Broadening the Scope of Reactivity for Neutral Organic Electron Donors

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Signed

Steven O'Sullivan, 2014

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I would like to thank Doctors Shengze Zhou and Eswararao Doni for giving me something to aspire to as well as laying the foundations upon which my chemistry was built.

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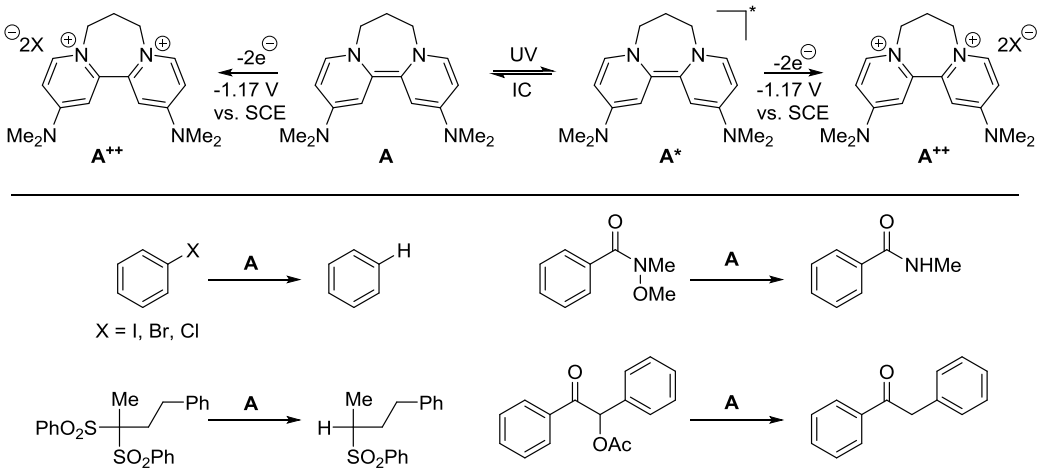
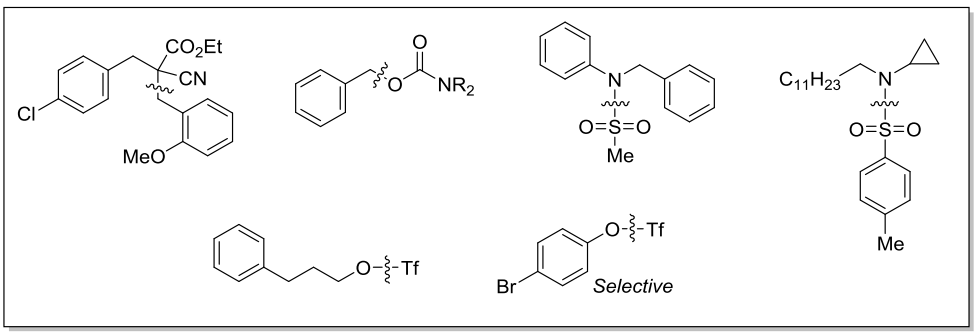
Abstract

Reduction and oxidation of functional groups are some of the fundamental transformations in inorganic and organic synthesis. Compound **A** has been shown to be a powerful neutral organic electron donor capable of the reductive bond cleavage of various σ-bonds

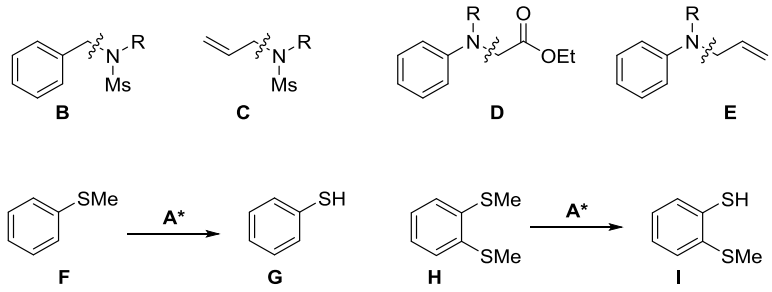


Photoactivation of donor **A** (to **A***) has been discovered to increase the reducing power of the species therefore allowing the reduction of less activated bonds and this body of work explores examples such as: carbon-nitrogen bonds of benzyl sulfonamides and aniline derivatives; carbon-oxygen bonds of benzyl ethers, esters and carbamates; carbon-carbon bonds of benzylated carbon acids; carbon-sulfur bonds of aryl methyl sulfides, oxygen-sulfur bonds of aryl and alkyl triflate esters; and nitrogen-sulfur bonds of tosylamides and activated mesylamides.



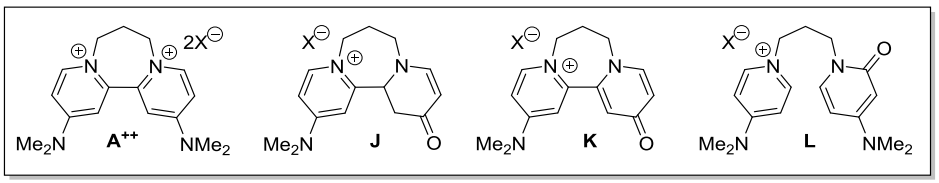
A series of nitrogen-containing substrates, **B-E**, was investigated for their reactivity with the photoactivated donor **A***. The results of these experiments were the high-yielding carbon-

nitrogen bond scissions, the details of which are reported herein including a mechanistic discussion and supporting evidence.



Likewise, aryl methyl sulfides **F** and **H** were cleaved in good yield with the photoactivated donor **A**. A number of related results demonstrate the scope of the chemistry and provide insights into the mechanism of the process.

Careful analysis of the reaction by-products from the above investigations has also allowed the elucidation of the structures of a number of compounds $\mathbf{A}^{++}$, **J**, **K**, **L**, derived from donor **A** under the reaction conditions. The mechanism of formation of these species and the insight offered into donor reactivity are discussed.



Contents

Abbreviations

Ac	acetyl
AIBN	Azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
aq	aqueous
Ar	aryl
ATR	attenuated total reflectance
B3LYP	Becke, three-parameter, Lee-Yang-Parr; a hybrid functional
Bn	benzyl
Boc	*tert*-Butyloxycarbonyl
bpy (bipy)	2,2'-bypyridyl
Bu	butyl
Bz	benzoyl
^{o}C	degrees Celsius
CAN	ceric ammonium nitrate
Cbz	Carboxybenzyl, (sometimes abbreviated to Z although not within this document)
cf.	*confere*, 'compare with'
CI	chemical ionization
cm^{-1}	wavenumber(s)
CoB	Coenzyme B
CoM	Coenzyme M
CV	cyclic voltammetry

DCM	dichloromethane
DET	double electron transfer
DFT	density functional theory
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*'-dimethylformamide
DMPU	*N*,*N*'-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
ε	dielectric constant
E	*entgegen*
ee	enantiomeric excess
e.g.	*exempli gratia*, 'for the sake of example'
EI	electron impact
EPSRC	Engineering and Physical Sciences Research Council
equiv.	equivalent(s)
Eqn.	equation
ESI	electrospray ionization
Et	ethyl
et al.	*et alii*, 'and others'
EWG	electron-withdrawing group
F_{430}	a nickel cofactor of MCR
fac	facial

FAD	flavin adenine dinucleotide
FT	Fourier transform
g	gram(s)
GC	gas chromatography
h	hour(s)
Hex	hexyl
HILIC	hydrophilic interaction liquid chromatography
HMPA	Hexamethylphosphoramide
HNESP	high resolution nano-electrospray
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
Hz	Hertz
i	*iso*
i.e.	*id est*, ‘that is (to say)’
IR	infra-red
ISC	inter-system crossing
J	coupling constant
kcal	kilocalorie
LC	liquid chromatography
LED	light-emitting diode
lit.	literature value
LUMO	lowest unoccupied molecular orbital
m-CPBA	*meta*-chloroperbenzoic acid

min	minute(s)
mL	millilitre(s)
mol	mole(s)
N	Normal
NAD^+	nicotinamide adenine dinucleotide
NHC	N-heterocyclic carbene
NHE	Normal Hydrogen Electrode/ Standard Hydrogen Electrode, SHE
nm	nanometer(s)
NMR	nuclear magnetic resonance
MALDI	matrix-assisted laser desorption ionization
MCR	methyl-coenzyme M reductase
Me	methyl
MLCT	metal-ligand charge transfer complex
mm	millimetre(s)
MM	multimode (in mass spectrometry)
M.pt.	melting point
MS	mass spectrometry
Ms	mesyl, methanesulfonyl
MTHF	5,10-methylenetetrahydrofolate
M.Wt.	molecular weight
NMR	nuclear magnetic resonance
Ph	Phenyl
Piv	pivaloyl

PMB	*para*-methoxybenzyl
PMHS	polymethylhydrosiloxane
ppm	part(s) per million
ppy	2-phenylpyridinato-
Pr	propyl
Pyr	pyridine
rt	room temperature
SCE	saturated calomel electrode
SET	single electron transfer
SG	silica gel
SHE	Standard Hydrogen Electrode/ Normal Hydrogen Electrode, NHE
SOMO	singly occupied molecular orbital
TDAE	tetrakis(dimethylamino)ethylene
t, *tert*	tertiary
Tf	triflyl, trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl, toluenesulfonyl, 4-methylbenzenesulfonyl
TTF	tetrathiafulvalene
UV	ultraviolet
V	volts
vs.	versus

W	watt(s)
Z	*zusammen*

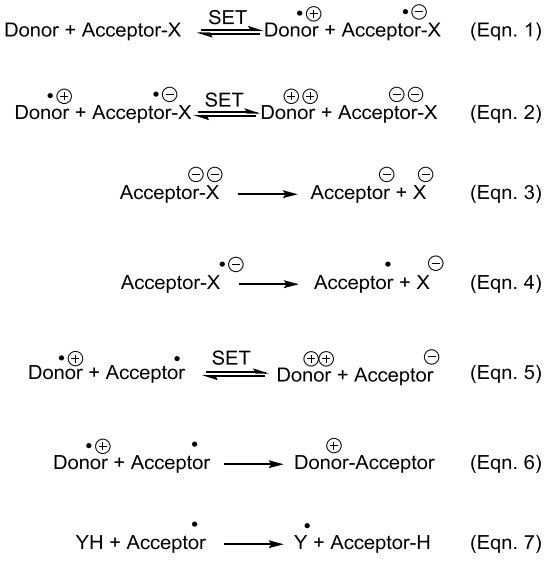
Introduction

Chapter 1. Introduction to Reductive Electron Transfer

Previous theses within the Murphy group have given quite a historic overview of electron transfer and reductive chemistry; but we have been lucky to find ourselves as a group with an established background in a field which is becoming more popular so, while I will give a brief summary of important processes (i.e. Birch reduction etc.), I will attempt to focus on current developments in the area as there have been many.

1.1. Electron Transfer

Henry Taube[1] and Rudolph A. Marcus[2] each received a Nobel Prize in Chemistry, in 1983 and 1992 respectively, for their work on electron transfer. It is an important chemical process, prevalent in metallic but also in organic systems, and involves the donation of an electron from one species to another (Eqn. 1) or from one part of a large molecule to another. In metals this can be self-exchange between two metal centres, identical save for their oxidation state, or it can be between two distinct species as is most often the case in our area of interest.



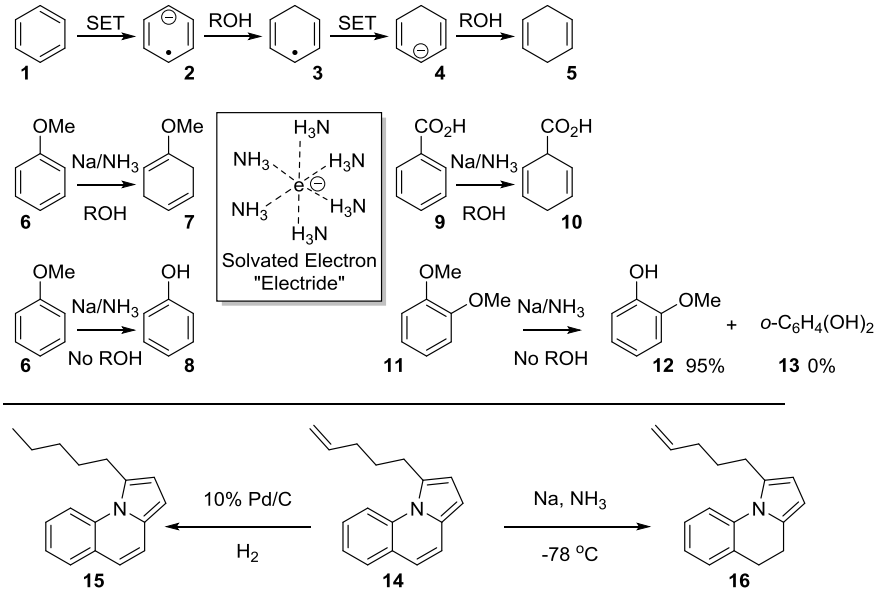
Much of the reduction discussed in this document relates to the reductive cleavage of bonds- shown above are various equations representing the relevant reactions in reductive bond scission. A donor can transfer an electron through space to an acceptor species to generate a radical cation and radical anion pair (Eqn. 1). The radical anion may then undergo cleavage to a radical and anion (Eqn. 4) or receive a second electron, giving rise to a dianion and dication pair (Eqn. 2); the dianion may undergo cleavage to give two anions (Eqn. 3). Equations 5-7 show additional reactions possible with the acceptor radical, respectively; further one-electron reduction to an anion, combination with the donor radical cation to give a closed-shell cation, or abstraction of a hydrogen atom from the reaction medium.

1.1.1. Redox Potential

Reduction and oxidation potentials provide a useful scale for the electron donating or accepting ability of a species and may be measured by cyclic voltammetry using a dilute, buffered solution and an electrochemical setup.[3] A more negative number represents a good donor or a substrate that is difficult to reduce; a more positive number represents a good oxidant or a substrate that should be easy to reduce. Redox potentials within this document will be reported for the various donors and acceptors in volts relative to a stated electrode in a specific solvent. Relative to the Normal Hydrogen Electrode (NHE or SHE), the Saturated Calomel Electrode (SCE) has a potential of +0.241 V and the Ag/AgCl a potential of +0.197 V (saturated) meaning that the SCE is +0.044 V relative to Ag/AgCl and the two can be compared without much adjustment.[4] Potentials measured in different solvents can vary to some degree but directly comparable figures aren't always available. Most of the measurements are quoted in DMF or acetonitrile however which normally don't show large deviations, and so should be representative.[5-6]

1.2. Birch Reduction

The Birch reduction[7-14] is the prototypical electron transfer reaction and was discovered by an Australian chemist, Arthur Birch, in 1944. Is has been investigated at length ever since and found to be both an interesting and very useful reaction: dissolution of metallic sodium or lithium in liquid ammonia gives rise to an intense blue colour resulting from the solvation of the electron as an 'electride' counter ion to the metal cation.[15-16] When an arene **1** is reacted under these conditions in the presence of a proton source, it reacts to yield the dihydroarene **5**.

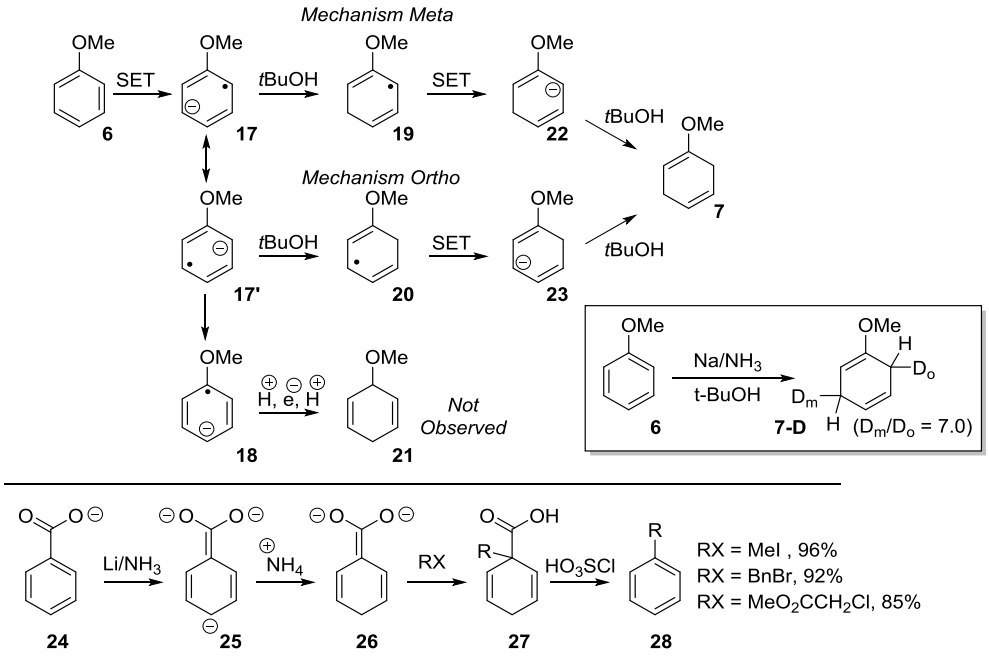


Scheme 1. Birch reduction of arenes

The reduction occurs by stepwise electron transfers and protonations (Scheme 1) and shows predictable regiochemistry for electron-donating **6** and electron-withdrawing substituents **9**. In the absence of a proton source it is possible to reductively cleave aryl alkyl ethers **6** to the corresponding phenol **8**, while arenes bearing two ether substitutions **11** show very selective monoreduction due to the difficulty of donating an electron to the anion intermediate.[17] Birch reductions also show chemoselectivity for more conjugated systems, and was shown by Gevorgyan and Kim[18] to be a complementary alternative to traditional hydrogenation which shows a preference for reduction of alkenes.

1.2.1. Birch Mechanism

Birch and Zimmerman published on the possible mechanisms[19-21] of the Birch reduction and how it applies to substituted substrates such as **6** and **9**. Computational and isotopic labelling evidence showed that the radical anion **17**/**17'** is protonated in the *ortho* position preferentially over the *meta* position (and never in the *ipso* or *para* position as evident by the absence of **21**). Benzoic acid is deprotonated under Birch reaction conditions to generate benzoate **24** which is then reduced to a trianion **25** before protonation to dianion **26**. Understanding of this mechanism allows for regioselective displacement of a carboxylic acid by reaction with an electrophile followed by decarbonylative elimination.[22-23]

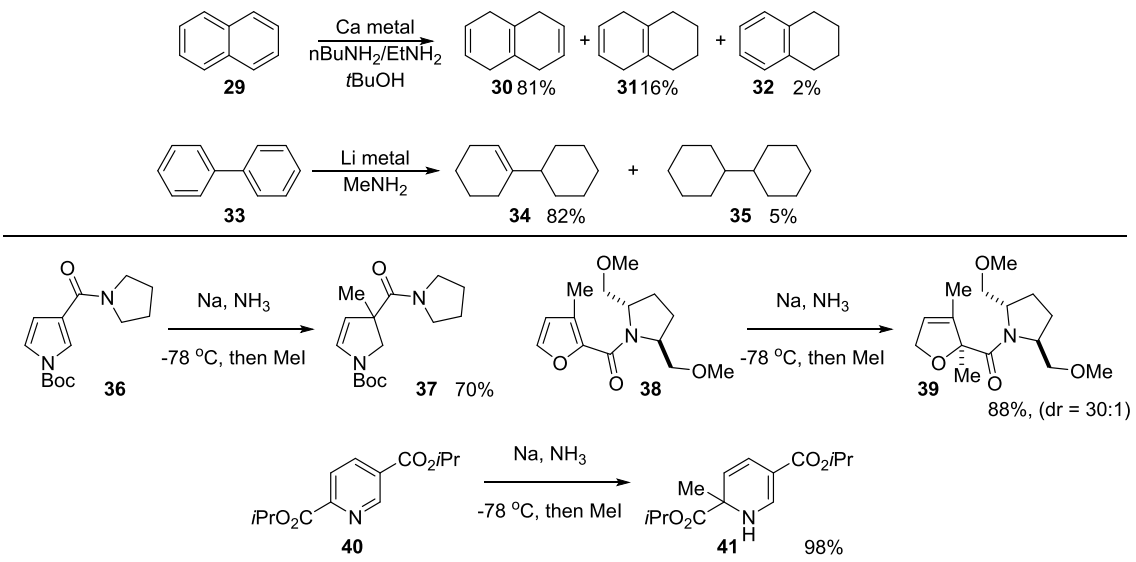


Scheme 2. Birch reduction regioselectivity

The Birch reduction is often described as being 'cumbersome and dangerous'[24] or the conditions 'a nuisance to handle'[25] but actually, it is quite straightforward and certainly a very inexpensive method to deliver electrons to a substrate. Where the Birch conditions are at a disadvantage however is in selectivity as such strongly reducing conditions are prone to reduce any and every functional group within a molecule; for this reason alternative, more selective methods have place in organic synthesis and these are discussed throughout the rest of the chapter.

1.2.2. Further Development and Modification of the Birch Reduction

Benkeser and co-workers[26-33] developed conditions under which low molecular weight amines could be used in place of ammonia as the solvent. They also utilized alternative metals such as calcium to achieve enhanced reactivity compared to more classical Birch conditions, Scheme 3.



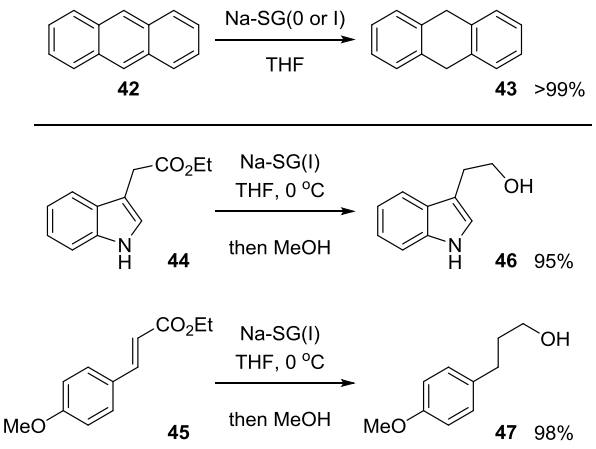
Scheme 3. Benkeser Reduction and Birch conditions applied to heterocycles

Prof. Timothy Donohoe[34-39] and his group have continued investigation of Birch reactivity in their reduction of electron-deficient pyrroles and other heterocycles, above, including stereoselective reactions. The co-workers have also worked with mediated electron transfer as discussed towards the end of this chapter.

1.2.3. Silica-Supported Alkali Metals

Another development which has been applied to the Birch reduction is that of liquid alloys of potassium and sodium adsorbed onto particles of silica.[40] The researchers identify different 'stages' (0, I and II) which can be generated; the first by adsorption of 35 wt% of a liquid Na/K alloy onto silica to form a shiny, black, air- and moisture-sensitive powder. Heating of

the stage 0 powder affords stage I, which is stable in dry air but upon further heating yields the stage II powder which can be handled in air but retains the reducing capacity (though not the power) of the other stages. The various stages have different reducing powers, as evident from their air stabilities, and can therefore be applied to different purposes.



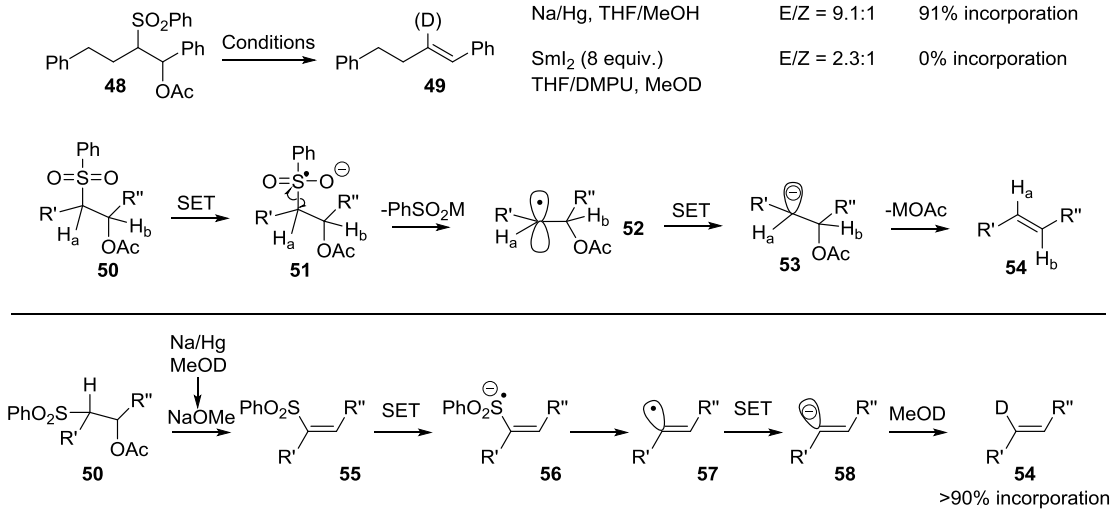
Scheme 4. Reduction by adsorbed alkali metals

Elution of a solution of anthracene, **42**, in THF over a short column containing stage 0 or I reductant yielded the mono-Birch reduced product, **43** (excess silica acting as the proton source) in excellent yield. A modified Bouveault-Blanc reduction[41-42] (a stepwise two-electron, two proton reduction of an ester **44**, **45** to an aldehyde followed by the same process from aldehyde to alcohol **46**, **47**) can also be effected using Stage I sodium on silica gel (Na-SG(I)) as shown in Scheme 4.[43] The co-workers report the powders as a practical source of clean hydrogen gas and they can also be used in reductive N-S and C-N bond cleavage as will be discussed in Chapter 3.

1.2.4. Julia-Lythgoe Olefination

In Chapter 4 we will discuss a series of carbon-sulfur σ-bond cleavages of sulfones and it therefore makes sense to discuss the Julia olefination; a common synthetic method which utilized electron transfer. The general mechanism involves deprotonation α to a sulfone to generate a stabilized carbanion, followed by addition to an aldehyde or ketone and quenching with e.g. acetyl or benzoyl chloride. The resultant beta-substituted sulfone **48** is

then reduced by sodium amalgam in an alcoholic solvent to yield, normally, the *E* alkene **49**.[44-45]



Scheme 5. Julia-Lythgoe Olefination mechanism

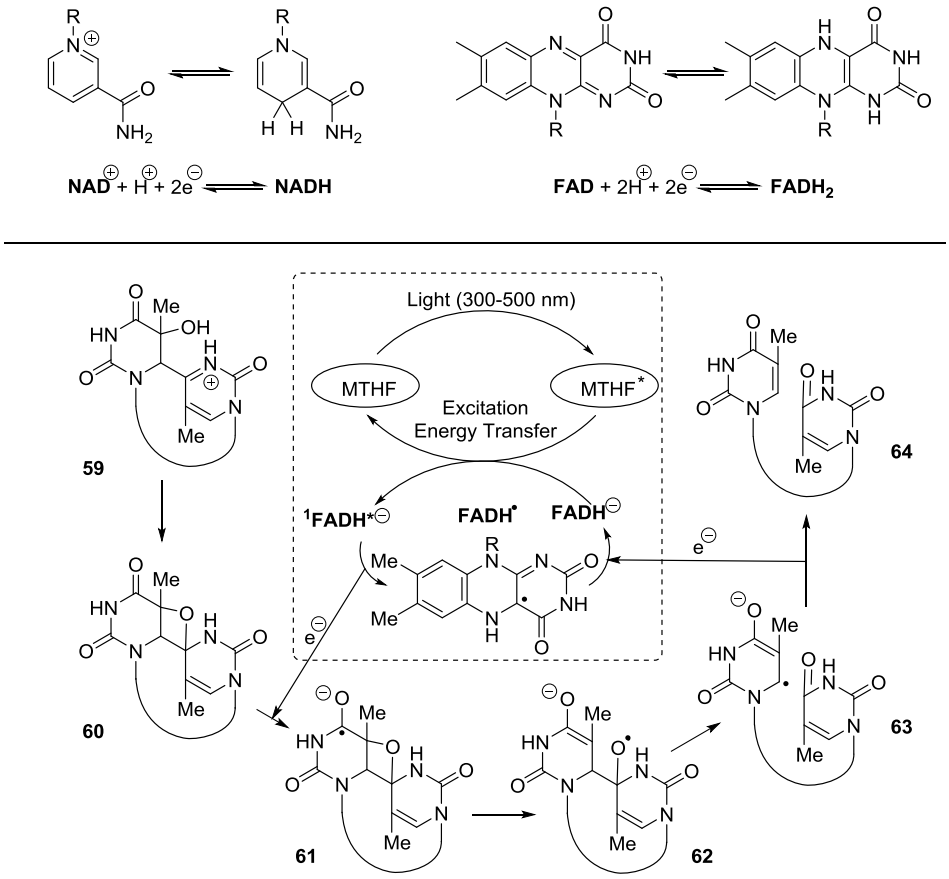
The mechanism of the reduction step is normally incorrectly taught however as shown in Scheme 5. In the classic mechanism, electron transfer followed by S-C bond cleavage yields an anion which eliminates the acetate or benzoate group whereas the alternative mechanism involves the formation of sodium ethoxide or methoxide from the solvent and E1cB elimination of the acetate or benzoate. The resulting vinyl sulfone **55** then undergoes the reductive cleavage to yield the observed products. This latter mechanism is supported by deuterium labelling experiments[46] which demonstrate good incorporation of deuterium into the alkene (e.g. **49**) which is not predicted by the classic mechanism. The issue of elimination beta to a sulfone is also discussed in Chapter 4 in reactions with a neutral organic electron donor.

Interestingly, Keck *et al.*[46] who were carrying out the mechanistic investigations found that under reductive conditions with samarium(II) iodide the classical mechanism was supported as no sufficiently strong base was present. Samarium(II) iodide reduction will be discussed in Section 1.4.

1.2. Electron Transfer in Nature

As with many important chemical processes, electron transfer is found widely in nature. Redox couples NADH/NAD^+ and $FADH_2$/FAD, Scheme 6, are used throughout biology for oxidative and reductive processes and are both based on nitrogen-containing heterocycles as are the synthetic, organic donors discussed later in the chapter.[47-48]

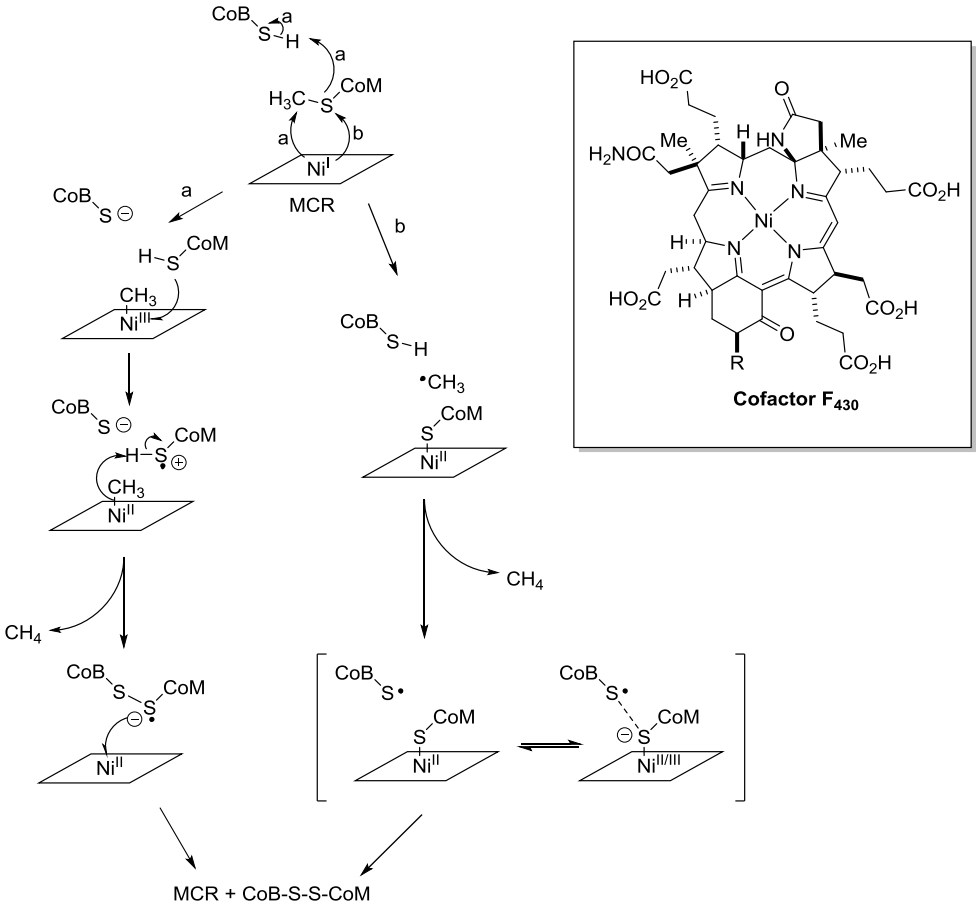
Nature utilizes electron transfer to repair damage to DNA caused by ultraviolet radiation. This elegant mechanism of repair is activated by the type of radiative conditions which cause the damaging pyrimidine dimerization: 5,10-methylenetetrahydrofolate, MTHF, within the skin is excited by UV-vis radiation and is able to transfer its excitation to $FADH^-$ to generate a singlet-excited electron donor. The donor species transfers an electron to a DNA dimer, brought into proximity by a photolyase enzyme, and a retro-radical cyclization occurs before return of an electron to the $FADH^{\bullet}$, Scheme 6. [49]



Scheme 6. Biological redox species in DNA repair by electron transfer

1.4.1. Methyl-Coenzyme M Reductase

Suffice to say, being able to harness an efficient route for the reduction of an environmentally harmful waste gas like carbon dioxide into a useful fuel (albeit also environmentally harmful) would be a great achievement. Naturally, biology has already achieved this but, by probing the process, insight may be gained which will allow the process to be carried out industrially.



Scheme 7. Methyl-Coenzyme M Reductase mechanism of methanogenesis

Methyl-Coenzyme M Reductase (MCR) reduces a methyl group to methane in the last step of methanogenesis from carbon dioxide in Methanogenic Archaea.[50] Investigation of the enzyme revealed a Nickel cofactor, F_{430}, which carries out the electron transfer step. Siegbahn[51-53] and Jaun[54-58] are two investigators who have proposed different mechanisms for this process in the past but currently favour the same mechanism as supported by computational and experimental results. Scheme 7 shows the two primary mechanisms

considered and path b is the presently accepted, whereby electron transfer from the nickel centre cleaves the S-methyl bond of methyl-coenzyme M to give a methyl radical and a thiolate anion which binds to the nickel. The methyl radical can then abstract a hydrogen atom from coenzyme B, held nearby by the enzyme, to generate a molecule of methane and a sulfur-centred radical. This radical attacks the bound sulfur and the 2-atom, three-electron system returns an electron to the nickel, regenerating the initial catalytic species and an equivalent of disulfide, CoB-S-S-CoM.

Figure 1 shows an X-ray crystal structure of Methyl-Coenzyme M Reductase from Methanothermobacter marburgensis containing cofactor F_{430} interacting with Coenzyme M and Coenzyme B.[59]

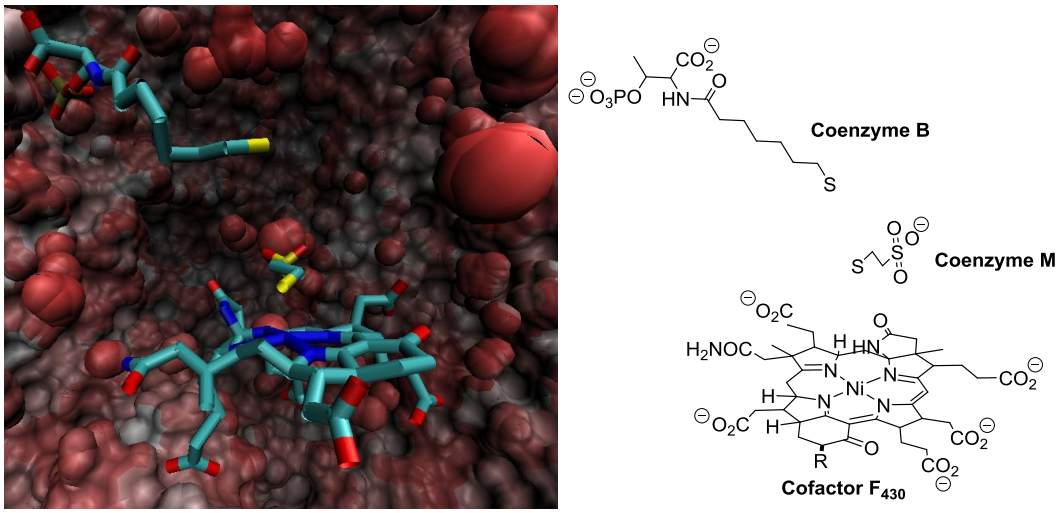
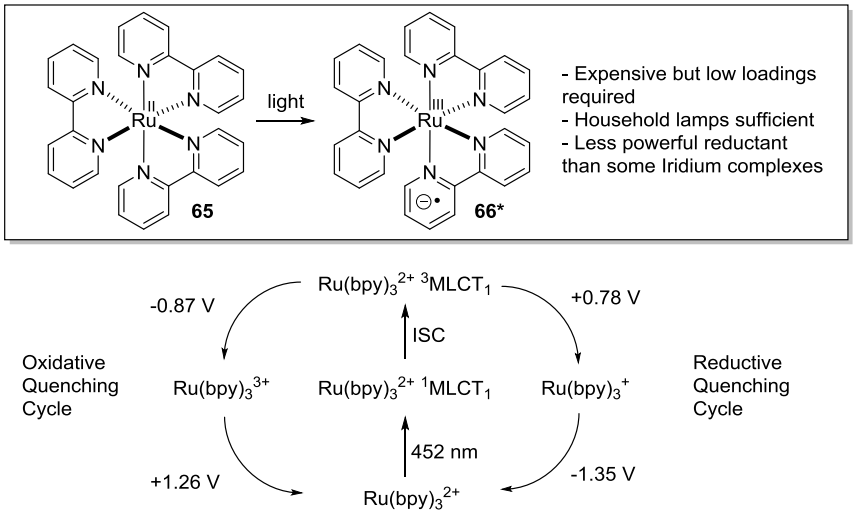


Figure 1. Crystal Structure of Methyl-Coenzyme M binding substrates[59]

1.3. Photoredox Catalysis

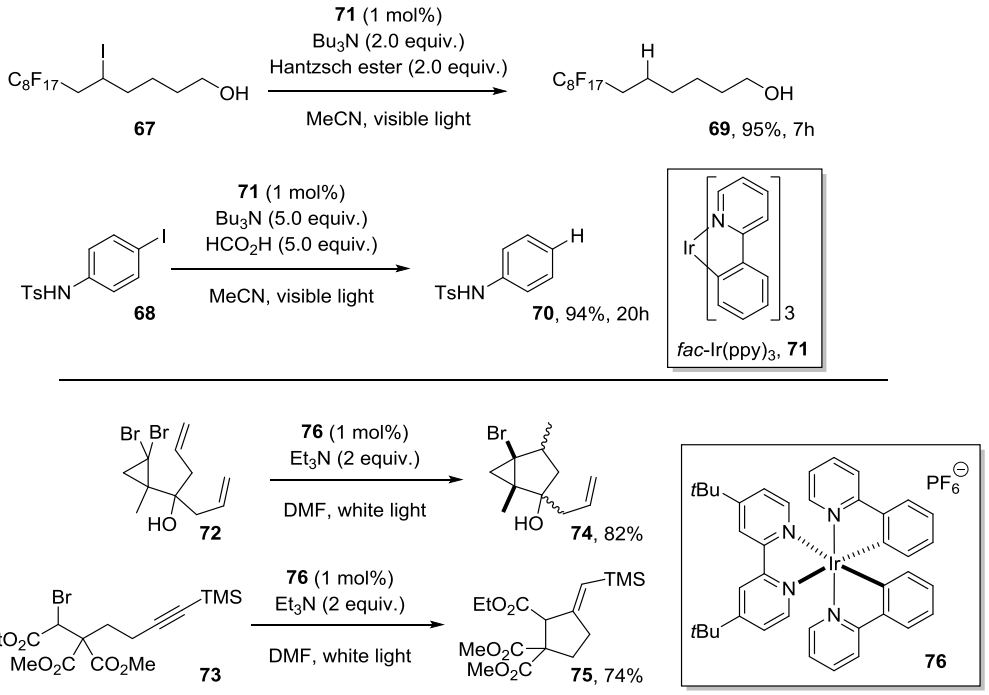
Photoredox catalysis is very much in-vogue in the literature at present as a method for carrying out both reductive and oxidative single electron transfer (SET).[60-61] This chemistry relies on the principle of photoexcitation giving rise to a high energy electron, able to be donated to an acceptor, and a low energy hole, able to receive an electron from a donor. Typically the excited state will be a triplet so recombination of the electron and hole are spin-forbidden, thereby giving the excited species a sufficient lifetime to react. Ruthenium and iridium complexes are the most common photoredox catalysts at present with tris(bipyridine)ruthenium(II) chloride, $Ru(bpy)_2Cl_2.6H_2O$, ("Rubipy") **65**, as shown in Scheme 8, being by far and away the most popular, but it has also been reported that organic dyes may be used and both will be discussed in this section. Excellent reviews of this topic have been written by two of the chemists at the centre of this growing field, Stephenson[60] and MacMillan.[61]



Scheme 8. $Ru(bpy)_3$ - a photoredox catalyst

Typically, catalytic photoredox reactions follow a general mechanism: photoactivation of the catalyst is followed by electron transfer and reductive bond cleavage in the substrate. The resulting radical then reacts by some well-established radical mechanism before picking up a hydrogen atom to complete the reaction. Normally the catalytic cycle is completed upon receiving an electron, often from the hydrogen atom donor, to recover the ground state photocatalyst. A simple example of such is the reduction of unactivated alkyl halides by Stephenson *et al.*[62] Herein, they report the excitation of *fac*-$Ir(ppy)_3$ **71** with visible light to

generate an activated donor **71***. This then donates an electron to halide **67**, reductively cleaving the C-I bond to give alkyl radical and an equivalent of iodide anion. The oxidized donor accepts an electron from tributylamine, activating it as an H-atom source to quench the alkyl radical and yield product alkane **69**. The same mechanism is followed for aryl iodides, e.g. **68**, yielding the corresponding arene **70** in high yield.

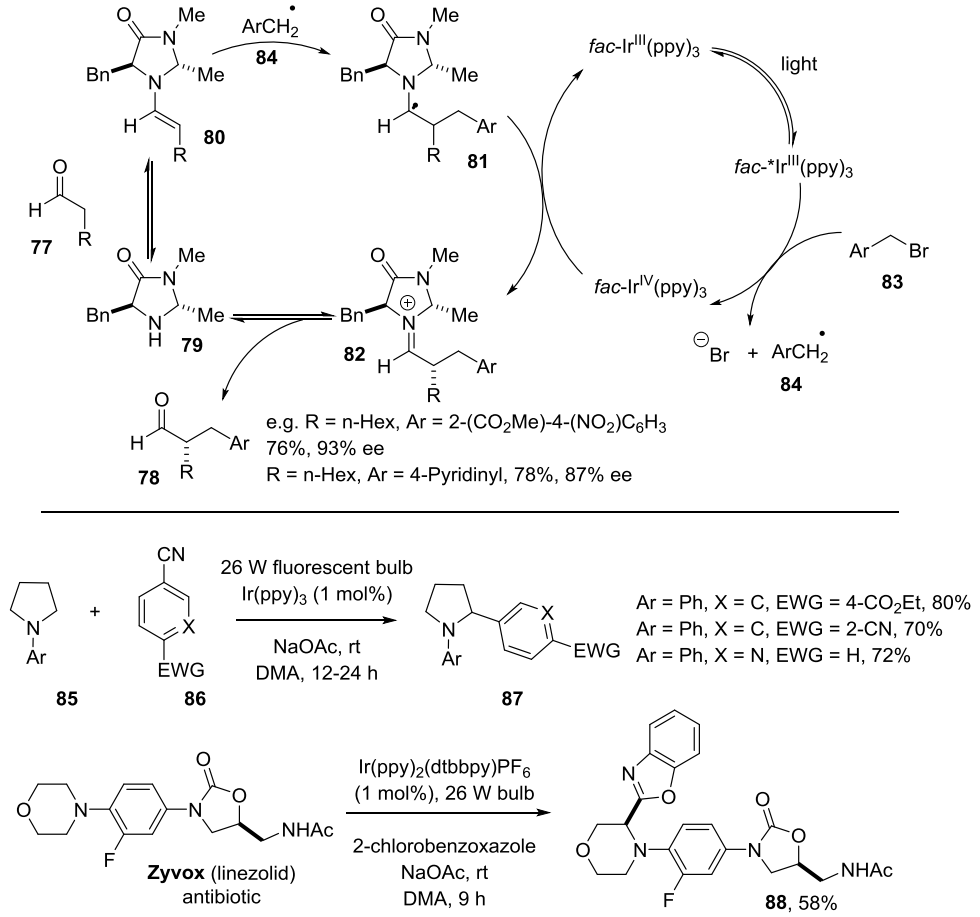


Scheme 9. Stephenson Group photoredox catalysis

In another paper they demonstrated the use of the alkyl radical for bond-forming cyclization reactions. This type of process might normally be initiated by AIBN and require stoichiometric tin hydride reagents but here 1 mol% catalyst and visible light delivered good yields of cyclized products **74** (as a mixture of diastereomers) and **75**, containing a reasonable level of complexity.

Most recently, Stephenson and co-workers published[63] a practical application for photoredox catalysis in the catalytic degradation of lignin into useful, low molecular weight aromatics (see also Mariano *et al.*).[64] The process is overall redox neutral and is carried out at ambient temperature unlike some of the alternative methods, potentially decreasing costs and tolerating more thermally sensitive species.

MacMillan and co-workers also made use of carbon-halogen bond cleavage for enantioselective benzylation of aldehydes **77** using 'SOMO catalysis'.[65] This combines chiral iminium organocatalysis with photoredox to deliver good yields of the alkylated products in high *ee*. This is restricted, however, to electron-deficient arenes as electron-neutral benzylic halides could not undergo the initial reduction.

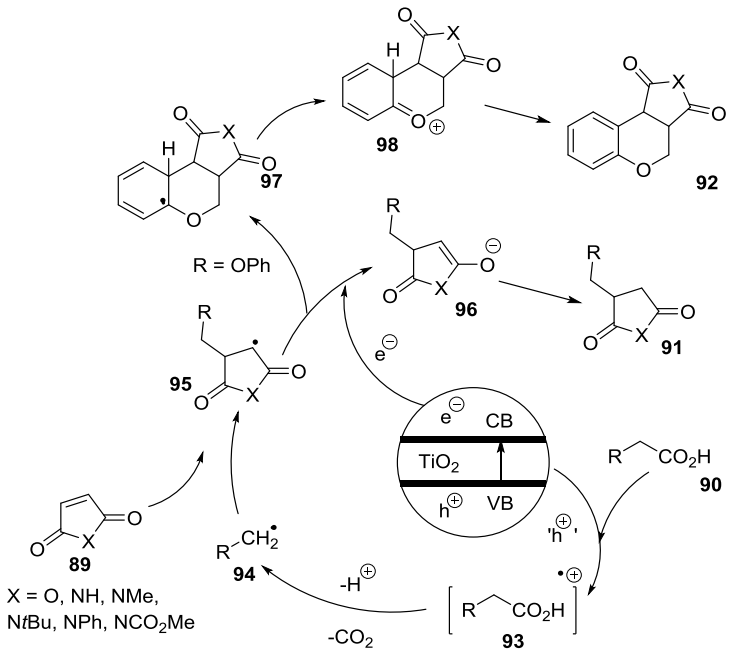


Scheme 10. MacMillan Group photoredox catalysis

Using their 'accelerated serendipity' method, MacMillan *et al.* also found photoredox to be applicable for α-amino C-H arylation.[66] The electron-deficient arene **86** is reduced by the excited catalyst and the resulting Ir(IV) species oxidizes the amine to complete the redox cycle. The amine radical cation can be easily deprotonated by a weak base to give an α-amino-alkyl radical. Radical coupling of the alkyl radical and radical anion of the arene is followed by elimination of cyanide to regenerate aromaticity and deliver the coupled product

87 in good yield. They were also able to apply a similar technique to a commercial pharmaceutical, **Zyvox**, to illustrate the potential utility of such a process.

An alternative to the more exotic ruthenium and iridium catalysts is highlighted by the work by Walton, Manley and co-workers in their investigation of titania photocatalysts.[67] They were able to show that TiO_2 nano-particles could be photoexcited at 385 nm, and the resultant excited catalyst was able to oxidatively decarboxylate carboxylic acids **90** giving rise to an alkyl radical **94**. They used this radical in a coupling reaction which was then quenched to an anion **96** by the catalyst to complete the catalytic cycle; protonation then yielded the alkylated heterocycle **91** in good yield. Depending on the substrate they were also able to observe a second, intramolecular radical reaction to add further molecular complexity, e.g. **92**. This work may be disadvantaged by its requirement of UVA light but benefits from its use of a relatively inexpensive titania photocatalyst which could lend itself more easily to solid support and/or flow chemistry.



Scheme 11. TiO_2 as a photoredox catalyst

This summary is by no means exhaustive but serves to show the general template for such reactions and the relatively wide synthetic range to which it can be applied. This work is comparable to that presented later in this thesis in that it features electron transfer, reductive

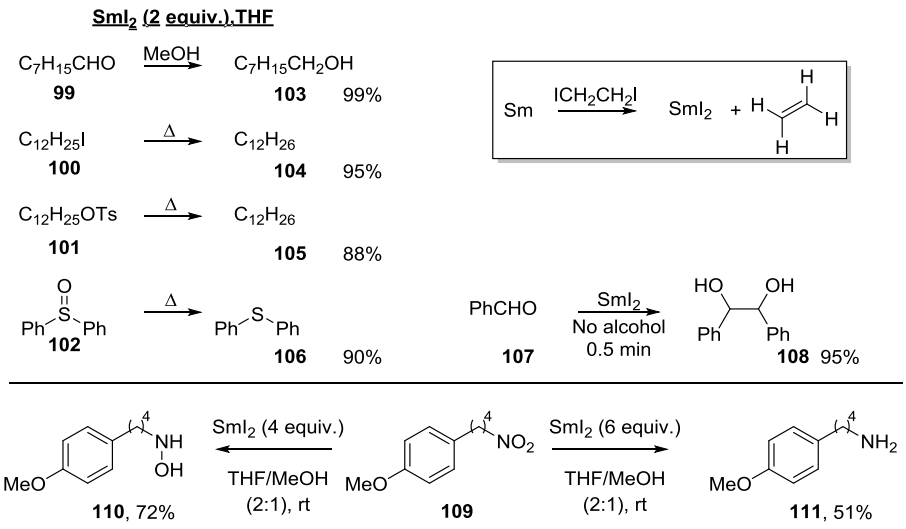
cleavage reactions, radical reactivity and photoactivation but is also distinct in its use of expensive metal reagents, visible light activation and catalytic turnover.

1.4. Samarium(II) Iodide

1.4.1. Samarium(II) Iodide- Discovery and Developments

Samarium chemistry is probably the most useful and selective method for electron transfer currently being researched.[68-70] Work in recent years, by the groups of Procter and Hilmersson into the addition of amines[71] and water[72] to reaction systems to enhance reduction potentials, has greatly increased the scope of this chemistry. The reductions that can be carried out with these samarium diiodide/amine/water systems have provided a benchmark against which to compare the work carried out in the writing of this thesis and therefore deserve discussion.

Samarium(II) iodide, samarium diiodide, SmI_2, is sometimes referred to as '*Kagan's reagent*' because of its discovery by Kagan and coworkers[73] in 1977. They published on its properties as a powerful electron donor, using it for the reduction of alkyl halides **100**, tosylates **101**, sulfoxides **102**, and aldehydes **99** and ketones, both directly to the alcohol **103** and towards pinacol-type products **108**, Scheme 12.[73-76] Having published a method for the straightforward generation of SmI_2 from the metal plus diiodoethane,[76] they were rapidly followed by a host of other groups keen to study such a useful new reagent.



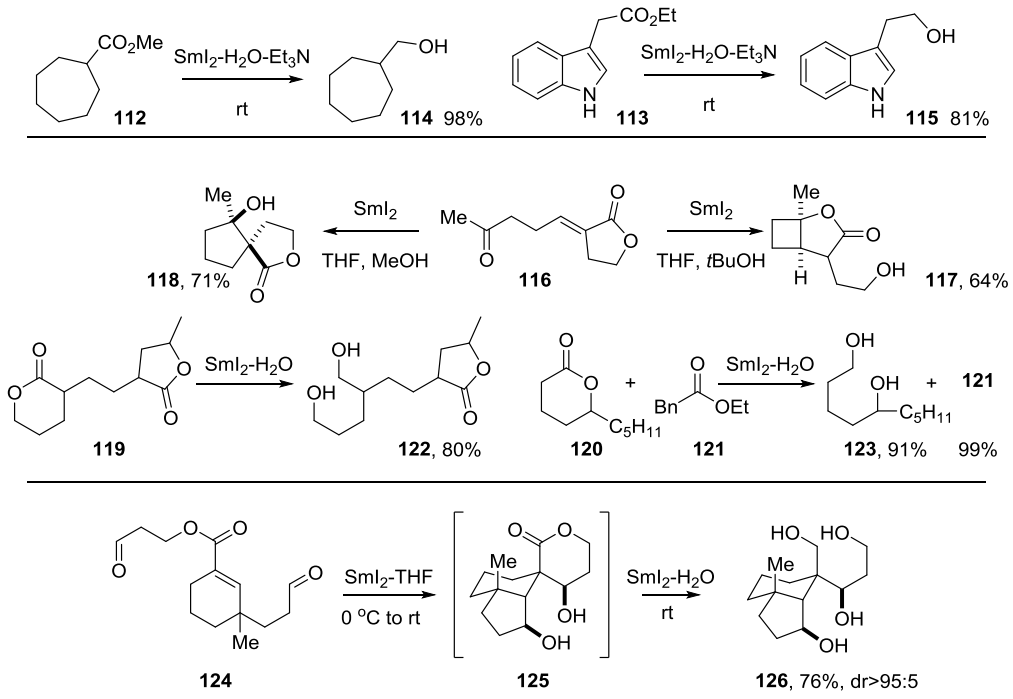
Scheme 12. Preparation of SmI_2 and some examples of reductions

Kende *et al.*[77] reported the reduction of nitroalkanes **109** to amines **111** and hydroxylamines **110** with SmI_2, depending on conditions, and Keck and co-workers[78] later explored the N-O bond cleavage of alkyl hydroxylamines and *N*-acyl derivatives.

Flowers and collaborators have carried out a series of mechanistic studies into the role of proton donors,[79] water,[80] additives[81-82] and catalytic transition metals[83] in reductive samarium chemistry but the vast majority of study into this field has come from the groups of Göran Hilmersson in Gothenburg, Sweden and David Procter in Manchester, UK.

1.4.2. Samarium(II) Iodide Chemistry- Procter Group

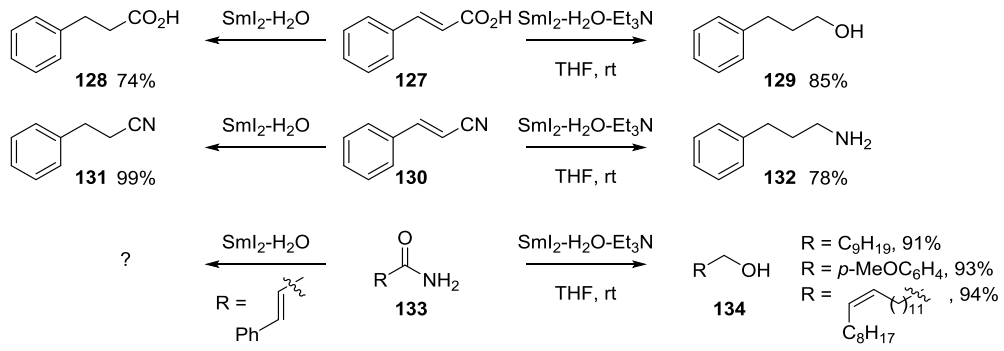
Procter's work in esters is remarkable in the selectivity that can be observed by careful control of the reaction conditions.[84] Lactones were shown to be reducible in the presence of other esters with excellent chemoselectivity in SmI_2-H_2O systems and that the reduction of six-membered lactones was also very selective over five- (substrate **119**), seven- or eight-membered rings. Reduction of unactivated esters, e.g. **112** and **113**, to the alcohol **114** and **115** could still be achieved in high yield using a SmI_2-H_2O-Et_3N cocktail or, as in a clever example **124** by activation of an ester as a six-membered lactone during the reaction.



