

Redox Transformations with Bismuth and Light

Dissertation

Zur Erlangung des Doktorgrades der Naturwissenschaften

(Dr. rer. nat.)

An der Fakultät für Chemie und Pharmazie

Der Universität Regensburg



vorgelegt von

Dominik Birnthal

aus Großetzenberg, Bayern

2025

The experimental work has been carried out between October 2020 and September 2024 under the supervision of Prof. Dr. Burkhard König at the University of Regensburg, Institute of Organic Chemistry

Date of submission: 25.07.2025

Date of colloquium: 02.09.2025

Board of examiners:

Prof. Dr. Jörg Heilmann	(chair)
Prof. Dr. Burkhard. König	(1 st referee)
Prof. Dr. Oliver Reiser	(2 nd referee)
Prof. Dr. Frank-Michael Matysik	(examiner)

*“No great discovery was ever made
without a bold guess.”*

Isaac Newton

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1 Metal Catalysis Initiated by Charge-Transfer-Processes

Recent developments in photoredox catalysis have demonstrated that direct photoinduced charge-transfer processes, such as ligand-to-metal charge (LMCT) and intra-ligand charge transfer (ILCT), can activate metal catalysts without the need for external reductants. These strategies have enabled efficient and sustainable C–N coupling and radical reactions using earth-abundant metals, such as nickel, cobalt, and iron, as well as lanthanides like samarium. By combining simple light-absorbing precursors with operationally straightforward conditions, this approach opens new avenues for redox-neutral and practical metal catalysis.

Manuscript under preparation

Author contribution: DB collected the presented literature and wrote the manuscript with input of BK

1.1 Introduction

Coordination compounds can undergo electron transfer processes upon light excitation. Intermolecular electron transfer from or to an external electron-donor or electron-acceptor changes the overall complex redox state. The two most important intramolecular processes are metal-to-ligand-charge-transfer (MLCT)^[1], in which the metal ion is oxidized or reduced by electron transfer to one of the ligands, and ligand-to-metal-charge-transfer (LMCT)^[2], by which the one-electron oxidation of a ligand reduces the metal ion. Both concepts have been widely applied in metal-photoredox catalysis. LMCT approaches are valuable for the photogeneration of hydrogen-atom abstraction reagents (HAT), as the electron transfer process, e.g., from an alkoxy ligand, generates an oxygen-centered radical.^[3] Additionally, radicals released by LMCT processes are valuable for anti-Markovnikov functionalization of alkenes or the alkylation of heteroarenes.^[4–6] Other charge-transfer processes, especially intra-ligand charge transfer processes (ILCT) are less applied so far, however, their photophysical principles are well known.^[7,8]

The change of the redox state of metal ions is likewise a key step in metal catalysis, as typically only specific metal redox states are catalytically active. The stoichiometric, photo- or electroreduction of catalyst precursors is a well-established concept in metal catalysis, primarily applied to transition metals such as copper, nickel, or cobalt^[9,10].

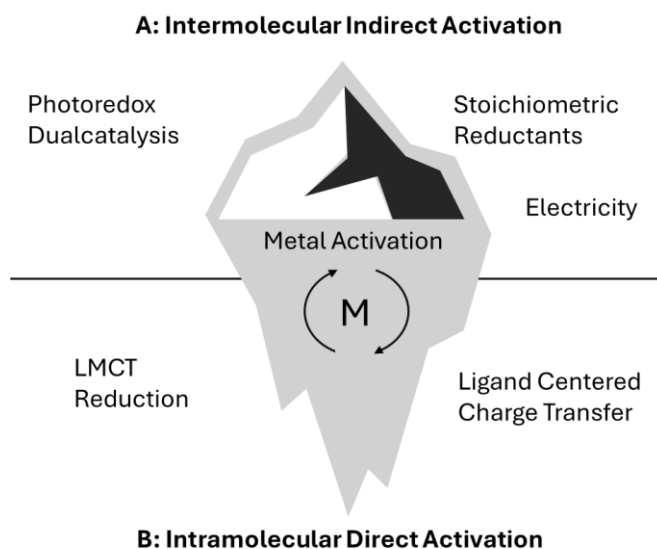


Figure 1.1 Overview of different pathways for metal activation

However, intramolecular charge-transfer processes that, in addition to the oxidized ligand, generate a reduced metal ion, have only been more recently applied as an activation strategy

for metal catalysis. Advantages of the approach are potential redox-neutral processes, no need for external reductants or dual catalytic systems, and its applicability to otherwise difficult to reduce lanthanide ions (Figure 1.1).

We highlight recent examples of metal-catalytic reactions initiated by a photoinduced charge transfer process in this perspective and discuss the opportunities for pursuing this approach in metal-photo catalysis. Special emphasis is given to examples with operational simplicity and high synthetic value.

1.2 Photoreduction of metals by ligand-to-metal charge transfer

The excitation of ligand-to-metal charge transfer bands can result in the net reduction of a metal center and the simultaneous dissociation of a ligand radical (Figure 1.2). This process is favored for metals in high oxidation states and electron-rich ligands such as halides, alkoxides, carboxylates or azides. Most applications of LMCT processes focus on selectively generating ligand-centered radicals, which are then harnessed for hydrogen atom transfer (HAT) reactions, hydrofunctionalization, or dual catalytic processes. In many of these transformations, the metal's role becomes secondary after the LMCT event, with the catalytic cycle often closed via a thermal oxidation step. A series of excellent review articles and perspectives continuously updated the progress in this direction.^[2,11–13] More recently, LMCT excitation has been exploited not just to access ligand radicals, but also to activate metals through reduction, thereby initiating traditional transition metal catalysis. This approach allows for transformations previously reliant on dual catalytic metallaphotoredox systems to be achieved with a single metal complex that simultaneously serves as the photocatalyst and the transition metal catalyst. Crucially, this is accomplished using simple, inexpensive, and commercially available precursors.

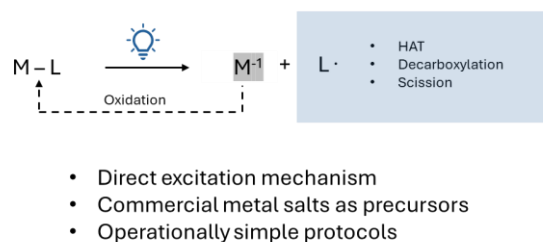
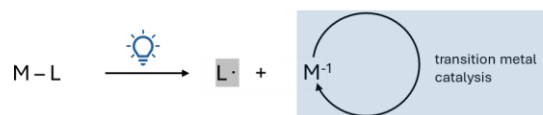
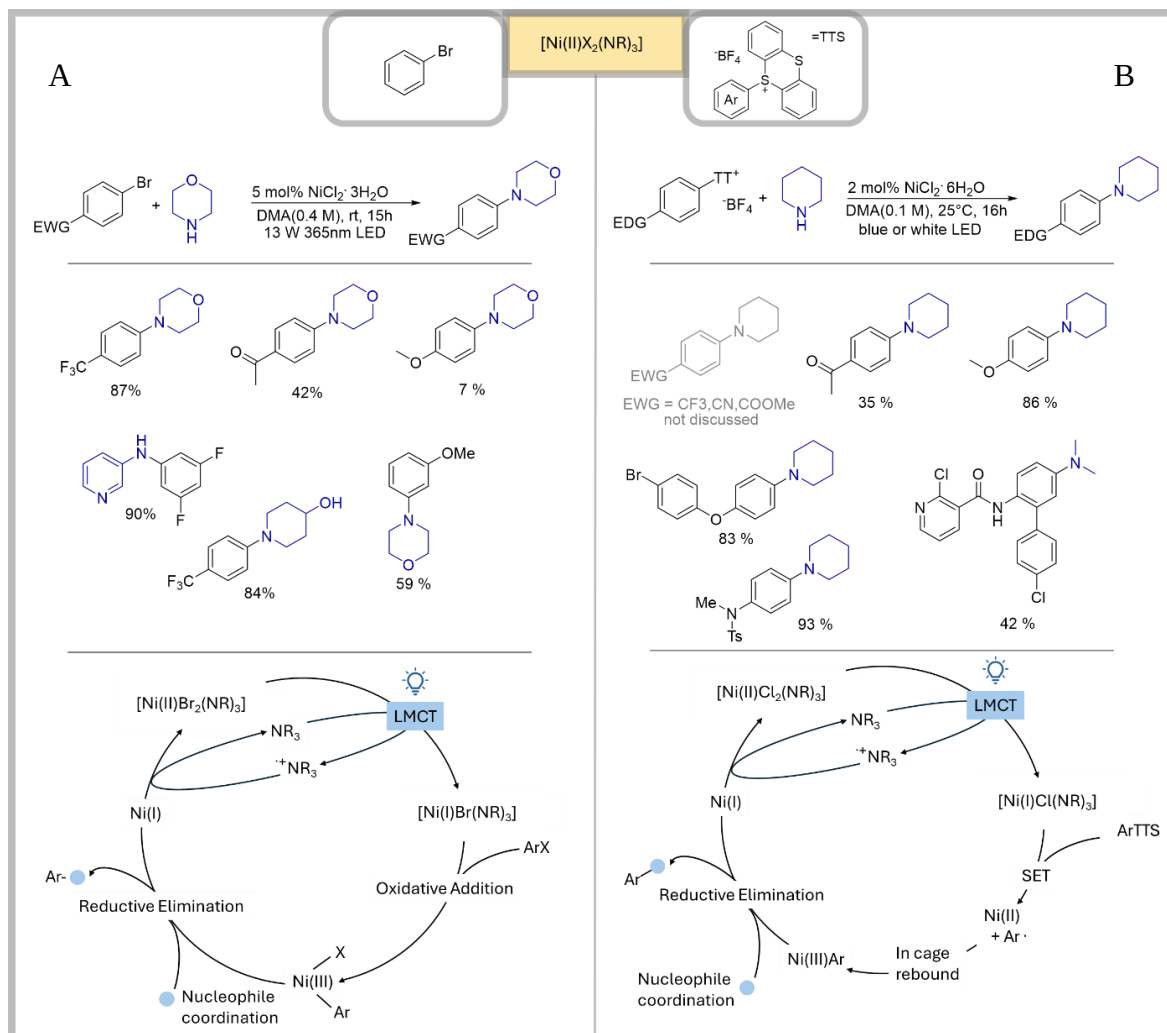
A: “Classical” LMCT Photocatalysts**B: LMCT Reduction**

Figure 1.2: Photoreduction of metals via a ligand-to-metal charge transfer

A pioneering example in this area was reported by Miyake and coworkers, who developed a nickel-catalyzed C–N coupling protocol (Scheme 1.1A).^[14] Instead of a dual catalytic system of photoredox and nickel catalyst they realized the coupling of aryl bromides with primary and secondary amines with Ni(II)Br₂ or Ni(II)Cl₂ as the sole precatalyst under basic conditions. UV-vis studies show that the amines present in the reaction mixture coordinate to nickel, forming a mixed [NiBr₂(amine)₃] nickel substrate assembly that can be excited at 365 nm. Density functional theory (DFT) calculations support a mechanism in which light irradiation leads to the formation of an amino radical and a reduced Ni(I) species, effectively activating nickel for transition metal catalysis. The authors propose that the amino radical cation engages in C–N bond formation via oxidative addition and reductive elimination or through bromine atom displacement at Ni(I). The method’s utility is demonstrated across numerous examples and was also successfully applied in a sequential C–S/C–N coupling, enabling the synthesis of complex structures such as flibanserin.

Building on this excitation concept, Ritter and coworkers later employed the direct excitation of nickel–amine complexes to facilitate C–heteroatom coupling with electron-rich arenes (Scheme 1.1B).^[15] This approach addresses the long-standing challenge of coupling electron-rich aryl electrophiles by replacing aryl halides with arylthianthrenium salts. These salts are activated by a single-electron transfer (SET) step with Ni(I), circumventing the sluggish oxidative addition typically associated with electron-rich aryl halides. The generation of paramagnetic Ni(I) species from [NiBr₂(amine)₃] via LMCT excitation was confirmed through EPR spectroscopy. Light on/off experiments further indicated the need for continuous irradiation, suggesting that a self-sustained Ni(I/III) catalytic cycle is unlikely. Overall single-

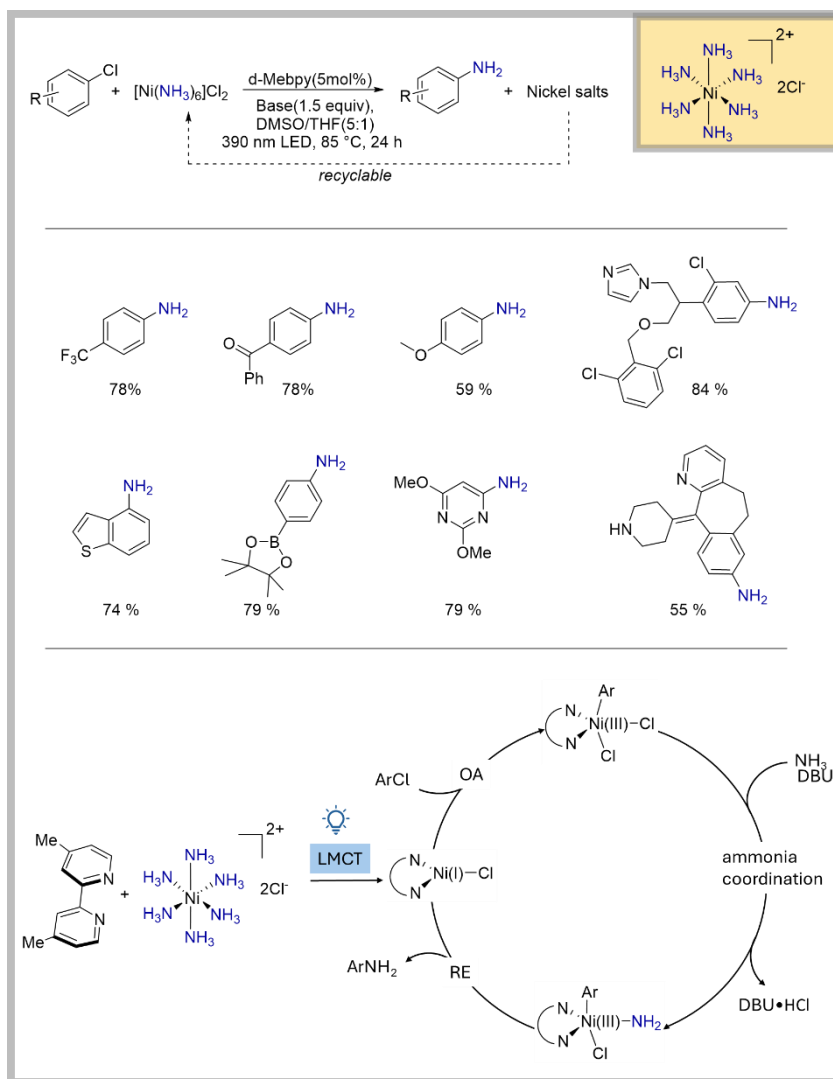
electron transfer and oxidative addition are complementary pathways that work best with matching substrate electronics.



Scheme 1.1 A: Nickel C-N cross coupling with aryl bromides by direct nickel excitation; B: Nickel C-N cross coupling of electron-rich arenes by direct nickel excitation

The next example illustrates the potential of LMCT for reductive activation of metal species. Hexamine complexes (Werner salts), long considered as a catalytically inactive species were shown to be photoactivatable by the group of Xue in 2023.^[16] (Scheme 1.2). In their work, the nickel hexamine complex $[\text{Ni}(\text{NH}_3)_6]\text{Cl}_2$ was successfully activated via direct LMCT excitation in the presence of a simple bipyridine ligand. Upon photoexcitation, ammonia is slowly released from the complex, which effectively overcomes the challenge of catalyst

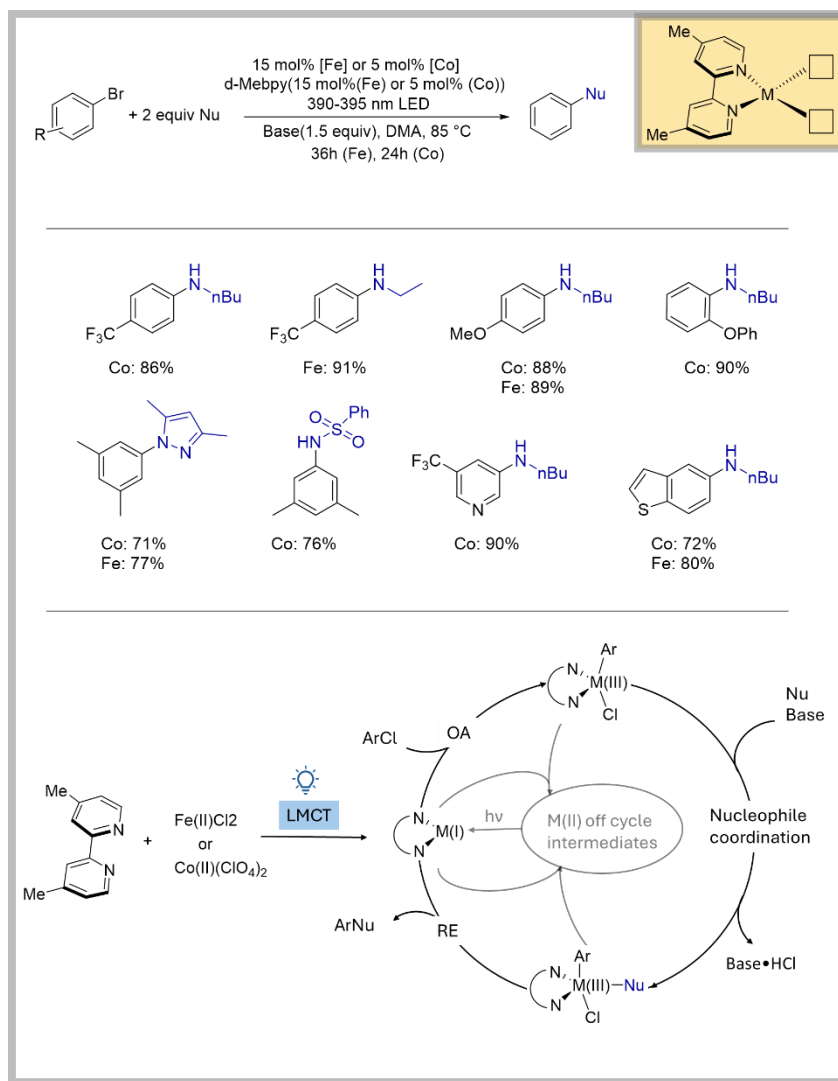
poisoning typically caused by strongly coordinating amines. The Werner salts uniquely function as both an active nickel catalyst and a source of ammonia, enabling the amination of aryl chlorides. The process employs stoichiometric amounts of nickel. However, this is well justified by its ease of recovery and recyclability. The method demonstrates remarkable functional group tolerance across more than 80 examples, with yields reaching up to 96%. Importantly, it is applicable to pharmaceutically relevant substrates, including motifs found in drugs such as isoconazole and desloratadine. Mechanistically, the transformation is initiated by the LMCT-induced dissociation of one ammonia ligand from the $[\text{Ni}(\text{NH}_3)_6]^+$ complex, yielding a Ni(I) species. The resulting vacant coordination site is then occupied by the bipyridine ligand, forming a catalytically active Ni(I) complex. This species enters a self-sustained Ni(I)/Ni(III) catalytic cycle that propagates C–N bond formation in the absence of light. Notably, continuous irradiation with purple LEDs ensures that the system remains redox-active, avoiding ammonia saturation, which could otherwise inhibit catalysis. EPR spectroscopy confirms the formation of both Ni(I) and amino radical intermediates. A key experiment supporting the proposed mechanism involves pre-irradiation of the nickel complex in the presence of bipyridine, followed by the addition of aryl chlorides in the dark. Product formation under these conditions confirms that the C–N coupling proceeds via a thermally driven dark cycle, with the LMCT step primarily serving as the initiation and reactivation of off-cycle intermediates.



Scheme 1.2: The direct excitation of nickel hexamine complexes for the amination of aryl chlorides

The authors note that product formation was also observed using manganese and cobalt hexamine complexes. This observation may have motivated further exploration into the direct photoexcitation of these earth-abundant metals for C–heteroatom bond formation. Indeed, the same group subsequently reported robust C–N coupling protocols involving aryl bromides and aryl chlorides, enabled by the direct excitation of iron^[17], cobalt^[18], and manganese^[19] complexes (Scheme 1.3). These protocols employ simple metal salts such as $FeCl_2$, $Co(ClO_4)_2$, or $Mn(OAc)_2$ combined with a standard ligand dimethylpyridine (d-Mebpy) at catalyst loadings of 5–15 mol% to form photoactive catalytic species. Upon light-induced reduction, these metal complexes also become active transition metal catalysts. Notably, in

the case of iron, this strategy circumvents the traditional requirement for stoichiometric reducing agents such as Grignard reagents, offering a milder and more sustainable alternative.^[20] Mechanistically, all three systems are proposed to operate through a light-initiated M(I)/M(III) redox cycle after photoactivation. Continuous photoexcitation serves to regenerate off-cycle intermediates, allowing them to reenter the catalytic cycle and maintain turnover. These methods exhibit broad functional group tolerance and high generality, enabling efficient coupling of a wide range of nucleophiles, including primary and secondary aliphatic and aromatic amines, amides, and heterocycles, with yields reaching up to 95%. Remarkably, even electron-rich aryl halides such as ortho-dimethylaryl chlorides perform well under the reaction conditions, achieving yields of 86% with cobalt and 88% with iron. While all three protocols show consistently high yields across many substrates, it is important to note that the reaction conditions are significantly harsher than those employed in the previously discussed nickel-based systems. The standard conditions require elevated temperatures (85 °C) and extended reaction times (24-36 hours).



Scheme 1.3: C-N coupling protocols enabled by direct excitation of iron and cobalt

Given the examples discussed so far, it is worth highlighting a key paradox in the use of LMCT processes for LMCT-driven metal reduction in cross-coupling protocols and the more classical LMCT pathways. In cross-coupling reactions, metals in the +2 oxidation state such as Ni(II), Fe(II), and Co(II) are typically employed as light-absorbing species to initiate redox catalysis. In contrast, classical LMCT processes utilize metals in the +3 oxidation state (e.g., Ni(III), Fe(III), or Co(III)), operating through (III/II) redox cycles. In these systems, the +2 oxidation state is generally viewed as stable and photochemically inactive. Metals in higher oxidation state are stronger electrophilic acceptors, making them better suited for LMCT. As a result, LMCT transitions from M(III) species should be more efficient than from M(II) species which might require higher-energy light sources, typically in the UV

range, to be effective. However, in the context of cross-coupling, a less effective LMCT step is not necessarily a drawback, as seen in the discussed systems.

1.3 Metal reduction by intra-ligand charge-transfer (ILCT)

Photoinduced ligand-centered charge-transfer processes have been already utilized in carefully designed systems with antenna-type ligands.^[21] Chromophore units are installed at the backbone of classical ligand scaffolds like bipyridines. More recently, common carbonyl chromophores can be effective scaffolds by reversibly coordination to Lewis acidic metal centers to facilitate their photoreduction (Figure 1.3). Their initial photophysical behavior parallels the well-established activation of unsaturated carbonyl compounds by Lewis acids, where coordination typically induces a bathochromic shift, enabling selective excitation.^[22,23] In classical systems, the Lewis acids serve purely as neutral catalysts without engaging in redox chemistry. A notable exception was reported by the Bach group in 2022.^[24] The excitation of a benzaldehyde - boron trichloride complex resulted in B–Cl bond cleavage, generating chlorine radicals capable of hydrogen atom transfer. When metal salts act as Lewis acids in such complexes, a subsequent reduction of the metal becomes feasible. Coordination to the carbonyl chromophore enhances its light absorption properties, and upon excitation, the ligand can become a strong reductant capable of reducing the coordinated metal center. The coordination increases the selectivity of the photoreduction to the metal, which then undergoes metal-specific downstream reactions.

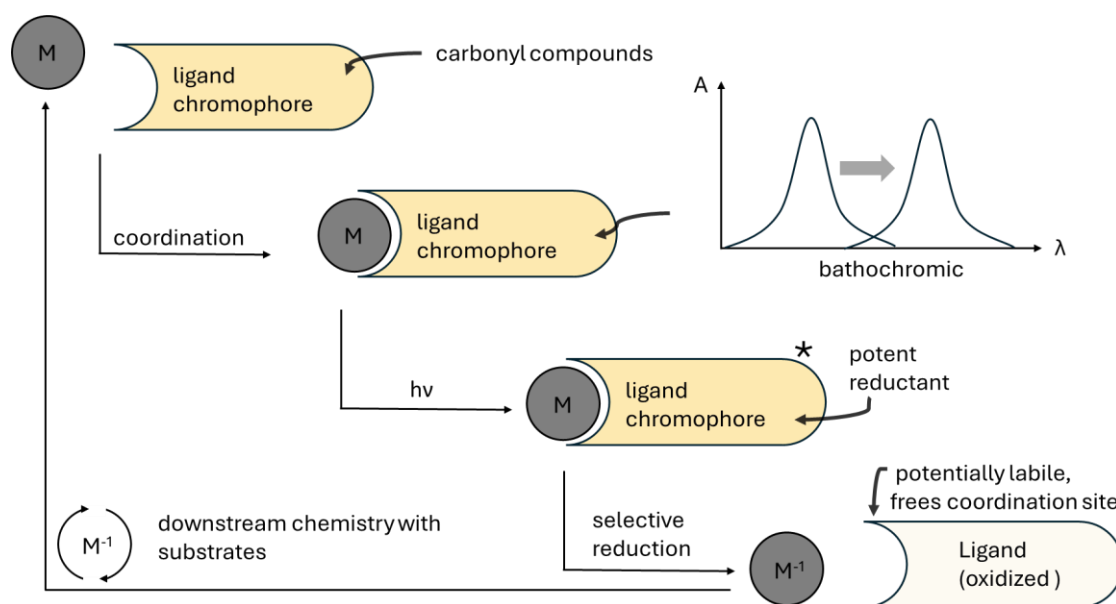
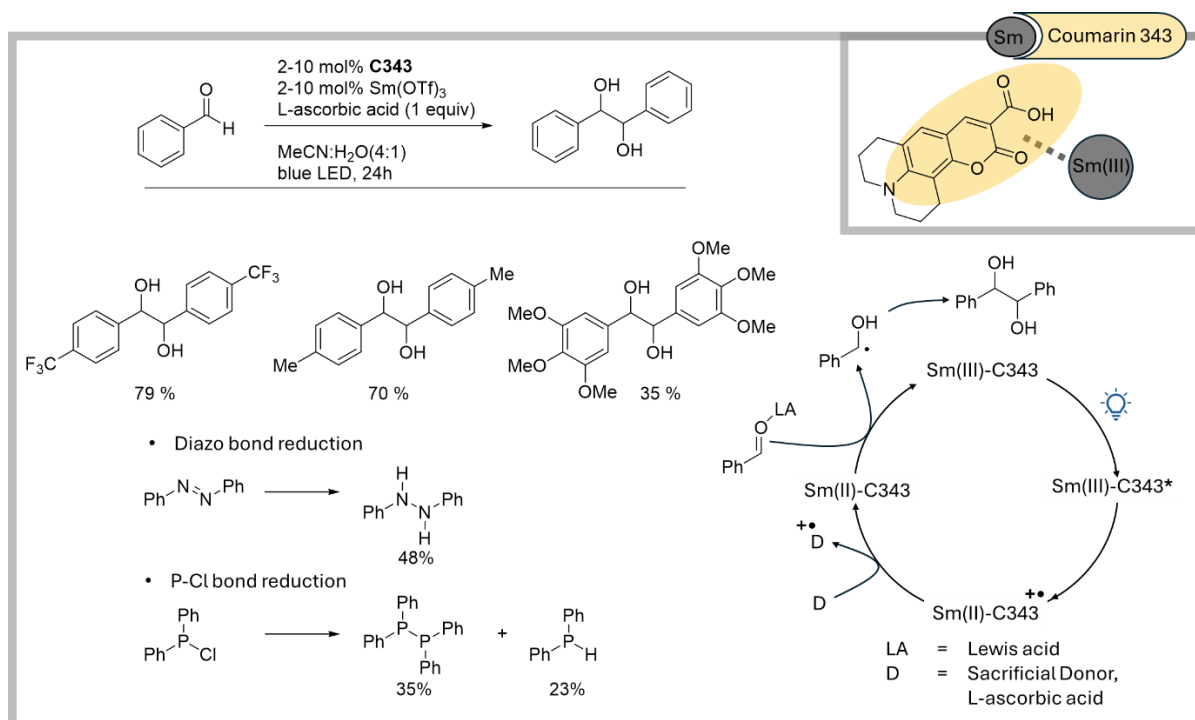


Figure 1.3: Metal reduction by intra-ligand charge-transfer with carbonyls

For this activation mode arguably the most prominent target is Samarium, which is widely utilized as a stoichiometric one-electron reductant for stereoselective pinacol couplings, reductive cyclization and radical cascade reactions.^[25] Its selectivity, mild reaction conditions and high functional group tolerance makes it a favorite in natural product synthesis for forming key carbon skeletons.^[26] Despite these excellent reagent properties, the large-scale use of samarium is inhibited by its high production cost being a lanthanoid making it economically impractical. To address these problems the catalytic use of samarium iodide is highly desirable and very recently pioneering works have been developed for the selective reduction of samarium(III)iodide enabling its catalytic use. Aside from electrochemistry,^[27] protocols used the photochemical reduction of samarium with carbonyl chromophores as ligands.

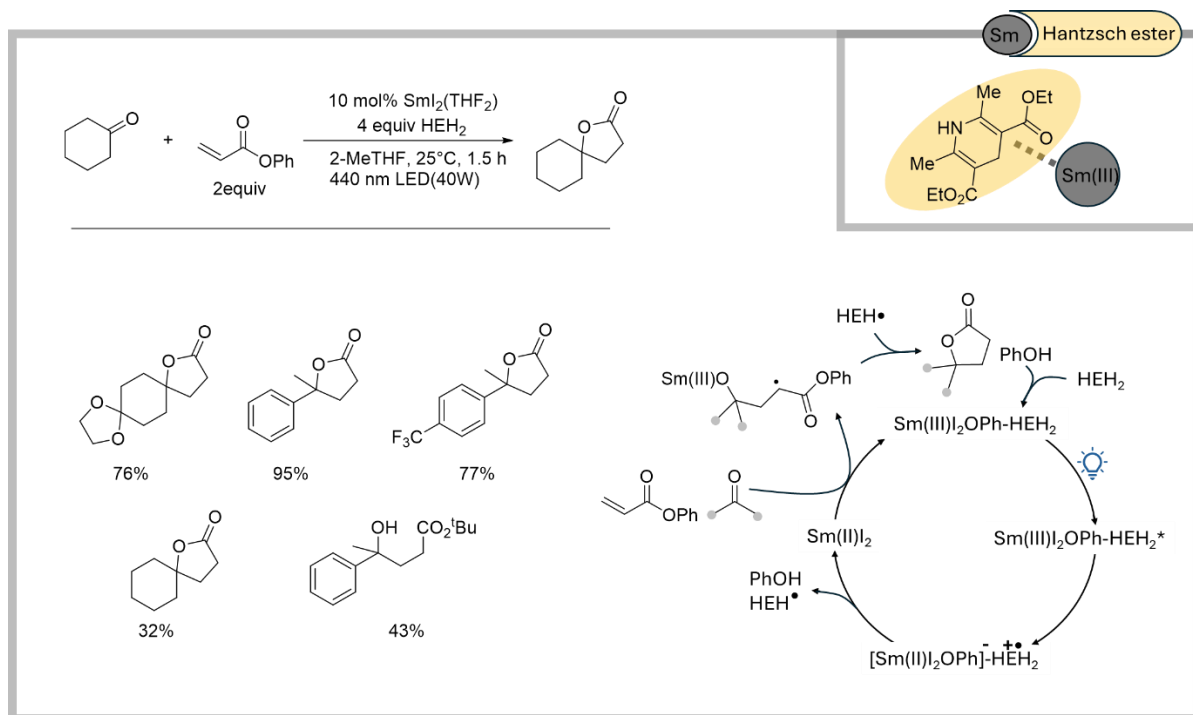
The group of Borbas developed a protocol utilizing commercially available coumarin343 as carbonyl chromophore for visible-light driven Sm(II) mediated reductions (Scheme 1.4).^[28] Pinacol couplings were enabled with several benzylic examples displaying diverse electronic properties. Additionally, carbon-halogen, phosphor-chloride and diazo-bonds reductions were successfully realized in good yields. The catalytic cycle starts with the excitation of coumarin coordinated to Sm(III), which reduces it to Sm(II). Then substrate downstream chemistry can take place. The inexpensive sacrificial, donor ascorbic acid, regenerates the oxidized coumarin catalyst. It is worth mentioning that not only samarium, but also europium

and ytterbium salts were potent catalysts in this reaction and could be reduced by photoexcited coumarin. UV-vis studies reveal an absorption maximum at 446 nm and the induction of a bathochromic shift when the coumarin is coordinated to these Lewis acidic metals.



Scheme 1.4 Photoreduction of samarium(III) with coumarin343 as carbonyl chromophore and L-ascorbic acid as sacrificial electron donor

Simultaneously, the group of Peters and coworkers utilized photoexcited Hantzsch ester as a photo reductant ($E(\text{HEH}_2^{++}/\text{HEH}_2) = -2.28$ vs SCE^[29]) for samarium (Scheme 1.5).^[30] Owing to its structural simplicity, the Hantzsch ester functions both as a carbonyl-based chromophore and as a sacrificial electron and hydrogen atom donor. In proof-of-concept studies, the authors demonstrated the utility of this system in intermolecular ketone–acrylate lactonizations, highlighting its effectiveness for Sm(II) -mediated transformations. The authors propose that the weak and reversible coordination of the Hantzsch ester to Lewis acidic Sm(III) center results in a more dynamic system, allowing for the generation of coordinatively unsaturated Sm(II) species upon photoinduced reduction. Importantly, the addition of base is critical to deprotonate the Hantzsch ester radical cation following electron transfer to samarium, thereby preventing rapid back-electron transfer and ensuring productive catalysis.



Scheme 1.5 Photoreduction of samarium(III) with Hantzsch ester as carbonyl chromophore

The use of Hantzsch ester as a reductant is also reported in combination with Cr(III)^[31,32], Gd(III)^[33] and Au(I)^[34]. Interactions between the Hantzsch ester and these metals are observed, but less critical for the reaction outcome.

1.4 Summary and future perspective

The activation and the modulation of the reactivity of metals by reduction have been crucial for transition metal and d-block catalysis. Dual catalytic approaches or sacrificial metal reductants have been used, but the direct excitation inducing reductive activation by well-established principles of dissociative LMCT and LC transfer processes of simple carbonyls has been mostly overlooked until recently. The examples discussed showcase the benefits of this strategy and expand the limitations of current methodology to the activation of catalytically metal species. The wide availability of photochemical setups enables the quick adoption of the developed protocols in various laboratory environments. However, developing and optimizing such protocols remains challenging. The reactivity of these systems stems from a cocktail of catalysts making mechanistic analysis and understanding challenging. Especially in ligand-free systems, dynamic assemblies of multiple species will likely occur,

and irradiation can dissociate inactive species, like dimers or oligomers, but also may lead to undesired demetallation and cleavages. Here, the choice of the optimal light source may be crucial for the reaction outcome: A broader emission might be beneficial for some applications, while in other cases, unwanted transformations are triggered. A better understanding of the LMCT process in cross-coupling procedures can help in the development of new transformations. What is the exact fate of the ligand radical? To what degree does the dissociation of ligand radicals play a role? Under what conditions can metals undergo consecutive LMCT e.g. from Fe(III) to Fe(I). In general, many more low-valent metal species should be accessible, although light of shorter wavelength may be necessary.

If an LMCT process is not feasible, the reduction *via* LC processes with a carbonyl compound is an alternative of similar simplicity. This strategy might be especially useful for the reductive activation of lanthanoids and main group metal ions with poor intrinsic photophysical properties. Metal ions are Lewis acidic and therefore close interactions with carbonyl chromophores are likely. While the use of Hantzsch esters is an excellent choice for net reductive procedures, the exploration of other chromophores may lead to novel reactivity. Particularly, the use of carbonyl ligands as substrates and metal reductants can be interesting.

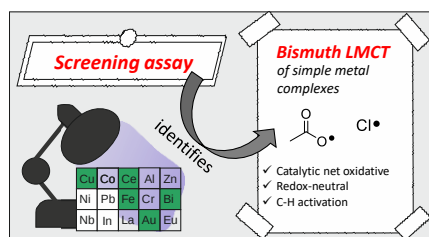
In summary, metal activation by direct photoreduction is a promising direction for the development of practical protocols and warrants further exploration in synthetic and mechanistic work.

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2 Exploration and Synthetic Application of Bismuth LMCT Photocatalysis for Radical Coupling Reactions



Abstract: Ligand-to-metal charge transfer (LMCT) photocatalysis allows the activation and synthetic utilization of halides and other heteroatoms in metal complexes. Many metals are known to undergo LMCT but so far remain underutilized in the field of catalysis. A screening assay identifying LMCT activity helped us to expand this catalysis concept to the application of bismuth LMCT in organic radical coupling reactions. We demonstrate its application for the generation of two different radicals (chlorine and carboxyl) in net-oxidative as well as redox-neutral photochemical reactions. Detailed investigation of the model Giese-type coupling revealed BiCl_4^- and BiCl_5^{2-} as catalytically active bismuth species under 385 nm irradiation. Combined cyclic voltammetry and UV-vis studies gave insight into the reactivity of the highly reactive bismuth(II) catalyst fragment.

This chapter has been published. For reference see: Dominik Birnthal, Rok Narobe, Eliseo Lopez-Berguno, Christoph Haag, and Burkhard König; Synthetic Application of Bismuth LMCT Photocatalysis in Radical Coupling Reactions; ACS Catalysis 2023 13 (2), 1125-1132; DOI: 10.1021/acscatal.2c05631, Reproduced with permission of the American Chemical Society.

Author Contribution: DB and RN contributed equally to the work. Both were involved in all stages of the project; LMCT activity assay design, screening and optimization of Giese coupling, synthetic scope investigations and mechanistic studies. ELP and CH assisted in the screening and optimizations. The manuscript was written by DB and RN with input of all the authors. BK supervised the project and is the corresponding author.

2.1 Introduction

Ligand-to-metal charge transfer (LMCT) photocatalysis has emerged into a powerful tool to easily access reactive electrophilic radicals from abundant and inexpensive metal complexes enabling diverse reactivity.^[1] Light absorption by a LMCT band induces a homolytic cleavage of a metal-ligand bond resulting in a reduced metal complex and an oxidized ligand radical.^[2] Even though these photophysical principles were never restricted to certain metals,^[3] modern synthetic applications have been limited mostly to cerium and its alkoxy^[4] and carboxyl^[5] radical chemistry. The recent utilisation of chlorine radicals generated from copper^[6] and iron salts^[7] serving as hydrogen atom abstractors expanded the portfolio of LMCT applications to C–H bond functionalisation of various hydrocarbons. In these transformations, the bond homolysis of a catalyst complex circumvents the requirements for long excited state lifetimes and matching redox potentials between substrate and catalyst thus allowing complementary reactivity patterns to classical single electron transfer (SET) catalysis.^[1c] Comparing the different LMCT complexes it becomes clear that metal character is crucially influencing, enabling and disabling certain reactivity modes. Benzoic acids, for example, while being utilized as fully recoverable ligands in synergistic cerium catalysis,^[8] readily undergo decarboxylation as copper-substrate complexes yielding phenyl radicals after excitation.^[9] Moreover, unique reaction outcomes are achieved when a single metal fulfils multiple roles besides LMCT activation. Of course, this behaviour is linked to specific elements - as an example efficient photocatalytic radical oxidation enabling cross-nucleophile coupling has so far only been achieved with copper.^[10] Furthermore, Doyle group demonstrated an intriguing combination of LMCT with multiple transition metal catalysis steps orchestrated by a single nickel catalyst.^[11] Despite these impressive developments, this research field is still in its infancy and new synthetic opportunities are to be discovered by exploring LMCT of different underutilized metals.

2.2 Development of an LMCT activity screening assay

To unlock access to the synthetic potential different elements may offer, we sought to design a systematic, rational screening assay for accelerated identification of LMCT activity across the periodic table. To begin, we focused on establishing a suitable test system allowing a conclusive qualitative readout. The reaction of choice should produce an easily detectable

product without any major side reactions. The only essential requirement for product formation should be a LMCT step of the metal catalyst. Leveraging net oxidative reactions with oxygen as terminal oxidant, using a 96-well plate setup becomes a simple choice for fast high-throughput screening (see Figure 2.8). Out of reported aerobic decarboxylative oxidation,^[12] benzylic C(sp³)-H oxidation,^[12b] oxidative cleavage of diols,^[13] and dehydrogenative lactonization of 2-arylbenzoic acids,^[14] the lastly mentioned transformation caught our attention. Cerium^[14a] and iron^[14b] based systems are described in literature to give the respective coumarin **1b** under diverse reaction conditions. In this reaction, the key intermediate - highly reactive carboxylate radical - undergoes rapid intramolecular addition to the tethered phenyl ring which then gets quickly oxidized and rearomatized.

We started to investigate the potential of simple bench stable metal chlorides available in our laboratories (Figure 2.1). A relatively high metal chloride loading (35 mol%) was selected to spot also minor LMCT activity. A set of differently coordinating solvents was used as their coordination has been proven to be beneficial in some cases (e.g., copper)^[6, 10] One set of conditions used additional chloride ligand to allow the formation of highly coordinated carboxylate, or mixed carboxylate-chloride complexes. Higher coordination generally improves absorption properties as demonstrated in the case of copper and cerium (e.g., CuCl₃⁻,^[6] FeCl₄⁻^[7a]). Based on previous reports,^[1] 375 nm LEDs were used, because they excite synthetically useful LMCT absorption bands. These bands typically appear higher than 300 nm and tail towards the visible region.

To verify the developed screening assay, cerium and iron chlorides were used as positive controls. Indeed, the positive outcome of these two metals made us confident that the selected parameters cover a correct range of conditions enabling LMCT. Moreover, an expected rediscovery of carboxyl radicals from copper complexes^[10, 12a] in a new transformation gave additional validity to the assay. Taking advantage of the experimental simplicity of this screening, also improbable metal chlorides like AlCl₃, ZnCl₂, NbCl₃, CdCl₂, InCl₃ and PbCl₂ were tested, and some gave product in detectable amounts. NiCl₂ and CoCl₂ showed no conversion even though their photophysical properties for LMCT were described before.^[15] The reason for inactivity is probably that higher oxidation state (III) was not achieved by oxidation with oxygen. Remarkable is the LMCT activity of gold across multiple reaction conditions.^[16] We did not further investigate this observation but hope that

the reactivity and synthetic use of these complexes will be further investigated in a different context.

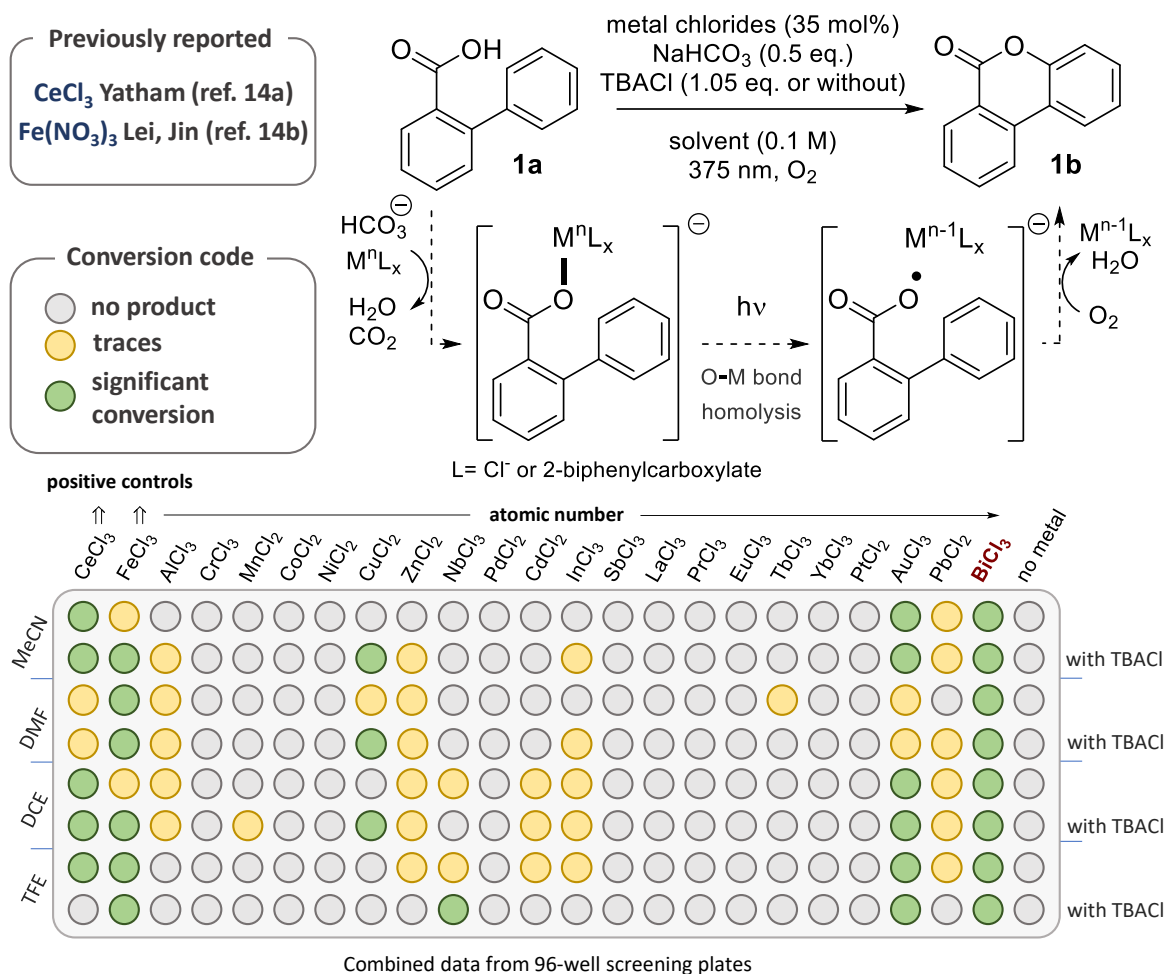


Figure 2.2: The developed LMCT reactivity assay along with combined screening results. 96-Well plate was analysed by qualitative TLC. TBACl = tetrabutylammonium chloride. For further experimental details of the screening see supporting information

For us, the biggest surprise and opportunity of the screening was the discovery of the exceptional performance of bismuth chloride in the lactonization. In all conditions we got significant amount of product **1b**, and in some cases, we even observed a complete consumption of the carboxylic acid **1a**. An additional experiment with a lower bismuth chloride loading (5 mol%) and TBACl ligand (15 mol%) in MeCN revealed high 78% yield of **1b** implicating that simple bismuth salts can act as a catalyst in this reaction (Scheme 2.5).

Knowing the right keywords, focused review of old photophysical literature brought us to the pioneering studies of Vogler.^[17] Therein, the photolysis of BiCl₃ in benzene was studied

which resulted in a formation of chlorobenzene and bismuth metal under 290 nm irradiation.^[17c] Over the years, investigations on photochemical^[18] and

Photoluminescent^[19] behaviour of different bismuth complexes have followed. However, it is important to note that the observed photochemical reactions were reported in the context of photodecomposition which have not been transferred to catalytic applications in organic synthesis.

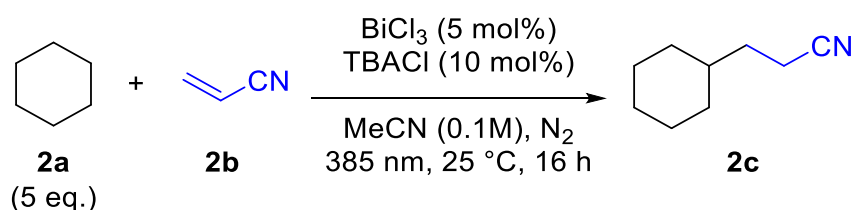
Rare examples of homogenous bismuth(II/III) catalysis are represented in the reactions of radical polymerizations,^[20] dehydrocouplings of TEMPO or phenol and hydrosilane,^[21] and radical cycloisomerization of δ -iodo-olefins.^[22] A plausible reason for the limited number of catalytic examples might be that bismuth(II) is a radical species.^[23] Seemingly the reactivity of such radicals is hard to control as they tend to undergo undesired side reactions. The catalytically active bismuth complexes in these reports contain carefully selected organic ligands and the reactions mostly proceed under thermal activation. An exception is light-initiated dehydrocoupling reported by Lichtenberg which has been performed under harsh mercury lamp irradiation.^[21b, c] In this transformation, the role of light is to generate an active bismuth(II) catalyst fragment, which interacts with stable oxygen-centered radicals (TEMPO or phenoxy radicals) and initiates a bismuth(II/III) catalytic cycle. While using TEMPO in the presence of the bismuth(II) radical is a unique and thoughtful strategy, such an approach is difficult to expand to reactions involving carbon-centered radicals. Such a persistent radical would actively interfere productive turnover, as they are commonly applied to trap carbon centered radical intermediates.^[24]

2.3 LMCT Catalysis of Bismuth

Building on our initial discovery of catalytic performance of simple bismuth salts in a net oxidative reaction, where an active stabilization strategy was not required, we sought to generalize the use of simple bismuth salts as homogenous photocatalysts in a redox-neutral Giese-type coupling reaction.^[25] In this reaction, no external oxidizing agent is added and therefore bismuth has to get reoxidized by transient organic radicals, before undergoing side reactions. This step is challenging and requires addition of a cocatalyst in some LMCT systems.^[4b, 26] With reports of Vogler^[17c] in mind, we considered chlorine radical generation

from bismuth chlorides for activation of aliphatic C(sp³)-H bonds relying on hydrogen atom transfer (HAT) strategy.^[27] To avoid mercury lamp irradiation, we utilized highly coordinated bismuth polychloride complexes which have absorption shifted towards higher, synthetically more appealing wavelengths. As an initial model reaction, we selected coupling of cyclohexane with acrylonitrile (Table 2.1). Gratifyingly, a combination of BiCl₃ and TBACl (1:2) in a relatively low 5% loading gave the desired coupling product **2c** in 72% yield under 385 nm LEDs irradiation (entry 1). The product yield without additional TBACl ligand is negligible (entry 2). Interestingly, heterogenous materials Bi₂O₃ and BiOCl lead to unproductive degradation of the alkene (entries 3 and 4) despite being established photocatalysts in environmental applications^[28] and in some synthetic procedures.^[29] Control experiments without BiCl₃ and in the absence of light confirmed essential role of both in this transformation (entries 5 and 6).

Table 2.1: Evaluation of the reaction conditions and control experiments for the C(sp³)-H functionalization of alkanes.^a



entry	deviation from optimized condi-	yield 2c
1	none	72 %
2	without TBACl	<5 %
3	BiOCl instead of BiCl ₃	<5 %
4	Bi ₂ O ₃ instead of BiCl ₃	0 %
5	without BiCl ₃	0 %
6	no light, 80 °C	0 %

^aReaction conditions: 0.2 mmol acrylonitrile, 5 mol% of bismuth salt, 10 mol% tetrabutylammonium chloride, 5 eq. cyclohexane, 2 ml MeCN (0.1 M) under N₂ atmosphere, 385 nm, 25 °C, 16 h. Yields were determined by GC-FID using benzonitrile as internal standard

During optimization of the ratio of BiCl₃ to TBACl ligand, an interesting reactivity pattern was observed (Figure 2.2). *In situ* formed BiCl₄⁻ and BiCl₅²⁻ are competent catalysts when irradiated at 385 nm giving comparable yields of **2c**, whereas at 400 nm only BiCl₅²⁻ is active. We followed the observation by performing UV-vis titration studies.^{18d} The sequential

addition of one equivalent TBACl to BiCl_3 resulted in a bathochromic shift, which increased upon addition of a second equivalent. Interestingly, the addition of third equivalent of TBACl did not lead to a different UV-Vis absorption maximum which would indicate a formation of new species (BiCl_6^{3-}). A less pronounced change in absorption revealed an isosbestic point at 324 nm. This isosbestic point corresponds to equilibrium between BiCl_4^- and BiCl_5^{2-} . It suggests that BiCl_5^{2-} is indeed the preferred coordination mode of bismuth chlorides. Consistent with this finding are Gibbs free energy calculations performed by the Hunt group. These show that Bi^{3+} ions favour a square pyramidal coordination in excess of chloride over other structures.³⁰

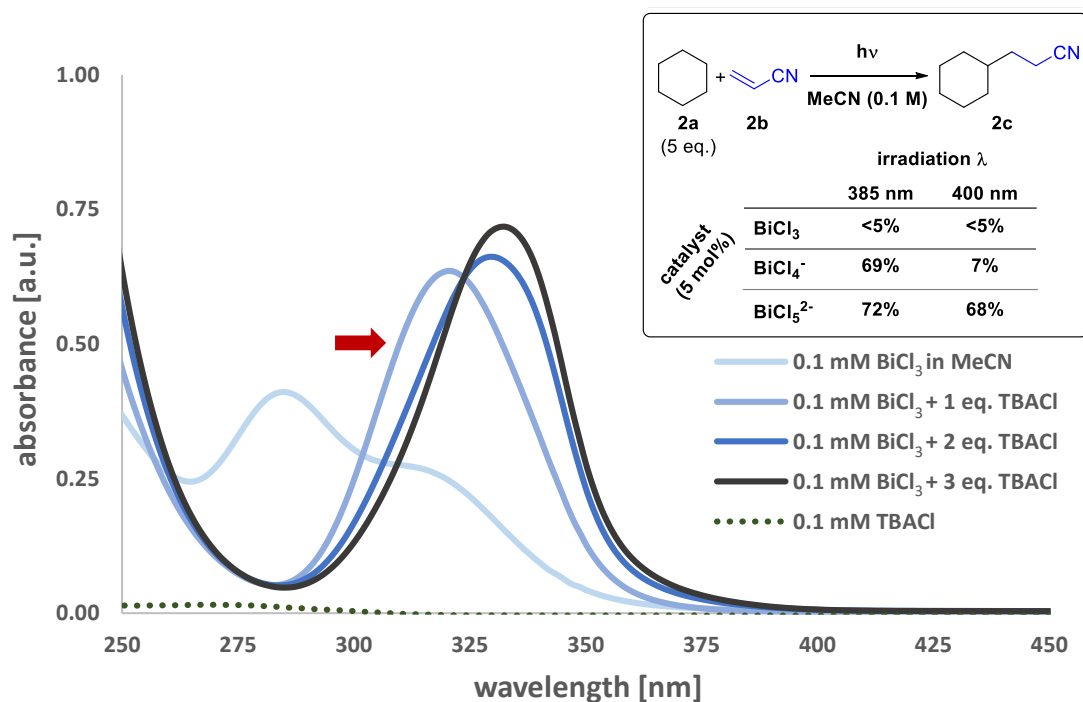


Figure 2.2: UV-vis spectra of different bismuth(III) chloride complexes in MeCN and display of their reactivity in the inset.

