Photoinduced Decarboxylation of *N*-Acyloxyphthalimides

Dissertation

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Christian Faderl

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Die Arbeit wurde angeleitet von: Prof. Dr. Oliver Reiser

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Herrn Prof. Dr. Oliver Reiser möchte ich herzlich für die Überlassung des interessanten Themas, die Freiheiten in der Bearbeitung desselben, die anregenden Diskussionen und die stete Unterstützung danken.

Regine und meiner Familie

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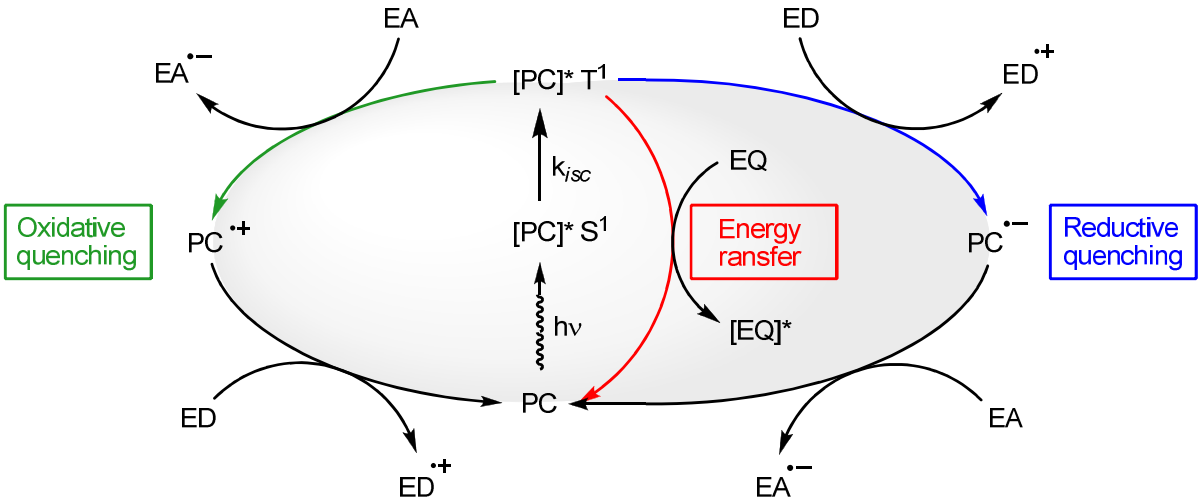
A Introduction

1 Photoredox chemistry

Photoredox catalysis using visible light is one of the few reaction processes, which can be performed directly using a renewable energy source, namely sunlight. The potential of photochemistry was realized from one of the early pioneers of this field of research, Giacomo Ciamician. In a talk at the Société Française de Chimie (French Chemical Society) in 1908, he established the idea of "green chemistry", highlighting the importance of sustainability. Further Giacomo Ciamician predicted that the study and exploration of solar energy would be necessary for the global society once the fossil fuels were depleted.[1]

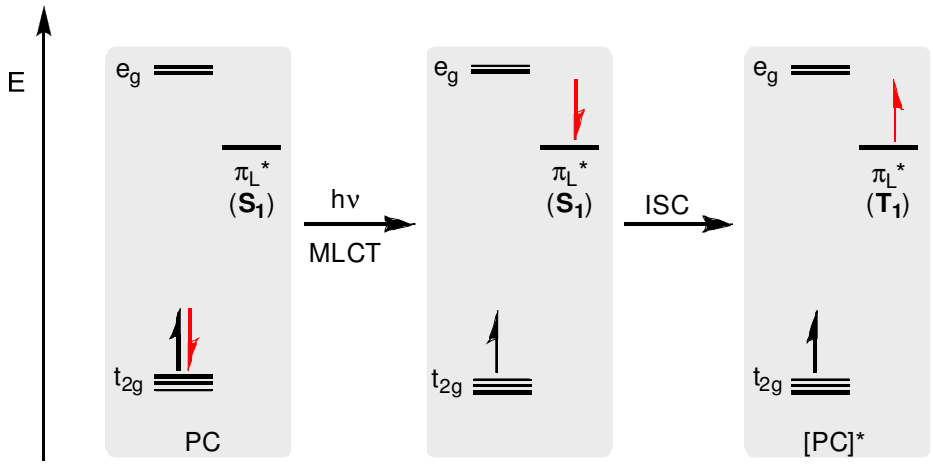
Since that time photochemistry has become a powerful methodology that generates reactive radical species without the use of toxic or explosive reagents, such as tin reagents or peroxides.[2] Only a few molecules absorb light in the visible range, therefore short wavelength and high energy ultra-violet (UV) irradiation is required to excite these molecules directly. Irradiation with UV light is problematic due to the stability of molecular bonds and occupational safety of researcher and employees. Instead of irradiation with short wavelength, various photosensitizers, which absorb photons from visible light and transfer the energy to the reagents, has been applied for the excitation of these non-absorbing molecules. Besides organic dyes and inorganic semiconductors, most commonly used photocatalysts in organic synthesis are transition-metal-pyridyl complexes, such as $[Ru(bpy)_3]Cl_2$ (bpy = 2,2´-bipyridine).[3] Under visible light irradiation, transition-metal based photocatalysts are able to undergo single-electron transfer (SET) processes. This grants access to reactive radical intermediates and new chemical transformations under ambient temperatures and mild reaction conditions.[4] Following, the mechanisms of different catalytic processes of the photocatalysts were described.

Visible light-induced transformations begin with the absorption of the emitted photons by the photocatalyst (PC). Subsequently the excited catalyst [PC*] can interact with suitable substrates in single electron transfer reactions or energy transfer. Distinction is made between the oxidative and reductive quenching cycle (Scheme 1).



Scheme 1. Photoredox catalysis of a photocatalyst (PC) by reductive, oxidative, or energy transfer pathways. EA = electron acceptor, ED = electron donor, EQ = energy quencher.

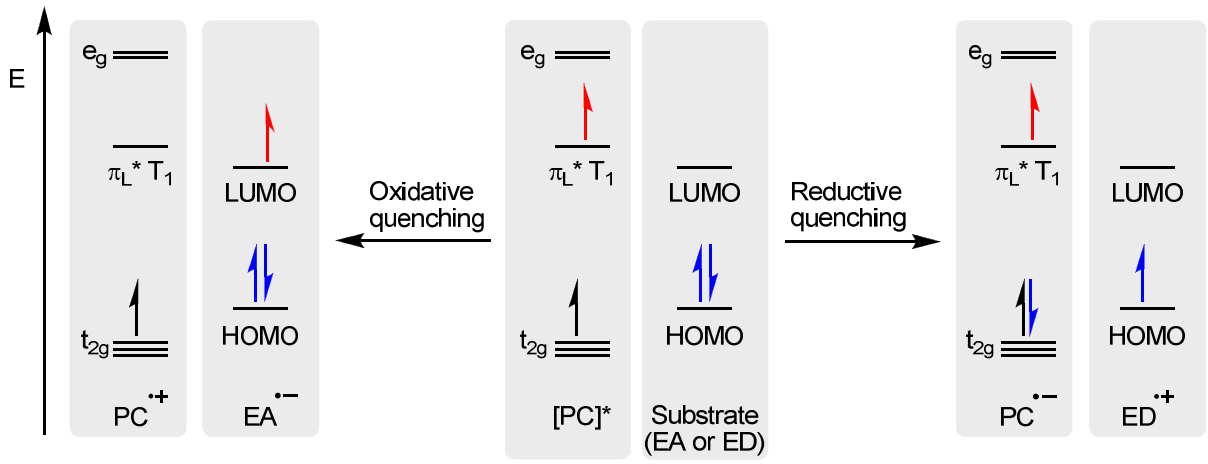
A closer look in the molecular orbital diagram illustrates the excitation of photocatalysts (Scheme 2). For octahedral complexes, such as $[Ru(bpy)_3]^{2+}$ or $Ir[(ppy)_2(dtb\text{-}bpy)]^+$ (ppy = phenylpyridine, dtb-bpy = 4,4´-di-*tert*-butyl-2,2´-bipyridine), the metal-centered t_{2g} orbital is fully occupied. Through absorption of visible light an electron is excited into the ligand-centered π_L^* (S_1) via metal to ligand charge transfer (MLCT). The singlet π_L^* (S_1) state rapidly undergoes intersystem crossing (ISC) and internal conversion to generate the first triplet excited state π_L^* (T_1). The energy in the excited photocatalyst $[PC]^*$ can lead to phosphorescence, alternate intersystem crossing, or intermolecular quenching. The latter enables electron transfer mechanisms and productive chemistry.[5,6]



Scheme 2. Jablonski diagram of a visible light-promoted excitation of a transition metal based photocatalyst (PC).

If a suitable electron donor (ED) is present in the reaction, the catalytic active photocatalyst $[PC]^*$ undergoes reductive quenching (Scheme 3). An electron of the highest occupied molecular orbital (HOMO) of the substrate donates into orbital t_{2g}, whereby the catalyst gets reduced (PC^-). In presence of an electron acceptor (EA), the catalyst $[PC]^*$ acts as a reductant and reduces the substrate via electron transfer from π_L^* state to the lowest unoccupied molecular orbital (LUMO) of the EA molecule. This oxidative quenching cycle leads to the cationic catalyst species PC^+.[7]

In order to regenerate the neutral photocatalyst a second redox reaction step is necessary. The reduced species PC^- has to react with an electron acceptor (EA), equally the oxidized catalyst PC^+ needs an electron from a suitable electron donor molecule (ED).

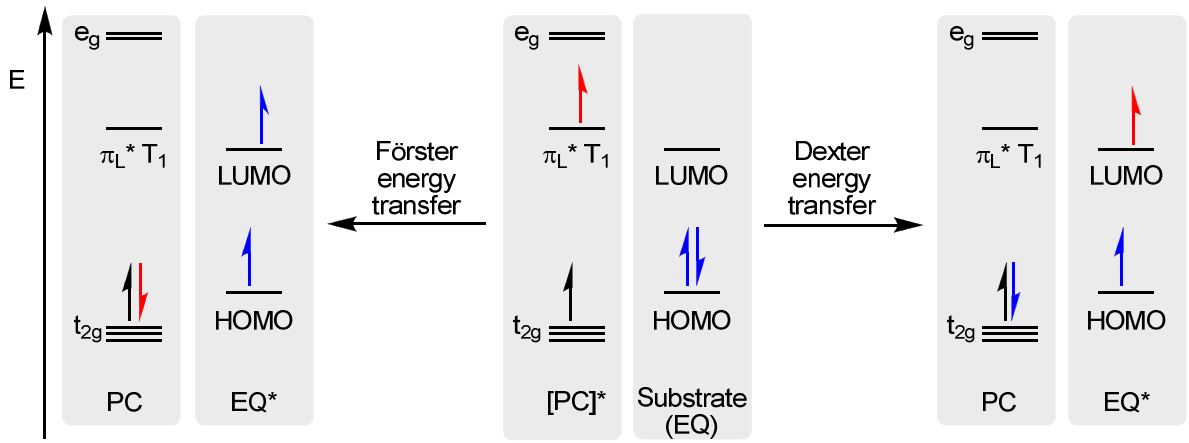


Scheme 3. Jablonski diagram of the oxidative and reductive quenching of $[PC]^*$. EA = electron acceptor, ED = electron donor, LUMO = lowest unoccupied molecular orbital, HOMO = highest occupied molecular orbital.

Besides the photoredox pathways – reduction and oxidation – the photocatalyst can serve as photosensitizer and transfer energy, which was received by visible light irradiation, onto the substrate (EQ). The energy transfer is equal to an excited state transfer and allows the excitation of molecules that do not have favorable redox potentials. Two most common energy transfer mechanisms are the Förster and the Dexter transfer (Scheme 4).

If an acceptor substrate (energy quencher, EQ) is closer than 10 nm to the catalyst the relaxation energy of the π_L^* (T_1) state funnels into a vibrational mode of the substrate. An electron of the energy quencher (EQ) is transferred from the highest occupied to the lowest unoccupied molecular orbital. For this Förster transfer mechanism the emission spectrum of the photocatalyst has to overlap with the ground state absorption spectrum of substrate EQ.

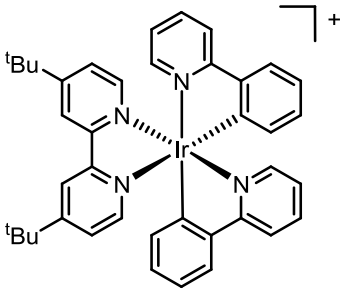
The Dexter energy transfer is a simultaneous double electron transfer mechanism. The excited catalyst $[PC]^*$ and the substrate (EQ) exchange their electron from HOMO to t_{2g} and π_L^* (T1) to LUMO. This exchange occurs through physical contact of the molecules (< 0.01 nm) and overlapping wavefunctions.[8]



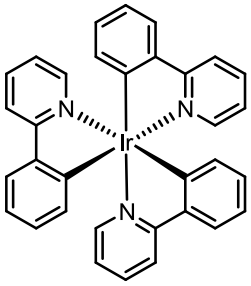
Scheme 4. Jablonski diagram of the Förster and Dexter energy transfer of $[PC]^*$.

Iridium and ruthenium based polypyridyl complexes were the most common photocatalysts in organic synthesis, due to their easy synthesis and the photoredox properties. As example for the photophysical behavior the catalysts $Ir[(ppy)_2(dtb\text{-}bpy)]^+$ (**1**), $Ir(ppy)_3$ (**2**), and $[Ru(bpy)_3]^{2+}$ (**3**) are mentioned (Table 1). With the absorption maxima in the visible range the catalysts can be excited into their long-lived triplet states via commercial light bulbs or light emitting diodes (LEDs). With relatively high oxidation [see $E_{1/2}$ (PC^+/PC) and $E_{1/2}$ (PC^*/PC^-)] and reduction [see $E_{1/2}$ (PC^+/PC^*) and $E_{1/2}$ (PC/PC^-)] potentials numerous substrates can be transformed via electron transfer.[9]

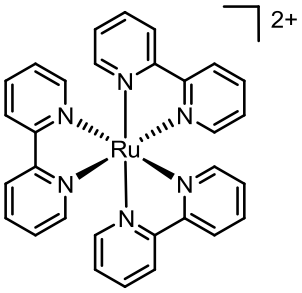
Table 1. Transition metal based photocatalysts $[Ir(ppy)_2(dtb\text{-}bpy)]^+$ (**1**), $Ir(ppy)_3$ (**2**), and $[Ru(bpy)_3]^{2+}$ (**3**) with corresponding photoredox potentials and photophysical properties.



$[Ir(ppy)_2(dtb\text{-}bpy)]^+$ (**1**)



$Ir(ppy)_3$ (**2**)



$[Ru(bpy)_3]^{2+}$ (**3**)

		1	**2**	**3**
Oxidative quenching	$E_{1/2}$ (PC^+/PC^*)	-0.96 V	-1.73 V	-0.81 V
	$E_{1/2}$ (PC^+/PC)	+1.21 V	+0.77 V	+1.29 V
Reductive quenching	$E_{1/2}$ (PC^*/PC^-)	+0.66 V	+0.31 V	+0.77 V
	$E_{1/2}$ (PC/PC^-)	-1.51 V	-2.19 V	-1.33 V
excited state lifetime: τ		0.56 µs	1.9 µs	1.1 µs
absorption wavelength: λ_{abs}		410 nm	375 nm	452 nm
emission wavelength: λ_{em}		581 nm	518 nm	652 nm

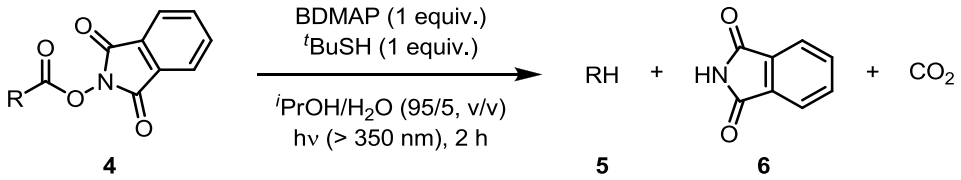
During the last decade a multitude of different chemical transformations were investigated, using the visible light-promoted photoredox catalysis. This elegant and mild radical reaction tool was applied to dehalogenations,[10] deoxygenations,[11] cycloadditions,[12] and atom transfer radical additions (ATRA),[13] to name but a few. Following the photoinduced decarboxylation reactions were discussed in more detail.

2 Decarboxylation of *N*-acyloxyphthalimides

Carboxylic acids are very common in nature and represent a substance class that can be extracted from renewable resources. The possibility to isolate or synthesize a multitude of acids from biomass makes them a group of abundant and inexpensive basic chemicals. For that reason carboxylic acids are widely used in the synthesis of high-value chemical products.[14] Especially the radical decarboxylation is an important tool to generate active intermediates for biological and chemical synthesis. Decarboxylation methods have been under investigation for a fairly long time and many different reactions were established, such as the Hunsdiecker reaction[15] or the Kolbe electrolysis.[16]

With regards to sustainable and "green" chemistry in recent years, more and more visible and UV light-mediated decarboxylation reactions were investigated.[17] One powerful photoinduced method is the Barton decarboxylation.[18] This classical radical reaction was discovered by Prof. D. Barton in 1983. Acids were transferred to the corresponding thiohydroxamate esters, which could be cleaved homolytically by photochemical or thermal conditions. The Barton protocol facilitates the generation of new bonds, such as carbon-carbon, carbon-sulfur, carbon-halogen, or carbon-nitrogen formations, and is still under investigation.[19]

In 1988 Okada *et al.* demonstrated an alternative synthetic tool for decarboxylation. Depending on the thiohydroxamate esters of the Barton decarboxylation, the group of Okada activated the acids with *N*-hydroxyphthalimide (Scheme 5).[20]

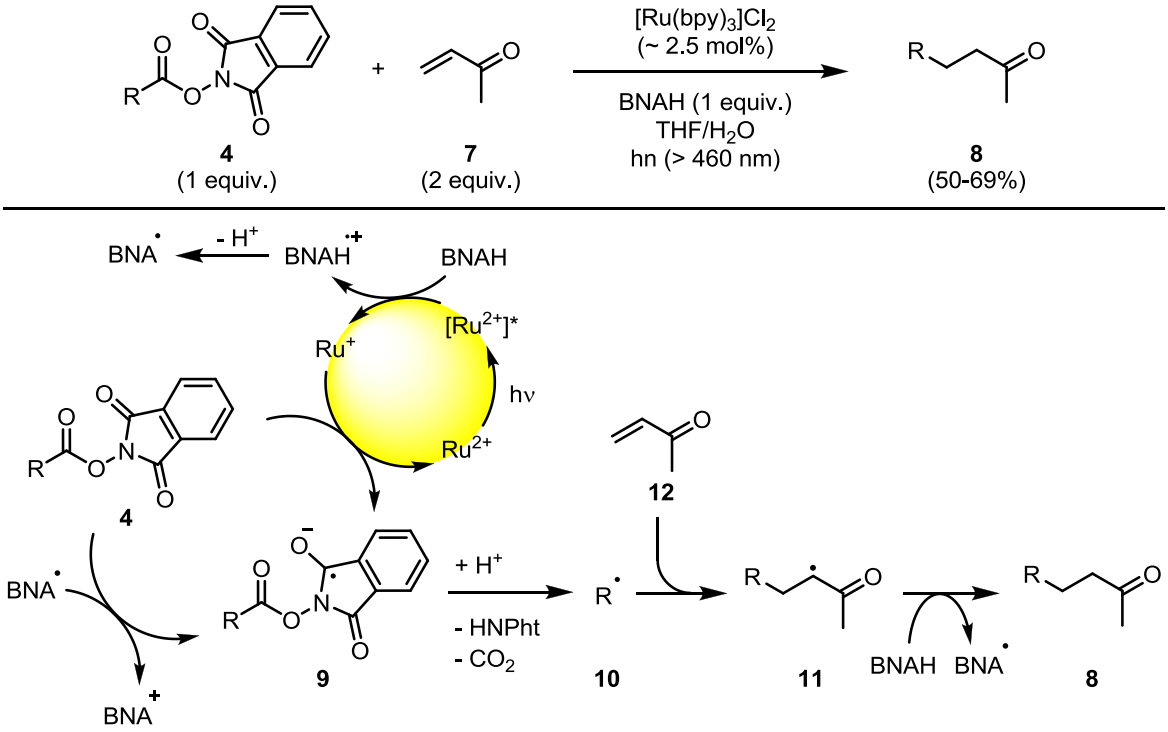


Scheme 5. First photosensitized decarboxylation of *N*-acyloxyphthalimides **l1**.

Reducing the phthalimide moiety of compound **4** via the photoexcited state of 1,6-bis(dimethyl-amino)pyrene (BDMAP) in presence of an aqueous solvent mixture and *tert*-butylthiol the decarboxylated products **5** and phthalimide (**6**) were obtained.

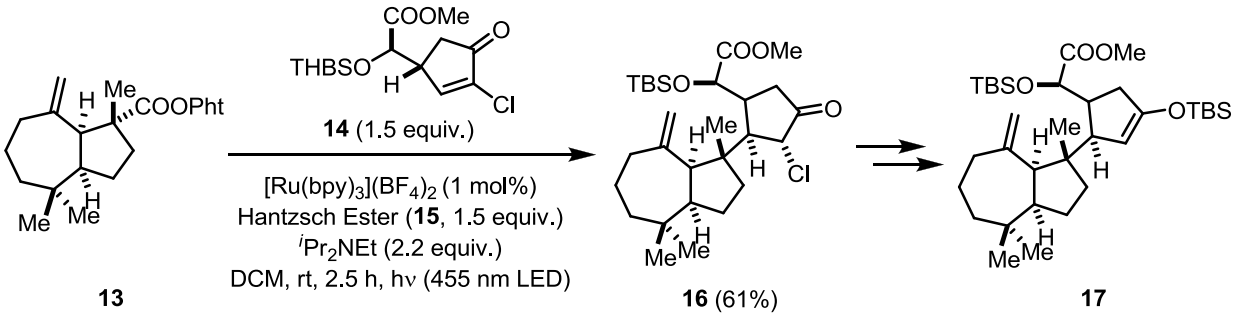
Extending the scope of this project the group investigated a photochemical chlorodecarboxylation of carboxylic acids.[21] *N*-Acyloxyphthalimide was transferred into its excited state via UV-light irradiation of a 100 W high pressure mercury lamp. Triethylendiamine (DABCO) was used as reducing agent for the phthalimide moiety and the obtained radical was trapped by carbon tetrachloride leading to the corresponding chlorides in 56-96% yield.

The application of this new visible light decarboxylation method was once more extended to include a photoredox catalyzed Michael addition (Scheme 6).[22] The excited photocatalyst $[Ru(bpy)_3]Cl_2$ was oxidized by 1-benzyl-1,4-dihydronicotinamide (BNAH) to serve as a reducing agent for phthalimide ester **4**. After phthalimide cleavage and decarboxylation alkyl radical **10** undergoes a Michael addition with methyl vinyl ketone (**12**).



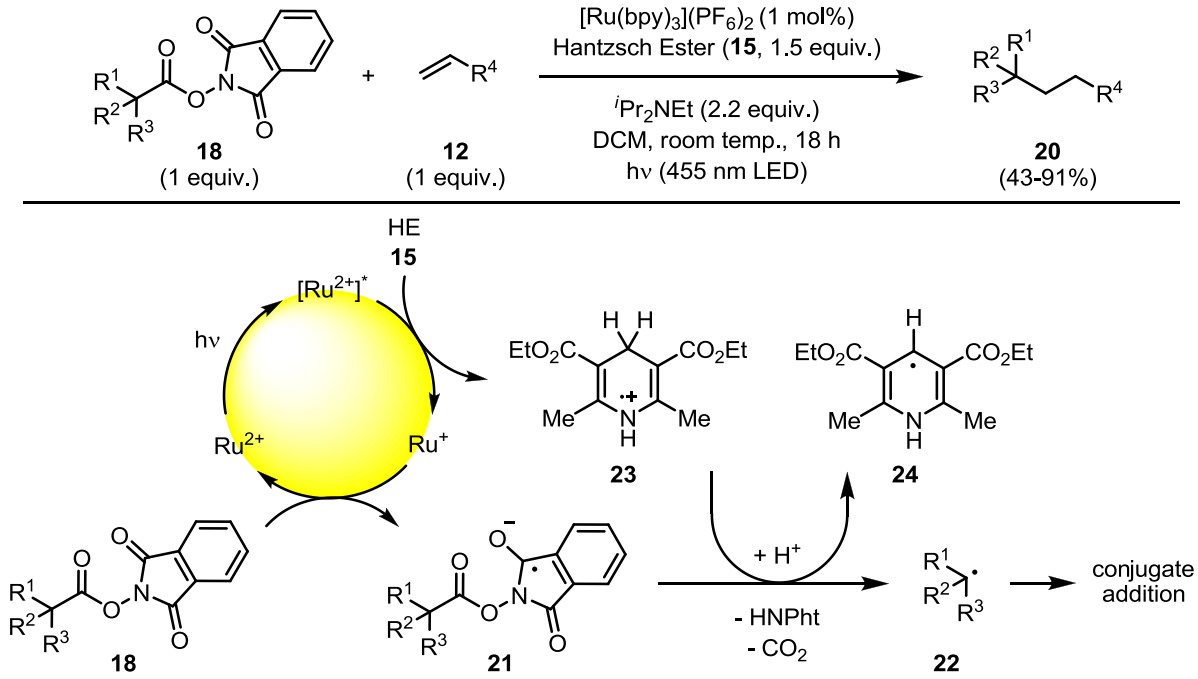
Scheme 6. Visible light decarboxylative Michael addition developed by Okada *et al.*

Taking the prior contributions of Okada and coworkers into account, Overman *et al.* established a slightly modified version of the visible light-mediated decarboxylation as key step for the total synthesis of (-)-aplyviolene (**17**, Scheme 7).[23]



Scheme 7. Visible light-mediated decarboxylation of **13** as a key step in the total synthesis of (-)-aplyviolene (**17**).

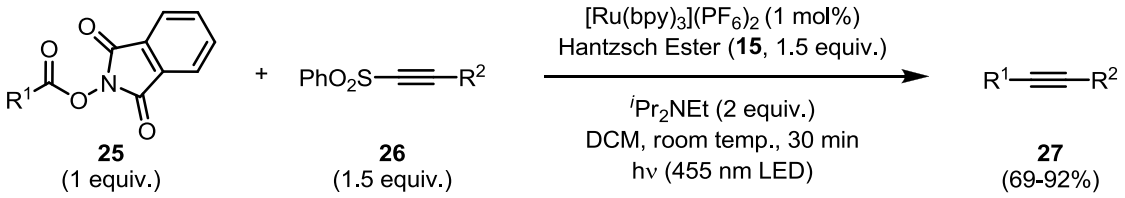
With this successful application the group extended the scope of the fragmentation under mild reaction conditions. Using $[Ru(bpy)_3](PF_6)_2$ as photocatalyst and Hantzsch ester (**15**) as well as *N,N´*-diisopropylethylamine (DIPEA) for sacrificial electron and hydrogen donors, tertiary radicals were generated from *N*-acyloxyphthalimide derivatives **18** (Scheme 8).[24] With this reaction system and the protonation of the reduced phthalimide moiety **21** by Hantzsch ester intermediate **23** the reaction could be performed in absence of water. Obtained radicals **22** are coupled with a variety of alkenes and undergo substitution reactions with allylic and vinylic halides forming new C-C bonds and quaternary carbons. In presence of highly reactive coupling partners the reaction proceeds also in absence of the photocatalyst. In these special cases the reduction of the phthalimide moiety by the photoexcited Hantzsch ester was assumed.



Scheme 8. Photoinduced decarboxylation of tertiary acids based *N*-acyloxyphthalimides **18**.

This modified reaction protocol was the source for several photoinduced decarboxylative coupling reactions. In the latest publication of Overman *et al.*, photodecarboxylation was performed in presence of methyl *N*-phthalimidoyl oxalate, leading to methoxycarbonyl radicals, which subsequently underwent conjugative additions to electron deficient olefins.[25] Fu and coworkers improved the visible light-mediated selenation reaction of Okada and synthesized with *N*-acyloxyphthalimides numerous chiral α-selenoamino acids.[26]

In 2015 Chen *et al.* performed a photoinduced decarboxylative alkynylation reaction using similar reaction conditions to the work of Overman and coworkers (Scheme 9).[27] After visible light-mediated fragmentation of **25**, induced by the photoredox system $[Ru(bpy)_3](PF_6)_2$, DIPEA, and Hantzsch ester, the corresponding primary, secondary, or tertiary alkyl radicals underwent addition to alkynyl sulfone **26**. The sulfone moiety served as leaving group yielding alkyne products **27**.



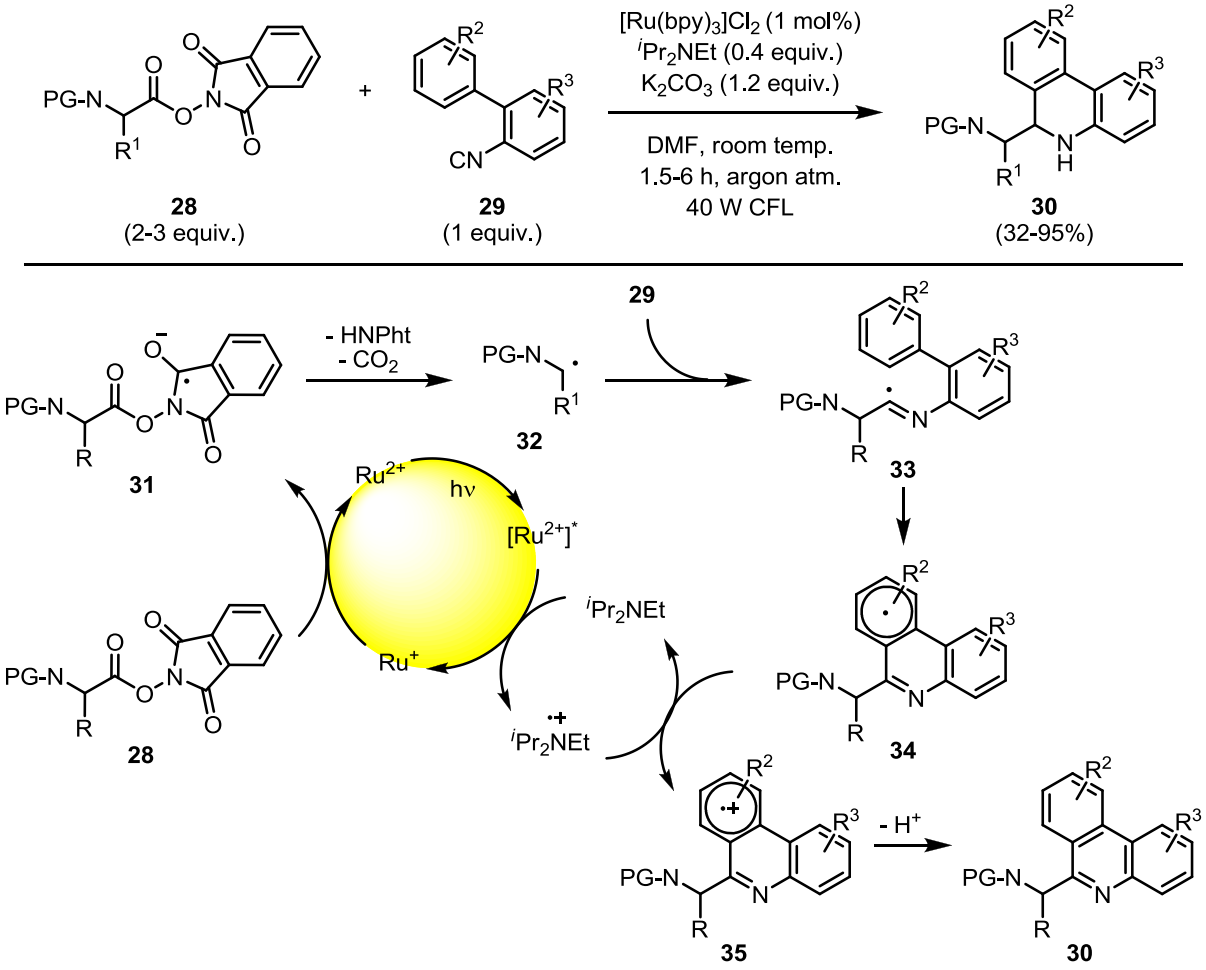
Scheme 9. Photoinduced decarboxylative alkynylation of *N*-acyloxyphthalimides **25**.

Continuing this project Chen and coworkers extended the reaction scope to a decarboxylative allylation using allyl sulfones as coupling reagents.[28]

Recently König *et al.* demonstrated the visible light initiated decarboxylative alkylation of phthalimide ester derivatives using the metal free eosin Y catalyst instead of common metal based photocatalysts, such as $[Ru(bpy)_3]Cl_2$ or $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$.[29]

Fu *et al.* developed an efficient method installing *N*-protected amino acids and peptide residues on *N*-heterocycles (Scheme 10).[30] Phthalimide activated α-amino acids **28** were decarboxylated via photoredox chemistry. Diisopropylethylamine (DIPEA) reduces the excited photocatalyst, which gives an electron to *N*-acyloxyphthalimide **28**. After N-O bond cleavage and decarboxylation, intermediate **32** undergoes a radical addition to substituted 2-isocyanobiphenyl **29**. Intramolecular cyclization of generated imidoyl radical **33** affords intermediate **34**, which regenerates DIPEA via reduction. Rearomatization yields to the desired product **30**. Because of the regeneration of diisopropylethylamine (DIPEA) the

reductive quencher can be added in catalytic amounts (0.4 equiv.). A multitude of α-amino acids were coupled on *N*-heterocycles and phenanthridine as well as oxindole derivatives with biological and pharmaceutical activity were prepared.

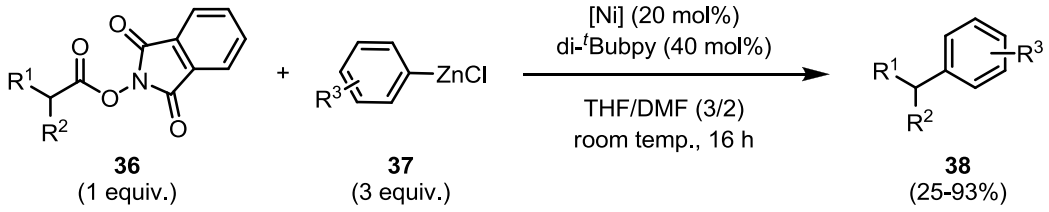


Scheme 10. Photodecarboxylative conjugation of amino acid based *N*-acyloxyphthalimides **28** and phenanthridine derivatives **29**.

Cheng *et al.* demonstrated in a similar mechanism to the reaction of Fu and coworkers (Scheme 10), a tandem radical cyclization of *N*-arylacrylamides to 3,3-dialkyl substituted oxindoles using *N*-acyloxyphthalimides of tertiary acids.[31]

One non-photochemical decarboxylation method with phthalimide ester derivatives was reported by Baran *et al.* (Scheme 11).[32] In contrast to the photoredox reactions, an aryl-Ni(I) complex, which was formed in situ from $NiCl_2 \cdot 6\,H_2O$, 2,2´-bipyridine (bpy), and Ar-ZnCl·LiCl, delivers an electron to the phthalimide ester **36**. After fragmentation and decarboxylation the radical species and phthalimide combine to a Ni(III)-complex, which upon reductive elimination afford the desired coupling product **38**. The Ni-catalyzed

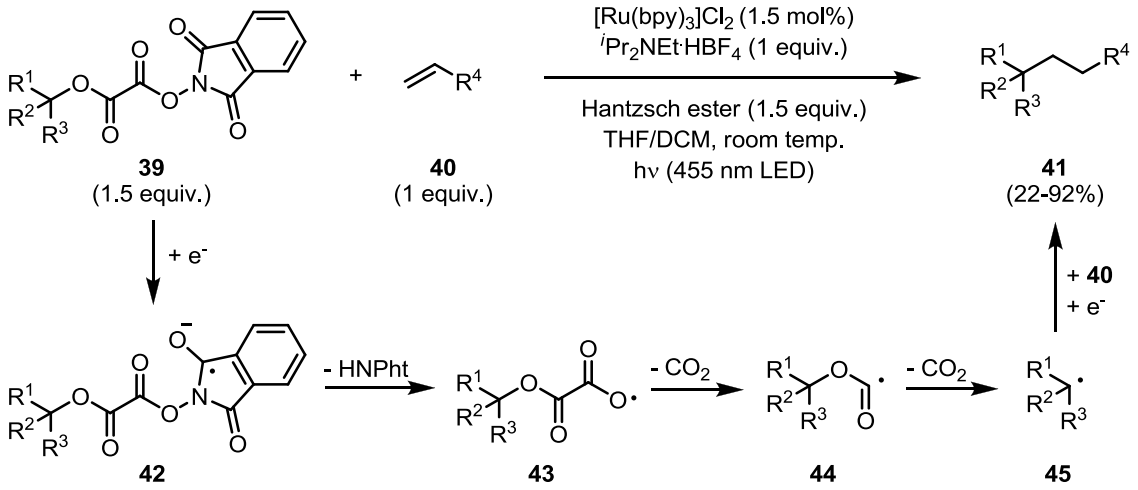
decarboxylative cross-coupling reaction can be performed on gram scale in moderate to very good yields.



Scheme 11. Nickel-catalyzed decarboxylative cross-coupling of *N*-acyloxyphthalimides **36**.

Phthalimide activation was not only used for decarboxylation, but also for deoxygenation reactions. Overman *et al.* established a photoredox-catalyzed fragmentation of *tert*-alkyl-*N*-phthalimidoyl oxalates **39** (Scheme 12).[33] The deoxygenation proceeds the same way as described for the decarboxylation reactions (see Scheme 8). The phthalimide moiety is reduced by the photocatalyst, followed by N-O bond cleavage and decarboxylation. Obtained alkoxycarbonyl radical **44** undergoes a second, slower decarboxylation, which leads to tertiary radical **45**. Addition to electron deficient alkenes **40** provides the products **41**. The decarboxylation of the alkoxycarbonyl radical is only efficient when performed on tertiary alcohols. Methoxycarbonyl radicals for example react almost completely with olefins generating corresponding γ-ketoesters.[25]

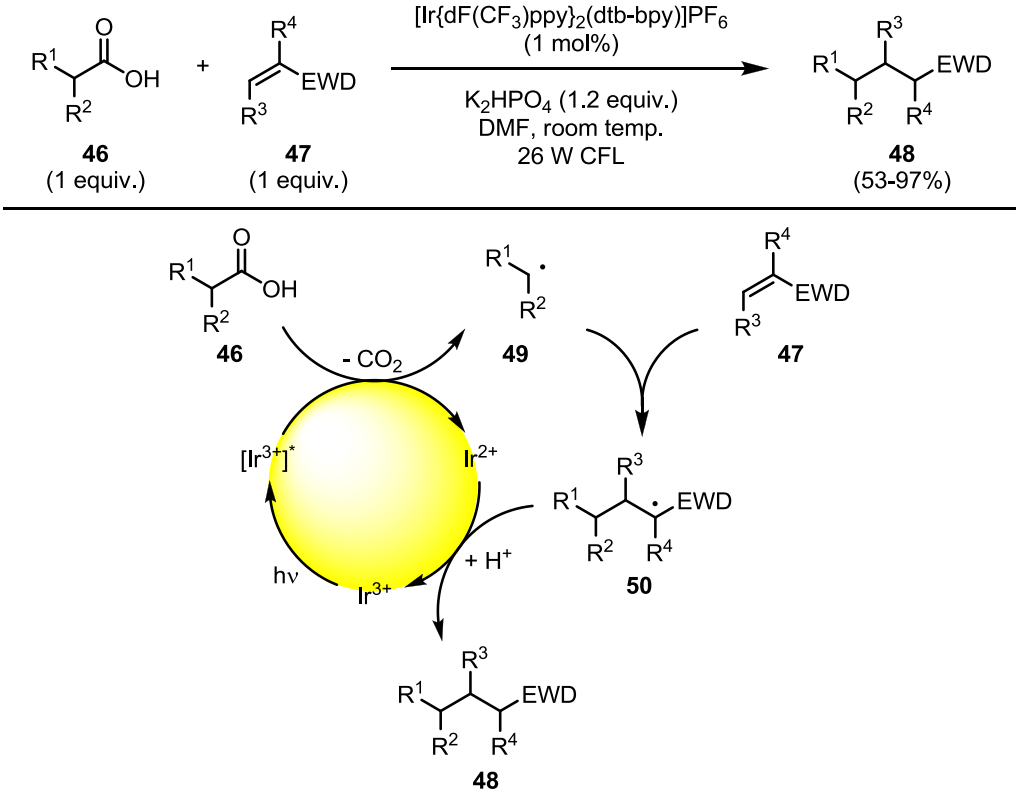
Chen *et al.* applied this photoinduced deoxygenation method for alkynylation reactions of tertiary alcohols with 1-(2-(arylsulfonyl)ethynyl)benzenes.[34]



Scheme 12. Visible light-mediated deoxygenation of *N*-phthalimidoyl oxalates **39**.

N-Phthalimidoyl oxalates **39** are very sensitive because of their instability to aqueous workup or flash chromatography.[33] For that reason Overman and MacMillan *et al.* improved the visible light-mediated deoxygenation by using simple oxalates. In presence of the photocatalyst $[Ir\{dF(CF_3)ppy\}_2(dtb\text{-}bpy)]PF_6$ (1 mol%), a solvent mixture of DME/DMF (3/1), water (10 equiv.) and the base CsF, alkyl radicals from secondary and tertiary alcohols were generated via simple oxalates. With these photoredox conditions no phthalimide activation was necessary and coupling products with Michael acceptors were obtained in 51-93% yield.[35] This concept was based on the prior contributions of MacMillan *et al.* in 2014 to the visible light-mediated decarboxylation.

For this photoinduced decarboxylation method no additional sacrificial electron donor was necessary to decarboxylate simple carboxylic acids (Scheme 13).[36] The excited photocatalyst oxidizes acid **46** in presence of K_2HPO_4 salt. After decarboxylation and conjugate addition to enolate **47**, radical **50** gets reduced to product **48**, while simultaneously regenerating the photocatalyst.



Scheme 13. Visible light-mediated decarboxylative Michael addition of carboxylic acids **46**.

Secondary, tertiary, and stabilized α-amino acids could be decarboxylated and cross coupled with Michael systems. This protocol was applied to various other useful transformations, although reactions with non stabilized primary acids were not successful. The group described a visible light-mediated decarboxylative arylation of α-amino acids with cyanoarenes, yielding benzylic amine structures in good yields.[37] By merging photoredox decarboxylation with nickel catalysis a decarboxylative cross-coupling of carboxylic acids with vinyl and aryl halides was established by MacMillan *et al*.[38]

During the last few years photoredox decarboxylation became a powerful tool for the synthesis of biological attractive molecules and fine chemicals.[39] With energy saving light emitting diodes (LEDs) and compact fluorescent lamps (CFLs) this sustainable and "green" method is under big interest in current research.

3 Photoreaction setup

Photochemistry is classified as a green chemical method. The photons, which initiate photochemical reactions, are regarded as a clean and traceless reagent.[40] With the invention of light-emitting diodes (LEDs) photochemistry became even more energy efficient. Because of narrow emission peaks, LEDs allow the irradiation with a defined wavelength. Depending on the absorption maximum of the catalysts the application of different LEDs, typically blue (λ_{max} = 455 nm) or green light (λ_{max} = 530 nm) leads to optimized excitation. In contrast to fluorescent light bulbs, less energy is wasted.

The widespread used photoreaction setup is build up by an external irradiation system, e.g. a light bulb or LED and the reaction vessel containing the reaction solution.

Dr. Peter Kreitmeier developed an alternative reaction setup in the working group of Prof. O. Reiser. The light of an external LED is guided via an optical fiber directly into the reaction mixture (Figure 1). Regarding external irradiation systems, this setup minimizes light scattering at the reaction vessel and guarantee optimal irradiation. In addition the light source is on top of the solution, whereby the solvent is not heated by the LED. Therefore temperature control, with heating and cooling, is easy to handle, without special precautions for the light source by using an oil- or ice bath.

All upcoming visible light-mediated photoreactions in this thesis were performed with this reaction setup unless noted in a different way.

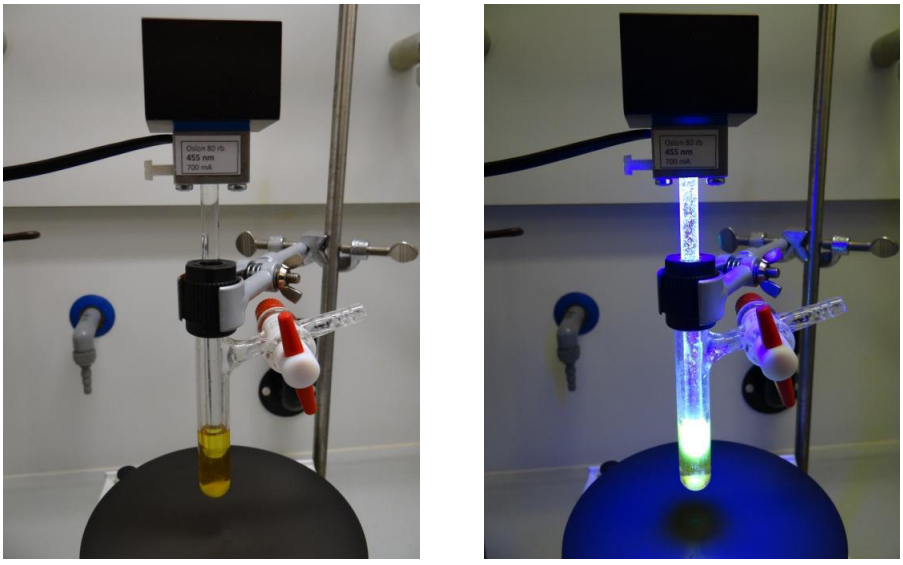


Figure 1. Irradiation system developed by Dr. Peter Kreitmeier. Blue light (λ_{max} = 455 nm) is channeled through a glass rod into the reaction mixture.

4 References

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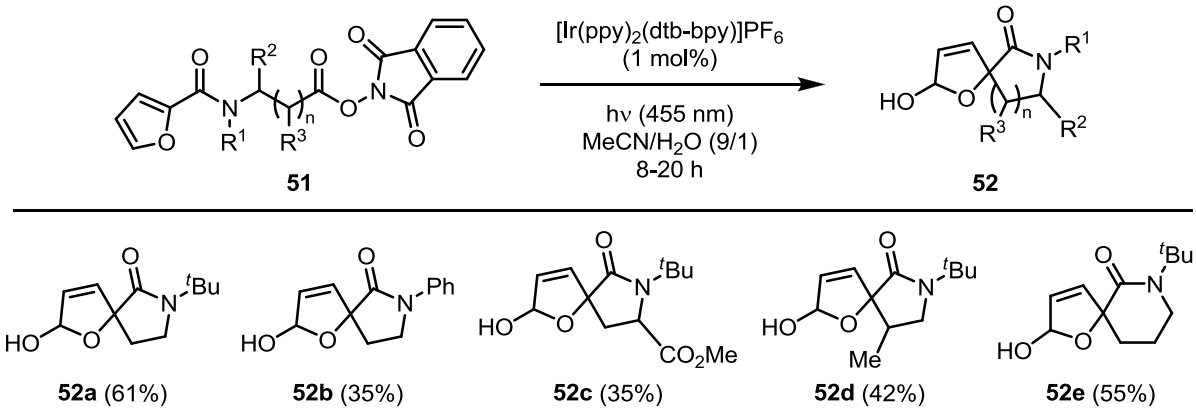
B Photoinduced Decarboxylation

1 Decarboxylation of ω-aryl-*N*-acyloxyphthalimides

1.1 Preliminary studies[a]

As previously shown in my master thesis, visible light mediated decarboxylation of phthalimide activated acids was used to develop an intramolecular spirocyclization prozess. Based on renewable resources, using furans and amino acids in the starting material synthesis, decarboxylation enables the formation of numerous spirolactames **52**.[41] The reaction tolerates a broad range of different substituents (Scheme 14). The driving force of this work was to develop a "green" approach to intermediates of relevance for fine chemicals or natural products.[41,42]

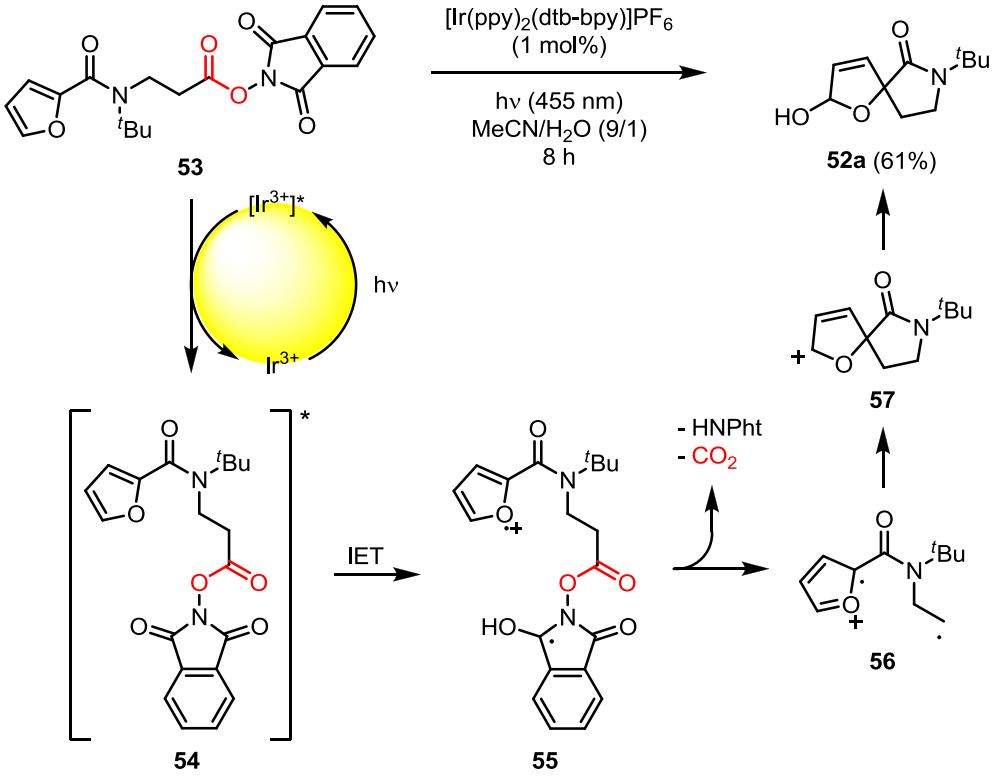


Scheme 14. Visible light mediated synthesis of spirolactame derivatives **52**.[41]

In contrast to preceding phthalimide assisted decarboxylations, where the phthalimide moiety was reduced directly by the photocatalyst, a sensitization mechanism was proposed for this reaction. The reducing power of the excited iridium based catalyst ($[Ir^{3+}]^* \rightarrow Ir^{4+}$ = -0.96 V *vs.* SCE)[43] is out of range of substrate **51** (-1.25 V *vs.* SCE). Therefore the oxidative quenching cycle is not possible. $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ serves as a sensitizer, transferring energy to the *N*-acyloxyphthalimide **51**. The excited molecule **54** undergoes an intramolecular electron transfer, which leads to the reduction of the phthalimide. Releasing phthalimide and carbon

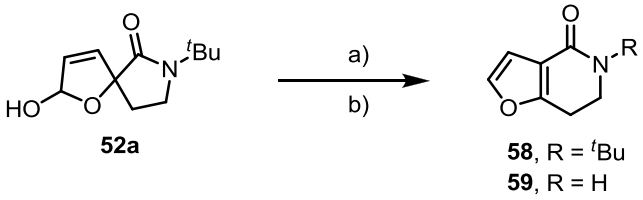
[a] This Chapter is mainly based on the results of my master thesis and Kachkovskyi, G.; Faderl, C.; Reiser, O.

dioxide, the alkyl radical **56** cyclizes in a 5-*exo*-trig manner, forming the spirocation **57** (Scheme 15).



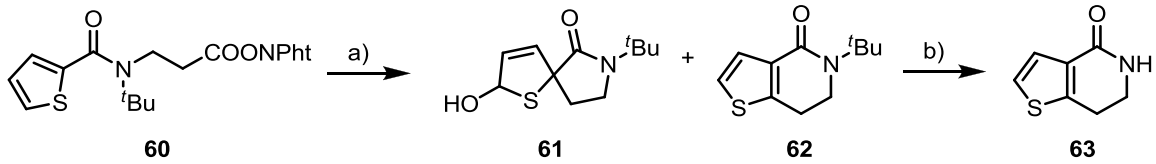
Scheme 15. Proposed sensitization mechanism.[41]

The field of application for spirolactame product **52a** was extended, using a vinylogous semipinacol rearrangement to get the more stable compounds **58** or **59**.[44] Treating lactame **52a** with TFA initiates a cleavage of the hydroxyl group. Subsequently the acyl moiety undergoes a 1,2-shift with a concurrent rearomatization of the furan group.[45] Depending on the solvent, the *N*-*tert*-butyl group was cleaved using neat TFA leading to product **59** or product **58** was obtained using a 0.2 M TFA in dichloromethane solvent (Scheme 16).



Scheme 16. Vinylogous semipinacol rearrangement of **52a**. a) 0.2 M TFA in DCM, rt, 48 h → **58** (85%). b) TFA (neat), room temp., 16 h → **59** (97%).

Replacing furan with thiophene the formation of an inseparable mixture of **61** and **62** was observed, after irradiation under standard photosensitization reaction conditions (Scheme 17). The thiophene moiety of compound **60** has a slightly different electron density than furan based *N*-acyloxyphthalimide **53**, whereby thienopyridinone **62** was formed simultaneously to **61**. Treating the crude product mixture with neat TFA the inseparable products were converted into compound **63** in overall yield of 45%



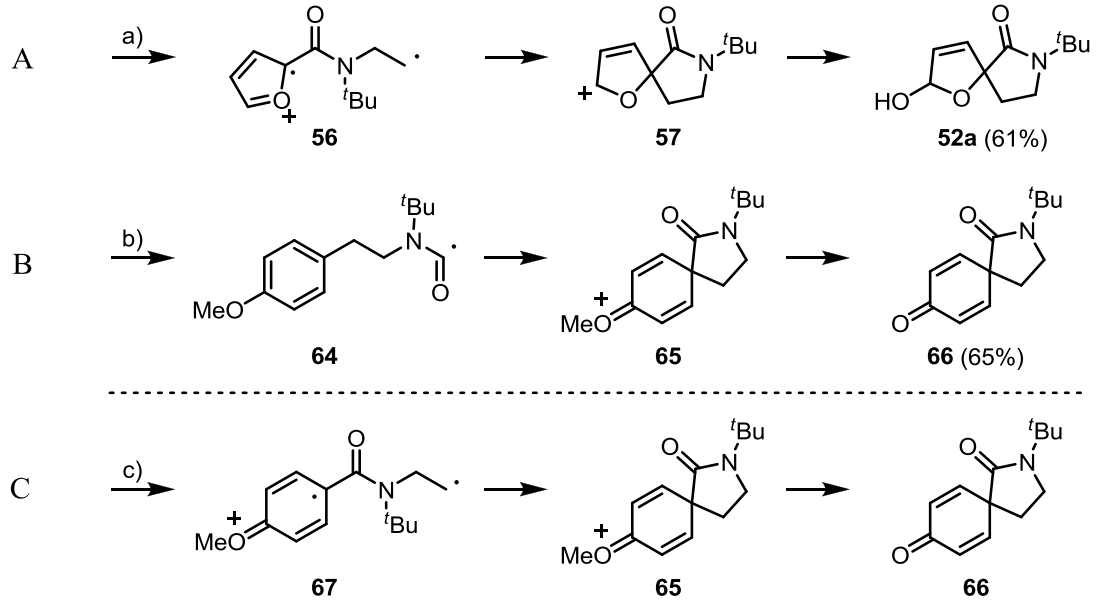
60 **61** **62** **63**

Scheme 17. Photoreaction of thiophene based *N*-acyloxyphthalimide **60**. a) $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), MeCN/H_2O (40/1, c = 0.1 mol/l), hν (455 nm LED), room temp., 16 h. b) TFA, room temp., 12 h. Overall yield: 45%.

1.2 Initial synthetic aim

After establishing the photodecarboxylation of *N*-acyloxyphthalimides with furan moieties, the work was continued employing phenyl rings as core structures. The aim of this continuative project was to yield spirodienonamides **66** by a similar cyclization reaction.

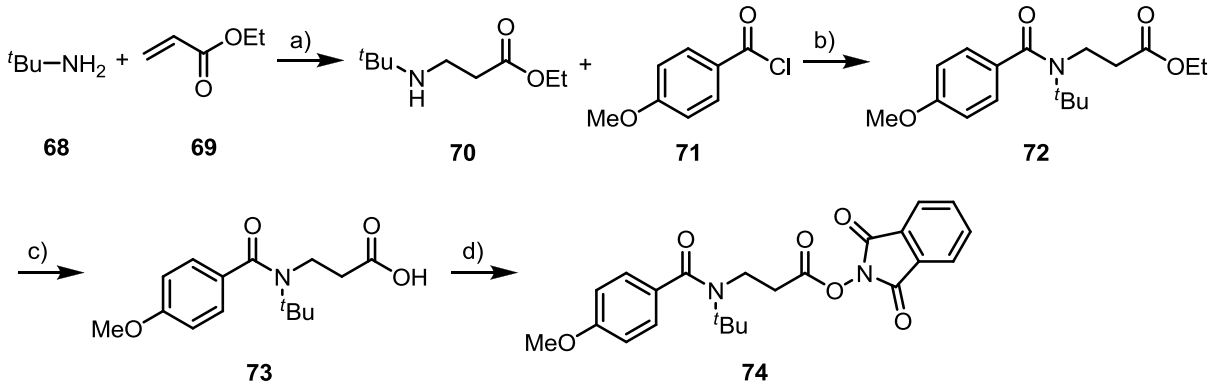
Recently Miranda *et al.* reported the synthesis of spirodienonamides **66** via a radical based dearomatizing spiroacylation process (Scheme 18, B).[46] The carbamoyl radical **64** was obtained using the corresponding carbamoylxanthate and triethylborane to initiate the radical formation. After spirocyclization and oxidation the desired spirointermediate **65** was formed, leading to product **66**. The starting material synthesis requires expensive and, because of their biological activity, strictly controlled phenylethylamines[47] and the very toxic triphosgene. Another disadvantage is the starting carbamoylxanthate itself, which is very temperature sensitive and unstable.[46] Regarding the established photoinduced decarboxylation method, changing the furan moiety to phenyl rings, intermediate **67** should form after the decarboxylation step (Scheme 18, C). The spirocyclization could lead to the same intermediate **65**, which was described by Miranda *et al.* and the product formation could be possible.



Scheme 18. Abstract of proposed radical mechanisms. **A:** Photodecarboxylation of furan based *N*-acyloxyphthalimides. a) MeCN/H_2O (9/1), $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), hν (455 nm), room temp., 8 h.[41] **B:** Radical based spiroacylation by Miranda *et al.* b) DCM, 0.5 equiv. Et_3B, -5 °C, 2.6 h.[46] **C:** Proposed mechanism of a photodecarboxylation of phenyl based *N*-acyloxyphthalimides.

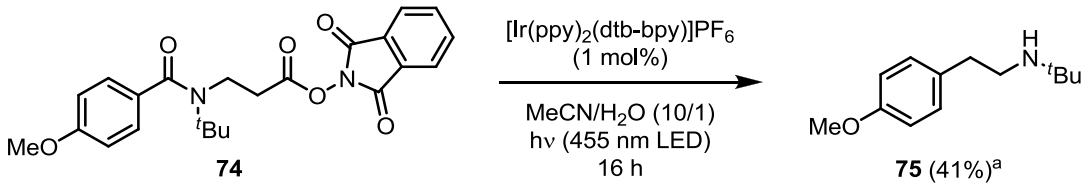
1.3 Starting material synthesis and first reaction attempts

N-acyloxyphthalimide **74** was synthesized as a model compound in four steps from cheap and easy available chemicals. The nucleophilic addition of *tert*-butylamine (**68**) and ethyl acrylate (**69**) and the following amide synthesis with benzoyl chloride **71**, as well as the hydrolysis were performed in nearly quantitative yields. The last coupling step with *N*-hydroxyphthalimide results in ω-aryl-*N*-acyloxyphthalimide **74**. Relating to the carbamoylxanthate starting materials described above, the big advantage of the phthalimide activated acid **74** is its stability. It can be stored at room temperature, on air and light for more than four years (Scheme 19).



Scheme 19. Starting material synthesis. a) EtOH, 0°C, overnight (97%). b) NEt_3 (1.1 equiv.), 0 °C-22 °C, DCM, 15 h (90%). c) EtOH, H_2O, KOH (1.1 equiv.), room temp., overnight (98%). d) THF, *N*-hydroxyphthalimide (1 equiv.), DCC (1 equiv.), room temp., 15 h (43%).

The model substrate **74** was applied to the earlier established reaction conditions. By irradiation of an aqueous acetonitrile solution containing *N*-acyloxyphthalimide **74**, via a blue light-emitting diode (LED, $\lambda_{max} = 455$ nm), in the presence of catalytic amounts of $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%) phenylethylamine derivative **75** was obtained (Scheme 20).



Scheme 20. Photoinduced decarboxylation of ω-aryl-*N*-acyloxypthalimide **74**. [a] Yield was determined by NMR analysis with 4-nitrobenzaldehyde as internal standard.

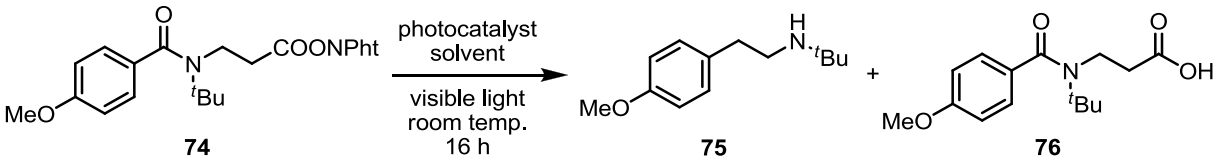
The synthesis of spirodienamides was not successful via this photochemical route. Instead, a new photochemical access to β-phenylethylamines via a smiles-type rearrangement was discovered. In this "green" photochemical reaction cheap and easy available substrates were transferred into phenylethylamine derivatives, which represent a comprehensive class of biological active compounds. Concerning atom efficiency of this reaction, 95% of the released phthalimide could be recovered, whereas only two carbon dioxides were lost in this reaction.

1.4 β-Phenylethylamine synthesis

1.4.1 Optimization and control experiments

Former studies and publications claim the necessity of water for this type of decarboxylation.[41,48] The phthalimide moiety is dependent on protonation, which allows the release of phthalimide followed by the decarboxylation. After a control experiment with pure acetonitrile as solvent, only traces of products were observable which consequently demonstrates the dependence on water (entry 1). During the reaction a substantial amount of acid (**76**) is formed as a side product. An explanation for the acid formation is simple hydrolysis and a redox fragmentation first described by Sammis *et al.* by irradiation of *N*-alkoxyphthalimides.[49]

Table 2. Solvent and catalyst dependence of the decarboxylation reaction.



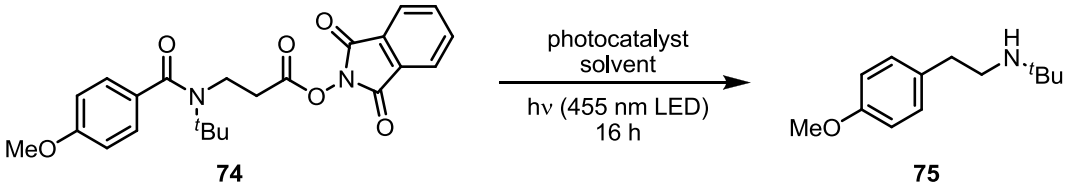
Entry	Catalyst (1 mol%)	Solvent[a]	Solvent/water ratio	Yield **2a**[b]
1	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	MeCN	-	Traces
2	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	$MeCN/H_2O$	10/1	41%
3	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	$MeCN/H_2O$	20/1	42%
4	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	$MeCN/H_2O$	30/1	51%
5	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	$MeCN/H_2O$	40/1	58%
6	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	$MeCN/H_2O$	50/1	48%
7	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	THF/H_2O	40/1	50%
8	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	$Acetone/H_2O$	40/1	49%
9	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	DMF/H_2O	40/1	41%
10	$[Ru(bpy)_3]Cl_2$	$MeCN/H_2O$	40/1	0%
11	$[Cu(dap)_2]Cl$	$MeCN/H_2O$	40/1	50%
12	$[Ir\{dF(CF_3)ppy\}_2(dtb\text{-}bpy)]PF_6$	$MeCN/H_2O$	40/1	0%
13	Perylene[c]	$MeCN/H_2O$	40/1	0%

[a] reaction concentration 0.1 mol/l. [b] yields were determined by NMR analysis with 4-nitrobenzaldehyde as internal standard. [c] 0.5 equiv.

The acid formation is correlated to the ratio of water. Therefore the amount of water was lowered in order to reduce the hydrolysis side reaction (Table 2; entry 2-6). The best results were achieved in an acetonitrile/water mixture of 40/1 in a 0.1 M concentrated solution, adding up to 13.5 equiv. of water (entry 5).

To optimize the reaction conditions, different solvent mixtures were screened. Changing acetonitrile to THF, acetone or DMF shows slight decreasing in the yield of β-phenylethylamine (entry 7-9). Afterwards different photocatalysts were screened. Instead of $[Cu(dap)_2]Cl$, which 50% of the β-phenylethylamine **75** was detected, the metal based photocatalysts $[Ru(bpy)_3]Cl_2$ and $[Ir\{dF(CF_3)ppy\}_2(dtb\text{-}bpy)]PF_6$ show no product formation. Also the reaction with the organic dye perylene showed no conversion after 16 h of irradiation (entry 10-13).

Table 3. Control experiments of the decarboxylation reaction.



Entry	Catalyst (1 mol%)	Solvent[a]	Modifications	Yield
1	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	$MeCN/H_2O$ (40/1)	40 °C	40%[b]
2	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	$MeCN/H_2O$ (40/1)	80 °C	17%[b]
3	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	$MeCN/H_2O$ (40/1)	no degassing	0%
4	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	$MeCN/H_2O$ (40/1)	no light	0%
5	-	$MeCN/H_2O$ (40/1)	no catalyst	0%

[a] reaction concentration 0.1 mol/l. [b] yields were determined by NMR analysis with 4-nitrobenz-aldehyde as internal standard.

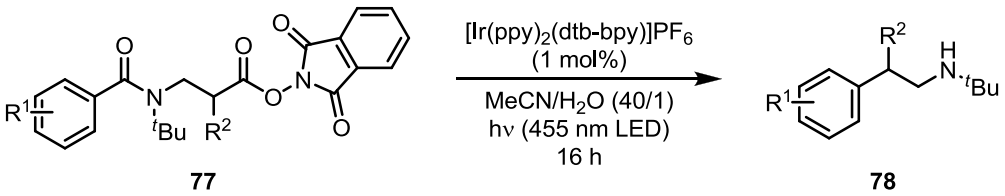
Increasing the reaction temperature to 40 °C and 80 °C leads to decreasing yields and only 40% and 17% of β-phenylethylamine **75** were obtained (Table 3, entry 1 and 2).

Further control experiments proofed, that this decarboxylation is a photoinduced process. Without removing the oxygen from the reaction, which also quenches the excited state of $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$, no β-phenylethylamine **75** could be detected (entry 3). The same result was found in the absence of light or photocatalyst (entry 4 and 5).

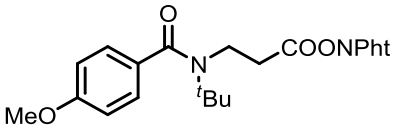
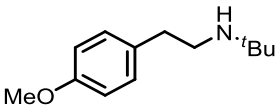
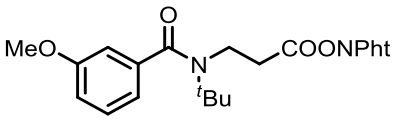
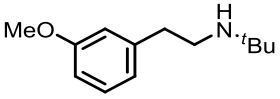
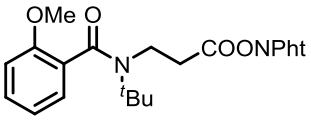
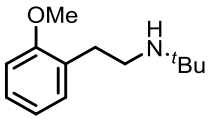
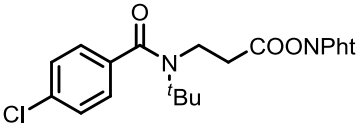
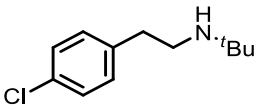
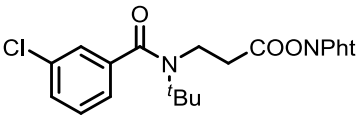
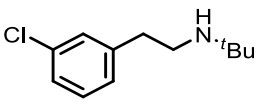
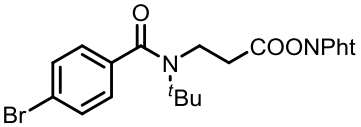
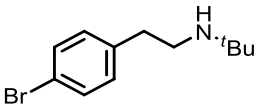
1.4.2 Substrate scope

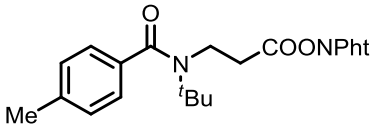
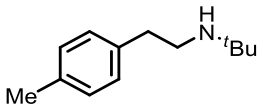
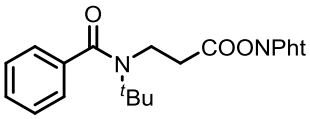
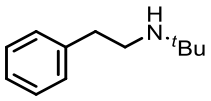
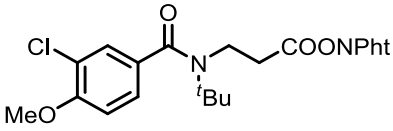
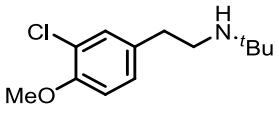
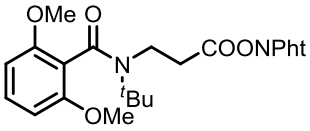
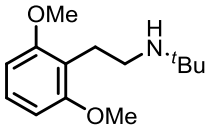
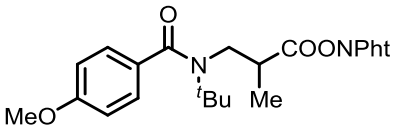
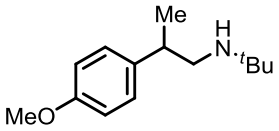
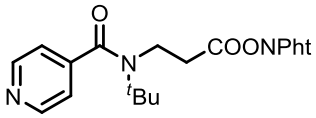
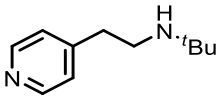
With the optimized conditions in hand, the scope of the decarboxylation/rearrangement reaction was evaluated (Table 4). The introduction of electron donating substituents, like methoxy- (entry 1-3) or halogenated-groups (entry 4-6), into the phenyl moiety was well tolerated and an array of different β-phenylethylamines **77** in good to moderate yields was obtained. *Para*-substituated compounds were most effective (entry 1,4,6,7), but *meta*- and *ortho*-substituents were tolerated as well (entry 2,3,5). However, decreasing the electron density of the phenyl ring led to a drastic drop in yield. Unsubstituted product **78h** was obtained in 29%, whereas the formation of **78l**, bearing electron deficient pyridine ring, was not possible. In the latter case only the corresponding acid was formed (entry 12).

Table 4. Scope of the β-phenylethylamine synthesis.

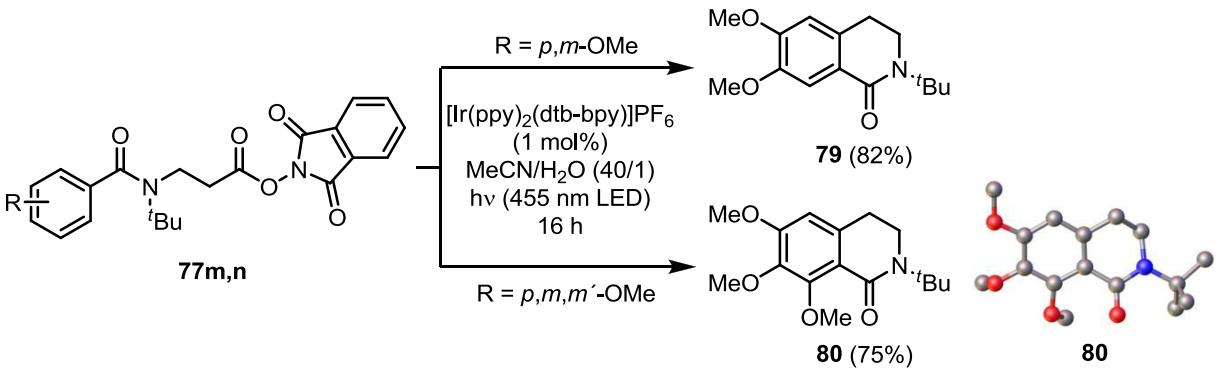


77 **78**

Entry	Substrate		Product		Yield
1		**77a**		**78a**	61%
2		**77b**		**78b**	33%
3		**77c**		**78c**	43%
4		**77d**		**78d**	45%
5		**77e**		**78e**	21%
6		**77f**		**78f**	49%

Entry	Substrate		Product		Yield
7		**77g**		**78g**	45%
8		**77h**		**78h**	29%
9		**77i**		**78i**	53%
10		**77j**		**78j**	38%
11		**77k**		**78k**	53%
12		**77l**		**78l**	0%

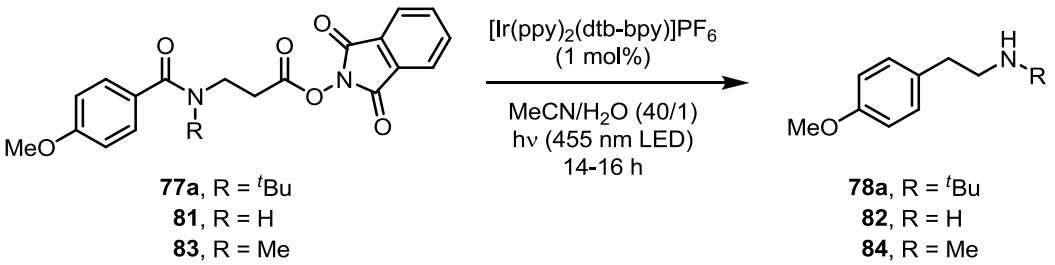
Interestingly, a further increase of the electron density via the introduction of two (**77m**) or even three (**77n**) methoxy groups led to the exclusive formation of dihydroisoquinolinones **79** and **80** in very good yields (Scheme 21). These products derive from the 1,2-acyl shift of the spiroradical intermediate. This 1,2-acyl shift was observed already in the further transformations of spirolactame product **52a** (Scheme 16, Section 1.1). Surprisingly the disubstituted *N*-acyloxyphthalimide **77i** does not form its dihydroisoquinolinone derivative (Table 4, entry 9). The chlorine substituent, which replaces one methoxy group, has a different influence on the phenyl ring, leading to β-phenylethylamine **78i**. Introducing two methoxy-groups in *ortho*-position, the rearrangement forming dihydroisoquinolinone is blocked (entry 10). In this case the transformation continuous towards the phenylethylamine product **78j**.



Scheme 21. Decarboxylation and rearrangement reaction of *N*-acyloxyphthalimide **77m** and **77n** with the crystal structure of the product **80**.

Until now the scope of the reaction was limited to the *N*-*tert*-butyl group, because of the starting material synthesis. Replacing this functional group with a methyl group would lead to an easy access to *N*-methylphenylethylamine derivatives. To test the group tolerance, *N*-hydrogen and *N*-methyl substituted *N*-acyloxyphthalimides were synthesized from β-alanine and ethyl 3-(methylamino)propanoate, following starting material synthesis protocol (Scheme 19, Section 1.3). Performing the reaction, employing the optimized conditions using 1 mol% $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$, a $MeCN/H_2O$ solvent mixture and a blue light emitting diode (λ_{max} = 455 nm), no product formation for the hydrogen- and methyl-substituted compounds was observed within 14-16 h (Table 5, entry 2,3). Although the product formation decreases at higher temperatures (Table 3, Section 1.4.1) this could lead to faster rotations and movements of the molecules. Unfortunately increasing the reaction temperature to 40 °C and 80 °C, there was still no *N*-methyl-β-phenylethylamine (**84**) formation (entry 4 and 5).

Table 5. Effect of *N*-protecting groups on the photoinduced decarboxylation.



Entry	R	Temperature	Yield
1	*tert*-Butyl	25 °C	61%
2	H	25 °C	0%
3	Me	25 °C	0%
4	Me	40 °C	0%
5	Me	80 °C	0%

The substitution pattern on the nitrogen plays a crucial role in the decarboxylation process. The sterical demanding *tert*-butyl group and the whole conformation of the ω-aryl-*N*-acyloxyphthalimide subjected to the Thorpe-Ingold effect.[50] Without the bulky *N*-substituent the molecule engages an unfavorable conformation for the reaction. Therefore an intramolecular decarboxylation process is obvious (see mechanistic discussion: Section 1.4.5).

1.4.3 Carbamate synthesis

A slight change in the reaction conditions leads to the formation of different products. By substitution water with alcohols corresponding carbamates were isolated (Figure 2). In the same way as water did before, the alcohols promote the protonation of the phthalimide moiety, which initiates the reaction. Subsequently the reaction intermediate is trapped by the alcohols forming carbamates **85**. The carbamates were efficiently synthesized using primary (methanol, ethanol, benzyl aclcohol), secondary (2-propanol) and tertiary (*tert*-butanol) alcohols. With the exception of the sterical demanding *tert*-butanol (**85c**, **85g**), the carbamates were isolated in good to fair yields.

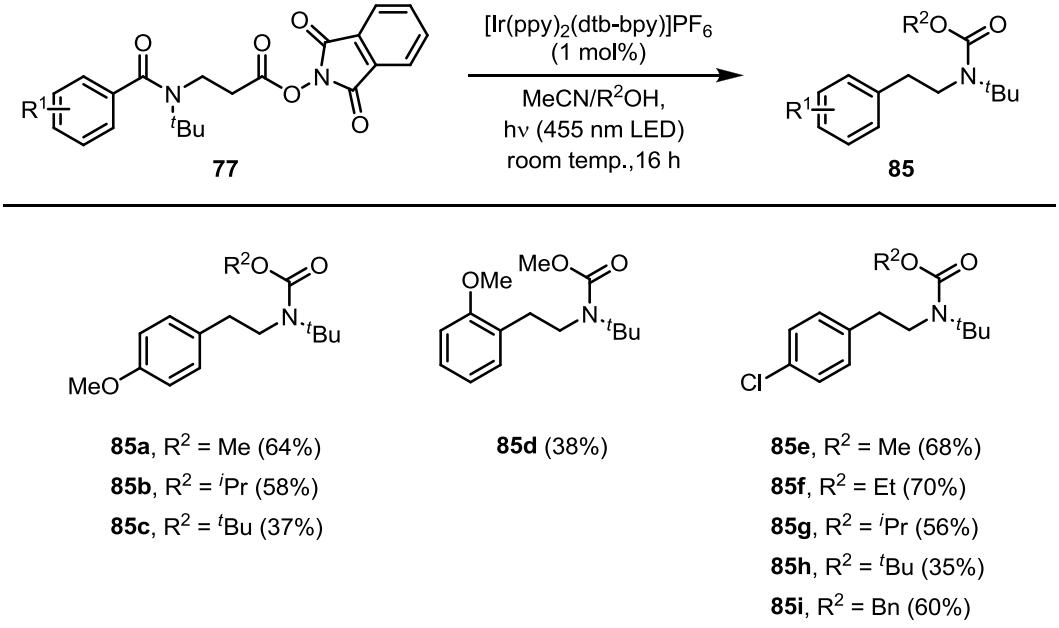
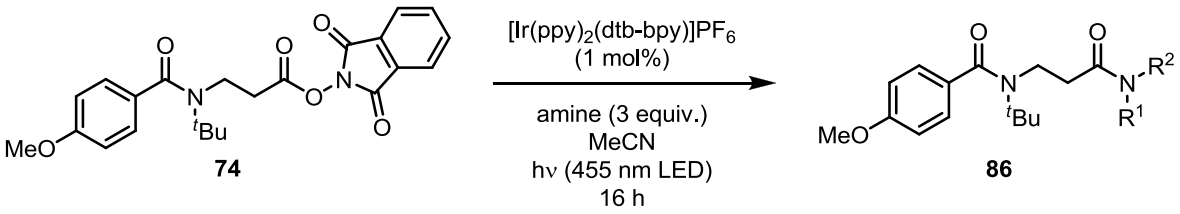


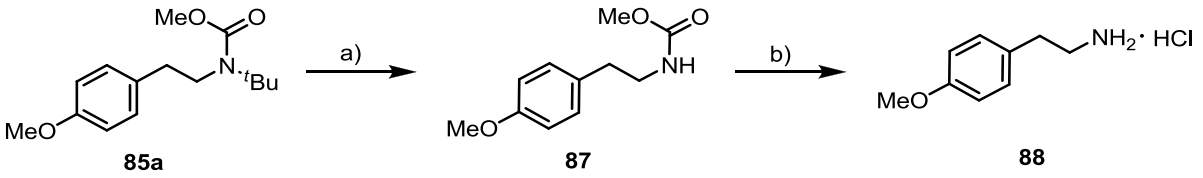
Figure 2. Photoinduced carbamate **85** synthesis.

Following the carbamate protocol, other additives were investigated in this reaction. Primary and secondary amines, as well as thiols can serve as hydrogen donors and nucleophiles simultaneously. Unfortunately applying benzylamine or 2-aminopropane, in order to synthesize carbamides, only hydrolysis occurs and the simple amide products **86a** were isolated (Scheme 22).[51] Using thiols in this reaction, only complex reaction mixtures were observed and no desired carbothioate product could be isolated.



Scheme 22. Transformation of *N*-acyloxyphthalimide **74** in presence of different amines. **86a**: R^1 = H, R^2 = ^{i}Pr (91%). **86b**: R^1 = R^2 = CH_3 (92%). **86c**: R^1 = H, R^2 = benzyl (90%)

As described previously, the *N-tert*-butyl group is responsible for the product formation (Table 5). Due to the carbamate synthesis this group can be seen as a typical protecting group. The *tert*-butyl moiety was easily cleaved from carbamate **85a** under mild conditions receiving the non-substituted carbamate **87** in quantitative yields (Scheme 23). In a further transformation it is possible to cleave of the carboxylate yielding the primary amine **88**.[52] Despite the required *tert*-butyl group the carbamate synthesis enables the generation of "free" β-phenylethylamines. Based on cheap and easy available starting materials and using a "green" photodecarboxylation process it is possible to extend the reaction scope from already shown *N-tert*-butyl β-phenylethylamines **78** and the corresponding carbamates **85** to *N*-substitution free β-phenylethylamines.

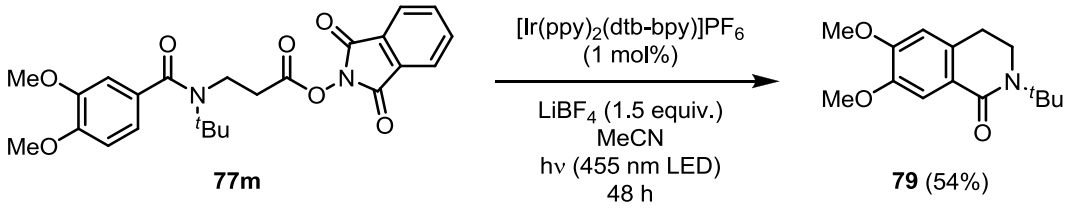


Scheme 23. Deprotaction of carbamate **85a** and further transformation, yielding β-phenylethyl-amine **88**. a) TFA, room temp., 15 h (97%). b) 2 M LiOH, THF, MeOH, Microwave, 120 °C, 10 min (88%).

1.4.4 Reaction improvements

To stabilize of the phthalimide during the decarboxylation reaction, water or alcohols were used yet. Sammis *et al.* avoided these proton sources in their study about photoinduced redox fragmentation of *N*-alkoxyphthalimides.[49] Instead they added $LiBF_4$ to the reactions, without going into detail about the effect of the lewis acid.

Using more water in the decarboxylation reaction leads to an increased formation of acid **76** side product. In order to decrease the side reaction and increasing the yield, lewis acids have been investigated to replace water. The photoreaction of the phthalimide ester **77m** needs water solely for the protonation of the phthalimide species and not as a nucleophile, like in the reactions yielding β-phenylethylamines. Therefore ω-aryl-*N*-acyloxyphthalimide **77m** was used in a test reaction. The irradiation, in presence of the photocatalyst $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$, water free acetonitrile and 1.5 equivalents of $LiBF_4$, took about 48 h until full conversion and 54% dihydroisoquinolinone **79** was isolated. The lewis acid $LiBF_4$ can therefore be used to stabilize the phthalimide moiety in this reaction, but compared to water (16 h, 82% yield) the reaction time is more than doubled and the yield is lower (Scheme 24).

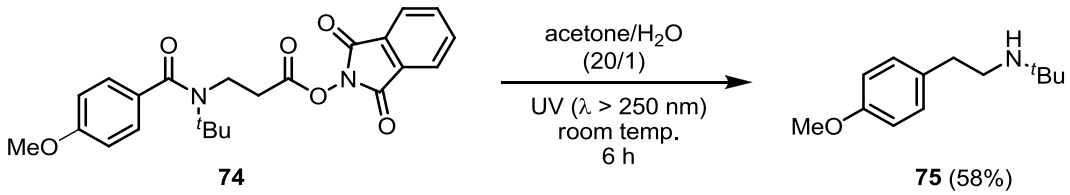


Scheme 24. Photoinduced decarboxylation using $LiBF_4$.

Common photoredox systems are based on electron transfer mechanisms of the excited photocatalysts. Also the former discussed visible light mediated decarboxylations of *N*-acyloxyphthalimides are based on the reduction of the phthalimide moiety by photocatalysts. The catalysts were regenerated by sacrificial electron donors or by further reacted substrates, mostly in consequence of Michael-additions. Using UV-light irradiation to decarboxylate *N*-acyloxyphthalimides, catalysts, which absorb the UV-light and reduce the phthalimide, were applied. For such UV supported decarboxylation reactions only two reports were published yet,[48a,b] although UV-photoreactions of phthalimide groups in general are well-known.[53]

In the developed decarboxylation reaction of ω–aryl-*N*-acyloxyphthalimides no additional compound, than the photocatalyst and the solvent, was used. In order to investigate the

function of the $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ and clarify the mechanism, one UV reaction was performed (Scheme 25).



Scheme 25. UV-mediated decarboxylation of ω-aryl-*N*-acyloxyphthalimide **75**.

The model compound **74** was diluted in acetone/water solvent mixture, degassed and irradiated at room temperature via high pressure mercury lamp. Acetone is known to be a good sensitizer in UV reactions.[54] After 6 h full conversion of the starting material was determined and 58% β-phenylethylamine derivative could be isolated. Either the UV light excites the acetone, which gives the energy to the *N*-acyloxyphthalimide **74**, or the phthalimide ester **74** is excited directly. Therefore the reaction is not dependent on the redox cycle of the photocatalyst.

1.4.5 Mechanistic considerations

Based on these results, a plausible mechanism for this decarboxylation and rearrangement reaction was proposed. The key step of this reaction is the reduction of the phthalimide moiety. The reduction potential of *N*-acyloxyphthalimide **74** was determined as -1.32 V versus SCE by CV in acetonitrile and is thermodynamically incompatible for photoredox reactions with the used $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ catalyst ($[Ir^{3+}]^* \rightarrow Ir^{4+}$ = -0.96 V vs SCE).[43] Because of the absence of a sacrificial electron donor, which could act as a reductant for the catalyst, the reductive quenching cycle of the photocatalyst was excluded. Additionally, direct UV-light irradiation of the phthalimide moiety, in absence of any catalyst, leads to product formation, therefore an alternative function for the iridium based catalyst as a sensitizer was assumed. Accordingly, the excited photocatalyst $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ transfers energy (ET) to the *N*-acyloxyphthalimide **90**. Calculations from the Schütz group of the analytic energy gradients for the ground and excited states in this system suggest the assumption that the excited phthalimide species **91** is protonated.[55] An intramolecular electron transfer (IET) of the S_1 and T_1 states of the protonated molecule **89** from the phenyl to the phthalimide moiety could be calculated (Figure 3). As already mentioned the *tert*-butyl group is decisive for the reaction. Although the energy barriers are suitable for a charge transfer, the crucial mechanistic step is only possible, if the phthalimide and phenyl group are sterical close to each other. The bulky *tert*-butyl group provides a suitable conformation, within which the intramolecular transfer can occur.

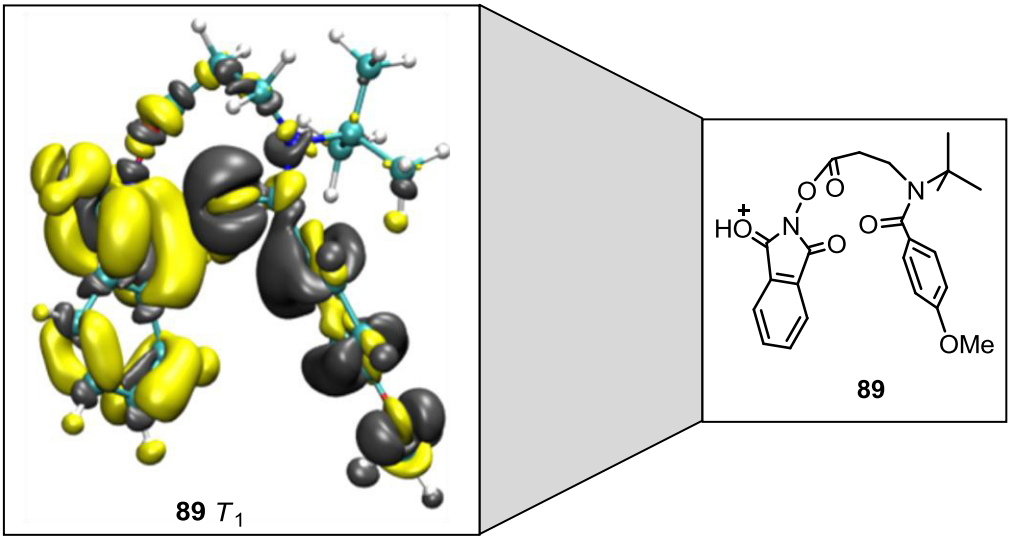


Figure 3. Orbital-relaxed electron density difference of the lowest triplet state T_1 of the protonated *N*-acyloxyphthalimide **89**; provided by Dr. Thomas Merz. Yellow = electron rich areas (phthalimide moiety), black = electron poor areas (phenyl group).

The biradical intermediate **92** undergoes N-O bond cleavage, facilitated by leaving of the neutral phthalimide molecule, and subsequent decarboxylation of the carboxyl radical. The calculated potential energy surface show that these two separations proceeds spontaneous under the reaction conditions (Figure 4).

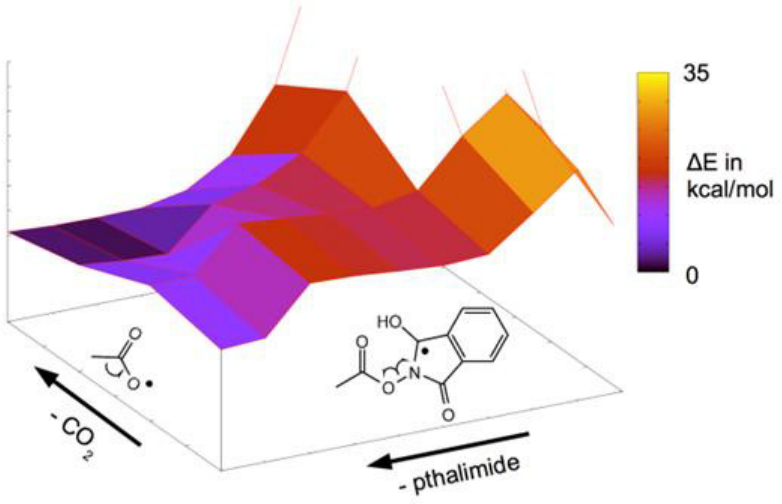
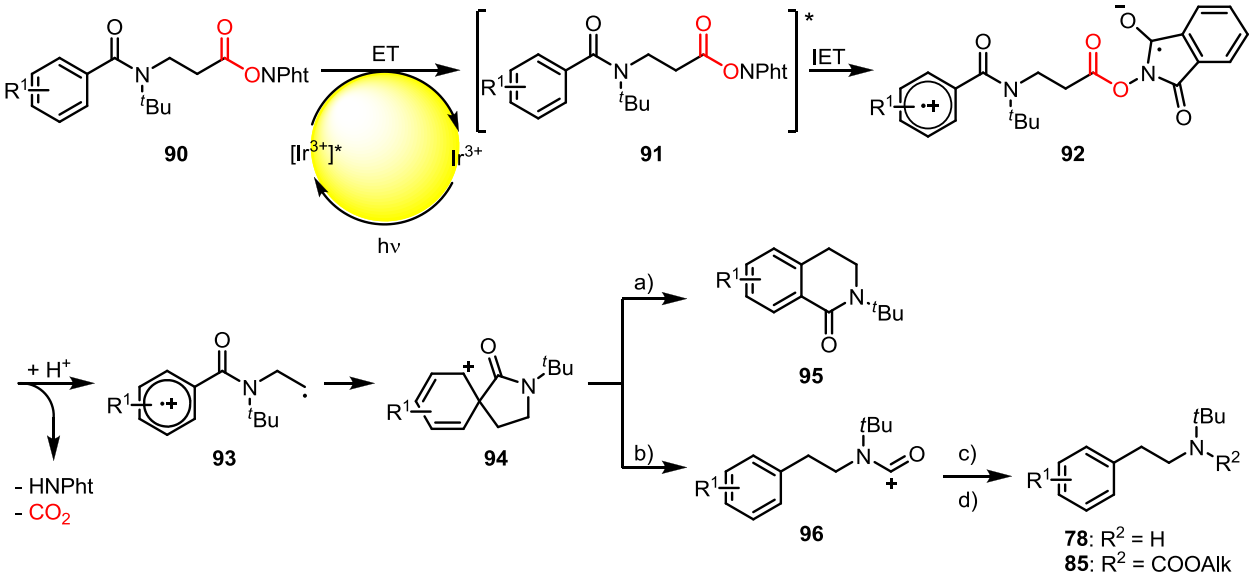


Figure 4. Potential energy surface of the phthalimide radical cleavage and decarboxylation of the carboxyl radical; provided by Dr. Thomas Merz.

An intramolecular radical recombination of the alkyl radical **93** affords the spiro-cation intermediate **94**. Depending on the phenyl substituents the already discussed 1,2-acyl shift (Scheme 16) leads to dihydroisoquinolinone products **95** or acyl cation **96**.[41,56] In aqueous reaction condition β-phenylethylamine derivatives **78** were isolated. Changing the solvent to acetonitrile/alcohol the corresponding carbamates **85** were obtained (Scheme 26).

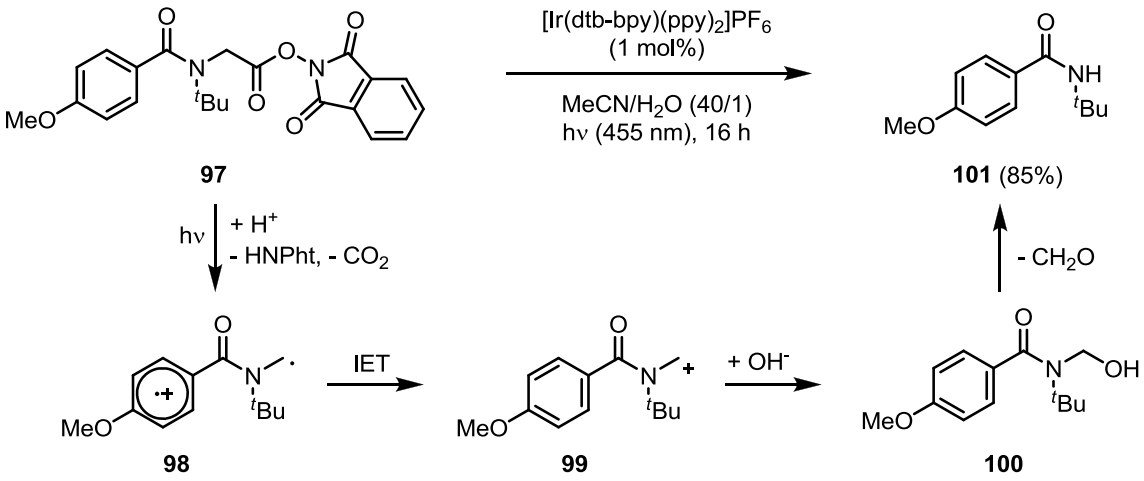


Scheme 26. Proposed reaction mechanism. a) R^1 = *p*,*m*-OMe; *p*,*m*,*m´*-OMe. b) R^1 = mono-substituted. c) MeCN/H_2O, R^2 = H; MeCN/alcohol, R^2 = COOAlk (Alk = alkyl group).

1.5 Further substrate investigations

1.5.1 Decarboxylation of hippuric acid derivatives

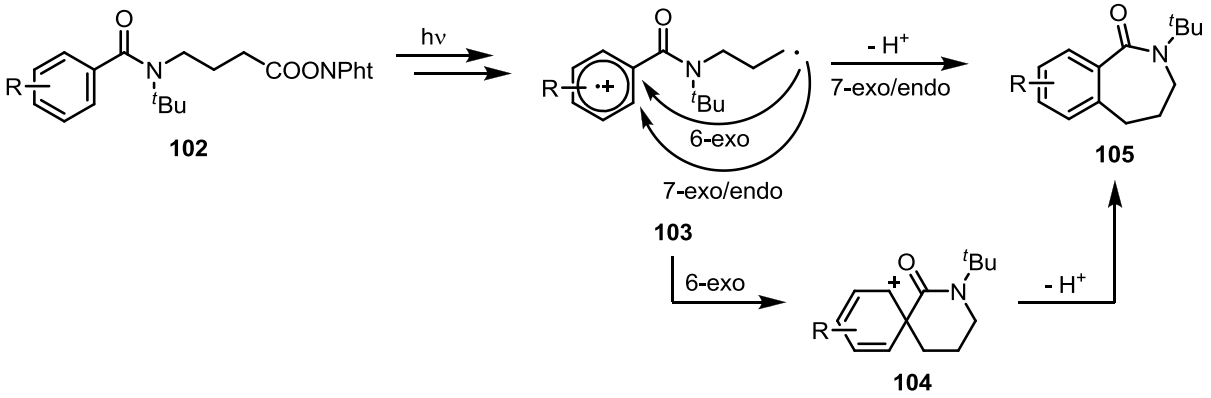
To extend the substrate scope, *N*-acyloxyphthalimide **97** was synthesized. In contrast to the starting phthalimide esters described earlier in the β-phenylethylamine synthesis (see Section 1.3) this starting material is based on the α-amino acid glycin. Interestingly the photodecarboxylation of **98**, using the common reaction conditions, leads to benzamide **101** in very good yields (85%). If the mechanism of this reaction includes a radical recombination step, some amounts of the rearranged product should be formed, but no benzylamine was detected. Due to this and because of the unfavored ring size the spirocyclization, which is necessary for the rearrangement process, is not assumed. Instead, a second intramolecular electron transfer (IET) is envisoned, which results in rearomatization and alkyl cation **99**. The water in the solvent mixture forms the amidomethanol **100** intermediate, which hydrolyses under the release of formaldehyde to isolated benzamide **101** (Scheme 27).[57]



Scheme 27. Photodecarboxylation and proposed reaction mechanism of *N*-acyloxyphthalimide **97**.

1.5.2 Decarboxylative tetrahydro-1*H*-benzazepinone synthesis

Applying molecules, based on α-amino acids did not show the desired reaction. Consequently the alkyl carbon chain was elongated by one CH_2-group, with respect to **74**, in order to obtain γ-phenylpropylamines. The reactions of the elongated ω-aryl-*N*-acyloxyphthalimides showed full conversion after 16 h of irradiation and phthalimide was identified as a side product. Surprisingly instead of the expected γ-phenylpropylamine a different product was obtained – tetrahydrobenzazepinone **105**. The photoinduced decarboxylation was successful, but no rearrangement took place. Regarding the product, two radical cyclizations are possible. A 6-*exo*-trig cyclization forms the six membered spirocyclized intermediate **104**, which was observed in previous studies. In contrast to the β-phenylethylamine reactions, no products which arise from an 1,2-acyl shift of the carbonyl group were detected at all. Either only the alkyl chain shifts after the formation of the spiro-intermediate **104**, or, more likely, the hydro-azepinone ring is formed directly via 7-*exo*/*endo*-trig cyclization (Scheme 28).



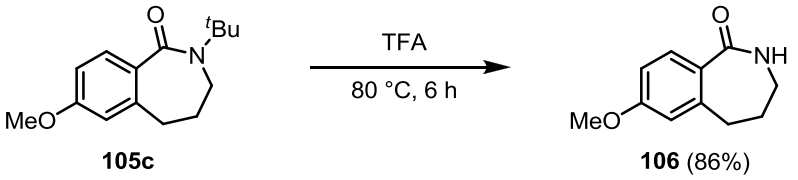
Scheme 28. Abstract of the proposed reaction mechanism.