Scheme 13. Reduction of esters with SmI_2

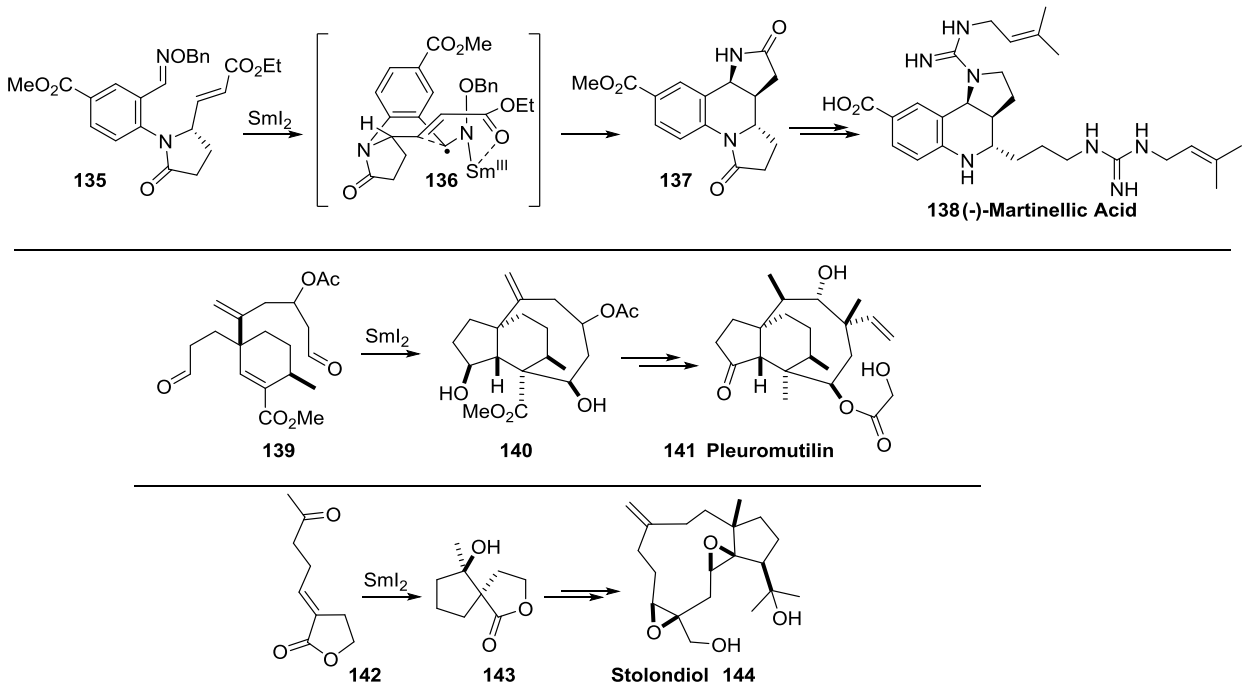
The lactone reactivity could also be extended to the selective mono-reduction of cyclic 1,3-diesters under reaction conditions which tolerate the presence of aryl bromides and acetates. Investigations[85] on lactone **116** revealed a substantial co-solvent effect when using methanol or *tert*-butanol as a proton source. This was proposed to be due to the slower rate of protonation with the bulkier alcohol, allowing two tandem cyclizations to occur.

The more reactive conditions, containing an amine additive, were found to reduce carboxylic acids or their salts to the corresponding alcohol while the SmI_2/H_2O conditions selectively reduce the alkene of an α,β-unsaturated carboxylic acid while preserving the carboxylate moiety, **127**. Similar selectivity is observed in the case of α,β-unsaturated nitrile species **130**.[86] Interestingly a recent paper on the reduction of amides **133** to alcohols[87] did not report the same type of comparison (although distal alkenes are tolerated) so it remains to be seen if selective conjugate reductions of α,β-unsaturated amides can be achieved. The amide reactions are of note, however for their reduction to the corresponding alcohol **134** rather than the amine as is the more common product of amide reduction with metal hydride reducing agents.[88]



Scheme 14. Selectivity in SmI_2 reduction of the CX_3 oxidation state

The depth of chemistry, extended to the aldehyde oxidation state, has allowed a number of natural product syntheses to be carried out, including that of Martinellic Acid **138**,[89] Stolondiol **144**[90-91] and Pleuromutilin **141**.[92-93] Scheme 15 shows the key steps in each of these syntheses as mediated by SmI_2. As can be seen, reductive annulation reactions mediated by samarium diiodide give a high level of stereo-control, facilitated by lanthanide complexation, in order to install a high level of complexity.

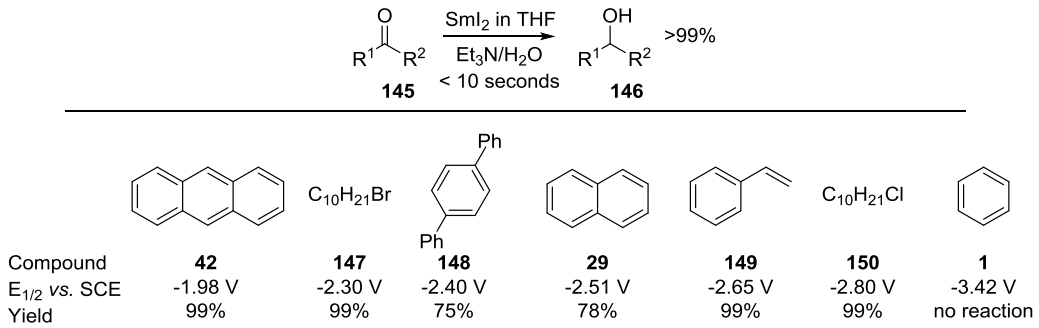


Scheme 15. Samarium diiodide applied to natural product synthesis

1.4.3. Samarium(II) Iodide Chemistry- Hilmersson Group

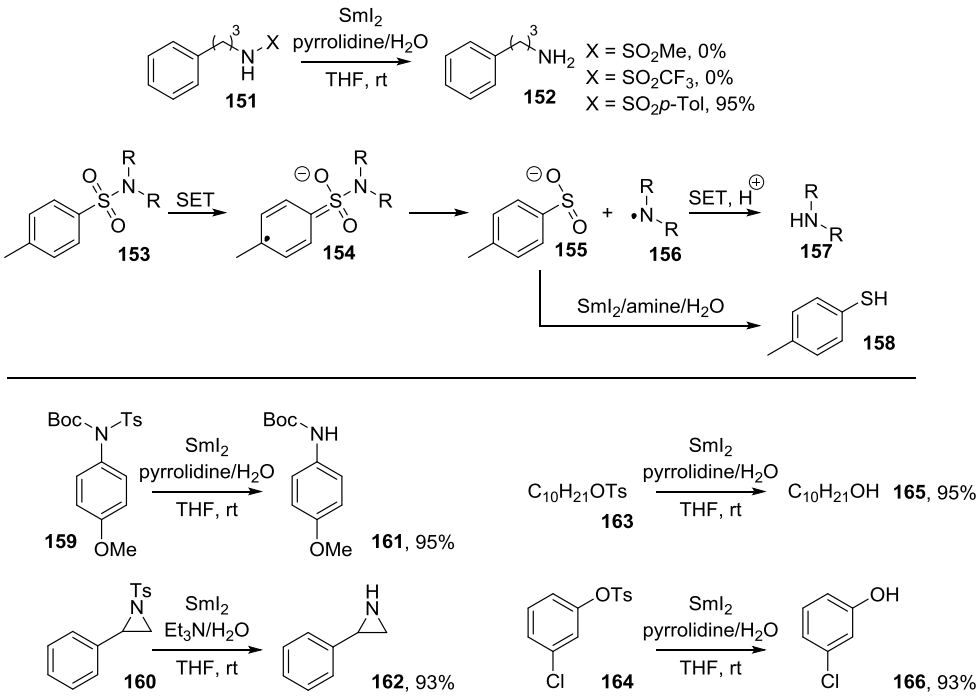
While the Procter group have studied an expanse of electron transfer focussed around carbonyl groups, Hilmersson and co-workers have had a focus more on aromatic acceptor species for bond cleavage and in this way the work is more related to that presented later in this thesis.

That being said, in 2002 they published a study on the reduction of ketones to alcohols and demonstrated that reduction by a SmI_2/H_2O/amine mixture was 100,00 times faster than SmI_2 with the amine or water alone.[94] In order to quantify the reducing power of the $SmI_2/H_2O/Et_3N$ mixture, a series of compounds with known reduction potentials was tested against the conditions in order to observe the limit of reactivity and infer a reduction potential for the cocktail.[71] A wide array of conjugated aromatic species and alkyl bromides were reduced with the most difficult being decyl chloride **150** at -2.8 V *vs.* SCE. The only attempted arene which could not be reduced was benzene **1** at -3.42 V and the same set of substrates found $YbI_2/H_2O/Et_3N$ mixture to be limited at -2.3 V *vs.* SCE (able to reduce decyl bromide **147** but not *p*-terphenyl **148**).



Scheme 16. Reductions by the Hilmersson group

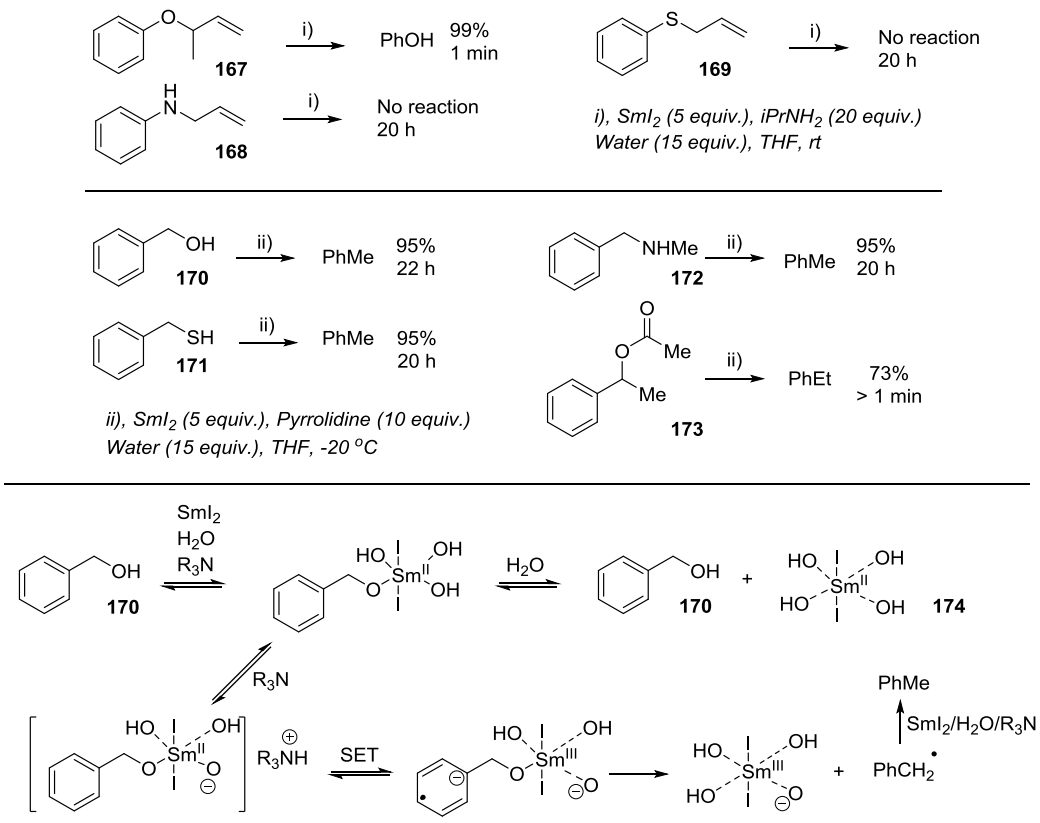
As well as π-bonds, Hilmersson *et al.* studied the reductive cleavage of N-S and O-S σ-bonds in tosylamides and tosylates, Scheme 17.[95] These reductions were again carried out using a SmI_2/H_2O/amine mixture and proceeded in excellent yield, as is required of a deprotective transformation such as this, and indeed in impressive reaction times of only a few seconds, although six equivalents of the samarium species and twelve equivalents of pyrrolidine were required to achieve such high conversions. In addition, because of the presence of a proton source, the cleaved sulfinate can be quenched and then further reduced to the thiol oxidation state **158**, leading to a foul-smelling product mixture. Nevertheless the reaction is certainly a useful one, operating for aliphatic and aromatic examples and tolerating aryl chlorides **164** and aziridines **160**.



Scheme 17. Sulfonates and sulfonamides with SmI_2/amine/H_2O conditions

The cleavage is restricted to (or selective for) arenesulfonamides, showing no cleavage for mesyl or triflyl cases which should be noted for comparison with other methods in section 5.7. The result of cleavage of aliphatic tosylate **163** to the corresponding alcohol **165** seems to be in conflict with the initial results by Kagan showing the cleavage of tosylates to the corresponding alkane (Scheme 12) but this is again a result of chemoselectivity under different additive conditions: the SmI_2/H_2O/ Et_3N conditions are powerful enough to directly reduce the tosylate by the mechanism shown above, while under the SmI_2/MeOH/THF conditions the tosylate cannot be reduced but is rather converted to the alkyl iodide (exchange from the samarium(II) iodide) which is then readily reduced to the alkane. This mechanism is supported by detection of small amounts of the alkyl halide from these reactions and enhancement of reactivity in the presence of sodium iodide.

Allyl and benzyl carbon-heteroatom bond cleavage reactions are key to the chemistry discussed in Chapter 3. Similar chemistry has been carried out by Hilmersson and co-workers over the years, involving benzyl alcohols **170**, esters **173**, amines **172** and thiols **171** as substrates, Scheme 18.[24]



Scheme 18. Benzyl and allyl reductions with samarium(II) iodide

Interestingly, allyl sulfides **169** and allyl amines **168** could not be cleaved under the conditions while allyl ethers **167** cleaved readily.[96] Also shown in Scheme 18 is the mechanism proposed by the researchers for the reduction of benzyl alcohol and how critical the Lewis acid/Lewis base interactions are to the process. This may account for why some of these processes are more difficult under metal-free conditions.

As should be evident from the above section, SmI_2 with or without additives is an extremely useful reagent for a wide range of reductive transformations across organic chemistry and has made a correspondingly large impact on electron transfer and radical chemistry. For balance, some of the disadvantages of the SmI_2 reactions include the practicality of using an excess of such a high molecular weight (404.17 g/mol) and expensive reagent[97] especially compared with alkali metals which are low atomic weight and cheap. As ever, with such a powerful reagent, selectivity is an issue although this is attenuated somewhat by the use of different additives to fine-tune the reactivity. A disadvantage often mentioned of samarium species is that samarium is radioactive but in reality samarium is approximately as

radioactive as potassium (Environmental Permitting Guidance 2011, UK) and is therefore of no concern. The use of highly toxic additives such as HMPA has been superseded by the used of water/amine mixtures which makes reductions using SmI_2 more attractive. Samarium diiodide chemistry is a valuable tool in reductive chemistry and new applications continue to be discovered.

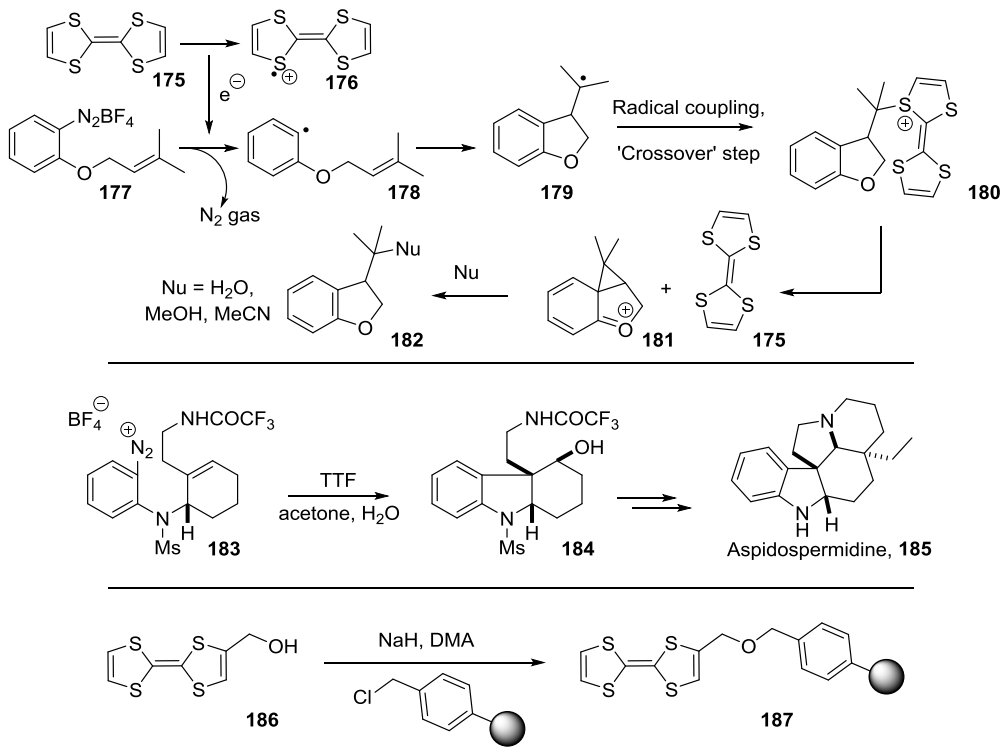
1.5. Organic Electron Donors

Most electron transfer processes involve metals as they have lower ionization energies than non-metals and tolerate more oxidation states. Such reagents have disadvantages however, e.g. the flammability of metallic sodium, the expense of exotic heavy metal complexes or the toxicity of SmI_2 reaction mixtures as mentioned above. Research has therefore been carried out into metal-free reductive chemistry featuring electron-rich species which are able to stabilize the positive charge generated from electron transfer.

The Murphy group found its way into electron transfer chemistry from more traditional radical chemistry via tetrathiafulvalene. Since then, great advances have been made in the area of organic electron donors, largely by our group although some other researchers have published in this area, and this section will outline the progression of reactivity to the current, highly reductive conditions used in the experimental work for this thesis. Excellent reviews of this area include Broggi *et al.* from 2013[98] and another from Doni and Murphy in 2014.[99]

1.5.1. Radical-Polar Crossover/ Tetrathiafulvalene

Tetrathiafulvalene[100] (TTF) **175** is an electron-rich, organic species capable of donating an electron at +0.38 and another at +0.82 V *vs.* SCE in MeCN;[101] sufficient to reduce an arenediazonium tetrafluoroborate salt (+0.16 V *vs.* SCE in MeCN)[102] e.g. **177**. Subsequent loss of nitrogen gas and generation of an aryl radical **178** can be followed by 5-*exo*-*trig* cyclization and recombination of the alkyl radical with the radical cation **176**. From this point on, normal nucleophile/electrophile chemistry occurs (yielding product **182**) and this net reaction is therefore referred to as the Radical-Polar Crossover Reaction.[103] Various nucleophiles may be used in the final step, allowing for functional diversity to be generated and TTF is regenerated at this stage, meaning that it acts catalytically.



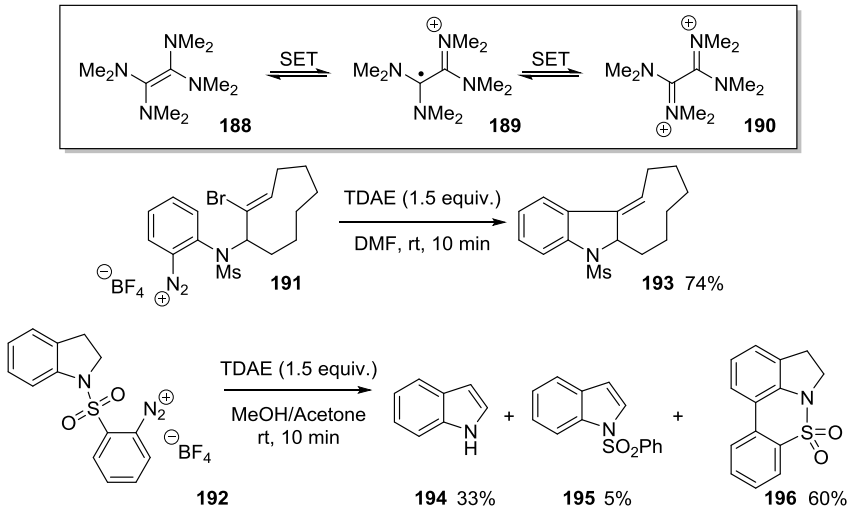
Scheme 19. Radical-Polar Crossover reaction

The reactivity of the radical-polar crossover could be exploited for useful heterocyclizations and in 1998[104]/1999[105], Murphy *et al.* reported the total synthesis of (±)-aspidospermidine **185**, utilizing TTF in one of the key steps. Collaboration with polymer chemists also allowed for generation of a polymer-bound TTF derivative **187** which could carry out Radical-Polar Crossover reactions catalytically and be recovered and reused as long as care was taken not to expose the polymer catalyst to air, or it could be regenerated with sodium borohydride in methanol, and then reused.[106]

1.5.2. Tetrakis(dimethylamino)ethylene (TDAE)

Tetrakis(dimethylamino)ethylene (TDAE) **188**, is a nitrogenous analogue of TTF with an enhanced reductive capability; -0.78 V and -0.61 V *vs.* SCE in MeCN.[107] This is not yet strong enough for the reduction of aryl iodides (E_p = -2.2 V *vs.* SCE in DMF)[108] but considerably stronger than tetrathiafulvalene with the results that arenediazonium salts (benzenediazonium tetrafluoroborate, E = +0.16 V *vs.* SCE in MeCN)[102] may be reduced

within minutes instead of days, and in high yield of C-C cyclized product. The reaction of these salts with TDAE also differed from that with TTF in that no trapping occurs between an alkyl radical and the radical cation of the donor. This means that the radical-polar-crossover reaction, typical of TTF chemistry, cannot be carried out under these accelerated reaction conditions.[109]



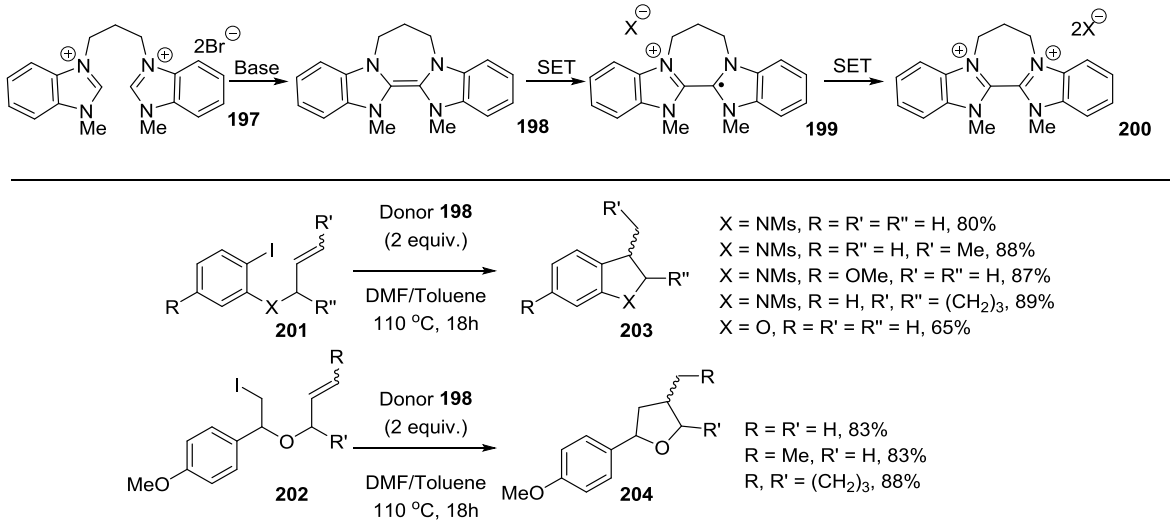
Scheme 20. Reductions with TDAE

As well as offering diversity in the reactivity of arenediazonium salts, TDAE also effected some N-S bond cleavage under electron transfer conditions, Scheme 20, a reaction to which we will return in a few pages.

1.5.3. 'Benzimidazole donor'

Benzimidazolylidene **198** combines the electron-rich enetetramine present in TDAE with the aromatic stabilization featured in the reactivity of TTF: the result being an electron donor more powerful than either, capable of donating an electron at a potential of -0.82 V and another at -0.76 V *vs.* SCE in DMF[110] and with the ability to reduce aryl and alkyl iodides to the corresponding radical, with loss of iodide; the first organic molecule to achieve such a feat.[111] While further reduction to the carbanion should be possible based on the potential ($Ar^{\bullet}$ to Ar^{-}, E^{0} = +0.05 V *vs.* SCE in MeCN),[102] this was not observed, rather radical

cyclization to an adjacent alkene could be utilized in useful bond-forming processes to generate heterocycles **203** and **204** as mixtures of diastereomers (from alkyl radicals).

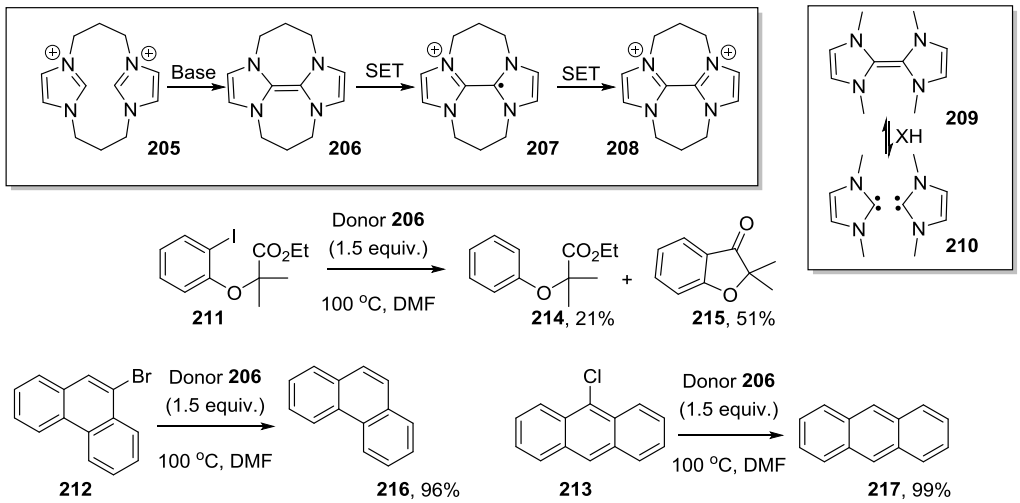


Scheme 21. Donor 198

Because donor **198** is aromatic, it gains less aromaticity upon oxidation than if it were non-aromatic. A stronger donor then may have the same number of electron-donating nitrogen atoms but no aromaticity: exactly such a structure is seen in **206** and it is indeed a powerful donor.

1.5.4. 'Doubly Bridged Donor'

First studied electrochemically by Thummel *et al.* in 1989[112] and isolated by Taton and Chen in 1996,[113] bis-imidazolylidene **206** enjoys an island of stability between **198**, which is stable as the dimer but a weaker donor, and **209**, in which the equilibrium between carbene and dimer lies to the former, meaning that the methylene bridges serve an important purpose.[114] The work of Murphy *et al.*[115] on compound **206** was something of a milestone in the development of organic electron donors as it was discovered to reduce aryl halides e.g. **211** to aryl anions under neutral, ground-state conditions; remarkable for an organic compound. Consequently it was dubbed the first 'super electron donor' and remains among relatively few neutral organic compounds capable of the feat, *vide infra*.



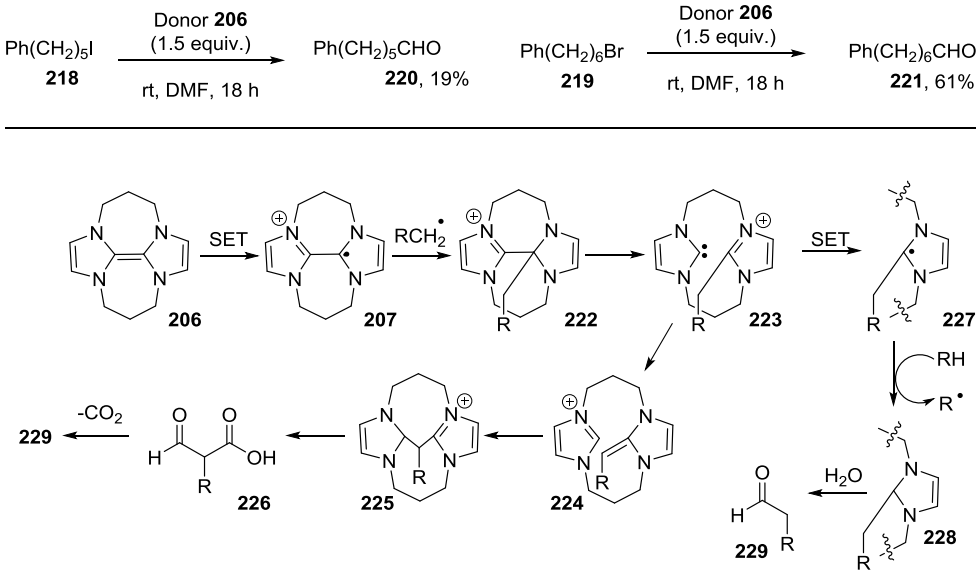
Scheme 22. Donor 206 and its reactions

Reduction of **208** to **206** has been measured[110] to occur at -1.20 V *vs.* SCE in DMF (two-electron wave) which until very recently (see below, section 1.5.13) was the most powerful neutral organic reductant. The aryl anions generated from reaction of this powerful donor from aryl iodides **211** can be used simply for dehalogenation to form **214** or for nucleophilic substitution onto an ester to generate a cyclic ketone **215**, as was observed in good yield. When extended aromatic systems were used then the reactivity could be extended to include bromides **212** and chlorides **213**. This is remarkable as even the more easily reduced iodoarenes have a reduction potential of -2.2 V *vs.* SCE in DMF, which should be out of reach for donor **206**. The successful reduction is attributed to the difference in conditions between the electrochemical measurement set-up and the reaction system wherein the donor is able to undergo intimate interactions with the substrates in solution, facilitating the transfer of electrons compared to a static electrode surface.[116]

1.5.5. 'Doubly Bridged Donor' - Trapping

For alkyl radicals generated from alkyl iodides, when no intramolecular cyclization is available (see examples **218**, **219**), it was observed that an aldehyde product **220**, **221** respectively was formed with an additional carbon atom added to the chain length. This was attributed to radical coupling between the newly generated radical (RCH_2•) and the radical

cation **207** of donor **206**. Two mechanisms are proposed (Scheme 23) for how the observed products might arise but both include incorporation of a carbon atom originating from donor **206**.

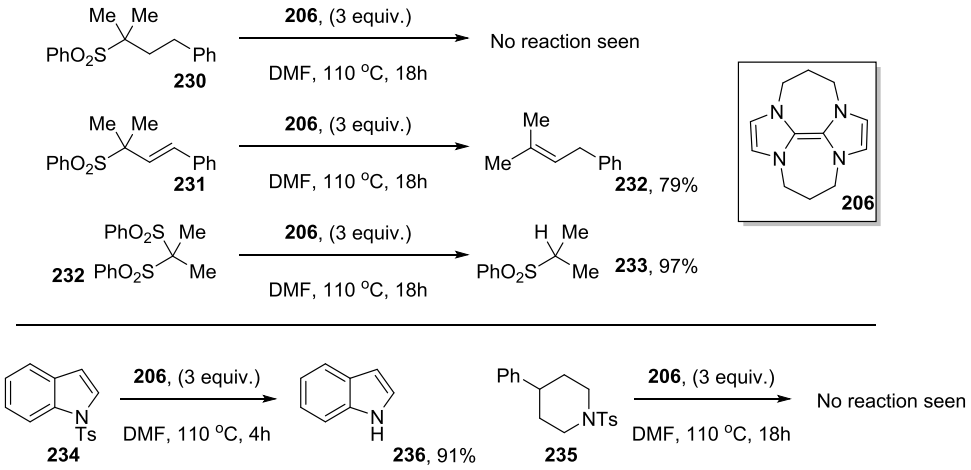


Scheme 23. Radical trapping with donor 206

One mechanism requires electron transfer to the trapped species **223**, to afford **227** followed by abstraction of a hydrogen atom to give **288** and hydrolysis upon workup to liberate aldehyde **229**. The other involves a series of intramolecular reactions followed by a final hydrolysis and decarboxylation of **226** to yield the same product **229**, but whichever mechanism is followed these observations were a clear indication of radical trapping between the substrate radical and the radical cation of the donor species.

1.5.6. 'Doubly Bridged Donor' – Sulfone Cleavage

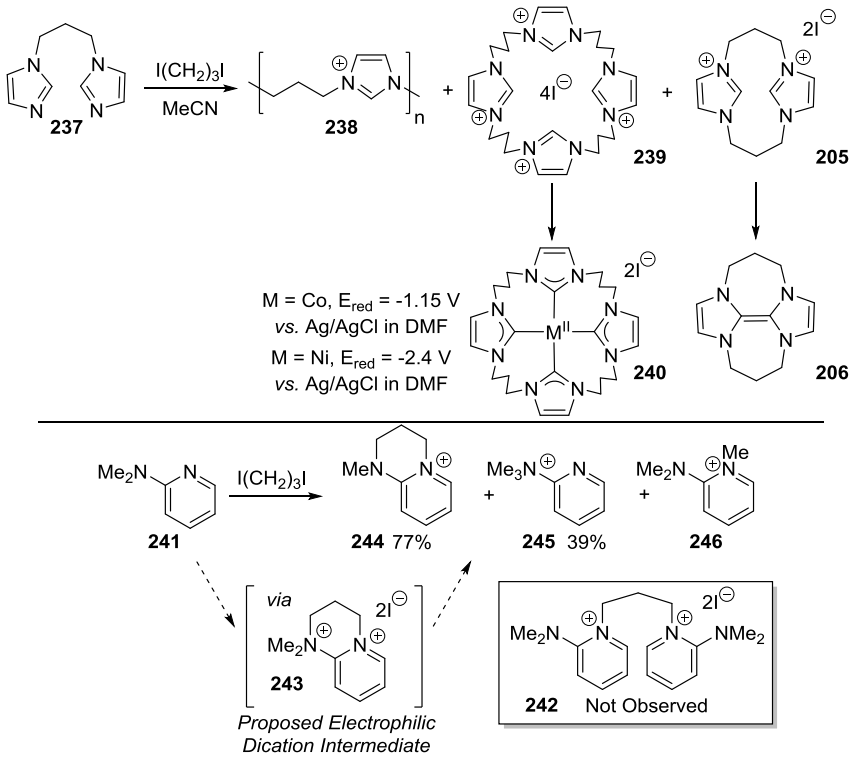
Having developed powerfully reducing reaction conditions with donor **206**, studies continued to investigate the substrate scope. Sulfones and sulfonamides, with a typical reduction potential of -2.3 V *vs.* SCE in DMF,[116] were selected for a series of experiments and found to give high yields of C-S and N-S bond cleavage, Scheme 24.[117]



Scheme 24. Reduction of activated sulfones and sulfonamides

The examples in Scheme 24 show these reactions to be selective for activated arenesulfonyl groups, in the sulfone cases cleaving bis-sulfones **232** and allyl sulfones **231** while leaving normal alkyl aryl sulfones **230** untouched, and in the case of tosylamides, cleaving the N-S bond of aromatic tosylamides **234** but not *N*,*N*-dialkyltosylamides **235**. The reasons for this could be the electron-withdrawing ability of these groups activating the substrate towards receiving an electron, or the stabilization of the resulting radical or anion to favour progress towards the cleavage products. Later in the chapter we will discuss conditions under which the unactivated examples may also be reductively cleaved by a neutral organic electron donor.

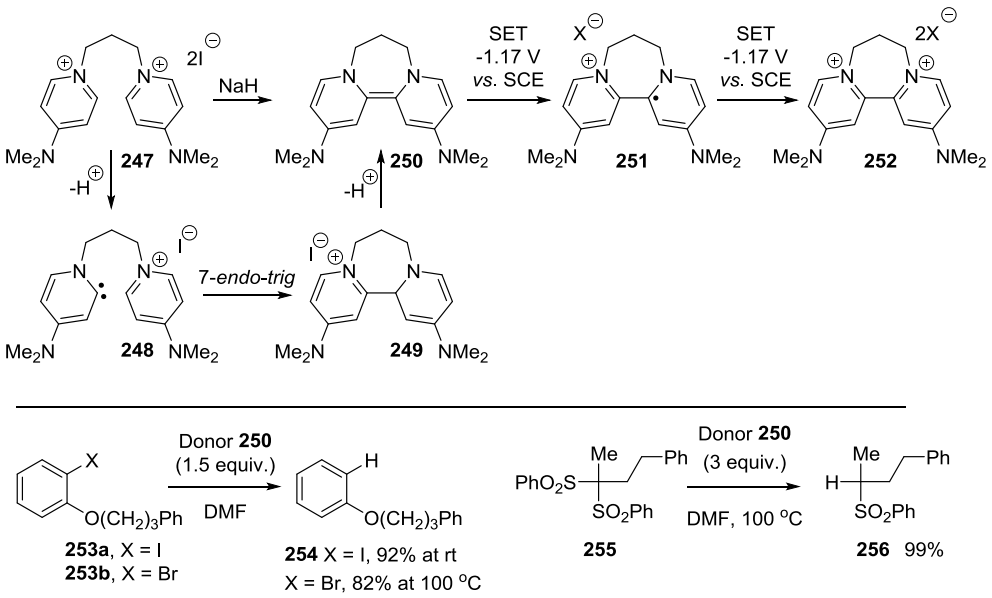
This success with donor **206** in the reduction of difficult substrates encouraged Murphy and co-workers to explore potential new donors and their properties. Another reason was that, while experience would eventually make synthesis of large quantities of **206** straightforward, at the time the conditions for synthesis of **205** also generated **238** and 2**39** (from which a number of redox-active transition metal complexes **240** could be formed)[118-119] meaning that yields were generally low and the purification somewhat complicated. The attempted synthesis of a precursor salt **242** for one such species led to a separate research project into superelectrophilic dications e.g. **243**.[120-121] Another similar attempt yielded, **250**,[122] a purple-black, air- and moisture-sensitive, crystalline solid which came to be the focus of a great deal of experimental chemistry including that presented within this thesis.[99,122-128]



Scheme 25. Synthesis of donor 206

1.5.7. A DMAP-Derived Donor

Species **250** is synthesized from 4-DMAP and 1,3-diiodopropane in quantative yield to generate a bis-pyridinium salt **247**.[122] Deprotonation of this salt gives rise to an *N*-heterocyclic carbene **248** which can nucleophilically attack the second pyridinium moiety. A second deprotonation of **249** yields bis-pyridinylidene **250**, often referred to as 'DMAP donor' in high yield. Oxidation of this species with iodine and cyclic voltammetry of the resulting disalt showed a pseudo-reversible two-electron wave at -1.17 V *vs.* SCE in DMF. This was roughly equivalent to the potential of donor **206** and with the high yielding and straightforward synthesis it was a prime candidate for further study.

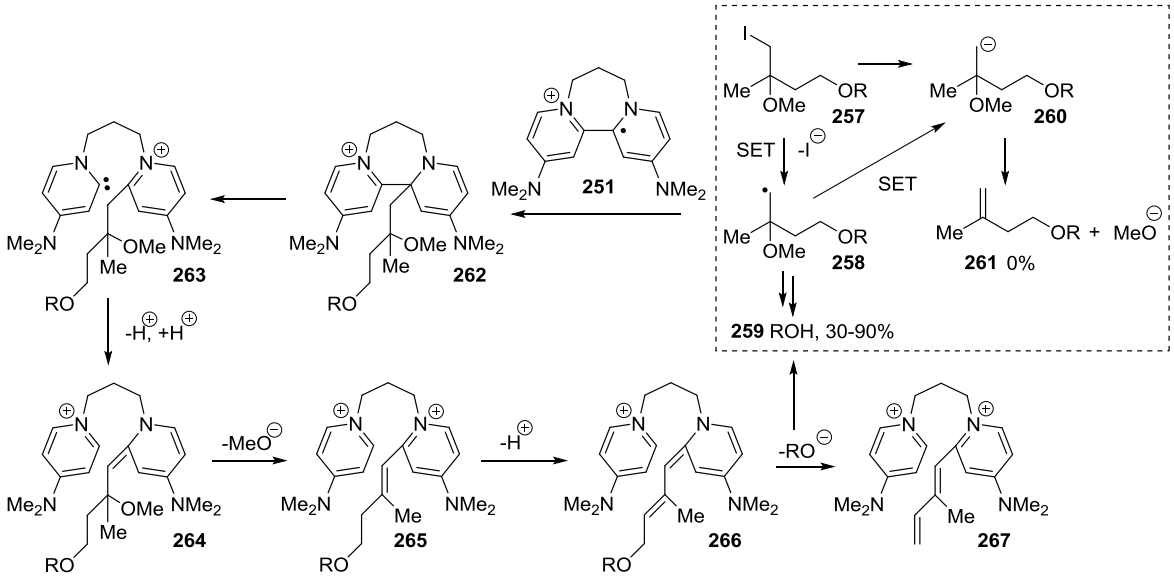


Scheme 26. Donor 250, synthesis and oxidation

Initial results compared the reactivity of donor **250** with donor **206** and showed it to be a similarly powerful donor, able to generate aryl anions from aryl iodides **253a** at room temperature and from the corresponding aryl bromide **253b** at 100 °C, as well as effecting the C-S bond cleavage of activated sulfones **255**.

1.5.8. Trapping of a DMAP-Derived Donor

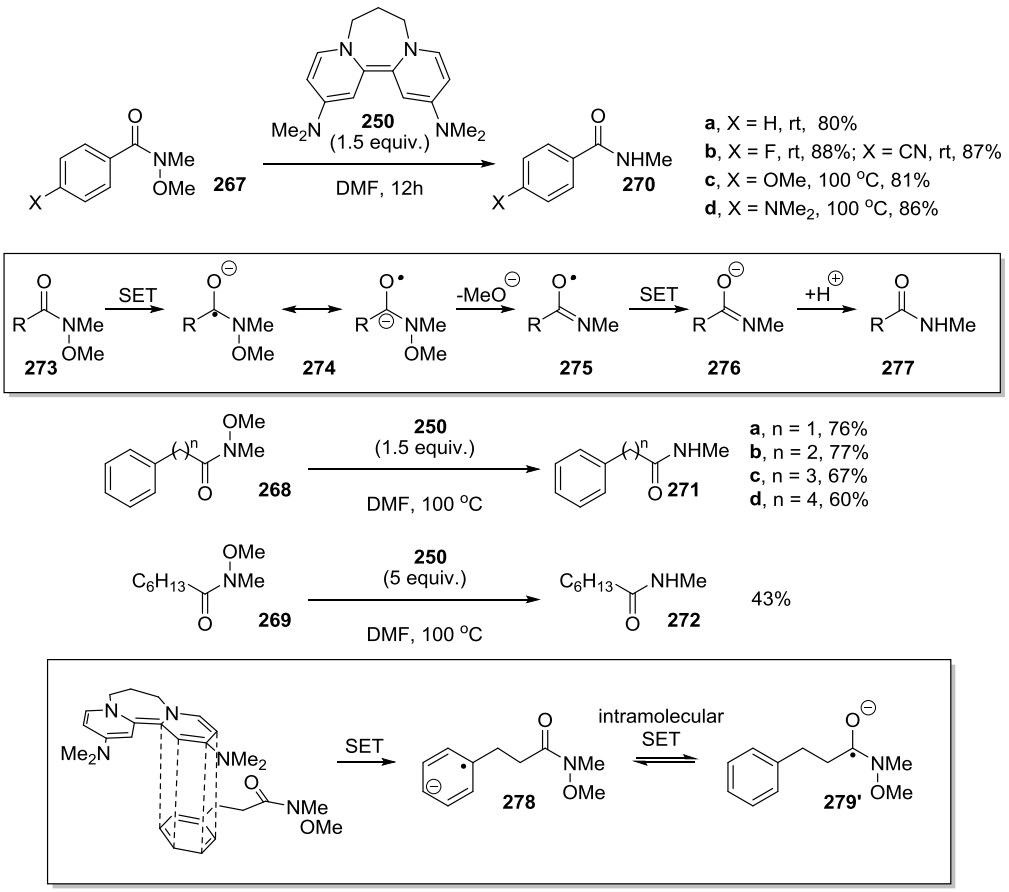
Another example of alkyl iodide cleavage featured a cleverly designed substrate **257** which is thought to undergo the expected reductive C-I bond cleavage followed by alkyl radical **258** being trapped by the radical cation **251** of the donor.[129] An elimination cascade then follows to deliver alcohol **259** as the final product. This is good supporting evidence for the trapping of a substrate radical with the donor radical cation as proposed at times within this thesis. None of the olefin product **261** of the other likely reaction (two-electron reduction followed by elimination of methoxide) was observed. Bis-pyridinium species **267** was also not observed and only inferred to have been generated because of the logical mechanism; Chapter 7 describes a series of experiments where pyridinium compounds derived from donor **250** were isolated and characterized.



Scheme 27. Radical trapping with donor 250

1.5.9. A DMAP-Derived Donor – Cleavage of Weinreb Amides

Further study soon revealed new chemistry of donor **250** that had not yet been explored with **206**, beginning with the reductive N-O σ-bond scission of Weinreb amides to the corresponding amide.[130] The reductions were proposed to proceed via a step-wise two-electron transfer and protonative quenching upon work-up (Scheme 28) and occurred in high yield for electron-rich and electron-deficient benzamides **267**, heterocyclic amides and, in poorer yield, alkyl amides **269**.

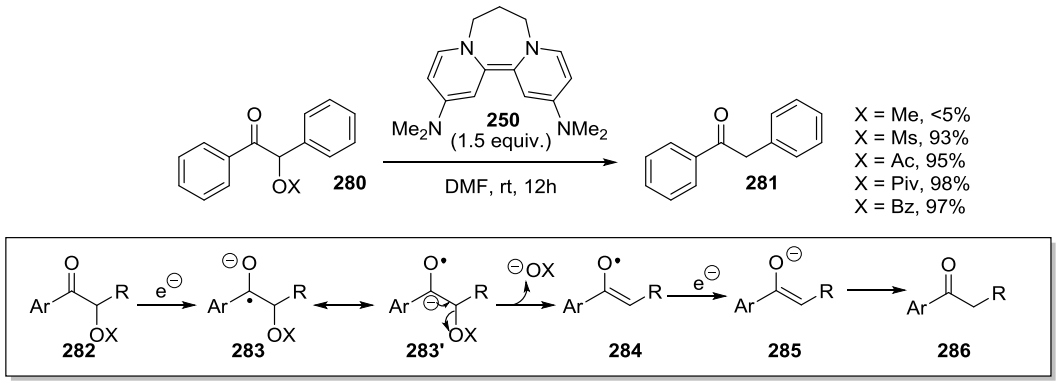


Scheme 28. Reduction of Weinreb amides

An additional proposition was made based on the observation that yields of the successful cleavage decreased for series **268a-d** as the amide was moved further from an aryl π-system. The assertion was that π-stacking interactions occur between the π-conjugated donor **250** and the arene of the substrate, Scheme 28, and that this intimate interaction assists in the electron transfer; this would explain why the proximity of the reducible group to the arene is important. It is also thought that electron transfer to the arene may occur, followed by intramolecular electron transfer to the Weinreb amide: such a through-space mechanism would also be explained by the observed effect of the arene-amide proximity on the yield. Precedent for such intramolecular electron transfer is seen in biology where some enzymes and peptides carry out long range transfer within the macromolecule.[131-132] Clearly in substrate **269**, such an interaction is impossible and as such the yield of product is the lowest observed even with additional equivalents of donor included in the reaction mixture.

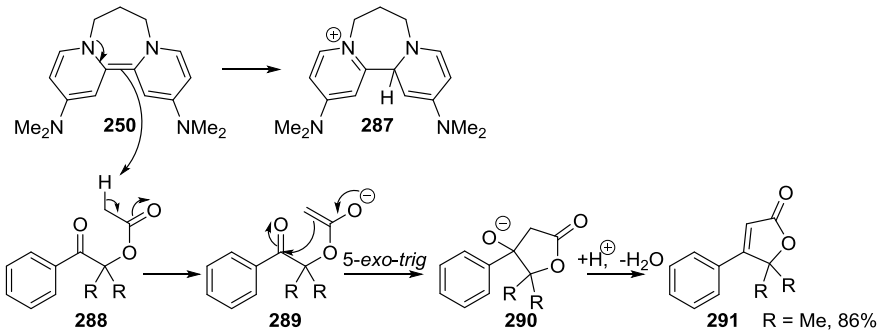
1.5.10. A DMAP-Derived Donor – Reduction of Acyloin Derivatives

Donor **250** was found to cleave C-O σ-bonds in acyloin derivatives **280**, typically synthesized from cyanide- or NHC-mediated benzoin condensation followed by protection of the alcohol. The reductive cleavage reactions proceeded cleanly and in high yield providing that the oxygen anion of the leaving group was stabilized (methoxide as a poor leaving group gave a correspondingly poor yield of C-O bond cleavage). The ketyl radical anion **283** is generated by electron transfer and the leaving group eliminated; a second electron reduces this intermediate **284** to the enolate **285** which upon protonation gives rise to the observed product, **286**.



Scheme 29. Acyloin reduction

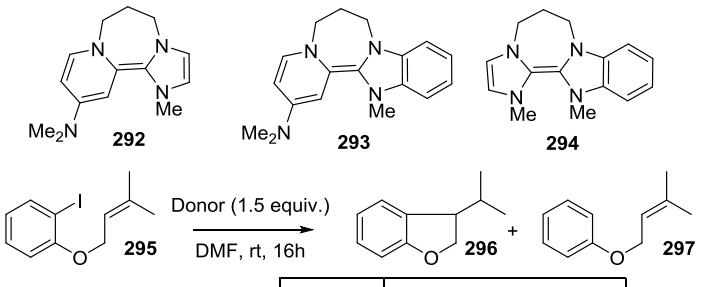
The enolate and enolyl intermediates are extendedly conjugated and therefore favour the forwards progression of the reaction. When R is alkyl rather than phenyl, however, a different reactivity was reported. Donor **250** is very electron-rich and stabilizes positive charge readily; it therefore acts as a strong base and is able to deprotonate acetate-protected substrates e.g. **288**. The resulting anion **289** can intramolecularly cyclize onto a carbonyl group to yield butenolide products **291** in good yield (e.g. R = Me, 86%). This was only observed for acetate esters and only when R was alkyl rather than phenyl, in which case the electron-transfer-induced C-O cleavage was still preferred.



Scheme 30. Donor 250 acting as a base

1.5.11. Asymmetrical Hybrid Donors

One of the benefits normally considered of organic reducing species compared to metallic ones is that they are able to be tailored and customized to have specific properties or for a particular purpose. An example of this is seen in the work of Garnier *et al.*[133] who developed a series of 'hybrid' electron donors **292-294**, which combined different heterocycle motifs common to other donors to make new donors combining the properties of the parent halves.



Donor **292**	0%	59%
Donor **293**	74%	12%
Donor **294**	25%	17%

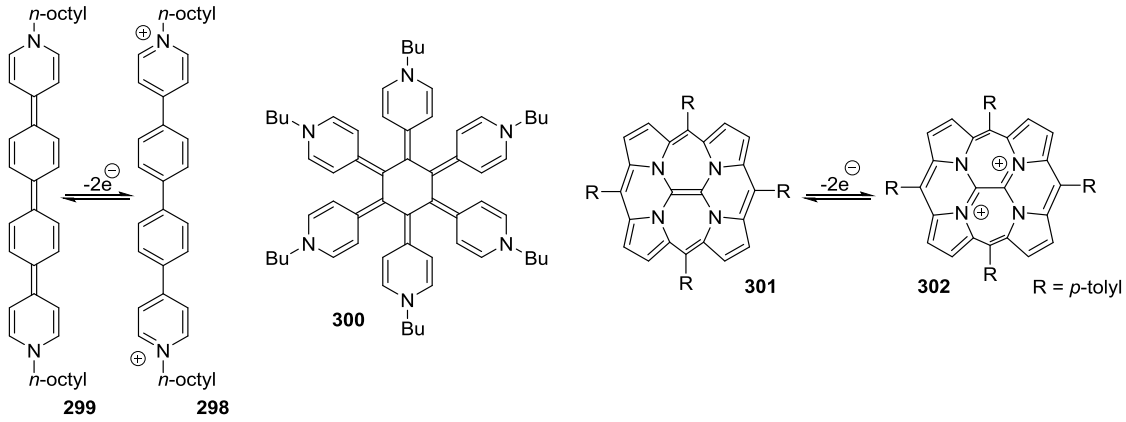
Scheme 31. Asymmetrical donors

Donor **292** had oxidation potentials of -1.30 and -1.18 V *vs.* SCE in DMF; donor **293** had oxidation potentials of -1.09 and -0.97 V *vs.* SCE in DMF, and donor **294** gave an irreversible electrochemical trace but all of these asymmetrical species were able to donate

one or two electrons to aryl halides **295** under mild conditions to deliver dehalogenated **297** and/or cyclized products **296** in good yield.

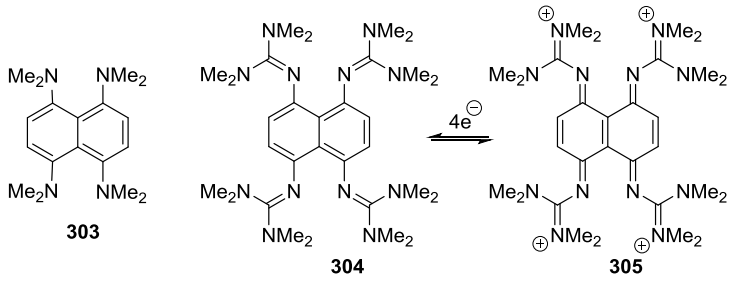
1.5.12. Other Organic Donors

Not all of the recent developments in the area of neutral organic electron donors have come from the Murphy group and another notable contribution comes from Vaid and co-workers.[134-136] The researchers have not focussed on probing the reactivity of the donors with reducible species but nevertheless report several powerful donors shown in Scheme 32.



Scheme 32. Extended, nitrogen-containing π-systems

The first of these, **299**, was reported in 2005[134] and was measured to have a reversible, two-electron oxidation at -1.48 V *vs.* Fc/Fc^+ in THF (equivalent to -0.92 V *vs.* SCE).[137] The 'extended viologen' systems are named for the parent 4,4-bypyridyl parent structure. More extended species **300**[135] was able to donate a total of six electrons, four at -1.14 V and another two at -1.33 V *vs.* Fc/Fc^+ in DMF (-0.69 and -0.88 V *vs.* SCE respectively). Porphyrin-based species **301**[136] was synthesized from the corresponding cobalt-containing porphyrin in three steps. It can donate two electrons at -0.03 V and +0.30 V and also receive two at -1.35 and -1.61 V *vs.* SCE in THF. While the central enetetramine moiety common in the Murphy group donors is present in **301**, its extended conjugated system means that the electron density is more spread out within the molecule, rendering it a less powerful reductant.

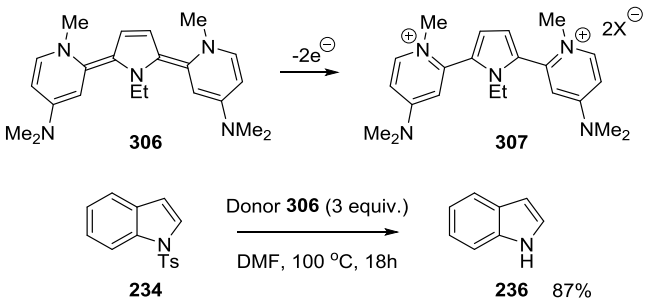


Scheme 33. Proton sponges as electron donors

The field of proton sponges has also given rise to some organic electron donors, which makes sense as each is designed to be electron-rich and able to stabilize positive charge. Species **303**[138] was measured to oxidize at -0.50 V *vs.* Ag/AgCl in MeCN while compound **304**[139] was found to donate four electrons, two at -0.25 and two at +0.50 V *vs.* SCE in MeCN. As in the cases immediately above, the donors were not probed for their reactivity with substrates but should be able to instigate reductive cleavage of arenediazonium salts and other readily reducible species.

1.5.13. Most Powerful Neutral Organic Electron Donor To-Date

Recently, the most powerful ground state organic electron donor to-date **306** was published by Murphy *et al.*[140] with a reversible two-electron transfer at -1.50 V *vs.* SCE in DMF. Three aromatic rings are formed upon donation of two electrons and five substituted nitrogens stabilize the resulting positive charge which accounts for its reducing power and indeed it is able to reduce substrates, e.g. **234**, to give higher yields compared to donors **206** and **250**.