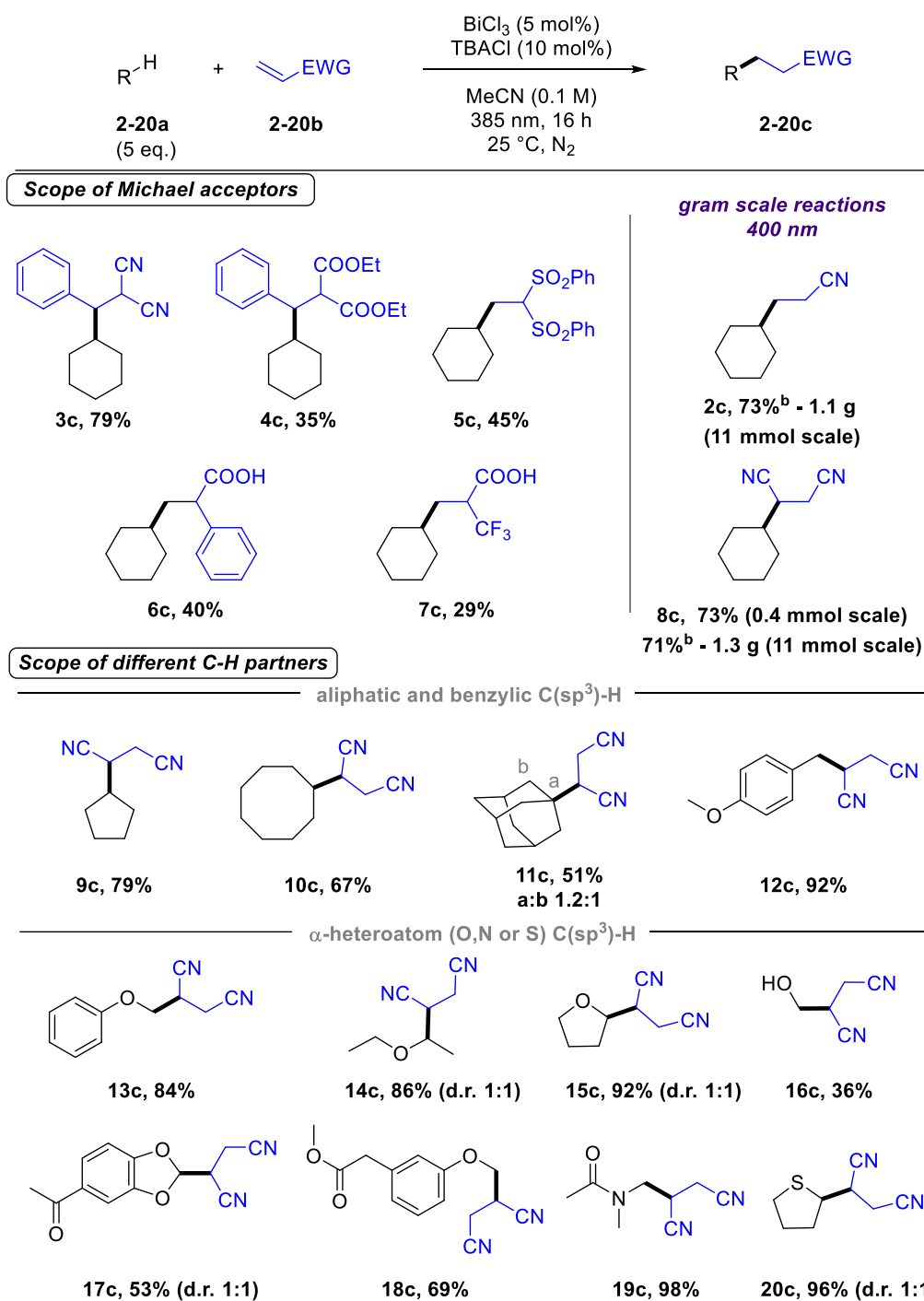
2.4 Synthetic application

The synthetic scope of this photocatalytic bismuth mediated Giese-type coupling was explored to showcase its generality (Scheme 2.1). Differently substituted electron-deficient alkenes bearing nitrile, carboxyl and sulfone groups were viable coupling partners (**2-8b**). Nitrile group containing radical traps gave best product yields. Less steric hindrance around the radical trap seemed to be beneficial, hinting at close interactions of reaction intermediates and bismuth catalyst. The free carboxylic acid functional group of **6c** and **7c** are tolerated

under the pH neutral conditions of this coupling. This shows that coordination of carboxylic acid to bismuth without base is unlikely to happen. The protocol was successfully upscaled to gram scale(**8c**) without any significant loss of efficiency at higher irradiation wavelength of 400 nm (Scheme 2.7).

The chlorine radical-mediated HAT allows the C–H bond activation of a broad range of starting materials. The selectivity of abstraction is steered to the most hydridic hydrogen atoms – an established abstraction pattern of the electrophilic chlorine radical.^[31] Compounds **12c** and **18c** illustrate the described selectivity. The benzylic -CH₃ group of 4-methylanisol (**12a**) is functionalized in the presence of -OCH₃ moiety which remains intact. In the case of more functionalized anisole derivative **18a**, the electron-withdrawing ester group deactivates the benzylic position enough that HAT is happening exclusively at the previously untouched aromatic -OCH₃ group.

Scheme 2.6: Synthetic scope of the bismuth-catalysed Giese-type coupling reaction.



^aReaction conditions: 0.4 mmol of the radical trap, 5 mol% of BiCl₃, 10 mol% tetrabutylammonium chloride, 5 eq. of alkane in 4 ml MeCN (0.1 M) under N₂ atmosphere, 385 nm, 25 °C, 16 h. ^bReaction performed on a 11 mmol scale in a different setup with irradiation at 400 nm. See SI for details.

Similarly, the α-keto-CH₃ group of benzodioxol **17a** is deactivated enough, that functionalisation occurs only at the dioxol motive. In general, α- to heteroatom C–H bond containing precursors are high-yielding. Particularly, **19a** gave an excellent yield of 98%.

Tetrahydrothiophene (**20a**) was converted to the desired product **20c** without any noticeable oxidation of the sulfide moiety. Diastereomeric products were obtained in 1:1 diastereomeric ratio.

2.5 Mechanistic investigation

In the synthetic scope investigation, a black precipitate was observed after the reaction, which did not appear under oxidative conditions. It is reasonable to assume that this precipitate originates from the decompositions of reduced bismuth(II) radical species.^[17c, 23, 32] To get additional insight into the behaviour of bismuth(II) in our catalytic system, we performed cyclic voltammetry (CV) studies. Electroreduction serves as a complementary approach to photochemical reduction offering us the opportunity to study bismuth(II) radical behaviour. The cyclic voltammogram of BiCl_5^{2-} revealed reversible behaviour (Figure 2.3A), whereas voltammogram of BiCl_3 showed an additional irreversible reduction peak (Figure 2.3A-I) indicating some chemical reaction.

Gratifyingly, this reaction could be identified by monitoring the bismuth species interconversions during the electrochemical reduction by UV-vis spectroscopy (Figures 2.3B and C). These combined spectro-electrochemical measurements display the shift of the absorption maximum of BiCl_3 from 280 nm to 340 nm in the first reduction step (Figure 2.3C-I). The absence of a clear isosbestic point, indicates the presence of more than one species during this process. Probably BiCl_4^- is the formed intermediate and gets quickly consumed resulting in the formation of BiCl_5^{2-} .^[33] Finding this newly formed bismuth species, still in oxidation state III is counterintuitive at the first sight. However, this suggests that the unstable bismuth(II) radical rapidly undergoes disproportionation to bismuth(III) and to a further reduced bismuth species without any absorption features. Hereby, the released chlorine is transferred to bismuth(III) to eventually form BiCl_5^{2-} as observed by UV-Vis. Indeed, the absorption and electrochemical behaviour of *in situ* generated BiCl_5^{2-} and preformed BiCl_5^{2-} is the same. Further reduction of BiCl_5^{2-} results in a complete disappearance of all absorption features (Figures 2.3B-II and 3C-II), likely indicating its complete reduction.^[34] Upon oxidation, the absorption features of BiCl_5^{2-} reappear (Figures 2.3B-III and 2.3C-III). Upon further oxidation, the concentration of Bi^{3+} ions increases, and in the absence of free chloride ions, Bi^{3+} ions start taking chloride atoms from BiCl_5^{2-} . As a consequence, we observed reappearance of the BiCl_3 signal at 280 nm (Figure 2.3C-IV). The process is not completely reversible as indicated by the slightly lower final UV-vis

absorption of BiCl_3 and formation of black precipitate on the electrode surface. Similarly, dissociative LMCT is also a SET reduction which triggers the abovementioned disproportionations leading to the black precipitate - $\text{Bi}(0)$.

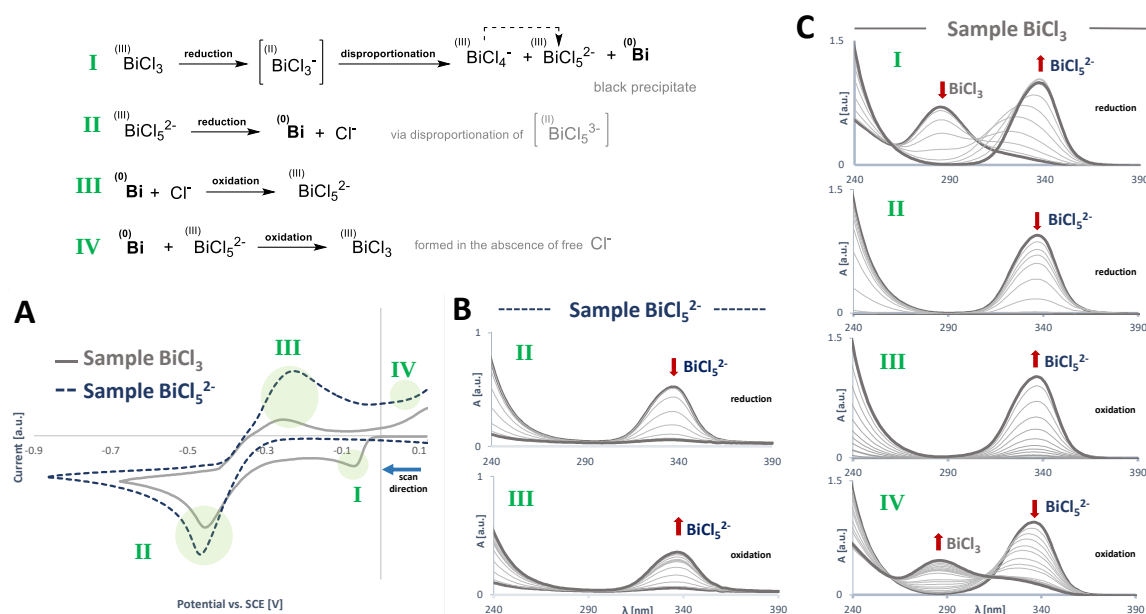
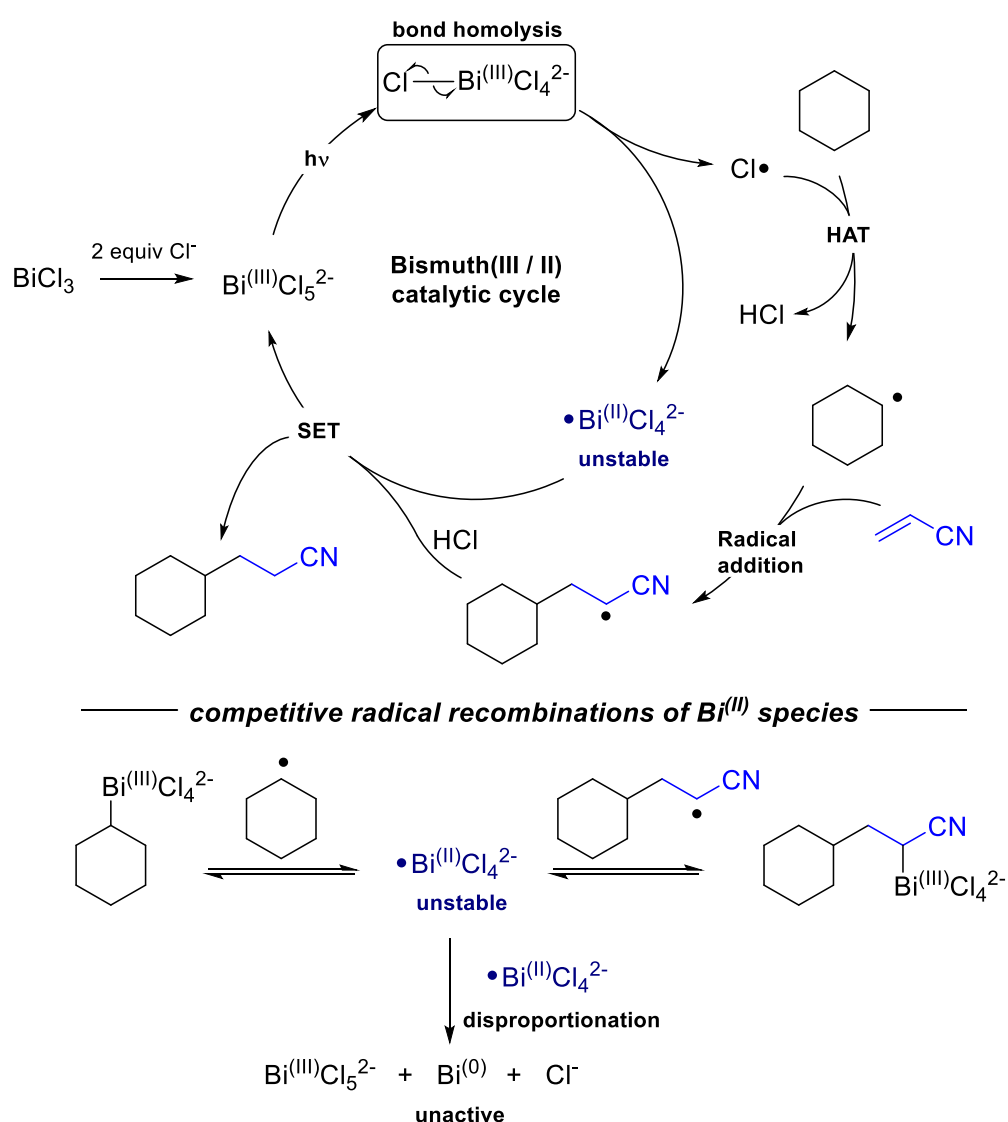


Figure 3.3: Cyclic voltammograms of two different bismuth(III) chlorides (BiCl_3 and BiCl_5^{2-}) (A), and on-line UV-vis spectra showing interconversions of the bismuth species during the CV measurements of two samples - BiCl_5^{2-} (B) and BiCl_3 (C). Each UV-vis spectrum corresponds to the change in the potential by 50 mV.

To better characterize the formed black solid, we conducted a direct photochemical synthesis by irradiating concentrated BiCl_5^{2-} solution without any reactants (Scheme 2.6). The analysis by powder diffraction identified the black precipitate as elemental bismuth (Figure 2.20) which was obtained in 51 % yield. In the context of our C–H activation protocol this disproportionation to bismuth(0) poses a loss of active catalyst and therefore termination of the reaction. However, judging on the high Giese coupling product yields (up to 98%) it seems that the disproportionation process is successfully interfered by much faster kinetics of the productive reaction. Reaction kinetic monitoring within the first hour gave a linear profile showing six catalyst turnovers (Figure 2.21). To determine whether the reaction is light initiated or light-driven, we measured the quantum yield (Table 2.9) and performed a light on-off experiment (Figure 2.22). The obtained quantum yield of 1.5% and the reaction not proceeding in the dark, makes a radical chain pathway to the coupling product unlikely. These measurements suggest that the photoactive catalytic species continuously catalyses

the reaction and remains intact as long as reactants and light are present. A plausible explanation for the efficiency of this catalytic system and neglectable disproportionation is an interaction of the open shell bismuth(II) radical fragment with carbon centred radicals. Such a rebound mechanism would stabilize the highly reactive bismuth(II), and at the same time assemble reaction partners for a fast turnover. Similar effects have been postulated for bismuth polymerisation catalysts.^[20c] Additionally, in a seminal report of the Cornella group on the nature of such bismuth(II) - carbon radical equilibria have been studied in detail in SET oxidative additions of redox active esters to bismuth(I).^[35]



Scheme 2.7: A plausible reaction mechanism.

Based on our mechanistic experiments and previous abovementioned studies on low valent bismuth, the following mechanism is proposed (Scheme 2.2). The addition of two equivalents of TBACl to BiCl₃ generates the active BiCl₅²⁻ catalyst. Under 385 nm irradiation this catalyst undergoes bismuth – chlorine bond homolysis releasing an electrophilic chlorine radical. This radical abstracts a hydrogen atom from the C–H bond precursor. The resulting carbon centred radical can recombine with bismuth(II). After radical addition of the cyclohexyl radical to an electron-deficient alkene, a reduction event gives the desired coupling product and regenerates photoactive bismuth(III). This can be either facilitated by an inner-sphere protodemetalation step or by an outer-sphere SET event followed by protonation. The regenerated bismuth(III) then perpetuates the bismuth(II/III) catalytic cycle.

2.6 Conclusion

In summary, we developed a screening assay which enables quick identification of dissociative LMCT activity. The developed assay revealed LMCT activity of simple bismuth(III) salts in a net oxidative lactonization reaction which turned out to be catalytic. The concept of photoinduced bismuth (II/III) LMCT catalysis was successfully extended to more challenging redox neutral Giese-type coupling. In these reactions, simple bismuth polychloride species were used as a source of chlorine radicals, which enabled the functionalization of different C(sp³)-H precursors. In the latter model reaction system we investigated the fate of bismuth(II) radical intermediates by combined cyclic voltammetry and spectro-electrochemical measurements. In the absence of organic substrates, we observed a pronounced bismuth(II) disproportionation which is not affecting catalytic applicability. In summary our findings are establishing bismuth as a generally working LMCT photocatalyst and present important mechanistic ground and considerations for more advanced catalytic applications in organic synthesis.

2.7 Experimental information

2.7.1 General information

Starting materials and reagents were purchased from commercial suppliers (Sigma Aldrich, Alfa Aesar, Acros or Fluka) and were used without further purification. Solvents were used as p.a. grade. Reactions were monitored by analytic thin layer chromatography (TLC) using Fluka silica gel plates with a fluorescent indicator. Visualization of the developed TLC chromatogram was performed using 254 nm UV light source or potassium permanganate stain. Organic solutions were concentrated using Büchi rotary evaporator. Flash column chromatography was performed either on a Biotage® Isolera™ Spektra or by hand for non-UV absorbing products. In both cases we used columns filled with Silica gel (60-200 μm). For non-UV-Vis absorbing product we used permanganate TLC stain for the visualization of the TLC spots.

NMR spectroscopy

All NMR spectra were recorded at room temperature using a Bruker Avance 300 (300 MHz for ^1H , 75 MHz for ^{13}C , 282 MHz for ^{19}F) or a Bruker Avance 400 (400 MHz for ^1H , 101 MHz for ^{13}C , 376 MHz for ^{19}F) NMR spectrometer. All chemical shifts are reported in δ -scale as parts per million [ppm] (multiplicity, coupling constant J, number of protons), relative to the solvent residual peaks as the internal standard. Coupling constants J are given in Hertz [Hz]. Abbreviations used for signal multiplicity: ^1H -NMR: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, and m = multiplet.

Gas chromatography

GC measurements were performed on a GC 7890 from Agilent Technologies system coupled to a FID. The system was equipped with a capillary column (HP-5ms UI, length 30 m, diam. 0.25 mm, film 0.25 μm) and worked with H_2 as carrier gas. GC program: The initial temperature of the GC was set to 40 $^\circ\text{C}$ and kept for 1.5 minutes. Subsequently, the oven temperature was increased at a rate of 25 $^\circ\text{C}/\text{min}$. until reaching 280 $^\circ\text{C}$, which was maintained for 3 min. Then, temperature was further increased (42 $^\circ\text{C}/\text{min}$) until reaching 300 $^\circ\text{C}$ and final temperature was hold for 5 minutes. Injector temperature was set to 280 $^\circ\text{C}$ and temperature of the detecting unit to 310 $^\circ\text{C}$. A split ratio of 30:1 (split flow 42 mL/min) was applied, and

the column flow was set to 1.4 mL/min. Data acquisition and evaluation was done with Agilent ChemStation Rev.C.01.04.

Mass spectrometry

High resolution mass spectrometry (HRMS) was performed at the Central Analytical Laboratory of the University of Regensburg. Mass spectra were measured on a Finnigan MAT 95, ThermoQuest Finnigan TSQ 7000, Finnigan MAT SSQ 710 A or Agilent Q-TOF 6540 UHD instrument and a Waters Acquity UPLC system equipped with Waters PDA, sample manager, sample organizer, column oven and Waters Xevo QTOF mass spectrometer.

UV-Vis

Absorption spectra were measured on an Agilent Cary 100 UV/Vis spectrometer in a 10 mm × 10 mm quartz cuvette at 25.0 °C under air atmosphere.

Cyclic voltammetry

Cyclic voltammetry was conducted using a three-electrode setup consisting of a glassy carbon disc working electrode 'WE' (d = 3.0 mm, BASi MF-2012), an Ag/AgCl wire reference electrode 'RE' (containing sat. aq. KCl) and a platinum wire counter-electrode 'CE'. Electrochemical measurements were carried out using an Metrohm Autolab PGSTAT 302N potentiostat at room temperature (298 K). Before use and between measurements, the working electrode was mechanically cleaned by polishing (Buehler Metadi Diamond polishing 1 Micron) and rinsed with distilled water repeatedly until its surface was reflective by eye, then allowed to air dry. The reference electrode was washed with electrolyte solution and distilled water and stored in 3.0 M aq. KCl when not in use/between measurements. The counter electrode was cleaned by soaking in 2.0 M HCl for 1-2 h, then rinsed with distilled water and allowed to air dry. Ferrocene was recrystallized twice from n-hexane prior to use. *n*-Bu₄NBF₄ (TBAB) was used as supplied commercially from TCI (98%+). Unless otherwise stated, all solutions were prepared at 10.0 mM concentration (in 0.1 M TBAB that had been bubbled for 5 min with Ar prior to the analyte being added) and were purged with Ar bubbling for 5 min prior to recording CV. After measuring one CV scan, Ferrocene (2.2 mg, 12 μmol) was added and the mixture purged with Ar bubbling for 5 min prior to recording CV again. Data acquisition and processing were performed with Metrohm Autolab Nova 42 1.10.4.

Spectro-electrochemical measurements

Chrono amperometry was measured in an Ottle Cell (optically transparent thin-layer electrochemical cell) with Pt mini grid as working and counter electrode. A silver wire was used as a pseudo-reference electrode. The optical path length of the cell is 0.02 cm. The potentials were controlled by Metrohm Autolab PGSTAT 302N potentiostat at room temperature (298 K). UV-Vis spectra were measured during the measurements by using Agilent 8453 spectrometer. Data acquisition and processing were performed with Metrohm Autolab Nova 42 1.10.4.

For further details about Ottle Cell, see:

<https://research.reading.ac.uk/spectroelectrochemistry/opticallytransparent-thin-layer-electrochemical-cells/room-temperature-ottle-cell/>

X-ray powder diffraction

For X-ray powder diffraction analysis, the samples were measured on a STADI P diffractometer (STOE & Cie GmbH, Darmstadt, Germany) in transmission geometry with Mo K α_1 radiation. The software package WinXPOW (STOE & Cie GmbH, Version 3.10, Darmstadt, Germany) was used for visualization and the software MATCH! (Match! - Phase Analysis using Powder Diffraction, Version 3.x, Crystal Impact - Dr. H. Putz & Dr. K. Brandenburg GbR, Kreuzherrenstr. 102, 53227 Bonn, Germany) for phase analysis.

Microscopy

The photos were taken with a modified microscope Swift SW380T equipped with a 15MP Swiftcam. The modified version has illumination from the top side, whereas the original had illumination from the bottom side.

2.7.2 Photochemical setups

Screenings of different metal chlorides for LMCT activity have been performed on 96-well plates (PP, 400 μ l well volume with flat bottom). Typically, a 96-well plate containing reaction mixtures was covered with a transparent foil and placed on a thermostated cooling block (**Figure 2.4**). The plate was irradiated from the top side with a LED array containing 96 LEDs (above each individual well). The reactor setup is a custom-made device (University of Regensburg workshop) and is not a commercially available product.

LED specifications: 375 nm Nichia NSSU100DT. Manufacturer optical power: 9.9 mW, measured: 6.4 mW, maximum current 20 mA, max voltage 3.3 V/LED.

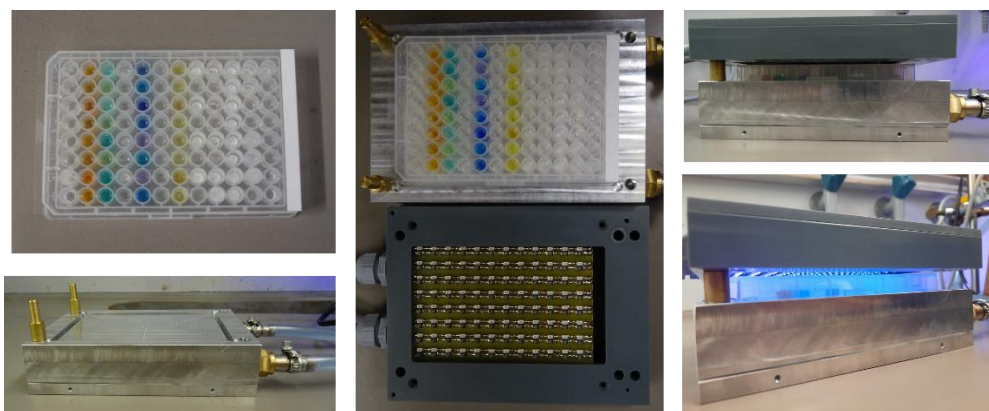


Figure 2.4: Equipment for 96-well plate irradiation.

Photochemical reactions were performed in closed crimp reaction vials, placed approximately 2 cm above a 385 nm LED array (2.5). The reactions were stirred under irradiation by magnetic stirrer under each reaction well. The reaction temperature was controlled by a thermostated (25 $^{\circ}$ C) metal cooling block. The reactor setup is a custom-made device (University of Regensburg workshop) and is not a commercially available product.

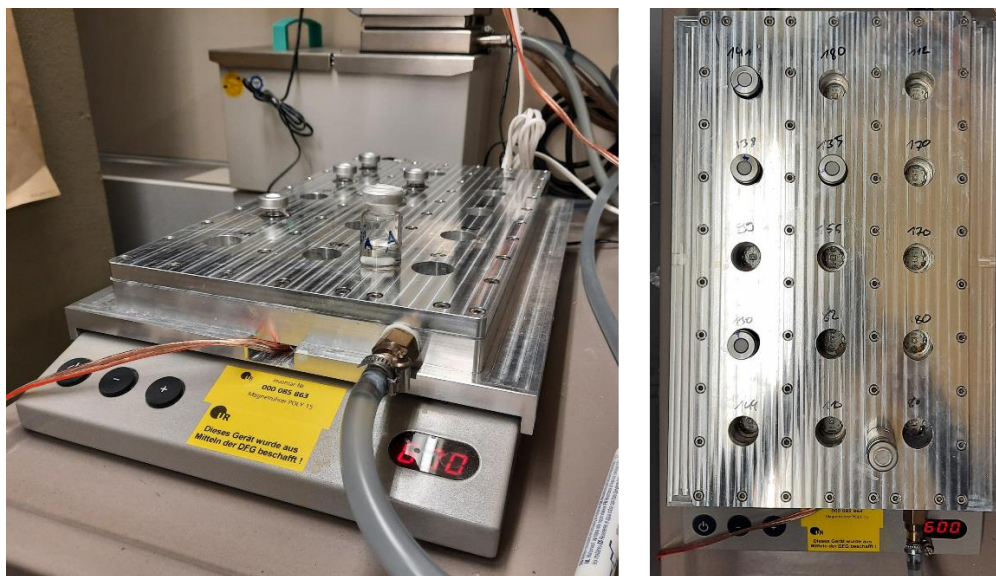


Figure 2.5: Equipment for screening and synthetic scope reactions.

Gram-scale reaction was performed in a custom build glass photoreactor which was irradiated from the sides by 18 LEDs (400 nm, 3 W electrical power each). The temperature of the inner part of the glass photoreactor was actively controlled by a thermostat (25 °C).

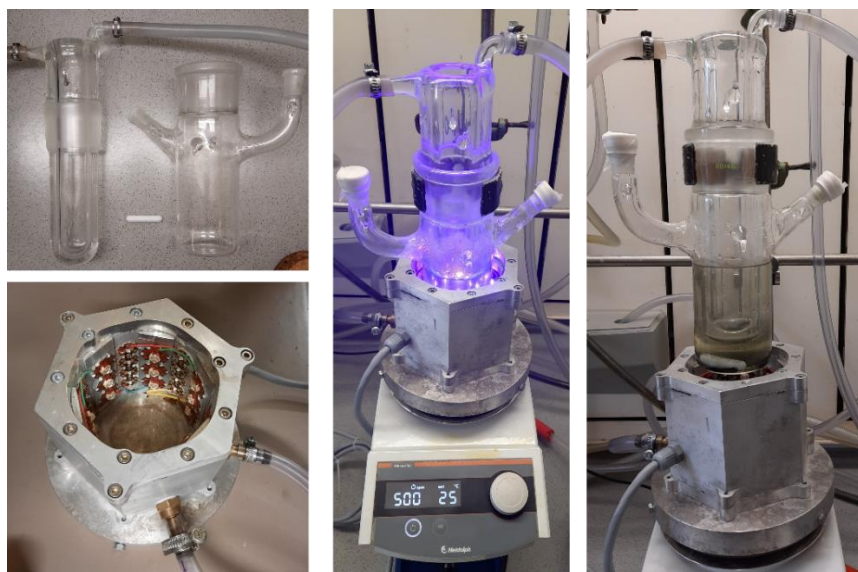


Figure 2.6: Gram-scale reactor before, during and after the photochemical reaction.

Quantum yield measurement was performed in a setup developed by Prof. Riedle.¹ For the sample we have used 10×10 mm fluorescence cuvette.

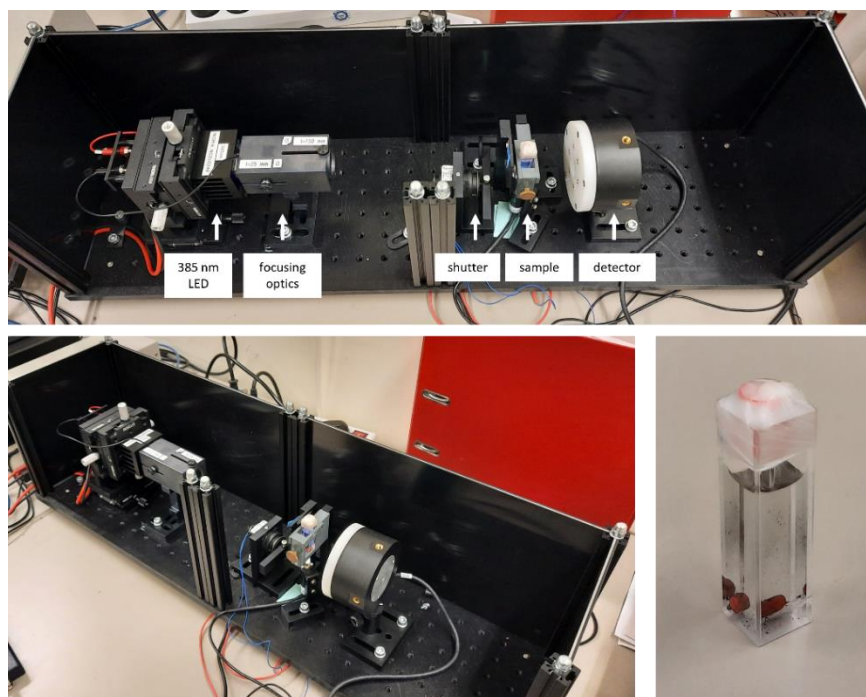


Figure 2.7: Quantum yield determination setup and the sample after completion of the reaction.

2.7.3 General experimental procedures

General procedure for the preparative scale reactions

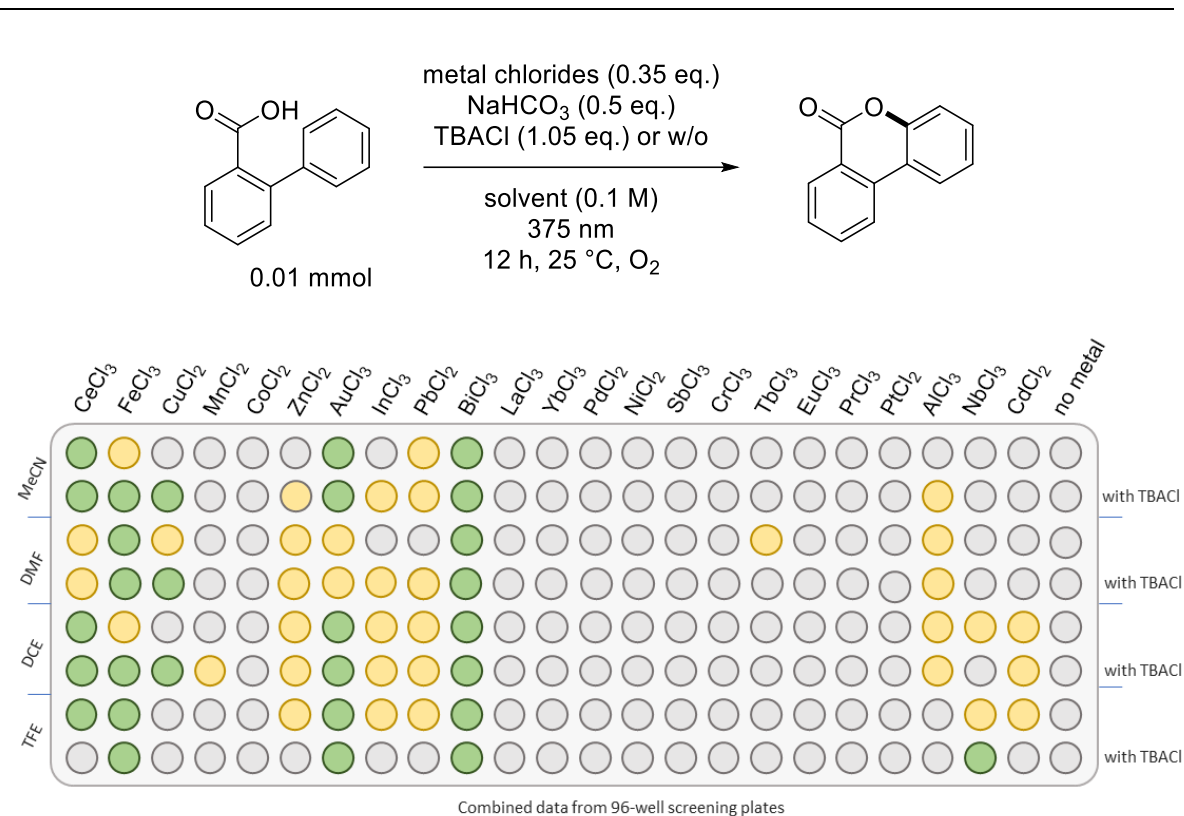
The preparative scale reactions were set in 2 parallel vials, each containing 0.2 mmol of a radical trap as the limiting reagent. If solid, radical trap (0.2 mmol, 1 eq.) and C–H substrate (1.0 mmol, 5 eq.) were weighed into a 5 ml crimp reaction vial. Then, 2.0 ml of a stock solution containing BiCl₃ (0.01 mmol, 3.2 mg, 10 mol%) and TBACl (0.02 mmol, 5.5 mg, 10 mol%) in dry MeCN were added and the vial was capped. The reaction mixture was degassed by 4 nitrogen-vacuum cycles. Afterwards any liquid reagents (radical trap or a C–H substrate) were added with syringe through the septum, and the vial was placed in a thermostated cooling block (25 °C) and irradiated through the plane bottom side of the vial by a 385 nm LED for 16 hours (see Figure 2.5). After the completion, the two reaction batches were combined in a 100 ml round bottom flask to which a spoon of silica was added before removing the solvent *in vacuo*. So prepared dry load was purified on the automatic column machine (Biotage® Isolera™ Spektra) or by hand column for non-UV absorbing products using a mixture of petrol ether and EtOAc. For non-UV-Vis absorbing product permanganate TLC stain was used for the visualization of the TLC spots.

General procedure for screening and optimization studies:

Bismuth precursors and tetrabutylammonium chloride were weighed into a crimp reaction vial together with any other solid materials. Then, 2 ml of an indicated solvent were added, and the vial was capped. The reaction mixture was degassed by 4 nitrogen-vacuum cycles. Afterwards, degassed acrylonitrile (13.1 µl, 0.2 mmol, 1 eq.) and degassed cyclohexane (108 µl, 1.0 mmol, 5 eq.) together with any other liquids were added through septum, and the vial was placed in a thermostated cooling block (25 °C) and irradiated through the plane bottom side of the vial by a 385 nm LED for 12 hours. After the reaction completion, internal standard benzotrifluoride (22.5 µl, 0.2 mmol) was added into the reaction vial. The sample was briefly shaken, filtered, and submitted for GC-FID analysis.

2.7.4 96-well plate screening of different metals for LMCT reactivity

The screening experiments were performed on a 0.01 mmol scale (0.1 M concentration in 100 μ l of the solvent) on 96-well plates (material: transparent PP). The compounds were applied on the 96-well plate by distributing them as stock solutions in volatile solvents which were later evaporated. First, sodium bicarbonate was added as a stock solution in water and the plate was left overnight in the oven to dry completely. Next, the substrate (stock solution in EtOAc) and metal chlorides were added. Some of the metal chlorides dissolved well in ethyl acetate and in the cases when they did not dissolve, we prepared fine suspensions by putting them on the ultrasound bath for 30 min. The organic solvents were evaporated in the flow of air in the fume hood (ca. 1 hour). Due to its hygroscopicity, TBACl was added as the last compound dissolved in a small amount of DCM which was evaporated within minutes after being put on the plate. Then, 100 μ l of each indicated reaction solvent was added. The plate was purged with oxygen and immediately closed with a transparent sticker foil. The plate was irradiated from the top site in a custom-built setup (**Figure 2.4**) for 12 hours. To analyse the reaction mixtures, we filled the wells to 200 μ l with EtOAc and transferred 25 μ l of each reaction mixture onto another 96-well plate and diluted them to 225 μ l. With the TLC capillaries, we applied 3 drops of each so-prepared sample on the TLC plate. For the spotting, we used fresh, brand new TLC capillaries. TLCs were developed using petrol ether/ EtOAc 3:1 solvent mixture containing a few drops of AcOH. The photos of the developed TLC plates in the **Figure 2.8** were taken in a dark lab under UV light irradiation.



Scheme 2.3: Summarized results of the 96-well plate screenings.

An important note: Care should be taken when using this reaction to probe for the LMCT reactivity because we observed some product formation without any metal at higher light intensities over extended time periods. Therefore, suitable negative control (without metal) and positive control (with known LMCT metals) experiments have to be carried out before screening any new reaction conditions.

Guide for the interpretation

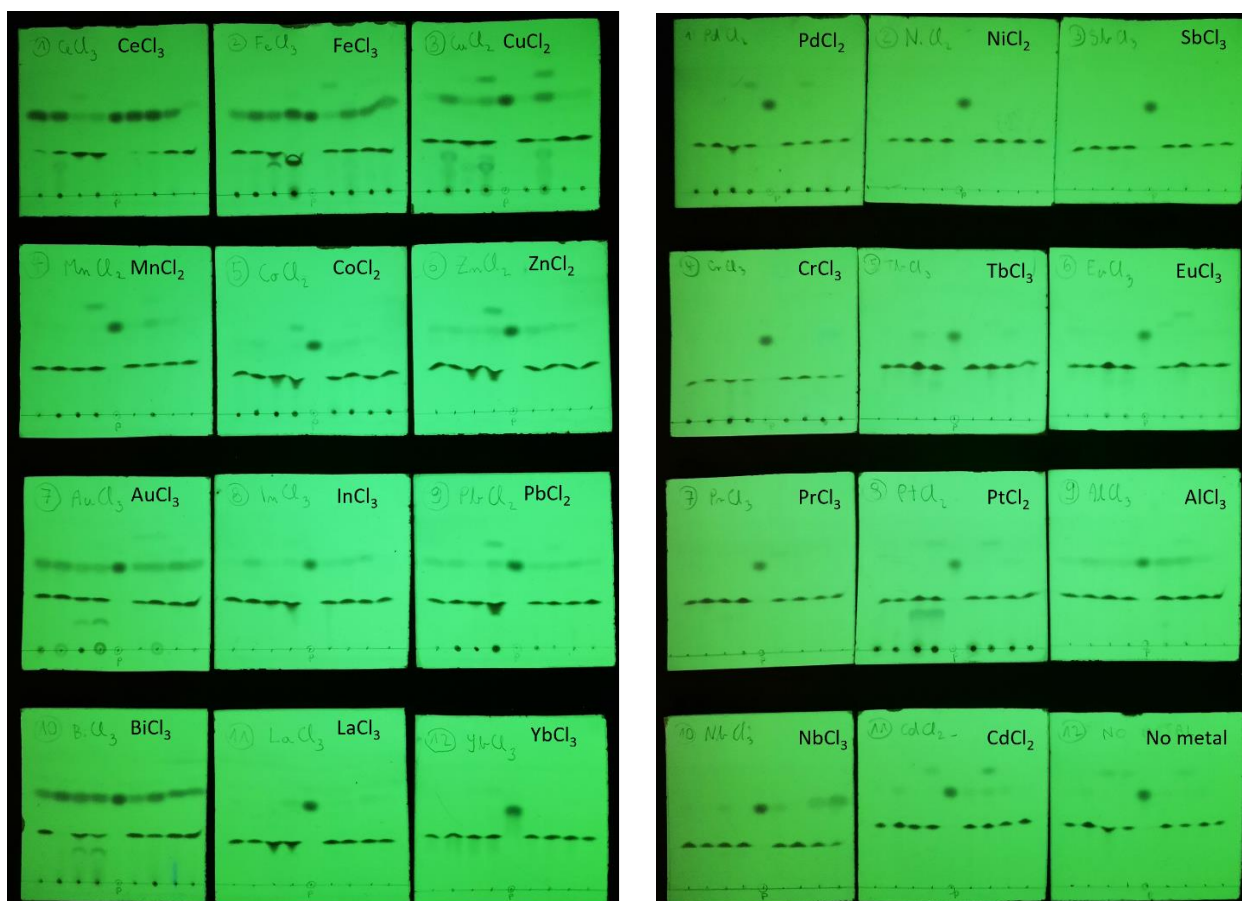
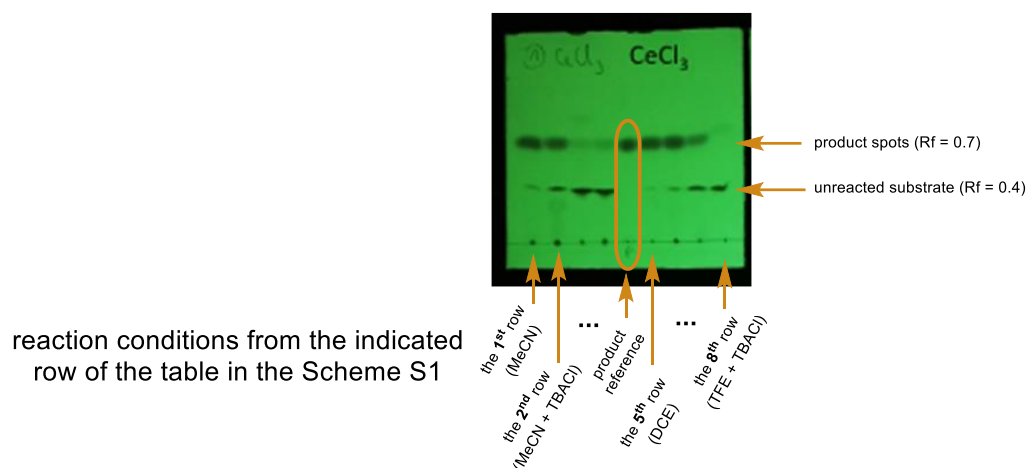
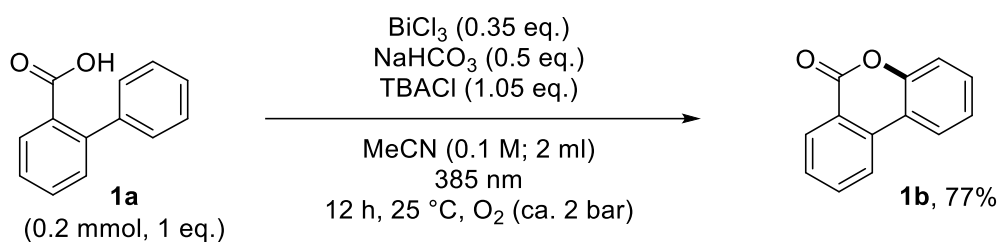


Figure 2.8: Raw data of the TLC analysis.

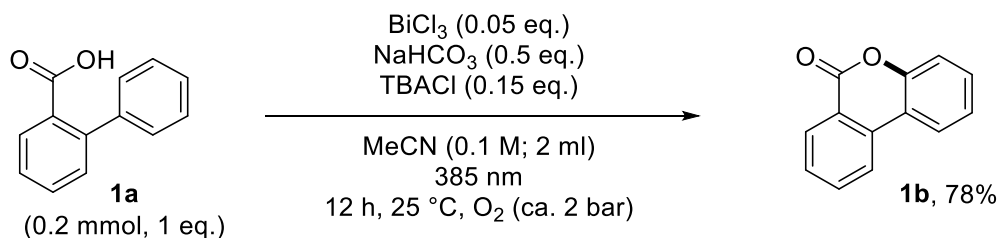
To additionally confirm the screening results obtained in 96-well plates, we repeated the reaction with BiCl_3 in conditions 2 (MeCN, additional TBACl ligand) also on a normal scale (0.2 mmol) and isolated the product **1b** (Scheme 2.3).



Scheme 2.4: Synthesis of the lactone **1b** on a normal 0.2 mmol scale.

2-phenylbenzoic acid (**1a**, 39.6 mg, 0.2 mmol, 1 eq.), NaHCO_3 (8.4 mg, 0.1 mmol, 0.5 eq.), tetrabutylammonium chloride (29 mg, 0.21 mmol, 1.05 eq.), and BiCl_3 (22 mg, 0.07 mmol, 0.35 eq.) were weighed in a 5 ml reaction vial. Then, 2 ml of dry MeCN were added and the vial was closed with a crimp cap with a septum. Then an oxygen balloon was attached to the vial and the atmosphere inside the vial was exchanged by pumping out 20 ml three times. At the end we removed the balloon and pumped additional 5 ml of oxygen into the vial with a syringe to create approximately 2 bar oxygen overpressure. The reaction mixture was shaken briefly, and the vial was placed approximately 2 cm above a 385 nm LED and stirred under irradiation at 25 °C for 12 hours. After completion of the reaction, the solvent was evaporated, and the suspension of the reaction mixture in DCM was prepared. Then we filtered the crude reaction mixture through a short basic alumina column (ca. 4 cm of basic alumina filled in a Pasteur pipette) to remove insoluble salts and any leftover carboxylic acid. We washed the column with more DCM (ca. 5 ml) to elute all the product. After evaporation of the organic solvent, 30 mg of the product **1b** (77% yield) was obtained as a white solid. The purity and identity were confirmed by ^1H -NMR and GC-FID analysis.

Following a similar procedure, we performed the same reaction as well with lower (5 mol%) bismuth catalyst loading. The reaction gave almost the same product yield.



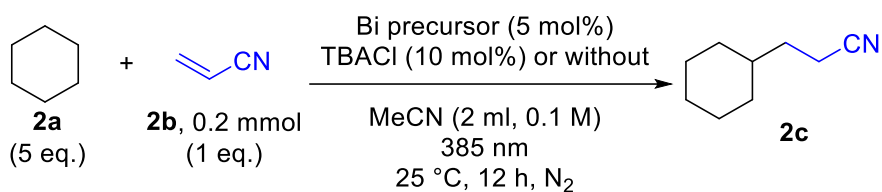
Scheme 2.5: Synthesis of the lactone **1b** on a normal 0.2 mmol scale using lower catalyst loading.

2.7.5 Optimization tables of C-H functionalization

2.7.5.1 Screening of bismuth precursors

We screened different simple and easily available bismuth sources as catalysts for our model reaction.

Table 2.2: Screening of different bismuth sources.



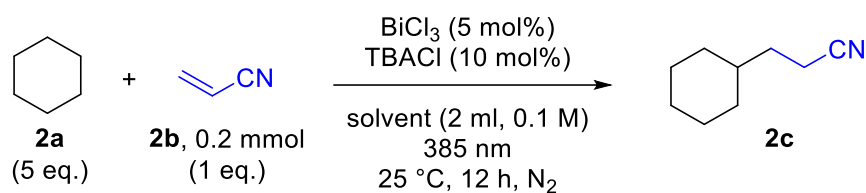
entry	Bi precursors	TBACl	GC Yield (%)
A	BiF ₃	10 mol%	0
B	BiCl ₃	10 mol%	72
C	BiBr ₃	10 mol%	1
D	Bi(OAc) ₃	10 mol%	0
E	BiOCl	10 mol%	0
F	BiOCl	-	0
G	Bi ₂ O ₃	10 mol%	0
H	Bi ₂ O ₃	-	0
I	Bismuth powder	10 mol%	4

GC yields determined by using benzonitrile as internal standard.

Bismuth chloride is the only one which showed significant catalytic activity. Importantly, heterogenous bismuth oxychloride and bismuth oxide which are frequently used in material/inorganic chemistry are completely inactive in our transformation.

2.7.5.2 Solvent screening and water content

Table 2.3: Screening of different solvents.

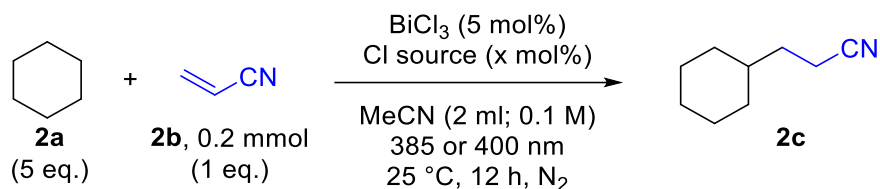


entry	reaction solvent	GC Yields (%)
A	MeCN	72
B	DMF	7
C	DMSO	0
D	TFE	4
E	DCE	14
F	PhCN	44
G	MeCN/H ₂ O (5 eq)	31
H	MeCN/H ₂ O (1:1)	0

GC yields determined by using benzonitrile as internal standard.

2.7.5.3 Screening of wavelengths for excitation of different bismuth chloride complexes

Table 2.4: Excitation of different complexes.

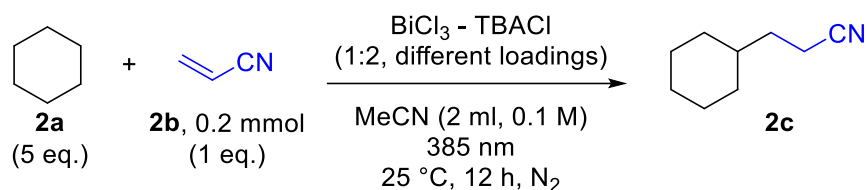


entry	TBACl (mol%)	Ratio BiCl ₃ : TBACl	385 nm	400 nm	GC Yield (%)
A	-	0	X		1
B	5	1 - 1	X		69
C	5	1 - 1		X	7
D	10	1 - 2	X		72
E	10	1 - 2		X	68
F	15	1 - 3	X		61
G	50	1 - 10	X		50

GC yields determined by using benzonitrile as internal standard

2.7.6 Catalyst loading and estimation of TON

Table 2.5: Attempts changing the catalyst loading



entry	BiCl ₃ (mol%)	TBACl (mol%)	GC Yield (%)
A	1	2	15
B	5	10	72
C	10	20	74
D	20	40	70

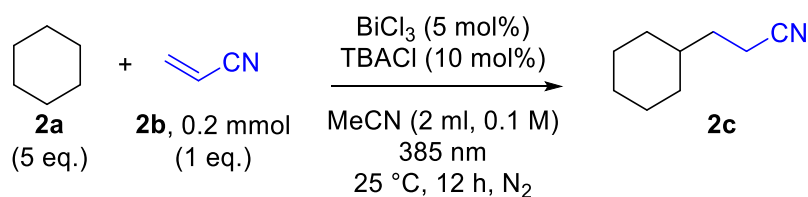
GC yields determined by using benzonitrile as internal standard.

From these entries we can estimate that each catalytic unit of bismuth can do approximately 14 catalytic turnovers before it loses its activity.

2.7.7 Control experiments

The performed control experiments show that indeed bismuth source in combination with UV irradiation are required for the reaction to proceed. Importantly, the reaction cannot be performed at elevated temperature instead of irradiation.

Table 2.6: Control experiments.



entry	deviation	GC yield (%)
A	no BiCl ₃	0
B	no light	0
C	80 °C, no light	0

GC yields determined by using benzonitrile as internal standard.

2.7.8 Mechanistic investigation

2.7.8.1 UV-VIS of bismuth(III) chloride complexes

The absorbing species in the reaction system was investigated

2.7.8.2 BiCl₃ titration with chloride anions

Upon addition of chloride anions to BiCl₃, new bismuth polychloride complexes are formed. These complexes have different spectral properties (**Figure 2.9**) and only sufficiently coordinated species are active reaction catalysts at 385 nm or 400 nm irradiation wavelength (**Figure 2.9**, in the inset).

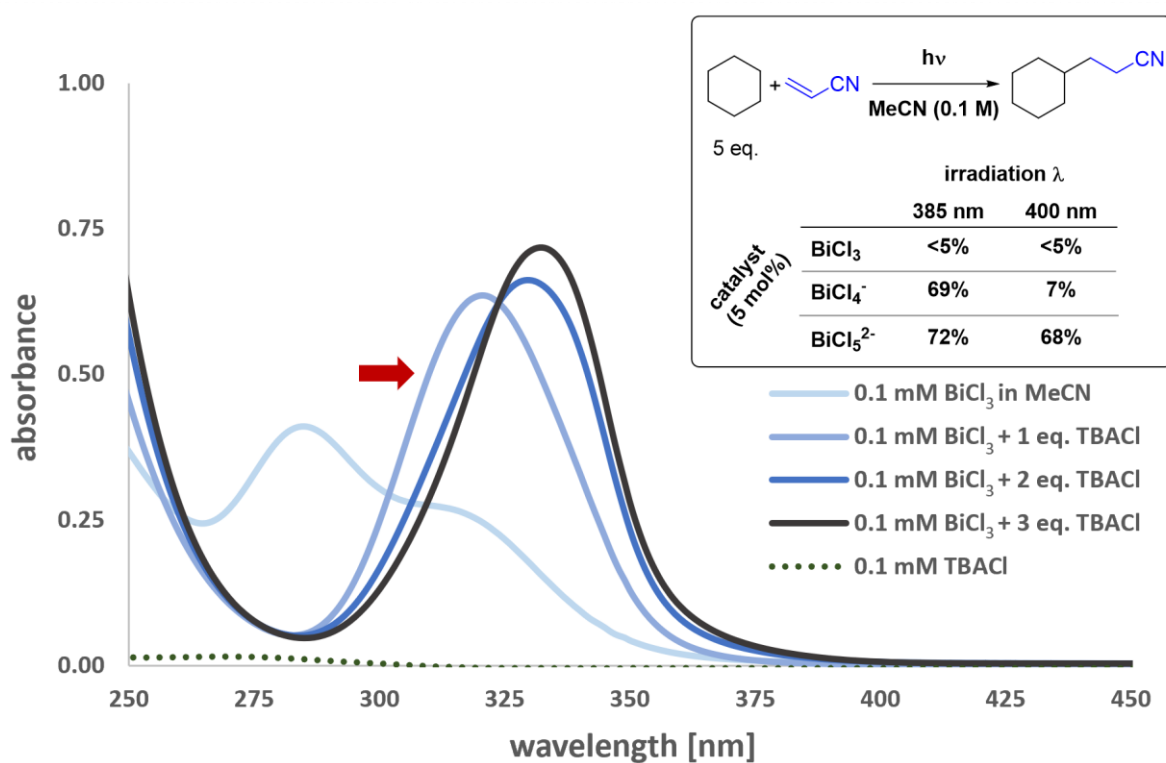


Figure 2.9: UV-Vis spectra of different bismuth(III) chloride complexes in acetonitrile and display of their reactivity in the inset.

2.7.9 BiCl₃ titration with water

When water was gradually added to the solution of BiCl₃ in MeCN, we noticed significant red shift in the light absorption (**Figure 2.10**). However, we did not observe any significant difference in the reactivity between dried and non-dried BiCl₃ from the commercial bottle. In general, small amount of water (e.g., from a wet TBACl) is well tolerated in the reaction conditions despite the possibility of coordination to BiCl₃.

