 (ArC), 136.9 (ArC), 129.6 (ArCH), 126.3 (ArCH), 115.6 (d, *J* = 22.2 Hz; ArCH), 114.2 (d, *J* = 7.2 Hz; ArCH), 83.6 (CO₂C(CH₃)₃), 56.3 (CHNH), 56.1 (CHCO₂CH₃), 52.5 (CO₂CH₃), 40.7 (CH₂), 28.1 (C(CH₃)₃), 21.2 ppm (Ar-CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3657 (w, N-H), 2980 (s), 2888 (m), 1747 (m, NC=O), 1696 (m, OC=O), 1510 (m); **HRMS** (ESI): *m/z* = 517.27081 ([M+H]⁺, calcd. for C₂₈H₃₈O₆N₂F⁺: 517.27084).

Data of *anti*-**79b**:

m.p. = 128 °C; ¹H NMR (400 MHz, CDCl₃): δ = 7.19 (d, *J* = 8.2 Hz, 2 H; ArH), 7.14–7.07 (m, 2 H; ArH), 6.76 (t, *J* = 8.8 Hz, 2 H; ArH), 6.48–6.39 (m, 2 H; ArH), 5.13 (dd, *J* = 7.6, 5.4 Hz, 1 H; CHCO₂CH₃), 4.34 (dd, *J* = 10.9, 4.5 Hz, 2 H; CHNH), 3.73 (s, 3 H; CO₂CH₃), 2.65–2.54 (m, 1 H; CH₂), 2.30 (s, 3 H; Ar-CH₃), 2.29–2.21 (m, 1 H; CH₂), 1.42 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = -128.48 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 172.0 (CO₂CH₃), 155.8 (d, *J* = 234.5 Hz; C-F), 152.0 (NC=O), 143.6 (ArC), 140.3 (ArC), 136.9 (ArC), 129.6 (ArCH), 126.2 (ArCH), 115.5 (d, *J* = 22.3 Hz; ArCH), 114.4

(d, $J = 7.2$ Hz; ArCH), 83.5 (CO₂C(CH₃)₃), 56.3 (CHNH), 56.2 (CHCO₂CH₃), 52.6 (CO₂CH₃), 40.1 (CH₂), 28.0 (C(CH₃)₃), 21.2 ppm (Ar-CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3657 (w, N-H), 2980 (s), 2888 (m), 1741 (w, NC=O), 1696 (m, OC=O), 1510 (w); **HRMS** (ESI): m/z = 517.27087 ([M+H]⁺, calcd. for C₂₈H₃₈O₆N₂F⁺: 517.27084).

Synthesis of compound **80**



Compound **80** was synthesised according to General Procedure **C** using *p*-anisaldehyde (0.024 mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 2.3:1. FC (SiO₂; pentane/acetone 95:5 to 90:10) gave **80a** (37 mg, 35%) as yellow oil and **80b** (60.5 mg, 57%) as yellow oil (**80**: 92% total isolated yield).

Data of **syn-80a**:

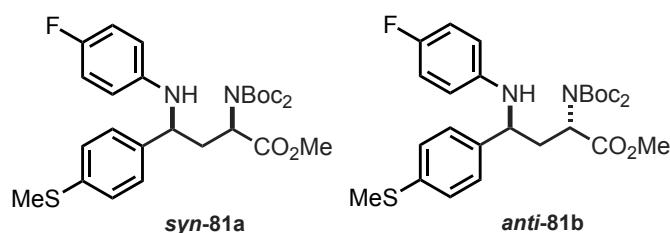
¹H NMR (400 MHz, CDCl₃): δ = 7.29 (d, $J = 8.7$ Hz, 2 H; ArH), 6.89–6.82 (m, 2 H; ArH), 6.78 (t, $J = 8.8$ Hz, 2 H; ArH), 6.44 (dd, $J = 9.0, 4.4$ Hz, 2 H; ArH), 4.98 (dd, $J = 7.0, 5.5$ Hz, 1 H; CHCO₂CH₃), 4.44 (dd, $J = 8.8, 4.8$ Hz, 1 H; CHNH), 3.77 (s, 3 H; CO₂CH₃), 3.72 (s, 3 H; OCH₃), 2.81–2.72 (m, 1 H; CH₂), 2.05 (ddd, $J = 14.5, 8.8, 5.6$ Hz, 1 H; CH₂), 1.48 ppm (s, 18 H; (C(CH₃)₃)₂); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = -128.50 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 171.3 (CO₂CH₃), 158.9 (ArC), 158.7 (C-F), 152.3 (NC=O), 143.9 (ArC), 135.3 (ArC), 127.5 (ArCH), 115.6 (d, $J = 22.9$ Hz; ArCH), 114.3 (d, $J = 7.2$ Hz; ArCH), 114.3 (ArCH), 83.6 (CO₂C(CH₃)₃), 56.2 (CHNH), 56.0 (CHCO₂CH₃), 55.4 (OCH₃), 52.4 (CO₂CH₃),

40.7 ($\underline{\text{C}}\text{H}_2$), 28.1 ppm ($\text{C}(\underline{\text{C}}\text{H}_3)_3$); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3380 (w, N–H), 2980 (s), 1744 (s, NC=O), 1697 (s, OC=O), 1510 (s); **HRMS** (ESI): m/z = 533.26587 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{28}\text{H}_{38}\text{O}_7\text{N}_2\text{F}^+$: 533.26576).

Data of **anti-80b**:

^1H NMR (400 MHz, CDCl_3): δ = 7.24–7.18 (m, 2 H; ArH), 6.87–6.81 (m, 2 H; ArH), 6.76 (t, J = 8.7 Hz, 2 H; ArH), 6.46–6.40 (m, 2 H; ArH), 5.11 (dd, J = 7.5, 5.4 Hz, 1 H; $\underline{\text{C}}\text{HCO}_2\text{CH}_3$), 4.33 (dd, J = 10.3, 4.1 Hz, 1 H; $\underline{\text{C}}\text{H}\text{NH}$), 3.77 (s, 3 H; OCH_3), 3.73 (s, 3 H; CO_2CH_3), 2.65–2.55 (m, 1 H; $\underline{\text{C}}\text{H}_2$), 2.24 (ddd, J = 14.9, 7.6, 4.1 Hz, 1 H; $\underline{\text{C}}\text{H}_2$), 1.42 ppm (s, 18 H; $(\text{C}(\underline{\text{C}}\text{H}_3)_3)_2$); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): δ = –128.44 ppm; ^{13}C NMR (101 MHz, CDCl_3): δ = 172.0 ($\underline{\text{C}}\text{O}_2\text{CH}_3$), 159.9 (ArC), 158.6 ($\underline{\text{C}}\text{--F}$), 152.0 ($\text{NC}=\text{O}$), 143.6 (ArC), 135.3 (ArC), 127.4 (ArCH), 115.5 (d, J = 22.3 Hz; ArCH), 114.5 (d, J = 7.2 Hz; ArCH), 114.3 (ArCH), 83.5 ($\text{CO}_2\underline{\text{C}}(\text{CH}_3)_3$), 56.3 ($\underline{\text{C}}\text{H}\text{NH}$), 56.0 ($\underline{\text{C}}\text{HCO}_2\text{CH}_3$), 55.4 (OCH_3), 52.6 (CO_2CH_3), 40.1 ($\underline{\text{C}}\text{H}_2$), 28.1 ppm ($\text{C}(\underline{\text{C}}\text{H}_3)_3$); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3393 (w, N–H), 2980 (m), 1742 (s, NC=O), 1699 (m, OC=O), 1510 (s); **HRMS** (ESI): m/z = 533.26581 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{28}\text{H}_{38}\text{O}_7\text{N}_2\text{F}^+$: 533.26576).

Synthesis of compound **81**



Compound **81** was synthesised according to General Procedure **C** using 4-(methylthio)benzaldehyde (0.027 mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for

24 h. Crude dr: 3.4:1. FC (SiO₂; pentane/acetone 95:5 to 90:10) gave **81a** (24.8 mg, 23%) as brown oil and **81b** (82.3 mg, 75%) as off-white solid (**81**: 98% total isolated yield).

Data of *syn*-**81a**:

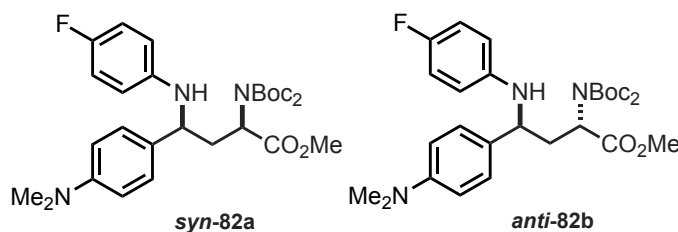
¹H NMR (400 MHz, CDCl₃): δ = 7.33–7.27 (m, 2 H; ArH), 7.20 (d, *J* = 8.4 Hz, 2 H; ArH), 6.77 (t, *J* = 8.8 Hz, 2 H; ArH), 6.46–6.35 (m, 2 H; ArH), 4.99 (dd, *J* = 7.2, 5.1 Hz, 1 H; CHCO₂CH₃), 4.45 (dd, *J* = 9.1, 4.4 Hz, 1H; CHNH), 3.72 (s, 3 H; CO₂CH₃), 2.78 (ddd, *J* = 14.5, 7.3, 4.4 Hz, 1 H; CH₂), 2.45 (s, 3 H; SCH₃), 2.01 (ddd, *J* = 14.5, 9.1, 5.2 Hz, 1 H; CH₂), 1.47 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = –128.30 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 171.3 (CO₂CH₃), 157.0 (C–F), 152.3 (NC=O), 143.8 (ArC), 140.4 (ArC), 137.2 (ArC), 127.2 (ArCH), 127.0 (ArCH), 115.6 (d, *J* = 22.3 Hz; ArCH), 114.3 (d, *J* = 7.2 Hz; ArCH), 83.7 (CO₂C(CH₃)₃), 56.5 (CHNH), 56.0 (CHCO₂CH₃), 52.5 (CO₂CH₃), 40.8 (CH₂), 28.1 (C(CH₃)₃), 16.1 ppm (SCH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3385 (w, N–H), 2982 (m), 2929 (w), 1745 (s, NC=O), 1698 (m, OC=O), 1510 (s); **HRMS** (ESI): *m/z* = 549.24261 ([M+H]⁺, calcd. for C₂₈H₃₈O₆N₂FS⁺: 549.24291).

Data of *anti*-**81b**:

m.p. = 120 °C; ¹H NMR (400 MHz, CDCl₃): δ = 7.25–7.15 (m, 4 H; ArH), 6.76 (t, *J* = 8.8 Hz, 2 H; ArH), 6.46–6.37 (m, 2 H; ArH), 5.13 (dd, *J* = 7.6, 5.4 Hz, 1 H; CHCO₂CH₃), 4.33 (dd, *J* = 10.5, 3.9 Hz, 1 H; CHNH), 3.73 (s, 3 H; CO₂CH₃), 2.58 (ddd, *J* = 15.0, 10.5, 5.5 Hz, 1 H; CH₂), 2.45 (s, 3 H; SCH₃), 2.25 (ddd, *J* = 15.0, 7.6, 3.8 Hz, 1 H; CH₂), 1.42 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} (377 MHz, CDCl₃): δ = –128.23 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 171.9 (CO₂CH₃), 157.1 (C–F), 152.0 (NC=O), 143.4 (ArC), 140.3 (ArC), 137.3 (ArC), 127.2 (ArCH), 126.8 (ArCH), 115.6 (d, *J* = 22.3 Hz; ArCH), 114.5 (d, *J* = 7.4 Hz; ArCH), 83.6 (CO₂C(CH₃)₃), 56.3 (CHNH), 56.2 (CHCO₂CH₃), 52.6 (CO₂CH₃), 40.0 (CH₂), 28.1 (C(CH₃)₃),

16.1 ppm (SCH_3); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3397 (w, N–H), 2984 (m), 2929 (m), 1740 (s, NC=O), 1699 (s, OC=O), 1510 (s); **HRMS** (ESI): m/z = 549.24274 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{28}\text{H}_{38}\text{O}_6\text{N}_2\text{FS}^+$: 549.24291).

Synthesis of compound **82**



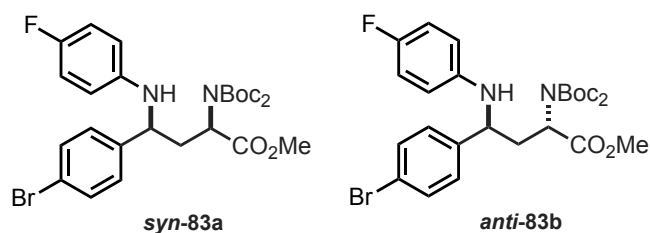
Compound **82** was synthesised according to General Procedure **C** using 4- dimethylaminobenzaldehyde (29.8 mg, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 48 h. Crude dr: 2.6:1. FC (SiO_2 ; pentane/acetone 95:5 to 90:10) gave an inseparable mixture of **82a** and **82b** (61.1 mg, 56%) as brownish oil.

Data of mixture **syn-82a** and **anti-82b**:

^1H NMR (400 MHz, CDCl_3): δ = 7.22 (d, J = 8.7 Hz, 2 H; ArH, **82a** or **82b**), 7.15 (d, J = 8.8 Hz, 2 H; ArH, **82a** or **82b**), 6.82–6.71 (m, 4 H; ArH, **82a** or **82b**), 6.72–6.61 (m, 4 H; ArH, **82a** or **82b**), 6.50–6.41 (m, 4 H; ArH, **82a** or **82b**), 5.12 (dd, J = 7.5, 5.5 Hz, 1 H; CHCO_2CH_3 , **82b**), 4.98 (dd, J = 6.8, 5.8 Hz, 1 H; CHCO_2CH_3 , **82a**), 4.39 (dd, J = 8.7, 5.1 Hz, 1 H; CHNH , **82a**), 4.30 (dd, J = 10.3, 4.2 Hz, 1 H; CHNH , **82b**), 3.73 (s, 3 H; CO_2CH_3 , **82b**), 3.71 (s, 3 H; CO_2CH_3 , **82a**), 2.91 (s, 6 H; $\text{N}(\text{CH}_3)_2$, **82a**), 2.91 (s, 6 H; $\text{N}(\text{CH}_3)_2$, **82b**), 2.76 (ddd, J = 14.5, 6.9, 5.3 Hz, 1 H; CH_2 , **82a**), 2.65–2.55 (m, 1 H; CH_2 , **82b**), 2.23 (ddd, J = 14.9, 7.5, 4.2 Hz, 1 H; CH_2 , **82b**), 2.06 (ddd, J = 14.5, 8.6, 5.8 Hz, 1 H; CH_2 , **82a**), 1.47 (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$, **82a**), 1.42 ppm (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$, **82b**); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): δ = –128.80

(**82b**), -128.83 ppm (**82a**); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 172.1, 171.4, 151.9, 149.9, 143.8, 130.9, 127.2, 127.0, 115.6, 115.3, 114.5, 114.4, 113.0, 83.5, 56.3, 55.8, 52.5, 50.9, 40.8, 40.0, 28.4, 28.1, 28.0$ ppm; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3389 (w, N–H), 2976 (w), 2933 (m), 1744 (s, NC=O), 1700 (s, OC=O), 1511 (s); **HRMS** (ESI): $m/z = 568.27942$ ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{29}\text{H}_{40}\text{O}_6\text{N}_3\text{FNa}^+$: 568.27934).

Synthesis of compound **83**



Compound **83** was synthesised according to General Procedure **C** using 4-bromobenzaldehyde (37 mg, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 2.6:1. FC (SiO_2 ; pentane/acetone 95:5 to 90:10) gave **83a** (25.1 mg, 22%) as off-white solid and **83b** (68 mg, 58%) as off-white solid (**83**: 80% total isolated yield).

Data of **syn-83a**:

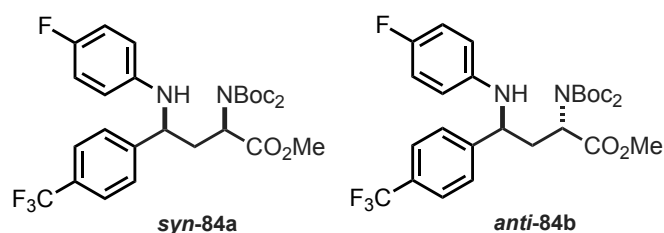
m.p. = 134 °C; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.46\text{--}7.40$ (m, 2 H; ArH), 7.27 (d, $J = 8.9$ Hz, 2 H; ArH), 6.78 (t, $J = 8.7$ Hz, 2 H; ArH), 6.43–6.38 (m, 2 H; ArH), 4.98 (dd, $J = 7.4, 4.8$ Hz, 1 H; CHCO_2CH_3), 4.54–4.42 (m, 2 H; CHNH), 3.73 (s, 3 H; CO_2CH_3), 2.78 (ddd, $J = 14.5, 7.5, 3.9$ Hz, 1 H; CH_2), 1.97 (ddd, $J = 14.5, 9.2, 4.9$ Hz, 1 H; CH_2), 1.48 ppm (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): $\delta = -128.04$ ppm; ^{13}C NMR (101 MHz, CDCl_3): $\delta = 171.2$ (CO_2CH_3), 152.3 (NC=O), 143.6 (ArC), 142.6 (ArC), 140.1 (ArC), 139.2 (ArC), 132.0 (ArCH), 128.2 (ArCH), 115.7 (d, $J = 22.2$ Hz; ArCH), 114.3 (d, $J = 7.3$ Hz; ArCH),

83.8 (CO₂C(CH₃)₃), 56.4 (CHNH), 55.8 (CHCO₂CH₃), 52.5 (CO₂CH₃), 40.9 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3657 (w, N-H), 2980 (s), 2988 (m), 1743 (w, NC=O), 1509 (s); **HRMS** (ESI): m/z = 581.16534 ([M+H]⁺, calcd. for C₂₇H₃₅O₆N₂BrF⁺: 581.16570).

Data of **anti-83b**:

m.p. = 144 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 7.43 (d, J = 8.4 Hz, 2 H; ArH), 7.19 (d, J = 8.4 Hz, 2 H; ArH), 6.76 (t, J = 8.8 Hz, 2 H; ArH), 6.43–6.34 (m, 2 H; ArH), 5.12 (dd, J = 7.6, 5.4 Hz, 1 H; CHCO₂CH₃), 4.39 (s, 1 H; NH), 4.32 (dd, J = 10.5, 3.8 Hz, 1 H; CHNH), 3.74 (s, 3 H; CO₂CH₃), 2.62–2.53 (m, 1 H; CH₂), 2.24 (ddd, J = 15.0, 7.6, 3.7 Hz, 1 H; CH₂), 1.43 ppm (s, 18 H; (C(CH₃)₃)₂); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = -127.94 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 171.9 (CO₂CH₃), 152.1 (NC=O), 142.5 (ArC), 140.1 (ArC), 132.0 (ArCH), 128.1 (ArCH), 121.1 (ArC), 115.6 (d, J = 22.3 Hz; ArCH), 114.5 (d, J = 7.2 Hz; ArCH), 83.7 (CO₂C(CH₃)₃), 56.2 (CHNH), 56.2 (CHCO₂CH₃), 52.7 (CO₂CH₃), 40.0 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3685 (w, N-H), 2993 (s), 1746 (w, NC=O), 1699 (s, OC=O), 1510 (m); **HRMS** (ESI): m/z = 581.16510 ([M+H]⁺, calcd. for C₂₇H₃₆O₆N₂F⁺: 581.16570).

Synthesis of compound **84**



Compound **84** was synthesised according to General Procedure **C** using 4- trifluoromethylben-

zaldehyde (0.027 mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 2.3:1. FC (SiO₂; pentane/acetone 95:5 to 90:10) gave **84a** (14.6 mg, 13%) as off-white amorphous solid and **84b** (33.6 mg, 29%) as yellow oil (**84**: 42% total isolated yield).

Data of *syn*-**84a**:

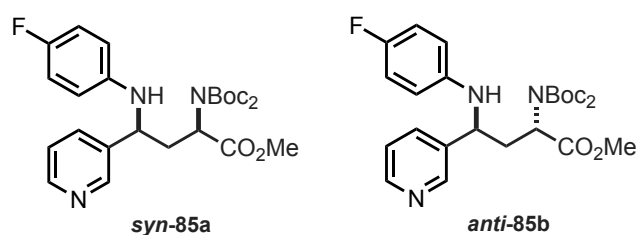
¹H NMR (400 MHz, CDCl₃): δ = 7.57 (d, *J* = 8.0 Hz, 2 H; ArH), 7.52 (d, *J* = 8.2 Hz, 2 H; ArH), 6.79 (t, *J* = 8.8 Hz, 2 H; ArH), 6.44–6.37 (m, 2 H; ArH), 5.01 (dd, *J* = 7.6, 4.6 Hz, 1 H; CHCO₂CH₃), 4.63–4.52 (m, 2 H; CHNH), 3.74 (s, 3 H; CO₂CH₃), 2.83 (ddd, *J* = 14.5, 7.6, 3.5 Hz, 1 H; CH₂), 2.00 (m, 1 H; CH₂), 1.47 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = –62.04 (3 F; CF₃), –127.87 ppm (1 F; Ar–F); ¹³C NMR (101 MHz, CDCl₃): δ = 171.1 (CO₂CH₃), 152.3 (NC=O), 147.7 (ArC), 143.5 (ArC), 126.7 (ArCH), 125.9 (ArCH), 115.7 (d, *J* = 22.5 Hz; ArCH), 114.3 (d, *J* = 7.2 Hz; ArCH), 83.9 (CO₂C(CH₃)₃), 56.7 (CHNH), 55.8 (CHCO₂CH₃), 52.6 (CO₂CH₃), 41.0 (CH₂), 28.1 ppm (C(CH₃)₃); FT-IR (thin film): ν_{max} (cm^{–1}) = 3657 (w, N–H), 2980 (s), 2888 (m), 1746 (m, NC=O), 1511 (m); HRMS (ESI): *m/z* = 571.24194 ([M+H]⁺, calcd. for C₂₈H₃₅O₆N₂F₄⁺: 571.24258). Note: ArC–F, ArC–CF₃, and ArC–CF₃ were not observed.

Data of *anti*-**84b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.66–7.51 (m, 2 H; ArH), 7.49–7.39 (m, 2 H; ArH), 6.77 (t, *J* = 8.8 Hz, 2 H; ArH), 6.47–6.31 (m, 2 H; ArH), 5.14 (dd, *J* = 7.7, 5.4 Hz, 1 H; CHCO₂CH₃), 4.41 (dd, *J* = 10.7, 3.8 Hz, 1 H; CHNH), 3.74 (s, 3 H; CO₂CH₃), 2.68–2.53 (m, 1 H; CH₂), 2.28 (ddd, *J* = 14.9, 7.6, 3.6 Hz, 1 H; CH₂), 1.43 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = –62.45 (3 F; CF₃), –127.76 ppm (1 F; Ar–F); ¹³C NMR (101 MHz, CDCl₃): δ = 171.8 (CO₂CH₃), 156.1 (d, *J* = 235.5 Hz; C–F), 152.1 (NC=O), 147.7 (ArC), 143.0 (ArC),

126.7 (ArCH), 125.9 (ArCH), 116.0 (d, $J = 22.3$ Hz; ArCH), 114.4 (d, $J = 7.3$ Hz; ArCH), 83.8 (CO₂C(CH₃)₃), 56.5 (CHNH), 56.2 (CHCO₂CH₃), 52.7 (CO₂CH₃), 40.0 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3658 (w, N-H), 2980 (s), 2888 (m), 1741 (w, NC=O), 1511 (m); **HRMS** (ESI): $m/z = 571.24188$ ([M+H]⁺, calcd. for C₂₈H₃₅O₆N₂F₄⁺: 571.24258). Note: ArC-CF₃, and ArC-CF₃ were not observed.

Synthesis of compound **85**



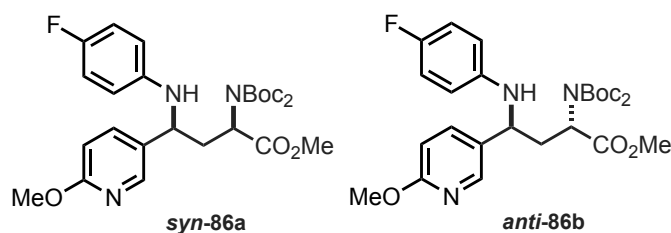
Compound **85** was synthesised according to General Procedure **C** using 3-pyridinecarboxaldehyde (0.019 mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 48 h. Crude dr: 1.2:1. FC (SiO₂; pentane/EtOAc 90:10 to 60:40) gave an inseparable mixture of **85a** and **85b** (44.4 mg, 44%) as yellow oil.

Data of mixture **syn-85a** and **anti-85b**:

¹H NMR (400 MHz, CDCl₃): $\delta = 8.66$ (dd, $J = 2.4, 0.9$ Hz, 1 H; ArH, **85a**), 8.58 (dd, $J = 2.3, 0.9$ Hz, 1 H; ArH, **85b**), 8.49 (ddd, $J = 4.8, 2.4, 1.7$ Hz, 2 H; ArH, **85a** and **85b**), 7.69 (dt, $J = 7.9, 2.0$ Hz, 1 H; ArH, **85a**), 7.64 (ddd, $J = 7.8, 2.3, 1.6$ Hz, 1 H; ArH, **85b**), 7.26–7.20 (m, 2 H; ArH, **85a** and **85b**), 6.84–6.72 (m, 4 H; ArH, **85a** and **85b**), 6.46–6.37 (m, 4 H; ArH, **85a** and **85b**), 5.15 (dd, $J = 7.6, 5.4$ Hz, 1 H; CHCO₂CH₃, **85b**), 5.02 (dd, $J = 7.5, 4.9$ Hz, 1 H; CHCO₂CH₃, **85a**), 4.60–4.53 (m, 1 H; CHNH, **85b**), 4.50 (s, 1 H; CHNH, **85b**), 4.42 (d, $J = 8.1$ Hz, 2 H; CHNH, **85a**), 3.74 (s, 3 H; OCH₃, **85b**), 3.73 (s, 3 H; OCH₃, **85a**), 2.82 (ddd,

$J = 14.5, 7.5, 4.0$ Hz, 1 H; $\underline{\text{CH}}_2$, **85a**), 2.63 (ddd, $J = 15.0, 10.7, 5.4$ Hz, 1 H; $\underline{\text{CH}}_2$, **85b**), 2.29 (ddd, $J = 15.0, 7.6, 3.1$ Hz, 1 H; $\underline{\text{CH}}_2$, **85b**), 2.03 (ddd, $J = 14.5, 9.3, 4.9$ Hz, 1 H; $\underline{\text{CH}}_2$, **85a**), 1.48 (s, 18 H; **85a**), 1.43 ppm (s, 18 H; **85b**); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): $\delta = -127.63$ (**85b**), -127.72 ppm (**85a**); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 206.0, 171.7, 170.9, 152.2, 152.0, 148.8, 148.7, 148.6, 148.5, 138.6, 133.9, 133.7, 123.7, 123.6, 115.7$ (d, $J = 4.1$ Hz), 115.5 (d, $J = 4.5$ Hz), 114.4 (d, $J = 7.8$ Hz), 114.2 (d, $J = 7.3$ Hz), $83.8, 83.7, 56.0, 55.6, 54.7, 54.4, 52.6, 52.4, 40.6, 39.7, 28.0, 27.9$ ppm; FT-IR (thin film): ν_{max} (cm^{-1}) = 3656 (w, N-H), 2980 (m), 2888 (m), 1744 (s, NC=O), 1509 (m); HRMS (ESI): $m/z = 504.25034$ ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{26}\text{H}_{35}\text{O}_6\text{N}_3\text{F}^+$: 504.25044).

Synthesis of compound **86**



Compound **86** was synthesised according to General Procedure **C** using 6-methoxy-3-pyridinecarboxaldehyde (27.4 mg, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 48 h. Crude dr: 2.9:1. FC (SiO_2 ; pentane/EtOAc 95:5 to 90:10) gave **86a** (24.3 mg, 23%) as yellow oil and **86b** (51.4 mg, 48%) as off-white solid (**86**: 71% total isolated yield).

Data of **syn-86a**:

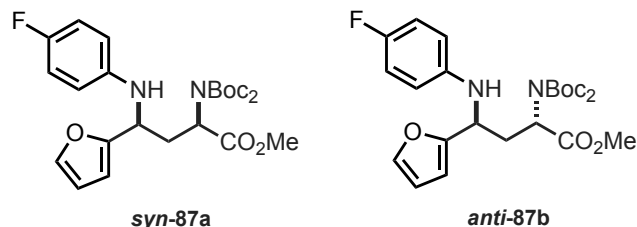
^1H NMR (400 MHz, CDCl_3): $\delta = 8.16$ (d, $J = 2.4$ Hz, 1 H; ArH), 7.58 (dd, $J = 8.6, 2.5$ Hz, 1 H; ArH), 6.79 (t, $J = 8.7$ Hz, 2 H; ArH), 6.69 (dd, $J = 8.5, 0.8$ Hz, 1 H; ArH), 6.49–6.39 (m, 2 H; ArH), 4.98 (dd, $J = 7.0, 5.5$ Hz, 1 H; $\underline{\text{CH}}\text{CO}_2\text{CH}_3$), 4.47 (dd, $J = 8.8, 4.8$ Hz, 1 H; $\underline{\text{CH}}\text{NH}$), 4.38

(s, 1H; CHNH), 3.91 (s, 3 H; OCH₃), 3.72 (s, 3 H; CO₂CH₃), 2.76 (ddd, $J = 14.6, 7.0, 4.7$ Hz, 1 H; CH₂), 2.11–2.01 (m, 1 H; CH₂), 1.48 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): $\delta = -127.92$ ppm; ¹³C NMR (101 MHz, CDCl₃): $\delta = 171.2$ (CO₂CH₃), 163.8 (C–F), 157.2 (ArC), 152.3 (NC=O), 145.4 (ArCH), 143.4 (ArC), 137.0 (ArCH), 131.2 (ArC), 115.7 (d, $J = 22.3$ Hz; ArCH), 114.4 (d, $J = 7.4$ Hz; ArCH), 111.2 (ArCH), 83.8 (CO₂C(CH₃)₃), 55.8 (CHCO₂CH₃), 54.2 (CHNH), 53.6 (OCH₃), 52.5 (CO₂CH₃), 40.4 (CH₂), 28.1 ppm (C(CH₃)₃); FT-IR (thin film): ν_{max} (cm^{−1}) = 3379 (w, N–H), 3011 (w), 2936 (w), 1745 (s, NC=O), 1697 (s, OC=O), 1607 (m), 1510 (s); HRMS (ESI): $m/z = 534.26086$ ([M+H]⁺, calcd. for C₂₇H₃₇O₇N₃F⁺: 534.26101).

Data of *anti*-**86b**:

m.p. = 116 °C; ¹H NMR (400 MHz, CDCl₃): $\delta = 8.09$ (dd, $J = 2.5, 0.8$ Hz, 1 H; ArH), 7.52 (dd, $J = 8.5, 2.5$ Hz, 1 H; ArH), 6.77 (t, $J = 8.8$ Hz, 2 H; ArH), 6.69 (dd, $J = 8.5, 0.8$ Hz, 1 H; ArH), 6.43 (dd, $J = 9.0, 4.4$ Hz, 2 H; ArH), 5.12 (dd, $J = 7.5, 5.5$ Hz, 1 H; CHCO₂CH₃), 4.42–4.28 (m, 2 H; CHNH), 3.90 (s, 3 H; OCH₃), 3.74 (s, 3 H; CO₂CH₃), 2.71–2.57 (m, 1 H; CH₂), 2.22 (ddd, $J = 15.0, 7.5, 4.0$ Hz, 1 H; CH₂), 1.42 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): $\delta = -127.86$ ppm; ¹³C NMR (101 MHz, CDCl₃): $\delta = 171.9$ (CO₂CH₃), 163.8 (C–F), 154.9 (ArC), 152.0 (NC=O), 145.2 (ArCH), 143.1 (ArC), 136.8 (ArCH), 131.2 (ArC), 115.7 (d, $J = 22.5$ Hz; ArCH), 114.5 (d, $J = 7.3$ Hz; ArCH), 111.3 (ArCH), 83.7 (CO₂C(CH₃)₃), 56.1 (CHCO₂CH₃), 53.9 (CHNH), 53.6 (OCH₃), 52.7 (CO₂CH₃), 39.8 (CH₂), 28.1 ppm (C(CH₃)₃); FT-IR (thin film): ν_{max} (cm^{−1}) = 3379 (w, N–H), 3014 (w), 2935 (w), 1740 (s, NC=O), 1699 (m, OC=O), 1510 (s); HRMS (ESI): $m/z = 534.26080$ ([M+H]⁺, calcd. for C₂₇H₃₇O₇N₃F⁺: 534.26101).

Synthesis of compound **87**



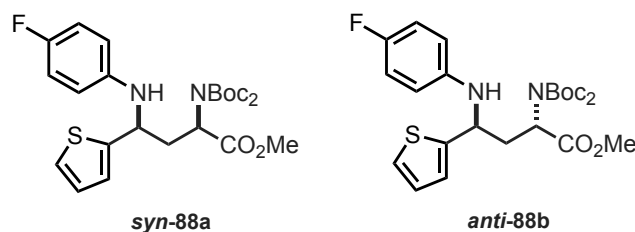
Compound **87** was synthesised according to General Procedure **C** using furfural (0.017 mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 5:2. FC (SiO₂; pentane/EtOAc 95:5 to 90:10) gave an inseparable mixture of **87a** and **87b** (49.8 mg, 51%) as yellow oil.

Data of mixture ***syn*-87a** and ***anti*-87b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.31 (dd, J = 1.8, 0.9 Hz, 2 H; C₄H₃O, **87a** and **87b**), 6.87–6.79 (m, 4 H; ArH, **87a** and **87b**), 6.60–6.52 (m, 4 H; ArH, **87a** and **87b**), 6.26 (dd, J = 3.2, 1.9 Hz, 2 H; C₄H₃O, **87a** and **87b**), 6.17 (dt, J = 3.2, 0.8 Hz, 1 H; C₄H₃O, **87a**), 6.15–6.11 (m, 1 H; C₄H₃O, **87b**), 5.12 (dd, J = 7.9, 5.3 Hz, 1 H; CHCO₂CH₃, **87b**), 5.04 (dd, J = 7.2, 6.0 Hz, 1 H; CHCO₂CH₃, **87a**), 4.65 (t, J = 6.7 Hz, 1 H; CHNH, **87a**), 4.54 (dd, J = 9.4, 4.9 Hz, 1 H; CHNH, 13b), 3.73 (s, 3 H; OCH₃, **87b**), 3.71 (s, 3 H; OCH₃, **87a**), 2.83 (dt, J = 14.5, 6.1 Hz, 1 H; CH₂, **87a**), 2.70 (ddd, J = 14.7, 9.4, 5.3 Hz, 1 H; CH₂, **87b**), 2.40 (ddd, J = 14.7, 7.9, 5.0 Hz, 1 H; CH₂, **87b**), 2.30 (dt, J = 14.5, 7.3 Hz, 1 H; CH₂, **87a**), 1.47 (s, 18 H; **87a**); 1.43 ppm (s, 18 H; **87b**); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = –127.42 (**87b**), –127.46 ppm (**87a**); **¹³C NMR** (101 MHz, CDCl₃): δ = 171.7, 157.5, 155.4, 155.1, 152.0, 143.3, 142.0, 141.9, 115.8, 115.8, 115.6, 115.5, 115.1, 115.0, 114.8, 110.3, 106.6, 106.4, 83.5, 83.5, 55.8, 55.6, 52.7, 52.5, 50.7, 50.5, 35.9, 35.9, 28.1, 28.1 ppm; **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3373 (w, N–H), 2923 (w), 1743 (s, NC=O), 1511 (m); **HRMS** (ESI): m/z = 493.23392 ([M+H]⁺, calcd.

for C₂₅H₃₄O₇N₂F⁺: 493.23446).

Synthesis of compound **88**



Compound **88** was synthesised according to General Procedure **C** using 2-thiophenecarboxaldehyde (0.02 mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 48 h. Crude dr: 2.4:1. FC (SiO₂; pentane/EtOAc 95:5 to 90:10) gave partial separation of **88a** (10.5 mg, 10%) as yellow oil, **88b** (27 mg, 27%) as yellow oil, and mixed fractions (8.2 mg, 8%) as brown oil (**88**: 45% total isolated yield).

Data of **syn-88a**:

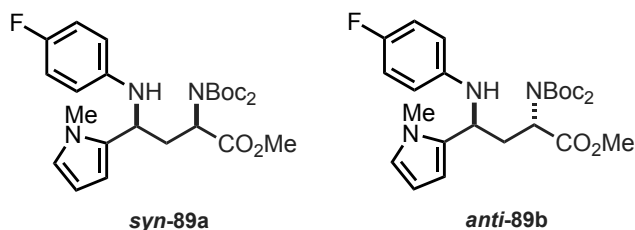
¹H NMR (400 MHz, CDCl₃): δ = 7.16 (dd, J = 5.0, 1.2 Hz, 1 H; C₄H₃S), 6.99 (dt, J = 3.5, 1.0 Hz, 1 H; C₄H₃S), 6.96–6.90 (m, 1 H; C₄H₃S), 6.82 (t, J = 8.8 Hz, 2 H; ArH), 6.54 (dd, J = 9.0, 4.4 Hz, 2 H; ArH), 5.05 (t, J = 6.4 Hz, 1 H; CHCO₂CH₃), 4.81 (dd, J = 8.3, 5.3 Hz, 1 H; CHNH), 3.72 (s, 3 H; CO₂CH₃), 2.88 (ddd, J = 14.5, 6.7, 5.3 Hz, 1 H; CH₂), 2.23 (ddd, J = 14.5, 8.3, 6.0 Hz, 1 H; CH₂), 1.47 ppm (s, 18 H; (C(CH₃)₃)₂); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = –127.55 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 171.2 (CO₂CH₃), 152.3 (NC=O), 148.3 (ArC), 143.5 (C₄H₃S), 127.0 (C₄H₃S), 124.2 (C₄H₃S), 124.0 (C₄H₃S), 115.7 (d, J = 22.2 Hz; ArCH), 114.7 (d, J = 7.2 Hz; ArCH), 83.7 (CO₂C(CH₃)₃), 55.8 (CHCO₂CH₃), 53.1 (CHNH), 52.5 (CO₂CH₃), 40.5 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3388 (w, N–H), 2933 (w), 2849 (w), 1744 (s, NC=O), 1699 (s, OC=O), 1510 (s); **HRMS** (ESI): m/z

= 509.21164 ($[M+H]^+$, calcd. for $C_{25}H_{34}O_6N_2FS^+$: 509.21161). Note: $ArC-F$ was not observed.

Data of **anti-88b**:

^1H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.13 (m, 1 H; C_4H_3S), 6.94–6.87 (m, 2 H; C_4H_3S), 6.81 (t, J = 8.8 Hz, 2 H; ArH), 6.54 (dd, J = 9.0, 4.4 Hz, 2 H; ArH), 5.14 (dd, J = 7.8, 5.3 Hz, 1 H; $CHCO_2CH_3$), 4.70 (dd, J = 9.9, 4.4 Hz, 1 H; $CHNH$), 3.74 (s, 3 H; CO_2CH_3), 2.77 (ddd, J = 15.0, 9.9, 5.4 Hz, 1 H; CH_2), 2.40 (ddd, J = 15.0, 7.8, 4.4 Hz, 1 H; CH_2), 1.43 ppm (s, 18 H; $(C(CH_3)_3)_2$); ^{19}F $\{^1H\}$ NMR (377 MHz, $CDCl_3$): δ = -127.47 ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.7 (CO_2CH_3), 156.3 (d, J = 235.3 Hz; $C-F$), 152.0 ($NC=O$), 148.1 (ArC), 143.2 (C_4H_3S), 127.0 (C_4H_3S), 124.2 (C_4H_3S), 123.8 (C_4H_3S), 115.7 (d, J = 22.3 Hz; $ArCH$), 114.9 (d, J = 7.2 Hz; $ArCH$), 83.6 ($CO_2C(CH_3)_3$), 56.0 ($CHCO_2CH_3$), 52.6 ($CHNH$), 52.6 (CO_2CH_3), 39.7 (CH_2), 28.1 ppm ($C(CH_3)_3$); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3388 (w, N-H), 2932 (br), 2852 (w), 1741 (s, $NC=O$), 1702 (m, $OC=O$), 1510 (s); **HRMS** (ESI): m/z = 509.21167 ($[M+H]^+$, calcd. for $C_{25}H_{34}O_6N_2FS^+$: 509.21161).

Synthesis of compound **89**

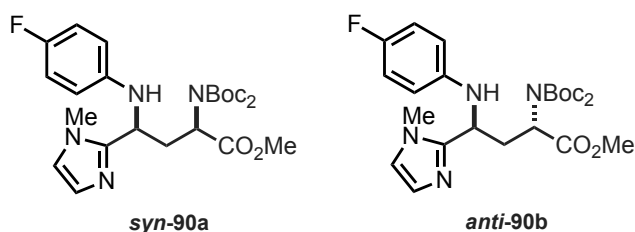


Compound **89** was synthesised according to General Procedure **C** using N-methyl-2-pyrrolecarboxaldehyde (0.02 mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 48 h. Crude dr: 1:1. FC (SiO_2 ; pentane/acetone 95:5 to 90:10) gave an inseparable mixture of **89a** and **89b** (72.2 mg, 71%) as yellow oil.