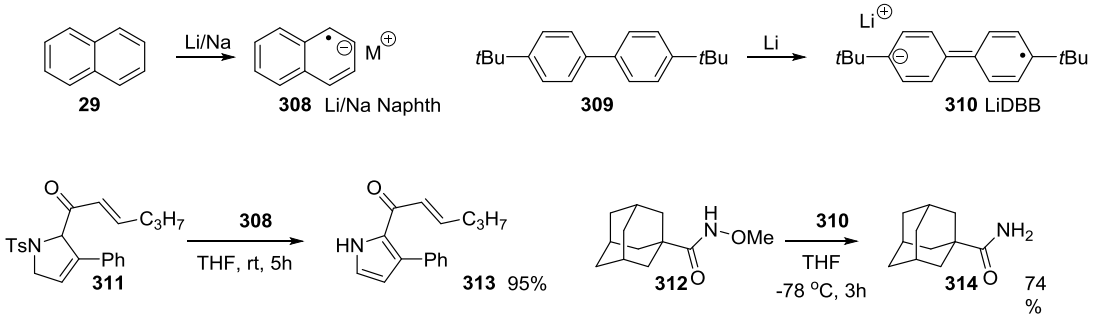


Scheme 34. Most powerful organic donor to-date

Unfortunately, the multi-step synthesis of **306** renders it impractical for general use so it is most useful as an example of what can be achieved with neutral organic electron donors rather than being suitable for research.

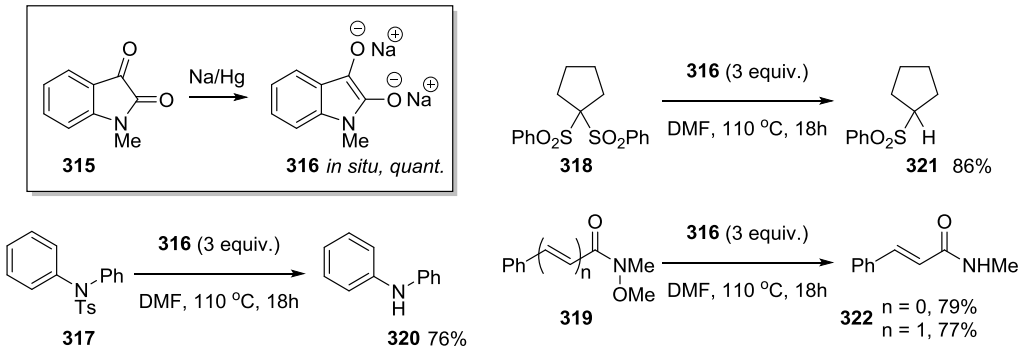
1.5.14. *N*-Methylisatin, DBB and Naphthalide Reagents – Electron Transfer Mediators

What some might call a compromise between organic donors and more traditional, metal reductants are the electron transfer mediators. Lithium or sodium naphthalide **308** and lithium 4, 4'-di-*tert*-butybiphenylide (LiDBB) **310** have proved to be useful for controlled electron transfer, normally associated with organic reductants, with the ultimate electron source remaining the readily available alkali metals. Sodium naphthalide can reduce toluenesulfonamides **311**,[141-143] methanesulfonamides, BOC groups, allyl and benzyl ethers and siloxanes[144] while lithium DBB has been reported to reduce alkoxyamides **312**,[144] acyl azides[144] and heterocycles[145] as seen in Scheme 35. In general these reactions are reported to occur in high yield although the cryogenic conditions required for the LiDBB reactions are inconvenient.



Scheme 35. Electron transfer mediators

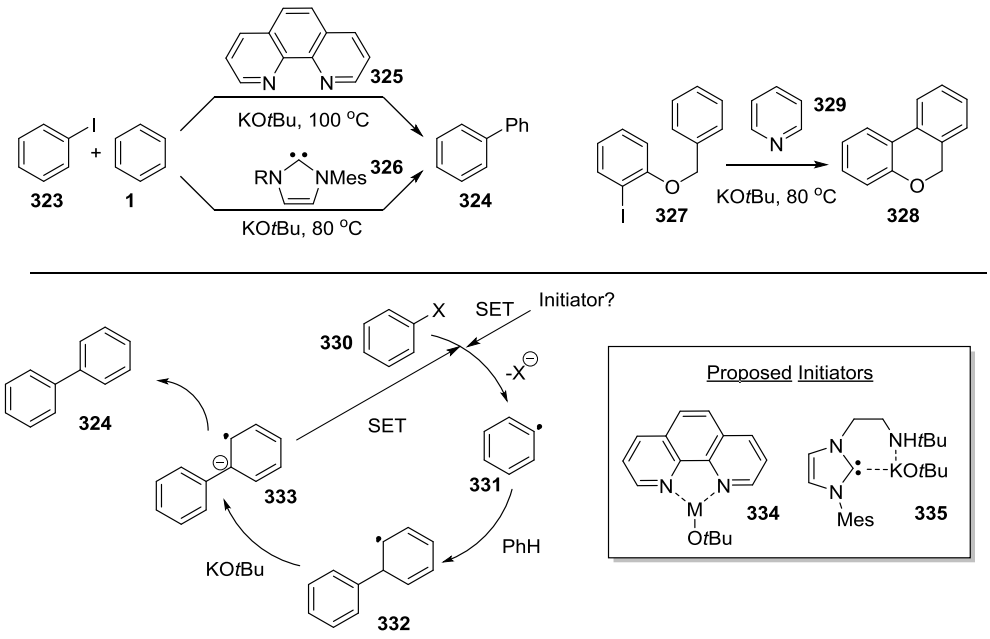
Similarly, *N*-methylisatin **315** can be reduced with sodium amalgam to generate a powerful electron donor **316** (two quasi-reversible one-electron oxidations occur at -0.9 and -1.9 V *vs.* Ag/AgCl in DMF) capable of the reduction of sulfones **318**, tosylamides **317** and Weinreb amides **319** in high yield (Scheme 36).[146] Advantages of **316** over some other donors are that it can be prepared *in situ* when required and, because of its use in the dye industry, isatin (readily converted in high yield to *N*-methylisatin) is remarkably inexpensive, as are sodium and mercury, making this a very economical option although arguments could be made against the use of mercury on the basis of toxicity and environmental impact.



Scheme 36. *N*-Methylisatin as electron transfer mediator

1.6. 'Transition Metal-Free' Coupling Reactions

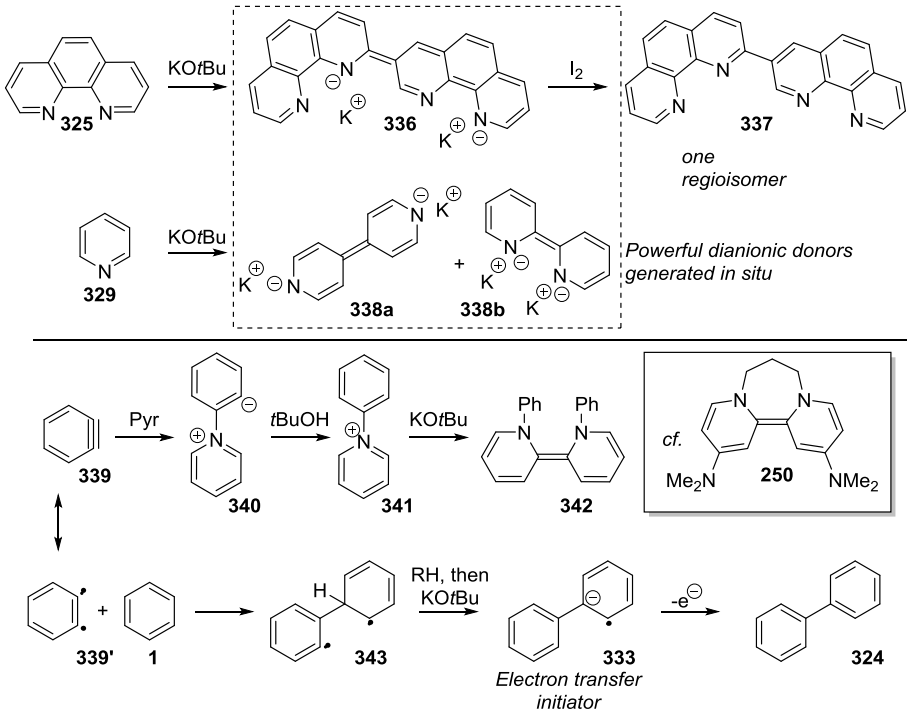
Recently, organic electron donors have been implicated in the mechanism of the in-vogue, transition metal-free coupling reactions of aryl halides with arenes. Previously constrained to metal-containing conditions, these reactions were recently found to operate in the absence of any transition metal during blank reactions carried out by Itami *et al.*[147] A glut of publications has followed featuring potassium *tert*-butoxide (and some other bases) in the presence of various additives to carry out coupling reactions but with a relative dearth of mechanistic insight.[148-158]



Scheme 37. 'Metal-free' coupling reactions

This raised questions into how the reaction was occurring and much speculation ensued, involving potassium *tert*-butoxide as an electron transfer agent stabilized by various ligands. Studer and Curran published an essay,[157] taking an overview of the results and proposing a plausible mechanism (bottom half of Scheme 37). Electron transfer to an aryl halide **330** leads to reductive cleavage to an aryl radical **331** and halide anion. Radical coupling of **331** with another arene yield an aryl cyclohexadienyl radical **332** which can be deprotonated under the reaction conditions to yield radical anion **333** which is a sufficiently powerful donor to reduce the halide substrate **330** to propagate the cycle and deliver the biphenyl product **324**. The issue with the mechanism is that it requires an initial electron transfer for initiation which they accounted for by the oxidation of a ligated sodium or potassium

alkoxide. Work from Murphy and collaborators[159] indicated that donation of an electron from KO*t*Bu would be highly endergonic (+59.5 kcalmol^{-1}), regardless of ligand interactions, and so have proposed a more energetically acceptable mechanism for the formation of organic electron donors under the reaction conditions, Scheme 38. The donors can be generated in sub-stoichiometric amounts from the heterocyclic solvents and additives to initiate the radical coupling reaction shown above. The proposed donors **336**, **338a** and **b**, and **342**, have much in common with the previous organic species, e.g. **250**, used within the Murphy group and the parallel reactivity adds credence to the proposed mechanism.



Scheme 38. Murphy explanation for the initiation of 'metal-free' coupling reactions

A recent paper from Wilden and co-workers reported the conversion or aryl halides to biaryls in the absence of any additives.[160] They see this as a justification for *tert*-butoxide acting as the donor as no other species are present and because product regiospecificity is seen which rules out coupling via a benzyne mechanism. The reactivity observed is explained, however, by the final mechanism shown above whereby a benzyne **339** (formed by deprotonation and elimination of an aryl halide) reacts with an arene **1** to yield biradical **343**; deprotonation of which gives rise to a radical anion **333** capable of reducing aryl halides

to the corresponding aryl radical as seen previously. The radical reaction will be regiospecific and tiny quantities of benzyne are sufficient to initiate the process which explains why none of the other regioisomer was observed.

Speculation and investigation will no doubt continue as this chemistry has much potential to be a useful and cost-effective alternative to more common transition metal-catalyzed coupling reactions. At present however, a hypothesis has been presented by Murphy *et al.* which stands up to scrutiny and is well supported by the synthetic and computational results.

1.7. Electron Donor and Acceptor Species in Organic Photovoltaics

An application of electron donors, outwith synthetic organic chemistry, is in photovoltaics. The photovoltaic effect is the excitation of electrons from the valence band of a substance in to the conductance band. By interaction with a junction to another material the electrons are able to flow energetically downhill, thereby generating a current as a result of the initial incident light. This is the principle underlying solar power generation, one of the potential solutions to the world's energy crisis and therefore studied at depth.[161] The photovoltaic systems require an electron donor and an electron acceptor species (sometimes within one larger molecule) and the electron-rich moieties are comparable to the donors discussed above. By fine-tuning the band gap of the organic substrates, chemists are able to select the desired attributes for the solar cells to make them more efficient, longer lasting and/or easier/less expensive to produce.

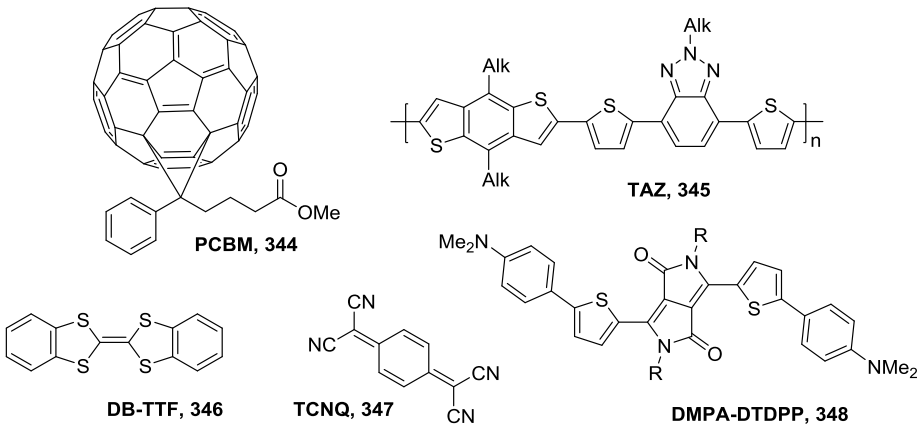


Figure 2. Some photoactive materials

Some examples are shown in Figure 2 of different donor-acceptor materials, featuring the high degree of conjugation and lots of nitrogen and sulfur atoms to increase the electron density of the species. Fullerene derivatives also feature heavily in this area of research due to the six separate potentials at which fullerene can accept an additional electron.[162] It is clear to see that, with the electronic characteristics depending on the structure and such a wide variety available, the desired characteristics may be tailored to fit.

The same type of organic semi-conductor technology is being applied to organic LEDs and field-effect transistors,[163-164] meaning that research into electron transfer in organic species has wide-reaching applications, confined not only to the type of synthetic transformations discussed within this thesis.

Results & Discussion

Chapter 2. Results and Discussion – General

This section will discuss what was accomplished during the course of the research project. The work will be sub-categorized by the type of bond being reductively cleaved i.e. C-N bond cleavage, which accounts for the majority of the work, along with N-S, C-O, C-C, S-O and S-C bond cleavage. Much of the work has been published and was carried out in collaboration with other chemists so care has been taken to accredit the collaborators for their work while including some of it to show a more complete picture of what can be achieved by photoactivated electron transfer with a neutral organic electron donor. A more general overview of the donor reactivity will preface the section.

2.1. Photochemical Experiments with Donor

Figure 3 (top left) shows the general reaction set-up used for the UV-activated reduction reactions carried out during the research of this thesis: two 100 W spot-lamps emitting at 365 nm were focused on a flattened 5 mL round-bottom flask (top right), typically for a reaction time of 72 hours.

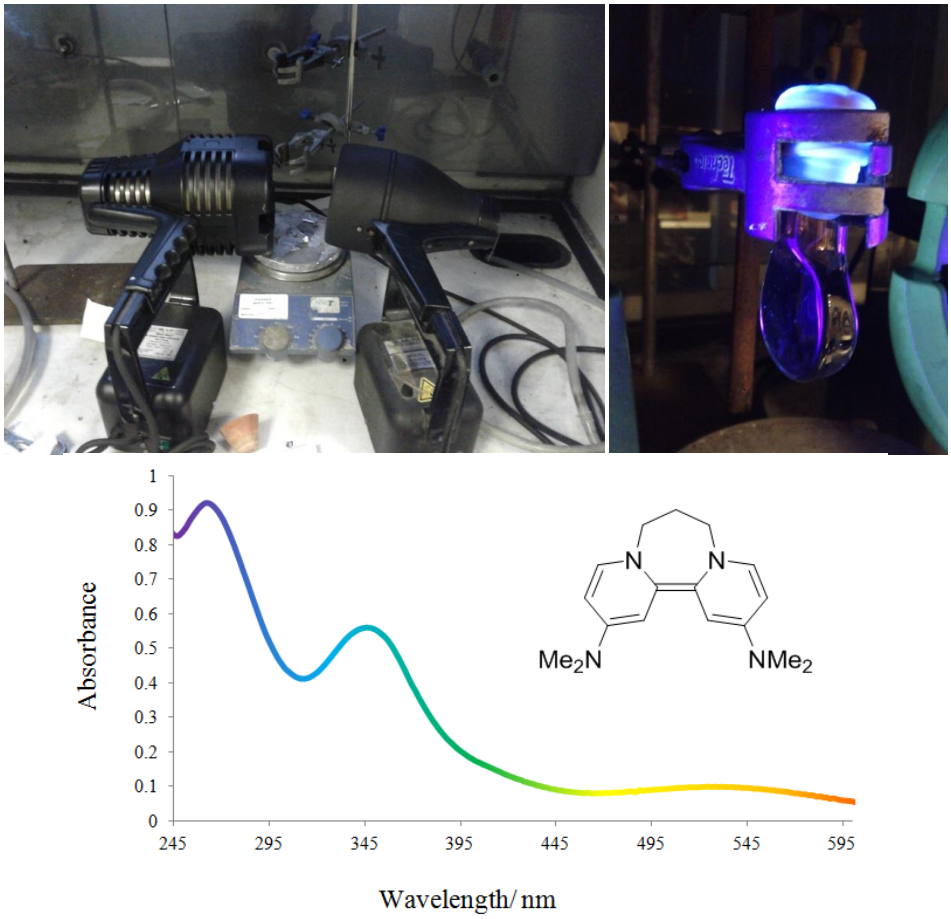


Figure 3. Top left- Standard reaction set-up; Top right- a flattened reaction flask clamped between the two activated UV lamps; Bottom- UV-vis Absorbance spectrum of Donor 250 in acetonitrile.

Excitation at a wavelength of 365 nm was based on the UV-visible absorbance spectrum measured in acetonitrile (above). Unfortunately, attempts to measure other photophysical properties of the donors were largely unsuccessful;[165] fluorescent and phosphorescent measurements revealed no information about the excited species. An excited state must exist, otherwise the photoactivation would not enhance the reactivity of donor **250** but for some reason, whether it be photo-bleaching (by which the incident light required for the measurement causes the photo-degradation of the analyte) or auto-quenching (whereby the analyte solution absorbs the fluorescent radiation, obscuring the measurement), the emission spectrum could not be measured.

2.2. Reducing Power of the Excited Donor Species

By the same method used by Stephenson *et al.*[60] to estimate the approximate strength of photoactivated ruthenium and iridium species, so can we add the excitation energy to the measured ground state oxidation potential of donor **250** to infer the potential of **250*** → **251** (as shown on page 33). The longest wavelength in the absorbance spectrum of **250** was 512 nm which is equivalent to 2.42 eV. Subtracting this value from the ground state redox potential (-1.17 V *vs.* SCE in DMF) gives a value of –3.59 V *vs.* SCE. This is an impressive value for a neutral organic species and is more negative than the potential required to reduce benzene, which could explain why ring opening was observed in aryl cyclopropanes as discussed in section 4.1.1, page 64. This estimation is based on a singlet excited state, however, which may not be sufficiently long-lived to transfer an electron to a substrate.

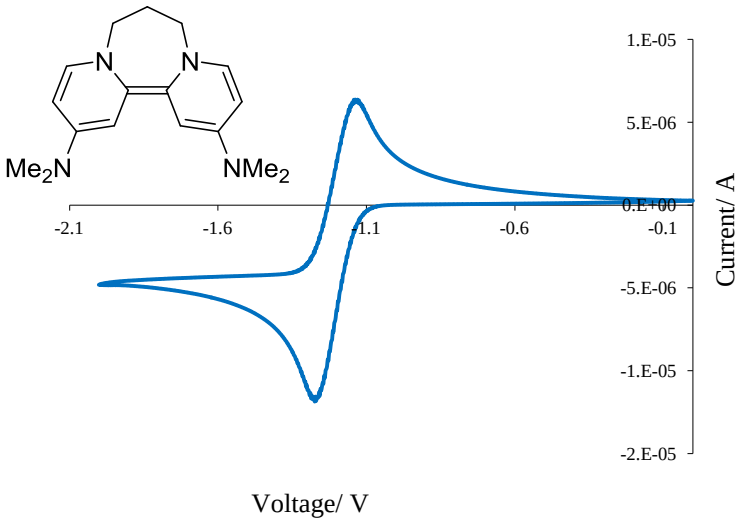


Figure 4. Cyclic Voltammogram of Donor 250 *vs.* Ag/AgCl in DMF[122]

The electron transfer would be more likely to occur (i.e. have more time to occur) if a triplet excited state were the active donor species (the phosphorescence from triplet excited state to singlet ground state is forbidden and therefore slow). As no phosphorescence could be measured, an alternative was to determine the energy gap computationally: DFT calculations run at 6-31G (d,p) level of theory using CPCM (Conductor-like Polarizable Continuum Model)[166-167] in DMF (ε = 37.219) were used to predict the energy of the frontier orbitals of the ground state and triplet excited state donor, Figure 5, and thereby calculate the energy

difference. This method predicts a potential of -2.13 V (phosphorescence at 1495 nm) which would also be an extremely strong reductant.

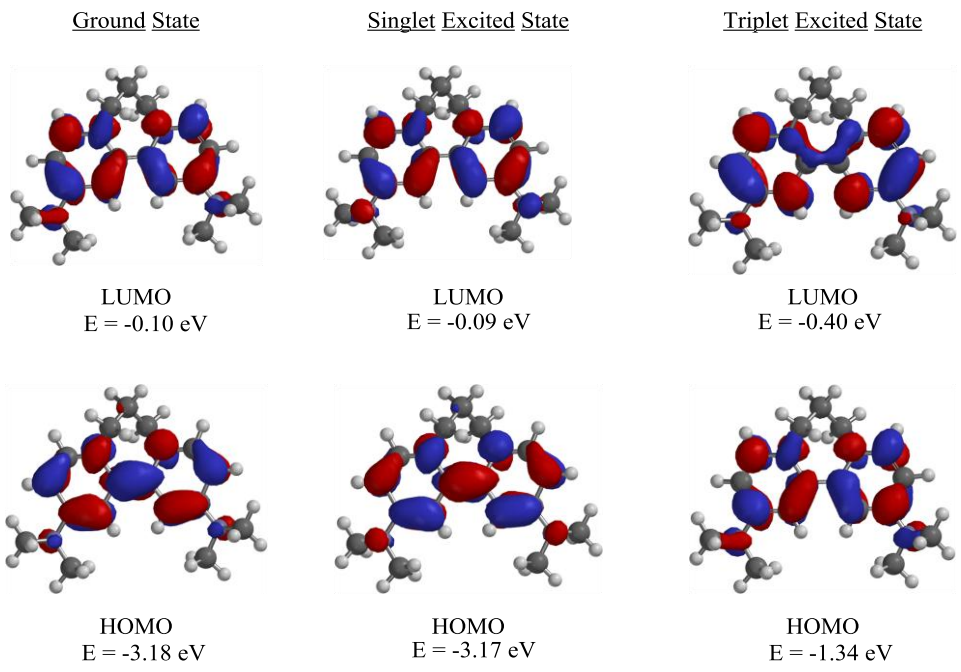


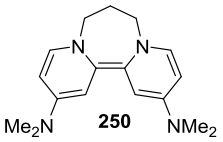
Figure 5. Excited state frontier orbital of donor 250, (DFT, B3LYP, 6-31G(d,p))

These approximations would be more satisfying if derived from a measured emission spectrum but nevertheless act as a useful guide to the donor strength under photoexcited conditions.

2.3. Donor Economy

Aside from difference in reactivity, practical considerations must be taken into account when choosing a chemical reagent- expense included. Considering modern electron transfer reagents, the three main options are SmI_2, Ru and Ir photoredox catalysts **65** and **71**, and organic electron donors such as **250**. The catalytic reagents would appear to have an advantage as they are typically used in 1 mol% but they are also expensive, high formula weight species. Standard conditions for reactions with donor **250** require six equivalents as often do those with SmI_2.

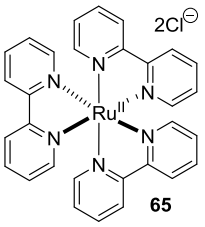
2.3.1. DMAP-Derived Donor



250

For 0.3 mmol of substrate using 6 equiv = 1.8 mmol
Synthesis of donor yield = 95%, M.Wt. of Donor = 284.40 g
Synthesis of salt yield = 100%, M.Wt. of Salt = 324.07 g
Dibromopropane, 1000 g = £60.10 (Alfa Aesar 17/01/2014), M.Wt. = 201.90 g, 0.06 £/g, 12.13 £/mole
DMAP, 100 g = £50 (Alfa Aesar 17/01/2014), M.Wt. = 122.17 g, 0.5 £/g, 61.08 £/mole
1 mole of donor costs 77.06 £/mole, 00.27 £/g
Price for 1.8 mmol = £0.14

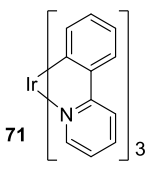
2.3.2. Photoredox Catalysts



65

$Ru(bpy)_2Cl_2.6H_2O$, 1 g = £79.90 (Sigma Aldrich 14/02/2014), M.Wt. = 748.62 g, 79.9 £/g, 59,815 £/mole.
For 0.3 mmol of substrate use 0.01 equiv., 0.003 mmol
Price for 0.003 mmol = £0.18

***fac*-$Ir(ppy)_3$**, 250 mg = £181.50 (Sigma Aldrich 14/02/2014), M.Wt. = 654.78 g, 726 £/g, 475,370 £/mole.
For 0.3 mmol of substrate use 0.01 equiv., 0.003 mmol
Price for 0.003 mmol = £1.42



71

2.3.3. Samarium(II) Iodide

For 0.3 mmol scale using 6 equiv. = 1.8 mmol

SmI_2 0.1 M solution in THF 100 mL = £46.80 (Sigma Aldrich 14/02/2014), 4680 £/mole.

Price of 1.8 mmol = £8.42

Researchers of samarium iodide chemistry would tend to generate their own from samarium metal and 1,2-diiodoethane which is a far more economic option and is believed to give better results.

It is evident from the above calculations that organic electron donor **250** is a very competitive electron source compared to the major alternatives. The possibility for *in situ* generation of the donor also means that no special apparatus is required for its use - it is therefore a very real alternative to its metal counterparts.

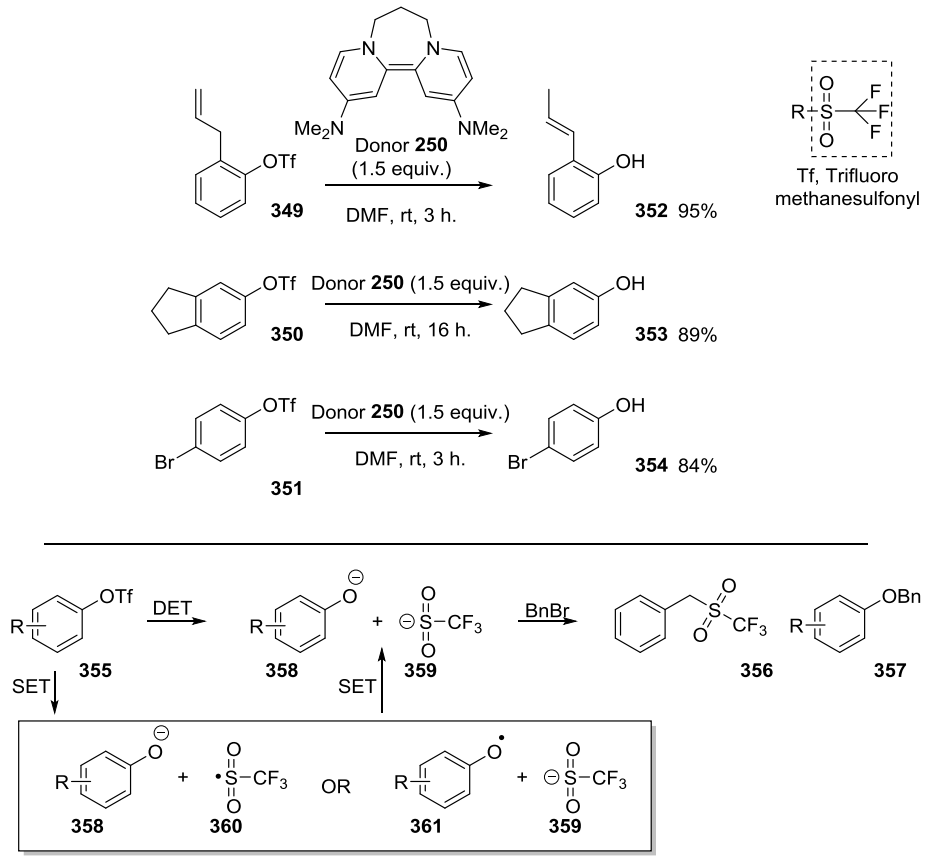
Chapter 3. Reductive Sulfur-Oxygen σ-Bond Cleavage in Aryl and Alkyl Triflates

(This work has been published. See: Jolly, P. I.; Fleary-Roberts, N.; O'Sullivan, S.; Doni, E.; Zhou, S.; Murphy, J. A. *Org. Biomol. Chem.* **2012**, *10*, 5807.[124] The work included in this section is my own unless stated otherwise).

3.1. Previous Results in Aryl Triflate Cleavage

Previous work in this area within the group had produced some promising results: the cleavage of aryl triflates **349**-**351** to the corresponding phenols **352**-**354** had been achieved in high yield in the presence of donor **250**. Our aim was then to determine whether the cleavage of the triflates proceeds through an electron transfer process or by some other means, and to explain some of the other results.

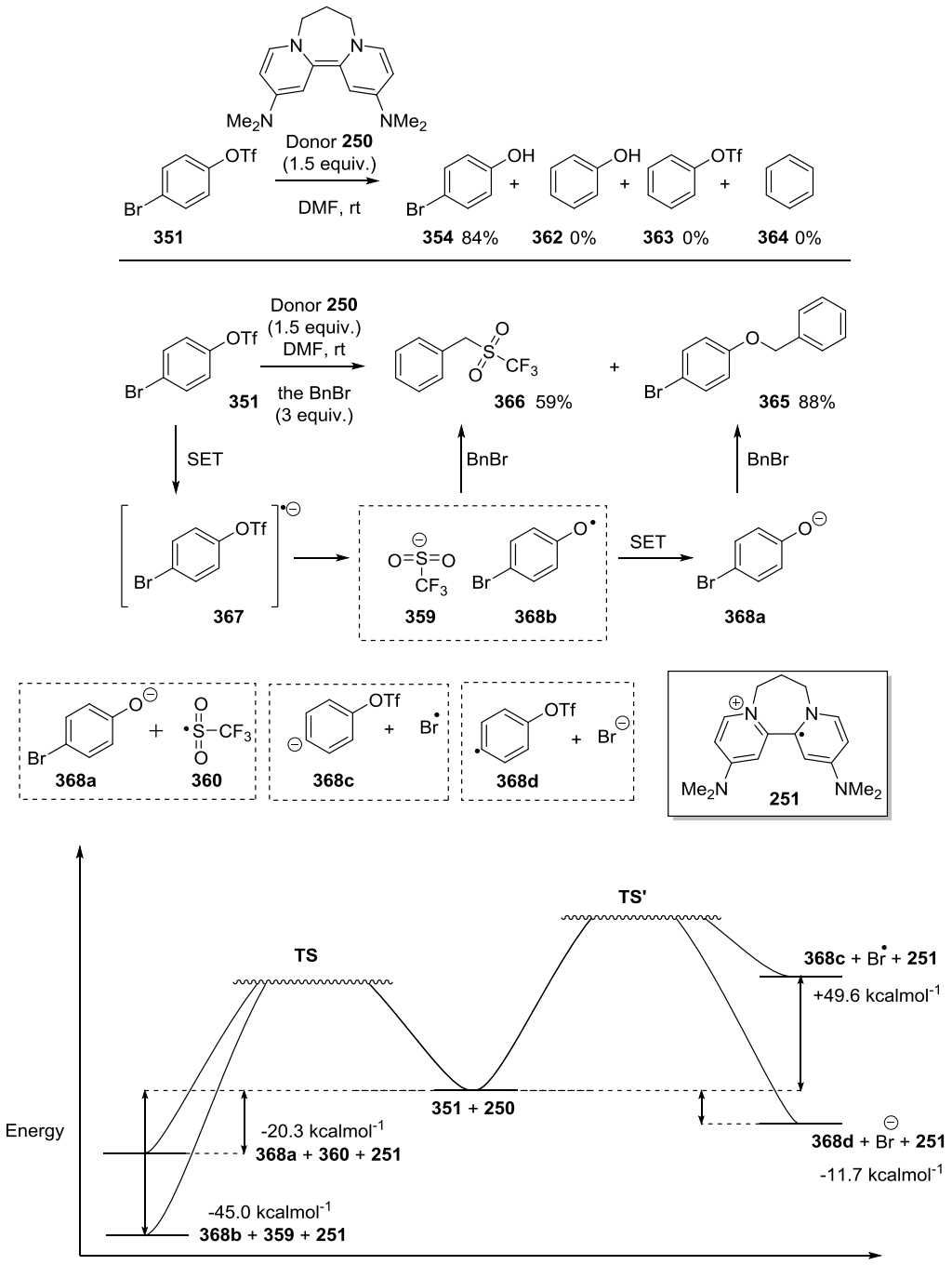
A trapping experiment (lower half of Scheme 39) had been devised in which the reaction was quenched with benzyl bromide to indicate which anions were present. The isolation of sulfone **356** and ether **357** is evidence of the generation of sulfinate **359** and phenoxide **358**, consistent with the proposition of an electron transfer process. Although two anions (**358** and **359**) are generated, it is thought that one electron acts to reductively cleave the bond and that the second electron reduces the resultant radical (**360** or **361**) to form the second anion.



Scheme 39. Previous results in aryl triflate cleavage

3.2. Chemoselectivity- Bromide *vs.* Triflate ester

One of the previous substrates **351** had shown an interesting selectivity so it was decided to carry out additional experiments. In the reaction of bromotriflate **351** with donor **250**, only 4-bromophenol **354** was observed but none of the products resulting from C-Br reduction, **362** and **363**. This is somewhat surprising as the reduction potential of aryl triflates and bromides are very similar; -2.63 and -2.70 V *vs.* SCE[168] respectively, so at least a mixture of products would be expected in the presence of excess donor **250**.



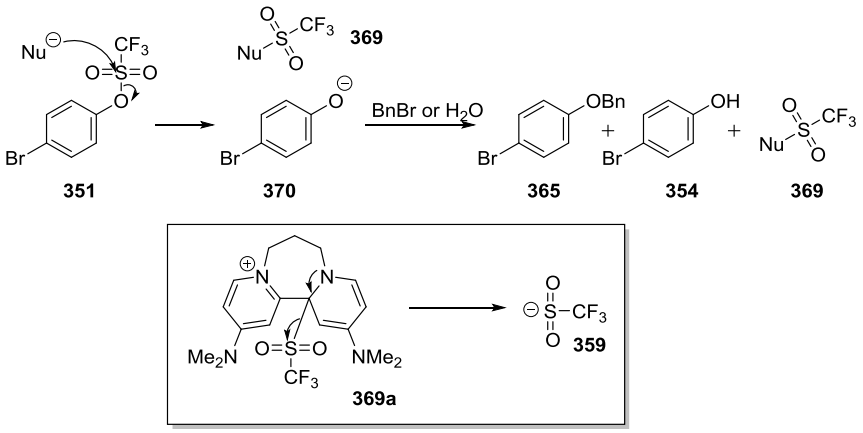
Scheme 40. Chemoselectivity in triflate cleavages

A computational model of radical anion **367** (DFT, B3LYP, 6-311G(d,p), CPCM DMF) exhibited spontaneous C-Br cleavage which suggests a barrierless transformation to cleavage products. In practice however, the S-O bond cleavage occurs in good yield and no debromination was ever observed which raised questions as to whether electron transfer was

occurring or if some other process was taking place. A more in-depth computational analysis of the competing electron transfer mechanisms was conducted (with the assistance of Greg Anderson) which showed the products of S-O bond cleavage to be more energetically favourable than that of C-Br cleavage and that the transition state for C-Br cleavage would be unreasonable high (greater than 49.6 $kcalmol^{-1}$). Previous experiments have shown that thermal activation is required for reduction of aryl bromides[122] which agrees with the calculations. Why then can aryl triflates be reduced when their reduction potential is almost the same as the bromides?

Because of the surprising reactivity, a trapping experiment, Scheme 40, was carried out, using benzyl bromide to quench the reaction of **351** with donor **250**, similar to that above, in the reaction of triflate **351** with donor **250**. This reaction proceeded as seen before; benzyl ether **365** was isolated in high yield and sulfone **366** in good yield. The fact that less sulfone was isolated than benzyl ether may offer an additional insight into the route of the bond cleavage: if the bond breaks such that the phenoxide anion **368a** and sulfonyl radical **360** are generated then some of the radical may be either trapped by another radical or abstract a hydrogen atom which would account for a decreased yield of sulfone **366**.

A mechanism may be proposed, Scheme 41, where the sulfonate ester **351** is nucleophilically attacked on sulfur, whether by water, donor **250** or the DMF solvent, to displace a phenoxide anion **370** which could then yield the observed phenol **354** or ether **365**, depending on the quench. In this case, the sulfinate anion **359** would be generated by elimination from adduct **369a** and could go on to react with benzyl bromide to yield observed sulfone **366**. Such a mechanism can explain the observations and could also explain the selectivity for the S-O bond scission over the C-Br. Although donor **250** is electron-rich, it is also quite a bulky species, meaning that it may be a poor nucleophile and disinclined to react in such a manner.

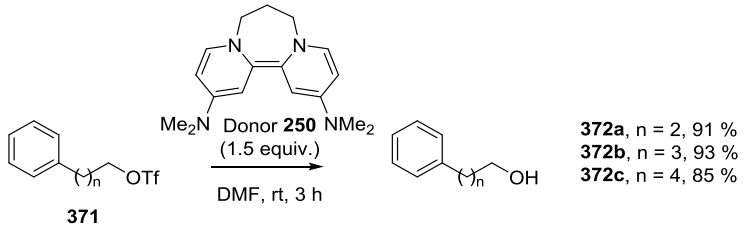


Scheme 41. Possible alternative route to cleavage

There is, therefore, supporting evidence that the cleavage occurs through a nucleophilic substitution/subsequent elimination mechanism rather than via electron transfer. Further study would demonstrate that the same is not true for alkyl triflates.

3.3. Existing Results of Alkyl Triflate Reductions

The work on the cleavage of triflate esters also included a number of alkyl examples **371a-c**, each containing a distal phenyl group. These varied in the length of carbon chain between the arene and triflate moieties and were intended to test the effect of chain length upon the yield as had been carried out on Weinreb amides (Section 1.5.9).



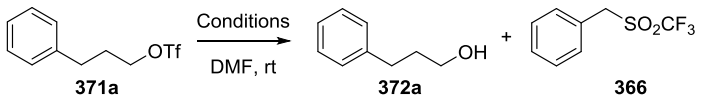
Scheme 42. Previous work on cleavage of alkyl triflates

The substrates cleaved in the presence of donor **250** in excellent yield to the corresponding alcohols **372a-c**. The yields of the three reactions do not follow perfectly the trend of decreasing with increasing chain length but certainly the longest chain shows a marked

decrease in yield, possibly due to less effective electron "shuttling" from the low lying LUMO of the aromatic ring to the reactive sulfonate ester.

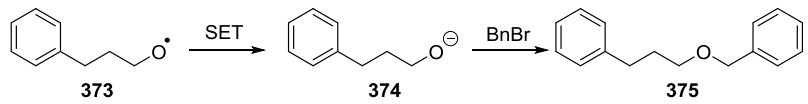
3.4. Additional Experiments Investigating Reduction of Alkyl Triflates

Unlike the aryl triflates discussed above, there is no precedent[169] for the cleavage of alkyl sulfonates by nucleophilic attack on sulfur, therefore further experiments were carried out to probe whether the reduction of alkyl triflates **371** to alcohols **372** occurred by electron transfer as had originally been proposed for their aryl counterparts. Benzyl bromide was used to quench the reaction of triflate **371a** with donor **250** in an attempt to trap the sulfinate anion as sulfone **366**. However, this reaction did not yield the sulfone despite numerous attempts under various conditions (Scheme 43).



371a **372a** **366**

371a	Donor **250**	BnBr	Time/h	**372a**	**366**
1	1.5	1.5	3 h	51%	0%
1	1.5	3	18 h	40%	0%
1	1.5	3	18 h	40%	0%
1	3	6	18 h	34%	0%

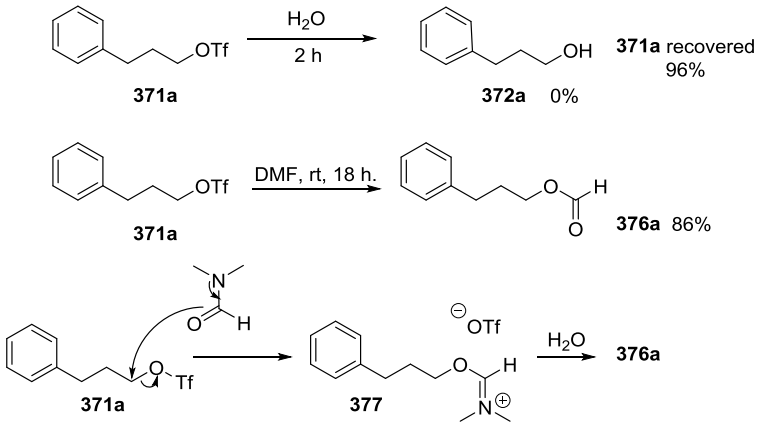


373 **374** **375**

Scheme 43. Benzyl bromide trapping experiment for alkyl triflates

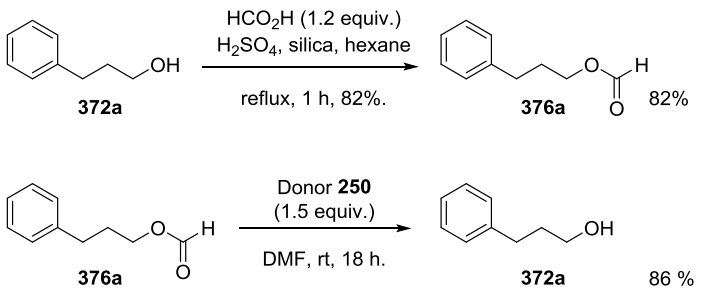
The observation that no benzyl ether **375** was recovered from the trapping experiments with the alkyl triflates is puzzling in the presence of such a large excess of benzyl bromide. This could be because the alkoxide **374** picks up a proton from the reaction mixture more quickly than the comparable phenoxide because of its greater basicity, and is therefore quenched before the bromide is added. The absence of sulfone **366** is not so easily explained and might indicate that cleavage is not occurring via an electron transfer mechanism but rather by nucleophilic substitution of the triflate by donor **250**, DMF or water (although the reactions were carried out under anhydrous conditions).

A simple test was therefore run to investigate the hydrolysis stability of the triflates. Triflate **371a** was stirred for two hours in de-ionized water in the open air at room temperature and then subjected to the standard work-up conditions of the reactions, using diethyl ether and water. The triflate was recovered in quantitative yield, indicating that the direct hydrolysis to the alcohol may not be as easy as initially thought.



Scheme 44. Blank reaction generates formate ester

A control reaction was run then to determine whether, in the absence of donor, any alcohol would be observed. The reaction yielded neither the triflate nor the alcohol but instead delivered the formate ester **376a** in good yield. This is formed from the nucleophilic attack of DMF upon the triflate and traces of the ester had been observed previously in crude reaction mixtures. A plausible mechanism for conversion of alkyl triflate to alcohol may then include the corresponding formate ester as an intermediate, followed by either reduction or hydrolysis. Fischer esterification[170] yielded an authentic sample of the formate ester **376a** which was reacted under the standard donor conditions and yielded alcohol **372a** in high yield.

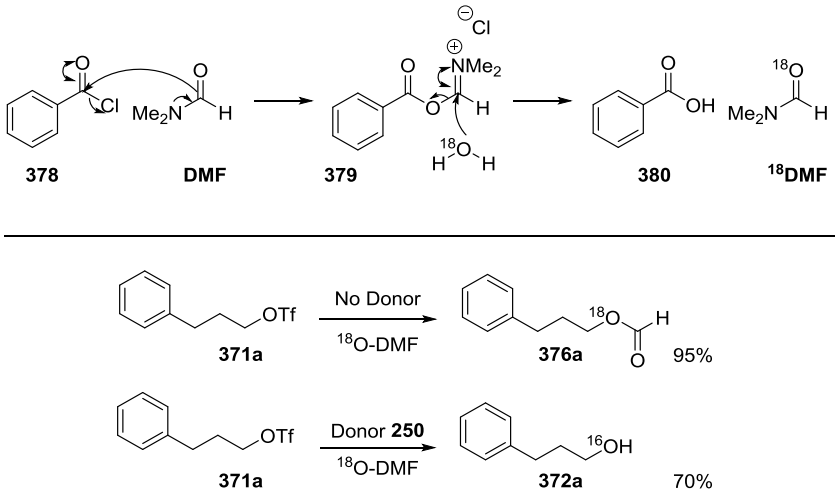


Scheme 45. Substrate designed to give evidence of electron transfer process

These results demonstrate that, under the reaction conditions, an alkyl triflate can be converted to a formate ester and a formate ester may be converted to the alcohol but neither yet served to clarify if donor **250** could directly reduce alkyl triflate esters to alcohols. Isotopic labelling was therefore proposed as a means to elucidate the mechanism, *vide infra*.

3.4.1. Labelling experiments

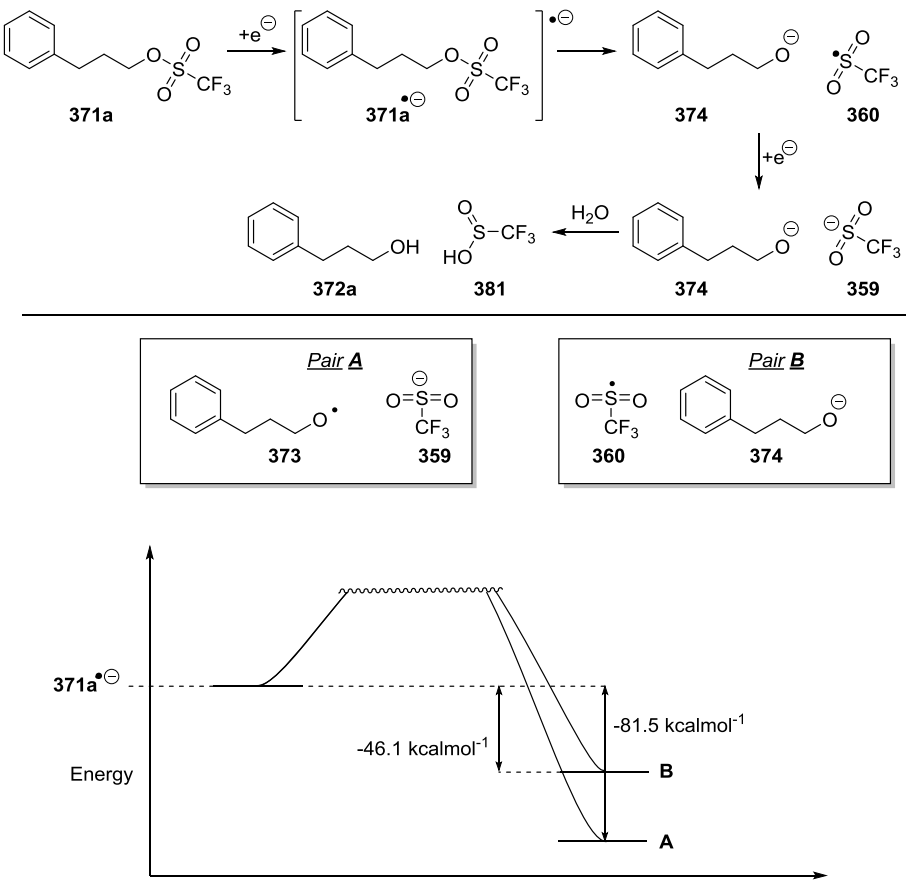
^{18}O-labelled DMF was synthesized using ^{18}O-enriched water (97% enriched $H_2{}^{18}O$ was obtained and then diluted down to ~ 20% enriched ^{18}O-H_2O) and benzoyl chloride **378** in DMF.[171] This reaction proceeded in good yield and with high incorporation of the isotope: delivering 5.6 g (77%) of ^{18}O-DMF (~13% enriched). The labelling of the DMF was carried out in cooperation with Eswararao Doni.[124]



Scheme 46. Isotope labelling

The ^{18}O labelled DMF was used as the solvent in a reduction reaction with donor **250** and also in a control reaction in the absence of the donor (Scheme 46). The blank reaction showed complete incorporation of the ^{18}O into the formate ester **376a** by mass spectrometry, showing that the ester is generated from the DMF nucleophilically attacking the triflate as was not really in dispute. Alcohol **372a** isolated from the donor reaction contained no ^{18}O enrichment which rules out the possibility that the alcohol generated in the presence of donor **250** is formed via the formate ester.

While the ester can be formed under the reaction conditions and can be reduced (or hydrolysed) to the alcohol, the triflate reduction occurs preferentially by another method. Combined with experiments showing the hydrolysis stability of the alkyl triflates, and knowing that donor **250** is bulky and more likely to yield elimination products rather than substitution, it is proposed that the reduction of triflates to alcohols occurs via electron transfer from donor **250** as originally thought (Scheme 47).

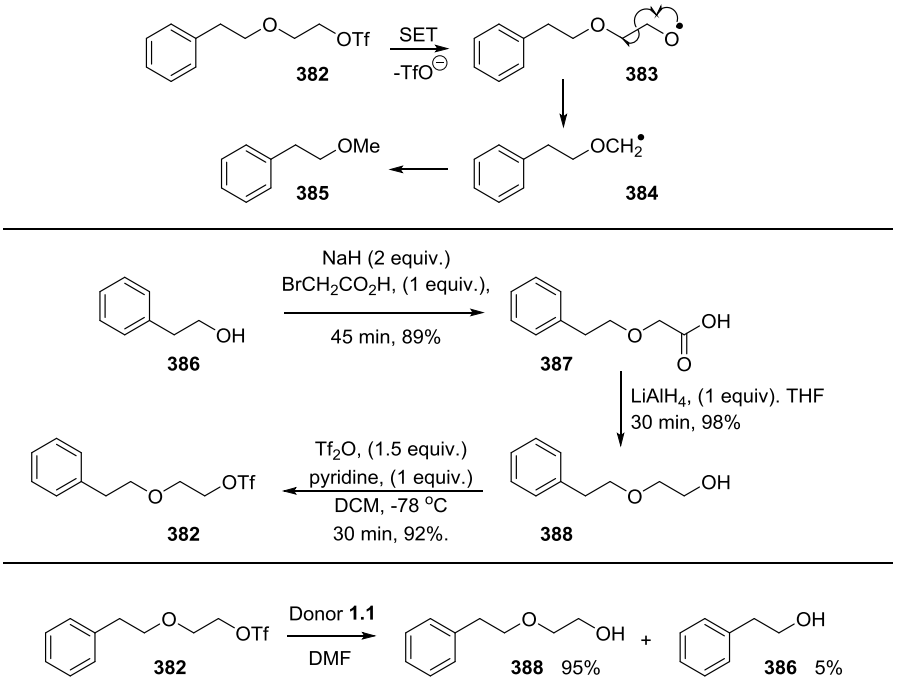


Scheme 47. Mechanism for electron transfer-induced cleavage of alkyl triflates. Calculations were run with DFT, B3LYP, 6-311G(d,p), CPCM DMF

A computational analysis (carried out with the assistance of Greg Anderson) of the possible cleavage processes of substrate **371a** was carried out and proved to be illuminating. Radical and anion pair **A** was calculated to be 35.4 kcalmol^{-1} more stable than the combined energy of **B**. Attempts to optimize a transition state structure for cleavage of the radical anion led to bond cleavage, indicating that the S-O scission is spontaneous. Given the possibility that the reactions to form pair A or pair B may have a shared transition state, it becomes difficult to predict the more likely outcome.

3.4.2. Trapping Experiment

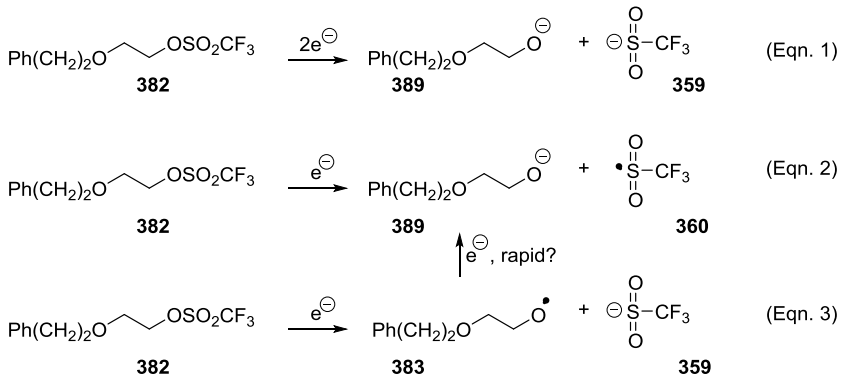
An additional series of experiments was carried out to observe the degradation of a radical intermediate and thereby confirm its presence. The theory behind this was that the radical adjacent to oxygen in **384** should be more stable than the oxyl radical in **383**. Elimination of formaldehyde should therefore occur and ether **385** would result. This substrate was synthesized quite simply in a number of high yielding steps as shown in the scheme below.



Scheme 48. Proposed intermediate and degradation to probe electron transfer

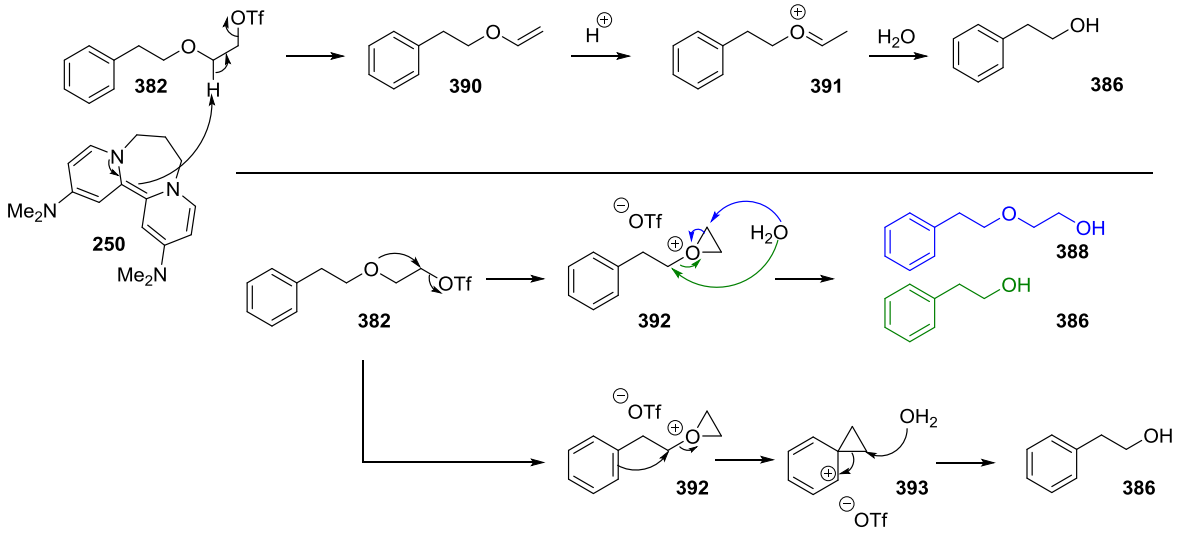
When the substrate was reacted in the presence of donor **250** none of the proposed ether **385** was seen; instead alcohol **388** (95%) and small quantities of alcohol **386** (5%) were isolated. The fact that the ether **385** is not observed seems to indicate that the donation of a second electron may be extremely rapid, before the radical can fragment to a more stable species. This relies on the supposition from the section above that the cleavage occurs by electron transfer rather than hydrolysis or some other process.

It could also be that the oxygen radical is never present in the electron transfer process; a two-electron transfer would give rise to the alkoxide **389** and sulfinate anion **359** and therefore no radical collapse would be seen. In the case of a single electron transfer occurring first, the lysis may proceed in two ways; either to give the alkoxide anion **389** and sulfinyl radical **360**, or to give the alkoxyl radical **383** and the sulfinate anion **359**. Only the latter would display any kind of radical process on the alkyl fragment.



Scheme 49. Cleavage mechanisms possible following electron transfer

The observation of alcohol **386**, may offer some insight as to what is occurring within the reaction mixture. It has been reported before[123] that donor **250** can act as a strong base and the formation of **382** may therefore proceed via elimination of the triflate to give a vinyl ether **390** which can be readily hydrolysed to the observed product, Scheme 50.



Scheme 50. Elimination mechanism for generation of alcohol

Two other possible mechanisms were also proposed to explain the unexpected outcome, based on neighbouring group effects. Firstly, the nucleophilic displacement of the triflate by the ethereal oxygen to give an oxiranium ion **392**.[172] Hydrolysis of this can then yield the two observed alcohols **388** and **386**, shown in the figure below. Secondly, the intramolecular nucleophilic substitution as above followed by an electrophilic aromatic substitution onto the carbon chain with displacement of an oxirane. Hydrolysis of the intermediate spirocyclic carbocation **393** then yields phenylethanol **386**.