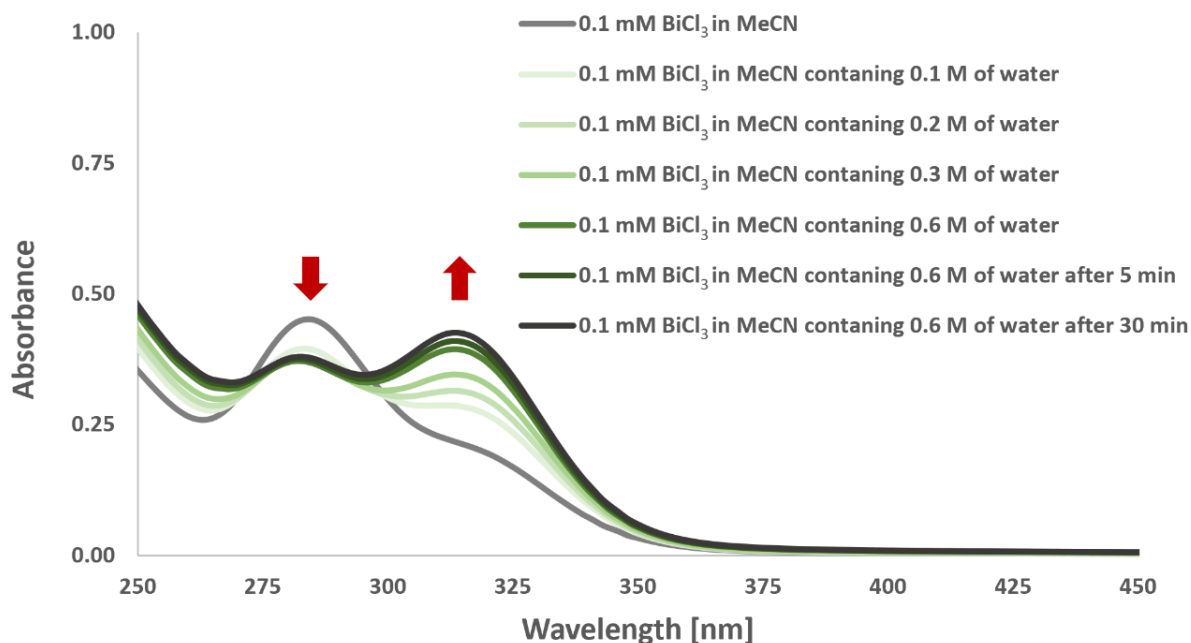


Figure 2.10: UV-Vis spectra of bismuth(III) chloride in acetonitrile upon gradual addition of water.

2.7.9.1 Cyclic voltammetry of bismuth chlorides

The potentials were measured against Ag/AgCl electrode. For comparability, the potential of the ferrocene/ferrocenium couple was corrected to +0.38 V vs. saturated calomel electrode (vs. SCE).

2.7.9.2 Cyclic voltammetry of BiCl_5^{2-}

Solutions were prepared by adding 1 mL of a 0.1 M BiCl_5^{2-} stock solution in MeCN to 6 mL of a 0.1 M conducting TBABF₄ salt in MeCN. The measurement was started in oxidative direction to get the ferrocene reference peaks and then were run in reductive direction for two cycles. However, starting directly in the reductive direction does not change the cyclic voltammogram. The ferrocene is overlapping with additional oxidation peaks. We do not want to speculate on the nature of these additional peaks as bismuth has five different possible oxidation states (0,I,II,III,V) and additional chemical reactions are possible. The CV peaks relevant for bismuth LMCT are the first reduction (Bi(III) to Bi(0)) and the first oxidation peak (Bi(0) to Bi(III)). The first and second CV cycle show a slightly altered curve.

Presumably this change is caused by the deposition of an elemental bismuth film on the carbon working electrode.

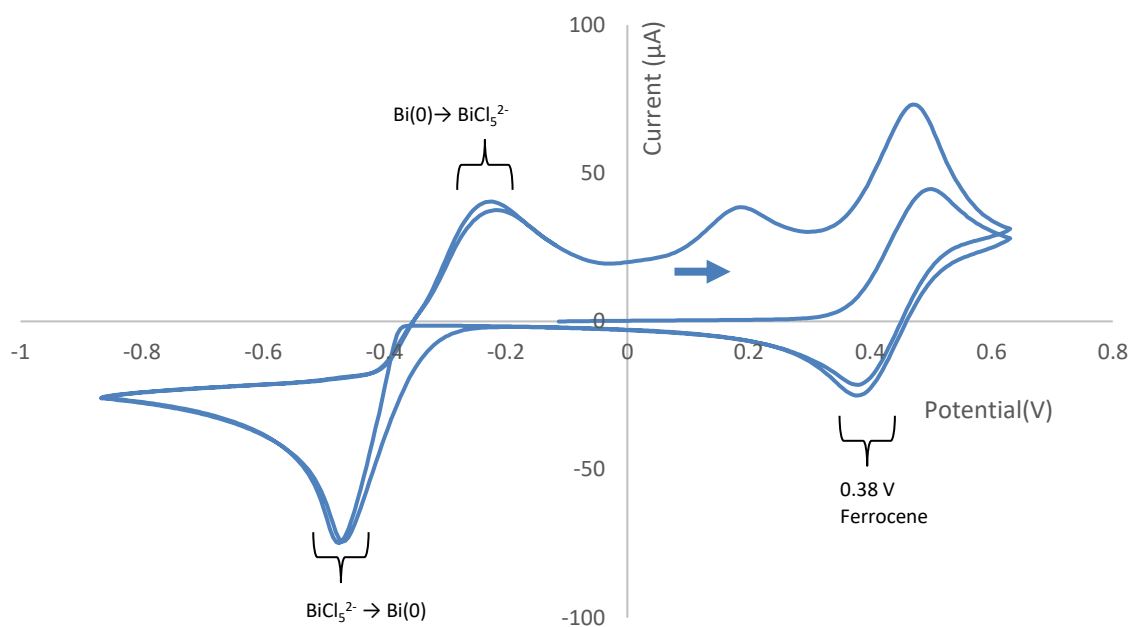


Figure 2.11: Cyclic voltammogram of BiCl_5^{2-} in MeCN.

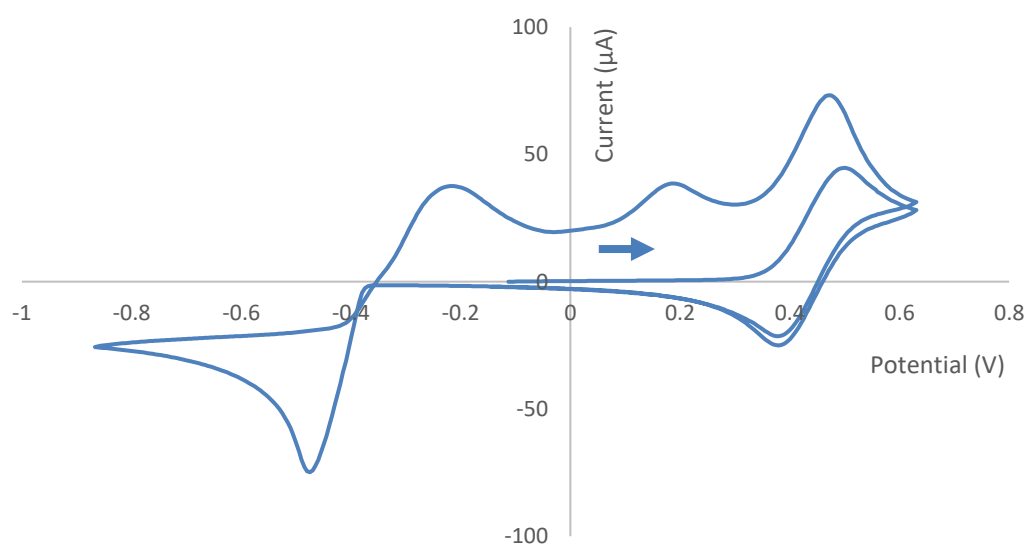


Figure 2.12: Only the first cycle of cyclic voltammogram of BiCl_5^{2-} in MeCN.

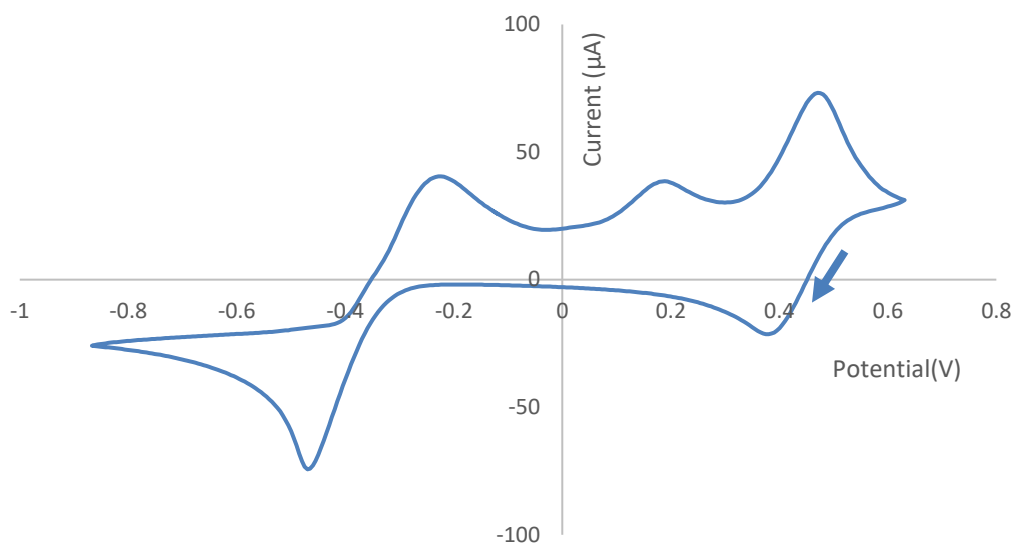


Figure 2.13: Only the second cycle of cyclic voltammogram of BiCl_5^{2-} in MeCN.

2.7.9.3 Cyclic voltammetry of BiCl_3

The measurement was performed similarly as with BiCl_5^{2-} . The only difference was that we started the measurements in reductive direction.

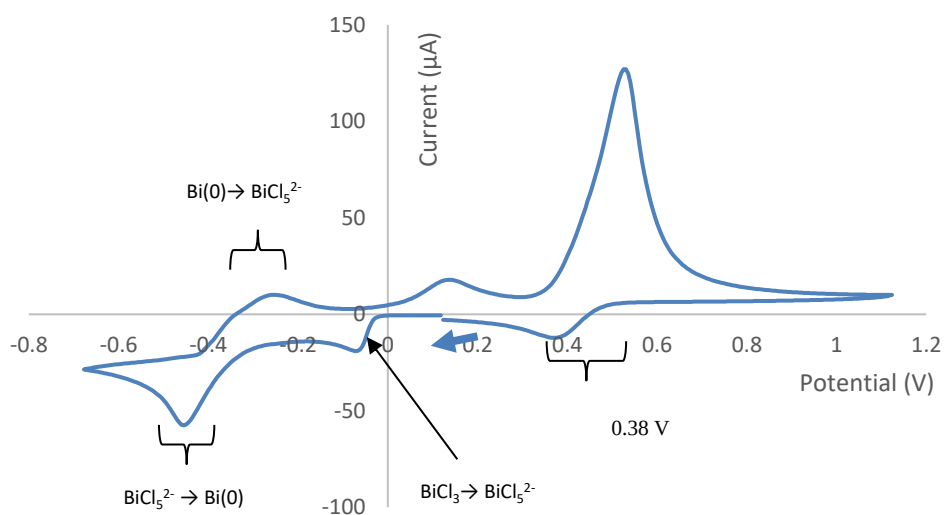


Figure 2.14: Cyclic voltammogram of BiCl_3 in MeCN.

2.7.9.4 Cyclic voltammetry of BiCl_4^-

We performed this measurement to support our spectro-electrochemical investigation. The measurement shows only a small reduction peak (at -0.2 V) for BiCl_4^- , indicating that the released chloride immediately reacts with the remaining BiCl_4^- to form BiCl_5^{2-} .

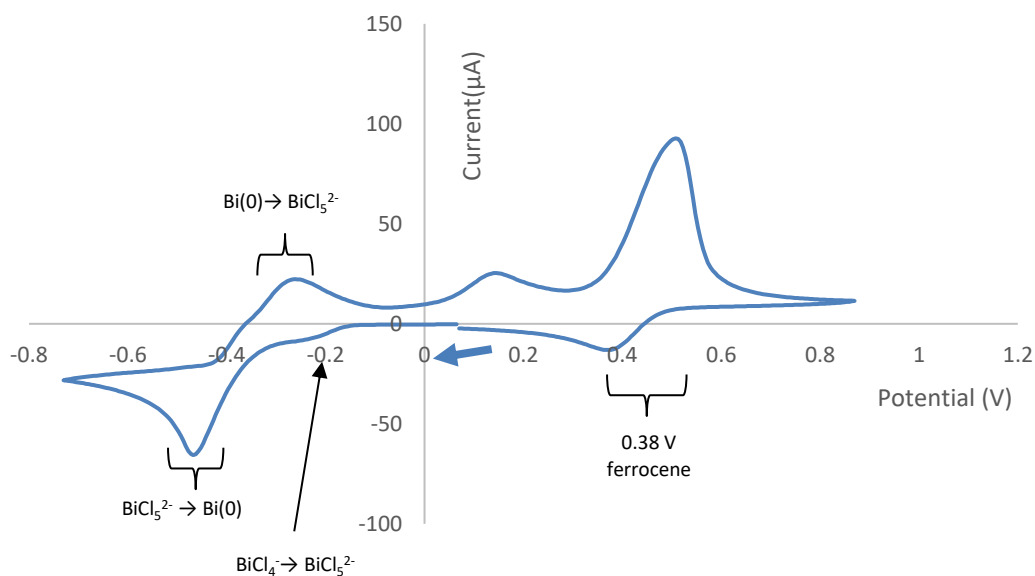


Figure 2.15: Cyclic voltammogram of BiCl_4^- in MeCN.

2.7.10 Spectro-electrochemical experiments

The samples dissolved in MeCN were purged with argon for 5 min before they were transferred in the Ottle cell. The reported potentials were measured against Ag/AgCl reference electrode. During the measurements, the potential was being changed slowly at rate 5 mV/s. The UV-Vis spectra were measured after each change of potential for 50 mV (corresponds to 10 seconds).

2.7.11 UV-vis monitoring of the reduction and oxidation of BiCl_5^{2-}

The absorption maximum peak of BiCl_5^{2-} at 340 nm disappears upon reduction (**Figure 2.16A**), and upon oxidation reappears without any noticeable intermediates or side reactions (**Figure 2.16B**).

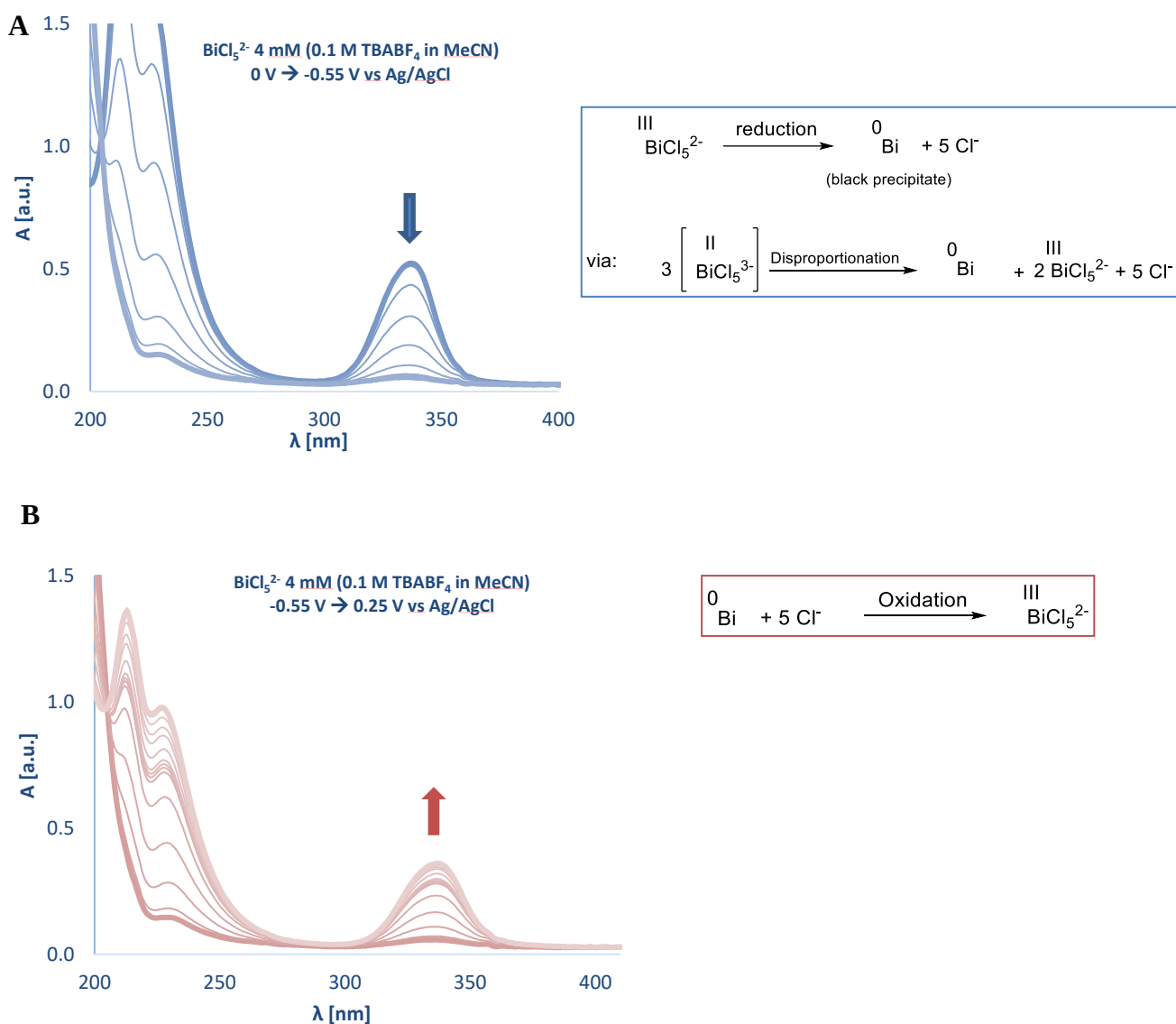


Figure 2.16: UV-vis monitoring of the reduction (A) and subsequent oxidation of BiCl_5^{2-} (B).

The reduction of $\text{Bi}^{(\text{III})}\text{Cl}_5^{2-}$ and oxidation of $\text{Bi}^{(0)}$ are complex processes. In both cases 3 electrons are transferred, but we could only observe a single peak in CV. This likely indicates that after the initial electron transfer, a fast series of disproportionations is triggered which results in $\text{Bi}(\text{III})$ and $\text{Bi}(0)$.

2.7.12 UV-vis monitoring of the reduction and oxidation of BiCl_3

The reduction of BiCl_3 (**Figure 2.17**) is a two-step process. In the first step BiCl_3 is reduced to BiCl_5^{2-} . The absorption maximum of BiCl_3 at 280 nm disappears, and a new peak at 340 nm appears indicating formation of BiCl_5^{2-} (**Figure 2.17**). The disproportionation should generate both BiCl_5^{2-} and BiCl_4^- (otherwise it is impossible to balance the chemical equation). We observed the bathochromic shift of the absorption without a clear isosbestic point, indicating the presence of more than one species. Probably the fast interconversion of BiCl_4^- by either reduction or addition of chlorine makes this species under the measurement conditions only short-lived. At the end of this stage, we observed absorption pattern which corresponds to previously measured BiCl_5^{2-} spectrum. This could be explained by the onset of the reduction of the BiCl_4^- (**Figure 2.15**) which releases some chloride. The released chloride reacts with BiCl_4^- to form BiCl_5^{2-} . In the second step (**Figure 2.17B**), when the reduction potential is further decreased, *in situ* generated BiCl_5^{2-} undergoes reduction - similarly as in **Figure 2.16**.

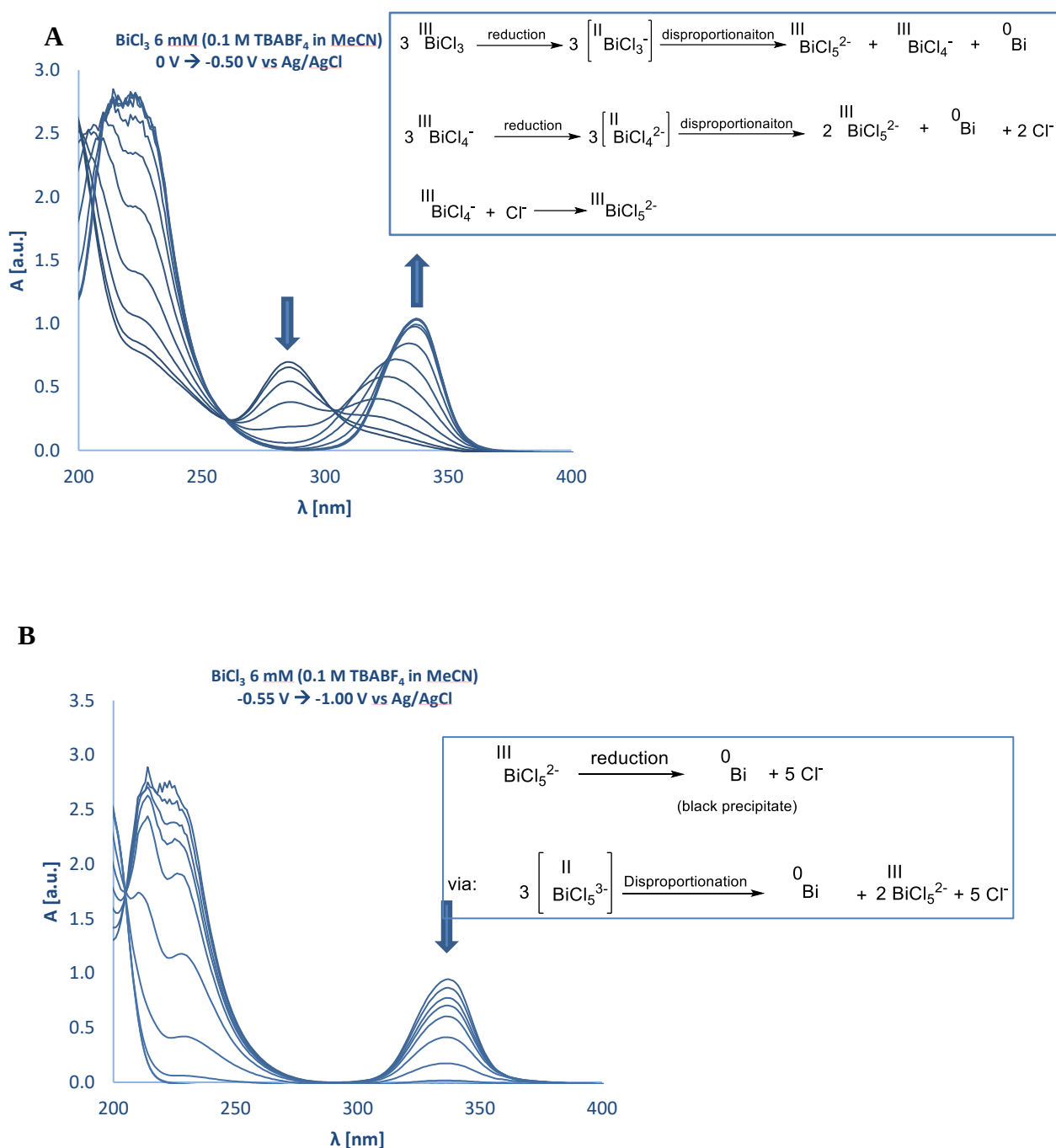


Figure 2.17: UV-vis monitoring of the reduction of BiCl_3 (A) and BiCl_5^{2-} (B).

In the first step of oxidation of $\text{Bi}(0)$ (**Figure 2.18A**), absorption maximum of BiCl_5^{2-} at 340 nm reappears – similarly as in **Figure 2.16B**. During further oxidation of bismuth(0) (**Figure 2.18B**), the disappearance of the band at 340 nm and formation of a new absorption maximum at 280 nm was observed. We can explain that by looking at the concentration of the chloride ions. Once, when the free Cl^- ions are used up, the newly formed Bi^{3+} ions start taking the chloride ions from BiCl_5^{2-} leading to formation of BiCl_3 .

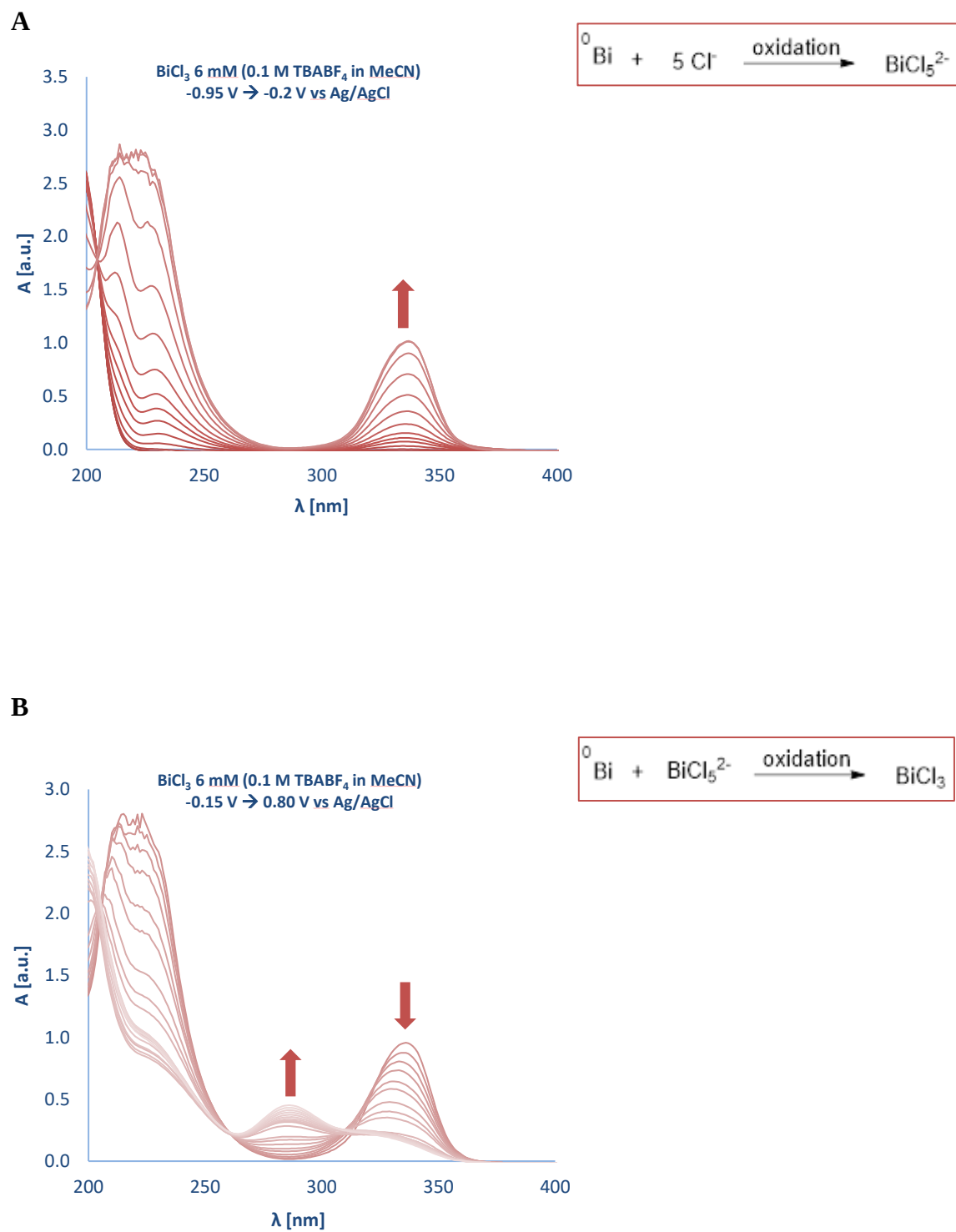


Figure 2.18: UV-vis monitoring of the oxidation of the previously reduced BiCl₃ sample.

2.7.13 Powder diffraction and microscopy of the black precipitate

The black powder which forms in redox neutral reactions corresponds to some reduced bismuth species. The main question we had, was whether we are getting bismuth in oxidation state (I), (so-called complex bismuth subchlorides) or is it elemental bismuth (0). The black precipitate was prepared by two different means. In one case, we analyzed the solid residue which was formed in large scale reaction between acrylonitrile and cyclohexane (**Scheme 2.8**). In the other case, we directly prepared the black precipitate by irradiation of the solution of the BiCl_5^{2-} complex in the absence of any reactants (**Scheme 2.6**).

The powder X-ray diffraction analysis unambiguously identified the black precipitate as elemental bismuth(0) in both cases (**Figure 2.19**). The unidentified peak areas were less than 4% in both samples. We estimate the purity of the samples to be 92+ %.

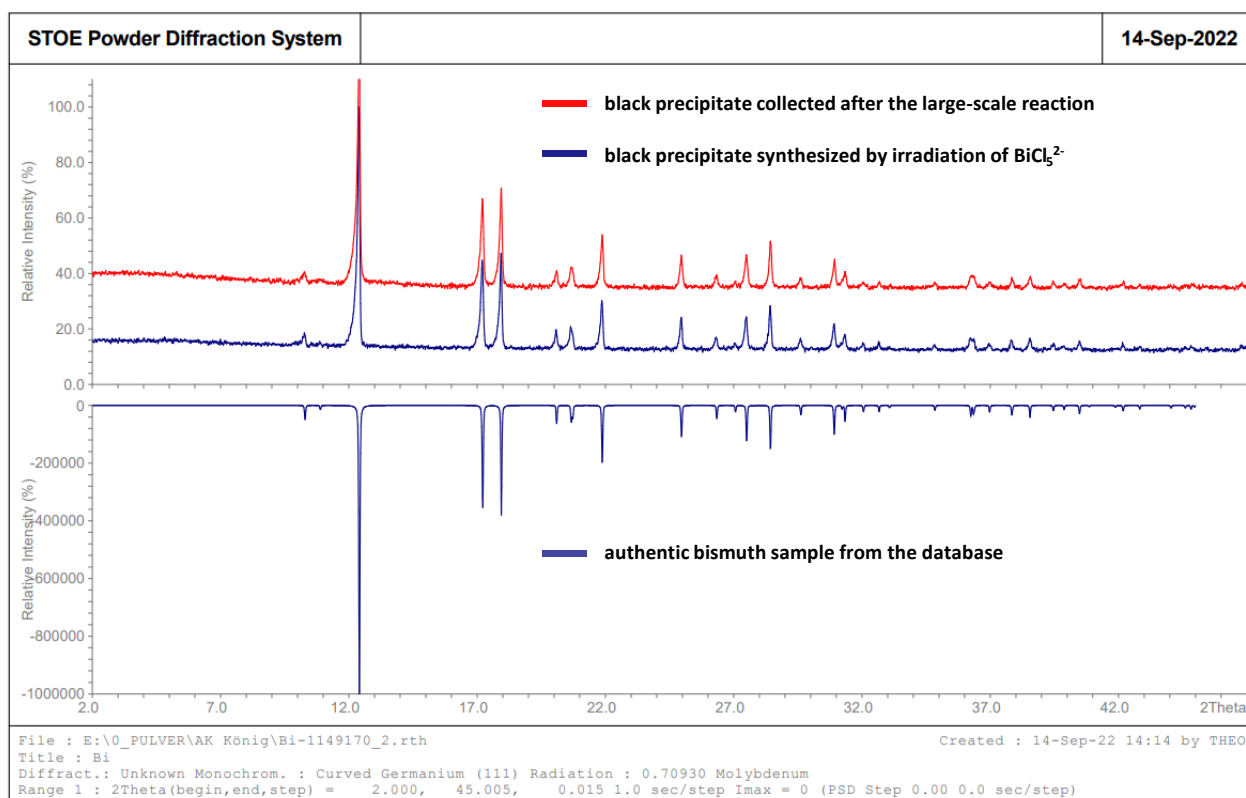


Figure 2.19: Comparison of the measured powder X-Ray diffractograms to the database bismuth reference.²

2.7.14 Kinetics of the reaction

The yield after one hour, 26% corresponds to 5 catalytic turnovers of the bismuth catalyst (5 mol% loading). The reaction profile in the first one hour is linear, likely indicating that the active catalytic species is not changing over time.

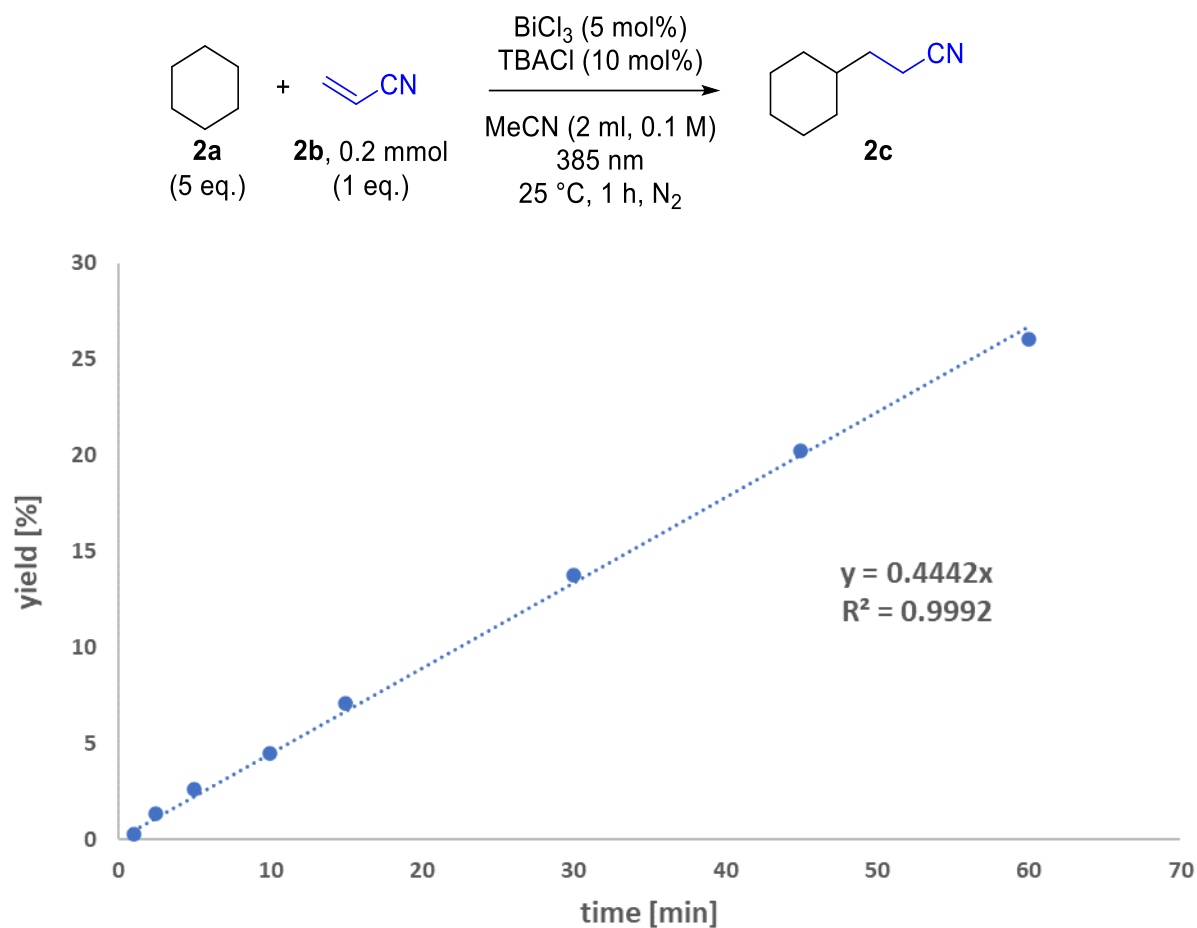


Figure 2.21: Initial kinetics of the model reaction.

2.7.15 Quantum yield of the model reaction

Experimental procedure for quantum yield determination

The method and instrument which we used was originally developed by Prof. Riedle.¹

BiCl₃ (6.3 mg, 0.02 mmol, 5 mol%) and TBACl (11.1 mg, 0.04 mmol, 10 mol%) were weighed into a crimp reaction vial. 4 ml of dry MeCN was added and the vial was closed. The reaction mixture was stirred for a few minutes and degassed by 4 argon-vacuum cycles. Then, 3.0 ml of the so-prepared reaction mixture was transferred using air-free techniques into a 10×10 mm fluorescence cuvette equipped with a stirring bar (see **Figure**). Afterwards, degassed internal standard benzotrifluoride (36.8 µl, 0.3 mmol, 1 eq.) and liquid reactants acrylonitrile (19.7 µl, 0.3 mmol, 1 eq.) and cyclohexane (162 µl, 1.5 mmol, 5 eq.) were added. The reaction mixture was irradiated with a single spot 385 nm LED in a quantum yield determination setup for 12 hours. 50 µl aliquots of the reaction mixture were and taken analysed by GC-FID after approximately 4, 8 and 12 hours of irradiation.

Table 2.9: Quantum yield determination.

2a (5 eq.) + **2b**, 0.3 mmol (1 eq.) $\xrightarrow[\text{MeCN (3 ml, 0.1 M), 385 nm, rt, Ar}]{\text{BiCl}_3 \text{ (5 mol\%), TBACl (10 mol\%)}}$ **2c**

En-try	Δt [min]	$P_{ref(solvent)}$ [mW]	P_{sample} [mW]	P_{abs} [mW]	GC yield	Quantum yield ϕ
1	265	50.7	13.9	38.5	11 %	1.6 %
2	455	50.7	13.5	38.9	17 %	1.5 %
3	715	50.7	11.9	40.6	25 %	1.3 %

average = **1.5 %**

More details on the calculation of the quantum yield (Φ) of the Entry 1.

$$\Phi = \frac{N_{prod}}{N_{ph,abs}} = N_A \cdot h \cdot c \frac{c_{prod} \cdot V}{P_{abs} \cdot \Delta t \cdot \lambda_{LED}}$$

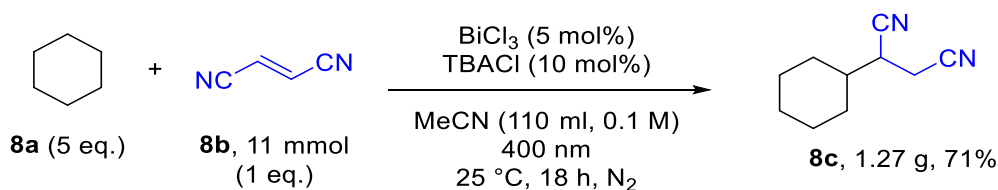
constants		
$N_A= 6.02214 \times 10^{23} \text{ mol}^{-1}$	Avogadro constant	
$h= 6.62607004 \times 10^{-34} \text{ Js}$	Planck constant	
$c= 299792458 \text{ m/s}$	Speed of light	
data for our system		
N_{prod}	Number of product molecules	
$N_{ph,abs}$	Number of photons absorbed	
c_{prod}	Product concentration	= 10.5 mmol/L
V	Reaction volume	= 3.00 mL
Δt	Illumination time	= 15908 s (4 h 25 min)
P_{abs}	Absorbed power	= 13.9 mW (calculated)
λ_{LED}	Illumination wavelength	= 385 nm

P_{abs} was calculated using the following equations:

$$P_{abs} = (P_{ref} - P_{sample})f \quad f = \frac{1 + R \frac{P_{sample}}{P_{ref}}}{1 - R}$$

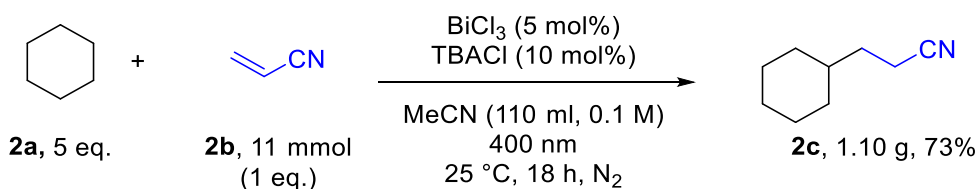
Data for our system		
P_{sample}	Average power during illumination	= 13.9 mW
P_{ref}	Reference power (solvent)	= 50.7 mW
f	Correction factor	= 1.049
R	Back reflection	= 0.0357 (parameter for fused silica cuvette)

2.7.16 Gram-scale reactions



Scheme 2.7: Gram-scale reaction for preparation of **8c**.

Fumaronitrile (858 mg, 11 mmol, 1 eq.), BiCl₃ (173 mg, 0.55 mmol, 5 mol%) and tetrabutylammonium chloride (305 mg, 1.1 mmol, 10 mol%) were weighed in a reaction vessel (see **Figure 2.6** for pictures of the setup). Then, dry MeCN (110 ml) was added, and the reaction vessel was closed and degassed by 4 nitrogen-vacuum cycles. Afterwards, degassed cyclohexane (5.9 ml, 55 mmol, 5 eq.) was added through a septum and the reaction mixture was stirred under irradiation for 18 hours at 25 °C. The conversion of the fumaronitrile was monitored by GC-FID. After the completion, the reaction mixture was transferred into a round bottom flask, 2 spoons of silica gel were added, and the solvent was removed by a rotary evaporator to prepare a dry load for the column. 5-20 % ethyl acetate/petrol ether solvent mixture was used as an eluent for the column. The spots on the TLC were visualized by permanganate stain. After the column and pentane wash, the product was obtained as a white crystalline solid in 71% yield.



Scheme 2.8: Gram-scale reaction for preparation of **2c**.

Gram-scale reaction for preparation of **2c** was done similarly as in above-described procedure (**Scheme 2.7**). Acrylonitrile **2b** was degassed in a separate reaction vial before it was added to the degassed reaction mixture. After the completion, the reaction mixture was transferred into a round bottom flask and the solvent was removed under reduced pressure. The crude reaction mixture was purified by Kugelrohr distillation. The purified product was obtained as a colorless oil in 73% yield.

2.7.17 Light on-off experiment

BiCl₃ (3.2 mg, 0.01 mmol, 5 mol%), TBACl (5.5 mg, 0.02 mmol, 10 mol%) and fumaronitrile (15.6 mg, 0.2 mmol, 1 eq) were weighed into a crimp reaction vial. 1.5 ml of dry MeCN was added and the vial was closed. The reaction mixture was stirred for a few minutes and degassed by 4 nitrogen-vacuum cycles. Afterwards, degassed internal standard benzotri-fluoride (12.3 μ L, 0.1 mmol) and cyclohexane (108 μ L, 1 mmol, 5 eq.) were added. The sample was periodically irradiated and left in the dark. During these light dark cycles, samples of 80 μ L were periodically taken and analysed by GC. Product formation is only observed when the sample is irradiated (**Figure 2.22**). Therefore, the reaction is light-driven.

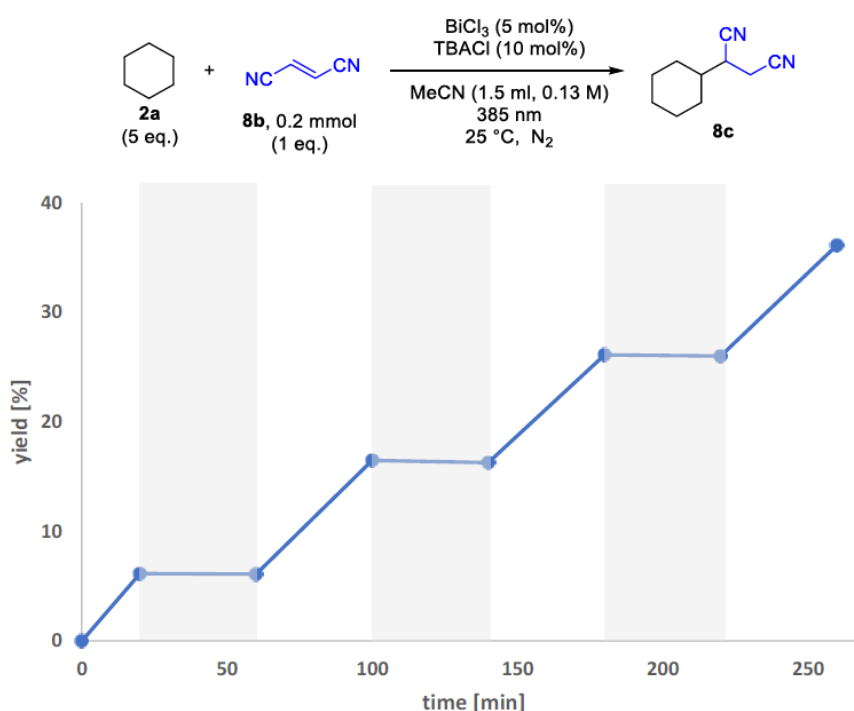
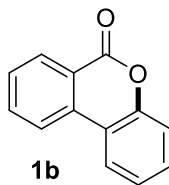


Figure 2.22 Light on-off experiment

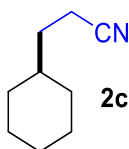
2.7.18 Characterization data

6H-benzo[c]chromen-6-one (1b)



Yield	77% (30 mg, 0.15 mmol), White solid
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 8.35 (dd, <i>J</i> = 8.1, 1.0 Hz, 1H), 8.06 (d, <i>J</i> = 8.1 Hz, 1H), 8.00 (dd, <i>J</i> = 7.9, 1.3 Hz, 1H), 7.79 (ddd, <i>J</i> = 8.1, 6.9, 1.3 Hz, 1H), 7.54 (ddd, <i>J</i> = 8.1, 6.9, 0.9 Hz, 1H), 7.44 (ddd, <i>J</i> = 8.3, 6.9, 1.3 Hz, 1H), 7.37 – 7.27 (m, 2H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 161.2, 151.3, 134.8, 134.7, 130.5, 130.4, 128.9, 124.6, 122.8, 121.7, 121.2, 118.0, 117.7.

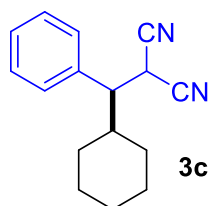
3-cyclohexylpropanenitrile (2c)



Yield	large scale (11 mmol): 73% (1.10 g, 8.0 mmol), colorless oil.
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 2.33 (t, <i>J</i> = 7.3 Hz, 2H), 1.75 – 1.60 (m, 5H), 1.53 (dt, <i>J</i> = 7.3, 7.3 Hz, 2H), 1.44 – 1.29 (m, 1H), 1.30 – 1.04 (m, 3H), 0.97 – 0.80 (m, 2H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 120.1, 36.6, 32.6, 32.5, 26.3, 26.0, 14.7.
HR-MS (EI)	(M ⁺ -H) ⁺ : calc. 136.1121, found 136.1120

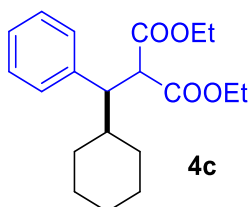
The compound is too volatile to be isolated on a normal scale (0.4 mmol) in a representative yield.

2-(cyclohexyl(phenyl)methyl)malononitrile (3c)



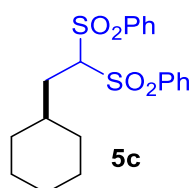
Yield	79% (75 mg, 0.32 mmol), colorless oil
^1H NMR	^1H NMR (400 MHz, CDCl_3) δ 7.46 – 7.28 (m, 5H), 4.20 (d, J = 5.5 Hz, 1H), 2.89 (dd, J = 9.8, 5.5 Hz, 1H), 2.10 – 1.97 (m, 1H), 1.97 – 1.89 (m, 1H), 1.89 – 1.77 (m, 1H), 1.77 – 1.60 (m, 2H), 1.53 – 1.29 (m, 2H), 1.29 – 0.96 (m, 3H), 0.90 – 0.76 (m, 1H).
^{13}C NMR	^{13}C NMR (101 MHz, CDCl_3) δ 136.8, 129.1, 128.7, 128.4, 112.4, 112.1, 52.3, 39.3, 31.2, 30.6, 27.2, 25.9, 25.9, 25.8.
HR-MS (EI)	(M) $^+$: calc. 238.1465, found 238.1459

diethyl 2-(cyclohexyl(phenyl)methyl)malonate (4c)



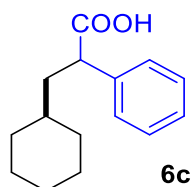
Yield	35% (47 mg, 0.14 mmol), colorless oil
^1H NMR	^1H NMR (400 MHz, CDCl_3) δ 7.26 – 7.08 (m, 5H), 4.30 – 4.16 (2H), 3.97 (d, J = 11.3 Hz, 1H), 3.91 – 3.78 (2H), 3.37 (dd, J = 11.3, 5.0 Hz, 1H), 1.74 – 1.48 (m, 6H), 1.35 – 1.04 (m, 5H), 1.01 – 0.75 (m, 6H).
^{13}C NMR	^{13}C NMR (101 MHz, CDCl_3) δ 168.9, 168.1, 139.0, 129.5, 127.7, 126.7, 61.5, 61.1, 55.4, 51.1, 40.9, 32.1, 28.4, 26.7, 26.5, 26.2, 14.1, 13.7.
HR-MS (ESI)	(M+H) $^+$: calc. 333.2060, found 333.2067

(2-cyclohexylethane-1,1-diyl)disulfonyl)dibenzene (5c)



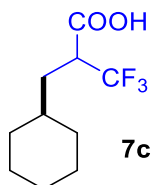
Yield	45% (71 mg, 0.18 mmol), White solid
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 7.95 (dt, <i>J</i> = 8.6, 1.6 Hz, 4H), 7.75 – 7.64 (m, 2H), 7.64 – 7.51 (m, 4H), 4.46 (t, <i>J</i> = 5.6 Hz, 1H), 1.99 (dd, <i>J</i> = 6.9, 5.7 Hz, 2H), 1.70 – 1.54 (m, 5H), 1.50 – 1.37 (m, 1H), 1.20 – 1.00 (m, 3H), 0.80 – 0.67 (m, 2H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 137.9, 134.6, 129.7, 129.2, 81.4, 35.7, 32.6, 32.5, 26.1, 25.8.
HR-MS (ESI)	(M+H) ⁺ : calc. 393.1197, found 393.1189

3-cyclohexyl-2-phenylpropanoic acid (6c)



Yield	40% (37 mg, 0.16 mmol), colorless oil
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 10.34 (s, 1H), 7.36 – 7.24 (m, 5H), 3.71 (t, <i>J</i> = 7.8 Hz, 1H), 2.02 – 1.94 (m, 1H), 1.80 – 1.56 (m, 6H), 1.26 – 1.10 (m, 4H), 0.97 – 0.84 (m, 2H)
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 180.7, 138.8, 128.7, 128.1, 127.4, 48.8, 40.6, 35.2, 33.3, 33.0, 26.5, 26.1, 26.1.
HR-MS (EI)	(M) ⁺ : calc. 232.1458, found 232.1462

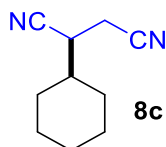
2-(cyclohexylmethyl)-3,3,3-trifluoropropanoic acid (7c)



Yield	29% (26 mg, 0.12 mmol), colorless oil
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 7.52 (bs, 1H), 3.42 – 3.03 (m, 1H), 2.05 – 1.52 (m, 7H, overlap with water), 1.44 – 1.07 (m, 5H), 1.07 – 0.80 (m, 2H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 173.5, 124.7 (q, <i>J</i> = 276.7 Hz), 47.8 (q, <i>J</i> = 28.0 Hz), 34.9, 33.5, 33.4, 32.1, 26.3, 26.0, 25.8.
¹⁹F NMR	¹⁹ F NMR (376 MHz, CDCl ₃) δ -68.9.
HR-MS (EI)	(M-HF) ⁺ : calc. 204.0956, found 204.0957

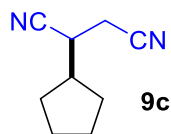
A similar complex ¹³C NMR pattern was observed for a related methyl ester compound.³

2-cyclohexylsuccinonitrile (8c)



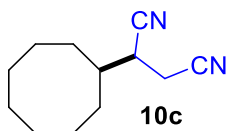
Yield	Normal scale (0.4 mmol): 73% (47 mg, 0.29 mmol), white solid Large scale (11 mmol): 71% (1.27 g, 7.8 mmol), white solid
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 2.81 – 2.73 (m, 1H), 2.73 – 2.59 (m, 2H), 1.92 – 1.56 (m, 6H), 1.35 – 1.02 (m, 5H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 118.5, 116.4, 38.5, 34.6, 30.8, 29.0, 25.6, 25.6, 25.5, 18.7.
HR-MS (EI)	(M ⁺ -H) ⁺ : calc. 161.1073, found 161.1073

2-cyclopentylsuccinonitrile (9c)



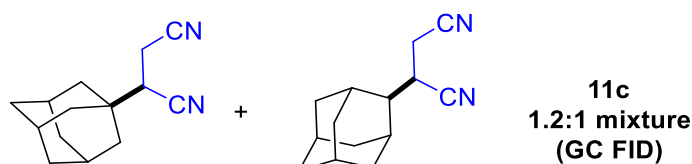
Yield	79% (47 mg, 0.32 mmol), colorless oil
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 2.95-2.87 (m, 1H), 2.80 – 2.61 (m, 2H), 2.28 – 2.10 (m, 1H), 2.05 – 1.81 (m, 2H), 1.81 – 1.51 (m, 4H), 1.51 – 1.19 (m, 2H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 118.5, 115.9, 41.0, 33.6, 30.9, 29.7, 25.2, 25.0, 20.5.
HR-MS (ESI)	(M+NH ₄) ⁺ : calc. 166.1339, found 166.1338

2-cyclooctylsuccinonitrile (10c)



Yield	67% (51 mg, 0.27 mmol), colorless oil
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 2.90 – 2.63 (m, 3H), 2.05 – 1.89 (m, 1H), 1.87 – 1.40 (m, 14H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 118.6, 116.0, 38.3, 35.8, 31.6, 28.9, 26.5, 26.3, 26.2, 25.6, 25.0, 19.2.
HR-MS (EI)	(M ⁺ -H) ⁺ : calc. 189.1386, found 189.1391

2-((3*r*,5*r*,7*r*)-adamantan-1-yl)succinonitrile / 2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yl)succinonitrile (11c)



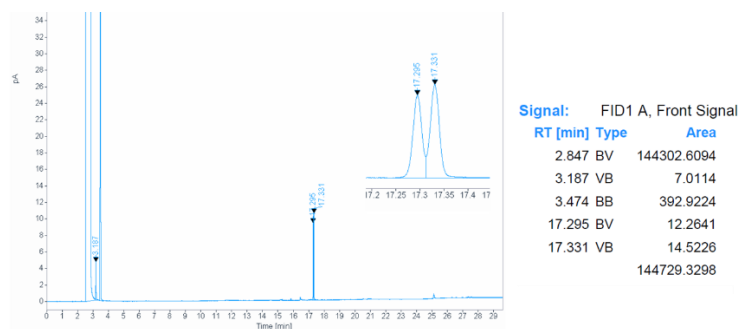
Yield 51% (44 mg, 0.20 mmol), white solid

¹H NMR (mixture) ¹H NMR (400 MHz, CDCl₃) δ 3.25 – 3.16 (m, 1H), 2.87 – 2.74 (m, 1H), 2.69 – 2.58 (m, 4H), 2.20 (s, 1H), 2.13 – 1.99 (m, 4H), 1.98 – 1.90 (m, 3H), 1.90 – 1.57 (m, 22H).

¹³C NMR (mixture) ¹³C NMR (101 MHz, CDCl₃) δ 118.9, 117.8, 116.9, 115.8, 45.2, 41.1, 39.4, 38.2, 38.1, 37.5, 36.2, 35.0, 31.5, 30.9, 30.8, 30.2, 28.2, 28.1, 27.3, 27.2, 19.0, 15.4.

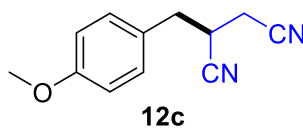
HR-MS (ESI) (M+NH₄)⁺: calc. 232.1808, found 232.1809

GC-FID



Ratio of the two isomers was determined from the GC-FID analysis. The isomers in the sample are not easy to separate on the column and therefore, we used very low concentration to minimize the overlap.

2-(4-methoxybenzyl)succinonitrile (12c)



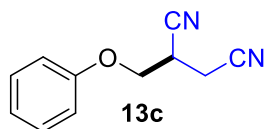
Yield 92% (74 mg, 0.37 mmol), yellowish oil

¹H NMR ¹H NMR (400 MHz, CDCl₃) δ 7.18 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.14 – 2.92 (m, 3H), 2.63 (dd, *J* = 6.3, 1.4 Hz, 2H).

¹³C NMR ¹³C NMR (101 MHz, CDCl₃) δ 159.4, 130.3, 126.5, 118.8, 115.8, 114.6, 55.4, 36.2, 30.3, 20.0.