Data of mixture *syn*-**89a** and *anti*-**89b**:

¹H NMR (400 MHz, CDCl₃): δ = 6.84 (ddt, J = 8.7, 5.9, 3.5 Hz, 4 H; ArH, **89a** and **89b**), 6.64–6.55 (m, 4 H; ArH, **89a** and **89b**), 6.52–6.46 (m, 2 H; C₄H₃NCH₃, **89a** or **89b**), 6.10 (td, J = 3.9, 1.7 Hz, 2 H; C₄H₃NCH₃, **89a** or **89b**), 6.07–6.03 (m, 2 H; C₄H₃NCH₃, **89a** or **89b**), 5.03 (ddd, J = 13.3, 7.3, 5.7 Hz, 2 H; CHCO₂CH₃, **89a** and **89b**), 4.71 (t, J = 7.2 Hz, 1 H; CHNH, **89a** or **89b**), 4.54 (br, t, J = 7.2 Hz, 1H; CHNH, **89a** or **89b**), 3.72 (s, 6 H; CO₂CH₃, **89a** and **89b**), 3.59 (s, 3 H; NCH₃, **89a** or **89b**), 3.55 (s, 3 H; NCH₃, **89a** or **89b**), 2.88–2.74 (m, 2 H; CH₂, **89a** and **89a**), 2.33–2.15 (m, 2 H; CH₂, **89a** and **89b**), 1.45 (s, 18 H; **89a** or **89b**), 1.44 ppm (s, 18 H; **89a** or **89b**); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = –127.93 (**89a** or **89b**), –128.04 ppm (**89a** or **89b**); **¹³C NMR** (101 MHz, CDCl₃): δ = 171.8, 171.3, 152.1, 152.0, 132.9, 132.7, 123.0, 116.0, 115.9, 115.8, 115.7, 114.5, 114.4, 114.1, 114.0, 107.0, 107.0, 106.4, 105.8, 83.6, 83.5, 56.3, 56.1, 52.4, 48.9, 48.6, 36.0, 35.9, 34.0, 34.0, 33.9, 28.5, 28.1 ppm; **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3389 (w, N–H), 2981 (m), 1740 (s, NC=O), 1698 (m, OC=O), 1510 (s); **HRMS** (ESI): m/z = 528.24799 ([M+Na]⁺, calcd. for C₂₆H₃₆O₆N₃FN⁺: 528.24804).

Synthesis of compound **90**



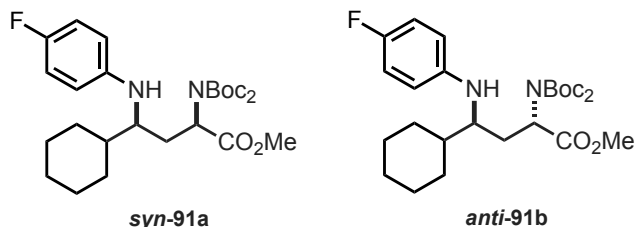
Compound **90** was synthesised according to General Procedure **C** using 1-methyl-2- imidazole-carboxaldehyde (22 mg, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 48 h. Crude dr: 1:1. FC (SiO₂; pentane/acetone 95:5 to 90:10) gave an inseparable

mixture of **90a** and **90b** (69.1 mg, 68%) as yellow foam.

Data of mixture *syn*-**90a** and *anti*-**90b**:

m.p. = 81 °C; ^1H NMR (400 MHz, CDCl_3): δ = 6.95 (d, J = 1.3 Hz, 1 H; $\text{C}_3\text{H}_2\text{N}_2\text{CH}_3$, **90a** or **90b**), 6.93 (d, J = 1.2 Hz, 1 H; $\text{C}_3\text{H}_2\text{N}_2\text{CH}_3$, **90a** or **90b**), 6.82 (td, J = 8.7, 2.0 Hz, 4 H; ArH , **90a** and **90b**), 6.78 (d, J = 1.3 Hz, 1 H; $\text{C}_3\text{H}_2\text{N}_2\text{CH}_3$, **90a** or **90b**), 6.74 (d, J = 1.2 Hz, 1 H; $\text{C}_3\text{H}_2\text{NCH}_3$, **90a** or **90b**), 6.58 (ddd, J = 16.8, 9.0, 4.4 Hz, 4 H; ArH , **90a** and **90a**), 5.18 (dd, J = 7.5, 5.9 Hz, 1 H; CHCO_2CH_3 , **90a** or **90a**), 5.11 (dd, J = 7.4, 6.0 Hz, 1 H; CHCO_2CH_3 , **90a** or **90b**), 4.78 (d, J = 7.2 Hz, 1 H; CHNH , **90a** or **90b**), 4.70 (t, J = 7.2 Hz, 1H; CHNH , **90a** or **90b**), 4.33 (br, 1H; CHNH , **90a** or **90b**), 4.14 (br, 1 H; CHNH , **90a** or **90b**), 3.73 (s, 3 H; CO_2CH_3 , **90a** or **90b**), 3.71 (s, 3 H; CO_2CH_3 , **90a** or **90b**), 3.66 (s, 3 H; NCH_3 , **90a** or **90b**), 3.60 (s, 3 H; NCH_3 , **90a** or **90b**), 2.88–2.75 (m, 2 H; CH_2 , **90a** and **90b**), 2.39 (ddd, J = 14.4, 7.4, 5.6 Hz, 1 H; CH_2 , **90a** or **90b**), 2.25–2.16 (m, 1 H; CH_2 , **90a** or **90b**), 1.45 (s, 18 H; **90a** or **90b**), 1.43 ppm (s, 18 H; **90a** or **90b**); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): δ = –126.69 (**90a** or **90b**), –126.90 ppm (**90a** or **90b**); ^{13}C NMR (101 MHz, CDCl_3): δ = 171.8, 171.6, 157.7, 155.3, 152.3, 152.0, 148.5, 148.1, 143.6, 143.3, 127.5, 127.5, 121.3, 121.2, 116.0, 115.9, 115.8, 115.7, 115.6, 115.5, 115.4, 115.4, 83.5, 83.5, 55.9, 55.6, 52.5, 52.4, 49.5, 49.1, 36.3, 36.6, 32.8, 32.7, 28.1, 28.1 ppm; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3254 (w, N–H), 2980 (m), 1742 (s, NC=O), 1700 (m, OC=O), 1509 (s); **HRMS** (ESI): m/z = 507.26117 ($[\text{M}+\text{H}]^+$, calcd. $\text{C}_{25}\text{H}_{36}\text{O}_6\text{N}_4\text{F}^+$: 507.26134).

Synthesis of compound **91**



Compound **91** was synthesised according to General Procedure **C** using cyclohexanecarboxaldehyde (0.024 mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 3.2:1. FC (SiO₂; pentane/EtOAc 95:5 to 90:10) gave **91a** (20.7 mg, 20%) as brown oil and **91b** (61.2 mg, 60%) as yellow oil (**91**: 80% total isolated yield).

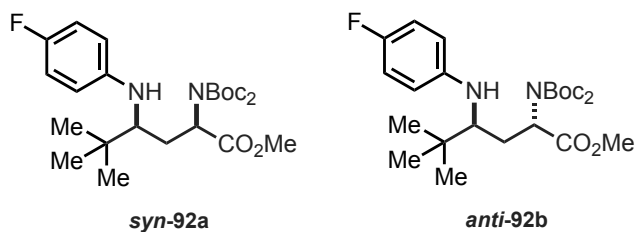
Data of ***syn*-91a**:

¹H NMR (400 MHz, CDCl₃): δ = 6.81 (t, J = 8.8 Hz, 2 H; ArH), 6.47 (dd, J = 9.0, 4.4 Hz, 2 H; ArH), 4.98 (dd, J = 7.3, 5.8 Hz, 1 H; CHCO₂CH₃), 3.69 (s, 3 H; CO₂CH₃), 3.41 (dt, J = 9.0, 4.4 Hz, 1 H; CHNH), 2.54 (ddd, J = 14.4, 7.3, 4.2 Hz, 1 H; CH₂), 1.81–1.69 (m, 3 H; C₆H₁₁), 1.68–1.59 (m, 4 H; C₆H₁₁ and CH₂), 1.45 (s, 18 H; (C(CH₃)₃)₂), 1.22–1.03 ppm (m, 5 H; C₆H₁₁); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = –129.25 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 171.6 (CO₂CH₃), 155.4 (d, J = 233.8 Hz; C–F), 152.3 (NC=O), 144.9 (ArC), 115.7 (d, J = 22.3 Hz; ArCH), 113.9 (d, J = 7.3 Hz; ArCH), 83.3 (CO₂C(CH₃)₃), 57.1 (CHNH), 56.6 (CHCO₂CH₃), 52.3 (CO₂CH₃), 42.0 (C₆H₁₁), 33.8 (CH₂), 29.0 (C₆H₁₁), 28.1 (C(CH₃)₃), 26.7 (C₆H₁₁), 26.6 (C₆H₁₁), 26.5 ppm (C₆H₁₁); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3391 (w, N–H), 2927 (m), 2852 (m), 1746 (s, NC=O), 1698 (m, OC=O), 1510 (s); **HRMS** (ESI): m/z = 509.30164 ([M+H]⁺, calcd. for C₂₇H₄₂O₆N₂F⁺: 509.30214).

Data of **anti-91b**:

¹H NMR (400 MHz, CDCl₃): δ = 6.81 (t, J = 8.7 Hz, 2 H; ArH), 6.46 (dd, J = 9.0, 4.4 Hz, 2 H; ArH), 5.06 (dd, J = 9.1, 4.6 Hz, 1 H; CHCO₂CH₃), 3.71 (s, 3 H; CO₂CH₃), 3.18 (d, J = 10.5 Hz, 1 H; CHNH), 2.22–2.07 (m, 2 H; CH₂), 1.75–1.71 (m, 2 H; C₆H₁₁), 1.68–1.57 (m, 4 H; C₆H₁₁ and CH₂); 1.41 (s, 18 H; (C(CH₃)₃)₂), 1.22–0.96 (m, 5 H; C₆H₁₁); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = –129.14 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 172.3 (CO₂CH₃), 155.5 (d, J = 233.8 Hz; C–F), 152.2 (NC=O), 144.4 (ArC), 115.7 (d, J = 22.2 Hz; ArCH), 114.2 (d, J = 7.3 Hz; ArCH), 83.2 (CO₂C(CH₃)₃), 56.2 (CHCO₂CH₃), 55.5 (CHNH), 52.5 (CO₂CC₃), 41.3 (C₆H₁₁), 31.9 (CH₂), 29.8 (C₆H₁₁), 28.0 (C(CH₃)₃), 26.7 (C₆H₁₁), 26.6 (C₆H₁₁), 26.5 ppm (C₆H₁₁); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3392 (w, N–H), 2926 (br), 2852 (m), 1740 (s, NC=O), 1702 (s, OC=O), 1510 (s); **HRMS** (ESI): m/z = 509.30096 ([M+H]⁺, calcd. for C₂₇H₄₂O₆N₂F⁺: 509.30214).

Synthesis of compound **92**



Compound **92** was synthesised according to General Procedure **C** using trimethylacetaldehyde (0.022 mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 3.8:1. FC (SiO₂; pentane/EtOAc 95:5 to 90:10) gave **92a** (23.3 mg, 24%) as brown oil and **92b** (66.8 mg, 69%) as off-white solid (**92**: 93% total isolated yield).

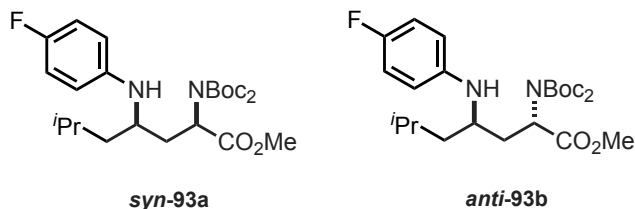
Data of ***syn-92a***:

^1H NMR (400 MHz, CDCl_3): δ = 6.79 (t, J = 8.8 Hz, 2 H; ArH), 6.48 (dd, J = 9.0, 4.4 Hz, 2 H; ArH), 4.91 (dd, J = 9.2, 3.3 Hz, 1 H; CHCO_2CH_3), 3.68 (s, 3 H; CO_2CH_3), 3.36 (d, J = 6.0 Hz, 1 H; CHNH), 2.72 (ddd, J = 14.0, 9.2, 2.5 Hz, 1 H; CH_2), 1.44 (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$), 1.34 (ddd, J = 14.0, 11.0, 3.4 Hz, 1 H; CH_2), 0.94 (s, 9 H; $\text{C}(\text{CH}_3)_3$); **^{19}F $\{^1\text{H}\}$ NMR** (377 MHz, CDCl_3): δ = -129.77 ppm; **^{13}C NMR** (101 MHz, CDCl_3): δ = 171.9 (CO_2CH_3), 156.3 (C-F), 152.1 (NC=O), 146.1 (ArC), 115.7 (d, J = 22.3 Hz; ArCH), 113.3 (d, J = 7.2 Hz; ArCH), 83.2 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 60.3 (CHNH), 56.3 (CHCO_2CH_3), 52.2 (CO_2CH_3), 37.0 ($\text{C}(\text{CH}_3)_3$), 35.7 (CH_2), 28.1 ($\text{C}(\text{CH}_3)_3$), 26.8 ppm ($\text{C}(\text{CH}_3)_3$); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3402 (w, N-H), 2978 (br), 1746 (s, NC=O), 1702 (m, OC=O), 1510 (m); **HRMS** (ESI): m/z = 483.28656 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{25}\text{H}_{40}\text{O}_6\text{N}_2\text{F}^+$: 483.28649).

Data of ***anti-92b***:

m.p. = 128 °C; **^1H NMR** (400 MHz, CDCl_3): δ = 6.78 (dd, J = 9.0, 8.5 Hz, 2 H; ArH), 6.47 (dd, J = 9.0, 4.4 Hz, 2 H; ArH), 4.99 (dd, J = 9.6, 4.2 Hz, 1 H; CHCO_2CH_3), 3.69 (s, 3 H; CO_2CH_3), 3.44 (br, 1 H; CHNH), 3.18–3.03 (m, 1 H; CHNH), 2.26 (ddd, J = 14.8, 9.6, 2.5 Hz, 1 H; CH_2), 2.04 (ddd, J = 14.8, 11.7, 4.2 Hz, 1 H; CH_2); 1.43 (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$), 0.90 (s, 9 H; $\text{C}(\text{CH}_3)_3$); **^{19}F $\{^1\text{H}\}$ NMR** (377 MHz, CDCl_3): δ = -129.98 ppm; **^{13}C NMR** (101 MHz, CDCl_3): δ = 172.5 (CO_2CH_3), 155.2 (d, J = 232.9 Hz; C-F), 152.3 (NC=O), 145.8 (ArC), 115.6 (d, J = 22.2 Hz; ArCH), 113.4 (d, J = 7.2 Hz; ArCH), 83.2 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 59.4 (CHNH), 56.4 (CHCO_2CH_3), 52.4 (CO_2CH_3), 36.9 ($\text{C}(\text{CH}_3)_3$), 32.0 (CH_2), 28.1 ($\text{C}(\text{CH}_3)_3$), 27.1 ppm ($\text{C}(\text{CH}_3)_3$); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3397 (w, N-H), 2952 (br), 1739 (s, NC=O), 1704 (m, OC=O), 1509 (m); **HRMS** (ESI): m/z = 483.28650 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{25}\text{H}_{40}\text{O}_6\text{N}_2\text{F}^+$: 483.28649).

Synthesis of compound **93**



Compound **93** was synthesised according to General Procedure **C** using isovaleraldehyde (0.02 mL, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 2.4:1. FC (SiO₂; pentane/EtOAc 95:5 to 90:10) gave **93a** (29.2 mg, 26%) as brown oil and **93b** (56.7 mg, 59%) as off-white solid (**93**: 85% total isolated yield).

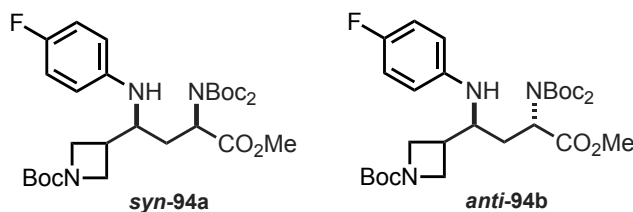
Data of ***syn*-93a**:

¹H NMR (400 MHz, CDCl₃): δ = 6.83 (t, J = 8.7 Hz, 2 H; ArH), 6.52–6.44 (m, 2 H; ArH), 5.04 (t, J = 6.6 Hz, 1 H; CHCO₂CH₃), 3.69 (s, 3 H; CO₂CH₃), 3.61–3.52 (m, 1 H; CHNH), 2.46 (ddd, J = 14.4, 6.5, 5.6 Hz, 1 H; CH₂), 1.82–1.70 (m, 2 H; CH₂ and CH(CH₃)₂), 1.46 (s, 18 H; C(CH₃)₃), 1.31 (d, J = 7.3 Hz, 1 H; CH₂), 1.28–1.21 (m, 1H; CH₂), 0.91 (dd, J = 33.5, 6.6 Hz, 6 H; CH(CH₃)₂); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = –128.87 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 172.6 (CO₂CH₃), 154.5 (C–F), 152.3 (NC=O), 144.3 (ArC), 115.8 (d, J = 21.9 Hz; ArCH), 113.9 (d, J = 7.3 Hz; ArCH), 83.3 (CO₂C(CH₃)₃), 55.6 (CHCO₂CH₃), 52.4 (CO₂CH₃), 49.9 (CHNH), 45.1 (CH₂), 36.6 (CH₂), 28.0 (C(CH₃)₃), 25.1 (CH(CH₃)₂), 22.8 ppm (CH(CH₃)₂); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3368 (w, N–H), 2980 (m), 2917 (m), 1740 (s, NC=O), 1701 (m, OC=O), 1509 (m); **HRMS** (ESI): m/z = 483.28653 ([M+H]⁺, calcd. for C₂₅H₄₀O₆N₂F⁺: 483.28649).

Data of **anti-93b**:

m.p. = 96 °C; ^1H NMR (400MHz, CDCl_3): δ = 6.83 (t, J = 8.8 Hz, 2 H; ArH), 6.61–6.38 (m, 2 H; ArH), 5.08 (dd, J = 8.2, 5.3 Hz, 1 H; CHCO_2CH_3), 3.72 (s, 3 H; CO_2CH_3), 3.41 (tt, J = 8.1, 5.3 Hz, 1 H; CHNH), 3.31 (br, 1 H; CHNH), 2.23–2.11 (m, 2 H; CH_2), 1.72–1.62 (m, 1 H; $\text{CH}(\text{CH}_3)_2$), 1.51–1.48 (m, 1 H; CH_2), 1.42 (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$), 1.31–1.23 (m, 1 H; CH_2), 0.89 (dd, J = 14.9, 6.6 Hz, 6 H; $\text{CH}(\text{CH}_3)_2$); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): δ = –128.79 ppm; ^{13}C NMR (101 MHz, CDCl_3): δ = 172.1 (CO_2CH_3), 155.7 (d, J = 233.9 Hz; $\text{C}-\text{F}$), 152.3 ($\text{NC}=\text{O}$), 144.0 (ArC), 115.7 (d, J = 22.3 Hz; ArCH), 114.3 (d, J = 7.7 Hz; ArCH), 83.3 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 55.8 (CHCO_2CH_3), 52.5 (CO_2CH_3), 49.4 (CHNH), 44.6 (CH_2), 35.3 (CH_2), 28.0 ($\text{C}(\text{CH}_3)_3$), 25.2 ($\text{CH}(\text{CH}_3)_2$), 23.4 ($\text{CH}(\text{CH}_3)_2$), 22.4 ppm ($\text{CH}(\text{CC}_3)_2$); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3370 (w, N–H), 2956 (br), 1740 (s, $\text{NC}=\text{O}$), 1700 (s, $\text{OC}=\text{O}$), 1510 (s); **HRMS** (ESI): m/z = 483.28674 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{25}\text{H}_{40}\text{O}_6\text{N}_2\text{F}^+$: 483.28649).

Synthesis of compound **94**

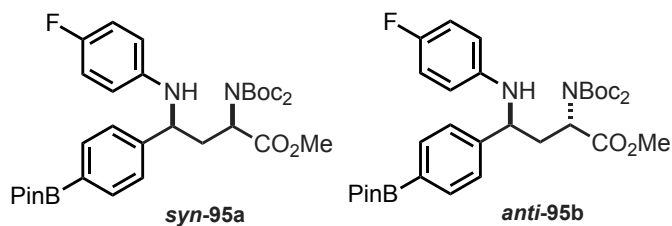


Compound **94** was synthesised according to General Procedure **C** using azetidine-3-carboxaldehyde (37 mg, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 3:2. FC (SiO_2 ; pentane/acetone 95:5 to 90:10) gave an inseparable mixture of **94a** and **94b** (72.6 mg, 65%) as yellow oil.

Data of mixture *syn*-**94a** and *anti*-**94b**:

^1H NMR (400 MHz, CDCl_3): δ = 6.88–6.78 (m, 4 H; ArH, **94a** and **94b**), 6.54 (dd, J = 9.0, 4.3 Hz, 4 H; ArH, **94a** and **94b**), 5.01 (dd, J = 8.6, 4.5 Hz, 1 H; CHCO_2CH_3 , **94b**), 4.95 (dd, J = 7.4, 5.6 Hz, 1 H; CHCO_2CH_3 , **94a**), 3.97–3.85 (m, 4 H; CHNH and CH_2 , **94a** or **94b**), 3.77–3.70 (m, 1 H; CHNH , **94a** or **94b**), 3.71 (s, 3 H; CO_2CH_3 , **94b**), 3.73 (s, 3 H; CO_2CH_3 , **94a**), 3.67–3.63 (m, 3 H; CHNH and CH_2 , **94a** or **94b**), 2.69 (td, J = 13.3, 6.7 Hz, 2 H; CH_2 , **94a** and **94b**), 2.23 (ddd, J = 14.1, 9.1, 4.5 Hz, 1 H; CH_2 , **94a** or **94b**), 2.13–2.04 (m, 1 H; CH_2 , **94a** or **94b**), 1.68–1.58 (m, 2 H; CHCHNH , **94a** and **94b**), 1.47 (s, 18 H; **94a**), 1.44 (s, 18 H; **94b**), 1.42 (s, 9 H; **94a**), 1.41 ppm (s, 9 H; **94b**); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): δ = –127.73 (**94b**), –127.83 ppm (**94a**); ^{13}C NMR (101 MHz, CDCl_3): δ = 171.6, 171.3, 156.4, 152.3, 143.8, 116.0, 116.0, 115.8, 115.8, 114.8, 114.7, 114.4, 114.3, 83.7, 83.6, 79.9, 55.4, 55.2, 54.3, 54.0, 52.6, 52.4, 33.9, 32.5, 28.5, 28.5, 28.1, 28.1 ppm; FT-IR (thin film): ν_{max} (cm^{-1}) = 3365 (w, N–H), 2978 (m), 1741 (s, NC=O), 1694 (m, OC=O), 1508 (s); HRMS (ESI): m/z = 582.31824 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{29}\text{H}_{45}\text{O}_8\text{N}_3\text{F}^+$: 582.31852).

Synthesis of compound **95**

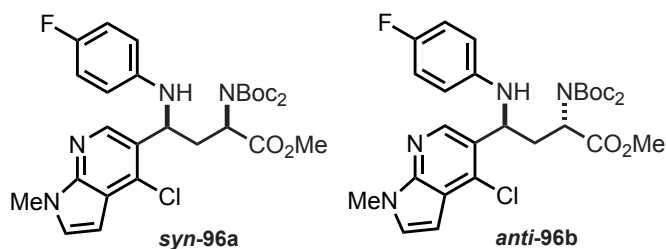


Compound **95** was synthesised according to General Procedure **C** using 4-formylphenylboronic acid pinacol ester (46.4 mg, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 2.2:1. FC (SiO_2 ; pentane/acetone 95:5 to 90:10) gave an inseparable mixture of **95a** and **95b** (83.1 mg, 66%) as yellow oil.

Data of mixture *syn*-**95a** and *anti*-**95b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.80–7.73 (m, 4 H; ArH, **95a** and **95b**), 7.41–7.36 (m, 2 H; ArH, **95a** or **95b**), 7.33–7.28 (m, 2 H; ArH, **95a** or **95b**), 6.75 (dtd, J = 8.7, 7.0, 2.3 Hz, 4 H; ArH, **95a** and **95b**), 6.47–6.35 (m, 4 H; ArH, **95a** and **95b**), 5.16 (dd, J = 7.8, 5.2 Hz, 1 H; CHCO₂CH₃, **95b**), 5.02 (dd, J = 7.5, 4.8 Hz, 1 H; CHCO₂CH₃, **95a**), 4.56–4.44 (m, 2 H; CHNH, **95a**), 4.36 (d, J = 4.2 Hz, 2 H; CHNH, **95b**), 3.73 (s, 3 H; CO₂CH₃, **95b**), 3.72 (s, 3 H; CO₂CH₃, **95a**), 2.80 (ddd, J = 14.5, 7.5, 3.9 Hz, 1 H; CH₂, **95a**), 2.57 (ddd, J = 15.3, 10.4, 4.7 Hz, 1 H; CH₂, **95b**), 2.31–2.24 (m, 1 H; CH₂, **95b**), 1.98 (ddd, J = 14.5, 9.3, 4.8 Hz, 1 H; CH₂, **95a**), 1.47 (s, 18 H; **95a**), 1.41 (s, 18 H; **95b**), 1.41 ppm (s, 22 H; 2x (CH₃)₄, **95a** and **95b**); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = –126.28 (**95b**), –128.39 ppm (**95a**); **¹³C NMR** (101 MHz, CDCl₃): δ = 171.9, 171.3, 152.2, 151.9, 146.8, 146.7, 135.4, 135.4, 125.8, 125.7, 115.7, 115.6, 114.5, 114.5, 114.3, 114.3, 83.9, 83.9, 83.7, 83.6, 57.0, 56.6, 56.3, 56.0, 53.6, 52.5, 50.9, 40.8, 40.0, 28.1, 28.1, 25.0, 25.0 ppm; **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3383 (w, N–H), 1743 (s, NC=O), 1699 (m, OC=O), 1511 (s); **HRMS** (ESI): m/z = 628.34369 ([M+H]⁺, calcd. for C₃₃H₄₇O₈N₂BF⁺: 628.34403).

Synthesis of compound **96**



Compound **96** was synthesised according to General Procedure **C** using 4-chloro-1-methyl-1H-

pyrrolepyridine-5-carboxaldehyde¹⁵ (38.9 mg, 0.2 mmol) and 4-fluoroaniline (0.02 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 1:1. FC (SiO₂; pentane/EtOAc 90:10 to 70:30) gave **96a** (27.7 mg, 23%) as yellow oil and **96b** (31.3 mg, 27%) as brown solid (**96**: 50% total isolated yield).

Data of *syn*-**96a**:

¹H NMR (400 MHz, CDCl₃): δ = 8.29 (s, 1 H; ArH), 7.19 (d, J = 3.5 Hz, 1 H; C₂H₂NCH₃), 6.81–6.69 (m, 2 H; ArH), 6.54 (d, J = 3.4 Hz, 1 H; C₂H₂NCH₃), 6.49–6.39 (m, 2 H; ArH), 5.19 (dd, J = 7.1, 5.7 Hz, 1 H; CHCO₂CH₃), 5.10 (dd, J = 9.8, 3.8 Hz, 1 H; CHNH), 4.63 (s, 1 H; CHNH), 3.84 (s, 3 H; NCH₃), 3.74 (s, 3 H; CO₂CH₃), 2.87 (ddd, J = 15.0, 7.1, 3.8 Hz, 1 H; CH₂), 2.19 (ddd, J = 15.0, 9.7, 6.0 Hz, 1 H; CH₂), 1.44 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = –128.11 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 171.1 (CO₂CH₃), 156.0 (d, J = 234.5 Hz; C–F), 152.3 (NC=O), 147.9 (ArC), 143.2 (ArC), 142.6 (ArCH), 134.6 (ArC), 130.0 (C₂H₂NCH₃), 126.8 (ArC), 120.1 (ArC), 115.64 (d, J = 22.3 Hz; ArCH), 114.3 (d, J = 7.2 Hz; ArCH), 98.3 (C₂H₂NCH₃), 83.7 (CO₂C(CH₃)₃), 56.1 (CHCO₂CH₃), 52.6 (CHNH), 52.5 (CO₂CH₃), 38.7 (CH₂), 31.6 (NCH₃), 28.1 ppm (C(CH₃)₃); FT-IR (thin film): ν_{max} (cm^{–1}) = 3388 (w, N–H), 2981 (m), 1745 (s, NC=O), 1695 (m, OC=O), 1510 (s); HRMS (ESI): m/z = 591.23779 ([M+H]⁺, calcd. for C₂₉H₃₇O₆N₄³⁵ClF⁺: 591.23802).

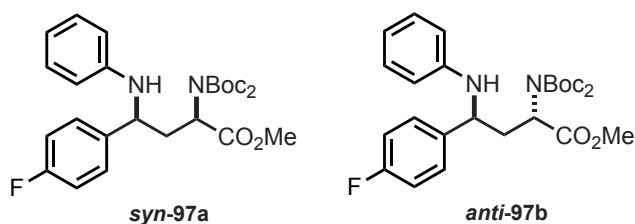
Data of *anti*-**96b**:

¹H NMR (400 MHz, CDCl₃): δ = 8.29 (s, 1 H; ArH), 7.18 (d, J = 3.5 Hz, 1 H; C₂H₂NCH₃), 6.73 (t, J = 8.8 Hz, 2 H; ArH), 6.52 (d, J = 3.5 Hz, 1 H; C₂H₂NCH₃), 6.47–6.37 (m, 2 H; ArH), 5.26 (dd, J = 7.6, 4.7 Hz, 1 H; CHCO₂CH₃), 5.00–4.88 (m, 1 H; CHNH), 4.60 (s, 1 H; CHNH), 3.83 (s, 3 H; NCH₃), 3.74 (s, 3 H; CO₂CH₃), 2.72–2.57 (m, 1 H; CH₂), 2.37 (ddd,

¹⁵this aldehyde was kindly provided by Astex Pharmaceuticals

$J = 15.1, 7.6, 3.3$ Hz, 1 H; CH_2), 1.42 ppm (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -127.99$ ppm; ^{13}C NMR (101 MHz, CDCl_3): $\delta = 172.0$ (CO_2CH_3), 156.0 (d, $J = 235.2$ Hz; CC-F), 151.9 (NC=O), 147.9 (ArC), 143.0 (ArC), 142.3 (ArCH), 134.5 (ArC), 130.0 ($\text{C}_2\text{H}_2\text{NCH}_3$), 126.7 (ArC), 119.9 (ArC), 115.6 (d, $J = 22.3$ Hz; ArCH), 114.4 (d, $J = 7.7$ Hz; ArCH), 98.1 ($\text{C}_2\text{H}_2\text{NCH}_3$), 83.6 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 56.5 (CHCO_2CH_3), 52.7 (CO_2CH_3), 52.1 (CHNH), 39.0 (CH_2), 31.6 (NCH_3), 28.0 ppm ($\text{C}(\text{CH}_3)_3$); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3382 (w, N-H), 2981 (m), 2934 (m), 1739 (s, NC=O), 1699 (m, OC=O), 1510 (s); **HRMS** (ESI): $m/z = 591.23779$ ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{29}\text{H}_{37}\text{O}_6\text{N}_4^{35}\text{ClF}^+$: 591.23802).

Synthesis of compound **97**



Compound **97** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and aniline (0.018 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 2.7:1. FC (SiO_2 ; pentane/EtOAc 95:5 to 90:10) gave **97a** (24.3 mg, 24%) as off-white solid and **97b** (69.2 mg, 69%) as off-white solid (**97**: 93% total isolated yield).

Data of **syn-97a**:

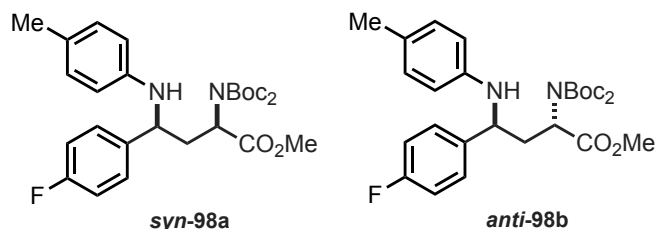
m.p. = 134 °C; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.44\text{--}7.32$ (m, 2 H; ArH), 7.14–7.04 (m, 2 H; ArH), 6.99 (t, $J = 8.7$ Hz, 2 H; ArH), 6.72–6.61 (m, 1 H; ArH), 6.50 (dt, $J = 7.8, 1.1$ Hz, 2 H; ArH), 4.99 (dd, $J = 7.4, 5.0$ Hz, 1 H; CHCO_2CH_3), 4.55 (dd, $J = 9.0, 4.4$ Hz, 2 H; CHNH and CHNH), 3.72 (s, 3 H; CO_2CH_3), 2.88–2.71 (m, 1 H; CH_2), 2.12–1.94 (m, 1 H; CH_2); 1.48 ppm

(s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = -116.02 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 171.2 (CO₂CH₃), 163.3 (C-F), 152.3 (NC=O), 147.3 (ArC), 139.2 (d, *J* = 3.2 Hz; ArC), 129.2 (ArCH), 128.0 (d, *J* = 8.0 Hz; ArCH), 117.5 (ArCH), 115.6 (d, *J* = 21.5 Hz; ArCH), 113.5 (ArCH), 83.7 (CO₂C(CH₃)₃), 55.9 (CHCO₂CH₃), 55.6 (CHNH), 52.5 (CO₂CH₃), 41.0 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3381 (w, N-H), 2934 (m), 1745 (s, NC=O), 1701 (m, OC=O), 1508 (m); **HRMS** (ESI): *m/z* = 503.25479 ([M+H]⁺, calcd. for C₂₇H₃₆O₆N₂F⁺: 503.25519).

Data of *anti*-**97b**:

m.p. = 108 °C; ¹H NMR (400MHz, CDCl₃): δ = 7.33–7.27 (m, 2 H; ArH), 7.09–7.03 (m, 2 H; ArH), 7.02–6.94 (m, 2 H; ArH), 6.65–6.59 (m, 1 H; ArH), 6.51–6.46 (m, 2 H; ArH), 5.11 (dd, *J* = 7.4, 5.4 Hz, 1 H; CHCO₂CH₃), 4.45 (dd, *J* = 10.4, 4.0 Hz, 2 H; CHNH), 3.74 (s, 3 H; CO₂CH₃), 2.62 (ddd, *J* = 15.0, 10.3, 5.4 Hz, 1 H; CH₂), 2.25 (ddd, *J* = 15.0, 7.4, 3.9 Hz, 1 H; CH₂), 1.43 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = -115.86 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 172.0 (CO₂CH₃), 162.0 (d, *J* = 245.1 Hz; C-F), 152.0 (NC=O), 147.0 (ArC), 139.2 (d, *J* = 3.1 Hz; ArC), 129.2 (ArCH), 127.8 (d, *J* = 8.0 Hz; ArCH), 117.6 (ArCH), 115.7 (d, *J* = 21.4 Hz; ArCH), 113.6 (ArCH), 83.6 (CO₂C(CH₃)₃), 56.3 (CHCO₂CH₃), 55.5 (CHNH), 52.6 (CO₂CH₃), 40.2 (CH₂), 28.0 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3401 (w, N-H), 2933 (m), 1741 (s, NC=O), 1699 (m, OC=O), 1508 (s); **HRMS** (ESI): *m/z* = 503.25439 ([M+H]⁺, calcd. for C₂₇H₃₆O₆N₂F⁺: 503.25519).

Synthesis of compound **98**



Compound **98** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and p-toluidine (21.4 mg, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 3:1. FC (SiO₂; pentane/acetone 95:5 to 90:10) gave **98a** (20.6 mg, 20%) as off-white solid and **98b** (55.5 mg, 54%) as off-white solid (**98**: 74% total isolated yield).

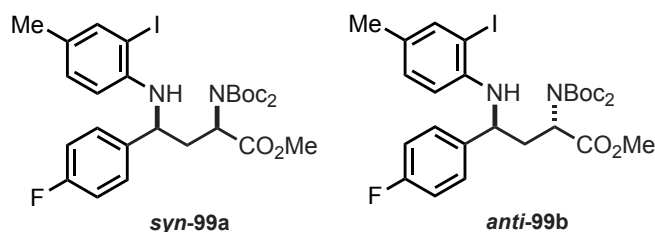
Data of **syn-98a**:

m.p. = 164 °C; ¹H NMR (400MHz, CDCl₃): δ = 7.37 (dd, *J* = 8.6, 5.4 Hz, 2 H; ArH), 6.98 (t, *J* = 8.7 Hz, 2 H; ArH), 6.93–6.83 (m, 2 H; ArH), 6.47–6.36 (m, 2 H; ArH), 4.97 (dd, *J* = 7.4, 5.0 Hz, 1 H; CHCO₂CH₃), 4.52 (dd, *J* = 9.1, 4.5 Hz, 1 H; CHNH), 4.40 (br, s, 1 H; CHNH), 3.72 (s, 3 H; CO₂CH₃), 2.78 (ddd, *J* = 14.5, 7.4, 4.5 Hz, 1 H; CH₂), 2.17 (s, 3 H; ArCH₃), 2.00 (ddd, *J* = 14.5, 9.0, 5.0 Hz, 1 H; CH₂), 1.48 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = –116.15 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 171.3 (CO₂CH₃), 161.9 (d, *J* = 259.8 Hz; C–F), 152.3 (NC=O), 145.0 (ArC), 139.4 (ArC), 129.7 (ArCH), 128.0 (d, *J* = 8.0 Hz; ArCH), 126.7 (ArC), 116.0 (d, *J* = 21.4 Hz, ArCH), 113.6 (ArCH), 83.7 (CO₂C(CH₃)₃), 55.9 (CHCO₂CH₃), 55.8 (CHNH), 52.5 (CO₂CH₃), 41.0 (CH₂), 28.1 (C(CH₃)₃), 20.5 ppm (ArCH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3389 (w, N–H), 2978 (m), 2927 (m), 1746 (s, NC=O), 1699 (s, OC=O), 1508 (s); **HRMS** (ESI): *m/z* = 517.27069 ([M+H]⁺, calcd. for C₂₈H₃₈O₆N₂F⁺: 517.27084).

Data of **anti-98b**:

m.p. = 148 °C; **¹H NMR** (400MHz, CDCl₃): δ = 7.32–7.26 (m, 2 H; ArH), 6.97 (t, J = 8.7 Hz, 2 H; ArH), 6.91–6.81 (m, 2 H; ArH), 6.40 (d, J = 8.4 Hz, 2 H; ArH), 5.10 (dd, J = 7.3, 5.4 Hz, 1 H; CHCO₂CH₃), 4.41 (dd, J = 10.4, 4.0 Hz, 1 H; CHNH), 4.35 (br, s, 1 H; CHNH), 3.73 (s, 3 H; CO₂CH₃), 2.67–2.54 (m, 1 H; CH₂), 2.22 (ddd, J = 15.0, 7.3, 4.0 Hz, 1 H; CH₂), 2.16 (s, 3 H; ArCH₃), 1.42 ppm (s, 18 H; (C(CH₃)₃)₂); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = –115.98 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 172.0 (CO₂CH₃), 162.0 (d, J = 244.8 Hz; C–F), 152.0 (NC=O), 144.6 (ArC), 139.4 (ArC), 129.2 (ArCH), 127.9 (d, J = 7.9 Hz; ArCH), 126.7 (ArC), 115.7 (d, J = 21.4 Hz, ArCH), 113.8 (ArCH), 83.6 (CO₂C(CH₃)₃), 56.4 (CHCO₂CH₃), 55.7 (CHNH), 52.6 (CO₂CH₃), 40.2 (CH₂), 28.1 (C(CH₃)₃), 20.5 ppm (ArCH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3395 (w, N–H), 2978 (m), 1746 (s, NC=O), 1699 (s, OC=O), 1508 (m); **HRMS** (ESI): m/z = 517.27081 ([M+H]⁺, calcd. for C₂₈H₃₈O₆N₂F⁺: 517.27084).

Synthesis of compound **99**



Compound **99** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and 3-iodo-4-methylamine (46.6 mg, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 3.3:1. FC (SiO₂; pentane/acetone 95:5 to 90:10) gave **99a** (25.7 mg, 20%) as yellow oil and **99b** (62.3 mg, 49%) as off-white solid (**99**: 69% total isolated yield).

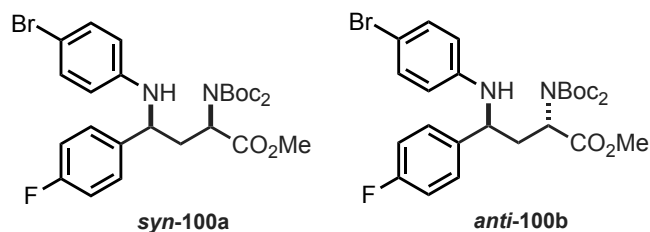
Data of *syn-99a*:

^1H NMR (400 MHz, CDCl_3): δ = 7.34 (dd, J = 8.8, 5.3 Hz, 2 H; ArH), 7.03–6.97 (m, 3 H; ArH), 6.89 (dd, J = 8.2, 0.7 Hz, 1 H; ArH), 6.36 (dd, J = 8.2, 2.5 Hz, 1 H; ArH), 4.96 (dd, J = 7.4, 5.1 Hz, 1 H; CHCO_2CH_3), 4.48 (d, J = 5.7 Hz, 2 H; CHNH), 3.73 (s, 3 H; CO_2CH_3), 2.76 (ddd, J = 14.5, 7.4, 3.8 Hz, 1 H; CH_2), 2.25 (s, 3 H; ArCH_3), 1.99 (ddd, J = 14.5, 9.2, 5.1 Hz, 1 H; CH_2), 1.48 ppm (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): δ = –115.79 ppm; ^{13}C NMR (101 MHz, CDCl_3): δ = 152.4 (NC=O), 146.2 (ArC), 129.8 (ArCH), 127.9 (d, J = 8.3 Hz; ArCH), 123.8 (ArCH), 115.7 (d, J = 21.5 Hz; ArCH), 113.7 (ArCH), 83.8 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 55.9 (CHNH), 52.5 (CO_2CH_3), 28.1 ($\text{C}(\text{CH}_3)_3$), 26.8 ppm (ArCH_3); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3375 (w, N–H), 2980 (m), 2931 (m), 1745 (s, NC=O), 1698 (s, OC=O), 1507 (s); **HRMS** (ESI): m/z = 643.16705 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{28}\text{H}_{37}\text{O}_6\text{N}_2\text{FI}^+$: 643.16748). Note: CO_2CH_3 , C–F , and two ArC were not observed.