Substrate **382** did not serve to offer any insight into the mechanism of cleavage of alkyl triflate esters but the evidence discussed previously serves as strong support for an electron transfer-induced S-O bond cleavage. The reductions occur in high yield under mild conditions and without requiring the use of any metal reagents.

From the results presented in this chapter it is clear that donor 250 is a powerful organic electron donor in the ground state, capable of the reductive cleavage of S-O bonds in high yield and under mind reaction conditions. The following chapters will discuss the new reactivity made possible by photoactivation.

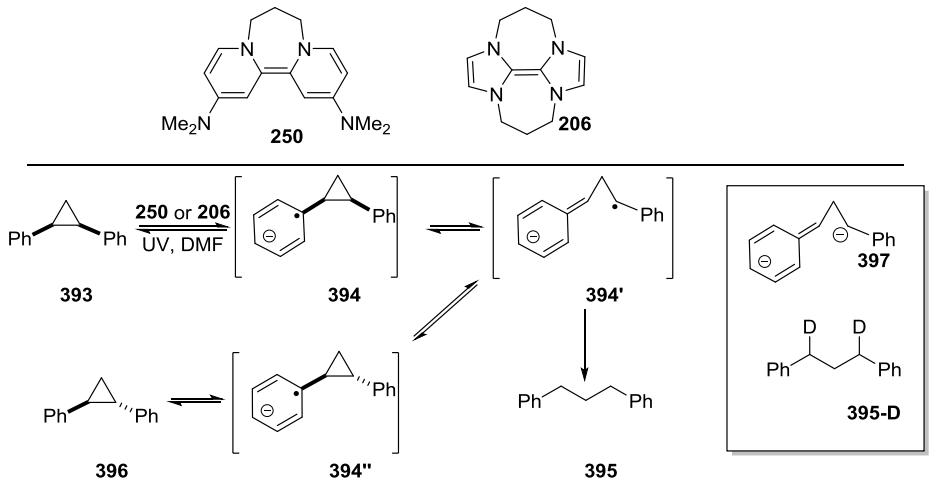
Chapter 4. C-O Bond Cleavage of Benzylic Ethers and Esters and C-C Bond Cleavage of Benzylic Malonates and Cyanoacetates

(This work has been published. See: Doni, E.; O'Sullivan, S.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2239[126] and Doni, E.; Mondal, B.; Tuttle, T.; Murphy, J. A.; O'Sullivan, S. *J. Am. Chem. Soc.* **2013**, *135*, 10934.[127] Some of the chemistry is also discussed at length in the PhD thesis of Eswararao Doni.[173] The work included in this section, unless stated otherwise, is my own).

4.1. Introduction to C-C Bond Cleavage of Benzylic Malonates and Cyanoacetates

4.1.1. Previous Results in C-C Bond Reduction

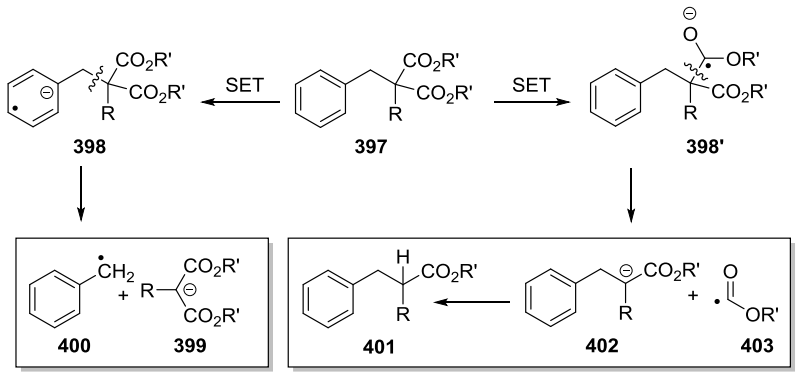
In 2012, Murphy and co-workers reported[125] the reduction of aryl cyclopropanes **393** with photoactivated neutral electron donors **206** and **250**. Such neutrally substituted arenes are almost equivalent to benzene (E^0 = -3.42 V *vs.* SCE)[174] in their ability to be reduced and therefore represent a significant challenge for electron transfer. Nevertheless, when donors **206** and **250** were excited with ultraviolet radiation (365 nm) they were able to afford in good yield, the *cis-trans* epimerized product **396** and 1,3-diarylpropane **395**. The mechanism proposed for the process is photoexcitation of the donor and electron transfer to arene **393** to yield radical anion **394**. This species can undergo radical ring opening to **394'** which in turn can recombine back to **394**, or if bond rotation occurs then recombine to **394''**. It is thought that the straight-chain product results from donation of a second electron to afford dianion **397** which is supported by isotopic labelling experiments (doubly deuterated alkane **395-D** was observed after a D_2O quench of the reaction).



Scheme 51. Reductions by photoactivated donor 250

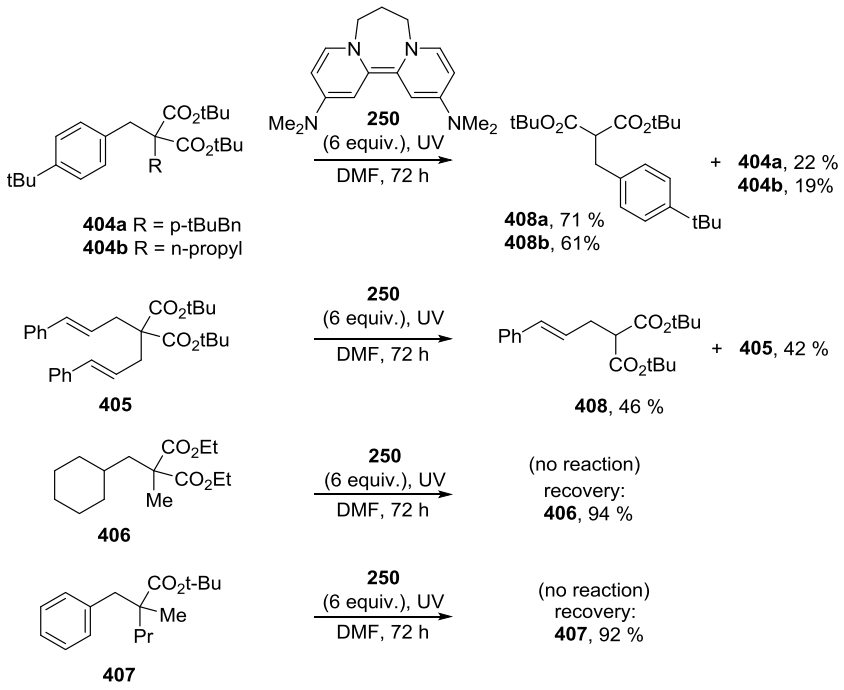
These results demonstrated the potential power of photoactivation to assist in the reduction of difficult substrates and led to the investigation of other functional groups that would previously have been out of reach. One such body of research involved C-C sigma-bond cleavage of benzyl malonates and cyanoacetates.

Eswararao Doni[173] conducted thorough investigations on the cleavage of C-C bonds of carbon acids such as malonates e.g. **397**. Two likely possibilities were considered for how the substrates may react under the conditions; knowing from the aryl cyclopropane results that unactivated arenes may be reduced, the substrate could have received an electron to become radical anion **398′** and undergone cleavage to radical and anion pair **402** and **403**; or one of the carbonyl groups could have been reduced to the ketyl radical anion **398** and a different C-C bond cleaved to anion **399** and radical **400**.



Scheme 52. Possible pathways for C-C cleavage reactions

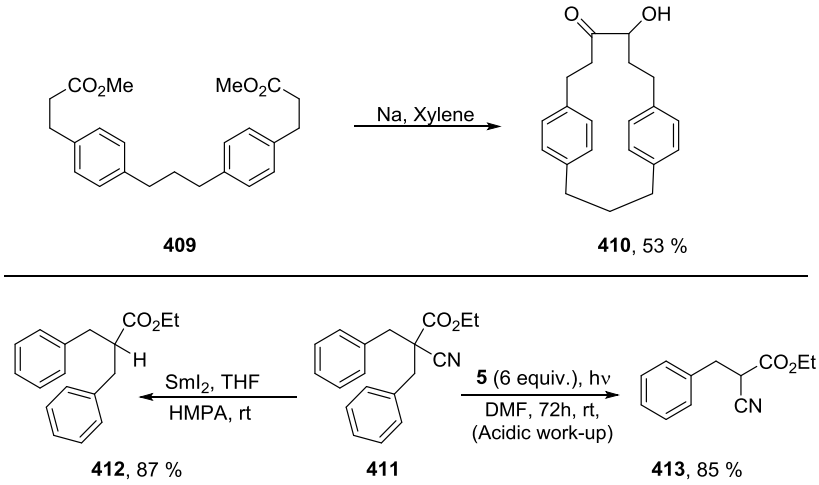
A series of substrates, **404**-**407**, Scheme 53, was tested under standard reaction conditions with donor **250** (6 equiv.), using 365 nm activation in DMF for 72 h. The results show that selective mono-debenzylation can be achieved in high yield for malonate esters. A benzyl group is not required, however, as can be seen for bis-cinnamyl substrate **405**, but conjugation to the cleaved bond *is* necessary as excellent recovery of starting material was observed for dialkyl example **406**. The recovery of substrate **407** from the reaction shows that a mono-ester is not sufficiently activated for the reductive cleavage to occur although other activating groups are discussed later. Quaternary carbons were always used in the substrates because the acidity of a proton between two esters would not be tolerated by the donor which has been shown to deprotonate acetates.[123]



Scheme 53. Reductive C-C bond cleavage

These results show that under the photoactivated neutral organic electron donor conditions used above for the reduction of aryl cyclopropanes, that substrates such as **404** undergo debenzylation rather than carbonyl reduction. This reactivity is interesting as an arene selectively reduced in the presence of a carbonyl group is complementary to some metal-based electron transfer reactions (**409** to **410**) where the opposite is seen. This was illustrated with the synthesis and reduction of substrate **411**, in comparison with a result reported by Kand *et al.* using samarium(II) iodide. The photoactivated organic donor effected benzyl C-

C bond cleavage (yielding **413**, 85%) while the lanthanide conditions cleaved the nitrile C-C sigma-bond to afford **412** in high yield.

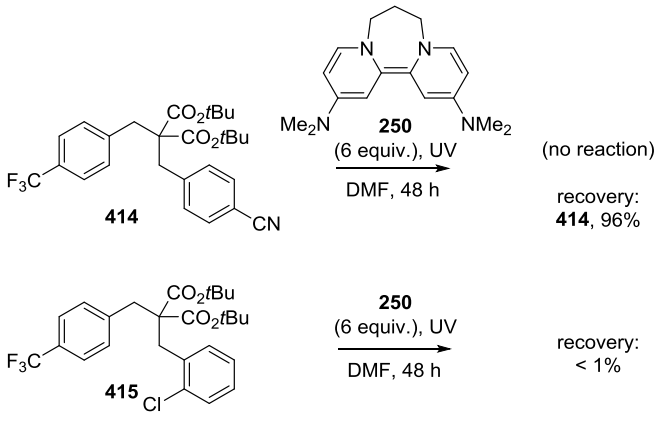


Scheme 54. Complementary metal-induced and metal-free C-C reductions

The cyanoacetate shows the same selectivity for the bond cleavage as the malonate esters and in similarly high yield. Work for this thesis involved exploring further examples of these types to probe the reactivity and gain clues to the mechanism.

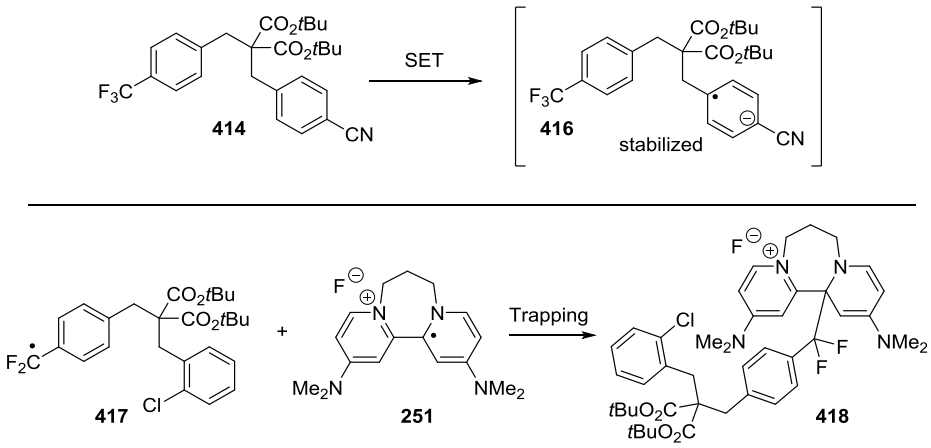
4.2. Results in Benzylic C-C Bond Cleavage

The substrates **414**-**415** shown in Scheme 55, chosen to explore a variety of substituents both electron-donating and withdrawing, proved to be informative about the nuances of the reaction mechanism.



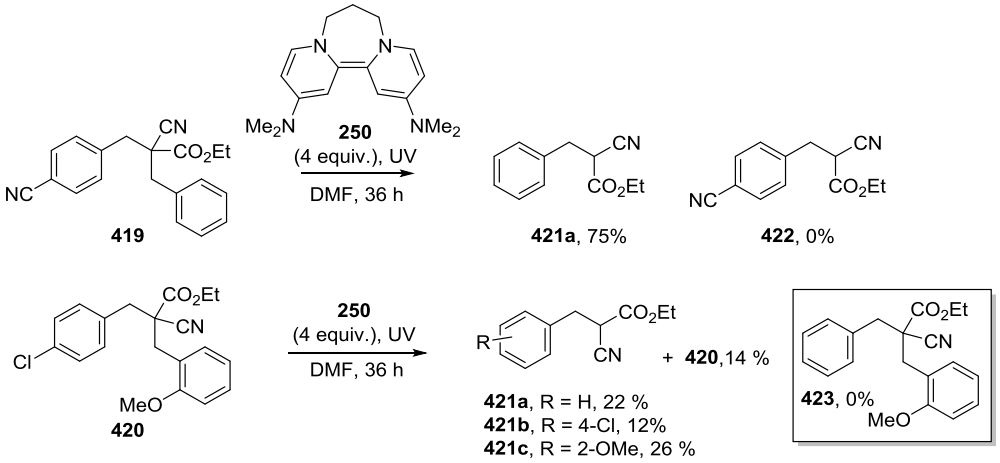
Scheme 55. Mixed benzyl malonate reductions

Focussing on substrate **415**, it can be seen that trifluoromethyl groups are not well tolerated in this reaction; the reason likely being that the fluoride substituents are in a benzyl position as are the carbon substituents to be cleaved. Perhaps unsurprisingly, the carbon-fluorine bond proves more easily cleaved and the resulting stabilized radical **417** is thought to be trapped by radical cation **251** which accounts for the poor recovery in the reaction of this substrate with donor **250**. In the case of substrate **414** this does not occur which is theorized to be due to the nitrile substituted π-system preferentially receiving the electron from donor **250**. Once the electron transfer occurs it is proposed that the resulting radical anion is too stabilized to result in the difficult carbon-carbon bond cleavage. This species is then quenched upon workup to yield the observed recovery of starting material.



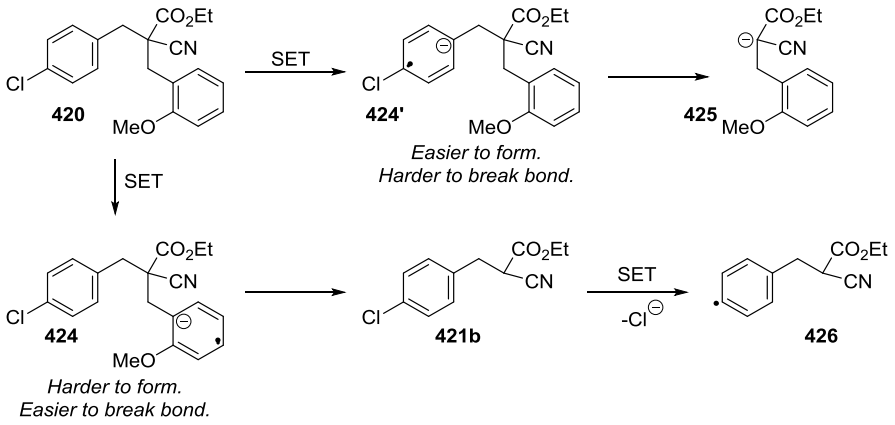
Scheme 56. Explanation of substrate reactivity

Having seen above that 4-cyanobenzyl substituted substrate **414** failed to be reduced it may be surprising that cleavage occurs in the reaction of substrate **419** with donor **250**. Complete selectivity is observed for product **421a** over **422** (which was not observed) so it is clear that the electron is being given to the electron-poor cyanoarene but in this case the cleavage is able to occur. This may be attributed to an improved leaving group ability of the cyanoacetate *vs.* a diester as indicated by a 2-3 unit pKa difference (diethyl malonate 16.4[175] in DMSO, ethyl cyanoacetate 13.1[176] in DMSO). When exploring the limits of the reducing power of donor **250** it is of interest to observe such a large reactivity difference which in a specific set of circumstances could give excellent chemoselectivity.



Scheme 57. Reductive cleavage of cyanoacetates

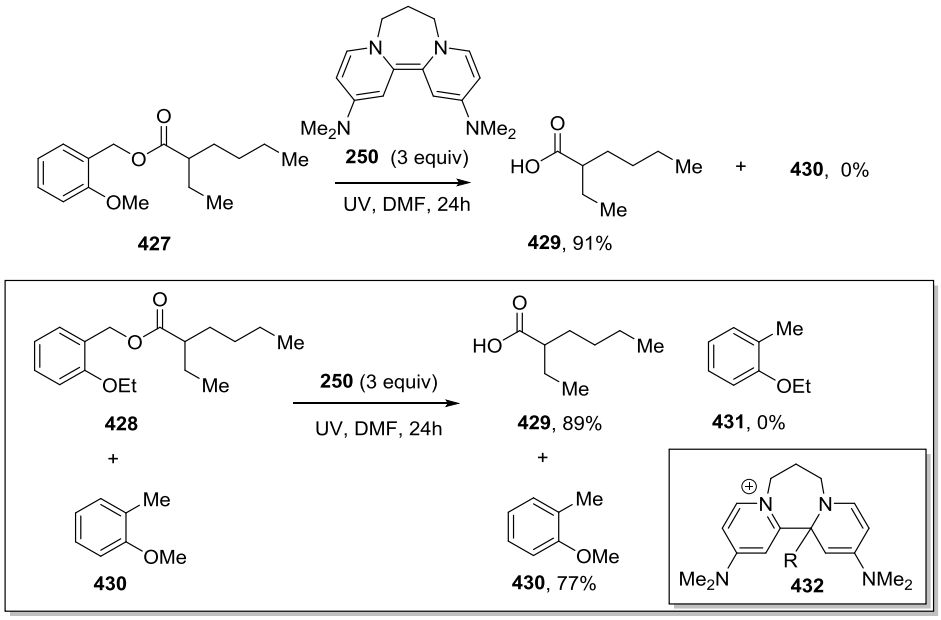
Cyanoacetate **420** is an example which shows the chemoselectivity of the reaction conditions for electron-richer arenes, albeit a minor effect. The results are somewhat masked by the competing dechlorination reaction but it is seen that products **421a** and **421b** (22 and 12% respectively) arise from methoxybenzyl C-C cleavage and that **421c** (26%) arises from reduction of the chlorobenzyl group. This is in stark contrast to reactivity seen in chapter 5 where an electron-deficient ring is preferentially cleaved by C-N bond scission in a mixed substrate. This may be attributed to a difference in rate-determining step, i.e. the electron-deficient ring will more readily accept electrons from donor **250** but the radical anion resulting will be more stabilized, slowing the cleavage while an electron-rich ring will be more reluctant to accept an electron but will more rapidly stabilize itself by reductive cleavage of a bond. This paradox leads to an overall lessening in selectivity and explains the substrate-dependent switching of preference. Because none of compound **423** was detected it can be inferred that **421a** results from the C-C bond cleavage followed by C-Cl bond cleavage, rather than *vice versa*. The combined yield then of C-C bond cleavage of the more electron-rich ring is therefore 34%, sufficiently higher than that of **421c** to be a genuine preference.

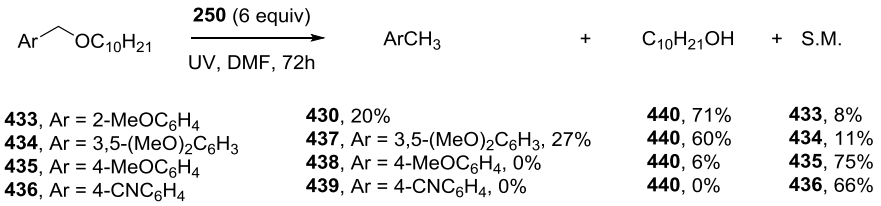


Scheme 58. Selective cleavage of benzyl groups

4.3. Introduction to Benzylic C-O Bond Cleavage of Benzylic Ethers and Esters

Having successfully reduced benzylic C-C bonds, Murphy *et al.* turned their attention to the benzylic C-O bonds of ethers and esters. Benzylic esters, e.g. **427**, could be cleaved to the corresponding acid **429** in high yield with 3 equivalents of donor **250** in 24 hour reaction times. In the absence of UV activation, excellent recovery of starting material was observed, indicating both that the excitation is necessary for the reaction and that electron tansfer is a likely mechanism for the cleavage.





433, Ar = 2-$MeOC_6H_4$
434, Ar = 3,5-$(MeO)_2C_6H_3$
435, Ar = 4-$MeOC_6H_4$
436, Ar = 4-CNC_6H_4

430, 20%
437, Ar = 3,5-$(MeO)_2C_6H_3$, 27%
438, Ar = 4-$MeOC_6H_4$, 0%
439, Ar = 4-CNC_6H_4, 0%

440, 71%
440, 60%
440, 6%
440, 0%

433, 8%
434, 11%
435, 75%
436, 66%

Scheme 59. Reduction of benzyl ethers and esters

The reductive C-O cleavage of the esters is thought to proceed via photoactivation of donor **250** followed by electron transfer to the benzyl group; σ-bond scission of the C-O bond to yield an oxygen anion and tolyl radical. Poor recovery of the aryl fragment serves as support for the intermediacy of the tolyl radical. In one reaction between ester **428** and donor **250**,

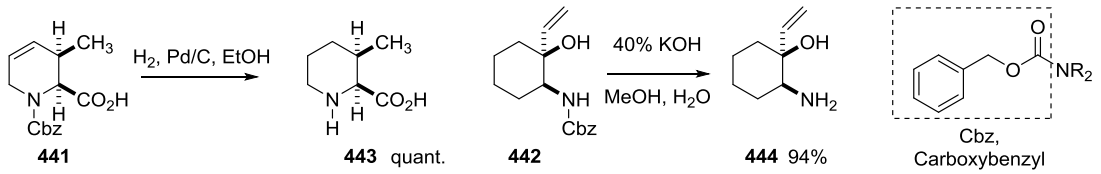
the mixture was doped with an equivalent of 2-methoxytoluene **430** as it is more volatile than and readily distinguishable from potential product 2-ethoxytoluene **431**. The result was good recovery of the dopant **430** and no observed traces of the fragment arising from the substrate **431**. This seems to be an indication that complete trapping of the intermediate benzyl radical occurs under the reaction conditions with formation of unisolated pyridinium species **432**.

Benzylic ethers **433**-**436** were also reported to cleave in good yield, although high conversion requiried six equivalents of donor **250** and 72 hours reaction time, with no product observed under milder conditions (3 equivalents, 24 h). This slower reactivity compared to their ester counterparts is attributed to the relative leaving group ability of the carboxylate over the alkoxide anion. 4-Cyanobenzyl substrate **436** showed none of the expected product **439** and good recovery of starting material indicating that a radical anion formed on an electron-deficient substrate is too stabilized to undergo bond scission. Cleavage of the ethers is thought to proceed via a two-electron transfer process to yield an alkoxide and a benzyl anion. This would account for the observation of the toluene fragment recovered in moderate yield from the reactions and highlight a difference in reactivity with the corresponding benzylic esters.

4.3.1 Carbamate Deprotection

Having reduced benzyl ethers and esters, benzyl carbamates were proposed as a target for investigation. Section 4.4 describes the novel results in carbamate cleavage after this brief introduction to more traditional carbamate removal methods.

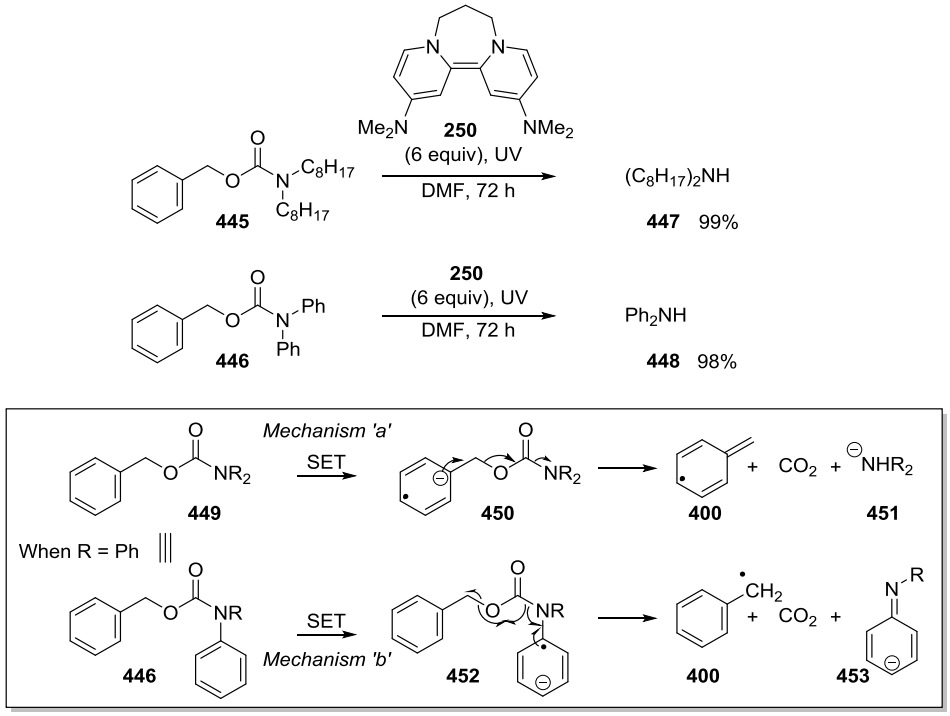
Greene's 'Protective Groups in Organic Synthesis'[177] lists nineteen methods for the deprotection of Cbz (Carboxybenzyl) protecting groups, many featuring hydrogenation with palladium on charcoal.[178] Other methods include photolysis,[179] electrolysis,[180] hydrolysis,[178] reduction under Birch conditions or with sodium borohydride. The photolysis was carried out a 254 nm and electrolysis at -2.9 V.



Scheme 60. Hydrogenation or hydrolysis for the deprotection of Cbz-amines

4.4. Results in Benzyl C-O bond Cleavage

Carboxybenzyl protecting groups, upon reaction with donor **250** under photoactivation, yield the parent amines in excellent yield. At first glance this may appear to be a C-N bond cleavage, more at home in chapter 5 but the reaction is proposed to proceed via reductive C-O bond cleavage, akin to that discussed above as is further discussed below.



Scheme 61. Carboxybenzyl group deprotection

The proposed mechanism (mechanism ‘a’ in Scheme 61) begins with photoactivation of donor **250** followed by electron transfer from donor **250*** to the benzyl group. The resulting radical anion **450** undergoes C-O bond cleavage and decarboxylation to afford a nitrogen-

centred anion **451** which is quenched by the reaction medium or upon workup. Mechanism 'b' can be proposed as an alternative when R is a phenyl group. This alternative mechanism involves electron transfer to the nitrogen-substituted arene, again to afford a radical anion **452**; decarboxylation in this case could give rise to the same products. However, a donated electron is perhaps more likely to enter the electron neutral benzyl group over the more electron-rich nitrogen-substituted arene. N, N-dialkyl substrate **445** has no π-system adjacent to the nitrogen for mechanism 'b' to occur and yet the reaction proceeds in excellent yield which is taken as support for proposed mechanism 'a'.

The quantitative yield of these reactions makes them a realistic option for deprotection of Cbz-protected amines, potentially giving different selectivity to more traditional deprotection techniques.

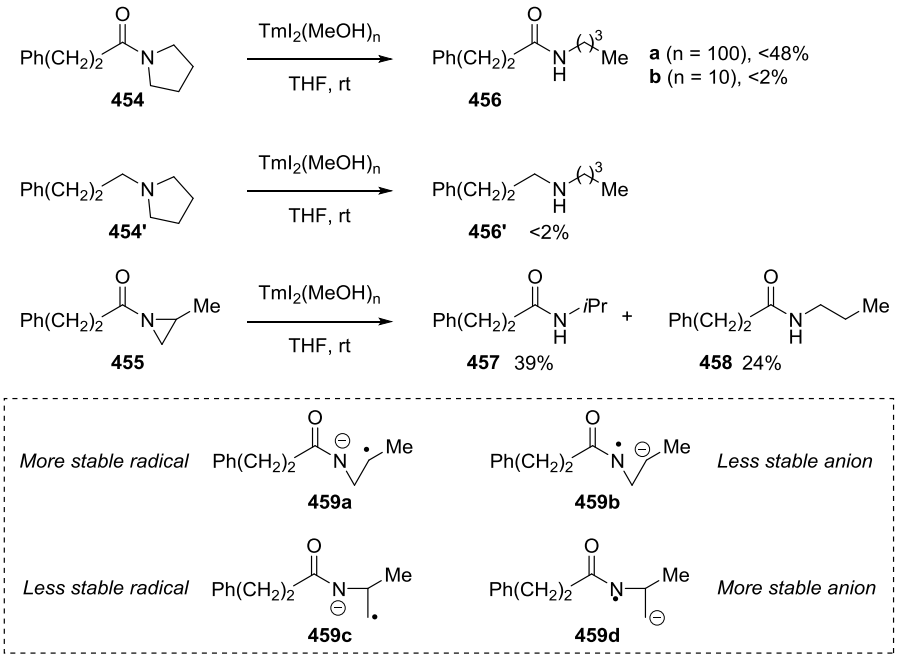
In this section, C-C and C-O bond cleavages have been shown to be effected in high yield and under metal-free reaction conditions using donor **250**. C-O bond cleavage occurs selectively in the presence of a variety of electron-rich and electron-deficient functional groups while the more difficult C-C bond scissions are less predictable but nevertheless of considerable interest.

Chapter 5. C-N Bond Cleavage of Sulfonamides and Amino Acid Analogues

(This chemistry has been published: O'Sullivan, S.; Doni, E.; Tuttle, T.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 474.[128] The majority of the chemistry in this paper is my own with some valuable additions from Dr Eswararao Doni in the N-S cleavage chemistry. Except where specifically stated otherwise the work presented within this chapter is my own.)

5.1. C-N Cleavage Literature

Reductive cleavage of C-N bonds has been explored recently by Procter *et al.*[181] using thulium iodide, another lanthanide reducing reagent and a more powerful alternative to samarium diiodide Tm^{III}/Tm^{II}: E^0 = -2.22 V *vs.* NHE compared to Sm^{III}/Sm^{II}: E^0 = -1.55 V *vs.* NHE). Under comparable reaction conditions to their samarium(II) iodide chemistry, the researchers observed the carbon-nitrogen bond cleavage of amides e.g. **454**. While samarium reagents struggled to generate traces of the product after extended reaction times, the thulium iodide was able to reduce the bond in reasonable yield within minutes. One hundred equivalents of the alcohol co-solvent/proton donor were required for significant conversion, however, with only 2% of product observed when ten equivalents were used.

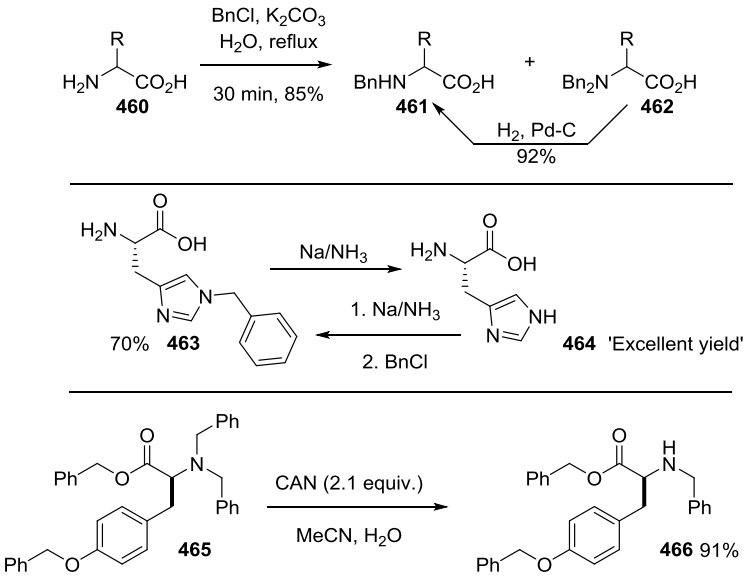


Scheme 62. Carbon-nitrogen σ-bond reduction in amides

Aziridinyl amide **455** served as a mechanistic probe, with the major product **457** arising from what would be the more stable carbanion intermediate **459d**. This leads to the conclusion that the cleavage occurs mainly via a nitrogen-centred radical and a carbanion **459d** rather than an alkyl radical and amide anion **459c**. The reactivity was selective for tertiary over secondary amides and N-methyl and N-aryl amides were not reduced under the reaction conditions. Under the same reaction conditions **454'**, the corresponding alkyl amine of **454**, showed only traces of C-N cleaved product, highlighting the importance of the carbonyl→lanthanide Lewis acid interaction and ketyl radical anion to the mechanism.

5.1.1. Debenzylation of amines

Typical conditions for deprotection of a benzylamine would be hydrogenation with palladium on charcoal or Birch reduction.[177]

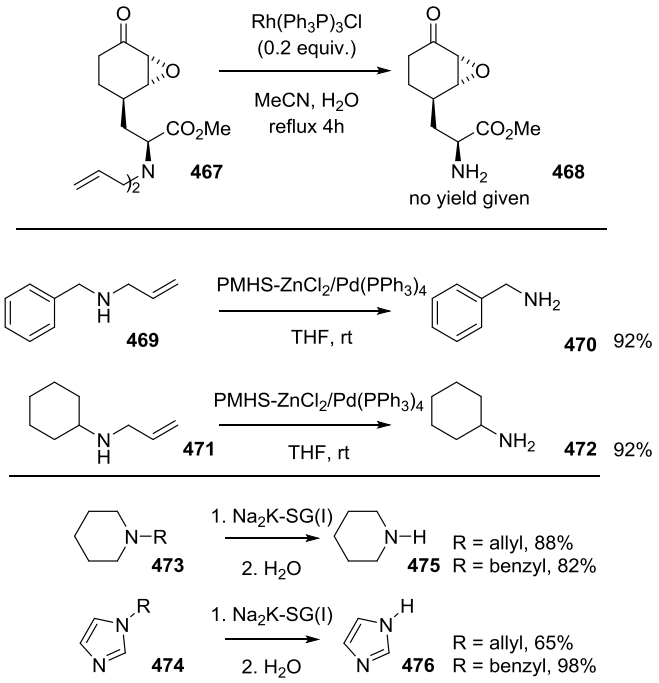


Scheme 63. Debenzylation reactions of amines

Hydrogenolysis is slow as is evident from the example where selective mono-debenzylation of **462** to afford **461** can be achieved in high yield. Interestingly, in the case of the Birch reduction the benzylated substrate **463** was prepared under Birch conditions to generate the anion followed by addition of benzyl chloride. Dissolving metal reduction then afforded the deprotected product **464** in 'excellent' yield. A very selective mono-debenzylation was reported by Smith *et al.*[182] under oxidative conditions with ceric ammonium nitrate (CAN).

5.1.2. Deallylation of Amines

Several procedures are reported for the deprotection of allyl amines.[177,183] Some representative examples are shown in Scheme 64 including a method from Gigg *et al.*[184-185] to isomerize the alkene with Wilkinson's catalyst followed by enamine hydrolysis.



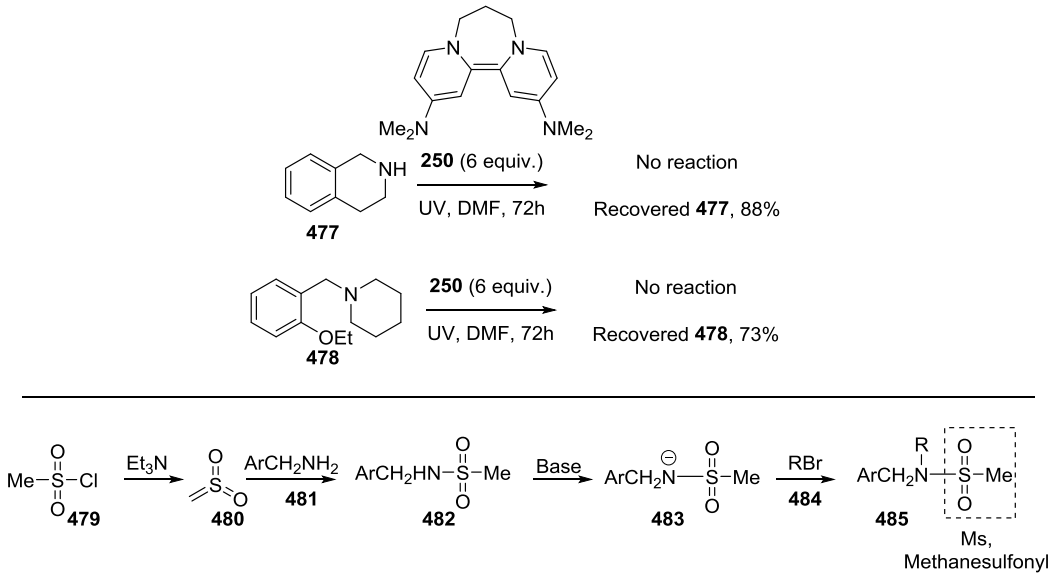
Scheme 64. N-Allyl deprotection

Rao *et al.* reported a proto-deallylation catalysed by palladium and therefore selectively cleaved allyl groups in the presence of benzyl groups (**469**) and in the absence of extended π-systems (**471**).[186] Silica-supported alkali metals were also reported by Jackson *et al.* to efficiently cleave both allyl and benzyl amines **473**-**474**, presumably by an electron transfer mechanism.[187]

5.2. Benzyl Methanesulfonamides

As an initial investigation into the reactivity of benzylamines, substrates **477** and **478** were reacted in the presence of photoactivated donor **250** for 72 hours in DMF. The result was good recovery of starting material which is to be expected; the work discussed in Chapter 3 highlighted the stark reactivity difference between benzyl ethers and esters in line with the carboxylate and alkoxide leaving-group ability. The anion of a secondary amine is a considerably poorer leaving group than either of these and as such cannot undergo the reductive cleavage under the reaction conditions. In order to explore carbon-nitrogen bond

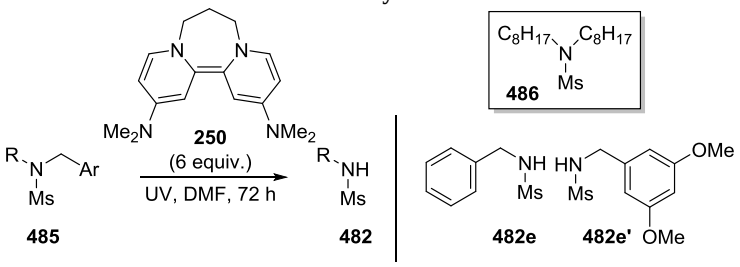
cleavage, therefore, methanesulfonamides were proposed as an alternative and their reactivity explored.



Scheme 65. Synthesis route to benzyl alkyl methanesulfonamides

Benzyl methanesulfonamide substrates **485** were generally prepared by sulfonylation of the substituted benzylamine followed by alkylation of the sulfonamide to add the second group, Scheme 65. This simple chemistry allowed the expedient synthesis of a series of electron-rich/neutral/and poor sulfonamides. These sulfonamides **485** were then investigated under standard reaction conditions: 6 equivalents of donor **250**, 0.3 mmol scale of substrate (normally around 100 mg) in 4 mL anhydrous DMF, 72 hour reaction time at room temperature, and photoactivation with two 100 W bulbs (λ_{max} = 365 nm). The reactions were set up in a nitrogen glovebox, typically at <0.1 ppm oxygen and <0.5 ppm water, and the reaction vessel carefully sealed to remain anaerobic for the duration of the reaction. The results of these experiments are shown in Table 1.

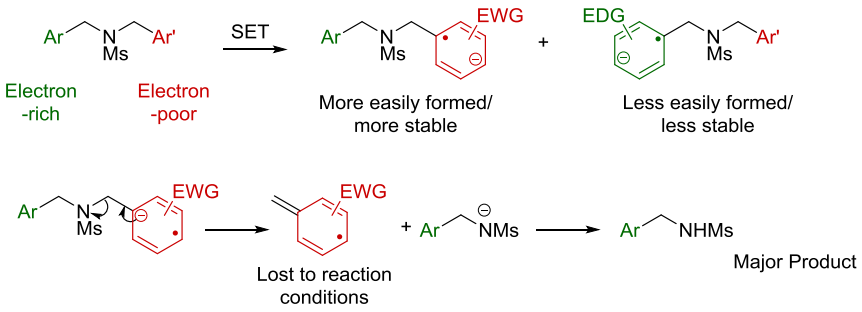
Table 1. Reduction of benzyl methanesulfonamides



Substrate[a]	R	Ar	**485** (%)	Product **482** isolated (%)
485a	$CyCH_2$	3,5-$(MeO)_2C_6H_3$	9	80
485b	*i*-pentyl	3,5-$(MeO)_2C_6H_3$	12	82
485c	*i*-butyl	3,5-$(MeO)_2C_6H_3$	0	79
485d	$C_{12}H_{25}$	3,5-$(MeO)_2C_6H_3$	21	64
485e	C_6H_5	3,5-$(MeO)_2C_6H_3$	7	35 (**482e'**) + 28(**482e**).
485f	$C_{12}H_{25}$	C_6H_5	15	80
485g	$CyCH_2$	C_6H_5	14	71
485h	*n*-butyl	4-$(CF_3)C_6H_4$	0	84
485i	Cy	4-$(CF_3)C_6H_4$	0	75

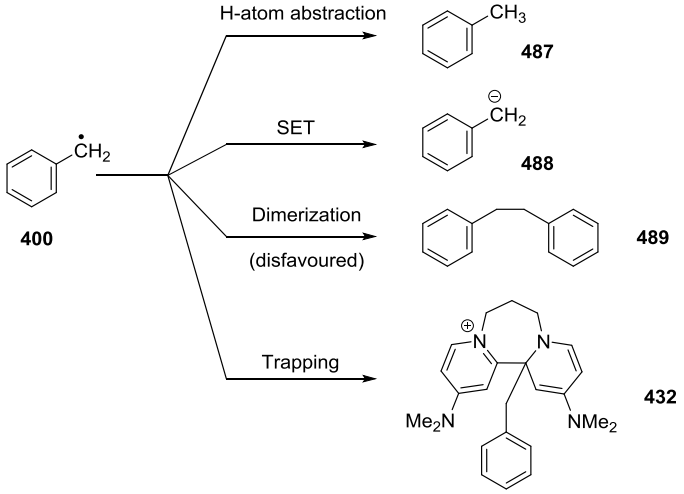
The products isolated were alkyl sulfonamides arising from C-N bond cleavage. The cleavage is proposed to occur via transfer of one electron from photoactivated donor **250*** to the arene of the benzyl sulfonamide. The resulting radical anion then undergoes bond scission to the sulfonamide anion and a tolyl radical. Upon work-up the sulfonamide anion is quenched to yield the observed product **482** while a toluene product is generally not observed.

For these cases, predictable chemoselectivity can be seen in the preferential cleavage of the more electron-deficient of two benzyl groups and in the selectivity for greater π conjugation, i.e. benzyl > allyl.



Scheme 66. Selectivity for electron-deficient arenes

Four main quenching pathways for the tolyl radical are considered: i) abstraction of a hydrogen atom from somewhere in the reaction medium to yield toluene **487**; ii) reduction with a second electron followed by quenching with a proton to yield toluene **487**; iii) dimerization with another tolyl radical to yield a diphenylethane **489**; iv) trapping of the radical with the radical cation **251**, derived from the donor.



Scheme 67. Pathways of tolyl radical loss

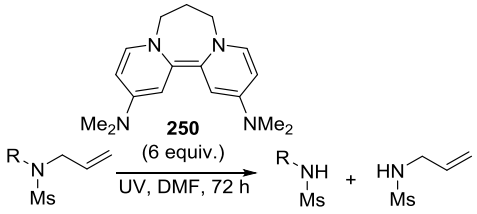
The lattermost of these options is the only one that explains disappearance of the aromatic fragment of the substrate (toluene **487** may be volatile but 3,5-dimethoxytoluene for example is less so and every care was taken to avoid loss of this product by evaporation). The

resulting alkylated cation **432** is then a water-soluble salt and likely lost to aqueous work-up; investigations into aqueous-soluble donor-derived cations are discussed in chapter 7.

5.3. Allyl Methanesulfonamide

To probe the boundaries of the carbon-nitrogen reductions a series of analogous allyl methanesulfonamides were reacted under the standard photoactivated donor conditions as used above. The result was moderate C-N cleavage to deallylate the substrates **490** and yield the corresponding N-H sulfonamide **491**. The reaction is effective with alkyl substituents and distal aromatic groups seem not to influence the reactivity greatly but substrate **490a** with benzyl and allyl substituents shows a > 6:1 preference for reduction of the benzyl group versus the allyl moiety.

Table 2. Reduction of allyl methanesulfonamides



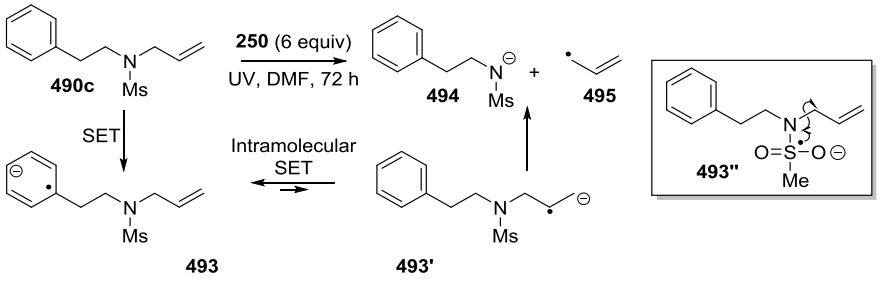
490 **491** **492**

Substrate[a]	R	Recovered **490** (%)	Product **491** isolated (%)	Product **492** isolated (%)
490a	$C_6H_5CH_2$	15	10	62
490b	$C_6H_5(CH_2)_2$	57	41	0
490c	$C_6H_5(CH_2)_3$	47	42	0
490d	$C_{12}H_{25}$	32	63	0
490e	*i*-pentyl	38	50	0

When investigating the reductive cleavage of these allyl methanesulfonamides it was interesting to observe a relative degradation in conversion when compared with the benzyl cases. The carbon-nitrogen cleavages discussed at the beginning of this chapter, using palladium-mediated conditions, show the opposite chemoselectivity, preferentially reducing allyl groups in the presence of benzyl as a result of the olefinophilic nature of palladium. This is another example, as seen in the C-C bond cleavages in Chapter 4, of organic donors allowing access to complementary reactivity to their metal counterparts and the reasons for

the observed reactivity are believed to be π-complexation between donor **250** and the arene of the substrate.

Charge-transfer complexes are a fundamental part of electron transfer chemistry; donors are inherently electron-rich and acceptors (relatively) electron-poor so interactions are inevitable. In metal-based reductive chemistry, with SmI_2 being a prime example, Lewis acid/base interactions predominate, whereas with donor **250** π-π interactions hold sway. An arene is a more extended π system than an alkene and therefore the interaction with the π-rich donor is greater. This greater interaction means the donor is brought into proximity with the acceptor more often and more strongly which favours the electron transfer to take place. It is also worth noting that upon electron transfer, the radical anion formed on the substrate will be more stabilized in the case of benzyl reduction compared with allyl, due to resonance.



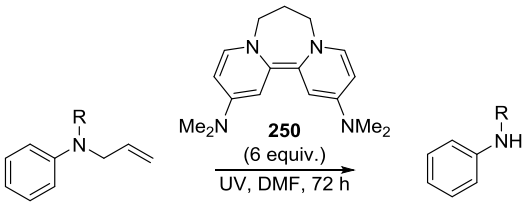
Scheme 68. Intramolecular electron transfer in allylsulfonamides

In the cases of **490b** and **c**, where an aromatic group is present but no benzyl cleavage may occur, it is considered likely that intramolecular electron transfer may be taking place. It has been observed that the electron is preferentially donated to the aromatic group in similar substrates so radical anion **493** should be readily generated under the reaction conditions. Reversible electron transfer between the aryl and allyl group may then occur and although the equilibrium no doubt lies away from the allyl radical anion **493'**, the bond cleavage is irreversible and the observed product is generated. If the intramolecular transfer leads to radical anion **493''** then C-N bond cleavage could likewise occur to yield the same products. Species **493''** should be more stable than **493'** and therefore should be present in a higher concentration but also should be less prone to undergo bond scission so it is proposed that both are intermediates leading to the generation of the isolated products.

5.4. Allyl Anilines

Having successfully carried out C-N bond cleavage of benzylic nitrogen species, attention then turned to the case where the C-N bond is simply the other way around; i.e. a substituted aniline. Typically, anilines would be expected to oxidize slowly in air and might therefore be thought of as being difficult to reduce. Indeed, Table 3 shows that examples **496a** and **b**, the most electron rich examples, show only low yields of the products of C-N bond cleavage.

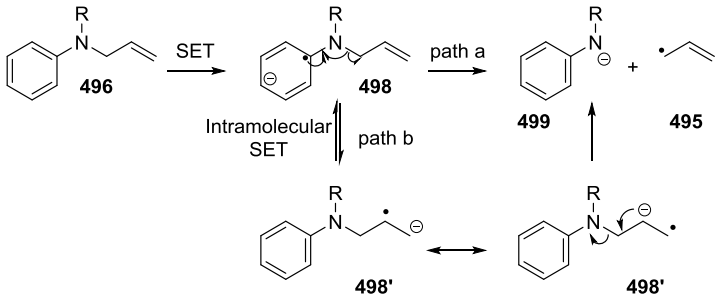
Table 3. Reduction of substituted allyl anilines



496 **497**

Substrate	R	**496** (%)	**497** (%)
496a	Me	62	6
496b	allyl	81	7
496c	COMe	59	33
496d	CO*t*Bu	8	83
496e	CO_2Et	37	58

More electron-deficient examples **496c-e** yielded higher degrees of cleavage although not as efficiently as in the benzyl examples above. As well as withdrawing electron density from the arene in the starting material, the electron-withdrawing amide and carbamate substituents also serve to stabilize the partial anion generated in the transition state and therefore favour the reaction compared to the methyl or allyl cases.



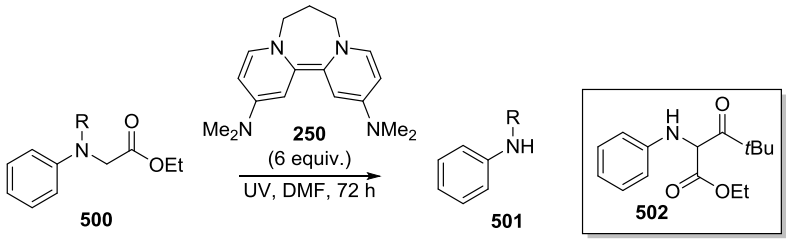
Scheme 69. Possible mechanisms of C-N bond cleavage

Proposed mechanisms for the reaction are shown in Scheme 69 above and both begin with photoactivated electron transfer to the arene **496**. Path 'a' then follows a radical bond-scission process to yield an allyl radical **495** and anilide anion **499** which is quenched upon work-up or by the reaction medium to yield the observed products. Path 'b' operates via intramolecular single electron transfer from radical anion in the ring **498** to generate radical anion **498'** which can then cleave to give the same products as above. Each of these mechanisms has its merits as species **498** should be more stable and form more readily while species **498'** should be less stable so if it does form, it should cleave more readily. An electron-rich amine substituent should render the cyclohexadienyl radical anion reactive enough to follow path 'a' and this is considered to be the favoured mechanism. In this case, no reasonable mechanism can be proposed for base-induced cleavage or for donor **250** acting as a nucleophile.

5.5. *N*-Phenyl Amino Acid Derivatives

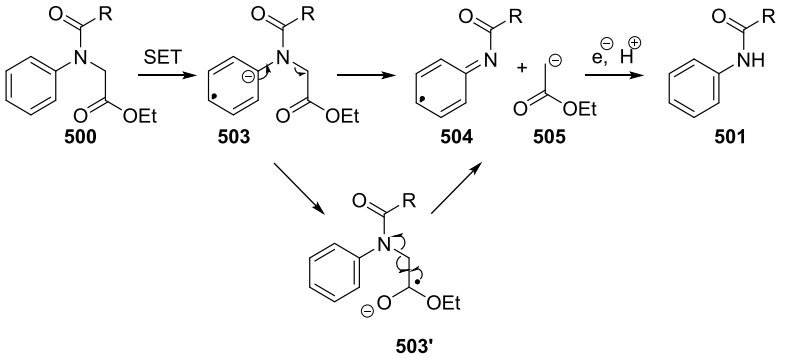
This series of 'amino acid derivatives' **500** was not, in fact, derived from amino acids for expedience of synthesis and were instead prepared by alkylation of substituted anilines. They nevertheless contain the characteristic α-amino-substituted carboxylate functionality which is so prevalent in chemistry and chemical biology. As a result of the commonality of this moiety, the exploration of their reactivity under our reductive conditions was a natural development and stood to be one of the most interesting. Table 4 shows the results of the reductive cleavage reactions under the same conditions as the C-N series above. It can be seen that the reactions proceed in moderate to high yield depending on the substituent, R.

Table 4. Reduction of *N*-phenyl amino acid derivatives



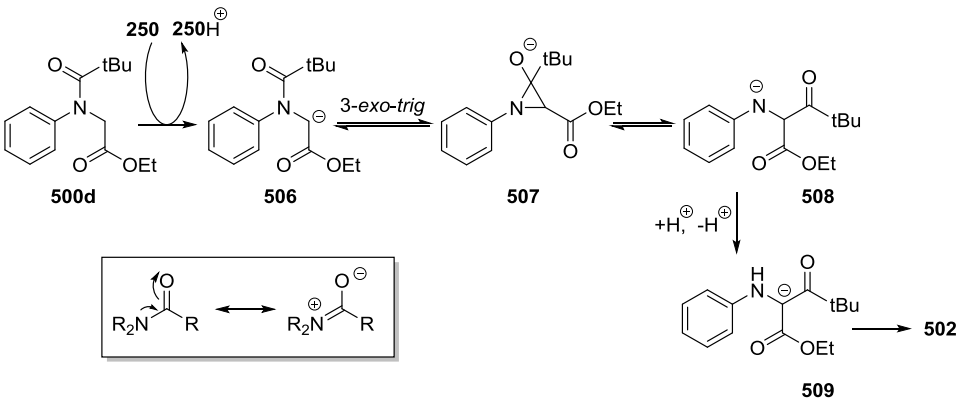
Substrate	R	Recovered **500** (%)	**501** (%)	**502** (%)
500a	Me	58	34	/
500b	COMe	25	74	/
500c	CO_2Et	0	92	/
500d	CO_2tBu	33	15	38

The reaction mechanism, Scheme 70, for this set of examples is believed to mirror that shown above for the allyl-substituted analogues. Electron transfer from the photoactivated donor into the aromatic π-system of **500** is followed by C-N bond scission to afford a nitrogen-centred radical **504** and an ethyl acetate anion **505**. Donation of a second electron affords the anilide which upon workup is quenched and can be isolated as reported. Compound **500a** is unsurprisingly the least reactive of the set: weakly electron-donating rather than electron-withdrawing, the methyl substituted example proceeds in low yield. Acetanilide **500b** shows enhanced reactivity, proceeding in good yield and carbamate **500c** is the best, cleaving in an excellent 92% yield.



Scheme 70. Mechanism for C-N bond cleavage in amino acid derivatives

The products arising from reaction of **500d** were not discussed in the publication[128] with the others as it would only have served to obfuscate the key reactions under discussion. They will be discussed here, however, for completeness and as an interesting example of an unexpected reactivity. Scheme 71 shows the proposed mechanism for the formation of **502**; deprotonation of **500d** by donor **250** is followed by 3-*exo*-*trig* cyclization and then retro-3-*exo*-*trig* to displace the anilide anion before quenching by an equivalent of starting material, or upon workup, to yield the isolated product **502**.

