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Designing Green Oxidation Reactions with Sulfoxides

by

Francesca Spagna

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For the degree of Doctor of Philosophy

“Science is magic that works.”

— Kurt Vonnegut, Cat's Cradle

Abstract

With increasing environmental concerns, the development of chemical reactions based on green chemistry protocols has a pivotal position in the organic synthetic community.

Chapter 1 is a review of the main developments on the employment of dimethyl sulfoxide. Dimethyl sulfoxide is one of the most used organic solvents. Numerous reports have recently appeared that demonstrate dimethyl sulfoxide acting as a substrate, building block, or synthon in organic chemistry.

Chapter 2 will discuss our studies on the thermal dehydrogenation reaction of amines to synthesised imine based on the sulfoxide group. This environmentally friendly reaction features no requirement of metal catalysts. A wide range of imines can be obtained in good yields. Chapter 3 will conclude the topic.

Chapter 4 is a literature review of the photochemistry of the sulfoxide group. The first section of this chapter will show different behaviours of the sulfoxide group upon irradiation. Subsequently, the second section will focus more specifically on the photodeoxygenation of dibenzothiophene sulfoxide. Historically, several mechanisms have been postulated for this reaction. Here, these postulated mechanisms will be introduced.

Chapter 5 will discuss our work in the photodeoxygenation reaction of dibenzothiophene sulfoxide. It will describe our numerous attempts to create a new catalytic cycle based on the photodeoxygenation of dibenzothiophene sulfoxide. Chapter 6 will summarise our findings keeping an eye on future opportunities.

I hereby certify that this doctoral thesis is my own work.

Acknowledgments

I wish to take advantage of this opportunity to particularly thank my supervisor Professor Chris J. Moody, for allowing me to work within his group and for providing me with constant support and advice.

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Last but not least, I would like to thank the Taekwondo Club of the University of Nottingham. Their constant presence and support helped me to get through the most difficult moments.

Designing Green Oxidation Reactions with Sulfoxides

List of Abbreviations

API	active pharmaceutical ingredient
DBT	dibenzothiophene
DBTO	dibenzothiophene sulfoxide
$DBTO_2$	dibenzothiophene sulfone
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	2-deoxydeoxyribonucleic acid
DPM	diphenylmethyl group
EPA	electron-pair acceptor
EPD	electron-pair donor
EPR	Electron Paramagnetic Resonance
GC–MS	gas chromatography – mass spectrometry
HBA	hydrogen-bond acceptor
HBD	hydrogen-bond donor
HPLC	high performance liquid chromatography
KIE	kinetic isotope effect
LC–MS	liquid chromatography – mass spectrometry
LOHC	liquid organic hydrogen carrier
*m*CPBA	*meta*-chloroperoxybenzoic acid
m/z	mass charge ratio
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NSAIDs	non-steroidal anti-inflammatory agents
SWNT	single-walled nanotube
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl

TGA–MS	thermal gravimetric analysis – mass spectrometry
THBC	tetrahydro-β-carbolines
THIQ	tetrahydroisoquinolines
TIC	total ion chromatogram
TLC	thin-layer chromatography
TPD–MS	temperature programmed desorption – mass spectrometry

1. The Application of Dimethyl Sulfoxide as a Reagent in Organic Chemistry

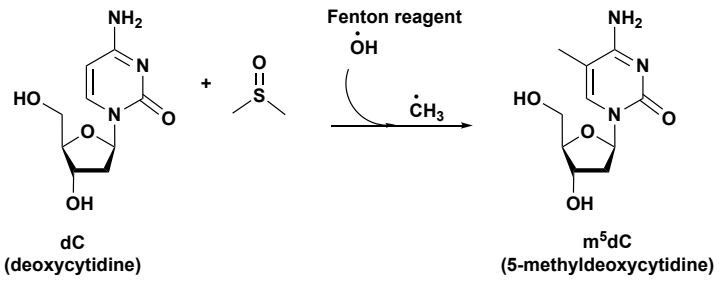
Dimethyl sulfoxide (DMSO) is an organosulfur compound with the chemical formula $(CH_3)_2SO$. It was first synthesised by the Russian scientist Alexander Zaytsev in 1866.[1] It is commercially produced by the oxidation of dimethyl sulfide with nitrogen dioxide or oxygen. It is a colourless liquid and an important polar aprotic solvent that dissolves both polar and nonpolar compounds; it is miscible in a wide range of organic solvents as well as water. It is also a naturally occurring substance and is present at low concentrations (0.11-3.7 ppm) in food products such as tomato paste, raspberries, and milk.[2] It is a part of Earth's complex sulfur cycle. DMSO is created in the atmosphere at a rate of 10-25 billion kilogrammes per year from dimethyl sulfide. [3] Metabolism of DMSO in soil by microorganisms results in the formation of sulfur and dimethyl sulfide. DMSO has low acute and chronic toxicity for animal, plant, and aquatic life. DMSO is not listed as a carcinogen by regulatory authorities and is not teratogenic in mice, rats or rabbits. Due to its low toxicity, DMSO is listed as a green solvent.[4] In organic synthesis, DMSO is employed not only as a cheap, low-toxic and aprotic polar solvent, but is also a well-known oxidant in reactions such as the Swern oxidation, Pfitzner-Moffatt oxidation, and in the Corey-Chaykovsky reaction. These reactions are not considered here. Moreover, DMSO is widely used for the treatment of rheumatic disorders because of its capacity of inhibiting inflammation processes of various aetiologies, due its similar properties to non-steroidal anti-inflammatory agents (NSAIDs).[5] DMSO is approved as an active pharmaceutical ingredient (API) and is currently being evaluated as an API in several orphan-status drugs worldwide.[6] DMSO is not often thought of as a substrate, building block or synthon in organic chemistry. However, in recent years lots of reports have emerged in which DMSO covers these roles. An overview of the literature on this topic is offered in the following sections.

1.1 As C_1 Sources

DMSO is known to be a valuable source of a variety of one-carbon synthons. Many reports have recently been published that demonstrate dimethyl sulfoxide acting in these roles. This Section will cover DMSO as a -CH_3 source (Section 1.1.1), -CH_2- source (Section 1.1.2), =CH- source (Section 1.1.3), -CN source (Section 1.1.4), and -CHO source (Section 1.1.5).

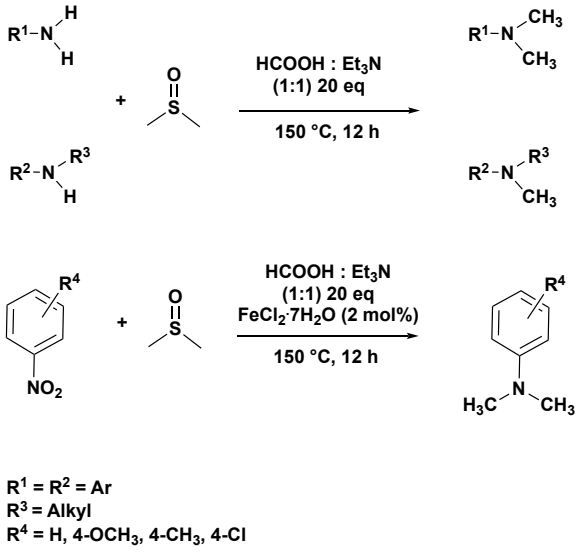
1.1.1 DMSO-Based Methylation (-CH_3 Source)

The presence of a methyl group can greatly alter or regulate the activities of biologically or pharmaceutically active molecules. Therefore, an intense research effort has been made to properly study its introduction. In this regard, DMSO has been successfully used as a methyl source. In 1966, Weiner discovered that the dimsyl anion, generated by the treatment of DMSO with sodium hydride, can readily methylate heteroaromatic hydrocarbons such as quinoline, isoquinoline, and benzisoxazoles.[7] More recently, Kasai and co-workers demonstrated the *in vitro* methylation of the C-5 carbon of the deoxycytosine nucleotide in DNA by DMSO under physiological conditions in the presence of the Fenton reagent. Chemical cytosine methylation is one of the mechanisms of DNA hypermethylation during carcinogenesis **(Scheme 1)**.[8] The implication of this finding is a new tool to study carcinogenesis processes.



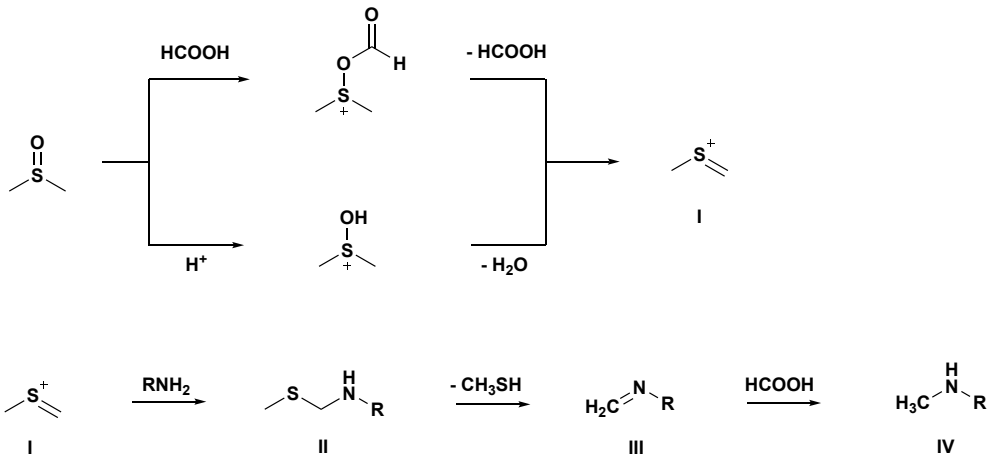
Scheme 1 Formation of m^5dC *via* methyl radicals from DMSO triggered by the Fenton reagent.

Furthermore, DMSO is a versatile methylation reagent for amines. Xiao and co-workers developed a new amine methylation protocol with a very broad substrate scope **(Scheme 2)**.[9] Substrates were heated at 150 °C in DMSO in the presence of an excess of formic acid and triethylamine. Extensive isotope-labelling experiments indicated that the carbon atom and two of the three H atoms of the methyl group originates from DMSO, while the third H atom is provided by formic acid. Aromatic nitro compounds could be directly converted into dimethylated amines in the presence of an iron catalyst.[9]



Scheme 2 *N*-methylation of primary and secondary amines in DMSO.

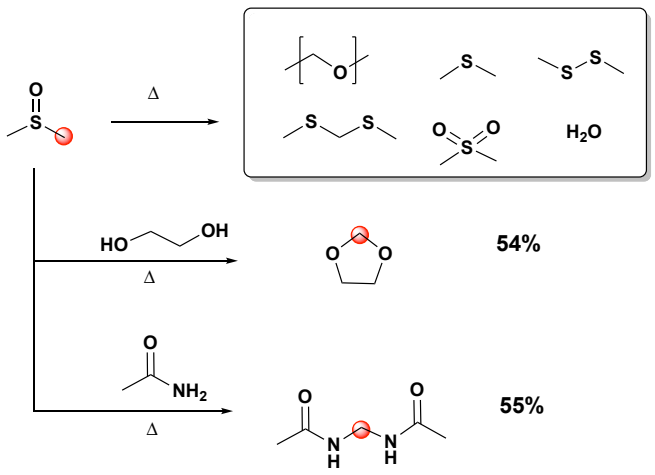
The mechanism proposed by the authors starts from the formation of the methyl(methylene) sulfonium species **(I)**. DMSO may be acylated or protonated by formic acid. The methyl(methylene) sulfonium species **(I)** will form in both cases. This reacts with the amine to form an intermediate **(II)**. The subsequent elimination of methanethiol results in imine formation **(III)**. In the final step, formic acid reduces the imine **(III)**, affording the methylated amine products **(IV) (Scheme 3)**.



Scheme 3 Putative mechanism for methylation of amines.

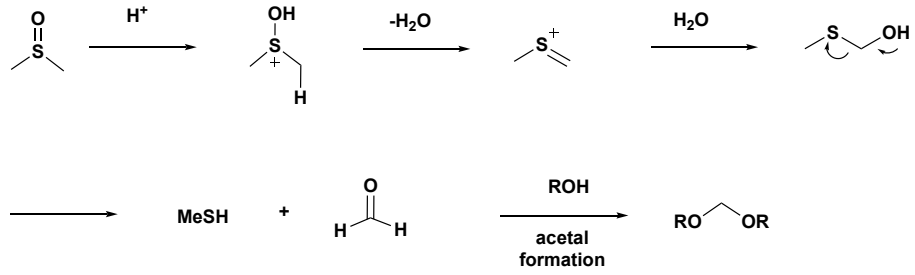
1.1.2 DMSO-Based Methylenation (-CH_2- Source)

In 1964, Traynelis and Hergenrother isolated the decomposition products of DMSO that were formed upon prolonged heating at reflux **(Scheme 4)**.[10] These were paraformaldehyde, dimethyl sulfide, dimethyl disulfide, bismethylthiomethane, dimethyl sulfone, and water. 1,3-Dioxolane and methylenebisacetamide were obtained respectively in 54% and 55% yield when ethylene glycol and acetamide were heated with DMSO.



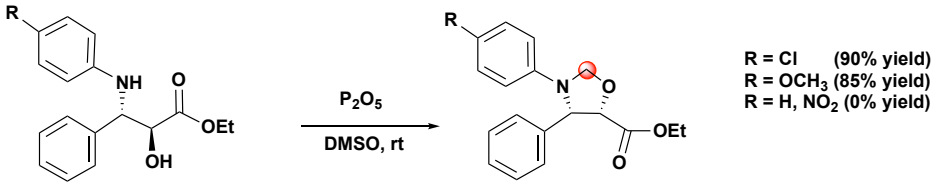
Scheme 4 Decomposition studies of DMSO.

The mechanism for acetal formation is unknown but presumably involves hydrolysis, followed by loss of methanethiol to generate formaldehyde **(Scheme 5)**.



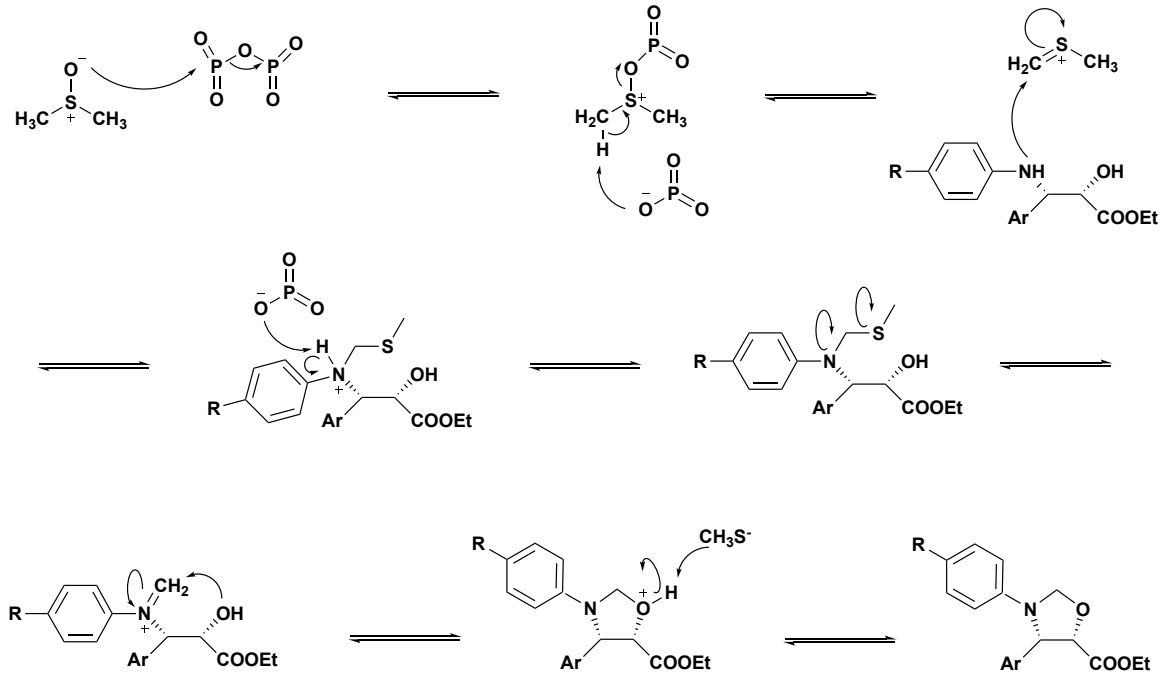
Scheme 5 Mechanistic rationale for methylenation with DMSO.

In 2007, Kayser reported the conversion of 1,2-aminoalcohols into oxazolidines when treated with phosphorus pentoxide in DMSO **(Scheme 6)**.[11] The reaction was highly dependent on the nature of the *para*-substituents of the aniline moiety. Methoxy and chloro-substitution were well tolerated, while no product was observed with a *para*-nitro substitution or in the absence of *para*-substituents. The mechanism proposed by the authors is similar to the general methylenation rationale discussed in **Scheme 5**.



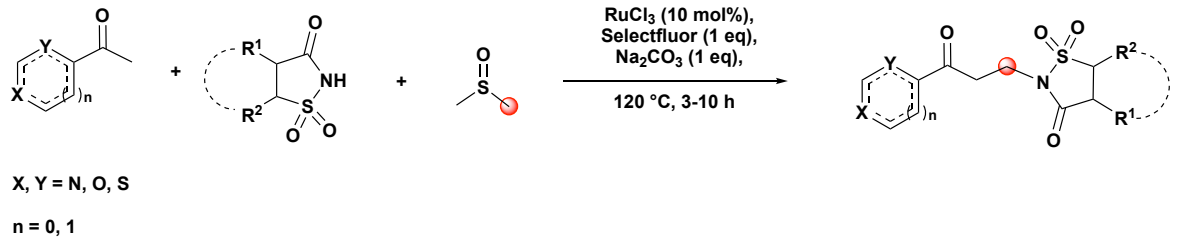
Scheme 6 Synthesis of oxazolidines using DMSO/P_2O_5.

The mechanism postulated by Kayser begins with the activation of DMSO by reaction with an electrophile, phosphorus pentoxide, with subsequent nucleophilic attack of the amino group on the sulfonium ion. The resulting intermediate possesses a potential leaving group (CH_3S^-) and a neighbouring electron-rich hydroxyl group. In the final step, the attack from the alcohol leads to the ring closure **(Scheme 7)**.



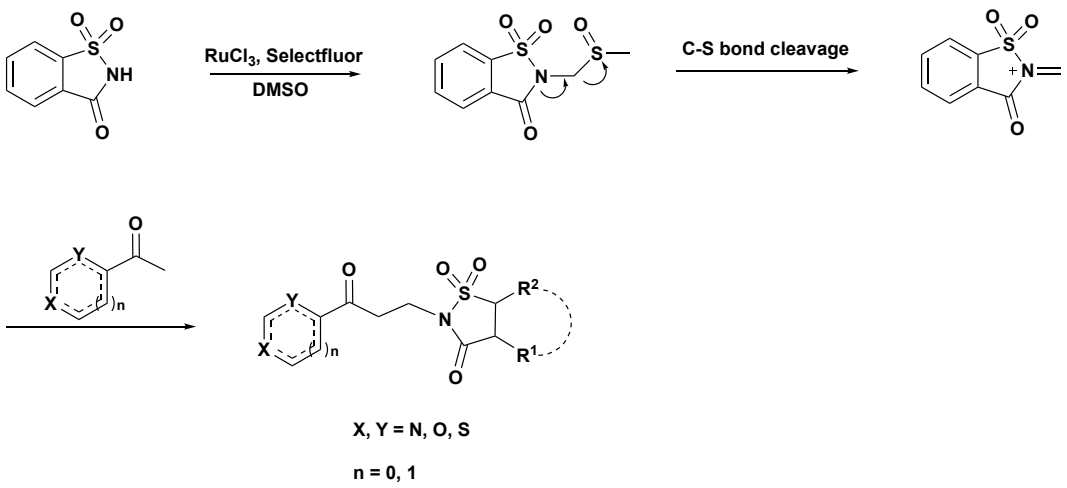
Scheme 7 Kayser's postulated pathway for formation of oxazolidine.

A novel C-S bond cleavage reaction of DMSO for dual C-C and C-N bond formation has been described by Wang and co-workers **(Scheme 8)**.[12] A series of acetyl heteroarenes could be converted into the corresponding β-amino ketones, commonly found in biologically active compounds. DMSO was used both as the solvent and the source of one-carbon bridge. A catalytic amount of $RuCl_3$, a stoichiometric amount of the electrophilic fluorinating agent Selectfluor® and sodium carbonate were used. The authors reported several examples showing that the reaction has a wide substrate scope.



Scheme 8 Formation for β-amino ketones by three-component Mannich reaction.

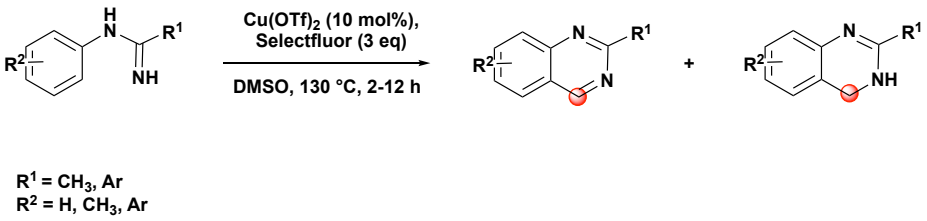
The use of d_6-DMSO firmly established that the new methylene adjacent to the nitrogen, (highlighted in red in **Scheme 8**) arises from DMSO. The authors believe that the mechanism proceeds *via* a Mannich-type iminium alkylation. The first step is proposed to be an oxidative amination process by $RuCl_3$ and Selectfluor®, followed by C-S bond cleavage that delivers the iminium intermediate. Finally, the desired product is formed by the reaction between the intermediate and the ketone **(Scheme 9)**.



Scheme 9 Wang's putative mechanism for C-C and C-N bond formation for β-amino ketones.

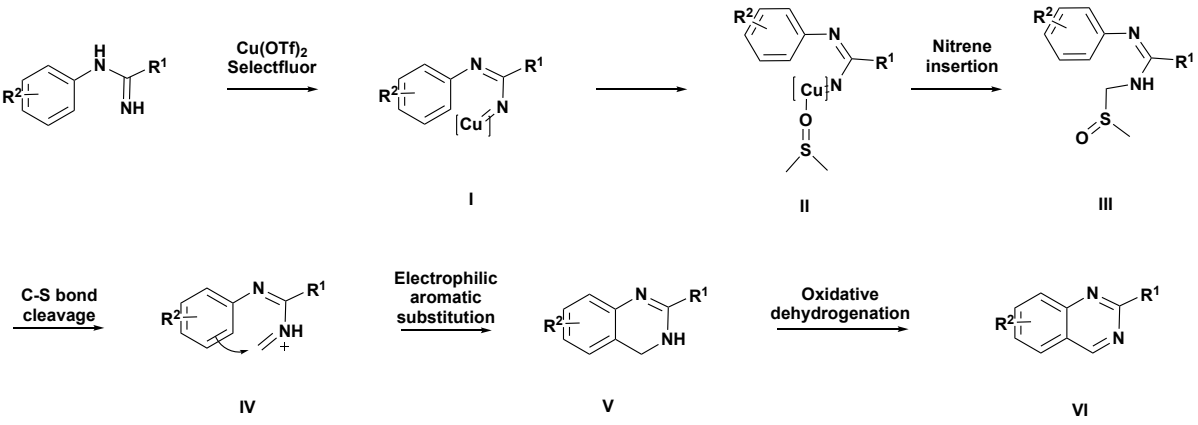
1.1.3 DMSO-Based Annulation/Aromatisation (=CH- Source)

Quinazoline derivatives are broadly distributed in biologically active molecules. Therefore, there are numerous methods for their synthesis.[13] One of the most prominent has been made by Zhang and co-workers **(Scheme 10)**.[14] They proposed an efficient Cu-catalysed synthesis of quinazolines *via* the C-N bond formation reaction between N-H bonds of amidines and C(sp^3)-H bonds adjacent to the sulfur atom of DMSO, followed by intramolecular C-C bond formation.



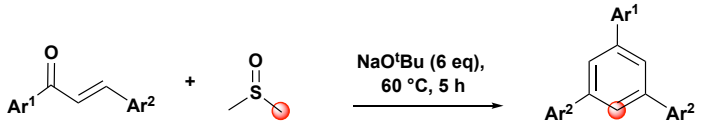
Scheme 10 Quinazoline synthesis incorporating a C atom from DMSO.

Electron-donating substituents favour the selectivity for aromatised quinazolines to the detriment of dihydroquinazolines. The mechanism proposed in this study begins with the oxidation of Cu(II) to Cu(III) by the F oxidant of Selectfluor® and formation of a copper-nitrene complex **(I)**. The subsequent coordination of intermediate **(II)** with DMSO provides a copper-nitrene complex **(II)**. This undergoes a C-N bond formation reaction *via* nitrene insertion into the C(sp^3)-H bond of DMSO **(III)**. The cleavage of C-S leads to an iminium species **(IV)**, which cyclises *via* an aromatic substitution mechanism to yield dihydroquinazolines **(V)**. For electron-rich substrates, a further oxidative dehydrogenation occurs to give fully aromatised quinazolines **(VI) (Scheme 11)**.



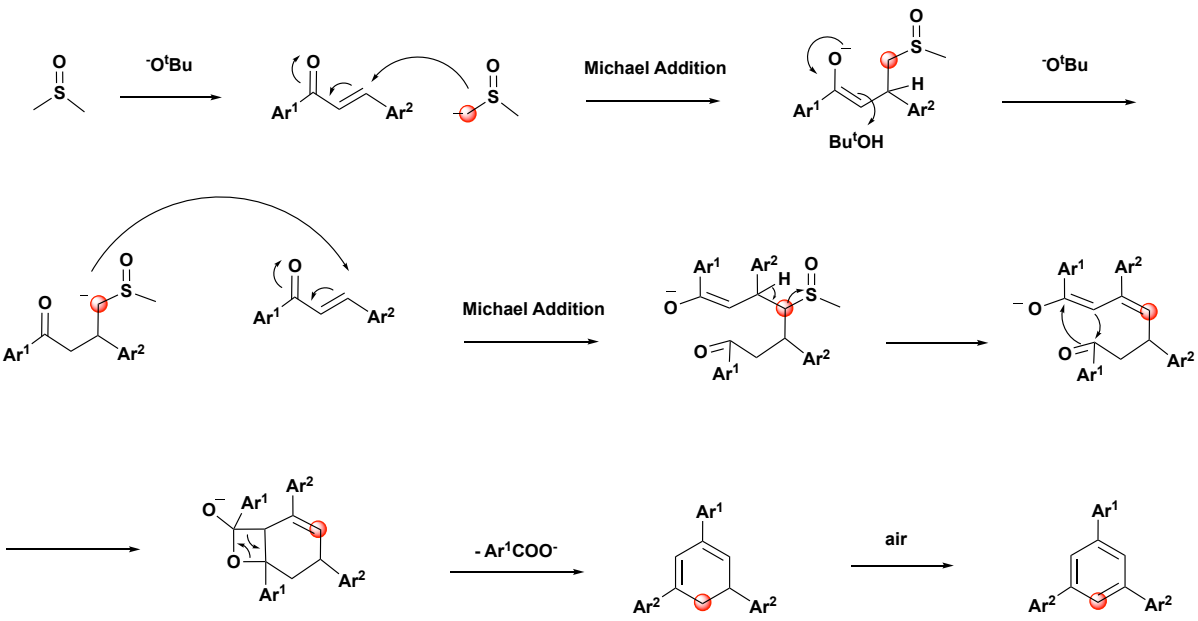
Scheme 11 Proposed mechanism for annulation/aromatisation reaction incorporating a C atom from DMSO.

In 2015, Cui and co-workers reported a new method for the synthesis of both symmetrical and unsymmetrical 1,3,5-triarylbenzenes starting from chalcones **(Scheme 12)**.[15]



Scheme 12 Triarylbenzene annulation incorporating a C atom from DMSO.

Isotopic labelling experiments proved that the central carbon highlighted in **Scheme 12** derives from DMSO. According to the authors, *tert*-butoxide promotes the deprotonation of DMSO with formation of the dimsyl anion. This undergoes two sequential Michael additions. A subsequent ring closure *via* demethylsulfinylation and [2+2]-cycloaddition gives the product **(Scheme 13)**, although the authors do not explain the apparent oxidation step.

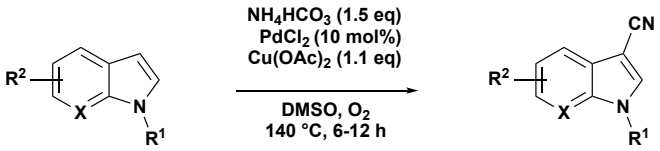


Scheme 13 Triarylbenzene annulation with a C atom deriving from DMSO.

1.1.4 DMSO-Based cyanation (-CN Source)

In 2011, Chan, Cheng and co-workers reported a palladium-catalysed cyanation of the sp^2 C-H bond of indole at the 3-position **(Scheme 14)**.[16] Aromatic nitriles were produced in moderate to good yield with a combination of NH_4HCO_3 and DMSO as the CN source. *N*-Unsubstituted indoles were not tolerated. Otherwise, indoles containing both electron-withdrawing and electron-donating substituents were suitable for the reaction. In order to validate the source of the CN, $Cu(OAc)_2$ was replaced by $CuCl_2$. The reaction led to cyano product under otherwise the same reaction conditions, which eliminated the possibility of the carbon atom in the cyano group deriving from $Cu(OAc)_2$. Moreover, when $NH_3{\cdot}H_2O$ or $(NH_4)_2SO_4$ replaced NH_4HCO_3 as the nitrogen source, the nitrile product was also isolated. Therefore, the carbon atom could not derive from NH_4HCO_3. Furthermore, a ^{13}C-DMSO labelled experiment confirmed the carbon in the cyano group came from DMSO. The authors of the study did not speculate about the mechanism by which DMSO may be converted to a nitrile. Nevertheless, this methodology represents a safe cyanation protocol. Although the

details of this way of generating cyano units are not clear at the present stage, it may be reasonable that the reaction involves the Cu-catalysed formylation of indole with DMSO and molecular oxygen, as discussed below (Section 1.1.5).[17] The formylation is followed by reaction with the ammonium.[18] The ammonia surrogate reacted with aldehyde with the help of molecular oxygen; after oxidative condensation, the nitrile was obtained.

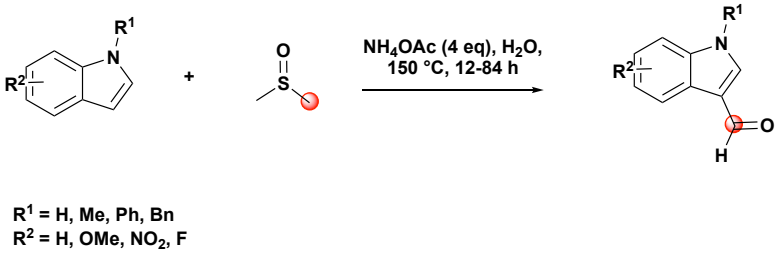


X = C, N
R^1 = Me, Ph, Bn
R^2 = H, Me, OMe, NO_2, F, Br

Scheme 14 C-H cyanation using ammonium formate and DMSO.

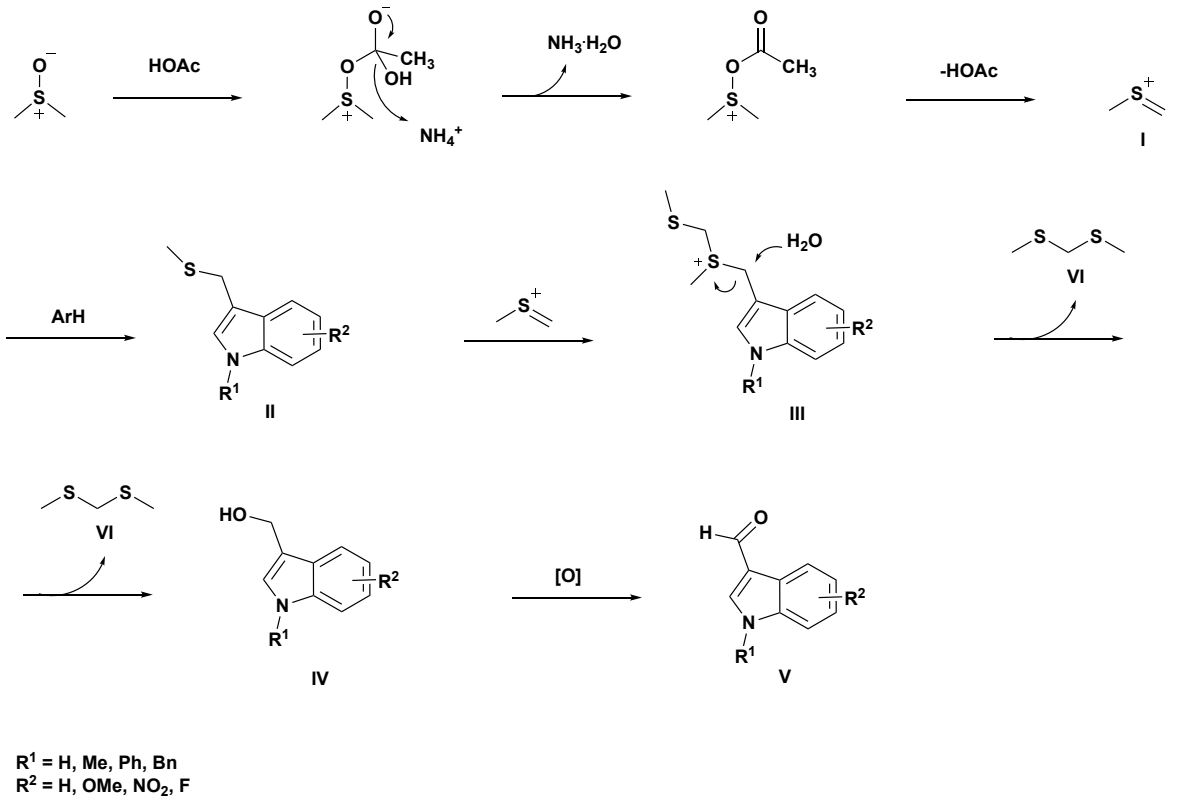
1.1.5 DMSO-Based formylation (-CHO Source)

In 2013, Cheng and co-workers showed that DMSO and H_2O is an efficient combination for the ammonium-promoted indole formylation **(Scheme 15)**.[19] Substrates with electron-withdrawing groups led to sluggish results, whilst substrates with electron-donating groups gave good to excellent yield. The transformation proceeds smoothly regardless of the *N*-substituent of the indoles. The authors observed that when D_2O was used, no deuterium was incorporated in the product. However, the use of d_6-DMSO led to deuterated aldehydic hydrogen. When $H_2{}^{18}O$ was used, the 3-formyl-*N*-methyl indole with ^{18}O in the carbonyl group was the major product. They concluded that the aldehydic hydrogen derived from DMSO, while the oxygen derived from water.



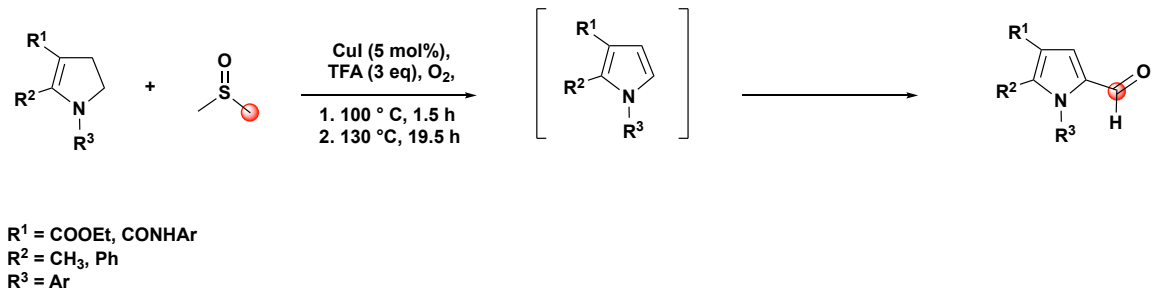
Scheme 15 Formylation of indoles promoted by ammonium acetate and DMSO.

The authors postulate a mechanism that begins with methyl(methylene)sulfonium species **(I)** formation in the presence of NH_4^+ and water. More specifically, NH_4OAc is decomposed to HOAc and NH_3. Then, HOAc activates DMSO. The role of NH_4^+ is likely to facilitate the cleavage of the C-OH bond. Therefore, the thionium ion is formed in the presence of $NH_3{\cdot}H_2O$ as a base. This is attacked by *N*-methyl indole forming 3-methylthiomethylindole as an intermediate **(II)**, which subsequently undergoes a second attack by a second thionium ion to form a sulfonium species **(III)** as an intermediate. This latter intermediate **(III)** is attacked by H_2O as the nucleophile to afford the hydroxymethylation product **(IV)**, which is oxidised to the formylation product **(V)**. Bis(methylthio)methane **(VI)** was detected by GC–MS **(Scheme 16)**.



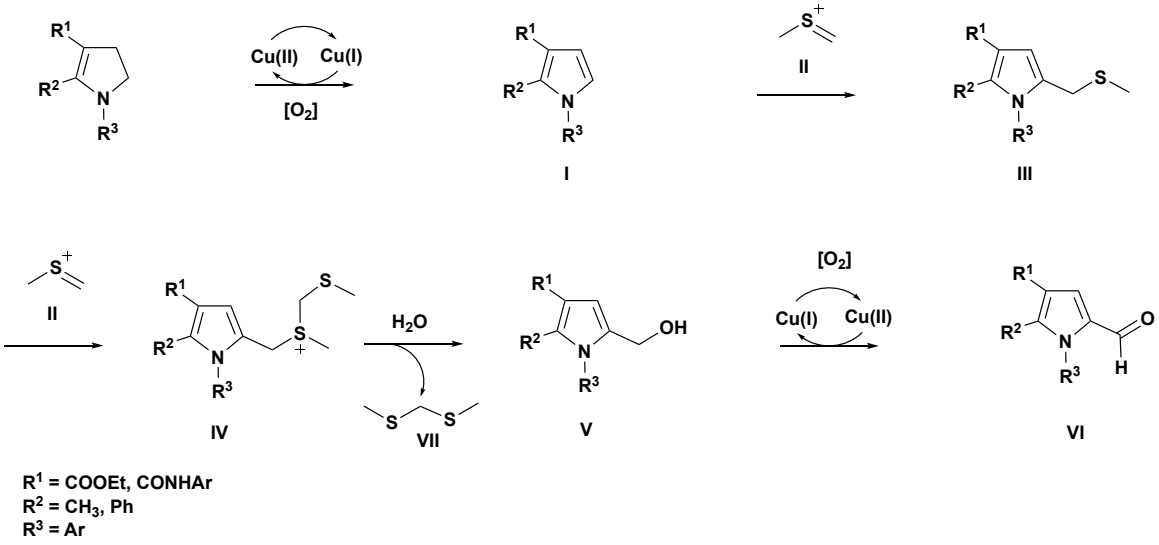
Scheme 16 Cheng's postulated mechanism for the formylation of indoles.

Highly functionalised pyrroles are widely present in pharmaceutical drugs.[20] In 2014, Zhang and co-workers disclosed a copper-catalysed tandem dehydrogenation/C-2 formylation reaction with DMSO acting both as a carbonyl source and as the solvent **(Scheme 17)**.[21] The reaction has a wide substrate scope and tolerates compounds with electron-donating or electron-withdrawing groups, as well as non-substituted compounds as well. The reaction works under an O_2 atmosphere; under a N_2 atmosphere only the dehydrogenative step worked partially. There was a completely deuterated formyl group at the α position of pyrrole when d_6-DMSO was used. These results indicates that the oxygen atom of the formyl group derives from O_2 atmosphere, whilst the proton derives from DMSO.



Scheme 17 Dehydrogenation and formylation of dihydropyrroles.

The mechanism postulated by the authors starts with a copper-catalysed aerobic oxidative dehydrogenation of the substrates to the corresponding pyrroles **(I)**. Subsequently, an electrophilic aromatic substitution reaction between the pyrrole at C-2 and the Pummerer-derived methyl(methylene)sulfonium **(II)** occurs. A second molecule of methyl(methylene)sulfonium **(II)** is attacked by the previous intermediate **(III)** to yield a sulfonium ion **(IV)**, which reacts with water to give an alcohol **(V)**. In the last step, a copper-catalysed aerobic benzylic oxidation of the alcohol gives the final aldehyde product **(VI)**. A large amount of bis(methylthio)methane **(VII)** was detected as a by-product by GC–MS **(Scheme 18)**.



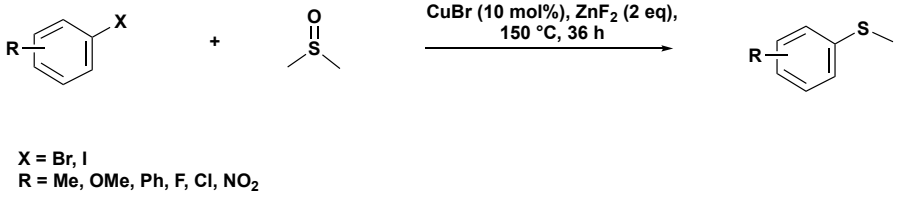
Scheme 18 Dehydrogenation and formylation of dihydropyrroles.

1.2 As $S(O)_XMe$ Sources

Synthetic transformations that have utilised the S-C or C-S-C fragments of dimethyl sulfoxide as building blocks are systematically summarised in the next section. This Section will review the main developments on the employment of DMSO as a source of -SMe (Section 1.2.1) and $-SO_2Me$ (Section 1.2.2).

1.2.1 DMSO-Based Thiomethylation (-SMe Source)

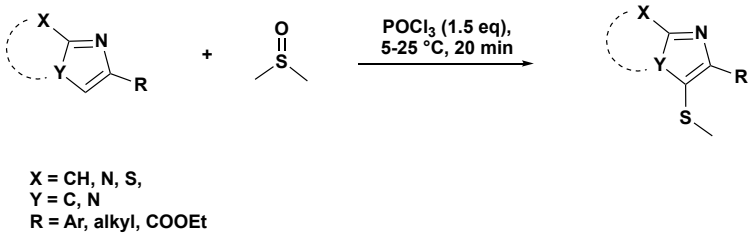
In 2011, Cheng and co-workers used DMSO as a thiomethyl source for a copper-mediated thiomethylation of aryl halides **(Scheme 19)**.[22] Several examples were reported from the corresponding bromo- or iodoarenes in good yields. The reaction tolerates both electron-withdrawing and electron-donating groups, with the latter giving better yields. The mechanism of the reaction remains unknown. Nevertheless, the authors conclude that a disulfide species may act as an intermediate in the reaction.



Scheme 19 Thiomethylation of aryl halides with DMSO.

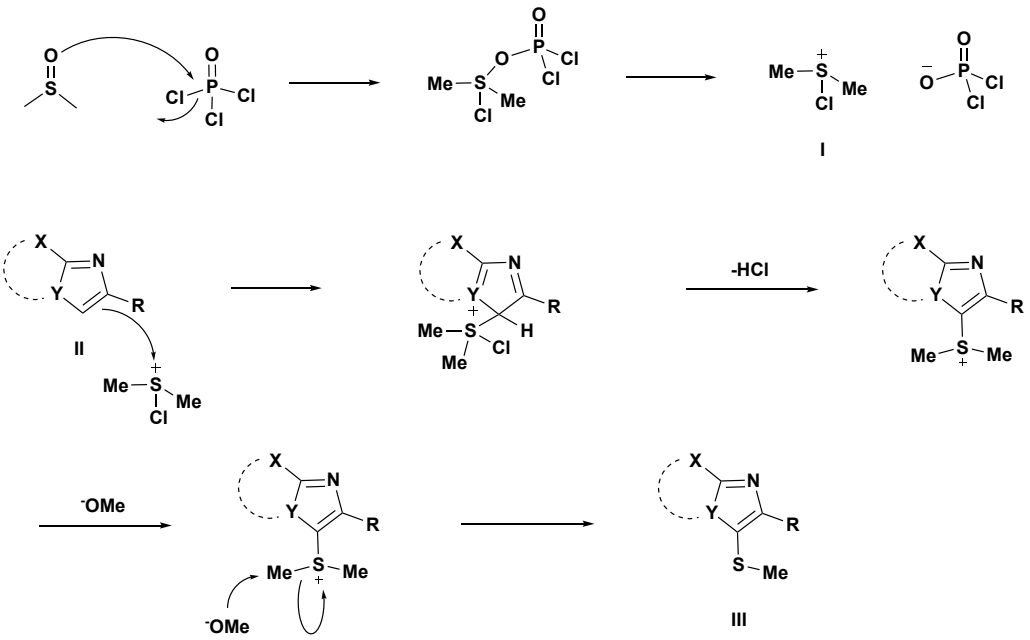
Imidazo-fused heterocycles are pharmaceutically important compounds. They are a widespread in biologically active molecules.[23] Their functionalisation with a thiomethyl moiety has great impact on the biological activity. Further, these compounds have found application as fluorescent dyes.[24] Roychowdhury and co-workers reported a method for the

methylthiolation of imidazo-fused heterocycles using a DMSO-$POCl_3$ complex **(Scheme 20)**.[25] Reactions proceed at room temperature to give good to excellent yield of products.



Scheme 20 C-H thiomethylation of heterocycles with DMSO.

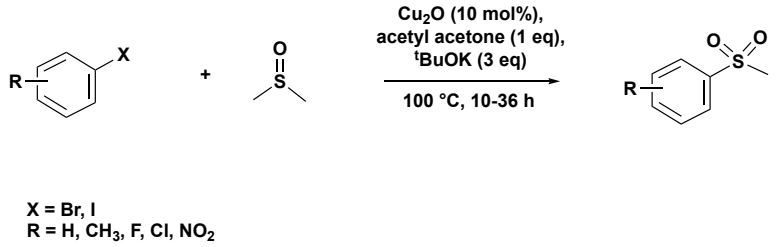
The authors proposed a reaction mechanism in which DMSO reacts with phosphorus oxychloride to give a chlorodimethylsulfonium intermediate **(I)**. This is attacked by the heterocycle **(II)** on the sulfur atom with subsequent demethylation presumably by the NaOMe added in the work-up, yielding the final product **(III) (Scheme 21)**.



Scheme 21 Roychowdhury's putative mechanism for the methylthiolation.

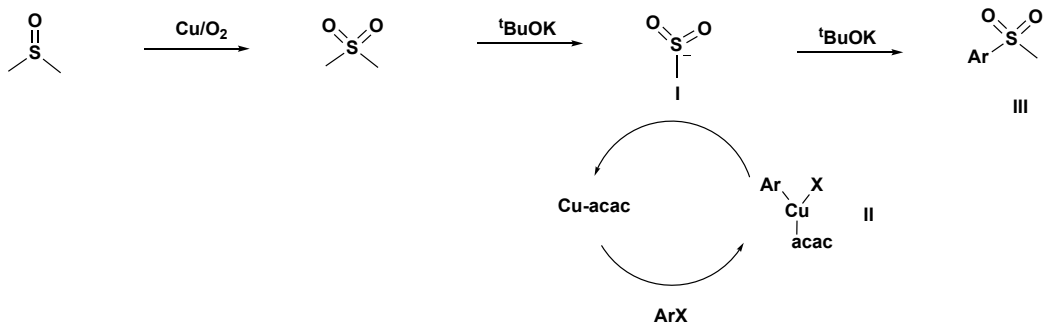
1.2.2 DMSO-Based methylsulfonylation (-SO_2Me Source)

The sulfone group has attracted lots of attention for its antitumour, antifungal, and antibacterial activities.[26] In 2012, Yuan and co-workers reported a new synthesis of aryl methyl sulfones from aryl halides and DMSO **(Scheme 22)**.[27] The reaction works well with both electron-donating and electron-withdrawing groups, with the latter being more reactive. Labelling experiments suggested that one of the oxygen atoms derives from molecular O_2.



Scheme 22 Methylsulfonylation of aryl halides with DMSO.

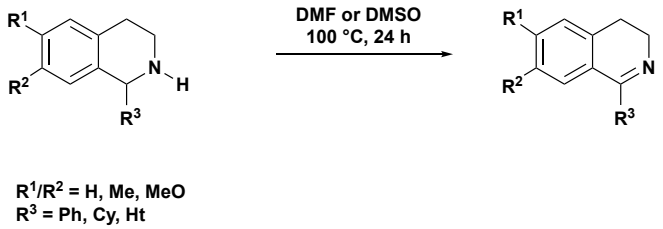
The authors suggested that the reaction begins with a copper-catalysed aerobic oxidation of DMSO to the corresponding sulfone. Subsequently, the *tert*-butoxide cleaves the C-S bond acting as a nucleophile, generating an anion as the first intermediate **(I)**. The copper catalyst undergoes oxidative addition to the aryl halide to provide the second intermediate **(II)**. These two intermediates **(I** and **II)** undergo a copper-mediated cross-coupling sequence to form the product **(III)** with release of the catalyst and X^- anions. Performing the reaction starting directly from the sulfone rather than DMSO leads to very low yields of the aryl methyl product **(III)** **(Scheme 23)**.



Scheme 23 Yuan's postulated mechanism for the methylsulfonylation of aryl halides with DMSO.

1.3 Dehydrogenation

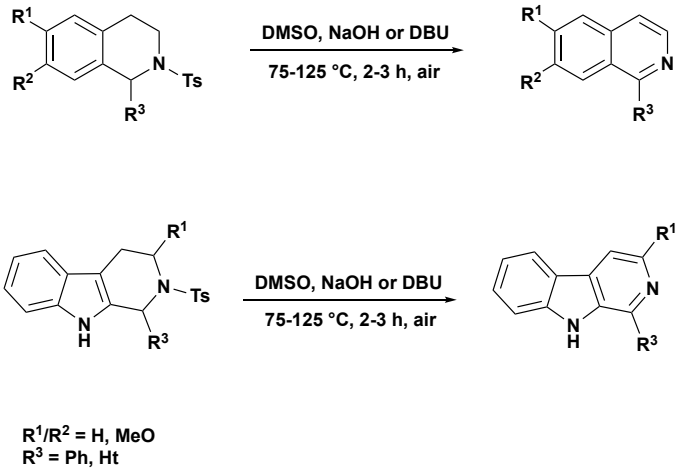
In 2016, Feng and co-workers reported a rare oxidation reaction of tetrahydroisoquinolines performed in *N,N*-dimethylformamide (DMF).[28] According to the authors, by simply stirring the substrates in DMF at 100 °C for 24 h under air, the corresponding 3,4-dihydroisoquinolines can be obtained in high yield and with high chemoselectivity **(Scheme 24)**. In a single experiment, air was carefully excluded from the reaction system. Even in these conditions the product was obtained in excellent yields. Although, DMF appeared to be the solvent of choice, it was also reported that the reaction worked in DMSO. However, only a single example was described, and no detailed solvent effects were examined.



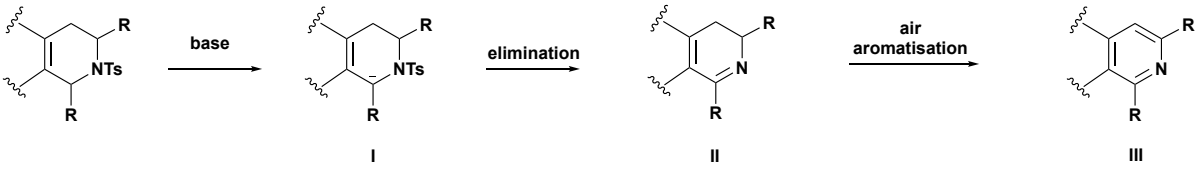
Scheme 24 Feng's DMF and DMSO-promoted thermal dehydrogenation.

The authors provided 18 examples of tetrahydroisoquinolines for this reaction in DMF. Nevertheless, extension of the reaction to other amines failed. The gas composition of the reaction system was analysed by Temperature Programmed Desorption-Mass Spectrometry (TPD–MS), and the signal for hydrogen gas (*m/z* = 2) was detected. However, the mechanism remained unclear.

In 2010, Dong and co-workers reported that treatment of *N*-tosyltetrahydroisoquinolines and *N*-tosyltetrahydro-β-carbolines with NaOH or DBU in DMSO at high temperature resulted in the corresponding isoquinolines and β-carbolines **(Scheme 25)**.[29] The authors suggested that the substrates first react with the base to create an anion **(I)**. This then undergoes β-elimination to give the partially dehydrogenated product **(II)** as intermediates. The final products **(III)** are achieved after oxidation by molecular oxygen **(Scheme 26)**. Nevertheless, the authors did not report any proof or experiment to support this hypothesis.

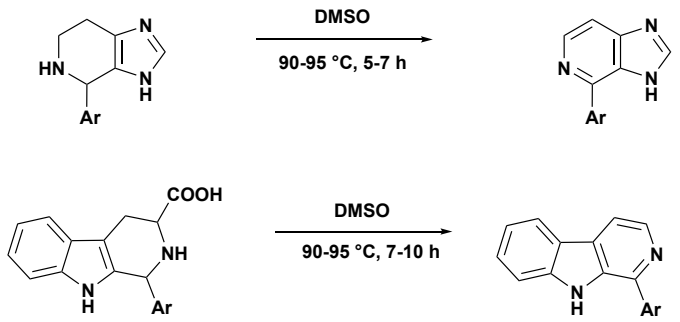


Scheme 25 Dong's conversion of *N*-tosyl-THIQ and *N*-tosyl-THBC into isoquinolines and β-carbolines in DMSO.