Data of *anti-99b*:

m.p. = 136 °C; ^1H NMR (400MHz, CDCl_3): δ = 7.28 (d, J = 5.3 Hz, 2 H; ArH), 7.03–6.94 (m, 3 H; ArH), 6.88 (dd, J = 8.2, 0.7 Hz, 1 H; ArH), 6.36 (dd, J = 8.2, 2.5 Hz, 1 H; ArH), 5.07 (dd, J = 7.1, 5.5 Hz, 1 H; CHCO_2CH_3), 4.42 (br, 1 H; CHNH), 4.37 (dd, J = 10.4, 4.0 Hz, 1 H; CHNH), 3.74 (s, 3 H; CO_2CH_3), 2.64–2.55 (m, 1 H; CH_2), 2.24 (s, 3 H; ArCH_3), 2.22–2.17 (m, 1 H; CH_2), 1.44 ppm (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): δ = –115.59 ppm; ^{13}C NMR (101 MHz, CDCl_3): δ = 172.0 (CO_2CH_3), 160.9 (C–F), 152.1 (NC=O), 146.9 (ArC), 138.8 (ArC), 129.9 (ArC), 129.7 (ArCH), 127.8 (d, J = 8.0 Hz; ArCH), 123.8 (ArCH), 115.8 (d, J = 21.4 Hz, ArCH), 113.6 (ArCH), 101.6 (ArC), 83.7 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 56.3 (CHCO_2CH_3), 55.6 (CHNH), 52.7 (CO_2CH_3), 40.1 (CH_2), 28.1 ($\text{C}(\text{CH}_3)_3$), 26.8 ppm (ArCH_3); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3384 (w, N–H), 2979 (m), 1739 (s, NC=O), 1699 (s, OC=O), 1507 (s); **HRMS** (ESI): m/z = 643.16699 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{28}\text{H}_{37}\text{O}_6\text{N}_2\text{FI}^+$: 643.16748).

Synthesis of compound **100**



Compound **100** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and 4-bromoaniline (34.4 mg, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 3.4:1. FC (SiO₂; pentane/EtOAc 95:5 to 90:10) gave an inseparable mixture of **100a** and **100b** (105.8mg, 91%) as yellow solid. Preparative thin layer chromatography of a small sample of **100** allowed separation of major and minor diastereoisomers for full characterization.

Data of mixture ***syn*-100a** and ***anti*-100b**:

m.p. = 160 °C; **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3386 (w, N-H), 2980 (m), 1742 (s, NC=O), 1700 (s, OC=O), 1508 (m); **HRMS** (ESI): m/z = 581.16583 ([M+H]⁺, calcd. for C₂₇H₃₅O₆N₂⁷⁹BrF⁺: 581.16570).

Data of ***syn*-100a**:

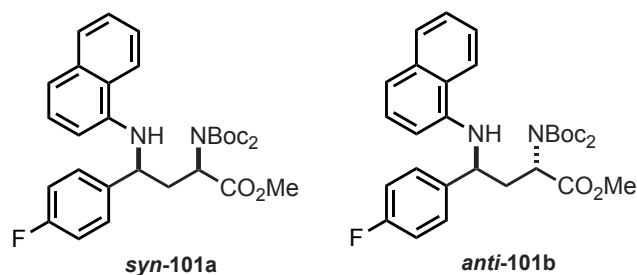
¹H NMR (400 MHz, CDCl₃): δ = 7.34 (dd, J = 8.6, 5.3 Hz, 2 H; ArH), 7.15 (d, J = 8.9 Hz, 2 H; ArH), 7.00 (t, J = 8.7 Hz, 2 H; ArH), 6.37 (d, J = 8.9 Hz, 2 H; ArH), 4.96 (dd, J = 7.4, 4.9 Hz, 1 H; CHCO₂CH₃), 4.66 (br, 1 H; CHNH), 4.53–4.47 (m, 1 H; CHNH), 3.73 (s, 3 H; CO₂CH₃), 2.79 (ddd, J = 14.5, 7.4, 4.2 Hz, 1 H; CH₂), 1.99 (ddd, J = 14.5, 9.3, 4.9 Hz, 1 H;

CH_2), 1.48 ppm (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): $\delta = -115.64$ ppm; ^{13}C NMR (101 MHz, CDCl_3): $\delta = 171.2$ (CO_2CH_3), 160.9 ($\text{C}-\text{F}$), 152.4 ($\text{NC}=\text{O}$), 146.3 (ArC), 131.9 (ArCH), 127.9 (d, $J = 8.0$ Hz; ArCH), 115.8 (d, $J = 21.4$ Hz; ArCH), 115.1 (ArCH), 109.2 (ArC), 83.8 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 55.8 (CHCO_2CH_3), 55.8 (CHNH), 52.6 (CO_2CH_3), 41.0 (CH_2), 28.1 ppm ($\text{C}(\text{CH}_3)_3$). Note: one ArC was not observed.

Data of ***anti*-100b**:

^1H NMR (400 MHz, CDCl_3): $\delta = 7.29$ – 7.23 (m, 2 H; ArH), 7.13 (d, $J = 8.8$ Hz, 2 H; ArH), 6.99 (t, $J = 8.7$ Hz, 2 H; ArH), 6.36 (d, $J = 8.9$ Hz, 2 H; ArH), 5.08 (dd, $J = 7.2, 5.5$ Hz, 1 H; CHCO_2CH_3), 4.59 (d, $J = 6.5$ Hz, 1 H; CHNH), 4.38 (br, 1 H; CHNH), 3.74 (s, 3 H; CO_2CH_3), 2.68–2.52 (m, 1 H; CH_2), 2.23 (ddd, $J = 15.0, 7.2, 4.0$ Hz, 1 H; CH_2), 1.43 ppm (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): $\delta = -115.45$ ppm; ^{13}C NMR (101 MHz, CDCl_3): $\delta = 172.0$ (CO_2CH_3), 162.1 (d, $J = 245.5$ Hz; $\text{C}-\text{F}$), 152.1 ($\text{NC}=\text{O}$), 146.0 (ArC), 138.6 (d, $J = 3.1$ Hz; ArC), 131.9 (ArCH), 127.8 (d, $J = 8.0$ Hz; ArCH), 115.8 (d, $J = 21.5$ Hz; ArCH), 115.2 (ArCH), 109.3 (ArC), 83.7 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 56.2 (CHCO_2CH_3), 55.7 (CHNH), 52.7 (CO_2CH_3), 40.2 (CH_2), 28.1 ppm ($\text{C}(\text{CH}_3)_3$).

Synthesis of compound **101**



Compound **101** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and 1-aminonaphthalene (28.6 mg, 0.2 mmol) and irradiated with blue

light for 24 h. Crude dr: 2:1. FC (SiO₂; pentane/acetone 95:5 to 90:10) gave **101a** (26 mg, 23%) as yellow oil and **101b** (57.3 mg, 52%) as brown oil (**101**: 75% total isolated yield).

Data of *syn*-**101a**:

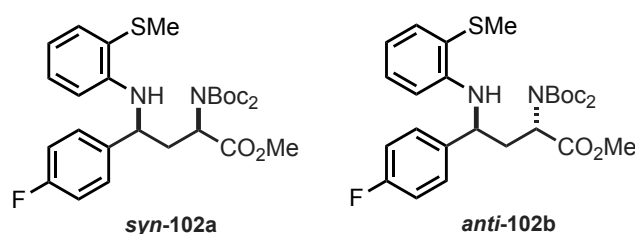
¹H NMR (400 MHz, CDCl₃): δ = 8.15–8.09 (m, 1 H; ArH), 7.79–7.73 (m, 1 H; ArH), 7.49–7.38 (m, 4 H; ArH), 7.19–7.09 (m, 2 H; ArH), 6.99 (t, *J* = 8.7 Hz, 2 H; ArH), 6.22 (dd, *J* = 6.5, 2.3 Hz, 1 H; ArH) 5.12 (dd, *J* = 7.4, 4.7 Hz, 1 H; CHCO₂CH₃), 4.75 (dt, *J* = 9.0, 4.2 Hz, 1 H; CHNH), 3.75 (s, 3 H; CO₂CH₃), 2.93 (ddd, *J* = 14.7, 7.4, 3.7 Hz, 1 H; CH₂), 2.24–2.16 (m, 1 H; CH₂), 1.45 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = –116.01 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 171.4 (CO₂CH₃), 160.9 (C–F), 152.5 (NC=O), 142.3 (ArC), 138.9 (ArC), 134.5 (ArC), 128.7 (ArCH), 127.9 (d, *J* = 8.0 Hz; ArCH), 126.6 (ArCH), 125.8 (ArCH), 124.7 (ArCH), 123.6 (ArC), 120.7 (ArCH), 117.3 (ArCH), 115.7 (d, *J* = 21.4 Hz, ArCH), 105.8 (ArCH), 83.8 (CO₂C(CH₃)₃), 56.2 (CHCO₂CH₃), 55.9 (CHNH), 52.6 (CO₂CH₃), 41.4 (CH₂), 28.1 ppm (C(CH₃)₃); FT-IR (thin film): ν_{max} (cm^{–1}) = 3416 (w, N–H), 2981 (m), 1744 (s, NC=O), 1695 (s, OC=O), 1508 (s); HRMS (ESI): *m/z* = 553.27063 ([M+H]⁺, calcd. for C₃₁H₃₈O₆N₂F⁺: 553.27084).

Data of *anti*-**101b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.99 (dd, *J* = 7.4, 1.9 Hz, 1 H; ArH), 7.80–7.71 (m, 1 H; ArH), 7.53–7.41 (m, 2 H; ArH), 7.41–7.32 (m, 2 H; ArH), 7.17–7.12 (m, 2 H; ArH), 6.99 (t, *J* = 8.7 Hz, 2 H; ArH), 6.27 (dd, *J* = 5.4, 3.3 Hz, 1 H; ArH), 5.57 (br, 1 H; CHNH), 5.15 (t, *J* = 5.8 Hz, 1 H; CHCO₂CH₃), 4.69 (dd, *J* = 10.4, 3.7 Hz, 1 H; CHNH), 3.77 (s, 3 H; CO₂CH₃), 2.88 (ddd, *J* = 15.1, 10.4, 5.9 Hz, 1 H; CH₂), 2.28 (ddd, *J* = 15.1, 5.8, 3.8 Hz, 1 H; CH₂), 1.42 ppm (s, 18 H; (C(CH₃)₃)₂); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = –115.73 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 172.5 (CO₂CH₃), 162.1 (d, *J* = C–F), 152.0 (NC=O), 142.0 (ArC), 138.9

(d, $J = 3.1$ Hz; ArC), 134.4 (ArC), 128.7 (ArCH), 127.8 (d, $J = 8.0$ Hz; ArCH), 126.6 (ArCH), 125.7 (ArCH), 124.8 (ArCH), 123.6 (ArC), 120.4 (ArCH), 117.4 (ArCH), 115.7 (d, $J = 21.5$ Hz; ArCH), 105.8 (ArCH), 83.7 (CO₂C(CH₃)₃), 56.8 (CHCO₂CH₃), 56.4 (CHNH), 52.8 (CO₂CH₃), 40.9 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3420 (w, N-H), 2979 (m), 1740 (s, NC=O), 1699 (s, OC=O), 1508 (m); **HRMS** (ESI): $m/z = 553.27075$ ([M+H]⁺, calcd. for C₃₁H₃₈O₆N₂F⁺: 553.27084).

Synthesis of compound **102**



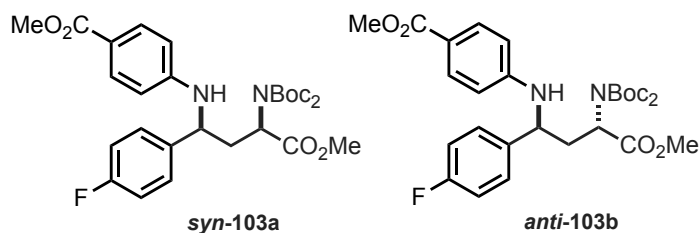
Compound **102** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and 2-(methylthio)aniline (0.025 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 1:1. FC (SiO₂; pentane/EtOAc 90:10 to 85:15) gave an inseparable mixture of diamine102.syn and diamine102.anti (77.7 mg, 71%) as yellow oil.

Data of mixture **syn-102a** and **anti-102b**:

¹H NMR (400 MHz, CDCl₃): $\delta = 7.37$ (td, $J = 7.7, 1.6$ Hz, 2 H; ArH, **102a** and **102b**), 7.30–7.21 (m, 4 H; ArH, **102a** and **102b**), 7.03–6.94 (m, 6 H; ArH, **102a** and **102b**), 6.57 (dd, $J = 7.5, 1.3$ Hz, 2 H; ArH, **102a** and **102b**), 6.38 (dd, $J = 8.3, 1.2$ Hz, 2 H; ArH, **102a** and **102b**), 5.17 (dd, $J = 8.7, 5.1$ Hz, 1 H; CHCO₂CH₃, **102b**), 5.09 (t, $J = 6.5$ Hz, 1 H; CHCO₂CH₃, **102a**), 4.68 (d, $J = 6.0$ Hz, 1 H; CHNH, **102a**), 4.52 (ddd, $J = 11.0, 7.4, 4.0$ Hz, 1 H; CHNH, **102a**), 3.75 (s, 3 H; CO₂CH₃, **102b**), 3.73 (s, 3 H; CO₂CH₃, **102a**), 2.79 (ddd, $J = 14.6, 6.8,$

5.1 Hz, 1 H; CH_2 , **102a**), 2.68–2.61 (m, 1 H; CH_2 , **102b**), 2.43–2.37 (m, 1 H; CH_2 , **102b**), 2.36 (s, 3 H; SCH_3 , **102a**), 2.35 (s, 3 H; SCH_3 , **102b**), 2.23–2.14 (m, 1 H; CH_2 , **102a**), 1.47 (s, 18 H; **102a**), 1.40 ppm (s, 18 H; **102b**); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): $\delta = -115.71$ (**102b**), -115.72 ppm (**102a**); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 171.6, 163.3, 160.8, 152.3, 152.1, 147.3, 147.1, 138.9, 138.9, 134.6, 134.4, 129.5, 129.4, 128.1, 128.0, 127.8, 127.7, 120.3, 117.6, 117.4, 115.8, 115.8, 115.6, 115.6, 111.7, 111.6, 83.6, 83.5, 56.1, 56.0, 55.2, 54.7, 52.6, 52.5, 40.5, 40.0, 28.1, 28.0, 18.7, 18.7$ ppm; FT-IR (thin film): ν_{max} (cm^{-1}) = 3366 (w, N-H), 2980 (m), 1741 (s, NC=O), 1699 (s, OC=O), 1506 (s); HRMS (ESI): $m/z = 549.24262$ ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{28}\text{H}_{38}\text{O}_6\text{N}_2\text{FS}^+$: 549.24291).

Synthesis of compound **103**



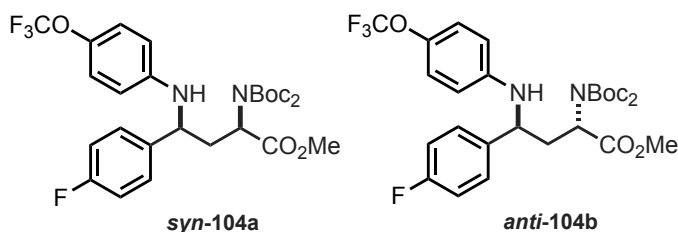
Compound **103** was synthesised according to General Procedure **C** using preformed imine **67a** (51.45 mg, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 2:1. FC (SiO_2 ; pentane/EtOAc 90:10) gave an inseparable mixture of **103a** and **103b** (101.1 mg, 90%) as brown solid.

Data of mixture **syn-103a** and **anti-103b**:

m.p. = 92 °C; ^1H NMR (400MHz, CDCl_3): $\delta = 7.81\text{--}7.67$ (m, 4 H; ArH, **103a** and **103b**), $7.22\text{--}7.08$ (m, 2 H; ArH, **103a** and **103b**), 7.00 (td, $J = 8.6, 1.2$ Hz, 4 H; ArH, **103a** and **103b**), 6.45 (dd, $J = 8.9, 2.2$ Hz, 4 H; ArH, **103a** and **103b**), 5.08 (t, $J = 6.2$ Hz, 1 H; CHCO_2CH_3 ,

103b), 5 4.96 (dd, $J = 7.5, 4.8$ Hz, 1 H; CHCO_2CH_3 , **103a**), 4.62 (dd, $J = 9.4, 4.0$ Hz, 1 H; CHNH , **103a**), 4.51 (dd, $J = 10.5, 3.9$ Hz, 1 H; CHNH , **103b**), 3.92 (s, 3 H; ArCO_2CH_3 , **103a**), 3.81 (s, 3 H; ArCO_2CH_3 , **103b**), 3.75 (s, 3 H; CO_2CH_3 , **103b**), 3.73 (s, 3 H; CO_2CH_3 , **103a**), 2.81 (dd, $J = 7.3, 3.3$ Hz, 1 H; CH_2 , **103a**), 2.72–2.60 (m, 1 H; CH_2 , **103b**), 2.23 (ddd, $J = 15.0, 6.7, 3.9$ Hz, 1 H; CH_2 , **103b**), 2.07–2.00 (m, 1 H; CH_2 , **103a**), 1.47 (s, 18 H; **103a**), 1.43 ppm (s, 18 H; **103b**); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): $\delta = -115.35$ (**103b**), -115.49 ppm (**103a**); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 172.0, 171.2, 167.6, 163.3, 160.9, 152.4, 152.0, 151.2, 150.9, 138.3, 131.5, 131.4, 130.9, 129.9, 129.8, 127.9, 127.8, 127.7, 119.6, 118.6, 116.1, 115.9, 115.7, 112.5, 112.4, 84.0, 83.9, 56.2, 55.8, 55.1, 52.7, 52.6, 52.2, 51.6, 50.7, 40.6, 40.0, 28.0, 28.0$ ppm; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3368 (w, N–H), 2981 (m), 1783 (m, NC=O), 1699 (s, OC=O), 1509 (m); **HRMS** (ESI): $m/z = 561.26068$ ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{29}\text{H}_{38}\text{O}_8\text{N}_2\text{F}^+$: 561.26067).

Synthesis of compound **104**



Compound **104** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and 4-trifluoromethoxyaniline (0.027 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 3.3:1. FC (SiO_2 ; pentane/acetone 95:5 to 90:10) gave **104a** (29.2 mg, 25%) as yellow oil and **104b** (86 mg, 73%) as off-white amorphous solid (**104**: 98% total isolated yield).

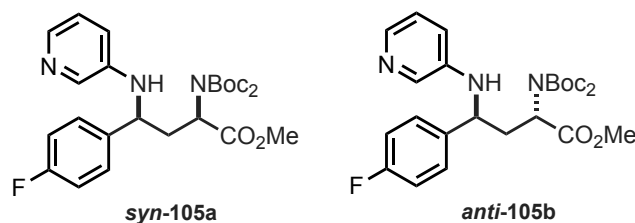
Data of **syn-104a**:

^1H NMR (400 MHz, CDCl_3): δ = 7.36 (dd, J = 8.6, 5.3 Hz, 2 H; ArH), 7.01 (t, J = 8.7 Hz, 2 H; ArH), 6.93 (dd, J = 9.1, 1.0 Hz, 2 H; ArH), 6.44 (d, J = 9.0 Hz, 2 H; ArH), 4.98 (dd, J = 7.4, 5.0 Hz, 1 H; CHCO_2CH_3), 4.49 (dd, J = 9.4, 4.0 Hz, 1 H; CHNH), 3.73 (s, 3 H; CO_2CH_3), 2.78 (ddd, J = 14.5, 7.4, 4.1 Hz, 1 H; CH_2), 2.01 (ddd, J = 14.5, 9.4, 5.1 Hz, 1 H; CH_2), 1.47 ppm (s, 18 H; $\text{C}(\text{CH}_3)_3$); **^{19}F $\{^1\text{H}\}$ NMR** (377 MHz, CDCl_3): δ = -58.51 (3 F, OCF_3), -115.61 ppm (1 F, ArF); **^{13}C NMR** (101 MHz, CDCl_3): δ = 171.2 (CO_2CH_3), 152.4 (NC=O), 146.1 (ArC), 127.9 (d, J = 8.0 Hz; ArCH), 122.4 (ArCH), 115.8 (d, J = 21.5 Hz; ArCH), 113.7 (ArCH), 83.9 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 56.0 (CHNH), 56.0 (CHCO_2CH_3), 52.6 (CO_2CH_3), 41.0 (CH_2), 28.1 ppm ($\text{C}(\text{CH}_3)_3$); **FT- IR** (thin film): ν_{max} (cm^{-1}) = 3392 (w, N-H), 2981 (m), 2932 (m), 1743 (m, NC=O), 1697 (m, OC=O), 1510 (m); **HRMS** (ESI): m/z = 587.23706 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{28}\text{H}_{35}\text{O}_7\text{N}_2\text{F}_4^+$: 587.23749). Note: C-F , two ArC, and OCF_3 were not observed.

Data of ***anti*-104b**:

^1H NMR (400 MHz, CDCl_3): δ = 7.32–7.26 (m, 2 H; ArH), 7.01 (t, J = 8.7 Hz, 2 H; ArH), 6.92 (dd, J = 9.0, 1.0 Hz, 2 H; ArH), 6.44 (d, J = 9.0 Hz, 2 H; ArH), 5.10 (dd, J = 7.5, 5.6 Hz, 1 H; CHCO_2CH_3), 4.37 (br, 1 H; CHNH), 4.37 (dd, J = 10.6, 3.8 Hz, 1 H; CHNH), 3.74 (s, 3 H; CO_2CH_3), 2.59 (ddd, J = 15.0, 10.5, 5.6 Hz, 1 H; CH_2), 2.27 (ddd, J = 15.0, 7.6, 3.8 Hz, 1 H; CH_2), 1.42 ppm (s, 18 H; $\text{C}(\text{CH}_3)_3$); **^{19}F $\{^1\text{H}\}$ NMR** (377 MHz, CDCl_3): δ = -58.54 (3 F, OCF_3), -115.44 ppm (1 F, ArF); **^{13}C NMR** (101 MHz, CDCl_3): δ = 171.9 (CO_2CH_3), 162.1 (d, J = 245.3 Hz; C-F), 152.1 (NC=O), 145.8 (ArC), 140.7 (ArC), 138.8 (ArC), 127.8 (d, J = 8.1 Hz; ArCH), 122.4 (ArCH), 115.8 (d, J = 21.8 Hz; ArCH), 113.8 (ArCH), 83.7 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 56.2 (CHCO_2CH_3), 55.8 (CHNH), 52.7 (CO_2CH_3), 40.2 (CH_2), 28.0 ppm ($\text{C}(\text{CH}_3)_3$); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3392 (w, N-H), 2981 (m), 1738 (m, NC=O), 1697 (m, OC=O), 1509 (m); **HRMS** (ESI): m/z = 587.23785 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{28}\text{H}_{35}\text{O}_7\text{N}_2\text{F}_4^+$: 587.23749). Note: OCF_3 was not observed.

Synthesis of compound **105**



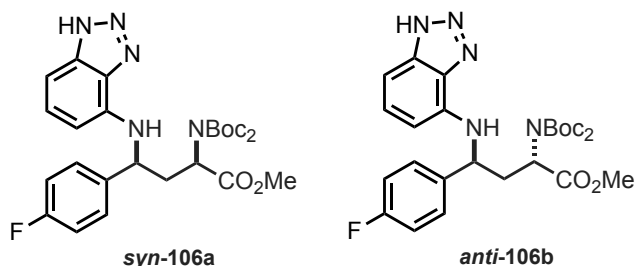
Compound **105** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and 3-aminopyridine (19 mg, 0.2 mmol) and irradiated with blue light for 48 h. Crude dr: 3.3:1. FC (SiO₂; pentane/acetone 70:30 to 50:50) gave an inseparable mixture of **105a** and **105b** (50.6 mg, 50%) as brown oil.

Data of mixture ***syn*-105a** and ***anti*-105b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.98 (d, *J* = 2.9 Hz, 1 H; ArH, **105b**), 7.95 (d, *J* = 2.9 Hz, 1 H; ArH, **105a**), 7.88 (t, *J* = 4.4 Hz, 2 H; ArH, **105a** and **105b**), 7.38–7.32 (m, 2 H; ArH, **105b**), 7.30–7.27 (m, 2 H; ArH, **105a**), 7.00 (dd, *J* = 8.5, 1.7 Hz, 4 H; ArH, **105a** and **105b**), 6.97–6.91 (m, 2 H; ArH, **105a** and **105b**), 6.69 (dddd, *J* = 9.7, 8.3, 3.2, 1.7 Hz, 2 H; ArH, **105a** and **105b**), 5.10 (dd, *J* = 7.3, 5.6 Hz, 1 H; CHCO₂CH₃, **105a**), 4.97 (dd, *J* = 7.3, 5.0 Hz, 1 H; CHCO₂CH₃, **105b**), 4.77 (d, *J* = 5.5 Hz, 1 H; CHNH, **105a**), 4.72 (br, 1 H; CHNH, **105a**), 4.53 (dd, *J* = 9.3, 4.6 Hz, 1 H; CHNH, **105b**), 4.41 (br, 1 H; CHNH, **105b**), 3.73 (s, 3 H; CO₂CH₃, **105a**), 3.73 (s, 3 H; CO₂CH₃, **105b**), 2.80 (ddd, *J* = 14.7, 7.4, 4.2 Hz, 1 H; CH₂, **105b**), 2.70–2.56 (m, 1 H; CH₂, **105a**), 2.26 (ddd, *J* = 15.0, 7.3, 3.9 Hz, 1 H; CH₂, **105a**), 2.04 (ddd, *J* = 14.5, 9.3, 5.0 Hz, 1 H; CH₂, **105b**), 1.47 (s, 18 H; **105b**), 1.42 ppm (s, 18 H; **105a**);
¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = −115.22 (**105a**), −115.40 ppm (**105a**); ¹³C NMR (101 MHz, CDCl₃): δ = 171.9, 171.1, 163.4, 160.9, 152.4, 152.1, 143.3, 143.0, 139.0, 138.9, 138.3,

136.8, 136.8, 127.9, 127.8, 127.7, 123.7, 123.6, 119.4, 119.2, 116.0, 115.9, 115.8, 115.7, 83.9, 83.7, 56.1, 55.9, 55.6, 55.5, 52.7, 52.6, 40.9, 40.1, 28.1, 28.0 ppm; **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3367 (w, N-H), 2982 (m), 1742 (s, NC=O), 1698 (s, OC=O), 1508 (s); **HRMS** (ESI): m/z = 504.24994 ([M+H]⁺, calcd. for C₂₆H₃₅O₆N₃F⁺: 504.25044).

Synthesis of compound **106**



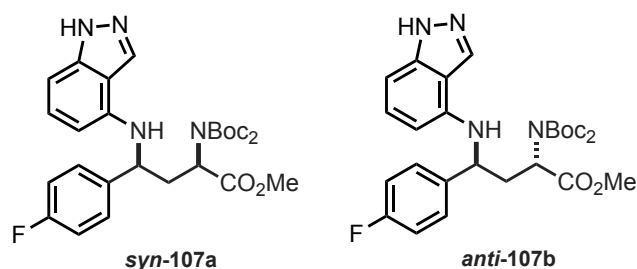
Compound **106** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and benzotriazole-4-amine (26.8 mg, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 1:1. FC (SiO₂; pentane/acetone 80:20) gave an inseparable mixture of **106a** and **106b** (93.9 mg, 86%) as yellow oil.

Data of mixture **syn-106a** and **anti-106b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.43 (dd, J = 8.6, 5.4 Hz, 2 H; ArH, **106a** and **106b**), 7.35 (dd, J = 8.6, 5.3 Hz, 3 H; ArH, **106a** and **106b**), 7.16–7.05 (m, 2 H; ArH, **106a** and **106b**), 7.03–6.93 (m, 5 H; ArH, **106a** and **106b**), 6.14 (d, J = 7.7 Hz, 2 H; ArH, **106a** and **106b**), 5.31–5.22 (m, 1 H; CHCO₂CH₃, **106a** or **106b**), 5.08 (t, J = 6.4 Hz, 1 H; CHCO₂CH₃, **106a** or **106b**), 4.91–4.80 (m, 1 H; CHNH, **106a** or **106b**), 4.70 (t, J = 10.1 Hz, 1 H; CHNH, **106a** or **106b**), 3.73 (s, 3 H; CO₂CH₃, **106a** or **106b**), 3.74 (s, 3 H; CO₂CH₃, **106a** or **106b**), 2.93–2.73 (m, 2 H; CH₂, **106a** and **106b**), 2.40 (ddd, J = 14.9, 8.4, 4.2 Hz, 2 H; CH₂, **106a** and **106b**), 1.44 (s, 18 H; **106a** or **106b**), 1.35 ppm (s, 18 H; **106a** or **106b**); **¹⁹F {¹H} NMR** (377 MHz,

CDCl₃): δ = -115.33 (**106a** or **106b**), -115.36 ppm (**106a** or **106b**); ¹³C NMR (101 MHz, CDCl₃): δ = 171.5, 171.4, 163.4, 160.9, 152.3, 151.9, 138.5, 138.2, 128.2, 128.1, 127.9, 127.8, 115.9, 115.9, 115.7, 115.7, 83.9, 83.7, 56.2, 56.0, 54.7, 52.7, 52.6, 40.6, 39.7, 28.1, 27.9 ppm; **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3259 (w, N-H), 2981 (m), 1740 (m, NC=O), 1697 (m, OC=O), 1508 (m); **HRMS** (ESI): m/z = 566.23865 ([M+Na]⁺, calcd. for C₂₇H₃₄O₆N₅FNa⁺: 566.23853).

Synthesis of compound **107**



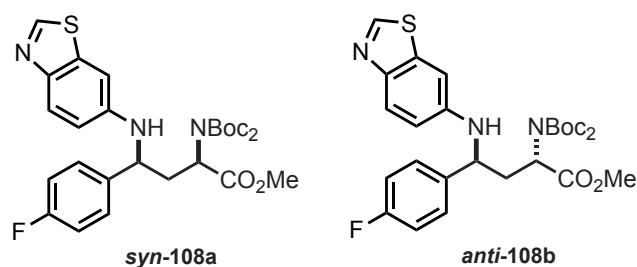
Compound **107** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and 7-amino-1H-indazole (26.6 mg, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 2.8:1. FC (SiO₂; pentane/acetone 80:20 to 50:50) gave an inseparable mixture of **107a** and **107b** (86.7 mg, 80%) as brown oil.

Data of mixture **syn-107a** and **anti-107b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.81 (br, 2 H; CHNH, **107a** and **107b**), 7.49–7.37 (m, 4 H; ArH and CHNNH, **107a** and **107b**), 7.32 (ddd, J = 8.7, 5.4, 2.7 Hz, 4 H; ArH, **107a** and **107a**), 7.70 (td, J = 8.7, 2.6 Hz, 4 H; ArH, **107a** and **107b**), 6.59 (dd, J = 8.7, 1.9 Hz, 1 H; ArH, **107a**), 6.53 (dd, J = 8.7, 1.9 Hz, 1 H; ArH, **107b**), 6.21 (dd, J = 13.7, 1.9 Hz, 2 H; ArH, **107a** and **107b**), 5.12 (dd, J = 7.0, 5.6 Hz, 1 H; CHCO₂CH₃, **107b**), 5.00 (dd, J = 7.5, 4.7 Hz, 1 H; CHCO₂CH₃, **107a**), 4.94 (br, 1 H; CHNH, **107a**), 4.88 (br, 1 H; CHNH, **107b**), 4.61–4.55 (m, 1 H; CHNH, **107a**), 4.52–4.44 (m, 1 H; CHNH, **107b**), 3.74 (s, 3 H; CO₂CH₃, **107b**), 3.73 (s,

3 H; CO₂CH₃, **107a**), 2.84 (ddd, $J = 14.5, 7.5, 4.1$ Hz, 1 H; CH₂, **107a**), 2.67 (ddd, $J = 15.0, 10.4, 5.7$ Hz, 1 H; CH₂, **107b**), 2.25 (ddd, $J = 15.0, 7.1, 4.0$ Hz, 1 H; CH₂, **107b**), 2.02 (ddd, $J = 14.5, 9.4, 4.7$ Hz, 1 H; CH₂, **107a**), 1.47 (s, 18 H; **107a**), 1.40 ppm (s, 18 H; **107b**); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): $\delta = -115.47$ (**107b**), -115.65 ppm (**107a**); ¹³C NMR (101 MHz, CDCl₃): $\delta = 172.0, 171.2, 163.3, 160.9, 152.4, 152.1, 147.3, 147.0, 142.2, 138.6, 134.9, 134.9, 127.9, 127.8, 121.5, 115.9, 115.7, 113.6, 89.6, 83.7, 56.3, 55.9, 52.7, 52.5, 41.0, 40.3, 28.1, 28.0$ ppm; FT-IR (thin film): ν_{max} (cm⁻¹) = 3368 (w, N-H), 2980 (m), 1739 (s, NC=O), 1697 (m, OC=O), 1508 (s); HRMS (ESI): $m/z = 543.26099$ ([M+H]⁺, calcd. for C₂₈H₃₆O₆N₄F⁺: 543.26134).

Synthesis of compound **108**



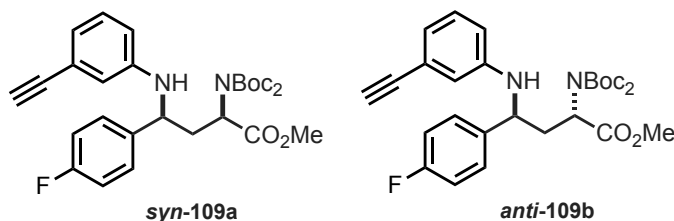
Compound **108** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and benzothiazol-6-amine (30 mg, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 3:1. FC (SiO₂; pentane/acetone 90:10 to 80:20) gave an inseparable mixture of **108a** and **108b** (87 mg, 78%) as yellow foam.

Data of mixture **syn-108a** and **anti-108b**:

m.p. = 70 °C; ¹H NMR (400MHz, CDCl₃): $\delta = 8.61$ (m, 2 H; NCHS, **108a** and **108b**), 7.43–7.37 (m, 2 H; ArH, **108a**), 7.36–7.30 (m, 2 H; ArH, **108b**), 7.01 (td, $J = 8.7, 2.6$ Hz, 4 H; ArH, **108a** and **108b**), 6.86–6.75 (m, 4 H; ArH, **108a** and **108b**), 5.13 (dd, $J = 7.2, 5.6$ Hz,

1 H; CHCO_2CH_3 , **108b**), 5.00 (dd, $J = 7.5, 4.8$ Hz, 1 H; CHCO_2CH_3 , **108a**), 4.91 (br, 1 H; CHNH , **108a**), 4.84 (br, 1 H; CHNH , **108b**), 4.65–4.57 (m, 1 H; CHNH , **108a**), 4.48 (dd, $J = 10.5, 3.9$ Hz, 1 H; CHNH , **108b**), 3.75 (s, 3 H; CO_2CH_3 , **108b**), 3.73 (s, 3 H; CO_2CH_3 , **108a**), 2.84 (ddd, $J = 14.5, 7.5, 4.1$ Hz, 1 H; CH_2 , **108a**), 2.67 (ddd, $J = 15.0, 10.5, 5.6$ Hz, 1 H; CH_2 , **108b**), 2.28 (ddd, $J = 15.0, 7.2, 3.9$ Hz, 1 H; CH_2 , **108b**), 2.04 (ddd, $J = 14.5, 9.4, 4.8$ Hz, 1 H; CH_2 , **108a**), 1.47 (s, 18 H; **108a**), 1.41 ppm (s, 18 H; **108b**); ^{19}F $\{^1\text{H}\}$ NMR (377 MHz, CDCl_3): $\delta = -115.36$ (**108b**), -115.55 ppm (**108a**); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 172.0, 171.2, 163.4, 160.9, 152.4, 152.1, 149.3, 146.2, 146.1, 145.8, 145.4, 138.6, 135.8, 135.7, 127.9, 127.8, 127.8, 123.8, 116.0, 115.9, 115.8, 115.7, 115.3, 115.3, 103.1, 103.0, 83.9, 83.7, 56.3, 56.1, 56.0, 55.9, 52.7, 52.6, 41.1, 40.3, 28.1, 28.0$ ppm; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3391 (w, N–H), 2980 (m), 1740 (s, NC=O), 1698 (m, OC=O), 1508 (m); **HRMS** (ESI): $m/z = 560.22198$ ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{28}\text{H}_{35}\text{O}_6\text{N}_3\text{FS}^+$: 560.22251).

Synthesis of compound **109**



Compound **109** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and 3-ethynylaniline (0.021 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 7:2. FC (SiO_2 ; pentane/acetone 95:5 to 90:10) gave **109a** (22.5 mg, 21%) as yellow oil and **109b** (73.8 mg, 70%) as yellow oil (**109**: 91% total isolated yield).

Data of ***syn*-109a**:

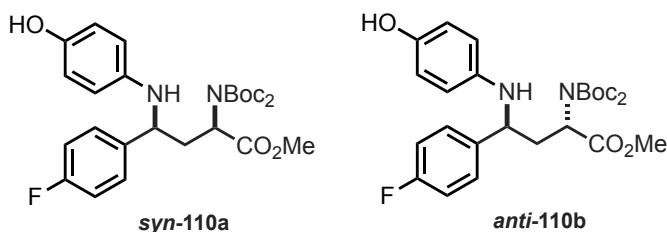
¹H NMR (400 MHz, CDCl₃): δ = 7.35 (dd, J = 8.6, 5.3 Hz, 2 H; ArH), 7.01 (td, J = 8.7, 8.2, 5.4 Hz, 3 H; ArH), 6.83–6.73 (m, 1 H; ArH), 6.62 (dd, J = 2.5, 1.5 Hz, 1 H; ArH), 6.49–6.43 (m, 1 H; ArH), 4.97 (dd, J = 7.4, 5.0 Hz, 1 H; CHCO₂CH₃), 4.65 (br, 1 H; CHNH), 4.54 (d, J = 8.8 Hz, 1 H; CHNH), 3.73 (s, 3 H; CO₂CH₃), 2.95 (s, 1 H; CCH), 2.78 (ddd, J = 14.5, 7.4, 4.1 Hz, 1 H; CH₂), 2.00 (ddd, J = 14.5, 9.3, 5.0 Hz, 1 H; CH₂), 1.48 ppm (s, 18 H; (C(CH₃)₃)₂); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = –115.79 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 171.2 (CO₂CH₃), 163.3 (C–F), 152.4 (NC=O), 147.2 (ArC), 138.9 (ArC), 129.2 (ArCH), 127.9 (d, J = 7.9 Hz; ArCH), 122.7 (ArC), 121.5 (ArCH), 116.8 (ArCH), 115.7 (d, J = 21.5 Hz; ArCH), 114.2 (ArCH), 84.3 (CCH), 83.8 (CO₂C(CH₃)₃), 76.3 (CCH), 55.9 (CHCO₂CH₃), 55.6 (CHNH), 52.5 (CO₂CH₃), 41.0 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3375 (w, N–H), 3298 (w, C–H), 2980 (m), 2932 (m), 1745 (s, NC=O), 1698 (s, OC=O), 1508 (s); **HRMS** (ESI): m/z = 527.25519 ([M+H]⁺, calcd. for C₂₉H₃₆O₆N₂F⁺: 527.25519).

Data of ***anti*-109b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.33–7.27 (m, 2 H; ArH), 7.00 (td, J = 8.3, 2.2 Hz, 3 H; ArH), 6.77 (dt, J = 7.6, 1.2 Hz, 1 H; ArH), 6.61 (dd, J = 2.5, 1.4 Hz, 1 H; ArH), 6.47 (ddd, J = 8.2, 2.5, 1.0 Hz, 1 H; ArH), 5.09 (dd, J = 7.3, 5.5 Hz, 1 H; CHCO₂CH₃), 4.42 (dd, J = 10.5, 3.9 Hz, 1 H; CHNH), 3.74 (s, 3 H; CO₂CH₃), 2.95 (s, 1 H; CCH), 2.60 (ddd, J = 15.0, 10.5, 5.5 Hz, 1 H; CH₂), 2.25 (ddd, J = 15.0, 7.3, 3.9 Hz, 1 H; CH₂), 1.43 ppm (s, 18 H; (C(CH₃)₃)₂); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = –115.60 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 172.0 (CO₂CH₃), 162.1 (d, J = 244.8 Hz; C–F), 152.1 (NC=O), 146.8 (ArC), 138.8 (ArC), 129.2 (ArCH), 127.78 (d, J = 8.0 Hz; ArCH), 122.7 (ArC), 121.6 (ArCH), 116.9 (ArCH), 115.8 (d, J = 21.5 Hz; ArCH), 114.4 (ArCH), 84.3 (CCH), 83.7 (CO₂C(CH₃)₃), 76.3 (CCH), 56.3 (CHCO₂CH₃), 55.4 (CHNH), 52.7 (CO₂CH₃), 40.2 (CH₂), 28.1 ppm (C(CH₃)₃); **FT-IR**

(thin film): ν_{max} (cm⁻¹) = 3388 (w, N-H), 3285 (w, C-H), 2980 (m), 1739 (s, NC=O), 1698 (s, OC=O), 1508 (m); **HRMS** (ESI): m/z = 527.25543 ([M+H]⁺, calcd. for C₂₉H₃₆O₆N₂F⁺: 527.25519).

