Institute of Organic Chemistry
Polish Academy of Sciences

Photochemical Generation of Carbenes and Radicals for C-C and C-X Bond Formations at the α-Position to the Carbonyl Moiety

Joseph Patrick Milton MSc

A monothematic series of publications, with commentary, submitted to the Scientific Council of the Institute of Organic Chemistry, Polish Academy of Sciences for the purpose of obtaining a doctoral degree

Supervisor: Prof. Dorota Gryko

Warsaw 2025

Doctoral thesis prepared as part of the Horizon 2020 Marie Skłodowska-Curie ITN "PhotoReAct"

"Photocatalysis as a Tool for Synthetic Organic Chemistry"

Grant Agreement No. 956324

I would like to thank everyone that inspired me along the way:

Prof. Dorota Gryko – for guidance and encouragement throughout my PhD journey,

Prof. John S. Fossey – for putting his faith in me and giving me encouragement to consider a doctoral position outside of the UK,

Group XV – to the many great friends I met along the way:

Adam, Antek, Asia, Basia, Kacper, Kasia O., Kitti, Klaudia, KRJ, Krzysiek D., Krzysiek G., Kuba D., Kuba P., Łukasz, Magda, Marianna, Marzena, Mateusz, Mohad, Monica, Ola P., Ola W., Piotrek B., Piotrek K., Shantanu, Souvik, Szymon, Victor, Wojtuś,

The Family & Magdalena – for their support and love.

Abstract

Photochemistry is a core methodology within modern day organic chemistry. It often enables alternative or complimentary chemistry to traditional reactivity but under milder and greener conditions and therefore is highly desirable.

The carbonyl moiety is ubiquitous within organic chemistry and is a constituent of many fundamental functional groups such as esters, aldehydes and amides. In classical chemistry, α-functionalisation of carbonyl compounds is easily achieved by displacing heteroatoms, for example, the conversion of acyl chlorides to carboxylic acids, however, α-functionalisation of alkyl groups is typically restricted to enolate-derived reactions. Photochemical methods have enabled a wide range of new reactivity within organic chemistry and are also highly relevant in the α-functionalisation of carbonyl compounds. In this context, direct irradiation of diazo compounds, primarily phenyl diazoacetates, within the last decade have been found as a convenient source of singlet carbenes, which can then undergo reactivity such as cycloadditions, X-H insertions and ylide generation.

The main objective of my work was to explore new reactivity of photochemically generated carbenes and radicals towards the construction of C-C and C-X bonds at the α-position to the carbonyl moiety.

Four publications are included as part of the doctoral thesis. The first paper is a book chapter that encapsulates all of the known reactions that utilise photochemically generated carbenes, primarily from diazo compounds but also from silyl ketones that undergo Brook rearrangement to form α-silyloxy carbenes.

The second publication discusses a photochemical cyclopropanation of diazo compounds in a micellar medium, which enables the usage of carbenes in an aqueous environment. We could also generate diazo compounds in-situ from hydrazones with the addition of a base, which yielded the cyclopropane typically in diminished yields but much higher diastereoselectivity.

The third publication describes the first instance of 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones being employed in a photochemical context, which facilitate O-H, S-H and C-H insertion reactions. In addition, I reported the first synthesis of a new group of diazo compounds, namely 4-diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides, and explored their reactivity under violet light irradiation.

The final paper, in collaboration with Dr. Geraldine Masson and Dr. Luc Neuville, reports a photochemical HAT reaction with chiral *N*-sulfinyl imines to synthesise highly diastereoselective amines. Removal of the sulfinyl group brandishes the unprotected amine in 99% ee.

In summary, I have described new bond forming reactions via the generation of reactive intermediates, namely carbenes and radicals, at the α-position to the carbonyl moiety. The majority of my work utilised diazo compounds, which are convenient sources of carbenes and undergo atom efficient reactions without the need for a photocatalyst.

Streszczenie w języku polskim

Fotochemia jest jedną z podstawowych metodologi we współczesnej chemii organicznej. Często jest podejściem komplementarnym lub alternatywnym do metod tradycyjnych, oferując łagodniejsze i bardziej zrównoważone warunki, co czyni ją szczególnie cennym narzędziem.

W chemii organicznej grupa karbonylowa jest kluczowym elementem wielu grup funkcyjnych, takich jak estry, aldehydy i amidy. Funkcjonalizacja tych związków w pozycji α jest stosunkowo łatwa, na przykład poprzez podstawienie heteroatomów podczas przekształcenia chlorków acylowych w kwasy karboksylowe. Jednak możliwości funkcjonalizacji grup alkilowych w tej pozycji są zazwyczaj ograniczone do reakcji przebiegających przez enolany. Metody fotochemiczne umożliwiły odkrycie szerokiego zakresu nowych transformacji w chemii organicznej, a także znajdują istotne zastosowanie w α-funkcjonalizacji związków karbonylowych. W tym kontekście, bezpośrednie naświetlanie związków diazowych, w szczególności 2-fenylodiazooctanów prowadzące do generowania karbenów singletowych, które mogą wstępowaćw reakcje cykloaddycji, insercji wiązania X-H oraz generowania ylidów jest ciekawym podejściem.

Głównym celem mojej pracy było opracowanie nowych fotochemicznych reakcji funkcjonalizacji związków organicznych w pozycji α do ugrupowania karbonylowego przebiegających z udziałem karbenów i rodników.

W skład rozprawy doktorskiej wchodzą cztery publikacje. Pierwsza z nich to rozdział w monografii podsumowujący wszystkie dotychczas znane reakcje z udziałem fotochemicznie generowanych karbenów, głównie z diazozwiązków, ale także z ketonów sililowych ulegających przegrupowaniu Brooka do α-sililoksykarbenów.

Druga publikacja opisuje fotochemiczne cyklopropanowanie związków diazowych w środowisku micelarnym, co umożliwia generowanie karbenów w układach wodnych. Ponadto udowodniłem, że możliwe jest otrzymanie związków diazowych *in situ* z hydrazonów poprzez dodatek zasady, co prowadziło do otrzymania cyklopropanów z nieco niższymi wydajnościami, lecz z wyraźnie wyższą diastereoselektywnością.

Trzecia publikacja przedstawia pierwsze zastosowanie 4-diazoizochinolino-1,3(2*H*,4*H*)-dionów w warunkach fotochemicznych prowadzące do insercji karbenów do wiązania O-H, S-H i C-H. Dodatkowo opracowałem pierwszą syntezę nowej klasy związków diazowych, mianowicie 4-diazo-2*H*-benzo[*e*][1,2]tiazyn-3(4*H*)-onów 1,1-dioksydów, oraz zbadałem ich reaktywność pod wpływem promieniowania w zakresie światła fioletowego.

Ostatnia publikacja, zrealizowana we współpracy z dr Geraldine Masson i dr. Lucem Neuville'em, dotyczy fotochemicznej reakcji HAT (transfer atomu wodoru) z udziałem chiralnych imin *N*-sulfinylowych, prowadzącej do wysoko diastereoselektywnej syntezy amin. Usunięcie grupy sulfinylowej pozwoliło na uzyskanie niezabezpieczonej aminy z enancjoselektywnością 99%.

Podsumowując, moja praca przedstawia nowe możliwości fotochemicznej funkcjonalizacji związków organicznych w pozycji α do ugrupowania karbonylowego. Większość badań koncentrowała się na zastosowaniu związków diazowych jako dogodnych prekursorów karbenów, które umożliwiają przeprowadzanie reakcji o wysokiej efektywności atomowej, bez konieczności stosowania fotokatalizatora.

Table of Contents

Abstract **7**

Streszczenie w języku polskim **8**

1. List of Publications in the Doctoral Thesis **11**

2. List of Publications Not Included in the Doctoral Thesis **12**

3. List of Abbreviations **13**

4. Foundation and Objective of the Thesis **15**

5. Photochemical Functionalisations at the α-Position to the Carbonyl Moiety **17**

5.1. Photochemistry – General Information 17

5.2. Carbene Chemistry 18

5.2.1. Diazo Compounds – A General Introduction 18

5.2.2. Direct Irradiation of Diazo Compounds 19

5.2.2.1. [2+1] Cycloaddition Reactions 21

5.2.2.2. Reactions Involving Ylide Intermediates 23

5.2.2.2.1. X-H Insertion Reactions 25

5.3. Radical Chemistry 28

5.3.1. Generation of Radicals from Diazo Compounds 28

5.3.2. Generation of Radicals in the α-Position to the Carbonyl Moiety 29

5.4. Summary 31

6. Own Research **32**

6.1. Photochemical Cyclopropanation of Diazo Compounds in Micellar Media 32

6.2. Photochemical X-H Insertion Reactions of 4-Diazoisoquinoline-1,3(2*H*,4*H*)-diones 35

6.3. Diastereoselective Synthesis of Amines via a Photochemical HAT Reaction 39

6.4. Conclusions 41

7. References **42**

8. Original Publications **49**

9. Supporting Information for the Original Publications **99**

10. Author Declarations **239**

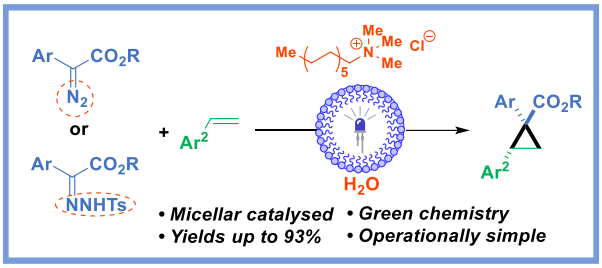
1. List of Publications in the Doctoral Thesis

1. *Photo-Induced Carbene Transformations to Heterocycles*

J. P. Milton, D. Gryko, *Top. Heterocycl. Chem.*, **2023**, *59*, 1 – 34

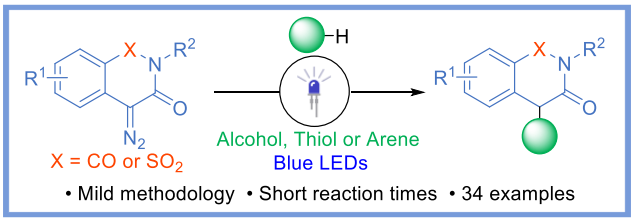
2. *Photochemical Cyclopropanation in Aqueous Micellar Media – Experimental and Theoretical Studies*

J. P. Milton, A. Milanowski, M. Anderrson, D. Gryko, *Chem. Commun.*, **2024**, *60* (33), 4483 – 4486



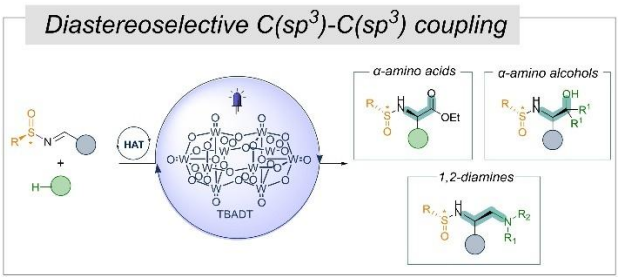
3. *Photochemical Functionalization of 4-Diazoisoquinoline-1,3(2H,4H)-diones and Their Sulfoxide Analogs*

J. P. Milton, D. Gryko, *ACS Org. Inorg. Au.*, **2025**, doi.org/10.1021/acsorginorgau.5c00017



4. *TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines*

M. Leone, **J. P. Milton**, D. Gryko, L. Neuville, G. Masson, *Chem. Eur. J.*, **2024**, *30*, e202400363



2. List of Publications Not Included in the Doctoral Thesis

1. *Azetidines and Their Applications in Asymmetric Catalysis*

J. P. Milton, J. S. Fossey, *Tetrahedron*, **2021**, *77*, 131767

3. List of Abbreviations

Ac	Acetyl group
Acr	Acridinium
Alk	Alkyl group
Ar	Aryl group
Boc	*tert*-Butoxycarbonyl group
BHT	Butylated hydroxytoluene; 2,6-di-*tert*-butyl-4-methylphenol
bpy	2,2'-Bipyridine
CMC	Critical Micellar Concentration
COSMO-RS	COnductor-like Screening MOdel for Real Solvents
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMC	Dimethyl carbonate
dmp	2,9-Dimethyl-1,10-phenanthroline; neocuproine
DMSO	Dimethyl sulfoxide
DoE	Design of Experiments
dr	Diastereomeric ratio
DTAC	Dodecyltrimethylammonium chloride
dtbpy	4,4-Di-*tert*-butyl-2,2-dipyridyl
EDG	Electron-donating group
ee	Enantioselective excess
EnT	Energy Transfer
Et	Ethyl
EWG	Electron-withdrawing group
EY	Eosin Y
HAT	Hydrogen Atom Transfer
HFIP	1,1,1,3,3,3-Hexafluoroisopropan-2-ol
$h\nu$	Light
ISC	Intersystem Crossing
LEDs	Light-Emitting Diodes
Me	Methyl
Mes	Mesityl; 2,4,6-trimethylphenyl
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
NHPI	*N*-hydroxyphthalimide
NMR	Nuclear Magnetic Resonance
NuH	Nucleophile
PC	Photocatalyst
Ph	Phenyl group
Piv	Pivaloyl group; 2,2-dimethylpropan-1-one
PMP	*para*-Methoxyphenyl
ppy	2-Phenylpyridine
R_f	Fluorine-containing alkyl chain
SET	Single-Electron Transfer
TBADT	Tetra-*n*-butylammoniumdecatungstate;
^{t}Bu	*tert*-Butyl group
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TFA	Trifluoroacetic Acid

THF	Tetrahydrofuran
THP	Tetrahydropyran
Tol	Tolyl group
Ts	Tosyl groupp, *p*-toluenesulfonyl
UV	Ultraviolet
UV-Vis	Ultraviolet-visible

4. Foundation and Objective of the Thesis

The carbonyl bond (C=O) is ubiquitous within organic compounds and is a constituent within a broad range of functional groups such as aldehydes, ketones and esters (Figure 1A). With their wide prominence, a vast number of transformations are known and available, which emphasises their usefulness in various synthetic routes, coupled with their high commercial availability and relatively low price. In the context of functionalising the α-position to the carbonyl moeity, chemists typically perform transformations at the heteroatom, such as converting carboxylic acids to acyl chlorides or amides. However, when an alkyl substituent is present at the α-position, with the addition of a base, it is possible to perform further transformations via enolate chemistry. This is widely explored in a plethora of known reactions (such as Aldol and Haloform) and condensations (such as Dieckmann and Knoevenagel) (Figure 1B).

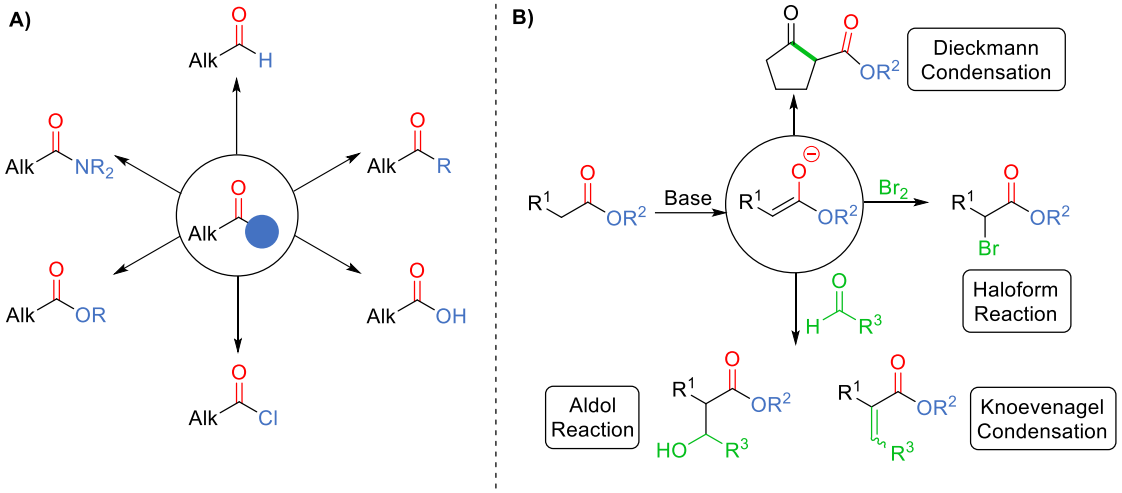


Figure 1: **A**) Carbonyl compounds **B**) Typical reactions that revolve around functionalisation of enolate intermediates

Photocatalytic reactions of carbonyl compounds usually involve the interaction of a photocatalyst in the excited state with the substrate. The resulting intermediate often undergoes cleavage of the relatively labile α-heteroatom group, such as the conversion of carboxylic acids to carboxylic radicals,[1] full decarboxylation of NHPI esters,[2] the formation of acyl radicals from acyl chlorides,[3] and others[4–6] (Figure 2A). Furthermore, we can also photochemically functionalise the α-methylene position with the use of diazo compounds, which are typically synthesised via enolate chemistry. Alternatively, they can also be synthesised by treating hydrazone compounds with an oxidant[7] or a base, which is also a viable strategy when performed in-situ.[8] Exposure of diazo compounds to high temperature, a metal-catalyst (typically rhodium) or, most relevant to this work, light, cleaves dinitrogen to brandish a carbene species. It is commonly accepted that under direct irradiation a singlet carbene is generated, whilst photosensitisation with a photocatalyst forms a triplet carbene;[9] radicals can also be formed with a photocatalyst, however there are limited literature reports on the matter.[10,11] With this in mind:

The aim of my PhD was to explore new reactivity of photochemically generated carbenes and radicals towards the construction of C-C and C-X bonds at the α-position to the carbonyl moiety.

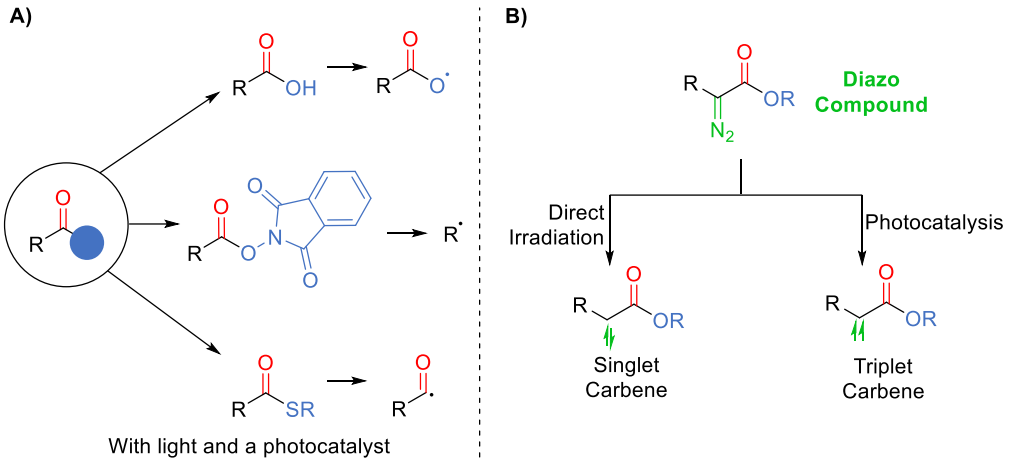


Figure 2: **A**) Photocatalytic α-functionalisations of carbonyl compounds **B**) General scheme for the formation of singlet and triplet carbenes from diazo compounds

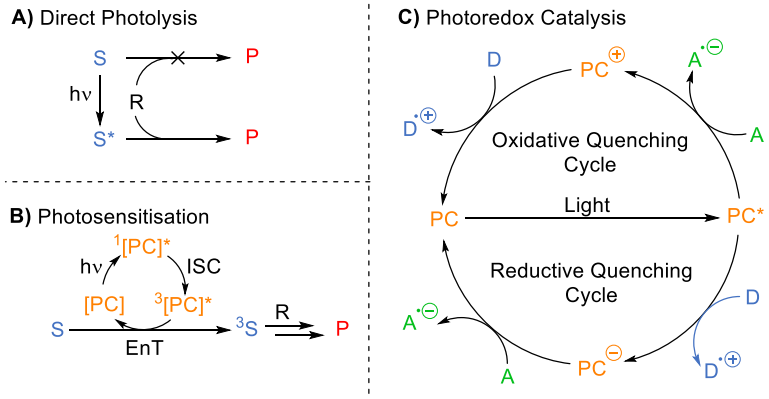
5. Photochemical Functionalisations at the α-Position to the Carbonyl Moiety

5.1. Photochemistry – General Information

Photochemistry is an integral methodology within modern organic chemistry. Sitting alongside electrochemistry and mechanochemistry, this trifecta in the present-day contribute to green chemistry, enabling reactions that are typically inaccessible via standard means in an eco-friendly manner removing the need for harsh or toxic reagents.[12]

Photochemistry has been used by nature since the dawn of time, where plants use light energy to convert water and carbon dioxide into oxygen, and is one of the most fundamental processes on the planet. In organic chemistry, the development of photochemistry is largely credited to Giacomo Ciamician for his work starting at the beginning of the 20th century, and is well-known with the famous photo of his reaction flasks atop the University of Bologna rooftop.[13]

In the 21st century, photochemistry is still a thriving field and can be broken down into three fields: direct photolysis, photosensitisation, and photoredox catalysis. **Direct photolysis** is the most straightforward and convenient method, because it simply relies on irradiating a substrate with light within a specific wavelength range (determined by UV-Vis spectroscopy), to undergo the desired transformation (Scheme 1A).[14] This is typically exploited with substrates that contain labile moieties, such as diazo or azide groups, that will undergo an energetically favourable process of losing dinitrogen. This also enables highly atom efficient reactions without the need for any external catalyst or additives in many cases. The latter two fields, both require a photocatalyst and are useful when compounds do not natively absorb light in a conveniently accessible region. The **photosensitisation** mechanism relies on the irradiation of a photocatalyst, which excites an electron to the singlet state. The excited species then undergoes intersystem crossing to the triplet state and subsequently engages in an energy transfer process with a substrate generating radical or triplet carbene species (Scheme 1B). Some deem this method as essentially enabling "indirect photoexcitation of a substrate".[15] **Photoredox** reactions require the excitation of a photocatalyst which subsequently oxidises or reduces a substrate typically generating a radical cation and a radical anion (Scheme 1C).[16,17] Photocatalysis can also take part in other crucial reactions such as hydrogen atom transfer (HAT) and halogen-atom transfer reactions (XAT).[18,19]



Scheme 1: General schematic for the three types of photochemical reactions: direct photolysis, photosensitisation and photoredox catalysis

The majority of photochemical reactions discussed in this thesis focusses on the direct photolysis of diazo compounds and this type of reactivity is covered in the literature section too. A smaller section is dedicated to photocatalytic radical-generating at the α-position to the carbonyl moiety.

5.2. Carbene Chemistry

Carbenes are typically used as reactive intermediates, although some persistent species are known, with *N*-heterocyclic carbenes (NHCs) being the most prominent.[20] The carbon atom of carbenes possesses only six valence electrons, which adopts a sp^2 configuration and these species are divided into two classes: singlet and triplet carbenes, depending on their spin state. Singlet carbenes bear a lone pair of electrons in the *p* orbital leaving an empty sp^2 orbital, whereas triplet carbenes have one unpaired electron in both the *p* orbital and the sp^2 orbital and thus can be considered as diradical species (Figure 3).[21] Carbenes were traditionally generated by the α-elimination of halogenated compounds (such as chloroform),[22] but now diazo compounds are the most common precursors and are discussed in-depth below.

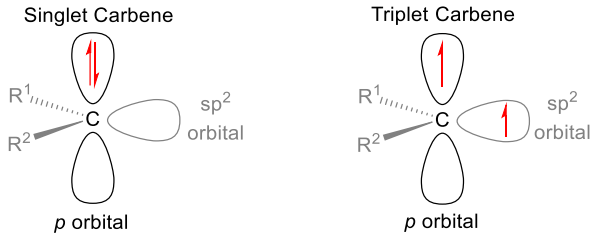


Figure 3: Orbital diagrams of singlet and triplet carbenes

5.2.1. Diazo Compounds – A General Introduction

The prototypical diazo compound is diazomethane, which exists as a yellow gas and is highly sensitive, explosive, and toxic. However, diazomethane is an incredible methylating reagent, which spontaneously methylates carboxylic acids[23] and is a crucial reagent in the Arndt-Eistert[24] and Büchner-Curtius-Schlotterbeck[25] reactions. Many other diazo compounds also suffer from instability and explosiveness, although to a significant lesser extent than diazomethane, and are stabilised with electron-withdrawing substituents, typically carbonyl-containing groups such as esters or ketones (Figure 4).[26] However, these more stable diazo compounds do not typically exhibit spontaneous reactivity and require activation via metal-catalytic, thermal, or photochemical means.

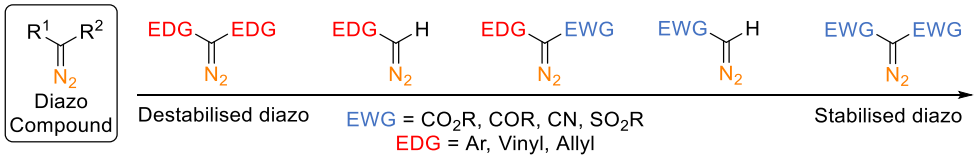
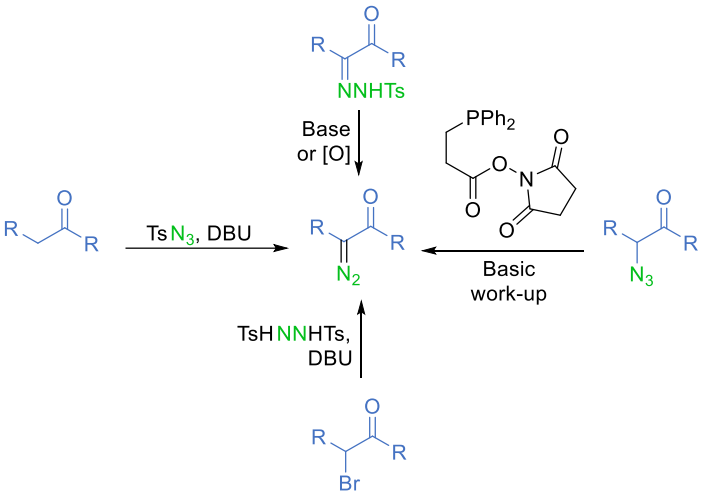


Figure 4: General schematic illustrating the stability of diazo compounds

Such compounds are typically synthesised via the Regitz diazo transfer method from compounds bearing a labile methylene group, such as malonates or esters of phenylacetic acid.[27] The reaction involves the generation of an enolate in the presence of an amine base, typically DBU or

triethylamine, and the addition of an azide, commonly *p*-toluenesulfonyl azide, which affords the desired diazo compound, with concomitant formation of *p*-toluenesulfonamide, in good yields (>70%). Several other methods are known, such as oxidising hydrazones[7] or treating them with a base,[8] conversion of azides with 2,5-dioxopyrrolidin-1-yl 3-(diphenylphosphaneyl)propanoate,[28] or displacement of halogens with *N*,*N*'-bis(*p*-toluenesulfonyl)hydrazine (Scheme 2).[29]

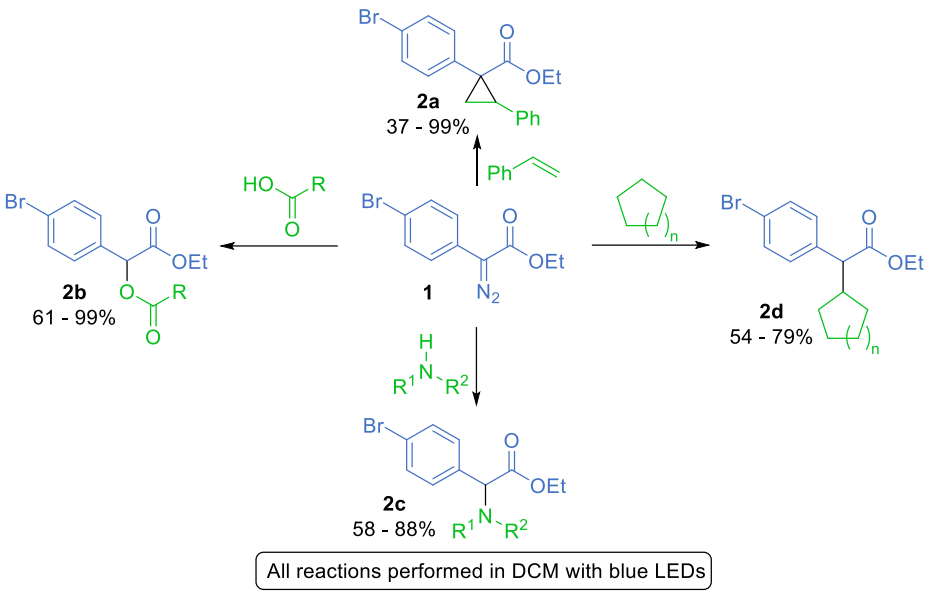


Scheme 2: Standard methods for the synthesis of diazo compounds

5.2.2. Direct Irradiation of Diazo Compounds

Direct photochemical activation of diazo compounds was limited for a long time because high-powered UV lamps were typically used as the light source. This severely constrained the number of available transformations as many functional groups could be unintentionally cleaved during the reaction, triggering numerous undesired side reactions.[30] A review article by Galkina and Rodina, published in 2016, exemplifies this trend cataloguing all known photochemical transformations of diazo compounds, where the majority of the reported reactions used a 300 nm (or lower) lamp.[31] In 2018, Jurberg and Davies found that the substituents attached to the diazo compound strongly influences their absorption spectra, where phenyl diazoacetates were shown to absorb in the blue region of light. In contrast, ethyl diazoacetate and dimethyl diazomalonate exhibit absorption in the UV or violet region respectively. To highlight the synthetic utility, they demonstrated that phenyl diazoacetates, primarily with ethyl 2-(4-bromophenyl)-2-diazoacetate (**1**), can undergo cyclopropanation with styrenes (**2a**), O-H insertion with carboxylic acids (**2b**), N-H insertion with amines (**2c**), and C-H insertion with cycloalkanes and electron-rich aromatics (**2d**) (Scheme 3).[32]

Koenigs and co-workers explored the effect of substituents attached to diazo compounds in further detail with biaryl diazo compounds. The maximum absorption of (4-methoxyphenyl)(4-nitrophenyl)diazomethane (**3a**) is 409 nm, however more electron-rich diazo compound such as diphenyldiazomethane (**3b**) and bis(4-methoxyphenyl)diazomethane (**3c**) exhibit much higher λ_{max} values of 522 nm and 543 nm respectively (Scheme 4A). Despite this, blue light irradiation still remained optimal for all three diazo compounds when examining their reactivity with aryl-substituted acetylenes and gave interesting divergent reactivity. Compound **3a** underwent cyclopropenation (**4**), while **3b** engaged in a radical cascade reaction to form indenes, whereas diazo **3c** performed a C-H insertion (**6**) reaction at the terminal position which is rather irregular outside of NHC chemistry (Scheme 4B). The reaction outcomes were justified

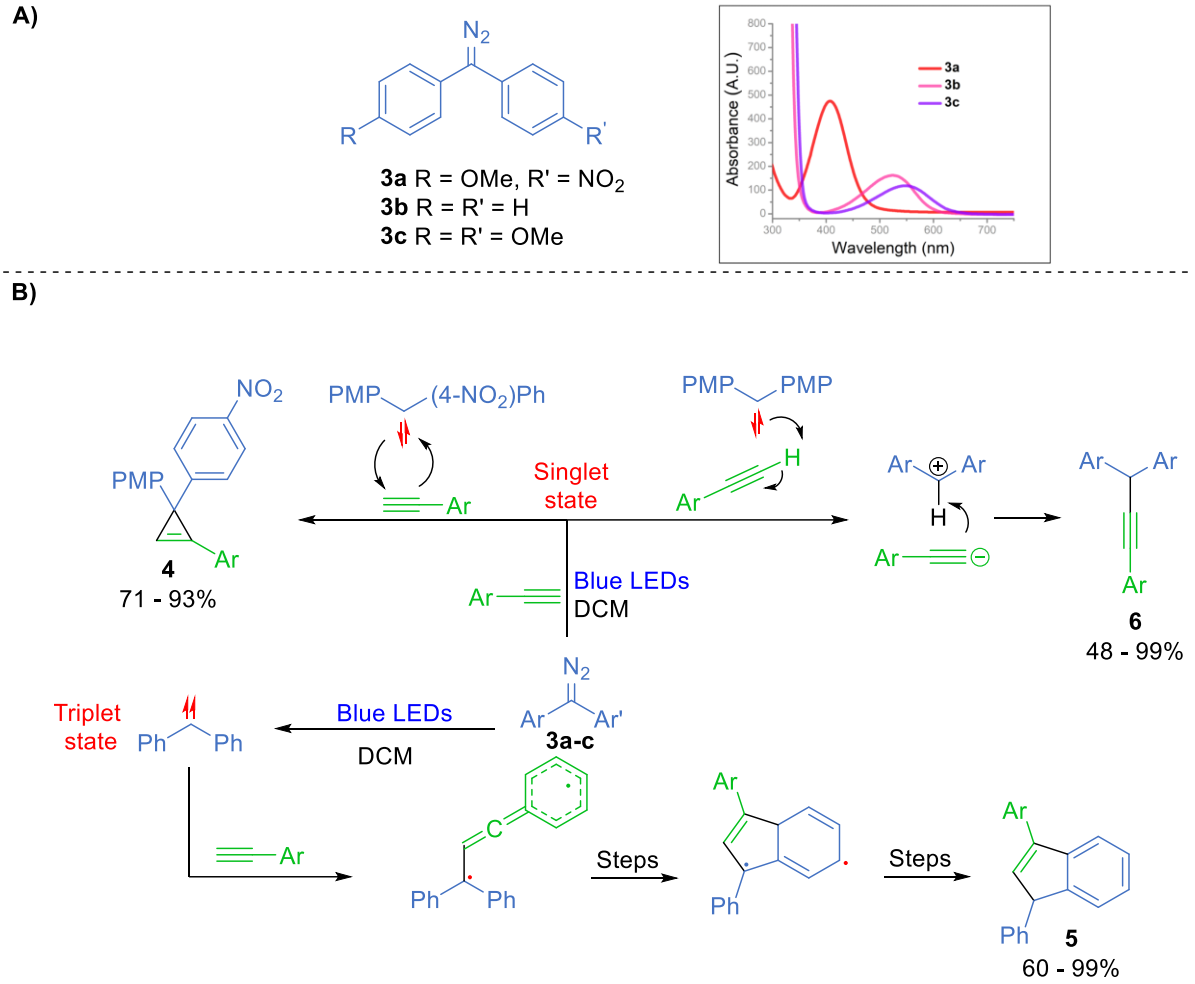


Scheme 3: O-H, N-H and C-H insertion reactions of ethyl 2-(4-bromophenyl)-2-diazoacetate (**1**)

with computational studies on the carbene formed from the series of diazo compounds, which showed that the substituents are affecting the polarity at the carbene-containing carbon and the spin-state of the resultant carbene. The carbene from **3a** and **3b** both exhibit a small energy difference in their singlet and triplet energies, and thus both spin states are accessible. However, the carbene of **3a** was slightly more favourable towards the singlet state and thus underwent a classical cycloaddition, whereas the carbene of **3b** was preferable to the triplet state, with the respective transition state also being lower in energy enabling the biradical species, which undergoes the cascade to the indene product. In the case of carbene generation from **3c**, hydrogen abstraction is highly favourable as the subsequent carbocation is stabilised with the electron-donating substituents, which can then undergo nucleophilic attack of the deprotonated alkyne.[33]

Naturally, not all diazo compounds are able to absorb visible light, but they can still be used in an indirect manner via the irradiation of a photocatalyst. Common photocatalysts in the area of diazo chemistry are tetra aryl porphyrins,[14,34] $Ru(bpy)_3$,[11,35] and $\{Ir[dF(CF_3)ppy]_2(dtbpy)\}PF_6$.[30,36,37] The use of a photocatalyst effects the generation of the carbene, typically furnishing a triplet carbene, whereas direct irradiation generates singlet carbenes, which can lead to new and diverse reactivity.[9] However, these methods are not discussed at length in the literature section as they are not relevant to my work, which primarily focussed on the direct irradiation of diazo compounds.

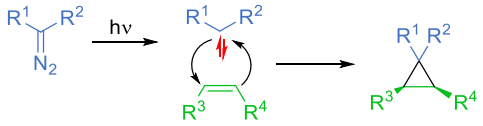
In summary, the nature of the substituents attached to the diazo moiety plays a significant role in its absorption spectra. Generally, electron-donating moieties enable bathochromic shifts of the absorption spectra allowing diazo compounds to undergo photochemical reactions with lower energy light such as green or red light.



Scheme 4: **A**) UV-Vis spectra of biaryl diazo compounds, UV-spectra from Ref. 33. **B**) Divergent reactivity of biaryl diazo compounds

5.2.2.1. [2+1] Cycloaddition Reactions

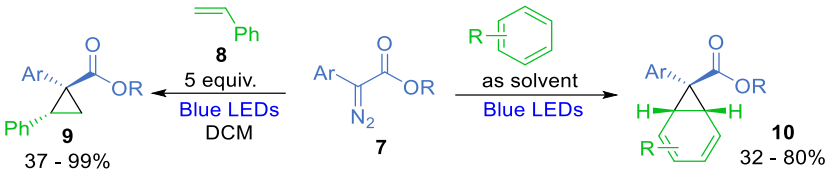
In the repertoire of carbene-based reactions, cycloadditions, and specifically [2+1] cycloadditions, are debatably one of the most fundamental. The reaction is particularly useful with singlet carbenes as the reaction proceeds in a concerted stereospecific manner, which enables retention of the olefin stereoselectivity (Scheme 5).[38]



Scheme 5: General mechanism for [2+1] cycloaddition reactions from singlet carbenes

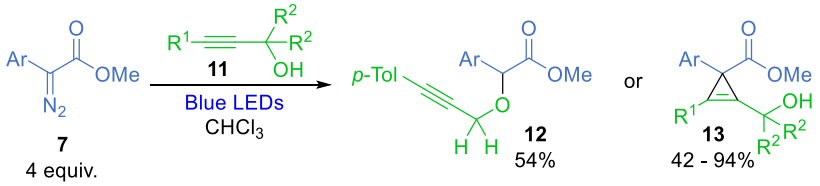
In Jurberg and Davies seminal work showing the blue LED irradiation of phenyl diazoacetates (**7**), they exemplified its effectiveness in one of the most iconic reactions of diazo compounds, cyclopropanation with styrene (**8**) (Scheme 6, left).[32] The influence of various functional groups were tested as the ester substituent including 2,2,2-trichloroethyl, (trimethylsilyl)methyl, and 2-(triisopropylsilyl)ethyl groups. The reaction delivered cycloadducts in high yields and excellent diastereoselectivity (typically >15:1 dr) (**9**). Guo et al. expanded on this reactivity by developing

the [2+1] cycloaddition with aromatic compounds and using them as solvents (Scheme 6, right).[39] Cycloaddition with common aromatic compounds such as benzene, toluene and xylenes yielded the products in high diastereoselectivity (**10**). Polyaromatics such as naphthalene, anthracene and triphenylene required solubilisation in DCM, as they are solids at room temperature, but still maintained the excellent diastereoselectivity. Later work from Guo et al. also demonstrated similar results for the cycloaddition with cyclooctatetraene.[40]



Scheme 6: Cycloaddition of diazo compounds with styrenes and arenes under blue LEDs irradiation

He and Koenigs explored the reaction of diazo esters **7** with propargylic alcohols **11**, which displayed divergent reactivity depending on the substituents at the α-position to the alcohol (Scheme 7).[41] Primary alcohols (R^2 = H) afforded exclusive formation of the O-H insertion product **12**, however when alkyl or aromatic substituents are present at the α-position, only the cyclopropenation reaction takes place (**13**); unfortunately, no explanation was given to justify this divergent reactivity. Yields were generally around 70% with different substituents upon the aromatic ring of the diazo compound and when altering the R^1 group.



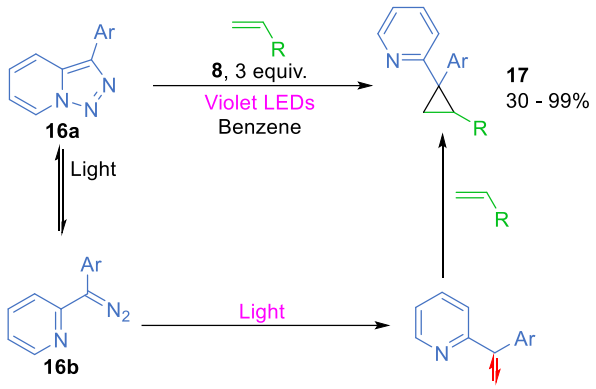
Scheme 7: Blue light irradiation of diazo compounds with propargylic alcohols

Klöpfer et al. reported the cyclopropanation of heteroaromatics **14** under photochemical flow conditions (Scheme 8).[42] After a substantial DoE optimisation of the reaction conditions, the majority of the reported reactions yielded the cycloadduct products **15** in approximately 55% yield, although furan performed optimally in 82% yield. However, the main allure of this methodology was its effectiveness in large-scale reactions. The optimum batch conditions produces a maximum of 0.41 gram per hour, whereas flow conditions, in their 2.7 ml reactor, enabled over one gram per hour highlighting the efficiency benefits of photochemistry in flow.

Scheme 8: Photochemical flow [2+1] cycloaddition of diazo compounds with carbo- and heterocycles.

Furthermore, Gevorgyan and co-workers reported an intriguing example of cyclopropanation with pyridotriazoles **16a**, which upon light irradiation undergo a rearrangement to form (2-pyridyl)diazo compounds **16b** (Scheme 9).[43] These, in turn, furnish a carbene, which subsequently undergoes the desired cyclopropanation; despite benzene being used as the solvent, no comment was made if any undesired cycloaddition with the solvent occurred. Yields were typically fairly good

(>70%), however diastereoselectivity was poor in most cases (~1:1). The in-situ generated (2-pyridyl)diazo compounds **16b** were further explored for other reactivity such as X-H insertions, and arylations with boronic acids.

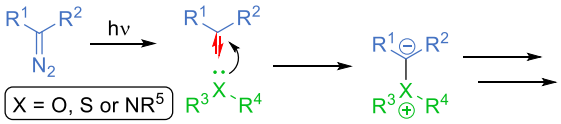


Scheme 9: Photochemical [2+1] cycloaddition of pyridotriazoles with olefins

In summary, singlet carbenes undergo cyclopropanation reactions from styrenes and heteroaromatics, such as indoles, with relative ease. Cyclopropenation is also known but is not as commonly observed in the literature as the reaction is not as general and depends on the substituents attached to the alkyne moiety.

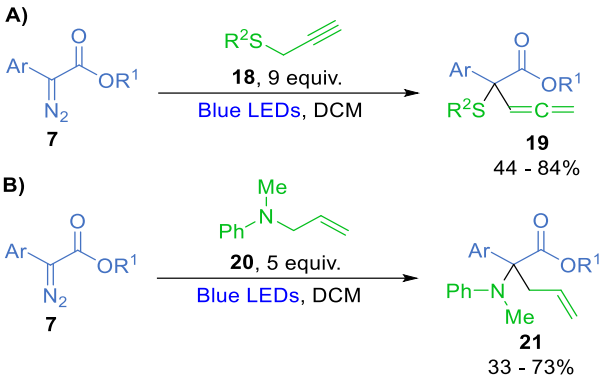
5.2.2.2. Reactions Involving Ylide Intermediates

Compounds bearing moieties with electronegative atoms, typically oxygen, sulfur, and nitrogen, attack singlet carbenes to generate ylides that undergo a plethora of further reactivity that is explored below (Scheme 10). Typically, the heteroatom cannot be substituted with hydrogen as X-H insertion takes place instead (section 5.2.2.2.1). Kirmse describes this interaction as analogous to the behaviour of Lewis acids and bases.[44]



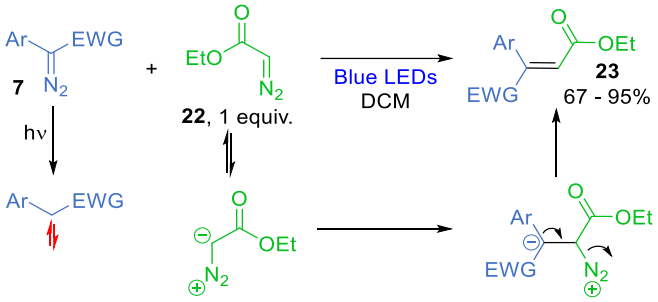
Scheme 10: General mechanism for the formation of ylides from singlet carbenes

Orłowska et al. reported a photochemical Doyle-Kirmse reaction of diazo compounds **7** with substituted propargyl sulfides **18** (Scheme 11A).[45] The optimisation revealed that adding the diazo reagent in two portions over three hours enables the optimum yield of 80%. The effect of different aryl substituents on the diazo compound was explored at length but yields held constant from 70 - 80%, with only notable drops being observed with strong electron-withdrawing (NO_2) or electron-donating (OMe) groups. The Koenigs group reported a similar Doyle-Kirmse rearrangement reaction from allyl amines **20** and diazo compounds (Scheme 11B).[46] Other photochemical Doyle-Kirmse reactions are known from 4-diazo-2-tosyl-1,4-dihydroisoquinolin-3(2*H*)-one,[47] *N*-sulfenyl phthalimides[48] and 3,3-difluoroallylsulfides.[49]



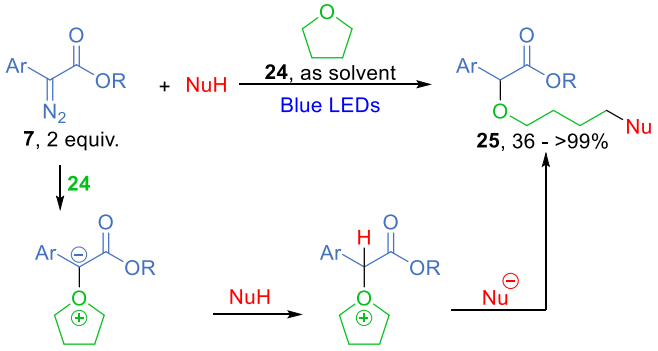
Scheme 11: Photochemical Doyle-Kirmse reaction with propargyl sulfides.

Zhou et al. ingeniously exploited the difference in the absorption spectra of diazo compounds to enable a "cross-coupling" of diazo compounds (Scheme 12).[50] Whilst phenyl diazoacetates (**7**) absorb in the blue region, ethyl diazoacetate (**22**) absorbs in the UV/violet region. Thus, upon blue LED irradiation, only the phenyl diazoacetate undergoes excitation with the concomitant loss of dinitrogen brandishing the carbene. This generates an ylide with compound **22** that can undergo an elimination reaction to give tri-substituted alkenes **23** with high *E*-selectivity in the majority of cases.



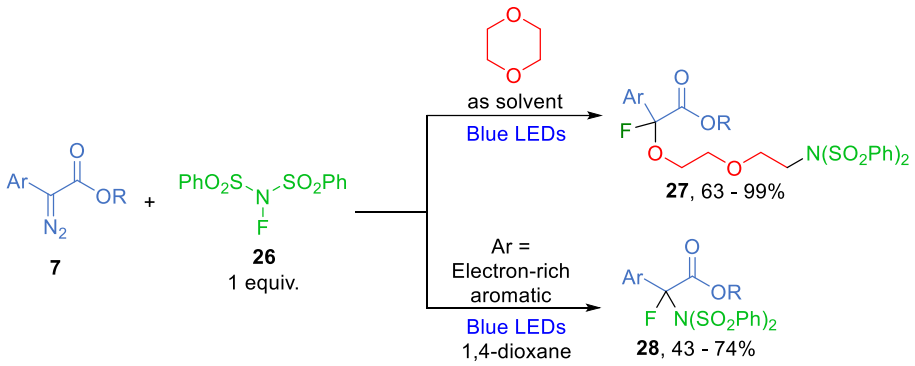
Scheme 12: "Cross-coupling" reaction of two different diazo compounds

Jurberg and co-workers explored the generation of oxygen-ylides from tetrahydrofuran (**24**) in a photochemical manner, which subsequently react with nucleophiles to give ring-opened products **25** (Scheme 13).[51] Yields were high in most situations with various nucleophiles such as carboxylic acids, water, alcohols, HCl, oximes and amides. Larger cyclic ethers were also compatible in the reaction but typically required more aggressive conditions, such as with tetrahydropyran and 1,4-dioxane that performed optimally only under photochemical conditions at 60 °C. This reaction is known under thermal conditions too.[52]



Scheme 13: Ring-opening of THF with a nucleophile via a photochemically-generated ylide.

He et al. utilised NFSI (**26**) to synthesise fluorine-containing compounds (Scheme 14).[53] The reaction undergoes an analogous mechanism, as in Scheme 13, with the ylide being first fluorinated by NFSI and subsequently attacked by the anionic amine intermediate **27**. Yields were typically high, even when using other cyclic ethers, including tetrahydropyran and oxepane without any modification of the reaction conditions. When performing the reaction with diazo compounds with electron-rich substituents such as *p*-tolyl, 4-ethoxyphenyl and benzo[*d*][1,3]dioxole, the reactivity of the carbene is significantly enhanced, bypassing the ylide intermediate, and undergoing direct N-F insertion **28**.

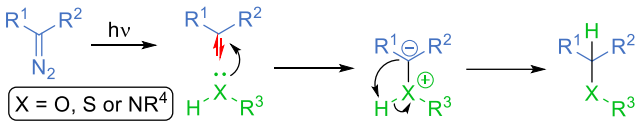


Scheme 14: Ring-opening of 1,4-dioxane with NFSI enabling fluorination of diazo compounds.

In summary, the generation of ylides from singlet carbenes enables a broad range of subsequent transformations. The ylides are typically derived from *O*-heterocycles but are also known from thiols and diazo compounds.

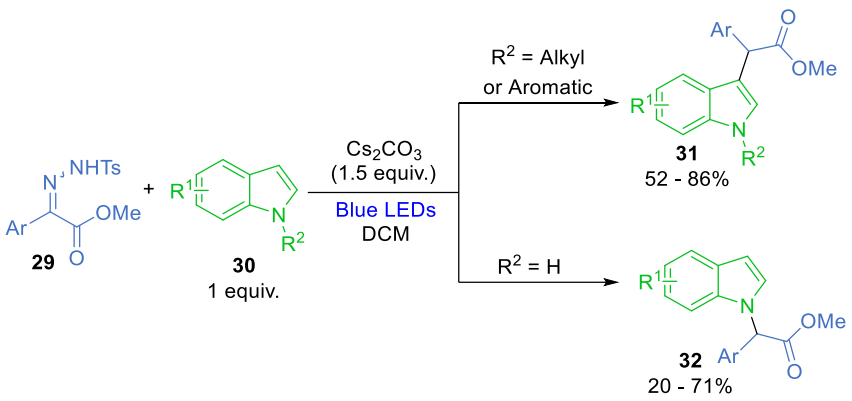
5.2.2.2.1. X-H Insertion Reactions

X-H insertion reactions proceeds via ylide formation, as seen previously (Scheme 10), but the subsequent carbanion intermediate captures the labile hydrogen atom attached to the cation to afford the product (Scheme 15). Typically, these reactions are achieved with alcohols, carboxylic acids, thiols and amines.



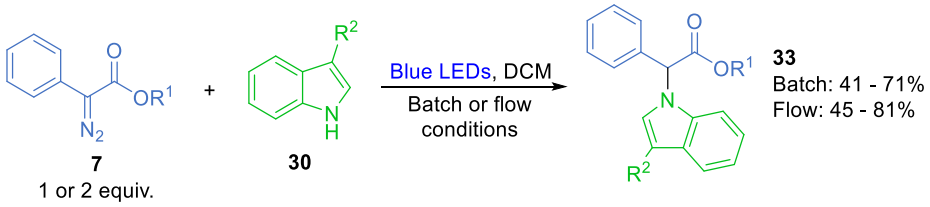
Scheme 15: General mechanism for X-H insertion reactions

Jana et al. explored the reactivity of in-situ generated diazo compounds, from hydrazones **29**, with indoles **30** to afford C3-substituted heterocycles **31** and N-H insertion products **32** (Scheme 16).[54] In respect to the C-H insertion reaction, they compared the efficiency of the reaction with methyl phenyldiazoacetate generated in-situ or used neat, which gave a 50% difference in the yield for the highlighted cases, although no justification was given. C-H insertion from the hydrazone proceeded in high yields in all cases regardless of the aryl substituents within the diazo or the indole. Generally, the *N*-substituent is also tolerable with a wide range of alkyl or aromatic substituents, but when nitrogen is substituted with a Boc or a Piv group, cyclopropanation takes place instead. When nitrogen is unsubstituted, predictably, N-H insertion took place instead and gives moderate yields from various *N*-heterocycles such as indoles, carbazoles and tetrahydroquinolines.



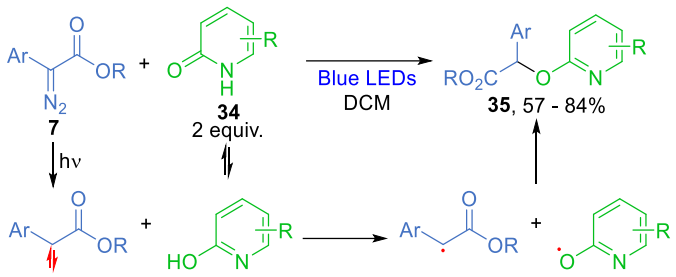
Scheme 16: C3-substituiton and N-H insertion of indoles from in-situ generated diazo compounds from hydrazones

N-H insertion of *N*-heterocycles is already known from previous reports from the groups of Koenigs[54,55] and Jurberg.[56] Maiti et al. took inspiration from these works and optimised the reaction for 3-substituted indoles **30** under batch and flow conditions (Scheme 17).[57] On average, all examples that were tested under both conditions observed an approximate 6% increase in yield when performed in flow conditions, with the added benefit of substantially shorter reaction times (22 hours in batch versus 3.15 hours in flow). They could also prove with a Hammett plot that the nature of the C-3 substituent plays a substantial role on the outcome of the reaction where electron-withdrawing moieties increase the acidity of the N-H proton, which subsequently increases the reaction rate and gives higher yields of the N-H insertion product **33**.



Scheme 17: Photochemical N-H insertion of 3-substituted indoles under batch and flow conditions

In addition to C-H and N-H insertions, O-H insertion represents another major pillar of X-H insertion chemistry. Many of these works on O-H insertion with alcohols have been reported by the Koenigs group and are discussed in greater detail in section 6.2.[58,59] Nevertheless, Huo and co-workers reported the O-H insertion of 2-pyridones **34**, which exist as lactam/lactim tautomers, that proceeds in high yields (**35**) (Scheme 18).[60] The mechanistic aspect of this reaction is particularly intriguing as the intermediates could be detected with radical traps such as BHT and TEMPO, implying the reaction proceeds via a radical intermediate, which is rather uncommon. Thus, they proposed that light irradiation affords the free carbene, which reacts with the lactim form of 2-pyridone and abstracts a proton. The two radicals generated subsequently combine together to give the O-H insertion product.

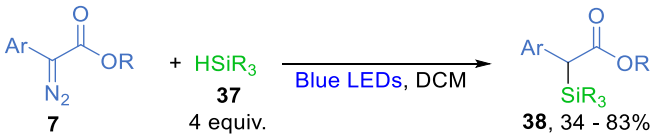


Scheme 18: O-H insertion reactions of 2-pyridones

As previously shown in Scheme 4A, biaryl diazo compounds can possess bathochromically shifted absorption spectra depending on the substituents, with bis(4-methoxyphenyl)diazomethane (**3c**) exhibiting a shoulder in the red region.[33] Orłowska et al. took advantage of this by using compound **3c** under direct red light irradiation for various O-H, N-H and S-H insertions reactions (**36**, Scheme 19).[14] Large excesses of the alcohol were required but for N-H or S-H insertion the diazo compound was used in excess; nevertheless, all reactions performed in minimum 55% yield and notably underwent almost quantitative O-H insertion into cholesterol.

Scheme 19: Red-light irradiation of electron-rich diazo compounds

Under photochemical conditions, X-H reactions typically revolve around electronegative atoms such as O-H, N-H and S-H insertions. Si-H insertions on the other hand, are little reported due to the difficulty of getting the reaction to work effectively because of the poor acidity of silanes **37**. Nevertheless, He et al. showed that insertion reactions are indeed viable, typically with triethylsilane as the coupling partner enabling the reaction in 34 – 82% yield (**38**, Scheme 20).[61]



Scheme 20: Photochemical Si-H insertion reaction

In summary, photochemically-generated singlet carbenes generate ylides that can undergo seamless X-H insertion reactions such as O-H, C-H and N-H insertions.

5.3. Radical Chemistry

Free radicals, or known simply as radicals, are fundamental reactive intermediates in organic chemistry that bears, typically, a singular free electron. They exist in a sp^2 configuration and are stabilised by electron-donating groups, similar to carbocations (Figure 5).[62] In modern times, photocatalysis offers a mild and versatile way to generate radicals, which has contributed to its widespread adoption.[63] Radical chemistry is usually explored with carbon-based radicals but is also widely explored with other atoms such as boron,[64,65] oxygen, nitrogen and sulfur.[66–68] Below, some examples of photocatalytic generation of radical species in the α-position to carbonyl bonds are highlighted.

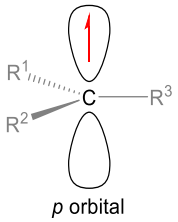
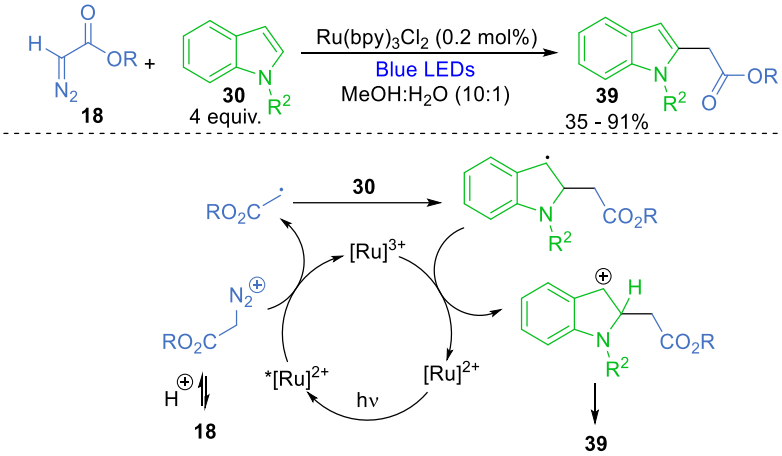


Figure 5: Orbital diagram of carbon free radicals

5.3.1. Generation of Radicals from Diazo Compounds

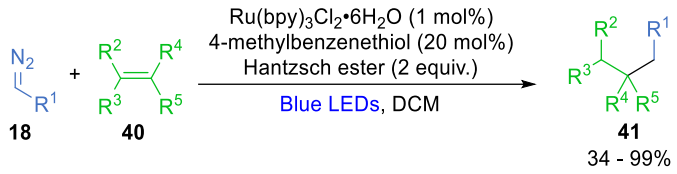
The alkylation of indoles **30** usually occurs at the C3-position as it is the most reactive position within the heterocycle.[69] However, Ciszewski et al. found that the C2-position can be selectively alkylated by radicals (**39**) generated from diazoacetates **18** under photoredox conditions (Scheme 21).[11] This offers complimentary reactivity to the direct irradiation of diazo compounds, which gives C3-alkylated products.[32,54] The C2-alkylation was effective with various indoles, including *N*-methyl and unsubstituted derivatives, as well as a selection of pyrroles too.



Scheme 21: Alkylation of indoles via photocatalytically generated radicals from diazo compounds

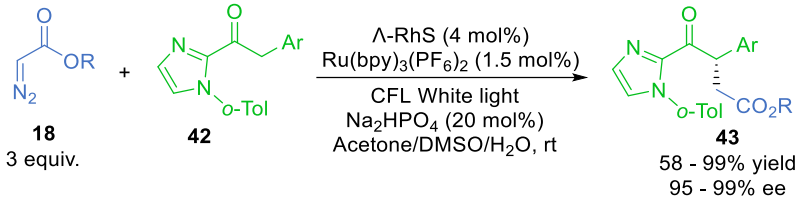
The Doyle group showed that the radical intermediate formed from diazo compounds reacts with olefins **40** to form "hydroalkylation" products **41** (Scheme 22).[70] A wide variety of olefins were viable under the reaction conditions with styrenes substituted with moieties such as pinacol boronate esters, carboxylic esters and pyridines. Dienes such as 2,3-dimethylbuta-1,3-diene and 2,3-diphenylbuta-1,3-diene enabled 1,4-addition products, however the substrate scope was limited with tetrasubstituted olefins and provided only traces of material. They also reported that

the reaction is viable in the absence of light with an iron catalyst and *tert*-butyl hydroperoxide as a stoichiometric oxidant.



Scheme 22: Radical coupling of styrenes from diazo compounds

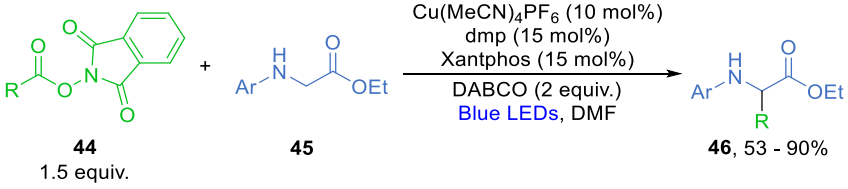
Enantioselective radical reactions from diazo compounds are relatively rare and commend high praise in the chemical community for successful examples. Along this line, Meggers and co-workers reported the enantioselective α-alkylation of 2-imidazoyl substituted ketones **42** (Scheme 23).[10] The key to the enantioselective control was the chiral Rh catalyst, that selectively co-ordinated the imidazole nitrogen and the ketone generating a rigid "Rh-enolate". Once again, the combination of a Ru photocatalyst and diazo compound generates a radical intermediate that reacts with the "Rh-enolate" giving the alkylation products **43** in high ee; similar reactivity is also reported from aryl azide reagents. One example was given for the selective removal of the imidazolyl group affording 1,4-diesters with only a diminutive reduction in ee.



Scheme 23: Photochemical enantioselective α-alkylation of ketones

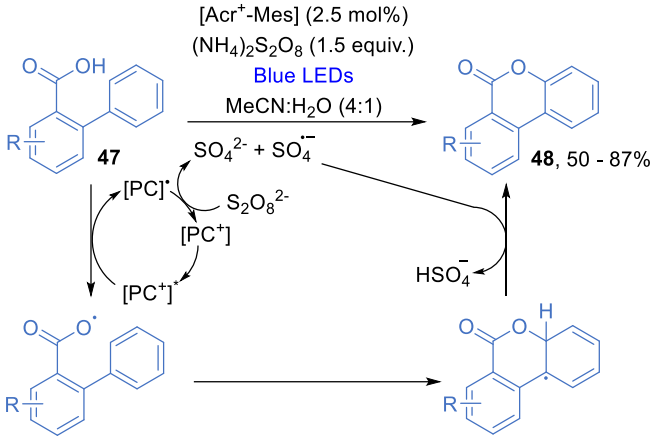
5.3.2. Generation of Radicals in the α-Position to the Carbonyl Moiety

Radicals can be photocatalytically generated from other moieties, not just diazo compounds. *N*-hydroxyphthalimide (NHPI) esters **44** are well-documented as convenient sources of alkyl radicals under photoredox conditions and has been reviewed recently by Zhang and co-workers.[71] Along this line, Wang et al. reported the α-functionalisation of glycine derivatives **45** by exploiting NHPI esters with an in-situ generated copper photocatalyst (Scheme 24).[72] Primary, secondary and tertiary radicals were all viable under the reaction conditions in high yields, including alkyl chlorides, *N*-substituted piperidines and adamantanes. The reaction was effective in site-selective modifications of peptides, and they also reported the synthesis of a collagen tripeptide analogue.



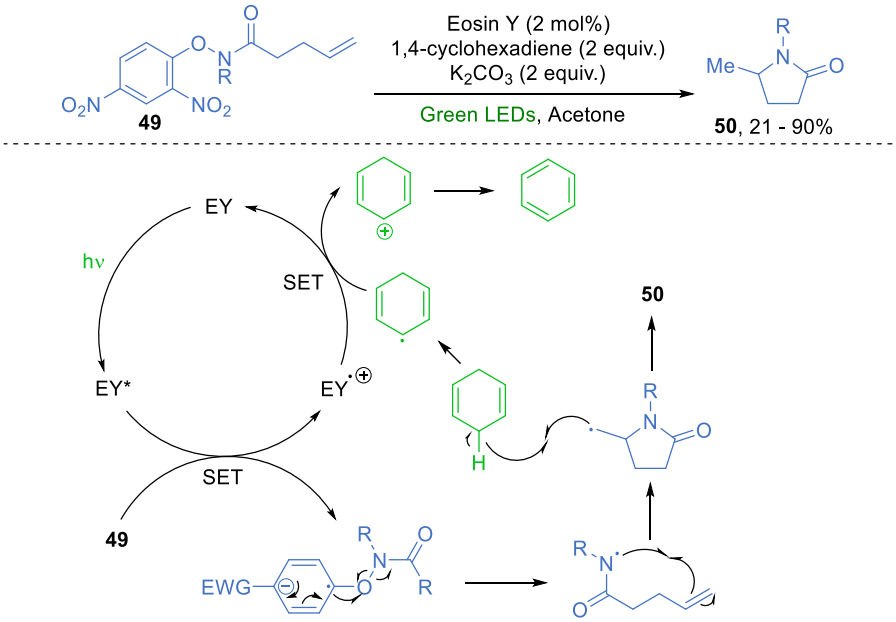
Scheme 24: Photocatalytic generation of alkyl radicals from NHPI esters for the α-functionalisation of glycine derivatives

Photocatalysis also enables the generation of heteroatomic radicals, for example, the generation of carboxylic radicals from biphenyl carboxylic acids **47** to generate lactones **48** from an acridinium photocatalyst (Scheme 25).[1] The cyclisation proceeds in high yields although the presence of strong electron-donating substituents diminishes the yields. No reason was suggested by the authors why this is, but the lowered yields could be countered by increasing the amount of ammonium persulfate.



Scheme 25: Photocatalytic dehydrogenative lactonisation of biphenyl carboxylic acids

The Leonori group reported the functionalisation of amidyl radicals towards the synthesis of 2-pyrrolidones (**50**) (Scheme 26).[73] The nature of the aryl substituent attached to substrate **49** is highly important as the N-O bond dissociation energy is significantly lower with 2,4-dinitrophenyl, in comparison to 4-cyanophenyl and phenyl, which enabled spontaneous fragmentation to the amidyl radical. The reaction was very general in regard to the R substituent with alkyl and aryl substituents being compatible and a wide array of bicyclic and spiro structures were synthesised too.



Scheme 26: Intramolecular cyclisation via amidyl radicals to afford pyrrolidines

In summary, photocatalytic reactions can conveniently generate radicals from a wide host of starting materials such as diazo compounds, carboxylic acids and NHPI esters.

5.4. Summary

Diazo compounds are convenient sources of reactive intermediates such as singlet carbenes, triplet carbenes and radicals. Direct irradiation of diazo compounds, primarily via blue LED irradiation from the works of Jurberg and Davies,[32] are convenient sources of singlet carbenes and can undergo diverse reactivity, which typically revolves around either cycloadditions, or ylide-formation, which then undergoes further functionalisation or X-H insertion. They can also be easily generated in-situ by treating hydrazones with a base, which drastically improves the safety aspect of the reaction in an industrial setting and/or large scales as diazo compounds can be a potential explosive whereas hydrazones are relatively inert during storage. Triplet carbenes and radicals are typically generated via photocatalytic pathways and offer an alternative paradigm in reactivity.

However, whilst the number of reactions explored with visible-light absorbing diazo compounds is relatively vast, there seems to be tunnel-vision towards phenyl diazoacetates with little work on exploring new diazo compounds. Koenigs has somewhat helped mitigate this issue with their development on aryl/aryl diazo compounds (Scheme 4) and were the first to explore the photochemistry of 3-diazooxindole (discussed at further length in section 6.2).[59] The Krasavin group have reported the synthesis of a plethora of new diazo compounds within recent years via novel methodologies, typically using their "sulfonyl-azide-free (SAFE)" method,[74,75] but so far very few of them have been explored outside of metal-catalysed conditions, and thus there is still plenty of untapped potential.

Naturally, carbenes have proven to be productive towards the synthesis of heterocycles. As part of my PhD, I catalogued all known examples where photochemically-generated carbenes are used to synthesise heterocycles, primarily from diazo compounds, but also from silyl ketones that undergo Brook rearrangement to form α-silyloxy carbenes. This book chapter is included as one of the publications in the thesis and was published as seen below:[76]

[P1] Photo-Induced Carbene Transformations to Heterocycles, **J. P. Milton**, D. Gryko, *Top. Heterocycl. Chem.*, **2023**, *59*, 1 - 34

6. Own Research

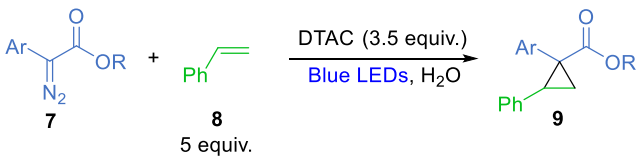
The aim of my PhD was to explore new reactivity of photochemically generated carbenes and radicals towards the construction of C-C and C-X bonds at the α-position to the carbonyl moiety. To meet this aim, I have worked on three research publications, which are attached to the thesis and summarised below.

6.1. Photochemical Cyclopropanation of Diazo Compounds in Micellar Media

Arguably, the most fundamental reaction of diazo compounds is cyclopropanation, which is commonly achieved via the addition of a rhodium catalyst; this can be performed enantioselectively with chiral ligands typically derived from proline-like skeletons.[77–79] However, the preparation of asymmetric cyclopropanes is not always required and thus we can conveniently generate carbenes via photolytic activation of diazo compounds, which also enhances the atom efficiency and toxicological profile of a reaction.

Carbenes are highly reactive intermediates and thus the choice of solvent in the reaction is highly important. Reactions with alcoholic solvents (methanol, ethanol, etc.), or acids (acetic acid, TFA, etc.) will undergo O-H insertion. Similarly, acetone, acetonitrile, and benzene undergo cycloadditions, whilst THF undergoes C-H insertion and ring-opening/O-H insertion.[32] As the majority of solvents give notable non-negligible amounts of side reactions, typically chlorinated solvents such as DCM or $CHCl_3$ are employed as they are relatively unreactive in most cases. However, DCM is notoriously toxic[80] and halogenated solvents are some of the most potent pollutants amongst organic solvents.[81] Naturally, if we want to consider a green, safe and non-toxic solvent, water is the first to come to mind, however the majority of organic substrates are typically insoluble in the medium, and, in the context of carbene chemistry, can also undergo O-H insertion. Thus, I envisioned performing these reactions in a micellar medium to counteract these negatives.

Surfactants generally consist of two main components: 1) a hydrophilic group bearing a formal charge, and 2) a long hydrophobic alkyl chain. When enough surfactant molecules are present in an aqueous solution (known as the critical micelle concentration (CMC)), they congregate together to form a micelle. The micelle consists of two main components, namely the interface layer, which mostly consists of the charged "heads" of the surfactant and the core, which consists of the hydrophobic alkyl chains (Figure 6). Generally, the components of the reaction will preferentially exist somewhere within the micellar system, instead of the hydrophilic aqueous bulk, with hydrophobic compounds in the core, or more polar compounds at the interface. This enables reactions typically inaccessible in an aqueous system to take place effectively. Indeed, we were able to exploit micellar systems for the cyclopropanation of carbenes with styrenes **8** (Scheme 27).



Scheme 27: Model reaction for the cyclopropanation of diazo compounds in a micellar medium

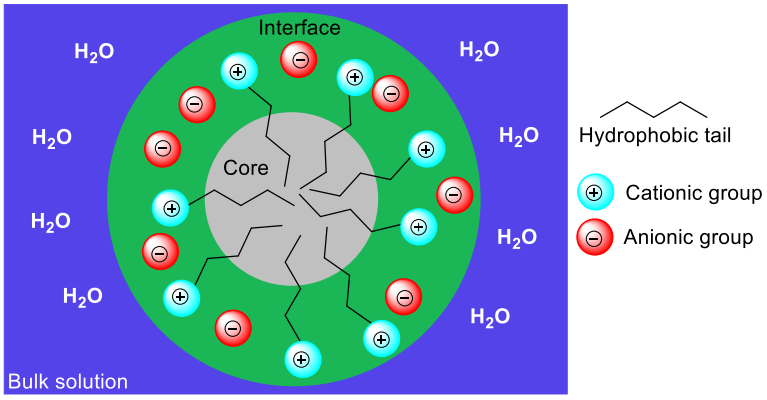
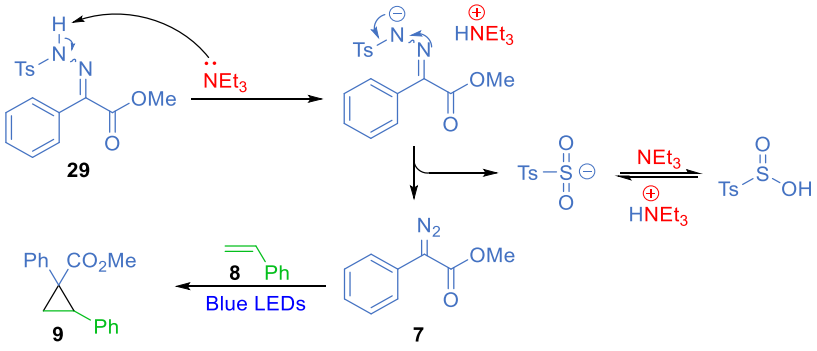


Figure 6: General schematic of a micellar system.

I found that as we increase the length of the alkyl chain, so does the yield of the reaction. COSMO-RS studies performed by our collaborator, Dr. Andersson, found that as the length of the alkyl chain at the ester increases, so does the CMC, which means less micelles are being formed in the reaction. We interpreted this information as the increase in CMC means that the alkyl chain is somewhat contributing to the micelle, thus with longer alkyl chains, fewer but larger micelles ones are formed, which enables higher amounts of styrene to be encapsulated within the system, which when the diazo compound transforms into the carbene, there is a greater chance of a successful collision instead of decomposition.

I also examined the possibility of generating diazo compounds in-situ from hydrazones with the addition of a base, which provided some interesting discussion points. I initially synthesised methyl 2-phenyl-2-(2-tosylhydrazineylidene)acetate (**29**) as a model hydrazone which afforded the desired product in the same yield as with methyl 2-diazo-2-phenylacetate (**7**), however, an improved diastereoselectivity was observed. There are two potential ways to rationalise this observation. Firstly, positioning of the hydrazone within the micelle is likely to be different than the diazo compound as it contains a polar nitrogen moiety, thus we can potentially have favourable hydrogen bonding between the hydrazone and the aqueous bulk solution. On the other hand, the application of triethylamine to the hydrazone indeed generates the diazo compound, but a triethylammonium cation, a sulfinate anion and excess triethylamine will be present as well in the solution (Scheme 28). How specifically this effects the diastereoselectivity is difficult to comment on but both parameters may affect the reactivity. Likewise, Koenigs and co-workers also observed stark differences in the reactivity of diazo compounds for C-H insertions with *N*-heterocycles depending if the diazo compound was generated in-situ or not, but they also could not find a rationale.[54]



Scheme 28: Mechanism for the conversion of hydrazones to diazo compounds

The alkyl chain effect was also no longer relevant, with hexyl and dodecyl alkyl chain providing detrimental yields in comparison to methyl or ethyl groups. We have no rationalisation for this behaviour, other than to state that other works within our group have also observed no beneficial effects with long alkyl chains.[82] Adam Milanowski found that isolating the *E*- and *Z*-hydrazones individually and assessing them in the reaction also provided different yields and diastereoselectivities. Again, our rationalisation is about localisation within the micellar system as above, but also the rates of deprotonation and other parameters within the reaction could be different.[83]

In summary, we reported a photochemical cyclopropanation reaction of diazo compounds (used neat and generated in-situ) in an aqueous environment via the application of micellar systems. Yields were optimal with dodecyl chains as the ester substituent, which enabled the synthesis of cyclopropanes in high yields. The reaction was also viable with hydrazones and triethylamine that enabled the formation of cyclopropanes, typically in slightly lower yields but with greater diastereoselectivity.

The above results were published in a scientific article:[84]

[P2] Photochemical Cyclopropanation in Aqueous Micellar Media – Experimental and Theoretical Studies, **J. P. Milton**, A. Milanowski, M. Anderrson, D. Gryko, *Chem. Commun.*, **2024**, *60* (33), 4483 - 4486

6.2. Photochemical X-H Insertion Reactions of 4-Diazoisoquinoline-1,3(2*H*,4*H*)-diones

Heterocyclic scaffolds are prevalent in the pharmaceutical industry as promising drug leads and candidates.[85] Isoquinoline-1,3(2*H*,4*H*)-diones have held a privileged position in this area and have been investigated for their biological activity for over 100 years[86] and is still actively studied today.[87–90] Along this line, fluorinated moieties have a pronounced impact on the pharmaceutical properties of drug candidates, and thus we sought to find a mild method for the introduction of fluorinated moieties to the periphery of the isoquinoline-1,3(2*H*,4*H*)-dione skeleton.

The discovery of new photolabile diazo compounds is of interest to those in the field. Along this line, 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones **51** have been reported for a plethora of metal-catalysed reactions but no reports have been made on their potential photochemical reactivity. However, I was aware that 3-diazooxindoles **52** have been used for a variety of photochemical reactions, as well as the closely related series of *N*-tosyl-4-diazo-1,4-dihydroisoquinolin-3(2*H*)-ones **53** (Figure 7). Thus, I decided to investigate the possibility of using 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones under photochemical conditions for the first time. Below highlights the known reactivity of these other heterocyclic diazo compounds under blue LED irradiation.

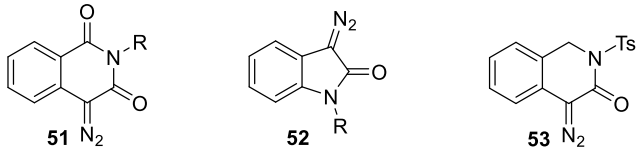
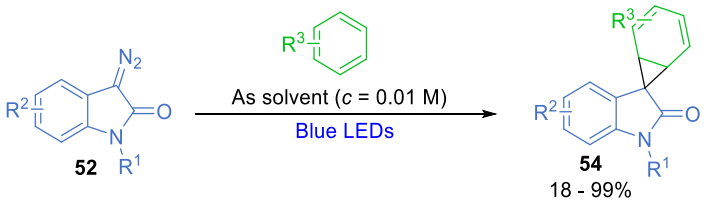


Figure 7: General structure of 3-diazooxindoles **51**, 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones **52** and *N*-tosyl-4-diazo-1,4-dihydroisoquinolin-3(2*H*)-ones **53**

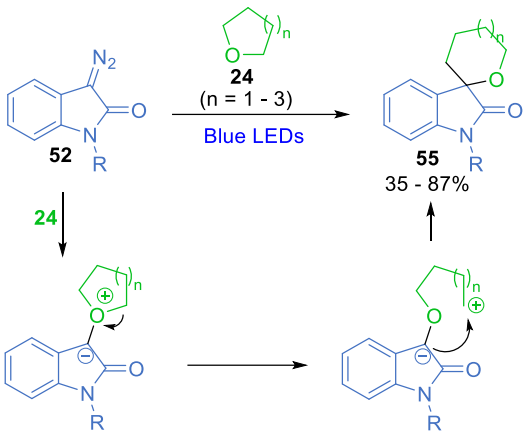
Zhoa et al. described the cyclopropanation of 3-diazooxindoles **52** with arenes (Scheme 29).[91] In regard to the reaction with benzene, the yields were typically high with alkyl protecting groups but are severely diminished when R^1 = H, Ac, or Boc. Electron-rich arenes were particularly interesting as the cyclopropane could not be isolated and only the C-H insertion products were identified such as in the case with anisole or *N*-methylpyrrole. The nocaradienes could be selectively converted into the C-H insertion product when subjecting them to mild heat with silica gel, in particular with the parent compound from benzene, which did so in quantitative yield.



Scheme 29: Cyclopropanation of 3-diazooxindoles with arenes to form novel norcaradienes

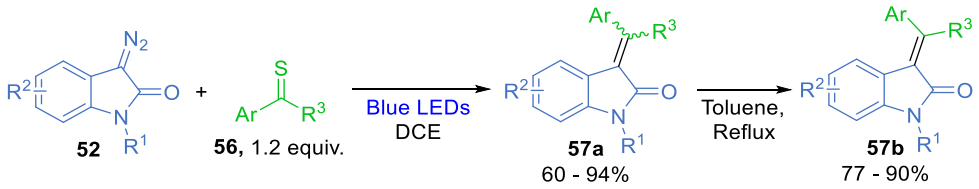
Simple *O*-heterocycles, such as THF and THP, are well-known to form ylides with singlet carbenes and have already been discussed previously (section 5.2.2.2). Xia and co-workers reported that 3-diazooxindoles **52** under photochemical conditions can react with cyclic ethers **24** to form spirocyclic oxindoles **55** (Scheme 30).[92] In general, the reaction is compatible with many aromatic substituents upon 3-diazooxindole, however, strongly electron-withdrawing moieties such as nitro groups are not compatible. 5-7-membered *O*-heterocycles are effective even when

possessing internal alkenes although the 7-membered rings examined had diminished yields in comparison to 5- and 6-membered rings. The reaction was performed on a gram-scale and flow conditions and was used a key step towards the synthesis of a CB2 agonist.



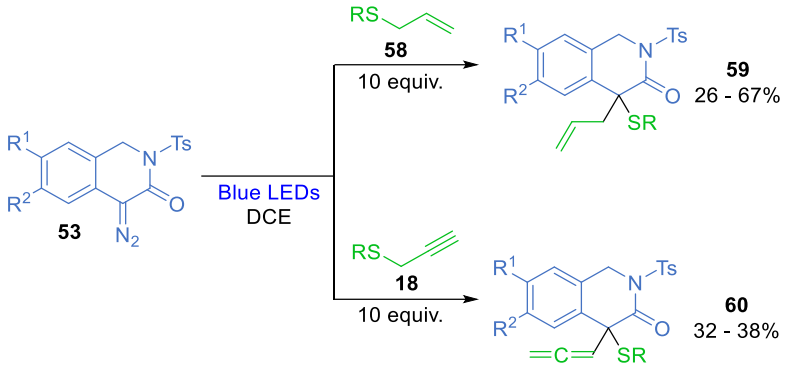
Scheme 30: Photochemical ring-expansion of *O*-heterocycles

Muthusamy and Ramesh proposed the formation of 3-methyleneindolin-2-ones **57** from thioketones **56** and 3-diazooxindoles **52** (Scheme 31).[93] The reaction was complete in high yields (84 – 94%) with symmetrical thioketones, however, unsymmetrical thioketones, whilst still giving high yields, had poor *E*/*Z* selectivity. The authors found that this could be rectified by a thermal isomerisation reaction by refluxing the product in toluene, which selectively rearranged to the *E*-product; this could be achieved in one pot too after a solvent swap. The reaction was scalable, up to a gram-scale, with only a small reduction in the yield.



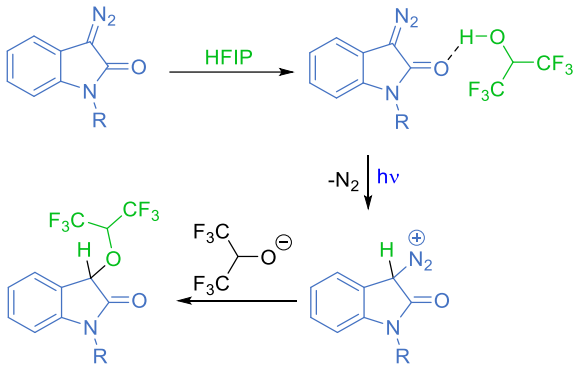
Scheme 31: Formation of disubstituted 3-methyleneindolin-2-ones from a photochemical ylide-based reaction

Xie et al. demonstrated that *N*-tosyl-4-diazo-1,4-dihydroisoquinolin-3(2*H*)-ones **53** are viable under photochemical conditions for a Doyle-Kirmse reaction (Scheme 32).[47] Various aryl allyl sulfides **58** were examined, with allyl phenyl sulfide typically giving moderate yields (~60% yield) whereas electron-withdrawing aromatics on the allyl sulfide would lower the reactivity. Propargyl sulfides **18** were also investigated to give allenes **60**, but the yields were noticeably poorer than the reaction with allyl sulfides.



Scheme 32: Photochemical Doyle-Kirmse reaction of *N*-tosyl-4-diazo-1,4-dihydroisoquinolin-3(2*H*)-ones

During the course of this work, the primary reaction that was focussed on was O-H insertion, mainly with HFIP and other fluorinated alcohols. I did not observe any product formation when performing the reaction with typical alcohols such as ethanol and *iso*propanol, which was intriguing. Koenigs and co-workers also reported O-H insertion reactions with HFIP and 3-diazooxindoles, where they proposed a photochemical proton-transfer as the key mechanistic step,[59] and is further discussed in one of their prior publications (Scheme 33).[58] In addition, it appears that 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones are notably less reactive than 3-diazooxindole. Koenigs' work only required 5 equivalents of HFIP, whilst when I performed the reaction with approximately 20 equivalents of HFIP, I had less than 20% yield and I could only attain serviceable yields when using solvent amount of HFIP. The lower reactivity can also be observed when comparing my results to those obtained by Koenigs such as with HFIP (97% vs. 67%), 2,2,2-trifluoroethanol (75% vs. 41%) and 2,2,3,3-tetrafluoropropan-1-ol (84% vs. 45%). Thus, in conclusion, the O-H insertion with 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones likely proceeds via the same proton-transfer mechanism as described by Koenigs and coworkers but its lower reactivity is why I could not achieve any noticeable product formation with less acidic alcohols.

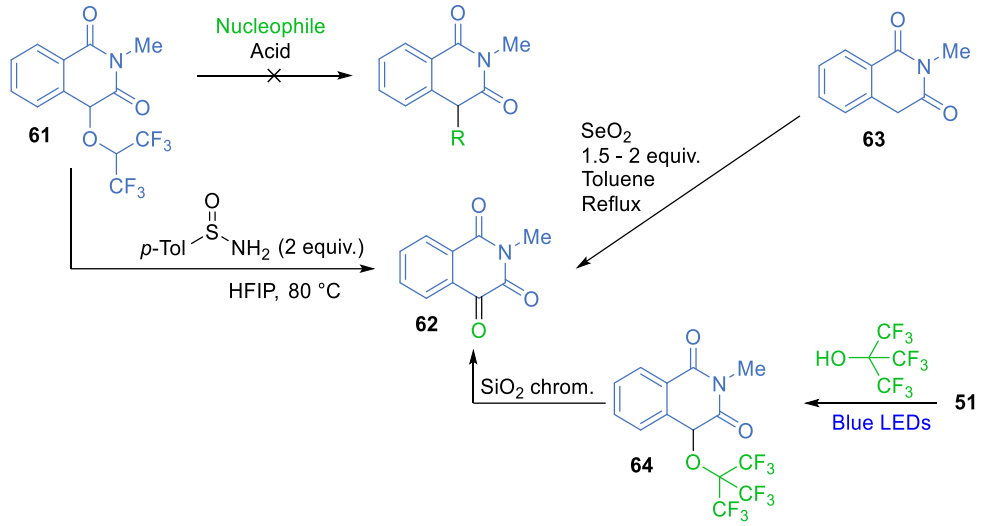


Scheme 33: Proposed O-H insertion mechanism by Koenigs and co-workers with fluorinated alcohols

I wanted to find further transformations of 4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**61**), the model O-H insertion product (Scheme 34). I believed I should be able to exploit the ether functionality with an acid and nucleophile. However, the compound was surprisingly unreactive under a variety of conditions with increasingly stronger acids and nucleophiles, such as TFA and *N*-methylpyrrole, methanesulfonic acid and mesitylene, or triflic acid and *p*-xylene. The only successful further transformation I found was the reaction of compound **61** and 4-methylbenzenesulfinamide, which afforded trione **62**, although it does not serve much practical purpose as the same product can be produced from

isoquinoline-1,3(2*H*,4*H*)-dione (**63**) and selenium dioxide, which is already know in the literature.[94,95] We observed the desired O-H insertion adduct **64** from the reaction of nonafluoro-*tert*-butyl alcohol and compound **51** by NMR, however, during silica gel column chromatography the product surprisingly underwent a rearrangement reaction to trione **62**, with no traces of substrate **64**.