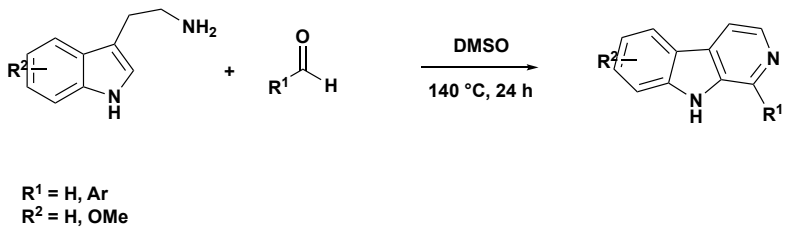
Scheme 26 Putative mechanism for Dong's conversion.

In 2014, Lomov and co-workers reported a similar reaction.[30] More specifically, they isolated the dehydrogenation and decarboxylation products of spinacine and carboline derivatives when the precursors were heated in DMSO at 90 – 95 °C **(Scheme 27)**. No explanation was attempted.



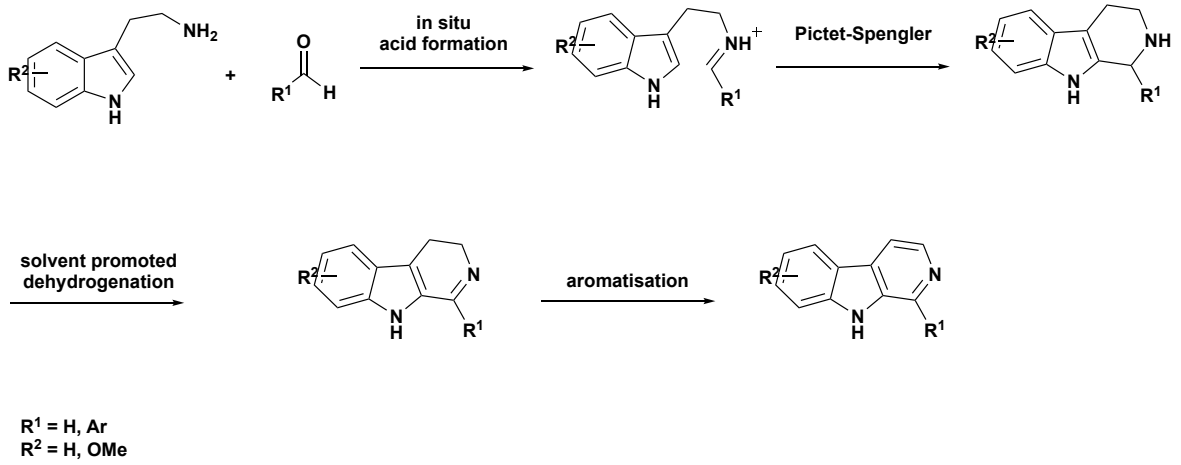
Scheme 27 Dehydrogenation of spinacine and carboline derivatives in DMSO.

Recently, an efficient one-pot β-carboline synthesis was reported involving a domino Pictet-Spengler reaction and aromatisation in DMSO.[31] β-Carbolines were obtained after heating tryptamine and an aldehyde in DMSO at 140 °C for 24 h **(Scheme 28)**. The transformation showed a great tolerance of functional groups.



Scheme 28 Metal-free one pot synthesis of β-carbolines in DMSO.

In an attempt to understand the mechanism, the authors heated every single intermediate independently. They observed the formation of the imine and cyclisation followed by aromatisation. Numerous reports in the literature reveal that the Pictet-Spengler reaction requires acid catalysis for both the imine formation and the cyclisation.[32] Since no acid was added in this study, the authors assumed that the acid needed to catalyse the Pictet-Spengler reaction was formed in *situ* by oxidation of the aldehyde **(Scheme 29)**.

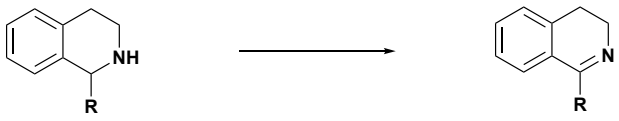


Scheme 29 Synthesis of β-carbolines *via* a domino Pictet-Spengler reaction and aromatisation.

1.4 Aims and Objectives

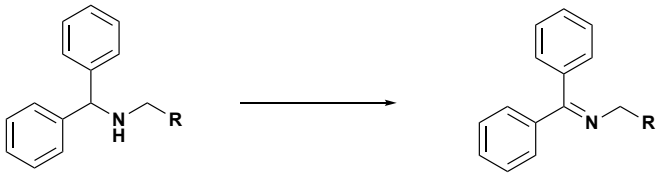
The dehydrogenation of organic compounds is of pivotal importance for both the fine chemical and pharmaceutical industries. Furthermore, it is also attracting attention for its potential application as liquid organic hydrogen carriers (LOHCs).[33] More specifically, the dehydrogenation of *N*-heterocycles has been at the centre of a broad research effort in the last few years because the introduction of a *N*-heteroatom into the ring can reduce the enthalpy, making the reaction less thermodynamically unfavourable.[34] The release of H_2 contributes positively to the entropic factor.

The introduction of C=N functionalities is traditionally performed *via* transition metals.[34,35] However, most of these systems show poor functional group tolerance, and the lack of mechanistic understanding makes the tuning of the catalyst difficult. The pharmaceutical industry avoids metals due to increased restrictions on trace-metal impurities. For these reasons, we posed as an objective the development of a new green protocol for the dehydrogenation of cyclic and acyclic amines with no need for a metal catalyst **(Scheme 30)**. More specifically, our substrates are based mainly on the 1,2,3,4-tetrahydroisoquinoline structure, naturally contained in several plants.[36] Isoquinolines represent an important class of alkaloids with antimicrobial, antimalarial, cytotoxic, and anti-HIV properties.[37]



Scheme 30 Dehydrogenation of cyclic amines.

However, we aim to extend the substrate scope to acyclic amines as well. For acyclic amines, our main focus is a structure based on benzhydrylic substrates **(Scheme 31)**. These substrates were chosen for their utility as a protecting group.



Scheme 31 Dehydrogenation of acyclic amines.

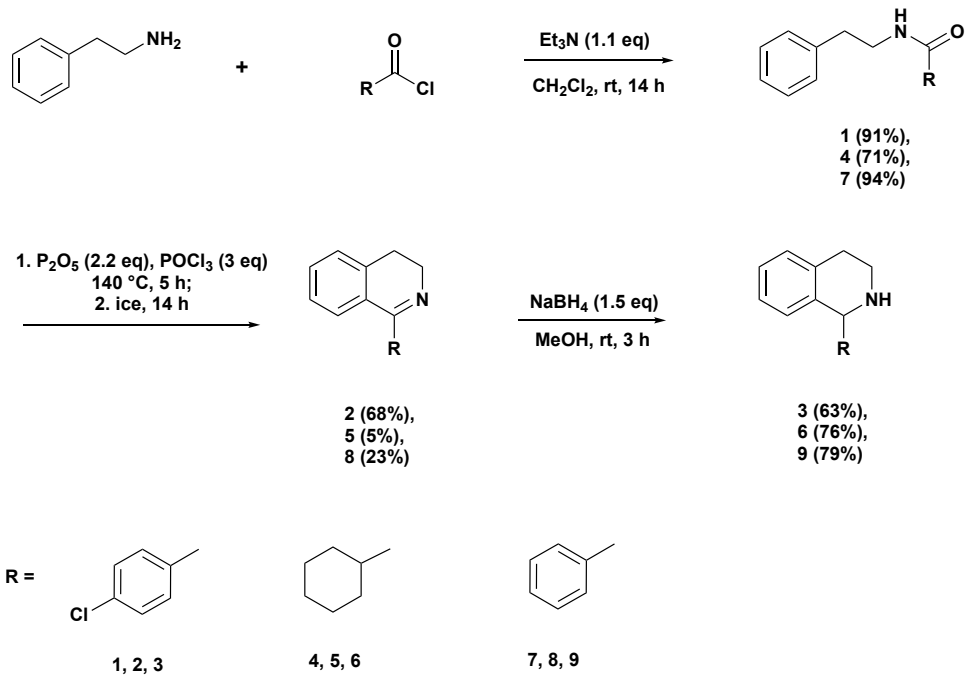
We also aimed to explore different conditions to gauge the system to achieve the best performance. Last but not least, we aim to understand the mechanism of the reaction.

2 Results and Discussion

This results Chapter has been divided into three Sections. The first Section (Section 2.1) discusses the substrate scope of the reaction. In the second Section (Section 2.2), the stoichiometry is studied; the last Section (Section 2.3), describes investigations into the mechanism of the reaction.

2.1 Substrate scope

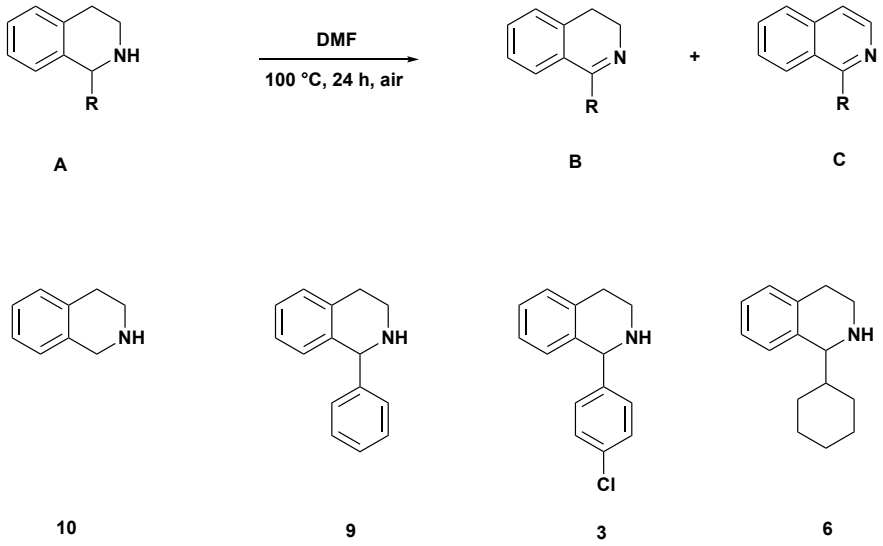
To begin our project on the thermal dehydrogenation of organic compounds, we started by repeating the literature protocol described by Feng and co-workers.[28] Thus, several tetrahydroisoquinolines were synthesised according to a literature procedure **(Scheme 32)**.[38] In the first step of the synthesis, phenethylamine was reacted with the corresponding benzoyl chloride in dichloromethane. In the second step, $POCl_3$ (3 eq.) and P_2O_5 (2.2 eq.) were added to the *N*-phenethylbenzamide in xylene. Finally, sodium borohydride (1.5 eq.) was added to the solution of 3,4-dihydroisoquinoline in methanol. After that, the reaction mixture was stirred at room temperature for 3 h, and the solvent concentrated. After purification by column chromatography, the corresponding 1,2,3,4-tetrahydroisoquinoline was isolated.



Scheme 32 Synthesis of various 1,2,3,4-tetrahydroisoquinolines.

Once the substrates were synthesised, they (0.1 mmol) were dissolved in anhydrous DMF (1 mL). Subsequently, the reaction flask was heated to 100 °C for 24 h under air. At the end, the reaction mixture was directly analysed by GC–MS, revealing that the thermal dehydrogenation was working effectively. However, several unidentified by-products were also observed. These were likely to have been formed from DMF decomposition, since it is well known that DMF may serve as a multipurpose building block for various units such as -CO, -NMe_2, -$CONMe_2$, -CHO, etc.[39] For this reason, even if the target products were formed, the corresponding yields were low. When the unsubstituted tetrahydroisoquinoline **10** was used, the reaction gave an extremely complex mixture **(Table 1, entry 1)**. When 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** was used, the partially dehydrogenated product was generated in reasonable yield (68%). Literature yields are higher (83%) **(Table 1, entry 2)**.[28] A large difference between our reaction and the literature reaction was noted with 1-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline **3** **(Table 1, entry 3)**. In our case, it gave mainly starting material (83%) whilst according to Feng and co-workers, the reaction went almost to completion (88%).[28] 1-Cyclohexyl-1,2,3,4-

tetrahydroisoquinoline **6** gave the product with very high selectivity (99%) **(Table 1, entry 4)**. Feng and co-workers performed the reaction of this substrate at lower temperature.[28] Therefore, a direct comparison is not possible. However, they also reported a good yield of dehydrogenation product for substrate **6** (64%).

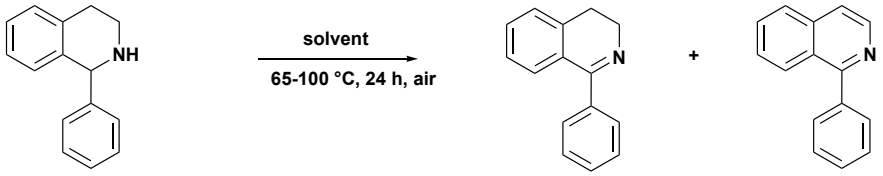


Entry	Substrate R	Product A:B:C GC–MS Ratio (%)	Literature (%) yields of B[28]
1	H **10**	39 : 60 : 0	–
2	Ph **9**	28 : 68 : 1	83
3	4-ClC_6H_4 **3**	83 : 12 : 5	88
4	Cy **6**	< 1 : 99 :0	64[a]

Table 1 Reaction of various tetrahydroisoquinolines in DMF, 100 °C, 24 h under air. Ratio of the peaks according to GC–MS. [a] 80 °C.

With these first encouraging results in hand, we decided to try to improve the reaction efficiency. It was decided that solvent, time, and temperature were all parameters that needed much closer inspection. It was interesting to see in which solvent the reaction performed best.

Therefore, a solvent survey was conducted. For this, the commercial 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** was chosen as the standard substrate. 1-Phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) was dissolved in the elected solvent (3 mL) and the reaction mixture was heated to 100 °C for 24 h under air. Solvents such as acetonitrile and methanol were considered because of their polarity, but because they have a low boiling point, in this case the reaction was conducted under reflux. Nevertheless, the dehydrogenation reaction of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** failed to give any product **(Table 2, entries 1 and 2)**. Toluene is a common laboratory solvent with a higher boiling point. However, it completely thwarted the reaction outcomes as well **(Table 2, entry 3)**. According to the literature, ethylene glycol, 1,2-dichlorobenzene, and *N*-methyl-2-pyrrolidone (NMP) worked partially in similar reactions.[31] In agreement with this study, ethylene glycol gave the partially dehydrogenated product in very low yield (10%) **(Table 2, entry 4)**, whilst better results were achieved with 1,2-dichlorobenzene (76%), *N*-methyl-2-pyrrolidone (57%), and acetamide (60%) **(Table 2, entries 5 – 7)**. DMSO provided excellent results **(Table 2, entries 8)**. DMSO was elected as solvent of choice due to its excellent results.



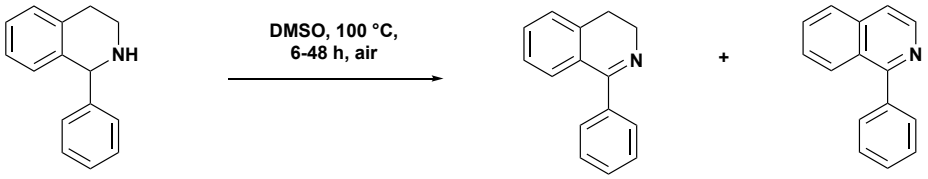
9 8 17

Entry	Solvent	Temperature (°C)	Product 9:8:17 GC–MS Ratio (%)
1	CH_3CN	80	100 : 0 : 0
2	MeOH	65	100 : 0 : 0
3	toluene	100	93 : 7 : 0
4	ethylene glycol	100	89 : 10 : 0
5	1,2-dichlorobenzene	100	24 : 76 : 0
6	NMP	100	43 : 57 : 0
7	acetamide	100	34 : 60 : 3
8	Dry DMSO	100	0 : 97 : 3

Table 2 Solvent survey. Reaction of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) in the elected solvent (3 mL), 100 °C, 24 h under air. Ratio of the peaks according to the GC–MS.

After the solvent survey, we performed the reaction for different times and with different temperatures to find the best conditions. First, 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) was heated to 100 °C in DMSO under air (3 mL) for different lengths of time **(Table 3)**. The idea was to discover if the reaction necessarily needs 24 h to go to completion. Furthermore, it would have been interesting to verify if, by leaving the reaction longer, the selectivity could have been more finely tuned between the partially dehydrogenated product **8** and the totally dehydrogenated by-product **17**. The reaction in a timeframe of 6 h yielded the partially dehydrogenated product **8** in very low yield (18%) **(Table 3, entry 1)**. After 12 h, the dehydrogenated product **8** was present in 52% yield, with no traces of the total

dehydrogenated by-product **17 (Table 3, entry 2)**. After 18 h, the partially dehydrogenated product **8** was present in high yield (88%) **(Table 3, entry 3)**. After 24 h, the partially dehydrogenated product **8** was the only product present (97%) **(Table 3, entry 4)**. The reaction did not yield more isoquinoline **17** after 48 h (1%) **(Table 3, entry 5)**. It was clear that a longer length of time does not improve the selectivity towards the totally dehydrogenated by-product **17**. Therefore, 24 h was selected as the standard reaction time.



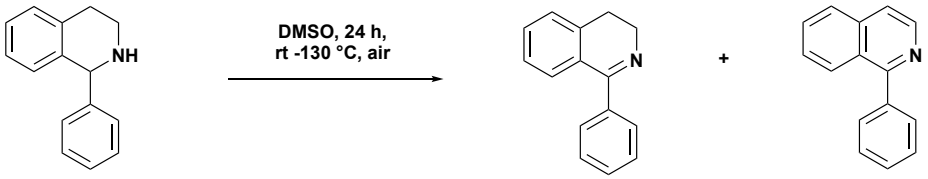
9 **8** **17**

Entry	Time (h)	Product 9:8:17 GC–MS Ratio (%)
1	6	81 : 18 : 0
2	12	47 : 52 : 0
3	18	1 : 88 : 11
4	24	0 : 97 : 3
5	48	30 : 69 : 1

Table 3 Time study. Reaction of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) in DMSO (3 mL), 100 °C, under air. Ratio of the peaks according to the GC–MS.

Secondly, the same reaction mixture was heated for the same amount of time at different temperatures **(Table 4)**. The question was at which temperature the reaction started, and if the selectivity between the partially dehydrogenated product **8** and the totally dehydrogenated by-product **17** could be tuned with a higher temperature. When 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) was heated in DMSO (3 mL) for 24 h at different

temperatures, the following data were collected. At room temperature and up to 70 °C, the reaction fails completely **(Table 4, entries 1 and 2)**. At 80 °C, the reaction gives a good yield of partially dehydrogenated product, however there is still some starting material **(Table 4, entry 3)**. At 90 – 100 °C, all of the starting material is consumed **(Table 4, entries 4 – 5)**. At higher temperature, the reaction outcome does not increase the formation of the totally dehydrogenated isoquinoline **(Table 4, entry 6)**. Therefore, 100 °C was selected as the standard temperature.

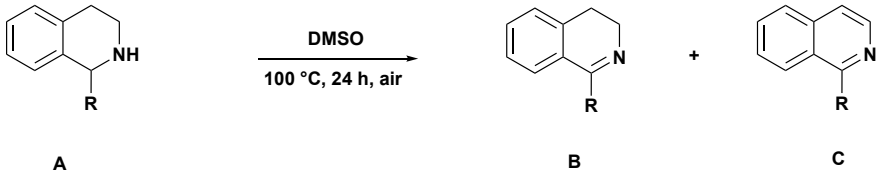


9 **8** **17**

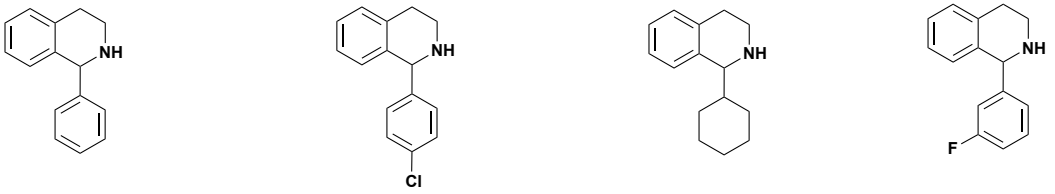
Entry	Temperature (°C)	Product 9:8:17 GC–MS Ratio (%)
1	21	100 : 0 : 0
2	70	99: < 1 : 0
3	80	5 : 95 : 0
4	90	0 : 91 : 9
5	100	0 : > 97 : < 3
6	130	3 : 89 : 7

Table 4 Temperature study. Reaction of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) in DMSO (3 mL), 24 h under air. Ratio of the peaks according to the GC–MS.

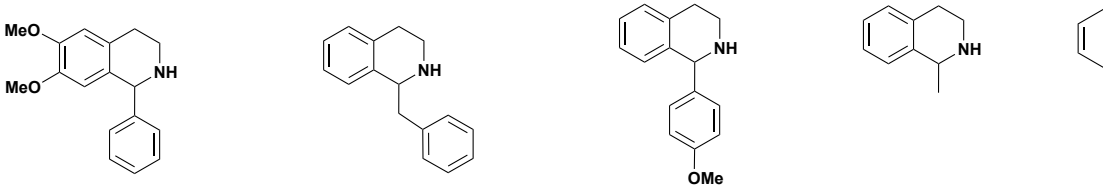
Slight differences in yield or selectivity are probably due to the quality of DMSO. DMSO is very hygroscopic. DMSO purity was regularly assessed by putting it in the fridge. Even a small amount of water reduces the DMSO freezing point drastically.[40] Therefore, if DMSO was not solidifying in the fridge, water may have been a contaminant. Another problem present in commercial DMSO is represented by molecular sieves. Molecular sieves are commonly used in dry DMSO bottles. However, they are slightly acidic. Acid can thwart the reaction outcome as shown in **Table 11**. Nevertheless, the best results for this reaction are obtained when using dry DMSO from a bottle without molecular sieves. From now on, if not otherwise stated, the reaction will be always performed under standard conditions. Under the established standard conditions, the substrates (0.48 mmol) were dissolved in dry DMSO (1 mL) and the mixture heated for 24 h at 100 °C. These standard conditions were applied to study the substrate scope. Substrates **9**, **3**, and **16** gave the product in excellent yield. Therefore, in these cases, the products were isolated by simply evaporating the DMSO. The isolated yields corresponded to the GC–MS yields **(Table 5, entries 1, 2, and 9)**. Substrates **6** and **11** gave the corresponding partially dehydrogenated products in moderate yield **(Table 5, entries 3 and 4)**. Substrate **13** gave the product in low yield **(Table 5, entry 6)**. However, the reaction did not work at all on substrates **12** and **14 (Table 5, entries 5 and 7)** probably because of the very electron-rich aromatic unit.



A B C



9 3 6 11



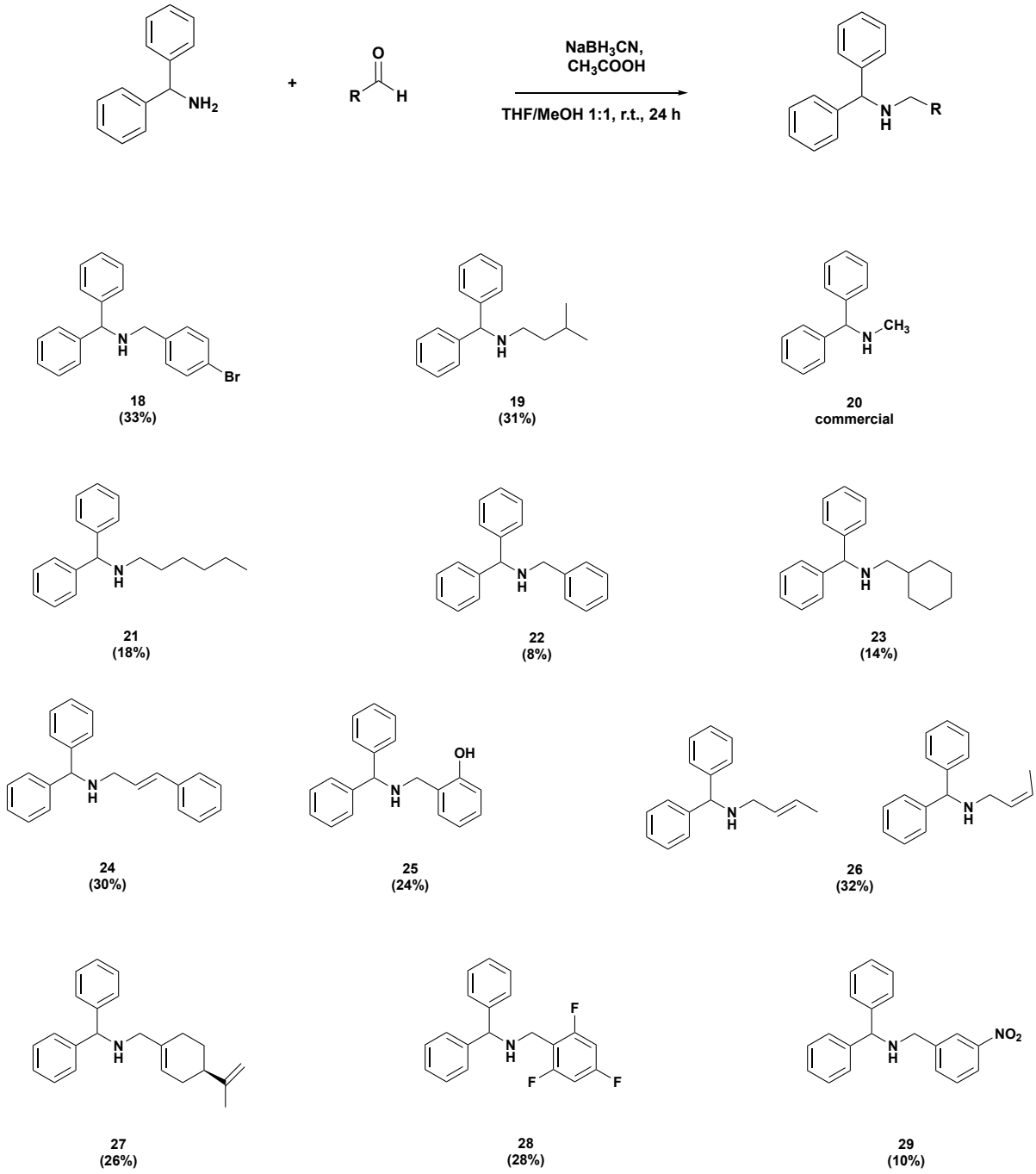
12 13 14 15 16

Entry	Substrate	Product A:B:C GC–MS Ratio (%)	Isolated yields % of B
1	**9**	0 : > 97 : < 3	95
2	**3**	0 : > 97 : 0	97
3	**6**	< 2 : 80 : 18	
4	**11**	22 : 77 : 0	
5	**12**	> 99 : 0 : 0	
6	**13**	84 : 16 : 0	
7	**14**	99 : 0 : 0	
8	**15**	< 1 : > 99 : 0	
9	**16**	< 3 : > 97 : 0	97

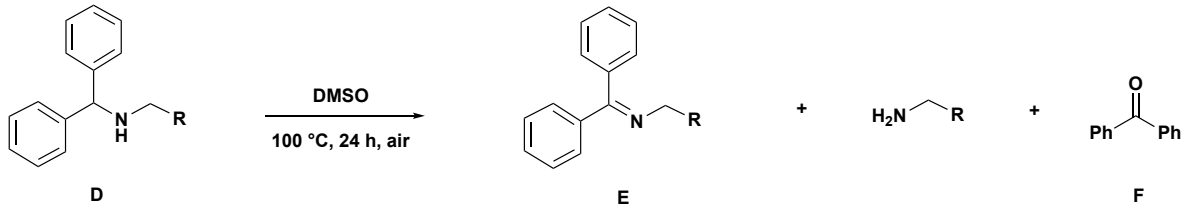
Table 5 Substrate scope for different substituted 1,2,3,4-tetrahydroisoquinolines.

Ratio of the peaks according to the GC–MS.

Subsequent to the tetrahydroisoquinoline substrates, it was decided to try the dehydrogenation reaction on benzhydrylamines. These substrates were chosen because the diphenylmethyl (DPM) group is a protecting group used primarily for carboxylic acids, alcohols and amines. Its removal is traditionally achieved with conditions such as Pd/C and hydrochloric acid or using an excess of triethylsilane in trifluoroacetic acid.[41,42] These conditions often lead to the cleavage of other functionalities with subsequent degradation of the substrate. If our protocol would have worked also on acyclic substrates, the corresponding imines would be obtained. Imines are not only interesting substrates *per se*, but diphenylmethyl imines can be easily hydrolysed afterwards with a simple acid treatment, thus releasing the corresponding free amines. Therefore, several benzhydrylamines were synthesised by alkylation of benzhydrylamine according to a literature procedure.[43] This was achieved by stirring the diphenylmethylamine with the chosen aldehyde in a mixture of THF/MeOH for 1 h, with subsequent addition of sodium cyanoborohydride and acetic acid **(Scheme 33)**. After purification, the substrates were ready to undergo the dehydrogenative reaction. The alkylated benzhydrylamines (0.3 mmol) were dissolved in DMSO (1 mL) and heated to 100 °C for 24 h under air. The reaction outcomes were again analysed by GC–MS, and the results are presented in **Table 6**. The reaction works on a wide range of substrates. However, there are only a few cases in which the starting material is above 90% at the end of the reaction **(Table 6, entries 2,4, and 11)**. For all the other substrates, the reaction gives a mixture of dehydrogenated imines and benzophenone **(Table 6, entries 1, 3, 5 – 10, and 12)**.



Scheme 33 Synthesis of benzhydrylamines.



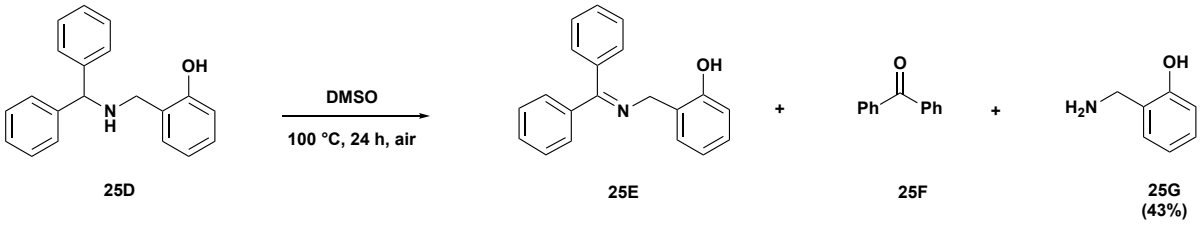
Entry	Substrate	Product D:E:F GC–MS Ratio (%)
1	**18**	**D** 53%, **E** 30%, **F** 17%
2	**19**	**D** 95%, **F** 2%
3	**20**	**D** 18%, **E** 64%, **F** 18%
4	**21**	**D** 99%
5	**22**	**D** 27%, **E** 27%, **F** 46%
6	**23**	**E** 69%, **F** 28%
7	**24**	**E** 6%, **F** 90%
8	**25**	**E** 14%, **F** 86%
9	**26**	**E** 50%, **E** 30%, **F** 20%
10	**27**	**D** 31%, **F** 66%
11	**28**	**D** 100%
12	**29**	**E** 39%, **F** 60%

Table 6 Dehydrogenation reaction on benzhydrylic substrates in DMSO.

Ratio of the peaks according to the GC–MS.

To our surprise, the reaction of alkylated benzhydrylamines often gave benzophenone such as on substrates **18F, 20F, 22F – 27F, 29F (Table 6, entries 1, 3, 5 – 10, and 12)**. This means that the reaction product is a mixture of the corresponding imine and free amine. Therefore, the cleavage of the benzhydrylic protecting group is already in place, eliminating the need for the following acid-treatment step, as was foreseen at

the outset. However, the corresponding free amines were not observed by GC–MS. This was probably due to the amine incapacity to run in the column. As a proof of concept, it was decided to isolate a sample of free amine. Thus, 2-((benzhydrylamino)methyl)phenol **25D** was heated in dry DMSO to 100 °C for 24 h under air. At the end of the reaction, no acid treatment was used during the work-up. In fact, excess of water was added, and the products were extracted into CH_2Cl_2 **(Scheme 34)**.



Scheme 34 Synthesis of 2-hydroxybenzylamine.

The TLC of the reaction mixture clearly revealed the spots of the corresponding imine **25E** and the benzophenone **25F**, but after treatment with a ninhydrin solution another spot **25G** appeared at the bottom of the TLC plate. This corresponds to the commercial 2-hydroxybenzylamine that was used as a reference **(Fig. 1)**.

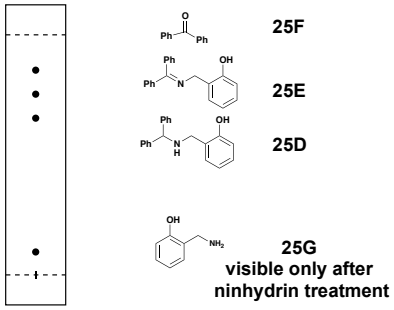


Fig. 1 TLC of 2-((benzhydrylamino)methyl)phenol reaction mixture in pure ethyl acetate.

Subsequently, the crude reaction mixture was purified by column chromatography, and 2-hydroxybenzylamine **25G** was isolated in 43% yield and confirmed by ^{1}H and ^{13}C-NMR spectroscopy **(Appendix Fig. A6–A7)**. The fact that 2-hydroxybenzylamine is at the bottom of the TLC plate proves the hypothesis that this kind of substrates does not run properly in the GC–MS. Furthermore, also the purification step by column chromatography proved to be extremely challenging. The newly isolated free amine and its commercial reference shows the same retention time *via* HPLC **(Fig. 2 and 3)**, and the same fragmentation pattern **(Fig. 4 and 5)**. More specifically, the molecular ion (*m/z* 124.07) is hardly visible in both of them. In fact, it is well known that benzylic cations rearrange into tropylium ions (*m/z* 107.05) **(Scheme 35)**.[44]

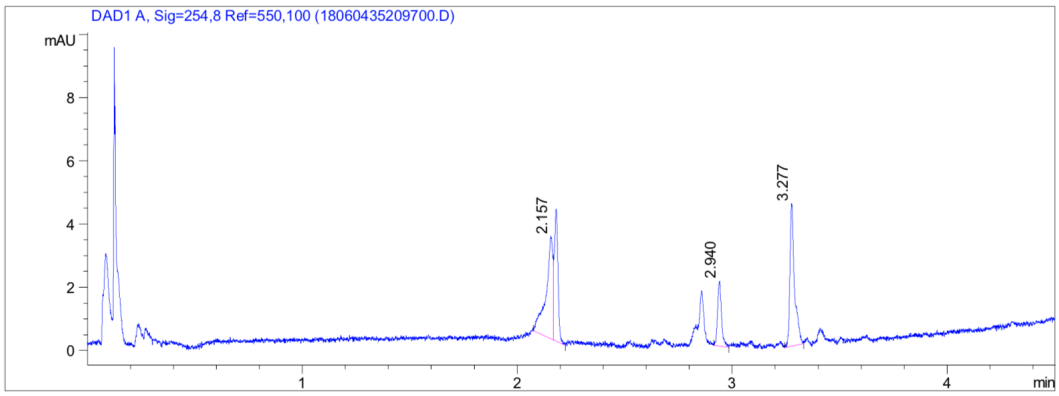


Fig. 2 Retention time by LC-MS of 2-hydroxybenzylamine after purification of reaction mixture.

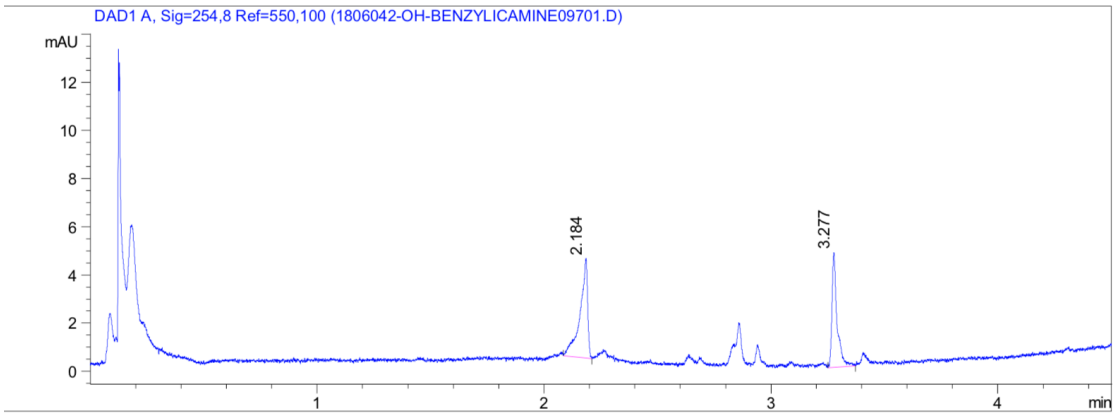


Fig. 3 Retention time by LC-MS of commercially available 2-hydroxybenzylamine.

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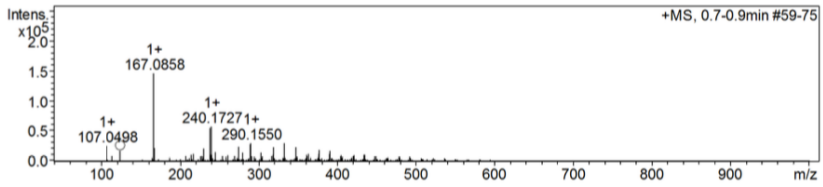
Sample-ID	f_spa_salicylamide	Lab	C13
Submitter	Francesca Spagna	Supervisor	Chris Moody
Analysis Name	f_spa_salicylamide_550008_17_01_46382.d	Acquisition Date	6/2/2017 1:49:13 PM
Ionisation Mode	ESI Positive	Instrument	Bruker MicroTOF

+MS, 0.7-0.9min #59-75



#	m/z	I %
1	107.0498	17.1
2	124.0764	12.3
3	167.0858	100.0
4	168.0884	15.3
5	231.1190	14.4
6	238.1593	37.6
7	240.1727	39.1
8	245.1298	10.5
9	275.1463	17.0
10	280.2063	9.5
11	289.1590	18.9
12	290.1550	20.7
13	303.1670	10.1
14	319.1715	16.0
15	333.1870	20.3
16	347.1982	16.1
17	363.1983	8.1
18	376.2306	8.4
19	377.2145	12.6
20	391.2279	11.8

Generate Molecular Formula Parameters

Charge	Tolerance	sigma limit	H/C Ratio	Electron Conf.	Nitrogen Rule	Chrom.BackGround	Calibration
+1	12 ppm	0.08	3 - 0	both	false	false	TRUE

Expected Formula C7 H9 N1 O1 **Adduct(s):** H, Na, NH4, C3H5N2, radical

#	meas. m/z	theo. m/z	|Err|[ppm]	Sigma	Formula	Adduct	Adduct Mass
1	124.0764	124.0757	5.40	0.0031	C7H10NO	M+H	1.0078

Note: Sigma fits < 0.05 indicates high probability of correct MF

Fig. 4 Mass Spectrum 2-hydroxybenzylamine after purification of reaction mixture.

Mass Spectrometry
Analytical Services
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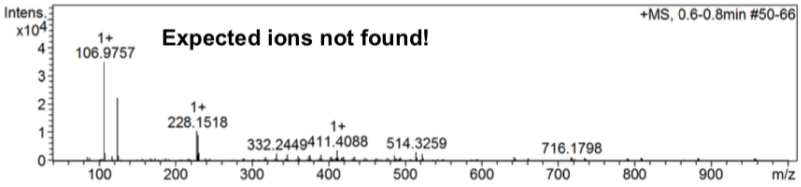
The University of Nottingham

Sample-ID	f_spa_2-hydroxybenzylamine	Lab	C13
Submitter	Francesca Spagna	Supervisor	Chris Moody
Analysis Name	f_spa_2-hydroxybenzylamine_5676_22_0 1_61241.d	Acquisition Date	6/4/2018 12:01:49 PM
Ionisation Mode	ESI Positive	Instrument	Bruker MicroTOF

+MS, 0.6-0.8min #50-66



#	m/z	I %
1	106.9757	100.0
2	107.9811	8.2
3	116.9348	4.9
4	124.0390	63.6
5	125.0436	5.3
6	228.1518	30.4
7	229.1541	5.7
8	230.1672	26.3
9	231.1686	7.9
10	332.2449	7.8
11	346.2476	6.8
12	360.2395	4.7
13	374.2426	4.9
14	376.2534	6.1
15	390.2588	6.3
16	411.4088	10.7
17	434.2672	4.4
18	486.2269	5.6
19	514.3259	8.9
20	522.3870	7.1

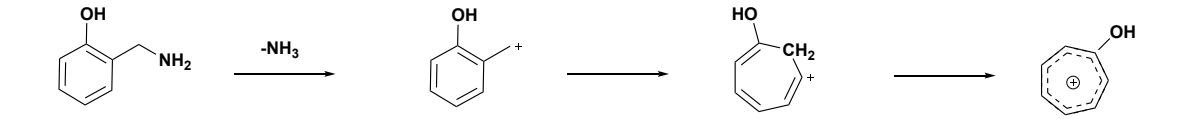
Generate Molecular Formula Parameters

Charge	Tolerance	sigma limit	H/C Ratio	Electron Conf.	Nitrogen Rule	Chrom.BackGround	Calibration
+1	12 ppm	0.08	3 - 0	both	false	false	TRUE

Expected Formula C7 H9 N1 O1 **Adduct(s):** H, Na, NH4, C3H5N2, radical

Note: Sigma fits < 0.05 indicates high probability of correct MF

Fig. 5 Mass Spectrum of commercially available 2-hydroxybenzylamine.



Chemical Formula: C_7H_9NO
M**+H:** $C_7H_{10}NO$
m/z: 124.07

Chemical Formula: $C_7H_7O^+$
m/z: 107.05

Chemical Formula: $C_7H_7O^+$
m/z: 107.05

Chemical Formula: $C_7H_7O^+$
m/z: 107.05

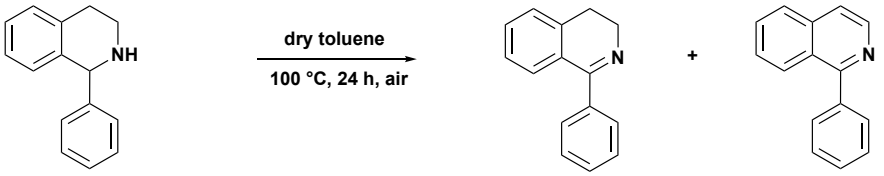
Scheme 35 Tropylium cation rearrangement.

When the reaction was performed on *N*-(4-bromobenzyl)-1,1-diphenylmethanamine **18**, the corresponding free-amine was formed and, therefore, detected by GC–MS **(Appendix Fig. A8 – A11)**.

One of the main problems in handling benzhydrylic substrates was their susceptibility to air. Generally, they are a yellowish oil. However, in contact with air they change appearance into a white powder. This process may take anywhere between a few minutes and a few days, depending on the exact substrate. Once they solidify, they do not solubilise in anything except water. According to the literature, this observation is in agreement with the reaction of amines with carbon dioxide.[45]

2.2 Studies on the stoichiometry of the reaction

At this point, it was decided to study the stoichiometry of the reaction with respect to the amount of DMSO. Again, 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) was used as the standard substrate. Reactions were performed in dry toluene (3 mL). Toluene was chosen as the reaction medium because it proved to be an inert solvent to the reaction. DMSO was added in different amounts. The reaction vessel was heated to 100 °C for 24 h. With only 0.5 eq. of DMSO, the reaction hardly proceeded **(Table 7, entry 1)**. When DMSO was added in only 1 eq. compared to the substrate, we found the product **8** present in 46% whilst the remaining 53% is starting material **9 (Table 7, entry 2)**. With 2 eq. of DMSO, the reaction proceeded only slightly further, with the starting material **9** at 40% and the product **8** at 59%. Interestingly, when performed under argon, only starting material **9** was seen **(Table 7, entry 3)**. With 5 eq. of DMSO, the starting material **9** was almost consumed as it was present only in 14%, whilst the product **8** gave very high yield with 86% **(Table 7, entry 4)**. However, it is only with 10 eq. of DMSO that product **17** starts to be present in traces, whilst product **8** was formed in high yield (90%) and the starting material **9** is present in small amount (6%) **(Table 7, entry 5)**. From these results, it was evident that the reaction is dependent upon the quantity of DMSO and the presence of air.

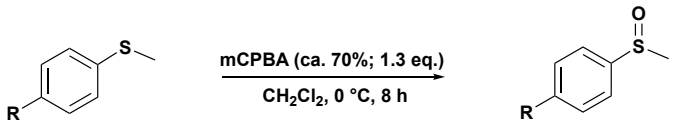


9 8 17

Entry	Equivalents of dry DMSO	GC–MS relative (%) Ratio
1	0.5	**9** 96%, **8** 4%
2	1	**9** 53%, **8** 46%
3	2 (Argon)	**9** 40%, **8** 59% (**9** 99%)
4	5	**9** 14%, **8** 86%
5	10	**9** 6%, **8** 90%, **17** 3%

Table 7 Stoichiometry of DMSO. Reaction of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** in toluene, 100 °C, 24 h under air. Ratio of the peaks according to the GC–MS.

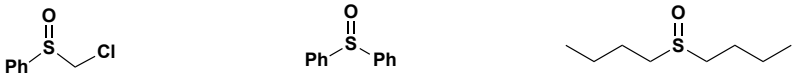
At this point, it was interesting to see if the reaction would depend not only on the quantity of sulfoxide, but also on its structure type. Therefore, DMSO was replaced with a range of different sulfoxides. Sulfoxides **30 – 39** were tested. Of these, only sulfoxides **37** and **38** were prepared in house **(Scheme 36)**. All the others are commercial products. Sulfoxides **37** and **38** were prepared by treating the corresponding sulfides with *m*CPBA at 0 °C for 8 h.



37 R = OMe (48%)
38 R = CF_3 (67%)

Scheme 36 Synthesis of sulfoxides **37** and **38**.

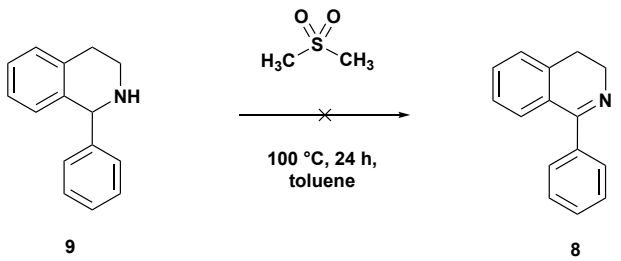
Chloromethyl phenyl sulfoxide **30**, diphenyl sulfoxide **31**, and dibutyl sulfoxide **32** were chosen for their steric hindrance. When sulfoxides **30 – 32** were used, no reaction was observed **(Scheme 37)**. These results were especially surprising for butyl sulfoxide, because its electronic properties are expected to be similar to those of DMSO.



30 **31** **32**

Scheme 37 Unreactive sulfoxides.

Dimethyl sulfone was also tested because it has a structure similar to DMSO, but with two oxygens instead of one. It would have been interesting to see how the addition of a second oxygen atom would influence the reaction outcome. However, dimethyl sulfone was found not to give any product after several attempts **(Scheme 38)**.

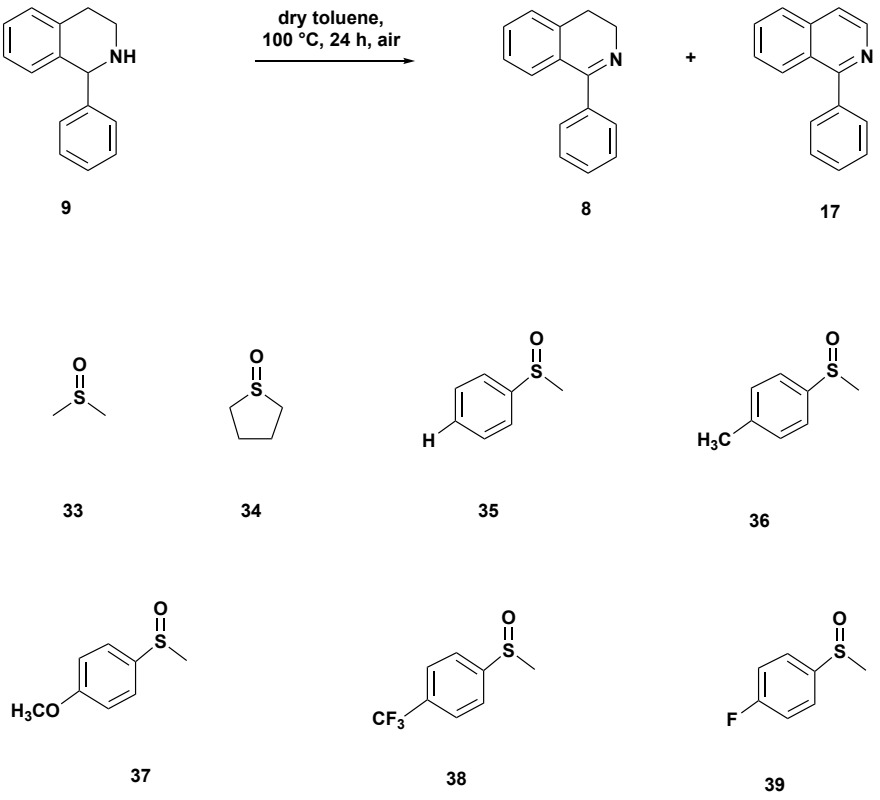


Scheme 38 Failed reaction with dimethyl sulfone.

When sulfoxides **30**, **31**, and **32** pictured in **Scheme 37** failed to produce any product, it was hypothesised that a methyl group next to the sulfoxide group was a key requirement for a successful reaction. Therefore, it was decided to try different sulfoxides with a structure that it was in some way related to DMSO, i.e. one of the substituents was a methyl group, whilst the other was a differently substituted aryl group. Thus, substrates from **35** to **39** were chosen **(Scheme 39)**.

On the basis of the aforementioned results with dibutyl sulfoxide **32**, tetrahydrothiophene-1-oxide **34** was thought likely to fail. Surprisingly, tetrahydrothiophene-1-oxide **34** was able to partially perform the reaction. In fact, only 2 eq. of sulfoxide with respect to the tetrahydroisoquinoline **9**, gives the product **8** in 25%. With 5 eq, the yield increases to 73%. With 10 eq. the outcome of the reaction was quite different. The yield decreased to 41% **(Table 8, entries 34 A - D)**. When methyl phenyl sulfoxide **35** was used, the outcome of the reaction was quite similar **(Table 8, 35 A – D)**. First of all, with only 1 eq. of sulfoxide, the reaction does not occur. The product **8** is present only in traces. However, with 2 eq. of sulfoxide, product **8** is present in 55%. Increasing the equivalents of sulfoxide to 5, the yield of product **8** increased again. However, increasing the number of sulfoxide equivalents to 10 had a deleterious effect on the reaction outcome. Differently from DMSO **33**, with methyl phenyl sulfoxide **35** the yield of product **8** decreased to 5%. Methyl *p*-tolyl sulfoxide **36**, gave no reaction with just 1 equivalent of sulfoxide as well. With 2 equivalents, the reaction gave the product **8** in low yield. Similarly to DMSO, when the reaction was performed under argon, it failed completely.

Increasing the equivalent of methyl *p*-tolyl sulfoxide to 5, the yield of product increased slightly. Similar to DMSO, increasing the equivalents to 10, gave the product **8** in 61%, whilst not achieving the same results as DMSO **(Table 8, entries 36 A – D)**. Methyl methoxyphenyl sulfoxide **37** did not give any reaction product **(Table 8, entries 37 A – D)**. Phenyl trifluoromethyl sulfoxide **38** gave the product **8** in traces when 1 or 2 equivalents were used. With 5 eq. the yield remained low. Increasing the equivalents to 10, the yield increased like with DMSO, but they remained not excellent achieving a maximum of 56% **(Table 8, entries 38 A – D)**. When 4-fluoro-phenyl methyl sulfoxide **39** was used, even with only 1 equivalent the reaction gave 29% of product **8**. Increasing the equivalents to 2 and 5, the yield increased to 36% and 47% respectively. However, once again, when 10 equivalents of sulfoxide **39** were used, the yield of product **8** decreased to 38% **(Table 8, entries 39 A – D)**.



Scheme 39 Reactive sulfoxides.

To summarise the key-finding found until this point, the reaction is both sensitive to the stoichiometry and to the type of sulfoxide. In fact, increasing the amount of DMSO in the reaction with the standard substrate 1,2,3,4-tetrahydroisoquinoline **9**, the amount of product 3,4-dihydroisoquinoline **8** increases accordingly. When different sulfoxides are used, the reaction works with different rates. Therefore, the reaction is also clearly dependent on the kind of sulfoxide employed. If we observe substrates from **35** to **39** of entry B of **Table 8**, it describes the effect of the substituent in the *para*-position of the phenyl group compared to neutral H **35** when the reaction is studied with 2 eq. of sulfoxide. More specifically, all substituents lead to a reduction of the product yields. The fact that certain sulfoxides reduce the yield of product when passing from 5 to 10 eq., (i.e. sulfoxides **34**, **35**, and **39**) is probably due to lack of solubility of the sulfoxide in the reaction medium.