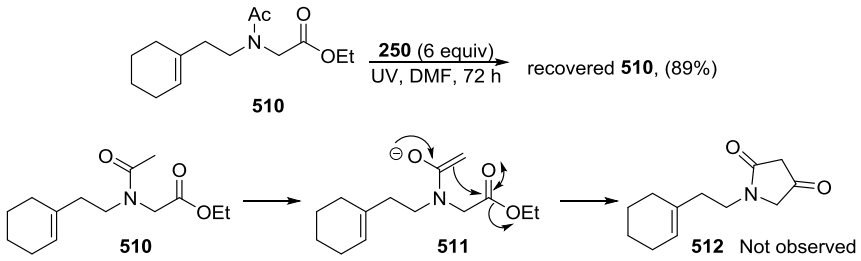


Scheme 71. Distorted pivalamide as electrophile

Normally an amide, and certainly a pivalamide, would be a poor electrophile for electronic and steric reasons; additionally a nitrogen-centred anion is a poor leaving group even when stabilized by an adjacent arene as is the case here. Nevertheless the reaction occurs so how can the observation be accounted for? Well, the poor electrophilicity of an amide is due to conjugation of the nitrogen's lone pair of electrons to the carbonyl π-system. In substrate **500d**, not only is the lone pair being partially drawn away from the amide into conjugation with the arene but the steric environment of the *tert*-butyl group and the pendant ester can lead to an out-of-plane twisting of the C-N bond of the amide which additionally decreases the electron density in the amide carbonyl group. In some cyclic examples it has been reported for twisted amides to be react more rapidly by hydrolysis than other amides,[188] in some ways like a pseudo-acyl halide, and in the case of substrate **500d** the activation is sufficient to allow an intramolecular substitution.

Formation of species **502** was confirmed to occur by a deprotonative mechanism rather than any peculiar electron transfer or post-electron transfer process by a control experiment with **500d** and sodium hydride in DMF. This afforded the same rearranged product **502** in a 76% yield.

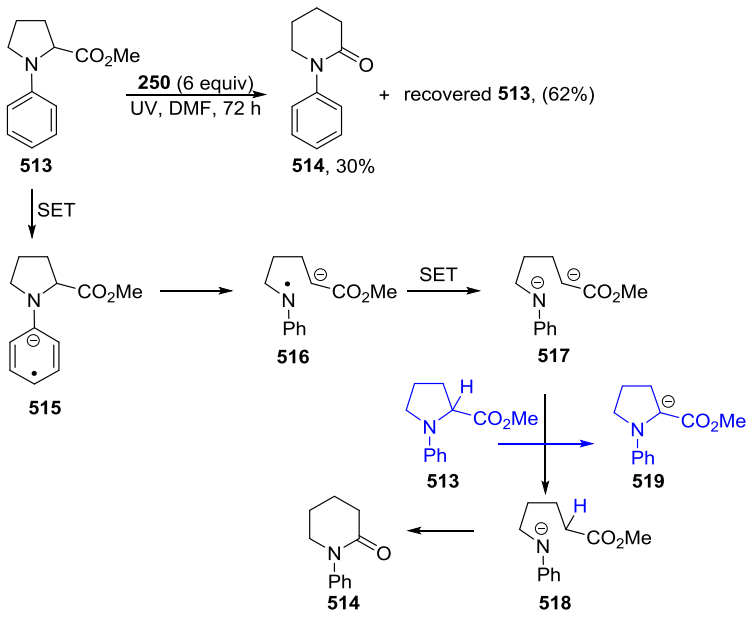
Save for this side-product, the pivalamide is thought to react via the same mechanism outlined above. Support for this mechanism comes from the reaction of alkyl acetamide **510** which is distinct from substrates **500a-d** above in its lack of an aromatic substituent on nitrogen. Evidently this proves critical, as no product of C-N bond cleavage is observed with this substrate, rather the starting material is recovered in high yield. It is curious however that no deprotonation/cyclization occurs with this substrate as might be expected. The ^{1}H NMR spectrum of substrate **510** shows evidence of slow rotation adjacent to the amide so it may be that the restriction of geometry is the reason for the absence of **512** from the reaction mixture.



Scheme 72. Unreactive alkyl amide

One of the most interesting results to come from the C-N cleavage work is the conversion of **513** to **514**. The reductive cleavage of a proline derivative gives rise to a nitrogen-centred anion **516** which is able to perform a 6-*exo*-*trig* cyclization onto the pendant methyl ester to give the ring-expanded piperidone **514**. This is an interesting and potentially very useful transformation but in this case the yield was limited by deprotonation, i.e. for the cyclization to occur the enolate anion must be quenched and the most acidic proton in the reaction mixture is the α-proton of the starting material **513**. Deprotonation of the starting material increases the electron density of the system making it too difficult for the photoactivated donor **250*** to reduce. This shuts down the reactivity after 30% conversion. Adding an

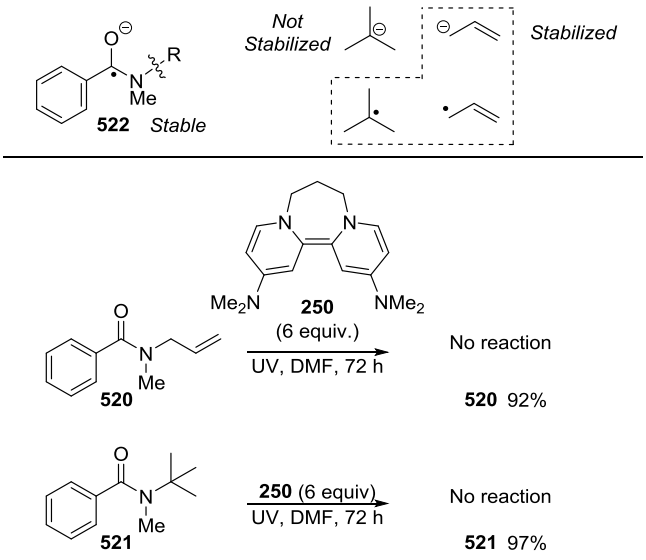
alternative proton source to shut down this pathway may be possible but it is difficult to find a proton source tolerated by donor **250**.



Scheme 73. An electron transfer-induced cyclization

5.6. Further C-N reactivity probes

To further test the established reactivity outlined in the sections above, benzamide compounds **520** and **521** were synthesized. The amide C-N bond is in a pseudo-benzylic position and the carbonyl moiety should help to extend the conjugation out onto the cleavable bond. Unlike the benzyl examples above, the bond proposed most likely to break would be the C-N σ-bond on the substituent rather than the amide, more similar to the Weinreb amide reductions reported in section 1.5.9. For ketyl radical anion **522**, the R fragment will be stable to cleave as a radical when R = allyl or *tert*-butyl but cleave as a stabilized carbanion only when R = allyl, Scheme 74. In this way any reactivity difference between **520** and **521** should provide clues towards the mode of cleavage.



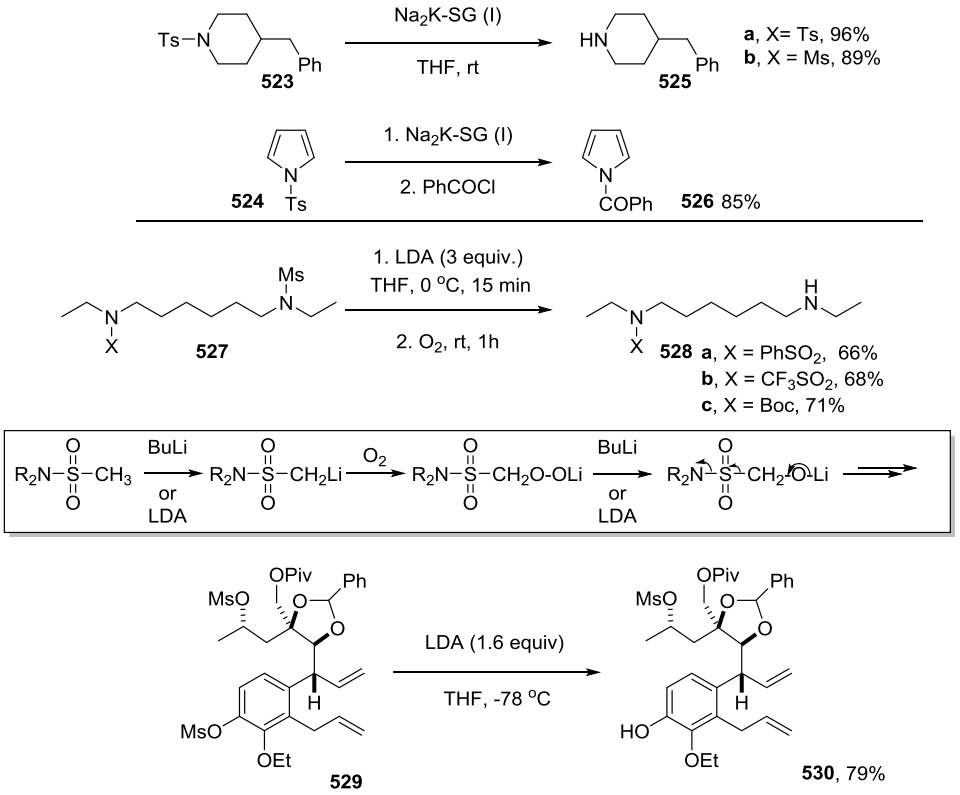
Scheme 74. Benzamide substrates

Testing the two substrates **520** and **521** under the standard photoactivated conditions with donor **250** showed only recovery of stating material in high yield. This could be an indication that the radical anion that forms from electron transfer to the substrate is too stabilized by the electron-withdrawing group. Alternatively, an argument could be made for the bulky substituents affecting the substrates ability to form a π-stacking interaction with the donor and therefore limiting the reactivity.

5.7. N-S Cleavage of Methanesulfonamides

5.7.1. Existing Examples of Methanesulfonamide Deprotection

Classical deprotection of a methanesulfonamide requires dissolving metal (Na, *t*-BuOH, HMPA, NH_3) reduction[189] or lithium aluminium hydride.[177] More recent procedures have been reported using either alkali metals adsorbed onto silica,[190] or strong bases such as BuLi or LDA.[191]



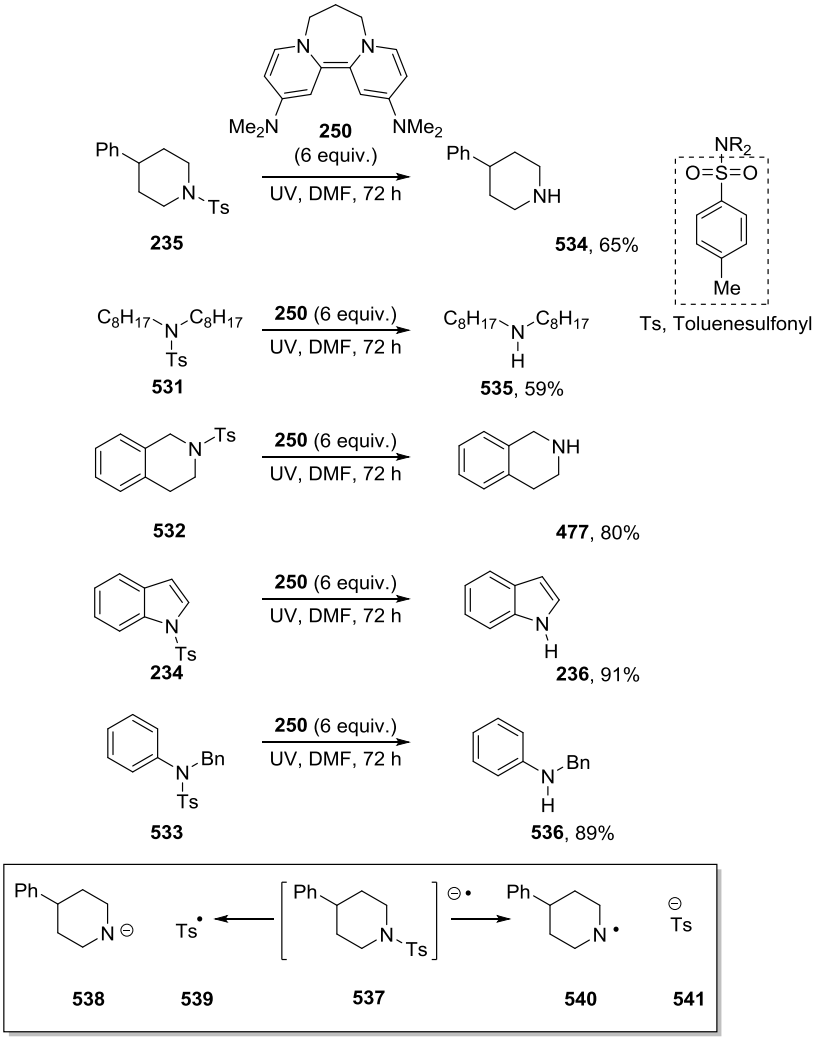
Scheme 75. Existing procedures for methanesulfonamide cleavage

Similar conditions were utilized by Carreira *et al.*[192] for the sulfur-oxygen σ-bond cleavage of mesylates, e.g. **529**, although this deprotection occurs by a simple deprotonative mechanism rather than the oxidative process believed to occur with sulfonamide **527**. Under the reaction conditions selectivity was seen for a phenolic ester over the aliphatic mesylate which is potentially very synthetically useful.

5.7.2. Toluenesulfonamide Deprotection

Recently Doni *et al.* utilized the photoactivation of donor **250** to achieve the reductive N-S bond cleavage of unactivated toluenesulfonamides.[128] Previous results had shown that under thermal conditions, aryl toluenesulfonamides could be deprotected in good yield although with extended reaction times. The same examples, **234** and **533**, carried out under photoexcited reduction conditions now cleave in high yield in just a few hours and, with

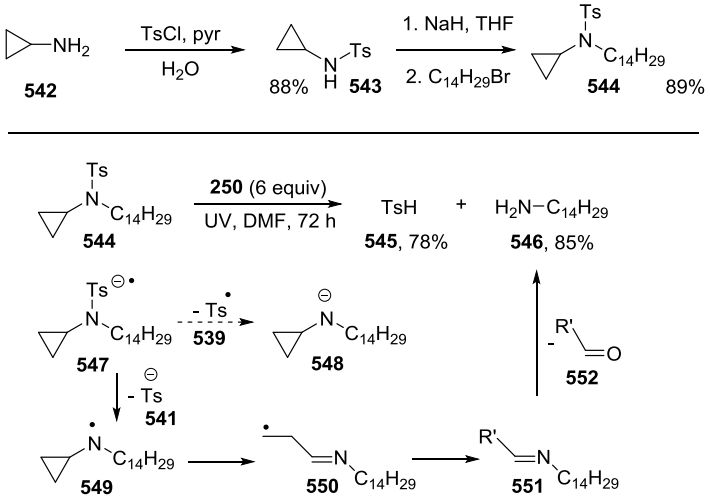
longer reaction times (3 days), dialkyl toluenesulfonamides **235** and **531**-**532** were reduced in excellent conversion and high isolated yield.



Scheme 76. Reductive N-S bond cleavage of tosylamides (E. Doni)

As part of the completion of the chemistry for this thesis, another substrate, **544**, was synthesized in addition to the above examples which would give an indication of the mechanism of the reaction. From the above example it was already clear that electron transfer to the toluenesulfonyl group was occurring, followed by cleavage of the radical anion **537** to give a radical and anion pair **538** + **539** or **540** + **541**. As ever, it was not so clear which fragment departed with one electron and which with two. Computational predictions had indicated that a nitrogen-centred radical **540** and sulfinate anion **541** would be more stable than the alternative and that the barrier for formation should also be more

feasible. The results of the reductive cleavage of **544** would come to agree with this prediction, *vide infra*.

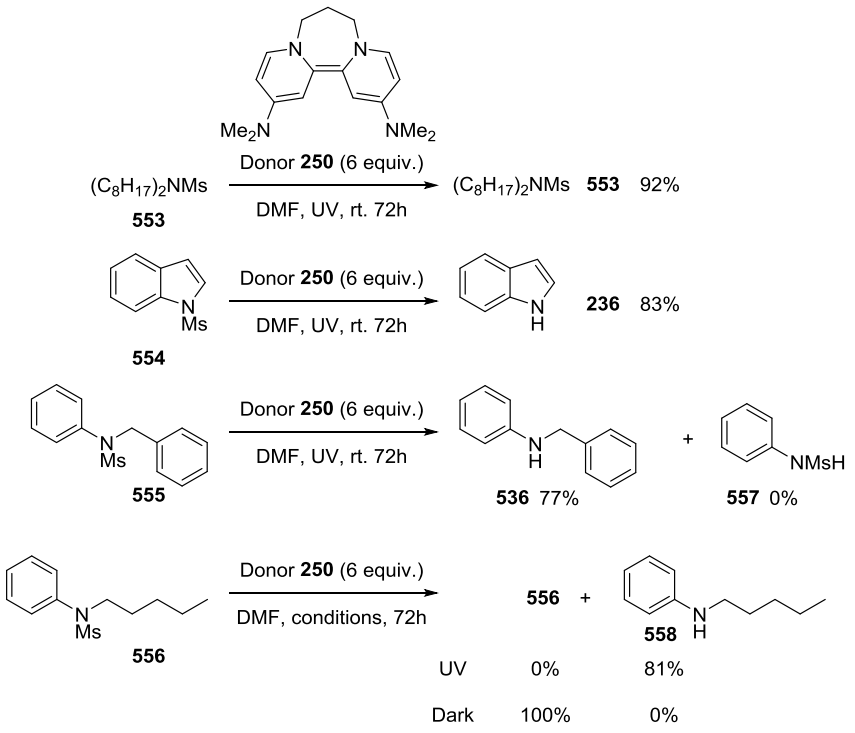


Scheme 77. Cyclopropyl mechanism probe

As can be seen, the product of the reaction of **544** with DMAP-derived donor under photoactivated conditions is that of ring-opening followed by hydrolysis. This ring-opening is taken to be an indication of a nitrogen-centred radical **549** after the bond scission process which clarifies two mechanistic aspects; i) the reaction proceeds via a one-electron reduction and ii) the N-S bond cleaves selectively in a particular way to generate a sulfinate anion **541** and aminyl radical **549**.

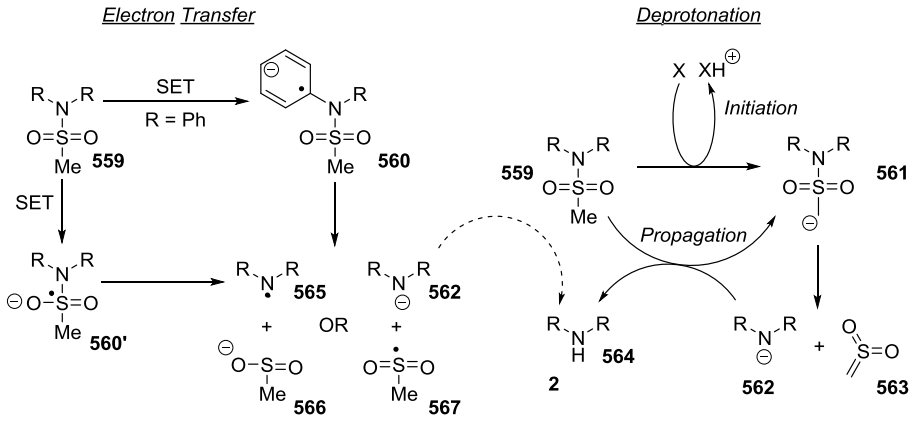
5.7.3. Methanesulfonamide N-S Cleavage Results

During the investigation of carbon-nitrogen bond cleavage above, certain methanesulfonamide substrates demonstrated complete chemoselectivity for a different reductive bond scission. Under the same reaction conditions, reductive nitrogen-sulfur σ-bond cleavage was observed in high yield. Previously in the cases of toluenesulfonamides it had been observed that tosylamides of aryl-substituted amines were cleaved more readily than alkyl-substituted counterparts. The same proved to be true of methanesulfonamides as demonstrated below in Scheme 78.



Scheme 78. Reduction of Methanesulfonamides- An alternative cleavage

Dioctylmethanesulfonamide **553** was recovered in high yield from reaction with donor **250** under the standard photoactivated conditions but reaction of more activated examples **554-556** yielded good conversion to the N-S cleaved products. Benzyl-substituted example **555** showed complete selectivity for nitrogen-sulfur cleavage (product **536**) over the normally observed carbon-nitrogen (product **557**) which is worthy of note.



Scheme 79. Mechanism of methanesulfonamide cleavage

Considering the result that no cleavage occurs with dialkyl example **553**, there are two likely possibilities; i) that electron transfer cannot occur as there is no π-system with a sufficiently low energy to receive an electron from the donor, ii) electron transfer can occur to the sulfonyl moiety but the unstabilised dialkyl amide is too poor a leaving group for bond cleavage to occur.

Mechanistically it is not necessarily clear if the reaction proceeds via electron transfer; deprotonation of the methyl substituent followed by elimination would yield the same product. The strength of **250** as a base is not entirely known but if it were able to deprotonate just a small fraction of the substrate **559** then the product of the cleavage **562** would also be a strong base and could propagate the deprotection. By the same argument, if electron transfer were able to convert a small amount of sulfonamide **559** to anion **562** then this would serve to initiate the process. The extended reaction times could then account for the reaction proceeding in high yield despite low concentrations of the anion **562**.

The observation that the control reaction of **556** in the absence of photoactivation afforded excellent recovery of starting material while the photoexcited reaction proceeded in good yield, would imply that electron transfer is a critical part of the process and that the excitation of the donor **250** is necessary for the reduction to occur. The proposed electron transfer mechanism is shown in Scheme 79 and begins with reduction of an arene to its radical anion. Bond scission then occurs to give an anion and radical pair which may undergo further reduction to two anions but are quenched upon workup to yield the observed amine product **564**.

A computational analysis (carried out with the assistance of Greg Anderson) of the possible cleavage processes of substrate **555** was carried out and proved to be illuminating, Figure 6. Radical and anion 'pair B' was calculated to be 23.8 $kcalmol^{-1}$ more stable than the combined energy of 'pair A'. Attempts to optimize a structure for radical anion **560** as a transition state or intermediate led to spontaneous bond cleavage, indicating that the N-S scission was barrierless and should occur in a concerted fashion towards the more stable products.

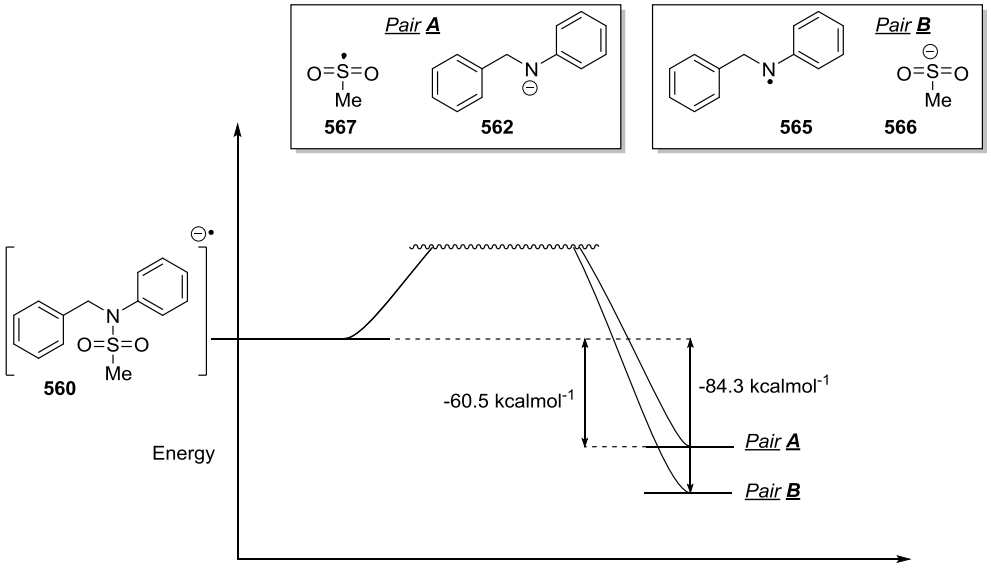
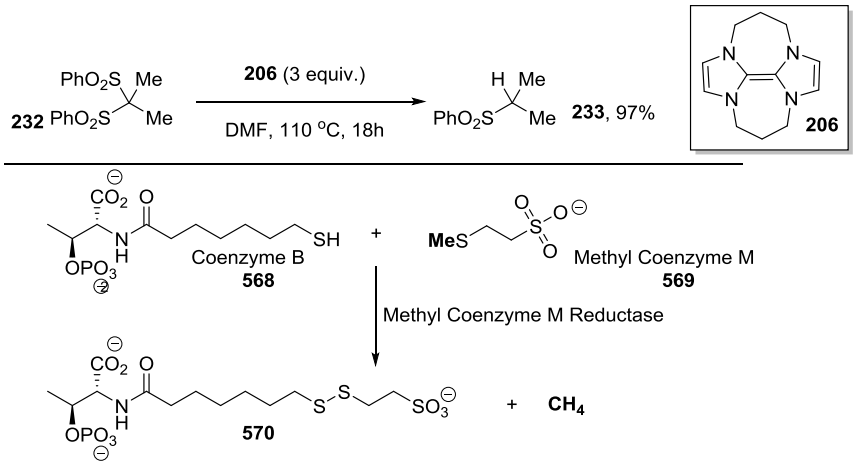


Figure 6. Computational results, (DFT, B3LYP, 6-311G(d,p), CPCM DMF)

In this chapter, an array of nitrogen-containing substrates has been shown to be reducible using donor **250** under mild reaction conditions. An electron transfer mechanism has been proposed and is supported by the experimental observations and computational predictions. Adjacent π systems play a key role in the reactivity and selectivity between C-N and N-S bond scission may be achieved by careful substrate. In addition to several examples of reductive cleavage, an avenue has been opened into a useful bond-forming reaction.

Chapter 6. Reductive Cleavage of S-Methyl and S-Alkyl Bonds

Having effected carbon-oxygen, carbon-carbon and carbon-nitrogen bond scissions by reductive electron transfer, the next logical avenue of research was the cleavage of carbon-sulfur bonds. The C-S σ-bond cleavage of activated sulfones had previously been shown to proceed in high yield with donor **206** and **250** (Sections 1.5.6 and 1.5.9 respectively) under thermally activated reaction conditions but the additional reactivity allowed by photoexcitation of the donor was expected to lead to the cleavage of less easily reduced species.

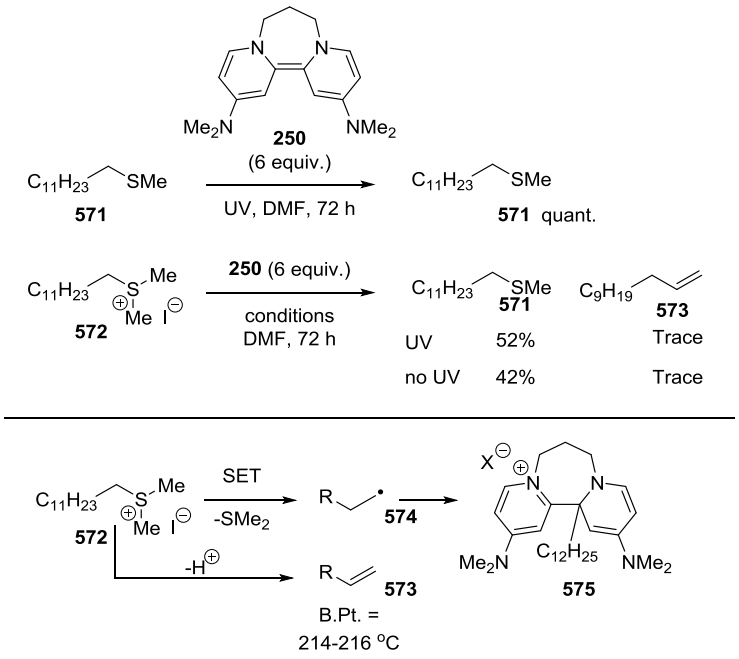


Scheme 80. Recap of carbon-sulfur cleavage

It was also discussed in section 1.4.1, that nature was able to carry out carbon-sulfur bond cleavage by electron transfer to yield methane in the final stage of methanogenesis. In synthetic chemistry, Beak and Sullivan reported the one-electron reduction of sulfonium salts to the corresponding sulfide using potassium in THF,[193] while diaryl sulfides could be cleaved in high yield with sodium and tetraphenylethylene[194] or under Birch-type reaction conditions.[195]

6.1. C-S Bond Cleavage

Normally a useful indicator as to whether the mechanism of a reaction with donor **250** is occurring via electron transfer is if the reduction proceeds with the added activation of photoexcitation and does not proceed under ground state conditions (as a nucleophile-electrophile or acid-base reaction will not be promoted by photochemistry). In the case of the alkyl sulfonium species **572**, however, the reaction occurs in both cases which could mean that the reaction is occurring via electron transfer but is easy enough not to require photoactivation, or that the reaction proceeds via another mechanism e.g. alkylation of the pyridinylidene nucleophile. Traces of a terminal alkene were detected in the crude reaction mixture are believed to be dodecene **573** which would result from elimination of dimethyl sulfide. As donor **250** is a bulky nucleophile, and DMF a polar solvent, the deprotonation may be expected to be faster than nucleophilic substitution which may act as evidence in favour of an electron transfer mechanism.

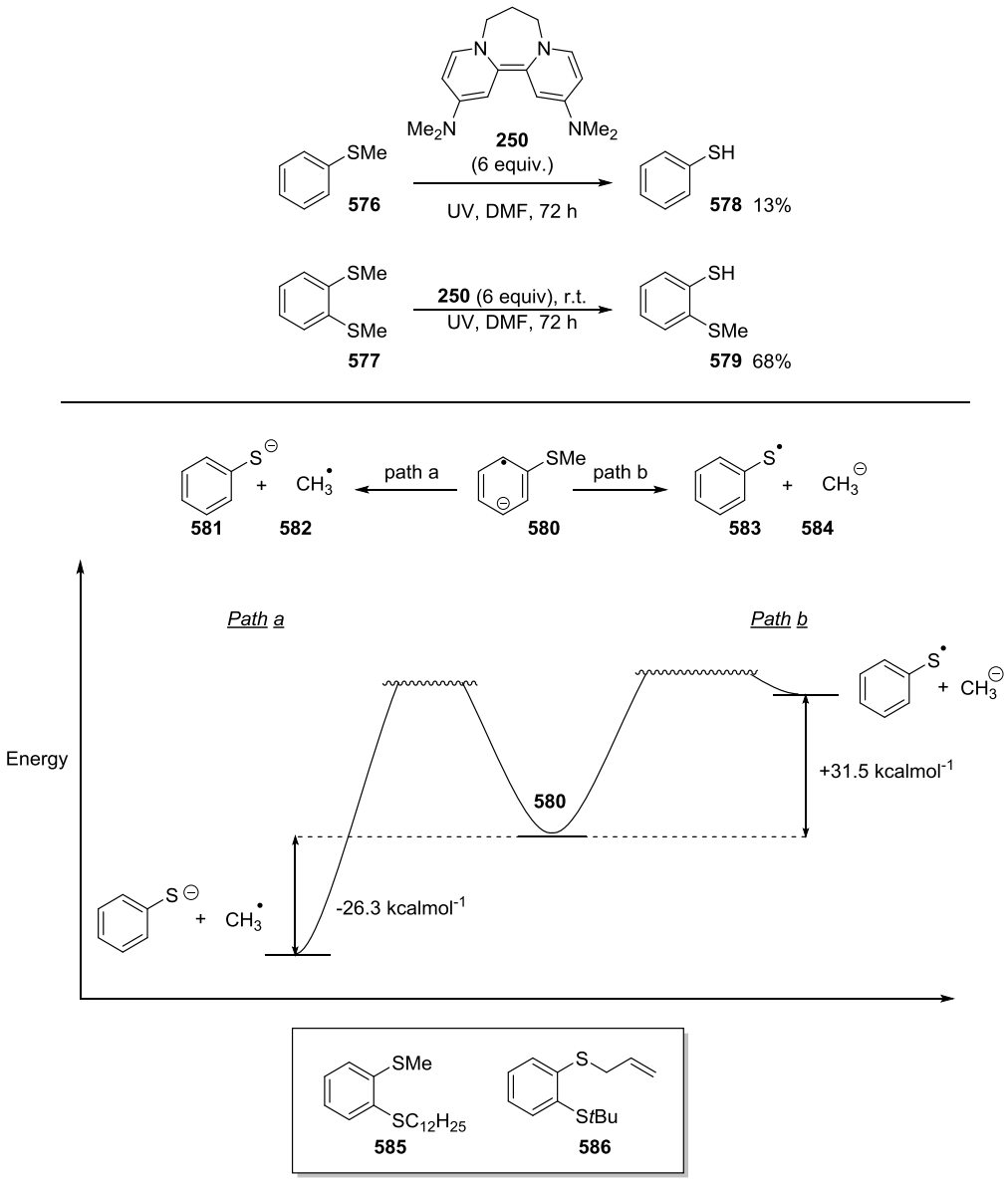


Scheme 81. Alkyl sulfides and sulfonium salts

The poor mass recovery from these reactions raises further questions, however. Speculation may be made into mechanisms that can account for loss of mass which include elimination followed by evaporation of volatile products and cleavage followed by radical trapping. The boiling point of the alkene **573** is 214-216 ^{o}C so such a large loss would not be expected,

even for such a non-polar species. As will be discussed in the chapter below, isolation of trapped radical species proves difficult so no traces of **575** were observed.

Unactivated substrate, dodecyl methyl sulfide **571** was tested under the same reaction conditions and the result was high recovery of the starting material. By comparison, thioanisole **576**, Scheme 82, was reduced in good yield to afford thiophenol **578** under the photoactivated reaction conditions with six equivalents of donor **250**. Generally ether-disubstituted arenes are more readily reduced than their mono-substituted counterparts as discussed in section 1.2, and for the same reasons, bis-sulfide **577** is reduced to the mono-deprotected product in a higher yield. These substrates are remarkable as they represent the least activated leaving groups that have been reduced by donor **250**. These cleavages are proposed to proceed via single electron transfer from photoexcited donor **250*** to the arene to yield radical anion **580**. This anion then undergoes carbon-sulfur bond cleavage to give either the thiolate anion **581** and methyl radical **582** or the thiyl radical **583** and methyl anion **584**. Comparison of a mixed methyl, alkyl bis-sulfide e.g. **585** should give some clue as to which mechanism is followed as could a substrate such as **586**. Unfortunately, time constraints meant that these experiments do not make up part of this body of work but density functional calculations offered some insight into which path may be favoured. The calculations showed products 'a' to be extremely energetically favoured (-58.32 $kcalmol^{-1}$) compared with the products of path 'b' and that products 'b' would be 31.5 $kcalmol^{-1}$ energetically uphill of the radical cation **580**. These results indicate that path 'a', giving rise to thiolate **581** and radical **582** is the more likely reaction mechanism followed.

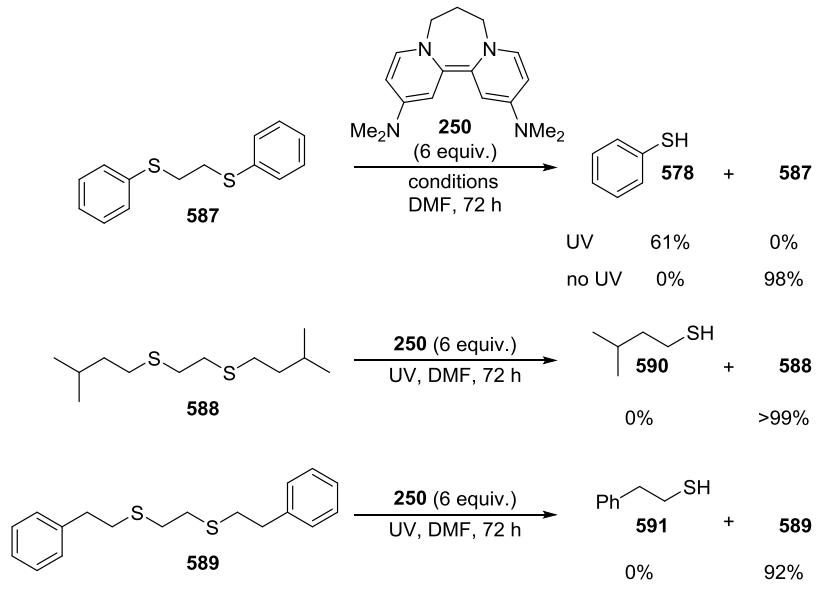


Scheme 82. S-Methyl cleavage

Indications from the more recent work of Jonathan Chua are that the anion resides on the sulfur and the radical on carbon as shown by an example where quenching with benzyl bromide afforded quantitative yield of phenyl benzyl sulfide while no extended alkane was observed.

6.2. Disulfur substrates

The S-C-C-S moiety is present in methyl coenzyme M **569** (albeit with a mixed oxidation state) in which a terminal methyl group is reductively transferred. To explore the reactivity of such a system in the presence of a neutral organic electron donor, probes into the reactivity of substrates bearing the S-C-C-S moiety were carried out (Scheme 83).



Scheme 83. S-C-C-S substrates

Having observed that reductive C-S σ-bond cleavage occurs for bis-sulfide **587** under photoactivated conditions but not in the ground state, an electron transfer mechanism is supported. Experiments with substrate **588** showed that reductive cleavage cannot be carried out on such an unactivated substrate so substrate **589** was synthesized to determine whether a distal π system would be sufficient to allow delivery of an electron to the sulfur-containing side chain. Good recovery of the starting material **589** even under photoactivated conditions make it apparent that conjugation to the π-system is important for the reductive cleavage to occur. The combination of these observations leads to the proposed mechanism: an electron is transferred for photoexcited donor **250** to aryl sulfide **587**. The radical anion then undergoes C-S bond scission and elimination to yield ethene, benzenethiolate and a benzenethiyl radical. Some trapping of this radical may occur which will account for the lower mass balance of the reaction but some must either abstract a hydrogen atom or receive

a second electron to yield a second thiolate as the yield is higher than 50% based on the expectation of two equivalents of thiol **578**.

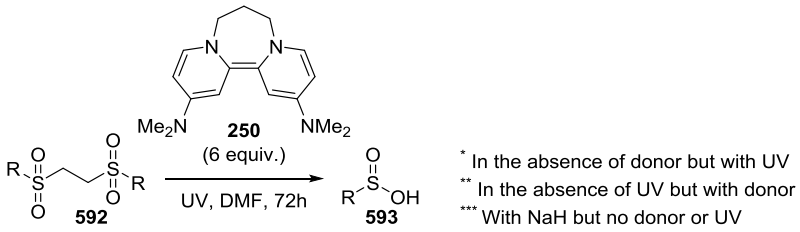
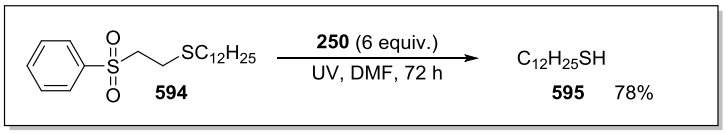
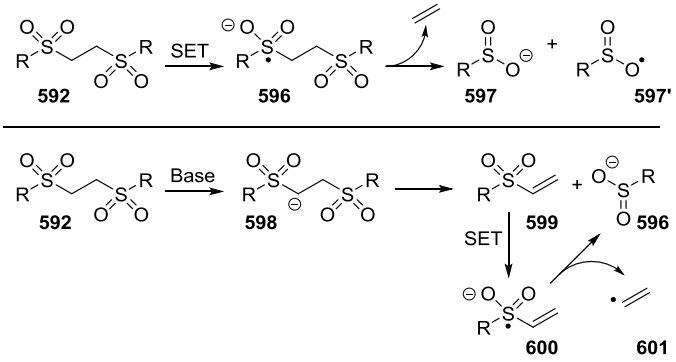


Table 5. Bis-sulfone cleavage

Compound	R	**593** (%)	Recovered **592** (%)
592a	Ph	64	
592a*	Ph		77
592b	$Ph(CH_2)_3$	41	
592b* **	$Ph(CH_2)_3$	82	
592c	isopentyl	35	
592c **	isopentyl	38	



An investigation of systems more similar to the mixed oxidation state of methyl coenzyme M was also proposed and substrates **592a-c** and **594** were synthesized. Investigation of these substrates under photoactivated conditions displayed similar reactivity to the examples above, giving rise to the corresponding sulfinic acids **593a-c** or thiol **595**. No reactivity difference was observed when the reactions were carried out in the absence of photoactivation meaning that an electron transfer mechanism was not apparent.



Scheme 84. Sulfone cleavage mechanisms

A base-induced elimination could be considered as quite likely for a sulfone derivative even given the relative crowding around the central protons and the bulk of donor **250**. The successful reaction of isopentyl substituted species **592c** may seem to indicate that electron transfer is not occurring because the corresponding sulfide **588** was not cleaved under electron transfer conditions but the two are not comparable as the sulfone is a more easily reduced moiety and therefore may not require the pendant arene to activate it. Observing fine differences in yield to glean further information from the examples was complicated by the inherent instability of sulfinic acids and their tendency to decompose and disproportionate.[196] Jonathan Chua, who collaborated on similar chemistry with different substrates, went on to use benzyl bromide as a trap for thiolate ions (the technique previously applied to isolate the products of the sulfur-oxygen bond cleavage of triflates, Chapter 2) to isolate sulfides and sulfones in high yield.

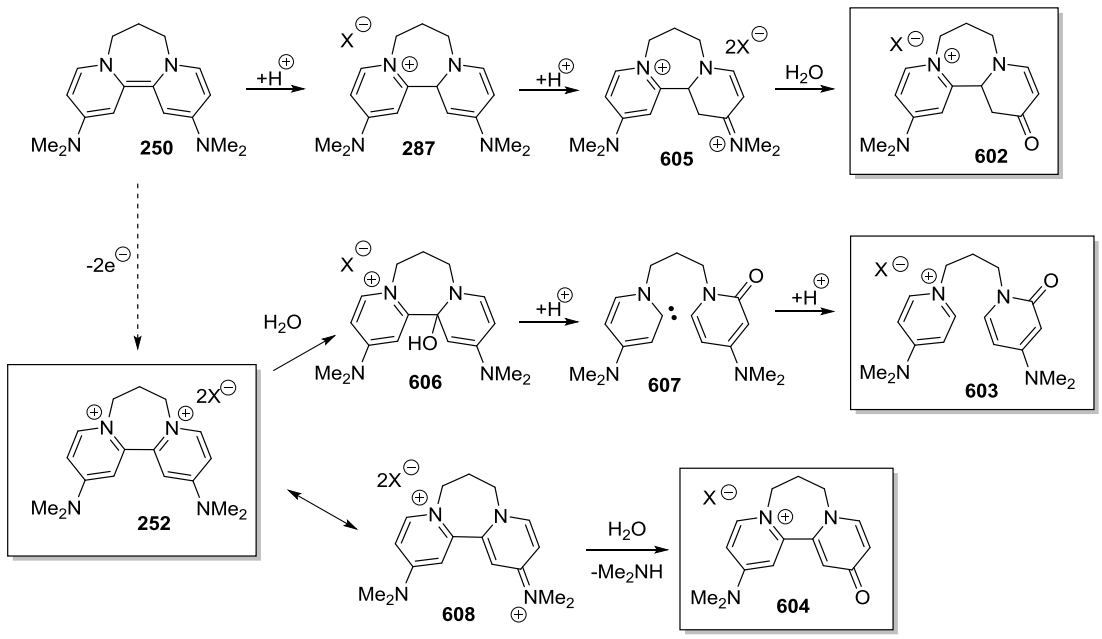
Time constraints towards the end of this body of work mean that some further examples were not carried out to resolve some of the uncertainty surrounding the mechanism. Based on the reported results, however, Jonathan Chua continues experiments to investigate whether the sulfone cleavage of unactivated α-substituted sulfones can be carried out using the photoactivated donor conditions and also whether the conditions may be applied to Julia-Lythgoe olefination reactions. Utilization of an anion-trapping electrophile such as benzyl bromide will help in the recovery of the products of these reactions and thereby hopefully elucidate the mechanism.

Chapter 7. Oxidation and Hydrolysis Products of a Neutral Organic Electron Donor- Mechanistic Insights

In all the time that donor **250** has been under study, great attention has been paid to the products arising from the electron acceptor, which is logical as **250** has been designed as a tool to transform the substrate of interest in order to isolate said products. Nothing was known, however, about the fate of the electron donor after it has reacted with the substrate except for quenching of donor **250** with excess iodine to afford **252**, initially done[197] in order to characterize the salt so to assist in confirming that the neutral donor had indeed formed.

7.1. Isolation of Four Donor-Derived Compounds

During the study of C-N bond cleavage, as discussed in chapter 5, an investigation into donor derivatives was made. The photoactivated electron transfer reactions were typically followed by aqueous workup as an initial purification step for the removal of DMF. Upon exposure to air and moisture the remaining donor or reactive species derived from the donor will become water-soluble and be separated from the substrate-derived products. In this way it was relatively straightforward to obtain a crude mixture of the donor-derived species present after the reactions. Concentration of the aqueous solution and crude NMR analysis revealed that no donor remained. This was as expected as powerful reductants are known to be air-sensitive. There were, however, other species present which looked to be similar in structure to donor **250** and therefore were assumed to have formed from it during the course of the reaction or work-up process.



Scheme 85. Oxidation and hydrolysis of donor 250

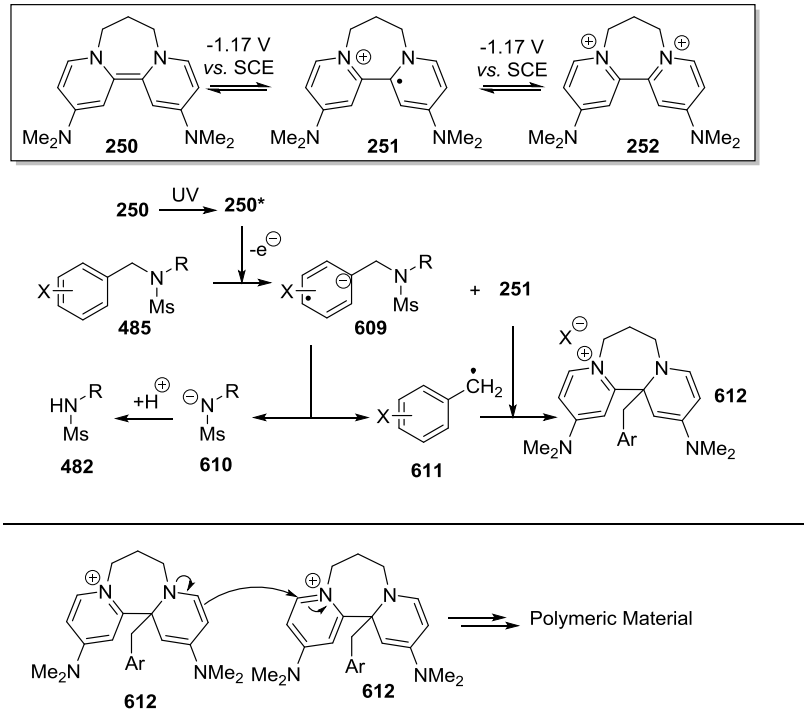
This crude mixture of similar salts with, presumably, a mixture of counter-ions did not lend itself readily to purification and isolation of the individual components and therefore quantitative recovery was not achieved. Serial recrystallization of the mixture did allow the isolation of clean samples of four compounds **252** and **602-604** which were the major components of the mixture. As can be seen in Scheme 85, compounds **252** and **602-604** share a number of common structural similarities, namely pyridinium and pyridone moieties, with donor **250** and are clearly derived from reaction of **250** with the substrate, air, or water. Compound **252** has been reported before as the product of quenching of the donor with iodine and is the main product one would expect to generate as a result of reaction with the substrate. Scheme 85 shows proposed mechanisms for the formation of **602-604**. Compound **252** forms from the two-electron oxidation of donor **250** and can then undergo hydrolysis to afford pyridones **603** and **604**. Dihydropyridone **602** is proposed to form by protonation of donor **250** directly followed by a second protonation and iminium hydrolysis.

The standard reaction conditions for the reduction of the benzyl and allyl methanesulfonamides were with six equivalents of donor **250** so it is not surprising that donor remained at the end of the reaction and was able to react with moisture and/or air, but these results serve to demonstrate that the donor tolerates the reaction conditions for the

duration of the experiment (typically 72 hours) and that if a substrate is not fully reduced by this time it is not because the donor has all been consumed.

One of the reasons it is important to understand what happens to the donor when it reacts is to understand what factors need to be addressed in order to design an effective donor for catalytic reduction reactions. From this point of view, it is useful to observe that the pyridinium species are prone to hydrolysis but that largely the donor is unscathed by the reaction conditions. Until the work-up only donor **250** and bis-pyridinium salt **252** are thought to be present in the mixture and hypothetically **252** can be recycled to **250** by Birch reduction or by electrochemistry. In order to recover and recycle all of the donor it would be necessary to quench the remaining active species (with e.g. iodine) to convert all of the species to the fully oxidized form before exposure to air. The salt could then be triturated from the reaction mixture rather than exposed to hydrolytic conditions in the workup. The effect of iodine upon the reduced products within the reaction mixture would be substrate-dependent but would need to be considered if such a protocol were to be put into practice. As a proof of concept, additional experiments were carried out using simply iodobenzene. The product of the reaction of iodobenzene with after work-up should be the iodide salt of **252** and benzene which was not isolated. Indeed carrying out the reaction with one equivalent of donor and quenching the excess with iodine delivered a 94% yield of bis-pyridinium iodide **252**. As discussed in section 2.3, donor **250** is in reality an inexpensive source of electrons and this factor reduces the worth of any more complicated procedures to recycle it. A more sensible way to utilize sub-stoichiometric electron donors for synthetic transformations would be as an initiator in a redox neutral coupling reaction as discussed in section 1.6.

7.2. Evidence of Radical Trapping



Scheme 86. Proposal of trapping

Often when examining reductive cleavage reactions it has only been possible to isolate one half of the molecule; in the case of the benzyl C-N bond cleavage the sulfonamide is isolated in good yield but at most traces of the toluene fragment are detected. This is attributed to the trapping of the tolyl radical **611** with radical cation **251** to yield **612**. Compound **612** is similar in structure to the isolated donor-derived species **602-604** and would be expected to be water-soluble so why is none of this detected or isolated alongside the others?

The reason is thought to be that species **612** has a nucleophilic enamine moiety and also contains an electrophilic pyridinium and is therefore likely to oligomerize or polymerize readily to yield higher molecular weight. Because recrystallization is used to purify the compounds, a polymer will not be isolated and attempts to separate the mixture by semi-preparative HPLC did not lead to resolution of the components. HPLC-MS analysis of the crude mixture revealed tantalizing traces of an ion corresponding to **612** but in such vanishingly small amounts that isolation from the complex mixture is unrealistic.

7.3. Quantification of Oxidation and Hydrolysis Products

As alluded to above, isolation of compounds **252** and **602**-**604** was complicated and reliable yields could not be measured directly. Nevertheless, isolation of compounds **252** and **602**-**604** did allow a calibration line to be generated for quantitative HPLC-MS which gave a better impression of the composition of the mixture.

7.3.1. Chromatography

Reverse phase HPLC resulted in short retention times and poor resolution of the crude salt mixture so an alternative chromatography method was used. HILIC (Hydrophilic Interaction Liquid Chromatography)[198-199] was suggested by Patricia Keating of our micro-analytics department and found to give far superior separation of the individual species. HILIC operates on the basis of the stationary particles suspending a layer of water around themselves during the column equilibration; for this reason HILIC columns are sometimes called 'ice columns' as they have water in a stationary phase. The solution of the analyte passes over the stationary phase and the particles interact with the water via hydrogen bonding and dipole to induced dipole interactions. The mobile phase then performs a kind of liquid/liquid extraction of the analytes from the water with the less polar species experiencing less retention. In the specific case of the donor reaction analyte mixture, a gradient of 5 to 100% acetonitrile in water was used and critically an additive of 5 μM ammonium acetate. Without this additive the separation degraded drastically and this is thought to be due to the effect that it has on the pH and ion strength of the mobile phase.

7.3.2. Results

An average of **252** (10%), **602** (3%), **603** (30%) and **604** (2%) was found to make up the crude reaction mixture. The total recovery of 45% implies the presence of additional donor-derived species in the mixture. The additional mass may be made up of a number of minor species and may also contain some of the polymerized **612** as discussed in the above paragraphs. The observation that pyridone **603** is the most abundant observed component of the mixture may indicate that upon exposure to the work-up conditions, oxidation occurs more quickly than hydrolysis of the donor. Another interpretation may be that the oxidation has already occurred under the reaction conditions and that perhaps only a small concentration of donor remains after 72 hours reaction time. This would be in keeping with

an observation from Doni[173] that increasing the reaction time for the reduction of substrates to 96 hours delivered little if any increase in isolated yield of the reduced substrate. On the other hand in an experiment discussed in section 5.5 above, reacting an amide for 72 hours with 6 equivalents of donor and then adding additional donor (6 equiv.) for a further 72 hours reaction time, did improve the yield considerably.

Another observation was that the composition of the reaction mixture did not change between the photoactivated and ground state control reactions so there is no consideration to be made for including excited-state structures in the mechanism of formation for **602**-**604**.

7.4. Conclusions

The fate of the donor after reaction with a substrate and whether it can be recovered and reused are two of the questions that are frequently asked in regard to the DMAP-derived donor chemistry. The work presented in this chapter makes strides towards answering those questions and shines some light on an area that was otherwise little understood. In terms of mechanistic insight, the individual compounds offer a little but the absence of any trapped species raises more questions than the investigation sought to answer.

Development of a method on a preparative or semi-preparative HPLC with a HILIC column would be the best course if this type of investigation were to be pursued. This would allow each individual experiment to be analysed for the make-up of its oxidation and hydrolysis products by a standard method which would save considerable time and labour compared to serial recrystallizations. This method would allow some of the more minor products to be isolated and characterised, possible to give further insight into the inner-workings of the reaction process. In this way perhaps a series of reactions could be run under different conditions to find any circumstances under which a trapped species is formed in observable quantities as even small amounts of such a species would serve as a proof of concept for the radical trapping proposition.

Chapter 8. Conclusions and Future Work

In the past three years, with the development of the photoactivation of donor **250**, it has been possible to expand the range of substrates which may be reduced using organic electron donors. Herein it is demonstrated that C-C, C-N, N-S and C-S bonds may all be reductively cleaved in useful synthetic processes by an understood mechanism; chemoselectivity can be predicted and then observed experimentally and access is granted to reactivity not before reported for other reductants.

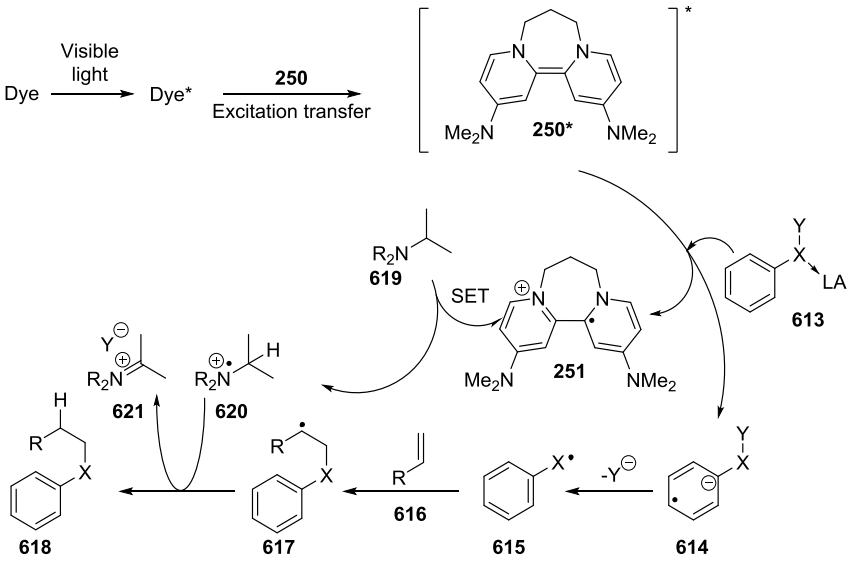
If all of the chemistry presented in this thesis worked perfectly then there would be no need to develop it further so, playing devil's advocate, criticism of the work and therefore areas for further development would include:

- The need for super-stoichiometric quantities of the donor (albeit a simply synthesized, low molecular weight species). It may therefore be wise to design reaction systems wherein the oxidized donor may be reduced and recycled catalytically. Hints towards this may come from the hybrid donors seen in section 1.5.11 which had a significant difference between the first and second oxidation potentials

- The use of potentially harmful UV radiation. Previous experiments have shown sunlight to be capable of activating the donor but visible light alone will not suffice and therefore modification of the donors to red-shift the absorption maxima could be a worthwhile endeavour. If an organic photoredox catalyst were developed that could be activated with LED bulbs and had the reducing power of donor **250** then it would certainly be an invaluable synthetic tool. It could be that the weaker LED bulbs would be most effective if used in conjunction with flow photochemistry so this too could be an avenue of development

- The breadth and depth of high impact literature coming from the metal-free coupling chemistry (Section 1.6) illustrates that there is more of a market for bond-forming than bond-breaking/deprotective chemistry and therefore any further work with donor **250** would profit from bearing this in mind. Transformation of proline derivative **513** into piperidone **514** shows the promise of this type of process so reaction systems may be developed where such reactivity may be exploited.