In conclusion, I reported the first reaction of 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones under photolytic conditions for the introduction of fluorinated moieties via O-H insertion. The reaction conditions were also viable for S-H and C-H insertion reactions with thiols and arenes respectively. I synthesised a novel series of related diazo compounds, namely, 4-diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides, which preferentially reacted under violet LED conditions and also effectively underwent O-H insertion with fluorinated alcohols and S-H insertion.



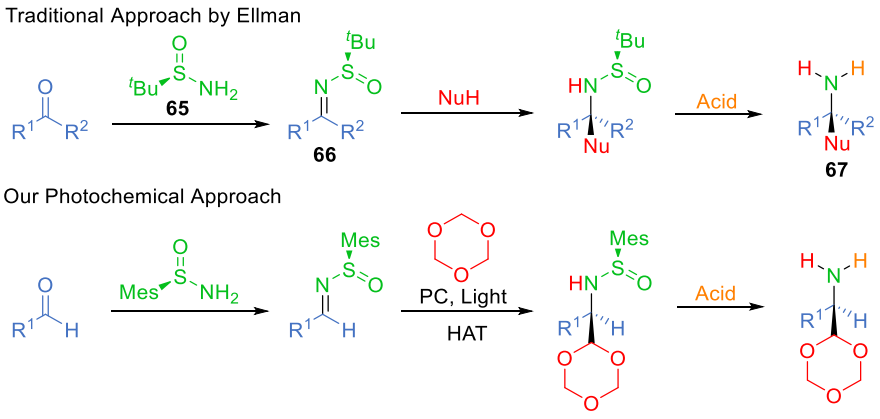
Scheme 34: Further transformations of 4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione

The above results were published in a scientific article:[96]

[P3] Photochemical Functionalization of 4-Diazoisoquinoline-1,3(2*H*,4*H*)-diones and Their 1-Sulfoxide Analogs, **J. P. Milton**, D. Gryko, *ACS Org. Inorg. Au*, **2025**, doi.org/10.1021/acsorginorgau.5c00017

6.3. Diastereoselective Synthesis of Amines via a Photochemical HAT Reaction

Chiral amines are pivotal moieties within the pharmaceutical industry with 40% of all active pharmaceutical ingredients and 35% of the top 200 small drugs containing at least one.[97–99] However, many of these chiral amines are synthesised via catalytic approaches with costly and toxic transition metals.[100,101] However, organocatalytic methods can provide high enantioselectivity transformations to chiral amines whilst mitigating the toxicity of the reaction. One classical way to achieve this is via the use of the Ellman auxiliary **65** (chiral *tert*-butanesulfinamides), which generates chiral (ket)imines **66** upon addition to carbonyl compounds. When attacked by a nucleophile, the chiral information of the sulfinamide is imparted into the respective product, which upon acidic deprotection of the amine brandishes the enantiomerically enriched amine **67**.[102,103] We envisioned that we could use Ellman-like auxiliaries to enable the synthesis of chiral amines via a photocatalytic pathway, namely, hydrogen atom transfer, which would expand the scope of chiral amines (Scheme 35).



Scheme 35: General scheme for the functionalisation of the Ellman auxiliary towards the synthesis of chiral amines and our approach via a photochemical HAT reaction.

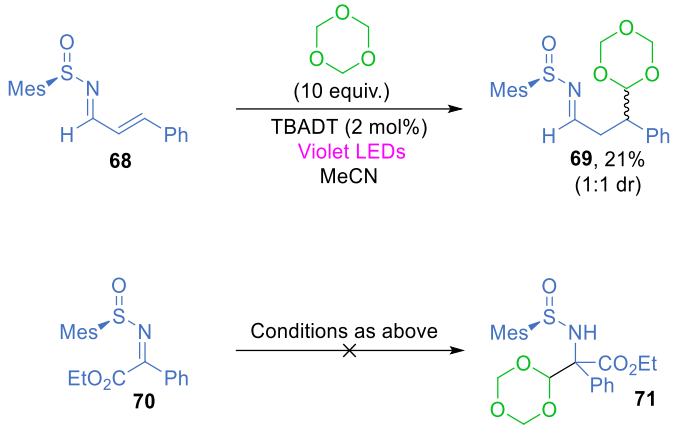
During the optimisation, Matteo Leone, found that the *tert*-butyl group on the sulfinamide provided rather ineffective diastereoselective control and likewise for the tosyl group, thus mesityl was used as the substituent as choice, as it provided >98:2 dr. The photocatalyst of choice, TBADT, was selected as other organic photocatalysts, such as benzophenone and 4,4'-dichlorobenzophenone, required 50 mol% catalyst loading to afford similar yields to the optimum catalyst. In contrast, TBADT only needed 5 mol% and has the benefit of being well documented for its capabilities in HAT reactions while also being relatively inexpensive.[104]

My work focussed on developing the scope of *N*-sulfinyl imines with 1,3,5-trioxane. It had been already established that electron-withdrawing groups on the phenyl ring, such as 4-cyanophenyl substituents, gave high yields, in comparison to electron-donating substituents such as 4-phenyl or 4-methoxy. My investigation into other electron-withdrawing groups examined imines with chlorine-substituted aromatics, which behaved similarly for the *meta*- and *para*-positions, with the *ortho*-position surprisingly giving a higher yield. All results gave high diastereoselectivity with >98/2 dr.

Other substrates performed rather poorly initially though. Imines derived from isovaleraldehyde and cyclohexanecarboxaldehyde gave 16% yield and no reaction respectively. Heteroaromatics as substituents also delivered diminutive yields such as with 2-thiophene and

3-benzo[*b*]thiophene in 14% and 13% yield respectively. However, we found that the addition of Na_2CO_3 as an additive in the reaction improved the yield. There is no literature precedence about this, nor do we have a clear reason why this helps, but our theory is that the radical species in the reaction could be oxidised by traces of oxygen, which would then generate a carboxylic acid and could cause the *N*-sulfinyl imide to hydrolyse back to an aldehyde. The addition of Na_2CO_3 instead would quench the carboxylic acid and hinder any acid formation during the reaction. This improved the reaction with the 2-thiophene substituent from 14% to 56%, and likewise with the isobutyl substituents from 16% to 43%.

A couple of interesting results that I investigated went unpublished that I would like to highlight here (Scheme 36). The chiral *N*-sulfinyl imine of *trans*-cinnamaldehyde (**68**) reacted exclusively with the alkene, giving product **69** with the imine moiety intact. The diastereoselectivity was very poor (1:1) as the sulfinyl group had no effect on the distal position. I also probed a *N*-sulfinyl ketimine (**70**), which gave no conversion under the reaction conditions, but we could not provide any rationale why this was.



Scheme 36: Unpublished results from the publication

This work was performed in collaboration with Dr. Geraldine Masson, Dr. Luc Neuville and Matteo Leone during June and July 2023, as part of the H2020 Marie Skłodowska-Curie PhotoReAct ITN during a secondment at the Centre National de la Recherche Scientifique (CNRS).

The above results were published in a scientific article:[105]

[P4] TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines, M. Leone, **J. P. Milton**, D. Gryko, L. Neuville, G. Masson, *Chem. Eur. J.*, **2024**, *30*, e202400363

6.4. Conclusions

The aim of my PhD was to explore new reactivity of photochemically generated carbenes and radicals towards the construction of C-C and C-X bonds at the α-position to the carbonyl moiety. To meet these aims, I performed:

1. **To gain knowledge in the area, I wrote a book chapter disclosing all know reactions to synthesise heterocycles from diazo compounds.** Many of these reactions involved the direct irradiation of phenyl diazoacetates, which allowed me to understand the wide type of reactivity available from singlet carbenes.

2. **I found that micellar solutions are a suitable media for photochemical reactions involving diazo compounds to minimise the usage of toxic and environmentally unfriendly solvents.** The use of diazo compounds with long alkyl chains attached to the ester groups enabled the construction of cyclopropanes in high yields within a dodecyltrimethylammonium chloride micellar system. Diazo compounds formed in-situ from hydrazones underwent cyclopropanation with minorly decreased yields in comparison to neat diazo compounds but exhibited better diastereoselectivity.

3. **I reported the first case of 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones being used under photochemical conditions for X-H insertion reactions.** The resultant carbene effectively underwent O-H insertions with fluorinated alcohols, S-H insertions with thiols and C-H insertions with aromatic compounds. The reaction was scalable and performed efficiently up to a gram scale. I synthesised a new family of diazo compounds, namely 4-diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides, which performed well under violet LED irradation and gave O-H and S-H insertion products.

4. **I expanded the scope of a diastereoselective HAT reaction with chiral *N*-sulfinyl imines and 1,3,5-trioxane.** Alkyl and aryl substituents attached to chiral *N*-sulfinyl imines resulted in >98:2 dr with yields in line with the rest of the scope. The addition of a base was crucial for a successful transformation, primarily with alkyl substituted imines. Deprotection of the sulfinyl group yielded the desired enantioenriched amine in 99% ee.

In summary, the research performed within my doctoral thesis significantly contributes to advancing the knowledge of reactions via the photochemical generation of carbenes and radicals at the α-position. In particular, much of my work has focussed on the chemistry of diazo compounds under direct visible light irradiation and provides valuable advancements to this field.

7. References

(1) Ramirez, N. P.; Bosque, I.; Gonzalez-Gomez, J. C. Photocatalytic Dehydrogenative Lactonization of 2-Arylbenzoic Acids. *Org. Lett.* **2015**, *17* (18), 4550–4553.

(2) Guo, Y.; Lin, G.; Zhang, M.; Xu, J.; Song, Q. Photo-Induced Decarboxylative C-S Bond Formation to Access Sterically Hindered Unsymmetric S-Alkyl Thiosulfonates and SS-Alkyl Thiosulfonates. *Nat. Commun.* **2024**, *15* (1), 1–13.

(3) Norman, A. R.; Yousif, M. N.; McErlean, C. S. P. Photoredox-Catalyzed Indirect Acyl Radical Generation from Thioesters. *Org. Chem. Front.* **2018**, *5* (22), 3267–3298.

(4) Banerjee, A.; Lei, Z.; Ngai, M.-Y. Acyl Radical Chemistry via Visible-Light Photoredox Catalysis. *Synthesis* **2019**, *51* (02), 303–333.

(5) Roy, M.; Sardar, B.; Mallick, I.; Srimani, D. Generation of Alkyl and Acyl Radicals by Visible-Light Photoredox Catalysis: Direct Activation of C–O Bonds in Organic Transformations. *Beilstein J. Org. Chem.* **2024**, *20*, 1348–1375.

(6) Wang, F.; Wang, B.; Wang, Q.; Wang, L. Photochemical-, Electrochemical-, and Photoelectrochemical- Catalyzed Hydrogen Atom Transfer from Aldehydes to Acyl Radicals and Their Transformations. *Eur. J. Org. Chem.* **2025**, *28* (6).

(7) Tanbouza, N.; Caron, L.; Khoshoei, A.; Ollevier, T. Catalytic Bismuth(V)-Mediated Oxidation of Hydrazones into Diazo Compounds. *Org. Lett.* **2022**, *24* (14), 2675–2678.

(8) Yan, K.; He, H.; Li, J.; Luo, Y.; Lai, R.; Guo, L.; Wu, Y. Blue Light-Promoted Cyclopropenizations of N-Tosylhydrazones in Water. *Chinese Chem. Lett.* **2021**, *32* (12), 3984–3987.

(9) Durka, J.; Turkowska, J.; Gryko, D. Lightening Diazo Compounds? *ACS Sustain. Chem. Eng.* **2021**, *9* (27), 8895–8918.

(10) Huang, X.; Webster, R. D.; Harms, K.; Meggers, E. Asymmetric Catalysis with Organic Azides and Diazo Compounds Initiated by Photoinduced Electron Transfer. *J. Am. Chem. Soc.* **2016**, *138* (38), 12636–12642.

(11) Ciszewski, L. W.; Durka, J.; Gryko, D. Photocatalytic Alkylation of Pyrroles and Indoles with α-Diazo Esters. *Org. Lett.* **2019**, *21* (17), 7028–7032.

(12) Crisenza, G. E. M.; Melchiorre, P. Chemistry Glows Green with Photoredox Catalysis. *Nat. Commun.* **2020**, *11* (1), 1–4.

(13) Albini, A.; Fagnoni, M. Green Chemistry and Photochemistry Were Born at the Same Time. *Green Chem.* **2004**, *6* (1), 1–6.

(14) Orłowska, K.; Łuczak, K.; Krajewski, P.; Santiago, J. V; Rybicka-Jasińska, K.; Gryko, D. Unlocking the Reactivity of Diazo Compounds in Red Light with the Use of Photochemical Tools. *Chem. Commun.* **2023**, *59* (99), 14649–14652.

(15) Strieth-Kalthoff, F.; Glorius, F. Triplet Energy Transfer Photocatalysis: Unlocking the Next Level. *Chem* **2020**, *6* (8), 1888–1903.

(16) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81* (16), 6898–6926.

(17) Dagousset, G.; Carboni, A.; Masson, G.; Magnier, E. 14 - Visible Light–Induced (Per)Fluoroalkylation by Photoredox Catalysis; Groult, H., Leroux, F. R., Tressaud, A. B. T.-

M. S. P. and R. of F. C., Eds.; Elsevier, 2017; pp 389–426.

(18) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, *2017* (15), 2056–2071.

(19) Juliá, F.; Constantin, T.; Leonori, D. Applications of Halogen-Atom Transfer (XAT) for the Generation of Carbon Radicals in Synthetic Photochemistry and Photocatalysis. *Chem. Rev.* **2022**, *122* (2), 2292–2352.

(20) Chakraborty, S.; Barik, S.; Biju, A. T. N-Heterocyclic Carbene (NHC) Organocatalysis: From Fundamentals to Frontiers. *Chem. Soc. Rev.* **2025**.

(21) de Frémont, P.; Marion, N.; Nolan, S. P. Carbenes: Synthesis, Properties, and Organometallic Chemistry. *Coord. Chem. Rev.* **2009**, *253* (7–8), 862–892.

(22) Platz, M. S. Dichlorocarbene: From Jack Hine to Robert Moss. *J. Phys. Org. Chem.* **2024**, *37* (1), e4563.

(23) Sammakia, T.; Ramazanov, I. R.; Yaroslavova, A. V. Diazomethane, CAS No. 334-88-3. In *Encyclopedia of Reagents for Organic Synthesis*; Wiley, 2021; pp 1–12.

(24) Arndt, F.; Eistert, B. Ein Verfahren Zur Überführung von Carbonsäuren in Ihre Höheren Homologen Bzw. Deren Derivate. *Berichte der Dtsch. Chem. Gesellschaft (A B Ser.* **1935**, *68* (1), 200–208.

(25) Büchner-Curtius-Schlotterbeck Reaction. In *Comprehensive Organic Name Reactions and Reagents*; 2010; pp 567–569.

(26) Green, S. P.; Wheelhouse, K. M.; Payne, A. D.; Hallett, J. P.; Miller, P. W.; Bull, J. A. Thermal Stability and Explosive Hazard Assessment of Diazo Compounds and Diazo Transfer Reagents. *Org. Process Res. Dev.* **2020**, *24* (1), 67–84.

(27) Regitz, M. New Methods of Preparative Organic Chemistry. Transfer of Diazo Groups. *Angew. Chemie Int. Ed. English* **1967**, *6* (9), 733–749.

(28) Myers, E. L.; Raines, R. T. A Phosphine-Mediated Conversion of Azides into Diazo Compounds. *Angew. Chemie - Int. Ed.* **2009**, *48* (13), 2359–2363.

(29) Toma, T.; Shimokawa, J.; Fukuyama, T. N,N'-Ditosylhydrazine: A Convenient Reagent for Facile Synthesis of Diazoacetates. *Org. Lett.* **2007**, *9* (16), 3195–3197.

(30) Orłowska, K.; Santiago, J. V.; Krajewski, P.; Kisiel, K.; Deperasińska, I.; Zawada, K.; Chaładaj, W.; Gryko, D. UV Light Is No Longer Required for the Photoactivation of 1,3,4-Oxadiazolines. *ACS Catal.* **2023**, *13* (3), 1964–1973.

(31) Galkina, O. S.; Rodina, L. L. Photochemical Transformations of Diazocarbonyl Compounds: Expected and Novel Reactions. *Russ. Chem. Rev.* **2016**, *85* (5), 537.

(32) Jurberg, I. D.; Davies, H. M. L. Blue Light-Promoted Photolysis of Aryldiazoacetates. *Chem. Sci.* **2018**, *9* (22), 5112–5118.

(33) Jana, S.; Pei, C.; Empel, C.; Koenigs, R. M. Photochemical Carbene Transfer Reactions of Aryl/Aryl Diazoalkanes—Experiment and Theory. *Angew. Chemie Int. Ed.* **2021**, *60* (24), 13271–13279.

(34) Rybicka-Jasińska, K.; Shan, W.; Zawada, K.; Kadish, K. M.; Gryko, D. Porphyrins as Photoredox Catalysts: Experimental and Theoretical Studies. *J. Am. Chem. Soc.* **2016**, *138*

(47), 15451–15458.

(35) Fu, X.; Tang, J.; Hua, R.; Li, X.; Kang, Z.; Qiu, H.; Hu, W. Functionalization of DNA-Tagged Alkenes with Diazo Compounds via Photocatalysis. *Org. Lett.* **2022**, *24* (11), 2208–2213.

(36) Ma, N.; Guo, L.; Qi, D.; Gao, F.; Yang, C.; Xia, W. Visible-Light-Induced Multicomponent Synthesis of γ-Amino Esters with Diazo Compounds. *Org. Lett.* **2021**, *23* (16), 6278–6282.

(37) Liu, G. X.; Liang, H. C.; Fu, X.; Tang, J.; Hu, W. H.; Qiu, H. Photoredox-Catalyzed Carbonyl Alkylative Amination with Diazo Compounds: A Three-Component Reaction for the Construction of γ-Amino Acid Derivatives. *Org. Lett.* **2022**, *24* (27), 4908–4913.

(38) Krishnan, K. K.; Thankachan, A. P.; Anilkumar, G. Recent Advances and Perspectives in the Synthesis of Heterocycles via Carbenes. *Tetrahedron* **2015**, *71* (16), 2333–2347.

(39) Guo, Y.; Nguyen, T. V.; Koenigs, R. M. Norcaradiene Synthesis via Visible-Light-Mediated Cyclopropanation Reactions of Arenes. *Org. Lett.* **2019**, *21* (21), 8814–8818.

(40) Guo, Y.; Empel, C.; Pei, C.; Atodiresei, I.; Fallon, T.; Koenigs, R. M. Photochemical Cyclopropanation of Cyclooctatetraene and (Poly-)Unsaturated Carbocycles. *Org. Lett.* **2020**, *22* (13), 5126–5130.

(41) He, F.; Koenigs, R. M. Visible Light Mediated, Metal-Free Carbene Transfer Reactions of Diazoalkanes with Propargylic Alcohols. *Chem. Commun.* **2019**, *55* (33), 4881–4884.

(42) Klöpfer, V.; Eckl, R.; Floß, J.; Roth, P. M. C.; Reiser, O.; Barham, J. P. Catalyst-Free, Scalable Heterocyclic Flow Photocyclopropanation. *Green Chem.* **2021**, *23* (17), 6366–6372.

(43) Zhang, Z.; Yadagiri, D.; Gevorgyan, V. Light-Induced Metal-Free Transformations of Unactivated Pyridotriazoles. *Chem. Sci.* **2019**, *10* (36), 8399–8404.

(44) Kirmse, W. CHAPTER 1 - Introduction. In *Carbene Chemistry, 2nd ed.*; Academic Press, 1971.

(45) Orłowska, K.; Rybicka-Jasińska, K.; Krajewski, P.; Gryko, D. Photochemical Doyle-Kirmse Reaction: A Route to Allenes. *Org. Lett.* **2020**, *22* (3), 1018–1021.

(46) Li, F.; He, F.; Koenigs, R. M. Catalyst-Free [2,3]-Sigmatropic Rearrangement Reactions of Photochemically Generated Ammonium Ylides. *Synthesis* **2019**, *51* (23), 4348–4358.

(47) Xie, J.; Suleman, M.; Wang, Z.; Mao, X.; Mao, B.; Fan, J.; Lu, P.; Wang, Y. Syntheses of 4-Allyl-/4-Allenyl-4-(Arylthio)-1,4-Dihydroisoquinolin-3-Ones via the Photochemical Doyle-Kirmse Reaction. *Org. Biomol. Chem.* **2021**, *19* (28), 6341–6345.

(48) Yang, Z.; Guo, Y.; Koenigs, R. M. Photochemical, Metal-Free Sigmatropic Rearrangement Reactions of Sulfur Ylides. *Chem. - A Eur. J.* **2019**, *25* (27), 6703–6706.

(49) Yang, J.; Wang, J.; Huang, H.; Qin, G.; Jiang, Y.; Xiao, T. Gem-Difluoroallylation of Aryl Diazoesters via Catalyst-Free, Blue-Light-Mediated Formal Doyle-Kirmse Reaction. *Org. Lett.* **2019**, *21* (8), 2654–2657.

(50) Xiao, T.; Mei, M.; He, Y.; Zhou, L. Blue Light-Promoted Cross-Coupling of Aryldiazoacetates and Diazocarbonyl Compounds. *Chem. Commun.* **2018**, *54* (64), 8865–8868.

(51) Stivanin, M. L.; Gallo, R. D. C.; Spadeto, J. P. M.; Cormanich, R. A.; Jurberg, I. D. A Visible Light-Mediated Three-Component Strategy Based on the Ring-Opening of Cyclic Ethers

with Aryldiazoacetates and Nucleophiles. *Org. Chem. Front.* **2022**, *9* (5), 1321–1326.

(52) Lu, L.; Chen, C.; Jiang, H.; Yin, B. Three-Component Ring-Opening Reactions of Cyclic Ethers, α-Diazo Esters, and Weak Nucleophiles under Metal-Free Conditions. *J. Org. Chem.* **2018**, *83* (23), 14385–14395.

(53) He, F.; Pei, C.; Koenigs, R. M. Photochemical Fluoro-Amino Etherification Reactions of Aryldiazoacetates with NFSI under Stoichiometric Conditions. *Chem. Commun.* **2020**, *56* (4), 599–602.

(54) Jana, S.; Li, F.; Empel, C.; Verspeek, D.; Aseeva, P.; Koenigs, R. M. Stoichiometric Photochemical Carbene Transfer by Bamford–Stevens Reaction. *Chem. - A Eur. J.* **2020**, *26* (12), 2586–2591.

(55) Empel, C.; Patureau, F. W.; Koenigs, R. M. Visible Light Induced Metal-Free Carbene N-Carbazolation. *J. Org. Chem.* **2019**, *84* (17), 11316–11322.

(56) Stivanin, M. L.; Fernandes, A. A. G.; da Silva, A. F.; Okada, C. Y.; Jurberg, I. D. Blue Light-Promoted N–H Insertion of Carbazoles, Pyrazoles and 1,2,3-Triazoles into Aryldiazoacetates. *Adv. Synth. Catal.* **2020**, *362* (5), 1106–1111.

(57) Maiti, D.; Das, R.; Sen, S. Blue LED-Mediated N-H Insertion of Indoles into Aryldiazoesters at Room Temperature in Batch and Flow: Reaction Kinetics, Density Functional Theory, and Mechanistic Study. *J. Org. Chem.* **2021**, *86* (3), 2522–2533.

(58) Jana, S.; Yang, Z.; Li, F.; Empel, C.; Ho, J.; Koenigs, R. M. Photoinduced Proton-Transfer Reactions for Mild O-H Functionalization of Unreactive Alcohols. *Angew. Chemie - Int. Ed.* **2020**, *59* (14), 5562–5566.

(59) Empel, C.; Verspeek, D.; Jana, S.; Koenigs, R. M. Photochemical O–H Functionalization Reactions of Cyclic Diazoamides. *Adv. Synth. Catal.* **2020**, *362* (21), 4716–4722.

(60) Yang, J.; Wang, G.; Zhou, H.; Li, Z.; Ma, B.; Song, M.; Sun, R.; Huo, C. Visible-Light-Promoted Selective: O -Alkylation of 2-Pyridones with α-Aryldiazoacetates. *Org. Biomol. Chem.* **2021**, *19* (2), 394–398.

(61) He, F.; Li, F.; Koenigs, R. M. Metal-Free Insertion Reactions of Silanes with Aryldiazoacetates. *J. Org. Chem.* **2020**, *85* (2), 1240–1246.

(62) Vasiļevska, A.; Slanina, T. Structure–Property–Function Relationships of Stabilized and Persistent C - and N -Based Triaryl Radicals. *Chem. Commun.* **2024**, *60* (3), 252–264.

(63) Huang, C.-Y.; Li, J.; Li, C.-J. Photocatalytic C(Sp3) Radical Generation via C–H, C–C, and C–X Bond Cleavage. *Chem. Sci.* **2022**, *13* (19), 5465–5504.

(64) Buettner, C. S.; Stavagna, C.; Tilby, M. J.; Górski, B.; Douglas, J. J.; Yasukawa, N.; Leonori, D. Synthesis and Suzuki–Miyaura Cross-Coupling of Alkyl Amine-Boranes. A Boryl Radical-Enabled Strategy. *J. Am. Chem. Soc.* **2024**, *146* (34), 24042–24052.

(65) Zhang, Z.; Tilby, M. J.; Leonori, D. Boryl Radical-Mediated Halogen-Atom Transfer Enables Arylation of Alkyl Halides with Electrophilic and Nucleophilic Coupling Partners. *Nat. Synth.* **2024**, *3* (10), 1221–1230.

(66) McLean, J. T.; Benny, A.; Nolan, M. D.; Swinand, G.; Scanlan, E. M. Cysteinyl Radicals in Chemical Synthesis and in Nature. *Chem. Soc. Rev.* **2021**, *50* (19), 10857–10894.

(67) Reyes, Y.; Adhikary, A.; Wnuk, S. F. Nitrogen-Centered Radicals Derived from Azidonucleosides. *Molecules* **2024**, *29* (10), 2310.

(68) Yuan, Y.; Yang, J.; Lei, A. Recent Advances in Electrochemical Oxidative Cross-Coupling with Hydrogen Evolution Involving Radicals. *Chem. Soc. Rev.* **2021**, *50* (18), 10058–10086.

(69) Sengul, I. F.; Wood, K.; Bowyer, P. K.; Bhadbhade, M.; Chen, R.; Kumar, N.; Black, D. S. Synthesis of New Di-(3-Indolyl)Arenes. *Tetrahedron* **2012**, *68* (36), 7429–7434.

(70) Su, Y.-L.; Liu, G.-X.; Liu, J.-W.; Tram, L.; Qiu, H.; Doyle, M. P. Radical-Mediated Strategies for the Functionalization of Alkenes with Diazo Compounds. *J. Am. Chem. Soc.* **2020**, *142* (32), 13846–13855.

(71) Zhang, Y.; Ma, D.; Zhang, Z. Utilization of Photocatalysts in Decarboxylative Coupling of Carboxylic N-Hydroxyphthalimide (NHPI) Esters. *Arab. J. Chem.* **2022**, *15* (7).

(72) Wang, C.; Guo, M.; Qi, R.; Shang, Q.; Liu, Q.; Wang, S.; Zhao, L.; Wang, R.; Xu, Z. Visible-Light-Driven, Copper-Catalyzed Decarboxylative C(Sp3)−H Alkylation of Glycine and Peptides. *Angew. Chemie - Int. Ed.* **2018**, *57* (48), 15841–15846.

(73) Davies, J.; Svejstrup, T. D.; Reina, D. F.; Sheikh, N. S.; Leonori, D. Visible-Light-Mediated Synthesis of Amidyl Radicals: Transition-Metal-Free Hydroamination and N -Arylation Reactions. *J. Am. Chem. Soc.* **2016**, *138* (26), 8092–8095.

(74) Dar'in, D.; Kantin, G.; Krasavin, M. A "Sulfonyl-Azide-Free" (SAFE) Aqueous-Phase Diazo Transfer Reaction for Parallel and Diversity-Oriented Synthesis. *Chem. Commun.* **2019**, *55* (36), 5239–5242.

(75) Bubyrev, A.; Dar'in, D.; Kantin, G.; Krasavin, M. Synthetic Studies towards CH-Diazomethane Sulfonamides: A Novel Type of Diazo Reagents. *Eur. J. Org. Chem.* **2020**, *2020* (27), 4112–4115.

(76) Milton, J. P.; Gryko, D. Photo-Induced Carbene Transformations to Heterocycles. *Top. Heterocycl. Chem.* **2023**, *59*, 1–34.

(77) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T. Chiral Rhodium(II) Carboxamides. A New Class of Catalysts for Enantioselective Cyclopropanation Reactions. *Tetrahedron Lett.* **1990**, *31* (46), 6613–6616.

(78) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. Asymmetric Cyclopropanations by Rhodium(II) N-(Arylsulfonyl)Prolinate Catalyzed Decomposition of Vinyldiazomethanes in the Presence of Alkenes. Practical Enantioselective Synthesis of the Four Stereoisomers of 2-Phenylcyclopropan-1-Amino Acid. *J. Am. Chem. Soc.* **1996**, *118* (29), 6897–6907.

(79) Briones, J. F.; Hansen, J.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. Highly Enantioselective Rh_2(S-DOSP)$_4$-Catalyzed Cyclopropenation of Alkynes with Styryldiazoacetates. *J. Am. Chem. Soc.* **2010**, *132* (48), 17211–17215.

(80) Vidal, S. Safety First: A Recent Case of a Dichloromethane Injection Injury. *ACS Cent. Sci.* **2020**, *6* (2), 83–86.

(81) Tobiszewski, M.; Namieśnik, J.; Pena-Pereira, F. Environmental Risk-Based Ranking of Solvents Using the Combination of a Multimedia Model and Multi-Criteria Decision Analysis. *Green Chem.* **2017**, *19* (4), 1034–1042.

(82) Depa, W. J.; Majumder, S.; Nadirova, M.; Cmoch, P.; Chaładaj, W.; Andersson, M. P.; Gryko, D. CO2 Utilization in a Micellar System: Synthesis of Cyclic Carbonates. **2024**, doi.org/10.26434/chemrxiv-2024-jd8vk.

(83) Tisovský, P.; Donovalová, J.; Sokolík, R.; Horváth, M.; Gáplovský, A. A New Strategy for the Preparation of E Isomers of Hydrazones and Anil-Like Compounds: Thermally Stimulated Isomerization of Z Isomers of Anions. *ChemistrySelect* **2021**, *6* (39), 10651–10654.

(84) Milton, J. P.; Milanowski, A.; Andersson, M.; Gryko, D. Photochemical Cyclopropanation in Aqueous Micellar Media – Experimental and Theoretical Studies. *Chem. Commun.* **2024**, *60* (33), 4483–4486.

(85) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87* (12), 1348–1349.

(86) Harriman, B. R.; Shelton, R. S.; Campen, M. G. Van; Warren, M. R. Homophthalimides as Hypnotic Agents. *J. Am. Chem. Soc.* **1945**, *67* (9), 1481–1482.

(87) Billamboz, M.; Bailly, F.; Lion, C.; Touati, N.; Vezin, H.; Calmels, C.; Andréola, M. L.; Christ, F.; Debyser, Z.; Cotelle, P. Magnesium Chelating 2-Hydroxyisoquinoline-1,3(2H,4H)-Diones, as Inhibitors of HIV-1 Integrase and/or the HIV-1 Reverse Transcriptase Ribonuclease H Domain: Discovery of a Novel Selective Inhibitor of the Ribonuclease H Function. *J. Med. Chem.* **2011**, *54* (6), 1812–1824.

(88) Billamboz, M.; Bailly, F.; Barreca, M. L.; De Luca, L.; Mouscadet, J. F.; Calmels, C.; Andréola, M. L.; Witvrouw, M.; Christ, F.; Debyser, Z.; Cotelle, P. Design, Synthesis, and Biological Evaluation of a Series of 2-Hydroxyisoquinoline-1,3(2H,4H)-Diones as Dual Inhibitors of Human Immunodeficiency Virus Type 1 Integrase and the Reverse Transcriptase RNase H Domain. *J. Med. Chem.* **2008**, *51* (24), 7717–7730.

(89) Malamas, M. S.; Hohman, T. C. N-Substituted Spirosuccinimide, Spiropyridazine, Spiroazetidine, and Acetic Acid Aldose Reductase Inhibitors Derived from Isoquinoline-1,3-Diones. 2. *J. Med. Chem.* **1994**, *37* (13), 2059–2070.

(90) Vernekar, S. K. V.; Liu, Z.; Nagy, E.; Miller, L.; Kirby, K. A.; Wilson, D. J.; Kankanala, J.; Sarafianos, S. G.; Parniak, M. A.; Wang, Z. Design, Synthesis, Biochemical, and Antiviral Evaluations of C6 Benzyl and C6 Biarylmethyl Substituted 2-Hydroxylisoquinoline-1,3-Diones: Dual Inhibition against HIV Reverse Transcriptase-Associated RNase H and Polymerase with Antiviral Activities. *J. Med. Chem.* **2015**, *58* (2), 651–664.

(91) Zhao, S.; Chen, X.-X.; Gao, N.; Qian, M.; Chen, X. Visible-Light-Mediated Cyclopropanation Reactions of 3-Diazooxindoles with Arenes. *J. Org. Chem.* **2021**, *86* (10), 7131–7140.

(92) Qi, D.; Bai, J.; Song, Z.; Li, B.; Yang, C.; Guo, L.; Xia, W. Photoinduced Synthesis of Functionalized Oxacyclic Spirooxindoles Via Ring Expansion. *Org. Lett.* **2023**, *25* (3), 506–511.

(93) Muthusamy, S.; Ramesh, C. Blue LED-Mediated Synthesis of 3-Arylidene Oxindoles. *J. Org. Chem.* **2023**, *88* (9), 5609–5621.

(94) You, Y.; Lu, W.-Y.; Xie, K.-X.; Zhao, J.-Q.; Wang, Z.-H.; Yuan, W.-C. Enantioselective Synthesis of Isoquinoline-1,3(2H,4H)-Dione Derivatives via a Chiral Phosphoric Acid Catalyzed Aza-Friedel–Crafts Reaction. *Chem. Commun.* **2019**, *55* (58), 8478–8481.

(95) Zhan, S.; Xu, H.; Hong, B.; Gu, Z. Quaternary Chiral Phthalides Enabled by Dirhodium(II)/Phosphine Catalyzed Asymmetric Carbonyl Addition Cascade. *Org. Lett.* **2024**, *26* (38), 8023–8027.

(96) Milton, J. P.; Gryko, D. Photochemical Functionalization of 4-Diazoisoquinoline-1,3(2*H*,4*H*)-Diones and Their 1-Sulfoxide Analogues. *ACS Org. Inorg. Au* **2025**,

doi.org/10.1021/acsorginorgau.5c00017.

(97) D. Patil, M.; Grogan, G.; Bommarius, A.; Yun, H. Recent Advances in ω-Transaminase-Mediated Biocatalysis for the Enantioselective Synthesis of Chiral Amines. *Catalysts* **2018**, *8* (7), 254.

(98) Yin, Q.; Shi, Y.; Wang, J.; Zhang, X. Direct Catalytic Asymmetric Synthesis of α-Chiral Primary Amines. *Chem. Soc. Rev.* **2020**, *49* (17), 6141–6153.

(99) Mathew, S.; Renn, D.; Rueping, M. Advances in One-Pot Chiral Amine Synthesis Enabled by Amine Transaminase Cascades: Pushing the Boundaries of Complexity. *ACS Catal.* **2023**, *13* (8), 5584–5598.

(100) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. *Chem. Rev.* **2020**, *120* (5), 2613–2692.

(101) Cabré, A.; Verdaguer, X.; Riera, A. Recent Advances in the Enantioselective Synthesis of Chiral Amines via Transition Metal-Catalyzed Asymmetric Hydrogenation. *Chem. Rev.* **2022**, *122* (1), 269–339.

(102) Liu, G.; Cogan, D. A.; Ellman, J. A. Catalytic Asymmetric Synthesis of Tert-Butanesulfinamide. Application to the Asymmetric Synthesis of Amines. *J. Am. Chem. Soc.* **1997**, *119* (41), 9913–9914.

(103) Ellman, J. A. Applications of Tert-Butanesulfinamide in the Asymmetric Synthesis of Amines. *Pure Appl. Chem.* **2003**, *75* (1), 39–46.

(104) Varlet, T.; Bouchet, D.; Van Elslande, E.; Masson, G. Decatungstate-Photocatalyzed Dearomative Hydroacylation of Indoles: Direct Synthesis of 2-Acylindolines. *Chem. – A Eur. J.* **2022**, *28* (56), e202201707.

(105) Leone, M.; Milton, J. P.; Gryko, D.; Neuville, L.; Masson, G. TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines. *Chem. – A Eur. J.* **2024**, *30* (24), e202400363.

8. Original Publications

Top Heterocycl Chem (2023) 59: 1–34
https://doi.org/10.1007/7081_2023_59

Published online: 30 March 2023

Photo-Induced Carbene Transformations to Heterocycles

Joseph P. Milton and Dorota Gryko

Contents

1 Introduction 2
2 Carbenes for the Photochemical Synthesis of Heterocycles 4
2.1 C-H Insertions Leading to Heterocyclic Scaffolds 4
2.2 O-H Insertions in Heterocycle Synthesis 8
2.3 Photochemically Generated Ylides in Heterocycle Synthesis 9
2.4 Photochemical Wolff Rearrangements and Subsequent Transformations 13
2.5 Light-Induced [2+1]-Cycloadditions Leading to Heterocycle Rings 18
2.6 Carbenes Generated Via Photochemical Brook Rearrangements 21
2.7 Nitrenes as Intermediates in Photochemical Synthesis of Heterocycles 24
2.8 Miscellaneous 25
3 Conclusion 28
References 28

Abstract Heterocycles are biologically relevant molecules with broad applications in pharmaceutical and agrochemical research. Among the countless approaches for their synthesis, those starting from various carbene/nitrene precursors occupy an important place. Undeniably, environmentally friendly methods for the generation of these reactive intermediates that exclude common transition metals, which are well known for their low abundance, high price, and toxicity, are of great interest. In this chapter, we present photochemical transformations of carbene/nitrene precursors leading to heterocyclic scaffolds. Under the irradiation of light, diazo or azido compounds are typically employed as convenient sources of these reactive species, which subsequently enable cyclizations via Wolff rearrangements, C-H and X-H insertions, or from cycloadditions, as well as various other mechanisms, with only the loss of dinitrogen.

Keywords Carbenes · Diazo compounds · Heterocycles · Photochemistry

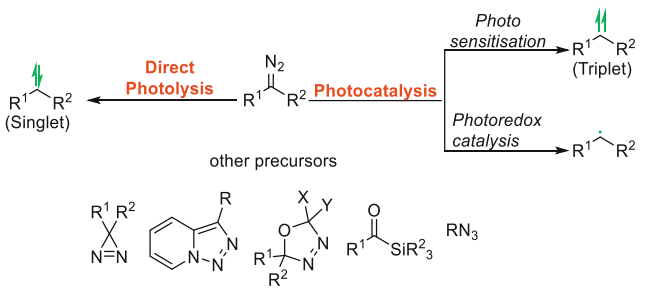
J. P. Milton and D. Gryko (✉)
Institute of Organic Chemistry Polish Academy of Sciences, Warsaw, Poland
e-mail: joseph.milton@icho.edu.pl; dorota.gryko@icho.edu.pl

1 Introduction

Photochemistry is a 'green' methodology that enables the synthesis of heterocycles in an efficient and sustainable manner, often without the need for a catalyst [1]. It provides an elegant way to access intermediates and pathways that are often not available or difficult to reach with typical ground-state reactions [2]. In photochemical reactions, absorption of a photon leads to the generation of an electronically excited state of a reagent and, in fact, contrary to thermal conditions, the reaction starts from a higher energy level [3]. This characteristic often '*facilitates a thermally unachievable, energetically uphill reactions*' [4]. For this reason, the potential of photochemistry has been widely recognised and has quickly attained the state of a mature field [5–9].

Light-induced processes have also proven to be efficient for generating carbenes/nitrenes from various precursors such as diazo compounds, diazirines [10, 11], pyridotriazoles [12, 13], oxadiazolines [14], silyl substituted ketones, and azides. Their reactivity has previously been reviewed with a focus on their use in either photochemical [15–19] or metal-mediated transformations [20–22]. In general, direct photolysis of such compounds leads to the formation of singlet carbenes and requires that the species being irradiated absorbs light of the applied energy. However, for those precursors that do not absorb the light source, a photocatalyst must be added, the role of which is to transfer either energy or donate/accept electrons (Scheme 1) [23]. In the first case, the catalyst acts as a photosensitiser that enables the generation of triplet carbenes, while a photoredox catalyst gives access to open-shell intermediates [15].

Currently, the photochemical synthesis of heterocycles via carbene intermediates mostly utilises the photolysis of the aforementioned photolabile precursors, of which diazo compounds prevail as carbene sources. Stabilised diazo reagents are categorised into three types: acceptor-acceptor (A/A, two electron-withdrawing groups), acceptor (A, one electron-withdrawing group), and acceptor-donor (A/D, one electron-withdrawing group and one electron-donating group), Fig. 1a [16]. Destabilised diazo compounds (D/D, two electron-donating groups) are, in general, highly unstable, but some diaryl diazo compounds can be stored [25]. The



Scheme 1 Photocatalytic transformations of carbene precursors

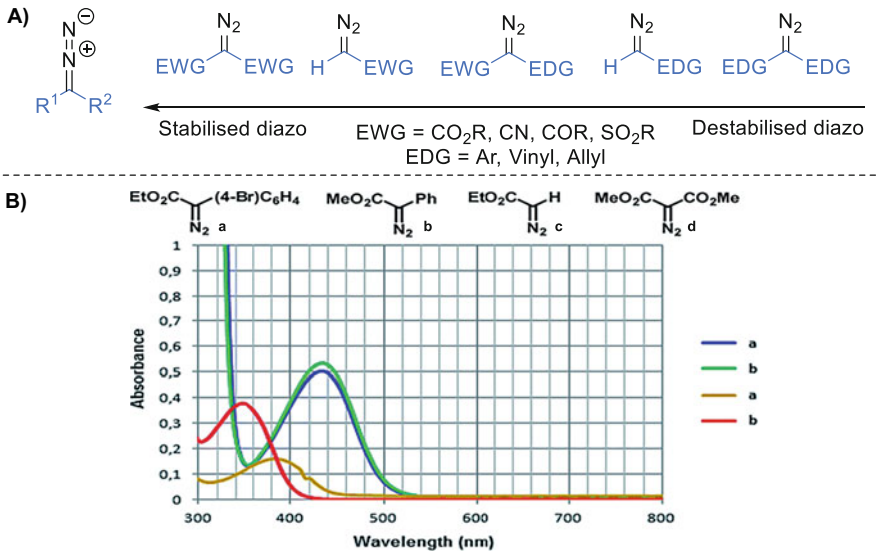


Fig. 1 (**a**) General structure of diazo compounds and their substituents, graded from 'stabilised' to 'destabilised'. (**b**) UV-vis absorbance spectra of some common diazo compounds. Courtesy of the Royal Society of Chemistry, 2018 [24]

nature of the substituents attached to the diazo group impacts their photophysical properties. Most stabilised A/A or acceptor diazo reagents do not absorb light in the visible region, while the absorption of D/A analogues is bathochromically shifted towards the blue region (Fig. 1b) [24]. On the other hand, those bearing two donor substituents, such as aryl-aryl diazoalkanes, can absorb even in the green or red region [25]. Since the seminal report by Jurberg and Davies in 2018 [24], a rise in blue light photochemistry of diazo reagents has been observed. However, even though protocols engaging triplet carbenes do exist, so far, to the best of our knowledge, they have not been utilised for the construction of heterocyclic scaffolds.

Photochemistry is regarded as an eco-friendly methodology and is of intense interest to industry. Its application to the synthesis of heterocycles, which is the core of pharmaceutical chemistry with over 85% of all biologically active compounds containing at least one heterocycle [26], is particularly relevant. Heterocycles are also widely used as agrochemicals, antioxidants, dyes, among others [27]. For decades, heterocyclic scaffolds have been constructed by catalytic reactions using transition metals. These methods are well-documented and reliable; however, they require extensive purification to ensure that the compound surpasses toxicological assessments [28], which has elevated interest in the industrial sector for photochemical methods leading to these key moieties.

Herein, we describe transformations of photochemically generated carbenes/nitrenes leading to heterocyclic scaffolds. The chapter is divided into sections based on the key carbene-mediated mechanistic step. To the best of our knowledge,

it collates all examples for the formation of heterocycles. We wish to stress that it strictly covers only photochemical carbene-based transformations; there are many other reports of photochemical transformations to heterocycles, but they involve other reactive intermediates and these can be found elsewhere [29, 30].

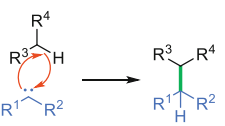
2 Carbenes for the Photochemical Synthesis of Heterocycles

2.1 C-H Insertions Leading to Heterocyclic Scaffolds

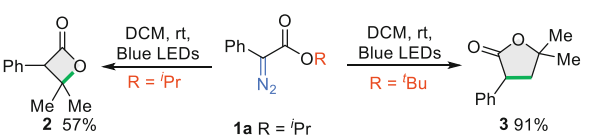
Carbenes insert into carbon-hydrogen bonds in a concerted fashion facilitating the functionalisation of inactivated sp^3, sp^2, and sp C-H bonds (Scheme 2) [31]. Insertion is preferred for more acidic protons, so having an electron-withdrawing group adjacent to the C-H bond undergoing insertion is advantageous, although not required.

Jurberg and Davies reported the photolysis of aryl diazoacetates **1**, under blue light to generate singlet carbenes that engage in C-H, O-H and N-H insertion reactions, as well as cyclopropanation. When C-H insertion is intramolecular, it gives straightforward access to diverse heterocyclic scaffolds. For example, a photochemical intramolecular reaction of isopropyl or *tert*-butyl phenyldiazoacetate (**1a, b**) leads to the corresponding β-propiolactone **2** or γ-butyrolactone **3** in 57 and 91% yield, respectively (Scheme 3) [24]. Of note is the fact that the reaction is mostly viable for bulky alkoxy moieties, otherwise only the extrusion of dinitrogen takes place [32].

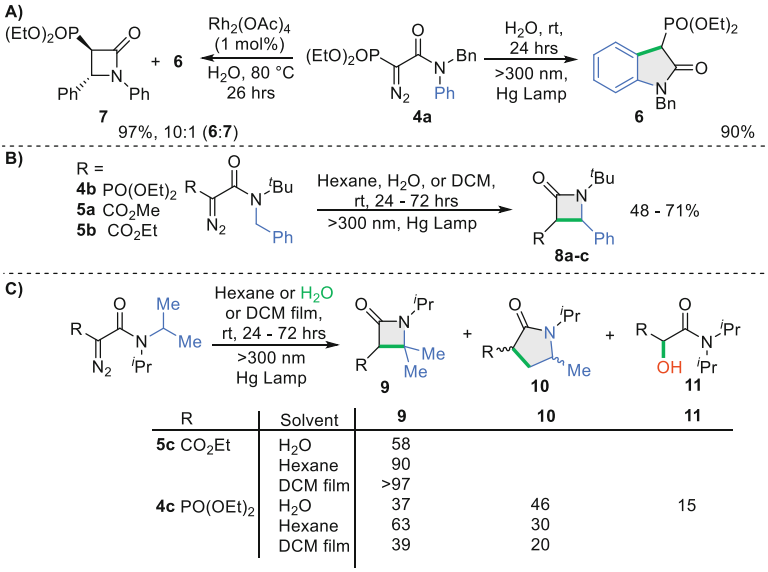
Likewise, α-diazo amides furnish lactams. Here, the amide moiety imposes close proximity of an alkyl group to the in-situ generated carbene, thus facilitating cyclisation [33, 34]. Recent ultrafast time-resolved infrared spectroscopy studies showed that these reactions happen either via a rearrangement in the excited state (RIES) or from a pathway involving a singlet carbene [35]. Along this line, the synthesis of several lactams **6–10** via photochemical C-H insertions was accomplished (Scheme 4) [36].



Scheme 2 General mechanism for a C-H insertion reaction



Scheme 3 Photochemical intramolecular C-H insertions affording lactones

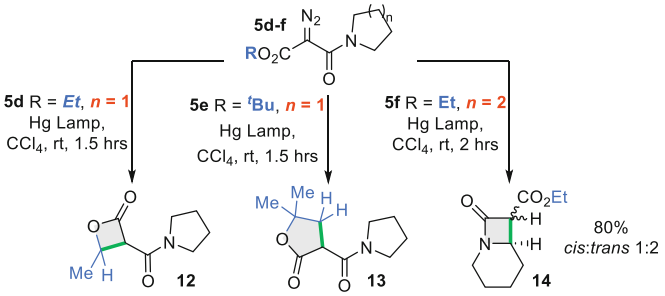


R	Solvent	9	10	11
5c CO_2Et	H_2O	58		
	Hexane	90		
	DCM film	>97		
4c $PO(OEt)_2$	H_2O	37	46	15
	Hexane	63	30	
	DCM film	39	20	

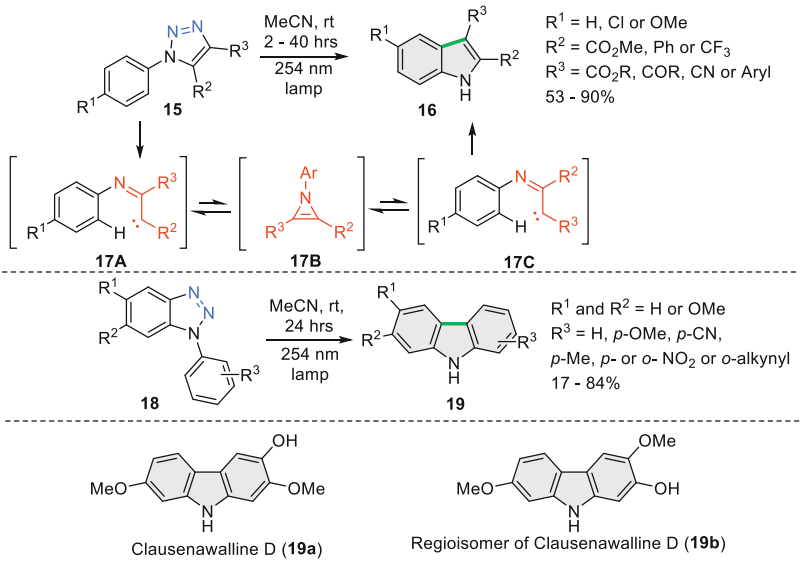
Scheme 4 Light-enabled the synthesis of lactams

While the photochemical reaction of diazo reagent **4a** yields benzo-γ-butyrolactam **6** as the sole product (90%), the reaction under dirhodium (II)-catalysis is less effective with the formation of β-lactam **7** as a pronounced side product (Scheme 4a). Diazo compounds **4b**, **5a**, and **5b** bearing a nitrogen substituted with *tert*-butyl and benzyl groups afford the corresponding β-lactams **8a–c** as the sole product (Scheme 4b). Moreover, in water, the reaction is highly *trans*-stereoselective with the *trans*-isomer being the only diastereoisomer when R = CO_2Et. The site-selectivity in these transformations is governed not only by the susceptibility of C-H bonds towards diazo insertions (Ph > Bn > ^{t}Bu) but also depends on the nature of a substituent at the position α to the diazo functionality. Consequently, for the bis(isopropyl)substituted diazo ester **5c**, only β-lactam **9** was isolated, but when R = $PO(OEt)_2$ (**4c**) a mixture of products forms including β-lactam **9** and γ-lactams **10**, as well as the respective O-H insertion product **11** when the reaction is conducted in water (Scheme 4c).

As is well represented by the studies of Lowe and Parker (Scheme 5) [37], the proximity of the reactive sites in C-H insertions is also important in determining reaction selectivity. Under UV irradiation, when the amide substituent of diazo compound **5d** is a pyrrolidine ring, the reaction favours C-H insertion into the alkyl ester substituent, analogous to Jurberg and Davies' work, forming β-propiolactone **12** (from the ethyl ester) or γ-butyrolactone **13** (from the *tert*-butyl ester). Conversely, when piperidine is the amide substituent (**5f**), C-H insertion occurs at the α-amino site forming fused β-lactam **14** in an approximate 2:1 *trans*:*cis* ratio. Corey and Felix made a similar observation for piperidinyl substituted



Scheme 5 The formation of 4- and 5-membered lactones and lactams via C-H insertions

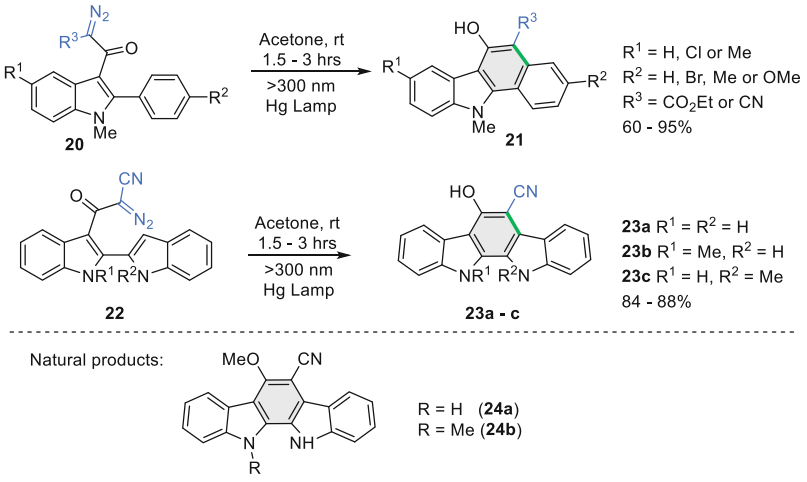


Scheme 6 Synthesis of indoles and carbazoles via irradiation of triazoles

α-diazo amide compounds, and such selectivity enabled the formation of penicillin derivatives [38].

C-H insertion reactions are also viable with respect to aromatic C-H bonds as illustrated by the synthesis of indoles and carbazoles under UV irradiation with the use of triazoles as carbene precursors (Scheme 6) [39].

Interestingly, the production of indoles **16** from the photolysis of *N*-aryl triazoles **15** is fully regioconvergent; substituents R^2 and R^3 can be organised either way, and the same product **16** forms. However, the yields are quite different due to the stability of the proposed intermediates **17A** and **17B**. The same method applied to benzotriazoles **18** gives carbazoles **19** in 22–84% yield. In this case, however, a mixture of regioisomers forms when the *N*-aryl group has two substituents. The



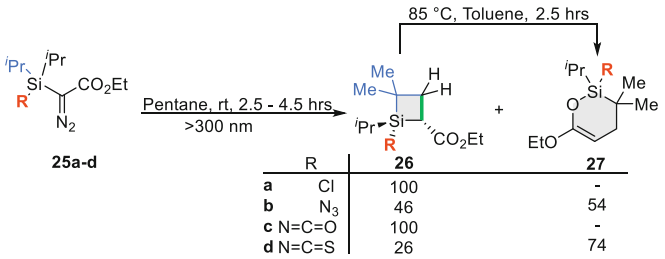
Scheme 7 Synthesis of benzocarbazoles and fused carbazoles from blue light irradiation of diazo compounds

synthetic utility of the procedure is represented by the total synthesis of Clausenawalline D **19a** and its isomer **19b**, which was isolated in six steps with an overall yield of 3% for each compound.

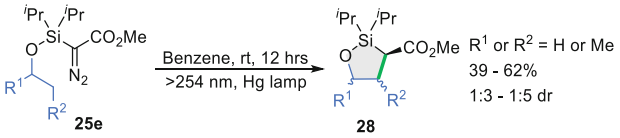
The photochemical methodology based on the intramolecular transformations of carbenes is also suitable for the synthesis of expanded systems, such as carbazole scaffolds (Scheme 7) [40]. With indole-based α-diazo reagent **20**, benzocarbazoles **21** form in over 60–95% yield under UV irradiation, with no major effect on the yield by changing the nature of the aryl substituents. The method also facilitates the synthesis of key intermediates **23a** and **23b** that allow the synthesis of two natural products (**24a,b**), which were isolated from the blue-green alga *Nostoc sphaericum*.

A straightforward method for carbene transformations into heterocycles would be to use α-heteroatom substituted carbene precursors. This strategy is dominated by transition metal-catalysed reactions, and they are exhaustively discussed by Cheng and Meth-Cohn in their review [41]. Until recently, photochemical transformations have not been widely utilised in this context. Along this line, under irradiation with a high-pressure mercury lamp, α-silyl diazo compounds **25a–d** afford siletanes **26** as a single *trans*-diastereoisomer from C-H insertion on alkyl groups of the silicon substituent (Scheme 8) [42]. When the silicon atom is substituted with chloride or isocyanate, only the four-membered ring is formed, contrasting with that when azido or isothiocyanate groups are present from which a mixture of 4- and 6-membered heterocycles **26** and **27** is furnished. All the siletanes can be transformed into the respective 3,4-dihydro-2H-1,2-oxasilines **27** by a thermally induced 1,3(C→O) silyl shift.

Similarly, the synthesis of oxasilolanes **28** from diazo compound **25e** can be accomplished when there is an alkoxy substituent on silicon (Scheme 9) [43]. The



Scheme 8 Photochemical synthesis of four-membered silicon-containing heterocycles



Scheme 9 Synthesis of oxasilolanes via a photochemical C-H insertion reaction

reaction, although affording product **28** in only moderate yields, is noteworthy to mention because C-H insertion typically occurs at the α-position with respect to oxygen, whereas here insertion occurs at the β-position.

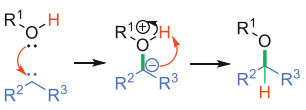
2.2 *O-H Insertions in Heterocycle Synthesis*

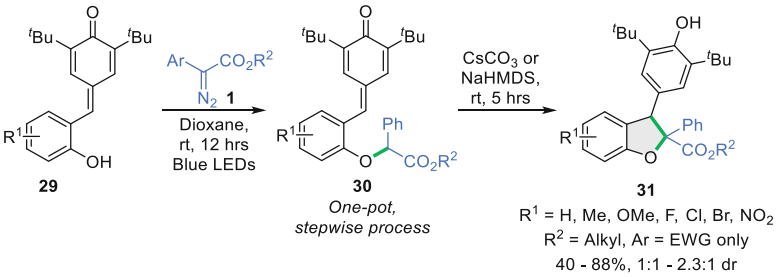
Oxygen-hydrogen insertion represents another key reaction in the repertoire of carbene-mediated reactions. The first step involves the attack of oxygen at the carbene to form an ylide, and its negatively charged carbon centre subsequently removes the proton from oxygen to yield an ether compound (Scheme 10) [44].

This transformation is the key to a two-step, one-pot photochemical process for the synthesis of 2,3-dihydrobenzofurans **31** (Scheme 11) [45].

The use of aryl diazoacetates **1** under blue light irradiation facilitates an O-H insertion reaction on the phenol **29** which, after subsequent treatment with a base, closes the ring in a yield of up to 88% and 2.3: 1 *dr*. The presence of *tert*-butyl groups on the quinone moiety has a strong influence on the reaction, with no cyclisation possible when they are replaced with isopropyl groups.

Scheme 10 General reaction mechanism for O-H insertion





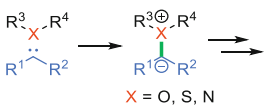
Scheme 11 Photochemical one-pot, stepwise synthesis of 2,3-dihydrobenzofuran derivatives

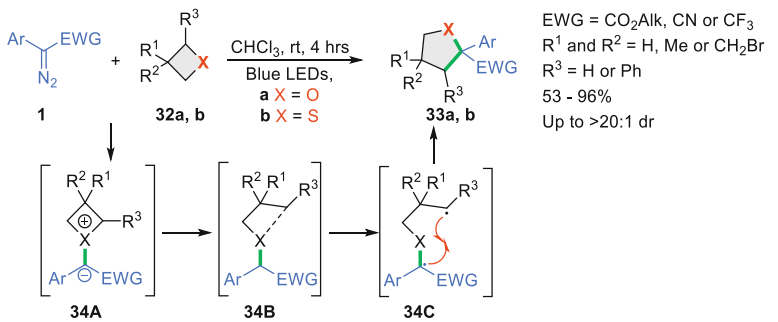
2.3 *Photochemically Generated Ylides in Heterocycle Synthesis*

Carbenes form ylides with electronegative atoms such as oxygen, sulfur, and nitrogen, providing they are unsubstituted with hydrogen (Scheme 12). Such behaviour is described by Kirmse as being analogous to the interaction between Lewis acids and Lewis bases [46].

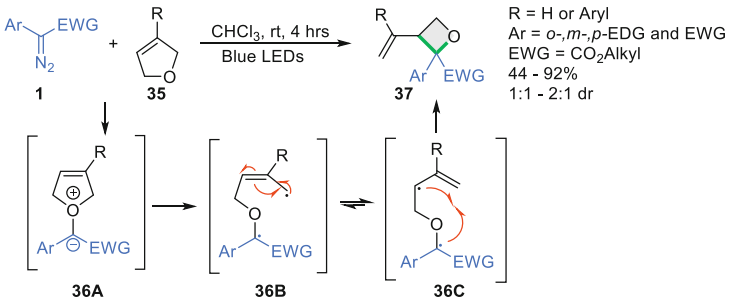
Ylide based transformations often facilitate ring-expansion or ring-contraction processes, leading to new heterocyclic structures. Along this line, the Koenig group described the photochemical ring-expansion of oxetanes **32a** and thietanes **32b** to their respective tetrahydrofurans **33a** and tetrahydrothiophenes **33b** (Scheme 13) [25]. A wide range of substituents on the aryl ring of diazo substrate **1**, regardless of its electronic nature or position, is tolerated enabling the formation of five-membered heterocycles **33a**,**b** in 53–98% yield. When chiral phenyldiazoacetates (e.g. bearing

Scheme 12 Formation of ylides from carbenes

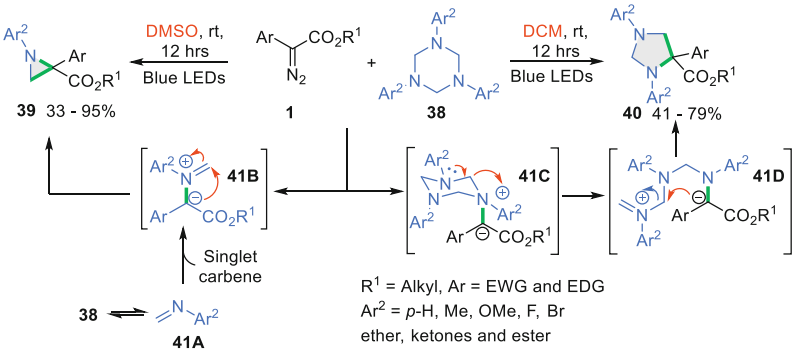




Scheme 13 Ring-expansion of oxetanes and thietanes to form the corresponding tetrahydrofuran and tetrahydrothiophene



Scheme 14 Ring-contraction of 2,5-dihydrofurans to form oxetanes



Scheme 15 Solvent-dependant reactions of diazo compounds with 1,3,5-triazinanes under blue light irradiation

a (−)-menthol group as the ester substituent) are used, the reaction leads to tetrahydrofuran **33a** in high diastereoselectivity (>20:1 *dr*). However, 3-, 5- and 6-membered heterocycles are incompatible with the ring-expansion reaction under the developed conditions.

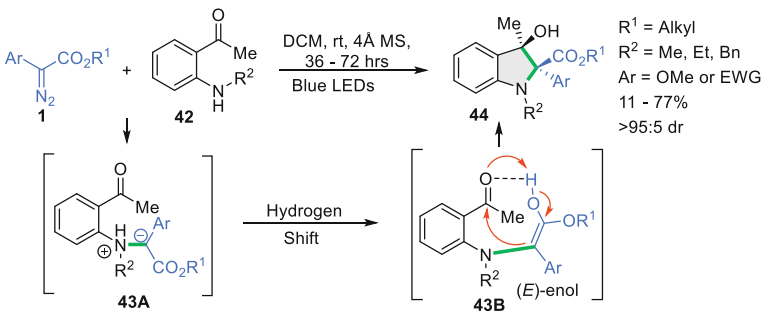
Conversely, the ring-contraction of 2,5-dihydrofurans **35** yields oxetanes **37** for which a mechanism similar to the one depicted in Scheme 13 operates (Scheme 14) [47]. Under blue light irradiation, diazo compound **1** forms a singlet carbene, which reacts with **35** to produce oxonium ylide **36A**. Subsequently, the C–O bond breaks, generating diradical **36B**, which rearranges to the more stable allylic radical species **36C**. Finally, a ring-contraction takes place to give oxetanes **37,** which consists of a broad variety of substituents in 44–92% yield. Computational studies show that the energy barrier between the two diastereomers is nearly identical, which is why the reaction is only moderately diastereoselective with the best result of only 2:1 *dr*.

This strategy is also viable for the generation of ammonium ylides and, hence, the synthesis of *N*-heterocyclic structures. In this regard, Cheng and co-workers reported a divergent solvent-dependant synthesis of both aziridines **39** and imidazolidines **40** using the same starting materials, triazines **38** and aryl diazoacetates **1** (Scheme 15)

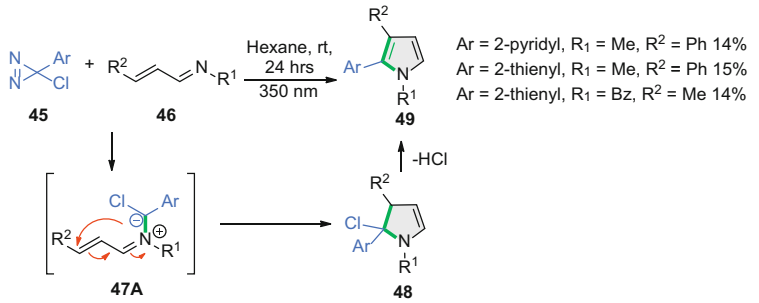
[48]. Under blue light irradiation, a [2+1]-cycloaddition occurs when DMSO is used as solvent, whereas a [4+1]-cycloaddition takes place in DCM. Reportedly, the solvent effect of DMSO facilitates in-situ formation of *N*-phenylmethanimine **41A**, from triazines **38**, which is not the case in DCM. Both transformations are highly tolerable with different aryl and ester substituents present in the diazo reagent **1**, as well as different aromatic groups on triazines **38**, enabling yields up to 95% for azirines **39** and up to 79% for imidazolidines **40**. The method proved to be viable for the modification of bioactive molecules.

The photochemical formation of ammonium ylides **43A** upon aniline derivative **42** is the key step in the synthesis of indolines **44** as reported by Hu and co-workers [49]. The final ring closure on the *Si*-face yields the pyrrolidine moiety in high diastereomeric ratio of >95:5 in all cases studied (Scheme 16). DFT calculations corroborate that the reaction proceeds via the formation of a singlet carbene and subsequent ylide formation. The idea of a triplet carbene pathway is excluded as it would trigger a radical mechanism; the energy barrier of such a transition state is approximately 2.5 times higher than the proposed singlet carbene route. The reaction gives indolines **44** in approximately 50% yield in most cases, although, when the aryl substituent on diazo compound **1** is highly electron-withdrawing (*p*-trifluoromethyl or *p*-nitro), the yield drops significantly to less than 30% even with the reaction time prolonged to 96 h. Interestingly, this example is rather unique as nitrogen atoms bearing hydrogen typically facilitate N-H insertion; therefore, ylide formation here is rather atypical.

However, diazo compounds are not the only source of carbenes generated in a photochemical manner. Heteroaryldiazirines **45** also give access to carbenes upon light irradiation although for their photolysis more energetic light is required as their absorption is hypsochromically shifted. Under UV light irradiation, diazirines similarly give access to carbenes; in this case, once generated they add to the imine nitrogen of substrate **46**, leading to intermediate **47A**, which triggers intramolecular Michael addition to form 2,3-dihydropyrroles **48** (Scheme 17) [50]. Concomitant expulsion of HCl then affords the respective pyrrole **49**. 2-Pyridyl and 2-thienyl

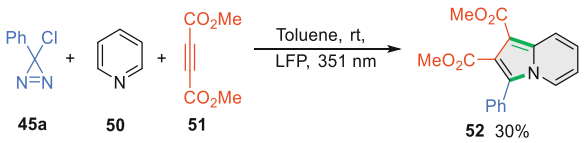


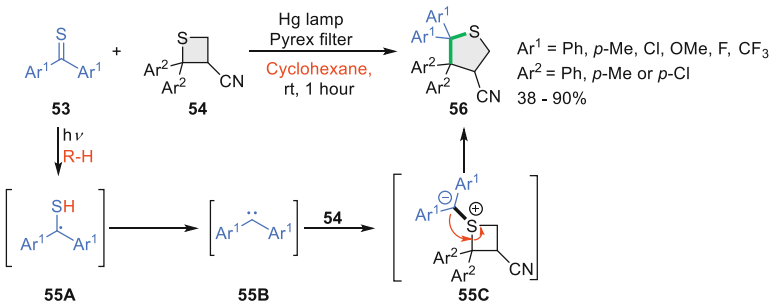
Scheme 16 Synthesis of highly substituted indolines via a formal [4+1]-annulation involving photochemically generated ylides



Scheme 17 Photochemical synthesis of pyrroles from diazirines and α,β-unsaturated imines

Scheme 18 Laser flash photolysis of a diazirine, pyridine and acetylene for the formation of an indolizine





Scheme 19 Generation of carbenes from thioketones enabling ring-expansion of thietanes

pyrroles **49** were synthesised, albeit in rather low yields of less than 15% in all cases, presumably because of the high reactivity of iminium starting material **46**.

Along this line, phenylchlorocarbenes generated from diazirines **45a** gives access to indolizine **52** upon laser flash photolysis of a three-component mixture (Scheme 18) [51]. In this transformation a photochemically generated singlet carbene adds to pyridine (**50**) to form an ylide that follows with a dipolar cyclisation with dimethyl acetylenedicarboxylate (**51**) facilitating the final ring closure. The subsequent removal of HCl affords indolizine **52** in 30% yield.

Aitkene and co-workers reported the rather uncommon photochemical formation of carbene **55B** from diaryl thioketones **53** enabling the ring-expansion of thietanes **54** (Scheme 19) [52]. Substrate **53** in the triplet excited state is proposed to abstract a hydrogen from cyclohexane, which generates radical **55A**, which subsequently transforms into carbene **55B** by the concomitant loss of sulfhydryl HS$^{\cdot}$; ylide **55C**

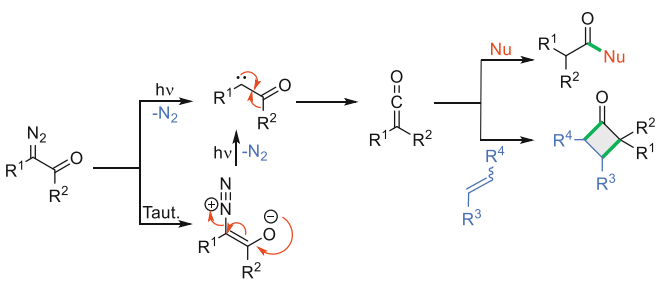
then undergoes a thia-Stevens rearrangement to form tetrahydrothiophenes **56**. The reaction is highly concentration dependant and requires highly dilute conditions (0.001 M), since at higher concentrations decomposition of thietane **54** to a 1,1-diaryl-2-cyanoethene takes place. Yields are generally good (66–90%) except when strongly electron-withdrawing trifluoromethyl groups are attached to the aryl rings of thioketone **53**.

2.4 *Photochemical Wolff Rearrangements and Subsequent Transformations*

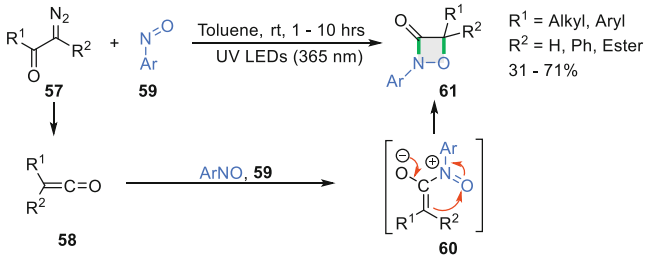
The Wolff rearrangement is a classic reaction in organic chemistry introduced by Ludwig Wolff [46]. Despite being discovered over 120 years ago, the mechanism of the reaction is still heavily debated [47]. Nevertheless, it is assumed to involve nitrogen extrusion, which forms a carbene and leads to a [1,2]-rearrangement. The reaction gives access to ketenes that can be quenched by nucleophilic reagents to form carboxylic acids, amides, and other species, or can react via [2+2]-cycloaddition leading to cyclobutanones (Scheme 20).

Photochemically generated ketenes **58** are highly versatile intermediates and can be utilised in the synthesis of heterocycles of many different sizes. When nitroso compounds **59** are applied as a reaction partner, formal [2+2]-cycloadditions furnishes a four-membered oxazetidine ring (**61**) in 31–71% yield (Scheme 21) [53]. The reaction can tolerate nitroso compounds which contain strongly electron-withdrawing groups (CF_3 or CN) at the *ortho*-position. When an electron-donating group (such as methyl) is present, the resultant cycloadduct is so unstable that a retro rearrangement occurs.

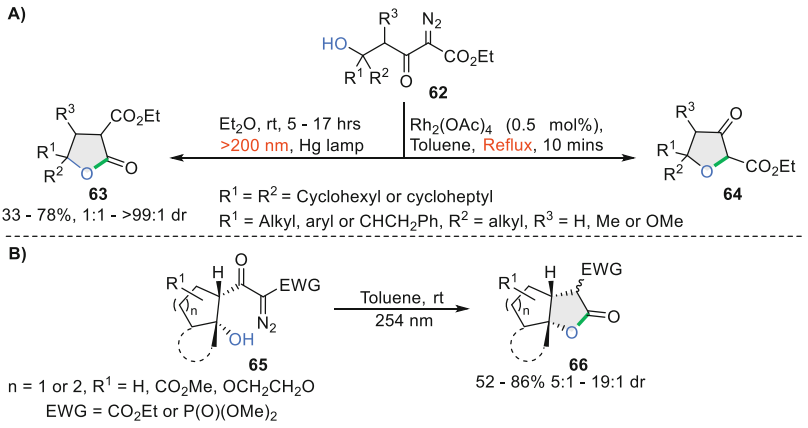
Photochemical Wolff rearrangement of α-diazocarbonyl compounds followed by an intramolecular reaction with a nucleophile leads to heterocycles, as reported by Liao and co-workers (Scheme 22a) [54]. In particular, diazo ketones **62** under UV light irradiation give access to five-membered lactones **63** in 33–78% yield with high diastereoselectivity. In contrast, a rhodium catalysed reaction relies solely on an O-H insertion and gives corresponding 3-oxotetrahydrofurans **64** in excellent yields (over



Scheme 20 Possible general mechanistic pathways for the Wolff rearrangement



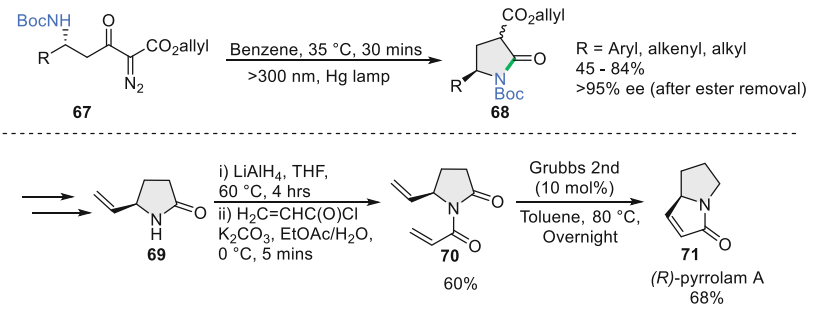
Scheme 21 Cycloaddition of nitroso aryl compounds with photochemically generated ketenes



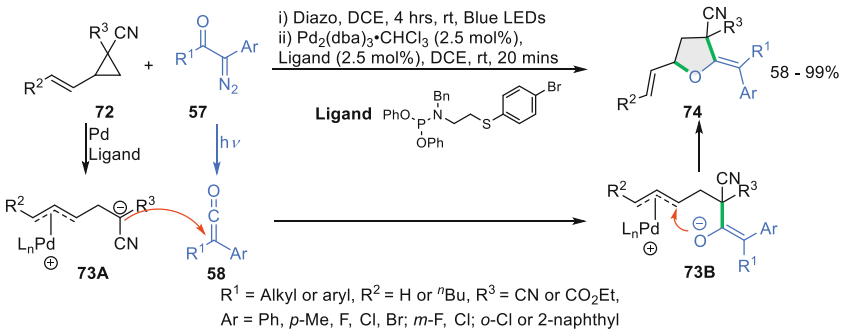
Scheme 22 Synthesis of γ-butyrolactones via photochemical Wolff rearrangements with intramolecular ring closure

90%) though with low diastereoselectivity. Along the same line, Zhang and Romo used diazo compounds **65** for the synthesis of bicyclic and tricyclic β-lactones **66** (Scheme 22b). In all cases, thermal conditions (toluene at reflux) proved less efficient in producing the desired heterocycle in comparison to the photochemical conditions. Similarly, Rh-catalysis can be utilised for such a compound through an O-H insertion to 3(*2H*)-furanones [55].

Likewise, the synthesis of γ-lactams **68** was accomplished (Scheme 23). Subjecting specifically designed diazo esters **67** to irradiation under a high-pressure mercury lamp produced 3,5-disubstitued pyrrolidones **68** in 45–84% yields whether R is an aryl or an alkyl substituent with relatively poor diastereoselectivity. Removing the ester group from lactam **68** reveals that the reaction maintains the pre-installed stereogenic centre with >95% *ee* in all cases [56]. The same group used this methodology towards the synthesis of alkaloid derivatives and even for the total synthesis of *(R)*-pyrrolam A (**71**) [57], while McDonald and co-workers prepared an enantiomerically pure *trans*-β-lactam from an α-amino acid under flow conditions [58].



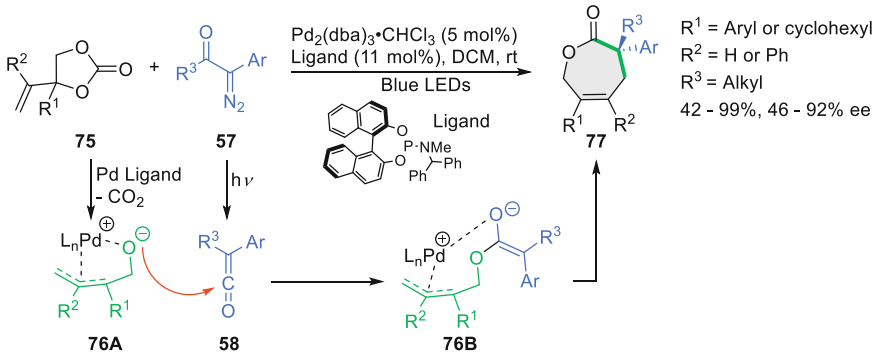
Scheme 23 Synthesis of lactams involving a photochemical Wolff rearrangement



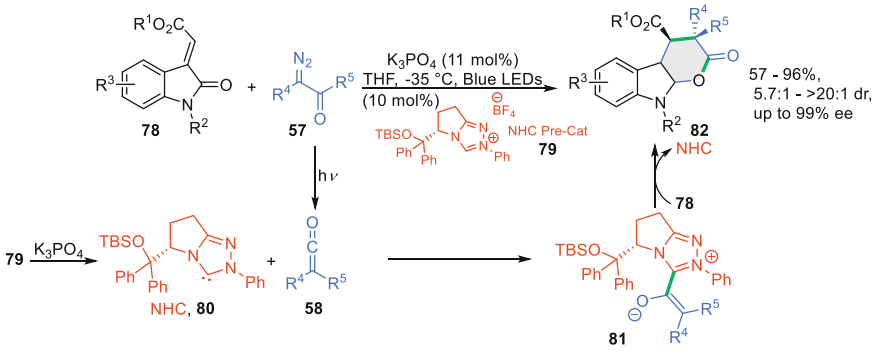
Scheme 24 Synthesis of tetrahydrofurans via a palladium-catalysed insertion into cyclopropanes followed by a chain reaction with photochemically generated ketenes

The formation of highly reactive ketenes **58** obtained from aryl diazo compounds **57** under photochemical conditions does not require any catalyst, thus predisposing them to be used in conjunction with traditional metal catalysis. The Xiao group merged a palladium-catalysed ring-opening of cyclopropanes **72** with the photochemical generation of ketenes **58** for the synthesis of tetrahydrofurans **74** (Scheme 24) [59]. The reaction is highly tolerant to a wide range of substituents on the aromatic ring of aryl diazo ketones **57** while the R group can contain double and triple bonds or an ether moiety with only a small effect on product yield. The use of a chiral ligand enabled the formation of the product also, but only with 50% *ee*.

A similar approach enabled the enantioselective synthesis of seven-membered lactones **77** with a chiral quaternary stereocenter (Scheme 25) [60]. The palladium-catalysed ring-opening of vinylethylene carbonates **75** with expulsion of carbon dioxide affords 1,5-dipolar intermediate **76A** that subsequently reacts with ketene **58** generated in the Wolff rearrangement. A number of cyclic carbonates **77** react with 2-diazo-1-phenylpropan-1-ones **57** with most proceeding in over 90% yield and *ee*, even on a gram-scale in a flow photoreactor. The reaction is highly tolerable to a range of functional groups including alkenyl, alkynyl and ethereal groups present in diazo compounds **57**. One example is given for a cyclic diazo compound that



Scheme 25 Wolff rearrangement of diazo compounds with simultaneous ring-opening of vinylethylene carbonates from seven-membered lactones

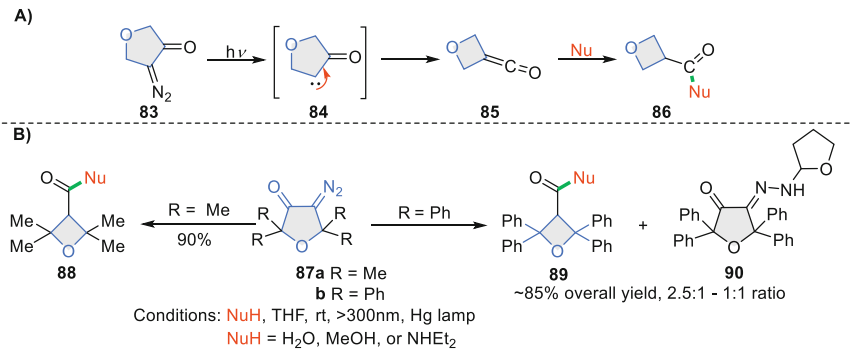


Scheme 26 Synthesis of fused tetrahydro[2,3-b] indoles via direct photolysis of diazo compound merged with NHC-catalysis

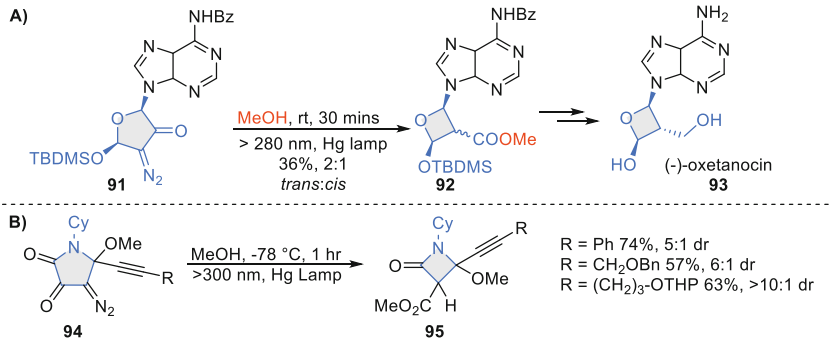
afforded a spiro-lactam in 83% yield and 76% *ee*. A similar reaction mechanism operates for the enantioselective synthesis of six-membered lactones, also by Xiao [61].

Direct photolysis of α-oxo-diazo compounds **57** can also be merged with *N*-heterocyclic carbene (NHC) catalysis (Scheme 26) [62]. In this context, tetrahydro [2,3-b]indoles **82** were synthesised in high yields and *ee* (57–96%, >20:1 *dr* and 99% *ee*) with good reaction scalability. However, the nature of the *N*-protecting group on substrates **78** is crucial for the reaction outcome, as introducing groups other than benzyl at the nitrogen atom diminished both *ee* and *dr*, with no product formation for unprotected or *N*-tosyl-indolinone being observed.

When, however, both diazo- and oxo-functionalities are present in the cyclic system, such as in diazo compound **83**, it is predisposed to undergo ring-contraction yielding new heterocyclic platforms (Scheme 27a). In this regard, Rodina and co-workers have extensively investigated the photochemical ring-contraction of tetrasubstituted 3-oxo-4-diazotetrahydrofurans **87** [63, 64]. Early data showed that



Scheme 27 Investigation into the Wolff rearrangement of tetrasubstituted 3-oxo-4-diazotetrahydrofurans



Scheme 28 Ring-contraction via a photochemical Wolff reaction for the synthesis of β-lactams

short-wave irradiation (>210 nm) of 2,2,5,5-tetraalkyltetrahydrofurans **87a** furnishes oxetanes **88** in near quantitative yield but gives lower yields in the case of tetraphenyl derivative **87b**. When the latter is exposed to high-wave irradiation (>300 nm), surprisingly it simultaneously undergoes C-H insertion into the α-position of THF with full retention of the nitrogen atoms to give side-product **90**. This is not, however, the case for the tetramethyl analogue **87a** (Scheme 27b). The ratio of products depends on the nucleophile used with a 1:1 mixture being formed when using water, whereas a 2.5:1 ratio was observed for diethylamine in favour of the ring-contracted product **89** [65]. The position of the phenyl groups does not have an impact on the reaction course, and such C-H insertion occurs independent of the aryl group position [66].

Norbeck and Kramer utilised a ring-contraction of 3-oxotetrahydrofuran **91** as the key step towards the total synthesis of (−)-oxetanocin (**93**) (Scheme 28a) [67]. The ring-forming step affords the respective oxetane **92** in 36% yield in an approximate 2:1 mixture, with the *trans,trans*-oxetane as the major product, enabling the

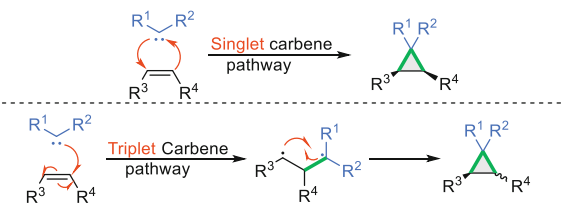
formation of desired product **93** in 5% overall yield after 12 steps. This is a significant improvement over the previous total synthesis of (−)-oxetanocin from Niitsuma and co-workers, which took 19 steps with an overall yield of only 0.008% [68, 69]. Similarly, the photoinduced ring-contraction works for *N*-heterocycles. For example, photolysis of 4-diazopyrrolidine-2,3-diones **94** furnishes β-lactams **95** in 57–74% yield in up to >10:1 *dr* (Scheme 28b). The utility of this strategy is represented by the synthesis of bicyclic β-lactams and generated a penicillin analogue in 72% isolated yield with exclusive formation of the *trans*-product [70]. Lowe and Yeung reported a similar ring-contraction of 3-diazopyrrolidine-2,4-diones [71].

2.5 *Light-Induced [2+1]-Cycloadditions Leading to Heterocycle Rings*

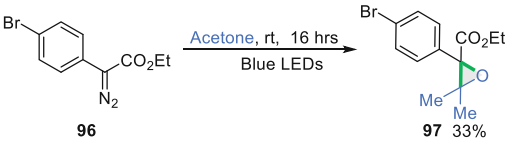
Cycloadditions are debatably the most fundamental reactions of carbenes. The stereochemical outcome of the reaction is dependent on the nature of a carbene; reactions with singlet carbenes proceed in a concerted and stereospecific manner, whereas triplet carbenes react in a stepwise fashion and are only stereoselective (Scheme 29) [72].

Such cycloadditions are typically used for cyclopropanation involving either singlet or triplet carbenes, but they can also be employed in the construction of heterocyclic scaffolds. Jurberg and Davies demonstrated that photochemically generated carbenes from aryldiazoacetates, such as ethyl (4-bromophenyl)diazoacetate (**96**), under blue light irradiation react with a large array of solvents as acceptors, among them, acetone. A [2+1]-cycloaddition occurs in such a case to form epoxide **97** in 33% yield (Scheme 30) [24].