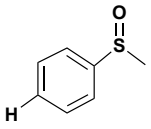
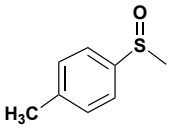
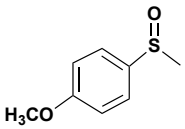
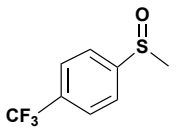
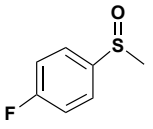
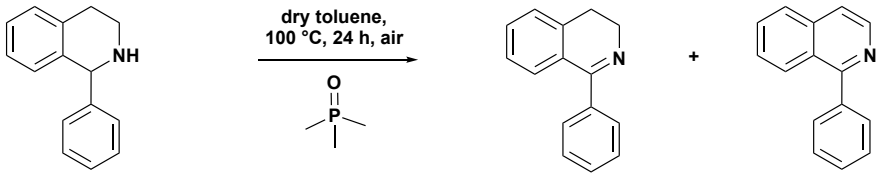
Entry	Equiv. of sulfoxide	**33**	**34**	**35**	**36**	**37**	**38**	**39**
								
A	1	**9** 53% **8** 46%		**9** 95% **8** 5%	**9** 94% **8** 5%	**9** > 99%	**9** > 99%	**9** 71% **8** 29%
B	2 (Argon)	**9** 40% **8** 59% (**9** 99%)	**9** 74% **8** 25%	**9** 45% **8** 55%	**9** 72% **8** 28% (**9** 99%)	**9** > 99%	**9** > 95% **8** < 5 %	**9** 62% **8** 36% **17** traces
C	5	**9** 14% **8** 86%	**9** 27% **8** 73%	**9** 24% **8** 76%	**9** 65% **8** 34%	**9** > 99%	**9** 68% **8** 32%	**9** 51% **8** 47% **17** traces
D	10	**9** 6% **8** 90% **17** 3%	**9** 59% **8** 41%	**9** 94% **8** 5%	**9** 38% **8** 61%	**9** > 99%	**9** 44% **8** 56%	**9** 62% **8** 38%

Table 8 Different sulfoxides with different stoichiometries. Dry toluene, 100 °C, 24 h, under air. Ratio of the peaks according to the GC–MS.

Next, we aimed to use a different heteroatom to replace the sulfur while maintaining the polarity. Our choice was the phosphorus atom. Therefore, we performed the reaction using trimethylphosphine oxide as a replacement of the sulfoxide group. To a solution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.47 mmol) in dry toluene (3 mL), different amounts of trimethylphosphine oxide **40** were added. The reaction mixture was heated to 100 °C for 24 h under air as usual. The results are described in **Table 9**. With just 0.5 eq. of trimethylphosphine oxide, the product **8** is already present in good yield, whilst with DMSO the product is totally absent **(Table 9, entry 1)**. However, with 1, 2, and 5 eq. of both phosphine oxide and DMSO, the yield of product **8** become comparable **(Table 9, entries 2 – 4)**. With 10 eq. of phosphine oxide, once again, the yield of product **8** is reduced, whilst with DMSO it increased even more **(Table 9, entry 5)**. Therefore, trimethylphosphine oxide proved that one of the main requirements for the reaction to succeed is to have a great polarity in its interaction.



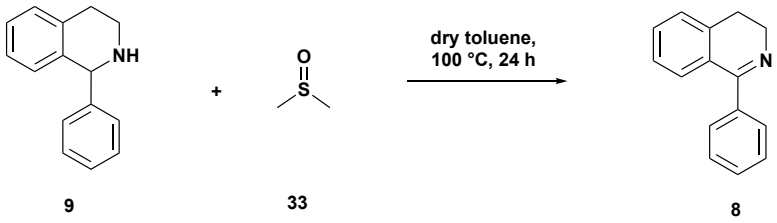
9 40 8 17

Entry	Equivalents	GC–MS ratio (%) with trimethyl phosphine oxide	GC–MS ratio (%) with dry DMSO
1	0.5	**9** 48% **8** 52%	**9** 96% **8** 4%
2	1	**9** 44% **8** 56%	**9** 53% **8** 46%
3	2	**9** 37% **8** 63%	**9** 40% **8** 59%
4	5	**9** 19% **8** 81%	**9** 14% **8** 86%
5	10	**9** 39% **8** 60%	**9** 6% **8** 90% **17** 3%

Table 9 Stoichiometry of trimethylphosphine oxide. Dry toluene, 100 °C, 24 h, under air.

Ratio of the peaks according to the GC–MS.

From these results, it is evident that the effectiveness of the sulfoxide is strongly dependent on the electronic properties. The reaction outcomes are clearly dependent not only on the specific sulfoxide in use, but also on its stoichiometry. Therefore, the presence of sulfoxide is necessary for achieving positive results. DMSO proved to be the best sulfoxide. If we plotted the disappearance of the starting material **9** at different concentrations of DMSO **33**, we obtain a curve **(Fig. 6)**. Also, if we plot the appearance of product **8** at different concentrations of DMSO **33**, we find the curve depicted in **Fig. 7**. When a similar plot was made with trifluoromethyl phenyl sulfoxide **38**, the results were similar **(Fig. 8** and **9)**. Once again, it is clear that the disappearance of **9** using sulfoxide **38** at different concentration gave a similar curve to the one of **Fig. 6**. Following the appearance of product **8**, the curve is again similar to the one depicted in **Fig. 7**. Nevertheless, the shapes of the curves for DMSO **32** are different from the shapes of curves for sulfoxide **38**. Therefore, it is clear that different sulfoxides with different electronic properties have different effects on the reaction outcomes.



9 33 8

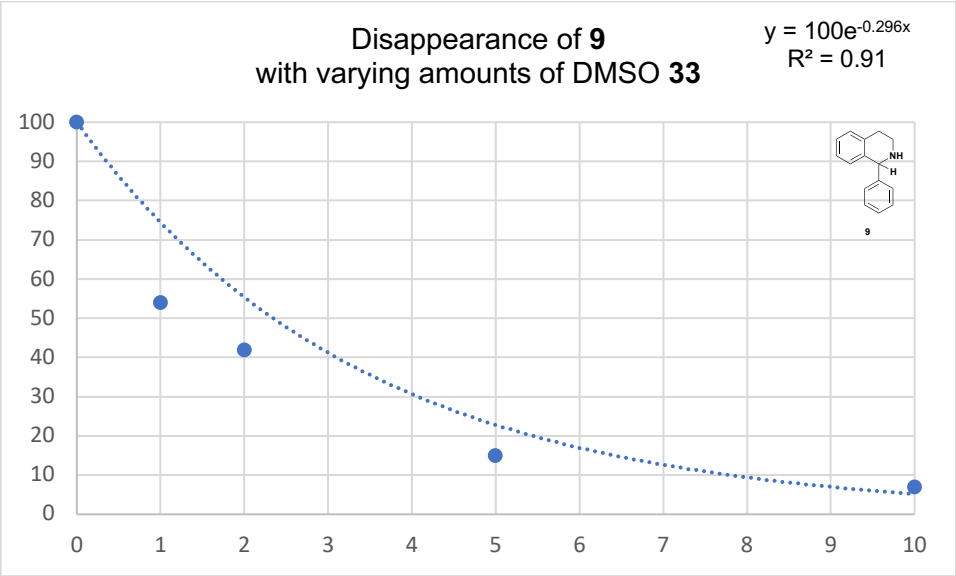


Fig. 6 X axis represent the equivalents of DMSO **33**; the Y axis represent the % of starting material **9** disappearing. R^2 is the goodness of fit.

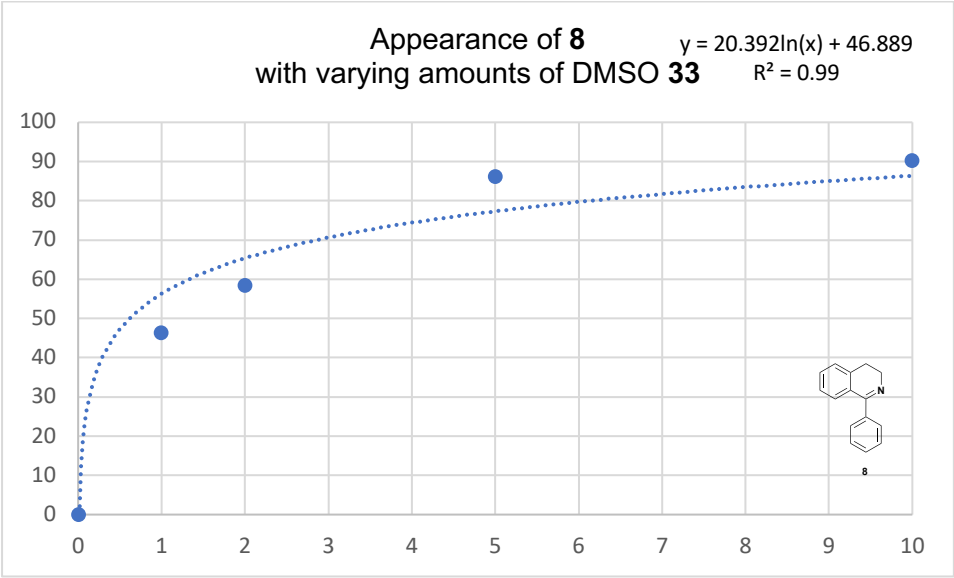
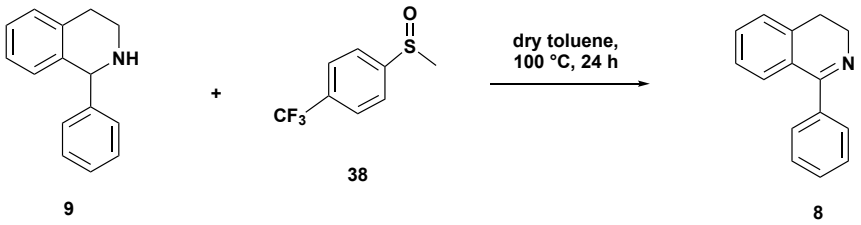


Fig. 7 X axis represent the equivalents of DMSO **33**; the Y axis represent the % of product **8** appearing. R^2 is the goodness of fit.



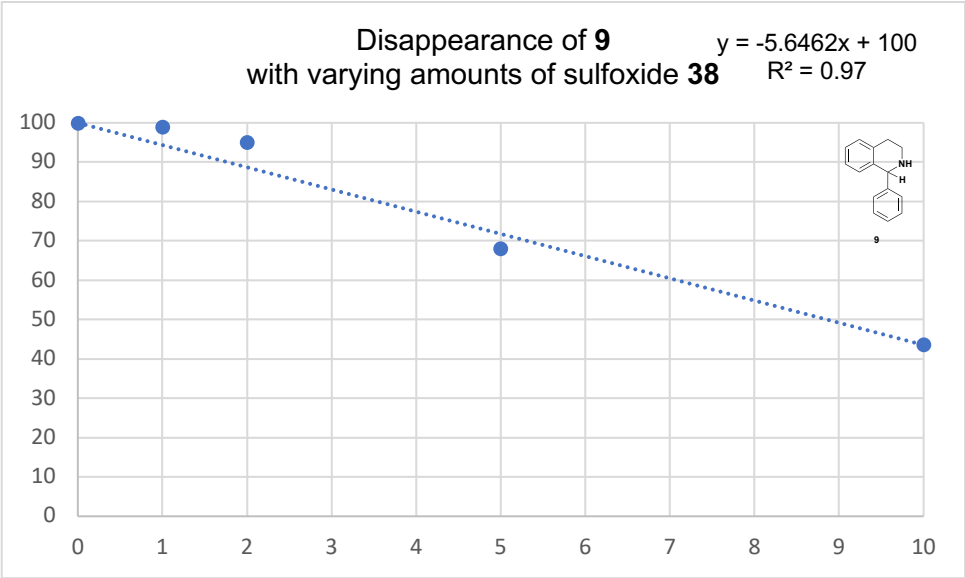


Fig. 8 X axis represent the equivalents of sulfoxide **38**; the Y axis represent the % of starting material **9** disappearing. R^2 is the goodness of fit.

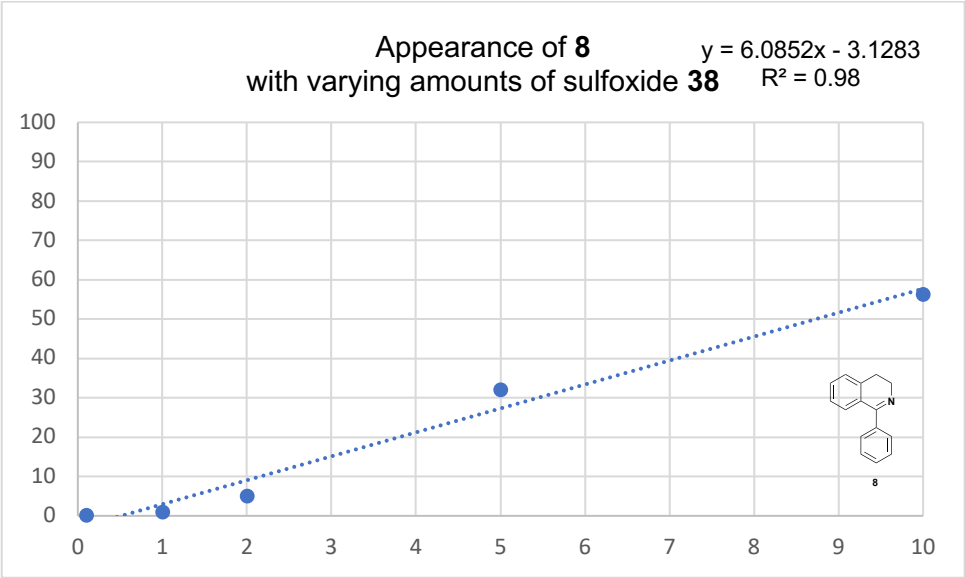
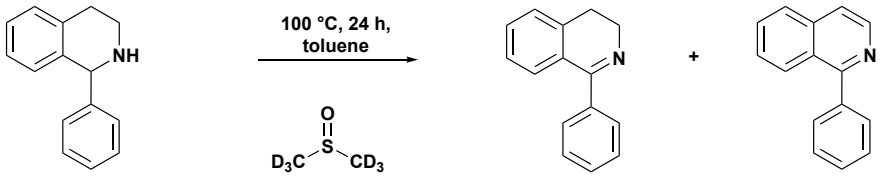


Fig. 9 X axis represent the equivalents of sulfoxide **38**; the Y axis represent the % of product **8** appearing. R^2 is the goodness of fit.

These same studies were also performed with deuterated DMSO. The goal was to make a direct comparison with protonated DMSO. Therefore, the same experimental conditions were maintained, but replacing normal DMSO with d_6-DMSO **(Table 10)**. The results show that, by substituting protonated DMSO with d_6-DMSO, the yield of product **8** increased, although the increases are small. Similar to before, the disappearance of **9** using deuterated DMSO **d_6-33** at different concentration gave the curve shown in **Fig. 10**. Following the appearance of product **8** using deuterated DMSO **d_6-33**, shown in the **Fig. 11**. Comparing the coefficients of the equations for DMSO and d_6-DMSO we can find a small KIE of 1.2 and may not be significant.



9 **8** **17**

Entry	Equiv. of sulfoxide	GC–MS Ratio (%) dry DMSO	GC–MS Ratio (%) d_6-DMSO
1	1	**9** 53% **8** 46%	**9** 42% **8** 57%
2	2	**9** 40% **8** 59%	**9** 35% **8** 65%
3	5	**9** 14% **8** 86%	**9** 15% **8** 84%
4	10	**9** 6% **8** 90% **17** 3%	**9** 3% **8** 96%

Table 10 Direct comparison between protonated and deuterated DMSO. Dry toluene, 100 °C, 24 h, under air. Ratio of the peaks according to the GC–MS.

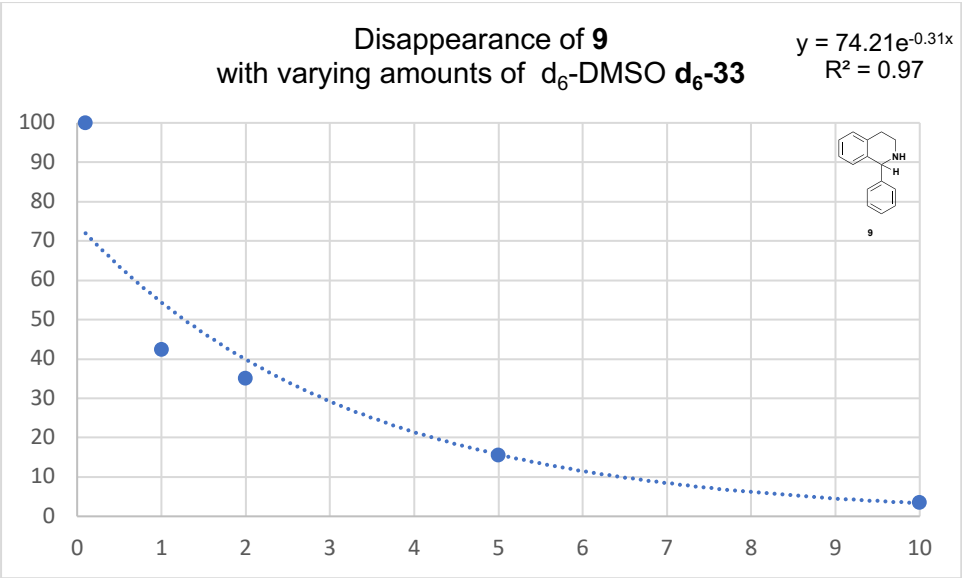


Fig. 10 X axis represent the equivalents of sulfoxide d_6-DMSO; the Y axis represent the % of starting material **9** disappearing. R^2 is the goodness of fit.

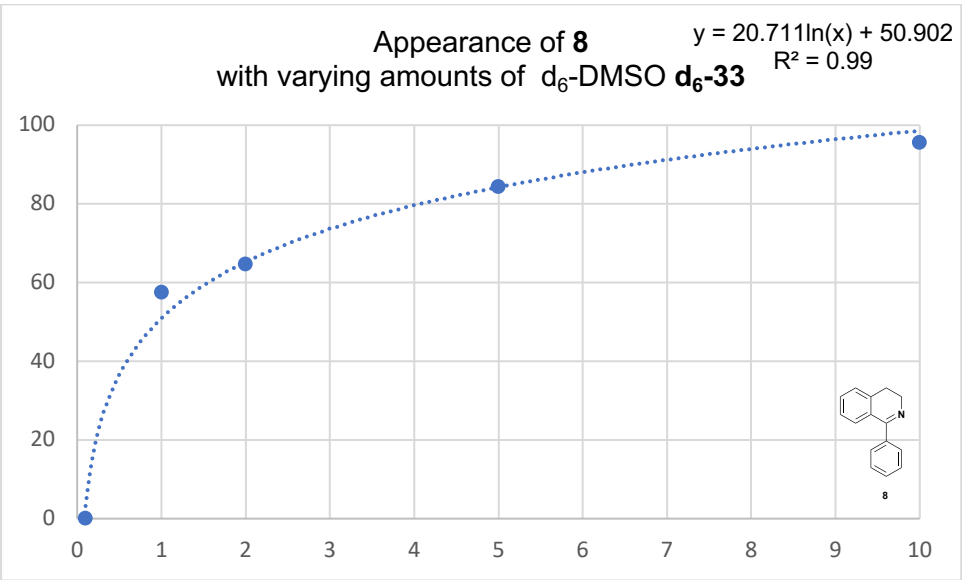
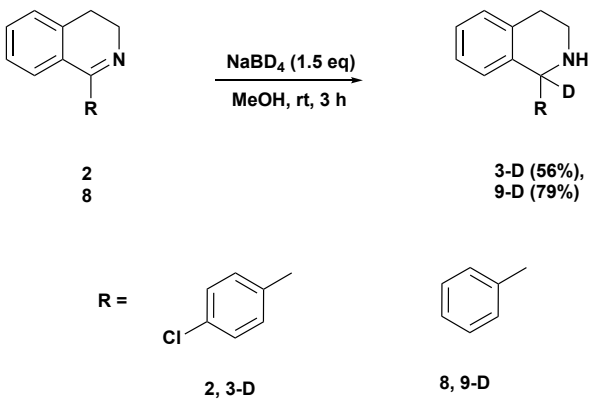


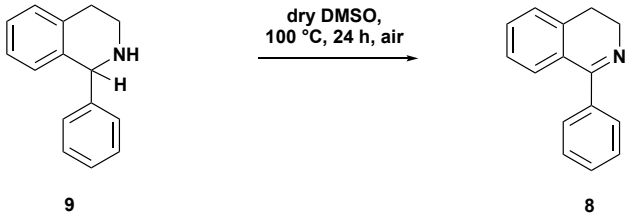
Fig. 11 X axis represent the equivalent of d_6-DMSO; the Y axis represent the % of product **8** appearing. R^2 is the goodness of fit.

Furthermore, we performed a kinetic study using LC–MS. The reaction was followed by LC–MS, giving the following results for protonated **9 (Fig. 12)** and deuterated **9-D (Fig. 13)**. These were synthesised reacting the corresponding dihydroisoquinoline with $NaBD_4$ (1.5 eq.) in MeOH at room temperature for 3 h **(Scheme 40)**.



Scheme 40 Synthesis of deuterated tetrahydroisoquinoline.

The *x* axis represents the time. The *y* axis represents the concentration of starting material **9** or **9-D**. The blue line follows the disappearance of the starting material **9**. The plain dots represent the specific data registered with the machine, whilst the dotted lines represent the trendline calculated. The reaction was conducted with 0.100 g of starting material in 1.5 mL of dry DMSO. Samples of 50 μL were taken at 15 min intervals. The KIE calculated in this way is again a small value of 1.2.



9 **8**

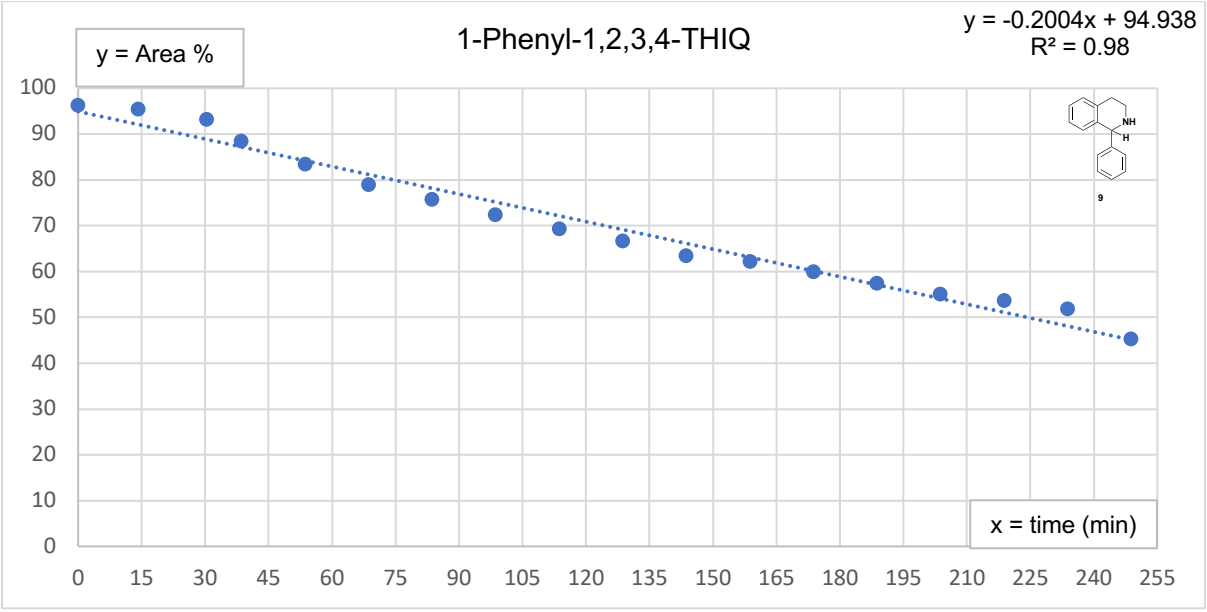
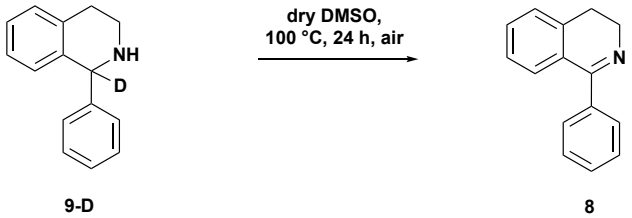


Fig. 12 Disappearance of **9** followed by LC–MS. R^2 is the goodness of fit.



9-D **8**

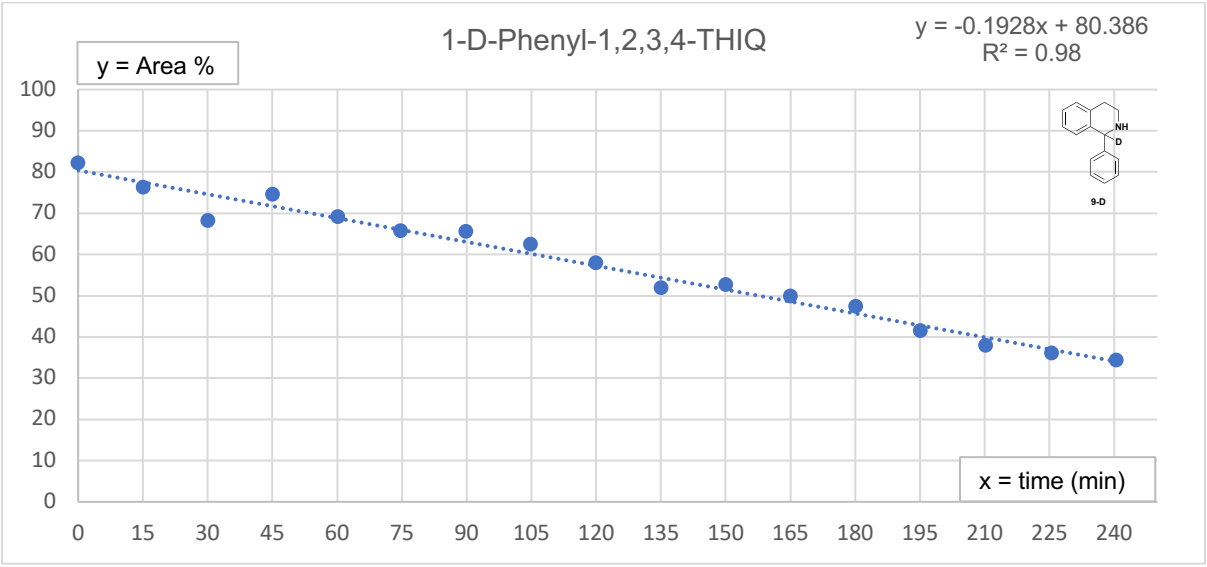
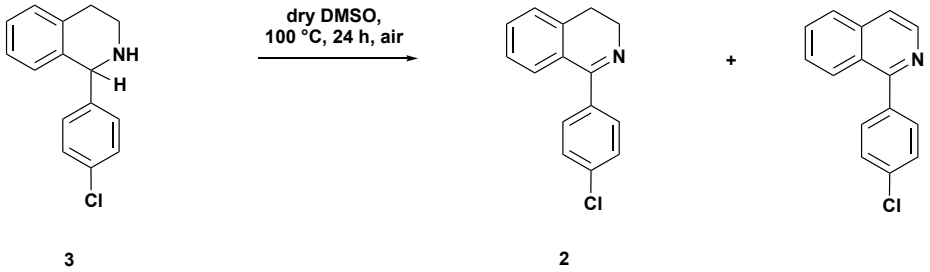


Fig. 13 Disappearance of deuterated **9-D** followed by LC–MS. R^2 is the goodness of fit.

The same experiment was also performed with another substrate. When 1-(4-chloro)-phenyl-1,2,3,4-tetrahydroisoquinoline **3** was used, the reaction was conducted with 0.100 g of starting material in 1.5 mL of dry DMSO. Samples of 50 μL were collected every hour for a total period of 10 h. In this way, the reaction was monitored for a longer period of time that reflected the whole reaction time with more precision. In **Fig. 14** and **15**, the blue line represents the disappearance of the starting material **3**. The orange line represents the appearance of the partially dehydrogenated product. The grey line represents the appearance of the totally dehydrogenated by-product. The plain dots represent the specific data registered with the machine, whilst the dotted lines represent the trendline calculated. From this, we can observe that a log curve well represents well the disappearance of **3**. The same is true for the appearance of the main product. Instead, the appearance of the by-product is linear. When the deuterated 1-D-(4-chloro)-phenyl-1,2,3,4-tetrahydroisoquinoline **3-D** was used, similar trends were found, but with different equation. If we compared the coefficient of the equations for the appearance of the protonated and deuterated form, we again find a small KIE of 1.2.



3 2

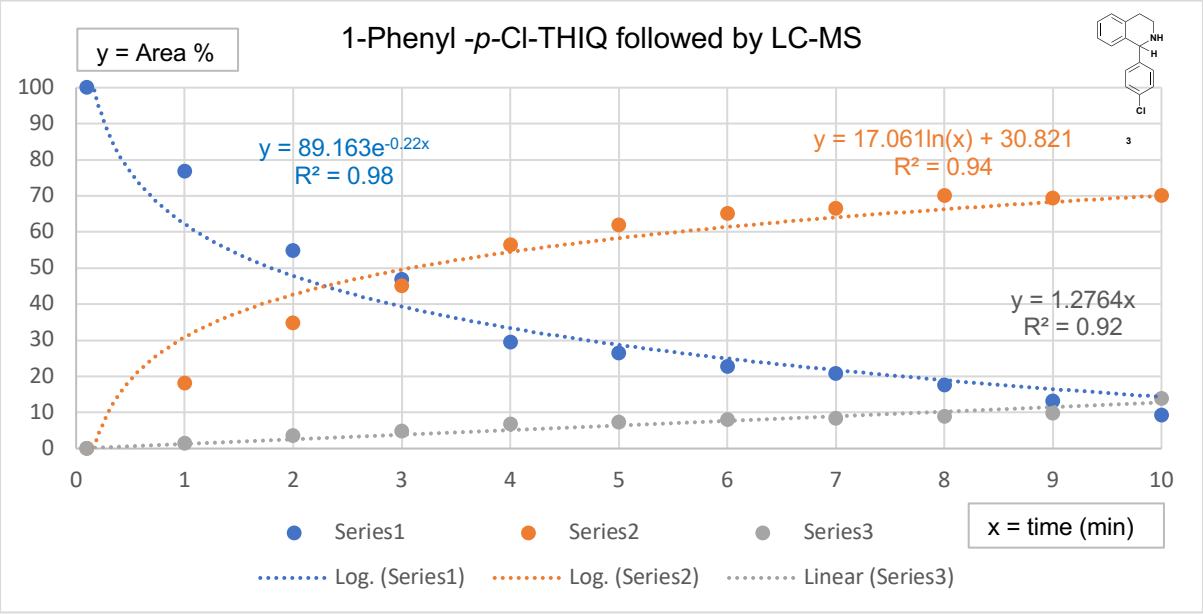


Fig. 14 1-Phenyl-(4-chloro)-1,2,3,4-tetrahydroisoquinoline **3** monitored by LC–MS. R^2 is the goodness of fit.

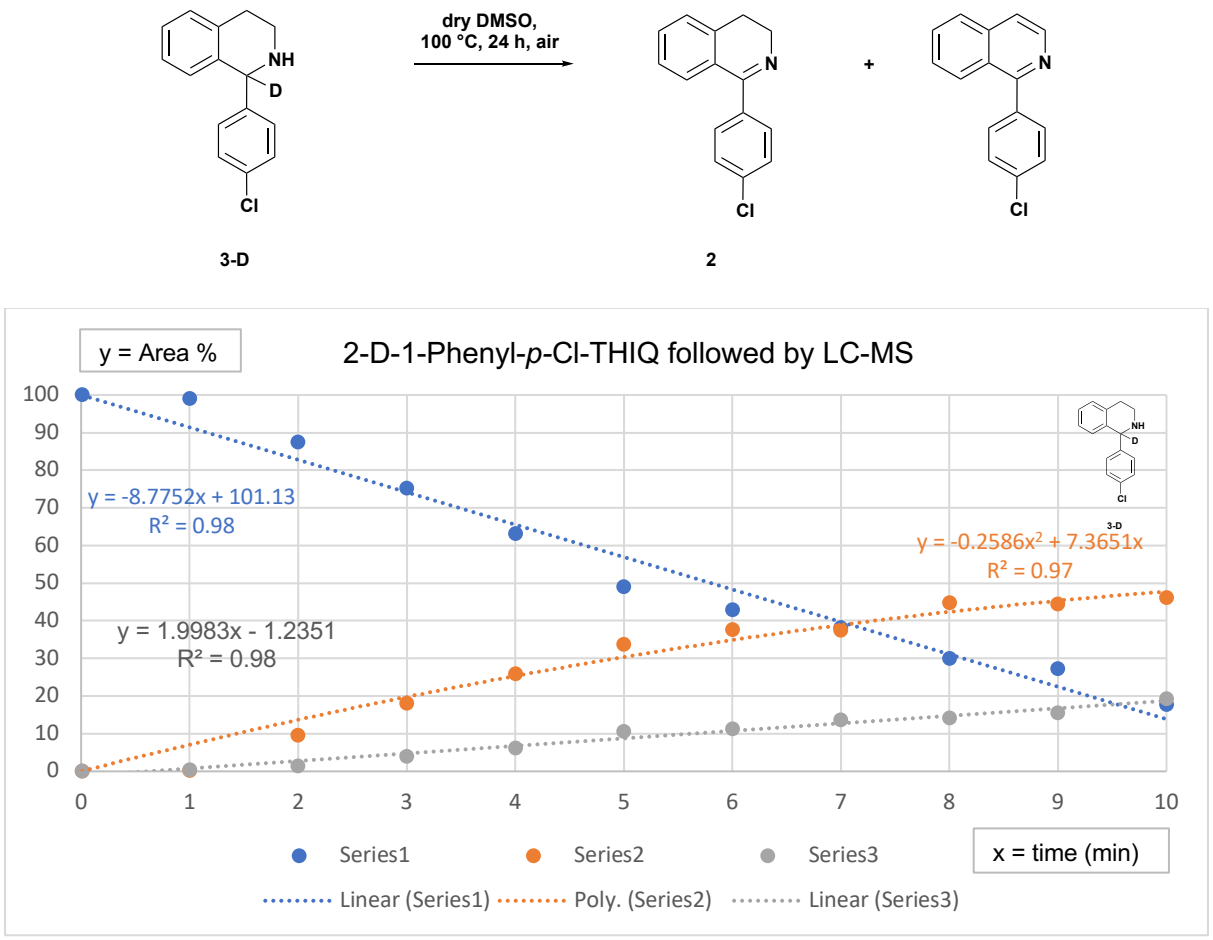
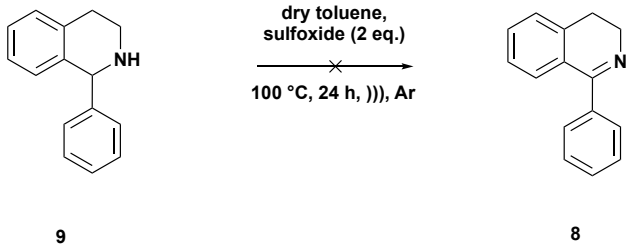


Fig. 15 1-D-phenyl-(4-chloro)-1,2,3,4-tetrahydroisoquinoline **3-D** monitored by LC–MS.

R^2 is the goodness of fit.

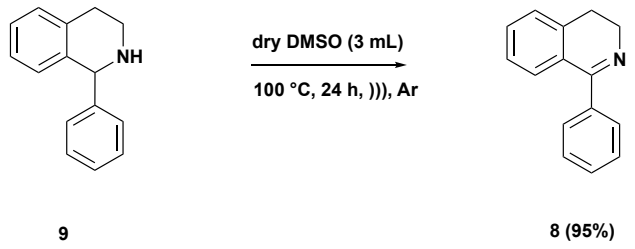
It is common to measure the primary KIE by direct rate measurement of the separate light and heavy isotopic species.[46] However, the interpretation of the KIE is not as simple as its measurement. The replacement of H with D at the position of C-H activation decreases the rate of reaction, leading to a relatively small normal KIE. The C-H bond cleavage step is irreversible, but this step is not the rate-determining step. The rate-determining step does not involve the substrate that ultimately undergoes C-H bond cleavage. For this reason, the overall rate of the reaction will be unaffected by the replacement of a C-H bond with a C-D bond. Therefore, no significant KIE can be measured.[47] The rate-determining step is probably the release of H_2 through the proton-hydride recombination.

Subsequently, the effect of anhydrous conditions was studied. 1-Phenyl-1,2,3,4-tetrahydroisoquinoline (0.48 mmol) was dissolved in dry toluene (3 mL). After the reaction mixture was prepared, this was sonicated for 20 min under an argon flow with the argon bubbling into the solvent. The reaction mixture was then heated to 100 °C for 24 h under with an argon balloon. It is worth pointing out that, when the reaction was performed in toluene with 2 equivalents of sulfoxide, the reaction was strongly inhibited. In fact, only starting material was found. This was true for both DMSO and methyl *p*-tolyl sulfoxide **(Table 8, entries 33B** and **36B**, and **Scheme 41)**.



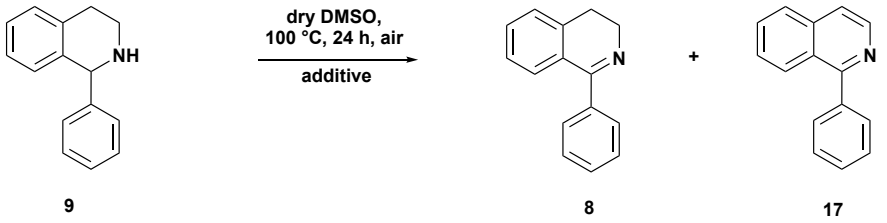
Scheme 41 Failed reaction under anhydrous conditions.

On the contrary, when dry toluene was replaced by dry DMSO as the only solvent, with otherwise identical conditions, the inhibition did not occur. The reaction gave the product **8** in more than 95% yield **(Scheme 42)**.



Scheme 42 Successful reaction under anhydrous conditions.

As mentioned previously, the effect of acid from molecular sieves was found to slow down the reaction outcome. Therefore, the effect of acid and base on the reaction was studied systematically. The reaction was always performed in dry DMSO (1 mL). 1-Phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) was used as the standard substrate. To the reaction medium, different amounts of acetic acid or 1,5-diazabicyclo(5.4.0)undec-7-ene (DBU) were added. Subsequently, the reactants were heated to 100 °C for 24 h under air. The corresponding results are presented in **Table 11**. For the acid, the results do not show a specific pattern. However, it is clear that the reaction outcomes are thwarted **(Table 11, entries 1 – 4).** This is in agreement with the literature, for which the presence of the acid favours the decomposition of DMSO.[10] For the base, 1 eq. does not make a great difference compared to the normal reaction conditions **(Table 11, entry 5)**. However, by increasing the amount of DBU the amount of by-product **17** become higher in yield. In fact, with 10 eq. of DBU by-product **17** is present in 83% yield **(Table 11, entry 6 – 8)**. If a stronger base such as NaOH (1 eq.) was used, the completely dehydrogenated by-product was generated in 14% **(Table 11, entry 9)**. This is in agreement with the work of Dong and co-workers.[29] They showed the effects of the treatment of several tetrahydroisoquinolines THIQs and tetrahydro-β-carbolines THBCs with different substituents patterns, with bases in DMSO. The molecules dehydrogenated into the corresponding isoquinolines and β-carbolines. These results are significant because they represent an example of perfect tuning between a partially dehydrogenated and a totally dehydrogenated product.



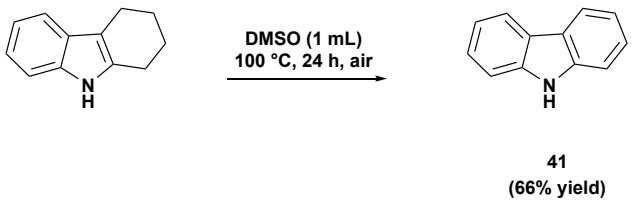
9 **8** **17**

additive: Acetic acid or DBU

Entry	Additive	Equivalents	Ratio (%) by GC–MS
1	CH_3COOH	1	**9** 50%, **8** 49%
2	CH_3COOH	2	**9** 4%, **8** 88% **17** 8%
3	CH_3COOH	5	**9** 73%, **8** 25% **17** traces
4	CH_3COOH	10	**9** 85%, **8** 15%
5	DBU	1	**9** 6%, **8** 94%
6	DBU	2	**9** 69%, **8** 23% **17** 8%
7	DBU	5	**9** 27%, **8** 26% **17** 47%
8	DBU	10	**9** 8%, **8** 9% **17** 83%
9	NaOH	1	**9** 85%, **17** 14%
10	No additive		**9** 93%, **8** 3%

Table 11 Effect of acid and base on the reaction. Dry DMSO, 100 °C, 24 h, under air. Ratio of the peaks according to the GC–MS.

The application of hydrogen as an energy carrier is hampered by serious deficiencies of storage technologies. The concept of storing hydrogen within Liquid Organic Hydrogen Carriers (LOHCs) is based on the dehydrogenation and subsequent hydrogenation of organic molecules.[48] In the liquid H_2 carrier scheme, a generalised hydrogenated carrier A_h gives up hydrogen to form the fully dehydrogenated form A_d through a catalysed thermal process. Muller and co-workers highlighted the importance of nitrogen-containing aromatics to be used as LOHCs.[49] An important patent by Pez and co-workers reports the use of a variety of aza and polyaza heterocycles, notably carbazoles, for hydrogen storage, and report DFT calculations on the thermodynamics of a much wider variety of A_h/A_d pairs.[50] For this reason, we also tried our conditions on carbazoles **(Scheme 43)**. More specifically, tetrahydrocarbazole (0.100 g) was dissolved in dry DMSO (1 mL). The reaction mixture was heated to 100 °C for 24 h. According to GC–MS, the fully dehydrogenated product was present in 66% yield. This product was isolated with difficulties in 66% yield to give white crystals which exhibit strong fluorescence. This characteristic is described in the literature.[51,129]



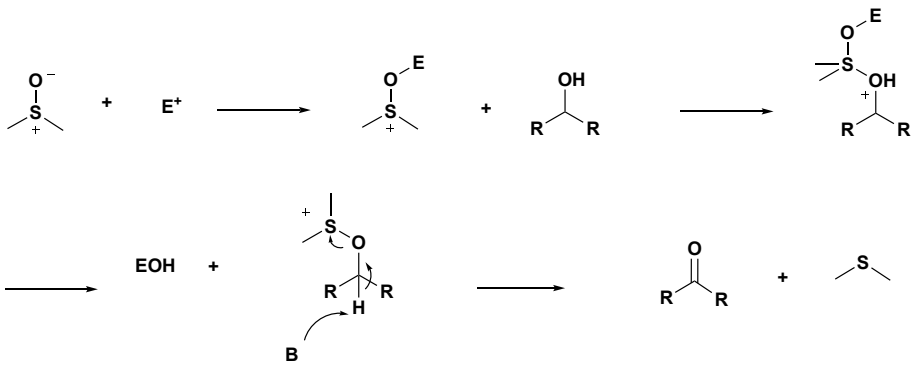
41
(66% yield)

Scheme 43 Dehydrogenation of 1,2,3,4-tetrahydrocarbazole into fully aromatised carbazole in DMSO.

2.3 Mechanistic Studies

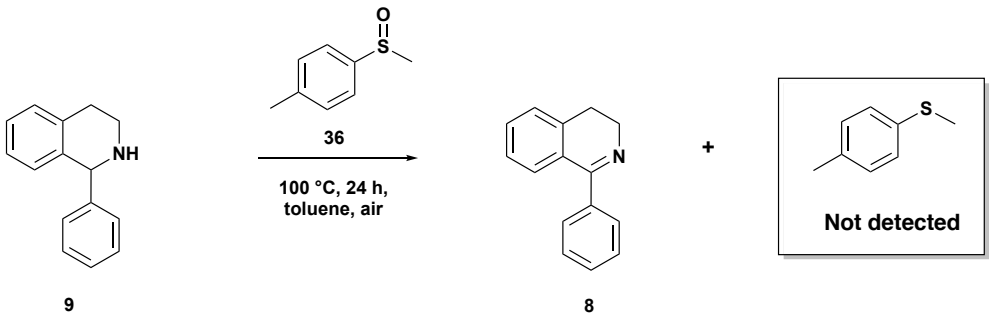
In the original article published by Feng and co-workers, it was claimed explicitly that the oxidation reaction of tetrahydroisoquinolines in DMF comes with a net production of hydrogen.[28] The authors proposed that hydrogen-bond interactions between DMF or DMSO and substrates may result in weakened N-H and C-H bonds and, consequently, in a low dehydrogenation energy barrier. They performed a Temperature Programmed-Desorption Mass Spectrometry (TPD–MS) experiment, and a signal for hydrogen (*m/z*=2) released from the substrate was detected. Nevertheless, no mechanistic explanation was attempted. Our goal at this stage was to attempt a mechanistic explanation for the oxidation of tetrahydroisoquinolines in DMSO under air. Therefore, several experiments were carried out to confirm or exclude certain reaction pathways. First of all, it was important to understand if the reaction was ionic or radical in nature. To this end, the radical trap TEMPO was used. When the radical inhibitor TEMPO (1.1 eq.) was added to the reaction mixture, the reaction was not inhibited. Therefore, a radical mechanism is probably excluded.

The oxidation of substrates such as alcohol with DMSO is well known **(Scheme 44)**. The oxidation was discovered by Moffatt, who used acetic anhydride to activate DMSO.[52] Moreover, a few of the subsequent modifications which improved the procedure have also become named reactions. These differ in how the alkoxysulfonium ion Me_2S^+-X is generated. Generally, a DMSO solution of the alcohol is treated with one of the several electrophilic reagents **(E^+)**. The alcohol is oxidised and DMSO is reduced to dimethyl sulfide. A drawback of this reaction is the production of the malodorous side-product dimethyl sulfide.



Scheme 44 Oxidation of alcohols by DMSO.

However, in our specific case, no trace of dimethyl sulfide was found. No obnoxious gas or smell was noted. This is remarkable considering that the extremely low threshold of dimethyl sulfide perception is between 0.1 and 0.02 ppm.[53] Dimethyl sulfide boils at 37 °C. Therefore, it is likely to evaporate in the reaction flask during GC–MS analysis, making its detection quite difficult. Therefore, a potential explanation for our DMSO-based oxidation being a simple variation of a reaction already known in the literature cannot be totally excluded at this stage. To verify this hypothesis, the reactions with more stable sulfoxides were studied in greater detail, focusing on the detection of any possible sign of the corresponding sulfide. For this reason, we chose to work with methyl *p*-tolyl sulfoxide **36** and its corresponding commercial sulfide **(Scheme 45)**. Commercial methyl *p*-tolyl sulfide was run in the GC–MS as a pure reference. Its signal was clear in a region normally clear from any signals due to other reaction components. The signal of methyl *p*-tolyl sulfoxide **36** was perfectly distinguishable from the signal of its corresponding sulfide. If the reaction mechanism consisted in a simple variation of a literature mechanism with consequent production of the corresponding sulfide, this sulfide would have definitely been visible as a by-product. Therefore, a solution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) in toluene (3 mL) with 2 eq. of *p*-tolyl sulfoxide **36** as the sulfoxide was heated to 100 °C for 24 h under air. As a result, the peak corresponding to product **8** was present in the GC–MS, whilst no traces of the corresponding sulfide were detected. This result excludes the formation of the sulfide as a by-product **(Scheme 45)**.



Scheme 45 Failed detection of methyl *p*-tolyl sulfide.

To confirm the validity of the results described above, it was decided to apply the same concept to a different analytical technique. This time, fluorine NMR spectroscopy was chosen. Commercial methyl *p*-fluorophenyl sulfide was chosen as a reference. This has a single signal at -60.7 ppm in the ^{19}F NMR spectrum **(Fig. 16)**. The ^{19}F-NMR signal of the corresponding sulfoxide **39** is at -110.2 ppm **(Fig. 17)**. Therefore, the signal of the sulfoxide **39** and its corresponding sulfide are readily distinguishable by ^{19}F-NMR spectroscopy**.**

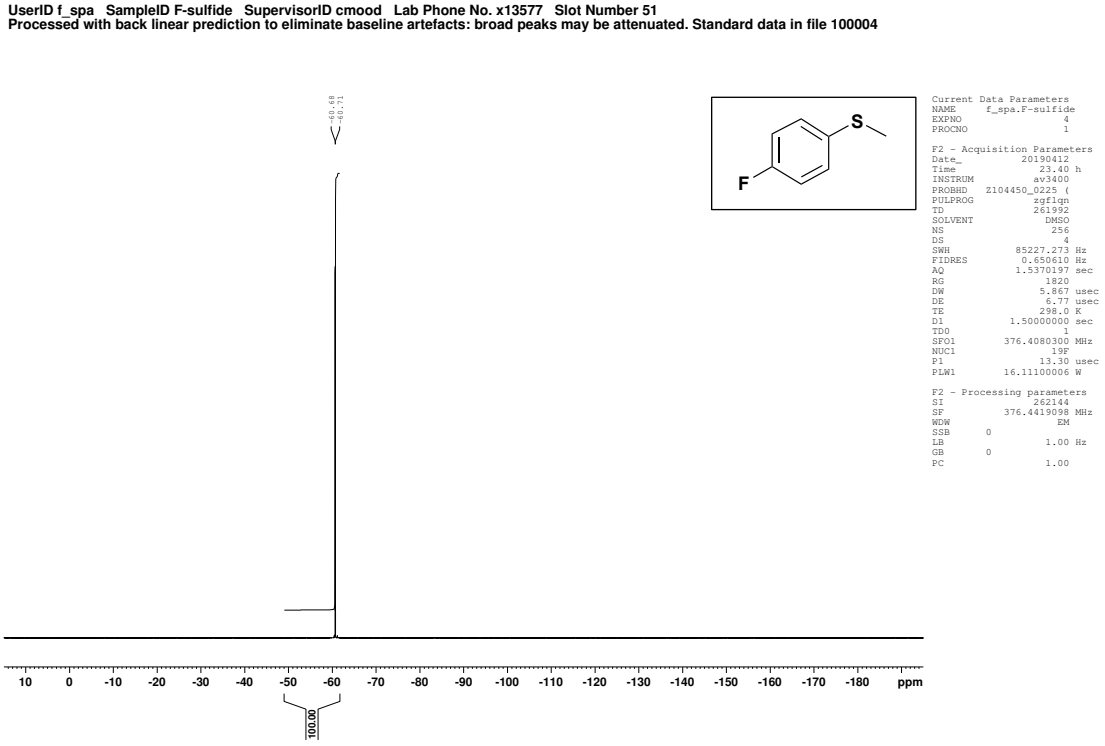


Fig. 16 ^{19}F-NMR of methyl *p*-fluorophenyl sulfide.

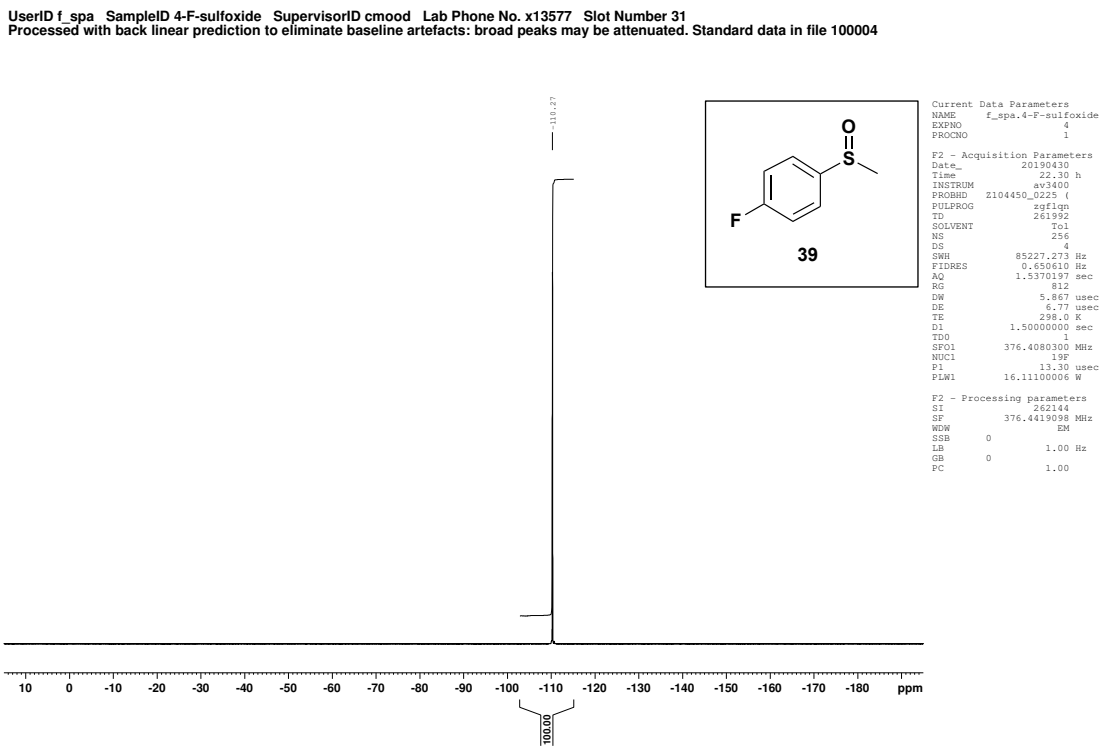


Fig. 17 ^{19}F-NMR of methyl *p*-fluorophenyl sulfoxide **39**.

Next, a solution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) in toluene (3 mL) and 2 eq. of methyl *p*-fluorophenyl sulfoxide **39** was heated to 100 °C for 24 h under air. Subsequently, the reaction mixture was analysed by ^{19}F-NMR spectroscopy. The result clearly shows that, after the reaction, the spectrum of the reaction outcome indicates the presence of the sulfoxide **39** at -110.2 ppm exclusively, whilst there was no evidence for the corresponding sulfide **(Fig. 18)**, whilst the product **8** was still forming in high yield.