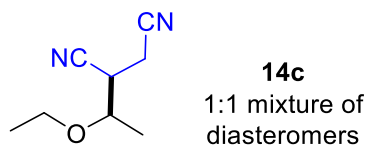
HR-MS (EI) (M)⁺: calc. 200.0944, found 200.0941

2-(phenoxymethyl)succinonitrile (**13c**)



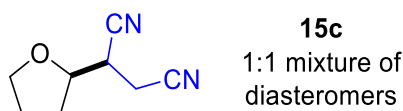
Yield	84% (63 mg, 0.34 mmol), yellowish oil
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 7.33 (dd, <i>J</i> = 8.7, 7.3 Hz, 2H), 7.06 (t, <i>J</i> = 7.3 Hz, 1H), 6.93 (d, <i>J</i> = 8.7, 2H), 4.30 – 4.18 (m, 2H), 3.40 – 3.32 (m, 1H), 2.94 (dd, <i>J</i> = 6.7, 1.1 Hz, 2H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 157.3, 129.9, 122.5, 116.9, 115.5, 114.8, 65.4, 29.0, 18.1.
HR-MS (EI)	(M) ⁺ : calc. 186.0788, found 186.0789

2-(1-ethoxyethyl)succinonitrile (**14c**)



Yield	86% (52 mg, 0.34 mmol), colorless oil
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 3.76 – 3.57 (m, 2H), 3.52 – 3.33 (m, 1H), 3.07 – 2.69 (m, 3H), 1.35 (dd, <i>J</i> = 7.9, 6.2 Hz, 3H), 1.27 – 1.14 (m, 3H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 117.6, 117.1, 116.2, 116.0, 73.3, 72.1, 65.1, 64.8, 35.2, 35.1, 17.7, 17.7, 17.5, 17.4, 15.2, 15.2.
HR-MS (EI)	(M ⁺ -H) ⁺ : calc. 151.0866, found 151.0866

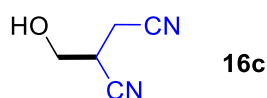
2-(tetrahydrofuran-2-yl)succinonitrile (**15c**)



Yield	92% (55 mg, 0.37 mmol), colorless oil
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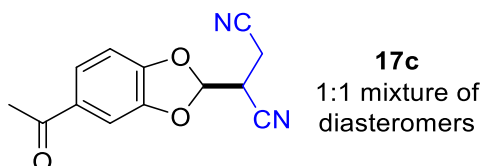
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 4.15 – 3.73 (m, 3H), 3.13 – 2.69 (m, 3H), 2.35 – 1.75 (m, 4H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 117.3, 117.2, 116.0, 115.7, 77.2, 76.4, 69.4, 69.1, 34.6, 34.3, 30.1, 29.9, 25.9, 25.5, 18.8, 18.5.
HR-MS (EI)	(M ⁺ -H) ⁺ : calc. 149.0709, found 149.0711

2-(hydroxymethyl)succinonitrile (16c)



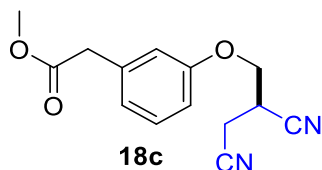
Yield	36% (16 mg, 0.14 mmol), yellowish oil
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 3.96 (dd, <i>J</i> = 5.2, 1.4 Hz, 2H), 3.11 (tt, <i>J</i> = 6.8, 5.2 Hz, 1H), 2.87 (dd, <i>J</i> = 6.8, 1.4 Hz, 2H), 2.44 (bs, 1H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 117.5, 115.6, 60.8, 31.1, 17.5.
HR-MS (EI)	(M) ⁺ : calc. 110.0475, found 110.0473

2-(5-acetylbenzo[d][1,3]dioxol-2-yl)succinonitrile (17c)



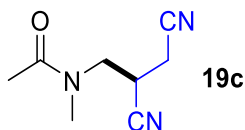
Yield	53% (51 mg, 0.21 mmol), slightly brownish oil
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 7.61 (dd, <i>J</i> = 8.2, 1.7 Hz, 1H), 7.50 (t, <i>J</i> = 1.8 Hz, 1H), 6.95 (dd, <i>J</i> = 8.2, 1.9 Hz, 1H), 6.45 (dd, <i>J</i> = 3.7, 2.4 Hz, 1H), 3.59 – 3.51 (m, 1H), 2.95 (dd, <i>J</i> = 7.0, 1.4 Hz, 2H), 2.54 (s, 3H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 196.2, 150.1, 146.9, 146.9, 133.1, 125.6, 114.7, 114.6, 114.1, 114.1, 108.7, 108.7, 107.2, 107.2, 34.2, 34.2, 26.6, 16.0, 15.9.
HR-MS (EI)	(M) ⁺ : calc. 242.0686, found 242.0691

methyl 2-(3-(2,3-dicyanopropoxy)phenyl)acetate (18c)



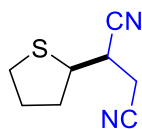
Yield	69% (71 mg, 0.28 mmol), yellowish oil
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 7.27 (dd, <i>J</i> = 7.9, 7.9 Hz, 1H), 6.94 (d, <i>J</i> = 7.9 Hz, 1H), 6.89 – 6.85 (m, 1H), 6.84 – 6.80 (m, 1H), 4.28 – 4.15 (m, 2H), 3.69 (s, 3H), 3.61 (s, 2H), 3.41 – 3.30 (m, 1H), 2.93 (d, <i>J</i> = 6.6 Hz, 2H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 171.8, 157.4, 136.0, 130.0, 123.4, 116.9, 115.9, 115.5, 113.4, 65.4, 52.2, 41.0, 29.0, 18.1
HR-MS (EI)	(M) ⁺ : calc. 258.0999, found 258.1001

N-(2,3-dicyanopropyl)-N-methylacetamide (19c)



Yield	98% (65 mg, 0.39 mmol), yellowish oil
¹H NMR	¹ H NMR (400 MHz, CDCl ₃) δ 3.82 – 3.74 (m, 1H), 3.53 – 3.35 (m, 2H), 3.15 (s, 3H), 2.82 – 2.63 (m, 2H), 2.09 (s, 3H).
¹³C NMR	¹³ C NMR (101 MHz, CDCl ₃) δ 172.3, 118.3, 115.8, 49.4, 38.2, 27.2, 21.8, 18.9.
HR-MS (EI)	(M) ⁺ : calc. 165.0897, found 165.0896

2-(tetrahydrothiophen-2-yl)succinonitrile (**20c**)



20c
1:1 mixture of
diastereomers

Yield	96% (combined yield of both diastereomers, 64 mg, 0.38 mmol), yellowish oil
^1H NMR	- isomer #1 (less polar, eluted first from the column) ^1H NMR (400 MHz, CDCl_3) δ 3.70 – 3.49 (m, 1H), 3.02 – 2.74 (m, 5H), 2.39 – 2.22 (m, 1H), 2.15 – 1.95 (m, 3H). - isomer #2 ^1H NMR (400 MHz, CDCl_3) δ 3.76 – 3.63 (m, 1H), 3.31 – 3.20 (m, 1H), 3.09 – 2.90 (m, 2H), 2.90 – 2.69 (m, 2H), 2.38 – 2.24 (m, 2H), 2.09 – 1.92 (m, 1H), 1.92 – 1.77 (m, 1H).
^{13}C NMR	- isomer #1 ^{13}C NMR (101 MHz, CDCl_3) δ 117.6, 115.4, 48.8, 35.7, 35.3, 33.2, 30.1, 20.8. - isomer #2 ^{13}C NMR (101 MHz, CDCl_3) δ 117.5, 115.5, 48.4, 35.9, 35.2, 33.3, 30.9, 20.8.
HR-MS (EI)	(M) $^+$: calc. 166.0559, found 166.0561

2.7.19 Copies of NMR spectra

The copies of the NMR spectra in the supporting information on the publisher's website free of charge.

<https://pubs.acs.org/doi/10.1021/acscatal.2c05631>

2.7.20 Notes and references

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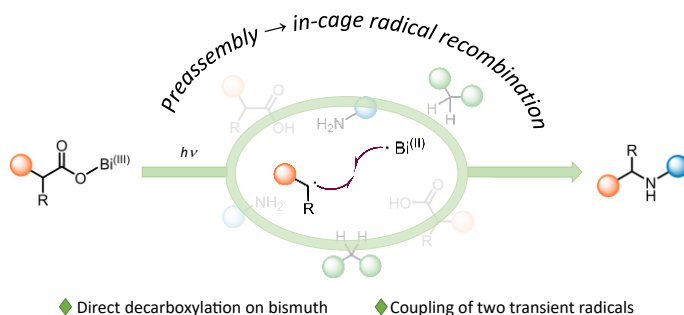
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33. See the description of Figure 2.22
34. The reduction of Bi^(III)Cl₅²⁻ and oxidation of Bi⁽⁰⁾ are complex processes. In both cases 3 electrons are transferred, but we could only observe a single peak in CV. This likely indicates that after the initial single electron transfer (SET), a fast series of disproportionations is triggered which results in Bi^(III) and Bi⁽⁰⁾. If the processes were stepwise, we should be able to observe more peaks in the CV. Similarly, dissociative LMCT is also a SET reduction which triggers the abovementioned disproportionations leading to the black precipitate - Bi⁽⁰⁾.
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3 Preassembly-Controlled Radical Recombination at Bismuth: Decarboxylative C–N Coupling with Sulfonamides

Abstract:

Persistent transition metal radicals form the foundation for many metallaphotoredox protocols. Their ability to efficiently trap organic radicals and convert them into various coupling products has inspired the exploration of selective radical reactions even beyond the d-block. Radical processes involving bismuth hold great potential but innovative strategies are required to control the reactivity of bismuth intermediates. Herein we report preassembly as a powerful strategy to enforce a selective recombination of a bismuth(II) radical and an organic radical. As a result, an inner-sphere pathway is accessed, enabling the formation of C–N coupling products.



This chapter has been published. For reference see: Taskinen, E.K., Birnthal, D., Kermelj, V. and König, B. (2025), Preassembly-Controlled Radical Recombination at Bismuth: Decarboxylative C–N Coupling with Sulfonamides. *Chem. Eur. J.*, 31: e202500396. <https://doi.org/10.1002/chem.202500396>

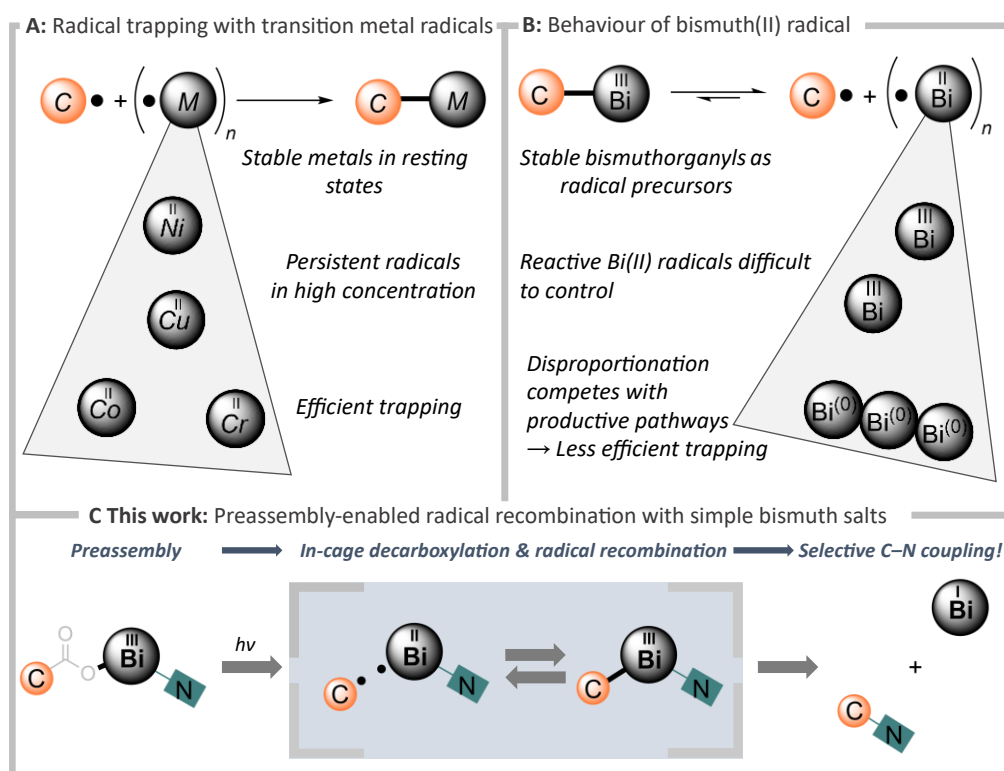
Author contribution: Elina Taskinen and Dominik Birnthal developed the concept of the project. Vid Kermelj and D.B. explored the general idea. E.K.T. and D.B. optimized the reaction, synthesized the starting materials and the products, and carried out mechanistic studies. E.K.T. and D.B. wrote the manuscript and modified the draft according to the feedback from other authors. All authors agreed on the final version of the manuscript. B.K. supervised the work.

3.1 Introduction

Photochemistry has provided mild and facile means to convert easily accessible, bench stable feedstock chemicals into corresponding radical intermediates.^[1–4] However, despite the ease of the radical generation, directing their downstream reactivity has turned out to be fundamentally more challenging due to their high reactivity and short lifetime.^[5] As a result, a swift radical trap-ping with organic radical acceptors such as activated olefins or electron-rich heteroarenes has been established as a successful strategy towards selective C–C bond formations.^[6,7] Moreover, the merger of transition metals with light-driven processes has enabled the trapping of the initially generated radical into organometallic intermediates, where the follow-up reactions of the organic fragment are highly dependent on the metal centre (Scheme 3.1a).^[8] For instance, with nickel, the trapped radical typically undergoes reductive elimination or is cleaved off from the metal centre by radical substitution (SH₂ mechanism).^[9–11] Cobalt, in contrast, provides access to unsaturated organic products via a β -hydride elimination.^[12,13] Organic substrates bound to chromium and titanium, in turn, display carbanion-like reactivity and are often used to attack carbonyl electrophiles.^[14,15] Copper is well known for its ability to oxidize radicals to carbocations and even simple copper salts are widely used as powerful terminal oxidants in many radical processes.^[16,17] Despite the diversity of these transition metal-based methods, their reactivity is largely based on the same concept: the persistent radical effect.^[18] While the stability of these metal radicals favours the radical trapping process, the resting nature of the radical (oxidation)states simultaneously makes them rather unreactive towards the closed-shell starting materials. Thus, a second catalyst is needed to activate the organic substrates, requiring fine adjustments between multiple catalytic systems.^[8,19]

In recent years bismuth redox chemistry has emerged as a transition metal like platform for synthesis and catalysis, broadening elementary steps like oxidative addition and reductive elimination beyond the d-block^[20–22] The enabling factor in the bismuth redox chemistry is the easy thermal or photochemical homolysis of bismuth-carbon and bismuth-heteroatom bonds combined with the metal's effortless shuttling between various oxidation states.^[23–27] In the realm of recent reports on bismuth redox transformation, we were particularly inspired by the work of Cornella detailing the radical recombination/dissociation equilibrium between their N,C,N-pincer ligand stabilized Bi(II) com-plex and an α -amino alkyl radical.^[28]

Given our previous report with ligand-free bismuth redox chemistry, we wondered whether we could utilize simple bismuth salts for a similar radical trapping process (Scheme 3.1B).^[29] However, in strong contrast to transition metals, main group metal without specially designed ligands radicals are usually transient in nature making them prone to undesired dimerization and disproportionation.^[30,31] Therefore, simple bismuth radicals cannot be added directly to the reaction mixture but need to be generated in situ. Although this presents a challenge, it also provides the opportunity to utilize a single metal centre in two consecutive key steps, first activating the organic substrate by SET and then trapping the formed radical intermediate. Herein, we realized that our success relied on making the rate of the desired cross-coupling faster than the competing homocoupling and disproportionation processes.^[18] Rather than relying on diffusion-controlled combination of reagents, we envisioned that bringing the reagents together prior to the onset of the reaction could increase the probability of the following cross-coupling event.



Scheme 8.1: Radical trapping with persistent transition metal radicals (a), behaviour of bismuth(II) radical (b) and the concept of this work (c).

Over the past years, preassembly has been established as an innovative strategy to make the unfavoured processes possible.^[32] As an example, earlier this year the Wolf group addressed

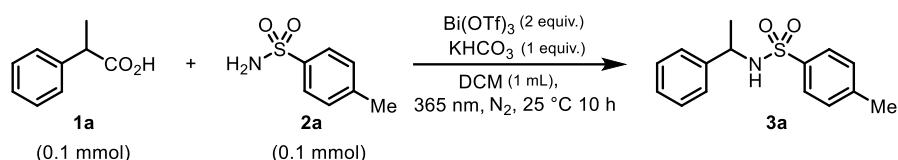
the challenges stemming from the short excited state lifetimes of their cobalt photocatalyst by pre-coordinating the excited state quencher before irradiation.^[33] To facilitate the preorganization in our system, we considered carboxylic acids as potent radical precursors as they typically form metal carboxylates setting the stage for LMCT reactivity. Upon excitation, the bismuth(II) radical and substrate derived radical are generated simultaneously in a codependent manner. Since LMCT decarboxylations most typically follow an inner-sphere mechanism,^[34,35] the substrate radical and bismuth radical are likely staying in close proximity favouring the subsequent radical recombination. While many molecular bismuth carboxylates have been structurally characterized,^[36–39] their potential for photochemical transformations has remained underutilized. However, indications on the photoactivity of bismuth carboxylates from our earlier study gave us confidence that this reaction mode could be obtainable with the right set of condition.^[29]

3.2 Reaction optimisation

We started our optimization studies by using equimolar amounts of the carboxylic acid **1a**, sulfonamide **2a** and a base to identify the best-performing bismuth precursor under 365 nm irradiation. Following our previous study on bismuth LMCT photoactivity, we decided to focus our screening on inexpensive and commercially available salts (Table 3.1 and 3.3). We found that the reaction outcome was highly dependent on the bismuth precursor utilized. While many salts (such as Bi(NO₃)₃, Bi(OAc)₃, and BiOCl) did not give any conversion of the starting material, both BiCl₃ and Bi(OTf)₃ were able to decarboxylate the benzylic acid **1a** (Entries 1 and 2). However, only Bi(OTf)₃ afforded the desired cross coupling product **3a** whereas with BiCl₃ the homocoupling of the benzylic radical was mainly observed. Similarly to previous observations on LMCT decarboxylations, we also found the combination of a hydrogencarbonate base and DCM as a solvent to give the best yield.^[17] After a broad screening of possible variables (see SI), a significant yield improvement was obtained when either the sulfonamide (Entry 3) or the acid (Entry 4) was used in excess. This observation led to two optimal conditions: in **conditions A** the acid partner serves as the limiting reagent combined with 3.5 equivalent of the nucleophile, whereas in **conditions B** the sulfonamide counterpart is the limiting reagent, and 3.0 equivalents of the carboxylic acid are used. Whereas conditions A worked reliably over a broad variety of carboxylic acids, conditions B proved to be particularly useful in the cases where the sulfonamides were only sparingly soluble in DCM. Apart from the solubility considerations, the dual nature of our optimized

conditions leaves room for a flexible choice of reagent in excess depending on other factors such as starting material availability and costs. Using Bi(OTf)₃ in catalytic amounts in combination with a chemical oxidant, such as NFSI, peroxides or persulfates, led into only trace amounts of the product (Entries 5 and 6, Table 3.1). Although the reoxidation of bismuth would be mechanistically interesting, the simplicity and economic feasibility of using stoichiometric bismuth triflate is well comparable to commonly used oxidants. Finally, control experiments confirmed the necessity of bismuth salt and photochemical nature of our transformation. In the absence of a bismuth source, no product could be detected (Entry 7). No product was also observed in the absence of light either at room temperature or upon heating to 60 °C (Entries 8 and 9).

Table 3.1: Optimization of the reaction



En-try	Deviation		Yield (%) ^[a]
1	As above		32
2	BiCl ₃ instead of Bi(OTf) ₃		<i>traces</i>
3 ^[b]	A	Sulfonamide (3.5 equiv.)	60
4 ^[b]	B	Acid (3.0 equiv.)	60
5	Bi(OTf) ₃ (20 mol%) + NFSI (2 equiv.)		11
6	Bi(OTf) ₃ (20 mol%) + (NH ₄) ₂ S ₂ O ₈ (2 equiv.)		<i>traces</i>
Control Experiments			
7	No Bismuth		n.d.
8	No Light		n.d.
9	60 °C dark		n.d.

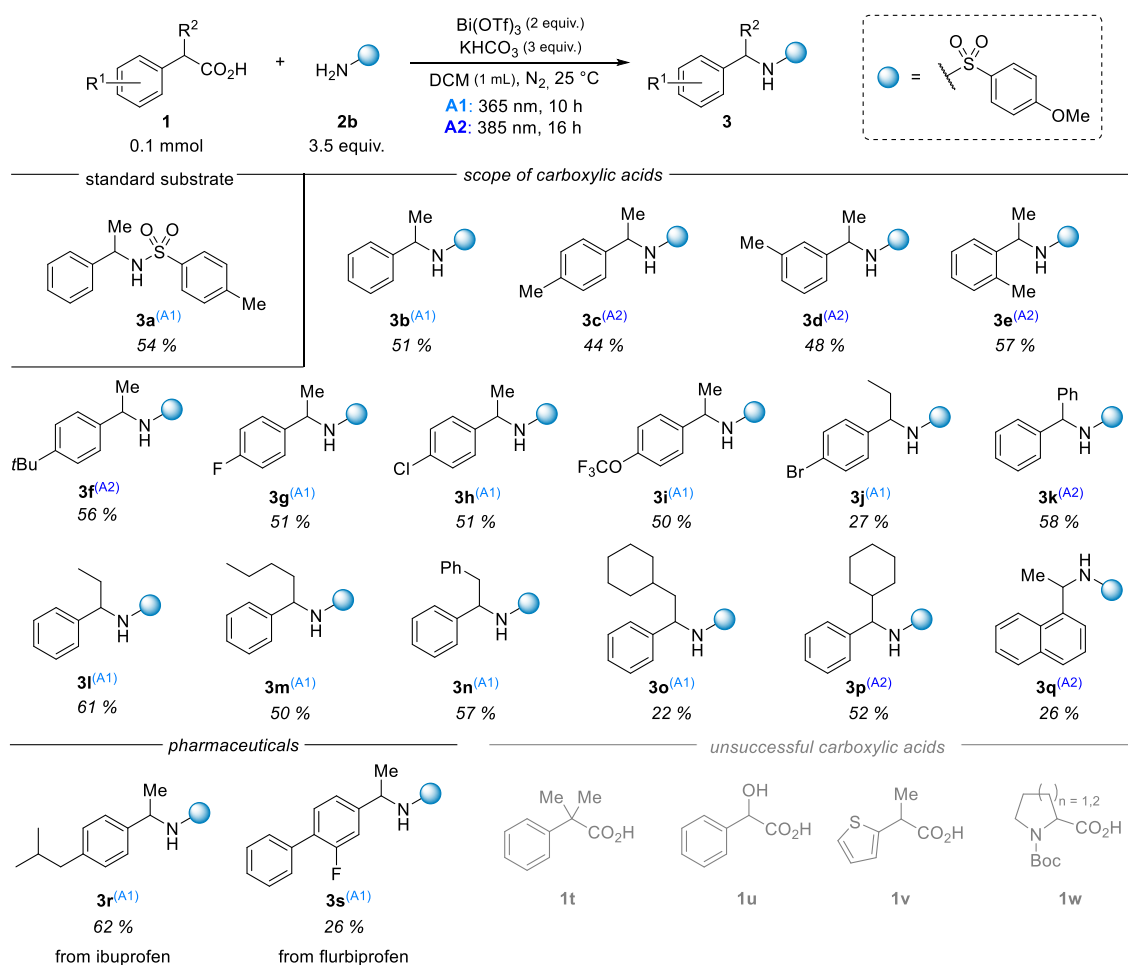
[a] Calibrated GC-FID yield. [b] KHCO₃ (3 equiv.). NFSI = *N*-Fluorobenzenesulfonimide

3.3 Scope of carboxylic acids

Next, we studied the scope of the transformation. ($\pm$)-2-Phenylpropanoic acid (**1a**) was smoothly converted into the C–N coupling products with *p*-methylphenyl and *p*-methoxyphenyl sulfonamides (products **3a** and **3b**). Different methylation patterns were well tolerated and particularly the *ortho*-methylated acid gave a high yield (**3c**, **3d** and **3e**). A *tert*-butyl group was also compatible as an electron donating substituent in the *para*-position (**3f**). We also noticed that the reactions of the electron rich carboxylic acids were best carried out with 385 nm irradiation to avoid undesired degradation. For electron withdrawing substituents, halogens such as fluorine (**3g**) and chlorine (**3h**) together with a trifluoromethoxy group (**3i**) gave comparable yields to the standard compound. The brominated compound **3j** was obtained in a somewhat lower yield due to the debromination accompanying the desired product-forming events.

Several *alpha*-substituted carboxylic acids were successfully converted to the products. A phenyl, ethyl and *n*-butyl substituents were well compatible (**3k**, **3l** and **3m**). An aliphatic cyclohexyl ring was also tolerated both with a CH₂-linker (**3o**) and when directly attached to the benzylic position (**3p**). The positive results obtained here were particularly encouraging as they demonstrate the significant selectivity of our method towards the C–N coupling over the alternative alkene formation. Particularly worth mentioning here is the conversion of 2,3-diphenylpropanoic acid to the desired coupling product **3n** without any observable stilbene generation. The 1-naphthyl substituted carboxylic acid also underwent the desired transformation although the yield might have been slightly reduced by the direct excitation of the aromatic system (**3q**). Finally, we applied our method for the late-stage modification of pharmaceutically active compounds giving products **3r** and **3s** stemming from ibuprofen and flurbiprofen, respectively.

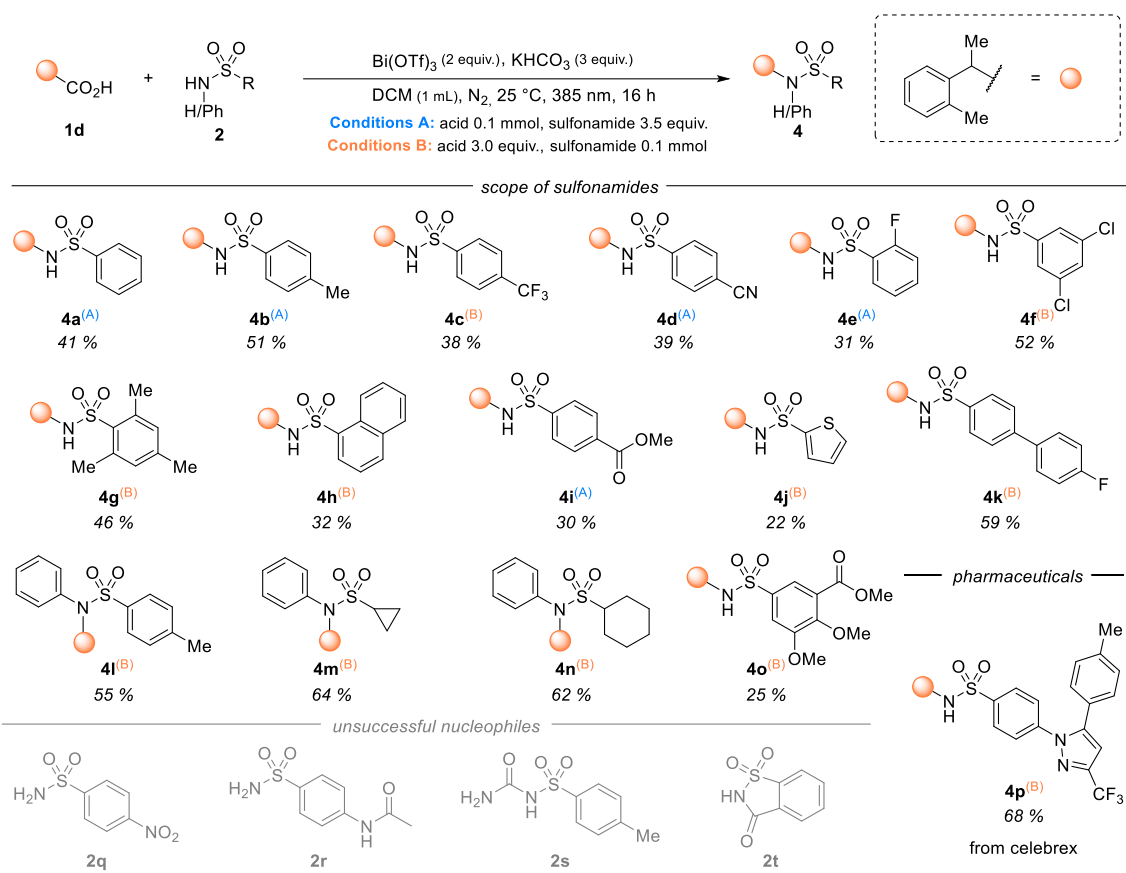
Regarding the limitations, tertiary carboxylic acids (such as **1t**) typically underwent decarboxylation but most likely due to the steric hindrance only homocoupling of the formed benzylic radical was observed. Addition of a free hydroxy group to the benzylic position (**1u**) effectively shut down the reaction probably by forming a bidentate ligand on bismuth from which no decarboxylation could take place. Aminoacids (such as **1w**) formed insoluble species with bismuth in DCM and no further reactivity was observed.



Scheme 3.2: Scope of carboxylic acids

3.4 Scope of nucleophiles

We then turned our attention to the scope of the nucleophiles. The phenyl-substituted sulfonamide yielded the desired product **4a** in a synthetically useful 41% yield, whereas an addition of a methyl group to the *para*-position gave a higher isolated yield of **4b**. In terms of electronic effects, *para*-trifluoromethyl and *ortho*-fluorine substituted sulfonamides (**4c** and **4e**) resulted in slightly lowered yields implying that extra electron density on the sulfonamide, which would also increase the nucleophilicity, is beneficial for the reaction. When electron withdrawing substituents were placed in non-conjugated *meta*-positions, high yields were retained (**4f**). Notably, selective coupling reactions were also obtained in the presence of a competing nucleophilic CN-group (**4d**) or a competing electrophilic ester-group (**4i**). For the electron donating group, a mesityl ring and 1-naphthyl substituents (**4g** and **4h**) as well as a 4'-F-biphenyl group (**4k**) could also be included in the sulfonamide. The thiophene-derived sulfonamide gave the desired product **4j** in 22% yield. Steric demand at secondary *N*-phenyl sulfonamides was well tolerated. *N*-phenyl-methylphenyl sulfonamide gave the tertiary product **4l** in a 55% yield. Moreover, sulfonamides with an aliphatic ring attached to the sulfonyl group were also compatible giving products **4m** and **4n** in over 60% yield. Moreover, the highly substituted sulfonamide product **4o** was obtained. Finally, the pharmaceutically active compound celebrex could be derivatized with our method giving the product **4p** in a good yield of 68%. With respect to the limitations on the sulfonamide side, a nitro substituent (**2q**) and an amide functionality (**2r**) were incompatible with the reaction and no conversion of the starting materials was observed. The carbamoyl-benzenesulfonamide **2s** and the cyclic sulfonamide saccharin **2t** failed to undergo the desired reaction perhaps by forming an unreactive chelated ligand to bismuth.



Scheme 3.3: Scope of nucleophiles

3.5 Mechanistic studies

To gain a better understanding of our reaction, a set of mechanistic studies was carried out. We started by measuring the UV-vis spectra of all the reaction components and their combination. As seen from Figure 3.1a, $\text{Bi}(\text{OTf})_3$ had its absorption maximum at 230 nm and did not show any absorbance above 300 nm (grey dotted line). The carboxylic acid **1a** (orange line) and sulfonamide **2a** (blue line) both exhibited their absorption band between 250 nm and 280 nm, but no absorption could be detected in the range of irradiation. The addition of $\text{Bi}(\text{OTf})_3$ to the mixture of carboxylic acid and sulfonamide significantly intensified the absorption features accompanied by prolonged tailing (yellow line). Indeed, the tailing of the absorbance reached the area of the irradiation wavelength, thus confirming the role of the in situ-formed bismuth-centred assembly as the light harvesting species (zoom-in spectrum).

We then measured the kinetic profile of our reaction (Figure 3.1b). From the measurement spanning over the first four hours of irradiation, we could see that the product formation was rapid at the beginning of the reaction (0–20 min) after which the rate of the reaction started to gradually decrease. The product formation was observed immediately upon the start of irradiation thus supporting our hypothesis that the active bismuth assembly is pre-formed in the mixture. The initial kinetics, in turn, followed a linear trend without detectable build-up of intermediates (Figure 3.1c). The accumulation of a black solid during the reaction suggests the full reduction of bismuth to its metallic form perhaps via disproportionation of bismuth(II) and/or bismuth(I) both of which are described as unstable species in the literature (Figure 3.1d).^[40,41] Furthermore, the light on/off experiment shows the necessity of continuous irradiation for the reaction progress, thus rendering a radical chain mechanism unlikely (Figure 3.1e).

The final C–N bond-forming step could either follow an inner-sphere reductive elimination pathway or go via an outer-sphere mechanism. Literature reports of decarboxylative C–N coupling reactions with copper and iron suggest an outer-sphere mechanism.^[17,42] With copper, a well-established radical oxidation to a carbocation is proposed whereas with iron a chlorinated intermediate stemming from a radical ligand transfer could be detected. In our system, the radical ligand transfer mechanism was found unlikely on a stereo electronic basis.

To evaluate the outer-sphere ionic nucleophilic coupling mechanism proceeding via a carbocation, we rationalized that the presence of this intermediate would most likely lead to a broad compatibility of nucleophiles. Instead, with our bismuth system, alternative nucleophiles such as pyrazole, amides, amines, and alcohols could not be coupled so far (Figure 4f). Furthermore, side-reactions like esterification or desaturation via α -deprotonation of a carbocation were rarely observed in our study. On the carboxylic acid side, sterically demanding substrates (such as **1t**), were not tolerated. Taken together, the C–N coupling step in our reaction most likely follows a reductive elimination pathway. We believe that the exact coordination sphere around bismuth in our system is rather dynamic and not limited to certain coordination patterns since the excess of either carboxylic acid or sulfonamide is beneficial to the reaction. When bismuth is used as a limiting reagent, the highest efficiency of bismuth as a consecutive one electron oxidant is achieved (96% yield, bismuth as limiting reagent, Figure 3.1g). Finally, the radical nature of the decarboxylation process was suggested by the trapping of the benzylic radical with TEMPO (Figure 3.1h).

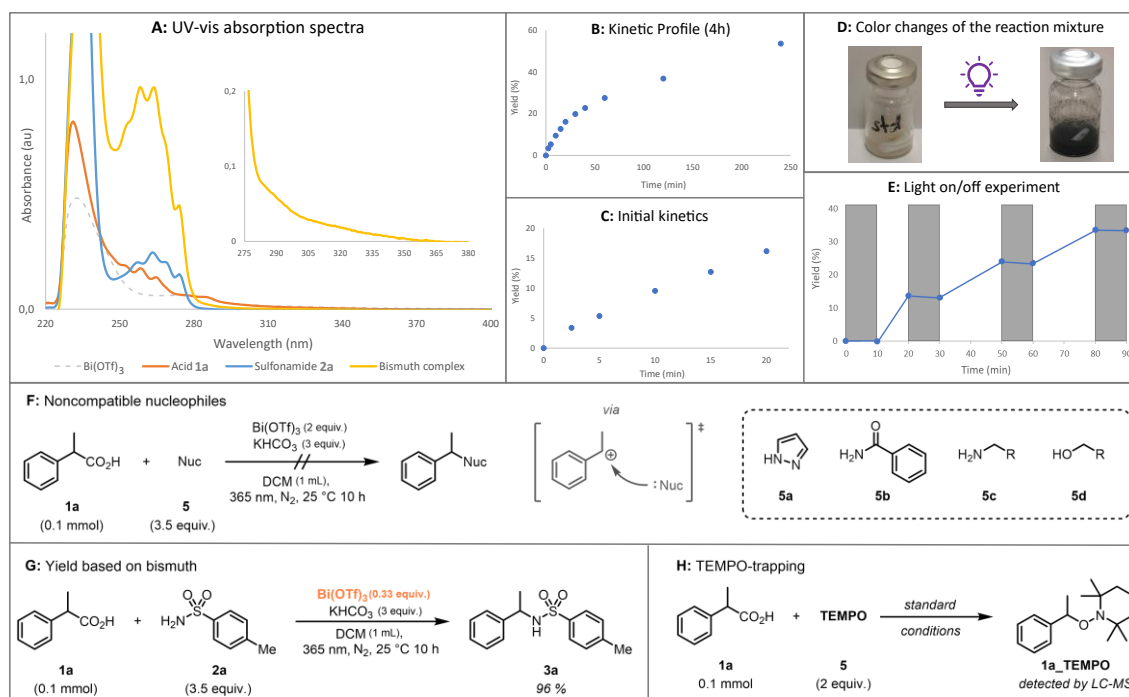
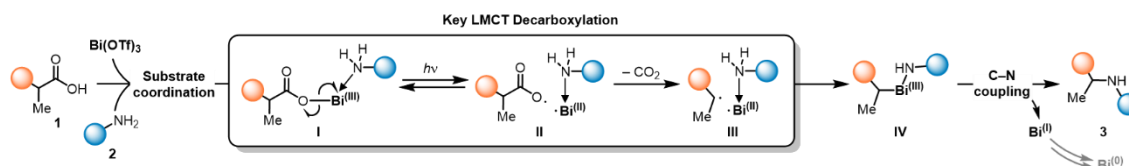


Figure 3.1. Key mechanistic studies. UV-vis absorption spectra of the reactants and the in situ-formed complex (a), kinetic profile of the reaction (b), initial kinetics (c), colour change of the reaction mixture (d), light on/off experiment (e), noncompatible nucleophiles tested (f), reaction using bismuth as limiting reagent (g) and TEMPO-trapping study (h).



Scheme 3.4. Proposed mechanism.

Based on our mechanistic considerations and the previous literature^[43,44], the following mechanism is proposed (Scheme 3.4): The product forming sequence starts with the coordination of the respective carboxylic acid **1** to the bismuth center assisted by KHCO_3 . The formed bismuth(III) carboxylate assembly **I** is irradiated resulting in the cleavage of the bismuth carboxylate. The formed carboxyl radical **II** can then either recombine with the Bi(II) re-generating the complex **I**, or undergo an irreversible decarboxylation to the carbon centered radical **III**. The preassembly of the complex **I** together with the codependent manner of the radical generation ensures the spatial proximity between the bismuth(II) radical and the carbon centered radical **III** thus favoring their recombination. The formed organobismuth compound **IV** then undergoes a reductive elimination to forge the C–N bond upon the release of the product **3**. The bismuth(I) formed in this process is unstable and eventually undergoes disproportionation to metallic bismuth.

3.6 Conclusion

In summary, we report the first direct decarboxylation on bismuth, giving access to C–N coupling products with sulfonamides. The direct use of nonfunctionalized starting materials allows a straight-forward and step-economical method. Importantly, pre-assembly allowed us to overcome the challenges of controlling the reactivity of transient radicals, thus enabling a selective coupling process. While preassembly has remained as underutilized strategy, we hope that our report encourages its further utilization. Furthermore, we believe that the observation of efficient decarboxylation provides an additional entry point to radical chemistry on bismuth.

3.7 Experimental

3.7.1 General information

Chemicals and solvents were purchased from commercial suppliers (Sigma Aldrich, TCI, BLD Pharma, Alfa Aesar, Acros, Fluka or Thermo Fischer) and, unless otherwise noted, used without further purification. Specifically, for the benchmark reaction the following chemicals were used: Bi(OTf)₃ (99% purity, Thermo Scientific), (±)-2-phenylpropionic acid (98% purity, ABCR), *p*-toluenesulfonamide (99% purity, Acros), KHCO₃ (Merck) and DCM (99.8% purity, anhydrous, Sigma Aldrich). All air- and moisture sensitive reactions including photoreactions were set up using pre-dried N₂ as shielding gas, whereas dry solvents were obtained from commercial suppliers. Evaporation of organic solvents was carried out in a rotary evaporator at temperatures below 40 °C and under reduced pressure.

Analytical thin layer chromatography (TLC) was routinely used for the monitoring of starting material synthesis and to quantify the elution of product. Silica-gel pre-coated aluminium sheets (Macherey-Nagel, silica gel 60G/UV254, 0.2 mm) served as stationary phase, whereas the mobile phase consisted of solvents and solvent mixtures, the ratios of which are reported as v/v solutions. Visualization was performed with a 254 nm UV-light source combined with chromatographic dyes if so noted.

Flash column chromatography (FCC) was done either by hand or by a Biotage® Isolera™ Spektra One machine. In the former case flash silica gel (Merck, particle size 40–63 µm, 230–440 mesh) was used as a stationary phase whereas in the latter case pre-packed Biotage® columns were used. For both techniques eluent mixtures, whenever possible consisting of pre-distilled petroleum ether (PE) and ethyl acetate (EtOAc), was used. For all eluents, the solvent ratios are reported as v/v ratios.

GC-FID and GC-MS measurements were performed on a GC 7890 from Agilent Technologies coupled with a FID detector. The system was equipped with a capillary column (HP-5MS UI, 30 m length, 0.25 mm diameter, 0.25 µm film) and run with He (flow rate 1 mL/min) as a carrier gas. (**NOTE:** The use of H₂ as carrier gas in this project was found to

result in a complex GC-spectrum, most likely due to reactions within the GC. Therefore, if change of carrier gas is desired, we recommend to test the suitability of the new carrier by comparing against the spectrum obtained with helium). Unless otherwise noted, sample volume of 1 μ L was injected (split injection, 40:1 split) at 280 °C with detector temperature 300 °C. The GC-MS measurements were done with a 7890AGC system with an Agilent 5975 MSD detector. For the GC program, the initial temperature of 40 °C was hold for 3 minutes, after which the temperature was increased on a rate of 15°C/min for over 16 minutes. The temperature was ramped until 280 °C, where the temperature was hold constant for 5 minutes. After this the temperature was increased with a rate of 25 °C/min for 48s, until the final temperature of 300 °C was reached and hold again for 5 minutes. Finally, data accumulation was done using Agilent ChemStation Rev.C.01.04.

Nuclear Magnetic Resonance Spectroscopy (NMR) was recorded at room temperature using a Bruker Avance 400 (400 MHz for ^1H , 101 MHz for ^{13}C , 376 MHz for ^{19}F) NMR spectrometer. All chemical shifts are reported δ -scale as part per million [ppm] (multiplicity, coupling constant J , number of protons) relative to the solvent residual peak. The coupling constants J are given in Herz [Hz] and the multiplicity of the signals are abbreviated as: singlet (s), broad singlet (br. s.), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), doublet of triplets (dt), triplet of doublets (td), quartet (q), doublet of quartets (dq), pentet (p) and multiplet (m). For the NMR measurements deuterated solvents (CDCl_3 from deutero, $\text{DMSO}-d_6$ from Sigma Aldrich) were used. The spectra were processed using MestreNova 9.0.1.

High Resolution Mass Spectra (HRMS) were performed at the Central Analytical Laboratory of the departments of chemistry and pharmacy at the University of Regensburg. For measurements, > 1 mg of the sample submitted, which was later dissolved to acetonitrile, DCM or ethyl acetate. The samples were then injected either to a Jeol AccuTOF GCX or to an Agilent Q-TOF 6540 UHD instrument.

3.7.2 1.1 Photosetups

365 nm (2.0 W) setup

For the photoreactions run at 365 nm (1.5 W to 2.0 W) were performed using custom-made photoreactors depicted below (Figure 3.2). At the core of the photoreactors reside a metal block to which six single-spot LEDs of desired wavelength are mounted. On top of the LED block sits a hollow cooling block made out of stainless-steel through which a constant flow of water is possible. This cooling block also contains holes made to perfectly fit 5 mL crimp-cap vials thus providing a sideways contact of the reaction vessels to the cooling system. Magnetic stirring for the reactions is imposed from underneath the LED blocks using Heidolph MR 3000 stirring plates. Finally, the water cooling is sustained with a Julabo Curio Co unit. **NOTE:** Due to the modular nature of these setups, they can be used to serve at any desired wavelength simply by changing the LED plate.



Figure 3.2: Pictures of the photosetup used for reactions run in 365 nm (1.5 W to 2.0 W optical power). General picture of the setup (left), picture from the top of the cooling block looking down to the LED plate (centre) and a sideways picture of the photosetup with lights on (right).

385 nm (0.5 W) setup

For the photoreactions run at 385 nm (0.5 W) were performed using custom-made photoreactors designed to allow for an increased number of simultaneously run reactions (Figure 3.3). At the core of the photoreactors reside a stainless-steel block to which fifteen single-spot LEDs with emission centered around 385 nm are mounted. On top of the LED block sits a hollow cooling block made of stainless-steel, through which a constant flow of water is possible. This cooling block also contains fifteen holes made to perfectly fit 5 mL crimp-cap vials, thus providing a sideways contact of the reaction vessels to the cooling system. Magnetic stirring for the reactions is imposed from underneath the LED blocks using Cimarec i Poly 15-point stirring plates. Finally, the water cooling is sustained with a Julabo Curio Co water cooling unit. Due to the modular principle of the reactors, these several wavelengths can be utilized on these setups by changing the LED plate.

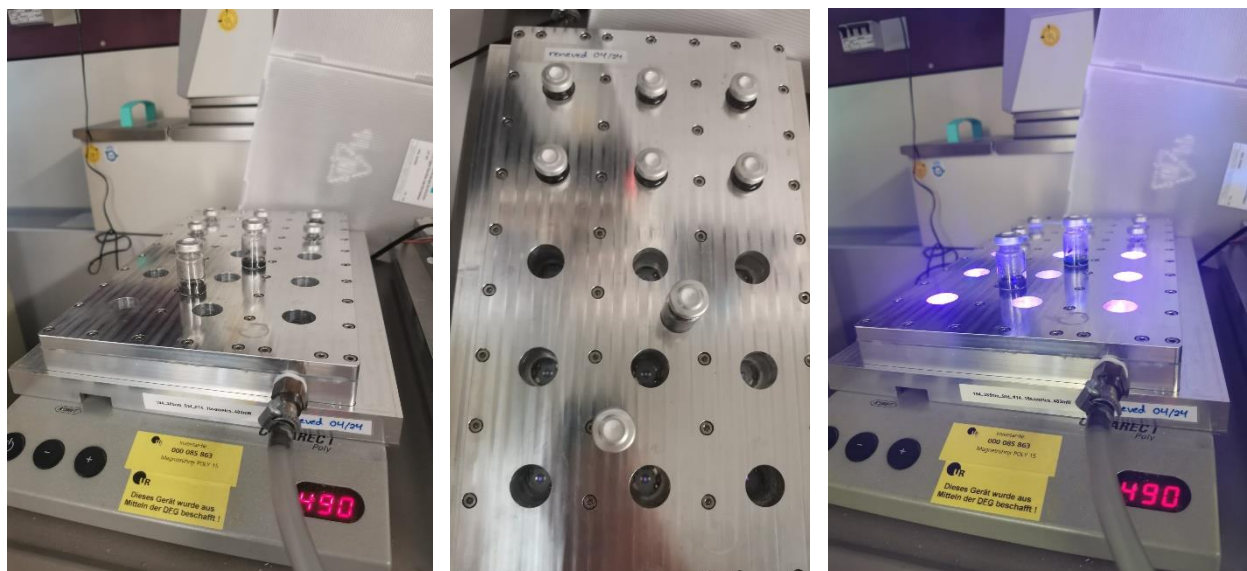


Figure 3.3: Pictures of the photosetup used for reactions run in 385 nm (0.5 W optical power). General picture of the setup (left), picture from the top of the cooling block looking down to the LED plate (centre) and a sideways picture of the photosetup with lights on (right).

Emission spectrum of the LEDs

The emission spectrum of the utilized LEDs (365 nm, Inolus and 385 nm, New Energy Luminus) was also measured to better characterize the actual emitted wavelengths of each setup. The measurement was carried out with Ocean Optics HR 2000+ spectrometer. The results are plotted in Figure 3.4.

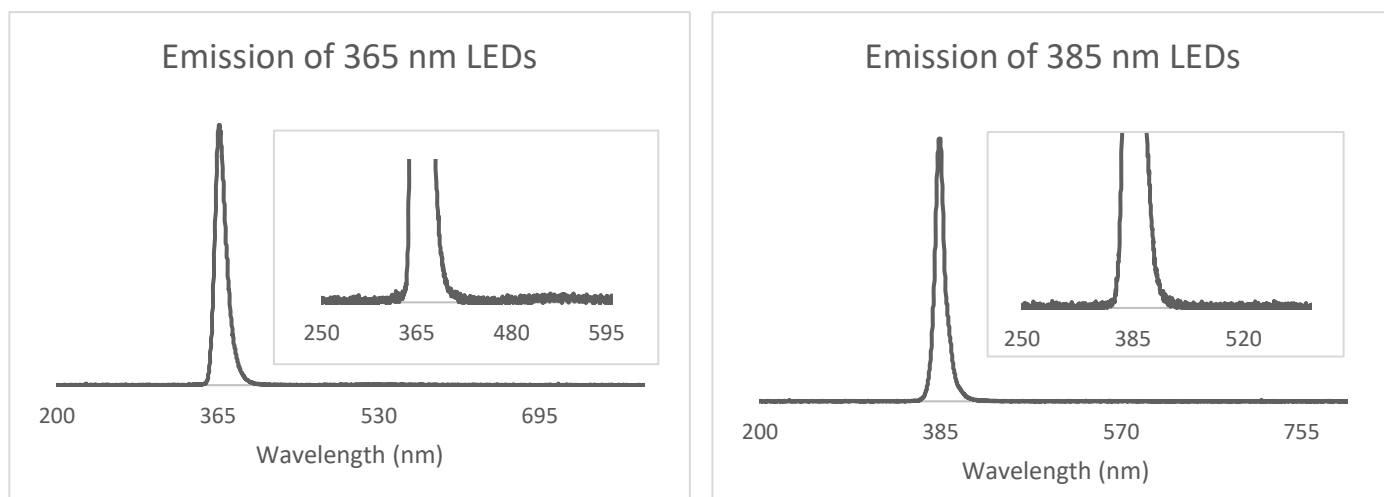


Figure 3.4: Emission spectra of the 365 nm LEDs (left) and 385 nm LEDs (right)

As can be easily observed from Figure 3.4, both of the utilized LEDs have their emission maxima around the desired wavelength, yet tailing is present for both LEDs. For the 365 nm LED, the actual emission starts around 350 nm and tails closer to 400 nm. For the 385 nm LEDs, on the other hand, the tailing is broader to both directions thus covering the area from around 360 nm to 440 nm.

3.7.3 1.1.4 Reaction mixtures before and after irradiation

The success of the decarboxylative oxidative coupling can be qualitatively assessed by the look of the reaction after the irradiation period. Before irradiation, the reaction mixture is (in most cases depending on the carboxylic acid and sulfonamide reactants) a white milky solution mostly due to the incomplete solubility of $\text{Bi}(\text{OTf})_3$ (Figure 3.5, left). After a successful reaction, the formation of fully reduced bismuth (elemental bismuth, “bismuth black”) gives the mixture a very dark, often black color (Figure 3.5, right).



Figure 3.5: Pictures of the reaction mixture in a 5 mL crimp-cap vial before the reaction (left) and after irradiation (right).

3.7.4 GC-FID calibration

For the calculation of the exact yields during the reaction optimization, a five-point calibration was carried out for the GC-FID. For this, a stock solution of the product **3a** in DCM was prepared, five samples were taken followed by dilution to the desired concentrations (see molarities below). Equal amounts of mesitylene were then added as internal standard, and the samples were submitted for GC-FID.

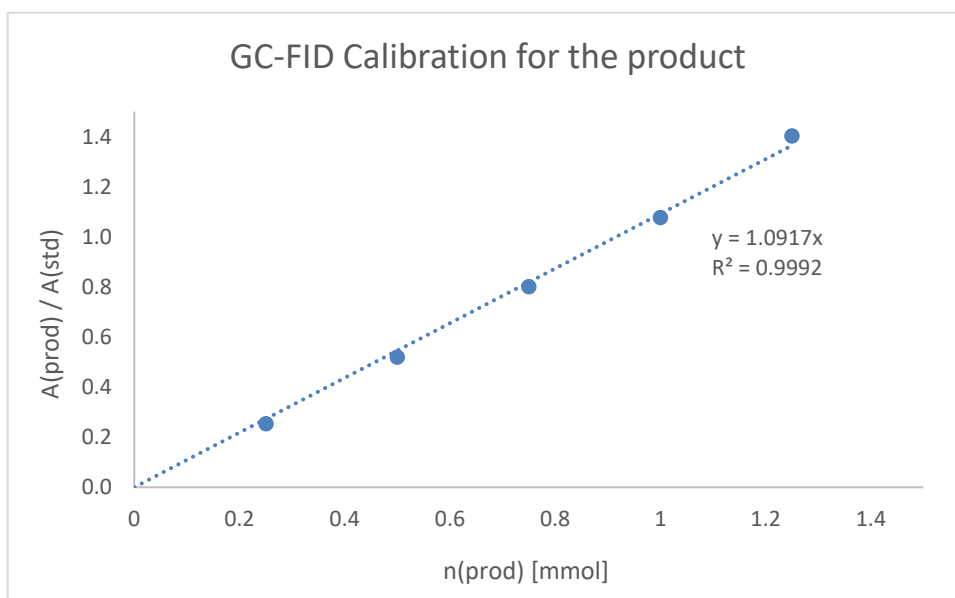


Figure 3.6: Calibration curve plotted with the ratio of product peak area to the area of internal standard as the y-axis and molar amount of the product given in each sample as x-axis as obtained from the GC-FID. Linear fit across the points and zero-point intersection added to obtain the equation for the line.

After the GC-FID analysis, the obtained areas of the peaks corresponding to the product and internal standard were then collected and plotted against the amounts of the product in moles. The linear fit was then applied, and the obtained curve set to intersect the origin. The equation of this line ($y = 1,0917x$) was utilized to calculate all GC-FID yields measured afterwards. Finally, the correlation coefficient (R^2) was analyzed to verify the accuracy of the calibration curve.

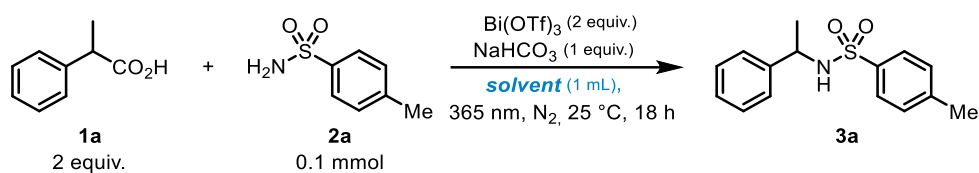
3.7.5 Extended optimization studies

General procedure for the optimization studies

4-Methylbenzenesulfonamide (n equiv.) and base (m equiv.) and were weighed into a 5 mL crimp-cap vial equipped with a stirring bar. The vial was sealed and set under an inert atmosphere by evacuating and back-filling with N_2 three times. A 0.1 M stock solution of ($\pm$)-2-phenylpropanoic acid in a pre-dried solvent was prepared under N_2 and 1 mL of this solution was added to the reaction mixture. Residual oxygen was then removed by freeze-pump thaw ($\times 3$), after which the reaction was irradiated with 365 nm LEDs (2 W) while maintaining the temperature at 25 °C with a water-cooling block. After the given reaction time, a 100 μ L of stock solution (1.0 M mesitylene in DCM) was added as internal standard and the reaction mixtures were filtered through a syringe filter. The reactions were then analyzed with GC-FID using helium as carrier gas and the final yields were calculated against a five-point calibration curve of product **3a** and mesitylene.

3.7.6 Solvent screening

Table 3.2: Full optimization of solvent.

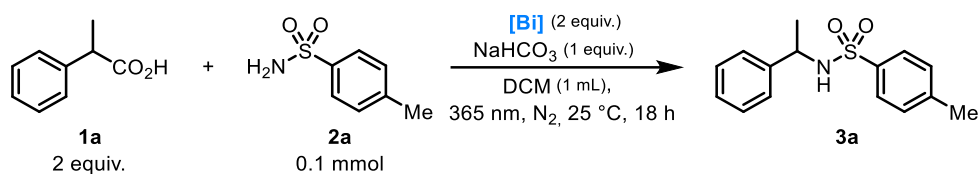


Entry	Solvent	Yield (%)
1	DCM	28
2	DCE	11
3	CHCl_3	9
4	MeCN	traces
5	TFE	n.d.
6	HFIP	n.d.
7	Toluene	n.d.
8	H_2O	traces
9	DMSO	n.d.
10	DMA	n.d.
11	THF	n.d.
12	EtOAc	traces
13	Acetone	traces

Reaction conditions: $\text{Bi}(\text{OTf})_3$ (130 mg, 0.20 mmol, 2.0 equiv.), 2-phenylpropanoic acid (30 mg, 0.20 mmol, 2.0 equiv.), NaHCO_3 (8.2 mg, 0.10 mmol, 1.0 equiv.) and 4-methylphenylsulfonamide (17.2 mg, 0.10 mmol, 1.0 equiv.) were dissolved into solvent in case (1 mL) under N_2 . After irradiation with 365 nm (18 h) at 25 °C internal standard was added and reactions analyzed with GC-FID. Abbreviations used: DCM=dichloromethane, DCE=dichloroethane, CHCl_3 =chloroform, MeCN=acetonitrile, TFE=trifluoroethanol, HFIP=hexafluoroisopropanol, DMSO=dimethylsulfoxide, DMA=dimethylacetamide, THF=tetrahydrofuran, EtOAc=ethyl acetate.