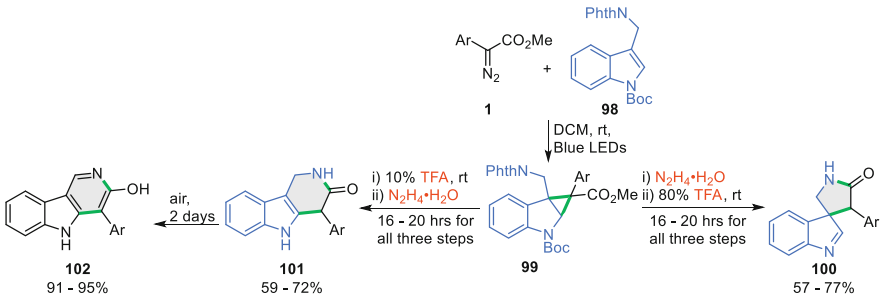
Photochemically generated carbenes were employed for the functionalisation of tethered *N*-Boc indole **98**; a three-step telescoped process formed either



Scheme 29 General mechanism for the [2+1]-cycloaddition leading to cyclopropanes

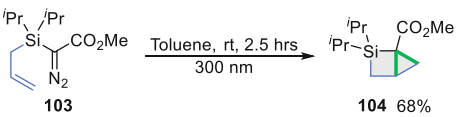


Scheme 30 [2+1]-cycloaddition of a diazo compound with acetone resulting in an epoxide



Scheme 31 Synthesis of γ-carbolinones and spiro[pyrrolidinone-3,3′]indoles via the cyclopropanation and selective deprotection of indoles

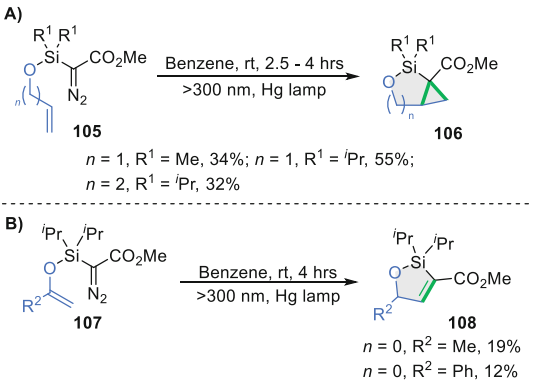
Scheme 32 A photochemical [2+1]-cycloaddition leading to a silicon-containing 'housane'



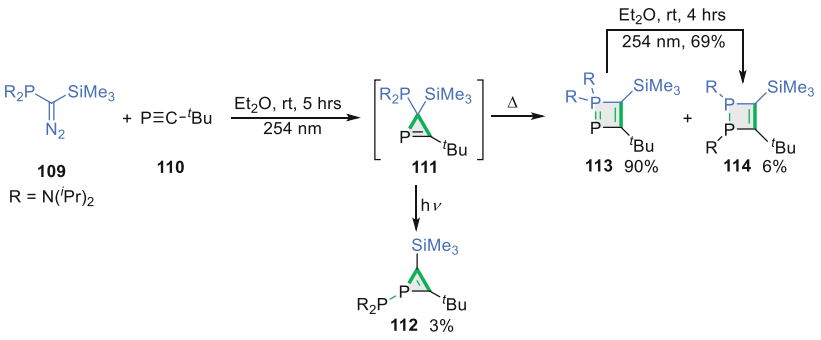
γ-carbolinones **101** or spiro[pyrrolidinone-3,3′]indoles **100**, depending on the order of removal of the protecting groups' steps (Scheme 31) [73]. In the first step, a light-induced reaction of aryl diazoacetates **1** with tethered *N*-Boc indole **98** occurs, forming the expected [2+1]-cyclopropane derivatives **99**. From this, the cycloadducts are subjected to phthalimide deprotection, followed by *N*-Boc removal which gives spiro pyrrolidones **100**. When the deprotection step follows treatment of compound **99** with TFA, γ-carbolinones **101** are formed instead. The carbolinones can be subsequently oxidised to fused pyridines **102** in over 90% yield by simple exposure to air. Of note is the fact that from the same starting materials, three distinctive heterocyclic scaffolds can be formed depending on the conditions used.

The photochemical intramolecular [2+1]-cycloaddition of specifically designed α-silyldiazo compound **103** bearing a silicon-bound allyl substituent yields 2-silabicyclo[2.1.0]pentane **104** (a silicon-containing 'housane') in 68% yield as reported by Maas and co-workers (Scheme 32) [74]. The same reaction under rhodium catalysis or under thermal conditions leads to a complex mixture of compounds, with no desired product being identified. Compound **104** is the first example of a silicon-containing housane derivative and is reported to be thermally stable, but in methanol can be opened to a non-fused cyclopropane.

The formation of 1,2-oxysila-heterocycles can be achieved by intramolecular cyclopropanation reactions of siloxy-substituted diazo compounds with tethered olefins **105**. Such substrates, when exposed to UV light, enable the formation of bicyclic oxasilolanes ($n = 1$) and an oxasilinane ($n = 2$) in 32–55% yield (Scheme 33a) [43]. Similarly, when (vinyloxy)silyldiazoacetates **107** are exposed to UV light, 2,5-dihydro-1,2-oxasiloles **108** are formed, presumably from a rearrangement of the initially formed unstable bicycloxasiletane (Scheme 33b) [75]. Such compounds are



Scheme 33 Synthesis of 1,2-oxasilolanes and 1,2-oxasilinanes from intramolecular cyclopropanation or C-H insertion



Scheme 34 Photochemical intramolecular cycloaddition of silyl diazo compounds with a phosphane

hydrolytically labile and, hence, could only be isolated in low yields, which were less than 20% for both substrates reported.

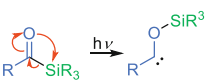
The synthesis of various phosphorus heterocycles from phosphinocarbenes, in particular those of diphosphetes **113** and dihydrophosphetes **114**, was accomplished by Sanchez and co-workers (Scheme 34) [76]. Under UV irradiation of compound **109** a singlet phosphinocarbene is produced, which undergoes a [2+1]-cycloaddition with (2,2-dimethylpropylidyne)phosphane (**110**) to furnish 2*H*-phosphirene **111** (detected by ^{31}P NMR). This intermediate **111** can undergo either a photochemical rearrangement to 1*H*-phosphirene **112** or a thermal rearrangement to a diphosphete and dihydrophosphete. Diphosphete **113**, known to act as a ligand for tungsten complexes [77], can be further converted to **114** as the exclusive product under photochemical conditions.

2.6 *Carbenes Generated Via Photochemical Brook Rearrangements*

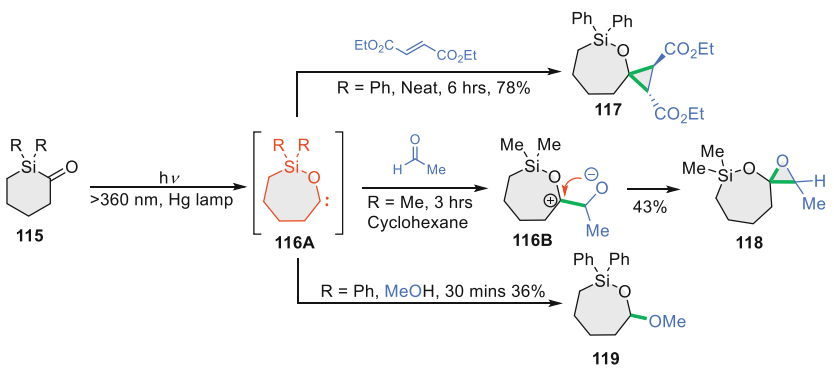
The Brook rearrangement is a transformation characteristic for silyl ketones giving access to heteroatom substituted carbenes having nucleophilic character (Scheme 35). This approach has been broadly utilised for the synthesis of heterocycles including those that contain a silicon atom [41]. The formation of silyloxy carbenes from Brook rearrangements is a pleasing alternative to diazo compounds as they maintain full atom economy. These rearrangements can occur under thermal conditions that are frequently realised under microwave conditions [78].

Initial work on the photochemical Brook rearrangement from Adrian Brook demonstrated the generation of cyclic silyloxy carbenes, such as **116A** from 1,1-diphenylsilacyclohexanones **115**, which can be trapped with various reagents, including olefins, alcohols, and aldehydes (Scheme 36) [79, 80].

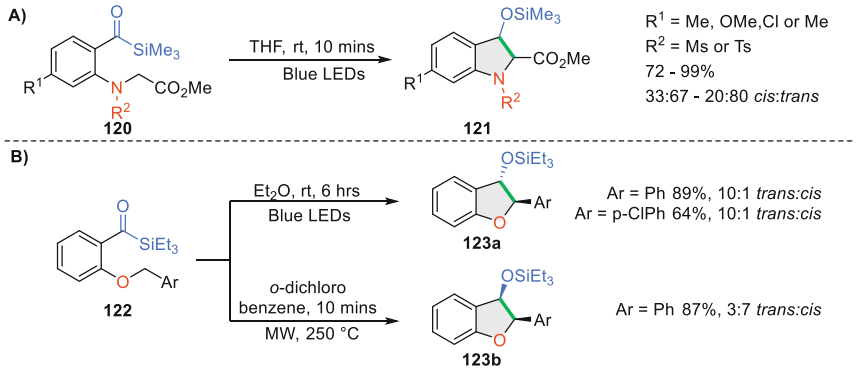
Predictably, [2+1]-cycloaddition of the carbene with the olefin leads to the respective 1,2-oxasila- spirocyclic scaffold **117**, while the reaction with acetaldehyde affords epoxide **118** as an inseparable mixture of diastereoisomers. Other aldehydes proved ineffective in giving the desired bicyclic heterocycle. O-H Insertion with methanol leads to 7-methoxy-1,2-oxasilepane (**119**) in 36% yield. Svarovsky and co-workers used such a transformation for the synthesis of potential silicon-containing pH-sensitive prodrugs from sugars that are active against tumours [81]. Under UV light irradiation, O-H insertion into various carbohydrates enabled the formation of the seven-membered ring in yields of over 90%.



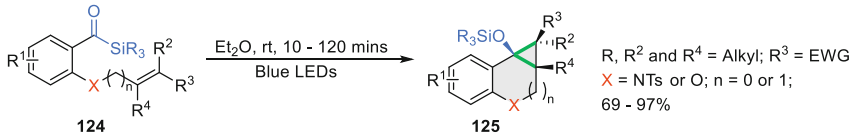
Scheme 35 General reaction mechanism for a photochemical Brook rearrangement



Scheme 36 Reactions of photochemically generated silyloxy carbenes



Scheme 37 Formation of five-membered heterocycles from the C-H insertion siloxy carbenes

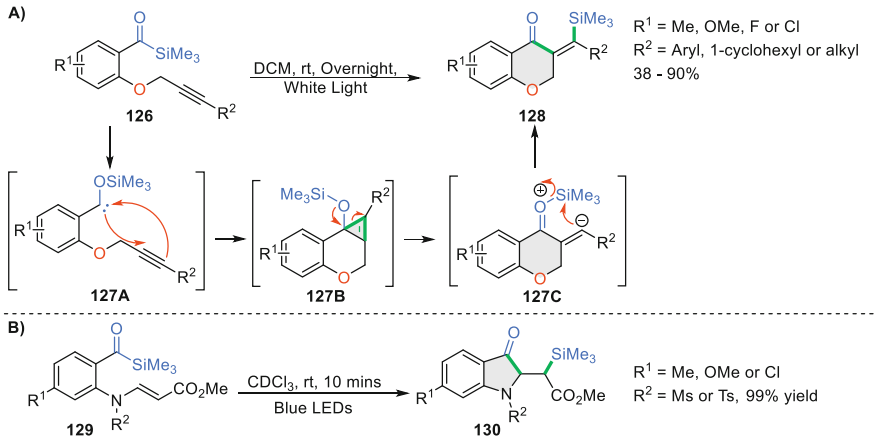


Scheme 38 Intramolecular [2+1]-cycloaddition of siloxy carbenes to afford cyclopropyl-fused O- and N-heterocyclic scaffolds

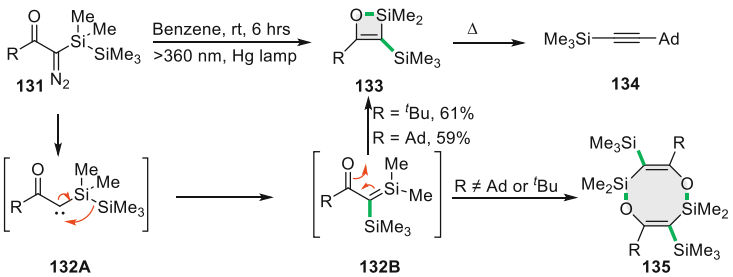
Becker et al. showed that the use of blue light is sufficient for the generation of silyloxy species from specifically designed *ortho*-aminated substrates **120** (Scheme 37a) [82]. The Brook rearrangement followed by C-H insertion enables the synthesis of indolines **121** in high yields (99% yield in most cases). Optimisation studies revealed that diastereoselectivity is solvent-dependent with THF proving to be the solvent of choice, giving *dr* ranging from 33:67 to 20:80. Priebbenow and co-workers found that a similar C-H insertion reaction generates 2,3-dihydrobenzofurans **123a** with high *trans*-selectivity (Scheme 37b) [83]. This complements Shen and Dong's work, where the same substrate under microwave conditions at 250°C produced 2,3-dihydrobenzofurans **123b** with high *cis*-selectivity instead [78].

A similar intramolecular approach merging blue light-induced Brook rearrangement with [2+1]-cycloaddition of nucleophilic siloxy carbenes leads to cyclopropyl-fused heterocycles **125** (Scheme 38) [83]. The *exo*-diastereomer forms exclusively from (*E*)-alkenes in only 10 min; longer reaction times are required for alkenes bearing poorly activating alkyl groups (for example, when R^1 or R^2 = Me and H or $R^1 = R^2$ = cyclohexyl). In general, the reaction is high yielding and tolerates many functional groups enabling the synthesis of fused heterocycles in 69–97% yield.

For propargyl derivatives **126** reactions of siloxy carbenes result in the formation of cyclopropene **127B**, and the instability of the three-membered ring triggers a retro Brook rearrangement, which enables the synthesis of chroman-4-ones **128** (Scheme



Scheme 39 Synthesis of chromon-4-ones and indolin-3-ones via cycloaddition and retro-Brook rearrangement



Scheme 40 Formation of 1,2-silaoxetenes and 1,5,2,6-dioxadisilocines from the silyl migration into carbenes

39a) [84]. The reaction furnishes **128** in high yields, up to 92%, with the *Z*-isomer as the only diastereoisomer in the majority of cases. The reaction is viable under solvent-free conditions although the *E*/*Z* ratio is eroded. Becker showed that this type of reactivity is also compatible with acrylates **129**, allowing the formation of 3-oxo-indolines **130** in >99% yield (Scheme 39b) [82].

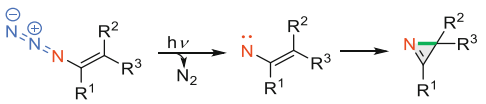
While not a Brook rearrangement, the synthesis of silaoxetenes **133** can be achieved through direct photolysis of α-silyl-α'-carbonyl compounds **131** (Scheme 40) [85]. The fate of silene **132B** depends on the bulkiness of the ketone substituent. Adamantyl or *tert*-butyl substituted silanes undergo a [2+2] intramolecular cycloaddition to form 1,2-silaoxetenes **133**. Sterically less hindered substrates (R = ^{i}Pr, Me or aryl) tend to dimerize to an 8-membered ring **135**, the formation of which is unclear but believed to either arise from cyclodimerisation of 1,2-silaoxetene **133** or the silene **132B**. Sekiguchi and co-workers reported that the silaoxetene is converted to 2-adamantan-1-yltrimethylsilylacetylene (**134**) under thermal conditions [86].

2.7 *Nitrenes as Intermediates in Photochemical Synthesis of Heterocycles*

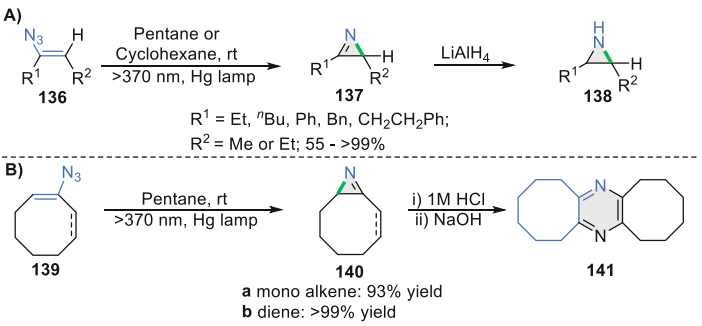
Nitrenes, the nitrogen analogues of carbenes, are reactive intermediates easily accessed from vinyl or aryl azides. Once formed, they subsequently react in an intramolecular manner to form azirines, which are highly strained molecules and are prone to ring-opening (Scheme 41).

Hassner and Fowler reported the photochemical synthesis of azirines **137** directly from vinyl azides **136** (Scheme 42a) [87]. While rather common, the azirines are only intermediates in various reactions and are typically not isolated. Sometimes, however, they can be isolated in high yields (over 80% yield), although when R = R^2 = ethyl the yield dropped to 55%. Isomura showed that under reductive conditions, *2H*-azirines produce aziridines **138** [88]. Unexpectedly, the cyclisation of azidocycloctenes **139** furnish aziridines **140a**,**b** in quantitative yields, which turned out to be highly stable even with two double bonds being present in the ring (Scheme 42b). These bicyclic heterocycles **140** readily hydrolyze under acidic conditions and treating the subsequent product with a base facilitates dimerization to yield a new heterocyclic scaffold, pyrazine **141** [87].

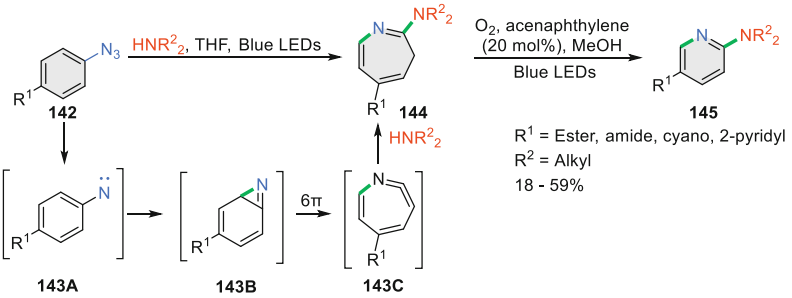
Under UV irradiation with a high-power mercury lamp, the direct conversion of benzene rings to pyridine rings via carbon-nitrogen exchange was initially described in 1972. However, because two azepines and two pyridines were produced as an inseparable mixture, the method was not synthetically useful [89]. It is now known, as shown by Patel and Burns, that the transformation of azidobenzenes **142** under less energetic blue light leads selectively to 3*H*-azepines **144** (Scheme 43) [90]. The



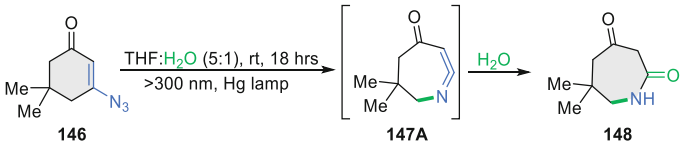
Scheme 41 General mechanism for the photochemical formation of nitrenes



Scheme 42 Synthesis of isolatable azirines under photochemical conditions; 9-aza-bicyclo[6.1.0] nonenes were reported to be highly stable



Scheme 43 Functional group interconversion of aryl azides to pyridines via an isolatable 3H-azepine



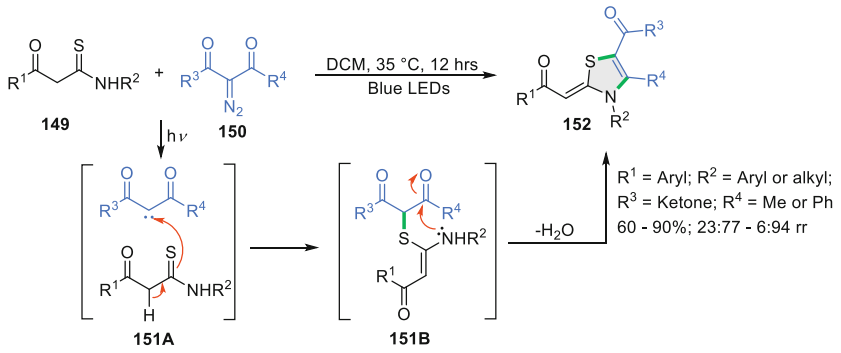
Scheme 44 Synthesis of 6,6-dimethylazepane-2,4-dione from photolysis of a vinyl azide

mechanism suggests the generation of nitrene **143A**, which subsequently produces azirine **143B**. 6π-Electrocyclization followed by attack of the amine generates azepine heterocycle **144,** which can further react with singlet oxygen to brandish a new scaffold, pyridine **145**. Both steps can be realised in a one-pot manner in yields of up to 59%.

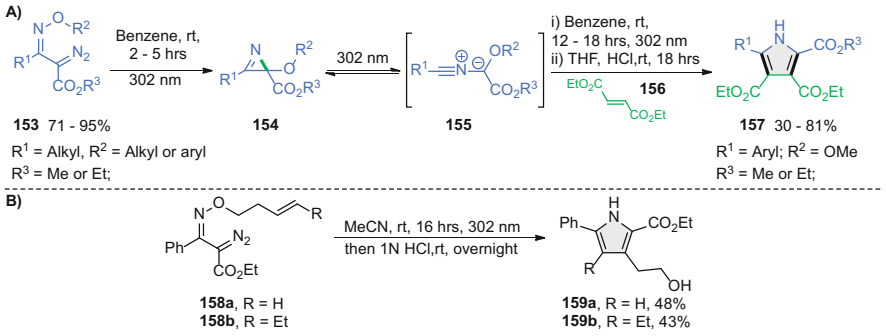
Along this line, irradiation of cyclic vinyl azide **146** results in a ring-expansion to an azepane-2,4-ketoamide **148** (Scheme 44) [91]. Interestingly, the mechanism of the reaction is suggested not to proceed via an azirine but instead via strained intermediate **147A**, that presumably results from a Curtius-type rearrangement. Subsequent hydrolysis leads to the formation of 6,6-dimethylazepane-2,4-dione (**148**) as the only product, although no comment on the yield was made.

2.8 Miscellaneous

Among the many heterocyclic scaffolds that have been synthesised based on photochemical transformations, thiazolines **152** are also part of this collection. This moiety forms regioselectively under blue light irradiation of α-diazo-1,3-diketones **150** with β-ketothioamides **149** in good yields (Scheme 45) [92]. The reaction is scalable and highly tolerant with a variety of electron-donating or electron-withdrawing substituents on the aryl rings of both substrates having no detrimental



Scheme 45 Photochemical synthesis of thiazolines from diazo 1,3-dicarbonyl diazo compounds and β-ketothioamides

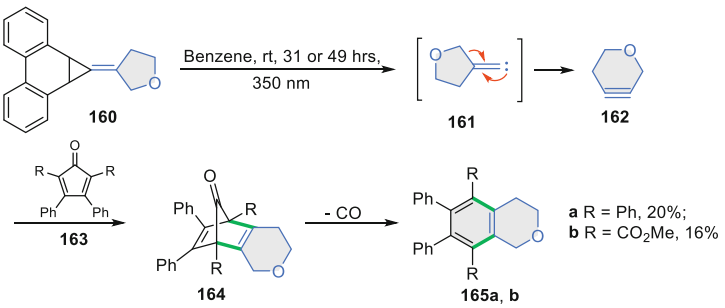


Scheme 46 Synthesis of 2H-azirines from intramolecular N-O insertion of carbenes

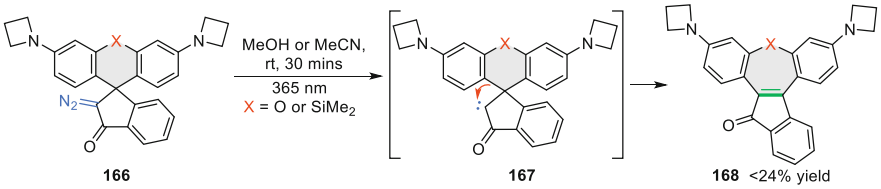
effect on product yields. For diaryl substituted diazo ketones **149**, regioselectivity in the formation of compound **152** erodes but is still relatively high (up to 94:6 *rr*).

Another five-membered valuable heterocycle, namely pyrrole **157**, is accessible from α-diazo-β-oxime esters **153**. Photochemically generated carbenes intramolecularly insert into the N-O bond to form 2*H*-azirines **154** in 71–95% yield (Scheme 46a) [93]. Prolonged irradiation with UV light induces rearrangement of the azirine scaffold to nitrile ylide **155** that subsequently undergoes cyclisation with diethyl fumarate (**156**) to yield a five-membered ring; treatment with hydrochloric acid forms the pyrrole **157** in 40–81% yields in a one-pot manner. The reaction is equally viable with pre-formed substrates, such as with **158a,b** that allowed an intramolecular tandem cyclization to pyrroles **159a**,**b** in 48 and 43% yield, respectively (Scheme 46b).

Thamattoor and co-workers explored the potential reactivity of putative alkenyl carbenes **161** originating from the light-induced extrusion of phenanthracene from **160** (Scheme 47) [94]. Upon irradiation, singlet carbene **161** is formed, which is corroborated with computational studies and subsequently undergoes a Fritsch–



Scheme 47 Synthesis of isochromanes from trapping of in-situ generated cycloalkynes

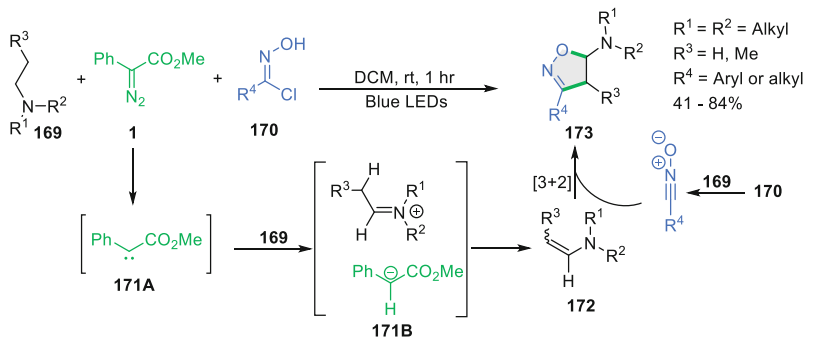


Scheme 48 Ring-expansion of diazoindanones facilitating a carbon-carbon bond migration

Buttenberg–Wiechell rearrangement to strained alkyne **162**. Such strained compounds are known to undergo Diels-Alder reactions that form isochromanes **165** in 16–20% yield. The Garg group has reported similar reactivity for the nitrogen analogue of intermediate **162** that is formed in-situ from a fluoride-induced 1,2-elimination reaction [95].

Even though complex molecules are typically regarded as unselective in photochemical activation, Grimm et al. utilised light for the modification of 'Janelia Fluor' dyes **166** [96]. In this case, the formation of carbene **167** induces an unintended unexpected ring-expansion of oxygen and silicon-containing heterocycles (Scheme 48). The generated singlet carbene facilitates a carbon-carbon bond migration transforming dibenzo[*a*,*e*]pyran **166** to the dibenzo[*b*,*f*]oxepine **168**, and a similar transformation took place for the silicon-analogue. Similar reactions were also reported by the groups of Belov [97] and Halabi [98].

The photolysis of aryldiazoacetates **1** can lead to diverse products, and they have been explored extensively. Jin and co-workers employed them in a blue light-induced three-component reaction leading to dihydroisoxaziles **173** (Scheme 49) [99]. Once the carbene forms, it abstracts hydrogen from amine **169**, leading to ion pairs **171B** and finally enamine **172** that undergoes a [3+2]-cycloaddition that furnishes 4,5-dihydroisooxazoles **173**. The role of aryldiazo compound **1** is rather unique in this case as it acts as both an electrophile and a base and is not present in the final product. The *N*-hydroximoyl chloride could be replaced with other reagents to enable the synthesis of additional heterocycles such as triazoles, furans and tetrahydroquinolines.



Scheme 49 Formation of 4,5-dihydroisoxazoles via [3+2]-cycloaddition of photochemically generated vinylamines

3 Conclusion

For a long period of time photochemistry has been regarded as just a curiosity, but recently it has been recognised as a valuable tool in organic chemistry. New reaction pathways and modes of reactivity have been opened giving access to structures that were inaccessible by other means. The photochemistry of carbenes/nitrenes is not an exception.

This review has covered the synthesis of heterocycles under photochemical conditions but is limited to those involving carbenes/nitrenes as the key reactive intermediates. These intermediates can be photogenerated from various precursors, among which diazo compounds and azides are dominant. Under light irradiation, dinitrogen extrusion typically occurs generating carbenes/nitrenes that subsequently form other reactive intermediates such as ylides, ketenes or diradicals giving access to a wide variety of oxygen-, nitrogen-, silicon- and phosphorus-containing heterocycles. In general, highly energetic UV light-induced reactions dominate this field, but it limits the library of potential reactions. However, since the seminal work by Davies and Jurberg, the use of visible light for activation has become the tool of choice for aryl diazo compounds, providing reactants absorbed in this region. Photocatalytic transformations are far less developed, and we look forward to seeing what developments will come in the future.

References

1. Verschueren RH, De Borggraeve WM (2019) Electrochemistry and photoredox catalysis: a comparative evaluation in organic synthesis. Molecules 24:2122
2. Crisenza GEM, Mazzarella D, Melchiorre P (2020) Synthetic methods driven by the photoactivity of electron donor-acceptor complexes. J Am Chem Soc 142:5461–5476

3. Protti S, Ravelli D, Fagnoni M, Albini A (2013) Smooth photogeneration of α,n-didehydrotoluenes (DHTs). Pure Appl Chem 85:1479–1486
4. Noyori R (2010) Insight: green chemistry: the key to our future. Tetrahedron 66:1028
5. Candish L, Collins KD, Cook GC, Douglas JJ, Gómez-Suárez A, Jolit A, Keess S (2022) Photocatalysis in the life science industry. Chem Rev 122:2907–2980
6. Allen AR, Noten EA, Stephenson CRJ (2022) Aryl transfer strategies mediated by photoinduced electron transfer. Chem Rev 122:2695–2751
7. Juliá F, Constantin T, Leonori D (2022) Applications of halogen-atom transfer (XAT) for the generation of carbon radicals in synthetic photochemistry and photocatalysis. Chem Rev 122:2292–2352
8. Capaldo L, Ravelli D, Fagnoni M (2022) Direct photocatalyzed hydrogen atom transfer (HAT) for aliphatic C–H bonds elaboration. Chem Rev 122:1875–1924
9. Pitre SP, Overman LE (2022) Strategic use of visible-light photoredox catalysis in natural product synthesis. Chem Rev 122:1717–1751
10. Moss RA (2006) Diazirines: carbene precursors par excellence. Acc Chem Res 39:267–272
11. Ollevier T, Carreras V (2022) Emerging applications of aryl trifluoromethyl diazoalkanes and diazirines in synthetic transformations. ACS Org Inorg Au 2:83–98
12. Zhang Z, Yadagiri D, Gevorgyan V (2019) Light-induced metal-free transformations of unactivated pyridotriazoles. Chem Sci 10:8399–8404
13. Akter M, Rupa K, Anbarasan P (2022) 1,2,3-triazole and its analogues: new surrogates for diazo compounds. Chem Rev 122:13108–13205
14. Orłowska K, Santiago JV, Krajewski P, Deperansińska I, Zawada K, Chaładaj W, Gryko D (2023) UV light is no longer required for the photoactivation activation of 1,3,4-oxadiazolines. ACS Catal 13(3):1964–1973. https://doi.org/10.1021/acscatal.2c05319
15. Durka J, Turkowska J, Gryko D (2021) Lightening diazo compounds? ACS Sustain Chem Eng 9:8895–8918
16. Ciszewski ŁW, Rybicka-Jasińska K, Gryko D (2019) Recent developments in photochemical reactions of diazo compounds. Org Biomol Chem 17:432–448
17. Galkina OS, Rodina LL (2016) Photochemical transformations of diazocarbonyl compounds: expected and novel reactions. Russ Chem Rev 85:537
18. Hua T-B, Yang Q-Q, Zou Y-Q (2019) Recent advances in enantioselective photochemical reactions of stabilized diazo compounds. Molecules 24
19. Candeias RN, Afonso AMC (2009) Developments in the photochemistry of diazo compounds. Curr Org Chem 13:763–787
20. Bergstrom BD, Nickerson LA, Shaw JT, Souza LW (2021) Transition metal catalyzed insertion reactions with donor/donor carbenes. Angew Chem Int Ed 60:6864–6878
21. Xiang Y, Wang C, Ding Q, Peng Y (2019) Diazo compounds: versatile synthons for the synthesis of nitrogen heterocycles *via* transition metal-catalyzed cascade C–H activation/carbene insertion/annulation reactions. Adv Synth Catal 361:919–944
22. Li YP, Li ZQ, Zhu SF (2018) Recent advances in transition-metal-catalyzed asymmetric reactions of diazo compounds with electron-rich (hetero-) arenes. Tetrahedron Lett 59:2307–2316
23. de Frémont P, Marion N, Nolan SP (2009) Carbenes: synthesis, properties, and organometallic chemistry. Coord Chem Rev 253:862–892
24. Jurberg ID, Davies HML (2018) Blue light-promoted photolysis of aryldiazoacetates. Chem Sci 9:5112–5118
25. Jana S, Yang Z, Pei C, Xu X, Koenigs RM (2019) Photochemical ring expansion reactions: synthesis of tetrahydrofuran derivatives and mechanism studies. Chem Sci 10:10129–10134
26. Jampilek J (2019) Heterocycles in medicinal chemistry. Molecules 24:3839
27. Ashitha KT, Krishna MSA, Basavaraja D, Somappa SB (2022) Recent advances in the transition metal-free synthesis of heterocycles from α,β-unsaturated ketones. Org Chem Front 9:5306–5358

28. Kiciński W, Dyjak S (2020) Transition metal impurities in carbon-based materials: pitfalls, artifacts and deleterious effects. Carbon 168:748–845
29. Lefebvre C, Fortier L, Hoffmann N (2020) Photochemical rearrangements in heterocyclic chemistry. Eur J Org Chem 2020:1393–1404
30. Latrache M, Hoffmann N (2021) Photochemical radical cyclization reactions with imines, hydrazones, oximes and related compounds. Chem Soc Rev 50:7418–7435
31. Davies HML, Beckwith REJ (2003) Catalytic enantioselective C-H activation by means of metal-carbenoid-induced C-H insertion. Chem Rev 103:2861–2903
32. Kirmse V, Dietrich H, Bücking HW (1967) Intramolekulare reaktiønen von alkoxycarbonylcarbenen. Tetrahedron Lett 8:1833–1835
33. Rando RR (1970) Conformational and solvent effects on carbene reactions. J Am Chem Soc 92: 6706–6707
34. Rando RR (1972) Conformational and medium effects on intramolecular carbene reactions. J Am Chem Soc 94:1629–1631
35. Zhang Y, Burdziński G, Kubicki J, Platz MS (2009) Ultrafast time-resolved infrared spectroscopy study of the photochemistry of *N*,*N*-diethyldiazoacetamide: rearrangement in the excited state. J Am Chem Soc 131:9646–9647
36. Candeias NR, Gois PMP, Veiros LF, Afonso CAM (2008) C-H carbene insertion of α-diazo acetamides by photolysis in non-conventional media. J Org Chem 73:5926–5932
37. Lowe G, Parker J (1971) Photochemical conversion of α-diazo-amides and -esters into β-lactams and β- and γ-lactones. J Chem Soc D 197:577–578
38. Corey EJ, Felix AM (1965) A new synthetic approach to the penicillins. J Am Chem Soc 87: 2518–2519
39. Alimi I, Remy R, Bochet CG (2017) Photochemical C–H activation: generation of indole and carbazole libraries, and first total synthesis of clausenawalline D. Eur J Org Chem 2017:3197–3210
40. Yang J, Zhang Q, Zhang W, Yu W (2014) Synthesis of benzo[*a*]carbazoles and indolo[2,3-a] carbazoles via photoinduced carbene-mediated C-H insertion reaction. RSC Adv 4:13704–13707
41. Cheng Y, Meth-Cohn O (2004) Heterocycles derived from heteroatom-substituted carbenes. Chem Rev 104:2507–2530
42. Maas G, Bender S (2000) Synthesis and ring enlargement of 2-ethoxycarbonyl-1-silacyclobutanes. Chem Commun:437–438
43. Maas G, Krebs F, Werle T, Gettwert V, Striegler R (1999) Silicon-oxygen heterocycles from thermal, photochemical, and transition-metal-catalyzed decomposition of α-(alkoxysilyl and alkenyloxysilyl)-α-diazoacetates. Eur J Org Chem:1939–1946
44. Clayden J, Greeves N, Warren S (2012) Organic chemistry.2nd edn. Oxford University Press
45. Zhou S, Cai B, Hu C, Cheng X, Li L, Xuan J (2021) Visible light and base promoted O-H insertion/cyclization of Para-quinone methides with aryl diazoacetates: an approach to 2,3-dihydrobenzofuran derivatives. Chin Chem Lett 32:2577–2581
46. Kirmse W (1971) Chapter 1 – Introduction. In: Carbene chemistry, 2nd edn. Academic Press
47. Qi D, Bai J, Zhang H, Li B, Song Z, Ma N, Guo L, Song L, Xia W (2022) Photoinduced synthesis of functionalized oxetanes via diradical-mediated ring contraction. Green Chem 24: 5046–5051
48. Cheng X, Cai BG, Mao H, Lu J, Li L, Wang K, Xuan J (2021) Divergent synthesis of aziridine and imidazolidine frameworks under blue LED irradiation. Org Lett 23:4109–4114
49. Chen J, Liu S, Lv X, Hong K, Lei J, Xu X, Hu W (2020) Blue light-promoted formal [4+1]-annulation of diazoacetates with *o*-aminoacetophenones: synthesis of polysubstituted indolines and computational study. J Org Chem 85:13920–13928
50. Romashin YN, Liu MTH, Ma W, Moss RA (1999) New synthesis of 2,2′-heteroarylpyrroles from heteroarylchlorocarbenes. Tetrahedron Lett 40:7163–7165

51. Jackson JE, Soundararajan N, Platz MS, Liu MTH (1988) Pyridine ylide formation by capture of phenylchlorocarbene and tert-butylchlorocarbene. Reaction rates of an alkylchlorocarbene by laser flash photolysis. J Am Chem Soc 110:5595–5596
52. Kassir AF, Guillot R, Scherrmann MC, Boddaert T, Aitken DJ (2020) Formation of tetrahydrothiophenes *via* a thia-Paternò-Büchi-initiated domino photochemical reaction. Org Lett 22:8522–8527
53. Roy S, Kumar G, Chatterjee I (2021) Photoinduced diverse reactivity of diazo compounds with nitrosoarenes. Org Lett 23:6709–6713
54. Liao M, Dong S, Deng G, Wang J (2006) Synthesis of oxygen-containing heterocyclic compounds based on the intramolecular O-H insertion and Wolff rearrangement of α-diazocarbonyl compounds. Tetrahedron Lett 47:4537–4540
55. Zhang W, Romo D (2007) Transformation of fused bicyclic and tricyclic β-lactones to fused γ-lactones and 3(2H)-furanones via ring expansions and O-H insertions. J Org Chem 72:8939–8942
56. Dong C, Mo F, Wang J (2008) Highly diastereoselective addition of the lithium enolate of α-diazoacetoacetate to *N*-sulfinyl imines: enantioselective synthesis of 2-oxo and 3-oxo pyrrolidines. J Org Chem 73:1971–1974
57. Mo F, Li F, Qiu D, Wang J (2010) Enantioselective synthesis of condensed and transannular ring skeletons containing pyrrolidine moiety. Tetrahedron 66:1274–1279
58. Vaske YSM, Mahoney ME, Konopelski JP, Rogow DL, McDonald WJ (2010) Enantiomerically pure *trans*-β-lactams from α-amino acids *via* compact fluorescent light (CFL) continuous-flow photolysis. J Am Chem Soc 132:11379–11385
59. Liu J, Li MM, Le QB, Lu LQ, Xiao WJ (2019) A photoinduced Wolff rearrangement/Pd-catalyzed [3+2] cycloaddition sequence: an unexpected route to tetrahydrofurans. Chem Commun 55:2031–2034
60. Wei Y, Liu S, Li M-M, Li Y, Lan Y, Lu L-Q, Xiao W-J (2019) Enantioselective trapping of Pd-containing 1,5-dipoles by photogenerated ketenes: access to 7-membered lactones bearing chiral quaternary stereocenters. J Am Chem Soc 141:133–137
61. Li MM, Le QB, Xiao YQ, Xiao WJ, Lu LQ (2021) Enantioselective trapping of palladium-stabilized oxo-1,4-dipoles with photochemically generated ketenes. Sci Bull 66:1719–1722
62. Wang C, Wang Z, Yang J, Shi SH, Hui XP (2020) Sequential visible-light and *N*-heterocyclic carbene catalysis: stereoselective synthesis of tetrahydropyrano[2,3-*b*]indoles. Org Lett 22:4440–4443
63. Korobitsina IK, Rodina LL (1965) Zh Org Khim 1:932
64. Korobitsina IK, Rodina LL, Shuvalova VG (1968) Zh Org Khim 4:2016
65. Rodina LL, Mishchenko VL, Malashikhin SA, Platz M, Nikolaev VA (2003) New photochemical reaction in the series of diazofuranones. Russ J Org Chem 39:1530–1532
66. Rodina LL, Malashikhin SA, Galkina OS, Nikolaev VA (2009) Photochemical reactions of regioisomeric 2,2-dimethyl-5,5-diphenyl- and 5,5-dimethyl-2,2-diphenyl-substituted diazo ketones of a tetrahydrofuran series. Helv Chim Acta 92:1990–1998
67. Norbeck DW, Kramer JB (1988) Synthesis of (−)-oxetanocin. J Am Chem Soc 110:7217–7218
68. Niitsuma S, Ichikawa Y, Kato K, Takita T (1987) Studies on the total synthesis of oxetanocin; I. The first synthesis of a nucleoside having oxetanosyl-*N*-glycoside. Tetrahedron Lett 28:3967–3970
69. Niitsuma S, Kato K, Takita T (1987) Studies on the total synthesis of oxetanocin; II. Total synthesis of oxetanocin. Tetrahedron Lett 28:4713–4714
70. Moore HW, Arnold MJ (1983) Photolysis of 4-diazopyrrolidine-2,3-diones. A new synthetic route to mono- and bicyclic β-lactams. J Org Chem 48:3365–3367
71. Lowe G, Yeung HW (1973) Synthesis of a β-lactam related to the cephalosporins. J Chem Soc Perkin Trans 1:2907–2910
72. Thu Le NN, Klinkerch EJ, Thamattoor DM (2019) Stereochemistry of dichlorocarbene addition to alkenes: a collaborative, discovery-based experiment for the organic chemistry laboratory. J Chem Educ 96:1727–1730

73. Guha S, Gadde S, Kumar N, Black DS, Sen S (2021) Orthogonal syntheses of γ-carbolinone and spiro[pyrrolidinone-3,3′]indole derivatives in one pot through reaction telescoping. J Org Chem 86:5234–5244
74. Maas G, Daucher B, Maier A, Gettwert V (2004) Synthesis and ring opening reactions of a 2-silabicyclo[2.1.0]pentane. Chem Commun 4:238–239
75. Daucher B, Gettwert V, Striegler R, Maas G (2004) Intramolecular carbene and carbenoid reactions of α-(vinyloxy)silyl-α-diazoacetates. Zeitschrift fur Naturforsch Sect B J Chem Sci 59:1444–1450
76. Sanchez M, Réau R, Marsden CJ, Regitz M, Bertrand G (1999) From 2-phosphino-2*H*-phosphirene to 1-phosphino-1*H*-phosphirene, $1\lambda^5,2\lambda^3$-diphosphete, and 1,2-dihydro-$1\lambda^3,2\lambda^3$-diphosphete: an experimental and theoretical study. Chem – A Eur J 5:274–279
77. Armbrust R, Bergsträsser U, Regitz M, Sanchez M, Réau R, Bertrand G (1995) Synthesis of a stable $1\lambda^5,2\lambda^3$-diphosphete: the first codimer of a λ^3-phosphaalkyne with a λ^5-phosphaalkyne. J Am Chem Soc 117:10785–10786
78. Shen Z, Dong VM (2009) Benzofurans prepared by C-H bond functionalization with acylsilanes. Angew Chem Int Ed 48:784–786
79. Brook AG, Kucera HW, Pearce R (1971) Photolysis of 1,1-diphenylsilacyclohexanone in diethyl fumarate. The trapping of a siloxycarbene by an electron-deficient olefin. Can J Chem 49:1618–1621
80. Brook AG, Pearce R, Pierce JB (1971) Nucleophilic attack of siloxycarbenes on carbonyl groups. The formation of oxiranes. Can J Chem 49:1622
81. Svarovsky SA, Taraban MB, Barchi JJ (2004) Facile photochemical synthesis of mixed siloxyacetal glycosides as potential pH-sensitized prodrugs for selective treatment of solid tumors. Org Biomol Chem 2:3155–3161
82. Becker P, Pirwerdjan R, Bolm C (2015) Acylsilanes in iridium-catalyzed directed amidation reactions and formation of heterocycles *via* siloxycarbenes. Angew Chem Int Ed 127:15713–15716
83. Bunyamin A, Hua C, Polyzos A, Priebbenow DL (2022) Intramolecular photochemical [2 + 1]-cycloadditions of nucleophilic siloxy carbenes. Chem Sci 13:3273–3280
84. Zhang HJ, Becker P, Huang H, Pirwerdjan R, Pan FF, Bolm C (2012) Photochemically induced silylacylations of alkynes with acylsilanes. Adv Synth Catal 354:2157–2161
85. Schneider K, Daucher B, Fronda A, Maas G (1990) Acylsilenes (3-Oxo-1-sila-1-propenes) from acyl(disilanyl)carbenes. Chem Ber 123:589–594
86. Akira S, Ando W (1984) 1,2-silaoxetene. J Am Chem Soc 106:1486–1487
87. Hassner A, Fowler FW (1968) Synthesis and reactions of 1-azirines. J Am Chem Soc 90:2869–2875
88. Isomura K, Okada M, Taniguchi H (1969) Azirine formation by decomposition of terminal vinyl azides. Tetrahedron Lett 10:4073–4076
89. Sundberg RJ, Suter SR, Brenner M (1972) Photolysis of *ortho*-substituted aryl azides in diethylamine. Formation and autoxidation of 2-diethylamino-1*H*-azepine intermediates. J Am Chem Soc 94:513–520
90. Patel SC, Burns NZ (2022) Conversion of aryl azides to aminopyridines. J Am Chem Soc 144:17797–17802
91. Sato S (1968) Azirines. IV. The photolysis of β-azidovinyl ketones. Bull Chem Soc Jpn 41:2524–2525
92. Ansari MA, Yadav D, Singh MS (2020) Visible-light-driven photocatalyst- and additive-free cross-coupling of β-ketothioamides with α-diazo 1,3-diketones: access to highly functionalized thiazolines. Chem Eur J 26:8083–8089
93. Qi X, Xu X, Park CM (2012) Facile synthesis of 2-alkyl/aryloxy-2H-azirines and their application in the synthesis of pyrroles. Chem Commun 48:3996–3998
94. Fan R, Wen Y, Thamattoor DM (2017) Photochemical generation and trapping of 3-oxacyclohexyne. Org Biomol Chem 15:8270–8275

95. McMahon TC, Medina JM, Yang YF, Simmons BJ, Houk KN, Garg NK (2015) Generation and regioselective trapping of a 3,4-piperidyne for the synthesis of functionalized heterocycles. J Am Chem Soc 137:4082–4085
96. Grimm JB, English BP, Choi H, Muthusamy AK, Mehl BP, Dong P, Brown TA, Lippincott-Schwartz J, Liu Z, Lionnet T, Lavis LD (2016) Bright photoactivatable fluorophores for single-molecule imaging. Nat Methods 13:985–988
97. Belov VN, Wurm CA, Boyarskiy VP, Jakobs S, Hell SW (2010) Rhodamines NN: a novel class of caged fluorescent dyes. Angew Chem Int Ed 49:3520–3523
98. Halabi EA, Thiel Z, Trapp N, Pinotsi D, Rivera-Fuentes P (2017) A photoactivatable probe for super-resolution imaging of enzymatic activity in live cells. J Am Chem Soc 139:13200–13207
99. Luo K, Zhao Y, Tang Z, Li W, Lin J, Jin Y (2022) Visible-light-induced dual C(sp^3)-H bond functionalization of tertiary amine *via* hydrogen transfer to carbene and subsequent cycloaddition. Org Lett 24:6335–6340

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2024, **60**, 4483

Received 20th February 2024,
Accepted 15th March 2024

DOI: 10.1039/d4cc00828f

rsc.li/chemcomm

Photochemical cyclopropanation in aqueous micellar media – experimental and theoretical studies†

Joseph P. Milton, [a] Adam Milanowski, [ab] Martin Andersson [*c] and Dorota Gryko*[a]

While in nature, reactions occur in water-based confined compartments, for a long time, water has been often regarded as an unsuitable medium for organic reactions. We have, however, found that photochemical cyclopropanation of styrenes with diazo compounds or their precursors can be performed in micellar systems. COSMO-RS studies revealed that the reactivity correlates with the predicted critical micelle concentration (CMC), with higher CMC values delivering higher yields.

Organic solvents comprise the majority of waste in the chemical industry, which is believed to account for more than 60% by mass in the pharmaceutical sector.[1] One way to minimise solvent waste is to implement water, which is non-toxic, non-flammable, cheap, safe,[2] and enables a reaction to adhere more closely to the 12 principles of green chemistry.[3] Of course, the prominent issue with water is the poor solubility of organic reagents in this medium, which leads to most chemists automatically ruling it out as a solvent choice;[4] undoubtedly, there are examples where photochemical reactions in water can successfully take place though.[5,6] To enhance the viability of reactions in water, a surfactant can be added, thus forming a micellar solution. They have been known for many years for their remarkable properties as solubilisers to dissolve compounds under aqueous conditions,[1] enabling organic synthesis in water that may not be possible otherwise.[7–14] With the reagents encapsulated inside of the micelle, the components of the reaction pre-organise themselves, which can also lead to increased selectivies.[15] Moreover, the lifetimes of short-lived species, such as carbenes and radicals, are prolonged in micelles.[9,16] Studies into the generation of UV-light *in situ via* triplet–triplet annihilation upconversion in micelles were recently reviewed by Næsborg and co-workers.[17]

Cyclopropanes are one of the top ten most frequently represented moieties in FDA-approved drugs, and hence greener approaches for their construction are of great benefit to the pharmaceutical sector.[18,19] With the copious number of methods for their synthesis, diazo compounds are one of the most atom economical starting materials that can be used, since only the concomitant loss of dinitrogen is required to generate the reactive species under thermal, photochemical, or metal-catalysed conditions.[20] Photochemical activation of diazo compounds often performs optimally with DCM, although it is notoriously toxic[21] and poses a high risk to the environment.[22] Using water would alleviate the toxicity issue and make these reactions safer, but reactions with carbenes in water pose an additional challenge as O–H insertion is always a viable side reaction.[23]

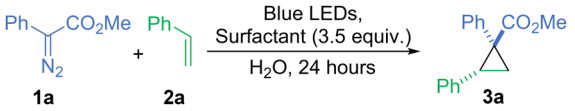
In turn, there are only a limited number of methods involving diazo compounds in water and most of them are metal-catalysed. Álvarez *et al.* used a copper catalyst to allow cyclopropanation and C–H insertion of diazo compounds in water,[24] while the use of a water-soluble Ru-porphyrin enabled N–H insertion reactions in a buffer solution.[25] Rh-catalysed lactam and lactone synthesis was also accomplished in this medium.[26–28] Li's group showed that [2+1]-cycloadditions can be performed in water without any external stimuli with the diazo moiety simply cleaved as a leaving group.[29]

Only two reports describe photochemical reactions of diazo compounds in water. UV irradiation of various α-diazo acetamides leads to intramolecular C–H insertions to form an assortment of lactams.[30] O–H insertion was also observed and the propensity towards hydroxylation was linked to the hydrophilicity of the diazo compound. Hydrophobic dibutyl acetamides formed lactams as the exclusive product, whereas acetamides bearing hydrophilic 2-methoxyethyl substituents

[a] *Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, Warsaw 01-224, Poland. E-mail: dorota.gryko@icho.edu.pl*
[b] *Department of Chemistry, Warsaw University of Technology, Noakowskiego 3, Warsaw 00-664, Poland*
[c] *Center for Integrative Petroleum Research, King Fahd University of Petroleum and Minerals, Dhahran 31261, Kingdom of Saudi Arabia. E-mail: martin.andersson@kfupm.edu.sa*

† Electronic supplementary information (ESI) available: General procedures, compound characterisation (NMR, HRMS), and NMR spectra. See DOI: https://doi.org/10.1039/d4cc00828f

Table 1 Optimisation of the reaction conditions[a]



1a 2a 3a

Entry	Surfactant[c]	Surfactant charge	Yield (%)
1	DTAC	Cationic	62[d] (59)[f]
2	TPGS-750-M	Neutral	16[e]
3	Potassium laurate	Anionic	54[e]
4	DOSS	Anionic	56[d]
5	None	N/A	53[d]
6[b]	DTAC	Cationic	66[d]

[a] Standard conditions: diazo reagent **1a** (0.1 mmol), styrene **2a** (0.5 mmol), surfactant (0.35 mmol), H_2O (5 mL), blue LEDs, and 24 h. [b] Diazo reagent **1a** (0.5 mmol), and styrene **2a** (0.1 mmol). [c] DTAC – dodecyltrimethylammonium chloride, TPGS-750-M – DL-α-tocopherol methoxypolyethylene glycol succinate, DOSS – dioctyl sulfosuccinate sodium salt, and SDS – sodium dodecyl sulfate. [d] ^{1}H NMR yield. [e] GC yield. [f] Isolated yield.

reacted only with water. Later, Yan *et al.* showed the *in situ* formation of diazo compounds from hydrazones in the presence of triethylamine in water and their subsequent reaction with acetylenes, olefins, anilines, and thiols under blue LED irradiation.[31]

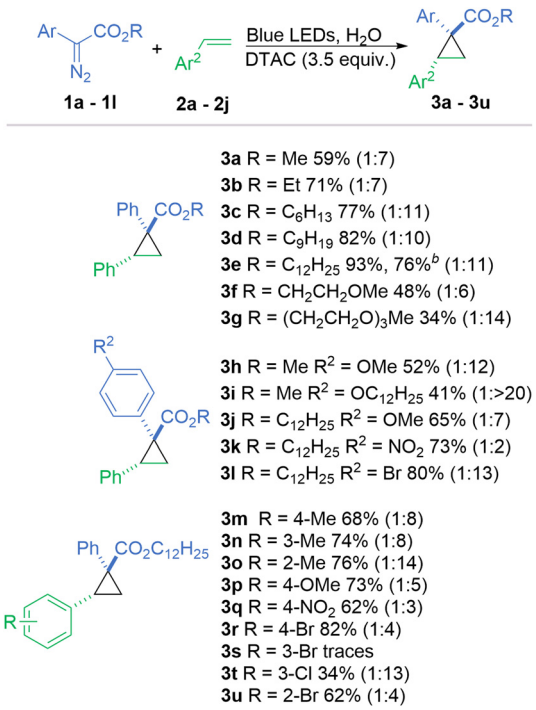
We hypothesised that photochemical cyclopropanation of diazo compounds could be performed in a micellar solution; in particular, Maaskant *et al.* has shown the beneficial effects of micelles for diazo compounds in an iron-catalysed process. In the presence of a cationic Fe-porphyrin in water, only traces of the desired cyclopropane were detected, whereas the addition of sodium dodecyl sulfate (SDS) increased the yields up to >99% in the best case.[32]

To begin our investigation, we tested the feasibility of methyl phenyldiazoacetate (**1a**) with styrene (**2a**) to form cyclopropane **3a** in a variety of micellar solutions, of which, a solution of cationic dodecyl trimethylammonium chloride (DTAC) proved the most effective (62%, Table 1, entry 1). Importantly, no evidence of side reactions such as O–H insertion with water or C–H insertion with the surfactant was observed. All neutral surfactants performed poorly with less than 20% yield, including Lipshutz's TPGS-750-M[4] (entry 2). Reactions in anionic surfactants such as dioctyl sulfosuccinate sodium salt (DOSS) or potassium laurate gave comparable results of 56% and 54%, respectively (entries 3 and 4). The control reaction in the absence of any surfactant proceeds with only a small decrease in the yield to 53% (entry 5). However, in this case, substrates **1a** and **2a** are both oils so it is reasonable to assume that this reaction takes place as an "on-water" reaction. To enable a more general reaction, with the improved dissolution of the starting materials, we continued using the DTAC micellar system.

All parameters of the reaction (light source, the addition of co-solvents, ratio of substrates, and surfactant concentration) were optimised leading to model cyclopropane **3a** in 59% isolated yield (entry 1). Once the concentration of the surfactant exceeds 40 mM, which surpasses the CMC by ~20 mM,[33] there is a notable bump in the yield, but increasing the concentration of DTAC further has a less pronounced impact (Fig. S1, see ESI†). Only a slight increase in the yield was observed when we used the diazo compound in excess instead of styrene (entry 6).

In a photochemical bimolecular reaction, short-lived species such as radicals and carbenes, with lifetimes in a nanoseconds range, do not diffuse out of the micelle within a period ranging from μs to ms, thus enabling a high chance of a successful collision, namely styrene in our case.[34,35] As compartmentalisation has a strong impact on reactions in micellar systems, the structure (lipophilicity) of the substrates potentially has a strong impact on the process. When using diazo compounds with longer hydrophobic alkyl chains on the ester group, the yield gradually increased, from 59% for methyl (**3a**), to 71% for ethyl (**3b**), 77% for *n*-hexyl (**3c**), 82% for *n*-nonyl (**3d**) and finally 93% for *n*-dodecyl (**3e**) (Scheme 1).

To see the impact of the diazo reagent localisation in the micelle on the reaction outcome, **1f** and **1g** with hydrophilic ester substituents were evaluated. The presence of oxygen atoms on their alkyl chain affects factors such as hydrophilicity, electrostatic interactions, and hydrogen bonding, which may change the position of the diazo reagent relative to styrene (**2a**) in the micellar compartment. In fact, reactions were less efficient compared to **3a**, with cyclopropane **3f**, with one glycol unit, being obtained in 48% yield with a dr of 1 : 6, while for cyclopropane **3g**, with three glycol units, the yield dropped to 34% but had a much-improved dr of 1 : 14. We may therefore



3a R = Me 59% (1:7)
3b R = Et 71% (1:7)
3c R = C_6H_{13} 77% (1:11)
3d R = C_9H_{19} 82% (1:10)
3e R = $C_{12}H_{25}$ 93%, 76%[b] (1:11)
3f R = CH_2CH_2OMe 48% (1:6)
3g R = $(CH_2CH_2O)_3Me$ 34% (1:14)

3h R = Me R^2 = OMe 52% (1:12)
3i R = Me R^2 = $OC_{12}H_{25}$ 41% (1:>20)
3j R = $C_{12}H_{25}$ R^2 = OMe 65% (1:7)
3k R = $C_{12}H_{25}$ R^2 = NO_2 73% (1:2)
3l R = $C_{12}H_{25}$ R^2 = Br 80% (1:13)

3m R = 4-Me 68% (1:8)
3n R = 3-Me 74% (1:8)
3o R = 2-Me 76% (1:14)
3p R = 4-OMe 73% (1:5)
3q R = 4-NO_2 62% (1:3)
3r R = 4-Br 82% (1:4)
3s R = 3-Br traces
3t R = 3-Cl 34% (1:13)
3u R = 2-Br 62% (1:4)

Scheme 1 Scope of the reaction. The major diastereoisomer is drawn. Reaction conditions: Diazo compounds **1a–1m** (0.1 mmol), styrene **2a–2i** (0.5 mmol), DTAC (0.35 mmol), H_2O (5 mL), and blue LEDs. [b] Diazo reagent **1e** (1.0 mmol), styrene **2a** (10 mmol), DTAC (3.5 mmol), H_2O (50 mL), blue LEDs, and 60 h.

assume that the reduced yield for the reaction involving these diazo compounds could be because of internal non-optimal alignment in the micelles. This type of alignment is not, however, considered in COSMO-RS calculations.

Furthermore, we investigated how the position of the dodecyl chain in the diazo compound structure affects their reactivity in the micellar system. Diazo **1h**, containing the 4-methoxyphenyl substituent and the methyl ester, yielded cyclopropane **3h** in 52% yield. Changing the alkyl substituent on the ester from methyl to dodecyl led to a 13% increase in the yield (**3i**). Conversely, changing the methoxy substituent upon the aromatic ring to a dodecyloxy group led to an approximate 10% decrease in yield (**3j**) demonstrating that the beneficial effect from an extended alkyl chain is only relevant when it is located near to the reaction centre. Two diazo compounds **3k** and **3l** with electron-withdrawing aromatic substituents provided cyclopropanes in good yields although the dr is significantly eroded for product **3k** possessing the nitro group.

Styrenes with electron-withdrawing and electron-donating substituents are equally effective. The substitution pattern (2-, 3- or 4-) in methyl styrenes does not influence the reaction yield in contrast to bromo styrenes (**2r**, **2u**, and **2s**), where the 3-bromo derivative only formed traces of product. Despite this, the reaction with 3-chlorostyrene (**2t**) could provide a serviceable amount of product **3t** (34%). Expectedly, the diastereoselectivity of the reaction is influenced by the position of the substituent.

To demonstrate the applicability of the developed conditions, the reaction of diazo reagent **1e** with styrene **2a** was performed on a one mmol scale. Increasing the amount of styrene to 10 mmol and extending the reaction time to 60 hours enabled the construction of cycloadduct **3e** in a satisfactory yield of 76% with identical dr as the 0.1 mmol scale.

Computational analysis (COSMO-RS) shows that the predicted critical micelle concentration (CMC)[36] changes depending on the diazo compound used with styrene (Fig. 1, blue). The higher the predicted CMC, the higher the experimental yield. Those with hexyl, nonyl, and dodecyl chains all had a CMC of 23.5 or above and were the higher performers in our reactions. The higher the CMC, the fewer surfactant molecules are available to stabilise the micelles (DTAC = 70 mM, for all points). This would, in general, lead to larger micelles and thus more reactants are in the micellar core compared to the micelle–water interface region. The yield *vs.* CMC trend is negligibly changed when running the predictions when accounting for 25% product formation (Fig. 1, green). No significant trends between experimental yields and interfacial concentrations of the reactant were found, which was consistent with the reaction taking place mainly in the micellar core. No evidence of OH-insertion was observed either, which further supported our conclusion that the reaction occurred in the core.

Whilst our method works efficiently, there is still an inherent risk present in the work as diazo compounds are well reported for their instability and potential explosive behaviour.[37] Following the work of Wu and co-workers, we explored the possibility of using bench-stable hydrazones, which can generate diazo compounds *in situ* with the addition of a base[21] or an oxidant.[38,39] Initially, we tried the reaction with a small selection of basic surfactants, namely DOSS, SDS and potassium laurate, with the idea that they could have a dual role for the reaction, as a base for the generation of the diazo compound and as a surfactant, being investigated (Scheme 2). Using DOSS or SDS only formed traces of product **3a**, but we could reach a 40% yield with potassium laurate. However, DTAC in combination with a small excess of triethylamine ensured the formation of cycloadduct **3a** in 59% isolated yield analogous to the reaction with the neat diazo compound and a slight increase in the diastereomeric ratio was observed too (1 : 7 to 1 : 10).

Even though the active species, *i.e.* the diazo reagent, generated in the reaction is the same, we can expect some differences in the reactivity between the *E*- and *Z*-hydrazones as their stability vary and thus their propensity for deprotonation is different.[40] Also, the two isomers may position themselves differently in the micelle to enable favourable electrostatic interactions and hydrogen bonding, thus influencing the rate of carbene generation.[9] Thus, *E*- and *Z*-hydrazones **4b** were evaluated; the *E*-hydrazone performed better by about 20% in terms of yield and the diastereoselectivity was significantly improved to 1 : 20, whereas the *Z*-hydrazone provided 1 : 8 dr.

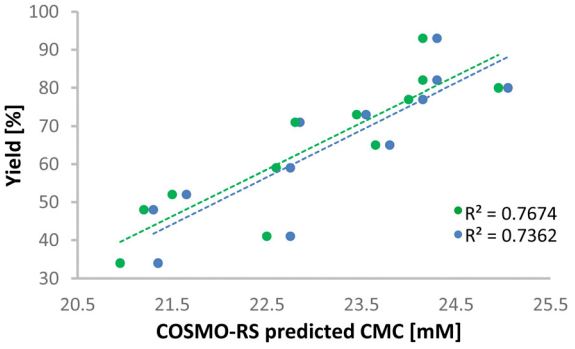
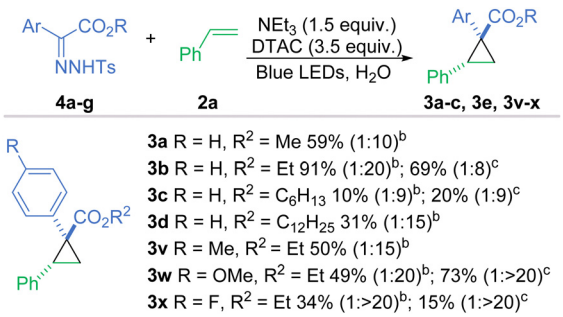


Fig. 1 COSMO-RS-predicted CMC *versus* experimental yields. Points marked in blue represent the CMC for the reaction before any product formation (the starting point of the reaction). Points marked in green represent the CMC for the reaction after 25% product formation.



Scheme 2 Scope of cyclopropanation with hydrazones. The major product is drawn. Conditions: Hydrazones (**4a–4g**) (0.1 mmol), styrene (1.0 mmol), DTAC (0.35 mmol), NEt_3 (0.15 mmol), H_2O (5 mL), blue LEDs, and 18–24 h. [b] The hydrazone starting material was predominantly *E*. [c] The hydrazone starting material was predominantly *Z*.

In contrast to diazo compounds, for hydrazones, increasing the length of the alkyl chain had a detrimental effect on the reaction with yields of 20% or below for hexyl esters (**3c**) and 31% for dodecyl ester (**3e**). Using hydrazones with substituents in the 4-position worked effectively and provided the products in sufficient yields. 4-Methoxy- and 4-fluoro-substituted hyrazones were highly effective for the diastereoselective synthesis of *cis*-cyclopropanes **3w** and **3x** with 1: $>$ 20 dr.

In summary, the synthesis of cyclopropanes constitutes one of the fundamental reactions in the repertoire of carbene-derived processes and can be accomplished in water-based systems. In micellar systems, the photochemical reaction of diazo compounds with styrenes in the absence of a metal catalyst gave products in moderate to excellent yields and with good diastereoselectivity. The synthetic utility of the reaction is showcased by a one mmol scale reaction producing cyclopropane **3d** in a satisfactory 76% yield. To further enhance the safety features of the reaction, the diazo compound was replaced with a hydrazone, enabling the generation of the carbene *in situ* by the addition of triethylamine. We believe that this work is a productive stepping stone to enable the further use of diazo compounds under photochemical conditions in the absence of organic solvents and we look forward to seeing further work in a similar vein.

J. P. M. and D. G. thank the European Union for funding under the H2020 Marie Skłodowska-Curie grant agreement No. 956324 (MSCA ITN: PhotoReAct). D. G. thanks the National Science Centre, Poland grant number Maestro UMO-2020-38/A/ST4/00185 for funding.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 F. Gallou, N. A. Isley, A. Ganic, U. Onken and M. Parmentier, *Green Chem.*, 2015, **18**, 14–19.
2 M. Billamboz, F. Mangin, N. Drillaud, C. Chevrin-Villette, E. Banaszak-Léonard and C. Len, *J. Org. Chem.*, 2014, **79**, 493–500.
3 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, 1998.
4 M. Cortes-Clerget, J. Yu, J. R. A. Kincaid, P. Walde, F. Gallou and B. H. Lipshutz, *Chem. Sci.*, 2021, **12**, 4237–4266.
5 C. Russo, F. Brunelli, G. C. Tron and M. Giustiniano, *J. Org. Chem.*, 2023, **88**, 6284–6293.
6 C. Chatgilialoglu, S. Barata-Vallejo and T. Gimisis, *Molecules*, 2024, **29**, 569.
7 G. Pölderl and L. Næsborg, *ChemPhotoChem*, 2024, e2023003.
8 B. H. Lipshutz, *Green Chem.*, 2023, **26**, 739–752.
9 L. Brüss, R. Jeyaseelan, J. C. G. Kürschner, M. Utikal and L. Næsborg, *ChemCatChem*, 2022, **15**, e202201146.
10 M. Banerjee, P. C. Panjikar, Z. T. Bhutia, A. A. Bhosle and A. Chatterjee, *Tetrahedron*, 2021, **88**, 132142.
11 G. La Sorella, G. Strukul and A. Scarso, *Green Chem.*, 2015, **17**, 644–683.
12 E. Borrego, A. Caballero and P. J. Pérez, *Organometallics*, 2022, **41**, 3084–3098.
13 H. K. Maurya, *Org. Chem. Ind. J.*, 2022, **16**, 1.
14 A. Steven, *Synthesis*, 2019, 2632–2647.
15 M. Banerjee, P. C. Panjikar, Z. T. Bhutia, A. A. Bhosle and A. Chatterjee, *Tetrahedron*, 2021, **88**, 132142.
16 M. Cybularczyk-Cecotka, J. Predygier, S. Crespi, J. Szczepanik and M. Giedyk, *ACS Catal.*, 2022, **12**, 3543–3549.
17 R. Jeyaseelan, M. Utikal and L. Næsborg, *Asian J. Org. Chem.*, 2024, e202300604.
18 R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859.
19 T. T. Talele, *J. Med. Chem.*, 2016, **59**, 8712–8756.
20 J. Durka, J. Turkowska and D. Gryko, *ACS Sustainable Chem. Eng.*, 2021, **9**, 8895–8918.
21 S. Vidal, *ACS Cent. Sci.*, 2020, **6**, 83–86.
22 M. Tobiszewski, J. Namieśnik and F. Pena-Pereira, *Green Chem.*, 2017, **19**, 1034–1042.
23 I. Nicolas, P. Le Maux and G. Simonneaux, *Coord. Chem. Rev.*, 2008, **252**, 727–735.
24 M. Álvarez, R. Gava, M. R. Rodríguez, S. G. Rull and P. J. Pérez, *ACS Catal.*, 2017, **7**, 3707–3711.
25 C.-M. Ho, J.-L. Zhang, C.-Y. Zhou, O.-Y. Chan, J. J. Yan, F.-Y. Zhang, J.-S. Huang and C.-M. Che, *J. Am. Chem. Soc.*, 2010, **132**, 1886–1894.
26 N. R. Candeias, C. Carias, L. F. R. Gomes, V. André, M. T. Duarte, P. M. P. Gois and C. A. M. Afonso, *Adv. Synth. Catal.*, 2012, **354**, 2921–2927.
27 N. R. Candeias, P. M. P. Gois and C. A. M. Afonso, *J. Org. Chem.*, 2006, **71**, 5489–5497.
28 N. R. Candeias, P. M. P. Gois and C. A. M. Afonso, *Chem. Commun.*, 2005, 391–393.
29 Q. Z. Li, X. Zhang, K. Xie, Q. S. Dai, R. Zeng, Y. Q. Liu, Z. Q. Jia, X. Feng and J. L. Li, *Green Chem.*, 2019, **21**, 2375–2379.
30 N. R. Candeias, P. M. P. Gois, L. F. Veiros and C. A. M. Afonso, *J. Org. Chem.*, 2008, **73**, 5926–5932.
31 K. Yan, H. He, J. Li, Y. Luo, R. Lai, L. Guo and Y. Wu, *Chin. Chem. Lett.*, 2021, **32**, 3984–3987.
32 R. V. Maaskant, E. A. Polanco, R. C. W. Van Lier and G. Roelfes, *Org. Biomol. Chem.*, 2020, **18**, 638–641.
33 S. K. Mehta, K. K. Bhasin, R. Chauhan and S. Dham, *Colloids Surf., A*, 2005, **255**, 153–157.
34 N. J. Turro, M. F. Chow, C. J. Chung, Y. Tanimoto and G. C. Weed, *J. Am. Chem. Soc.*, 1981, **103**, 4574–4576.
35 N. J. Turro, G. Sidney Cox and M. A. Paczkowski, *Photochemistry in micelles*, Springer Berlin Heidelberg, Berlin, Heidelberg, 1985.
36 M. Turchi, A. P. Karcz and M. P. Andersson, *J. Colloid Interface Sci.*, 2022, 618–627.
37 S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller and J. A. Bull, *Org. Process Res. Dev.*, 2020, **24**, 67–84.
38 W. Liu, J. Twilton, B. Wei, M. Lee, M. N. Hopkins, J. Bacsa, S. S. Stahl and H. M. L. Davies, *ACS Catal.*, 2021, **11**, 2676–2683.
39 N. Tanbouza, L. Caron, A. Khoshoei and T. Ollevier, *Org. Lett.*, 2022, **24**, 2675–2678.
40 P. Tisovský, J. Donovalová, R. Sokolík, M. Horváth and A. Gáplovský, *ChemistrySelect*, 2021, **6**, 10651–10654.

ACS ORGANIC & INORGANIC Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

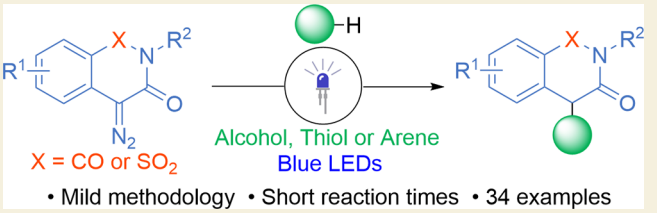
pubs.acs.org/orginorgau
Article

Photochemical Functionalization of 4-Diazoisoquinoline-1,3(2*H*,4*H*)-diones and Their 1-Sulfoxide Analogues

Joseph P. Milton and Dorota Gryko*

Cite This: https://doi.org/10.1021/acsorginorgau.5c00017
Read Online

ABSTRACT: Isoquinoline-1,3(2*H*,4*H*)-diones have been the subject of numerous studies toward new pharmaceuticals, and therefore novel, mild functionalizations of this scaffold are highly desirable. As diazo compounds are versatile reagents in organic synthesis, 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones should give access to a broad range of various derivatives. Indeed, they enable the introduction of fluorinated moieties via photochemical O−H insertion reactions in serviceable yields, typically in under 2 h. Exchanging the 1-carbonyl group with the sulfoxide moiety causes a hypsochromic shift in the absorption of the diazo compounds, and thus, violet light is required for effective O−H and S−H insertion reactions.



KEYWORDS: *photochemistry, photolysis, diazo compounds, insertion reactions, isoquinoline-1,3(2H,4H)-diones*

Heterocyclic scaffolds are highly prevalent in natural compounds, drugs, and lead candidates.[1] Among them, isoquinoline-1,3(2*H*,4*H*)-diones draw particular interest in biological assays, where they have been probed as inhibitors of HIV-1 integrase[2,3] and ALR2,[4] antagonists for progesterone receptors, among others in recent years (Figure 1A).[5−8] In fact, they have been investigated as potential hypnotic agents since the 1920's,[9] illustrating that interest in this class of compounds has been constant over the last 100 years. Nevertheless, the development of mild, efficient, and practical modifications of this skeleton still presents a challenge and is highly desirable.[10]

With the well-documented impact of fluorine on the pharmacokinetic and physicochemical properties of a compound and approximately 20% of pharmaceuticals containing a fluorinated moiety,[11−13] *we sought a straightforward methodology to introduce fluorinated moieties into the isoquinoline-1,3(2H,4H)-dione scaffold.*

In the past decade, reactions of 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones have only been probed with a rhodium catalyst in combination with nitriles,[14] heterocycles,[15] and carboxylic acids[16,17] by Krasavin and Dar'in (Figure 1B). Recently, the Fan group has used them to synthesize a variety of spirocyclic heterocycles under either Rh or dual catalytic conditions (Rh and Cu).[18−20] One of these diazo compound was tested in a three-component acyloxylation reaction with a ruthenium catalyst.[21] Eliminating the need for transition metals, it has been shown that strong acids such as hydrofluoric and triflic acid enable the introduction of fluorine atoms or aryl moieties to the 4-position.[22] On the other hand, some closely related heterocyclic diazo compounds such as 3-diazooxindoles[23−26] and 4-diazo-2-tosyl-1,4-dihydroisoquinolin-3(2*H*)-ones[27] are known to react effectively under blue light-emitting diode (LED) conditions. With our previous experience in the photochemistry of diazo compounds,[28−30] we envisaged *that 4-diazoisoquinoline-1,3(2H,4H)-diones should productively react with fluorinated alcohols under mild photochemical conditions.*

Changes at the 4-position of isoquinoline-1,3(2*H*,4*H*)-diones have a pronounced impact on their pharmaceutical activity (Figure 1A). As the 1,1,1,3,3,3-hexafluoroisopropoxy moiety has already provided promising results in biological screenings,[31−34] we decided to start our investigation with 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**1a**) with 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) under blue LED irradiation to undergo the classical photochemical O−H insertion reaction.[30,35,36]

Using a 2:8 solution of EtOAc and HFIP enabled the formation of the desired product **2**, but in a low yield (17% by NMR, Table 1, entry 1). The more HFIP we used, the better the yield became; thus, the reaction was performed in neat HFIP (entries 2 and 3); reducing the concentration did not improve the yield to any substantial effect (entry 4) but increasing it to 0.2 M or higher started to have adverse effects (entries 5 and 6). Kinetics studies showed that a yield of 80% was consistently achieved for the timespan of 1−4 h; however, the product slowly decomposes when exposed to prolonged irradiation (see SI Figure 2.3). After 2 h, product **2** was isolated in 67% yield (entry 7).

Received: February 11, 2025
Revised: March 18, 2025
Accepted: March 19, 2025

https://doi.org/10.1021/acsorginorgau.5c00017
ACS Org. Inorg. Au XXXX, XXX, XXX−XXX

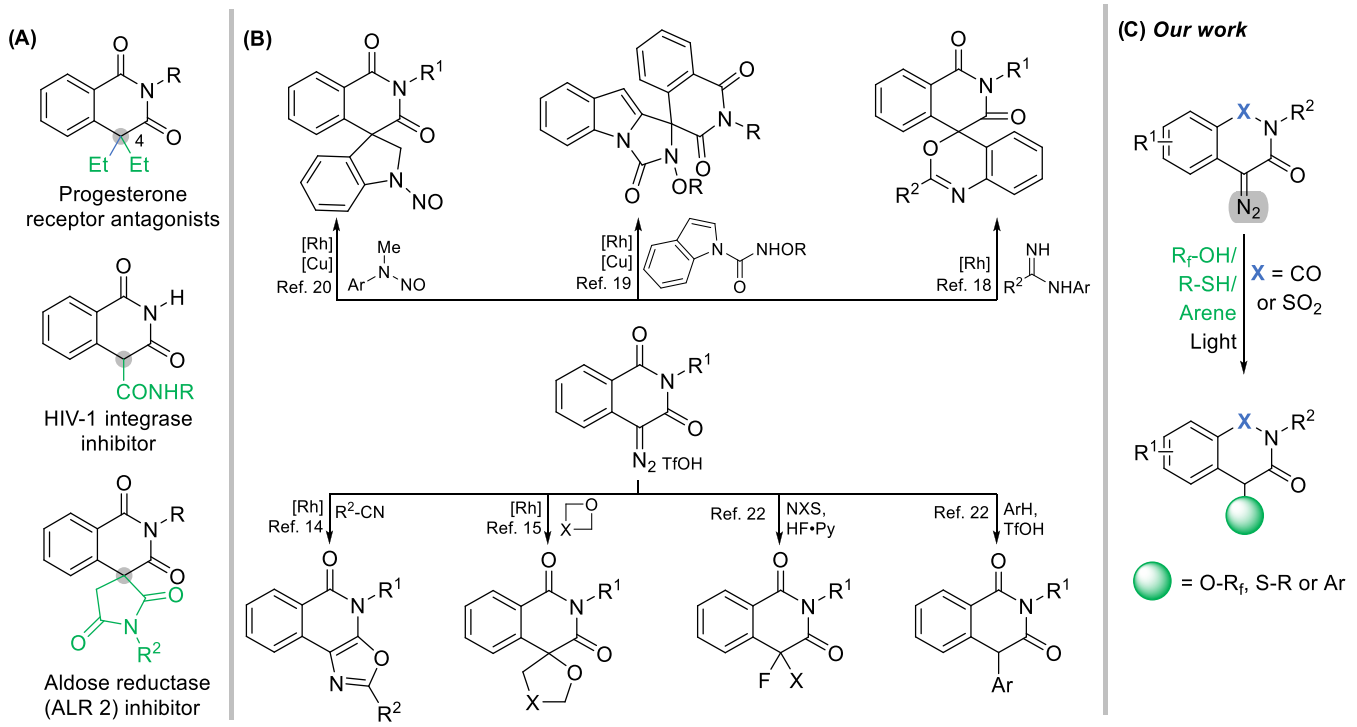
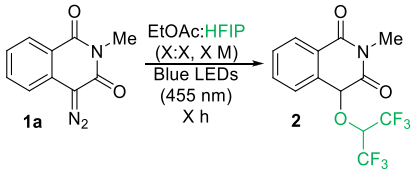


Figure 1. (A) Examples of bioactive isoquinoline-1,3(2*H*,4*H*)-diones, (B) known reactions of 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones, and (C) our work.

Table 1. Optimization Studies[a]



entry	HFIP/EtOAc	*c* (M)	time (h)	yield (%)[b]
1	2:8	0.1	18	17
2	6:4	0.1	18	45
3	1:0	0.1	18	60
4	1:0	0.05	18	57
5	1:0	0.2	18	53
6	1:0	0.4	18	46
7	1:0	0.1	2	80 (67)[c]

[a]**1a** (0.1 mmol), blue LEDs (455 nm). [b]NMR yields determined with trichloroethene as the internal standard. [c]Isolated yield.

Other *N*-alkyl-substituted 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones performed relatively consistently, allowing fluorinated derivatives to be synthesized in 60−71% yield (Scheme 1, **2**−**6**). However, the reaction with 4-diazo-2-phenylisoquinoline-1,3(2*H*,4*H*)-dione led to product **7** in a diminished yield because of the lower stability of the substrate and product under the reaction conditions. Furthermore, the presence of electron-withdrawing or electron-donating substituents at position 7 of the aromatic ring slightly diminishes the reaction yield in comparison to the unsubstituted analogues (**8**−**10**). In the case of the 6- and 7-methoxy derivatives, prolongation of the reaction time was required to achieve products **11** and **12** in serviceable yield. Intriguingly, the presence of halogens at the 6-position destabilizes these compounds (**13** and **14**), and thus, they could not be successfully isolated. A similar issue was encountered with compound **15**, which possesses a chlorine atom with an analogous electron-withdrawing effect, which gave a diminished yield, highlighting the problematic nature of the electron-withdrawing substituents in the *ortho*-position. Furthermore, reactions with other fluorinated alcohols were less efficient than HFIP (**17** − **21**); however, the reaction with 1,1,1-trifluoroisopropanol provided a satisfactory diastereomeric ratio of 1:10 (**18**). The O−H insertion product with nonafluoro-*tert*-butyl alcohol (**21a**) underwent an interesting rearrangement reaction to a ketone forming the respective trione compound (**21b**) under silica gel column chromatography.

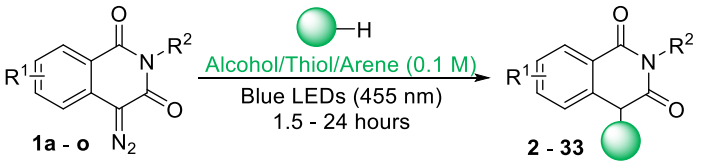
For more typical alcohols, such as ethanol and isopropanol, no product formation was observed, which might suggest that the mechanism reported by Koenigs and co-workers may operate instead of a formal carbene O−H insertion. They proposed that the relatively acidic HFIP coordinates to the α-carbonyl moiety, which upon light irradiation triggers a photoexcited proton transfer to generate an unstable diazonium-like intermediate, which is immediately attacked by the deprotonated alcohol. This would also justify why other examined fluorinated alcohols give lower yields, as they are less acidic and, thus, the coordination to the amide would be weaker.[24,37]

The introduction of fluorinated moieties is easily scalable and is demonstrated by performing the reaction on a gram scale (5.0 mmol) with diazo compound **1a** in 50 mL of HFIP, with an extended reaction time of 7 h that yielded over 1 g of product **2** in 66% yield, a comparable yield to the smaller-scale reaction. With HFIP still being a commodity solvent[34,38] and having a relatively high cost, we recycled the solvent (>80% efficiency) by distilling the excess after the reaction completion.

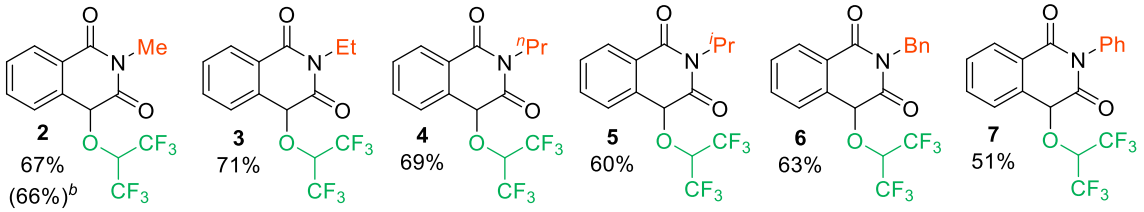
With the photochemical insertion of O−H working successfully, we tested the developed method for similar reactions such as S−H and C−H insertions.

https://doi.org/10.1021/acsorginorgau.5c00017
ACS Org. Inorg. Au XXXX, XXX, XXX−XXX

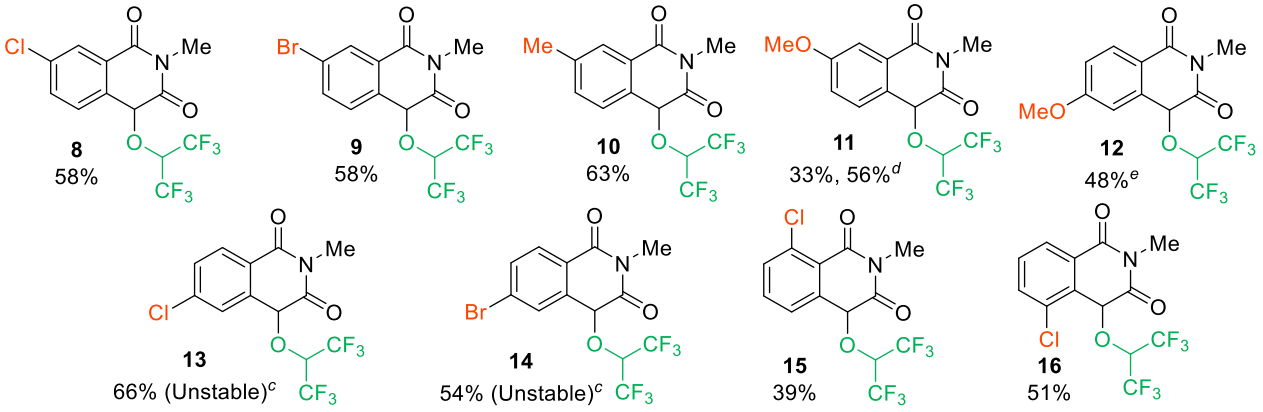
Scheme 1. Scope of Insertion Reactions with 4-Diazoisoquinoline-1,3(2*H*,4*H*)-diones[a]



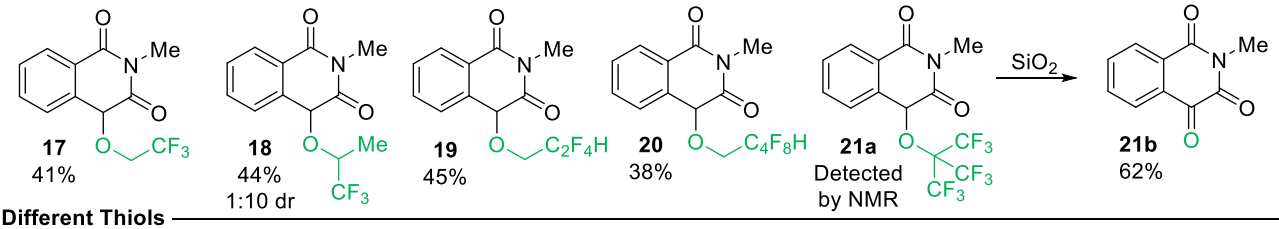
Different *N*-substituents



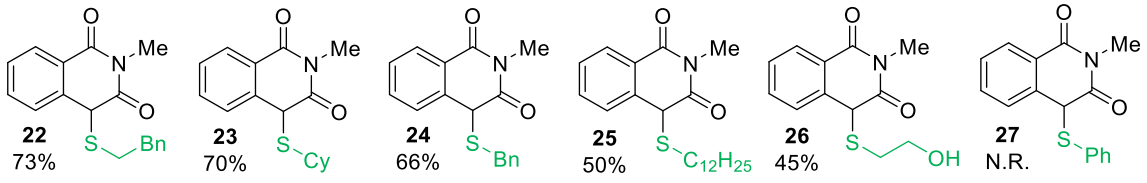
Different Aryl Substituents



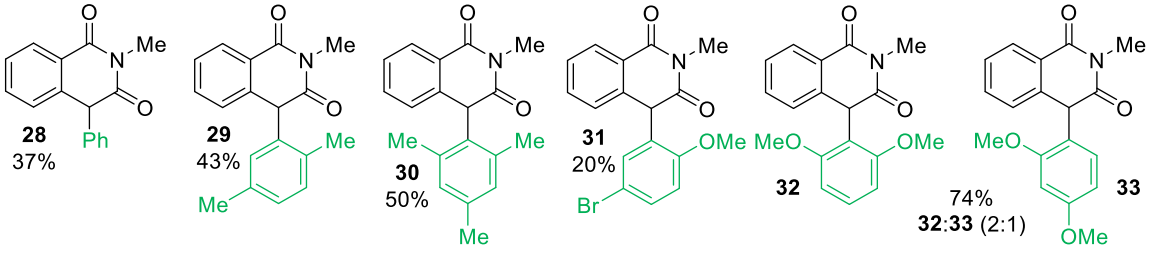
Different Alcohols



Different Thiols



Different Arenes[f]



[a]Reaction conditions: 4-diazoisoquinoline-1,3(2*H*,4*H*)-dione (0.2 mmol), alcohol or thiol (0.1 M), blue LEDs (455 nm), 1.5 h, unless otherwise stated, isolated yields are given. [b]Gram-scale reaction, 7 h. [c]0.1 mmol scale reaction, yield determined by ^{19}F NMR with methyl 4-(trifluoromethyl)benzoate as the internal standard, the product was not isolated. [d]4.5 h. [e]20 h. [f]4-Diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (0.2 mmol), arene (0.1 M), blue LEDs (455 nm), 24 h.