This reaction represents a new method for the synthesis of benzazepinones.[58] Therefore a set of tetrahydrobenzazepinones with different substituents was synthesized in fair to good yields (Table 6). In contrast to the synthesis of β-phenylethylamines **78**, the electron density of the phenyl group had less influence on the reaction and the product yields. Remarkably after irradiation of the electron deficient *N*-acyloxyphthalimide **102b** the corresponding hydrobenzazepinone was isolated with a yield of 35%. However, the β-phenylethylamine **78l** of the pyridine based phthalimide ester was not observed at all (Table 4, entry 12). Also the yield of the unsubstituted tetrahydrobenzazepinone **102a** is significantly higher with 43% (compared to 29% for **78h**). As expected, the reaction is an unsymmetrical substitution of the phenyl ring at the *N*-acyloxyphthalimides **102d** and **102e**. The reaction leads to two respective

isomers (**105d´**,**105d´´** and **105e´**, **105e´´**), which were isolated separately. The yield of benzazepinone **105e´** (48%) is five times higher than **105e´´** (10%), due to sterical bulkiness of the methoxy group in *meta* position. Surprisingly, changing the substituent to chloride, we observe the reverse effect and product **105d´** was isolated in 18% and **105d´´** in 44% (1:2). Blocking both *ortho*-positions (**102f**, **102g**) led to the isolation of the formal reductive decarboxylation products **105f** and **105g**, together with significant amount of the corresponding acid, formed apparently via competitive electron abstraction by the carboxylic group. This result is a hint for the mechanism. The *ortho*-substituents (-Me, -OMe) have no big sterical demand and the reaction towards the *ortho*-substituted β-phenylethylamine **78j** is able to undergo a 5-*exo*-trig cyclization (Table 4, entry 10, Section 1.4.2). Therefore the spirocyclization leading to γ-phenylpropylamine products could occur, but these products were not detected.

In case of the trisubstituted *N*-acyloxyphthalimide **102h**, whose analog **77m** gave the dihydroisoquinolinone **80** in very good yields (75%, Scheme 21), only 43% of the tetrahydro-1*H*-benzazepinone **105h** was isolated. Simple decarboxylation and reduction, according to the products of entry 7 and 8, formed the *N*-propylbenzamide in substantial amount (38%).

To clarify the molecule structure of this cyclization reaction the *tert*-butyl group of benzazepinone **105c** was removed, using neat TFA and reflux conditions (Scheme 29).

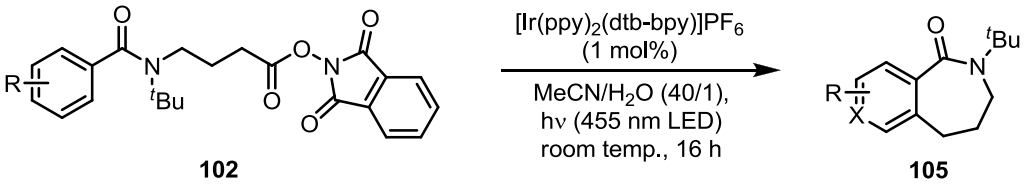


105c **106** (86%)

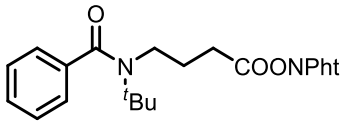
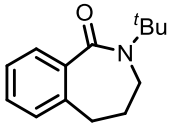
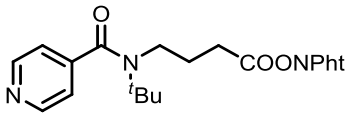
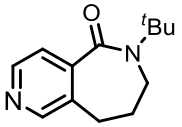
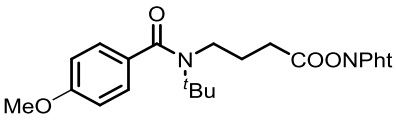
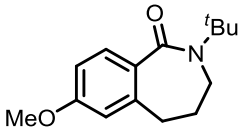
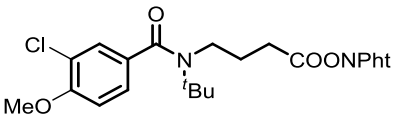
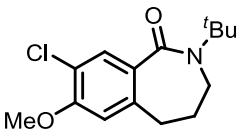
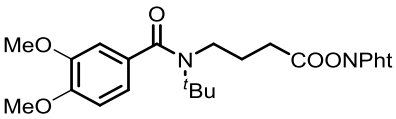
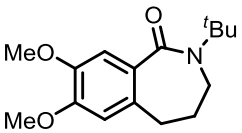
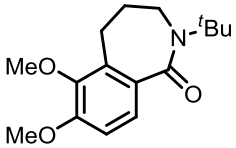
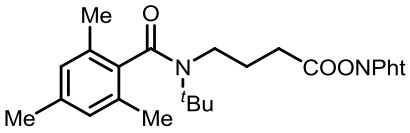
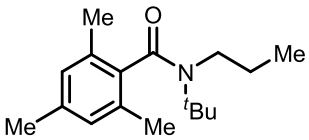
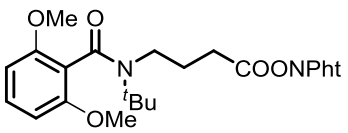
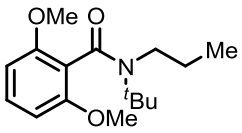
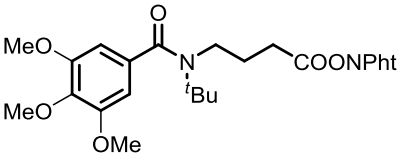
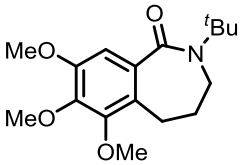
Scheme 29. Removing of the *tert*-butyl group of **105c**.

Pure *N*-deprotected benzazepinone **106** was isolated in 86% and the NMR signals of the product were in accordance to the literature.[59] This shows that under photodecarboxylative conditions ω-aryl-*N*-acyloxyphthalimides based on γ-amino acid preferably undergo the already discussed 7-*exo/endo*-trig cyclization instead of the 6-*exo* spirocyclization.

Table 6. Scope of the tetrahydro-1*H*-benzoazepinone **105** synthesis.



102 **105**

Entry	Substrate		Product		Yield
1		**102a**		**105a**	43%
2		**102b**		**105b**	35%
4		**102c**		**105c**	60%
5		**102d**	 **105d´**, 18%	 **105d´´**, 44%	
6		**102e**	 **105e´**, 48%	 **105e´´**, 10%	
7		**102f**		**105f**	24%
8		**102g**		**105g**	45%[a]
9		**102h**		**105h**	43%

[a] incomplete conversion after 24 h.

1.6 Decarboxylation of naphthalene diimide esters

The crucial step of this decarboxylation method is the excitation of the *N*-acyloxyphthalimide, which enables the intramolecular charge transfer and consequently decarboxylation. So far the substrates were excited either indirectly by a visible light excited photocatalyst or directly via UV-light irradiation without a catalyst. Each process has its disadvantages. Using UV irradiation, you have to follow special safety regulations, special glassware and high energy is needed. On the other hand, visible light conditions with light emitting diodes, less power leads to a greener chemistry, but expensive photocatalysts were used in the reactions. If the *N*-acyloxyphthalimides would absorb light in the visible range, no catalyst would be needed to initiate the decarboxylation process. Therefore particular attention is drawn to naphthalene diimides, which are known as organic dyes and triplet photosensitizers.[60]

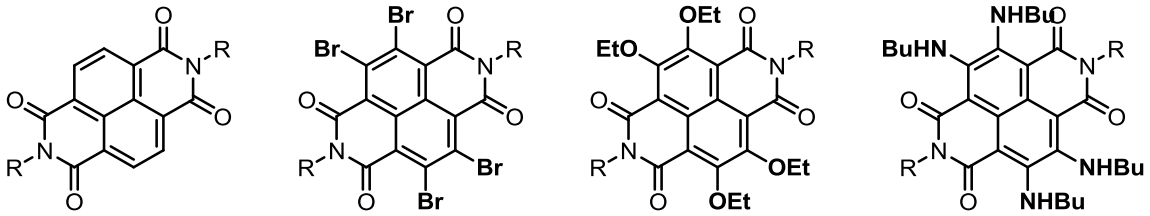
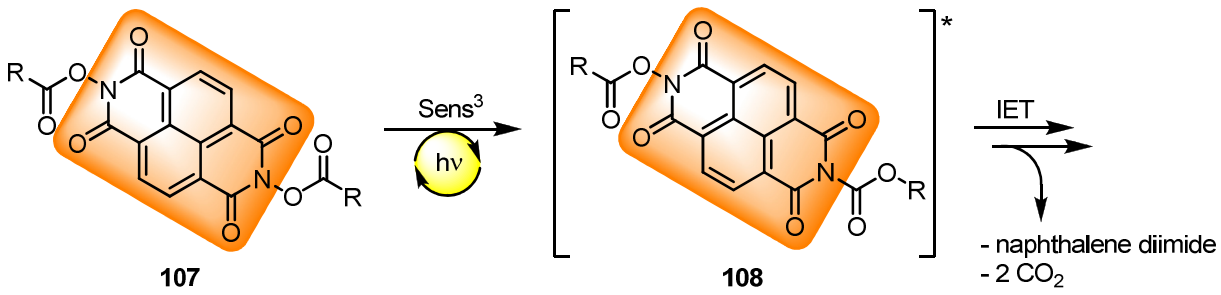


Figure 5. Absorption maxima of substituted naphthalenediimides (R = alkyl chain, n > 5).

Most naphthalene diimides absorb in the visible range. Depending on the substituents of the naphthalene core structure and the *N*-substituents the absorption maxima changes (Figure 5). Replacing so far used phthalimides with naphthalene diimides would allow direct sensitization, which avoids the detour via the photocatalyst. The naphthalene diimide core **107** is excited by visible light. This excited species **108** undergoes the intramolecular energy transfer. After naphthalene diimide separation, two decarboxylations take place and the product is formed (Scheme 30). This direct excitation could lead to shorter reaction times and higher yields at the same time.



Scheme 30. Mechanism of the direct sensitization of colored naphthalene diimide compounds **107**.

To investigate if naphthalene diimides could activate acids and lead to decarboxylation like phthalimides, compounds **109** and **110** were synthesized. The naphthalene diimides **109** and **110** were yellow solids and the UV-Vis absorption spectra of **109** shows absorption in the visible range, therefore the compounds are accessible for 455 nm LEDs (Figure 6).

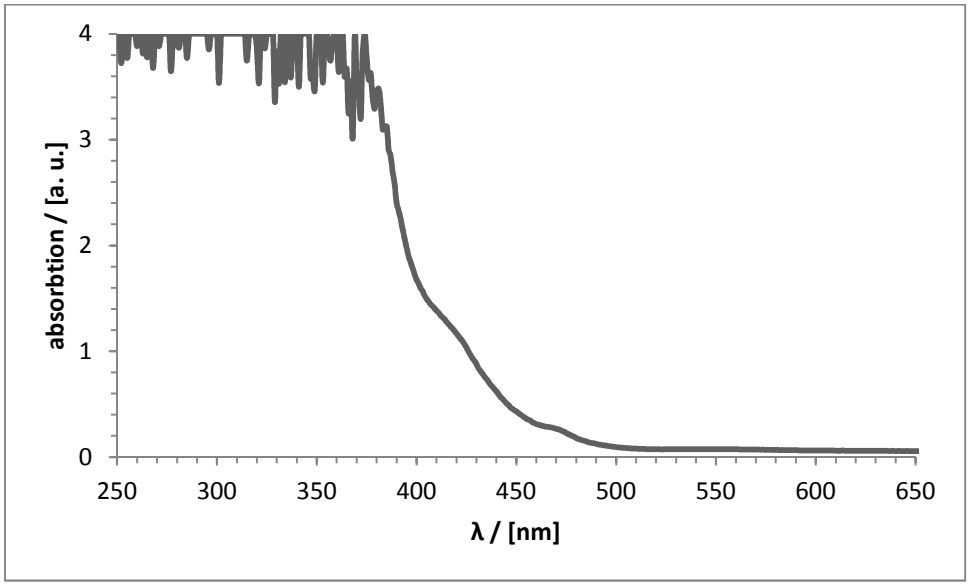
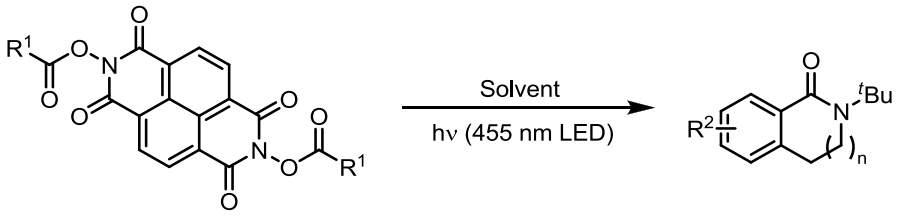


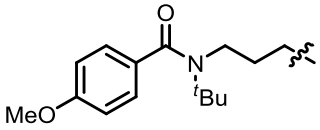
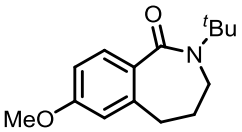
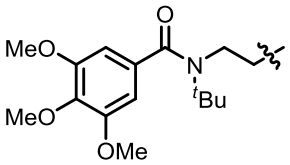
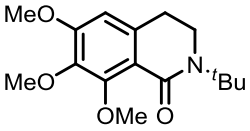
Figure 6. Absorption spectra of compound **109**.

Due to solubility problems the photoreactions were performed in DMF/water and DMSO/water solvent mixtures (Table 7). The reaction mixture of **109** turned dark brown during irradiation, so the reaction time was elongated to 36 h until full conversion was obtained (entry 1). Performing the reaction in DMSO, full conversion was obtained after 6 h (entry 2). In contrast to the reaction in DMF the mixture turned red within 2 h of irradiation, whereby the light still could reach the naphthalene diimide derivative **110**. The isolated yields of **105c** (40%) and **80** (52%) were around 20% less than the former reactions with phthalimide activation (**105c** – 60% and **80** – 75%). In conclusion, using strongly colored

starting materials, which absorb light in the visible range, direct irradiation enables the decarboxylation reaction and no additional sensitizer is necessary.

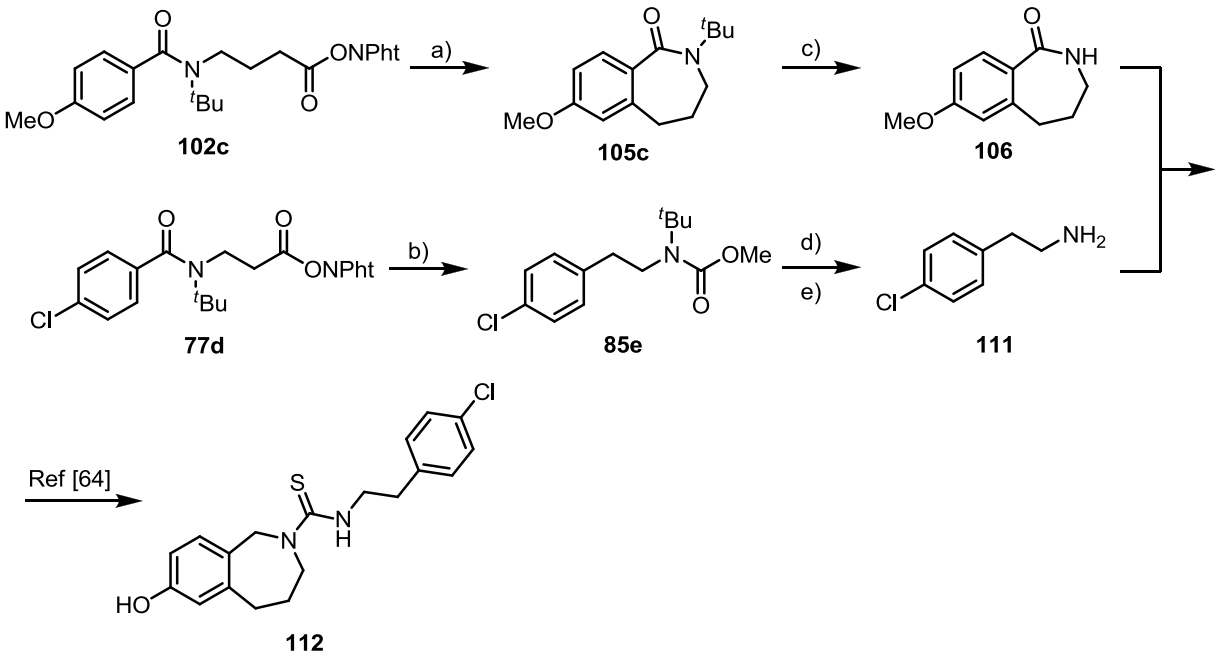
Table 7. Decarboxylation reaction of naphthalene diimide based compounds **109** and **110**.



Entry	R^1		Solvent	Time	Product		Yield
1		**109**	DMF/H_2O (40/1)	32 h		**105c**	40%
2		**110**	DMSO/H_2O (40/1)	6 h		**80**	52%

1.7 Capsazepinoid synthesis

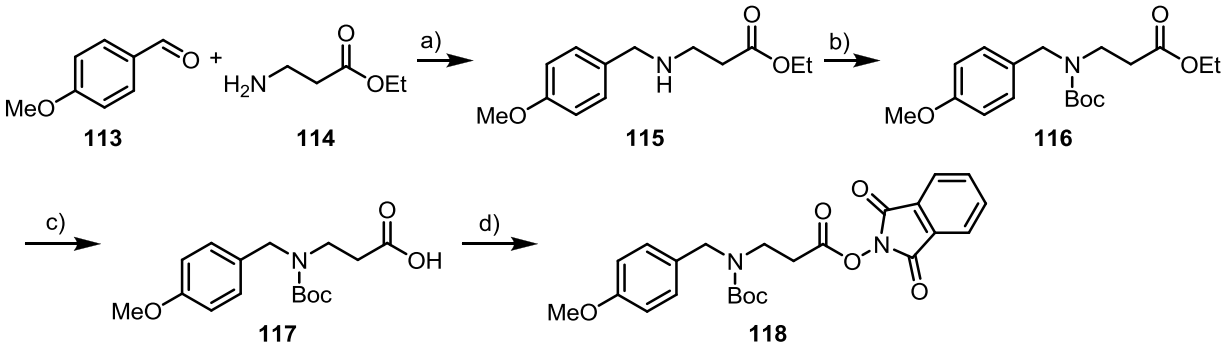
The products – β-phenylethylamines **78**, dihydroisoquinolinones **79**, **80** and benzazepinones **105** – of the developed visible light mediated transformation of ω-aryl-*N*-acyloxyphthalimides can serve as precursors for numerous biological active compounds.[61] One application is the preparation of key intermediates **106** and **111**, used in the convergent synthesis of bronchodilator capsazepinoid **112**.[62] The starting materials **102c** and **77d** could be synthesized each in 4 steps from readily and commercial available benzoyl chlorides, ethyl 4-bromobutyrate, ethyl acrylate and *N*-hydroxyphthalimide in overall yields of 41% (**102c**) and 55% (**77d**). After the visible light-mediated decarboxylation products **105c** and **85e** were isolated in 60% and 68% yield. The *tert*-butyl groups were removed using TFA and the methyl carbamate was cleaved under microwave conditions, described by Scobie *et al.*[63] The obtained benzoazepinone **106** and unprotected β-phenylethylamine **111** can be transformed to capsazepinoid **112** as reported by Sterner *et al.* (Scheme 31). With this strategy it is possible to synthesize numerous other active capsazepinoids, which acts as inhibitors of constriction of human airways.[64]



Scheme 31. Formal synthesis of capsazepinoid **112**. a) $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), $MeCN/H_2O$ (40/1), 455 nm LED, room temp., 16 h (60%). b) $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), MeCN/MeOH (3 equiv.), 455 nm LED, room temp., 16 h (68%). c) TFA, reflux, 6 h (86%). d) TFA, room temp., overnight. e) 2 M LiOH/THF/MeOH (1/1/1), MW, 120 °C, 10 min (89%).

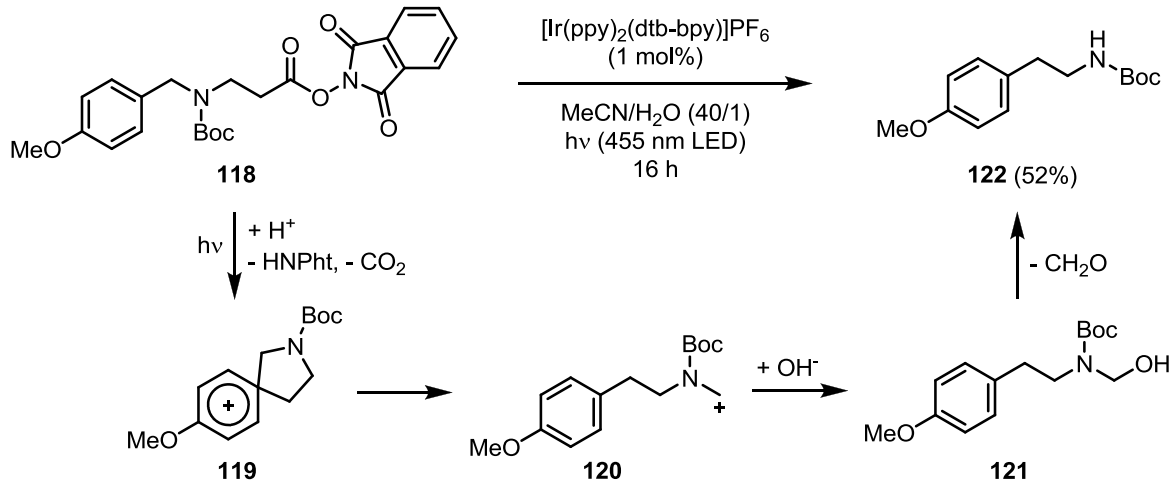
1.8 Decarboxylative phenylalanine synthesis

Until now the used substrates were synthesized from benzoyl chlorides, giving benzamides. Therefore the limitation of the reaction scope is liable to suitable amines with the sterical demanding *tert*-butyl group. In order to gain access to a broader substrate range, ω-aryl-*N*-acyloxyphthalimide **118** was synthesized from 4-anisaldehyde (**113**) and β-amino acid **114** (Scheme 32). Due to the convenient amine Boc-protection, which replaces the so far used bulky *tert*-butyl group, all β-amino acids can be utilized in the starting material synthesis.



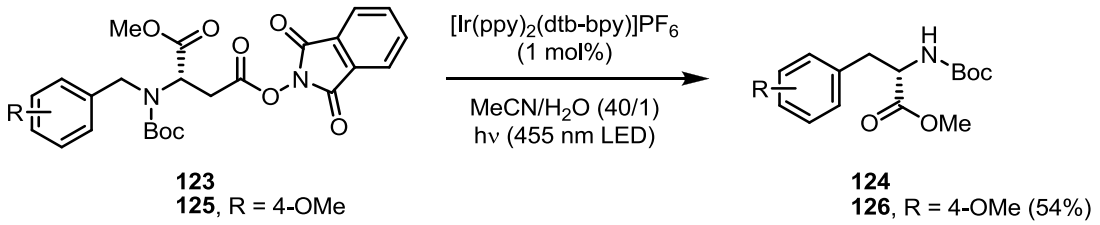
Scheme 32. Synthesis of ω-aryl-*N*-acyloxyphthalimide **118**. a) MeOH, NEt_3 (1 equiv.), $NaBH_4$ (1 equiv.), room temp., overnight (90%). b) DCM, NEt_3 (1 equiv.), Boc_2O (1 equiv.), room temp., overnight (56%). c) EtOH, H_2O, KOH (1.9 equiv.) (98%). d) THF, *N*-hydroxyphthalimide (1 equiv.), DCC (1 equiv.), room temp., overnight (67%).

The decarboxylation of **118**, using the established photoreaction conditions, yields the Boc-protected β-phenylethylamine **122** in 52% (Scheme 33). Similar to the previous results, the formation of spiro-intermediate **119** is assumed, in course of the reaction. Rearomatization leads to cation intermediate **120**, which is trapped by the solvent, releasing formaldehyde, similar to the reaction of *N*-acyloxyphthalimide **97** (Scheme 27).



Scheme 33. Photodecarboxylation and proposed reaction mechanism of *N*-acyloxyphthalimide **118**.

Using commercially available L-aspartic acid and substituted benzaldehydes in the starting material synthesis, numerous of unnatural phenylalanine derivatives **124** can be synthesized via this visible light-mediated decarboxylation (Scheme 34). In contrast to the *N-tert*-butyl substituted β-phenylethylamines **78**, the received amino acids **124** have commonly used *tert*-butyloxycarbonyl and methyl ester protecting groups. As an example the *para*-methoxy substituted phenylalanine **126** was synthesized from **125** in 54% yield.[b] Ongoing experiments in the Reiser group by M.Sc. Simon Budde are extending the scope of the reaction, giving rise to a library of unnatural phenylalanine derivatives **124**.



Scheme 34. Synthesis of phenylalanine derivatives from *N*-acyloxyphthalimides **123**.

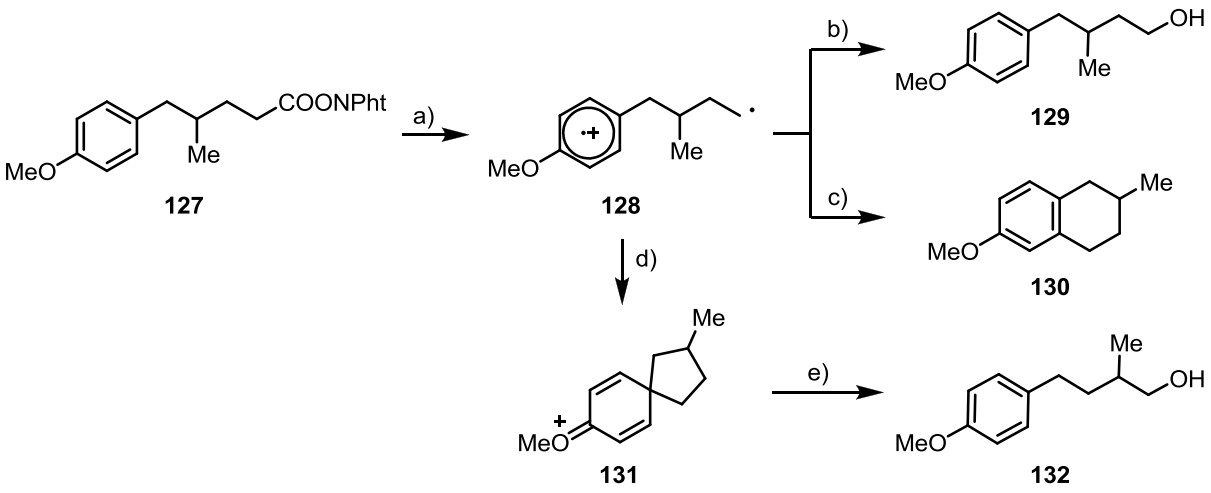
[b] The photoreaction of **125** was performed by M.Sc. Simon Budde in course of his PhD thesis.

1.9 Decarboxylative tetralin synthesis

In the previous chapters the visible light-mediated decarboxylation was limited to ω-aryl amino acids. After decarboxylation and spirocyclization an 1,2-acyl shift lead to β-phenylethylamines **78** and tetrahydroisoquinolinones **105**. This rearrangement was observed using benzamide- or benzylamine based starting materials.

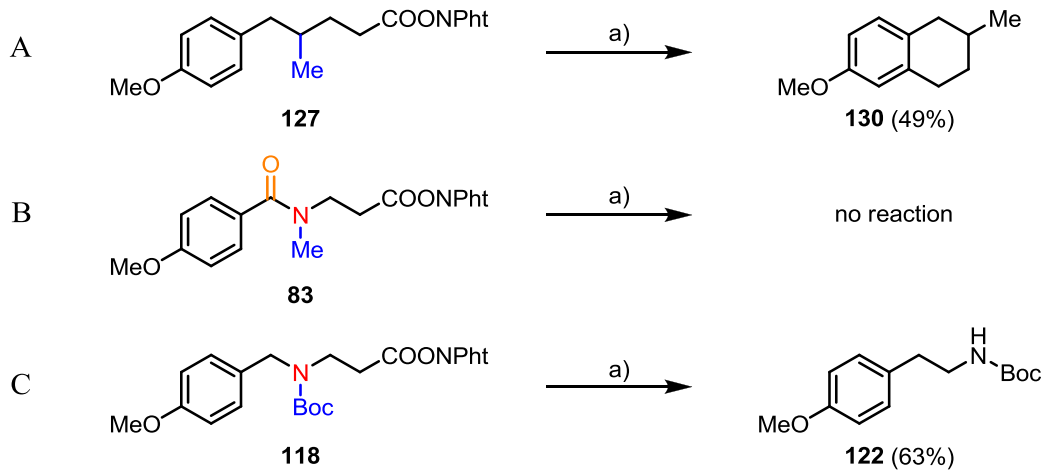
In the next step the function of the amine in the spirocyclization process was investigated. For this ω-aryl-*N*-acyloxyphthalimide **127** was synthesized. Starting from 4-methoxy benzaldehyde and propionaldehyde the key step of the synthesis was a Horner-Wadsworth-Emmons reaction. After hydrogenation and ester hydrolysis the desired product **127** was obtained after the coupling with N-hydroxyphthalimide.

Using previous investigated photoreaction conditions, the intramolecular reduction of the phthalimide moiety and following decarboxylation should lead to the biradical **128**. This intermediate **128** was assumed to undergo several transformations (Scheme 35). One possible mechanism continuous with an intramolecular electron back transfer to the phenyl moiety forms the primary alkyl cation, which was observed in the reaction with *N*-acyloxy-phthalimide **97** (Scheme 27, Section 1.4.5). A reaction with water leads to the alcohol **129**. Another possible product based on intermediate **128** is the tetralin derivative **130**, which concludes from a 6-*exo*-trig cyclization and rearomatization. Spirocyclization of biradical **128** forms the intermediate **131**, which could undergo ring opening, obtaining again compound **129** or a smiles-type rearrangement leading to compound **132**. By observing the positions of the methyl group in the alkyl chain the assumed mechanisms and products can be differentiated.



Scheme 35. Photodecarboxylation of **127** and the possible reaction products **129**, **130** and **132**. a) reaction conditions: $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), MeCN/H_2O (40/1), hν (455 nm LED), room temp., 16 h. b) Intramolecular electron transfer and hydroxyl addition. c) Cyclization and rearomatization. d) 5-*Exo*-trig spirocyclization. e) Ring opening and hydroxyl addition.

N-acyloxyphthalimide **127** was irradiated with a 455 nm LED in presence of $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%) and an acetonitrile/water solvent mixture (40/1, c = 1 mol/l). After the photoreaction the cyclized tetralin derivative **130** was isolated in 49% yield (Scheme 36, A) together with the corresponding hydrolyzed acid side product.

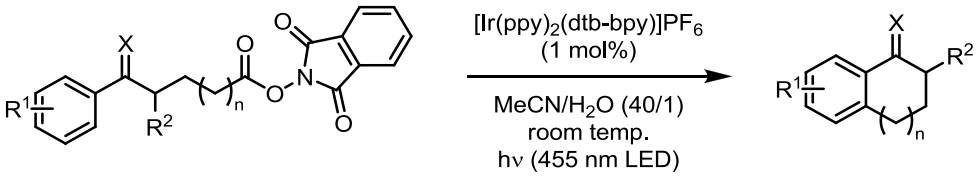


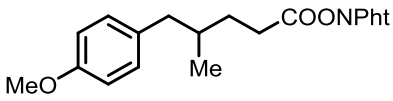
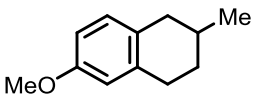
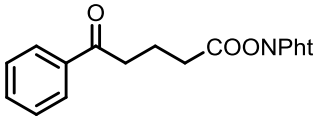
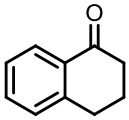
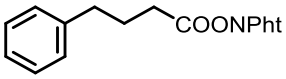
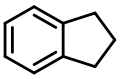
Scheme 36. Reaction comparison of compound **127** with *N*-methyl benzamide derivative **83** and *N*-Boc protected benzylamine derivative **118**. a) $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), MeCN/H_2O (40/1, c = 1 mol/l), 455 nm LED, room temp., 16 h.

Incorporating an amide group into the molecule **127** the already investigated benzamide derivative **83** is received (Scheme 36). Regarding the photoredox mechanism of photocatalytic reactions, the carbonyl group in this molecule is necessary to prevent the nitrogen from oxidation by the photocatalyst. Former reaction studies show no product formation for the benzamide derivative **83** (Table 5, Section 1.4.2). The *N*-methyl group is not bulky enough to engage a favorable conformation for the reaction (Scheme 36, B). A sterical demanding *N*-protecting group enables the decarboxylation and rearrangement forming phenylethylamine derivatives (Scheme 36, C).

In contrast to amide containing analogs of these *N*-acyloxyphthalimides, compound **127** is able to undergo the intramolecular electron transfer from the phenyl to the phthalimide moiety, without any bulky substituents. Although decarboxylation occurs, no spirocyclization was assumed. Instead of that, direct 6-*exo*-trig cyclization is forming tetralin **130**.

Table 8. Decarboxylative tetralin synthesis.



Entry	ω-Aryl-*N*-acyloxyphthalimide		Time	Product		Yield
1		**127**	16 h		**130**	49%
2		**133**	36 h		**134**	33%[a]
3		**135**	65 h		**136**	0%

[a] incomplete conversion after 36 h of irradiation.

Electron density of the phenyl group plays still a crucial role in product formation. The intramolecular reduction of the phthalimide is favored by increased presence of electron donating substituents (Table 4, Section 1.4.2). Performing the photoreaction with *N*-acyloxyphthalimide **133**, which has an electron withdrawing carbonyl group, after 36 h of irradiation the reaction was still incomplete and only 33% of the corresponding tetralin **134** was isolated (Table 8, entry 2). The synthesis of hydro-indene **136** failed in spite of the

absence of the carbonyl group. In all likelihood sterical effects disable the intramolecular phthalimide reduction.

In contrast to the photoreaction of *N*-acyloxyphthalimides **77** and **118**, phenylpentanoic phthalimide ester derivatives reacted in a 6-*exo*-trig cyclization, without any additional rearrangement. On the basis of these simple examples the synthesis of tetralin derivatives via visible light-mediated decarboxylation was shown. Further investigations regarding reaction conditions would allow for improving yields, but were not performed as part of this thesis.

1.10 Conclusion

In summary, a visible light-promoted decarboxylative Smiles-type rearrangement was developed. ω-Aryl-*N*-acyloxyphthalimides were easily synthesized from commercially inexpensive compounds and decarboxylated via energy transfer mechanism from a visible light excited photocatalyst. Depending on the aryl substituents and different solvent mixtures a multitude of β-phenylethylamines, β-phenylethylcarbamates and dihydroisoquinolinones were synthesized under mild and environmentally friendly reactions.

A further substrate scope extension via the elongation of the alkyl carbon chain of the starting materials afforded tetrahydrobenzazepinones in good yields. After the decarboxylation of these substrates no additional rearrangement reaction was observed.

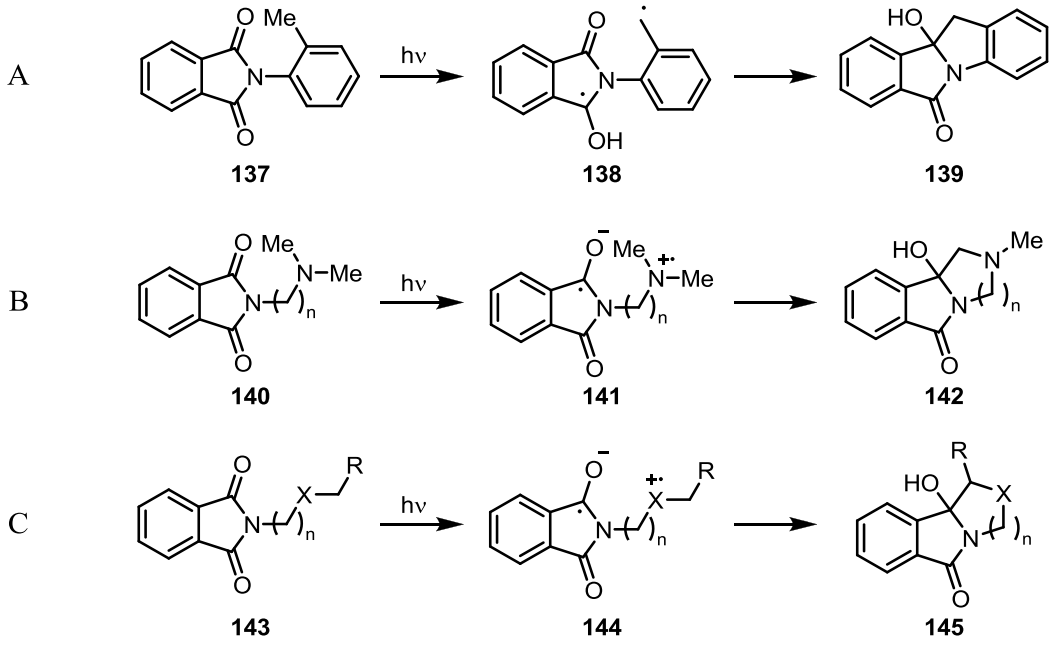
As an application for the developed visible light mediated transformation of ω-aryl-*N*-acyloxyphthalimides both key intermediates for the convergent synthesis of the bronchodilator capsazepinoid were prepared. This photoinduced process was also used in the synthesis of unnatural phenylalanine derivatives based on L-aspartic acid and substituted benzaldehydes and the synthesis of tetralin derivatives from the decarboxylation of phenylpentanoic acids.

2 UV light-mediated reactions of phthalimides[c]

2.1 Scientific bases

The photophysical[65] as well as the electrochemical[66] properties of phthalimides are well investigated. The absorption spectra of non substituted phthalimide, *N*-acetyl- or *N*-benzoylphthalimide show the absorption maxima at around λ_{max} = 235 nm, λ_{max} = 340 nm, and λ_{max} = 350 nm, respectively.[67] Light absorption in the UV range enables the access to the excited triplet state of *N*-substituted phthalimides with an average lifetime between 2 µs and 10 µs at room temperature in absence of oxygen. This excited state of the phthalimide has a remarkably high oxidizing power, which can lead to electron transfer reactions in presence of suitable electron donor groups.[68]

In the 1970s Kanaoka *et al.* utilized this behavior and demonstrated a number of phthalimide based photochemical reactions.[69] The group focused especially on intramolecular cyclizations, using phthalimides with *N*-substituted ω-benzyl (A),[70] ω-alkene,[71] ω-dialkylamines (B),[72] ω-thionyl (C)[73] or ether (C)[74] moieties (Scheme 37).



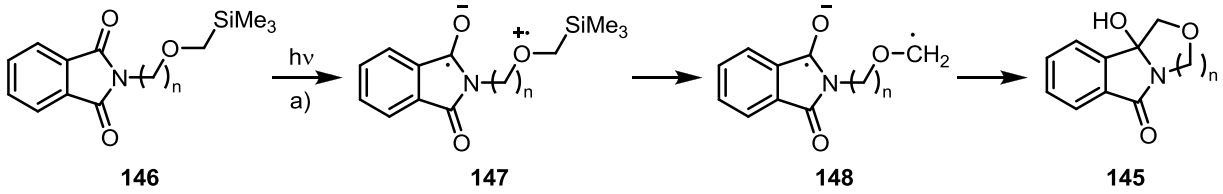
Scheme 37. Photoinduced intramolecular cyclization of *N*-substituted phthalimides. A: *tert*-Butanol, 1 kW high pressure mercury lamp, 3 h (65%). B: 0.2 M solution acetone/petroleum ether (3/1), 500 W high pressure mercury lamp, 0.5 h, n = 2 (29%). C: Acetone, 400 W high pressure mercury lamp, 3 h; a) X = S, n = 3, R = H (86%); b) X = O, n = 1, R = Ph (60%).

[c] The results of this chapter were prepared during a four month research intership at James Cook University of Townsville/Australia. College of Science, Technology & Engineering. Supervisor: A/Prof. Michael Oelgemöller.

Using usually acetone as a triplet sensitizer, the phthalimide derivatives were excited via UV irradiation. In the excited state, the molecules undergo charge transfer from the particular reactive end of the molecule to the phthalimide moiety. The oxidized part of the molecule cleaves off hydrogen atom and a radical ion combination yields the cyclization products **139**, **142** and **145**.

Apart from the intramolecular cyclizations, intermolecular additions were also investigated. Based on the same process, benzylic donors,[75] alkenes,[76] or ethers (e.g. tetrahydrofuran)[77] were used as reducing agent in a photoaddition reaction, resulting in the alkylated phthalimide derivatives.

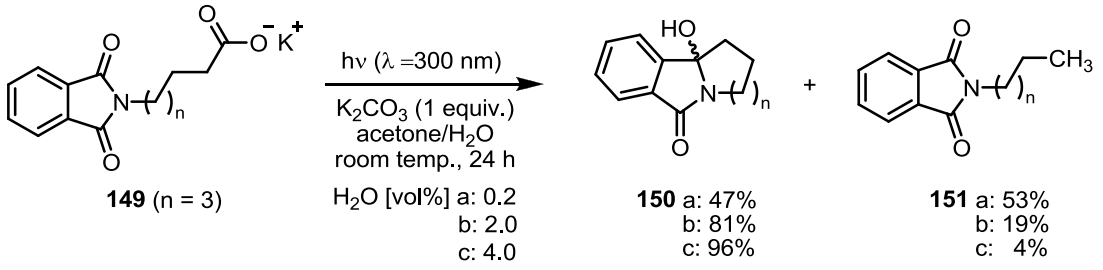
Mariano *et al.* and Yoon *et al.* continued the work of Kanaoka *et al.* and introduced trimethylsilyl (TMS) as a leaving group. In this study, TMS is placed in β-position to the active donor group, like ethers[78] or amides.[79] After the reduction of the phthalimide moiety, trimethylsilane is cleaved off, generating the alkyl radical **148**, which undergoes intramolecular cyclization and to form compound **145** (Scheme 38).[80] In contrast to the hydrogen atom cleavage, the alkyl radical is generated faster, which lowers the reaction time and increases the yield. Also intermolecular conditions with phthalimides and alkoxymethyl-trimethoxysilanes, which react in a competitive single electron transfer manner, were investigated.[81]



Scheme 38. Photocyclization reaction of ω-trimethylsilyl-phthalimide **146**. a) MeOH, 450 W Hanovia medium pressure mercury vapor lamp, 2 h (98%).

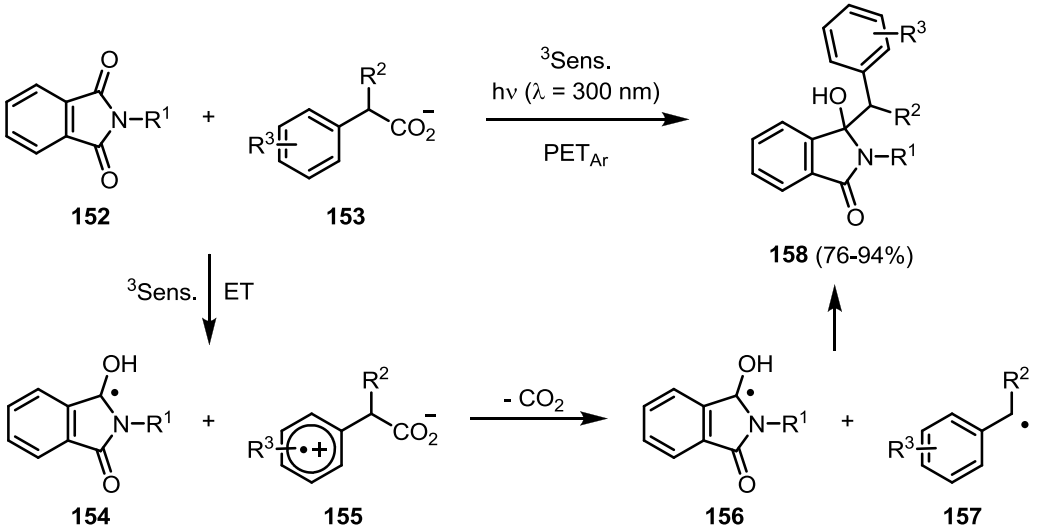
Griesbeck *et al.* and Oelgemöller *et al.* expanded the scope of this intramolecular phthalimide addition. They used UV irradiation to oxidize free carboxylic acids with the excited phthalimide moiety. After decarboxylation the cyclized phthalimide derivatives **150** were isolated. Depending on the amount of water in the reaction solvent, the simple decarboxylated side products **151** were obtained. By increasing the water ratio, less side product was observed, which could form after the decarboxylation in a second back electron transfer (Scheme 39).[82] Via the application of aqueous nontoxic solvents and omitting further

additives, this process offered a new possibility for mild decarboxylation and in the spirit of green chemistry.[83]



Scheme 39. Photoinduced decarboxylation of phthalimide **149** and the influence of the water amount on the product ratios.

Intermolecular additions were investigated mainly with phenylacetic acids. The phthalimide reduction was performed either by the acid group or, in case of a high electron density of the phenyl ring (R^3 = 3,4,5-OMe; 3,4-OMe), by the phenyl moiety. The oxidized phenylacetic acid **155** loses carbon dioxide, generating the benzyl radical **157**. Radical recombination leads to the desired benzylated phthalimides **158** in excellent to very good yields (Scheme 40).[84]



Scheme 40. Proposed mechanism of the decarboxylative benzylation of phthalimides.
R^1 = H, Alk, Ar; R^2 = H, Alk; R^3 = OMe, OAc, Hal, Alk.

Many target molecules of these reactions, specifically the benzylation products **158**, which can easily be transformed into **159** or **160** via acid treatment, lead to useful and pharmaceutical active compounds.[85,86] E.g. the 4-methoxyphenylmethylene derivative **160** (AL-12), known for its local anesthetic activity, is superior to tetracaine and the E-phenylethylidene derivative **161** (AKS-186), which inhibits tromboxane A_2 analogue (U-46619) induced vasoconstriction.[87,88] In a simple aryl-aryl-coupling arylmethylene-isoindolin-1-ones (**159**) can be transformed into aristolactams (**162**), which are components of many plants such as *Aristolochia* and *Asarum* (Figure 7).[89]

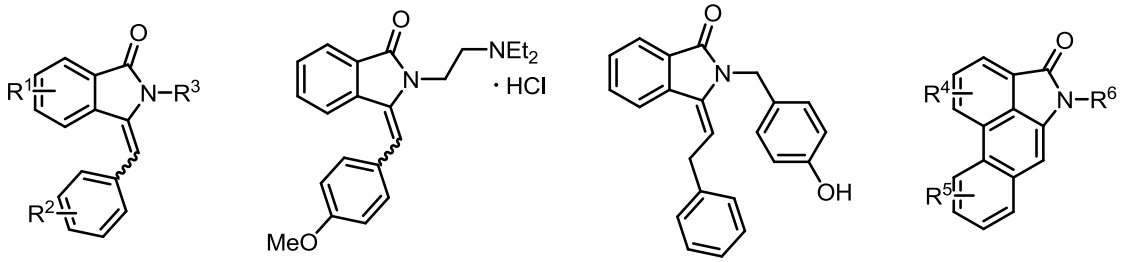


Figure 7. The core structure of arylmethylene-isoindolin-1-ones (**159**), 4-methoxyphenylmethylene derivative **160** (Al-12), E-phenylethylidene derivative **161** (AKS-186) and the core structure of aristolactams (**162**).

2.2 Investigation of the light-promoted dual decarboxylation

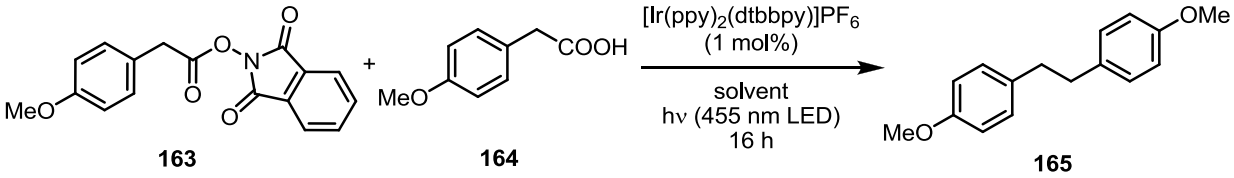
2.2.1 Visible light-mediated dual decarboxylation

Thanks to the work of Okada *et al.* and the recently published papers the mechanism of the light induced decarboxylation of activated phthalimide esters is widely explained the phthalimide moiety is reduced before CO_2 is cleaved off.[48,90] As already mentioned Griesbeck *et al.* and Oelgemöller *et al.* explored a UV-light induced decarboxylation of free carboxylic acids, which is also initiated by the reduction of the phthalimide group (see Section 2.1).[82,83,84,85]

Based on these findings a special method for decarboxylation reactions, combining both systems in one reaction, was investigated. Phthalimide esters should get reduced by external carboxylic acids, which undergo decarboxylation. Subsequently phthalimide is cleaved and the second decarboxylation occurs.

Therefore *N*-acyloxyphthalimid **163** was synthesized as a model substrate for the test reactions. The electron-rich phenyl group could reduce the phthalimide moiety in an intramolecular way, as seen in the decarboxylation/rearrangement reactions of compound **77** (Scheme 26, Section 1.4), without requiring the addition of phenylacetic acid. For that reason first experiments were carried out under visible light conditions using $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ for the energy transfer to the molecule (Table 9). Under the commonly used reaction conditions for photosensitized decarboxylation reactions of *N*-acyloxyphthalimides, 1 mol% of the catalyst $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ and an acetonitrile/water (40/1) solvent mixture, there was still incomplete conversion of compound **163**. Only traces of the dihydrostilbene product **165** were determined (entry 1).

Table 9. Dihydrostilbene **165** synthesis under visible light conditions.



Entry	**163**	**164**	Solvent	Yield **165**[a]
1	1 equiv.	-	MeCN/H_2O (40/1)	traces[b]
2	1 equiv.	-	acetone/H_2O (20/1)	34%
3	1 equiv.	1 equiv.	acetone/H_2O (20/1)	37%
4	1 equiv.	3 equiv.	acetone/H_2O (20/1)	36%

[a] Yields are based on **163**. [b] Incomplete conversion after 16 h.

By increasing the amount of water and changing the solvent to acetone, full conversion was observed and 34% of product, based on *N*-acyloxyphthalimide **E1**, was isolated (entry 2). Oelgemöller *et al.* used phenylacetic acid to reduce the phthalimide.[84] The presence of additional 4-methoxyphenylacetic acid (**E2**) had no notable impact on the yields (entry 3 and 4). In all reactions, 4-methoxybenzyl alcohol and 4-methoxybenzaldehyde were detected as side products.

2.2.2 Experimental set up of UV-reactions

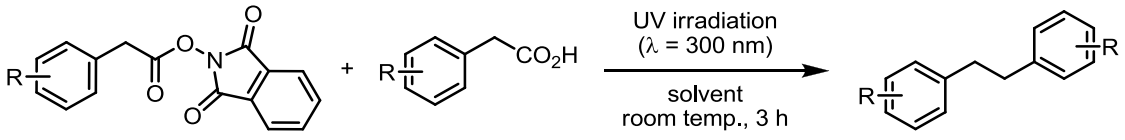
The following UV reactions were performed in a Rayonet chamber reactor, equipped with 16 x 8 W RPR-3000 Å lamps ($\lambda = 300 \pm 25$ nm; Figure 8). The reaction mixture was irradiated in a Pyrex Schlenk flask ($\lambda \geq 290$ nm) with cooling finger to keep a constant reaction temperature of approximately 15-20 °C. With a Teflon tube a slight stream of nitrogen was inserted, to generate a continuous movement of the solvent.

Figure 8. Rayonet photoreactor (1) and the experimental setup with 16 x 8 W RPR-3000 Å lamps (2), pyrex tube (3), cooling finger (4) and in/outlet for N_2 (5).

2.2.3 UV light-mediated dihydrostilbene synthesis

Using visible light in combination with the sensitizer $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ only resulted in moderate yields (see Section 2.2.1). Therefore, UV-light was applied to excite the phthalimide moiety directly to harness the reducing power of phenylacetic acid, which was not observed under visible light conditions. Performing the dihydrostilbene synthesis under UV-light irradiation the product yield was increased slightly. After 3 h of irradiation in an acetone / water solvent mixture, in absence of additional acid, 40% of dihydrostilbene **165** was isolated (Table 10, entry 1). For these types of UV reactions, acetone is known to be the best solvent as it is serving as a triplet sensitizer. The carboxylic acid functionality of phenylacetic acid reduces the phthalimide. Electron rich phenyl rings have the property that also the phenyl moiety can act as a reductant, which leads to decarboxylation of the phenylacetic acid derivatives. Therefore, the *N*-acyloxyphthalimide with *para*-methyl substituent and thereby with a lower electron density in comparison to the *para*-methoxy group, only 18% of the corresponding dihydrostilbene was obtained (entry 2). In presence of 1 equiv. phenylacetic acid the yield increased only to 48%, whereas with 3 equiv. acid 72% yield was isolated (entry 3 and 4). Based on the experiences of Oelgemöller *et al.* 1.5 equiv. potassium carbonate was added in the reactions in order to deprotonate the acid and enable a better and faster reduction of the phthalimide moiety.[84]

Table 10. Dihydrostilbene synthesis under UV-light conditions.

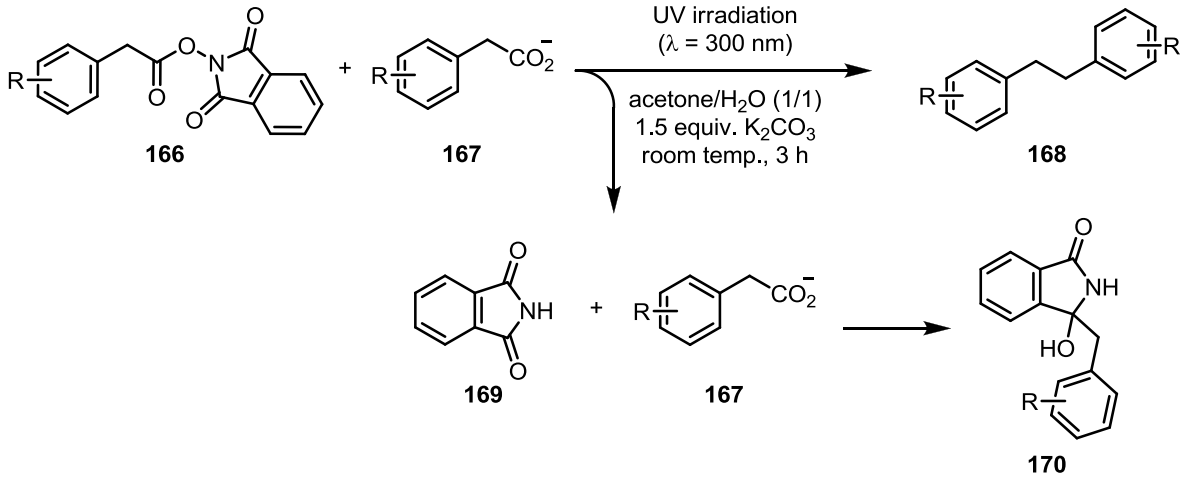


166 167 168

Entry	**166**	**167**	R	Solvent	Yield[a]
1	1 equiv.	-	*p*-OMe	acetone/H_2O (1/1)	40%
2[b]	1 equiv.	-	*p*-Me	acetone/H_2O (1/1)	18%
3[c]	1 equiv.	1 equiv.	*p*-OMe	acetone/H_2O (1/1)	48%
4[c]	1 equiv.	3 equiv.	*p*-OMe	acetone/H_2O (1/1)	72%
5[d]	1 equiv.	1 equiv.	*p*-OMe	acetone/buffer (1/1)	20%
6	-	1 equiv.	*p*-OMe	acetone/H_2O (10/1)	-
7[e]	1 equiv.	1 equiv.	*p*-OMe	acetone/H_2O (1/1)	-

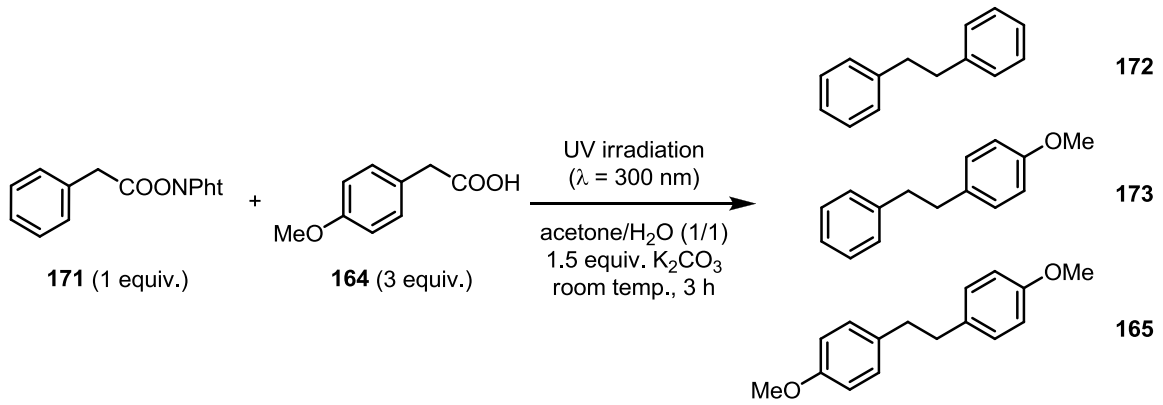
[a] Yields are based on *N*-acyloxyphthalimide. [b] 4 h reaction time. [c] additional 1.5 equiv. K_2CO_3. [d] pH 7 buffer solution (Fixanal®), without K_2CO_3. [e] no light irradiation for 20 h.

During the photoreaction, free phthalimide (**169**) was formed. Due to the UV light, the well-precedented alkylation of phthalimides takes place, forming compound **170**. This competing reaction decreased the amount of acid available for the dihydrostilbene synthesis, thereby reducing its efficiency (Scheme 41). The best results (72% yield; Table 10; entry 4) were obtained using 3 equiv. of the phenylacetic acid additive. Using a pH 7 buffer solution (Fixanal®) for the reactions,[85b] which was generally used for the alkylation reactions to "free" phthalimides only 20% dihydrostilbene was isolated (entry 5). Without the phthalimide activation and without light irradiation, no reaction was determined (entry 6 and 7).



Scheme 41. Phthalimide alkylation as a side reaction of the dihydrostilbene synthesis.

In order to find out, whether the last step of the mechanism is a radical dimerization, the photoreaction of the non-substituted phthalimide activated acid **171** with 4-methoxyphenylacetic acid (**164**) was performed. After the reaction, three dihydrostilbenes, originating from the combination of both benzyl radicals, were obtained in a total yield of approximately 78%, based on **166**, and a product ratio of 1:2.4:2.1 (**172**:**173**:**165**; determined by NMR analysis (Scheme 42). In addition to this reaction, the alkylated phthalimide side product **170** (R = *para*-OMe), which only reacted with the acid **164** was isolated in 87% yield, based on maximum released amount of phthalimide.

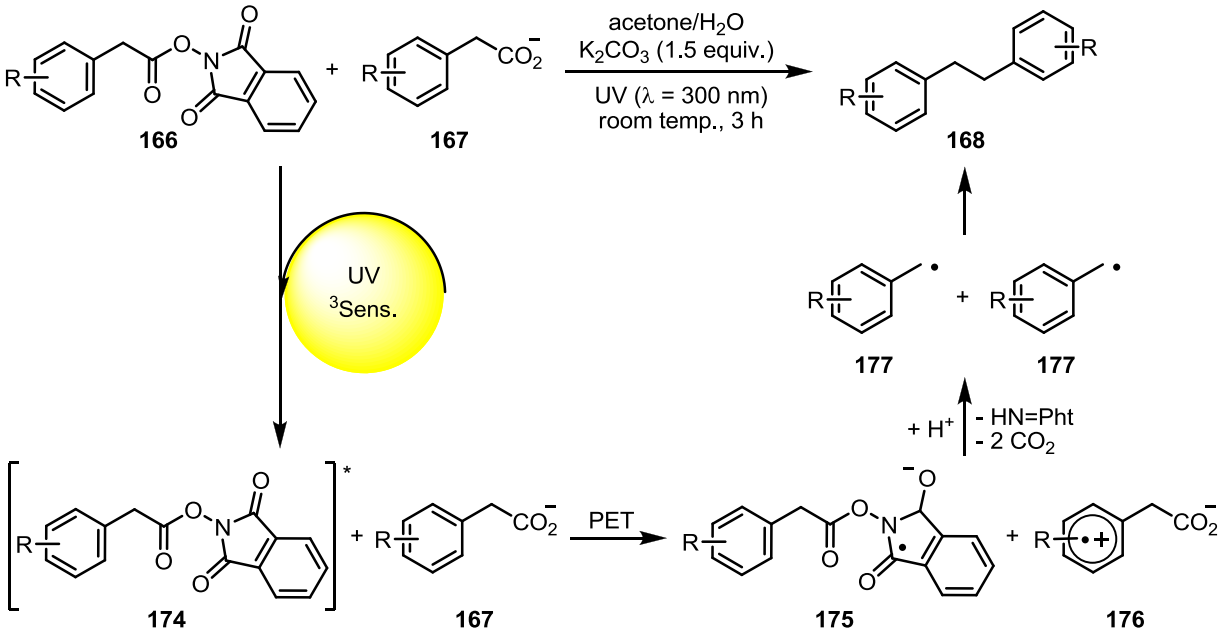


Scheme 42. Simultaneous decarboxylation of different phenylacetic acid derivatives.

The amount of mixed heterocoupling product **173** was 2.4 times higher than homocoupled dihydrostilbene **172** formed by the phthalimide ester **171**. During the reduction of the phthalimide moiety by phenylacetic acid **164**, the molecules are sterically close to each other. This proximity could be increased by the possibility of π-stacking.[91] Nevertheless the amount of **172** and **165** product is still too high, to use this reaction for a selective, preparative useful C-C coupling between different acids.

2.2.4 Mechanistic aspects of the UV decarboxylation reaction

With these results in hand the following sensitization reaction mechanism was proposed. The UV irradiation of the acetone/water reaction mixture leads to the triplet sensitization of *N*-acyloxyphthalimide **166**. The excited species **174** is reduced by the phenylacetic acid (**167**). Depending on the substituents and therefore the electron density of the phenyl group, a different phenylacetic acid moiety reduces the phthalimide group. In case of a high electron density in the phenyl ring, the moiety itself reduces the excited phthalimide species. If no electron donor substituents were present, the acid group is performing the reduction. The reduced phthalimide **175** gets protonated by the solvent and undergoes a phthalimide cleavage followed by the decarboxylation. The oxidized phenylacetic acid derivative **176** decarboxylates spontaneously, whereby two benzyl radicals **177** are obtained. After dimerization of the radicals the desired dihydrostilbene **168** is formed (Scheme 43).

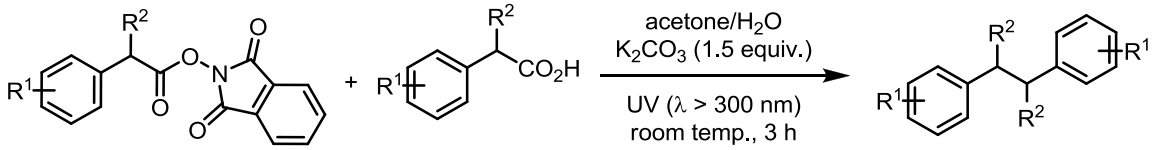


Scheme 43. Proposed reaction mechanism for the UV light mediated decarboxylation of **166** and **167** (PET = photoinduced electron transfer).

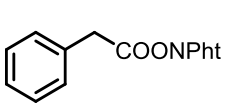
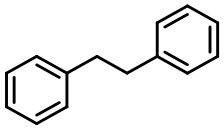
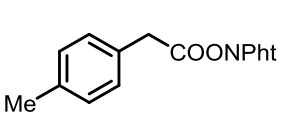
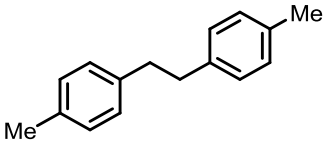
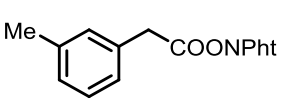
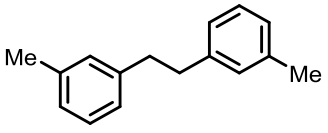
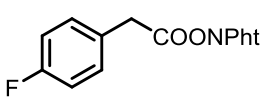
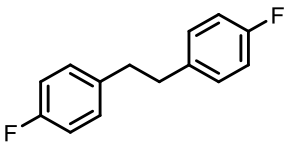
2.2.5 Scope of the dihydrostilbene synthesis

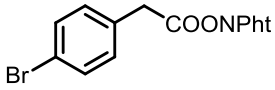
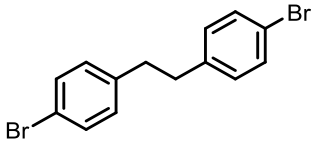
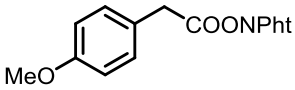
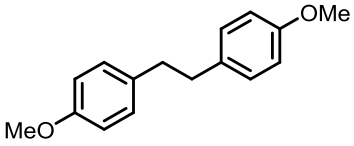
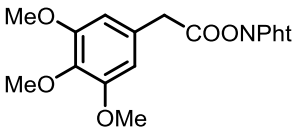
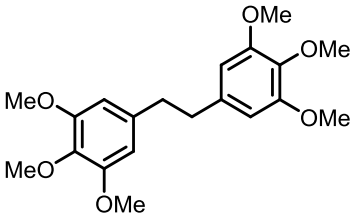
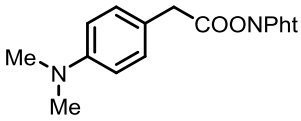
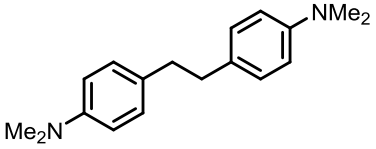
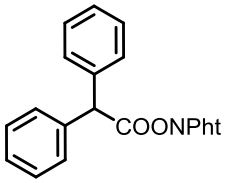
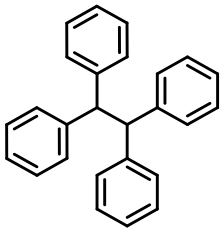
Different dihydrostilbenes were prepared starting from phenylacetic acid derivatives and their *N*-acyloxyphthalimides via UV-light irradiation. The phthalimide activated acids could be synthesized in fair to very good (52-87%) yields from the corresponding phenylacetic acid and *N*-hydroxyphthalimide. The yield of unsubstituted and *para*-methylated phenylacetic acids were in the same range of 59-62%. Therefore it was surprising that 1,2-di-*meta*-tolylethane (**168c**) was isolated in 82% yield (entry 3). Also halogenated derivatives, such as fluoro- or bromo-dihydrostilbenes could be synthesized (entry 4 and 5). The phthalimide coupled *para*-methoxyphenylacetic acid gave 72% yield (entry 6). For the decarboxylation of the trimethoxy-substituted phenylacetic acid (**168g**) only 1 equivalent of the corresponding acid was used, wherefore only 28% yield was isolated (entry 7). The phthalimide activated 4-(dimethylamino)phenylacetic acid **168h** is very light sensitive, for this reason the yield drops to only 17% (entry 8). Finally the secondary acid derivative **166i** was decarboxylated isolating dihydrostilbene **168i** in 43% yield (entry 9).

Table 11. Dihydrostilbene synthesis via light induced decarboxylation.



166 (1 equiv.) + **167** (3 equiv.) → **168**

Entry	Substrate		Product		Yield
1		**166a**		**168a**	59%
2		**166b**		**168b**	62%
3		**166c**		**168c**	82%
4		**166d**		**168d**	50%

Entry	Substrate		Product		Yield
5		**166e**		**168e**	61%
6		**166f**		**168f**	72%
7[a]		**166g**		**168g**	28%
8		**166h**		**168h**	17%[a]
9[b]		**166i**		**168i**	43%

[a] 1 equiv. of 2-(3,4,5-trimethoxyphenyl)acetic acid. [b] irradiated with an high pressure mercury lamp.

2.2.6 Conclusion

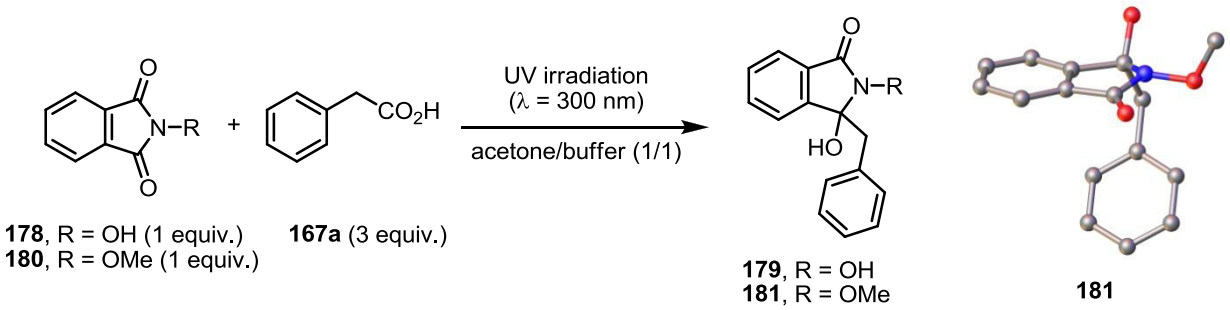
A feasible “dual” decarboxylation method via UV-light irradiation, using phthalimide activated acids and phenylacetic acids, was investigated. In a light sensitized mechanism the phthalimide moiety was reduced by the phenylacetic acid. After simultaneous decarboxylation of both substrates the stabilized radicals combine in a crosscoupling reaction. A library of different dihydrostilbenes with fair to very good yields was established.

2.3 Photodecarboxylative benzylation of *N*-methoxy-phthalimides[d]

2.3.1 Benzylation of *N*-substituted phthalimides

The photochemical behavior of phthalimides is well investigated and many papers were published in this research area.[68,92] The photo excited species of the phthalimide moieties can be reduced by a multiplicity of compounds, like arenes, alkenes, ethers, amines and thioethers.[69] Griesbeck *et al.* and Oelgemöller *et al.* investigated an impressive alkylation method for phthalimides using carboxylic acids. Regardless if the reaction is inter- or intramolecular, this protocol was extended to *N*-substitution free phthalimide derivatives and a multitude of *N*-alkylphthalimides.[93,94] At this juncture, the well-known benzylation reaction was observed as a side reaction in the decarboxylation project forming dihydrostilbenes, as described before (Scheme 41).

Considering former studies, the established protocol for the photodecarboxylative addition of carboxylates to phthalimides were extended to *N*-hydroxy and *N*-methoxy substituents. The expected *N*-substituted phthalimide products are attractive precursors in the synthesis of novel isoindolinone derivatives and aristolactames.[95]



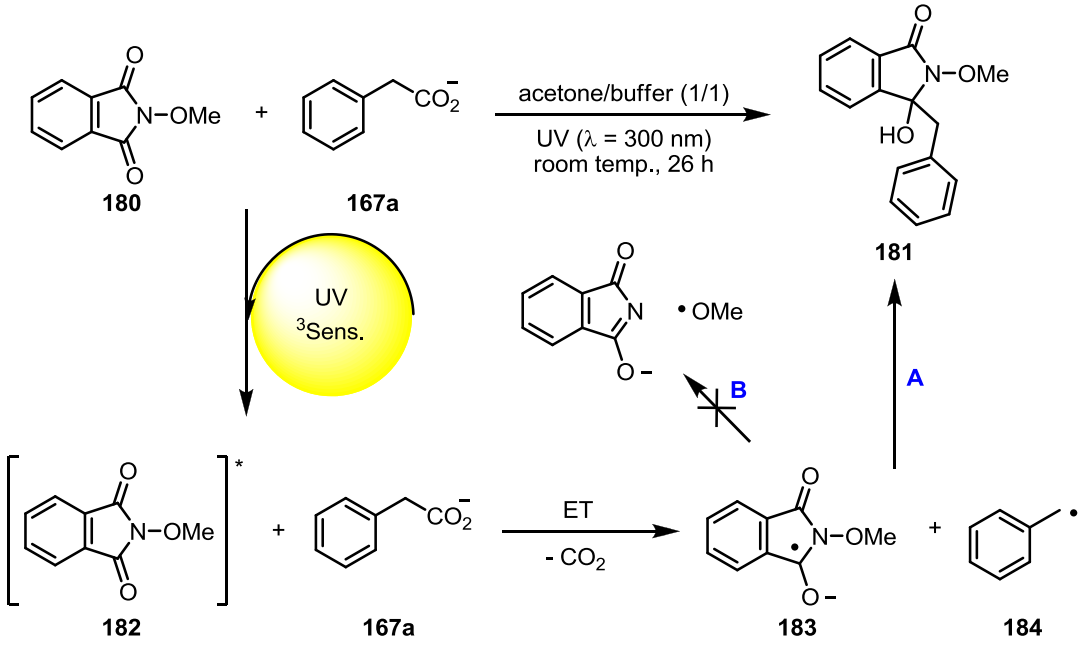
Scheme 44. Photodecarboxylative benzylation of phthalimide **178** and **180**. **179**, 23h (0%); **181**, 26 h (73%).

First decarboxylation experiments were performed in a 1/1 solvent mixture of acetone and pH 7 buffer (Fixanal®), because of salt effects of the phenylacetic acid. Former publications in this field of research showed that the reaction efficiency is correlated to the pH level of the solvent.[85b] Using 3 equiv. of acid **167a** and *N*-hydroxypthalimide (**178**), no conversion was

[d] This Chapter is based on Pordanjani, H. M.; Faderl, C.; Wang, J.; Motti, C. A.; Junk, P. C.; Oelgemöller, M. *Aust. J. Chem.* **2015**, *68*, 1662-1667. Appropriate copyrights have been obtained where necessary.

observed after 23 h of irradiation. The reaction with *N*-methoxyphthalimide (**180**) was successful, forming 2-methoxyisoindolinone **181** after 26 h in 73% yield (Scheme 44).

The mechanistic discussion starts with the triplet sensitization of *N*-methoxyphthalimide (**180**) by UV irradiated acetone. The intermolecular electron transfer from the phenylacetic acid to the excited phthalimide leads to the reduced phthalimide **183** and the decarboxylation of the oxidiezed acid to the alkyl radical **184**. Sammis et al. reported a photoredox catalyzed fragmentation of *N*-alkoxyphthalimides.[96] In their mechanism they claim a homolysis and a simultaneous acting intramolecular elimination of the reduced *N*-alkoxyphthalimide **183**. This phthalimide cleavage (path B) couldn´t be observed, whereby protonation and C-C bond formation yielded the benzylated *N*-methoxyphthalimide **181** (path A, Scheme 45).



Scheme 45. Proposed reaction mechanism of the photodecarboxylative benzylation of *N*-methoxyphthalimide **180**.

Hossein Mohammadkhani Pordanjani, a grad student in the Oelgemöller group, optimized the conditions for that reaction and benzylated *N*-methoxyphthalimides with a couple of different phenylacetic acid derivatives.[97]

2.3.2 Benzylation of *N*-methoxyphthalimide under flow conditions[e]

An important step to commercialize a reaction and make it attractive for industry, is to develop a continuous flow setup for this reaction.[98] The advantages over batch techniques are numerous, such as a better control of reaction parameter, like temperature or reaction time. Also in many reactions the yields increase, because products were removed from the irradiated zone and there is less chance of photodecomposition.[99] Furthermore faster operation times and quick optimizations of the reactions are possible, to name but a few.[100]

Accordingly the benzylated *N*-methoxyphthalimide **181** was prepared by continuous-flow photochemistry. For the flow studies the commercially available Vapourtec easy-Photochem reactor (Figure 9) was used. The UV-150 reactor chamber was equipped with a 150 W medium pressure pure mercury lamp, which operated during the reaction with 82 W at around 30 °C. A so called "gold filter" in the reactor guarantees wavelengths of $\lambda = 290$ nm.

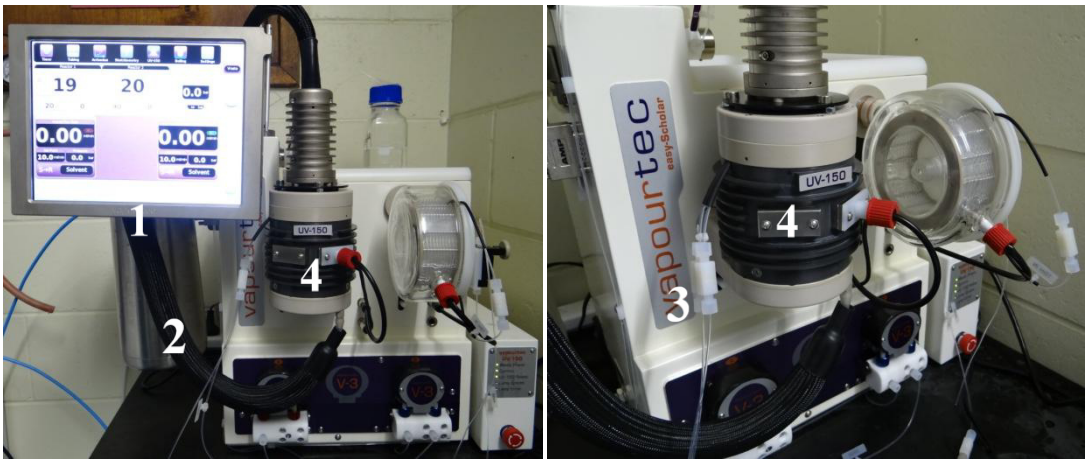


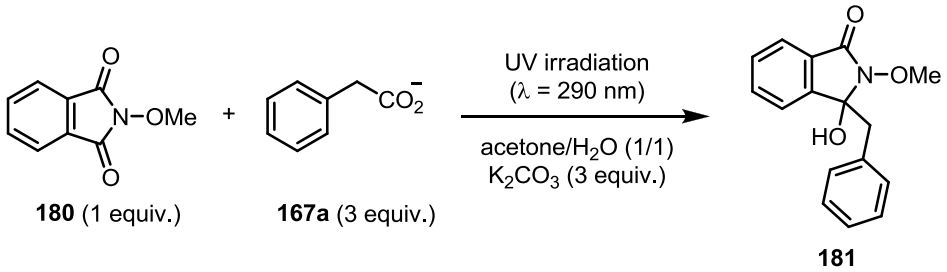
Figure 9. Vapourtec easy-Photochem module: digital display (1), cooling system (2), in- and outlet (3) and UV-150 chamber (4).

After the optimization reactions of Hossain M. Pordanjani the reaction time could be shortened to 1 h, which comes along with a decreasing yield from 73% to 52% (Table 12).[97] With these reaction conditions in hand, the concentration studies were performed with a constant flow rate of 5 ml/min (= 120 s irradiation / residence time; entry 1-4). Full conversion was achieved with 0.01 mmol/l concentration of the substrate, and 67% 2-methoxyisoindolinone **181** was isolated. Despite the application of a relatively small reaction coil (internal diameter: 1.30 mm) and a strong UV irradiation the conversion dropped with

[e] Hossein M. Pordanjani and I myself performed the following concentration and flow rate studies under my supervision.

increasing substrate concentration. In a second step, the flow rate was changed to lower the reaction time (entry 5-9), which resulted in a reduction of conversion rates. The best result, with full conversion and 74% isolated yield, was achieved with 0.01 mmol/l concentration and a flow rate of 6 ml/min (100 s irradiation / residence time; entry 6).

Table 12. Experimental details for the photoinduced benzylation of **180** with **166a** in the flow reactor.



Entry	Conc. of **180** [mmol/l]	Flow rate [ml/min]	irradiation time [s]	Conversion [%][a]
1	0.01	5	120	100 (67[b])
2	0.015	5	120	88
3	0.025	5	120	39
4	0.1	5	120	trace
5	0.01	6	100	100 (74[b])
6	0.01	7	86	92
7	0.01	8	75	81
8	0.01	9	67	71
9	0.01	10	60	61

[a] Conversion was determined by ^{1}H NMR spectroscopy (± 3%). [b] Isolated yields.

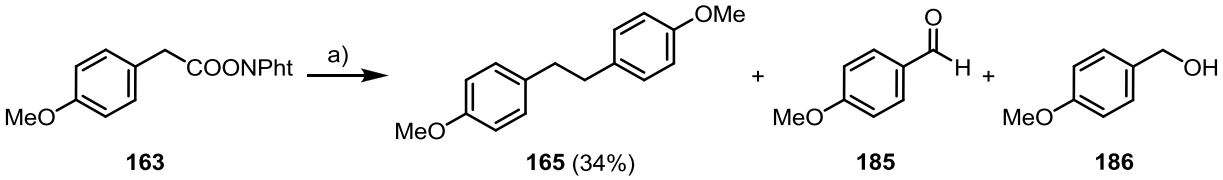
2.3.3 Conclusion

In conclusion, the photoinduced decarboxylation protocol was applied for the benzylation of *N*-methoxyphthalimide. A cleavage of the methoxy group, as previously described in literature, was not observed.[96] The reaction protocol was successfully transferred and optimized from batch condition to a meso-scale continuous flow photoreactor.

3 Decarboxylative hydroxylation/alkoxylation[f]

3.1 Preliminary studies and state of the art

In preliminary studies using visible light and a photocatalyst for the synthesis of dihydrostilbene **165**, decarboxylation of *N*-acyloxyphthalimide **163** generated aldehyde **185** and a significant amount of benzyl alcohol **186** as side products (Scheme 46 and Section 2.2.1). Slightly changing of the reaction conditions, e.g. using acetonitrile instead of acetone as solvent, led to a dramatically change of the product formation. UV-light irradiation turned out to be the most efficient way synthesizing dihydrostilbenes (50-82%), following this decarboxylation procedure (Table 11, Section 2.2.5). Vice versa visible light photochemistry seemed to be the method of choice transforming phenylacetic acid derivatives into benzyl alcohols.



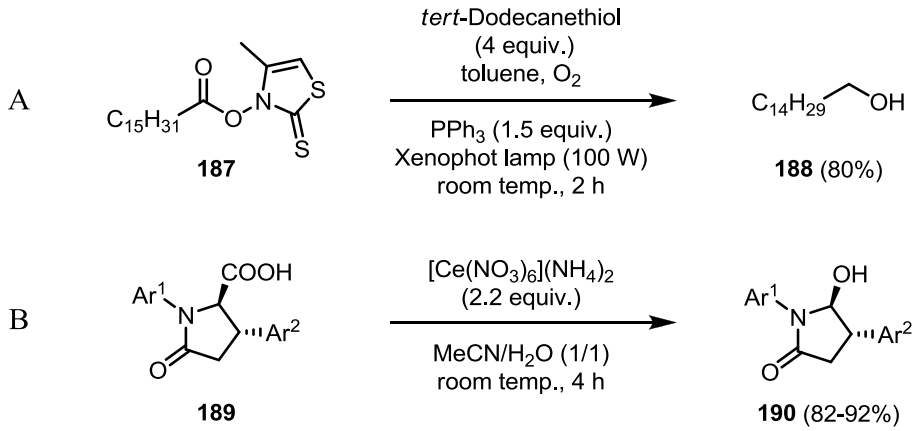
163 **165** (34%) **185** **186**

Scheme 46. Visible light-mediated decarboxylation of **163**. a) $[Ir(dtb\text{-}bpy)(ppy)_2]PF_6$ (1 mol%), acetone/H_2O (20/1, c = 0.1 mol/l), hν (455 nm), room temp., 16 h.

Analysis of the literature showed that only few examples of decarboxylation/hydroxylation protocols are known.[101] These reactions include complex reaction mixtures with excess of harmful and expensive chemicals. First Barton *et al.* reported the decarboxylation/hydroxylation reaction using a Barton decarboxylation with 2 equiv. $(PhS)_3Sb$ and oxygen.[101a,102] A few years later, this reaction was improved by the same working group replacing the antimony compound with 4 equiv. *tert*-dodecanethiol and 1.5 equiv. triphenylphosphine in toluene using visible light (Scheme 47, A.). Another very special method, because it was only done for *N*-aryl-γ-lactame carboxylic acids **189**, was investigated by Ray *et al.* Performing the reaction in presence of 2.2 equiv. ceric ammonium nitrate (CAN) not only hydroxylations, but also alkoxylations were possible, while the sterical

[f] This Chapter is based on a cooperation with M.Sc. Simon Budde, who conducted investigations for this project in his master thesis "*Decarboxylation of N-Hydroxyphthalimide esters: Attempted synthesis of annulated indoles and investigations of a new reaction pathway*". Appropriate copyrights have been obtained where necessary.

information is retained. (Scheme 47, B).[101c] This is also the only example where free acids were applied.



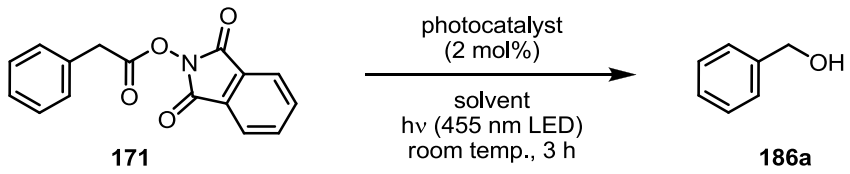
Scheme 47. Literature examples of decarboxylation/hydroxylation reactions (A[101b], B[101c]).

The decarboxylative hydroxylation/alkoxylation is a useful tool in organic synthesis. Acids, which are very common in nature and the synthesis of fine chemicals, can be transferred into further important hydroxyl/alkoxy derivatives. For example the Barton decarboxylation and hydroxylation employing $(PhS)_3Sb$ was used in natural compound synthesis of debromoflustramide B,[103] (-)-Paeoniflorin),[104] or (-)-Verrucarol.[105]

Below the visible light-mediated decarboxylative hydroxylation of *N*-acyloxyphthalimides was investigated, which represents an easy and chemical saving alternative to the literature known methods.

3.2 Optimization experiments and mechanistic considerations[g]

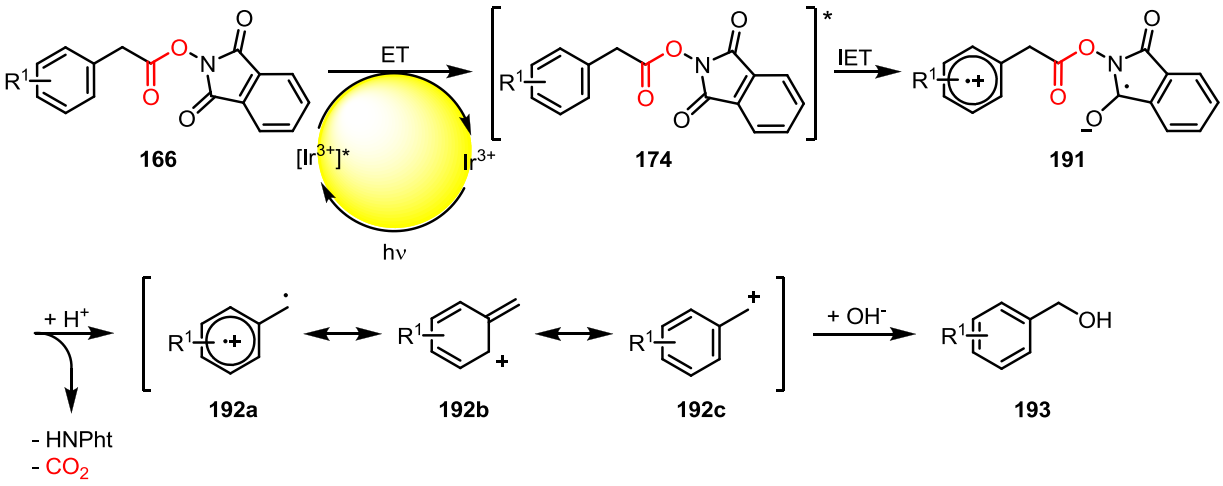
To optimize the reaction conditions phenylacetic acid based phthalimide ester **171** was used (Scheme 48). M.Sc. Simon Budde performed the optimization reactions regarding solvents, catalysts and catalyst amount. Water plays a crucial role in this reaction. Besides the protonation of the phthalimide moiety, water is also necessary for the hydroxyl addition. Therefore only water miscible solvents were screened.



Scheme 48. Model reaction for the decarboxylative hydroxylation.

Compound **171** was irradiated in presence of 2 mol% $[Ir(dtb\text{-}bpy)(ppy)_2]PF_6$ in 0.1 molar reaction mixtures in 4/1 ratios of acetone/water, MeCN/water, DMF/water and THF/water. The biggest amount of benzyl alcohol was obtained using MeCN/water, which is in agreement to the results of the dihydrostilbene synthesis (see Section 2.2.1). Subsequently the amount of water was changed in the reaction. Performing the reaction in a 0.1 molar solution with different MeCN/water ratios from 8/1 to 1/4 the highest yield of 85% was achieved with a 2/1 reaction mixture. The photocatalyst screening suggests a photosensitization mechanism. Application of $[Ru(bpy)_3]Cl_2$ showed no reaction and the photoreactions with $[Cu(dap)_2]Cl$ and $[Ir\{dF(CF_3)ppy\}_2(dtb\text{-}bpy)]PF_6$ only low conversions were observed. The best yields were obtained using $[Ir(dtb\text{-}bpy)(ppy)_2]PF_6$, whose redox potential of the excited state ($[Ir^{3+}]^* \rightarrow Ir^{4+}$ = -0.96 V vs SCE)[43] is too low for direct reduction of the phthalimide moiety of compound **171** ($E_{1/2}$ = -1.22 V vs SCE). Therefore the catalyst serves as a sensitizer in the reaction, transferring energy to *N*-acyloxyphthalimide **166** (Scheme 49).

[g] The optimization reactions of this chapter were performed by M.Sc. Simon Budde.

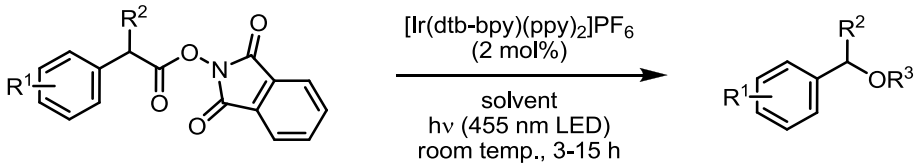


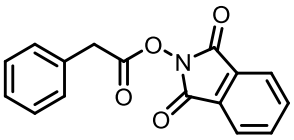
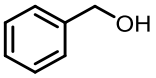
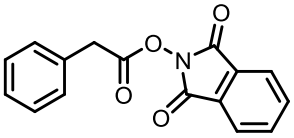
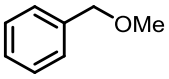
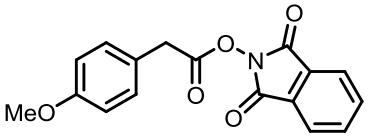
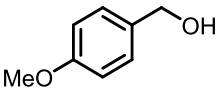
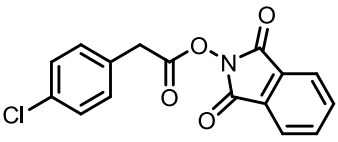
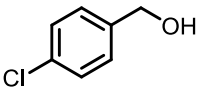
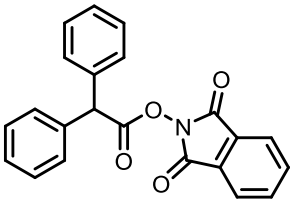
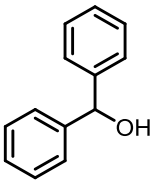
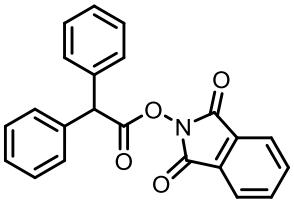
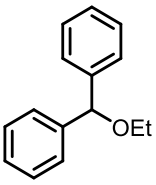
Scheme 49. Proposed visible light-mediated decarboxylation/hydroxylation mechanism.

The excited molecule **174** undergoes an intramolecular electron transfer, reducing the phthalimide moiety by the phenyl group. After protonation of intermediate **191** phthalimide cleavage occurs, followed by decarboxylation. Nucleophilic addition of the mesomeric stabilized benzyl radical **192**, via the water containing solvent, leads to appropriate benzyl alcohol **194** (Scheme 49). In a side reaction, which is caused by photosensitization of the catalyst, dihydrostilbene was synthesized (Section 2.2.1).

The photoinduced decarboxylation/hydroxylation reaction of phenylacetic acid derivatives leads to corresponding benzyl alcohols in good yields (Table 13). Besides the non-substituted compound **171**, which gave 85% of benzyl alcohol (**186a**, entry 1), 4-methoxy and 4-chloro substituted phenylacetic acid derivatives were applied in this reaction leading to the alcohols **186b** and **186c** in 92% and 71% yield (entry 3 and 4). Also secondary alcohol **186d** could be isolated in a good yield (entry 5). Changing the solvent to acetonitrile/alcohol reaction mixture, alkoxylation of the cation intermediate **192c** is the consequence. According to this the ethers **194** and **195** were synthesized (entry 2 and 5). Side reactions with the solvent acetonitrile were not detected.

Table 13. Decarboxylative hydroxylation and alkoxylation of phenylacetic acid derivatives.

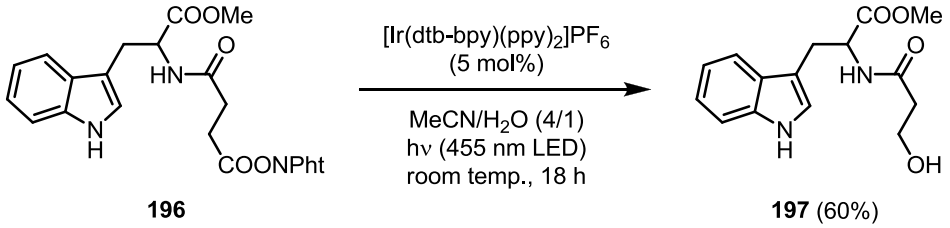


Entry	*N*-Acyloxyphthalimide		Solvent[a]	Product		Yield
1[b]		**171**	MeCN/H_2O		**186a**	85%
2[b]		**171**	MeCN/MeOH		**194**	76%
3		**163**	MeCN/H_2O		**186b**	92%
4		**166j**	MeCN/H_2O		**186c**	71%
5		**166i**	MeCN/H_2O		**186d**	73%
6		**166i**	MeCN/EtOH		**195**	68%

[a] c = 0.1 M solution. [b] Performed by M.Sc. Simon Budde.

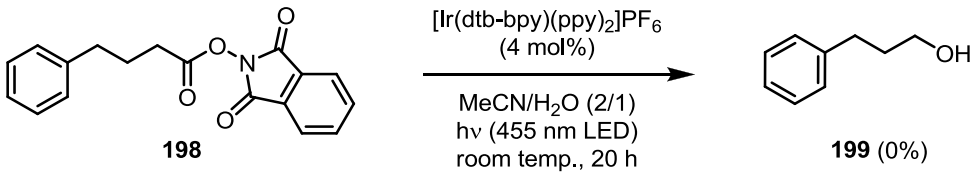
3.3 Further decarboxylative hydrogenation investigations

Regarding the mechanism, decarboxylation of phenylacetic acid derivative **166** leads to the ω-alkyl cation intermediate **192c** via mesomeric effects. Other phthalimide esters need another mechanism to generate the cation intermediate. Photodecarboxylation of compound **196**, which was performed by M.Sc. Simon Budde, yields 60% of hydroxyl product **197** (Scheme 50). Instead of mesomeric effects, a second intramolecular electron transfer from the alkyl radical to the phenyl moiety forming the ω-alkyl cation intermediate was assumed. This second charge transfer was already observed in the photoreaction of *N*-acyloxyphthalimide **97** (Scheme 27, Section 1.5.1).



Scheme 50. Photodecarboxylation of **196**.[h]

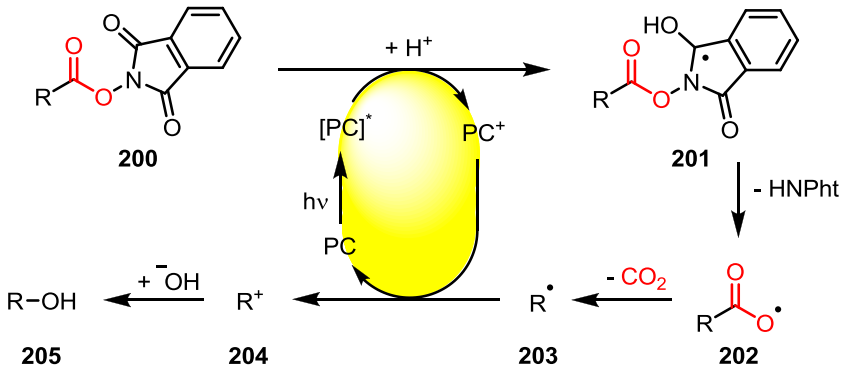
Unfortunately using simple ω-aryl-phthalimide esters, such as compound **198** or the phthalimide ester of cinnamic acid, no reaction was observed (Scheme 51). These molecules were not able to undergo the intramolecular electron transfer, accompanied by phthalimide cleavage and decarboxylation.



Scheme 51. Photoreaction of **198**.

This sensitization mechanism limits the reaction scope not only to ω-aryl compounds, but also linear molecules with a disfavored conformation show no reaction. In order to use alkyl acid derivatives in general for this decarboxylation/hydroxylation reaction, another reaction with a different mechanism was proposed (Scheme 52).

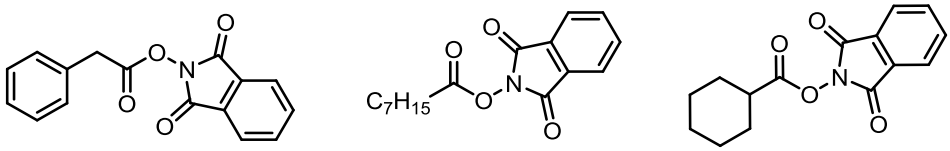
[h] Reaction was performed by M.Sc. Simon Budde.



Scheme 52. Proposed decarboxylation/hydroxylation mechanism for alkyl acid derivatives **200**.

This reaction is based on photocatalysts, whose excited states have redox potentials which are high enough to reduce the phthalimide moiety directly. After phthalimide cleavage and decarboxylation, the alkyl radicals should get oxidized via the oxidized species of the photocatalyst, such as in ATRA (atom transfer radical addition) reactions.[106] The cation intermediate **204** can be trapped by the water containing solvent.

In order to find suitable photocatalysts the redox potentials of several *N*-acyloxyphthalimides were measured (Figure 10). The potentials of the phthalimide esters of phenylacetic acid (**171**), octanoic acid (**206**) and cyclohexane carboxylic acid (**207**) were all in the same range of -1.22 V to -1.25 V (vs. SCE).



171 ($E_{1/2}$ = -1.22 V) **206** ($E_{1/2}$ = -1.25 V) **207** ($E_{1/2}$ = -1.23 V)

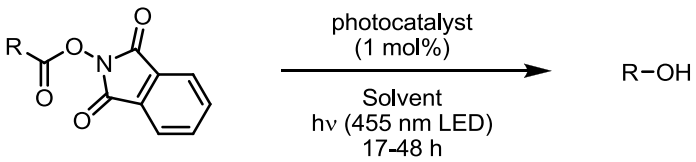
Figure 10. Redox potentials of **171**, **206**, and **207**. Measured in acetonitrile and calculated vs. SCE.

The metal based photocatalysts *fac*-Ir(ppy)$_3$ ($E_{1/2}$ $Ir^{4+}/[Ir^{3+}]^*$ = -1.73 V vs. SCE) and [Cu(dap)$_2$]Cl ($E_{1/2}$ $Cu^{2+}/[Cu^{+}]^*$ = -1.43 V vs. SCE) come into consideration for the reduction of these phthalimide ester derivatives.

Irradiation of primary carboxylic acid derivative **206** in presence of *fac*-Ir(ppy)$_3$ or [Cu(dap)$_2$]Cl and acetonitrile/water solvent mixture no conversion was observed (Table 14, entry 1 and 2). The addition of formic acid to the reaction in order to support the phthalimide protonation did not lead to any conversion of the starting material (entry 3).

Applying compound **207**, which should form stabilized secondary radicals after decarboxylation, no product formation was observed. This applies analogously to the reaction with $[Ir(dtb\text{-}bpy)(ppy)_2]PF_6$ (entry 6). The formation of 1-adamantanol was also not successful using *fac*-$Ir(ppy)_3$ and $[Cu(dap)_2]Cl$ as catalysts (entry 7 and 8). Switching the solvent to DMF/water no influence on the reaction was observable (entry 9). Also the increasing of the temperature to 60 °C leads only to small amount of hydrolyzation, but has no effect on decarboxylation (entry 10).

Table 14. Decarboxylation/hydroxylation reactions of primary, secondary, and tertiary acid derivatives.



Entry	R	Catalyst	Solvent	Modification	Yield
1	*n*-heptyl	*fac*-$Ir(ppy)_3$	$MeCN/H_2O$		0%
2	*n*-heptyl	$[Cu(dap)_2]Cl$	$MeCN/H_2O$		0%
3	*n*-heptyl	*fac*-$Ir(ppy)_3$	$MeCN/H_2O$	formic acid[a]	0%
4	ω-phenylpropanyl	*fac*-$Ir(ppy)_3$	$MeCN/H_2O$		0%
5	cyclohexyl	*fac*-$Ir(ppy)_3$	$MeCN/H_2O$		0%
6	cyclohexyl	$[Ir(dtb\text{-}bpy)(ppy)_2]PF_6$	$MeCN/H_2O$		0%
7	1-adamantyl	*fac*-$Ir(ppy)_3$	$MeCN/H_2O$		0%
8	1-adamantyl	$[Cu(dap)_2]Cl$	$MeCN/H_2O$		0%
9	1-adamantyl	*fac*-$Ir(ppy)_3$	DMF/H_2O		0%
10	1-adamantyl	*fac*-$Ir(ppy)_3$	DMF/H_2O	60°C	0%

[a] 1 equiv. of formic acid.