Synthesis of compound **110**



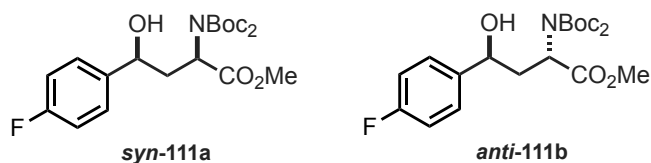
Compound **110** was synthesised according to General Procedure **C** using 4-fluorobenzaldehyde (0.02 mL, 0.2 mmol) and 4-aminophenol (21.8 mg, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 2.8:1. FC (SiO₂; pentane/acetone 80:20) gave an inseparable mixture of **110a** and **110b** (57.3 mg, 55%) as off-white foam.

Data of mixture **syn-110a** and **anti-110b**:

m.p. = 78 °C; ¹H NMR (400MHz, CDCl₃): δ = 7.39–7.30 (m, 2 H; ArH, **110a**), 7.31–7.21 (m, 2 H; ArH, **110b**), 6.98 (td, J = 8.7, 3.4 Hz, 4 H; ArH, **110a** and **110b**), 6.65–6.52 (m, 4 H; ArH, **110a** and **110b**), 6.47–6.32 (m, 4 H; ArH, **110a** and **110b**), 5.13 (dd, J = 7.8, 5.3 Hz, 1 H; CHCO₂CH₃, **110b**), 4.99 (dd, J = 7.3, 5.2 Hz, 1 H; CHCO₂CH₃, **110a**), 4.46 (dd, J = 9.1, 4.6 Hz, 1 H; CHNH, **110a**), 4.34 (dd, J = 10.6, 3.9 Hz, 1 H; CHNH, **110b**), 3.73 (s, 3 H; CO₂CH₃, **110b**), 3.72 (s, 3 H; CO₂CH₃, **110a**), 2.76 (ddd, J = 14.5, 7.3, 4.6 Hz, 1 H; CH₂, **110a**), 2.57 (ddd, J = 15.0, 10.3, 5.3 Hz, 1 H; CH₂, **110b**), 2.23 (ddd, J = 15.0, 7.7, 4.0 Hz, 1 H; CH₂, **110b**), 2.00 (ddd, J = 14.5, 9.0, 5.2 Hz, 1 H; CH₂, **110a**), 1.47 (s, 18 H; **110a**), 1.42 ppm (s, 18 H; **110b**); ¹⁹F {¹H} NMR (377 MHz, CDCl₃): δ = –115.90 (**110b**), –116.04

ppm (**110a**); ^{13}C NMR (101 MHz, CDCl_3): δ = 171.9, 160.8, 152.3, 152.1, 141.1, 139.4, 128.0, 127.9, 127.8, 116.1, 115.8, 115.7, 115.6, 115.1, 114.9, 83.7, 83.6, 56.3, 56.1, 56.0, 52.6, 52.5, 40.9, 40.1, 28.1, 28.1 ppm; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3400 (w, N-H), 3012 (br, O-H), 2984 (m), 2936 (m), 1736 (s, NC=O), 1696 (s, OC=O), 1513 (s); **HRMS** (ESI): m/z = 519.24994 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{27}\text{H}_{36}\text{O}_7\text{N}_2\text{F}^+$: 519.25011).

5.2.6 Synthesis of β -Amino Alcohol



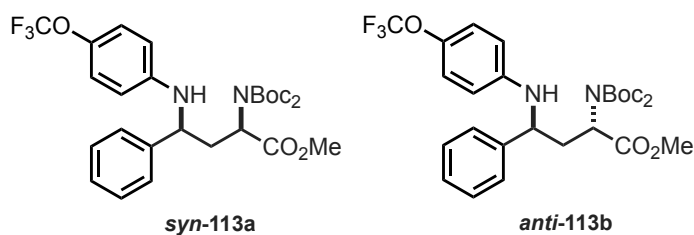
To a 1.6 mL glass vial equipped with a microstirrer, was charged 4-fluorobenzaldehyde (0.2 mmol, 1 eq), coupling partner **68** (0.4 mmol, 2 eq), diethyl 4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate HE **75** (99 mg, 0.3 mmol, 1.5 eq), and $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (**[Ir2]** PF_6 , 2.24 mg, 0.002 mmol, 1 mol%). To the vial were sequentially added anhydrous DMSO (0.4 mL) and dry MeOH (0.6 mL). Nitrogen was then bubbled through the stirred solution for 5 minutes. The vial was then sealed and then irradiated with blue light while stirring for 24 h. The reaction mixture was then diluted in EtOAc (20 mL), H_2O (10 mL) and brine (10 mL), the organic phase extracted and the aqueous phase re-extracted with EtOAc (2x 20 mL). The combined organic phases were dried over MgSO_4 , filtered, and concentrated under reduced pressure. An aliquot from the crude residue was dissolved in CDCl_3 to determine the diastereomeric ratio; crude dr 3:2. FC (SiO_2 ; pentane/acetone 95:5 to 90:10) gave an inseparable mixture of **111a** and **111b** (72.5 mg, 85%) as yellow oil.

Data of mixture **syn-111a** and **anti-111b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.38–7.29 (m, 4 H; ArH, **111a** and **111b**), 7.02 (t, J = 8.7 Hz, 4 H; ArH, **111a** and **111b**), 5.11 (dd, J = 10.1, 4.4 Hz, 1 H; CHCO₂CH₃, **111a**), 5.03 (dd, J = 6.8, 5.6 Hz, 1 H; CHCO₂CH₃, **111b**), 4.95 (dd, J = 8.3, 4.2 Hz, 1 H; CHNH, **111b**), 4.63 (dd, J = 11.0, 2.6 Hz, 1 H; CHNH, **111a**), 3.73 (s, 3 H; CO₂CH₃, **111a**), 3.72 (s, 3 H; CO₂CH₃, **111b**), 2.71 (ddd, J = 14.5, 6.9, 4.3 Hz, 1 H; CH₂, **111b**), 2.45 (ddd, J = 15.1, 10.8, 4.4 Hz, 1 H; CH₂, **111a**), 2.26–2.16 (m, 1 H; CH₂, **111a**), 2.09 (ddd, J = 14.5, 8.3, 5.7 Hz, 1 H; CH₂, **111b**), 1.51 (s, 18 H; **111a**), 1.48 ppm (s, 18 H; **111b**); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = –115.34 (**111b**), –115.41 ppm (**111a**); **¹³C NMR** (101 MHz, CDCl₃): δ = 171.8, 171.4, 163.5, 161.1, 152.7, 152.2, 140.0, 139.6, 139.6, 127.5, 127.4, 127.4, 115.5, 115.5, 115.3, 115.3, 84.0, 83.6, 71.5, 70.1, 56.1, 55.6, 52.6, 52.5, 40.6, 40.1, 28.1, 28.1 ppm; **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3511 (br, O–H), 2980 (m), 1744(s, NC=O), 1700 (s, OC=O), 1509 (m); **HRMS** (ESI): m/z = 450.18954 ([M+Na]⁺, calcd. for C₂₁H₃₀O₇NFNa⁺: 450.18985).

5.2.7 Synthesis of α -Amino- γ -Lactam

Synthesis of compound **113**



Compound **113** was synthesised according to General Procedure **C** using benzaldehyde (0.02 mL, 0.2 mmol) and 4-trifluoromethoxyaniline (0.03 mL, 0.2 mmol) and irradiated with blue light for 24 h. Crude dr: 3.4:1. FC (SiO₂; pentane/acetone 95:5 to 90:10) gave **113a** (32 mg, 28%) as yellow oil and **113b** (81.1 mg, 71%) as off-white solid (**113**: 99% total isolated yield).

Data of ***syn*-113a**:

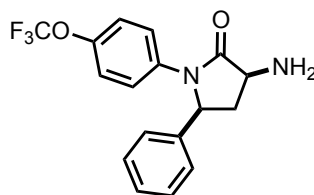
^1H NMR (400 MHz, CDCl_3): δ = 7.42–7.36 (m, 2 H; ArH), 7.36–7.28 (m, 2 H; ArH), 7.23 (d, J = 7.2 Hz, 1 H; ArH), 6.92 (dd, J = 9.0, 1.0 Hz, 2 H; ArH), 6.46 (d, J = 9.0 Hz, 2 H; ArH), 5.01 (dd, J = 7.3, 5.3 Hz, 1 H; CHCO_2CH_3), 4.69 (br, 1 H; CHNH), 4.52 (dd, J = 9.8, 3.9 Hz, 1 H; CHNH), 3.73 (s, 3 H; CO_2CH_3), 2.81 (ddd, J = 14.7, 7.3, 4.2 Hz, 1 H; CH_2), 2.05 (ddd, J = 14.7, 9.4, 5.3 Hz, 1 H; CH_2), 1.47 ppm (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$); **^{19}F $\{^1\text{H}\}$ NMR** (377 MHz, CDCl_3): δ = –58.50 ppm; **^{13}C NMR** (101 MHz, CDCl_3): δ = 171.2 (CO_2CH_3), 152.4 (NC=O), 146.3 (ArC), 143.3 (ArC), 128.9 (ArCH), 127.4 (ArCH), 126.3 (ArCH), 122.4 (ArCH), 113.7 (ArCH), 83.8 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 56.6 (CHNH), 56.1 (CHCO_2CH_3), 52.5 (CO_2CH_3), 40.8 (CH_2), 28.1 ppm ($\text{C}(\text{CH}_3)_3$); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3392 (w, N–H), 2981 (m), 1745 (m, NC=O), 1697 (m, OC=O), 1515 (m); **HRMS** (ESI): m/z = 569.24707 ($[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{28}\text{H}_{36}\text{O}_7\text{N}_2\text{F}_3^+$: 569.24691). Note: OCF_3 and one ArC were not observed.

Data of ***anti*-113b**:

m.p. = 128 °C; **^1H NMR** (400MHz, CDCl_3): δ = 7.32 (d, J = 4.3 Hz, 4 H; ArH), 7.26–7.21(m, 1 H; ArH), 6.91 (dd, J = 9.0, 1.0 Hz, 2 H; ArH), 6.46 (d, J = 9.0 Hz, 2 H; ArH), 5.13 (dd, J = 7.7, 5.5 Hz, 1 H; CHCO_2CH_3), 4.59 (br, 1 H; CHNH), 4.38 (dd, J = 10.6, 3.8 Hz, 1 H; CHNH), 3.74 (s, 3 H; CO_2CH_3), 2.61 (ddd, J = 15.0, 10.6, 5.5 Hz, 1 H; CH_2), 2.31 (ddd, J = 15.0, 7.7, 3.8 Hz, 1 H; CH_2), 1.42 ppm (s, 18 H; $(\text{C}(\text{CH}_3)_3)_2$); **^{19}F $\{^1\text{H}\}$ NMR** (377 MHz, CDCl_3): δ = –58.54 ppm; **^{13}C NMR** (101 MHz, CDCl_3): δ = 172.0 (CO_2CH_3), 152.1 (NC=O), 146.0 (ArC), 143.1 (ArC), 140.1 (ArC), 129.0 (ArCH), 127.5 (ArCH), 126.2 (ArCH), 122.4 (ArCH), 113.8 (ArCH), 83.6 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 56.3 (CHNH), 56.3 (CHCO_2CH_3), 52.7 (CO_2CH_3), 40.1 (CH_2), 28.0 ppm ($\text{C}(\text{CH}_3)_3$); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3392 (w, N–H), 2980 (s), 1739 (m, NC=O), 1699 (m, OC=O), 1517 (m); **HRMS** (ESI): m/z = 569.24701 ($[\text{M}+\text{H}]^+$, calcd. for

C₂₈H₃₆O₇N₂F₃⁺: 569.24691). Note: OCF₃ was not observed.

Synthesis of compound **112**



112

A solution of major diastereoisomer **113b** (330 mg, 0.58 mmol, 1 eq) in anhydrous MeOH (14.5 mL) under Ar atmosphere was treated by dropwise addition of aq. HCl solution (1 M, 13.6 mL) at 25 °C. The resulting mixture was warmed up to 65 °C and stirred for 5 h. The reaction mixture was diluted with CH₂Cl₂ (30 mL), basified to pH 8-9 with aq. sat. NaHCO₃ solution, and extracted with CH₂Cl₂ (3x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. FC (SiO₂; Et₂O/MeOH 80:20) afforded title compound **39** (148 mg, 76%) as yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.35 (d, *J* = 9.1 Hz, 2 H; ArH), 7.30–7.16 (m, 5 H; ArH), 7.06 (dd, *J* = 9.1, 1.0 Hz, 2 H; ArH), 5.09 (dd, *J* = 9.3, 6.4 Hz, 1 H; CHNH₂), 3.79 (dd, *J* = 10.8, 8.3 Hz, 1 H; CHC₆H₅), 2.98 (ddd, *J* = 12.9, 8.3, 6.4 Hz, 1 H; CH₂), 1.84–1.71 ppm (m, 3 H; CH₂ and NH₂); **¹⁹F {¹H} NMR** (377 MHz, CDCl₃): δ = −58.01 (3 F); **¹³C NMR** (101 MHz, CDCl₃): δ = 176.1 (NC=O), 140.0, 136.2, 129.2, 128.3, 126.7, 124.2, 121.2, 60.5 (CHNH₂), 53.8 (CHC₆H₅), 40.21 ppm (CH₂); **FT-IR** (thin film): ν_{max} (cm^{−1}) = 3366 (w, N–H₂), 2925 (m), 2932 (m), 1699 (s), 1509 (s); **HRMS** (ESI): *m/z* = 337.11627 ([M+H]⁺, calcd. for C₁₇H₁₆O₂N₂F₃⁺: 337.11584).

5.3 Experimental Details for Chapter 3

5.3.1 General Procedure D: Ketal Substrates - Method 1

A solution of relevant ketone/aldehyde (1 eq) in dry MeOH (0.4 M) under N₂ atmosphere was treated with PTSA (10 mol%) in one-portion, followed by addition of orthoformate (3 eq) at 25 °C and stirred at the same temperature for 18 h. The reaction was quenched with Et₃N (ca. 20 mol%) and concentrated under reduced pressure. The compounds were purified by flash column chromatography (see individual experiments).

5.3.2 General Procedure E: Ketal Substrates - Method 2

A solution of relevant ketone (1 eq) in dry MeOH (0.5 M) under N₂ atmosphere was treated with TBABr₃ (1 mol%) in one-portion, followed by addition of orthoformate (1.1 eq) at 25 °C and stirred at the same temperature for 18 h. The reaction was poured into a sat. aq. solution of NaHCO₃ (10 mL) and extracted with EtOAc (3x 20 mL). The compounds were purified by flash column chromatography (see individual experiments).

5.3.3 General Procedure F: Ether Products - DHA as Coupling Partner

A 1.6 mL glass vial equipped with a microstirrer was charged with relevant ketal (or acetal) (0.2 mmol), compound **68** (0.4 mmol, 2 eq), diethyl 4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate HE **75** (99mg, 0.3 mmol, 1.5 eq.), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (**[Ir2]**PF₆, 2.24 mg, 0.002 mmol, 1 mol%), and dissolved in dry DMA (0.8 mL, 0.25 M). Nitrogen was bubbled to the stirred solution for 1 min. The vial was closed and treated by dropwise addition of TMSOTf (36 µL, 0.2 mmol). After addition, the vial was sealed with parafilm[®] and then irradiated with blue light for 16 h. The reaction mixture was then diluted in EtOAc (20 mL), H₂O (10 mL) and brine (10 mL), the organic phase extracted and the aqueous phase re-extracted with EtOAc (2x 20 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. Prior to purification by flash column chromatography (see

individual experiments), an aliquot from the crude residue was dissolved in CDCl₃ to determine the diastereomeric ratio and/or NMR yield.

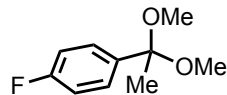
Note: When necessary, in order to ease separation by flash column chromatography from excess DHA **68**, prior to the above mentioned work-up, the vial was taken out from the photoreactor and charged with cysteamine (47 mg, 3 eq), Et₃N (112 μ L, 4 eq) and stirred at room temperature for 1–2 h.

5.3.4 General Procedure G: Ether Products - Acrylate-type Coupling Partners

A 1.6 mL glass vial equipped with a microstirrer was charged with relevant ketal (or acetal) (0.2 mmol), relevant coupling partner (0.6 mmol, 3 eq), diethyl 4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate HE **75** (132 mg, 0.4 mmol, 2 eq), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (**[Ir2]**PF₆, 2.24 mg, 0.002 mmol, 1 mol%), and dissolved in dry DMA (0.8 mL, 0.25 M). While nitrogen was bubbled to the stirred solution, 1,4-cyclohexadiene **143** (0.3 mmol, 1.5 eq) was added to the reaction mixture. Then, the vial was closed and treated by dropwise addition of TMSOTf (36 μ L, 0.2 mmol). After addition, the vial was sealed with parafilm[®] and irradiated with blue light for 16 h. The reaction mixture was then diluted in EtOAc (20 mL), H₂O (10 mL) and brine (10 mL), the organic phase extracted and the aqueous phase re-extracted with EtOAc (2x 20 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. Prior to purification by flash column chromatography (see individual experiments), an aliquot from the crude residue was dissolved in CDCl₃ to determine the diastereomeric ratio and/or NMR yield.

5.3.5 Synthesis of Substrates

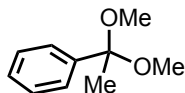
1-(1,1-dimethoxyethyl)-4-fluorobenzene (**136**)



The above compound was prepared according to General Procedure **D** using 4'-fluoroacetophenone (2.43 mL, 20 mmol) and trimethyl orthoformate (6.56 mL, 60 mmol). FC (SiO₂; pentane/EtOAc 9:1 with 3% Et₃N) gave title compound **136** (3.03 g, 82%) as colorless oil. NMR Spectra and physical properties matched those from reported literature.^[184]

¹H NMR (400 MHz, CDCl₃): δ = 7.46 (dd, J = 8.9, 5.5 Hz, 2 H; ArH), 7.02 (t, J = 8.8 Hz, 2 H; ArH), 3.17 (s, 6 H; OCH₃), 1.52 (s, 3 H; CH₃); ¹⁹F NMR (377 MHz, CDCl₃): δ = -115.47 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 162.4 (d, J = 245.6 Hz), 138.9 (d, J = 3.1 Hz), 128.2 (d, J = 7.9 Hz), 114.9 (d, J = 21.3 Hz), 101.4, 48.9, 26.2 ppm.

(1,1-dimethoxyethyl)benzene (**145**)

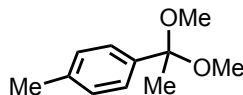


The above compound was prepared according to General Procedure **D** using acetophenone (1.52 mL, 13 mmol) and trimethyl orthoformate (4.27 mL, 39 mmol). FC (SiO₂; pentane/EtOAc 9:1 with 3% Et₃N) gave title compound **145** (2.02 g, 94%) as yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.53–7.49 (m, 2 H; ArH), 7.39–7.33 (m, 2 H; ArH), 7.32–7.28 (m, 1 H; ArH), 3.20 (s, 6 H; OCH₃), 1.55 ppm (s, 3 H; CH₃); ¹³C NMR (101 MHz, CDCl₃): δ = 143.0 (ArC), 128.2 (ArCH), 127.6 (ArCH), 126.4 (ArCH), 101.8 (ArC(OCH₃)₂CH₃), 49.1 (OCH₃), 26.2 (CH₃) ppm; FT-IR (thin film): ν_{max} (cm⁻¹) = 2990 (m), 2830 (w), 1686 (s),

1447 (m), 1359 (m), 1264 (s), 1080 (s); **HRMS** (ESI): $m/z = 189.0888$ ($[M+Na]^+$, calcd. for $C_{10}H_{14}O_2Na^+$: 189.08860).

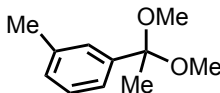
1-(1,1-dimethoxyethyl)-4-methylbenzene (146)



The above compound was prepared according to General Procedure **D** using 4'-methylacetophenone (671 mg, 5 mmol) and trimethyl orthoformate (1.64 mL, 15 mmol). FC (SiO_2 ; pentane/EtOAc 9:1 with 3% Et_3N) gave title compound **146** (845 mg, 94%) as colorless oil. NMR Spectra and physical properties matched those from reported literature.^[185]

^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$ – 7.38 (m, 2 H; H_3), 2.37 (s, 3 H; $ArCH_3$), 1.55 ppm (s, 3 H; CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): $\delta = 140.1$, 137.2, 128.9, 126.3, 101.2, 49.0, 26.2, 21.2 ppm.

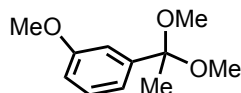
1-(1,1-dimethoxyethyl)-3-methylbenzene (147)



The above compound was prepared according to General Procedure **D** using 3'-methylacetophenone (0.68 mL, 5 mmol) and trimethyl orthoformate (1.64 mL, 15 mmol). FC (SiO_2 ; pentane/EtOAc 9:1 with 3% Et_3N) gave title compound **147** (870 mg, 97%) as colorless oil. NMR Spectra and physical properties matched those from reported literature.^[186]

^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$ – 7.27 (m, 2 H; ArH), 7.26–7.21 (m, 1 H; ArH), 7.12–7.08 (m, 1 H; ArH), 3.20 (s, 6 H; OCH_3), 2.37 (s, 3 H; $ArCH_3$), 1.53 ppm (s, 3 H; CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): $\delta = 142.9$, 137.7, 128.3, 128.1, 127.0, 123.4, 101.8, 49.0, 26.2, 21.7 ppm.

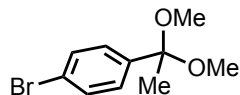
1-(1,1-dimethoxyethyl)-3-methoxybenzene (148)



The above compound was prepared according to General Procedure **D** using 3'-methoxyacetophenone (0.69 mL, 5 mmol) and trimethyl orthoformate (1.64 mL, 15 mmol). FC (SiO₂; pentane/EtOAc 9:1 with 3% Et₃N) gave title compound **148** (960 mg, 98%) as colorless oil. NMR Spectra and physical properties matched those from reported literature.^[186]

¹H NMR (400 MHz, CDCl₃): δ = 7.30–7.22 (m, 1 H; ArH), 7.10–7.04 (m, 2 H; ArH), 6.83 (ddd, J = 8.2, 2.5, 1.2 Hz, 1 H; ArH), 3.82 (s, 3 H; ArOCH₃), 3.20 (s, 6 H; OCH₃), 1.53 ppm (s, 3 H; CH₃); ¹³C NMR (101 MHz, CDCl₃): δ = 159.7, 144.8, 129.2, 118.7, 113.2, 112.0, 101.7, 55.3, 49.1, 26.1 ppm.

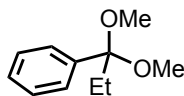
1-bromo-4-(1,1-dimethoxyethyl)benzene (149)



The above compound was prepared according to General Procedure **D** using 4'-bromoacetophenone (1 g, 5 mmol) and trimethyl orthoformate (1.64 mL, 15 mmol). FC (SiO₂; pentane/EtOAc 9:1 with 3% Et₃N) gave title compound **149** (96.8 mg, 79%) as yellow oil. NMR Spectra and physical properties matched those from reported literature.^[185]

¹H NMR (400 MHz, CDCl₃): δ = 7.50–7.45 (m, 2 H; ArH), 7.37 (d, J = 8.6 Hz, 2 H; ArH), 3.17 (s, 6 H; OCH₃), 1.51 ppm (s, 3 H; CH₃); ¹³C NMR (101 MHz, CDCl₃): δ = 141.9, 131.2, 128.1, 121.6, 101.3, 48.9 ppm.

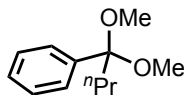
(1,1-dimethoxypropyl)benzene (150)



The above compound was prepared according to General Procedure **D** using propiophenone (0.67 mL, 5 mmol) and trimethyl orthoformate (1.64 mL, 15 mmol). FC (SiO₂; pentane/EtOAc 9:1 with 3% Et₃N) gave title compound **150** (785 mg, 87%) as colorless oil. NMR Spectra and physical properties matched those from reported literature.^[187]

¹H NMR (400 MHz, CDCl₃): δ = 7.48–7.43 (m, 2 H; ArH), 7.38–7.32 (m, 2 H; ArH), 7.31–7.25 (m, 1 H; ArH), 3.16 (s, 6 H; OCH₃), 1.91 (q, J = 7.5 Hz, 2 H; CH₂), 0.59 ppm (t, J = 7.5 Hz, 3 H; CH₃); ¹³C NMR (101 MHz, CDCl₃): δ = 140.8, 127.9, 127.6, 121.2, 104.3, 48.7, 30.0, 7.8 ppm.

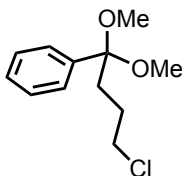
((1,1-dimethoxybutyl)benzene (151)



The above compound was prepared according to General Procedure **D** using butyrophenone (0.73 mL, 5 mmol) and trimethyl orthoformate (1.64 mL, 15 mmol). FC (SiO₂; pentane/EtOAc 9:1 with 3% Et₃N) gave title compound **151** (940 mg, 97%) as colorless oil. NMR Spectra and physical properties matched those from reported literature.^[184]

¹H NMR (400 MHz, CDCl₃): δ = 7.46–7.42 (m, 2 H; ArH), 7.37–7.32 (m, 2 H; ArH), 7.31–7.27 (m, 1 H; ArH), 3.16 (s, 6 H; OCH₃), 1.89–1.81 (m, 2 H; CH₂), 1.05–0.92 (m, 2 H; CH₂), 0.77 ppm (t, J = 7.3 Hz, 3 H; CH₃); ¹³C NMR (101 MHz, CDCl₃): δ = 141.2, 127.9, 127.6, 127.0, 103.7, 48.6, 39.6, 16.7, 14.1 ppm.

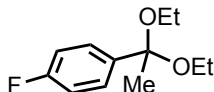
(4-chloro-1,1-dimethoxybutyl)benzene (152)



The above compound was prepared according to General Procedure **D** using 4-chlorobutyrophenone (0.8 mL, 5 mmol) and trimethyl orthoformate (1.64 mL, 15 mmol). FC (SiO₂; pentane/EtOAc 9:1 with 3% Et₃N) gave title compound **152** (1 g, 87%) as yellow oil. NMR Spectra and physical properties matched those from reported literature.^[188]

¹H NMR (400 MHz, CDCl₃): δ = 7.48–7.42 (m, 2 H; ArH), 7.38–7.32 (m, 2 H; ArH), 7.32–7.28 (m, 1 H; ArH), 3.37 (t, J = 6.6 Hz, 2 H; CH₂), 3.17 (s, 6 H; OCH₃), 2.07–2.00 (m, 2 H; CH₂), 1.52–1.42 ppm (m, 2 H; CH₂); ¹³C NMR (101 MHz, CDCl₃): δ = 140.6, 128.1, 127.9, 126.9, 103.2, 48.7, 45.0, 34.7, 27.1 ppm.

1-(1,1-diethoxyethyl)-4-fluorobenzene (153)

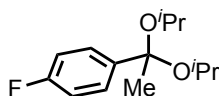


The above compound was prepared according to General Procedure **D** using 4'-fluoroacetophenone (2.43 mL, 5 mmol) and triethyl orthoformate (2.5 mL, 15 mmol) in EtOH (12.5 mL). FC (SiO₂; pentane/EtOAc 9:1 with 3% Et₃N) gave title compound **153** (948 mg, 89%) as colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.53–7.45 (m, 2 H; ArH), 7.04–6.95 (m, 2 H; ArH), 3.51–3.41 (m, 2 H; OCH₂), 3.39–3.29 (m, 2 H; OCH₂), 1.53 (s, 3 H; CH₃), 1.20 (t, J = 7.4 Hz, 6 H; OCH₂CH₃); ¹⁹F NMR (377 MHz, CDCl₃): δ = –115.75 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 162.3 (d, J = 244.9 Hz; C–F), 139.8 (d, J = 3.1 Hz; ArC), 128.0 (d, J = 8.1 Hz; ArCH), 114.7

(d, $J = 21.3$ Hz; ArCH), 101.0 (C(OCH₂CH₃)₂CH₃), 56.7 (OCH₂CH₃), 27.2 (CH₃), 15.4 ppm (OCH₂CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 2976 (m), 2886 (w), 1690 (m), 1507 (s), 1265 (s), 1154 (m), 1048 (s); **HRMS** (ESI): $m/z = 235.1107$ ([M+Na]⁺, calcd. for C₁₂H₁₇O₂FNa⁺: 235.1105).

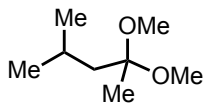
1-(1,1-diisopropoxyethyl)-4-fluorobenzene (154)



The above compound was prepared according to an adapted literature procedure.^[189] To a solution of 4'-fluoroacetophenone (0.12 mL, 1 mmol) in dry iPrOH (1 M) and toluene (1 M) under N₂ atmosphere was added Ce(OTf)₃ (5.9 mg, 0.01 mmol) in one-portion. The reaction mixture was treated by dropwise addition of triisopropyl orthoformate (0.67 mL, 3 mmol) at 0 °C. The reaction was allowed to warm up to 25 °C and stirred for 24 h (full conversion was not achieved), quenched with Et₃N (1 mmol), passed through a short plug of silica (pentane/EtOAc 95:5 with 5% Et₃N) and concentrated under reduced pressure. The clear yellow oil residue was used without further purification (86 mg, 36%).

¹H NMR (400 MHz, CDCl₃): $\delta = 7.61$ – 7.53 (m, 2 H; ArH), 7.03 – 6.93 (m, 2 H; ArH), 4.04 – 3.96 (m, 2 H; CH(CH₃)₂), 1.62 (s, 3 H; CH₃), 1.19 (d, $J = 6.2$ Hz, 6 H; CH(CH₃)₂), 0.97 ppm (d, $J = 6.1$ Hz, 6 H; CH(CH₃)₂); **¹⁹F NMR** (377 MHz, CDCl₃): $\delta = -115.78$ ppm; **¹³C NMR** (101 MHz, CDCl₃): $\delta = 162.3$ (d, $J = 245.4$ Hz; C–F), 140.4 (d, $J = 2.3$ Hz; ArC), 128.7 (d, $J = 7.9$ Hz; ArCH), 114.30 (d, $J = 21.3$ Hz; ArCH), 100.7 (C(OCH(CH₃)₂)₂CH₃), 63.7 (OCH(CH₃)₂), 28.1 (CH₃), 24.7 (OCH(CH₃)₂), 24.0 ppm (OCH(CH₃)₂).

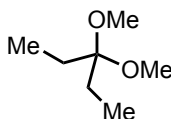
2,2-dimethoxy-4-methylpentane (**155**)



The above compound was prepared according to General Procedure **E** using 4-methyl-2-pentanone (0.63 mL, 5 mmol) and trimethyl orthoformate (0.6 mL, 5.5 mmol). FC (SiO₂; pentane/EtOAc 9:1 with 3% Et₃N) gave title compound **155** (558 mg, 76%) as colorless oil. NMR Spectra or physical properties matched those from reported literature.^[190]

¹H NMR (400 MHz, CDCl₃): δ = 3.11 (s, 6 H; OCH₃), 1.75–1.64 (m, 1 H; CH(CH₃)₂), 1.47 (d, J = 6.3 Hz, 2 H; CH₂), 1.24 (s, 3 H; CH₃), 0.90 ppm (d, J = 6.7 Hz, 6 H; CH(CH₃)₂); ¹³C NMR (101 MHz, CDCl₃): δ = 101.9, 47.9, 44.9, 24.5, 24.0, 21.3 ppm.

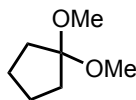
3,3-dimethoxypentane (**156**)



The above compound was prepared according to General Procedure **E** using 3-pentanone (0.53 mL, 5 mmol) and trimethyl orthoformate (0.6 mL, 5.5 mmol). FC (SiO₂; pentane/EtOAc 9:1 with 3% Et₃N) gave title compound **156** (520 mg, 79%) as colorless oil. NMR Spectra and physical properties matched those from reported literature.^[191]

¹H NMR (400 MHz, CDCl₃): δ = 3.10 (s, 6 H; OCH₃), 1.54 (q, J = 7.5 Hz, 4 H; CH₂), 0.79–0.73 ppm (m, 6 H; CH₃); ¹³C NMR (101 MHz, CDCl₃): δ = 104.2, 47.7, 24.4, 7.9 ppm.

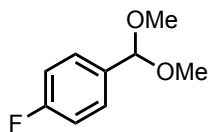
1,1-dimethoxycyclopentane (**157**)



The above compound was prepared according to General Procedure **D** using cyclopentanone (0.44 mL, 5 mmol) and trimethyl orthoformate (1.64 mL, 15 mmol). FC (SiO₂; pentane/EtOAc 9:1 with 3% Et₃N) gave title compound **157** (449 mg, 69%) as colorless oil. NMR Spectra and physical properties matched those from reported literature.^[191]

¹H NMR (400 MHz, CDCl₃): δ = 3.17 (s, 6 H; OCH₃), 1.77–1.69 (m, 4 H; CH₂), 1.66–1.58 ppm (m, 4 H; CH₂); ¹³C NMR (101 MHz, CDCl₃): δ = 112.3, 49.4, 34.3, 23.7 ppm.

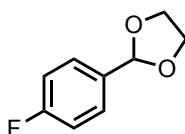
1-(dimethoxymethyl)-4-fluorobenzene (**172**)



The above compound was prepared according to a literature procedure.^[130] A 2-neck round-bottom flask equipped with reflux condenser was charged with 4'-fluorobenzaldehyde (0.54 mL, 5 mmol) under N₂ atmosphere. Trimethyl orthoformate (2.2 mL, 20 mmol) and PTSA (57 mg, 0.3 mmol) were sequentially added at 25 °C. The reaction mixture was then warmed up to 105 °C and stirred for 5 h. The reaction mixture was cooled down to room temperature and quenched by addition of solid NaHCO₃. The resulting mixture was passed through a short pad of silica (EtOAc as eluent) and concentrated under reduced pressure. FC (SiO₂; pentane/EtOAc 100:1 to 90:10 with 3% Et₃N) gave title compound **172** (764 mg, 90%) as colorless oil. NMR Spectra and physical properties matched those from reported literature.^[130]

¹H NMR (400 MHz, CDCl₃): δ = 7.46–7.39 (m, 2 H; ArH), 7.10–6.99 (m, 2 H; ArH), 5.37 (s, 1 H; CH(OCH₃)₂), 3.31 ppm (s, 6 H; OCH₃); **¹⁹F NMR** (377 MHz, CDCl₃): δ = –113.86 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 162.9 (d, J = 246.4 Hz), 134.2 (d, J = 3.2 Hz), 128.6 (d, J = 8.0 Hz), 115.2 (d, J = 21.4 Hz), 102.7, 52.7 ppm.

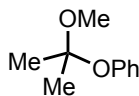
2-(4-fluorophenyl)-1,3-dioxolane (173)



The above compound was prepared according to a literature procedure.^[192] To a solution of 4'-fluorobenzaldehyde (0.32 mL, 3 mmol) in dry DCM (15 mL) under N₂ atmosphere was added NBS (16 mg, 0.09 mmol) in one-portion, and 1,2-Bis(trimethylsiloxy)ethane (0.96 mL, 3.9 mmol) at 25 °C and stirred for 16h. A cold aq. solution of NaOH (5%, 35 mL) and extracted with CH₂Cl₂ (3x 20 mL). The combined organic layers were washed with aq. NaOH (5%, 20 mL), H₂O (4x 20 mL), dried over MgSO₄, and concentrated under reduced pressure. The crude yellow oil residue (484 mg, 96%) was used without further purification. NMR Spectra and physical properties matched those from reported literature.^[193]

¹H NMR (400 MHz, CDCl₃): δ = 7.51–7.42 (m, 2H; ArH), 7.10–7.00 (m, 2H; ArH), 5.78 (s, 1 H; CH(OCH₂)₂), 4.15–4.07 (m, 2 H; CH₂), 4.07–3.99 ppm (m, 2 H; CH₂); **¹⁹F NMR** (377 MHz, CDCl₃): δ = –112.63 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 163.4 (d, J = 247.1 Hz), 133.9 (d, J = 3.2 Hz), 128.5 (d, J = 8.7 Hz), 115.4 (d, J = 21.6 Hz), 103.2, 65.4 ppm.

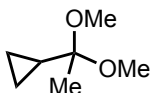
((2-methoxypropan-2-yl)oxy)benzene (190)



The above compound was prepared according to an adapted literature procedure.^[194] A flame-dried round-bottom flask under N₂ atmosphere was charged with N,N'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea catalyst (15 mg, 0.03 mmol), phenol (0.28 g, 3 mmol), and 2-methoxypropene (0.58 mL, 6 mmol). The reaction mixture was stirred at 25 °C for 24 h. Excess 2-methoxypropene was evaporated under reduced pressure without warming. Crude residue was purified via short plug of silica to afford desired compound **190** (270 mg, 54%) as yellow oil. NMR Spectra and physical properties matched those from reported literature.^[194]

¹H NMR (400 MHz, CDCl₃): δ = 7.30–7.23 (m, 2 H; ArH), 7.12–7.09 (m, 2 H; ArH), 7.06–7.01 (m, 1 H; ArH), 3.43 (s, 3 H; OCH₃), 1.48 ppm (s, 6 H; C(CH₃)₂); ¹³C NMR (101 MHz, CDCl₃): δ = 155.3, 129.2, 122.7, 121.2, 103.6, 49.2, 25.3 ppm.

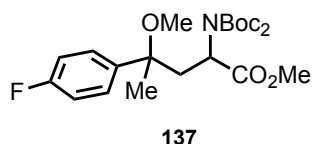
(1,1-dimethoxyethyl)cyclopropane (192)



A solution of cyclopropyl methyl ketone (1 mL, 10 mmol) in dry MeOH (3.3 mL) under N₂ atmosphere was treated with trimethyl orthoformate (1.42 mL, 13 mmol, 1.3 eq) and PTSA at 25 °C (1.90 mg, 0.01 mmol, 10 mol%) and stirred at the same temperature for 2 h. Then, the reaction was treated with NaOMe (1.1 mg, 0.02 mmol, 20 mol%) at 25 °C and vigorously stirred for 5 min. The reaction mixture was concentrated under reduced pressure, washed with brine, and dried over MgSO₄. The crude residue (yellow oil) was used in the next step without further purification.

5.3.6 Synthesis of Ether Products

Synthesis of compound **137**



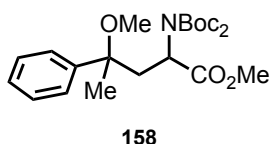
Compound **137** was synthesised according to General Procedure **F** using **136** (37 mg, 0.2 mmol) and irradiated with blue light for 5 h. Crude dr: 1.7:1. FC (SiO₂; pentane/EtOAc 100 to 80:20) gave an inseparable mixture of **137** (*syn*-**137a** and *anti*-**137b**, 60 mg, 66%) as yellow oil.