Indeed, all thiols examined performed well, especially 2-phenylethyl mercaptan and cyclohexanethiol (**22** and **23**, respectively). 2-Mercaptoethanol (**26**) gave high chemoselectivity with only exclusive formation of the S−H insertion

https://doi.org/10.1021/acsorginorgau.5c00017
ACS Org. Inorg. Au XXXX, XXX, XXX−XXX

product; we presume this is due to nonfluorinated alcohols being unproductive in the reaction, whereas alkyl thiols perform effectively. Furthermore, reactions with aromatic solvents provided C−H insertion products as the main constituents of the product mixture (Scheme 1). The yield gradually improved with an increased electron richness of the aromatic ring from benzene (**28**, 37%), *p*-xylene (**29**, 43%) to mesitylene (**30**, 50%). 4-Bromoanisole, despite having a strong electron-donating methoxy group, gave a poor yield of only 20%, showing that the electron-withdrawing bromine group significantly affects the reactivity (**31**). 1,3-Dimethoxybenzene provided the highest yield of arenes tested, which afforded a statistical amount of the two regioisomers despite the steric hindrance present at the 2-position (**32** and **33**). While the yields are generally relatively moderate with arenes, Golushko et al. reported that such a reaction only provides traces of material under microwave-assisted rhodium-catalyzed conditions.[22] Alternative methods for such a transformation either involve the use of triflic acid[22] or a palladium cross-coupling,[39] thus demonstrating the mildness of the developed photochemical reaction. We also attempted to perform N−H insertion reactions, but a rearrangement reaction takes place that is analogous to that described by Li et al.[40] and similar to works by Wakchaure et al.[41,42]

2*H*-Benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide, a closely related heterocycle, where, effectively, the 1-carbonyl group is replaced with a sulfoxide moiety, has previously been reported to possess impressive anti-inflammatory properties, some displaying even higher activity than indomethacin,[43] which is part of the WHO list of essential medicines.[44] We, thus, examined this novel series of diazo compounds (**34a−c**) in our new method to introduce fluorinated moieties.

Ultraviolet−visible (UV−vis) spectra of these new diazo compounds are similar in shape to the 4-diazoisoquinoline-1,3(2*H*,4*H*)-dione (**1a**) but the λ_{max} is hypsochromically shifted approximately 35 nm (Figure 2); consequently, violet

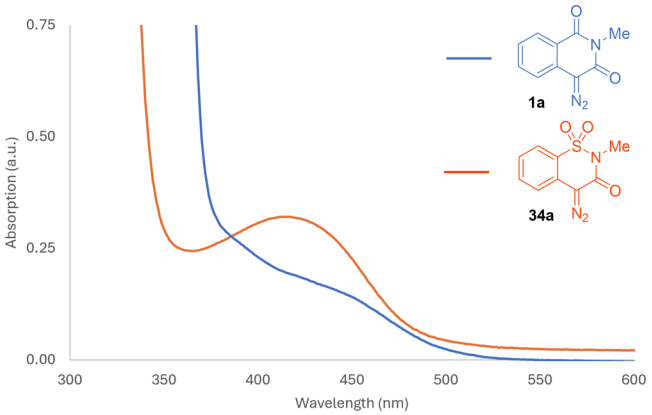
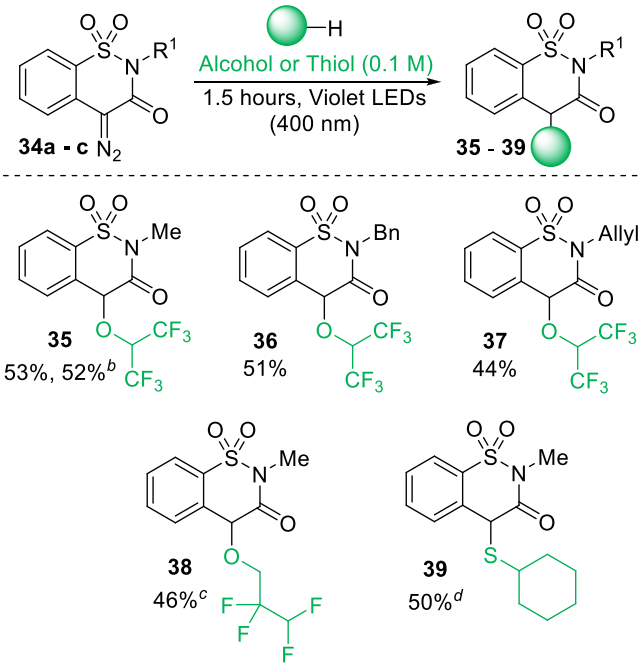


Figure 2. UV−vis spectra of 4-diazo-2-methylisoquinoline-1,3-(2*H*,4*H*)-dione (**1a**) and 4-diazo-2-methyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (**34a**) (c = 0.006 M in DCM).

LED irradiation instead of blue LEDs is preferable for their activation. The O−H insertion reaction of diazo compound **34a** with HFIP formed the desired product (**35**) in 53% yield with violet LEDs in 1.5 h; blue LED irradiation led to product **35** in a comparable yield (52%), with an extended reaction time (2.5 h, Scheme 2).

Scheme 2. Scope of O−H and S−H Insertions with 4-Diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-Dioxides[a]



[a]Reaction conditions: 4-diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (0.15 mmol), alcohol or thiol (0.1 M), violet LEDs (400 nm), 1.5 h. [b]Blue LEDs (455 nm), 2.5 h. [c]4 h. [d]7 h.

Similar reactivity was observed with other *N*-substituted derivatives, such as *N*-benzyl (**36**, 51%) and *N*-allyl (**37**, 44%). The X−H insertion reaction was also viable with 2,2,3,3-tetrafluoropropan-1-ol (**38**, 46%) and cyclohexanethiol (**39**, 50%) in similar moderate yields but both required extended reaction times of 4 and 7 h, respectively. In brief, this new series of diazo compounds is generally less reactive compared to 4-diazoisoquinoline-1,3(2*H*,4*H*)-diones while requiring a different light source and an extended reaction time in more situations.

In conclusion, fluorinated moieties can be effectively introduced into the isoquinoline-1,3(2*H*,4*H*)-dione scaffold under mild blue LED irradiation. Gratifyingly, the reaction is compatible up to a gram scale with HFIP as the reagent and solvent and is also recyclable and scalable. The developed conditions are also compatible with S−H and C−H insertion reactions. A novel series of diazo compounds, 4-diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides, were synthesized and efficiently react under violet LED irradiation, providing O−H and S−H insertion reactions in slightly diminished yields compared to 4-diazoisoquinoline-1,3-(2*H*,4*H*)-diones. We believe that this work will provide a useful stepping stone for further investigations of photochemical reactions of heterocyclic diazo compounds.

EXPERIMENTAL SECTION

General Procedures

All solvents and commercially available reagents were used as purchased without further purification. Dry solvents were obtained from a Solvent Purification System (SPS). All reactions were monitored by gas chromatography (GC) or TLC on Merck silica gel (GF254, 0.20 mm thickness) and were visualized with UV light. Column chromatography was performed using Merck silica gel 60

https://doi.org/10.1021/acsorginorgau.5c00017
ACS Org. Inorg. Au XXXX, XXX, XXX−XXX

(230−400 mesh). Unless otherwise noted, all reactions were performed without the exclusion of air or moisture. Unless otherwise noted, all photochemical reactions were performed in 10 mL vials with an aluminum cap and a rubber septum.

^{1}H and ^{13}C NMR spectra were recorded at 25 °C on a Bruker 400 MHz, Bruker 500 MHz, Varian 500 MHz or a Varian 600 MHz instrument. NMR chemical shifts are reported in ppm and referenced to the residual solvent peak: ^{1}H NMR 7.26 ppm ($CDCl_3$) or 2.50 ppm (DMSO-d_6); ^{13}C NMR 77.16 ppm ($CDCl_3$) or 39.52 ppm (DMSO-d_6). In cases where the $CDCl_3$ peak could not be identified, TMS was instead used as the reference at 0.00 ppm. Multiplicities are indicated by singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (hept), and multiplet (m). Coupling constants (J) are reported in hertz. All data analyses were performed using the MestReNova software package. Elemental analysis (C, H, N, S, Br, Cl, and F) was performed on a PerkinElmer 240 Elemental Analyzer. High-resolution mass spectra were recorded on a Waters SYNAPT G2-S HDMS using electrospray ionization (ESI) or atmospheric-pressure chemical ionization (APCI) with a time-of-flight (TOF) detector. Gas chromatography analysis coupled with a flame ionization detector (GC-FID) was performed on a Shimadzu GCMS-QP2010 SE with helium as the carrier gas and a Zebron ZB 5MSi column.

General Procedure for the Insertion Reactions of 4-Diazoisoquinoline-1,3(2*H*,4*H*)-dione

4-Diazoisoquinoline-1,3(2*H*,4*H*)-dione (0.2 mmol) is charged in a vial and dissolved in the respective alcohol, thiol, or arene (2 mL), and then the vial is capped. The vial is irradiated with blue LEDs for typically 1.5 h (24 h with arenes) at approximately 15 °C and then the cap is removed.

For Volatile Solvents. The solution is transferred to a flask with DCM and all of the volatiles are removed in vacuo. The crude residue is purified by column chromatography (SiO_2, 10% EtOAc in hexane) to afford the X−H insertion product.

For Nonvolatile Solvents. The crude reaction mixture is pipetted directly on top of a prepacked column and subjected to column chromatography (SiO_2, 10% EtOAc in hexane) to afford the X−H insertion product.

General Procedure for the Insertion Reactions of 4-Diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides

4-Diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (0.15 mmol) is charged in a vial and dissolved in the respective alcohol or thiol (1.5 mL), and then the vial is capped. The vial is irradiated with violet LEDs for 1.5 h at approximately 15 °C, then the reaction mixture is transferred to a flask with DCM, and all of the volatiles are removed in vacuo. The crude residue is purified by column chromatography (SiO_2, 10% EtOAc in hexane) to afford the X−H insertion product.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and the Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.5c00017.

Experimental details and procedures; optimization studies; and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Dorota Gryko − *Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw 01-224, Poland;* orcid.org/0000-0002-5197-4222; Email: dorota.gryko@icho.edu.pl

Author

Joseph P. Milton − *Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw 01-224, Poland;* orcid.org/0000-0002-3907-5136

Complete contact information is available at: https://pubs.acs.org/10.1021/acsorginorgau.5c00017

Author Contributions

CRediT: J.P.M.: conceptualization, methodology, investigation, data curation, writing—original draft, writing—review and editing; D.G.: conceptualization, writing—review and editing, supervision, funding acquisition.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project has received funding from European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska−Curie Grant Agreement No. 956324 (MSCA ITN: PhotoReAct).

■ REFERENCES

(1) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87* (12), 1348−1349.

(2) Billamboz, M.; Bailly, F.; Lion, C.; Touati, N.; Vezin, H.; Calmels, C.; Andréola, M. L.; Christ, F.; Debyser, Z.; Cotelle, P. Magnesium Chelating 2-Hydroxyisoquinoline-1,3(2H, 4H)-Diones, as Inhibitors of HIV-1 Integrase and/or the HIV-1 Reverse Transcriptase Ribonuclease H Domain: Discovery of a Novel Selective Inhibitor of the Ribonuclease H Function. *J. Med. Chem.* **2011**, *54* (6), 1812−1824.

(3) Billamboz, M.; Bailly, F.; Barreca, M. L.; De Luca, L.; Mouscadet, J. F.; Calmels, C.; Andréola, M. L.; Witvrouw, M.; Christ, F.; Debyser, Z.; Cotelle, P. Design, Synthesis, and Biological Evaluation of a Series of 2-Hydroxyisoquinoline-1,3(2H,4H)-Diones as Dual Inhibitors of Human Immunodeficiency Virus Type 1 Integrase and the Reverse Transcriptase RNase H Domain. *J. Med. Chem.* **2008**, *51* (24), 7717−7730.

(4) Malamas, M. S.; Hohman, T. C. N-Substituted Spirosuccinimide, Spiropyridazine, Spiroazetidine, and Acetic Acid Aldose Reductase Inhibitors Derived from Isoquinoline-1,3-Diones. 2. *J. Med. Chem.* **1994**, *37* (13), 2059−2070.

(5) Vernekar, S. K. V.; Liu, Z.; Nagy, E.; Miller, L.; Kirby, K. A.; Wilson, D. J.; Kankanala, J.; Sarafianos, S. G.; Parniak, M. A.; Wang, Z. Design, Synthesis, Biochemical, and Antiviral Evaluations of C6 Benzyl and C6 Biarylmethyl Substituted 2-Hydroxylisoquinoline-1,3-Diones: Dual Inhibition against HIV Reverse Transcriptase-Associated RNase H and Polymerase with Antiviral Activities. *J. Med. Chem.* **2015**, *58* (2), 651−664.

(6) Chen, Y. L.; Tang, J.; Kesler, M. J.; Sham, Y. Y.; Vince, R.; Geraghty, R. J.; Wang, Z. The Design, Synthesis and Biological Evaluations of C-6 or C-7 Substituted 2-Hydroxyisoquinoline-1,3-Diones as Inhibitors of Hepatitis C Virus. *Bioorg. Med. Chem.* **2012**, *20* (1), 467−479.

(7) Kankanala, J.; Marchand, C.; Abdelmalak, M.; Aihara, H.; Pommier, Y.; Wang, Z. Isoquinoline-1,3-Diones as Selective Inhibitors of Tyrosyl DNA Phosphodiesterase II (TDP2). *J. Med. Chem.* **2016**, *59* (6), 2734−2746.

(8) Lu, X. Y.; Chen, Y. D.; Sun, N. Y.; Jiang, Y. J.; You, Q. D. Molecular-Docking-Guided 3D-QSAR Studies of Substituted Isoquinoline-1,3-(2H,4H)-Diones as Cyclin-Dependent Kinase 4 (CDK4) Inhibitors. *J. Mol. Model.* **2010**, *16* (2), 163−173.

(9) Harriman, B. R.; Shelton, R. S.; Campen, M. G. Van.; Warren, M. R. Homophthalimides as Hypnotic Agents. *J. Am. Chem. Soc.* **1945**, *67* (9), 1481−1482.
(10) Niu, Y. N.; Xia, X. F. Recent Developments in the Synthesis of the Isoquinoline-1,3(2H,4H)-Dione by Radical Cascade Reaction. *Org. Biomol. Chem.* **2022**, *20* (40), 7861−7885.
(11) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5* (19), 10633−10640.
(12) Smart, B. E. Fluorine Substituent Effects (on Bioactivity). *J. Fluorine Chem.* **2001**, *109* (1), 3−11.
(13) Shah, P.; Westwell, A. D. The Role of Fluorine in Medicinal Chemistry. *J. Enzyme Inhib. Med. Chem.* **2007**, *22* (5), 527−540.
(14) Kantin, G.; Dar'in, D.; Krasavin, M. RhII-Catalyzed Cycloaddition of α-Diazo Homophthalimides and Nitriles Delivers Oxazolo[5,4-c]Isoquinolin-5(4H)-One Scaffold. *Eur. J. Org. Chem.* **2018**, *2018* (35), 4857−4859.
(15) Guranova, N. I.; Dar'in, D.; Kantin, G.; Novikov, A. S.; Bakulina, O.; Krasavin, M. Rh(II)-Catalyzed Spirocyclization of α-Diazo Homophthalimides with Cyclic Ethers. *J. Org. Chem.* **2019**, *84* (7), 4534−4542.
(16) Dar'in, D.; Kantin, G.; Chupakhin, E.; Sharoyko, V.; Krasavin, M. Natural-Like Spirocyclic Δα,β-Butenolides Obtained from Diazo Homophthalimides. *Chem. - Eur. J.* **2021**, *27* (31), 8221−8227.
(17) Malkova, K.; Tatarinov, I.; Kantin, G.; Dar'in, D. Utilizing Allenic Acids and Heterocyclic Diazo Compounds in the Synthesis of Polysubstituted Spirocyclic Butenolides and β-Methylidene 2-Furanones. *J. Org. Chem.* **2024**, *89* (4), 2782−2786.
(18) Zhou, Q.; Song, X.; Zhang, X.; Fan, X. Synthesis of Spiro[Benzo[d][1,3]Oxazine-4,4′-Isoquinoline]s via [4 + 1+1] Annulation of N-Aryl Amidines with Diazo Homophthalimides and O2. *Org. Lett.* **2022**, *24* (6), 1280−1285.
(19) Wang, M.; Zhou, Q.; Zhang, X.; Fan, X. Condition-Controlled Divergent Synthesis of Imidazoindolone Spiroisoquinolinones from N-Alkoxycarboxamide Indoles and Diazo Homophthalimides. *Adv. Synth. Catal.* **2023**, *365* (8), 1255−1261.
(20) Wang, K.; Sun, Y.; Li, B.; Zhang, X.; Fan, X. Expeditious Synthesis of Spiroindoline Derivatives via Tandem C(Sp2)-H and C(Sp3)-H Bond Functionalization of N-Methyl-N-Nitrosoanilines. *Org. Lett.* **2024**, *26* (15), 3091−3096.
(21) Lin, M. L.; Zheng, T.; Liu, H.; Wang, Y. X.; Dong, L. Three-Component Acyloxylation of Diazo Compounds with Carboxylic Acids and Azadienes. *Org. Biomol. Chem.* **2023**, *21* (5), 925−929.
(22) Golushko, A.; Dar'in, D.; Kantin, G.; Guranova, N.; Vasilyev, A. V.; Krasavin, M. Medicinally Relevant Modification of the Isoquinoline-1,3-Dione Scaffold via Metal-Free Arylation and Fluorination of Diazo Homophthalimides in Brønsted Acids. *Synthesis* **2019**, *51* (20), 3815−3824.
(23) Zhao, S.; Chen, X. X.; Gao, N.; Qian, M.; Chen, X. Visible-Light-Mediated Cyclopropanation Reactions of 3-Diazooxindoles with Arenes. *J. Org. Chem.* **2021**, *86* (10), 7131−7140.
(24) Empel, C.; Verspeek, D.; Jana, S.; Koenigs, R. M. Photochemical O−H Functionalization Reactions of Cyclic Diazoamides. *Adv. Synth. Catal.* **2020**, *362* (21), 4716−4722.
(25) Muthusamy, S.; Ramesh, C. Blue LED-Mediated Synthesis of 3-Arylidene Oxindoles. *J. Org. Chem.* **2023**, *88* (9), 5609−5621.
(26) Qi, D.; Bai, J.; Song, Z.; Li, B.; Yang, C.; Guo, L.; Xia, W. Photoinduced Synthesis of Functionalized Oxacyclic Spirooxindoles Via Ring Expansion. *Org. Lett.* **2023**, *25* (3), 506−511.
(27) Xie, J.; Suleman, M.; Wang, Z.; Mao, X.; Mao, B.; Fan, J.; Lu, P.; Wang, Y. Syntheses of 4-Allyl-/4-Allenyl-4-(Arylthio)-1,4-Dihydroisoquinolin-3-Ones via the Photochemical Doyle-Kirmse Reaction. *Org. Biomol. Chem.* **2021**, *19* (28), 6341−6345.
(28) Milton, J. P.; Milanowski, A.; Andersson, M.; Gryko, D. Photochemical Cyclopropanation in Aqueous Micellar Media − Experimental and Theoretical Studies. *Chem. Commun.* **2024**, *60* (33), 4483−4486.
(29) Wosińska-Hrydczuk, M.; Anzabi, M. Y.; Przeździecki, J.; Danylyuk, O.; Chaładaj, W.; Gryko, D. Unique Reactivity of Triazolyl Diazoacetates under Photochemical Conditions. *ACS Org. Inorg. Au* **2024**, *4* (4), 418−423.
(30) Orłowska, K.; Łuczak, K.; Krajewski, P.; Santiago, J. V.; Rybicka-Jasińska, K.; Gryko, D. Unlocking the Reactivity of Diazo Compounds in Red Light with the Use of Photochemical Tools. *Chem. Commun.* **2023**, *59* (99), 14649−14652.
(31) Chang, J. W.; Cognetta, A. B.; Niphakis, M. J.; Cravatt, B. F. Proteome-Wide Reactivity Profiling Identifies Diverse Carbamate Chemotypes Tuned for Serine Hydrolase Inhibition. *ACS Chem. Biol.* **2013**, *8* (7), 1590−1599.
(32) Butler, C. R.; Beck, E. M.; Harris, A.; Huang, Z.; McAllister, L. A.; am Ende, C. W.; Fennell, K.; Foley, T. L.; Fonseca, K.; Hawrylik, S. J.; Johnson, D. S.; Knafels, J. D.; Mente, S.; Noell, G. S.; Pandit, J.; Phillips, T. B.; Piro, J. R.; Rogers, B. N.; Samad, T. A.; Wang, J.; Wan, S.; Brodney, M. A. Azetidine and Piperidine Carbamates as Efficient, Covalent Inhibitors of Monoacylglycerol Lipase. *J. Med. Chem.* **2017**, *60* (23), 9860−9873.
(33) Cisar, J. S.; Weber, O. D.; Clapper, J. R.; Blankman, J. L.; Henry, C. L.; Simon, G. M.; Alexander, J. P.; Jones, T. K.; Ezekowitz, R. A. B.; O'Neill, G. P.; Grice, C. A. Identification of ABX-1431, a Selective Inhibitor of Monoacylglycerol Lipase and Clinical Candidate for Treatment of Neurological Disorders. *J. Med. Chem.* **2018**, *61* (20), 9062−9084.
(34) Motiwala, H. F.; Armaly, A. M.; Cacioppo, J. G.; Coombs, T. C.; Koehn, K. R. K.; Norwood, V. M.; Aubé, J. HFIP in Organic Synthesis. *Chem. Rev.* **2022**, *122* (15), 12544−12747.
(35) Jurberg, I. D.; Davies, H. M. L. Blue Light-Promoted Photolysis of Aryldiazoacetates. *Chem. Sci.* **2018**, *9* (22), 5112−5118.
(36) Empel, C.; Jana, S.; Pei, C.; Nguyen, T. V.; Koenigs, R. M. Photochemical O−H Functionalization of Aryldiazoacetates with Phenols via Proton Transfer. *Org. Lett.* **2020**, *22* (18), 7225−7229.
(37) Jana, S.; Yang, Z.; Li, F.; Empel, C.; Ho, J.; Koenigs, R. M. Photoinduced Proton-Transfer Reactions for Mild O-H Functionalization of Unreactive Alcohols. *Angew. Chem., Int. Ed.* **2020**, *59* (14), 5562−5566.
(38) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. Hexafluoroisopropanol as a Highly Versatile Solvent. *Nat. Rev. Chem.* **2017**, *1* (11), No. 0088.
(39) Yang, Y.; Li, Y.; Cheng, C.; Yang, G.; Zhang, J.; Zhang, Y.; Zhao, Y.; Zhang, L.; Li, C.; Tang, L. Synthesis of 4-Aryl Isoquinolinedione Derivatives by a Palladium-Catalyzed Coupling Reaction of Aryl Halides with Isoquinoline-1,3(2 H,4 H)-Diones. *J. Org. Chem.* **2018**, *83* (6), 3348−3353.
(40) Li, Y.; Feng, X.; Jia, X.; Jin, H.; Chen, F.; Zhao, Y.; Zhang, J.; Wang, J.; Guo, B.; Tang, L.; Yang, Y. Regiodivergent Functionalization of Isoquinoline-1,3(2 H, 4 H)-dione Derivatives via Aerobic Umpolung. *Asian J. Org. Chem.* **2021**, *10* (6), 1508−1513.
(41) Wakchaure, P. B.; Easwar, S.; Puranik, V. G.; Argade, N. P. Facile Air-Oxidation of N-Homopiperonyl-5,6-Dimethoxyhomophthalimide: Simple and Efficient Access to Nuevamine. *Tetrahedron* **2008**, *64* (8), 1786−1791.
(42) Wakchaure, P.; Argade, N. Intramolecular Chemoselective Acylation of a Suitably Substituted Isoindole: Synthesis of (±)-Chilenine and (±)-Deoxychilenine. *Synthesis* **2011**, *2011* (17), 2838−2842.
(43) Lombardino, J. G.; Wiseman, E. H. Antiinflammatory 3,4-Dihydro-2-Alkyl-3-Oxo-2H-1,2-Benzothiazine-4-Carboxamide 1,1-Dioxides. *J. Med. Chem.* **1971**, *14* (10), 973−977.
(44) WHO Model List of Essential Medicines - 23rd list 2023, https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02. (accessed November 28, 2024).

https://doi.org/10.1021/acsorginorgau.5c00017
ACS Org. Inorg. Au XXXX, XXX, XXX−XXX

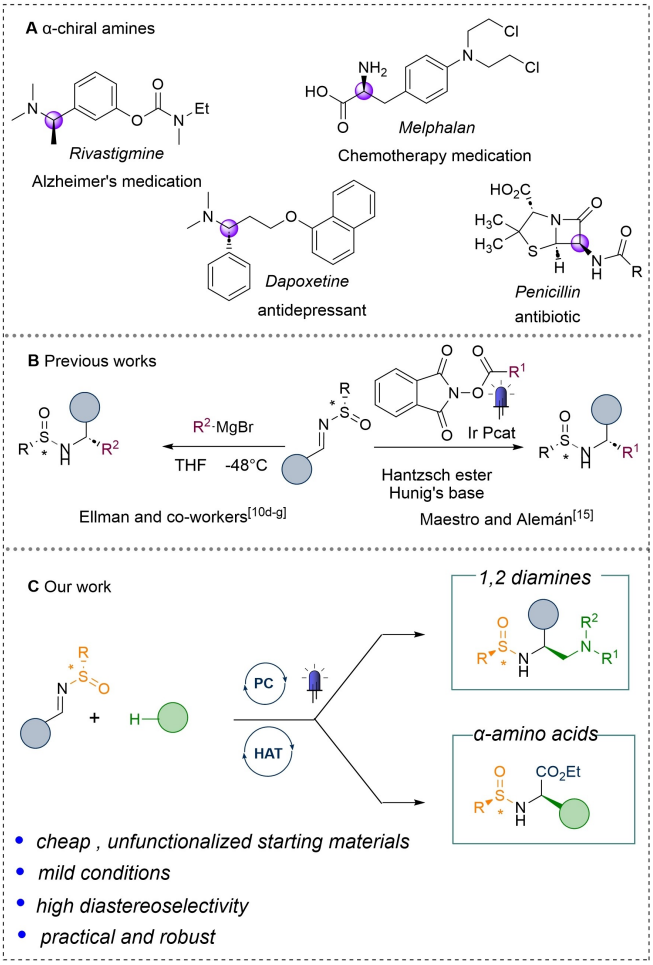
Chemistry–A European Journal
Research Article
doi.org/10.1002/chem.202400363
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines

Matteo Leone,[a] Joseph P. Milton,[b] Dorota Gryko,[b] Luc Neuville,*[a, c] and Géraldine Masson*[a, c]

Herein we describe a sustainable and efficient photocatalytic method for the stereoselective radical alkylation of chiral sulfinyl imines. By employing readily available non-prefunctionalized radical precursors and the cost-effective TBADT as a direct HAT photocatalyst, we successfully obtain diverse chiral amines with high yields and excellent diastereoselectivity under mild conditions. This method provides an efficient approach for accessing a diverse array of medicinally relevant compounds, including both natural and synthetic α-amino acids, aryl ethyl amines, and other structural motifs commonly found in approved pharmaceuticals and natural product.

Chiral amines serve as essential building blocks in the development of pharmaceutical ingredients (Scheme 1A).[1] Illustrative data reveals that approximately 35% of the top 200 small molecule drugs marketed in 2018 feature at least one chiral amine center.[2] Furthermore, these compounds are prevalent in natural substances and can be utilized in organic synthesis as resolving agents or chiral auxiliaries.[3] Among the various strategies for the industrial synthesis of chiral amines, many of them still rely on traditional synthetic methods involving resolution[4] or costly precious metals-based catalytic approaches.[5] Furthermore, most of these metal-catalyzed methods require either harsh conditions or expensive chiral ligands.[6,7] Therefore, the high demand for the production of chiral amines, due to their varied applications, has pushed the scientific community to find alternative and sustainable ways towards their effective preparation.[3c,8] Chiral auxiliaries represent a valid alternative for the generation of chiral amines.[9] Among the various auxiliaries applied in asymmetric synthesis, chiral sulfoxides represent a powerful tool for the development



Scheme 1. (A) Examples of achiral amines of pharmaceutical interest (B) Previous examples of diastereoselective transformations: using metal-based reagents or photocatalyzed SET (C) Proposed asymmetric radical C(sp3)-C(sp3) coupling through a photocatalyzed HAT process.

[a] M. Leone, Dr. L. Neuville, Dr. G. Masson
Institut de Chimie des Substances Naturelles (ICSN) CNRS, Université Paris-Saclay, 1 Avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France
E-mail: luc.neuville@cnrs.fr
geraldine.masson@cnrs.fr
Homepage: https://eq51power.wixsite.com/power
[b] J. P. Milton, Prof. D. Gryko
Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
[c] Dr. L. Neuville, Dr. G. Masson
HitCat, Seqens-CNRS joint laboratory, Seqens'Lab, 8 Rue de Rouen, 78440 Porcheville France

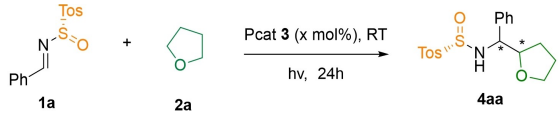
Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202400363

of a wide variety of enantioselective reactions.[10] The widespread use of chiral sulfoxides is mainly due to its significant asymmetric induction exhibited by the sulfinyl fragment, its high configurational stability and its easy and straightforward preparation. Several review articles have detailed the diverse applications of chiral sulfoxides in the field of organic synthesis,[9,11] such as for the preparation of α- and β-amino acids[12,13] and various substituted aziridines.[14] Nevertheless, most of these transformations require the use of expensive, highly reactive, and toxic metal-based compounds. Alemán and coworkers pioneered a potential substitute to circumvent these harsh conditions by introducing the first photocatalyzed asymmetric reaction utilizing chiral sulfinyl imines (Scheme 1B).[15] Following this example, several other reports have been developed exploiting the asymmetric induction and the electrophilic properties of sulfinyl imines in order to trap a wide variety of nucleophilic radicals generated under mild catalytic conditions.[16] However, in most cases the preparation of specific radical precursors such as redox active esters derived from *N*-hydroxyphthalimide (NHPI) as well as the use of stoichiometric amounts of reducing agent, need to be considered (Scheme 1B). To the best of our knowledge, only a limited number of procedures have documented the direct addition of alkyl radicals to chiral sulfinyl imines using non-pre-functionalized starting materials. In 2020, Martin and co-workers developed a photocatalytic, stereoselective alkylation of chiral *N*-sulfinyl imines with adamantane through Hydrogen Atom Transfer (HAT).[17] Although the resulting amines were generally isolated with high diastereoselectivity, the report was restricted to only adamantyl-containing substrates. One year later, Kärkäs and co-workers described a photodecarboxylative C–H alkylation of chiral glyoxylate-derived *N*-sulfinyl imines using carboxylic acids, providing access to various enantioenriched unnatural α-amino acids.[18] Very recently, Maruoka and coworkers disclosed an efficient asymmetric C–H aminoalkylation of chiral *N*-sulfinyl imines derived from glyoxylate employing an indirect HAT process with primary and secondary alcohol.[19] In spite of these notable achievements, it is noteworthy that the majority of these alkylations are primarily restricted to activated imines or to selected alkylating sources. Hence, the development of general photocatalytic asymmetric alkylations of chiral *N*-sulfinyl imines using non-prefunctionalized radical precursors is of significant interest. Pursuing our exploration in asymmetric photocatalyzed transformations,[20] we, herein, present an effective catalytic alkylation reaction of chiral imines with various non-activated alkylating substrates. This methodology yields a diverse array of chiral amines, encompassing both natural and unnatural amino acids,[21,22] α-amino alcohols,[23] amino aldehydes,[24] and 1,2-diamines.[25]

Based on our work involving photocatalyzed HAT processes[20e] and inspired by the methodologies developed by the groups of Alemàn[15] and Kärkäs,[18] we became interested in establishing a method for a diastereoselective radical addition to chiral *N*-sulfinyl imines. Our goal was to employ effective and readily available photocatalysts, utilizing common non-activated radical sources.[26] To develop this approach, we initiated our study by selecting THF (**2a**), serving both as a solvent and as a radical source, owing to the low C–H bond dissociation energy (BDE) in the α-position relative to the oxygen atom (92 kcal/mol).[27] We began by screening various photocatalysts for the alkylation of *N*-sulfinyl imines **1a** (Table 1). Several benzophenone (BP) derivatives were found to catalyze the desired transformation when exposed to the appropriate light source, offering good yields of adduct **4aa** in moderate diastereoselectivity (entry 1–3). Other organocatalysts known to perform direct HAT, such as thioxanthone, anthraquinone, and eosin Y,[26] did not afford the desired product (entry 4–6). In 2019, Dilman and coworkers reported TBADT as an efficient photocatalyst for promoting the radical alkylation of *N*-tosylimines.[28,29] Guided by their findings, the performance of such catalyst was subsequently evaluated. To our delight, TBADT exhibited superior results, achieving a higher yield and diastereoselectivity with a catalytic loading 10 times lower than that required by the aforementioned organo-photocatalysts (entry 7). It should be noted that the addition of a co-solvent was important for a successful transformation. Among the co-solvents dry acetonitrile played a key role in solubilizing the TBADT,[30] and was optimal compared to other tested solvents.

Optimization was pursued by examining the effect of various chiral *N*-sulfinyl auxiliaries. To address the diastereoselectivity issue, THF was replaced by 1,3,5-trioxane (**2b**) as the radical precursor. The reaction with **1a** resulted in the formation of product **4ab** with promising diastereoselectivity (Table 2, entry 1). The *tert*-butyl substituted *N*-sulfinyl imine **1b** showed poor performance (Table 2, entry 2), giving a low yield, moderate diastereoselectivity, and some side products. This unsatisfactory result may be attributed to partial cleavage of the *tert*-butyl-sulfur bond, initiated by radical migration or via fragmentation of a transient aminyl or alkylsulfinamide radical

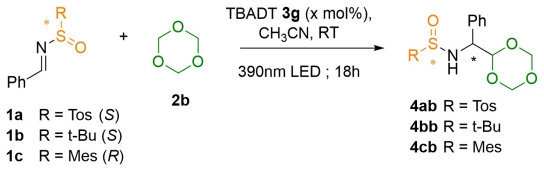
Table 1. Survey of Reaction Conditions with THF **2a** as Alkyl Radical.[a]



Entry	3 (x mol %)	hv (nm)	dr[b]	4aa Yield [%][c]
1	**3a**, BP (50 mol%)	390	6.4:3:3: 1	73
2	**3b**, DmBP (50 mol%)	390	6.4:3:3:1	50
3	**3c**, BcBP (50 mol%)	390	6.5:3:3:1	80
4	**3d**, AQ (50 mol%)	390	–	
5	**3e**, TX (50 mol%)	405	–	
6	**3f**, Eosin Y (50 mol%)	456	–	
7[d]	**3g**, TBADT (5 mol%)	390	6.9:3.1:3:1	80

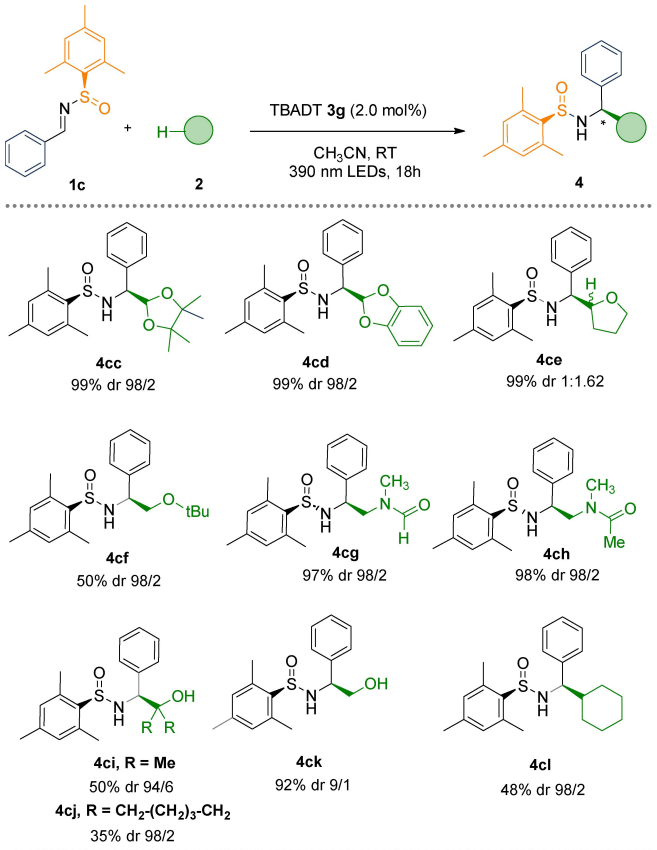
[a] Reaction conditions: **1a** (0.1 mmol), and **3** (5 to 50 mol%) in 1.0 mL of THF under argon, for 24 h. [b] dr Determined by 1H NMR analysis of the crude mixture. [c] ^{1}H NMR yield of **4** determined using 1,1,2-trichloroethene as internal standard. [d] Reaction was performed with an addition of CH_3CN 0.05 M. BP: Benzophenone; DmBP: 4,4′-Dimethoxybenzophenone DcBP: 4,4′-Dichlorobenzophenone AQ: Anthraquinone TX: Thioxanthone.

Table 2. Survey of Reaction Conditions of Photocatalyzed Alkylation of N-Sulfinyl Imines [a].[a]



Entry	1 (R*)	3g (x mol%)	hv (nm)	dr[b]	4 Yield [%][c]
1	**1a** (Tos)	5 mol%	390	6:1	**4ab**, 54
2	**1b** (*t*-Bu)	5 mol%	390	1.7:1	**4bb**, 38
3	**1c** (Mes)	5 mol%	390	>98:2	**4cb**, 70
4	**1c** (Mes)	2 mol%	390	>98:2	**4cb**, 75 (70)[d]
5	**1c** (Mes)	1 mol%	405	>98:2	**4cb**, 63
6[e]	**1c** (Mes)	2 mol%	390	>98:2	**4cb**, 50
7	**1c** (Mes)	–	390	–	–
8[f]	**1c** (Mes)	2 mol%	–	–	–
9[g]	**1c** (Mes)				

[a] Reaction conditions: **1** (0.1 mmol), and **3** (5 to 1 mol%) in CH_3CN 0.1 M, under argon, for 18 h. [b] dr Determined by ^1H NMR analysis of the crude mixture. [c] ^1H NMR yield of **4** determined using 1,1,2-trichloroethene as internal standard. [d] Yields refer to chromatographically pure product **4**. [e] in DCM. [f] No light irradiation. [g] Under air.

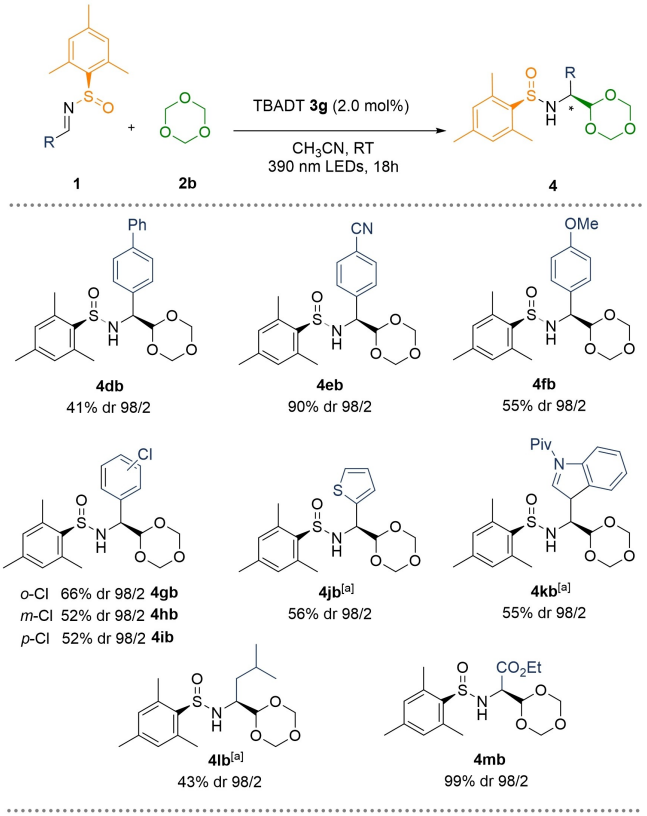


Scheme 2. Scope for the HAT radical addition to N-sulfinyl imine **1c**. Reaction conditions: **1** (0.1 mmol), **2** (1.0 mmol, 10 equiv.), and **3g** (2 mol%) in 1.0 mL of CH_3CN under argon and 390 nm irradiated with Kessil 40 W blue LED for 18 h. Yields are based on isolated pure product after column chromatography. dr Determined by ^1H NMR analysis of the crude mixture.

intermediate.[31,32] Pleasingly, optimal results were achieved with the mesityl-substituted *N*-sulfinyl imine **1c**,[15–19] providing **4cb** as a single diastereomer (entry 3). The catalyst loading was also investigated, affording comparable results with 1 mol% TBADT (entry 5). Acetonitrile was identified as the optimal solvent (entry 4 vs 6). Control experiments showed that the reaction is fully inhibited in the presence of air or in the absence of light or photocatalyst (entries 7–9).

With these results, we proceeded to investigate the asymmetric radical addition of diverse non-prefunctionalized radical precursors to imine **1c** (Scheme 2). We decided to focus our attention on the use of a cheap source of alkyl radicals, such as commonly used solvents or other easily accessible compounds to explore the scope. In analogy to 1,3,5-trioxane (**2b**), 4,4,5,5-tetramethyl-1,3-dioxolane (**2c**) and benzo[*d*][1,3]dioxole (**2d**) performed well in the reaction delivering corresponding adducts **4cc** and **4cd** in nearly quantitative yield and in near perfect diastereoselectivity (Scheme 2). The reaction involving THF and sulfonyl imine **1c** delivered product **4ce** with an enhanced yield (nearly quantitative) and improved diastereoselectivity compared to compound **4aa** obtained from imine **1a**. Indeed, among the four possible diastereoisomers, only two of them could be detected with a ratio of 1.6:1 highlighting the poor β-diastereoselectivity but a nearly perfect α-diastereoselectivity. Interestingly, acyclic methyl *tert*-butyl ether could also be used, albeit delivering the corresponding adduct **4cf** in a comparatively reduced but still valuable yield. We were pleased to find that DMF and DMA were suitable partners, providing direct access to 1,2-diamines **4cg** and **4ch** that are prevalent in numerous pharmaceutical compounds.[25] Most notably, the HAT process worked well with unprotected secondary alcohols such as isopropanol or cyclohexanol under optimized conditions, allowing the synthesis of 1,2-amino-alcohols **4ci** and **4cj** with excellent diastereoselectivity, albeit in moderate yields. Methanol could also be used in the reaction delivering corresponding adduct **4ck** in excellent yield (92%) albeit with slightly reduce dr (9:1). In addition, the fully aliphatic radical precursor cyclohexane participated successfully in the reaction to deliver **4cl** in a satisfactory yield and with again excellent diastereoselectivity.[33]

Subsequently, we evaluated a diverse range of substituted *N*-2,4,6-trimethylbenzene sulfinyl imines as radical acceptors using 1,3,5-trioxane (**2b**) as the radical donor (Scheme 3). The procedure tolerated various substituted aryl imines and consistently furnished the corresponding adduct with high diastereoselectivity. While slightly diminished yields (**4db** and **4fb**) were noted when using less reactive electron-rich imines, aryl imines bearing a strong electron-withdrawing group were particularly effective as seen with the synthesis of compound **4eb** isolated in 90% yield with 98:2 dr. The (*ortho, meta* and *para*)-substituted aromatic imines worked well leading to desired products **4gb**–**4ib** with similar yield and diastereoselectivity, thus indicating that the reaction is not sensitive to

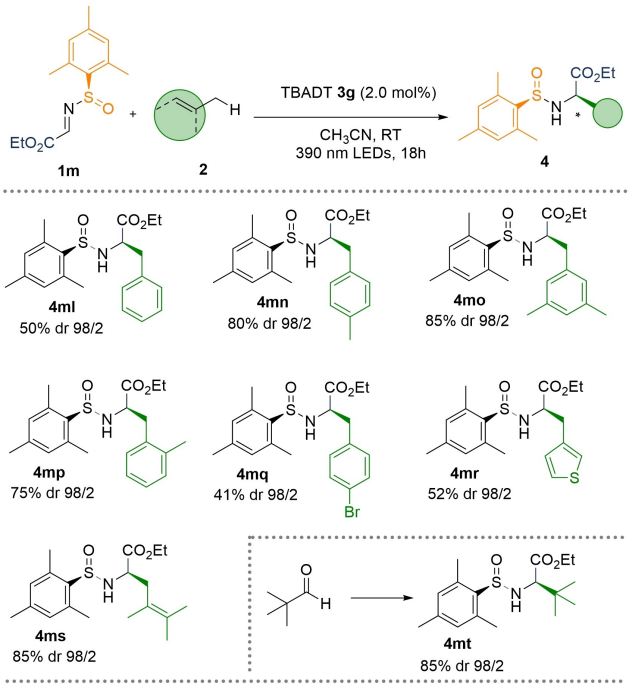


Scheme 3. Scope for the HAT radical addition of 1,3,5-trioxane (**2b**) to **1**. Reaction conditions: **1** (0.1 mmol), **2** (1.0 mmol, 10 equiv.), and **3g** (2 mol%) in 1.0 mL of CH_3CN under argon and 390 nm irradiated with Kessil 40 W blue LED for 18 h. Yields are based on isolated pure product after column chromatography. dr Determined by ^1H NMR analysis of the crude mixture. [a] Addition of Na_2CO_3 (0.1 mmol, 1 equiv.).

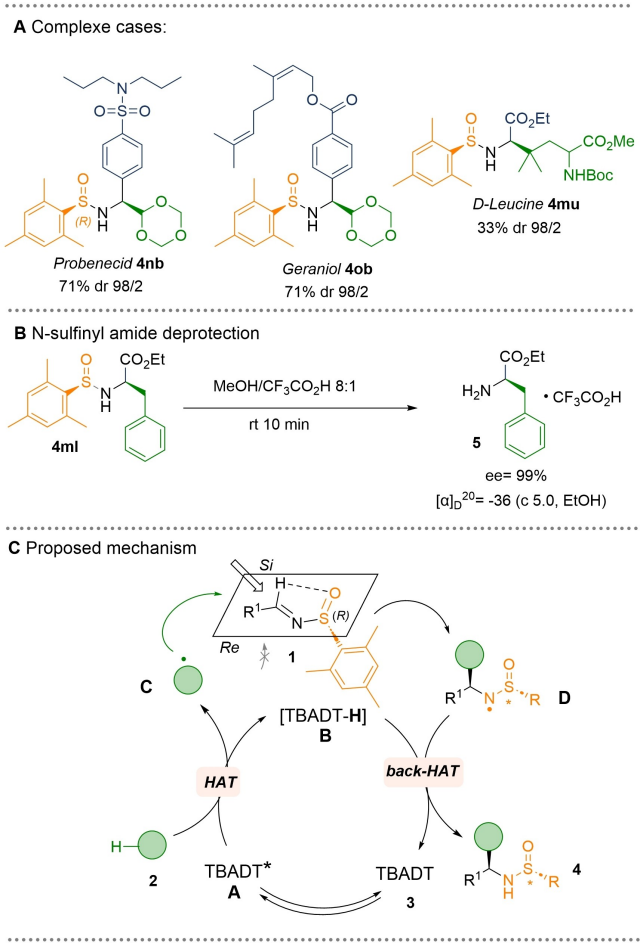
steric hindrance. The scope can be extended to different hetero-aromatic compounds, yielding the desired products in good yields (**4jb**; **4kb**). Ethyl glyoxylate-derived imine was also a suitable radical trap, leading to compound **4mb** in quantitative yield and with excellent diastereoselectivity. To our delight, reaction could be further extended to the use of challenging enolizable aliphatic imines like the one derived from isovaleraldehyde, resulting in the formation of enantioenriched desired product **4lb** in a satisfying yield of 43%.

In order to enlarge the scope, we next sought to explore more challenging alkyl radicals. Therefore, we explored the feasibility of conducting a diastereoselective addition of benzylic radicals generated by HAT of toluene.[27] However, reaction with *N*-sulfinyl imine **1c** and dry toluene under our standard conditions resulted in the recovery of the starting material. Lack of reactivity was probably not due to the absence of radical generation in the reaction given that the BDE of toluene (88 kcal/mol)[27] is lower than that of THF and that TBADT mediated benzylation of alkenes has precedent.[34] The unsuccessful result could however be attributed to the mild nucleophilicity of the benzyl radical. Consequently, we postulated that a more electrophilic imine might lead to a successful benzylation. Indeed, when the *N*-sulfinyl imine **1m** derived from ethyl glyoxylate was subjected to the standard conditions with toluene, it yielded product **4ml** in a 50% yield with high diastereoselectivity (Scheme 4). With this result we evaluated several other benzylic radical precursors. The use of *ortho* and *para*-xylene as well as mesitylene provided the desired enantioenriched products **4mp**, **4mn** and **4mo** in similar yields and dr. In contrast, electron-deficient toluene derivatives, such as *p*-bromotoluene, was less successful, affording only 41% yield of **4mq** albeit with no erosion of diastereoselectivity. To our delight, 3-methylthiophene was also competent, affording **4mr** in moderate yield and high dr (98:2). Tetramethylethylene turned out to be a good HAT substrate to afford the desired enantioenriched allylated product **4ms** in 88%. Finally, the tertiary alkyl radical, originating from the decarbonylation of the acyl radical produced from pivaldehyde, underwent an efficient reaction, leading to the formation of the enantioenriched protected *tert*-leucine compound **4mt**.

To further illustrate the practicality of this protocol, we conducted a series of late-stage functionalizations on imines derived from complex natural products and bioactive compounds (Scheme 5A). Pleasingly, the alkylation of imines derived from Probenecid[35] and geraniol[36] was successfully accomplished, yielding **4nb**, **4ob** in good yields. Moreover, we could selectively add the radical generated at the γ-position of *D*-leucine to **1m** resulting in the desired product **4mu** with a yield of 33%. Next, the reaction was scaled up on a 1 mmol scale under our optimized conditions and the product **4mb** was formed in 85% yield, validating the practicability of this protocol. Furthermore, the cleavage of the *N*-sulfinyl amide group of **4ml** under mild acidic conditions furnished *D*-phenyl-



Scheme 4. Scope for the HAT radical addition to N-sulfinyl imine **1m**. Reaction conditions: **1** (0.1 mmol), **2** (1.0 mmol, 10 equiv.), and **3g** (2 mol%) in 1.0 mL of CH_3CN under argon and 390 nm irradiated with Kessil 40 W blue LED for 18 h. Yields are based on isolated pure product after column chromatography. dr Determined by ^1H NMR analysis of the crude mixture.



Scheme 5. (**A**) Functionalization of complex molecules (**B**) Chiral auxiliary cleavage and determination of the absolute configuration of **5**. (**C**) Proposed mechanism for the photocatalyzed HAT transformation.

alanine amino ester **4** with 99% enantioselectivity in nearly quantitative yields (Scheme 5B). The absolute configuration was determined as (*R*) by comparing it with an independently synthesized authentic sample of compound **4**, thereby confirming the configuration. (For more details see Supporting Information).

Based on selected experiments and literature precedents,[20e,28,29] a mechanism for the developed transformation can be proposed (Scheme 5C). As shown in Table 2, light is mandatory, and an ON-OFF experiment was performed providing no evidence of a radical chain propagation mechanism in the reaction (see Supporting Information). As such, upon visible light irradiation of TBADT, a long-lived excited state, TBADT* (**A**), can form; this species subsequently abstracts a hydrogen atom from the respective alkyl compound (**2**) delivering an alkyl radical (**C**). Controlled by the chiral auxiliary, this radical undergoes a diastereoselective addition to N-sulfinyl imine leading to the N-centered radical (**D**). Previous studies, as well as, computational studies[18,30] has established that, because of the hydrogen bond between the sulfinyl-oxygen and the hydrogen of the imine, N-sulfinyl imine **1** adopts a well-defined *s-cis* conformation in which the mesityl group of (*S*)-2,4,6-trimethylbenzenesulfinamide shields the Re-face. Therefore, addition of the radical (**C**) is taking place from the less hindered face (Si-face) to form the enantioenriched N-centered radical (**D**). Finally, this radical species undergoes a back hydrogen atom transfer (BHAT) with the protonated TBADT–H (**B**) closing the catalytic cycle and generating the final product **4**.

In summary, we have established a practical and sustainable alkylative method for chiral *N*-sulfinyl imines, employing visible light and TBADT as the photocatalyst. The process exhibits excellent diastereoselectivity, delivering a range of chiral amine products, covering natural and unnatural amino acids, α-amino alcohols, amino aldehydes, and 1,2-diamines. Notably, its effectiveness with challenging substrates, including toluene-derived radicals, highlights its versatility. The late-stage functionalization of imines derived from complex compounds further emphasizes the practicality of this approach.

Experimental Section

General procedure for the HAT radical addition to N-sulfinyl imine: In a flame dried vial tube equipped with a stirring bar and a septum were placed **1** (0.1 mmol), the TBADT **3 g** (0.002 mmol, 2 mol%) and, if solid, the radical precursor **2** (1 mmol 10 equiv.). The solids were evacuated and back-filled with Argon three times, followed by addition of dry solvent and, if liquid, the radical precursor. Argon was bubbled for 1 min in the reaction tube through a long needle. Thereafter, the reaction mixture was placed ca. 5 cm from the light source (390 nm 40 W Kessil LED) and stirred with a fan cooling or air flow system. The reaction was monitored by TLC. Upon completion, the crude mixture is concentrated by rotary evaporator and dried under vacuo. Dr was determined by ^{1}H NMR from the crude mixture. The crude is concentrated and purified by column chromatography (silica gel PET/EtOAc).

Acknowledgements

We thank ICSN and CNRS for financial support; M. L. and J. P. M. received funding from the European Union H2020 research and innovation program under the Marie S. Curie Grant Agreement No. 956324 (MSCA ITN: Photoreact)

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Photocatalysis · HAT · Decatungstate · Sulfinyl imine · chiral auxiliary · diastereoselectivity

[1] S. Zhang, J. Del Pozo, F. Romiti, Y. Mu, S. Torker, A. H. Hoveyda, *Science* **2019**, *364*, 45–51.
[2] Q. Yin, Y. Shi, J. Wang, X. Zhang, *Chem. Soc. Rev.* **2020**, *49*, 6141–6153.
[3] a) C. Xie, Q. Guo, X. Wu, W. Ye, G. Hou, *J. Org. Chem.* **2023**, *88*, 15726–15738; b) A. Umanzor, N. A. Garcia, C. C. Roberts, *ACS Org. Inorg. Au* **2024**, *4* (1), 97–101; c) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383–394.
[4] R. Kuhn, F. Erni, T. Bereuter, J. Haeusler, *Anal. Chem.* **1992**, *64*, 2815–2820.

[5] A. Trowbridge, S. M. Walton, M. J. Gaunt, *Chem. Rev.* **2020**, *120*, 2613–2692.
[6] J. L. Tucker, *Org. Process Res. Dev.* **2006**, *10*, 315–319.
[7] G. Grogan, *Curr. Opin. Chem. Biol.* **2018**, *43*, 15–22.
[8] a) G. Bernadat, G. Masson, *Synlett* **2014**, *25*, 2842–2867; b) J. Merad, C. Lalli, G. Bernadat, J. Maury, G. Masson, *Chem. Eur. J.* **2018**, *24*, 3925–3943; c) D. Bouchet, T. Varlet, G. Masson, *Acc. Chem. Res.* **2022**, *55*, 3265–3283.
[9] G. Diaz-Muñoz, I. L. Miranda, S. K. Sartori, D. C. De Rezende, M. Alves Nogueira Diaz, *Chirality* **2019**, *31*, 776–812.
[10] Selected references a) J. Han, V. A. Soloshonok, K. D. Klika, J. Drabowicz, A. Wzorek, *Chem. Soc. Rev.* **2018**, *47*, 1307–1350; b) I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651–3706; c) E. Wojaczyńska, J. Wojaczyński, *Chem. Rev.* **2020**, *120*, 4578–4611; d) D. A. Cogan, G. Liu, J. Ellman, *Tetrahedron* **1999**, *55*, 8883–8904; e) T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 12–13; f) J. W. Evans, J. A. Ellman, *J. Org. Chem.* **2003**, *68*, 9948–9957; g) T. Kochi, T. P. Tang, J. A. Ellman, *J. Am. Chem. Soc.* **2003**, *125*, 11276–11282.
[11] a) E. Wojaczyńska, J. Wojaczyński, *Chem. Rev.* **2010**, *110*, 4303–4356; b) S. Otocka, M. Kwiatkowska, L. Madalińska, P. Kiełbasiński, *Chem. Rev.* **2017**, *117*, 4147–4181.
[12] a) T. Guo, R. Song, B.-H. Yuan, X.-Y. Chen, X.-W. Sun, G.-Q. Lin, *Chem. Commun.* **2013**, *49*, 5402; b) F. A. Davis, P. S. Portonovo, R. E. Reddy, Y. Chiu, *J. Org. Chem.* **1996**, *61*, 440–441.
[13] F. A. Davis, J. M. Szewczyk, R. E. Reddy, *J. Org. Chem.* **1996**, *61*, 2222–2225.
[14] a) F. A. Davis, H. Liu, P. Zhou, T. Fang, G. V. Reddy, Y. Zhang, *J. Org. Chem.* **1999**, *64*, 7559–7567; b) F. A. Davis, S. H. Lee, H. Xu, *J. Org. Chem.* **2004**, *69*, 3774–3781; c) F. A. Davis, W. McCoull, D. D. Titus, *Org. Lett.* **1999**, *1*, 1053–1055.
[15] A. F. Garrido-Castro, H. Choubane, M. Daaou, M. C. Maestro, J. Alemán, *Chem. Commun.* **2017**, *53*, 7764–7767.
[16] a) S. Ni, A. F. Garrido-Castro, R. R. Merchant, J. N. de Gruyter, D. C. Schmitt, J. J. Mousseau, G. M. Gallego, S. Yang, M. R. Collins, J. X. Qiao, K. Yeung, D. R. Langley, M. A. Poss, P. M. Scola, T. Qin, P. S. Baran, *Angew. Chem. Int. Ed.* **2018**, *57*, 14560–14565; b) K. M. Baker, A. Tallon, R. P. Loach, O. P. Bercher, M. A. Perry, M. P. Watson, *Org. Lett.* **2021**, *23*, 7735–7739; c) Z. Zhou, Z. S. Sales, D. J. Pippel, M. Qian, C. L. Martin, *J. Org. Chem.* **2022**, *87*, 14948–14952; d) G. Levitre, S. Keess, G. A. Molander, *Org. Lett.* **2023**, *25*, 3864–3869.
[17] W. K. Weigel III, H. T. Dang, H.-B. Yang, D. B. C. Martin, *Chem. Commun.* **2020**, *56*, 9699–9702.
[18] A. Shatskiy, A. Axelsson, E. V. Stepanova, J.-Q. Liu, A. Z. Temerdashev, B. P. Kore, B. Blomkvist, J. M. Gardner, P. Dinér, M. D. Kärkäs, *Chem. Sci.* **2021**, *12*, 5430–5437.
[19] J. Caner, A. Matsumoto, K. Maruoka, *Chem. Sci.* **2023**, *14*, 13879–13884.
[20] a) L. Jarrige, A. Carboni, G. Dagousset, G. Levitre, E. Magnier, G. Masson, *Org. Lett.* **2016**, *18*, 2906–2909; b) G. Levitre, C. Audubert, A. Dumoulin, N. Goual, P. Retailleau, X. Moreau, G. Masson, *ChemCatChem* **2019**, *11*, 5723–5727; c) J. Lyu, A. Claraz, M. R. Vitale, C. Allain, G. Masson, *J. Org. Chem.* **2020**, *85*, 12843–12855; d) J. Lyu, M. Leone, A. Claraz, C. Allain, L. Neuville, G. Masson, *RSC Adv.* **2021**, *11*, 36663–36669; e) T. Varlet, D. Bouchet, E. Van Elslande, G. Masson, *Chem. Eur. J.* **2022**, *28*, e202201707.
[21] *Biochemistry of the Amino Acids*, *Elsevier*, ***1965***.
[22] L. Pollegioni, S. Servi, Eds., *Unnatural Amino Acids: Methods – Protocols*, *Humana Press*, Totowa, NJ, **2012**.
[23] a) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–876; b) D. Ghislieri, N. J. Turner, *Top. Catal.* **2014**, *57*, 284–300; c) O. K. Karjalainen, A. M. P. Koskinen, *Org. Biomol. Chem.* **2012**, *10*, 4311; d) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824; e) T. Sehl, Z. Maugeri, D. Rother, *J. Mol. Catal. B* **2015**, *114*, 65–71; f) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576.
[24] a) J. F. Hooper, S. Seo, F. R. Truscott, J. D. Neuhaus, M. C. Willis, *J. Am. Chem. Soc.* **2016**, *138*, 1630–1634; b) D. Gryko, J. Chałko, J. Jurczak, *Chirality* **2003**, *15*, 514–541; c) M. T. Reetz, *Chem. Rev.* **1999**, *99*, 1121–1162; d) R. Hili, S. Baktharaman, A. K. Yudin, *Eur. J. Org. Chem.* **2008**, 5201–5213.
[25] a) G.-Q. Lin, M.-H. Xu, Y.-W. Zhong, X.-W. Sun, *Acc. Chem. Res.* **2008**, *41*, 831–840; b) D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627; c) S. R. S. Saibabu Kotti, C. Timmons, G. Li, *Chem. Biol. Drug Des.* **2006**, *67*, 101–114.
[26] L. Capaldo, D. Ravelli, M. Fagnoni, *Chem. Rev.* **2022**, *122*, 1875–1924.
[27] a) G. W. Gribble, *Indole Ring Synthesis: From Natural Products to Drug* Y.-R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, **2007**.
[28] V. I. Supranovich, V. V. Levin, A. D. Dilman, *Org. Lett.* **2019**, *21*, 4271–4274.
[29] For selected reviews on decatungstate anion-photocatalysis, see: a) C. L. Hill, *Synlett* **1995**, *1995*, 127–132; b) M. D. Tzirakis, I. N. Lykakis, M. Orfanopoulos, *Chem. Soc. Rev.* **2009**, *38*, 260–2621; c) D. Ravelli, S. Protti, M. Fagnoni, *Acc. Chem. Res.* **2016**, *49*, 2232–2242; d) D. Ravelli, M. Fagnoni, T. Fukuyama, T. Nishikawa, I. Ryu, *ACS Catal.* **2018**, *8*, 701–713; e) K. Suzuki, N. Mizuno, K. Yamaguchi, *ACS Catal.* **2018**, *8*, 10809–10825; f) Y. Xiaoya, Y. Guoping, Y. Bing, *Chin. J. Org. Chem.* **2020**, *40*, 3620–3632; See also: g) R. F. Renneke, C. L. Hill, *J. Am. Chem. Soc.* **1986**, *108*, 3528–3529; h) R. F. Renneke, C. L. Hill, *Angew. Chem. Int. Ed.* **1988**, *27*, 1526–1527; i) V. De Waele, O. Poizat, M. Fagnoni, A. Bagno, D. Ravelli, *ACS Catal.* **2016**, *6*, 7174–7182; For a selection of recent examples of decatungstate-photocatalyzed reactions, see: j) A. Jorea, C. Raviola, M. Giustiniano, D. Ravelli, *ChemCatChem* **2023**, *15*, e202300042. k) R. Canton-Vitoria, M. Quintana, N. G. Malliaros, N. Tagmatarchis, *Adv. Mater. Interfaces* **2023**, *10*, 2201575; l) K. El-Chami, R. Madsen, *ChemCatChem* **2023**, *15*, e202301143; m) D. Kolb, A. A. Almasalma, M. Morgenstern, L. Ganser, I. Weidacher, B. König, *ChemPhotoChem* **2023**, *7*, e202300167; n) W.-H. Lu, D. Yang, G.-Q. Wang, T. Wang, Y.-X. Zhou, L.-H. Jing, *Org. Biomol. Chem.* **2023**, *21*, 2822–2827; o) F. Raymenants, T. M. Masson, J. Sanjosé-Orduna, T. Noël, *Angew. Chem. Int. Ed.* **2023**, *62*, e202308563; p) R. Wang, C. Wang, *Chem. Sci.* **2023**, *14*, 6449–6456; q) A. Cruise, M. Baumann, *ChemCatChem* **2023**, *15*, e202201328; r) P. S. Gowda, D. S. Sharada, G. Satyanarayana, *Chem. Commun.* **2023**, *59*, 9094–9097; s) A. Pulcinella, S. Bonciolini, F. Lukas, A. Sorato, T. Noël, *Angew. Chem. Int. Ed.* **2023**, *62*, e202215374; t) S. Bonciolini, A. Pulcinella, M. Leone, D. Schiroli, A. L. Ruiz, A. Sorato, M. Dubois, R. Gopalakrishnan, G. Masson, N. Della Ca, S. Protti, M. Fagnoni, E. Zysman-Colman, M. Johansson, T. Noël, *Nat. Commun.* **2024**, *15*, 1509, doi: 10.1038/s41467-024-45804-.
[30] T. Yamase, N. Takabayashi, M. Kaji, *J. Chem. Soc. Dalton Trans.* **1984**, 793.
[31] J. A. Fernández-Salas, M. C. Maestro, M. M. Rodríguez-Fernández, J. L. García-Ruano, I. Alonso, *Org. Lett.* **2013**, *15*, 1658–1661.
[32] a) W. Huang, J.-L. Ye, W. Zheng, H.-Q. Dong, B.-G. Wei, *J. Org. Chem.* **2013**, *78*, 11229–11237; b) M. Oliva, G. A. Coppola, E. V. Van Der Eycken, U. K. Sharma, *Adv. Synth. Catal.* .**2021**, *363*, 1810–1834; c) F. Xue, F. Wang, J. Liu, J. Di, Q. Liao, H. Lu, M. Zhu, L. He, H. He, D. Zhang, H. Song, X. Liu, Y. Qin, *Angew. Chem. Int. Ed.* **2018**, *57*, 6667–6671.
[33] Unsuccessful reagents can be found in the SI.
[34] a) S. Montanaro, D. Ravelli, D. Merli, M. Fagnoni, A. Albini, *Org. Lett.* **2012**, *14*, 4218–4221; b) X. Fan, J. Rong, H. Wu, Q. Zhou, H. Deng, J. D. Tan, C. Xue, L. Wu, H. Tao, J. Wu, *Angew. Chem. Int. Ed.* **2018**, *57*, 8514–8518.
[35] R. M. Mason, *Ann. Rheum. Dis.* **1954**, *13*, 120–130.
[36] W. Chen, A. M. Viljoen, *S. Afr. J. Bot.* **2010**, *76*, 643–651.

Manuscript received: January 27, 2024
Accepted manuscript online: February 20, 2024
Version of record online: March 21, 2024

9. Supporting Information for the Original Publications

Note: NMR spectra are available online from the respective articles.

Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information for

Photochemical Cyclopropanation in Aqueous Micellar Media – Experimental and Theoretical Studies

Joseph P. Milton,[a] Adam Milanowski,[a,b] Martin Peter Andersson[c]* and Dorota Gryko[a]*

[a]Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

[b]Department of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland

[c]Center for Intergrative Petroleum Research, King Fahd University of Petroleum and Minerals, Dhahran 31261, Kingdom of Saudi Arabia

correspondence: dorota.gryko@icho.edu.pl

for correspondence regarding computational calculations: martin.andersson@kfupm.edu.sa

Table of Contents

1. General Information 4

2. Optimisation Details 5

2.1. Surfactant (by GC) 5

2.2. Surfactant (by NMR)[a] 5

2.3. Concentration of DTAC[a] 6

2.4. Co-solvent[a] 6

2.5. Light Source[a] 6

2.6. Ratio of Reactants[a] 7

3. Experiments with the Concentration of DTAC 8

4. General Procedures 9

4.1. Synthesis of Diazo Compounds - General Procedure A 9

4.2. Synthesis of Hydrazones - General Procedure B 9

4.3. General Procedure C - Synthesis of Cyclopropanes from Diazo Compounds 9

4.4. General Procedure D - Synthesis of Cyclopropanes from Hydrazones 10

5. Scope and Characterisation of Products 11

5.1. Diazo Compounds 11

5.2. Hydrazone Compounds 15

5.3. Cyclopropanes 19

6. Computational Methods and Additional Results 32

7. References 33

8. NMR Spectra 34

hexyl-2-diazo-2-phenylacetate (**1c**) 34

nonyl 2-diazo-2-phenylacetate (**1d**) 35

dodecyl 2-diazo-2-phenylacetate (**1e**) 36

2-methoxyethyl 2-diazo-2-phenylacetate (**1f**) 37

2-(2-(2-methoxyethoxy)ethoxy)ethyl 2-diazo-2-phenylacetate (**1g**) 38

methyl 2-diazo-2-(4-(dodecyloxy)phenyl)acetate (**1i**) 39

dodecyl 2-diazo-2-(4-methoxyphenyl)acetate (**1j**) 40

dodecyl 2-diazo-2-(4-nitrophenyl)acetate (**1k**) 41

dodecyl 2-(4-bromophenyl)-2-diazoacetate (**1l**) 42

hexyl (E)-2-phenyl-2-(2-tosylhydrazineylidene)acetate (*E*-**4c**) 43

dodecyl (E)-2-phenyl-2-(2-tosylhydrazineylidene)acetate (*E*-**4d**) 44

ethyl (E)-2-(4-fluorophenyl)-2-(2-tosylhydrazineylidene)acetate (*E*-**4e**) 45

ethyl (Z)-2-(4-fluorophenyl)-2-(2-tosylhydrazineylidene)acetate (*Z*-**4e**) 47

ethyl-(Z)-2-(p-tolyl)-2-(2-tosylhydrazineylidene)acetate (*Z*-**4f**) 49

ethyl (E)-2-(4-methoxyphenyl)-2-(2-tosylhydrazineylidene)acetate (*E*-**4g**) 50
ethyl (Z)-2-(4-methoxyphenyl)-2-(2-tosylhydrazineylidene)acetate (*Z*-**4g**) 51
methyl-1,2-diphenylcyclopropane-1-carboxylate (**3a**) (dr 1:7) 52
ethyl 1,2-diphenylcyclopropane-1-carboxylate (**3b**) (dr 1:7) 53
hexyl 1,2-diphenylcyclopropane-1-carboxylate (**3c**) (dr 1:11) 54
nonyl 1,2-diphenylcyclopropane-1-carboxylate (**3d**) (dr 1:10) 55
dodecyl 1,2-diphenylcyclopropane-1-carboxylate (**3e**) (dr 1:11) 56
2-methoxyethyl 1,2-diphenylcyclopropane-1-carboxylate (**3f**) (dr 1:6) 57
2-(2-(2-methoxyethoxy)ethoxy)ethyl 1,2-diphenylcyclopropane-1-carboxylate (**3g**) (dr 1:14) 58
methyl 1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (**3h**) (dr 1:12) 59
methyl 1-(4-(dodecyloxy)phenyl)-2-phenylcyclopropane-1-carboxylate (**3i**) (dr 1:>20) 60
dodecyl 1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (**3j**) (dr 1:7) 61
dodecyl 1-(4-nitrophenyl)-2-phenylcyclopropane-1-carboxylate (**3k**) (dr 1:2) 62
dodecyl 1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate (**3l**) (dr 1:13) 63
dodecyl 1-phenyl-2-(p-tolyl)cyclopropane-1-carboxylate (**3m**) (dr 1:8) 64
dodecyl 1-phenyl-2-(m-tolyl)cyclopropane-1-carboxylate (**3n**) (dr 1:8) 65
dodecyl 1-phenyl-2-(o-tolyl)cyclopropane-1-carboxylate (**3o**) (dr 1:14) 66
dodecyl 2-(4-methoxyphenyl)-1-phenylcyclopropane-1-carboxylate (**3p**) (dr 1:5) 67
dodecyl 2-(4-nitrophenyl)-1-phenylcyclopropane-1-carboxylate (**3q**) (dr 1:3) 68
dodecyl 2-(4-bromophenyl)-1-phenylcyclopropane-1-carboxylate (**3r**) (dr 1:4) 69
dodecyl 2-(3-chlorophenyl)-1-phenylcyclopropane-1-carboxylate (**3t**) (dr 1:13) 70
dodecyl 2-(2-bromophenyl)-1-phenylcyclopropane-1-carboxylate (**3u**) (dr 1:4) 71
ethyl 2-phenyl-1-(p-tolyl)cyclopropane-1-carboxylate (**3v**) (dr 1:15) 72
ethyl 1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (**3w**) (dr 1:>20) 73
ethyl 1-(4-fluorophenyl)-2-phenylcyclopropane-1-carboxylate (**3x**) (dr 1:>20) 74

1. General Information

General - Reactions were monitored by gas chromatography (GC) or TLC on Merck silica gel (GF254, 0.20 mm thickness), visualising with UV-light. Column chromatography was performed using Merck silica gel 60 (230 - 400 mesh) or with commercially available cartridges with a CombiFlash. Unless otherwise noted, all reactions were performed without the exclusion of air or moisture. Unless otherwise stated, all photochemical reactions were performed in 10 mL test tubes with a B14 neck and sealed with a rubber septum.

Materials - All solvents and commercially available reagents were purchased as reagent grade and were used without further purification. Methyl 2-diazo-2-phenylacetate (**1a**),[1] ethyl 2-diazo-2-phenylacetate (**1b**),[1] methyl 2-diazo-2-(4-methoxyphenyl)acetate (**1h**),[1] methyl 2-(4-(dodecyloxy)phenyl)acetate,[2] methyl 2-phenyl-2-(2-tosylhydrazineylidene)acetate (**4a**),[3] ethyl 2-phenyl-2-(2-tosylhydrazineylidene)acetate (**4b**),[4] ethyl 2-(4-fluorophenyl)-2-oxoacetate,[5] ethyl 2-oxo-2-(p-tolyl)acetate,[5] ethyl 2-(4-methoxyphenyl)-2-oxoacetate[5] and 3-chlorostyrene[6] were synthesised according to the literature.

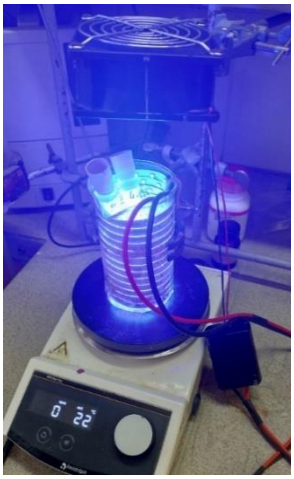
NMR - ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on a Bruker 400 MHz, Bruker 500 MHz, Varian 500 MHz or a Varian 600 MHz instrument. NMR chemical shifts are reported in ppm and referenced to the residual solvent peak of $CDCl_3$, 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR or to TMS as an internal standard. Multiplicities are indicated by singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), multiplet (m). Coupling constants (J) are reported in Hertz. All data analysis was performed using the MestReNova software package.

GC - Gas chromatography coupled with a flame ionisation detector (GC-FID) were performed on a Shimadzu GCMS-QP2010 SE with helium as the carrier gas and a Zebron ZB 5MSi column.

EA - Elemental analysis (C, H, N, F, S, Br) were performed on a PERKIN-ELMER 240 Elemental Analyzer

HRMS - High resolution mass spectrometry was recorded on a Waters SYNAPT G2-S HDMS using ESI with a TOF detector.

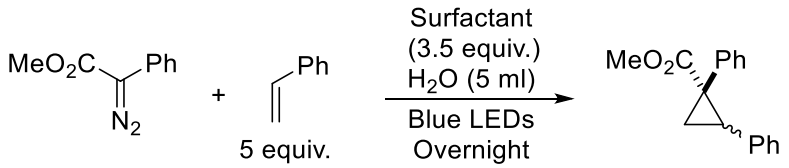
Setup for photoreactions



All photochemical reaction were performed in a beaker that contains blue LED tape (455 nm, 9 W) and are cooled with a fan.

2. Optimisation Details

2.1. Surfactant (by GC)



NOTE: The obtained yields are only approximate values and we found that more accurate values could be obtained when analysing the reactions by NMR. Nevertheless, we used GC as an initial screening for various surfactants.

Entry	Surfactant	Yield (%)[b]
1	DTAC	74
2	Aliquat 336	60
3	CTAB	50
4	CTAC	47
5	DOSS	44
6	DTAB	54
7	Potassium Laurate	54
8	None	>99
9	Tween 60	20
10	BZK	10
11	SDS	39
12	SLES	21
13	TPGS-750-M	16
14	Triton X-45	10
15	Triton X-100	12

[a]Reaction conditions: methyl 2-diazo-2-phenylacetate (0.1 mmol, 1 equiv.), styrene (5 equiv.), surfactant (3.5 equiv.), H_2O (5 mL), blue LEDs (9W, 455 nm), overnight (~20 hours); [b]Yield determined by GC with dodecane as internal standard.

2.2. Surfactant (by NMR)[a]

Entry	Surfactant	Yield (%)[b]
1	DTAC	62
2	Aliquat 336	26
3	CTAB	36
4	CTAC	53
5	DOSS	39
6	DTAB	56
7	Potassium Laurate	43
8	None	53

[a]Reaction conditions: methyl 2-diazo-2-phenylacetate (0.1 mmol, 1 equiv.), styrene (5 equiv.), surfactant (3.5 equiv.), H_2O (5 mL), blue LEDs (9W, 455 nm), overnight (~20 hours); [b]Yield determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

2.3. Concentration of DTAC[a]

Entry	DTAC Concentration (M)	Yield (%)[b]
1	0.14	44
2	0.07	62
3	0.0466	53
4	0.035	63

[a]Reaction conditions: methyl 2-diazo-2-phenylacetate (0.1 mmol, 1 equiv.), styrene (5 equiv.), DTAC (3.5 equiv.), H_2O (X mL), blue LEDs (9W, 455 nm), overnight (~20 hours); [b]Yield determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

2.4. Co-solvent[a]

Entry	Co-Solvent	Equivalents	Yield (%)[b]
1	None	None	62
2	Acetone	10	47
3		30	53
4		50	43
5	THF	10	48
6		30	47
7		50	31
8	MeCN	10	51
9		30	52
10		50	43
11	^{i}PrOH	10	44
12		30	52
13		50	49
14	^{n}BuOH	10	54
15		30	47
16		50	37

[a]Reaction conditions: methyl 2-diazo-2-phenylacetate (0.1 mmol, 1 equiv.), styrene (5 equiv.), DTAC (3.5 equiv.), H_2O (5 mL), Co-solvent (10 - 50 equiv.), blue LEDs (9W, 455 nm), overnight (~20 hours) [b]Yield determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

2.5. Light Source[a]

Entry	Light Source (Blue)	Yield (%)[b]
1	LED Tape, 9W, 455 nm, Beaker	62
2[c]	UOSlab 25% power	56
3[c]	UOSlab 50% power	46
4[c]	UOSlab75% power	38
5[c]	UOSlab 100% power	60
6[d]	Custom Photoreactor, 3 W	45
7[d]	Custom Photoreactor, 6 W	60
8[e]	Kessil Lamp, 440 nm, 100% power	46

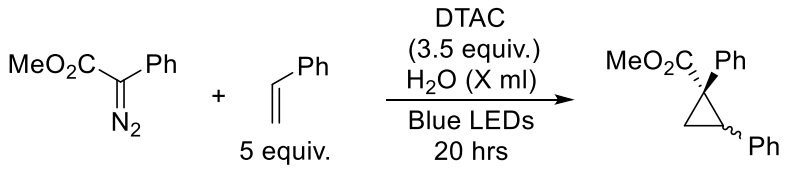
[a]Reaction conditions: methyl 2-diazo-2-phenylacetate (0.1 mmol, 1 equiv.), styrene (5 equiv.), DTAC (3.5 equiv.), H_2O (5 mL), blue LEDs, overnight (~20 hours); [b]Yield determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard; [c]See the supporting information in reference 7 to find more detailed information on the photoreactor; [d]See the supporting information in reference 8 to find more detailed information on the photoreactor; [e]Reaction time: 1 hour.

2.6. Ratio of Reactants[a]

Entry	Diazo:styrene	Yield (%)[b]
1	1:10	48
2	1:5	62
3	1:3	40
4	1:2	21
5	1:1.5	20
6	1:1	26
7	1.5:1	29
8	2:1	44
9	3:1	46
10	5:1	66
11	10:1	59

[a]Reaction conditions: methyl 2-diazo-2-phenylacetate (0.1 - 1.0 mmol), styrene (0.1 - 1.0 mmol), DTAC (3.5 equiv.), H_2O (5 mL), blue LEDs (9W, 455 nm), overnight (~20 hours); [b]Yield determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

3. Experiments with the Concentration of DTAC



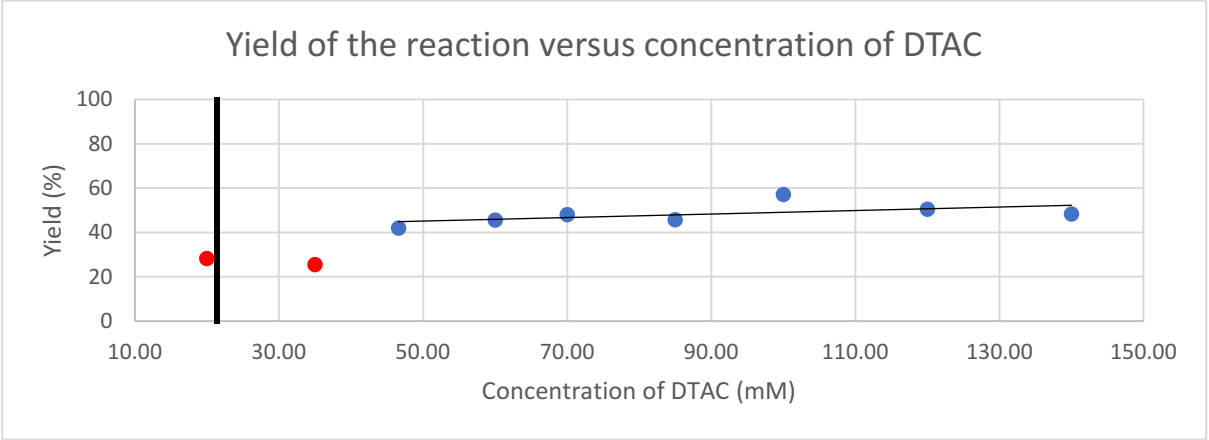
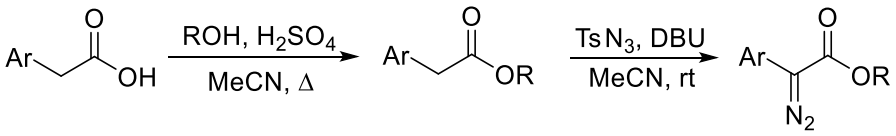


Figure S1: Yield of the reaction versus the concentration of DTAC. As the concentration of DTAC increases the yield gradually improves, particularly when surpassing 40 mM

All experiments used 0.1 mmol of diazo compound, 0.5 mmol of styrene and 0.35 mmol of DTAC with the concentration being modified by changing the amount of water. Yields were calculated by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. The solid black vertical line represents the CMC of DTAC at 25 °C (0.0213 mol/kg).[7] We can see an increase in the yield once the concentration surpasses 0.04 M; the average yield below 40 mM was 27% where as it was 48% when above 40 mM. This shows that once the reaction sufficiently surpasses the CMC of DTAC, the reaction can work more efficiently with a weak positive trend showing the higher concentration of DTAC, the higher the yield.

4. General Procedures

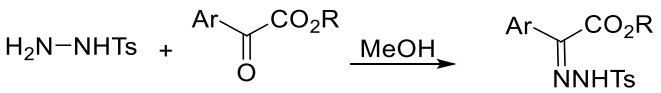
4.1. Synthesis of Diazo Compounds - General Procedure A



Esterification was performed by a modified procedure as reported by Claveau et al.[8] Diazo formation was performed analogously as reported by Keipour.[9]

The corresponding phenylacetic acid was dissolved in MeCN (0.5 M) followed by the addition of the corresponding alcohol (1.5 equiv.) and sulfuric acid (25 mol%), which was then refluxed overnight (~16 hours). The reaction was cooled down to room temperature and poured into a separating funnel. Water was added and the aqueous layer was extracted thrice with EtOAc. The organic layer was washed with water, saturated $NaHCO_3$, and brine successively, dried (Na_2SO_4) and filtered. EtOAc and residual MeCN was removed in vacuo. The corresponding crude mixture was then dissolved in MeCN (0.5 M) and DBU was added (1.5 equiv.). After 10 minutes, tosyl azide (1.5 equiv.) was then added, and the reaction was stirred until completed by TLC (~16 hours). MeCN was then removed in vacuo and the resultant crude was dissolved in EtOAc and washed with water once. The aqueous phase was extracted with EtOAc thrice and the combined organic layer was then washed twice with water, dried (Na_2SO_4), filtered and evaporated in vacuo. The crude mixture was subjected to column chromatography (SiO_2, 2-5% EtOAc in hexane) which, afforded the pure diazo compound typically as an orange compound.

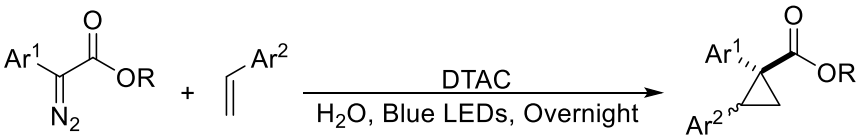
4.2. Synthesis of Hydrazones - General Procedure B



Hydrazones were synthesised according to the procedure by Li et al.[3]

p-Toluenesulfonyl hydrazide (1.1 equiv.) was dissolved in MeOH (1 M) followed by the corresponding β-keto ester dropwise/portionwise and stirred for 4 - 16 hours (sometimes the product will precipitate out of the solution indicating the end of the reaction). Upon completion, MeOH is removed in vacuo and the resultant solid was recrystallised in MeOH to afford the pure product. In cases where the product could not be recrystallised, it was purified by column chromatography (SiO_2, 10% EtOAc in hexane) instead.