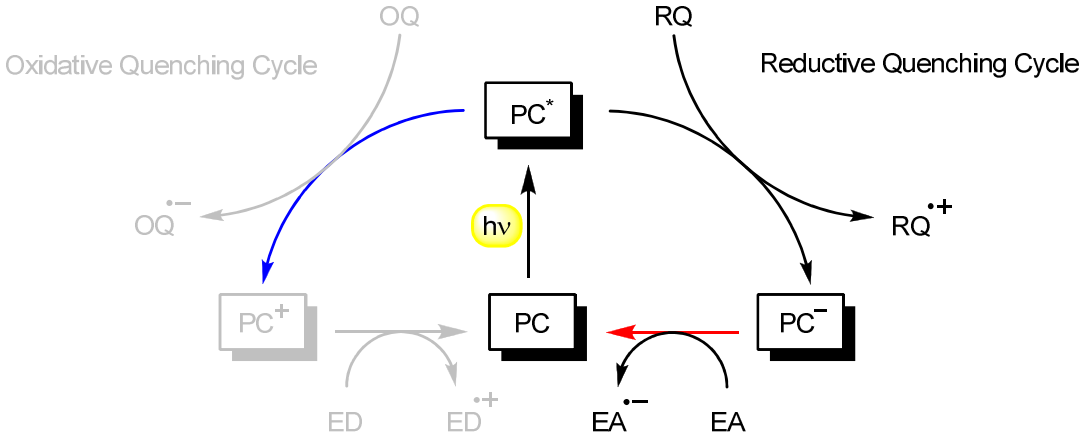
3.4 Conclusion

In summary, a protocol for the visible light mediated decarboxylative hydroxylation/alkoxylation was developed. Irradiation of *N*-acyloxyphthalimides based on phenylacetic acid derivatives in presence of $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ and aqueous acetonitrile the corresponding benzyl alcohols were isolated in good yields. Using alcohol instead of water in the solvent mixture allowed the isolation of benzyl ethers. Applying this reaction to other phthalimide coupled aliphatic acids was not successful. Changing the reaction conditions utilizing direct phthalimide reduction via photoredox chemistry, instead of a sensitization mechanism, showed no product formation. Consequently the reaction scope of this decarboxylative hydroxylation was limited to phenylacetic acid derivatives.

4 Photoredox catalyzed decarboxylative α-amination

4.1 Introduction

Photoredox chemistry is a mild and elegant tool for the reduction of certain compounds. The underlying mechanism has been studied thoroughly in the last decades.[107] Regarding common photocatalysts, the reduction potential of the PC^--species (Scheme 53, red) is much higher than the potential of its excited states (blue).[108] Therefore usually the reductive quenching cycle is applied for these reactions. After excitation of the photocatalyst (PC) via visible light, a reductive quencher (RQ) accepts an electron, forming the reduced species PC^-.



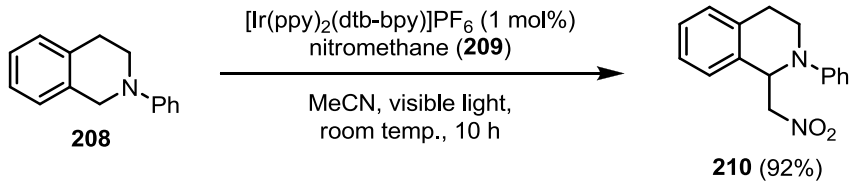
PC	$E_{1/2}(PC/PC^-)$	$E_{1/2}(PC^+/PC^*)$
$Ru(bpy)_3^{2+}$	-1.33 V	-0.81 V
$Ir[dF(CF_3)ppy]_2(dtb\text{-}bpy)^+$	-1.37 V	-0.89 V
$Ir(ppy)_2(dtb\text{-}bpy)^+$	-1.51 V	-0.96 V
fac-$Ir(ppy)_3$	-2.19 V	-1.73 V

Scheme 53. Oxidative and reductive quenching cycle and redox potentials of selected photocatalysts. PC = photocatalyst, RQ = reductive quencher, OQ = oxidative quencher, EA = electron acceptor, ED = electron donor.[108]

To get access to the high reductive power of photocatalysts, sacrificial electron donors, like NEt_3, DIPEA, BNAH or Hantzsch ester were added.[108] These consumables usually accumulate as waste and are only rarely used in subsequently occurring reactions. Using triethylamine (NEt_3), for example, after its oxidation by the excited photocatalyst, the α-C-H

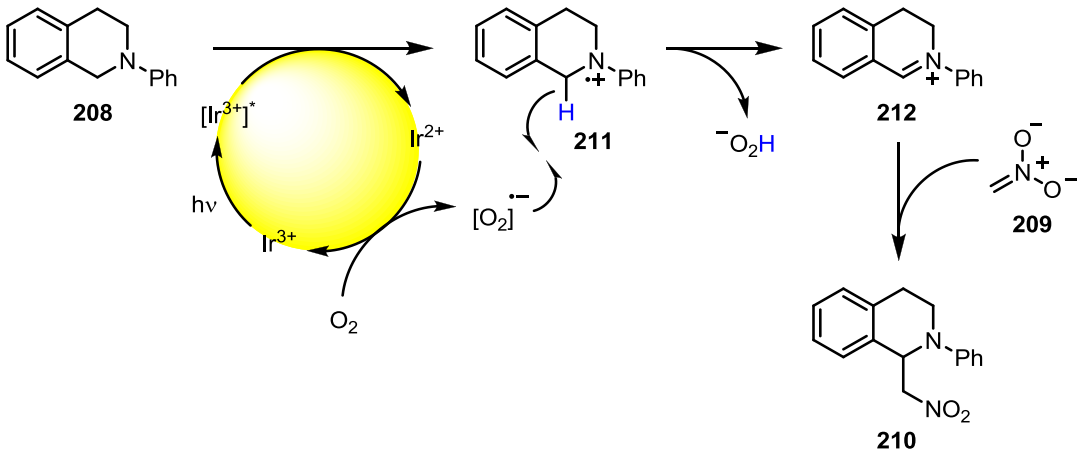
bond of the cation radical is weakened to approximately 42 kcal/mol, which could lead to proton abstraction.[109]

One possible application for using photoredox chemistry is the field of α-amino functionalizations. Stephenson *et al.* applied this functionalization using tetrahydroisoquinoline **208** in an oxidative *aza*-Henry reaction. In the presence of a photocatalyst and nitromethane, tetrahydroisoquinoline **208** undergoes an oxidative C-H functionalization, concluding in the formation of nitro compound **210** in 92% yield (Scheme 54).[110]



Scheme 54. Photocatalytic *aza*-Henry reaction of tetrahydroisoquinoline **208**.

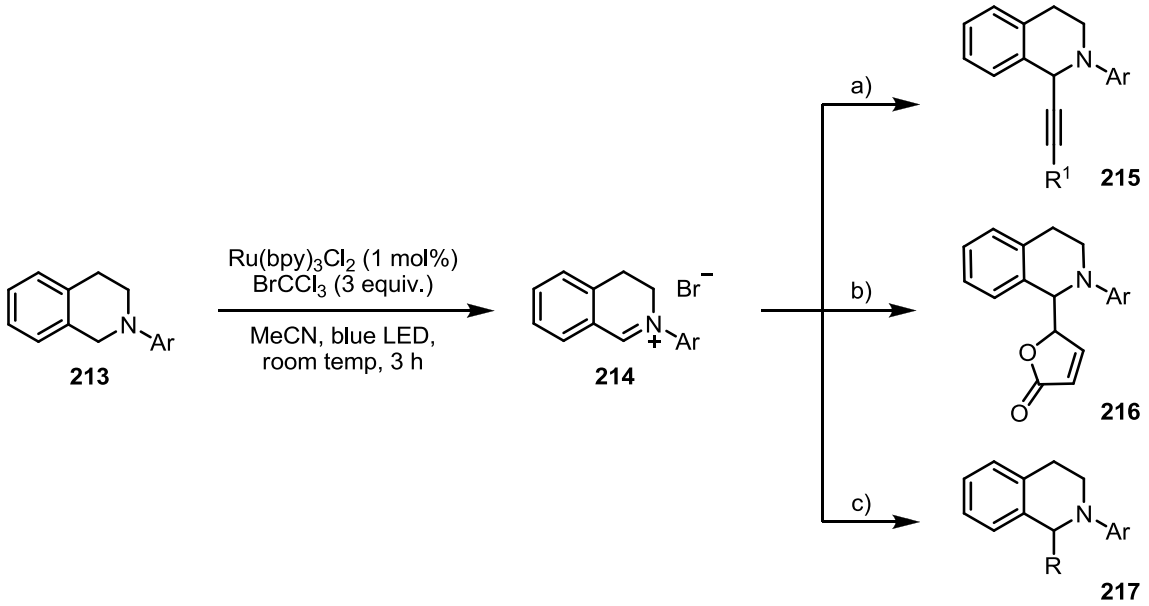
The best results were obtained using $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ as photocatalyst. The excited iridium based catalyst oxidizes tetrahydroisoquinoline **208**. Afterwards oxygen oxidizes the catalyst, regenerating the initial state. The generated superoxide radical subsequently abstracts a hydrogen from the cationic species **211**. The iminium ion **212** is the key intermediate in this reaction mechanism and is attacked by a deprotonated nitromethane (**209**), forming the product **210** (Scheme 55).



Scheme 55. Reaction mechanism of the photocatalytic *aza*-Henry reaction.[110]

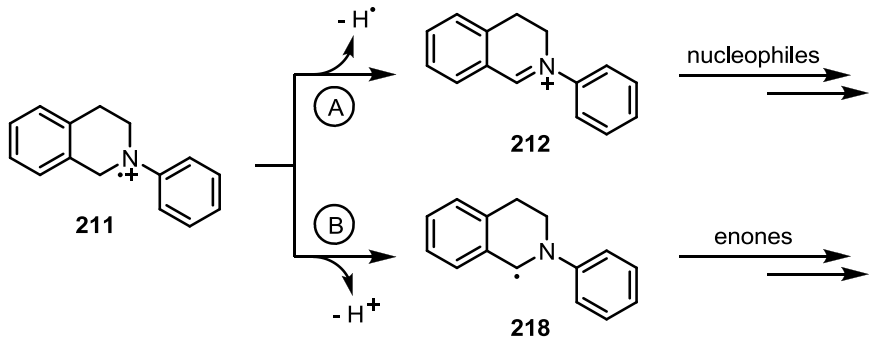
Applying oxygen in the reaction limits the scope and increases the reaction time for this oxidative *aza*-Henry reaction since the species can interact with the catalyst or other reactive

substrates.[111] To prevent these side reactions Stephenson *et al.* introduced bromotrichloromethane ($BrCCl_3$) for the synthesis of the iminium salt **214** instead. The photocatalyst is regenerated by the reduction of $BrCCl_3$, which splits into bromine anion and trichloromethane radical. Under the formation of chloroform, iminium salt **214** was obtained.[111] This iminium salt synthesis was the basis for several nucleophilic addition reactions (Scheme 56).



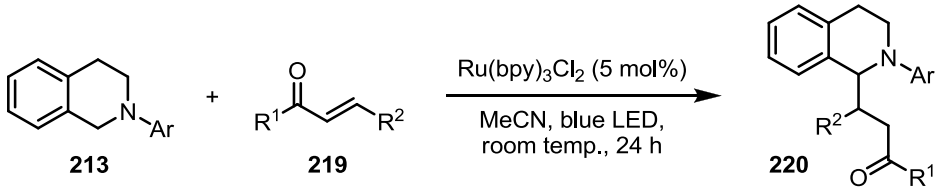
Scheme 56. Synthesis and transformation of the iminium salt **214**. a) NEt_3 (5 equiv.), CuBr (15 mol%), alkyne (5 equiv.), DMF, R = Ph, CH_2CH_2Ph (53-82%).[111] b) trimethylsiloxyfuran (5 equiv.), DMF, 55%.[111] c) RMgBr (2 equiv.), MeCN, 0 °C, N_2, < 5 min, R = alkyl, vinyl, phenyl (66-90%).[112]

In 2015 Zeitler *et al.* proved, that this iminium salt formation does not require any photocatalyst.[113] Under the same reaction conditions, but in absence of the photocatalyst, the desired products, in even higher yields, were isolated. By blue light irradiation of a $BrCCl_3$ solution, the formation of oxidative reagents was detected. Therefore the light promotes homolytic bond fission and the direct formation of bromine and CCl_3 radicals. Additionally a tetrahydroisoquinoline **208** solution containing $BrCCl_3$ seems to build an amine polyhalomethane electron donor acceptor (EDA) complex. Irradiating this complex leads to cation radical **211** and the decomposition of $CBrCl_3$ into CCl_3 radical. Both pathways promote the synthesis of iminium salt **214**, which can be used in subsequent nucleophilic addition reactions.[113]



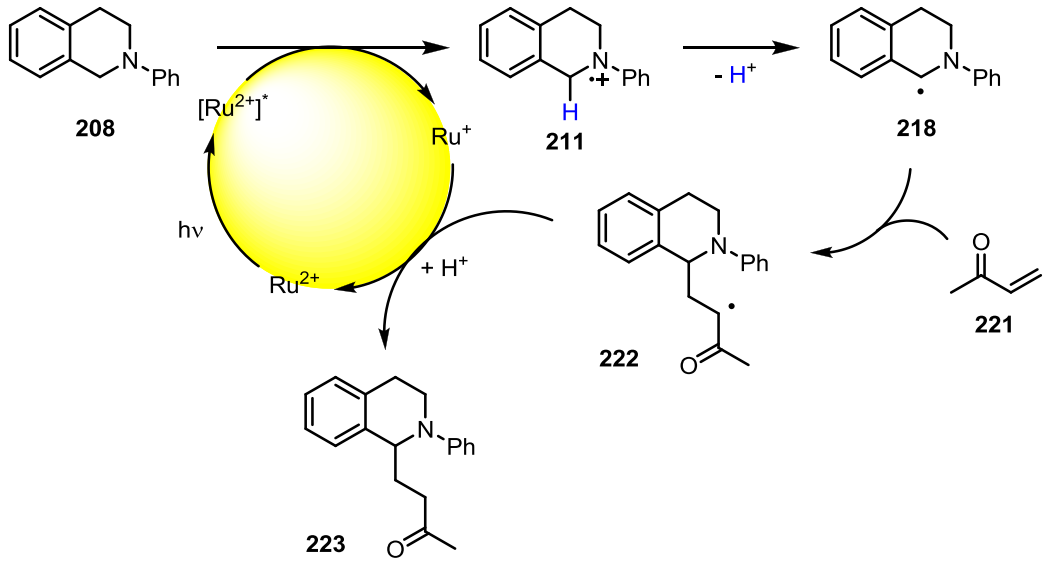
Scheme 57. Possible reaction pathways of the amino radical cation **211**.

So far oxidized tetrahydroisoquinoline species **211** was transformed into its iminium salt via photoredox chemistry followed by an irradiation independent nucleophilic addition reaction (Scheme 57, Pathway A). Recently Reiser *et al.* developed a photoreaction to generate α-amino radicals from tetrahydroisoquinoline **211** (Pathway B).[114] These radicals were coupled with a variety of Michael acceptors **219** in moderate to good yields (Scheme 58).



Scheme 58. Photocatalyzed α-functionalization of *N*-aryl-isoquinoline (**213**). $R^{1,2}$ = alkyl, phenyl.

No electron donor or acceptor is needed in this reaction. In the proposed mechanism the oxidation of tetrahydroisoquinoline **208** via the visible light excited ruthenium based photocatalyst, leads to the radical cation **211**. In contrast to the iminium synthesis, the cation **211** abstracts a proton forming the radical intermediate **218** followed by a coupling reaction with enones, such as methyl vinyl ketone (**221**). The cation **222** accepts an electron from the photocatalyst and resulting in the desired product **223** (Scheme 59).[114] Yoon *et al.* improved this reaction by adding TFA. Yields were increased and the reaction time was shortened from 24 h to 5 h. The lewis acid (TFA) subsequently protonates enone **219**, leading to an increased reactivity of the species, allowing for an easier attack by radical **218**.[115]



Scheme 59. Proposed mechanism of the α-amino radical conjugate addition to methyl vinyl ketone (**221**).

Besides the commonly used *N*-aryl-tetrahydroisoqinolines **213**,[110-115] photocatalyzed α-C-H-activations were also performed with *N*-methyl-9,10-dihydroacridine,[116] DMF[117] or 1-phenylpyrrolidine,[118] to name but a few.

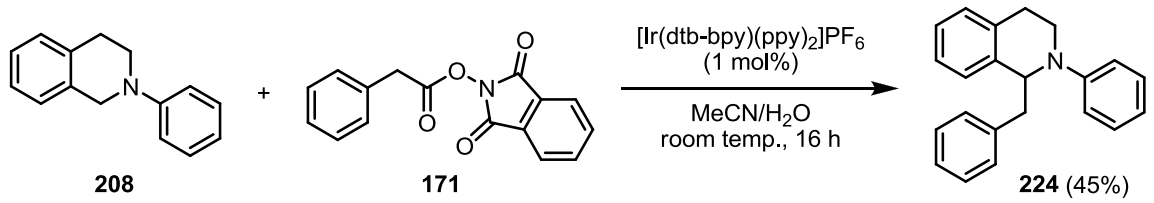
4.2 Decarboxylative α-amination via visible light

4.2.1 Optimization and control experiments

Earlier in the thesis the photoredox catalyzed decarboxylation of *N*-acyloxyphthalimides of Okada *et al.*[48] and Overman *et al.*[90] were described. To reduce the phthalimide moiety the working groups utilize the reductive quenching cycle of the photocatalysts (Scheme 53). A sacrificial electron donor reduces the excited catalyst, which donates an electron to the phthalimide moiety, leading to decarboxylation.

In the following project it was envisioned to combine this phthalimide assisted decarboxylation reaction with the photocatalyzed α-amino activation of tetrahydro-isoquinolines, generating a new C-C bond.

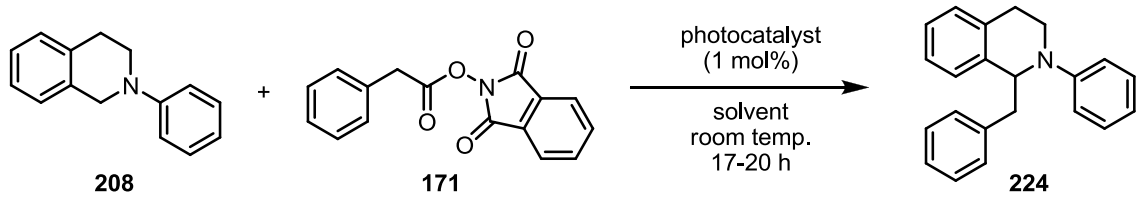
As a test reaction *N*-phenyl-tetrahydroisoquinoline (**208**) and *N*-acyloxyphthalimide **171** were irradiated under previously established photoreaction conditions (Section 1.4.1), using 1 mol% $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ in an acetonitrile water solvent mixture (ratio 40/1, c = 0.1 M). After 16 h the benzylated tetrahydroisoquinoline **224** was isolated in 45% yield (Scheme 60).



Scheme 60. Photoredox reaction of *N*-phenyl-tetrahydroisoquinoline (**208**) and *N*-acyloxy-phthalimide **171**.

Solvent screening showed that no additional proton source for the phthalimide protonation is necessary and the reaction can be performed in water free solvents (Table 15). Apart from DCM, where only 8% product was isolable (entry 8), moderate to good yields were obtained with common solvents. Using $[Ru(bpy)_3]Cl_2$ as catalyst no full conversion of the starting material and lower yields were observed, within 20 h of irradiation.

Table 15. Catalyst and solvent screening of the α-amino benzylation.



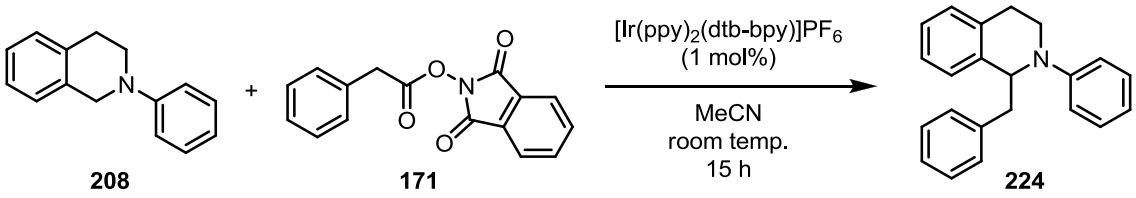
208 **171** **224**

Entry	Catalyst (1 mol%)	Solvent	Yield[b]
1	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	MeCN/H_2O (40/1)[a]	45%
2	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	MeCN	65%
3	$[Ru(bpy)_3]Cl_2$		32%[c]
4	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	DMF	36%
5	$[Ru(bpy)_3]Cl_2$		41%
6	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	THF	36%
7	$[Ru(bpy)_3]Cl_2$		15%[c]
8	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	DCM	8%
9	$[Ru(bpy)_3]Cl_2$		9%[c]
10	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	acetone	46%

[a] reaction concentration 0.1 mol/l. [b] Yields were determined by NMR analysis with 4-nitrobenzaldehyde as internal standard. [c] no full conversion after 20 h.

Further optimizations proved, that neither using an additional base (Table 16, entry 2), for improving proton abstraction of tetrahydroisoquinoline **208**, nor formic acid (entry 3), protonating the phthalimide moiety of **171**, improved the product formation. Employing Hantzsch ester in this reaction, which is able to act as an additional sacrificial electron and hydrogen donor,[119] product **224** was not isolated (entry 2). In the absence of light or photocatalyst no reaction takes place (entries 4 and 5). Oxygen reduces the reaction rate, although 22% yield was still observed in a non-degassed system (entry 6).

Table 16. Control and optimization experiments of the α-amino benzylation.



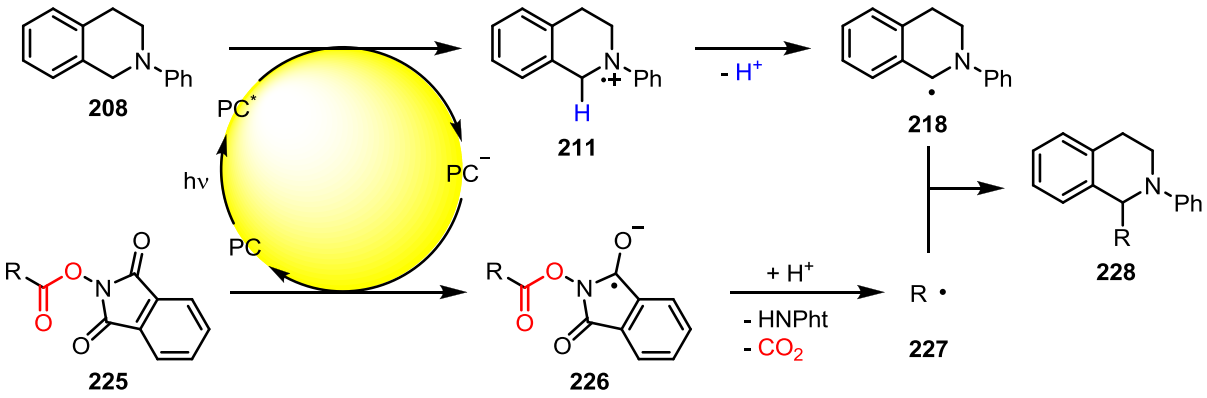
208 **171** **224**

Entry	Catalyst (1 mol%)	Modifications	Yield[a]
1	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	pyridine (1 equiv.)	46%
2	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	Hantzsch ester (1 equiv.)	0%[b]
3	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	formic acid (1 equiv.)	43%
4	-	no catalyst	0%
5	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	no light	0%
6	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	not degassed	22%[c]

[a] Yields were determined by NMR analysis with 4-nitrobenzaldehyde as internal standard. [b] full conversion but no product formation. [c] no full conversion of **171**.

4.2.2 Mechanistic aspects

With regard to the publications of the photoredox catalyzed α-amino functionalization[114,115], the decarboxylation using *N*-acyloxyphthalimides[41,48,90] and the previously presented optimization and control experiments (see Section 4.2.1), a plausible mechanism for this reaction was proposed (Scheme 61). Light irradiation in the visible spectrum leads to the excited photocatalyst (PC), which oxidizes *N*-phenyl-tetrahydroisoquinoline (**208**) to the radical cation **211**. The reduced photocatalyst species has a higher reduction potential compared to its excited state (Scheme 53) and is able to reduce the phthalimide moiety of **225**.[90] The oxidized tetrahydroisoquinoline species **211** abstracts a proton and forms radical **218**. Former optimization reactions show that no additional proton source is needed in the experiment. Therefore the reduced phthalimide moiety accepts the proton that was previously cleaved from **211**. Afterwards phthalimide is released and decarboxylation occurs, which leads to alkyl radical **227**. After radical recombination the desired product **228** is formed.

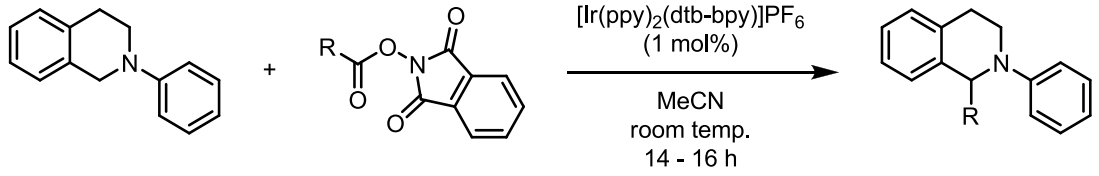


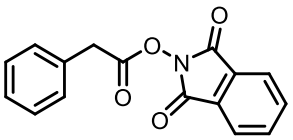
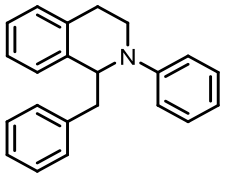
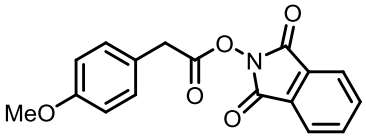
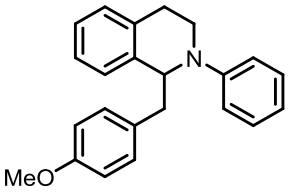
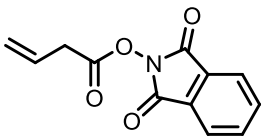
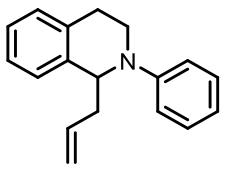
Scheme 61. Proposed reaction mechanism. PC = photocatalyst, R = alkyl.

4.2.3 Substrate scope

The decarboxylative benzylation of tetrahydroisoquinoline **208** under visible light conditions was successful. With the optimized reaction conditions in hand the reaction was applied in a 1 mmol scale and different phthalimide esters were used. Performing the reaction in a 1 mmol scale, 79% of the benzylated *N*-Phenyl-tetrahydroisoquinoline **224** was isolated after 14 h of irradiation (Table 17, entry 1). Similar results were obtained by the reaction with the *para*-methoxy derivative of the starting material (entry 2). Decarboxylation of **230** yielded 52% of isoquinoline **231**, however 36% tetrahydroisoquinoline **208** was recovered (entry 3). During the reaction *N*-acyloxyphthalimide **230** was consumed without taking part in product formation. Therefore 2 equiv. of phthalimide ester **230** was set in subsequent reaction, for achieving full conversion and higher yields. Contrary to expectations, no increase of yields was observed.

Table 17. Reactions with phenyl-/vinylacetic acid derivatives.

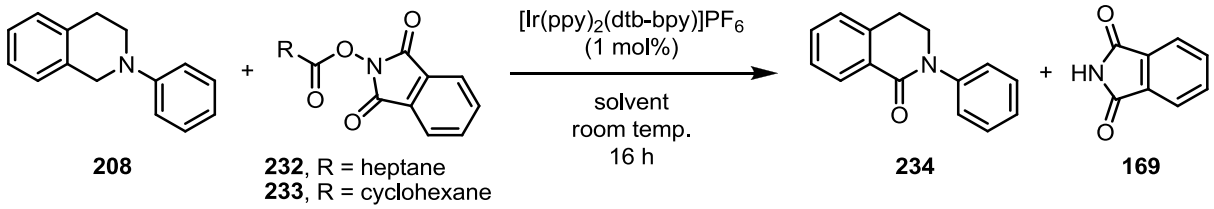


Entry	*N*-Acyloxyphthalimide		Product		Yield
1		**171**		**224**	79%
2		**163**		**229**	66%
3		**230**		**231**	52%[a]

[a] 36% of the starting material *N*-phenyl-tetrahydroisoquinoline **208** was reisolated.

Photodecarboxylation of phenyl- and vinylacetic acid derivatives **171**, **163** and **230** leads to radicals, which are stabilized and able to undergo the proposed radical recombination in good yields (Table 17).

In order to enlarge the scope of the reaction primary, secondary and tertiary carboxylic acid derivatives were synthesized (Table 18). Compounds **232** and **233** have a redox potential of -1.25 V and -1.23 V, respectively. Therefore these *N*-acyloxyphthalimides can get reduced by all common metal based photocatalysts (Scheme 53, Section 4.1). Performing the reaction with the acid derivatives **232**, **233** and **238** no product formation was observed (Table 18, entries 1-3). Using either the formerly established acetonitrile/water or non dried solvents, such as DMF, in the reaction with **232** or **236**, products of oxidized isoquinoline species **234** and simple phthalimide (**169**) were isolated (Scheme 62). This can be explained by initial coupling of radical **218** (Scheme 61) with present water.

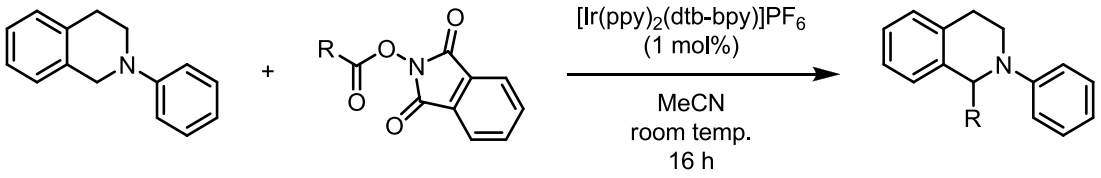


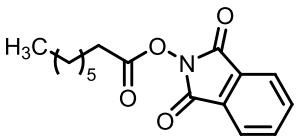
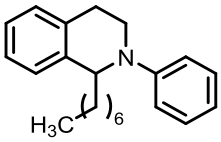
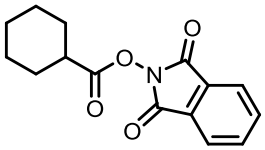
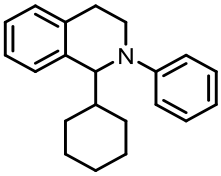
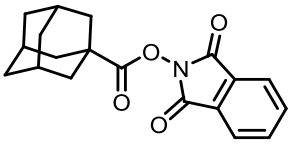
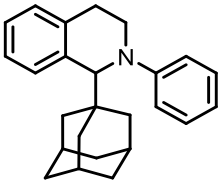
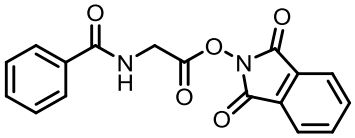
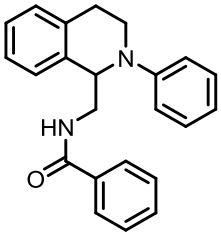
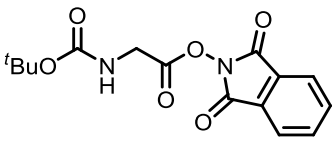
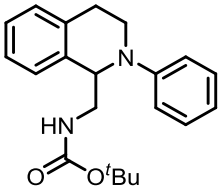
Scheme 62. Photoreaction of **232** and **233** with tetrahydroisoquinoline **208** using MeCN/H_2O and non dried DMF as solvent.

In the next step two phthalimide activated amino acids were applied in the reaction. The coupling with hippuric acid derivative **240** yielded in 46% of desired product **241** (Table 18, entry 5). In contrast to this moderate product formation, the decarboxylation of Boc-protected glycine **242** yielded only 18% of **243** (entry 6). Since the radical intermediates of **241** and **242** were both stabilized by the α-amide moiety, a second reason has to play a role in product formation to explain these differences in yields. One notable difference is the ability of the hippuric acid derivative **241** to interact with *N*-phenyl-tetrahydroisoquinoline (**208**) by π-π-stacking. This would place those reaction partners in a sterically close proximity to each other, which would facilitate the radical coupling step. This π-π-stacking is not possible for *N*-acyloxyphthalimide **242**, for which reason the product formation is more inefficient.

For the same reason the reactions with aliphatic acids (**232**, **233**, **238**) were also unsuccessful, since apart from being stabilized radicals, the reactants have to be sterically close to each other to initiate coupling.

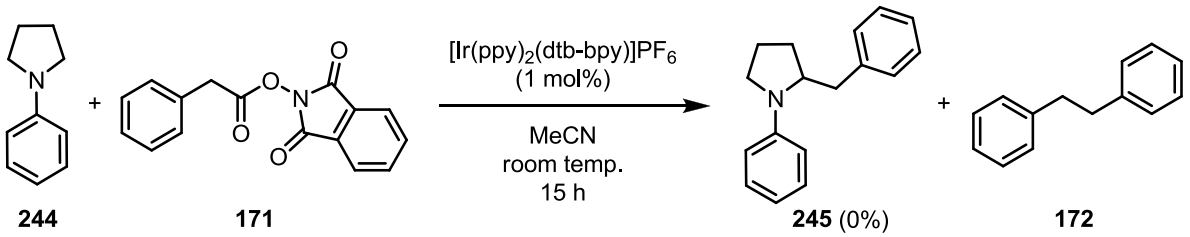
Table 18. Photoredox α-amination using primary, secondary, and tertiary phthalimide esters.



Entry	*N*-Acyloxyphthalimide		Product		Yield
1		**232**		**235**	0%
3		**236**		**237**	0%
4		**238**		**239**	0%
5		**240**		**241**	46%
6		**242**		**243**	18%

The photoredox catalyzed α-amino activation of *N*-phenylpyrrolidine (**244**) is challenging and it has been previously shown that these types of coupling reactions generally result in low yields.[114] Without an activating substituent on the α-position the radical or even iminium cation formation is unfavorable.[110] Nevertheless benzylation of *N*-phenylpyrrolidine (**244**)

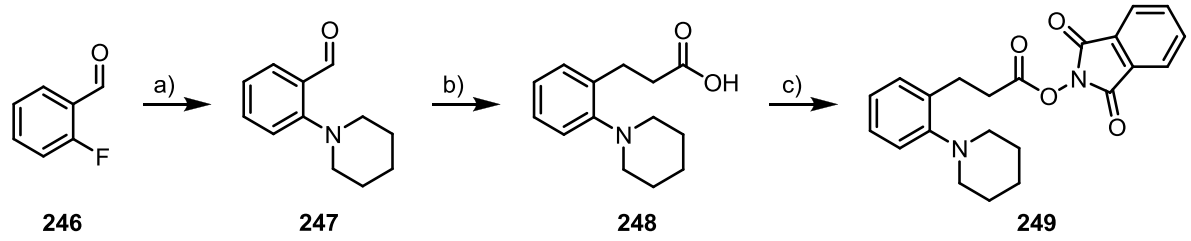
was explored using $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%) in acetonitrile (Scheme 63). After 15 h of irradiation no benzylated product **245** was synthesized. Under light irradiation in the visible spectrum *N*-acyloxyphthalimide **171** undergoes decarboxylation and forms dihydrostilbene **172** in a side reaction. This mechanism was already investigated and discussed in section 2.2.



Scheme 63. Photoinduced α-amino activation of *N*-phenylpyrrolidine (**244**).

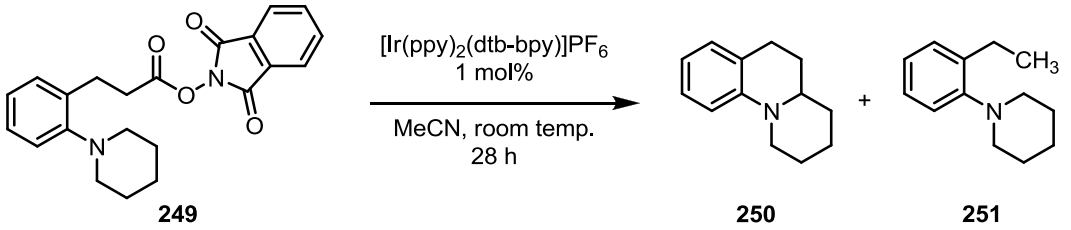
4.2.4 Intramolecular reaction

Intermolecular reactions were investigated for the combined photoredox decarboxylation/α-amino activation so far. One limitation of these intermolecular reactions was the necessity of the reactants being sterically close. Simultaneously this reaction is limited to *N*-aryl-tetrahydroisoquinolines to activate the α-amino position. In order to circumvent these problems and enlarge the substrate scope the reaction protocol was applied to an intramolecular version. To that end *N*-acyloxyphthalimide **249** was synthesized from 2-fluorobenzaldehyde (**246**), piperidine and malonic acid (Scheme 64).



Scheme 64. Synthetic route of *N*-acyloxyphthalimide **249**. a) piperidine (1.1 equiv.), K_2CO_3 (2.2 equiv.), DMF, 155 °C, 20 h (83%). b) Malonic acid (1.5 equiv.), pyridine, 120 °C, 2 h, 10% Pd/C, EtOH, overnight (93%). c) *N*-hydroxyphthalimide (1 equiv.), DCC (1 equiv.), THF, 2 d, room temp. (18%).

The cyclization reaction of compound **249** was performed in acetonitrile under visible light irradiation, using $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%) as photocatalyst. After a reaction time of 28 h an inseparable mixture of the desired cyclized product **250** and the simple decarboxylated side product **251** was obtained with an approximately yield of 19% (Scheme 65).



Scheme 65. Photoredox catalyzed intramolecular decarboxylative cyclization of **249**.

An intramolecular cyclization via photoredox catalyzed decarboxylation and subsequent α-amino activation is possible. An additional activation by a benzyl group is necessary for the α-activation and crucial for a successful cyclization.

4.3 Conclusion

Based on two well established photochemical reactions a dual visible light-promoted system of decarboxylation and α-amino activation was investigated. With this strategy the bifunctional property of the photoredox catalyst could be efficiently utilized. Tetrahydroisoquinoline serves as an electron donor for the photocatalyst to enable the reduction and subsequent decarboxylation of a phthalimide activated acid derivative. The corresponding α-amino and alkyl radicals, which were derived from the same catalytic cycle, can then react in a cross coupling process. Although being limited to phenylacetic-, vinylacetic-, and amino acids so far, the examples demonstrate the feasibility of this process, which allows the efficient synthesis of benzylation, allylation, and α-amino derivative products. Preliminary results suggest that an intramolecular version of this reaction gave rise to the desired product. This reaction will be optimized and investigate in future.

5 References

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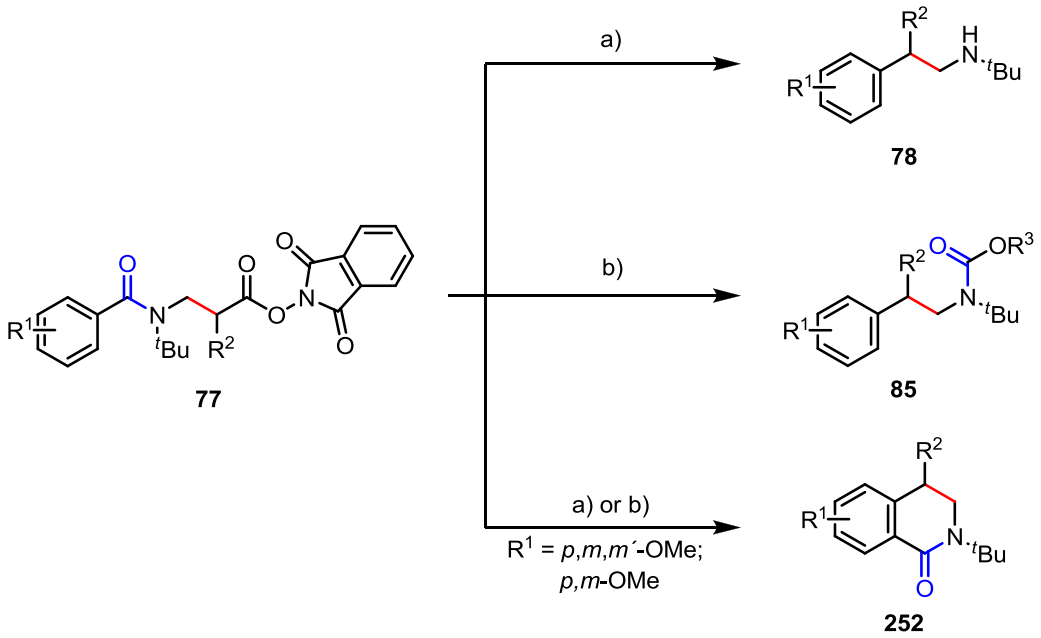
C Summary/Zusammenfassung

1 Summary

This PhD thesis demonstrates new applications for photoinduced decarboxylation of *N*-acyloxyphthalimides.

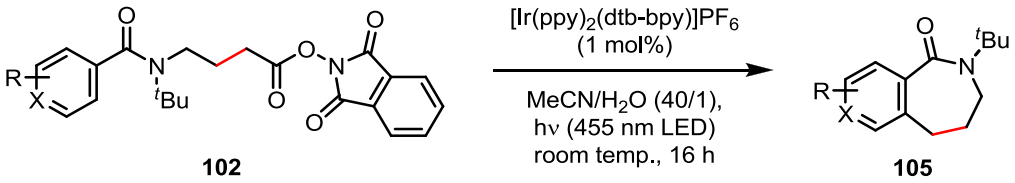
The **first chapter**, "Decarboxylation of ω-aryl-*N*-acyloxyphthalimides", discusses the decarboxylation of phthalimide activated amino acid derivatives via visible light irradiation. Performing the reaction of *N*-acyloxyphthalimides **77** in presence of photocatalyst $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ and a solvent mixture $MeCN/H_2O$ give rise to β-phenylethylamine derivatives **78** (Scheme 66). Initiated by energy transfer of the catalyst, an intramolecular electron transfer from the phenyl group to the phthalimide moiety enables the decarboxylation and a Smiles-type rearrangement occurs. Reaction conditions were optimized and a set of β-phenylethylamine derivatives were synthesized to evaluate the scope of the reaction. A slight change in the reaction conditions – substitution of H_2O on alcohol in the solvent mixture – allows the isolation of carbamate **85** of corresponding β-phenylethylamines. The carbamates were efficiently synthesized using primary, secondary and even tertiary alcohols.



Scheme 66. Scope of the visible light promoted decarboxylation of *N*-acyloxyphthalimides **77**. Reaction conditions: $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), hν (455 nm LED), room temp., 16 h. Solvent: a) $MeCN/H_2O$ (40/1) (v/v). b) MeCN, R^3OH (3 equiv.).

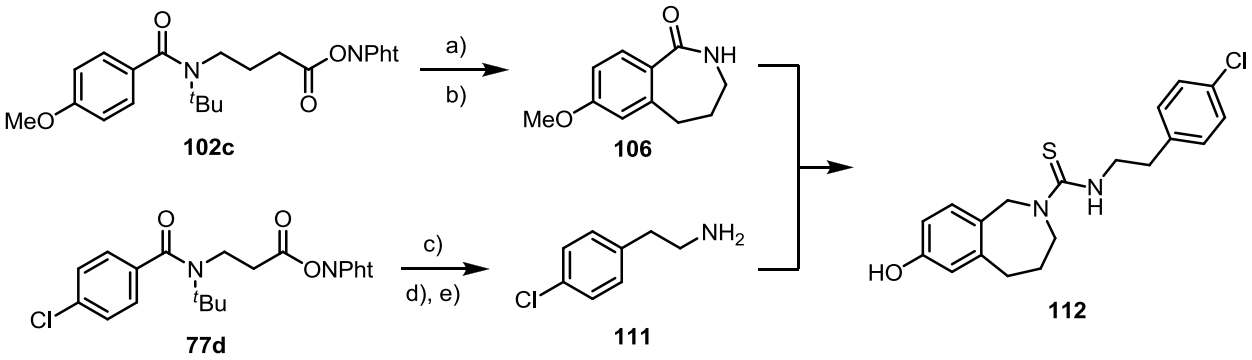
Interestingly increasing the electron density in the phenyl moiety via introduction of two or three methoxy groups led to the exclusive formation of dihydroisoquinolinones **252** in very good yields.

A further substrate scope extension via the elongation of the alkyl carbon chain afforded tetrahydrobenzazepinones **105** in good yields (Scheme 67). In this reaction no rearrangement was observed, the primary alkyl radical rather undergoes a 7-*exo/endo*-trig cyclization after decarboxylation instead of the 6-*exo* spirocyclization of *N*-acyloxyphthalimides **77**.



Scheme 67. Photodecarboxylative tetrahydrobenzazepinone **105** synthesis.

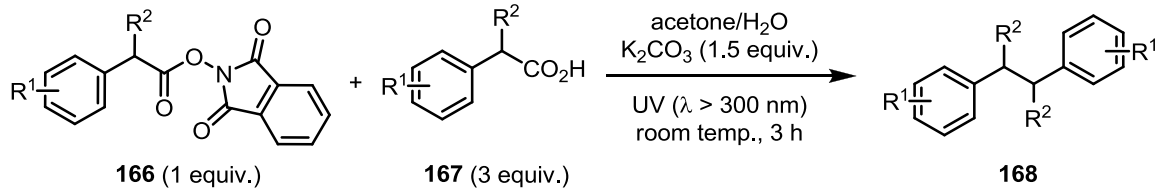
The developed visible light mediated transformation of ω-aryl-*N*-acyloxyphthalimides **77** and **102** was applied for the preparation of both key intermediates **106** and **111**, used in the convergent synthesis of the bronchodilator capsazepinoid **112** (Scheme 68).



Scheme 68. Formal synthesis of capsazepinoid **112**. a) $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), $MeCN/H_2O$ (40/1), 455 nm LED, room temp., 16 h (60%). b) TFA, reflux, 6 h (86%). c) $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), MeCN/MeOH (3 equiv.), 455 nm LED, room temp., 16 h (68%). d) TFA, room temp., overnight. e) 2 M LiOH/THF/MeOH (1/1/1), MW, 120 °C, 10 min (89%).

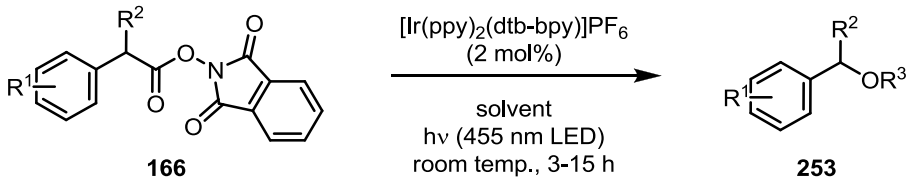
Another application of this decarboxylative rearrangement reaction was demonstrated with the synthesis of Boc-protected unnatural phenylalanine derivatives starting from commercially available L-aspartic acid and substituted benzaldehydes.

As the mechanism of these decarboxylations is based on energy transfer, hence a feasible dual decarboxylation method via UV-light irradiation was investigated in the **second chapter**, "UV light-mediated reactions of phthalimides". Excited *N*-acyloxyphthalimides **166** were reduced by phenylacetic acids **167**, which leads to a simultaneous decarboxylation of both substrates. In a subsequent crosscoupling reaction dihydrostilbenes **168** were isolated in fair to very good yields (Scheme 69).



Scheme 69. Dihydrostilbene **168** synthesis under UV-light irradiation.

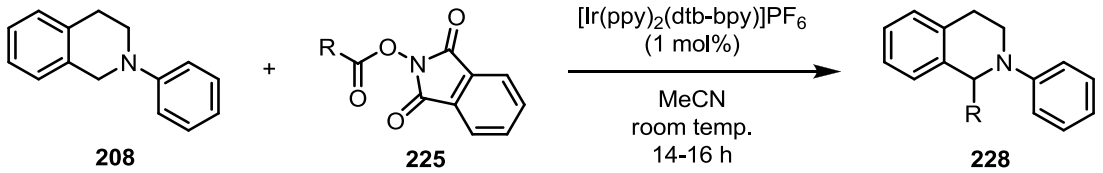
In the **third chapter**, a "Decarboxylative hydroxylation/alkoxylation" was investigated. Performing the sensitized decarboxylation reaction of *N*-acyloxyphthalimides **166** using visible light and the photocatalyst $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$, instead of UV irradiation, benzyl alcohols **253** (R^3 = H) were obtained as major products in good yields (Scheme 70). Using alcohol instead of water in the solvent mixture gave rise to corresponding benzyl ethers **253** (R^3 = Alk). Applying this reaction to other phthalimide-coupled aliphatic acids, via visible light-induced photoredox chemistry, was not successful. Consequently the reaction scope of this decarboxylative hydroxylation/alkoxylation was limited to phenylacetic acid derivatives.



Scheme 70. Visible light-promoted decarboxylative hydroxylation/alkoxylation. Solvent:
a) MeCN/H_2O, R^3 = H. b) MeCN/Alk-OH, R^3 = Alk.

In **Chapter four**, "Photoredox catalyzed decarboxylative α-amination", two well established photochemical reactions were combined into a dual visible light-promoted system of decarboxylation and α-amino activation (Scheme 71). With this strategy the bifunctional property of the photoredox catalyst could be efficiently utilized. Tetrahydroisoquinoline **208** serves as an electron donor for the photocatalyst to enable the reduction and subsequent

decarboxylation of *N*-acyloxyphthalimide **225**. The corresponding α-amino and alkyl radicals, which were derived from the same catalytic cycle, can then react in a cross coupling process. Although being limited to phenylacetic-, vinylacetic-, and amino acids so far, the examples demonstrate the feasibility of this meaningful process, which allows the efficient synthesis of benzylation, allylation, and α-amino derivative products.

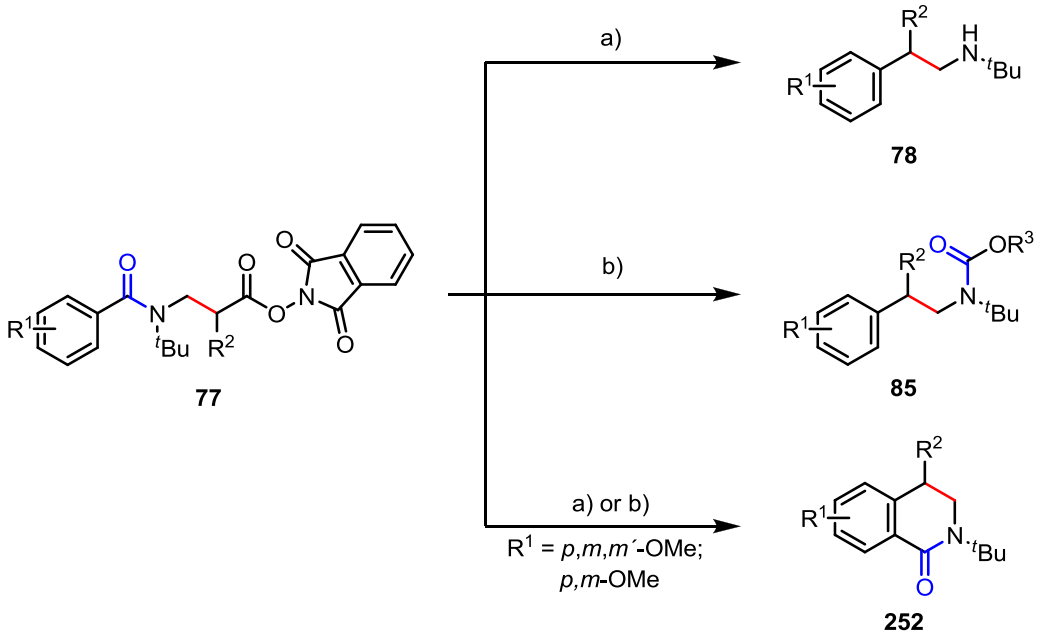


Scheme 71. Photoredox catalyzed decarboxylative α-amination.

2 Zusammenfassung

Die vorliegende Arbeit behandelt die photochemische Decarboxylierung von *N*-Acyloxyphthalimiden.

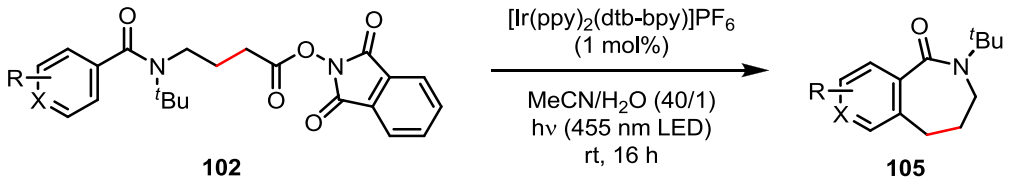
Im **ersten Kapitel** „Decarboxylation of ω-aryl-*N*-acyloxyphthalimides“ wurde das photochemische Verhalten von Phthalimid aktivierten Benzoylaminosäurederivaten untersucht. Die *N*-Acyloxyphthalimide **77** dienten hierbei als Ausgangsmoleküle. Durch Belichtung mit blauen LEDs und unter Einsatz des Photokatalysators $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ unterlief *N*-Acyloxyphthalimid **77** eine Decarboxylierung und wurde zum β-Phenylethylaminderivat **78** umgelagert (Schema 1). Initiiert durch eine Energieübertragung des Katalysators auf das Substrat findet ein intramolekularer Elektronentransfer von der Phenylgruppe hin zum Phthalimidrest statt. Daraufhin spaltet sich die reduzierte Phthalimiduntereinheit ab, was eine Decarboxylierung mit anschließender „Smiles-Umlagerung“ ermöglicht. Die Reaktionsbediungungen wurden daraufhin optimiert und eine Reihe an β-Phenylethylaminderivaten hergestellt. Durch Änderung des Lösungsmittelgemisches zu Acetonitril/Alkohol-Mischungen konnten, mittels primärer, sekundärer sowie tertiärer Alkohole, die entsprechenden Carbamate **85** isoliert werden.



Schema 1. Photoinduzierte Decarboxylierung der *N*-acyloxyphthalimide **77**.
Reaktionsbedingungen: $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), hν (455 nm LED), rt, 16 h.
Lösungsmittel: a) $MeCN/H_2O$ (40/1) (v/v). b) MeCN, R^3OH (3 equiv.).

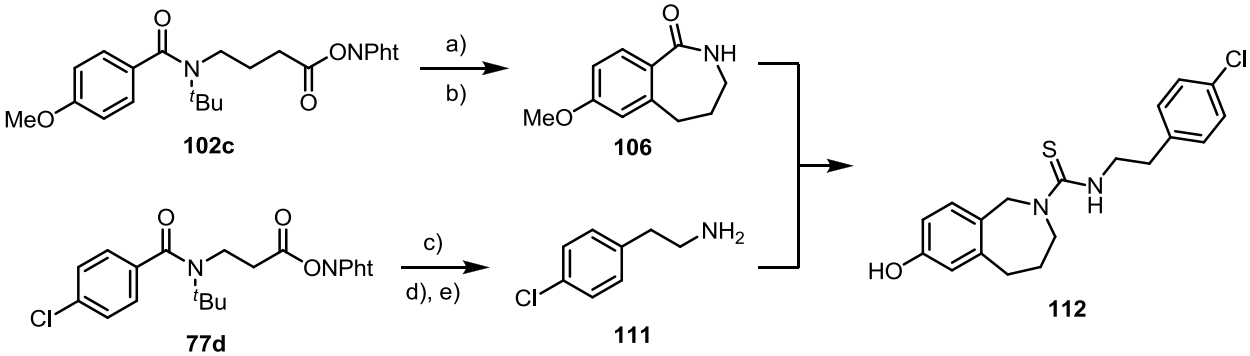
Durch Einführung von zwei oder drei Methoxy-Substituenten wurde die Elektrondichte am Phenylring erhöht und nach der photoinduzierten Decarboxylierung ausschließlich Dihydroisochinoline **252** in sehr guten Ausbeuten erhalten.

Bei der Erweiterung des Substratbereichs dieser photoinduzierten Decarboxylierungsreaktion wurden um eine Alkylgruppe verlängerte *N*-Acyloxyphthalimide **102** eingesetzt. Nach der Photoreaktion konnten Tetrahydrobenzoazepinone **105** in guten Ausbeuten isoliert werden (Schema 2). In dieser Reaktion war keine Umlagerung zu beobachten, weshalb nach der Decarboxylierung eine 7-*exo/endo*-trig Zyklisierung des *N*-Acyloxyphthalimids **102** angenommen wird.



Schema 2. Photoinduzierte Synthese von Tetrahydrobenzoazepinon **105**.

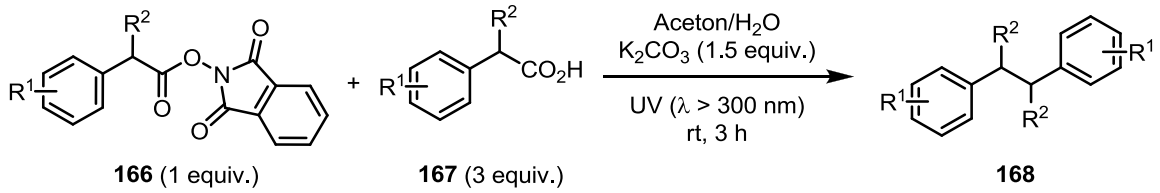
Die entwickelte photoinduzierte Decarboxylierung von ω-Aryl-*N*-acyloxyphthalimiden **102** und **77** wurden anschließend zur Synthese der beiden Schlüsselsubstrate **106** und **111** genutzt, welche bei der Herstellung des Broncholytikums **112** zum Einsatz kommen (Schema 3).



Schema 3. Synthese von Capsazepinoid **112**. a) $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), $MeCN/H_2O$ (40/1), 455 nm LED, rt, 16 h (60%). b) TFA, reflux, 6 h (86%). c) $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1 mol%), MeCN/MeOH (3 equiv.), 455 nm LED, rt, 16 h (68%). d) TFA, rt, über Nacht. e) 2 M LiOH/THF/MeOH (1/1/1), MW, 120 °C, 10 min (89%).

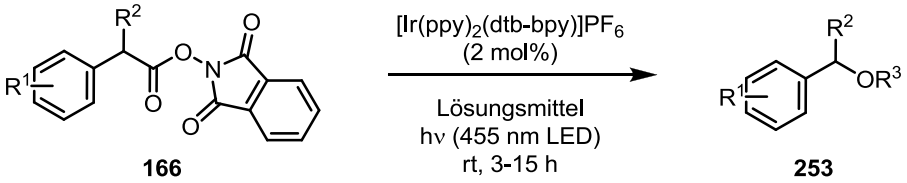
Eine weitere Anwendung dieser photoinduzierten Umlagerungsreaktion wurde mit der Herstellung von unnatürlichen Phenylalaninen ausgehend von billiger, kommerziell erhältlicher L-Asparaginsäure und unterschiedlich substituierter Benzaldehyde gezeigt.

Im **zweiten Kapitel** „UV light-mediated reactions of phthalimides" wurde eine auf Energietransfer basierte doppelte Decarboxylierung mittels UV-Belichtung entwickelt. Das angeregte *N*-Acyloxyphthalimid **166** wurde hierbei von der Phenylessigsäure **167** reduziert, wodurch die Decarboxylierung beider Substrate erfolgte. In einer anschließenden Kopplungsreaktion wurde Dihydrostilbene **168** in ordentlichen bis sehr guten Ausbeuten erhalten (Schema 4).



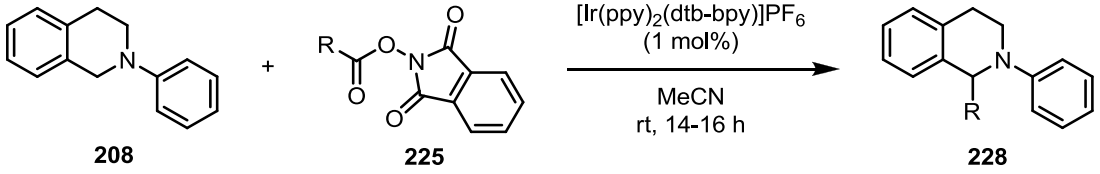
Schema 4. Synthese von Dihydrostilben **168** mittels UV-Belichtung.

Im **dritten Kapitel** „Decarboxylative hydroxylation/alkoxylation" werden die Forschungsergebnisse einer photoinduzierten Decarboxylierung mit anschließender Hydroxylierung bzw. Alkoxylierung beschrieben. Wird das *N*-Acyloxyphthalimid **166** anstelle von UV-Licht mit sichtbarem Licht unter Einsatz des Photokatalysators $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ bestrahlt, so wurde anstelle der Dihydrostilbene **168** der entsprechende Benzylalkohol **253** (R^3 = H) als Hauptprodukt erhalten. Bei einem Acetonitril/Alkohol Lösungsmittelgemisch konnten die entsprechenden Ether **253** (R^3 = Alk) in guten Ausbeuten isoliert werden (Schema 5). Diese neuartige Transformation konnte allerdings mittels Photoredoxkatalyse nicht auf andere aliphatische Säuren übertragen werden, weshalb der Substratbereich vorerst auf Phenylessigsäurederivate beschränkt bleibt.



Schema 5. Hydroxylierung/Alkoxylierung mittels photoinduzierter Decarboxylierung von **166**. Lösungsmittel: a) MeCN/H_2O, R^3 = H. b) MeCN/Alk-OH, R^3 = Alk.

In **Kapitel vier** „Photoredox catalyzed decarboxylative α-amination“ wurden zwei etablierte Photoreaktionen zu einem neuen gemeinsamen Photoredox-katalysierten Prozess kombiniert. Tetrahydroisochinolin **208** diente dabei als Elektronendonator und wurde vom Photokatalysator $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ oxidiert. Anschließend konnte die reduzierte Katalysatorspezies das *N*-Acyloxyphthalimid **225** reduzieren, wodurch ein N-O-Bindungsbruch mit anschließender Decarboxylierung induziert wurde. Die entstandenen Radikale der Substrate rekombinierten in einer Kreuzkopplungsreaktion und die α-Aminierungsprodukte **228** wurden isoliert (Schema 6). Nach aktuellem Forschungsstand ist dieser Decarboxylierungs- und Aminierungsprozess auf stabilisierte Radikale beschränkt, wonach bisher benzylierte (R = Benzyl), allylierte (R = Allyl) und α-amino (R = CH_2NHAlk) Produkte synthetisiert wurden.



Schema 6. Photoredox katalysierte Decarboxylierung und *N*-α-Funktionalisierung.

D Experimental Part

1 General information

Solvents and chemicals

All commercially available compounds were used as received. Absolute THF was taken from a MB-SPS solvent purification system. Other absolute solvents were prepared by established laboratory procedures. Ethyl acetate, hexanes (40/60) and DCM for chromatography were distilled prior to use. $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ was prepared according to literature.[120]

NMR spectroscopy

^{1}H-NMR spectra were recorded on BRUKER Avance 300 (300 MHz), BRUKER Avance III 400 "Nanobay" (400 MHz), and Oxford 300 MHz spectrometers. ^{13}C-NMR spectra were recorded on BRUKER Avance 300 (75 MHz) and BRUKER Avance III 400 "Nanobay" (100 MHz) spectrometers. The spectra were recorded in $CDCl_3$. The Chemical shifts for ^{1}H-NMR were reported as δ, parts per million, relative to the signal of $CDCl_3$ at 7.26 ppm.

The Chemical shifts for **^{13}C-NMR** were reported as δ, parts per million, relative to the center line signal of the $CDCl_3$ triplet at 77.0 ppm.

For **column chromatography** silica gel (Merck, Geduran 60, 0.063-0.200 mm particle size) and flash silica gel 60 (Merck, 0.040-0.063 mm particle size) was used.

The **thin layer chromatography** (TLC) analysis was done on a silica gel 60 F_{254} (Merck) coated on aluminium sheets and visualized with UV, ninhydrin solution (300 mg ninhydrin, 5 ml conc. acetic acid, 35 ml isopropyl alcohol) or $KMnO_4$ solution (1.0 g $KMnO_4$, 2 g Na_2CO_3, 100 ml water).

ATR-IR spectroscopy was carried out on a Biorad Excalibur FTS 3000 spectrometer, equipped with a Specac Golden Gate Diamond Single Reflection ATR-System. Solid and liquid compounds were measured neatly and wave numbers are reported in cm^{-1}.

The **melting points** were measured with a Büchi SMP-20 apparatus in silicon oil bath.

Mass spectrometry was done by the Central Analytical Laboratory of the University of Regensburg on a Varian MAT 311A, Finnigan MAT 95, ThermoQuest Finnigan TSQ 7000, Agilent Q-TOF 6540 UHD or Finnigan MAT SSQ 710 A.

X-Ray crystallographic analyses were recorded on a Bruker APEX-II CCD diffractometer.

Elementary analysis was measured on a Vario EL III or Mikro-Rapid CHN (Heraeus) - Microanalytic section of the University of Regensburg.

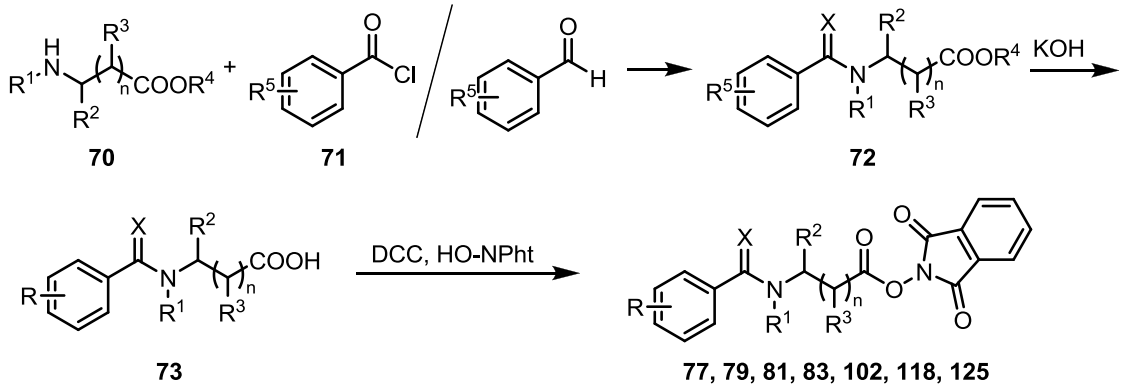
As **light source** in batch process CREE XLamp XP-E D5-15 LED (λ = 450 - 465 nm) were used. The UV-batch reactions were performed in a Rayonet chamber reactor (RPR-200; Southern New England Ultraviolet Co., USA) equipped with 16 x 8 W RPR-3000 Å lamps at 15-20 °C.

Microwave reactions were performed in a CEM Discover S-Class microwave oven using pressure stable sealed 10 ml vials.

Cyclic voltammetry measurements were carried out on an Autolab PGSTAT 302N set-up at 20 °C in acetonitrile, containing tetrabutyl ammonium tetrafluoroborate as supporting electrolyte. A conventional undivided electrochemical cell equipped with a glassy carbon working electrode, platinum wire as the counter electrode and silver wire as the reference electrode was used. The solvent was degassed by vigorous nitrogen bubbling prior to the measurements Redox potentials were referenced against ferrocene as an internal standard. All values are reported in reference to the SCE electrode.

2 Synthesis of *N*-acyloxyphthalimides

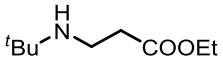
Amino acid based *N*-acyloxyphthalimides were mainly synthesized in a 5 step procedure: α-, β-, and γ-amino-carboxylate **70**, as well as benzoyl chloride **71** synthesis, *N*-acylation to **72** followed by ester hydrolysis. The coupling of the acids **73** and *N*-hydroxyphthalimide was mediated by DCC (Scheme 72).



Scheme 72. General synthesis of amino acid based *N*-acyloxyphthalimides.

Synthesis of α-, β-, and γ-aminocarboxylates 70

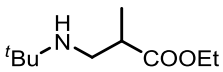
Ethyl 3-(*tert*-butylamino)propionate (70a).



To a 30 ml ethanol solution of *tert*-butylamine (30.0 ml, 287.1 mmol, 4 equiv.) was added dropwise a 30 ml ethanol solution of ethyl acrylate (7.70 ml, 72.3 mmol, 1 equiv.) at 0 °C. The reaction was stirred overnight at the same temperature. The solvent was removed under reduced pressure, and the residue was destilled under vacuum (3 mbar). One fraction of clear, colorless liquid was collected (12.20 g, 70.42 mmol, 97%; B.P. 60 °C (3 mbar)). ^{1}H NMR (300 MHz, CDCl3) δ = 4.14 (q, *J* = 7.1 Hz, 2H), 3.34 (s, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, CDCl3) δ = 173.0, 60.3, 50.3, 38.1, 35.7, 29.0 (3 C), 14.2.

Analytical data match to the reported data.[121]

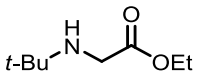
Ethyl 3-(*tert*-butylamino)-2-methylpropanoate (70b).



A solution of *tert*-butylamine (40 ml, 377.37 mmol, 2.9 equiv.) and ethyl methacrylate (15.15 g, 132.73 mmol, 1 equiv.) in 80 ml EtOH was heated under reflux for four days (60 °C). The solvent and *tert*-butylamine was removed by distillation (50 °C) and product was purified by vacuum disillation (8.7 mbar). One fraction of clear, colorless liquid was collected (14.80 g, 79.03 mmol, 60%; 70 °C (8.7 mbar)). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 (qd, *J* = 7.1, 0.6 Hz, 2H), 2.87 – 2.69 (m, 1H), 2.53 (td, *J* = 12.6, 5.8 Hz, 2H), 1.24 (td, *J* = 7.1, 0.6 Hz, 3H), 1.20 – 1.11 (m, 3H), 1.06 (d, *J* = 0.6 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.1, 60.2, 50.2, 45.8, 41.1, 29.0 (3 C), 15.5, 14.3.

Analytical data match to the reported data.[121]

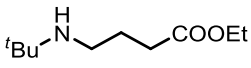
Ethyl 2-(*tert*-butylamino)acetate (70c).



Tert-butylamine (17.0 ml, 162.71 mmol, 4 equiv.) was dissolved in dry acetonitrile (30 ml) and ethyl 2-bromoacetate (6.07 g, 39.68 mmol, 1 equiv.) was added at 0 °C. The reaction mixture was stirred for overnight. After evaporation of the solvent under reduced pressure the maintained solution was extracted with 1 M HCl solution (2 x 20 ml) solution. The hydrous phase was basified with a 1 M KOH solution (50 ml) and extracted with ethylacetate (3 x 30 ml). The solvent was dried under $MgSO_4$ and removed under reduced pressure, yielding a orange to brown oil (5.04 g, 31.65 mmol, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.14 (q, *J* = 7.1 Hz, 2H), 3.34 (s, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.00, 60.78, 50.18, 44.85, 28.71 (3 C), 14.16.

Analytical data match to the reported data.[122]

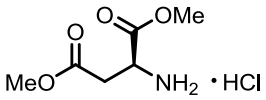
Ethyl 3-(*tert*-butylamino)butanoate (70d).



Ethyl 4-bromobutyrate (7.04 ml, 36.09 mmol, 1 equiv.), *tert*-butylamine (15.0 ml, 143.57 mmol, 4 equiv.) and K_2CO_3 (16.70 g, 120.83 mmol, 3.5 equiv.) were dissolved in acetonitrile (50 ml) and stirred at room temperature for 2.5 days. Precipitate was filtered and the solvent was removed under reduced pressure. The obtained oil was distilled under vacuum (3 mbar) to get a slightly yellow oil (5.41 g, 28.88 mmol, 80%, B.P. 60 °C (3 mbar)). ^{1}H NMR (400 MHz, CDCl3) δ = 4.10 (q, *J* = 7.1 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.74 (p, *J* = 7.3 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H), 0.61 (s, 1H). ^{13}C NMR (101 MHz, CDCl3) δ = 173.6, 60.2, 50.2, 41.9, 32.4, 29.1 (3 C), 26.5, 14.2.

Analytical data match to the reported data.[121]

(S)-Dimethyl 2-aminosuccinate hydrochloride (70e).

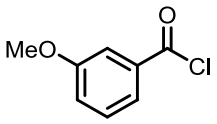


Chlorotrimethylsilane (35 ml, 275.77 mmol, 3.5 equiv.) was added dropwise to a solution of L-aspartic acid (10.01 g, 75.21 mmol, 1 equiv.) in methanol (absolute, 100 ml) at 0 °C and stirred for overnight. The solvent was removed under reduced pressure and a clear oil was obtained. The residue was consecutively diluted in methanol (50 ml) and diethylether (50) and the particular solvent was evaporated again, yielding a white solid (14.14 g, 71.55 mmol, 95%). ^{1}H NMR (400 MHz, MeOD) δ = 4.38 (t, *J* = 15.7 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.06 (d, *J* = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ = 171.63, 169.84, 54.20, 53.22, 50.60, 34.97.

Analytical data match to the reported data.[123]

Synthesis of benzoyl chlorides 71

3-Methoxybenzoyl chloride (71a).

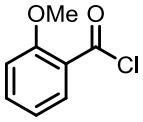


General protocol A

3-Methoxybenzoic acid (3.07 g, 20.18 mmol, 1 equiv.) was dissolved in thionyl chloride (14.00 ml, 192.99 mmol, 10 equiv.) and heated under reflux conditions for 3 h (until no more gas was produced). The solvent was removed by distillation of the warm reaction mixture and then again by vacuum distillation. A red oil was obtained (3.28 g, 19,23 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.73 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.57 (dd, *J* = 2.4, 1.9 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.21 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.32, 159.83, 134.42, 129.91, 124.14, 121.95, 115.34, 55.60.

Analytical data match to the reported data.[124]

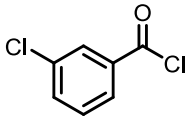
2-Methoxybenzoyl chloride (71b).



2-Methoxybenzoyl chloride (**71b**) was prepared from 2-methoxybenzoic acid (3.12 g, 20.51 mmol, 1 equiv.) and thionyl chloride (15.00 ml, 206.77 mmol, 10 equiv.) following *general protocol A*. Yield: 3.34 g (19.58 mmol, 95%), orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.09 (dd, *J* = 8.0, 1.7, 1H), 7.59 (ddd, *J* = 8.5, 7.4, 1.8, 1H), 7.09 – 6.97 (m, *J* = 11.3, 8.9, 4.7, 2H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.98, 159.67, 136.31, 134.74, 122.20, 120.37, 112.04, 56.11.

Analytical data match to the reported data.[125]

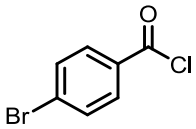
3-Chlorobenzoyl chloride (71c).



3-Chlorobenzoyl chloride (**71c**) was prepared from 3-chlorobenzoic acid (6.88 g, 43.94 mmol, 1 equiv.) and thionyl chloride (15.00 ml, 206.77 mmol, 4 equiv.) following *general protocol A*. Yield: 7.60 g (43.43 mmol, 99%), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.10 – 8.04 (m, 1H), 8.03 – 7.96 (m, 1H), 7.65 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.32, 135.30 (2 C), 134.80, 131.11, 130.24, 129.42.

Analytical data match to the reported data.[126]

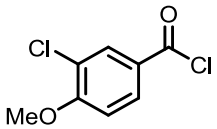
4-Bromobenzoyl chloride (71d).



4-Bromobenzoyl chloride (**71d**) was prepared from 4-bromobenzoic acid (2.38 g, 11.84 mmol, 1 equiv.) and thionyl chloride (30.00 ml, 413.55 mmol, 35 equiv.) following *general protocol A*. Yield: 2.54 g (11.16 mmol, 94%), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.68, 132.65, 132.42 (2 C), 132.09 (2 C), 131.21.

Analytical data match to the reported data.[127]

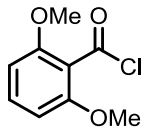
3-Chloro-4-methoxybenzoyl chloride (71e).



3-Chloro-4-methoxybenzoyl chloride (**71e**) was prepared from 3-chloro-4-methoxybenzoic acid (3.90 g, 43.94 mmol, 1 equiv.) and thionyl chloride (12.00 ml, 165.42 mmol, 8 equiv.) following *general protocol A*. Yield: 3.73 g (18.19 mmol, 87%), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.14 (d, *J* = 2.3 Hz, 1H), 8.05 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 4.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.40, 160.65, 133.33, 132.28, 126.11, 123.38, 111.46, 56.69.

Analytical data match to the reported data.[128]

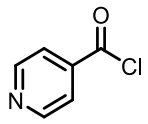
2,6-Dimethoxybenzoyl chloride (71f).



2,6-Dimethoxybenzoyl chloride (**71f**) was prepared from 2,6-dimethoxybenzoic acid (6.69 g, 36.72 mmol, 1 equiv.) and thionyl chloride (16.00 ml, 220.56 mmol, 6 equiv.) following *general protocol A*. Yield: 6.98 g (34.79 mmol, 95%), red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 (t, *J* = 8.5 Hz, 1H), 6.57 (d, *J* = 8.5 Hz, 2H), 3.87 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.08, 156.19 (2 C), 132.63, 117.71, 104.00 (2 C), 56.21 (2 C).

Analytical data match to the reported data.[129]

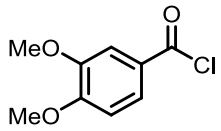
Isonicotinoyl chloride (71g).



Isonicotinoyl chloride (**71g**) was prepared from Isonicotinic acid (4.04 g, 32.82 mmol, 1 equiv.) and thionyl chloride (35.0 ml, 482.47 mmol, 15 equiv.) following *general protocol A* with a reaction time of 18 h. Yield: 3.61 g (25.50 mmol, 78%), yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.21 (d, *J* = 6.6 Hz, 2H), 8.56 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.52, 147.19 (2 C), 143.58, 125.34 (2 C).

Analytical data match to the reported data.[130]

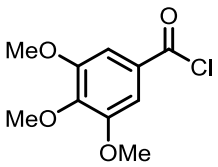
3,4-Dimethoxybenzoyl chloride (71h).



3,4-Dimethoxybenzoyl chloride (**71h**) was prepared from 3,4-dimethoxybenzoic acid (8.13 g, 44.63 mmol, 1 equiv.) and thionyl chloride (30.00 ml, 413.55 mmol, 10 equiv.) following *general protocol A*. Yield: 8.80 g (43.86 mmol, 98%), grey solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.84 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.53 (d, *J* = 2.2 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.34, 155.19, 148.65, 127.28, 124.61, 112.71, 110.40, 56.32, 56.13.

Analytical data match to the reported data.[131]

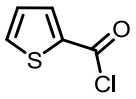
3,4,5-Trimethoxybenzoyl chloride (71i).



3,4,5-Trimethoxybenzoyl chloride (**71i**) was prepared from 3,4,5-trimethoxybenzoic acid (4.21 g, 19.84 mmol, 1 equiv.) and thionyl chloride (14.00 ml, 192.99 mmol, 10 equiv.) following *general protocol A*. Yield: 4.25 g (18.44 mmol, 93%), red solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36 (s, 2H), 3.95 (s, 3H), 3.92 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.80, 152.99 (2 C), 143.01, 124.11, 107.43 (2 C), 60.98, 56.26 (2 C).

Analytical data match to the reported data.[132]

Thiophene-2-carbonyl chloride (71j).

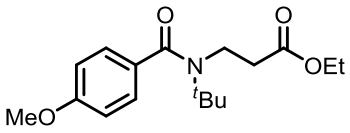


Thiophene-2-carbonyl chloride (**71j**) was prepared from thiophene-2-carboxylic acid (6.02 g, 46.98 mmol, 1 equiv.) and thionyl chloride (10.00 ml, 141.21 mmol, 3 equiv.) following *general protocol A*. Yield: 6.7 g (45.7 mmol, 97%) red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.98 (dd, *J* = 3.9, 1.3 Hz, 1H), 7.83 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.20 (dd, *J* = 5.0, 4.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.75, 138.00, 137.69, 137.42, 128.69.

Analytical data match to the reported data.[133]

Synthesis of compounds 72

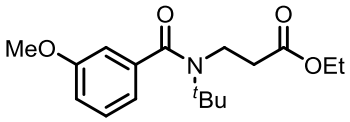
Ethyl 3-(N-*tert*-butyl-4-methoxybenzamido)propanoate (72a).



General protocol B

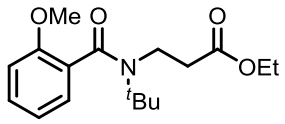
A solution of 4-methoxybenzoyl chloride (3.05 g, 17.88 mmol, 1 equiv.) in 30 ml DCM was added dropwise to an ice cooled solution of amine **70a** (3.36 g, 19.39 mmol, 1.1 equiv.) and triethylamine (2.80 ml, 20.20 mmol, 1.1 equiv.) in 50 ml DCM. The reaction was allowed to warm up to room temperature (22 °C) and was stirred for 15 h. The solution was washed with 1M HCl (20 ml), saturated $NaHCO_3$ solution (20 ml) and brine (20 ml). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was dried in vacuo to give 4.93 g (16.04 mmol, 90%) of the product as a pale yellow oil. IR (neat): 2978, 2840, 1730, 1636, 1607, 1513, 1461, 1375, 1297, 1245, 1170, 1111, 1025, 947, 842, 809, 768, 664 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.68 – 3.58 (m, 2H), 2.50 – 2.41 (m, 2H), 1.51 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.69, 170.87, 160.18, 131.68, 128.15 (2 C), 113.71 (2 C), 60.58, 57.02, 55.29, 42.99, 36.31, 28.96 (3C), 14.08.

Ethyl 3-(N-*tert*-butyl-3-methoxybenzamido)propanoate (72b).



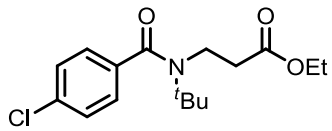
Compound **72b** was prepared from 3-methoxybenzoyl chloride (**71a**, 3.28 g, 19.23 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 3.23 g, 18,64 mmol, 1 equiv.) and triethylamine (2.70 ml, 19.48 mmol, 1 equiv.) following *general protocol B*. Yield: 5.67 g (18.45 mmol, 96%), yellow oil. IR (neat): 2978, 1730, 1641, 1580, 1536, 1484, 1428, 1394, 1320, 1290, 1238, 1182, 1033, 865, 790, 753, 675 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.31 – 7.24 (m, 1H), 6.92 – 6.81 (m, 3H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.64 – 3.54 (m, 2H), 2.53 – 2.42 (m, 2H), 1.53 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.18, 170.76, 159.60, 140.55, 129.66, 118.21, 114.88, 111.41, 60.59, 57.22, 55.34, 42.74, 36.44, 28.90 (3 C), 14.06.

Ethyl 3-(N-*tert*-butyl-2-methoxybenzamido)propanoate (72c).



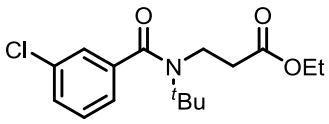
Compound **72c** was prepared from 2-methoxybenzoyl chloride (**71b**, 3.34 g, 19.58 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 3.35 g, 19,34 mmol, 1 equiv.) and triethylamine (3.00 ml, 21.64 mmol, 1.1 equiv.) following *general protocol B*. Yield: 5.79 g (18.84 mmol, 96%), yellow oil. IR (neat): 2978, 1730, 1640, 1599, 1490, 1461, 1439, 1394, 1364, 1290, 1245, 1185, 1156, 1099, 1021, 767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.27 (ddd, *J* = 8.3, 7.5, 1.8 Hz, 1H), 7.12 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.92 (ddd, *J* = 22.6, 11.3, 4.6 Hz, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.64 – 3.33 (m, 2H), 2.60 – 2.30 (m, 2H), 1.53 (s, 9H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.01, 170.48, 154.66, 129.65, 128.93, 126.91, 120.79, 111.09, 60.44, 57.28, 55.55, 42.27, 36.22, 28.96 (3 C), 14.08.

Ethyl 3-(N-*tert*-butyl-4-chlorobenzamido)propanoate (72d).



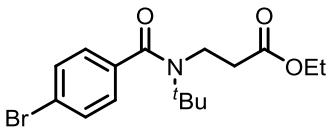
Compound **72d** was prepared from 4-chlorobenzoyl chloride (1.2 ml, 9.33 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 1.64 g, 9.47 mmol, 1 equiv.) and triethylamine (1.30 ml, 9.38 mmol, 1 equiv.) following *general protocol B*. Yield: 2.50 g (8.02 mmol, 86%), white solid. IR (neat): 2971, 1730, 1629, 1487, 1394, 1320, 1293, 1223, 1193, 1156, 1088, 1040, 1010, 839, 872, 738, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.31 (dd, *J* = 27.7, 8.6 Hz, 4H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.63 – 3.54 (m, 2H), 2.49 – 2.40 (m, 2H), 1.51 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.46, 170.59, 137.65, 134.98, 128.78 (2 C), 127.71 (2 C), 60.73, 57.36, 42.84, 36.24, 28.88 (3 C), 14.07.

Ethyl 3-(N-*tert*-butyl-3-chlorobenzamido)propanoate (72e).



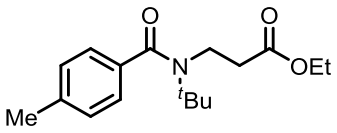
Compound **72e** was prepared from 3-Chlorobenzoyl chloride (**71c**, 2.00 g, 10.89 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 2.00 g, 11.54 mmol, 1 equiv.) and triethylamine (2.40 ml, 17.31 mmol, 1.5 equiv.) following *general protocol B*. Yield: 3.30 g (10.58 mmol, 93%), orange oil. IR (neat): 2982, 1730, 1640, 1566, 1476, 1390, 1320, 1286, 1252, 1185, 1149, 1096, 1044, 880, 798, 753, 716, 664 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.28 (m, 3H), 7.21 (dt, *J* = 6.8, 1.7 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.63 – 3.50 (m, 2H), 2.51 – 2.40 (m, 2H), 1.52 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.87, 170.57, 140.81, 134.48, 129.96, 129.18, 126.33, 124.26, 60.74, 57.46, 42.79, 36.26, 28.83 (3 C), 14.06.

Ethyl 3-(4-bromo-N-*tert*-butylbenzamido)propanoate (72f).



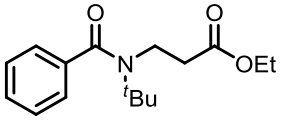
Compound **72f** was prepared from 4-bromobenzoyl chloride (**71d**, 1.49 g, 6.79 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 1.19 g, 6.87 mmol, 1 equiv.) and triethylamine (1.00 ml, 7.21 mmol, 1 equiv.) following *general protocol B*. Yield: 1.93 g (5.42 mmol, 80%), orange oil. IR (neat): 3306, 2960, 1730, 1705, 1633, 1592, 1539, 1483, 1439, 1379, 1320, 1260, 1226, 1182, 1070, 1010, 928, 850, 798, 750, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 2H), 7.24 – 7.17 (m, 2H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.64 – 3.50 (m, 2H), 2.52 – 2.35 (m, 2H), 1.51 (s, 9H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.43, 170.56, 138.12, 131.71 (2 C), 127.93 (2 C), 123.17, 60.72, 57.36, 42.81, 36.22, 28.87 (3 C), 14.08.

Ethyl 3-(N-*tert*-butyl-4-methylbenzamido)propanoate (72g).



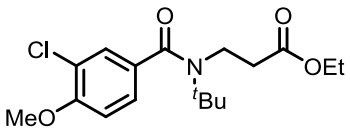
Compound **72g** was prepared from 4-toluoyl chloride (2.04 g, 13.20 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 2.30 g, 13.28 mmol, 1 equiv.) and triethylamine (2.00 ml, 14.43 mmol, 1.1 equiv.) following *general protocol B*. Yield: 3.44 g (11.81 mmol, 89%), clear oil. IR (neat): 2978, 2930, 1730, 1640, 1506, 1375, 1320, 1252, 1178, 1111, 1040, 947, 831, 757, 664 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.25 – 7.18 (m, 2H), 7.18 – 7.11 (m, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.66 – 3.54 (m, 2H), 2.50 – 2.39 (m, 2H), 2.33 (s, 3H), 1.51 (s, 9H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.79, 170.82, 138.90, 136.46, 129.06 (2 C), 126.18 (2 C), 60.54, 57.05, 42.83, 36.32, 28.94 (3 C), 21.34, 14.05.

Ethyl 3-(N-*tert*-butylbenzamido)propanoate (72h).



Compound **72h** was prepared from benzoyl chloride (1.13 g, 8.04 mmol, 1.1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 1.27 g, 7.32 mmol, 1 equiv.) and triethylamine (1.30 ml, 9.38 mmol, 1.2 equiv.) following *general protocol B*. Yield: 1.83 g (6.60 mmol, 90%), pale yellow oil. IR (neat): 2978, 1789, 1730, 1640, 1446, 1394, 1320, 1252, 1185, 1114, 1040, 924, 857, 783, 734, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.39 – 7.29 (m, 5H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.65 – 3.55 (m, 2H), 2.52 – 2.40 (m, 2H), 1.53 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.55, 170.75, 130.60, 128.98 (2 C), 128.51 (2 C), 126.07, 60.60, 57.19, 42.78, 36.32, 28.94 (3 C), 14.07.

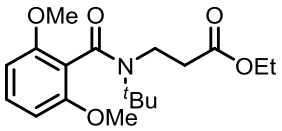
Ethyl 3-(N-*tert*-butyl-3-chloro-4-methoxybenzamido)propanoate (72i).



Compound **72i** was prepared from 3-chloro-4-methoxybenzoyl chloride (**71e**, 1.98 g, 9.66 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 1.66 g, 9.58 mmol, 1 equiv.)

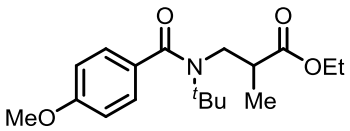
and triethylamine (2.00 ml, 14.43 mmol, 1.5 equiv.) following *general protocol B*. Yield: 3.11 g (9.10 mmol, 94%), orange oil. IR (neat): 2978, 2844, 1785, 1730, 1630, 1599, 1498, 1461, 1368, 1260, 1185, 1062, 1018, 891, 858, 820, 764, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 2.1 Hz, 1H), 7.23 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 3.66 – 3.57 (m, 2H), 2.51 – 2.39 (m, 2H), 1.49 (s, 9H), 1.20 – 1.12 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.11, 170.71, 155.60, 132.36, 128.64, 126.36, 122.37, 111.71, 60.69, 57.22, 56.21, 43.00, 36.25, 28.86 (3 C), 14.07.

Ethyl 3-(N-*tert*-butyl-2,6-dimethoxybenzamido)propanoate (72j).



Compound **72j** was prepared from 2,6-dimethoxybenzoyl chloride (**71f**, 2.97 g, 14.80 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 2.51 g, 14.49 mmol, 1 equiv.) and triethylamine (3.00 ml, 20.73 mmol, 1.4 equiv.) following *general protocol B*. Yield: 4.14 g (12.27 mmol, 83%), orange oil. IR (neat): 2974, 2840, 1730, 1640, 1592, 1472, 1394, 1364, 1290, 1249, 1185, 1107, 1021, 947, 876, 731, 664 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.19 (t, *J* = 8.4 Hz, 1H), 6.52 (dd, *J* = 8.4, 6.0 Hz, 3H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 6H), 3.49 – 3.42 (m, 2H), 2.50 – 2.42 (m, 2H), 1.54 (s, 9H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.36, 167.87, 155.97 (2 C), 129.59, 117.77, 104.06 (2 C), 60.33, 57.32, 55.81, 42.25, 36.05, 28.99 (3 C), 14.12.

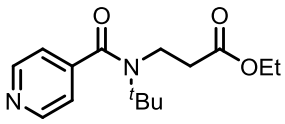
Ethyl 3-(N-*tert*-butyl-4-methoxybenzamido)-2-methylpropanoate (72k).



Compound **72k** was prepared from 4-methoxybenzoyl chloride (2.04 g, 11.96 mmol, 1 equiv.), ethyl 3-(tert-butylamino)-2-methylpropanoate (**70b**, 2.24 g, 11.97 mmol, 1 equiv.) and triethylamine (1.90 ml, 13.71 mmol, 1.1 equiv.) following *general protocol B*. Yield: 2.43 g (7.55 mmol, 63%), orange oil. IR (neat): 2974, 2840, 1730, 1633, 1607, 1510, 1461, 1387, 1334, 1301, 1245, 1170, 1141, 1085, 1055, 1029, 932, 842, 809, 768, 716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.42 – 7.27 (m, 2H), 6.92 – 6.79 (m, 2H), 4.05 (dd, *J* = 7.1, 4.0

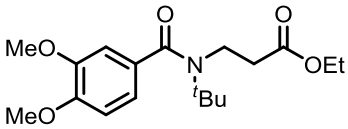
Hz, 2H), 3.85 – 3.73 (m, 4H), 3.52 (dd, *J* = 15.0, 7.9 Hz, 1H), 2.73 (dd, *J* = 14.5, 7.0 Hz, 1H), 1.52 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.38, 174.10, 160.45, 131.53, 129.44 (2 C), 113.58 (2 C), 60.62, 56.88, 55.31, 50.68, 41.07, 29.03 (3 C), 14.46, 14.13.

Ethyl 3-(N-*tert*-butylisonicotinamido)propanoate (72l).



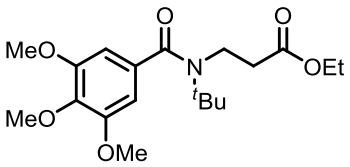
Compound **72l** was prepared from isonicotinoyl chloride (**71g**, 2.07 g, 14.62 mmol, 1.5 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 1.65 g, 9,52 mmol, 1 equiv.) and triethylamine (2.00 ml, 14.43 mmol, 1.5 equiv.) following *general protocol B*. Yield: 1.60 g (5.75 mmol, 59%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65 (d, *J* = 5.7 Hz, 2H), 7.22 (d, *J* = 6.0 Hz, 2H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.59 – 3.50 (m, 2H), 2.50 – 2.41 (m, 2H), 1.53 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.63, 170.23, 150.24 (2 C), 146.60, 120.44 (2 C), 60.80, 57.69, 42.55, 36.20, 28.78 (3 C), 14.05.

Ethyl 3-(N-*tert*-butyl-3,4-dimethoxybenzamido)propanoate (72m).



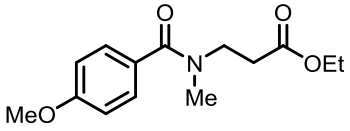
Compound **72m** was prepared from 3,4-Dimethoxybenzoyl chloride (**71h**, 4.12 g, 20.54 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 3.76 g, 21,70 mmol, 1.1 equiv.) and triethylamine (3.00 ml, 21.64 mmol, 1.1 equiv.) following *general protocol B*. Yield: 5.83 g (17.28 mmol, 84%), orange oil. Ir (neat): 2971, 2840, 1730, 1633, 1603, 1514, 1461, 1320, 1264, 1223, 1174, 1137, 1021, 921, 869, 816, 768 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.90 (m, *J* = 7.5 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.69 – 3.59 (m, 2H), 2.55 – 2.42 (m, 2H), 1.52 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.55, 170.83, 149.72, 148.89, 131.81, 119.13, 110.59, 109.94, 60.61, 57.14, 55.98, 55.93, 43.00, 36.47, 28.93 (3 C), 14.08.

Ethyl 3-(N-*tert*-butyl-3,4,5-trimethoxybenzamido)propanoate (72n).



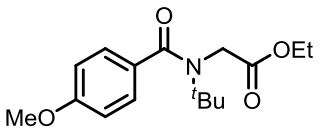
Compound **72n** was prepared from 3,4,5-Trimethoxybenzoyl chloride (**71i**, 2.05 g, 8.89 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 1.59 g, 9,18 mmol, 1.1 equiv.) and triethylamine (1.40 ml, 10.10 mmol, 1.1 equiv.) following *general protocol B*. Yield: 2.78 g (7.75 mmol, 85%), orange oil. Ir (neat): 2941, 2837, 1730, 1640, 1584, 1506, 1461, 1412, 1327, 1226, 1178, 1122, 1055, 1006, 865, 831, 768, 731 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.52 (s, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 3.69 – 3.53 (m, 2H), 2.61 – 2.39 (m, 2H), 1.52 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.17, 170.70, 153.32 (2 C), 134.75, 106.70 (2 C), 103.36, 60.89, 60.68, 57.29, 56.22 (2 C), 42.89, 36.68, 28.86 (3 C), 14.07.

Ethyl 3-(4-methoxy-N-methylbenzamido)propanoate (72o).



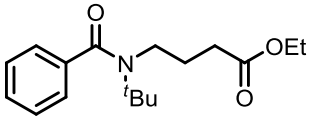
Compound **72o** was prepared from 4-methoxybenzoyl chloride (3.61 g, 21.16 mmol, 1 equiv.), ethyl 3-(methylamino)propanoate (2.73 g, 20.81 mmol, 1 equiv.) and triethylamine (4.40 ml, 31.74 mmol, 1.5 equiv.) following *general protocol B*. Yield: 5.52 g (20.81 mmol, 100%) clear oil. IR (neat): 2937, 2840, 1730, 1607, 1513, 1489, 1443, 1398, 1301, 1245, 1174, 1074, 1025, 842, 798, 764, 716 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.39 – 7.32 (m, 2H), 6.93 – 6.85 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.73 (s, 2H), 3.03 (d, *J* = 1.6 Hz, 3H), 2.64 (s, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.78, 160.68, 132.15, 128.94, 128.13 (2 C), 113.65 (2 C), 60.77, 55.33, 44.47, 38.68, 32.51, 14.18.

Ethyl 2-(N-*tert*-butyl-4-methoxybenzamido)acetate (72p).



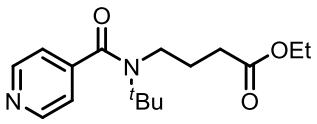
Compound **72p** was prepared from 4-methoxybenzoyl chloride (3.02 g, 17.70 mmol, 1 equiv.), ethyl 2-(*tert*-butylamino)acetate (**70c**, 3.23 g, 20.29 mmol, 1.1 equiv.) and triethylamine (2.70 ml, 19.48 mmol, 1.1 equiv.) following *general protocol B*. Yield: 5.10 g (17.38 mmol, 98%), yellow oil. IR (neat): 2971, 2937, 1744, 1640, 1607, 1513, 1461, 1428, 1379, 1297, 1249, 1170, 1111, 1025, 977, 842, 768, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.42 – 7.35 (m, 2H), 6.87 – 6.80 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 2H), 3.79 (s, 3H), 1.50 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.57, 171.37, 160.39, 131.20, 128.17 (2 C), 113.69 (2 C), 61.26, 57.64, 55.30, 49.97, 28.09 (3 C), 14.13.

Ethyl 4-(N-*tert*-butylbenzamido)butanoate (72q).



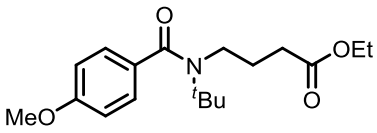
Compound **72q** was prepared from benzoyl chloride (1.84 g, 13.09 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)butanoate (**70d**, 2.51 g, 13,40 mmol, 1 equiv.) and triethylamine (2.00 ml, 14.44 mmol, 1.1 equiv.) following *general protocol B*. Yield: 3.72 g (12.77 mmol, 97%), pale yellow oil. IR (neat): 3313, 2937, 1707, 1629, 1539, 1577, 1450, 1375, 1312, 1238, 1174, 1095, 1025, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.39 – 7.27 (m, 5H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.29 (dd, *J* = 8.9, 6.9 Hz, 2H), 2.00 (t, *J* = 7.2 Hz, 2H), 1.77 (dq, *J* = 10.1, 7.5 Hz, 2H), 1.54 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.37, 139.56, 135.38, 131.44, 128.91, 128.42, 126.12, 60.47, 57.02, 46.82, 31.39, 28.92 (3 C), 27.02, 14.15. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.37, 172.54, 131.44, 128.91 (2 C), 128.42 (2 C), 126.12, 60.47, 57.02, 46.82, 31.39, 28.92 (3 C), 27.02, 14.15.

Ethyl 4-(N-*tert*-butylisonicotinamido)butanoate (72r).



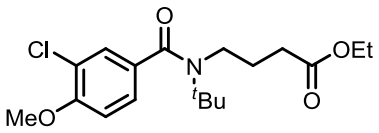
Compound **72r** was prepared from Isonicotinoyl chloride (**71g**, 2.02 g, 14.27 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)butanoate (**70d**, 1.74 g, 9.56 mmol, 1 equiv.) and triethylamine (1.50 ml, 10.82 mmol, 1.1 equiv.) following *general protocol B*. Yield: 2.09 g (7.15 mmol, 75%), orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.64 (dd, *J* = 4.5, 1.3 Hz, 2H), 7.20 (dd, *J* = 4.4, 1.6 Hz, 2H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.26 – 3.17 (m, 2H), 2.00 (t, *J* = 7.1 Hz, 2H), 1.83 – 1.70 (m, 2H), 1.54 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.19, 170.39, 150.17 (2 C), 146.82, 120.41 (2 C), 60.58, 57.58, 46.55, 31.23, 28.76 (3 C), 27.02, 14.13.

Ethyl 4-(N-*tert*-butyl-4-methoxybenzamido)butanoate (72s).



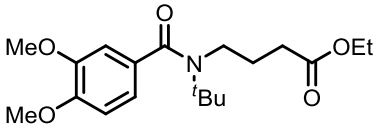
Compound **72s** was prepared from 4-methoxybenzoyl chloride (3.09 g, 18.11 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)butanoate (**70d**, 3.65 g, 19.49 mmol, 1.1 equiv.) and triethylamine (3.00 ml, 21.64 mmol, 1.2 equiv.) following *general protocol B*. Yield: 5.09 g (15.84 mmol, 87%), pale yellow oil. IR (neat): 2967, 1730, 1633, 1607, 1513, 1461, 1390, 1297, 1245, 1170, 1111, 1062, 1029, 809, 768 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32 – 7.24 (m, 2H), 6.89 – 6.81 (m, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.39 – 3.28 (m, 2H), 2.02 (t, *J* = 7.3 Hz, 2H), 1.76 (dt, *J* = 18.8, 7.4 Hz, 2H), 1.52 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.50, 172.62, 159.99, 131.94, 128.16 (2 C), 113.64 (2 C), 60.45, 56.87, 55.29, 47.01, 31.40, 28.97 (3 C), 27.01, 14.14.

Ethyl 4-(N-*tert*-butyl-3-chloro-4-methoxybenzamido)butanoate (72t).



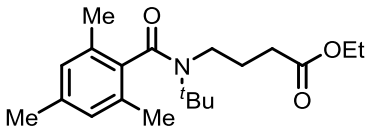
Compound **72t** was prepared from 3-chloro-4-methoxybenzoyl chloride (**71e,** 1.75 g, 8.54 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)butanoate (**70d**, 1.60 g, 8.54 mmol, 1 equiv.) and triethylamine (2.00 ml, 14.43 mmol, 1.7 equiv.) following *general protocol B*. Yield: 3.03 g (8.51 mmol, 99%), pale yellow oil. IR (neat): 2974, 1730, 1633, 1603, 1502, 1461, 1394, 1293, 1260, 1178, 1111, 1062, 1021, 887, 820, 768, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 2.1 Hz, 1H), 7.22 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.36 – 3.27 (m, 2H), 2.03 (t, *J* = 7.2 Hz, 2H), 1.75 (dt, *J* = 15.1, 7.3 Hz, 2H), 1.50 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.49, 171.90, 155.41, 132.60, 128.61, 126.33, 122.29, 111.67, 60.52, 57.12, 56.20, 47.01, 31.30, 28.86, 26.96 (3 C), 14.13.