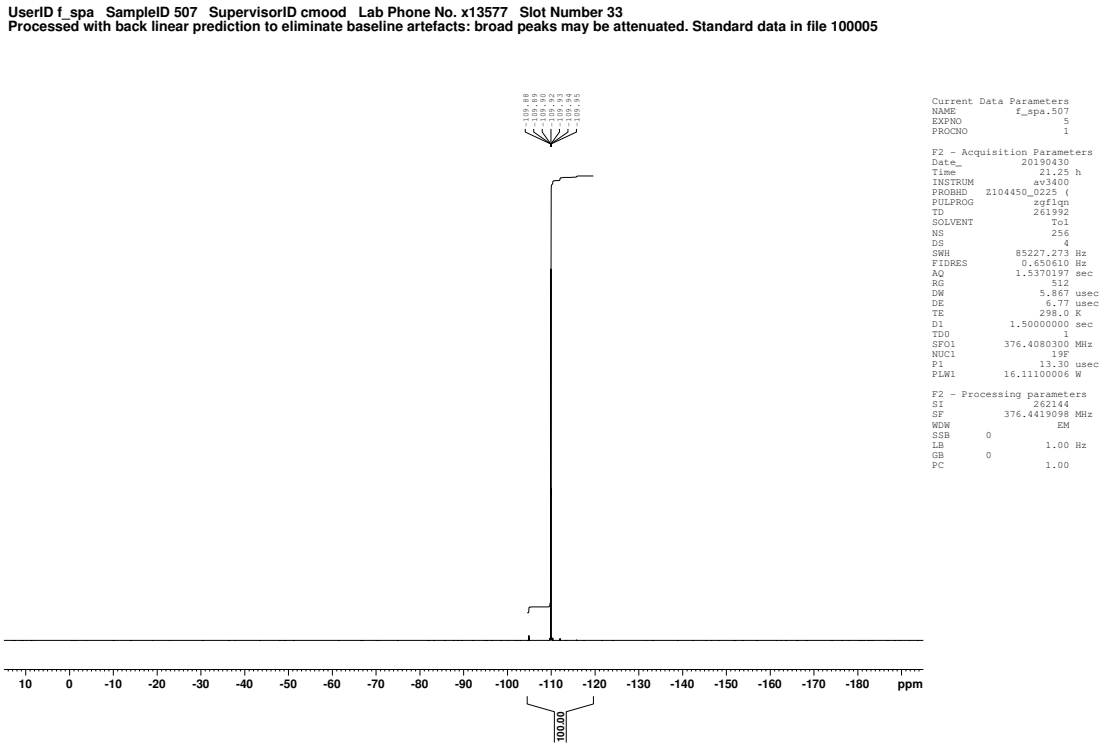
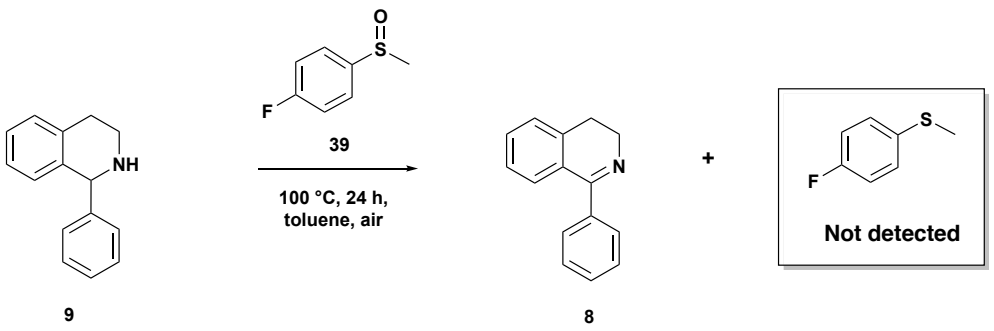


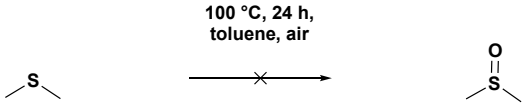
Fig. 18 ^{19}F-NMR of the reaction mixture.

Once again, this result excluded the formation of the sulfide as a by-product **(Scheme 46)**.



Scheme 46 Failed detection of methyl *p*-fluorophenyl sulfide**.**

Exactly, the same result was achieved using CF_3-sulfoxide **38** and its corresponding CF_3-sulfide. CF_3-sulfide gives a single signal in its ^{19}F NMR spectrum that was completely absent in the NMR spectrum after the reaction with CF_3-sulfoxide. It was plausible, though unlikely, that the sulfide is oxidised by atmospheric oxygen under the reaction conditions, regenerating the sulfoxide. Dimethyl sulfide is reported to be photochemically converted into oxidised sulfur species such as DMSO and SO_2.[54] To verify this hypothesis, pure commercial dimethyl sulfide was dissolved in dry toluene. The solution was heated to 100 °C for 24 h under air. However, no trace of sulfoxide was detected by GC-MS **(Scheme 47)**.



Scheme 47 Failed oxidation of sulfide to DMSO.

These results discredit the idea that the DMSO-based oxidation of tetrahydroisoquinoline produces the corresponding dimethyl sulfide as a by-product. In fact, not only did the content of the reaction flask failed to give any smell, but also the reaction failed to give any trace of sulfide both by GC–MS and fluorine NMR spectroscopy. At this point, it seemed clear that DMSO or any other sulfoxide were not consumed during the reaction, at least not by

conversion to the sulfide. To highlight this, a solution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) in DMSO (3 mL) was heated to 100 °C for 24 h under air. A sample of this reaction was taken every hour timely and ran by GC–MS (100 μL of reaction mixture in 1 mL of CH_3CN). The results were analysed all together as stacked graphs. The aliquots have been analysed at different time by the hour, as described in the box. The *x* axis represents the retention time of the corresponding molecule, whilst the *y* axis represents the intensity of the signal according to Total Ion Chromatogram (TIC). The results show that DMSO concentration does not change **(Fig. 19)**. Its signal is approximately constant, taking into consideration the sensitivity of the machine. On the other side, the signals corresponding to the product 1-phenyl-3,4-dihydroisoquinoline **8** increase with time **(Fig. 20)**.

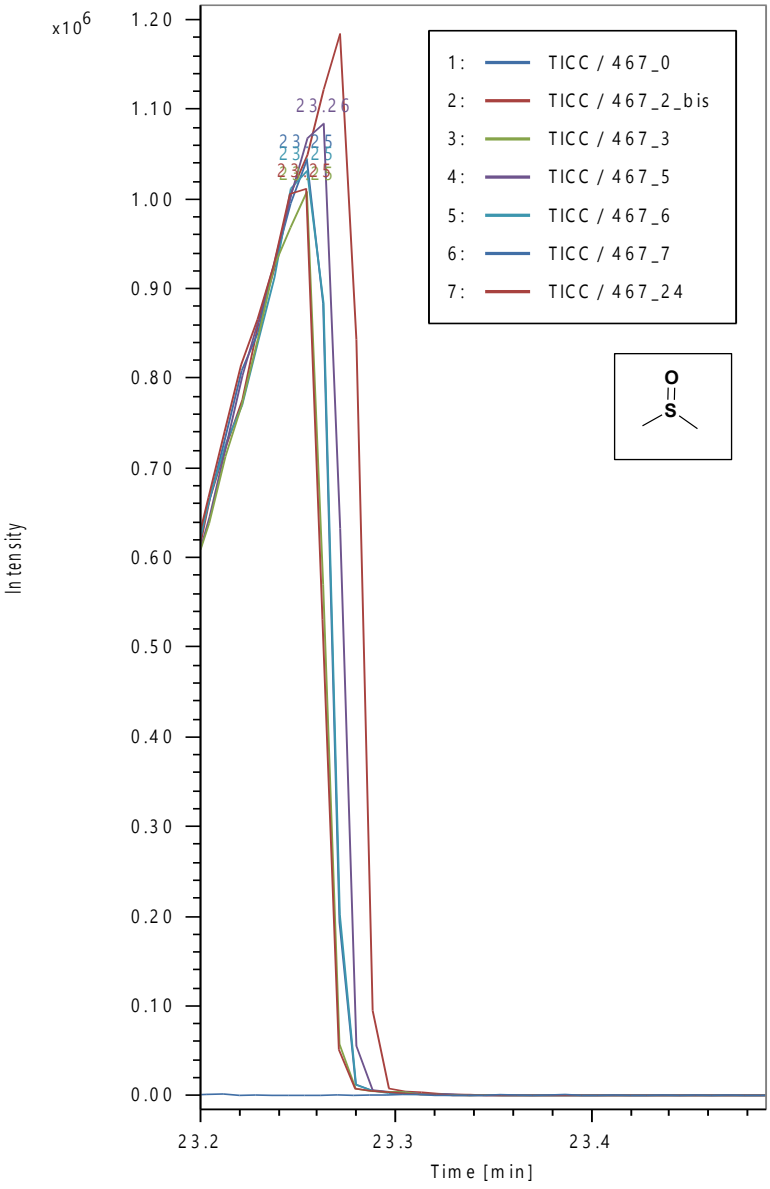


Fig. 19 Signals of DMSO by GC–MS remaining constant with time.

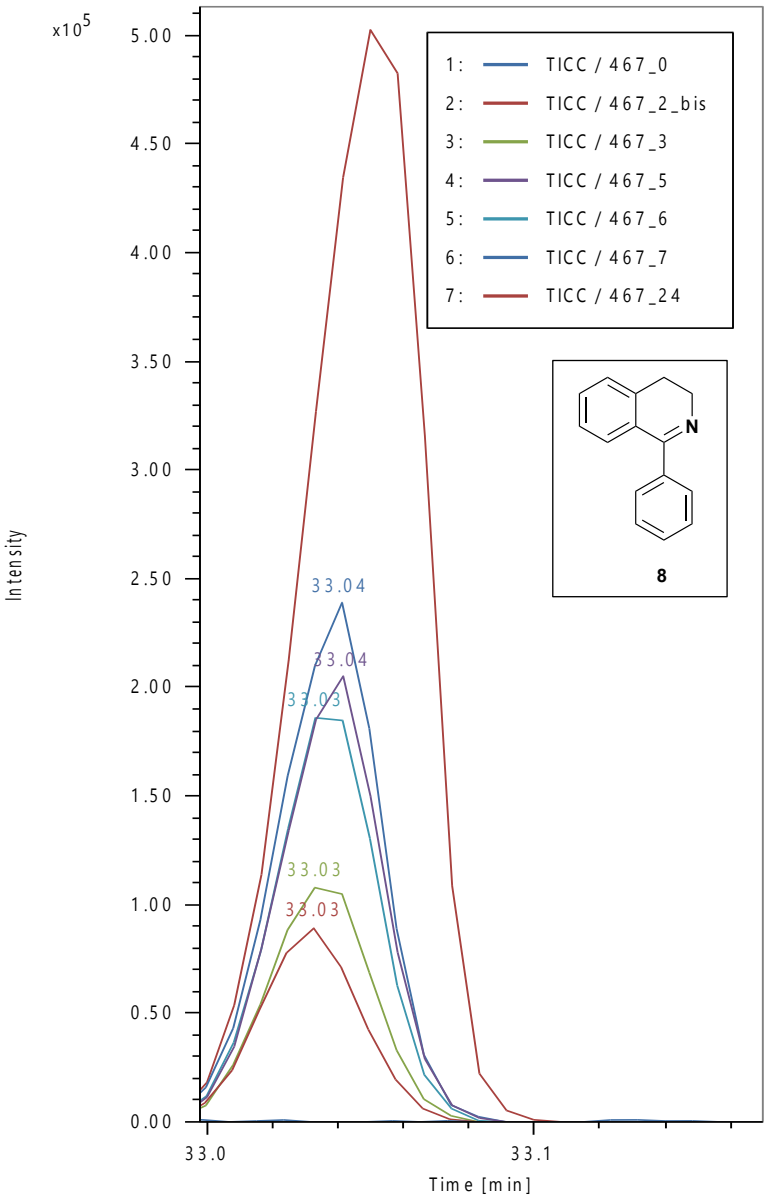


Fig. 20 Signals of 1-phenyl-3,4-dihydroisoquinoline **8** by GC–MS increasing with time.

At this point, unequivocal proof for the evolution of hydrogen gas was needed. Therefore, several experiments were undertaken. First of all, the reaction mixture was analysed by Thermal Gravimetric Analysis/Mass Spectrometry (TGA–MS). The method used consisted of heating the sample dissolved in DMSO from room temperature to 100 °C with an increase rate of 5 °C/min under air flow. After that, isothermal conditions were left for 24 h. The large loss of weight recorded is due to the evaporation of DMSO **(Fig. 21 – 23)**. In fact, the sample was dry at the end of the experiment. Nevertheless, the mass spectrometer detected a peak for molecular hydrogen (*m/z*=2) **(Fig. 22)**. Furthermore, the sample at the end of the TGA–MS analysis was subjected to GC–MS. This did not reveal any starting material, but only product, strengthening the hypothesis that the hydrogen peak detected was gas released from the reaction. Even if it is true that the hydrogen peak is not particularly large, it must be taken into consideration that the analysis has been performed on a sample of 28 mg. Therefore, due to technical limitations, the amount of sample analysed cannot be increased. This is in agreement with Feng and co-workers. According to them, a peak for molecular hydrogen (*m/z*=2) has been detected by TPD–MS.[28] A second attempt at the TGA–MS experiment was performed. However, this time the reaction was run under argon, and the TGA–MS failed to detect any trace of hydrogen (*m/z*=2). Accordingly, the final sample analysed by GC–MS gave only starting material.

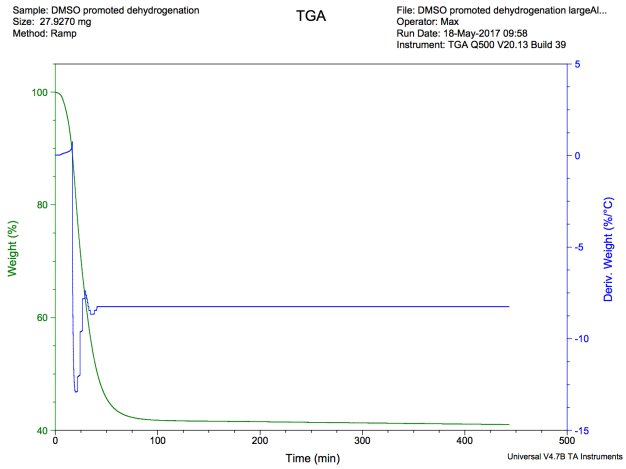


Fig. 21 TGA-MS Analysis: Plot of Time (min) vs Weight loss (%)

m/z=2

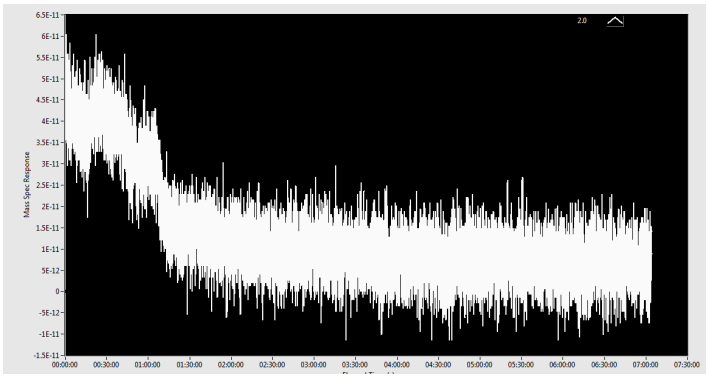


Fig. 22 TGA-MS *m/z*=2

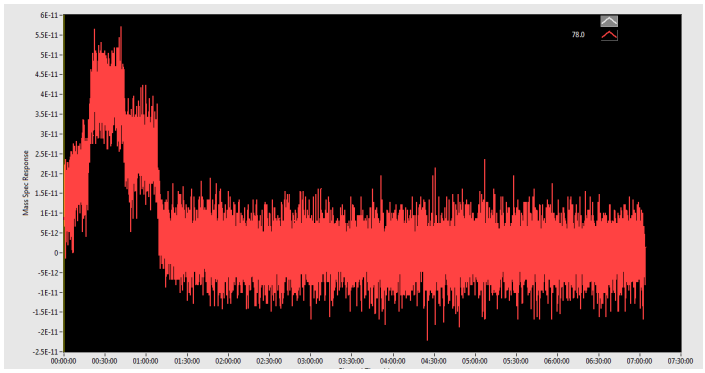
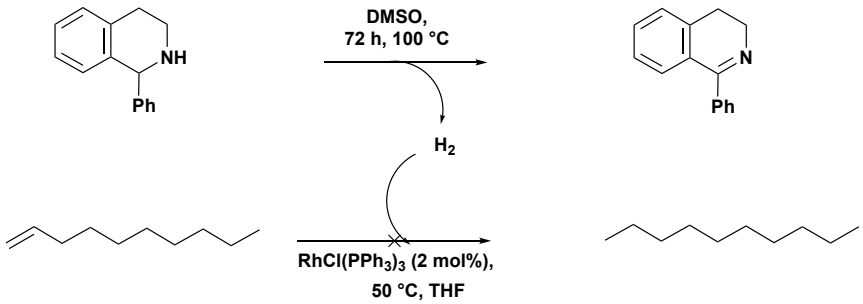


Fig. 23 TGA-MS *m/z*=78 Evaporation of DMSO

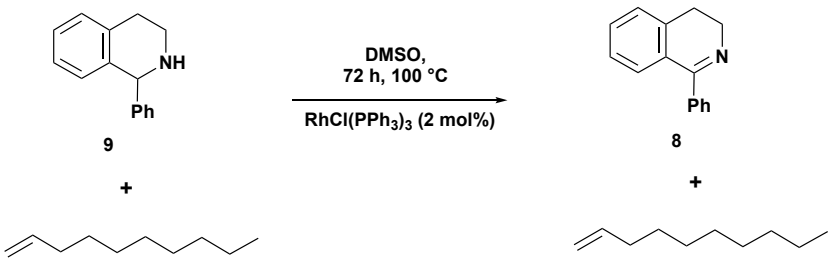
More experiments were carried out to confirm the formation of hydrogen. A double reaction involving the dehydrogenation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** and the hydrogenation of 1-decene was attempted several times. Therefore, a solution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) in DMSO (3 mL) was heated to 100 °C for 72 h under air. The dehydrogenation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** was conducted in a flask connected through a rubber tube to another flask. In this second flask was a solution of 1-decene (1 eq) in THF (3 mL) with various catalytic amounts (4-15 mol%) of Wilkinson's catalyst.[55] This second reaction flask was heated to 50 °C for 72 h **(Scheme 48)**. The idea was that the hydrogen gas generated in the former flask would transfer through the rubber tube to the second flask, reducing 1-decene to 1-decane. The experimental procedure is similar to that described in the literature.[55] At the end of the experiment, the partially dehydrogenated product was detected by GC–MS. However, this experiment did not show any sign of 1-decane as a reaction product by GC–MS.



Scheme 48 Dual reaction involving dehydrogenation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** and hydrogenation of 1-decene in different flasks.

A different approach was attempted in which all of the reagents were placed in the same flask **(Scheme 49)**. Briefly, in a single flask, the starting material 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** (0.48 mmol) and 1-decene (1 eq) were dissolved in DMSO (5 mL). To this solution, the Wilkinson's catalyst (2-15 mol%) was added. The reaction mixture was

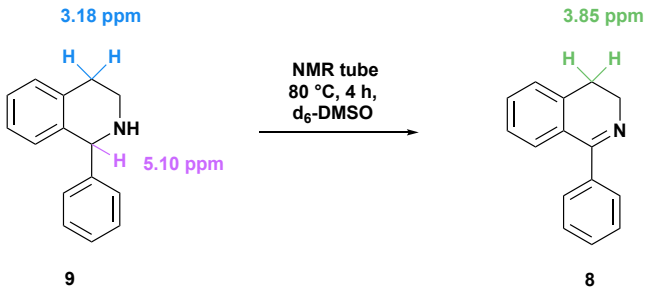
heated to 100 °C for 72 h under air. The outcomes were equally inconclusive despite several attempts.



Scheme 49 Dual reaction involving dehydrogenation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** and hydrogenation of 1-decene in the same flask.

Exactly the same results were achieved when Pd/C (10 mol%) was used in both experiment as a replacement for the Wilkinson's catalyst, as described in literature.[56]

According to the literature, the hydrogen molecule has a NMR peak at 4.6 ppm in DMSO.[57] Therefore, even if it is uncommon procedure, we thought to try to observe the formation of the hydrogen by NMR spectroscopy. An NMR experiment was designed in which a solution of the substrate 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** in d_6-DMSO was heated to 80 °C for 4 h in a NMR tube directly in the instrument. Spectra were recorded every 30 min **(Fig. 23)**, with the aim of following the characteristic signals shown in **(Scheme 50)**. The *x* axis represents the ppm. The *y* axis represents the time.



Scheme 50 NMR signals followed in the NMR experiment.

From **Fig. 24** it is clear that no signal was observed in the NMR spectrum between 4.5 – 4.7 ppm over 4 h of experimental time. Therefore, no peak directly attributable to H_2 is present. However, the signal at 3.3 ppm is constantly increasing. This is attributable to water. At the same time, at 10.3 ppm a very small peak appears. This may be attribute to H_2O_2. Considering that the NMR sample was not prepared under an inert atmosphere in a glove box, it is possible that H_2 liberated from the reaction and kept at high temperature for several hours may have reacted with molecular oxygen to generate water and hydrogen peroxide.[58] By providing an oxygen source to fix the product hydrogen, the endothermic dehydrogenation process may be converted to a more favourable exothermic one.

In concordance with this theory, the signal of the starting material **9** is clearly gradually disappearing. At 5.0 – 5.3 ppm, the signal of the benzylic proton of the starting material C<u>H</u>-NH (purple in **Scheme 50**) is not only gradually disappearing, but also shifting downfield at higher ppm (+δ). This may indicate a hydrogen bond formation between the substrate and the DMSO molecule. At the same time, the signal of the benzylic C<u>H</u>$_2$ at 3.2 ppm (blue in **Scheme 50**) is gradually disappearing. A signal at 3.8 ppm appears for the benzylic C<u>H</u>$_2$ of the product **8** (green in **Scheme 50**). This experiment was inconclusive probably due to insufficient reaction time. The duration of the analysis or the temperature cannot be increased without damaging the spectrometer.

Another attempt was made performing the reaction in a closed air-tight NMR tube (Young's NMR tube). The reaction was performed directly in the closed NMR tube, heating-up the solution with the heat-gun and running the sample immediately after. After 5 min of heating, traces of product were already visible in the spectrum. However, no hydrogen was detected between 4.5 – 4.7 ppm. The experiment could not go any further because the heat-gun could have deformed the NMR tube, leading it to break in the machine.

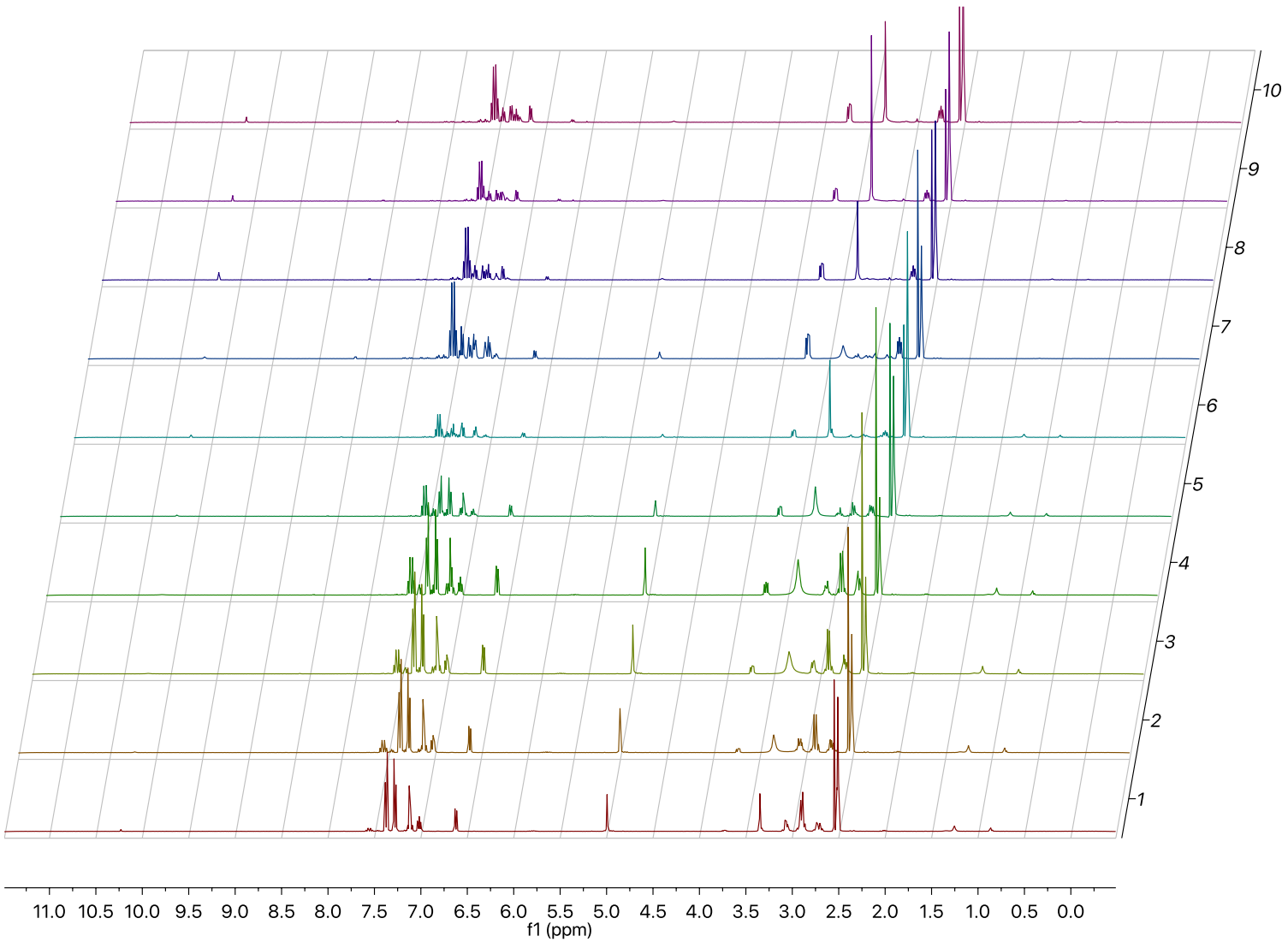


Fig. 24 1-Phenyl-1,2,3,4-tetrahydroisoquinoline **9** in d_6-DMSO heated in a NMR tube at 80 °C directly in the NMR machine. Spectra were run every 30 min (Y axis).

A rudimentary hydrogen gas volume measuring experiment was also performed. The reaction was conducted in a conventional stirring sealed flask containing the reagents. 1-Phenyl-1,2,3,4-tetrahydroisoquinoline **9** (1.0 g) was dissolved in dry DMSO (5 mL). The solution was heated to 100 °C for 24 h. The gas generated from the reaction was channelled through a needle into an upturned water-filled measuring cylinder in a reservoir containing water. In theory, the water should have been displaced from the measuring cylinder by the incoming gas. The volume of gas collected should be read off of the cylinder. The water displacement method is applicable to the collection of any gas that has low solubility in water, included hydrogen. This method was based on that described in the literature.[59] The apparatus used for the water displacement experiment is depicted in **Fig**. **25**.

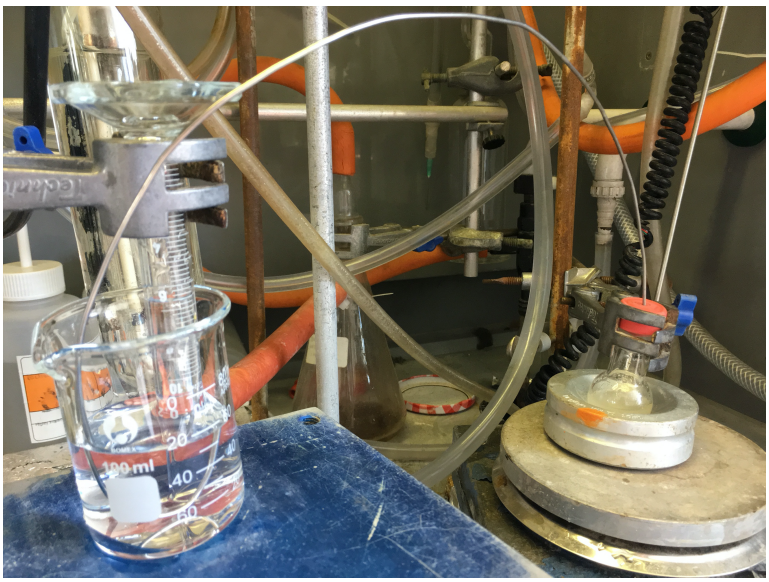


Fig. 25 Apparatus for the water displacement experiment.

With this method, water displacement was clearly seen. In fact, at the beginning of the experiment, the water has a level of 5.1 mL **(Fig. 26)**, whilst at the end of the experiment, the water read off 5.3 mL **(Fig. 27)**. However, every attempt to see the characteristic combustion of hydrogen with a flame failed.

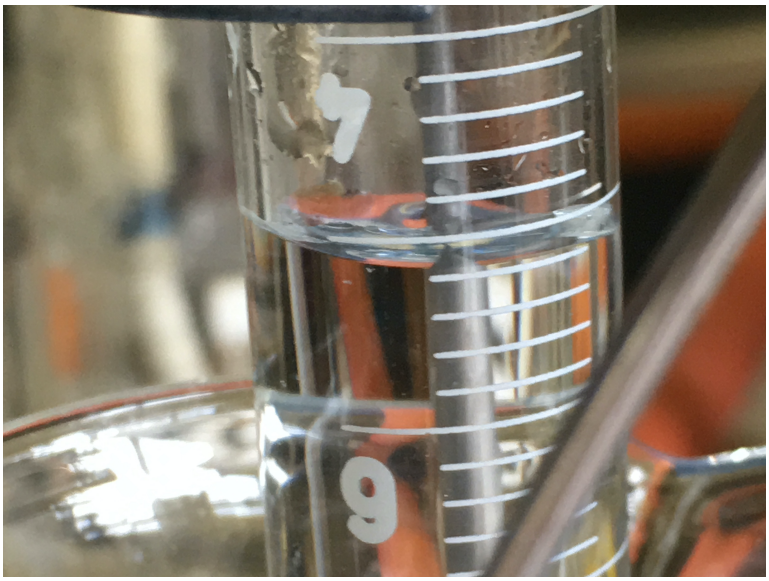


Fig. 26 Graduated cylinder at the beginning of the reaction.

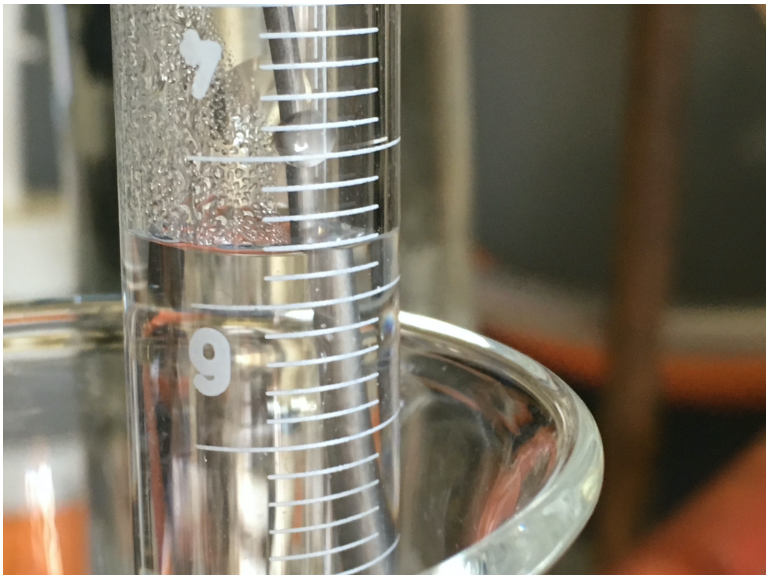
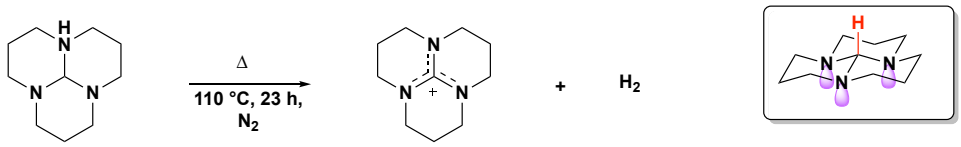


Fig. 27 Graduated cylinder at the end of the reaction.

Even if rare, hydrogen release from carbon-hydrogen bonds is known to occur. Already in 1980, Wuest and co-workers showed that orthoformamide and related compounds are remarkably active substrates for protonolysis.[56,60] They created a compound that incorporates a carbon-hydrogen bond designed especially to be a good formal hydride donor **(Scheme 51)**. Under mild conditions, the central carbon-hydrogen bond (highlighted in red in **Scheme 51**) liberates H_2. Hydrogen was released simply heating up the substrate with no solvent to 110 °C for 23 h under a nitrogen atmosphere. Hydrogen was captured by reduction of *trans*-stilbene in the presence of 10% Pd/C in 39% yield. However, when the authors used d_6-DMSO, the guanidinium product was present in 90% yield.[56] According to them, this remarkable reactivity is a consequence of its conformation. The central carbon-hydrogen bond is antiperiplanar to three nitrogen lone pairs.



Scheme 51 Wuest's generation of H_2 from orthoformamides with an activated carbon-hydrogen bond.

According to Salehzadeh and Maleki, there are three limiting trajectories for the protonolysis of the central carbon-hydrogen bond.[61] The first one is a colinear approach **A**. The second one is an orthogonal approach that produces a triangular transition state **B**. Alternatively, in the third one, the formation and release of H_2 molecules occurs *via* a transition state in an orthogonal approach that produces a square structure **C**, this being the favourite one **(Fig. 28)**.

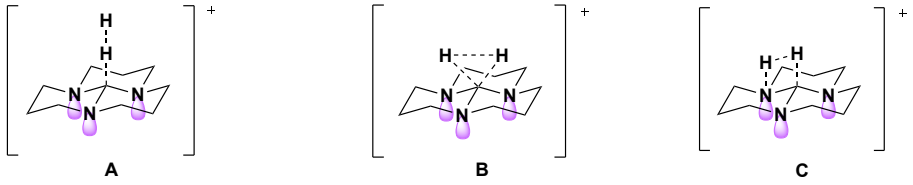
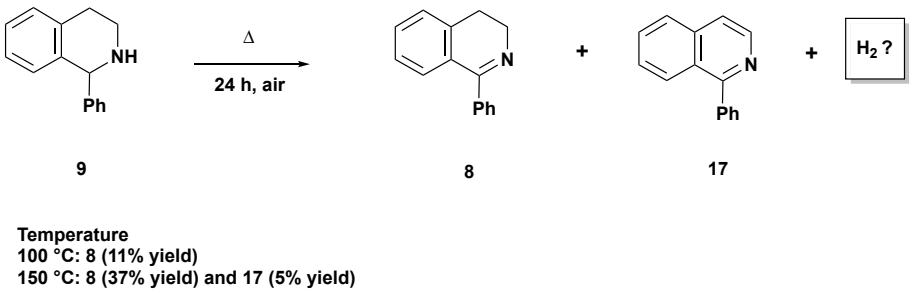


Fig. 28 Alternative transition states with either a linear configuration **A**, a triangular configuration **B**, or the favorite one, square configuration **C.**

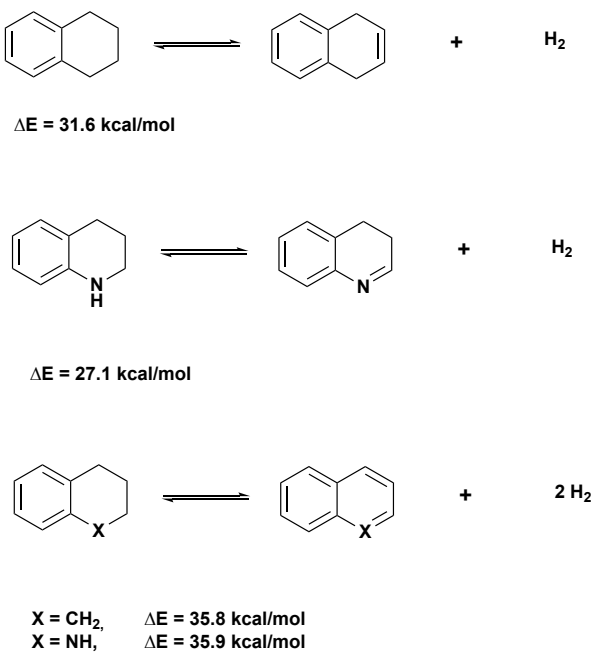
For these reasons, we also sought to try our reaction with no solvent. Therefore, 0.5 g of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9** was heated neat with no solvent to 100 °C for 24 h under air atmosphere **(Scheme 52)**. The substrate melted at 87–90 °C without decomposition, but after 2 h, the melt turned yellow. Interestingly, when no solvent was used, the GC–MS analysis showed clearly that product **8** was still formed, even if only in very low yield at 11%. Increasing the temperature to 150 °C, the neat reaction produces the product **8** in 37% and by-product **17** in 5% **(Appendix Fig. A12 – A16)**.



Scheme 52 Neat dehydrogenation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **9**.

Catalytic hydrogen release from substrates, such as cyclohexane to give benzene, are strongly endothermic. These kinds of reactions usually require really high temperature. Crabtree and Muller showed that the inclusion of heteroatoms into the organic structure, especially nitrogen, can favour hydrogen release.[49b.56,60] According to them, not only N-H bonds are slightly weaker than analogous C-H or O-H bonds, but they also have a weakening

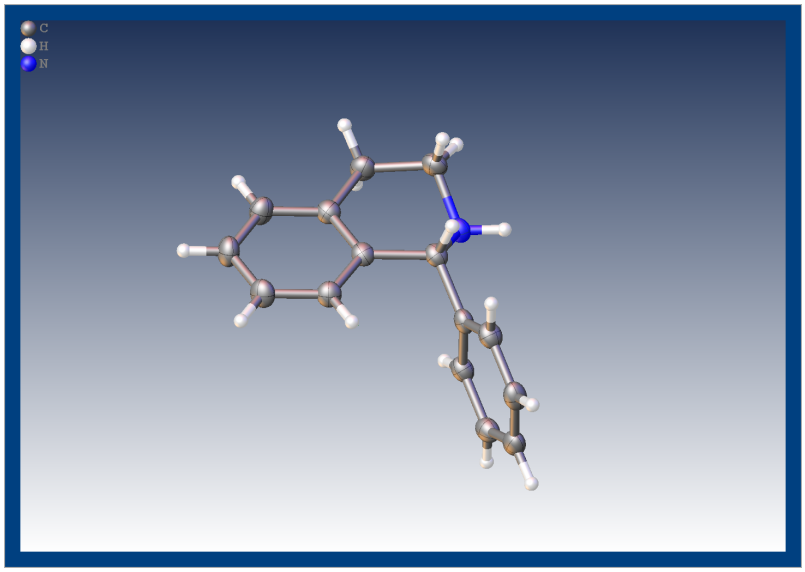
effect on adjacent C-H bonds. Crabtree showed theoretically and experimentally that the dehydrogenation is possible even at modest temperature.[60c] The presence of one or more nitrogen atoms lowers the unfavourable enthalpy of the reaction. When double dehydrogenation is considered, the enthalpies shift from 27.1 to 35.9 kcal/mol. These numbers are not much higher than those obtained for mono-dehydrogenation because the molecules formed are aromatic **(Scheme 53)**.



Scheme 53 Crabtree's calculation of the reaction enthalpies for dehydrogenation.

Salehzadeh and Maleki published a comparative DFT study on hydride release from a number of known orthoamides both in the gas phase and in solution.[61] The data showed that orthoamides release hydride more easily upon dissolving in polar solvent. The values of Gibbs free energy ΔG_{soln} decrease with increasing polarity of the solvent. In some examples, Gibbs free energy ΔG_{soln} reaches negative values, indicating that these compounds will probably release the hydride upon dissolving in related solutions. Therefore, the chemical reaction in solution may show unexpected properties in comparison with the gas phase. The

computational data clearly show that the most significant impact on ΔG value for the release of hydride are due to the hyperconjugation interactions in the initial orthoamide compound and the proper mixing of the empty *p* orbital of the central carbon atom with adjacent lone-pair orbitals of nitrogen atoms ($lp\text{N} \rightarrow \sigma^*_{\text{CH}}$). In these compounds, the hyperconjugation interaction facilitates the anion release. The values of Gibbs free energy ΔG_{soln} decrease with an increase of the value of the hyperconjugation interaction. Furthermore, the C-H bond is notably weakened and polarised by proper mixing of σ^*_{CH} with adjacent lone-pair orbitals of nitrogen atoms ($lp\text{N} \rightarrow \sigma^*_{\text{CH}}$). The antibonding orbital of C-H bond is anti-periplanar to the adjacent lone pairs of nitrogen atoms. This leads to a significant effect on the ΔG value for the hydride releasing compounds. Indeed, the above orbital interaction significantly stabilises the resulting carbocations and considerably decreases the ΔG value for hydride-releasing process. The values of Gibbs free energies are reduced even further due to the solvent effect. Following this theory, we wished to verify if 1-phenyl-1,2,3,4-tetrahydroisoquinoline possesses the characteristics described above. Therefore, it was subjected to X-ray crystal analysis **(Fig. 29)**. This revealed that the C-H bond is effectively antiperiplanar to the nitrogen lone-pair.



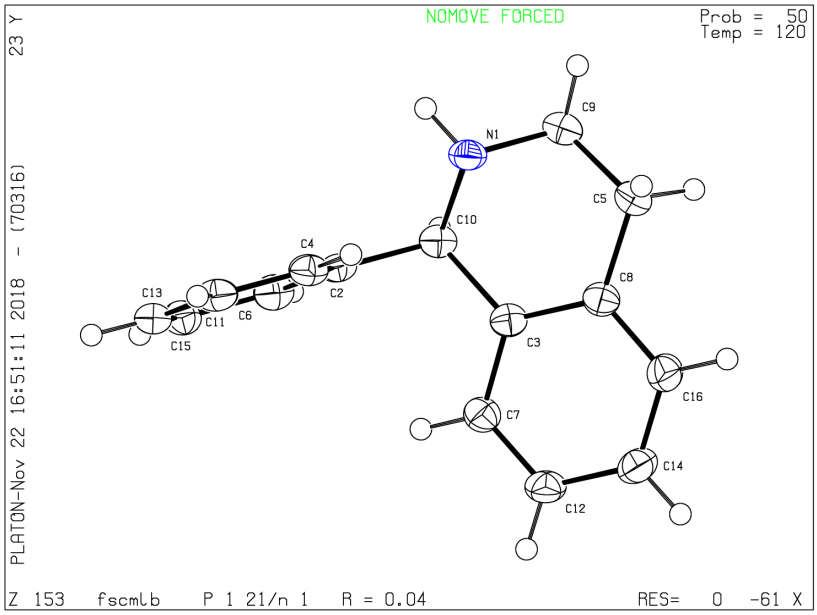


Fig. 29 X-ray Crystal structure of 1-phenyl-1,2,3,4-tetrahydroisoquinoline.

A peculiar behaviour of the dehydrogenation reaction that should be highlighted is the observation on air/argon atmospheres. When DMSO is the bulk solvent, the presence of air or argon atmospheres does not make any difference **(Table 8, Entry B)**. This is in agreement with Feng and co-workers.[28] However, when the reaction is conducted in toluene as the bulk solvent, with minimal amount of DMSO, the air atmosphere is of pivotal importance for the success of the reaction. In fact, it has been seen on several occasion that an argon atmosphere hampers the reaction, making it fail completely **(Fig. 30)**.

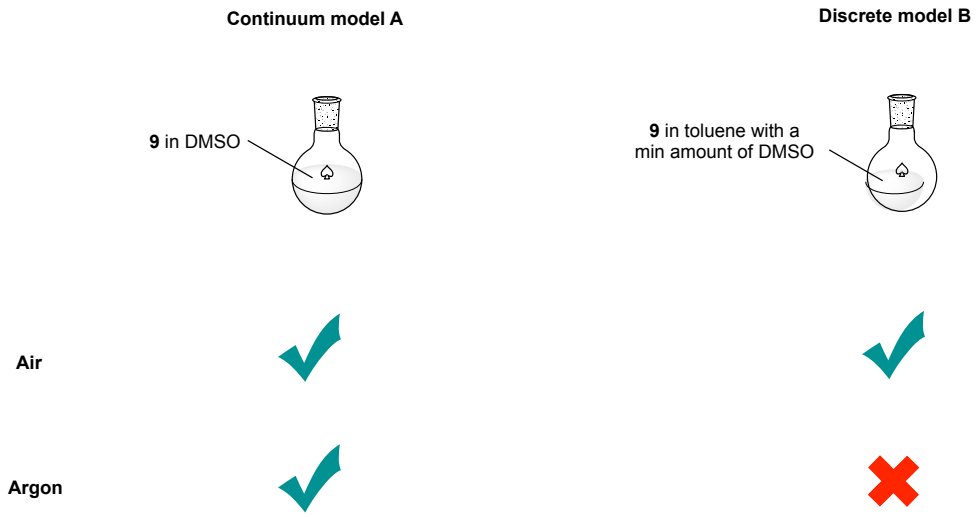


Fig. 30 Role of the atmosphere on the reaction.

The reason for this behaviour may be due to solvent effects. It is widely accepted that a change of solvent can considerably change the rate of a chemical reaction. There are important differences between polar solvents, those that have high dielectric constants, and nonpolar solvent media. In the two cases described above, the bulk of the reaction is different.

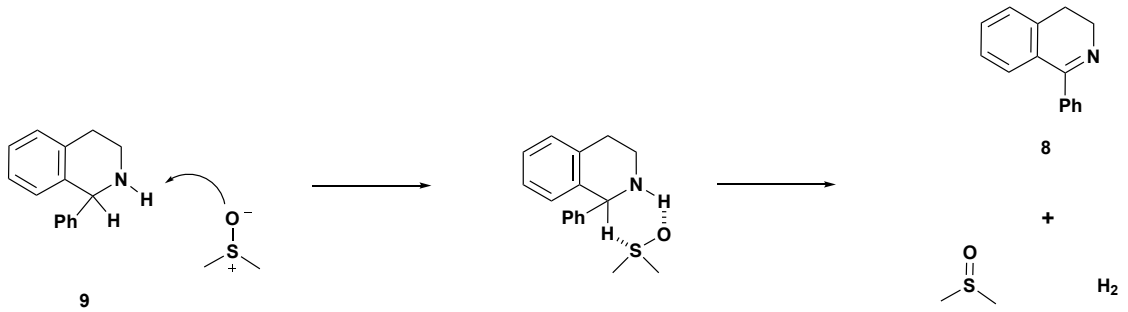
Furthermore, when discussing solvent effects, it is important to distinguish between the macroscopic effects and those that depend upon details of structure. Macroscopic properties

refer to properties of the bulk solvent. One example is the dielectric constant ε. Microscopic dielectric constant ε around the reactants may be different to the macroscopic dielectric constant ε of the bulk solvent.[62] An important property of solvent molecules is the response to changes in charge distribution as reaction occurs. The dielectric constant of a solvent is a good indicator of its ability to accommodate separation of charge. A solvent should not be considered a macroscopic continuum characterised only by its macroscopic physical constants such as boiling point, vapour pressure, density, cohesive pressure, index of refraction, relative permittivity, thermal conductivity, surface tension, etc. From the molecular-microscopic point of view, a solvent is a discontinuum which consists of individual, mutually interacting solvent molecules, characterised by their molecular properties such as dipole moment, electronic polarisability, hydrogen-bond donor (HBD) and hydrogen-bond acceptor (HBA) capability, electron-pair donor (EPD) and electron-pair acceptor (EPA) capability, etc.[63] Theoretical modelling of the environmental modulation of solute properties is receiving increasing attention nowadays. The study of the interaction between a solute and solvent is complicated and has been handled theoretically through models with varying degrees of sophistication. These models can be divided into two groups: **A** the discrete model, and **B** the continuum model. In the discrete model **A**, a finite number of solvent molecules are assumed to surround the solute molecules and all molecules, of the solutes or solvents, are treated explicitly. The model focuses on the description of short-range interactions and the results often depend on the number of solvent molecules used in modelling the surrounding of the solute species. Models of this kind may be suitable for describing specific solvent effects such as hydrogen bonding and charge transfer between the solute and solvent. In the continuum models **B**, the solvent is described by a homogeneous continuous medium characterised by a macroscopic dielectric constant. The solute molecule is assumed to interact with the surrounding polarisable dielectric medium. The continuum models allow one to take into account long-range interactions.[64]

The reaction that contains a small amount of DMSO in toluene is approximated to a discrete model **A**. In this case, only short-range interactions between solute and solvent must be taken into consideration. The reaction in which DMSO is the bulk is approximated to a continuum model **B**. In this case, macroscopic properties and long-range interactions must also be taken into account. This may explain why the reaction performed under argon does work when DMSO is the bulk of the solvent, and not when toluene is the bulk of the solvent. A literature example of this concept is presented by Privalov.[65] They studied the Pd-catalysed aerobic oxidation of alcohol in DMSO. In this study, DMSO represents both the ligand for the metal and the solvent. The authors define as ligands those DMSO molecules that are bound in the first coordination sphere of Pd. The rest is considered solvent. They concluded that in the continuum model, DMSO in the second coordination sphere is important for the stability and the geometry of $Pd(DMSO)_x$ complex. Weak intermolecular interactions become less important when dielectric constant is considered.

Now, the only question left on the argument is why the reaction works in toluene under air atmosphere. One possible answer is that, by providing an oxygen source to fix the product hydrogen as water, the endothermic dehydrogenation process may be converted to a more favourable exothermic one.

Taking everything into account, a possible mechanism is proposed **(Scheme 54)**. Initially, DMSO coordinates with the amine group forming a hydrogen bond. A six-atom transition state is formed with a hydrogen bond forming between the oxygen atom of the DMSO and the hydrogen of amine, and a second hydrogen bond is formed between the sulfur atom of the DMSO and the C-H bond of the compound. Finally, rearrangement lead to the formation of hydrogen molecule with consequent formation of the partially dehydrogenated by-product, and regeneration of DMSO.



Scheme 54 Postulated mechanism for DMSO-promoted dehydrogenation.

The reasons that support this postulated mechanism are the following. DMSO is an ambidentate molecule. The oxygen atom in DMSO has two lone-pairs and partially negative charge. It is common for the oxygen atom of DMSO to engage in hydrogen-bonds. The sulfur atom of DMSO also has a lone-pair and is partially positively charged. It is generally considered a soft nucleophile.[66] It is assumed that DMSO is catalytic. Therefore, at the end of the reaction, it is not consumed. This was shown in the stoichiometry experiments, in which DMSO works well at 0.5 eq compared to the substrate **(Table 8)**. Moreover, no generation of sulfide was detected by GC–MS or NMR spectroscopy **(Fig. 16-18**, and **Scheme 45-47)**. The GC–MS shows a constant concentration of DMSO along the reaction whilst the product is forming **(Fig. 19-20)**. The detection of hydrogen gas generated in the reaction has been investigated in several ways. The TGA–MS has clearly seen a peak corresponding to hydrogen (*m/z*=2) **(Fig. 21-23)**. This is in agreement with Feng and co-workers.[28] Measuring cylinder displacement has been noticed, even if it failed to pop in contact with a flame **(Fig. 25-27)**. In the NMR experiment **(Fig. 24)**, the signal of the hydrogen peak failed to appear in the expected range 4.5 – 4.7 ppm. However, the signal of water at 3.3 ppm was increasing constantly during the reaction. Furthermore, at the end of the reaction, a signal between 10 – 11 ppm started to appear. This could be attributable to hydrogen peroxide.

The influence of the solvent dielectric constant has been tested **(Fig. 6-9)**. Causing the reaction to occur in a series of mixed solvents (toluene and DMSO) of increasing polarity, the yield of the product increased accordingly.

The kinetic studies in **Fig. 14** and **Fig. 15** suggest a consecutive mechanism of the kind,

starting material ⟶ [*X*] ⟶ product

In **Fig. 14**, the half-time for the starting material is about 2 h, but the product is present in 50% yield after 3 h. This is even more evident with the deuterated version **(Fig. 15)**. The starting material has a half-time of 5 h, while the product reaches the 50% yield after 10 h. This suggest that the reactant is converted in an intermediate **[*X*]**, which subsequently forms the product.

2.4 Conclusion

In conclusion, a green protocol for accessing cyclic and acyclic imines with good to excellent yield has been developed. The simplicity of the operations, the lack of mutagenic reagents, and the environmental benignity of the process are all advantages that make the reaction particularly attractive for industrial purposes. Furthermore, this methodology can be applied for the removal of a diphenylmethyl protecting group. Traditionally, this protecting group is very robust, and therefore not used very widely. This way, its application can be employed more broadly. Under the established conditions, the substrates are dissolved in dry DMSO and the mixture heated for 24 h at 100 °C.

The traditional path in which a sulfide is formed after a sulfoxide-mediated oxidation is excluded. Therefore, the reaction probably occurs through a rare example of thermal dehydrogenation, as has already been postulated by Feng and co-workers.[28] There are several problems that hamper hydrogen detection, for example its rapid diffusion. Hydrogen molecules are smaller than all other gases, and can diffuse through many materials, sometimes even if they are airtight or impermeable to other gases. Therefore, hydrogen is more difficult to contain than other gases.