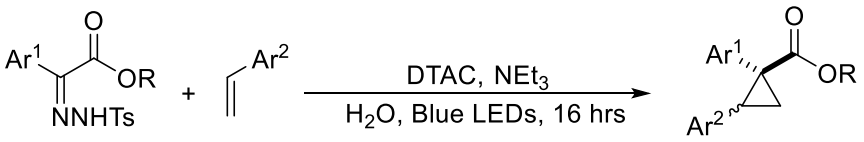
4.3. General Procedure C - Synthesis of Cyclopropanes from Diazo Compounds



A test tube was charged with DTAC (3.5 equiv.) followed by the addition of H_2O (0.07 M in respect to DTAC) and the solution was sonicated to ensure full dissolution. The diazo compound (0.1 mmol) was then added to the solution followed by the addition of olefin (5 equiv.) and the resulting mixture was then irradiated with blue LEDs overnight (16 - 24 hours). The reaction mixture was then diluted with brine and was extracted with EtOAc thrice. The combined organic phase was washed with water and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude mixture was then subjected to

column chromatography (SiO_2, 0 -> 5% EtOAc in hexane gradient) to afford the corresponding cyclopropanes as a mixture of *cis*- and *trans*-isomers.

4.4. General Procedure D - Synthesis of Cyclopropanes from Hydrazones

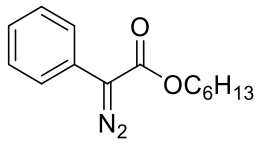


A test tube was charged with the corresponding hydrazone (0.1 mmol) and a 0.07 M solution of DTAC in water was added (5 mL per 0.1 mmol of hydrazone). Styrene (10 equiv.). and triethylamine (NEt_3, 1.5 equiv.) were sequentially added to the reaction vessel. The resulting mixture was stirred for 5 minutes without irradiation and then irradiated with blue LEDs for 16 hours. The reaction mixture was diluted with brine and extracted with EtOAc thrice. The combined organic phases were washed with water and brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude mixture was then subjected to column chromatography (SiO_2, 0 -> 5% EtOAc in hexane gradient) to afford the corresponding cyclopropanes as a mixture of *cis*- and *trans*-isomers.

5. Scope and Characterisation of Products

5.1. Diazo Compounds

hexyl 2-diazo-2-phenylacetate (**1c**)



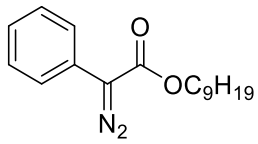
The title compound was synthesised according to General Procedure A from phenylacetic acid (5 mmol) in 24% yield (287 mg) as an orange oil (solidifies upon storage in a freezer).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.20 – 7.16 (m, 1H), 4.28 (t, *J* = 6.7 Hz, 2H), 1.71 (p, *J* = 6.9 Hz, 2H), 1.43 – 1.31 (m, 6H), 0.91 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.4, 129.1, 125.9, 125.8, 124.1, 65.3, 31.5, 28.9, 25.7, 22.7, 14.1.

The spectroscopic data is consistent with that previously reported in the literature.[10]

nonyl 2-diazo-2-phenylacetate (**1d**)



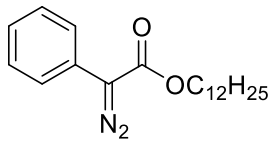
The title compound was synthesised according to General Procedure A from phenylacetic acid (5 mmol) in 34% yield (485 mg) as an orange oil (solidifies upon storage in a freezer).

^{1}H NMR ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 1.71 (p, *J* = 6.8 Hz, 2H), 1.42 – 1.28 (m, 12H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.4, 129.1, 125.9, 125.8, 124.1, 65.3, 32.0, 29.6, 29.37, 29.36, 29.0, 26.0, 22.8, 14.2.

HRMS (EI$^+$): Calc'd for $C_{17}H_{24}N_2O_2^+$: 288.1838, found: 288.1833.

dodecyl 2-diazo-2-phenylacetate (**1e**)



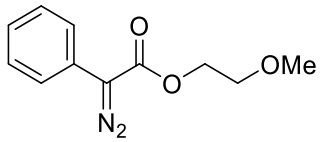
The title compound was synthesised according to General Procedure A from phenylacetic acid (20 mmol) in 59% yield (389 mg) as a pale orange solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 4.28 (t, *J* = 6.7 Hz, 2H), 1.71 (p, *J* = 6.8 Hz, 2H), 1.41 – 1.28 (m, 19H), 0.90 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.4, 129.0, 125.9, 125.8, 124.1, 65.3, 32.1, 29.78, 29.76, 29.69, 29.64, 29.5, 29.4, 28.9, 26.0, 22.8, 14.2.

The spectroscopic data is consistent with that previously reported in the literature.[10]

2-methoxyethyl 2-diazo-2-phenylacetate (**1f**)



The title compound was synthesised according to General Procedure A from phenylacetic acid (10 mmol) in 58% yield (1.27 g) as an orange solid.

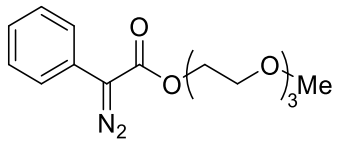
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 – 7.47 (m, 2H), 7.40 – 7.37 (m, 2H), 7.19 (tt, *J* = 7.4, 1.2 Hz, 1H), 4.43 – 4.42 (m, 2H), 3.68 – 3.66 (m, 2H), 3.41 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 165.2, 129.1, 126.0, 125.6, 124.2, 70.7, 64.0, 59.2.

HRMS (EI$^+$): Calc'd for $C_{11}H_{12}N_2O_3^+$: 220.0848; found: 220.0844.

The spectroscopic data is consistent with that previously reported in the literature.[11]

2-(2-(2-methoxyethoxy)ethoxy)ethyl 2-diazo-2-phenylacetate (**1g**)



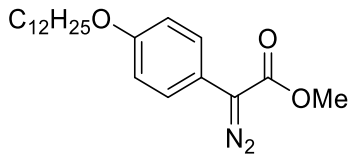
The title compound was synthesised according to General Procedure A from phenylacetic acid (5 mmol) in 50% yield (776 mg) as an orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 – 7.44 (m, 2H), 7.34 (dd, *J* = 8.6, 7.3 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 4.40 – 4.38 (m, 2H), 3.75 – 3.73 (m, 2H), 3.66 – 3.61 (m, 6H), 3.52 – 3.50 (m, 2H), 3.34 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.0, 128.9, 125.8, 125.4, 124.0, 71.9, 70.65, 70.61, 70.56, 69.2, 63.9, 59.0.

HRMS (EI$^+$): Calc'd for $C_{15}H_{20}N_2O_5^+$: 308.1372; found: 308.1370.

methyl 2-diazo-2-(4-(dodecyloxy)phenyl)acetate (**1i**)



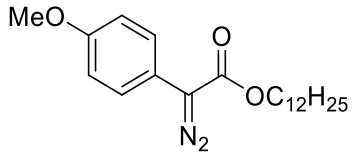
The title compound was synthesised according to General Procedure A from methyl 2-(4-(dodecyloxy)phenyl)acetate (1.0 mmol) in 17% yield (63 mg) as an orange solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.35 (m, 2H), 6.95 – 6.92 (m, 2H), 3.95 (t, *J* = 6.6 Hz, 2H), 3.85 (s, 3H), 1.77 (p, *J* = 6.7 Hz, 2H), 1.48 – 1.42 (m, 2H), 1.36 – 1.27 (m, 16H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.3, 157.9, 126.1, 116.7, 115.4, 68.3, 52.1, 32.1, 29.80, 29.77, 29.73, 29.71, 29.53, 29.49, 29.38, 26.2, 22.8, 14.2.

HRMS (EI$^+$): Calc'd for $C_{21}H_{32}N_2O_3^+$: 360.2413; found: 360.2395.

dodecyl 2-diazo-2-(4-methoxyphenyl)acetate (**1j**)



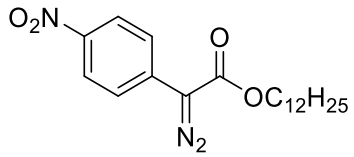
The title compound was synthesised according to General Procedure A from 4-methoxyphenylacetic acid (3 mmol) in 24% yield (262 mg) as an orange solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 – 7.37 (m, 2H), 6.95 – 6.93 (m, 2H), 4.25 (t, *J* = 6.7 Hz, 2H), 3.81 (s, 3H), 1.71 – 1.67 (m, 2H), 1.40 – 1.27 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0, 158.2, 126.1, 117.2, 114.7, 65.2, 55.5, 32.1, 29.78, 29.78, 29.70, 29.65, 29.5, 29.4, 29.0, 26.0, 22.8, 14.3.

HRMS (EI$^+$): Calc'd for $C_{21}H_{32}N_2O_3^+$: 360.2413; found: 360.2407.

dodecyl 2-diazo-2-(4-nitrophenyl)acetate (**1k**)



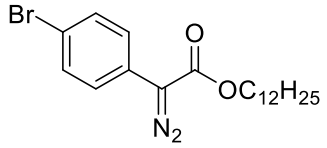
The title compound was synthesised according to General Procedure A from 4-nitrophenylacetic acid (5 mmol) in 30% yield (531 mg) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 – 8.21 (m, 2H), 7.67 – 7.65 (m, 2H), 4.30 (t, *J* = 6.7 Hz, 2H), 1.72 (p, *J* = 6.8 Hz, 2H), 1.40 – 1.26 (m, 19H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.9, 145.2, 134.2, 124.4, 123.3, 65.9, 32.1, 29.78, 29.77, 29.69, 29.63, 29.5, 29.3, 28.9, 26.0, 22.8, 14.2.

HRMS (EI$^+$): Calc'd for $C_{20}H_{29}N_3O_4^+$: 375.2158; found: 375.2166.

dodecyl 2-(4-bromophenyl)-2-diazoacetate (**1l**)



The title compound was synthesised according to General Procedure A from 4-bromophenylacetic acid (5 mmol) in 13% yield (273 mg) as an orange solid.

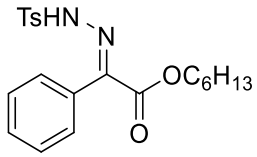
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 4.26 (t, *J* = 6.7 Hz, 2H), 1.70 (p, *J* = 6.8 Hz, 2H), 1.39 – 1.27 (m, 19H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.0, 132.1, 125.5, 125.1, 119.4, 65.5, 32.1, 29.78, 29.77, 29.70, 29.6, 29.5, 29.4, 28.9, 26.0, 22.8, 14.2.

HRMS (EI^+): Calc'd for $C_{20}H_{29}N_2O_2Br^+$: 408.1412; found 408.1419.

5.2. Hydrazone Compounds

hexyl (E)-2-phenyl-2-(2-tosylhydrazineylidene)acetate (*E*-**4c**)



The title compound was synthesised according to General Procedure B from hexyl 2-oxo-2-phenylacetate (3.83 mmol) in 65% yield (1.00 g). Purified by recrystallisation affording a white solid.

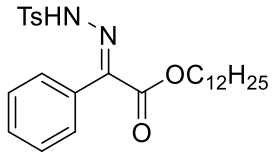
^{1}H NMR (600 MHz, $CDCl_3$): δ 11.55 (s, 1H), 7.88 – 7.86 (m, 2H), 7.52 – 7.50 (m, 2H), 7.39 – 7.30 (m, 5H), 4.28 (t, *J* = 6.7 Hz, 2H), 2.42 (s, 3H), 1.70 – 1.65 (m, 2H), 1.35 – 1.25 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 162.3, 144.5, 138.4, 135.7, 134.2, 129.9, 129.5, 128.7, 128.14, 128.11, 66.6, 31.3, 28.3, 25.6, 22.6, 21.8, 14.0. [One peak from the alkyl region could not be found].

HRMS (ESI$^+$): Calc'd for $C_{21}H_{26}N_2O_4SNa^+$: 425.1511; found: 425.1515.

Elemental Anal.: Calc'd (%) for $C_{21}H_{26}N_2O_4S$: C - 62.66 H - 6.51 N - 6.96; found C - 62.45 H - 6.44 N - 6.99

dodecyl (E)-2-phenyl-2-(2-tosylhydrazineylidene)acetate (*E*-**4d**)



The title compound was synthesised according to General Procedure B from dodecyl 2-oxo-2-phenylacetate (3.9 mmol) in 69% yield (1.31 g). Purified by recrystallisation affording a white solid.

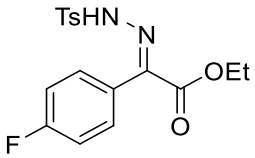
^{1}H NMR (600 MHz, $CDCl_3$): δ 11.56 (s, 1H), 7.88 – 7.86 (m, 2H), 7.52 - 7.50 (m, 2H), 7.38 – 7.30 (m, 5H), 4.27 (t, *J* = 6.7 Hz, 2H), 2.42 (s, 3H), 1.69 – 1.65 (m, 2H), 1.33 – 1.25 (m, 17H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 162.4, 144.5, 138.4, 135.7, 134.2, 129.9, 129.5, 128.7, 128.14, 128.11, 66.6, 32.1, 29.8, 29.63, 29.56, 29.48, 29.2, 28.4, 26.0, 22.8, 21.8, 14.3.

HRMS (ESI$^+$): Calc'd for $C_{27}H_{38}N_2O_4SNa^+$: 509.2450; found: 509.2453.

Elemental Anal: Calc'd (%) for $C_{27}H_{36}N_2O_4S$: C - 66.64 H - 7.87 N - 5.76; found: C - 66.70 H - 7.90 N - 5.95.

ethyl (E)-2-(4-fluorophenyl)-2-(2-tosylhydrazineylidene)acetate (*E*-**4e**)



The title compound was synthesised according to General Procedure B from ethyl 2-(4-fluorophenyl)-2-oxoacetate acid (0.55 mmol) in 39% yield for the *E*-isomer (26 mg). Purified by column chromatography affording a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.59 (s, 1H), 7.87 – 7.85 (m, 2H), 7.52 – 7.48 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.05 – 7.00 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).

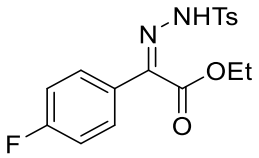
^{13}C NMR (126 MHz, $CDCl_3$): δ 163.5 (d, *J* = 250.0 Hz), 162.0, 144.6, 137.1, 135.6, 130.7 (d, *J* = 8.4 Hz), 130.3 (d, *J* = 3.3 Hz), 129.9, 128.1, 115.3 (d, *J* = 21.9 Hz), 62.6, 21.8, 14.1.

^{19}F NMR (470 MHz, $CDCl_3$): δ MAJOR: -111.4 (tt, *J* = 8.5, 5.3 Hz), MINOR: -114.1 (tt, *J* = 8.7, 5.3 Hz).

HRMS (ESI$^+$): Calc'd for $C_{17}H_{18}N_2O_4SF^+$: 365.0971; found: 365.0970.

Elemental Anal: Calc'd (%) for $C_{17}H_{17}FN_2O_4S$: C - 56.04 H - 4.70 N - 7.69 S - 8.80 F - 5.21; found C - 56.03 H - 4.55 N - 7.65 S - 8.82 F - 5.10.

ethyl (Z)-2-(4-fluorophenyl)-2-(2-tosylhydrazineylidene)acetate (*Z*-**4e**)



The title compound was synthesised according to General Procedure B from ethyl 2-(4-fluorophenyl)-2-oxoacetate acid (0.55 mmol) in 13% yield for the *Z*-isomer (26 mg). Purified by column chromatography and further purified by recrystallisation affording white crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.86 – 7.84 (m, 2H), 7.35 – 7.33 (m, 2H), 7.24 – 7.20 (m, 2H), 7.19 – 7.16 (m, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 2.45 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

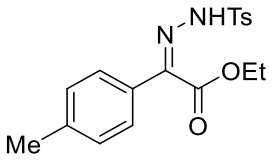
^{13}C NMR (126 MHz, $CDCl_3$): δ 163.5 (d, *J* = 252.3 Hz), 163.1, 145.0, 143.2, 134.9, 130.8 (d, *J* = 8.6 Hz), 129.9, 128.3, 124.1 (d, *J* = 3.7 Hz), 117.0 (d, *J* = 21.9 Hz), 62.2, 21.8, 14.2.

^{19}F NMR (470 MHz, $CDCl_3$): δ -108.3 (tt, *J* = 8.4, 5.3 Hz)

HRMS (ESI$^+$): Calc'd for $C_{17}H_{17}N_2O_4SFNa^+$: 387.0791; found 387.0793.

Elemental Anal: Calc'd (%) for $C_{17}H_{17}FN_2O_4S$: C - 56.04 H - 4.70 N - 7.69 S - 8.80 F - 5.21; found C - 56.05 H - 4.55 N - 7.72 S - 8.98 F - 5.08.

ethyl (Z)-2-(p-tolyl)-2-(2-tosylhydrazineylidene)acetate (*Z*-**4f**)



The title compound was synthesised according to General Procedure B from ethyl 2-oxo-2-(*4*-tolyl)acetate (1.15 mmol) in 42% yield (152 mg) for the *E*-isomer. Purified by column chromatography affording a viscous yellow oil.

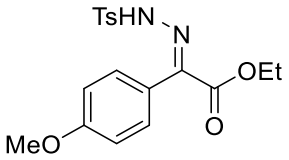
^{1}H NMR (600 MHz, $CDCl_3$): δ 11.42 (s, 1H), 7.88 – 7.86 (m, 2H), 7.43 – 7.41 (m, 2H), 7.32 – 7.30 (m, 2H), 7.16 – 7.14 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 162.3, 144.4, 139.7, 138.7, 135.7, 131.3, 129.8, 128.9, 128.5, 128.1, 62.5, 21.7, 21.4, 14.1.

HRMS (EI^{+}): Calc'd for $C_{18}H_{20}N_2O_4S^{+}$: 360.1144; found: 360.1149.

Elemental Anal: Calc'd for $C_{18}H_{20}N_2O_4S$: C 59.98 H 5.59 N 7.77 S 8.89; found: C - 60.08 H - 5.55 N - 7.88 S - 8.78.

ethyl (E)-2-(4-methoxyphenyl)-2-(2-tosylhydrazineylidene)acetate (*E*-**4g**)



The title compound was synthesised according to General Procedure B from ethyl 2-(4-methoxyphenyl)-2-oxoacetate (3.37 mmol) in 34% yield (431 mg) for the *E*-isomer. Purified by column chromatography affording a brown oil.

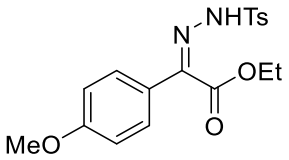
^{1}H NMR (600 MHz, $CDCl_3$): δ 11.29 (s, 1H), 7.88 – 7.85 (m, 2H), 7.50 – 7.47 (m, 2H), 7.32 – 7.30 (m, 2H), 6.87 – 6.85 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.41 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 162.4, 160.8, 144.4, 138.6, 135.7, 130.1, 129.8, 128.1, 126.6, 113.7, 62.5, 55.5, 21.8, 14.2.

HRMS (ESI^{+}): Calc'd for $C_{18}H_{21}N_2O_5S^{+}$: 377.1171; found 377.1173.

Elemental Anal: Calc'd (%) for $C_{18}H_{20}N_2O_5S$: C - 57.43 H - 5.36 N - 7.44 S - 8.52; found: C - 57.41 H - 5.42 N - 7.36 S - 8.44.

ethyl (Z)-2-(4-methoxyphenyl)-2-(2-tosylhydrazineylidene)acetate (*Z*-**4g**)



The title compound was synthesised according to General Procedure B from ethyl 2-(4-methoxyphenyl)-2-oxoacetate (3.37 mmol) in 10% yield for the *Z*-isomer (126 mg). Purified by column chromatography affording a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.86 – 7.84 (m, 2H), 7.34 – 7.32 (m, 2H), 7.18 – 7.15 (m, 2H), 6.99 – 6.96 (m, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.44 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.4, 161.2, 144.8, 144.3, 135.1, 130.1, 129.8, 128.2, 120.0, 115.0, 62.0, 55.6, 21.8, 14.2.

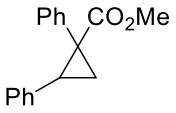
HRMS (EI^{+}): Calc'd for $C_{18}H_{20}N_2O_5S^{+}$: 376.1093; found 376.1088.

Elemental Anal: Calc'd (%) for $C_{18}H_{20}N_2O_5S$: C - 57.43 H - 5.36 N - 7.44 S - 8.52; found: C - 57.45, H - 5.50 N - 7.45 S - 8.58.

5.3. Cyclopropanes

NOTE CAREFULLY: Only the major diastereoisomer is reported due to the high number of overlapping peaks from the two diastereoisomers when the cyclopropane contains long alkyl chains. For ^{1}H NMR, only key peaks are identifiable such as those from the cyclopropane ring and the aromatic region.

methyl 1,2-diphenylcyclopropane-1-carboxylate (**3a**)



The title compound was synthesised according to General Procedure C from methyl 2-diazo-2-phenylacetate (0.1 mmol, 17.6 mg) in 59% yield (15 mg) as a white solid in 1:7 dr.

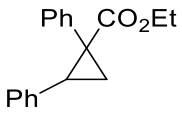
The title compound was synthesised according to General Procedure D from methyl 2-phenyl-2-(2-tosylhydrazineylidene)acetate (0.1 mmol, 33.2 mg) in 59% yield (15 mg) as a white solid in 1:10 dr.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 – 7.11 (m, 3H), 7.08 – 7.02 (m, 5H), 6.79 – 6.77 (m, 2H), 3.67 (s, 3H), 3.13 (dd, *J* = 9.4, 7.3 Hz, 1H), 2.15 (dd, *J* = 9.3, 4.9 Hz, 1H), 1.89 (dd, *J* = 7.3, 4.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.5, 136.5, 134.9, 132.1, 128.2, 127.83, 127.81, 127.2, 126.4, 52.8, 37.5, 33.3, 20.6.

The spectroscopic data is consistent with that previously reported in the literature.[12]

ethyl 1,2-diphenylcyclopropane-1-carboxylate (**3b**)



The title compound was synthesised according to General Procedure C from ethyl 2-diazo-2-phenylacetate (0.1 mmol, 19.0 mg) in 71% yield (19 mg) as a white solid in 1:7 dr.

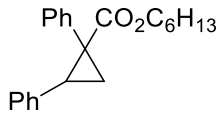
The title compound was synthesised according to General Procedure D from (*E*)-2-phenyl-2-(2-tosylhydrazineylidene)acetate (0.1 mmol, 34.6mg) in 91% yield (24 mg) as a white solid in 1:20 dr. The reaction with ethyl (*Z*)-2-phenyl-2-(2-tosylhydrazineylidene)acetate obtained the title compound in 69% yield (18 mg) in 1:8 dr.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 – 7.10 (m, 3H), 7.06 – 7.01 (m, 5H), 6.78 – 6.76 (m, 2H), 4.20 – 4.07 (m, 2H), 3.10 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.13 (dd, *J* = 9.3, 4.9 Hz, 1H), 1.87 (dd, *J* = 7.2, 4.9 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 136.6, 135.0, 132.0, 128.2, 127.8, 127.7, 127.0, 126.4, 61.4, 37.7, 33.0, 20.3, 14.3.

The spectroscopic data is consistent with that previously reported in the literature.[13]

hexyl 1,2-diphenylcyclopropane-1-carboxylate (**3c**)



The title compound was synthesised according to General Procedure C from hexyl 2-diazo-2-phenylacetate (0.1 mmol, 24.6 mg) in 77% yield (25 mg) as a yellow solid in 1:11 dr.

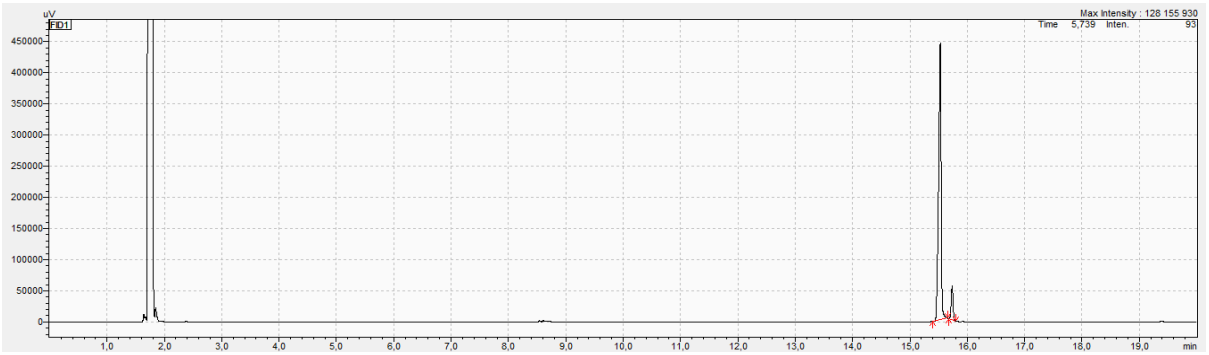
The title compound was synthesised according to General Procedure D from (*E*)-2-phenyl-2-(2-tosylhydrazineylidene)acetate (0.1 mmol, 40.3 mg) in 10% yield (3 mg) as a yellow solid in 1:9 dr. The reaction with ethyl (*Z*)-2-phenyl-2-(2-tosylhydrazineylidene)acetate obtained the title compound in 20% yield (6 mg) in 1:10 dr.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 – 7.01 (m, 8H), 6.77 (dd, *J* = 6.4, 2.9 Hz, 2H), 4.06 (ddt, *J* = 40.7, 10.8, 6.6 Hz, 2H), 3.09 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.12 (dd, *J* = 9.2, 4.9 Hz, 1H), 1.87 (dd, *J* = 7.3, 4.9 Hz, 1H).

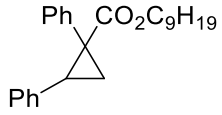
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 136.7, 135.0, 132.0, 128.2, 127.8, 127.7, 127.0, 126.4, 65.5, 37.8, 33.0, 31.4, 28.6, 25.5, 22.6, 20.3, 14.1.

HRMS (ESI$^+$): Calc'd for $C_{22}H_{26}O_2Na^+$: 345.1830; found: 345.1833.

GC (FID): 92% *cis* / 8% *trans*



nonyl 1,2-diphenylcyclopropane-1-carboxylate (**3d**)



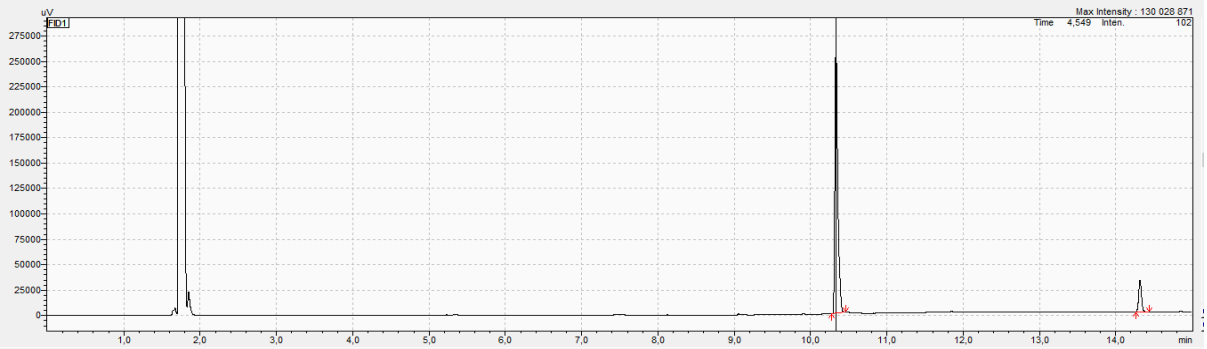
The title compound was synthesised according to General Procedure C from nonyl 2-diazo-2-phenylacetate (0.1 mmol, 28.8 mg), in 82% yield (30 mg) as a yellow oil in 1:10 dr.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 – 7.01 (m, 8H), 6.78 (dd, *J* = 6.6, 3.0 Hz, 2H), 4.06 (ddt, *J* = 40.8, 10.7, 6.6 Hz, 2H), 3.10 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.13 (dd, *J* = 9.3, 4.9 Hz, 1H), 1.87 (dd, *J* = 7.3, 4.9 Hz, 1H).

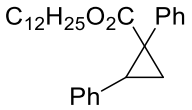
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 136.7, 135.0, 132.0, 128.2, 127.8, 127.7, 127.0, 126.4, 65.5, 37.8, 33.0, 32.0, 29.6, 29.3, 29.2, 28.6, 25.9, 22.8, 20.3, 14.2.

HRMS (ESI$^+$): Calc'd for $C_{25}H_{32}O_2Na^+$: 387.2300; found: 387.2298.

GC (FID): 90% *cis* / 10% *trans*



dodecyl 1,2-diphenylcyclopropane-1-carboxylate (**3e**)



The title compound was synthesised according to General Procedure C from dodecyl 2-diazo-2-phenylacetate (0.1 mmol, 33.0 mg) in 93% yield (38 mg) as a yellow oil in 1:11 dr.

1 mmol scale reaction: dodecyl 2-diazo-2-phenylacetate (1.0 mmol, 330.4 mg), styrene (10.0 mmol, 1040 mg), DTAC (3.5 mmol, 924 mg) and water (50 mL) were charged in a 50 mL round bottomed flask and was subjected to blue light irradiation for 60 hours. The work up and purification procedures were analogous to General Procedure C, which obtained the title compound in 76% yield (309 mg) as a yellow oil in 1:11 dr.

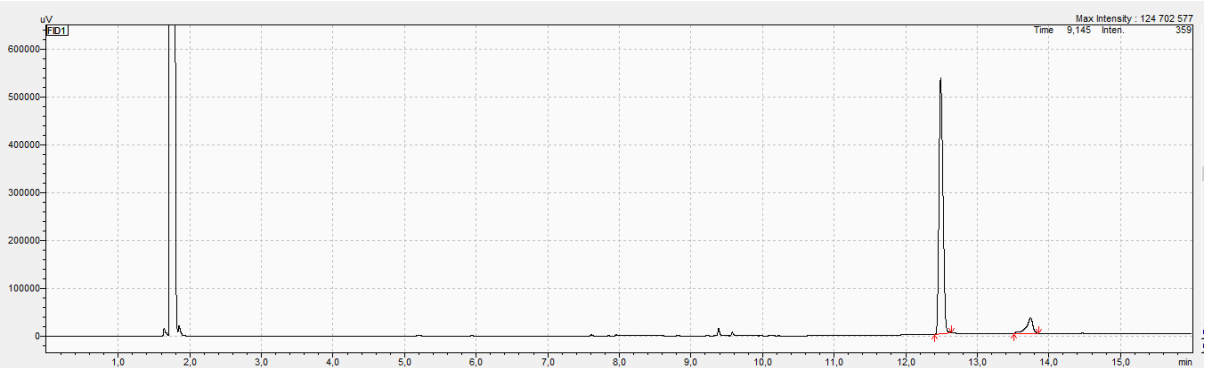
The title compound was synthesised according to General Procedure D from (*E*)-2-phenyl-2-(2-tosylhydrazineylidene)acetate (0.1 mmol, 34.6mg) in 31% yield (12 mg) as a yellow oil in 1:15 dr.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 – 7.00 (m, 8H), 6.79 – 6.76 (m, 2H), 4.14 – 3.99 (m, 2H), 3.10 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.13 (dd, *J* = 9.3, 4.9 Hz, 1H), 1.87 (dd, *J* = 7.2, 4.9 Hz, 1H).

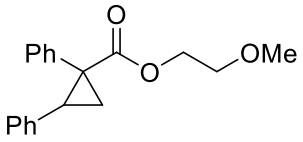
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 136.7, 135.0, 132.0, 128.2, 127.8, 127.7, 127.0, 126.4, 65.5, 37.8, 33.0, 32.1, 29.79, 29.78, 29.65, 29.63, 29.5, 29.2, 28.6, 25.9, 22.8, 20.3, 14.2.

HRMS (ESI$^+$): Calc'd for $C_{28}H_{38}O_2Na^+$: 429.2770; found: 429.2771.

GC (FID): 92% *cis* / 8% *trans*



2-methoxyethyl 1,2-diphenylcyclopropane-1-carboxylate (**3f**)



The title compound was synthesised according to General Procedure C from 2-methoxyethyl 2-diazo-2-phenylacetate (0.1 mmol, 22.0 mg) in 48% yield (14 mg) as a colourless semi-solid in 1:6 dr.

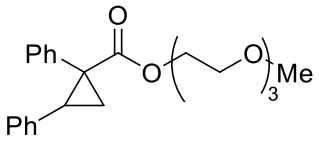
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 – 7.03 (m, 8H), 6.80 – 6.77 (m, 2H), 4.23 (ddt, *J* = 41.9, 11.9, 4.7 Hz, 2H), 3.52 (t, *J* = 4.9 Hz, 2H), 3.25 (s, 3H), 3.15 – 3.11 (m, 1H), 2.16 (dd, *J* = 9.3, 5.0 Hz, 1H), 1.90 (dd, *J* = 7.2, 4.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8, 136.5, 134.8, 132.1, 128.2, 127.8, 127.7, 127.1, 126.4, 70.4, 64.7, 59.2, 37.6, 33.2, 20.3.

HRMS (ESI$^+$): Calc'd for $C_{19}H_{20}O_3Na^+$: 319.1310; found: 319.1313.

Elemental Anal: Calc'd (%) for $C_{19}H_{20}O_3$: C - 77.00 H - 6.80; found: C - 76.59 H - 7.04.

2-(2-(2-methoxyethoxy)ethoxy)ethyl 1,2-diphenylcyclopropane-1-carboxylate (**3g**)



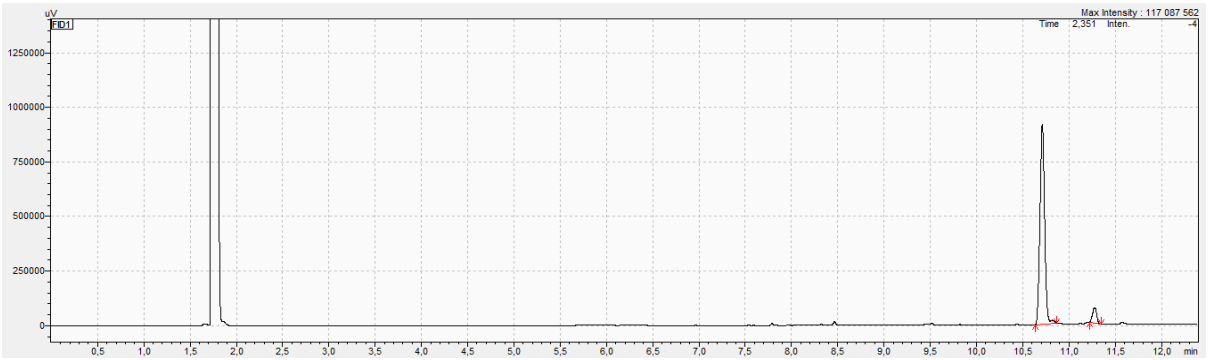
The title compound was synthesised according to General Procedure C from 2-(2-(2-methoxyethoxy)ethoxy)ethyl 2-diazo-2-phenylacetate (0.1 mmol, 30.8 mg), in 34% yield (13 mg) as a colourless semi-solid in 1:14 dr.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 – 7.01 (m, 8H), 6.77 (dd, *J* = 6.7, 3.0 Hz, 2H), 4.22 (ddt, *J* = 36.0, 11.8, 4.9 Hz, 2H), 3.62 – 3.58 (m, 4H), 3.53 (dd, *J* = 5.5, 3.2 Hz, 4H), 3.47 – 3.45 (m, 2H), 3.37 (s, 3H), 3.12 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.15 (dd, *J* = 9.3, 4.9 Hz, 1H), 1.88 (dd, *J* = 7.3, 4.9 Hz, 1H).

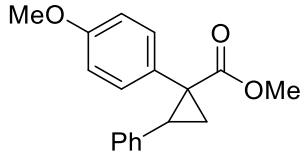
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8, 136.5, 134.9, 132.1, 128.2, 127.8, 127.7, 127.1, 126.4, 72.1, 70.81, 70.78, 70.68, 69.0, 65.0, 59.2, 37.6, 33.2, 20.4.

HRMS (ESI$^+$): Calc'd for $C_{23}H_{28}O_5Na^+$: 407.1834; found: 407.1841.

GC (FID): 93% *cis* / 7% *trans*



*methyl 1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (***3h**)



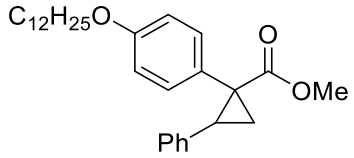
The title compound was synthesised according to General Procedure C from methyl 2-diazo-2-(4-methoxyphenyl)acetate (0.1 mmol, 20.6 mg) in 52% yield (15 mg) as a white solid in 1:12 dr.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09 – 7.04 (m, 3H), 6.94 – 6.92 (m, 2H), 6.78 – 6.76 (m, 2H), 6.68 – 6.65 (m, 2H), 3.72 (s, 3H), 3.66 (s, 3H), 3.07 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.12 (dd, *J* = 9.3, 4.8 Hz, 1H), 1.82 (dd, *J* = 7.3, 4.8 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.8, 158.6, 136.6, 133.1, 128.2, 127.9, 126.9, 126.4, 113.3, 55.2, 52.8, 36.8, 33.3, 20.9.

The spectroscopic data is consistent with that previously reported in the literature.[14]

methyl 1-(4-(dodecyloxy)phenyl)-2-phenylcyclopropane-1-carboxylate (**3i**)



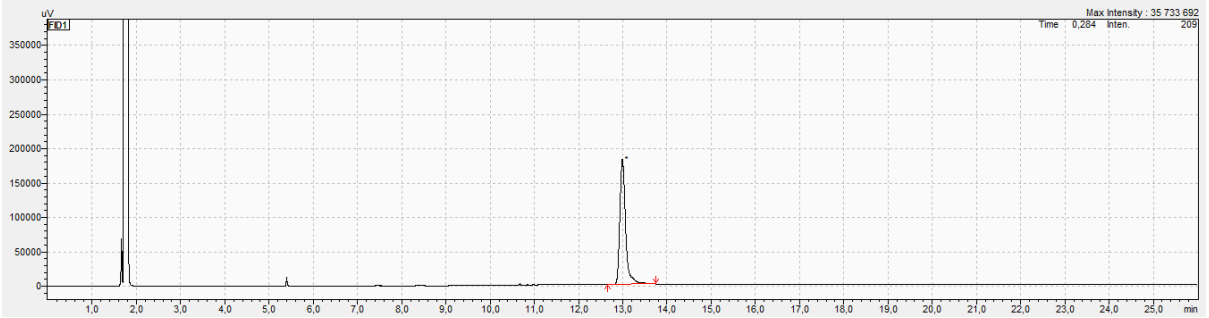
The title compound was synthesised according to General Procedure C from methyl 2-diazo-2-(4-(dodecyloxy)phenyl)acetate (0.1 mmol, 36.0 mg) in 41% yield (18 mg) as a colourless oil in >1:20 dr.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 – 7.04 (m, 3H), 6.92 – 6.90 (m, 2H), 6.78 – 6.76 (m, 2H), 6.66 – 6.64 (m, 2H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.67 (s, 3H), 3.08 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.13 (dd, *J* = 9.3, 4.8 Hz, 1H), 1.81 (dd, *J* = 7.2, 4.8 Hz, 1H), 1.74 – 1.69 (m, 1H).

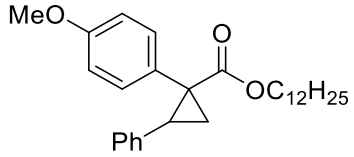
^{13}C NMR (151 MHz, $CDCl_3$) δ 174.9, 158.2, 136.7, 133.0, 128.2, 127.8, 126.7, 126.4, 113.9, 68.0, 52.7, 36.8, 33.3, 32.1, 29.81, 29.78, 29.75, 29.72, 29.6, 29.5, 29.4, 26.2, 22.8, 21.0, 14.3.

HRMS (ESI$^+$): Calc'd for $C_{29}H_{40}O_3Na^+$: 459.2875; found 459.2880.

GC (FID): Inseperable mixture of two diastereoisomers.



dodecyl 1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (**3j**)



The title compound was synthesised according to General Procedure C from methyl dodecyl 2-diazo-2-(4-methoxyphenyl)acetate (0.1 mmol, 36.0 mg) in 65% yield (28 mg) as a colourless oil in 1:7 dr.

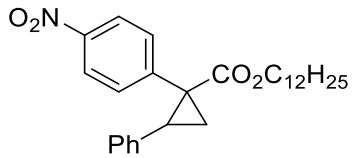
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 – 7.05 (m, 3H), 6.95 – 6.90 (m, 2H), 6.78 (dd, *J* = 7.3, 2.3 Hz, 2H), 6.67 – 6.65 (m, 2H), 4.13 – 4.00 (m, 2H) 3.72 (s, 3H), 3.05 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.11 (dd, *J* = 9.3, 4.8 Hz, 1H), 1.81 (dd, *J* = 7.2, 4.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.2, 158.5, 136.8, 133.0, 130.4, 128.2, 127.8, 126.3, 113.2, 65.5, 55.2, 40.7, 37.0, 33.0, 32.1, 29.77, 29.67, 29.66, 29.5, 29.3, 28.6, 25.9, 22.8, 20.5, 14.2.

HRMS (ESI$^+$): Calc'd for $C_{29}H_{40}O_3Na^+$: 459.2875; found: 459.2878.

Elemental Anal: Calc'd (%) for $C_{29}H_{40}O_3$: C - 79.77 H - 9.23; found: C - 79.65 H - 9.31.

dodecyl 1-(4-nitrophenyl)-2-phenylcyclopropane-1-carboxylate (**3k**)



The title compound was synthesised according to General Procedure C from dodecyl 2-diazo-2-(4-nitrophenyl)acetate (0.1 mmol, 37.5 mg) in 73% yield (45 mg) as a yellow oil in 1:2 dr.

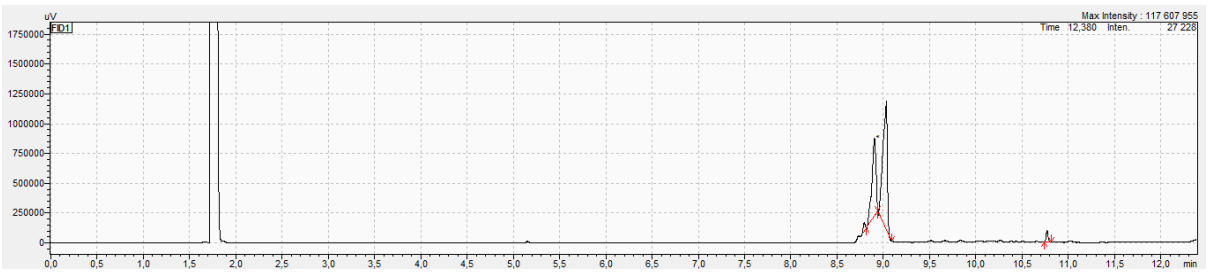
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.31 (m, 2H), 7.20 – 7.18 (m, 2H), 7.09 – 7.07 (m, 3H), 6.79 (dd, *J* = 6.6, 2.9 Hz, 2H), 4.08 (ddt, *J* = 29.8, 10.8, 6.7 Hz, 2H), 3.19 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.21 (dd, *J* = 9.3, 5.2 Hz, 1H), 1.94 (dd, *J* = 7.4, 5.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) Unable to unambiguously assign ^{13}C peaks due to the low dr.

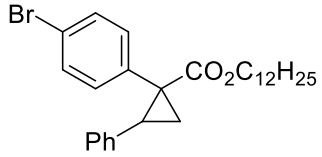
HRMS [APCI$^+$): Calc'd for $C_{28}H_{38}NO_4^+$: 452.2801; found: 452.2804.

Elemental Anal: Calc'd: (%) for $C_{28}H_{37}NO_4$ C - 74.47 H - 8.26 N - 3.10; found C - 74.46 H - 8.27 N - 3.20.

GC (FID): 64% *cis* / 36% *trans*



dodecyl 1-(4-bromophenyl)-2-phenylcyclopropane-1-carboxylate (**3l**)



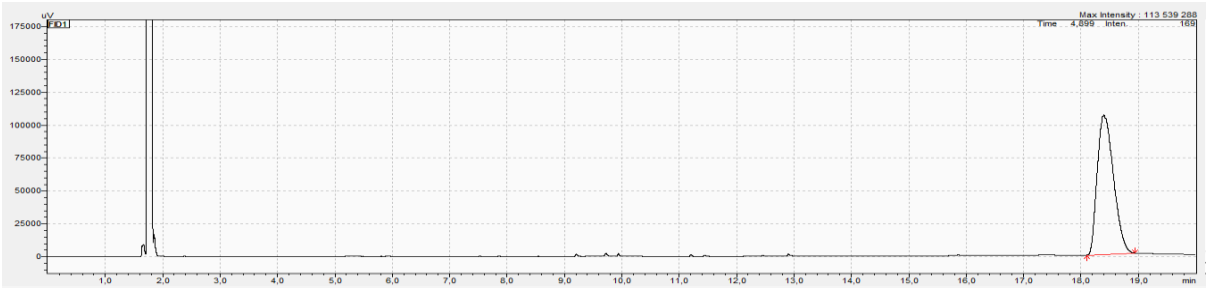
The title compound was synthesised according to General Procedure C from dodecyl 2-diazo-2-(4-bromophenyl)acetate (0.1 mmol, 40.9 mg) in 80% yield (39 mg) as a colourless semi-solid in 1:13 dr.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.22 (m, 2H), 7.10 – 7.06 (m, 3H), 6.89 – 6.87 (m, 2H), 6.78 – 6.77 (m, 2H), 4.05 (ddt, *J* = 33.5, 10.8, 6.6 Hz, 2H), 3.09 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.12 (dd, *J* = 9.3, 4.9 Hz, 1H), 1.82 (dd, *J* = 7.3, 5.0 Hz, 1H).

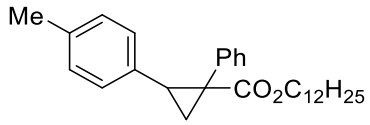
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.4, 136.1, 134.3, 133.7, 130.9, 128.2, 128.0, 126.6, 121.2, 65.7, 37.1, 33.1, 32.1, 29.80, 29.77, 29.66, 29.64, 29.5, 29.2, 28.6, 25.9, 22.8, 20.2, 14.3.

HRMS (ESI$^+$): Calc'd for $C_{28}H_{37}O_2BrNa^+$: 507.1875; found: 507.1877.

GC (FID): Inseperable mixture of two diastereoisomers.



dodecyl 1-phenyl-2-(p-tolyl)cyclopropane-1-carboxylate (**3m**)



The title compound was synthesised according to General Procedure C from dodecyl 2-diazo-2-phenylacetate (0.1 mmol, 33.0 mg) in 68% yield (29 mg) as a colourless semi-solid in 1:8 dr.

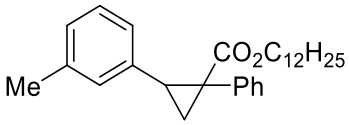
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 – 7.11 (m, 3H), 7.03 (dd, *J* = 6.6, 3.0 Hz, 2H), 6.87 (d, *J* = 7.8 Hz, 2H), 6.66 (d, *J* = 7.9 Hz, 2H), 4.06 (ddt, *J* = 40.8, 10.8, 6.6 Hz, 2H), 3.06 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.21 (s, 3H), 2.11 (dd, *J* = 9.3, 4.8 Hz, 1H), 1.82 (dd, *J* = 7.3, 4.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.0, 135.9, 135.2, 133.6, 132.1, 128.6, 128.0, 127.7, 126.9, 65.4, 37.6, 32.8, 32.1, 29.80, 29.78, 29.66, 29.64, 29.5, 29.2, 28.6, 25.9, 22.8, 21.1, 20.4, 14.3.

HRMS (ESI$^+$): Calc'd for $C_{29}H_{40}O_2Na^+$: 443.2926; found: 443.2923.

Elemental Anal: Calc'd (%) for $C_{29}H_{40}O_2$: C - 82.81 H - 9.59; found: C - 82.65 H - 9.70.

dodecyl 1-phenyl-2-(m-tolyl)cyclopropane-1-carboxylate (**3n**)



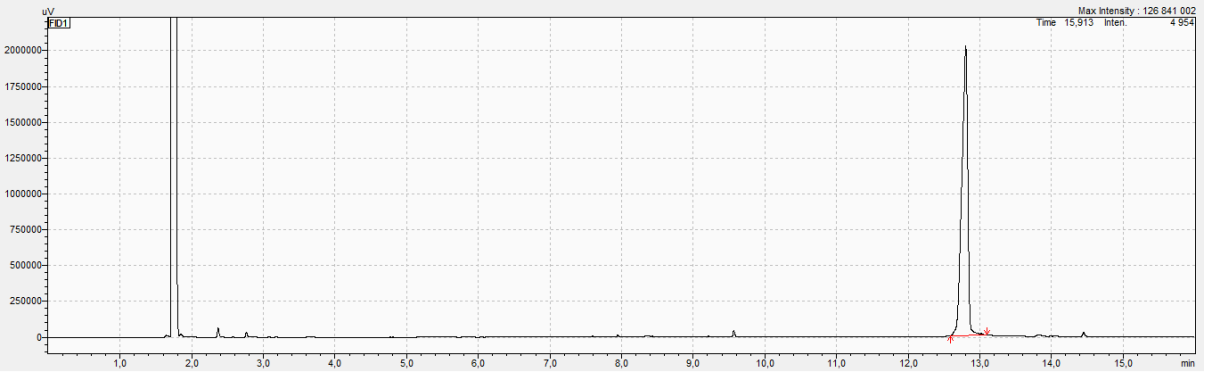
The title compound was synthesised according to General Procedure C from dodecyl 2-diazo-2-phenylacetate (0.1 mmol, 33.0 mg) in 74% yield (31 mg) as a yellow oil in 1:8 dr.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.12 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.04 – 7.02 (m, 2H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.62 (s, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 4.06 (ddt, *J* = 48.4, 10.8, 6.6 Hz, 2H), 3.05 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.15 (s, 3H), 2.11 (dd, *J* = 9.3, 4.8 Hz, 1H), 1.85 (dd, *J* = 7.3, 4.9 Hz, 1H).

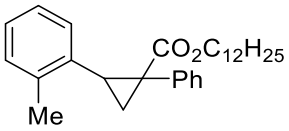
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.0, 137.3, 136.6, 135.1, 132.0, 129.2, 127.63, 127.62, 127.1, 127.0, 125.0, 65.5, 37.7, 33.0, 32.1, 29.79, 29.78, 29.65, 29.63, 29.5, 29.2, 28.6, 25.9, 22.8, 21.4, 20.4, 14.3.

HRMS (ESI$^+$): Calc'd for $C_{29}H_{40}O_2Na^+$: 443.2926; found: 443.2927.

GC (FID): Inseperable mixture of two diastereoisomers



dodecyl 1-phenyl-2-(o-tolyl)cyclopropane-1-carboxylate (**3o**)



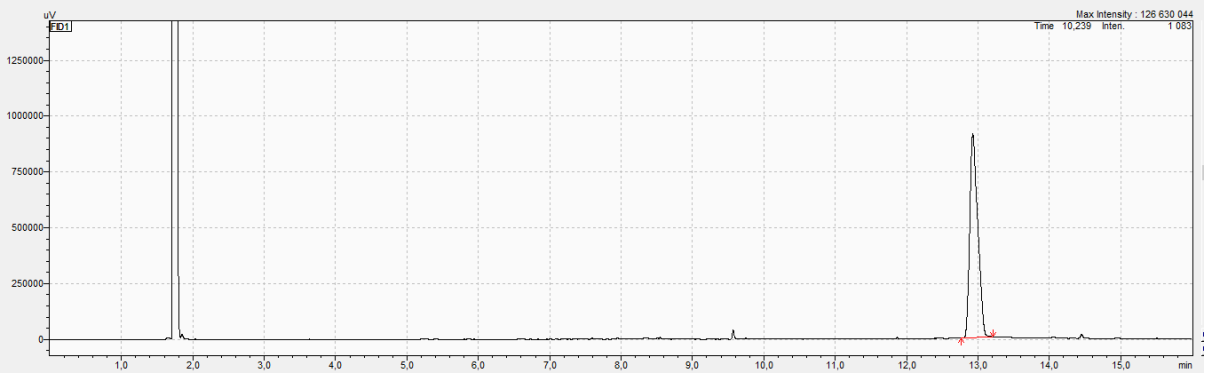
The title compound was synthesised according to General Procedure C from dodecyl 2-diazo-2-phenylacetate (0.1 mmol, 33.0 mg) in 76% yield (29 mg) as a colourless semi-solid in 1:14 dr.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.10 (d, *J* = 7.1 Hz, 1H), 7.05 (dd, *J* = 5.2, 2.0 Hz, 3H), 6.98 – 6.96 (m, 3H), 6.79 (t, *J* = 7.5 Hz, 1H), 6.41 (dd, *J* = 7.8, 1.3 Hz, 1H), 4.10 (ddt, *J* = 59.4, 10.8, 6.6 Hz, 2H), 3.12 (dd, *J* = 9.1, 7.6 Hz, 1H), 2.48 (s, 3H), 2.08 – 2.03 (m, 2H).

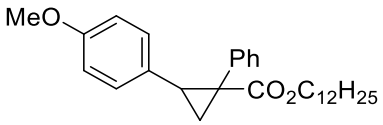
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.1, 137.9, 135.2, 134.5, 131.3, 129.8, 127.6, 126.9, 126.5, 125.8, 125.4, 65.4, 36.8, 32.1, 31.1, 29.80, 29.78, 29.67, 29.66, 29.5, 29.3, 28.7, 25.9, 22.8, 20.2, 18.5, 14.3.

HRMS (ESI$^+$): Calc'd for $C_{29}H_{40}O_2Na^+$: 443.2926; found: 443.2927.

GC (FID): Inseperable mixture of two diastereoisomers.



dodecyl 2-(4-methoxyphenyl)-1-phenylcyclopropane-1-carboxylate (**3p**)



The title compound was synthesised according to General Procedure C from dodecyl 2-diazo-2-phenylacetate (0.1 mmol, 33.0 mg) in 73% yield (32 mg) as a yellow solid in 1:5 dr.

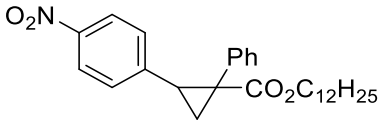
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (mHz, 3H), 7.03 (dd, *J* = 6.6, 3.0 Hz, 2H), 6.71 – 6.68 (m, 2H), 6.62 – 6.59 (m, 2H), 4.06 (ddt, *J* = 41.0, 10.8, 6.6 Hz, 2H), 3.69 (s, 3H), 3.05 (dd, *J* = 9.4, 7.3 Hz, 1H), 2.11 (dd, *J* = 9.4, 4.8 Hz, 1H), 1.80 (dd, *J* = 7.3, 4.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 174.0, 158.2, 135.2, 132.1, 129.1, 128.6, 127.7, 126.9, 113.3, 65.4, 55.2, 37.4, 32.5, 32.1, 29.79, 29.77, 29.64, 29.62, 29.5, 29.2, 28.6, 25.9, 22.8, 20.3, 14.3.

HRMS (ESI$^+$): Calc'd for $C_{29}H_{40}O_3Na^+$: 459.2875; found: 459.2881.

Elemental Anal: Calc'd (%) for $C_{29}H_{40}O_3$: C - 79.77 H - 9.23; found: C - 79.62 H - 9.39.

dodecyl 2-(4-nitrophenyl)-1-phenylcyclopropane-1-carboxylate (**3q**)



The title compound was synthesised according to General Procedure C from dodecyl 2-diazo-2-phenylacetate (0.1 mmol, 33.0 mg) in 62% yield (28 mg) as a colourless semi-solid in 1:3 dr.

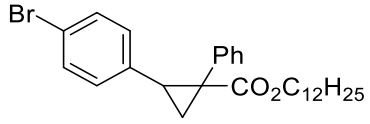
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 – 7.89 (m, 2H), 7.14 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.01 – 6.99 (m, 2H), 6.90 – 6.88 (m, 2H), 4.07 (ddt, *J* = 38.4, 10.8, 6.6 Hz, 2H), 3.18 (dd, *J* = 9.1, 7.1 Hz, 1H), 2.22 (dd, *J* = 9.1, 5.2 Hz, 1H), 1.94 (dd, *J* = 7.1, 5.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.2, 146.5, 145.1, 134.0, 131.8, 128.7, 128.1, 127.6, 123.0, 65.9, 38.9, 32.3, 32.1, 29.78, 29.76, 29.63, 29.60, 29.5, 29.2, 28.5, 25.8, 22.8, 21.1, 14.3.

HRMS [APCI$^+$): Calc'd for $C_{28}H_{38}NO_4^+$: 452.2801; found: 452.2805.

Elemental Anal: Calc'd (%) for $C_{28}H_{37}NO_4$: C - 74.47 H - 8.26; found: C - 74.45 H - 8.28.

dodecyl 2-(4-bromophenyl)-1-phenylcyclopropane-1-carboxylate (**3r**)



The title compound was synthesised according to General Procedure C from dodecyl 2-diazo-2-phenylacetate (0.1 mmol, 33.0 mg) in 82% yield (40 mg) as a yellow oil in 1:4 dr.

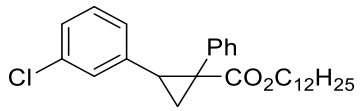
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 – 7.13 (m, 5H), 7.01 (dd, *J* = 6.5, 3.1 Hz, 2H), 6.64 – 6.62 (m, 2H), 4.06 (ddt, *J* = 39.7, 10.8, 6.6 Hz, 2H), 3.04 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.13 (dd, *J* = 9.3, 5.0 Hz, 1H), 1.81 (dd, *J* = 7.2, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.7, 135.9, 134.6, 131.9, 130.9, 129.8, 127.9, 127.2, 120.3, 65.6, 37.9, 32.3, 32.1, 29.79, 29.77, 29.64, 29.62, 29.5, 29.2, 28.6, 25.9, 22.8, 20.5, 14.3.

HRMS (ESI$^+$): Calc'd for $C_{28}H_{37}O_2BrNa^+$: 507.1875; found: 507.1878.

Elemental Anal: Calc'd (%) for $C_{28}H_{37}BrO_2$: C - 69.27, H - 7.68 Br - 16.46; found C - 69.19, H - 7.67, Br - 16.42.

dodecyl 2-(3-chlorophenyl)-1-phenylcyclopropane-1-carboxylate (**3t**)



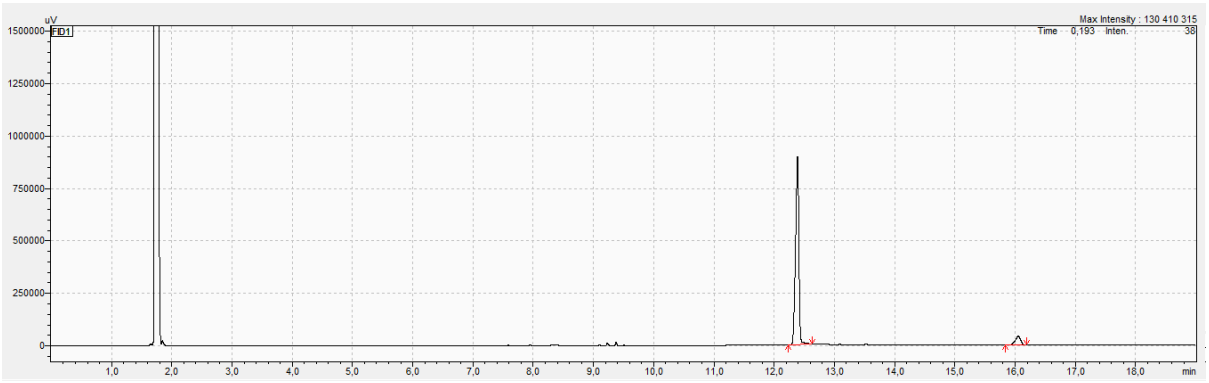
The title compound was synthesised according to General Procedure C from dodecyl 2-diazo-2-phenylacetate (0.1 mmol, 33.0 mg) in 34% yield (15 mg) as a yellow oil in 1:13 dr.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 – 7.12 (m, 3H), 7.02 (dd, *J* = 6.7, 2.8 Hz, 3H), 6.95 (t, *J* = 7.8 Hz, 1H), 6.80 (t, *J* = 1.9 Hz, 1H), 6.59 (dt, *J* = 7.8, 1.5 Hz, 1H), 4.06 (ddt, *J* = 41.3, 10.8, 6.6 Hz, 2H), 3.05 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.12 (dd, *J* = 9.3, 5.0 Hz, 1H), 1.84 (dd, *J* = 7.2, 5.0 Hz, 1H).

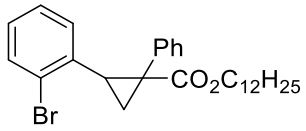
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.6, 139.0, 134.5, 133.7, 131.9, 128.9, 128.5, 127.9, 127.3, 126.5, 126.1, 65.7, 37.9, 32.4, 32.1, 29.79, 29.78, 29.65, 29.62, 29.5, 29.2, 28.6, 25.9, 22.8, 20.4, 14.3.

HRMS [APCI$^+$): Calc'd for $C_{28}H_{38}O_2Cl$: 441.2560; found: 441.2561.

GC (FID): 92% *cis* / 8% *trans*



dodecyl 2-(2-bromophenyl)-1-phenylcyclopropane-1-carboxylate (**3u**)



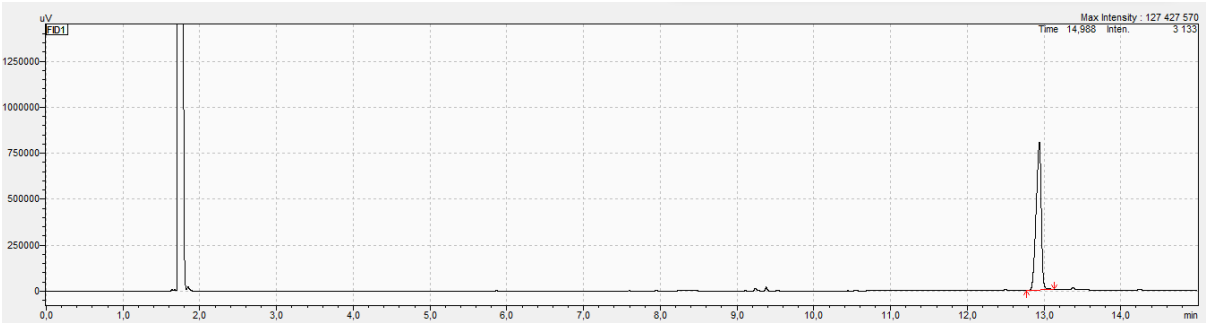
The title compound was synthesised according to General Procedure C from dodecyl 2-diazo-2-phenylacetate (0.1 mmol, 33.0 mg) in 62% yield (30 mg) as a yellow oil in 1:4 dr.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.12 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.09 – 7.05 (m, 3H), 6.91 (pd, *J* = 7.4, 1.8 Hz, 2H), 6.49 (dd, *J* = 7.4, 2.1 Hz, 1H), 4.12 (ddt, *J* = 77.0, 10.7, 6.6 Hz, 2H), 3.35 (dd, *J* = 7.9 Hz, 1H), 2.11 (dd, *J* = 9.1, 5.0 Hz, 1H), 2.02 (dd, *J* = 7.5, 5.1 Hz, 1H).

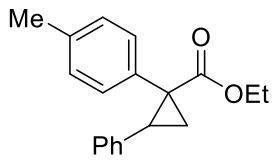
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.5, 136.1, 135.0, 132.5, 131.4, 128.1, 127.8, 127.7, 127.0, 126.8, 65.5, 36.9, 34.1, 32.1, 29.80, 29.78, 29.68, 29.5, 29.3, 28.7, 25.9, 22.8, 18.5, 14.3. [One peak from the aromatic region cannot be unambiguously assigned and the typical second peak around δ 29.7 is not observed].

HRMS (ESI$^+$): Calc'd for $C_{28}H_{37}O_2BrNa^+$: 507.1875; found 507.1872.

GC (FID): Inseperable mixture of two diastereoisomers.



ethyl 2-phenyl-1-(p-tolyl)cyclopropane-1-carboxylate (**3v**)



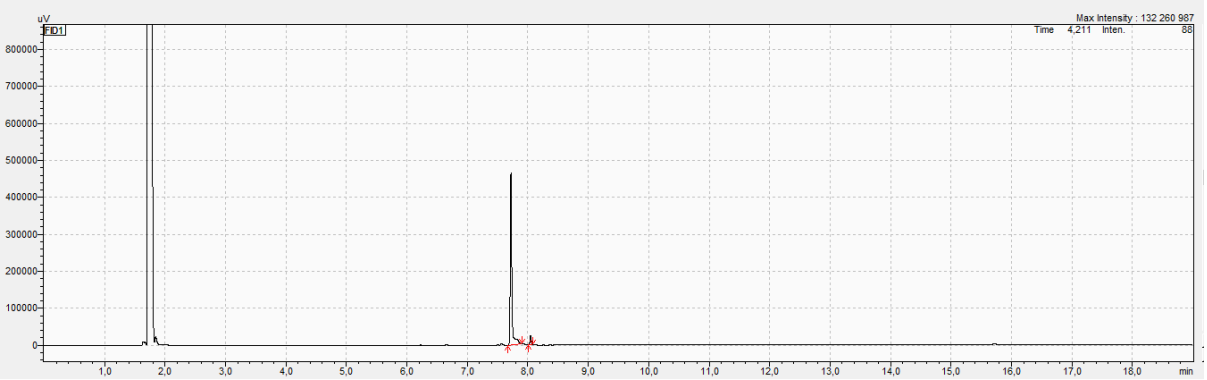
The title compound was synthesised according to General Procedure D from ethyl (*E*)-2-(*p*-tolyl)-2-(2-tosylhydrazineylidene)acetate (0.1 mmol, 36.0 mg), in 50% yield (14 mg) as a colourless semi-solid in 1:15 dr.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (dd, *J* = 5.2, 1.9 Hz, 3H), 6.93 – 6.89 (m, 4H), 6.79 – 6.77 (m, 2H), 4.20 – 4.06 (m, 2H), 3.07 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.24 (s, 3H), 2.10 (dd, *J* = 9.3, 4.8 Hz, 1H), 1.83 (dd, *J* = 7.2, 4.8 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H).

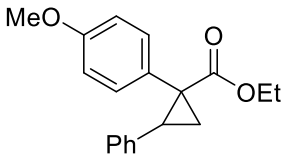
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 136.8, 136.6, 131.9, 131.8, 128.5, 128.2, 127.8, 126.3, 61.3, 37.4, 33.0, 21.3, 20.4, 14.3.

HRMS (EI$^+$): Calc'd for $C_{19}H_{20}O_2$: 280.1463; found 280.1470.

GC (FID): 96% *cis* / 4% *trans*



ethyl 1-(4-methoxyphenyl)-2-phenylcyclopropane-1-carboxylate (**3w**)



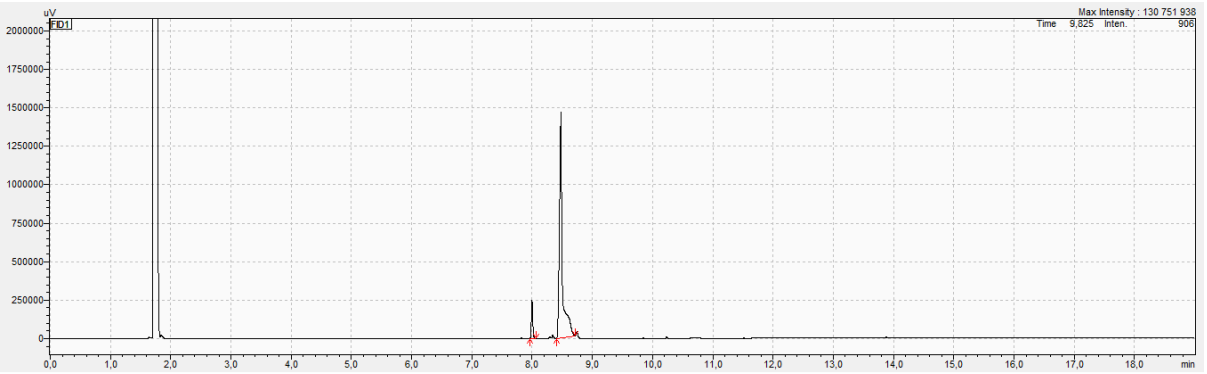
The title compound was synthesised according to General Procedure D from ethyl (*E*)-2-(4-methoxyphenyl)-2-(2-tosylhydrazineylidene)acetate (0.1 mmol, 37.6 mg) in 49% yield (15 mg) as a colourless semi-solid in 1:20 dr. The same reaction with ethyl (*Z*)-2-(4-methoxyphenyl)-2-(2-tosylhydrazineylidene)acetate obtained the title compound in 73% yield (22 mg) in 1:>20 dr.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 – 7.05 (m, 3H), 6.95 – 6.91 (m, 2H), 6.78 (dd, *J* = 7.5, 2.2 Hz, 2H), 6.67 – 6.64 (m, 2H), 4.20 – 4.05 (m, 2H), 3.72 (s, 3H), 3.06 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.11 (dd, *J* = 9.3, 4.9 Hz, 1H), 1.81 (dd, *J* = 7.2, 4.9 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H).

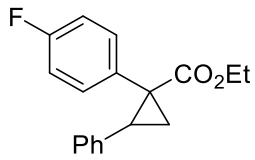
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.2, 158.5, 136.8, 133.0, 128.2, 127.8, 127.1, 126.3, 113.2, 61.3, 55.2, 37.0, 33.1, 20.6, 14.3.

HRMS (ESI^{+}): Calc'd for $C_{19}H_{20}O_3Na^{+}$: 319.1310; found 319.1316.

GC (FID): 93% *cis* / 7% *trans.*



ethyl 1-(4-fluorophenyl)-2-phenylcyclopropane-1-carboxylate (**3x**)



The title compound was synthesised according to General Procedure D from ethyl (*E*)-2-(4-fluorophenyl)-2-(2-tosylhydrazineylidene)acetate (0.1 mmol, 36.4 mg) in 34% yield (10 mg) as a colourless oil in 1:>20 dr. The same reaction with ethyl (*Z*)-2-(4-fluorophenyl)-2-(2-tosylhydrazineylidene)acetate obtained the title compound in 15% yield (4 mg) in 1:>20 dr.

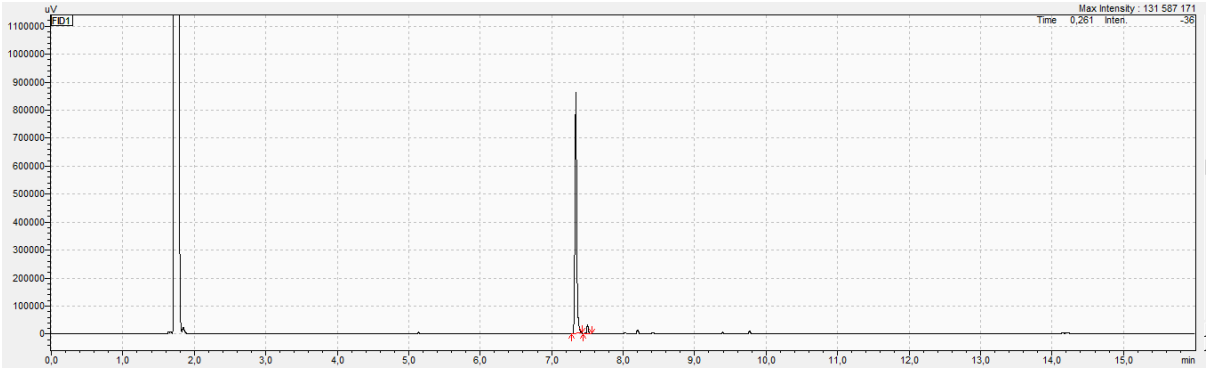
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 – 7.05 (m, 3H), 7.00 – 6.97 (m, 2H), 6.83 – 6.76 (m, 4H), 4.20 – 4.08 (m, 2H), 3.09 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.14 (dd, *J* = 9.3, 5.0 Hz, 1H), 1.84 (dd, *J* = 7.2, 5.0 Hz, 1H) 1.19 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.7, 162.8, 160.9, 136.3, 133.6 (d, *J* = 8.2 Hz), 128.2, 127.9, 126.6, 114.7 (d, *J* = 21.5 Hz), 61.5, 36.9, 33.1, 20.3, 14.3.

^{19}F NMR (470 MHz, $CDCl_3$): δ MINOR = -115.10 (tt, *J* = 8.5, 5.4 Hz), MAJOR = -115.33 (tt, *J* = 8.9, 5.4 Hz).

HRMS (ESI$^+$): Calc'd for $C_{18}H_{18}O_2F^+$: 285.1291; found: 285.1293.

GC (FID): 97% *cis* / 3% *trans*



6. Computational Methods and Additional Results

The density functional theory (DFT) calculations were performed using Turbomole 7.3[15]. We used the BP functional[16,17] and the TZVP basis set[18] along with the COSMO implicit solvent model[19] using an infinite dielectric constant, in order to allow for COSMO-RS[20] calculations. The ensuing COSMO-RS calculations were performed using COSMOtherm 21 and the BP_TZVP_C30_1601 parameterisation. The DTAC surfactant was modelled as a contact ion pair, to make it a neutral molecule, which is a requirement for the interfacial tension calculations.

We predicted the critical micellar concentration (CMC) using our recent method[21] with dodecane as the equivalent tail model for the surfactant. The method is based on our COSMO-RS based method for predicting liquid-liquid interfacial tension (IFT)[22] and allows to calculate the interfacial mole fraction of all components at the liquid-liquid interface, which in our case is the micelle-water interface. The first part of any liquid-liquid IFT calculation is a liquid extraction calculation, an equilibrium calculation between the two bulk phases, which were

1. Surfactant + water
2. Dodecane (modelling surfactant tail), styrene and diazo reagents (+ product)

In short, for the system including all components in the calculation (including the styrene and diazo reagents), the CMC was found by changing the surfactant concentration in the calculations until the computed IFT was equal to 0. Thermodynamically, this is the concentration at which the free energy cost for creating the micelle-water interface vanishes, and micelles can start to form spontaneously. For more details on the procedure, see [21]. This initial equilibration also allows for calculating the partition coefficient P between any compound in the calculation between the micellar core and the aqueous phase. All $\log(P_{water\text{-}core})$ values were lower than 0.00013, which means the concentration of diazo compounds in the aqueous phase are negligible, including the ones with more hydrophilic side chains.

7. References

1 H. Keipour, A. Jalba, L. Delage-Laurin and T. Ollevier, *J. Org. Chem.*, 2017, **82**, 3000–3010.

2 S. Y. Sit, C. M. Conway, K. Xie, R. Bertekap, C. Bourin and K. D. Burris, *Bioorganic Med. Chem. Lett.*, 2010, **20**, 1272–1277.

3 P. Li, J. Zhao, C. Wu, R. C. Larock and F. Shi, *Org. Lett.*, 2011, **13**, 3340–3343.

4 A. Y. Ji, A. Thirupathi, J. Y. Hwang, Y. Kim, G. Han, K.-H. Ahn, K. Kang and E. J. Kang, *Org. Lett.*, 2023, **25**, 1541–1546.

5 S. Xie, D. Li, H. Huang, F. Zhang and Y. Chen, *J. Am. Chem. Soc.*, 2019, **141**, 16237–16242.

6 N. Hu, H. Jung, Y. Zheng, J. Lee, L. Zhang, Z. Ullah, X. Xie, K. Harms, M. Baik and E. Meggers, *Angew. Chemie*, 2018, **130**, 6350–6354.

7 S. K. Mehta, K. K. Bhasin, R. Chauhan and S. Dham, *Colloids Surfaces A Physicochem. Eng. Asp.*, 2005, **255**, 153–157.

8 R. Claveau, B. Twamley and S. J. Connon, *Chem. Commun.*, 2018, **54**, 3231–3234.

9 D. Y. Li, W. Fang, Y. Wei and M. Shi, *Chem. - A Eur. J.*, 2016, **22**, 18080–18084.

10 S. Zhou, B. Cai, C. Hu, X. Cheng, L. Li and J. Xuan, *Chinese Chem. Lett.*, 2021, **32**, 2577–2581.

11 S. Harada, K. Tanikawa, H. Homma, C. Sakai, T. Ito and T. Nemoto, *Chem. - A Eur. J.*, 2019, **25**, 12058–12062.

12 R. Sambasivan and Z. T. Ball, *Angew. Chemie - Int. Ed.*, 2012, **51**, 8568–8572.

13 J. D. Pizarro, F. Molina, M. R. Fructos and P. J. Pérez, *Chem. - A Eur. J.*, 2020, **26**, 10330–10335.

14 A. Dasgupta, R. Babaahmadi, B. Slater, B. F. Yates, A. Ariafard and R. L. Melen, *Chem*, 2020, **6**, 2364–2381.

15 R. Ahlrichs, M. Bar, M. Haser, H. Horn and C. Kolmel, *Chem. Phys. Lett.*, 1989, **162**, 165–169.

16 A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098.

17 J. P. Perdew, *Phys. Rev. B*, 1986, **33**, 8822–8824.

18 F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297–3305.

19 A. Klamt and G. Schüürmann, *J. Chem. Soc. Perkin Trans. 2*, 1993, 799–805.

20 A. Klamt, F. Eckert and W. Arlt, in *Annual Review of Chemical and Biomolecular Engineering, Vol 1*, 2010, vol. 1, pp. 101–122.

21 M. Turchi, A. P. Karcz and M. P. Andersson, *J. Colloid Interface Sci.*, 2022, **606**, 618–627.

22 M. P. Andersson, M. Bennetzen, A. Klamt and S. L. S. Stipp, *J. Chem. Theory Comput.*, 2014, **10**, 3401–3408.

SUPPORTING INFORMATION FOR:

PHOTOCHEMICAL FUNCTIONALIZATION OF 4-DIAZOISOQUINOLINE-1,3(2*H*,4*H*)-DIONES AND THEIR 1-SULFOXIDE ANALOGS

Joseph P. Milton, Dorota Gryko*

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224, Warsaw, Poland

**Correspondence: dorota.gryko@icho.edu.pl*

Table of Contents

1. General Information **5**

2. Optimisation of the HFIP Insertion with 4-Diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione **7**

2.1. Amount of HFIP vs. Reaction Yield 7

2.2. Effect of Concentration on the Reaction Yield 8

2.3. Reaction Profile over Time 8

2.4. Assessing the Reaction with DCM 9

3. UV-Vis Spectra of Diazo Compounds **10**

3.1. Influence of *N*-substituents 10

3.2. Influence of the Position of Cl-Substituents on the Aryl Ring 10

3.3. Influence of Substituents at the 7-Position 11

3.4. UV-Vis of Sulfoxide-Containing Diazo Compounds 11

3.5. Comparing the Two Families of Diazo Compounds 12

4. Mechanistic Considerations **13**

5. General Procedures **14**

5.1. General Procedure A - Synthesis of Substituted (2-(Carboxymethyl)benzoic acids) 14

5.2. General Procedure B - Synthesis of Substituted *N*-Methylisoquinoline-1,3(2*H*,4*H*)-diones 14

5.3. General Procedure C - Synthesis of 2*H*-Benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides 15

5.4. General Procedure D - Synthesis of Diazo Compounds 16

5.5. General Procedure E - O-H and S-H Insertion Reactions of 4-Diazoisoquinoline-1,3(2*H*,4*H*)-diones 16

5.6. General Procedure F – Arene Insertion Reactions of 4-Diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-diones 17

5.7. General Procedure G - O-H and S-H Insertion Reactions of 4-Diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides 17

6. (2-(Carboxymethyl))benzoic acids **18**

7. Isoquinoline-1,3(2*H*,4*H*)-diones **21**

8. 2*H*-Benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides **30**

9. 4-Diazo-2-methylisoquinoline-1,3(2H,4H)-diones **33**

10. 4-Diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide **38**

10. O-H Insertion Products **40**

11. S-H Insertion Products **58**

12. Arene Insertions **62**

13. Reactions of 4-diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides **66**

14. References **71**

15. NMR Spectra **73**

4-methoxy-2-methylbenzoic acid (**S1**) 73
2-(carboxymethyl)-4-methoxybenzoic acid (**S2**) 74
2-(carboxymethyl)-5-chlorobenzoic acid (**S3**) 75
2-(carboxymethyl)-3-chlorobenzoic acid (**S4**) 76
4-bromo-2-(carboxymethyl)benzoic acid (**S5**) 77
7-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**S6**) 78
7-bromo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**S7**) 79
2,7-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (**S8**) 80
7-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**S9**) 81
6-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**S10**) 82
6-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**S11**) 83
6-bromo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**S12**) 84
8-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**S13**) 85
5-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**S14**) 86
2-methyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (**S15**) 87
2-benzyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (**S16**) 88
2-allyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (**S17**) 89
7-chloro-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**1g**) 90
7-bromo-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**1h**) 91
4-diazo-2,7-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (**1i**) 92
4-diazo-7-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**1j**) 93
4-diazo-6-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**1k**) 94
6-chloro-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**1l**) 95
6-bromo-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**1m**) 96
8-chloro-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**1n**) 97
5-chloro-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**1o**) 98
2-methyl-4-diazo-2H-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (**34a**) 99
2-benzyl-4-diazo-2H-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (**34b**) 100
4-diazo-2-allyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (**34c**) 101
4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**2**) 102
2-ethyl-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)isoquinoline-1,3(2*H*,4*H*)-dione (**3**) 103
4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-propylisoquinoline-1,3(2*H*,4*H*)-dione (**4**) 105
4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-isopropylisoquinoline-1,3(2*H*,4*H*)-dione (**5**) 106
2-benzyl-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)isoquinoline-1,3(2*H*,4*H*)-dione (**6**) 108

4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-phenylisoquinoline-1,3(2*H*,4*H*)-dione (**7**)..... 109

7-chloro-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**8**) 111

7-bromo-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**9**) 112

4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2,7-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (**10**). 114

4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-7-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**11**)..... 115

4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-6-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**12**)..... 117

8-chloro-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**15**)..... 118

5-chloro-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**16**)..... 120

2-methyl-4-(2,2,2-trifluoroethoxy)isoquinoline-1,3(2*H*,4*H*)-dione)(**17**)..... 121

2-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)isoquinoline-1,3(2*H*,4*H*)-dione (**18**) (dr 1:10)..... 123

2-methyl-4-(2,2,3,3-tetrafluoropropoxy)isoquinoline-1,3(2*H*,4*H*)-dione (**19**) 124

2-methyl-4-((2,2,3,3,4,4,5,5-octafluoropentyl)oxy)isoquinoline-1,3(2*H*,4*H*)-dione (**20**) 126

2-methylisoquinoline-1,3,4(2*H*)-trione (**21b**) 128

2-methyl-4-(phenethylthio)isoquinoline-1,3(2*H*,4*H*)-dione (**22**) 129

4-(cyclohexylthio)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**23**) 130

4-(benzylthio)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**24**) 131

4-(dodecylthio)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**25**)..... 132

4-((2-hydroxyethyl)thio)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**26**)..... 133

2-methyl-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (**28**)..... 134

4-(2,5-dimethylphenyl)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**29**) 135

4-mesityl-2-methylisoquinoline-1,3(*2H,4H*)-dione (**30**) 136

4-(5-bromo-2-methoxyphenyl)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (**31**) 137

4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methyl-2H-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (**35**)..... 139

2-benzyl-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2H-benzo[e][1,2]thiazin-3(4H)-one 1,1-dioxide (**36**)..... 140

2-allyl-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (**37**)..... 142

2-methyl-4-(2,2,3,3-tetrafluoropropoxy)-2H-benzo[e][1,2]thiazin-3(4*H*)-one 1,1-dioxide (**38**) 143

4-(cyclohexylthio)-2-methyl-2H-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (**39**) 145

1. General Information

General - All solvents and commercially available reagents were used as purchased without any further purification. Dry solvents were obtained from a Solvent Purification System (SPS). All reactions were monitored by gas chromatography (GC) or TLC on Merck silica gel (GF254, 0.20 mm thickness) and were visualised with UV-light. Column chromatography was performed using Merck silica gel 60 (230 – 400 mesh). Unless otherwise noted, all reactions were performed without the exclusion of air or moisture. Unless otherwise noted, all photochemical reactions were performed in 10 mL vials with an aluminium cap with a rubber septum.

NMR - ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded at 25 °C on a Bruker 400 MHz, Bruker 500 MHz, Varian 500 MHz or a Varian 600 MHz instrument. NMR chemical shifts are reported in ppm and referenced to the residual solvent peak: ^{1}H NMR - 7.26 ppm ($CDCl_3$) or 2.50 ppm (DMSO-d_6); ^{13}C{^{1}H} NMR - 77.16 ppm ($CDCl_3$) or 39.52 ppm (DMSO-d_6). In cases where the $CDCl_3$ peak could not be identified, TMS was instead used as the reference at 0.00 ppm. Multiplicities are indicated by singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (hept), multiplet (m). Some multiplicities are preceded with "obs." meaning that we observed this multiplicity even if theoretically it should be different. Coupling constants (*J*) are reported in hertz. All data analysis was performed using the MestReNova software package.

EA – Elemental Analysis (C, H, N, S, Br, Cl, F) was performed on a Perkin-Elmer 240 Elemental Analyzer

HRMS – High resolution mass spectra were recorded on a Waters SYNAPT G2-S HDMS using electrospray ionization (ESI) or atmospheric-pressure chemical ionization (APCI) with a time-of-flight (TOF) detector.

GC – Gas chromatography analysis coupled with a flame ionisation detector (GC-FID) were performed on a Shimadzu GCMS-QP2010 SE with helium as the carrier gas and a Zebron ZB 5MSi column.

All GCs were recorded with the following parameters:

Pressure: 90.8 kPA; Total flow: 5.3 mL/min; Column flow: 1.11 mL/min; Linear velocity: 27.5 cm/s; Purge flow: 2.0 mL/min; Split ratio: 2.0

With the following method:

Rate (°C/min)	Temperature (°C)	Hold Time (minutes)
-	100	1.00
40	180	1.50
40	260	1.50
45	300	1.00
50	325	2.00

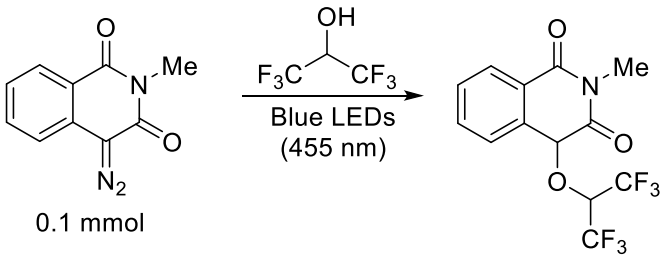
Photochemical Setup:

All photochemical reactions were performed using a homemade photoreactor composed of a cooling block (connected to a Huber MiniChiller 300 set at 15 °C) and a plate containing 6 LEDs of the desired wavelength. The photochemical vials were placed directly atop of the LEDs thus there is minimal distance between the light source and reaction mixture. Both blue (455 nm) and violet plates (400 nm) are rated at 21 V and 0.7 A, thus the power at each well for the light source is approximately 3W.

Figure S1: Left: Standard photochemical set ups with violet LEDs (400 nm) and blue LEDs (455 nm) accompanied by the chiller. Right: Aerial view of the wells of the photochemical reactors.

2. Optimisation of the HFIP Insertion with 4-Diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione

Model reaction procedure:



4-Diazoisoquinoline-1,3(2*H*,4*H*)-dione (20 mg, 0.1 mmol) is charged in a vial and dissolved in a HFIP/EtOAc mixture (X:X *c* = X M) then the vial is capped. The vial is irradiated with blue LEDs for X hours at approximately 15 °C then the cap is removed. The solvent is removed in vacuo and dried under a vacuum pump. Trichloroethene (0.1 mmol) is added, and the solution is dissolved in $CDCl_3$ and analyzed by NMR.