Ethyl 4-(N-*tert*-butyl-3,4-dimethoxybenzamido)butanoate (72u).



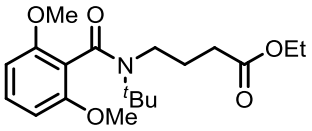
Compound **72u** was prepared from 3,4-Dimethoxybenzoyl chloride (**71h**, 4.10 g, 20.44 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)butanoate (**70d**, 3.79 g, 20,24 mmol, 1 equiv.) and triethylamine (2.90 ml, 20.92 mmol, 1 equiv.) following *general protocol B*. Yield: 6.15 g (17.50 mmol, 86%), orange oil. IR (neat): 3295, 2937, 2840, 1726, 1625, 1580, 1543, 1510, 1457, 1413, 1267, 1238, 1178, 1133, 1096, 1018, 845, 753, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 6.92 – 6.86 (m, 2H), 6.81 (d, *J* = 8.7 Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.88 (s, 3H), 3.35 (m, *J* = 8.8, 6.9 Hz, 2H), 2.03 (t, *J* = 7.3 Hz, 2H), 1.79 (dt, *J* = 14.7, 7.2 Hz, 2H), 1.53 (s, 9H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.36, 172.59, 149.50, 148.82, 132.08, 119.11, 110.56, 109.99, 60.49, 56.99, 55.99, 55.93, 47.06, 31.47, 28.94 (3 C), 27.19, 14.14.

Ethyl 4-(N-*tert*-butyl-2,4,6-trimethylbenzamido)butanoate (72v).



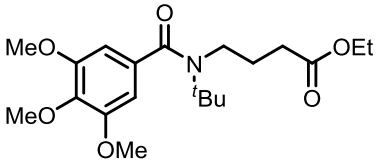
Compound **72v** was prepared from 2,4,6-trimethylbenzoyl chloride (1.50 g, 8.21 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)butanoate (**70d**, 1.57 g, 8,38 mmol, 1 equiv.) and triethylamine (1.20 ml, 8.66 mmol, 1 equiv.) following *general protocol B*. Yield: 1.24 g (3.70 mmol, 45%) yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.77 (s, 2H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.15 – 3.00 (m, 2H), 2.23 (s, 3H), 2.20 (s, 6H), 1.94 (t, *J* = 7.1 Hz, 2H), 1.73 – 1.61 (m, 2H), 1.57 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.49, 172.13, 137.21, 135.72, 132.88 (2 C), 128.34 (2 C), 60.45, 57.45, 46.19, 31.76, 28.89 (3 C), 26.52, 21.05, 19.07 (2 C), 14.10.

Ethyl 4-(N-*tert*-butyl-2,6-dimethoxybenzamido)butanoate (72w).



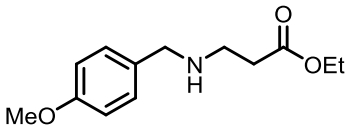
Compound **72w** was prepared from 2,6-Dimethoxybenzoyl chloride (**71f**, 2.01 g, 10.02 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)butanoate (**70d**, 1.89 g, 10.09 mmol, 1 equiv.) and triethylamine (3.00 ml, 21.64 mmol, 2.3 equiv.) following *general protocol B*. Yield: 3.04 g (8.65 mmol, 86%), yellow oil. IR (neat): 2967, 2840, 1730, 1636, 1592, 1472, 1394, 1364, 1290, 1249, 1178, 1029, 1107, 1030, 876, 790, 738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.17 (t, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 6H), 3.14 – 3.08 (m, 2H), 1.93 (t, *J* = 7.4 Hz, 2H), 1.73 (dq, *J* = 10.8, 7.7 Hz, 2H), 1.53 (s, 9H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.84, 167.69, 155.99 (2 C), 129.42, 117.89, 103.91 (2 C), 60.33, 57.21, 55.77 (2 C), 46.36, 31.83, 28.97 (3 C), 26.65, 14.17.

Ethyl 4-(N-*tert*-butyl-3,4,5-trimethoxybenzamido)butanoate (72x).



Compound **72x** was prepared from 3,4,5-Trimethoxybenzoyl chloride (**71i**, 4.05 g, 17.56 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)butanoate (**70d**, 3.31 g, 17,67 mmol, 1 equiv.) and triethylamine (2.50 ml, 18.04 mmol, 1 equiv.) following *general protocol B*. Yield: 5.90 g (15.47 mmol, 88%), orange oil. IR (neat): 3302, 2941, 2840, 1729, 1633, 1580, 1536, 1502, 1465, 1413, 1375, 1334, 1234, 1178, 1122, 1036, 992, 850, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 6.52 (s, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 3.39 – 3.25 (m, 2H), 2.04 (t, *J* = 6.7 Hz, 2H), 1.81 (dq, *J* = 15.3, 7.5 Hz, 2H), 1.54 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.98, 172.50, 153.26 (2 C), 138.33, 135.03, 103.33 (2 C), 60.88, 60.52, 57.13, 56.21 (2 C), 46.97, 31.52, 28.85 (3 C), 27.41, 14.14.

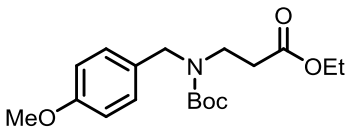
Ethyl 3-(4-methoxybenzylamino)propanoate (72y).



β-Alanine ethyl ester hydrochloride (3.19 g, 20.77 mmol, 1 equiv.) was dissolved in methanol (absolute, 20 ml). Anisaldehyde (2.8 g, 20.57 mmol, 1 equiv.) and NEt_3 (3 ml, 21.64 mmol, 1 equiv.) were added to the solution and stirred at room temperature for 3 h. $NaBH_4$ (781.6 mg, 20.66 mmol, 1 equiv.) was added slowly and the solution was stirred for overnight. Saturated NH_4Cl solution (20 ml) was added to quench the reaction and the mixture was extracted with diethylether (2 x 30 ml). The organic phases were combined, dried over Na_2SO_4, filtered and evaporated, which gave 4.41 g (18.58 mmol, 90%) of white solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 2H), 2.88 (t, *J* = 6.5 Hz, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 1.78 (s, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.83, 158.70, 132.16, 129.32 (2 C), 113.84 (2 C), 60.46, 55.29, 53.15, 44.38, 34.72, 14.23.

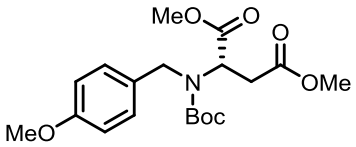
Analytical data match to the reported data.[134]

Ethyl 3-(*tert*-butoxycarbonyl(4-methoxybenzyl)amino)propanoate (72z).



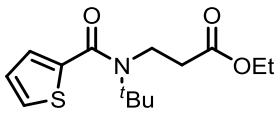
Compound **72y** (4.41 g, 18.58 mmol, 1 equiv.) and NEt_3 (2.7 ml, 19.48 mmol, 1 equiv.) were dissolved in dichloromethane (50 ml), treated with di-*tert*-butyl dicarbonate (4.16 g, 19.06 mmol, 1 equiv.) and stirred at room temperature for overnight. Solvent was evaporated and product was purified by column chromatography. Yield: 3.53 g (10.46 mmol, 56%). R_f (hexanes/EtOAc = 2/1) = 0.54. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (s, 2H), 6.89 – 6.80 (m, 2H), 4.38 (s, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.54 – 3.32 (m, 2H), 2.49 (d, *J* = 10.2 Hz, 2H), 1.47 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.96, 158.89, 155.53 (d) 130.43, 128.87 (d, 2 C), 113.94 (2 C), 79.95, 60.50, 55.28, 50.29 (d), 42.63 (d), 33.57 (d), 28.45 (3 C), 14.19.

(S)-Dimethyl 2-(*tert*-butoxycarbonyl(4-methoxybenzyl)amino)succinate (72aa).



Amine **70e** (2.40 g, 14.89 mmol, 1 equiv.) was dissolved in methanol (absolute, 20 ml). Anisaldehyde (1.8 ml, 14.81 mmol, 1 equiv.) and NEt_3 (2.0 ml, 14.83 mmol, 1 equiv.) were added to the solution and stirred at room temperature for 1 h. $NaBH_4$ (561.0 mg, 14.83 mmol, 1 equiv.) was added slowly and the solution was stirred for 5 h. Saturated NH_4Cl solution (20 ml) was added to quench the reaction and the mixture was extracted with diethylether (3 x 30 ml). The organic phases were combined, washed with brine (30 ml), dried over Na_2SO_4, filtered and evaporated. The residue was used directly for the Boc-protection. The residue was dissolved in dichloromethane (50 ml) and treated with NEt_3 (2.o ml, 14.43 mmol, 1 equiv.) and di-*tert*-butyl dicarbonate (3.26 g, 14.94 mmol, 1 equiv.) and stirred at room temperature for overnight. Solvent was evaporated and product was purified by column chromatography. Yield: 3.91 g (10.26 mmol, 69%). R_f (hexanes/EtOAc = 3/1) = 0.38. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 – 7.16 (m, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.63 – 4.21 (m, 3H), 3.78 (s, 3H), 3.61 (d, *J* = 1.5 Hz, 6H), 3.12 (dd, *J* = 16.2, 7.5 Hz, 1H), 2.65 – 2.37 (m, 1H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.82, 171.30, 146.76, 132.00, 129.96, 129.26 (d, 2 C), 113.91, 113.79 (d, 2 C), 85.17, 56.34, 55.23, 52.24, 51.86, 51.55, 35.99, 27.85 (d, 3 C).

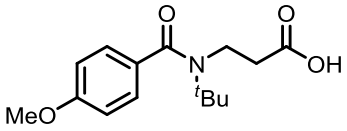
Ethyl 3-(N-*tert*-butylthiophene-2-carboxamido)propanoate (72ab).



Compound **S31-2** was prepared from thiophene-2-carbonyl chloride (**71j**, 2.50 g, 17.05 mmol, 1 equiv.), ethyl 3-(*tert*-butylamino)propanoate (**70a**, 2.92 g, 16.85 mmol, 1 equiv.) and triethylamine (2.40 ml, 17.31 mmol, 1 equiv.) following *general protocol B*. Yield: 2.57 g (9.05 mmol, 53%), orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32 – 7.26 (m, 1H), 7.17 (dt, *J* = 3.6, 1.1 Hz, 1H), 6.92 (ddd, *J* = 5.0, 3.6, 1.2 Hz, 1H), 4.00 (qd, *J* = 7.1, 1.1 Hz, 2H), 3.84 – 3.70 (m, 2H), 2.55 (dd, *J* = 9.1, 6.6 Hz, 2H), 1.44 (d, *J* = 1.0 Hz, 9H), 1.13 (td, *J* = 7.1, 1.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.72, 166.45, 140.57, 127.69, 127.39, 126.58, 60.64, 57.88, 42.99, 36.81, 28.77 (3 C), 14.10.

Synthesis of compounds 73

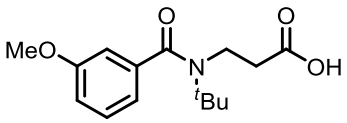
3-(N-*tert*-butyl-4-methoxybenzamido)propanoic acid (73a).



General protocol C

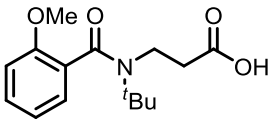
Ethylester **72a** (4.93 g, 16.04 mmol, 1 equiv.) was dissolved in 50 ml ethanol and a solution of KOH (992.40 mg, 17.69 mmol, 1.1 equiv.) in 40 ml water was added slowly. The reaction mixture was stirred at room temperature (22 °C) for overnight and ethanol was evaporated. The aqueous solution was acidified with concentrated HCl dropwise (2.10 ml, 24.47 mmol, 1.5 equiv.) and stirred additionally for 5 min. The white precipitate was filtered and dried in vacuo to give 4.40 g (15.75 mmol, 98%) of the product as white solid. IR (neat): 3004, 2967, 2930, 2557, 1714, 1588, 1517, 1489, 1420, 1364, 1305, 1264, 1204, 1111, 1029, 973, 924, 846, 813, 727 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.27 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.67 – 3.57 (m, 2H), 2.53 – 2.42 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.10, 174.13, 160.26, 131.25, 128.15 (2 C), 113.78 (2 C), 57.29, 55.30, 42.87, 35.88, 29.00 (3 C).

3-(N-*tert*-butyl-3-methoxybenzamido)propanoic acid (73b).



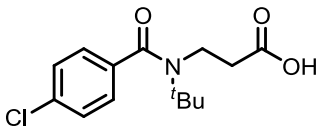
Compound **73b** was prepared from ester **72b** (5.66 g, 18.41 mmol, 1 equiv.) and potassium hydroxide (1.21 g, 21.57 mmol, 1.1 equiv.) following *general protocol C*. After the acidification with concentrated HCl, a yellow oil was observed, which was extracted with DCM (2 x 30 ml). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was dried in vacuo to give 5.79 g (18.84 mmol, 96%), of the product as white solid. IR (neat): 3075, 2971, 2930, 2837, 2661, 2553, 2486, 1718, 1580, 1461, 1398, 1286, 1181, 1033, 910, 872, 787, 746, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.30 – 7.23 (m, 1H), 6.93 – 6.80 (m, 3H), 3.80 (s, 3H), 3.65 – 3.55 (m, 2H), 2.57 – 2.48 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.06, 173.38, 159.63, 140.30, 129.69, 118.22, 115.06, 111.49, 57.40, 55.35, 42.46, 35.88, 28.97 (3 C).

3-(N-*tert*-butyl-2-methoxybenzamido)propanoic acid (73c).



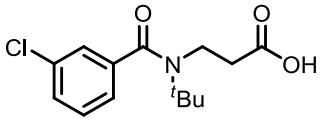
Compound **73c** was prepared from ester **72c** (5.78 g, 18.80 mmol, 1 equiv.) and potassium hydroxide (1.12 g, 19.96 mmol, 1.1 equiv.) following *general protocol C*. After the acidification with concentrated HCl, a yellow oil was observed, which was extracted with DCM (2 x 30 ml). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was dried in vacuo to give 4.90 g (17.54 mmol, 93%) of the product as orange oil. IR (neat): 2971, 2840, 1722, 1595, 1491, 1461, 1435, 1401, 1286, 1245, 1185 1148, 1021, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.28 (dt, *J* = 8.3, 2.2 Hz, 1H), 7.11 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.96 – 6.89 (m, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 3.49 (m, 2H), 2.48 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.45, 170.72, 154.69, 129.84, 128.60, 126.95, 120.83, 111.18, 57.52, 55.60, 42.03, 35.75, 29.00 (3 C).

3-(N-*tert*-butyl-4-chlorobenzamido)propanoic acid (73d).



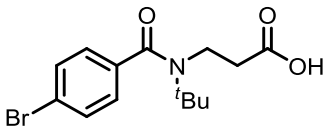
Compound **73d** was prepared from ester **72d** (3.48 g, 11.16 mmol, 1 equiv.) and potassium hydroxide (898.0 mg, 16.01 mmol, 1.4 equiv.) following *general protocol C*. Yield: 2.89 g (10.18 mmol, 91%), white solid. IR (neat): 3310, 2971, 2926, 2550, 2654, 1718, 1633, 1588, 1566, 1483, 1424, 1305, 1267, 1185, 1115, 1036, 1010, 924, 820, 760, 723 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.38 – 7.31 (m, 2H), 7.28 – 7.24 (m, 2H), 4.16 (s, 1H), 3.62 – 3.53 (m, 2H), 2.54 – 2.44 (m, 2H), 1.51 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.44, 172.78, 137.26, 135.18, 128.83 (2 C), 127.71 (2 C), 57.60, 42.58, 35.75, 28.91 (3 C).

3-(N-*tert*-butyl-3-chlorobenzamido)propanoic acid (73e).



Compound **73e** was prepared from ester **72e** (3.30 g, 10.58 mmol, 1 equiv.) and potassium hydroxide (977.1 mg, 17.42 mmol, 1.5 equiv.) following *general protocol C*. Yield: 2.62 g (9.23 mmol, 87%), white solid. IR (neat): 3075, 2978, 2922, 2661, 2557, 1715, 1592, 1483, 1397, 1364, 1305, 1193, 1092, 1040, 917, 880, 794, 760, 708 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.27 (m, 3H), 7.19 (dt, *J* = 7.2, 1.5 Hz, 1H), 3.68 – 3.50 (m, 2H), 2.59 – 2.38 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.59, 172.09, 140.49, 134.53, 129.99, 129.35, 126.36, 124.26, 57.66, 42.53, 35.77, 28.87 (3 C).

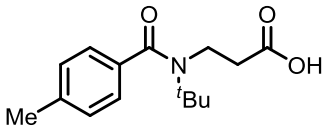
3-(4-bromo-N-*tert*-butylbenzamido)propanoic acid (73f).



Compound **73f** was prepared from ester **72f** (1.92 g, 5.39 mmol, 1 equiv.) and potassium hydroxide (367.35 mg, 6.55 mmol, 1.1 equiv.) following *general protocol C*. Yield: 1.36 g (4.14 mmol, 77%), white solid. IR (neat): 2974, 2922, 2855, 2658, 2490, 1677, 1633, 1588, 1484, 1379, 1320, 1290, 1192, 1010, 924, 835, 801, 757, 682 cm^{-1}. ^1H NMR (300 MHz,

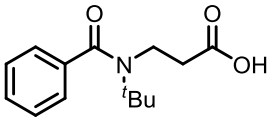
$CDCl_3$) δ = 7.54 – 7.46 (m, 2H), 7.24 – 7.16 (m, 2H), 3.58 (dd, *J* = 8.7, 6.7 Hz, 2H), 2.49 (dd, *J* = 8.7, 6.8 Hz, 2H), 1.51 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.21, 172.72, 137.80, 131.77 (2 C), 127.92 (2 C), 123.39, 57.59, 42.54, 35.74, 28.93 (3 C).

3-(N-*tert*-butyl-4-methylbenzamido)propanoic acid (73g).



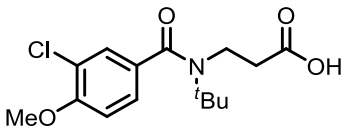
Compound **73g** was prepared from ethyl ester **72g** (3.41 g, 11.70 mmol, 1 equiv.) and potassium hydroxide (745.2 mg, 13.28 mmol, 1.1 equiv.) following *general protocol C*. Yield: 2.96 g (11.24 mmol, 96%), white solid. IR (neat): 2967, 2915, 1722, 1595, 1487, 1394, 1361, 1305, 1275, 1223, 1189, 1040, 951, 828, 764, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.20 (s, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 3.64 – 3.56 (m, 2H), 2.48 (dd, *J* = 8.8, 6.8 Hz, 2H), 2.34 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.89, 174.17, 139.16, 136.10, 129.13 (2 C), 126.17 (2 C), 57.33, 42.64, 35.82, 29.00 (3 C), 21.35.

3-(N-*tert*-butylbenzamido)propanoic acid (73h).



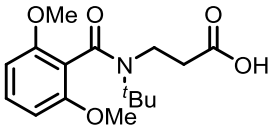
Compound **73h** was prepared from ester **72h** (4.09 g, 14.75 mmol, 1 equiv.) and potassium hydroxide (1.42 g, 25.31 mmol, 1.5 equiv.) following *general protocol C*. Yield: 3.31 g (13.28 mmol, 90%), white solid. IR (neat): 2967, 2822, 2661, 2564, 1715, 1592, 1577, 1446, 1424, 1401, 1364, 1305, 1204, 1189, 1111, 1073, 1040, 943, 876, 824, 794, 731, 705, 667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.94 (s, 1H), 7.38 – 7.32 (m, 3H), 7.32 – 7.27 (m, 2H), 3.62 – 3.53 (m, 2H), 2.48 (dd, *J* = 8.9, 6.7 Hz, 2H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.63, 173.93, 138.91, 129.15 (2 C), 128.54 (2 C), 126.07, 57.47, 42.63, 35.99, 28.98 (3 C).

3-(N-*tert*-butyl-3-chloro-4-methoxybenzamido)propanoic acid (73i).



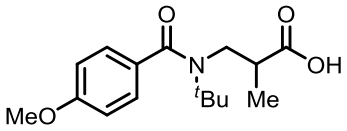
Compound **73i** was prepared from ester **72i** (3.11 g, 9.10 mmol, 1 equiv.) and potassium hydroxide (784.8 mg, 13.99 mmol, 1.5 equiv.) following *general protocol C*. Yield: 2.44 g (7.77 mmol, 85%), white solid. IR (neat): 2967, 2933, 2680, 2572, 1722, 1584, 1476, 1416, 1368, 1320, 1267, 1185, 1062, 1025, 954, 883, 813, 768, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 2.1 Hz, 1H), 7.26 – 7.21 (m, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 3.69 – 3.59 (m, 2H), 2.57 – 2.47 (m, 2H), 1.51 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.73, 172.45, 155.73, 132.00, 128.68, 126.40, 122.46, 111.75, 57.47, 56.23, 42.80, 35.84, 28.93 (3 C).

3-(N-*tert*-butyl-2,6-dimethoxybenzamido)propanoic acid (73j).



Compound **73j** was prepared from ester **72j** (4.11 g, 12.18 mmol, 1 equiv.) and potassium hydroxide (1.15 g, 20.50 mmol, 1.5 equiv.) following *general protocol C*. Yield: 2.35 g (7.60 mmol, 62%), white solid. IR (neat): 2974, 2937, 2840, 1722, 1648, 1592, 1476, 1435, 1420, 1365, 1290, 1252, 1185, 1111, 1025, 913, 877, 805, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.19 (t, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 6H), 3.48 – 3.40 (m, 2H), 2.53 – 2.41 (m, 2H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.76, 168.07, 155.97 (2 C), 129.75, 117.46, 104.10 (2 C), 57.51, 55.84 (2 C), 42.01, 35.47, 28.97 (3 C).

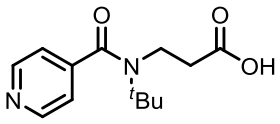
3-(N-*tert*-butyl-4-methoxybenzamido)-2-methylpropanoic acid (73k).



Compound **73k** was prepared from ester **72k** (2.42 g, 7.53 mmol, 1 equiv.) and potassium hydroxide (656.0 mg, 11.69 mmol, 1.5 equiv.) following *general protocol C*. Yield: 2.02 g (6.89 mmol, 91%), white solid. IR (neat): 2974, 2937, 2840, 1733, 1685, 1588, 1517, 1457,

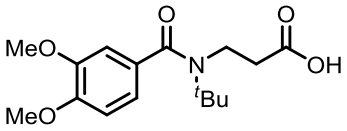
1420, 1364, 1305, 1257, 1200, 1137, 1029, 921, 839, 771 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.28 (m, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.85 – 3.78 (m, 1H), 3.81 (s, 3H), 3.54 (dd, *J* = 15.1, 8.0 Hz, 1H), 2.77 (dd, *J* = 14.4, 7.0 Hz, 1H), 1.53 (s, 9H), 1.00 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 179.33, 174.41, 160.51, 131.23, 129.46 (2 C), 113.62 (2 C), 57.08, 55.30, 50.48, 40.76, 29.08 (3 C), 14.24.

3-(N-*tert*-butylisonicotinamido)propanoic acid (73l).



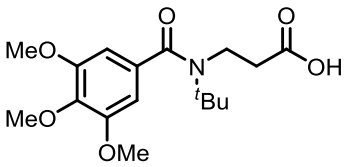
Compound **73l** was prepared from ester **72l** (1.36 g, 4.89 mmol, 1 equiv.) and potassium hydroxide (309.4 mg, 5.52 mmol, 1.1 equiv.) following *general protocol C*. Yield: 240.05 mg (0.961 mmol, 20%), ochre solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.59 (d, *J* = 5.3 Hz, 1H), 7.32 (d, *J* = 6.0 Hz, 1H), 3.57 – 3.47 (m, 1H), 2.55 – 2.46 (m, 1H), 1.56 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.76, 169.98, 148.36 (2 C), 148.24, 121.06 (2 C), 57.90, 42.55, 36.40, 28.66 (3 C).

3-(N-*tert*-butyl-3,4-dimethoxybenzamido)propanoic acid (73m).



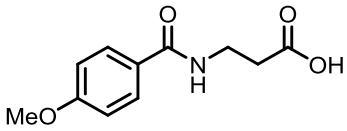
Compound **73m** was prepared from ester **72m** (5.79 g, 17.16 mmol, 1 equiv.) and potassium hydroxide (1.21 g, 21.57 mmol, 1.1 equiv.) following *general protocol C*. Yield: 4.59 g (14.84 mmol, 86%), white solid. IR (neat): 3086, 2967, 25575, 1714, 1677, 1569, 1521, 1469, 1424, 1398, 1305, 1264, 1230, 1178, 1148m, 1118, 1025, 902, 820, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 6.92 – 6.84 (m, 2H), 6.81 (d, *J* = 8.7 Hz, 1H), 3.87 (d, *J* = 2.0 Hz, 6H), 3.64 (dd, *J* = 8.8, 6.7 Hz, 2H), 2.53 (dd, *J* = 8.7, 6.8 Hz, 2H), 1.51 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.88, 173.89, 149.82, 148.92, 131.42, 119.11, 110.54, 109.94, 57.35, 55.95, 55.91, 42.80, 36.06, 28.96 (3 C).

3-(N-*tert*-butyl-3,4,5-trimethoxybenzamido)propanoic acid (73n).



Compound **73n** was prepared from ester **72n** (2.21 g, 6.02 mmol, 1 equiv.) and potassium hydroxide (398.1 mg, 7.10 mmol, 1.2 equiv.) following *general protocol C*. Yield: 1.89 mg (5.13 mmol, 85%), white solid. IR (neat): 3399, 2971, 2840, 1715, 1629, 1580, 1547, 1502, 1454, 1416, 1334, 1271, 1193, 1122, 1059, 1025, 917, 857, 760, 723, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.53 (s, 3H), 3.85 (s, 8H), 3.84 (s, 4H), 3.68 – 3.57 (m, 3H), 2.62 – 2.51 (m, 3H), 1.53 (s, 14H).). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.29, 173.36, 153.32 (2 C), 138.61, 134.56, 103.38 (2 C), 60.90, 57.44, 56.22 (2 C), 42.74, 36.35, 28.90 (3 C).

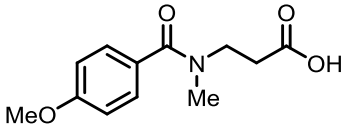
3-(4-Methoxybenzamido)propanoic acid (73o).



β-Alanine (1.33 g, 14,93 mmol, 1 equiv.) and sodium hydroxide (1.12 g, 28 mmol, 2 equiv.) were dissolved in H_2O (10 ml) and cooled to 0 °C. A solution of 4-methoxybenzoyl chloride (3.00 g, 17.59 mmol, 1.2 equiv.) in THF (20 ml) was added slowly and stirred for 20 h. The THF was removed under reduced pressure and the precipitated solid was filtered of. Yield: 2.19 g (9.81 mmol, 67%) white solid. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.57 – 7.47 (m, 2H), 6.65 (m, 2H), 3.59 (s, 3H), 3.40 (q, *J* = 6.3 Hz, 2H), 2.36 (t, *J* = 6.4 Hz, 2H).

Analytical data match to the reported data.[135]

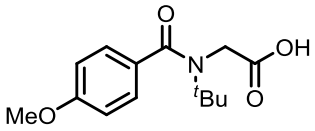
3-(4-Methoxy-N-methylbenzamido)propanoic acid (73p).



Compound **73p** was prepared from ester **72o** (5.50 g, 20.73 mmol, 1 equiv.) and potassium hydroxide (1.81 g, 32.26 mmol, 1.5 equiv.) following *general protocol C*. Yield: 4.32 g (18.23 mmol, 88%), white solid. IR (neat): 2937, 2840, 1722, 1595, 1517, 1487, 1439, 1402,

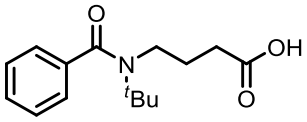
1301, 1249, 1174, 1077, 1025, 951, 902, 839, 764, 719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.26 (s, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.92 – 6.85 (m, 2H), 3.81 (s, 3H), 3.74 (s, 2H), 3.03 (s, 3H), 2.68 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.26, 160.83, 132.30, 129.07 (2 C), 127.60, 113.70 (2 C), 58.36, 55.35, 53.49, 18.20.

2-(N-*tert*-Butyl-4-methoxybenzamido)acetic acid (73q).



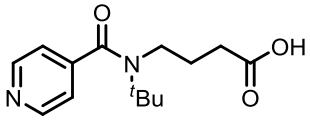
Compound **73q** was prepared from ester **72p** (5.02 g, 17.11 mmol, 1 equiv.) and potassium hydroxide (1.12 g, 19.96 mmol, 1.1 equiv.) following *general protocol C*. Yield: 3.63 g (13.69 mmol, 80%), white solid. IR (neat): 2967, 2933, 2844, 2717, 2658, 2579, 2509, 1730, 1644, 1588, 1513, 1480, 1431, 1390, 1305, 1252, 1193, 1025, 977, 842, 772, 712 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.40 – 7.37 (m, 2H), 6.88 – 6.81 (m, 2H), 3.79 (s, 3H), 3.78 (s, 2H), 1.50 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.61, 168.43, 160.89, 128.17 (2 C), 114.19 (2 C), 58.28, 55.39, 47.84, 28.05 (3 C).

4-(N-*tert*-butylbenzamido)butanoic acid (73r).



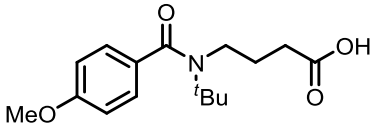
Compound **73r** was prepared from ester **72q** (3.72 g, 12.77 mmol, 1 equiv.) and potassium hydroxide (799.1 mg, 14.24 mmol, 1.1 equiv.) following *general protocol C*. After acidification a white oil obtained, which was extracted by EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was dried in vacuo to give 2.33 g (8.85 mmol, 69%), of the product as white solid. IR (neat): 3064, 2937, 2646, 2568, 1703, 1573, 1491, 1413, 1364, 1323, 1293, 1241, 1185, 1118, 1025, 887, 850, 790, 746, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 10.78 (s, 1H), 7.37 – 7.28 (m, 5H), 3.39 – 3.23 (m, 2H), 2.03 (t, *J* = 7.2 Hz, 2H), 1.77 (dt, *J* = 10.0, 7.3 Hz, 2H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.84, 173.76, 139.08, 130.13 (2 C), 128.46 (2 C), 126.03, 57.31, 46.75, 31.08, 28.91 (3 C), 26.74.

4-(N-*tert*-butylisonicotinamido)butanoic acid (73s).



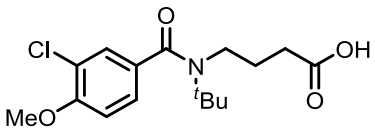
Compound **73s** was prepared from ester **72r** (1.79 g, 6.12 mmol, 1 equiv.) and potassium hydroxide (382.5 mg, 6.82 mmol, 1.1 equiv.) following *general protocol C*. After acidification a white oil obtained, which was extracted by dichloromethane (2 x 30 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was dried in vacuo to give 937 mg (3.54 mmol, 58%), of the product as white solid. IR (neat): 2930, 2445, 1890, 1700, 1610, 1554, 1491, 1409, 1349, 1293, 1249, 1215, 1159, 1118, 1066, 973, 842, 801, 764 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.51 (d, *J* = 6.1 Hz, 2H), 7.36 (dd, *J* = 4.7, 1.4 Hz, 2H), 3.43 – 3.33 (m, 2H), 2.22 – 2.14 (m, 2H), 1.83 (m, 2H), 1.57 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.60, 169.85, 148.41 (2 C), 147.70, 121.61 (2 C), 57.62, 46.33, 30.91, 28.73 (3 C), 27.21.

4-(N-*tert*-butyl-4-methoxybenzamido)butanoic acid (73t).



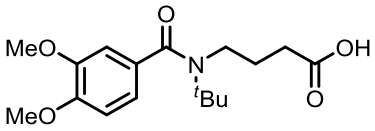
Compound **73t** was prepared from ester **72s** (4.98 g, 15.49 mmol, 1 equiv.) and potassium hydroxide (921.78 mg, 16.43 mmol, 1.05 equiv.) following *general protocol C*. Yield: 4.46 g (15.20 mmol, 98%), white solid. IR (neat): 2933, 2710, 2568, 1722, 1610, 1566, 1416, 1368, 1301, 1256, 1174, 1025, 936, 835, 768, 727 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.32 – 7.22 (m, 2H), 6.89 – 6.80 (m, 2H), 3.79 (s, 3H), 3.42 – 3.27 (m, 2H), 2.05 (t, *J* = 7.2 Hz, 2H), 1.77 (dd, *J* = 15.1, 7.4 Hz, 2H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.55, 173.79, 160.03, 131.56, 128.14 (2 C), 113.66 (2 C), 57.08, 55.26, 46.88, 30.98, 28.97 (3 C), 26.73.

4-(N-*tert*-butyl-3-chloro-4-methoxybenzamido)butanoic acid (73u).



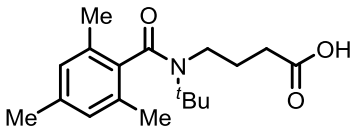
Compound **73u** was prepared from ethyl 4-(N-*tert*-butyl-3-chloro-4-methoxy-benzamido)butanoate (**72t**, 3.03 g, 8.51 mmol, 1 equiv.) and potassium hydroxide (727.5 mg, 12.97 mmol, 1.5 equiv.) following *general protocol C*. Yield: 2.43 g (7.41 mmol, 87%), white solid. IR (neat): 2982, 2956, 1730, 1629, 1580, 1505, 1454, 1368, 1297, 1174, 1062, 1021, 924, 880, 846, 768, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 2.1 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 3.41 – 3.31 (m, 2H), 2.10 (t, *J* = 7.1 Hz, 2H), 1.83 – 1.73 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.78, 172.13, 155.48, 132.30, 128.60, 126.37, 122.32, 111.69, 57.29, 56.17, 46.85, 30.87, 28.90 (3 C), 26.66.

4-(N-*tert*-butyl-3,4-dimethoxybenzamido)butanoic acid (73v).



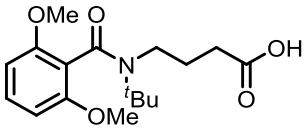
Compound **73v** was prepared from ester **72u** (6.15 g, 17.5 mmol, 1 equiv.) and potassium hydroxide (1.12 g, 19.96 mmol, 1.1 equiv.) following *general protocol C*. After the acidification with concentrated HCl, a yellow oil was observed, which was extracted with EtOAc (2 x 40 ml). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was dried in vacuo to give 5.32 g (16.45 mmol, 94%) of the product as orange oil. IR (neat): 3317, 2937, 2840, 1707, 1580, 1513, 1461, 1416, 1301, 1264, 1230, 1182, 1021, 924, 869, 820, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 6.90 – 6.84 (m, 2H), 6.79 (d, *J* = 8.7 Hz, 1H), 3.86 (s, 6H), 3.44 – 3.31 (m, 2H), 2.07 (t, *J* = 7.2 Hz, 2H), 1.86 – 1.70 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.71, 173.64, 149.56, 148.80, 131.65, 119.11, 110.51, 109.97, 57.16, 55.94, 55.85, 46.93, 31.00, 28.92 (3 C), 26.84.

4-(N-*tert*-Butyl-2,4,6-trimethylbenzamido)butanoic acid (73w).



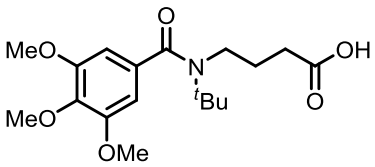
Compound **73w** was prepared from ester **72v** (1.24g, 3.72 mmol, 1 equiv.) and potassium hydroxide (0.211 g, 3.77 mmol, 1 equiv.) following *general protocol C*. Yield: 1.06 g (3.46 mmol, 93%), pale yellow solid. IR (neat): 2978, 2922, 2866, 1722, 1610, 1435, 1379, 1264, 1170, 1081, 1036, 936, 850, 779, 717 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.79 (s, 2H), 3.15 – 3.03 (m, 2H), 2.24 (s, 3H), 2.21 (s, 6H), 1.97 (t, *J* = 7.2 Hz, 2H), 1.69 (dt, *J* = 15.2, 7.3 Hz, 2H), 1.58 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.12, 172.20, 137.32, 135.63, 132.88 (2 C), 128.36 (2 C), 57.48, 46.09, 31.23, 28.91 (3 C), 26.25, 21.09, 19.11 (2 C).

4-(N-*tert*-butyl-2,6-dimethoxybenzamido)butanoic acid (73x).



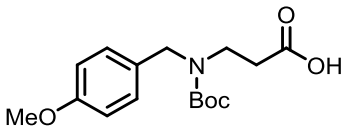
Compound **73x** was prepared from ester **72w** (3.04 g, 8.65 mmol, 1 equiv.) and potassium hydroxide (728.0 mg, 12.98 mmol, 1.5 equiv.) following *general protocol C*. Yield: 2.53 g (7.82 mmol, 90%), white solid. IR (neat): 2967, 2840, 2535, 1726, 1636, 1580, 1472, 1416, 1290, 1249, 1200, 1174, 1107, 1033, 947, 854, 790, 738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.17 (t, *J* = 8.4 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 6H), 3.12 (dd, *J* = 11.6, 4.4 Hz, 2H), 1.94 (t, *J* = 7.3 Hz, 2H), 1.73 (dq, *J* = 15.4, 7.5 Hz, 2H), 1.53 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.58, 168.00, 156.01 (2 C), 129.57, 117.60, 103.95 (2 C), 57.38, 55.79 (2 C), 46.35, 31.49, 28.96 (3 C), 26.41.

4-(N-*tert*-butyl-3,4,5-trimethoxybenzamido)butanoic acid (73y).



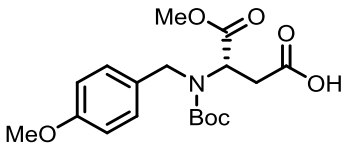
Compound **73y** was prepared from ester **72x** (5.79 g, 15.18 mmol, 1 equiv.) and potassium hydroxide (1.1 g, 19.61 mmol, 1.1 equiv.) following *general protocol C*. After acidification an orange oil obtained, which was extracted by EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was dried in vacuo to give 4.84 g (13.70 mmol, 90%) of the product as orange oil. IR (neat): 2964, 2840, 2632, 1715, 1580, 1506, 1461, 1416, 1326, 1237, 1174, 1022, 999, 939 857, 708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 6.52 (s, 2H), 3.83 (s, 6H), 3.81 (s, 3H), 3.39 – 3.27 (m, 2H), 2.10 (t, *J* = 7.2 Hz, 2H), 1.83 (dd, *J* = 15.2, 7.4 Hz, 2H), 1.53 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.83, 173.27, 153.24 (2 C), 138.39, 134.65, 103.38 (2 C), 60.87, 57.30, 56.19 (2 C), 46.88, 31.08, 28.85 (3 C), 27.02.

3-(*tert*-Butoxycarbonyl(4-methoxybenzyl)amino)propanoic acid (73z).



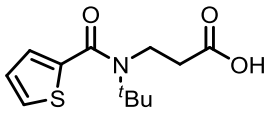
Compound **73z** was prepared from ester **72z** (3.52 g, 10.43 mmol, 1 equiv.) and potassium hydroxide (1.11 g, 19.82 mmol, 1.9 equiv.) following *general protocol C*. Yield: 3.15 g (10.18 mmol, 98%), clear solid. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.16 (d, *J* = 6.9 Hz, 2H), 6.89 – 6.80 (m, 2H), 4.39 (s, 2H), 3.79 (s, 3H), 3.43 (s, 2H), 2.53 (s, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.44, 158.95, 155.68, 130.19, 128.9 (d, 2 C), 114.00 (2 C), 80.33, 55.27, 50.41 (d), 42.46, 33.30, 28.43 (3 C).

(S)-3-(*tert*-Butoxycarbonyl(4-methoxybenzyl)amino)-4-methoxy-4-oxobutanoic acid (73aa).



Ester **72aa** (3.91 g, 10.25 mmol, 1 equiv.) was dissolved in 90 ml methanol and a 1 M KOH solution (110.0 ml, 11.0 mmol, 1 equiv.) was added slowly. The reaction mixture was stirred at room temperature for overnight and methanol was evaporated. The aqueous solution was acidified with 1 M HCl and extracted with ethyl acetate (2 x 100 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give 2.94 g (8.01 mmol, 78%) of the product as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.24 (dd, *J* = 6.6, 4.1 Hz, 2H), 6.84 (dd, *J* = 8.8, 2.3 Hz, 2H), 4.64 – 4.20 (m, 3H), 3.78 (d, *J* = 1.9 Hz, 3H), 3.67 – 3.55 (m, 3H), 3.14 (td, *J* = 16.6, 7.7 Hz, 1H), 2.67 – 2.38 (m, 1H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.96, 171.33, 159.10, 154.75, 132.08, 129.98 (2 C), 113.91 (2 C), 81.36, 60.47, 55.24, 52.33, 51.75 (d), 35.99, 28.30 (3 C).

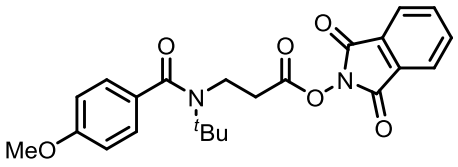
3-(N-*tert*-Butylthiophene-2-carboxamido)propanoic acid (73ab).



Compound **73ab** was prepared from ester **72ab** (2.57 g, 9.07 mmol, 1 equiv.) and potassium hydroxide (1.154 g, 20.57 mmol, 1.1 equiv.) following *general protocol C*. Yield: 0.845 g (3.31 mmol, 36%), white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.24 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.00 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.92 – 3.77 (m, 2H), 2.67 (dd, *J* = 8.9, 6.7 Hz, 2H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.46, 166.77, 140.20, 127.85, 127.60, 126.66, 58.07, 42.74, 36.25, 28.85 (3 C).

Synthesis of compounds 77

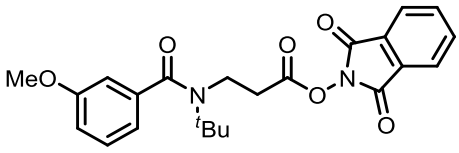
1,3-dioxoisoindolin-2-yl 3-(N-tert-butyl-4-methoxybenzamido)propanoate (74/77a).



General protocol D

A solution of DCC (1.65 g, 8.00 mmol, 1 equiv.) in 30 ml anhydrous THF was added to a solution of acid **73a** (2.20 g, 7.88 mmol, 1 equiv.) and N-hydroxyphthalimide (1.29 g, 7.91 mmol, 1 equiv.) in 40 ml of anhydrous THF. The reaction mixture was stirred at room temperature for 15 h, filtered and evaporated. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/1, $R_f = 0.31$) gave 1.45 g (3.42 mmol, 43%) of white solid, m.p. = 135-139 °C. IR (neat): 3127, 2930, 2851, 1789, 1711, 1603, 1577, 1461, 1297, 1245, 1178, 1137, 1081, 1014, 977, 842, 768, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.88 – 7.82 (m, 2H), 7.78 (m, 2H), 7.37 – 7.30 (m, 2H), 6.94 – 6.87 (m, 2H), 3.82 (s, 3H), 3.81 – 3.74 (m, 2H), 2.86 (dd, *J* = 8.6, 6.6 Hz, 2H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.89, 167.10, 161.66, 160.50 (2 C), 134.85 (2 C), 131.31, 128.83 (2 C), 128.14 (2 C), 124.02 (2 C), 114.00 (2 C), 57.35, 55.32, 42.46, 33.22, 29.07 (3 C). HRMS: (ES-MS) m/z calculated for $C_{23}H_{25}N_2O_6$ [M+H]: 425.1707, found 425.1719. The redox potential of **1a** was determined as -1.32 V (vs. SCE, irreversible peak) by cyclic voltametry.

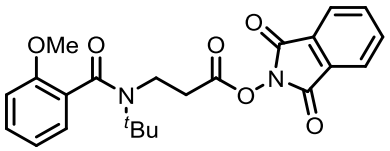
1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-3-methoxybenzamido)propanoate (77b).



Compound **77b** was prepared from acid **73b** (1.09 g, 3.90 mmol, 1 equiv.), N-hydroxyphthalimide (639.9 mg, 3.92 mmol, 1 equiv.) and DCC (807.8 mg, 3.92 mmol, 1 equiv.) following *general protocol D*. The precipitated DCC urea was removed by filtration and the solvent was evaporated. R_f (hexanes/EtOAc = 1/1) = 0.55. Yield: 1.15 g (2.71 mmol, 69%) pale yellow solid, m.p. = 132-136 °C. IR (neat): 2967, 2840, 1815, 1789, 1741, 1640, 1580, 1465, 1428, 1364, 1290, 1219, 1185, 1133, 1077, 1029, 965, 876, 839, 787, 753, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.90 – 7.82 (m, 2H), 7.79 (m, 2H), 7.36 – 7.27 (m,

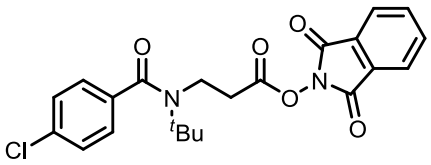
1H), 6.91 (dtd, *J* = 9.3, 3.6, 1.4 Hz, 3H), 3.82 (s, 3H), 3.79 – 3.70 (m, 2H), 2.94 – 2.82 (m, 2H), 1.57 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.38, 166.98, 161.64 (2 C), 159.79, 140.16, 134.86, 129.90 (2 C), 128.80 (2 C), 124.02 (2 C), 118.10, 115.26, 111.47, 57.55, 55.37, 42.27, 33.31, 28.99 (3 C). HRMS: (ES-MS) m/z calculated for $C_{23}H_{25}N_2O_6$ [M+H]: 425.1707, found 425.1719.

1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-2-methoxybenzamido)propanoate (77c).



Compound **77c** was prepared from acid **73c** (3.90 g, 13.96 mmol, 1 equiv.), N-hydroxyphthalimide (2.31 g, 14.16 mmol, 1 equiv.) and DCC (2.90 g, 14.06 mmol, 1 equiv.) following *general protocol D*. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/1, R_f = 0.6) gave 4.49 g (10.58 mmol, 76%) pale yellow solid, m.p. = 129-134 °C. IR (neat): 2967, 2840, 2482, 1815, 1789, 1741, 1640, 1599, 1491, 1465, 1439, 1394, 1364, 1290, 1245, 1185, 1133, 1077, 1021, 962, 876, 753, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 – 7.82 (m, 2H), 7.80 – 7.76 (m, 2H), 7.30 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H), 7.15 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.97 (td, *J* = 7.4, 0.8 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 3.87 (s, 3H), 3.76 – 3.68 (m, 1H), 3.64 – 3.56 (m, 1H), 2.97 – 2.89 (m, 1H), 2.86 – 2.78 (m, 1H), 1.58 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.45, 170.72, 154.69 (2 C), 133.81, 129.84 (2 C), 128.60 (2 C), 126.95 (2 C), 122.14, 120.83, 111.68, 111.18, 57.52, 55.60, 42.03, 35.75, 29.00 (3 C). HRMS: (ES-MS) m/z calculated for $C_{23}H_{25}N_2O_6$ [M+H]: 425.1707, found 425.1719.

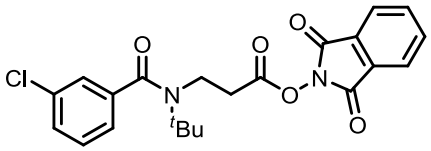
1,3-dioxoisoindolin-2-yl 3-(N-*tert*-butyl-4-chlorobenzamido)propanoate (77d).



Compound **77d** was prepared from acid **73d** (1.73 g, 6.10 mmol, 1 equiv.), N-hydroxyphthalimide (1.01 g, 6.19 mmol, 1 equiv.) and DCC (1.30 g, 6.30 mmol, 1 equiv.) following *general protocol D*. Purification by column chromatography on flash silica gel

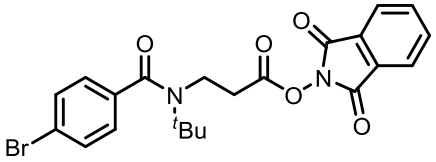
(hexanes/EtOAc = 2/1, R_f = 0.25) gave 1.92 g (4.48 mmol, 73%) white solid, m.p. = 119-121 °C. IR (neat): 3355, 3142, 2933, 1789, 1733, 1640, 1592, 1528, 1465, 1357, 1305, 1252, 1185, 1033, 1137, 1077, 1033, 917, 876, 839, 787, 757, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.90 – 7.83 (m, 2H), 7.80 (dt, *J* = 5.2, 3.6 Hz, 2H), 7.40 – 7.34 (m, 2H), 7.34 – 7.28 (m, 2H), 3.74 (dd, *J* = 8.5, 6.6 Hz, 2H), 2.86 (dd, *J* = 8.6, 6.6 Hz, 2H), 1.55 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.62, 166.91, 161.64 (2 C), 137.28, 134.92 (2 C), 129.02 (2 C), 128.75 (2 C), 127.71 (2 C), 124.09 (2 C), 57.65, 42.34, 33.10, 29.01 (3 C). HRMS: (ES-MS) m/z calculated for $C_{22}H_{22}ClN_2O_5$ [M+H]: 429.1212, found 429.1217.

1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-3-chlorobenzamido)propanoate (77e).



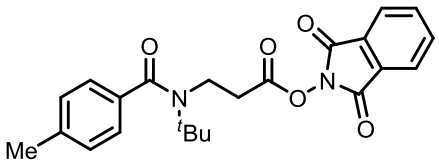
Compound **77e** was prepared from acid **73e** (2.61 g, 9.21 mmol, 1 equiv.), N-hydroxyphthalimide (1.52 g, 9.32 mmol, 1 equiv.) and DCC (1.92 g, 9.31 mmol, 1 equiv.) following *general protocol D*. For Purification the residue was dissolved in dichloromethane (20 ml) and cooled to 0 °C. The precipitated DCC urea was removed by filtration and the solvent was evaporated. Recrystallization from EtOH gave 3.13 g (7.30 mmol, 79%) as a white solid, m.p. = 114-117 °C. IR (neat): 2971, 2930, 1815, 1789, 1733, 1636, 1566, 1469, 1394, 1372, 1293, 1256, 1185, 1161, 1090, 1025, 965, 783, 780, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.87 - 7.84 (m, 2H), 7.81 – 7.75 (m, 2H), 7.39 – 7.31 (m, 3H), 7.26 – 7.21 (m, 1H), 3.78 – 3.70 (m, 2H), 2.89 – 2.82 (m, 2H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.98, 166.87, 161.61 (2 C), 140.51, 134.91 (2 C), 134.76, 130.16, 129.55, 128.77 (2 C), 126.40, 124.18, 124.07 (2 C), 57.76, 42.31, 33.13, 28.97 (3 C). HRMS: (ES-MS) m/z calculated for $C_{22}H_{22}ClN_2O_5$ [M+H]: 429.1212, found 429.1218.

1,3-dioxoisoindolin-2-yl 3-(4-bromo-N-tert-butylbenzamido)propanoate (77f).



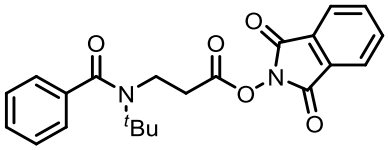
Compound **77f** was prepared from acid **73f** (1.35 g, 4.11 mmol, 1 equiv.), N-hydroxyphthalimide (679.9 mg, 4.17 mmol, 1 equiv.) and DCC (856.0 mg, 4.15 mmol, 1 equiv.) following *general protocol D*. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/1, $R_f = 0.75$) gave 1.23 g (2.60 mmol, 63%) white solid, m.p. = 111-114 °C. IR (neat): 2967, 2933, 1823, 1789, 1744, 1710, 1640, 1603, 1461, 1364, 1264, 1185, 1137, 1073, 977, 880, 835, 805, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.90 – 7.83 (m, 2H), 7.83 – 7.75 (m, 2H), 7.56 – 7.50 (m, 2H), 7.27 – 7.21 (m, 2H), 3.81 – 3.65 (m, 2H), 2.91 – 2.77 (m, 2H), 1.55 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.67, 166.90, 161.63 (2 C), 137.70, 134.92 (2 C), 131.96 (2 C), 128.74 (2 C), 127.90 (2 C), 124.09 (2 C), 123.64, 57.70, 42.33, 33.07, 29.00 (3 C). HRMS: (ES-MS) m/z calculated for $C_{22}H_{22}BrN_2O_5$ [M+H]: 473.0707, found 473.0707.

1,3-dioxoisoindolin-2-yl 3-(N-*tert*-butyl-4-methylbenzamido)propanoate (77g).



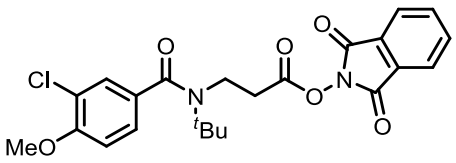
Compound **77g** was prepared from acid **73g** (1.55 g, 5.89 mmol, 1 equiv.), N-hydroxyphthalimide (966.2 mg, 5.92 mmol, 1 equiv.) and DCC (1.27 g, 6.16 mmol, 1 equiv.) following *general protocol D*. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/1, $R_f = 0.77$) gave 2.01 g (4.92 mmol, 84%) white solid, m.p. = 82-89 °C. IR (neat): 3138, 3034, 2967, 2922, 2658, 1789, 1711, 1595, 1461, 1398, 1364, 1282, 1185, 1137, 1081, 1040, 973, 828, 753, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.89 – 7.82 (m, 2H), 7.82 – 7.74 (m, 2H), 7.25 (m, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 3.80 – 3.69 (m, 2H), 2.89 – 2.79 (m, 2H), 2.35 (s, 3H), 1.56 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.00, 167.06, 161.68 (2 C), 139.40, 136.05, 134.89 (2 C), 129.33 (2 C), 128.76 (2 C), 126.12 (2 C), 124.04 (2 C), 57.42, 42.33, 33.15, 29.04 (3 C), 21.39. HRMS: (ES-MS) m/z calculated for $C_{23}H_{25}N_2O_5$ [M+H]: 409.1758, found 409.1761.

1,3-dioxoisoindolin-2-yl 3-(N-tert-butylbenzamido)propanoate (77h).



Compound **77h** was prepared from acid **73h** (4.02 g, 16.12 mmol, 1 equiv.), N-hydroxyphthalimide (2.91 mg, 17.84 mmol, 1.1 equiv.) and DCC (3.69 g, 17.88 mmol, 1.1 equiv.) following *general protocol D*. Purification by recrystallization from ethanol. Yield: 3.56 g (9.03 mmol, 56%) white solid, m.p. = 86-88 °. IR (neat): 2974, 2930, 1812, 1781, 1744, 1640, 1489, 1357, 1293, 1256, 1185, 1140, 1081, 1010, 980, 921, 876, 842, 799, 753, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.85 (dt, *J* = 6.8, 3.6 Hz, 2H), 7.82 – 7.75 (m, 2H), 7.43 – 7.32 (m, 5H), 3.80 – 3.69 (m, 2H), 2.93 – 2.80 (m, 2H), 1.57 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.69, 166.98, 161.64 (2 C), 138.97 (2 C), 134.88 (2 C), 130.67, 129.34, 128.74 (2 C), 126.03 (2 C), 124.03 (2 C), 57.50, 42.30, 33.23, 29.04 (3 C). HRMS: (ES-MS) m/z calculated for $C_{22}H_{23}N_2O_5$ [M+H]: 395.1609, found 395.1601.

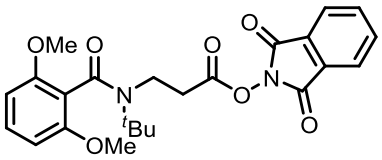
1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-3-chloro-4-methoxybenzamido)propanoate (77i).



Compound **77i** was prepared from acid **73i** (2.44 g, 7.77 mmol, 1 equiv.), N-hydroxyphthalimide (1.28 g, 7.85 mmol, 1 equiv.) and DCC (1.60 g, 7.76 mmol, 1 equiv.) following *general protocol D*. For Purification the residue was dissolved in dichloromethane (20 ml) and cooled to 0 °C. The precipitated DCC urea was removed by filtration and the solvent was evaporated. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/1, R_f = 0.23) gave 2.10 g (4.58 mmol, 59%) white solid, m.p. = 139-142 °C. IR (neat): 2926, 2844, 1815, 1785, 1744, 1633, 1599, 1504, 1460, 1405, 1367, 1264, 1186, 1081, 842, 760, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.91 – 7.83 (m, 2H), 7.79 (dt, *J* = 5.2, 3.6 Hz, 2H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.28 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 3.77 (dd, *J* = 8.4, 6.7 Hz, 2H), 2.87 (dd, *J* = 8.4, 6.7 Hz, 2H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.46, 166.99, 161.65 (2 C), 155.91, 134.92 (2 C), 131.82, 128.75, 128.68 (2 C), 126.25, 124.07 (2 C), 122.72, 111.91, 57.66, 56.22, 42.50,

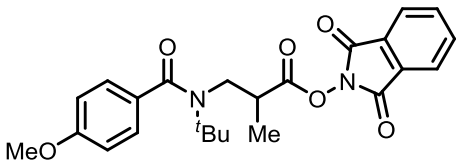
33.09, 28.98 (3 C). HRMS: (ES-MS) m/z calculated for $C_{23}H_{24}ClN_2O_6$ [M+H]: 459.1317, found 459.1319.

1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-2,6-dimethoxybenzamido)propanoate (77j).



Compound **77j** was prepared from acid **73j** (2.28 g, 7.37 mmol, 1 equiv.), N-hydroxyphthalimide (1.33 g, 8.15 mmol, 1.1 equiv.) and DCC (1.69 g, 8.19 mmol, 1.1 equiv.) following *general protocol D*. For Purification the residue was dissolved in diethylether (20 ml) and cooled to 0 °C. The precipitated DCC urea was removed by filtration and the solvent was evaporated. Column chromatography and recrystallization from EtOH gave 2.12 g (4.66 mmol, 63%) as a white solid, m.p. = 131-133 °C. R_f (hexanes/EtOAc = 1/1) = 0.39. IR (neat): 2982, 2823, 2839, 1807, 1744, 1643, 1592, 1472, 1440, 1383, 1300, 1249, 1189, 1166, 1111, 1081, 989, 924, 872, 794, 740, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.85 – 7.82 (m, 2H), 7.79 – 7.74 (m, 2H), 7.20 (t, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 3.83 (s, 6H), 3.66 – 3.59 (m, 2H), 2.90 – 2.83 (m, 2H), 1.59 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.13, 167.45, 161.71 (2 C), 155.88 (2 C), 134.85, 129.97 (2 C), 128.81 (2 C), 123.98 (2 C), 117.25, 104.21 (2 C), 57.55, 55.87 (2 C), 41.90, 33.00, 29.03 (3 C). HRMS: (ES-MS) m/z calculated for $C_{24}H_{27}N_2O_7$ [M+H]: 455.1813, found 455.1821.

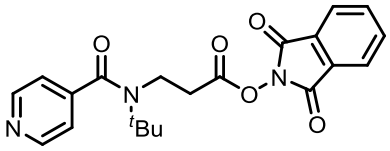
1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-4-methoxybenzamido)-2-methylpropanoate (77k).



Compound **77k** was prepared from acid **73k** (2.42 g, 8.25 mmol, 1 equiv.), N-hydroxyphthalimide (1.36 g, 8.34 mmol, 1 equiv.) and DCC (1.76 g, 8.53 mmol, 1 equiv.) following *general protocol D*. For Purification the residue was dissolved in dichloromethane (20 ml) and cooled to 0 °C. The precipitated DCC urea was removed by filtration and the

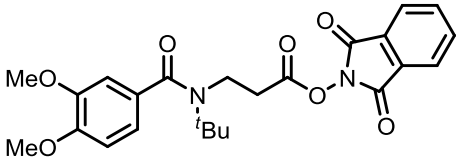
solvent was evaporated. Recrystallization from EtOH gave 2.38 g (5.43 mmol, 66%) as a white solid, m.p. = 134-139 °C. IR (neat):2982, 2112, 1804, 1778, 1741, 1633, 1599, 1513, 1450, 1398, 1361, 1305, 1252, 1182, 1111, 1021, 1062, 962, 835, 872, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (td, *J* = 5.3, 2.0 Hz, 2H), 7.81 – 7.75 (m, 2H), 7.41 – 7.34 (m, 2H), 6.90 – 6.84 (m, 2H), 3.96 (dd, *J* = 15.0, 5.1 Hz, 1H), 3.81 (s, 3H), 3.77 (dd, *J* = 15.0, 9.0 Hz, 1H), 3.18 (ddd, *J* = 8.9, 7.0, 5.2 Hz, 1H), 1.57 (s, 9H), 1.21 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.40, 170.69, 161.77, 160.70 (2 C), 134.85 (2 C), 131.23, 129.54 (2 C), 128.87 (2 C), 124.01 (2 C), 113.80 (2 C), 57.20, 55.33, 50.02, 38.77, 29.22 (3 C), 14.23. HRMS: (ES-MS) m/z calculated for $C_{24}H_{27}N_2O_6$ [M+H]: 439.1864, found 439.187.

1,3-Dioxoisoindolin-2-yl 3-(N-tert-butylisonicotinamido)propanoate (77l).



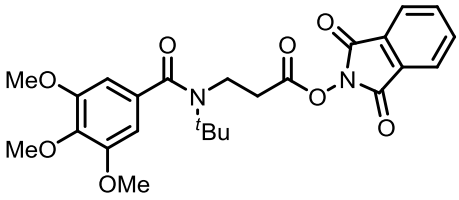
Compound **77l** was prepared from acid **73l** (240 mg, 0.959 mmol, 1 equiv.), N-hydroxyphthalimide (174 mg, 1.07 mmol, 1.1 equiv.) and DCC (219.6 mg, 1.06 mmol, 1.1 equiv.) following *general protocol D*. Purification by recrystallization from toluene. Yield: 313 mg (0.791 mmol, 83%) pale yellow solid, m.p. = 121-126 °C. IR (neat): 3131, 2930, 2851, 1789, 1710, 1633, 1461, 1413, 1327, 1290, 1185, 1137, 1066, 977, 880, 835, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.70 (d, *J* = 4.6 Hz, 2H), 7.89 – 7.83 (m, 2H), 7.83 – 7.77 (m, 2H), 7.31 (d, *J* = 5.9 Hz, 2H), 3.71 (dd, *J* = 8.3, 6.6 Hz, 2H), 2.88 (dd, *J* = 8.3, 6.6 Hz, 2H), 1.57 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.46, 166.69, 161.55 (2 C), 149.63, 134.94 (2 C), 128.74 (2 C), 124.12 (2 C), 123.18 (2 C), 120.78 (2 C), 58.06, 42.09, 33.13, 28.93 (3 C). LRMS: (ES-MS) m/z calculated for $C_{21}H_{22}N_3O_5$ [M+H]: 396.0317, found 396.0608.

1,3-dioxoisoindolin-2-yl 3-(N-*tert*-butyl-3,4-dimethoxybenzamido)propanoate (77m).



Compound **77m** was prepared from acid **73m** (4.48 g, 14.48 mmol, 1 equiv.), N-hydroxyphthalimide (2.38 g, 14.59 mmol, 1 equiv.) and DCC (3.03 g, 14.69 mmol, 1 equiv.) following *general protocol D* using $CHCl_3$ as solvent. For Purification the residue was dissolved in diethylether (20 ml) and cooled to 0 °C. The precipitated DCC urea was removed by filtration and the solvent was evaporated. Recrystallization from $CHCl_3$ gave 4.56 g (10.03 mmol, 69%) as a white solid, m.p. = 118-120 °C. IR (neat): 2963, 2933, 2840, 1819, 1789, 1744, 1629, 1603, 1513, 1465, 1413, 1264, 1230, 1182, 1137, 1074, 1021, 969, 880, 782, 757, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.85 (m, *J* = 5.7, 3.0 Hz, 2H), 7.81 – 7.74 (m, 2H), 6.96 – 6.84 (m, 3H), 3.89 (s, 6H), 3.83 – 3.72 (m, 2H), 2.95 – 2.79 (m, 2H), 1.55 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.80, 167.10, 161.68 (2 C), 150.03, 149.10, 134.91, 131.36 (2 C), 128.73 (2 C), 124.03 (2 C), 119.08, 110.72, 109.89, 57.43, 55.99, 55.93, 42.51, 33.36, 28.99 (3 C). HRMS: (ES-MS) m/z calculated for $C_{24}H_{27}N_2O_7$ [M+H]: 455.1813, found 455.1813.

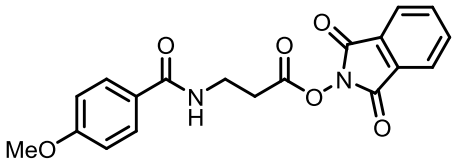
1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-3,4,5-trimethoxybenzamido)propanoate (77n).



Compound **77n** was prepared from acid **73n** (1.89 g, 5.57 mmol, 1 equiv.), N-hydroxyphthalimide (989.6 mg, 6.07 mmol, 1 equiv.) and DCC (1.16 g, 5.62 mmol, 1 equiv.) following *general protocol D* using $CHCl_3$ as solvent. For Purification the residue was dissolved in diethylether (20 ml) and cooled to 0 °C. The precipitated DCC urea was removed by filtration and the solvent was evaporated. Recrystallization from $CHCl_3$ gave 4.56 g (10.03 mmol, 69%) of pale yellow solid, m.p. = 134-139 °C. IR (neat): 2952, 2840, 1815, 1789, 1744, 1633, 1584, 1461, 1364, 1331, 1238, 1185, 1126, 1066, 995, 965, 876, 794, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.89 – 7.82 (m, 2H), 7.82 – 7.74 (m, 2H), 6.56 (s, 2H), 3.88 (s, 6H), 3.84 (s, 3H), 3.83 – 3.75 (m, 2H), 2.94 – 2.85 (m, 2H), 1.56 (s, 9H). ^{13}C

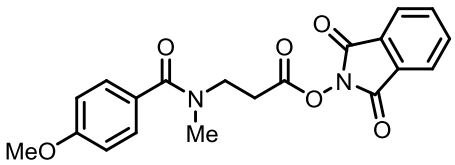
NMR (75 MHz, $CDCl_3$) δ = 173.35, 166.96, 161.66 (2 C), 153.48 (2 C), 138.92, 134.92 (2 C), 134.31, 128.73 (2 C), 124.06 (2 C), 103.42 (2 C), 60.92, 57.58, 56.28, 42.47, 33.47, 28.98 (3 C). HRMS: (ES-MS) m/z calculated for $C_{25}H_{29}N_2O_8$ [M+H]: 485.1918, found 485.1920.

1,3-Dioxoisoindolin-2-yl 3-(4-methoxybenzamido)propanoate (81).



Compound **81** was prepared from acid **73o** (1.98 g, 8.87 mmol, 1 equiv.), N-hydroxyphthalimide (1.32 g, 8.09 mmol, 0.9 equiv.) and DCC (1.67 g, 8.09 mmol, 0.9 equiv.) following *general protocol D*. Recrystallization from MeOH gave 2.43 g (6.60 mmol, 74%) of white solid. IR (neat): 3370, 3317, 3086, 2922, 2840, 1812, 1785, 1707, 1629, 1543, 1502, 1461, 1323, 1252, 1182, 1081, 1033, 965, 876, 764, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.95 – 7.87 (m, 2H), 7.85 – 7.78 (m, 4H), 6.95 – 6.91 (m, 2H), 3.96 – 3.86 (m, 2H), 3.84 (s, 3H), 3.04 – 2.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.78, 167.14, 162.32, 161.99 (2 C), 134.98 (2 C), 128.96 (2 C), 128.80 (2 C), 126.25, 124.18 (2 C), 113.78 (2 C), 55.42, 35.62, 32.21. HRMS: (ES-MS) m/z calculated for $C_{19}H_{17}N_2O_6$ [M+H]: 369.1081, found 369.1089.

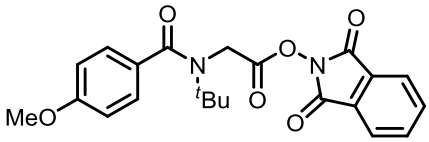
1,3-Dioxoisoindolin-2-yl 3-(4-methoxy-N-methylbenzamido)propanoate (83).



Compound **83** was prepared from acid **73p** (4.32 g, 18.23 mmol, 1 equiv.), N-hydroxyphthalimide (2.99 g, 18.33 mmol, 1 equiv.) and DCC (3.77 g, 18.27 mmol, 1 equiv.) following *general protocol D*. For Purification the residue was dissolved in diethylether (20 ml) and cooled to 0 °C. The precipitated DCC urea was removed by filtration and the solvent was evaporated. Yield: 4.10 g (10.72 mmol, 59%) pale yellow solid. IR (neat): 2933, 2844, 1722, 1595, 1517, 1487, 1443, 1402, 1301, 1249, 1174, 1077, 1025, 969, 842, 794, 764, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.87 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 6.89 (dd, *J* = 6.7, 4.8 Hz, 2H), 3.87 (d, *J* = 3.8 Hz, 2H),

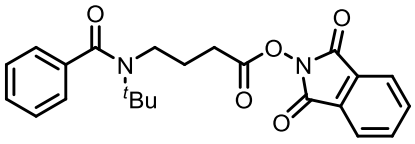
3.80 (s, 3H), 3.15 – 3.02 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.92, 161.81 (2 C), 160.85, 134.90 (2 C), 133.82, 129.17, 128.84 (2 C), 127.93 (2 C), 124.06 (2 C), 113.72 (2 C), 55.35, 33.76, 29.77, 24.90. HRMS: (ES-MS) m/z calculated for $C_{20}H_{19}N_2O_6$ [M+H]: 383.1238, found 383.1244.

1,3-Dioxoisoindolin-2-yl 2-(N-*tert*-butyl-4-methoxybenzamido)acetate (97).



Compound **97** was prepared from acid **73q** (3.60 g, 13.57 mmol, 1 equiv.), N-hydroxyphthalimide (2.45 g, 15.02 mmol, 1.1 equiv.) and DCC (3.11 g, 15.07 mmol, 1.1 equiv.) following *general protocol D*. For purification the solvent of the reaction mixture was removed and the product was precipitated by adding diethylether. Yield: 3.22 g (7.85 mmol, 58%) white solid. IR (neat): 2967, 2933, 1830, 1789, 1744, 1644, 1603, 1580, 1510, 1469, 1416, 1357, 1308, 1249, 1138, 1174, 1077, 1029, 951, 876, 846, 790, 734, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.91 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.82 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.43 (s, 2H), 3.84 (s, 3H), 1.58 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.73, 168.37, 161.66 (2 C), 160.88, 135.02 (2 C), 130.08, 128.76 (2 C), 128.13 (2 C), 124.14 (2 C), 114.20 (2 C), 58.35, 55.36, 47.85, 28.06 (3 C).

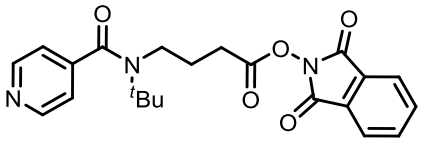
1,3-dioxoisoindolin-2-yl 4-(N-tert-butylbenzamido)butanoate (102a).



Compound **102a** was prepared from acid **73r** (2.33 g, 8.85 mmol, 1 equiv.), N-hydroxyphthalimide (1.49 g, 9.13 mmol, 1 equiv.) and DCC (1.91 g, 9.26 mmol, 1 equiv.) following *general protocol D*. Purification by column chromatography on flash silica gel (hexanes/DCM = 1/2 to hexanes/EtOAc = 1/1, R_f = 0.56) gave 1.98 g (4.89 mmol, 56%) pale yellow solid, m.p. = 100-109 °C. IR (neat): 3064, 2933, 2605, 1789, 1707, 1589, 1484, 1446, 1409, 1368, 1305, 1241, 1185, 1070, 973, 783, 749, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.90 – 7.82 (m, 2H), 7.82 – 7.75 (m, 2H), 7.37 – 7.31 (m, 10H), 3.46 – 3.35 (m, 2H), 2.36

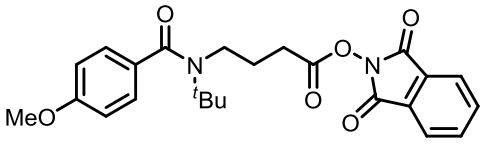
(t, *J* = 7.2 Hz, 2H), 1.93 (dt, *J* = 19.7, 7.5 Hz, 2H), 1.56 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.55, 168.71, 161.80 (2 C), 139.25 (2 C), 134.91 (2 C), 128.93, 128.76, 128.60 (2 C), 125.98 (2 C), 124.03 (2 C), 57.34, 46.43, 28.97 (3 C), 28.34, 26.66. HRMS: (ES-MS) m/z calculated for $C_{23}H_{25}N_2O_8$ [M+H]: 409.1758, found 409.1763.

1,3-dioxoisoindolin-2-yl 4-(N-*tert*-butylisonicotinamido)butanoate (102b).



Compound **102b** was prepared from acid **73s** (936 mg, 3.54 mmol, 1 equiv.), N-hydroxyphthalimide (637.4 mg, 3.91 mmol, 1.1 equiv.) and DCC (805.7 mg, 3.90 mmol, 1.1 equiv.) following *general protocol D*. Recrystallization from toluene gave 1.21 g (2.96 mmol, 83%) white solid, m.p. = 134-151 °C. IR (neat): 3127, 2930, 1789, 1707, 1625, 1461, 1409, 1364, 1297, 1252, 1215, 1185, 1133, 1062, 973, 880, 835, 764, 731, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.66 (d, *J* = 5.6 Hz, 2H), 7.87 (td, *J* = 5.3, 2.0 Hz, 2H), 7.80 (td, *J* = 5.2, 1.9 Hz, 2H), 7.26 – 7.22 (m, 2H), 3.41 – 3.32 (m, 2H), 2.42 (t, *J* = 6.9 Hz, 2H), 1.94 (ddd, *J* = 15.0, 10.9, 7.0 Hz, 2H), 1.56 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.22, 169.84, 164.61 (2 C), 148.51, 147.78 (2 C), 134.13 (2 C), 129.25 (2 C), 123.24 (2 C), 121.59 (2 C), 57.79, 46.38, 30.92, 28.72 (3 C), 27.08. HRMS: (ES-MS) m/z calculated for $C_{22}H_{24}N_3O_5$ [M+H]: 410.1710, found 410.1716.

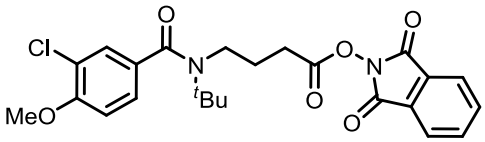
1,3-dioxoisoindolin-2-yl 4-(N-*tert*-butyl-4-methoxybenzamido)butanoate (102c).



Compound **102c** was prepared from acid **73t** (2.49 g, 8.49 mmol, 1 equiv.), N-hydroxyphthalimide (1.41 g, 8.64 mmol, 1 equiv.) and DCC (1.77 g, 8.58 mmol, 1 equiv.) following *general protocol D*. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/1, R_f = 0.45) gave 2.25 g (5.13 mmol, 60%) white solid, m.p. = 109-114 °C. IR (neat):2967, 2110, 1815, 1789, 1744, 1607, 1513, 1465, 1394, 1297, 1249, 1170, 1133, 1080, 1029, 969, 880, 839, 768, 734, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (dt, *J* = 7.1, 3.6 Hz, 2H), 7.80 (td, *J* = 5.2, 2.0 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* =

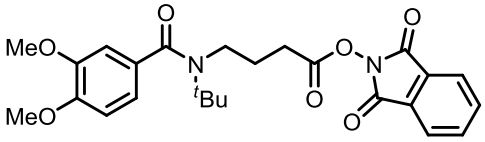
8.7 Hz, 2H), 3.81 (d, *J* = 4.0 Hz, 3H), 3.50 – 3.42 (m, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.99 – 1.87 (m, 2H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.61, 168.74, 161.79 (2 C), 160.11, 134.87 (2 C), 131.73, 128.84 (2 C), 128.09 (2 C), 124.02 (2 C), 113.83 (2 C), 57.12, 55.28, 46.64, 29.04 (3 C), 28.40, 26.70. HRMS: (ES-MS) m/z calculated for $C_{24}H_{27}N_2O_6$ [M+H]: 439.1864, found 439.1866.

1,3-dioxoisoindolin-2-yl 4-(N-tert-butyl-3-chloro-4-methoxybenzamido)butanoate (102d).



Compound **102d** was prepared from acid **73u** (2.43 g, 7.41 mmol, 1 equiv.), N-hydroxyphthalimide (1.22 g, 7.48 mmol, 1 equiv.) and DCC (1.53 g, 7.43 mmol, 1 equiv.) following *general protocol D*. For Purification the residue was dissolved in dichloromethane (20 ml) and cooled to 0 °C. The precipitated DCC urea was removed by filtration and the solvent was evaporated. Recrystallization from EtOH gave 2.04 g (4.31 mmol, 58%) white solid, m.p. = 134-139 °C. IR (neat):2974, 2922, 1812, 1785, 1744, 1625, 1506, 1405, 1290, 1264, 1223, 1185, 1085, 1018, 958, 876, 824, 787, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (dt, *J* = 7.1, 3.6 Hz, 2H), 7.83 – 7.77 (m, 2H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.29 – 7.26 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 3.45 (dd, *J* = 9.1, 7.0 Hz, 2H), 2.43 (t, *J* = 7.1 Hz, 2H), 1.99 – 1.88 (m, 2H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.99, 168.65, 161.77 (2 C), 155.52, 134.89 (2 C), 132.40, 128.79, 128.54 (2 C), 126.26, 124.05 (2 C), 122.48, 111.82, 57.34, 56.18, 46.62, 28.94 (3 C), 28.35, 26.65. HRMS: (ES-MS) m/z calculated for $C_{24}H_{26}ClN_2O_6$ [M+H]: 473.1474, found 473.1483.

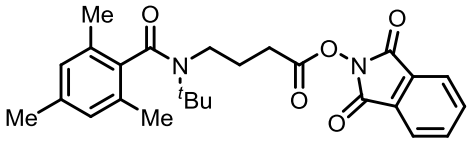
1,3-dioxoisoindolin-2-yl 4-(N-tert-butyl-3,4-dimethoxybenzamido)butanoate (102e).



Compound **102e** was prepared from acid **73v** (2.51 g, 7.76 mmol, 1 equiv.), N-hydroxyphthalimide (1.29 g, 7.91 mmol, 1 equiv.) and DCC (1.61 g, 7.80 mmol, 1 equiv.) following *general protocol D* using $CHCl_3$ as solvent. Purification by column

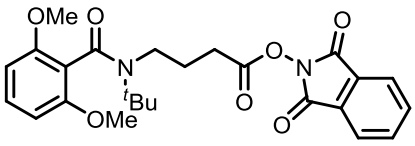
chromatography on flash silica gel (hexanes/EtOAc = 1/1, R_f = 0.5) gave 2.29 g (4.89 mmol, 63%) white solid, m.p. = 113-118 °C. IR (neat): 2922, 2651, 1782, 1744, 1618, 1513, 1412, 1327, 1293, 1260, 1182, 1144, 1092, 1047, 962, 869, 779, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.86 (dt, *J* = 7.1, 3.6 Hz, 2H), 7.83 – 7.75 (m, 2H), 6.94 – 6.87 (m, 2H), 6.80 (d, *J* = 8.1 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.46 (dd, *J* = 9.1, 6.9 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.99 – 1.90 (m, 2H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.60, 168.67, 161.77 (2 C), 149.64, 148.95, 134.87 (2 C), 131.72, 128.83 (2 C), 124.02 (2 C), 119.01, 110.71, 109.84, 57.32, 56.00, 55.86, 46.70, 29.00, 28.46 (3 C), 26.83. HRMS: (ES-MS) m/z calculated for $C_{25}H_{29}N_2O_7$ [M+H]: 469.1969, found 469.1975.

1,3-Dioxoisoindolin-2-yl 4-(N-tert-butyl-2,4,6-trimethylbenzamido)butanoate (102f).



Compound **102f** was prepared from acid **73w** (0.30 g, 0.982 mmol, 1 equiv.), N-hydroxyphthalimide (0.167 g, 1.02 mmol, 1 equiv.) and DCC (0.206 g, 0.999 mmol, 1 equiv.) following *general protocol D*. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/1, R_f = 0.55) gave 0.311 g (0.69 mmol, 70%) yellow solid. IR (neat): 3138, 3034, 2960, 1789, 1737, 1703, 1625, 1461, 1416, 1390, 1305, 1352, 1189, 1137, 1055, 977, 939, 880, 853, 787, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.89 – 7.81 (m, 2H), 7.81 – 7.75 (m, 2H), 6.79 (s, 2H), 3.26 – 3.16 (m, 2H), 2.31 (t, *J* = 7.1 Hz, 2H), 2.23 (s, 6H), 2.20 (s, 3H), 1.82 (tt, *J* = 11.3, 7.2 Hz, 2H), 1.58 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.10, 168.65, 161.80 (2 C), 137.36, 135.69, 134.90 (2 C), 132.84 (2 C), 128.77 (2 C), 128.48 (2 C), 124.01 (2 C), 57.54, 45.74, 28.94 (3 C), 28.47, 26.04, 21.06, 19.12 (2 C). HRMS: (ES-MS) m/z calculated for $C_{26}H_{31}N_2O_5$ [M+H]: 451.2227, found 451.2236.

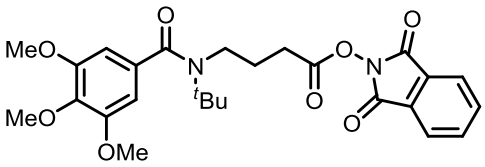
1,3-Dioxoisoindolin-2-yl 4-(N-*tert*-butyl-2,6-dimethoxybenzamido)butanoate (102g).



Compound **102g** was prepared from acid **73x** (2.53 g, 7.82 mmol, 1 equiv.), N-hydroxyphthalimide (1.28 g, 7.88 mmol, 1 equiv.) and DCC (1.62 g, 7.83 mmol, 1 equiv.)

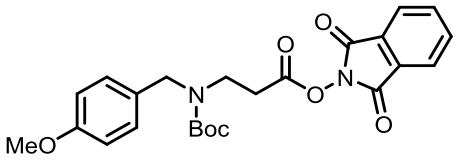
following *general protocol D*. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/1, R_f = 0.29) and recrystallization from EtOH gave 2.73 g (5.83 mmol, 75%) as a white solid, m.p. = 173-175 °C. IR (neat): 2967, 2844, 1812, 1744, 1636, 1588, 1472, 1440, 1394, 1361, 1252, 1219, 1152, 1107, 1073, 988, 876, 831, 794, 749, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.86 (m, 2H), 7.81 – 7.76 (m, 2H), 7.18 (t, *J* = 8.4 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 2H), 3.81 (s, 6H), 3.25 (dd, *J* = 9.2, 7.0 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.91 (dt, *J* = 15.4, 7.5 Hz, 2H), 1.57 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.86, 167.84, 161.84 (2 C), 156.05 (2 C), 134.85 (2 C), 129.61, 128.88 (2 C), 123.99 (2 C), 117.79, 104.06 (2 C), 57.44, 55.85 (2 C), 45.97, 29.04 (3 C), 28.62, 26.26. HRMS: (ES-MS) m/z calculated for $C_{25}H_{29}N_2O_7$ [M+H]: 469.1969, found 469.1976.

1,3-dioxoisoindolin-2-yl 4-(N-tert-butyl-3,4,5-trimethoxybenzamido)butanoate (102h).



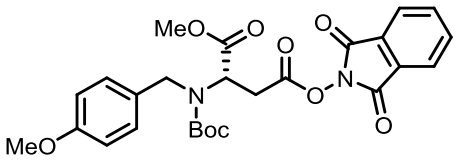
Compound **102h** was prepared from acid **73y** (2.50 g, 7.07 mmol, 1 equiv.), N-hydroxyphthalimide (1.21 g, 7.42 mmol, 1 equiv.) and DCC (1.49 g, 7.22 mmol, 1 equiv.) following *general protocol D* using $CHCl_3$ as solvent. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/1, R_f = 0.34) gave 1.98 g (4.89 mmol, 56%) white solid, m.p. = 132-139 °C. IR (neat): 3125, 3015, 2930, 2848, 1812, 1750, 1737, 1636, 1584, 1461, 1409, 1361, 1234, 1185, 1126, 1043, 880, 805, 783, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.87 (m, 2H), 7.79 (m, 2H), 6.54 (s, 2H), 3.86 (s, 6H), 3.78 (s, 3H), 3.43 (dd, *J* = 9.2, 6.9 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.02 – 1.93 (m, 2H), 1.56 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.09, 168.65, 161.77 (2 C), 153.39 (2 C), 138.60, 134.88 (2 C), 134.79, 128.84 (2 C), 124.04 (2 C), 103.42 (2 C), 60.85, 57.33, 56.27 (2 C), 46.56, 28.95 (3 C), 28.47, 27.06. HRMS: (ES-MS) m/z calculated for $C_{26}H_{31}N_2O_8$ [M+H]: 499.2075, found 499.2078.

1,3-Dioxoisoindolin-2-yl 3-(*tert*-butoxycarbonyl(4-methoxybenzyl)amino)propanoate (118).



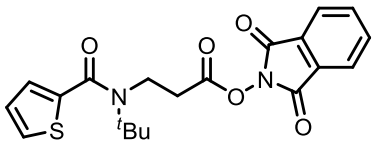
Compound **118** was prepared from acid **73z** (3.14 g, 10.15 mmol, 1 equiv.), N-hydroxyphthalimide (1.66 g, 10.18 mmol, 1 equiv.) and DCC (2.01 g, 9.74 mmol, 1 equiv.) following *general protocol D*. Purification by column chromatography gave 3.11 g (6.84 mmol, 67%) of white solid. R_f (hexanes/EtOAc = 2/1) = 0.35). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.93 – 7.84 (m, 2H), 7.82 – 7.75 (m, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.90 – 6.81 (m, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 3.56 (d, *J* = 8.5 Hz, 2H), 2.88 (d, *J* = 39.3 Hz, 2H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.58, 171.09, 159.08 (2 C), 154.80, 132.29 (2 C), 130.23, 129.98 (2 C), 129.40 (2 C), 129.14 (2 C), 113.79 (2 C), 81.18, 55.26, 52.26, 51.89, 51.57, 28.31 (3 C).

(S)-4-(1,3-Dioxoisoindolin-2-yl) 1-methyl 2-(*tert*-butoxycarbonyl(4-methoxybenzyl)-amino)succinate (125).



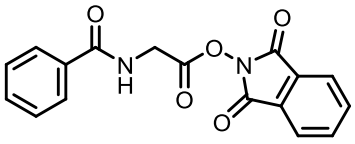
Compound **125** was prepared from acid **73aa** (2.93 g, 7.98 mmol, 1 equiv.), N-hydroxyphthalimide (1.33 g, 8.18 mmol, 1 equiv.) and DCC (1.65 g, 7.97 mmol, 1 equiv.) following *general protocol D*. After evaporation of the solvent, the residue was dissolved in dichloromethane at 0 °C and the precipitated urea was removed by filtration. Column chromatography gave 2.43 g (4.74 mmol, 59%) of colorless oil. R_f (hexanes/EtOAc = 1/1) = 0.34). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.91 – 7.85 (m, 2H), 7.82 – 7.76 (m, 2H), 7.28 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.72 – 4.59 (m, 1H), 4.35 (dd, *J* = 22.2, 10.9 Hz, 1H), 3.79 (d, *J* = 1.7 Hz, 3H), 3.65 (d, *J* = 23.3 Hz, 3H), 3.59 – 3.43 (m, 1H), 3.32 – 2.97 (m, 1H), 2.94 – 2.55 (m, 1H), 1.52 (d, *J* = 23.2 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.08, 167.70, 161.67 (2 C), 161.35, 159.17, 134.84 (2 C), 130.10 (2 C), 129.40, 128.84 (2 C), 124.02 (2 C), 113.99 (2 C), 81.63, 55.91, 55.27, 52.61, 51.75, 33.36, 28.32 (3 C).

1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butylthiophene-2-carboxamido)propanoate (60).



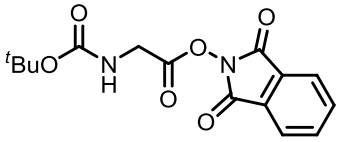
Compound **60** was prepared from acid **73ab** (0.823 g, 3.22 mmol, 1 equiv.), N-hydroxyphthalimide (527.8 mg, 3.24 mmol, 1 equiv.) and DCC (664.4 mg, 3.22 mmol, 1 equiv.) following *general protocol D*. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/1, R_f = 0.65) Yield: 812 mg (2.03 mmol, 63%) yellow solid. IR (neat): 3101, 2978, 1789, 1707, 1625, 1521, 1461, 1424, 1379, 1282, 1249, 1185, 1137, 1077, 958, 902, 880, 805, 746, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.84 (dt, *J* = 6.8, 3.6 Hz, 2H), 7.77 (dt, *J* = 5.3, 3.6 Hz, 2H), 7.38 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.01 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.03 – 3.86 (m, 2H), 3.08 – 2.92 (m, 2H), 1.53 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.13, 166.85, 161.68 (2 C), 139.84, 134.94 (2 C), 128.73, 128.12 (2 C), 127.83, 126.91 (2 C), 124.06, 58.24, 42.51, 33.80, 28.81 (3 C). HRMS: (ES-MS) m/z calculated for $C_{20}H_{21}N_2O_5S$ [M+H]: 401.1166, found 401.1167.

1,3-Dioxoisoindolin-2-yl 2-benzamidoacetate (240).



Compound **240** was prepared from hippuric acid (2.02 g, 11.25 mmol, 1 equiv.), N-hydroxyphthalimide (1.85 g, 11.34 mmol, 1 equiv.) and DCC (2.33 g, 11.29 mmol, 1 equiv.) following *general protocol D*. Recrystallization in DCM gave a white solid. Yield: 2.86 g (8.82 mmol, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.86 – 7.77 (m, 4H), 7.56 – 7.40 (m, 3H), 7.26 (s, 1H), 6.64 (s, 1H), 5.30 (s, 1H), 4.70 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.45, 167.01, 161.45 (2 C), 134.98 (2 C), 133.23, 132.15 (2 C), 128.79 (2 C), 128.75 (2 C), 127.20 (2 C), 124.19 (2 C), 39.58. HRMS: (ES-MS) m/z calculated for $C_{17}H_{13}N_2O_5$ [M+H]: 325.0819, found 325.0825.

1,3-Dioxoisoindolin-2-yl 2-(*tert*-butoxycarbonylamino)acetate (242).

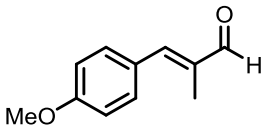


Compound **242** was prepared from 2-(tert-butoxycarbonylamino)acetic (1.50 g, 8.59 mmol, 1 equiv.), N-hydroxyphthalimide (1.42 g, 8.70 mmol, 1 equiv.) and DCC (1.83 g, 8.87 mmol, 1 equiv.) following *general protocol D*. Recrystallization in DCM gave a white solid. Yield: 2.21 g (6.90 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.04 (s, 1H), 4.35 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.21, 161.50 (2 C), 134.93 (2 C), 128.77 (2 C), 124.13 (2 C), 80.76, 40.36, 33.62, 28.27 (3 C).

Analytical data match to the reported data.[136]

N-acyloxyphthalimides for tetralin synthesis

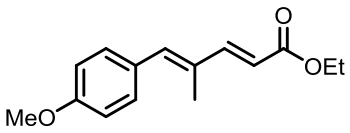
(E)-3-(4-Methoxyphenyl)-2-methylacrylaldehyde (254).



Propanal (13 ml, 179.07 mmol, 1.2 equiv.) in benzene (20 ml) was added dropwise to a solution of 4-methoxybenzaldehyde (18 ml, 148.7 mmol, 1 equiv.) in benzene (30 ml). Potassium hydroxide (1.24 g, 22 mmol, 0.15 equiv.) and tetrabutylammonium hexafluorophosphate (5.7 g, 14.7 mmol, 0.1 equiv.) was powdered into the solution and stirred at room temperature for 36 h. The solvent was evaporated and the residue was distilled under vacuum (1.9 mbar). One fraction of yellow oil was collected (B.P. 70-75 °C). After column chromatography a yellow oil was obtained (2.82 g, 16 mmol, 11%). R_f (hexanes/EtOAc = 4/1) = 0.4. IR (neat): 2960, 2840, 2714, 1670, 1599, 1510, 1443, 1405, 1305, 1252, 1174, 1115,1014, 891, 820, 768 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.52 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.17 (s, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 3H), 2.06 (d, *J* = 1.3 Hz, 3H).

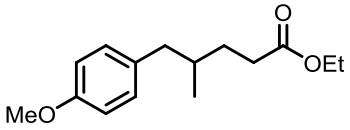
Analytical data match to the reported data.[137]

(2E,4E)-Ethyl 5-(4-methoxyphenyl)-4-methylpenta-2,4-dienoate (255).



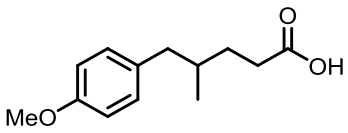
Triethyl phosphonoacetate (4.03 g, 17.98 mmol, 1.1 equiv.) was added to a solution of NaH (60% dispersion in mineral oil, 667.3 mg, 16.88 mmol, 1.05 equiv.) in THF (20 ml) and stirred for 30 min at 0 °C. Aldehyde **254** was added dropwise at 0 °C and stirred for additional 15 h at room temperature. The reaction was quenched with brine (30 ml) and the THF was removed under reduced pressure. The aqueous layer was extracted with DCM (2 x 30 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. Purification via column chromatography gave a yellow oil (2.54 g, 10.31 mmol, 65%). R_f (hexanes/EtOAc = 10/1) = 0.33. IR (neat): 3474, 2982, 2840, 1707, 1633, 1603, 1513, 1461, 1368, 1305, 1249, 1163, 1029, 984, 828, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 16.0 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 5.7 Hz, 2H), 6.78 (s, 1H), 5.93 (dd, *J* = 15.6, 0.5 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.04 (d, *J* = 1.2 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.45, 161.33, 144.32, 131.04, 129.72 (2 C), 127.19, 115.71, 114.32, 113.83 (2 C), 60.39, 55.39, 14.37, 14.24. LRMS: (APCI-MS) m/z calculated for $C_{15}H_{19}O_3$ [M+H]: 247.13, found 247.1332.

Ethyl 5-(4-methoxyphenyl)-4-methylpentanoate (256).



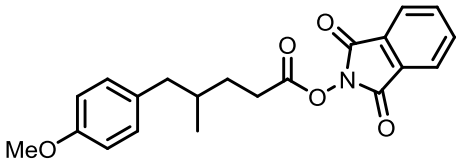
Compound **255** (2.54 g, 10.31 mmol, 1 equiv.) and 10% palladium on activated charcoal (100 mg, 0.1 mmol, 0.01 equiv.) was dissolved in EtOH (absolute, 30 ml). The mixture was stirred under hydrogen atmosphere overnight. The mixture was filtered through Celite and the solvent was removed under reduced pressure to give a pale yellow oil (2.37 g, 9.47 mmol, 92%). IR (neat): 2930, 1733, 1614, 1584, 1513, 1461, 1372, 1342, 1301, 1245, 1178, 1107, 1036, 939, 824, 708 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.15 – 7.09 (m, 2H), 6.86 – 6.78 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.89 (t, *J* = 7.8 Hz, 1H), 2.62 – 2.55 (m, 2H), 2.39 – 2.28 (m, 2H), 1.76 – 1.65 (m, 1H), 1.52 – 1.42 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.87 (dd, *J* = 8.9, 5.3 Hz, 3H). LRMS: (ES-MS) m/z calculated for $C_{15}H_{23}O_3$ [M+H]: 251.16, found 251.1655.

5-(4-Methoxyphenyl)-4-methylpentanoic acid (257).



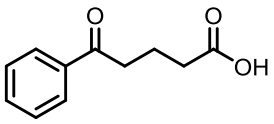
Compound **257** was prepared from ester **256** (1.37 g, 5.47 mmol, 1 equiv.) and potassium hydroxide (0.307 g, 5.47 mmol, 1 equiv.) following *general protocol C*. Yield: 0.915 g (4.12 mmol, 75%), white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.17 – 7.10 (m, 2H), 6.86 – 6.83 (m, 2H), 3.79 (s, 4H), 2.91 (t, *J* = 7.7 Hz, 2H), 2.58 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.44 – 2.28 (m, 2H), 1.81 – 1.62 (m, 2H), 1.56 – 1.40 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 180.04, 158.17, 132.84, 130.02 (2 C), 113.66 (2 C), 55.27, 42.42, 35.88, 34.65, 31.24, 18.96. LRMS: (ES-MS) m/z calculated for $C_{13}H_{17}O_3$ [M-H]: 221.13, found 221.1189.

1,3-Dioxoisoindolin-2-yl 5-(4-methoxyphenyl)-4-methylpentanoate (127).



Compound **127** was prepared from acid **257** (0.915 g, 4.12 mmol, 1 equiv.), N-hydroxyphthalimide (0.739 g, 4.53 mmol, 1.1 equiv.) and DCC (0.936 g, 4.54 mmol, 1.1 equiv.) following *general protocol D*. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/1, R_f = 0.61) gave 0.431 g (1.17 mmol, 29%) white solid. IR (neat): 3097, 2960, 2933, 1785, 1703, 1607, 1510, 1461, 1413, 1297, 1245, 1174, 1133, 1074, 1033, 973, 932, 880, 846, 783, 693 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.93 – 7.84 (m, 2H), 7.82 – 7.75 (m, 2H), 7.12 – 7.05 (m, 2H), 6.87 – 6.80 (m, 2H), 3.79 (s, 3H), 2.78 – 2.56 (m, 3H), 2.40 (dd, *J* = 13.6, 7.7 Hz, 1H), 1.93 – 1.78 (m, 2H), 1.64 (ddd, *J* = 11.8, 8.4, 5.3 Hz, 1H), 0.92 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.70, 160.96 (2 C), 156.81, 133.72 (2 C), 131.52, 128.99 (2 C), 127.88 (2 C), 122.92 (2 C), 112.64 (2 C), 54.19, 41.31, 33.41, 30.10, 27.87, 17.87. HRMS: (ES-MS) m/z calculated for $C_{21}H_{22}NO_5$ [M+H]: 368.1492, found 368.1498.

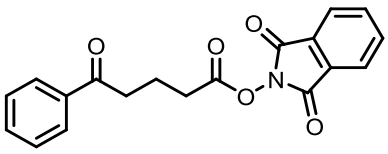
5-Oxo-5-phenylpentanoic acid (258).



A suspension of $AlCl_3$ (3.4 g, 25.5 mmol, 1 equiv.) and benzene (6 ml, 67.6 mmol, 3 equiv.) was treated with DCM (10 ml). Glutaric anhydride (2.9 g, 25.42 mmol, 1 equiv.) in DCM (10 ml) was added to the suspension and stirred for overnight. The black solution was quenched with ice cooled water and the phases were separated. The aqeous layer was extracted with ethyl acetate (2 x 10 ml) and the solvent of the combined organic phases was removed. The obtained solid was diluted again with ethyl acetate and washed with water (2 x 10 ml). The organic layer was extracted with a saturated $NaHCO_3$ solution, which was acidified by concentrated HCl. The product was extracted with ethyl acetate, dried over $MgSO_4$, filtered and evaporated off. Yield: 1.24 g (6.45 mmol, 29%) white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.03 (s, 1H), 7.95 (dd, *J* = 5.3, 3.3 Hz, 2H), 7.61 – 7.52 (m, 1H), 7.51 – 7.41 (m, 2H), 3.08 (t, *J* = 7.1 Hz, 2H), 2.53 – 2.41 (m, 2H), 2.11 – 2.04 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.40, 179.65, 136.71, 133.17, 128.62 (2 C), 128.03 (2 C), 37.29, 33.09, 18.96.

Analytical data match to the reported data.[138]

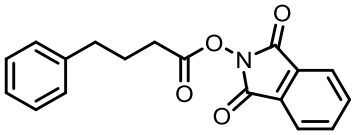
1,3-Dioxoisoindolin-2-yl 5-oxo-5-phenylpentanoate (133).



Compound **133** was prepared from acid **258** (0.500 g, 2.6 mmol, 1 equiv.), N-hydroxyphthalimide (0.469 g, 2.87 mmol, 1.1 equiv.) and DCC (0.594 g, 2.88 mmol, 1.1 equiv.) following *general protocol D*. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 2/1, R_f = 0.51) gave 0.439 g (1.30 mmol, 50%) white solid. IR (neat): 3056, 2922, 1815, 1789, 1737, 1689, 1595, 1446, 1413, 1379, 1320, 1267, 1185, 1044, 965, 880, 790, 734, 690 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.04 – 7.97 (m, 2H), 7.93 – 7.86 (m, 2H), 7.83 – 7.76 (m, 2H), 7.61 – 7.53 (m, 1H), 7.52 – 7.44 (m, 2H), 3.20 (t, *J* = 7.1 Hz, 2H), 2.84 (t, *J* = 7.0 Hz, 2H), 2.25 (p, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ =

198.88, 169.39, 161.95 (2 C), 136.73, 134.79 (2 C), 133.22, 128.95 (2 C), 128.68 (2 C), 128.10 (2 C), 124.02 (2 C), 36.75, 30.27, 19.17.

1,3-Dioxoisoindolin-2-yl 4-phenylbutanoate (135).