Today, hydrogen is considered an important fuel for the future. It would allow significant amounts of electrical power to be obtained using a pollution-free source of energy that can be

used as fuel for cars and other vehicles. The major H_2 storage approaches are physical, such as high-pressure tanks or cryogenic methods, or chemical such as reversible absorption in metal or hydrides. High pressure tanks are very voluminous and may pose practical problem. They are hazardous and have an historical "bad reputation" after the Hindenburg disaster.[67] Condensation into liquid is, of course, particularly attractive from the point of view of increasing the mass per volume, but the condensation temperature of hydrogen at 1 bar is -252 °C, and it has a critical temperature of -241 °C. Cryogenic storage requires very low temperature, implying a large energy loss in the liquefaction step. Energy input is constantly required to maintain cooling. Chemical methods such as metal hydride have been extensively studied. MgH_2 or $LiBH_4$ have been proposed under several forms.[68] However, scalability has not been considered in these approaches. These elements are not available on a scale needed to make an impact on global level and, therefore, they are unrealistic candidates.

Liquid organic hydrogen carriers (LOHCs) have significant advantages compared to other methods. They can be readily pumped not just for distribution and delivery, but also within the vehicle during operation. Only a small aliquot would be pumped into the dehydrogenation chamber for heating to reaction temperature at any given time. Once dehydrogenated, the spent storage material would be off-loaded at the fuel station and substituted with fresh material by trained personnel. H_2 has a high diffusivity, leading to enhanced risk from leaks. It can cause embrittlement of metals, generating potential leaks and problems at engineering. The H_2 flame is also invisible. These elements all represent dangers that are avoided with a liquid storage material strategy. For many years, the possibility of storage of hydrogen in organic compounds has not been thought to be feasible. Hydrogen is release from all covalent carbon hydrogen compounds only when heated above 800 °C.[69] However, in the last two decades research focused on modification of carbon hydrogen compounds to favour H_2 release. Several groups focused their studies on reducing the enthalpies and favouring the thermodynamic of H_2 release both theoretically and experimentally. Useful structure activity trends have been identified and patented.[50,70]

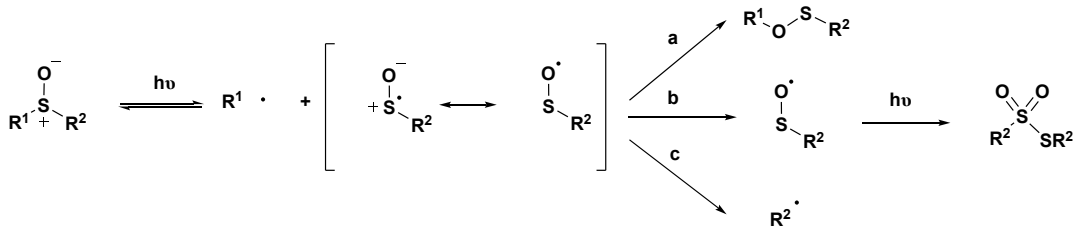
The fuelling and refuelling reactions of a chemical storage system correspond to dehydrogenation and hydrogenation processes. Metal-free hydrogenation/dehydrogenation processes of *N*-heterocycles are rare, but have been proposed by the pioneering work of Stephan and co-workers, and by Berke and co-workers. In both cases, dehydrogenated compounds reacted with H_2 in solution at 25 – 30 °C.[71] Hydrogen storage in new materials and devices is an active field for research worldwide. Attractive performances have been seen in carbon-based solids.[72] Single-walled nanotubes (SWNTs) or microporous metal-organic frameworks are both under study to improve their performance before practical applications.[73,74] With our system, not only are lower release temperatures achieved, but the metallurgic degradation of the catalyst is also avoided.

3 Photochemistry of sulfoxides

The sulfoxide functional group has been compared to the carbonyl group for a very long time, due to its apparent similarity. Both of them have polarised bonds. However, there are significant differences between the two groups. The main one is the hybridisation. Whilst the carbon atom in the carbonyl group is sp^2 hybridised, the sulfur atom in the sulfoxide is approximately sp^3 hybridised. Moreover, unlike the carbonyl group, the bond between S and O is not a real π bond. However, it cannot be represented as a single bond either.[75] Another important aspect of the sulfoxide functional group is its intermediate oxidation state. In a sulfoxide, the group with sulfur in (+IV) oxidation state, can be either reduced to a sulfide (+II) or oxidised to a sulfone (+VI). A sulfoxide can undergo four different unimolecular chemical changes under irradiation conditions, i.e., α-cleavage (Section 3.1), hydrogen abstraction (Section 3.2), stereomutation (Section 3.3), and deoxygenation (Section 3.4). In the next Section, the photochemical deoxygenation and photophysics of some aromatic sulfoxides will be discussed. Deoxygenation is only a minor process for most sulfoxides, but the sulfoxides investigated in this work were designed to show deoxygenation as the major photochemical reaction.

3.1 α-Cleavage

Under photochemical conditions, homolytic cleavage between the sulfur and the adjacent carbon atoms occurs, and two radicals are formed, a carbon-centred radical and a sulfinyl radical **(Scheme 55)**. The latter has two resonance structures. A sulfenic ester will form when the organic radical and the sulfinyl radical recombine at the oxygen terminus **(Path a)**. A thiosulfonate is formed following the dimerisation of the sulfinyl radical **(Path b)**. In case of extra driving force, the sulfinyl radical can lose SO **(Path c)**.

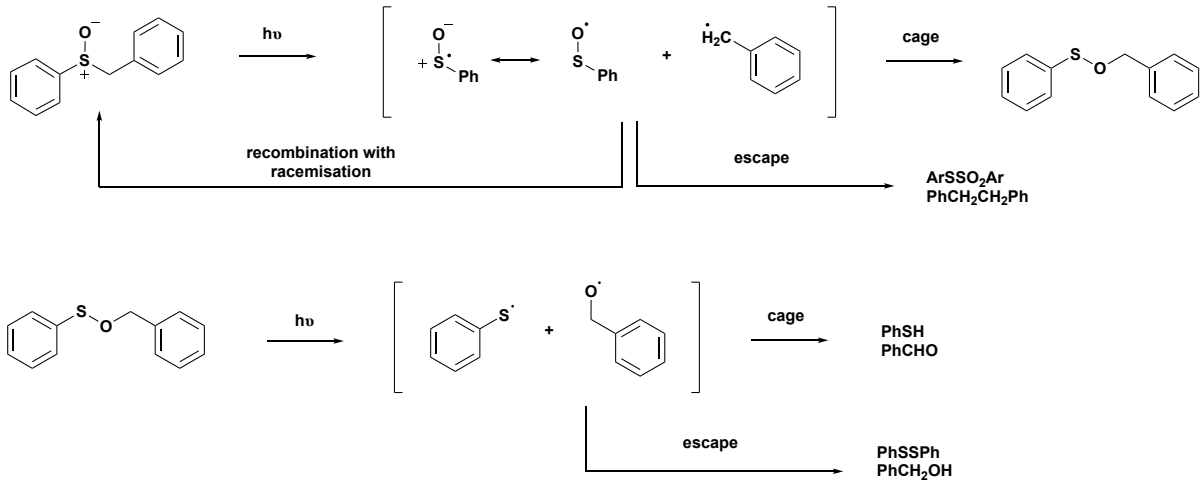


Scheme 55 The α-cleavage reaction of sulfoxides.

Direct detection of several sulfinyl radicals and their spin-trapping products has been performed in electron paramagnetic resonance (EPR) experiments at low temperature. These studies provided evidence for the α-cleavage mechanism.[76] Moreover, flash photolysis of thiosulfinate was used to observe the phenyl sulfinyl radical at room temperature.[77]

Guo and Jenks studied the photolysis of sulfoxides in detail.[78] The irradiation of phenyl benzyl sulfoxide until all of the starting material was consumed generated a complex reaction mixture, mainly the result of secondary photolysis. The exact composition of this complex mixture depended on several parameters, including the viscosity of the solvent, and the wavelength of excitation. To avoid this problem, the reaction mixtures reported were 3-5 mM in initial concentration, and the irradiations were carried out to modest conversions (≤ 20%). Sulfoxides are particularly susceptible to secondary photolysis because several of the photoproducts have large absorption extinction coefficients, at wavelength above 290 nm. The problem was alleviated by tuning the excitation wavelength to 267 nm with a 150 W Xe lamp filtered through a monochromator. The initial product from photolysis of phenyl benzyl sulfoxide is a radical pair formed by an α-cleavage reaction. Since the benzyl radical is more stable than the phenyl radical, the cleavage pattern forming the benzyl radical is the only one observed **(Scheme 56)**. This radical pair forms the sulfenic ester. This is subjected to a second photolysis to create a second radical pair. When optically pure *(S)*-sulfoxide was used, the first radical pair also gave the starting material back with racemisation through to a random recombination that leads to a loss of configuration (Section 3.3). The first radical pair also gave a certain amount of escape products. These products were observed only when the

photolysis was carried out in low viscosity solvents and are consistent with a S-C bond cleavage followed by escape to form freely diffusing radical pairs. The result of the combination between separation and recombination depends substantially on the viscosity of the solvent.

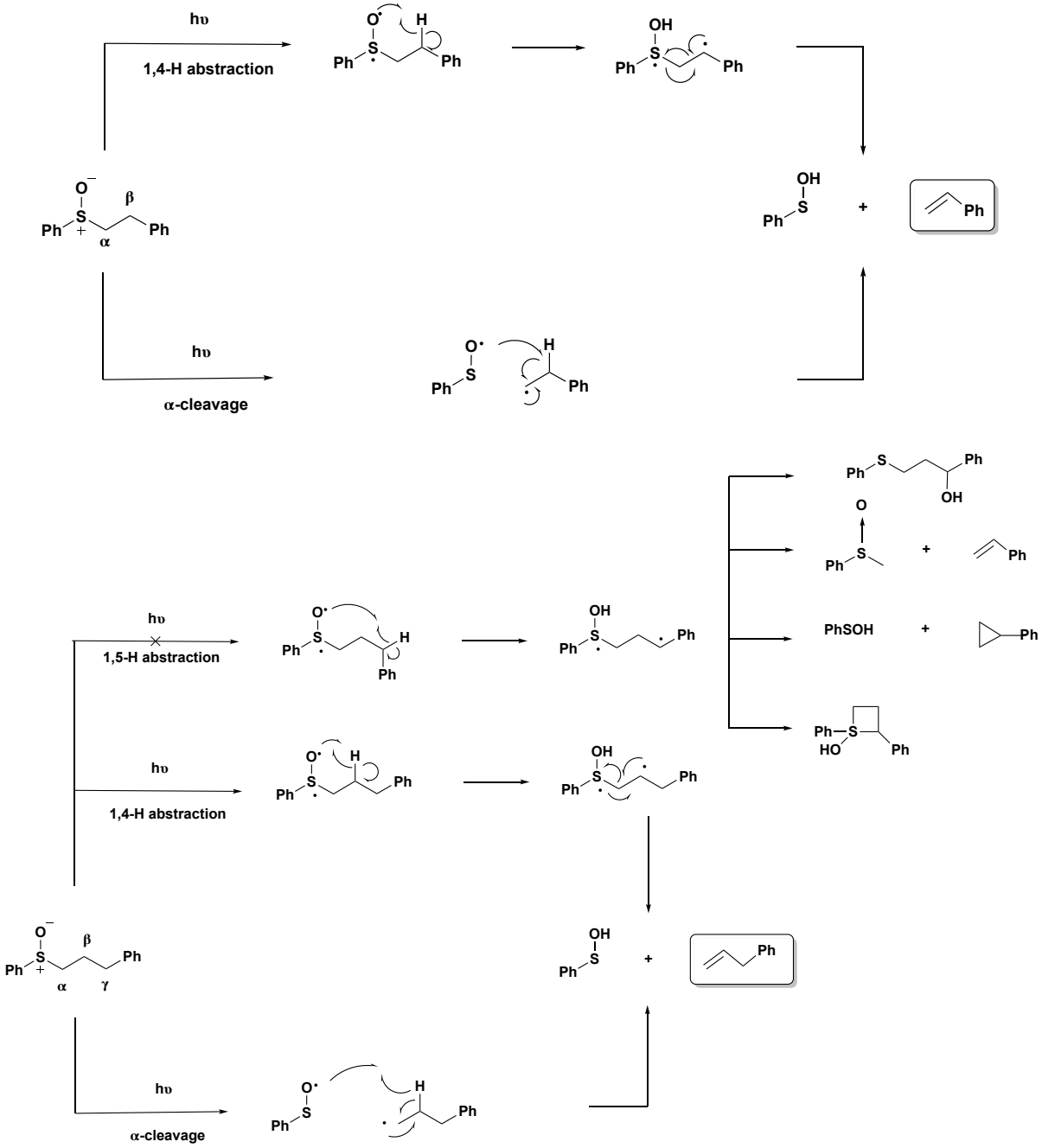


Scheme 56 Guo and Jenks's proposed overall reaction scheme for photolysis of sulfoxides.

3.2 Hydrogen abstraction

The hydrogen abstraction reaction is a very common reaction for both sulfoxide and carbonyl compounds under irradiation conditions. Due to the analogy of the sulfoxide group with the carbonyl group, hydrogen abstraction reactions of sulfoxides were originally explained by the same mechanism. However, now that there is more knowledge about the differences between the sulfoxide group and the carbonyl group, those results are no longer applicable. The same results of products formed *via* hydrogen abstraction can also be explained *via* an α-cleavage mechanism. Guo and Jenks designed an experiment to clarify this issue.[79] They chose an aryl alkyl sulfoxide in which there were β- and γ-hydrogen atoms **(Scheme 57)**. To reduce secondary chemistry, the product yields were measured at $\leq$ 10% conversion. Solutions between 3-5 mM of these sulfoxides in *tert*-butanol were irradiated at 267 nm. No products

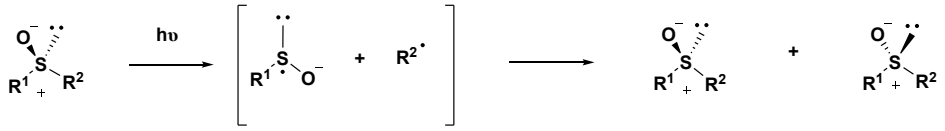
whose formation was due to a γ-hydrogen abstraction mechanism exclusively were formed. The highlighted olefinic products were the only ones observed. Their formation can be explained by both 1,4-hydrogen abstraction mechanism and α-cleavage mechanism. In the example given in **Scheme 54** both mechanisms are shown. For this reason, the 1,4-hydrogen abstraction mechanism cannot be supported, but neither can it be ruled out.



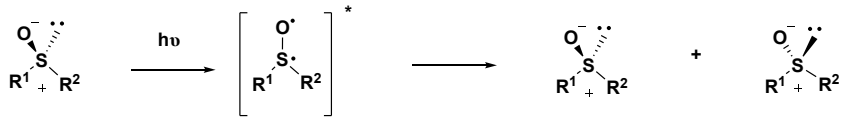
Scheme 57 Postulated sulfoxide photochemistry with *H*-abstraction *vs.* α-cleavage. Only products shown in boxes were observed.

3.3 Stereomutation

When two different groups are attached to the sulfur atom, the sulfoxide group is asymmetric. However, racemisation of chiral sulfoxides may occur photochemically through two different mechanisms. In the first, an α-cleavage reaction followed by recombination of the radical pair leads to the stereomutation **(Scheme 58)**. The second mechanism consists of a direct inversion, when the inversion barrier is low **(Scheme 59)**.

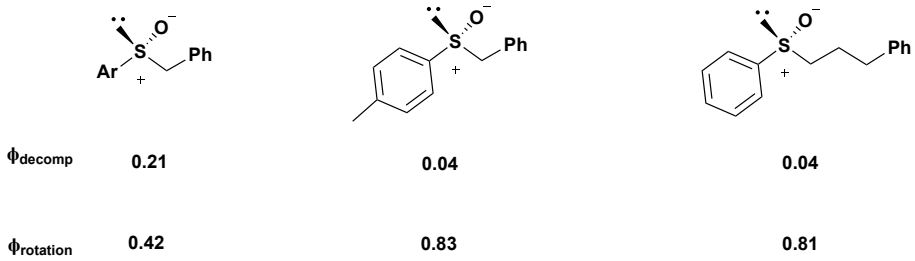


Scheme 58 Stereomutation of sulfoxides by α-cleavage reaction.



Scheme 59 Stereomutation of sulfoxides by direct inversion.

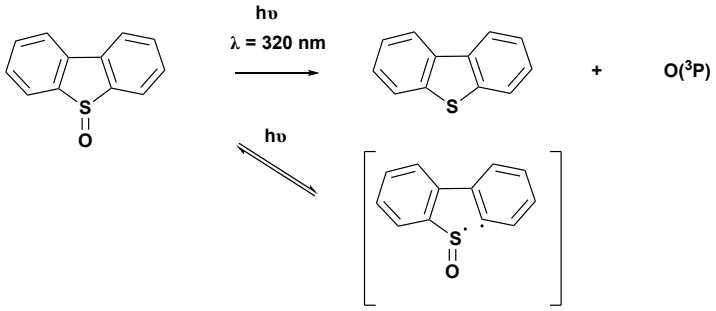
Guo and Jenks investigated the stereomutation of sulfoxides in further detail.[78,79] They studied the racemisation of different aryl alkyl sulfoxides **(Scheme 60)**. Photolysis of chiral sulfoxides were carried out in *tert*-butanol at 267 nm with a concentration of the starting material of 4-6 mM. In **Scheme 60** ϕ_{decomp} represents the total quantum yield for chemical conversion and $\phi_{rotation}$ is the quantum yield for loss of optical rotation. Comparing the quantum yield for loss of optical rotation to the quantum yield for loss of starting material, it was suggested that the α-cleavage reaction is not the only mechanism that leads to stereomutation. In fact, despite a very low value for ϕ_{decomp} they have a very high value for $\phi_{rotation}$.



Scheme 60 Stereomutation of aryl alkyl sulfoxides in ^{t}Bu-OH at 267 nm with a concentration of 4-6 mM.

3.4 Deoxygenation

In 1973, Shelton and Posner reported for the first time the deoxygenation of aromatic sulfoxides upon photoirradiation.[80,81] The sulfur-oxygen bond cleavage is generally a minor reaction compared to α-cleavage. However, in compounds in which α-cleavage is energetically disfavoured, or when the diradical cleavage products have no choice but to recombine giving back the starting material, the deoxygenation process is more marked. Dibenzothiophene oxide DBTO is a unique case, in which only deoxygenation is observed. α-Cleavage is a low quantum yield process, and the recombination to DBTO is fast **(Scheme 61)**.[82,83]

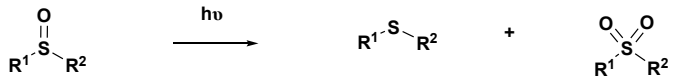


Scheme 61 Fast recombination of DBTO diradical with 320 nm irradiation by 150 W Xe lamp.

In this Section, all of the many proposed mechanisms for deoxygenation will be described. Disproportionation (Section 3.4.1), dimer mechanism (Section 3.4.2), sulfinyl mechanism (Section 3.4.3), hydrogen abstraction (Section 3.4.4), and unimolecular homolytic cleavage (Section 3.4.5) have all been proposed in the literature.

3.4.1 Disproportionation

In simple sulfoxides such as DMSO, the reaction of two sulfoxide molecules to produce one molecule of sulfone and one molecule of sulfide has often been observed **(Scheme 62)**. However, in the case of DBTO, the sulfone molecule has never been detected. For this reason, the disproportionation mechanism has been excluded.[81]

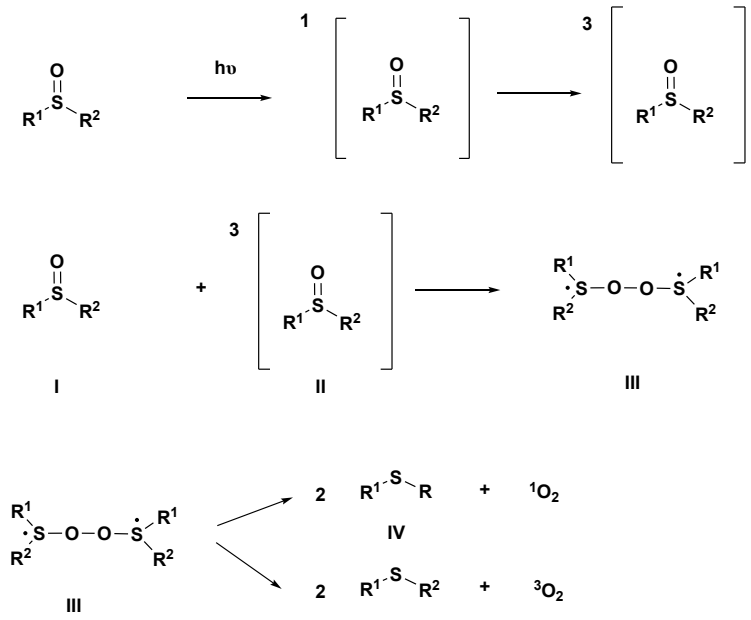


Scheme 62 Photochemical disproportionation reaction of sulfoxides.

3.4.2 Dimer mechanism

Posner and Shelton independently and almost concurrently proposed a dimer mechanism for the photochemical deoxygenation of sulfoxides.[80,83] According to their mechanism, a ground-state sulfoxide **(I)** and a photochemically generated triplet sulfoxide **(II)** form a peroxide type sulfoxide dimer **(III)**. This species decomposes to form the corresponding sulfide **(IV)** and molecular oxygen **(Scheme 63)**. The key step of this mechanism is the formation of the triplet state **(II)** of sulfoxide. Whilst Posner proposed that the oxygen formed would be a singlet, Shelton argued that it would form ground state molecular oxygen. The assignment of singlet oxygen by Posner was based on the isolation of cyclohexenol when DBT was photolysed in the presence of cyclohexene, as a singlet oxygen quencher. The fact that cyclohexene is not

a good chemical quencher was proved a few years later.[84] The assignment of an excited sulfoxide triplet state by Shelton was based on sensitised experiments. When benzophenone was added as a sensitiser, an increase in yield of the sulfide was observed. However, it is now clear that benzophenone does not have sufficient energy for direct triplet energy transfer to sulfoxides.



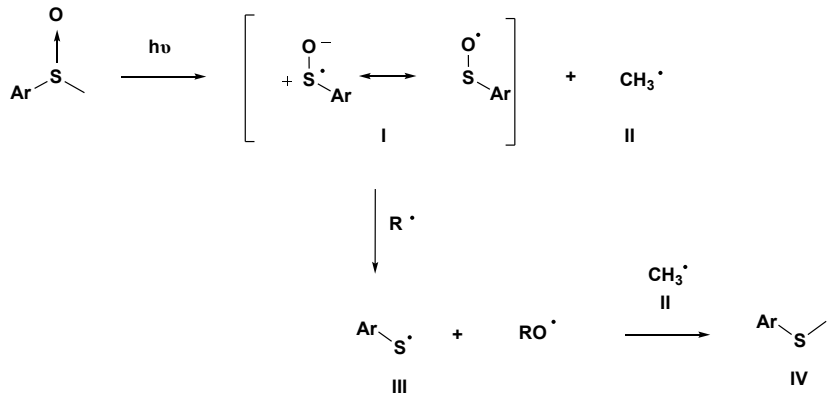
Scheme 63 Dimer mechanism in the photo-deoxygenation of sulfoxides.

The dimer mechanism has been investigated experimentally many times since it was first proposed. The reaction is proposed to proceed *via* an excited triplet state. This triplet state sulfoxide should form a dimer with another ground state sulfoxide molecule. Therefore, the lifetime of the triplet state should be sufficiently long to allow triplet state quenching. Photolysis of the sulfoxide in the presence of a triplet quencher should decrease the quantum yield of the deoxygenation. However, photolysis of DBTO in the presence of triplet quenchers such as isoprene, cyclopentadiene, and oxygen do not decrease the quantum yield of the deoxygenation reaction.[82] From these experiments it can be concluded that pre-association of

the sulfoxides is not a requirement for the photo-deoxygenation of dibenzothiophene sulfoxide. This suggests that the dimer mechanism is not occurring.

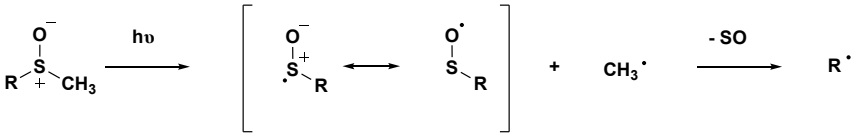
3.4.3 Sulfinyl mechanism

In the sulfinyl mechanism suggested by Lüdersdorf in 1981, the key step is α-cleavage to generate a sulfinyl radical **(I)** and a carbon-centred radical **(II)**.[85] The former facilitates the oxygen transfer to another radical in solution, resulting in the sulfenyl radical **(III)**. This couples with a methyl radical **(II)** to form the final sulfide **(IV) (Scheme 64)**.



Scheme 64 Sulfinyl mechanism in the photo-deoxygenation of sulfoxides.

According to the authors, other radicals in solution are generated by a rare SO extrusion process **(Scheme 65)**.[85]

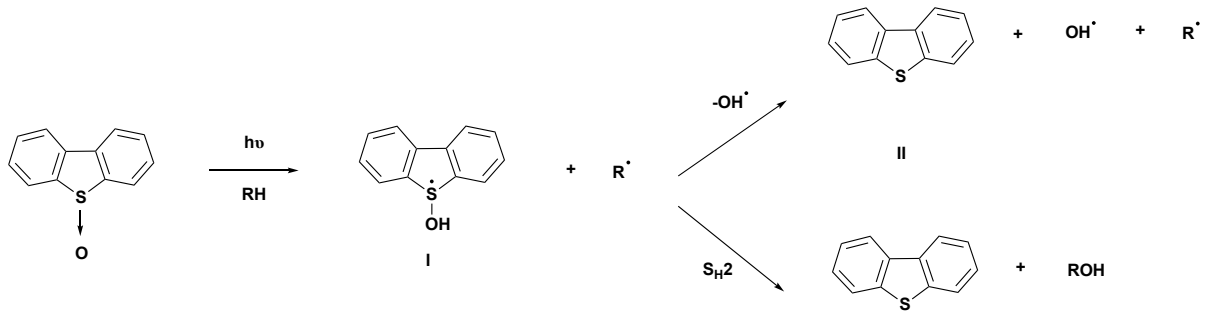


Scheme 65 Elimination of SO according to Lüdersdorf.

The energetics of the sulfinyl radical ruled out this mechanism. In fact, the bond dissociation energy of the S-O bond of the sulfoxide is higher than that of the S-Ph bond by 35 kcal/mol. Thus, one would expect cleavage of the S-Ph bond before the S-O bond. Moreover, the oxygen transfer from the sulfinyl radical to the carbon radical is an endothermic process. Due to these considerations, the sulfinyl mechanism was ruled out.

3.4.4 Hydrogen abstraction

In the hydrogen abstraction mechanism, the excited state sulfoxide abstracts a hydrogen atom from the solvent to form a radical **(I)**. This decomposes, generating the sulfide **(II)** by loss of hydroxyl radical or by an S_H2 type mechanism where R• radical attacks the hydroxyl group **(Scheme 66)**.



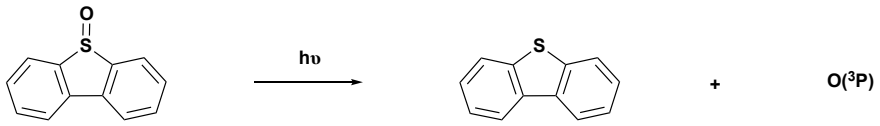
Scheme 66 Hydrogen abstraction mechanism for the photo-deoxygenation of sulfoxides.

The hydrogen abstraction mechanism implies that the hydrogen donating ability of the solvent would severely affect the quantum yield of the deoxygenation process. Solvents that can donate hydrogen atoms more easily should lead to higher quantum yields. Jenks and co-workers showed that the rate of deoxygenation of DBTO is essentially constant across a wide variety of solvents with different hydrogen-donating abilities.[81] Therefore, this mechanism was ruled out because of the lack of dependence between solvents and deoxygenation quantum yield. The quantitative yield of sulfide in solvents as diverse as 2-propanol, benzene,

acetonitrile, and toluene are nearly identical. In Freon 113, which has no hydrogen to abstract, the quantum yield of DBTO deoxygenation is of 0.024.

3.4.5 Unimolecular homolytic cleavage

In 2001, Greer and co-workers proposed a direct cleavage of the S-O bond, forming the corresponding sulfide and a triplet oxygen atom O(^{3}P). Subsequently, the triplet oxygen reacts with the solvent oxidising it from benzene to phenol **(Scheme 67)**.[86]



Scheme 67 Mechanism for the direct homolysis of the S-O bond.

The reactivity of the oxygen atom in its ground state, O(^{3}P), has been extensively studied in the gas phase. However, its reactivity in solution has not been well established. The lack of information about O(^{3}P) reactivity in solution is mainly due to a lack of knowledge about organic systems that generate triplet oxygen atoms cleanly. Scaiano and co-workers presented evidence for the formation of O(^{3}P) in acetonitrile solution upon flash photolysis of pyridine *N*-oxide.[87] Greer and Mazur studied the oxidation products of styrene and made a direct comparison between the oxidation O(^{3}P) styrene oxidation pattern arising from *N*-oxide and the one from active oxygen species produces in the photolysis of DBTO.[86b,88] The results of this comparison are shown in **Table 12**. The O(^{3}P) generated by N_2/N_2O discharge reacts with styrene, forming four oxidation products. The difference in selectivity between these four products is noticeable. In the absence of oxygen, the epoxide and phenylacetaldehyde are formed in a 62:31 ratio. Acetophenone and benzaldehyde are formed in traces **(Table 12, entry 1)**. When molecular oxygen O_2 was present, the yield of acetophenone and

benzaldehyde increased **(Table 12, entry 2)**. Thereafter, an argon-saturated solution of DBTO and styrene in acetonitrile was irradiated with a 350-nm light. DBTO deoxygenated to give styrene oxide and phenylacetaldehyde in 58:42 ratio. **(Table 12, entry 3)**. When molecular oxygen remains in solution, yields of acetophenone and benzaldehyde increased **(Table 12, entry 4)**. Within experimental error, the results are identical. Product studies in the presence of DBTO are consistent with the expectations of $O(^3P)$.

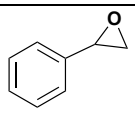
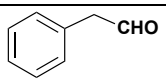
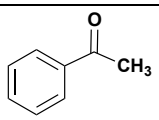
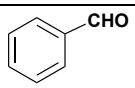
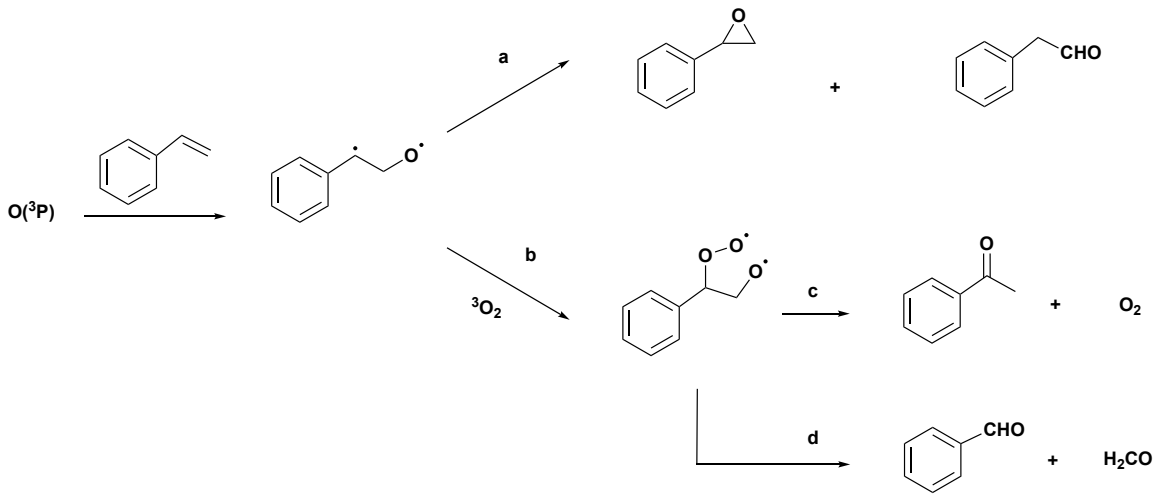
Entry	**Putative source of $O(^3P)$**				
1	MDM-N_2O/N_2 [a]	62	31	2	5
2	MDM-N_2O/N_2-O_2 [a]	44	25	12	19
3	DBTO + hν	58	42	0	0
4	DBTO-O_2 + hν	47	32	5	16

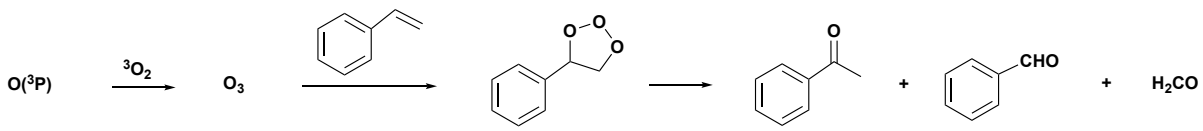
Table 12 Comparison of product distribution in relative yields for styrene oxidation. [a] Microwave Discharge Method (MDM) generates $O(^3P)$.

Greer and Mazur suggested that oxygen was responsible for the formation of by-products, such as acetophenone and benzaldehyde.[86b,88] These were the results of a 3-step mechanism in which $O(^3P)$ attacks styrene, followed by the addition of O_2, forming a peroxyl diradical. This undergoes either cleavage of the C-C bond to form benzaldehyde **(Path d)** or rearrangement to give acetophenone and evolution of O_2 **(Path c) (Scheme 68)**.



Scheme 68 Greer's and Mazur reaction of styrene in the absence **(Path a)** and presence **(Path b)** of molecular oxygen.[86b,88]

Klaning suggested that O(^{3}P) may react with O_2 to yield ozone, then ozonide, and ultimately acetophenone, and benzaldehyde **(Scheme 69)**.[89]

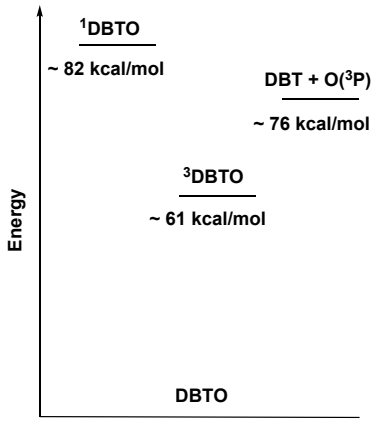


Scheme 69 Ozone formation and reaction with styrene.

Oxygen O(^{3}P) atoms balance reactivity and selectivity. O(^{3}P) reacts with alkanes typically insensitive to other oxidants, such as peracids, dioxiranes, ozone, and singlet molecular oxygen. Moreover, the origin of the oxygen atom was tested.[81] Dibenzothiophene sulfoxide containing 5.5% of ^{18}O was produced by exchange of H_2O^{18} into ordinary sulfoxides. Photolysis of [^{18}O]-DBTO in benzene resulted in the formation of phenol that contained 5.1% of ^{18}O.

The energetic feasibility is another important point to establish the deoxygenation mechanism for dibenzothiophene oxide. The excited singlet energy state of DBTO is about 82 kcal/mol,

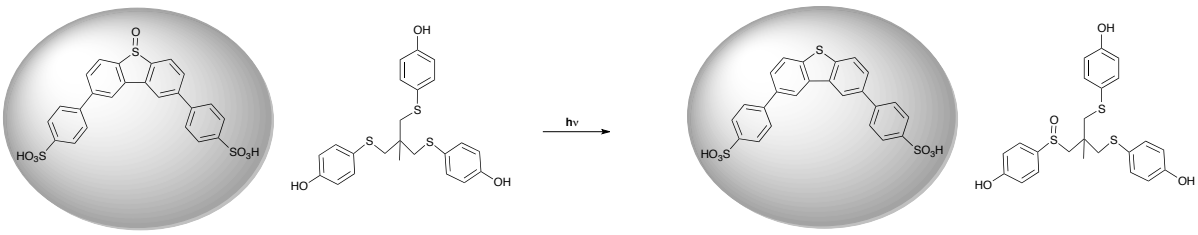
whilst the excited triplet energy state is about 61 kcal/mol. The S-O bond breaking energy was calculated to be about 75-77 kcal/mol **(Scheme 70)**. The authors based these values on the experimental bond dissociation energy of DMSO and diphenyl sulfoxide. From a mechanistic point of view, this is compelling evidence for simple S-O cleavage that generates the sulfide and O(^{3}P), even if there is no direct evidence for the formation of this intermediate.[90]



Scheme 70 Energetics for DBTO excited states and S-O dissociation.

McCulla and co-workers recently published new results that are consistent with freely diffusing O(^{3}P) as the oxidant.[91] They proposed an experiment in which DBTO-derivative-loaded nanocapsules are irradiated in the presence of a O(^{3}P)-trap **(Scheme 71)**. Nanocapsules are made of porous shells of polymers and are used as barriers. They are capable of physically separating relatively large molecules, allowing for diffusion of only small molecules of < 1 nm of diameter through pores in the nanocapsule shell. The O(^{3}P)-trap was a molecule containing three sulfide groups. This O(^{3}P)-trap was chosen because it offered several advantages. First, it was known to have a high reaction rate with O(^{3}P). Secondly, its symmetry allowed for a single oxidation product. Finally, its chromophore made easy detection by UV. DBTO-derivative-loaded nanocapsules were irradiated with broadly emitting UV light (325 – 375 nm) in the presence of a solution of non-encapsulated O(^{3}P)-trap. The formation of oxidised O(^{3}P)-trap following irradiation confirmed a freely diffusing oxidant. No measurable efflux of

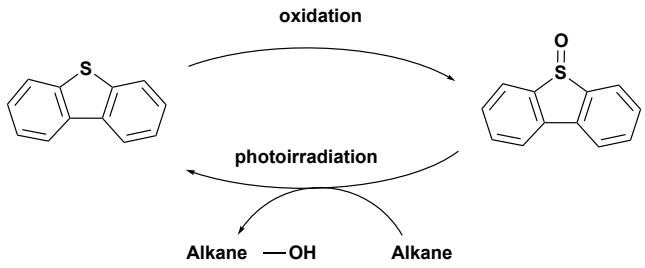
molecules larger than the pore size in the nanocapsules was detected in long-term stability studies over five years.



Scheme 71 DBTO-derivatives nanocapsules irradiated in the presence of O(^{3}P)-trap.

3.5 Objectives

In the presence of light, dibenzothiophene sulfoxide can react with several alkanes to afford the corresponding alcohols. The postulated mechanism involves an atomic oxygen species, $O(^3P)$, generated upon irradiation of the sulfoxide. One of the most seminal and longstanding problems in organic chemistry is the selective oxidation of hydrocarbons. Therefore, a reagent, such as $O(^3P)$, capable of selectively transforming hydrocarbons into materials of a higher oxidation state would have useful applications. In our long-standing interest for the environment, our goal was to create a strategy to make this reaction greener. Our intention was to create a catalytic cycle **(Scheme 72)**. In this way, dibenzothiophene DBT would be oxidised to dibenzothiophene oxide DBTO. Subsequently, upon irradiation, the DBTO molecule would lose its oxygen atom, oxidising the alkane to the corresponding alcohol, and regenerating the dibenzothiophene DBT molecule. If successful, this project would lead to high chemical yields for the oxidation of alkanes, in spite of the low quantum yields ϕ usually reported for DBTO deoxygenation reaction.



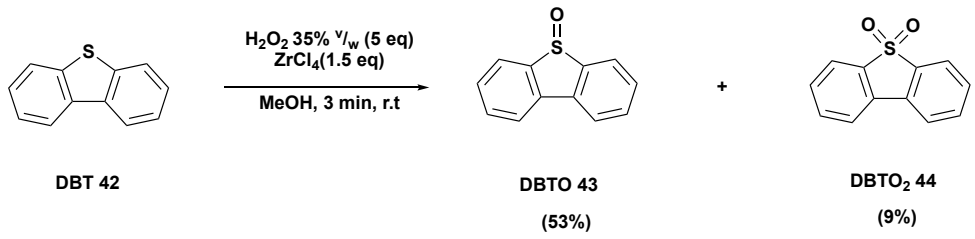
Scheme 72 Ideal catalytic cycle for DBT/DBTO deoxygenation reactions.

4 Results and Discussion

To create a catalytic cycle for the oxidation of organic molecules involving dibenzothiophene and dibenzothiophene *S*-oxide (DBT/DBTO), the first step was the study of the photodeoxygenation of dibenzothiophene (DBTO). We started with the synthesis of dibenzothiophene oxide (DBTO), starting from the commercial dibenzothiophene (DBT).

Sulfur-containing polycondensed aromatic compounds such as dibenzothiophenes and homologues are common contaminants in fossil fuels. Due to their toxicity, there has been extensive research effort centred on their removal. It has been noticed that DBT is stable to photooxidation and to photolysis.[92,93] Nevertheless, DBT in sea water, for example within an oil spill, oxidises to dibenzothiophene *S*-oxide (DBTO) and to dibenzothiophene *S,S*-dioxide ($DBTO_2$) upon irradiation with sunlight.[94] Several reports discuss the DBT oxidation with H_2O_2/TiO_2, Ti-containing zeolite, H_2O_2/TAPC, and $H_2O_2/ZrCl_4$.[94-97]

H_2O_2 as the terminal oxidant is particularly useful due to the oxygen content, low cost, and environmental benignity of H_2O_2. The applicability of the $H_2O_2/ZrCl_4$ system for the oxidation of sulfides to sulfoxides was shown by Bahrani **(Scheme 73)**.[98] Thus, to a solution of dibenzothiophene DBT **42** in methanol, aqueous hydrogen peroxide (35% v/w) (5 eq.) and $ZrCl_4$ (1.5 eq.) were added. Although it was reported that the reaction gave the corresponding sulfoxide DBTO **43** in quantitative yield as the sole oxidation product, we found this not to be the case. In fact, the best outcome was when a precise ratio of 1.0:5.0:1.5 (sulfide/$H_2O_2/ZrCl_4$) was used. These conditions oxidised DBT **42** into DBTO **43** in 3 min in 53% isolated yield.



Scheme 73 Synthesis of DBTO.

One difficulty lay in the fact that the reaction time was so short that there was no opportunity to run a TLC analysis whilst the reaction was in progress. If the reaction time had had been longer, the sulfide **42** would have been over-oxidised to the sulfone **44**. On TLC, the sulfoxide and sulfone spots were extremely close **(Fig. 31)**. Therefore, such a mixture would have made purification particularly challenging. Given this, it was preferable to maintain a higher quantity of unreacted starting material, rather a high yield of the sulfone. The starting material could be recovered and recycled.

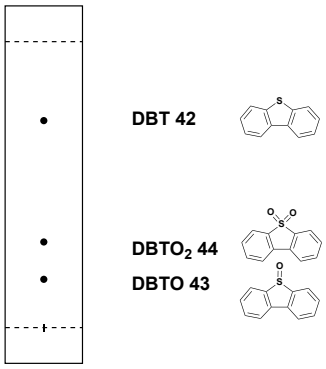


Fig. 31 Petroleum : EtOAc 8:2. TLC of DBT **42**, $DBTO_2$ **44** and DBTO **43** reaction mixture.

Jenks performed the irradiation of dibenzothiophene sulfoxide **43** in several solvents, with the formation of the oxidised solvents as products.[82] They irradiated a solution of DBTO **43** in the elected solvent (1 mM) at 320 nm at room temperature. When the elected solvent was cyclohexane, this was converted to cyclohexanol and cyclohexene **(Table 13, entry 1)**. Benzene and xylene are converted to the corresponding benzyl alcohols/phenols **(Table 13, entry 2 and 3)**. Cyclohexene formed 2-cyclohexen-1-ol and epoxycyclohexane **(Table 13, entry 4)**. Tertiary hydroxylation is observed with branched alkanes **(Table 13, entry 5)**.

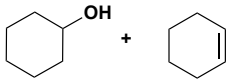
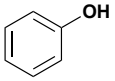
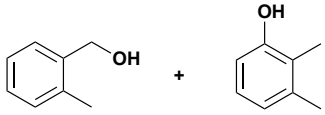
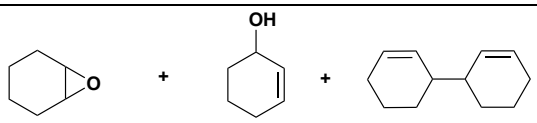
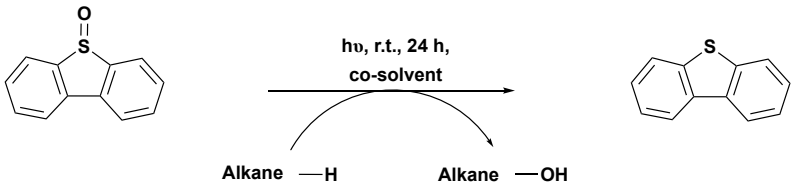
Entry	Substrate	Products
1		
2		
3		
4		
5		

Table 13 Oxidation of several solvents by DBTO irradiation performed by Jenks.[82]

The authors of the study claimed that benzene or xylene are not sensitive to O_2, but the presence of O_2 with alkane solvents resulted in oxidised products in excess of 100%.[82] In this paper, yields of oxygenated products were expressed as a fraction of deoxygenated DBT. However, the article does not mention how much DBT was found at the end of the reaction. Therefore, the relative yields of oxidised products are not clear. It is only in another paper that Jenks and co-workers reported that the conversion of DBTO to DBT under photo-irradiation conditions was moderately low, typically less than 25%.[81] Therefore, several attempts were made to reproduce these results. Product identifications were made by comparison to authentic samples with GC and LC–MS. The reaction mixture was prepared in a quartz tube and irradiated with a 400 W Hg lamp for 24 h at room temperature under continuous stirring. The concentration range of 1-5 mM mentioned by Jenks and co-workers was not possible, because the solubility of DBTO was a limitation. In a few instances, to overcome this issue, co-solvents were used. We started with a 1 mM solution of DBTO in cyclohexane. However, no trace of cyclohexanol was observed by GC–MS.

To improve DBTO solubility, it was decided to include a co-solvent. Although Jenks mentioned the use of benzene and xylene, it was decided that the UV cut-off of these solvents may have been too high, 278 nm and 288 nm respectively.[82] Dichloromethane has a much lower UV cut-off 233 nm. Therefore, CH_2Cl_2 was used as a co-solvent. In this case, the total concentration of the DBTO solution was about 10 mM. However, the reaction failed to give any trace of product with any of the substrates attempted **(Table 14, entries 1 – 3)**. Subsequently, CH_2Cl_2 was replaced by DMSO as the co-solvent with a UV cut-off of 268 nm. With DMSO, some traces of DBT were found by LC–MS **(Table 14, entries 4 – 5)**. More specifically, when cyclohexane was the substrate, DBT was found in 3%. With cyclohexene, traces of DBT were found in 2.5%, whilst with styrene and toluene, the reaction failed to give any trace of DBT or product **(Table 14, entries 6 – 7)**.

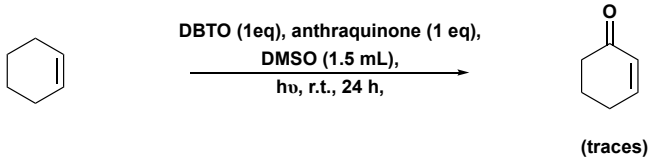


co-solvent: CH_2Cl_2 or DMSO

Entry	Substrate	Co-solvent	LC–MS DBT
1	cyclohexane	CH_2Cl_2	Not detected
2	toluene	CH_2Cl_2	Not detected
3	benzene	CH_2Cl_2	Not detected
4	cyclohexane	DMSO	3%
5	cyclohexene	DMSO	2.5%
6	styrene	DMSO	Not detected
7	toluene	DMSO	Not detected

Table 14 Deoxygenation of DBTO in the presence of CH_2Cl_2 or DMSO as co-solvents.

In related work, Olivé and co-workers reported the irradiation of a solution of sulfoxide in benzene with benzophenone.[99] Sensitised photolysis of DBTO may result in deoxygenation but not by the same mechanism as direct irradiation. Sensitised reactions may occur through an electron-transfer mechanism, even if details are unknown.[100] Benzophenone and anthraquinone were chosen as sensitisers. Therefore, anthraquinone was added to a solution of cyclohexene and DBTO in DMSO. When the solution was irradiated with a 400 W medium pressure Hg lamp for 24 h, traces of cyclohexen-1-one were found by GC–MS **(Scheme 74)**. Nevertheless, when the same conditions were repeated with other substrates, such as cyclohexanone and toluene, no reaction product was found.

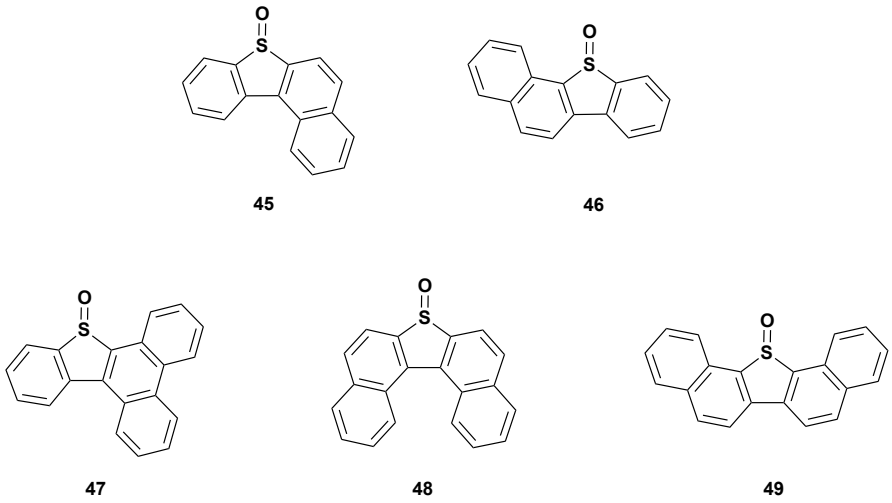


Scheme 74 Sensitised reaction with anthraquinone.

After that, anthraquinone was replaced by benzophenone. Results were in agreement with those reported in the literature, for which the presence of benzophenone accelerated the desulfurisation of DBT by about 7.6 times after 10 h of photo-irradiation.[101] However, in all cases, no traces of products were observed. Furthermore, anthraquinone and benzophenone are known hydrogen abstractors.[102] $O(^3P)$ is not produced by benzophenone-sensitization and direct photolysis of DBTO has not been observed.[103] Due to the scarcity of results and the problem concerning the mechanism, we decided to abandon on this strategy.

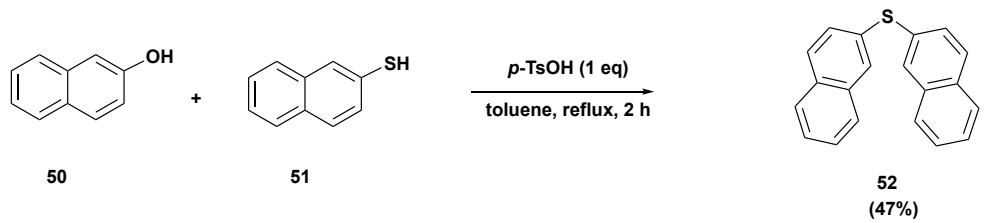
Subsequently, the problem was approached from a different point of view. One of the most common tactics to facilitate the path in a photochemical reaction is the modulation of the chromophore. Extending the chromophore, the reaction occurs at higher wavelength. This strategy has already been exploited for the chemistry of DBTO. McCulla and co-workers red-shifted the absorption spectrum of the sulfoxide by extending its chromophore.[104]

For compounds **45** and **46**, the absorption was extended to 350 nm, whilst for **47**, **48**, and **49** the absorption was extended into the visible range above 400 nm **(Scheme 75)**.



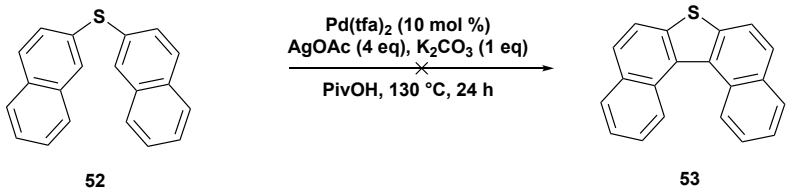
Scheme 75 Examples of McCulla's DBTO-derivatives with extension of the chromophore.

Therefore, the new approach consisted of extending the chromophore of DBTO analogues in order to red-shift the absorption spectrum. Irradiation of the sulfoxide with the new chromophore was hypothesised to generate O(^{3}P) and the corresponding thiophene similarly to DBTO. The new chosen target was dinaphtho[2,1-*b*:1',2'-*d*]thiophene *S*-oxide **48**, because this sulfoxide has the most red-shifted absorption spectrum from those depicted in **Scheme 72**. The absorption of dinaphtho[2,1-*b*:1',2'-*d*]thiophene *S*-oxide **48** extends the furthest into the visible region with its extinction coefficient ε falling at 437 nm.[105] Retrosynthetic analysis suggested that the precursor for the photochemical reaction could be dinaphthyl sulfide **52**, which could be derived straightforwardly from the acid-mediated nucleophilic aromatic substitution between 2-naphthol **50** and 2-naphthalenethiol **51**.[105] The reaction of 2-naphthol **50** and 2-naphthalenethiol **51** was thus carried out in the presence of *p*-TsOH in boiling toluene for 2 h. The desired dinaphthyl sulfide **52** was obtained in 47% yield **(Scheme 76)**.