- Samarium diiodide chemistry and photoredox chemistry both make use of additives to alter or enhance reactivity so it may be that exploring the use of e.g. amines, Lewis acids or sensitizing dyes could improve on this chemistry without changes to the donor itself.



Scheme 87. Possible developments

That being said, our reaction system is complementary to SmI_2, photoredox and alkali metal reductants and has carved out its own niche in the field of reductive chemistry.

Chapter 9. The Roll of Aluminium in Thermal Organic Chemistry

During my studies, I came up with an alternative to oil baths and machined aluminium heating mantles. The idea came from a dislike of oil baths because: they look messy, they can catch fire, they cover your flask in an oily film (affecting yield measurements on a small scale) and they must be changed periodically- creating unpleasant oily waste. The solution was as simple and obvious as so many discoveries in research. Aluminium foil which is a common sight in most labs but several years ago I found that by layering aluminium foil around the bottom half of a round-bottomed flask it is possible to create an aluminium heating mantle (Figure 7). These mantles quickly replaced almost all of the oil baths in our lab and the technology has since spread to other labs in the department.

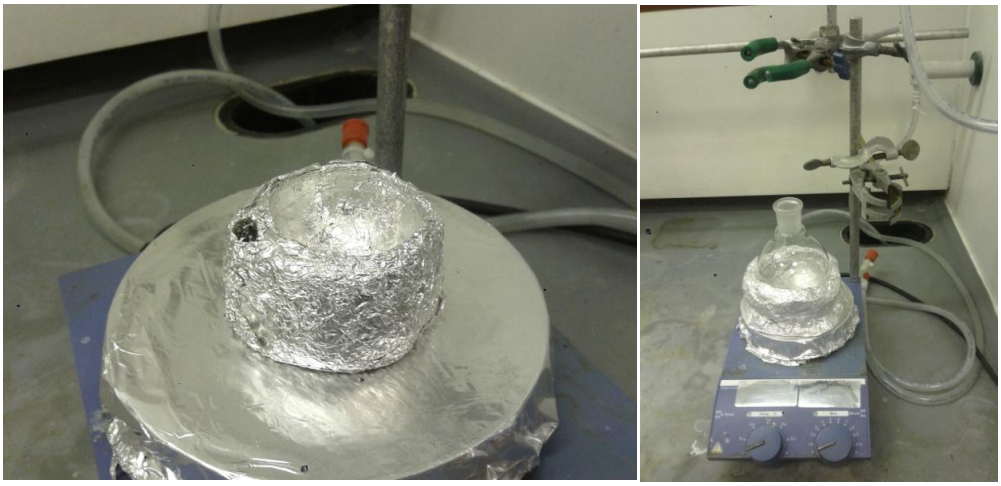
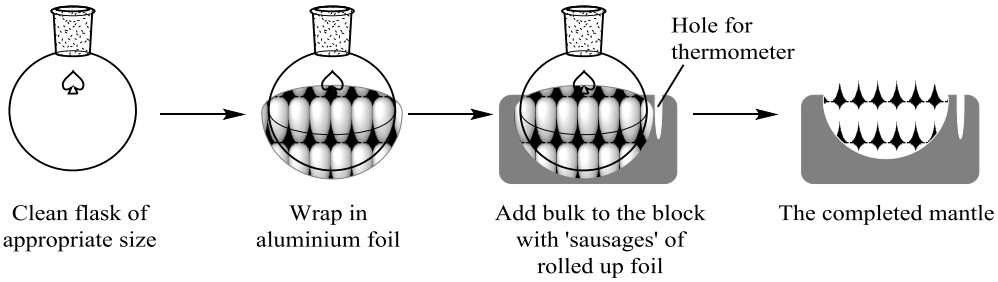


Figure 7. Foil mantles in the lab

Advantages of these mantles include that they are quick and easy to make, are safe, leave no oily residue, heat up much more quickly than oil, also cool more quickly after use, are much cheaper than commercial aluminium heating blocks, can also be used as cork ring and are re-useable indefinitely.

I encourage trying them for yourself and include a short method below for how they are made.

General Method for Construction of Aluminium Heating Block:



A clean round-bottom flask of appropriate size was taken as a template and several layers of aluminium foil wrapped around it in a hemisphere. ‘Sausages’ of rolled up aluminium foil were then be used to fill out the bottom of the shape to give a flatter base. This may also be done in layers and it is important to compress the aluminium with a finger at each stage as the denser the block, the more efficient the heating. Sometimes a cork ring may be used as a template for the outer circumference of the block. Remember to make a hole for a thermometer and another for a temperature probe if needed. This is best done between layers rather than trying to add it at the end; if this can be done easily at the end then the block has not been compressed enough. Finally one or two layers of foil were added over the entire block for aesthetic purposes and to help hold it together in one piece (the thermometer can be poked through this thin layer to the pre-formed hole). The mantle is now ready for use.

It was found that one roll of kitchen foil (79p) was enough to make a mantle for each of the most common flask sizes in our lab (2, 5, 10, 25, 50, 100 and 250 mL). For flask sizes above 500 mL these become less practical but can still be made and our 1 L mantle is certainly preferable to a huge oil bath. We have never tried a 2.5 L example and would probably recommend a traditional heating mantle for such a case. While inappropriate for cooling reactions, a mantle that has been chilled in the fridge or freezer (only a few minutes needed as it’s made of metal) can be useful for low-temperature recrystallizations.

Experimental

Chapter 10. Experimental Details

10.1. General

All chemicals and reagents were obtained from commercial suppliers and reactions were carried out under anhydrous conditions unless otherwise stated.

Acetonitrile was distilled over phosphorus pentoxide. Hexane, CH_2Cl_2, Et_2O and THF were all kept anhydrous by purification by an Innovative Technology inc. PURESOLV SPS-400-5 solvent purification apparatus. Solvents were deoxygenated by bubbling dry argon through with stirring for 1 hour.

Ultra-violet experiments were carried out using two Blak Ray® B-100 Series high intensity inspection lamps, with 100 W, 365 nm spot bulbs.

Chromatography was carried out on silica gel 60 (200-400 mesh). TLC analysis was carried out on aluminium sheets of silica gel 60 F_{245} and developed in acidic ethanolic vanillin or a phosphomolybdic acid solution.

^{1}H NMR and ^{13}C NMR analyses were carried out on a Bruker Avance AV3 400 spectrometer, operating at 400 and 100 MHz respectively or on a Bruker DRX500 spectrometer operating at 500 and 125 MHz respectively. $CDCl_3$, DMSO-d_6 or benzene-d_6, was taken as the solvent. Chemical shifts are reported in parts per million shift (δ value) calibrated against the residual solvent peak. Signal patterns are indicated as s, singlet; br. s, broad singlet; d, doublet; dd, double doublet; t, triplet; dt, double triplet; q, quartet; m, multiplet. Coupling constants (*J*) are given in hertz (Hz).

Infra-red analyses were carried out on a SHIMADZU IRAffinity-1 FTIR Spectrophotometer with a Pike Technologies MIRacle™ Single Reflection Horizontal ATR Accessory with a ZnSe crystal.

High Resolution Mass spectral analyses were carried out at EPSRC National Mass Spectrometry Service Centre in Swansea on a LTQ Orbitrap XL using Atmospheric Pressure Chemical Ionisation (APCI) or High Resolution Nano-Electrospray (HNESP), and masses observed are accurate to within 5 ppm.

Low resolution mass spectral analyses were carried out on a Thermofinnigan LCQ DUO LDU 00377 Mass Spectrometer operating electrospray ionisation (ESI).

HPLC-MS was carried out on an Agilent Technologies 1200 Series LCMS with a KINETEX C18 column, 4.6 x 150mm (5 μm particles size) and Agilent Technologies 6130 Quadropole MS. Conditions were 5 to 100 acetonitrile in water buffered with 5μM ammonium acetate.

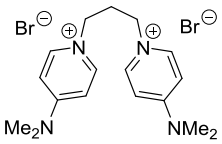
HILIC chromatography was carried out on an Agilent Technologies 1200 Series LCMS with an Agilent Zorbax Hilic Plus Narrow Bore 2.1 x 50 mm column (3.5 μm particles size) and G1315D diode-array detector (190-950 nm).

GC/CI was carried out using Agilent Technologies 7890A GC System, 5975C Inert XL EI/CI MSD with Triple Axis Detector with an Agilent DB5-MS 30 m x 0.25 mm column with 0.25 μm packing. The carrier gas was helium at 1 mL/min and the reagent gas was methane. GC/EI was carried out using ThermoFinnigan PolarisQ Ion Trap Spectrometer with an Agilent DB5-MS 30 m x 0.25 mm column with 0.25 μ packing. The carrier gas was helium at 1 mL/min. MALDI-MS was carried out on a Shimadzu Axima-CFR system with no matrix.

Melting points were measured on a Gallenkamp Griffin SG94/05/530 Melting Point Apparatus and are unamended.

Computational predictions were carried out using Spartan 2010 software and Density Functional Theory as a method. B3LYP and 6-31G(d,p) were used as a level of theory and generally calculations were run in a DMF solvent continuum (ε = 37.219).

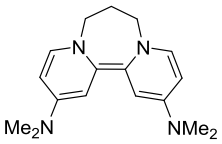
Synthesis of 1,3-bis(*N*',*N*'-dimethyl-4-aminopyridinium)propane dibromide 247



A solution of 4-(dimethylamino)pyridine (9.16 g, 75 mmol, 2.5 equiv.) and 1,3-dibromopropane (6.06 g, 30 mmol, 1.0 equiv.) in a flask containing acetonitrile (60 mL) was stirred at reflux for 16 h, under argon. Diethyl ether (10 mL) was added to the reaction flask and the product precipitated instantaneously, and was then filtered. To precipitate more of the solid, an additional amount of diethyl ether (20 mL) was added to the filtrate. After

filtration, the solid was washed with diethyl ether (3 x 50 mL) and dried under vacuum to give 1,3-bis(*N*',*N*'-dimethyl-4-aminopyridinium)propane dibromide **247**[126] (13 g, 97%) as a white solid M.pt. 199-203 °C (lit.[126] 199-203 °C); [Found: (ESI$^+$) (M-Br)$^+$ 365.1338 and 367.1317. $C_{17}H_{26}BrN_4$ (M-Br) requires 365.1336 and 367.1315]; ν_{max}(ATR)/cm^{-1} 3027, 2725, 2468, 1649, 1571, 1403; δ_H (400 MHz, DMSO-d_6) 2.36 (2H, quintet, *J* = 7.2 Hz, $CH_2CH_2CH_2$), 3.18 (12H, s, NCH_3), 4.28 (4H, t, *J* = 7.2 Hz, NCH_2), 7.04 (4H, d, *J* = 7.6 Hz, Ar*H*), 8.34 (4H, d, *J* = 7.6 Hz, Ar*H*); δ_C (100 MHz, DMSO-d_6) 31.2, 39.8, 53.7, 107.8, 141.8, 155.8.

Synthesis of *N*,*N*,*N*',*N*'-tetramethyl-7,8-dihydro-6H-dipyrido[1,2-a;2',1'-c][1,4] diazepine-2,12-diamine 250



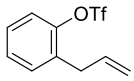
To a Schlenk flask in a nitrogen glovebox was added 1,3-bis(*N*',*N*'-dimethyl-4-aminopyridinium)propane dibromide **247** (13.38 g, 30 mmol, 1.0 equiv.) and pre-washed NaH (stored in glovebox, 4.55 g, 180 mmol, 6 equiv.). The flask was removed to a fumehood, fitted with a dry ice condenser, and the atmosphere was made oxygen-free by flushing with argon. At this point, anhydrous ammonia (75 mL) was condensed and the reaction mixture allowed to reflux for 4 h before leaving to evaporate overnight (14 h) under a steady flow of argon. The flask was sealed and transferred to a nitrogen glove box. The solid was extracted with dry diethyl ether (300 mL) and the solvent removed by distillation under reduced pressure (10-20 mbar) to yield pure *N*,*N*,*N*',*N*'-tetramethyl-7,8-dihydro-6*H*-dipyrido-[1,2-a;2',1'-c][1,4]-diazepine-2,12-diamine **250**[126] (7.61 g, 89%) as a purple-black, moisture- and oxygen-sensitive solid. δ_H (400 MHz, C_6D_6) 1.00 (2H, quintet, *J* = 6.3 Hz, $CH_2CH_2CH_2$), 2.46 (12H, s, $N(CH_3)_2$), 3.03 (4H, t, *J* = 6.3 Hz, NCH_2), 4.91 (2H, dd, *J* = 7.5, 2.2 Hz, Ar*H*), 5.14 (2H, d, *J* = 2.2 Hz, Ar*H*), 5.64 (2H, d, *J* = 7.5 Hz, Ar*H*); δ_C (100 MHz, benzene-d_6) 24.5, 40.8, 52.6, 95.8, 96.2, 116.0, 138.7, 143.7. λ_{max} (MeCN) = 260 nm (ε = 30000 M^{-1} cm^{-1}), 345 nm (ε = 15000 M^{-1} cm^{-1}), 512 nm (ε = 2500 M^{-1} cm^{-1}).

10.2. Experimental Details for Chapter 3

General Procedure A-Preparation of triflates

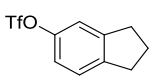
Alcohol or phenol starting material (1.0 equiv.) was dissolved in dry dichloromethane (2 mL), pyridine (1.0 equiv.) was added and the flask cooled to -78 ^{o}C. A solution of trifluoromethanesulfonic anhydride (1.5 equiv.) in dichloromethane (2 mL) at -78 ^{o}C was added dropwise to the stirred alcohol or phenol solution. The dry-ice bath was removed and the reaction mixture allowed to warm to room temperature. After 30 min, water (10 mL) was added, followed by dichloromethane (10 mL). The reaction solution was then washed with further portions of water (3 x 10 mL), dried over Na_2SO_4 and the solvent evaporated. The crude organic residue was then eluted over silica in dichloromethane, to afford the pure corresponding trifluoromethanesulfonate ester.

2-Allylphenyl trifluoromethanesulfonate 349



2-Allylphenol (268 mg, 2.0 mmol, 1.0 equiv.) was reacted according to general procedure A to afford 2-allylphenyl trifluoromethanesulfonate **349**[200] as a colourless oil (493 mg, 1.85 mmol, 93%); [Found: $(M)^+$ 266.0219. $C_{10}H_9F_3O_3S$ requires $(M)^+$, 266.0219]; ν_{max} (Thin film) 3085, 2985, 2923, 1642, 1488, 1454, 1422, 1250, 1214, 1140, 1105, 1073, 891, 181, 767 and 606 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.49 (2H, dt, J = 6.6, 1.3 Hz, ArCH_2), 5.11-5.18 (2H, m, $ArCH_2CHCH_2$), 5.89-5.97 (1H, m, $ArCH_2CH$), 7.28-7.36 (4H, m, ArH); δ_C (125 MHz, $CDCl_3$) 34.3, 117.8, 119.0 (q, J_{C-F} = 318 Hz, CF_3), 121.7, 128.5, 128.7, 131.8, 133.2, 134.9, 148.3.

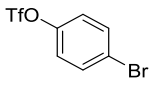
2,3-Dihydro-1*H*-inden-5-yl trifluoromethanesulfonate 350



2,3-Dihydro-1*H*-inden-5-ol **353** (201 mg, 1.5 mmol, 1.0 equiv.) was reacted according to general procedure A to afford 2,3-dihydro-1H-inden-5-yl trifluoromethanesulfonate **350**[201] as

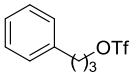
a colourless oil (359 mg, 90%); [Found: $(M)^+$, 266.0220. $C_{10}H_9F_3O_3S$ requires (M), 266.0219]; ν_{max} (Thin film)/cm^{-1} 2957, 2850, 1611, 1593, 1480, 1423, 1250, 1212, 1142, 1100, 933, 870, 852, 608, 502; δ_H (400 MHz, $CDCl_3$) 2.45 (2H, quintet, J = 7.4 Hz, $ArCH_2CH_2CH_2Ar$), 2.93 (2H, t, J = 7.4 Hz, $ArCH_2$), 2.96 (2H, t, J = 7.4 Hz, $ArCH_2$), 7.02-7.05 (1H, m, Ar*H*), 7.12 (1H, d, J = 1.8 Hz, Ar*H*), 7.25 (1H, d, J = 7.2 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 26.1, 32.7, 33.3, 117.7, 119.1 (q, J_{C-F} = 319 Hz, CF_3), 119.2, 125.8, 145.0, 147.2, 148.6.

4-Bromophenyl trifluoromethanesulfonate 351



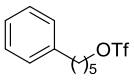
4-Bromophenol **354** (346 mg, 2.0 mmol, 1.0 equiv.) was reacted according to general procedure A to afford 4-bromophenyl-1-trifluoromethanesulfonate **354**[202] as a colourless oil (591 mg, 1.94 mmol, 97%); [Found: $(M)^+$ 303.9011, 305.8992. $C_7H_4BrF_3O_3S$ (M) requires, 303.9017, 305.8996]; ν_{max} (Thin film)/cm^{-1} 3103, 1481, 1428, 1401, 1251, 1216, 1174, 1141, 1071, 1013, 886, 832, 779, 750, 628, 607, 525; δ_H (400 MHz, $CDCl_3$) 7.18 (2H, d, J = 9.0 Hz, Ar*H*), 7.60 (2H, d, J = 9.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$): 119.0 (q, J_{C-F} = 319 Hz, CF_3), 122.4, 123.4, 133.8, 148.8.

3-Phenylpropyl-1-trifluoromethanesulfonate 372a



Phenylpropan-1-ol **373a** (161 mg, 0.6 mmol, 1.0 equiv.) was reacted according to general procedure A to afford 3-phenylpropyl-1-trifluoromethanesulfonate **372a**[203] as a colourless oil (153 mg, 95%); ν_{max} (Thin film)/cm^{-1} 3066, 3030, 2935, 2865,1498, 1455, 1412, 1360, 1246, 1207, 1145, 984, 930, 831, 800, 747, 700, 615, 576, 519; δ_H (400 MHz, $CDCl_3$) 2.14-2.20 (2H, m), 2.78 (2H, t, J = 7.3 Hz), 4.54 (2H, t, J = 6.3 Hz), 7.20 (2H, d, J = 7.4 Hz), 7.25 (1H, t, J = 7.4 Hz), 7.33 (2H, t, J = 7.4 Hz); δ_C (100 MHz, $CDCl_3$) 31.1, 31.5, 76.9, 119.0 (q, J_{C-F} = 318 Hz, CF_3) 126.9, 128.7, 129.1, 139.8. *m/z* (ESI^+) 268.0 ($[M]^+$, 18%), 118.0 (35), 117.0 (71), 91.0 (100).

5-Phenylpentyl-1-trifluoromethanesulfonate 371c

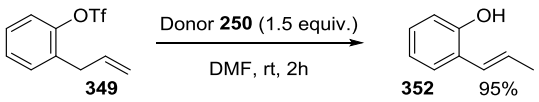


5-Phenylpentan-1-ol **372c** (164 mg, 1.0 mmol, 1.0 equiv.) was reacted according to general procedure A to afford 5-phenylpentyl-1-trifluoromethanesulfonate **371c**[204] as a colourless oil (279 mg, 0.94 mmol, 94%); ν_{max} (Thin film)/cm^{-1} 3030, 2934, 2865, 1412, 1247, 1207, 1145, 930, 799, 746, 616; δ_H (400 Hz, $CDCl_3$) 1.55-1.61 (2H, m, $(CH_2)_2CH_2(CH_2)_2$), 1.66-172 (2H, m, $ArCH_2CH_2$), 1.84-1.90 (2H, m, CH_2CH_2OTf), 2.69 (2H, t, J = 7.4 Hz, $ArCH_2CH_2$), 4.58 (2H, t, J = 6.3 Hz, CH_2CH_2OTf), 7.17-7.22 (3H, m, Ar*H*), 7.26-7.31 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 25.0, 29.5, 31.0, 35.9, 77.8, 119.0 (q, J_{C-F} = 317 Hz, CF_3), 126.2, 128.7, 128.7, 142.2; *m/z* (ESI$^+$) 295.9 ([M]$^+$, 22%), 146.1 (32), 104.1 (38). 91.2 (100), 65.1 (22).

General Procedure B – Reaction of triflate esters with donor 250

Donor **250** (128 mg, 0.45 mmol, 1.5 equiv.) was dissolved in degassed DMF (2 mL) in a glovebox. This solution was directly pipetted onto the dry and degassed selected substrate (0.3 mmol, 1.0 equiv.). The mixture was left to stir for 3 h at ambient temperature, then added to water (10 mL), before extracting with diethyl ether (4 x 10 mL). The combined organic layers were then washed with water (2 x 15 mL), brine (10 mL) and dried over Na_2SO_4. The crude organic residue, obtained after evaporation under reduced pressure, was eluted with ethyl acetate on silica gel, to afford the pure corresponding products as reported.

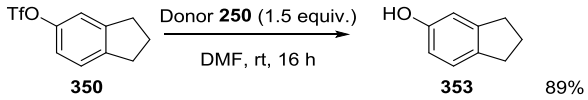
Reaction of 2-allylphenyl trifluoromethanesulfonate 349 with donor 250



2-Allylphenyl trifluoromethanesulfonate **349** (80 mg, 0.3 mmol, 1.0 equiv.), was reacted according to procedure B to afford 2-(prop-1-enyl)phenol **352**[124] as a colourless oil, (38 mg, 0.286 mmol, 95%); ν_{max} (Thin Film)/cm^{-1} 3410, 3034, 2912, 2852, 1654, 1581, 1446, 1284,

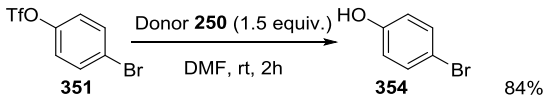
1172, 964, 746; δ_H (400 MHz, $CDCl_3$): 1.93 (3H, dd, *J* = 6.6, 1.7 Hz, C*H*$_3$), 4.96 (1H, s, O*H*), 6.23 (1H, dq, *J* = 15.9, 6.6 Hz, ArCHC*H*), 6.59-6.63 (1H, m, ArC*H*), 6.81 (1H, dd, *J* = 8.0, 1.0 Hz, Ar*H*), 6.91 (1H, ddd, *J* = 7.7, 7.4, 1.0 Hz, Ar*H*), 7.12 (1H, ddd, *J* = 8.0, 7.4, 1.6 Hz, Ar*H*), 7.32 (1H, dd, *J* = 7.7, 1.6 Hz, Ar*H*); δ_C (125 MHz, $CDCl_3$) 19.3, 116.0, 121.2, 125.4, 125.7, 127.7, 128.3, 128.7, 152.7. *m*/*z* (ESI^-) 133.10 ($[M-H]^-$, 100%).

Reaction of 2,3-dihydro-1H-inden-5-yl trifluoromethanesulfonate with donor 250



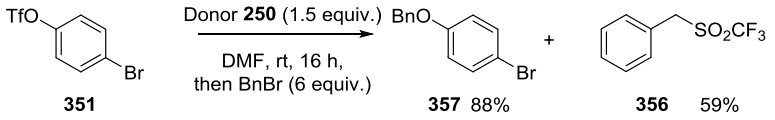
2,3-Dihydro-1H-inden-5-yl trifluoromethanesulfonate **350** (80 mg, 0.3 mmol, 1.0 equiv.), was reacted according to procedure B to afford 2,3-dihydro-1H-inden-5-ol **353** as a white solid (36 mg, 89%); M.pt. 56-57 ^oC (lit.[205] 56 ^oC); δ_H (400 MHz, $CDCl_3$) 2.08 (2H, quintet, *J* = 7.3 Hz, $CH_2CH_2CH_2$), 2.84 (2H, t, *J* = 7.3 Hz, ArC*H*$_2$), 2.87 (2H, t, *J* = 7.3 Hz, ArC*H*$_2$), 6.61 (1H, dd, *J* = 8.0, 2.2 Hz, Ar*H*), 6.72 (1H, d, *J* = 2.2 Hz, Ar*H*), 7.08 (1H, d, *J* = 8.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 26.2, 32.3, 33.4, 111.7, 113.3, 123.3, 136.7 146.4, 154.5; *m*/*z* (ESI^-) 133.07 ($[M-H]^-$, 100%).

Reaction of 4-Bromophenyl-1-trifluoromethanesulfonate with donor 250



4-Bromophenyl-1-trifluoromethanesulfonate **351** (92 mg, 0.3 mmol, 1.0 equiv.), was reacted according to procedure B to afford 4-bromophenol **354** as a colourless crystalline solid, (44 mg, 84%); M.pt. 66-68 ^oC (lit.[206] 66-68 ^oC); ν_{max} (Thin film)/cm^{-1} 3342, 3062, 2943, 2665, 1588, 1487, 1437, 1331, 1211, 1116, 1070, 999, 936, 827, 695, 632; δ_H (400 MHz, $CDCl_3$): 4.69 (1H, s, O*H*), 6.73 (2H, d, *J* = 8.9 Hz, Ar*H*), 7.35 (2H, d, *J* = 8.9 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 113.3, 117.5, 132.8, 155.0; *m*/*z* (ESI^-) 172.9 ($[M-H]^-$, 98%), 170.9 ($[M-H]^-$, 100).

Reaction of 4-bromophenyl trifluoromethanesulfonate with donor 250 and quenching with benzyl bromide



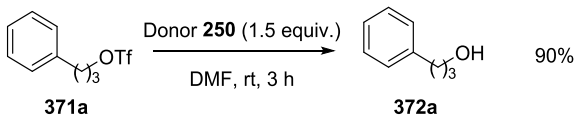
351 **357** 88% **356** 59%

Donor **250** (427 mg, 1.5 mmol, 1.5 equiv.) was dissolved in degassed DMF (5 mL) in a glovebox. This solution was directly pipetted onto the dry and degassed 4-bromophenyl trifluoromethanesulfonate (305 mg, 1.0 mmol, 1.0 equiv.). The mixture was left to stir for 16 h at ambient temperature, before benzyl bromide (1.03 g, 6.0 mmol, 6.0 equiv.) was added to the reaction mixture and stirred overnight. The reaction vessel was sealed and removed to a fumehood and water (25 mL) added, before extraction with ethyl acetate (4 x 30 mL). The combined organic layers were then washed with water (2 x 30 mL), brine (25 mL) and dried over Na_2SO_4. The crude organic obtained after evaporation under reduced pressure was purified by column chromatography in diethyl ether and petroleum ether (40-60 ^oC) to give 1-(benzyloxy)-4-bromobenzene **357** as a white crystalline solid (231 mg, 0.88 mmol, 88%) and (trifluoromethylsulfonyl)methylbenzene **356** as a white crystalline solid (132 mg, 59%);

1-(benzyloxy)-4-bromobenzene **357** (231 mg, 0.88 mmol, 88%); M.pt. 59-60 ^oC (lit.[207] 59-60 ^oC); [Found $(M)^+$, 261.9986, 263.9966. $C_{13}H_{11}BrO$ (M) requires 261.9993, 263.9973]. ν_{max} (ATR)/cm^{-1} 3034, 2891, 1573, 1491, 1453, 1379, 1285, 1233, 1112, 1073, 1047, 993, 909, 823, 739; δ_H (400 MHz, $CDCl_3$) 5.06 (2H, s, ArCH_2O), 6.87 (2H, d, J = 9.0 Hz, ArH), 7.45-7.33 (7H, m, ArH); δ_C (100 MHz, $CDCl_3$) 69.7, 112.6, 116.2, 126.9, 127.6, 128.1, 131.8, 136.1, 157.4.

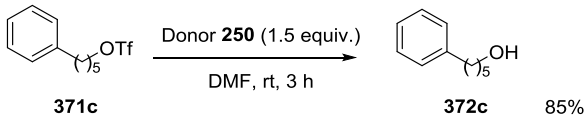
(Trifluoromethylsulfonyl)methylbenzene **356** (132 mg, 59%); M.pt. 100-101^oC (lit.[208] 104 ^oC); [Found $(M)^+$, 224.0114. $C_8H_7F_3O_2S$ (M) requires 224.0113]. ν_{max} (KBr)/cm^{-1} 3007, 2953, 1625, 1494, 1459, 1361, 1202, 1120, 774, 720, 697, 634, 525, 507; δ_H (400 MHz, $CDCl_3$) 4.49 (2H, s, ArCH_2SO_2), 7.43-7.48 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 56.5, 120.1 (q, J = 326 Hz, CF_3), 123.5, 129.6, 130.4, 131.6.

Reaction of 3-phenylpropyl-1-trifluoromethanesulfonate with donor 250



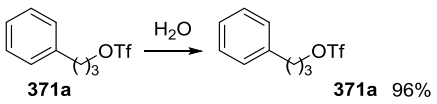
3-Phenylpropyl-1-trifluoromethanesulfonate **371a** (81 mg, 0.3 mmol, 1.0 equiv.), was reacted according to procedure B to afford 3-phenylpropan-1-ol **372c**[209] as a colourless oil, (37 mg, 0.27 mmol, 90%); ν_{max} (Thin film)/cm^{-1} 3335, 3033, 2932, 2941, 1605, 1495, 1450, 1055, 1032, 749, 701; δ_H (400 MHz, $CDCl_3$) 1.62 (1H, s, O*H*), 1.89-1.95 (2H, m, $CH_2CH_2CH_2OTf$), 2.72 (2H, t, *J* = 7.7 Hz, $ArCH_2$), 3.70 (2H, t, *J* = 6.5 Hz, CH_2OTf), 7.20-7.23 (3H, m, Ar*H*), 7.31 (2H, t, *J* = 7.4, Ar*H*); δ_C (100 MHz, $CDCl_3$) 32.4, 34.5, 62.6, 126.2, 128.7, 128.8, 142.1. *m*/*z* (GC-MS EI$^+$) 135.93 ([M]$^+$, 100%).

Reaction of 5-Phenylpentyl-1-trifluoromethanesulfonate with donor 250



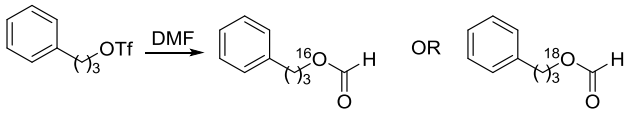
5-Phenylpentyl-1-trifluoromethanesulfonate **371c** (89 mg, 0.3 mmol, 1.0 equiv.), was reacted according to procedure B to afford 5-phenylpentan-1-ol **372c**[210] as a colourless oil, (42 mg, 0.26 mmol, 85%); ν_{max} (Thin film)/cm^{-1} 3101, 2957, 2850, 1611, 1593, 1480, 1423, 1250, 1212, 1142, 1100, 933, 870, 852, 608, 502; δ_H (400 MHz, $CDCl_3$) 1.39-1.45 (2H, m, $(CH_2)_2CH_2(CH_2)_2$), 1.59-1.64 (2H, m, $ArCH_2CH_2$), 1.65-1.70 (2H, m, CH_2CH_2OH), 2.64 (2H, t, *J* = 7.7 Hz, $ArCH_2$), 3.65 (2H, t, *J* = 6.6 Hz, CH_2CH_2OH), 7.18-7.12 (3H, m, Ar*H*), 7.27-7.30 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 25.7, 31.6, 33.0, 36.2, 63.3, 126.0, 128.6, 128.7, 142.9; *m*/*z* (ESI$^+$) 186.93 ([M+Na]$^+$, 100%).

Hydrolysis stability of 3-phenylpropyl trifluoromethanesulfonate



3-Phenylpropyl trifluoromethanesulfonate **371a** (81 mg, 0.3 mmol, 1 equiv.) was weighed into a small flask and water (2 mL) added, then stirred for 1 h before addition of water (10 mL) and extraction with diethyl ether (4 x 20 mL). The combined organic layers were then washed with water (3 x 15 mL) and dried over Na_2SO_4. The crude organic product obtained after evaporation under reduced pressure was 3-phenylpropyl trifluoromethanesulfonate **371a** as a colourless oil (78 mg, 0.28 mmol, 96%) with data matching those of the original material.

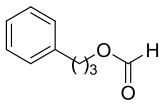
Preparation of 3-phenylpropyl formate 376a from 3-phenylpropyl trifluoromethanesulfonate 371a



3-Phenylpropyl trifluoromethanesulfonate **371a** (81 mg, 0.3 mmol, 1 equiv.) was dissolved in degassed DMF (2 mL) in a glovebox. This solution was left to stir for 16 h at ambient temperature, before being removed to a fumehood and water (25 mL) added, before extraction with diethyl ether (4 x 20 mL). The combined organic layers were then washed with water (3 x 15 mL) and dried over Na_2SO_4. The crude organic product obtained after evaporation under reduced pressure was purified by column chromatography in diethyl ether and petroleum ether (40-60 ^oC) to give 3-phenylpropyl formate **376a**[170] as a colourless oil (46 mg, 93%); [Found: $(M+NH_4)^+$, 182.1176. $C_{10}H_{16}NO_2$ $(M+NH_4)$ requires 182.1176]; ν_{max} (Thin film)/cm^{-1} 3032, 2939, 1722, 1504, 1455, 1384, 1161, 1090, 1017, 922, 819, 745; δ_H (400 MHz, $CDCl_3$) 1.99-2.06 (2H, m, $CH_2CH_2CH_2$), 2.74 (2H, d, J = 7.4 Hz, $ArCH_2CH_2$), 4.22 (2H, d, J = 6.5 Hz, CH_2CH_2O, *found to have additional minor interaction with peak at 8.10 in COSY spectrum*), 7.20-7.25 (3H, m, Ar*H*), 7.30-7.34 (2H, m, Ar*H*), 8.10 (1H, s, C*H*O, *found to have additional minor interaction with peak at 4.22 in COSY spectrum*); δ_C (100 MHz, $CDCl_3$) 29.6, 31.5, 62.8, 125.6, 127.9, 128.0, 140.4, 160.6; *m*/*z* (GC-MS CI^+) 165.1 ($[M+H]^+$, 100%).

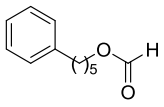
The same experiment carried out with DMF ^{18}O enrichment (~ 13%) gave rise to the labelled ester, ^{18}O-3-phenylpropyl formate (also ~ 13% enriched in the minor isotope) was seen in GC/CI-MS, with other data matching those of the unlabelled material. Peak seen for the ^{16}O $[M+H]^+$: 165.1; Peak seen for the ^{18}O $[M+H]^+$: 167.1

Preparation of 3-phenylpropyl formate 376a



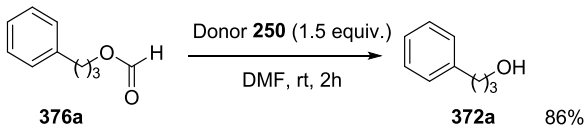
3-Phenylpropanol **372a** (681 mg, 5.0 mmol, 1 equiv.) was dissolved in hexane (10 mL) and then added to formic acid (276 mg, 6 mmol, 1.2 equiv.), silica (1 g) and a few drops of conc. sulfuric acid.[170] The suspension was allowed heat at reflux for 1 h, then allowed to cool. The silica was filtered off and water (25 mL) added, before extraction with ethyl acetate (3 x 25 mL). The combined organic layers were then washed with water (3 x 25 mL) and dried over Na_2SO_4. The crude organic product obtained after evaporation under reduced pressure was purified by column chromatography with 20% diethyl ether in petroleum ether (40-60 ^oC) to give 3-phenylpropyl formate **376a** as a colourless oil (672 mg, 82%). Data were as reported above.

Preparation of 5-phenylpentyl formate, 376c



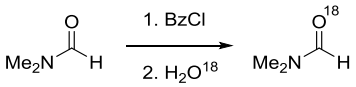
5-Phenylpentyl trifluoromethanesulfonate **371c** (89 mg, 0.3 mmol, 1 equiv.) was dissolved in degassed DMF (2 mL) in a glovebox. This solution was left to stir for 16 h at ambient temperature, before being removed to a fumehood and water (25 mL) added, before extraction with diethyl ether (4 x 20 mL). The combined organic layers were then washed with water (3 x 15 mL) and dried over Na_2SO_4. The crude organic product obtained after evaporation under reduced pressure was purified by column chromatography on silica gel (Et_2O/petroleum ether (40-60 ^oC)) to give *5-phenylpentyl formate* **376c** as a colourless oil (54 mg, 94%); ν_{max} (Thin film)/cm^{-1} 3101, 2928, 2852, 1724, 1662, 1505, 1379, 1174, 1114, 911, 844, 817, 747; δ_H (400 MHz, $CDCl_3$) 1.42-1.48 (2H, m, $(CH_2)_2CH_2(CH_2)_2$), 1.76-1.65 (4H, m, $CH_2CH_2CH_2CH_2CH_2$), 2.65 (2H, t, J = 7.7 Hz, $ArCH_2CH_2$), 4.18 (2H, t, J = 6.7 Hz, CH_2CH_2O), 7.22-7.19 (3H, m, Ar*H*), 7.32-7.29 (2H, m, Ar*H*), 8.07 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 25.0, 27.9, 30.5, 35.3, 63.5, 125.3, 127.8, 127.9, 141.8, 160.7; *m*/*z* (ESI^+) 215.0 ($[M+Na]^+$, 100%).

Reaction of 3-phenylpropyl formate 376a with donor 250



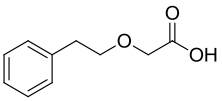
3-Phenylpropyl formate **376a** (150 mg, 1.0 mmol, 1.0 equiv.) was reacted according to procedure B to afford 3-phenylpropanol **372a** as a colourless oil (36 mg, 0.26 mmol, 86%); Data were as reported previously.

Preparation of ^{18}O- dimethylformamide[171]



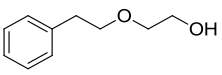
Dry dimethylformamide (7.7 mL, 0.1 mol) and dry benzoyl chloride (11.6 mL, 0.1 mol) were taken in a three-necked flask equipped with a calcium chloride drying tube. The flask was then cooled to 0 ° C and ^{18}O-labelled water (20% mole of ^{18}O isotope, 1.83 g, 0.1 mol) was introduced slowly into the reaction flask. The contents solidified instantaneously due to the formation of benzoic acid. Mass spectrometry of the crude reaction mixture indicated the presence of ^{18}O labelled dimethylformamide. Petroleum ether (40-60 ^{o}C, 10 mL) was added to the reaction flask and stirred for 10 min and sodium bicarbonate (8.4 g, 0.1 mol) was added to the reaction flask. When the evolution carbon dioxide ceased, the contents were extracted with acetone (3 x 20 mL). The combined acetone layers were dried over anhydrous potassium carbonate and the resulting solution was concentrated under vacuum. The crude product was purified by distillation and provided ^{18}O-labelled dimethylformamide as a colourless oil (~13% mole of ^{18}O isotope, 5.6 g, 78%). ν_{max} (Thin film)/cm^{-1} 3480, 2939, 1660, 1388, 1257, 1092, 1060; δ_H (400 MHZ, $CDCl_3$) 2.80 (3H, s, NC*H*$_3$), 2.89 (3H, s, NC*H*$_3$), 7.94 (1H, s, C(O)*H*); δ_C (100 MHz, $CDCl_3$) 31.3, 36.4, 162.4; *m*/*z* (ESI$^+$) 76.2 (13%), 74.2 (100).

2-Phenethoxyacetic acid 387



2-Phenylethanol **386** (6.11 g, 50 mmol, 1.0 equiv.), in a solution of dry DMF (100 mL) was added slowly to sodium hydride (4.0 g, 100 mmol, 2.0 equiv.) at 0 ^{o}C. Once the addition was complete, the suspension was brought to 60 ^{o}C and left to stir for 15 min before addition of 2-bromoacetic acid (6.95 g, 50 mmol, 1.0 eq) in DMF (10 mL). Following a further 45 min reaction time at 60 ˚ C the reaction mixture was allowed to cool and then water (100 mL) added and extracted with diethyl ether (2 x 100 mL). The aqueous layer was acidified to pH 1 and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were then washed with aqueous 2N HCl (100 mL) and dried over Na_2SO_4. The crude organic obtained after evaporation under reduced pressure was purified by column chromatography on silica gel (ethyl acetate/petroleum ether (40-60 ^{o}C)) to give 2-phenethoxyacetic acid **387**[211] as a white solid (8.00 g, 89%); M.pt. 41-43 ^{o}C (lit.[211] 46-48 ^{o}C); [Found $(M+NH_4)^+$, 198.1125. $C_{10}H_{16}NO_3$ $(M+NH_4)$ requires 198.1125]. ν_{max} (KBr)/cm^{-1} 2889, 2577, 1750, 1453, 1313, 1244, 1229, 1131, 1026, 920, 750; δ_H (400 MHz, $CDCl_3$) 2.98 (2H, t, J = 7.0 Hz, ArCH_2CH$_2$), 3.83 (2H, t, J = 7.0 Hz, CH$_2$CH_2O), 4.12 (2H, s, OCH_2CO$_2$H), 7.24-7.28 (3H, m, Ar*H*), 7.32-7.36 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 35.6, 67.4, 72.3, 126.1, 128.1, 128.4, 137.6, 173.7.

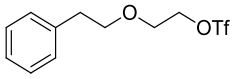
2-Phenethoxyethanol 388



To $LiAlH_4$ (759 mg, 20 mmol, 1.0 equiv.) suspended in dry THF (25 mL) was slowly added 2-phenethoxyacetic acid **387** (3.6 g, 20 mmol, 1.0 equiv.) as a solution in dry THF (25 mL). The reaction mixture was left stirring for 30 min before slow quenching with 2N aqueous HCl. The resulting suspension was extracted with ethyl acetate (3 x 100 mL). The aqueous layer was acidified to pH 1 and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were then washed with aqueous 2N HCl (100 mL) and dried over Na_2SO_4. The crude organic product obtained after evaporation under reduced pressure was purified by column chromatography on silica gel (Et_2O/petroleum ether (40-60 ^{o}C)) to give 2-

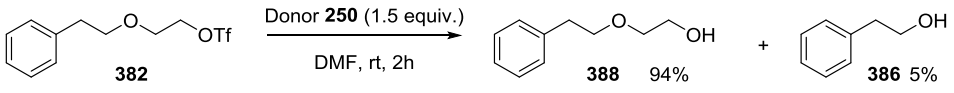
phenethoxyethanol **388**[211] as a colourless oil (3.25 g, 98%); [Found $(M+NH_4)^+$, 184.1331. $C_{10}H_{18}NO_2$ $(M+NH_4)$ requires 184.1332]; ν_{max} (Thin film)/cm^{-1} 3353, 3023, 2926, 1602, 1494, 1453, 1356, 1116, 1047, 888, 879, 849; δ_H (400 Hz, $CDCl_3$) 1.89 (1H, t, J = 6.1 Hz, CH_2OH), 2.94 (2H, t, J = 7.1 Hz, $ArCH_2$), 3.60-3.57 (2H, m, CH_2CH_2OH), 3.75-3.71 (4H, m, CH_2OCH_2), 7.26-7.22 (3H, m, Ar*H*), 7.35-7.30 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 35.8, 61.3, 71.4, 71.6, 125.8, 127.9, 128.4, 138.3.

2-Phenethoxyethyl trifluoromethanesulfonate 382



2-Phenethoxyethanol **388** (831 mg, 5.0 mmol, 1.0 equiv.) was reacted according to general procedure A to give 2-phenethoxyethyl trifluoromethanesulfonate **382**[212] as a colourless oil (1.37 g, 4.6 mmol, 92%); [Found $(M+NH_4)^+$, 316.0830. $C_{11}H_{17}F_3NO_4S$ $(M+NH_4)$ requires 316.0825]; ν_{max} (Thin film)/cm^{-1} 2872, 1496, 1244, 1200, 1144, 1060, 989, 974; δ_H (400 MHz, $CDCl_3$) 2.93 (2H, t, J = 6.3 Hz, $ArCH_2$), 3.78-3.72 (4H, m, CH_2OCH_2), 4.63 (2H, t, J = 4.5 Hz, CH_2CH_2OTf), 7.26-7.23 (3H, m, Ar*H*), 7.34-7.31 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 36.2, 68.0, 72.5, 75.5, 119.6 (q, J = 312 Hz, CF_3), 126.4, 128.4, 128.9, 138.5.

Reaction of 2-Phenethoxyethyl trifluoromethanesulfonate 382 with donor 250



2-Phenethoxyethyl trifluoromethanesulfonate **382** (149 mg, 0.5 mmol, 1.0 equiv.) was reacted according to procedure B to afford 2-phenethoxyethanol **388** (78 mg, 94%) and 2-phenylethanol **386** (3 mg, 5%).

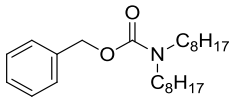
2-Phenethoxyethanol **388** was a colourless oil (78 mg, 94%). Data were as reported previously.

2-Phenylethanol **386**[213] was a colourless oil (3 mg, 5%); ν_{max} (Thin film)/cm^{-1} 3325, 3064, 2939, 2876, 1497, 1451, 1081, 1044, 855, 744, 697; δ_H (400 MHz, $CDCl_3$) 1.86 (1H, s, O*H*),

2.89 (2H, t, J = 6.6 Hz, ArCH_2), 3.87 (2H, t, J = 6.6 Hz, CH_2OH), 7.28-7.25 (3H, m, ArH), 7.37-7.34 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 39.2, 63.7, 126.5, 128.6, 129.0, 135.5; m/z (ESI^+) 144.87 ($[M+Na]^+$, 100%), 128.93 ($[M+Li]^+$, 33).

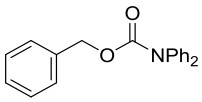
10.3. Experimental Details for Chapter 4

Benzyl dioctylcarbamate 445



Di-*N*-octylamine **447** (5.31 g, 22 mmol, 1.1 equiv.) and triethylamine (2.43 g, 24 mmol, 1.2 equiv.) were cooled to 0 ^{o}C in dry dichloromethane (25 mL). Benzyl chloroformate (3.41 g, 20 mmol, 1 equiv. was then added dropwise with stirring and the reaction stirred at room temperature overnight. Water (50 mL) was then added, followed by dichloromethane (2 x 30 mL). The solution was then washed with further portions of water (2 x 25 mL) and one of brine (10 mL), dried over Na_2SO_4 and the solvent evaporated. The crude organic residue was then eluted over silica in 30% ethyl acetate in petroleum ether v/v, to afford benzyl dioctylcarbamate **445**[214] (6.48 g, 86%) as a colourless oil; ν_{max} (thin film)/cm^{-1} 2953, 2922, 2854, 1697, 1465, 1419, 1211, 1186, 1147, 1089, 767, 727, 696; δ_H (400 MHz, $CDCl_3$) 0.90 (6H, t, J = 6.8 Hz, $(CH_2)_7CH_3$), 1.18-1.37 (20H, m, $CH_3(CH_2)_5CH_2CH_2$), 1.50-1.56 (4H, m, $NCH_2CH_2(CH_2)_5CH_3$), 3.19-3.30 (4H, m, $NCH_2(CH_2)_6CH_3$), 5.15 (2H, s, $ArCH_2O$), 7.29-7.38 (5H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 26.8, 28.1, 28.7, 29.2, 29.3, 31.8, 46.9, 47.6, 66.7,127.7, 127.8, 128.4, 137.2, 156.2; *m*/*z* (APCI$^+$) 376.4 ([M+H]$^+$, 100%).

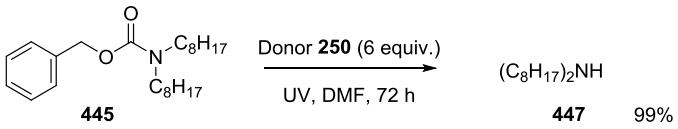
Benzyl diphenylcarbamate 446



To a solution of diphenylamine **448** in dry THF (20 mL) at 0 ^{o}C was slowly added *n*-BuLi (2.17 mL of a 2.3 M solution in hexanes, 5 mmol, 1 equiv.). The reaction mixture was then stirred for 30 min before being added to a cooled solution of benzyl chloroformate (850 mg, 5 mmol, 1 equiv.) in dry THF (10 mL). The reaction mixture was allowed to come to room temperature and stirred overnight. Water (50 mL) was added and extracted with dichloromethane (4 x 30 mL). The organic solution was then washed with further portions of water (2 x 20 mL) and one of brine (10 mL), dried over Na_2SO_4 and the solvent evaporated. The crude organic residue was then eluted over silica in 5-10% ethyl acetate in petroleum ether v/v, to afford benzyl diphenylcarbamate **446** (1.49 g, 99%) as white solid; M.pt. 106-

108 °C (lit.[215] 109 °C); [Found: $(M+H)^+$, 304.1337. $C_{20}H_{18}NO_2^+$ (M+H) requires 304.1332]; ν_{max} (ATR)/cm^{-1} 3113, 3055, 3034, 2968, 1703, 1662, 1490, 1373, 1309, 1205, 1045, 1020, 883, 756, 690, 667; δ_H (400 MHz, $CDCl_3$) 5.24 (2H, s, ArCH_2O), 7.21-7.37 (15H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 67.5, 126.2, 127.0, 127.7, 128.0, 128.5, 129.0, 136.4, 142.5, 156.6; *m*/*z* ($APCI^+$) 304.1 ($[M+H]^+$, 100%).

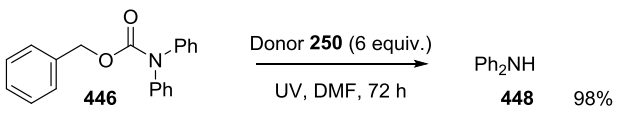
Reaction of benzyl dioctylcarbamate 445 with donor 250



445 **447** 99%

Donor **250** (512 mg, 1.8 mmol, 6 equiv.) was dissolved in degassed DMF (4 mL) in a glovebox. This solution was directly pipetted into benzyl dioctylcarbamate **445** (112 mg, 0.3 mmol, 1 equiv.). The solution was removed to a fumehood and stirred at room temperature for 72 h under UV radiation (365 nm, 2 x 100 W). Water (20 mL) was added to the mixture before extracting with ethyl acetate (4 x 15 mL). The combined organic layers were then washed with water (2 x 15 mL) and brine (10 mL) and dried over Na_2SO_4. The crude organic residue, obtained after evaporation under reduced pressure, was eluted with ethyl acetate on silica gel, to afford dioctylamine **447**[118] as a colourless oil (72 mg, 99%); ν_{max} (ATR)/cm^{-1} 3118, 2954, 2922, 2852, 1460, 1377, 1130, 721; δ_H (400 MHz, $CDCl_3$) 0.89 (6H, t, J = 7.0 Hz, $(CH_2)_7CH_3$), 1.27-1.33 (20H, m, $CH_3(CH_2)_5CH_2CH_2$), 1.45-1.55 (4H, m, $CH_3(CH_2)_5CH_2CH_2$), 2.05-2.45 (1H, bs, N*H*), 2.62 (4H, t, J = 7.5 Hz, $CH_3(CH_2)_6CH_2N$); δ_C (100 MHZ, $CDCl_3$);14.1, 22.6, 27.4, 29.2, 29.5, 29.8, 32.8, 49.8; *m*/*z* ($APCI^+$) 242.3 ($[M+H]^+$, 100%).

Reaction of benzyl diphenylcarbamate with donor



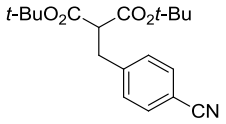
446 **448** 98%

Donor **250** (512 mg, 1.8 mmol, 6 equiv.) was dissolved in degassed DMF (4 mL) in a glovebox. This solution was directly pipetted into benzyl diphenylcarbamate **446** (91 mg, 0.3 mmol, 1 equiv.). The solution was removed to a fumehood and stirred at room temperature

for 72 h under UV radiation (365 nm, 2 x 100 W). Water (20 mL) was added to the mixture before extracting with ethyl acetate (4 x 15 mL). The combined organic layers were then washed with water (2 x 15 mL) and brine (10 mL) and dried over Na_2SO_4. The crude organic residue, obtained after evaporation under reduced pressure, was eluted with ethyl acetate on silica gel, to afford to afford diphenylamine **448** as a white solid (50 mg, 98%); M.pt. 49-50 ^oC (lit.[216] 48-50 ^oC); ν_{max} (ATR)/cm^{-1} 3381, 3039, 2981, 1581, 1514, 1315, 1147, 977, 875, 740, 686; δ_H (400 MHz, $CDCl_3$) 5.62-5.89 (1H, bs, N*H*), 6.95 (2H, t, *J* = 7.4 Hz, Ar*H*), 7.11 (4H, d, *J* = 7.7 Hz, Ar*H*), 7.30 (4H, dd, *J* = 7.7, 7.4 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 117.9, 121.1, 129.4, 143.1; *m*/*z* ($APCI^+$) 170.1 ($[M+H]^+$, 100%).

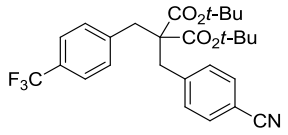
Synthesis of di-*tert*-butyl 2-(4-cyanobenzyl)-2-(4-(trifluoromethyl)benzyl)-malonate 414

i) Synthesis of di-*tert*-butyl 2-(4-cyanobenzyl)malonate 422



Di-*tert*-butyl malonate (0.870 g, 4.0 mmol, 1 equiv.) was added to a suspension of sodium hydride (~60%, 0.177 g, 4.4 mmol, 1.1 equiv.) in dry tetrahydrofuran (20 mL) at 0 ^oC under argon gas. The resulting solution was stirred for 15 min at 0 ^oC and 4-cyanobenzyl bromide (0.790 g, 4.0 mmol, 1 equiv.) in dry tetrahydrofuran (10 mL) was added slowly into the reaction flask. The reaction mixture was further stirred at reflux conditions for 16 h under argon gas. At this point, the reaction was quenched with water (10 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed once again with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulfate. The concentrated solution was purified by column chromatography (10% diethyl ether in petroleum ether) to yield *di-tert-butyl 2-(4-cyanobenzyl)malonate* **422** (1.186 g, 89%) as a white solid. M.pt. 95-97 ^oC; ν_{max}(ATR) /cm^{-1} 2978, 2935, 2226, 1724, 1367, 1306, 1250, 1142, 995, 841, 828; δ_H (400 MHz, $CDCl_3$) 1.40 (18H, s, *t*-Bu), 3.17 (2H, d, *J* = 7.8 Hz, ArCH_2), 3.46 (1H, t, *J* = 7.8 Hz, $ArCH_2CH$), 7.32 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.56 (2H, d, *J* = 8.2 Hz, Ar*H*); δ_C (125 MHz, $CDCl_3$) 27.3, 34.0, 54.3, 81.5, 110.0, 118.3, 129.3, 131.6, 143.6, 167.2; *m/z* (ESI^+) 353.9 ($[M+Na]^+$, 67%), 297.8 (100), 241.8 (25).

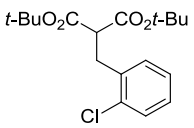
ii) Synthesis of di-*tert*-butyl 2-(4-cyanobenzyl)-2-(4-(trifluoromethyl)benzyl)-malonate 414



Di-*tert*-butyl 2-(4-cyanobenzyl)malonate **422** (0.870 g, 4.0 mmol) was added to a suspension of sodium hydride (~60%, 0.177 g, 4.4 mmol) in dry tetrahydrofuran (20 mL) at 0 ^{o}C under argon gas. The resulting solution was stirred for 15 min at 0 ^{o}C and 1-(bromomethyl)-4-(trifluoromethyl)benzene (0.790 g, 4.0 mmol) in dry tetrahydrofuran (10 mL) was added slowly into the reaction flask. The reaction mixture was further stirred at reflux conditions for 16 h under argon gas. At this point, the reaction was quenched with water (10 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed once again with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulfate. The concentrated solution was purified by column chromatography (10% diethyl ether in petroleum ether) to yield *di-tert-butyl 2-(4-cyanobenzyl)-2-(4-(trifluoromethyl)benzyl)-malonate* **414** (773 mg, 79%) as a white solid. M.pt. 87-89 ^{o}C; ν_{max}(ATR) /cm^{-1}; 2974, 2934, 2226, 1735, 1708, 1614, 1317, 1258, 1159, 1142, 1105, 1069, 839, 821, 729; δ_H (400 MHz, $CDCl_3$) 1.40 (18H, s, *t*-Bu), 3.22 (2H, s, ArCH_2), 3.25 (2H, s, ArCH_2), 7.30-7.35 (4H, m, Ar*H*), 7.54-7.59 (4H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 27.2, 39.1, 39.2, 59.5, 82.0, 110.3, 118.2, 123.7 (q, $J_{C\text{-}F}$ = 272.0 Hz, CF_3), 124.5 (q, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.4 Hz), 128.7 (q, $J_{C\text{-}C\text{-}F}$ = 32.0 Hz), 130.1, 130.7, 131.3, 142.0, 140.2, 169.0; *m/z* (ESI$^+$) 512.0 ([M+Na]$^+$, 90%), 455.9 (78), 399.9 (100), 297.9(44).