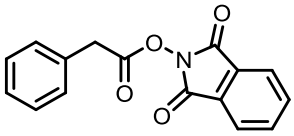


Compound **135** was prepared from 4-phenylbutanoic acid (1.50 g, 9.14 mmol, 1 equiv.), N-hydroxyphthalimide (1.66 g, 10.18 mmol, 1.1 equiv.) and DCC (2.12 g, 10.27 mmol, 1.1 equiv.) following *general protocol D*. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 2/1, R_f = 0.60) gave 2.62 g (8.47 mmol, 93%) white solid. IR (neat): 3027, 2945, 2874, 1785, 1737, 1603, 1491, 1461, 1375, 1290, 1252, 1185, 1141, 1077, 965, 917, 876, 787, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.95 – 7.85 (m, 2H), 7.84 – 7.74 (m, 2H), 7.32 (ddd, *J* = 7.2, 4.5, 2.0 Hz, 2H), 7.27 – 7.18 (m, 3H), 2.78 (t, *J* = 7.5 Hz, 2H), 2.68 (t, *J* = 7.4 Hz, 2H), 2.12 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.46, 162.00 (2 C), 140.68, 134.79 (2 C), 128.95 (2 C), 128.60 (2 C), 128.56 (2 C), 126.25, 124.00 (2 C), 34.63, 30.23, 26.32. HRMS: (ES-MS) m/z calculated for $C_{18}H_{16}NO_4$ [M+H]: 310.1074, found 310.1076.

Analytical data match to the reported data.[139]

Phenylacetic acid based *N*-acyloxyphthalimides

1,3-Dioxoisoindolin-2-yl 2-phenylacetate (171/166a).



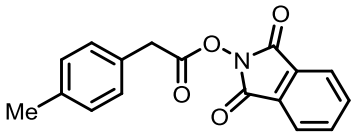
General protocol E

N-(3-dimethylaminopropyl)-N´-ethylcarbodiimide hydrochloride (EDAC, 430 mg, 2.2 mmol, 1.1 equiv.) was dissolved in dichloromethane (20 ml) and added slowly to a solution of phenylacetic acid (270 mg, 2.0 mmol, 1 equiv.) and N-hydroxyphthalimide (326 mg, 2.0 mmol, 1 equiv.) in THF (30 ml). The reaction was stirred at room temperature for overnight and washed with water (2x 30 ml) and brine (1x 30 ml). The pure compound was

obtained after an additional washing step with a saturated $NaHCO_3$ solution. The organic phase was dried over $NaSO_4$, filtered and evaporated. Compound **171** was isolated as white solid (0.433 g, 1.54 mmol, 77%), m.p. = 102-109 °C. Ir (neat): 3131, 2922, 1812, 1789, 1733, 1705, 1607, 1461, 1409, 1364, 1185, 1133, 1058, 973, 880, 824, 783, 723, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.86 (ddd, *J* = 4.9, 3.7, 2.0 Hz, 2H), 7.81 – 7.75 (m, 2H), 7.45 – 7.27 (m, 5H), 4.00 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.69, 161.84 (2 C), 141.78, 134.80 (2 C), 131.54, 129.31 (2 C), 128.89 (2 C), 127.82 (2 C), 124.01 (2 C), 37.73. HRMS: (APCI-MS) m/z calculated for $C_{16}H_{15}N_2O_4$ [M+NH_4]: 299.1026, found 299.1031.

Analytical data match to the reported data.[140]

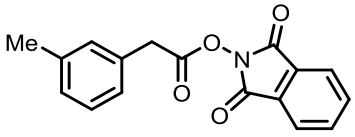
1,3-Dioxoisoindolin-2-yl 2-p-tolylacetate (166b).



Compound **166b** was prepared from *p*-tolylacetic acic (0.700 g, 4.66 mmol, 1.2 equiv.), N-hydroxyphthalimide (0.633 g, 3.88 mmol, 1 equiv.) and EDAC (0.894 g, 4.66 mmol, 1.2 equiv.) following *general protocol E*. Purification by column chromatography (hexanes/EtOAc = 1/1, R_f = 0.72) gave a yellow solid (0.673 g, 2.28 mmol, 59%), m.p. = 97-100 °C. IR (neat): 3131, 2922, 1823, 1789, 1737, 1610, 1517, 1469, 1422, 1357, 1185, 1141, 1055, 969, 880, 839, 775, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.88 (ddd, *J* = 9.2, 4.3, 2.8 Hz, 2H), 7.83 – 7.74 (m, 2H), 7.31 – 7.24 (m, 2H), 7.19 (d, *J* = 7.4 Hz, 2H), 3.95 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.95, 161.96 (2 C), 141.87, 137.62, 134.89 (2 C), 129.67 (2 C), 129.03 (2 C), 128.57 (2 C), 124.09 (2 C), 37.45, 21.25.

Analytical data match to the reported data.[141]

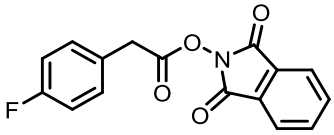
1,3-Dioxoisoindolin-2-yl 2-m-tolylacetate (166c).



Compound **166c** was prepared from 2-*m*-tolylacetic acic (0.800 g, 5.33 mmol, 1.1 equiv.), N-hydroxyphthalimide (0.790 g, 4.84 mmol, 1 equiv.) and EDAC (1.0 g, 5.21 mmol, 1.1 equiv.)

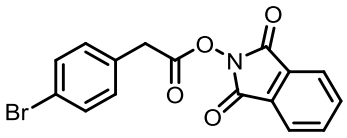
following *general protocol E*. After extraction work up a yellow solid (1.01 g, 3.42 mmol, 71%) was obtained; m.p. = 105-113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.91 – 7.84 (m, 2H), 7.81 – 7.74 (m, 2H), 7.27 (dd, *J* = 8.7, 6.3 Hz, 1H), 7.24 – 7.07 (m, 3H), 3.96 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.74, 161.98 (2 C), 137.22, 134.90 (2 C), 130.68, 130.47, 130.38, 129.00 (2 C), 128.28, 126.52, 124.08 (2 C), 35.99, 19.64. HRMS: (ES-MS) m/z calculated for $C_{17}H_{14}NO_4$ [M+H]: 269.0917, found 296.0919.

1,3-Dioxoisoindolin-2-yl 2-(4-fluorophenyl)acetate (166d).



Compound **166d** was prepared from 4-fluorophenylacetic acic (0.700 g, 4.54 mmol, 1.2 equiv.), N-hydroxyphthalimide (0.617 g, 3.78 mmol, 1 equiv.) and EDAC (0.870 g, 4.54 mmol, 1.2 equiv.) following *general protocol E*. After extraction work up a yellow solid (0.988 g, 3.3 mmol, 87%) was obtained; m.p. = 103-105 °C. Ir (neat): 3116, 2926, 2658, 1789, 1696, 1607, 1510, 1467, 1410, 1342, 1290, 1223, 1185, 1137, 1062, 973, 932, 880, 828, 783, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.91 – 7.83 (m, 2H), 7.82 – 7.74 (m, 2H), 7.41 – 7.30 (m, 2H), 7.12 – 7.01 (m, 2H), 3.96 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.62, 161.83 (2 C), 134.88 (2 C), 131.05 (2 C), 130.94, 128.84 (2 C), 124.04 (2 C), 115.97, 115.69 (2 C), 36.91. HRMS: (ES-MS) m/z calculated for $C_{16}H_{11}FNO_4$ [M+H]: 300.0667, found 300.0670.

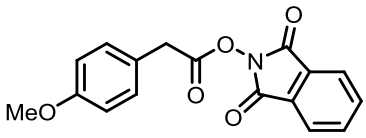
1,3-Dioxoisoindolin-2-yl 2-(4-bromophenyl)acetate (166e).



Compound **166e** was prepared from 4-bromophenylacetic acic (1.0 g, 4.65 mmol, 1.2 equiv.), N-hydroxyphthalimide (0.632 g, 3.88 mmol, 1 equiv.) and EDAC (0.891 g, 4.65 mmol, 1.2 equiv.) following *general protocol E*. Recrystallization by EtOH gave a yellow solid (1.02 g, 2.83 mmol, 73%), m.p. = 11-114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.92 – 7.84 (m, 2H), 7.82 – 7.76 (m, 2H), 7.55 – 7.46 (m, 2H), 7.32 – 7.21 (m, 2H), 3.95 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.37, 161.90 (2 C), 134.99 (2 C), 132.14 (2 C), 131.13 (2 C), 130.60, 128.94 (2 C), 124.17 (2 C), 122.11, 37.25.

Analytical data match to the reported data.[139]

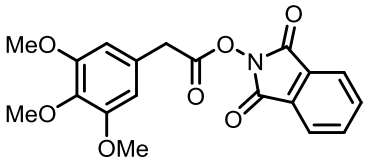
1,3-Dioxoisoindolin-2-yl 2-(4-methoxyphenyl)acetate (163/166f).



2-*p*-Methoxyphenylacetic acid (2.02 g, 12.16 mmol, 1 equiv.) and N-hydroxyphthalimide (2.01 g, 12.32 mmol, 1 equiv.) was dissolved in anhydrous THF (40 ml). *N*,*N*′-Dicyclohexylcarbodiimid (DCC, 2.57 g, 12.46 mmol, 1 equiv.) in THF (15 ml) was added dropwise at 0 °C and the reaction mixture was stirred for overnight. The solvent was evaporated under reduced pressure and after purification by column chromatography (hexanes/EtOAc = 2/1, R_f = 0.26) pure product **163** (3.16 g, 10.15 mmol, 84%) was obtained as a pale yellow solid, m.p. = 94-96 °C. Ir (neat): 2977, 1823, 1785, 1737, 1610, 1513, 1469, 1420, 1357, 1249, 1186, 1118, 1081, 1029, 969, 872, 816, 768, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.90 – 7.84 (m, 2H), 7.82 – 7.75 (m, 2H), 7.33 – 7.27 (m, 2H), 6.94 – 6.87 (m, 2H), 3.93 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.09, 162.00 (2 C), 159.27, 134.92 (2 C), 130.52 (2 C), 128.99 (2 C), 124.11 (2 C), 123.61, 114.39 (2 C), 55.40, 36.98. HRMS: (ES-MS) m/z calculated for $C_{17}H_{17}N_2O_5$ [M+NH_4]: 329.1132, found 329.1136.

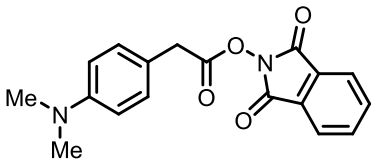
Analytical data match to the reported data.[139]

1,3-Dioxoisoindolin-2-yl 2-(3,4,5-trimethoxyphenyl)acetate (166g).



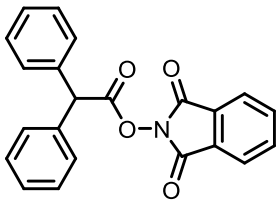
Compound **166g** was prepared from 2-(3,4,5-trimethoxyphenyl)acetic acid (1.37 g, 6.07 mmol, 1.1 equiv.), N-hydroxyphthalimide (0.900 g, 5.52 mmol, 1 equiv.) and EDAC (1.16 g, 6.05 mmol, 1.1 equiv.) following *general protocol E*. Recrystallization by EtOH gave a beige solid (1.71 g, 4.60 mmol, 83%), m.p. = 130-131 °C. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.88 (dt, *J* = 7.3, 3.6 Hz, 2H), 7.84 – 7.75 (m, 2H), 6.61 (s, 2H), 3.93 (s, 2H), 3.89 (s, 6H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.72, 161.97 (2 C), 153.56 (2 C), 137.56, 134.98 (2 C), 128.96 (2 C), 127.20, 124.15 (2 C), 106.28 (2 C), 60.98, 56.30 (2 C), 38.08.

1,3-Dioxoisoindolin-2-yl 2-(4-(dimethylamino)phenyl)acetate (166h).



Compound **166h** was prepared from 4-dimethylaminophenylacetic acic (1.0 g, 5.58 mmol, 1.1 equiv.), N-hydroxyphthalimide (0.830 g, 5.09 mmol, 1 equiv.) and EDAC (1.0 g, 5.21 mmol, 1 equiv.) following *general protocol E*. After extraction work up a yellow solid (0.972 g, 3.0 mmol, 59%) was obtained; m.p. = 108-115 °C. IR (neat): 3131, 2956, 2922, 1789, 1707, 1606, 1513, 1461, 1379, 1282, 1230, 1185, 1133, 1081, 973, 880, 816, 783, 738, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.91 – 7.83 (m, 2H), 7.80 – 7.74 (m, 2H), 7.24 (dd, *J* = 6.7, 4.5 Hz, 2H), 6.76 – 6.71 (m, 2H), 3.90 (s, 2H), 2.94 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.36, 162.04 (2 C), 141.88, 134.85 (2 C), 130.09 (2 C), 129.07, 124.06 (2 C), 112.99 (2 C), 40.72 (2 C), 36.92. HRMS: (ES-MS) m/z calculated for $C_{18}H_{17}N_2O_4$ [M+H]: 325.1183, found 325.1189.

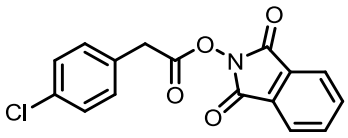
1,3-Dioxoisoindolin-2-yl 2,2-diphenylacetate (166i).



Compound **166i** was prepared from 2,2-diphenylacetic acid (2.00 g, 9.42 mmol, 1 equiv.), N-hydroxyphthalimide (1.54 g, 9.42 mmol, 1 equiv.) and DCC (1.94 g, 9.42 mmol, 1 equiv.) following *general protocol D*. For purification the solvent filtered and removed under reduced pressure. Ethanol (80 ml) was added and heated to 100 °C for 1 h. The white undiluted solid was filtered and dried in vacuum. Yield: 2.71 g (7.58 mmol, 80%) white solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.46 – 7.35 (m, 8H), 7.35 – 7.28 (m, 2H), 5.42 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.08, 161.86 (2 C), 136.78 (2 C), 134.83 (2 C), 128.91 (4 C), 128.73 (4 C), 127.93 (2 C), 124.01 (2 C), 54.04. HRMS: (APCI-MS) m/z calculated for $C_{22}H_{19}N_2O_4$ [M+NH_4]: 375.1339, found 375.1346.

Analytical data match to the reported data.[140]

1,3-Dioxoisoindolin-2-yl 2-(4-chlorophenyl)acetate (166j).

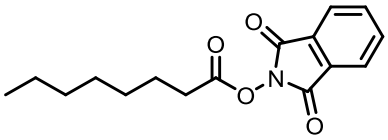


Compound **166j** was prepared from 4-chlorophenylacetic acic (1.0 g, 5.86 mmol, 1.2 equiv.), N-hydroxyphthalimide (0.797 g, 4.88 mmol, 1 equiv.) and EDAC (1.2 g, 5.86 mmol, 1.2 equiv.) following *general protocol E*. Purification by column chromatography (hexanes/EtOAc, 1/1, $R_f = 0.62$) gave a yellow solid (0.673 g, 2.28 mmol, 59%), m.p. = 93-96 °C. IR (neat): 3101, 2971, 2903, 2654, 1819, 1789, 1737, 1700, 1602, 1491, 1413, 1351, 1290, 1252, 1178, 1115, 1059, 969, 928, 880, 805, 738, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.93 – 7.85 (m, 2H), 7.83 – 7.74 (m, 2H), 7.38 – 7.28 (m, 4H), 3.96 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.39, 161.83 (2 C), 134.90 (2 C), 130.78, 130.70 (2 C), 129.97, 129.08 (2 C), 128.82 (2 C), 124.08 (2 C), 37.06.

Analytical data match to the reported data.[141]

Aliphatic acid based *N*-acyloxyphthalimides

1,3-Dioxoisoindolin-2-yl octanoate (206/232).

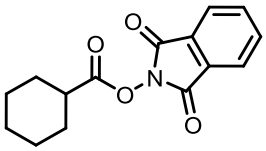


Octanoyl chloride (1.50 mL, 13.28 mmol, 1.0 equiv.) in THF (20 ml) was added dropwise to a solution of N-hydroxyphthalimide (2.11 g, 12.93 mmol, 1 equiv.) and NEt_3 (2.00 ml, 14.43 mmol, 1.1 equiv.) in THF (30 ml) and stirred at room temperature for overnight. The reaction mixture was washed with water (50 ml), a half-saturated $NaHCO_3$ solution (50 ml) and a saturated NaCl solution (50 ml). The organic phase was dried over $MgSO_4$, filtrated and the solvent was removed under reduced pressure, which gave a white solid (1.99 g, 6.88 mmol, 52%). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.95 – 7.84 (m, 2H), 7.83 – 7.72 (m, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 1.95 – 1.63 (m, 2H), 1.55 – 1.17 (m, 8H), 1.03 – 0.70 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.70, 162.06, 134.76, 128.95, 123.98, 33.96, 31.58, 31.00, 28.80, 24.68, 22.59, 14.08. HRMS: (APCI-MS) m/z calculated for $C_{16}H_{23}N_2O_4$ $[M+NH_4]$: 307.1652, found 307.1657.

Analytical data match to the reported data.[142]

The redox potential of **P8** was determined as -1.25 V (vs. SCE, irreversible peak) by cyclic voltametry.

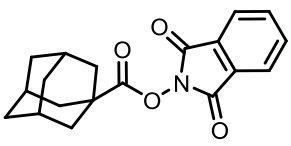
1,3-Dioxoisoindolin-2-yl cyclohexanecarboxylate (207/236).



Cyclohexanecarboxylic acid (2.0 g, 15.6 mmol, 1 equiv.) was diluted in THF (30 ml). Thionyl chloride (2.3 ml, 31.71 mmol, 2 equiv.) was added and stirred at room temperature for 20 min. A solution of N-hydroxyphthalimide (2.56 g, 15.69 mmol, 1 equiv.) and NEt_3 (4.3 ml, 31.02 mmol, 2 equiv.) in THF (50 ml), was added to the reaction mixture and stirred at room temperature for overnight. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (50 ml). The organic phase was washed with water (50 ml), 1 M HCl (50 ml) and a half-saturated $NaHCO_3$ solution (50 ml). The organic layer was dried over $MgSO_4$, filtrated and the solvent was removed. Purification by column chromatography (hexanes/EtOAc = 3/1, R_f = 0.56) and recrystallization with ethanol gave a white solid (3.10 g, 11.34 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 2.74 (tt, *J* = 10.9, 3.7 Hz, 1H), 2.16 – 2.05 (m, 2H), 1.89 – 1.78 (m, 2H), 1.66 (td, *J* = 14.0, 3.2 Hz, 3H), 1.36 (qdd, *J* = 11.1, 8.4, 2.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.86, 162.13 (2 C), 134.71 (2 C), 129.02 (2 C), 123.93 (2 C), 40.48, 28.80 (2 C), 25.47, 25.04 (2 C). The redox potential of **P7** was determined as -1.23 V (vs. SCE, irreversible peak) by cyclic voltametry.

Analytical data match to the reported data.[142]

1,3-Dioxoisoindolin-2-yl adamantanate (238).

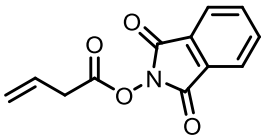


Adamantanecarboxylic acid (1.83 g, 9.21 mmol, 1 equiv.) in DCM (20 ml) was added to a solution of N-hydroxyphthalimide (1.53 g, 9.38 mmol, 1 equiv.) and NEt_3 (1.30 ml,

9.38 mmol, 1 equiv.) in DCM (80 ml) and stirred at room temperature for 2 h. The reaction mixture was washed with water (100 ml), a half-saturated $NaHCO_3$ solution (100 ml) and a saturated NaCl solution (100 ml). The organic phase was dried over $MgSO_4$, filtrated and the solvent was removed under reduced pressure, which gave a white solid (2.42 g, 7.44 mmol, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.93 – 7.83 (m, 2H), 7.82 – 7.73 (m, 2H), 2.13 (m, *J* = 6.0 Hz, 9H), 1.78 (d, *J* = 2.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.30, 162.19, 134.65, 129.09, 123.87, 40.53, 38.46, 36.20, 27.64.

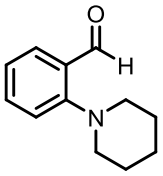
Analytical data match to the reported data.[143]

1,3-Dioxoisoindolin-2-yl but-3-enoate (230).



N-hydroxyphthalimide (1.92 g, 11.77 mmol, 1 equiv.) was added to a solution of 3-butanoic acid (1.0 ml, 11.77 mmol, 1 equiv.) in THF (80 ml). The solution was treated with DCC (2.45 g, 11.87 mmol, 1 equiv.) and stirred at room temperature for overnight. The solvent was removed under reduced pressure and the product was purified by column chromatography (hexanes/EtOAc = 3/1). Yield: 2.10 g (9.08 mmol, 77%) yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 – 7.86 (m, 2H), 7.83 – 7.76 (m, 2H), 5.97 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.41 – 5.29 (m, 2H), 3.46 (dt, *J* = 6.7, 1.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.53, 161.86 (2 C), 134.84 (2 C), 128.86 (2 C), 127.57, 124.03 (2 C), 120.63, 35.53. HRMS: (APCI-MS) m/z calculated for $C_{12}H_{10}NO_4$ [M+H]: 232.0607, found 232.0604.

2-(piperidin-1-yl)benzaldehyde (247).

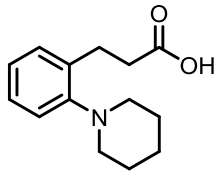


A solution of 2-Fluorobenzaldehyde (**246**, 1.06 ml, 10.06 mmol, 1 equiv.), piperidine (1.1 ml, 11.14 mmol, 1.1 equiv.) and potassium carbonate (2.2 g, 15.92 mmol, 2.2 equiv.) in DMF (25 ml) was heated at 155 °C for 20 h. Water was added to the cooled reaction mixture and the solution was extracted with ethyl acetate (3x 50 ml). The combined organic phases were

washed with water (3x 50 ml) and brine (1x 50 ml), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, yielding 1.58 g (8.35 mmol, 83%) of dark orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.29 (d, *J* = 0.7 Hz, 1H), 7.78 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.49 (ddd, *J* = 8.2, 7.2, 1.8 Hz, 1H), 7.12 – 7.00 (m, 2H), 3.09 – 2.98 (m, 4H), 1.75 (dt, *J* = 10.9, 5.6 Hz, 4H), 1.59 (ddd, *J* = 7.7, 5.6, 3.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.78, 157.02, 134.85, 129.18, 128.59, 121.97, 118.99, 55.64 (2 C), 26.20 (2 C), 24.06.

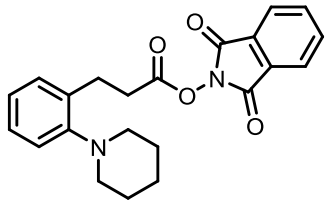
Analytical data match to the reported data.[144]

3-(2-(piperidin-1-yl)phenyl)propanoic acid (248).



To a solution of benzaldehyde **247** (1.58 g, 8.35 mmol, 1 equiv.) in pyridine (20 ml) were added dropwise a solution of malonic acid (1.30 g, 12.52 mmol, 1.5 equiv.) in pyridine (10 ml). The reaction mixture was stirred under reflux conditions (120 °C) for 2 h. The mixture was acidified with 1 M HCl and extracted with ethyl acetate (3x 50 ml). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was dissolved in EtOH and a catalytic amount of 10% palladium on activated carbon (300 mg) was added. The reaction was stirred under hydrogen atmosphere and room temperature for overnight. The mixture was filtered through Celite pat and the solvent was removed under reduced pressure yielding 1.82 g (7.79 mmol, 93%) of brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22 – 7.12 (m, 2H), 7.11 – 7.06 (m, 1H), 7.02 (td, *J* = 7.3, 1.4 Hz, 1H), 3.03 – 2.90 (m, 3H), 2.87 – 2.82 (m, 3H), 2.66 (t, *J* = 7.6 Hz, 2H), 1.71 (dd, *J* = 10.5, 5.4 Hz, 4H), 1.55 (d, *J* = 5.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.84, 150.77, 136.49, 130.38, 127.51, 125.15, 120.30, 54.81, 44.18, 37.09, 26.41, 25.90, 23.92, 22.69. HRMS: (ES-MS) m/z calculated for $C_{14}H_{20}NO_2$ [M+H]: 234.1489, found 234.1493.

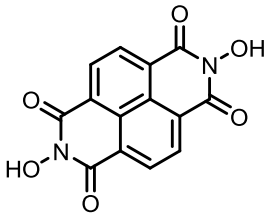
1,3-dioxoisoindolin-2-yl 3-(2-(piperidin-1-yl)phenyl)propanoate (249).



Compound **249** was prepared from acid **248** (1.81 g, 7.76 mmol, 1 equiv.), N-hydroxyphthalimide (1.28 g, 7.85 mmol, 1 equiv.) and DCC (1.61 g, 7.80 mmol, 1 equiv.) following *general protocol D*. Column chromatography (hexanes/EtOAc = 4:1 → 2:1) and recrystallization in EtOH gave a yellow solid. Yield: 0.53 g (1.40 mmol, 18%). R_f (hexanes/EtOAc = 5/1) = 0.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94 – 7.85 (m, 2H), 7.83 – 7.76 (m, 2H), 7.25 – 7.18 (m, 2H), 7.17 – 7.11 (m, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 3.18 – 3.03 (m, 4H), 2.89 – 2.79 (m, 4H), 1.79 – 1.68 (m, 4H), 1.58 (d, *J* = 5.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.57, 162.04, 134.88, 134.76 (2 C), 129.80 (2 C), 128.98 (2 C), 127.71 (2 C), 124.06, 123.98 (2 C), 120.89, 54.43 (2 C), 31.59, 26.95, 26.70 (2 C), 24.34. HRMS: (ES-MS) m/z calculated for $C_{22}H_{23}N_2O_4$ [M+H]: 379.1652, found 379.1658.

3 Naphthalindiimide ester derivatives

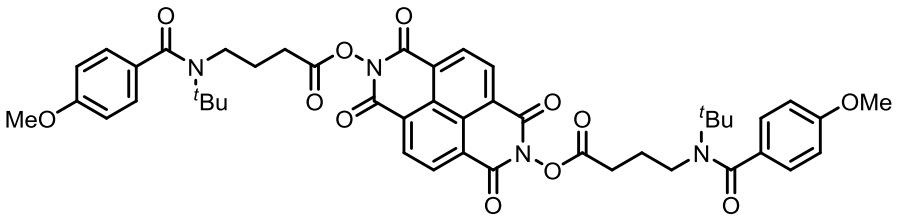
2,7-dihydroxybenzo[lmn][3,8]phenanthroline-1,3,6,8(2H,7H)-tetraone (259).



Naphthalene[1,8:4,5]tetracarboxylic acid dianhydride (1.54 g, 5.74 mmol, 1 equiv.) and hydroxylamine hydrochloride (0.834 mg, 12 mmol, 2 equiv.) were dissolved in DMF (25 ml). Tributylamine (3 ml, 12 mmol, 2 equiv.) were added and the stirred at 140 °C for 1 h. The reaction was cooled to room temperature and diluted with acetonitrile (25 ml). The brown precipitate was filtrated and washed with acetonitrile and diethylether. Yield: 1.46 g (4.89 mmol, 85%). IR (neat): 3474, 3422, 3261, 3086, 2654, 1659, 1580, 1446, 1413, 1346, 1238, 1208, 1126, 1003, 895, 839, 738, 671 cm^{-1}. ^{1}H NMR (300 MHz, DMSO) δ = 11.02 (s, 2H), 8.67 (s, 4H). ^{13}C NMR (75 MHz, DMSO) δ = 159.97 (4 C), 130.48 (4 C), 126.80 (6 C). LRMS: (ES-MS) m/z calculated for $C_{14}H_7N_2O_6$ [M+H]: 299.21, found 299.0297.

Analytical data match to the reported data.[145]

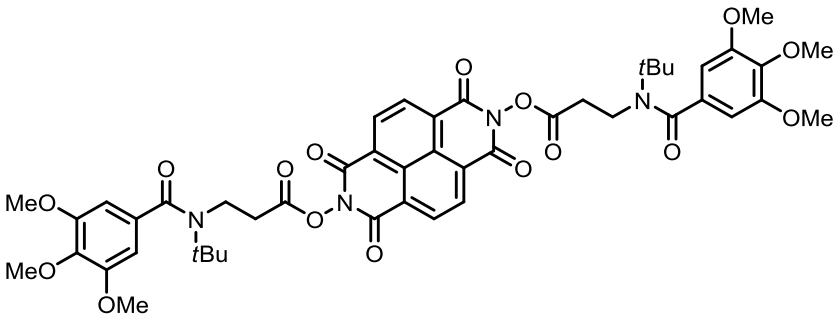
1,3,6,8-tetraoxobenzo[lmn][3,8]phenanthroline-2,7(1H,3H,6H,8H)-diyl bis(4-(N-*tert*-butyl-4-methoxybenzamido)butanoate) (109).



Compound **109** was prepared from acid **73t** (1.0 g, 3.41 mmol, 2 equiv.), naphthalindiimid **259** (0.506 g, 1.70 mmol, 1 equiv.) and DCC (0.778 g, 3.77 mmol, 2.2 equiv.) following *general protocol D*. The solvent was evaporated and ice cooled dichloromethane was added. The precipitated urea was removed by filtration and the solvent was removed under reduced pressure. Purification by column chromatography on flash silica gel (hexanes/EtOAc = 1/2, R_f = 0.53) 0.25 g (0.295 mmol, 17%) yellow solid. IR (neat): 3325, 2930, 2848, 1800, 1730, 1633, 1510, 1446, 1394, 1334, 1293, 1245, 1200, 1096, 1059, 980, 876, 839, 697, 749 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.80 (s, 4H), 7.36 – 7.31 (m, 4H), 6.89 – 6.86 (m, 4H), 3.78 (s, 6H), 3.57 – 3.49 (m, 4H), 2.50 (t, *J* = 7.2 Hz, 4H), 2.05 – 1.96 (m, 4H), 1.56 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.66, 168.47, 160.10, 157.82, 131.83, 131.75, 128.14, 127.04, 126.51, 113.81, 57.15, 55.27, 46.74, 29.06, 28.59, 26.80. HRMS: (ES-MS) m/z calculated for $C_{46}H_{49}N_4O_{12}$ [M+H]: 849.3341, found 849.3352.

1,3,6,8-Tetraoxobenzo[lmn][3,8]phenanthroline-2,7(1H,3H,6H,8H)-diyl bis(3-(N-*tert*-butyl-3,4,5-trimethoxybenzamido)propanoate) (110).



Compound **110** was prepared from acid **73n** (0.521 g, 1.54 mmol, 2 equiv.), naphthalindiimid **259** (0.23 g, 0.772 mmol, 1 equiv.) and DCC (0.318 g, 1.54 mmol, 2 equiv.) following *general protocol D*. Purification by column chromatography (hexanes/EtOAc = 1/4, R = 0.40). Desired product was insoluble in methanol. Yield: 117.3 mg (0.125 mmol, 16%) yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.76 (s, 4H), 6.58 (s, 4H), 3.88 (s, 12H), 3.87 – 3.83 (m, 4H), 3.83 (s, 6H), 2.99 (dd, *J* = 8.9, 6.4 Hz, 4H), 1.59 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.39 (2 C), 166.58 (2 C), 157.69 (4 C), 153.47 (4 C), 138.84 (2 C), 134.34 (2 C), 131.87 (4 C), 126.95 (4 C), 126.48 (2 C), 103.36 (4 C), 60.90 (2 C), 57.64 (2 C), 56.28 (4 C), 42.61 (2 C), 33.76 (2 C), 28.99 (6 C). LRMS: (ES-MS) m/z calculated for $C_{48}H_{53}N_4O_{16}$ [M+H]: 941.3394, found 941.3458.

4 Photochemical decarboxylations

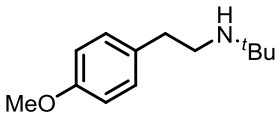
4.1 Photoinduced β-phenylethylamine synthesis

General protocol F

General procedure for visible light-promoted decarboxylations:

A Schlenk tube with a magnetic stir bar was charged with N-acyloxyphthalimide (1 mmol, 1 equiv.) and the photocatalyst $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (10 µmol, 1 mol%) in 10 ml acetonitrile/water (40/1, v/v) mixture (0.1 M concentration). The solution was degassed using three freeze-pump-thaw cycles and closed with a Teflon-sealed inlet for a glass rod, through which irradiation with a 455 nm high power LED took place. The photochemical reaction was stirred at room temperature and monitored by TLC analysis. After completion the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography or by extraction. For this the solvent was evaporated, the residue dissolved in EtOAc and extracted with 1 M HCl (3 x). The water phase was basified with KOH and extracted with dichloromethane (3 x). The side product phthalimide (hexanes/EtOAc = 2/1; R_f = 0.51) could be isolated in > 95% yield.

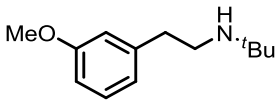
N-(4-methoxyphenethyl)-2-methylpropan-2-amine (75/78a).



Compound **75** was prepared from **74** (205.2 mg, 0.483 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (4.5 mg, 4.9 µmol, 1 mol%) following *general protocol F*. Yield: 77.8 mg (0.293 mmol, 61%) orange oil. R_f (dichloromethane/EtOAc = 5/1) = 0.23. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.17 – 7.09 (m, 2H), 6.87 – 6.80 (m, 2H), 3.78 (s, 3H), 2.84 – 2.72 (m, 4H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.25, 130.77, 129.72 (2 C), 113.99 (2 C), 55.27, 53.21, 43.75, 33.91, 27.38 (3 C). HRMS: (CI-MS) m/z calculated for $C_{13}H_{22}NO$ [M+H]: 208.1696, found 208.1699.

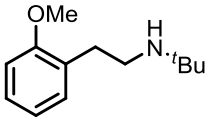
Analytical data match to the reported data.[146,147]

N-(3-methoxyphenethyl)-2-methylpropan-2-amine (78b).



Compound **78b** was prepared from **77b** (430.4 mg, 1.01 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (10.0 mg, 10.9 µmol, 1 mol%) following *general protocol F*. Yield: 70.0 mg (0.338 mmol, 33%) yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25 – 7.16 (m, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.75 (dt, *J* = 2.6, 1.9 Hz, 2H), 3.79 (s, 3H), 2.90 – 2.72 (m, 4H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.67, 141.68, 129.44, 121.06, 114.38, 111.52, 55.17, 50.71, 43.92, 36.95, 28.81 (3 C). HRMS: (CI-MS) m/z calculated for $C_{13}H_{22}NO$ [M+H]: 208.1696, found 208.1698.

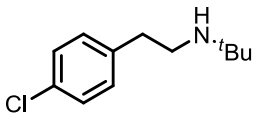
N-(2-methoxyphenethyl)-2-methylpropan-2-amine (78c).



Compound **78c** was prepared from **77c** (524.0 mg, 1.23 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (11.5 mg, 12.5 µmol, 1 mol%) following *general protocol F*. Yield: 110.0 mg (0.53 mmol, 43%) yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.23 – 7.14 (m, 2H), 6.92 – 6.81 (m, 2H), 3.81 (s, 3H), 2.79 (s, 4H), 1.08 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.66, 130.30, 128.69, 127.39, 120.42, 110.38, 55.27, 50.42, 42.74, 31.86, 29.00 (3 C). HRMS: (ES-MS) m/z calculated for $C_{13}H_{22}NO$ [M+H]: 208.1696, found 208.1696.

Analytical data match to the reported data.[146]

N-(4-chlorophenethyl)-2-methylpropan-2-amine (78d).

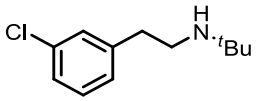


Compound **78d** was prepared from **77d** (456.7 mg, 1.07 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (10.0 mg, 10.9 µmol, 1 mol%) following *general protocol F*. Yield: 102.3 mg (0.483 mmol, 45%) yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 2.80 (m, 2H), 2.75 (m, 2H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.24,

132.65, 130.13 (2 C), 128.83 (2 C), 55.21, 43.03, 32.66, 26.35 (3 C). HRMS: (CI-MS) m/z calculated for $C_{12}H_{19}ClN$ [M+H]: 212.1201, found 212.1205.

Analytical data match to the reported data.[146,148]

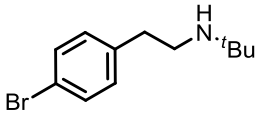
N-(3-chlorophenethyl)-2-methylpropan-2-amine (78e).



Compound **78e** was prepared from **77e** (425.0 mg, 0.991 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.2 mg, 10.1 µmol, 1 mol%) following *general protocol F*. Yield: 44.8 mg (0.212 mmol, 21%) yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 – 7.15 (m, 3H), 7.10 (d, *J* = 7.1 Hz, 1H), 2.84 – 2.78 (m, 2H), 2.77 – 2.71 (m, 2H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.25, 133.12, 128.62, 127.73, 125.86, 125.31, 49.38, 42.78, 35.86, 27.92 (3 C). HRMS: (ES-MS) m/z calculated for $C_{12}H_{19}ClN$ [M+H]: 212.1201, found 212.1202.

Analytical data match to the reported data.[148]

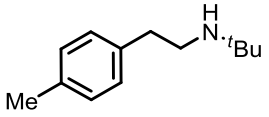
N-(4-bromophenethyl)-2-methylpropan-2-amine (78f).



Compound **78f** was prepared from **77f** (330.2 mg, 0.698 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (7.0 mg, 7.7 µmol, 1 mol%) following *general protocol F*. Yield: 87.5 mg (0.342 mmol, 49%) orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 2.80 (m, 2H), 2.75 (m, 2H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.16, 131.91 (2 C), 130.49 (2 C), 120.95, 56.66, 43.09, 32.36, 26.12 (3 C). HRMS: (ES-MS) m/z calculated for $C_{13}H_{22}N$ [M+H]: 256.0695, found 256.0700.

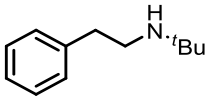
Analytical data match to the reported data.[146]

2-Methyl-N-(4-methylphenethyl)propan-2-amine (78g).



Compound **78g** was prepared from **77g** (409 mg, 1.0 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.4 mg, 10.3 µmol, 1 mol%) following *general protocol F*. Yield: 86.3 mg (0.451 mmol, 45%) orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.15 – 7.05 (m, 4H), 2.91 – 2.73 (m, 4H), 2.32 (s, 3H), 1.13 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.30, 135.84, 129.21 (2 C), 128.60 (2 C), 52.00, 43.91, 35.35, 28.04 (3 C), 21.04. HRMS: (ES-MS) m/z calculated for $C_{13}H_{22}N$ [M+H]: 192.1747, found 192.1747.

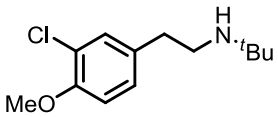
2-Methyl-N-phenethylpropan-2-amine (77h).



Compound **77h** was prepared from **78h** (312.9 mg, 0.793 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.5 mg, 10.4 µmol, 1.3 mol%) following *general protocol F*. Yield: 40.2 mg (0.227 mmol, 29%) pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.26 – 7.12 (m, 5H), 2.92 (qd, *J* = 7.7, 4.4 Hz, 4H), 1.99 (s, 1H), 1.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.79, 134.18, 128.79, 128.71, 126.80, 123.47, 55.23, 43.20, 33.26, 26.32 (3 C). HRMS: (CI-MS) m/z calculated for $C_{13}H_{22}NO$ [M+H]: 178.1589, found 178.1590.

Analytical data match to the reported data.[146, 147]

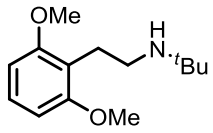
N-(3-chloro-4-methoxyphenethyl)-2-methylpropan-2-amine (78i).



Compound **78i** was prepared from **77i** (298.1 mg, 0.650 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (7.2 mg, 7.87 µmol, 1.2 mol%) following *general protocol F*. Yield: 93.5 mg (0.387 mmol, 60%) colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 2.1 Hz, 1H), 7.06 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H), 2.83 – 2.74 (m, 2H), 2.74 – 2.66 (m, 2H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.38, 133.34, 130.30, 127.86, 122.19,

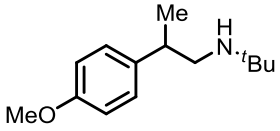
112.05, 56.17, 50.48, 44.01, 35.96, 28.94 (3 C). HRMS: (ES-MS) m/z calculated for $C_{13}H_{21}ClNO$ [M+H]: 242.1306, found 242.1308.

N-(2,6-dimethoxyphenethyl)-2-methylpropan-2-amine (78j).



Compound **78j** was prepared from **77j** (463.8 mg, 1.02 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (10.2 mg, 11.1 µmol, 1.1 mol%) following *general protocol F*. Yield: 92.3 mg (0.398 mmol, 38%) yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.12 (t, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 2H), 3.80 (s, 6H), 2.84 – 2.79 (m, 2H), 2.70 – 2.64 (m, 2H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.51 (2 C), 127.02, 116.93, 103.65 (2 C), 55.66 (2 C), 50.26, 42.09, 29.05 (3 C), 24.71. HRMS: (ES-MS) m/z calculated for $C_{14}H_{24}NO_2$ [M+H]: 238.1802, found 238.1803.

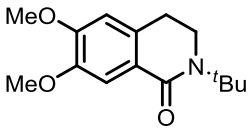
N-*tert*-butyl-2-(4-methoxyphenyl)propan-1-amine (78k).



Compound **78k** was prepared from **77k** (425.2 mg, 0.970 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.7 mg, 10.6 µmol, 1.1 mol%) following *general protocol F*. Yield: 113.2 mg (0.512 mmol, 53%) yellow oil. R_f (hexanes/EtOAc = 1/1, with 10% NEt_3) = 0.32. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.14 – 7.10 (m, 2H), 6.85 – 6.81 (m, 2H), 3.76 (s, 3H), 2.87 – 2.75 (m, 1H), 2.74 – 2.67 (m, 2H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.06, 137.49, 128.07 (2 C), 113.91 (2 C), 55.22, 50.10, 49.83, 39.77, 28.89 (2 C), 20.87. HRMS: (APCI-MS) m/z calculated for $C_{14}H_{24}NO$ [M+H]: 222.1852, found 222.1857.

Analytical data match to the reported data.[146]

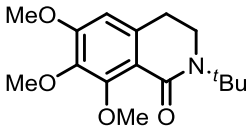
2-*tert*-butyl-6,7-dimethoxy-3,4-dihydroisoquinolin-1(2H)-one (79).



Compound **79** was prepared from **77m** (456 mg, 1.0 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.5 mg, 10.3 µmol, 1 mol%) following *general protocol F*. Yield: 214.7 mg (0.815 mmol, 82%) pale yellow solid, m.p. = 138-140 °C. R_f (hexanes/EtOAc = 1/1) = 0.45. IR (neat): 2997, 2960, 2930, 1726, 1633, 1599, 1510, 1465, 1429, 1357, 1334, 1219, 1148, 1070, 992, 880, 808, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.60 (s, 1H), 6.60 (s, 1H), 3.90 (d, *J* = 2.2 Hz, 6H), 3.62 – 3.52 (m, 2H), 2.91 – 2.78 (m, 2H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.76, 151.49, 147.90, 131.79, 124.14, 110.57, 108.60, 57.29, 56.03, 56.00, 42.62, 29.01 (3 C). HRMS: (ES-MS) m/z calculated for $C_{15}H_{21}NO_3$ [M+]: 263.1521, found 263.1525.

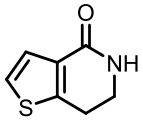
Analytical data match to the reported data.[146]

2-*tert*-butyl-6,7,8-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one (80).



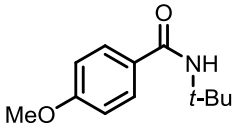
Compound **80** was prepared from **77n** (490.0 mg, 1.01 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.5 mg, 10.3 µmol, 1 mol%) following *general protocol F*. Yield: 222.7 mg (0.759 mmol, 75%) pale yellow solid, m.p. = 98-101 °C. R_f (hexanes/EtOAc = 2/1) = 0.18. IR (neat): 2963, 2926, 1633, 1595, 1487, 1457, 1402, 1357, 1308, 1260, 1215, 1190, 1148, 1118, 1025, 969, 928, 850, 824, 734, 667 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 6.41 (s, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.51 – 3.44 (m, 2H), 2.79 – 2.71 (m, 2H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.67, 155.00, 154.93, 141.81, 136.07, 119.00, 104.66, 61.75, 61.09, 57.25, 55.95, 42.27, 31.08, 29.24 (3 C). HRMS: (ES-MS) m/z calculated for $C_{15}H_{22}NO_2$ [M+H]: 294.17, found 294.1706.

6,7-Dihydrothieno[3,2-c]pyridin-4(5H)-one (63).



Compound **63** was prepared from **60** (408.2 mg, 0.986 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (10.1 mg, 11.0 µmol, 1.1 mol%) following *general protocol F*. The crude product was treated with TFA and stirred at room temperature for 12 h. TFA was removed under reduced pressure and product was purified by column chromatography (eluted with pure MeOH).Yield: 68.0 mg (0.444 mmol, 45%) yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.43 (d, *J* = 5.2 Hz, 1H), 7.12 (d, *J* = 5.2 Hz, 1H), 6.35 (s, 1H), 3.66 (td, *J* = 6.9, 2.7 Hz, 2H), 3.07 (t, *J* = 6.9 Hz, 2H). HRMS: (ES-MS) m/z calculated for C_7H_8NOS [M+H]: 154.0321, found 154.0322.

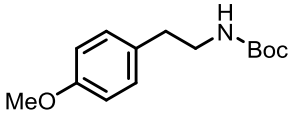
N-*tert*-butyl-4-methoxybenzamide (101).



Compound **101** was prepared from **97** (412.0 mg, 1.0 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.0 mg, 9.9 µmol, 1 mol%) following *general protocol F*. Yield: 175.3 mg (0.846 mmol, 85%) white solid. R_f (hexanes/EtOAc = 1/1) = 0.70. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.74 – 7.62 (m, 2H), 6.93 – 6.85 (m, 2H), 5.88 (s, 1H), 3.83 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.45, 161.84, 128.46 (2 C), 128.18, 113.61 (2 C), 55.40, 51.47, 28.95 (3 C). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.45, 161.84, 128.46 (2 C), 128.18 (2 C), 113.61, 55.40, 51.47, 28.95 (3 C).

Analytical data match to the reported data.[149]

***tert*-Butyl 4-methoxyphenethylcarbamate (122).**



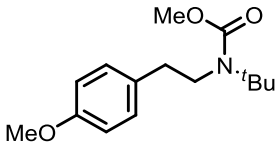
Compound **122** was prepared from **118** (234 mg, 0.515 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (5.1 mg, 5.6 µmol, 1.1 mol%) following *general protocol F*. Yield: 67.3 mg (268 mmol, 52%) colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H),

4.53 (s, 1H), 3.79 (s, 3H), 3.33 (d, *J* = 6.6 Hz, 2H), 2.73 (t, *J* = 7.0 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.24, 155.92, 131.03, 129.75 (2 C), 114.02 (2 C), 79.19, 55.28, 41.99, 35.30, 28.43 (3 C). LRMS: (ES-MS) m/z calculated for $C_{10}H_{14}NO_3$ [M-C_4H_8]: 296.22, found 296.0903.

Analytical data match to the reported data.[150]

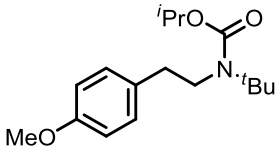
4.2 Photoinduced carbamate synthesis

Methyl *tert*-butyl(4-methoxyphenethyl)carbamate (85a).



Compound **85a** was prepared from **77a** (224.4 mg, 0.528 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (3.2 mg, 3.5 µmol, 0.7 mol%) following *general protocol F*. As solvent 4 ml MeCN and 70 µl methanol (3 equiv.) was used. Yield: 89.0 mg (0.335 mmol, 64%) pale yellow oil. R_f (DCM/EtOAc = 19/1) = 0.84. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.11 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.78 (d, *J* = 4.1 Hz, 3H), 3.68 (s, 3H), 3.49 – 3.40 (m, 2H), 2.74 (dd, *J* = 9.4, 7.0 Hz, 2H), 1.42 (d, *J* = 4.8 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.12, 156.58, 131.59, 129.64 (2 C), 113.90 (2 C), 55.84, 55.28, 51.88, 46.94, 36.63, 29.39 (3 C). HRMS: (ES-MS) m/z calculated for $C_{15}H_{24}NO_3$ [M+H]: 266.1751, found 266.1745.

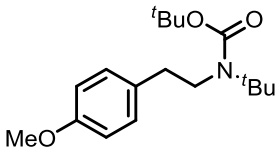
Isopropyl *tert*-butyl(4-methoxyphenethyl)carbamate (85b).



Compound **85b** was prepared from **77a** (206.8 mg, 0.487 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (2.9 mg, 3.2 µmol, 0.7 mol%) following *general protocol F*. As solvent 4 ml MeCN and 120 µl 2-propanol (3 equiv.) was used. Yield: 83.2 mg (0.284 mmol, 58%) yellow oil. R_f (DCM/EtOAc = 19/1) = 0.87. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.96 (dt, *J* = 12.5, 6.2 Hz, 1H), 3.79 (s, 3H), 3.48 – 3.39 (m, 2H), 2.74 (dd, *J* = 9.4, 7.0 Hz, 2H), 1.43 (s, 9H), 1.29 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (101 MHz,

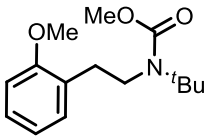
$CDCl_3$) δ = 158.13, 155.72, 131.75, 129.62 (2 C), 113.94 (2 C), 67.74, 55.66, 55.28, 47.00, 36.73, 29.54 (3 C), 22.36 (2 C). HRMS: (ES-MS) m/z calculated for $C_{17}H_{28}NO_3$ [M+H]: 294.2064, found 294.2068.

tert-butyl _tert_-butyl(4-methoxyphenethyl)carbamate (85c).



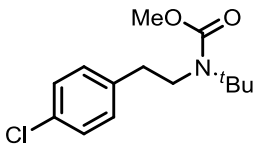
Compound **85c** was prepared from **77a** (200.1 mg, 0.471 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (3.1 mg, 3.4 µmol, 0.7 mol%) following *general protocol F*. As solvent 4 ml MeCN and 140 µl *tert*-butyl alcohol (3 equiv.) was used. Yield: 53.3 mg (0.173 mmol, 37%) yellow oil. R_f (DCM/EtOAc = 19/1) = 0.88. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.44 – 3.35 (m, 2H), 2.74 (dd, *J* = 9.5, 7.0 Hz, 2H), 1.50 (s, 9H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.09, 131.85, 129.87, 129.64 (2 C), 113.92 (2 C), 79.08, 55.39, 55.28, 47.20, 36.68, 29.67 (3 C), 28.67 (3 C). HRMS: (ES-MS) m/z calculated for $C_{18}H_{30}NO_3$ [M+H]: 308.222, found 308.222.

Methyl _tert_-butyl(2-methoxyphenethyl)carbamate (85d).



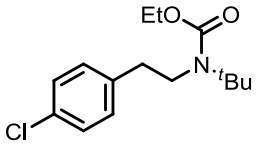
Compound **85d** was prepared from **77c** (520.0 mg, 1.23 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (11.0 mg, 12.0 µmol, 1 mol%) following *general protocol F*. As solvent 10 ml MeCN and 140 µl methanol (3 equiv.) was used. Yield: 122.5 mg (0.462 mmol, 38%) yellow oil. R_f (DCM/EtOAc = 19/1) = 0.77. IR (neat): 2960, 2840, 1700, 1588, 1491, 1465, 1361, 1290, 1241, 1178, 1081, 1029, 775, 753 cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 (td, *J* = 7.9, 1.7 Hz, 1H), 7.14 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.89 (td, *J* = 7.4, 1.0 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.49 – 3.43 (m, 2H), 2.82 (dd, *J* = 9.1, 7.0 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.64, 156.66, 130.56, 127.93, 127.56, 120.53, 110.18, 55.89, 55.16, 51.76, 45.05, 32.13, 29.31 (3 C). LRMS: (ES-MS) m/z calculated for $C_{15}H_{24}NO_3$ [M+H]: 266.1751, found 266.1754.

Methyl *tert*-butyl(4-chlorophenethyl)carbamate (85e).



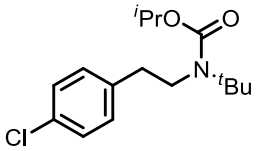
Compound **85e** was prepared from **77d** (206.8 mg, 0.483 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (4.2 mg, 4.6 µmol, 1 mol%) following *general protocol F*. As solvent 5 ml MeCN and 60 µl methanol (3 equiv.) was used. Yield: 88.6 mg (0.328 mmol, 68%) colorless oil. R_f (hexanes/EtOAc = 2/1) = 0.82. IR (neat): 2960, 1703, 1491, 1439, 1364, 1288, 1256, 1178, 1149, 1085, 1014, 850, 775, 701, 682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 3.67 (s, 3H), 3.48 – 3.42 (m, 2H), 2.80 – 2.72 (m, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.54, 137.92, 132.07, 130.08 (2 C), 128.60 (2 C), 55.91, 51.93, 46.58, 36.91, 29.41 (3 C). HRMS: (ES-MS) m/z calculated for $C_{14}H_{21}ClNO_2$ [M+H]: 270.1255, found 270.1262.

Ethyl *tert*-butyl(4-chlorophenethyl)carbamate (85f).



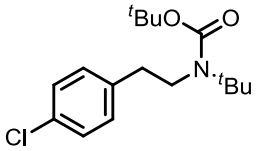
Compound **85f** was prepared from **77d** (429.8 mg, 1.00 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.4 mg, 10.3 µmol, 1 mol%) following *general protocol F*. As solvent 10 ml MeCN and 120 µl ethanol (3 equiv.) was used. Yield: 199.7 mg (0.704 mmol, 70%) colorless oil. R_f (hexanes/EtOAc = 2/1) = 0.84. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.28 – 7.22 (m, 2H), 7.11 (dd, *J* = 8.7, 2.1 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.49 – 3.40 (m, 2H), 2.76 (dd, *J* = 9.3, 7.0 Hz, 2H), 1.42 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.11, 137.99, 132.04, 130.06 (2 C), 128.61 (2 C), 60.65, 55.80, 46.62, 36.94, 29.47 (3 C), 14.69. HRMS: (ES-MS) m/z calculated for $C_{15}H_{23}ClNO_2$ [M+H]: 284.1412, found 284.1418.

Isopropyl tert-butyl(4-chlorophenethyl)carbamate (85g).



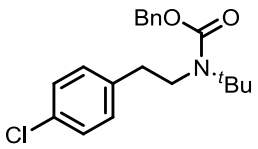
Compound **85g** was prepared from **77d** (241.4 mg, 0.563 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (5.2 mg, 5.7 µmol, 1 mol%) following *general protocol F*. As solvent 2 ml MeCN and 200 µl 2-propanol (4 equiv.) was used. Yield: 94.4 mg (0.317 mmol, 56%) colorless oil. R_f (hexanes/EtOAc = 2/1) = 0.87. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 4.95 (hept, *J* = 6.2 Hz, 1H), 3.49 – 3.38 (m, 2H), 2.76 (dd, *J* = 9.4, 7.0 Hz, 2H), 1.42 (s, 9H), 1.28 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.67, 138.05, 132.02, 130.05 (2 C), 128.61 (2 C), 67.89, 55.69, 46.64, 36.96, 29.54 (3 C), 22.33. HRMS: (ES-MS) m/z calculated for $C_{16}H_{25}ClNO_2$ [M+H]: 298.1568, found 298.157.

***tert*-butyl *tert*-butyl(4-chlorophenethyl)carbamate (85h).**



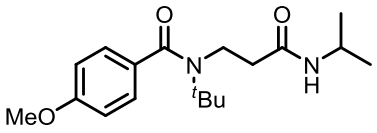
Compound **85h** was prepared from **77d** (78.7 mg, 0.184 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1.8 mg, 2.0 µmol, 1.1 mol%) following *general protocol F*. As solvent 2 ml MeCN and 100 µl *tert*-butyl alcohol (5 equiv.) was used. Yield: 20.2 mg (65 µmol, 35%) colorless oil. R_f (hexanes/EtOAc = 2/1) = 0.90. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21 (dd, *J* = 6.7, 1.6 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 3.40 – 3.32 (m, 2H), 2.72 (dd, *J* = 9.4, 6.9 Hz, 2H), 1.45 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.36, 138.14, 131.96, 130.07 (2 C), 128.58 (2 C), 79.28, 55.42, 46.81, 36.91, 29.69 (3 C), 28.64 (3 C). HRMS: (ES-MS) m/z calculated for $C_{17}H_{27}ClNO_2$ [M+H]: 312.1725, found 312.1728.

Benzyl *tert*-butyl(4-chlorophenethyl)carbamate (85i).



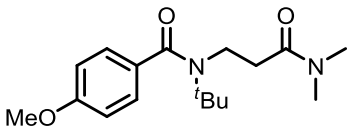
Compound **85i** was prepared from **77d** (232.6 mg, 0.542 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (5.4 mg, 5.9 µmol, 1 mol%) following *general protocol F*. As solvent 2 ml MeCN and 200 µl benzyl alcohol (2 equiv.) was used. Yield: 112.4 mg (0.325 µmol, 60%) colorless oil. R_f (hexanes/EtOAc = 2/1) = 0.85. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42 – 7.32 (m, 5H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 5.13 (s, 2H), 3.53 – 3.42 (m, 2H), 2.76 (dd, *J* = 9.3, 7.0 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.72, 137.78, 136.91, 132.04, 130.05 (2 C), 128.58 (2 C), 128.53 (2 C), 128.08 (2 C), 128.00, 66.80, 56.07, 46.73, 37.02, 29.40 (3 C). HRMS: (ES-MS) m/z calculated for $C_{20}H_{25}ClNO_2$ [M+H]: 346.1568, found 346.1574.

N-*tert*-Butyl-N-(3-(*iso*propylamino)-3-oxopropyl)-4-methoxybenzamide (86a).



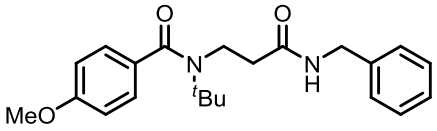
Compound **86a** was prepared from **74** (208.4 mg, 0.491 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (3.1 mg, 3.4 µmol, 1 mol%) following *general protocol F*. As solvent 4 ml MeCN and 85 µl isopropylamine (2 equiv.) was used. Yield: 143.2 mg (0.447 µmol, 91%) yellow solid. R_f (hexanes/EtOAc = 1/1) = 0.15. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34 – 7.27 (m, 2H), 6.90 – 6.84 (m, 2H), 5.17 (s, 1H), 3.97 – 3.83 (m, 1H), 3.81 (d, *J* = 8.7 Hz, 3H), 3.70 – 3.56 (m, 2H), 2.34 – 2.20 (m, 2H), 1.49 (s, 9H), 1.00 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.65, 169.15, 160.17, 131.89, 128.06 (2 C), 113.78, (2 C) 57.23, 55.30, 43.93, 41.20, 38.88, 29.15 (3 C), 22.61 (2 C). LRMS: (ES-MS) m/z calculated for $C_{18}H_{29}N_2O_3$ [M+H]: 321.43, found 321.2183.

N-*tert*-Butyl-N-(3-(dimethylamino)-3-oxopropyl)-4-methoxybenzamide (86b).



Compound **86b** was prepared from **74** (212.1 mg, 0.450 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (3.3 mg, 3.6 µmol, 1 mol%) following *general protocol F*. As solvent 4 ml MeCN and 70 µl dimethylamine (2 equiv.) was used. Yield: 126.4 mg (0.413 µmol, 92%) colorless oil. R_f (hexanes/EtOAc = 1/1) = 0.22. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.28 – 7.21 (m, 2H), 6.82 – 6.75 (m, 2H), 3.72 (s, 3H), 3.67 – 3.54 (m, 2H), 2.74 (s, 3H), 2.70 (s, 3H), 2.40 – 2.31 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.62, 170.09, 160.10, 131.71, 128.09 (2 C), 113.73 (2 C), 57.16, 55.30, 43.68, 36.85, 35.09, 34.98, 29.10.

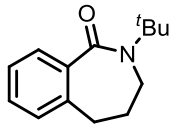
N-(3-(Benzylamino)-3-oxopropyl)-N-*tert*-butyl-4-methoxybenzamide (86c).



Compound **86c** was prepared from **74** (210.6 mg, 0.496 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (3.5 mg, 3.8 µmol, 1 mol%) following *general protocol F*. As solvent 4 ml MeCN and 110 µl dimethylamine (2 equiv.) was used. Yield: 164.5 mg (0.446 µmol, 90%) white solid. R_f (hexanes/EtOAc = 1/1) = 0.20. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.26 (m, 5H), 7.17 – 7.09 (m, 2H), 6.86 – 6.79 (m, 2H), 5.88 (s, 1H), 4.48 (d, *J* = 5.7 Hz, 1H), 4.26 (d, *J* = 5.5 Hz, 2H), 3.77 (s, 3H), 3.72 – 3.60 (m, 2H), 2.41 – 2.24 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.67, 169.03, 160.20, 137.80, 134.54, 130.36, 128.78 (2 C), 128.73 (2 C), 128.44, 128.07, 127.87 (2 C), 127.75, 127.60, 113.79 (2 C), 57.25, 55.30, 44.15, 43.50, 38.59, 29.20 (3 C).

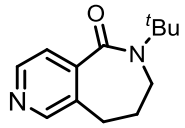
4.3 Photoinduced benzoazepinone synthesis

2-*tert*-butyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105a).



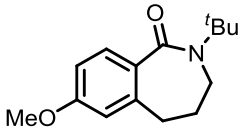
Compound **105a** was prepared from **102a** (300.0 mg, 0.734 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (7.9 mg, 8.6 µmol, 1.2 mol%) following *general protocol F*. Purification by column chromatography (hexanes/EtOAc = 2/1, $R_f = 0.62$) gave 69.0 mg (0.318 mmol, 43%) colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.70 – 7.64 (m, 1H), 7.32 – 7.27 (m, 2H), 7.11 – 7.04 (m, 1H), 3.23 (t, *J* = 6.3 Hz, 2H), 2.78 (t, *J* = 7.0 Hz, 2H), 1.89 (p, *J* = 6.8 Hz, 2H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.99, 138.39, 137.22, 130.47, 128.67, 127.95, 126.88, 57.03, 42.74, 31.49, 30.10, 28.82 (3 C). HRMS: (ES-MS) m/z calculated for $C_{14}H_{19}NO$ [M+]: 218.1539, found 218.1544.

6-*tert*-butyl-6,7,8,9-tetrahydro-5H-pyrido[4,3-c]azepin-5-one (105b)



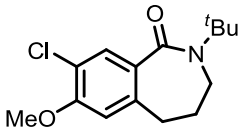
Compound **105b** was prepared from **102b** (412.8 mg, 1.01 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.4 mg, 10.3 µmol, 1 mol%) following *general protocol F*. For column chromatography neutral alumina oxide (DCM/EtOAc = 1/1, $R_f = 0.54$) was used. Yield: 76.6 mg (0.351 µmol, 35%) yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.60 (d, *J* = 5.0 Hz, 1H), 8.42 (s, 1H), 7.56 (d, *J* = 5.0 Hz, 1H), 3.24 (t, *J* = 6.3 Hz, 2H), 2.82 (t, *J* = 7.1 Hz, 2H), 2.00 – 1.92 (m, 2H), 1.56 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.57, 148.86, 148.74, 145.76, 131.47, 122.18, 57.57, 42.43, 30.91, 28.65 (3 C), 26.67. HRMS: (CI-MS) m/z calculated for $C_{13}H_{19}N_2O$ [M+H]: 219.1492, found 219.1496.

2-*tert*-butyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105c).

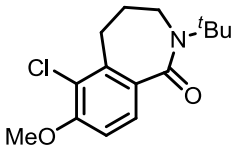


Compound **105c** was prepared from **102c** (440.2 mg, 1.01 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.4 mg, 10 µmol, 1 mol%) following *general protocol F*. For column chromatography neutral alumina oxide (DCM/EtOAc = 9/1, R_f = 0.59) was used. Yield: 152.3 mg (0.61 mmol, 60%) yellow oil. IR (neat):2960, 2863, 1785, 1737, 1633, 1599, 1491, 11457, 1387, 1316, 1249, 1197, 1167, 1092, 1036, 831, 779, 716 cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 8.5 Hz, 1H), 6.80 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.62 (d, *J* = 2.6 Hz, 1H), 3.81 (s, 3H), 3.25 (t, *J* = 6.3 Hz, 2H), 2.77 (t, *J* = 7.0 Hz, 2H), 1.89 (p, *J* = 6.8 Hz, 2H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.04, 161.28, 139.49, 130.95, 130.79, 113.66, 111.60, 56.89, 55.26, 42.92, 31.46, 30.61, 28.84 (3 C). HRMS: (ES-MS) m/z calculated for $C_{15}H_{22}NO_2$ [M+H]: 248.1645, found 248.1648.

2-*tert*-butyl-8-chloro-7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105d´).



2-*tert*-butyl-6-chloro-7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105d´´).



Compound **105d´** and **105d´´** were prepared from **102d** (459.7 mg, 1.03 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.5 mg, 10.4 µmol, 1 mol%) following *general protocol F*. Purification by column chromatography (dichloromethane/EtOAc = 10/1) gave **105d´** in 52.8 mg (0.187 mmol, 18%) as white solid and **105d´´** in 127.4 mg (0.452 mmol, 44%) as white solid.

Compound **105d´**:

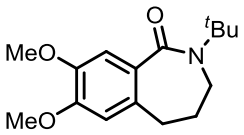
M.p. = 135-138 °C. R_f (DCM/EtOAc = 10/1) = 0.69. IR (neat): 3012, 2933, 2863, 1722, 1628, 1595, 1491, 1446, 1409, 1361, 1301, 1223, 1148, 1051, 936, 898, 842, 775, 712 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 6.64 (s, 1H), 3.91 (s, 3H), 3.24 (t, *J* = 6.3 Hz, 2H),

2.77 (t, *J* = 7.0 Hz, 2H), 1.91 (p, *J* = 6.7 Hz, 2H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.76, 156.32, 137.83, 131.48, 131.02, 120.70, 111.44, 57.10, 56.22, 42.79, 31.36, 30.44, 28.75 (3 C). HRMS: (ES-MS) m/z calculated for $C_{15}H_{21}ClNO_2$ [M+H]: 282.1255, found 282.1260.

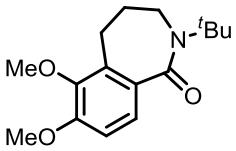
Compound **105d´´**:

M.p. = 135-138 °C. R_f (DCM/EtOAc = 10/1) = 0.45. IR (neat): 3194, 3079, 2952, 2862, 1726, 1633, 1592, 1562, 1476, 1439, 1387, 1301, 1260, 1189, 1141, 1062, 917, 883, 801, 716, 671 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 3.91 (s, 3H), 3.21 (t, *J* = 6.2 Hz, 2H), 3.06 (t, *J* = 6.8 Hz, 2H), 1.88 (p, *J* = 6.6 Hz, 2H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.05, 156.55, 136.52, 134.28, 132.44, 128.07, 123.57, 120.62, 109.62, 57.18, 56.29, 42.86, 30.26, 28.85 (3 C), 25.82. HRMS: (ES-MS) m/z calculated for $C_{15}H_{21}ClNO_2$ [M+H]: 282.1255, found 282.1261.

2-*tert*-butyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105e´).



2-*tert*-butyl-6,7-dimethoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105e´´).



Compound **105e´** and **105e´´** were prepared from **102e** (468.5 mg, 1.0 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.3 mg, 10.2 µmol, 1 mol%) following *general protocol F*. For column chromatography neutral alumina oxide (hexanes/EtOAc = 4/1) was used. Yield **105e´**: 134.0 mg (0.483 mmol, 48%) pale yellow solid. Yield **105e´´**: 28.6 mg (0.103 mmol, 10%) pale yellow solid.

Compound **105e´**:

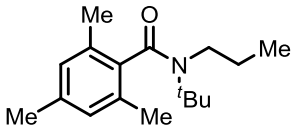
R_f (hexanes/EtOAc = 4/1) = 0.24. Ir (neat): 2963, 2930, 2863, 1625, 1599, 1536, 1446, 1415, 1368, 1334, 1282, 1261, 1215, 1033, 1088, 1029, 957, 869, 783 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25 (s, 1H), 6.58 (s, 1H), 3.88 (s, 6H), 3.25 (t, *J* = 6.3 Hz, 2H), 2.73 (t, *J* = 7.0 Hz, 2H), 1.89 (p, *J* = 6.7 Hz, 2H), 1.53 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.20,

150.42, 147.52, 130.93, 130.19, 111.90, 110.93, 56.98, 56.00, 55.93, 43.01, 31.86, 30.08, 28.90, 28.81 (3 C). HRMS: (ES-MS) m/z calculated for $C_{16}H_{24}NO_3$ [M+H]: 278.1751, found 278.1757.

Compound **105e´´**:

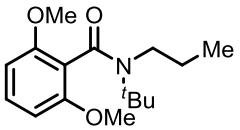
R_f (hexanes/EtOAc = 4/1) = 0.33. Ir (neat): 2963, 2930, 2863, 1629, 1599, 1510, 1450, 1417, 1383, 1359, 1260, 1215, 1077, 1029, 958, 869, 749 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 3.23 (t, *J* = 6.3 Hz, 2H), 2.89 (t, *J* = 6.9 Hz, 2H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.73, 153.36, 143.99, 130.97, 130.42, 124.14, 108.84, 60.18, 55.91, 54.66, 41.90, 29.99, 27.80 (3 C), 20.43. HRMS: (ES-MS) m/z calculated for $C_{16}H_{24}NO_3$ [M+H]: 278.1751, found 278.1753.

N-*tert*-Butyl-2,4,6-trimethyl-N-propylbenzamide (105f).



Compound **105f** was prepared from **102f** (225.0 mg, 0.5 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (4.7 mg, 5.1 µmol, 1 mol%) following *general protocol F*. Yield: 31.9 mg (0.122 mmol, 24%) white solid. R_f (hexanes/EtOAc = 4/1) = 0.58. IR (neat): 2960, 2922, 2874, 1625, 1454, 1387, 1361, 1297, 1252, 1200, 1144, 1070, 1036, 887, 753, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 6.79 (d, *J* = 0.4 Hz, 2H), 3.04 – 2.95 (m, 2H), 2.26 (s, 3H), 2.22 (s, 6H), 1.57 (s, 9H), 1.46 – 1.33 (m, 2H), 0.58 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.80, 136.97, 136.22, 132.92 (2 C), 128.23 (2 C), 57.11, 48.61, 28.91 (3 C), 24.69, 21.10, 19.12 (2 C), 11.29. LRMS: (ES-MS) m/z calculated for $C_{17}H_{28}NO$ [M+H]: 262.21, found 262.2178.

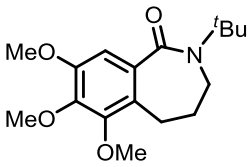
N-*tert*-butyl-2,6-dimethoxy-N-propylbenzamide (105g).



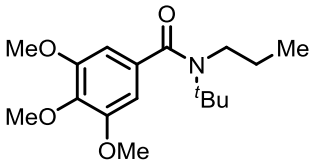
Compound **105g** was prepared from **102g** (424.0 mg, 0.905 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (10.1 mg, 11.1 µmol, 1.2 mol%) following *general protocol F*. Purification by column chromatography (hexanes/EtOAc = 1/1, R_f = 0.30) gave 113.5 mg (0.406 mmol, 45%) pale

yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.19 (t, *J* = 8.4 Hz, 1H), 6.52 (d, *J* = 8.4 Hz, 2H), 3.78 (s, 6H), 3.06 – 2.98 (m, 2H), 1.55 (s, 9H), 1.48 – 1.37 (m, 2H), 0.56 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.59, 156.12 (2 C), 129.21, 118.37, 103.96 (2 C), 57.03, 55.81 (2 C), 48.83, 29.00 (3 C), 24.69, 11.28. HRMS: (ES-MS) m/z calculated for $C_{16}H_{26}NO_3$ [M+H]: 280.1907, found 280.1915.

2-*tert*-butyl-6,7,8-trimethoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105h).



N-*tert*-butyl-3,4,5-trimethoxy-N-propylbenzamide (260).



Compound **105h** and **260** were prepared from **102h** (50.0 mg, 0.1 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1.87 mg, 10.2 µmol, 2 mol%) following *general protocol F*. For column chromatography neutral alumina oxide (hexanes/EtOAc = 4/1) was used. Yield **105h**: 20 mg (65 µmol, 43%) pale yellow solid. Yield **260**: 15 mg (48 µmol, 38%) yellow oil.

Compound **105h**:

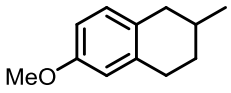
R_f (hexanes/EtOAc = 4/1) = 0.52. IR (neat): 2960, 2937, 1752, 1722, 1636, 1592, 1484, 1457, 1416, 1387, 1323, 1241, 1193, 1111, 1074, 1033, 954, 917, 857, 809, 690 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.04 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.77 (s, 3H), 3.22 (t, *J* = 6.2 Hz, 2H), 2.79 (t, *J* = 6.9 Hz, 2H), 1.89 – 1.76 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.66, 151.75, 150.02, 144.07, 133.94, 123.73, 108.05, 61.57, 60.87, 57.12, 56.01, 42.93, 31.35, 28.79 (3 C), 20.97. HRMS: (ES-MS) m/z calculated for $C_{17}H_{26}NO_4$ [M+H]: 308.1856, found 308.1863.

Compound **260**:

R_f (hexanes/EtOAc = 4/1) = 0.35. IR (neat): 2933, 2837, 1722, 1633, 1584, 1502, 1457, 1394, 1327, 1293, 1230, 1126, 1006, 951, 850, 775, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.54 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.21 (dd, *J* = 9.7, 6.0 Hz, 2H), 1.54 (s, 11H), 0.67 (t,

J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.05, 153.22 (2 C), 138.28, 135.45, 103.47 (2 C), 60.96, 56.97, 56.26 (2 C), 49.43, 28.88 (3 C), 25.61, 11.19. HRMS: (ES-MS) m/z calculated for $C_{17}H_{28}NO_4$ [M+H]: 310.2013, found 310.2017.

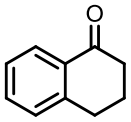
6-methoxy-2-methyl-1,2,3,4-tetrahydronaphthalene (130).



Compound **130** was prepared from **127** (214 mg, 0.58 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (5 mg, 5.5 µmol, 1 mol%) following *general protocol F*. Purification via column chromatography with pure hexanes. Yield: 50 mg (0.284 mmol, 49%) white solid. IR (neat): 2960, 2922, 2855, 1715, 1607, 1498, 1461, 1379, 1260, 1085, 1010, 865, 787, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.97 (d, *J* = 8.3 Hz, 1H), 6.68 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 3.77 (s, 3H), 2.82 – 2.72 (m, 3H), 2.37 – 2.27 (m, 1H), 1.92 – 1.78 (m, 2H), 1.43 – 1.33 (m, 1H), 1.05 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.40, 137.75, 129.84, 129.12, 113.40, 111.77, 55.26, 37.32, 31.47, 29.64, 29.52, 22.03.

Analytical data match to the reported data.[151]

3,4-Dihydronaphthalen-1(2H)-one (134).



Compound **134** was prepared from **133** (189.6 mg, 0.56 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (7.3 mg, 8.0 µmol, 1.4 mol%) following *general protocol F*. Yield: 15.3 mg (0.105 mmol, 19%) white solid. R_f (hexanes/EtOAc = 3/1) = 0.71. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.99 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.42 (td, *J* = 7.5, 1.5 Hz, 1H), 7.26 (ddd, *J* = 7.9, 1.2, 0.6 Hz, 1H), 7.21 (t, *J* = 3.8 Hz, 1H), 2.93 (t, *J* = 6.1 Hz, 2H), 2.66 – 2.57 (m, 2H), 2.16 – 2.04 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.41, 144.51, 133.40, 132.65, 128.78, 127.19, 126.65, 39.19, 29.73, 23.31.

Analytical data match to the reported data.[152]

4.4 UV light-mediated reactions

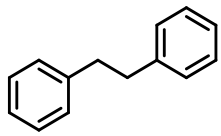
General protocol G

General procedure for UV light-promoted decarboxylations:

N-acyloxyphthalimide (1 mmol, 1 equiv.) was dissolved in acetone (60 ml) and a solution of corresponding phenylacetic acid (3 mmol, 3 equiv.) and potassium carbonate (1.5 mmol, 1.5 equiv.) in water (60 ml) was added. The mixture was degassed for 10 min in a Pyrex Schlenk flask (internal diameter (ID): 30 mm) equipped with a cold finger (outer diameter (OD): 20 mm) with a slow stream of nitrogen. While the continuous stream of nitrogen the solution was irradiated until full conversion of the starting material (judged by TLC, typically 3 h) in a Rayonet chamber reactor equipped with 16 x 8 W RPR-3000 Å lamps. The acetone was evaporated under reduced pressure and the remaining water phase was extracted with dichloromethane (3 x 40 ml). The organic layer was washed with a saturated $NaHCO_3$ solution (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated. Purification by column chromatography.

Dihydrostilbene synthesis

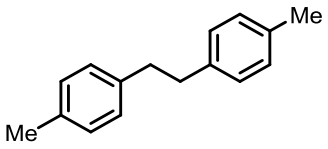
1,2-Diphenylethane (172/168a).



Compound **168a** was prepared from **171** (168.6 mg, 0. 60 mmol, 1 equiv.), phenylacetic acic (248 mg, 1.82 mmol, 3 equiv.) and K_2CO_3 (126 mg, 1.82 mmol, 1.5 equiv.) following *general protocol G*. Yield: gave 65.1 mg (0.360 mmol, 59%) as a white solid. R_f (hexanes/EtOAc, 1/1) = 0.94. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 – 7.26 (m, 2H), 7.21 (ddd, *J* = 6.8, 3.8, 1.2 Hz, 3H), 2.93 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.92 (2 C), 128.59 (4 C), 128.47 (4 C), 126.05 (2 C), 38.09 (2 C).

Analytical data match to the reported data.[153]

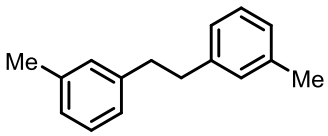
1,2-Di-*p*-tolylethane (168b).



Compound **168b** was prepared from **166b** (284.5 mg, 0.96 mmol, 1 equiv.), *p*-tolylacetic acic (445.3 mg, 2.97 mmol, 3 equiv.) and K_2CO_3 (203 mg, 1.47 mmol, 1.5 equiv.) following *general protocol G*. Yield: 125.8 mg (0.598 mmol, 62%), white solid, m.p. = 75-76 °C. R_f (hexanes/EtOAc, 1/1) = 0.96. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.10 (s, 4H), 2.87 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.01 (2 C), 135.43 (2 C), 129.14 (4 C), 128.43 (4 C), 37.79 (2 C), 21.16 (2 C).

Analytical data match to the reported data.[153]

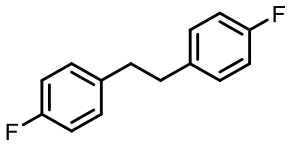
1,2-Di-*m*-tolylethane (168c).



Compound **168c** was prepared from **166c** (284.9 mg, 0.96 mmol, 1 equiv.), 2-*m*-tolylacetic acic (449.1 mg, 2.99 mmol, 3 equiv.) and K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv.) following *general protocol G*. Yield: 165.9 mg (0. 79 mmol, 82%), white solid. R_f (hexanes/EtOAc, 1/1) = 0.9. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21 (t, *J* = 7.2 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 6H), 2.89 (s, 4H), 2.36 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.06 (2 C), 138.01 (2 C), 129.40 (2 C), 128.40 (2 C), 126.79 (2 C), 125.56 (2 C), 38.17 (2 C), 21.56 (2 C).

Analytical data match to the reported data.[154]

1,2-Bis(4-fluorophenyl)ethane (168d).

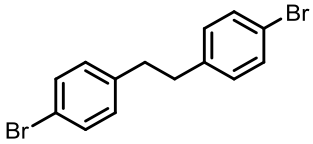


Compound **168d** was prepared from **166d** (295.2 mg, 0.986 mmol, 1 equiv.), 4-fuorophenylacetic acic (450 mg, 2.92 mmol, 3 equiv.) and K_2CO_3 (205 mg, 1.48 mmol, 1.5 equiv.) following *general protocol G*. Yield: 106.9 mg (0.490 mmol, 50%), yellow solid,

m.p. = 89-91 °C. R_f (hexanes/EtOAc, 1/1) = 0.94. ^{1}H NMR (300 MHz, CDCl3$_3$) δ = 7.12 (ddd, *J* = 8.0, 5.4, 2.3 Hz, 4H), 7.06 – 6.92 (m, 4H), 2.90 (d, *J* = 2.2 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.47 (d, *J* = 243.5 Hz, 2 C), 137.09 (d, *J* = 3.2 Hz, 2 C), 129.96 (d, *J* = 7.8 Hz, 4 C), 115.18 (d, *J* = 21.1 Hz, 4 C), 37.26 (s, 2 C).

Analytical data match to the reported data.[153]

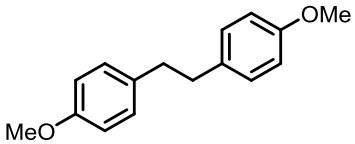
1,2-Bis(4-bromophenyl)ethane (168e).



Compound **168e** was prepared from **166e** (249.3 mg, 0.692 mmol, 1 equiv.), 4-bromophenylacetic acic (443.9 mg, 2.06 mmol, 3 equiv.) and K_2CO_3 (143 mg, 1.03 mmol, 1.5 equiv.) following *general protocol G*. Yield: 143.9 mg (0.423 mmol, 61%), yellow solid, m.p. = 101-106 °C. R_f (hexanes/EtOAc, 1/1) = 0.81. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42 – 7.35 (m, 4H), 7.03 – 6.96 (m, 4H), 2.85 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.22 (2 C), 131.55 (4 C), 130.38 (4 C), 119.95 (2 C), 37.15 (2 C).

Analytical data match to the reported data.[153]

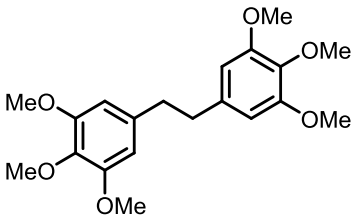
1,2-Bis(4-methoxyphenyl)ethane (165/168f).



Compound **168f** was prepared from **163** (311.6 mg, 1.00 mmol, 1 equiv.), 2-*p*-methoxyphenylacetic acid (454.6 mg, 2.74 mmol, 2.7 equiv.) and K_2CO_3 (230 mg, 1.66 mmol, 1.6 equiv.) following *general protocol G*. Yield: 173.9 mg (0.718 mmol, 72%), white solid, m.p. = 127-128 °C. R_f (hexanes/EtOAc, 1/1) = 0.86. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.15 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 3.84 (s, 3H), 2.90 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.86 (2 C), 134.01 (2 C), 129.44 (4 C), 113.77 (4 C), 55.27 (2 C), 37.36 (2 C). HRMS: (EI-MS) m/z calculated for $C_{16}H_{18}O_2$ [M+]: 242.1307, found 242.1305.

Analytical data match to the reported data.[155]

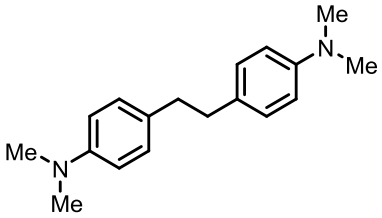
1,2-Bis(3,4,5-trimethoxyphenyl)ethane (168g).



Compound **168g** was prepared from **166g** (369.4 mg, 1.00 mmol, 1 equiv.), 2-(3,4,5-trimethoxyphenyl)acetic acid (235.1 mg, 1.04 mmol, 1 equiv.) and K_2CO_3 (204 mg, 1.48 mmol, 1.5 equiv.) following *general protocol G*. Yield: 100.8 mg (0.278 mmol, 28%), yellow solid, m.p. = 135-137 °C. R_f (hexanes/EtOAc, 1/1) = 0.56. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.36 (s, 4H), 3.82 (s, 18H), 2.84 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.17 (4 C), 137.46 (2 C), 136.34 (2 C), 105.60 (4 C), 61.00 (2 C), 56.19 (4 C), 38.57 (2 C).

Analytical data match to the reported data.[156]

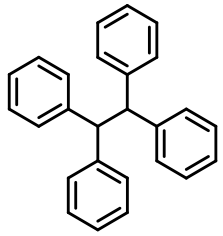
4,4'-(Ethane-1,2-diyl)bis(*N*,*N*-dimethylaniline) (168h).



Compound **168h** was prepared from **166h** (320.9 mg, 0.99 mmol, 1 equiv.), 4-dimethylaminophenylacetic acic (533.1 mg, 2.97 mmol, 3 equiv.) and K_2CO_3 (230 mg, 1.66 mmol, 1.6 equiv.) following *general protocol G*. Yield: 44.5 mg (0.166 mmol, 17%), brown solid. R_f (hexanes/EtOAc, 1/1) = 0.89. ^{1}H NMR (300 MHz, $cdcl_3$) δ = 7.10 (d, *J* = 8.8 Hz, 4H), 6.72 (d, *J* = 6.2 Hz, 4H), 2.92 (d, *J* = 5.0 Hz, 12H), 2.80 (s, 4H). ^{13}C NMR (75 MHz, $cdcl_3$) δ = 149.08 (2 C), 129.44 (2 C), 129.04 (4 C), 113.11 (4 C), 41.03 (4 C), 37.37 (2 C).

Analytical data match to the reported data.[157]

1,1,2,2-tetraphenylethane (168i).

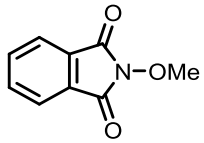


Compound **168i** was prepared from **166i** (356.5 mg, 1.68 mmol, 1 equiv.), diphenylacetic acic (636.1 mg, 2.97 mmol, 3 equiv.) and K_2CO_3 (240 mg, 1.74 mmol, 1.5 equiv.) following *general protocol G*. Yield: 242.9 mg (0.726 mmol, 43%), pale yellow solid. R_f (hexanes/EtOAc, 4/1) = 0.87. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.19 – 7.08 (m, 6H), 7.04 – 6.98 (m, 4H), 4.78 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.50 (4 C), 128.55 (8 C), 128.19 (8 C), 125.89 (4 C), 56.36 (2 C).

Analytical data match to the reported data.[158]

UV light-mediated benzylation of *N*-methoxyphthalimide

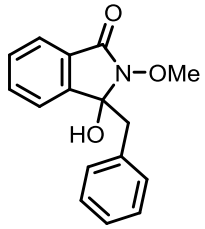
2-Methoxyisoindoline-1,3-dione (261).



Methyl iodide (1.05 ml, 16.8 mmol, 1.1 equiv.) was added dropwise to a solution of N-hydroxyphthalimide (2.5 g, 15.33 mmol, 1 equiv.) and K_2CO_3 (2.54 g, 18.4 mmol, 1.2 equiv.) in DMF (50 ml). The reaction mixture was stirred for overnight. Water (60 ml) was added and the orange solution was extracted with dichloromethane (2x 100 ml). The combined organic phases were washed with water (2x 100 ml), dried with Na_2SO_4 and removed under reduced pressure. Purification by column chromatography (hexanes/EtOAc = 1/1, R_f = 0.58) gave the product **261** (2.0 g, 11.3 mmol, 83%) as pale yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.86 – 7.77 (m, 2H), 7.77 – 7.69 (m, 2H), 4.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.33 (2 C), 134.61 (2 C), 128.97 (2 C), 123.62 (2 C), 65.92.

Analytical data match to the reported data.[159]

3-Benzyl-3-hydroxy-2-methoxyisoindolin-1-one (181).[160]



Photodecarboxylative benzylation under batch conditions

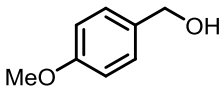
N-Methoxyphthalimide (**261**, 170 mg, 0.96 mmol, 1 equiv.) was dissolved in acetone (30 ml). A solution of phenylacetic acid (400 mg, 2.94 mmol, 3 equiv.) in a pH 7 buffer (Fixanal®, 30 ml) was added, and the mixture was irradiated in a Pyrex Schlenk tube for 26 h, while purging with a slow stream of nitrogen. Acetone was removed under reduced pressure and the remaining solution was extracted with dichloromethane (2 x 30 ml), dried over Na_2SO_4, filtered, and the solvent was evapurated. Purification by column chromatography (hexanes/EtOAc = 1/1, R_f = 0.27) and crystallization (DCM/n-hexane) gave a colorless solid (188.1 mg, 70 mmol, 73%). M.p. = 133-134 °C. IR (neat): 3228, 3030, 2930, 1688, 1498, 1485, 1456, 1435, 1368, 1339, 1297, 1223, 1194, 1126, 1077, 1036, 999, 951, 902, 775, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.51 (dd, *J* = 11.8, 4.3 Hz, 2H), 7.40 – 7.34 (m, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.10 – 7.04 (m, 3H), 6.93 (dd, *J* = 7.2, 2.3 Hz, 2H), 4.14 (s, 3H), 3.47 (d, *J* = 13.5 Hz, 1H), 3.40 (d, *J* = 13.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.62, 143.09, 133.92, 132.55, 130.40 (2 C), 129.78, 128.70, 127.94 (2 C), 127.01, 123.31, 122.48, 91.70, 77.37, 77.05, 76.74, 66.09, 42.02. HRMS: (ES-MS) m/z calculated for $C_{16}H_{16}NO_3$ [M+H]: 270.1125, found 270.1125.

Photodecarboxylative benzylation under continuous-flow condition[160]

A solution of *N*-methoxyphthalimide (**261**, 1-10 mmol) was dissolved in acetone (50 ml) and a solution of potassium phenylacetate (3-30 mmol) in water (50 ml) was added. The mixture was degassed and pumped through the UV-150 easy-Photochem reactor (Vapourtec Ltd, UK)[161] at various flow rates while irradiated with a lamp power of 82 W. After complete collection of the product the reactor coil was flushed with additional acetone/water (~ 20 ml). Acetone was removed under reduced pressure and the remaining solution was extracted with dichloromethane (2 x 50 ml). The combined organic layer was washed eith saturated $NaHCO_3$ (1 x 50 ml) and brine (1 x 50 ml), dried over Na_2SO_4, filtered, and the solvent was evapurated. Conversion rates were subsequently determined via ^1H NMR analysis.

4.5 Decarboxylative hydroxylation reactions

(4-Methoxyphenyl)methanol (186b).

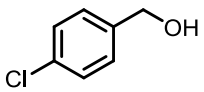


General protocol H

General procedure for the photochemical decarboxylaitive hydroxylation: A Schlenk tube with a magnetic stir bar was charged with N-acyloxyphthalimide **163** (416 mg, 1.34 mmol, 1 equiv.) and the photocatalyst $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (11.2 mg, 1.2 µmol, 1 mol%) in 10 ml acetonitrile/water (2/1, v/v) mixture (0.1 M concentration). The solution was degassed using three freeze-pump-thaw cycles and closed with a Teflon-sealed inlet for a glass rod, through which irradiation with a 455 nm high power LED took place. The photochemical reaction was stirred at room temperature and monitored by TLC analysis. After completion the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography. Yield: 170.3 mg (1.23 mmol, 92%) white solid. R_f (hexanes/EtOAc = 1/2) = 0.86. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31 – 7.25 (m, 2H), 6.92 – 6.84 (m, 2H), 4.60 (s, 2H), 3.80 (s, 3H), 2.03 (s, 1H).

Analytical data match to the reported data.[162]

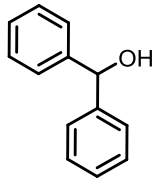
(4-Chlorophenyl)methanol (186c).



Compound **186c** was prepared from **166j** (408 mg, 1.29 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (10.9 mg, 11.9 µmol, 1 mol%) following *general protocol H*. Yield: 131.2 mg (0.92 mmol, 71%) white solid. R_f (hexanes/EtOAc = 1/2) = 0.85.^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36 – 7.30 (m, 4H), 4.68 (s, 2H), 1.25 (s, 1H).

Analytical data match to the reported data.[162]

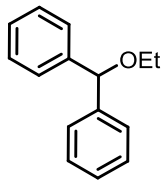
Diphenylmethanol (186d).



Compound **186d** was prepared from **166i** (72.2 mg, 0.202 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (2.1 mg, 2.3 µmol, 1.1 mol%) following *general protocol H*. Yield: 27.1 mg (0.147 mmol, 73%) white solid. R_f (hexanes/EtOAc = 1/1) = 0.70. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.43 – 7.26 (m, 10H), 5.84 (s, 1H), 2.24 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.81 (2 C), 128.54 (4 C), 127.62 (2 C), 126.58 (4 C), 76.28. HRMS: (APCI-MS) m/z calculated for $C_{13}H_{11}$ [MH^+-H_2O]: 167.0855, found 167.0863.

Analytical data match to the reported data.[163]

(Ethoxymethylene)dibenzene (195).



Compound **195** was prepared from **166i** (70 mg, 0.196 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (3.1 mg, 3.4 µmol, 1.5 mol%) following *general protocol H* with a solvent mixture of MeCN/EtOH (1/1, conc.: 0.1 M). Yield: 28.4 mg (0.134 mmol, 68%) white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.28 (m, 8H), 7.23 (ddd, *J* = 6.2, 3.9, 1.6 Hz, 2H), 5.36 (s, 1H), 3.53 (q, *J* = 7.0 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.55 (2 C), 128.38 (4 C), 127.36 (2 C), 126.96 (4 C), 83.50, 64.56, 15.37.

Analytical data match to the reported data.[164]

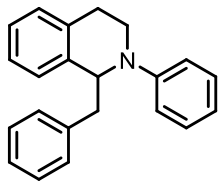
4.6 Photoreactions of the decarboxylative α-amination

General protocol I

General procedure for visible light-promoted decarboxylative α-amination:

A Schlenk tube with a magnetic stir bar was charged with N-acyloxyphthalimide (1 mmol, 1 equiv.), *2*-phenyl-1,2,3,4-tetrahydroisoquinoline (1 mmol, 1 equiv.) and the photocatalyst $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (10 µmol, 1 mol%) in 10 ml acetonitrile/water (40/1, v/v) mixture (0.1 M concentration). The solution was degassed using three freeze-pump-thaw cycles and closed with a Teflon-sealed inlet for a glass rod, through which irradiation with a 455 nm high power LED took place. The photochemical reaction was stirred at room temperature and monitored by TLC analysis. After completion the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography.

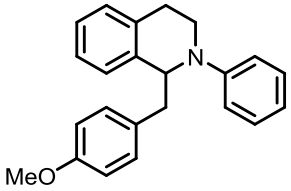
1-Benzyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (224).



Compound **224** was prepared from **171** (281.6 mg, 1.0 mmol, 1 equiv.), 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**208**, 209.6 mg, 1.0 mmol, 1 equiv.) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.1 mg, 1.0 µmol, 1 mol%) following *general protocol I*. Yield: 236.6 mg (0.79 mmol, 79%) brown oil. R_f (hexanes/EtOAc = 2/1) = 0.87. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.24 (dd, *J* = 7.0, 1.4 Hz, 5H), 7.17 (dd, *J* = 6.3, 1.1 Hz, 2H), 7.07 – 7.02 (m, 3H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 2H), 4.97 – 4.88 (m, 1H), 3.68 (ddd, *J* = 12.5, 7.6, 5.0 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.28 (dd, *J* = 13.3, 5.8 Hz, 1H), 3.06 – 2.95 (m, 2H), 2.82 – 2.72 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.35, 138.89, 137.65, 135.12, 129.83 (2 C), 129.27 (2 C), 128.28, 128.19 (2 C), 127.69, 126.64, 126.30, 125.55, 117.21, 113.64 (2 C), 61.54, 42.45, 42.14, 27.51. HRMS: (ES-MS) m/z calculated for $C_{22}H_{22}N$ [M+H]: 300.1747, found 300. 1749.

Analytical data match to the reported data.[165]

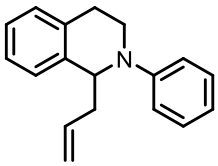
1-(4-Methoxybenzyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (229).



Compound **229** was prepared from **163** (170.5 mg, 0.548 mmol, 1.1 equiv.), 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**208**, 103.7 mg, 0.496 mmol, 1 equiv.) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (3.4 mg, 3.7 µmol, 0.74 mol%) following *general protocol I*. Yield: 108.6 mg (0.329 mmol, 66%) yellow oil. R_f (hexanes/EtOAc = 3/1) = 0.74. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (dd, *J* = 8.8, 7.3 Hz, 2H), 7.24 – 7.18 (m, 2H), 7.13 (td, *J* = 7.5, 1.8 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H), 6.83 (dd, *J* = 14.0, 7.9 Hz, 4H), 4.99 – 4.91 (m, 1H), 3.84 (s, 3H), 3.70 (ddd, *J* = 12.4, 7.5, 5.0 Hz, 1H), 3.64 – 3.55 (m, 1H), 3.27 (dd, *J* = 13.5, 5.6 Hz, 1H), 3.09 – 3.01 (m, 2H), 2.84 – 2.75 (m, 1H).

Analytical data match to the reported data.[165]

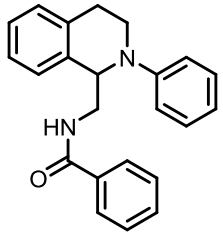
1-Allyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (231).



Compound **231** was prepared from **230** (230 mg, 0.995 mmol, 1 equiv.), 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**208**, 208.2 mg, 0.994 mmol, 1 equiv.) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (9.3 mg, 1.0 µmol, 1 mol%) following *general protocol I*. Yield: 128.4 mg (0.515 mmol, 52%) yellow oil. R_f (hexanes/EtOAc = 5/1) = 0.83. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.27 (m, 2H), 7.25 – 7.13 (m, 4H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.81 (t, *J* = 7.2 Hz, 1H), 5.93 (ddt, *J* = 17.2, 10.2, 7.2 Hz, 1H), 5.18 – 5.08 (m, 2H), 4.82 (t, *J* = 6.8 Hz, 1H), 3.76 – 3.60 (m, 2H), 3.09 (ddd, *J* = 15.7, 7.9, 5.7 Hz, 1H), 2.94 (dt, *J* = 15.9, 5.4 Hz, 1H), 2.81 (dt, *J* = 13.8, 6.8 Hz, 1H), 2.56 (dt, *J* = 14.3, 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.43, 138.16, 135.69, 135.00, 129.28 (2 C), 128.53, 127.38, 126.58, 125.75, 117.24, 117.05, 113.88 (2 C), 59.40, 41.93, 40.95, 27.42. HRMS: (ES-MS) m/z calculated for $C_{18}H_{20}N$ [M+H]: 250.1590, found 250.1593.

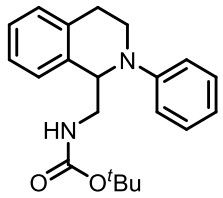
Analytical data match to the reported data.[165]

N-((2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)benzamide (241).



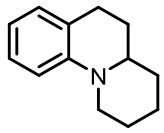
Compound **241** was prepared from **240** (33.6 mg, 0.104 mmol, 1 equiv.), 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**208**, 21.7 mg, 0.104 mmol, 1 equiv.) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (1.0 mg, 1.1 µmol, 1.1 mol%) following *general protocol I*. Yield: 16.4 mg (48 µmol, 46%) yellow solid. R_f (hexanes/EtOAc = 3/1) = 0.29. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.28 – 7.20 (m, 5H), 7.18 – 7.13 (m, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.79 (t, *J* = 7.2 Hz, 1H), 6.49 (s, 1H), 5.02 (dd, *J* = 8.6, 6.0 Hz, 1H), 3.96 – 3.84 (m, 1H), 3.76 (ddd, *J* = 13.6, 9.0, 4.4 Hz, 1H), 3.69 – 3.60 (m, 2H), 3.12 – 2.99 (m, 1H), 2.81 (dt, *J* = 16.0, 4.5 Hz, 1H). LRMS: (ES-MS) m/z calculated for $C_{23}H_{23}N_2O$ [M+H]: 343.4300, found 343.1811.

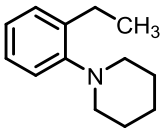
***tert*-Butyl (2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methylcarbamate (243).**



Compound **243** was prepared from **242** (33.1 mg, 0.103 mmol, 1 equiv.), 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**208**, 21.4 mg, 102 mmol, 1. equiv.) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (0.9 mg, 1.0 µmol, 1 mol%) following *general protocol I*. Yield: 6.8 mg (20.1 µmol, 18%) yellow oil. R_f (hexanes/EtOAc = 3/1) = 0.63. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.02 (m, 6H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.73 (t, *J* = 7.2 Hz, 1H), 4.83 (s, 1H), 3.68 – 3.43 (m, 3H), 3.38 (s, 1H), 3.04 – 2.93 (m, 1H), 2.69 (d, *J* = 15.9 Hz, 1H), 1.41 (s, 9H). HRMS: (ES-MS) m/z calculated for $C_{21}H_{27}N_2O_2$ [M+H]: 339.2067, found 339.2073.

2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoline (250) and 1-(2-ethylphenyl)piperidine (251).



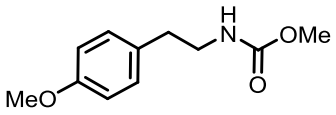


Compounds **250** and **251** were prepared from *N*-acyloxyphthalimide **249** (155.6 mg, 0.411 mmol) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (4.0 mg, 4.3 µmol, 1 mol%) following *general protocol F*. Purification by column chromatography (hexanes/EtOAc = 2/1), $R_f = 0.94$) gave an inseparable mixture of **250** and **251**. Yield: 29.3 mg (~19%).

Compound **250**: HRMS: (ES-MS) m/z calculated for $C_{13}H_{18}N$ [M+H]: 188.1434, found 188.1438. Compound **251**: HRMS: (ES-MS) m/z calculated for $C_{13}H_{20}N$ [M+H]: 190.1590, found 190.1592.

5 *N*-deprotection and synthesis of capsazepinoid precursor derivatives

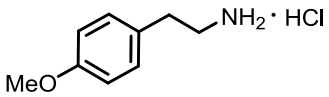
Methyl 4-methoxyphenethylcarbamate (87).



Compound **85a** (214.6 mg, 0.809 mmol) was dissolved in TFA (3 ml) and stirred at room temperature for 15 h. The solvent was removed under reduced pressure and a brown oil was isolated. Yield: 163.9 mg (0.783 mmol, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.10 (d, *J* = 8.6 Hz, 2H), 6.88 – 6.82 (m, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.40 (s, 2H), 2.79 – 2.68 (m, 2H) 1.36 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.60, 158.30, 129.73 (2 C), 126.92, 114.12 (2 C), 55.32, 55.12, 35.03, 29.66. HRMS: (APCI-MS) m/z calculated for $C_{11}H_{16}NO_3$ [M+H]: 210.1125, found 210.1131.