2.1. Amount of HFIP vs. Reaction Yield

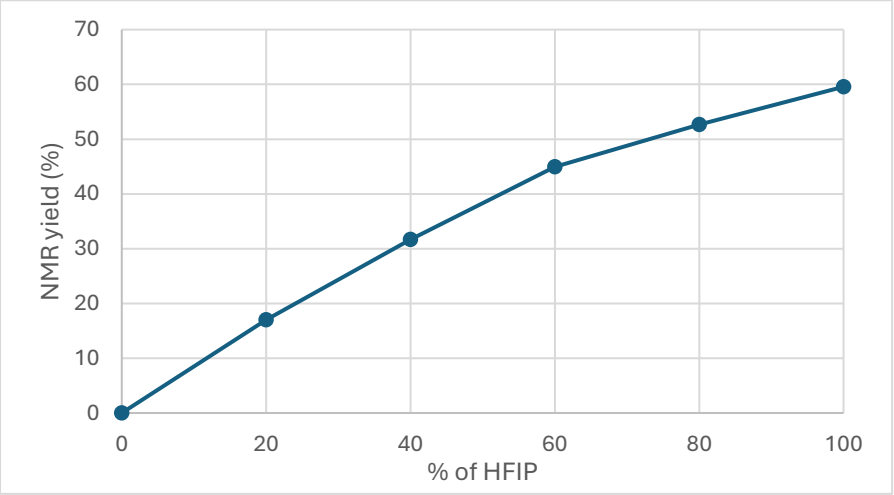


Figure S2: Graph showing the yield versus the % of HFIP in the solvent

Entry	HFIP:EtOAc	Yield (%)[a]
1	2:8	17
2	4:6	32
3	6:4	45
4	8:2	53
5	**1:0**	**60**

Reactions conditions: 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (0.1 mmol), solvent (*c* = 0.1 M), blue LEDs, 18 hours. [a]Yield determined by ^{1}H NMR with trichloroethene as the internal standard.

2.2. Effect of Concentration on the Reaction Yield

Entry	HFIP Conc. (M)	Yield (%)[a]
1	0.050	57
2	0.066	61
3	**0.100**	**60**
4	0.133	56
5	0.200	53
6	0.400	46

Reaction conditions: 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (0.1 mmol), HFIP (*c* = X M), blue LEDs, 18 hours. [a]Yield determined by ^{1}H NMR with trichloroethene as the internal standard.

2.3. Reaction Profile over Time

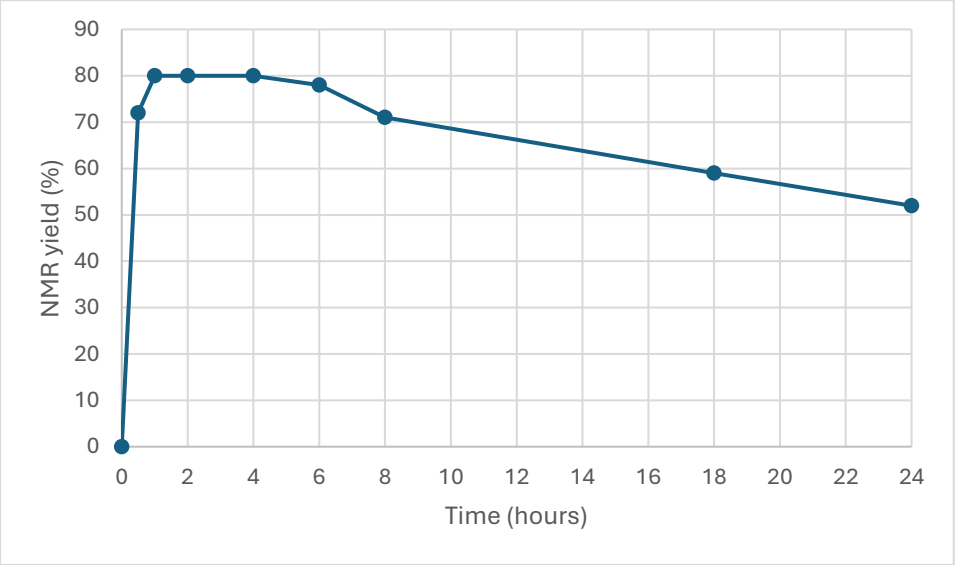


Figure S3: Kinetics study of the reaction between **1a** and HFIP

Entry	Time (hours)	Yield (%)[a]
1	0.5	72
2	**1**	**80**
3	2	80
4	4	80
5	6	78
6	8	71
7	18	59
8	24	52

Reaction conditions: 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (0.1 mmol), HFIP (*c* = 0.1 M), blue LEDs, X hours. [a]Yield determined by ^{1}H NMR with trichloroethene as the internal standard.

2.4. Assessing the Reaction with DCM

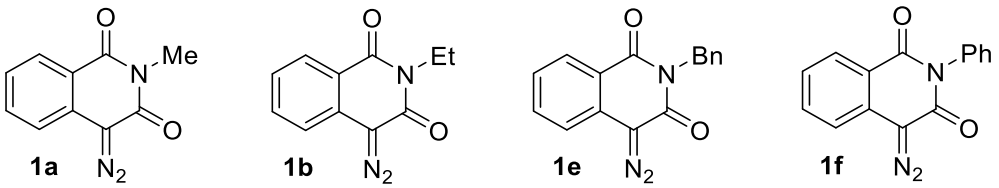
Entry	HFIP:DCM	Yield (%)[a]
1	2:8	49
2	4:6	50
3	6:4	60

Reactions conditions: 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (0.1 mmol), solvent (*c* = 0.1 M), blue LEDs, 1.5 hours. [a]Yield determined by ^{1}H NMR with trichloroethene as the internal standard.

Conclusions: All photochemical X-H insertion reactions were performed for 1.5 hours in neat HFIP to ensure that full conversion of the diazo compound is achieved for all substrates. Sustained reaction time gradually decomposes the product under the reaction conditions.

3. UV-Vis Spectra of Diazo Compounds

3.1. Influence of *N*-substituents



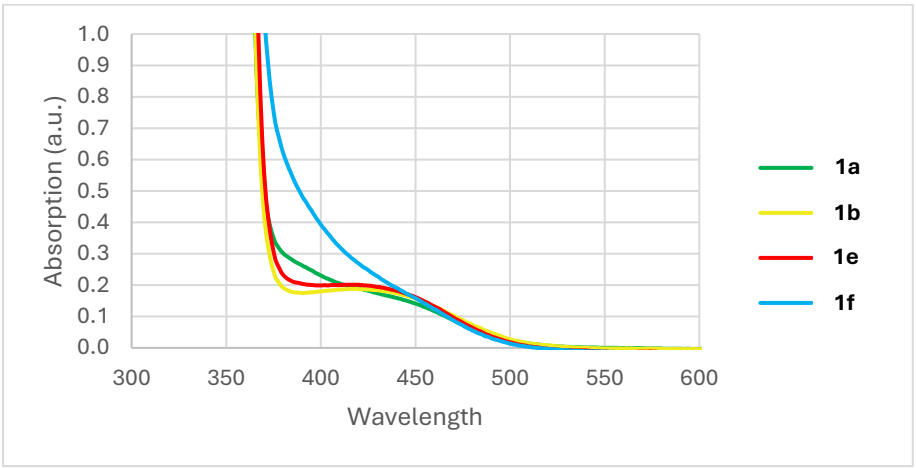
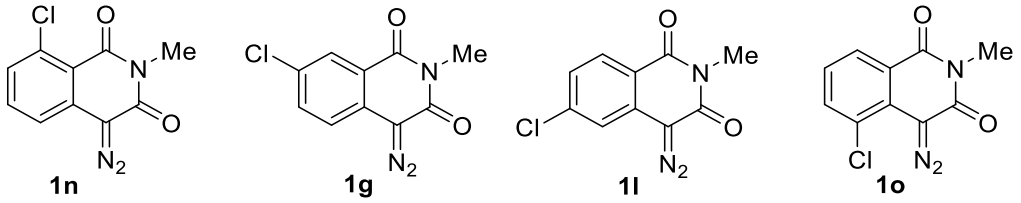


Figure S4: Influence of *N*-substituents on UV-Vis spectra. *c* = 0.006 M (DCM).

3.2. Influence of the Position of Cl-Substituents on the Aryl Ring



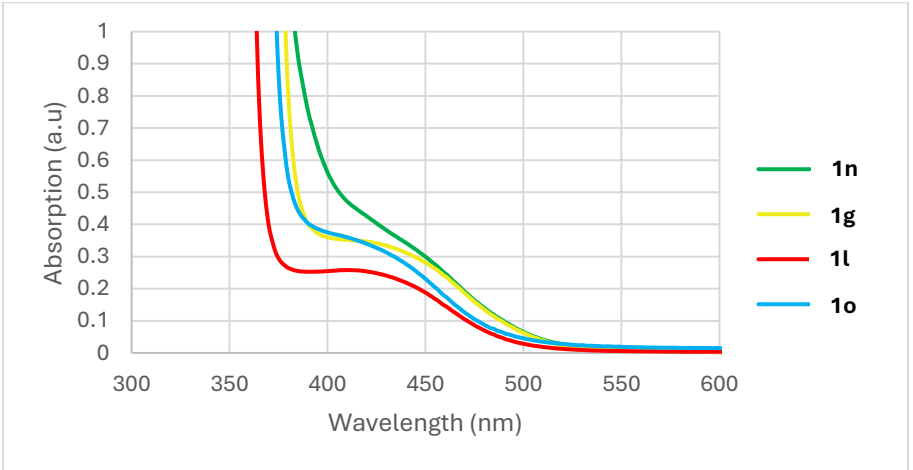


Figure S5: Influence of the position of Cl-substituents on the UV-Vis spectra. *c* = 0.006 M (DCM)

3.3. Influence of Substituents at the 7-Position

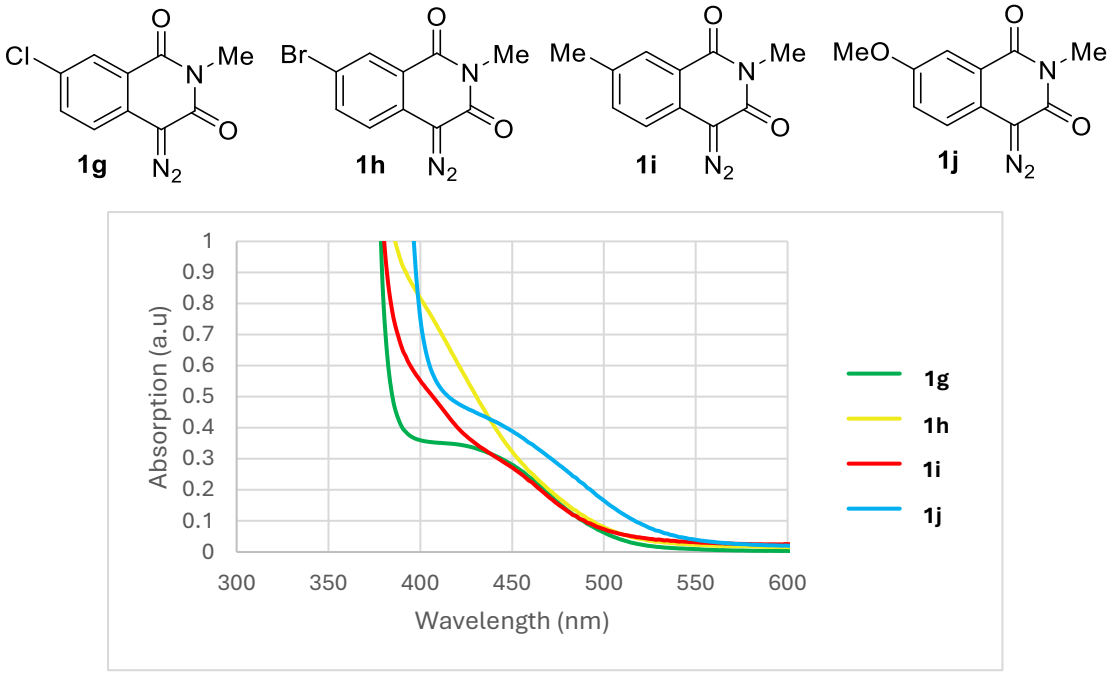


Figure S6: Influence of different functional groups at the 7-position on the UV-Vis spectra. *c* = 0.006 M (DCM)

3.4. UV-Vis of Sulfoxide-Containing Diazo Compounds

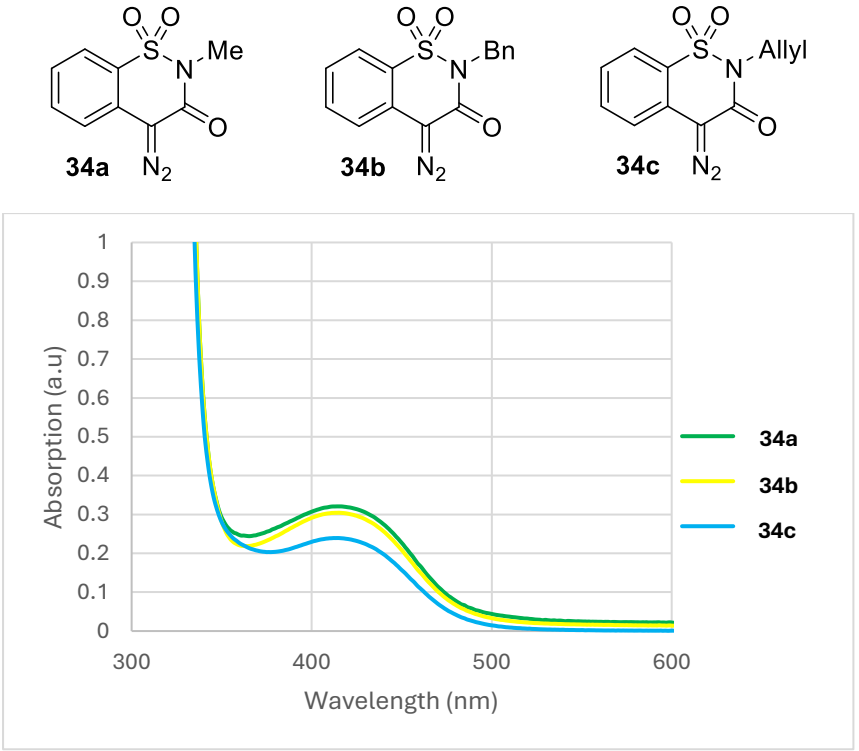


Figure S7: UV-Vis spectra of 4-diazo-2H-benzo[e][1,2]thiazin-3(4H)-one 1,1-dioxides. *c* = 0.006 M (DCM)

3.5. Comparing the Two Families of Diazo Compounds

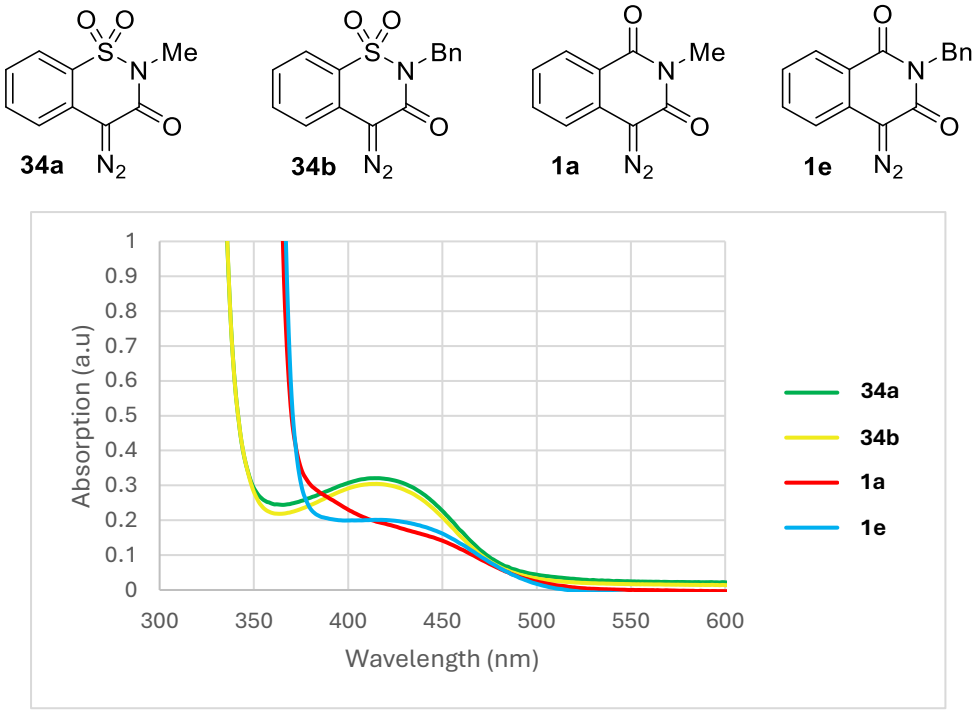
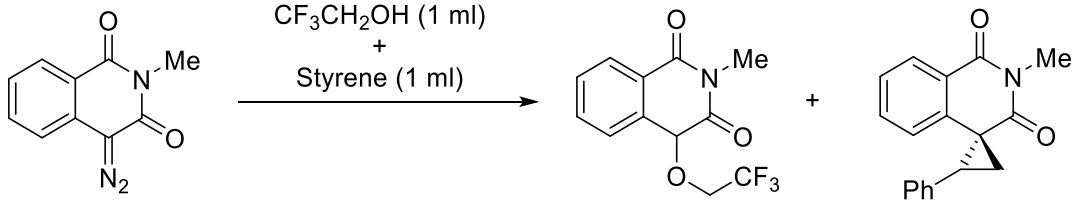
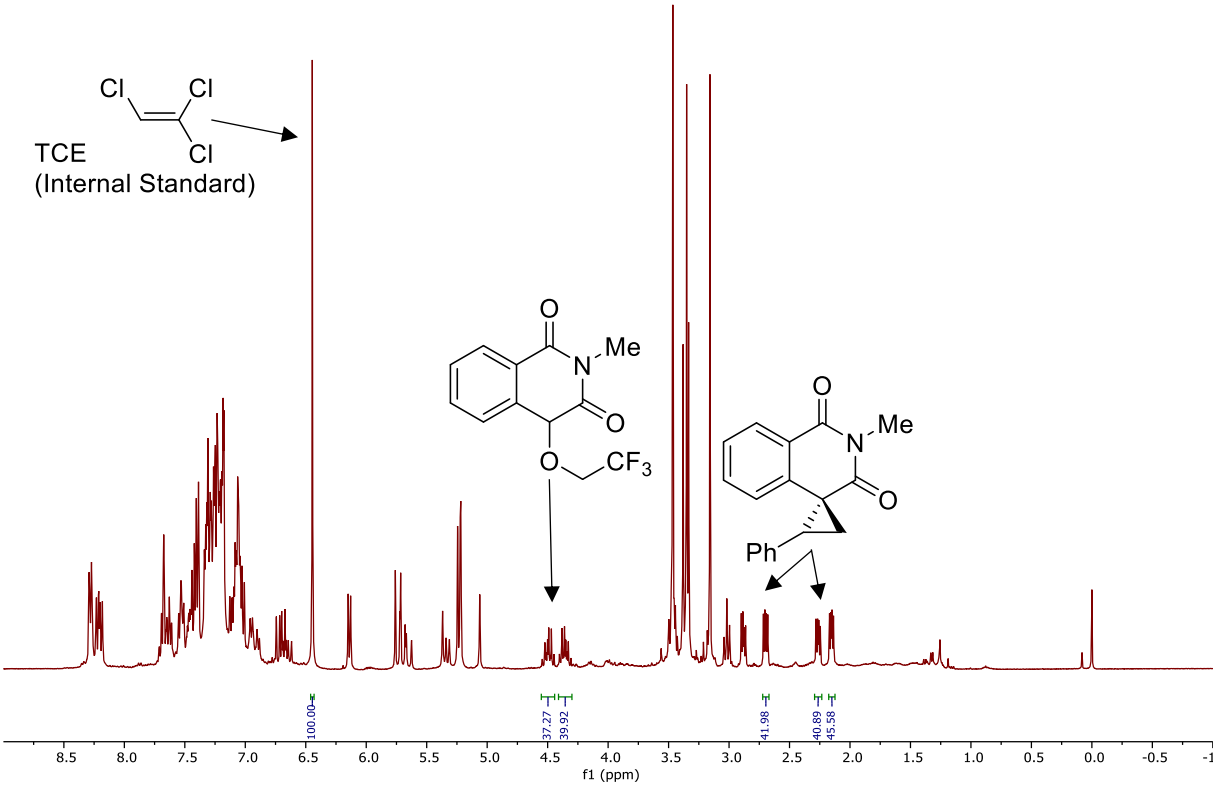


Figure S8: Comparing the UV-Vis spectra of the two families of diazo compound.
c = 0.006 M (DCM)

4. Mechanistic Considerations

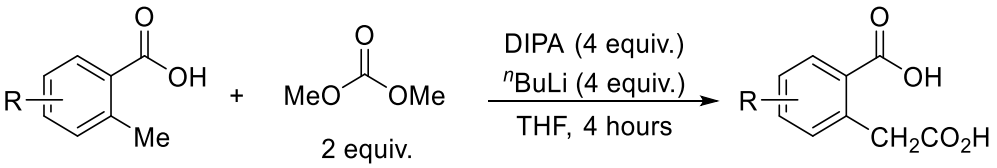
To confirm that the reaction forms carbenes, we performed a control experiment with a 1:1 mixture (by volume) of trifluoroethanol (TFE) and styrene. 4-Diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) was dissolved in a 1:1 mixture of TFE and styrene (2 ml total) and irradiated for 1.5 hours. The volatiles were removed in vacuo and dried on a vacuum pump. Trichloroethene was added as internal standard, and the crude mixture was subjected to ^{1}H NMR analysis to afford approximately 21% O-H insertion adduct and 24% cyclopropanation adduct. Therefore, the reaction indeed forms a carbene intermediate.





5. General Procedures

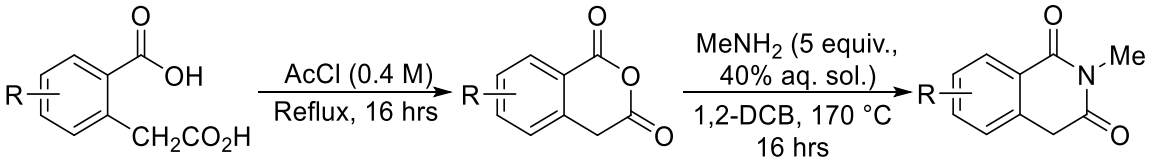
5.1. General Procedure A - Synthesis of Substituted (2-(Carboxymethyl)benzoic acids)



Slightly modified procedure to that reported by Tsou et al. [1]

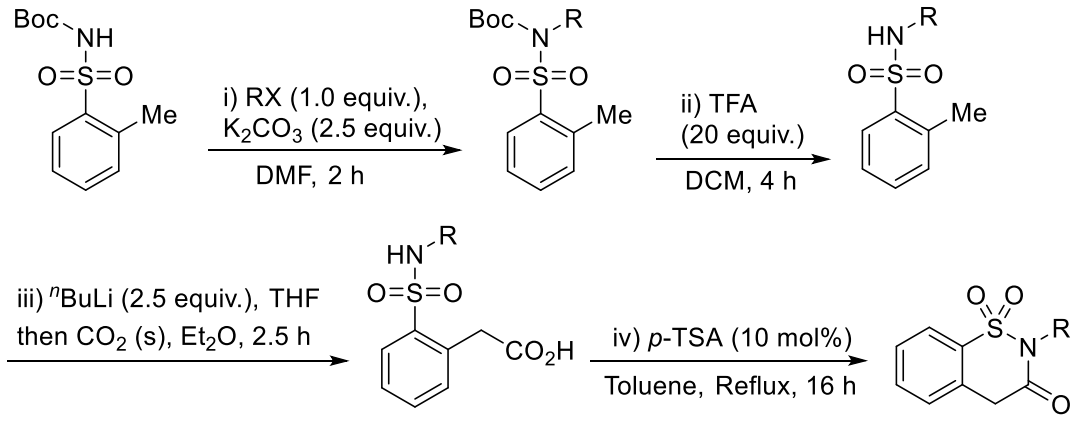
Diisopropylamine (DIPA, 4.0 equiv.) is added to a flame-dried flask followed by the addition of dry THF (*c* = 3 M with respect to DIPA) then the flask is cooled to -78 °C. ^{n}BuLi (2.5 M in hexanes, 4.0 equiv.) is added dropwise to the solution, warmed to 0 °C and maintained at 0 °C for 5 minutes, then cooled to -78 °C. A solution of dimethyl carbonate (2.0 equiv.) and substituted 2-methylbenzoic acid (1.0 equiv.) in the minimum amount of dry THF, is added dropwise to the freshly prepared LDA solution. After the addition, the reaction is kept at -78 °C for 15 minutes, then warmed to room temperature and stirred for 4 hours. The reaction mixture gradually became turbid over time. After 4 hours, the mixture is diluted with water until the turbidity of the solution significantly reduced, stirred for 30 minutes and the layers are separated. The bottom aq. layer is acidified to pH ~2 with 2 M HCl and extracted with EtOAc thrice. The organic layers are washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The crude residue is triturated in boiling chloroform (60 °C) to afford the diacid.

5.2. General Procedure B - Synthesis of Substituted *N*-Methylisoquinoline-1,3(2*H*,4*H*)-diones



Substituted 2-(carboxymethyl)benzoic acid (1.0 equiv.) is charged in a flask and dissolved in acetyl chloride (*c* = 0.4 M with respect to the benzoic acid). The reaction mixture is refluxed for 16 hours, cooled to room temperature and the remaining acetyl chloride is removed in vacuo and the crude residue is dried on a vacuum pump. Once dry, methylamine (40% aq. solution, 5.0 equiv.) is added to the crude solid and stirred for 5 minutes, then 1,2-dichlorobenzene (1,2-DCB, *c* = 0.35 M with respect to the intermediate isochromane-1,3-dione) is added, a water-cooled reflux condenser is attached to the flask and the reaction is heated to 170 °C for 16 hours. The flask is cooled to room temperature and the crude reaction mixture is pipetted on top of a prepacked silica column and subjected to column chromatography (SiO_2, 20% EtOAc in hexane) to afford the desired isoquinoline-1,3(2*H*,4*H*)-dione.

5.3. General Procedure C - Synthesis of 2*H*-Benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides



tert-Butyl (*o*-tolylsulfonyl)carbamate was synthesised according to the procedure described by Liu et al.[2] Steps i) and ii) are slightly modified procedures of Barbazanges et al.[3] Steps iii) and iv) are modified procedures of Lombardino and Wiseman.[4]

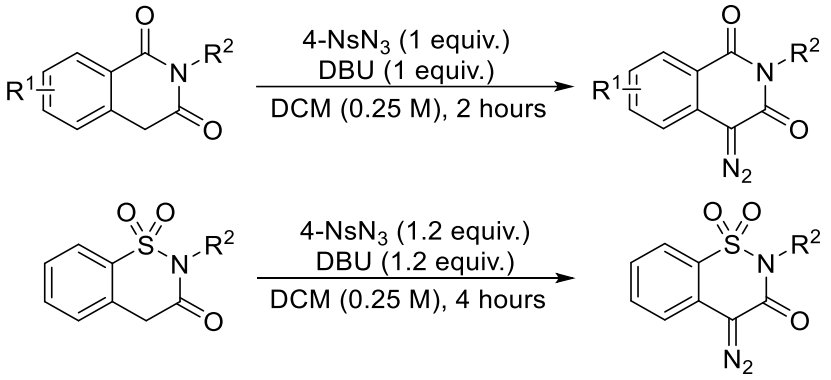
i) *tert*-Butyl (*o*-tolylsulfonyl)carbamate (1.0 equiv.) is charged in a flask followed by the addition of K_2CO_3 (2.5 equiv.) and DMF (*c* = 0.8 M with respect to the carbamate), then the reaction is vigorously stirred for 1 hour. Alkyl bromide/iodide (1.0 equiv.) is added dropwise and stirred for an additional hour. The reaction mixture is diluted with water and transferred to a separating funnel and extracted with diethyl ether thrice. The organic layer is washed with water and brine, dried (Na_2SO_4), filtered and concentrated and used immediately in the next step.

ii) The trisubstituted amine is charged in a flask and dissolved in DCM (*c* = 0.16 M with respect to the amine) followed by the dropwise addition of trifluoroacetic acid (TFA) (20.0 equiv.). After 4 hours, sat. aq. $NaHCO_3$ is added slowly to the reaction flask to quench the excess TFA. The contents of the flask is transferred to a separating funnel, then extracted with DCM thrice. The organic layer is washed with sat. aq. $NaHCO_3$ thrice and brine, dried (Na_2SO_4), filtered, concentrated and extensively dried on a vacuum pump.

iii) The solid thus obtained is transferred to a flame-dried flask, dissolved in dry THF (*c* = 0.2 M with respect to the sulfonamide) and cooled to 0 °C. ^{n}BuLi (2.5 M in hexanes, 2.5 equiv.) is added dropwise to the solution, which turns yellow and after further addition, red, then the ice bath is removed, and the reaction is allowed to stir for a further 30 minutes at room temperature. The contents of the flask are transferred via a syringe to a second flask containing dry ice and diethyl ether (*c* = 0.1 M with respect to the sulfonamide) with a stir bar and is left to stir for 2 hours. After this time, the reaction is quenched with 2 M HCl (same volume as THF in the reaction), and the solution is transferred to a separating funnel, where the aq. layer is extracted with chloroform thrice. The organic layer is washed with brine, dried (Na_2SO_4), filtered, concentrated and used immediately in the next step.

iv) Toluene (*c* = 0.0625 M with respect to the carboxylic acid) is added to the carboxylic acid followed by the addition of *p*-toluenesulfonic acid monohydrate (10 mol%) and the reaction is heated at reflux for 16 hours. Toluene is removed in vacuo and the crude residue is subjected to column chromatography (SiO_2, 10 -> 20% EtOAc in hexane) to afford the 2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide product.

5.4. General Procedure D - Synthesis of Diazo Compounds

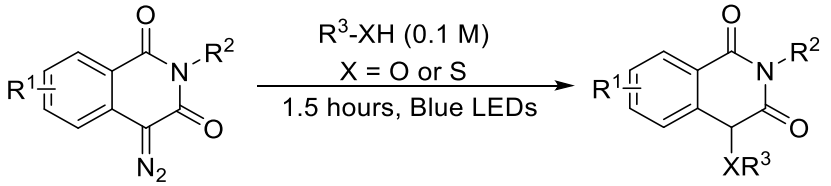


Diazo compounds were synthesised via an analogous procedure as reported by Kantin et al.[5]

A) Isoquinoline-1,3(2*H*,4*H*)-dione and 4-nitrobenzenesulfonyl azide[6] (4-NsN_3, 1.0 equiv.) are charged in a flask and dissolved in DCM (*c* = 0.25 M with respect to the isoquinoline-1,3(2*H*,4*H*)-dione). 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) (1.0 equiv.) is then added dropwise to the flask and an immediate colour change is observed. After two hours, the solution is pipetted on top of a pre-packed column and subjected to column chromatography (SiO_2, 20% EtOAc in hexane) to afford the respective diazo compound.

B) An analogous general procedure is used for the synthesis of 4-diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides, with 1.2 equiv. of 4-NsN_3 and 1.2 equiv. of DBU and the reaction time is extended to 4 hours.

5.5. General Procedure E - O-H and S-H Insertion Reactions of 4-Diazoisoquinoline-1,3(2*H*,4*H*)-diones

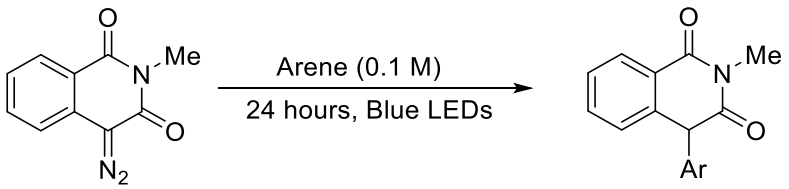


4-Diazoisoquinoline-1,3(2*H*,4*H*)-dione (0.20 mmol) is charged in a vial and dissolved in the respective alcohol or thiol (2 ml) then the vial is capped. The vial is irradiated with blue LEDs for typically 1.5 hours at approximately 15 °C then the cap is removed.

For volatile alcohols/thiols: The solution is transferred to a flask with DCM and all the volatiles are removed in vacuo. The crude residue is purified by column chromatography (SiO_2, 10% EtOAc in hexane) to afford the X-H insertion product.

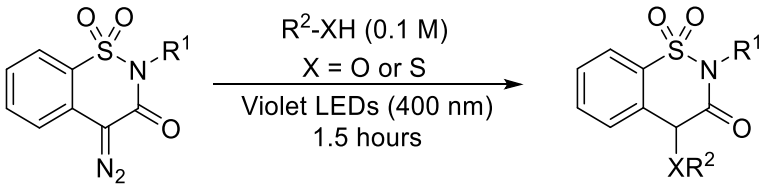
For non-volatile alcohols/thiols: The solution is directly pipetted on top of a prepacked column and subjected to column chromatography (SiO_2, 10% EtOAc in hexane) to afford the X-H insertion product.

5.6. General Procedure F – Arene Insertion Reactions of 4-Diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-diones



4-Diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (0.20 mmol) is charged in a vial and dissolved in the respective arene (2 ml) then the vial is capped. The vial is irradiated with blue LEDs for 24 hours at approx. 15 °C then the cap is removed, and the crude residue is pipetted on top of a prepacked silica column (SiO_2, 10% - 20% EtOAc in hexane) to afford the C-H insertion product.

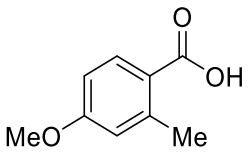
5.7. General Procedure G - O-H and S-H Insertion Reactions of 4-Diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides



General Procedure: 4-Diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (0.15 mmol) is charged in a vial and dissolved in the respective alcohol or thiol (1.5 ml) then the vial is capped. The vial is irradiated with violet LEDs for 1.5 hours at approx. 15 °C then the reaction mixture is transferred to a flask with DCM and all the volatiles are removed in vacuo. The crude residue is purified by column chromatography (SiO_2, 10% EtOAc in hexane) to afford the X-H insertion product.

6. (2-(Carboxymethyl))benzoic acids

4-methoxy-2-methylbenzoic acid (S1)



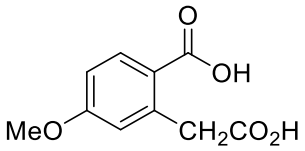
The title compound was synthesised from 4-hydroxy-2-methylbenzoic acid (2.28 g, 15.0 mmol) via an analogous procedure by Lobb et al. for the methylation of 2-chloro-4-methoxybenzoic acid[7] in 94% yield (2.34 g) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 7.84 (d, J = 8.2 Hz, 1H), 6.84 – 6.81 (m, 2H), 3.79 (s, 3H), 2.52 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.9, 161.7, 142.1, 132.7, 122.1, 116.7, 111.1, 55.2, 21.8.

The spectroscopic data is consistent with that previously reported in the literature.[8]

2-(carboxymethyl)-4-methoxybenzoic acid (S2)



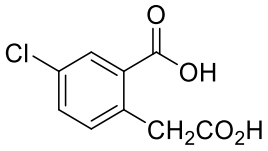
The title compound was synthesised according to General Procedure A from 4-methoxy-2-methylbenzoic acid (2.50 g, 15.0 mmol) in 53% yield (1.66 g) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 2H), 7.89 (d, J = 8.4 Hz, 1H), 6.93 – 6.89 (m, 2H), 3.92 (s, 2H), 3.81 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.3, 167.6, 161.7, 139.2, 132.7, 122.4, 117.9, 111.9, 55.3. (One peak overlaps with the residual DMSO peaks.)

The spectroscopic data is consistent with that previously reported in the literature.[9]

2-(carboxymethyl)-5-chlorobenzoic acid (S3)



The title compound was synthesised according to General Procedure A from 5-chloro-2-methylbenzoic acid (2.13 g, 12.5 mmol) in 84% yield (2.26 g) as a white solid.

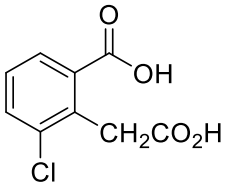
^{1}H NMR (500 MHz, DMSO-d_6) δ 12.74 (s, 2H), 7.85 (d, J = 2.4 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.38 (dd, J = 8.3, 3.1 Hz, 1H), 3.93 (s, 2H).

^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 172.1, 167.0, 135.5, 134.3, 132.5, 131.5, 129.8. (CH_2 peak is overlapping with one of the DMSO residual solvent peaks. One of the quaternary aromatic peaks were not observed).

m.p. 195 – 198 °C (lit. 195 – 198 °C)[10]

The spectroscopic data is consistent with that previously reported in the literature.[11]

2-(carboxymethyl)-3-chlorobenzoic acid (S4)



The title compound was synthesised according to General Procedure A from 3-chloro-2-methylbenzoic acid (2.13 g, 12.5 mmol) in 83% yield (2.24 g) as a yellow solid.

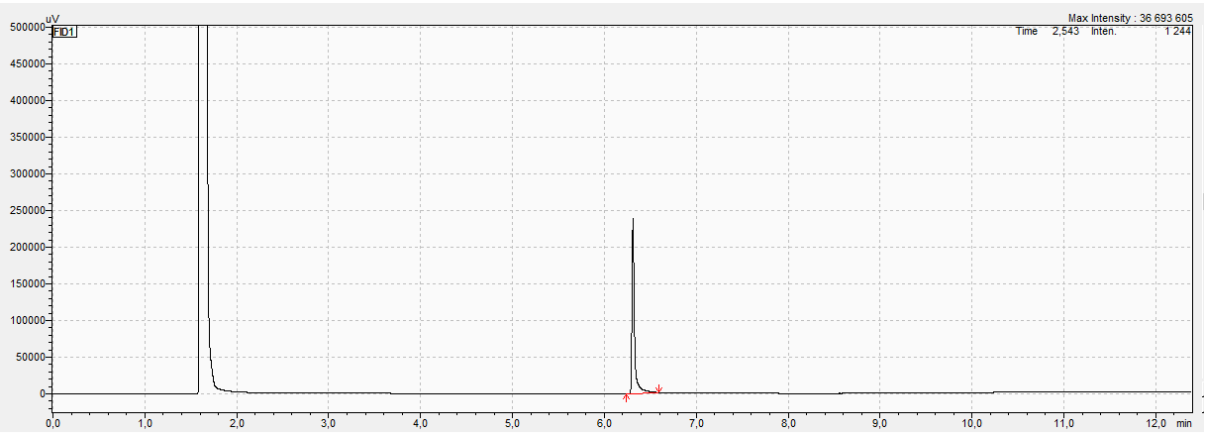
^{1}H NMR (500 MHz, DMSO-d_6) δ 12.82 (s, 2H), 7.84 (dd, J = 7.8, 1.4 Hz, 1H), 7.69 – 7.67 (m, 1H), 7.40 (td, J = 8.0, 4.6 Hz, 1H), 4.13 (s, 2H).

^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 171.1, 167.7, 135.6, 133.8, 133.4, 132.5, 129.2, 128.3, 35.8.

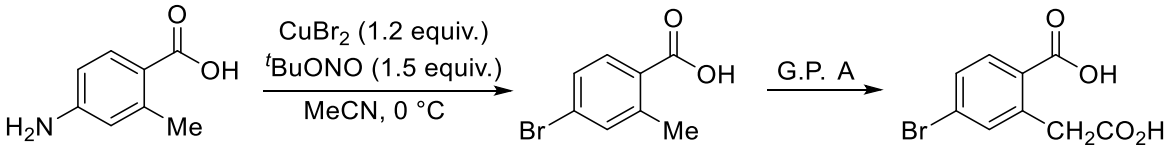
HRMS (ESI^{-}) m/z calc'd for $C_9H_6O_4Cl^{-}$: 212.9955; found: 212.9957 [M-H^{+}]

m.p. 171 – 172 °C (lit. 174 – 176 °C)[10]

GC (FID):



4-bromo-2-(carboxymethyl)benzoic acid (S5)



4-Bromo-2-methylbenzoic acid was synthesised according to an analogous procedure by Glennon et al. for the bromination of 4-amino-2-hydroxybenzoic acid.[12]

Copper (II) bromide (5.36 g, 24.0 mmol) is charged in a flask followed by the addition of MeCN (60 mL) and cooled to 0 °C. *tert*-Butyl nitrite (3.6 mL, 30 mmol) is added in one portion to the reaction mixture and 4-amino-2-methylbenzoic acid (3.02 g, 20.0 mmol) is added portionwise and the reaction is stirred for a further two hours at 0 °C. After this time, the solution is basified to pH ~10 with 3 M NaOH and washed with Et_2O twice. The aq. layer is acidified to pH ~2 and extracted with EtOAc thrice, the organic layer is washed with brine twice, dried (Na_2SO_4), filtered and concentrated. 4-bromo-2-methylbenzoic acid (2.32 g) was afforded in approximately 90% purity and used immediately in General Procedure A, without any further purification, to afford the title compound in 35% yield (2 steps, 1.79 g) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.66 (s, 2H), 7.82 (d, J = 8.3 Hz, 1H), 7.62 – 7.57 (m, 2H), 3.94 (s, 2H).

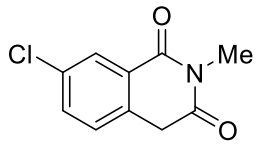
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.0, 167.5, 139.2, 135.0, 132.4, 130.0, 129.9, 125.4, 39.4.

Despite drying on a vacuum pump at 65 °C for 72 hours, traces of EtOAc and $CHCl_3$ remained in the product and are identified in the spectra. Nevertheless, the peaks corresponding to the product are consistent with those reported by Trost and Kalnmals.[13]

7. Isoquinoline-1,3(2*H*,4*H*)-diones

2-Methylisoquinoline-1,3(2*H*,4*H*)-dione was synthesised according to the procedure reported by Jangir et al.[14] 2-Ethylisoquinoline-1,3(2*H*,4*H*)-dione, 2-propylisoquinoline-1,3(2*H*,4*H*)-dione, 2-isopropylisoquinoline-1,3(2*H*,4*H*)-dione, 2-benzylisoquinoline-1,3(2*H*,4*H*)-dione, and 2-phenylisoquinoline-1,3(2*H*,4*H*)-dione were all synthesised according to the procedures reported by Kantin et al.[5] When substituents are present on the aromatic rings, we found these methods were unsuccessful or gave low yields, thus we developed General Procedure B instead.

7-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (S6)



The title compound was synthesised according to General Procedure B from 5-chloro-2-(carboxymethyl)benzoic acid 2.15 g (10.0 mmol) in 83% yield (1.74 g) as a beige solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

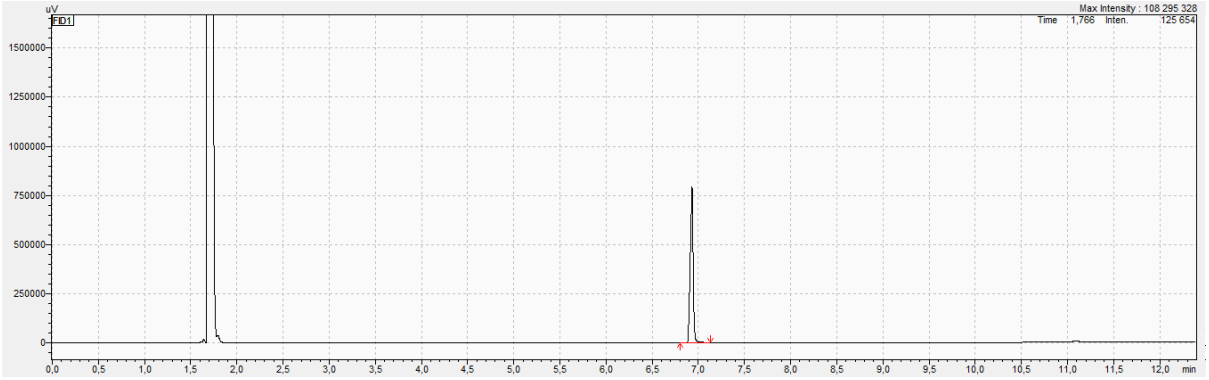
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 2.3 Hz, 1H), 7.53 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 4.00 (s, 2H), 3.36 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.7, 164.1, 134.1, 133.8, 132.3, 129.0, 128.8, 126.9, 36.0, 27.0.

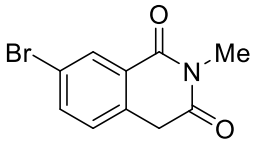
HRMS (ESI$^-$) m/z calc'd for $C_{10}H_7NO_2Cl^-$: 208.0165; found: 208.0166 [M-H$^+$]

m.p. 116 – 118 °C (lit. 116 – 118 °C)[15]

GC (FID):



7-bromo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (S7)



The title compound was synthesised according to General Procedure B from 5-bromo-2-(carboxymethyl)benzoic acid[16] (1.91 g, 7.37 mmol) in 70% yield (1.31 g) as a white solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

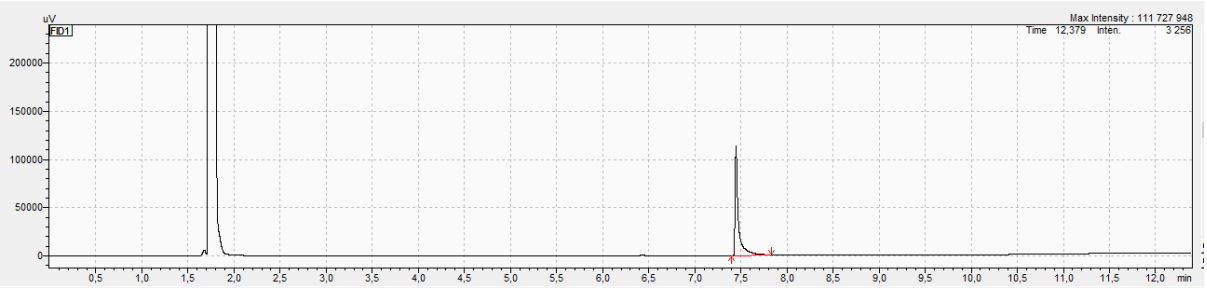
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 2.1 Hz, 1H), 7.67 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 3.97 (s, 2H), 3.34 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.6, 164.0, 136.7, 132.8, 131.9, 128.9, 127.1, 121.7, 36.0, 27.0.

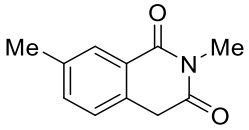
HRMS (ESI$^-$) m/z calc'd for $C_{10}H_7NO_2Br^-$: 251.9660; found: 251.9663 $[M\text{-}H^+]^-$

m.p. 132 – 134 °C

GC (FID):



2,7-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (S8)



The title compound was synthesised according to General Procedure B from 2-(carboxymethyl)-5-methylbenzoic acid[17] (457 mg, 2.35 mmol) in 61% yield (271 mg) as a yellow solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.40 – 7.38 (m, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 4.00 (s, 2H), 3.36 (s, 3H), 2.42 (s, 3H).

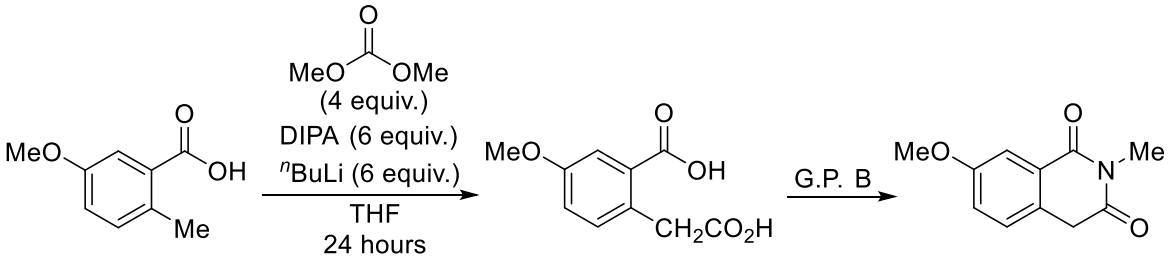
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 170.6, 165.5, 137.8, 134.8, 131.2, 129.3, 127.2, 125.2, 36.2, 26.9, 21.2.

HRMS (ESI$^+$) m/z calc'd for $C_{11}H_{12}NO_2^+$: 190.0868; found: 190.0874 $[M+H]^+$

m.p. 134 – 136 °C

GC (FID):

7-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (S9)



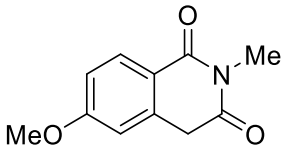
Diisopropylamine (7.31 g, 72.0 mmol, 6.00 equiv.) is added to a flame-dried flask followed by the addition of dry THF (24 mL) then the flask is cooled to -78 °C. ^{n}BuLi (29 mL, 2.5 M in hexanes, 72.0 mmol, 6.00 equiv.) is added dropwise to the solution, warmed to 0 °C and maintained at 0 °C for 5 minutes, then cooled to -78 °C. A solution of dimethyl carbonate (4.34 g, 4.00 equiv.) and 5-methoxy-2-methylbenzoic acid (2.00 g, 12.0 mmol, 1.0 equiv.) in the minimum amount of dry THF, is added dropwise to the freshly prepared LDA solution. After the addition, the reaction is kept at -78 °C for 1 hour, then warmed to room temperature and stirred for 18 hours. The reaction mixture gradually became turbid over time. After 18 hours, the mixture is diluted with water until the turbidity of the solution significantly reduced, stirred for 30 minutes and the layers are separated. The bottom aq. layer is acidified to pH ~2 with 2 M HCl and extracted with EtOAc thrice. The organic layers are washed with water and brine, dried (Na_2SO_4), filtered and concentrated. The crude residue is triturated in boiling chloroform (60 °C) which afforded 962 mg of 2-(carboxymethyl)-5-methoxybenzoic acid in approximately 90% purity. The beige solid was used in General Procedure B, without any further purification, to afford the title compound in 27% yield (2 steps, 674 mg) as a yellow solid. Eluent for column chromatography (SiO_2): gradually from 20% of EtOAc in hexane to 30%.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.6 Hz, 1H), 7.18 – 7.14 (m, 2H), 3.98 (s, 2H), 3.88 (s, 3H), 3.37 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 170.6, 165.3, 159.2, 128.5, 126.3, 122.1, 111.4, 55.8, 35.8, 27.0.

The spectroscopic data is consistent with that previously reported in the literature [18]

6-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (S10)



The title compound was synthesised according to General Procedure B from 2-(carboxymethyl)-4-methoxybenzoic acid (1.22 g, 5.82 mmol) in 62% yield (745 mg) as a colourless solid. Eluent for column chromatography (SiO_2): gradually from 20% of EtOAc in hexane to 30%.

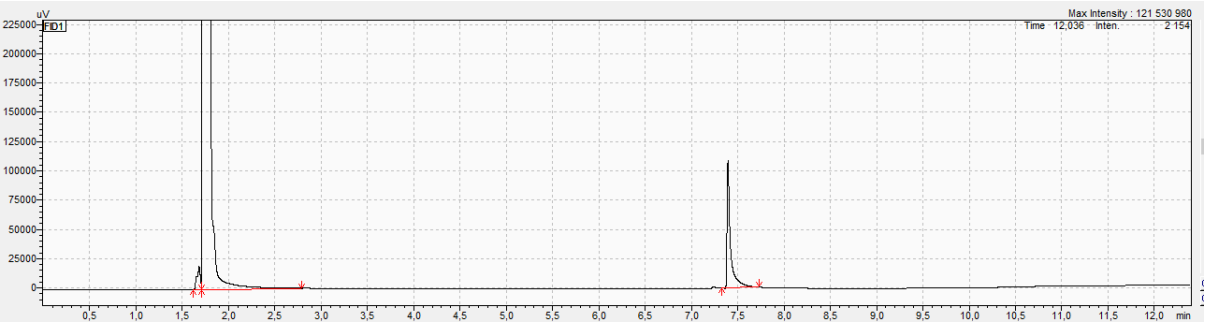
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.9, 1.8 Hz, 1H), 6.95 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.71 – 6.70 (m, 1H), 4.00 (s, 2H), 3.88 (s, 3H), 3.35 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 170.4, 164.9, 164.0, 136.4, 131.4, 118.3, 114.5, 111.4, 55.8, 36.7, 26.8.

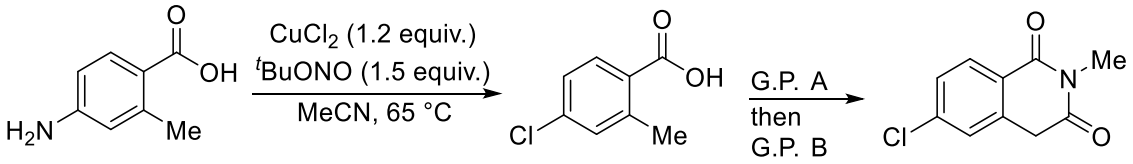
HRMS (ESI$^+$) m/z calc'd for $C_{11}H_{12}NO_3^+$: 206.0817; found: 206.0818 $[M+H]^+$

m.p. 169 – 171 °C

GC (FID):



6-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (S11)



4-chloro-2-methylbenzoic acid was synthesised according to an analogous procedure by Doyle et al. for the chlorination of 2-aminobenzoic acid.[19]

To a flame-dried flask under argon was added copper(II) chloride (3.23 g, 24.0 mmol) and dry MeCN (40 mL), then the flask was cooled to 0 °C. *tert*-Butyl nitrite (3.09 g, 30.0 mmol) was added in one portion followed by the portionwise addition of 4-amino-2-methylbenzoic acid (3.02 g, 20.0 mmol), then the reaction mixture was heated to 65 °C for 1 hour. After this time, the reaction was cooled to room temperature and poured into a 20% conc. HCl solution and extracted with diethyl ether twice. The organic layers were washed with a 20% conc. HCl solution and brine, dried (Na_2SO_4), filtered and concentrated which afforded 2.78 g of 4-chloro-2-methylbenzoic acid in approximately 85% purity. The impure 4-chloro-2-methylbenzoic acid was subjected to General Procedure A and General Procedure B successively to afford the title compound as a beige solid in overall 14% yield (574 mg). Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

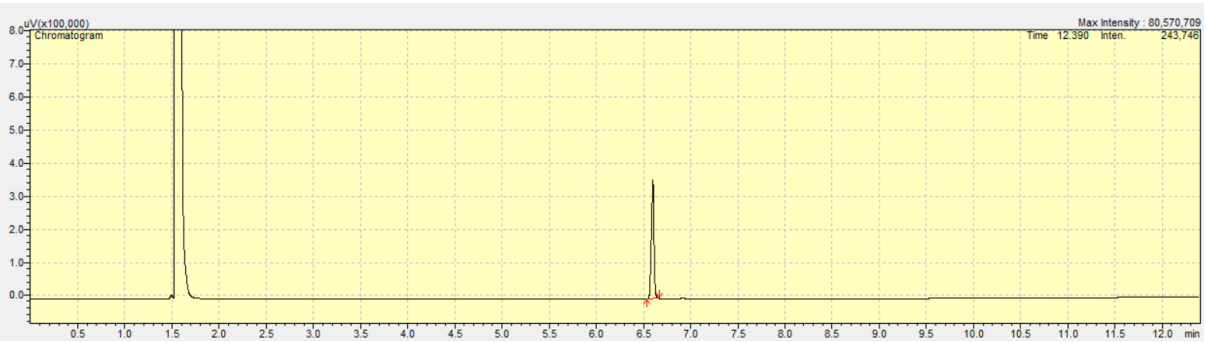
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 1H), 7.43 – 7.41 (m, 1H), 7.29 (s, 1H), 4.02 (s, 2H), 3.37 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.5, 164.4, 140.3, 135.7, 130.8, 128.5, 127.3, 124.0, 36.2, 27.0.

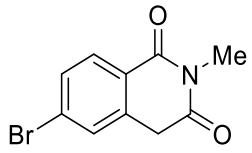
HRMS (APCI$^+$) m/z calc'd for $C_{10}H_9NO_2Cl^+$: 210.0322; found: 210.0326 $[M+H]^+$

m.p. 110 °C (dec., purple discolouration observed)

GC (FID):



6-bromo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (S12)



The title compound was synthesised according to General Procedure B from 4-bromo-2-(carboxymethyl)benzoic acid (1.69 g, 6.52 mmol) in 56% yield (929 mg) as a beige solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

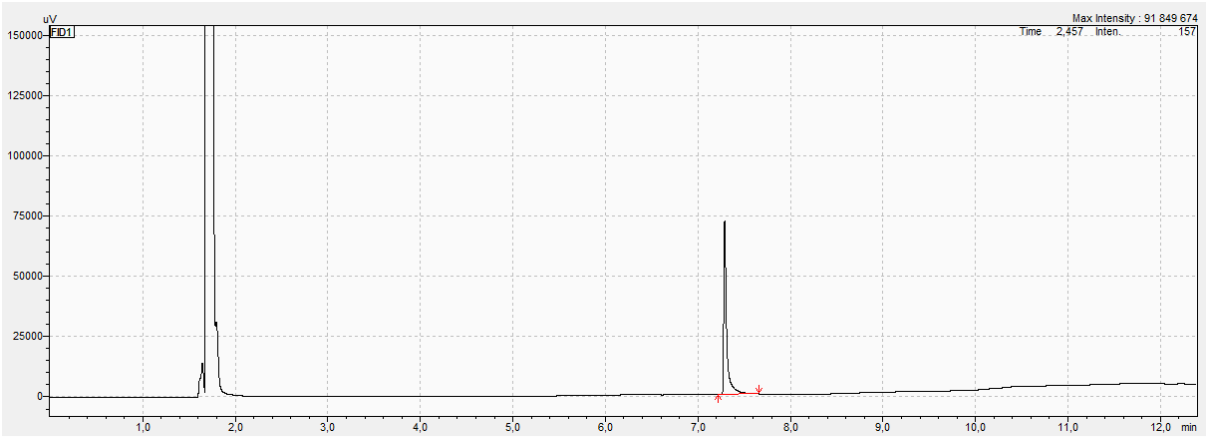
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.46 (s, 1H), 4.02 (s, 2H), 3.36 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.5, 164.6, 135.8, 131.5, 130.8, 130.3, 128.9, 124.4, 36.1, 27.0.

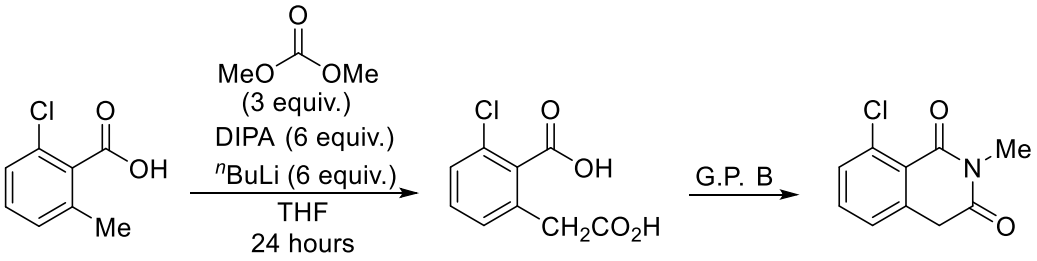
HRMS (ESI$^-$) m/z calc'd for $C_{10}H_7NO_2Br^-$: 251.9660; found: 251.9661 $[M\text{-}H^+]^-$

m.p. 150 °C (purple discolouration observed)

GC (FID):



8-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (S13)



Diisopropylamine (DIPA) (7.59 g, 75.0 mmol, 6.00 equiv.) is added to a flame-dried flask followed by the addition of dry THF (30 mL) then the flask is cooled to -78 °C. ^{n}BuLi (30 mL, 2.5 M in hexanes, 75.0 mmol, 6.00 equiv.) is added dropwise to the solution, warmed to 0 °C and maintained at 0 °C for 5 minutes, then cooled to -78 °C. A solution of dimethyl carbonate (3.38 g, 37.5 mmol, 3.0 equiv.) and 2-chloro-6-methylbenzoic acid (2.13 g, 12.5 mmol) in the minimum amount of dry THF, is added dropwise to the freshly prepared LDA solution. After the addition, the reaction is kept at -78 °C for 1 hour, then warmed to room temperature and stirred for 18 hours. The solution is then diluted with water (75 mL) until the turbidity of the mixture significantly reduced, stirred for 30 minutes and the layers are separated. The bottom aq. layer is acidified to pH ~2 with 2 M HCl and extracted with EtOAc thrice. The organic layers are washed with water and brine, dried (Na_2SO_4), filtered and concentrated and dried further on a vacuum pump. The brown sticky residue was subjected to General Procedure B, without further purification, to afford the title compound in 26% yield (670 mg) as a brown solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

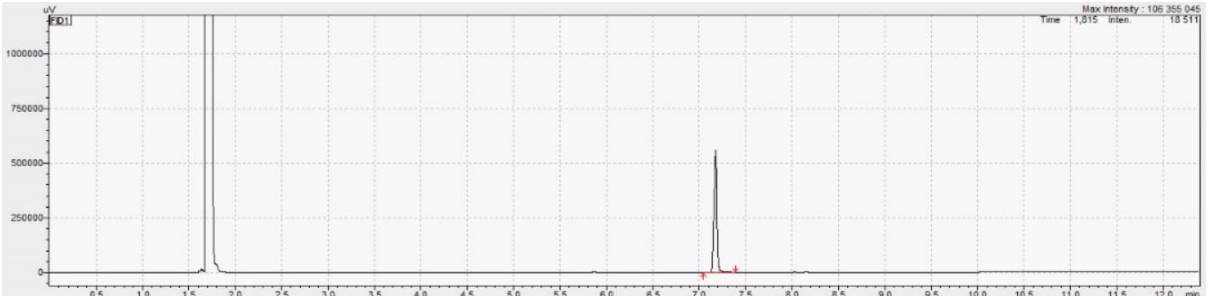
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.21 – 7.19 (m, 1H), 4.05 (s, 2H), 3.36 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.0, 163.0, 136.9, 136.6, 133.3, 131.8, 126.3, 122.5, 37.1, 27.2.

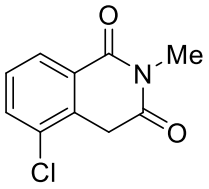
HRMS (ESI$^-$) m/z calc'd for $C_{10}H_7NO_2Cl^-$: 208.0165; found: 208.0167 $[M\text{-}H^+]^-$

m.p. 195 °C (dec.)

GC (FID):



5-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (S14)



The title compound was synthesised according to General Procedure B from 2-(carboxymethyl)-3-chlorobenzoic acid (2.13 g, 9.91 mmol) in 93% yield (1.94 g) as a white solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

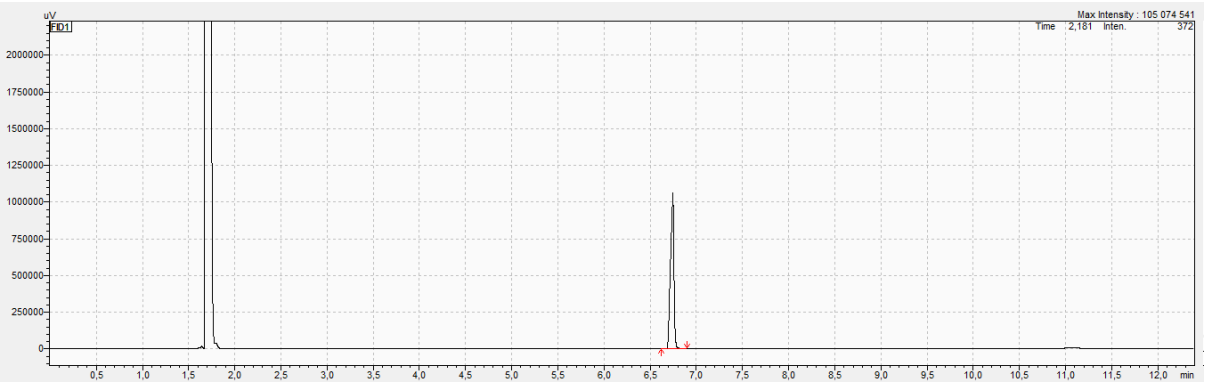
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 4.02 (s, 2H), 3.37 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.1, 164.3, 134.1, 132.9, 132.3, 128.8, 127.8, 127.3, 35.0, 27.0.

HRMS (ESI$^-$) m/z calc'd for $C_{10}H_7NO_2Cl^-$: 208.0165; found: 208.0166 $[M\text{-}H^+]^-$

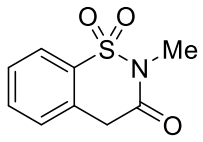
m.p. 126 – 128 °C

GC (FID):



8. 2*H*-Benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides

2-methyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (S15)



The title compound was synthesised according to General Procedure C, from *tert*-butyl (*o*-toylsulfonyl)carbamate (2.71 g, 10.0 mmol) in 43% yield (899 mg) as a white solid. Eluent for column chromatography (SiO_2): gradually from 10% of EtOAc in hexane to 20%.

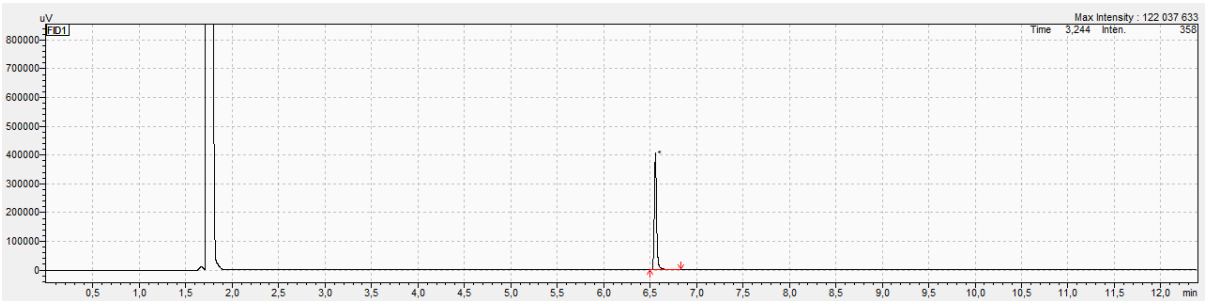
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.60 (td, *J* = 7.6, 1.3 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 4.09 (s, 2H), 3.28 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.3, 135.9, 133.7, 131.3, 128.8, 128.1, 123.1, 39.5, 27.2.

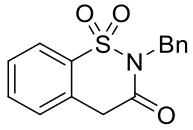
HRMS (ESI$^-$) m/z calc'd for $C_9H_8NO_3S^-$: 210.0225; found: 210.0224 $[M\text{-}H^+]^-$

m.p. 88 – 91 °C (lit. 89 - 91 °C)[20]

GC (FID):



2-benzyl-2*H*-benzo[e][1,2]thiazin-3(4*H*)-one 1,1-dioxide (S16)



The title compound was synthesised according to General Procedure C, from *tert*-butyl (*o*-toylsulfonyl)carbamate (2.17 g, 8.00 mmol) in 43% yield (988 mg) as a white solid. Eluent for column chromatography (SiO_2): gradually from 10% of EtOAc in hexane to 20%.

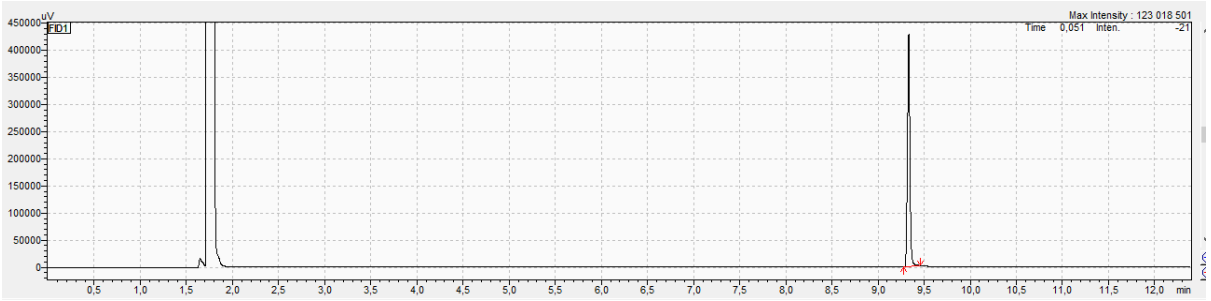
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.59 (td, *J* = 7.6, 1.3 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.42 – 7.40 (m, 2H), 7.38 – 7.36 (m, 1H), 7.32 – 7.29 (m, 2H), 7.27 – 7.24 (m, 1H), 5.00 (s, 2H), 4.12 (s, 2H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.2, 136.4, 136.0, 133.7, 131.4, 128.9, 128.7, 128.6, 128.1, 128.0, 123.0, 45.4, 39.9.

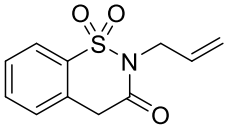
HRMS (ESI$^-$) m/z calc'd for $C_{15}H_{12}NO_3S^-$: 286.0538; found: 286.0537 $[M\text{-}H^+]^-$

m.p. 149 – 152 °C (lit. 152 – 155 °C)[4]

GC (FID):



2-allyl-2H-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (S17)



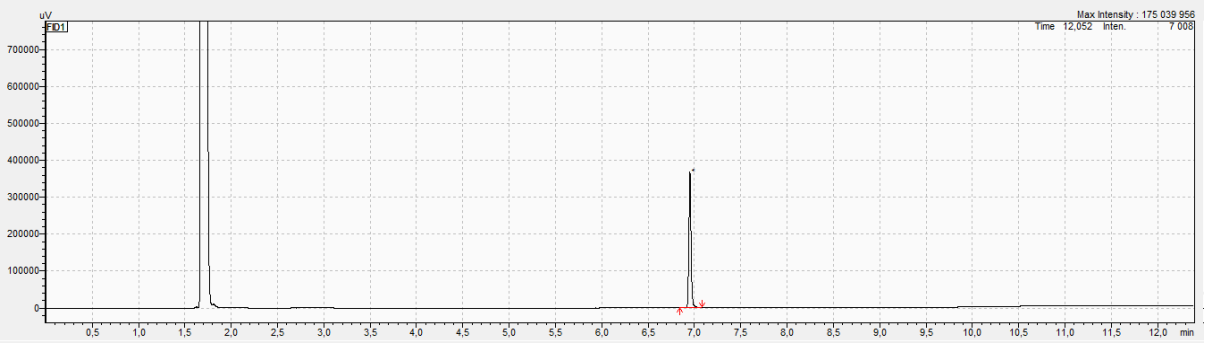
The title compound was synthesised according to General Procedure C, from *tert*-butyl (*o*-toylsulfonyl)carbamate (2.71 g, 10.0 mmol) in 45% yield (1.06 g) as a viscous colourless oil. Eluent for column chromatography (SiO_2): gradually from 10% of EtOAc in hexane to 20%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.7 Hz, 1H), 7.60 (td, *J* = 7.6, 1.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 5.88 (ddt, *J* = 17.2, 10.2, 5.7 Hz, 1H), 5.30 (dq, *J* = 17.1, 1.4 Hz, 1H), 5.21 (dq, *J* = 10.3, 1.2 Hz, 1H), 4.45 (dt, *J* = 5.8, 1.5 Hz, 2H), 4.12 (s, 2H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.0, 136.4, 133.6, 131.7, 131.4, 128.9, 128.1, 123.0, 118.8, 44.1, 39.8.

HRMS (ESI$^-$) m/z calc'd for $C_{11}H_{10}NO_3S^-$: 236.0381; found: 236.0384 $[M\text{-}H^+]^-$

GC (FID):

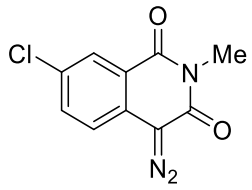


9. 4-Diazo-2-methylisoquinoline-1,3(2H,4H)-diones

4-Diazo-2-methylisoquinoline-1,3(2H,4H)-dione (**1a**), 4-diazo-2-ethylisoquinoline-1,3(2H,4H)-dione (**1b**), 4-diazo-2-propylisoquinoline-1,3(2H,4H)-dione (**1c**), 4-diazo-2-isopropylisoquinoline-1,3(2H,4H)-dione (**1d**), 2-benzyl-4-diazoisoquinoline-1,3(2H,4H)-dione (**1e**), 4-diazo-2-isopropylisoquinoline-1,3(2H,4H)-dione (**1f**) were synthesised according to the procedure reported by Kantin et al.[5]

Note: The ^{13}C NMR peak for the $C{=}N_2$ moiety is not observed in any case and this is consistent with literature reports.[5]

7-chloro-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (1g)



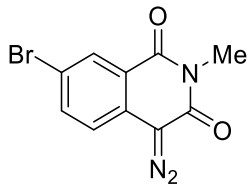
The title compound was synthesised according to General Procedure DA from 7-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (839 mg, 4.00 mmol) in 69% yield (648 mg) as a yellow solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 2.3 Hz, 1H), 7.61 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 3.46 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.4, 162.0, 134.5, 131.9, 130.0, 125.0, 122.1, 120.1, 27.7.

HRMS (APCI$^+$) m/z calc'd for $C_{10}H_7N_3O_2Cl^+$: 236.0227; found 236.0228 $[M+H]^+$

7-bromo-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (1h)



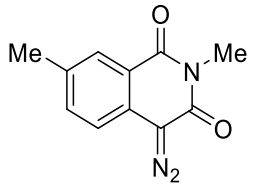
The title compound was synthesised according to General Procedure DA from 7-bromo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (867 mg, 3.41 mmol) in 74% yield (700 mg) as a yellow solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.1 Hz, 1H), 7.75 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 3.45 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.4, 161.9, 137.2, 133.0, 125.5, 122.3, 120.3, 119.3, 27.7.

HRMS (APCI$^+$) m/z calc'd for $C_{10}H_7N_3O_2Br^+$: 279.9722; found: 279.9720 $[M+H]^+$

4-diazo-2,7-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (1i)



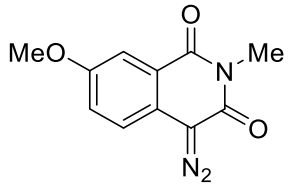
The title compound was synthesised according to General Procedure DA from 2,7-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (269 mg, 1.42 mmol) in 95% yield (290 mg) as an orange solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.47 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 3.45 (s, 3H), 2.43 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.21, 163.15, 136.0, 135.4, 130.3, 123.5, 120.9, 118.7, 27.5, 21.2.

HRMS (APCI$^+$) m/z calc'd for $C_{11}H_{10}N_3O_2^+$: 216.0773; found: 216.0771 $[M+H]^+$

4-diazo-7-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (1j)



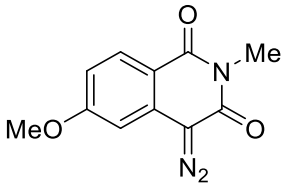
The title compound was synthesised according to General Procedure DA from 7-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (600 mg, 2.92 mmol) in 95% yield (640 mg) as an orange solid. Eluent for column chromatography (SiO_2): gradually from 20% of EtOAc in hexane to 30%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 2.8 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 3.89 (s, 3H), 3.46 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.3, 163.0, 158.1, 123.6, 122.0, 120.3, 118.6, 112.2, 55.9, 27.6.

HRMS (APCI$^+$) m/z calc'd for $C_{11}H_{10}N_3O_3^+$: 232.0722; found: 232.0723 $[M+H]^+$

4-diazo-6-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (1k)



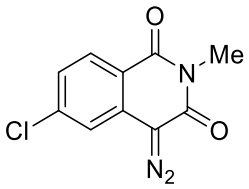
The title compound was synthesised according to General Procedure DA from 6-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (419 mg, 2.00 mmol) in 30% yield (210 mg) as an orange solid. Eluent for column chromatography (SiO_2): gradually from 20% of EtOAc in hexane to 30%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.8 Hz, 1H), 6.86 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 3.90 (s, 3H), 3.43 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.4, 163.0, 162.8, 132.5, 128.7, 114.3, 113.0, 102.6, 55.9, 27.4.

HRMS (APCI$^+$) m/z calc'd for $C_{11}H_{10}N_3O_3^+$: 232.0722; found: 232.0720 $[M+H]^+$

6-chloro-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (1l)



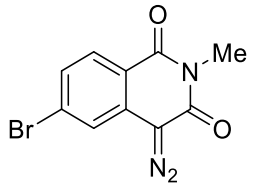
The title compound was synthesised according to General Procedure DA from 6-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (560 mg, 2.67 mmol) in 81% yield (510 mg) as a yellow solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.11 (d, *J* = 1.9 Hz, 1H), 3.45 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.4, 162.3, 141.0, 131.8, 128.4, 126.4, 119.2, 118.5, 27.6.

HRMS (APCI$^+$) m/z calc'd for $C_{10}H_7N_3O_2Cl^+$: 236.0227; found: 236.0230 $[M+H]^+$

6-bromo-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (1m)



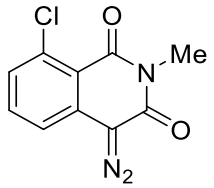
The title compound was synthesised according to General Procedure DA from 6-bromo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (762 mg, 3.0 mmol) in 62% yield (521 mg) as a yellow solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.5 Hz, 1H), 7.44 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 3.44 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.5, 162.2, 131.7, 129.5, 129.2, 128.4, 121.4, 119.6, 27.6.

HRMS (APCI$^+$) m/z calc'd for $C_{10}H_7N_3O_2Br^+$: 279.9722; found: 279.9723 $[M+H]^+$

8-chloro-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (1n)



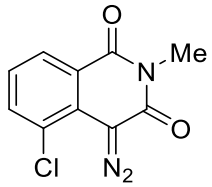
The title compound was synthesised according to General Procedure DA from 8-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (419 mg, 2.00 mmol) in 59% yield (276 mg) as an orange solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (t, *J* = 8.0 Hz, 1H), 7.36 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.02 (dd, *J* = 7.9, 1.1 Hz, 1H), 3.44 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.7, 161.0, 138.4, 133.6, 129.7, 129.5, 117.5, 117.4, 27.7.

HRMS (ESI$^+$) *m/z* calc'd for $C_{10}H_6N_3O_2ClNa^+$: 258.0046; found: 258.0048 $[M+Na]^+$

5-chloro-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (1o)



The title compound was synthesised according to General Procedure DA from 5-chloro-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (839 mg, 4.00 mmol) in 96% yield (900 mg) as an orange solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

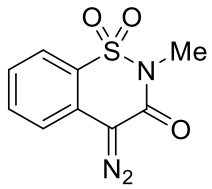
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 1H), 3.46 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.2, 162.0, 135.5, 129.1, 126.7, 126.2, 124.3, 122.5, 28.1.

HRMS (ESI$^+$) *m/z* calc'd for $C_{10}H_6N_3O_2NaCl^+$: 258.0046; found: 258.0047 $[M+Na]^+$

10. 4-Diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide

2-benzyl-4-diazo-2H-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (34a)



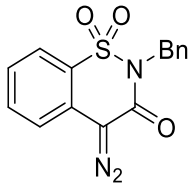
The title compound was synthesised according to General Procedure DB from 2-methyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (423 mg, 2.00 mmol) in 66% yield (314 mg) as an orange solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.97 (m, 1H), 7.69 – 7.66 (m, 1H), 7.41 – 7.38 (m, 1H), 7.18 – 7.16 (m, 1H), 3.39 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.7, 134.0, 129.2, 126.1, 124.2, 123.2, 120.2, 26.8.

HRMS (APCI$^+$) *m/z* calc'd for $C_9H_8N_3O_3S^+$: 238.0286; found: 238.0284 $[M+H]^+$

2-benzyl-4-diazo-2H-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (34b)



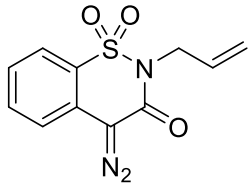
The title compound was synthesised according to General Procedure DB from 2-benzyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (575 mg, 2.00 mmol) in 45% yield (284 mg) as an orange solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.96 (m, 1H), 7.66 – 7.63 (m, 1H), 7.48 – 7.46 (m, 2H), 7.40 – 7.36 (m, 1H), 7.33 – 7.30 (m, 2H), 7.28 – 7.25 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 5.12 (s, 2H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.7, 135.9, 133.9, 129.7, 129.0, 128.6, 128.1, 126.1, 124.1, 123.2, 120.3, 44.8.

HRMS (APCI$^+$) *m/z* calc'd for $C_{15}H_{12}N_3O_3S^+$: 314.0599; found: 314.0598 $[M+H]^+$

4-diazo-2-allyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (34c)



The title compound was synthesised according to General Procedure DB from 2-allyl-2*H*-benzo[e][1,2]thiazin-3(4*H*)-one 1,1-dioxide (475 mg, 2.00 mmol) in 86% yield (453 mg) as an orange solid. Eluent for column chromatography (SiO_2): 20% EtOAc in hexane.

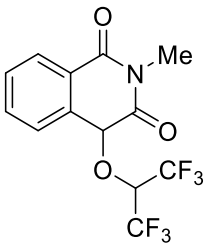
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.96 (m, 1H), 7.67 (td, *J* = 8.0, 1.3 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.18 – 7.16 (m, 1H), 5.96 (ddt, *J* = 16.5, 10.3, 6.1 Hz, 1H), 5.38 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.27 (dq, *J* = 10.2, 1.2 Hz, 1H), 4.56 (dt, *J* = 6.1, 1.4 Hz, 2H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.5, 133.9, 132.0, 129.8, 126.1, 124.0, 123.3, 120.3, 119.3, 44.1.

HRMS (APCI$^+$) *m/z* calc'd for $C_{11}H_{10}N_3O_3S$: 264.0443$^+$; found: 264.0447 $[M+H]^+$

10. O-H Insertion Products

4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (2)



The title compound was synthesised according to General Procedure E from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and HFIP (2 mL) in 67% yield (46 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

For gram-scale reaction: 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (1.00 g, 4.97 mmol) is charged in a 500 mL flask followed by the addition of HFIP (50 mL). The flask is irradiated with the whole blue LED plate for 7 hours. After completion of the reaction, HFIP is removed via distillation affording 41 mL of HFIP. The crude residue is subjected to column chromatography affording the title compound as a white solid in 66% yield (1.12 g) as a yellow solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.7 Hz, 1H), 7.74 – 7.71 (m, 1H), 7.63 – 7.59 (m, 2H), 5.45 (hept, *J* = 5.9 Hz, 1H), 5.35 (s, 1H), 3.37 (s, 3H).

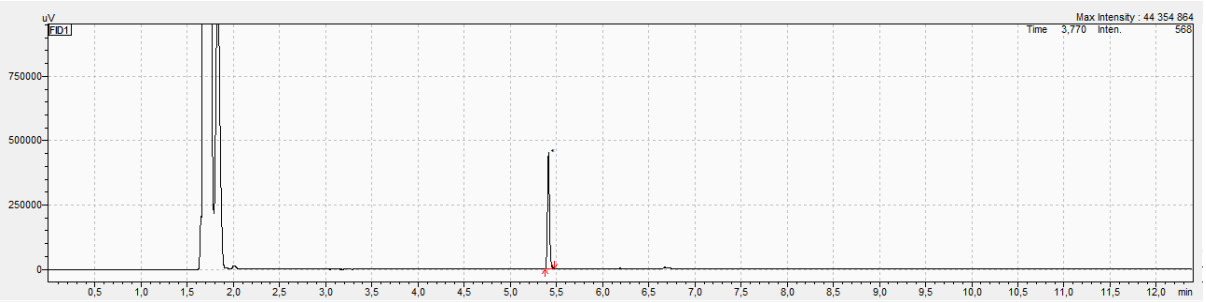
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.8, 163.5, 134.5, 132.8, 130.4, 129.3, 128.1, 125.2, 124.3 – 117.5 (m), 74.6 (obs. p, *J* = 31.9 Hz), 74.2, 27.1.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.0 (qd, *J* = 9.0, 5.9 Hz, 3F), -73.4 (qd, *J* = 9.1, 5.8 Hz, 3F).

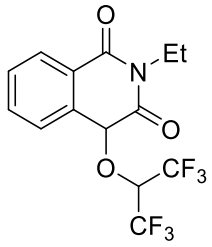
HRMS (ESI$^-$) *m/z* calc'd for $C_{13}H_8NO_3F_6^-$: 340.0408; found: 340.0414 $[M\text{-}H^+]^-$

m.p. 117 – 120 °C

GC (FID):



2-ethyl-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)isoquinoline-1,3(2*H*,4*H*)-dione (3)



The title compound was synthesised according to General Procedure E from 4-diazo-2-ethylisoquinoline-1,3(2*H*,4*H*)-dione (43 mg, 0.20 mmol) and HFIP (2 mL) in 71% yield (51 mg) as a yellow solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.60 (t, *J* = 7.4 Hz, 2H), 5.46 (hept, *J* = 5.9 Hz, 1H), 5.32 (s, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

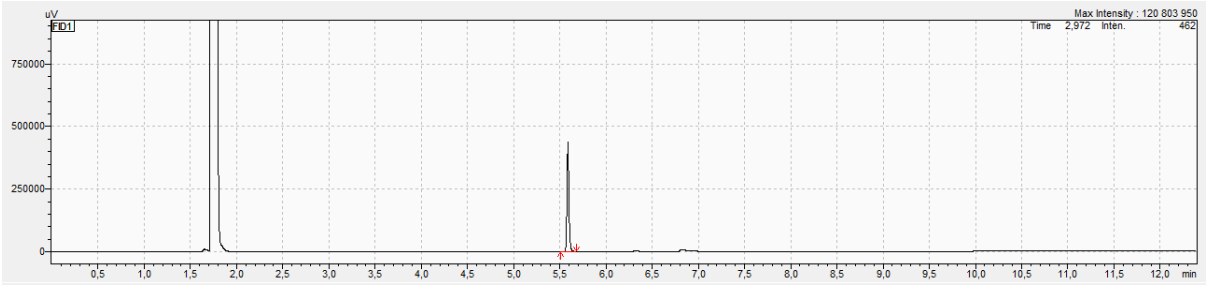
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.2, 162.9, 134.3, 132.7, 130.3, 129.1, 128.0, 125.2, 123.2 – 119.6 (m), 74.3 (obs. p, J = 32.3 Hz), 74.0, 35.7, 13.0.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.1 (qd, *J* = 9.1, 5.8 Hz, 3F), -73.4 (qd, *J* = 9.1, 5.8 Hz, 3F).

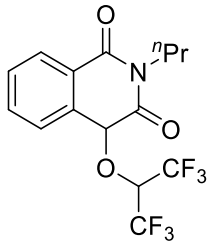
HRMS (ESI$^-$) *m/z* calc'd for $C_{14}H_{10}NO_3F_6^-$: 354.0565; found: 354.0564 $[M\text{-}H^+]^-$

m.p. 69 – 71 °C

GC (FID):



4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-propylisoquinoline-1,3(2*H*,4*H*)-dione (4)



The title compound was synthesised according to General Procedure E from 4-diazo-2-propylisoquinoline-1,3(2*H*,4*H*)-dione (46 mg, 0.20 mmol) and HFIP (2 mL) in 69% yield (51 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 – 8.22 (m, 1H), 7.74 – 7.71 (m, 1H), 7.62 – 7.58 (m, 2H), 5.47 (hept, *J* = 5.9 Hz, 1H), 5.33 (s, 1H), 3.94 – 3.91 (m, 2H), 1.69 – 1.62 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

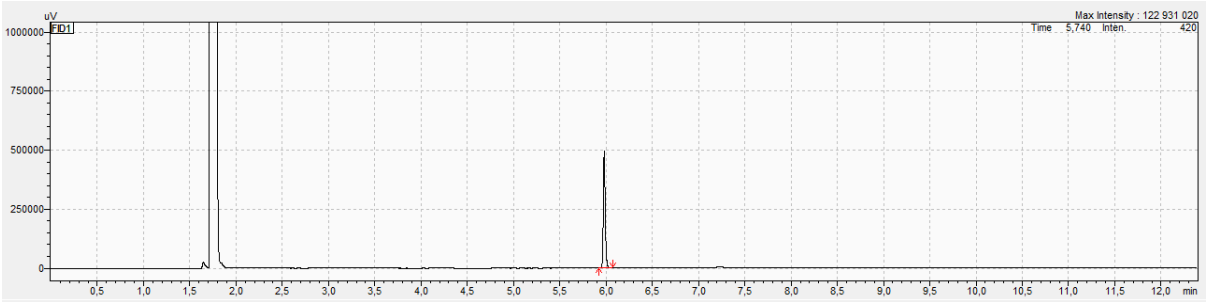
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.6, 163.3, 134.5, 132.8, 130.4, 129.3, 128.1, 125.3, 124.3 – 119.8 (m), 74.6 (obs. p, J = 32.8 Hz), 74.1, 42.2, 21.3, 11.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.0 (qd, *J* = 9.0, 5.9 Hz, 3F), -73.4 (qd, *J* = 9.0, 5.7 Hz, 3F).