Data of mixture *syn*-**137a** and *anti*-**137b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.38–7.31 (m, 4 H; ArH, **137a** and **137b**), 7.03–6.95 (m, 4 H; ArH, **137a** and **137b**), 5.04 (dd, *J* = 8.1, 2.9 Hz, 1 H; CHCO₂CH₃, **137a** or **137b**), 4.96 (dd, *J* = 8.3, 2.4 Hz, 1 H; CHCO₂CH₃, **137a** or **137b**), 3.66 (s, 3 H; CO₂CH₃, **137a** or **137b**), 3.64 (s, 3 H; CO₂CH₃, **137a** or **137b**), 3.07 (s, 3 H; OCH₃, **137a** or **137b**), 3.05 (s, 3 H; OCH₃, **137a** or **137b**), 2.79–2.67 (m, 2 H; CH₂, **137a** and **137b**), 2.37–2.27 (m, 2 H; CH₂, **137a** and **137b**), 1.54 (s, 3 H; CH₃, **137a** or **137b**), 1.53 (s, 3 H; CH₃, **137a** or **137b**), 1.46 (s, 18 H; NCO₂C(CH₃)₃, **137a** or **137b**), 1.46 ppm (s, 18 H; NCO₂C(CH₃)₃, **137a** or **137b**); ¹⁹F NMR (377 MHz, CDCl₃): δ = –116.39 (**137a** or **137b**), –116.53 ppm (**137a** or **137b**); ¹³C NMR (101 MHz, CDCl₃): δ = 171.2 (CO₂CH₃, **137a** or **137b**), 171.8 (CO₂CH₃, **137a** or **137b**), 161.9 (d, *J* = 245.5 Hz; C–F, **137a** or **137b**), 161.9 (d, *J* = 245.3 Hz; C–F, **137a** or **137b**), 152.1 (NC=O, **137a** and **137b**), 140.7 (d, *J* = 3.2 Hz; ArC, **137a** or **137b**), 140.6 (d, *J* = 3.1 Hz; ArC, **137a** or **137b**), 128.0 (d, *J* = 8.0 Hz; ArCH, **137a** or **137b**), 127.9 (d, *J* = 7.9 Hz; ArCH, **137a** or **137b**), 115.1 (d, *J* = 21.3 Hz; ArCH, **137a** or **137b**), 115.0 (d, *J* = 20.9 Hz; ArCH, **137a** or **137b**), 82.9 (CO₂C(CH₃)₃, **137a** or **137b**), 82.9 (CO₂C(CH₃)₃, **137a** or **137b**),

78.0 ($\underline{\text{C}}(\text{OCH}_3)\text{CH}_3$, **137a** or **137b**), 77.9 ($\underline{\text{C}}(\text{OCH}_3)\text{CH}_3$, **137a** or **137b**), 55.0 ($\underline{\text{CHCO}}_2\text{CH}_3$, **137a** or **137b**), 54.7 ($\underline{\text{CHCO}}_2\text{CH}_3$, **137a** or **137b**), 52.5 (2C; $\text{CO}_2\underline{\text{CH}}_3$, **137a** and **137b**), 50.3 (OCH_3 , **137a** or **137b**), 50.2 (OCH_3 , **137a** or **137b**), 42.3 ($\underline{\text{CH}}_2$, **137a** or **137b**), 42.1 ($\underline{\text{CH}}_2$, **137a** or **137b**), 28.1 ($\text{C}(\underline{\text{CH}}_3)_3$, **137a** and **137b**), 23.7 ($\text{C}(\text{OCH}_3)\underline{\text{CH}}_3$, **137a** or **137b**), 23.5 ppm ($\text{C}(\text{OCH}_3)\underline{\text{CH}}_3$, **137a** or **137b**); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2980 (m), 1742 (s), 1697 (m), 1366 (s), 1142 (s); **HRMS** (ESI): m/z = 478.2212 ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{23}\text{H}_{34}\text{O}_7\text{FNa}^+$: 478.2212).

Synthesis of compound **158**



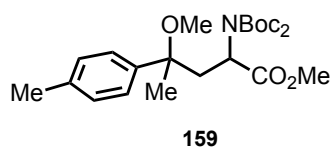
Compound **158** was synthesised according to General Procedure **F** using **145** (33.2 mg, 0.2 mmol) and irradiated with blue light for 18 h. Crude dr: 1.6:1. FC (SiO_2 ; pentane/EtOAc 100 to 90:10) gave an inseparable mixture of **158** (*syn*-**158a** and *anti*-**158b**, 52.7 mg, 60%) as yellow oil.

Data of mixture *syn*-**158a** and *anti*-**158b**:

^1H NMR (400 MHz, CDCl_3): δ = 7.42–7.36 (m, 4 H; ArH, **158a** and **158b**), 7.35–7.29 (m, 4 H; ArH, **158a** and **158b**), 7.25–7.19 (m, 2 H; ArH, **158a** and **158b**), 5.09 (dd, J = 8.0, 3.0 Hz, 1 H; $\underline{\text{CHCO}}_2\text{CH}_3$, **158a** or **158b**), 5.04 (dd, J = 8.3, 2.4 Hz, 1 H; $\underline{\text{CHCO}}_2\text{CH}_3$, **158a** or **158b**), 3.66 (s, 3 H; $\text{CO}_2\underline{\text{CH}}_3$, **158a** or **158b**), 3.64 (s, 3 H; $\text{CO}_2\underline{\text{CH}}_3$, **158a** or **158b**), 3.09 (s, 3 H; OCH_3 , **158a** or **158b**), 3.05 (s, 3 H; OCH_3 , **158a** or **158b**), 2.79 (dd, J = 15.5, 2.4 Hz, 1 H; $\underline{\text{CH}}_2$, **158a** or **158b**), 2.71 (dd, J = 15.5, 3.0 Hz, 1 H; $\underline{\text{CH}}_2$, **158a** or **158b**), 2.39–2.29 (m, 2 H; $\underline{\text{CH}}_2$, **158a** and **158b**), 1.56 (s, 3 H; $\underline{\text{CH}}_3$, **158a** or **158b**), 1.55 (s, 3 H; $\underline{\text{CH}}_3$, **158a** or **158b**),

1.47 (s, 18 H; NCO₂C(CH₃)₃, **158a** or **158b**), 1.47 ppm (s, 18 H; NCO₂C(CH₃)₃, **158a** or **158b**); ¹³C NMR (101 MHz, CDCl₃): δ = 172.1 (C=O, **158a** or **158b**), 171.9 (C=O, **158a** or **158b**), 152.1 (NC=O, **158a** and **158b**), 145.0 (ArC, **158a** or **158b**), 144.9 (ArC, **158a** or **158b**), 128.3 (ArCH, **158a** and **158b**), 127.0 (ArC, **158a** and **158b**), 126.2 (ArCH, **158a** and **158b**), 82.9 (CO₂C(CH₃)₃, **158a** or **158b**), 82.8 (CO₂C(CH₃)₃, **158a** or **158b**), 78.3 (C(OCH₃)CH₃, **158a** and **158b**), 55.1 (CHCO₂CH₃, **158a** or **158b**), 54.8 (CHCO₂CH₃, **158a** or **158b**), 52.5 (CO₂CH₃, **158a** and **158b**), 50.4 (OCH₃, **158a** or **158b**), 50.3 (OCH₃, **158a** or **158b**), 42.4 (CH₂, **158a** or **158b**), 42.0 (CH₂, **158a** or **158b**), 28.1 (C(CH₃)₃, **158a** and **158b**), 23.7 (C(OCH₃)CH₃, **158a** or **158b**), 23.3 ppm (C(OCH₃)CH₃, **158a** or **158b**); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 2980 (m), 1745 (s), 1698 (m), 1508 (m), 1367 (s), 1144 (s); **HRMS** (ESI): m/z = 460.2296 ([M+Na]⁺, calcd. for C₂₃H₃₅O₇NNa⁺: 460.2306).

Synthesis of compound **159**



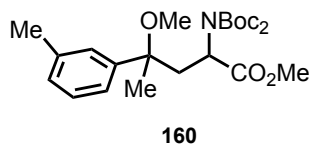
Compound **159** was synthesised according to General Procedure **F** using **146** (36 mg, 0.2 mmol) and irradiated with blue light for 18 h. Crude dr: 1.3:1. FC (SiO₂; pentane/EtOAc 100 to 90:10) gave an inseparable mixture of **159** (*syn*-**159a** and *anti*-**159b**, 51.4 mg, 57%) as yellow oil.

Data of mixture *syn*-**159a** and *anti*-**159b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.30–7.23 (m, 4 H; ArH, **159a** and **159b**), 7.16–7.10 (m, 4 H; ArH, **159a** and **159b**), 5.07 (dd, *J* = 7.9, 3.0 Hz, 1 H; CHCO₂CH₃, **159a** or **159b**), 5.02 (dd, *J* = 8.2, 2.4 Hz, 1 H; CHCO₂CH₃, **159a** or **159b**), 3.66 (s, 3 H; CO₂CH₃, **159a** or **159b**), 3.64 (s, 3 H; CO₂CH₃, **159a** or **159b**), 3.07 (s, 3 H; OCH₃, **159a** or **159b**), 3.03 (s,

3 H; OCH₃, **159a** or **159b**), 2.78 (dd, $J = 15.4, 2.4$ Hz, 1 H; CH₂, **159a** or **159b**), 2.71 (dd, $J = 15.3, 3.0$ Hz, 1 H; CH₂, **159a** or **159b**), 2.36–2.28 (m, 8 H; CH₂ and ArCH₃, **159a** and **159b**), 1.54 (s, 3 H; CH₃, **159a** or **159b**), 1.52 (s, 3 H; CH₃, **159a** or anti- **5**), 1.47 ppm (s, 36 H; NCO₂C(HH₃)₃, **159a** and **159b**); ¹³C NMR (101 MHz, CDCl₃): $\delta = 172.1$ (C=O, **159a** or **159b**), 171.9 (C=O, **159a** or **159b**), 152.1 (NC=O, **159a** and **159b**), 141.9 (ArC, **159a** and **159b**), 136.5 (ArC, **159a** and **159b**), 129.0 (ArCH, **159a** and **159b**), 126.2 (ArCH, **159a** and **159b**), 82.8 (CO₂C(CH₃)₃, **159a** or **159b**), 82.7 (CO₂C(CH₃)₃, **159a** or **159b**), 78.2 (C(OCH₃)CH₃, **159a** and **159b**), 55.1 (CHCO₂CH₃, **159a** or **159b**), 54.9 (CHCO₂CH₃, **159a** or **159b**), 52.4 (CO₂CH₃, **159a** and **159b**), 50.3 (OCH₃, **159a** or **159b**), 50.2 (OCH₃, **159a** or **159b**), 42.4 (CH₂, **159a** or **159b**), 42.1 (CH₂, **159a** or **159b**), 28.1 (C(CH₃)₃, **159a** and **159b**), 23.7 (C(OCH₃)CH₃, **159a** or **159b**), 23.3 (C(OCH₃)CH₃, **159a** or **159b**), 21.1 ppm (ArCH₃, **159a** and **159b**); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 2980 (m), 1745 (s), 1698 (m), 1367 (s), 1143 (s); **HRMS** (ESI): $m/z = 474.2459$ ([M+Na]⁺, calcd. for C₂₄H₃₇O₇NNa⁺: 474.2462).

Synthesis of compound **160**



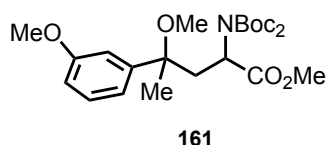
Compound **160** was synthesised according to General Procedure **F** using **147** (36 mg, 0.2 mmol) and irradiated with blue light for 18 h. Crude dr: 1.5:1. FC (SiO₂; pentane/EtOAc 100 to 90:10) gave an inseparable mixture of **160** (*syn*-**160a** and *anti*-**160b**, 56 mg, 62%) as yellow oil.

Data of mixture *syn*-**160a** and *anti*-**160b**:

¹H NMR (400 MHz, CDCl₃): $\delta = 7.24$ – 7.13 (m, 6 H; ArH, **160a** and **160b**), 7.07 – 7.01 (m, 2 H; ArH, **160a** and **160b**), 5.10 (dd, $J = 7.9, 3.0$ Hz, 1 H; CHCO₂CH₃, **160a** or **160b**), 5.04 (dd,

$J = 8.3, 2.4$ Hz, 1 H; CHCO_2CH_3 , **160a** or **160b**), 3.66 (s, 3 H; CO_2CH_3 , **160a** or **160b**), 3.64 (s, 3 H; CO_2CH_3 , **160a** or **160b**), 3.09 (s, 3 H; OCH_3 , **160a** or **160b**), 3.04 (s, 3 H; OCH_3 , **160a** or **160b**), 2.78 (dd, $J = 15.5, 2.4$ Hz, 1 H; CH_2 , **160a** or **160b**), 2.70 (dd, $J = 15.3, 3.0$ Hz, 1 H; CH_2 , **160a** or **160b**), 2.38–2.28 (m, 8 H; CH_2 and ArCH_3 , **160a** and **160b**), 1.55 (s, 3 H; CH_3 , **160a** or **160b**), 1.53 (s, 3 H; CH_3 , **160a** or **160b**), 1.47 ppm (s, 36 H; $\text{NCO}_2\text{C}(\text{CH}_3)_3$, **160a** and **160b**); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 172.1$ (CO_2CH_3 , **160a** or **160b**), 172.0 (CO_2CH_3 , **160a** or **160b**), 152.2 ($\text{NC}=\text{O}$, **160a** or **160b**), 152.1 ($\text{NC}=\text{O}$, **160a** or **160b**), 145.0 (ArC , **160a** and **160b**), 137.7 (ArC , **160a** and **160b**), 128.2 (ArCH , **160a** and **160b**), 127.8 (ArCH , **160a** and **160b**), 127.0 (ArCH , **160a** or **160b**), 126.9 (ArCH , **160a** or **160b**), 123.3 (ArCH , **160a** and **160b**), 82.8 ($\text{CO}_2\text{C}(\text{CH}_3)_3$, **160a** or **160b**), 82.7 ($\text{CO}_2\text{C}(\text{CH}_3)_3$, **160a** or **160b**), 78.2 ($\text{C}(\text{OCH}_3)\text{CH}_3$, **160a** and **160b**), 55.1 (CHCO_2CH_3 , **160a** or **160b**), 54.9 (CHCO_2CH_3 , **160a** or **160b**), 52.4 (CO_2CH_3 , **160a** and **160b**), 50.4 (OCH_3 , **160a** or **160b**), 50.3 (OCH_3 , **160a** or **160b**), 42.3 (CH_2 , **160a** or **160b**), 41.9 (CH_2 , **160a** or **160b**), 28.1 ($\text{C}(\text{CH}_3)_3$, **160a** and **160b**), 23.8 ($\text{C}(\text{OCH}_3)\text{CH}_3$, **160a** or **160b**), 23.4 ($\text{C}(\text{OCH}_3)\text{CH}_3$, **160a** or **160b**), 21.8 ppm (ArCH_3 , **160b** and **160b**); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2980 (m), 1744 (s), 1699 (m), 1367 (s), 1142 (s); **HRMS** (ESI): $m/z = 474.2458$ ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{24}\text{H}_{37}\text{O}_7\text{NNa}^+$ **160b**: 474.2462).

Synthesis of compound **161**

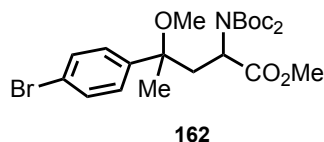


Compound **161** was synthesised according to General Procedure **F** using **148** (39 mg, 0.2 mmol) and irradiated with blue light for 18 h. Crude dr: 1.3:1. FC (SiO_2 ; pentane/Et₂O 70:30 to 50:50) gave an inseparable mixture of **161** (*syn*-**161a** and *anti*-**161b**, 60 mg, 64%) as yellow oil.

Data of mixture *syn*-**161a** and *anti*-**161b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.23 (td, *J* = 8.0, 1.8 Hz, 2 H; ArH, **161a** and **161b**), 6.99–6.92 (m, 4 H; ArH, **161a** and **161b**), 6.77 (ddd, *J* = 8.3, 2.5, 1.1 Hz, 2 H; ArH, **161a** and **161b**), 5.08 (dd, *J* = 8.0, 3.0 Hz, 1 H; CHCO₂CH₃, **161a** or **161b**), 5.04 (dd, *J* = 8.4, 2.3 Hz, 1 H; CHCO₂CH₃, **161a** or **161b**), 3.80 (s, 6 H; ArOCH₃, **161a** and **161b**), 3.66 (s, 3 H; CO₂CH₃, **161a** or **161b**), 3.64 (s, 3 H; CO₂CH₃, **161a** or **161b**), 3.09 (s, 3 H; OCH₃, **161a** or **161b**), 3.05 (s, 3 H; OCH₃, **161a** or **161b**), 2.77 (dd, *J* = 15.4, 2.4 Hz, 1 H; CH₂, **161a** or **161b**), 2.70 (dd, *J* = 15.3, 3.0 Hz, 1 H; CH₂, **161a** or **161b**), 2.43–2.28 (m, 2 H; CH₂, **161a** and **161b**), 1.54 (s, 3 H; CH₃, **161a** or **161b**), 1.53 (s, 3 H; CH₃, **161a** or **161b**), 1.47 ppm (s, 36 H; NCO₂C(CH₃)₃, **161a** and **161b**); ¹³C NMR (101 MHz, CDCl₃): δ = 172.1 (CO₂CH₃, **161a** or **161b**), 171.9 (CO₂CH₃, **161a** or **161b**), 159.7 (ArC, **161a** and **161b**), 152.2 (NC=O, **161a** or **161b**), 152.1 (NC=O, **161a** or **161b**), 146.8 (ArC, **161a** and **161b**), 129.3 (ArCH, **161a** and **161b**), 118.7 (ArCH, **161a** and **161b**), 112.3 (ArCH, **161a** and **161b**), 82.9 (CO₂C(CH₃)₃, **161a** or **161b**), 82.8 (CO₂C(CH₃)₃, **161a** or **161b**), 78.3 (C(OCH₃)CH₃, **161a** or **161b**), 78.2 (C(OCH₃)CH₃, **161a** or **161b**), 55.3 (ArOCH₃, **161a** and **161b**), 55.1 (CHCO₂CH₃, **161a** or **161b**), 54.8 (CHCO₂CH₃, **161a** or **161b**), 52.5 (CO₂CH₃, **161a** and **161b**), 50.5 (OCH₃, **161a** or **161b**), 50.4 (OCH₃, **161a** or **161b**), 42.4 (CH₂, **161a** or **161b**), 42.0 (CH₂, **161a** or **161b**), 28.1 (C(CH₃)₃, **161a** and **161b**), 23.7 (C(OCH₃)CH₃, **161a** or **161b**), 23.3 ppm (C(OCH₃)CH₃, **161a** or **161b**); FT-IR (thin film): ν_{max} (cm⁻¹) = 2980 (m), 1742 (s), 1698 (m), 1366 (s), 1140 (s); HRMS (ESI): *m/z* = 490.2402 ([M+Na]⁺, calcd. for C₂₄H₃₇O₈NNa⁺: 490.2411).

Synthesis of compound **162**



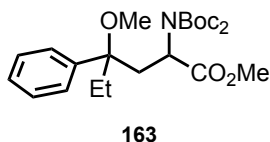
Compound **162** was synthesised according to General Procedure **F** using **149** (49 mg, 0.2 mmol) and irradiated with blue light for 18 h. Crude dr: 1.2:1. FC (SiO₂; pentane/EtOAc 100 to 90:10) gave an inseparable mixture of **162** (*syn*-**162a** and *anti*-**162b**, 34 mg, 33%) as yellow oil.

Data of mixture *syn*-**162a** and *anti*-**162b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.46–7.41 (m, 4 H; ArH, **162a** and **162b**), 7.27–7.23 (m, 4 H; ArH, **162a** and **162b**), 5.06 (dd, *J* = 8.2, 2.8 Hz, 1 H; CHCO₂CH₃, **162a** or **162b**), 4.95 (dd, *J* = 8.4, 2.4 Hz, 1 H; CHCO₂CH₃, **162a** or **162b**), 3.66 (s, 3 H; CO₂CH₃, **162a** or **162b**), 3.64 (s, 3 H; CO₂CH₃, **162a** or **162b**), 3.08 (s, 3 H; OCH₃, **162a** or **162b**), 3.08 (s, 3 H; OCH₃, **162a** or **162b**), 2.77–2.67 (m, 2H; CH₂, **162a** and **162b**), 2.38–2.24 (m, 2H; CH₂, **162a** and **162b**), 1.53 (s, 3 H; CH₃, **162a** or **162b**), 1.52 (s, 3 H; CH₃, **162a** or **162b**), 1.47 (s, 18 H; NCO₂C(CH₃)₃, **162a** or **162b**), 1.46 ppm (s, 18 H; NCO₂C(CH₃)₃, **162a** or **162b**);
¹³C NMR (101 MHz, CDCl₃): δ = 172.0 (CO₂CH₃, **162a** or **162b**), 171.8 (CO₂CH₃, **162a** or **162b**), 152.2 (NC=O, **162a** and **162b**), 144.3 (ArC, **162a** or **162b**), 144.0 (ArC, **162a** or **162b**), 131.4 (ArCH, **162a** or **162b**), 131.4 (ArCH, **162a** or **162b**), 128.2 (ArCH, **162a** and **162b**), 128.0 (ArCH, **162a** and **162b**), 121.1 (ArC, **162a** or **162b**), 120.9 (ArC, **162a** or **162b**), 83.0 (CO₂C(CH₃)₃, **162a** or **162b**), 82.9 (CO₂C(CH₃)₃, **162a** or **162b**), 78.1 (C(OCH₃)CH₃, **162a** or **162b**), 77.9 (C(OCH₃)CH₃, **162a** or **162b**), 55.0 (CHCO₂CH₃, **162a** or **162b**), 54.6 (CHCO₂CH₃, **162a** or *anti*- **162b**), 52.5 (CO₂CH₃, **162a** and **162b**), 50.4 (OCH₃, **162a** or **162b**), 50.3 (OCH₃, **162a** or **162b**), 41.9 (CH₂, **162a** or **162b**), 41.8 (CH₂, **162a** or **162b**), 28.1 (C(CH₃)₃, **162a** and **162b**), 23.6 (C(OCH₃)CH₃, **162a** or **162b**), 23.5 ppm (C(OCH₃)CH₃, **162a** or **162b**).

162a or **162b**); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 2980 (m), 1741 (s), 1697 (m), 1366 (s), 1142 (s); **HRMS** (ESI): m/z = 538.1401 ([M+Na]⁺, calcd. for C₂₃H₃₄O₇NBrNa⁺: 538.1411).

Synthesis of compound **163**



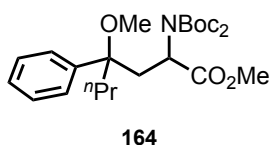
Compound **163** was synthesised according to General Procedure **F** using **150** (36 mg, 0.2 mmol) and irradiated with blue light for 18 h. Crude dr: 1.2:1. FC (SiO₂; pentane/EtOAc 100 to 90:10) gave an inseparable mixture of **163** (*syn*-**163a** and *anti*-**163b**, 49 mg, 54%) as yellow oil.

Data of mixture *syn*-**163a** and *anti*-**163b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.41–7.27 (m, 8 H; ArH, **163a** and **163b**), 7.23–7.16 (m, 2 H; ArH, **163a** and **163b**), 4.99 (dd, J = 8.4, 2.4 Hz, 1 H; CHCO₂CH₃, **163a** or **163b**), 4.79 (dd, J = 8.6, 2.0 Hz, 1 H; CHCO₂CH₃, **163a** or **163b**), 3.66 (s, 3 H; CO₂CH₃, **163a** or **163b**), 3.62 (s, 3 H; CO₂CH₃, **163a** or **163b**), 3.10 (s, 3 H; OCH₃, **163a** or **163b**), 3.09 (s, 3 H; OCH₃, **163a** or **163b**), 2.93 (dd, J = 15.7, 2.4 Hz, 1 H; CH₂, **163a** or **163b**), 2.81 (dd, J = 15.9, 2.0 Hz, 1 H; CH₂, **163a** or **163b**), 2.65–2.57 (m, 1 H; CH₂, **163a** or **163b**), 2.47 (dd, J = 15.7, 8.4 Hz, 1 H; CH₂, **163a** or **163b**), 1.98–1.88 (m, 2 H; C(OCH₃)CH₂CH₃, **163a** and **163b**), 1.83–1.72 (m, 2 H; C(OCH₃)CH₂CH₃, **163a** and **163b**), 1.48 (s, 18 H; NCO₂C(CH₃)₃, **163a** or **163b**), 1.43 (s, 18 H; NCO₂C(CH₃)₃, **163a** or **163b**), 0.68–0.52 ppm (m, 6 H; C(OCH₃)CH₂CH₃, **163a** and **163b**); ¹³C NMR (101 MHz, CDCl₃): δ = 172.2 (CO₂CH₃, **163a** or **163b**), 171.9 (CO₂CH₃, **163a** or **163b**), 152.2 (NC=O, **163a** or **163b**), 152.1 (NC=O, **163a** or **163b**), 143.4 (ArC, **163a** or **163b**), 143.3 (ArC, **163a** or **163b**), 128.0 (ArCH, **163a** and **163b**), 126.7 (ArCH, **163a** or **163b**), 126.5 (ArCH, **163a** or **163b**), 82.8 (CO₂C(CH₃)₃, **163a** or **163b**), 82.7 (CO₂C(CH₃)₃,

163a or **163b**), 81.1 ($\underline{\text{C}}(\text{OCH}_3)\text{CH}_2\text{CH}_3$, **163a** or **163b**), 80.4 ($\underline{\text{C}}(\text{OCH}_3)\text{CH}_2\text{CH}_3$, **163a** or **163b**), 55.2 ($\underline{\text{CHCO}}_2\text{CH}_3$, **163a** or **163b**), 54.5 ($\underline{\text{CHCO}}_2\text{CH}_3$, **163a** or **163b**), 52.5 ($\text{CO}_2\underline{\text{CH}}_3$, **163a** or **163b**), 52.4 ($\text{CO}_2\underline{\text{CH}}_3$, **163a** or **163b**), 49.6 ($\text{O}\underline{\text{CH}}_3$, **163a** or **163b**), 49.4 ($\text{O}\underline{\text{CH}}_3$, **163a** or **163b**), 35.5 ($\underline{\text{CH}}_2$, **163a** or **163b**), 35.4 ($\underline{\text{CH}}_2$, **163a** or **163b**), 30.1 ($\text{C}(\text{OCH}_3)\underline{\text{CH}}_2\text{CH}_3$, **163a** and **163b**), 28.1 ($\text{C}(\underline{\text{CH}}_3)_3$, **163a** and **163b**), 7.6 ($\text{C}(\text{OCH}_3)\text{CH}_2\underline{\text{CH}}_3$, **163a** or **163b**), 7.5 ppm ($\text{C}(\text{OCH}_3)\text{CH}_2\underline{\text{CH}}_3$, **163a** or **163b**); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2980 (m), 1742 (s), 1698 (m), 1367 (s), 1144 (s); **HRMS** (ESI): m/z = 474.2455 ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{24}\text{H}_{37}\text{O}_7\text{NNa}^+$: 474.2462).

Synthesis of compound **164**



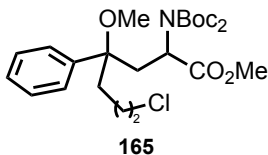
Compound **164** was synthesised according to General Procedure **F** using **151** (39 mg, 0.2 mmol) and irradiated with blue light for 18 h. Crude dr: 1.5:1. FC (SiO_2 ; pentane/EtOAc 100 to 80:20) gave an inseparable mixture of **164** (*syn*-**164a** and *anti*-**164b**, 46.4 mg, 50%) as yellow oil.

Data of mixture *syn*-**164a** and *anti*-**164b**:

^1H NMR (400 MHz, CDCl_3): δ = 7.40–7.34 (m, 4 H; ArH, **164a** and **164b**), 7.32–7.27 (m, 4 H; ArH, **164a** and **164b**), 7.24–7.16 (m, 2 H; ArH, **164a** and **164b**), 4.96 (dd, J = 8.4, 2.3 Hz, 1 H; $\underline{\text{CHCO}}_2\text{CH}_3$, **164a** or **164b**), 4.83 (dd, J = 8.6, 1.8 Hz, 1 H; $\underline{\text{CHCO}}_2\text{CH}_3$, **164a** or **164b**), 3.66 (s, 3 H; $\text{CO}_2\underline{\text{CH}}_3$, **164a** or **164b**), 3.63 (s, 3 H; $\text{CO}_2\underline{\text{CH}}_3$, **164a** or **164b**), 3.09 (s, 3 H; $\text{O}\underline{\text{CH}}_3$, **164a** or **164b**), 3.08 (s, 3 H; $\text{O}\underline{\text{CH}}_3$, **164a** or **164b**), 2.92 (dd, J = 15.7, 2.4 Hz, 1 H; $\underline{\text{CH}}_2$, **164a** or **164b**), 2.83 (dd, J = 15.9, 1.9 Hz, 1 H; $\underline{\text{CH}}_2$, **164a** or **164b**), 2.61 (dd, J = 15.9, 8.6 Hz, 1 H; $\underline{\text{CH}}_2$, **164a** or **164b**), 2.47 (dd, J = 15.7, 8.4 Hz, 1 H; $\underline{\text{CH}}_2$,

164a or **164b**), 1.90–1.79 (m, 2 H; C(OCH₃)CH₂CH₂CH₃, **164a** and **164b**), 1.76–1.61 (m, 2 H; C(OCH₃)CH₂CH₂CH₃, **164a** and **164b**), 1.48 (s, 18 H; NCO₂C(CH₃)₃, **164a** or **164b**), 1.44 (s, 18 H; NCO₂C(CH₃)₃, **164a** or **164b**), 1.12–0.98 (m, 2 H; C(OCH₃)CH₂CH₂CH₃, **164a** and **164b**), 0.96–0.85 (m, 2 H; C(OCH₃)CH₂CH₂CH₃, **164a** and **164b**), 0.79 ppm (q, J = 7.3 Hz, 6 H; C(OCH₃)CH₂CH₂CH₃, **164a** and **164b**); ¹³C NMR (101 MHz, CDCl₃): δ = 172.2 (CO₂CH₃, **164a** or **164b**), 171.9 (CO₂CH₃, **164b** or **164b**), 152.2 (NC=O, **164a** or **164b**), 152.1 (NC=O, **164a** or **164b**), 143.7 (ArC, **164a** and **164b**), 128.0 (ArCH, **164a** and **164b**), 126.8 (ArCH, **164a** or **164b**), 126.7 (ArCH, **164a** or **164b**), 126.6 (ArCH, **164a** or **164b**), 126.5 (ArCH, **164a** or **164b**), 82.8 (CO₂C(CH₃)₃, **164b** or **164b**), 82.7 (CO₂C(CH₃)₃, **164a** or **164b**), 80.8 (C(OCH₃)CH₂CH₂CH₃, **164a** or **164b**), 80.1 (C(OCH₃)CH₂CH₂CH₃, **164a** or **164b**), 55.1 (CHCO₂CH₃, **164a** or **164b**), 54.5 (CHCO₂CH₃, **164a** or **164b**), 52.5 (CO₂CH₃, **164a** and **164b**), 49.6 (OCH₃, **164a** or **164b**), 49.5 (OCH₃, **164a** or **164b**), 40.3 (CH₂, **164a** or **164b**), 39.7 (CH₂, **164a** or **164b**), 36.0 (C(OCH₃)CH₂CH₂CH₃, **164a** or **164b**), 35.2 (C(OCH₃)CH₂CH₂CH₃, **164a** or **164b**), 28.1 (C(CH₃)₃, **164a** and **164b**), 16.6 (C(OCH₃)CH₂CH₂CH₃, **164a** or **164b**), 16.5 (C(OCH₃)CH₂CH₂CH₃, **164a** or **164b**), 14.4 (C(OCH₃)CH₂CH₂CH₃, **164a** or **164b**), 14.3 ppm (C(OCH₃)CH₂CH₂CH₃, **164b** or **164b**); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 2980 (m), 1742 (s), 1698 (m), 1366 (s), 1143 (s); **HRMS** (ESI): m/z = 488.2618 ([M+Na]⁺, calcd. for C₂₅H₃₉O₇NNa⁺: 488.2619).

Synthesis of compound **165**



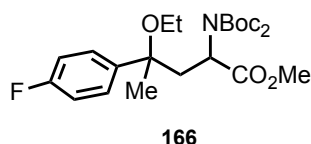
Compound **165** was synthesised according to General Procedure **F** using **152** (45.7 mg, 0.2 mmol) and irradiated with blue light for 18 h. Crude dr: 1.2:1. FC (SiO₂; pentane/EtOAc 100 to 80:20) gave an inseparable mixture of **165** (*syn*-**165a** and *anti*-**165b**, 35.6 mg, 36%) as yellow oil.

Data of mixture *syn*-**165a** and *anti*-**165b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.42–7.28 (m, 8 H; ArH, **165a** and **165b**), 7.25–7.18 (m, 2 H; ArH, **165a** and **165b**), 4.97 (dd, *J* = 8.3, 2.4 Hz, 1 H; CHCO₂CH₃, **165a** or **165b**), 4.76 (dd, *J* = 8.5, 1.9 Hz, 1 H; CHCO₂CH₃, **165a** or **165b**), 3.67 (s, 3 H; CO₂CH₃, **165a** or **165b**), 3.62 (s, 3 H; CO₂CH₃, **165a** or **165b**), 3.43–3.33 (m, 4 H; C(OCH₃)CH₂CH₂CH₂Cl, **165a** and **165b**), 3.15 (s, 3 H; OCH₃, **165a** or **165b**), 3.13 (s, 3 H; OCH₃, **165a** or **165b**), 2.97 (dd, *J* = 15.9, 2.4 Hz, 1 H; CH₂, **165a** or **165b**), 2.84 (dd, *J* = 15.9, 2.0 Hz, 1 H; CH₂, **165a** or **165b**), 2.68–2.60 (m, 1 H; CH₂, **165a** or **165b**), 2.49 (dd, *J* = 15.8, 8.3 Hz, 1 H; CH₂, **165a** or **165b**), 2.12–2.03 (m, 2 H; C(OCH₃)CH₂CH₂CH₂Cl, **165a** and **165b**), 1.94–1.77 (m, 2 H; C(OCH₃)CH₂CH₂CH₂Cl, **165a** and **165b**), 1.49 (s, 18 H; NCO₂C(CH₃)₃, **165a** or **165a165b**), 1.43 ppm (s, 18 H; NCO₂C(CH₃)₃, **165a** or **165b**); ¹³C NMR (101 MHz, CDCl₃): δ = 172.1 (CO₂CH₃, **165a** or **165b**), 171.8 (CO₂CH₃, **165a** or **165b**), 152.3 (NC=O, **165a** or **165b**), 152.1 (NC=O, **165a** or **165b**), 143.1 (ArC, **165a** or **165b**), 143.0 (ArC, **165a** or **165b**), 128.3 (ArCH, **165a** and **165b**), 127.1 (ArCH, **165a** or **165b**), 126.9 (ArCH, **165a** or **165b**), 126.5 (ArCH, **165a** or **165b**), 126.3 (ArCH, **165a** or **165b**), 83.0 (CO₂C(CH₃)₃, **165a** or **165b**), 82.9 (CO₂C(CH₃)₃, **165a** or **165b**), 80.4 (C(OCH₃)CH₂CH₂CH₂Cl, **165a** or **165b**), 79.5 (C(OCH₃)CH₂CH₂CH₂Cl, **165a** or **165b**),

55.1 ($\underline{\text{CHCO}}_2\text{CH}_3$, **165a** or **165b**), 54.3 ($\underline{\text{CHCO}}_2\text{CH}_3$, **165a** or **165b**), 52.6 ($\text{CO}_2\underline{\text{CH}}_3$, **165a** or **165b**), 52.5 ($\text{CO}_2\underline{\text{CH}}_3$, **165a** or **165b**), 49.6 ($\text{O}\underline{\text{CH}}_3$, **165a** or **165b**), 49.4 ($\text{O}\underline{\text{CH}}_3$, **165a** or **165b**), 45.5 ($\text{C}(\text{OCH}_3)\text{CH}_2\text{CH}_2\underline{\text{CH}}_2\text{Cl}$, **165a** or **165b**), 45.4 ($\text{C}(\text{OCH}_3)\text{CH}_2\text{CH}_2\underline{\text{CH}}_2\text{Cl}$, **165a** or **165b**), 36.3 ($\underline{\text{CH}}_2$, **165a** or **165b**), 35.7 ($\underline{\text{CH}}_2$, **165a** or **165b**), 35.1 ($\text{C}(\text{OCH}_3)\underline{\text{CH}}_2\text{CH}_2\text{CH}_2\text{Cl}$, **165a** and **165b**), 34.9 ($\text{C}(\text{OCH}_3)\text{CH}_2\underline{\text{CH}}_2\text{CH}_2\text{Cl}$, **165a** and **165b**), 28.1 ppm ($\text{C}(\underline{\text{CH}}_3)_3$, **165a** and **165b**); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2979 (m), 1740 (s), 1697 (m), 1366 (s), 1142 (s); **HRMS** (ESI): m/z = 522.2234 ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{25}\text{H}_{38}\text{O}_7\text{NClNa}^+$: 522.2229).

Synthesis of compound **166**



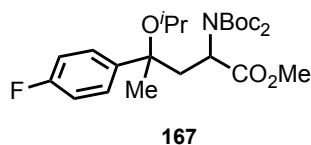
Compound **166** was synthesised according to General Procedure **F** using **153** (42.5 mg, 0.2 mmol) and irradiated with blue light for 18 h. Crude dr: 1.6:1. FC (SiO_2 ; pentane/EtOAc 100 to 80:20) gave an inseparable mixture of **166** (*syn*-**166a** and *anti*-**166b**, 52 mg, 55%) as yellow oil.

Data of mixture *syn*-**166a** and *anti*-**166b**:

^1H NMR (400 MHz, CDCl_3): δ = 7.38–7.31 (m, 4 H; ArH , **166a** and **166b**), 7.02–6.94 (m, 4 H; ArH , **166a** and **166b**), 5.08 (dd, J = 8.2, 3.1 Hz, 1 H; $\underline{\text{CHCO}}_2\text{CH}_3$, **166a** or **166b**), 5.04 (dd, J = 8.4, 2.5 Hz, 1 H; $\underline{\text{CHCO}}_2\text{CH}_3$, **166a** or **166b**), 3.65 (s, 3 H; $\text{CO}_2\underline{\text{CH}}_3$, **166a** or **166b**), 3.64 (s, 3 H; $\text{CO}_2\underline{\text{CH}}_3$, **166a** or **166b**), 3.34–3.23 (m, 2 H; OCH_2CH_3 , **166a** and **166b**), 3.18–3.07 (m, 2 H; OCH_2CH_3 , **166a** and **166b**), 2.74 (dd, J = 15.3, 2.5 Hz, 1 H; $\underline{\text{CH}}_2$, **166a** or **166b**), 2.64 (dd, J = 15.3, 3.1 Hz, 1 H; $\underline{\text{CH}}_2$, **166a** or **166b**), 2.31 (dd, J = 15.3, 8.3 Hz, 2 H; $\underline{\text{CH}}_2$, **166a** and **166b**), 1.55 (s, 3 H; $\underline{\text{CH}}_3$, **166a** or **166b**), 1.54 (s, 3 H; $\underline{\text{CH}}_3$, **166a** or **166b**), 1.46

(s, 36 H; $\text{NCO}_2\text{C}(\text{CH}_3)_3$, **166a** and **166b**), 1.14 ppm (t, $J = 7.0, 1.0$ Hz, 6 H; OCH_2CH_3 , **166a** and **166b**); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -116.56$ (**166a** or **166b**), -116.75 ppm (**166a** or **166b**); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 172.1$ (CO_2CH_3 , **166a** or **166b**), 171.9 (CO_2CH_3 , **166a** or **166b**), 161.9 (d, $J = 248.8$ Hz; $\text{C}-\text{F}$, **166a** or **166b**), 161.9 (d, $J = 240.8$ Hz; $\text{C}-\text{F}$, **166a** or **166b**), 151.2 ($\text{NC}=\text{O}$, **166a** and **166b**), 141.6 (d, $J = 3.1$ Hz; ArC , **166a** or **166b**), 141.4 (d, $J = 3.1$ Hz; ArC , **166a** or **166b**), 127.9 (d, $J = 7.9$ Hz; ArCH , **166a** or **166b**), 128.0 (d, $J = 7.9$ Hz; ArCH , **166a** or **166b**), 115.0 (d, $J = 21.3$ Hz; ArCH , **166a** or **166b**), 114.9 (d, $J = 21.2$ Hz; ArCH , **166a** or **166b**), 82.9 ($\text{CO}_2\text{C}(\text{CH}_3)_3$, **166a** or **166b**), 82.8 ($\text{CO}_2\text{C}(\text{CH}_3)_3$, **166a** or **166b**), 77.5 ($\text{C}(\text{OCH}_2\text{CH}_3)\text{CH}_3$, **166a** and **166b**), 57.7 (OCH_2CH_3 , **166a** or **166b**), 57.6 (OCH_2CH_3 , **166a** or **166b**), 54.9 (CHCO_2CH_3 , **166a** or **166b**), 54.7 (CHCO_2CH_3 , **166a** or **166b**), 52.5 (2C; CO_2CH_3 , **166a** and **166b**), 42.8 (CH_2 , **166a** or **166b**), 42.4 (CH_2 , **166a** or **166b**), 28.1 ($\text{C}(\text{CH}_3)_3$, **166a** and **166b**), 24.2 (OCH_2CH_3 , **166a** or **166b**), 23.8 (OCH_2CH_3 , **166a** or **166b**), 15.8 ppm ($\text{C}(\text{OCH}_2\text{CH}_3)\text{CH}_3$, **166a** and **166b**); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2977 (m), 1744 (s), 1698 (m), 1367 (s), 1143 (s); **HRMS** (ESI): $m/z = 492.2362$ ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{24}\text{H}_{36}\text{O}_7\text{NFNa}^+$: 492.2368).

Synthesis of compound **167**

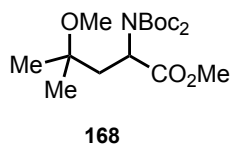


Compound **167** was synthesised according to General Procedure **F** using **154** (48 mg, 0.2 mmol) and irradiated with blue light for 18 h. Crude dr: 1.4:1. FC (SiO_2 ; pentane/EtOAc 100 to 90:10) gave an inseparable mixture of **167** (*syn*-**167a** and *anti*-**167b**, 39.4 mg, 41%) as yellow oil.