Analytical data match to the reported data.[166]

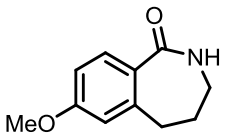
2-(4-Methoxyphenyl)ethanamine hydrochlorid (88).



Compound **87** (150 mg, 0.717 mmol) was dissolved in a mixture of THF, MeOH and 2 M LiOH (1:1:1, 3 ml) and heated at 120 °C for 10 min in a microwave oven. The reaction mixture was treated with ethylacetate (10 ml) and 1 M NaOH solution and the phases were separated. The organic phase was extracted with 1 M HCl solution (2 x 10 ml) and the aqueous phase was removed under reduced pressure. 2-(4-Methoxyphenyl)ethanamine hydrochlorid (**88**) was received as a white solid. Yield: 118.9 mg (0.634 mmol, 88%). ^{1}H NMR (400 MHz, D_2O) δ = 7.30 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H), 3.26 (t, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 7.3 Hz, 2H), 1.37 (s, 1H). ^{13}C NMR (101 MHz, D_2O) = δ 157.99, 130.14, 129.15 (2 C), 114.51 (2 C), 55.40, 40.70, 31.86.

Analytical data match to the reported data.[167]

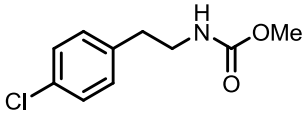
7-Methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (106).



Benzoazepinone **105c** (93 mg, 0.376 mmol) was dissolved in 4 ml trifluoroacetic acid and heated under reflux conditions for 13 h. TFA was removed under reduced pressure and brown oil was purified by flash chromatography (hexanes/EtOAc = 2:1 to EtOAc) on deactivated silica (pretreated with 10% Et_3N in hexanes) to give 61.8 mg (0.323 mmol, 86%) of compound **106** as pale beige solid. IR (neat):3340, 3250, 3056, 2956, 2866, 1689, 1644, 1607, 1498, 1461, 1402, 1361, 1312, 1262, 1208, 1152, 1036, 973, 831, 798, 719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 8.5 Hz, 1H), 6.83 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.70 (d, *J* = 2.5 Hz, 1H), 3.83 (s, 3H), 3.11 (q, *J* = 6.5 Hz, 2H), 2.82 (t, *J* = 7.1 Hz, 2H), 2.00 (p, *J* = 6.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.16, 161.89, 140.74, 130.96, 127.20, 114.30, 111.80, 55.33, 39.79, 30.74, 30.47. HRMS: (ES-MS) m/z calculated for $C_{11}H_{14}NO_2$ [M+H]: 192.1019, found 192.1017.

Analytical data match to the reported data.[168]

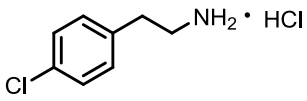
Methyl 4-chlorophenethylcarbamate (262).



Compound **85c** (87.0 mg, 0.809 mmol) was dissolved in TFA (5 ml) and stirred at room temperature for 15 h. The solvent was removed under reduced pressure and a yellow oil was isolated. Yield: 60.2 mg (0.282 mmol, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.22 (m, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 4.73 (s, 1H), 3.65 (s, 3H), 3.40 (d, *J* = 6.3 Hz, 2H), 2.77 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.07, 137.21, 132.37, 130.14 (2 C), 128.75 (2 C), 52.18, 46.04, 42.11, 35.54, 8.53. HRMS: (APCI-MS) m/z calculated for $C_{10}H_{12}ClNO_2$ [M+H]: 214.0629, found 214.0632.

Analytical data match to the reported data.[169]

2-(4-Chlorophenyl)ethanamine hydrochloride (111).



Compound **262** (49 mg, 0.229 mmol) was dissolved in a mixture of THF, MeOH and 2 M LiOH (1:1:1, 3 ml) and heated at 120 °C for 10 min in a microwave oven. The reaction mixture was treated with ethylacetate (10 ml) and 1 M KOH solution (10 ml) and the phases were separated. The organic phase was extracted with 1 M HCl solution (2 x 10 ml) and the aqueous phase was removed under reduced pressure. 2-(4-chlorophenyl)ethanamine (**111**) was received as a white solid. Yield: 39 mg (0.203 mmol, 89%). ^{1}H NMR (300 MHz, D_2O) δ = 7.28 – 7.20 (m, 2H), 7.16 – 7.09 (m, 2H), 3.10 (t, *J* = 7.3 Hz, 2H), 2.82 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, D_2O) δ = 135.19, 132.46, 130.42 (2 C), 128.90 (2 C), 40.40, 32.13. HRMS: (ES-MS) m/z calculated for $C_8H_{11}ClN$ [M+H]: 156.0575, found 156.0573.

Analytical data match to the reported data.[170]

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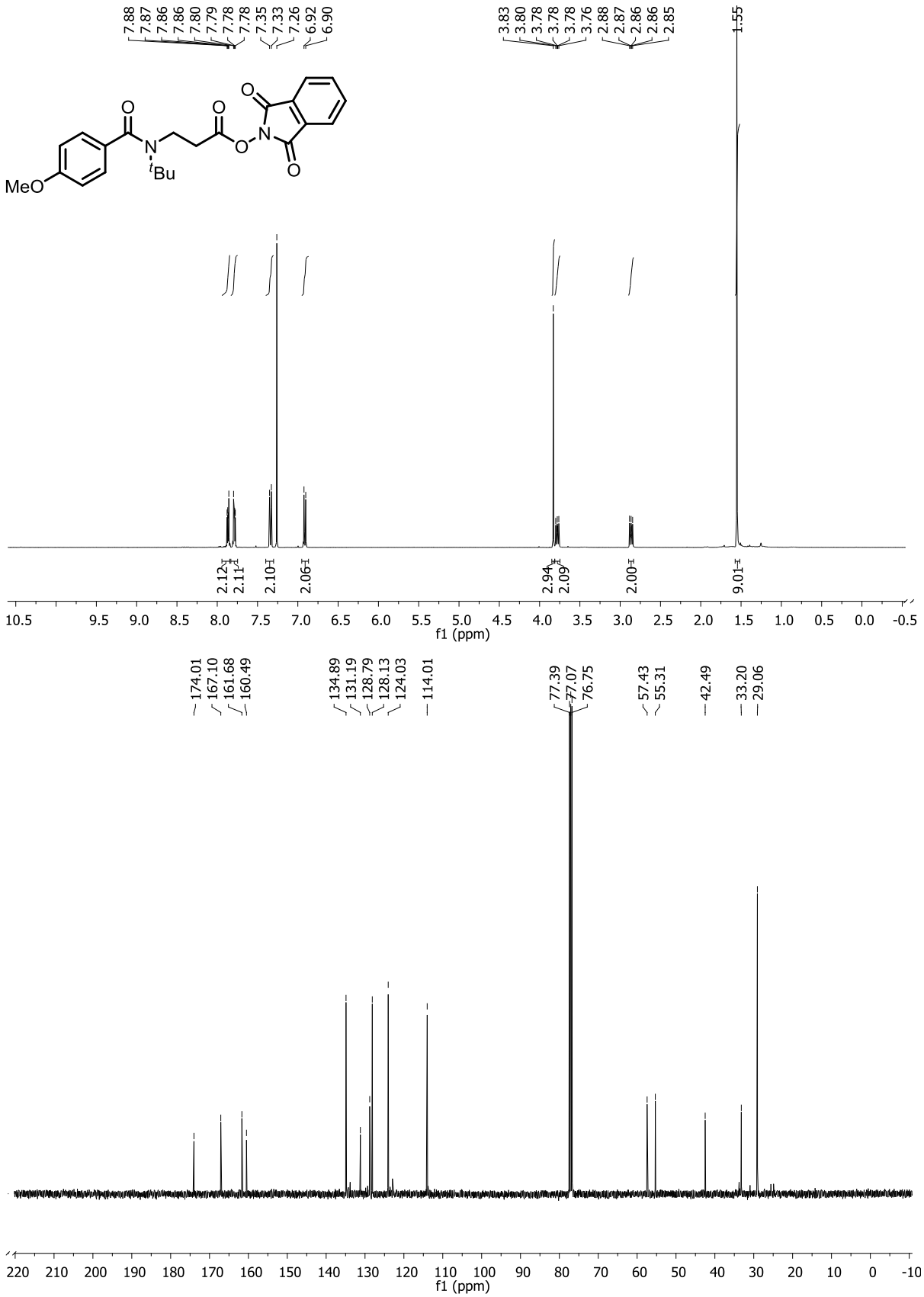
E Appendix

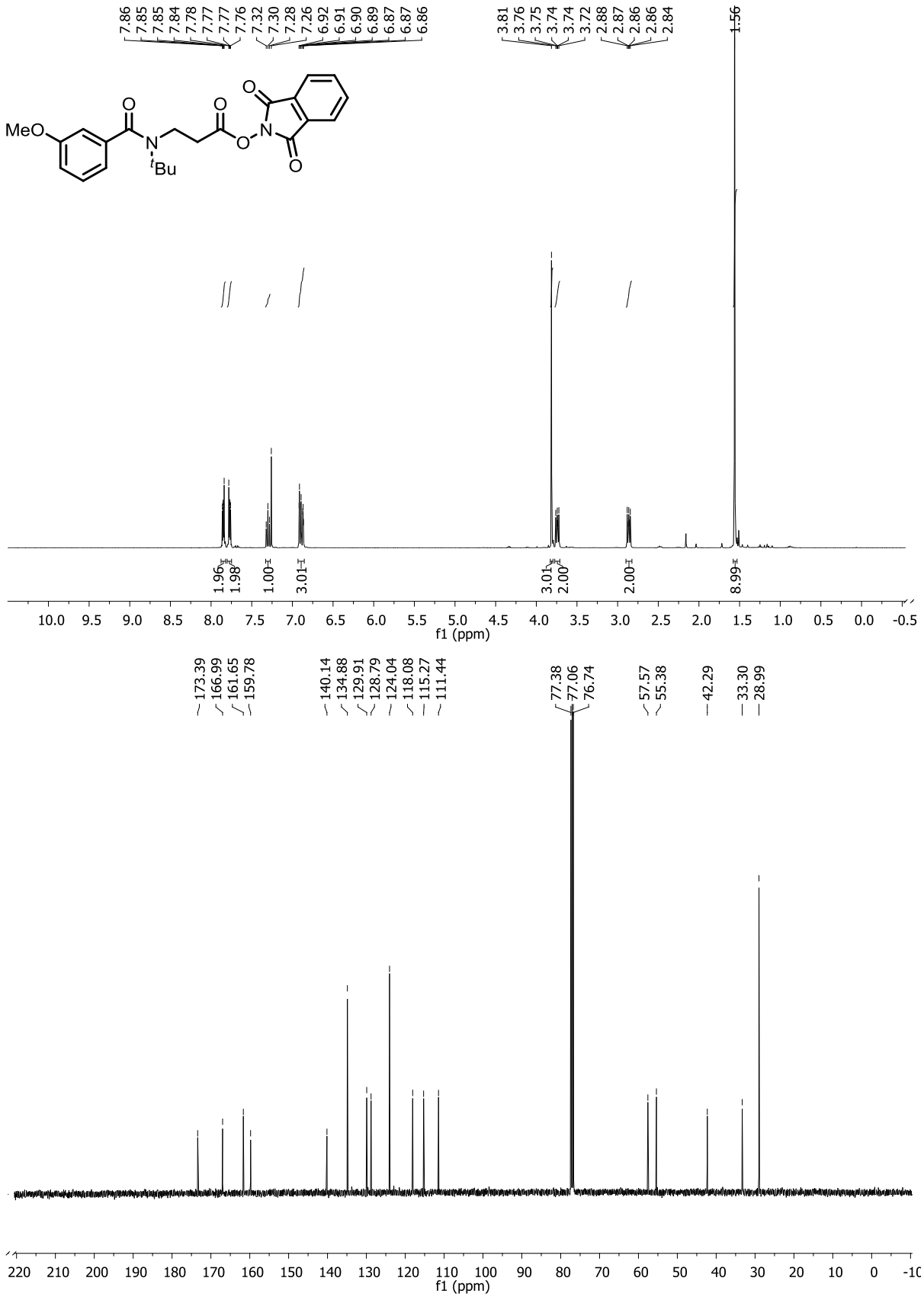
1 NMR spectra

^{1}H-NMR (upper image) followed by ^{13}C-NMR (lower image) spectra of new *N*-acyl-oxyphthalimides and new compounds arose from photoreactions are depicted.

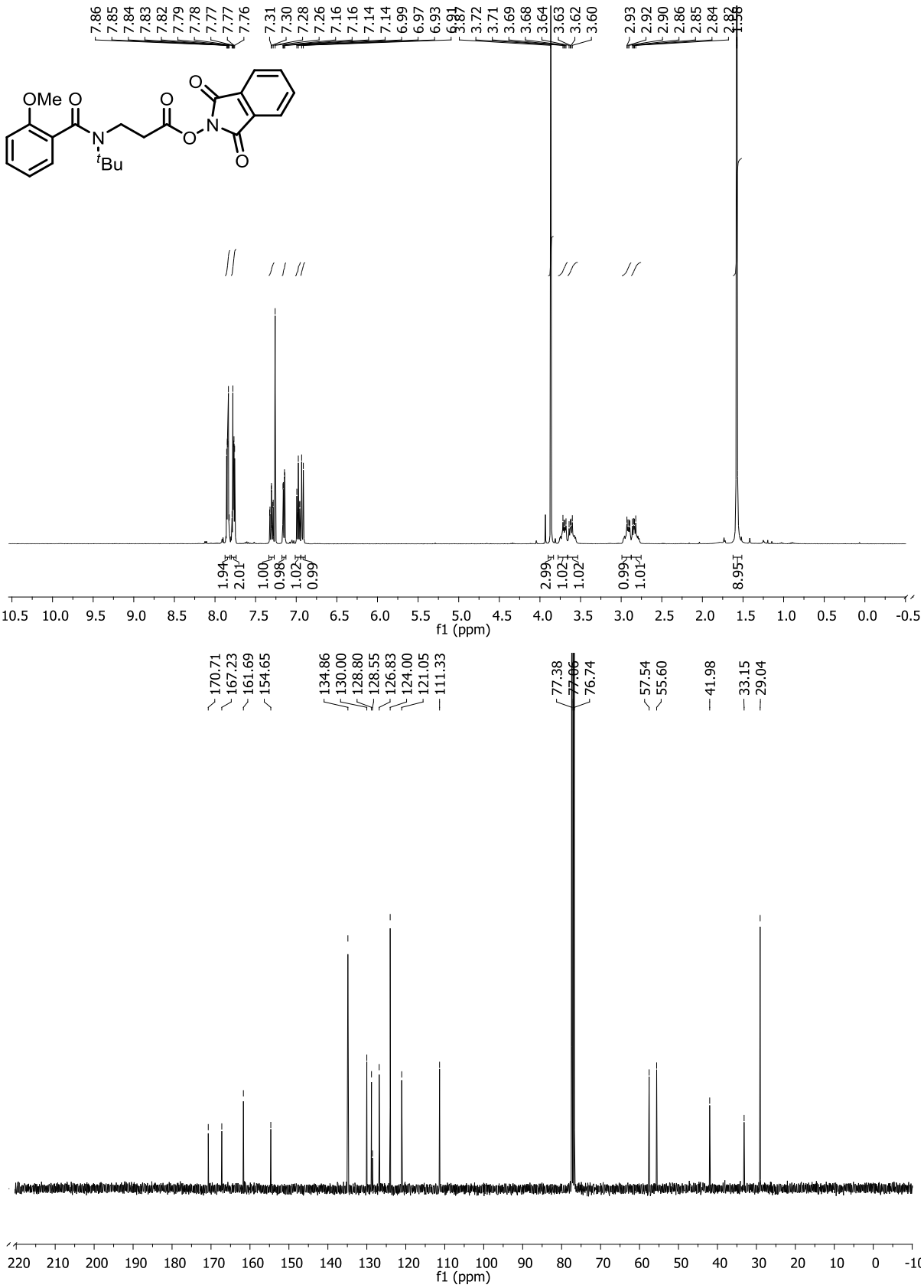
1,3-dioxoisoindolin-2-yl 3-(N-tert-butyl-4-methoxybenzamido)propanoate (74/77a).



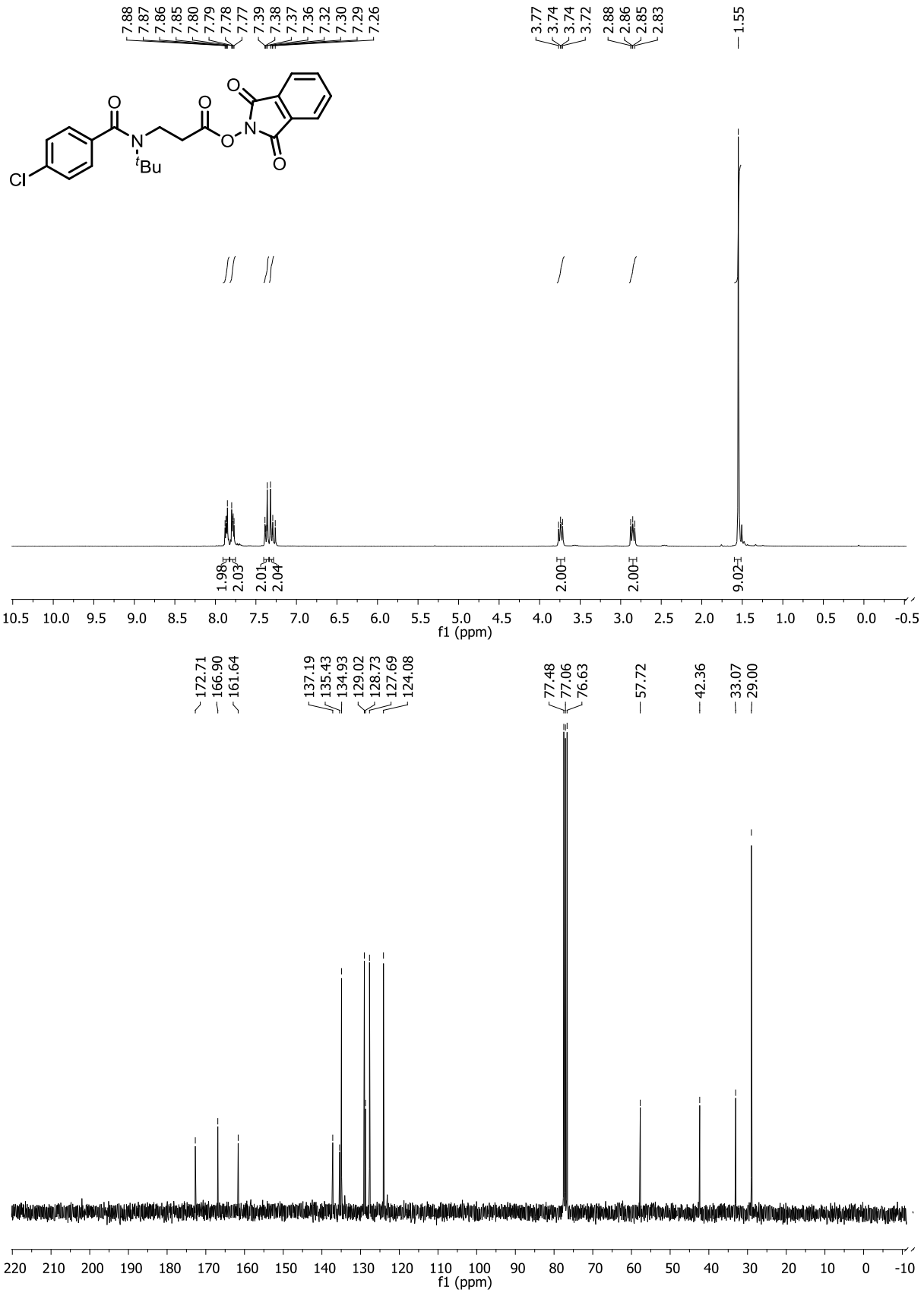
1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-3-methoxybenzamido)propanoate (77b).



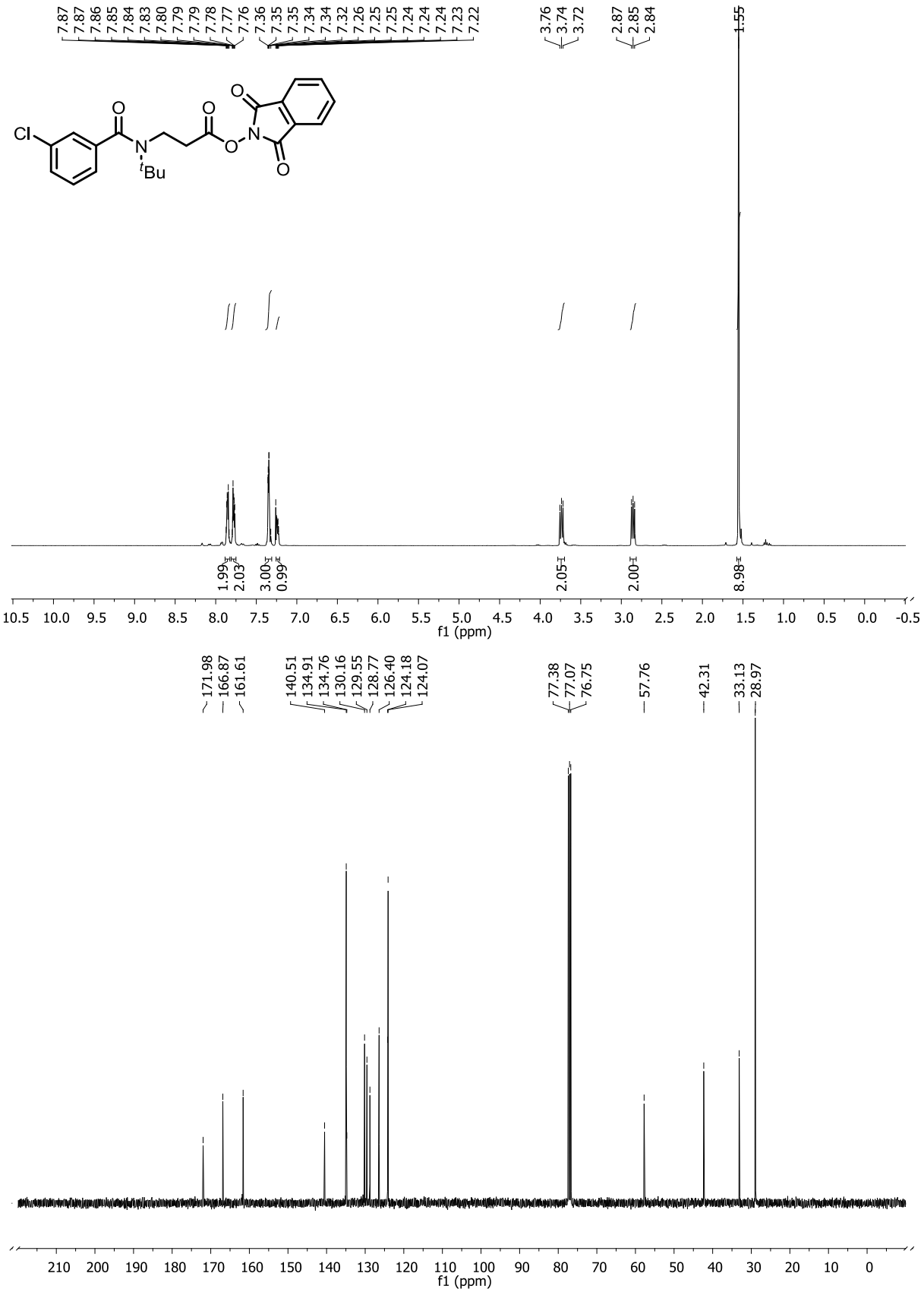
1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-2-methoxybenzamido)propanoate (77c).



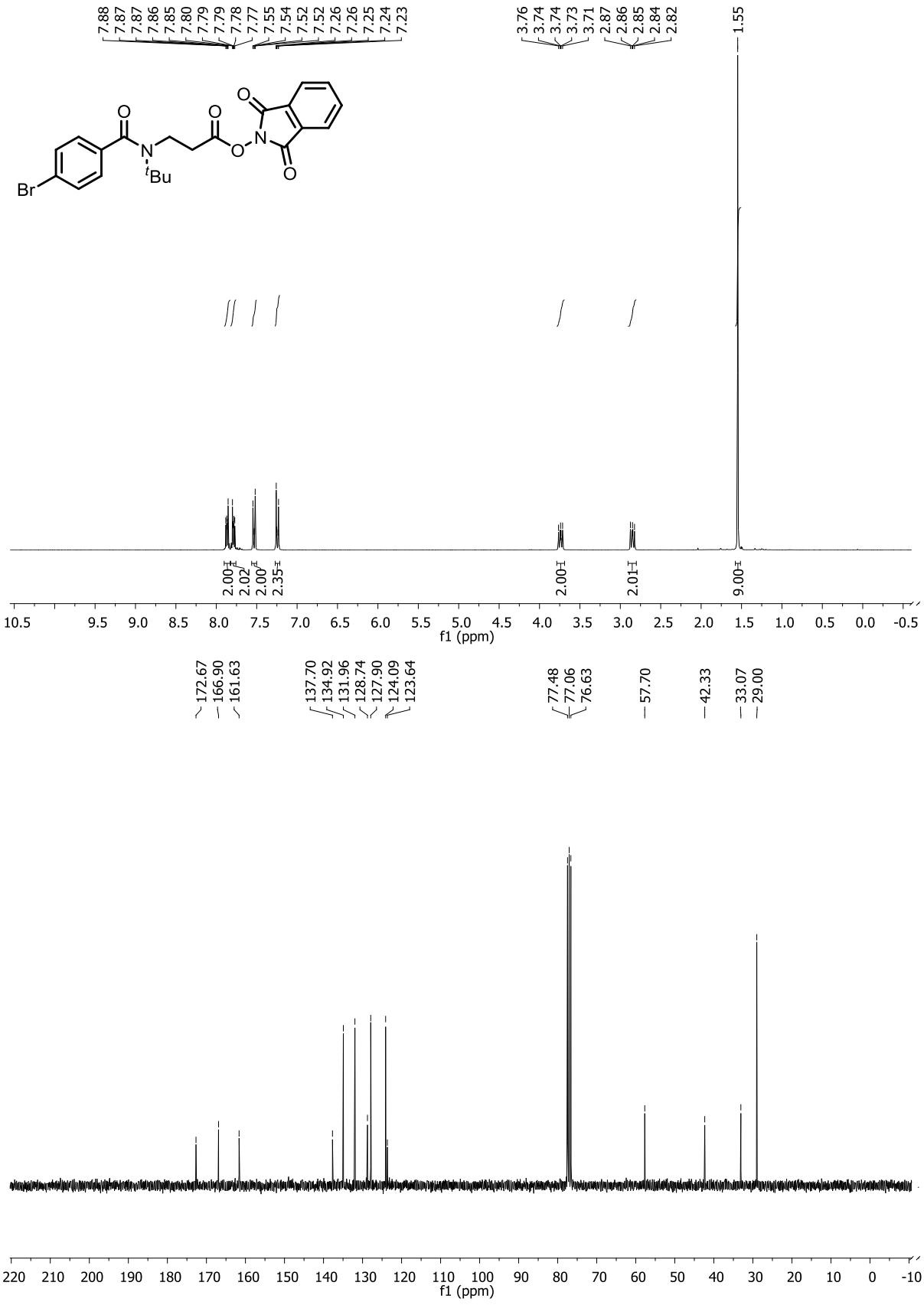
1,3-dioxoisoindolin-2-yl 3-(N-*tert*-butyl-4-chlorobenzamido)propanoate (77d).



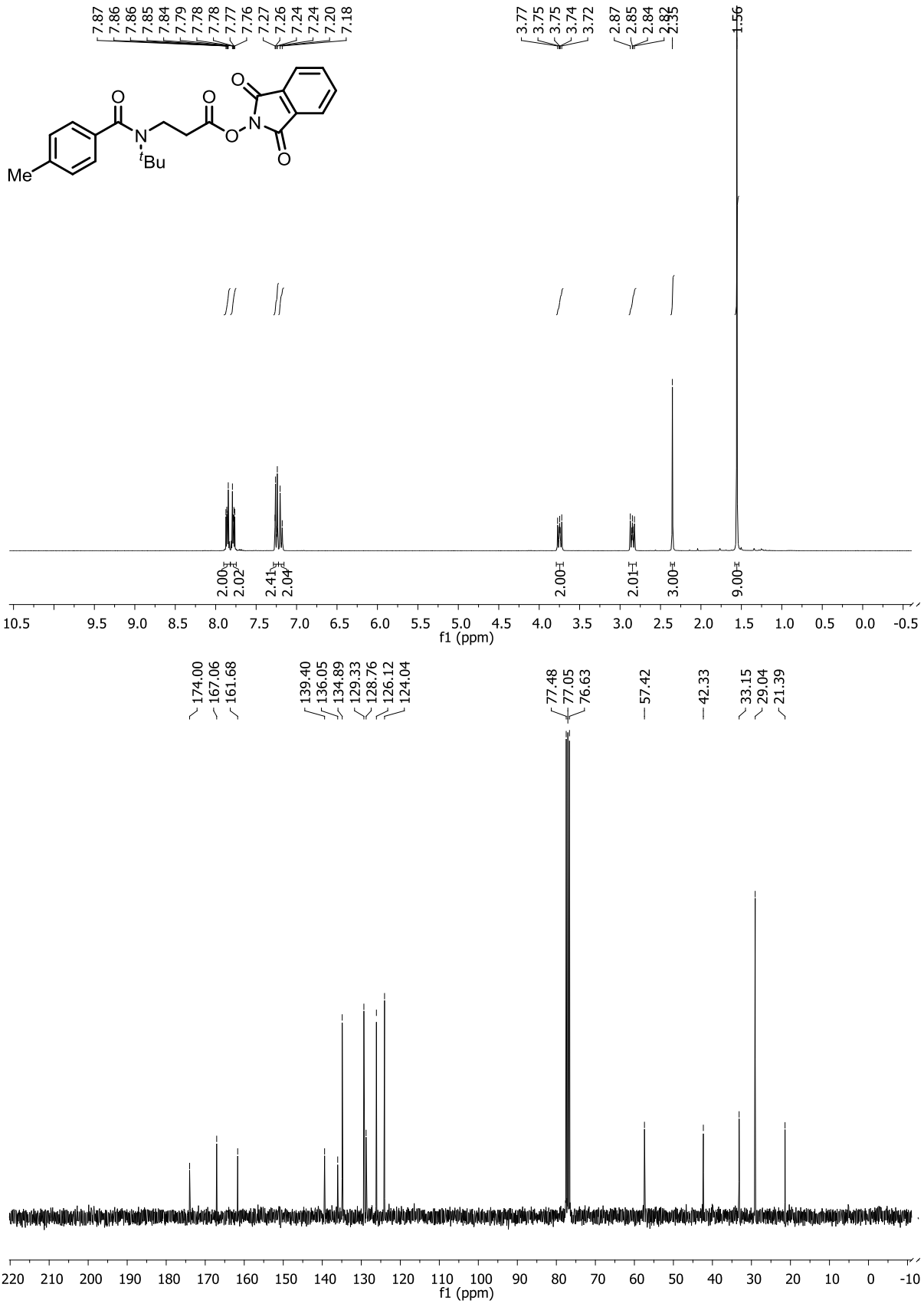
1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-3-chlorobenzamido)propanoate (77e).



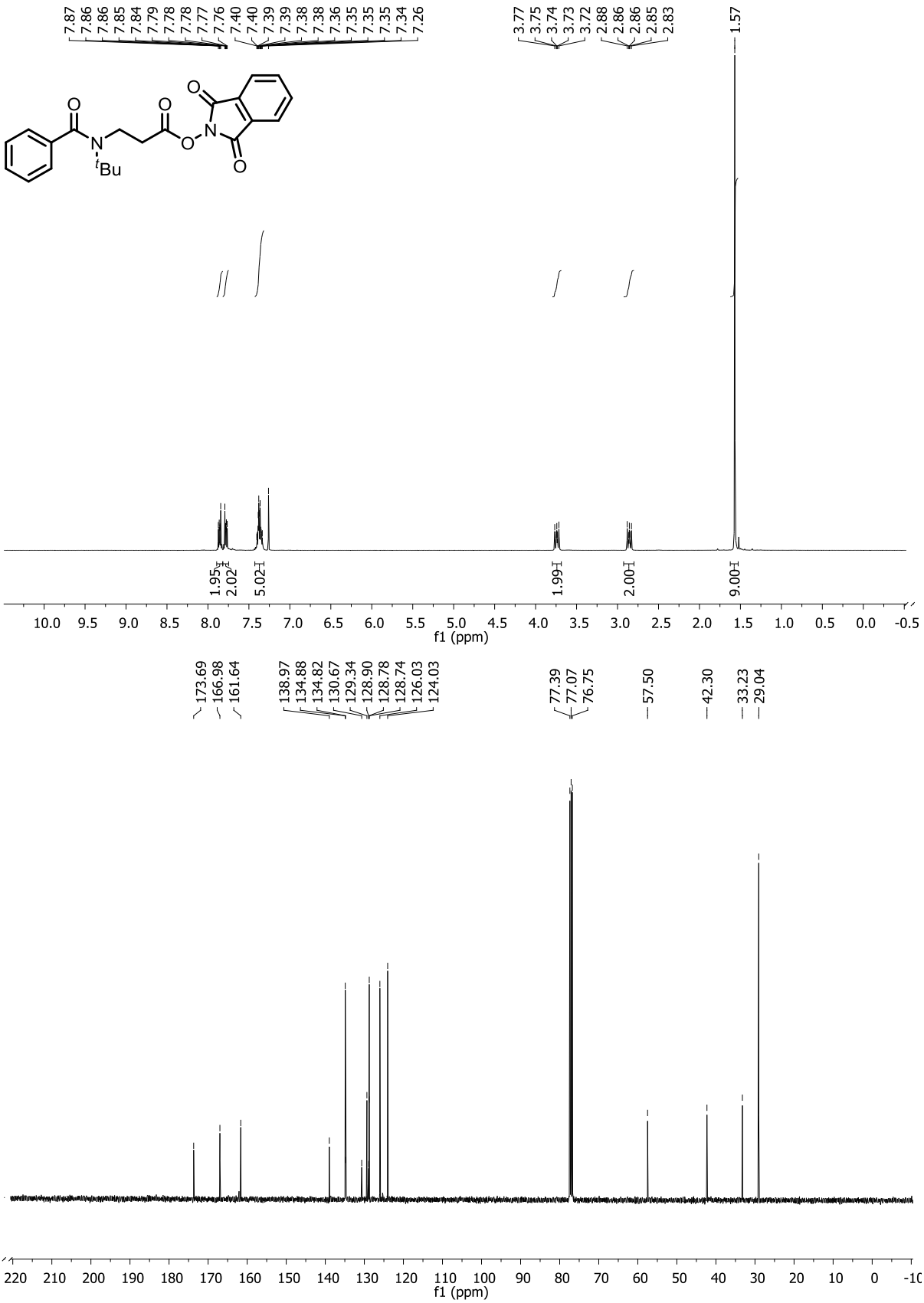
1,3-dioxoisoindolin-2-yl 3-(4-bromo-N-tert-butylbenzamido)propanoate (77f).



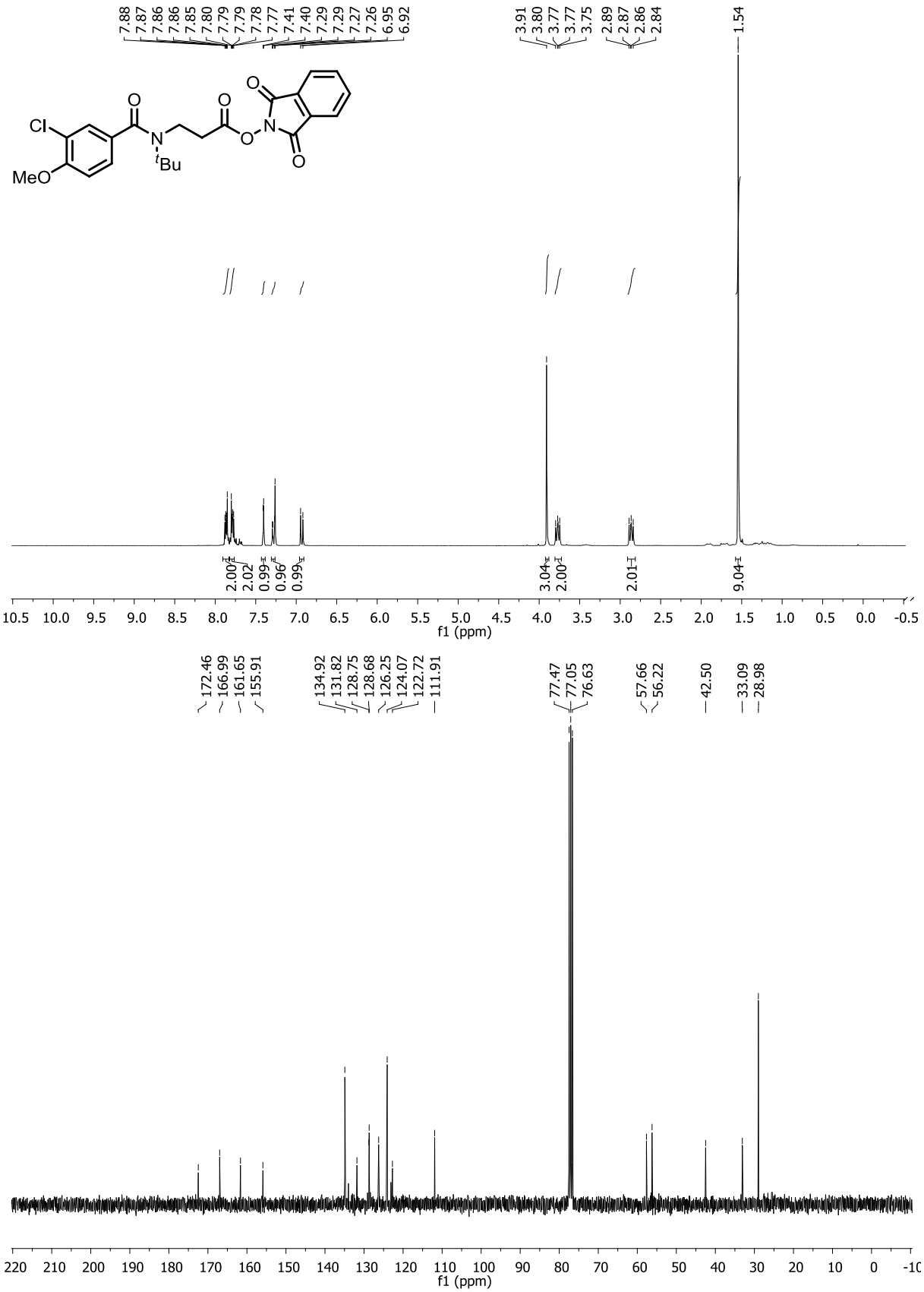
1,3-dioxoisoindolin-2-yl 3-(N-*tert*-butyl-4-methylbenzamido)propanoate (77g).



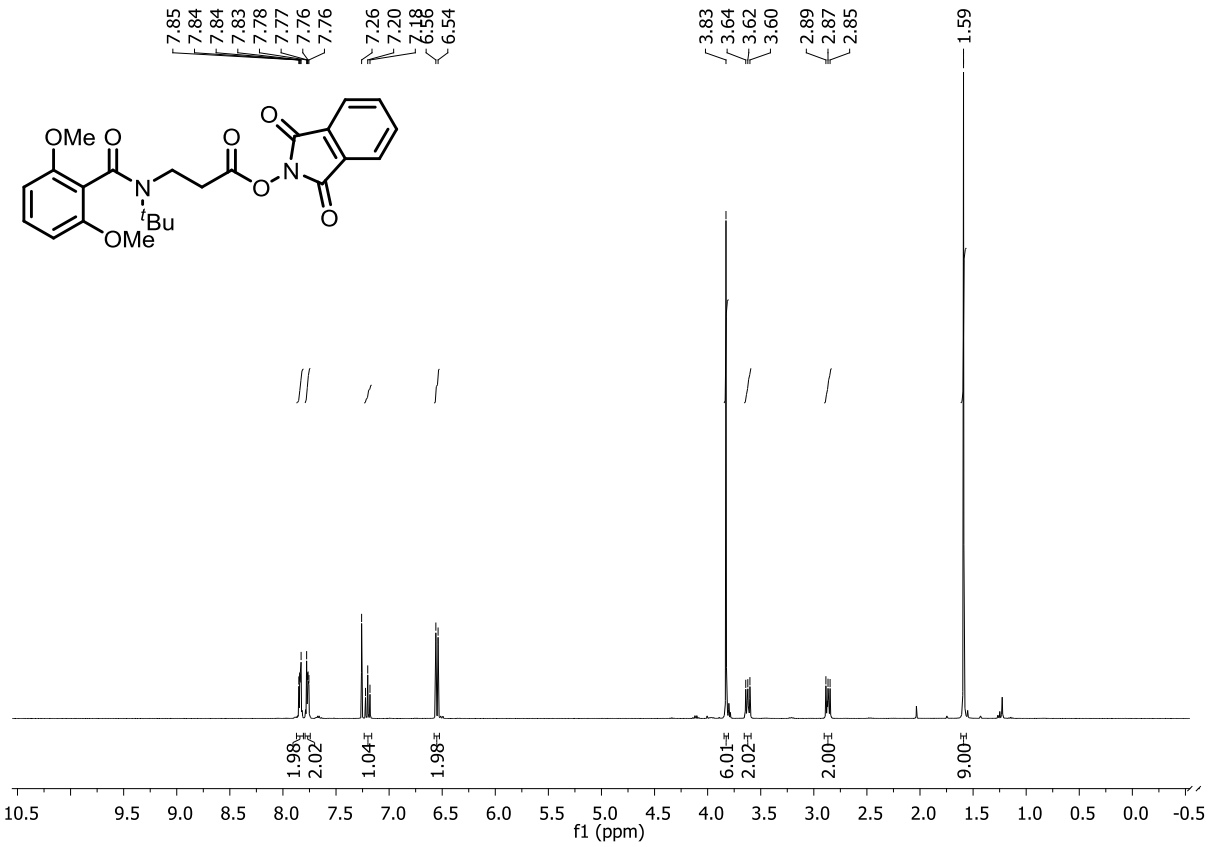
1,3-dioxoisoindolin-2-yl 3-(N-tert-butylbenzamido)propanoate (77h).

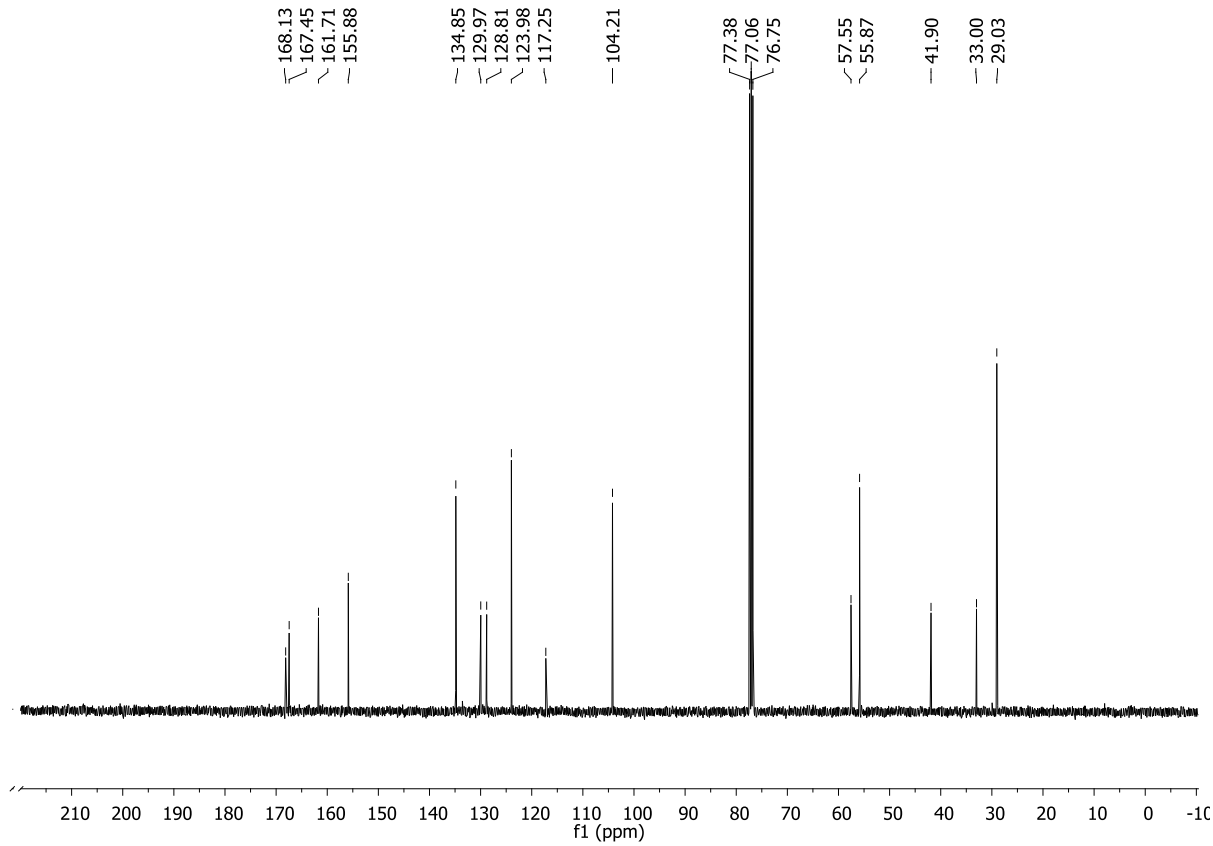


1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-3-chloro-4-methoxybenzamido)propanoate (77i).

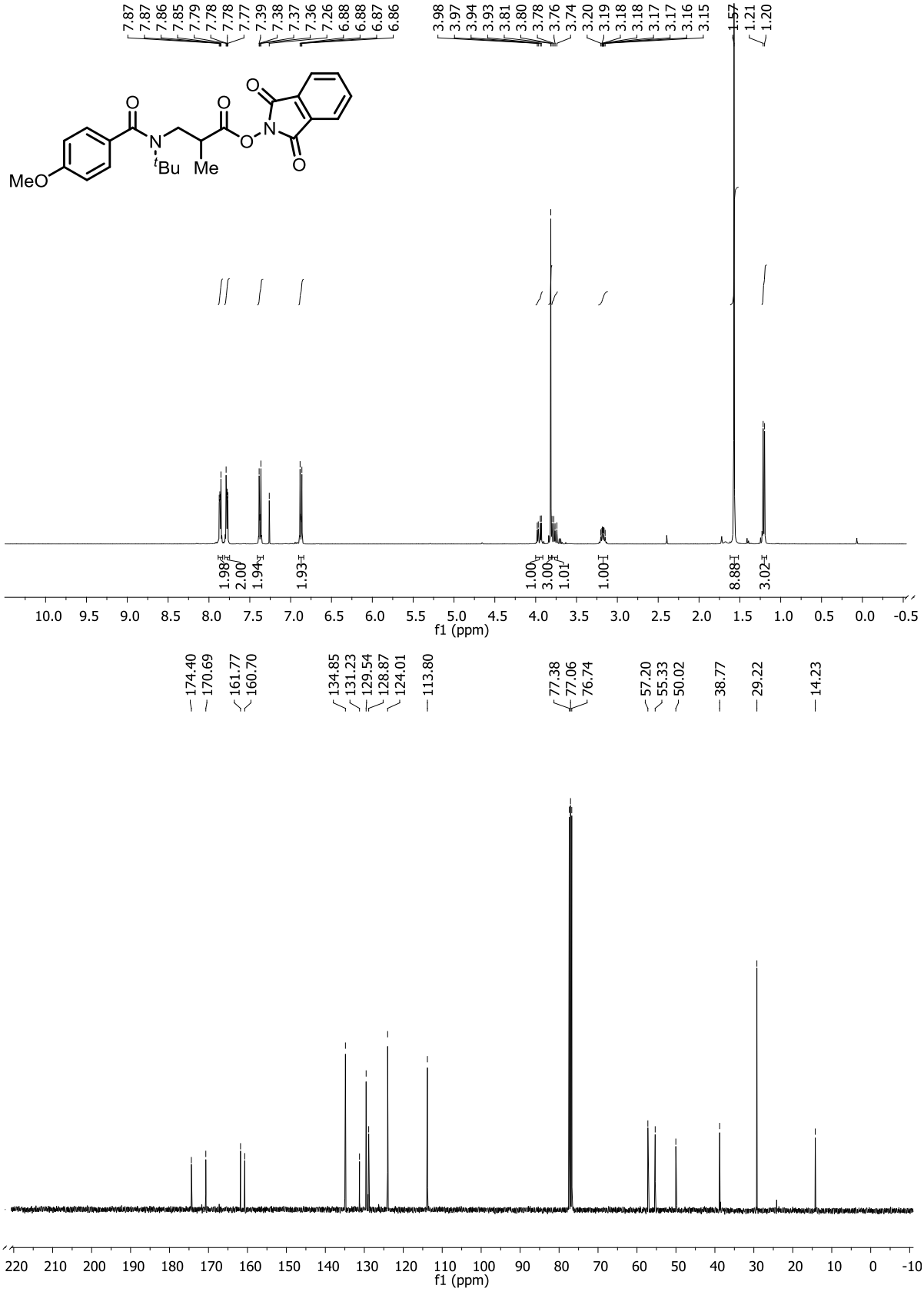


1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-2,6-dimethoxybenzamido)propanoate (77j).

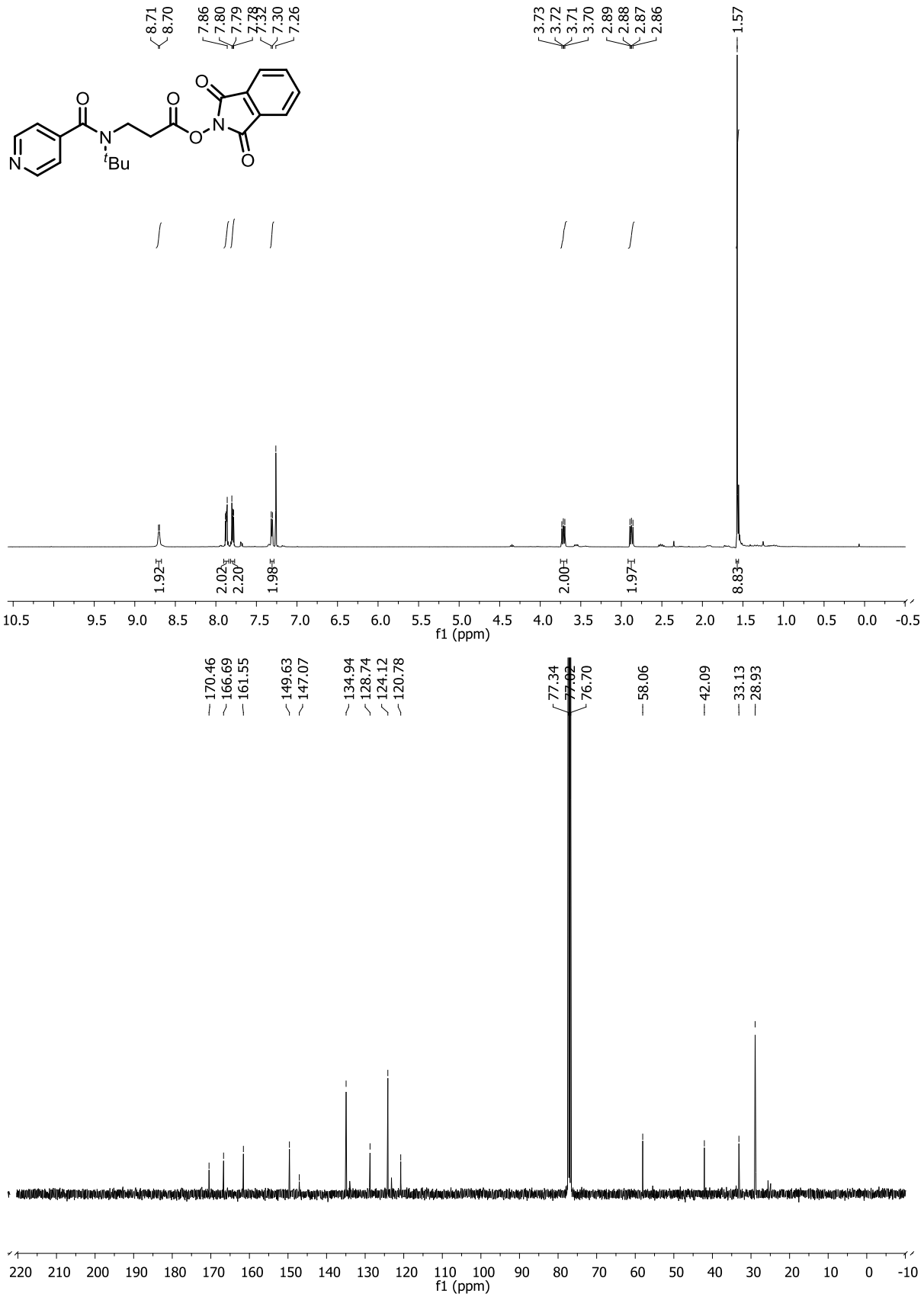




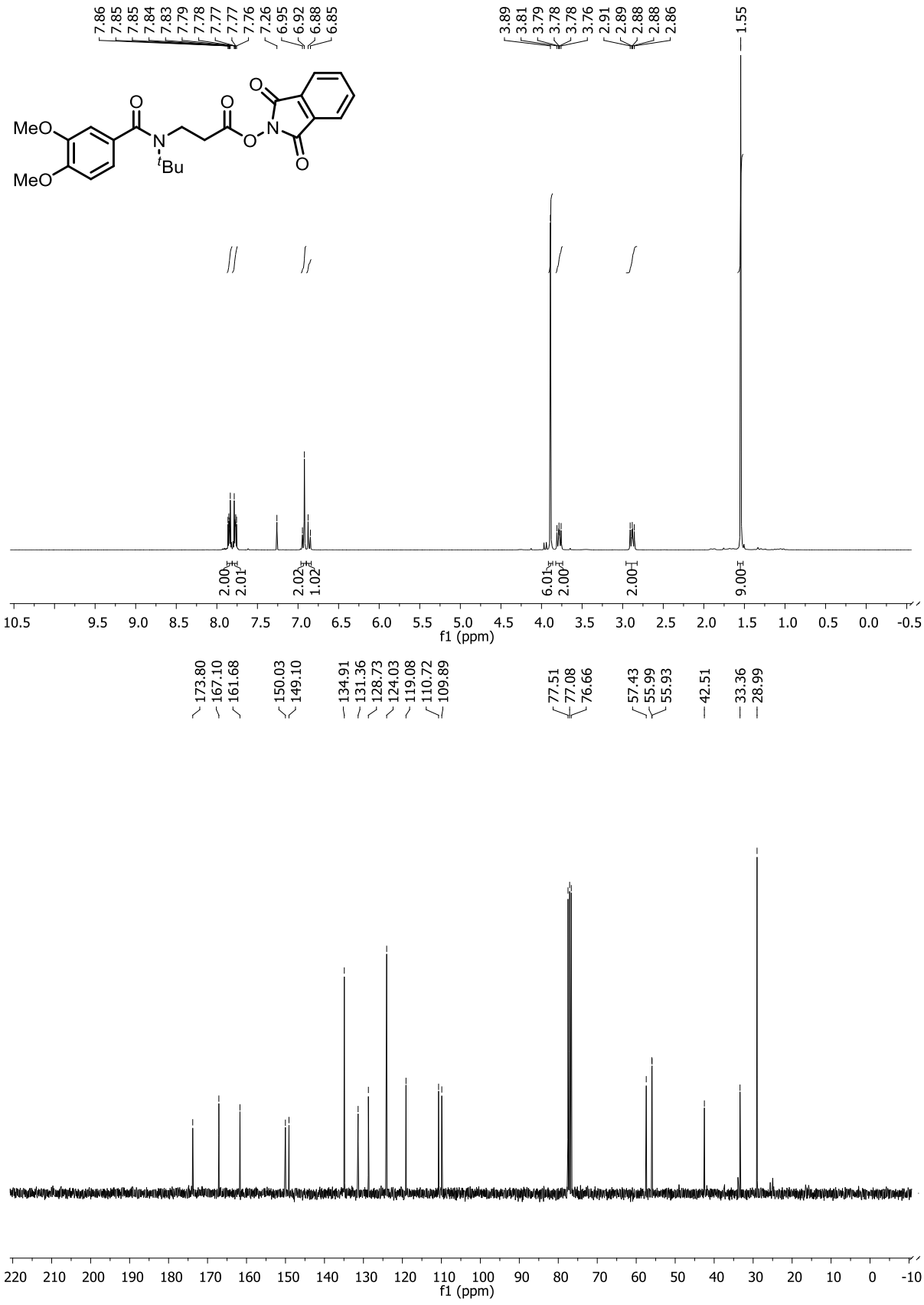
1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-4-methoxybenzamido)-2-methylpropanoate (77k).



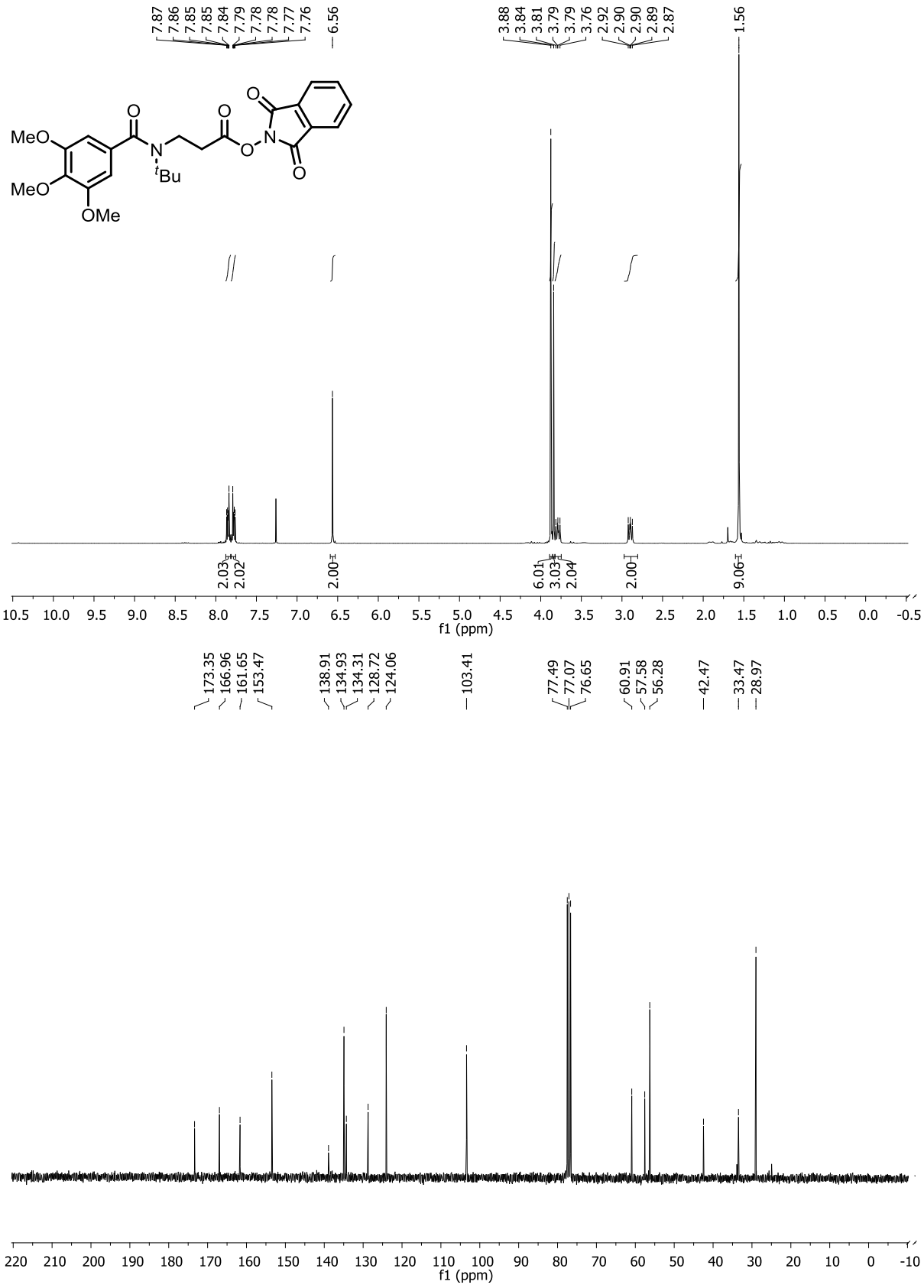
1,3-Dioxoisoindolin-2-yl 3-(N-tert-butylisonicotinamido)propanoate (77l).



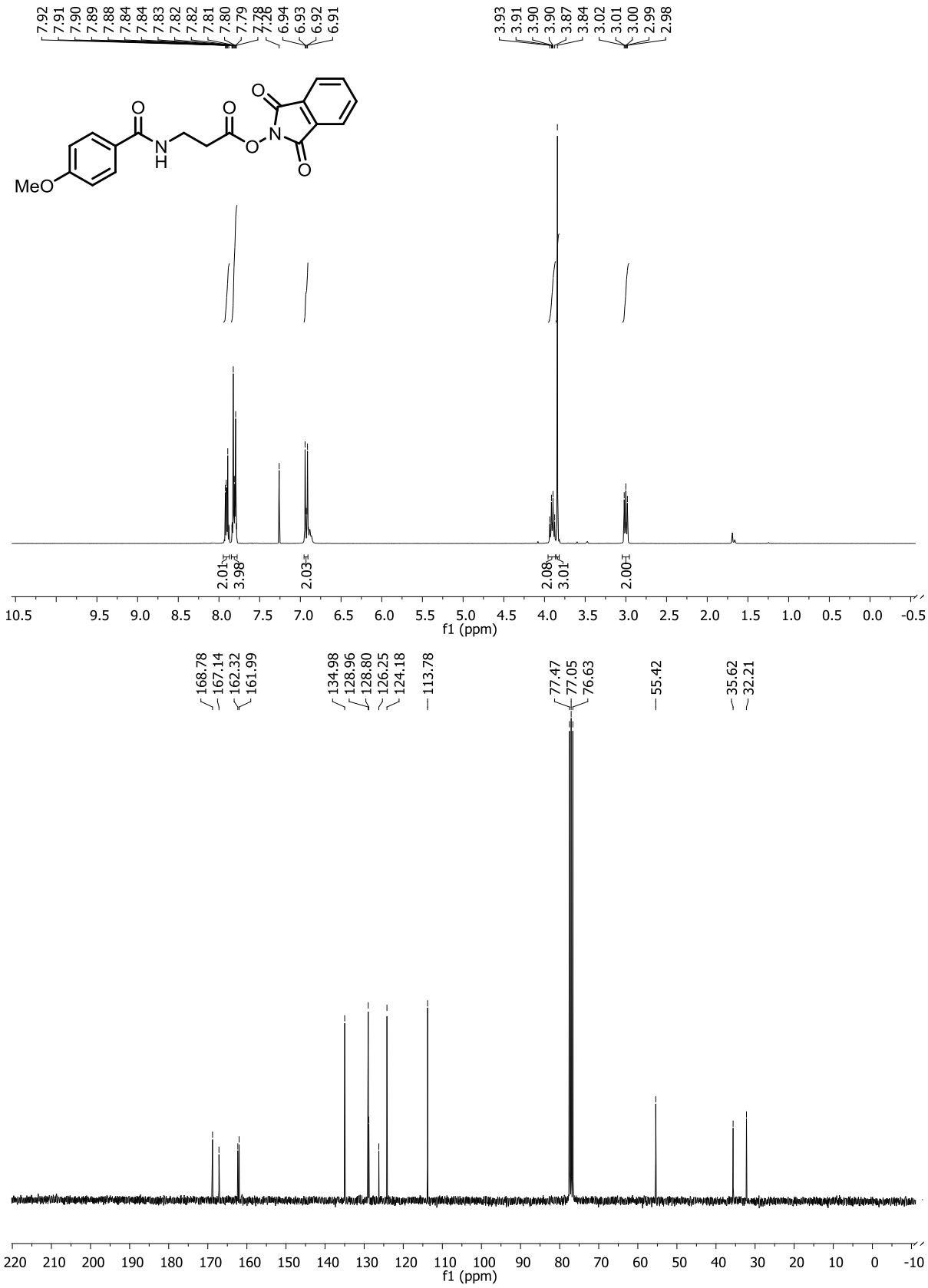
1,3-dioxoisoindolin-2-yl 3-(N-*tert*-butyl-3,4-dimethoxybenzamido)propanoate (77m).



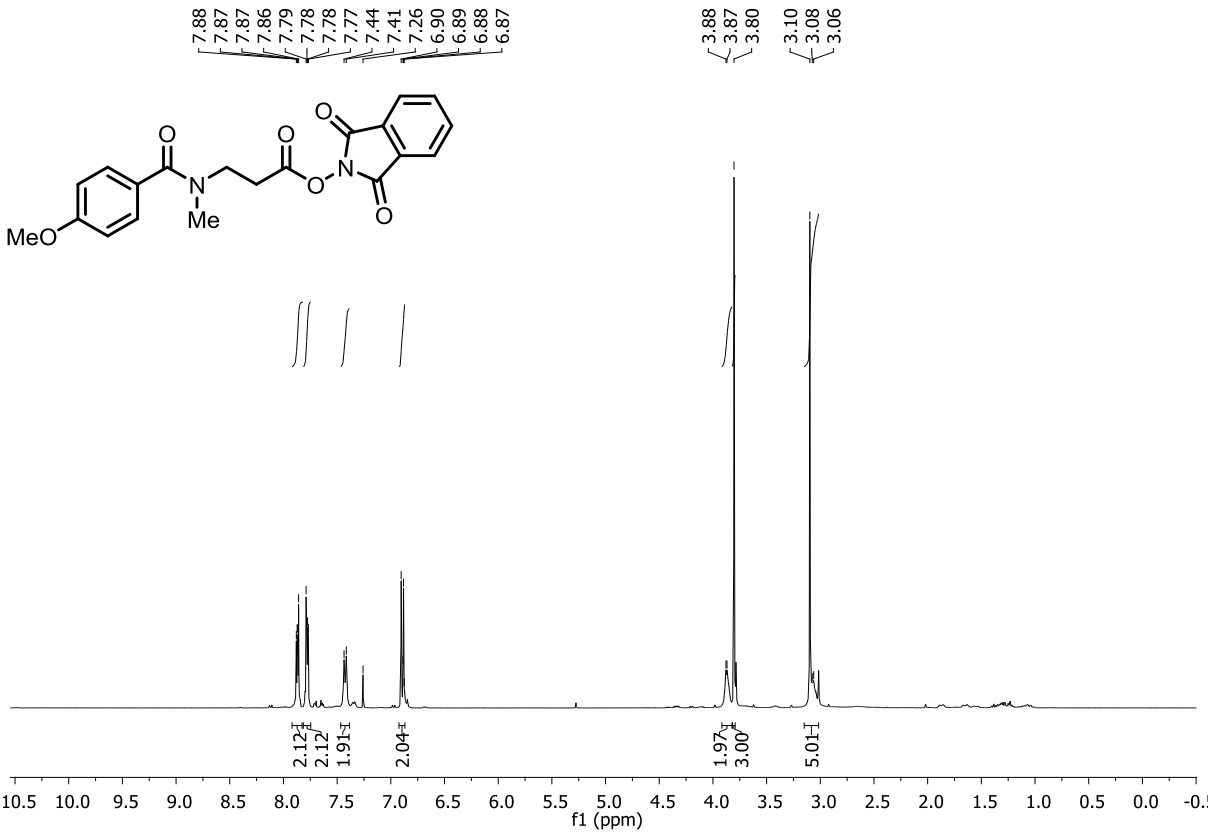
1,3-Dioxoisoindolin-2-yl 3-(N-*tert*-butyl-3,4,5-trimethoxybenzamido)propanoate (77n).

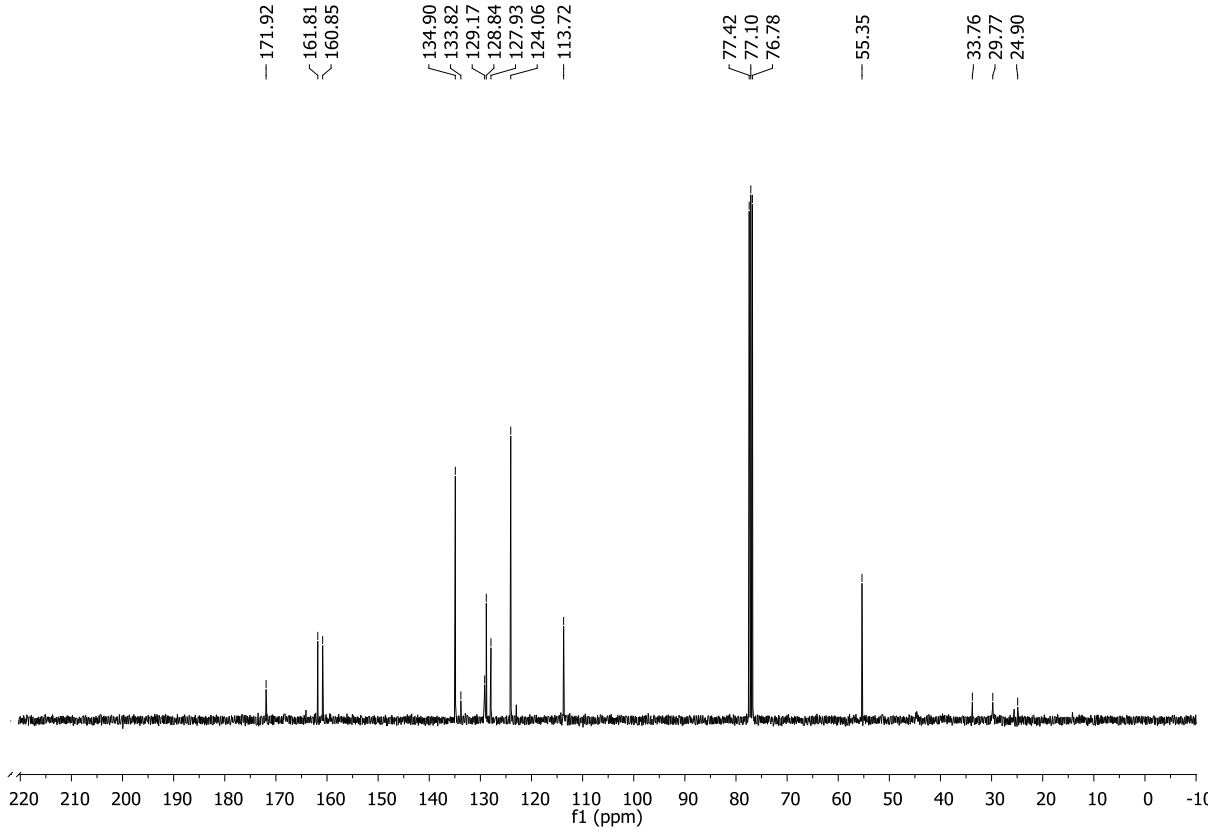


1,3-Dioxoisoindolin-2-yl 3-(4-methoxybenzamido)propanoate (81).

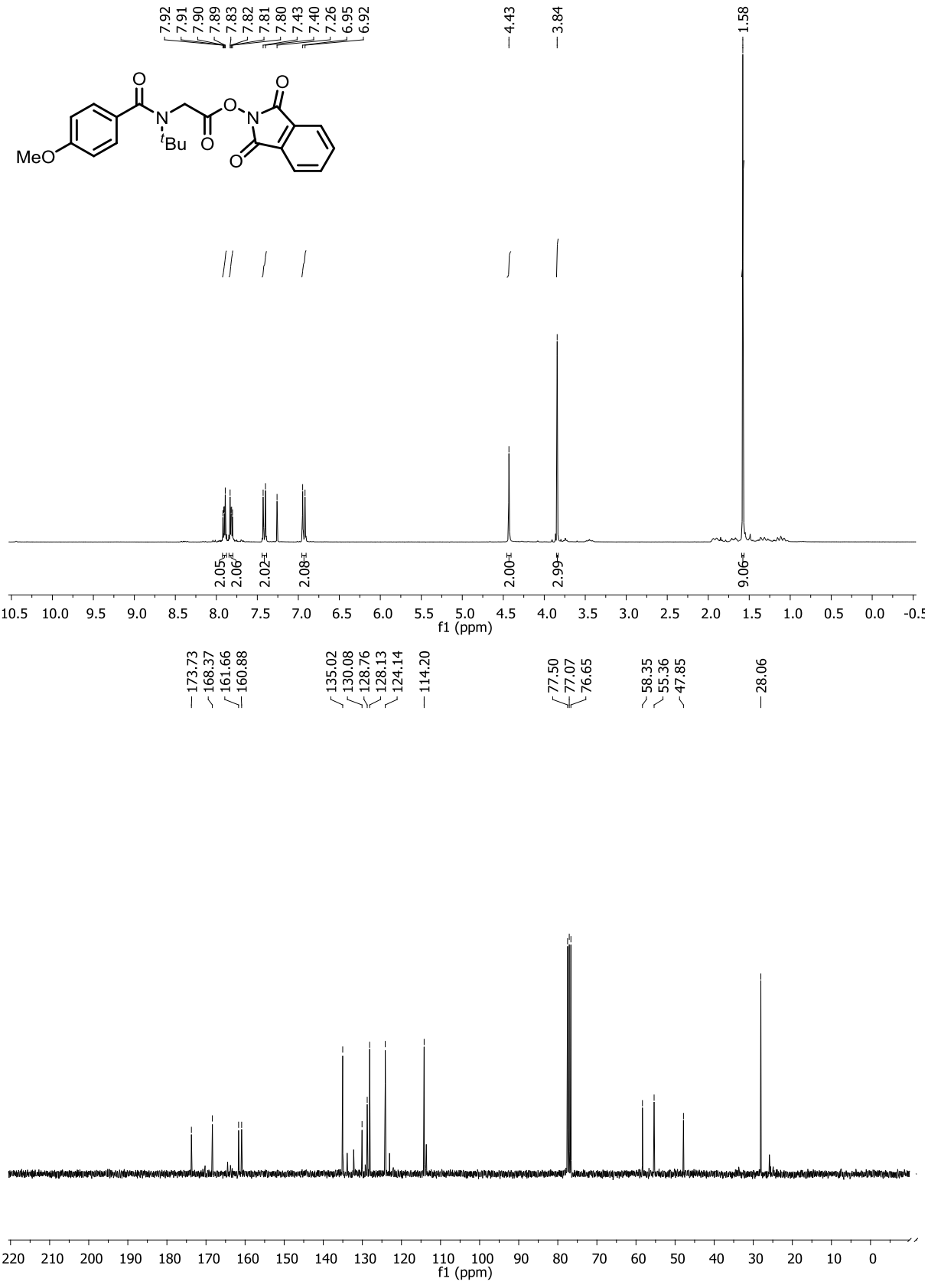


1,3-Dioxoisoindolin-2-yl 3-(4-methoxy-N-methylbenzamido)propanoate (83).

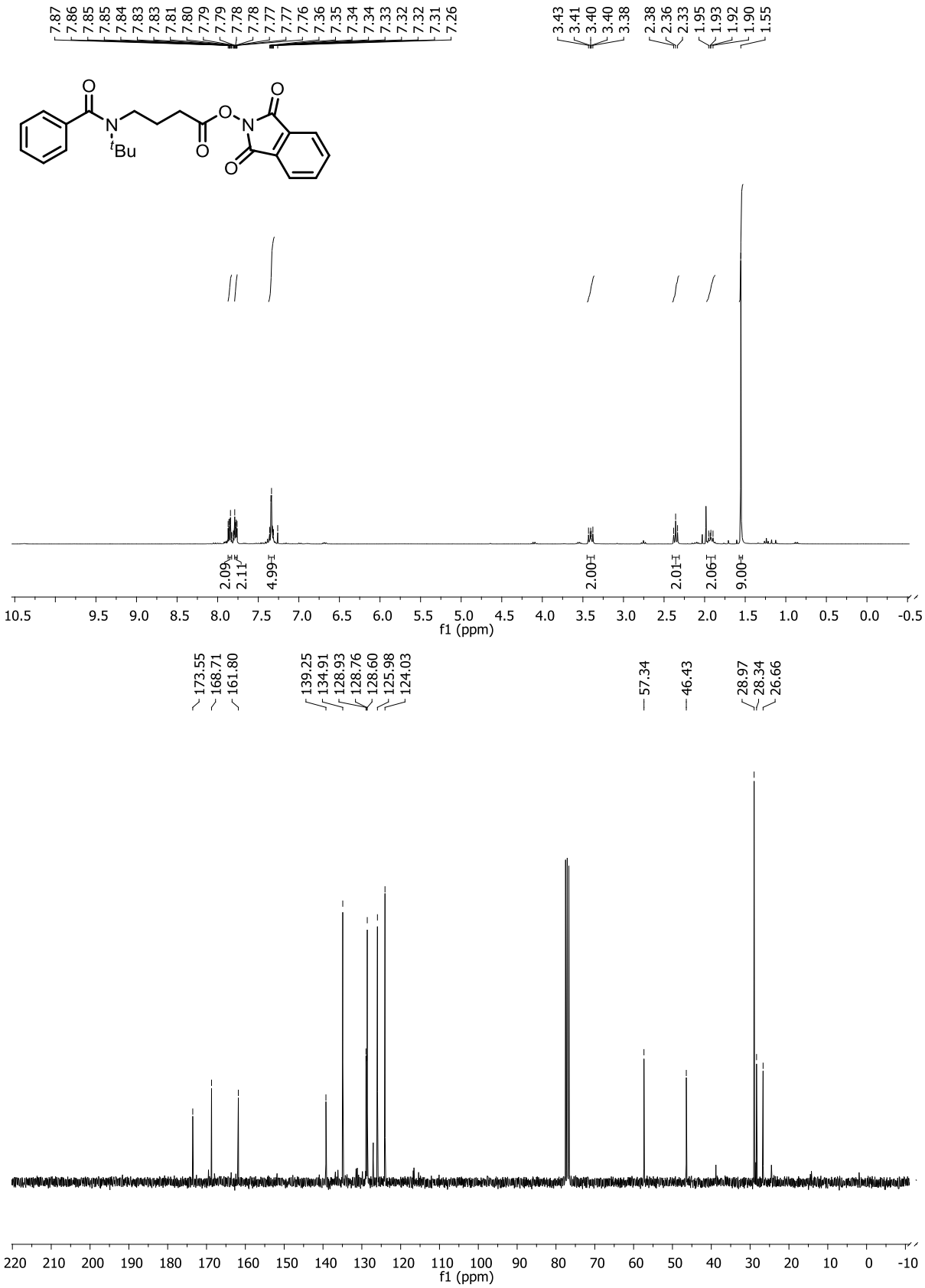




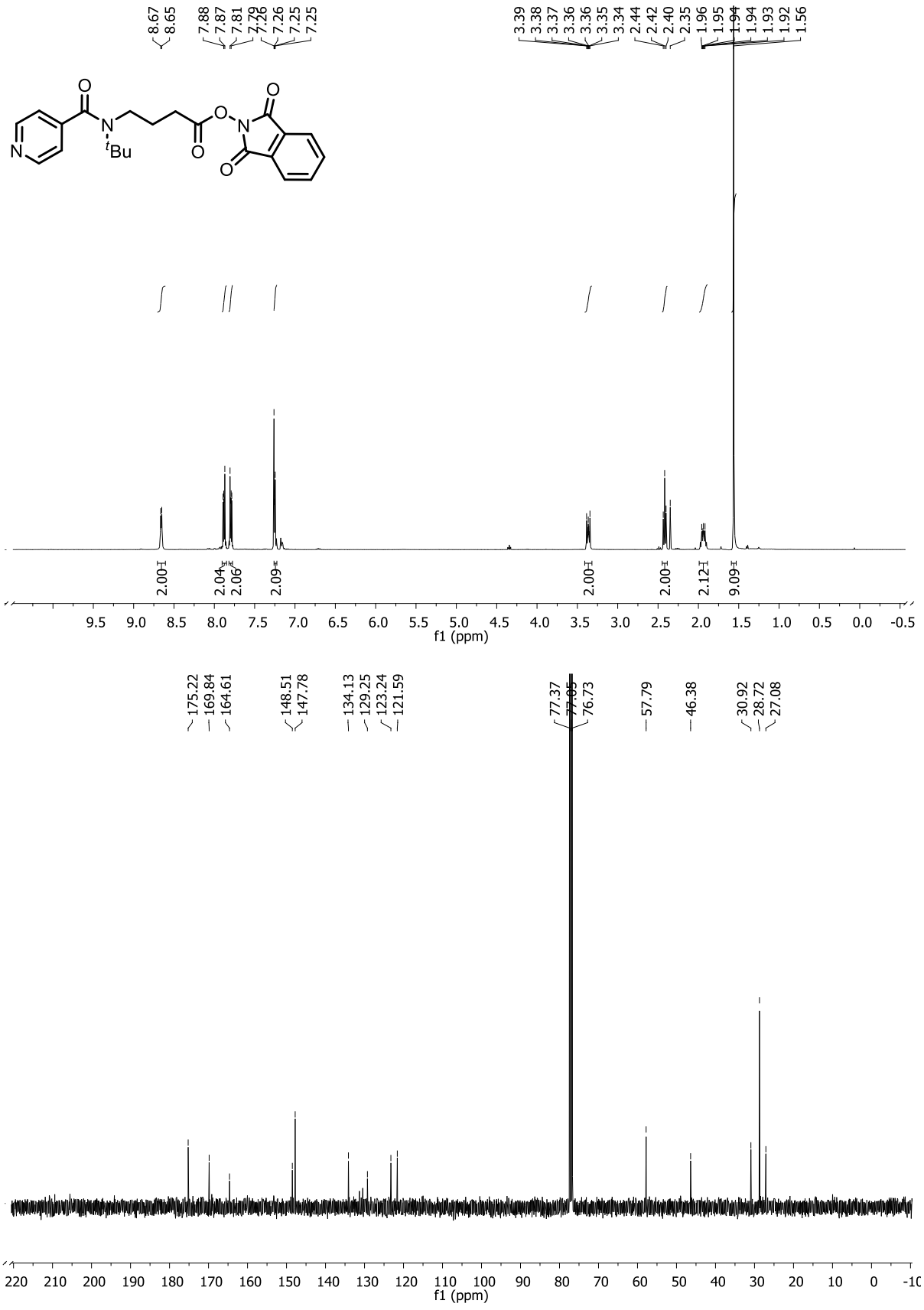
1,3-Dioxoisoindolin-2-yl 2-(N-*tert*-butyl-4-methoxybenzamido)acetate (97).



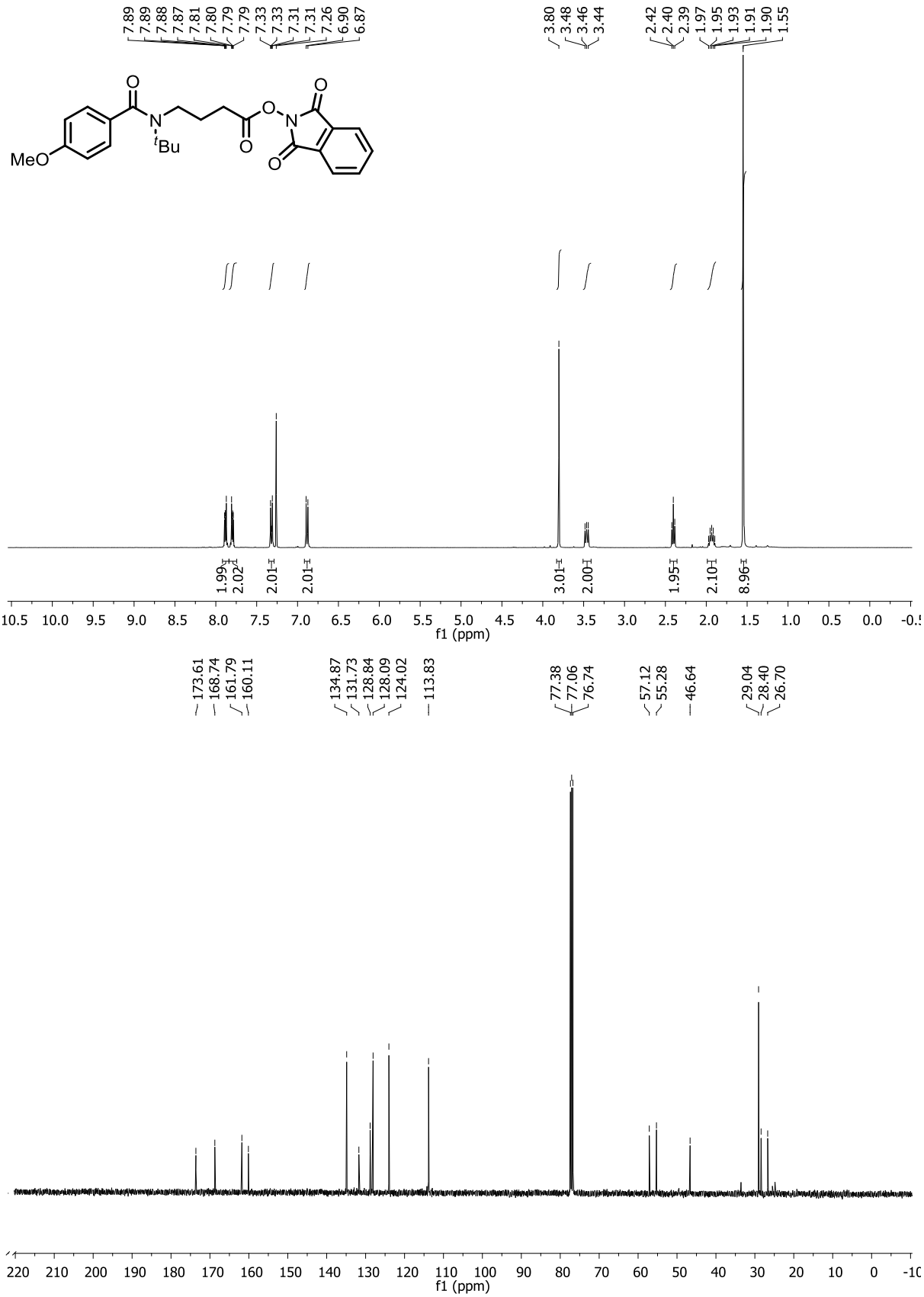
1,3-dioxoisoindolin-2-yl 4-(N-tert-butylbenzamido)butanoate (102a).



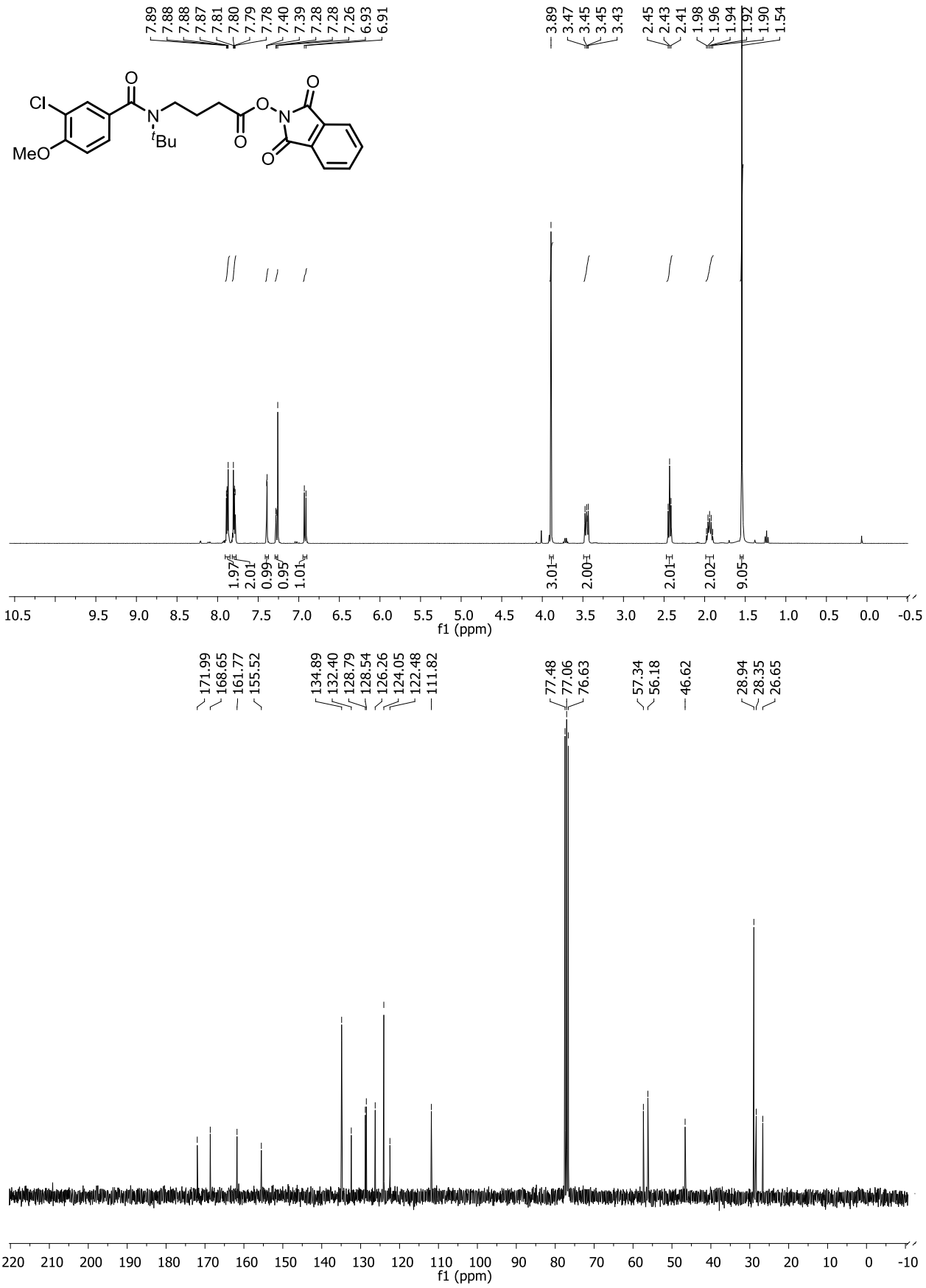
1,3-dioxoisoindolin-2-yl 4-(N-*tert*-butylisonicotinamido)butanoate (102b).



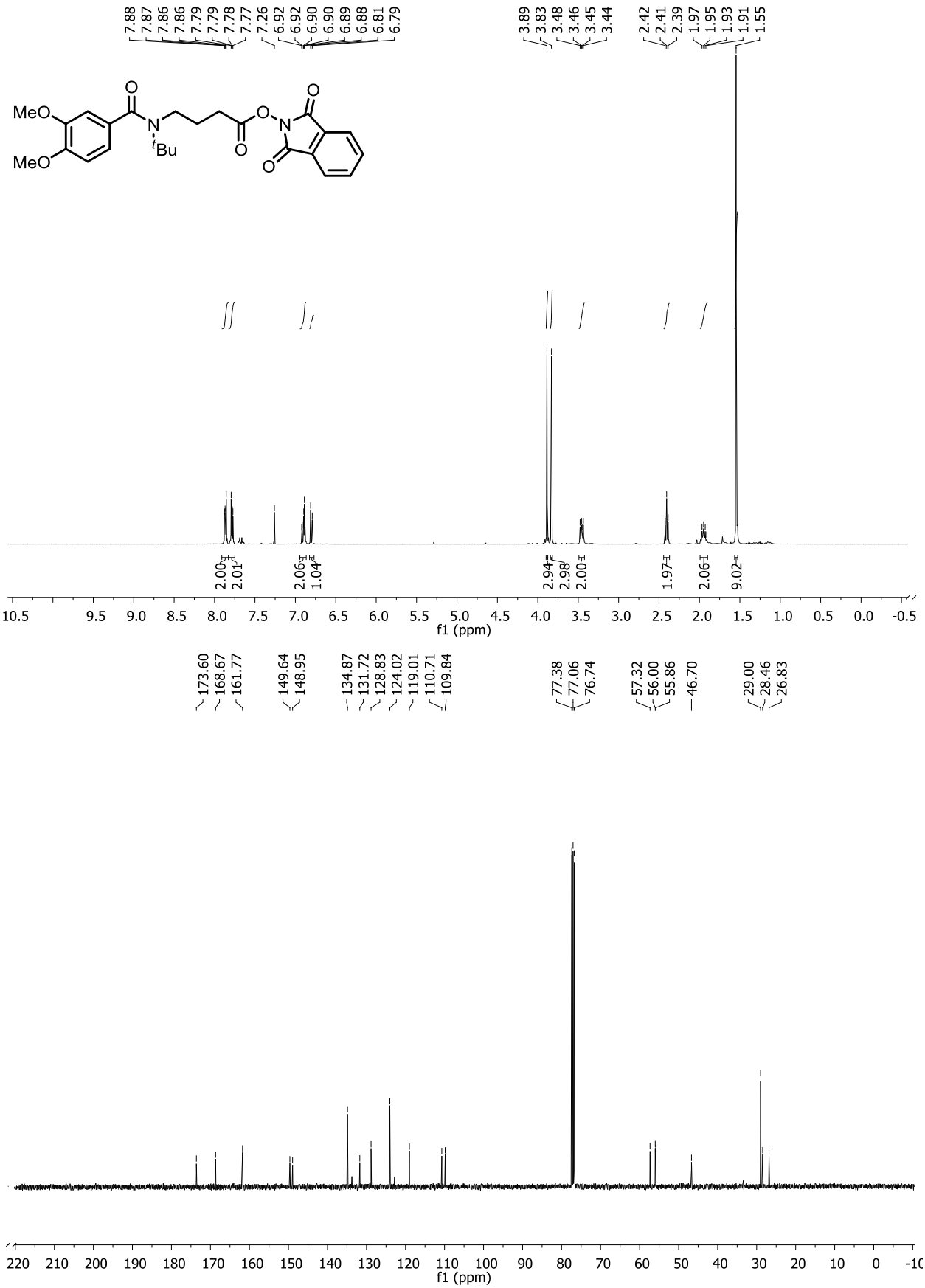
1,3-dioxoisoindolin-2-yl 4-(N-*tert*-butyl-4-methoxybenzamido)butanoate (102c).



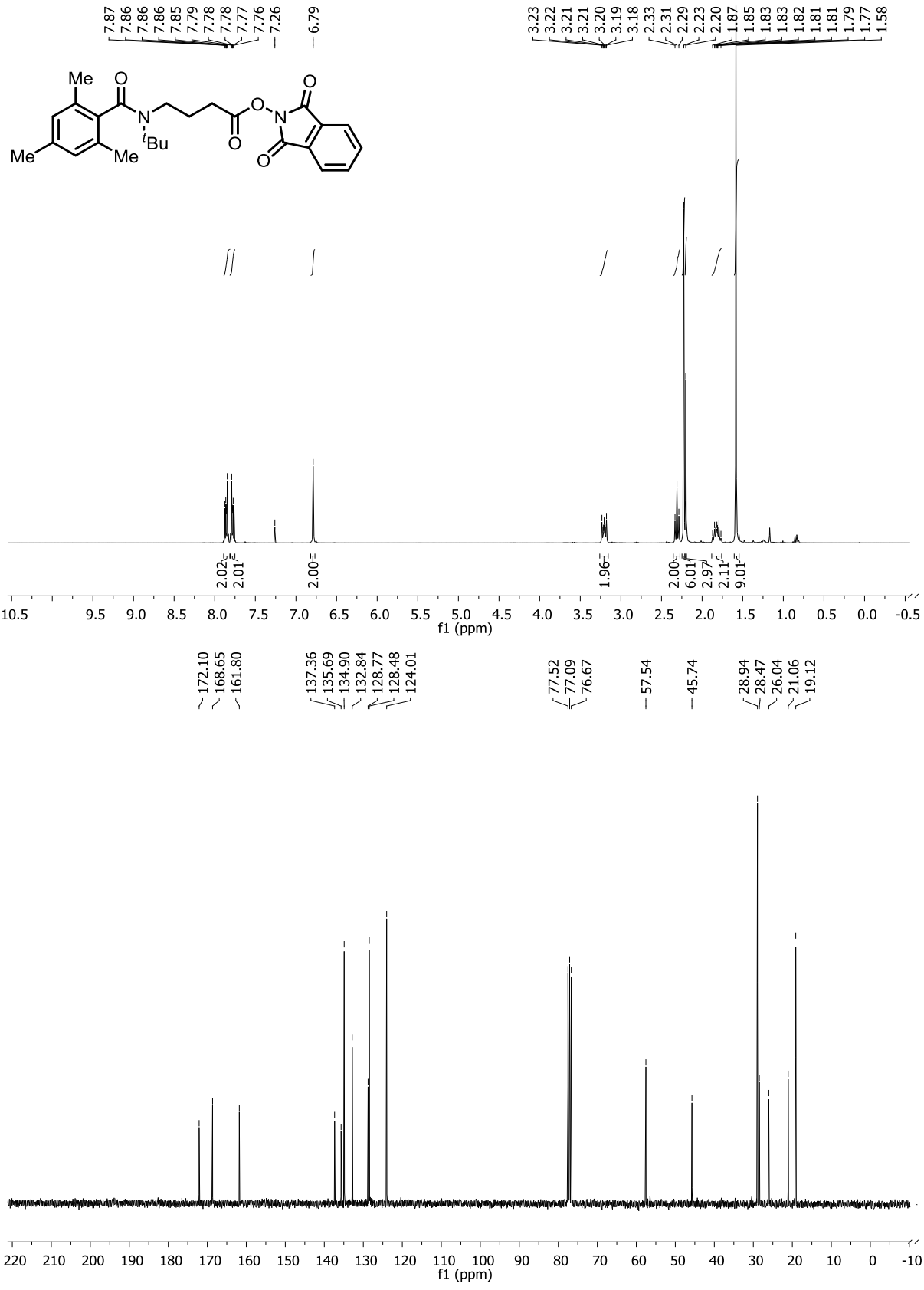
1,3-dioxoisoindolin-2-yl 4-(N-tert-butyl-3-chloro-4-methoxybenzamido)butanoate (102d)



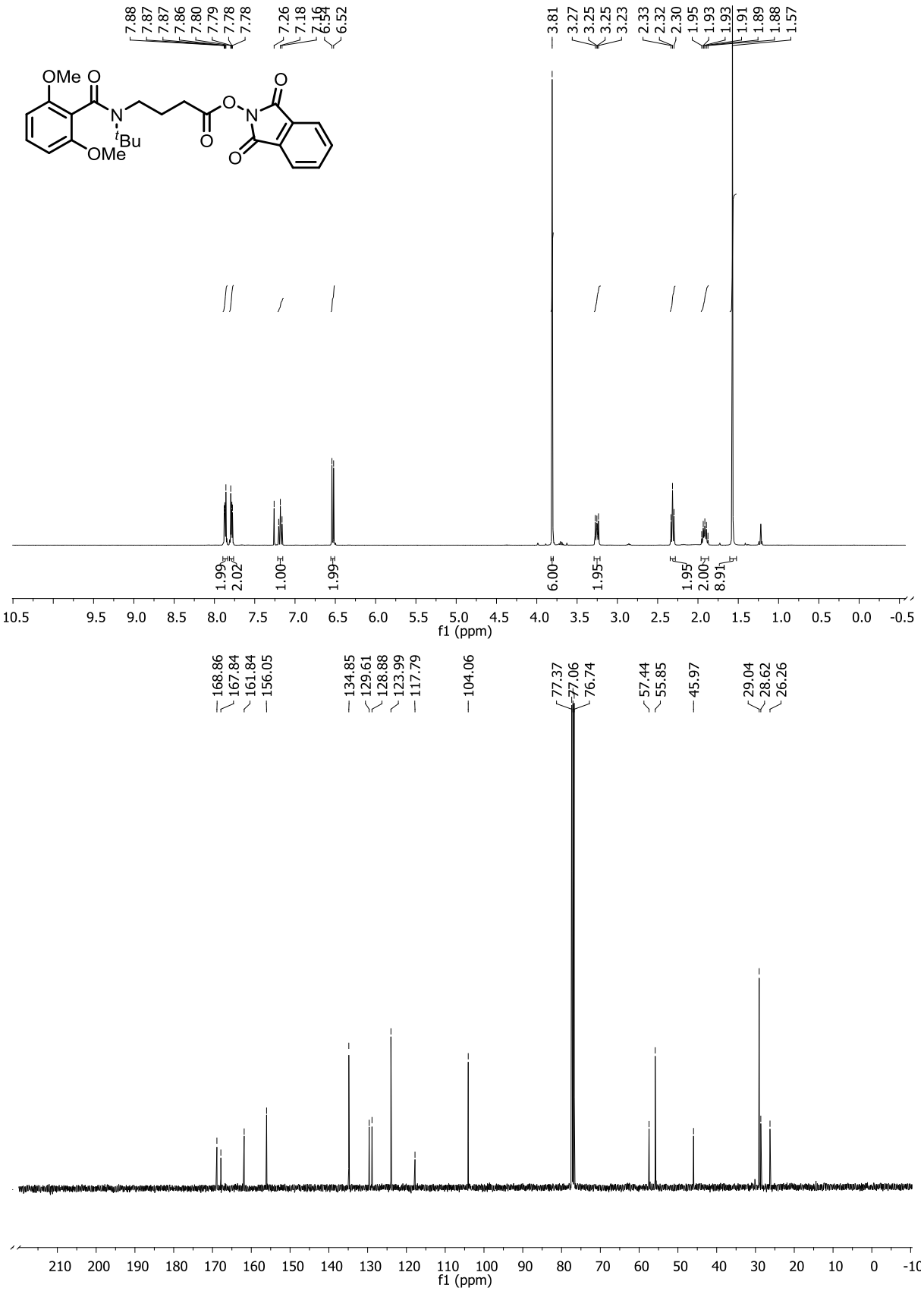
1,3-dioxoisoindolin-2-yl 4-(N-tert-butyl-3,4-dimethoxybenzamido)butanoate (102e).