3.7.7 Bismuth source screening

Table 3.3: Full optimization of the bismuth source.

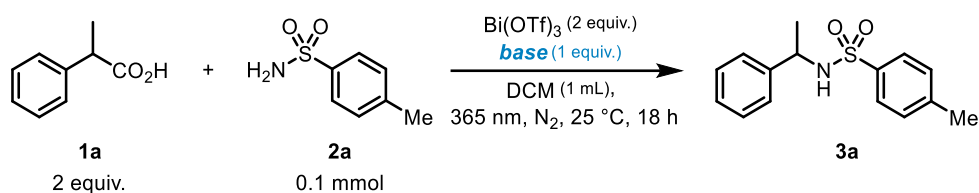


Entry	Catalyst screening	Yield (%)
1	$\text{Bi}(\text{OTf})_3$	28
2	BiCl_3	traces
3	BiF_3	n.d.
4	BiBr_3	n.d.
5	BiPh_3	10
6	$\text{Bi}^{(0)}$	n.d.
7	Bi_2O_3	n.d.
8	BiOCl	n.d.
9	$\text{Bi}(\text{OAc})_3$	n.d.
10	$\text{Bi}(\text{NO}_3)_3$	n.d.

Reaction conditions: the bismuth source (0.20 mmol, 2.0 equiv.), 2-phenylpropanoic acid (30 mg, 0.20 mmol, 2.0 equiv.), NaHCO_3 (8.2 mg, 0.10 mmol, 1.0 equiv.) and 4-methylphenylsulfonamide (17.2 mg, 0.10 mmol, 1.0 equiv.) were dissolved into DCM (1 mL) under N_2 . After irradiation with 365 nm (18 h) at 25 °C, internal standard was added and reactions analyzed with GC-FID.

3.7.8 Base screening

Table 3.4: Full optimization of bases.

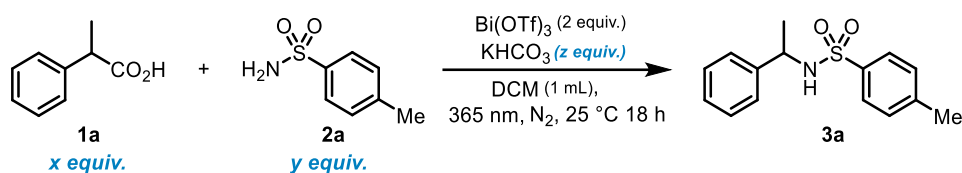


Entry	Base	Yield (%)
1	none	traces
2	NaHCO_3	28
3	KHCO_3	37
4	K_2CO_3	14
5	K_3PO_4	14
6	K_2HPO_4	27
7	Na_2HPO_4	7
8	KOtBu	30
9	DBU	traces
10	DABCO	30
11	2,6-Lutidine	5
12	TBD	traces
13	TMG	traces
14	Tetramethylpiperidine	traces

Reaction conditions: $\text{Bi}(\text{OTf})_3$ (130 mg, 0.20 mmol, 2.0 equiv.), 2-phenylpropanoic acid (30 mg, 0.20 mmol, 2.0 equiv.), the base in question (0.10 mmol, 1.0 equiv.) and 4-methylphenylsulfonamide (17.2 mg, 0.10 mmol, 1.0 equiv.) were dissolved into DCM (1 mL) under N_2 . After irradiation with 365 nm (18 h) at 25 °C, internal standard was added and reactions analyzed with GC-FID. Abbreviations used: DBU=1,8-diazabicyclo[5.4.0]undec-7-ene, DABCO=1,4-diazabicyclo[2.2.2]octane, TBD=1,5,7-triazabicyclo[4.4.0]dec-5-en, TMG=tetramethylguanidine.

3.7.9 Stoichiometry screening

Table 3.5: Full screening of the reaction stoichiometry.

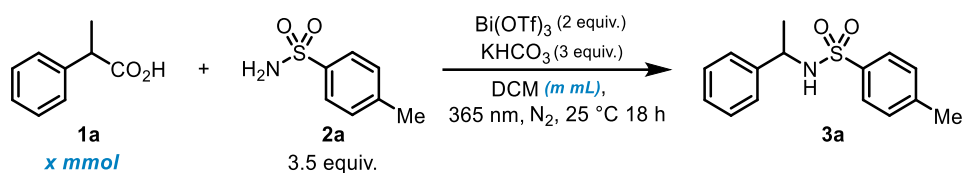


Entry	1a (equiv.)	2a (equiv.)	Base (equiv.)	Yield (%)
1	1.0	1.0	1.0	38
2	2.0	1.0	0.5	27
3	2.0	1.0	1.5	38
4	2.0	1.0	2.0	42
5	2.0	1.0	2.5	22
6	3.0	1.0	1.0	45
7	3.0	1.0	2.0	60
8	3.0	1.0	3.0	46
9	4.0	1.0	3.0	16
10	1.0	2.0	2.0	16
11	1.0	2.0	3.0	48
12	1.0	2.0	1.0	40
13	1.0	3.0	2.0	25
14	1.0	3.0	3.0	62
15	1.0	4.0	2.0	62
16	1.0	4.0	3.0	31
17	1.0	3.5	2.0	52
18	1.0	3.5	3.0	60

Reaction conditions: $\text{Bi}(\text{OTf})_3$ (130 mg, 0.20 mmol, 2.0 equiv.), 2-phenylpropanoic acid (*x* equiv.), KHCO_3 (*y* equiv.) and 4-methylphenylsulfonamide (*z* equiv.) were dissolved into DCM (1 mL) under N_2 . After irradiation with 365 nm (18 h) at 25 °C, internal standard was added and reactions analyzed with GC-FID.

3.7.10 Concentration screening

Table 3.6: Full screening of reaction concentration.

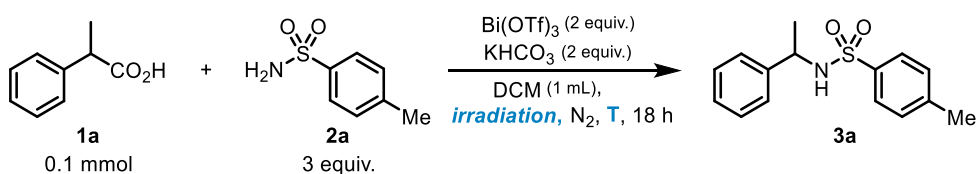


Entry	n(acid) (mmol)	V(DCM) (mL)	Concentration (M)	Yield (%)
1	0.05	1	0.05	31
2	0.075	1	0.075	33
3	0.15	1	0.15	51
4	0.2	1	0.2	30
5	0.1	0.5	0.2	20
6	0.1	0.75	0.13	31
7	0.1	1.0	0.1	60
8	0.1	1.5	0.66	49
9	0.1	2.0	0.05	47

Reaction conditions: $\text{Bi}(\text{OTf})_3$ (2.0 equiv.), 2-phenylpropanoic acid (x mmol, 1.0 equiv.), KHCO_3 (3.0 equiv.) and 4-methylphenylsulfonamide (3.5 equiv.) were dissolved into DCM (m mL) under N_2 . After irradiation with 365 nm (18 h) at 25 °C, internal standard was added and reactions analyzed with GC-FID.

3.7.11 Irradiation source and temperature screening

Table 3.7: Full screening of irradiation wavelength and temperature.



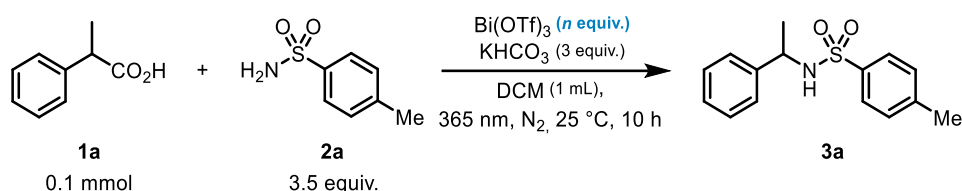
Entry	LED	Temperature (°C)	Yield (%)
1	365 nm (3W)	25	39
2	365 nm (0.8W)	25	4
3	340 nm (0.8W)	25	6
4	385 nm (0.8W)	25	44

5	385 nm (3W)	25	43
6	365 nm (2W)	10	34
7	365 nm (2W)	15	39
8	365 nm (2W)	20	55
9	365 nm (2W)	25	60
10	365 nm (2W)	30	42

Reaction conditions: Bi(OTf)₃ (130 mg, 0.2 mmol, 2.0 equiv.), 2-phenylpropanoic acid (15.0 mg, 0.1 mmol, 1.0 equiv.), KHCO₃ (30.0 mg, 0.3 mmol, 3.0 equiv.) and 4-methylphenylsulfonamide (65.5 mg, 0.35 mmol, 3.5 equiv.) were dissolved into DCM (1 mL) under N₂. After irradiation with the wavelength in question for the given times at given temperatures, internal standard was added and reactions analyzed with GC-FID.

3.7.12 Bismuth loading screening

Table 3.8: Full optimization of bismuth triflate loading.

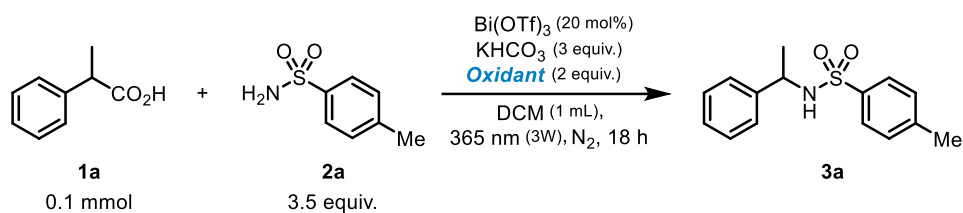


Entry	Bi Loading	Yield (%)
1	1.0 equiv.	22
2	1.5 equiv.	44
3	1.6 equiv.	44
4	1.7 equiv.	60
5	2.0 equiv.	60
6	2.5 equiv.	52

Reaction conditions: Bi(OTf)₃ (*n* equiv.), 2-phenylpropanoic acid (15.0 mg, 0.1 mmol, 1.0 equiv.), KHCO₃ (30.0 mg, 0.3 mmol, 3.0 equiv.) and 4-methylphenylsulfonamide (65.5 mg, 0.35 mmol, 3.5 equiv.) were dissolved into DCM (1 mL) under N₂. After irradiation with 365 nm for 10 h at 25 °C, internal standard was added and reactions analyzed with GC-FID.

3.7.13 Oxidant screening

Table 3.9: Full optimization of the terminal oxidant.

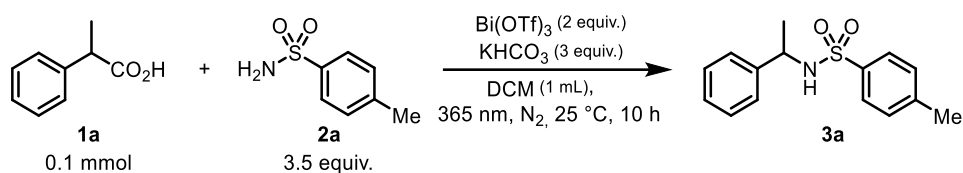


Entry	Oxidant	Yield (%)
1	$\text{Bi}(\text{OTf})_3$	60
2	none	11
3	Air	n.d.
4	Oxone	traces
5	$\text{Na}_2\text{S}_2\text{O}_8$	traces
6	$\text{K}_2\text{S}_2\text{O}_8$	traces
7	$(\text{NH}_4)_2\text{S}_2\text{O}_8$	5
8	NFSI	11
9	PIDA	14
10	Benzoyl peroxide	traces

Reaction conditions: $\text{Bi}(\text{OTf})_3$ (13.0 mg, 0.02 mmol, 20 mol%), 2-phenylpropanoic acid (15.0 mg, 0.1 mmol, 1.0 equiv.), KHCO_3 (30.0 mg, 0.3 mmol, 3.0 equiv.), 4-methylphenylsulfonamide (65.5 mg, 0.35 mmol, 3.5 equiv.) and the terminal oxidant (2.0 equiv.) were dissolved into DCM (1 mL) under N_2 . After irradiation with 365 nm for 18 h at 25 °C, internal standard was added and reactions analyzed with GC-FID. Abbreviations used: NFSI=N-fluorobenzene-sulfonimide, PIDA=(diazetoxyiodo)benzene.

3.7.14 Control Experiments

Table 3.10: Control experiments.



Entry	Variation	Yield (%)
1	Under air	traces
2 ^{a)}	$\text{BiBr}_3 + \text{Na}(\text{OTf})_3$	n.d.
3	No bismuth	n.d.
4	No light	n.d.
5	60 °C dark	n.d.

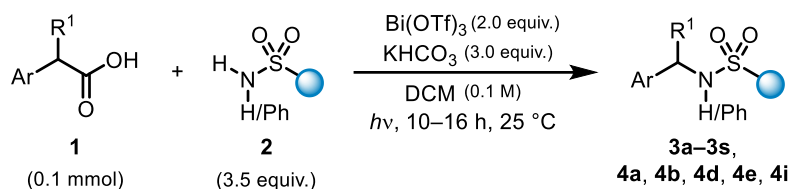
^{a)} BiBr_3 (2 equiv.) + $\text{Na}(\text{OTf})_3$ (2 equiv) used instead of $\text{Bi}(\text{OTf})_3$.

Reaction conditions: $\text{Bi}(\text{OTf})_3$ (130 mg, 0.20 mmol, 0.2 equiv.), 2-phenylpropanoic acid (15.0 mg, 0.1 mmol, 1.0 equiv.), KHCO_3 (30.0 mg, 0.3 mmol, 3.0 equiv.) and 4-methylphenylsulfonamide (65.5 mg, 0.35 mmol, 3.5 equiv.) were dissolved into DCM (1 mL) under N_2 . After irradiation with 365 nm for 10 h at 25 °C, internal standard was added and reactions analyzed with GC-FID.

3.8 Synthesis and characterization of products

3.8.1 General procedures for the photocatalyzed nucleophilic couplings

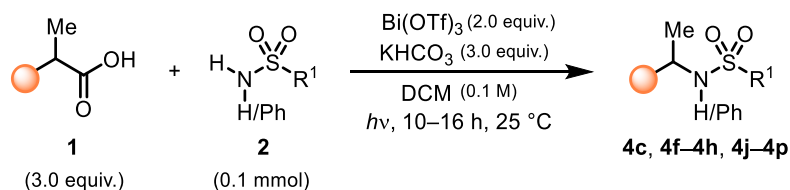
Carboxylic acid as a limiting reagent (GP1) [see details for each substrate below]



Four identical reactions were set up as following: Sulfonamide (0.35 mmol, 3.50 equiv.), KHCO₃ (30.0 mg, 0.30 mmol, 3.00 equiv.), Bi(OTf)₃ (130 mg, 0.20 mmol, 2.00 equiv.) and, if solid, the corresponding carboxylic acid (0.10 mmol, 1.00 equiv.) were weighed into a 5 mL crimp-cap vial equipped with a stirring bar. The vial was sealed and set under an inert atmosphere by evacuating and back-filling with N₂ (×3). If liquid, a stock solution of the corresponding carboxylic acid was prepared in dry DCM (0.1 M), and either 1 mL of this solution or 1 mL of dry DCM was added *via* syringe to the reaction mixture. The reaction mixture was degassed three times with a freeze-pump thaw, after which the reaction was irradiated either with 365 nm (1.8 W) for 10 hours or with 385 nm (0.5 W) for 16 hours while maintaining the temperature at 25 °C with a water-cooling block.

After completion, the reactions were combined, and crude reaction mixture was absorbed to silica. The reaction solvent was then removed under reduces pressure. Purification by flash column chromatography on silica (typically Acetone/PE 20% → 40% or EtOAc/PE 20% → 40%) followed by solvent evaporation yielded the desired products.

Sulfonamide as a limiting reagent (GP2) [see details for each substrate below]



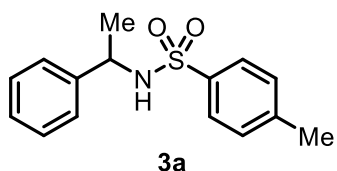
Four identical reactions were set up as following: Sulfonamide (0.10 mmol, 1.00 equiv.), KHCO₃ (30.0 mg, 0.30 mmol, 3.00 equiv.), Bi(OTf)₃ (130 mg, 0.20 mmol, 2.00 equiv.) and

carboxylic acid (0.30 mmol, 3.00 equiv.) were weighed into a 5 mL crimp-cap vial equipped with a stirring bar. The vial was sealed and set under an inert atmosphere by evacuating and back-filling with N₂ (×3). If liquid, a stock solution of the corresponding carboxylic acid was prepared in dry DCM (0.1 M), and either 1 mL of this solution or 1 mL of dry DCM was added *via* syringe to the reaction mixture. The reaction mixture was degassed three times with a freeze-pump thaw, after which the reaction was irradiated either with 365 nm (1.8 W) for 10 hours or with 385 nm (0.5 W) for 16 hours while maintaining the temperature at 25 °C with a water-cooling block.

After completion, the reactions were combined, and crude reaction mixture was absorbed to silica. The reaction solvent was then removed under reduced pressure. Purification by flash column chromatography on silica (typically Acetone/PE 20% → 40% or EtOAc/PE 20% → 40%) followed by solvent evaporation yielded the desired products.

3.8.2 Scope of carboxylic acids

Synthesis of 4-methyl-*N*-(1-phenylethyl)benzenesulfonamide (**3a**)



4-Methyl-*N*-(1-phenylethyl)benzenesulfonamide (**3a**) was synthesized according to **GP1** using (±)-2-phenylpropionic acid (in total 60.0 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and irradiated at 365 nm for 10 h. After purification with reverse-phase flash column chromatography (H₂O+0.5% TFA/MeCN, 10% → 100%) the title compound was obtained as a colorless oil which crystallized to white solid upon standing under ambient conditions (59 mg, 54%).

R_f (silica, 50% EtOAc/PE): 0.87 [potassium permanganate];

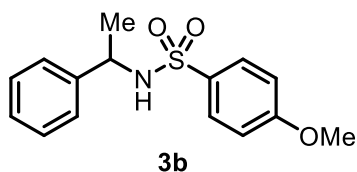
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.60–7.65 (m, 2H), 7.14–7.19 (m, 5H), 7.09–7.12 (m, 2H), 5.33 (d, *J* = 7.0 Hz, 1H), 4.45 (pent., *J* = 7.0 Hz, 1H), 2.37 (s, 3H), 1.41 (d, *J* = 7.0 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 143.1, 142.1, 137.7, 129.4, 128.5, 127.4, 127.1, 126.1, 53.7, 23.6, 21.5;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₅H₁₇NO₂SN_a 298.0878, found 298.0874, Δ = 0.4 mDa.

NOTE: An improved chromatographic separation was observed upon changing the *p*-methyl group of the nucleophile to a *p*-methoxy group. Therefore, the nucleophile **2b** was further on used as the standard nucleophile.

Synthesis of 4-methoxy-*N*-(1-phenylethyl)benzenesulfonamide (**3b**)



4-Methoxy-*N*-(1-phenylethyl)benzenesulfonamide (**3b**) was synthesized according to **GP1** using ($\pm$)-2-phenylpropionic acid (in total 60.0 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg,

1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 365 nm for 10 h. After purification with flash column chromatography (EtOAc/PE, 20% $\rightarrow$ 40%) the title compound was obtained as a colorless oil which slowly crystallized to a white solid upon standing under ambient conditions (59 mg, 51%).

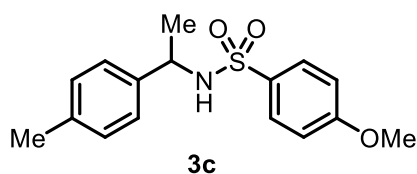
R_f (silica, 50% EtOAc/PE): 0.73 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.63–7.67 (m, 2H), 7.17–7.22 (m, 3H), 7.08–7.11 (m, 2H), 6.82–6.86 (m, 2H), 4.90 (d, J = 6.7 Hz, 1H), 4.45 (pent., J = 6.7 Hz, 1H), 3.83 (s, 3H), 1.42 (d, J = 6.8 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.7, 142.0, 132.2, 129.2, 128.6, 127.5, 126.1, 114.0, 55.6, 53.6, 23.6;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₅H₁₇NO₃Na 314.0827, found 314.0821, Δ = 0.6 mDa.

Synthesis of 4-methoxy-*N*-(1-(*p*-tolyl)ethyl)benzenesulfonamide (**3c**)



4-Methoxy-*N*-(1-(*p*-tolyl)ethyl)benzenesulfonamide (**3c**) was synthesized according to **GP1** using 2-(4-methylphenyl)propanoic acid (in total 65.6 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-

methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column

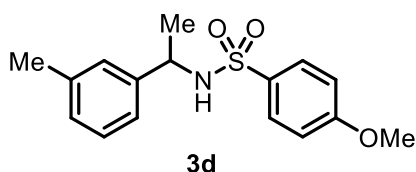
chromatography (Acetone/PE, 30%) the title compound was obtained as a pale solid (54 mg, 44%).

R_f (silica, 50% EtOAc/PE): 0.80 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.65–7.68 (m, 2H), 6.99 (s, 4H), 6.82–6.86 (m, 2H), 5.14 (br. s., 1H), 4.40 (pent., 6.2 Hz, 1H), 3.83 (s, 3H), 2.27 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.6, 139.2, 137.1, 132.3, 129.3, 129.2, 126.1, 113.9, 55.6, 53.4, 23.5, 21.0;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₆H₁₉NO₃SNa 328.0983, found 328.0982, Δ = 0.1 mDa.



Synthesis of 4-methoxy-*N*-(1-(*m*-tolyl)ethyl)benzenesulfonamide (**3d**)

4-Methoxy-*N*-(1-(*p*-tolyl)ethyl)benzenesulfonamide (**3d**) was synthesized according to **GP1** using 2-(4-methylphenyl)propanoic acid (in total 65.6 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (Acetone/PE, 30%) the title compound was obtained as a colorless oil (59 mg, 48%).

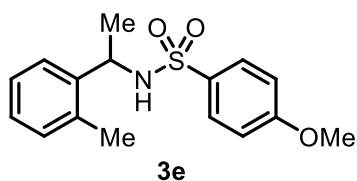
R_f (silica, 50% EtOAc/PE): 0.77 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.63–7.67 (m, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.90–6.97 (m, 2H), 6.84 (br. s., 1H), 6.80–6.84 (m, 2H), 5.33 (d, *J* = 6.8 Hz, 1H), 4.40 (pent., *J* = 6.8 Hz, 1H), 3.82 (s, 3H), 2.20 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.6, 142.0, 138.1, 132.4, 129.2, 128.4, 128.1, 126.9, 123.2, 113.9, 55.6, 53.7, 23.6, 21.3;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₆H₁₉NO₃SNa 328.0983, found 328.0978, Δ = 0.5 mDa.

Synthesis of 4-methoxy-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**3e**)



4-Methoxy-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**3e**) was synthesized according to **GP1** using 2-(4-methylphenyl)propanoic acid (in total 65.6 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (Acetone/PE, 30%) the title compound was obtained as a pale yellowish oil (70 mg, 57%).

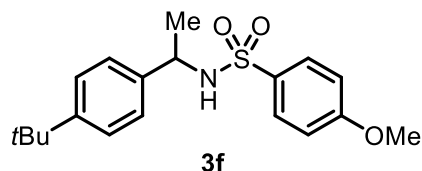
R_f (silica, 50% EtOAc/PE): 0.78 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.60–7.65 (m, 2H), 7.11–7.14 (m, 1H), 6.99–7.05 (m, 3H), 6.77–6.82 (m, 2H), 5.40 (d, *J* = 6.8 Hz, 1H), 4.72 (pent., *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 2.21 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.6, 140.3, 134.4, 132.3, 130.4, 129.1, 127.1, 126.4, 125.4, 113.9, 55.6, 49.7, 23.1, 19.0;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₆H₁₉NO₃SNa 328.0983, found 328.0980, Δ = 0.3 mDa.

Synthesis of *N*-(1-(4-(*tert*-butyl)phenyl)ethyl)-4-methoxybenzenesulfonamide (**3f**)



N-(1-(4-(*tert*-butyl)phenyl)ethyl)-4-methoxybenzenesulfonamide (**3f**) was synthesized according to **GP1** using 2-(4-(*tert*-butyl)phenyl)propanoic acid (in total 82.4 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent

and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (Acetone/PE, 30%) the title compound was obtained as an off-white solid (78 mg, 56%).

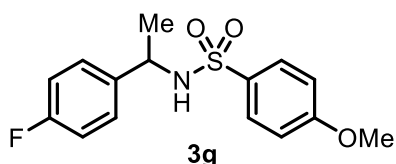
R_f (silica, 50% EtOAc/PE): 0.69 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.52–7.57 (m, 2H), 7.07–7.10 (m, 2H), 6.91–6.95 (m, 2H), 6.68–6.73 (m, 2H), 5.30 (d, *J* = 6.9 Hz, 1H), 4.35 (pent., *J* = 6.9 Hz, 1H), 3.72 (s, 3H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.17 (s, 9H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.5, 150.2, 139.0, 132.4, 129.2, 125.9, 125.3, 113.8, 55.5, 53.4, 34.4, 31.3, 23.5;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₉H₂₅NO₃SNa 370.1453, found 370.1442, Δ = 1.1 mDa.

Synthesis of *N*-(1-(4-fluorophenyl)ethyl)-4-methoxybenzenesulfonamide (**3g**)



N-(1-(4-Fluorophenyl)ethyl)-4-methoxybenzenesulfonamide (**3g**) was synthesized according to **GP1** using 2-(4-fluorophenyl)propanoic acid (in total 67.2 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 365 nm for 10 h. After purification with flash column chromatography (EtOAc/PE, 20% → 40%) the title compound was obtained as a pale orange oil (62 mg, 51%).

R_f (silica, 50% EtOAc/PE): 0.75 [potassium permanganate];

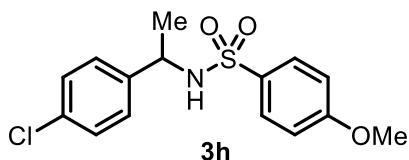
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.61–7.65 (m, 2H), 7.04–7.10 (m, 2H), 6.81–6.88 (m, 4H), 5.34 (br. s, 1H), 4.43 (q., 6.7 Hz, 1H), 3.83 (s, 3H), 1.38 (d, *J* = 6.7 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.7, 161.9 (d, *J* = 246 Hz), 137.9, (d, *J* = 3.1 Hz), 132.1, 129.2, 127.9 (d, *J* = 8.2 Hz), 115.2 (d, *J* = 21.7 Hz), 114.0, 55.6, 53.0, 23.6;

¹⁹F-NMR (376 MHz, CDCl₃, PhCF₃ as internal standard): δ (ppm) –116.0 – (–)116.1 (m)

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₅H₁₆FNO₃SNa 332.0733, found 332.0727, Δ = 0.6 mDa.

Synthesis of *N*-(1-(4-chlorophenyl)ethyl)-4-methoxybenzenesulfonamide (**3h**)



N-(1-(4-Chlorophenyl)ethyl)-4-methoxybenzenesulfonamide (**3h**) was synthesized according to **GP1** using 2-(4-chlorophenyl)propanoic acid (in total 73.8 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 365 nm for 10 h. After purification with flash column

chromatography (Acetone/PE, 30% → 40%) the title compound was obtained as a white solid (67 mg, 51%).

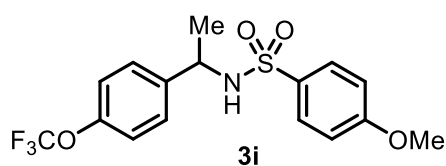
R_f (silica, 50% EtOAc/PE): 0.78 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.59–7.63 (m, 2H), 7.09–7.13 (m, 2H), 7.01–7.04 (m, 2H), 6.79–6.84 (m, 2H), 5.38–5.50 (m, 1H), 4.42 (pent., *J* = 6.9 Hz, 1H), 3.83 (s, 3H), 1.37 (d, *J* = 6.9 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.7, 140.77, 133.0, 132.0, 129.2, 128.5, 127.7, 124.1, 114.0, 55.6, 53.0, 23.5;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₅H₁₆ClNO₃SNa 348.0437, found 348.0428, Δ = 0.9 mDa.

Synthesis of *N*-(1-(4-trifluoromethoxyphenyl)ethyl)-4-methoxybenzenesulfonamide (**3i**)



N-(1-(4-Trifluoromethoxyphenyl)ethyl)-4-methoxybenzenesulfonamide (**3i**) was synthesized according to **GP1** using 2-(4-(trifluoromethoxy)phenyl)propanoic acid (in total 72.9 mg, 0.30 mmol, 1.0 equiv.) as

the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 365 nm for 10 h. After purification with flash column chromatography (Acetone/PE, 30% → 40%) the title compound was obtained as a pale yellow solid (54 mg, 50%).

R_f (silica, 50% EtOAc/PE): 0.81 [potassium permanganate];

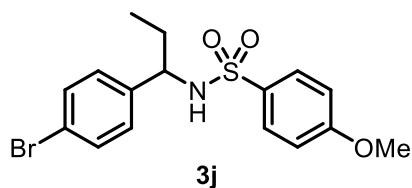
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.58–7.62 (m, 2H), 7.11–7.15 (m, 2H), 6.97–7.02 (m, 2H), 6.77–6.82 (m, 2H), 5.48 (d, *J* = 7.0 Hz, 1H), 4.48 (pent., *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 1.39 (d, *J* = 7.0 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.8, 148.2, 140.9, 132.0, 129.1, 127.7, 124.2, 121.7, 120.9, 120.3 (q, *J* = 257 Hz), 119.0, 116.6, 55.5, 53.0, 23.6;

¹⁹F-NMR (376 MHz, CDCl₃, PhCF₃ as internal standard): δ (ppm) – 58.97 (s)

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₆H₁₆F₃NO₃SNa 398.0650, found 398.0650, Δ = 0.0 mDa.

Synthesis of *N*-(1-(4-bromophenyl)propyl)-4-methoxybenzenesulfonamide (**3j**)



N-(1-(4-bromophenyl)propyl)-4-methoxybenzenesulfonamide (**3j**) was synthesized according to **GP1** using 2-(4-bromophenyl)butanoic acid (in total 97.2 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-

methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 365 nm for 10 h. After purification with flash column chromatography (EtOAc/PE, 20% → 40%) the title compound was obtained as a pale yellow solid (42 mg, 27%).

R_f (silica, 50% EtOAc/PE): 0.85 [potassium permanganate];

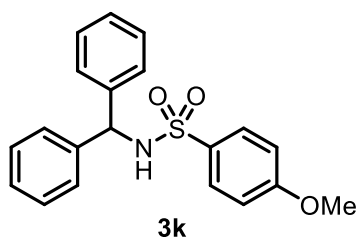
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.50–7.54 (m, 2H), 7.22–7.26 (m, 2H), 6.86–6.90 (m, 2H), 6.74–6.78 (m, 2H), 5.32 (d, *J* = 6.8 Hz, 1H), 4.14 (q., *J* = 7.1 Hz, 1H), 3.83 (s, 3H), 1.74 (sept., *J* = 7.1 Hz, 1H), 1.66 (sept. *J* = 7.2 Hz, 1H), 0.78 (t, *J* = 7.2 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.7, 139.8, 132.1, 131.4, 129.1, 128.5, 121.0, 113.8, 59.3, 55.6, 30.4, 10.4;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₆H₁₈BrNO₃SNa 406.0089, found 406.0085, Δ = 0.4 mDa.

Synthesis of *N*-bezhydryl-4-methoxybenzenesulfonamide (**3k**)

N-Bezhydryl-4-methylbenzenesulfonamide (**3k**) was synthesized according to **GP1** using diphenyl acetic acid (in total 84.8 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column



chromatography (Acetone/PE, 25%) the title compound was obtained as an off-white solid (82 mg, 58%).

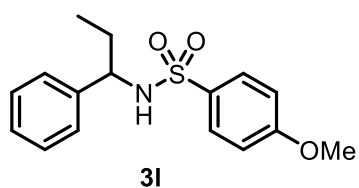
R_f (silica, 50% EtOAc/PE): 0.77 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.58–7.62 (m, 2H), 7.18–7.24 (m, 6H), 7.10–7.13 (m, 4H), 6.77–6.80 (m, 2H), 5.56 (d, *J* = 7.2 Hz, 1H), 5.32 (d, *J* = 7.2 Hz, 1H), 3.82 (s, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.7, 140.6, 132.0, 129.3, 128.6, 127.6, 127.4, 113.9, 61.4, 55.6;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₂₀H₁₉NO₃SNa 376.0983, found 376.0981, Δ = 0.2 mDa.

Synthesis of 4-methoxy-*N*-(1-phenylpropyl)benzenesulfonamide (**3l**)



4-Methoxy-*N*-(1-phenylpropyl)benzenesulfonamide (**3l**) was synthesized according to **GP1** using 2-phenylbutanoic acid (in total 65.6 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 365 nm for 10 h.

After purification with flash column chromatography (EtOAc/PE, 20% → 40%) the title compound was obtained as a white solid (74 mg, 61%).

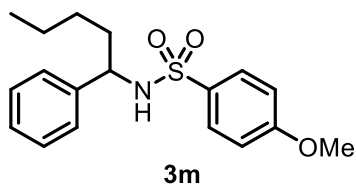
R_f (silica, 50% EtOAc/PE): 0.81 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.56–7.60 (m, 2H), 7.12–7.17 (m, 3H), 7.00–7.03 (m, 2H), 6.74–6.78 (m, 2H), 5.25–5.34 (m, 1H), 4.13–4.20 (m, 1H), 3.80 (s, 3H), 1.80 (sept., *J* = 7.2 Hz, 1H), 1.70 (sept., *J* = 7.2 Hz, 1H), 0.78 (t, *J* = 7.2 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.5, 140.8, 132.4, 129.1, 128.7, 127.3, 126.6, 113.8, 59.8, 55.6, 30.6, 10.5;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₆H₁₉NO₃SNa⁺ 328.0983, found 328.0978, Δ = 0.5 mDa.

Synthesis of 4-methoxy-*N*-(1-phenylpentyl)benzenesulfonamide (**3m**)



4-Methoxy-*N*-(1-phenylpentyl)benzenesulfonamide (**3m**) was synthesized according to **GP1** using 2-phenylhexanoic acid (in total 76.8 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 365 nm for 10 h. After purification with flash column chromatography (Acetone/PE, 20% → 30%) the title compound was obtained as a white solid (67 mg, 50%).

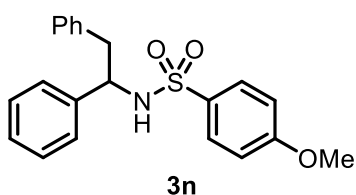
R_f (silica, 50% EtOAc/PE): 0.86 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.54–7.58 (m, 2H), 7.12–7.16 (m, 3H), 6.99–7.02 (m, 2H), 6.73–6.78 (m, 2H), 5.06–5.19 (m, 1H), 4.24 (q, *J* = 7.2 Hz, 1H), 3.80 (s, 3H), 1.70–1.80 (m, 1H), 1.61–1.70 (m, 1H), 1.17–1.27 (m, 3H), 1.04–1.13 (m, 1H), 0.80 (t, *J* = 7.2 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.5, 141.1, 132.4, 129.1, 128.4, 127.2, 126.5, 113.8, 58.3, 55.6, 37.4, 28.0, 22.2, 13.9;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₈H₂₃NO₃SN⁺ 356.1296, found 356.1290, Δ = 0.6 mDa.

Synthesis of *N*-(1,2-diphenylethyl)-4-methoxybenzenesulfonamide (**3n**)



N-(1,2-Diphenylethyl)-4-methoxybenzenesulfonamide (**3n**) was synthesized according to **GP1** using 2-phenylhexanoic acid (in total 90.4 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 365 nm for 10 h. After purification with flash column chromatography (Acetone/PE, 20% → 30%) the title compound was obtained as a white solid (84 mg, 57%).

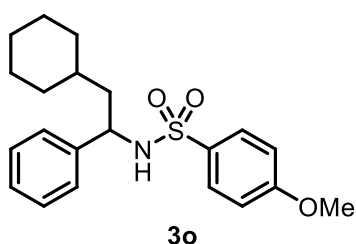
R_f (silica, 50% EtOAc/PE): 0.86 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.46–7.50 (m, 2H), 7.15–7.18 (m, 6H), 7.03–7.06 (m, 2H), 6.91–6.95 (m, 2H), 6.71–6.75 (m, 2H), 5.12–5.19 (m, 1H), 4.50 (q, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 2.96–3.00 (m, 2H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.5, 140.5, 136.5, 131.8, 129.3, 129.1, 128.5, 128.3, 127.4, 126.8, 126.7, 113.4, 59.3, 55.6, 44.1;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₂₁H₂₁NO₃SNa 390.1140, found 390.1132, Δ = 0.8 mDa.

Synthesis of *N*-(2-cyclohexyl-1-phenylethyl)-4-methoxybenzenesulfonamide (**3o**)



N-(2-cyclohexyl-1-phenylethyl)-4-methoxybenzenesulfonamide (**3o**) was synthesized according to **GP1** using 3-cyclohexyl-2-phenylpropanoic acid (in total 92.9 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 365 nm for 10 h. After purification with flash column chromatography (Acetone/PE, 30%) the title compound was obtained as a pale yellowish oil (33 mg, 22%).

R_f (silica, 50% EtOAc/PE): 0.74 [potassium permanganate];

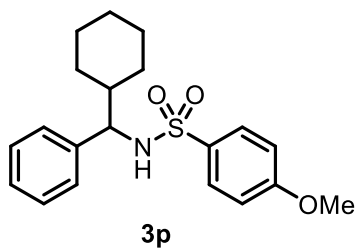
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.54–7.58 (m, 2H), 7.11–7.16 (m, 3H), 7.00–7.03 (m, 2H), 6.74–6.78 (m, 2H), 5.04 (d, *J* = 7.5 Hz, 1H), 4.35 (q., *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 1.54–1.67 (m, 6H), 1.51 (sept., *J* = 7.1 Hz, 1H), 1.02–1.19 (m, 4H), 0.75–0.92 (m, 2H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.5, 141.6, 132.4, 129.1, 128.4, 127.2, 126.4, 113.8, 55.7, 55.6, 45.7, 33.9, 33.2, 32.8, 26.4, 26.1, 26.0;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₂₁H₂₇NO₃SNa⁺ 396.1609, found 396.1608, Δ = 0.1 mDa.

Synthesis of *N*-cyclohexyl(phenyl)methyl-4-methoxybenzenesulfonamide (**3p**)

N-Cyclohexyl(phenyl)methyl-4-methoxybenzenesulfonamide (**3p**) was synthesized according to **GP1** using 2-cyclohexyl-2-phenylacetic acid (in total 87.2 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40



mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 365 nm for 10 h. After purification with flash column chromatography (Acetone/PE, 20% → 30%) the title compound was obtained as a white solid (75 mg, 52 %).

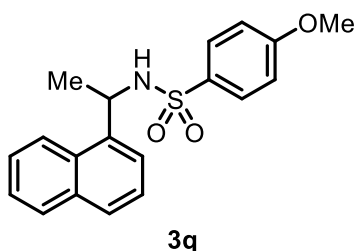
R_f (silica, 50% EtOAc/PE): 0.83 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.49–7.53 (m, 2H), 7.07–7.11 (m, 3H), 6.89–6.93 (m, 2H), 6.67–6.72 (m, 2H), 5.28 (d, *J* = 8.3 Hz, 1H), 3.78 (s, 3H), 1.93–1.98 (m, 1H), 1.69–1.76 (m, 2H), 1.53–1.63 (m, 3H), 1.24–1.28 (m, 1H), 1.03–1.11 (m, 2H), 0.82–0.96 (m, 2H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.4, 140.0, 132.4, 129.1, 128.1, 127.0, 126.9, 113.7, 63.5, 55.5, 43.8, 29.8, 29.5, 26.2, 25.9 (2C);

HRMS (ESI⁺): calc. [M+Na]⁺ for C₂₀H₂₅NO₃Na 382.1453, found 382.1451, Δ = 0.2 mDa.

Synthesis of 4-methoxy-*N*-(1-naphthalen-1-yl)ethyl)benzenesulfonamide (**3q**)



4-Methoxy-*N*-(1-naphthalen-1-yl)ethyl)benzenesulfonamide (**3q**) was synthesized according to **GP1** using 2-(naphthalen-1-yl)propanoic acid (in total 60.0 mg, 0.30 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in

excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (Acetone/PE, 30%) the title compound was obtained as a white solid (27 mg, 26%).

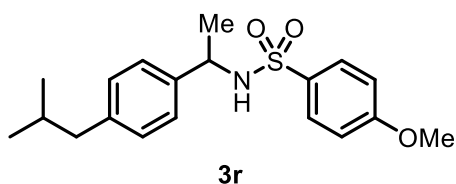
R_f (silica, 50% EtOAc/PE): 0.68 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.89–7.93 (m, 1H), 7.78–7.81 (m, 1H), 7.66–7.70 (m, 1H), 7.57–7.61 (m, 2H), 7.43–7.47 (m, 2H), 7.35–7.38 (m, 1H), 7.28–7.33 (m, 1H), 6.67–6.72 (m, 2H), 5.28 (pent., *J* = 6.8 Hz, 1H), 5.14–5.20 (m, 1H), 3.78 (s, 3H), 1.59 (d, *J* = 6.8 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.6, 137.7, 133.8, 132.0, 130.2, 129.2, 128.8, 128.1, 126.3, 125.6, 125.3, 123.4, 122.6, 113.8, 55.5, 49.8, 23.3;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₉H₁₉NO₃SNa 364.0983, found 364.0980, Δ = 0.3 mDa.

Synthesis of *N*-(1-(4-isobutylphenyl)ethyl)-4-methoxybenzenesulfonamide (**3r**)



N-(1-(4-Isobutylphenyl)ethyl)-4-methylbenzenesulfonamide (**3r**) was synthesized according to **GP1** using 2-(4-isobutylphenyl)propanoic acid (rac. ibuprofen, in total 82.4 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (EtOAc/PE, 5% → 50%) the title compound was obtained as a white solid (87 mg, 63%).

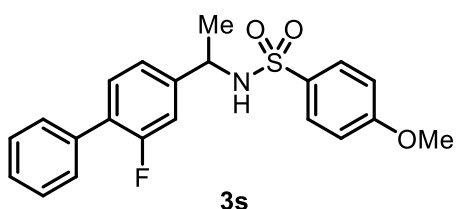
R_f (silica, 50% EtOAc/PE): 0.84 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.62–7.67 (m, 2H), 6.95–7.01 (m, 4H), 6.81–6.85 (m, 2H), 4.92 (br. s., 1H), 4.39–4.46 (m, 1H), 3.82 (s, 3H), 2.39 (d, *J* = 6.9 Hz, 2H), 1.79 (sept., *J* = 6.9 Hz, 1H), 1.42 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 6H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.6, 141.1, 139.3, 132.4, 129.2 (2C), 125.9, 113.9, 55.5, 53.4, 45.0, 30.2, 23.6, 22.3;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₉H₂₅NO₃SNa 370.1453, found 370.1453, Δ = 0.0 mDa.

Synthesis of *N*-(1-(2-fluoro-[1,1′biphenyl]-4-yl)ethyl)-4-methylbenzenesulfonamide (**3s**)



N-(1-(2-Fluoro-[1,1′biphenyl]-4-yl)ethyl)-4-methylbenzenesulfonamide (**3s**) was synthesized according to **GP1** using 2-(2-fluoro-[1,1′biphenyl]-4-yl)propanoic acid (rac. flurbiprofen, in total 97.6 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methoxybenzenesulfonamide (in total 262 mg, 1.40 mmol, 3.50 equiv.) as nucleophile in

excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (EtOAc/PE, 5% → 50%) the title compound was obtained as a white solid (40 mg, 26%).

R_f (silica, 50% EtOAc/PE): 0.80 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.56–7.61 (m, 2H), 7.32–7.40 (m, 4H), 7.25–7.30 (m, 1H), 7.14–7.19 (m, 1H), 6.89 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.79 (dd, *J* = 11.4, 1.8 Hz, 1H), 6.73–6.77 (m, 2H), 5.13–5.20 (m, 1H), 4.38–4.45 (m, 1H), 3.69 (s, 3H), 1.36 (d, *J* = 6.9 Hz, 3H);

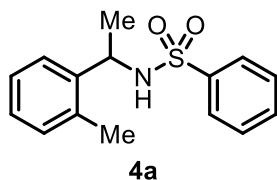
¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.8, 159.5 (d, *J* = 250 Hz), 143.6 (d, *J* = 7.0 Hz), 135.3 (d, *J* = 1.0 Hz), 132.1, 130.7 (d, *J* = 3.9 Hz), 129.3, 128.8 (d, *J* = 2.9 Hz), 128.4, 128.0 (d, *J* = 13.5 Hz), 127.7, 122.2 (d, *J* = 3.3 Hz), 114.0 (d, *J* = 23.7 Hz), 113.9, 55.5, 53.0, 23.4;

¹⁹F-NMR (376 MHz, CDCl₃, PhCF₃ as internal standard): δ (ppm) –118.6 – (–)118.7 (m)

HRMS (ESI⁺): calc. [M+Na]⁺ for C₂₁H₂₀FNO₃SNa 408.1046, found 408.1037, Δ = 0.9 mDa.

3.8.3 Scope of nucleophiles

Synthesis of *N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4a**)



N-(1-(*o*-Tolyl)ethyl)benzenesulfonamide (**4a**) was synthesized according to **GP1** using 2-(*o*-tolyl)propanoic acid (in total 65.7 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and benzenesulfonamide (in total 220 mg, 1.40 mmol, 3.50 equiv.) as nucleophile. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (Acetone/PE, 20% → 40%) the title compound was obtained as a colorless oil (45 mg, 41%).

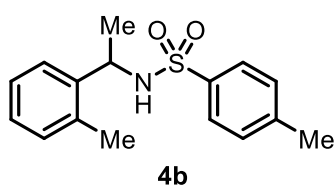
R_f (silica, 50% EtOAc/PE): 0.87 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.67–7.71 (m, 2H), 7.47 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.32–7.37 (m, 2H), 7.08–7.11 (m, 1H), 6.98–7.05 (m, 3H), 5.10 (d, *J* = 6.7 Hz, 1H), 4.76 (pent., *J* = 6.7 Hz, 1H), 2.19 (s, 3H), 1.40 (d, *J* = 6.7 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 140.6, 140.0, 134.5, 132.3, 130.4, 128.7, 127.3, 126.9, 126.4, 125.2, 49.8, 23.2, 18.9;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₅H₁₇NO₂SNa 298.0878, found 298.0874, Δ = 0.4 mDa.

Synthesis of 4-methyl-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4b**)



4-Methyl-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4b**) was synthesized according to **GP1** using 2-(*o*-tolyl)propanoic acid (in total 65.7 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-methylbenzenesulfonamide (in total 240 mg, 1.40 mmol, 3.50 equiv.) as nucleophile. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (Acetone/PE, 20% → 40%) the title compound was obtained as a colorless oil (59 mg, 51%).

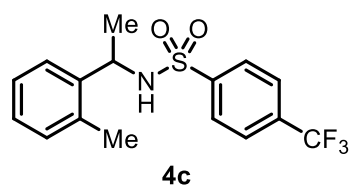
R_f (silica, 50% EtOAc/PE): 0.90 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.58–7.62 (m, 2H), 7.12–7.15 (m, 3H), 6.98–7.06 (m, 3H), 5.37 (d, *J* = 6.6 Hz, 1H), 4.73 (pent., *J* = 6.6 Hz, 1H), 2.36 (s, 3H), 2.20 (s, 3H), 1.37 (d, *J* = 6.6 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 143.0, 140.4, 137.7, 134.4, 130.4, 129.3, 127.1, 127.0, 126.4, 125.4, 49.7, 23.1, 21.5, 19.0;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₆H₁₉NO₂SNa 312.1034, found 312.1031, Δ = 0.3 mDa.

Synthesis of *N*-(1-(*o*-tolyl)ethyl)-4-(trifluoromethyl)benzenesulfonamide (**4c**)



N-(1-(*o*-Tolyl)ethyl)-4-(trifluoromethyl)benzenesulfonamide (**4c**) was synthesized according to **GP2** using 4-(trifluoromethyl)benzenesulfonamide (in total 90.0 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-(*o*-tolyl)propa-

noic acid (in total 197 mg, 1.20 mmol, 3.0 equiv.) as acid in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (Acetone/PE, 20% → 40%) the title compound was obtained as an off-white solid (52 mg, 38%).

R_f (silica, 50% EtOAc/PE): 0.95 [potassium permanganate];

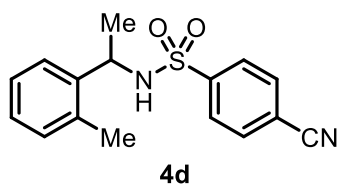
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.73 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 6.96–7.04 (m, 3H), 6.88–6.94 (m, 1H), 5.53 (d, *J* = 7.3 Hz, 1H), 4.87 (pent., *J* = 6.9 Hz, 1H), 2.26 (s, 3H), 1.43 (d, *J* = 6.9 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 144.1, 139.3, 134.4, 133.8 (q, *J* = 33 Hz), 130.4, 127.4, 127.3, 126.4, 125.6 (q, *J* = 3.7 Hz), 125.3, 123.2 (q, *J* = 272 Hz), 50.0, 29.7, 23.1, 19.0;

¹⁹F-NMR (376 MHz, CDCl₃, PhCF₃ as internal standard): δ (ppm) – 63.23 (s)

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₆H₁₆F₃NO₂SNa 366.0752, found 366.0748, Δ = 0.4 mDa.

Synthesis of 4-cyano-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4d**)



4-Cyano-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4d**) was synthesized according to **GP1** using 2-(*o*-tolyl)propanoic acid (in total 65.7 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 4-cyanobenzenesulfonamide (in total 255 mg, 1.40 mmol, 3.5 equiv.) as nucleophile in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (EtOAc/PE, 20% → 40%) the title compound was obtained as a pale oil which crystallized to a white solid upon standing under the ambient conditions (47 mg, 39%).

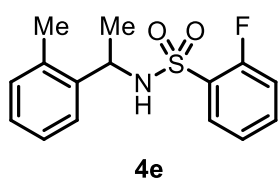
R_f (silica, 50% EtOAc/PE): 0.76 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.63–7.67 (m, 2H), 7.53–7.57 (m, 2H), 7.03–7.08 (m, 1H), 7.00–7.03 (m, 1H), 4.93 (d, *J* = 6.7 Hz, 1H), 4.88 (pent., *J* = 6.7 Hz, 1H), 2.25 (s, 3H), 1.44 (d, *J* = 6.7 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 144.9, 139.1, 134.7, 132.4, 130.6, 127.6, 127.4, 126.4, 125.2, 117.4, 115.8, 50.1, 23.2, 19.0;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₆H₁₆N₂O₂SNa 323.0830, found 323.0826, Δ = 0.4 mDa.

Synthesis of 2-fluoro-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4e**)



2-Fluoro-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4e**) was synthesized according to **GP1** using 2-(*o*-tolyl)propanoic acid (in total 65.7 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-fluorobenzenesulfonamide (in total 210 mg, 1.40 mmol, 3.5 equiv.) as nucleophile in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (EtOAc/PE, 20% → 40%) the title compound was obtained as a colorless oil which crystallized to white solid upon standing under the ambient conditions (36 mg, 31%).

R_f (silica, 50% EtOAc/PE): 0.86 [potassium permanganate];

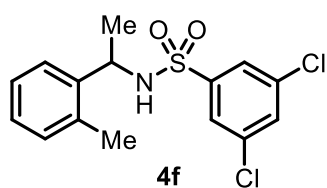
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.71 (td, *J* = 7.5, 1.8 Hz, 1H), 7.38–7.41 (m, 1H), 7.13–7.16 (m, 1H), 7.10 (dt, *J* = 7.7, 0.9 Hz, 1H), 6.97–7.05 (m, 3H), 6.92–6.97 (m, 1H), 5.15 (d, *J* = 7.6 Hz, 1H), 4.81 (pent., *J* = 7.0 Hz, 1H), 2.19 (s, 3H), 1.42 (d, *J* = 7.0 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): (ppm) 158.6 (d, *J* = 252 Hz), 139.6, 134.6 (d, *J* = 8.9 Hz), 134.4, 130.4, 129.7, 128.6 (d, *J* = 12.7 Hz), 126.8 (d, *J* = 102 Hz), 124.8, 124.1 (d, *J* = 3.8 Hz), 116.5 (d, *J* = 21.1 Hz), 49.9, 23.0, 18.9;

¹⁹F-NMR (376 MHz, CDCl₃, PhCF₃ as internal standard):

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₅H₁₆FNO₂SNa 316.0784, found 316.0777, Δ = 0.7 mDa.

Synthesis of 3,5-dichloro-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4f**)



3,5-Dichloro-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4f**) was synthesized according to **GP2** using 3,5-dichlorobenzenesulfonamide (in total 90.4 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-(*o*-tolyl)propanoic acid

(in total 197 mg, 1.20 mmol, 3.0 equiv.) as acid in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (Acetone/PE, 20% → 40%) the title compound was obtained as a cream-white solid (72 mg, 52%).

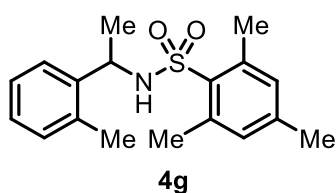
R_f (silica, 50% EtOAc/PE): 0.92 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.40–7.42 (m, 2H), 7.33 (t, *J* = 1.8 Hz, 1H), 7.03–7.05 (m, 2H), 6.97–7.00 (m, 2H), 5.49 (br. s., 1H), 4.87 (pent., *J* = 7.0 Hz, 1H), 2.29 (s, 3H), 1.45 (d, *J* = 7.0 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 143.4, 138.9, 135.4, 134.5, 132.1, 130.5, 127.7, 126.3, 125.3, 125.2, 50.1, 23.1, 19.0;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₅H₁₅Cl₂NO₂SNa 366.0098, found 366.0095, Δ = 0.3 mDa.

Synthesis of 2,4,6-trimethyl-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4g**)



2,4,6-Trimethyl-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4g**) was synthesized according to **GP2** using 2,4,6-trimethylbenzenesulfonamide (in total 79.7 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-(*o*-tolyl)propanoic acid (in total 197 mg, 1.20 mmol, 3.0 equiv.) as acid in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (Acetone/PE, 20% → 40%) the title compound was obtained as a cream-white solid (58 mg, 46%).

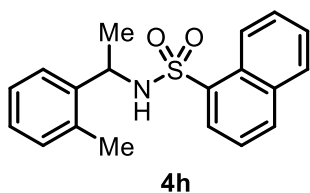
R_f (silica, 50% EtOAc/PE): 0.92 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.09–7.13 (m, 1H), 6.98–7.07 (m, 3H), 6.85 (s, 2H), 4.77 (d, *J* = 5.6 Hz, 1H), 4.71 (pent., *J* = 6.4 Hz, 1H), 2.53 (s, 6H), 2.26 (s, 3H), 2.17 (s, 3H), 1.36 (d, *J* = 6.4 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 141.9, 140.3, 138.8, 134.6, 134.5, 131.8, 130.5, 127.2, 126.2, 125.1, 49.5, 23.0, 22.8, 20.9, 18.8;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₈H₂₃NO₂SNa 340.1347, found 340.1345, Δ = 0.2 mDa.

Synthesis of *N*-(1-(*o*-Tolyl)ethyl)naphthalene-1-sulfonamide (**4h**)



N-(1-(*o*-Tolyl)ethyl)naphthalene-1-sulfonamide (**4h**) was synthesized according to **GP2** using naphthalene-1-sulfonamide (in total 82.9 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-(*o*-tolyl)propanoic acid (in total 197 mg, 1.20 mmol, 3.0 equiv.) as acid in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (Acetone/PE, 30% → 40%) the title compound was obtained as a cream-white solid (41 mg, 32%).