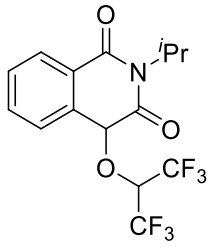
HRMS (ESI$^-$) *m/z* calc'd for $C_{15}H_{12}NO_3F_6^-$: 368.0721; found: 368.0731 $[M\text{-}H^+]^-$

m.p. 59 – 62 °C

GC (FID):



4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-isopropylisoquinoline-1,3(2*H*,4*H*)-dione (5)



The title compound was synthesised according to General Procedure E from 4-diazo-2-isopropylisoquinoline-1,3(2*H*,4*H*)-dione (46 mg, 0.20 mmol) and HFIP (2 mL) in 60% yield (44 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.9 Hz, 1H), 7.70 (td, *J* = 7.6, 1.4 Hz, 1H), 7.61 – 7.57 (m, 2H), 5.39 (hept, *J* = 5.9 Hz, 1H), 5.26 (s, 1H), 5.13 (hept, *J* = 7.0 Hz, 1H), 1.48 (dd, *J* = 6.9, 1.6 Hz, 6H).

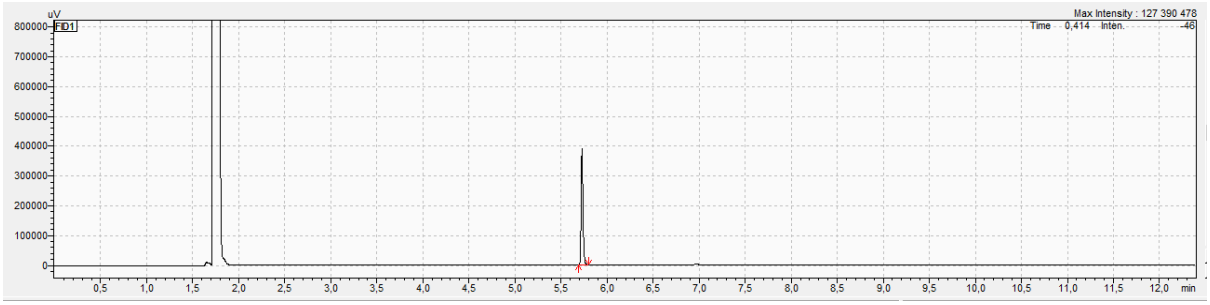
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.8, 163.6, 134.3, 132.7, 130.4, 129.3, 128.0, 126.0, 124.3 – 119.8 (m), 74.8, 74.5 (obs. p, *J* = 32.8 Hz), 46.2, 19.63, 19.61.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.1 (qd, *J* = 9.0, 5.8 Hz, 3F), -73.4 (qd, *J* = 9.0, 5.8 Hz, 3F).

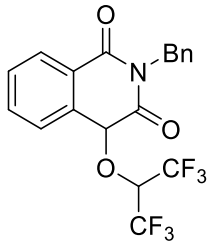
m.p. 62 – 65 °C

HRMS (ESI$^-$) *m/z* calc'd for $C_{15}H_{12}NO_3F_6^-$: 368.0721; found: 368.0728 $[M\text{-}H^+]^-$

GC (FID):



2-benzyl-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)isoquinoline-1,3(2*H*,4*H*)-dione (6)



The title compound was synthesised according to General Procedure E from 2-benzyl-4-diazoisoquinoline-1,3(2*H*,4*H*)-dione (56 mg, 0.20 mmol) and HFIP (2 mL) in 63% yield (52 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.9 Hz, 1H), 7.73 (td, *J* = 7.6, 1.4 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.45 – 7.42 (m, 2H), 7.33 – 7.25 (m, 3H), 5.48 (hept, *J* = 5.9 Hz, 1H), 5.37 (s, 1H), 5.22 (d, *J* = 13.9 Hz, 1H), 5.10 (d, *J* = 13.9 Hz, 1H).

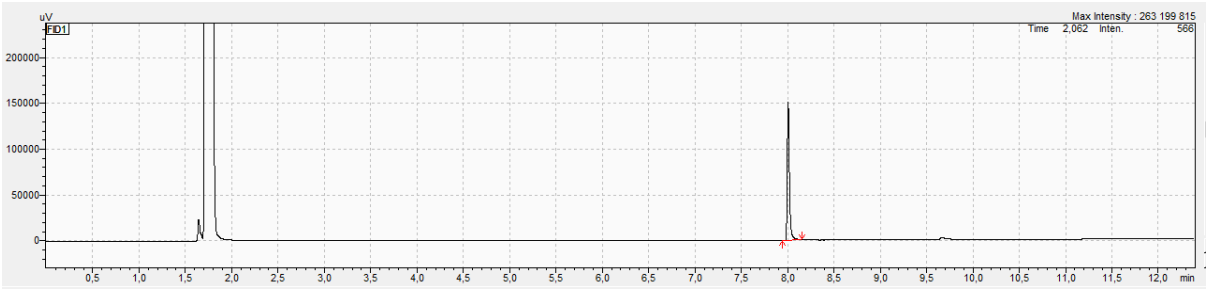
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.5, 163.2, 136.3, 134.6, 132.9, 130.4, 129.4, 129.1, 128.7, 128.1, 128.0, 125.2, 124.3 – 119.7 (m), 75.2 – 74.4 (m), 74.1 (m), 43.7.

^{19}F NMR (470 MHz, $CDCl_3$) δ -72.9 (qd, *J* = 8.7, 5.6 Hz, 3F), -73.3 (qd, *J* = 9.1, 5.7 Hz, 3F).

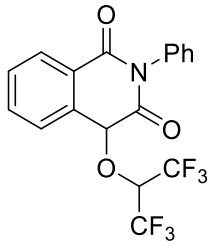
HRMS (ESI$^-$) *m/z* calc'd for $C_{19}H_{12}NO_3F_6^-$: 416.0721; found: 416.0728 $[M\text{-}H^+]^-$

m.p. 109 – 112 °C

GC (FID):



4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-phenylisoquinoline-1,3(2*H*,4*H*)-dione (7)



The title compound was synthesised according to General Procedure E from 4-diazo-2-phenylisoquinoline-1,3(2*H*,4*H*)-dione (53 mg, 0.20 mmol) and HFIP (2 mL) in 51% yield (21 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.8 Hz, 1H), 7.80 (td, *J* = 7.6, 1.4 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.50 – 7.46 (m, 1H), 7.22 – 7.19 (m, 2H), 5.52 (s, 1H), 5.39 (hept, *J* = 5.9 Hz, 1H).

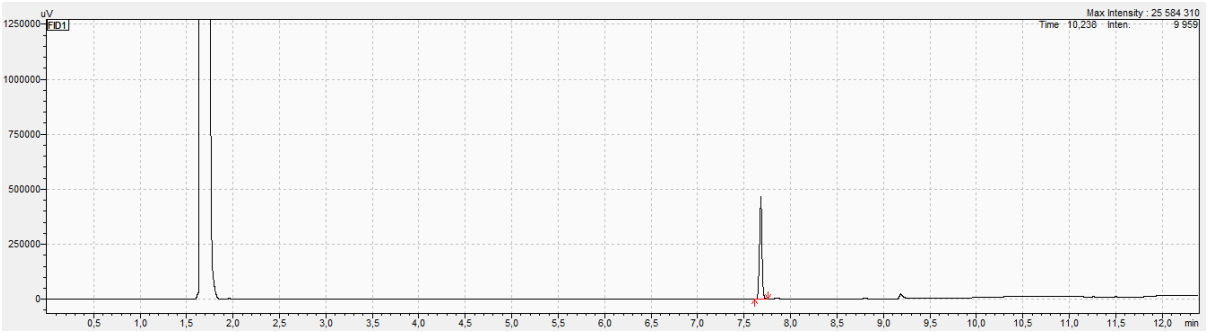
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.4, 163.5, 134.9, 134.0, 132.9, 130.7, 129.7, 129.6, 129.3, 128.4, 128.3, 125.4, 125.6 – 117.5 (m), 74.9, 74.5 (obs. p, *J* = 32.5 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.0 (qd, *J* = 9.0, 5.8 Hz, 3F), -73.3 (qd, *J* = 9.0, 5.7 Hz, 3F).

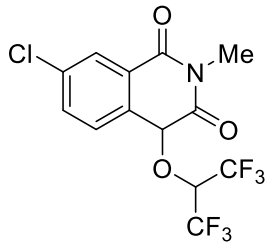
HRMS (ESI$^-$) *m/z* calc'd for $C_{18}H_{10}NO_3F_6^-$: 402.0565; found: 402.0570 $[M\text{-}H^+]^-$

m.p. 119 – 121 °C

GC (FID):



7-chloro-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (8)



The title compound was synthesised according to General Procedure E from 7-chloro-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (47 mg, 0.20 mmol) and HFIP (2.0 mL) in 58% yield (43 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 2.2 Hz, 1H), 7.69 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 5.43 (hept, *J* = 6.0 Hz, 1H), 5.32 (s, 1H), 3.37 (s, 3H).

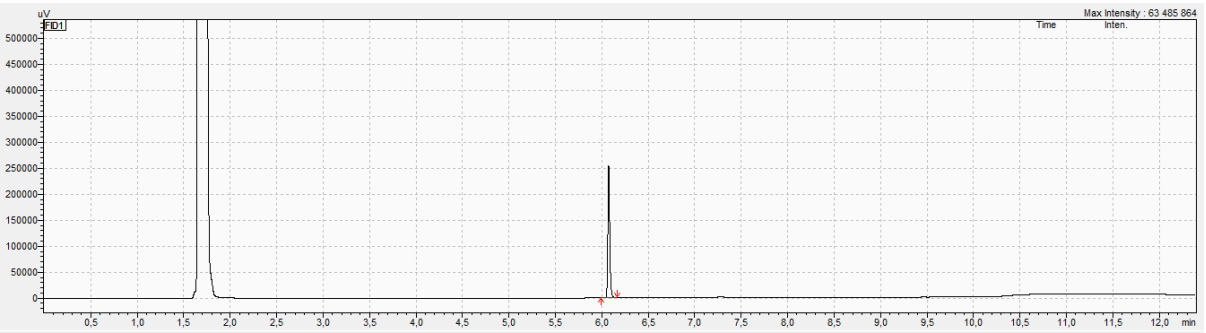
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.4, 162.4, 137.1, 134.7, 131.0, 129.6, 129.1, 126.7, 123.4 – 117.3 (m), 74.6 (obs. p, *J* = 32.5 Hz), 73.7, 27.3.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.0 – -73.1 (m, 3F), -73.4 – -73.5 (m, 3F).

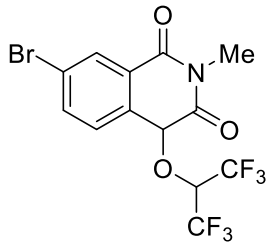
HRMS (ESI$^-$) *m/z* calc'd for $C_{13}H_7NO_3F_6Cl^-$: 374.0019; found: 374.0020 $[M\text{-}H^+]^-$

m.p. 77 – 80 °C

GC (FID):



7-bromo-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (9)



The title compound was synthesised according to General Procedure E from 7-bromo-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (56 mg, 0.20 mmol) and HFIP (2.0 mL) in 58% yield (49 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.1 Hz, 1H), 7.84 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 5.43 (hept, *J* = 5.9 Hz, 1H), 5.30 (s, 1H), 3.37 (s, 3H).

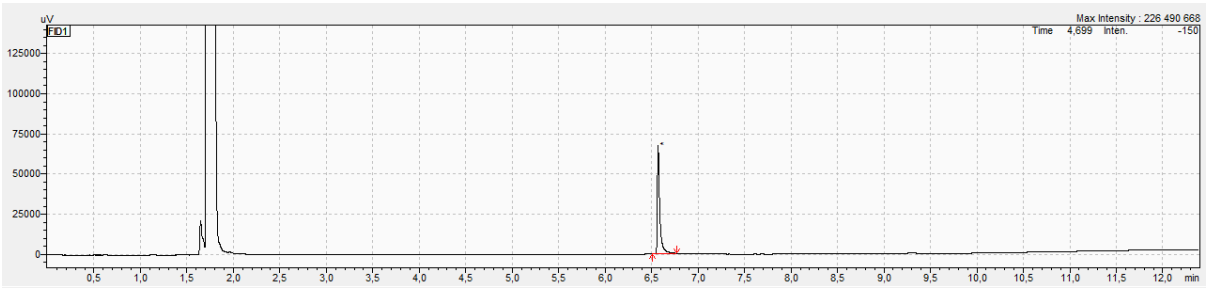
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 169.3, 162.3, 137.6, 132.1, 131.5, 129.7, 126.7, 124.9, 125.3 – 119.6 (m), 75.1 – 74.1 (m), 73.7, 27.3.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.0 (qd, *J* = 9.0, 5.9 Hz, 3F), -73.4 (qd, *J* = 9.0, 5.7 Hz, 3F).

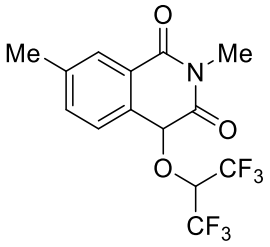
HRMS (ESI$^-$) *m/z* calc'd for $C_{13}H_7NO_3F_6Br^-$: 417.9514; found: 417.9516 [M-H$^+$]$^-$

m.p. 96 – 99 °C

GC (FID):



4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2,7-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (10)



The title compound was synthesised according to General Procedure E from 4-diazo-2,7-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (43 mg, 0.20 mmol) and HFIP (2 mL) in 63% yield (45 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.53 – 7.48 (m, 2H), 5.41 (hept, *J* = 5.9 Hz, 1H), 5.29 (s, 1H), 3.36 (s, 3H), 2.46 (s, 3H).

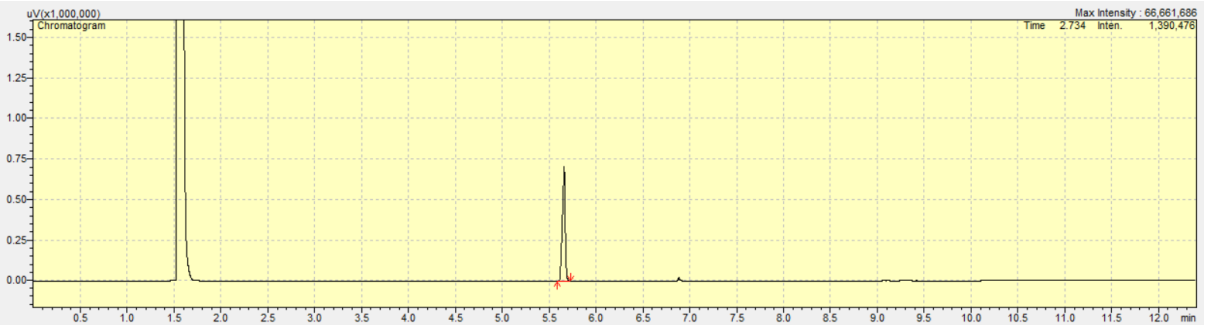
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.9, 163.7, 141.0, 135.4, 129.9, 129.4, 128.2, 125.0, 123.6 – 119.6 (m), 74.4 (obs. p, *J* = 32.5 Hz), 74.2, 27.0, 21.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.1 (qd, *J* = 9.0, 5.9 Hz, 3F), -73.5 (qd, *J* = 9.0, 5.8 Hz, 3F).

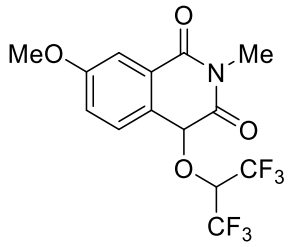
HRMS (ESI$^-$) *m/z* calc'd for $C_{14}H_{10}NO_3F_6^-$: 354.0565; found: 354.0569 $[M\text{-}H^+]^-$

m.p. 117 – 119 °C

GC (FID):



4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-7-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (11)



The title compound was synthesised according to General Procedure E from 4-diazo-7-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (46 mg, 0.20 mmol) and HFIP (2 mL) in 33% yield (25 mg) as a white solid. Extending the reaction time to 4.5 hours afforded the title compound in 56% yield (41 mg). Eluent for column chromatography (SiO_2): gradually from 10% of EtOAc in hexane to 15%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.7 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.25 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.39 (hept, *J* = 5.9 Hz, 1H), 5.25 (s, 1H), 3.90 (s, 3H), 3.36 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.8, 163.6, 161.3, 130.0, 126.7, 124.8, 122.2, 123.3 – 117.6 (m), 112.0, 74.3 (obs. p, *J* = 32.4 Hz), 74.1, 55.9, 27.1. (One carbon missing due to ^{19}F splitting).

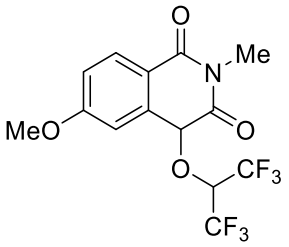
^{19}F NMR (470 MHz, $CDCl_3$) δ -73.2 (qd, *J* = 9.1, 6.1 Hz, 3F), -73.6 (qd, *J* = 8.9, 5.5 Hz, 3F).

HRMS (ESI$^-$) *m/z* calc'd for $C_{14}H_{10}NO_4F_6^-$: 370.0514; found: 370.0519 $[M\text{-}H^+]^-$

m.p. 99 – 101 °C

GC (FID):

4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-6-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (12)



The title compound was synthesised according to General Procedure E from 4-diazo-6-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (46 mg, 0.20 mmol) and HFIP (2 mL) with an extended reaction time of 20 hours in 48% yield (36 mg) as a beige solid. Eluent for column chromatography (SiO_2): gradually from 10% of EtOAc in hexane to 15%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 1H), 7.09 – 7.05 (m, 2H), 5.46 (hept, *J* = 5.9 Hz, 1H), 5.31 (s, 1H), 3.91 (s, 3H), 3.34 (s, 3H).

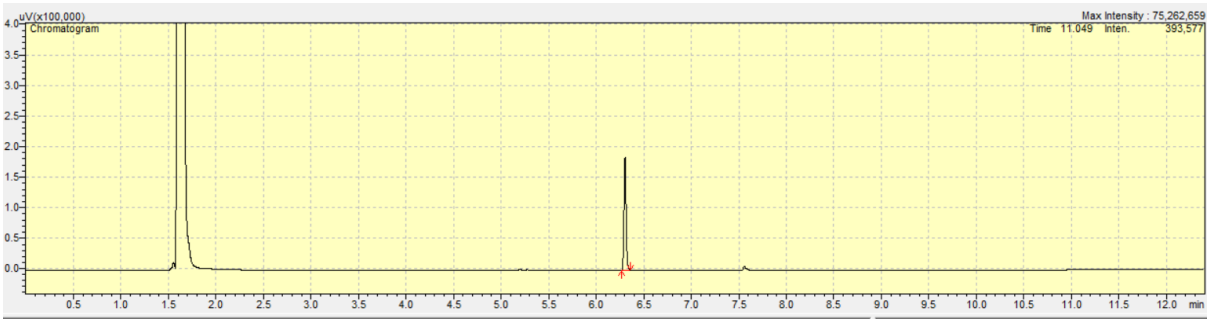
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.0, 164.5, 163.1, 135.1, 131.5, 126.0 – 119.6 (m), 117.8, 116.6, 112.3, 75.5 – 74.0 (m), 74.2, 55.8, 26.9.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.0 (qd, *J* = 9.0, 5.9 Hz, 3F), -73.4 (qd, *J* = 9.1, 5.9 Hz, 3F).

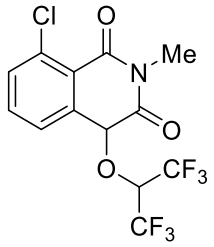
HRMS (APCI^{+}) *m/z* calc'd for $C_{14}H_{12}NO_4F_6^{+}$: 372.0671; found: 372.0673 $[M+H]^{+}$

M.P 118 – 121 °C

GC (FID):



8-chloro-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (15)



The title compound was synthesised according to General Procedure E from 8-chloro-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (47 mg, 0.20 mmol) and HFIP (2.0 mL) in 39% yield (30 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.56 – 7.54 (m, 1H), 5.36 – 5.31 (m, 2H), 3.36 (s, 3H).

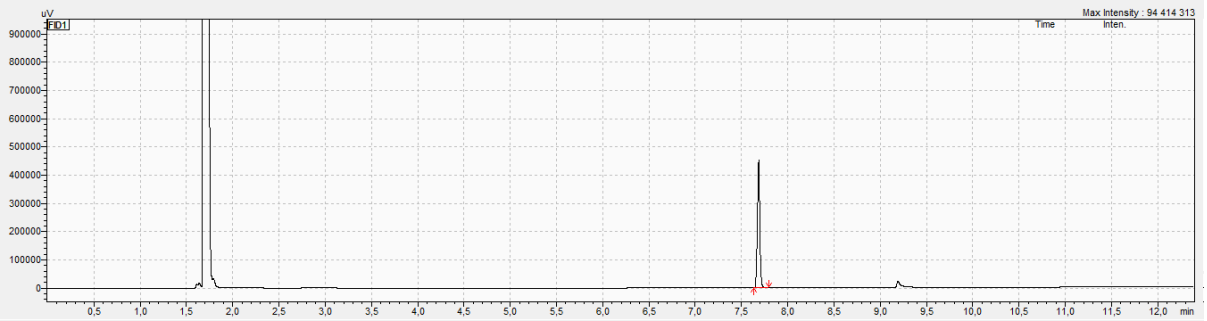
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.5, 161.3, 136.7, 135.2, 134.3, 134.1, 127.0, 122.4, 124.2 – 119.7 (m), 74.5, 74.9 – 73.9 (m), 27.4.

^{19}F NMR (470 MHz, $CDCl_3$) δ -73.1 (qd, *J* = 9.0, 5.8 Hz, 3F), -73.5 (qd, *J* = 9.0, 5.7 Hz, 3F).

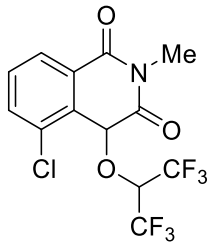
HRMS (ESI$^+$) *m/z* calc'd for $C_{13}H_8NO_3ClF_6Na^+$: 397.9995; found: 397.9991 $[M+Na]^+$

m.p. 137 – 140 °C

GC (FID):



5-chloro-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (16)



The title compound was synthesised according to General Procedure E from 5-chloro-4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (47 mg, 0.20 mmol) and HFIP (2.0 mL) in 51% yield (38 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 5.48 (s, 1H), 5.15 (hept, *J* = 6.0 Hz, 1H), 3.37 (s, 3H).

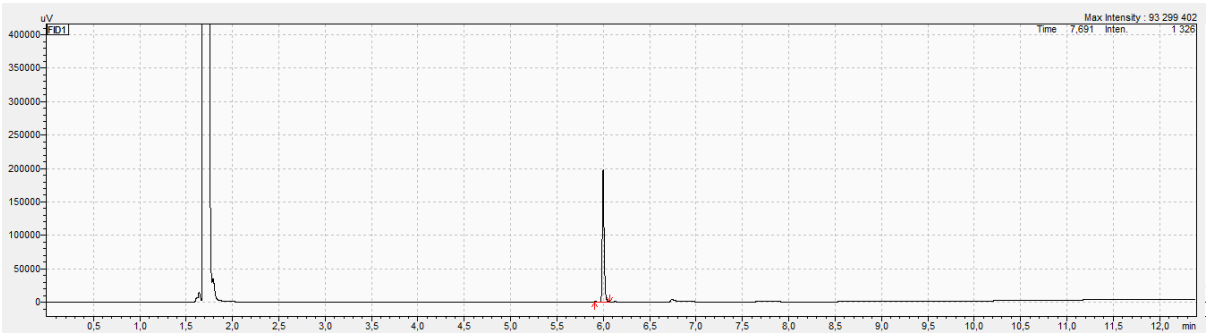
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.0, 162.9, 135.7, 135.3, 132.1, 129.7, 128.4, 128.3, 72.6, 72.4 (t, *J* = 33.1 Hz), 27.3. (One carbon missing due to ^{19}F splitting).

^{19}F NMR (470 MHz, $CDCl_3$) δ -72.7 (qd, *J* = 9.0, 5.9 Hz, 3F), -74.0 (qd, *J* = 9.0, 6.2 Hz, 3F).

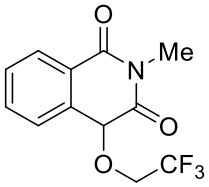
HRMS (ESI$^-$) *m/z* calc'd for $C_{13}H_7NO_3F_6Cl^-$: 374.0019; found 374.0020 $[M\text{-}H^+]^-$

m.p. 82 – 84 °C

GC (FID):



2-methyl-4-(2,2,2-trifluoroethoxy)isoquinoline-1,3(2*H*,4*H*)-dione (17)



The title compound was synthesised according to General Procedure E from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and 2,2,2-trifluoroethan-1-ol (2 mL) in 41% yield (23 mg) as a brown solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 – 8.19 (m, 1H), 7.72 – 7.69 (m, 1H), 7.68 – 7.67 (m, 1H), 7.57 – 7.54 (m, 1H), 5.24 (s, 1H), 4.50 (dq, *J* = 12.5, 8.7 Hz, 1H), 4.37 (dq, *J* = 12.6, 8.4 Hz, 1H), 3.36 (s, 3H).

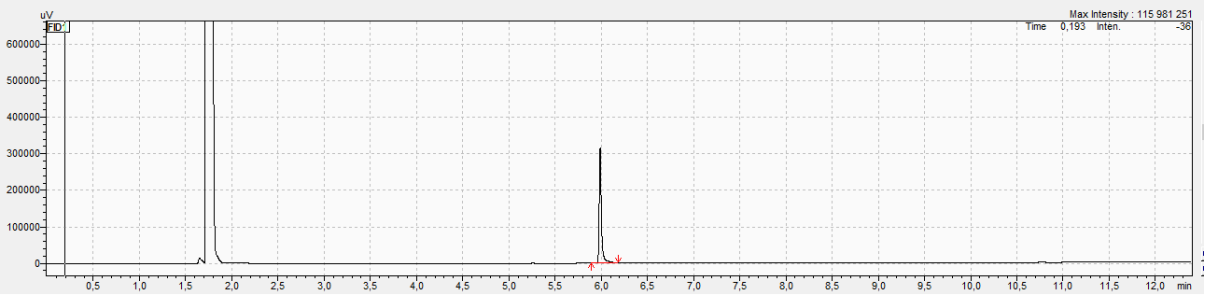
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.0, 163.9, 134.4, 134.3, 129.7, 129.1, 127.0, 124.9, 122.0 (q, *J* = 278.9 Hz), 75.6, 68.9 (q, *J* = 34.3 Hz), 27.2.

^{19}F NMR (470 MHz, $CDCl_3$) δ -74.4 (t, *J* = 8.6 Hz, 3F).

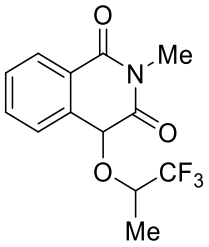
HRMS (ESI$^-$) *m/z* calc'd for $C_{12}H_9NO_3F_3^-$: 272.0535; found 272.0540 $[M\text{-}H^+]^-$

m.p. 65 – 68 °C

GC (FID):



2-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)isoquinoline-1,3(2*H*,4*H*)-dione (18)



The title compound was synthesised according to General Procedure E from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and 1,1,1-trifluoropropan-2-ol (2 mL) in 44% yield (1:10 dr, 25 mg) as a white solid. Only ^{1}H and ^{13}C peaks from the major product are reported as the intensity from the minor product is not sufficient to identify all peaks. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

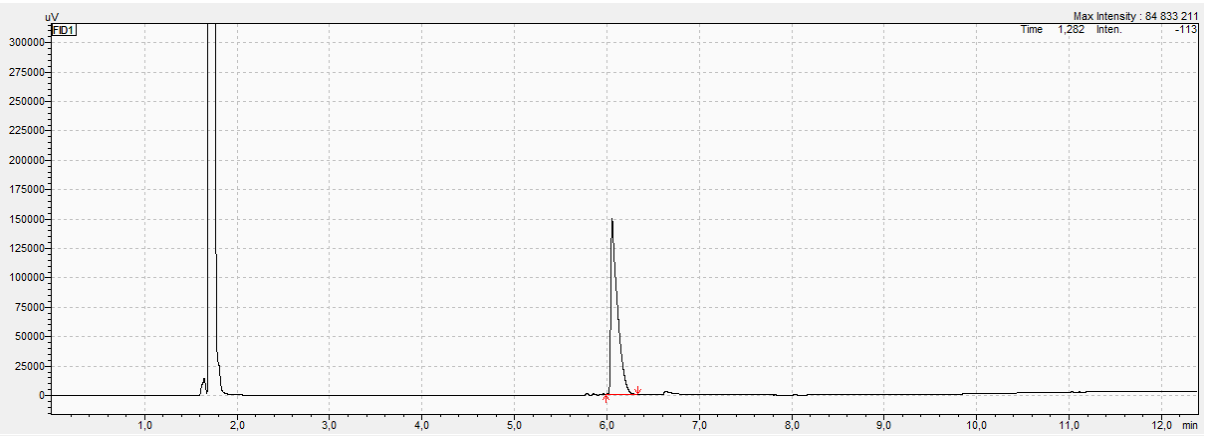
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.70 – 7.68 (m, 2H), 7.56 – 7.51 (m, 1H), 5.36 (s, 1H), 4.72 (hept, *J* = 6.5 Hz, 1H), 3.36 (s, 3H), 1.54 (d, *J* = 6.6, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.8, 164.1, 134.9, 134.4, 129.4, 128.9, 126.9, 124.7, 76.0 (t, *J* = 30.1 Hz), 75.6, 27.1, 14.9 (q, *J* = 2.1 Hz). (One carbon missing due to ^{19}F splitting within the diastereomeric peaks).

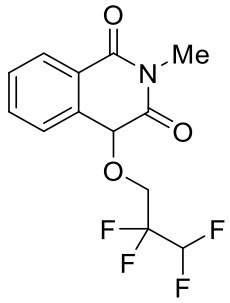
^{19}F NMR (470 MHz, $CDCl_3$) δ -78.6 (Major, t, *J* = 6.4 Hz, 3F), -78.9 (Minor, t, *J* = 6.5 Hz, 3F).

HRMS (ESI$^-$) *m/z* calc'd for $C_{13}H_{11}NO_3F_3^-$: 286.0691; found: 286.0696 $[M\text{-}H^+]^-$

GC (FID):



2-methyl-4-(2,2,3,3-tetrafluoropropoxy)isoquinoline-1,3(2*H*,4*H*)-dione (19)



The title compound was synthesised according to General Procedure E from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and 2,2,3,3-tetrafluoropropan-1-ol (2 mL) in 45% yield (28 mg) as a colourless oil. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

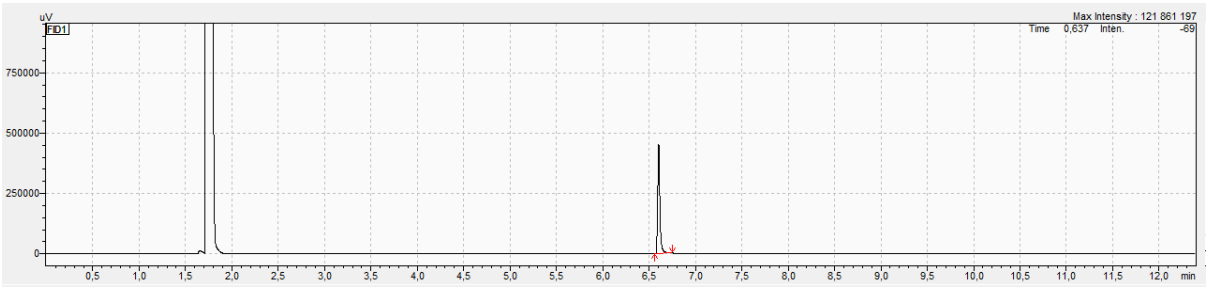
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.9 Hz, 1H), 7.71 (td, *J* = 7.5, 1.4 Hz, 1H), 7.64 – 7.62 (m, 1H), 7.58 – 7.54 (m, 1H), 6.01 (tdd, *J* = 53.2, 5.1, 4.1 Hz, 1H), 5.20 (s, 1H), 4.53 (dtd, *J* = 14.1, 11.8, 2.2 Hz, 1H), 4.27 – 4.19 (m, 1H), 3.37 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.7, 163.9, 134.4, 134.3, 129.8, 129.2, 126.9, 125.1, 115.0 (tt, *J* = 249.9, 27.4 Hz), 109.4 (tt, *J* = 249.9, 35.1 Hz), 75.7, 68.3 (t, *J* = 28.3 Hz), 27.2.

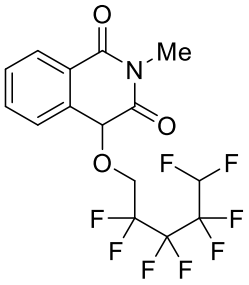
^{19}F NMR (470 MHz, $CDCl_3$) δ -124.2 – -125.8 (m, 2F), -137.8 – -139.7 (m, 2F).

HRMS (ESI$^-$) *m/z* calc'd for $C_{13}H_{10}NO_3F_4^-$: 304.0597; found: 304.0596 $[M\text{-}H^+]^-$

GC (FID):



2-methyl-4-((2,2,3,3,4,4,5,5-octafluoropentyl)oxy)isoquinoline-1,3(2*H*,4*H*)-dione (20)



The title compound was synthesised according to General Procedure E from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and 2,2,3,3,4,4,5,5-octafluoropentan-1-ol (2 mL) in 38% yield (31 mg) as a colourless oil. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

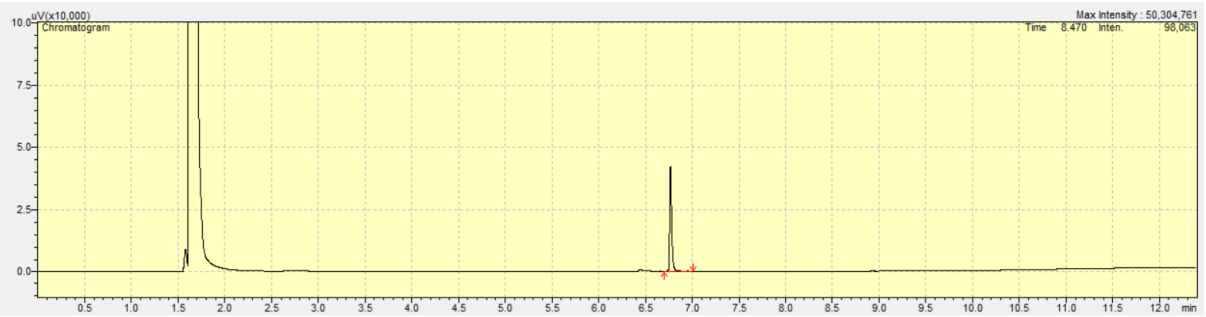
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.8 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.57 – 7.54 (m, 1H), 6.07 (tt, *J* = 52.0, 5.4 Hz, 1H), 5.23 (s, 1H), 4.75 – 4.66 (m, 1H), 4.43 (q, *J* = 13.5 Hz, 1H), 3.37 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.0, 163.9, 134.4, 134.2, 129.7, 129.1, 127.0, 124.9, 118.1 – 105.4 (m), 76.0, 68.3 (t, *J* = 25.0 Hz), 27.2.

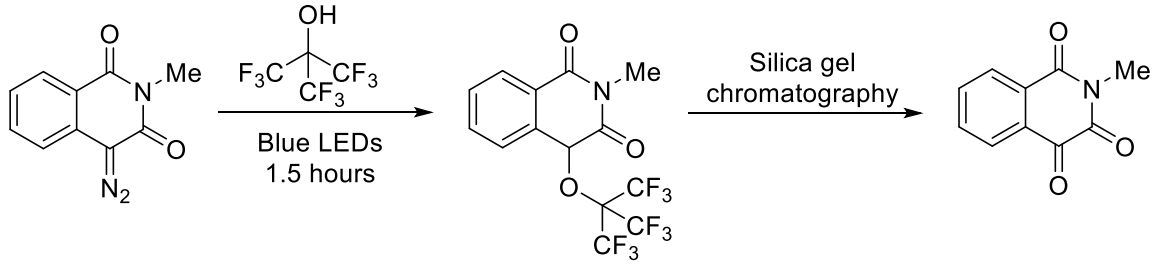
^{19}F NMR (470 MHz, $CDCl_3$) δ -120.4 (p, *J* = 12.7 Hz, 2F), -125.1 (t, *J* = 8.7 Hz, 2F), -129.9 – -130.1 (m, 2F), -137.1 – -137.3 (m, 2F).

HRMS (ESI$^-$) *m/z* calc'd for $C_{15}H_{10}NO_3F_8^-$: 404.0533; found: 404.0536 $[M\text{-}H^+]^-$

GC (FID):



2-methylisoquinoline-1,3,4(2H)-trione (21b)



4-Diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) was charged in a vial and dissolved in nonafluoro-*tert*-butanol (2 ml) and irradiated with blue LEDs for 1.5 hours. After this time, the solution was transferred to a flask with DCM and all the volatiles are removed in vacuo. ^{1}H and ^{13}C**{^{1}H}** NMR of the crude material showed evidence for the formation of 4-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione. During silica column chromatography (10% EtOAc in hexane) the compound rearranged to the title compound in 62% yield (24 mg).

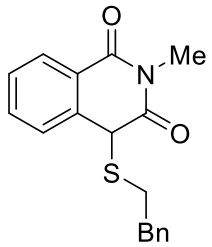
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.21 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.90 (td, *J* = 7.6, 1.4 Hz, 1H), 7.83 (td, *J* = 7.5, 1.4 Hz, 1H), 3.47 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.6, 162.5, 157.4, 136.2, 134.6, 130.8, 130.0, 129.9, 127.9, 27.7.

The spectroscopic data is consistent with that previously reported in the literature.[21]

11. S-H Insertion Products

2-methyl-4-(phenethylthio)isoquinoline-1,3(2*H*,4*H*)-dione (22)



The title compound was synthesised according to General Procedure E from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and 2-phenylethanethiol (2 mL) in 73% yield (45 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.5 Hz, 1H), 7.60 (td, *J* = 7.5, 1.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.22 (m, 3H), 4.62 (s, 1H), 3.37 (s, 3H), 3.20 (ddd, *J* = 12.2, 8.9, 6.1 Hz, 1H), 3.00 – 2.84 (m, 3H).

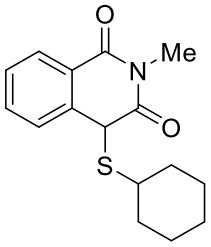
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.0, 164.4, 139.8, 135.1, 133.9, 129.1, 128.83, 128.82, 128.71, 128.70, 126.8, 125.7, 44.9, 35.8, 33.8, 27.4.

HRMS (ESI$^-$) *m/z* calc'd for $C_{18}H_{16}NO_2S^-$: 310.0902; found: 310.0905 $[M\text{-}H^+]^-$

m.p. 75 – 77 °C

EA calc'd (%) for $C_{18}H_{17}NO_2S$: C – 69.43, H – 5.50, N – 4.50, S – 10.30; found: C – 69.24, H – 5.49, N – 4.39, S – 10.36

4-(cyclohexylthio)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (23)



The title compound was synthesised according to General Procedure E from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and cyclohexanethiol (2 mL) in 70% yield (41 mg) as a beige solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

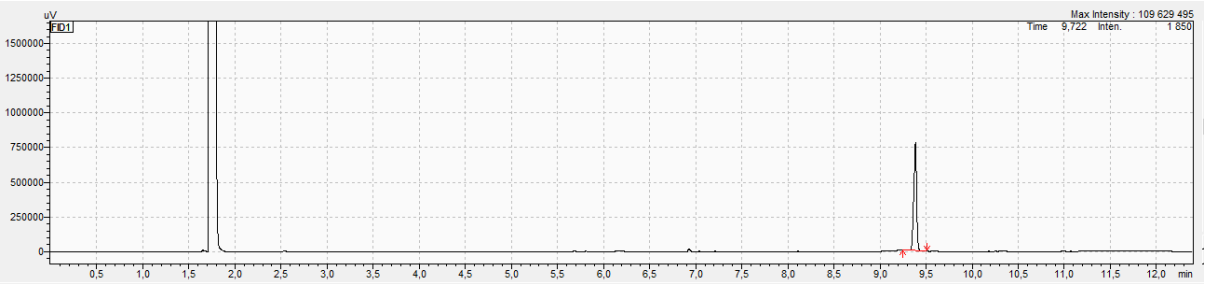
1H NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.59 (td, *J* = 7.5, 1.4 Hz, 1H), 7.46 – 7.42 (m, 2H), 4.76 (s, 1H), 3.36 (s, 3H), 3.15 (tt, *J* = 10.5, 3.7 Hz, 1H), 2.33 – 2.28 (m, 1H), 1.84 – 1.69 (m, 2H), 1.65 – 1.60 (m, 1H), 1.53 – 1.22 (m, 6H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.5, 164.4, 135.6, 133.8, 129.0, 128.7, 128.6, 125.7, 44.6, 43.5, 33.8, 32.4, 27.3, 26.1, 25.9, 25.8.

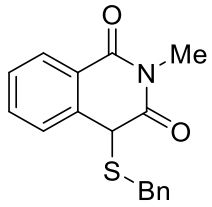
HRMS (ESI$^-$) *m/z* calc'd for $C_{16}H_{18}NO_2S^-$: 288.1058; found: 288.1059 $[M\text{-}H^+]^-$

m.p. 107 - 111 °C

GC (FID)



4-(benzylthio)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (24)



The title compound was synthesised according to General Procedure E from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and benzyl mercaptan (2 mL) in 66% yield (39 mg) as a colourless oil. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

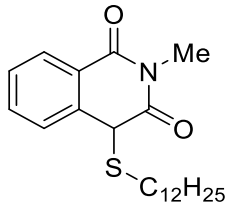
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.55 (td, *J* = 7.6, 1.4 Hz, 1H), 7.45 – 7.42 (m, 3H), 7.37 – 7.34 (m, 2H), 7.30 – 7.25 (m, 2H), 4.48 (s, 1H), 4.08 (d, *J* = 13.7 Hz, 1H), 3.81 (d, *J* = 13.7 Hz, 1H), 3.31 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.1, 164.3, 136.9, 135.0, 133.9, 129.5, 128.9, 128.83, 128.79, 128.69, 127.7, 125.8, 43.5, 36.9, 27.2.

HRMS (ESI$^+$) *m/z* calc'd for $C_{17}H_{15}NO_2SNa^+$: 320.0721; found: 320.0723 $[M+Na]^+$

EA: calc'd (%) for $C_{17}H_{15}NO_2S$: C – 68.66, H – 5.08, N – 4.71, S – 10.78; found: C – 68.49, H – 5.14, N 4.94, S – 10.58

4-(dodecylthio)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (25)



The title compound was synthesised according to General Procedure E from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and 1-dodecanethiol (2 mL) in 50% yield (37 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.62 (td, *J* = 7.6, 1.4 Hz, 1H), 7.51 – 7.45 (m, 2H), 4.67 (s, 1H), 3.38 (s, 3H), 2.86 (ddd, *J* = 12.6, 8.4, 5.8 Hz, 1H), 2.57 (ddd, *J* = 12.6, 8.6, 6.7 Hz, 1H), 1.67 – 1.54 (m, 3H), 1.30 – 1.25 (m, 16H), 0.88 (t, *J* = 6.9 Hz, 3H).

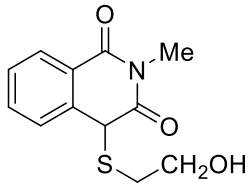
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.2, 164.4, 135.5, 133.9, 129.0, 128.7, 128.7, 125.7, 45.1, 32.5, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.3, 29.0, 28.9, 27.4, 22.8, 14.3.

HRMS (ESI$^-$) *m/z* calc'd for $C_{22}H_{32}NO_2S^-$: 374.2154; found: 374.2155 $[M-H^+]^-$

m.p. 60 – 62 °C

EA calc'd (%) for $C_{22}H_{33}NO_2S$: C – 70.36, H – 8.86, N – 3.73, S – 8.54; found: C – 70.30, H – 8.90, N – 3.83, S – 8.31

4-((2-hydroxyethyl)thio)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (26)



The title compound was synthesised according to General Procedure E from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and 2-mercaptoethanol (2 mL) in 45% yield (23 mg) as a colourless oil. Eluent for column chromatography (SiO_2): 20% -> 40% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 – 8.17 (m, 1H), 7.63 (td, *J* = 7.5, 1.4 Hz, 1H), 7.55 – 7.53 (m, 1H), 7.50 – 7.47 (m, 1H), 4.90 (s, 1H), 3.94 – 3.84 (m, 2H), 3.38 (s, 3H), 3.14 (ddd, *J* = 14.3, 6.6, 4.5 Hz, 1H), 2.84 (ddd, *J* = 14.3, 6.7, 4.7 Hz, 1H), 2.47 (s, 1H).

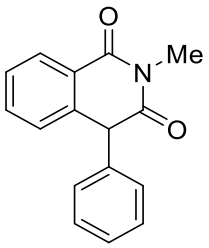
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.6, 164.2, 135.2, 134.1, 129.2, 129.0, 128.8, 125.5, 62.0, 44.8, 35.9, 27.5.

HRMS (ESI$^+$) *m/z* calc'd for $C_{12}H_{13}NO_3SNa^+$: 274.0514; found: 274.0516 $[M+Na]^+$

EA calc'd (%) for $C_{12}H_{13}NO_3S$: C – 57.35, H – 5.21, N – 5.57, S – 12.76; found: C – 57.25, H – 5.38, N – 5.66, S – 13.03

12. Arene Insertions

2-methyl-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (28)



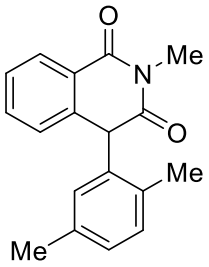
The title compound was synthesised according to General Procedure F from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and benzene (2 mL) in 37% yield (19 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.55 (td, *J* = 7.5, 1.5 Hz, 1H), 7.49 – 7.46 (m, 1H), 7.32 – 7.26 (m, 3H), 7.14 – 7.11 (m, 3H), 5.09 (s, 1H), 3.35 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.1, 165.1, 139.2, 138.4, 134.0, 129.2, 128.9, 128.7, 128.5, 128.1, 128.1, 125.5, 52.6, 27.4.

The spectroscopic data is consistent with that previously reported in the literature.[22]

4-(2,5-dimethylphenyl)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (29)



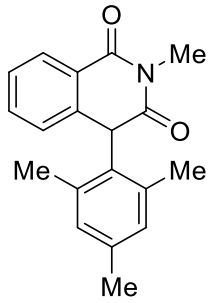
The title compound was synthesised according to General Procedure F from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and *p*-xylene (2 mL) in 43% yield (24 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.49 (td, *J* = 7.5, 1.6 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.71 (s, 1H), 5.24 (s, 1H), 3.40 (s, 3H), 2.23 (s, 6H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.2, 165.1, 139.1, 137.4, 136.2, 134.0, 133.5, 131.4, 130.7, 129.0, 128.8, 127.9, 127.8, 125.3, 49.9, 27.3, 21.0, 19.6.

The spectroscopic data is consistent with that previously reported in the literature.[22]

4-mesityl-2-methylisoquinoline-1,3(*2H,4H*)-dione (30)



The title compound was synthesised according to General Procedure F from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and mesitylene (2 mL) in 50% yield (30 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

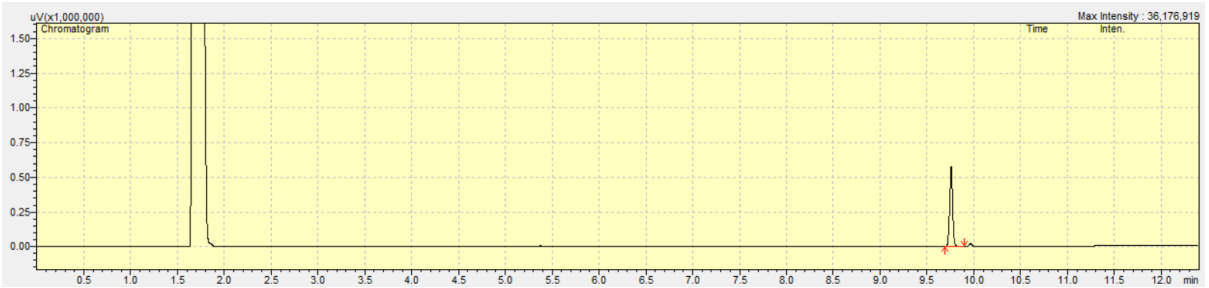
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.01 (s, 1H), 6.83 (dt, *J* = 7.6, 1.5 Hz, 1H), 6.80 (s, 1H), 5.44 (s, 1H), 3.45 (s, 3H), 2.49 (s, 3H), 2.29 (s, 3H), 1.62 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.2, 165.0, 138.9, 137.8, 137.7, 136.3, 134.1, 133.0, 130.8, 129.2, 129.0, 127.6, 126.5, 125.3, 47.1, 27.2, 21.15, 21.08, 20.0.

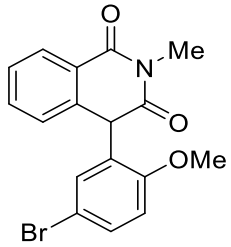
HRMS (ESI$^+$) m/z calc'd for $C_{19}H_{19}NO_2Na^+$: 316.1313; found: 316.1316 $[M+Na]^+$

m.p. 148 – 151 °C

GC (FID):



4-(5-bromo-2-methoxyphenyl)-2-methylisoquinoline-1,3(2H,4H)-dione (31)



The title compounds were synthesised according to General Procedure F from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and 4-bromoanisole (2 mL) in 20% yield (14 mg) as an off-white solid. Eluent for column chromatography (SiO_2): gradually from 20% of EtOAc in hexane to 35%.

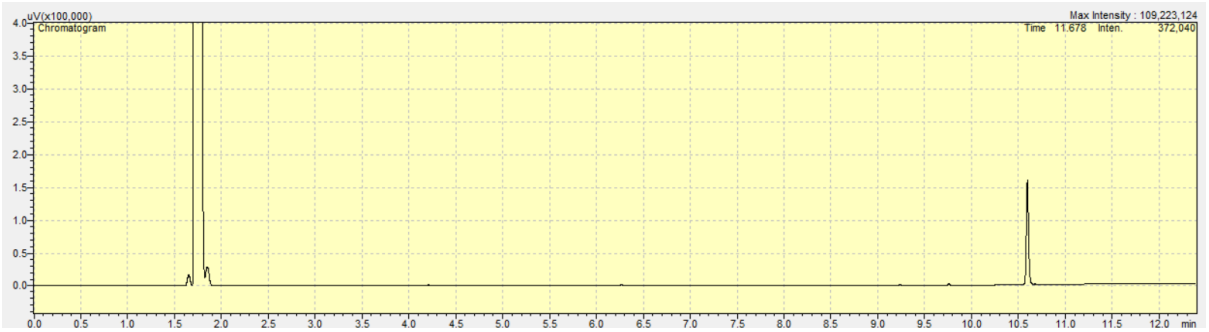
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.48 (td, *J* = 7.5, 1.5 Hz, 1H), 7.43 – 7.38 (m, 3H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.73 (d, *J* = 8.6 Hz, 1H), 5.07 (s, 1H), 3.58 (s, 3H), 3.42 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.8, 165.2, 156.0, 138.1, 134.0, 133.7, 132.3, 130.4, 128.7, 127.7, 127.3, 125.2, 113.6, 113.3, 56.1, 48.3, 27.2.

HRMS (ESI$^+$) *m/z* calc'd for $C_{17}H_{14}NO_3NaBr^+$: 382.0055; found: 382.0056 $[M+Na]^+$

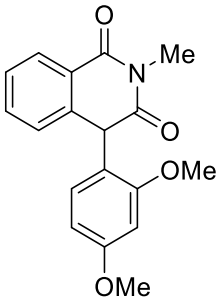
m.p. 170 – 173 °C

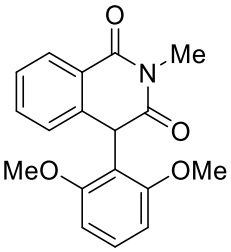
GC (FID):



4-(2,4-dimethoxyphenyl)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (32) and

4-(2,6-dimethoxyphenyl)-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (33)





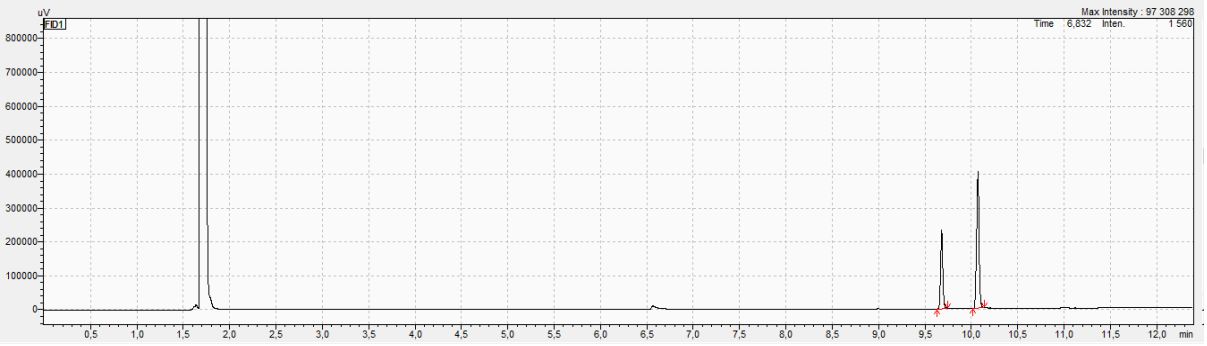
The title compounds were synthesised according to General Procedure F from 4-diazo-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (40 mg, 0.20 mmol) and 1,3-dimethoxybenzene (2 mL) in 74% yield (46 mg) as a white foam. The product was isolated as an inseparable 2:1 (**32**:**33**) mixture of regioisomers. Eluent for column chromatography (SiO_2): gradually from 30% of EtOAc in hexane to 40%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.22 (td, *J* = 7.5, 1.5 Hz, 2H + 33), 7.90 (td, *J* = 7.6, 1.4 Hz, 1H), 7.83 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47 – 7.32 (m, 4H + 33), 7.27 – 7.22 (m, 1H + 33), 7.14 (d, *J* = 8.2 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.50 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 5.67 (s, 1H), 5.06 (s, 1H), 3.96 (s, 3H), 3.79 (s, 3H), 3.58 (s, 3H), 3.49 (s, 3H), 3.43 (s, 3H), 3.41 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) Unable to unambiguously assign the ^{13}C peaks due to the low rr.

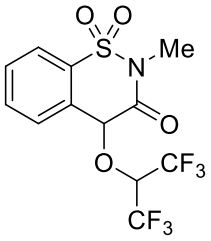
HRMS (ESI$^+$) *m/z* calc'd for $C_{18}H_{17}NO_4Na^+$: 334.1055; found: 334.1052 $[M+Na]^+$

GC (FID): 2:1 mixture.



13. Reactions of 4-diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxides

4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methyl-2H-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (35)



The title compound was synthesised according to General Procedure G from 4-diazo-2-methyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (36 mg, 0.15 mmol) and HFIP (1.5 mL) in 53% yield (30 mg) as a white solid. Performing the reaction on the same scale with blue LEDs for 2.5 hours yielded the title compound in 52% yield (29 mg). Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.84 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.75 (td, *J* = 7.7, 1.3 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 5.92 (s, 1H), 5.02 (hept, *J* = 5.6 Hz, 1H), 3.32 (s, 3H).

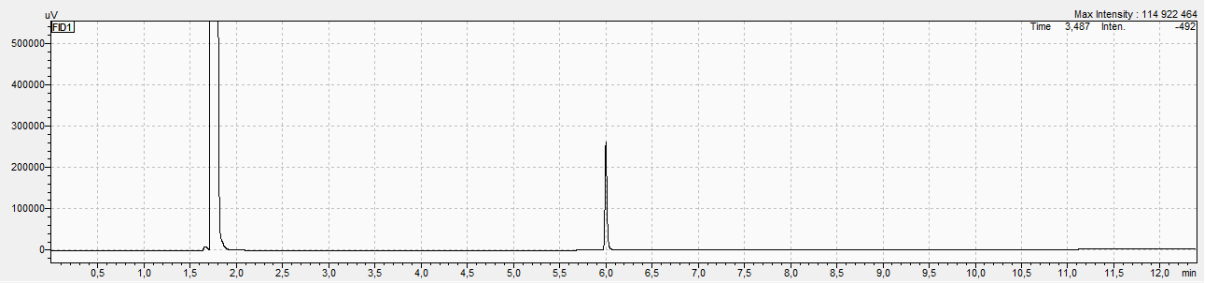
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.6, 134.2, 134.1, 131.4, 129.3, 125.5, 123.2, 123.0 – 118.3 (m), 76.1, 75.5 (obs. p, *J* = 33.6 Hz), 27.8.

^{19}F NMR (470 MHz, $CDCl_3$) δ -72.6 – -72.6 (m, 3F), -72.7 – -72.8 (m, 3F).

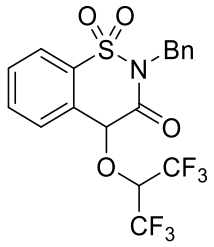
HRMS (ESI$^-$) *m/z* calc'd for $C_{12}H_8NO_4F_6S^-$: 376.0078; found: 376.0080 $[M\text{-}H^+]^-$

m.p. 92 – 96 °C

GC (FID):



2-benzyl-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (36)



The title compound was synthesised according to General Procedure G from 2-benzyl-4-diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (47 mg, 0.15 mmol) and HFIP (1.5 mL) in 51% yield (35 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.74 (td, *J* = 7.7, 1.3 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.44 – 7.42 (m, 2H), 7.36 – 7.28 (m, 3H), 5.97 (s, 1H), 5.04 (d, *J* = 15.2 Hz, 1H), 5.00 – 4.95 (m, 2H).

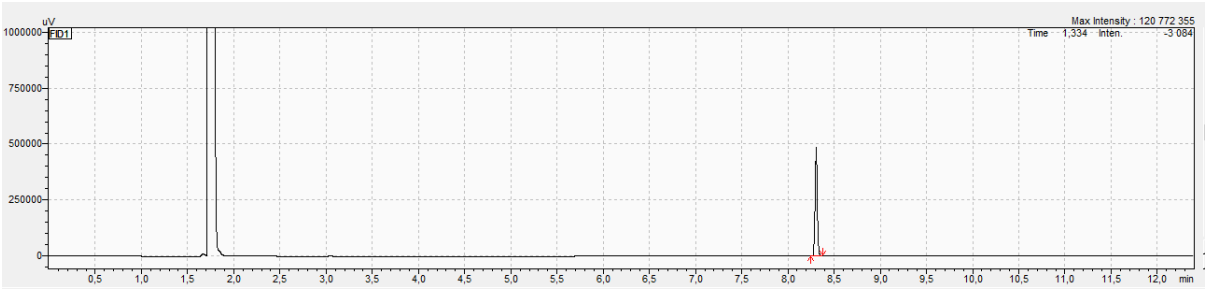
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.4, 135.3, 134.5, 134.2, 131.6, 129.3, 128.9, 128.8, 128.4, 125.5, 123.0, 122.8 – 118.5 (m), 76.3, 75.5 (obs. p, *J* = 33.0 Hz), 46.3.

^{19}F NMR (470 MHz, $CDCl_3$) δ -72.5 – -72.6 (m, 3F), -72.6 – -72.7 (m, 3F).

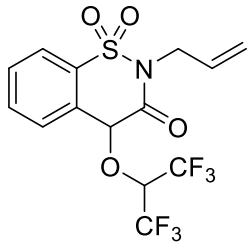
HRMS (ESI$^-$) *m/z* calc'd for $C_{18}H_{12}NO_4SF_6^-$:452.0391; found: 452.0399 $[M\text{-}H^+]^-$

m.p. 140 – 143 °C

GC (FID):



2-allyl-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (37)



The title compound was synthesised according to General Procedure G from 2-allyl-4-diazo-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (39 mg, 0.15 mmol) and HFIP (1.5 mL) in 44% yield (27 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.74 (td, *J* = 7.7, 1.3 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 5.97 (s, 1H), 5.87 (ddt, *J* = 17.1, 10.2, 5.8 Hz, 1H), 5.33 (dq, *J* = 17.0, 1.3 Hz, 1H), 5.25 (dq, *J* = 10.3, 1.1 Hz, 1H), 5.00 (hept, *J* = 5.5 Hz, 1H), 4.51 (ddt, *J* = 15.8, 5.8, 1.4 Hz, 1H), 4.41 (ddt, *J* = 15.7, 6.0, 1.4 Hz, 1H).

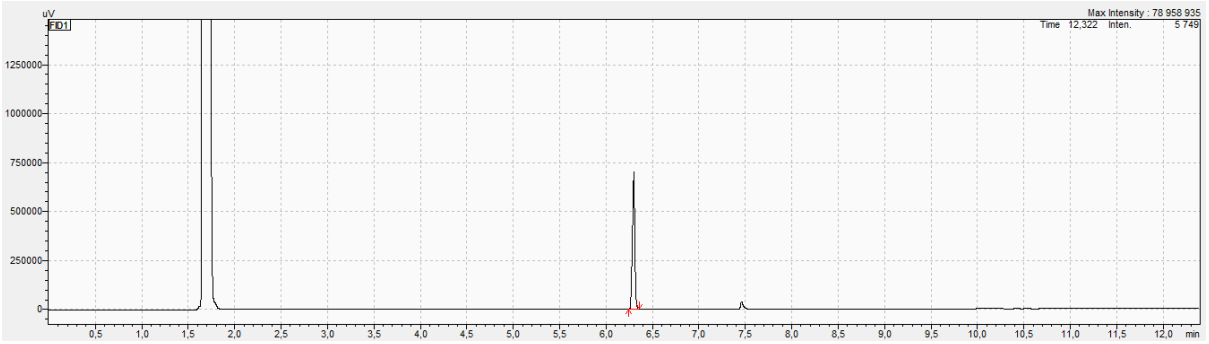
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.2, 134.5, 134.2, 131.5, 130.9, 129.3, 125.5, 123.0, 119.6, 76.3, 75.5 (obs. p, *J* = 32.2 Hz), 44.9. (One carbon is missing due to ^{19}F splitting).

^{19}F NMR (470 MHz, $CDCl_3$) δ -72.5 – -72.6 (m, 3F), -72.6 – -72.7 (m, 3F).

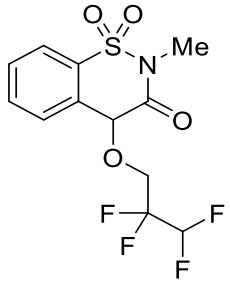
HRMS (APCI$^+$) *m/z* calc'd for $C_{14}H_{12}NO_4F_6S^+$: 404.0391; found: 404.0390. $[M+H]^+$

m.p. 65 – 67 °C

GC (FID):



2-methyl-4-(2,2,3,3-tetrafluoropropoxy)-2H-benzo[e][1,2]thiazin-3(4*H*)-one 1,1-dioxide (38)



The title compound was synthesised according to General Procedure G from 4-diazo-2-methyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (36 mg, 0.15 mmol) and 2,2,3,3-tetrafluoropropan-1-ol (1.5 mL) with an extended reaction time of 4 hours in 46% yield (24 mg) as a colourless oil. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

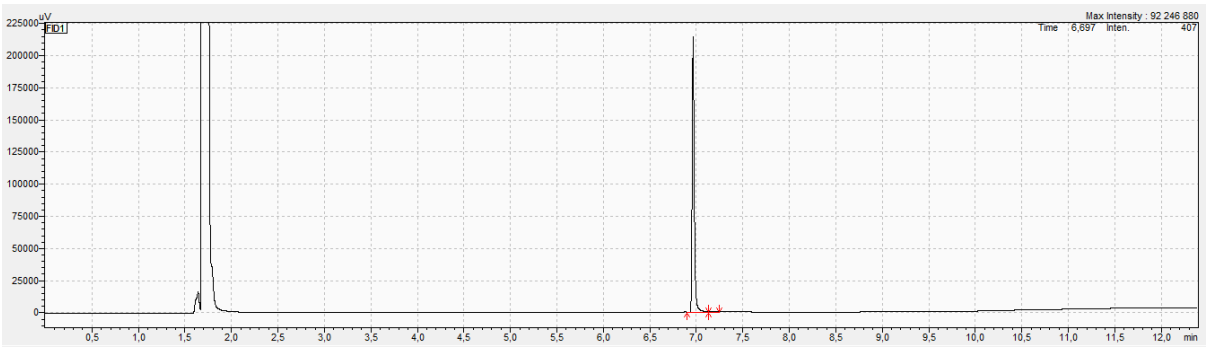
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.71 (td, *J* = 7.7, 1.2 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 6.09 (tdd, *J* = 53.2, 5.2, 3.2 Hz, 1H), 5.64 (s, 1H), 4.72 – 4.64 (m, 1H), 4.15 (qd, *J* = 11.8, 2.3 Hz, 1H), 3.30 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.7, 134.2, 134.0, 132.7, 128.9, 125.3, 123.0, 114.8 (tt, *J* = 249.9, 27.7 Hz), 109.5 (tdd, *J* = 250.0, 36.8, 34.8 Hz), 68.9 (dd, *J* = 29.7, 27.1 Hz), 27.9. (One peak is missing and overlaps with the $CDCl_3$ peak).

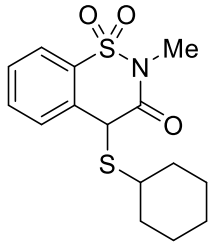
^{19}F NMR (470 MHz, $CDCl_3$) δ -123.5 – -125.6 (m, 2F), -136.7 – -139.3 (m, 2F).

HRMS (APCI^{+}) *m/z* calc'd for $C_{12}H_{12}NO_4F_4S^{+}$: 342.0423; found: 342.0425 $[M+H]^{+}$

GC (FID):



4-(cyclohexylthio)-2-methyl-2H-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (39)



The title compound was synthesised according to General Procedure G from 4-diazo-2-methyl-2*H*-benzo[*e*][1,2]thiazin-3(4*H*)-one 1,1-dioxide (36 mg, 0.15 mmol) and cyclohexanethiol (2 mL) with an extended reaction time of 7 hours in 50% yield (24 mg) as a white solid. Eluent for column chromatography (SiO_2): 10% EtOAc in hexane.

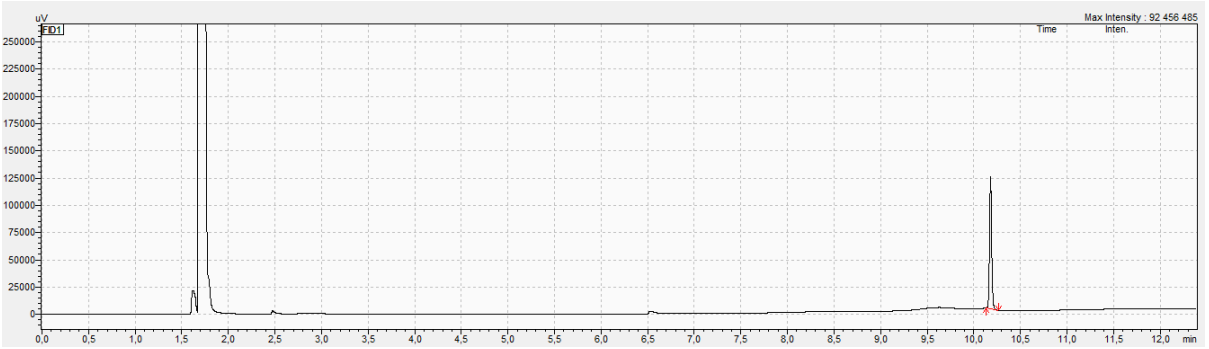
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.65 (td, *J* = 7.6, 1.3 Hz, 1H), 7.54 – 7.50 (m, 2H), 4.85 (s, 1H), 3.35 (s, 3H), 3.17 – 3.11 (m, 1H), 2.26 (d, *J* = 12.6 Hz, 1H), 2.02 – 1.98 (m, 1H), 1.85 – 1.76 (m, 2H), 1.66 – 1.62 (m, 1H), 1.53 – 1.24f (m, 5H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.9, 135.1, 134.1, 132.8, 129.5, 128.8, 123.8, 45.9, 45.8, 33.6, 32.8, 27.1, 26.1, 25.9, 25.8.

HRMS (APCI$^-$) *m/z* calc'd for $C_{15}H_{18}NO_3S_2^-$: 324.0728; found: 324.0730 $[M-H]^+$

m.p. 122 – 124 °C

GC (FID):



14. References

(1) Tsou, H. R.; Otteng, M.; Tran, T.; Floyd, M. B.; Reich, M.; Birnberg, G.; Kutterer, K.; Ayral-Kaloustian, S.; Ravi, M.; Nilakantan, R.; Grillo, M.; McGinnis, J. P.; Rabindran, S. K. 4-(Phenylaminomethylene)Isoquinoline-1,3(2H,4H)-Diones as Potent and Selective Inhibitors of the Cyclin-Dependent Kinase 4 (CDK4). *J. Med. Chem.* **2008**, *51* (12), 3507–3525.

(2) Liu, Z.; Shibata, N.; Takeuchi, Y. Novel Methods for the Facile Construction of 3,3-Disubstituted and 3,3-Spiro-2H,4H-Benzo[e]1,2-Thiazine-1,1-Diones: Synthesis of (11S,12R,14R)-2-Fluoro-14-Methyl-11-(Methylethyl)Spiro[4H]Benzo[e]-1,2-Thiazine-3,2'-Cyclohexane]-1,1-Dione, an Agent for The . *J. Org. Chem.* **2000**, *65* (22), 7583–7587.

(3) Barbazanges, M.; Augé, M.; Moussa, J.; Amouri, H.; Aubert, C.; Desmarets, C.; Fensterbank, L.; Gandon, V.; Malacria, M.; Ollivier, C. Enantioselective IrI-Catalyzed Carbocyclization of 1,6-Enynes by the Chiral Counterion Strategy. *Chem. - A Eur. J.* **2011**, *17* (49), 13789–13794.

(4) Lombardino, J. G.; Wiseman, E. H. Antiinflammatory 3,4-Dihydro-2-Alkyl-3-Oxo-2H-1,2-Benzothiazine-4-Carboxamide 1,1-Dioxides. *J. Med. Chem.* **1971**, *14* (10), 973–977.

(5) Kantin, G.; Dar'in, D.; Krasavin, M. RhII-Catalyzed Cycloaddition of α-Diazo Homophthalimides and Nitriles Delivers Oxazolo[5,4-c]Isoquinolin-5(4H)-One Scaffold. *Eur. J. Org. Chem.* **2018**, *2018* (35), 4857–4859.

(6) Eom, S.; Kwon, T.; Lee, D. Y.; Park, C. H.; Kim, H. J. Copper-Mediated Three-Component Reaction for the Synthesis of N-Acylsulfonamide on DNA. *Org. Lett.* **2022**, *24* (27), 4881–4885.

(7) Lobb, K. L.; Hipskind, P. A.; Aikins, J. A.; Alvarez, E.; Cheung, Y. Y.; Considine, E. L.; De Dios, A.; Durst, G. L.; Ferritto, R.; Grossman, C. S.; Giera, D. D.; Hollister, B. A.; Huang, Z.; Iversen, P. W.; Law, K. L.; Li, T.; Lin, H. S.; Lopez, B.; Lopez, J. E.; Martin Cabrejas, L. M.; McCann, D. J.; Molero, V.; Reilly, J. E.; Richett, M. E.; Shih, C.; Teicher, B.; Wikel, J. H.; White, W. T.; Mader, M. M. Acyl Sulfonamide Anti-Proliferatives: Benzene Substituent Structure-Activity Relationships for a Novel Class of Antitumor Agents. *J. Med. Chem.* **2004**, *47* (22), 5367–5380.

(8) Venkateswarlu, V.; Aravinda Kumar, K. A.; Gupta, S.; Singh, D.; Vishwakarma, R. A.; Sawant, S. D. DMSO/I_2 Mediated C-C Bond Cleavage of α-Ketoaldehydes Followed by C-O Bond Formation: A Metal-Free Approach for One-Pot Esterification. *Org. Biomol. Chem.* **2015**, *13* (29), 7973–7978.

(9) Deady, L. W.; Rodemann, T. Reduced Benzimidazo[2,1-a]Isoquinolines. Synthesis and Cytotoxicity Studies. *Aust. J. Chem.* **2001**, *54* (8), 529.

(10) Dey, A. S.; Rosowsky, A.; Modest, E. J. Direction of Cyclization of l,2-Bis-(Cyanomethyl)Benzenes. *J. Org. Chem.* **1970**, *35* (2), 536–539.

(11) Billamboz, M.; Bailly, F.; Barreca, M. L.; De Luca, L.; Mouscadet, J. F.; Calmels, C.; Andréola, M. L.; Witvrouw, M.; Christ, F.; Debyser, Z.; Cotelle, P. Design, Synthesis, and Biological Evaluation of a Series of 2-Hydroxyisoquinoline-1,3(2H,4H)-Diones as Dual Inhibitors of Human Immunodeficiency Virus Type 1 Integrase and the Reverse Transcriptase RNase H Domain. *J. Med. Chem.* **2008**, *51* (24), 7717–7730.

(12) Glennon, R. A.; Raghupathi, R.; Bartyzel, P.; Teitler, M.; Leonhardt, S. Binding of Phenylalkylamine Derivatives at 5-HT1C and 5-HT2 Serotonin Receptors: Evidence for a

Lack of Selectivity. *J. Med. Chem.* **1992**, *35* (4), 734–740.

(13) Trost, B. M.; Kalnmals, C. A. Sulfones as Synthetic Linchpins: Transition-Metal-Free Sp3–Sp2 and Sp2–Sp2 Cross-Couplings Between Geminal Bis(Sulfones) and Organolithium Compounds. *Chem. - A Eur. J.* **2018**, *24* (36), 9066–9074.

(14) Jangir Narshinha P., R. A. Total Synthesis of Tetrahydroisoquinoline-Based Bioactive Natural Products Laudanosine, Romneine, Glaucine, Dicentrine, and Their Unnatural Analogues Isolaudanosine and Isoromneine. *Synthesis* **2017**, *49* (07), 1655–1663.

(15) Horning, D. E.; Lacasse, G.; Muchowski, J. M. Spiroalkylation of Some Homophthalimides and Oxindoles with 1-Bromo-2-Chloroethane. *Can. J. Chem.* **1971**, *49* (2), 246–254.

(16) Deliömeroğlu, M. K.; Özcan, S.; Balcia, M. A Short and Efficient Construction of the Dibenzo[c,h]Chromen-6-One Skeleton. *Arkivoc* **2010**, *2010* (2), 148–160.

(17) Jaiswal, A. K.; Kushawaha, A. K.; Pandey, S.; Kumar, A.; Sashidhara, K. V. Halogen-Free Oxidation of Aryl Ketones and Benzyl Nitrile Derivatives to Corresponding Carboxylic Acids by Using NaOH/ TBHP in Aqueous Medium. *Tetrahedron* **2023**, *136*, 133359.

(18) Yang, Y.; Li, Y.; Cheng, C.; Yang, G.; Zhang, J.; Zhang, Y.; Zhao, Y.; Zhang, L.; Li, C.; Tang, L. Synthesis of 4-Aryl Isoquinolinedione Derivatives by a Palladium-Catalyzed Coupling Reaction of Aryl Halides with Isoquinoline-1,3(2 H,4 H)-Diones. *J. Org. Chem.* **2018**, *83* (6), 3348–3353.

(19) Doyle, M. P.; Siegfried, B.; Dellaria, J. F. Alkyl Nitrite-Metal Halide Deamination Reactions. 2. Substitutive Deamination of Arylamines by Alkyl Nitrites and Copper(II) Halides. A Direct and Remarkably Efficient Conversion of Arylamines to Aryl Halides. *J. Org. Chem.* **1977**, *42* (14), 2426–2431.

(20) Pfizer Patent - DE1943265, 1970, A1.

(21) Di Mola, A.; Tedesco, C.; Massa, A. Metal-Free Air Oxidation in a Convenient Cascade Approach for the Access to Isoquinoline-1,3,4(2H)-Triones. *Molecules* **2019**, *24* (11), 2177.

(22) Golushko, A.; Dar'in, D.; Kantin, G.; Guranova, N.; Vasilyev, A. V.; Krasavin, M. Medicinally Relevant Modification of the Isoquinoline-1,3-Dione Scaffold via Metal-Free Arylation and Fluorination of Diazo Homophthalimides in Brønsted Acids. *Synthesis* **2019**, *51* (20), 3815–3824.

Chemistry–A European Journal

Supporting Information

TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines

Matteo Leone, Joseph P. Milton, Dorota Gryko, Luc Neuville,* and Géraldine Masson*

Supplementary Information

TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines

Matteo Leone,[a] Joseph Milton,[b] Dorota Gryko,[b] Luc Neuville*[a,c] and Geraldine Masson*[a,c]

[a] Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

[b] Institute of Organic Chemistry Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

[c] Labcom HitCat, Seqens-CNRS joint laboratory, Seqens'Lab, 8 Rue de Rouen, 78440 Porcheville, France

E-mail: luc.neuville@cnrs.fr, geraldine.masson@cnrs.fr

Table of contents

General Information 3
General procedure for the synthesis of *N*-sulfinyl imines: 5
Procedure A: 5
Procedure B: 5
N-sulfinyl imines used in the Study 6
Optimization of the reaction conditions 7
General procedure for the HAT radical addition to *N*-sulfenyl imine 1 10
Procedure for 1.0 mmol scale synthesis of compound 4mb 10
N-sulfinyl amide deprotection and determination of the absolute configuration of product 4ml 12
Synthesis of 5 from 4ml: 12
Synthesis of 5 from D-α-phenyl alanine 12
Light ON-OFF experiment 14
Analytical data of new sulfinamides 15
Compound 1g 15
Compound 1k 15
Compound 1l 16
Compound 1n 16
Compound 1o 17
Analytical data of HAT adducts 4 18
Compound 4cb 18
Compound 4cc 18
Compound 4cd 19
Compound 4ce 19
Compound 4cf 20
Compound 4cg 20
Compound 4ch 21
Compound 4ci 21
Compound 4cj 22
Compound 4ck 22
Compound 4cl 23
Compound 4db 23
Compound 4eb 24

Compound 4fb 24
Compound 4gb 25
Compound 4hb 25
Compound 4ib 26
Compound 4jb 26
Compound 4kb 27
Compound 4lb 27
Compound 4mb 28
Compound 4ml 28
Compound 4mn 29
Compound 4mo 29
Compound 4mp 30
Compound 4mq 30
Compound 4mr 31
Compound 4ms 31
Compound 4mt 32
Compound 4mu 32
Compound 4nb 33
Compound 4ob 33
Unsuccessful transformation with selected reagents 34
NMR Spectra 34
References 73

General Information

All reactions were carried out in oven-dried glassware with magnetic stirring. Reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. When specified, acetonitrile and DCM were distilled with CaH_2. When specified THF was distilled with Na, Benzophenone and stored over 4A molecular sieves. Every purified solvent was stored under argon atmosphere. Analytical thin layer chromatography (TLC) plates were purchased from Merck KGaA (silica gel 60 F254 on aluminum support). Visualization was accomplished by irradiation with a UV light at 254 nm. Flash column chromatography was carried out using kieselgel 35-70 μm particle sized silica gel (200-400 mesh). Preparative TLC plates were purchased from Macherey-Nagel (0.25 mm silica gel 60). ^{1}H NMR and ^{13}C NMR and ^{19}F NMR spectra were recorded with Bruker 300 MHz instruments. ^{1}H and ^{13}C chemical

shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance as the internal standard. The following calibration values have been used for ^{1}H NMR: $CDCl_3$ (7.26 ppm); for ^{13}C NMR: $CDCl_3$ (77.2 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, h = hexuplet, hept = heptuplet, m = multiplet), coupling constants (Hz) and integration. UPLC-MS analysis was run using an Acquity Waters UPLC equipped with a Waters LCT Premier XE (ESI ionization) and a Waters Acquity PDA detector, using a column BEH C18 1.7 µm, 2.1 mm × 50 mm. Gradients were run using water and acetonitrile (1:1) with 0.1% of acetic acid at 40°C with a UV detection 4 from 210 to 410 nm and ESI+ and ESI- detection in the 80−1500 m/z range or with an Agilent 6546 Q-Tof spectrometer equipped with an APPI source with a detection in the 100-1700 m/z range. Optical rotations were performed on an Anton Paar MCP 300 Modular Circular (589 nm) using a 700-µL cell with a path length of 1 dm. Chiral HPLC analysis was performed on Hitachi LaChrom-Elite apparatus equipped with diode array UV detector (UV detection monitored at 254 nm), using Daicel Chiralcel IA column. The enantiomeric excess was determined by HPLC analysis by comparing with reported data. The photoreactions were carried out in 4 mL borosilicate vials equipped with a stirring bar and a septum unless otherwise noted. The reaction vials were placed in a holder (distance between the reaction vial and the lamp is ca. 5 cm, Figure S1) and illuminated with 390 nm LED (40 W, Kessil PR160, set to maximum intensity or 18 W 405 nm EvoluChem LED spotlight) with continuous stirring at 700 rpm. The diastereomeric ratio was determined by the crude NMR spectra.

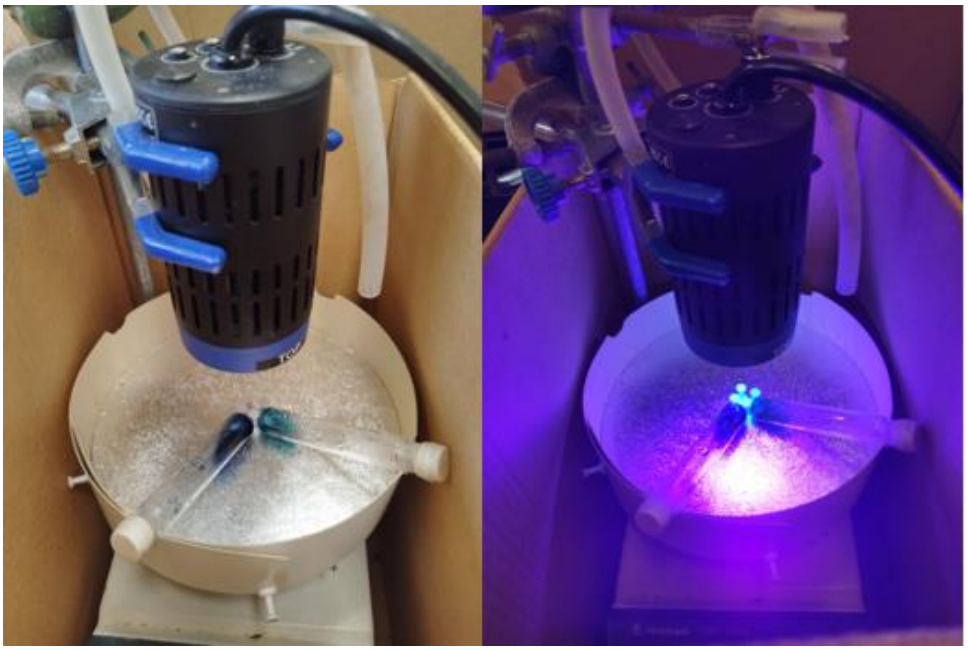
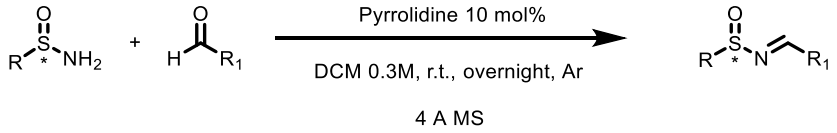


Figure S 1 The reaction setup for optimization of the reaction conditions and substrate scope evaluation

General procedure for the synthesis of *N*-sulfinyl imines:

Procedure A:

Reported procedure, described below, was used for selected imines **1**:[1]

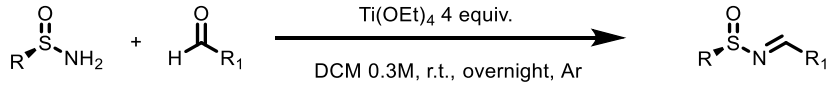


N-Sulfinyl amide (1.0 equiv.), 4 Å activated molecular sieves, and the aldehyde (1.0 equiv.), were placed in a dry round-bottom flask equipped with a stirring bar and a septum. The reaction vessel was evacuated and back-filled with Argon three times. Subsequently, anhydrous DCM (0.3 M) and pyrrolidine (10 mol %) were added. The reaction mixture was stirred at room temperature under an Argon balloon. After 19 hours, the reaction mixture was filtered through Celite, washed with DCM, and concentrated on a rotary evaporator. The crude product was purified by column chromatography (silica gel, PET/ethyl acetate). The combined fractions were concentrated on a rotary evaporator and dried under vacuum, resulting in the desired product.

Products **1a**[2], **1b**[3], and **1m**[4] were synthetized with this procedure and the NMR spectra agree with the previously reported data.

Procedure B:

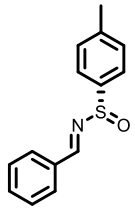
Reported procedure, described below, was used for selected imines **1**.[5]



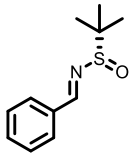
N-sulfinyl amide (1.0 equiv.), $Ti(OEt)_4$ (4.0 equiv.) and if in solid form, the aldehyde (1.0 equiv.) were placed in a dry round-bottom flask equipped with a stirring bar and a septum. The reaction vessel was evacuated and back-filled with Argon three times. Subsequently, anhydrous DCM (0.3 M) and pyrrolidine (10 mol %) were added. The reaction mixture was stirred at room temperature under an Argon balloon. *In the case of a liquid aldehyde (1.0 equiv.), it was introduced at the same stage as DCM (0.3 M) and pyrrolidine (10 mol %).*

After 19h, the mixture was quenched with a saturated aqueous solution of sodium hydrogen carbonate with rapid stirring. The resulting suspension was filtered through a plug of Celite, and the filter cake was washed 3 times with EtOAc. The combined organic portions were concentrated on rotary evaporator and purified by column chromatography (silica gel, PET/ethyl acetate). The combined fractions were concentrated on rotary evaporator, and dried under vacuum, resulting in the desired product. Products (**1c-1l**, **1n-1p**) were synthetized with this procure and the NMR spectras agree with the previously reported data.

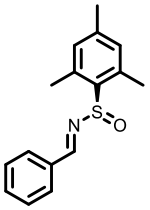
N-sulfinyl imines used in the Study



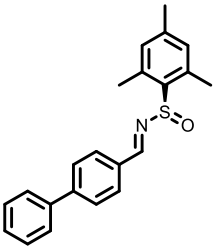
1a[2]



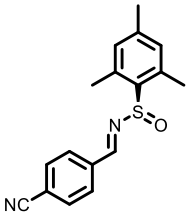
1b[3]



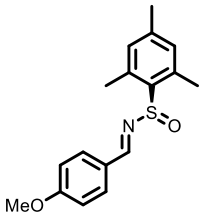
1c[2]



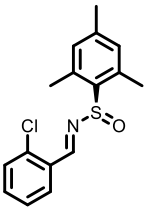
1d[6]



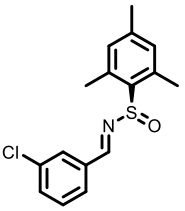
1e[7]



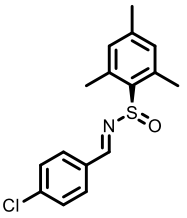
1f[7]



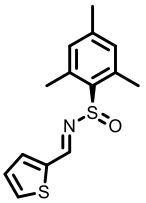
1g



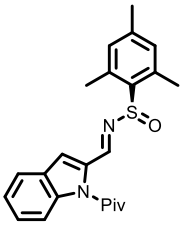
1h[8]



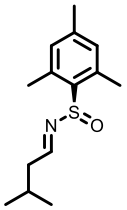
1i[6]



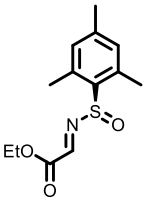
1j[7]



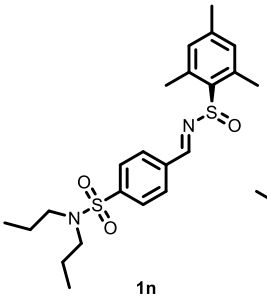
1k



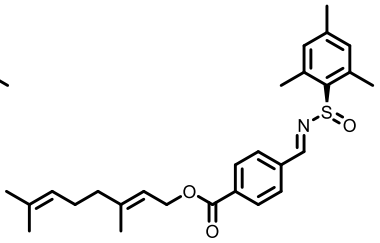
1l



1m[4]

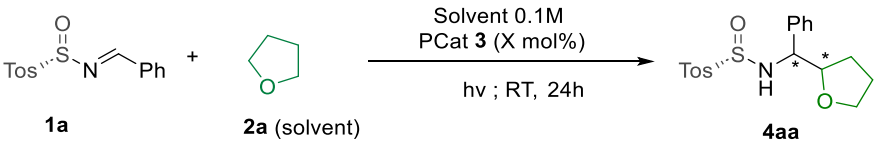


1n



1o

Optimization of the reaction conditions

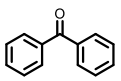


The reactions were performed on 0.1 mmol scale. The *N*-sulfinyl imine **1a** and the photocatalyst (X mol%) were placed in the reaction vial equipped with a stirring bar and a septum. The vial was evacuated and back-filled with Argon three times and dry THF was then added. Argon was bubbled through the reaction tube for 1 minute using a long needle. Thereafter, the reaction mixture was placed ca. 5 cm from the light source (see Figure S1) and stirred with either fan cooling or air flow. The completion of the reactions was monitored by TLC. Yields and dr were determined by ^{1}H NMR with Trichloroethylene (6.41 ppm) serving as external standard.