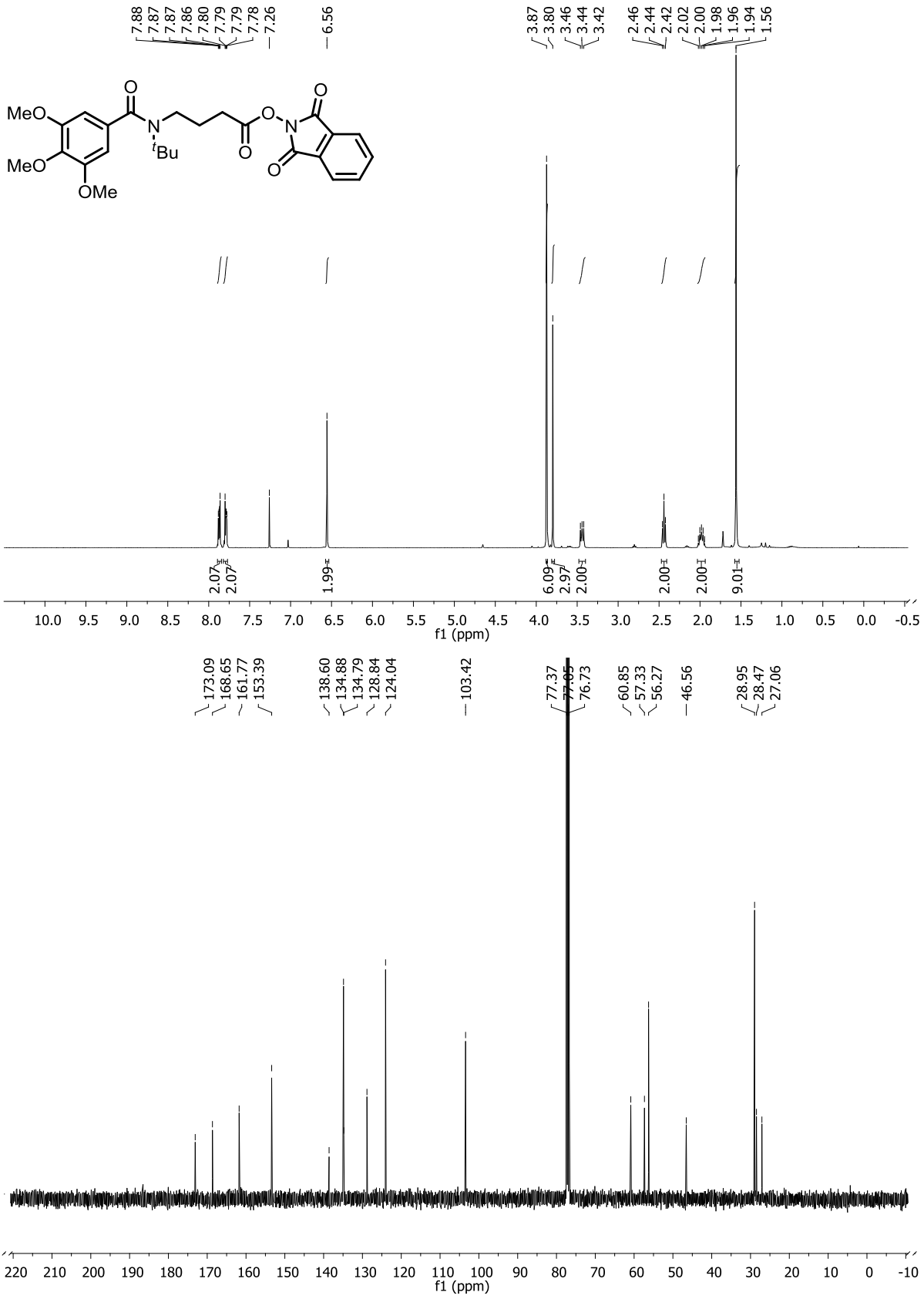
1,3-Dioxoisoindolin-2-yl 4-(N-tert-butyl-2,4,6-trimethylbenzamido)butanoate (102f).



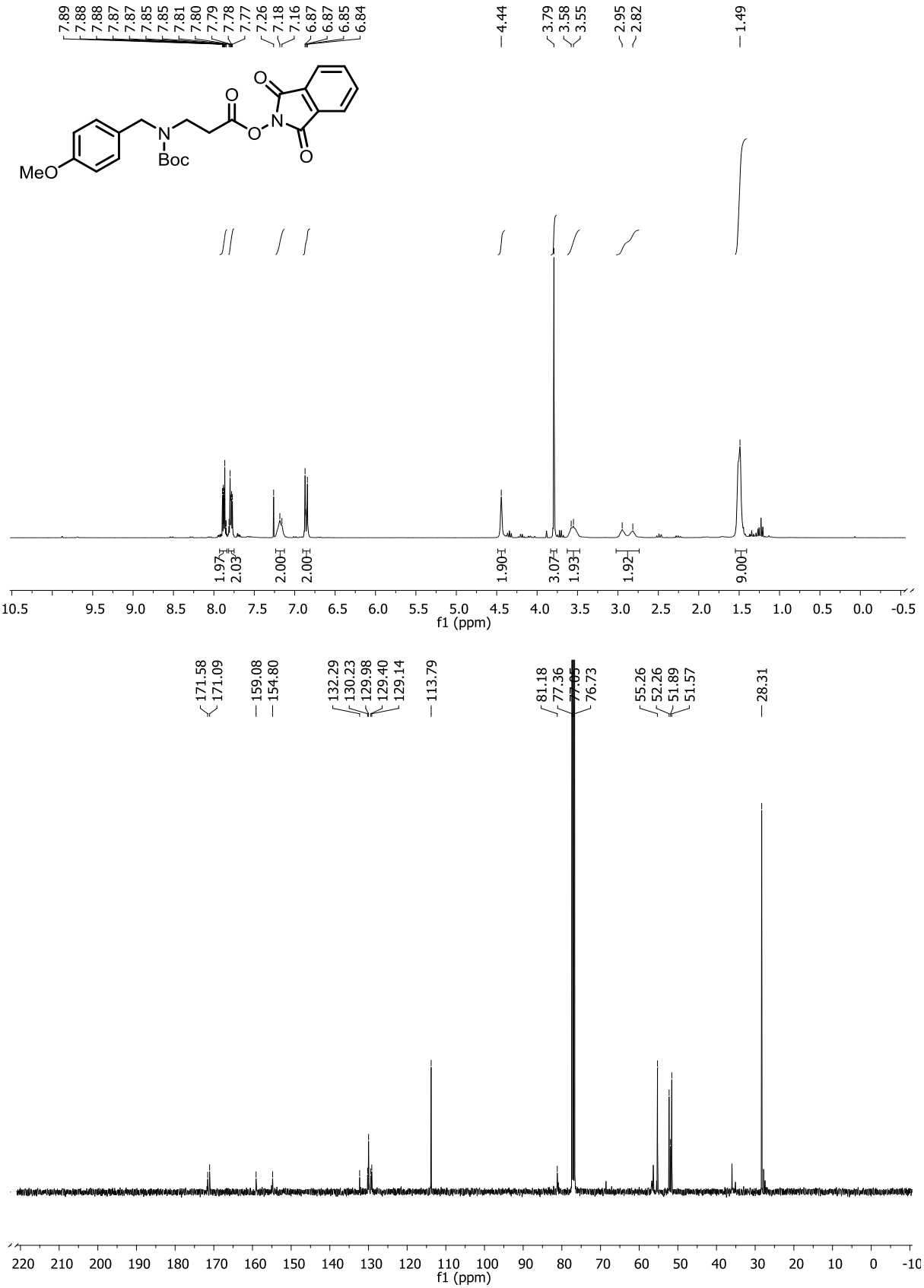
1,3-Dioxoisoindolin-2-yl 4-(N-*tert*-butyl-2,6-dimethoxybenzamido)butanoate (102g).



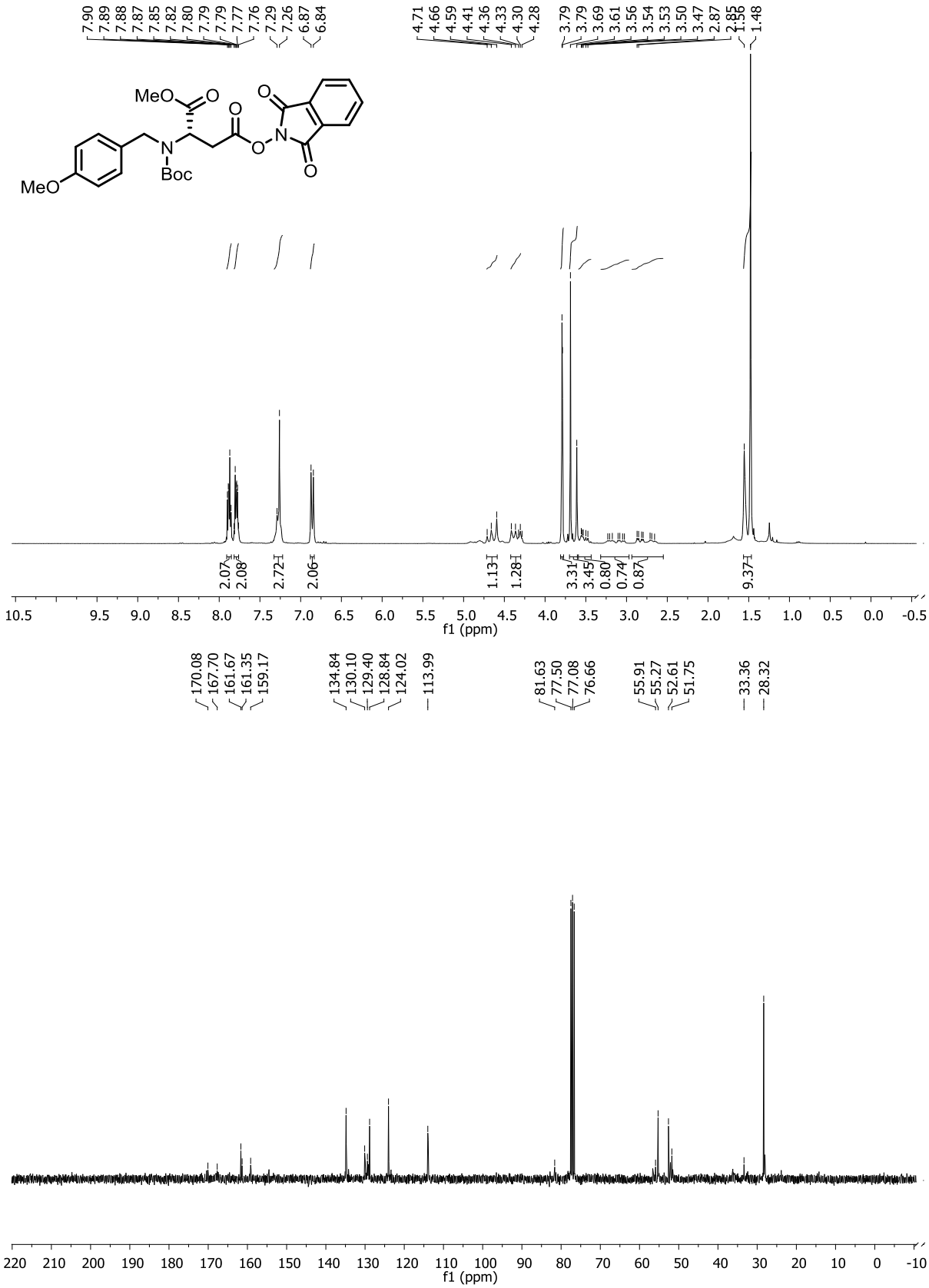
1,3-dioxoisoindolin-2-yl 4-(N-tert-butyl-3,4,5-trimethoxybenzamido)butanoate (102h).



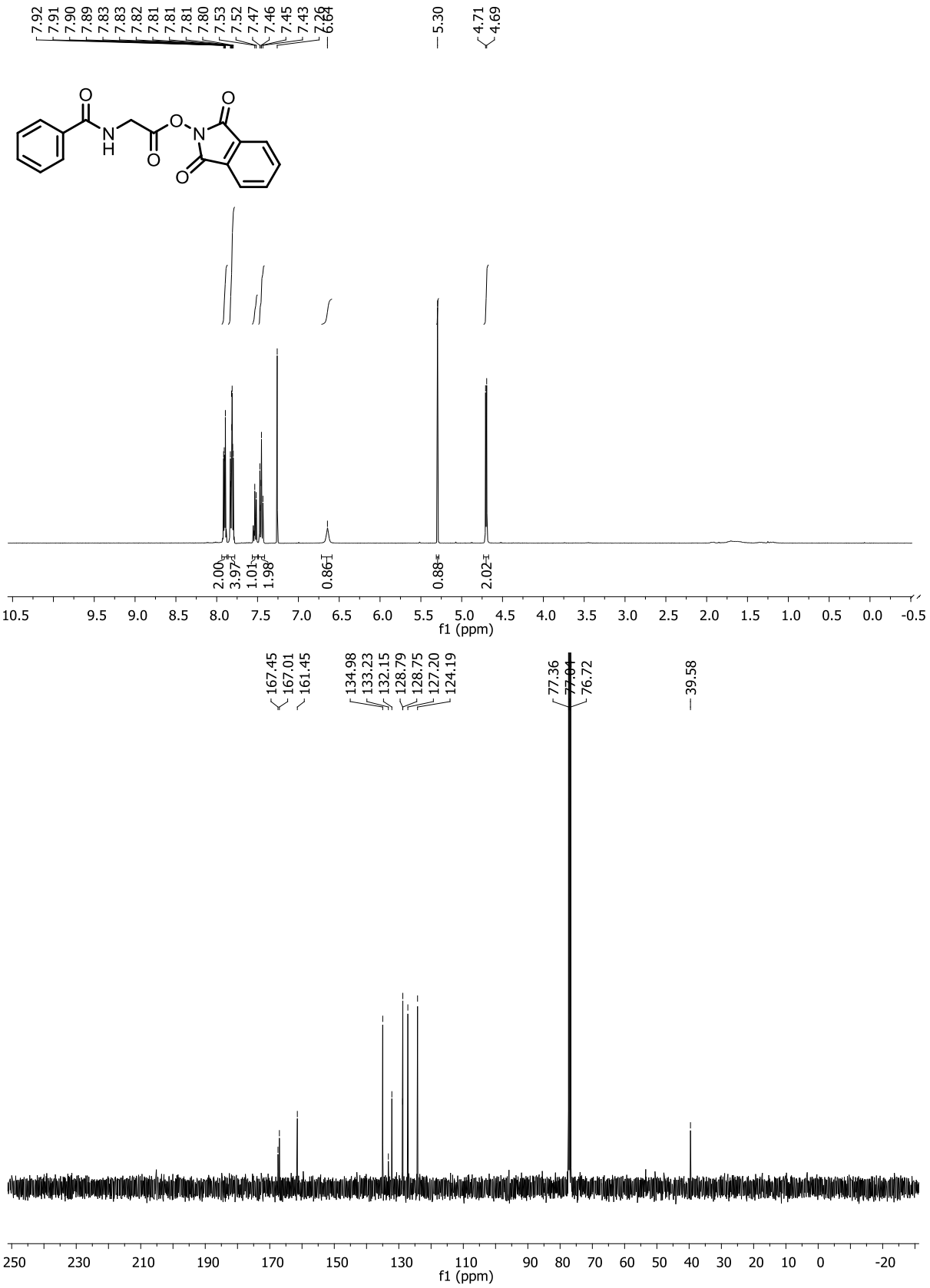
1,3-Dioxoisoindolin-2-yl 3-(*tert*-butoxycarbonyl(4-methoxybenzyl)amino)propanoate (118).



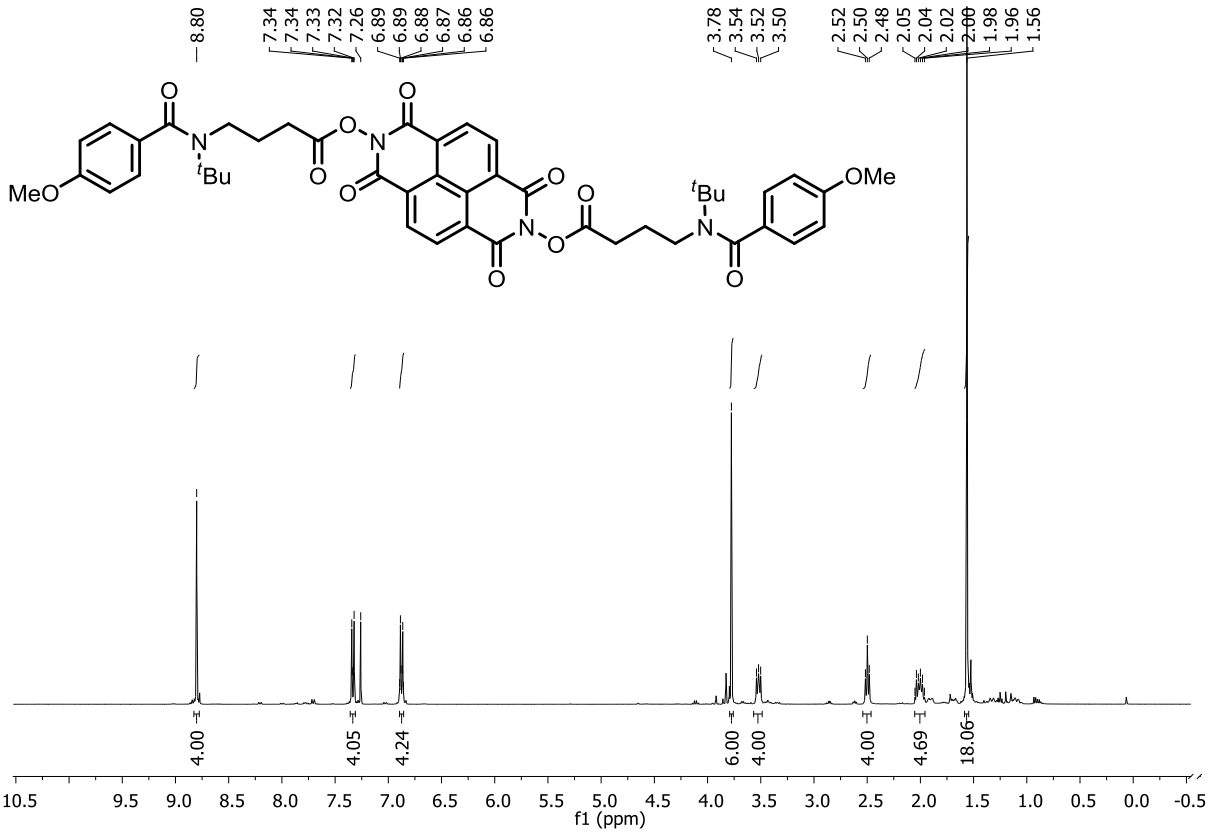
(S)-4-(1,3-Dioxoisoindolin-2-yl) 1-methyl 2-(*tert*-butoxycarbonyl(4-methoxybenzyl)-amino)succinate (125).

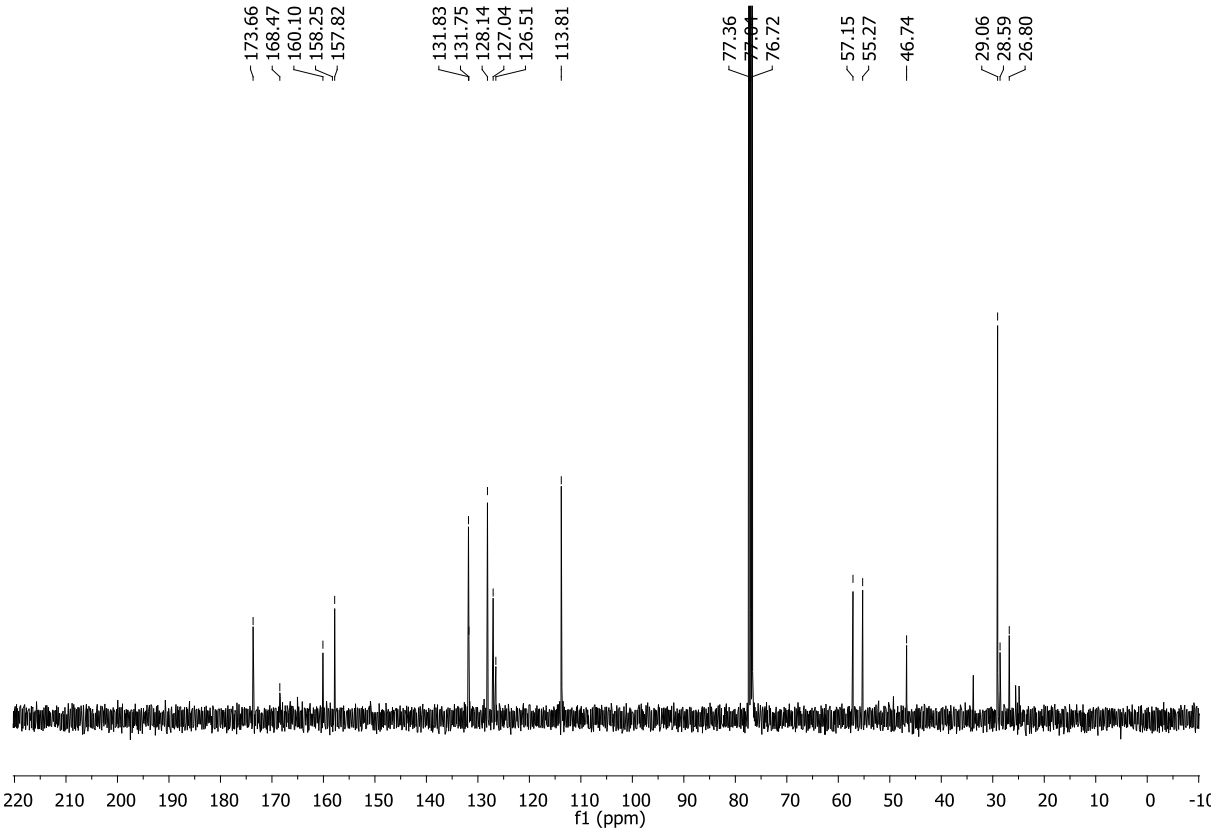


1,3-Dioxoisoindolin-2-yl 2-benzamidoacetate (240).

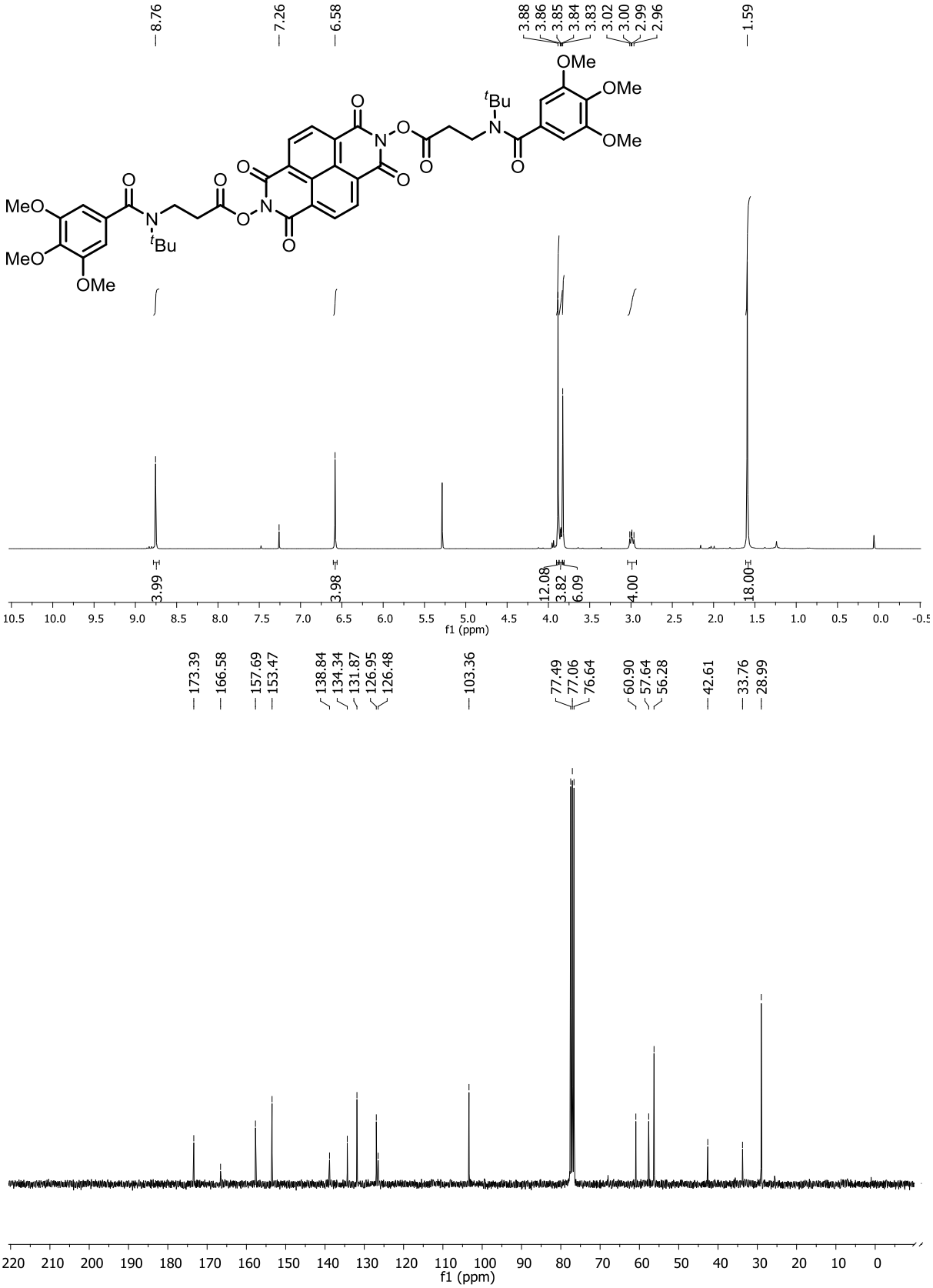


1,3,6,8-tetraoxobenzo[lmn][3,8]phenanthroline-2,7(1H,3H,6H,8H)-diyl bis(4-(N-*tert*-butyl-4-methoxybenzamido)butanoate) (109).

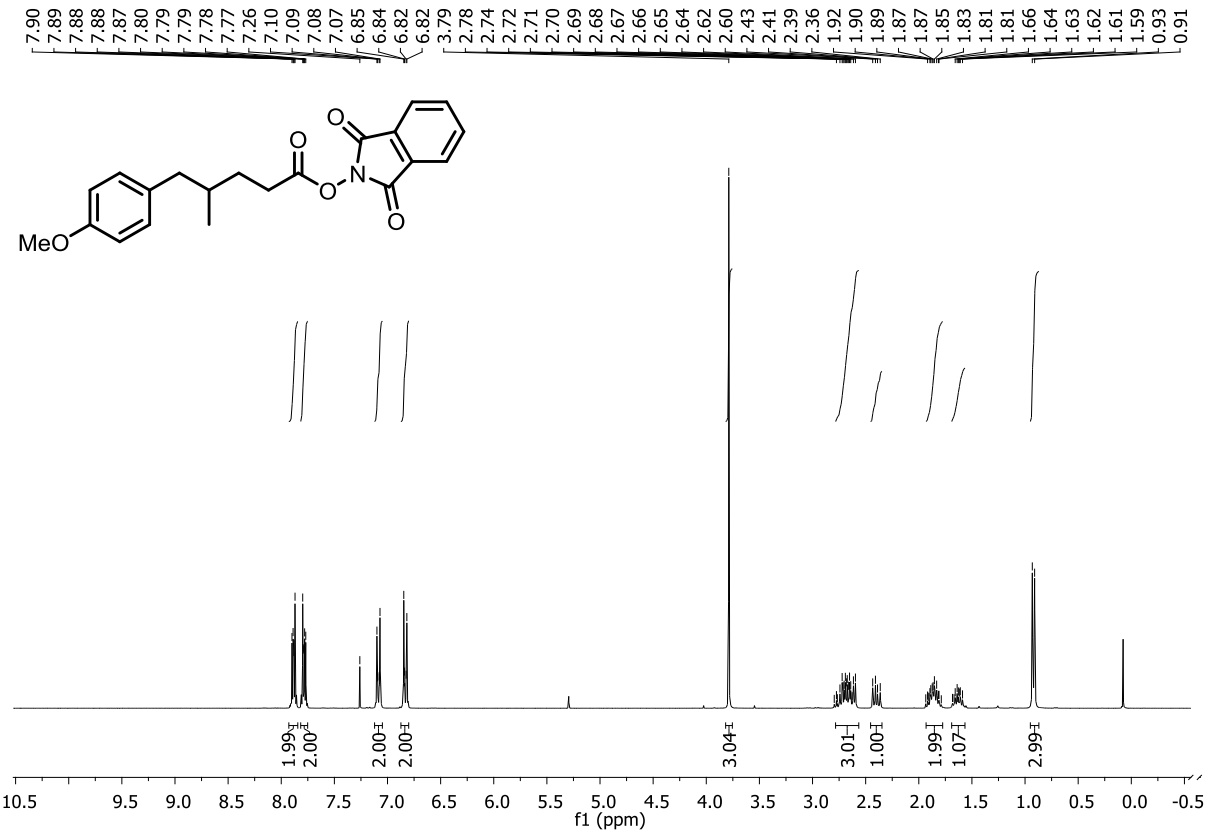


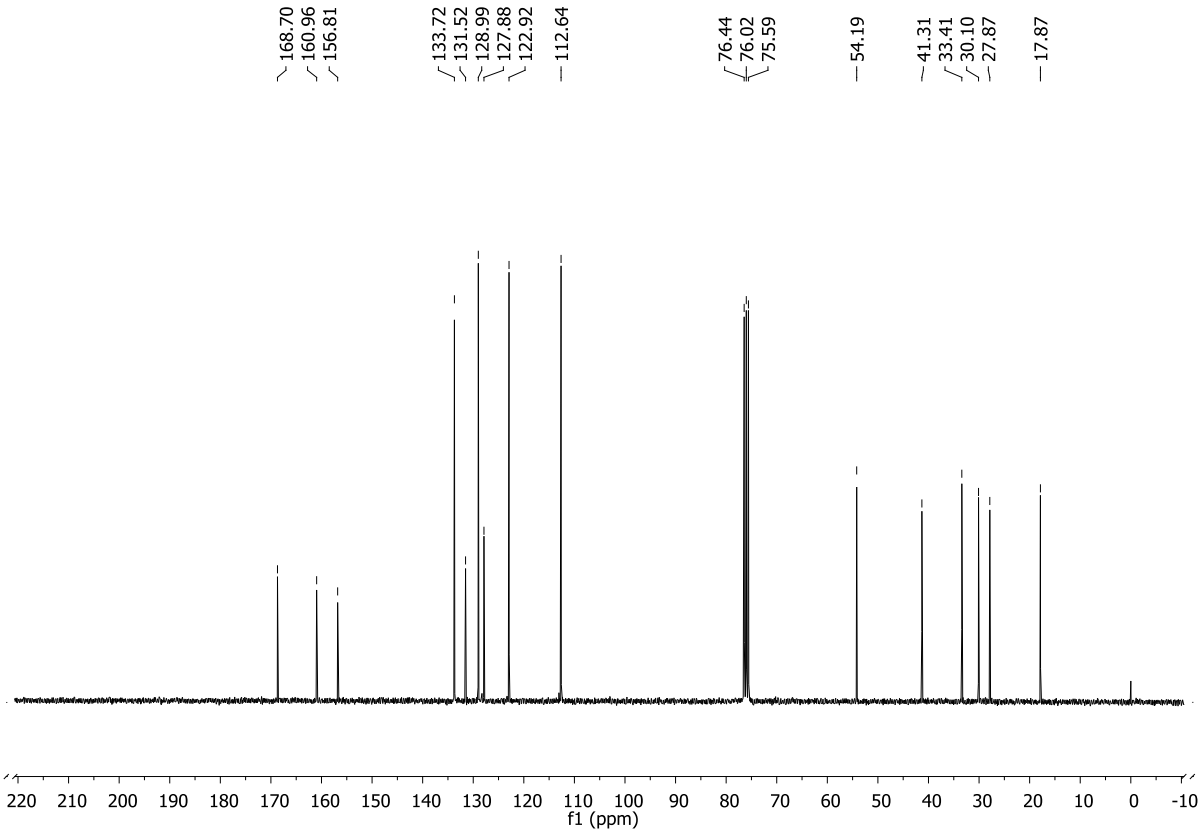


1,3,6,8-Tetraoxobenzo[lmn][3,8]phenanthroline-2,7(1H,3H,6H,8H)-diyl bis(3-(N-*tert*-butyl-3,4,5-trimethoxybenzamido)propanoate) (110).

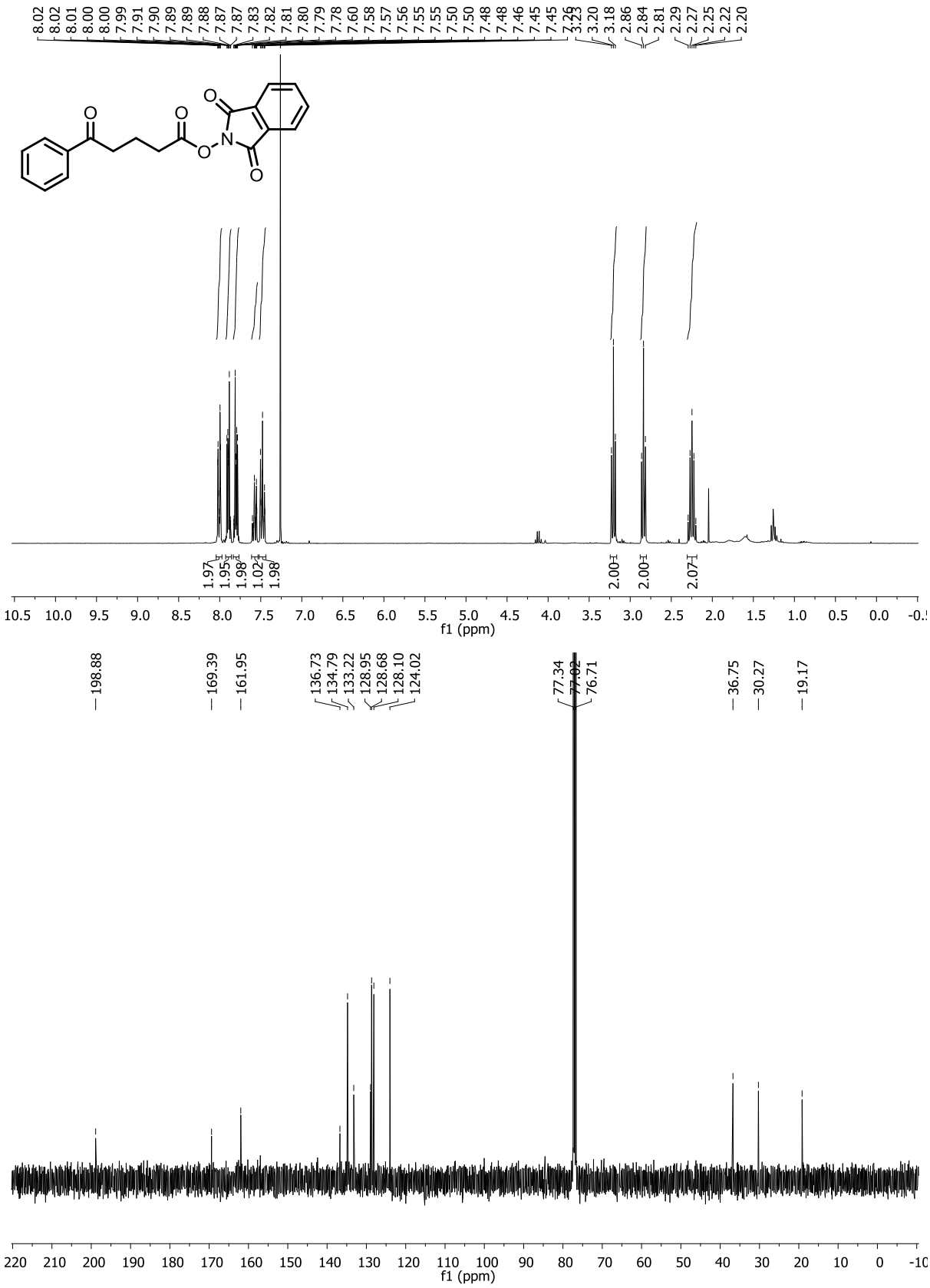


1,3-Dioxoisoindolin-2-yl 5-(4-methoxyphenyl)-4-methylpentanoate (127).

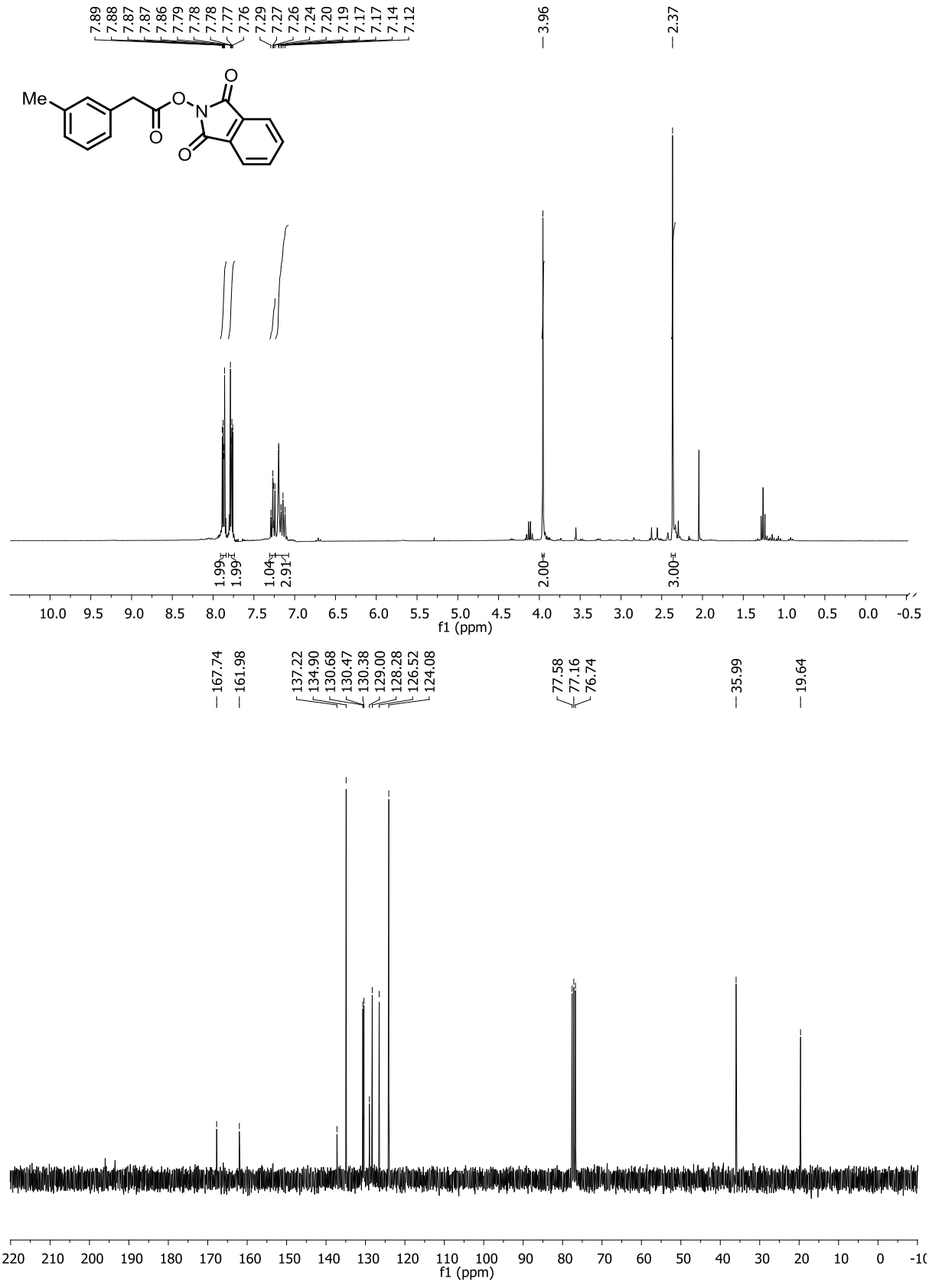




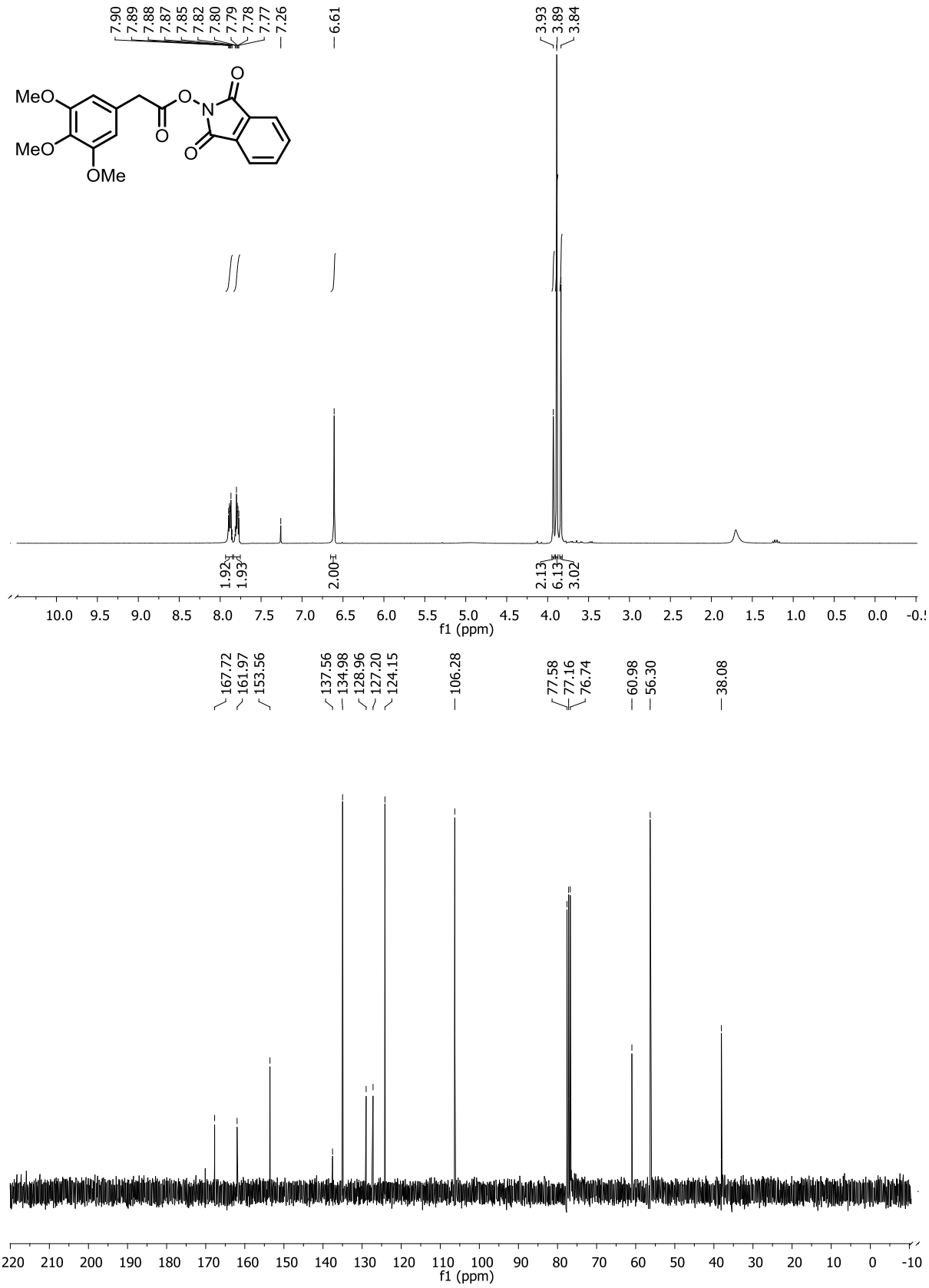
1,3-Dioxoisoindolin-2-yl 5-oxo-5-phenylpentanoate (133).



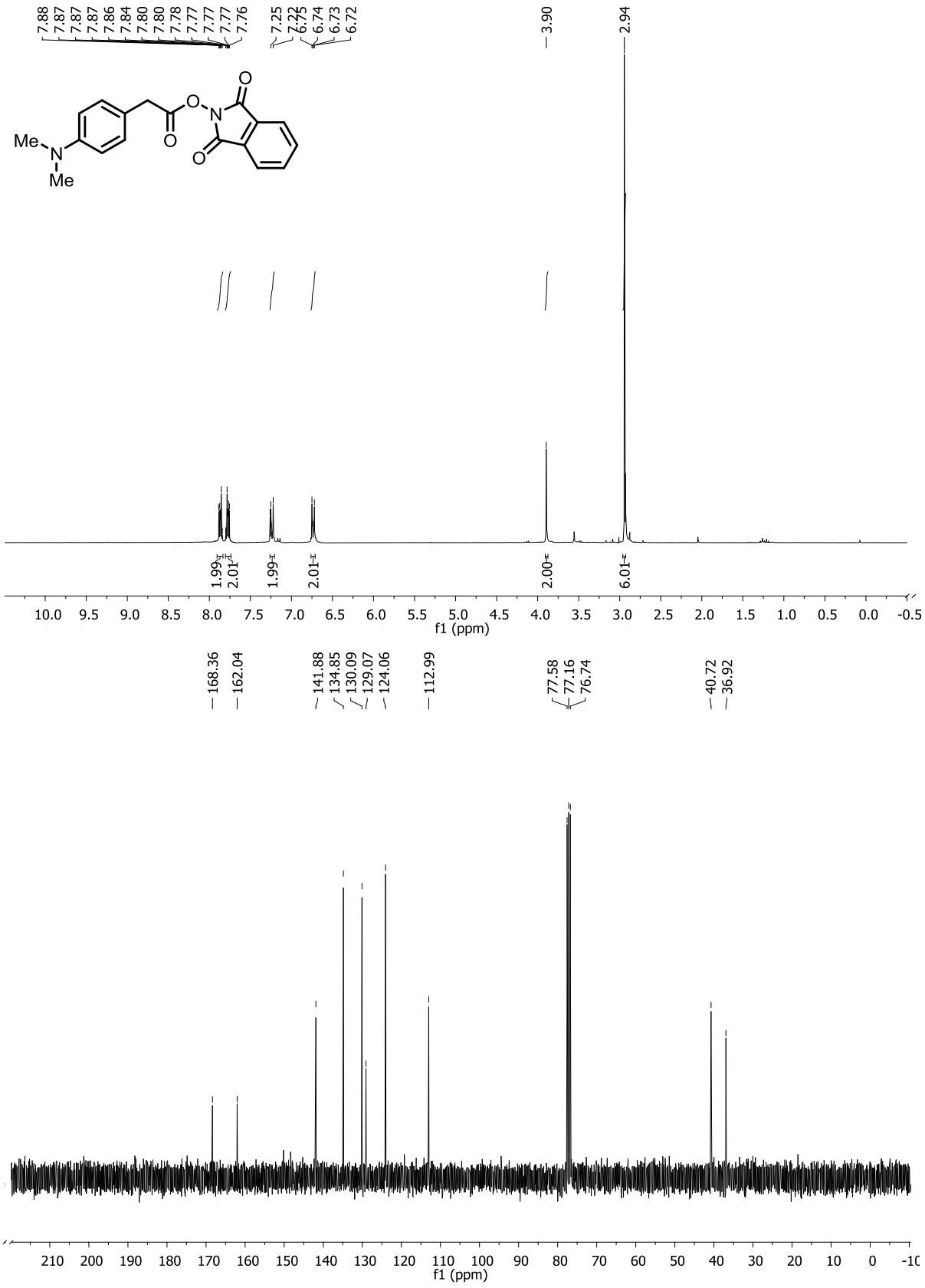
1,3-Dioxoisoindolin-2-yl 2-m-tolylacetate (166c).



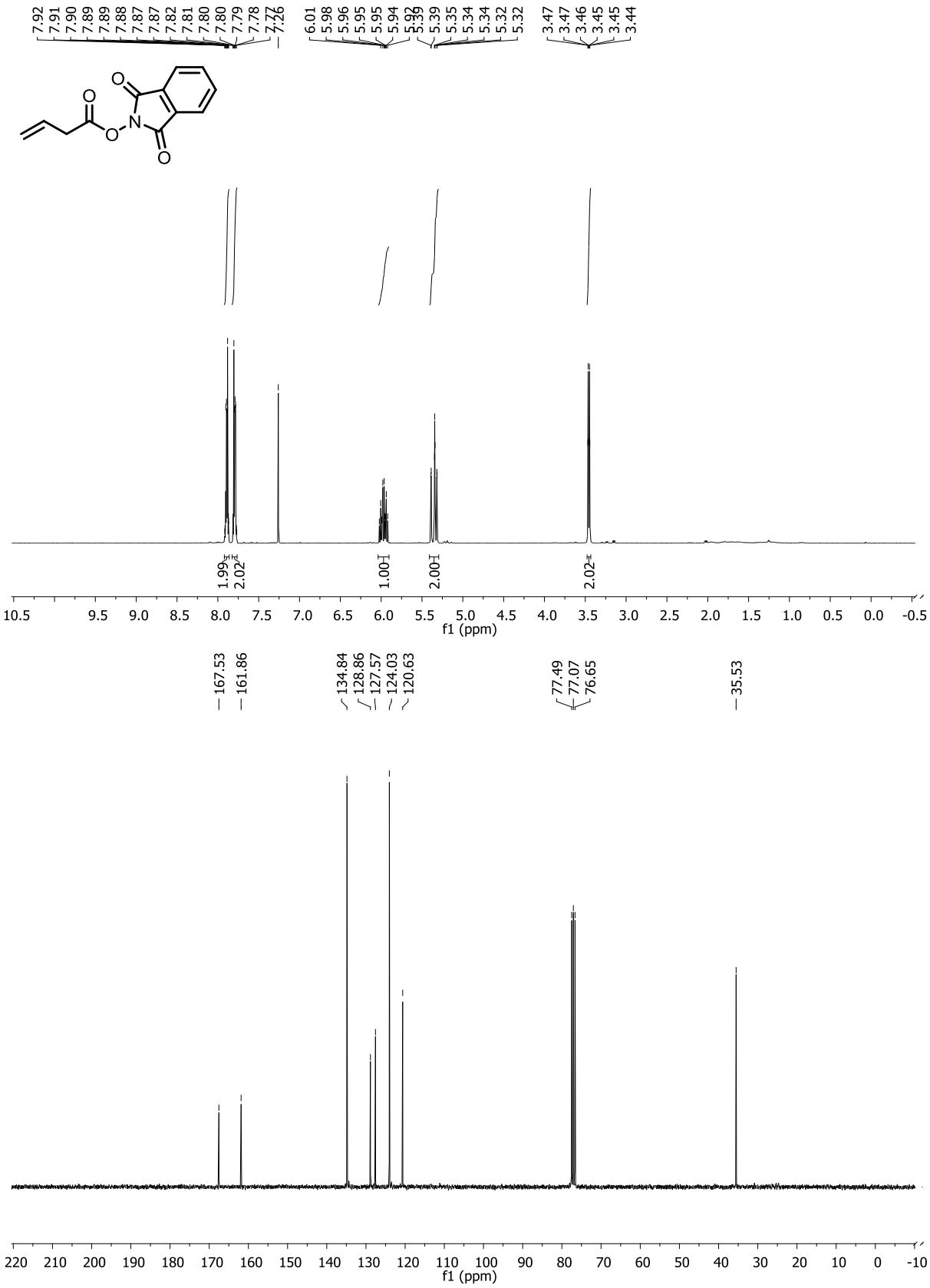
1,3-Dioxoisoindolin-2-yl 2-(3,4,5-trimethoxyphenyl)acetate (166g).



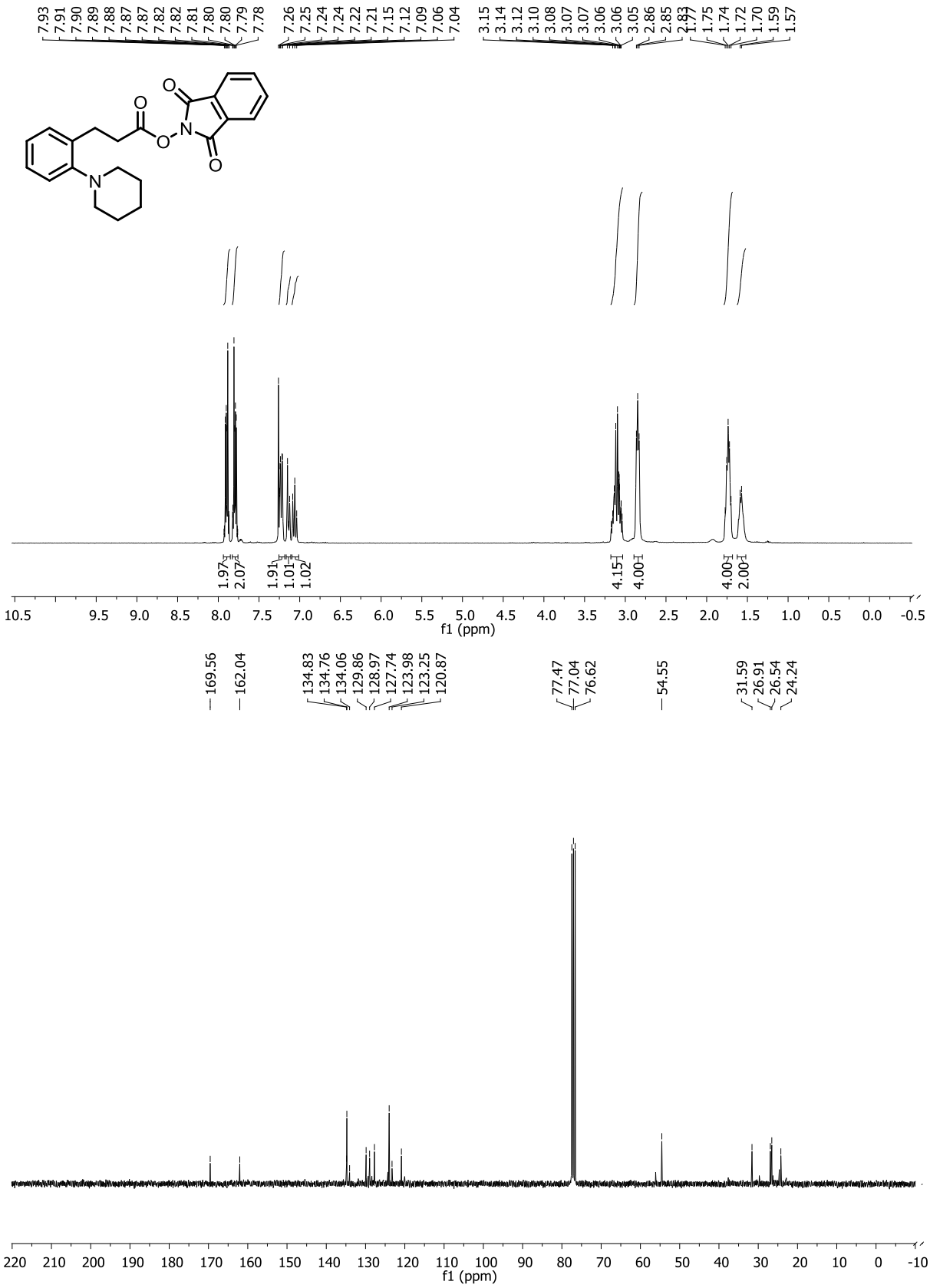
1,3-Dioxoisoindolin-2-yl 2-(4-(dimethylamino)phenyl)acetate (166h).



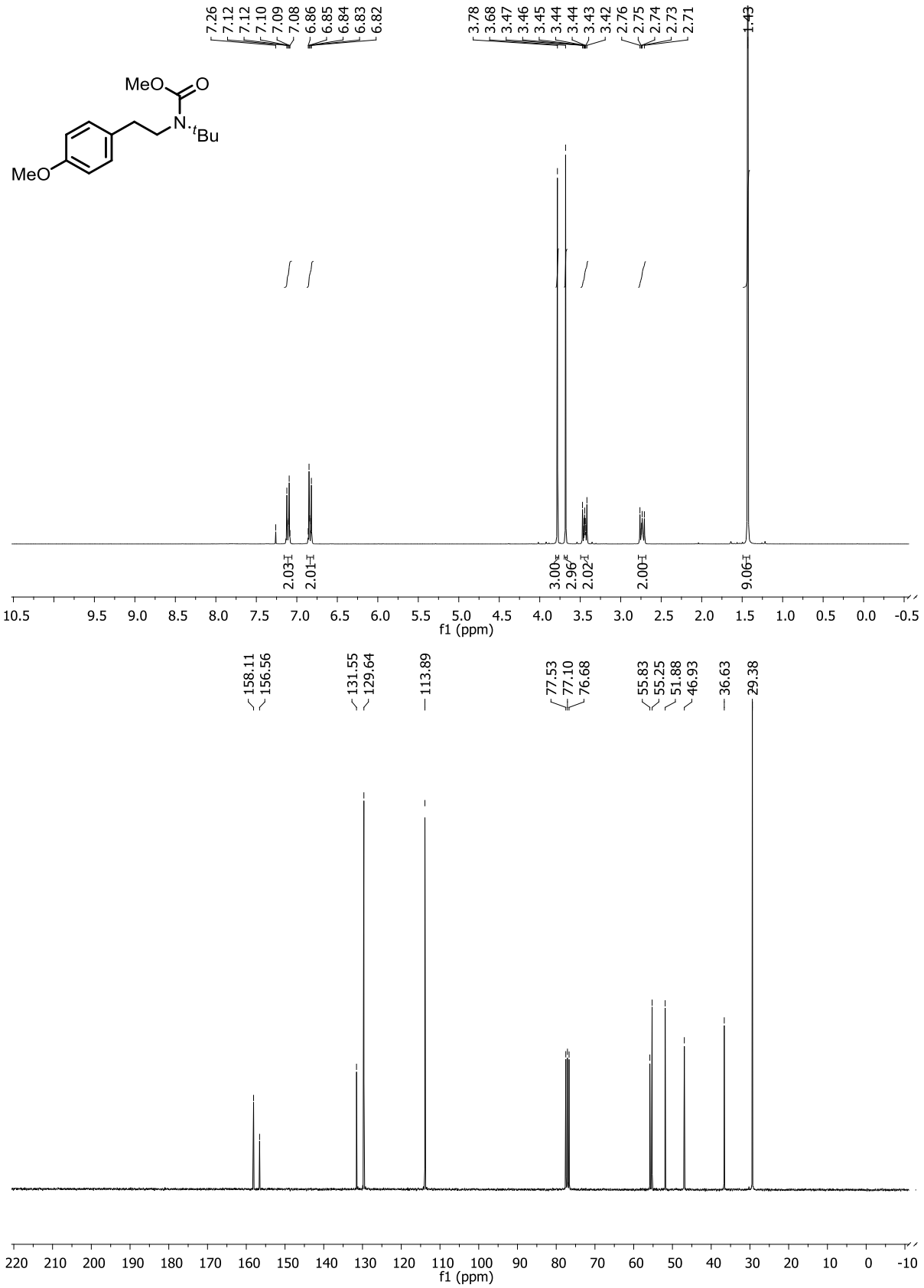
1,3-Dioxoisoindolin-2-yl but-3-enoate (230).



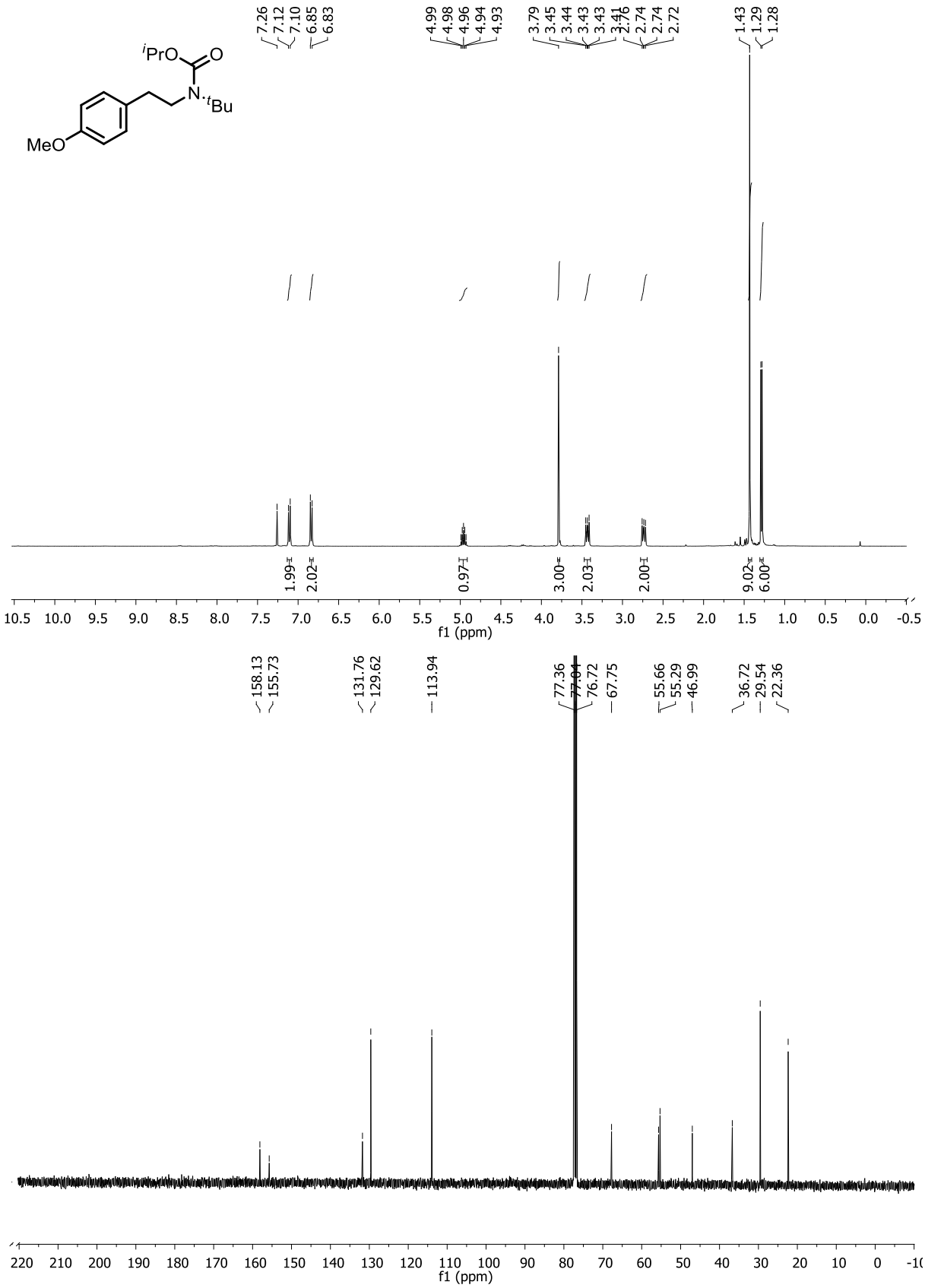
1,3-dioxoisoindolin-2-yl 3-(2-(piperidin-1-yl)phenyl)propanoate (249).



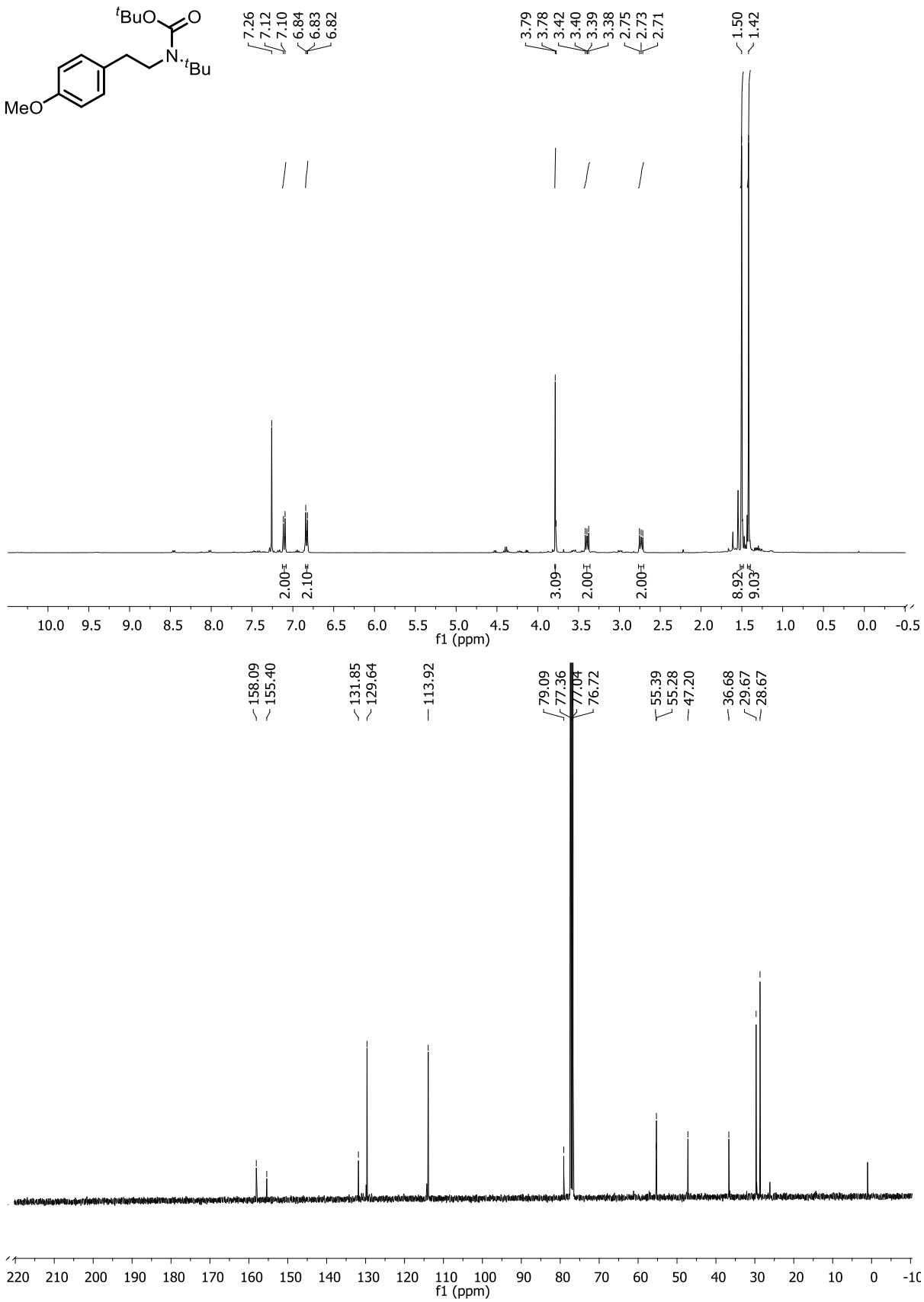
Methyl *tert*-butyl(4-methoxyphenethyl)carbamate (85a).



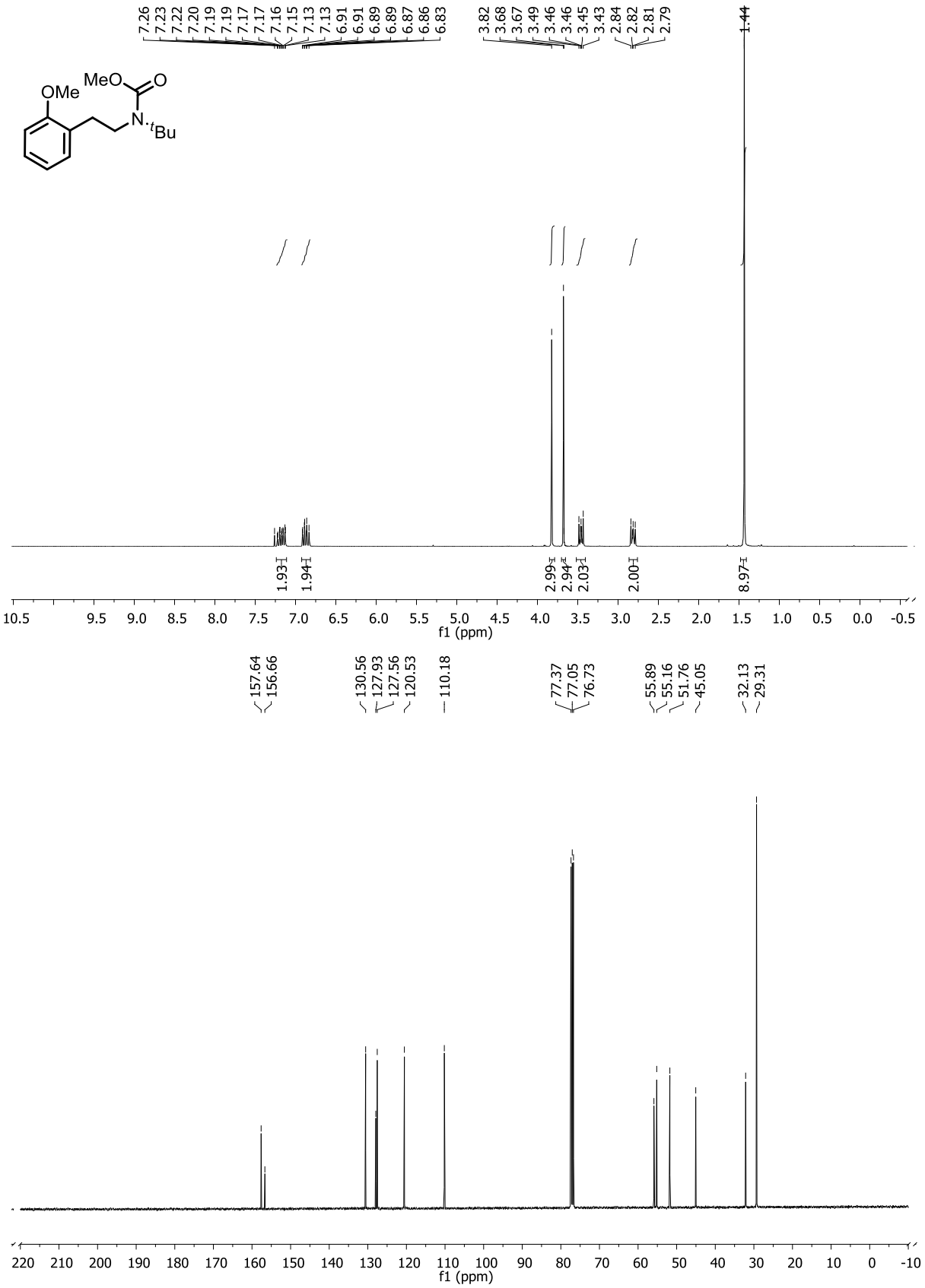
Isopropyl *tert*-butyl(4-methoxyphenethyl)carbamate (85b).



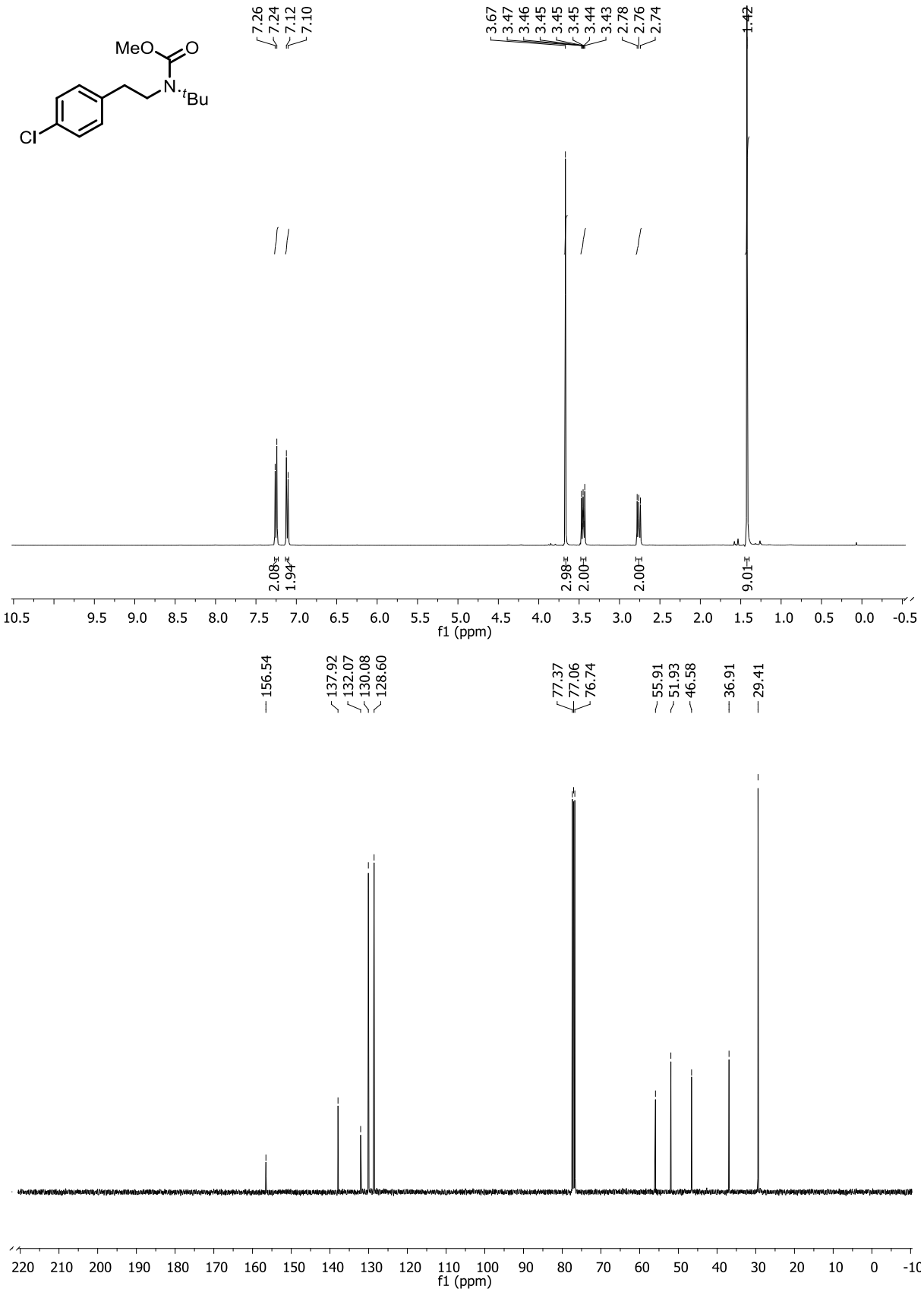
***tert*-butyl *tert*-butyl(4-methoxyphenethyl)carbamate (85c).**



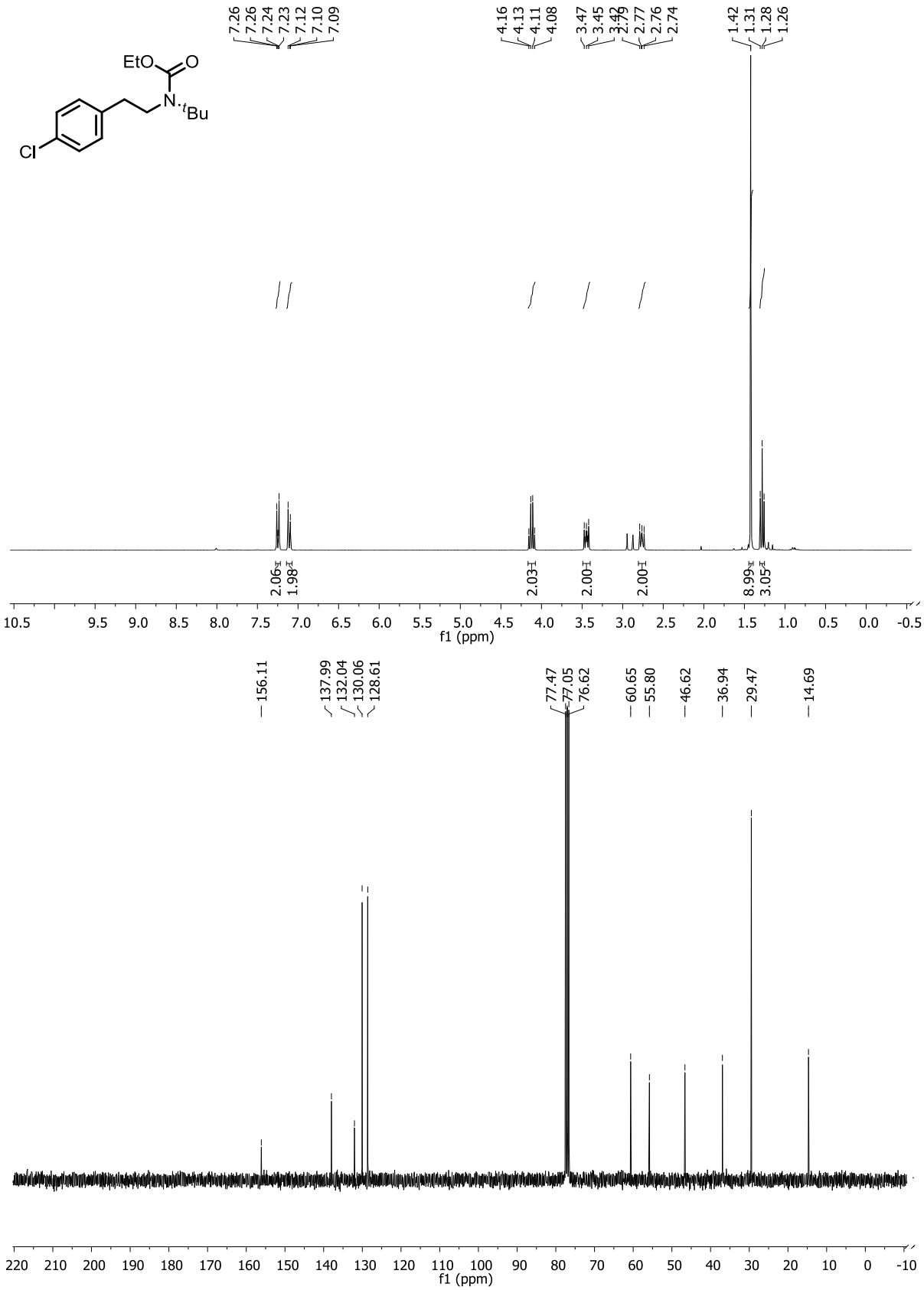
Methyl *tert*-butyl(2-methoxyphenethyl)carbamate (85d).



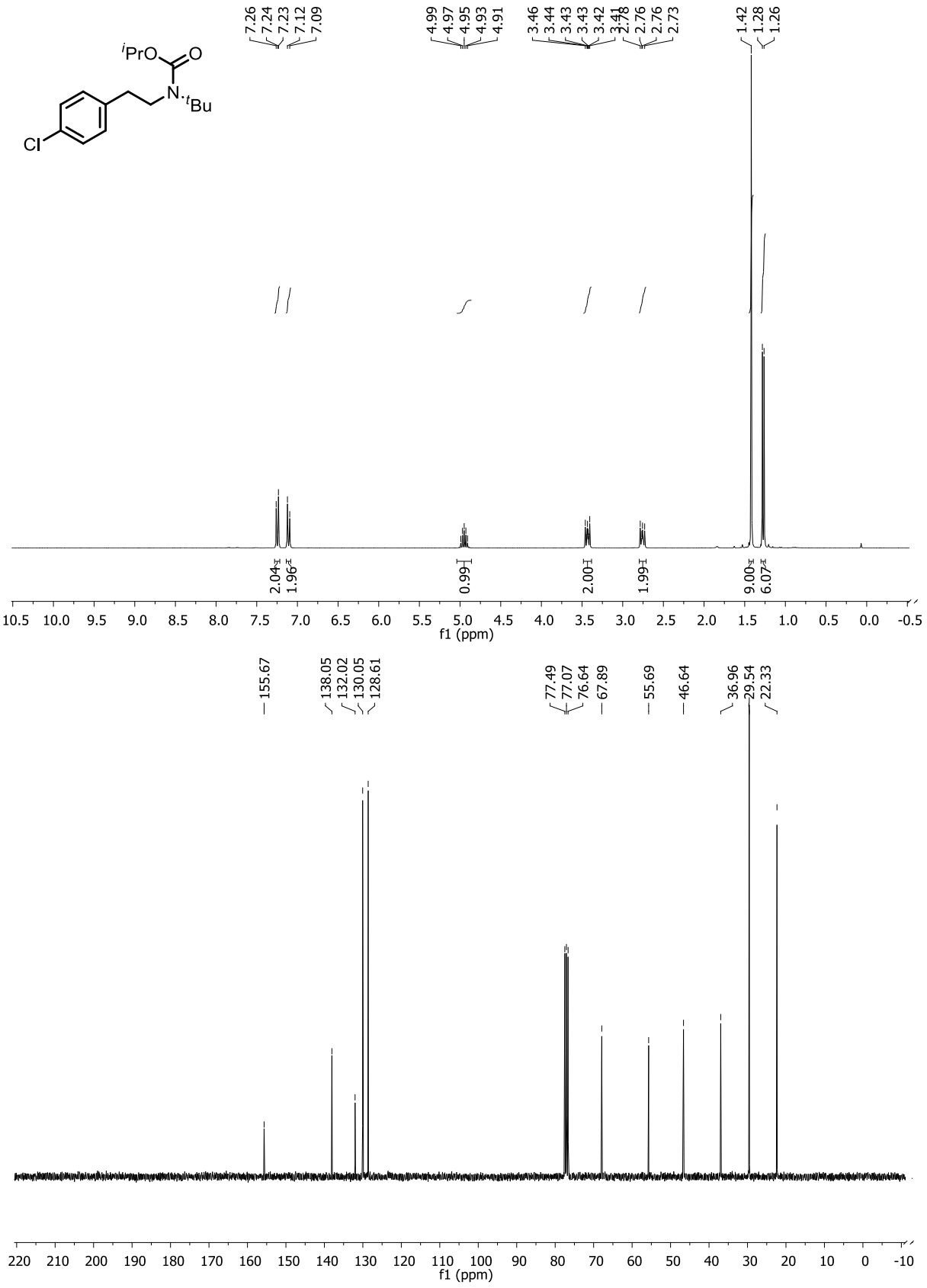
Methyl *tert*-butyl(4-chlorophenethyl)carbamate (85e).



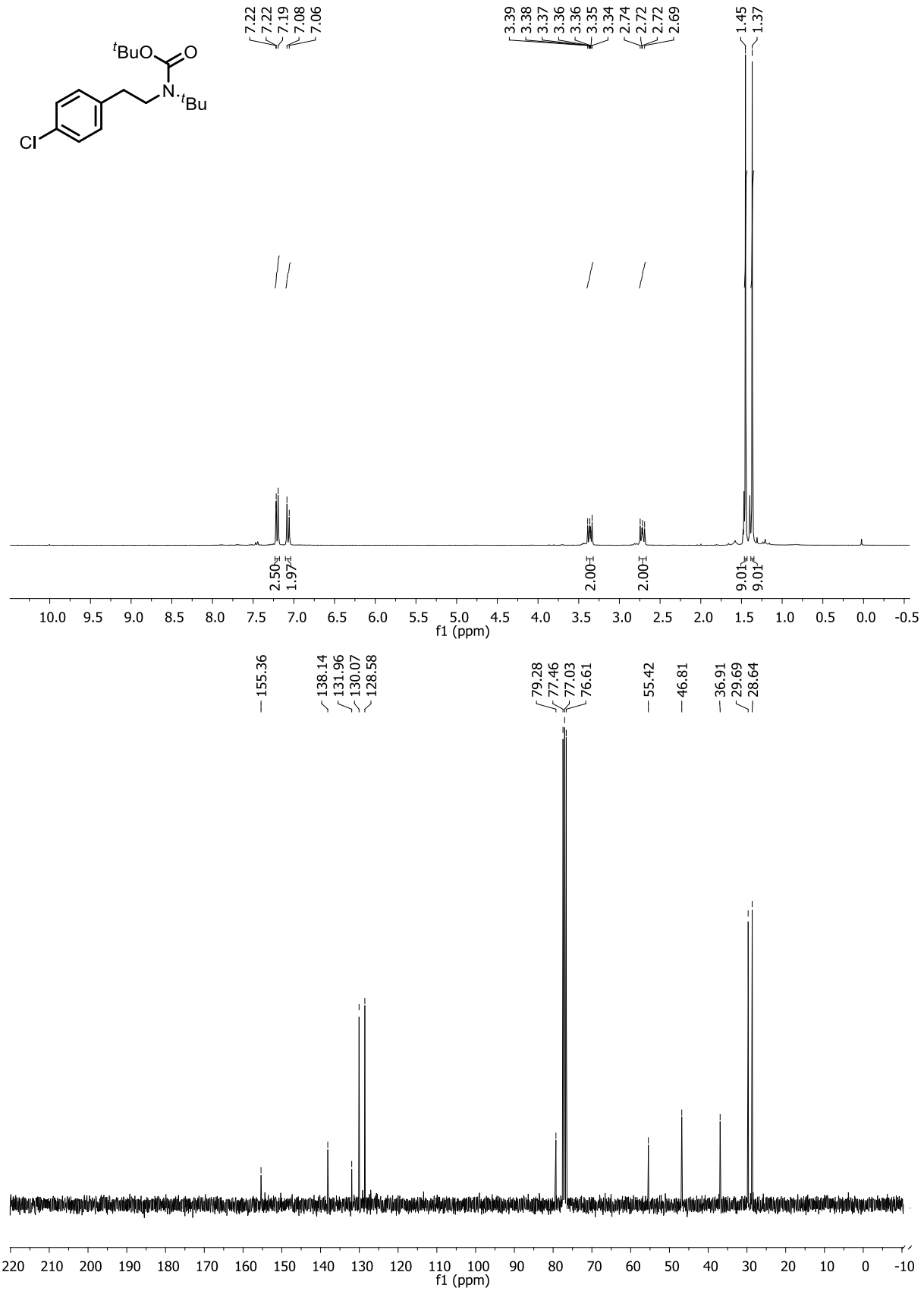
Ethyl *tert*-butyl(4-chlorophenethyl)carbamate (85f).



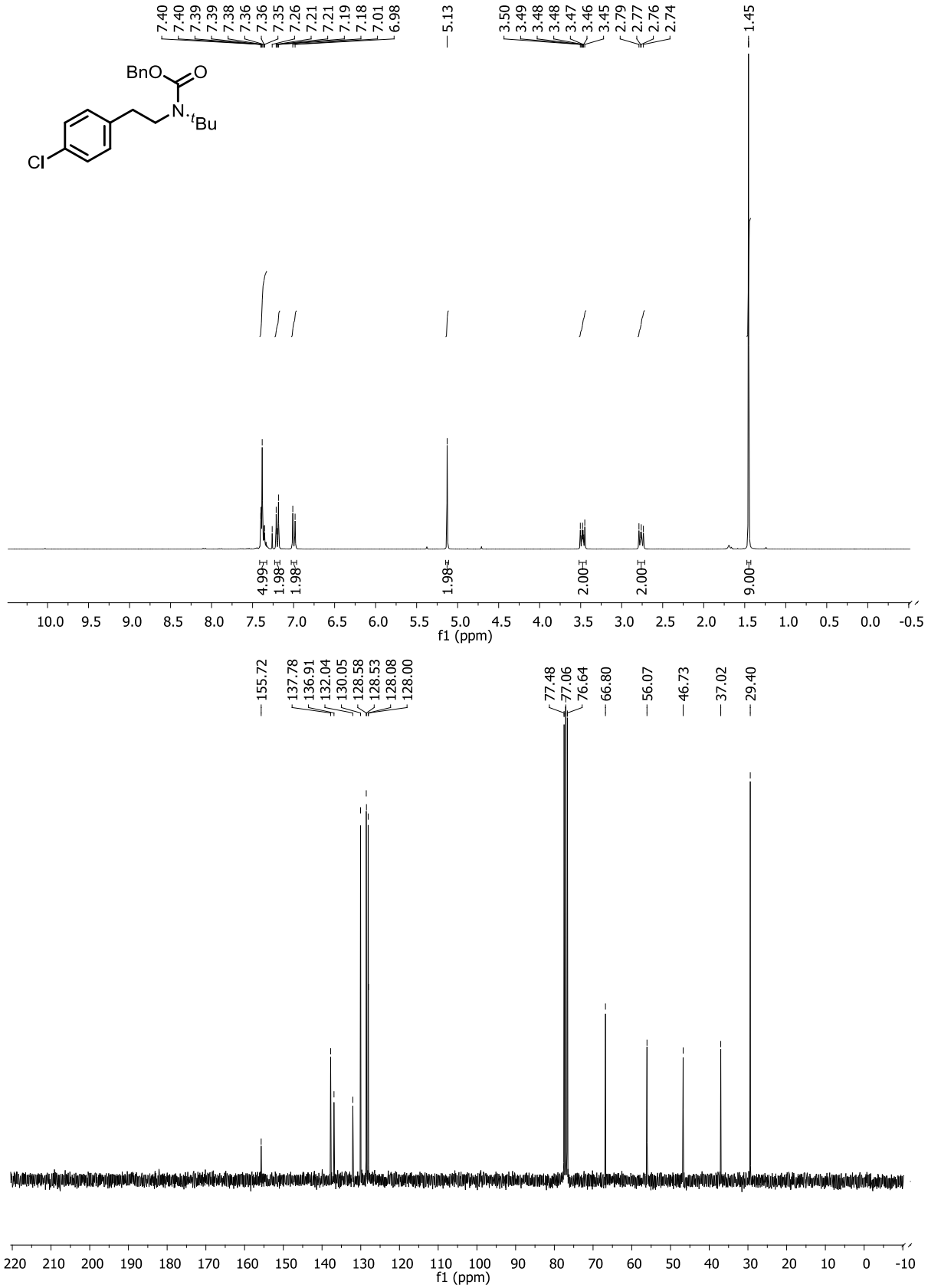
Isopropyl tert-butyl(4-chlorophenethyl)carbamate (85g).



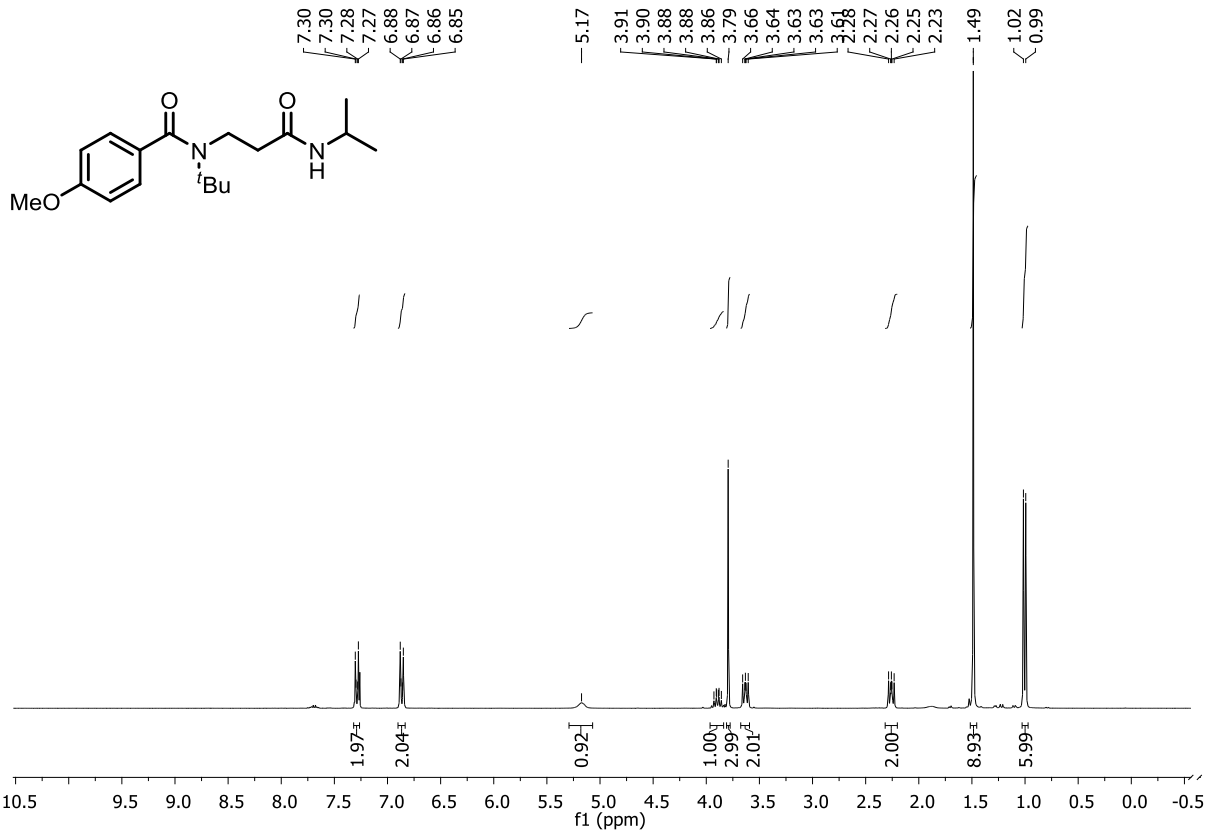
***tert*-butyl *tert*-butyl(4-chlorophenethyl)carbamate (85h).**

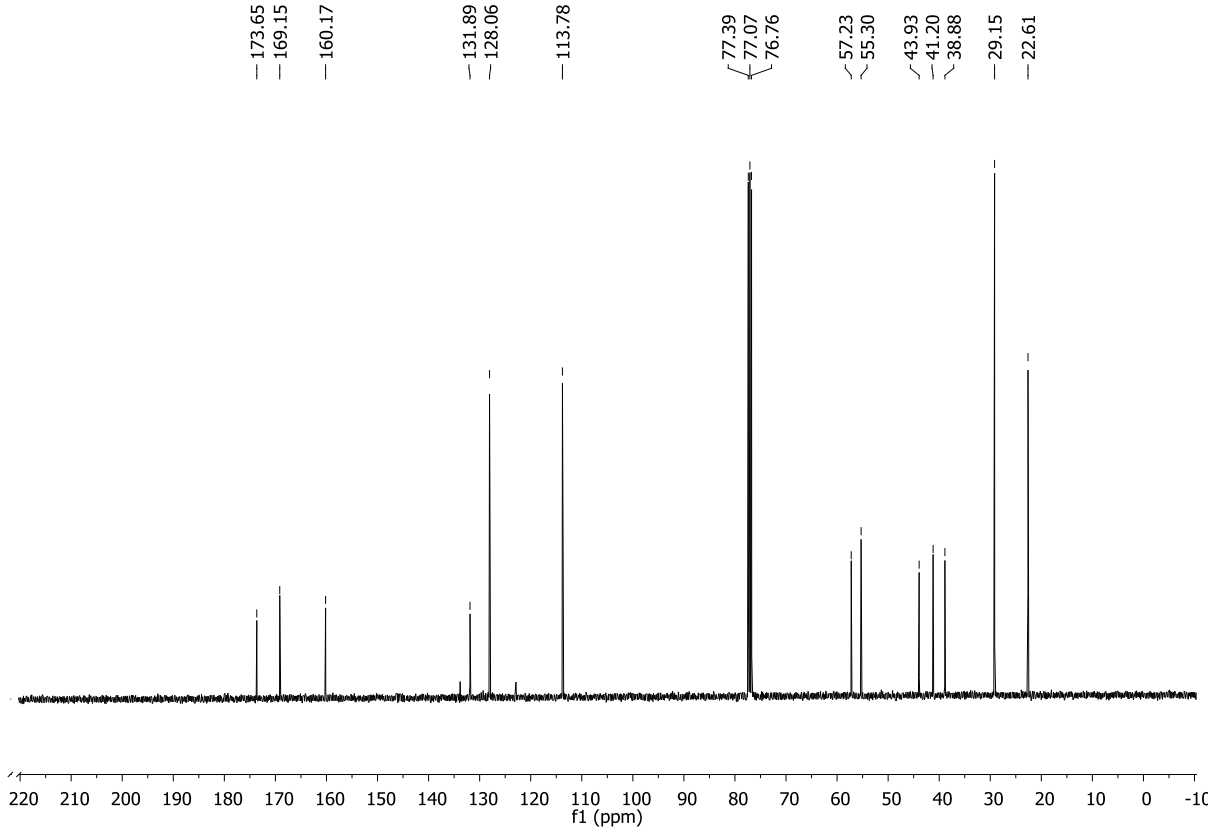


Benzyl *tert*-butyl(4-chlorophenethyl)carbamate (85i).

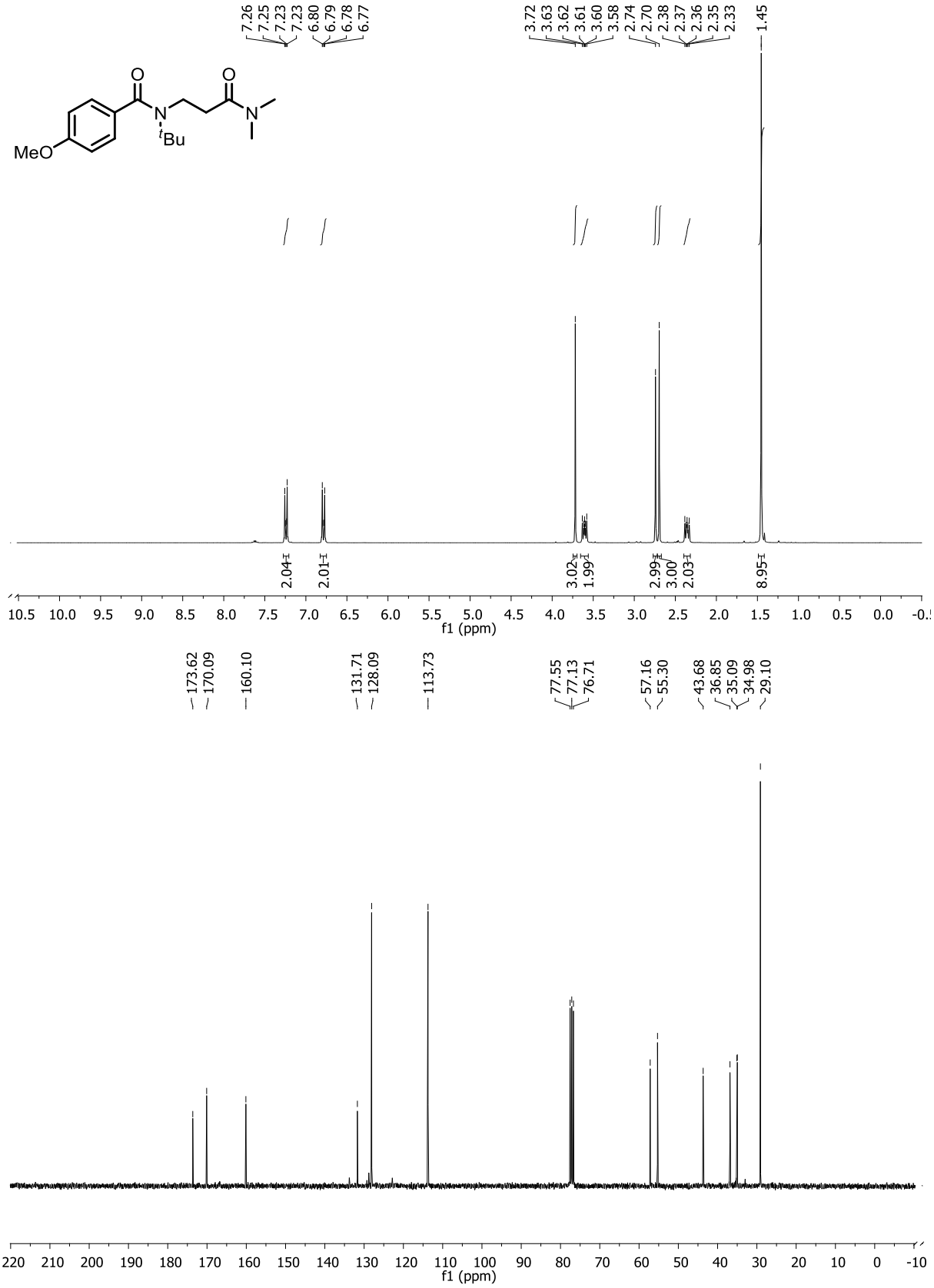


N-*tert*-Butyl-N-(3-(*iso*propylamino)-3-oxopropyl)-4-methoxybenzamide (86a).