Synthesis of di-*tert*-butyl 2-(2-chlorobenzyl)-2-(4-(trifluoromethyl)benzyl)malonate 415

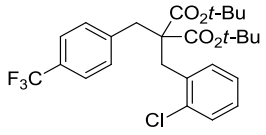
i) Synthesis of di-*tert*-butyl 2-(2-chlorobenzyl)malonate



Di-*tert*-butyl malonate (2.16 g, 10.0 mmol, 1 equiv.) was added to a suspension of sodium hydride (~60%, 0.440 g, 11.0 mmol, 1.1 equiv.) in dry tetrahydrofuran (20 mL) at 0 ^{o}C under argon gas. The resulting solution was stirred for 15 min at 0 ^{o}C and 2-chlorobenzyl bromide

(2.05 g, 10.0 mmol, 1 equiv.) in dry tetrahydrofuran (10 mL) was added slowly into the reaction flask. The reaction mixture was further stirred at reflux conditions for 16 h under argon gas. At this point, the reaction was quenched with water (10 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed once again with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulfate. The concentrated solution was purified by column chromatography (10% diethyl ether in petroleum ether) to yield *di-tert-butyl 2-(2-chlorobenzyl)malonate* (2.453 g, 72%) as a colourless oil. ν_{max}(ATR) /cm^{-1} 2978, 2933, 1724, 1368, 1240, 1155, 847, 748; δ_H (400 MHz, $CDCl_3$) 1.43 (18H, s, *t*-Bu), 3.26 (2H, d, *J* = 7.9 Hz, ArC*H*$_2$), 3.67 (1H, t, *J* = 7.9 Hz, ArCH$_2$C*H*), 7.13-7.18 (2H, m, Ar*H*), 7.22-7.27 (1H, m, Ar*H*), 7.32-7.36 (1H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 27.4, 32.0, 52.6, 81.1, 126.1, 127.6, 129.0, 131.0, 133.7, 135.4, 167.6; *m/z* (ESI$^+$) 362.9 ([M+Na]$^+$, 100%), 306.7 (36), 250.9 (26).

ii) Synthesis of di-*tert*-butyl 2-(2-chlorobenzyl)-2-(4-(trifluoromethyl)benzyl)malonate 415

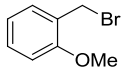


Di-*tert*-butyl 2-(2-chlorobenzyl)malonate (0.870 g, 4.0 mmol) was added to a suspension of sodium hydride (~60%, 0.177 g, 4.4 mmol) in dry tetrahydrofuran (20 mL) at 0 ^oC under argon gas. The resulting solution was stirred for 15 min at 0 ^oC and 1-(bromomethyl)-4-(trifluoromethyl)benzene (0.790 g, 4.0 mmol) in dry tetrahydrofuran (10 mL) was added slowly into the reaction flask. The reaction mixture was further stirred at reflux conditions for 16 h under argon gas. At this point, the reaction was quenched with water (10 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed once again with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulfate. The concentrated solution was purified by column chromatography (10% diethyl ether in petroleum ether) to yield *di-tert-butyl 2-(2-chlorobenzyl)-2-(4-(trifluoromethyl)benzyl)malonate* **415** (848 mg, 85%) as a white solid. M.pt. 83-85 ^oC; ν_{max}(ATR) /cm^{-1}; 2976, 2938, 1726, 1703, 1325, 1277, 1159, 1113, 1067, 835, 760, 745, 679; δ_H (400 MHz, $CDCl_3$) 1.37 (18H, s, *t*-Bu), 3.35 (2H, s, ArC*H*$_2$), 3.42 (2H, s, ArC*H*$_2$), 7.12-7.21 (2H, m, Ar*H*), 7.25-7.31 (2H, m, Ar*H*), 7.29-7.39 (1H, m, Ar*H*), 7.41-7.48 (1H, m,

Ar*H*), 7.48-7.56 (2H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 27.2, 35.3, 39.3, 59.5, 81.6, 123.8 (q, $J_{C\text{-}F}$ = 271.5 Hz, CF_3), 124.3 (q, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.6 Hz), 126.0, 127.4, 128.7 (q, $J_{C\text{-}C\text{-}F}$ = 32.0 Hz), 130.3, 130.7, 131.3, 134.7, 134.9, 140.7, 169.3; *m/z* (ESI^+) 520.9 ($[M+Na]^+$, 100%), 449.4 (67), 408.9 (46), 221.0 (35), 161.0 (27).

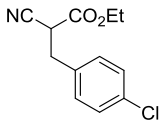
Synthesis of ethyl 2-(4-chlorobenzyl)-2-cyano-3-(2-methoxyphenyl)propanoate 420

i) Synthesis of 1-(bromomethyl)-2-methoxybenzene



To a solution of (2-methoxyphenyl)methanol (1.38 g, 10 mmol, 1 equiv.) in DCM (20 mL) at 0 ^oC was slowly added phosphorus tribromide (0.95 mL, 2.71 g, 15 mmol, 1.5 equiv.) under argon. The reaction mixture was allowed naturally to come to room temperature while stirring for 3 h. The reaction was quenched with water (25 mL) and the aqueous phase extracted with DCM (2 x 25 mL). The combined organic fractions were rinsed with brine (25 mL) and dried over sodium sulfate. Evaporation of the solvent gave rise to an off-white crystalline solid; 1-(bromomethyl)-2-methoxybenzene (2.01 g, quantitative); M.pt. 47-49 ^oC (lit.[217] 47-50 ^oC); ν_{max}(ATR) /cm^{-1} 3003, 2959, 2835, 1599, 1493, 1464, 1250, 1028, 752; δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, OCH_3), 4.62 (2H, s, ArCH_2Br), 6.92 (1H, d, *J* = 8.3 Hz, Ar*H*), 6.97 (1H, ddd, *J* = 7.5, 7.5, 0.9 Hz, Ar*H*), 7.31-7.39 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 28.6, 55.1, 110.5, 120.2, 125.7, 129.7, 130.4, 157.0; *m/z* (GCMS, CI^+) 202.9 ($[M+H]^+$, 8%), 200.9 ($[M+H]^+$, 9), 149.0 (11), 121.1($[M-Br]^+$, 100).

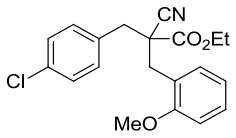
ii) Synthesis of ethyl 3-(4-chlorophenyl)-2-cyanopropanoate 421b



4-Chlorobenzaldehyde (703 mg, 5 mmol, 1 equiv.), benzene-1,2-diamine (270 mg, 2.5 mmol, 0.5 equiv.) and proline (115 mg, 1 mmol, 20 mol%) were added to a solution of ethyl 2-cyanoacetate (283 mg, 2.5 mmol, 0.5 equiv.) in ethanol (5 mL). The reaction mixture was stirred at room temperature for 16 h then DCM was added and filtered through a sintered

funnel. The concentrated solution was purified by column chromatography (60% DCM in petroleum ether) to yield *ethyl 3-(4-chlorophenyl)-2-cyanopropanoate* **421b**[218] (524 mg, 44%) as a pale orange oil; ν_{max}(ATR) /cm^{-1} 2984, 2940, 2907, 2251, 1740, 1493, 1447, 1369, 1260, 1196, 1094, 1016, 852, 833, 806, 718; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, J = 7.1 Hz, OCH_2CH_3), 3.15 (1H, dd, J = 14.0, 8.1 Hz, $ArCH_2$), 3.24 (1H, dd, J = 14.0, 5.8 Hz, $ArCH_2CH$), 4.21 (2H, q, J = 7.1 Hz, OCH_2CH_3), 7.20 (2H, d, J = 8.4 Hz, Ar*H*), 7.29 (2H, d, J = 8.4 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.9, 34.9, 39.4, 63.0, 116.0, 129.0, 130.5, 133.7, 133.9, 165.3; *m/z* (MM-ES+APCI$^+$) 236.0 ([M-H]$^+$, 94%), 162.1 (100).

iii) Synthesis of ethyl 2-(4-chlorobenzyl)-2-cyano-3-(2-methoxyphenyl)propanoate 420

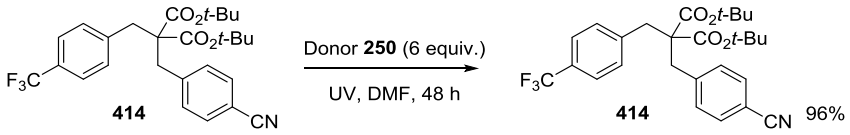


Ethyl 3-(4-chlorophenyl)-2-cyanopropanoate **421b** (0.262 g, 1.1 mmol, 1 equiv.) as a solution in dry THF (2 mL) was added to a suspension of sodium hydride (~60%, 0.048 g, 1.21 mmol, 1.1 equiv.) in dry THF (3 mL) under an argon atmosphere. The resulting solution was stirred for 15 min and 1-(bromomethyl)-2-methoxybenzene (0.243 g, 1.21 mmol, 1.1 equiv.) as a solution in dry THF (2 mL) was added slowly into the reaction flask. The reaction mixture was further stirred at 35 ^oC for 16 h under argon gas. At this point, the reaction was diluted with diethyl ether (25 mL) and poured into HCl (1N aq., 50 mL). The aqueous phase was extracted with further diethyl ether (2 x 25 mL) then the combined organic phases washed once with brine (25 mL) and dried over anhydrous sodium sulfate. The concentrated solution was purified by column chromatography (50% DCM in petroleum ether) to yield *ethyl 2-(4-chlorobenzyl)-2-cyano-3-(2-methoxyphenyl)propanoate* **420** (214 mg, 54%) as a colourless wax; ν_{max}(ATR) /cm^{-1}; 2980, 2938, 2837, 2245, 1736, 1493, 1248, 1123, 1028, 1016, 835, 754, 718; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, t, J = 7.2 Hz, OCH_2CH_3), 3.04 (1H, d, J = 13.6 Hz, ArC*H*), 3.30 (d, J = 13.4 Hz, ArC*H*), 3.36 (1H, d, J = 13.6 Hz, ArC*H*), 3.42 (1H, d, J = 13.4 Hz, ArC*H*), 3.84 (3H, s $ArOCH_3$), 4.09 (q, J = 7.2 Hz, OCH_2CH_3), 6.91-6.98 (2H, m, Ar*H*), 7.26-7.33 (6H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.3, 36.5, 41.4, 51.8, 54.8, 62.1, 110.2, 118.0, 120.0, 122.1, 128.1, 128.9, 131.0, 131.1, 132.7, 133.2, 157.4, 167.7; *m/z* (MM-ES+APCI$^+$) 358.1 ([M+H]$^+$, 36%), 160.1 (100).

General Procedure C- UV-activated electron-transfer reactions using donor 250:

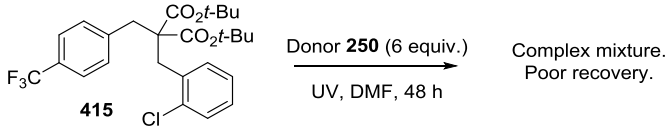
In a dry nitrogen-containing glovebox, a solution of donor **250** in dry *N*,*N*-dimethylformamide (4 mL) was added to a flask containing appropriate substrate. The sealed flask was then reacted under UV irradiation for a specified time, using two focused UV lamps (365 nm, each 100 watts). The reaction mixture was added to aqueous HCl (1N, 25 mL), before extracting with diethyl ether (3 x 25 mL). The combined organic layers were then washed with water (3 x 25 mL), brine (10 mL) and dried over Na_2SO_4. The crude product was adsorbed onto silica gel and purified by column chromatography, providing the corresponding products in yields as stated.

Reaction of di-*tert*-butyl 2-(4-cyanobenzyl)-2-(4-(trifluoromethyl)benzyl)malonate 414 with donor 250



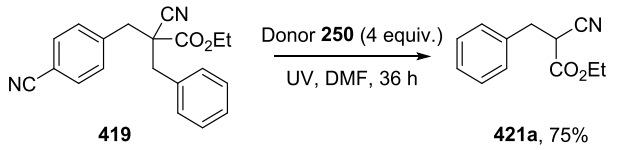
The general procedure C for electron transfer reactions under UV conditions for 48 h was applied to di-*tert*-butyl 2-(4-cyanobenzyl)-2-(4-(trifluoromethyl)benzyl)malonate **414** (0.147 g, 0.3 mmol, 1 equiv.) using the donor **250** (0.511 g, 1.8 mmol, 6 equiv.). The general acidic work-up procedure gave rise to good recovery of *di-tert-butyl 2-(4-cyanobenzyl)-2-(4-(trifluoromethyl)benzyl)malonate* **414** (140 mg, 96%) with data as reported above.

Reaction of di-*tert*-butyl 2-(2-chlorobenzyl)-2-(4-(trifluoromethyl)benzyl)malonate 415 with donor 250



The general procedure C for electron transfer reactions under UV conditions for 48 h was applied to di-*tert*-butyl 2-(2-chlorobenzyl)-2-(4-(trifluoromethyl)benzyl)malonate **415** (0.150 g, 0.3 mmol, 1 equiv.) using the donor **250** (0.511 g, 1.8 mmol, 6 equiv.). The general acidic work-up procedure gave rise to a complex mixture of products and poor mass recovery.

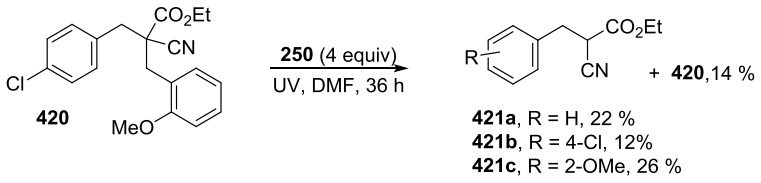
Reaction of ethyl 2-benzyl-2-cyano-3-(4-cyanophenyl)propanoate 419 with donor 250



419 **421a**, 75%

The general procedure C for electron transfer reactions under UV conditions for 36 h was applied to ethyl 2-benzyl-2-cyano-3-(4-cyanophenyl)propanoate **419** (0.050 g, 0.16 mmol, 1 equiv.) using the donor **250** (0.182 g, 0.64 mmol, 4 equiv.). The general acidic work-up procedure gave rise to ethyl 2-cyano-3-phenylpropanoate **421a**[219] as a colourless oil (27.5 mg, 75%). ν_{max} (ATR) /cm^{-1} 2986, 2924, 2361, 1739, 1498, 1453, 1265, 1206, 1039; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, J = 7.2 Hz, CH_2CH_3), 3.20 (1H, dd, J = 14.0, 8.0 Hz, $ArCH_2$), 3.29 (1H, dd, J = 14.0, 5.6 Hz, $ArCH_2$), 3.72 (1H, dd, J = 8.4, 5.6 Hz, $ArCH_2CH$), 4.25 (2H, q, J = 7.2 Hz, $CO_2CH_2CH_3$), 7.27-7.38 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1, 35.9, 39.8, 63.1, 116.3, 127.9, 129.0, 129.2, 135.4, 165.7.

Reaction of ethyl 2-(4-chlorobenzyl)-2-cyano-3-(2-methoxyphenyl)propanoate 420 with donor 250



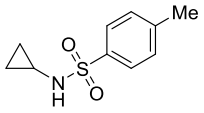
420

The general procedure for electron transfer reactions under UV conditions for 36 h was applied to ethyl 2-(4-chlorobenzyl)-2-cyano-3-(2-methoxyphenyl)propanoate **420** (0.107 g, 0.3 mmol, 1 equiv.) using the donor **250** (0.329 g, 1.2 mmol, 4 equiv.). The general acidic work-up procedure followed by column chromatography in 20-40% DCM petroleum ether yielded ethyl 2-cyano-3-phenylpropanoate **421a** (13 mg, 22%) with data as reported above, ethyl 3-(4-chlorophenyl)-2-cyanoprop-anoate **421b** (9 mg, 12%) with data as reported above, ethyl 2-cyano-3-(2-methoxyphenyl)propanoate **421c** (18 mg, 26%), and recovered ethyl 2-(4-chlorobenzyl)-2-cyano-3-(2-methoxyphenyl)propanoate **420** (15 mg, 14%).

Ethyl 2-cyano-3-(2-methoxyphenyl)propanoate **421c**[220] was a pale yellow oil; ν_{max}(ATR) /cm^{-1} 2982, 2941, 2839, 2249, 1742, 1495, 1244, 1113, 1026, 858, 752; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 3.13 (1H, dd, *J* = 13.4, 8.9 Hz, ArC*H*), 3.38 (1H, dd, *J* = 13.4, 6.6 Hz, ArC*H*), 3.95 (1H, dd, *J* = 8.9, 6.6 Hz, $ArCH_2CH$), 4.22-4.28 (2H, m, OCH_2CH_3), 6.90 (1H, d, *J* = 8.3 Hz, Ar*H*), 6.94 (1H, ddd, *J* = 7.4, 7.4, 1.0 Hz, Ar*H*), 7.22 (1H, dd, *J* = 7.4, 1.6 Hz, Ar*H*), 7.28-7.33 (1H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.5, 31.1, 36.9, 54.8, 62.2, 109.9, 116.0, 120.2, 123.2, 128.7, 130.6, 157.0, 165.5; *m/z* (GCMS, CI$^+$) 262.1 ($[M+C_2H_5]^+$, 16%), 234.1 ($[M+H]^+$, 53), 188.0 (32), 121.0 (100).

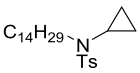
10.4. Experimental Details for Chapter 5

Synthesis of *N*-cyclopropyl-4-methylbenzenesulfonamide 543



To a solution of cyclopropylamine **542** (1.14 g, 20 mmol, 1 equiv) and pyridine (1.90 g, 24 mmol, 1.2 equiv.) in water (20 mL) was added toluenesulfonyl chloride (4.19 g, 22 mmol, 1.1 equiv.) portion-wise with stirring. The reaction mixture was then stirred at room temperature for 1 h before filtering and rinsing the precipitate with additional 10 mL water. The yellow solid was then dissolved in ether, dried over sodium sulfate and concentrated in vacuo to yield an off-white solid. Recrystallization from ethyl acetate/hexane gave rise to *N-cyclopropyl-4-methylbenzenesulfonamide* **543** as a white crystalline solid (3.72 g, 88%); M.pt. 72-74 ^{o}C; ν_{max} (ATR)/cm^{-1} 3271, 2993, 1599, 1409, 1362, 1315, 1155, 1093, 881, 816; δ_H (400 MHz, $CDCl_3$) 0.59-0.63 (4H, m, cyclopropyl-*H*), 2.23-2.29 (1H, m, NC*H*), 2.46 (3H, s, ArCH_3), 4.95 (1H, s, N*H*), 7.34 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.81 (2H, d, *J* = 8.4 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 5.6, 21.0, 23.8, 127.0, 129.1, 136.2, 143.0; *m*/*z* (GCMS, CI$^+$, CH_4) 252.0 (5%), 212.0 ([M+H]$^+$, 100), 154.9 (78).

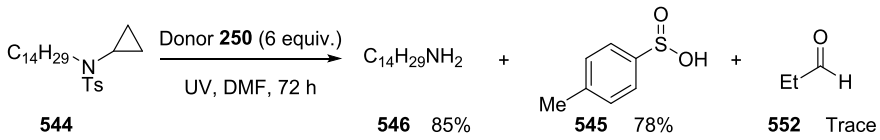
Synthesis of *N*-cyclopropyl-*N*-tetradecyl-4-methylbenzenesulfonamide 544



To sodium hydride (as a 60% suspension in mineral oil, 440 mg, 11 mmol, 1.1 equiv.) dispersed in dry THF (20 mL) was added a solution of *N*-cyclopropyl-4-methylbenzenesulfonamide **543** (2.32 g, 11 mmol, 1.1 equiv.) in dry THF (15 mL) under argon. A dense slurry formed which did not disperse upon addition of more dry THF (20 mL) so further dry DMF (10 mL) was added and stirred for 1 h before addition of 1-bromotetradecane (2.44 mL, 10 mmol, 1 equiv.) then stirring overnight at reflux. The reaction mixture was then allowed to return to room temperature and quenched with HCl (aqueous, 2N, 50 mL) and diethyl ether (150 mL) then extracted with further ether (2 x 50 mL). This solution was then sequentially washed with HCl (aqueous, 2N, 50 mL), water (50 mL), brine (25 mL), dried over sodium sulfate, filtered and evaporated under reduced

pressure. The resulting oil was purified by column chromatography in 10% diethyl ether/petroleum ether to yield *N-cyclopropyl-N-tetradecyl-4-methylbenzenesulfonamide* **544** as a white solid (3.62 g, 89%); M.pt. 35-37 ^{o}C; ν_{max} (ATR)/cm^{-1} 2922, 2852, 1456, 1344, 1161, 1091, 1026, 814, 713; δ_H (400 MHz, $CDCl_3$) 0.66-0.73 (2H, m, cyclopropyl-*H*), 0.84-0.88 (2H, m, cyclopropyl-*H*), 0.90 (3H, t, *J* = 6.8 Hz, CH_2CH_3) 1.24-1.38 (22H, m, $(CH_2)_{11}$), 1.57-1.64 (2H, m, NCH_2CH_2), 2.00-2.06 (1H, m, NC*H*), 2.45 (3H, s, $ArCH_3$), 3.15-3.19 (2H, m, NCH_2), 7.32 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.76 (2H, d, *J* = 8.1 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 6.7, 13.5, 20.8, 22.1, 26.4, 27.9, 28.7, 28.8, 29.0, 29.0, 29.1, 29.2, 29.8, 31.4, 50.7, 127.0, 128.9, 135.3, 142.5; *m*/*z* (GCMS, CI+, CH4) 436.2 ($[M+C_2H_5]^+$, 15%), 408.2 ($[M+H]^+$, 100), 252.2 (18).

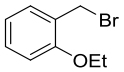
Reaction of *N*-cyclopropyl-*N*-tetradecyl-4-methylbenzenesulfonamide 544 with photoactivated donor 250



N-cyclopropyl-*N*-tetradecyl-4-methylbenzenesulfonamide **544** (105 mg, 0.3 mmol, 1 equiv.) was reacted under standard conditions with photoactivated donor **250** (512 mg, 1.8 mmol, 6 equiv.). After 72 h reaction time the reaction mixture was poured into HCl (2N, aq., 25 mL) and diethyl ether (25 mL), The aqueous fraction was washed with an additional 2 x 25 mL ether and the combined organic fractions rinsed with HCl (2N, aq., 25 mL), water (25 mL) and brine, then dried over sodium sulfate and concentrated under reduced pressure to yield 4-methylbenzenesulfinic acid **545**, *N*-cyclopropyl-4-methyl-*N*-tetradecylbenzenesulfonamide **544** and propionaldehyde **552** (trace). The original acidic aqueous fractions from above were basified to pH 10 with sodium hydroxide then extracted with ether (3 x 25 mL). The combined organic fractions were then rinsed with water (25 mL) and brine (2 x 25 mL), dried (sodium sulfate) and concentrated in vacuo to afford tetradecylamine **546** as an off-white solid (58 mg, 85%); M.pt. 36-38 ^{o}C (lit.[221] 40 ^{o}C); ν_{max} (ATR)/cm^{-1} 3334, 2955, 2918, 2851, 1570, 1487, 1468, 1262, 1096, 1022, 802, 719; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t , *J* = Hz, $(CH_2)_{13}CH_3$), 1.24-1.39 (24H, m, $NCH_2(CH_2)_{12}$), 1.43-1.51 (2H, m, NCH_2), 2.78-2.91 (2H, bs, NH_2); δC (100 MHz, $CDCl_3$) 13.6, 22.2, 28.9, 28.9, 29.1, 29.2, 29.2, 31.4; *m*/*z* (GCMS, CI$^+$, CH_4) 242.2 ($[M+C_2H_5]^+$, 24%), 214.1 ($[M+H]^+$, 97), 212.1 (100). Basification

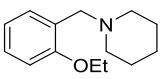
followed by re-extraction of the mixture of 4-methylbenzenesulfinic acid **545** and *N*-cyclopropyl-4-methyl-*N*-tetradecylbenzenesulfonamide **544** yielded the two products (36 mg, 78%) and (6 mg, 9%) respectively with data as reported above. Propionaldehyde was tentatively detected in low concentration by a signature aldehyde peak in ^{1}H NMR (9.77, t, *J* = 1.7 Hz).

Synthesis of 1-(Bromomethyl)-2-ethoxybenzene



A solution of (2-ethoxyphenyl)methanol (1.52 g, 10 mmol) in dry dichloromethane (10 mL) was cooled to 0 °C in an atmosphere of argon. To this was slowly added tribromophosphine (0.38 mL, 4 mmol) and the solution stirred at room temperature for 24 h. To the mixture was added water (20 mL) which was then extracted with diethyl ether (3 x 20 mL) and these combined extracts were rinsed with water (3 x 20 mL), dried over sodium sulfate and concentrated *in vacuo* to afford 1-(bromomethyl)-2-ethoxybenzene[222] as a colourless oil (1.94 g, 90%). ν_{max} (Thin film)/cm^{-1} 3027, 2978, 1599, 1495, 1245, 1045, 749; δ_H (400 MHz, $CDCl_3$) 1.48 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 4.12 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.60 (2H, s, $ArCH_2$), 6.87 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.93 (1H, td, *J* = 7.5, 1.6 Hz, Ar*H*), 7.26-7.29 (1H, m, Ar*H*), 7.34 (1H, dd, *J* = 7.5, 1.6 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.9, 29.2, 63.9, 111.9, 120.5, 126.3, 130.1, 130.9, 156.9; *m*/*z* (ESI$^+$) 134.93 ([M-Br]$^+$, 100%).

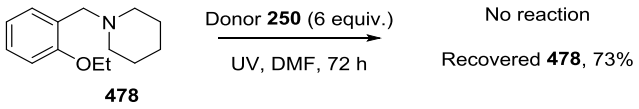
1-(2-Ethoxybenzyl)piperidine 478



To a solution of 1-(bromomethyl)-2-ethoxybenzene (1.16 g, 7.5 mmol) and piperidine (1.48 mL, 15 mmol) in dry THF (30 mL) was added *N*-ethyl-*N*-isopropylpropan-2-amine (3.9 mL, 22.5 mmol). The suspension was stirred at room temperature for 72 h. To the mixture was added water (25 mL) which was then extracted with diethyl ether (3 x 25 mL) and these combined and rinsed with water (3 x 25 mL). The organic solution was dried over sodium sulfate, concentrated *in vacuo* and purified by silica gel column chromatography (petroleum ether/ethyl acetate, 1:1, v/v) to afford *1-(2-ethoxybenzyl)piperidine* **478** as a yellow oil (592

mg, 36%); [Found: $(M+H)^+$, 220.1696. $C_{14}H_{22}NO^+$ $(M+H)^+$ requires 220.1696]; ν_{max} (KBr)/cm^{-1} 3032, 2923, 1599, 1454, 1231, 1048, 754; δ_H (400 MHz, $CDCl_3$) 1.45-1.50 (5H, m, $CH_2CH_2CH_2/OCH_2CH_3$), 1.55–1.65 (4H, m, $N(CH_2CH_2)_2$), 2.40-2.50 (4H, bs, $N(CH_2)_2$), 3.56 (2H, s, $ArCH_2$), 4.05 (2H, q, J = 7.0 Hz, OCH_2CH_3), 6.85 (1H, dd, J = 7.6, 1.4 Hz, Ar*H*), 6.92 (1H, td, J = 7.6, 1.6 Hz, Ar*H*), 7.20 (1H, td, J = 7.7, 1.4, Ar*H*), 7.37 (1H, dd, J = 7.7, 1.6 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.9, 24.4, 26.1, 54.5, 56.6, 63.7, 111.5, 120.1, 127.0, 127.6, 130.5, 157.2.

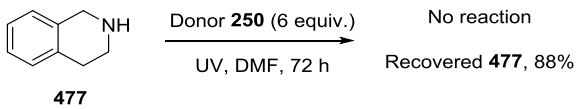
Reaction of 1-(2-ethoxybenzyl)piperidine 478 with donor 250 under photoactivation



478

1-(2-Ethoxybenzyl)piperidine **478** (66 mg, 0.3 mmol, 1.0 equiv.) was taken into a glovebox under an argon atmosphere and donor **250** (512 mg, 1.8 mmol, 6.0 equiv.) in DMF (5 mL) was added. The solution was stirred at room temperature for 72 h under high intensity UV radiation (365 nm). To the mixture was added water (25 mL) which was then extracted with diethyl ether (3 x 25 mL) and these combined and rinsed with water (3 x 25 mL). The organic solution was dried over sodium sulfate, concentrated *in vacuo* to recover the starting material 1-(2-ethoxybenzyl)piperidine **478** (58 mg, 73%) as a colourless oil. Data were as reported previously.

Reaction of 1,2,3,4-tetrahydroisoquinoline 477 with donor 250 under photoactivation



477

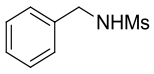
1,2,3,4-Tetrahydroisoquinoline **477** (40 mg, 0.3 mmol, 1.0 equiv.) was taken into a glovebox under an argon atmosphere and donor **250** (512 mg, 1.8 mmol, 6.0 equiv.) in DMF 5 mL) was added. The solution was stirred at room temperature for 72 h under high intensity UV radiation (365 nm). To the mixture was added water (25 mL) which was then extracted with diethyl ether (3 x 25 mL) and these combined and rinsed with water (3 x 25 mL). The organic solution was dried over sodium sulfate, concentrated *in vacuo* to recover the starting

material 1,2,3,4-tetrahydroisoquinoline **477**[223] as a light yellow oil (35 mg, 88%); ν_{max} (Thin film)/cm^{-1} 3282, 3020, 2926, 2828, 1664, 1454, 1327, 1260, 1122, 941, 805, 745, 637; δ_H (400 MHz, $CDCl_3$) 2.82 (2H, t, J = 6.0 Hz, $ArCH_2CH_2$), 3.16 (2H, t, J = 6.0 Hz, $ArCH_2$), 4.04 (2H, s, $ArCH_2N$), 6.02 (1H, s, Ar*H*), 7.02-7.04 (1H, m, Ar*H*), 7.10-7.16 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 28.7, 43.4, 47.8, 125.3, 125.5, 125.7, 128.8, 134.3, 135.4; *m*/*z* (ESI$^+$) 134.0 ([M+H]$^+$, 100%).

General Procedure D- for the methanesulfonylation of amines:

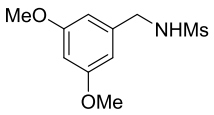
The amine (1 equiv.) was dissolved in dry dichloromethane (20 mL) and triethylamine (4 equiv.) added with stirring. Methanesulfonyl chloride (2 equiv.) was added dropwise to the stirred solution under a flow of argon then left stirring at room temperature overnight. Aqueous 2N NaOH (50 mL) was then added, and extracted with dichloromethane (3 x 25 mL). The aqueous fraction was acidified with aqueous HCl (37%) then washed with further portions of DCM (4 x 25 mL). The organic fractions were rinsed with water (3 x 20 mL), dried over Na_2SO_4 and the solvent evaporated. The crude organic residue was then filtered through celite (DCM), to afford the pure corresponding methanesulfonamide.

***N*-Benzylmethanesulfonamide 482e**



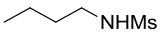
Benzylamine (5.36 g, 50 mmol, 1 equiv.) was reacted according to procedure D to afford *N*-benzylmethanesulfonamide **482e** as a white solid (7.87 g, 87%); M.pt. 61-63 ^oC (lit.[224] 63-64 ^oC); ν_{max} (ATR)/cm^{-1} 3232, 3014, 1461, 1438, 1320, 1134, 1062, 972, 864, 769; δ_H (400 MHz, $CDCl_3$) 2.90 (3H, s, SO_2CH_3), 4.35 (2H, d, J = 6.0 Hz, $ArCH_2N$), 4.67 (1H, br. s, N*H*), 7.33-7.42 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 40.7, 46.7, 127.4, 127.7, 128.5, 136.1; *m*/*z* (ESI$^+$) 184.00 ([M-H]$^+$, 100%).

_N_-(3,5-dimethoxybenzyl)methanesulfonamide 482e′



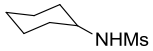
(3,5-Dimethoxyphenyl)methanamine (16.72 g, 100 mmol, 1 equiv.) was reacted according to procedure D to afford *N-(3,5-dimethoxybenzyl)methanesulfonamide* **482e′** as a white solid (8.50 g, 69%). M.pt. 77-79 ^{o}C; [Found: (HNESP^{+}) $(M+NH_4)^{+}$, 263.1063. $C_{10}H_{19}N_2O_4S$ $(M+NH_4)$, requires 263.1060; $(M+H)^{+}$, 246.0797. $C_{10}H_{16}NO_4S$ (M+H) requires 246.0795]; ν_{max} (ATR)/cm^{-1} 2935, 2846, 1595, 1459, 1321, 1205, 1146, 1064, 924, 791, 737; δ_H (500 MHz, $CDCl_3$) 2.92 (3H, s, SO_2CH_3), 3.80 (6H, s, $ArOCH_3$), 4.27 (2H, d, J = 6 Hz, $ArCH_2N$), 4.50-4.58 (1H, bs, N*H*), 6.41 (1H, t, J = 2.5 Hz, Ar*H*), 6.49 (2H, d, J = 2.5 Hz, Ar*H*); δ_C (125 MHz, $CDCl_3$) 41.2, 47.3, 55.4, 99.9, 105.7, 139.0, 161.3.

_N_-butylmethanesulfonamide 482b



Butan-1-amine (7.31 g, 100 mmol, 1equiv.) was reacted according to procedure D to afford *N*-butylmethanesulfonamide **482b**[225] as a colourless oil (6.56 g, 42%); ν_{max} (ATR)/cm^{-1} 3504, 3202, 3094, 2958, 2874, 1565, 1461, 1308, 1164, 1052, 786; δ_H (500 MHz, $CDCl_3$) 0.95 (3H, t, J = 7.4 Hz, CH_2CH_3), 1.36-1.44 (2H, m, $CH_2CH_2CH_3$), 1.54-1.60 (2H, m, $NCH_2CH_2CH_2CH_3$), 2.92 (3H, s, SO_2CH_3), 3.15 (2H, dt, J = 7.0, 6.8 Hz, NCH_2CH_2), 4.17-4.26 (1H, bs, N*H*); δ_C (125 MHz, $CDCl_3$) 13.6, 19.7, 32.1, 40.1, 43.0; *m*/*z* (ESI^{-}) 149.9 ([M-H]$^{-}$, 100%).

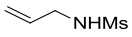
_N_-cyclohexylmethanesulfonamide 482i



Cyclohexylamine (9.92 g, 100 mmol, 1 equiv.) was reacted according to procedure D to afford *N*-cyclohexylmethanesulfonamide **482i** as an off-white solid (16.2 g, 91%); M.pt. 101-103 ^{o}C (lit.[226] 103 ^{o}C); ν_{max} (ATR)/cm^{-1} 3260, 2924, 2855, 1446, 1305, 1149, 1082, 1002, 881, 756; δ_H (400 MHz, $CDCl_3$) 1.15-1.42 (6H, m, $NCHCH_2CH_2CH_2CH_2$), 1.73-1.79

(2H, m, NCHCH_2), 2.00-2.04 (2H, m, NCHCH_2) 3.30 (3H, s, SO_2CH_3), 3.32-3.38 (1H, m, NC*H*), 4.09-4.18 (1H, bs, N*H*); δ_C (100 MHz, $CDCl_3$) 24.3, 24.6, 33.1, 41.5, 52.3; *m*/*z* ($APCI^+$) 195.1 ($[M+NH_4]^+$, 100%).

_N_-allylmethanesulfonamide 492

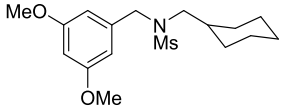


Allylamine (2.85 g, 50 mmol. 1 equiv.) was reacted according to procedure D to afford *N*-allylmethanesulfonamide **492**[227] as a yellow oil (4.71 g, 70%); ν_{max} (ATR)/cm^{-1} 3506, 3277, 3096, 1625, 1438, 1308, 1147, 1054, 970, 926, 836, 748; δ_H (500 MHz, $CDCl_3$) 2.98 (3H, s, SO_2CH_3), 3.78-3.81 (2H, m, NCH_2), 4.36 (1H, s, N*H*), 5.23-5.34 (2H, m, CH=CH_2), 5.85-5.93 (1H, m, C*H*=CH_2); δ_C (125 MHz, $CDCl_3$) 41.1, 45.7, 117.8, 133.5; *m*/*z* (ESI^-) 133.9 ($[M-H]^-$, 100%).

General Procedure E- for the alkylation of methanesulfonamides:

Sulfonamide (1.0 equiv.) and alkyl halide (1.2 equiv.) were dissolved in DMF (25 mL) and potassium carbonate (2 equiv.) added. The suspension was heated at 90 ^oC for 72 h and then allowed to cool to room temperature. Water (30 mL) was then added, followed by ethyl acetate (3 x 30 mL). The solution was then washed with a further portions of water (30 mL) and one of brine (30 mL), dried over Na_2SO_4 and the solvent evaporated. The crude organic residue was then eluted over silica in ethyl acetate, to afford the pure corresponding methanesulfonamide.

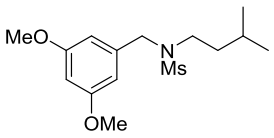
_N_-(Cyclohexylmethyl)-_N_-(3,5-dimethoxybenzyl)methanesulfonamide 485a



N-(3,5-Dimethoxybenzyl)methanesulfonamide (1.96 g, 8 mmol, 1.0 equiv.), was reacted with (bromomethyl)cyclohexane (1.70 g, 9.6 mmol, 1.2 equiv.) according to procedure E to afford *N-(cyclohexylmethyl)-N-(3,5-dimethoxybenzyl)methanesulfonamide* **485a** as a white

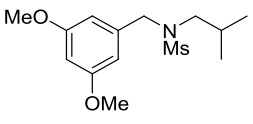
solid (1.12 g, 54%). M.pt. 59-61 ^{o}C; [Found: (HNESP^{+}) $(2M+NH_4)^+$, 700.3662. $C_{34}H_{58}N_3O_8S_2^+$ $(2M+NH_4)^+$, requires 700.3660; $(M+NH_4)^+$, 359.2001. $C_{17}H_{31}N_2O_4S^+$ $(M+NH_4)^+$, requires 359.1999; $(M+H)^+$, 342.1738. $C_{17}H_{28}NO_4S$ $(M+H)^+$ requires 342.1734]; ν_{max} (ATR)/cm^{-1} 2934, 2855, 1608, 1431, 1321, 1155, 1045, 1023, 976; δ_H (500 MHz, $CDCl_3$) 0.88-1.00 (3H, m, cyclohexyl), 1.16-1.29 (3H, m, cyclohexyl), 1.55-1.75 (5H, m, cyclohexyl), 2.83 (3H, s, SO_2CH_3), 3.01 (2H, d, J = 7.2 Hz, NCH_2CH), 3.82 (6H, s, $ArOCH_3$), 4.35 (2H, s, NCH_2Ar), 6.42 (1H, t, J = 2 Hz, Ar*H*), 6.52 (2H, d, J = 2 Hz, Ar*H*); δ_C (125 MHz, $CDCl_3$) 25.8, 26.4, 30.8, 36.0, 39.0, 51.9, 53.8, 55.4, 99.7, 106.5, 138.5, 161.0.

_N_-(3,5-Dimethoxybenzyl)-_N_-isopentylmethanesulfonamide 485b



N-(3,5-Dimethoxybenzyl)methanesulfonamide (491 mg, 2 mmol, 1 equiv.), was reacted with 1-bromo-3-methylbutane according to procedure E (362 mg, 2.4 mmol, 1.2 equiv.) to afford *N-(3,5-dimethoxybenzyl)-N-isopentylmethanesulfonamide* **485b** as a white solid (347 mg, 55%). M.pt. 49-51 ^{o}C; [Found: (HNESP^{+}) $(M+H)^+$, 316.1579. $C_{15}H_{26}NO_4S$ (M+H), requires 316.1577]; ν_{max} (ATR)/cm^{-1} 3005, 2945, 2872, 2837, 1588, 1465, 1437, 1320, 1288, 1211, 1144, 1059, 971, 913, 857, 799, 785, 691; δ_H (400 MHz, $CDCl_3$) 0.86 (6H, d, J = 6.5 Hz, CH_2CHCH_3), 1.43-1.47 (2H, m, NCH_2CH_2CH), 1.49-1.57 (1H, m, $NCH_2CH_2CHCH_3$), 2.87 (3H, s, SO_2CH_3), 3.20-3.24 (2H, m, NCH_2CH_2), 3.82 (6H, s, $ArOCH_3$), 4.33 (2H, s, NCH_2Ar), 6.52 (2H, d, J = 2.2 Hz, Ar*H*), 6.42 (1H, t, J = 2.2 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.9, 25.3, 36.2, 38.7, 45.3, 50.5, 54.9, 99.3, 105.8, 138.1, 160.6.

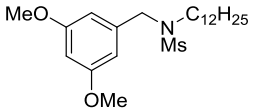
_N_-(3,5-Dimethoxybenzyl)-_N_-isobutylmethanesulfonamide 485c



N-(3,5-Dimethoxybenzyl)methanesulfonamide (490.6 mg, 2.0 mmol, 1 equiv.), was reacted with 1-iodo-2-methylpropane (441.6 mg, 2.4 mmol, 1.2 equiv.) according to procedure E to afford *N-(3,5-dimethoxybenzyl)-N-isobutylmethanesulfonamide* **485c** as a yellow oil (376

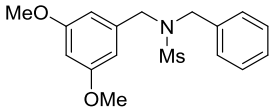
mg, 63%). [Found: (HNESP$^+$) (M+H)$^+$, 302.1423. $C_{14}H_{24}NO_4S$ (M+H), requires 302.1421]; ν_{max} (ATR)/cm^{-1} 2964, 2841, 1599, 1471, 1428, 1323, 1210, 1146, 1040, 950, 881, 833, 699; δ_H (400 MHz, $CDCl_3$) 0.91 (6H, d, J = 6.4 Hz, NCH_2CHCH_3), 1.83-1.93 (1H, m, NCH_2CHCH_3), 2.84 (3H, s, SO_2CH_3), 3.01 (2H, d, J = 7.6 Hz, NCH_2CH), 3.82 (6H, s, $ArOCH_3$), 4.35 (2H, s, NCH_2Ar), 6.42 (1H, t, J = 2.4 Hz, Ar*H*), 6.53 (2H, d, J = 2.4 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 19.5, 26.2, 38.3, 51.4, 54.7, 54.9, 99.2, 106.0, 137.9, 160.5.

_N_-(3,5-dimethoxybenzyl)-_N_-dodecylmethanesulfonamide 485d



N-(3,5-Dimethoxybenzyl)methanesulfonamide (1.23 g, 5 mmol, 1 equiv.), was reacted with dodecylbromide (2.49 g, 10 mmol, 2 equiv.) according to procedure E to afford *N-(3,5-dimethoxybenzyl)-N-dodecylmethanesulfonamide* **485d** as a colourless oil (1.54 g, 74%). [Found: (HNESP$^+$) (M+H)$^+$, 414.2660. $C_{22}H_{40}NO_4S$ (M+H), requires 414.2673]; ν_{max} (ATR)/cm^{-1} 2922, 2852, 1597, 1462, 1323, 1296, 1203, 1145, 1062, 10339, 958, 929, 833, 788, 721; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J = 6.8 Hz, $CH_2CH_2CH_3$), 1.21-1.35 (18H, m, $NCH_2CH_2(CH_2)_9CH_3$), 1.51-1.55 (2H, m, $NCH_2CH_2CH_2$), 2.85 (3H, s, SO_2CH_3), 3.17 (2H, t, J = 7.7 Hz, NCH_2CH_2), 3.80 (6H, s, $ArOCH_3$), 4.32 (2H, s, NCH_2Ar), 6.40 (1H, t, J = 2.2 Hz, Ar*H*), 6.51 (2H, d, J = 2.2 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 26.7, 28.0, 29.3, 29.5, 29.5, 31.9, 39.1, 47.5, 51.1, 55.4, 99.7, 106.3, 138.7, 161.0.

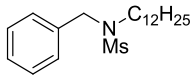
_N_-benzyl-_N_-(3,5-dimethoxybenzyl)methanesulfonamide 485e



N-(3,5-Dimethoxybenzyl)methanesulfonamide (1.23 g, 5 mmol, 1 equiv.), was reacted with benzyl bromide (1.28 g, 7.5 mmol, 1.5 equiv.) according to procedure E to afford *N-benzyl-N-(3,5-dimethoxybenzyl)methanesulfonamide* **485e** as a colourless oil (1.07 g, 64%). [Found: (HNESP$^+$) (M+H)$^+$, 336.1269. $C_{17}H_{22}NO_4S$ (M+H), requires 336.1264]; ν_{max} (ATR)/cm^{-1} 2931, 2839, 1595, 1456, 1319, 1203, 1141, 1049, 927, 788, 698, 686; δ_H (400 MHz, $CDCl_3$)

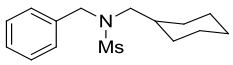
2.82 (3H, s, SO_2CH_3), 3.80 (6H, s, $ArOCH_3$), 4.30 (2H, s, NCH_2Ar), 4.39 (2H, s, NCH_2Ar), 6.42 (1H, t, *J* = 2.2 Hz, Ar*H*), 6.48 (2H, d, *J* = 2.2 Hz, Ar*H*), 7.28-7.39 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 39.7, 49.5, 54.9, 99.3, 106.1, 12.6, 128.2, 128.3, 135.0, 137.3, 160.6.

_N_-benzyl-_N_-dodecylmethanesulfonamide 485f



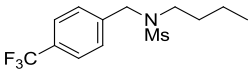
N-Benzylmethanesulfonamide (1.11 g, 6 mmol, 1.2 equiv.), was reacted with dodecyl bromide (1.25 g, 5 mmol, 1 equiv.) according to procedure E to afford *N-benzyl-N-dodecylmethanesulfonamide* **485f** as a white solid (1.18 g, 66%); M.pt. 35-37 ^oC; [Found: (HNESP$^+$) $(M+NH_4)^+$, 371.2731. $C_{20}H_{39}N_2O_2S^+$ $(M+NH_4)$, requires 371.2727]; ν_{max} (ATR)/cm^{-1} 2916, 2848, 1589, 1467, 1327, 1145, 964, 808, 792, 723, 694; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* = 6.8 Hz, CH_2CH_3), 1.20-1.38 (18H, m, $NCH_2CH_2(CH_2)_9CH_3$), 1.51-1.62 (2H, m, $NCH_2CH_2CH_2$), 2.85 (3H, s, SO_2CH_3), 3.18 (2H, dd, *J* = 7.8, 7.5 Hz, NCH_2CH_2), 4.41 (2H, s, NCH_2Ar), 7.29-7.39 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.6, 22.2, 26.1, 27.5, 28.7, 28.8, 29.5, 29.0, 29.1, 31.4, 38.7, 46.9, 50.5, 127.4, 127.9, 128.2, 135.7.

_N_-benzyl-_N_-(cyclohexylmethyl)methanesulfonamide 485g



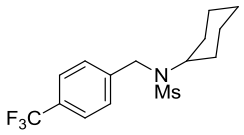
N-Benzylmethanesulfonamide (1.11 g, 6 mmol, 1.1 equiv.), was reacted with cyclohexylmethyl bromide (885 mg, 5 mmol, 1 equiv.) according to procedure E to afford *N-benzyl-N-(cyclohexylmethyl)methanesulfonamide* **485g** as a white solid (1.36 g, 97%); M.pt. 97-99 ^oC; [Found: (HNESP$^+$) $(M+H)^+$, 282.1526. $C_{15}H_{24}NO_2S^+$ (M+H), requires 282.1522]; ν_{max} (ATR)/cm^{-1} 2918, 2845, 1444, 1323, 1143, 1020, 964, 885, 796, 788, 754, 719, 698; δ_H (400 MHz, $CDCl_3$) 0.81-0.96 (2H, m, cyclohexyl), 1.11-1.22 (3H, m, cyclohexyl), 1.49-1.60 (2H, m, cyclohexyl), 1.62-1.79 (4H, m, cyclohexyl), 2.79 (3H, s, SO_2CH_3), 3.02 (2H, d, *J* = 7.4 Hz, NCH_2CH), 4.41 (2H, s, NCH_2Ar), 7.29-7.39 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 25.2, 25.9, 30.2, 35.5, 38.5, 51.3, 53.2, 127.5, 128.2, 128.2, 135.6.

_N_-Butyl-_N_-(4-(trifluoromethyl)benzyl)methanesulfonamide 485h



N-(3,5-Dimethoxybenzyl)bromide (1.20 g, 5 mmol, 1 equiv.), was reacted with *N*-butylmethanesulfonamide (832 mg, 5.5 mmol, 1.1 equiv.) according to procedure E to afford *N-butyl-N-(4-(trifluoromethyl)benzyl)methanesulfonamide* **485h** as a white solid (789 mg, 51%); M.pt. 52-54 ^{o}C; [Found: (HNESP^{+}) (M+H)$^{+}$, 310.1091. $C_{13}H_{19}F_3NO_2S^{+}$ (M+H), requires 310.1083]; ν_{max} (ATR)/cm^{-1} 2964, 2933, 2864, 1319, 1288, 1109, 1066, 1014, 966, 906, 785, 732, 694; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J = 7.6 Hz, CH_2CH_3), 1.32-1.33 (2H, m, $CH_3CH_2CH_3$), 1.47-1.56 (2H, m, $NCH_2CH_2CH_2$), 2.91 (3H, s, SO_2CH_3), 3.20 (2H, m, NCH_2CH_2), 4.46 (2H, s, NCH_2Ar), 7.51 (2H, d, J = 7.8, Ar*H*), 7.64 (2H, d, J = 7.8, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.5, 19.8, 30.1, 38.8, 47.8, 50.8, 122.7, 124.1 (q, $J_{C\text{-}F}$ = 272.5 Hz, CF_3), 125.5 (q, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.8 Hz), 129.0 (q, $J_{C\text{-}C\text{-}F}$ = 31.3 Hz), 141.0.

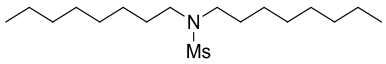
_N_-Cyclohexyl-_N_-(4-(trifluoromethyl)benzyl)methanesulfonamide 485i



Sodium hydride (as a 60% suspension in mineral oil, 160 mg, 4 mmol, 2 equiv.) was rinsed with dry hexane (3 x 20 mL) and blown dry under argon. To this was added dry DMF (10 mL) followed by a solution of cyclohexylmethanesulfonamide (478 mg, 2 mmol, 1 equiv.) in dry DMF (10 mL). 1-(Bromomethyl)-4-(trifluoromethyl)benzene (355 mg, 2 mmol, 1 equiv.) was dissolved in dry DMF (10 mL) and added to the mixture which was then stirred overnight at room temperature. The reaction mixture was poured into water (40 mL) and ethyl acetate (40 mL) and rinsed with further ethyl acetate (3 x 40 mL). This solution was then sequentially rinsed with water (3 x 30 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The precipitate was eluted over silica (30% ethyl acetate in petroleum ether) to afford *N-cyclohexyl-N-(4-(trifluoromethyl)benzyl)-methanesulfonamide* **485i** as a white solid (633 mg, 89%); M.pt. 106-108 ^{o}C; [Found: (HNESP^{+}) (M+H)$^{+}$, 336.1249. $C_{15}H_{21}F_3NO_2S^{+}$ (M+H), requires 336.1240]; ν_{max} (ATR)/cm^{-1}

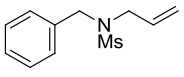
2943, 2862, 1319, 1139, 1070, 974, 850, 810, 783, 742; δ_H (400 MHz, $CDCl_3$) 0.95-1.06 (1H, m, cyclohexyl), 1.27-1.41 (4H, m, cyclohexyl), 1.60-1.64 (1H, m, cyclohexyl), 1.78-1.80 (4H, m, cyclohexyl), 2.87 (3H, s, SO_2CH_3), 3.69-3.76 (1H, m, $NCHCH_2$), 4.44 (2H, s, NCH_2Ar), 7.53 (2H, d, J = 7.8, Ar*H*), 7.60 (2H, d, J = 7.8, Ar*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 25.5, 31.6, 39.8, 46.2, 58.0, 123.8. (q, $J_{C\text{-}F}$ = 271.6 Hz, CF_3), 124.8 (q, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.6 Hz), 127.3, 129.1(q, $J_{C\text{-}C\text{-}F}$ = 32.8 Hz), 142.6.

Synthesis of *N*,*N*-dioctylmethanesulfonamide 486



To a solution of *N*,*N*-dioctylamine (15.11 mL, 50 mmol, 1 equiv.) and triethylamine (10.4 mL, 75 mmol, 1.5 equiv.) in dichloromethane (50 mL) at 0 ^oC, was added methanesulfonyl chloride (4.64 mL, 60 mmol, 1.2 equiv.). The reaction mixture was allowed to warm to room temperature and left stirring overnight, then quenched with 2N aqueous HCl (50 mL). The aqueous fraction was extracted with further dichloromethane (2 x 30 mL) and the combined organic fractions washed with additional aqueous HCl (2 x 30 mL), water (30 mL) and brine (30 mL), and then dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield *N*,*N*-dioctylmethanesulfonamide **486**[191] as a pale yellow oil (15.50 g, 97%); [Found: (HNESP$^+$) $(M+H)^+$, 320.2624. $C_{17}H_{38}NO_2S^+$ (M+H), requires 320.2618]; ν_{max} (ATR)/cm^{-1} 2924, 2854, 1465, 1332, 1143, 958, 783, 736; δ_H (400 MHz, $CDCl_3$) 0.85 (6H, t, J = 7.2 Hz, CH_2CH_3), 1.25-1.28 (20H, m, $NCH_2CH_2(CH_2)_5CH_3$), 1.54-1.60 (4H, m, $NCH_2CH_2CH_2$), 2.79 (3H, s, SO_2CH_3), 3.13 (4H, t, J = 7.7 Hz, NCH_2CH_2); δ_C (100 MHz, $CDCl_3$) 13.6, 22.1, 26.2, 28.2, 28.7, 31.3, 37.6, 47.3.

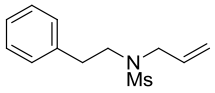
***N*-Allyl-*N*-benzylmethanesulfonamide 490a**



N-Benzylmethanesulfonamide (1.21 g, 10 mmol, 1 equiv.), was reacted with allyl bromide (1.81 g, 15 mmol, 1.5 equiv.) according to procedure E to afford *N*-allyl-*N*-benzylmethanesulfonamide **490a**[228] as a colourless oil (1.60 g, 71%); ν_{max} (ATR)/cm^{-1} 3083, 3032, 2924, 2857, 1642, 1500, 1448, 1323, 1146, 1045, 929, 898, 754; δ_H (400 MHz, $CDCl_3$)

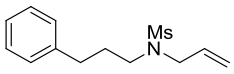
2.89 (3H, s, SO_2CH_3), 3.81 (2H, d, J = 6.4 Hz, NCH_2CH), 4.42 (2H, s, NCH_2Ar), 5.24-5.31 (2H, m, NCH_2CHCH), 5.79-5.89 (1H, m, NCH_2CHCH), 7.42-7.41 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 39.6, 48.5, 49.4, 119.4, 127.5, 128.0, 128.2, 131.6, 135.2; m/z (ESI^+) 225.9 ($[M+H]^+$).

_N_-Allyl-_N_-phenethylmethanesulfonamide 490b



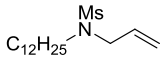
(2-Bromoethyl)benzene (925 mg, 5 mmol, 1 equiv.), was reacted with *N*-allylmethanesulfonamide (811 mg, 6 mmol, 1.2 equiv.) according to procedure E to afford *N-allyl-N-phenethylmethanesulfonamide* **490b** as a white solid (550 mg, 46%); M.pt. 55-57 ^oC; [Found: (HNESP$^+$) $(M+H)^+$, 240.1056. $C_{12}H_{18}NO_2S$ (M+H), requires 240.1053]; ν_{max} (ATR)/cm^{-1} 3012, 2943, 2870, 1460, 1319, 1280, 1138, 1105, 923, 756, 732, 702; δ_H (400 MHz, $CDCl_3$) 2.73 (3H, s, SO_2CH_3), 2.92 (2H, t, J = 7.5 Hz, $ArCH_2CH_2N$), 3.47 (2H, t, J = 7.5 Hz, $ArCH_2CH_2N$), 3.86 (2H, d, J = 6.8 Hz, NCH_2CH), 5.28-5.33 (2H, m, NCH_2CHCH), 5.79-5.89 (1H, m, NCH_2CHCH), 7.22-7.35 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 34.8, 38.7, 48.0, 49.7, 118.8, 126.2, 128.1, 128.4, 132.4, 138.0.