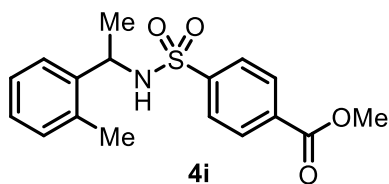
R_f (silica, 50% EtOAc/PE): 0.86 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.22 (d, *J* = 1.4 Hz, 1H), 7.79–7.86 (m, 3H), 7.67 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.54–7.63 (m, 2H), 7.06–7.10 (m, 1H), 6.98–6.95 (m, 3H), 4.94 (d, *J* = 6.6 Hz, 1H), 4.82 (pent., *J* = 6.6 Hz, 1H), 2.17 (s, 3H), 1.41 (d, *J* = 6.6 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 139.9, 137.4, 134.6, 134.5, 132.0, 130.4, 129.2, 129.1, 128.6, 128.3, 127.8, 127.3 (2C), 126.3, 125.1, 122.2, 49.9, 29.7, 23.1, 18.9;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₉H₁₉NO₂SNa 348.1034, found 348.1031, Δ = 0.3 mDa.

Synthesis of methyl 4-(*N*-(1-(*o*-tolyl)ethyl)sulfamoyl)benzoate (**4i**)



Methyl 4-(*N*-(1-(*o*-tolyl)ethyl)sulfamoyl)benzoate (**4i**) was synthesized according to **GP1** using 2-(*o*-tolyl)propanoic acid (in total 65.7 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and methyl 4-sulfamoylbenzoate (in total 301 mg,

1.40 mmol, 3.5 equiv.) as nucleophile in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (EtOAc/PE, 20% → 40%) the title compound was obtained as an off-white solid (40 mg, 30%).

R_f (silica, 50% EtOAc/PE): 0.73 [potassium permanganate];

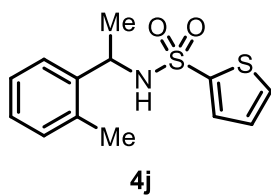
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.95–8.00 (m, 2H), 7.67–7.72 (m, 2H), 6.95–7.05 (m, 4H), 4.90 (d, *J* = 6.7 Hz, 1H), 4.82 (pent., *J* = 6.7 Hz, 1H), 3.94 (s, 3H), 2.22 (s, 3H), 1.42 (d, *J* = 6.7 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 165.6, 144.7, 139.5, 134.6, 133.4, 130.6, 129.9, 127.5, 126.9, 126.4, 125.2, 52.6, 49.9, 23.1, 19.0;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₇H₁₉NO₄SNa 356.0933, found 356.0927, Δ = 0.6 mDa.

Synthesis of *N*-(1-(*o*-tolyl)ethyl)thiophene-2-sulfonamide (**4j**)

N-(1-(*o*-Tolyl)ethyl)thiophene-2-sulfonamide (**4j**) was synthesized according to **GP2** using thiophene-2-sulfonamide (in total 65.2 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-(*o*-tolyl)propanoic acid (in total 197 mg, 1.20 mmol, 3.0 equiv.) as acid in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (EtOAc/PE, 20% → 40%) the title compound was obtained as a colorless



oil which crystallized to white solid upon standing under the ambient conditions (25 mg, 22%).

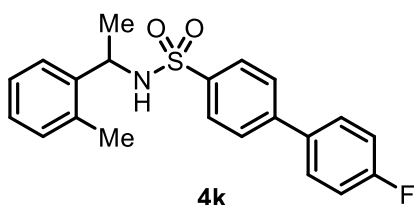
R_f (silica, 50% EtOAc/PE): 0.87 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.46 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.38 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.14–7.17 (m, 1H), 7.04–7.10 (m, 3H), 5.11 (d, *J* = 5.7 Hz, 1H), 4.83 (pent., *J* = 6.6 Hz, 1H), 2.25 (s, 3H), 1.44 (d, *J* = 6.8 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 141.7, 140.0, 134.5, 132.1, 131.7, 130.5, 127.4, 127.1, 126.5, 125.1, 50.2, 23.2, 19.0;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₃H₁₅NO₂S₂Na 304.0442, found 304.0434, Δ = 0.8 mDa.

Synthesis of 4'-fluoro-*N*-(1-(*o*-tolyl)ethyl)-[1,1'-biphenyl]-4-sulfonamide (**4k**)



4'-Fluoro-*N*-(1-(*o*-tolyl)ethyl)-[1,1'-biphenyl]-4-sulfonamide (**4k**) was synthesized according to **GP2** using 4'-fluoro-[1,1'-biphenyl]-4-sulfonamide (in total 100.4 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-(*o*-

tolyl)propanoic acid (in total 197 mg, 1.20 mmol, 3.0 equiv.) as acid in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (Acetone/PE, 20% → 40%) the title compound was obtained as a white solid (87 mg, 59%).

R_f (silica, 50% EtOAc/PE): 0.73 [potassium permanganate];

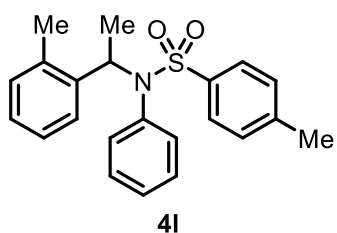
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.96–8.00 (m, 1H), 7.65–7.69 (m, 1H), 7.54–7.59 (m, 1H), 7.27–7.33 (m, 1H), 7.15–7.21 (m, 4H), 5.03 (br. s., 1H), 3.99 (q., *J* = 7.2 Hz, 1H), 2.38 (s, 3H), 1.49 (d, *J* = 7.2 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 180.0, 161.9, 144.8, 140.5, 137.0 (d, *J* = 246 Hz), 135.9, 130.6, 130.4 (d, *J* = 13.6 Hz), 129.0 (d, *J* = 8.5 Hz), 129.0 (d, *J* = 9.0 Hz), 127.4 (d, *J* = 41.3 Hz), 127.1, 126.5 (d, *J* = 9.6 Hz), 116.1 (d, *J* = 21.7 Hz), 41.0, 19.6, 17.6;

¹⁹F-NMR (376 MHz, CDCl₃, PhCF₃ as internal standard): δ (ppm) –114.4 – (–)114.5 (m)

HRMS (ESI⁺): calc. [M+Na]⁺ for C₂₁H₂₀FNO₂SNa 392.1097, found 392.1082, Δ = 1.5 mDa.

Synthesis of 4-methyl-*N*-phenyl-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4l**)



4-Methyl-*N*-phenyl-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4l**) was synthesized according to **GP2** using 4-methyl-*N*-phenylsulfonamide (in total 98.2 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-(*o*-tolyl)propanoic acid (in total 197 mg, 1.20 mmol, 3.0 equiv.) as acid in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (EtOAc/PE, 20% → 40%) the title compound was obtained as a white solid (80 mg, 55%).

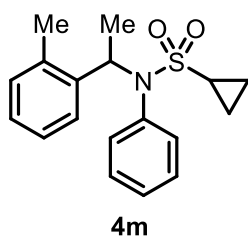
R_f (silica, 50% EtOAc/PE): 0.90 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.62–7.67 (m, 2H), 7.17–7.22 (m, 4H), 7.11–7.13 (m, 2H), 6.99–7.03 (m, 2H), 6.94–6.98 (m, 2H), 4.24 (q., *J* = 7.1 Hz, 1H), 2.37 (s, 3H), 2.17 (s, 3H), 1.54 (d, *J* = 7.1 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 143.7, 143.6, 143.5, 136.2, 136.0, 134.3, 130.4, 129.6, 128.5, 127.3, 126.6, 126.2, 126.1, 121.9, 40.4, 21.9, 21.6, 19.7;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₂₂H₂₃NO₂SNa 388.1347, found 388.1345, Δ = 0.2 mDa.

Synthesis of *N*-phenyl-*N*-(1-(*o*-tolyl)ethyl)cyclopropanesulfonamide (**4m**)



N-Phenyl-*N*-(1-(*o*-tolyl)ethyl)cyclopropanesulfonamide (**4m**) was synthesized according to **GP2** using *N*-phenylcyclopropanesulfonamide (in total 78.9 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-(*o*-tolyl)propanoic acid (in total 197 mg, 1.20 mmol, 3.0 equiv.) as acid in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (H₂O+0.5% TFA/MeCN, 10% → 100%) the title compound was obtained as a colorless oil (81 mg, 64%).

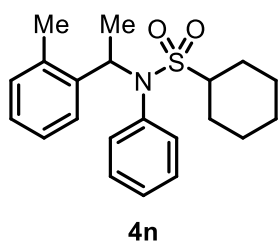
R_f (silica, 50% EtOAc/PE): 0.97 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.13–7.31 (m, 9H), 6.88 (br. s., 1H), 4.33 (q., *J* = 7.2 Hz, 1H), 2.49 (tt, *J* = 8.0, 4.8 Hz, 1H), 2.26 (s, 3H), 1.63 (d, *J* = 7.2 Hz, 3H), 1.14–1.19 (m, 2H), 0.92–0.98 (m, 2H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 143.7, 143.6, 136.0, 134.5, 130.5, 128.6, 126.6, 126.2, 126.1, 122.3, 40.5, 29.7, 22.1, 19.8, 5.6;

HRMS (ESI⁺): calc. [M+NH₄]⁺ for C₁₈H₂₁NO₂SNH₄ 333.1637, found 333.1633, Δ = 0.4 mDa.

Synthesis of *N*-phenyl-*N*-(1-(*o*-tolyl)ethyl)cyclohexanesulfonamide (**4n**)



N-Phenyl-*N*-(1-(*o*-tolyl)ethyl)cyclohexanesulfonamide (**4n**) was synthesized according to **GP2** using *N*-phenylcyclohexanesulfonamide (in total 95.7 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-(*o*-tolyl)propanoic acid (in total 197 mg, 1.20 mmol, 3.0 equiv.) as acid in excess. The reaction

was irradiated at 385 nm for 16 h. After purification with flash column chromatography (H₂O+0.5% TFA/MeCN, 10% → 100%) the title compound was obtained as a yellow-orange oil (88 mg, 62 %).

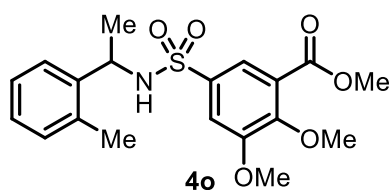
R_f (silica, 50% EtOAc/PE): 0.95 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.27–7.31 (m, 1H), 7.21–7.26 (m, 1H), 7.11–7.19 (m, 6H), 6.99 (s, 1H), 4.32 (q., *J* = 7.1 Hz, 1H), 3.02 (tt, *J* = 12.0, 3.2 Hz, 1H), 2.27 (s, 3H), 2.19 (d, *J* = 12.0 Hz, 2H), 1.88 (d, *J* = 10.6 Hz, 2H), 1.67–1.72 (m, 1H), 1.63 (d, *J* = 7.1 Hz, 3H), 1.53–1.59 (m, 2H), 1.13–1.30 (m, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 130.5, 128.7 (2C), 126.6, 126.2, 126.1, 120.5 (2C), 60.3, 40.4, 26.3, 25.1, 22.1, 19.8;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₂₁H₂₇NO₂SNa 380.1660, found 380.1658, Δ = 0.2 mDa.

Synthesis of methyl 2,3-dimethoxy-5-(*N*-(1-(*o*-tolyl)ethyl)sulfamoylbenzoate (**4o**)



Methyl 2,3-dimethoxy-5-(*N*-(1-(*o*-tolyl)ethyl)sulfamoylbenzoate (**4o**) was synthesized according to **GP2** using methyl 2,3-dimethoxy-5-sulfamoylbenzoate (in total 110.0 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-(*o*-tolyl)propanoic acid (in total 197 mg, 1.20 mmol, 3.0 equiv.) as acid in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (EtOAc/PE, 20% → 40%) the title compound was obtained as a colorless oil which crystallized to white solid upon standing under the ambient conditions (40 mg, 25%).

R_f (silica, 50% EtOAc/PE): 0.77 [potassium permanganate];

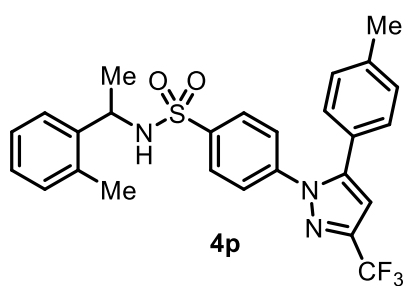
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.65 (d, *J* = 2.2 Hz, 1H), 7.15 (d, *J* = 2.2 Hz, 1H), 6.94–7.02 (m, 4H), 5.32 (d, *J* = 7.3 Hz, 1H), 4.81 (pent., *J* = 6.9 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.23 (s, 3H), 1.42 (d, *J* = 6.9 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 165.0, 153.3, 152.2, 139.7, 135.6, 134.4, 130.3, 127.3, 126.2, 125.3, 121.5, 113.3, 110.0, 61.6, 56.1, 52.4, 49.9, 23.4, 19.0;

HRMS (ESI⁺): calc. [M+H]⁺ for C₁₉H₂₄NO₆SN_a 394.1324, found 394.1320, Δ = 0.4 mDa.

Synthesis of 4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (**4p**)

4-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)-*N*-(1-(*o*-tolyl) ethyl)benzenesulfonamide (**4p**) was synthesized according to **GP2** using 4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (celebrex, in total 152.4 mg, 0.40 mmol, 1.0 equiv.) as the limiting reagent and 2-(*o*-tolyl)propanoic acid (in total 197 mg, 1.20 mmol, 3.0 equiv.) as acid in excess. The reaction was irradiated at 385 nm for 16 h. After purification with flash column chromatography (EtOAc/PE, 20% → 40%) the title compound was obtained as a



colorless oil which crystallized to white solid upon standing under the ambient conditions (136 mg, 68%).

R_f (silica, 50% EtOAc/PE): 0.95 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.63–7.67 (m, 2H), 7.29–7.32 (m, 2H), 7.15–7.18 (m, 2H), 7.03–7.11 (m, 6H),

7.67 (s, 1H), 5.07 (d, *J* = 6.6 Hz, 1H), 4.79 (pent., *J* = 6.7 Hz, 1H), 2.38 (s, 3H), 2.24 (s, 3H), 1.40 (d, *J* = 6.7 Hz, 3H);

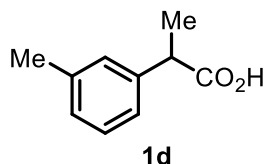
¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 145.1, 144.1 (q, *J* = 38 Hz), 142.2, 140.2, 139.8, 139.7, 134.5, 130.6, 129.7, 128.7, 127.9, 127.6, 126.5, 125.8, 125.3, 125.1, 121.0 (q, *J* = 268 Hz), 49.9, 23.1, 21.3, 19.1;

¹⁹F-NMR (376 MHz, CDCl₃, PhCF₃ as internal standard): δ (ppm) – 63.5 (s)

HRMS (ESI⁺): calc. [M+H]⁺ for C₂₆H₂₅F₃N₃O₂S 500.1620, found 500.1617, Δ = 0.3 mDa.

3.8.4 List of synthesized carboxylic acids

Synthesis of 2-(*m*-tolyl)propanoic acid (**1d**)



Synthesized according to **GP3** using 2-(*m*-tolyl)acetic acid (3.00 g, 20.0 mmol, 1.00 equiv.) as starting material. After purification with flash column chromatography (MeOH/DCM, 5%), the title compound was obtained as a yellowish oil which eventually crystallized

to a pale solid under ambient conditions (1.45 g, 44%).

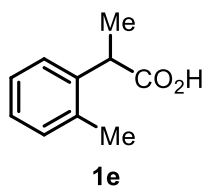
R_f (silica, 5% MeOH/DCM) 0.26 [bromocresol green]

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 11.96 (br. s., 1H), 7.34–7.39 (m, 1H), 7.21–7.30 (m, 3H), 3.85 (q, *J* = 7.15 Hz, 1H), 2.49 (s, 3H), 1.65 (d, *J* = 7.15 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 181.5, 139.9, 138.5, 128.8, 128.5, 128.3, 124.8, 45.5, 21.5, 18.2;

HRMS (EI⁺): calc. [M]⁺ for C₁₀H₁₂O₂⁺ 164.08318, found 164.08304, Δ = 0.14 mDa.

Synthesis of 2-(*o*-tolyl)propanoic acid (**1e**)



Synthesized according to **GP3** using 2-(*o*-tolyl)acetic acid (3.00 g, 20.0 mmol, 1.00 equiv.) as a starting material. After purification with flash column chromatography (MeOH/DCM, 5%), the title compound was obtained as a white hard solid (2.11 g, 64%).

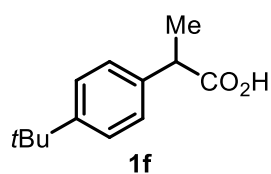
R_f (silica, 5% MeOH/DCM) 0.44 [bromocresol green]

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.28–7.31 (m, 1H), 7.16–7.23 (m, 3H), 3.99 (q, *J* = 7.15 Hz, 1H), 2.39 (s, 3H), 1.50 (d, *J* = 7.15 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 180.7, 138.3, 135.9, 130.6, 127.2, 126.6, 126.5, 41.1, 19.7, 17.5;

HRMS (EI⁺): calc. [M]⁺ for C₁₀H₁₂O₂⁺ 164.08318, found 164.08321, Δ = − 0.03 mDa.

Synthesis of 2-(4-(*tert*-butyl)phenyl)propanoic acid (**1f**)



Synthesized according to **GP3** using 2-(4-*tert*-butyl)phenylacetic acid (3.85 g, 20.0 mmol, 1.00 equiv.) as a starting material. After purification with flash column chromatography (MeOH/DCM, 5%), the title compound was obtained as an off-white solid (1.20 g, 29%).

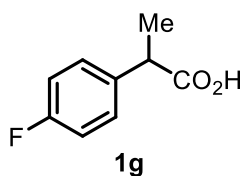
R_f (silica, 5% MeOH/DCM) 0.41 [bromocresol green]

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.25–7.29 (m, 2H), 7.15–7.19 (m, 2H), 3.63 (q, *J* = 7.1 Hz, 1H), 1.42 (d, *J* = 7.1 Hz, 3H), 1.23 (s, 9H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 181.0, 150.3, 136.6, 127.2, 125.6, 44.9, 34.5, 31.3, 18.0;

HRMS (EI⁺): calc. [M]⁺ for C₁₃H₁₈O₂⁺ 206.13013, found 206.13037, Δ = − 0.24 mDa.

Synthesis of 2-(4-fluorophenyl)propanoic acid (**1g**)



Synthesized according to **GP3** using 2-(4-fluorophenyl)acetic acid (3.80 g, 20.0 mmol, 1.00 equiv.) as starting material. After purification with flash column chromatography (MeOH/DCM, 5%) and drying in high vacuo, the title compound was obtained as a yellow oil (2.9 g, 86%).

R_f (silica, 5% MeOH/DCM) 0.64 [bromocresol green]

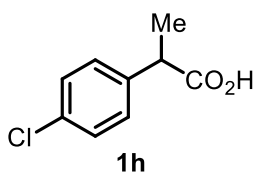
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 11.42 (br. s., 1H), 7.27–7.33 (m, 2H), 7.00–7.05 (m, 2H), 3.70–3.77 (m, 1H), 1.49–1.53 (m, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 181.0, 162.2 (d, *J* = 246 Hz), 131.0 (d, *J* = 8.1 Hz), 129.2 (d, *J* = 7.8 Hz), 115.5 (d, *J* = 21.5 Hz), 44.7, 18.2;

¹⁹F-NMR (376 MHz, CDCl₃, PhCF₃ as internal standard): δ (ppm) –115.31 – (–)115.40 (m)

HRMS (EI⁺): calc. [M]⁺ for C₉H₉FO₂⁺ 168.05811, found 168.05833, Δ = – 0.22 mDa.

Synthesis of 2-(4-chlorophenyl)propanoic acid (**1h**)



Synthesized according to a modified literature procedure over two steps.^[21] 2-(4-chlorophenyl)acetonitrile (3.82 mL, 30.0 mmol, 1.00 equiv.) was dissolved in THF (30 mL) cooled to 0 °C. NaH (60% in mineral oil, 1.32 g, 33.0 mmol, 1.10 equiv.) was added portionwise and the reaction mixture was stirred for 3 h while allowing to warm towards room temperature. After this the mixture was cooled again to 0 °C and MeI (2.05 mL, 33.0 mmol, 1.10 equiv.) was added dropwise. Cooling bath was then removed and the reaction was stirred overnight at room temperature. The reaction was quenched with sat. NH₄Cl (20 mL), diluted with water (200 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL), dried over Mg₂SO₄, filtrated and the solvent was removed under reduced pressure. The so-obtained crude product (3.98 g, 80 %) was used in the following step without further purification.

For the hydrolysis of the nitrile, the afore mentioned crude product (3.98 g, 24.0 mmol, 1.00 equiv.) was dissolved into ethylene glycol (40 mL) and KOH (14 g, 150 mmol, 6 equiv.)

was added. The reaction was then refluxed at 168 °C overnight. After cooling to room temperature water and ethyl acetate were added, the reaction was acidified with 2M HCl (pH=1) and the phases then separated. The aqueous phase was extracted with EtOAc (3×), the combined organic phases dried over Mg₂SO₄, filtered and concentrated under reduced pressure. Purification with flash column chromatography (EtOAc/PE, 30%) followed by removal of the solvents afforded the title compound as a white solid (1.36 g, 31 %; overall yield over two steps 25%).

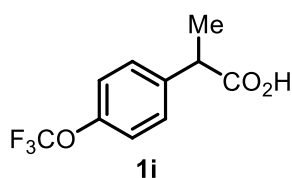
R_f (silica, 5% MeOH/DCM) 0.36 [bromocresol green]

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.26–7.35 (m, 5H), 3.75 (q, *J* = 7.2 Hz, 1H), 1.53 (d, *J* = 7.2 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 179.9, 138.1, 133.3, 129.0, 128.8, 128.6, 127.3, 44.7, 26.2, 18.1;

HRMS (EI⁺): calc. [M]⁺ for C₉H₉ClO₂⁺ 184.02856, found 184.02935, Δ = – 0.79 mDa.

Synthesis of 2-(4-trifluoromethoxy)phenyl)propanoic acid (**1i**)



Synthesized according to **GP3** using 2-(4-trifluoromethoxy)phenyl)acetic acid (780 mg, 3.5 mmol, 1.00 equiv.) as starting material. After purification with flash column chromatography (MeOH/DCM, 5%) and drying in high vacuo, the title compound was obtained as a yellow oil (606 mg, 73%).

R_f (silica, 5% MeOH/DCM) 0.80 [bromocresol green]

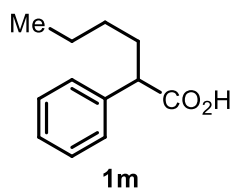
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 11.52 (br. s., 1H), 7.35–7.40 (m, 2H), 7.20 (app. d., *J* = 8.0 Hz, 2H), 3.78 (q, *J* = 7.2 Hz, 1H), 1.54 (d, *J* = 7.2 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 180.8, 148.5, 138.3, 129.1, 121.1, 120.4 (q., *J* = 257 Hz) 44.8, 18.0;

¹⁹F-NMR (376 MHz, CDCl₃, PhCF₃ as internal standard): δ (ppm) – 58.90 (s)

HRMS (EI⁺): calc. [M]⁺ for C₁₀H₉F₃O₂⁺ 234.04983, found 234.04999, Δ = – 0.16 mDa.

Synthesis of 2-phenylhexanoic acid (1m)



Synthesized according to **GP4** using phenylacetic acid (2.0 g, 15.0 mmol, 1.0 equiv.) as limiting reagent and *n*-bromobutane (1.1 equiv.) as electrophilic coupling partner. After purification with flash column chromatography (MeOH/DCM, 2.5%) the title compound was obtained as a yellow oil (2.29 g, 79 %).

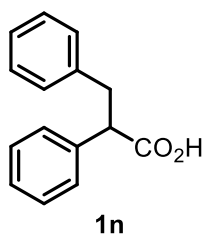
R_f (silica, 5% MeOH/DCM) 0.75 [bromocresol green]

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 11.11 (br. s, 1H), 7.28–7.37 (m, 5H), 3.57 (t, *J* = 7.7 Hz, 1H), 2.06–2.16 (m, 1H), 1.77–1.87 (m, 1H), 1.19–1.41 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 180.4, 138.6, 128.6, 128.1, 127.4, 51.6, 32.8, 29.6, 22.4, 13.8;

HRMS (EI⁺): calc. [M]⁺ for C₁₂H₁₆O₂⁺ 192.11448, found 192.11447, Δ = 0.01 mDa.

Synthesis of 2,3-diphenylpropanoic acid (1n)



Synthesized according to **GP4** using phenylacetic acid (2.0 g, 15.0 mmol, 1.0 equiv.) as limiting reagent and benzyl bromide (1.1 equiv.) as electrophilic coupling partner. After purification with flash column chromatography (MeOH/DCM, 2.5%) the title compound was obtained as a white solid (1.25 g, 37 %).

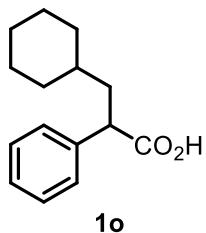
R_f (silica, 5% MeOH/DCM) 0.28 [bromocresol green]

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.10–7.27 (m, 8H), 7.04–7.08 (m, 2H), 3.81 (dd, *J* = 8.7, 7.0 Hz, 1H), 3.36 (dd, *J* = 14.2, 8.4 Hz, 1H), 2.99 (dd, *J* = 14.2, 7.0 Hz, 1H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm)

HRMS (EI⁺): calc. [M]⁺ for C₁₅H₁₄O₂⁺ 226.09883, found 226.09852, Δ = 0.31 mDa.

Synthesis of 3-cyclohexyl-2-phenylpropanoic acid (**1o**)



Synthesized according to **GP4** using phenylacetic acid (2.0 g, 15.0 mmol, 1.0 equiv.) as limiting reagent and (bromomethyl)cyclohexane (1.1 equiv.) as electrophilic coupling partner. After purification with normal phase flash column chromatography (MeOH/DCM, 5 %) on silica followed by a reverse-phase column chromatography (H₂O+0.5% TFA/MeCN, 10%

→ 100%), the title compound was obtained as a white solid (875 mg, 25 %).

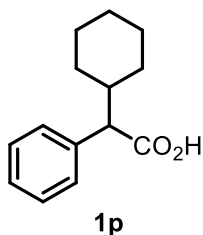
R_f (silica, 5% MeOH/DCM) 0.45 [bromocresol green]

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.24–7.33 (m, 5H), 3.70 (t, *J* = 7.8 Hz, 1H), 1.93–2.02 (m, 1H), 1.71–1.77 (m, 1H), 1.57–1.70 (m, 4H), 1.09–1.22 (m, 4H), 0.84–0.96 (m, 2H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 179.0, 138.8, 128.7, 128.1, 127.4, 48.5, 40.7, 35.1, 33.3, 32.9, 26.5, 26.1, 26.0;

HRMS (EI⁺): calc. [M]⁺ for C₁₅H₂₀O₂⁺ 232.14578, found 232.14632, Δ = − 0.54 mDa.

Synthesis of 2-cyclohexyl-2-phenylacetic acid (1p)



Synthesized according to **GP4** using phenylacetic acid (2.0 g, 15.0 mmol, 1.0 equiv.) as limiting reagent and cyclohexyl bromide (1.1 equiv.) as electrophilic coupling partner. After purification with normal phase flash column chromatography (MeOH/DCM, 5 %) on silica followed by a reverse-phase column chromatography (H₂O+0.5% TFA/MeCN, 10% → 100%), the title compound was obtained as a white solid (1.03 g, 32 %).

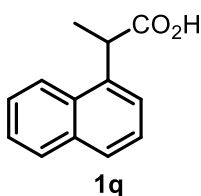
R_f (silica, 5% MeOH/DCM) 0.38 [bromocresol green]

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 10.5 (br. s., 1H), 7.28–7.39 (m, 5H), 3.26 (d, *J* = 10.9 Hz, 1H), 2.05 (qt, *J* = 10.9, 3.3 Hz, 1H), 1.91–1.98 (m, 1H), 1.75–1.82 (m, 1H), 1.60–1.70 (m, 2H), 1.29–1.41 (m, 2H), 1.06–1.24 (m, 3H), 0.73–0.83 (m, 1H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 180.4, 137.3, 128.7, 128.5, 127.4, 58.9, 40.7, 32.0, 30.3, 26.3, 26.0, 25.9;

HRMS (EI⁺): calc. [M]⁺ for C₁₄H₁₈O₂ 218.13013, found 218.13019, Δ = – 0.16 mDa.

Synthesis of 2-(naphthalen-1-yl)propanoic acid (1q)



Synthesized according to **GP3** using 2-(naphthalen-1-yl)acetic acid (3.72 g, 20.0 mmol, 1.00 equiv.) as starting material. After purification with flash column chromatography (MeOH/DCM, 5%) and drying in high-vacuo, the title compound was obtained as an off-white solid (1.09 g, 18%).

R_f (silica, 5% MeOH/DCM) 0.29 [bromocresol green]

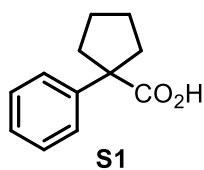
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.10 (d, *J* = 8.4 Hz, 1H), 7.88 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.44–7.58 (m, 4H), 4.55 (q, *J* = 7.2 Hz, 1H), 1.68 (d, *J* = 7.2 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 180.7, 135.9, 133.9, 131.3, 129.0, 128.0, 126.5, 125.7, 125.5, 124.6, 123.0, 41.0, 17.8;

HRMS (EI⁺): calc. [M]⁺ for C₁₃H₁₂O₂ 200.08318, found 200.08357, Δ = – 0.39 mDa.

List of synthesized unsuccessful carboxylic acids

Synthesis of 1-phenylcyclopentane-1-carboxylic acid (S1)



Synthesized in a two-step manner starting from 2-phenylacetonitrile following a literature-reported procedure.^[3] NaH (60% suspension in mineral oil, 1.92 g, 48 mmol, 2.4 equiv.) was suspended into DMF (14 mL) and cooled to 0 °C. A solution of 2-phenylacetonitrile (2.34 g, 20.00 mmol, 1.00 equiv.) in DMF (22 mL) was added dropwise to the suspension and the reaction was stirred for 1 h while allowing to warm towards room temperature. 1,4-Dibromobutane (5.16 g, 24 mmol, 1.2 equiv.) was added dropwise at room temperature, after which the reaction was stirred for 5 hours. The reaction was then quenched with water (10 mL). The mixture was extracted with EtOAc (3 × 15 mL), the combined organic layers washed with brine (20 mL) and eventually dried over MgSO₄. The drying agent was filtered off and the solvent removed under reduced pressure. After purification with flash column chromatography (EtOAc/PE, 10%), the 1-phenylcyclopentane-1-carbonitrile was obtained as a yellow oil (1.03 g, 30%).

For the hydrolysis of the nitrile group into carboxylic acid, the previously obtained 1-phenylcyclopentane-1-carbonitrile (1.03 g, 6.00 mmol, 1.00 equiv.) was dissolved in ethylene glycol (10 mL) and KOH (2.0 g, 36.0 mmol, 6.00 equiv.) was added. The reaction was then refluxed at 168 °C overnight. After cooling to room temperature water and ethyl acetate were added, the reaction was acidified with 2M HCl (pH=1) and the phases then separated. The aqueous phase was extracted with EtOAc (3×), the combined organic phases dried over Mg₂SO₄, filtered and concentrated under reduced pressure. Purification with flash column chromatography (EtOAc/PE, 30%), the 1-phenylcyclopentane-1-carboxylic acid was obtained as a white solid (0.45 g, 39%).

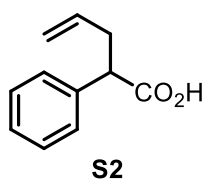
R_f (silica, 5% MeOH/DCM) 0.35 [bromocresol green]

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 11.2 (br. s., 1H), 7.38–7.42 (m, 2H), 7.29–7.34 (m, 2H), 7.22–7.27 (m, 1H), 2.63–2.70 (m, 2H), 1.88–1.97 (m, 2H), 1.71–1.77 (m, 4H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 182.0, 142.8, 128.3, 127.1, 110.0, 58.8, 36.0, 23.6;

HRMS (EI⁺): calc. [M]⁺ for C₁₂H₁₄O₂⁺ 190.09883, found 190.09862, Δ = 0.21 mDa.

Synthesis of 2-phenylpent-4-enoic acid (S2)



Synthesized according to **GP4** using phenylacetic acid (2.0 g, 15.0 mmol, 1.0 equiv.) as limiting reagent and allyl bromide (1.1 equiv.) as electrophilic coupling partner. After purification with flash column chromatography (MeOH/DCM, 2.5%) the title compound was obtained as a white solid (1.44 g, 54 %).

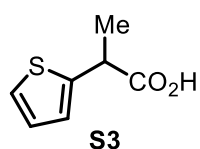
R_f (silica, 5% MeOH/DCM) 0.39 [bromocresol green]

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 11.00 (br.s., 1H), 7.28–7.38 (m, 5H), 5.77 (ddt, *J* = 17.2, 10.3, 6.8 Hz, 1H), 5.13 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.04–5.08 (m, 1H), 3.69 (dd, *J* = 8.8, 7.2 Hz, 1H), 2.83–2.91 (m, 1H), 2.54–2.62 (m, 1H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 179.8, 137.8, 134.9, 128.7, 128.1, 127.6, 117.3, 51.4, 37.1;

HRMS (EI⁺): calc. [M]⁺ for C₁₁H₁₂O₂⁺ 176.08318, found 176.08274, Δ = 0.44 mDa.

Synthesis of 2-(thiophen-2-yl)propanoic acid (S3)



Synthesized according to **GP3** using 2-(thiophen-2-yl)acetic acid (2.84 g, 20.0 mmol, 1.00 equiv.) as starting material. After purification with flash column chromatography (MeOH/DCM, 5%) and drying in high-vacuo, the title compound was obtained as a yellow oil (1.09 g, 18%).

R_f (silica, 5% MeOH/DCM) 0.65 [bromocresol green]

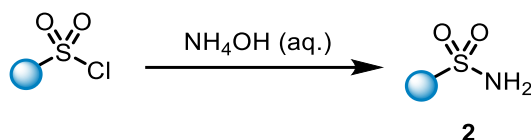
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 9.16 (br. s., 1H), 7.23 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.99–7.01 (m, 1H), 6.97 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.04 (q., *J* = 7.3 Hz, 1H), 1.62 (d, *J* = 7.3 Hz, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 179.7, 142.0, 126.7, 125.2, 124.6, 40.7, 19.1;

HRMS (EI⁺): calc. [M]⁺ for C₇H₈O₂S⁺ 156.02395, found 156.02396, Δ = − 0.01 mDa.

3.8.5 Synthesis of sulfonamide nucleophiles

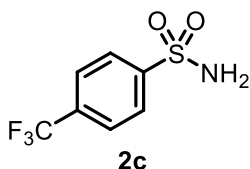
General Procedure for the sulfonamide synthesis from sulfonyl chlorides (GP5)



Typically, the prepared sulfonamides were synthesized as following (see details at each sulfonamide): The respective sulfonyl chloride (1.00 equiv.) was either dissolved directly into the ammonium hydroxide (25 % solution in water) or into the noted organic solvent under ambient conditions. If not used as a solvent, ammonium hydroxide was added, and the reaction was stirred first at room temperature followed by heating up to 100 °C. The reaction was followed with thin-layer chromatography (TLC) and when full conversion of the starting material was indicated, the reaction was cooled down to room temperature and quenched by adding a 1:1 mixture of water and ethyl acetate. The phases were separated and the aqueous phase extracted with EtOAc (3×), and the combined organic phases were washed with brine. The organic phases were then dried over MgSO_4 , the drying agent filtered off and solvent removed under reduced pressure upon which a white solid was obtained. The purity of the crude product was determined with $^1\text{H-NMR}$ spectroscopy and if needed the product was purified by passing through a short silica plug eluting with 1:1 EtOAc/PE. Removal of the solvent then gave the final product.

List of synthesized sulfonamides

Synthesis of 4-trifluoromethylbenzenesulfonamide (2c)



Synthesized according to a modified literature-reported procedure.^[4]

4-Trifluoromethylbenzenesulfonyl chloride (2.46 g, 10.0 mmol, 1.00 equiv.) was dissolved in ammonium hydroxide (25% solution in H₂O, 4 mL) under ambient conditions. The reaction mixture was stirred overnight at room temperature, after which the reaction was quenched by addition of a mixture of water and ethyl acetate (1:1, 10 mL). The phases were separated, aqueous phase extracted with EtOAc (3 × 10 mL) and combined organic layers washed with brine (20 mL). After drying over Mg₂SO₄ the drying agent was filtered off and the solvent removed under reduced pressure. The crude product was purified by a short column (EtOAc/PE, 50%) and after removal of solvent the title compound was obtained as a white solid (1.85 g, 82 %).

R_f (silica, 50% EtOAc/PE) 0.73 [potassium permanganate];

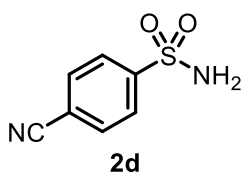
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.06 (d, *J* = 8.3 Hz, 2H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.64 (s, 2H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 148.3, 132.18 (q, *J* = 32.2 Hz), 127.1, 126.7 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 274.0 Hz);

¹⁹F-NMR (376 MHz, CDCl₃, PhCF₃ as internal standard): δ (ppm) – 63.39 (s)

HRMS (ESI⁺): calc. [M+H]⁺ for C₇H₇F₃NO₂S⁺ 226.0150, found 226.0145, Δ = 0.5 mDa.

Synthesis of 4-cyanobenzenesulfonamide (2d)



Synthesized according to a modified literature procedure.^[5] 4-cyanobenzenesulfonyl chloride (1.5 g, 7.4 mmol, 1.0 equiv.) was dissolved in 25% ammonium hydroxide (10 mL) at room temperature. The mixture was then heated up and refluxed at 100 °C for 1 h. After cooling

back to room temperature, the formed white precipitate was filtered, and the crude product

was washed with water (3×10 mL). The residual water was removed via lyophilization after which the title compound was obtained as an off-white powder (1.0 g, 74%).

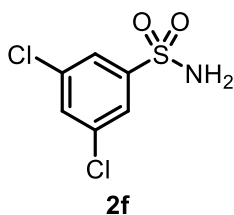
R_f (silica, 50% EtOAc/PE) 0.51 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.07–8.10 (m, 2H), 7.97–8.00 (m, 2H), 7.59 (br. s., 2H), 3.43 (s, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 148.4, 133.7, 126.9, 118.3, 114.8;

HRMS (ESI+): calc. $[M+H]^+$ for C₇H₇N₂O₂S⁺ 183.0228, found 183.0221, Δ = 0.7 mDa.

Synthesis of 3,5-dichlorobenzenesulfonamide (2f)



Synthesized according to a literature-reported procedure.^[6] 3,5-Dichlorobenzenesulfonyl chloride (1.47 g, 6.00 mmol, 1.00 equiv.) was dissolved in ammonium hydroxide (25% solution in H₂O, 16 mL) under ambient conditions. The reaction was stirred at room temperature for 3 h, after which it was quenched by addition of a mixture of water and ethyl acetate (1:1, 12 mL). The formed layers were separated, the aqueous layer extracted with EtOAc (3×10 mL) and combined organic layers washed with brine (20 mL). After drying over Mg₂SO₄ the drying agent was filtered off and the solvent removed under reduced pressure. The crude product was purified by a short column (EtOAc/PE, 50%) and after removal of solvent the title compound was obtained as a white solid (305 mg, 23 %).

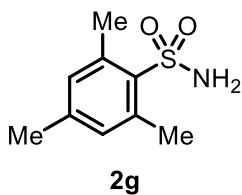
R_f (silica, 50% EtOAc/PE) 0.83 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.92–7.94 (m, 1H), 7.80 (d, J = 1.9 Hz, 2H), 7.65 (br. s., 2H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 147.5, 135.2, 131.9, 124.8;

HRMS (ESI+): calc. $[M+H]^+$ for C₆H₆Cl₂NO₂S⁺ 225.9496, found 225.9491, Δ = 0.5 mDa.

Synthesis of 2,4,6-trimethylbenzenesulfonamide (2g)



Synthesized according to a modified literature-reported procedure.^[4] 2,4,6-Trimethoxybenzenesulfonyl chloride (1.09 g, 5.00 mmol, 1.00 equiv.) was dissolved in ammonium hydroxide (25% solution in H₂O, 25 mL) at 0 °C. After 15 minutes the cooling bath was removed, and the reaction was stirred for 4 hours at room temperature. The reaction was quenched by addition of a mixture of water and ethyl acetate (1:1, 10 mL) and the formed layers were separated. The aqueous layer was acidified with 2M HCl (pH=1) after which it was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over Mg₂SO₄, the drying agent filtered off and the solvent removed under reduced pressure. The crude product was purified by passing through a short silica plug eluting with 50% EtOAc/PE. After evaporation of the solvent the product was obtained as an off-white solid (659 mg, 66 %).

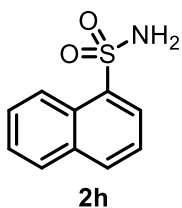
R_f (silica, 50% EtOAc/PE) 0.75 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.17 (br. s., 2H), 6.99 (s, 3H), 2.55 (s, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 141.0, 138.7, 137.6, 131.8, 23.0, 20.8;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₉H₁₃NO₂SNa⁺ 222.0565, found 222.0560, Δ = 0.5 mDa.

Synthesis of naphthalene-1-sulfonamide (2h)



Synthesized according to a literature-known procedure.^[7] Naphthalene-1-sulfonyl chloride (904 mg, 4.00 mmol, 1.00 equiv.) was dissolved in THF (13 mL). Ammonium hydroxide (25% solution in H₂O, 8.7 mL) was added slowly to the mixture under ambient conditions, after which the reaction was stirred for three hours at room temperature. THF was then removed under reduced pressure, and the crude was dissolved in a mixture of EtOAc and H₂O. The layers were then separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Mg₂SO₄, the drying agent filtered off and the solvent removed under reduced

pressure. The formed pale solid was washed with hexane and Et₂O and after drying under high vacuo the title compound was obtained as a white solid.

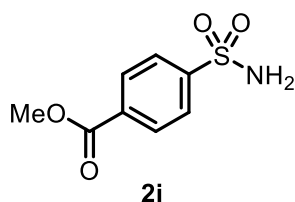
R_f (silica, 50% EtOAc/PE) 0.58 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.44 (d, *J* = 1.5 Hz, 2H), 8.11–8.16 (m, 2H), 8.03–8.06 (m, 1H), 7.90 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.65–7.72 (m, 2H), 7.46 (br. s., 2H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 141.7, 134.3, 132.2, 129.5 (2C), 128.9, 128.3, 127.9, 126.2, 122.6;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₀H₉N₂O₂SNa⁺ 244.0282, found 244.0245, Δ = 3.7 mDa.

Synthesis of methyl 4-sulfamoylbenzoate (**2i**)



Synthesized according to a modified literature-reported procedure.^[8] 4-Sulfamoylbenzoic acid (2.00 g, 9.94 mmol, 1.00 equiv.) was dissolved in MeOH (18 mL) followed by the addition of conc. H₂SO₄ (0.5 mL). The reaction was then refluxed for 7 h, after which

it was cooled down to room temperature. Methanol was removed under reduced pressure, and the residue dissolved in CHCl₃. The organic layer was then washed with H₂O, aq. sat. Na₂CO₃ solution and finally again with H₂O. The organic phase was dried over Mg₂SO₄, the drying agent filtered off and solvent removed under reduced pressure. Purification with flash column chromatography (EtOAc/PE, 20% → 80%) gave the title compound as a white solid (1.6 g, 75%).

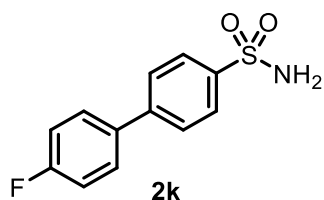
R_f (silica, 50% EtOAc/PE) 0.54 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.12–8.15 (m, 2H), 7.94–7.98 (m, 2H), 7.56 (s, 2H), 3.89 (s, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 165.7, 148.5, 132.8, 130.3, 126.5, 53.0;

HRMS (ESI⁺): calc. [M+H]⁺ for C₈H₁₀NO₄S⁺ 216.0331, found 216.0324, Δ = 0.7 mDa.

Synthesis of 4'-fluoro-[1,1'-biphenyl]-4-sulfonamide (2k)



Synthesized according to a modified patented procedure.^[9] 4'-fluoro-[1,1'-biphenyl]-4-sulfonyl chloride (1.0 g, 3.7 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (10 mL) at room temperature. Ammonium hydroxide (25% solution in H₂O, 5.8 mL, 37.0 mmol, 10.0 equiv.) was added and the reaction was stirred for 1 h under ambient conditions. The reaction was quenched by adding a mixture of water and hexane (1:1, 10 mL) followed by solid NaCl. The mixture was further stirred for 30 minutes, after which the formed white precipitate was filtered and the washed with H₂O (3 × 10 mL). The residual water was then removed via lyophilization after which the title compound was obtained as an off-white solid (678 mg, 73%).

R_f (silica, 50% EtOAc/PE) 0.63 [potassium permanganate];

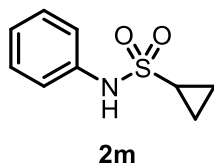
¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.84–7.93 (m, 4H), 7.77–7.82 (m, 2H), 7.42 (br. s., 2H), 7.32–7.38 (m, 2H),

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 162.9 (d, *J* = 247 Hz), 143.1 (d, *J* = 64 Hz), 135.6 (d, *J* = 3.1 Hz), 129.7, 129.6, 127.6, 126.8, 116.4 (d, *J* = 21.2 Hz);

¹⁹F-NMR (376 MHz, CDCl₃, PhCF₃ as internal standard): δ (ppm) –116.71 – (–)116.79 (m)

HRMS (EI+): (ESI+): calc. [M+Na]⁺ for C₁₂H₁₀FNO₂SN⁺ 274.0314, found 274.0310, Δ = 0.4 mDa.

Synthesis of *N*-phenylcyclopropanesulfonamide (2m)



Synthesized according to a modified literature procedure.^[10] Cyclopropanesulfonyl chloride (1.0 mL, 9.90 mmol, 1.0 equiv.) was dissolved to a mixture of pyridine (2 mL) and DCM (2 mL). Aniline (0.9 mL, 9.90 mmol, 1.0 equiv.) was added to the mixture under ambient conditions, after which the reaction was heated to reflux at 50 °C overnight. After cooling down to room temperature, the mixture was diluted with Et₂O (20 mL) and the organic layer was washed with water (2 × 20 mL) and brine (20 mL).

The organic layer was dried over MgSO₄, the drying agent filtered off and the organic layer concentrated under reduced pressure. The crude product was purified with flash column chromatography (EtOAc/PE) and after removal of solvents the title compound was obtained as a white solid.

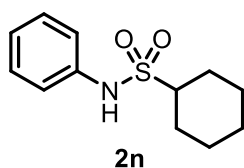
R_f (silica, 50% EtOAc/PE) 0.87 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.32–7.38 (m, 2H), 7.26–7.30 (m, 2H), 7.17–7.22 (m, 1H), 6.77 (br. s., 1H), 2.46–2.54 (m, 1H), 1.15–1.21 (m, 2H), 0.93–0.99 (m, 2H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 136.8, 129.5, 125.5, 121.8, 29.8, 5.61;

HRMS (ESI⁺): calc. [M+H]⁺ for C₉H₁₂NO₂S⁺ 198.0589, found 198.0583, Δ = 0.6 mDa.

Synthesis of *N*-phenylcyclopentanesulfonamide (**2n**)



Synthesized according to a modified literature procedure.^[10] Cyclohexanesulfonyl chloride (1.5 g, 8.20 mmol, 1.0 equiv.) was dissolved to a mixture of pyridine (2 mL) and DCM (2 mL). Aniline (0.84 mL, 9.20 mmol, 1.1 equiv.) was added to the mixture under ambient conditions, after which the reaction was heated to reflux at 50 °C overnight. After cooling down to room temperature, the mixture was diluted with Et₂O (20 mL) and the organic layer was washed with water (2 × 20 mL) and brine (20 mL). The organic layer was dried over MgSO₄, the drying agent filtered off and the organic layer concentrated under reduced pressure. The crude product was purified with flash column chromatography (EtOAc/PE) and after removal of solvents the title compound was obtained as a pale yellow solid (1.51 g, 77 %).

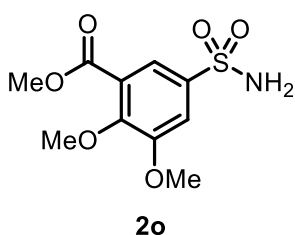
R_f (silica, 50% EtOAc/PE) 0.74 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.32–7.37 (m, 2H), 7.25–7.29 (m, 1H), 7.11–7.18 (m, 2H), 3.04 (tt, *J* = 12.1, 3.5 Hz, 1H), 2.19 (d, *J* = 13.0 Hz, 2H), 1.84–1.91 (m, 2H), 1.54–1.70 (m, 3H), 1.14–1.29 (m, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 137.4, 129.6, 124.6, 120.0, 60.4, 26.3, 25.1, 25.0;

HRMS (ESI⁺): calc. [M+Na]⁺ for C₁₂H₁₇NO₂SNa 262.0878, found 262.0874, Δ = 0.4 mDa.

Synthesis of methyl 2,3-dimethoxy-5-sulfamoylbenzoate (2o)



Synthesized according to a literature-reported procedure.^[8] 5-(Aminosulfonyl)-2,3-dimethoxybenzoic acid (5.1 g, 20 mmol, 1.00 equiv.) MeOH (15 mL) followed by the addition of conc. H₂SO₄ (0.3 mL). The reaction was then refluxed for 7 h, after which it was cooled down to room temperature. Methanol was removed under

reduced pressure, and the residue dissolved in CHCl₃. The organic layer was then washed with H₂O, aq. sat. Na₂CO₃ solution and finally again with H₂O. The organic phase was dried over Mg₂SO₄, the drying agent filtered off and solvent removed under reduced pressure. Recrystallization from a mixture of MeOH and H₂O yielded the final product as a white solid (1.58 g, 29% yield over three steps).

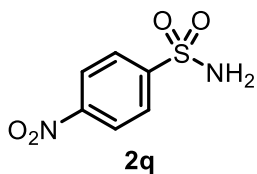
R_f (silica, 50% EtOAc/PE) 0.36 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.66 (d, *J* = 16.6, 2.2 Hz, 2H), 7.42 (br. s., 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 165.5, 153.7, 150.9, 140.1, 126.1, 119.3, 113.3, 61.7, 56.9, 53.0;

HRMS (ESI⁺): calc. [M+H]⁺ for C₁₀H₁₄NO₆S⁺ 276.0542, found 276.0535, Δ = 0.7 mDa.

Synthesis of 4-nitrobenzenesulfonamide (2q)



Synthesized according to a modified literature-reported procedure.^[4] 4-Nitrobenzenesulfonyl chloride (1.04 g, 5.00 mmol, 1.00 equiv.) was dissolved in ammonium hydroxide (25% solution in H₂O, 25 mL) at

0 °C. After 15 minutes the cooling bath was removed, and the reaction was stirred for 4 hours at room temperature. The reaction was quenched by addition of a mixture of water and ethyl acetate (1:1, 10 mL) and the formed layers were separated. The aqueous layer was acidified with 2M HCl (pH=1) after which it was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over Mg₂SO₄, the drying agent filtered off and the solvent removed under reduced pressure. The formed white crude product (which was not adequately pure based on ¹H NMR analysis) was then passed through a short silica plug (EtOAc/PE, 50%) to remove the formed sulfonic acid. After evaporation of the solvent the product was obtained as a white solid (315 mg, 31 %).

R_f (silica, 50% EtOAc/PE) 0.60 [potassium permanganate];

¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.39–8.43 (m, 2H), 8.05–8.09 (m, 2H), 7.73 (br. s., 2H);

¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 149.9, 149.7, 127.7, 124.9;

HRMS (ESI+): calc. [M+H]⁺ for C₆H₇N₂O₄S⁺ 203.0127, found 203.0120, Δ = 0.7 mDa.

3.8.6 Mechanistic studies

3.8.7 UV-vis measurements

Uv-vis in Acetonitrile

All UV-vis measurements in MeCN were carried out in a 0.1 cm × 1.0 cm quartz cuvette with 0.1 cm light path and an internal volume of about 0.2 mL. The spectra were recorded with Agilent Cary 4000 UV-vis spectrophotometer scanning the spectral window from 900 nm to 200 nm using 11 nm data intervals. The temperature was hold constant at 25.6 °C during the measurements with water-cooling running through the probe chamber. The samples were prepared as following: Bi(OTf)₃ (13.0 mg, 0.2 mmol) was set under an inert atmosphere through evacuation and back-filling with N₂ (3×). Dry MeCN (1 mL) was added, and the formed stock solution was shaken to ensure even distribution of components. Then, 0.25 mL of this stock solution was transferred to another vial under N₂, and the vial was filled up to a final volume of 1.0 mL with dry MeCN. 0.2 mL from the final solution was then transferred to the afore described quartz cuvette for measurements. With respect to the other components, 2-phenylpropanoic acid (2.75 µL, 0.05 mmol) or 4-methylsulfonamide (3.0 mg, 0.05 mmol) were both dissolved into dry MeCN (1 mL) in separate vials under N₂ to form the samples of appropriate concentrations. Other components, KHCO₃ (5 mg) and H₂O (5 µL), were then added stepwise to the 1 mL sample volumes, shaken, and 0.2 mL transferred again *via* syringe to the cuvette. For the measurement of the complex, a stock solution containing 0.2 mmol of Bi(OTf)₃, 2-phenylpropanoic acid **1a** and 4-methylsulfonamide **2a** in MeCN (1 mL) was first formed followed by 1/4 dilution as described for the pure bismuth triflate. Background spectrum of pure MeCN was measured first and subtracted from other spectra.

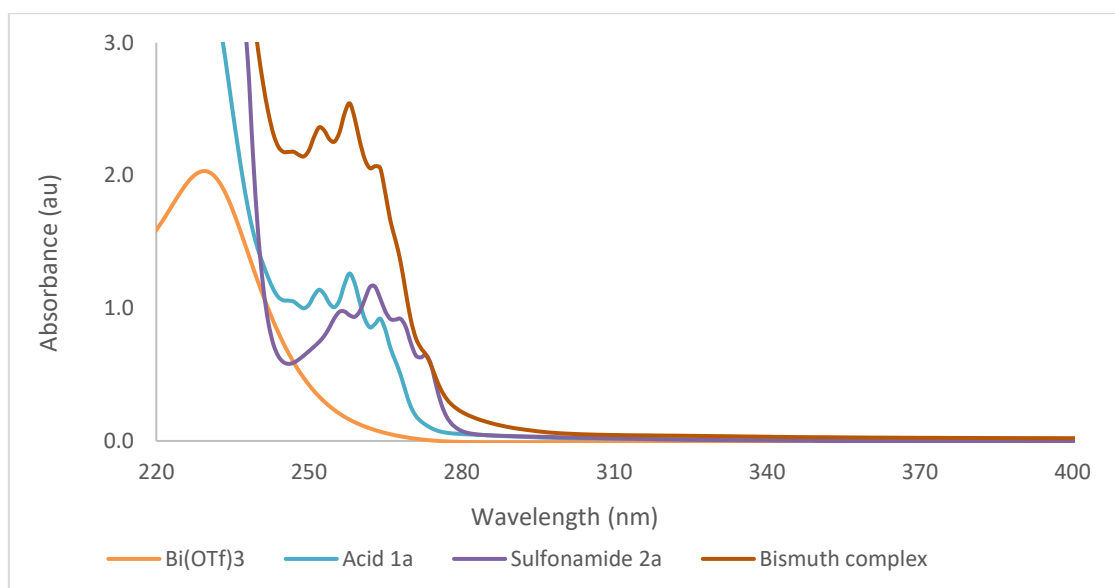


Figure 3.7: UV-vis spectrum of the reaction components: $\text{Bi}(\text{OTf})_3$ as a gray dotted line, 2-phenylpropanoic acid (**1a**) as an orange line, 4-methylphenylsulfonamide (**2a**) as a blue line and the combination of the above as a yellow line. All components measured in 0.05 mmol dissolved in 0.5 mL of MeCN. Samples of acid **1a**, sulfonamide **2a** and complex also containing KHCO_3 (5 mg) as a base and H_2O (5 μL).