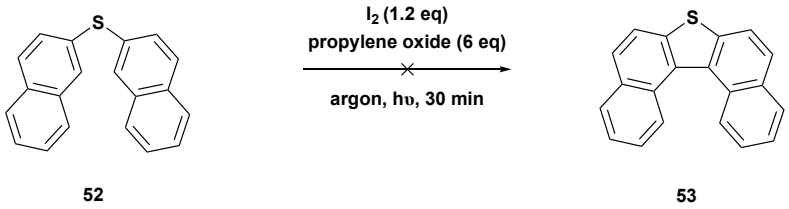
Scheme 76 Synthesis of dinaphthyl sulfide.

The synthesis of dinaphthyl thiophene **53** was attempted by a Pd-catalysed C-H/C-H oxidative cyclisation.[106] The system consisted of the use of $Pd(tfa)_2$, AgOAc, and K_2CO_3 in PivOH at 130 °C for 24 h. **(Scheme 77)** According to the literature, the reaction should tolerate a wide range of substrates; however, no product was ever isolated, in spite of numerous attempts.



Scheme 77 Synthesis of dinaphthothiophene *via* ring-closure with $Pd(tfa)_2$.

Another strategy for the reaction was an oxidative photocyclisation in the presence of I_2 and propylene oxide **(Scheme 78)**.[105] It was expected that electrocyclic ring closure of dinaphthyl sulfide would provide a cyclic intermediate which, upon reaction with I_2, would yield the final product, dinaphthothiophene **53**. Propylene oxide was supposed to function as a quencher of hydroiodic acid (HI) that is generated by this oxidising system. However, this strategy also failed to produce any product.



52 53

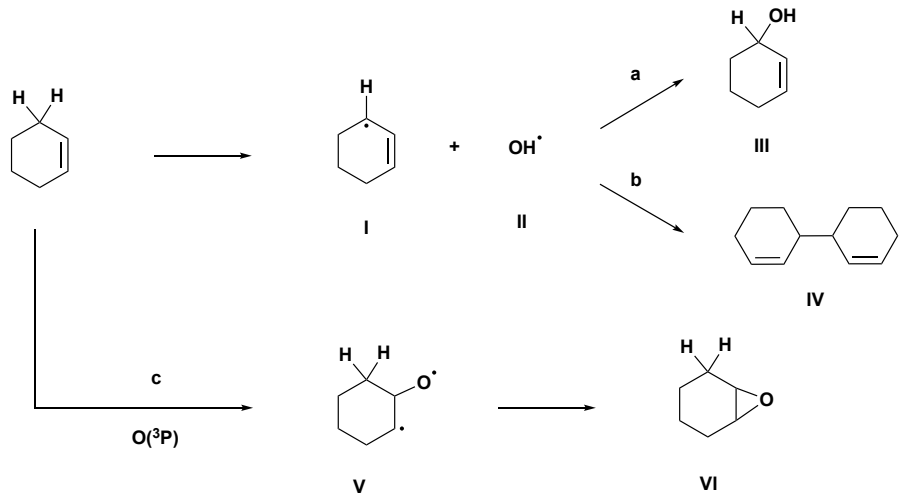
Scheme 78 Synthesis of dinaphthothiophene *via* ring closure with I_2.

Polyaromatic thiophenes are known for being toxic.[107] Benzo[b]naphtho(2,1-*d*)thiophene **45** has a carcinogenic activity comparable to chrysene whilst benzo[b]naphtho(1,2-*d*)thiophene **46** has mutagenic activity. Dibenzothiophene DBT **42**, on the other hand, is not associated with any carcinogenic risks. Therefore, considering this and the paucity of the results, it was decided to focus exclusively on the DBTO structure.

At this point, we noticed a discrepancy in the literature. Both Jenks and Greer claim that molecular oxygen does not affect the yield of the reaction, but only the distribution of products.[82,86] As mentioned before, Greer and Mazur suggested that oxygen was responsible for the formation of by-products, such as acetophenone and benzaldehyde.[86b,88]

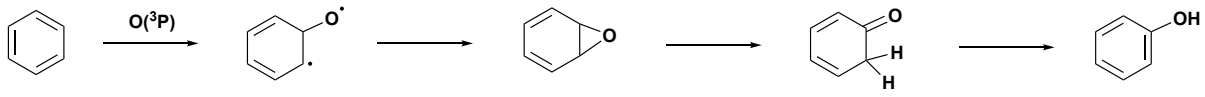
Oxygen is well known to be a very good quencher for both singlet and triplet states.[108] Hence, we reasoned that oxygen may be deleterious for the reaction, and it would have been good practice to try oxygen-free conditions. A sample reaction of DBTO in cyclohexane was prepared in the usual concentration range 1-5 mM. However, this time, the sample was flushed with N_2 for ca. 20 min before leaving the reaction mixture in front of the 400 W medium pressure lamp overnight. To our delight, the LC–MS analysis revealed that DBT was present in the reaction mixture in ca. 30%. The same reaction conditions were used with cyclohexene and benzene as substrates. Cyclohexene gave a complex mixture of products, including cyclohexene oxide 1%, cyclohexanone in 2%, cyclohexen-1-ol in 17%, and bi-2-cyclohexenyl dimer in 36%. It is important to show how O(^{3}P) can lead to all these products **(Scheme 79)**. Abstraction of an allylic hydrogen from cyclohexene will form the cyclohexenyl radical **(I)** and the hydroxyl radical **(II)**. Recombination of these two **(I and II)** will yield the allylic alcohol **(III)**

(Path a). The recombination of two cyclohexenyl radicals **(I)** yields the cyclohexenyl dimer **(IV)** **(Path b)**. Electrophilic addition of the triplet oxygen atom into the π system of the alkene forms a biradical **(V)** that yields the epoxide after recombination **(VI) (Path c)**.



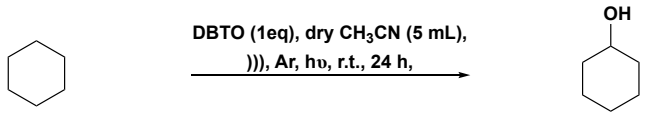
Scheme 79 Oxidation of cyclohexene by triplet oxygen O(^{3}P).

However, even under these conditions, no products were observed when benzene was used as a substrate. This is in contrast to the work of Jenks and co-workers, who claimed that O(^{3}P) reacts with benzene *via* electrophilic attack into the π system, forming an arene oxide as an intermediate. According to them, this rearomatizes to form phenol as the main product **(Scheme 80)**.[81]



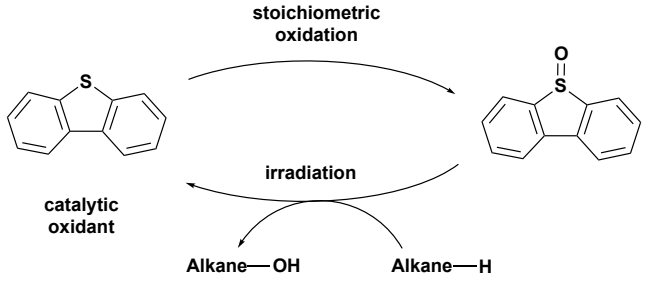
Scheme 80 Oxidation of benzene with triplet oxygen O(^{3}P).

Thus, after so many efforts, we finally understood the conditions for the successful transfer of oxygen from a DBTO molecule to a simple alkane/alkene molecule **(Scheme 81)**. A solution of DBTO (100 mg, 0.5 mmol) in dry acetonitrile (5 mL) was inserted in a quartz tube. The substrate (1 eq.) was added. The reaction mixture was sonicated for ca. 20 min under argon flow. After that, the samples were irradiated with a 400 W Mercury lamp for 24 h at room temperature with continuous magnetic stirring.



Scheme 81 Successful transfer of oxygen from DBTO to cyclohexane.

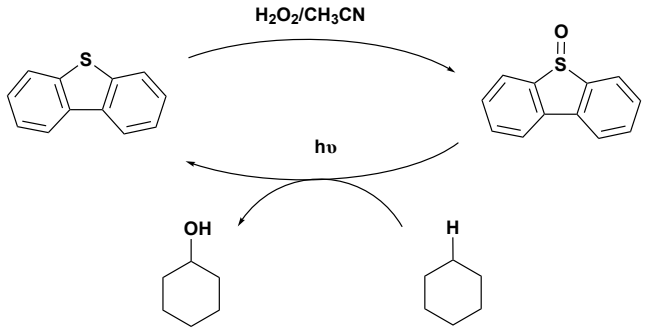
Thereafter, we decided to develop a catalytic cycle in which DBT is oxidised in situ. The newly-formed DBTO transfers its oxygen to the substrates under irradiating conditions, generating DBT again, ready for a new catalytic cycle **(Scheme 82)**.



Scheme 82 Ideal catalytic cycle for DBT/DBTO deoxygenation reactions.

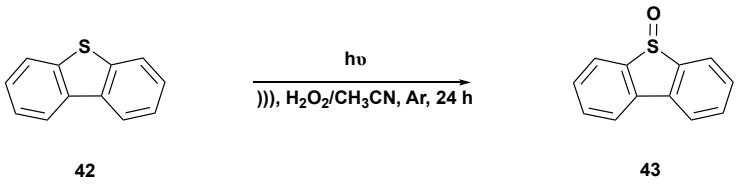
With this ambitious goal in mind, the first step was the investigation of DBT photo-oxidation. Several papers have investigated sunlight photo-oxidation of DBTs to the corresponding sulfoxides and sulfones in spilled crude oil in the marine environment.[109] The presence of sunlight and atmospheric oxygen and/or other oxidants has been suggested to be part of the

photooxidation process. DBTO was reported as a product after DBT was irradiated with a middle- and high-pressure Hg lamp. Ibusuki and co-workers studied the photooxidation of DBT with a medium-pressure Hg lamp.[110] In the course of their studies, they found a solution of DBT in H_2O_2/CH_3CN gives DBTO even in absence of any photocatalyst. Considering this, we believed we could create our catalytic cycle simply by direct irradiation of DBT in a system of H_2O_2/CH_3CN in the presence of an appropriate substrate **(Scheme 83)**.



Scheme 83 Catalytic cycle formed by direct irradiation of DBT in a system of H_2O_2/CH_3CN in the presence of an appropriate substrate.

The first step was to study the photooxidation of DBT in H_2O_2/CH_3CN. A solution of DBT **42** in a mixture of H_2O_2/CH_3CN (5 mM) was sonicated for 20 min under an argon flow. Subsequently it was irradiated for 24 h with a medium-pressure Hg lamp **(Scheme 84)**. The aqueous H_2O_2 solution was at 30% $^{v}/_{w}$, and it was maintained at no more than 3% compared to CH_3CN. We believed that an increased water content in the acetonitrile solution would be deleterious to the reaction, in agreement with the literature.[110,111]



42 43

Scheme 84 Oxidation of DBT to DBTO by irradiation in a H_2O_2/CH_3CN mixture.

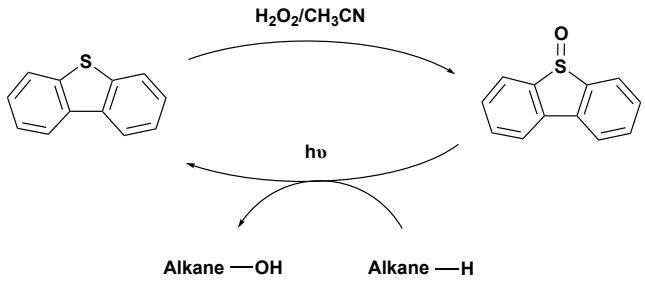
Under these conditions, DBTO was observed by TLC and detected by LC–MS in 31% yield. Subsequently, the same conditions were kept, but cyclohexane was added as a substrate. To a solution of DBT in dry acetonitrile, cyclohexane (1 eq) and H_2O_2 (1 eq) (30% $^{v}/_{w}$) were added. The reaction was sonicated for 20 min under an argon flow. The sample was then irradiated for 24 h. When the irradiation was stopped, the sample had a strong yellow colouration. GC–MS analysis of the sample revealed the presence of cyclohexanol **(Table 15, entry 1)**. However, this could not be quantified accurately with this technique, because the parent starting material cyclohexane is highly volatile. This GC–MS analysis also revealed the presence of DBT, but no DBTO. In contrast, LC–MS analysis revealed a ratio of DBT/DBTO of 2:1. To explain this discrepancy, it was hypothesised that DBTO, not being very stable, degrades inside the GC–MS, losing its oxygen and forming DBT. As a result of this, a peak of the same molecular weight and retention time of DBT will be generated, making it indistinguishable from DBT. DBTO does not decompose in the LC–MS, this being a milder technique. Therefore, the distinction between DBT and DBTO is highlighted through the formation of two distinct peaks with different retention times and molecular ions **(Appendix Fig. A20 – A21)**. To verify this hypothesis, a sample of a mixture of DBT and DBTO was submitted to both LC–MS and GC–MS. Whilst LC–MS analysis clearly gave two distinct peaks of, respectively, *m/z* 184 and *m/z* 200, the GC–MS gave a single peak of *m/z* 184, with a retention time identical to that of pure DBT. This is in agreement with the literature in which it is reported that DBTO decomposes to the parent compound at 250 °C.[110]

Another problem encountered was the extrusion of the sulfur atom from DBTO. Hirai reported the photodecomposition of DBTs by the use of a high-pressure Hg lamp at room temperature

and atmospheric pressure. The sulfur atom leads to its conversion to sulfate ions SO_4^{2-}.[99] We confirmed this disadvantage by addition of $BaCl_2$ into the resulting water phase, which made precipitates with SO_4^{2-}. Barium ions react with sulfate ions to form insoluble white barium sulfate.

$$Ba^{2+}\ (aq) + SO_4^{2-}\ (aq) \rightarrow BaSO_4\ (s)$$

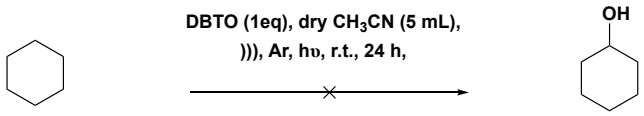
Nevertheless, we were excited by these preliminary results. The fact that cyclohexanol was identified in a system composed by DBT in H_2O_2/CH_3CN after irradiation represents a proof of concept. It is possible to oxidise DBT to DBTO and, subsequently, to a simple alkane in one pot. Hopefully, DBT would have been regenerated ready for another cycle. When cyclohexene was used as a substrate under the same reaction conditions, a complex mixture of products was found. 2-Cyclohexen-1-ol was detected in 8%, 2-cyclohexen-1-one was detected in 31%, and 2-(1-cyclohexenyl)cyclohexanone was present in traces. The DBT/DBTO ratio was found by LC–MS; DBTO was present in small amounts (7%), whilst the rest was DBT. **(Table 15, entry 2)**. In an attempt to expand the substrate scope, the same reaction conditions were used on other simple alkanes, but with poor results. Benzene, adamantane, cycloheptane were all investigated. According to the LC–MS analysis, in the reaction with benzene, there was a DBT content of 59% and DBTO content of 38% **(Table 15, entry 3)**. Similarly, with adamantane, the DBT content was of 81%, whilst DBTO was at 12% **(Table 15, entry 4)**. In contrast, cycloheptane gave a DBT yield of only 2% and DBTO of 97% **(Table 15, entry 5)**. However, in these reactions, no product was detected by GC–MS analysis. It was assumed that the deoxygenation step was working, whilst the subsequent oxidation step was failing for unknown reasons.



Entry	Substrate	LC–MS (%) Ratio	GC–MS (%) Ratio
1	cyclohexane	DBT 60%	cyclohexanol
2	cyclohexene	DBT 83%	2-cyclohexen-1-ol 8%, 2-cyclohexen-1-one 31%,
3	benzene	DBT 59%	Not detected
4	adamantane	DBT 81%	Not detected
5	cycloheptane	DBT 2%	Not detected

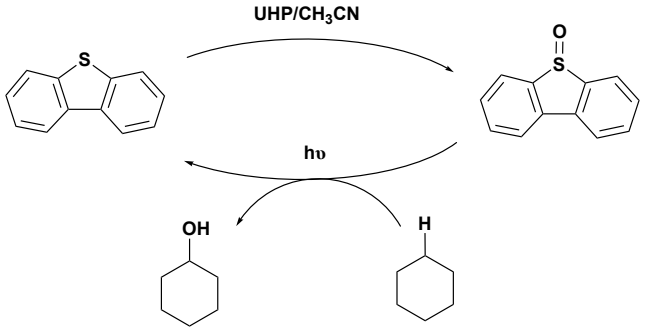
Table 15 Alkane oxidation in a system composed by DBT in H_2O_2/CH_3CN after irradiation.

At this point, it was decided to take a step back, and to study the reaction with cyclohexane in more detail. Once the reaction conditions had been optimised, attention could be focused on extending the substrate scope. However, with extreme disappointment, the previous results were not reproducible. Despite numerous attempts, no product was observed. Even with cyclohexane and cyclohexene, the only substrates that were successfully oxidised, the reactions were consistently failing without apparent reason **(Scheme 85)**.



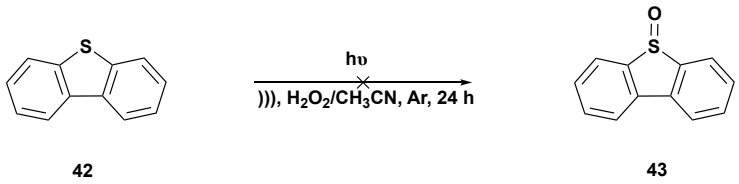
Scheme 85 Unsuccessful transfer of oxygen from DBTO to cyclohexane.

Therefore, some attempts to modify the reaction conditions were made. We hypothesised that a reduction of the water content of the reaction solution would have been beneficial.[110,111] A way to reduce the water content in the reaction was sought trying to replicate the previous results. For this reason, aqueous hydrogen peroxide H_2O_2 was substituted with hydrogen peroxide urea (UHP). Therefore, the DBT (1 eq.) was dissolved in a minimum amount of dry acetonitrile. UHP (3 eq.) and cyclohexane (1 eq.) were added to this solution. The reaction mixture was sonicated for ca. 20 min under an argon flow and then irradiated for 24 h **(Scheme 86)**.



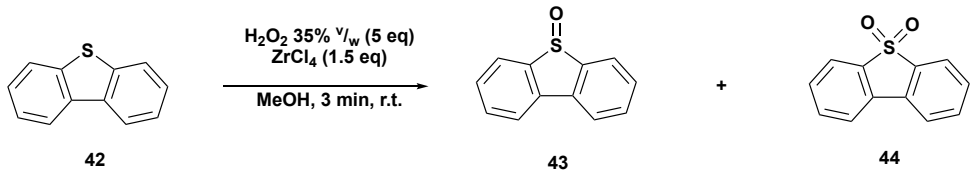
Scheme 86 Catalytic cycle formed by direct irradiation of DBT in a system of UHP/CH_3CN in the presence of an appropriate substrate.

Even with this switch, numerous attempts were all fruitless. Hirai and co-workers confirmed that UHP is a poor oxidant for the oxidation of sulfides.[112] Therefore, we decided to take a further step back. The oxidation of DBT in a system of H_2O_2/CH_3CN was attempted again. Once more, the previous results were not reproducible despite several attempts **(Scheme 87)**.



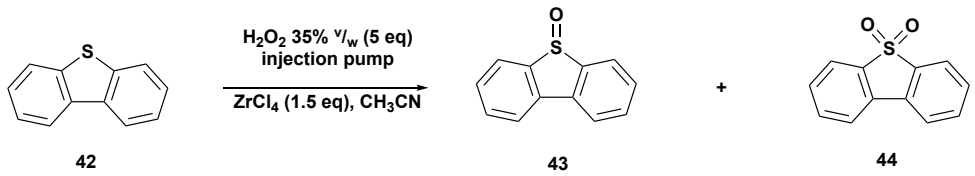
Scheme 87 Oxidation of DBT to DBTO by irradiation.

Under UV irradiation, H_2O_2 is easily decomposed into hydroxy radicals. Therefore, H_2O_2 acts in two different ways in the reaction with DBT. First, it works as a direct mild oxidising agent. Second, the hydroxyl radical generated by H_2O_2 photodecomposition acts as a strong oxidising agent. Hirai and co-workers concluded that the dominant mechanism is the former one.[99] They conducted the reactions under air and used a filter to block radiation above $\lambda > 280$ nm to hamper hydroxyl radical generation. Nevertheless, DBT oxidation was still occurring, indicating that H_2O_2 acts as an oxidant. However, when a filter $\lambda > 325$ was used, no reaction was seen. The 325 nm wavelength corresponds to the excited singlet energy of DBT. With this latest filter, DBT could not be photoexcited, and the reaction did not occur. Therefore, with these results in hand, the authors deduced that H_2O_2 oxidised the photoexcited state of DBT. At this point, we decided that the addition of $ZrCl_4$ to the reaction mixture would have been beneficial for the oxidation of DBT **42** to DBTO **43 (Scheme 85)**. Even if $ZrCl_4$ cannot be considered "green", it had already been used in our previous experiments for the successful synthesis of DBTO from the parent DBT.[96] Environmental concerns would have been addressed in a later stage of the project.



Scheme 85 Synthesis of DBTO.

Therefore, we studied the slow addition of H_2O_2 (5 eq., 1.3 mL) to a mixture of DBT **42** (1 eq.) and $ZrCl_4$ (1.5 eq.) in dry CH_3CN. H_2O_2 was added *via* syringe pump at a rate of 1 mL/h. Immediately after the injection had finished, the reaction was quenched with water, and the products extracted with CH_2Cl_2. The organic layer was analysed, and it was found that after 1 h, there were no traces of DBT **42**, whilst DBTO **43** was present in 52% and $DBTO_2$ **44** in 46% **(Table 16, entry 1)**. Considering that the photoreaction of DBTO takes 24 h, it would not be acceptable to already have a substantial amount of $DBTO_2$ as a by-product that in ca. 1 h. $DBTO_2$ is photoinactive, and the overoxidation of DBT to $DBTO_2$ erodes the source of DBT/DBTO.[81,113] This problem represents a limitation. Therefore, the speed of the injection pump was reduced by half. Even if the time of the reaction was double, the results were only slightly better. According to the LC–MS, DBTO was present in 58%, while $DBTO_2$ was present in 36%. The starting material DBT was detected in 2% **(Table 16, entry 2)**. Subsequently, the conditions were further modified. This time, the catalyst $ZrCl_4$ was reduced by half (0.75 eq.), whilst the rate of the injection pump was maintained at 0.5 mL/h. After 2 h, the major product was DBTO at 59%, whilst the $DBTO_2$ fraction was slightly lowered to 34%. DBT was still present in a small amount with 7% **(Table 16, entry 3)**. When the rate of the injection pump was reduced further to 0.25 mL/h, it was found that DBTO was present in 24% relative yield, $DBTO_2$ 4%, and DBT 70% **(Table 16, entry 4)**.

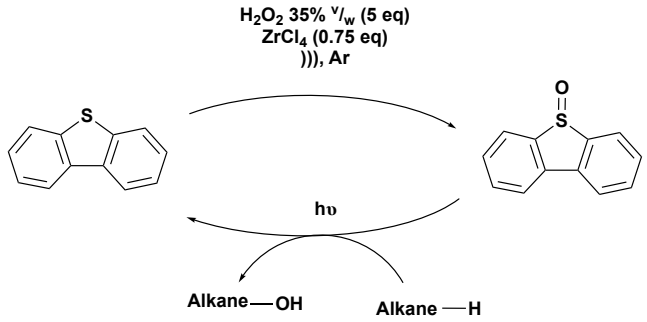


42 43 44

Entry	Rate (mL/h) of addition	$ZrCl_4$ (Eq.)	DBT/DBTO (%) Ratio by LC–MS
1	1	1.5	DBTO 52% $DBTO_2$ 46%
2	0.5	1.5	DBTO 58% $DBTO_2$ 36% DBT 2%
3	0.5	0.75	DBTO 59% $DBTO_2$ 34% DBT 7%
4	0.25	0.75	DBTO 24% $DBTO_2$ 4% DBT 70%

Table 16 Calibration of the oxidation of DBT to DBTO *via* injection pump.

At this point, these new conditions were used with some simple alkanes as substrates. To a solution of DBT (1 eq.) and $ZrCl_4$ (0.75 eq.) in dry CH_3CN, an alkane (2 eq.) was added. The solution was sonicated for 20 min under argon flow. Subsequently, H_2O_2 (5 eq.) was added *via* injection pump at a rate of 0.25 mL/h. The reaction was stirred under irradiation for 24 h. **(Scheme 88)**.



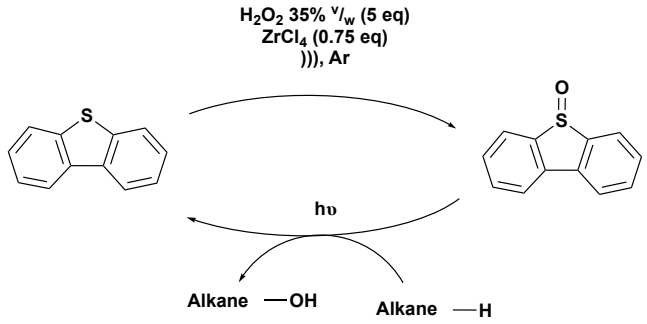
Scheme 88 Catalytic cycle formed by direct irradiation of DBT in a system of $H_2O_2/ZrCl_4$ in CH_3CN in the presence of an appropriate substrate.

When cyclohexane was used as a substrate, cyclohexanol was detected as the single product in 49% yield **(Table 17, entry 1)**. With cyclohexene as a substrate, a mixture of 1,2-dichlorocyclohexane and 2-chlorocyclohexanol was found **(Table 17, entry 2)**. When benzene was used, only chlorobenzene was detected in 8% yield. The chlorine atom clearly derived from $ZrCl_4$, this being the only possible source **(Table 17, entry 3)**. Interestingly, when cycloheptane was used as a substrate, cycloheptanol was present only in 5% yield, whilst cycloheptanone was present in 18%. Unreacted cycloheptane was present in 76% yield. This represents a sharp contrast in respect to cyclohexane, to which cycloheptane is structurally very similar **(Table 17, entry 4)**. Adamantane did not react very well. Unreacted adamantane represented 95% yield. Traces of 1-chloro-adamantane, and both 1- and 2-adamantanol were detected **(Table 17, entry 5)**. The low results achieved with adamantane may be caused by the low solubility of the substrate in the system. When norbornane was used as a substrate, exo-norborneol was detected as a single product in 26% yield **(Table 17, entry 6)**.

Entry	Substrate	LC–MS (%) Ratio	GC (%) Ratio
1	Cyclohexane	DBTO 4% $DBTO_2$ 72% DBT 5%	Cyclohexane 51% Cyclohexanol 49%
2	Cyclohexene	DBTO 31% $DBTO_2$ 9% DBT 56%	1,2dichlorocyclohexane 6% 2-chlorocyclohexanol 12%
3	Benzene	DBTO 12% $DBTO_2$ 55% DBT 21%	Benzene 92% Chloro-benzene 8%
4	Cycloheptane	DBTO 2% $DBTO_2$ 77% DBT 10%	Cycloheptane 76% Cycloheptanol 5% Cycloheptanone 18%
5	Adamantane	DBTO 44% $DBTO_2$ 41% DBT 6%	Adamantane 95% 1-chloro-adamantane 3% 2-adamantanol 1% 1-adamantanol 1%
6	Norbornane	DBTO 1% $DBTO_2$ 73% DBT 11%	Norbornane 74% Exo-norborneol 26%

Table 17 Products formed by direct irradiation of DBT in a system of $H_2O_2/ZrCl_4$ in CH_3CN in the presence of a substrate.

Control reactions were performed to check that every single element of our system was necessary. Thus, the usual reaction was performed, but eliminating a single element every time. In the absence of light, all DBT was over-oxidised to $DBTO_2$. Clearly, the oxidation step was working properly thanks to the mixture of H_2O_2 and $ZrCl_4$, but the deoxygenation step was not happening. This confirmed that UV irradiation is a minimum requisite for the photo-deoxygenation of DBTO **(Table 18, entry 1)**. In another control reaction, $ZrCl_4$ was omitted. In this case, no reaction was detected, showing that $ZrCl_4$ is necessary as catalyst for H_2O_2. This result is in agreement with the literature, which reports that the reaction without $ZrCl_4$ as a catalyst is sluggish.[91] In the absence of H_2O_2 there was no reaction. Both $ZrCl_4$ and H_2O_2 are necessary for the oxidation of DBT to DBTO **(Table 18, entries 2 and 3)**. When DBT was omitted, there was some kind of reaction. The cyclohexane was converted into a complex mixture of chlorinated by-products. However, no cyclohexanol was detected **(Table 18, entry 4)**. The reaction was also attempted in the dark at a temperature of 100 °C, with unsuccessful results **(Table 18, entry 5)**. These studies confirm that our conditions are critical to the successful oxidation of alkanes.



Entry	Element	Outcome
1	Dark	$DBTO_2$
2	Without $ZrCl_4$	No reaction
3	Without H_2O_2	No reaction
4	Without DBT	Chlorinated by-products
5	100 °C	No reaction

Table 18 Control reactions.

4.1 Conclusions

Despite its potential as an oxidising agent, $O(^3P)$ is not usually regarded as a useful reagent in organic chemistry. The findings from this study establish a potential method to generate high-value oxygenated hydrocarbons under mild photolysis conditions of DBTO, which would lead to a synthetic use of atomic oxygen, $O(^3P)$. Encouraging lessons about the viability of some sulfoxides, such as DBTO, to produce $O(^3P)$ can be learnt. The main aim of this study was to create a catalytic cycle, and this was investigated under a range of experimental conditions. Compared to the previous literature, DBT is added directly to the reaction vessel, instead of its oxidised form, DBTO. This make the operations more simple, quicker, and with a net saving of solvent. However, difficulties in the reproduction of literature results considerably change the results. For example, whilst Jenks and Greer claims that oxygen does not have a deleterious effect on the reaction, we found instead that it thwarted it completely.[78,86b] According to them, the reaction also works on aromatic substrates.[78,79,86b] We have not been able to reproduce this element.

Future work may focus on extending the chromophore, so to switch the light source from middle-pressure Hg lamp to LED. With these changes, we foresee a major control on parameters such as light intensity and frequencies.

5 Experimental

General

Commercially available reagents were used without further purification, unless otherwise stated. All anhydrous solvents were used as supplied. Reactions which required anhydrous conditions were conducted under an inert atmosphere of dry argon in flame-dried apparatus. Bottled wet solvents were used for work ups. Light petroleum refers to the fractions with bp 40-60 °C. Ether refers to diethyl ether.

Thin Layer Chromatography (TLC) was performed using Merck aluminium foil-backed plates, pre-coated with silica gel 60 F_{254}. Visualisation was carried out *via* U.V. fluorescence (λ_{max} = 254 nm and/or 360 nm) and/or staining with potassium permanganate and heating. Flash chromatography was carried out using Davisil silica 60 Å. The eluent has been specified.

NMR spectroscopy experiments were performed on a Bruker DPX400 or Bruker AV400 spectrometer at 400 MHz for ^{1}H NMR, corresponding ^{13}C frequencies 100 MHz, at room temperature. Proton magnetic resonance shifts (δH), recorded in parts per million (ppm), are referenced to residual H in the deuterated solvent. Coupling constants (*J*) are quoted in Hertz (Hz). The multiplicity of each signal is designated by a combination of the following abbreviations; s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Proton-decoupled carbon chemical shifts (δC), recorded in ppm, are recorded to one decimal place. In the ^{13}C spectra, signals corresponding to CH, CH_2, CH_3 groups are assigned from DEPT; all others are quaternary C.

Infrared spectra were obtained on a Bruker Avatar 320 FTIR spectrometer. Absorption maxima (ν_{max}) of major, peaks are reported in wavenumbers, quoted to the nearest integral wavenumber.

Mass spectra were recorded on a Bruker MicroTOF II (ESI) mass spectrometer which uses electrospray ionisation (ESI).

TGA was performed on an Agilent Q500 instrument. Temperature programme: from 30 °C to 100 °C with a ramp of 5 °C/min up to 100 °C. After that, isotherm for 24 h.

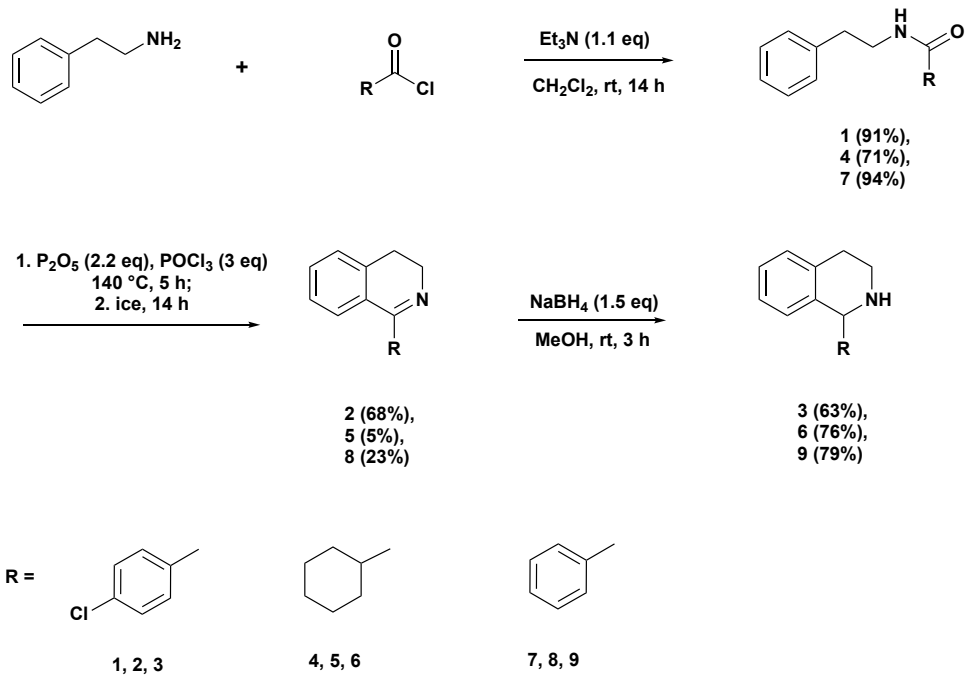
LC–MS was performed using an Agilent HPLC Infinity 1260, MS Quadrupole 6120. The HPLC contains a C18 PR HPLC column with a DAD detector at a flow rate of 208 μL/min.

GC was performed on a Varian Agilent 430-GC instrument with a column of 15 m x 0.53 mm x 1.5 μm with He at a flow rate of 2.0 mL/min. The temperature of the injector was 100 °C. Programme of temperature for the oven: 50 °C (2 min) to 100 °C (5 min), and from 100 °C to 200 °C (3 min) at a heating rate of 20 °C/min.

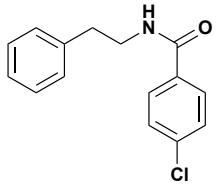
GC–MS was performed on a Thermo Single Quadrupole TraceGold TG SQC instrument with a column of 15 m x 0.25 mm x 25 μm with He at a flow rate of 1.5 mL/min. The temperature of the injector was 200 °C. Programme of temperature for the oven: 50 °C (5 min) to 350 °C (20 min) at a heating rate of 10 °C/min.

A 400 W medium pressure Hg lamp was used as the light source for photoirradiation.

General procedure for the synthesis of various 1,2,3,4-tetrahydroisoquinolines



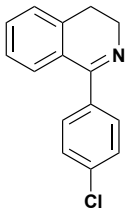
4-Chloro-*N*-phenethylbenzamide 1



1

2-Phenylethylamine (2.1 mL, 16.5 mmol) was added to a flask containing CH_2Cl_2 (20 mL) at 0 °C. 4-Chlorobenzoyl chloride (2.1 mL, 16.5 mmol) was added dropwise over a period of 15 min. Et_3N (2.5 mL, 18.1 mmol) was added to the resulting suspension over a period of 10 min at 0 °C. The reaction mixture was heated to reflux for 5 h. After that, it was stirred at room temperature for 14 h. Deionised water (20 mL) was added, and the phases were separated. The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to yield a colourless solid (3.9 g, 91%), mp = 128 – 130 °C (lit.,[114] 137 – 138 °C); ν_{max} (neat) 3344, 3065, 3028, 2930, 1635, 1593, 1569, 1536 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.67 – 7.62 (2 H, m, ArH), 7.46 – 7.18 (7 H, m, ArH), 6.16 (1 H, s, ArCONH), 3.73 (2 H, td, *J* 6.9, 5.9, CH_2), 2.95 (2 H, t, *J* 6.9, CH_2); δ_C (100 MHz; $CDCl_3$) 166.4 (C), 138.7 (C), 137.6 (C), 133.0 (C), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.2 (CH), 126.6 (CH), 41.2 (CH_2), 35.6 (CH_2); *m/z* (ESI) $C_{15}H_{14}NO^{35}Cl$ (M^+) *calc.* 282.0656 (M+Na)*; found* 282.0661 (M+Na). This is a known compound, and the spectroscopic data are similar to those reported in literature.[114]

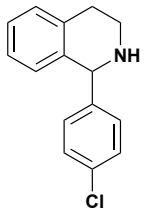
1-(4-Chlorophenyl)-3,4-dihydroisoquinoline 2



2

4-Chloro-*N*-phenethylbenzamide **1** (3.9 g, 0.015 mol) was dissolved in xylene (30 mL). To the mixture, $POCl_3$ (6.9 g, 0.045 mol) and P_2O_5 (4.7 g, 0.033 mol) were added. The resulting suspension was heated at 140 °C for 5 h. After that, the reaction mixture was cooled to room temperature, and ice (10 g) was carefully added. The reaction mixture was stirred at room temperature for 14 h. Subsequently, the two phases were separated. The pH of the water phase was adjusted to 10 using a NaOH (1 M) solution. The product was then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated by rotary evaporation. Further purification was achieved by column chromatography (petroleum : EtOAc 8:2) to yield a yellow oil (2.49 g, 68%), ν_{max} (neat) 2941, 2841, 1606, 1560, 1481, 1086 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.61 – 7.54 (2 H, m, ArH), 7.47 – 7.33 (3 H, m, ArH), 7.36 – 7.21 (3 H, m, ArH), 3.91 – 3.82 (2 H, m, CH_2), 2.87 – 2.78 (2 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 166.2 (C), 138.8 (C), 137.4 (C), 135.3 (C), 130.8 (CH), 130.1 (CH), 128.4 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 126.6 (CH), 47.6 (CH_2), 26.2 (CH_2); *m/z* (ESI) $C_{15}H_{12}N^{35}Cl$ (M^+) *calc.* (M+H) 242.0731, (M+Na) 264.05500, *found* (M+H) 242.0731, (M+Na) 264.0549. This is a known compound, and the spectroscopic data are identical to those reported in literature.[28]

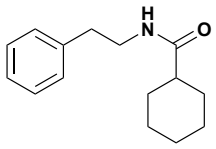
1-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline 3



3

1-(4-Chlorophenyl)-3,4-dihydroisoquinoline **2** (2.49 g, 0.01 mol) was dissolved in methanol (20 mL). $NaBH_4$ (0.58 g, 0.015 mol) was added. The reaction mixture was stirred at room temperature for 3 h. After that, the solvent was concentrated by rotary evaporation, and the product purified by column chromatography (petroleum : EtOAc 7:3) to yield a colourless solid (1.59 g, 63%), mp = 66 – 68 °C (lit.,[115] 65 – 67 °C); ν_{max} (KBr) 3247, 2962, 2922, 2803, 1491, 1085 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.38 – 7.13 (6 H, m, ArH), 7.13 – 7.01 (1 H, m, ArH), 6.78 – 6.70 (1 H, m, ArH), 5.11 (1 H, s, C<u>H</u>NH), 3.34 – 3.21 (1 H, m, CH_2), 3.18 – 3.00 (2 H, m, CH_2), 2.85 (1 H, m, CH_2), 1.85 (1 H, s, NH); δ_C (100 MHz; $CDCl_3$) 143.4 (C), 137.8 (C), 135.4 (C), 133.1 (C), 130.3 (CH), 129.1 (CH), 128.5 (CH), 127.9 (CH), 126.4 (CH), 125.7 (CH), 61.4 (CH), 42.2 (CH_2), 29.7 (CH_2); *m/z* (ESI) $C_{15}H_{14}N^{35}Cl$ (M^+) *calc.* for (M+H) 244.0888, (M+Na) 266.0707, *found* (M+H) 244.0884, (M+Na) 266.0695 (M+Na). This is a known compound, and the spectroscopic data are identical to those reported in literature.[115]

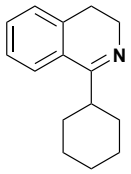
_N_-Phenethylcyclohexanecarboxamide 4



4

2-Phenylethylamine (2.0 g, 16.5 mmol) was added to a flask containing CH_2Cl_2 (20 mL) at 0 °C. Cyclohexanecarbonyl chloride (2.4 mL, 18.1 mmol) was added dropwise over a period of 15 min. Et_3N (2.5 mL, 18.1 mmol) was added to the resulting suspension over a period of 10 min at 0 °C. The reaction mixture was heated to reflux for 5 h. After that, it was stirred at room temperature for 14 h. Deionised water (20 mL) was added, and the phases were separated. The organic phase was dried over Na_2SO_4, and concentrated to yield a colourless solid (2.69 g, 71%), mp = 84 – 85 °C (lit.,[116] 94 – 97 °C; lit.,[117] 97 – 98 °C); ν_{max} (KBr) 3313, 2933, 2923, 2872, 1644, 1504, 1486, 1459 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.36 – 7.17 (5 H, m, ArH), 5.55 (1 H, s, NH), 3.55 – 3.45 (2 H, m, CH_2), 2.83 (2 H, t, *J* 6.9, CH_2), 1.86 – 1.73 (4 H, s, $2CH_2$), 1.46 – 1.34 (2 H, m, CH_2), 1.32 – 1.11 (4 H, m, $2CH_2$); δ_C (100 MHz; $CDCl_3$) 176.0 (C), 139.0 (C), 128.8 (CH), 128.6 (CH), 126.4 (CH), 45.5 (CH), 40.3 (CH_2), 35.7 (CH_2), 29.6 (CH_2), 25.7 (CH_2), (1 CH_2 not observed); *m/z* (ESI) $C_{15}H_{21}NO$ (M^+) *calc.* (M+H) 232.1696, (M+Na) 254.1515 (M+Na), *found* (M+H) 232.1696, (M+Na) 254.1514. This is a known compound, and the spectroscopic data are identical to those reported in literature.[116,117]

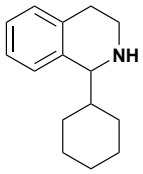
1-Cyclohexyl-3,4-dihydroisoquinoline 5



5

N-Phenethylcyclohexanecarboxamide **4** (2.50 g, 0.01 mol) was dissolved in xylene (30 mL). To the mixture, $POCl_3$ (4.97 g, 0.03 mol) and P_2O_5 (3.38 g, 0.02 mol) were added. The resulting suspension was heated at 140 °C for 5 h. After that, the reaction mixture was cooled to room temperature, and ice (10 g) was carefully added. The reaction mixture was stirred at room temperature for 14 h. Subsequently, the two phases were separated. The pH of the water phase was adjusted to 10 using a NaOH (1 M) solution. The product was then extracted in CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated by rotary evaporation. Further purification was achieved by column chromatography (petroleum : EtOAc 8:2) to yield a yellow oil (0.13 g, 5%); ν_{max} (KBr) 3022, 3059, 2848, 2925, 1255, 1488, 1621 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.53 (1 H, dd, *J* 7.1, 1.8, ArH), 7.33 (2 H, m, ArH) 7.20 (1 H, dd, *J* 7.1, 2.0, ArH), 3.67 (2 H, dd, *J* 8.5, 6.2, CH_2), 2.96 – 2.88 (1 H, m), 2.69 – 2.63 (2 H, m, CH_2), 1.95 – 1.83 (4 H, m, $2CH_2$), 1.76 (1 H, dtt, *J* 12.5, 3.5, 1.5, CH), 1.50 – 1.34 (5 H, m, $3CH_2$); δ_C (100 MHz; $CDCl_3$) 170.7 (C), 138.2 (C), 130.0 (CH), 128.8 (C), 127.6 (CH), 126.7 (CH), 124.5 (CH), 46.8 (CH_2), 42.0 (CH), 31.3 (CH_2), 26.6 (CH_2), 26.6 (CH_2), 25.7 (CH_2); *m/z* (ESI) $C_{15}H_{19}N$ (M^+) *calc.* (M+H) 214.1590, (M+Na) 236.1410, *found* (M+H) 214.1595, (M+Na) 236.1412. This is a known compound, and the spectroscopic data are identical to those reported in literature.[28]

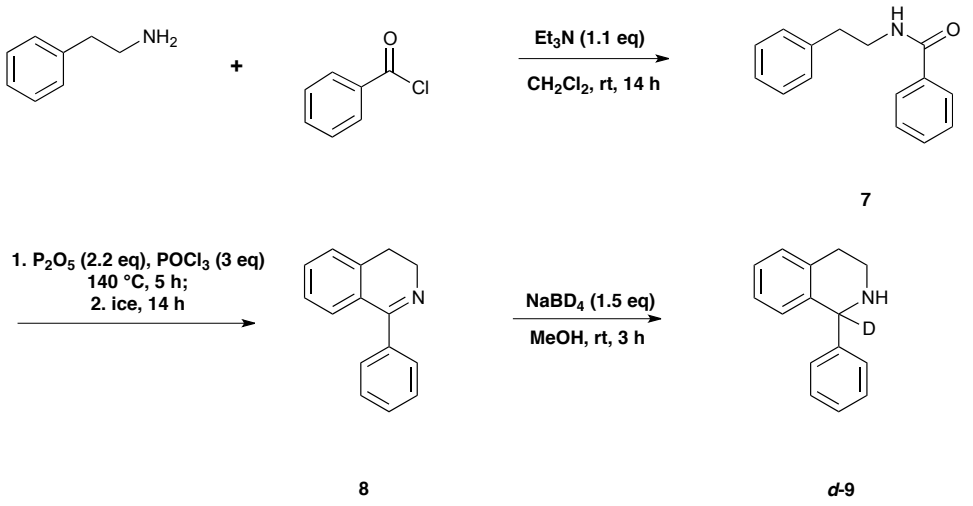
1-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline 6



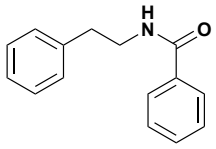
6

1-Cyclohexyl-3,4-dihydroisoquinoline **5** (0.13 g, 0.61 mmol) was dissolved in methanol (5 mL). $NaBH_4$ (34 mg, 0.091 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. After that, the solvent was concentrated by rotary evaporation, and the product purified by column chromatography (petroleum : EtOAc 7:3) to yield a yellow oil (0.10 mg, 76%); ν_{max} (KBr) 3348, 2921, 2849 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.38 – 7.20 (1 H, m, ArH), 7.19 – 7.16 (2 H, m, ArH), 7.11 (1 H, m, ArH), 3.94 (1 H, d, *J* 4.1), 3.30 (1 H, ddd, *J* 11.8, 5.2, 3.7, CH), 2.98 – 2.82 (2 H, m), 2.70 (1 H, dt, *J* 5.8, 3.9), 1.91 – 1.68 (5 H, m), 1.47 – 1.16 (6 H, m), (NH not observed); δ_C (100 MHz; $CDCl_3$) 138.5 (C), 136.2 (C), 129.1 (CH), 126.0 (CH), 125.6 (CH), 125.5 (CH), 60.7 (CH), 43.0 (CH), 42.3 (CH_2), 30.9 (CH_2), 30.3 (CH_2), 27.1 (CH_2), 26.6 (CH_2), 26.6 (CH_2), 26.4 (CH_2); *m/z* (ESI) $C_{15}H_{21}N$ (M^+) *calc.* (M+H) 216.1746, (M+Na) 238.1566, *found* (M+H) 216.1748, (M+Na) 238.1557. This is a known compound, and the spectroscopic data are identical to those reported in literature.[118]

Synthesis of the deuterated 1-D-phenyl-1,2,3,4-tetrahydroisoquinoline *d*-9.



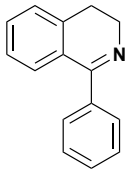
_N_-Phenethylbenzamide 7



7

To a flask containing 2-phenethylamine (2.0 g, 16.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C, benzoyl chloride (2.1 mL, 16.5 mmol) was added dropwise over a period of 15 min. Et_3N (2.5 mL, 18.1 mmol) was added to the resulting suspension over a period of 10 min at 0 °C. The reaction mixture was heated to reflux for 5 h. After that, it was stirred at room temperature for 14 h. Deionised water (20 mL) was added, and the phase were separated. The organic phases were dried over Na_2SO_4, and concentrated to yield a colourless solid (3.5 g, 94%), mp = 110 – 112 °C (lit.,[119] 113 – 116 °C (CH_2Cl_2); lit.,[120] 118 – 120.5 °C (MeOH); lit.,[121] 80.3 – 80.6 °C); ν_{max} (neat) 3341, 3058, 3025, 1637, 1537, 1453, 1484 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.73 – 7.68 (2 H, m, ArH), 7.53 – 7.48 (1 H, m, ArH), 7.46 – 7-39 (2 H, m, ArH), 7.38 – 7.31 (2 H, m, ArH), 7.30 – 7.25 (3 H, m, ArH), 6.21 (1 H, s, NH), 3.75 (2 H, td *J* 6.9, 5.8, CH_2), 2.96 (2 H, t, *J* 6.9, CH_2); δ_C (100 MHz, $CDCl_3$) 167.4 (C), 138.9 (C), 134.6 (C), 131.4 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 126.8 (CH), 126.6 (CH), 41.1 (CH_2), 35.7 (CH_2); *m/z* (ESI) $C_{15}H_{15}NO$ *calc.* (M+H) 226.1231, (M+Na), 248.1051, *found* (M+H) 226.1226, (M+Na) 248.1046. This is a known compound, and the spectroscopic data are identical to those reported in literature.[119,122]

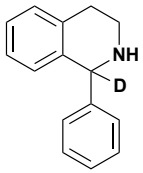
1-Phenyl-3,4-dihydroisoquinoline 8



8

N-Phenethylbenzamide **7** (3.50 g, 0.015 mol) was dissolved in xylene (30 mL). To the mixture, $POCl_3$ (6.58 g, 0.045 mol) and P_2O_5 (4.68 g, 0.033 mol) were added. The resulting suspension was heated at 140 °C for 5 h. After that, the reaction mixture was cooled to room temperature, and ice (10 g) was carefully added. The reaction mixture was stirred at room temperature for 14 h. Subsequently, the two phases were separated. The pH of the water phase was adjusted to 10 using a NaOH (1 M) solution. The product was then extracted in CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried over Na_2SO_4, and concentrated by rotary evaporation to yield a yellow oil (0.73 g, 23%); ν_{max} (neat) 3058, 3024, 2937, 2891, 2836, 1606, 1563, 1444, 1316, 1305 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.66 – 7.60 (2 H, m, ArH), 7.49 – 7.37 (4 H, m, ArH), 7.31 – 7.23 (3 H, m, ArH), 3.92 – 3.84 (2 H, m, CH_2-N), 2.86 – 2.79 (2 H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 167.2 (C), 139.0 (C), 138.8 (C), 130.6 (CH), 129.3 (CH), 128.8 (CH), 128.1 (CH), 127.9 (CH), 127.9 (CH), 127.4 (CH), 126.6 (CH), 47.7 (CH_2), 26.3 (CH_2); *m/z* (ESI) $C_{15}H_{13}N$ *calc.* (M+H) 208.1121, *found* (M+H) 208.1128. This is a known compound, and the spectroscopic data are identical to those reported in literature.[28,123]

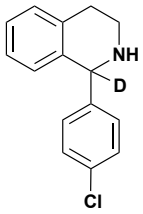
1-D-Phenyl-1,2,3,4-tetrahydroisoquinoline 9-*D*



d-9

1-Phenyl-3,4-dihydroisoquinoline **8** (0.73 mg, 3.5 mmol) was dissolved in MeOH (10 mL). $NaBD_4$ (0.22 g, 5.3 mmol) was added to the resulting solution. The reaction mixture was stirred at room temperature for 3 h. After that, the solvent was concentrated under reduced pressure, and the product was purified by column chromatography (petroleum : EtOAc 1:1) to yield a colourless solid (0.58 g, 79%), mp = 92 – 94 °C; ν_{max} (neat) 3255, 2960, 2819, 2783, 1117 cm^{-1}; δ_H (400 MHz; DMSO) 7.35 – 7.23 (5 H, m, ArH), 7.17 – 7.06 (2 H, m, ArH), 7.00 (1 H, ddd, *J* 7.6, 6.6, 2.1, ArH), 6.63 (1 H, dd *J* 7.5, 1.2, ArH), 3.14 – 3.03 (1 H, m), 2.97 – 2.85 (2 H, m), 2.74 (1 H, dd *J* 5.2, 2.7), 2.73 – 2.86 (1 H, m); δ_C (100 MHz; DMSO) 145.8 (C), 139.2 (C), 135.9 (C), 129.3 (CH), 129.3 (CH), 128.4 (CH), 128.0 (CH), 127.3 (CH), 126.3 (CH), 125.7 (CH), 61.3 (CD, t, *J* 35.0), 42.0 (CH_2), 29.7 (CH_2); *m/z* (ESI) $C_{15}H_{14}ND$ *calc.* (M+H) 211.1340, *found* (M+H) 211.1341.