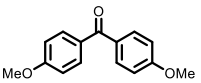
Table S1. Optimization of the reaction conditions with **1a** and THF as the radical precursor

entry	*Photocat.*	*Additive*	*hv*	*Dr[a]*	*Yield[b]*
1	**3a**, BP, 50mol%	-	390nm	6.4: 3 : 3 : 1	73%
2	**3b,** DmBP, 50mol%	-	390nm	6.4: 3 : 3 : 1	50%
3	**3d**, AQ 50mol%	-	405nm	-	-
4	**3e**, TX 50mol%	-	405nm	-	-
5	**3f**, Eosin Y 50mol%	-	456nm	-	-
6	**3c**, BcBP 50mol%	-	390nm	6.5 : 3 : 3 : 1	80%
7	**3c**, BcBP 50mol%	CPA 10mol%	390nm	6 : 2.8 : 2.8 : 1	50%
8	**3c**, BcBP 50mol%	$ZnCl_2$ 10mol%.	390nm	-	35%
9	**3g**, TBADT 5mol%	-	390nm	6.9 : 3.1 : 3 : 1	56%
10	**3g**, TBADT 5mol%	0.05M ACN_{dry}	390nm	6.9 : 3.1 : 3 : 1	80%

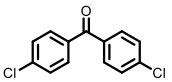
Reactions were performed on a 0.1 mmol scale using N-sulfinyl imine and THF as radical source and solvent. [a] determined by crude ^{1}H NMR [b] Yield determined by NMR with 1,1,2-trichloroethene as external standard.



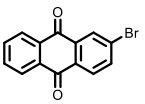
Benzophenone (BP), **3a**



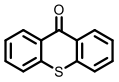
4,4'-Dimethoxy-benzophenone (DmBP), **3b**



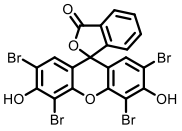
4,4'-Dichloro-benzophenone (DcBP), **3c**



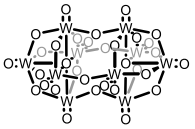
Anthraquinone (AQ), **3d**



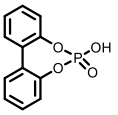
Thioxanthone. (Tx), **3e**



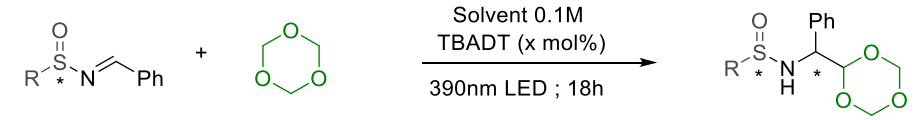
Eosin Y **3f**



TBADT, **3g**



Dibenzo[d,f][1,3,2]dioxaphosphepin-6-ol 6-oxide (Phosphoric Acid , PA),



1a R = Tos (*S*)
1b R = t-Bu (*S*)
1c R = Mes (*R*)

2b

4ab R = Tos
4bb R = t-Bu
4cb R = Mes

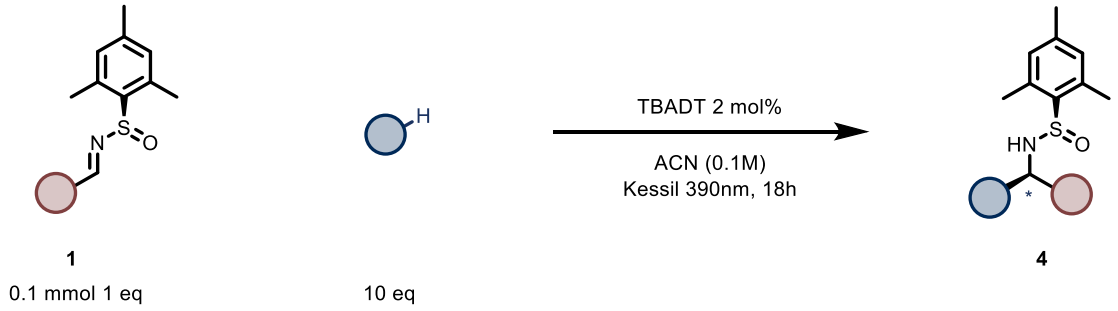
The reactions were performed on 0.1 mmol scale. The *N*-sulfinyl imine **1**, the photocatalyst (x mol%) and 1,3,5 trioxane **2b** were placed in the reaction vial equipped with a stirring bar and a septum. The vial was evacuated and back-filled with Argon three times and solvent was then added. Argon was bubbled through the reaction tube for 1 minute using a long needle. Thereafter, the reaction mixture was placed ca. 5 cm from the light source (see Figure S1) and stirred with a fan cooling or air flow. The completion of the reaction was monitored by TLC. Yields and dr were determined by ^{1}H NMR with Trichloroethylene (6.41 ppm) serving as external standard.

Table S2. Optimization of the reaction conditions with *N*-sulfenyl imine and Trioxane **2b** as the radical precursor

Entry	*N-sulfenyl imine*	*Solvent (0.1M)*	*PC (TBADT), x mol%*	*2b*	*dr[a]*	*Yield[b]*
1	**1a**	ACN	5 mol%	5eq	6 : 1	33%
2	**1a**	ACN	5 mol%	10eq	6 : 1	54%
3	**1b**	ACN	5 mol%	10eq	1.7: 1	38%
4	**1c**	ACN	5 mol %	10 eq	>98 : 2	70%
5	**1c**	ACN	2 mol %	10 eq	>98 : 2	75%
6	**1c**	ACN	1 mol %	10 eq	>98 : 2	63%
7	**1c**	ACN/TFT 1 : 1	2 mol %	10 eq	>98 : 2	50%
8	**1c**	TFT	2 mol %	10 eq	>98 : 2	35%
9	**1c**	Acetone	2 mol %	10 eq	>98 : 2	61%
10	**1c**	DCM	2 mol %	10 eq	>98 : 2	50%
11	**1c**	ACN/DCM 1 : 1	2 mol %	10 eq	>98 : 2	55%
			Deviations from conditions entry 5			
12	**1c**	No Photocat	390nm	10 eq	-	0%
13	**1c**	No light	-	10 eq	-	0%
14	**1c**	Air	390nm	10 eq	-	0%

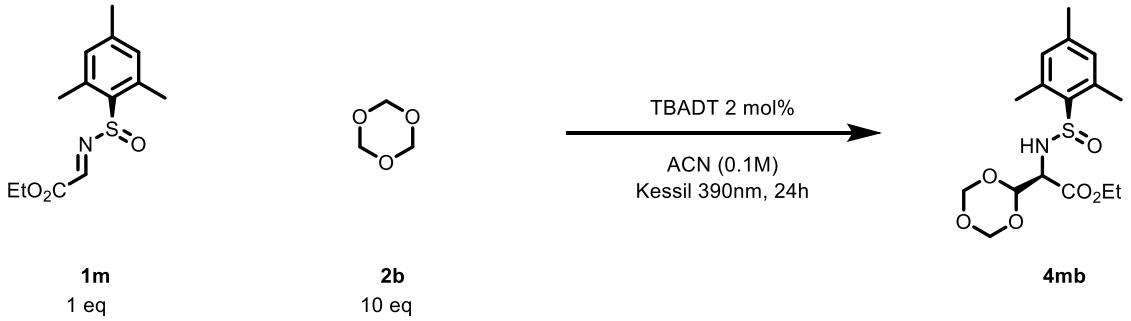
Reactions were performed on a 0.1 mmol scale using N-sulfinyl imine and 10 equiv. of 1,3,5-trioxane with 1 ml solvent. [a] determined by ^{1}H NMR on crude [b] Yield determined by NMR with 1,1,2-trichloroethene as external standard

General procedure for the HAT radical addition to *N*-sulfenyl imine 1



In a flame dried vial equipped with a stirring bar and a septum were placed **1** (0.1 mmol), TBADT (0.002 mmol 2 mol%) and, if solid, the radical precursor (1 mmol, 10 equiv.). The vial was evacuated and back-filled with Argon three times and dry CH_3CN was then added. *In the case of a liquid radical precursor (1.0 equiv.), it was introduced at the same stage as* CH_3CN. Argon was bubbled through the reaction tube for 1 minute using a long needle. Thereafter, the reaction mixture was placed ca. 5 cm from the light source (see Figure S1) and stirred with a fan cooling or air flow. The completion of the reaction was monitored by TLC. Upon completion of the reaction, the crude mixture is concentrated by rotary evaporator and dried under vacuo. Dr was determined by ^1H NMR from the crude mixture. The crude product is concentrated and purified by column chromatography (silica gel PET / EtOAc).

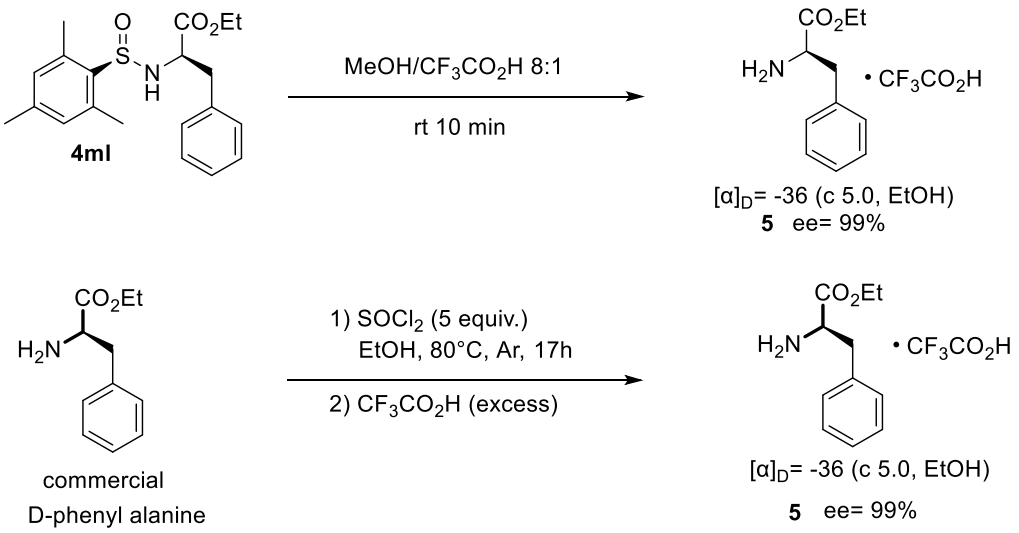
Procedure for 1.0 mmol scale synthesis of compound 4mb



In a flame dried vial tube equipped with a stirring bar and a septum were placed **1** (1.0 mmol), TBADT (0.02 mmol 2 mol%) and 1,3,5 trioxane **2b** (10 mmol, 10 equiv.). The vial was evacuated and back-filled with Argon three times and dry CH_3CN was then added. Argon was bubbled through the reaction tube for 1 minute using a long needle. Thereafter, the reaction mixture was placed ca. 5 cm from the light source (see Figure S2) and stirred with a fan cooling or air flow. The completion of the reaction was monitored by TLC. Upon completion of the reaction, the crude mixture is concentrated by rotary evaporator and dried under vacuo. Dr was determined by ^1H NMR from the crude mixture. The crude product is concentrated and purified by column chromatography (silica gel PET / EtOAc). The desired product was obtained as a colorless oil (303.5 mg, 85% yield).

Figure S 2 The reaction setup for 1.0 mmol scale reaction

N-sulfinyl amide deprotection and determination of the absolute configuration of product 4ml



The determination of absolute configuration of the α-stereocenter in the model product **4ml** was accomplished by comparing the optical rotation and enantiomeric excess with a commercially available α-amino acid ethyl ester and the deprotected model product 5.

The (R) absolute configuration of the α-stereocenter in the model product **4ml** was confirmed by comparing specific optical rotation of the corresponding deprotected α-amino acid ethyl ester **5** obtained from **4ml** ($[\alpha]_D = -36$ (c 5.0, EtOH)) and specific optical rotation of a reference compound **4** synthesized from commercial D-α-phenyl alanine ($[\alpha]_D = -36$ (c 5.0, EtOH)).

To further support the (R) absolute configuration, the enantiomeric excess of both compounds was determined by HPLC on a chiral column with an IA phase. Both, the α-amino acid ethyl ester 5 obtained from **4ml,** and the compound **5** synthesized from commercial D-α-phenylalanine exhibited a single enantiomer with a similar retention time.The given (R) absolute configuration of the α-stereocenter in **4ml** is in agreement with previous reports on radical addition reactions to chiral (R)-sulfinyl imines.

Synthesis of 5 from 4ml:

N-sulfinyl amide **4ml** (18 mg, 0.05 mmol) was placed in a flame dried vial tube. The vial was evacuated and back-filled with Argon three times, followed by addition of 1 mL MeOH and, once dissolved, a solution of CF_3CO_2H (0.25 mL) in 1 mL of MeOH was added. The reaction mixture was stirred at room temperature under Argon for 10 min and the solvent was removed on rotary evaporator. The solid residue was purified by column chromatography (silica gel DCM/MeOH) and dried in vacuo. Product **5** was obtained as a white solid (15.0 mg, 99% yield).

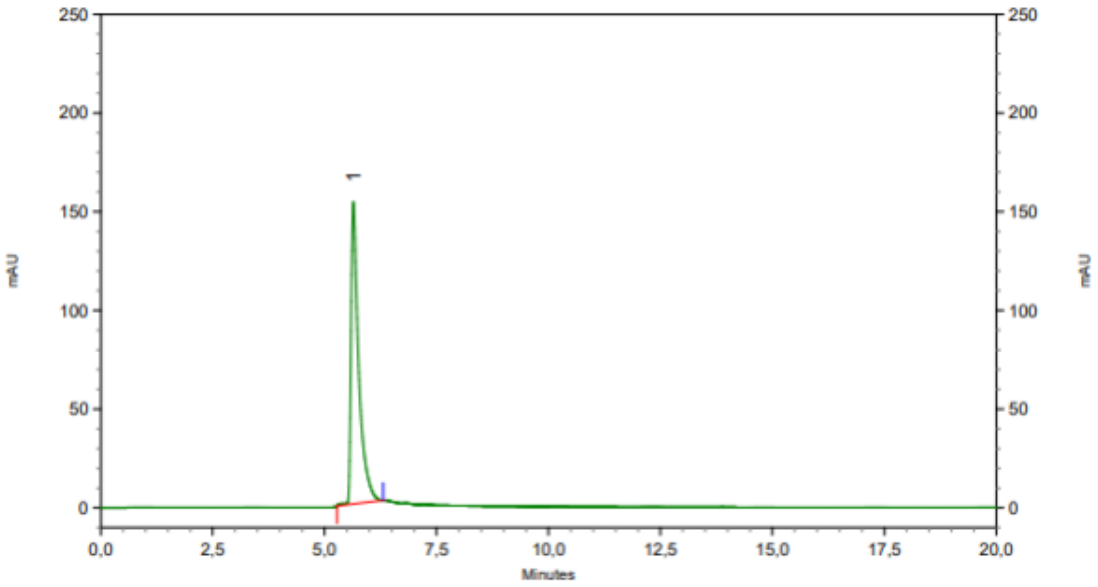
Synthesis of 5 from D-α-phenyl alanine:

In a 25mL round bottom flask equipped with a reflux condenser was placed D-α-phenyl alanine (165 mg, 1.0 mmol). The vial was evacuated and back-filled with Argon three times, followed by the subsequent addition of 4 mL of absolute ethanol and Thionyl chloride (363 µL, 5.0 mmol). The mixture was heated at 80°C overnight. Once the reaction is complete, the mixture was concentrated on rotary evaporator and the obtained residue was suspended in n-hexane (3

mL) and extracted with water (3 x 3 mL). To the combined water extracts CF_3CO_2H (2 mL) was carefully added, and the resulting solution was extracted with ethyl acetate (3 x 8 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The crude was purified by column chromatography (silica gel DCM/MeOH) and dried in vacuo. Product **5** was obtained as a white solid (123 mg, 40% yield). The ^{1}H NMR and ^{13}C NMR were identical for product **5** obtained from **4ml** and in agreement with previously reported data:[9]

Analytical data for compound **5:**

HPLC analysis (Daicel Chiralpak IA, Heptane/iPrOH, 90/10, flow rate 1.0 mL/min, 214 nm): t_R = 5.65 min,



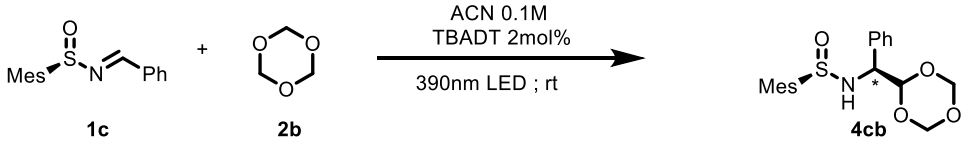
DAD-CH3 214 nm

Results

Pk #	Retention Time	Area	Area %
1	5,65	7258891	100,00

*Figure S 3 IA chiral column Hept/iPrOH 90/10 214nm **5** from **4ml***

Light ON-OFF experiment



In a flame dried vial tube equipped with a stirring bar and a septum were placed **1c** (0.1 mmol 1 equiv.), TBADT (0.002mmol 2 mol%) trioxane **2b** (1 mmol 10 equiv.). The vial was evacuated and back-filled with Argon three times and dry CH_3CN was then added. Argon was bubbled through the reaction tube for 1 minute using a long needle. Thereafter, the reaction mixture was placed ca. 5 cm from the light source (see Figure S1) and stirred with a fan cooling or air flow. The reaction progress was followed by ^1H NMR taking little aliquots of the crude mixture under Argon atmosphere. From the experiment, it is possible to assume that a chain reaction mechanism is not involved. (See figure S4)

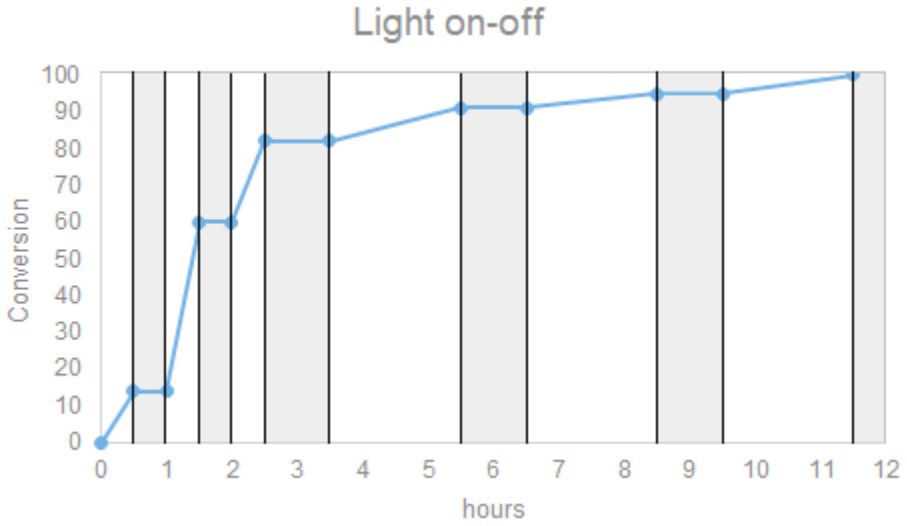
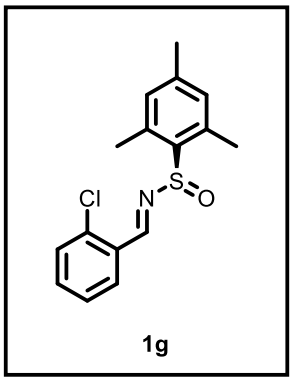


Figure S 4 Light ON-OFF experiment.

Analytical data of new sulfinamides

Compound 1g



1g

(R,E)-*N*-(2-chlorobenzylidene)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure B on 0.3 mmol scale. The product is a white solid (47 mg, 51% yield).

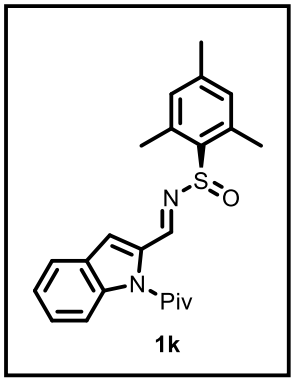
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72 (d, *J* = 0.7 Hz, 1H), 8.42 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.93 – 7.75 (m, 2H), 7.69 (dddd, *J* = 8.5, 7.7, 2.2, 1.2 Hz, 1H), 2.91 (s, 6H), 2.68 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 141.9, 138.6, 136.6, 135.3, 133.2, 131.5, 131.0, 130.3, 129.6, 127.2, 21.2, 19.0.

HRMS (ESI+, m/z): Calculated for $C_{18}H_{19}N_2OSClNa^+$: (M + MeCN + Na): 369.0804; found 369.0818.

$[\alpha]^{D}_{20}$ = -308.2 (c = 0.4 in CH_2Cl_2)

Compound 1k



1k

(R,E)-2,4,6-trimethyl-N-((1-pivaloyl-1H-indol-2-yl)methylene)benzenesulfinamide

Synthesized according to the general procedure B on 0.3 mmol scale.

The product is a yellow solid (101 mg, 85% yield).

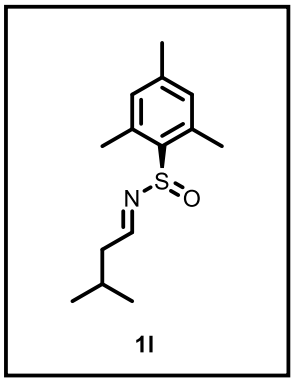
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.08 – 8.98 (m, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.32 – 8.19 (m, 2H), 7.41 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.31 (td, *J* = 7.6, 1.1 Hz, 1H), 6.87 (s, 2H), 2.54 (s, 6H), 2.30 (s, 3H), 1.55 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 177.1, 155.1, 141.7, 138.6, 138.1, 136.0, 132.4, 131.0, 126.7, 126.0, 124.9, 122.2, 118.4, 117.3, 41.7, 28.8, 21.2, 19.1.

HRMS (ESI+, m/z): calculated for $C_{23}H_{27}N_2O_2S$ $[M+H]^+$: 395.1793, found 395.1788.

$[\alpha]^{D}_{20}$ = +121.0 (c = 0.7, CH_2Cl_2)

Compound 1l



(R,E)-2,4,6-trimethyl-N-(3-methylbutylidene)benzenesulfinamide

Synthesized according to the general procedure B on 0.3 mmol scale. The product is a colorless oil (52 mg, 68% yield).

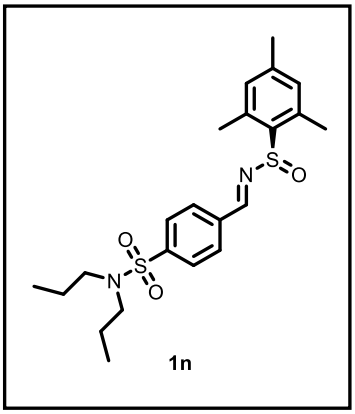
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (t, *J* = 5.4 Hz, 1H), 6.84 (s, 2H), 2.46 (s. el, 5H), 2.41 (dd, *J* = 6.9, 5.4 Hz, 2H), 2.26 (s, 3H), 2.04 (dqt, *J* = 13.4, 6.7 Hz, 1H), 0.99 (2d, *J* = 6.6 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 141.7, 138.3, 135.3, 131.0, 44.8, 26.5, 22.8, 22.6, 21.2, 18.9.

HRMS (ESI+, m/z): calculated for $C_{16}H_{24}N_2OSNa^+$ (M + MeCN + Na): 315.1507; found: 315.1511

$[\alpha]^{D}_{20}$ = -248.1 (c = 0.7, CH_2Cl_2)

Compound 1n



(R,E)-4-(((mesitylsulfinyl)imino)methyl)-N,N-dipropylbenzenesulfonamide

Synthesized according to the general procedure B on 0.3 mmol scale. The product is a white solid (115 mg, 88% yield).

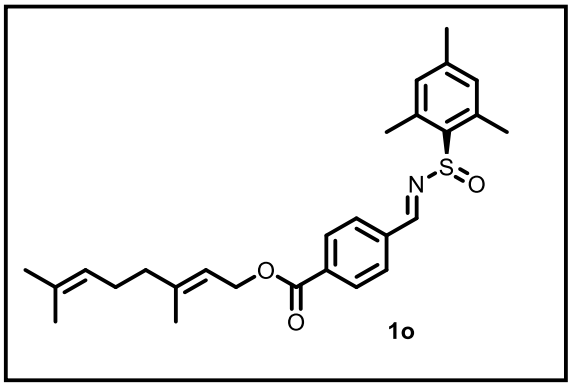
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H), 6.87 (s, 2H), 3.15 – 3.05 (m, 4H), 2.49 (s, 6H), 2.29 (s, 3H), 1.62 – 1.47 (m, 4H), 0.87 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 143.7, 142.1, 138.6, 137.0, 134.9, 131.1, 130.0, 127.7, 50.1, 22.1, 21.2, 19.0, 11.3

$[\alpha]^{D}_{20}$ = -40.4 (c = 0.9, CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{22}H_{31}N_2O_3S_2$ $[M+H]^+$: 435.1776; found: 435.1789.

Compound 1o



(E)-3,7-dimethylocta-2,6-dien-1-yl 4-((E)-(((R)-mesitylsulfinyl)imino)methyl)benzoate

Synthesized according to the general procedure B on 0.3 mmol scale. The product is a white solid (58 mg, 25% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.12 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 8.1 Hz, 2H), 6.87 (s, 2H), 5.53 – 5.52 – 5.39 (m, 1H), 5.16 – 5.03 (m, 1H), 4.86 (d, *J* = 7.3 Hz, 2H), 2.49 (s, 6H), 2.28 (s, 3H), 2.22 – 2.01 (m, 4H), 1.77 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H).

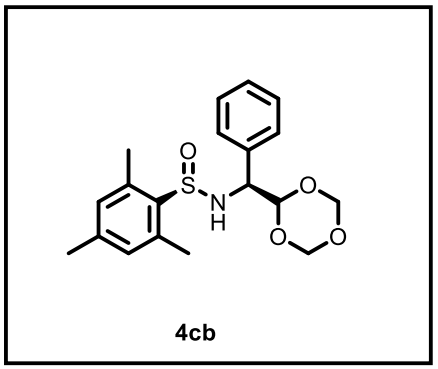
^{13}C NMR (75 MHz, CDCl3): δ 165.9, 160.8, 142.9, 142.0, 138.6, 137.4, 135.1, 133.9, 132.0, 131.0, 130.2, 129.4, 123.8, 118.2, 62.4, 39.7, 26.4, 25.8, 21.2, 19.0, 17.8, 16.7.

$[\alpha]^{D}_{20}$ = -37.0 (c=2.15 $CHCl_3$)

HRMS (ESI+, m/z): calculated for $C_{27}H_{34}NO_3S$ $[M+H]^+$: 452.2259; found: 452.2251.

Analytical data of HAT adducts 4

Compound 4cb



(R)-2,4,6-trimethyl-N-((S)-phenyl(1,3,5-trioxan-2-yl)methyl)benzenesulfinamide

Synthesized according to the general procedure. The product is a colorless oil (25.30 mg, 70% yield).

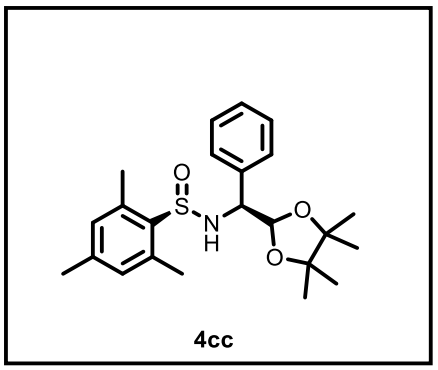
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H), 6.77 (s, 2H), 5.27 (d, *J* = 4.9 Hz, 1H), 5.23 -5.15 (2d, *J* = 12.3 Hz, 2H), 5.07 (2d, *J* = 7.6 Hz, 2H), 4.96 (d, *J* = 5.1 Hz, 1H), 4.54 (t, *J* = 5.0 Hz, 1H), 2.50 (s, 6H), 2.24 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 137.7, 137.0, 136.4, 130.9, 128.5, 128.37, 128.3, 102.1, 93.3, 93.2, 60.8, 21.0, 19.4.

$[\alpha]^{D}_{20}$ = -0.79 (c=2.1 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{19}H_{24}NO_4S$ $[M+H]^+$: 362.1426, found 362.1438.

Compound 4cc



(R)-2,4,6-trimethyl-N-((S)-phenyl(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)methyl)benzenesulfinamide

Synthesized according to the general procedure. The product is a colorless oil (40.0 mg, 99% yield). Rotamers were observed.

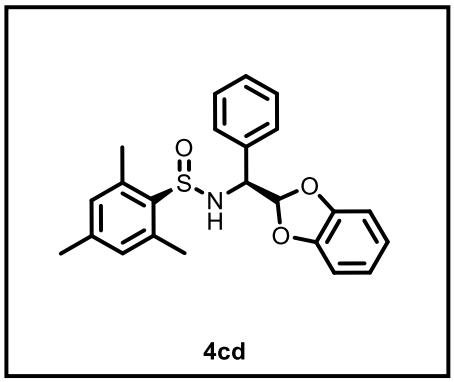
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 5H), 6.78 (s, 2H), 5.24 (d, *J* = 4.9 Hz, 1H), 4.82 (d, *J* = 5.7 Hz, 1H), 4.35 (t, *J* = 5.3 Hz, 1H), 2.53 (s, 6H), 2.24 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.00 (s, 3H). 0.98 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5, 138.4, 138.1, 136.7, 130.7, 128.3, 127.9, 101.7, 82.8, 82.6, 62.6, 24.1, 23.8, 22.5, 22.3, 21.1, 19.4. One aromatic C-H carbon is missing due to overlapping of signals.

$[\alpha]^{D}_{20}$ = -36.1 (c=3.3 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{23}H_{32}NO_3S$ $[M+H]^+$: 402.2103, found 402.2108.

Compound 4cd



(*R*)-N-((S)-benzo[*d*][1,3]dioxol-2-yl(phenyl)methyl)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure. The product is a colorless oil (39.0 mg, 99% yield).

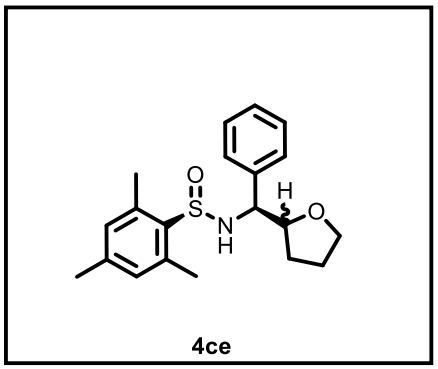
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.30 (m, 5H), 6.83 – 6.69 (m, 6H), 6.46 – 6.39 (m, 1H), 4.82 (m, 2H), 2.47 (s, 6H), 2.24 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 147.3, 141.0, 136.8, 136.2, 130.9, 128.9, 128.7, 128.2, 121.7, 121.7, 120.5, 115.3, 111.0, 108.6, 61.0, 21.1, 19.3.

$[\alpha]^{D}_{20}$ = -583.4 (c=3.6 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{23}H_{24}NO_3S$ $[M+H]^+$: 394.1477, found 394.1472.

Compound 4ce



(R)-2,4,6-trimethyl-N-((1S)-phenyl(tetrahydrofuran-2-yl)methyl)benzenesulfinamide

Synthesized according to the general procedure, with a dr of 1.6:1. The product is a colorless oil (34.0 mg, 99% yield).

Major Diastereoisomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 5H), 6.74 (s, 2H), 5.04 (d, *J* = 3.8 Hz, 1H), 4.24 – 4.11 (m, 2H), 3.80 (m, 2H), 2.50 (s, 6H), 2.22 (s, 3H), 1.89 – 1.72 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5, 139.5, 137.9, 136.9, 130.8, 128.5, 127.9, 82.5, 68.5, 62.2, 28.9, 25.8, 21.0, 19.5. One aromatic C-H carbon is missing due to overlapping of signals (127.9).

$[\alpha]^{D}_{20}$ = +8.3 (c=1.6 CH_2Cl_2)

Minor Diastereoisomer:

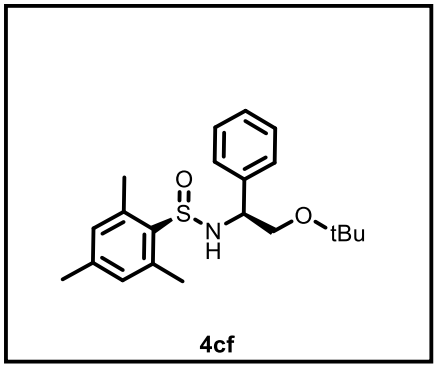
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 5H), 6.79 (s, 2H), 4.72 (d, *J* = 5.4 Hz, 1H), 4.43 (t, *J* = 5.2 Hz, 1H), 4.26 (td, *J* = 7.0, 5.1 Hz, 1H), 3.73 (ddd, *J* = 8.5, 5.1, 2.2 Hz, 2H), 2.50 (s, 6H), 2.25 (s, 3H), 1.99 – 1.57 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 139.4, 136.8, 130f.9, 128.5, 128.0, 127.9, 81.9, 68.8, 61.7, 27.9, 25.8, 21.1, 19.4. One aromatic quaternary carbon is missing due to overlapping of signals (136.8)

$[\alpha]^{D}_{20}$ = -93.0 (c=0.5 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{20}H_{26}NO_2S$ $[M+H]^+$: 344.1684, found 344.1688.

Compound 4cf



4cf

(R)-N-((S)-2-(tert-butoxy)-1-phenylethyl)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure. The product is a colorless oil (36.0 mg, 99% yield).

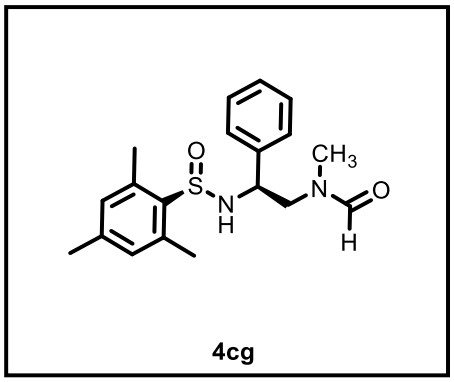
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 5H), 6.78 (s, 2H), 4.96 (d, *J* = 3.1 Hz, 1H), 4.36 (td, *J* = 6.3, 3.2 Hz, 1H), 3.57 (d, *J* = 6.3 Hz, 2H), 2.51 (s, 6H), 2.24 (s, 3H), 1.15 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 139.3, 137.9, 137.1, 130.8, 128.5, 127.9, 127.7, 73.7, 66.2, 58.6, 27.6, 21.1, 19.4.

$[\alpha]^{D}_{20}$ = -21.5 (c=1.1 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{21}H_{30}NO_2S$ $[M+H]^+$: 360.1997, found 360.1993.

Compound 4cg



4cg

N-((S)-2-(((R)-mesitylsulfinyl)amino)-2-phenylethyl)-N-methylformamide

Synthesized according to the general procedure. The product was isolated as mixture of rotamers. It is a colorless oil (33.4 mg, 97% yield). Strong rotamer signals were observed in the NMRs analysis.

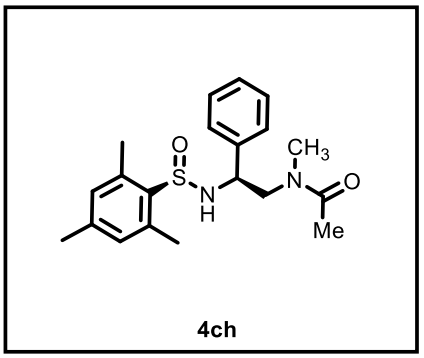
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 0.5H), 7.80 (s, 0.5H), 7.40-7.25 (m, 3H), 7.21 (s, 2H), 6.82 (s, 1H), 6.68 (s, 1H), 5.11 (d, *J* = 5.2 Hz, 0.5H), 4.79 (dt, *J* = 9.1, 5.3 Hz, 0.5H), 4.65 (td, *J* = 6.8, 4.5 Hz, 0.5H), 4.57 (d, *J* = 4.5 Hz, 0.5H), 4.00 (dd, *J* = 14.0, 9.1 Hz, 0.5H), 3.77 (dd, *J* = 14.2, 7.2 Hz, 0.5H), 3.50 (dd, *J* = 14.2, 6.4 Hz, 0.5H), 3.30 (dd, *J* = 14.0, 5.3 Hz, 0.5H), 2.91 (s, 1.5H), 2.88 (s, 1.5H), 2.49 (2s, 6H), 2.26 (s, 1.5H), 2.18 (s, 1.5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 163.3, 141.3, 140.5, 139.8, 139.0, 136.8, 136.8, 131.1, 130.9, 129.3, 128.8, 128.6, 127.9, 127.1, 126.7, 56.1, 55.6, 55.3, 50.8, 35.5, 30.7, 21.1, 21.0, 19.5, 19.4.

$[\alpha]^{D}_{20}$ = -121.6 (c=2.1 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{19}H_{25}N_2O_2S$ $[M+H]^+$: 345.1636, found 345.1640.

Compound 4ch



4ch

N-((S)-2-(((R)-mesitylsulfinyl)amino)-2-phenylethyl)-N-methylacetamide

Synthesized according to the general procedure. The product was isolated as mixture of rotamers. It is a colorless oil (35.1 mg, 98% yield). Strong rotamer signals were observed in the NMRs analysis.

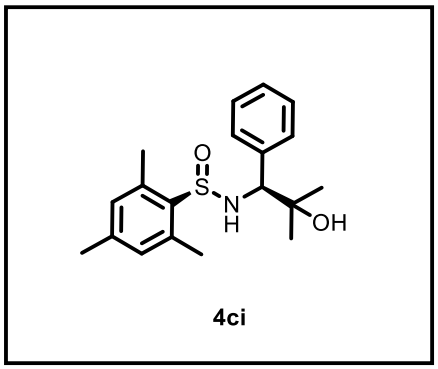
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 5.2, 3.1 Hz, 1.2H), 7.19 – 7.11 (m, 3.9H), 6.83 (s, 0.4H), 6.64 (s, 1.5H), 5.49 (d, *J* = 5.0 Hz, 0.7H), 4.75 (dt, *J* = 9.7, 4.7 Hz, 0.8H), 4.64 (td, *J* = 6.9, 3.8 Hz, 0.2H), 4.54 (d, *J* = 3.9 Hz, 0.2H), 4.16 (dd, *J* = 14.0, 9.8 Hz, 0.9H), 3.94 (dd, *J* = 14.5, 6.3 Hz, 0.2H), 3.48 (dd, *J* = 14.5, 7.5 Hz, 0.2H), 3.10 (dd, *J* = 14.0, 4.6 Hz, 0.9H), 2.98 (s, 2.3H), 2.84 (s, 0.6H), 2.51 (s, 1.4H), 2.49 (s, 4.5H), 2.26 (s, 0.7H), 2.16 (s, 2.3H), 2.04 (s, 2.5H), 1.84 (s, 0.6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 141.3, 140.4, 140.3, 136.9, 131.3, 130.8, 129.3, 128.8, 128.4, 127.5, 127.1, 126.6, 56.7, 56.4, 54.2, 37.2, 34.4, 21.9, 21.2, 21.1, 20.9, 19.6, 19.4. Few carbon are missing due to overlapping of signals.

$[\alpha]^D_{20}$ = -70.6 (c=2.0 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{20}H_{27}N_2O_2S$ $[M+H]^+$: 359.1793, found 359.1799.

Compound 4ci



4ci

(R)-N-((S)-2-hydroxy-2-methyl-1-phenylpropyl)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure. The product was isolated as a colorless oil (16.6 mg, 50% yield).

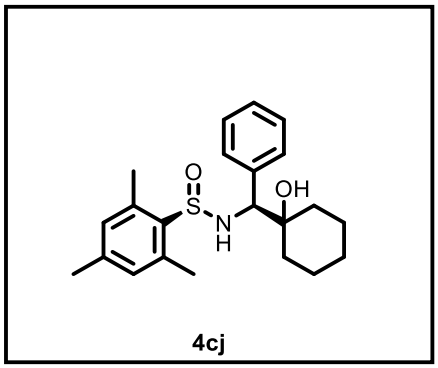
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 – 7.19 (m, 5H), 6.76 (s, 2H), 5.03 (d, *J* = 7.1 Hz, 1H), 4.18 (d, *J* = 7.1 Hz, 1H), 2.47 (s, 6H), 2.24 (s, 3H), 1.27 (s, 3H), 1.09 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 140.0, 136.9, 131.0, 128.4, 128.3, 128.0, 127.8, 72.9, 67.9, 28.0, 25.8, 21.1, 19.5.

$[\alpha]^D_{20}$ = -5.4 (c=0.7 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{19}H_{26}NO_2S$ $[M+H]^+$: 332.1684, found 332.1681.

Compound 4cj



4cj

(R)-N-((S)-(1-hydroxycyclohexyl)(phenyl)methyl)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure. The product was isolated as a colorless oil (13.0 mg, 35% yield).

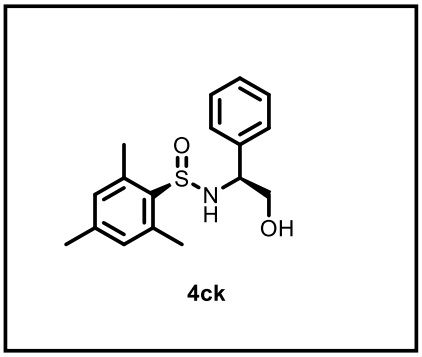
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 – 7.20 (m, 5H), 6.76 (s, 2H), 5.02 (d, *J* = 7.7 Hz, 1H), 4.19 (d, *J* = 7.7 Hz, 1H), 2.47 (s, 6H), 2.24 (s, 3H), 1.81 (d, *J* = 13.5 Hz, 2H), 1.62 – 1.50 (m, 3H), 1.48 – 1.40 (m, 3H), 1.27 – 1.20 (m, 2H).

^{13}C NMR (75 MHz, CDl_3): δ 140.3, 139.6, 137.2, 136.7, 130.9, 128.3, 128.2, 127.7, 73.5, 67.5, 35.6, 34.4, 25.7, 21.97, 21.7, 21.1, 19.6.

$[\alpha]^{D}_{20}$ = -123.2 (c=0.6 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{22}H_{30}NO_2S$ $[M+H]^+$: 372.1997, found 372.1993.

Compound 4ck



4ck

(R)-N-((S)-2-hydroxy-1-phenylethyl)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure. The product is a pale yellow oil (28.0 mg, 92% yield).

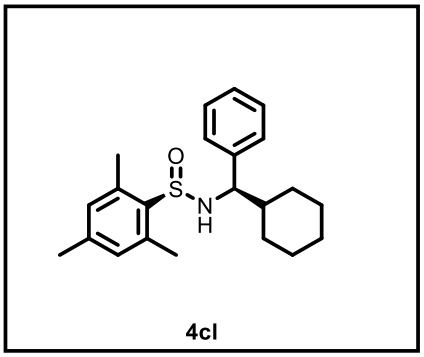
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.13 (m, 5H), 6.80 (s, 2H), 4.98 (d, *J* = 6.4 Hz, 1H), 4.53 – 4.41 (m, 1H), 3.97 – 3.77 (m, 2H), 2.52 (s, 6H), 2.25 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 139.1, 137.3, 131.2, 128.7, 127.9, 127.5, 127.0, 66.0, 60.8, 21.0, 19.8.

$[\alpha]^{D}_{20}$ = -48.0 (c=1.4 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{17}H_{22}NO_2S$ $[M+H]^+$: 304.1371, found 304.1378.

Compound 4cl



4cl

(R)-N-((R)-cyclohexyl(phenyl)methyl)-2,4,6-trimethylbenzenesulfinamide [10]

Synthesized according to the general procedure. The product was isolated as a colorless oil (17.0 mg, 48% yield). The NMR spectra agrees with the previously reported data.[10]

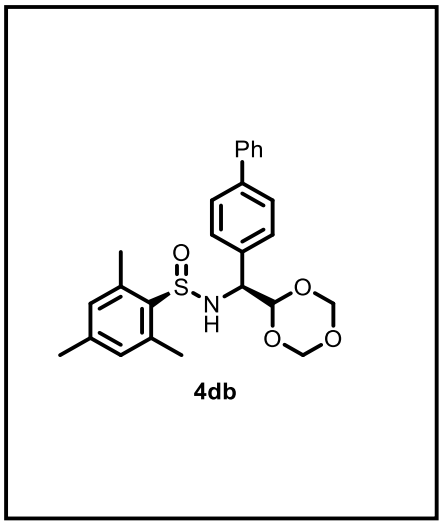
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.12 (m, 5H), 6.81 (s, 2H), 4.45 (d, *J* = 5.7 Hz, 1H), 4.25 – 4.12 (m, 1H), 2.51 (s, 6H), 2.26 (s, 3H), 2.00 – 1.88 (m, 1H), 1.85 – 1.47 (m, 6H), 1.29 – 1.12 (m, 2H), 0.99 – 0.86 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 140.6, 138.5, 136.6, 130.9, 128.4, 127.5, 127.5, 64.7, 43.1, 30.1, 29.3, 26.5, 26.3, 26.1, 21.1, 19.5.

$[\alpha]^{D}_{20}$ = -43.7 (c=1.4 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{22}H_{30}NOS$ $[M+H]^+$: 356.2048, found 356.2055.

Compound 4db



4db

(R)-N-((S)-[1,1'-biphenyl]-4-yl(1,3,5-trioxan-2-yl)methyl)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure. The product was isolated as a colorless oil (17.9 mg, 41% yield).

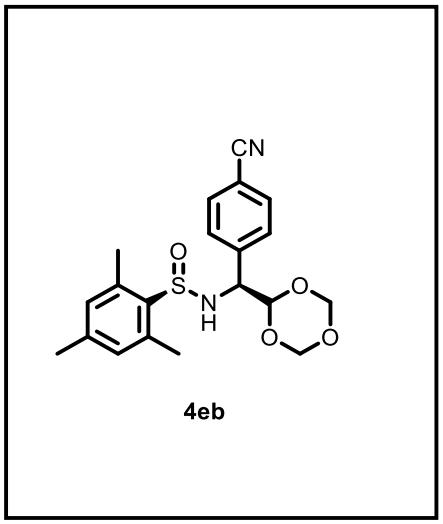
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.51 (m, 4H), 7.48 – 7.40 (m, 4H), 7.39 – 7.31 (m, 1H), 6.78 (s, 2H), 5.32 (d, *J* = 4.9 Hz, 1H), 5.29 – 5.19 (m, 2H), 5.15 – 5.08 (m, 2H), 5.00 (d, *J* = 5.0 Hz, 1H), 4.60 (t, *J* = 4.9 Hz, 1H), 2.52 (s, 6H), 2.23 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 140.9, 140.8, 137.6, 137.0, 135.4, 130.9, 128.9, 128.8, 127.5, 127.2, 102.1, 93.3, 93.3, 60.5, 21.1, 19.5. One aromatic CH carbon is missing due to overlapping of signals (127.5).

$[\alpha]^{D}_{20}$ = -13.9 (c=1.3 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{25}H_{28}NO_4S$ $[M+H]^+$: 438.1739, found: 438.1745.

Compound 4eb



4eb

(R)-N-((S)-(4-cyanophenyl)(1,3,5-trioxan-2-yl)methyl)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure. The product was isolated as a colorless oil (34.7 mg, 90% yield).

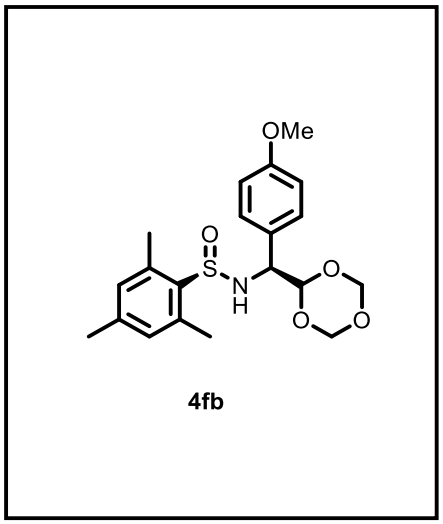
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 6.72 (s, 2H), 5.29 – 5.13 (m, 3H), 5.10 – 5.00 (m, 3H), 4.65 (dd, *J* = 5.6, 4.0 Hz, 1H), 2.49 (s, 6H), 2.22 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 141.2, 137.1, 136.5, 131.9, 131.0, 129.1, 118.7, 111.8, 101.4, 93.2, 93.2, 59.4, 21.0, 19.5.

$[\alpha]^{D}_{20}$ = -9.6 (c=2.0 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{20}H_{23}N_2O_4S$ $[M+H]^+$: 387.1378, found: 387.1372.

Compound 4fb



4fb

(R)-N-((S)-(4-methoxyphenyl)(1,3,5-trioxan-2-yl)methyl)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure. The product was isolated as a colorless oil (21.5 mg, 55% yield).

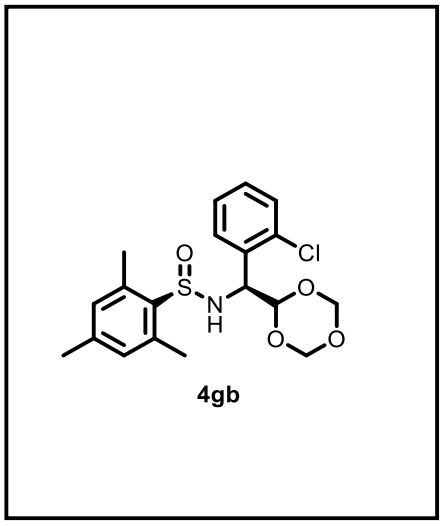
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.79 (s, 2H), 5.26 (d, *J* = 5.3 Hz, 1H), 5.21 (dd, *J* = 15.4, 6.4 Hz, 2H), 5.08 (dd, *J* = 13.3, 6.2 Hz, 2H), 4.90 (d, *J* = 4.7 Hz, 1H), 4.47 (t, *J* = 4.9 Hz, 1H), 3.79 (s, 3H), 2.49 (s, 6H), 2.25 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 140.8, 137.8, 137.0, 130.9, 129.7, 128.2, 114.0, 102.2, 93.3, 93.2, 60.5, 55.3, 21.1, 19.4.

$[\alpha]^{D}_{20}$ = -49.3 (c=2.1 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{20}H_{26}NO_5S$ [M+H]+: 392.1531, found: 392.1536.

Compound 4gb



4gb

(R)-N-((S)-(2-chlorophenyl)(1,3,5-trioxan-2-yl)methyl)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure. The product was isolated as a yellow oil (27.0 mg, 66% yield).

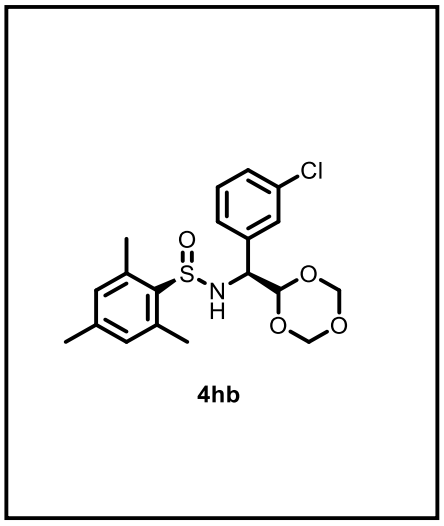
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 1H), 7.32 – 7.28 (m, 1H), 7.21 – 7.14 (m, 2H), 6.73 (s, 2H), 5.31 (d, *J* = 3.8 Hz, 1H), 5.24 – 5.07 (m, 5H), 5.02 (d, *J* = 6.2 Hz, 1H), 2.53 (s, 6H), 2.21 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 137.3, 137.1, 134.3, 133.3, 130.9, 130.3, 129.5, 129.2, 126.7, 100.6, 93.3, 93.2, 57.3, 21.0, 19.5.

$[\alpha]^{D}_{20}$ = +18.5 (c=2.7 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{19}H_{22}NO_4SClNa$ $[M+Na]^+$: 418.0856; found: 418.0845.

Compound 4hb



4hb

(R)-N-((S)-(3-chlorophenyl)(1,3,5-trioxan-2-yl)methyl)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure. The product was isolated as a yellow oil (21.4 mg, 52% yield).

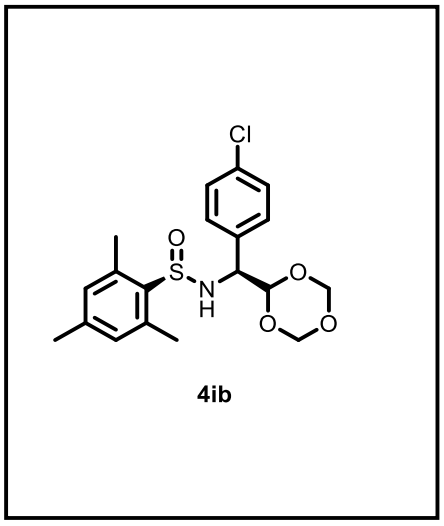
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 4H), 6.73 (s, 2H), 5.23 – 5.17 (m, 3H), 5.06 (dd, *J* = 6.4, 2.0 Hz, 2H), 4.98 (d, *J* = 5.0 Hz, 1H), 4.55 (t, *J* = 4.7 Hz, 1H), 2.50 (s, 6H), 2.22 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 138.7, 137.2, 134.2, 131.8, 131.0, 129.5, 128.4, 128.2, 126.5, 101.8, 93.3, 93.2, 59.5, 21.0, 19.5.

$[\alpha]^{D}_{20}$ = +195.5 (c=1.5 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{19}H_{22}NO_4SClNa$ $[M+Na]^+$: 418.0856; found: 418.0855.

Compound 4ib



(R)-N-((S)-(4-chlorophenyl)(1,3,5-trioxan-2-yl)methyl)-2,4,6-trimethylbenzenesulfinamide

Synthesized according to the general procedure. The product was isolated as a yellow oil (21.4 mg, 52% yield).

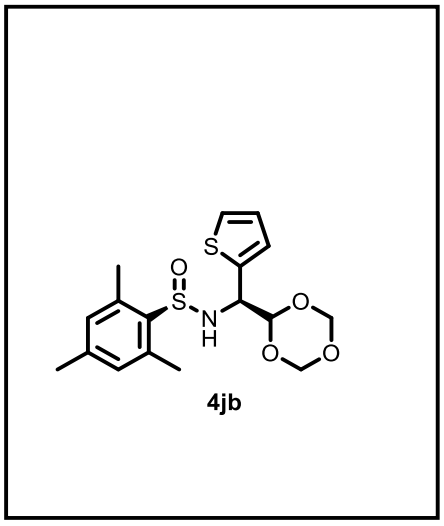
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (s, 4H), 6.76 (s, 2H), 5.25 – 5.16 (m, 3H), 5.07 (dd, *J* = 6.4, 3.2 Hz, 2H), 4.95 (d, *J* = 5.1 Hz, 1H), 4.54 (t, *J* = 4.9 Hz, 1H), 2.49 (s, 6H), 2.24 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 137.1, 135.1, 135.0, 131.0, 129.8, 128.6, 101.9, 93.3, 93.3, 59.9, 21.1, 19.5. One carbon in missing due to overlapping of signals (137.1).

$[\alpha]^{D}_{20}$ = +24.0 (c=0.2 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{19}H_{22}NO_4SClNa$ $[M+Na]^+$: 418.0856; found: 418.0875.

Compound 4jb



(R)-2,4,6-trimethyl-N-((R)-thiophen-2-yl(1,3,5-trioxan-2-yl)methyl)benzenesulfinamide

Synthesized according to the general procedure. The product was isolated as a yellow oil (20.6 mg, 56% yield).

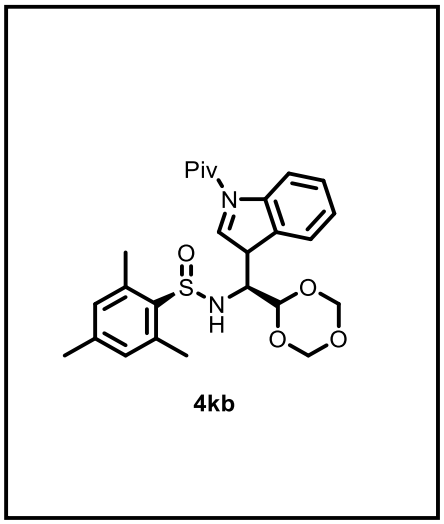
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 1H), 7.10 (dt, *J* = 3.5, 1.1 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.82 (s, 2H), 5.36 (d, *J* = 4.5 Hz, 1H), 5.27 – 5.22 (m, 2H), 5.14 (dd, *J* = 9.7, 6.2 Hz, 2H), 4.95 (d, *J* = 6.2 Hz, 1H), 4.82 (t, *J* = 5.4 Hz, 1H), 2.54 (s, 6H), 2.26 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 139.1, 137.5, 137.1, 131.0, 127.1, 126.8, 126.1, 101.9, 93.3, 93.2, 57.3, 21.1, 19.5.

$[\alpha]^{D}_{20}$ = -9.5 (c=1.3 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{17}H_{22}NO_4S_2$ $[M+H]^+$: 368.0990; found 368.0985.

Compound 4kb



(R)-2,4,6-trimethyl-N-((1S)-(1-pivaloyl-3H-1l4-indol-3-yl)(1,3,5-trioxan-2-yl)methyl)benzenesulfinamide

Synthesized according to the general procedure. The product was isolated as a yellow solid (33.9 mg, 70% yield).

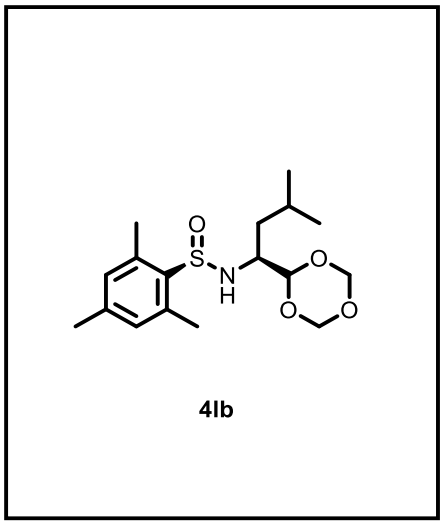
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 1.0 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.34 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 6.80 (s, 2H), 5.60 (d, *J* = 4.9 Hz, 1H), 5.27 (d, *J* = 6.4 Hz, 2H), 5.19 (dd, *J* = 6.4, 4.2 Hz, 2H), 4.97 (d, *J* = 5.0 Hz, 1H), 4.88 (td, *J* = 4.9, 1.0 Hz, 1H), 2.47 (s, 6H), 2.26 (s, 3H), 1.52 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 177.2, 141.0, 137.3, 137.2, 137.1, 131.0, 128.3, 125.8, 125.6, 123.6, 119.0, 117.5, 115.4, 101.6, 93.4, 53.9, 41.5, 28.8, 21.1, 19.5. One carbon in missing due to overlapping of signals (137.1).

$[\alpha]^{D}_{20}$ = -105.7 (c=1.1 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{26}H_{33}N_2O_5S$ $[M+H]^+$: 485.2110; found 485.2121.

Compound 4lb



(R)-2,4,6-trimethyl-N-((S)-3-methyl-1-(1,3,5-trioxan-2-yl)butyl)benzenesulfinamide

Synthesized according to the general procedure. The product was isolated as a colorless oil (14.7 mg, 43% yield).

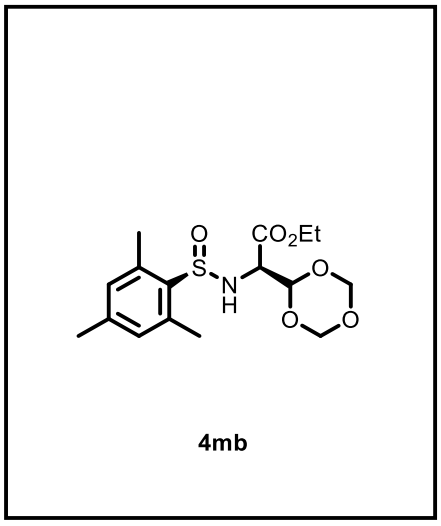
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 2H), 5.20 (t, *J* = 6.6 Hz, 2H), 5.13 (dd, *J* = 5.3, 3.0 Hz, 2H), 5.10 (d, *J* = 6.0 Hz, 1H), 4.49 (d, *J* = 6.8 Hz, 1H), 3.43 (ddt, *J* = 10.8, 6.9, 4.1 Hz, 1H), 2.57 (s, 6H), 2.27 (s, 3H), 1.80 – 1.70 (m, 1H), 1.61 (ddd, *J* = 14.6, 10.7, 4.1 Hz, 1H), 1.49 (ddd, *J* = 14.1, 10.1, 3.7 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 138.0, 136.9, 131.0, 102.8, 93.3, 93.3, 56.3, 37.3, 24.1, 23.8, 21.1, 19.6.

$[\alpha]^{D}_{20}$ = -181.7 (c=0.3 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{17}H_{27}NO_4SNa$ $[M+Na]^+$: 364.1559; found 364.1541.

Compound 4mb



4mb

Ethyl (R)-2-(((R)-mesitylsulfinyl)amino)-2-(1,3,5-trioxan-2-yl)acetate

Synthesized according to the general procedure. The product was isolated as a colorless oil (35.3 mg, 99% yield).

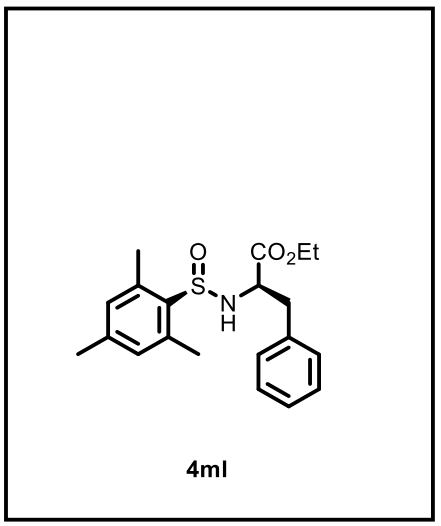
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 2H), 5.33 – 5.14 (m, 4H), 5.07 (dd, *J* = 10.2, 6.2 Hz, 2H), 4.39 – 4.11 (m, 3H), 2.60 (s, 6H), 2.28 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 141.1, 137.7, 137.1, 130.9, 100.2, 93.3, 62.4, 59.8, 21.2, 19.5, 14.2.

$[\alpha]^{D}_{20}$ = -44.7 (c=0.7 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{16}H_{24}NO_6S$ $[M+H]^+$: 358.1324, found: 358.1323.

Compound 4ml



4ml

Ethyl ((R)-mesitylsulfinyl)-D-phenylalaninate [11]

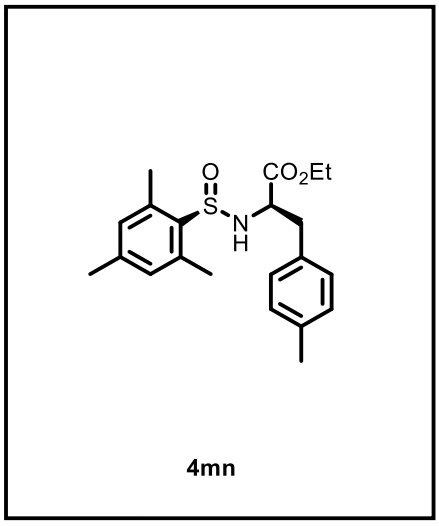
Synthesized according to the general procedure. The product was isolated as a colorless oil (18.0 mg, 50% yield). The NMR spectra agree with the previously reported data.[11]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.14 (m, 5H), 6.85 (s, 2H), 5.11 (d, *J* = 8.7 Hz, 1H), 4.34 – 4.16 (m, 3H), 3.18 (dd, *J* = 13.8, 5.2 Hz, 1H), 2.93 (dd, *J* = 13.8, 8.5 Hz, 1H), 2.45 (s, 6H), 2.30 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 141.0, 137.8, 136.9, 136.6, 130.9, 129.6, 128.5, 127.0, 61.9, 58.8, 40.6, 21.1, 19.2, 14.2.

HRMS (ESI+, m/z): calculated for $C_{20}H_{26}NO_3S$ $[M+H]^+$: 360.1633, found: 360.1639.

Compound 4mn



4mn

Ethyl (R)-2-(((R)-mesitylsulfinyl)amino)-3-(p-tolyl)propanoate

Synthesized according to the general procedure. The product was isolated as a colorless oil (29.9 mg, 80% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 – 6.99 (m, 4H), 6.82 (s, 2H), 5.05 (d, *J* = 8.6 Hz, 1H), 4.28 – 4.09 (m, 3H), 3.10 (dd, *J* = 13.8, 5.3 Hz, 1H), 2.87 (dd, *J* = 13.8, 8.2 Hz, 1H), 2.43 (s, 6H), 2.31 (s, 3H), 2.27 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H).

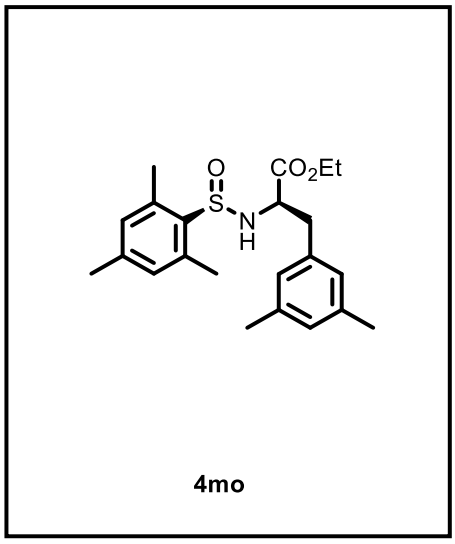
^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 140.9, 136.9, 136.5, 133.5, 130.9, 129.4, 129.2, 61.8, 58.8, 40.1, 21.1, 19.2, 14.2.

2CH_3 (21.1) and 2 quaternary C were overlapping.

$[\alpha]^{D}_{20}$ = -157.0 (c=0.1 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{21}H_{28}NO_3S$ $[M+H]^+$: 374.1790, found: 374.1796.

Compound 4mo



4mo

Ethyl (R)-3-(3,5-dimethylphenyl)-2-(((R)-mesitylsulfinyl)amino)propanoate

Synthesized according to the general procedure. The product was isolated as a colorless oil (18.0 mg, 85% yield).

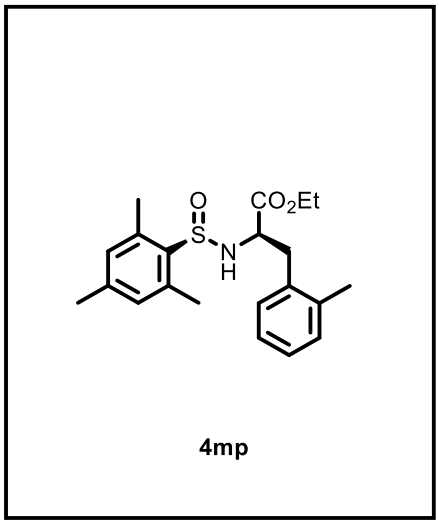
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 2H), 6.82 (s, 2H), 6.77 (d, *J* = 1.6 Hz, 2H), 5.06 (d, *J* = 8.6 Hz, 1H), 4.20 (tdd, *J* = 9.6, 4.5, 2.4 Hz, 3H), 3.06 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.80 (dd, *J* = 13.7, 8.6 Hz, 1H), 2.43 (s, 6H), 2.27 (s, 3H), 2.24 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 140.9, 138.0, 137.9, 136.9, 136.5, 130.8, 128.6, 127.4, 61.8, 58.9, 40.4, 21.3, 21.1, 19.2, 14.2.

$[\alpha]^{D}_{20}$ = -54.0 (c=1.4 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{22}H_{30}NO_3S$ $[M+H]^+$: 388.1946, found: 388.1944.

Compound 4mp



4mp

Ethyl (R)-2-(((R)-mesitylsulfinyl)amino)-3-(o-tolyl)propanoate

Synthesized according to the general procedure. The product was isolated as a colorless oil (28.0 mg, 75% yield).

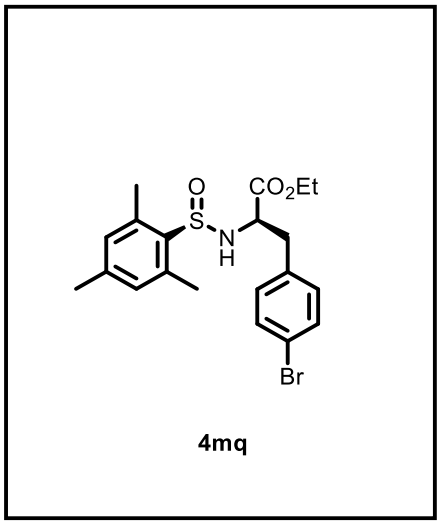
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.01 (m, 4H), 6.82 (s, 2H), 5.11 (d, *J* = 9.0 Hz, 1H), 4.26 – 4.10 (m, 3H), 3.12 (dd, *J* = 13.9, 5.4 Hz, 1H), 2.87 (dd, *J* = 13.9, 9.1 Hz, 1H), 2.40 (s, 6H), 2.30 (s, 3H), 2.27 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 141.0, 137.9, 136.9, 136.6, 135.1, 130.8, 130.5, 130.4, 127.1, 126.0, 61.9, 58.2, 38.1, 21.1, 19.6, 19.2, 14.1.

$[\alpha]^{D}_{20}$ = -22.8 (c=1.2 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{21}H_{28}NO_3S$ $[M+H]^+$: 374.1790, found: 374.1794.

Compound 4mq



4mq

Ethyl (R)-3-(4-bromophenyl)-2-(((R)-mesitylsulfinyl)amino)propanoate

Synthesized according to the general procedure. The product was isolated as a colorless oil (17.9 mg, 41% yield).

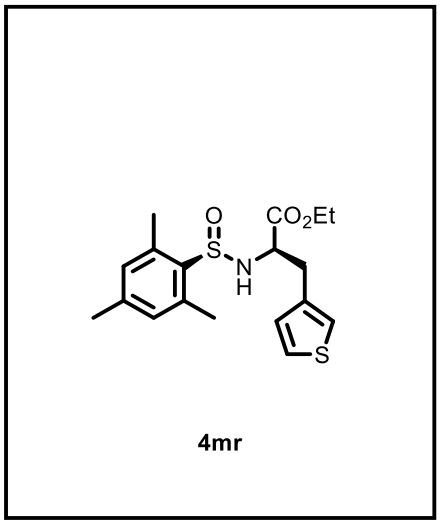
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H), 7.09 – 6.98 (m, 2H), 6.83 (s, 2H), 5.07 (d, *J* = 8.4 Hz, 1H), 4.24 – 4.15 (m, 3H), 3.10 (dd, *J* = 13.8, 5.1 Hz, 1H), 2.85 (dd, *J* = 13.8, 8.4 Hz, 1H), 2.42 (s, 6H), 2.28 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 141.1, 137.7, 136.9, 135.7, 131.6, 131.4, 130.9, 121.0, 62.1, 58.5, 39.8, 21.2, 19.2, 14.20.

$[\alpha]^{D}_{20}$ = -11.8 (c=1.0 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{20}H_{25}BrNO_3S$ $[M+H]^+$: 438.0738, found: 438.0732.

Compound 4mr



Ethyl (R)-2-(((R)-mesitylsulfinyl)amino)-3-(thiophen-3-yl)propanoate

Synthesized according to the general procedure. The product was isolated as a colorless oil (19.0 mg, 52% yield).

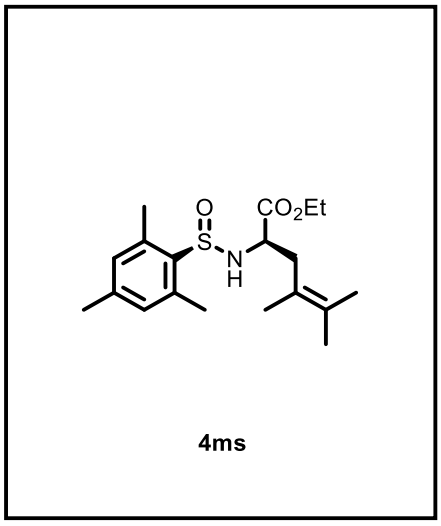
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.01 – 6.98 (m, 1H), 6.92 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.84 (s, 2H), 5.10 (d, *J* = 8.2 Hz, 1H), 4.28 – 4.14 (m, 3H), 3.16 (dd, *J* = 14.5, 5.6 Hz, 1H), 3.00 (dd, *J* = 14.3, 7.8 Hz, 1H), 2.48 (s, 6H), 2.27 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 141.0, 137.5, 136.9, 136.7, 130.9, 128.5, 125.7, 122.9, 61.9, 58.0, 34.8, 21.1, 19.3, 14.1.

$[\alpha]^{D}_{20}$ = -49.3 (c=1.2 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{18}H_{24}NO_3S_2$ $[M+H]^+$: 366.1197, found: 366.1193.

Compound 4ms



Ethyl (R)-2-(((R)-mesitylsulfinyl)amino)-4,5-dimethylhex-4-enoate

Synthesized according to the general procedure. The product was isolated as a colorless oil (29.8 mg, 85% yield).

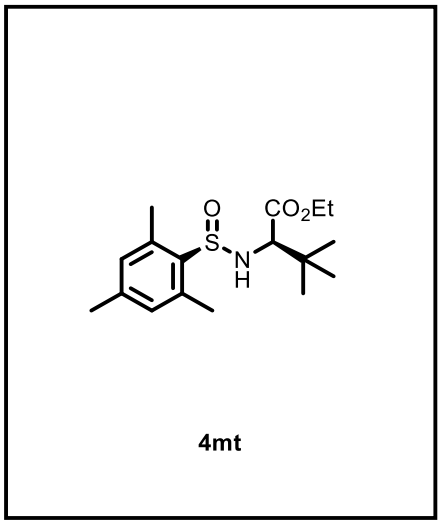
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 2H), 4.99 (d, *J* = 8.9 Hz, 1H), 4.27 – 4.02 (m, 3H), 2.55 (s, 6H), 2.50-2.30 (m, 2H), 2.27 (s, 3H), 1.68 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 140.9, 136.8, 136.8, 130.9, 128.7, 122.8, 61.6, 56.6, 39.49, 21.1, 20.9, 20.7, 19.32, 18.7, 14.2.

$[\alpha]^{D}_{20}$ = -139.4 (c=2.3 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{19}H_{30}NO_3S$ $[M+H]^+$: 352.1946, found: 352.1943.

Compound 4mt



4mt

Ethyl (R)-2-(((R)-mesitylsulfinyl)amino)-3,3-dimethylbutanoate

Synthesized according to the general procedure. The product was isolated as a colorless oil (19.5 mg, 60% yield).

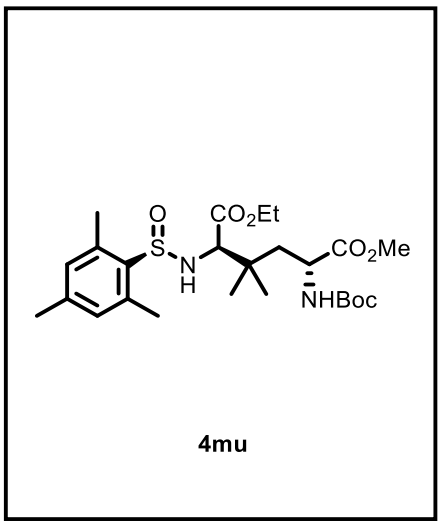
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, *J* = 0.6 Hz, 2H), 5.05 (d, *J* = 10.1 Hz, 1H), 4.35 – 4.11 (m, 2H), 3.60 (d, *J* = 10.1 Hz, 1H), 2.57 (s, 6H), 2.29 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.96 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 141.0, 138.2, 136.9, 130.9, 66.6, 61.4, 35.1, 26.6, 21.2, 19.4, 14.3.

$[\alpha]^{D}_{20}$ = -239.3 (c=1.3 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{17}H_{28}NO_3S$ $[M+H]^+$: 326.1790, found: 326.1798.

Compound 4mu



4mu

1-ethyl 6-methyl (2R,5R)-5-((tert-butoxycarbonyl)amino)-2-(((R)-mesitylsulfinyl)amino)-3,3-dimethylhexanedioate

Synthesized according to the general procedure. The product was isolated as a colorless oil (16.9 mg, 33% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 2H), 5.05 (d, *J* = 10.3 Hz, 1H), 4.99 (d, *J* = 9.8 Hz, 1H), 4.41 (m, 1H), 4.28 – 4.13 (m, 2H), 3.79 (d, *J* = 10.3 Hz, 1H), 3.71 (s, 3H), 2.57 (s, 6H), 2.29 (s, 3H), 1.77 (dd, *J* = 14.6, 3.5 Hz, 1H), 1.66 (d, *J* = 9.7 Hz, 1H), 1.45 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.05 (s, 3H), 1.00 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 169.6, 156.0, 137.5, 132.0, 131.0, 130.9, 64.3, 62.0, 54.6, 48.7, 43.0, 33.9, 28.5, 23.0, 20.9, 20.4, 19.2, 14.3.

$[\alpha]^{D}_{20}$ = -71.4 (c=0.7 CH_2Cl_2)

HRMS (ESI+, m/z): calculated for $C_{25}H_{41}N_2O_7S$ $[M+H]^+$: 513.2634, found: 513.2631.

References

[1] S. Morales, F. G. Guijarro, J. L. García Ruano, M. B. Cid, *J. Am. Chem. Soc.* **2014**, *136*, 1082–1089.
[2] C. Roe, H. Hobbs, R. A. Stockman, *Chem. Eur. J.* 2011, 17, 2704–2708.
[3] K. W. Kells, J. M. Chong, *J. Am. Chem. Soc.* **2004**, *126*, 15666–15667.
[4] A. Shatskiy, A. Axelsson, E. V. Stepanova, J.-Q. Liu, A. Z. Temerdashev, B. P. Kore, B. Blomkvist, J. M. Gardner, P. Dinér, M. D. Kärkäs, *Chem. Sci.* **2021**, *12*, 5430–5437.
[5] F. A. Davis, Y. Zhang, Y. Andemichael, T. Fang, D. L. Fanelli, H. Zhang, *J. Org. Chem.* **1999**, *64*, 1403–1406.
[6] R. Shelp, R. R. Merchant, J. M. E. Hughes, P. J. Walsh, *Org. Lett.* **2022**, *24*, 110–114.
[7] A. F. Garrido-Castro, H. Choubane, M. Daaou, M. C. Maestro, J. Alemán, *Chem. Commun.* **2017**, *53*, 7764–7767.
[8] S. Ni, N. M. Padial, C. Kingston, J. C. Vantourout, D. C. Schmitt, J. T. Edwards, M. M. Kruszyk, R. R. Merchant, P. K. Mykhailiuk, B. B. Sanchez, S. Yang, M. A. Perry, G. M. Gallego, J. J. Mousseau, M. R. Collins, R. J. Cherney, P. S. Lebed, J. S. Chen, T. Qin, P. S. Baran, *J. Am. Chem. Soc.* **2019**, *141*, 6726–6739.
[9] I. V. Kapitanov, A. Jordan, Y. Karpichev, M. Spulak, L. Perez, A. Kellett, K. Kümmerer, N. Gathergood, *Green Chem.* **2019**, *21*, 1777–1794.
[10] C. Roe, T. M. Solá, L. Sasraku-Neequaye, H. Hobbs, I. Churcher, D. MacPherson, R. A. Stockman, *Chem. Commun.* **2011**, *47*, 7491.
[11] S. Ni, A. F. Garrido-Castro, R. R. Merchant, J. N. de Gruyter, D. C. Schmitt, J. J. Mousseau, G. M. Gallego, S. Yang, M. R. Collins, J. X. Qiao, K. Yeung, D. R. Langley, M. A. Poss, P. M. Scola, T. Qin, P. S. Baran, *Angew. Chem. Int. Ed.* **2018**, *57*, 14560–14565.

10. Author Declarations

Institute of Organic Chemistry
Polish Academy of Sciences

Joseph Milton, MSc

PhD Student, Group XV

+48 22 343 2119

joseph.milton@icho.edu.pl

Institute of Organic Chemistry, Polish Academy of Sciences

Kasprzaka 44/52

Warsaw, 01-224, Poland

Warsaw, 25/03/2025

I declare that my contribution to the creation of the following publications included:

- Photo-Induced Carbene Transformations to Heterocycles, **J. P. Milton**, D. Gryko, *Top. Heterocycl. Chem.* **2023**, 1 - 34

Conducting a literature review and preparation of all parts of the manuscript, including schemes and text.

- Photochemical Cyclopropanation in Aqueous Micellar Media – Experimental and Theoretical Studies, **J. P. Milton**, A. Milanowski, M. Anderrson, D. Gryko, *Chem. Commun.*, **2024**, 4483 - 4486

Preparation of starting materials, optimisation of the cyclopropanation reaction of diazo compounds, assessing the scope of diazo compounds (**3a** – **3u**, Scheme 1) and initial testing of the reaction with hydrazones (the synthesis of **3a**) and all relevant data collection for the compounds synthesised. Preparation of all parts of the manuscript including the supporting information.

- Photochemical Functionalization of 4-Diazoisoquinoline-1,3(2*H*,4*H*)-diones and Their 1-Sulfoxide Analogs, **J. P. Milton**, D. Gryko, *ACS Org. Inorg. Au,* ***2025***, doi.org/10.1021/acsorginorgau.5c00017

Conceptulisation of the project, preparation of all starting materials, optimisation of the O-H insertion, the scope of all reactions in the paper and all relevant data collection for the compounds synthesised. UV-Vis studies were also performed. Preparations of all parts of the manuscript including the supporting information.

- TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines, M. Leone, **J. P. Milton**, D. Gryko, L. Neuville, G. Masson, *Chem. Eur. J.*, **2024**, 30, e202400363

Preparation of starting materials, investigating the scope of *N*-sulfinyl imines (compounds **4gb**, **4hb**, **4ib**, **4jb**, and **4lb**) and all relevant data collection for the compounds synthesised. Assistance in proof-reading and drafting the manuscript.

I confirm that the above statements are true: Dorota Gryko Digitally signed by Dorota Gryko Date: 2025.03.25 15:59:24 +01'00' ..... (Supervisor signature)

Joseph Milton

Institute of Organic Chemistry
Polish Academy of Sciences

Prof. Dorota Gryko

Group Leader, Group XV

+48 22 343 2051

dorota.gryko@icho.edu.pl

Institute of Organic Chemistry, Polish Academy of Sciences

Kasprzaka 44/52

Warsaw, 01-224, Poland

Warsaw, 25/03/2025

I declare that my contribution to the creation of the following publications included:

- Photo-Induced Carbene Transformations to Heterocycles, **J. P. Milton**, D. Gryko, *Top. Heterocycl. Chem.* **2023**, 1 - 34

Assistance, guidance and corrections during the preparation of the manuscript.

- Photochemical Cyclopropanation in Aqueous Micellar Media – Experimental and Theoretical Studies, **J. P. Milton**, A. Milanowski, M. Anderrson, D. Gryko, *Chem. Commun.*, **2024**, 4483 - 4486

Conceptulisation of the project, assistance and guidance on the direction of the project and creation of the manuscript.

- Photochemical Functionalization of 4-Diazoisoquinoline-1,3(2*H*,4*H*)-diones and Their 1-Sulfoxide Analogs, **J. P. Milton**, D. Gryko, *ACS Org. Inorg. Au*, **2025**, doi.org/10.1021/acsorginorgau.5c00017

Conceptulisation of the project, assistance and guidance on the direction of the project and creation of the manuscript.

- TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines, M. Leone, **J. P. Milton**, D. Gryko, L. Neuville, G. Masson, *Chem. Eur. J.*, **2024**, 30, e202400363

Assistance in proof-reading and drafting the manuscript.

.....

Institute of Organic Chemistry
Polish Academy of Sciences

mgr Adam Milanowski

PhD Student, Group XV

+48 22 343 2119

adam.milanowski@icho.edu.pl

Institute of Organic Chemistry, Polish Academy of Sciences

Kasprzaka 44/52

Warsaw, 01-224, Poland

Warsaw, 20/02/2025

I declare that my contribution to the creation of the following publications included:

- Photochemical Cyclopropanation in Aqueous Micellar Media – Experimental and Theoretical Studies, J. P. Milton, A. Milanowski, M. Anderrson, D. Gryko, *Chem. Commun.*, **2024**, 4483 – 4486

Preparation of starting materials, development of the substrate scope with hydrazones (**3b-d**, **3v-x**) and all relevant data collection for the compounds synthesised.

Adam Milanowski

King Fahd University of Petroleum & Minerals
College of Petroleum Engineering & Geosciences
Center for Integrative Petroleum Research
(036)

جامعة الملك فهد للبترول و المعادن
كلية هندسة البترول وعلوم الأرض
مركز بحوث البترول المتكاملة
(٠٣٦)

Co-author statement

Date	:	Feb 20, 2025
To	:	whomever it concerns
From	:	Dr. Martin P. Andersson Research Scientist I (Program Leader – Modelling), Center for Integrative Petroleum Research
Subject	:	Co-author statement

I declare that my contribution to the creation of the publication:

> Photochemical Cyclopropanation in Aqueous Micellar Media – Experimental and Theoretical Studies, **J. P. Milton**, A. Milanowski, M. P. Andersson, D. Gryko, *Chem. Commun.*, **2024**, 4483 - 4486

was performing the COSMO-RS calculations for modelling the cyclopropanation reaction of diazo compounds with styrenes in a micellar environment and subsequent data analysis of the computational results.

Best regards,

Dr. Martin Andersson

ص.ب ٥٠٨٦ • الظهران ٣١٢٦١ • المملكة العربية السعودية • تلفون: ٣٨٨٨-٨٦٠ (٠١٣) • فاكس: ٣٩٨٩-٨٦٠ (٠١٣) • بريد الكتروني: cipr@kfupm.edu.sa
Box: 5086 • DHAHRAN, 31261 • SAUDI ARABIA • Telephone: (013) 860-3888 • Fax: (013) 860-3989 • E-mail:cipr@kfupm.edu.sa

UNIVERSITÀ DI PAVIA
Department of Chemistry

Dr. Matteo Leone

Postdoctoral Student

mat.leone23@gmail.com

Department of Chemistry, University of Pavia,

Viale Taramelli 12,

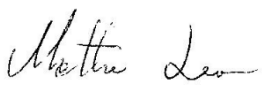
27100 Pavia, Italy

Pavia, 24/02/2025

I declare that my contribution to the creation of the following publications included:

- TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines, M. Leone, **J. P. Milton**, D. Gryko, L. Neuville, G. Masson, *Chem. Eur. J.*, **2024**, 30, e202400363

Conceptualization of the work, synthesis and characterization of starting materials, optimisation of the HAT reaction, substrate scope except (**4db**, **4eb**, **4fb**, **4kb**, **4mb**). Mechanistic studies and post transformations. Full characterization of compounds. Preparation of the manuscript and the supporting information.



Institut de Chimie des Substances Naturelles

Dr. Luc Neuville
CNRS Research Director
luc.neuville@cnrs.fr

Gif-sur-Yvette, le 21 Febuary 2025

To whom it may concern,

I, Luc Neuville, hereby declare my contribution to the creation of the following publication:

TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines, M. Leone, J. P. Milton, D. Gryko, L. Neuville, G. Masson, Chem. Eur. J., 2024, 30, e202400363

- Conceptualization of the project
- Supervision of the project
- Manuscript preparation

Dr. Luc Neuville

Institut de Chimie des Substances Naturelles

Dr. Géraldine Masson
Research Director
geraldine.masson@cnrs.fr

Gif-sur-Yvette, le 21 Febuary 2025

To whom it may concern,

I, Géraldine Masson, hereby declare my contribution to the creation of the following publication:

TBADT-Mediated Photocatalytic Stereoselective Radical Alkylation of Chiral N-Sulfinyl Imines: Towards Efficient Synthesis of Diverse Chiral Amines, M. Leone, J. P. Milton, D. Gryko, L. Neuville, G. Masson, Chem. Eur. J., 2024, 30, e202400363

- Conceptualization of the project
- Supervision of the project
- Manuscript preparation

Dr. Géraldine MASSON