Due to the well-soluble nature of $\text{Bi}(\text{OTf})_3$ and other reaction components in MeCN, relatively concentrated samples could be prepared. It should be noted that polar protic solvents, such as MeCN, are known to coordinate to metal centers, and therefore the existence of acetonitrile ligands in the measured bismuth compounds cannot be ruled out. However, to enhance the coordination of the desired ligands (carboxylic acids and sulfonamides), concentrated solutions were prepared for the UV-vis studies. As can be seen from Figure 3.7, $\text{Bi}(\text{OTf})_3$ has its broad absorption maximum around 230 nm and tails until 280 nm. The 2-phenylpropanoic acid (**1a**) and 4-methylphenylsulfonamide (**2a**) both have a more complex absorption spectra centered around 260 nm and tailing towards 300 nm. When $\text{Bi}(\text{OTf})_3$ is added to the mixture containing both components, a significant enhancement in the absorbance is observed around 260 nm, with the absorption of the complex tailing to longer wavelengths than that of either components alone.

Uv-vis in DCM

To obtain a better representation of the species present in the reaction mixtures, we changed the solvent to DCM. Unlike in MeCN, the bismuth species have only a limited solubility in the medium. For this reason, a notably more diluted solutions were measured combined with an increased light path length. For the measurements in DCM, a 1.0 cm × 1.0 cm quartz cuvette was utilized. Stock solutions of Bi(OTf)₃, carboxylic acid **1a** and sulfonamide **2a** were all prepared separately in 0.1 M concentration in DCM, followed by dilution with DCM to the final concentration of 0.002 M. The bismuth complex was prepared by mixing all three components in a 1:1:1 ratio (0.1 M each in DCM) followed by dilution to 0.002 M. The spectra were recorded with Agilent Cary 4000 UV-vis spectrophotometer scanning the spectral window from 900 nm to 200 nm using 11 nm data intervals. The temperature was hold constant at 25.6 °C during the measurements with water-cooling running through the probe chamber. The results can be seen in Figure 3.8.

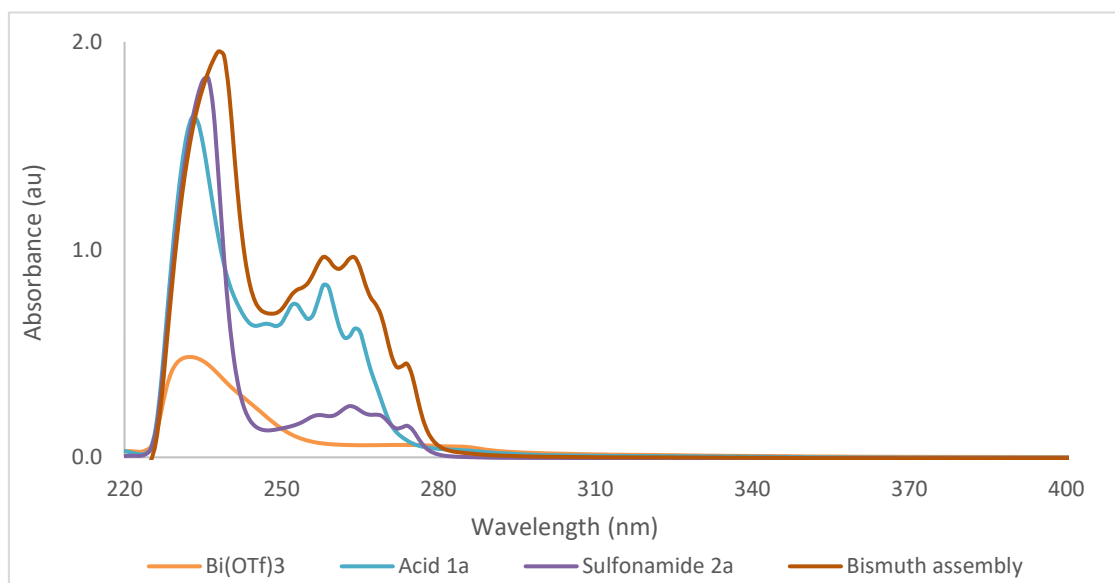


Figure 3.8: UV-vis spectrum of the reaction components in DCM: Bi(OTf)₃ as a gray dotted line, 2-phenylpropanoic acid (**1a**) as an orange line, 4-methylphenylsulfonamide (**2a**) as a blue line and the combination of the above as a yellow line. All components measured in 0.02 mmol concentrations.

As seen from Figure 3.8, the absorption spectra of each component in DCM closely resembles the respective spectra measured in MeCN both in the terms of the shape of the absorption band as well as the location of the absorption maxima. Here as well the addition of $\text{Bi}(\text{OTf})_3$ to the mixture of acid **1a** and sulfonamide **2a** causes a significant enhancement of absorption at the area covering the absorption maximum. In this case, however, the exact form of the absorption band slightly differs from that seen in MeCN perhaps due to the lack of the solvent ligands in DCM.

To gain a more precise look to the absorption spectrum around the irradiation wavelength (365 nm), we decided to measure the previously formed bismuth complex (1:1:1 of acid **1a**, sulfonamide **2a** and $\text{Bi}(\text{OTf})_3$, 0.002 M for each in DCM) with a 4 cm $\times$ 2 cm quartz cuvette (pathlength 4 cm, sample volume 6 mL). The measurement was carried out with Agilent Cary 60 UV-vis spectrophotometer at 25 °C in the scanning window from 1100 nm to 190 nm using the data interval of 0.5 nm. The result of this measurement can be seen in Figure 3.9.

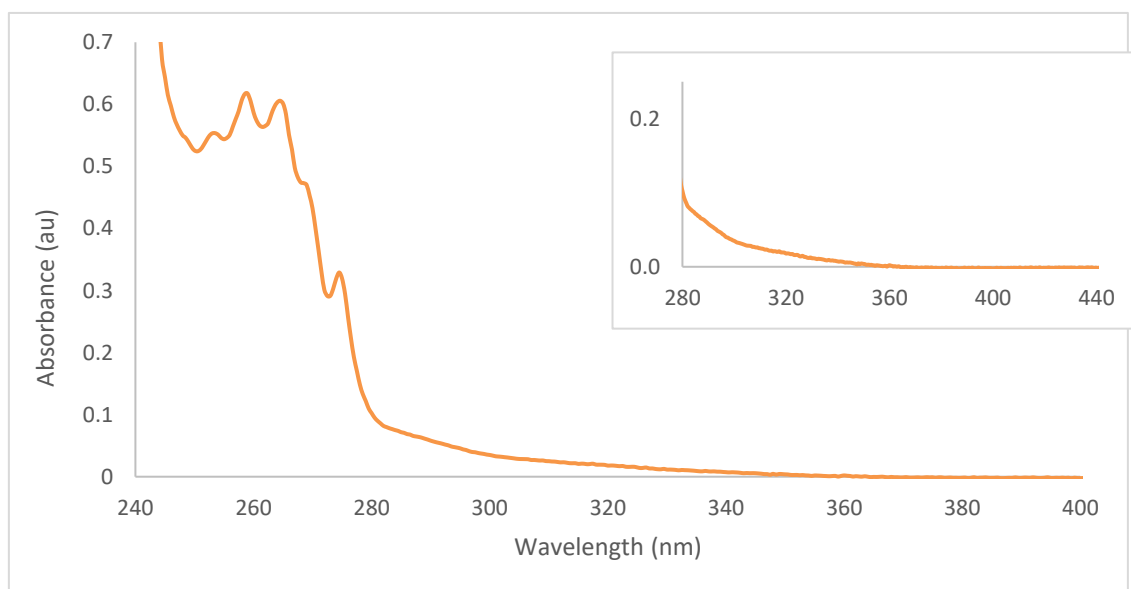


Figure 3.9: UV-vis spectrum of the bismuth complex containing $\text{Bi}(\text{OTf})_3$, 2-phenylpropanoic acid (**1a**) and 4-methylphenylsulfonamide (**2a**) as 0.02 mmol

concentration each in DCM. To gain a better look to the absorbance around the irradiation wavelength (365 nm), a 4.0 cm quartz cuvette was utilized.

Comparing the UV-vis spectrum obtained using the 4 cm pathlength to the one obtained with 1 cm pathlength gratifyingly shows significantly better-defined spectral region above 300 nm. Importantly, slight tailing of the UV-vis absorption of the complex can be easily observed starting around 360 nm which intersects the emission spectrum of the LEDs utilized (see section 1.1). Moreover, the low absorption coefficient around the irradiation wavelength in part accounts for the relatively high intensity needed for the product formation (Table 3.7). Although the exact intensity of the absorption around 365 nm is naturally dependent on the concentration of the complex, the UV-vis spectrum above demonstrates clearly how the absorption tails to the critical regions.

3.8.8 Kinetic studies

For the kinetic studies, one reaction vial was prepared as following: ($\pm$)-2-phenylpropanoic acid (15.1 mg, 0.10 mmol, 1.0 equiv.), KHCO_3 (30 mg, 0.30 mmol, 3.0 equiv.) and *p*-toluenesulfonamide (59 mg, 0.35 mmol, 3.5 equiv.) were weighed into a 5 mL crimp cap vial. The vial was then sealed and set under an inert atmosphere by evacuating and backfilling with pre-dried N_2 ($\times 3$). Anhydrous DCM (1 mL) was added, and the reaction mixture was degassed by freeze-pump thaw ($\times 3$). Then reaction was then irradiated with 365 nm (1.5 W) LEDs.

To obtaining each data point, a 25 μL sample was drawn from the reaction mixture, to which 250 μL of the stock solution containing internal standard was added (0.01 M mesitylene in DCM). Finally, the samples were analyzed by GC-FID and the yield were calculated against the calibration curve of the product and mesitylene.

Reaction kinetics

To obtain an overall picture of the reaction kinetics, the rate of the reaction was first monitored for the first four hours, the result of which mostly resembles a logarithmic reaction kinetic (Figure 3.10). A notable feature of this reaction is indeed its rapid initial kinetics, which results in a 28 % yield during the first hour of the reaction. It thus seems like the turbidness of the reaction mixture does not prevent the adequate amounts of light from entering the reaction mixture during the first hour of the reaction time.

Time (min)	Yield (%)
0	0
2.5	3.4
5	5.4
10	9.5
15	13
20	16
30	20
40	23
60	28
120	37
240	54

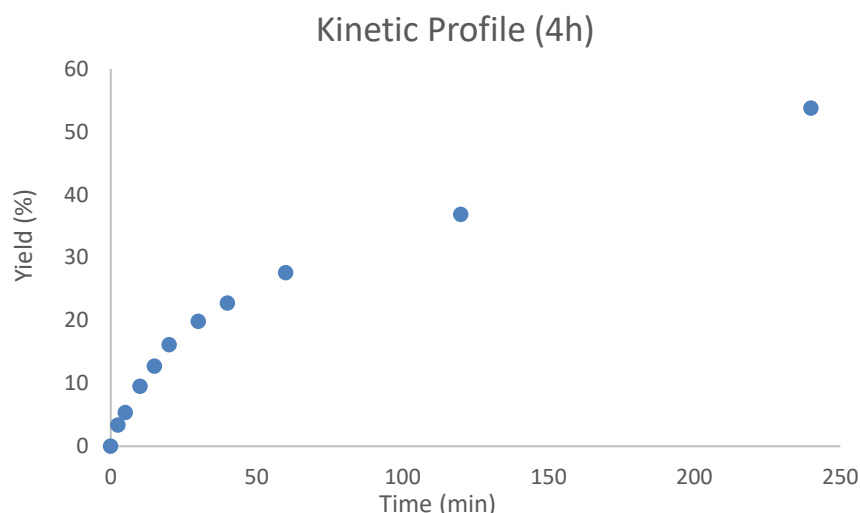
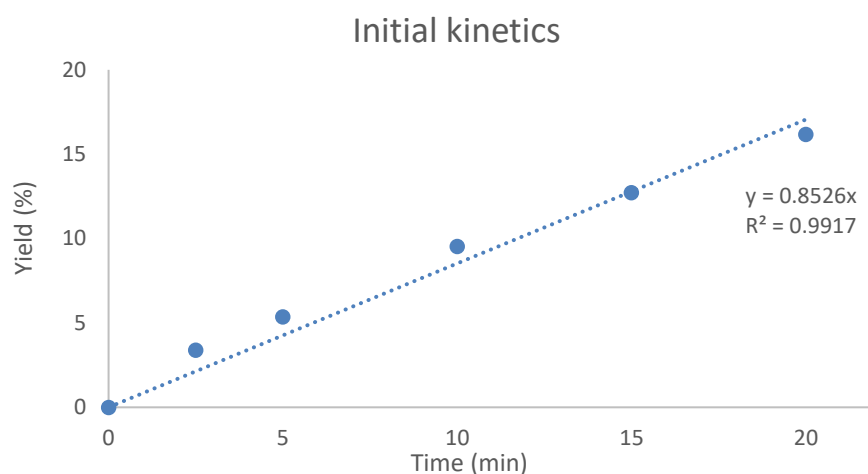


Figure 3.10: Kinetic profile of the reaction during the first four hours.

As a part of the observation of the fast initial kinetic is also the significant reduction of the product forming rate after the first hour. This decrease in the productive reaction can in to at least some extend be hypothesized to come from the formation of fully reduced $\text{Bi}^{(0)}$ (also referred to as “bismuth black”) which results into a significant darkening of the reaction mixture therefore diminishing the light penetration (see section 1.1.4).

Initial kinetics

To gain a deeper look to the initial kinetics of the reaction, the rate measurement was repeated during the first twenty minutes (Figure 3.11). During this time period the reaction could be said to follow a linear reaction rate although slight features of logarithmic rate could also be argued to appear. The single points obtained from each time point could also be joined with a direct line with very high experimental correlation coefficient.



Time (min)	Yield (%)
0	0
2.5	3.4
5	5.4
10	9.5
15	13
20	16

Figure 3.11: Initial reaction kinetics.

Strikingly, small amounts of product can be observed already after 2.5 minutes of irradiation time implying that the reaction starts (almost) immediately when the light is turned on. Moreover, the linear kinetic is often expected in the cases where the product is directly formed from the reactants without the need to build up any intermediates or to activate a pre-catalytic species. It is worth mentioning that a linear kinetics was also observed in our previous work with the BiCl_3 -catalyzed Giese-coupling reactions, which further supports the use of simple bismuth salts as efficient catalytic species requiring light as the sole source of activation.

3.8.9 Light on/off experiment

Finally, we concluded the kinetic experiments by carrying out a light on/off- experiment. Due to the turbid nature of our initial reaction mixture, we considered quantum yield measurement to give results that would be uncertain or difficult to interpret. Therefore, we decided to monitor the product formation by irradiating the reaction mixture 10 or 20 minutes followed by a ten-minute dark period. Results of this experiment can be seen in Figure 3.12.

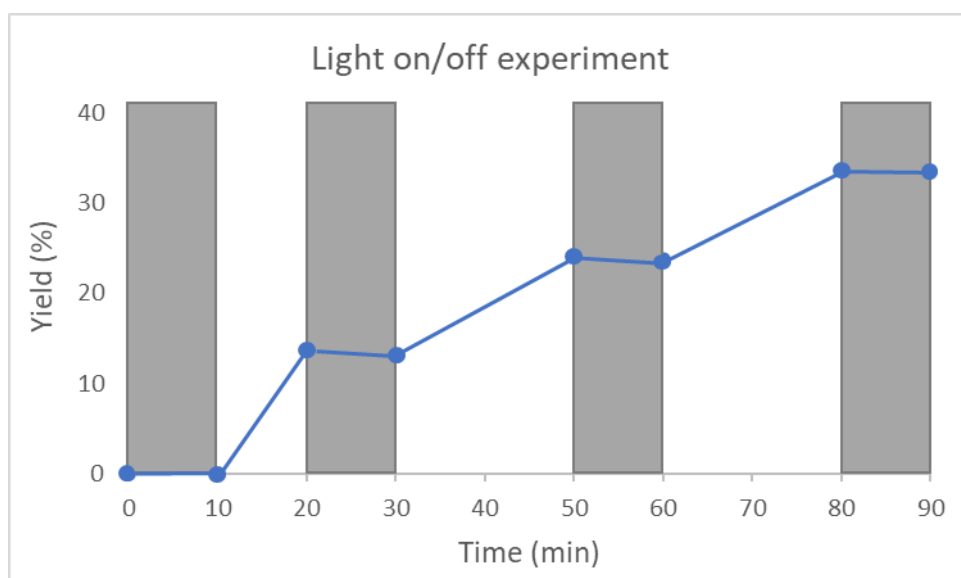


Figure 3.12: Light on/off experiment measuring the rate of product formation.

As can be seen from Figure 3.12, the reaction clearly progresses only when the light is on. This in turn implies that the reaction is dependent on continuous irradiation and a radical chain, if present at all, is short and does not serve as the main product-forming mechanism. Gratifyingly, the formed product also appears to be rather stable during the dark phases and no significant degradation was observed when the light was off.

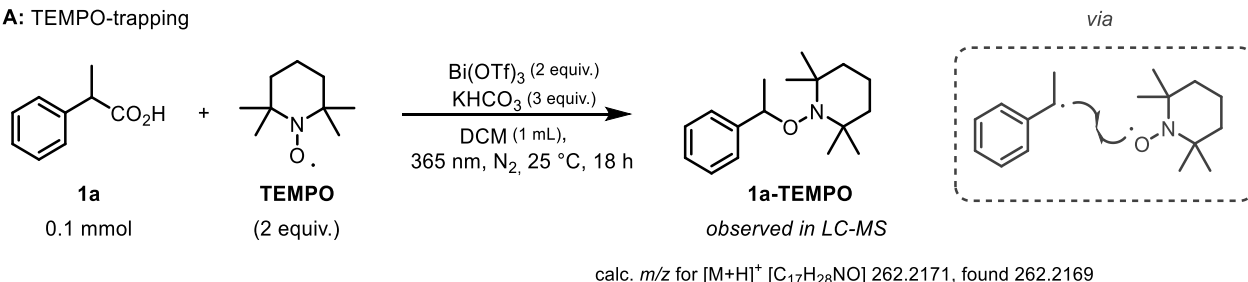
3.8.10 Experiments towards later elementary steps

3.8.11 TEMPO trapping studies

After establishing the nature of the light-harvesting species, we next turned our attention towards identification of some of the reaction intermediates. We started by carrying out a TEMPO-trapping experiment, which was set up as following: 2-phenylpropanoic acid (15.0 mg, 0.10 mmol, 1.00 equiv.), Bi(OTf)₃ (130 mg, 0.20 mmol, 2.00 equiv.), KHCO₃ (30.0 mg, 0.30 mmol, 3.00 equiv) and TEMPO (32.0 mg, 0.2 mmol, 2.00 equiv.) were weighed into a 5 mL crimp-cap vial equipped with a stirring bar. The vial was then sealed and set under an inert atmosphere by evacuating and back-filling with N₂ for three times. DCM (1 mL) was added *via* syringe against a flow of N₂, and the reaction mixture was further degassed by freeze-pump thaw (3×). The reaction was then irradiated with 365 nm LEDs for 18 hours while keeping the temperature at 25 °C by water-cooling.

After completion of the reaction, the solids were removed by filtering with a syringe filter. The so-obtained crude reaction mixture was then analyzed by LC-MS.

A: TEMPO-trapping

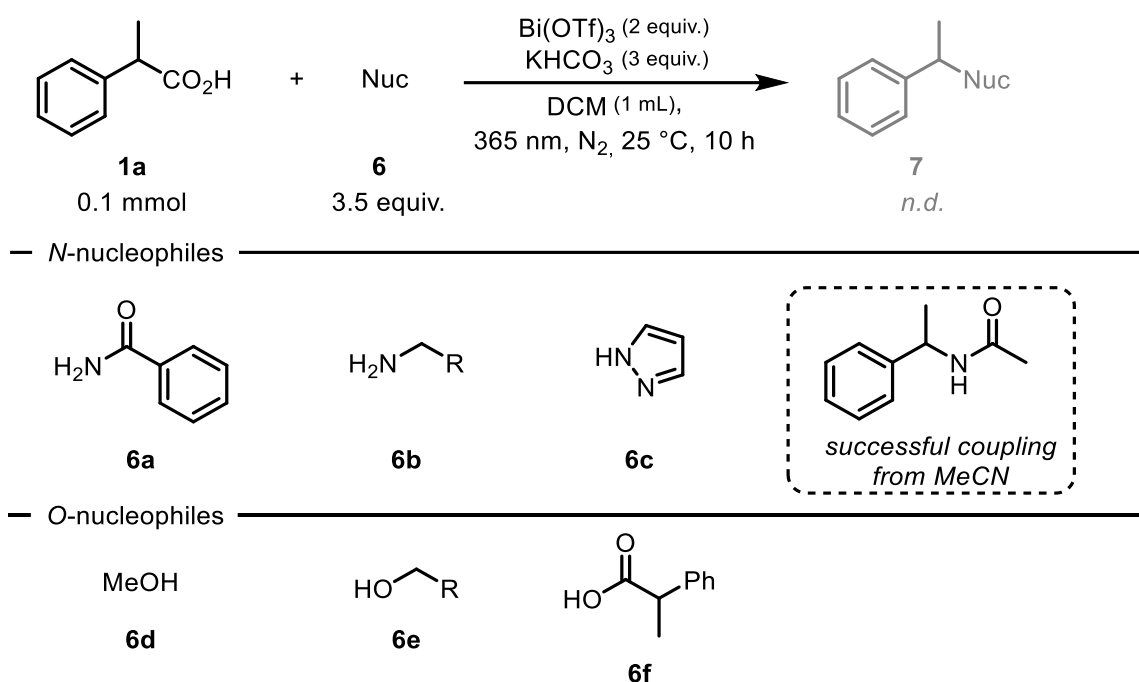


Scheme 3.5: TEMPO-trapping experiment.

As can be seen from Scheme 3.5, the TEMPO-trapping study was able to identify the expected benzylic radical formed from the radical decarboxylation. The found *m/z* of this trapped intermediate was in good agreement with the expected mass of the [M+H]⁺ ion. Importantly, this was the only product formed during the reaction, and no traces of the radical homocoupling or Kharasch products were observed.

3.8.12 Studies towards the presence/absence of benzylic carbocations

To gather indirect evidence on the presence or absence of a benzylic carbocation, we decided to turn towards testing different nucleophiles in our reaction. We rationalized that in the case of a “free” carbocation intermediate, nucleophilic coupling with various *N*- and *O*-centred nucleophiles should be feasible. For this, we set up the reactions according to the **GP1** but instead of 4-methylbenzenesulfonamide we tested a benzylamide (**6a**), selected primary amines **6b** and pyrazole **6c** as *N*-centred nucleophiles. For the *O*-centred nucleophiles, different alcohols were tried (**6d–6e**) together with the homocoupling to the 2-phenylpropanoic acid (**6f**) to form the benzylic ester (Kharasch product). The results are summarized in Scheme 3.6.



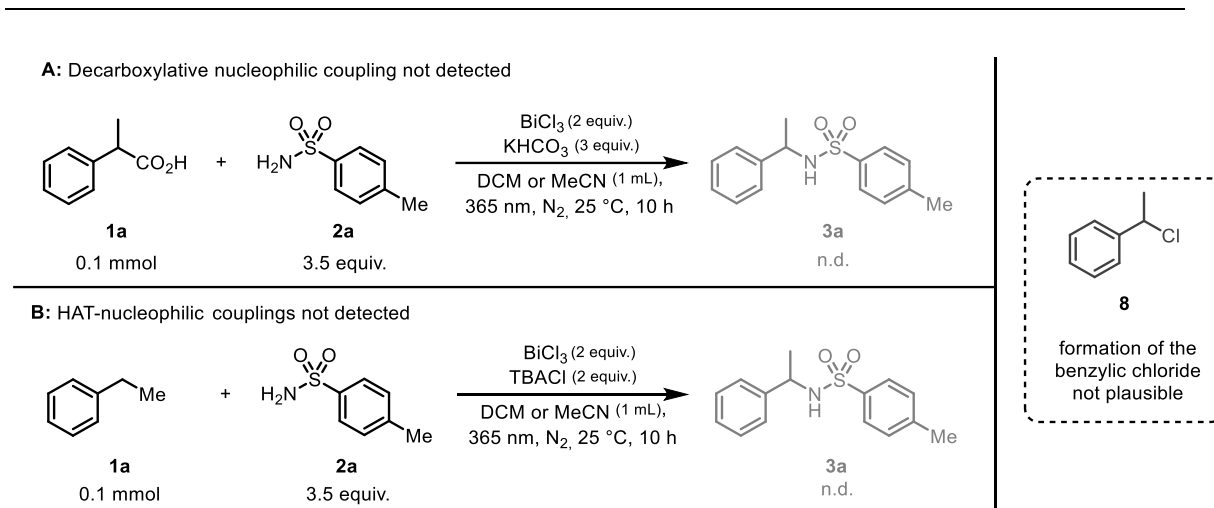
Scheme 3.6: List of unsuccessful nucleophiles.

Upon changing the sulfonamide nucleophiles other *N*-centred nucleophiles we observed clear suppression on the LMCT reactivity. Similar results were also obtained with alcohols as *O*-centred nucleophiles. While this hampering of reactivity might stem from numerous

reasons, we believe that factors worth considering include: 1) full saturation of the bismuth centre by tight coordination of alternative nucleophiles, thus leaving no room for the coordination of carboxylic acids, 2) diminishing from the UV-vis absorption properties *via* changing the ligands, and 3) the inability of other nucleophiles to undergo C–N coupling because no carbocation intermediates are present and the reductive elimination strongly favours the sulfonamides. While many of the afore-mentioned factors might explain the lack of reactivity with other nucleophiles, we were also unable to observe the Kharasch product stemming from nucleophilic attack of the 2-phenylpropanoic acid – an event likely to happen in the absence of other reactants. This, together with the absence of desaturation products formed by *alpha* deprotonation of the carbocation, indicate that a carbocationic intermediate is most likely not present. It also should be noted that successful CN coupling was observed with MeCN which also can coordinate to bismuth although in a reversible manner.

3.8.13 BiCl₃ as bismuth precatalyst

To differentiate between the possible outer-sphere mechanisms (radical ligand transfer vs. radical oxidation), we set up further reactions utilizing BiCl₃ as bismuth precursor (Scheme 3.7). If our reaction would follow the radical ligand transfer, a benzyl chloride **8** would be formed as an intermediate followed by nucleophilic substitution by the sulfonamides. When BiCl₃ was used for the decarboxylation of the acid **1a**, the reaction yielded a low concentration of the radical homocoupling product while C–N coupling product **3a** could not be detected (Scheme 3.7a). We then attempted to generate the intermediate **8** *via* a HAT reaction from ethylbenzene with over-stoichiometric amount of chlorine source (Scheme 3.7b). However, the desired product could not be observed. Taken together, these results suggest that the radical ligand transfer, as suggested with iron chloride, did not represent the key mechanistic pathway in our reaction.



Scheme S3.7: Mechanistic studies using bismuth(III)chlorides in LMCT decarboxylation (a) and HAT coupling (b). **Reactions using substoichiometric bismuth**

We set out to study the effects of using bismuth as a limiting reagent in our reaction to gain further insight into the efficiency of bismuth in our reaction. The reactions were set up following **GP1**, though lowered bismuth loading was used as described in Table 3.11.

Table 3.11: Full optimization of bismuth triflate loading.

Entry	Bi Loading	Yield (based on acid, %)	Yield (based on bismuth, %)
1	0.33 equiv.	31	0.94
2	0.66 equiv.	45	0.68

Reaction conditions: Bi(OTf)₃ (n equiv.), 2-phenylpropanoic acid (15.0 mg, 0.1 mmol, 1.0 equiv.), KHCO₃ (30.0 mg, 0.3 mmol, 3.0 equiv.) and 4-methylphenylsulfonamide (65.5 mg, 0.35 mmol, 3.5 equiv.) were dissolved into DCM (1 mL) under N₂. After irradiation with 365 nm for 10 h at 25 °C, internal standard was added and reactions analyzed with GC-FID.

With 0.33 equivalents of bismuth, the yield of 94% yield was obtained (Entry 1). This result suggests a high activity of bismuth, serving as an efficient subsequent one electron oxidizing agent. Moreover, this result can also be seen as supporting our mechanistic hypothesis that the bismuth centre participating the radical generation further traps the substrate radical resulting into the product formation. When 0.66 equivalents of bismuth was used, 68% yield was obtained (Entry 2).

3.9 NMR data

The NMR data to the compounds described is available free of charge on the publishers website:

<https://chemistry-europe.onlinelibrary.wiley.com/doi/full/10.1002/chem.202500396>

3.10 Notes and references

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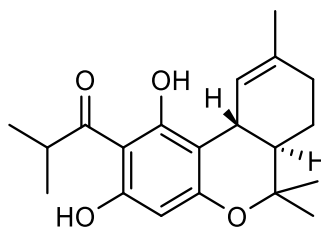
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4 Synthesis and Biological Evaluation of Acylphloroglucinol – Cannabinoid Hybrid Molecules



Abstract: This chapter describes the synthesis and biological evaluation of acylphloroglucinol-cannabinoid analogs and their biological evaluation. The synthesized compounds show promising antibiotic properties. One derivative showed high affinity for the human CB₂ receptor and additionally good selectivity versus the CB₁ receptor.

Author contribution

DB conceptualized the work and explored synthetic routes towards target compounds during his master studies. During the first year of the PhD synthetic procedures were optimized and compounds were synthesized in sufficient amount together with the research intern Hannes Schneider. Julia Brunner performed purification for biological testing and antibacterial testing studies in the Heilmann group. In cooperation with Christa Müller at the university of Bonn affinity studies towards the cannabinoid receptors were performed. Jörg Heilmann and Burkhard König supervised the work. JH coordinated the cooperation with CM.

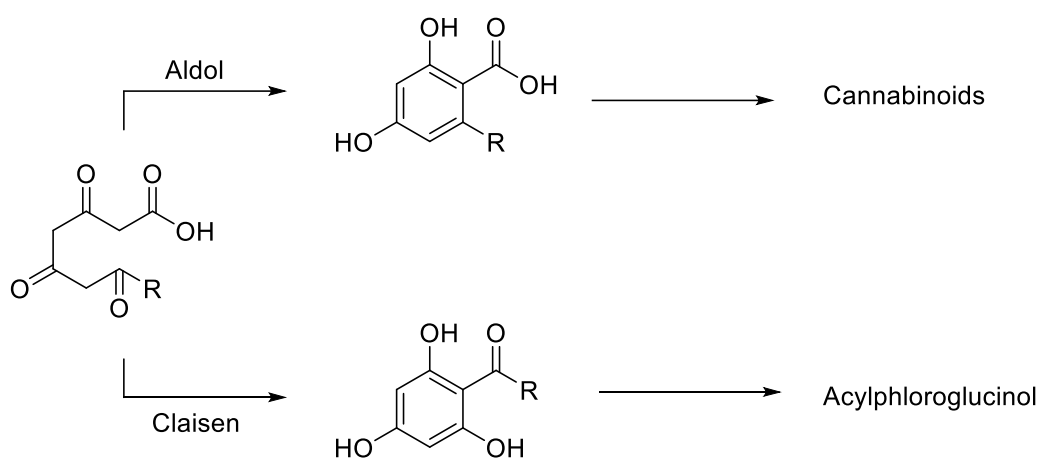
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4.1 Introduction

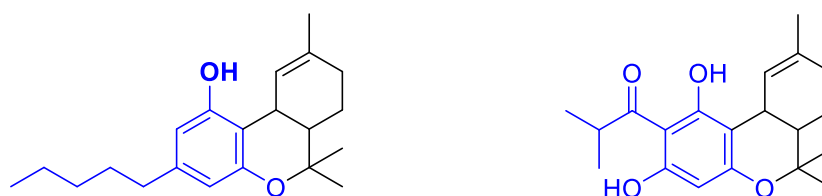
Prenylated natural products are a large class of bioactive molecules with demonstrated medical properties. Prominent examples with aromatic cores include prenyl-flavanoids, prenyl-phloroglucinols and cannabinoids.^[1–4] Biosynthetically the cores are derived from the polyketide pathway by three malonyl-CoA (coenzyme A) reacting with an activated acetyl-CoA to form an intermediate polyketide.^[5] A Claisen-like reaction enzymatically catalyzes this intermediate to acylphloroglucinols in the Genus *Hypericum*,^[6] whereas an enzymatic aldol reaction gives access to cannabinoids in “*cannabis sativa*”.^[7] From here on nature, developed both similar but also highly diverse prenylation patterns, which then can be additionally cyclized and oxidized to complex compounds.^[8] Representatives of acylphloroglucinol are reported to exhibit anti-bacterial, cytotoxic, anti-oxidative and anti-depressant effects.^[8–10] Hyperforin, likely the most prominent acylphloroglucinol derivative has been reported to exhibit anti-proliferative effects.^[11]

Historically phytocannabinoids have been notorious for their therapeutic and recreational applications.^[12] With more than 100 compounds known, *cannabis sativa* is the primary source for bioactive natural products^[13]. Tetrahydrocannabinol (THC), despite its psychotropic effects limiting its medical utility holds promise for treating conditions like pain, anxiety and cachexia.^[14–17] With the discovery of the endocannabinoid system comprised of cannabinoid receptors (CB1 and CB2)^[18], selective agonists were designed for studying these receptors. For therapeutic use, ligands binding selectively to the CB2 receptor, situated in the periphery are particularly interesting.^[19] So far synthetic cannabinoids mimicking their plant origin have been mostly modified at their terpenoid structure as important pharmacophores are the phenolic hydroxyl group and a lipophilic side chain, while the olivetol core of cannabinoids has been rarely changed.^[20] Nevertheless, we were wondering what impact a core-swap to an acylphloroglucinol on the biological properties could have in this type of molecules.

Biogenic relationship between resorcinyll and flavinoid meroterpenoids



This work: Core swap in THC to an Acylphloroglucinol

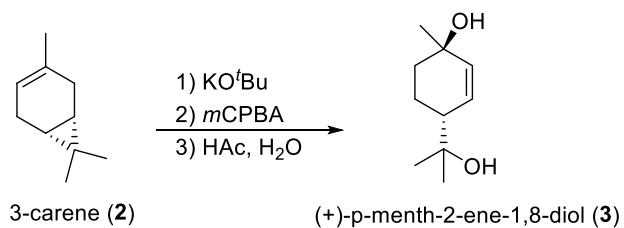


Scheme 4.1: Biogenic relationship between acylphloroglucinols and cannabinoids and planned core swap

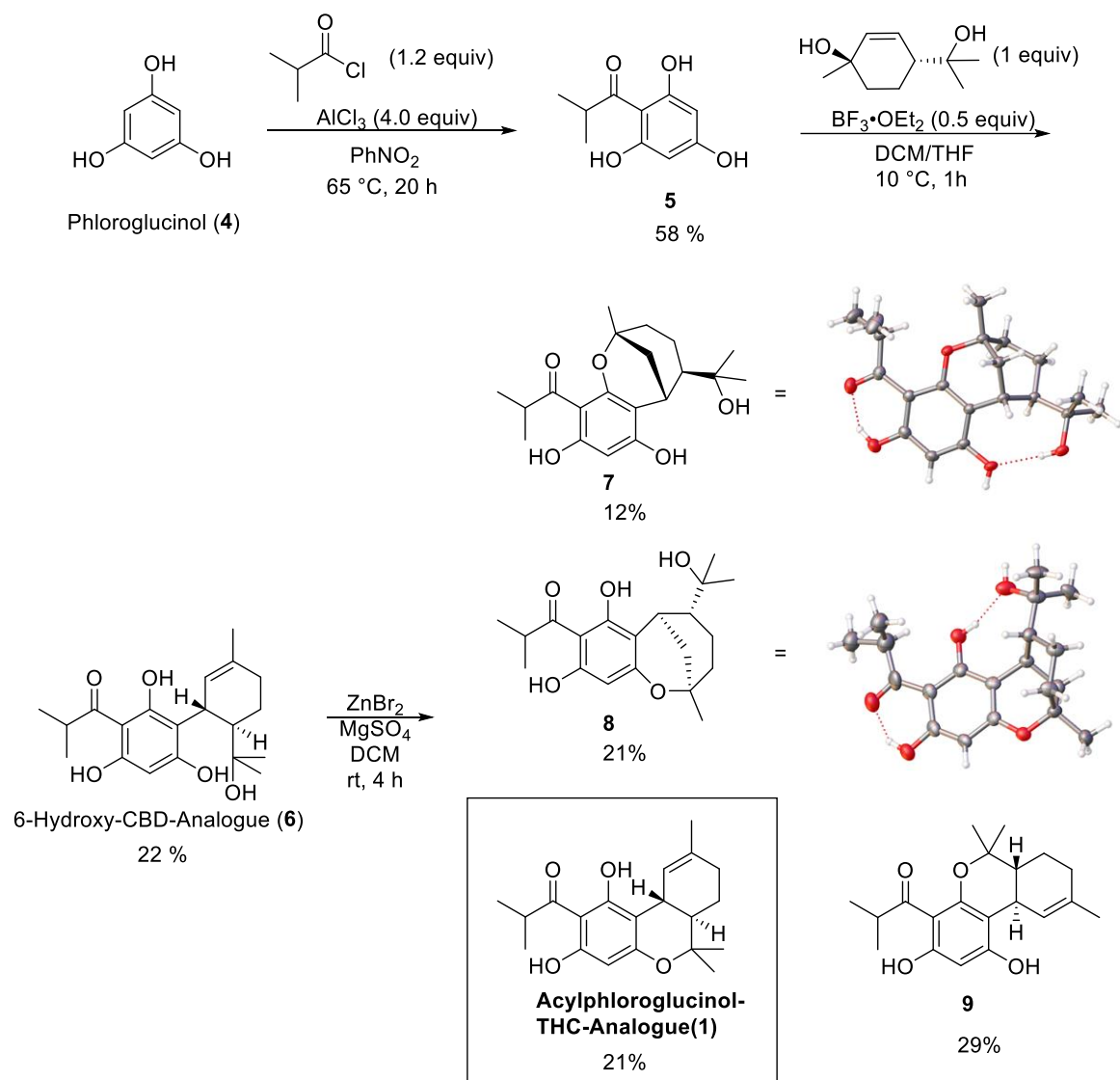
4.2 Synthesis

Retrosynthetically, we decided to employ a terpenoid chiral pool approach to install the key (–)-trans- Δ^9 -THC structure to an acylphloroglucinol. This strategy provides direct access to enantiopure cannabinoids and avoids typically more complex asymmetric transformations.^[21] While this approach is accompanied by broad regioselectivity profiles and thus challenging purification protocols, it also yields analogous structures for biological profiling. We employed p-menth-2-ene-1,8-diol (**3**) first used by Razdan and coworkers, because this two-step protocol with the isolation of a 6-hydroxy-CBD derivative (**6**) enables improved purity of products compared to other terpenoids^[22]. p-Menth-2-ene-1,8-diol (**3**) is synthesized from 3-carene (**2**), an inexpensive natural bulk terpenoid in a three-step protocol derived from literature^[23]. First, compound **2** is isomerized by heating with KOtBu overnight, which gives a 40:60 mixture of 2- and 3-carene. This mixture is then treated with *m*CPBA, giving access to the respective epoxides. Next, a selective epoxide opening of the 2-careneepoxide in the presence of acetic acid with water forms p-menth-2-ene-1,8-diol, which can be isolated by crystallization in 23 % yield over three steps. For the acylphloroglucinol core we decided on an isopropyl sidechain, a motive often found in acylphloroglucinols of hypericum. A Friedel-Crafts acylation of phloroglucinol (**4**) with isobutyryl chloride gave compound (**5**) in 58% yield. Then acylphloroglucinol (**5**) was reacted with terpenoid **3** in the presence 0.5 equivalents of BF₃ at 10 °C for one hour to provide the 6-hydroxy-CBD analogue **6** in 22 % yield. Temperature control is critical during this step to avoid further undesired cyclisation and a mixture which is difficult to purify. Compound **6** is further cyclized in the presence of anhydrous ZnBr₂ as Lewis acid giving access to the desired acylphloroglucinol-THC analogue (**1**) in 21% yield together with its regioisomer **9** and two additional products **7** and **8** with a cyclization pattern found in the carbon structure of Rhodonoid G. These products are the result of an attack of a phenolic hydroxyl group to the double bond. Compound **7** and **8** could be crystallized. The crystal structures show the extensive hydrogen bond networks found in this type of molecules. One hydrogen bond is formed between the *iso*-propanol group and the phenol. The orientation of the second hydrogen bond is dictated by the regioselectivity of the cyclisation. Overall, the synthesis delivered fast access to the desired acylphloroglucinols in sufficient quantities to be further purified by HPLC for biological testing.

Synthesis of (+)-p-menth-2-ene-1,8-diol



Synthesis of an Acylphloroglucinol-THC-Analogue(1)



Scheme 4.2: Synthesis of Acylphloroglucinol-THC analogues

4.3 Reaction chromatogram of the key cyclisation

As shown in the chromatogram in Figure 4.1, compounds **7** and **8** are easily separable from each other, as well as from the undesired side products **1** and **9** by using reversed phase flash chromatography. The latter two can only be separated from each other by using a very careful gradient at the preparative HPLC.

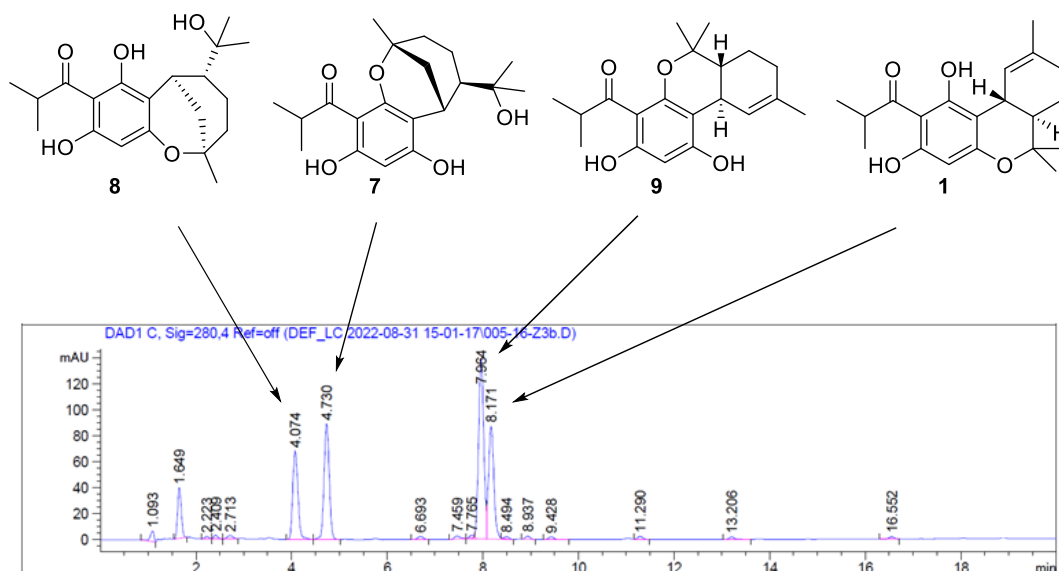


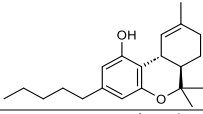
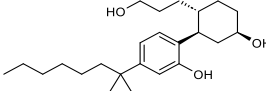
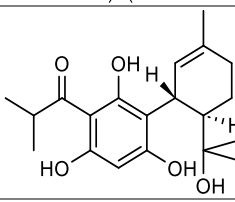
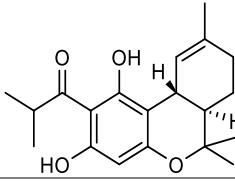
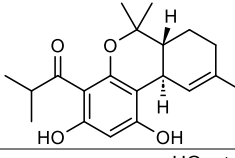
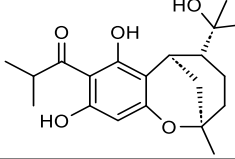
Figure 4.1: Reaction chromatogram of the key cyclisation step (70% → 98% MeCN in H₂O, C-18).

4.4 Cannabinoid receptor affinity tests

Testing studies were performed by Prof. Müller in Bonn. A series of compounds related to cannabinoids were tested in radioligand binding studies at CB₁ and CB₂ receptors (Table 4.1 and Figure 4.3). Selected compounds were further evaluated in β -arrestin recruitment assays (Figure 4.4). Data for standard compounds are provided for comparison.

Table 4.1: Affinities and potencies of the test compounds at human cannabinoid CB₁ and CB₂ receptors

ID	Structure	Radioligand binding assay		β -Arrestin-2 recruitment assay	
		Human CB ₁ receptor	Human CB ₂ receptor	Human CB ₁ receptor	Human CB ₂ receptor
		K _i ± SEM (nM)	K _i ± SEM (nM)	EC ₅₀ ± SEM (nM)	EC ₅₀ ± SEM (nM)
		vs.	vs.	[efficacy] ^a	[efficacy] ^a
		[³ H]CP55,940	[³ H]CP55,940		

		(or percent inhibition of at 10 000 nM)	(or percent inhibition of at 10 000 nM)		
THC		6.62 ± 0.86	5.97 ± 2.71	0.979 ± 0.316 [32%]	4.13 ± 0.52 [25%]
CP55,940		0.758 ± 0.94	0.293 ± 0.083	0.574 ± 0.201 [100%]	0.890 ± 0.332 [100%]
6		>10 000 (29)	5040 ± 918	n.d ^b	2824 ± 529 [107%]
1		1200 ± 190	34.1 ± 4.9	1243 ± 50 [30%]	24.1 ± 9.7 [118%]
9		2330 ± 316	1480 ± 91	1234 ± 13 [38%]	310 ± 56 [91%]
8		>10 000 (20)	2310 ± 62	n.d	1047 ± 638 [64%]

^a Efficacy relative to the maximal effect of the standard agonist CP55940 at 1 μ M set at 100%.

^b n.d = not determined. Compound **1** showed high affinity for the CB₂ receptors and lower affinity to the CB₁ receptor subtype.

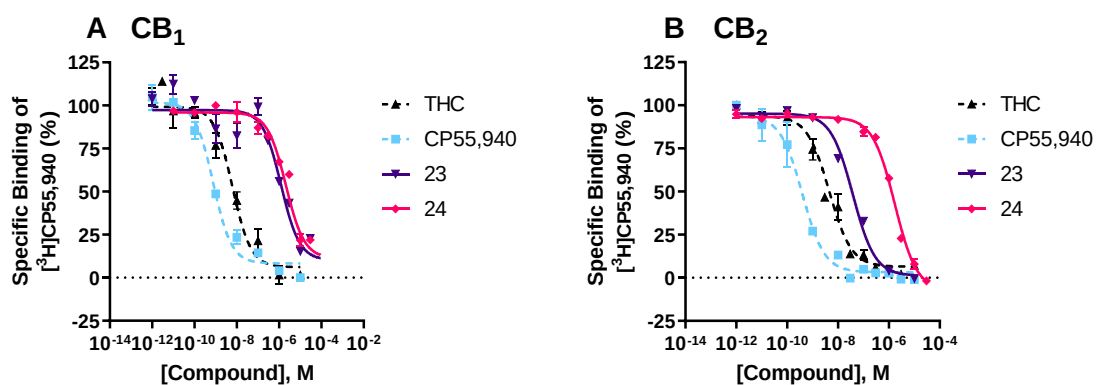


Figure 4.3: (A) Concentration-dependent inhibition of specific [³H]CP55,940 binding by **THC** (K_i 6.62 ± 0.86 nM), **CP55,940** (K_i 0.758 ± 0.94 nM), and compounds **1** (K_i 1198 ± 194 nM) and **9** (K_i 2326 ± 316 nM) at the human CB₁ receptor, determined in radioligand binding assays. (B) Concentration-dependent inhibition of specific [³H]CP55,940 binding

by **THC** (K_i 5.97 ± 2.71 nM), **CP55,940** (K_i 0.293 ± 0.083 nM), and compounds **1** (K_i 34.1 ± 4.9 nM) and **9** (K_i 1480 ± 91 nM) at the human CB₂ receptor, determined in radioligand binding assays. Data points represent means $\pm$ SEM of three independent experiments, performed in duplicates.

In order to investigate whether compound **1** is an agonist or an antagonist at CB receptors, we performed functional studies, measuring β -arrestin-2 recruitment induced by receptor activation. Compound **1** behaved as a full agonist towards the CB₂ receptor and as a partial agonist against the CB₁ receptor

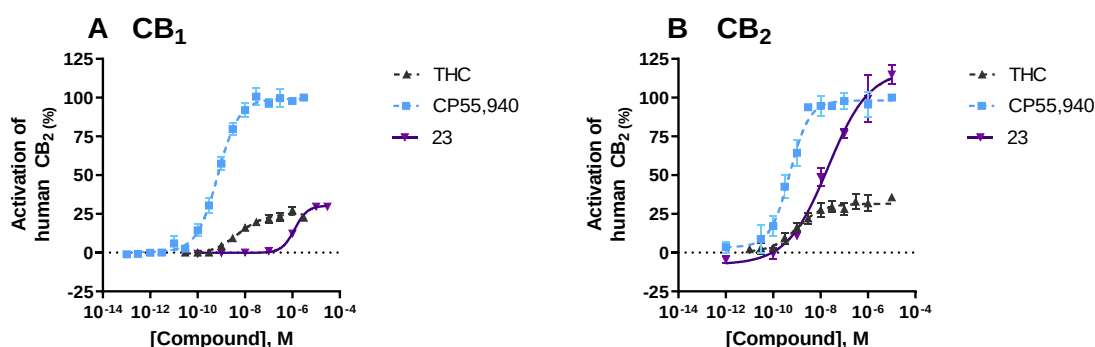


Figure 4.4: CB receptor-dependent β -arrestin-2 recruitment assays.

(A) Concentration-dependent activation of the CB₁ receptor by **THC** (EC_{50} : 0.979 ± 0.316 nM, E_{max} 32%; partial agonist), **CP55,940** (EC_{50} : 0.574 ± 0.201 nM, E_{max} 100%; full agonist), and compound **1** (EC_{50} : 1243 ± 50 nM, E_{max} 30%; partial agonist), determined in β -arrestin-2 recruitment assays.

(B) Concentration-dependent activation of the CB₂ receptor by **THC** (EC_{50} : 4.13 ± 0.52 nM, E_{max} 25%; partial agonist), **CP55,940** (EC_{50} : 0.890 ± 0.332 nM, E_{max} 100%; full agonist), and compound **1** (EC_{50} : 24.1 ± 9.7 nM, E_{max} 118%; full agonist), determined in β -arrestin-2 recruitment assay.

All data were normalized to the maximum response of full agonist, CP55,940 (1 μ M, set as 100%). Data points represent means $\pm$ SEM from a minimum of three independent experiments, performed in duplicates.

4.5 Conclusion

Derivatives of Acylphloroglucinol-Cannabinoid analogues have been successfully synthesized. Compound **1** demonstrated a high affinity for the human CB₂ receptor, with a K_i value of 34.1 nM, and exhibited 35-fold selectivity in favor of the CB₂ receptor over the CB₁ receptor. In β -arrestin-2 recruitment assays, compound **1** acted as a full agonist, showing an EC₅₀ of 24.1 ± 9.7 nM and an Emax of 118% when compared to the reference full agonist CP55,940. In contrast, at the CB₁ receptor, compound **1** behaved as a partial agonist, with an EC₅₀ of 1240 ± 50 nM and an Emax of 30% relative to CP55,940. These findings indicate that compound **1** is a potent and selective full agonist of the CB₂ receptor. Additionally, the structure-activity relationship analysis revealed that the activity of the compounds was highly sensitive to structural changes, with minor modifications leading to a significant reduction or loss of activity. Future research should explore the activity of compound **1** in G protein-dependent functional assays to further elucidate its pharmacological profile. Additional biological studies, potentially including in vivo investigations, are suggested. Moreover, evaluating the pharmacokinetic properties of compound **1**, such as its metabolic stability, absorption, and brain penetration, would be valuable for its further development.

4.6 Synthetic details

4.6.1 General Considerations

Chemicals and solvents were purchased from commercial suppliers (Sigma Aldrich, TCI, BLD Pharma, Alfa Aesar, Acros, Fluka or Thermo Fischer) and, unless otherwise noted, used without further purification.

Analytical thin layer chromatography (TLC) was routinely used for the monitoring of starting material synthesis and to quantify the elution of product. Silica-gel pre-coated aluminium sheets (Macherey-Nagel, silica gel 60G/UV254, 0.2 mm) served as stationary phase, whereas the mobile phase consisted of solvents and solvent mixtures, the ratios of which are reported as v/v solutions. Visualization was performed with a 254 nm UV-light source combined with chromatographic dyes if so noted.

Flash column chromatography (FCC) was done either by hand or by a Biotage® Isolera™ Spektra One machine. In the former case flash silica gel (Merck, particle size 40–63 µm, 230–440 mesh) was used as a stationary phase whereas in the latter case pre-packed Biotage® columns were used. For both techniques eluent mixtures, whenever possible consisting of pre-distilled petroleum ether (PE) and ethyl acetate (EtOAc), was used. For all eluents, the solvent ratios are reported as v/v ratios.

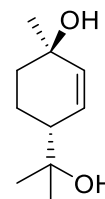
Nuclear Magnetic Resonance Spectroscopy (NMR) was recorded at room temperature using a Bruker Avance 400 (400 MHz for ^1H , 101 MHz for ^{13}C) NMR spectrometer. All chemical shifts are reported δ -scale as part per million [ppm] (multiplicity, coupling constant J , number of protons) relative to the solvent residual peak. The coupling constants J are given in Herz [Hz] and the multiplicity of the signals are abbreviated as: singlet (s), broad singlet (br. s.), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), doublet of triplets (dt), triplet of doublets (td), quartet (q), doublet of quartets (dq), pentet (p) and multiplet (m). For the NMR measurements deuterated solvents (CDCl_3 from deuterio, $\text{DMSO}-d_6$ from Sigma Aldrich) were used.

High Resolution Mass Spectra (HRMS) were performed at the Central Analytical Laboratory of the departments of chemistry and pharmacy at the University of Regensburg. For measurements, > 1 mg of the sample submitted, which was later dissolved to acetonitrile,

DCM or ethyl acetate. The samples were then injected either to a Jeol AccuTOF GCX or to an Agilent Q-TOF 6540 UHD instrument.

4.6.2 Synthetic procedures

(+)-p-Menth-2-ene-1,8-diol (3)



KO^tBu (5.4 g, 48 mmol, 0.33 eq) was dissolved in DMSO (250 mL), 3-carene (20 g, 146 mmol, 1.0 eq) was added and the mixture was heated to 110 °C over night. The mixture was cooled down to room temperature, H₂O (50 mL) was added and 3- and 2-carene was extracted with EtOAc (2·300 mL), washed with H₂O and brine and concentrated *in vacuo*.

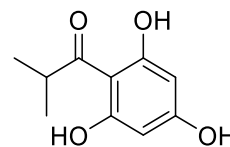
The residue was dissolved in H₂O (120 mL) and DCM (40 mL) and NaHCO₃ (30 g, 360 mmol, 2.45 eq) was added. 3-Chloroperoxybenzoic acid (77%, 35.1 g, 160 mmol, 1.1 eq) was added in portions and the mixture was stirred over night. The reaction was quenched with Na₂S₂O₃·5 H₂O (20 g, 80 mmol, 0.55 eq) and a KI test was made. Since the KI solution remained colourless, the mixture was extracted with EtOAc (3·150 mL) and washed with sat. NaHCO₃ and brine.

Acetic acid (5 mL) in H₂O (20 mL) was added to the EtOAc solution and the mixture was stirred for two days at room temperature. After concentrating under reduced pressure, the orange crude product was recrystallized in EtOAc and heptane at -18 °C. (+)-p-Menth-2-ene-1,8-diol was obtained as white needles (5.8 g, 34.1 mmol, 23% over three steps).

¹H-NMR (300 MHz, DMSO-*d*₆): δ = 5.60 (d, J = 10.6 Hz, 1H), 5.51 (d, J = 10.6 Hz, 1H), 4.41 (s, 1H), 4.21 (s, 1H), 2.03-1.95 (m, 1H), 1.74-1.63 (m, 2H), 1.58-1.46 (m, 1H), 1.30-1.13 (m, 1H), 1.09 (s, 3H), 1.02 (s, 3H), 0.95 (s, 3H).

¹³C-NMR (75 MHz, DMSO-*d*₆): 137.0, 127.4, 71.2, 68.1, 47.4, 38.5, 29.2, 28.0, 26.0, 23.4.

HRMS: *m/z* calculated for C₁₀H₁₈O₂ [M+NH₄]⁺: 188.1645, found 188.1642.