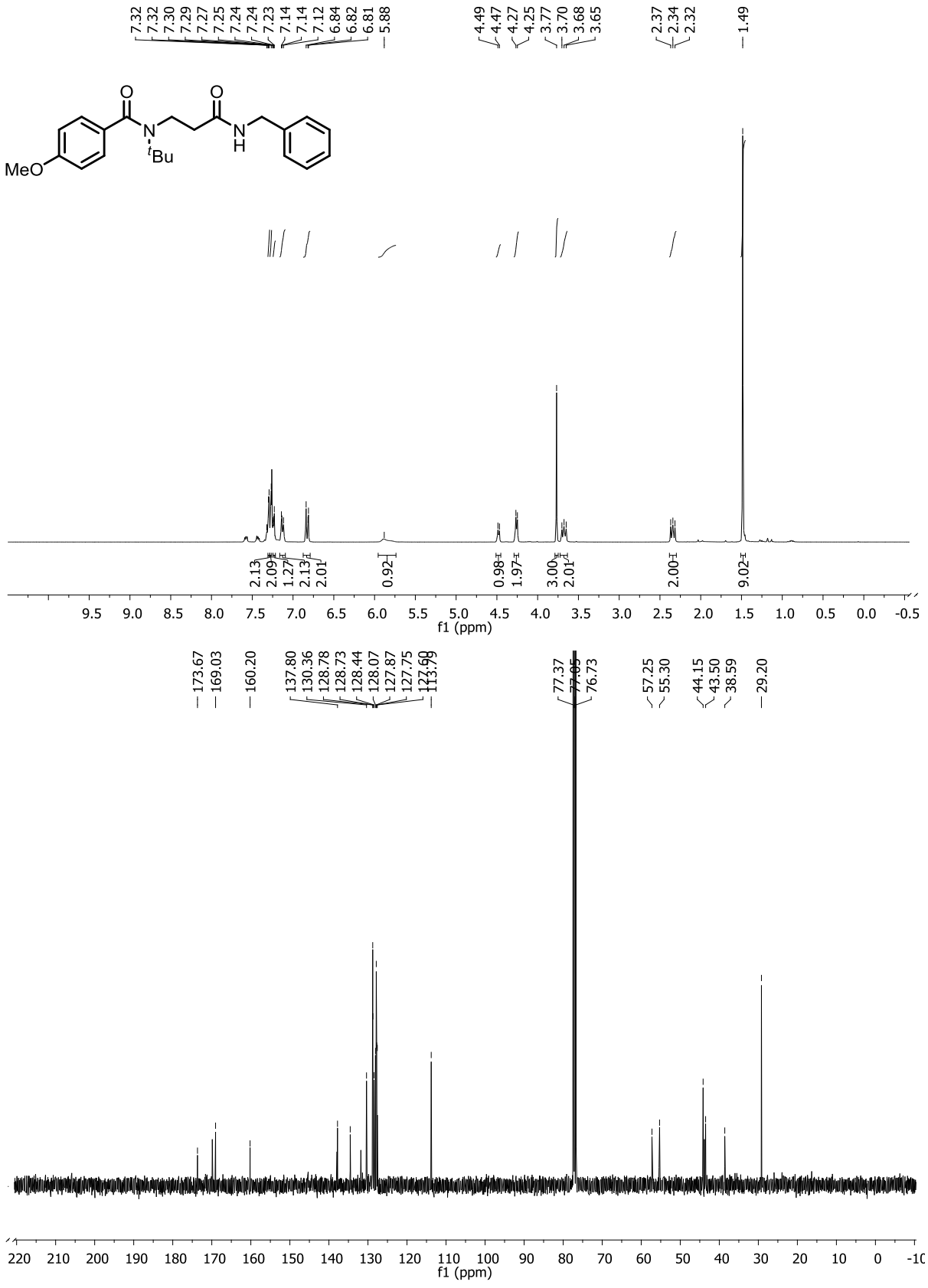




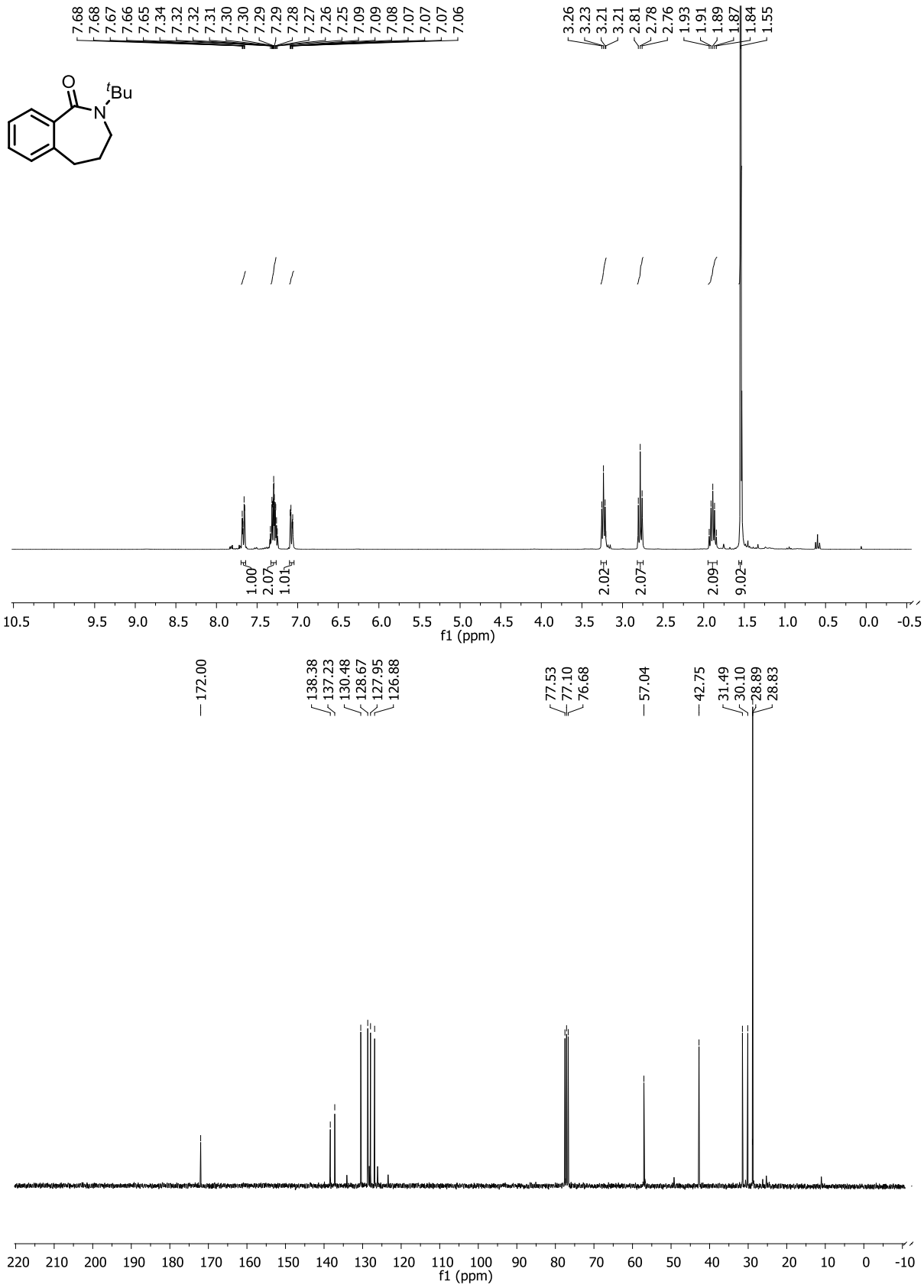
N-*tert*-Butyl-N-(3-(dimethylamino)-3-oxopropyl)-4-methoxybenzamide (86b).



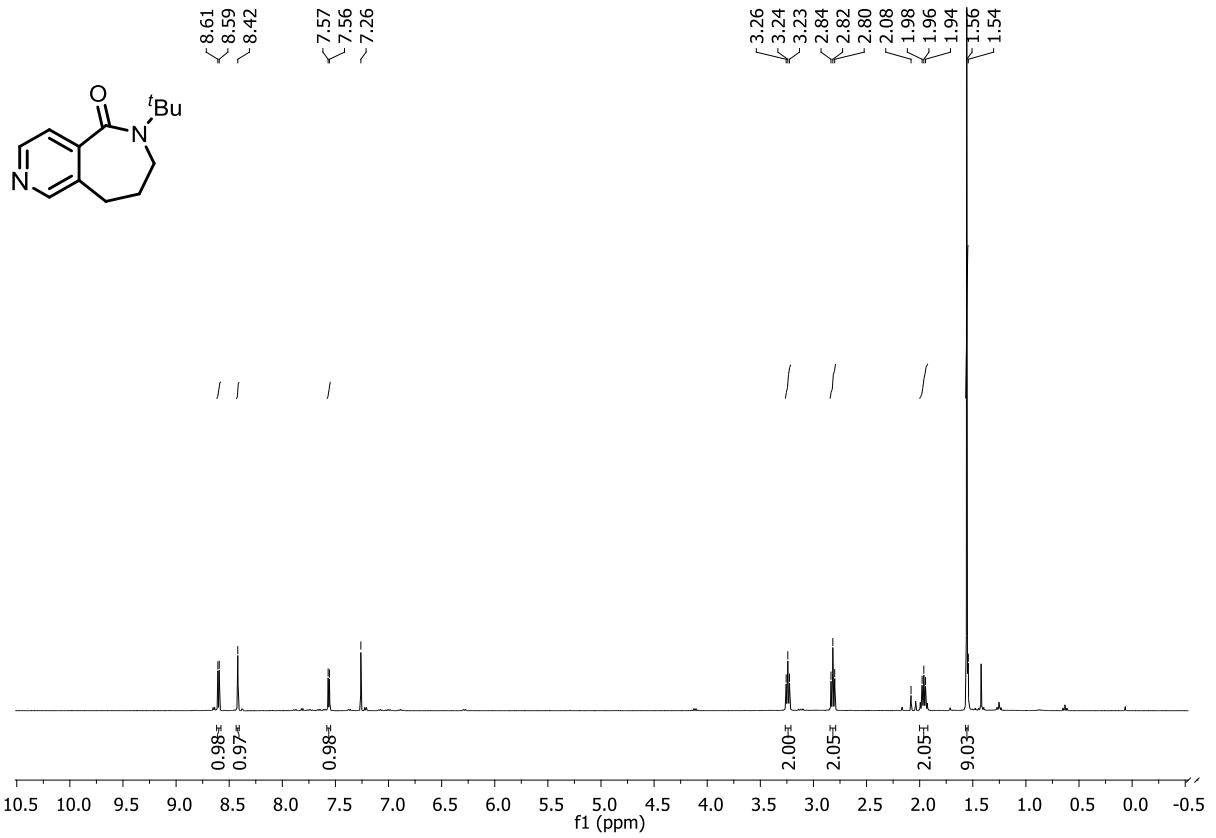
N-(3-(Benzylamino)-3-oxopropyl)-N-*tert*-butyl-4-methoxybenzamide (86c).

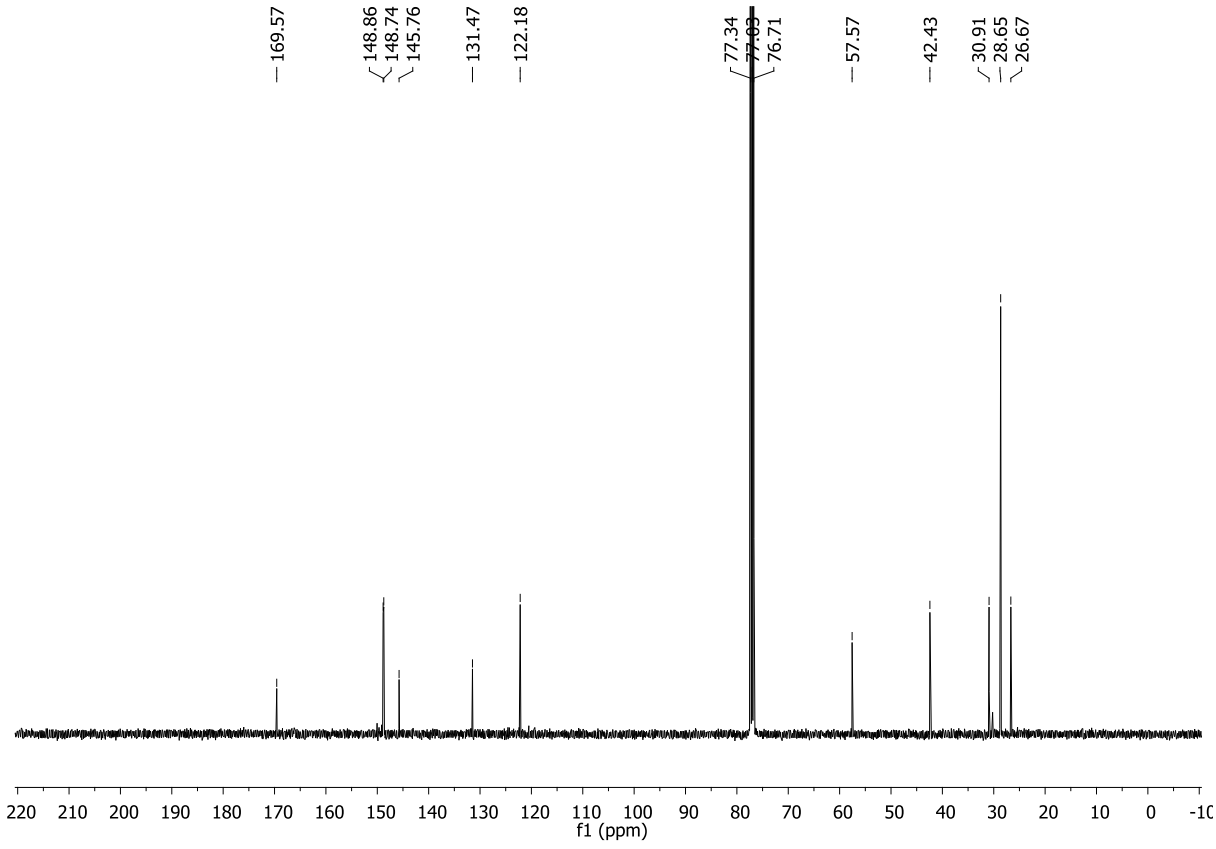


2-*tert*-butyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105a).

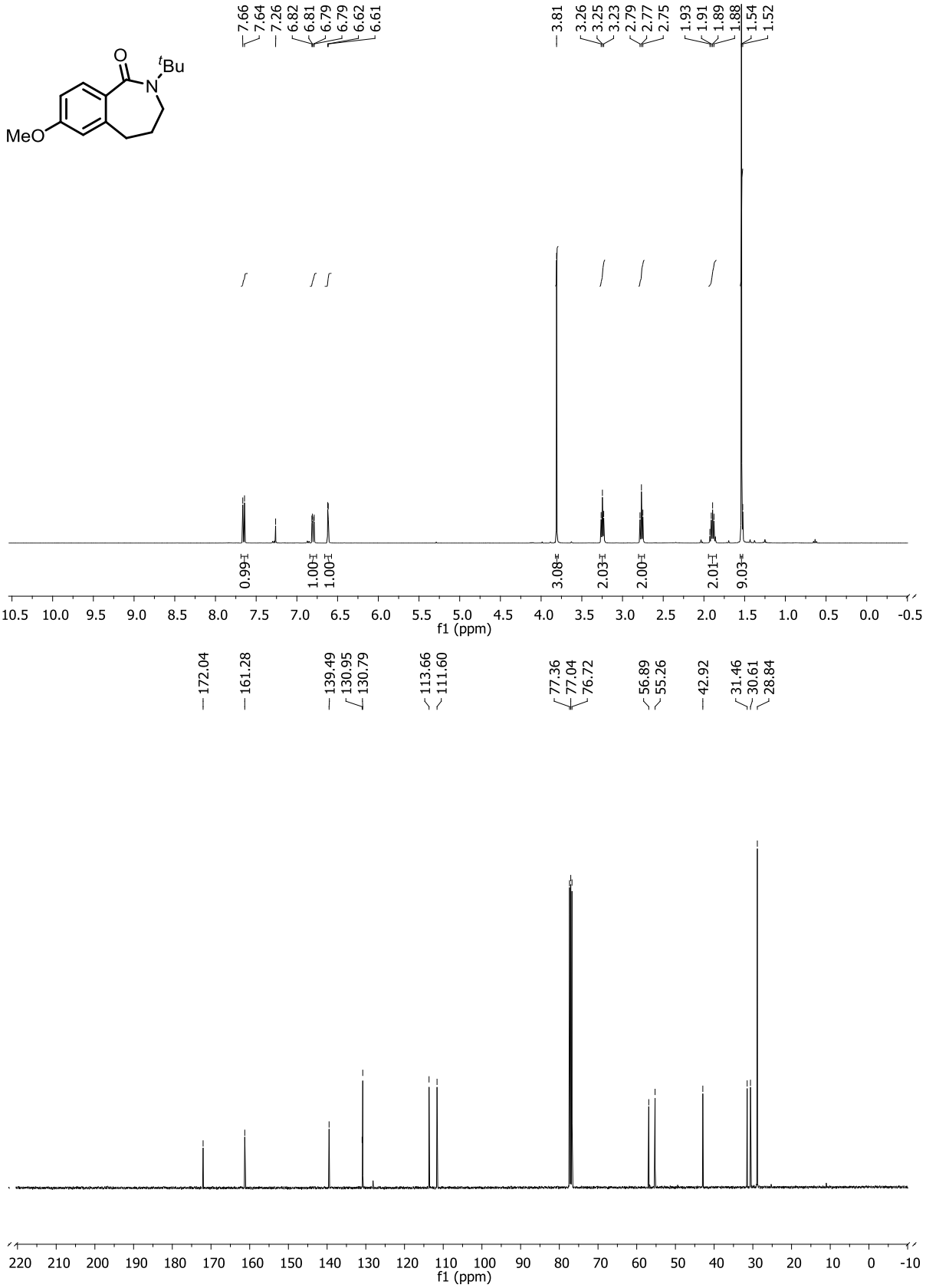


6-*tert*-butyl-6,7,8,9-tetrahydro-5H-pyrido[4,3-c]azepin-5-one (105b).

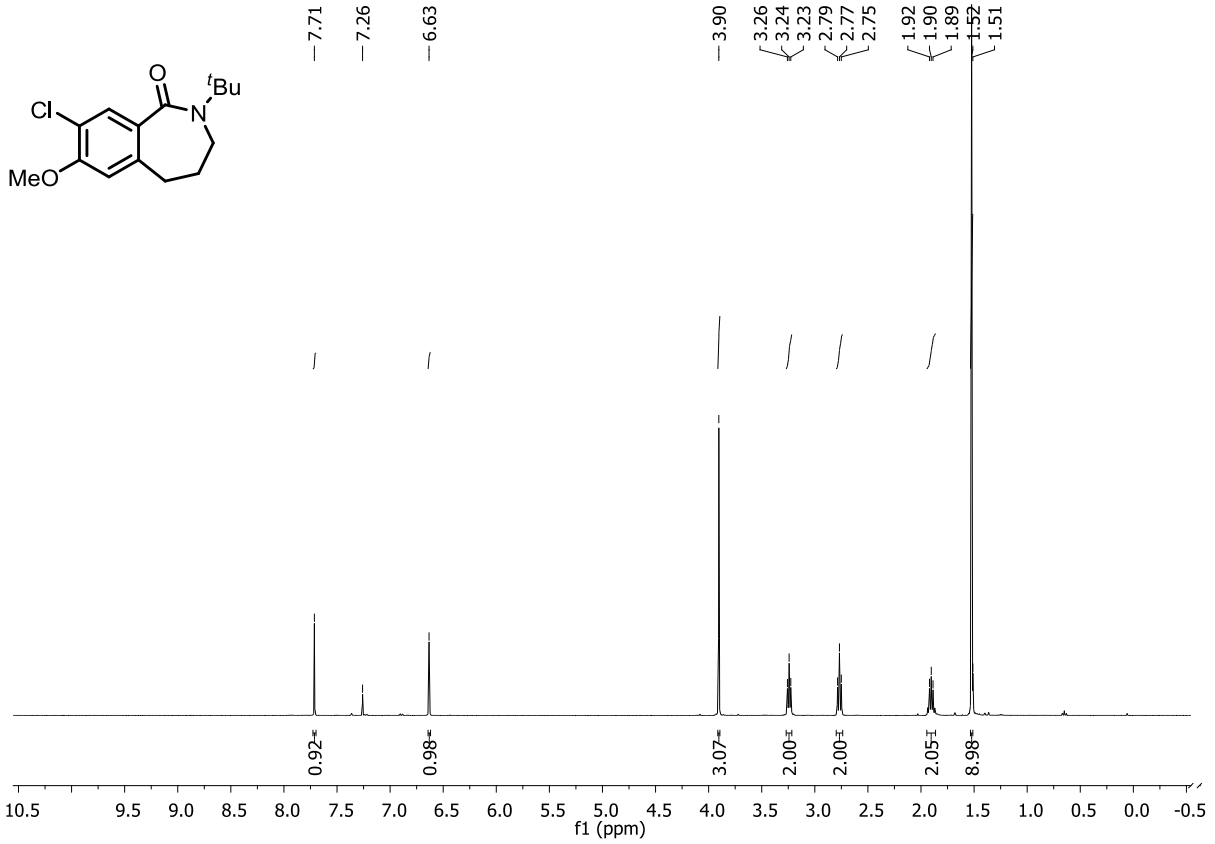


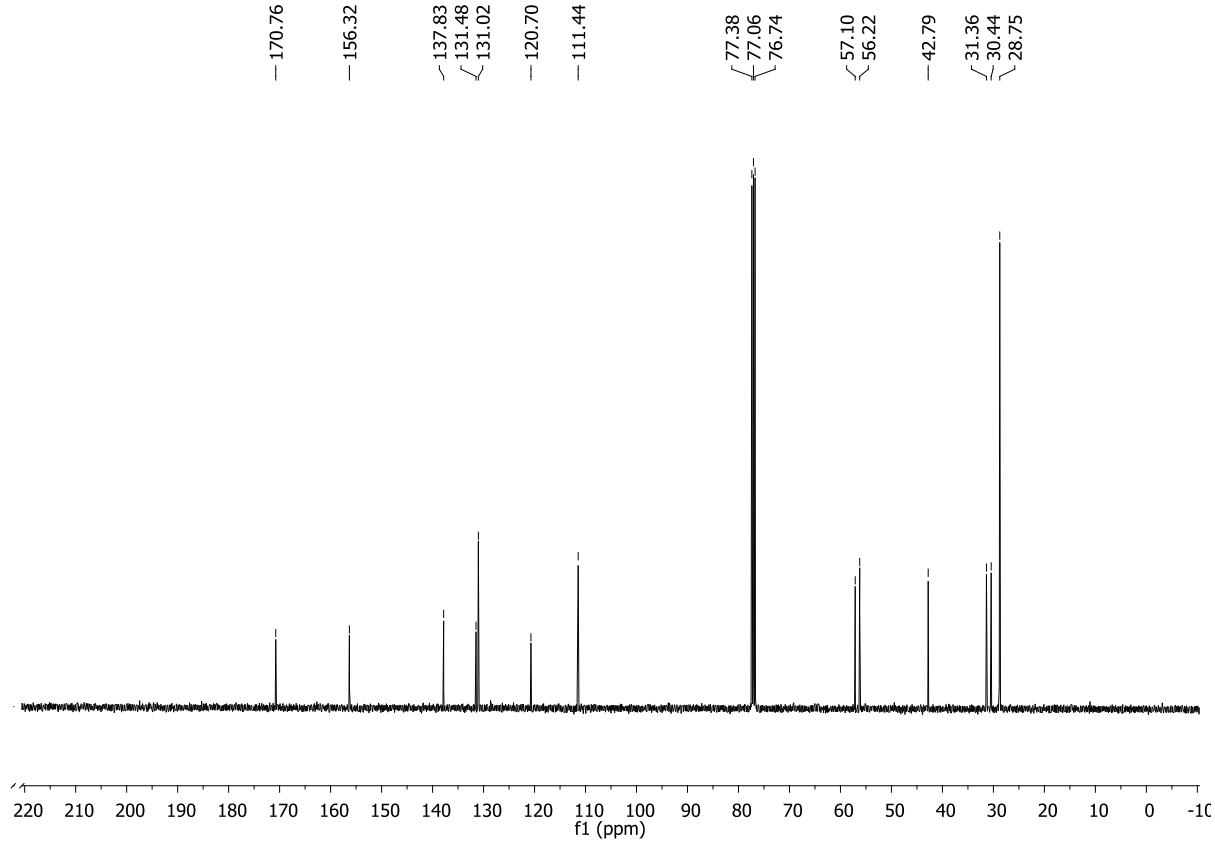


2-*tert*-butyl-7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105c).

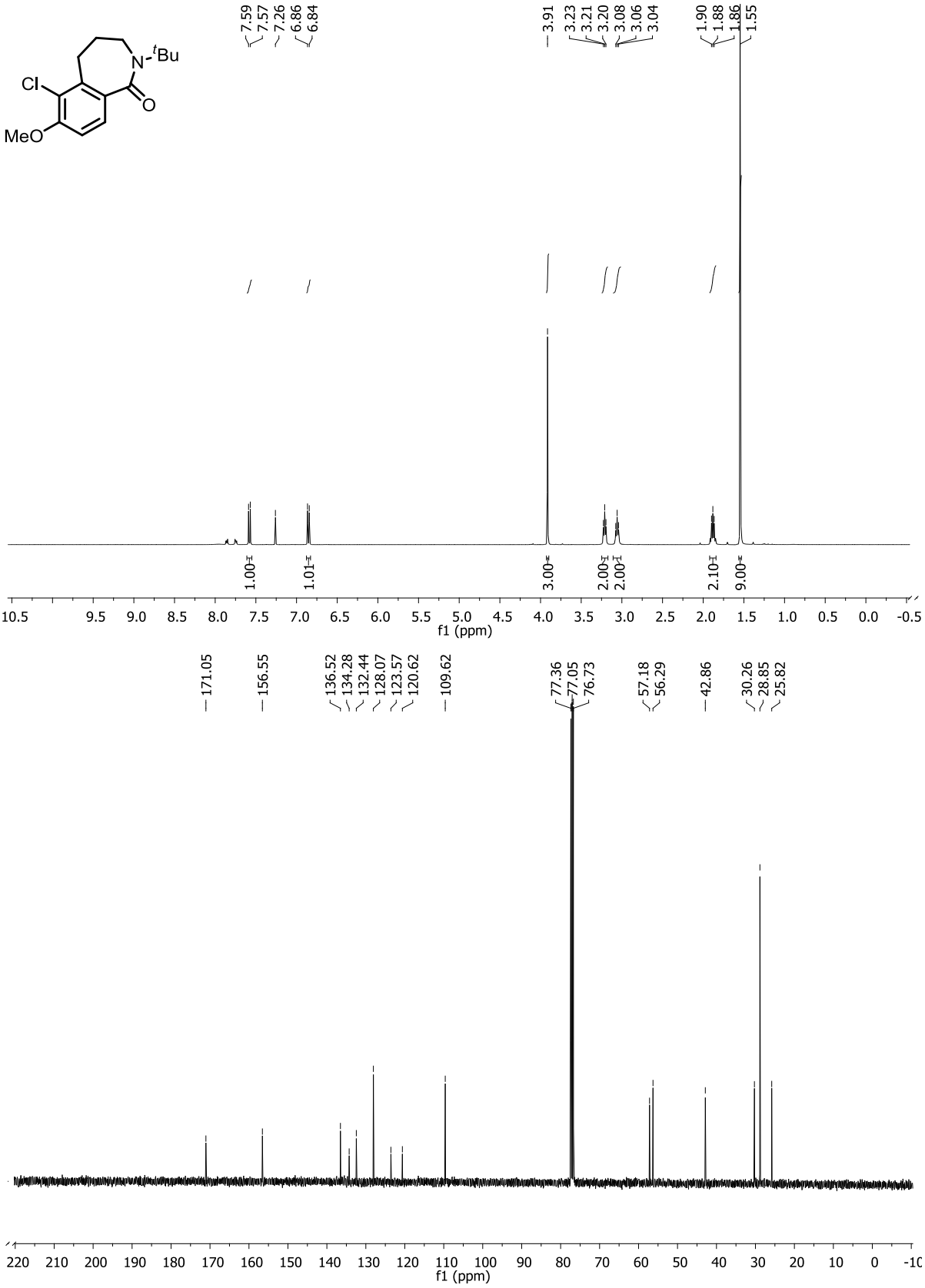


2-*tert*-butyl-8-chloro-7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105d´).

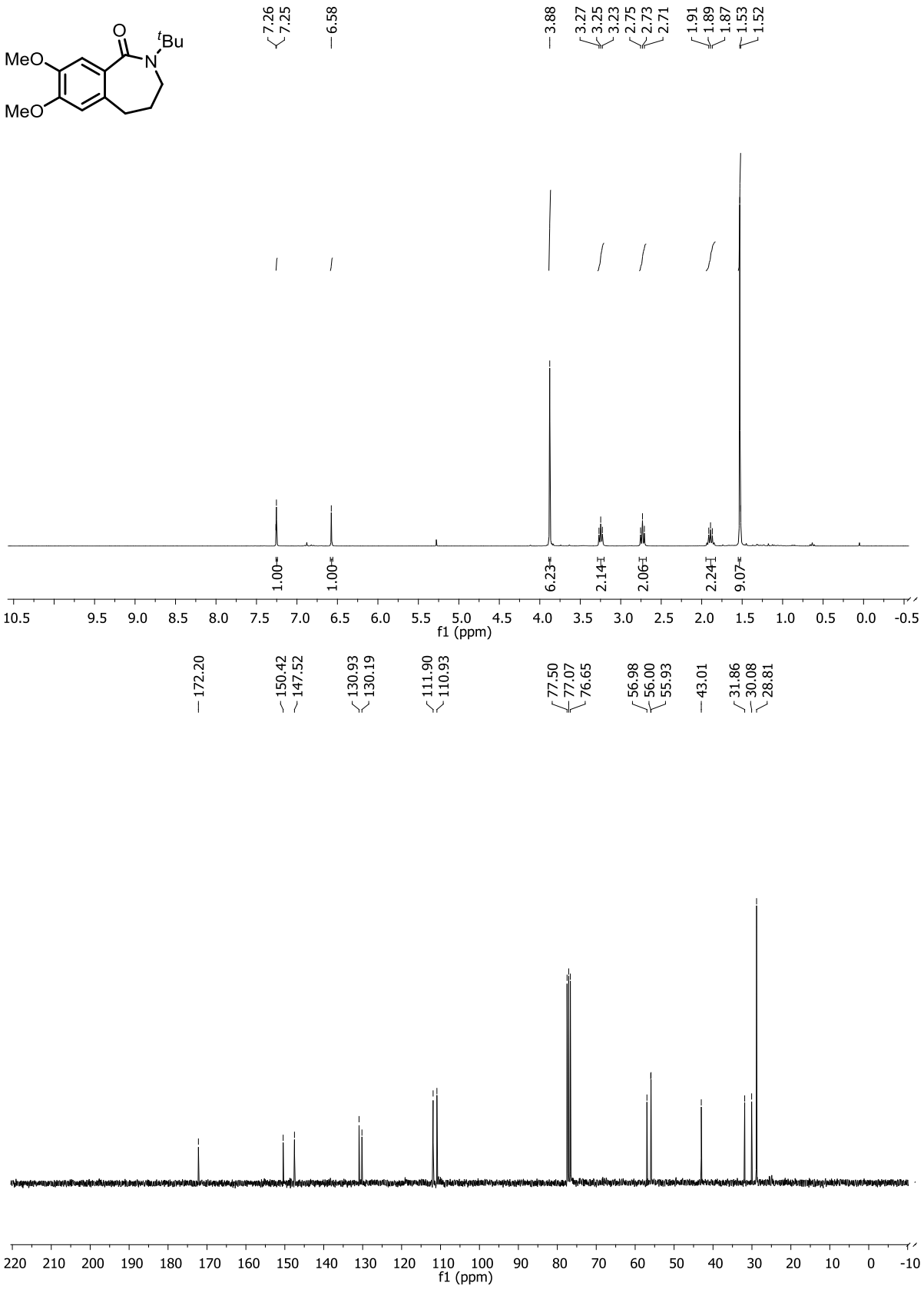




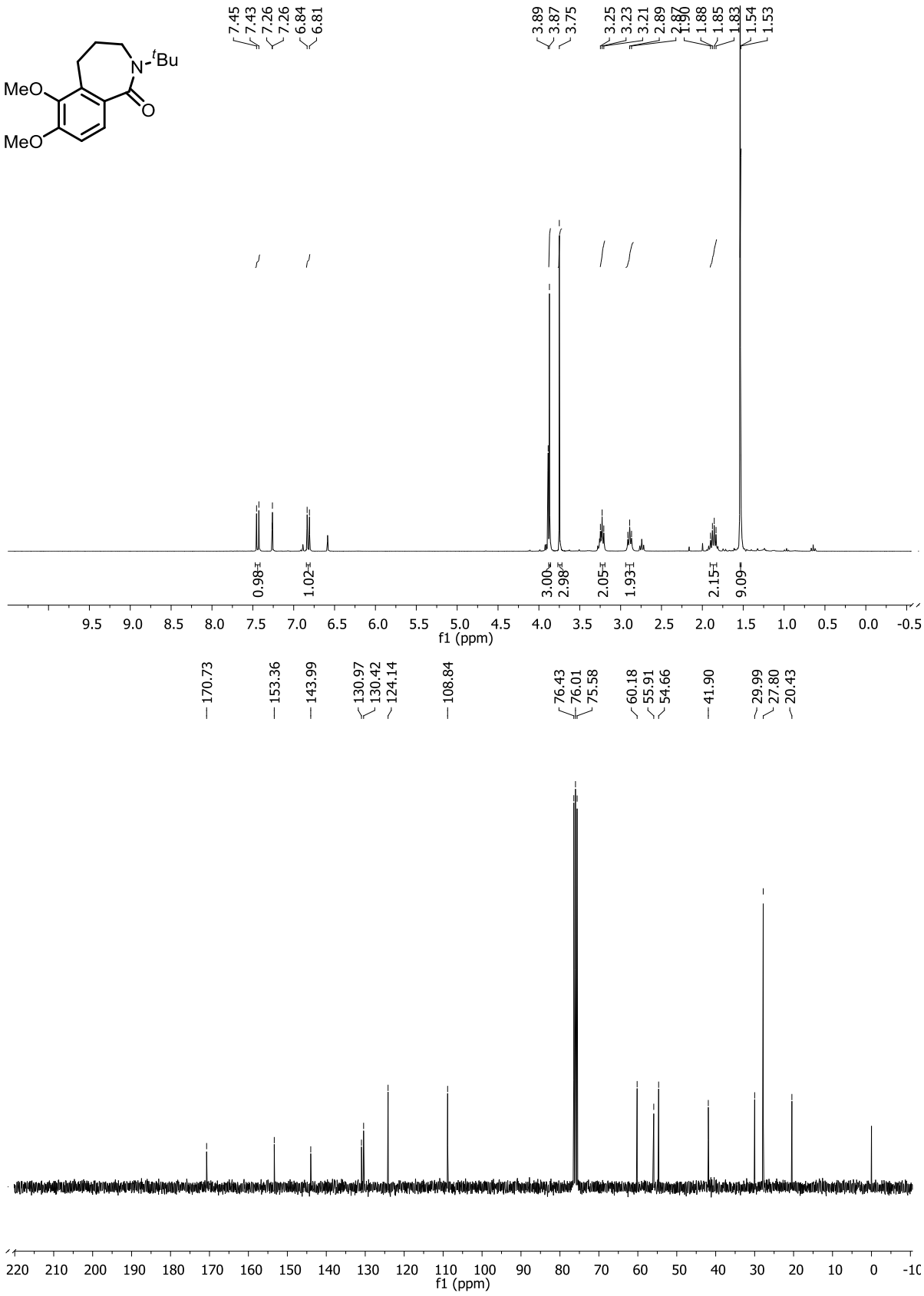
2-*tert*-butyl-6-chloro-7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105d´´).



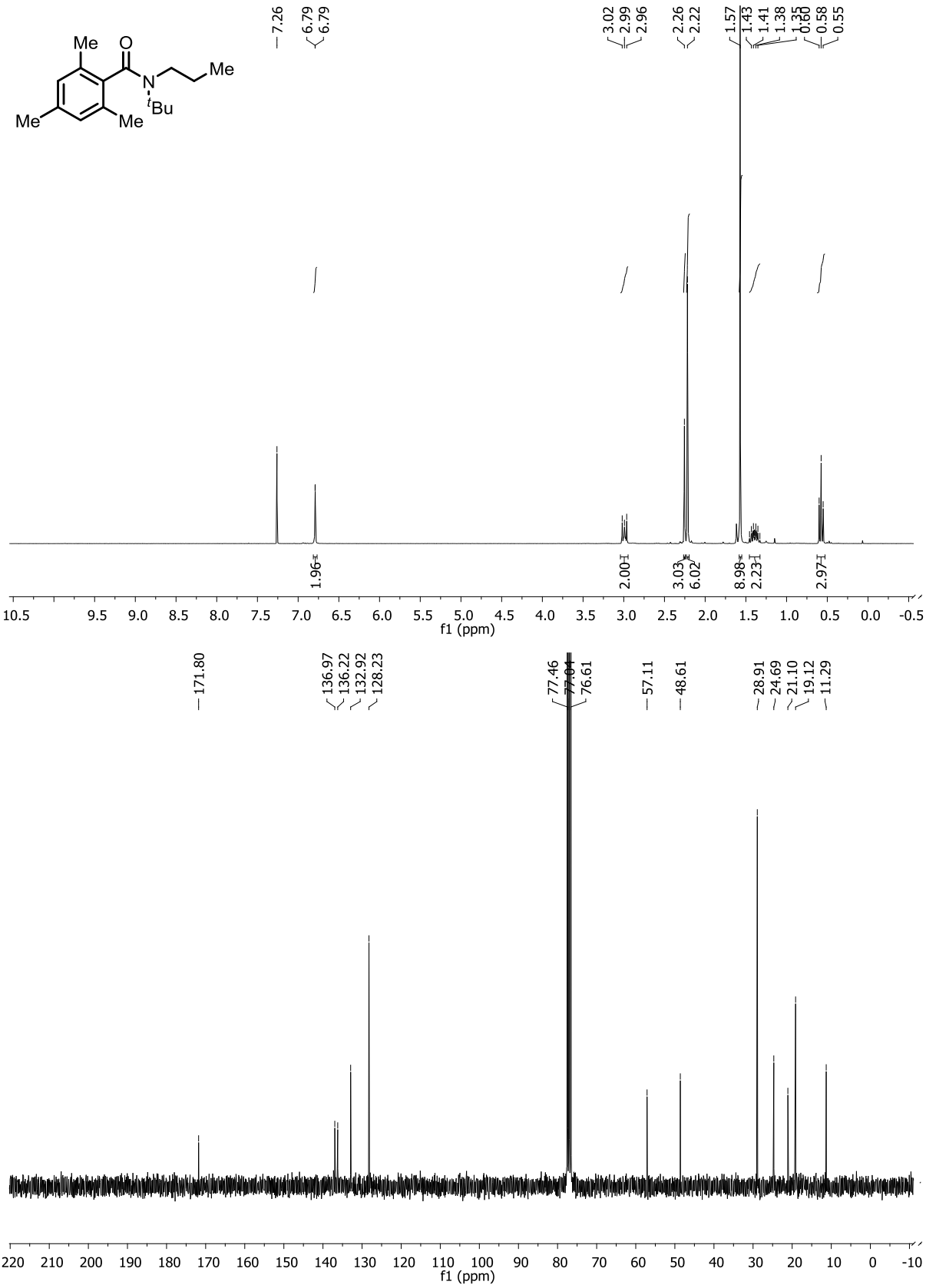
2-*tert*-butyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105e´).



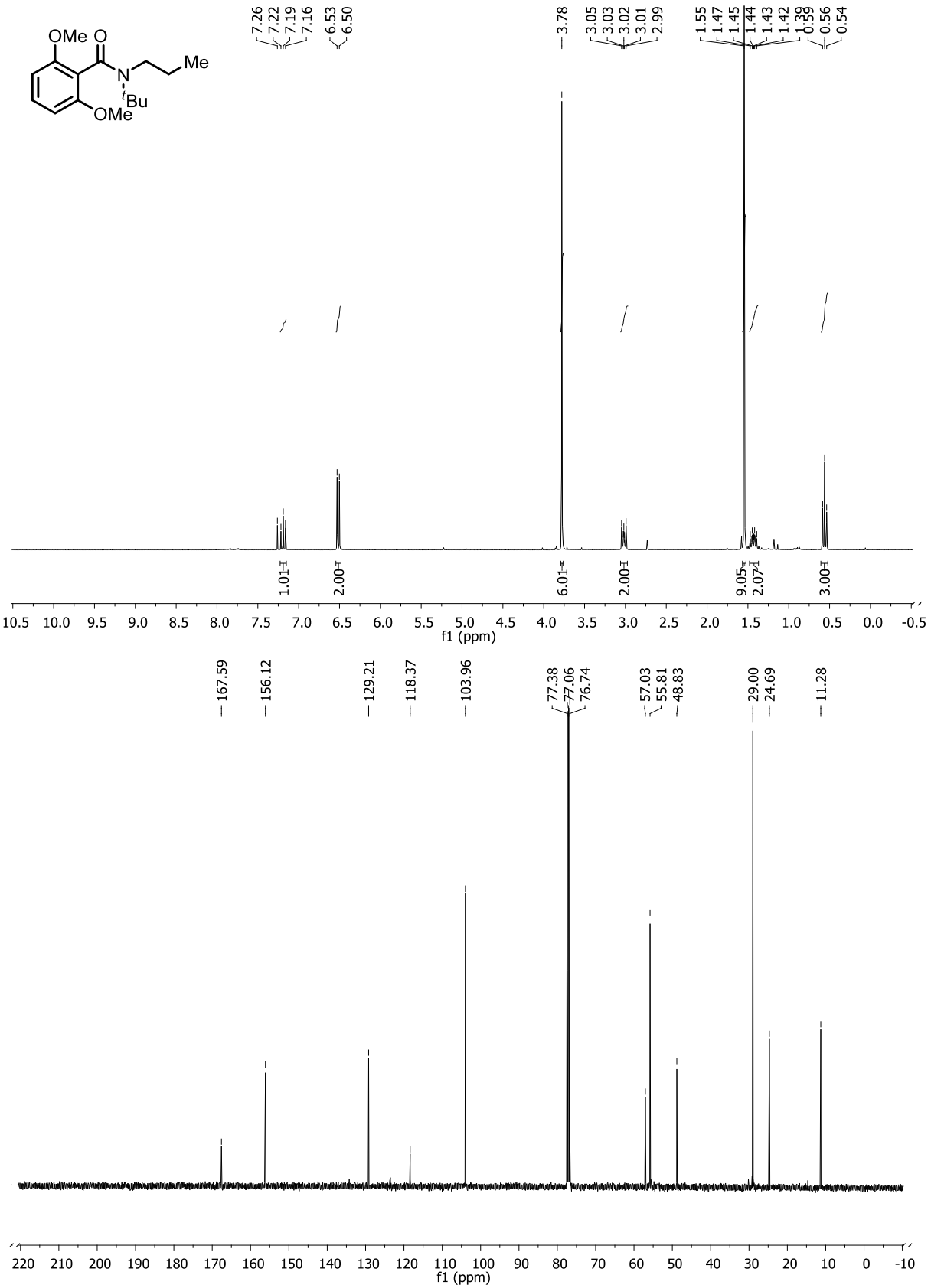
2-*tert*-butyl-6,7-dimethoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105e´´).



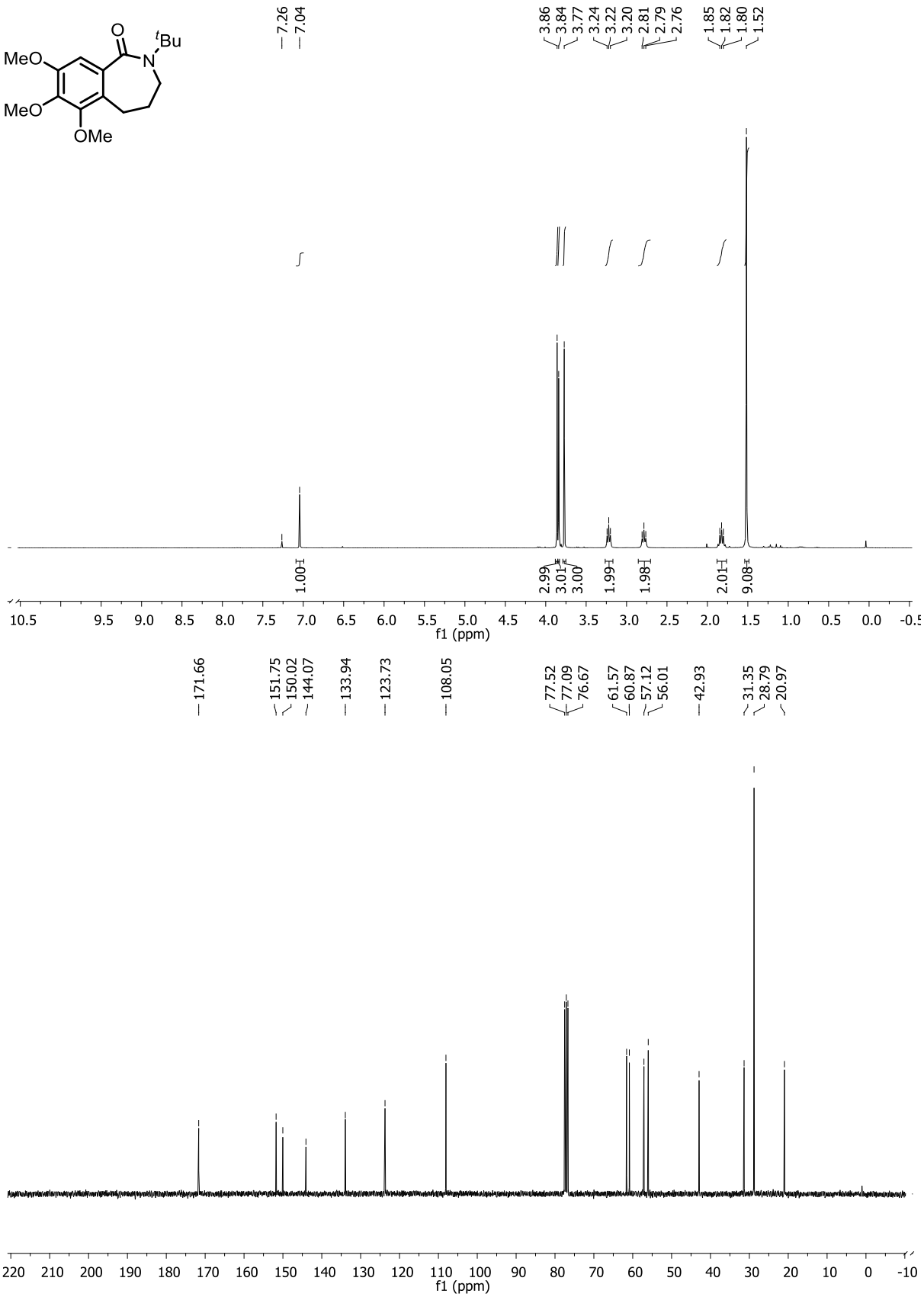
N-*tert*-Butyl-2,4,6-trimethyl-N-propylbenzamide (105f).



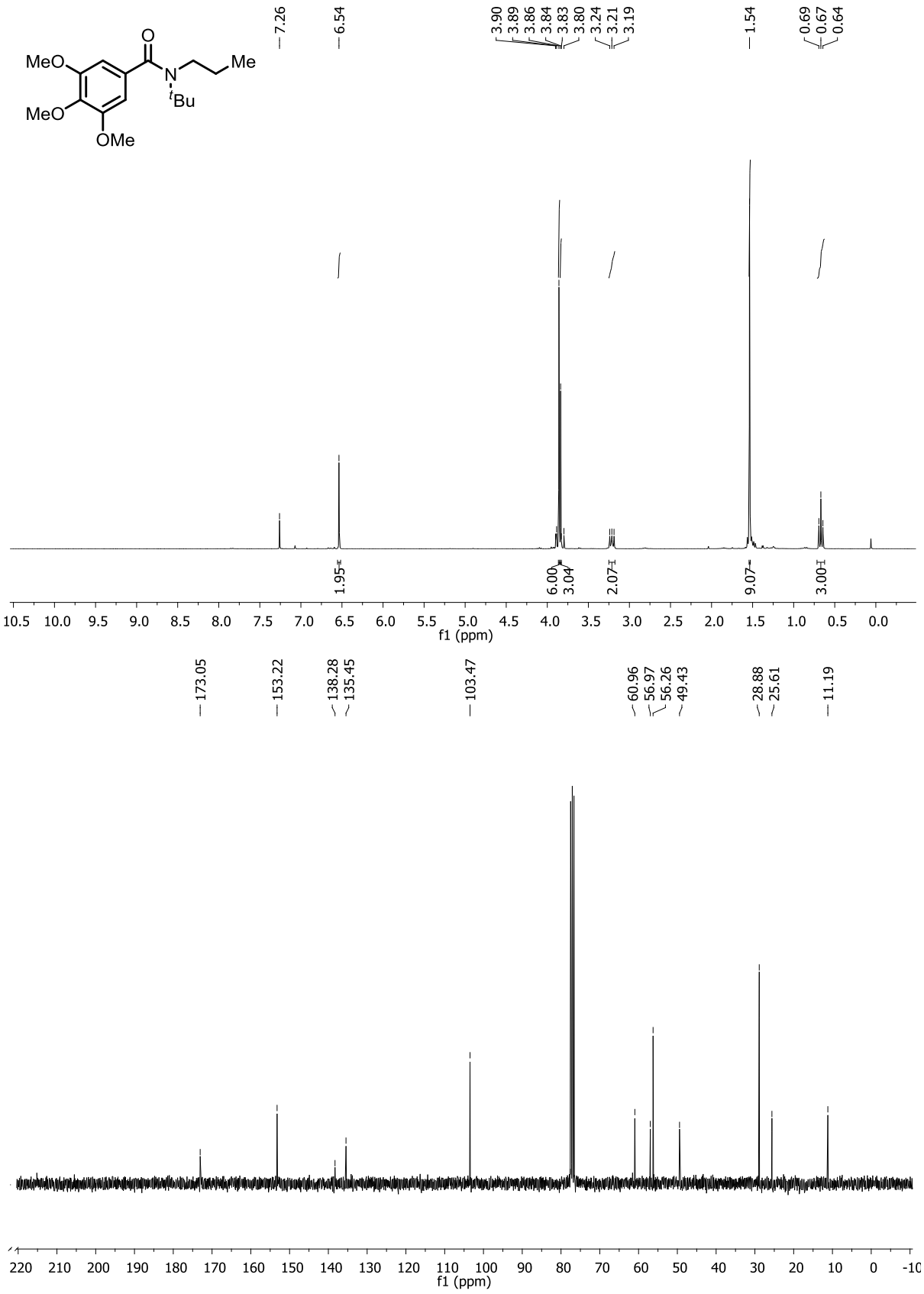
N-*tert*-butyl-2,6-dimethoxy-N-propylbenzamide (105g).



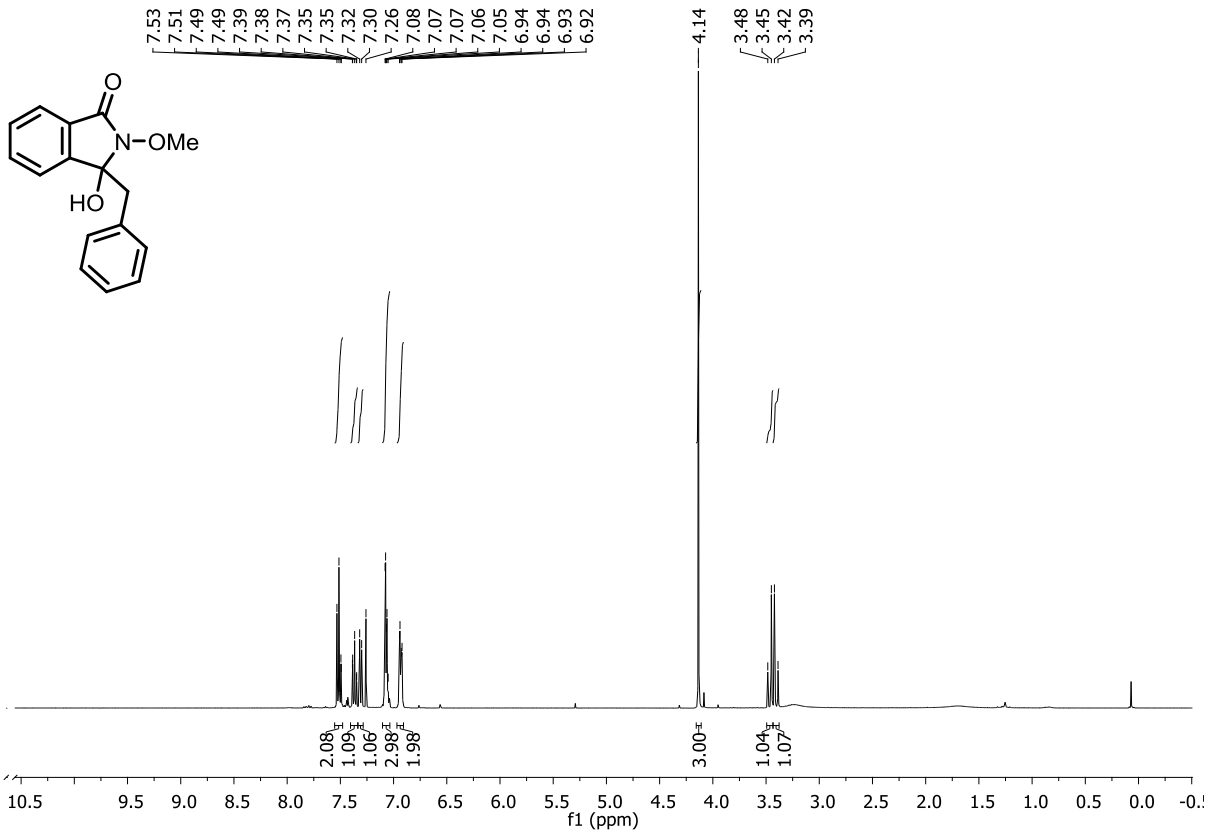
2-*tert*-butyl-6,7,8-trimethoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (105h).

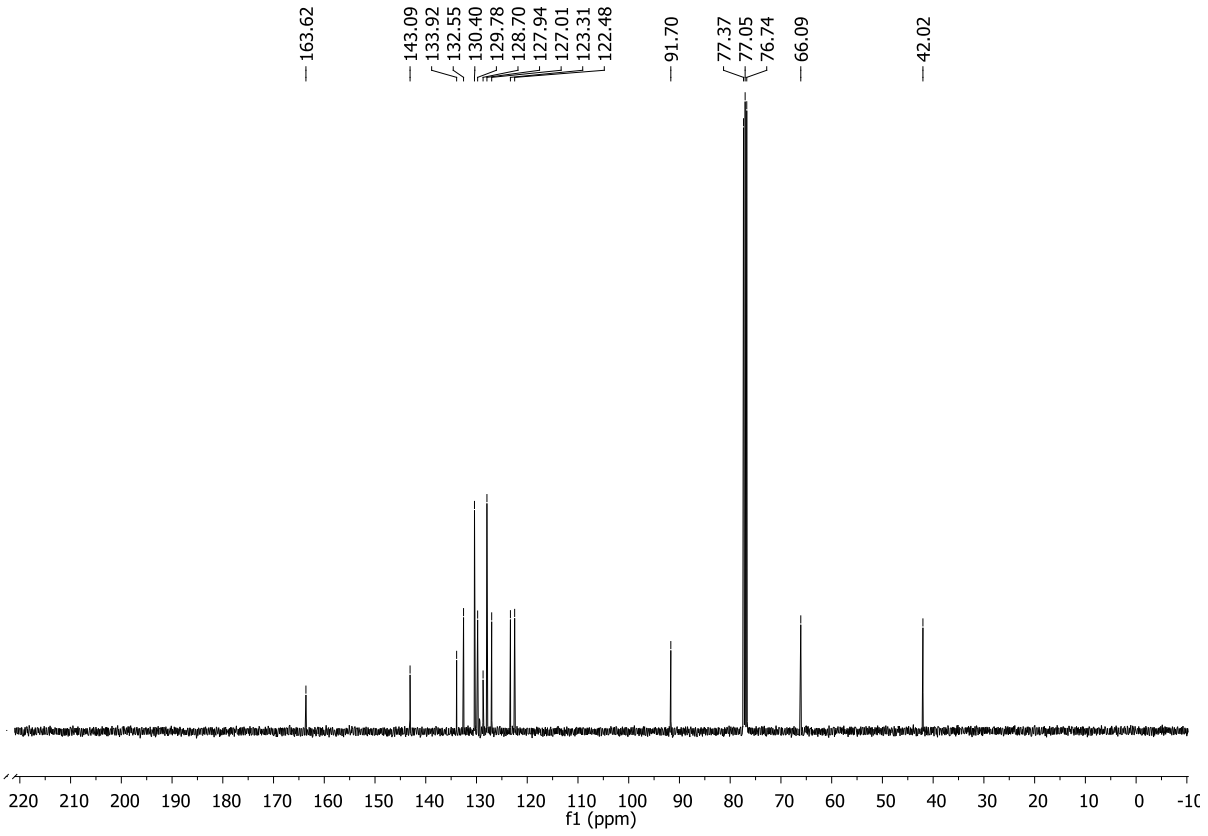


N-*tert*-butyl-3,4,5-trimethoxy-N-propylbenzamide (260).



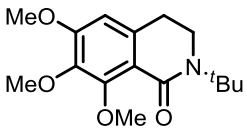
3-Benzyl-3-hydroxy-2-methoxyisoindolin-1-one (181).



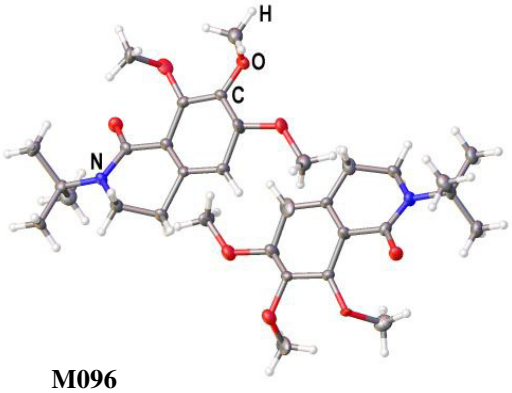


2 X-ray crystallographic data

2-*tert*-Butyl-6,7,8-trimethoxy-3,4-dihydroisoquinolin-1(2H)-one (80).



80



Compound	**M096**
CCDC	n/a
Formula	$C_{16}H_{23}NO_4$
$D_{calc.}$/ g cm^{-3}	1.260
μ/mm^{-1}	0.735
Formula Weight	293.35
Colour	colourless
Shape	block
Max Size/mm	0.17
Mid Size/mm	0.13
Min Size/mm	0.07
T/K	162.46(10)
Crystal System	orthorhombic
Flack Parameter	0.1(4)
Hooft Parameter	0.36(18)
Space Group	$Pca2_1$
a/Å	13.7745(2)
b/Å	9.69517(16)
c/Å	23.1634(4)
α/°	90
β/°	90
γ/°	90
V/Å^3	3093.38(9)
Z	8
Z'	2
Θ_{min}/°	3.817
Θ_{max}/°	73.533
Measured Refl.	17335
Independent Refl.	5726
Reflections Used	5000
R_{int}	0.0379
Parameters	474
Restraints	1
Largest Peak	0.259
Deepest Hole	-0.335
GooF	1.056
wR_2 (all data)	0.1642
wR_2	0.1529
R_1 (all data)	0.0581
R_1	0.0516

Table 1: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **M096**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
C1	-95(4)	22(3)	-924(2)	19.4(10)
C2	329(4)	98(3)	-337(3)	21.3(9)
C5	1593(4)	1(3)	-1253(3)	23.1(12)
C6	167(4)	-10(3)	-1984(3)	20.8(10)
C7	-460(3)	-1298(5)	-2100(2)	30.1(10)
C8	-422(3)	1316(5)	-2084(2)	32.3(10)
C9	1005(4)	-21(3)	-2426(2)	25.7(12)
C12	1009(4)	-154(4)	800(3)	27.9(11)
C3	1236(3)	-435(4)	-223(2)	16.9(8)
C4	1852(3)	-867(5)	-735(2)	21.4(10)
C10	-209(3)	645(5)	140(2)	18.6(8)
C11	120(3)	489(5)	700(2)	18.8(8)
C13	1588(3)	-619(6)	338(2)	18.9(9)
C14	-1002(4)	2603(5)	-239(3)	29.7(10)
C15	-304(4)	2325(5)	1292(3)	33.0(8)
C16	2178(4)	-1048(6)	1476(3)	33.0(8)
O2	-1066(2)	1339(4)	82(2)	21.9(8)
O3	-413(3)	899(3)	1164.6(19)	23.9(6)
O4	1277(3)	-348(4)	1365(2)	26.5(7)
C3A	1212(14)	390(20)	-219(11)	16.9(8)
C4A	1877(13)	900(20)	-754(11)	21.4(10)
C10A	-205(13)	-640(20)	139(11)	18.6(8)
C11A	86(13)	-574(18)	696(8)	18.8(8)
C13A	1594(13)	570(20)	339(11)	18.9(9)
C16A	2192(18)	1080(20)	1460(12)	33.0(8)
C14A	-986(15)	-2620(20)	-229(11)	27(4)
C15A	-286(16)	-2290(20)	1311(10)	33.0(8)
O2A	-1057(12)	-1354(16)	79(9)	28(4)
O3A	-395(11)	-869(14)	1161(9)	23.9(6)
O4A	1286(13)	321(19)	1355(9)	26.5(7)
C17	2577(4)	4972(3)	1939(2)	19.7(10)
C18	2155(4)	4896(3)	1340(3)	22.2(10)
C21	901(4)	4983(3)	2260(3)	23.1(11)
C22	2334(4)	5024(3)	2998(3)	22.8(11)
C23	1513(4)	5014(3)	3431(3)	30.1(14)
C24	2944(3)	3728(5)	3097(2)	32.3(10)
C25	2930(4)	6322(5)	3096(2)	33.3(10)
C28	1469(4)	5143(4)	205(3)	27.2(11)
N1	546(3)	-38(2)	-1379(2)	19.1(9)
N2	1951(3)	5023(2)	2386(2)	22.4(10)
O1	-976(3)	-8(2)	-994.3(19)	26.8(9)
O5	3479(3)	5016(2)	2001.9(18)	24.2(9)
C30	3510(4)	2403(5)	1259(3)	31.8(12)
C31	2809(5)	2645(5)	-271(3)	45.4(13)
O6	3566(2)	3655(4)	925.1(19)	20.9(8)
C19	1243(3)	5435(5)	1235(3)	18.6(9)
C20	661(3)	5858(5)	1741(2)	22.3(9)
C26	2698(3)	4342(5)	871(2)	17.6(8)
C27	2354(3)	4554(4)	308(2)	18.2(8)
C29	907(3)	5633(6)	674(3)	21.4(9)
C32	321(3)	6029(6)	-471(3)	26.2(9)
O7	2907(3)	4082(3)	-157.7(19)	22.6(6)
O8	1221(3)	5358(4)	-359(2)	27.4(7)
O7A	2910(11)	5931(15)	-156(9)	27.4(7)
O8A	1230(12)	4663(18)	-365(9)	27.4(7)
C27A	2317(12)	5350(20)	311(9)	18.2(8)
C19A	1215(13)	4530(20)	1233(10)	18.6(9)
C20A	689(16)	4140(20)	1730(11)	27(4)

Atom	x	y	z	U_{eq}
C26A	2677(12)	5640(20)	875(11)	17.6(8)
C29A	915(19)	4340(20)	672(13)	35(5)
C32A	343(13)	4000(20)	-491(11)	26.2(9)
O6A	3585(10)	6353(15)	921(8)	21(3)
C30A	3537(16)	7590(20)	1265(13)	31.8(12)
C31A	2920(20)	7400(20)	-221(11)	45.4(13)

Table 2: Anisotropic Displacement Parameters ($\times 10^4$) **M096**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + ... + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	18(2)	22(2)	18(3)	-2.1(10)	3.8(19)	1.5(9)
C2	17.5(19)	29.4(19)	17(2)	-0.2(14)	2.6(17)	-2.0(11)
C5	19(3)	31(3)	18(3)	0.8(11)	-0.5(19)	-0.8(10)
C6	25(3)	17(2)	20(3)	0.4(9)	-1(2)	-1(1)
C7	37(2)	26.3(19)	27(2)	-6.0(19)	-3.8(19)	-11.8(18)
C8	36(2)	28(2)	33(2)	6(2)	-4(2)	8.8(19)
C9	28(2)	33(3)	16(3)	1.3(11)	7(2)	-0.7(11)
C12	25(2)	45(2)	14(2)	0.3(19)	-1.2(17)	-4.9(14)
C3	19(2)	15(2)	17(2)	0.3(15)	1.8(15)	-2.3(13)
C4	12.4(18)	32(2)	20(2)	-0.1(14)	2.1(17)	0.8(13)
C10	17.6(19)	16.7(17)	21(2)	0.1(11)	0.4(15)	-2.4(11)
C11	18(2)	22(2)	17(2)	0.4(13)	3.8(15)	-1.7(12)
C13	13.3(19)	23(2)	20(2)	1.3(13)	-1.2(16)	-1.0(12)
C14	33(2)	21.2(19)	35(3)	1.8(16)	-4(2)	5.6(14)
C15	41.5(18)	30.4(16)	27.1(18)	-0.7(11)	1.0(14)	-2.8(11)
C16	41.5(18)	30.4(16)	27.1(18)	-0.7(11)	1.0(14)	-2.8(11)
O2	17.0(15)	23.9(16)	25(2)	0.1(16)	-0.1(14)	1.8(13)
O3	26.0(14)	25.9(13)	19.7(15)	-3.1(10)	7.4(11)	-1.4(10)
O4	27.0(15)	37.2(17)	15.4(17)	1.5(17)	-4.6(12)	0.6(16)
C3A	19(2)	15(2)	17(2)	0.3(15)	1.8(15)	-2.3(13)
C4A	12.4(18)	32(2)	20(2)	-0.1(14)	2.1(17)	0.8(13)
C10A	17.6(19)	16.7(17)	21(2)	0.1(11)	0.4(15)	-2.4(11)
C11A	18(2)	22(2)	17(2)	0.4(13)	3.8(15)	-1.7(12)
C13A	13.3(19)	23(2)	20(2)	1.3(13)	-1.2(16)	-1.0(12)
C16A	41.5(18)	30.4(16)	27.1(18)	-0.7(11)	1.0(14)	-2.8(11)
C14A	31(9)	30(8)	21(9)	-7(6)	-5(7)	-2(6)
C15A	41.5(18)	30.4(16)	27.1(18)	-0.7(11)	1.0(14)	-2.8(11)
O2A	35(8)	26(7)	23(9)	11(7)	-3(6)	9(6)
O3A	26.0(14)	25.9(13)	19.7(15)	-3.1(10)	7.4(11)	-1.4(10)
O4A	27.0(15)	37.2(17)	15.4(17)	1.5(17)	-4.6(12)	0.6(16)
C17	19(2)	20(2)	20(3)	-0.6(10)	-5(2)	0.0(9)
C18	16.9(19)	31(2)	19(2)	0.6(15)	0.0(18)	-2.9(11)
C21	17(3)	34(3)	18(3)	1.5(11)	2.7(18)	-1.1(10)
C22	25(3)	30(2)	13(3)	-0.5(10)	-5(2)	1.7(10)
C23	37(3)	34(3)	19(3)	-1.3(11)	-5(2)	2.4(12)
C24	36(2)	36(2)	25(2)	5(2)	-0.6(19)	7.5(19)
C25	38(2)	37(2)	24(2)	-7(2)	-2.4(19)	-6(2)
C28	20(2)	43(2)	19(3)	3.4(18)	0.8(17)	-1.6(14)
N1	16(2)	25.8(19)	16(2)	-1.2(9)	1.9(16)	1.0(8)
N2	20(2)	30(2)	17(2)	-1.0(9)	-3.3(17)	-0.7(9)
O1	18.0(19)	38(2)	24(2)	-1.6(8)	-1.1(15)	0.0(8)
O5	14.5(18)	35(2)	23(2)	-1.9(8)	-0.4(15)	-1.1(7)
C30	31(2)	21(2)	44(3)	2.7(16)	-2(2)	4.3(14)
C31	78(4)	26(2)	33(3)	-13.5(17)	16(2)	-7.6(19)
O6	17.0(16)	22.6(16)	22.9(19)	2.1(16)	5.3(14)	6.0(13)
C19	14.2(19)	22(2)	19(2)	-0.4(15)	0.7(15)	-4.1(13)
C20	16.2(17)	28(2)	23(2)	-1.8(15)	2.3(17)	0.8(14)
C26	14.5(19)	18.7(17)	19(2)	0.2(12)	0.4(14)	-2.3(10)
C27	21(2)	16(2)	18(2)	0.5(15)	4.1(15)	-4.3(13)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C29	16(2)	25(2)	23(2)	4.8(15)	0.0(15)	-1.4(14)
C32	16.3(16)	38(2)	25(2)	8.3(15)	-8.4(15)	-3.0(14)
O7	25.3(13)	24.0(13)	18.4(14)	-5.1(10)	4.6(11)	-2.1(10)
O8	27.4(16)	35.8(17)	19.1(18)	3.2(16)	-1.3(12)	1.6(15)
O7A	27.4(16)	35.8(17)	19.1(18)	3.2(16)	-1.3(12)	1.6(15)
O8A	27.4(16)	35.8(17)	19.1(18)	3.2(16)	-1.3(12)	1.6(15)
C27A	21(2)	16(2)	18(2)	0.5(15)	4.1(15)	-4.3(13)
C19A	14.2(19)	22(2)	19(2)	-0.4(15)	0.7(15)	-4.1(13)
C20A	30(9)	28(8)	22(9)	0(6)	-4(7)	7(6)
C26A	14.5(19)	18.7(17)	19(2)	0.2(12)	0.4(14)	-2.3(10)
C29A	58(13)	15(7)	31(11)	-6(6)	5(9)	7(7)
C32A	16.3(16)	38(2)	25(2)	8.3(15)	-8.4(15)	-3.0(14)
O6A	18(6)	26(6)	19(7)	-6(6)	10(5)	-13(5)
C30A	31(2)	21(2)	44(3)	2.7(16)	-2(2)	4.3(14)
C31A	78(4)	26(2)	33(3)	-13.5(17)	16(2)	-7.6(19)

Table 3: Bond Lengths in Å for **M096**.

Atom	Atom	Length/Å
C1	C2	1.482(8)
C1	N1	1.376(7)
C1	O1	1.224(8)
C2	C3	1.377(7)
C2	C10	1.432(7)
C2	C3A	1.28(2)
C2	C10A	1.51(2)
C5	C4	1.507(8)
C5	C4A	1.50(2)
C5	N1	1.472(6)
C6	C7	1.541(5)
C6	C8	1.537(6)
C6	C9	1.543(7)
C6	N1	1.495(7)
C12	C11	1.393(7)
C12	C13	1.409(8)
C12	O4	1.372(8)
C12	C11A	1.356(18)
C12	C13A	1.51(2)
C12	O4A	1.42(2)
C3	C4	1.518(7)
C3	C13	1.398(7)
C10	C11	1.383(7)
C10	O2	1.365(6)
C11	O3	1.362(6)
C14	O2	1.436(6)
C15	O3	1.422(6)
C16	O4	1.438(7)
C3A	C4A	1.62(3)
C3A	C13A	1.40(3)
C10A	C11A	1.35(3)
C10A	O2A	1.37(2)
C11A	O3A	1.30(3)
C16A	O4A	1.47(3)
C14A	O2A	1.42(3)
C15A	O3A	1.43(3)
C17	C18	1.506(8)
C17	N2	1.348(7)
C17	O5	1.251(8)
C18	C19	1.382(7)
C18	C26	1.423(7)
C18	C19A	1.367(18)
C18	C26A	1.48(2)
C21	N2	1.476(6)
C21	C20	1.508(8)
C21	C20A	1.51(2)
C22	C23	1.512(8)
C22	C24	1.529(6)
C22	C25	1.520(6)
C22	N2	1.513(7)
C28	C27	1.368(7)
C28	C29	1.416(8)
C28	O8	1.367(8)
C28	O8A	1.44(2)
C28	C27A	1.210(18)
C28	C29A	1.54(3)
C30	O6	1.441(7)
C31	O7	1.424(6)
O6	C26	1.375(6)
C19	C20	1.477(8)
C19	C29	1.395(7)
C26	C27	1.402(7)
C27	O7	1.398(6)
C32	O8	1.425(6)
O7A	C27A	1.47(2)
O7A	C31A	1.43(2)
O8A	C32A	1.41(2)
C27A	C26A	1.43(3)
C19A	C20A	1.41(3)
C19A	C29A	1.38(3)
C26A	O6A	1.43(2)
O6A	C30A	1.44(3)

Table 4: Bond Angles in ° for **M096**

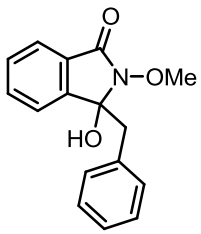
Atom	Atom	Atom	Angle/°
N1	C1	C2	116.9(5)
O1	C1	C2	120.9(5)
O1	C1	N1	122.2(6)
C1	C2	C10A	117.1(9)
C3	C2	C1	120.9(5)
C3	C2	C10	117.4(5)
C10	C2	C1	121.5(5)
C3A	C2	C1	125.6(12)
C3A	C2	C10A	114.4(15)
N1	C5	C4	112.1(4)
N1	C5	C4A	115.1(8)
C7	C6	C9	107.3(4)
C8	C6	C7	110.8(5)
C8	C6	C9	107.5(4)
N1	C6	C7	110.1(4)
N1	C6	C8	109.9(4)
N1	C6	C9	111.1(4)
C11	C12	C13	120.9(6)
O4	C12	C11	117.2(5)
O4	C12	C13	121.9(5)
C11A	C12	C13A	120.9(13)
C11A	C12	O4A	120.7(12)
O4A	C12	C13A	110.3(11)
C2	C3	C4	117.5(5)
C2	C3	C13	122.7(5)
C13	C3	C4	119.8(4)
C5	C4	C3	109.5(4)
C11	C10	C2	120.9(4)
O2	C10	C2	123.6(5)
O2	C10	C11	115.4(5)
C10	C11	C12	119.5(5)
O3	C11	C12	118.2(5)
O3	C11	C10	122.2(4)
C3	C13	C12	118.0(4)
C10	O2	C14	114.7(4)
C11	O3	C15	113.1(4)
C12	O4	C16	118.0(5)
C2	C3A	C4A	116.3(18)
C2	C3A	C13A	125.5(18)
C13A	C3A	C4A	117.1(16)
C5	C4A	C3A	105.4(14)
C11A	C10A	C2	122.0(15)
C11A	C10A	O2A	112.1(18)
O2A	C10A	C2	125.7(17)
C10A	C11A	C12	117.5(15)
O3A	C11A	C12	113.5(16)
O3A	C11A	C10A	129.0(17)
C3A	C13A	C12	113.2(15)
C10A	O2A	C14A	115.3(17)
C11A	O3A	C15A	111.1(16)
C12	O4A	C16A	122.8(17)
N2	C17	C18	117.6(5)
O5	C17	C18	119.5(5)
O5	C17	N2	122.9(5)
C19	C18	C17	119.5(5)
C19	C18	C26	119.1(5)
C26	C18	C17	121.2(5)
C19A	C18	C17	123.0(11)
C19A	C18	C26A	117.2(14)
C26A	C18	C17	117.2(9)
N2	C21	C20	110.9(4)
N2	C21	C20A	111.4(9)
C23	C22	C24	107.8(4)
C23	C22	C25	108.1(4)
C23	C22	N2	111.2(4)
C25	C22	C24	111.2(5)
N2	C22	C24	109.4(4)
N2	C22	C25	109.1(4)
C27	C28	C29	119.5(6)
O8	C28	C27	117.0(5)
O8	C28	C29	123.1(5)
O8A	C28	C29A	111.7(12)
C27A	C28	O8A	117.6(13)
C27A	C28	C29A	114.9(15)
C1	N1	C5	118.3(5)
C1	N1	C6	119.5(4)
C5	N1	C6	121.9(4)
C17	N2	C21	118.3(5)
C17	N2	C22	119.8(4)
C21	N2	C22	121.7(4)
C26	O6	C30	114.2(4)
C18	C19	C20	117.4(5)
C18	C19	C29	121.1(5)
C29	C19	C20	121.4(4)
C19	C20	C21	110.9(4)
O6	C26	C18	124.8(5)
O6	C26	C27	116.7(5)
C27	C26	C18	118.5(4)
C28	C27	C26	121.7(5)
C28	C27	O7	119.1(5)
O7	C27	C26	119.1(4)
C19	C29	C28	119.2(5)
C27	O7	C31	114.3(4)
C28	O8	C32	117.4(4)
C31A	O7A	C27A	117.6(17)
C32A	O8A	C28	122.4(16)
C28	C27A	O7A	116.9(16)
C28	C27A	C26A	123.8(16)
C26A	C27A	O7A	114.0(15)
C18	C19A	C20A	114.1(18)
C18	C19A	C29A	119.3(19)
C29A	C19A	C20A	125.6(19)
C19A	C20A	C21	114.9(17)
C27A	C26A	C18	113.6(14)
C27A	C26A	O6A	117.9(17)
O6A	C26A	C18	127.1(17)
C19A	C29A	C28	117(2)
C26A	O6A	C30A	113.7(15)

Table 5: Torsion Angles in ° for **M096**.

Atom	Atom	Atom	Atom	Angle/°
C1	C2	C3	C4	10.5(6)
C1	C2	C3	C13	-167.8(4)
C1	C2	C10	C11	168.4(4)
C1	C2	C10	O2	-11.3(7)
C1	C2	C3A	C4A	8(2)
C1	C2	C3A	C13A	174.8(16)
C1	C2	C10A	C11A	-176.0(15)
C1	C2	C10A	O2A	-1(2)
C2	C1	N1	C5	-1.0(4)
C2	C1	N1	C6	-175.5(2)
C2	C3	C4	C5	29.1(6)
C2	C3	C13	C12	-4.2(7)
C2	C10	C11	C12	3.0(7)
C2	C10	C11	O3	-174.5(4)
C2	C10	O2	C14	-62.8(6)
C2	C3A	C4A	C5	-40(2)
C2	C3A	C13A	C12	23(3)
C2	C10A	C11A	C12	-18(3)
C2	C10A	C11A	O3A	162.6(17)
C2	C10A	O2A	C14A	71(2)
C7	C6	N1	C1	-63.8(4)
C7	C6	N1	C5	122.0(4)
C8	C6	N1	C1	58.6(4)
C8	C6	N1	C5	-115.6(4)
C9	C6	N1	C1	177.5(2)
C9	C6	N1	C5	3.2(3)
C12	C11	O3	C15	98.7(5)
C12	C11A	O3A	C15A	-90.3(18)
C3	C2	C10	C11	-7.8(7)
C3	C2	C10	O2	172.5(4)
C4	C5	N1	C1	41.4(5)
C4	C5	N1	C6	-144.3(4)
C4	C3	C13	C12	177.5(5)
C10	C2	C3	C4	-173.3(4)
C10	C2	C3	C13	8.5(6)
C10	C11	O3	C15	-83.7(6)
C11	C12	C13	C3	-1.0(7)
C11	C12	O4	C16	178.1(4)
C11	C10	O2	C14	117.5(5)
C13	C12	C11	C10	1.4(7)
C13	C12	C11	O3	179.1(4)
C13	C12	O4	C16	0.1(7)
C13	C3	C4	C5	-152.6(4)
O2	C10	C11	C12	-177.3(4)
O2	C10	C11	O3	5.1(7)
O4	C12	C11	C10	-176.6(4)
O4	C12	C11	O3	1.0(7)
O4	C12	C13	C3	177.0(4)
C3A	C2	C10A	C11A	22(2)
C3A	C2	C10A	O2A	-163.5(18)
C4A	C5	N1	C1	-35.6(11)
C4A	C5	N1	C6	138.8(11)
C4A	C3A	C13A	C12	-169.9(15)
C10A	C2	C3A	C4A	167.9(16)
C10A	C2	C3A	C13A	-25(3)
C10A	C11A	O3A	C15A	89(3)
C11A	C12	C13A	C3A	-17(2)
C11A	C12	O4A	C16A	-165.5(17)
C11A	C10A	O2A	C14A	-114(2)
C13A	C12	C11A	C10A	16(2)
C13A	C12	C11A	O3A	-164.5(15)
C13A	C12	O4A	C16A	-16(2)
C13A	C3A	C4A	C5	151.6(18)
O2A	C10A	C11A	C12	166.6(14)
O2A	C10A	C11A	O3A	-13(3)
O4A	C12	C11A	C10A	161.9(16)
O4A	C12	C11A	O3A	-19(2)
O4A	C12	C13A	C3A	-166.1(16)
C17	C18	C19	C20	-9.7(6)
C17	C18	C19	C29	167.2(4)
C17	C18	C26	O6	10.1(7)
C17	C18	C26	C27	-167.1(4)
C17	C18	C19A	C20A	-4(2)
C17	C18	C19A	C29A	-173.2(15)
C17	C18	C26A	C27A	171.2(12)
C17	C18	C26A	O6A	5(2)
C18	C17	N2	C21	0.8(4)
C18	C17	N2	C22	176.8(2)
C18	C19	C20	C21	-30.4(6)
C18	C19	C29	C28	6.5(8)
C18	C26	C27	C28	-7.0(7)
C18	C26	C27	O7	176.5(4)
C18	C19A	C20A	C21	39(2)
C18	C19A	C29A	C28	-26(3)
C18	C26A	O6A	C30A	-69(2)
C23	C22	N2	C17	-177.2(2)
C23	C22	N2	C21	-1.4(3)
C24	C22	N2	C17	-58.2(4)
C24	C22	N2	C21	117.7(4)
C25	C22	N2	C17	63.7(4)
C25	C22	N2	C21	-120.5(4)
C28	C27	O7	C31	-96.6(5)
C28	C27A	C26A	C18	35(3)
C28	C27A	C26A	O6A	-157.6(16)
N1	C1	C2	C3	-26.6(5)
N1	C1	C2	C10	157.3(4)
N1	C1	C2	C3A	15.2(12)
N1	C1	C2	C10A	-144.6(9)
N1	C5	C4	C3	-54.2(5)
N1	C5	C4A	C3A	53.3(16)
N2	C17	C18	C19	26.6(5)
N2	C17	C18	C26	-156.6(4)
N2	C17	C18	C19A	-17.3(11)
N2	C17	C18	C26A	144.0(9)
N2	C21	C20	C19	55.4(5)
N2	C21	C20A	C19A	-53.5(19)
O1	C1	C2	C3	152.3(4)
O1	C1	C2	C10	-23.8(5)
O1	C1	C2	C3A	-165.9(12)
O1	C1	C2	C10A	34.3(10)
O1	C1	N1	C5	-179.8(3)
O1	C1	N1	C6	5.7(4)
O5	C17	C18	C19	-151.8(4)
O5	C17	C18	C26	25.0(5)
O5	C17	C18	C19A	164.3(11)
O5	C17	C18	C26A	-34.4(10)
O5	C17	N2	C21	179.1(3)
O5	C17	N2	C22	-4.9(4)

Atom	Atom	Atom	Atom	Angle/°
C30	O6	C26	C18	61.8(6)
C30	O6	C26	C27	-121.0(5)
O6	C26	C27	C28	175.6(4)
O6	C26	C27	O7	-0.9(6)
C19	C18	C26	O6	-173.2(4)
C19	C18	C26	C27	9.7(6)
C20	C21	N2	C17	-41.0(5)
C20	C21	N2	C22	143.2(4)
C20	C19	C29	C28	-176.7(5)
C26	C18	C19	C20	173.4(4)
C26	C18	C19	C29	-9.6(7)
C26	C27	O7	C31	80.0(6)
C27	C28	C29	C19	-3.6(7)
C27	C28	O8	C32	-177.2(4)
C29	C28	C27	C26	4.0(7)
C29	C28	C27	O7	-179.5(4)
C29	C28	O8	C32	-4.2(7)
C29	C19	C20	C21	152.7(5)
O8	C28	C27	C26	177.2(4)
O8	C28	C27	O7	-6.3(6)
O8	C28	C29	C19	-176.4(4)
O7A	C27A	C26A	C18	-171.9(14)
O7A	C27A	C26A	O6A	-4(3)
O8A	C28	C27A	O7A	37(2)
O8A	C28	C27A	C26A	-170.9(17)
O8A	C28	C29A	C19A	168.2(17)
C27A	C28	O8A	C32A	160.6(17)
C27A	C28	C29A	C19A	31(2)
C27A	C26A	O6A	C30A	125(2)
C19A	C18	C26A	C27A	-26(2)
C19A	C18	C26A	O6A	167.4(17)
C20A	C21	N2	C17	31.9(10)
C20A	C21	N2	C22	-144.0(10)
C20A	C19A	C29A	C28	165.5(18)
C26A	C18	C19A	C20A	-165.0(17)
C26A	C18	C19A	C29A	26(2)
C29A	C28	O8A	C32A	25(2)
C29A	C28	C27A	O7A	171.1(15)
C29A	C28	C27A	C26A	-36(2)
C29A	C19A	C20A	C21	-153(2)
C31A	O7A	C27A	C28	86(2)
C31A	O7A	C27A	C26A	-69(2)

3-Benzyl-3-hydroxy-2-methoxyisoindolin-1-one (181).



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Crystal data	
Chemical formula	$C_{16}H_{15}NO_3$
M_r	269.29
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	100
a, b, c (Å)	9.0510 (18), 10.638 (2), 14.281 (3)
V (Å^3)	1375.0 (5)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.09
Crystal size (mm)	0.12 × 0.08 × 0.05
Data collection	
Diffractometer	?
Absorption correction	Multi-scan
T_{min}, T_{max}	0.989, 0.995
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	13342, 2344, 2334
R_{int}	0.111
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.594
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.047, 0.123, 1.13
No. of reflections	2344
No. of parameters	186
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.24, −0.26
Absolute structure	Flack x determined using 987 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	0.0 (5)

Crystal data

$C_{16}H_{15}NO_3$	$F(000) = 568$
$M_r = 269.29$	$D_x = 1.301$ Mg m^{-3}
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 9.0510$ (18) Å	$\mu = 0.09$ mm^{-1}
$b = 10.638$ (2) Å	$T = 100$ K
$c = 14.281$ (3) Å	Prism, colorless
$V = 1375.0$ (5) Å^3	0.12 × 0.08 × 0.05 mm
$Z = 4$	

Data collection

Absorption correction: multi-scan	$R_{int} = 0.111$
$T_{min} = 0.989$, $T_{max} = 0.995$	$\theta_{max} = 25.0°$, $\theta_{min} = 2.7°$
13342 measured reflections	$h = -10 \rightarrow 10$
2344 independent reflections	$k = -12 \rightarrow 12$
2334 reflections with $I > 2\sigma(I)$	$l = -16 \rightarrow 16$

Refinement

Refinement on F^2	Hydrogen site location: mixed
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.047$	$w = 1/[\sigma^2(F_o^2) + (0.0747P)^2 + 0.2092P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.123$	$(\Delta/\sigma)_{max} = 0.001$
$S = 1.13$	$\Delta\rho_{max} = 0.24$ e Å^{-3}
2344 reflections	$\Delta\rho_{min} = -0.26$ e Å^{-3}
186 parameters	Absolute structure: Flack x determined using 987 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
0 restraints	Absolute structure parameter: 0.0 (5)

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{iso}*/U_{eq}
O1	0.43782 (17)	0.57477 (15)	0.25714 (12)	0.0173 (4)
N1	0.5911 (2)	0.58154 (17)	0.26503 (14)	0.0132 (4)
C9	0.3933 (3)	0.6076 (3)	0.16350 (17)	0.0232 (6)
H1A	0.4278	0.6927	0.1488	0.035*
H1B	0.2853	0.6047	0.1589	0.035*
H1C	0.4364	0.5478	0.1190	0.035*
O2	0.65760 (18)	0.79842 (16)	0.27454 (12)	0.0180 (4)
C1	0.6585 (2)	0.6828 (2)	0.32124 (16)	0.0133 (5)
O3	0.63180 (17)	0.37395 (15)	0.22574 (12)	0.0200 (4)
C2	0.8153 (2)	0.6336 (2)	0.32560 (15)	0.0133 (5)
C7	0.8227 (2)	0.5124 (2)	0.29043 (15)	0.0137 (5)
C8	0.6738 (2)	0.4753 (2)	0.25705 (15)	0.0148 (5)
C6	0.9542 (3)	0.4464 (2)	0.28695 (16)	0.0170 (5)
H6	0.9575	0.3624	0.2644	0.020*
C5	1.0812 (2)	0.5069 (2)	0.31742 (17)	0.0193 (5)
H5	1.1734	0.4644	0.3149	0.023*
C4	1.0747 (3)	0.6294 (2)	0.35172 (17)	0.0194 (5)
H4	1.1630	0.6696	0.3716	0.023*
C3	0.9412 (3)	0.6941 (2)	0.35737 (16)	0.0158 (5)
H3	0.9366	0.7769	0.3822	0.019*
C10	0.5835 (3)	0.6925 (2)	0.41836 (17)	0.0175 (5)
H10A	0.6398	0.7527	0.4574	0.021*
H10B	0.4826	0.7267	0.4102	0.021*
C11	0.5736 (3)	0.5685 (2)	0.46938 (16)	0.0169 (5)
C12	0.4445 (3)	0.4975 (3)	0.46567 (16)	0.0211 (5)
H12	0.3608	0.5298	0.4336	0.025*
C13	0.4360 (3)	0.3809 (3)	0.50777 (18)	0.0279 (6)
H13	0.3468	0.3340	0.5047	0.034*
C14	0.5577 (3)	0.3321 (3)	0.55453 (18)	0.0292 (7)
H14	0.5525	0.2515	0.5829	0.035*
C15	0.6867 (3)	0.4019 (3)	0.55950 (17)	0.0266 (6)
H15	0.7703	0.3690	0.5915	0.032*
C16	0.6943 (3)	0.5196 (2)	0.51793 (16)	0.0206 (5)
H16	0.7826	0.5674	0.5226	0.025*
H1	0.570 (4)	0.824 (3)	0.278 (3)	0.035 (9)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0071 (7)	0.0215 (9)	0.0231 (9)	−0.0020 (6)	−0.0030 (6)	0.0021 (7)
N1	0.0069 (9)	0.0131 (10)	0.0197 (9)	−0.0010 (7)	−0.0028 (7)	−0.0007 (8)
C9	0.0183 (11)	0.0290 (13)	0.0224 (12)	0.0000 (10)	−0.0059 (10)	0.0040 (11)
O2	0.0142 (8)	0.0116 (8)	0.0283 (9)	0.0011 (6)	−0.0003 (7)	0.0063 (7)
C1	0.0121 (11)	0.0100 (10)	0.0179 (11)	−0.0012 (8)	−0.0021 (9)	0.0003 (8)
O3	0.0163 (8)	0.0138 (9)	0.0299 (9)	−0.0030 (6)	−0.0001 (7)	−0.0061 (7)
C2	0.0133 (11)	0.0124 (11)	0.0143 (10)	0.0007 (9)	0.0014 (8)	0.0017 (8)
C7	0.0138 (10)	0.0124 (10)	0.0149 (10)	−0.0014 (9)	0.0008 (8)	0.0014 (8)
C8	0.0138 (10)	0.0146 (12)	0.0158 (10)	−0.0018 (8)	0.0010 (9)	0.0011 (9)
C6	0.0174 (11)	0.0147 (10)	0.0189 (11)	0.0017 (9)	−0.0005 (9)	−0.0001 (9)
C5	0.0136 (10)	0.0208 (11)	0.0235 (12)	0.0038 (9)	0.0007 (9)	0.0034 (10)
C4	0.0147 (11)	0.0227 (12)	0.0209 (11)	−0.0037 (9)	−0.0027 (9)	0.0019 (10)
C3	0.0156 (11)	0.0132 (11)	0.0185 (11)	−0.0009 (9)	−0.0018 (9)	−0.0003 (9)
C10	0.0167 (11)	0.0142 (11)	0.0216 (12)	0.0032 (9)	0.0014 (9)	−0.0035 (9)
C11	0.0190 (12)	0.0170 (12)	0.0147 (10)	0.0013 (9)	0.0032 (9)	−0.0020 (9)
C12	0.0165 (11)	0.0282 (12)	0.0187 (11)	0.0007 (10)	0.0027 (9)	0.0012 (10)
C13	0.0303 (14)	0.0291 (14)	0.0244 (12)	−0.0097 (11)	0.0072 (11)	−0.0001 (12)
C14	0.0449 (17)	0.0234 (14)	0.0191 (11)	0.0003 (12)	0.0058 (11)	0.0039 (10)
C15	0.0352 (15)	0.0281 (14)	0.0166 (11)	0.0094 (11)	−0.0028 (11)	0.0023 (10)
C16	0.0205 (11)	0.0250 (12)	0.0162 (11)	0.0005 (10)	−0.0018 (9)	−0.0020 (9)

Geometric parameters (Å, º)

O1—N1	1.394 (2)	C5—C4	1.393 (4)
O1—C9	1.440 (3)	C4—H4	0.9500
N1—C1	1.475 (3)	C4—C3	1.394 (3)
N1—C8	1.360 (3)	C3—H3	0.9500
C9—H1A	0.9800	C10—H10A	0.9900
C9—H1B	0.9800	C10—H10B	0.9900
C9—H1C	0.9800	C10—C11	1.510 (3)
O2—C1	1.399 (3)	C11—C12	1.393 (4)
O2—H1	0.84 (4)	C11—C16	1.394 (3)
C1—C2	1.514 (3)	C12—H12	0.9500
C1—C10	1.547 (3)	C12—C13	1.380 (4)
O3—C8	1.228 (3)	C13—H13	0.9500
C2—C7	1.385 (3)	C13—C14	1.388 (4)
C2—C3	1.385 (3)	C14—H14	0.9500
C7—C8	1.483 (3)	C14—C15	1.386 (4)
C7—C6	1.383 (3)	C15—H15	0.9500

C6—H6	0.9500	C15—C16	1.388 (4)
C6—C5	1.387 (3)	C16—H16	0.9500
C5—H5	0.9500		
N1—O1—C9	109.96 (17)	C4—C5—H5	119.7
O1—N1—C1	119.56 (17)	C5—C4—H4	119.4
C8—N1—O1	119.88 (18)	C5—C4—C3	121.3 (2)
C8—N1—C1	115.12 (18)	C3—C4—H4	119.4
O1—C9—H1A	109.5	C2—C3—C4	117.7 (2)
O1—C9—H1B	109.5	C2—C3—H3	121.2
O1—C9—H1C	109.5	C4—C3—H3	121.2
H1A—C9—H1B	109.5	C1—C10—H10A	108.8
H1A—C9—H1C	109.5	C1—C10—H10B	108.8
H1B—C9—H1C	109.5	H10A—C10—H10B	107.7
C1—O2—H1	105 (2)	C11—C10—C1	113.58 (18)
N1—C1—C2	99.07 (17)	C11—C10—H10A	108.8
N1—C1—C10	110.81 (18)	C11—C10—H10B	108.8
O2—C1—N1	112.34 (18)	C12—C11—C10	120.4 (2)
O2—C1—C2	109.20 (17)	C12—C11—C16	118.3 (2)
O2—C1—C10	111.46 (18)	C16—C11—C10	121.3 (2)
C2—C1—C10	113.40 (17)	C11—C12—H12	119.4
C7—C2—C1	110.60 (18)	C13—C12—C11	121.2 (2)
C7—C2—C3	120.8 (2)	C13—C12—H12	119.4
C3—C2—C1	128.6 (2)	C12—C13—H13	120.0
C2—C7—C8	108.69 (18)	C12—C13—C14	120.1 (3)
C2—C7—C6	121.8 (2)	C14—C13—H13	120.0
C6—C7—C8	129.5 (2)	C13—C14—H14	120.2
N1—C8—C7	104.62 (18)	C15—C14—C13	119.6 (2)
O3—C8—N1	126.1 (2)	C15—C14—H14	120.2
O3—C8—C7	129.2 (2)	C14—C15—H15	119.9
C7—C6—H6	121.1	C14—C15—C16	120.2 (2)
C7—C6—C5	117.8 (2)	C16—C15—H15	119.9
C5—C6—H6	121.1	C11—C16—H16	119.6
C6—C5—H5	119.7	C15—C16—C11	120.7 (2)
C6—C5—C4	120.6 (2)	C15—C16—H16	119.6

3 List of abbreviations

Å	angstrom
abs	absolute
Ac	acetyl
alk	alkyl
Ar	aryl
ATRA	atom transfer radical addition
BDMAP	1,6-bis(dimethylamino)-pyrene
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
BNAH	1-benzyl-1,4-dihydronicotinamide
bpy	2,2´-bipyridine, 2,2´bipyridyl
^{13}C-NMR	carbon NMR
°C	degrees Celsius
CAN	ceric ammonium nitrate
Cbz	carboxybenzyl
CFL	compact fluorescent lamp
CI	chemical ionization
cm	centimeter
cm^{-1}	wavenumber(s)
conc.	concentrated
CT	charge transfer
d	day(s); doublet (spectral)
DABCO	1,4-diazabicyclo[2.2.2]octane
dap	dianisol phenanthrolin
DCM	dichloromethane
DCC	N-N´-dicyclohexylcarbodiimide
dF(CF_3)ppy	2-(2,4-difluorophenyl)-5-trifluoromethylpyridine
DIPEA	N,N-diisopropylethylamine
DME	dimethyl ether
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dtb-bpy	4-4´-di-*tert*-butyl-2,2´-bipyridine
$E_{1/2}$	standard reduction potential
EA	electron acceptor
ED	electron donor
EDA	electron donor acceptor
e. g.	for example
equiv.	equivalents
ET	energy transfer
Et	ethyl
et al.	and others (co-authors)
EtOAc	ethyl acetate
ESI	electrospray ionization
eV	electron volt
EWD	electron withdrawing
fac	facial

g	gram(s)
GC	gas chromatography
^{1}H-NMR	proton NMR
h	hour
hal	halogen
hν	light
hp	high pressure
HRMS	high resolution mass spectrometry
Hz	Hertz
IET	intramolecular electron transfer
IR	infrared spectroscopy
^{i}Pr	*iso*-propyl
^{i}PrOH	*iso*-propyl alcohol
J	coupling constant (in NMR analysis)
k	kilo
l	liter
LED	light emitting diode
λ_{max}	max. UV-vis wavelength
m	meter; milli; multiplet (spectral)
M	molar (moles per liter)
µ	micro
max	maximum
Me	methyl
MeCN	acetonitrile
min	minute(s)
ml	milliliter
mol	mole(s)
mp	melting point
MS	mass spectrometry
NEt_3	triethylamine
NMR	nuclear magnetic resonance
Nu	nucleophile
OQ	oxidative quencher
PC	photocatalyst
PET	photoinduced electron transfer
Ph	phenyl
Phth	phthaloyl
ppm	parts per million
ppy	2-phenylpyridine
q	quartet (spectral)
R	arbitrary residue
redox	reduction-oxidation
Ref	reference
R_f	retention factor
RQ	reductive quencher
room temp.	room temperature
rt	Raumtemperatur
s	second(s)
sat.	saturated

SCE	saturated calomel electrode
t	triplet (spectral)
^{t}Bu	*tert*-butyl
temp.	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultra violet
UV-Vis	ultraviolet-visible absorption spectroscopy
vis.	visible
vs	versus

4 List of publications

1) Faderl, C.; Kachkovskyi, G.; Rackl, D.; Reiser, O.
"Visible light-mediated decarboxylation and rearrangement of ω-aryl-N-acyloxyphthalimides with [Ir(ppy)$_2$(dtb-bpy)]PF$_6$",
Manuscribt in preparation.

2) Hallare, A. V.; Bolinao, J. M. N.; Go, J. G. T.; Rubio, P. Y. M.; Faderl, C.; Macabeo, A. P. G.
"Comparative Toxicological Analysis of Polycyclic Aromatic Hydrocarbon (PAH)-Rich Soot Extracts from Gasoline and LPG-fueled Taxis Using the Zebrafish Embryo Toxicity (ZFET) Test",
Res. J. Pharm., Biol. Chem. Sci. **2016**, *7*, 159-169.

3) Pordanjani, H. M.; Faderl, C.; Wang, J.; Motti, C. A.; Junk, P. C.; Oelgemöller, M.
"Photodecarboxylative Benzylations of N-Methoxyphthalimide under Batch and Continuous-Flow Conditions",
Aust. J. Chem. **2015**, *68*, 1662-1667.

4) Kachkovskyi, G.; Faderl, C.; Reiser, O.
"Visible Light-Mediated Synthesis of (Spiro)anellated Furans",
Adv. Synth. Catal. **2013**, *355*, 2240-2248.

5 Congresses and scientific meetings

1) *„Visible light-mediated decarboxylation of N-acyloxyphthalimides“*
GDCh-Wissenschaftsforum, Dresden, Deutschland, August 2015.

2) *“Visible light-mediated decarboxylation of phthalimide activated acids bearing aromatic moieties"*
OZOM 8 Australasian Organometallics Symposium, Magnetic Island-Townsville, Australia, July 2014.

3) *„Visible light-mediated decarboxylation of N-acyloxyphthalimides“*
GRK 1626 Annual Report Meeting, Kloster Kostenz, Deutschland, April 2014.

4) *„Photoinduced decarboxylation of amino acids bearing aromatic moieties”*
GDCh Wissenschaftsforum, Darmstadt, Deutschland, September 2013.

5) *“Photoinduced decarboxylation of amino acids bearing furan moieties”*
4th EuCheMS (European Association for Chemical and Molecular Science) Chemistry Congress, Prag, Czech Republic, August 2012.

6 Curriculum Vitae

M. Sc. **Christian H. Faderl**

Rotteneckstr. 20, 93053 Regensburg
+49 176 56892532; +49 941 38214447
c.faderl@gmx.de

Personal details

Date and place of birth:	July, 23th 1986 in Hirschau (Germany)
Nationality:	German
Marital status:	Married

Professional Record

Since 10/2012	Research Assistant and Doctoral Student, University of Regensburg, Germany Thesis: "*Photoinduced decarboxylation of N-acyloxyphthalimides"* Supervisor: Prof. Dr. Oliver Reiser
07/2014-10/2014	Research stay at James Cook University Townsville (Australia) in the group of A/Prof. Dr. Michael Oelgemöller.

Education

10/2010-09/2012	Master Studies, Chemistry, University of Regensburg (Germany) Subjects: organic chemistry, bioanalytical chemistry and biochemistry. Thesis: *"Photoinduced decarboxylation of carboxylic acids bearing furan moieties"* Supervisor: Prof. Dr. Oliver Reiser Master of Science: 1,2
10/2007-09/2010	Bachelor Studies, Chemistry, University of Regensburg (Germany) Thesis: *"ATP sensitive Sonden"* Supervisor: Prof. Dr. Otto S. Wolfbeis Bachelor of Science: 2,3
08/2006-04/2007	Civilian service at the district hospital Landshut-Achdorf
09/1997-06/2006	Abitur, Hansl-Leinberger Gymnasium in Landshut, Germany. Degree: 2,7

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G Declaration

Herewith I declare that this present thesis is a presentation of my original work prepared single-handed. Wherever contributions from others are involved, all of them are marked clearly, with reference to the literature, license and acknowledgement of collaborative research.

Christian Faderl

Regensburg, 19.07.2016