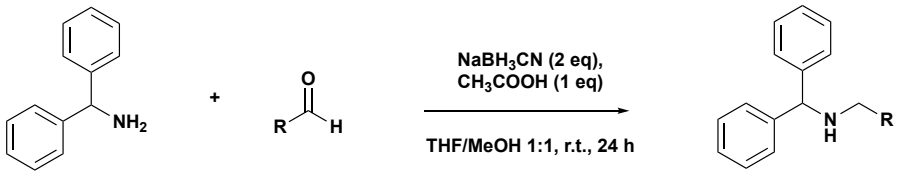
1-D-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline 3-*D*



d-3

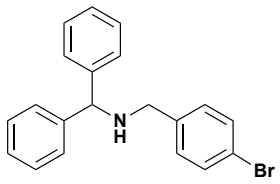
1-Phenyl-3,4-dihydroisoquinoline **2** (2.90 g, 12.0 mmol) was dissolved in MeOH (30 mL). $NaBD_4$ (0.76 g, 18.0 mmol) was added to the resulting solution. The reaction mixture was stirred at room temperature for 3 h. After that, the solvent was concentrated under reduced pressure, and the product was purified by column chromatography (petroleum : EtOAc 1:1) to yield a colourless solid (1.63 g, 56%), mp = 78 – 79 °C; ν_{max} (neat) 3245, 1085, 736 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.31 (2 H, t, *J* 8.8 ArH), 7.26 – 7.21 (2 H, m, ArH), 7.20 – 7.16 (2 H, m, ArH), 7.07 (1 H, t, *J* 8.5, 4.4, ArH), 6.78 – 6.72 (1 H, m, ArH), 3.28 (1 H, dt, *J* 10.7, 4.7, C$\underline{H_2}$-NH), 3.17 – 3.00 (2 H, m, CH_2), 2.85 (1 H, dt, *J* 16.1, 4.0,), 1.89 (1 H, s, NH); δ_C (100 MHz; $CDCl_3$) 143.3 (C), 137.6 (C), 135.4 (C), 133.1 (C), 130.3 (CH), 129.1 (CH), 128.5 (CH), 127.9 (CH), 126.4 (CH), 125.7 (CH), 61.1 (CD t, *J* 21.0) 42.1 (CH_2), 29.6 (CH_2); *m/z* (ESI) $C_{15}H_{13}N^{35}ClD$ *calc.* (M+H) 245.0950, (M+Na) 267.0770, *found* (M+H) 208.0950, (M+Na) 267.0766.

General Procedure for Preparation of Dpm Amines



Diphenylmethylamine (2.8 mL, 16 mmol) was dissolved in a 1:1 mixture of THF/MeOH (40 mL). The aldehyde (19 mmol) was added and the mixture was stirred at room temperature for 1 h followed by addition of sodium cyanoborohydride (2.01 g, 32 mmol) and glacial acetic acid (1 mL, 16 mmol). The resulting reaction mixture was stirred for 24 h. The solvents were then removed *in vacuo.* The resulting solid residue was dissolved in toluene (10 mL), washed with water (2 x 5 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The clear oils were further purified by column chromatography in CH_2Cl_2.

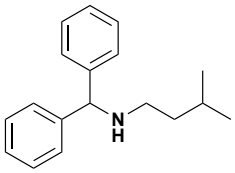
N-(4-Bromobenzyl)-1,1-diphenylmethanamine 18



18
(33%)

Pale yellow oil (1.35 g, 33%). ν_{max} (neat) 3059, 3025, 2828, 699 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.65 – 7.16 (14 H, m, Ar), 4.61 (1 H, s, C<u>H</u>NH), 3.81 (2 H, s, C<u>H</u>$_2$NH), 2.50 (1 H, s, NH); δ_C (100 MHz; $CDCl_3$) 143.7 (C), 139.4 (C), 131.6 (CH), 130.0 (CH), 128.8 (CH), 127.5 (CH), 127.3 (CH), 121.3 (C), 66.4 (CH), 51.2 (CH_2); *m/z* (ESI) $C_{20}H_{18}{}^{79}BrN$ (M^+) *calc.* (M+H) 352.0695, *found* (M+H) 352.0691.

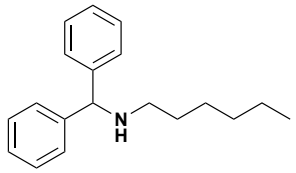
N-Benzhydryl-3-methylbutan-1-amine 19



19
(31%)

Pale yellow oil (1.28 g, 31%). ν_{max} (neat) 3083, 3025, 2954, 1597, 1491, 1452 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.48 – 7.44 (4 H, m, ArH), 7.38 – 7.33 (4 H, m, ArH), 7.30 – 7.26 (2 H, m, ArH), 4.91 (1 H, s, C<u>H</u>NH), 2.74 – 2.60 (2 H, m, C<u>H</u>$_2$NH), 1.69 (1 H, dt, *J* 13.4, 6.7, CH), 1.55 – 1.45 (2 H, m, CH_2), 0.92 (6 H, d, *J* 6.6, $2CH_3$), (NH not observed); δ_C (100 MHz; $CDCl_3$) 143.0 (C), 128.6 (CH), 127.3 (CH), 127.2 (CH), 67.6 (CH), 46.4 (CH_2), 38.6 (CH_2), 26.1 (CH), 22.6 (CH_3); *m/z* (ESI) $C_{18}H_{23}N$ (M^+) *calc.* (M+H) 254.1903, *found* (M+H) 254.1901. This is a known compound, and the spectroscopic data are identical to those reported in literature.[124]

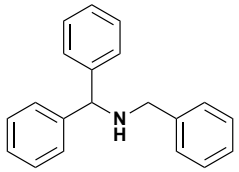
N-Benzhydrylhexan-1-amine 21



21
(18%)

Pale yellow oil (0.79 g, 18%). ν_{max} (KBr) 3083, 3061, 3024, 2954, 2924, 2868, 2854, 1597, 1491, 1451 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.52 – 7.46 (4 H, m, ArH), 7.37 (4 H, dd, *J* 8.6, 6.8, ArH), 7.37 – 7.25 (2 H, m, ArH), 4.90 (1 H, s, C<u>H</u>NH), 2.66 (2 H, t, *J* 7.1, C<u>H</u>$_2$NH), 1.78 (1 H, s, NH), 1.59 (2 H, q, *J* 7.5, CH_2), 1.46 – 1.30 (6 H, m, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 1.00 – 0.92 (3 H, m, C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 144.4 (C), 128.4 (CH), 127.3 (CH), 126.9 (CH), 67.7 (CH), 46.4 (CH_2), 31.8 (CH_2), 30.3 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.6 (CH_3); *m/z* (ESI) $C_{19}H_{25}N$ (M^+) *calc.* (M+H) 268.2060*, found* (M+H) 268.2061. This is a known compound, and the spectroscopic data are identical to those reported in literature.[124]

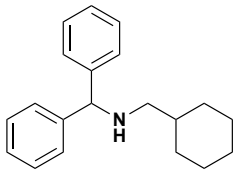
***N*-Benzyl-1,1-diphenylmethanamine 22**



22
(8%)

Pale yellow oil (0.36 g, 8%). ν_{max} (KBr) 3082, 3059, 3024, 1599, 1491, 1451 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.56 – 7.45 (4 H, m, ArH), 7.46 – 7.32 (9 H, m, ArH), 7.37 – 7.25 (2 H, m, ArH), 4.95 (1 H, s, C<u>H</u>NH), 3.84 (2 H, s, C<u>H</u>$_2$NH), 1.94 (1 H, s NH); δ_C (100 MHz; $CDCl_3$) 144.0 (C), 140.5 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.4 (CH), 127.1 (CH), 126.9 (CH), 66.5 (CH), 51.9 (CH_2); *m/z* (ESI) $C_{20}H_{19}N$ (M^+) *calc.* (M+H) 274.1590, *found* (M+H) 274.1593.

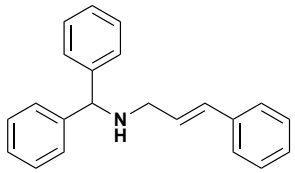
N-(Cyclohexylmethyl)-1,1-diphenylmethanamine 23



23
(14%)

Pale yellow oil (0.62 g, 14%). ν_{max} (KBr) 3328, 3079, 3060, 3020, 2918, 2844, 1491, 1446 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.51 – 7.45 (4 H, m, ArH), 7.40 – 7.31 (4 H, m, ArH), 7.29 – 7.22 (2 H, m, ArH), 4.85 (1 H, s, C<u>H</u>NH), 2.49 (2 H, d, *J* 6.6, C<u>H_2</u>NH), 1.90 – 1.70 (5 H, m), 1.55 (2 H, dddd, *J* 14.5, 11.2, 6.7, 3.2), 1.38 – 1.15 (3 H, m), 1.07 – 0.91 (2 H, m); δ_C (100 MHz; $CDCl_3$) 144.5 (C), 128.4 (CH), 127.3 (CH), 126.9 (CH), 67.7 (CH), 55.0 (CH_2), 38.3 (CH), 31.5 (CH_2), 26.7 (CH_2), 26.1 (CH_2); *m/z* (ESI) $C_{20}H_{25}N$ (M^+) *calc.* (M+H) 280.2060, *found* (M+H) 280.2066. This is a known compound, and the spectroscopic data are identical to those reported in literature.[124]

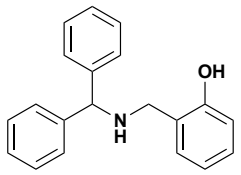
(*E*)-*N*-Benzhydryl-3-phenylprop-2-en-1-amine 24



24
(30%)

Pale yellow oil (1.47 g, 30%). ν_{max} (KBr) 3058, 3023, 1491, 1449 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.53 – 7.48 (4 H, m, ArH), 7.48 – 7.43 (2 H, m, ArH), 7.42 – 7.36 (6 H, m, ArH), 7.32 – 7.27 (3 H, m, ArH), 6.64 – 6.55 (1 H, d, *J* 15.8, CH), 6.41 (1 H, dt, *J* 15.8, 6.2, CH), 5.01 (1 H, s, C<u>H</u>NH), 3.46 (2 H, dd, *J* 6.2, 1.5, C<u>H</u>$_2$NH), 1.80 (1 H, s, NH); δ_C (100 MHz; $CDCl_3$) 144.0 (C), 137.2 (C), 131.3 (CH), 128.6 (CH), 121.6 (CH), 128.5 (CH), 127.4 (CH), 127.4 (CH), 127.1 (CH), 126.4 (CH), 66.5 (CH), 49.9 (CH_2); *m/z* (ESI) $C_{22}H_{21}N$ (M^+) *calc.* (M+H) 300.1746, (M+Na) 322.1566, *found* (M+H) 300.1747, (M+Na) 322.1570. This is a known compound, and the spectroscopic data are identical to those reported in literature.[125]

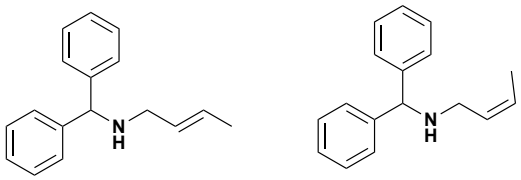
2-((Benzhydrylamino)methyl)phenol 25



25
(24%)

Pale yellow oil (1.14 g, 24%). ν_{max} (KBr) 3286, 3057, 3025, 1587, 1489, 1451 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.40 – 7.33 (8 H, m, ArH), 7.32 – 7.27 (2 H, m, ArH), 7.21 (1 H, td *J* 7.7, 1.8, ArH), 6.97 – 6.87 (2 H, m, ArH), 6.80 (1 H, td, *J* 7.4, 1.2, ArH), 4.93 (1 H, s, C<u>H</u>NH), 3.93 (2 H, s, C<u>H_2</u>NH) (NH and OH not observed); δ_C (100 MHz; $CDCl_3$) 157.9 (C), 141.9 (C), 128.9 (CH), 128.8 (CH), 128.5 (CH), 127.5 (CH), 127.3 (CH), 122.5 (C), 119.2 (CH), 116.4 (CH), 65.9 (CH), 50.6 (CH_2); *m/z* (ESI) $C_{20}H_{19}NO$ (M^+) *calc.* (M+H) 290.1539, (M+Na) 312.1359, *found* (M+H) *290*.1550, (M+Na) 312.1371.

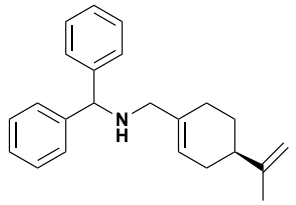
(*Z*) and (*E*)-*N*- Benzhydrylbut-2-en-1-amine 26



26
(32%)

Yellow oil (0.84 g, 32%). ν_{max} (KBr) 3024, 2956, 2927, 1491, 1451 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.60 – 7.52 (8 H, m, ArH), 7.46 – 7.40 (8 H, m, ArH), 7.37 – 7.31 (4 H, ArH), 5.76 – 5.71 (2 H, m, CH_2, *E*), 5.01 (1 H, s, CHNH, *E*), 4.97 (1 H, s, CHNH, *Z*), 3.33 – 3.27 (2 H, m, 2CH, *E*), 2.74 (2 H, t, *J* 7.1, CH_2, *Z*), 2.25 (2 H, s, 2NH), 1.84 (3 H, dd, *J* 3.4, 1.4, CH_3, *E*), 1.73 – 1.61 (1 H, m, CH, *Z*), 1.51 (1 H, h, *J* 7.3, CH, 7.1, CH, *Z*), 1.06 (3 H, t, *J* 7.3, CH_3, *Z*); δ_C (75 MHz; $CDCl_3$) 144.3 (C), 144.1 (C), 129.5 (CH), 128.8 (CH), 127.4 (CH), 127.4 (CH), 127.1 (CH), 67.8 (CH), 66.7 (CH), 49.9 (CH_2), 48.1 (CH_2), 32.4 (CH), 20.6 (CH), 18.0 (CH_3), 14.2 (CH_3) (the number of resonance reported are less than those expected probably due to overlap of the signal); *m/z* (ESI) $C_{17}H_{19}N$ (M^+) *calc.* (M+H) 238.1590, (M+Na) 260.1409, *found* (M+H) 238.1593, (M+Na) 260.1404.

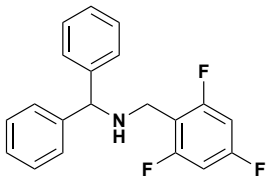
(*R*)-1,1-Diphenyl-*N*-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)methanamine 27



27
(26%)

Pale yellow oil (0.90 g, 26%). ν_{max} (KBr) 3024, 2916, 2834, 1642, 1491, 1450 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.56 – 7.50 (5 H, m, ArH), 7.42 – 7.35 (5 H, m, ArH), 5.69 (1 H, s, C<u>H</u>NH), 4.91 (1 H, s, CH), 4.84 (1 H, s, CH), 3.20 (2 H, s, NHC<u>H</u>$_2$), 2.30 – 2.18 (4 H, m, $2CH_2$), 2.12 – 1.99 (2 H, m, CH_2), 1.94 (1 H, ddt, *J* 10.4, 4.2, 2.2, CH), 1.85 (3 H, s, CH_3), 1.75 (1 H, s, NH), 1.60 (1 H, ddt, *J* 11.9, 8.8, 5.4, CH); δ_C (100 MHz; $CDCl_3$) 150.0 (C), 144.4 (C), 136.0 (C), 128.5 (CH), 127.4 (CH), 126.9 (CH), 122.3 (CH), 108.6 (CH_2), 66.4 (CH), 54.0 (CH_2), 41.3 (CH) 30.7 (CH_2), 27.8 (CH_2), 27.5 (CH_2), 20.9 (CH); *m/z* (ESI) $C_{23}H_{27}N$ (M^+) *calc.* (M+Na) 340.2036, *found* (M+Na) 340.2045.

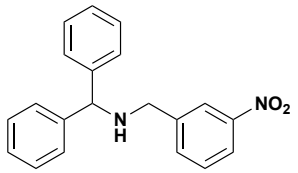
1,1-Diphenyl-*N*-(2,4,6-trifluorobenzyl)methanamine 28



28
(28%)

Pale yellow oil (1.0 g, 28%). ν_{max} (KBr) 3028, 2852, 1602, 1495, 1439 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.44 (4 H, dd, *J* 7.6, 1.4, ArH), 7.32 (4 H, dd, *J* 8.4, 6.8, ArH), 7.26 – 7.21 (2 H, m, ArH), 6.71 – 6.63 (2 H, m, ArH), 4.85 (1 H, s, C<u>H</u>NH), 3.83 (2 H, s, C<u>H</u>$_2$NH), 1.92 (1 H, s, NH); δ_C (100 MHz; $CDCl_3$) 163.3 – 162.9 (m, CF), 160.8 – 160.5 (m, CF), 143.5 (C), 128.5 (CH), 127.3 (CH), 127.2 (CH), 112.3 (t, *J* 3, C), 100.3 – 99.8 (m, CH), 66.7 (CH), 38.8 (t, *J* 3, CH_2); *m/z* (ESI) $C_{20}H_{16}F_3N$ (M^+) *calc*. (M+H) 328.1308, *found* (M+H) 328.1305.

N-(3-Nitrobenzyl)-1,1-diphenylmethanamine 29



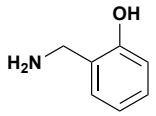
29
(10%)

Pale yellow oil (0.35 g, 10%). ν_{max} (KBr) 3321, 3083, 3060, 3025, 2831, 1523, 1491, 1451, 1345 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.28 (1 H, t, *J* 1.9, ArH), 8.14 (1 H, ddd, *J* 8.2, 2.4, 1.1, ArH), 7.72 (1H, dt, *J* 7.8, 1.3, ArH), 7.54 – 7.46 (5 H, m, ArH), 7.37 – 7.32 (4H, m, ArH), 7.30 – 7.27 (2 H, m, ArH), 4.91 (1 H, s, C<u>H</u>-NH), 3.89 (2 H, s, C<u>H</u>$_2$-NH), 1.96 (1 H, s, NH); δ_C (100 MHz; $CDCl_3$) 148.4 (C), 143.4 (C), 142.7 (C), 134.2 (CH), 129.2 (CH), 128.6 (CH), 127.3 (CH), 122.9 (CH), 122.0 (CH), 66.7 (CH), 51.1 (CH_2); *m/z* (ESI) $C_{20}H_{18}N_2O_2$ (M^+) *calc*. (M) 318.1362, (M+Na) 341.1260, *found* (M) 318.1364, (M+Na) 341.1268.

General procedure for Dehydrogenation of Amines

The amines (0.3 mmol) were placed in a flask with 1 mL of solvent. The mixture was stirred at 100 °C for 24 h. Subsequently, the mixture was cooled to room temperature over 30 min. The solvent was removed under reduced pressure. The results are reported in **Chapter 2**, **Table 5** and **Table 6**.

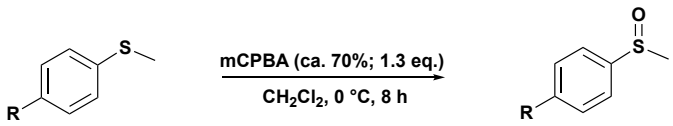
2-(Aminomethyl)phenol 25G



25G
(43%)

2-((Benzhydrylamino)methyl)phenol **25F** (1 g) was heated in dry DMSO (5 mL) for 24 h at 100 °C. The reaction was cooled down to room temperature over a period of 30 min. Deionised water (20 mL) was added to the reaction mixture and the products were extracted in CH_2Cl_2, (2x15 mL), dried over Na_2SO_4, and concentrated under reduce pressure to give a yellow oil. Further purification was achieved by column chromatography in CH_2Cl_2 to give an oil (0.18 g, 43%), δ_H (400 MHz; $CDCl_3$) 7.51 – 6.71 (4 H, m, ArH), 4.15 (2 H, s, CH_2) (OH and NH_2 are not observed); δ_C (100 MHz; $CDCl_3$) 158.4 (C), 128.6 (CH), 127.9 (CH), 123.9 (C), 119.0 (CH), 116.7 (CH), 45.5 (CH_2). This is a known compound, and the spectroscopic data are identical to those reported in literature.[126]

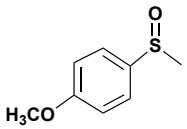
General procedure for the preparation of sulfoxides from sulfides



37 R = OMe (48%)
38 R = CF_3 (67%)

A solution of sulfide (1.6 mmol) in dichloromethane (20 mL) was cooled to 0 °C. After addition of *m*CPBA (ca. 70%; 1.3 eq.) the solution was stirred for 8 h. The reaction mixture was washed with deionised water (2x15 mL), and dried over Na_2SO_4 anhydrous. The solvent was removed under reduced pressure. Further purification was achieved by column chromatography (petroleum : EtOAc 1:1).

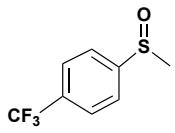
1-Methoxy-4-(methylsulfinyl)benzene 37



37

Colourless solid (1.16 g, 48%), mp 44 – 45 °C; ν_{max} (KBr) 2988, 1246, 1032 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.60 (2 H, d, *J* 8.8, ArH), 7.04 (2 H, d, *J* 8.8, ArH), 3.86 (3 H, s, CH_3), 2.71 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 161.9 (C), 136.6 (C), 125.4 (CH_2), 114.8 (CH_2), 55.5 (OCH_3), 44.0 (CH_3); *m/z* (ESI) $C_8H_{10}O_2S$ (M^+) *calc.* (M+H) 171.0474, (M+Na) 193.0294, *found* (M+H) 171.0494, (M+Na) 193.0303. This is a known compound, and the spectroscopic data are identical to those reported in literature.[127,128]

1-(Methylsulfinyl)-4-(trifluoromethyl)benzene 38



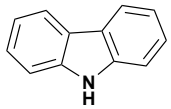
38

Colourless solid (1.60 g, 67%), mp 41 – 42 °C; ν_{max} (KBr) 3001, 2992, 2925, 2911, 1318, 1129, 1058, 1044 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.87 – 7.76 (4 H, m, ArH), 2.78 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 150.1 (C), 133.1 (q, *J* 32.7, C), 126.3 (q, *J* 3.7, CH), 124.0 (CH), 123.5 (q, *J* 271, CF_3), 43.9 (CH_3); δ_F (376 MHz; $CDCl_3$) – 62.9 (s); *m/z* (ESI) $C_8H_7OF_3S$ (M^+) *calc.* (M+H) 209.0242, (M+Na) 231.0062, *found.* (M+H) 209.0246, (M+Na) 231.0064.

General procedure for the Dehydrogenation of 1,2,3,4-tetrahydrocarbazole

1,2,3,4-Tetrahydrocarbazole (0.6 mmol, 100 mg) was placed in a flask with anhydrous DMSO (1 mL). The mixture was stirred at 100 °C for 24 h. Subsequently, the mixture was cooled to room temperature over a period of 30 min. The solvent was removed under reduced pressure.

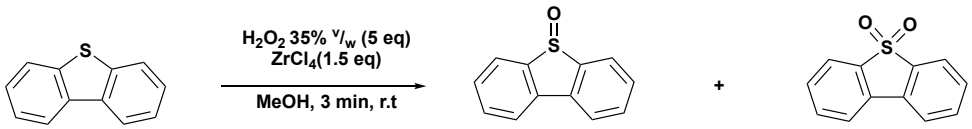
Synthesis of 9*H*-carbazole 41



41
(66% yield)

Colourless solid (0.04 g, 38%), mp 241 – 243 °C (lit[126] 243 – 246 °C); ν_{max} (KBr) 3417, 3048, 2934, 2872, 1599, 1449, 1324, 1235 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.11 (2 H, d, *J* 7.8, ArH), 7.45 (4 H, d, *J* 6.5, ArH), 7.26 (2 H, d, *J* 7.0, ArH) (NH not observed); δ_C (100 MHz; $CDCl_3$) 139.5 (C), 125.8 (CH), 123.9 (C), 120.3 (CH), 119.4 (CH), 110.5 (CH); *m/z* (ESI) $C_{12}H_9N$ (M^+) *calc*. (M+H) 168.0808, *found*. (M+H) 168.0806. This is a known compound, and the spectroscopic data are identical to those reported in literature.[129]

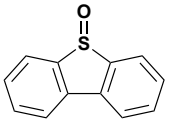
General procedure for the oxidation of DBT



DBT 42 **DBTO 43 (53%)** **$DBTO_2$ 44 (9%)**

In a round-bottomed flask, a solution of sulfide (0.74 g, 4.0 mmol) in CH_3OH (15 mL) was prepared. H_2O_2 (35%, 2 mL, 20 mmol) and $ZrCl_4$ (1.54 g, 6.0 mmol) were added. The mixture was stirred at room temperature for 5 min. After that, the reaction mixture was quenched by deionised water (15 mL) and extracted in CH_2Cl_2 (3 x 15 mL). The organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Further purification was achieved by column chromatography (petroleum : EtOAc 8:2) to yield DBTO **43** as a colourless solid (0.43 g, 53%) and $DBTO_2$ **44** as a colourless solid (80 mg, 9%).

Dibenzothiophen-5-oxide 43

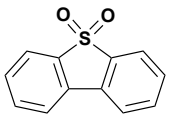


43

(53%)

mp = 181 – 183 °C (lit[127] 195 °C); ν_{max} (neat) 1019 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.02 (2 H, ddd, *J* 7.6, 1.1, 0.6, ArH), 7.84 (2 H, ddd, *J* 7.6, 0.9, ArH), 7.63 (2 H, ddd, *J* 7.6, 1.2, ArH), 7.53 (2 H, ddd, *J* 7.6, 1.1, ArH); δ_C (100 MHz; $CDCl_3$) 145.1 (C), 137.1 (C), 132.5 (CH), 129.5 (CH), 127.5 (CH), 121.8 (CH); *m/z* (ESI) $C_{12}H_8SO$ (M^+) *calc.* (M+H) 201.0369, (M+Na) 223.0188, *found* (M+H) 201.0369, (M+Na) 223.0194. This is a known compound, and the spectroscopic data are identical to those reported in literature.[130]

Dibenzothiophene-5,5-dioxide 44



44

(9%)

mp = 218 – 220 °C (lit,[127] 237 °C; lit,[128]232 – 232.5 °C); ν_{max} (neat) 1282, 1160 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.89 – 7.79 (4 H, m, ArH), 7.67 (2 H, td, *J* 7.6, 1.1, ArH), 7.56 (2 H, td, *J* 7.6, 1.0, ArH); δ_C (100 MHz; $CDCl_3$) 137.7 (C), 133.8 (CH), 131.6 (CH), 130.3 (CH), 122.2 (CH), 121.5 (CH); *m/z* (ESI) $C_{12}H_8SO_2$ (M^+) *calc.* (M+H) 217.0318, (M+Na) 239.0137, *found* (M+H) 217.0318, (M+Na) 239.0137. This is a known compound, and the spectroscopic data are identical to those reported in literature.[130,131]

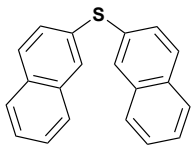
Photodeoxygenation of DBTO

DBTO (100 mg, 0.5 mmol) and the substrate (1 eq.) were inserted in a quartz tube containing anhydrous CH_3CN (5 mL). The reaction mixture was sonicated twice for 20 min each time under an Ar flow. After that, the samples were irradiated with a 400 W Mercury lamp for 24 h at room temperature with continuous magnetic stirring. The products were analysed by LC–MS.

DBT/DBTO Catalytic cycle

To a solution of DBT (50 mg, 2.7 mmol) in dry CH_3CN, the substrate (2 eq) and $ZrCl_4$ (0.47 g, 2.0 mmol) were added in a quartz tube. The resulting solution was sonicated twice for 4 min each under an Ar flow. After that, H_2O_2 (35%, 1.3 mL, 13.6 mmol) was injected by injection pump at a rate of 0.10 mL/h. The reaction mixture was irradiated with a 400 W Mercury lamp for 24 h at room temperature with continuous magnetic stirring. The products were analysed by LC–MS for the DBT/DBTO ratio and by GC or GC–MS for the products. The results are reported in **Chapter 4, Table 17**.

Dinaphthyl sulfide 52



52

A solution of 2-naphthol (1.24 g, 8.60 mmol) and 2-naphthalenethiol (2.07 g, 12.90 mmol) was refluxed in toluene for 14 h in the presence of *p*-TsOH (1.64 g, 8.60 mmol). The reaction was cooled down to room temperature and quenched with saturated $NaHCO_3$ solution (20 mL). The product was then extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated. Further purification was achieved through column chromatography (petroleum : EtOAc 8:2) to yield a colourless solid (1.15 g, 47%), mp = 142 – 144 °C; ν_{max} (neat) 734 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.92 – 7.87 (2 H, m), 7.84 – 7.74 (6 H, m, ArH), 7.52 – 7.45 (6 H, m, ArH); δ_C (100 MHz; $CDCl_3$) 133.8 (C), 133.0 (C), 132.3 (C), 129.7 (CH), 128.8 (CH), 128.6 (CH), 127.7 (CH), 127.4 (CH), 126.6 (CH), 126.2 (CH). This is a known compound, and the spectroscopic data are identical to those reported in literature.[10]

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7 Appendix

GC–MS analysis of reaction of 1-phenyl-1,2,3,4-tetrahydroisoquinoline *9*

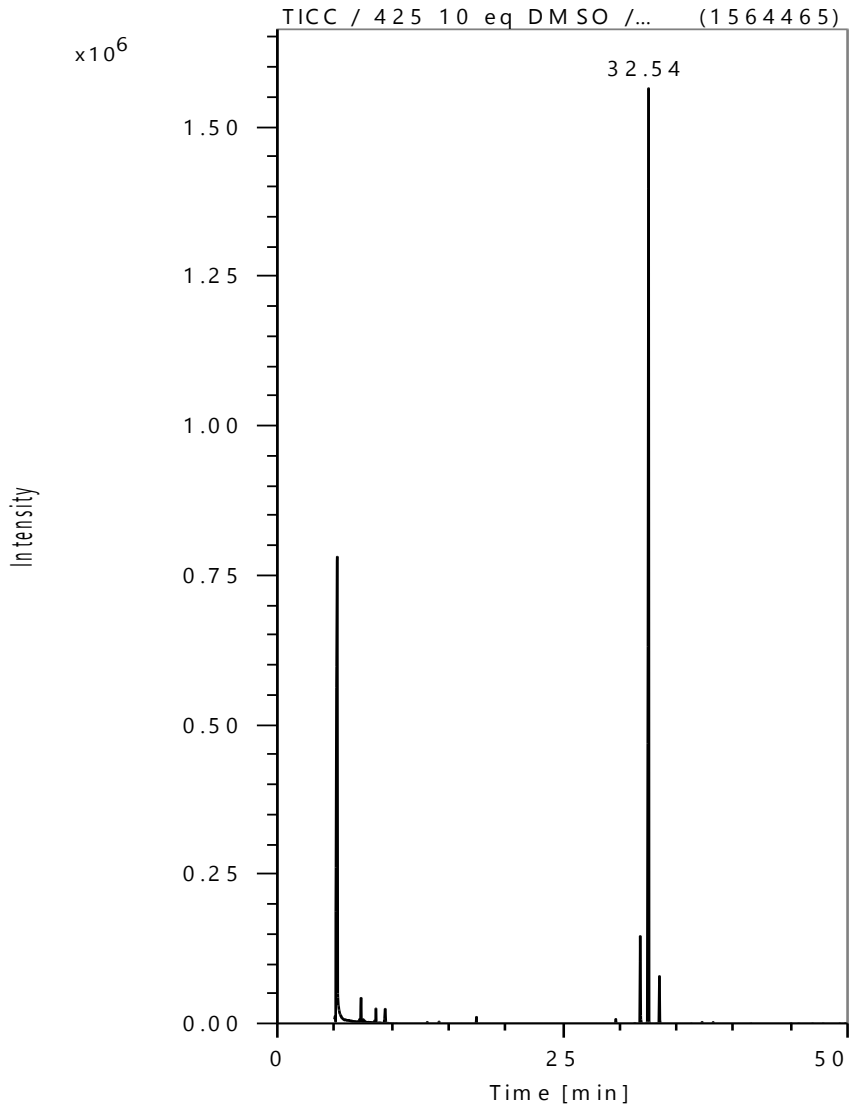


Fig. A1 GC–MS analysis of substrate **9** reaction mixture in DMSO for 24 h at 100 °C.

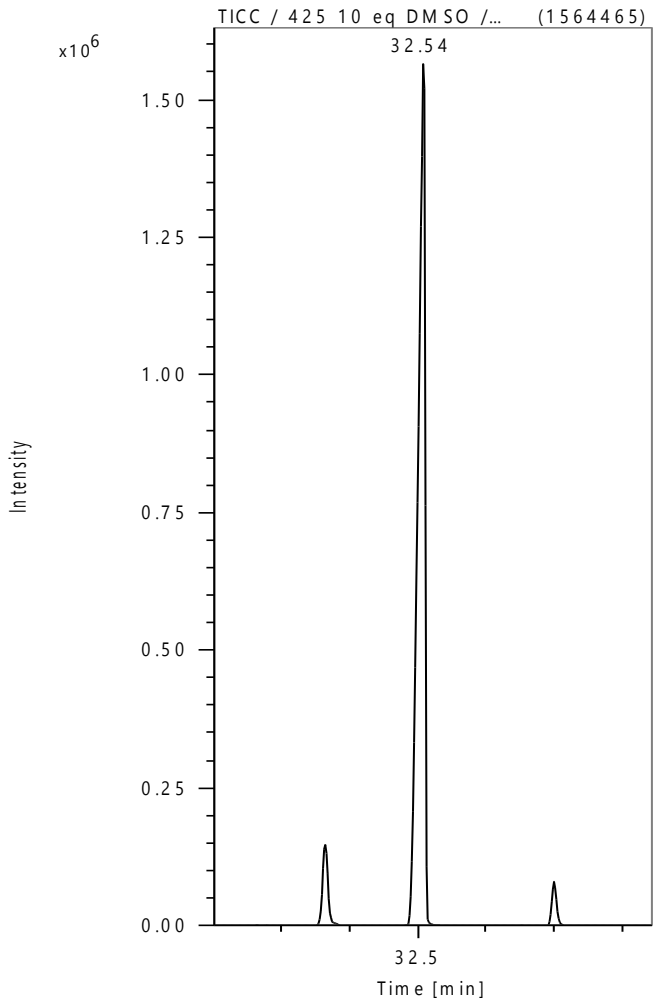
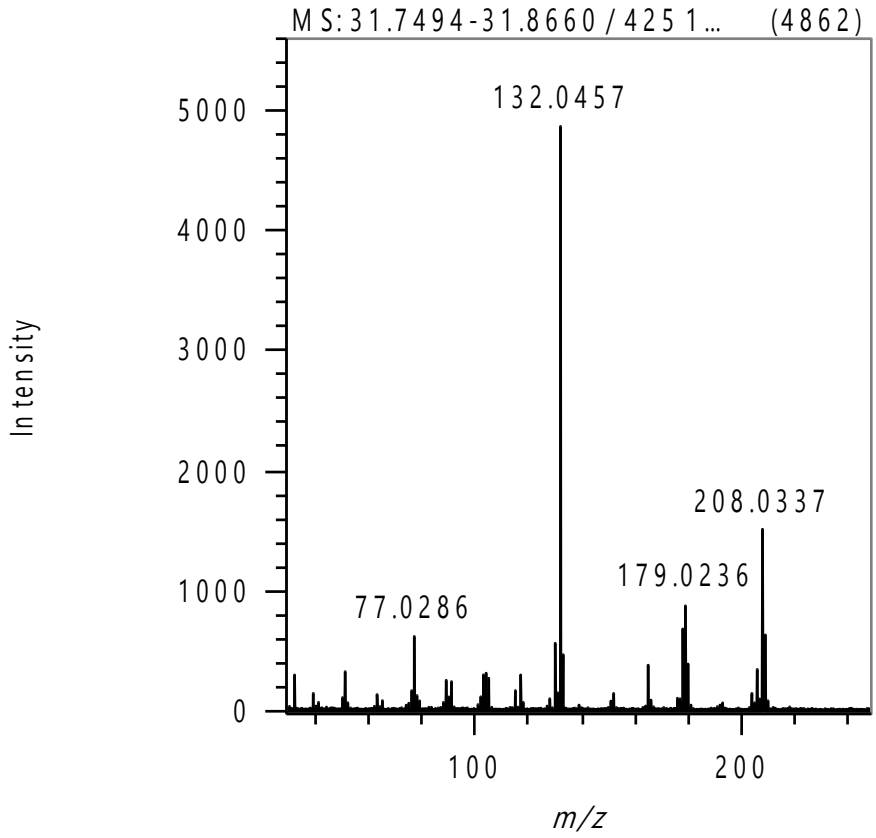
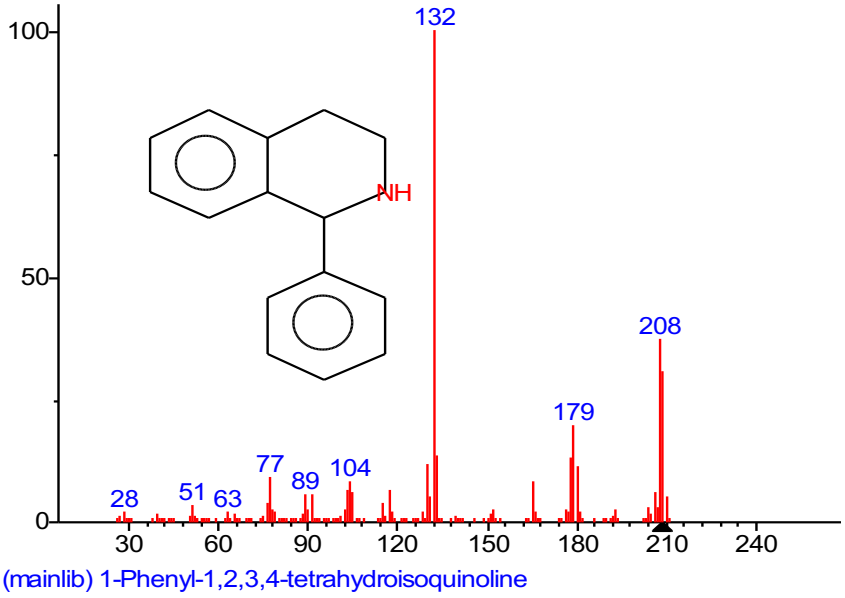


Fig. A2 Enlargement of the GC–MS analysis of substrate **9** in DMSO for 24 h at 100 °C.

No.	Time [min] End [min]	Type	Area	Area [%]	Area [% of Total]		Height	Start [min]
1	31.8244 31.9326	BB	409927.10	7.31	6.61	146266.00	31.7661	
2	32.5407 32.6573	BB	5607337.37	100.00	90.36	1564465.00	32.3991	
3	33.4985 33.5651	BB	188572.22	3.36	3.04	79242.00	33.4569	

min 31.8





(mainlib) 1-Phenyl-1,2,3,4-tetrahydroisoquinoline

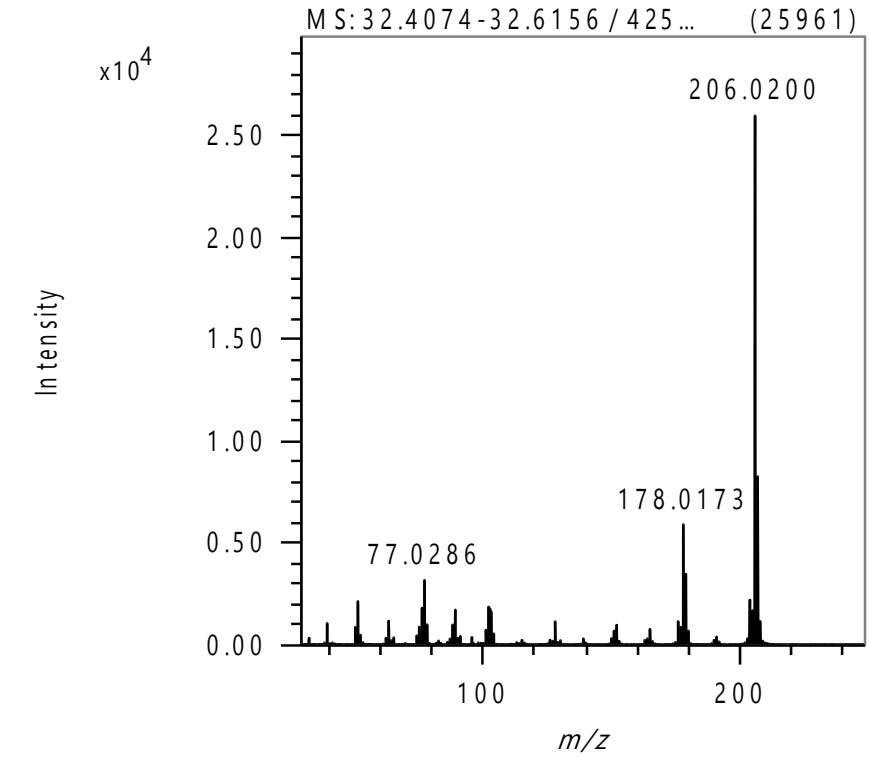
Name: 1-Phenyl-1,2,3,4-tetrahydroisoquinoline

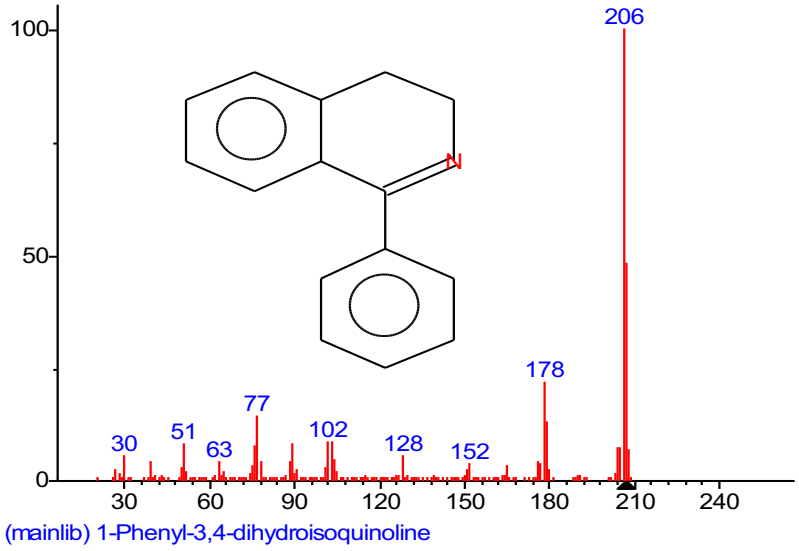
Formula: $C_{15}H_{15}N$

MW: 209 Exact Mass: 209.120449 CAS#: 22990-19-8

Fig. A3 Analysis of the first peak at 31.8 min.

min 32.5





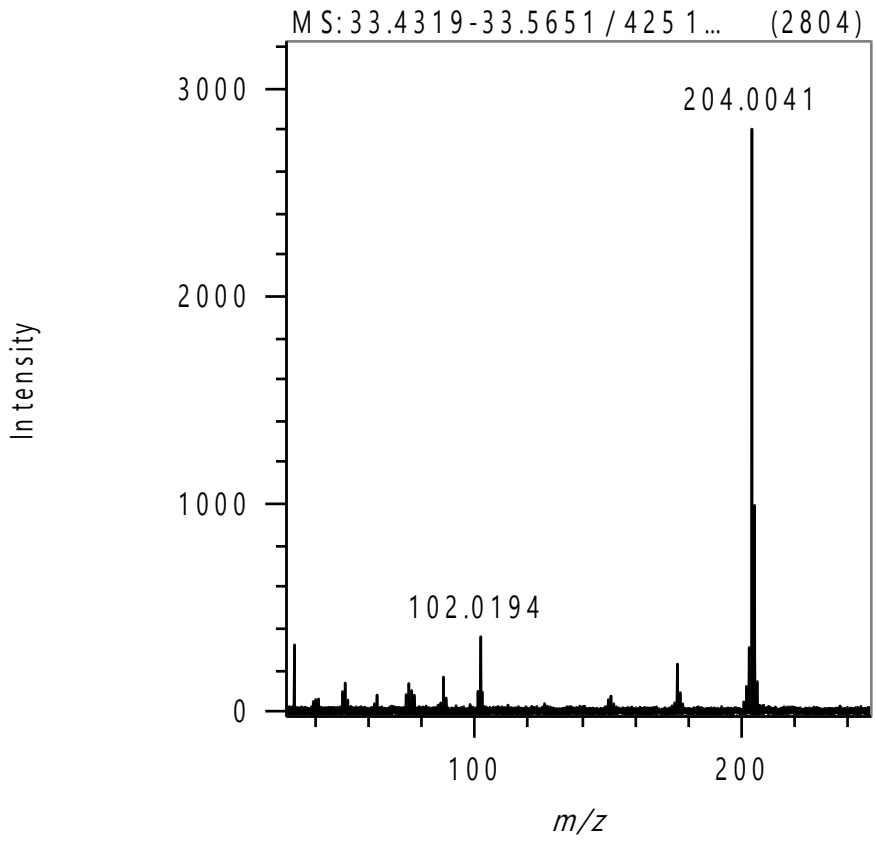
Name: 1-Phenyl-3,4-dihydroisoquinoline

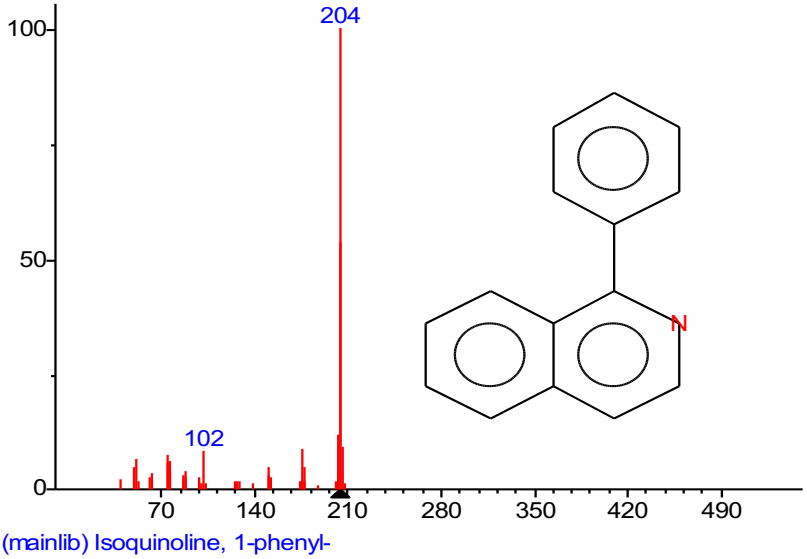
Formula: $C_{15}H_{13}N$

MW: 207 Exact Mass: 207.104799 CAS#: 52250-50-7

Fig. A4 Analysis of the second peak at 32.5 min.

min 33.4





Name: Isoquinoline, 1-phenyl-

Formula: $C_{15}H_{11}N$

MW: 205 Exact Mass: 205.089149 CAS#: 3297-72-1

Fig. A5 Analysis of the third peak at 33.4 min.

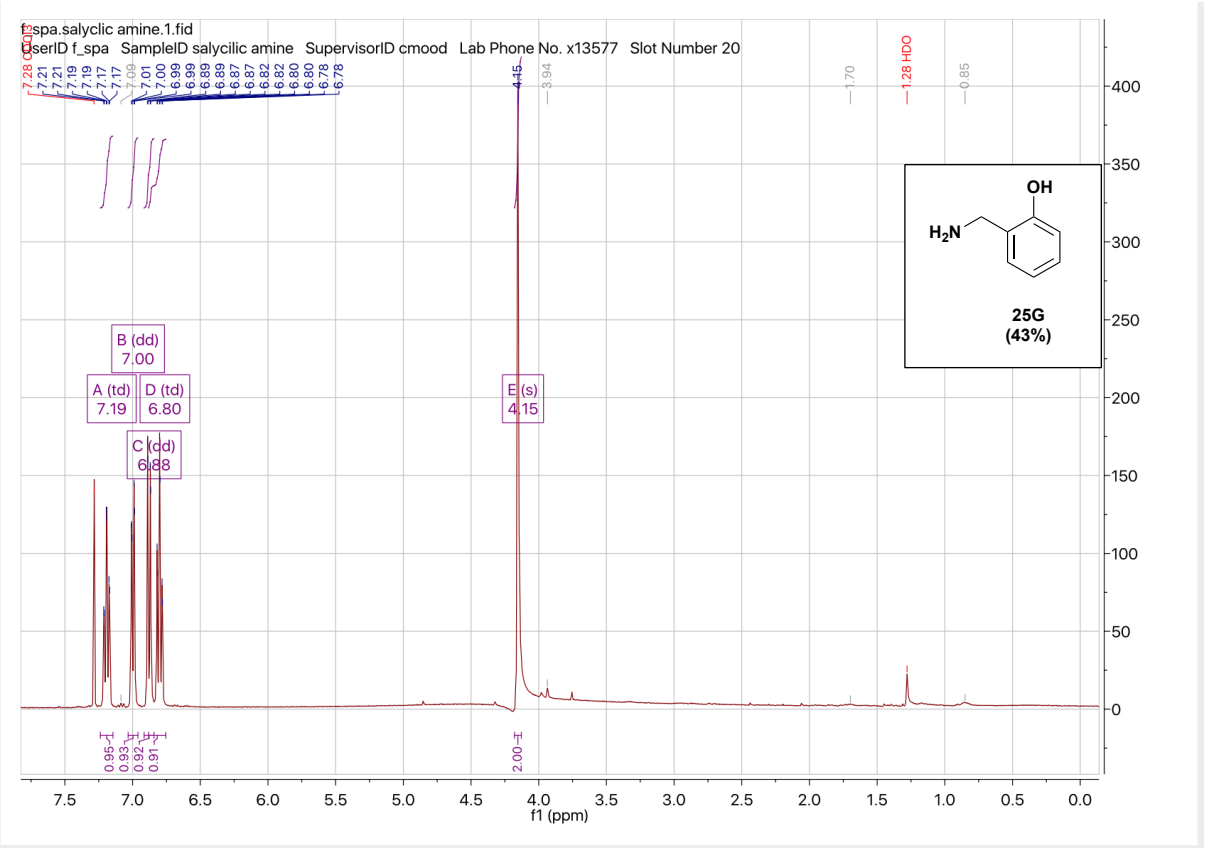


Fig. A6 ^{1}H NMR of isolated 2-hydroxybenzylamine **25G**.