2-Methyl-1-(2,4,6-trihydroxyphenyl)propan-1-one (5)

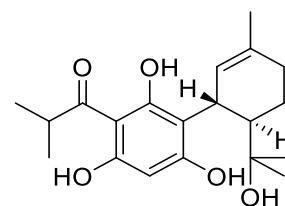
Phloroglucinol (5.0 g, 39.7 mmol, 1.0 eq) was suspended in nitrobenzene (50 mL), AlCl_3 (21.2 g, 159 mmol, 4.0 eq) was added slowly and the mixture was stirred for 15 min. Isobutyrylchloride (4.6 mL, 43.6 mmol, 1.1 eq) was added dropwise and the mixture was heated to 65 °C over night. After cooling down to room temperature, the reaction mixture was quenched by pouring it into ice-water and extracted with EtOAc (3·50 mL). The product was then extracted into NaOH solution (2 M, 2·100 mL), neutralized with conc. HCl and extracted back into EtOAc (3·100 mL). The solution was washed with H_2O and brine, dried over MgSO_4 and concentrated *in vacuo*. The product was obtained after purification by column chromatography (20% → 50% EtOAc in PE) as a yellow solid (4.52 g, 23.0 mmol, 58%).

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): δ = 12.25 (s, 2H), 10.33 (s, 1H), 5.81 (s, 2H), 3.87 (h, J = 6.7 Hz, 1H), 1.07 (d, J = 6.7 Hz, 6H).

$^{13}\text{C-NMR}$ (75 MHz, $\text{DMSO-}d_6$): 209.8 (q), 164.9 (q), 164.6 (q), 103.3 (q), 95.2 (p/t), 38.6 (p/t), 19.6 (p/t).

HRMS: m/z calculated for $\text{C}_{10}\text{H}_{12}\text{O}_4$ $[\text{M}]^+$: 196.0736, found 196.0727.

Acylphloroglucinol-6-hydroxy-CBD analogue (6)



Acylphloroglucinol **5** (981 mg, 5.0 mmol, 1.0 eq) and p-menth-2-ene-2,8-diol (851 mg, 5.0 mmol, 1.0 eq) were dissolved in dry DCM/THF (1:1, 25 mL) and cooled to 0 °C. $\text{BF}_3 \cdot \text{OEt}_2$ (310 μL , 2.5 mmol, 0.5 eq) was added and the mixture was stirred at 10 °C for 1 h. The reaction was quenched with sat. NaHCO_3 (25 mL), extracted with EtOAc (3·50 mL), dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by reversed phase flash column chromatography (20% $\rightarrow$ 70% MeCN in H_2O). The product was obtained as slightly yellow solid (359 mg, 1.0 mmol, 20%).

^1H -NMR (400 MHz, CDCl_3): δ = 14.27 (m, br, 1H), 10.47 (s, 1H), 10.10 (m, br, 1H), 5.94 (s, 1H), 4.83 (s, 1H), 3.90 (h, J =6.7 Hz, 1H), 3.66 (m, br, 1H), 2.33 (m, 1H), 2.12 (m, 1H), 2.02 (m, 1H), 1.83 (m, 1H), 1.58 (s, 3H), 1.32-1.21 (m, br, 2H), 1.08 (d, 6.7 Hz, 6H), 0.97 (s, 3H), 0.83 (s, 3H)

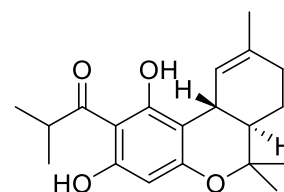
^{13}C -NMR (101 MHz, CDCl_3): δ = 209.9, 165.7, 163.8, 162.2, 159.9, 131.4, 126.2, 111.7, 103.1, 95.1, 72.1, 45.4, 38.4, 33.6, 30.6, 30.3, 25.4, 25.3, 23.7, 19.9

HRMS: m/z calculated for $\text{C}_{20}\text{H}_{28}\text{O}_5$ $[\text{M}+\text{H}]^+$: 349.2010, found 349.2012.

Acylphloroglucinol-Tetrahydrocannabinoid-Analogues

The 6-hydroxy-CBD analogue **6** (359 mg, 1.0 mmol, 1.0 eq), ZnBr₂ (452 mg, 2.0 mmol, 2.0 eq) and MgSO₄ (240 mg, 2.0 mmol, 2.0 eq) were suspended in DCM (12 mL). The mixture was stirred for 4.5 h at room temperature, quenched with NaHCO₃ (24 mL), extracted into EtOAc (3·20 mL), dried over MgSO₄ and concentrated under reduced pressure. Compound **7** and **8** were obtained after purification by reversed phase flash column chromatography (20% → 70% MeCN in H₂O) as a white powders, compound **7** (42 mg, 0.12 mmol, 12%) and **8** (77 mg, 0.22 mmol, 21%) respectively whereas the acylphloroglucinol-THC analogue was isolated together with its regioisomer together. An additional careful normal flash column chromatography (5% EtOAc in PE) was necessary to separate the two regioisomers **9** (96 mg, 0.29 mmol, 29%) and **1** (70 mg, 0.21 mmol, 21%)

1-((6aR,10aR)-1,3-dihydroxy-6,6,9-trimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-2-yl)-2-methylpropan-1-one (**1**)

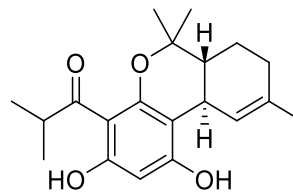


¹H-NMR (400 MHz, DMSO-d₆): δ = 14.35 (s, br, 1H), 6.90 (s, br, 1H), 6.35 (t, J = 1.44 Hz, 1H), 5.76 (s, 1H), 3.92, (h, J = 6.7 Hz, 1H), 3.15 (dt, J = 10.9, 2.1 Hz, 1H), 2.21-2.11 (m, 2H), 1.93-1.84 (m, 1H), 1.67 (s, 3H), 1.65-1.61 (m, 1H), 1.44-1.36 (m, 1H), 1.40 (s, 3H), 1.18 (d, J = 6.7 Hz, 6H), 1.09 (s, 3H).

¹³C-NMR (101 MHz, DMSO-d₆): δ = 210.9, 165.4, 160.5, 157.9, 133.8, 123.7, 104.8, 103.7, 96.0, 79.2, 45.8, 39.1, 33.0, 31.2, 27.3, 24.9, 23.3, 19.5, 19.5, 19.2.

HRMS: *m/z* calculated for C₂₀H₂₆O₄ [M+H]⁺: 331.1904, found 331.1909.

1-((6aR,10aR)-1,3-dihydroxy-6,6,9-trimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-4-yl)-2-methylpropan-1-one (9)

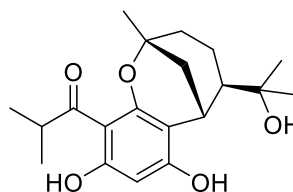


¹H-NMR (400 MHz, CDCl₃): δ = 13.80 (s, 1H), 6.13 (m, 1H), 5.93 (s, 1H), 5.66 (s, br, 1H), 3.81, (h, J = 6.7 Hz, 1H), 3.15 (dt, J = 10.9, 2.1 Hz, 1H), 2.21-2.13 (m, 2H), 1.96-1.89 (m, 1H), 1.69 (td, J = 12.78, 2.15 Hz, 1H), 1.68 (s, 3H), 1.49 (s, 3H), 1.45-1.37 (m, 1H), 1.18 (s, 3H), 1.15 (d, J = 6.7 Hz, 6H).

¹³C-NMR (101 MHz, CDCl₃): δ = 210.7 (q), 165.2 (q), 160.3 (q), 157.2 (q), 134.6 (q), 123.9 (p/t), 103.2 (q), 96.3 (p/t), 79.5 (q), 77.2 (q), 45.3 (p/t), 39.3 (p/t), 33.1 (p/t), 31.0 (s), 27.2 (p/t), 24.7 (s), 23.3 (p/t), 19.6 (p/t), 19.3 (p/t), 19.2 (p/t).

HRMS: m/z calculated for C₂₀H₂₆O₄ [M+H]⁺: 331.1904, found 331.1908.

1-((2R,5R,6R)-7,9-dihydroxy-5-(2-hydroxypropan-2-yl)-2-methyl-3,4,5,6-tetrahydro-2H-2,6-methanobenzo[b]oxocin-10-yl)-2-methylpropan-1-one (7)

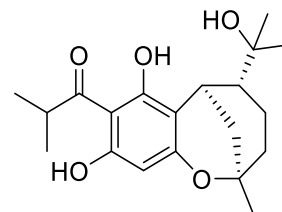


¹H-NMR (400 MHz, CDCl₃): δ = 13.75 (s, 1H), 6.05 (s, 1H), 3.81 (h, J = 6.7 Hz, 1H), 3.15 (t, J = 2.7 Hz, 1H), 2.03 (dt, J = 15.6, 3.7 Hz, 1H), 1.73-1.62 (m, 3H), 1.52 (s, 3H), 1.49-1.41 (m, 2H), 1.30 (s, 6H), 1.16 (d, J = 6.7 Hz, 3H), 1.16 (d, J = 6.7 Hz, 3H), 1.04-0.93 (m, 1H).

¹³C-NMR (101 MHz, CDCl₃): δ = 210.2 (q), 165.8 (q), 161.0 (q), 154.9 (q), 107.3 (q), 104.9 (q), 96.9 (p/t), 75.6 (q), 75.1 (q), 51.9 (p/t), 39.3 (p/t), 35.0 (s), 29.9 (s), 29.8 (p/t), 28.8 (p/t), 24.0 (p/t), 23.2 (p/t), 19.6 (p/t), 19.3 (p/t), 18.8 (s).

HRMS: m/z calculated for C₂₀H₂₈O₅ [M+H]⁺: 349.2010, found 349.2011.

1-((2R,5S,6R)-7,9-dihydroxy-5-(2-hydroxypropan-2-yl)-2-methyl-3,4,5,6-tetrahydro-2H-2,6-methanobenzo[b]oxocin-8-yl)-2-methylpropan-1-one (8)



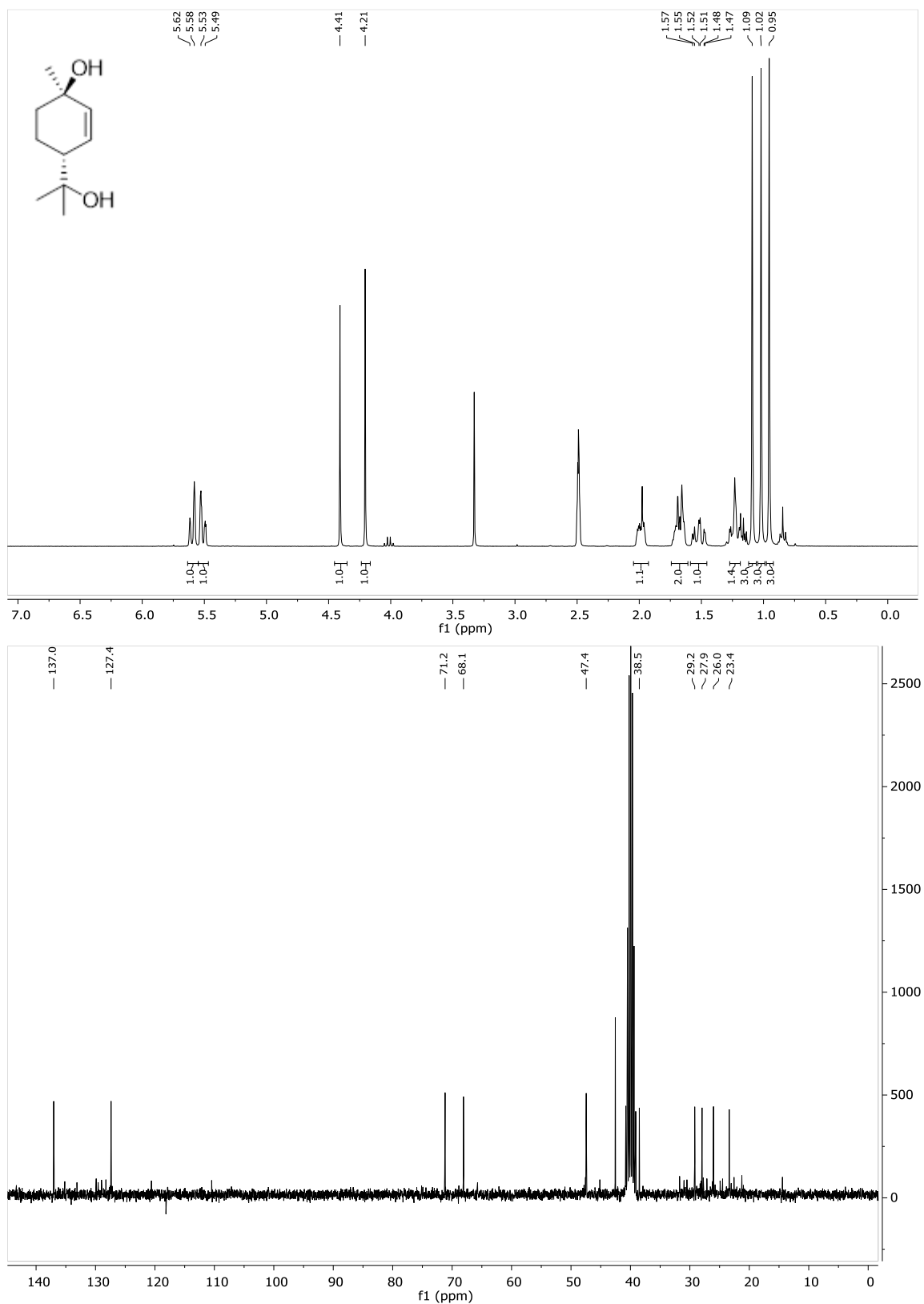
¹H-NMR (400 MHz, CDCl₃): δ = 12.88 (s, br, 1H), 9.75 (s, br, 1H), 5.92 (s, 1H), 3.98 (h, J = 6.8 Hz, 1H), 3.14 (t, J = 2.5 Hz, 1H), 1.99 (dt, J = 15.0, 3.8 Hz, 1H), 1.74 (dd, J = 13.5, 2.7 Hz, 1H), 1.67 (dd, J = 12.2, 6.7 Hz, 1H), 1.61 (td, J = 14.6, 4.3 Hz, 1H), 1.51 (dd, J = 13.2, 3.9 Hz, 1H), 1.46 (s, m, overlapping, 4H), 1.31 (s, 6H), 1.17 (d, J = 6.7 Hz, 3H), 1.16 (d, J = 6.7 Hz, 3H), 1.05 - 0.95 (m, 1H).

¹³C-NMR (101 MHz, CDCl₃): δ = 211.1 (q), 158.9 (q), 158.0 (q), 107.7 (q), 104.5 (q), 96.8 (p/t), 75.5 (q), 74.6 (q), 51.9 (p/t), 39.2 (p/t), 35.2 (s), 30.8 (s), 29.8 (p/t), 28.9 (p/t), 24.1 (p/t), 23.4 (p/t), 19.7 (p/t), 19.2 (s), 19.1 (p/t).

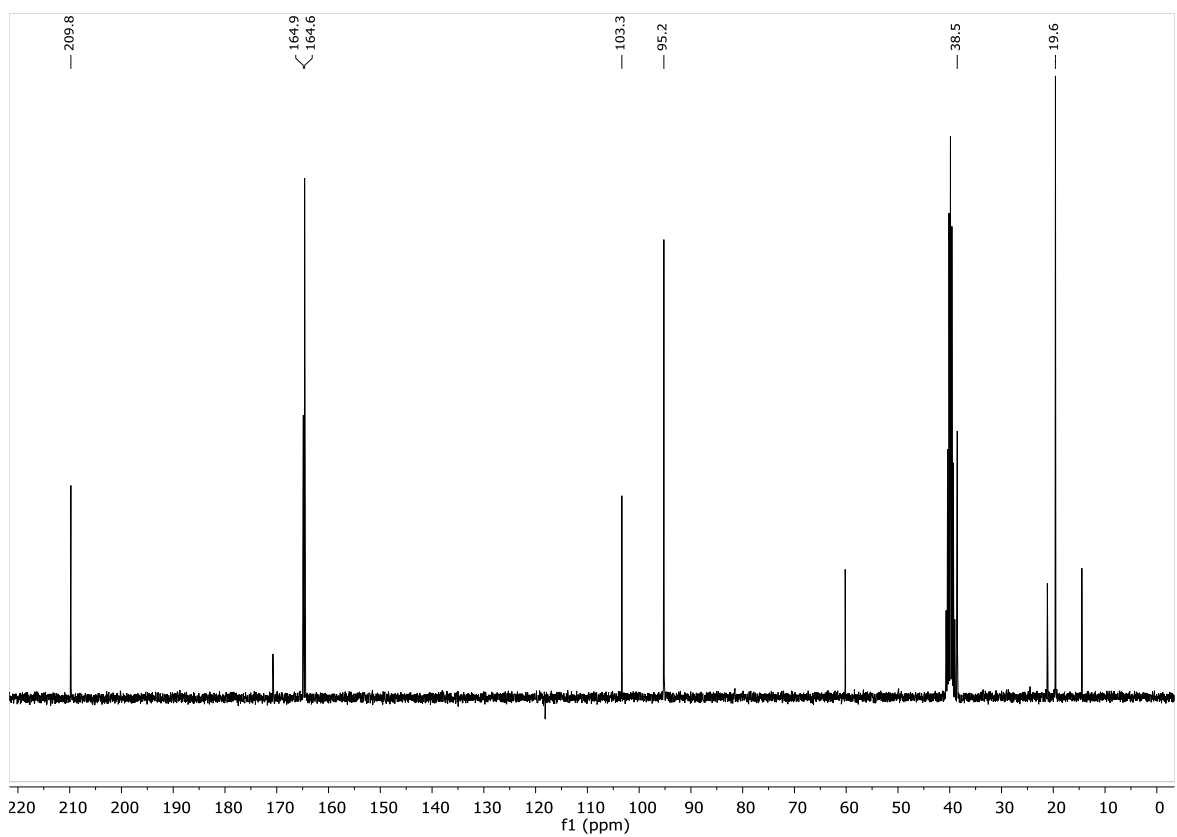
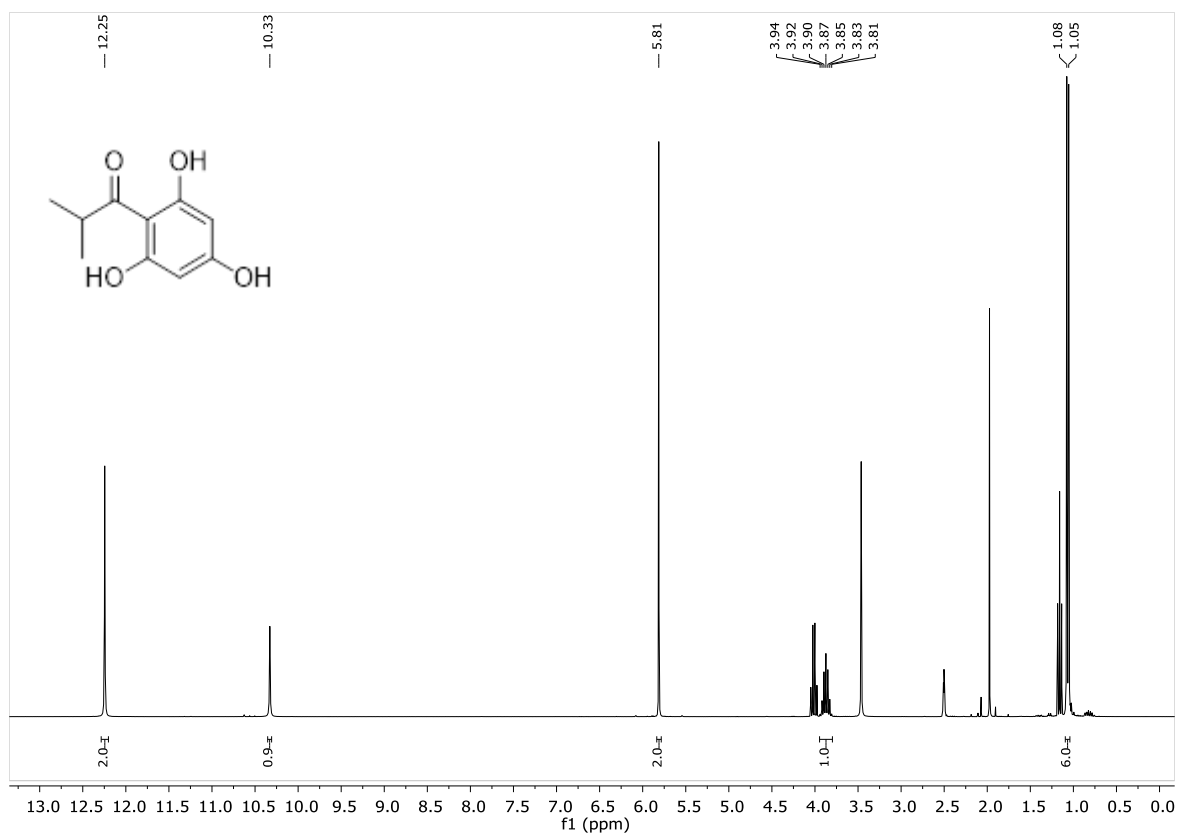
HRMS: m/z calculated for C₂₀H₂₈O₅ [M+H]⁺: 349.2010, found 349.2012.

4.7 NMR spectra

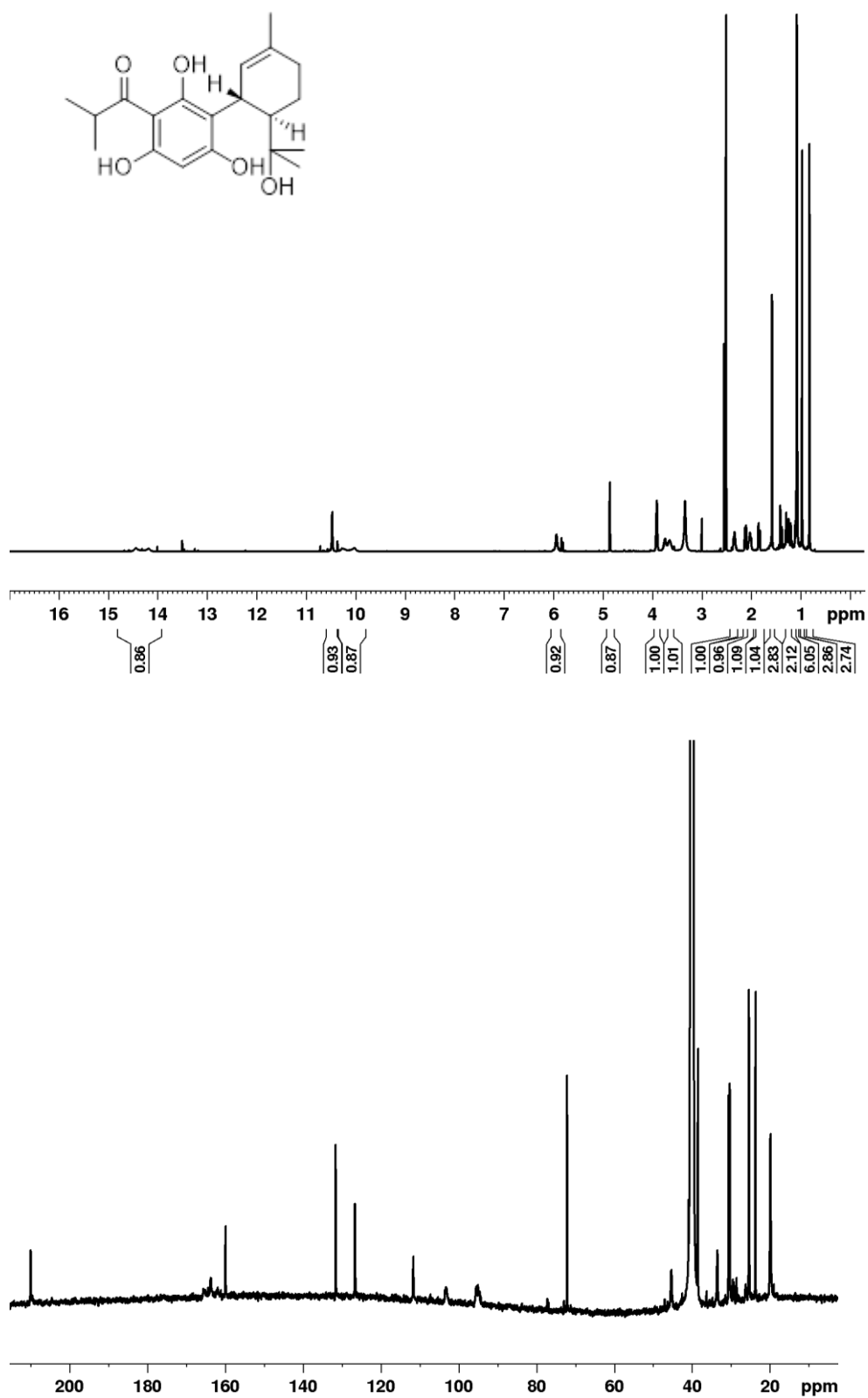
^1H -NMR and ^{13}C -NMR spectrum of (+)-p-Menth-2-ene-1,8-diol (3)



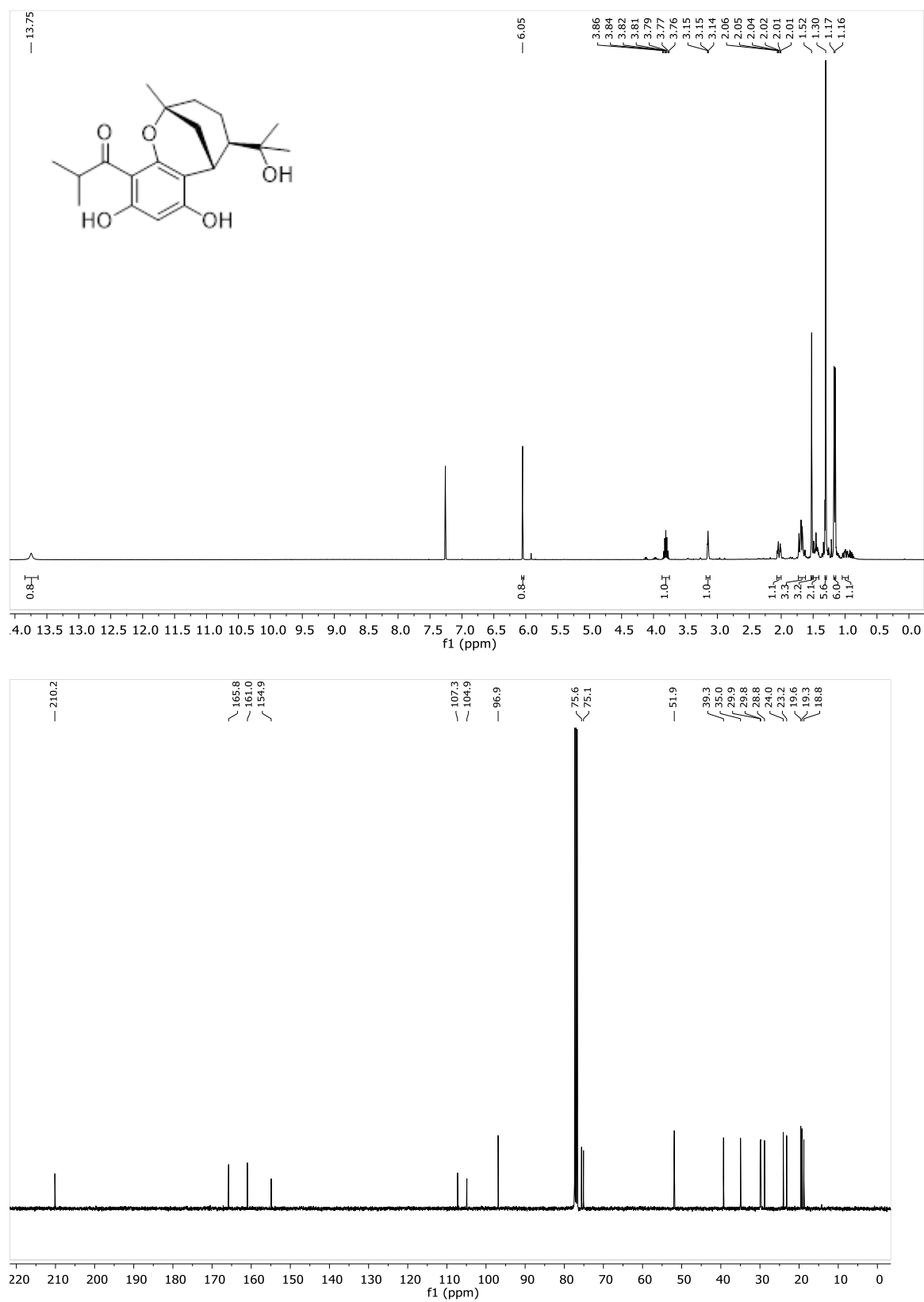
¹H-NMR and ¹³C-NMR of 2-Methyl-1-(2,4,6-trihydroxyphenyl)propan-1-one (5)



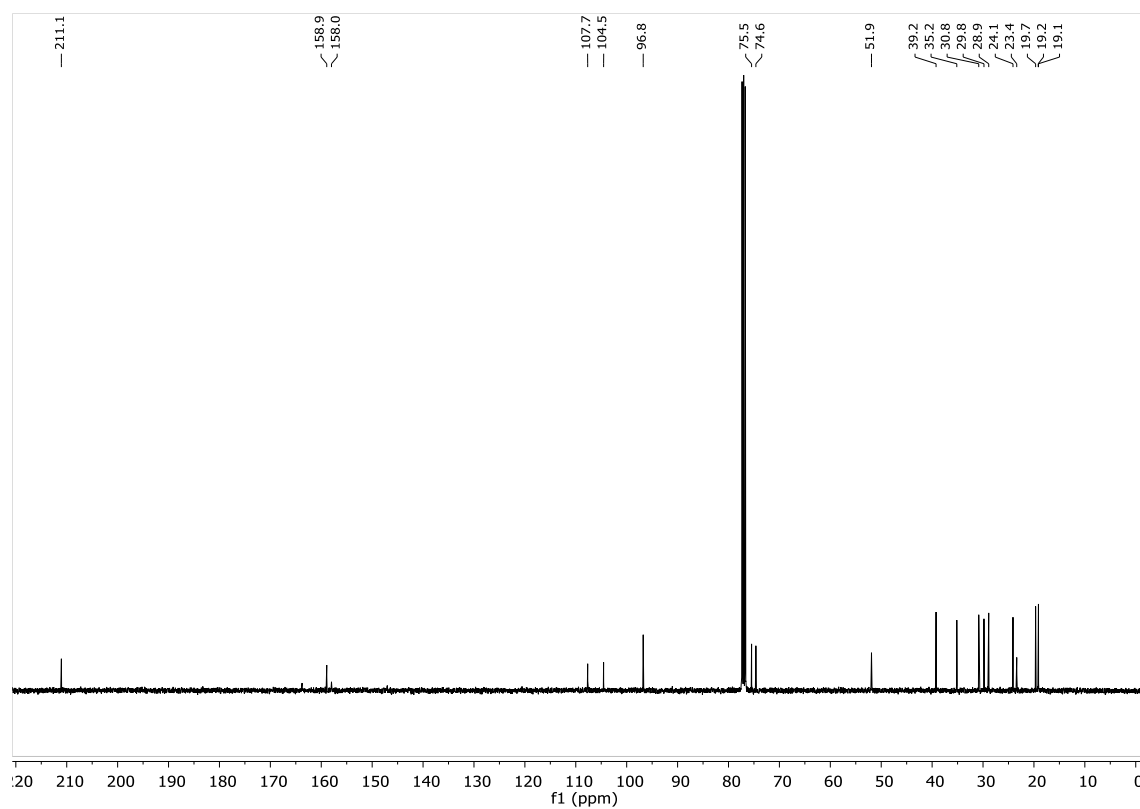
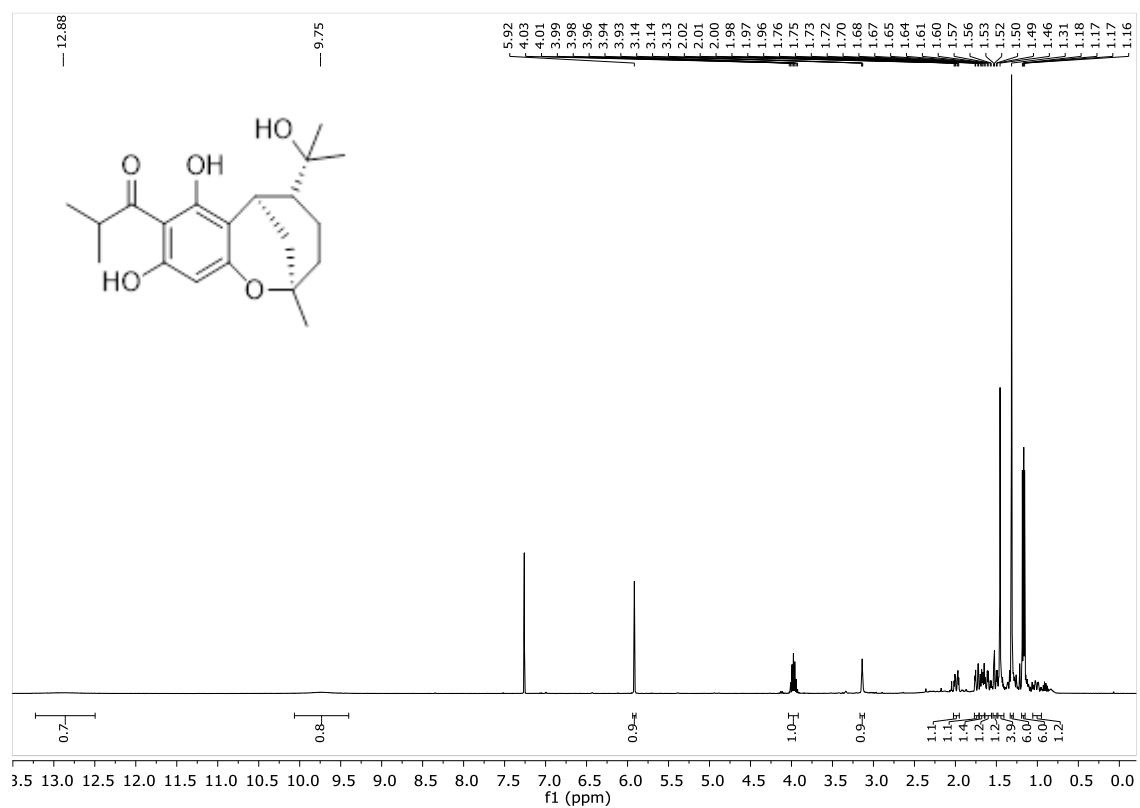
^1H -NMR and ^{13}C -NMR spectrum of 2-Methyl-1-((1'R,2'R)-2,4,6-trihydroxy-2'-(2-hydroxypropan-2-yl)-5'-methyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-yl)propan-1-one
(6)



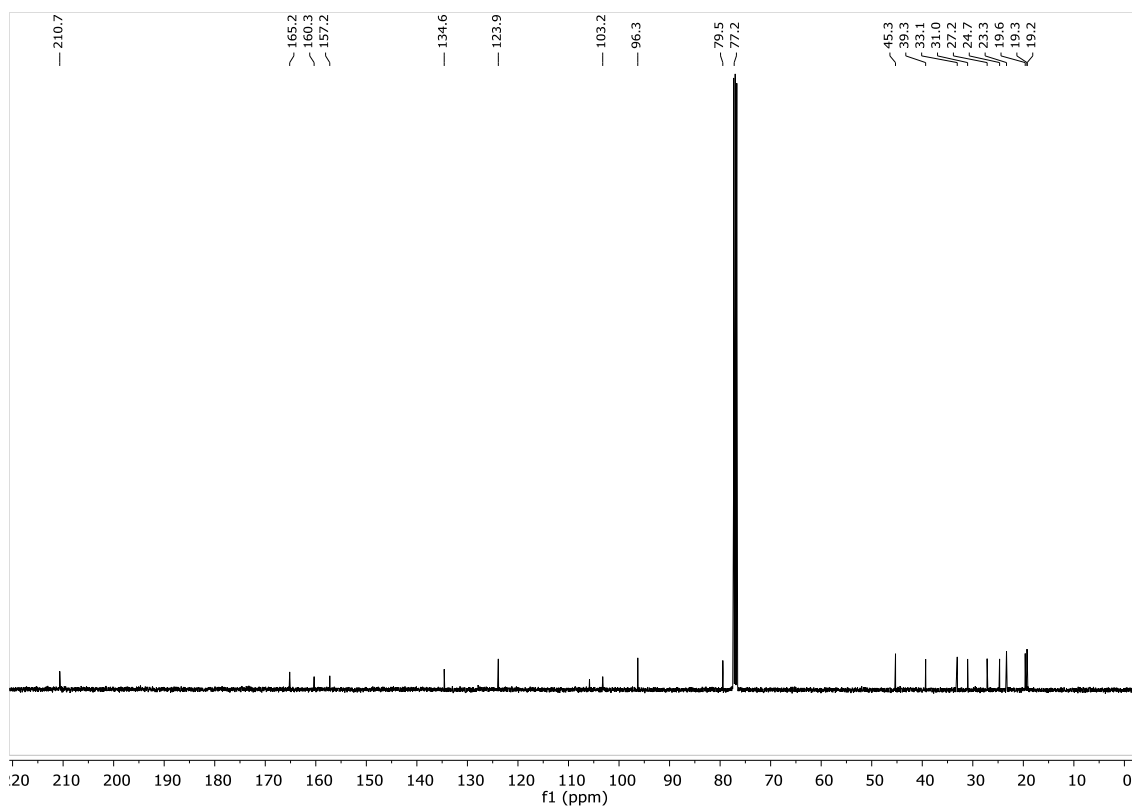
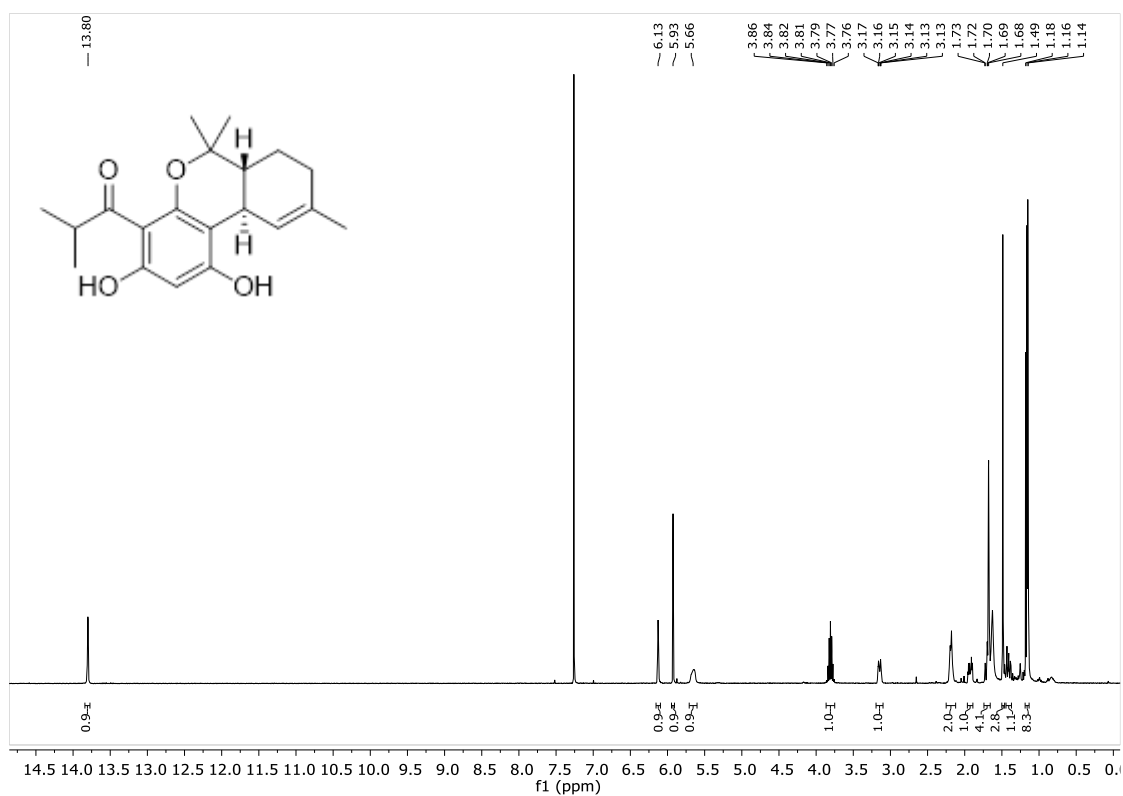
^1H -NMR and ^{13}C -NMR spectrum of 1-((2R,5R,6R)-7,9-dihydroxy-5-(2-hydroxypropan-2-yl)-2-methyl-3,4,5,6-tetrahydro-2H-2,6-methanobenzo[b]oxcin-10-yl)-2-methylpropan-1-one (7)



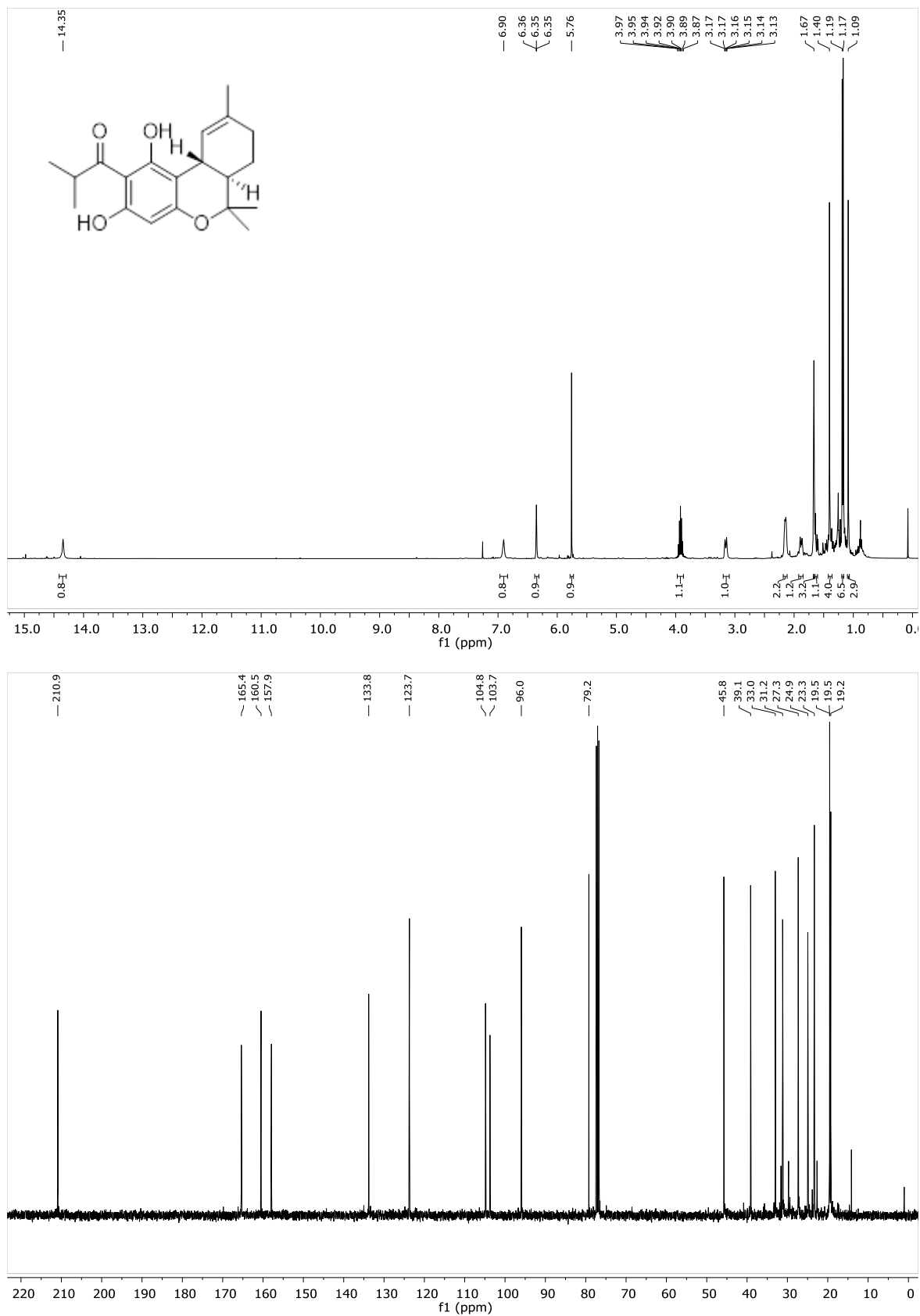
^1H -NMR and ^{13}C -NMR spectrum of 1-((2R,5S,6R)-7,9-dihydroxy-5-(2-hydroxypropan-2-yl)-2-methyl-3,4,5,6-tetrahydro-2H-2,6-methanobenzo[b]oxocin-8-yl)-2-methylpropan-1-one (8)



^1H -NMR and ^{13}C -NMR spectrum of 1-((6aR,10aR)-1,3-dihydroxy-6,6,9-trimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-4-yl)-2-methylpropan-1-one (9)



^1H -NMR and ^{13}C -NMR spectrum of 1-((6aR,10aR)-1,3-dihydroxy-6,6,9-trimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-2-yl)-2-methylpropan-1-one (1)



4.8 Notes and References

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5 Summary

Photocatalysis offers a mild approach for the generation of reactive radical intermediates for organic synthesis. Simple metal salts are an attractive alternative to more complex catalyst structures. In this thesis, we discovered and explored the application of simple bismuth complexes in different reactions

Chapter 1 gives an overview of very recent developments in the direct excitation of simple metal organics for activating these metals in coupling procedures. The concepts discussed here hold promise for future directions in the field

Chapter 2 describes the development of a systematic screening assay for the identification of ligand-to-metal- charge transfer (LMCT) activity of simple metal salts. This assay allowed us to discover the LMCT activity of bismuth salts. Two different electrophilic radicals (chlorine and carboxyl) were generated and used in net-oxidative lactonization reactions and in redox-neutral radical coupling reactions with electron deficient alkenes. Thorough mechanistic studies based on cyclovoltammetry and UV-vis spectroscopy revealed that the highly reactive bismuth(II) radical fragment undergoes disproportionation, which is a competing reaction pathway leading to catalyst inactivation.

Chapter 3 explores preassembly control of radical recombination at bismuth for decarboxylate C-N coupling protocols. While the reactivity bismuth of radical(II) fragments generated from simple bismuth(III) salts is typically hard to control, we used bismuth carboxylate assemblies to access an inner sphere coupling pathway, which led to the successful formation of C-N coupling products

Chapter 4 describes the synthesis and pharmacological evaluation of acylphloroglucinol cannabinoid analogues. One compound shows high affinity for the human CB₂ receptor and exhibits high selectivity in favor of the CB₂ receptor over the CB₁ receptor. This chapter is not closely related to other content in this thesis and is a continuation of results obtained in my master's studies.

6 Zusammenfassung

Photokatalyse ermöglicht die milde Erzeugung reaktiver Radikal-Zwischenprodukte für die organische Synthese. Dabei stellen einfache Metallsalze eine attraktive Alternative zu aufwendigeren Katalysatorstrukturen dar. In dieser Arbeit haben wir den Einsatz einfacher Bismutkomplexe in verschiedenen Reaktionen entdeckt und eingehend untersucht.

Kapitel 1 gibt einen Überblick über aktuelle Entwicklungen zur direkten photoinduzierten Anregung einfacher metallorganischer Verbindungen, mit dem Ziel, die enthaltenen Metalle für Kupplungsreaktionen zu aktivieren. Die in diesem Kapitel vorgestellten Konzepte eröffnen vielversprechende und potenziell wegweisende Perspektiven für dieses Forschungsgebiet.

Kapitel 2 beschreibt die Entwicklung eines systematischen Screening-Assays zur Identifikation von Ligand-zu-Metall-Ladungstransfer (LMCT) in einfachen Metallsalzen. Mithilfe dieses Assays konnten wir erstmals die LMCT-Aktivität von Bismutsalzen nachweisen. Dabei wurden zwei verschiedene elektrophile Radikale – Chlor- und Carboxylradikale – generiert und sowohl in net-oxidativen Laktonisierungsreaktionen als auch in redox-neutralen, radikalischen Kupplungsreaktionen mit elektronenarmen Alkenen eingesetzt. Umfassende mechanistische Untersuchungen mittels Cyclovoltammetrie und UV/Vis-Spektroskopie zeigten, dass hochreaktive Bismut(II)-Radikalfragmente zur Disproportionierung neigen – eine konkurrierende Nebenreaktion, die den Reaktionsverlauf jedoch nicht maßgeblich beeinflusst.

Kapitel 3 untersucht einen Vororganisationsansatz zur kontrollierten Radikalrekombination an Bismut im Rahmen decarboxylierender C–N-Kupplungen. Während Bismut(II)-Radikalfragmente typischerweise schwer kontrollierbar sind und C-Radikale nicht effizient abfangen, ermöglicht die Vororganisation von Carbonsäuren – nach lichtinduzierter Decarboxylierung – die gezielte Rekombination am Bismutmetallzentrum. Dadurch wird eine C–N-Kupplung mit Sulfonamiden ermöglicht.

Kapitel 4 beschreibt die Synthese und pharmakologische Evaluierung eines Acylphloroglucinol-Cannabinoid-Analogons. Eine der untersuchten Verbindungen zeigte eine hohe Affinität zum humanen CB2-Rezeptor sowie eine ausgeprägte Selektivität gegenüber dem CB1-Rezeptor. Dieses Kapitel steht thematisch nicht in direktem Zusammenhang

mit den übrigen Inhalten der Arbeit und stellt eine Fortführung von Forschungsergebnissen aus meiner Masterarbeit dar.

7 Appendix

7.1 Abbreviations

λ	wavelength
APCI	atmospheric-pressure chemical ionization
Ar	arene
calc	calculated
CPS	counts per second
CV	cyclic voltammetry
DCE	1,2- dichloroethane
DCM	dichloromethane
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
e.g.	for example (lat. <i>exempli grata</i>)
eq. or (equiv)	equivalent
EI	electron ionization
ESI	electrospray ionization
Et al.	and others (lat. <i>Et alii</i>)
EA	ethyl acetate
Fc	ferrocene
FID	flame ionization detector
GC	gas chromatography
HAT	hydrogen atom transfer
HE	Hantzsch ester
HRMS	high resolution mass spectrometry

h ν	incident photon energy
IR	infra red
J	coupling constant
LED	light emitting diode
LMCT	Ligand-to-metal charge transfer
LRMS	low resolution mass spectrometry
mCPBA	meta-Chloroperoxybenzoic acid
MS	mass spectrometry
n.d	not detected
NMR	nuclear magnetic resonance
Nu	nucleophile
p.a.	per analysis
ppm	pars per million
PC	photocatalyst
PE	petroleum ether
pKa	acid dissociation constant at logarithmic scale
R	allyl-, aryl- or functional groups
rt	room temperature
SCE	saturated calomel electrode
SET	singe electron transfer
TFA	trifluoracetic acid
THF	tetrahydrofuran
Ts	toluene sulfonyl
UV	ultraviolet
Vis	visible

Vs.	against (lat. versus)
XAT	halogen atom transfer

7.2 Curriculum Vitae

Personal Data

Name:	Dominik Birnthal
Date and place of birth:	20.10.1995
Place of birth:	Burglengenfeld (Germany)
Nationality:	German

EDUCATION

10/2020 – 07/2025	Ph.D. in Organic Chemistry University of Regensburg <i>“Redox Transformations with Bismuth and Light”</i> Supervisor: Prof. Dr. Burkhard König
10/2017 – 09/2020	M.Sc. Chemistry, University of Regensburg <i>“Synthesis and biological evaluation of a novel acylphloroglucinol-cannabinoid analog”</i> Supervisors: Prof. Jörg Heilmann & Prof. Burkhard König
10/2014 – 09/2017	B.Sc. in Chemistry University of Regensburg <i>“Reactivity of a hydrophosphacyclohexadienyl iron complex”</i> Supervisor: Prof. Robert Wolf
09/2006 – 06/2014	Abitur, Gymnasium Parsberg

Conference visits

- | | |
|---|------|
| [5] Poster – ORGCHEM Conference, Regensburg, Germany | 2024 |
| [4] Flash Presentation – Sustainable Chemistry Conference, Goa, India | 2024 |
| [3] Poster – International Conference on Photochemistry and Industry, Wuhan, China | 2023 |
| <i>ACS Award</i> for best Poster | |
| [2] Poster – Conference on Light Induced Transformations, Regensburg, Germany | 2023 |
| [1] Poster & Flash Presentation – CaRLa Winter School, Heidelberg, Germany | 2023 |

Publications

[2] Preassembly-Controlled Radical Recombination at Bismuth:Decarboxylative C–N Coupling with Sulfonamides; Taskinen, E.K., Birnthal, D., Kermelj, V. and König, B. (2025), . Chem. Eur. J. e202500396. <https://doi.org/10.1002/chem.202500396>

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Selected as Editor's Choice article

8 Acknowledgment

Allen voran gilt mein größter Dank Prof. Dr. Burkhard König für die Möglichkeit meine Doktorarbeit unter seiner Aufsicht anfertigen zu dürfen. Vielen Dank für die Freiheit und das Vertrauen in mich bei der Umsetzung meiner eigenen Ideen, die wir zusammen und mit deinen Beiträgen erfolgreich ins Ziel bringen konnten.

Des Weiteren möchte ich den Mitgliedern des Prüfungsausschusses danken. Ich danke Prof. Dr. Oliver Reiser für die Übernahme des Zweitgutachten, Prof. Dr. Frank-Michael Matysik für die Rolle als Drittprüfers, sowie Prof. Dr. Jörg Heilmann für die Übernahme des Prüfungsvorsitzes.

Ein spezieller Dank gilt all meinen Projekt Kollaboratoren, Elina Taskinen, Rok Narobe, Vid Kermelj, Eliseo Lopez und Christoph Haag, dessen Beiträge maßgeblich zum Erfolg der Bismuthprojekte waren. Danke an Julia Brunner und Hannes Schneider für die Zusammenarbeit an den Cannabionoid Projekt.

Vielen Dank an allen festangestellten Mitarbeitern des AK Königs, die den Laden am Laufen halten. Ein herzliches Dankeschön an Barbara Bauer, Ernst Lautenschlager, Britta Badziura, Rudolf Vasold, Julia Zach und Simone Strauß. Besonders möchte ich mich bei Regina Hoheisel bedanken für schönen Spektroelektrochemie-Messungen. Mein Dank gilt Petra Hilgers und Debayan Sarkar für die gemeinsame Organisation unseres DAAD Projektes und der internationalen Zusammenarbeit.

Ausserdem gilt mein Dank allen Mitarbeitern der Zentralen Analytik, der NMR-Abteilung, der Röntgenstrukturabteilung für die gute Zusammenarbeit, sowie Marc Schlosser für die Messung von Pulverdiffraktion.

Vielen Dank an Alena Hölzl-Hobmeier für die hervorragende Organisation des CRC325, das so eine echte Bereicherung zur Arbeit war.

Ein herzliches Dankeschön an alle ehemaligen und aktuellen Mitglieder des AK Königs. Danke für alle Tipps und Ratschläge insbesondere im am Anfang, für die fachliche Expertise, Ermutigungen bei Rückschlägen, gemeinsamen Feiern von Erfolgen und das Teilen schöner Momente.

Hier möchte ich besonders Elina, Vincent, Indra und Jonas erwähnen. Ohne euch wäre jeder Tag viel schwerer gewesen und mein PhD Journey nur ein ganz normaler Job.

Vielen Dank an meinen Laborpartner Sascha für das gute Miteinander im Labor 32.1.13.
Ich hätte mir keine besseren Wegbegleiter für diese Zeit wünschen können.

Zusätzlich bedanke ich mich bei Michela, Rok, Lea, Nico, Jose, Becky, Matthias, Tobi, Uli, Karsten, Jessica, Martin für die schöne Zeit.

Weiterhin möchte ich mich bei Alexander Falk und Sebastian Hauer für die langjährige Freundschaft und die guten Erinnerungen an das Chemiestudium bedanken.

Zu guter Letzt gilt mein großer Dank meinen Eltern Uta und Fritz, sowie meinem Bruder Matthias. Vielen Dank, dass ihr mir diesen Weg ermöglicht habt und mich jeder Zeit so gut wie möglich unterstützt habt.

Danke

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