Data of mixture *syn*-**167a** and *anti*-**167b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.45–7.36 (m, 4 H; ArH, **167a** and **167b**), 7.00–6.92 (m, 4 H; ArH, **167a** and **167b**), 5.04 (dd, *J* = 8.3, 2.7 Hz, 1 H; CHCO₂CH₃, **167a** or **167b**), 4.97 (dd, *J* = 8.4, 2.9 Hz, 1 H; CHCO₂CH₃, **167a** or **167b**), 3.66 (s, 3 H; CO₂CH₃, **167a** or **167b**), 3.64 (s, 3 H; CO₂CH₃, **167a** or **167b**), 3.57–3.42 (m, 2 H; OCH(CH₃)₂, **167a** and **167b**), 2.77 (dd, *J* = 15.2, 2.7 Hz, 1 H; CH₂, **167a** or **167b**), 2.61–2.54 (m, 1 H; CH₂, **167a** or **167b**), 2.31 (dd, *J* = 15.3, 8.4 Hz, 1 H; CH₂, **167a** or **167b**), 2.20 (dd, *J* = 15.2, 8.3 Hz, 1 H; CH₂, **167a** or **167b**), 1.62 (s, 3 H; CH₃, **167a** or **167b**), 1.61 (s, 3 H; CH₃, **167a** or **167b**), 1.47 (s, 18 H; NCO₂C(CH₃)₃, **167a** or **167b**), 1.44 (s, 18 H; NCO₂C(CH₃)₃, **167a** or **167b**), 1.11 (dd, *J* = 6.1, 1.7 Hz, 6 H; OCH(HH₃)₂, **167a** or **167b**), 0.94 ppm (dd, *J* = 14.7, 6.1 Hz, 6 H; OCH(CH₃)₂, **167a** or **167b**); ¹⁹F NMR (377 MHz, CDCl₃): δ = –116.34 (**167a** or **167b**), –116.51 ppm (**167a** or **167b**); ¹³C NMR (101 MHz, CDCl₃): δ = 172.0 (CO₂CH₃, **167a** or **167b**), 171.9 (CO₂CH₃, **167a** or **167b**), 162.0 (d, *J* = 245.6 Hz; C–F, **167a** or **167b**), 161.9 (d, *J* = 245.1 Hz; C–F, **167a** or **167b**), 152.2 (NC=O, **167a** or **167b**), 152.1 (NC=O, **167a** or **167b**), 141.8 (d, *J* = 3.2 Hz; ArC, **167a** or **167b**), 141.5 (d, *J* = 3.2 Hz; ArC, **167b** or **167b**), 128.7 (d, *J* = 7.9 Hz; ArCH, **167a** or **167b**), 128.4 (d, *J* = 8.0 Hz; ArCH, **167a** or **167b**), 114.7 (d, *J* = 21.5 Hz; ArCH, **167a** or **167b**), 114.7 (d, *J* = 21.4 Hz; ArCH, **167a** or **167b**), 82.9 (CO₂C(CH₃)₃, **167a** or **167b**), 82.8 (CO₂C(CH₃)₃, **167a** or **167b**), 77.9 (C(OCH(CH₃)₂)CH₃, **167a** or **167b**), 77.7 (C(OCH(CH₃)₂)CH₃, **167a** or **167b**), 65.3 (OCH(CH₃)₂, **167a** or **167b**), 65.2 (OCH(CH₃)₂, **167a** or **167b**), 55.0 (CHCO₂CH₃, **167a** and **167b**), 52.5 (2C; CO₂CH₃, **167a** and **167b**), 44.5 (CH₂, **167a** or **167b**), 43.9 (CH₂, **167a** or **167b**), 28.2 (C(CH₃)₃, **167a** or **167b**), 28.1 (C(CH₃)₃, **167a** or **167b**), 25.2 (OCH(CH₃)₂, **167a** or **167b**), 25.0 (OCH(CH₃)₂, **167a** or **167b**), 24.7 (OCH(CH₃)₂, **167a** or **167b**), 24.5 (OCH(CH₃)₂, **167a** or **167b**), 23.6 (C(OCH(CH₃)₂)CH₃, **167a** or **167b**), 23.2 ppm (C(OCH(CH₃)₂)CH₃, **167a** or **167b**); FT-IR (thin film): ν_{max} (cm^{–1}) = 2978 (m), 1744 (s), 1697 (m), 1366 (s), 1140 (br, s); HRMS (ESI): *m/z* = 506.2519 ([M+Na]⁺, calcd. for C₂₅H₃₈O₇NFNa⁺: 506.2525).

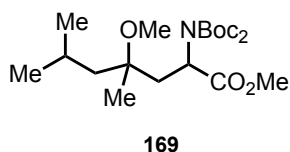
Synthesis of compound **168**



Compound **168** was synthesised according to General Procedure **F** using 2,2-Dimethoxypropane (25 μ L, 0.2 mmol) and irradiated with blue light for 18 h. FC (SiO₂; pentane/EtOAc 100 to 90:10) gave **168** (32 mg, 43%) as yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 5.10 (dd, J = 7.9, 2.9 Hz, 1 H; CHCO₂CH₃), 3.70 (s, 3 H; CO₂CH₃), 3.14 (s, 3 H; OCH₃), 2.44 (dd, J = 15.5, 2.9 Hz, 1 H; CH₂), 2.03 (dd, J = 15.5, 7.9 Hz, 1 H; CH₂), 1.49 (s, 18 H; NCO₂C(CH₃)₃), 1.18 (s, 3 H; CH₃), 1.17 ppm (s, 3 H; CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ = 172.2 (CO₂CH₃), 152.3 (NC=O), 83.0 (CO₂C(CH₃)₃), 73.9 (C(CH₃)₂OCH₃), 55.0 (CHCO₂CH₃), 52.5 (CO₂CH₃), 49.4 (OCH₃), 39.9 (CH₂), 28.2 (C(CH₃)₃), 25.4 (CH₃), 25.3 ppm (CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 2976 (w), 1745 (s), 1698 (m), 1366 (s), 1135 (s); **HRMS** (ESI): m/z = 398.2144 ([M+Na]⁺, calcd. for C₁₈H₃₃O₇NNa⁺: 398.2149).

Synthesis of compound **169**

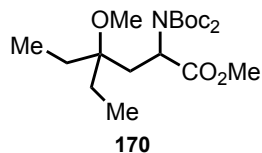


Compound **169** was synthesised according to General Procedure **F** using **155** (29 mg, 0.2 mmol) and irradiated with blue light for 18 h. FC (SiO₂; pentane/EtOAc 100 to 90:10) gave **169** (*syn*-**169a** and *anti*-**169b**, 23.5 mg, 28%) as yellow oil.

Data of mixture *syn*-**169a** and *anti*-**169b**:

¹H NMR (400 MHz, CDCl₃): δ = 5.12–5.10 (m, 1 H; CHCO₂CH₃, **169a** or **169b**), 5.10–5.08 (m, 1 H; CHCO₂CH₃, **169a** or **169b**), 3.69 (s, 6 H; CO₂CH₃, **169a** and **169b**), 3.10 (s, 3 H; OCH₃, **169a** or **169b**), 3.08 (s, 3 H; OCH₃, **169a** or **169b**), 2.48 (dd, *J* = 15.6, 2.4 Hz, 1 H; CH₂, **169a** or **169b**), 2.39 (dd, *J* = 15.5, 3.0 Hz, 1 H; CH₂, **169a** or **169b**), 2.10–1.96 (m, 2 H; CH₂, **169a** and **169b**), 1.79–1.69 (m, 2 H; CH(CH₃)₂, **169a** and **169b**), 1.49 (s, 36 H; NCO₂C(CH₃)₃, **169a** and **169b**), 1.46–1.30 (m, 4 H; CH₂CH(CH₃)₂, **169a** and **169b**), 1.15 (s, 3 H; CH₃, **169a** or **169b**), 1.14 (s, 3 H; CH₃, **169a** or **169b**), 0.96–0.87 ppm (m, 12 H; CH(CH₃)₂, **169a** and **169b**); ¹³C NMR (101 MHz, CDCl₃): δ = 172.4 (CO₂CH₃, **169a** or **169b**), 172.3 (CO₂CH₃, **169a** or **169b**), 152.3 (NC=O, **169a** or **169b**), 152.2 (NC=O, **169a** or **169b**), 83.0 (CO₂C(CH₃)₃, **169a** or **169b**), 82.9 (CO₂C(CH₃)₃, **169a** or **169b**), 76.4 (C(CH₃)OCH₃, **169a** or **169b**), 76.3 (C(CH₃)OCH₃, **169a** or **169b**), 54.8 (CHCO₂CH₃, **169a** or **169b**), 54.7 (CHCO₂CH₃, **169a** or **169b**), 52.5 (CO₂CH₃, **169b** and **169b**), 49.0 (OCH₃, **169a** and **169b**), 46.4 (CH₂, **169a** or **169b**), 46.1 (CH₂, **169a** or **169b**), 38.7 (CH₂CH(CH₃)₂, **169a** or **169b**), 38.2 (CH₂CH(CH₃)₂, **169a** or **169b**), 28.2 (C(CH₃)₃, **169a** and **169b**), 24.9 (CH₃, **169a** or **169b**), 24.8 (CH₃, **169a** or **169b**), 24.6 (CH₂CH(CH₃)₂, **169a** or **169b**), 24.5 (CH₂CH(CH₃)₂, **169a** or **169b**), 24.1 (CH₂CH(CH₃)₂, **169a** or **169b**), 23.9 (CH₂CH(CH₃)₂, **169a** or **169b**), 23.1 ppm (CH₂CH(CH₃)₂, **169a** and **169b**); FT-IR (thin film): ν_{max} (cm⁻¹) = 2952 (w), 1746 (s), 1699 (m), 1367 (s), 1135 (s); HRMS (ESI): *m/z* = 440.2616 ([M+Na]⁺, calcd. for C₂₁H₃₉O₇NNa⁺: 440.2619).

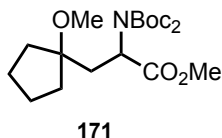
Synthesis of compound **170**



Compound **170** was synthesized according to General Procedure **F** using **156** (26.5 mg, 0.2 mmol) and irradiated with blue light for 18 h. FC **170** (33 mg, 41%) as yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 5.04 (dd, J = 8.1, 2.3 Hz, 1 H; CHCO_2CH_3), 3.69 (s, 3 H; CO_2CH_3), 3.07 (s, 3 H; OCH_3), 2.42 (dd, J = 16.0, 2.3 Hz, 1 H; CH_2), 2.09–1.96 (m, 1 H; CH_2), 1.55–1.37 (m, 22 H; CH_2CH_3 and $\text{NCO}_2\text{C}(\text{CH}_3)_3$), 0.84–0.72 ppm (m, 6 H; CH_2CH_3); **¹³C NMR** (101 MHz, CDCl₃): δ = 172.3 (CO_2CH_3), 152.3 (NC=O), 83.0 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 78.5 ($\text{C}(\text{CH}_2\text{CH}_3)_2\text{OCH}_3$), 55.0 (CHCO_2CH_3), 52.5 (CO_2CH_3), 48.6 (OCH_3), 33.5 (CH_2), 28.1 ($\text{C}(\text{CH}_3)_3$), 26.3 (CH_2CH_3), 26.2 (CH_2CH_3), 7.7 ppm (CH_2CH_3); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2975 (w), 1744 (s), 1698 (m), 1366 (s), 1130 (br, s); **HRMS** (ESI): m/z = 424.2455 ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{20}\text{H}_{37}\text{O}_7\text{NNa}^+$: 426.2462).

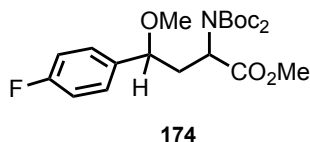
Synthesis of compound **171**



Compound **171** was synthesized according to General Procedure **F** using **157** (26 mg, 0.2 mmol) and irradiated with blue light for 18 h. FC (SiO₂; pentane/EtOAc 100 to 90:10) gave **171** (42.4 mg, 53%) as yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 5.10 (dd, J = 8.4, 2.8 Hz, 1 H; $\underline{\text{CH}}\text{CO}_2\text{CH}_3$), 3.70 (s, 3 H; CO_2CH_3), 3.08 (s, 3 H; OCH_3), 2.54 (dd, J = 15.7, 2.8 Hz, 1 H; $\underline{\text{CH}}_2$), 2.14 (dd, J = 15.7, 8.4 Hz, 1 H; $\underline{\text{CH}}_2$), 1.94–1.75 (m, 2 H; cyclopentyl- $\underline{\text{CH}}_2$), 1.73–1.53 (m, 4 H; cyclopentyl- $\underline{\text{CH}}_2$), 1.49 (s, 18 H; $\text{NCO}_2\text{C}(\underline{\text{CH}}_3)_3$), 1.45–1.32 ppm (m, 2 H; cyclopentyl- $\underline{\text{CH}}_2$); **¹³C NMR** (101 MHz, CDCl₃): δ = 172.3 ($\underline{\text{CO}}_2\text{CH}_3$), 152.3 ($\text{NC}=\text{O}$), 85.7 ($\underline{\text{C}}(\text{CH}_2\text{CH}_2)_2\text{OCH}_3$), 82.9 ($\text{CO}_2\underline{\text{C}}(\text{CH}_3)_3$), 55.6 ($\underline{\text{CH}}\text{CO}_2\text{CH}_3$), 52.5 ($\text{CO}_2\underline{\text{CH}}_3$), 49.4 (OCH_3), 36.0 ($\underline{\text{CH}}_2\text{CH}_2$), 35.9 ($\text{CH}_2\underline{\text{CH}}_2$), 35.5 ($\underline{\text{CH}}_2$), 28.2 ($\text{C}(\underline{\text{CH}}_3)_3$), 24.0 ($\underline{\text{CH}}_2\text{CH}_2$), 23.4 ppm ($\text{CH}_2\underline{\text{CH}}_2$); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 2951 (w), 1744 (s), 1698 (m), 1366 (s), 1130 (s); **HRMS** (ESI): m/z = 424.2300 ($[\text{M}+\text{Na}]^+$, calcd. for C₂₀H₃₅O₇NNa⁺: 424.2306).

Synthesis of compound **174**



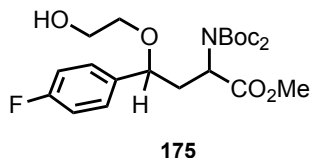
Compound **174** was synthesized according to General Procedure **F** using **172** (34 mg, 0.2 mmol) and irradiated with blue light for 18 h. Crude dr: 1.6:1. FC (SiO₂; pentane/EtOAc 100 to 90:10)

gave an inseparable mixture of **174** (*syn*-**174a** and *anti*-**174b**, 52 mg, 59%) as yellow oil.

Data of mixture *syn*-**174a** and *anti*-**174b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.33–7.21 (m, 4 H; ArH, **174a** and **174b**), 7.09–6.97 (m, 4 H; ArH, **174a** and **174b**), 5.24 (dd, *J* = 10.3, 4.2 Hz, 1 H; CHCO₂CH₃, **174a** or **174b**), 5.18–5.05 (m, 1 H; CHCO₂CH₃, **174a** or **174b**), 4.34 (dd, *J* = 9.2, 4.3 Hz, 1 H; CH₂OCH₃, **174a** or **174b**), 4.07 (dd, *J* = 10.5, 3.2 Hz, 1 H; CH₂OCH₃, **174a** or **174b**), 3.71 (s, 3 H; CO₂CH₃, **174a** or **174b**), 3.70 (s, 3 H; CO₂CH₃, **174a** or **174b**), 3.16 (s, 3 H; OCH₃, **174a** or **174b**), 3.15 (s, 3 H; OCH₃, **174a** or **174b**), 2.54–2.44 (m, 2 H; CH₂, **174a** and **174b**), 2.20–2.04 (m, 2 H; CH₂, **174a** and **174b**), 1.50 ppm (s, 36 H; NCO₂C(CH₃)₃, **174a** and **174b**); ¹⁹F NMR (377 MHz, CDCl₃): δ = –114.93 (**174a** or **174b**), –115.03 ppm (**174a** or **174b**); ¹³C NMR (101 MHz, CDCl₃): δ = 171.6 (CO₂CH₃, **174a** or **174b**), 171.5 (CO₂CH₃, **174a** or **174b**), 162.5 (d, *J* = 245.5 Hz; C–F, **174a** or **174b**), 162.4 (d, *J* = 245.2 Hz; C–F, **174a** or **174b**), 152.3 (NC=O, **174a** or **174b**), 152.1 (NC=O, **174a** or **174b**), 137.7 (d, *J* = 3.2 Hz; ArC, **174a** or **174b**), 137.5 (d, *J* = 3.2 Hz; ArC, **174a** or **174b**), 128.4 (d, *J* = 8.1 Hz; ArCH, **174a** or **174b**), 128.2 (d, *J* = 8.1 Hz; ArCH, **174a** or **174b**), 115.6 (d, *J* = 21.4 Hz; ArCH, **174a** or **174b**), 115.5 (d, *J* = 21.3 Hz; ArCH, **174a** or **174b**), 83.2 (CO₂C(CH₃)₃, **174a** and **174b**), 81.0 (CH₂OCH₃, **174a** or **174b**), 79.6 (CH₂OCH₃, **174a** or **174b**), 56.8 (OCH₃, **174a** and **174b**), 55.6 (CHCO₂CH₃, **174a** or **174b**), 55.5 (CHCO₂CH₃, **174a** or **174b**), 52.4 (CO₂CH₃, **174b** or **174b**), 52.3 (CO₂CH₃, **174a** or **174b**), 39.7 (CH₂, **174a** or **174b**), 39.0 (CH₂, **174a** or **174b**), 28.2 ppm (C(CH₃)₃, **174a** and **174b**); FT-IR (thin film): ν_{max} (cm^{–1}) = 2935 (w), 1745 (s), 1702 (m), 1366 (s), 1144 (s); HRMS (ESI): *m/z* = 464.2050 ([M+Na]⁺, calcd. for C₂₂H₃₂O₇NFNa⁺: 464.2055).

Synthesis of compound **175**



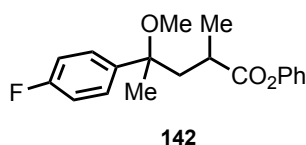
Compound **175** was synthesized according to General Procedure **F** using **173** (34 mg, 0.2 mmol) and irradiated with blue light for 48 h. Crude dr: 1.4:1. FC (SiO₂; pentane/EtOAc 75:15 to 50:50) gave an inseparable mixture of **175** (*syn*-**175a** and *anti*-**175b**, 64.6 mg, 69%) as yellow oil.

Data of mixture *syn*-**175a** and *anti*-**175b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.29–7.21 (m, 4 H; ArH, **175a** and **175b**), 7.06–6.97 (m, 4 H; ArH, **175a** and **175b**), 5.42 (dd, *J* = 11.1, 3.6 Hz, 1 H; CHCO₂CH₃, **175a** or **175b**), 5.29 (dd, *J* = 7.1, 6.0 Hz, 1 H; CHCO₂CH₃, **175a** or **175b**), 4.43 (dd, *J* = 10.3, 2.6 Hz, 1 H; CHCHOCH₂CH₂OH, **175a** or **175b**), 4.20 (dd, *J* = 11.2, 2.7 Hz, 1 H; CHCHOCH₂CH₂OH, **175a** or **175b**), 3.71 (s, 6 H; CO₂CH₃, **175a** and **175b**), 3.68–3.53 (m, 4 H; OCH₂CH₂OH, **175a** and **175b**), 3.46–3.33 (m, 2 H; OCH₂CH₂OH, **175a** and **175b**), 3.30–3.16 (m, 2 H; OCH₂CH₂OH, **175a** and **175b**), 2.58–2.39 (m, 2 H; CH₂, **175a** and **175b**), 2.24–2.12 (m, 2 H; CH₂, **175a** and **175b**), 1.51 ppm (s, 36 H; NCO₂C(CH₃)₃, **175a** and **175b**); ¹⁹F NMR (377 MHz, CDCl₃): δ = –114.55 (**175a** or **175b**), –114.74 ppm (**175a** or **175b**); ¹³C NMR (101 MHz, CDCl₃): δ = 171.5 (CO₂CH₃, **175a** or **175b**), 171.4 (CO₂CH₃, **175a** or **175b**), 162.5 (d, *J* = 246.2 Hz; C–F, **175a** or **175b**), 162.5 (d, *J* = 244.9 Hz; C–F, **175a** or **175b**), 152.8 (NC=O, **175a** or **175b**), 152.5 (NC=O, **175a** or **175b**), 137.8 (d, *J* = 3.2 Hz; ArC, **175a** or **175b**), 137.3 (d, *J* = 3.2 Hz; ArC, **175a** or **175b**), 128.2 (d, *J* = 7.9 Hz; ArCH, **175a** or **175b**), 128.0 (d, *J* = 8.0 Hz; ArCH, **175a** or **175b**), 115.7 (d, *J* = 21.4 Hz; ArCH, **175a** or **175b**), 115.6 (d, *J* =

21.4 Hz; ArCH, **175a** or **175b**), 83.8 (CO₂C(CH₃)₃, **175a** and **175b**), 80.2 (CHOCH₂CH₂OH, **175a** or **175b**), 78.0 (CHOCH₂CH₂OH, **175a** or **175b**), 71.0 (OCH₂CH₂OH, **175a** or **175b**), 70.6 (OCH₂CH₂OH, **175a** or **175b**), 62.1 (OCH₂CH₂OH, **175a** or **175b**), 62.0 (OCH₂CH₂OH, **175a** or **175b**), 56.0 (CHCO₂CH₃, **175a** or **175b**), 55.0 (CHCO₂CH₃, **175a** or **175b**), 52.5 (CO₂CH₃, **175a** or **175b**), 52.4 (CO₂CH₃, **175a** or **175b**), 39.7 (CH₂, **175a** or **175b**), 38.5 (CH₂, **175a** or **175b**), 28.2 ppm (C(CH₃)₃, **175a** and **175b**); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3535 (br, m), 2935 (w), 1740 (s), 1701 (br, m), 1368 (s), 1147 (m), 1122 (s); **HRMS** (ESI): m/z = 494.2155 ([M+Na]⁺, calcd. for C₂₃H₃₄O₈NFNa⁺: 494.2161).

Synthesis of compound **142**



Compound **142** was synthesized according to General Procedure **G** using **136** (37 mg, 0.2 mmol), **140** (90 μ L, 0.6 mmol), and irradiated with blue light for 18 h. Crude dr: 1.2:1. FC (SiO₂; pentane/EtOAc 100 to 90:10) gave an inseparable mixture of **142** (*syn*-**142a** and *anti*-**142b**, 46.8 mg, 74%) as colourless oil.

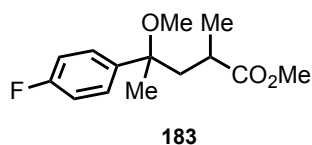
Data of mixture *syn*-**142a** and *anti*-**142b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.36–7.25 (m, 8 H; ArH, **142a** and **142b**), 7.17–7.08 (m, 2 H; ArH, **142a** and **142b**), 7.01–6.92 (m, 8 H; ArH, **142a** and **142b**), 3.07 (s, 3 H; OCH₃, **142b**, **142a** or **142b**), 3.00 (s, 3 H; OCH₃, **142a** or **142b**), 2.76–2.68 (m, 1 H; CHCO₂C₆H₅, **142a** or **142b**), 2.63–2.55 (m, 1 H; CHCO₂C₆H₅, **142a** or **142b**), 2.48–2.34 (m, 2 H; CH₂, **142a** and **142b**), 1.70–1.59 (m, 2 H; CH₂, **142a** and **142b**), 1.57 (s, 3 H; C(OCH₃)CH₃, **142a** or **142b**), 1.51 (s, 3 H; C(OCH₃)CH₃, **142a** or **142b**), 1.19 (d, J = 7.0 Hz, 3 H; CH₃, **142a** or **142b**).

142b), 1.14 ppm (d, $J = 7.1$ Hz, 3 H; $\underline{\text{CH}}_3$, **142a** or **142b**); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -116.12$ (**142a** or **142b**), -116.35 ppm (**142a** or **142b**); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 175.8$ ($\text{CO}_2\text{C}_6\text{H}_5$, **142a** or **142b**), 175.3 ($\text{CO}_2\text{C}_6\text{H}_5$, **142a** or **142b**), 162.0 (d, $J = 245.1$ Hz; $\underline{\text{C}}\text{-F}$, **142a** or **142b**), 161.9 (d, $J = 245.3$ Hz; $\underline{\text{C}}\text{-F}$, **142a** or **142b**), 151.1 ($\text{Ar}\underline{\text{C}}$, **142a** and **142b**), 140.8 (d, $J = 3.0$ Hz; $\text{Ar}\underline{\text{C}}$, **142a** or **142b**), 140.5 (d, $J = 3.2$ Hz; $\text{Ar}\underline{\text{C}}$, **142a** or **142b**), 129.4 ($\text{Ar}\underline{\text{CH}}$, **142a** and **142b**), 128.0 (d, $J = 7.7$ Hz; $\text{Ar}\underline{\text{CH}}$, **142a** or **142b**), 128.0 (d, $J = 7.8$ Hz; $\text{Ar}\underline{\text{CH}}$, **142a** or **142b**), 125.7 ($\text{Ar}\underline{\text{CH}}$, **142a** or **142b**), 125.6 ($\text{Ar}\underline{\text{CH}}$, **142a** or **142b**), 121.6 ($\text{Ar}\underline{\text{CH}}$, **142a** and **142b**), 115.2 (d, $J = 21.3$ Hz; $\text{Ar}\underline{\text{CH}}$, **142a** or **142b**), 115.1 (d, $J = 21.3$ Hz; $\text{Ar}\underline{\text{CH}}$, **142a** or **142b**), 78.6 ($\underline{\text{C}}(\text{OCH}_3)\text{CH}_3$, **142a** or **142b**), 78.4 ($\underline{\text{C}}(\text{OCH}_3)\text{CH}_3$, **142a** or **142b**), 50.6 ($\underline{\text{OCH}}_3$, **142a** or **142b**), 50.5 ($\underline{\text{OCH}}_3$, **142a** or **142b**), 48.3 ($\underline{\text{CH}}_2$, **142a** or **142b**), 47.3 ($\underline{\text{CH}}_2$, **142a** or **142b**), 36.1 ($\underline{\text{CHCO}}_2\text{C}_6\text{H}_5$, **142a** or **142b**), 35.6 ($\underline{\text{CHCO}}_2\text{C}_6\text{H}_5$, **142a** or **142b**), 24.0 ($\text{C}(\text{OCH}_3)\underline{\text{CH}}_3$, **142a** or **142b**), 22.2 ($\text{C}(\text{OCH}_3)\underline{\text{CH}}_3$, **142a** or **142b**), 19.7 ($\underline{\text{CH}}_3$, **142a** or **142b**), 19.5 ppm ($\underline{\text{CH}}_3$, **142b** or **142b**); FT-IR (thin film): ν_{max} (cm^{-1}) = 2936 (w), 1756 (s), 1507 (s), 1161 (s); HRMS (ESI): $m/z = 339.1367$ ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{19}\text{H}_{21}\text{O}_3\text{FNa}^+$: 339.1367).

Scale up: reaction performed on a 1 mmol scale without further modifications gave an inseparable mixture of of **142** (*syn*-**142a** and *anti*-**142b**, 224 mg, 71%, crude dr 1.2:1) as colourless oil.

Synthesis of compound **183**



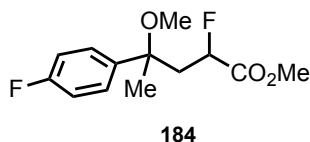
Compound **183** was synthesized according to General Procedure **G** using **136** (37 mg, 0.2 mmol), **176** (65 μL , 0.6 mmol), and irradiated with blue light for 18 h. Crude dr: 1.1:1. FC (SiO_2 ; pentane/EtOAc 100 to 95:5) gave an inseparable mixture of **183** (*syn*-**183a** and *anti*-**183b**,

31.6 mg, 62%) as yellow oil.

Data of mixture *syn*-**183a** and *anti*-**183b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.36–7.27 (m, 4 H; ArH, **183a** and **183b**), 7.11–6.89 (m, 4 H; ArH, **183a** and **183b**), 3.57 (s, 3 H; CO₂CH₃, **183a** or **183b**), 3.52 (s, 3 H; CO₂CH₃, **183a** or **183b**), 3.05 (s, 3 H; OCH₃, **183a** or **183b**), 3.04 (s, 3 H; OCH₃, **183a** or **183b**), 2.57–2.46 (m, 2 H; CHCO₂CH₃, **183a** and **183b**), 2.41–2.24 (m, 2 H; CH₂, **183a** and **183b**), 1.66 (td, *J* = 14.3, 3.2 Hz, 2 H; CH₂, **183a** and **183b**), 1.54 (s, 3 H; C(OCH₃)CH₃, **183a** or **183b**), 1.49 (s, 3 H; C(OCH₃)CH₃, **183a** or **183b**), 1.07 ppm (dd, *J* = 7.6, 7.1 Hz, 6 H; CH₃, **183a** and **183b**); ¹⁹F NMR (377 MHz, CDCl₃): δ = –116.38 (**183a** or **183b**), –116.43 ppm (**183a** or **183b**); ¹³C NMR (101 MHz, CDCl₃): δ = 177.7 (C=O₂CH₃, **183a** or **183b**), 177.5 (C=O₂CH₃, **183a** or **183b**), 161.9 (d, *J* = 245.3 Hz; C–F, **183a** or **183b**), 161.9 (d, *J* = 245.2 Hz; C–F, **183a** or **183b**), 140.6 (d, *J* = 3.2 Hz; ArC, **183a** or **183b**), 140.5 (d, *J* = 3.5 Hz; ArC, **183a** or **183b**), 128.1 (d, *J* = 7.9 Hz, ArCH, **183a** and **183b**), 115.0 (d, *J* = 20.7 Hz; ArCH, **183a** and **183b**), 78.4 (C(OCH₃)CH₃, **183a** or **183b**), 78.3 (C(OCH₃)CH₃, **183a** or **183b**), 51.6 (CO₂CH₃, **183a** or **183b**), 51.5 (CO₂CH₃, **183a** or **183b**), 50.4 (OCH₃, **183a** and **183b**), 47.6 (CH₂, **183a** or **183b**), 47.0 (CH₂, **183a** or **183b**), 35.5 (CHCO₂CH₃, **183a** or **183b**), 35.4 (CHCO₂CH₃, **183a** or **183b**), 23.3 (C(OCH₃)CH₃, **183a** or **183b**), 22.8 (C(OCH₃)CH₃, **183a** or **183b**), 19.7 (CH₃, **183a** or **183b**), 19.5 ppm (CH₃, **183b** or **183b**); FT-IR (thin film): ν_{max} (cm^{–1}) = 2939 (w), 1736 (s), 1508 (s), 1162 (m); HRMS (ESI): *m/z* = 277.1211 ([M+Na]⁺, calcd. for C₁₄H₁₉O₃FNa⁺: 277.1210).

Synthesis of compound **184**



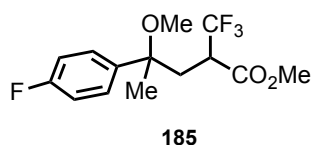
Compound **184** was synthesized according to General Procedure **G** using **136** (37 mg, 0.2 mmol), **177** (60 μ L, 0.6 mmol), and irradiated with blue light for 18 h. Crude dr: 1.3:1. FC (SiO₂; pentane/EtOAc 100 to 95:5) gave an inseparable mixture of **184** (*syn*-**184a** and *anti*-**184b**, 23 mg, 45%) as yellow oil.

Data of mixture *syn*-**184a** and *anti*-**184b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.40–7.32 (m, 4 H; ArH, **184a** and **184b**), 7.11–6.99 (m, 4 H; ArH, **184a** and **184b**), 5.25 (ddd, J = 49.6, 8.9, 2.3 Hz, 1 H; CHFCO₂CH₃, **184a** or **184b**), 4.82–4.62 (m, 1 H; CHFCO₂CH₃, **184a** or **184b**), 3.75 (s, 3 H; CO₂CH₃, **184a** or **184b**), 3.74 (s, 3 H; CO₂CH₃, **184a** or **184b**), 3.09 (s, 3 H; OCH₃, **184a** or **184b**), 3.07 (s, 3 H; OCH₃, **184a** or **184b**), 2.43–2.05 (m, 4 H; CH₂, **184a** and **184b**), 1.65 (d, J = 1.2 Hz, 3 H; CH₃, **184a** or **184b**), 1.63 ppm (d, J = 2.0 Hz, 3 H; CH₃, **184a** or **184b**); ¹⁹F NMR (377 MHz, CDCl₃): δ = –115.40 (ArF, **184a** or **184b**), –115.62 (ArF, **184a** or **184b**), –187.29 (CHF, **184a** or **184b**), –188.62 ppm (CHF, **184a** or **184b**); ¹³C NMR (101 MHz, CDCl₃): δ = 170.8 (d, J = 24.2 Hz; CO₂CH₃, **184a** or **184b**), 170.5 (d, J = 23.9 Hz; CO₂CH₃, **184a** or **184b**), 162.2 (d, J = 246.1 Hz; ArC–F, **184a** or **184b**), 162.1 (d, J = 245.9 Hz; ArC–F, **184a** or **184b**), 140.5 (d, J = 3.2 Hz; ArC, **184a** or **184b**), 139.1 (d, J = 3.2 Hz; ArC, **184a** or **184b**), 128.2 (d, J = 8.0 Hz; ArCH, **184a** or **184b**), 127.8 (d, J = 7.9 Hz; ArCH, **184a** or **184b**), 115.4 (d, J = 21.3 Hz; ArCH, **184a** or **184b**), 115.3 (d, J = 21.2 Hz; ArCH, **184a** or **184b**), 86.6 (d, J = 184.1 Hz; CHFCO₂CH₃, **184a** or **184b**), 86.3 (d, J = 183.6 Hz; CHFCO₂CH₃, **184a** or **184b**), 77.7 (C(OCH₃)CH₃, **184a** or **184b**), 77.0 (C(OCH₃)CH₃, **184a** or **184b**), 52.6 (CO₂CH₃, **184a** and

184b), 50.6 (OCH₃, **184a** or **184b**), 50.4 (OCH₃, **184a** or **184b**), 46.0 (d, $J = 19.6$ Hz; CH₂, **184a** or **184b**), 45.7 (d, $J = 19.9$ Hz; CH₂, **184a** or **184b**), 23.1 (d, $J = 3.3$ Hz; C(OCH₃)CH₃, **184a** or **184b**), 22.8 ppm (d, $J = 3.3$ Hz; C(OCH₃)CH₃, **184b** or **184b**); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 2916 (w), 1764 (s), 1508 (s), 1223 (s), 1162 (m); **HRMS** (ESI): $m/z = 281.0960$ ([M+Na]⁺, calcd. for C₁₃H₁₆O₃F₂Na⁺: 281.0960).

Synthesis of compound **185**

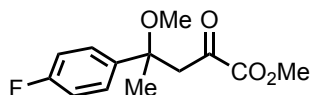


Compound **185** was synthesized according to General Procedure **G** using **136** (37 mg, 0.2 mmol), **178** (70 μ L, 0.6 mmol), and irradiated with blue light for 18 h. Crude dr: 1.3:1. FC (SiO₂; pentane/EtOAc 100 to 95:5) gave an inseparable mixture of **185** (*syn*-**185a** and *anti*-**185b**, 23 mg, 43%) as yellow oil.

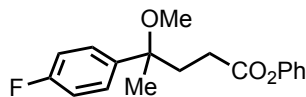
Data of mixture *syn*-**185a** and *anti*-**185b**:

¹H NMR (400 MHz, CDCl₃): $\delta = 7.35$ – 7.28 (m, 4 H; ArH, **185a** and **185b**), 7.10 – 6.95 (m, 4 H; ArH, **185a** and **185b**), 3.73 (s, 3 H; CO₂CH₃, **185a** or **185b**), 3.54 (s, 3 H; CO₂CH₃, **185a** or **185b**), 3.44 – 3.24 (m, 1 H; CHCO₂CH₃, **185a** or **185b**), 3.15 – 3.01 (m, 7 H; CHCO₂CH₃ and OCH₃, **185a** and **185b**), 2.62 – 2.54 (m, 1 H; CH₂, **185a** or **185b**), 2.49 (dd, $J = 14.3, 11.0$ Hz, 1 H; CH₂, **185a** or **185b**), 2.05 (dd, $J = 14.4, 1.7$ Hz, 1 H; CH₂, **185a** or **185b**), 2.00 (dd, $J = 14.3, 1.6$ Hz, 1 H; CH₂, **185a** or **185b**), 1.59 (s, 3 H; C(OCH₃)CH₃, **185a** or **185b**), 1.52 ppm (s, 3 H; C(OCH₃)CH₃, **185a** or **185b**); **¹⁹F NMR** (377 MHz, CDCl₃): $\delta = -68.72$ (CF₃, **185a** or **185b**), -68.80 (CF₃, **185a** or **185b**), -115.55 (ArF, **185a** or **185b**), -115.57 (ArF, **185a** or **185b**); **¹³C NMR** (101 MHz, CDCl₃): $\delta = 168.6$ (q, $J = 3.2$ Hz; CO₂CH₃, **185a** or **185b**);

185b), 168.1 (q, $J = 3.2$ Hz $\underline{\text{C}}\text{O}_2\text{CH}_3$, **185a** or **185b**), 162.1 (d, $J = 246.0$ Hz; $\underline{\text{C}}\text{-F}$, **185a** and **185b**), 139.3 (d, $J = 3.2$ Hz; $\text{Ar}\underline{\text{C}}$, **185a** or **185b**), 139.2 (d, $J = 3.1$ Hz; $\text{Ar}\underline{\text{C}}$, **185a** or **185b**), 127.8 (d, $J = 8.1$ Hz; $\text{Ar}\underline{\text{CH}}$, **185a** or **185b**), 127.0 (d, $J = 8.0$ Hz; $\text{Ar}\underline{\text{CH}}$, **185a** or **185b**), 125.1 (q, $J = 280.3$ Hz; $\underline{\text{C}}\text{F}_3$, **185a** or **185b**), 125.0 (q, $J = 280.3$ Hz; $\underline{\text{C}}\text{F}_3$, **185a** or **185b**), 115.4 (d, $J = 21.2$ Hz; $\text{Ar}\underline{\text{CH}}$, **185a** or **185b**),), 115.2 (d, $J = 21.2$ Hz; $\text{Ar}\underline{\text{CH}}$, **185a** or **185b**), 77.5 ($\underline{\text{C}}(\text{OCH}_3)\text{CH}_3$, **185a** and **185b**), 52.9 ($\text{CO}_2\underline{\text{CH}}_3$, **185a** or **185b**), 52.7 ($\text{CO}_2\underline{\text{CH}}_3$, **185b** or **185b**), 50.7 ($\text{O}\underline{\text{CH}}_3$, **185a** or **185b**), 50.5 ($\text{O}\underline{\text{CH}}_3$, **185a** or **185b**), 46.3 (q, $J = 27.3$ Hz; $\underline{\text{CH}}\text{CO}_2\text{CH}_3$, **185a** or **185b**), 46.2 (q, $J = 27.6$ Hz; $\underline{\text{CH}}\text{CO}_2\text{CH}_3$, **185a** or **185b**), 39.7 ($\underline{\text{CH}}_2$, **185a** or **185b**), 38.8 ($\underline{\text{CH}}_2$, **185a** or **185b**), 24.0 ($\text{C}(\text{OCH}_3)\underline{\text{CH}}_3$, **185a** or **185b**), 22.7 ppm ($\text{C}(\text{OCH}_3)\underline{\text{CH}}_3$, **185a** or **185b**); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2921 (w), 1751 (s), 1508 (s), 1219 (m); **HRMS** (ESI): fragmentation product $m/z = 277.0842$ ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{13}\text{H}_{15}\text{O}_4\text{FNa}^+$: 277.0847). Fragmentation product:



Synthesis of compound **186**



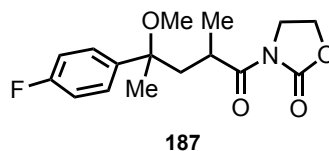
186

Compound **186** was synthesized according to General Procedure **G** using **136** (37 mg, 0.2 mmol), **179** (0.28 mL, 2 mmol), and irradiated with blue light for 18 h. FC (SiO_2 ; pentane/EtOAc 100 to 95:5) gave **186** (14.4 mg, 25%) as yellow oil. The reaction was also performed with 3 eq of **179** (83 μL , 0.6 mmol) affording **186** (13 mg, 22%) as yellow oil.

^1H NMR (400 MHz, CDCl_3): $\delta = 7.49\text{--}7.32$ (m, 4 H; $\text{Ar}\underline{\text{H}}$), 7.24–7.17 (m, 1 H; $\text{Ar}\underline{\text{H}}$), 7.10–6.97 (m, 4 H; $\text{Ar}\underline{\text{H}}$), 3.13 (s, 3 H; OCH_3), 2.60–2.42 (m, 2 H; $\underline{\text{CH}}_2\text{CO}_2\text{C}_6\text{H}_5$), 2.30–2.11 (m, 2 H;

$\text{CH}_2\text{CH}_2\text{CO}_2\text{C}_6\text{H}_5$), 1.59 ppm (s, 3 H; $\text{C}(\text{OCH}_3)\text{CH}_3$); ^{19}F NMR (377 MHz, CDCl_3): δ = -116.07 ppm; ^{13}C NMR (101 MHz, CDCl_3): δ = 172.3 ($\text{CO}_2\text{C}_6\text{H}_5$), 162.0 (d, J = 245.5 Hz; $\text{C}-\text{F}$), 150.9 (ArC), 140.2 (d, J = 3.3 Hz; ArC), 129.5 (ArCH), 127.9 (d, J = 8.0 Hz; ArCH), 125.9 (ArCH), 121.6 (ArCH), 115.2 (d, J = 21.2 Hz; ArCH), 78.0 ($\text{C}(\text{OCH}_3)\text{CH}_3$), 50.5 (OCH_3), 37.6 ($\text{CH}_2\text{CH}_2\text{CO}_2\text{C}_6\text{H}_5$), 29.5 ($\text{CH}_2\text{CO}_2\text{C}_6\text{H}_5$), 23.5 ppm (CH_3); FT-IR (thin film): ν_{max} (cm^{-1}) = 2936 (w), 1758 (s), 1507 (s), 1162 (m); HRMS (ESI): m/z = 325.1210 ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{18}\text{H}_{19}\text{O}_3\text{FNa}^+$: 325.1221).