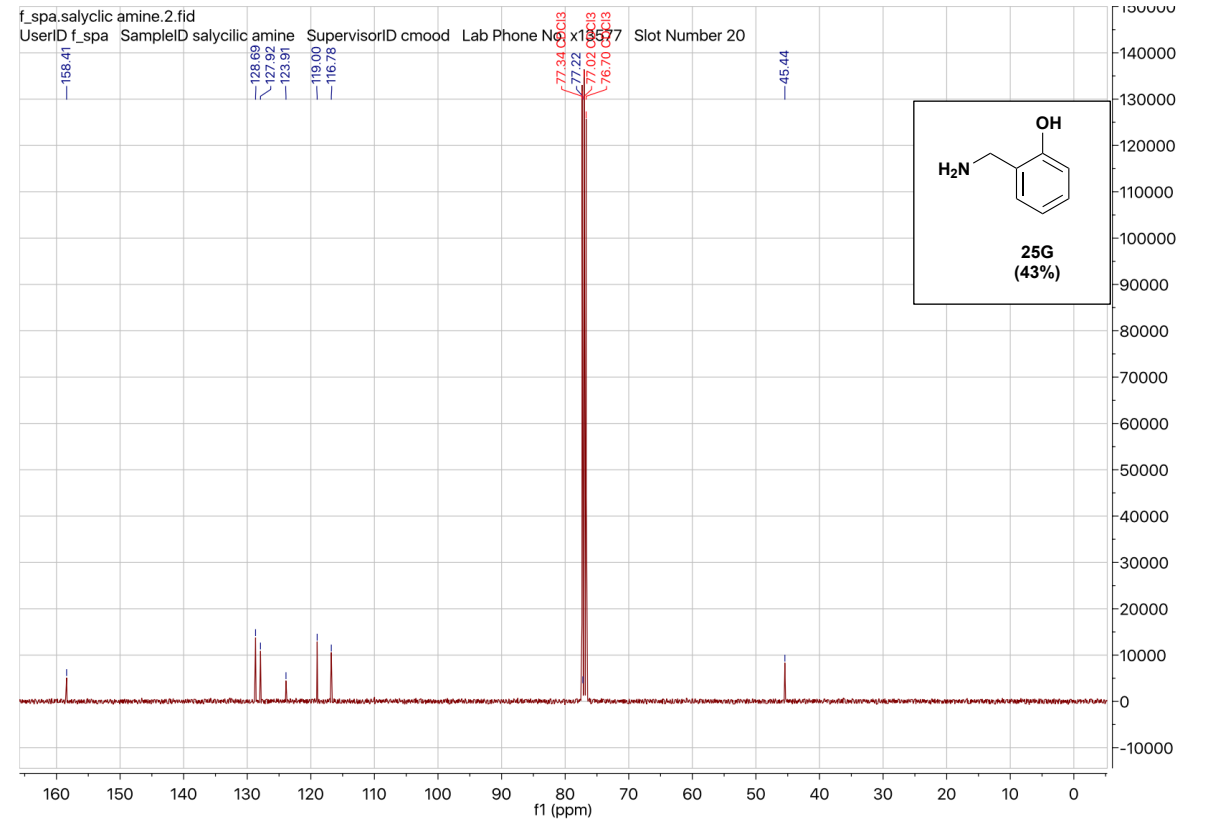
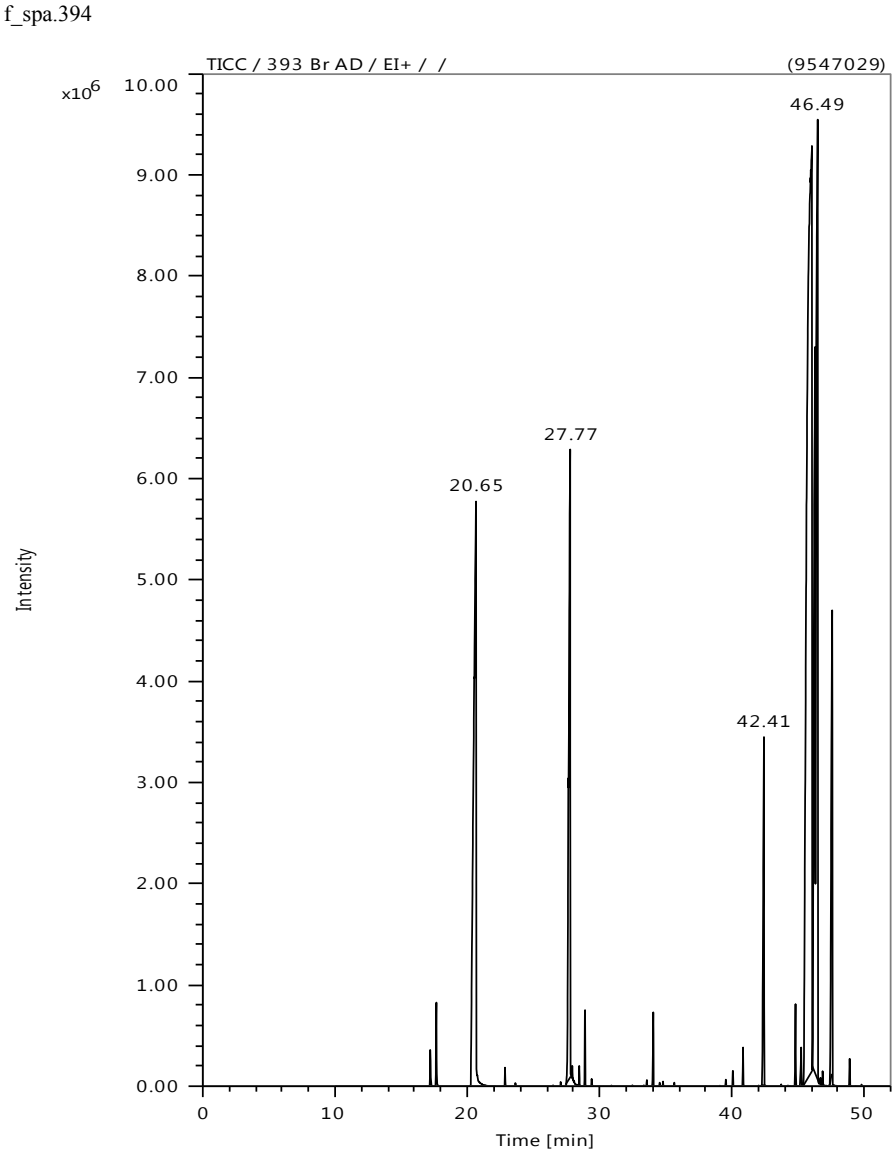


Fig. A7 ^{13}C NMR of isolated 2-hydroxybenzylamine **25G**.

GC–MS analysis of reaction of *N*-(4-bromobenzyl)1,1-diphenylmethanamine *18*



No.	Time [min]	Type	Area	Area [%]	Area [% of Total]		Height	Start [min]	End [min]
1	20.6490	BB	77153279.27	31.98	14.00	5776288.00	20.2076	22.2066	
2	27.7704	BB	50964328.48	21.13	9.25	6286975.52	27.4372	28.3035	
3	42.4129	BB	16058540.04	6.66	2.91	3445770.91	42.2380	42.5795	
4	46.0444	BB	241217195.14	100.00	43.78	9138118.37	45.3781	46.0777	
5	46.4859	BB	138054706.39	57.23	25.06	9485915.08	46.0861	46.5941	
6	47.5770	BB	27511456.22	11.41	4.99	4585275.66	47.3937	47.6020	

Fig. A8 GC–MS analysis of substrate **18** in DMSO for 24 h at 100 °C.

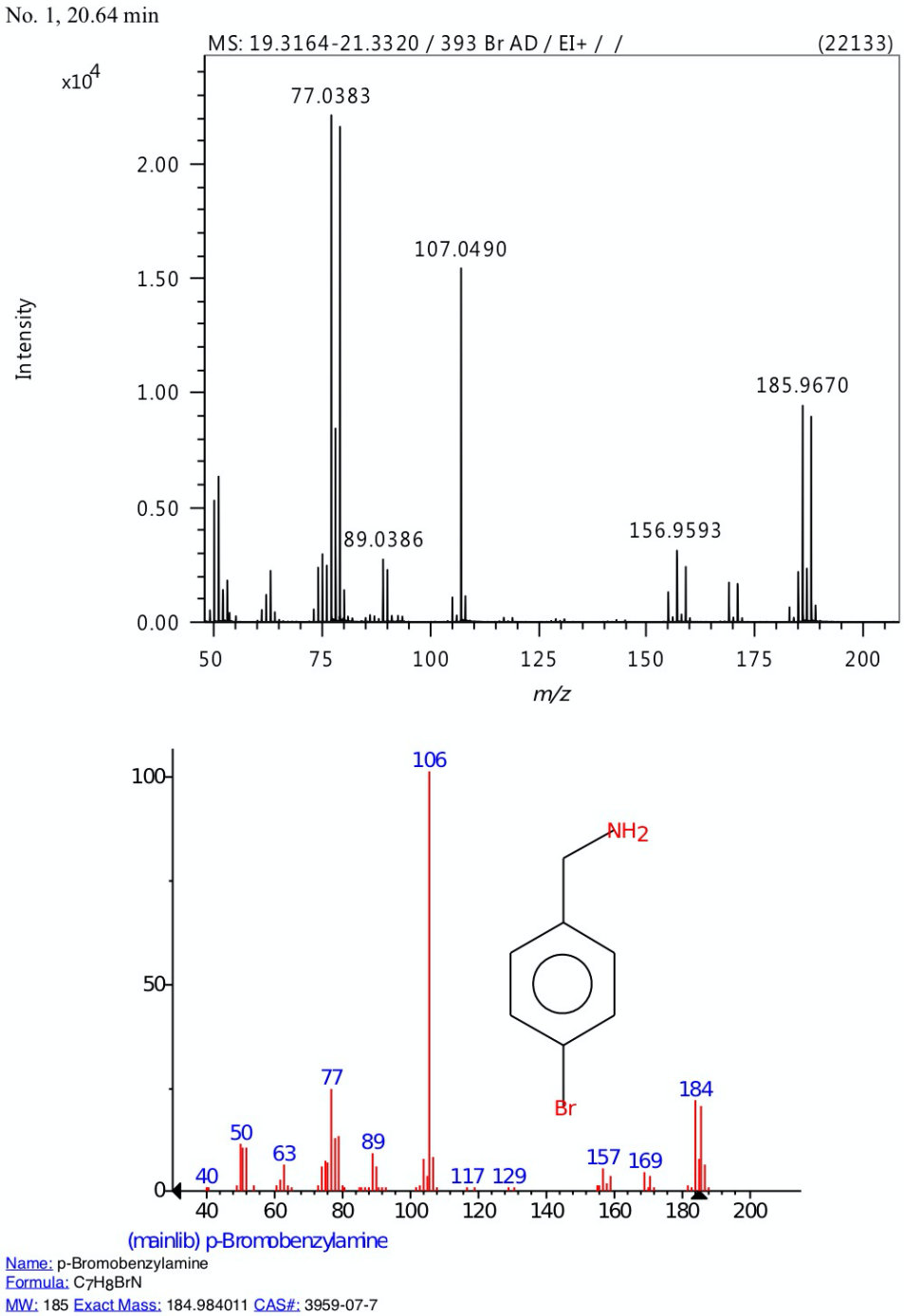


Fig. A9 GC–MS analysis of substrate **18** in DMSO for 24 h at 100 °C.

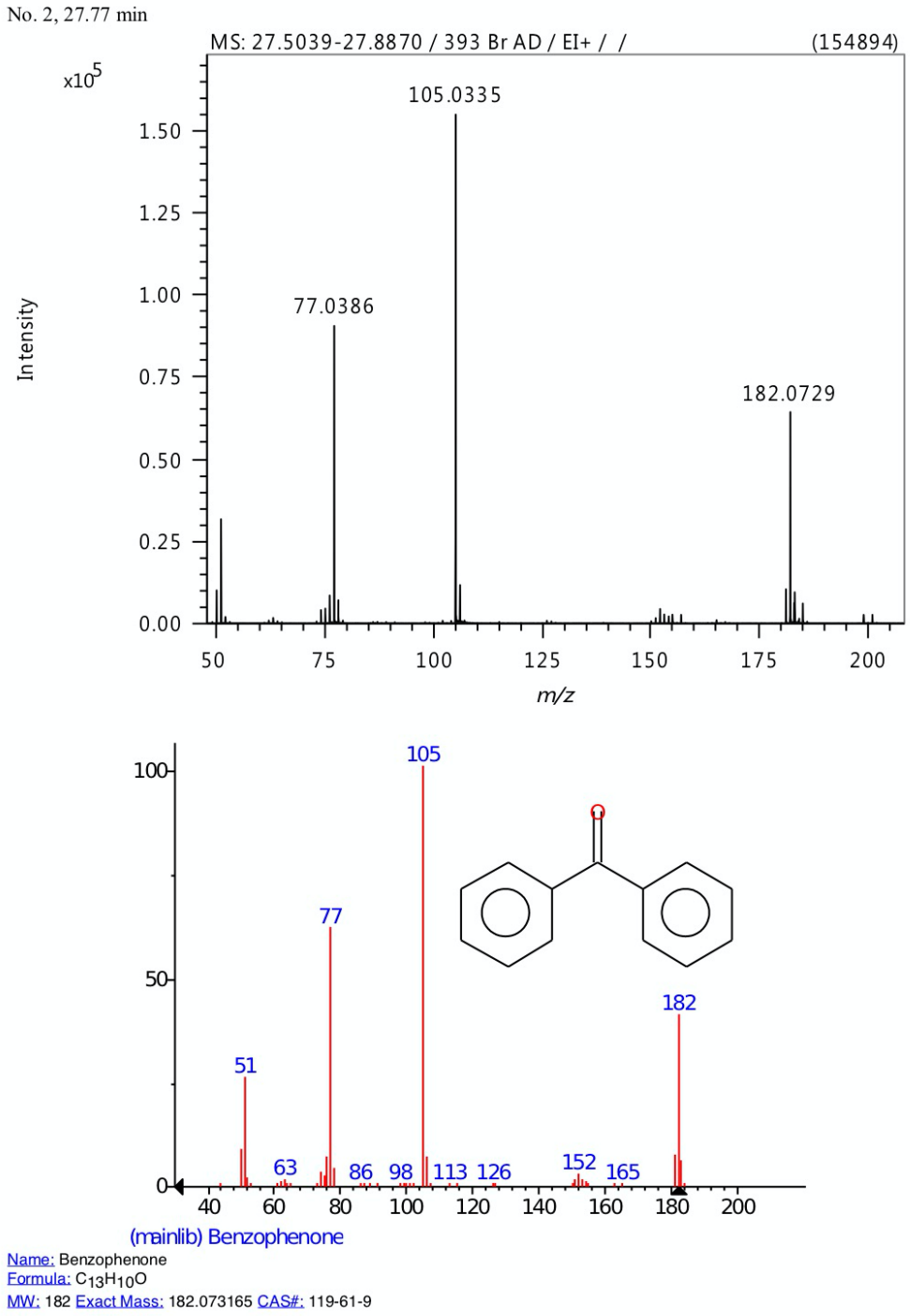


Fig. A10 GC–MS analysis of substrate **18** in DMSO for 24 h at 100 °C.

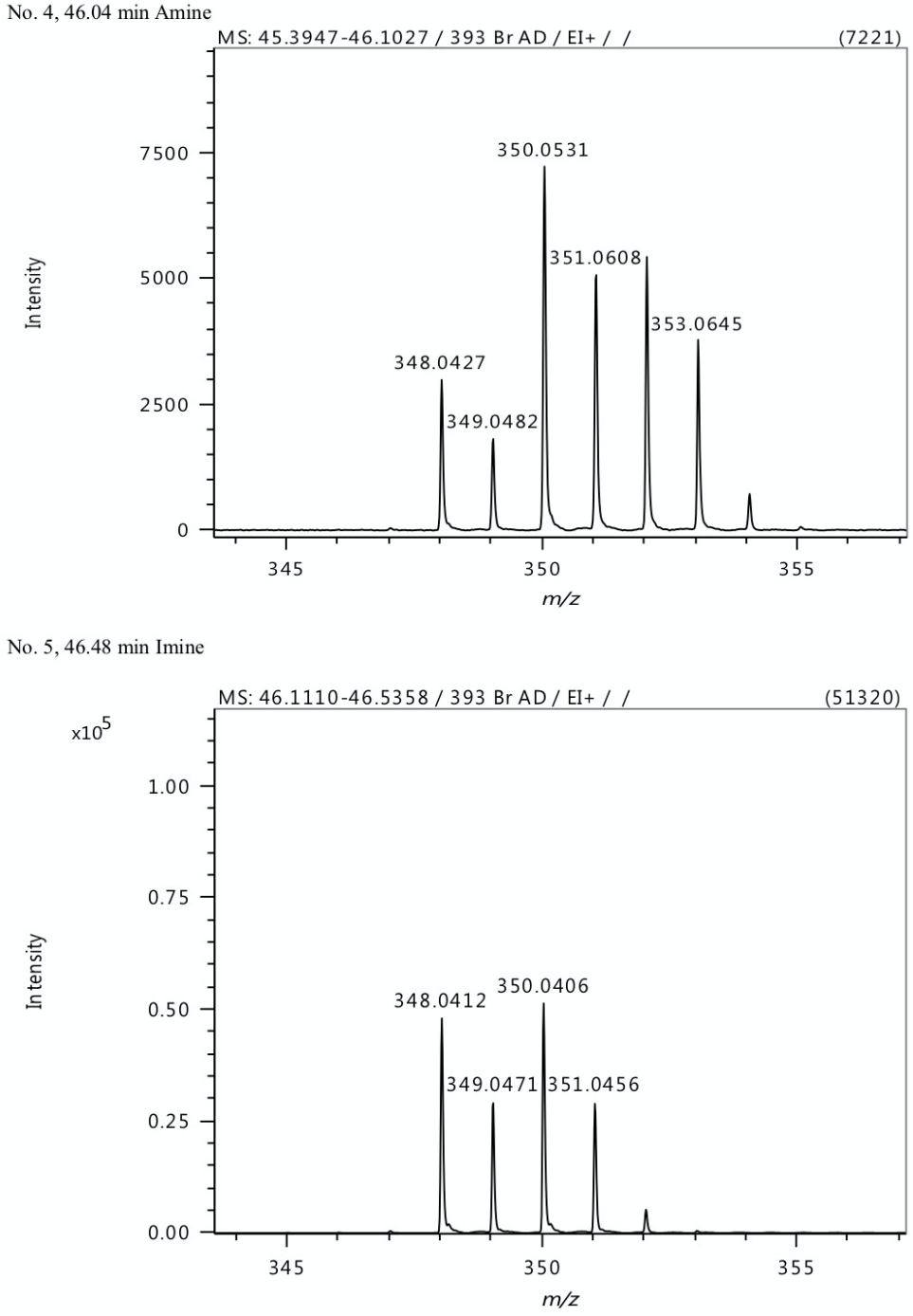


Fig. A11 GC–MS analysis of substrate **17** in DMSO for 24 h at 100 °C.

GC–MS analysis of a neat reaction of 1-phenyl-1,2,3,4-tetrahydroisoquinoline *9*

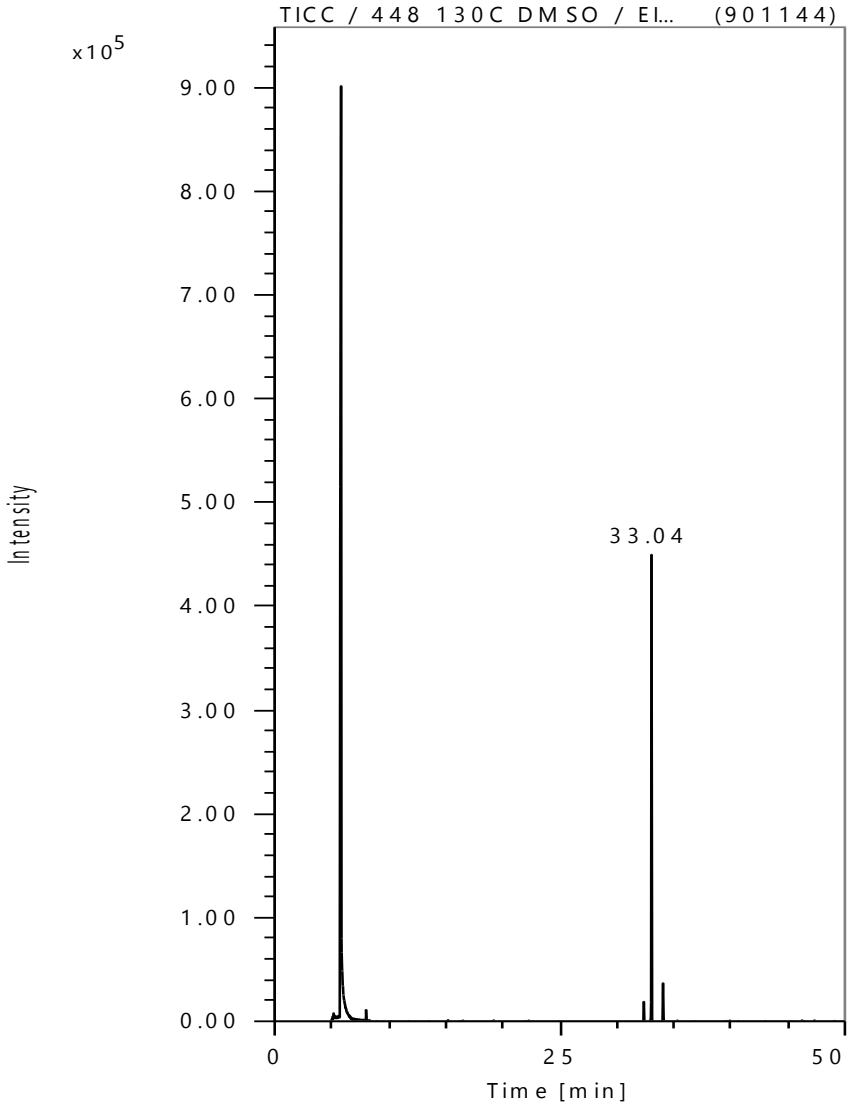
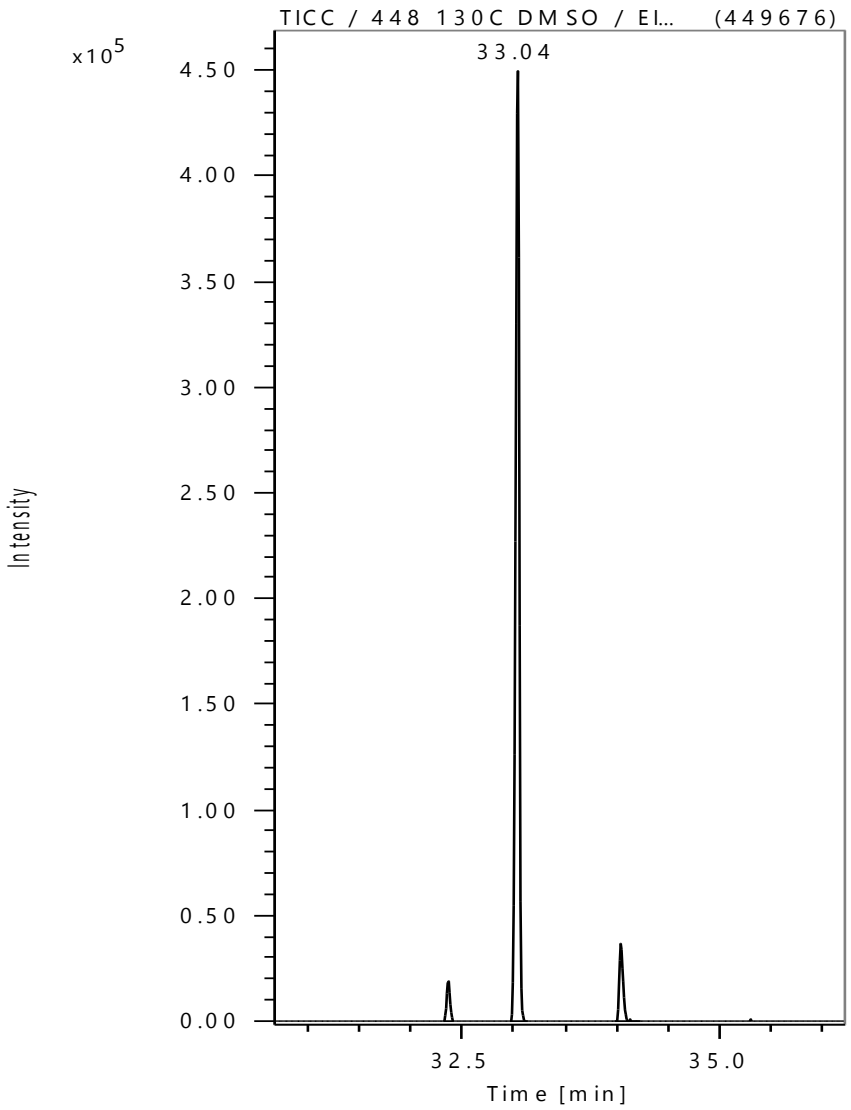


Fig. A12 GC–MS GC-MS analysis of substrate **9** reaction mixture for 24 h at 100 °C neat.



No.	Time [min] End [min]	Type	Area	Area [%]	Area [% of Total]	Height	Start [min]
1	32.3657 32.4074	BB	42908.20	3.79	3.38	18888.00	32.3241
2	33.0404 33.1487	BB	1133626.38	100.00	89.28	449676.00	32.9571
3	34.0399 34.2314	BB	93235.31	8.22	7.34	36660.00	33.9899

Fig. A13 Enlargement of the GC–MS analysis of substrate **9** for 24 h at 100 °C neat.

32.4 Min, first peak.

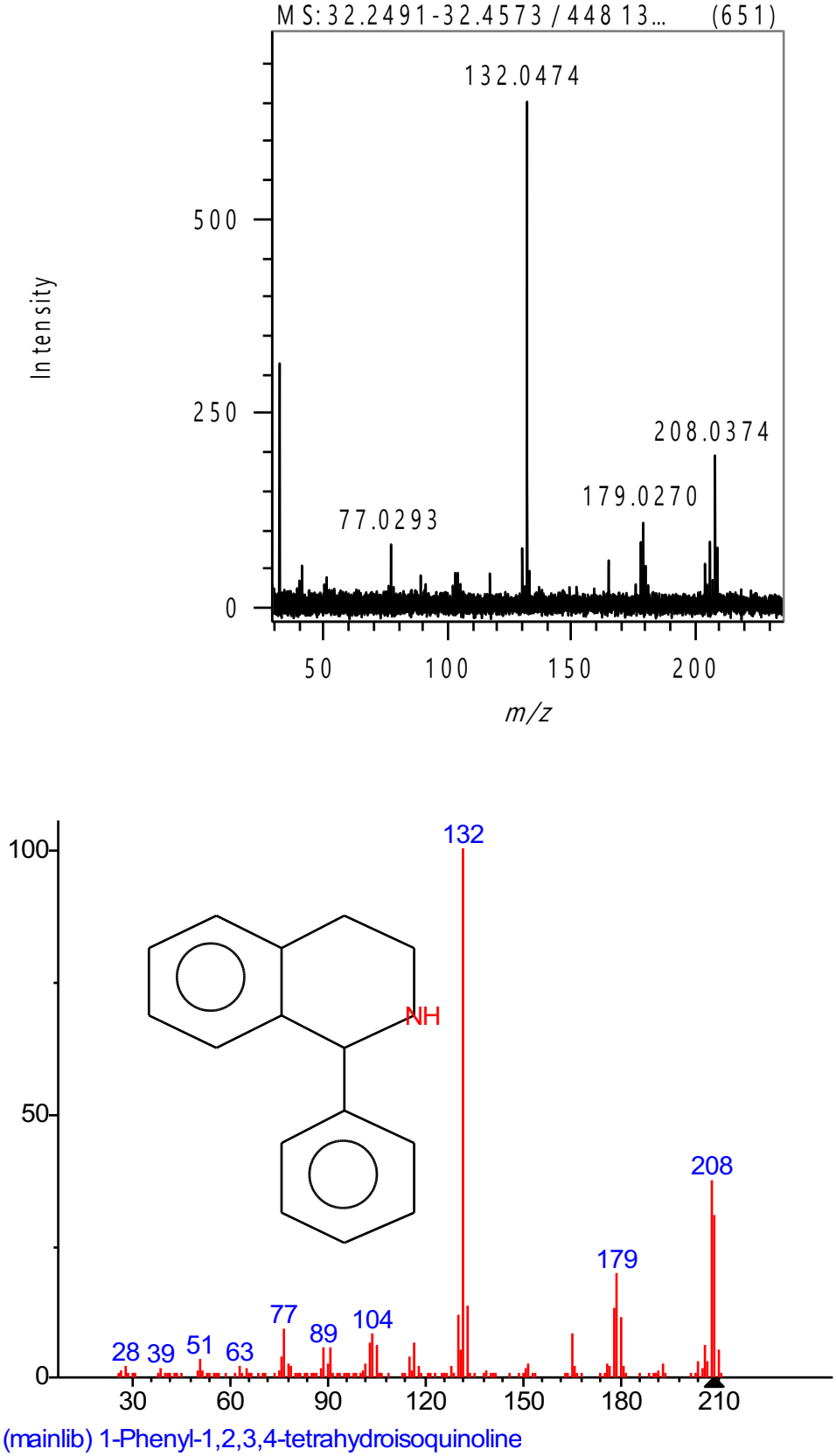
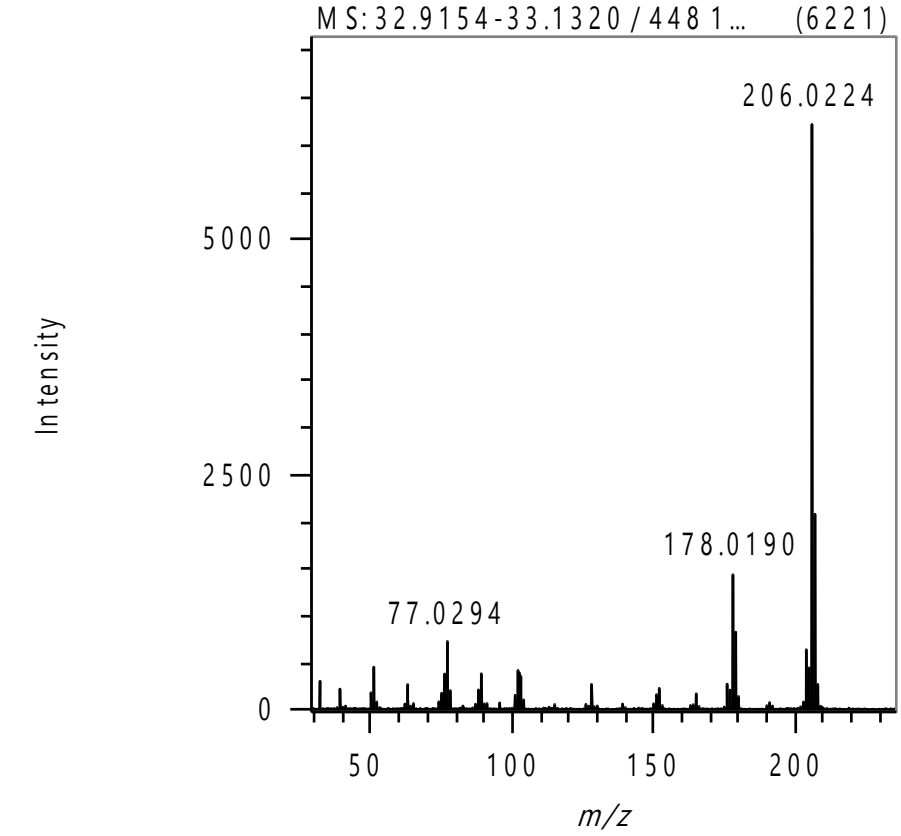


Fig. A14 Analysis of the first peak at 32.4 min.

Second peak, 32.9 min



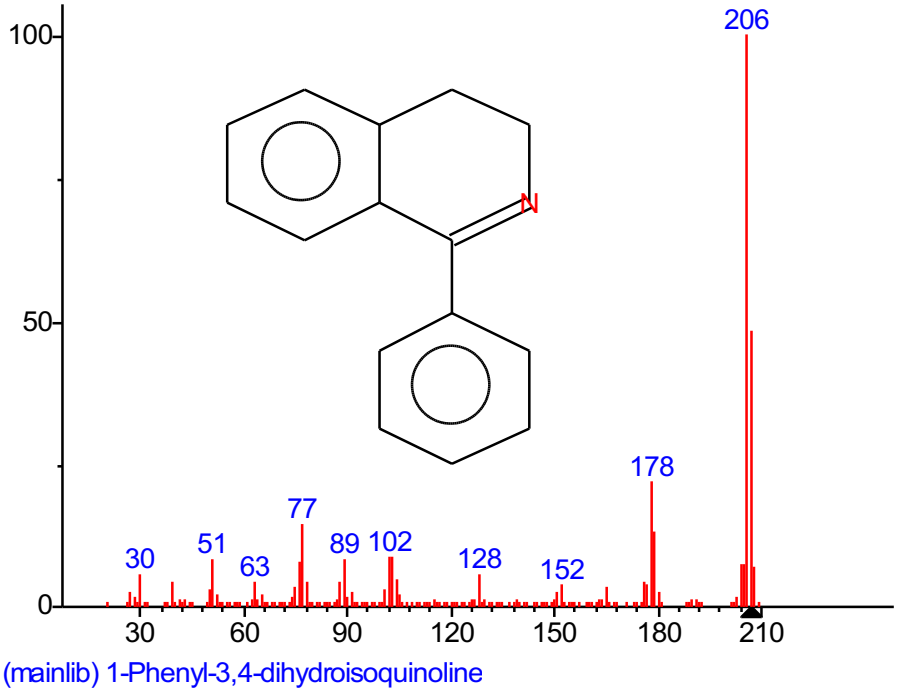
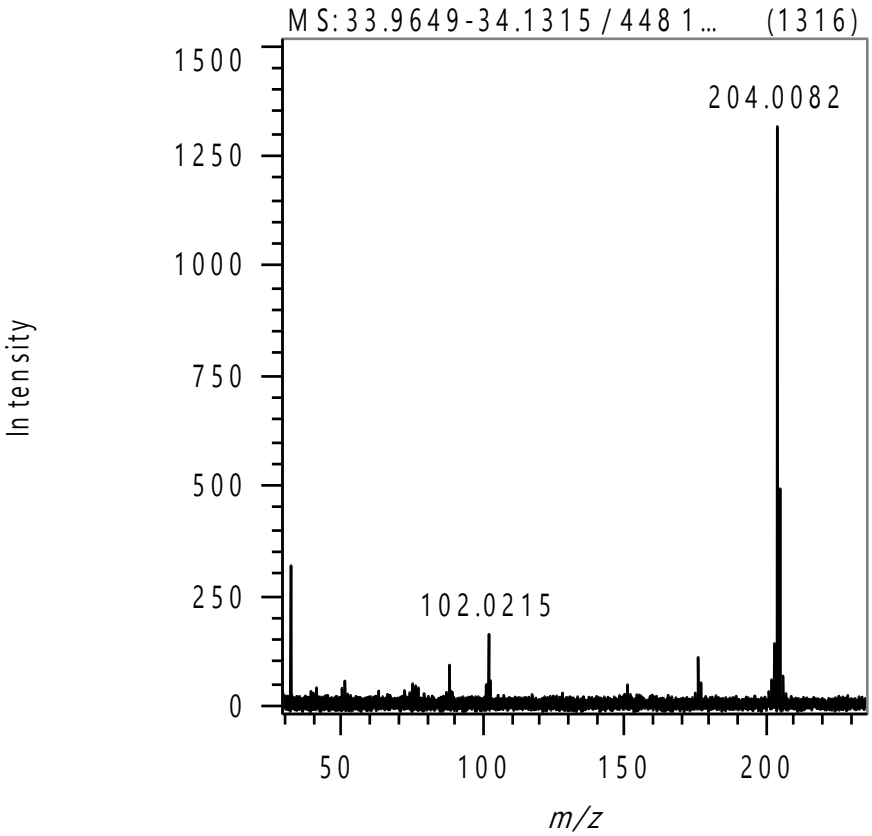


Fig. A15 Analysis of the second peak at 32.9 min.

Third peak, min 34.0



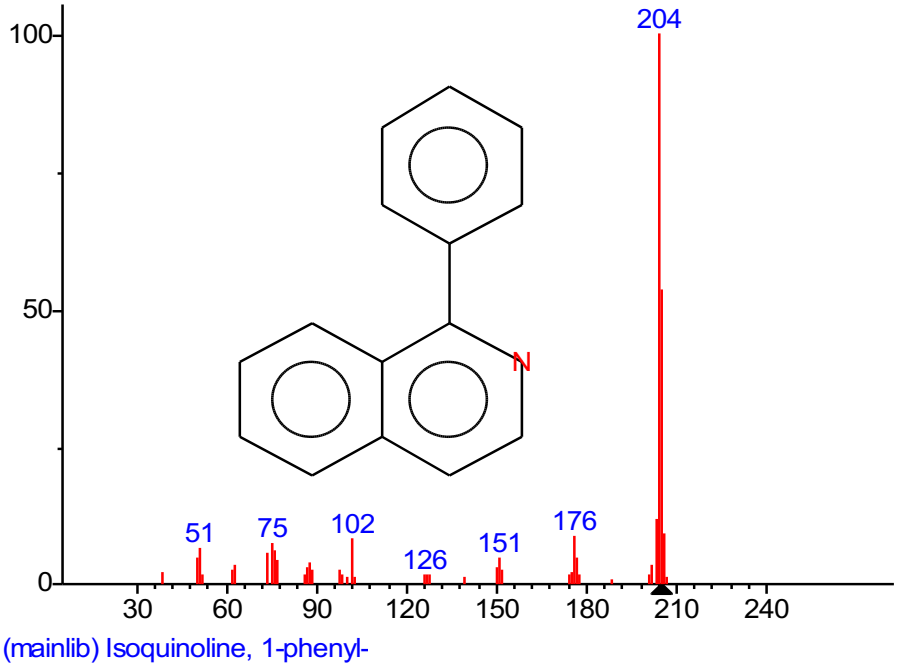


Fig. A16 Analysis of the third peak at 34.0 min.

TGA Images

A Thermal Gravimetric Analysis/Mass Spectrometer (TGA-MS) analysis was performed. The method used consisted in heating the sample dissolved in DMSO from room temperature to 100 °C with an increase rate of 5 °C/min. After that, isothermal conditions were left for 24 h. The big loss of weight recorded is due to the evaporation of DMSO **(Fig. A17** and **A19)**. In fact, the sample was dried at the end of the experiment. Nevertheless, the mass spectrometer detected a hydrogen peak (*m/z*=2) **(Fig. A18)**. The sample at the end of the TGA-MS analysis was subjected to GC-MS. This did not reveal any starting material, strengthening the hypothesis that the hydrogen peak detected was gas released from the reaction.

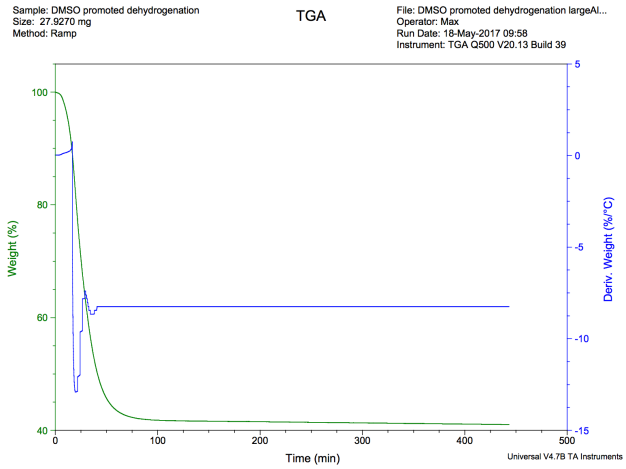


Fig. A17 TGA-MS Analysis: Plot of Time (min) vs Weight loss (%)

m/z=2

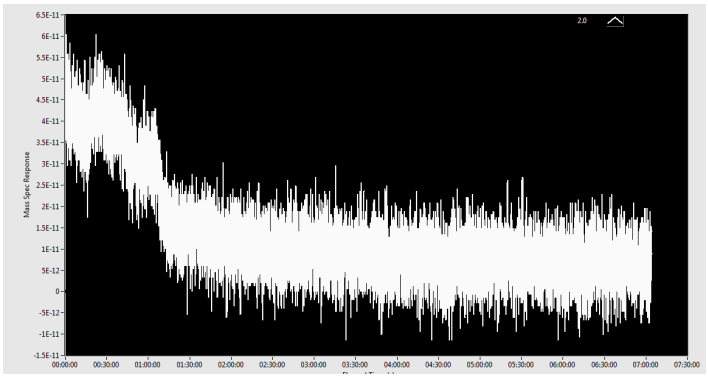


Fig. A18 TGA-MS *m/z*=2

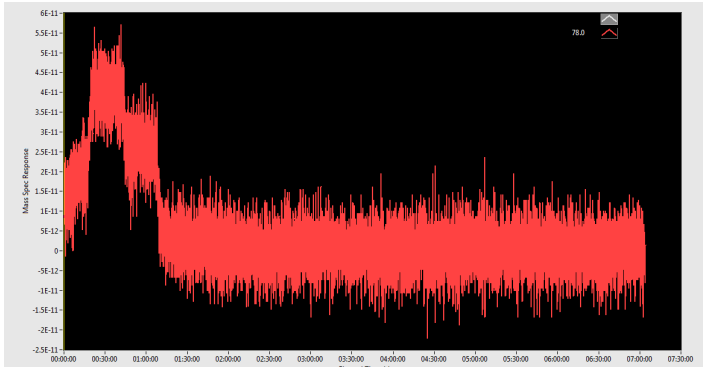
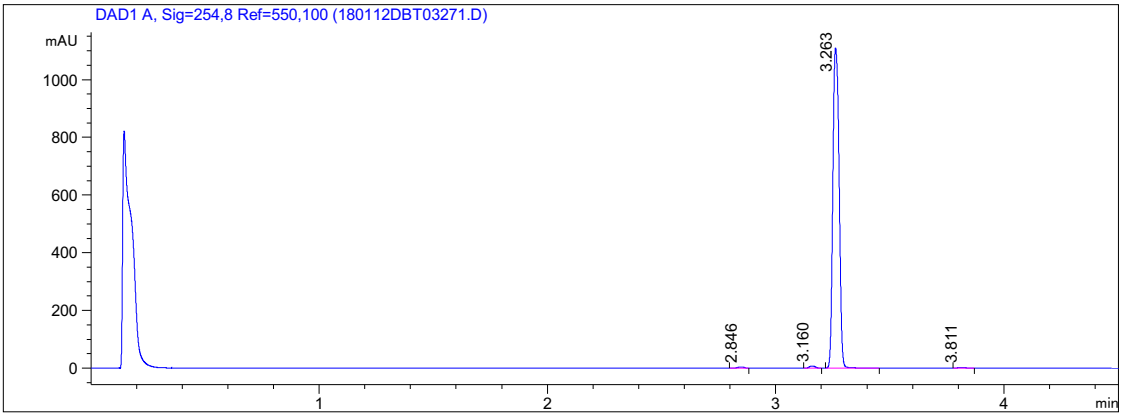


Fig. A19 TGA-MS *m/z*=78 Evaporation of DMSO

LC – MS analysis of DBT and DBTO

University of Nottingham- HPLC-MS report for DBT

Data File name: D:\WALKUP\PCXFS1\18-01\180112DBT03271.D
DBT
Walkup method: 'A9505A-UG'
Data acquired by: Admin
on: 12-Jan-18 at 1:21:19 PM
Method: C:\Chem32\1\METHODS\A9505A-UG.M
Injection Vol : 2.0 ul
Column: 30.00MM Sunfire
Vial: Vial 4



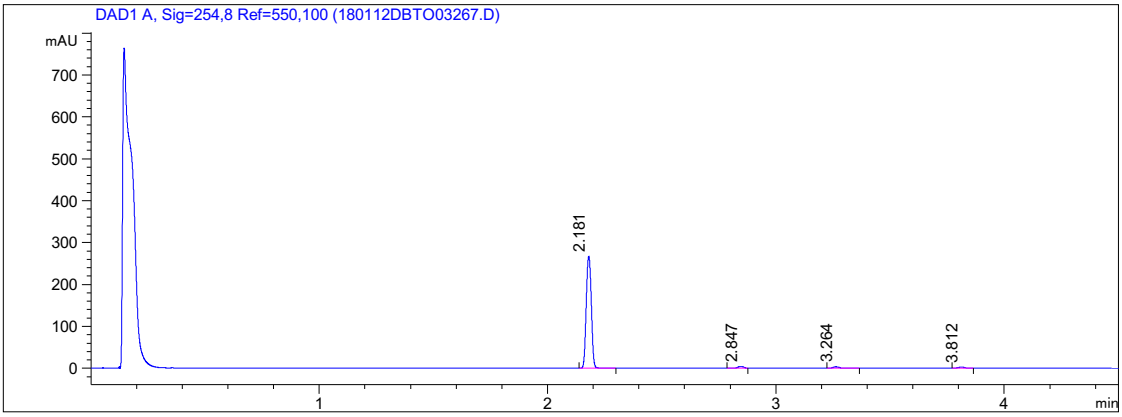
#	Meas. RT	Peak Type	Height	Width	Area	Area %
1	2.846	BB	4.285	0.031	8.172	0.382
2	3.160	BB	7.592	0.030	13.991	0.654
3	3.263	BB	1108.868	0.031	2110.554	98.724
4	3.811	BB	2.313	0.031	5.108	0.239

Report created on: 12-Jan-18 at 1:26:24 PM

Fig. A20 LC–MS analysis of DBT.

University of Nottingham- HPLC-MS report for dbto

Data File name: D:\WALKUP\PCXFS1\18-01\180112DBTO03267.D
dbto
Walkup method: 'A9505A-UG'
Data acquired by: Admin
on: 12-Jan-18 at 12:25:14 PM
Method: C:\Chem32\1\METHODS\A9505A-UG.M
Injection Vol : 2.0 ul
Column: 30.00MM Sunfire
Vial: Vial 80



#	Meas. RT	Peak Type	Height	Width	Area	Area %
1	2.181	BB	266.798	0.026	413.755	95.416
2	2.847	BB	4.308	0.031	8.145	1.878
3	3.264	BB	3.455	0.032	6.964	1.606
4	3.812	BB	2.449	0.027	4.768	1.100

Report created on: 12-Jan-18 at 12:30:16 PM

Page 1 of 3

Fig. A21 LC–MS analysis of DBT.

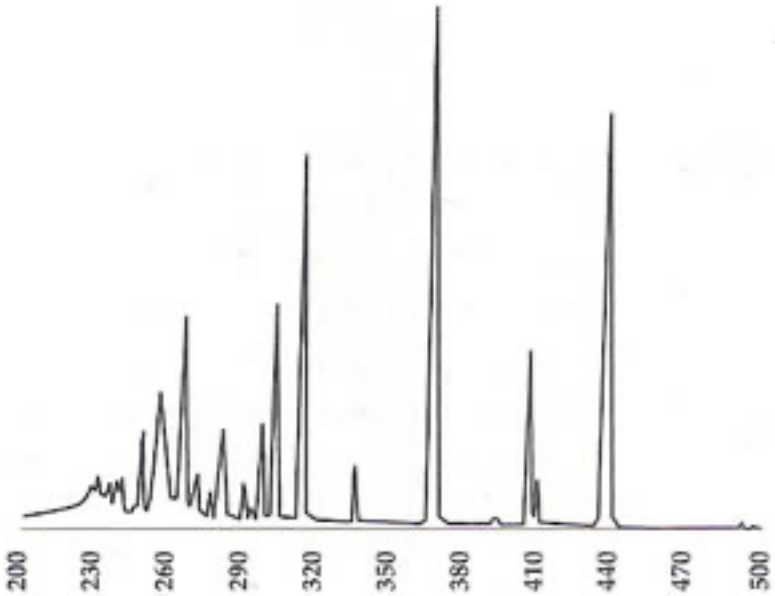


Fig. A22 400 W Middle Pressure Hg lamp UV output.

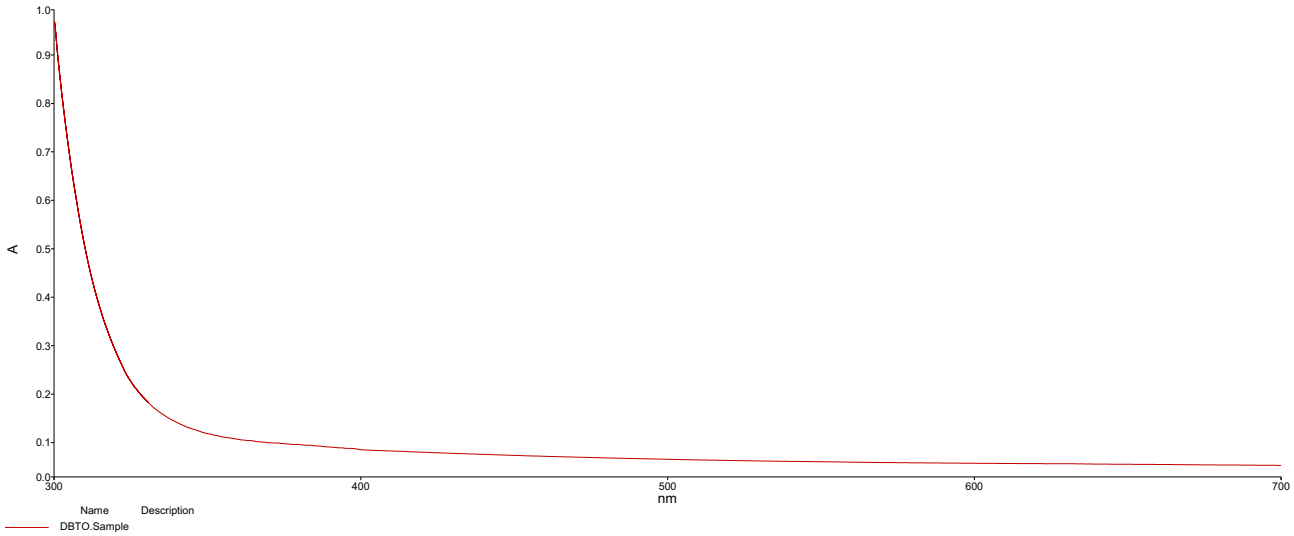
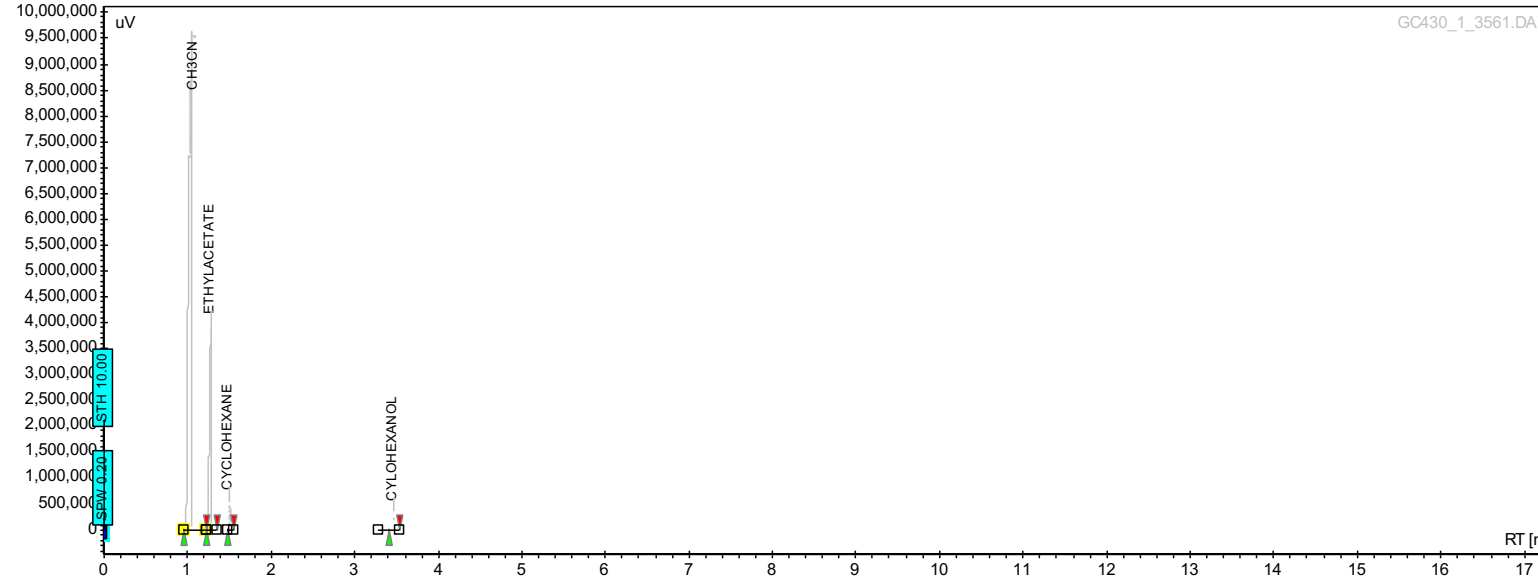
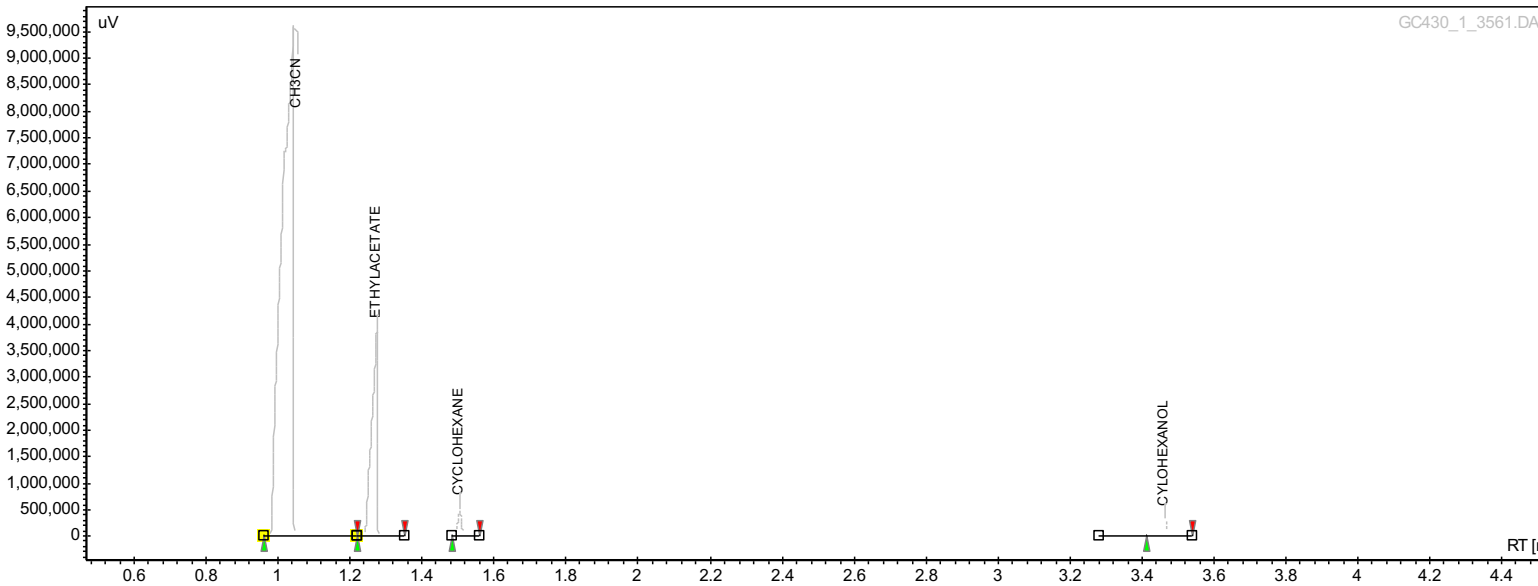


Fig. A23 DBTO UV reading.





#	Name	Time [Min]	[% Area]	Height [uV]	Area [uV.Min]	Area % [%]
1	CH3CN	1.04	81.30	9619131.5	343562.5	81.304
2	ETHYLACETATE	1.27	16.01	3880186.9	67643.4	16.008
3	CYCLOHEXANE	1.50	1.37	502880.4	5783.9	1.369
4	CYLOHEXANOL	3.46	1.32	335538.3	5577.6	1.320
	Total		100.00	14337737.1	422567.3	100.000

Fig. A24 GC analysis of the cyclohexanol product by photodeoxygenation of DBTO.