Synthesis of compound **187**



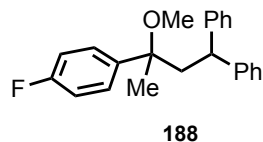
Compound **187** was synthesized according to General Procedure **G** using **136** (18.5 mg, 0.1 mmol), **180** (38 mg, 0.3 mmol), and irradiated with blue light for 18 h. Crude dr: 1.5:1. FC (SiO_2 ; pentane/EtOAc 100 to 85:15) gave an inseparable mixture of **187** (*syn*-**187a** and *anti*-**187b**, 13.7 mg, 44%) as yellow oil.

Data of mixture *syn*-**187a** and *anti*-**187b**:

^1H NMR (400 MHz, CDCl_3): δ = 7.35–7.29 (m, 4 H; ArH, **187a** and **187b**), 7.03–6.94 (m, 4 H; ArH, **187a** and **187b**), 4.39–4.19 (m, 4 H; $\text{NCH}_2\text{CH}_2\text{O}$, **187a** and **187b**), 4.14–4.07 (m, 1 H; $\text{CH}(\text{CH}_3)\text{CON}$, **187a** or **187b**), 3.92–3.75 (m, 3 H; $\text{CH}(\text{CH}_3)\text{CON}$ and $\text{NCH}_2\text{CH}_2\text{O}$, **187a** or **187b**), 3.71–3.51 (m, 2 H; $\text{NCH}_2\text{CH}_2\text{O}$, **187a** and **187b**), 3.06 (s, 3 H; OCH_3 , **187a** or **187b**), 3.02 (s, 3 H; OCH_3 , **187a** or **187b**), 2.61 (dd, J = 14.1, 9.8 Hz, 1 H; CH_2 , **187a** or **187b**), 2.52 (dd, J = 14.3, 10.1 Hz, 1 H; CH_2 , **187a** or **187b**), 1.74–1.69 (m, 2 H; CH_2 , **187a** and **187b**), 1.57 (s, 3 H; $\text{C}(\text{OCH}_3)\text{CH}_3$, **187a** or **187b**), 1.55 (s, 3 H; $\text{C}(\text{OCH}_3)\text{CH}_3$, **187a** or **187b**), 1.10 ppm

(d, $J = 7.0$ Hz, 6 H; $\underline{\text{CH}}_3$, **187a** and **187b**); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -116.03$ (**187a** or **187b**), -116.49 ppm (**187a** or **187b**); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 177.7$ ($\underline{\text{CON}}$, **187a** or **187b**), 177.4 ($\underline{\text{CON}}$, **187a** or **187b**), 162.0 (d, $J = 245.4$ Hz; $\underline{\text{C}}-\text{F}$, **187a** or **187b**), 161.9 (d, $J = 245.3$ Hz; $\underline{\text{C}}-\text{F}$, **187a** or **187b**), 153.2 ($\underline{\text{NCO}}_2$, **187a** or **187b**), 153.1 ($\underline{\text{NCO}}_2$, **187a** or **187b**), 140.6 (d, $J = 3.2$ Hz; $\text{Ar}\underline{\text{C}}$, **187a** or **187b**), 149.7 (d, $J = 3.3$ Hz; $\text{Ar}\underline{\text{C}}$, **187a** or **187b**), 128.8 (d, $J = 7.9$ Hz, $\text{Ar}\underline{\text{CH}}$, **187a** or **187b**), 128.4 (d, $J = 7.8$ Hz, $\text{Ar}\underline{\text{CH}}$, **187a** or **187b**), 114.7 (d, $J = 21.0$ Hz; $\text{Ar}\underline{\text{CH}}$, **187a** and **187b**), 78.6 ($\underline{\text{C}}(\text{OCH}_3)\text{CH}_3$, **187a** $\underline{\text{C}}(\text{OCH}_3)\text{CH}_3$, **187a** or **187b**), 61.8 ($\text{NCH}_2\underline{\text{CH}}_2\text{O}$, **187a** or **187b**), 61.7 ($\text{NCH}_2\underline{\text{CH}}_2\text{O}$, **187a** or **187b**), 50.5 ($\text{O}\underline{\text{CH}}_3$, **187a** or **187b**), 50.4 ($\text{O}\underline{\text{CH}}_3$, **187a** or **187b**), 48.1 ($\underline{\text{CH}}_2$, **187a** or **187b**), 47.6 ($\underline{\text{CH}}_2$, **187a** or **187b**), 43.0 ($\text{N}\underline{\text{CH}}_2\text{CH}_2\text{O}$, **187b** or **187b**), 42.9 ($\text{N}\underline{\text{CH}}_2\text{CH}_2\text{O}$, **187a** or **187b**), 32.8 ($\underline{\text{CH}}(\text{CH}_3)\text{CON}$, **187a** or **187b**), 32.4 ($\underline{\text{CH}}(\text{CH}_3)\text{CON}$, **187a** or **187b**), 23.1 ($\text{C}(\text{OCH}_3)\underline{\text{CH}}_3$, **187a** or **187b**), 22.7 ($\text{C}(\text{OCH}_3)\underline{\text{CH}}_3$, **187a** or **187b**), 20.1 ($\underline{\text{CH}}_3$, **187a** or **187b**), 19.8 ppm ($\underline{\text{CH}}_3$, **187a** or **187b**); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2921 (w), 1775 (s), 1698 (s), 1507 (s), 1222 (m); **HRMS** (ESI): $m/z = 332.1269$ ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_4\text{NFNa}^+$: 332.1269).

Synthesis of compound **188**

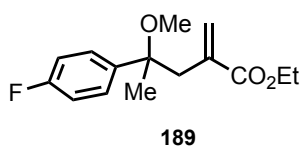


Compound **188** was synthesized according to General Procedure **G** using **136** (18.5 mg, 0.1 mmol), **181** (0.18 mL, 1 mmol), and irradiated with blue light for 18 h. FC (SiO_2 ; pentane/EtOAc 100 to 95:5) gave **188** (24 mg, 72%) as yellow oil.

^1H NMR (400 MHz, CDCl_3): $\delta = 7.29\text{--}7.23$ (m, 2 H; $\text{Ar}\underline{\text{H}}$), $7.22\text{--}7.05$ (m, 10 H; $\text{Ar}\underline{\text{H}}$), $7.02\text{--}6.89$ (m, 2 H; $\text{Ar}\underline{\text{H}}$), 3.91 (t, $J = 6.4$ Hz, 1 H; $\underline{\text{CH}}(\text{C}_6\text{H}_5)_2$), 2.98 (s, 3 H; $\text{O}\underline{\text{CH}}_3$), 2.62 (d, $J = 6.4$ Hz, 2 H; $\underline{\text{CH}}_2$), 1.30 ppm (s, 3 H; $\text{C}(\text{OCH}_3)\underline{\text{CH}}_3$); ^{19}F NMR (377 MHz, CDCl_3): $\delta =$

–116.43 ppm; ^{13}C NMR (101 MHz, CDCl_3): δ = 161.9 (d, J = 245.1 Hz; $\text{C}-\text{F}$), 146.1 (2C, ArC), 146.0 (2C, ArC), 140.7 (d, J = 3.3 Hz; ArC), 128.5 (2C, ArCH), 128.3 (d, J = 7.9 Hz; ArCH), 127.9 (ArCH), 127.8 (ArCH), 126.0 (2C, ArCH), 114.9 (d, J = 21.2 Hz; ArCH), 79.2 ($\text{C}(\text{OCH}_3)\text{CH}_3$), 50.2 (OCH_3), 48.8 (CH_2), 47.3 ($\text{CH}(\text{C}_6\text{H}_5)_2$), 23.3 ppm (CH_3); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3026 (m), 2935 (m), 1507 (s), 1160 (m); **HRMS** (ESI): mass not detected.

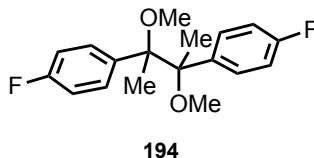
Synthesis of compound **189**



Compound **189** was synthesized according to General Procedure **G** (without 1,4-CHD **143**) using **136** (37 mg, 0.2 mmol), **182** (152.6 mg, 0.6 mmol), and irradiated with blue light for 18 h. FC (SiO_2 ; pentane/EtOAc 100 to 95:5) gave **189** (16 mg, 30%) as yellow oil.

^1H NMR (400 MHz, CDCl_3): δ = 7.34–7.26 (m, 2 H; ArH), 7.08–6.83 (m, 2 H; ArH), 6.10 (d, J = 1.7 Hz, 1 H; $\text{C}(\text{CO}_2\text{CH}_2\text{CH}_3)\text{CH}_2$), 5.33–5.31 (m, 1 H; $\text{C}(\text{CO}_2\text{CH}_2\text{CH}_3)\text{CH}_2$), 4.07–3.98 (m, 2 H; $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.07 (s, 3 H; OCH_3), 2.76 (dd, J = 2.4, 0.9 Hz, 2 H; CH_2), 1.52 (s, 3 H; $\text{C}(\text{OCH}_3)\text{CH}_3$), 1.21 ppm (t, J = 7.1 Hz, 3 H; $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{19}F NMR (377 MHz, CDCl_3): δ = –116.26 ppm; ^{13}C NMR (101 MHz, CDCl_3): δ = 167.8 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 162.0 (d, J = 245.6 Hz; $\text{C}-\text{F}$), 139.8 (d, J = 3.0 Hz; ArC), 137.0 ($\text{C}(\text{CO}_2\text{CH}_2\text{CH}_3)\text{CH}_2$), 128.5 (d, J = 8.0 Hz; ArCH), 128.2 ($\text{C}(\text{CO}_2\text{CH}_2\text{CH}_3)\text{CH}_2$), 114.8 (d, J = 21.2 Hz; ArCH), 78.9 ($\text{C}(\text{OCH}_3)\text{CH}_3$), 60.8 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 50.5 (OCH_3), 44.7 (CH_2), 22.0 (CH_3), 14.3 ppm ($\text{CO}_2\text{CH}_2\text{CH}_3$); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2826 (w), 1717 (s), 1507 (s), 1160 (m); **HRMS** (ESI): m/z = 289.1210 ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{15}\text{H}_{19}\text{O}_3\text{FNa}^+$: 289.1210).

Synthesis of compound **194**



Compound **194** was synthesized according to General Procedure **F** using **136** (18.5 mg, 0.1 mmol) and irradiated with blue light for 18 h (No coupling partner). Crude dr: 1:1. FC (SiO₂; pentane/EtOAc 100 to 95:5) gave an inseparable mixture of **194** (*syn*-**194a** and *anti*-**194b**, 16 mg, 52%) as an amorphous white solid.

Data of mixture *syn*-**194a** and *anti*-**194b**:

¹H NMR (400 MHz, CDCl₃): δ = 7.24–7.15 (m, 4 H; ArH, **194a** and **194b**), 7.02–6.85 (m, 4 H; ArH, **194a** and **194b**), 6.81–6.70 (m, 8 H; ArH, **194a** and **194b**), 3.06 (s, 6 H; OCH₃, **194a** or **194b**), 3.02 (s, 6 H; OCH₃, **194a** or **194b**), 1.64 (s, 6 H; CH₃, **194a** or **194b**), 1.39 ppm (s, 6 H; CH₃, **194a** or **194b**); ¹⁹F NMR (377 MHz, CDCl₃): δ = –116.97 (**194a** or **194b**), –117.07 ppm (**194a** or **194b**); ¹³C NMR (101 MHz, CDCl₃): δ = 161.8 (d, J = 244.7 Hz; C–F, **194a** or **194b**), 161.7 (d, J = 244.7 Hz; C–F, **194a** or **194b**), 137.3 (d, J = 3.3 Hz; ArC, **194a** or **194b**), 136.8 (d, J = 3.3 Hz; ArC, **194a** or **194b**), 130.6 (d, J = 7.8 Hz; ArCH, **194a** or **194b**), 130.5 (d, J = 8.0 Hz; ArCH, **194a** or **194b**), 113.6 (d, J = 20.9 Hz; ArCH, **194a** or **194b**), 113.1 (d, J = 20.9 Hz; ArCH, **194a** or **194b**), 83.5 (C(OCH₃)CH₃, **194a** or **194b**), 83.1 (C(OCH₃)CH₃, **194a** or **194b**), 50.6 (OCH₃, **194a** or **194b**), 50.4 (OCH₃, **194a** or **194b**), 19.1 (CH₃, **194a** or **194b**), 18.7 ppm (CH₃, **194b** or **194b**); FT-IR (thin film): ν_{max} (cm^{–1}) = 2925 (w), 1602 (m), 1507 (s), 1224 (m), 1131 (m); HRMS (ESI): decomposition of compound **194**. Decomposition of similar compounds has been reported previously.^[195]

5.4 Experimental Details for Chapter 4

5.4.1 General Procedure H: Hantzsch Ester Synthesis

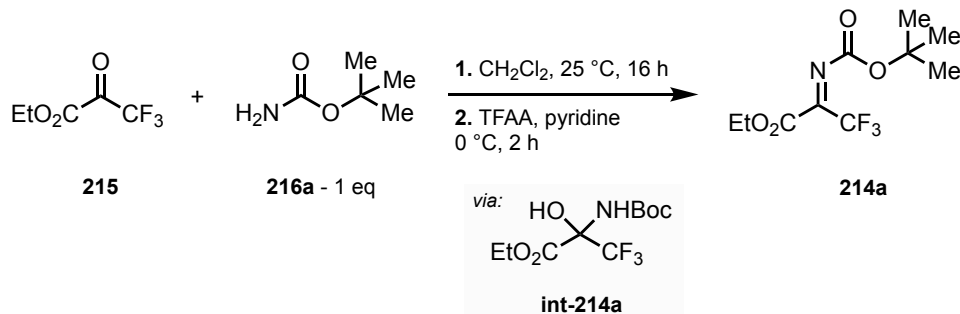
A solution of methyl acetoacetate **222** (1 eq), methyl 3-aminocrotonate **223** (1 eq) and relevant aldehyde (1 eq) in ethylene glycol (2.5 M) under N₂ atmosphere was treated with tetrabutylammonium hydrogensulfate (TBAHS, 12 mol%) in one-portion at 25 °C. The resulting solution was heated up to 100 °C and stirred for 5 h. The reaction was cooled down to room temperature, then poured into brine (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated. The compounds were purified by flash column chromatography (see individual experiments).

5.4.2 General Procedure I: Synthesis of α -Tfm Amino Acids

A 8 mL glass vial equipped with a microstirrer was charged with relevant imino ester **214** (0.2 mmol), Hantzsch ester (0.6 mmol, 3 eq), and dissolved in dry CH₂Cl₂ (2 mL, 0.1 M). Nitrogen was bubbled to the stirred solution for 1 min, then the vial was closed and irradiated with blue light for 24 h. The reaction mixture was diluted in EtOAc (20 mL), H₂O (10 mL) and brine (10 mL), the organic phase extracted and the aqueous phase re-extracted with EtOAc (2x 20 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. Prior to purification by flash column chromatography (see individual experiments), an aliquot from the crude residue was dissolved in CDCl₃ to determine the diastereomeric ratio and/or NMR yield.

5.4.3 Synthesis of Substrates

ethyl-2-((tert-butoxycarbonyl)imino)-3,3,3-trifluoropropanoate (**214a**)



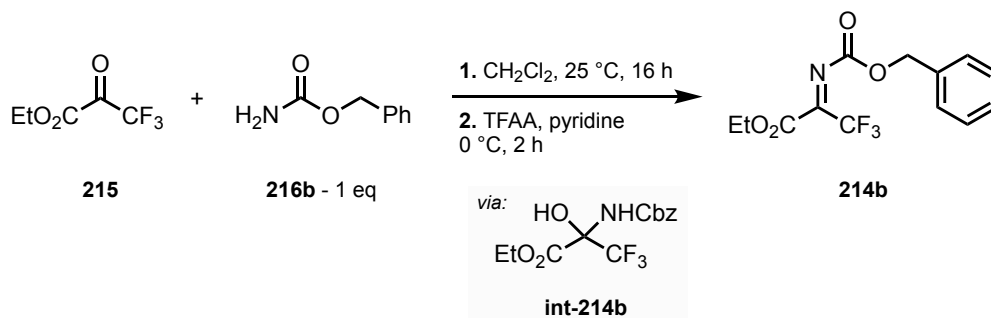
A solution of *tert*-butyl carbamate **216a** (2.34 g, 20 mmol) in CH_2Cl_2 (20 mL) under N_2 atmosphere was treated with ethyl 3,3,3-trifluoropyruvate **215** (2.64 mL, 20 mmol) and stirred at 25 °C for 16 h. The resulting solution was concentrated under reduced pressure to afford intermediate **int-214a** as a white solid. Then, a solution of **int-214a** in Et_2O (100 mL) was treated with trifluoroacetic anhydride (2.8 mL, 20 mmol) and pyridine (3.24 mL, 40 mmol) over 1 h at 0 °C. After complete addition, the resulting mixture was stirred for 1 h at 0 °C. Precipitate was filtered off and the filtrate concentrated under reduced pressure. The residue was taken up in hexane, filtered again, and the filtrate concentrated under reduced pressure. The resulting residue was purified by distillation (20mbar, bp 106 °C) to afford **214a** (4.39 g, 82%) as a colorless oil, which was stored under N_2 atmosphere in the fridge. NMR spectra and physical properties matched those from reported literature.^[167]

^1H NMR (400 MHz, CDCl_3): δ = 4.40 (q, J = 7.1 Hz, 2 H; $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.57 (s, 9 H; $\text{NCO}_2\text{C}(\text{CH}_3)_3$), 1.37 ppm (t, J = 7.1 Hz, 3 H; $\text{CO}_2\text{CH}_2\text{CH}_3$); **^{19}F NMR** (377 MHz, CDCl_3): δ = -70.16 ppm; **^{13}C NMR** (101 MHz, CDCl_3): δ = 157.2, 155.3, 146.6 (q, J = 38.5 Hz), 118.2 (q, J = 277.7 Hz), 85.5, 64.1, 27.9, 13.9 ppm.

Data for **int-214a**: **^1H NMR** (400 MHz, CDCl_3): δ = 5.70 (s, br, 1 H; NH), 5.34 (s, br, 1 H; OH), 4.49–4.30 (m, 2 H; $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.45 (s, 9 H; $\text{NCO}_2\text{C}(\text{CH}_3)_3$), 1.34 ppm (t, J = 7.1 Hz,

3 H; CO₂CH₂CH₃); ¹⁹F NMR (377 MHz, CDCl₃): δ = −80.68 ppm.

ethyl-2-(((benzyloxy)carbonyl)imino)-3,3,3-trifluoropropanoate (214b)



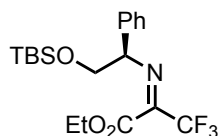
A solution of benzyl carbamate **216b** (3.02 g, 20 mmol) in CH₂Cl₂ (20 mL) under N₂ atmosphere was treated with ethyl 3,3,3-trifluoropyruvate **215** (2.64 mL, 20 mmol) and stirred at 25 °C for 16 h. The resulting solution was concentrated under reduced pressure to afford intermediate **int-214b** as a white solid. Then, a solution of **int-214b** in Et₂O (100 mL) was treated with trifluoroacetic anhydride (2.8 mL, 20 mmol) and pyridine (3.24 mL, 40 mmol) over 1 h at 0 °C. After complete addition, the resulting mixture was stirred for 1 h at 0 °C. Precipitate was filtered off and the filtrate concentrated under reduced pressure. The residue was taken up in hexane, filtered again, and the filtrate concentrated under reduced pressure. The resulting residue was purified by distillation (20 mbar, bp 175 °C) to afford **214b** (3.1 g, 51%) as a colorless oil, which was stored under N₂ atmosphere in the fridge. NMR spectra and physical properties matched those from reported literature.^[167]

¹H NMR (400 MHz, CDCl₃): δ = 7.46–7.34 (m, 5 H; ArH), 5.34 (s, 2 H; CO₂CH₂C₆H₅), 4.32 (q, *J* = 7.1 Hz, 2 H; CO₂CH₂CH₃), 1.31 ppm (t, *J* = 7.1 Hz, 3 H; CO₂CH₂CH₃); ¹⁹F NMR (377 MHz, CDCl₃): δ = −70.16 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 165.8, 158.7, 147.8 (q, *J* = 38.0 Hz), 134.3, 129.1, 129.0, 128.9, 117.9 (q, *J* = 279.2 Hz), 69.7, 64.4, 13.8 ppm.

Data for **int-214b**: ¹H NMR (400 MHz, CDCl₃): δ = 7.41–7.31 (m, 5 H; ArH), 5.93 (s, br, 1 H; NH), 5.33 (s, br, 1 H; OH), 5.14 (s, 2 H; CO₂CH₂C₆H₅), 4.44–4.27 (m, 2 H; CO₂CH₂CH₃),

1.31 ppm (t, $J = 7.1$ Hz, 3 H; $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{19}F NMR (377 MHz, CDCl_3): $\delta = -80.69$ ppm.

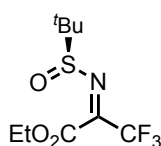
Synthesis of substrate **214c**



214c

The above compound was prepared according to an adapted literature procedure.^[196] To a solution of (*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethan-1-amine (2.3 g, 9.15 mmol) in toluene (0.076 M) under N_2 atmosphere was added **215** (1.34 mL, 10.07 mmol, 1.1 eq) dropwise at 25 °C. Then, PTSA (10 mol%) was added in one-portion and the mixture was refluxed with a Dean-Stark apparatus overnight. The resulting solution was cooled down to 0 °C, filtered, and concentrated under reduced pressure. The residue was taken up in a 5:1 mixture of Et_2O /hexane (ca. 100 mL) and stored in the freezer overnight. The solution was filtered and concentrated under reduced pressure to give a yellow oil (3.5 g, 95%) which was used in the next step without further purification.

Synthesis of substrate **214d**



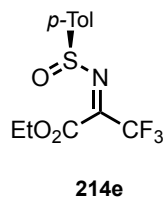
214d

Compound **214d** was synthesized according to a known literature procedure.^[197] To a solution of **215** (2 mL, 15 mmol) and (*S*)-*tert*-butanesulfinamide (2 g, 16.5 mmol, 1.1 eq) in CH_2Cl_2 (30 mL) under N_2 atmosphere, crushed 4 Å molecular sieves (30 g) and pyrrolidine (0.13 mL, 1.5 mmol, 0.1 eq) were added at room temperature. The resulting reaction mixture was heated to

reflux and stirred for 24 h. After cooling to room temperature, the mixture was filtered through a short pad of Celite[®] and concentrated under reduced pressure. The residue was purified by FC (SiO₂; pentane/EtOAc 95:5 to 80:20) to give **214d** (1.46 g, 36%) as a yellow oil. NMR Spectra and physical properties matched those from reported literature.^[197]

¹H NMR (400 MHz, CDCl₃): δ = 4.39 (qq, *J* = 7.2, 3.6 Hz, 2 H; CO₂CH₂CH₃), 1.37 (t, *J* = 7.2 Hz, 3 H; CO₂CH₂CH₃), 1.32 ppm (s, 9 H; C(CH₃)₃); ¹⁹F NMR (377 MHz, CDCl₃): δ = −69.49 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 160.7 (CO₂CH₂CH₃), 154.1 (q, *J* = 38.1 Hz; CCF₃), 117.8 (q, *J* = 280.8 Hz; CF₃), 63.6 (CO₂CH₂CH₃), 60.9 (C(CH₃)₃), 22.9 (C(CH₃)₃), 13.9 ppm (CO₂CH₂CH₃).

Synthesis of substrate **214e**



Compound **214e** was synthesized according to a known literature procedure.^[198] To a solution of (*S*)-*para*-toluenesulfinamide (400 mg, 2.63 mmol) in THF (10.5 mL) under N₂ atmosphere was added triphenylphosphine (690 mg, 2.63 mmol). The resulting mixture was cooled down to 0 °C and treated by dropwise addition of diethyl azodicarboxylate (0.52 mL, 2.63 mmol). After complete addition, the reaction mixture was warmed up to room temperature and stirred for 1 h. Then, concentrated under reduced pressure to give a yellow residue, which was purified by FC (SiO₂; pentane/EtOAc 80:20 to 10:90) to give (*S*)-4-methyl-*N*-(triphenylphosphaneylidene)benzenesulfinamide (1.1 g, quant.) as a yellow oil. To a solution of (*S*)-4-methyl-*N*-(triphenylphosphaneylidene)benzenesulfinamide (1.1 g, 2.63 mmol) in THF (4.5 mL) under N₂ atmosphere, **215** (0.35 mL, 2.63 mmol) was added dropwise at room temperature. After complete addition, the reaction mixture was heated up to 40 °C and stirred at

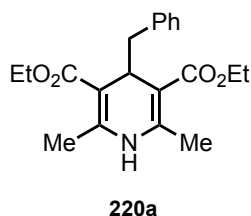
the same temperature for 2 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, then taken up in Et₂O, sonicated and filtered. Resulting compound **214e** (yellow oil) was used for the next step without further purification (unstable to silica gel).^[198]

Data of crude **214e**: ¹H NMR (400 MHz, CDCl₃): δ = 7.66–7.63 (m, 2 H; ArH), 7.38–7.33 (m, 2 H; ArH), 4.47 (qd, *J* = 7.2, 3.0 Hz, 2 H; CO₂CH₂CH₃), 2.43 (s, 3 H; ArCH₃), 1.42 ppm (t, *J* = 7.2 Hz, 3 H; CO₂CH₂CH₃); ¹⁹F NMR (377 MHz, CDCl₃): δ = –69.63 ppm.

Data of intermediate: ¹H NMR (400 MHz, CDCl₃): δ = H, 7.58–7.52 (m, 3 H; ArH), 7.51–7.42 (m, 6 H; ArH), 7.19 (d, *J* = 7.9 Hz, 2 H; ArH), 2.34 ppm (s, 3 H; ArCH₃); ³¹P NMR (162 MHz, CDCl₃): δ = 23.35 ppm; ¹³C NMR (101 MHz, CDCl₃): δ = 150.0 (d, *J* = 23.3 Hz), 139.5, 133.1 (d, *J* = 10.1 Hz), 132.5 (d, *J* = 2.9 Hz), 129.1, 128.8 (d, *J* = 12.4 Hz), 128.8 (d, *J* = 100.1 Hz), 125.2, 21.4 ppm.

5.4.4 Synthesis of Hantzsch Esters

Synthesis of Hantzsch ester **220a**

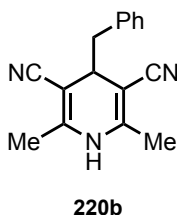


A flask equipped with a reflux condenser was charged with ethyl acetoacetate (5.06 mL, 40 mmol), phenylacetaldehyde (2.34 mL, 20 mmol) and ethanol (100 mL). The solution was treated by addition of NH₄OAc (1.54 g, 20 mmol) in one-portion at 25 °C. The resulting mixture was heated to reflux and stirred for 16 h. The reaction was cooled down to room temperature and concentrated. The residue was taken up in CH₂Cl₂, poured into brine (50 mL), and extracted with CH₂Cl₂

(3x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via silica gel column chromatography (Pentane/EtOAc 90:10 to 70:30) to afford compound **253** (1.85 g, 27%) as an off-white solid. NMR Spectra and physical properties matched those from reported literature.^[199]

¹H NMR (400 MHz, CDCl₃): δ = 7.20–7.10 (m, 3 H; ArH), 7.05–6.99 (m, 2 H; ArH), 5.19 (s, br, 1 H; NH), 4.20 (t, J = 5.5 Hz, 1 H; CHCH₂C₆H₅), 4.12–4.10 (m, 4 H; 2 x CO₂CH₂CH₃), 2.58 (d, J = 5.5 Hz, 2 H; CH₂C₆H₅), 2.18 (s, 6 H; 2 x NHCH₃), 1.23 ppm (t, J = 7.1 Hz, 6 H; 2 x CO₂CH₂CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ = 167.9, 145.4, 139.4, 130.2, 127.4, 125.8, 102.1, 59.7, 42.5, 35.6, 19.2, 14.5 ppm.

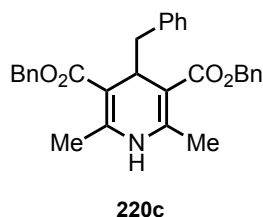
Synthesis of Hantzsch ester **220b**



A solution of 3-aminocrotonitrile (2.7 g, 33.3 mmol) in acetic acid (13 mL) under N₂ atmosphere was treated with phenylacetaldehyde (1.94 mL, 16.6 mmol) at 25 °C. The reaction mixture was heated to reflux and stirred for 16 h. After cooling to room temperature, the precipitate was filtered to give **220b** (1.35 g, 33%) as an off-white solid. The compound was used without further purification as ¹H NMR showed 95% purity.

¹H NMR (400 MHz, CDCl₃): δ = 7.29–7.26 (m, 1 H; ArH), 7.26–7.22 (m, 2 H; ArH), 7.21–7.13 (m, 2 H; ArH), 5.41 (s, br, 1 H; NH), 3.64 (t, J = 4.3 Hz, 1 H; CHCH₂C₆H₅), 2.88 (d, J = 4.3 Hz, 2 H; CH₂C₆H₅), 1.91 ppm (s, 6 H; 2 x NHCH₃).

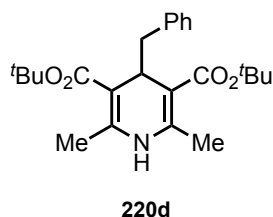
Synthesis of Hantzsch ester **220c**



A flask equipped with a reflux condenser was charged with benzyl acetoacetate (1.73 ml, 10 mmol), phenylacetaldehyde (0.59 mL, 5 mmol) and ethanol (10 mL). The solution was treated by dropwise addition of NH_4OH (35% aq. solution, 1.93 mL, 35 mmol) at 25 °C. The resulting mixture was heated to reflux and stirred for 16 h. The reaction was cooled down to room temperature and concentrated. The residue was taken up in CH_2Cl_2 , poured into water (20 mL) and extracted with CH_2Cl_2 (3x 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via silica gel column chromatography (pentane/EtOAc 95:5 to 30:70) to afford compound **220c** (1.17 g, 50%) as a yellow oil.

^1H NMR (400 MHz, CDCl_3): δ = 7.41–7.29 (m, 8 H; ArH), 7.20–7.05 (m, 3 H; ArH), 7.02–6.89 (m, 2 H; ArH), 5.63 (s, br, 1 H; NH), 5.13 (d, J = 12.6 Hz, 2 H; $\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$), 4.99 (d, J = 12.6 Hz, 2 H; $\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$), 4.36 (t, J = 5.5 Hz, 1 H; $\text{CHCH}_2\text{C}_6\text{H}_5$), 2.63 (d, J = 5.6 Hz, 2 H; $\text{CHCH}_2\text{C}_6\text{H}_5$), 2.20 ppm (s, 6 H; 2 x CH_3); **^{13}C NMR** (101 MHz, CDCl_3): δ = 167.6 ($\text{C}=\text{O}$), 146.2 (NHCH $\text{C}=\text{CH}_3$), 139.1 (C), 130.2 (ArCH), 128.5 (ArCH), 127.9 (ArCH), 127.4 (ArCH), 125.4 (ArCH), 101.7 ($\text{C}=\text{C}$), 65.6 ($\text{CO}_2\text{CH}_2\text{C}_6\text{H}_5$), 42.5 ($\text{CHCH}_2\text{C}_6\text{H}_5$), 35.5 ($\text{CHCH}_2\text{C}_6\text{H}_5$), 19.3 ppm (2 x CH_3); **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3371 (w), 2927 (m), 1739 (m), 1239 (s), 1174 (s); **HRMS** (ESI): m/z = 490.1987 ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_{30}\text{H}_{29}\text{O}_4\text{NNa}^+$: 490.1989).

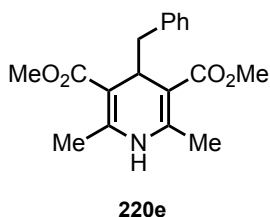
Synthesis of Hantzsch ester **220d**



A flask equipped with a reflux condenser was charged with tert-butyl acetoacetate (1.66 ml, 10 mmol), phenylacetaldehyde (0.59 mL, 5 mmol) and ethanol (10 mL). The solution was treated by dropwise addition of NH_4OH (35% aq. solution, 1.93 mL, 35 mmol) at 25 °C. The resulting mixture was heated to reflux and stirred for 16 h. The reaction was cooled down to room temperature and concentrated. The residue was taken up in CH_2Cl_2 , poured into water (20 mL) and extracted with CH_2Cl_2 (3x 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified via silica gel column chromatography (pentane/EtOAc 95:5 to 80:20) to afford compound **220d** (600 mg, 30%) as an off-white solid. NMR Spectra and physical properties matched those from reported literature.^[176]

^1H NMR (400 MHz, CDCl_3): δ = 7.22–7.10 (m, 3 H; ArH), 7.05–6.99 (m, 2 H; ArH), 5.21 (s, br, 1 H; NH), 4.14 (t, J = 5.7 Hz, 1 H; $\text{CHCH}_2\text{C}_6\text{H}_5$), 2.54 (d, J = 5.7 Hz, 2 H; $\text{CH}_2\text{C}_6\text{H}_5$), 2.15 (s, 6 H; 2 x NHCH_3), 1.42 ppm (s, 18 H; 2 x $\text{CO}_2\text{C}(\text{CH}_3)_3$); ^{13}C NMR (101 MHz, CDCl_3): δ = 167.3, 144.5, 139.7, 130.3, 127.6, 125.7, 103.4, 79.4, 42.0, 36.1, 28.4, 19.4 ppm.

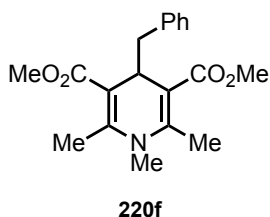
Synthesis of Hantzsch ester **220e**



Compound **220e** was synthesized according to General Procedure **H** using phenylacetaldehyde (1.17 mL, 10 mmol). FC (SiO₂; Pentane/EtOAc 95:5 to 35:65) gave compound **220e** (1.96 g, 62%) as an off-white solid.

m.p. = 140 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 7.20–7.10 (m, 3 H; ArH), 7.04–6.96 (m, 2 H; ArH), 5.38 (s, br, 1 H; NH), 4.18 (t, J = 5.5 Hz, 1 H; CHCH₂C₆H₅), 3.59 (s, 6 H; 2 x CO₂CH₃), 2.56 (d, J = 5.5 Hz, 2 H; CH₂C₆H₅), 2.17 ppm (s, 6 H; 2 x CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ = 168.4 (CO₂CH₃), 145.8 (NHCCH₃), 139.2 (ArC), 130.3 (ArCH), 127.4 (ArCH), 125.8 (ArCH), 101.7 (CCO₂CH₃), 51.0 (CO₂CH₃), 42.5 (CH₂C₆H₅), 35.6 (CHCH₂C₆H₅), 19.3 ppm (CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3370 (w), 2927 (m), 1739 (s), 1460 (m), 1222 (s), 1174 (s); **HRMS** (ESI): m/z = 315.1544 ([M+H]⁺, calcd. for C₁₈H₂₂O₄N⁺: 316.1543).

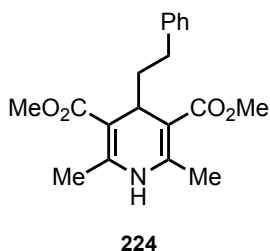
Synthesis of Hantzsch ester **220f**



A solution of **X** (100 mg, 0.32 mmol) in THF (1.3 mL) was treated with NaH (60% mineral oil, 38.4 mg, 0.96 mmol) in one-portion at 25 °C. The resulting mixture was heated up to 70 °C and stirred for 30 min, then treated by dropwise addition of MeI (0.1 mL, 1.6 mmol) and stirred at 80 °C for 2.5 h. The reaction mixture was cooled down to room temperature, poured into brine (15 mL) and extracted with EtOAc (3x 15 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified via silica gel column chromatography (SiO₂; pentane/EtOAc 95:5 to 85:15) to afford compound **220f** (68 mg, 65%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.22–7.15 (m, 2 H; ArH), 7.13–7.05 (m, 1 H; ArH), 7.02–6.95 (m, 2 H; ArH), 4.16 (t, J = 5.0 Hz, 1 H; CHCH₂C₆H₅), 3.67 (s, 6 H; 2 x CO₂CH₃), 2.48 (d, J = 5.6 Hz, 5 H; CH₂C₆H₅ and NCH₃), 2.26 ppm (s, 6 H; 2 x CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ = 168.6 (CO₂CH₃), 150.6 (N(CH₃)CCH₃), 139.7 (ArC), 129.9 (ArCH), 127.0 (ArCH), 125.9 (ArCH), 103.9 (CCO₂CH₃), 51.2 (CO₂CH₃), 41.6 (CH₂C₆H₅), 35.0 (CHCH₂C₆H₅), 33.3 (NCH₃), 16.3 ppm (CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3370 (w), 2927 (m), 1739 (s), 1460 (m), 1222 (s), 1174 (s); **HRMS** (ESI): m/z = 330.1700 ([M+H]⁺, calcd. for C₁₉H₂₄O₄N⁺: 330.1700).

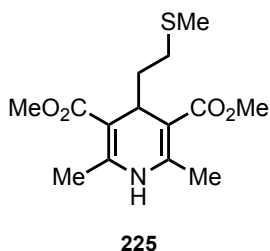
Synthesis of Hantzsch ester **224**



Compound **224** was synthesized according to General Procedure **H** using 3-phenylpropionaldehyde (0.66 mL, 5 mmol). FC (SiO₂; pentane/EtOAc 90:10 to 50:50) gave compound **224** (1.16 g, 70%) as an off-white solid.

m.p. = 110 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 7.25–7.20 (m, 2 H; ArH), 7.16–7.10 (m, 3 H; ArH), 5.70 (s, 1 H; NH), 4.04 (t, J = 5.7 Hz, 1 H; CHCH₂CH₂C₆H₅), 3.72 (s, 6 H; 2 x CO₂CH₃), 2.56–2.47 (m, 2 H; CH₂C₆H₅), 2.30 (s, 6 H; 2 x CH₃), 1.70–1.60 (m, 2 H; CH₂CH₂C₆H₅); **¹³C NMR** (101 MHz, CDCl₃): δ = 168.5 (CO₂CH₃), 145.5 (NHCH₃), 143.1 (ArC), 128.4 (ArCH), 128.3 (ArCH), 125.6 (ArCH), 102.8 (CCO₂CH₃), 51.1 (CO₂CH₃), 38.4 (CH₂CH₂C₆H₅), 33.3 (CHCH₂CH₂C₆H₅), 31.3 (CH₂C₆H₅), 19.6 ppm (CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3370 (w), 2925 (m), 1739 (m), 1597 (m), 1480 (m), 1239 (s); **HRMS** (ESI): m/z = 352.1519 ([M+Na]⁺, calcd. for C₁₉H₂₃O₄NNa⁺: 352.1519).

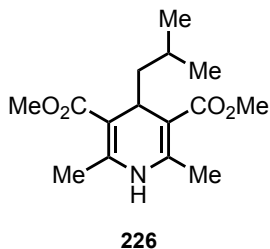
Synthesis of Hantzsch ester **225**



Compound **225** was synthesized according to General Procedure **H** using 3-(methylthio)propionaldehyde (0.5 mL, 5 mmol). FC (SiO₂; pentane/EtOAc 90:10 to 40:60) gave compound **225** (1 g, 67%) as a yellow solid.

m.p. = 96 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 5.71 (s, 1 H; NH), 3.98 (t, J = 5.7 Hz, 1 H; CHCH₂CH₂SCH₃), 3.71 (s, 6 H; 2 x CO₂CH₃), 2.41–2.34 (d, 2 H; CH₂SCH₃), 2.29 (s, 6 H; 2 x CH₃), 2.04 (s, SCH₃), 1.67–1.56 (m, 2 H; CH₂CH₂SCH₃); **¹³C NMR** (101 MHz, CDCl₃): δ = 168.3 (CO₂CH₃), 145.7 (NHCCH₃), 102.4 (CCO₂CH₃), 51.2 (CO₂CH₃), 36.4 (CH₂CH₂SCH₃), 33.1 (CHCH₂CH₂SCH₃), 30.1 (CH₂SCH₃), 19.6 (CH₃), 15.6 ppm (SCH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3370 (w), 2926 (m), 1739 (m), 1596 (m), 1222 (s), 1174 (s); **HRMS** (ESI): m/z = 322.1085 ([M+Na]⁺, calcd. for C₁₄H₂₁O₄NNaS⁺: 322.1084).

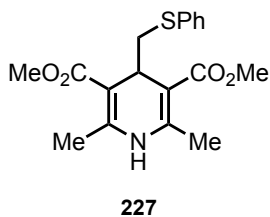
Synthesis of Hantzsch ester **226**



Compound **226** was synthesized according to General Procedure **H** using isovaleraldehyde (0.54 mL, 5 mmol). FC (SiO₂; pentane/EtOAc 90:10 to 40:60) gave compound **226** (1 g, 71%) as yellow solid. NMR Spectra and physical properties matched those from reported literature.^[200]

¹H NMR (400 MHz, CDCl₃): δ = 5.78 (s, 1 H; NH), 3.93 (t, J = 6.8 Hz, 1 H; CHCH₂CH(CH₃)₂), 3.70 (s, 6 H; 2 x CO₂CH₃), 2.28 (s, 6 H; 2 x CH₃), 1.44 (dp, J = 13.2, 6.6 Hz, 1 H; CHCH₂CH(CH₃)₂), 1.10 (t, J = 6.9 Hz, 2 H; CHCH₂CH(CH₃)₂), 0.85 ppm (d, J = 6.5 Hz, 6 H; CHCH₂CH(CH₃)₂); **¹³C NMR** (101 MHz, CDCl₃): δ = 168.7 (C=O₂CH₃), 144.9 (NHC=CH₃), 104.1 (C=CO₂CH₃), 50.9 (CO₂CH₃), 46.9 (CHCH₂CH(CH₃)₂), 31.0 (CHCH₂CH(CH₃)₂), 23.9 (CHCH₂CH(CH₃)₂), 23.0 (CHCH₂CH(CH₃)₂), 19.5 ppm (CH₃).

Synthesis of Hantzsch ester **227**

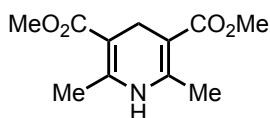


Compound **227** was synthesized according to General Procedure **H** using 2-(phenylthio)acetaldehyde (440 mg, 2.9 mmol). FC (SiO₂; pentane/EtOAc 95:5 to 40:60) gave compound **227** (762 mg, 44%) as an off-white solid.¹⁶

¹⁶2-(phenylthio)acetaldehyde was previously synthesised by J. A. P. Maitland, PhD Student.

m.p. = 140 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 7.30 (d, J = 7.7 Hz, 2 H; ArH), 7.23 (t, J = 7.6 Hz, 2 H; ArH), 7.10 (t, J = 7.3 Hz, 1 H; ArH), 6.35 (s, 1 H; NH), 4.32 (t, J = 5.9 Hz, 1 H; CHCH₂SC₆H₅), 3.64 (s, 6 H; 2 x CO₂CH₃), 2.97 (d, J = 6.0 Hz, 2 H; CHCH₂SC₆H₅), 2.26 ppm (s, 6 H; 2 x CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ = 168.1 (CO₂CH₃), 146.3 (NHCCH₃), 137.9 (ArC), 128.6 (ArCH), 127.6 (ArCH), 124.9 (ArCH), 101.5 (CCO₂CH₃), 51.0 (CO₂CH₃), 39.3 (CHCH₂SC₆H₅), 33.1 (CHCH₂SC₆H₅), 19.2 ppm (CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3335 (w), 2948 (w), 1679 (s), 1433 (s), 1215 (s); **HRMS** (ESI): m/z = 370.1084 ([M+Na]⁺, calcd. for C₁₈H₂₁O₄NNaS⁺: 370.1084).

Synthesis of Hantzsch ester **229**

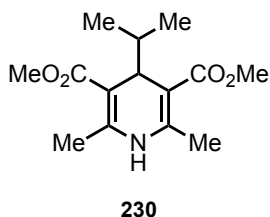


229

Compound **229** was synthesized according to General Procedure **H** using formaldehyde (0.41 mL, 5 mmol, aq. solution). FC (SiO₂; pentane/EtOAc 80:20 to 20:80) gave compound **229** (0.75 g, 67%) as yellow solid. NMR Spectra and physical properties matched those from reported literature.^[174]

¹H NMR (400 MHz, (CD₃)₂SO): δ = 8.31 (s, 1 H; NH), 3.58 (s, 6 H; 2 x CO₂CH₃), 3.13 (s, 2 H; CH₂), 2.11 ppm (s, 6 H; 2 x CH₃); **¹³C NMR** (101 MHz, (CD₃)₂SO): δ = 167.4 (CO₂CH₃), 146.7 (NHCCH₃), 96.9 (CCO₂CH₃), 50.6 (CO₂CH₃), 24.8 (CH₂), 17.8 ppm (CH₃).

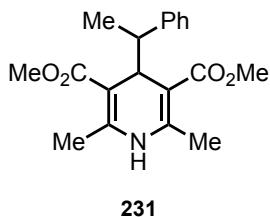
Synthesis of Hantzsch ester **230**



Compound **230** was synthesized according to General Procedure **G** using isobutyraldehyde (0.46 mL, 5 mmol). FC (SiO₂; pentane/EtOAc 95:5 to 50:50) gave compound **230** (0.99 g, 74%) as an off-white solid. NMR Spectra and physical properties matched those from reported literature.^[201]

¹**H NMR** (400 MHz, CDCl₃): δ = 5.80 (s, br, 1 H; NH), 3.87 (d, J = 5.4 Hz, 1 H; CHCH(CH₃)₂), 3.69 (s, 6 H; 2 x CO₂CH₃), 2.29 (s, 6 H; 2 x NCCH₃), 1.56 (pd, J = 6.9, 5.4 Hz, 1 H; CH(CH₃)₂), 0.72 ppm (d, J = 6.9 Hz, 6 H; CH(CH₃)₂); ¹³**C NMR** (101 MHz, CDCl₃): δ = 169.3 (CO₂CH₃), 145.0 (NHCCH₃), 101.6 (CCO₂CH₃), 51.0 (CO₂CH₃), 38.9 (CHCH(CH₃)₂), 35.6 (CHCH(CH₃)₂), 19.4 (NHCCH₃), 18.4 ppm (CHCH(CH₃)₂).

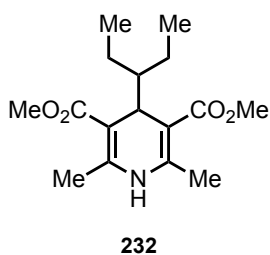
Synthesis of Hantzsch ester **231**



Compound **231** was synthesized according to General Procedure **H** using 2-phenylpropanal (0.67 mL, 5 mmol). FC (SiO₂; pentane/EtOAc 90:10 to 40:60) gave compound **231** (968 mg, 59%) as an off-white solid.

m.p. = 150 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 7.39–7.33 (m, 2 H; ArH), 7.32–7.27 (m, 1 H; ArH), 7.27–7.23 (m, 2 H; ArH), 5.63 (s, 1 H; NH), 4.41 (d, J = 5.2 Hz, 1 H; CHCHCH₃C₆H₅), 3.76 (s, 3 H; CO₂CH₃), 3.66 (s, 3 H; CO₂CH₃), 2.90 (qd, J = 7.2, 5.1 Hz, 1 H; CHCHCH₃C₆H₅), 2.37 (s, 6 H; 2 x CH₃), 1.32 ppm (d, J = 7.2 Hz, 3 H; CHCHCH₃C₆H₅); **¹³C NMR** (101 MHz, CDCl₃): δ = 168.9 (CO₂CH₃), 168.8 (CO₂CH₃), 145.5 (NHCCH₃), 145.4 (NHCCH₃), 144.1 (ArC), 128.6 (ArCH), 127.3 (ArCH), 125.9 (ArCH), 101.0 (CCO₂CH₃), 100.9 (CCO₂CH₃), 50.9 (CO₂CH₃), 50.8 (CO₂CH₃), 46.1 (CHCHCH₃C₆H₅), 40.3 (CHCHCH₃C₆H₅), 19.3 (CH₃), 19.2 (CH₃), 15.4 ppm (CHCHCH₃C₆H₅); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3339 (w), 2949 (w), 1678 (m), 1433 (m), 1215 (s); **HRMS** (ESI): m/z = 352.1516 ([M+Na]⁺, calcd. for C₁₉H₂₃O₄NNa⁺: 352.1519).

Synthesis of Hantzsch ester **232**

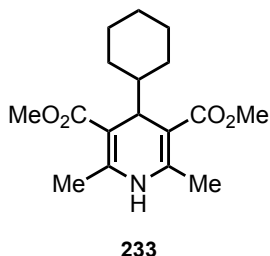


Compound **232** was synthesized according to General Procedure **H** using 2-ethylbutyraldehyde (0.62 mL, 5 mmol). FC (SiO₂; pentane/EtOAc 80:20 to 50:50) gave compound **232** (0.895 g, 61%) as yellow solid.

m.p. = 130 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 5.70 (s, 1 H; NH), 4.09 (d, J = 4.7 Hz, 1 H; CHCH(CH₂CH₃)₂), 3.69 (s, 6 H; 2 x CO₂CH₃), 2.27 (s, 6 H; 2 x CH₃), 1.22–1.07 (m, 4 H; CHCH(CH₂CH₃)₂), 1.03 (qd, J = 6.4, 4.7 Hz, 1 H; CHCH(CH₂CH₃)₂), 0.83 ppm (t, J = 7.3 Hz, 6 H; CHCH(CH₂CH₃)₂); **¹³C NMR** (101 MHz, CDCl₃): δ = 169.3 (CO₂CH₃), 144.9 (NHCCH₃), 102.2 (CCO₂CH₃), 50.9 (CO₂CH₃), 49.7 (CHCH(CH₂CH₃)₂), 35.0 (CHCH(CH₂CH₃)₂), 21.3 (CHCH(CH₂CH₃)₂), 19.4 (CH₃), 11.6 ppm (CHCH(CH₂CH₃)₂); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3339 (w), 2957 (w), 1721 (s), 1434 (m), 1283 (s); **HRMS** (ESI): m/z = 318.1676

([M+Na]⁺, calcd. for C₁₆H₂₅O₄NNa⁺: 318.1676).

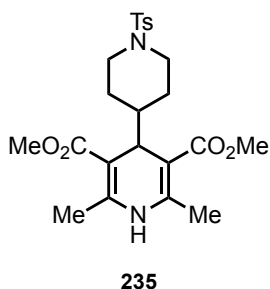
Synthesis of Hantzsch ester **233**



Compound **233** was synthesized according to General Procedure **H** using cyclohexanecarboxaldehyde (0.61 mL, 5 mmol). FC (SiO₂; pentane/EtOAc 90:10 to 40:60) gave compound **233** (1.18 g, 77%) as an off-white solid. NMR Spectra and physical properties matched those from reported literature.^[202]

¹H NMR (400 MHz, CDCl₃): δ = 5.77 (s, 1 H; NH), 3.88 (d, *J* = 5.8 Hz, 1 H; CHCHC₅H₁₀), 3.70 (s, 6 H; 2 x CO₂CH₃), 2.29 (s, 6 H; 2 x CH₃), 1.64 (dq, *J* = 13.3, 3.3 Hz, 2 H; CHC₅H₁₀), 1.58–1.46 (m, 3 H; CHC₅H₁₀), 1.19 (tdt, *J* = 11.9, 6.1, 3.2 Hz, 1 H; CHC₅H₁₀), 1.12–0.97 (m, 3 H; CHC₅H₁₀), 0.88 ppm (qd, *J* = 12.1, 11.7, 3.1 Hz, 2 H; CHC₅H₁₀); ¹³C NMR (101 MHz, CDCl₃): δ = 169.3 (CO₂CH₃), 145.0 (NHCCH₃), 101.7 (CCO₂CH₃), 51.0 (CO₂CH₃), 45.8 (CHC₅H₁₀), 38.5 (CHCHC₅H₁₀), 28.8 (CHC₅H₁₀), 26.8 (CHC₅H₁₀), 26.7 (CHC₅H₁₀), 19.5 ppm (CH₃).

Synthesis of Hantzsch ester **235**

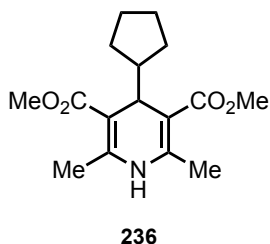


Compound **235** was synthesized according to General Procedure **H** using 1-tosylpiperidine-4-carbaldehyde (1.34 g, 5 mmol). FC (SiO₂; pentane/EtOAc 90:10 to 40:60) gave compound **235** (1.87 g, 81%) as yellow solid.¹⁷

m.p. = 190 °C; ¹**H NMR** (400 MHz, CDCl₃): δ = 7.63–7.52 (m, 2 H; ArH), 7.30–7.26 (m, 2 H; ArH), 5.90 (s, 1 H; NH), 3.93 (d, J = 5.3 Hz, 1 H; CHCH(CH₂)₄NSO₂Ar), 3.75–3.69 (m, 2 H; (CH₂)₂NSO₂Ar), 3.67 (s, 6 H; 2 x CO₂CH₃), 2.41 (s, 3 H; ArCH₃), 2.27 (s, 6 H; 2 x CH₃), 2.05 (td, J = 11.9, 2.5 Hz, 2 H; (CH₂)₂NSO₂Ar), 1.56–1.46 (m, 2 H; CHCH(CH₂)₂), 1.30 (qd, J = 12.6, 4.2 Hz, 2 H; CHCH(CH₂)₂), 1.18–1.06 ppm (m, 1 H; CHCH(CH₂)₄NSO₂Ar); ¹³**C NMR** (101 MHz, CDCl₃): δ = 168.6 (CO₂CH₃), 145.9 (NHCH₃), 143.5 (ArC), 133.2 (ArC), 129.6 (ArCH), 127.8 (ArCH), 100.5 (CCO₂CH₃), 51.1 (CO₂CH₃), 46.9 ((CH₂)₂NSO₂Ar), 43.1 (CHCH(CH₂)₂), 37.3 (CHCH(CH₂)₂), 27.1 (CHCH(CH₂)₂), 21.6 (ArCH₃), 19.5 ppm (CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3351 (w), 2949 (w), 1687 (m), 1434 (m), 1217 (s); **HRMS** (ESI): m/z = 463.1895 ([M+H]⁺, calcd. for C₂₃H₃₁O₆N₂S⁺: 463.1897).

¹⁷1-tosylpiperidine-4-carbaldehyde was previously synthesised by J. A. P. Maitland, PhD Student.

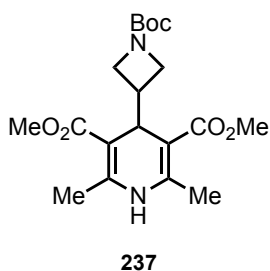
Synthesis of Hantzsch ester **236**



Compound **236** was synthesized according to General Procedure **H** using cyclopentanecarboxaldehyde (0.53 mL, 5 mmol). FC (SiO₂; pentane/EtOAc 90:10 to 40:60) gave compound **236** (783 mg, 53%) as yellow solid.

m.p. = 154 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 5.78 (s, 1 H; NH), 3.96 (d, J = 7.1 Hz, 1 H; CHCH(CH₂)₄), 3.70 (s, 6 H; 2 x CO₂CH₃), 2.29 (s, 6 H; 2 x CH₃), 1.78–1.64 (m, 1 H; CHCH(CH₂)₄), 1.60–1.33 (m, 6 H; CHCH(CH₂)₄), 1.18–1.04 ppm (m, 2 H; CHCH(CH₂)₄); **¹³C NMR** (101 MHz, CDCl₃): δ = 169.2 (CO₂CH₃), 145.0 (NHCCH₃), 102.6 (CCO₂CH₃), 51.0 (CO₂CH₃), 48.4 (CHCH(CH₂)₄), 36.0 (CHCH(CH₂)₄), 28.4 (CHCH(CH₂)₄), 24.2 (CHCH(CH₂)₄), 19.5 ppm (CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3338 (w), 2949 (w), 1676 (m), 1434 (m), 1215 (s); **HRMS** (ESI): m/z = 316.1514 ([M+Na]⁺, calcd. for C₁₆H₂₃O₄NNa⁺: 316.1519).

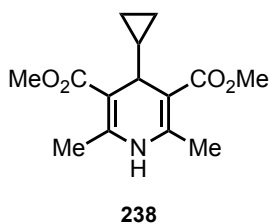
Synthesis of Hantzsch ester **237**



Compound **237** was synthesized according to General Procedure **G** using azetidine-3-carboxaldehyde (0.93 g, 5 mmol). FC (SiO₂; pentane/EtOAc 80:20 to 20:80) gave compound **237** (1.75 g, 92%) as yellow oil.

¹**H NMR** (400 MHz, CDCl₃): δ = 6.62 (s, 1 H; NH), 4.10 (d, J = 6.7 Hz, 1 H; CHCH(CH₂)₂N), 3.72 (s, 6 H; 2 x CO₂CH₃), 3.71–3.61 (m, 4 H; CH(CH₂)₂NCO₂C(CH₃)₃), 2.63 (tq, J = 8.6, 6.8 Hz, 1 H; CH(CH₂)₂NCO₂C(CH₃)₃), 2.30 (s, 6 H; 2 x CH₃), 1.40 ppm (s, 9 H; NCO₂C(CH₃)₃); ¹³**C NMR** (101 MHz, CDCl₃): δ = 168.4 (CO₂CH₃), 156.6 (NCO₂C(CH₃)₃), 147.1 (NHCCH₃), 99.8 (CCO₂CH₃), 79.3 (NCO₂C(CH₃)₃), 51.2 (CO₂CH₃ and CH(CH₂)₂NCO₂C(CH₃)₃), 35.1 (CH(CH₂)₂NCO₂C(CH₃)₃), 34.2 (CHCH(CH₂)₂NCO₂C(CH₃)₃), 28.5 (CH(CH₂)₂NCO₂C(CH₃)₃), 19.5 ppm (CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3306 (w), 2975 (w), 1673 (s), 1431 (m), 1214 (s); **HRMS** (ESI): m/z = 403.1840 ([M+Na]⁺ calcd. for C₁₉H₂₈O₆N₂Na⁺: 403.1840).

Synthesis of Hantzsch ester **238**

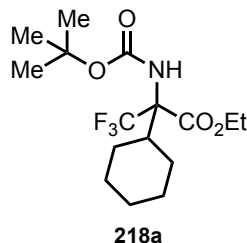


Compound **238** was synthesized according to General Procedure **G** using cyclopropanecarbaldehyde (0.37 mL, 5 mmol). FC (SiO₂; pentane/EtOAc 90:10 to 40:60) gave compound **238** (1.19 g, 90%) as an off-white solid.

m.p. = 160 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 5.87 (s, 1 H; NH), 3.70 (s, 6 H; 2 x CO₂H₃), 3.59 (d, J = 7.7 Hz, 1 H; CHCHC₂H₄), 2.30 (s, 6 H; 2 x CH₃), 0.85–0.69 (m, 1 H; CHC₂H₄), 0.22–0.17 ppm (m, 4 H; CHC₂H₄); **¹³C NMR** (101 MHz, CDCl₃): δ = 168.9 (CO₂CH₃), 145.1 (NHCCH₃), 102.5 (CCO₂CH₃), 51.0 (CO₂CH₃), 35.2 (CHCHC₂H₄), 19.5 (CH₃), 18.0 (CHCHC₂H₄), 1.90 ppm (CHCHC₂H₄); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3370 (w), 2925 (m), 1739 (m), 1462 (m), 1239 (s); **HRMS** (ESI): m/z = 266.1388 ([M+H]⁺, calcd. for C₁₄H₂₀O₄N⁺: 266.1387).

5.4.5 Synthesis of α -Tfm Amino Acids

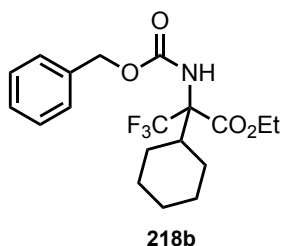
Synthesis of compound **218a**



Compound **218a** was synthesized according to General Procedure **I** using **233** (189.2 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 99:1 to 95:5) gave **218a** (65 mg, 92%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 4.99 (s, 1 H; NH), 4.28 (tt, J = 9.0, 4.1 Hz, 2 H; CO₂CH₂CH₃), 2.25–2.10 (m, 1 H; CH(CH₂)₅), 1.88–1.63 (m, 5 H; CH(CH₂)₅), 1.43 (s, 9 H; NHCO₂C(CH₃)₃), 1.30 (t, J = 7.2 Hz, 3 H; CO₂CH₂CH₃), 1.28–1.12 ppm (m, 5 H; CH(CH₂)₅); **¹⁹F NMR** (377 MHz, CDCl₃): δ = –67.35 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 166.4 (CO₂CH₂CH₃), 153.7 (NHCO₂(CH₃)₃), 124.7 (q, J = 288.3 Hz; CF₃), 80.9 (NHCO₂C(CH₃)₃), 68.8 (br; CCF₃), 62.2 (CO₂CH₂CH₃), 43.2 (CH(CH₂)₅), 28.3 (NHCO₂C(CH₃)₃), 27.8 (CH(CH₂)₅), 27.8 (CH(CH₂)₅), 26.8 (CH(CH₂)₅), 26.7 (CH(CH₂)₅), 26.1 (CH(CH₂)₅), 14.1 ppm (CO₂CH₂CH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3296 (w), 2933 (w), 1740 (m), 1703 (s), 1491 (m), 1157 (s); **HRMS** (ESI): m/z = 376.1704 ([M+Na]⁺, calcd. for C₁₆H₂₆O₄NF₃Na⁺: 376.1706).

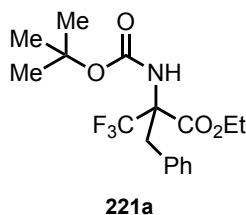
Synthesis of compound **218b**



Compound **218b** was synthesized according to General Procedure **I** using **233** (189.2 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 99:1 to 94:6) gave **218b** (72.1 mg, 93%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.41–7.30 (m, 5 H; ArH), 5.29 (s, 1 H; NH), 5.11 (d, J = 3.4 Hz, 2 H; NHCO₂CH₂C₆H₅), 4.38–4.18 (m, 2 H; CO₂CH₂CH₃), 2.34–2.22 (m, 1 H; CCH(CH₂)₅), 1.87–1.63 (m, 6 H; CCH(CH₂)₅), 1.37–1.07 ppm (m, 7 H; CCH(CH₂)₅ and CO₂CH₂CH₃); **¹⁹F NMR** (377 MHz, CDCl₃): δ = –67.15 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 166.1 (CO₂CH₂CH₃), 154.3 (NHCO₂CH₂C₆H₅), 136.0 (ArC), 128.7 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 124.5 (q, J = 288.4 Hz; CF₃), 68.2 (q, J = 27.1 Hz; CCF₃), 67.5 (NHCO₂CH₂C₆H₅), 62.6 (CO₂CH₂CH₃), 42.7 (CCH(CH₂)₅), 27.7 (d, J = 3.2 Hz; CCH(CH₂)₅), 26.6 (d, J = 3.2 Hz; CCH(CH₂)₅), 26.0 (CCH(CH₂)₅), 14.1 ppm (CO₂CH₂CH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3361 (w), 2936 (w), 1741 (s), 1502 (m), 1269 (s), 1175 (s); **HRMS** (ESI): m/z = 410.1550 ([M+Na]⁺, calcd. for C₁₉H₂₄O₄NF₃Na⁺: 410.1550).

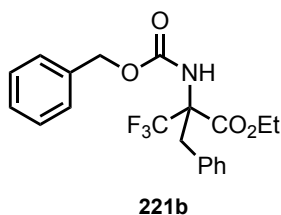
Synthesis of compound **221a**



Compound **221a** was synthesized according to General Procedure **I** using **220e** (189.2 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 100 to 95:5) gave **221a** (58.2 mg, 81%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.31–7.23 (m, 3 H; ArH), 7.20 (dt, J = 6.6, 2.3 Hz, 2 H; ArH), 5.55 (s, 1 H; NH), 4.40–4.22 (m, 2 H; CO₂CH₂CH₃), 4.19–4.06 (br, m, 1 H; CH₂C₆H₅), 3.41 (d, J = 13.9 Hz, 1 H; CH₂C₆H₅), 1.47 (s, 9 H; NHCO₂C(CH₃)₃), 1.33 ppm (t, J = 7.2 Hz, 3 H; CO₂CH₂CH₃); **¹⁹F NMR** (377 MHz, CDCl₃): δ = –72.96 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 166.5 (CO₂CH₂CH₃), 153.6 (NHCO₂(CH₃)₃), 133.8 (ArC), 130.3 (ArCH), 128.5 (ArCH), 127.6 (ArCH), 124.2 (q, J = 288.8 Hz; CF₃), 80.3 (NHCO₂C(CH₃)₃), 66.8 (q, J = 27.9 Hz; CCF₃), 63.5 (CO₂CH₂CH₃), 33.7 (CH₂C₆H₅), 28.3 (NHCO₂C(CH₃)₃), 14.0 ppm (CO₂CH₂CH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3417 (w), 2981 (w), 1732 (s), 1495 (m), 1157 (s); **HRMS** (ESI): m/z = 384.1393 ([M+Na]⁺, calcd. for C₁₇H₂₂O₄NF₃Na⁺: 384.1394).

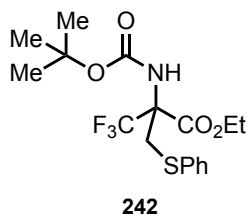
Synthesis of compound **221b**



Compound **221b** was synthesized according to General Procedure **I** using **220e** (189.2 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 99:1 to 96:4) gave **221b** (43.5 mg, 55%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.44–7.31 (m, 5 H; ArH), 7.24–7.14 (m, 3 H; ArH), 7.11–7.04 (m, 2 H; ArH), 5.86 (s, 1 H; NH), 5.24 (d, J = 12.2 Hz, 1 H; CO₂CH₂C₆H₅), 5.08 (d, J = 12.2 Hz, 1 H; CO₂CH₂C₆H₅), 4.43–4.09 (m, 3 H; CO₂CH₂CH₃ and CH₂C₆H₅), 3.41 (d, J = 13.9 Hz, 1 H; CH₂C₆H₅), 1.33 ppm (t, J = 7.2 Hz, 3 H; CO₂CH₂CH₃); **¹⁹F NMR** (377 MHz, CDCl₃): δ = –73.02 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 166.2 (CO₂CH₂CH₃), 154.2 (NHCO₂CH₂C₆H₅), 136.2 (ArC), 133.3 (ArC), 130.1 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 127.6 (ArCH), 124.1 (q, J = 288.8 Hz; CF₃), 67.1 (CO₂CH₂C₆H₅), 67.1 (q, J = 28.1 Hz; CCF₃), 63.8 (CO₂CH₂CH₃), 33.4 (CH₂C₆H₅), 13.9 ppm (CO₂CH₂CH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3407 (w), 2985 (w), 1737 (s), 1499 (m), 1266 (s), 1192 (s); **HRMS** (ESI): m/z = 396.1420 ([M+H]⁺, calcd. for C₂₀H₂₁O₄NF₃⁺: 396.1417).

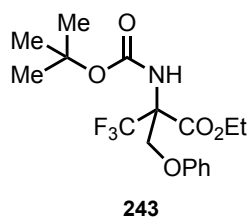
Synthesis of compound **242**



Compound **242** was synthesized according to General Procedure **I** using **227** (208.5 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 100 to 96:4) gave **242** (54.3 mg, 69%) as colorless oil.

¹**H NMR** (400 MHz, CDCl₃): δ = 7.45–7.41 (m, 2 H; ArH), 7.31–7.21 (m, 3 H; ArH), 5.87 (s, 1 H; NH), 4.49 (d, J = 13.5 Hz, 1 H; CH₂SC₆H₅), 4.18–4.05 (m, 1 H; CO₂CH₂CH₃), 3.79 (dq, J = 10.7, 7.1 Hz, 1 H; CO₂CH₂CH₃), 3.62 (d, J = 13.5 Hz, 1 H; CH₂SC₆H₅), 1.42 (s, 9 H; NHCO₂C(CH₃)₃), 1.11 ppm (t, J = 7.1 Hz, 3 H; CO₂CH₂CH₃); ¹⁹**F NMR** (377 MHz, CDCl₃): δ = –73.59 ppm; ¹³**C NMR** (101 MHz, CDCl₃): δ = 165.8 (CO₂CH₂CH₃), 153.3 (NHCO₂(CH₃)₃), 134.7 (ArC), 132.4 (ArCH), 129.1 (ArCH), 127.7 (ArCH), 123.7 (q, J = 289.3 Hz; CF₃), 80.8 (NHCO₂CC(CH₃)₃), 66.2 (q, J = 28.3 Hz; CCF₃), 63.7 (CO₂CH₂CH₃), 34.6 (CH₂C₆H₅), 28.3 (NHCO₂C(CC₃)₃), 13.7 ppm (CO₂CH₂CH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3415.2 (w), 2981 (w), 1734 (s), 1492 (m), 1309 (m), 1161 (s); **HRMS** (ESI): m/z = 416.1115 ([M+Na]⁺, calcd. for C₁₇H₂₂O₄NF₃NaS⁺: 416.1114).

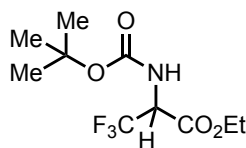
Synthesis of compound **243**



Compound **243** was synthesized according to General Procedure **I** using **228** (199 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 99:1 to 95:5) gave **243** (37.2 mg, 49%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.32–7.24 (m, 2 H; ArH), 6.99 (tt, J = 7.3, 1.1 Hz, 1 H; ArH), 6.95–6.89 (m, 2 H; ArH), 5.72 (s, 1 H; NH), 5.08 (br s, 1 H; CCH₂C₆H₅), 4.55 (dd, J = 9.4, 1.2 Hz, 1 H; CCH₂C₆H₅), 4.34 (q, J = 7.1 Hz, 2 H; CO₂CH₂CH₃), 1.40 (s, 9 H; NHCO₂C(CH₃)₃), 1.29 ppm (t, J = 7.1 Hz, 3 H; CO₂CH₂CH₃); **¹⁹F NMR** (377 MHz, CDCl₃): δ = –72.50 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 165.3 (CO₂CH₂CH₃), 158.1 (ArC), 153.6 (NHCO₂(CH₃)₃), 129.6 (ArCH), 123.3 (q, J = 287.6 Hz; CF₃), 122.0 (ArCH), 115.3 (ArCH), 81.0 (NHCO₂C(CH₃)₃), 65.7 (q, J = 28.3 Hz; CCF₃), 64.5 (CCH₂C₆H₅), 63.7 (CO₂CH₂CH₃), 28.2 (NHCO₂C(CH₃)₃), 14.0 ppm (CO₂CH₂CH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3413 (w), 2982 (w), 1736 (s), 1706 (s), 1497 (m), 1239 (s); **HRMS** (ESI): m/z = 400.1345 ([M+Na]⁺, calcd. for C₁₇H₂₂O₅NF₃Na⁺: 400.1342).

Synthesis of compound **244a**

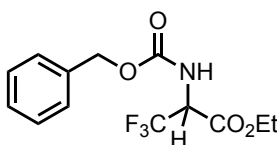


244a

Compound **244a** was synthesized according to General Procedure **I** using **229** (135.1 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 100 to 95:5) gave **244a** (37 mg, 68%) as a colorless oil. NMR Spectra and physical properties matched those from reported literature.^[167]

¹H NMR (400 MHz, CDCl₃): δ = 5.45–5.33 (m, 1 H; NH), 4.96 (p, J = 7.9 Hz, 1 H; CHCF₃), 4.40–4.21 (m, 2 H; CO₂CH₂CH₃), 1.46 (s, 9 H; NHCO₂C(CH₃)₃), 1.32 ppm (t, J = 7.1 Hz, 3 H; CO₂CH₂CH₃); ¹⁹F NMR (377 MHz, CDCl₃): δ = –73.04 ppm (d, J = 8.1 Hz); ¹³C NMR (101 MHz, CDCl₃): δ = 165.2 (CO₂CH₂CH₃), 154.7 (NHCO₂C(CH₃)₃), 122.7 (q, J = 282.5 Hz; CF₃), 81.5 (NHCO₂C(CH₃)₃), 63.2 (CO₂CH₂CH₃), 55.6 (q, J = 32.4 Hz; CCF₃), 28.3 (NHCO₂C(CH₃)₃), 14.0 ppm (CO₂CH₂CH₃).

Synthesis of compound **244b**



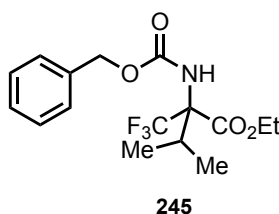
244b

Compound **244b** was synthesized according to General Procedure **I** using **229** (135.1 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 98:2 to 90:10) gave **244b** (52 mg, 85%) as a white solid. NMR Spectra and physical properties matched those from

reported literature.^[167]

¹H NMR (400 MHz, CDCl₃): δ = 7.43–7.30 (m, 5 H; ArH), 5.66 (d, J = 9.4 Hz, 1 H; NH), 5.16 (s, 2 H; NHCO₂CH₂C₆H₅), 5.10–4.97 (m, 1 H; CHCF₃), 4.39–4.24 (m, 2 H; CO₂CH₂CH₃), 1.32 ppm (t, J = 7.1 Hz, 3 H; CO₂CH₂CH₃); **¹⁹F NMR** (377 MHz, CDCl₃): δ = –72.97 (d, J = 7.7 Hz); **¹³C NMR** (101 MHz, CDCl₃): δ = 164.8 (CO₂CH₂CH₃), 155.5 (NHCO₂CH₂C₆H₅), 135.7 (ArC), 128.8 (ArCH), 128.6 (ArCH), 128.4 (ArCH), 122.7 (q, J = 282.8 Hz; CF₃), 68.1 (NHCO₂CH₂C₆H₅), 63.4 (CO₂CH₂CH₃), 56.0 (q, J = 32.4 Hz; CCF₃), 14.0 ppm (CO₂CH₂CH₃).

Synthesis of compound **245**

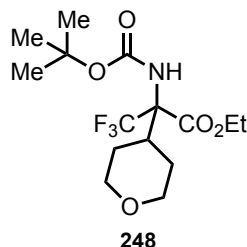


Compound **245** was synthesized according to General Procedure **I** using **230** (160.4 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 99:1 to 92:8) gave **245** (44.1 mg, 64%) as colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.41–7.30 (m, 5 H; ArH), 5.29 (s, 1 H; NH), 5.11 (s, 2 H; NHCO₂CH₂C₆H₅), 4.39–4.18 (m, 2 H; CO₂CH₂CH₃), 2.75–2.60 (m, 1 H; CH(CH₃)₂), 1.36–1.20 (m, 3 H; CO₂CH₂CH₃), 1.08 ppm (ddd, J = 7.0, 3.7, 1.2 Hz, 6 H; CH(CH₃)₂); **¹⁹F NMR** (377 MHz, CDCl₃): δ = –67.83 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 166.1 (CO₂CH₂CH₃), 154.3 (NHCO₂(CH₃)₃), 136.0 (ArC), 128.7 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 124.6 (q, J = 288.2 Hz; CF₃), 68.1 (q, J = 27.0 Hz; CCF₃), 67.5 (NHCO₂CH₂C₆H₅), 62.7 (CO₂CH₂CH₃), 32.2 (CH(CH₃)₂), 17.8 (d, J = 1.9 Hz; CH(CH₃)₂), 17.6 (d, J = 2.3 Hz; CH(CH₃)₂), 14.1 ppm (CO₂CH₂CH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3350 (w), 2982 (w), 1742 (s), 1511 (m), 1260

(s), 1227 (s); **HRMS** (ESI): $m/z = 348.1418$ ($[M+H]^+$, calcd. for $C_{16}H_{21}O_4NF_3^+$: 348.1417).

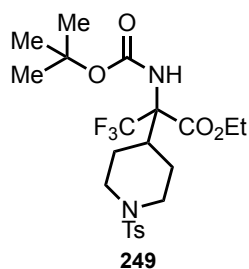
Synthesis of compound **248**



Compound **248** was synthesized according to General Procedure **I** using **234** (185.6 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 95:5 to 85:15) gave **248** (61 mg, 86%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): $\delta = 5.11$ (s, 1 H; NH), 4.31 (q, $J = 7.1$ Hz, 2 H; CO₂CH₂CH₃), 4.10–3.97 (m, 2 H; CH(CH₂)₂(CH₂)₂O), 3.47–3.30 (m, 2 H; CH(CH₂)₂(CH₂)₂O), 2.67 (br s, 1 H; CH(CH₂)₂(CH₂)₂O), 1.73–1.56 (m, 4 H; CH(CH₂)₂(CH₂)₂O), 1.44 (s, 9 H; NHCO₂C(CH₃)₃), 1.33 ppm (t, $J = 7.1$ Hz, 3 H; CO₂CH₂CH₃); **¹⁹F NMR** (377 MHz, CDCl₃): $\delta = -68.23$ ppm; **¹³C NMR** (101 MHz, CDCl₃): $\delta = 165.8$ (CO₂CH₂CH₃), 153.4 (NHCO₂(CH₃)₃), 124.3 (q, $J = 288.6$ Hz; CF₃), 80.9 (NHCO₂C(CH₃)₃), 67.9 (CH(CH₂)₂(CH₂)₂O), 67.8 (CH(CH₂)₂(CH₂)₂O), 67.4 (q, $J = 26.7$ Hz; CCF₃), 62.7 (CO₂CH₂CH₃), 38.9 (CH(CH₂)₂(CH₂)₂O), 28.1 (NHCO₂C(CH₃)₃), 27.9 (CH(CH₂)₂(CH₂)₂O), 27.7 (CH(CH₂)₂(CH₂)₂O), 14.0 ppm (CO₂CH₂CH₃); **FT-IR** (thin film): ν_{max} (cm⁻¹) = 3287 (w), 2979 (w), 1752 (m), 1705 (s), 1368 (m), 1244 (m), 1158 (s); **HRMS** (ESI): $m/z = 378.1500$ ($[M+Na]^+$, calcd. for $C_{15}H_{24}O_5NF_3Na^+$: 378.1499).

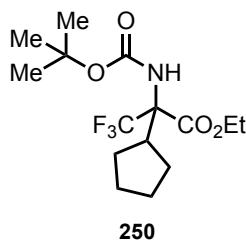
Synthesis of compound **249**



Compound **249** was synthesized according to General Procedure **I** using **235** (277.5 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 99:1 to 90:10) gave **249** (48 mg, 47%) as a white solid.

m.p. = 154 °C; **¹H NMR** (400 MHz, CDCl₃): δ = 7.64–7.59 (m, 2 H; ArH), 7.32 (d, J = 8.0 Hz, 2 H; ArH), 5.22 (s, 1 H; NH), 4.29 (qd, J = 7.1, 1.6 Hz, 2 H; CO₂CH₂CH₃), 3.92–3.82 (m, 2 H; N(CH₂)₂), 2.58–2.46 (m, 1 H; CH(CH₂)₂), 2.44 (s, 3 H; CH₃), 2.18 (td, J = 12.0, 2.6 Hz, 2 H; N(CH₂)₂), 1.88–1.78 (m, 2 H; CH(CH₂)₂), 1.78–1.69 (m, 1 H; CH(CH₂)₂), 1.61–1.50 (m, 1 H; CH(CH₂)₂), 1.41 (s, 9 H; CO₂C(CH₃)₃), 1.31 ppm (t, J = 7.2 Hz, 3 H; CO₂CH₂CH₃); **¹⁹F NMR** (377 MHz, CDCl₃): δ = –68.51 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 165.9 (CO₂CH₂CH₃), 153.5 (NHCO₂(CH₃)₃), 143.9 (ArC), 132.7 (ArC), 129.9 (ArCH), 127.9 (ArCH), 124.2 (q, J = 288.7 Hz; CF₃), 81.2 (NHCO₂C(CH₃)₃), 67.5 (q, J = 27.3 Hz; CCF₃), 63.2 (CO₂CH₂CH₃), 30.3 (CH(CH₂)₂), 28.3 (NHCO₂C(CH₃)₃), 26.8 (CH(CH₂)₂), 26.7 (CH(CH₂)₂), 21.7 (CH₃), 14.1 ppm (CO₂CH₂CH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3363 (w), 2981 (w), 1752 (m), 1731 (m), 1702 (m), 1509 (m), 1160 (s); **HRMS** (ESI): m/z = 531.1743 ([M+Na]⁺, calcd. for C₂₂H₃₁O₆N₂F₃NaS⁺: 531.1747).

Synthesis of compound **250**



Compound **250** was synthesized according to General Procedure **I** using **236** (176 mg, 0.6 mmol) and irradiated with blue light for 24 h. FC (SiO₂; pentane/EtOAc 99:1 to 95:5) gave **250** (58.2 mg, 86%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 4.89 (s, 1 H; NH), 4.27 (qd, J = 8.6, 4.2 Hz, 2 H; CO₂CH₂CH₃), 2.63 (br s, 1 H; (CCH(CH₂)₄), 1.85–1.70 (m, 2 H; CCH(CH₂)₄), 1.72–1.48 (m, 6 H; CCH(CH₂)₄), 1.44 (s, 9 H; NHCO₂C(CH₃)₃), 1.30 ppm (t, J = 7.1 Hz, 3 H; CO₂CH₂CH₃); **¹⁹F NMR** (377 MHz, CDCl₃): δ = –70.28 ppm; **¹³C NMR** (101 MHz, CDCl₃): δ = 166.4 (CO₂CH₂CH₃), 153.7 (NHCO₂(CH₃)₃), 124.8 (q, J = 287.9 Hz; CF₃), 80.9 (NHCO₂C(CH₃)₃), 66.5 (q, J = 28.1 Hz; CCF₃), 62.2 (CO₂CH₂CH₃), 42.7 (CCH(CH₂)₄), 28.3 (NHCO₂C(CH₃)₃), 27.6 (CCH(CH₂)₄), 27.4 (CCH(CH₂)₄), 25.4 (CCH(CH₂)₄), 25.0 (CCH(CH₂)₄), 14.1 ppm (CO₂CH₂CH₃); **FT-IR** (thin film): ν_{max} (cm^{–1}) = 3286 (w), 2979 (w), 1750 (m), 1706 (s), 1367 (m), 1159 (s); **HRMS** (ESI): m/z = 362.1549 ([M+Na]⁺, calcd. for C₁₅H₂₄O₄NF₃Na⁺: 362.1550).

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