_N_-Allyl-_N_-(3-phenylpropyl)methanesulfonamide 495c



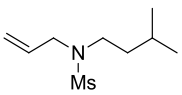
N-Allylmethanesulfonamide (675 mg, 5 mmol, 1 equiv.) and (3-bromopropyl)benzene (1.49 g, 7.5 mmol, 1.5 equiv.) were reacted according to procedure E to afford *N-allyl-N-(3-phenylpropyl)methanesulfonamide* **495c** as a colourless oil (1.01 g, 80%); [Found: (HNESP$^+$) $(M+H)^+$, 254.1209. $C_{13}H_{20}NO_2S^+$ (M+H), requires 254.1212]; ν_{max} (ATR)/cm^{-1} 3026, 2931, 2862, 1454, 1321, 1141, 993, 960, 925, 785, 746, 698; δ_H (400 MHz, $CDCl_3$) 1.91-1.99 (2H, m, $ArCH_2CH_2CH_2N$), 2.64-2.68 (2H, m, $ArCH_2CH_2CH_2N$), 3.22-3.27 (2H, m, $ArCH_2CH_2CH_2N$), 3.86 (2H, d, J = 6.4 Hz, NCH_2CHCH), 5.24-5.31 (2H, m, NCH_2CHCH), 5.79-5.89 (1H, m, NCH_2CHCH), 7.19-7.24 (3H, m, Ar*H*), 7.28-7.33 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 29.5, 32.3, 38.5, 46.3, 49.6, 118.7, 125.6, 127.8, 128.0, 132.3, 140.7.

_N_-Allyl-_N_-dodecylmethanesulfonamide 495d



N-Allylmethanesulfonamide (675 mg, 5 mmol, 1 equiv.) and dodecyl bromide (1.87 g, 7.5 mmol, 1.5 equiv.) were reacted according to procedure E to afford *N-allyl-N-dodecylmethanesulfonamide* **495d** as a white solid (1.22 g, 80%); M.pt. 40-42 ^{o}C; [Found: (HNESP^{+}) (M+H)$^{+}$, 304.2311. $C_{16}H_{34}NO_2S^{+}$ (M+H), requires 304.2305]; ν_{max} (ATR)/cm^{-1} 2914, 2845, 1323, 1141, 1112, 939, 916, 806, 786; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, J = 6.4 Hz, CH_2CH_3), 1.24-1.33 (18H, m, $NCH_2CH_2(CH_2)_9CH_3$), 1.55-1.62 (2H, m, $NCH_2CH_2CH_2$), 2.87 (3H, s, SO_2CH_3), 3.16-3.22 (2H, m, NCH_2CH_2), 3.87 (2H, d, J = 6.4 Hz, NCH_2CH), 5.25-5.33 (2H, m, NCH_2CHCH_2), 5.85 (1H, ddt, J = 17.0, 10.2, 6.4 Hz, NCH_2CHCH_2); δ_C (100 MHz, $CDCl_3$) 13.6, 22.2, 26.1, 26.1, 17.8, 28.7, 28.8, 29.0, 29.1, 31.4, 38.6, 46.6, 49.4, 117.5, 132.5.

Synthesis of _N_-allyl-_N_-isopentylmethanesulfonamide 495e

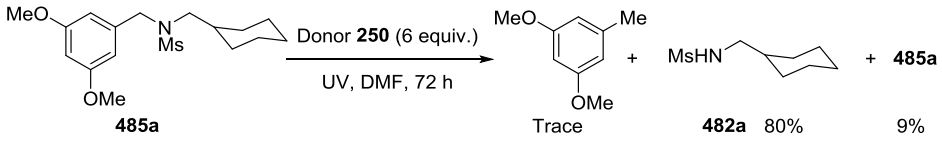


To a solution of *N*-allylmethanesulfonamide (744 mg, 5.5 mmol, 1.1 equiv.) and allyl bromide (599 μL, 5 mmol, 1 equiv.) in DMF (10 mL) was added potassium carbonate (1.38 g, 10 mmol, 2 eq). The reaction mixture was left stirring at room temperature overnight, then quenched with 2N aqueous NaOH (25 mL). The aqueous fraction was rinsed with diethyl ether (3 x 20 mL) and the combined organic fractions rinsed with additional aqueous NaOH (2 x 15 mL), water (30 mL) and brine (30 mL) then dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield *N-allyl-N-isopentylmethanesulfonamide* **495e** (982 mg, 87%) as a colourless oil; [Found: (HNESP^{+}) (M-H)$^{+}$, 204.1051. $C_9H_{18}NO_2S^{+}$ (M-H), requires 204.1053]; ν_{max} (ATR)/cm^{-1} 2958, 2870, 1321, 1141, 960, 916, 786; δ_H (400 MHz, $CDCl_3$) 0.93 (6H, d, J = 6.3 Hz, $CHCH_3$), 1.49 (2H, dt, J = 7.4, 7.0 Hz, NCH_2CH_2CH), 1.56-1.64 (1H, m, NCH_2CH_2CH), 2.87 (3H, s, SO_2CH_3), 3.22 (2H, t, J = 7.5 Hz, NCH_2CH_2), 3.86 (2H, d, J = 6.2 Hz, NCH_2CHCH_2), 5.26-5.34 (2H, m, NCH_2CHCH_2), 5.80-5.91 (1H, m, NCH_2CHCH_2); δ_C (100 MHz, $CDCl_3$) 22.3, 22.7, 37.0, 39.0, 45.4, 49.8, 118.9, 130.0.

General procedure F- for the reaction of sulfomamides with donor 250

Donor (512 mg, 1.8 mmol, 6 equiv.) was dissolved in degassed DMF (4 mL) in a glovebox. This solution was directly pipetted into the substrate (0.3 mmol, 1.0 equiv.). The solution was removed to a fumehood and stirred at room temperature for 72 h under UV radiation (365 nm). The mixture was poured into aqueous 2N HCl (25 mL) and ethyl acetate (25 mL) before extracting with ethyl acetate (4 x 15 mL). The combined organic layers were then washed with water (3 x 20 mL) and brine (10 mL) and dried over Na_2SO_4. The crude organic residue, obtained after evaporation under reduced pressure, was eluted with ethyl acetate on silica gel, to afford the pure corresponding products as reported.

Reaction of *N*-(cyclohexylmethyl)-*N*-(3,5-dimethoxybenzyl)methanesulfonamide 485a with donor 250



N-(Cyclohexylmethyl)-*N*-(3,5-dimethoxybenzyl)methanesulfonamide **485a** (102 mg, 0.3 mmol), was reacted according to procedure F to afford the products given below.

N-(Cyclohexylmethyl)methanesulfonamide **482a**[229] was isolated as a white solid (46 mg, 80%); M.pt. 70-72 ^{o}C (lit.[229] 71-73 ^{o}C); ν_{max} (ATR)/cm^{-1} 3280, 2928, 2854, 1459, 1435, 1301, 1144, 1059, 978, 954, 837, 755, 688; δ_H (400 MHz, $CDCl_3$) 0.89-1.01 (2H, m, cyclohexyl), 1.13-1.32 (3H, m, cyclohexyl), 1.44-1.56 (1H, m, cyclohexyl), 1.65-1.79 (5H, m, cyclohexyl), 2.96 (3H, s, SO_2CH_3) overlapping with 2.96-3.00 (2H, m, NCH_2CH), 4.40-4.49 (1H, bs, N*H*); δ_C (100 MHz, $CDCl_3$) 25.2, 25.8, 30.1, 37.6, 39.8, 49.0; *m*/*z* (EI$^+$) 191.0 ([M]$^+$, 6%), 110.0 (32), 108.0 (100), 96.0 (47), 83.0 (38), 54.9 (30).

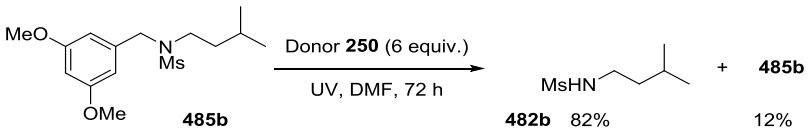
In the NMR spectrum of the crude reaction product, peaks (at 2.33 (3H, s, $ArCH_3$), 3.80 (6H, s, $ArOCH_3$), 6.32 (1H, d, *J* = 2.1 Hz, Ar*H*), 6.36 (2H, d, *J* = 2.1Hz, Ar*H*)) tentatively identified 3,5-dimethoxytoluene,[230] when compared to the authentic material.

N-(cyclohexylmethyl)-*N*-(3,5-dimethoxybenzyl)methanesulfonamide **485a** was recovered as a white solid (9 mg, 9%) with data matching those of the previously isolated material.

Blank reaction of *N*-(cyclohexylmethyl)-*N*-(3,5-dimethoxybenzyl)methanesulfonamide 485a with donor 250 without photoactivation

In parallel, *N*-(cyclohexylmethyl)-*N*-(3,5-dimethoxybenzyl)methanesulfonamide **485a** (102 mg, 0.3 mmol), was reacted according to procedure F with the omission of the UV activation to afford only recovery of *N*-(cyclohexylmethyl)-*N*-(3,5-dimethoxybenzyl)methane sulfonamide **485a** (96 mg, 94%) with data as reported previously.

Reaction of *N*-(3,5-dimethoxybenzyl)-*N*-isopentylmethanesulfonamide 485b with donor 250

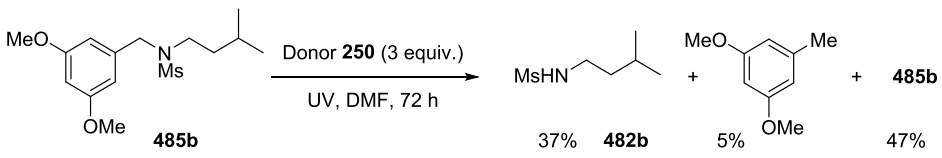


N-(3,5-Dimethoxybenzyl)-*N*-isopentylmethanesulfonamide **485b** (95 mg, 0.3 mmol), was reacted according to procedure F to afford the mixture of products given below.

N-isopentylmethanesulfonamide[231] was isolated as a colourless oil (41 mg, 82%); ν_{max} (ATR)/cm^{-1} 3271, 2963, 2872, 1464, 1440, 1295, 1127, 1069, 1039, 991, 972, 941, 881, 816, 715; δ_H (400 MHz, $CDCl_3$) 0.94 (6H, d, J = 6.8 Hz, $CHCH_3$), 1.48 (2H, dt, J = 7.3, 6.8 Hz, NCH_2CH_2), 1.69 (1H, nonet, J = 6.8 Hz, CH_2CHCH_3), 2.97 (3H, s, SO_2CH_3), 3.16 (2H, dt, J = 7.6, 7.3 Hz, NCH_2CH_2), 4.29-4.28 (1H, bs, NH); δ_C (100 MHz, $CDCl_3$) 21.8, 25.0, 38.4, 39.7, 41.1; *m/z* (ESI$^-$) 164.00 ([M-H]$^-$, 100%).

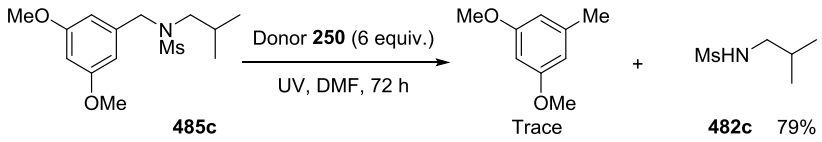
N-(3,5-dimethoxybenzyl)-*N*-isopentylmethanesulfonamide was recovered as a white solid (11 mg, 12%) with data matching those of the previously isolated material.

Reaction of *N*-(3,5-dimethoxybenzyl)-*N*-isopentylmethanesulfonamide 485b in the presence of less donor 250



When *N*-isopentyl-*N*-(3,5-dimethoxybenzyl)methanesulfonamide **485b** (95 mg, 0.3 mmol), was reacted according to procedure F with only 3 equiv. donor **250** the following were isolated: *N*-(3,5-dimethoxybenzyl)-*N*-isopentylmethanesulfonamide **485b** (74 mg, 47%), *N*-isopentylmethanesulfonamide **482b** was isolated as a colourless oil (28 mg, 37%) and 3,5-dimethoxytoluene[230] as a colourless oil (4 mg, 5%); ν_{max} (ATR)/cm^{-1} 2497, 3213, 1593, 1476, 1153, 1060, 786; δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, ArCH_3), 3.80 (6H, s, ArOCH_3), 6.32 (1H, t, J = 2.1 Hz, ArH), 6.36 (2H, d, J = 2.1Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.3, 54.7, 97.0, 106.6, 139.7, 160.2; *m/z* (ESI$^+$) 153.00 ([M+H]$^+$, 100%).

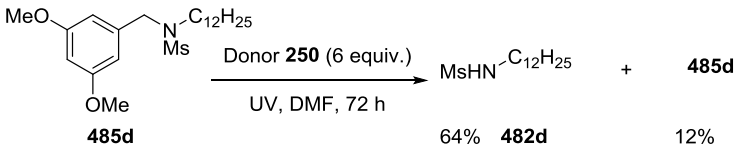
Reaction of *N*-(3,5-dimethoxybenzyl)-*N*-isobutylmethanesulfonamide 485c with donor 250



N-(3,5-dimethoxybenzyl)-*N*-isobutylmethanesulfonamide **485c** (72 mg, 0.3 mmol), was reacted according to procedure F to afford *N*-isobutylmethanesulfonamide **482c** as a colourless oil (36 mg, 79%); ν_{max} (ATR)/cm^{-1} 3256, 3016, 2958, 2868, 1474, 1448, 1304, 1136, 1067, 976, 881, 817, 762; δ_H (400 MHz, $CDCl_3$) 0.96 (6H, d, J = 6.5 Hz, CHCH_3), 1.77-1.87 (1H, m, CH_2CHCH_3), 2.93-2.96 (2H, m, NCH_2CH), 2.96 (1H, s, NH), 4.72 (3H, s, SO_2CH_3); δ_C (100 MHz, $CDCl_3$) 19.4, 28.3, 39.6, 50.1; *m/z* (ESI$^-$) 149.93 ([M-H]$^-$, 100%).

Peaks at δ 2.33 (3H, s, ArCH_3), 3.80 (6H, s, ArOCH_3), 6.32 (1H, d, J = 2.1 Hz, ArH), 6.36 (2H, d, J = 2.1Hz, ArH)) tentatively identified 3,5-dimethoxytoluene in trace amounts in a ^{1}H NMR spectrum of the crude reaction mixture when compared to the authentic material.

Reaction of *N*-(3,5-dimethoxybenzyl)-*N*-dodecylmethanesulfonamide 485d with donor 250

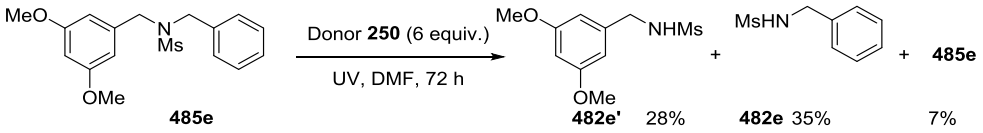


N-(3,5-Dimethoxybenzyl)-*N*-dodecylmethanesulfonamide **485d** (124 mg, 0.3 mmol), was reacted according to procedure F to afford the products given below.

N-Dodecylmethanesulfonamide **482d** was isolated as a white solid (50 mg, 64%); M.pt. 75-77 ^{o}C; [Found: (HNESP^{+}) $(M+NH_4)^{+}$, 281.2262. $C_{13}H_{33}N_2O_2S^{+}$ $(M+NH_4)$, requires 281.2258]; ν_{max} (ATR)/cm^{-1} 3267, 2957, 2957, 2850, 1415, 1031, 1141, 1132, 10664, 983, 889, 761, 717; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, J = 7.7 Hz, CH_2CH_3), 1.22-1.41 (18H, m, $NCH_2CH_2(CH_2)_9CH_3$), 1.50-1.55 (2H, m, $NCH_2CH_2CH_2$), 2.95 (3H, s, SO_2CH_3), 3.11 (q, J = 6.9 Hz, NCH_2CH_2), 4.40-4.50 (1H, bs, N*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 26.6, 29.1, 29.3, 29.4, 29.5, 29.6, 30.1, 31.9, 40.2, 43.4.

Residual *N*-(3,5-dimethoxybenzyl)-*N*-dodecylmethanesulfonamide **485d** was recovered as a white solid (26 mg, 21%). Data were as reported previously.

Reaction of *N*-benzyl-*N*-(3,5-dimethoxybenzyl)methanesulfonamide 485e with donor 250



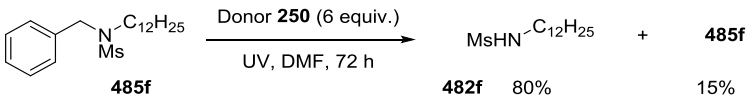
N-benzyl-*N*-(3,5-dimethoxybenzyl)methanesulfonamide **485e** (100.6 mg, 0.3 mmol), was reacted according to procedure F to afford the mixture of products given below.

N-(3,5-dimethoxybenzyl)methanesulfonamide **485e′** was isolated as a white solid (21 mg, 28%). Data were as reported previously.

N-benzylmethanesulfonamide **485e**[224] was isolated as a white solid (20 mg, 35%). Data were as reported previously.

N-benzyl-N-(3,5-dimethoxybenzyl)methanesulfonamide **485e** was recovered as a white solid (7 mg, 7%). Data were as reported previously.

Reaction of *N*-benzyl-*N*-dodecylmethanesulfonamide 485f with donor 250

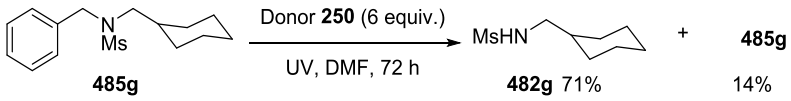


N-benzyl-*N*-dodecylmethanesulfonamide **485f** (106 mg, 0.3 mmol), was reacted according to procedure F to afford the products below.

N-dodecylmethanesulfonamide **482f** was isolated as a white solid (64 mg, 80%) with data as reported previously.

N-benzyl-*N*-dodecylmethanesulfonamide **485f** was recovered as a white solid (16 mg, 15%). Data were as reported previously.

Reaction of *N*-benzyl-*N*-(cyclohexylmethyl)methanesulfonamide 485g with donor 250

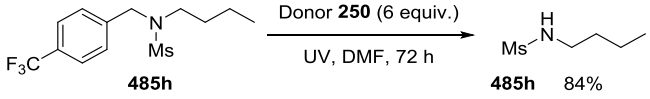


N-benzyl-*N*-(cyclohexylmethyl)methanesulfonamide **485g** (84 mg, 0.3 mmol), was reacted according to procedure F to afford the products given below.

N-cyclohexylmethylmethanesulfonamide **482g** was isolated as a white solid (41 mg, 71%). Data were as reported previously.

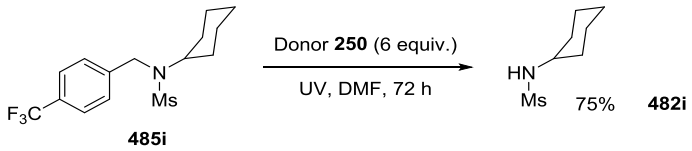
N-benzyl-*N*-(cyclohexylmethyl)methanesulfonamide **485g** was recovered as a white solid (12 mg, 14%). Data were as reported previously.

Reaction of N-butyl-N-(4-(trifluoromethyl)benzyl)methanesulfonamide 485h with donor 250



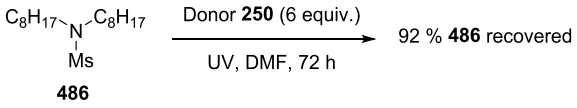
N-butyl-*N*-(4-(trifluoromethyl)benzyl)methanesulfonamide **485h** (92 mg, 0.3 mmol), was reacted according to procedure F to afford *N*-butylmethanesulfonamide **482h** as a pale yellow oil (38 mg, 84%). Data were as reported previously.

Reaction of N-cyclohexyl-N-(4-(trifluoromethyl)benzyl)methanesulfonamide 485i with donor 250



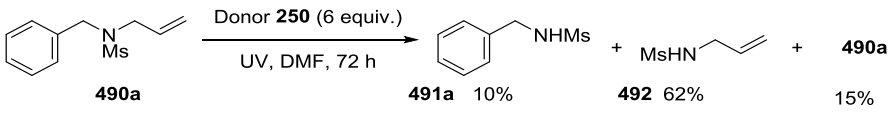
N-cyclohexyl-N-(4-(trifluoromethyl)benzyl)methanesulfonamide **485i** (102 mg, 0.3 mmol), was reacted according to procedure F to afford *N*-cyclohexyl)methanesulfonamide **482i** as a white solid (40 mg, 75%). Data were as reported previously.

Reaction of *N*,*N*-dioctylmethanesulfonamide 486 with photoactivated donor



N,*N*-dioctylmethanesulfonamide **486** (96 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford *N*,*N*-dioctylmethanesulfonamide as a pale yellow oil (88 mg, 92%) with data matching those reported previously.

Reaction of *N*-allyl-*N*-benzylmethanesulfonamide 490a with donor 250

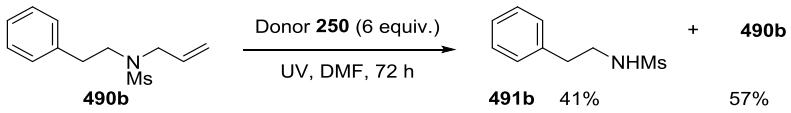


N-allyl-*N*-benzylmethanesulfonamide **490a** (68 mg, 0.3 mmol), was reacted according to procedure F to afford the mixture of products given below.

N-benzylmethanesulfonamide **491a** and *N*-allylmethanesulfonamide **492** were obtained as a mixture as a colourless oil (30.5 mg) which was tentatively identified by NMR in the following amounts: *N*-allylmethanesulfonamide **492** (25.1 mg, 62%) and *N*-benzylmethanesulfonamide **491a** (5.4 mg, 10%).

N-allyl-*N*-benzylmethanesulfonamide **490a** was recovered as a white solid (12 mg, 15%). Data were as reported previously.

Reaction of *N*-allyl-*N*-phenethylmethanesulfonamide 490b with donor 250



N-allyl-*N*-phenethylmethanesulfonamide **490b** (72 mg, 0.3 mmol), was reacted according to procedure F to afford the products given below.

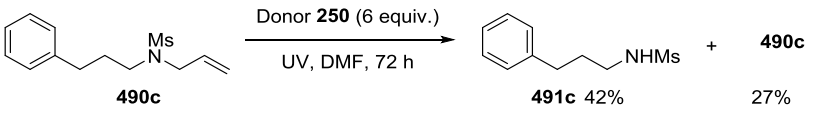
N-phenethylmethanesulfonamide **491b**[232] was isolated as a colourless oil (24 mg, 41%); ν_{max} (ATR)/cm^{-1} 3288, 3026, 2929, 2858, 1408, 1309, 1139, 1072, 970, 893, 815, 765, 748, 698; δ_H (400 MHz, $CDCl_3$) 2.83 (3H, s, SO_2CH_3), 2.88 (2H, t, J = 6.6 Hz, NCH_2CH_2Ar), 3.41 (2H, t, J = 6.6 Hz, NCH_2CH_2Ar), 4.30-4.40 (1H, bs, N*H*), 7.20-7.27 (3H, m, Ar*H*), 7.30-7.36 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 36.5, 40.4, 44.4, 127.0, 128.9, 128.9, 137.8; *m*/*z* (APCI$^+$) 198.1 ([M+H]$^+$, 100%).

N-Allyl-*N*-phenethylmethanesulfonamide **490b** was recovered as a white solid (41 mg, 57%). Data were as reported previously.

Blank reaction of *N*-allyl-*N*-phenethylmethanesulfonamide 490b with donor 250 in the absence of photoactivation

In parallel with the reaction above, *N*-allyl-*N*-phenethylmethanesulfonamide **490b** (72 mg, 0.3 mmol), was reacted according to procedure F with the omission of the UV activation, to afford quantative recovery of *N*-allyl-*N*-phenethylmethanesulfonamide **490b** with data as reported previously.

Reaction of *N*-allyl-*N*-(3-phenylpropyl)methanesulfonamide 490c with donor 250

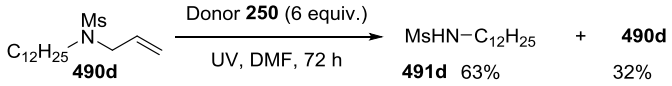


N-allyl-*N*-(3-phenylpropyl)methanesulfonamide **490c** (91 mg, 0.3 mmol), was reacted according to procedure F to afford the mixture of products given below.

N-(3-phenylpropyl)methanesulfonamide **491c**[233] was isolated as a white solid (33 mg, 42%); [Found: $(HNESP^+)$ $(M+H)^+$, 214.0898. $C_{10}H_{16}NO_2S^+$ (M+H), requires 214.0896]; M.pt. 44-46 ^oC (no literature M.pt. reported); ν_{max} (ATR)/cm^{-1} 3251, 3022, 2933, 2864, 1438, 1415, 1307, 1136, 1058, 1022, 970, 846, 777, 761, 705; δ_H (400 MHz, $CDCl_3$) 1.89-1.96 (2H, m, $ArCH_2CH_2CH_2N$), 2.71 (2H, t, J = 7.6 Hz, $ArCH_2CH_2CH_2N$), 2.94 (3H, s, SO_2CH_3), 3.16 (2H, q, J = 6.7 Hz, $ArCH_2CH_2CH_2N$), 7.18-7.24 (3H, m, Ar*H*), 7.28-7.33 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 31.6, 32.8, 40.3, 42.7, 126.2, 128.3, 128.5, 140.8.

N-allyl-*N*-(3-phenylpropyl)methanesulfonamide **490c** was recovered as a colourless oil (42 mg, 27%). Data were as reported previously.

Reaction of *N*-allyl-*N*-dodecylmethanesulfonamide 490d with donor 250

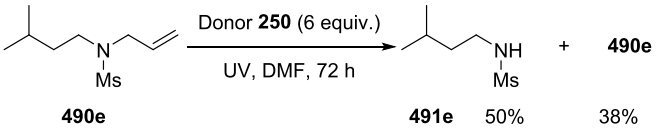


N-allyl-*N*-dodecylmethanesulfonamide **490d** (91 mg, 0.3 mmol), was reacted according to procedure F to afford the products given below.

N-dodecylmethanesulfonamide **491d** was isolated as a white solid (50 mg, 63%). Data were as reported previously.

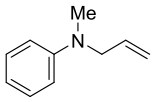
N-allyl-*N*-dodecylmethanesulfonamide **490d** was recovered as a white solid (29 mg, 32%). Data were as reported previously.

Reaction of *N*-allyl-*N*-isopentylmethanesulfonamide 490e with donor 250



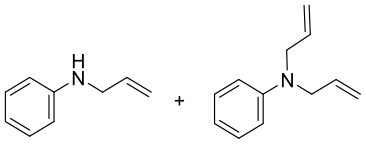
N-allyl-*N*-isopentylmethanesulfonamide **490e** (62 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford *N*-isopentylmethanesulfonamide **491e** (25 mg, 50%) and *N*-allyl-*N*-isopentylmethanesulfonamide **490e** (23 mg, 38%) with data matching those reported previously.

Synthesis of *N*-allyl-*N*-methylaniline 496a



To a solution of *N*-methylaniline **497a** (5.41 mL, 50 mmol, 1 equiv.) in ethanol (100 mL) was added sodium carbonate (7.95 g, 55 mmol, 1.5 equiv.) and allyl bromide (6.08 mL, 55 mmol, 1.1 eq) and the suspension stirred at reflux for 14 h. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic fractions were washed with water (4 x 50 mL) and brine (25 mL) then, dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. Silica column chromatography (0.5-1% ethyl acetate/ petroleum ether) afforded *N*-allyl-*N*-methylaniline **496a**[234] as a pale yellow oil (6.55 g, 89%); ν_{max} (ATR)/cm^{-1} 2894, 2806, 1597, 1502, 1365, 1207, 991, 916, 744, 688; δ_H (400 MHz, $CDCl_3$) 2.98 (3H, s, NCH_3), 3.95 (2H, ddd, J = 5.1, 1.6, 1.5 Hz, NCH_2), 5.17-5.24 (2H, m, NCH_2CHCH_2), 5.88 (1H, ddt, J = 17.2, 10.3, 5.1 Hz, NCH_2CH), 6.72 (1H, t, J = 7.3 Hz, ArH), 6.76 (2H, d, J = 8.4 Hz, ArH), 7.26-7.28 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 37.5, 54.8, 112.0, 115.6, 115.9, 128.6, 133.4, 149.0; *m*/*z* (MM-ES+APCI$^+$) 148.21 ([M+H]$^+$, 18%), 107.2 (100).

Synthesis of *N*-allylaniline 497b and *N*,*N*-diallylaniline 496b

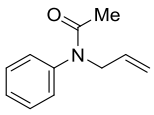


To DMF (25 mL) at 0 °C was added aniline (913 μL, 10 mmol, 1 equiv.), allyl bromide (950 μL, 11 mmol, 1.1 equiv.) and potassium carbonate (1.66 g, 12 mmol, 1.2 eq). The reaction mixture was allowed to come to room temperature and left stirring at room temperature for 24 h, and then quenched with water (50 mL). The aqueous fraction was extracted with diethyl ether (3 x 30 mL) and the combined organic fractions washed with additional water (4 x 25 mL) and brine (10 mL) then dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting organic residue was purified by flash column chromatography (10-50% ethyl acetate in petroleum ether) to yield *N*-allylaniline **497b**[235] and *N*,*N*-diallylaniline **496b**.[236]

N-allylaniline **497b** was a pale yellow oil (480 mg, 36%); [Found: (HASP$^+$) (M+H)$^+$, 134.0962. $C_9H_{12}N^+$ (M+H), requires 134.0964]; ν_{max} (ATR)/cm^{-1} 3410, 3051, 2839, 1600, 1502, 1313, 1251, 991, 916, 746, 690; δ_H (400 MHz, $CDCl_3$) 3.81 (2H, dt, *J* = 5.4, 1.5 Hz, ArNC*H*$_2$) overlapping with bs (1H, 3.80-3.90, N*H*), 5.20 (1H, ddt, *J* = 10.4, 1.5, 1.5 Hz, NCH$_2$CHC*H*$_2$), 5.34 (1H, ddt, *J* = 17.2, 1.5, 1.5 Hz, NCH$_2$CHC*H*$_2$), 5.98 (1H, ddt, *J* = 17.2, 10.4, 5.4 Hz, NCH$_2$C*H*), 6.67 (2H, d, *J* = 8.0 Hz, Ar*H*), 6.75 (1H, t, *J* = 7.2 Hz, Ar*H*), 7.21 (2H, dd, *J* = 8.0, 7.2 Hz, Ar*H*) ; δ_C (100 MHz, $CDCl_3$) 46.1, 112.5, 115.7, 117.1, 128.8, 135.0, 147.6.

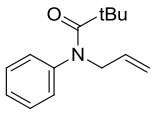
N,*N*-diallylaniline **496b** was a pale yellow oil (918 mg, 53%); [Found: (HNESP$^+$) (M+H)$^+$, 174.1276. $C_{12}H_{16}N^+$ (M+H), requires 174.1277]; ν_{max} (ATR)/cm^{-1} 3078, 2860, 1597, 1502, 1230, 914, 744, 690; δ_H (400 MHz, $CDCl_3$) 3.95 (4H, ddd, *J* = 4.9, 1.8, 1.5 Hz, 2 x ArNC*H*$_2$), 5.17-5.24 (4H, m, NCH$_2$CHC*H*), 5.89 (2H, ddt, *J* = 17.2, 10.3, 4.9 Hz, NCH$_2$C*H*), 6.70-6.75 (3H, m, Ar*H*), 7.22-7.26 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 52.3, 111.9, 115.6, 115.9, 128.7, 133.6, 148.3.

Synthesis of *N*-allyl-*N*-phenylacetamide 496c



Sodium hydride (as a 60% suspension in mineral oil, 480 g, 12 mmol, 1.2 equiv.) was rinsed with dry hexane (3 x 30 mL) and blown dry under argon. To this was added dry DMF (10 mL) followed by a solution of *N*-phenylacetamide 1.49 g, 11 mmol, 1.1 equiv.) in dry DMF (10 mL). Allyl bromide (864 µl, 10 mmol, 1 equiv.) was added to the mixture which was then stirred overnight at room temperature. The reaction mixture was poured into 2N aqueous NaOH (30 mL) and diethyl ether (50 mL) and extracted with further diethyl ether (3 x 25 mL). This solution was then sequentially washed with 2N aqueous NaOH (2 x 25 mL), water (50 mL) and brine (25 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The resulting precipitate was purified by flash column chromatography (25% ethyl acetate in petroleum ether) to afford *N*-allyl-*N*-phenylacetamide **496c**[237] as a pale yellow oil (1.17 g, 67%); [Found: (HNESP$^+$) $(M+H)^+$, 176.1070. $C_{11}H_{14}NO^+$ (M+H), requires 176.1070]; ν_{max} (ATR)/cm^{-1} 2905, 1656, 1494, 1382, 1274, 920, 698; δ_H (400 MHz, $CDCl_3$) 1.86 (3H, s, C(O)C*H*$_3$), 4.29-4.31 (2H, m, NC*H*$_2$), 5.04-5.12 (2H, m, NCH$_2$CHC*H*$_2$), 5.86 (1H, ddt, J = 16.9, 10.4, 6.3 Hz, NCH$_2$C*H*), 7.15-7.17 (2H, m, Ar*H*), 7.32-7.42 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.2, 51.5, 117.3, 127.4, 127.6, 129.1, 132.7, 142.5, 169.7.

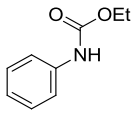
Synthesis of *N*-allyl-*N*-phenylpivalamide 496d



To a solution of *N*-allylaniline (266 mg, 2 mmol, 1 equiv.) and triethylamine (418 µL, 3 mmol, 1.5 equiv.) in dichloromethane (10 mL) was added pivaloyl chloride (271 µL, 2.2 mmol, 1.1 equiv.), slowly at 0 ^oC. The solution was then stirred at room temperature overnight before quenching with 2N aqueous HCl (25 mL). The aqueous fraction was extracted with further dichloromethane (3 x 10 mL) and the combined organic fractions washed with additional aqueous HCl (2 x 20 mL), water (20 mL) and brine (10 mL) then dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resultant pale yellow oil was purified by flash column chromatography (10% ethyl acetate in

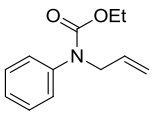
petroleum ether) to yield *N*-allyl-*N*-phenylpivalamide **496d**[238] (254 mg, 58%); [Found: (HNESP$^+$) (M+H)$^+$, 218.1537. $C_{14}H_{20}NO^+$ (M+H), requires 218.1539]; ν_{max} (ATR)/cm^{-1} 2956, 1631, 1593, 1494, 1195, 920, 702; δ_H (400 MHz, $CDCl_3$) 1.00 (9H, s, C*H*$_3$), 4.16 (2H, ddd, *J* = 6.3, 1.1, 1.1 Hz, NC*H*$_2$), 4.96 (1H, ddt, *J* = 17.1, 1.1, 1.1 Hz, NCH$_2$CHC*H*), 5.04 (1H, ddt, *J* = 10.2, 1.1, 1.1 Hz, NCH$_2$CHC*H*), 5.88 (1H, ddt, *J* = 17.1, 10.2, 6.3 Hz, NCH$_2$C*H*), 7.12-7.16 (2H, m, Ar*H*), 7.16-7.33 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 28.8, 40.2, 55.2, 116.9, 127.2, 128.3, 129.1, 132.7, 142.8, 176.4.

Synthesis of ethyl phenylcarbamate 501b



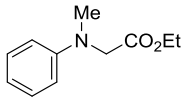
To a solution of aniline (1.00 mL, 11 mmol, 1.1 equiv.) and ethyl chloroformate (952 μL, 10 mmol, 1 equiv.) in chloroform (20 mL) was added potassium carbonate (2.76 g, 20 mmol, 2 equiv.). The solution was then stirred at reflux overnight before allowing to cool and quenching with water (25 mL). The aqueous fraction was extracted with dichloromethane (3 x 20 mL) and the combined organic fractions washed with additional aqueous HCl (2 x 20 mL), water (20 mL) and brine (10 mL), and then dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The precipitate was recrystallized (hot ethanol) to yield ethyl phenylcarbamate **501b**[239] as pale pink crystals (1.62 g, 98%); M.pt. 48-50 ^oC (lit.[239] 48-50 ^oC); [Found: (HNESP$^+$) (M+H)$^+$, 166.0858. $C_9H_{12}NO_2^+$ (M+H), requires 166.0863]; ν_{max} (ATR)/cm^{-1} 3315, 2981, 1701, 1597, 1529, 1440, 1226, 1058, 900, 740, 692; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$), 4.25 (2H, q, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 6.70-6.81 (1H, bs, N*H*), 7.05-7.10 (1H, m, Ar*H*), 7.29-7.35 (2H, m, Ar*H*), 7.40-7.43 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 60.7, 118.2, 122.8, 128.5, 137.5, 153.2; *m*/*z* (APCI$^+$) 165.2 ([M+H]$^+$, 100%).

Synthesis of ethyl allyl(phenyl)carbamate 496c



Sodium hydride (as a 60% suspension in mineral oil, 240 mg, 6 mmol, 1.2 equiv.) was rinsed with dry hexane (3 x 20 mL) and blown dry under argon. To this was added dry THF (20 mL) followed by a solution of ethyl phenylcarbamate (825 mg, 5 mmol, 1.1 equiv.) in dry THF (10 mL). To the resultant solution was slowly added allyl bromide (648 μL, 7.5 mmol, 1.5 equiv.). The solution was then stirred at room temperature overnight before quenching with water (35 mL). The aqueous fraction was extracted with further diethyl ether (3 x 10 mL) and the combined organic fractions washed with additional water (3 x 20 mL) and brine (10 mL) then dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resultant pale yellow oil was purified by flash column chromatography (5% ethyl acetate in petroleum ether) to yield ethyl allyl(phenyl)carbamate **496c**[240] (780 mg, 76%); ν_{max} (ATR)/cm^{-1} 2980, 1697, 1597, 1496, 1377, 1226, 1145, 1020, 921, 765, 696; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, J = 7.1 Hz, OCH_2CH_3), 4.19 (2H, q, J = 7.1 Hz, OCH_2CH_3) 4.28 (2H, ddd, J = 5.8, 1.5, 1.3, NCH_2), 5.14-5.20 (2H, m, NCH_2CHCH_2), 5.89-5.99 (1H, m, NCH_2CH), 7.22-7.26 (3H, m, Ar*H*), 7.34-7.38 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 52.7, 61.2, 116.4, 125.7, 126.2, 128.3, 113.4, 141.8, 155.0; *m*/*z* (MM-ES+APCI$^+$) 206.1 ([M+H]$^+$, 17%), 178.1 (34), 134.2 (100).

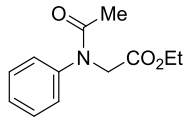
Synthesis of ethyl 2-[methyl(phenyl)amino]acetate 500a



To a solution of *N*-methylaniline (1.08 mL, 10 mmol, 1 equiv.) in ethanol (20 mL) was added sodium carbonate (1.59 g, 15 mmol, 1.5 equiv.) and ethyl bromoacetate (1.22 mL, 11 mmol, 1.1 eq) and the suspension stirred at reflux for 14 h. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic fractions were washed with water (4 x 25 mL) and brine (20 mL) and then dried with anhydrous sodium sulfate, filtered and concentrated under vacuum. Purification over silica (5% ethyl acetate/ petroleum ether) afforded ethyl 2-(methyl(phenyl)amino)acetate **500a**[241] as a colourless oil (1.91 g, 99%); ν_{max} (ATR)/cm^{-1} 2980, 2899, 1743, 1598, 1504, 1365, 1184, 1026, 945, 746, 688; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, J = 7.1 Hz, OCH_2CH_3), 3.11 (3H, s, NCH_3), 4.10 (2H, s, NCH_2), 4.22 (2H, q, J = 7.1 Hz, OCH_2CH_3), 6.73-6.76 (2H, m, Ar*H*), 6.76-6.82 (1H, m, Ar*H*), 7.27-7.31 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.8, 39.0, 54.0,

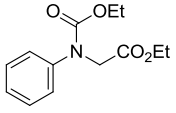
60.4, 111.8, 116.8, 128.7, 128.4, 170.6; *m/z* (MM-ES+APCI$^+$) 194.2 ([M+H]$^+$, 81%), 120.2 (100).

Synthesis of ethyl 2-(*N*-phenylacetamido)acetate 500b



Sodium hydride (as a 60% suspension in mineral oil, 480 g, 12 mmol, 1.2 equiv.) was rinsed with dry hexane 3 x 30 mL and blown dry under argon. To this was added dry DMF (10 mL) followed by a solution of *N*-phenylacetamide 1.49 g, 11 mmol, 1.1 equiv.) in dry DMF (10 mL). Ethyl bromoacetate (1.11 mL, 10 mmol, 1 equiv.) was added to the mixture which was then stirred overnight at room temperature. The reaction mixture was poured into 2N aqueous NaOH (30 mL) and diethyl ether (50 mL) and extracted with further diethyl ether (3 x 25 mL). This solution was then sequentially washed with 2N aqueous NaOH (2 x 25 mL), water (50 mL) and brine (25 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The resulting precipitate was purified over silica (25% ethyl acetate in petroleum ether) to afford ethyl 2-(*N*-phenylacetamido)acetate **500b**[242] as a pale yellow oil (1.61 g, 66%); [Found: (HNESP$^+$) (M+H)$^+$, 222.1127. $C_{12}H_{16}NO_3^+$ (M+H), requires 222.1125]; ν_{max} (ATR)/cm^{-1} 2981, 1745, 1664, 1375, 1190, 1020, 698; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.94 (3H, s, $C(O)CH_3$), 4.22 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.39 (2H, s, NCH_2), 7.35-7.46 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.6, 21.6, 50.7, 60.7, 127.4, 127.7, 129.2, 142.9, 168.7, 170.4.

Synthesis of ethyl 2-((ethoxycarbonyl)(phenyl)amino)acetate 500c

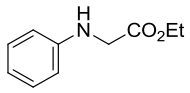


Sodium hydride (as a 60% suspension in mineral oil, 200 mg, 5 mmol, 1 equiv.) was rinsed with dry hexane 3 x 20 mL and blown dry under argon. To this was added dry THF (10 mL) followed by a solution of ethyl phenylcarbamate (826 mg, 5 mmol, 1 equiv.) in dry THF (10 mL). Ethyl bromoacetate (553 µl, 5 mmol, 1 equiv.) was dissolved in dry THF (10 mL) and

added to the mixture which was then stirred overnight at room temperature. The reaction mixture was poured into water (40 mL) and ethyl acetate (40 mL) and extracted with further ethyl acetate (3 x 40 mL). This solution was then sequentially washed with water (3 x 30 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The resulting precipitate was eluted over silica in 60-80% ethyl acetate in petroleum ether to afford ethyl 2-((ethoxycarbonyl)(phenyl)amino)acetate **500c**[243] as a pale yellow oil (1.17 g, 93%); [Found: (HNESP$^+$) (M+H)$^+$, 252.1225. $C_{13}H_{18}NO_4^+$ (M+H), requires 252.1230]; ν_{max} (ATR)/cm^{-1} 2980, 1749, 1699, 1597, 1375, 1193, 1024, 767, 696; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, bs, OCH_2CH_3), 1.30 (3H, *J* = 7.0 Hz, OCH_2CH_3), 4.15-4.27 (2H, m, OCH_2CH_3), overlapping with 4.22 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.35 (2H, s, NCH_2), 7.24-7.39 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.7, 14.0, 51.8, 60.7, 61.6, 125.8 (br.), 126.2 (br.), 128.4, 141.6 (br.), 155.1 (br.), 169.1.

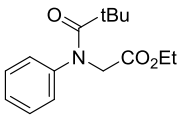
Synthesis of ethyl 2-(*N*-phenylpivalamido)acetate 500d:

i) Synthesis of ethyl 2-(phenylamino)acetate



To a solution of aniline (931 mg, 10 mmol, 1 equiv.) in ethanol (15 mL) was added sodium acetate (820 mg, 10 mmol, 1 equiv.) followed by ethyl bromoacetate (1.65 g, 10 mmol, 1 equiv.). The solution was heated at reflux for 6 h before dilution with water (10 mL). The aqueous suspension was extracted with diethyl ether (4 x 30 mL) and the combined organic fractions washed with additional water (3 x 20 mL) and brine (20 mL) then dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resultant pale yellow solid was recrystallized from ethanol to yield ethyl 2-(phenylamino)acetate as an off-white solid (1.02 g, 57%); M.pt. 53-55 ^oC (lit.[244] 48-49 ^oC); ν_{max} (ATR)/cm^{-1} 3388, 2978, 1728, 1604, 1450, 1369, 1217, 1024, 746, 692; δ_H (400 MHZ, $CDCl_3$) 1.33 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 3.93 (2H, s, NCH_2), 4.27 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 6.63-6.66 (2H, m, Ar*H*), 6.76-6.80 (1H, m, Ar*H*), 7.20-7.24 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.7, 45.4, 60.8, 112.5, 117.7, 128.8, 146.5, 170.6; *m*/*z* (MM-ES+APCI$^+$) 180.1 ([M+H]$^+$, 15%), 106.2 (100).

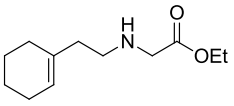
ii) Synthesis of ethyl 2-(*N*-phenylpivalamido)acetate 500d



To a solution of ethyl 2-(phenylamino)acetate (388 mg, 2 mmol, 1 equiv.) and triethylamine (418 μL, 3 mmol, 1.5 equiv.) in dichloromethane (10 mL) was added pivaloyl chloride (271 μL, 2.2 mmol, 1.1 equiv.), slowly at 0 ^{o}C. The solution was then stirred at room temperature overnight before quenching with 2N aqueous HCl (25 mL). The aqueous fraction was extracted with further dichloromethane (3 x 10 mL) and the combined organic fractions washed with additional aqueous HCl (2 x 20 mL), water (20 mL) and brine (10 mL) then dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resultant pale yellow oil was purified by flash column chromatography (10% ethyl acetate in petroleum ether) to yield *ethyl 2-(N-phenylpivalamido)acetate* **500d** (469 mg, 89%); [Found: (HNESP^{+}) $(M+H)^{+}$, 264.1594. $C_{15}H_{22}NO_3^{+}$ (M+H), requires 264.1594]; ν_{max} (ATR)/cm^{-1} 2970, 1747, 1639, 1595, 1359, 1186, 1014, 704; δ_H (400 MHz, $CDCl_3$) 1.03 (9H, s, C(O)CCH_3), 1.25 (3H, t, J = 7.1 Hz, OCH_2CH_3), 4.17 (2H, q, J = 7.1 Hz, OCH_2CH_3), overlapping with 4.19 (2H, s, NCH_2), 7.30-7.42 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.6, 28.7, 40.2, 54.3, 60.4, 127.8, 128.7, 129.1, 143.7, 168.9, 177.4.

Synthesis of Ethyl 2-(*N*-(2-(cyclohex-1-en-1-yl)ethyl)acetamido)acetate 510

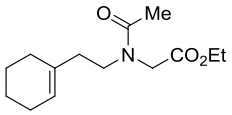
i) Ethyl 2-((2-(cyclohex-1-en-1-yl)ethyl)amino)acetate



To a solution of 2-(cyclohex-1-en-1-yl)ethanamine (2.50 g, 20 mmol, 1 equiv.) in chloroform (25 mL) was added triethylamine (4.18 mL, 30 mmol, 1.5 equiv.) followed slowly by ethyl bromoacetate (2.21 mL, 20 mmol, 1 equiv.). The reaction mixture was stirred overnight at reflux, then poured into water (50 mL) and rinsed with chloroform (3 x 30 mL). This solution was then sequentially rinsed with water (2 x 30 mL) and brine (2 x 30 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was eluted over silica (10% diethyl ether in dichloromethane) to afford *ethyl 2-((2-(cyclohex-1-en-1-yl)ethyl)amino)acetate* as a colourless oil (3.71 g, 88%); [Found: (HNESP^{+}) $(M+H)^{+}$,

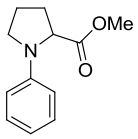
212.1646. $C_{12}H_{22}NO_2^+$ (M+H), requires 212.1645]; ν_{max} (ATR)/cm^{-1} 2922, 1735, 1436, 1369, 1182, 1026, 918, 742; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.50-1.67 (4H, m, cyclohexyl), 1.88-1.97 (4H, m, cyclohexyl), 2.10 (2H, t, J = 6.8 Hz, NCH_2CH_2) 2.65 (2H, t, J = 6.8 Hz, NCH_2CH_2), 3.36 (2H, s, NCH_2COOEt), 4.14 (2H, q, J = 7.1 Hz, OCH_2CH_3), 5.41-5.46 (1H, m, C=CH); δ_C (100 MHz, $CDCl_3$) 13.7, 21.9, 22.4, 24.7, 27.5, 37.9, 46.7, 50.4, 60.0, 122.3, 134.6, 171.9; *m*/*z* (MM-ES+APCI$^+$) 212.1 ([M+H]$^+$, 28%), 116.2 (100).

ii) Ethyl 2-(*N*-(2-(cyclohex-1-en-1-yl)ethyl)acetamido)acetate 510



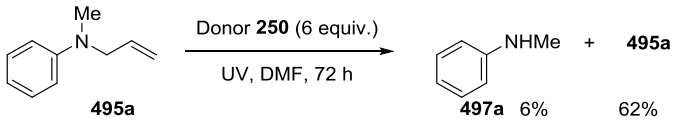
To a solution of ethyl 2-((2-(cyclohex-1-en-1-yl)ethyl)amino)acetate (2.13 g, 10 mmol, 1 equiv.) in chloroform (10 mL) was added imidazole (817 mg, 12 mmol, 1.2 equiv.) followed slowly by acetyl chloride (0.785 mL, 11 mmol, 1.1 equiv.). The reaction mixture was stirred overnight at reflux, then poured into water (25 mL) and rinsed with chloroform (3 x 25 mL). This solution was then sequentially rinsed with water (25 mL) and brine (25 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was eluted over silica (10% diethyl ether in dichloromethane) to afford *ethyl 2-(N-(2-(cyclohex-1-en-1-yl)ethyl)acetamido)acetate* **510** as a colourless oil (1.64 g, 65%); [Found: (HNESP$^+$) (M+H)$^+$, 254.1753. $C_{14}H_{24}NO_3^+$ (M+H), requires 254.1751]; ν_{max} (ATR)/cm^{-1} 2984, 2929, 2835, 1743, 1649, 1425, 1182, 1026, 920, 802, 711; δ_H (500 MHz, $CDCl_3$) [two rotamers in a ratio of 1:0.3] 1.29 (3H, t, J = 7.1 Hz, OCH_2CH_3, major isomer), 1.32 (0.9H, t J = 7.1 Hz, OCH_2CH_3, minor isomer), 1.62-1.67 (5.2H, m, CH_2CH_2, major and minor isomers), 2.01 (0.9H, s, $NC(O)CH_3$, minor isomer), 2.14 (3H, s, $NC(O)CH_3$, major isomer), 2.11-2.20 (5.2H, m, $CH_2C{=}CCH_2$, major and minor isomers), 3.36-3.01 (2H, m, NCH_2CH_2, major isomer), 3.41-3.47 (2H, m, NCH_2CH_2, minor isomer), 4.98 (0.6H, s, NCH_2CO_2Et, minor isomer), 4.04 (2H, s, NCH_2CO_2Et, major isomer), 4.17 (2H, q, J = 7.1 Hz, OCH_2CH_3, major isomer), 4.21 (0.6H, q, J = 7.1 Hz, OCH_2CH_3, minor isomer), 5.42-5.46 (0.3H, m, C=CH, minor isomer), 5.46-5.53 (1H, m, C=CH, major isomer); δ_C (125 MHz, $CDCl_3$) [two isomers] 14.1, 20.9, 21.6, 22.2, 22.3, 22.8, 22.9, 25.2, 25.3, 28.3, 28.5, 35.7, 36.9, 45.8, 47.5, 48.8, 50.7, 61.1, 61.6, 123.0, 124.0, 133.8, 134.8, 169.3, 169.5, 170.6, 170.9; *m*/*z* (MM-ES+APCI$^+$) 254.2 ([M+H]$^+$, 100%).

Methyl 1-phenylpyrrolidine-2-carboxylate 513



Under a flow of argon, CuI (200 mg, 1 mmol, 0.1 equiv.) and potassium carbonate (4 g, 20 mmol, 2 equiv.) were added to a solution of L-proline (1.14 g, 10 mmol, 1 equiv.) and bromobenzene (1.2 mL, 11.5 mmol, 1.15 equiv.) in DMF (10 mL). The reaction mixture was stirred overnight at 100 ^{o}C and then allowed to cool to room temperature, diluted with additional DMF (10 mL) and dimethyl sulfate (1.5 mL, 15 mmol, 1.5 equiv.) added. The reaction mixture was stirred for a further 20 h then the DMF removed by vacuum distillation. The resulting residue was dissolved in ethyl acetate (50 mL) and water (50 mL) and extracted with further ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (3 x 25 mL) and brine (25 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was eluted over a short column of silica (10% ethyl acetate in petroleum ether) to afford methyl 1-phenylpyrrolidine-2-carboxylate **513**[245] as a colourless oil (1.42 g, 69%); ν_{max} (ATR)/cm^{-1} 2957, 2841, 1729, 1597, 1504, 1361, 1343, 1272, 1188, 1154, 992, 743; δ_H (400 MHz, $CDCl_3$) 2.12-2.37 (4H, m, CH_2CH_2), 3.37.3.43 (1H, m, NC*H*H), 3.59-3.64 (1H, m, NCH*H*), 3.75 (3H, s, OCH_3), 4.29 (1H, dd, J = 8.5, 2.1 Hz, NC*H*CO_2Me), 6.58 (2H, d, J = 8.5 Hz, Ar*H*), 6.76 (1H, t, J = 7.2 Hz, Ar*H*), 7.26 (2H, dd, J = 8.5, 7.2 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 23.4, 30.4, 47.8, 51.6, 60.3, 111.5, 116.2, 128.8, 146.2, 174.5; *m*/*z* (MM-ES+APCI$^+$) 206.1 ([M+H]$^+$, 54%), 146.1 (100).

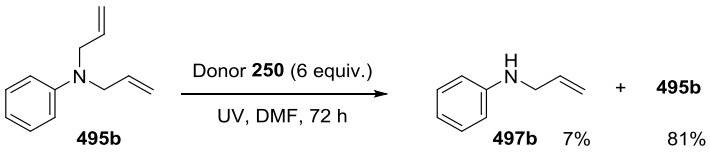
Reaction of *N*-allyl-*N*-methylaniline 495a with photoactivated donor 250



N-allyl-*N*-methylaniline **495a** (44 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford *N*-methylaniline **497a**[246] (2 mg, 6%) and recovery of *N*-allyl-*N*-methylaniline **495a** as a colourless oil (27 mg, 62%) with data as recorded previously. *N*-methylaniline **497a** was a pale brown oil; ν_{max} (ATR)/cm^{-1} 3412, 3049, 2879, 2812, 1600, 1504, 1317, 1261, 1178, 1151, 1070, 857, 746, 690; δ_H (400 MHz, $CDCl_3$) 2.89 (3H, s, NCH_3), 3.50-3.71 (1H, bs, N*H*), 6.66-6.70 (2H, m, Ar*H*), 6.79 (1H, td, J = 7.2, 1.1 Hz, Ar*H*),

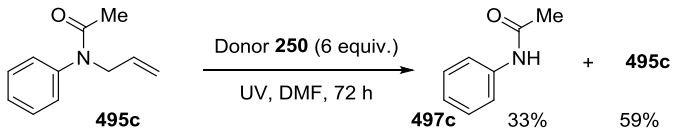
7.25-7.29 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 30.2, 111.9, 116.8, 128.7, 148.9; *m*/*z* (MM-ES+APCI$^+$) 108.2 ($[M+H]^+$, 100%).

Reaction of *N*,*N*-diallylaniline 495b with photoactivated donor 250



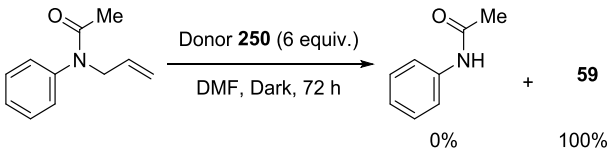
N,*N*-diallylaniline **495b** (52 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford *N*-allylaniline **497b** as a pale yellow oil (9 mg, 7%) and recovered *N*,*N*-diallylaniline **495b** as a colourless oil (42 mg, 81%) with data as reported previously.

Reaction of *N*-allyl-*N*-phenylacetamide 495c with photoactivated donor 250



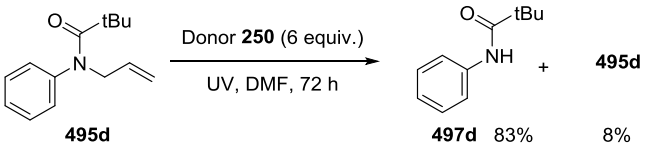
N-allyl-*N*-phenylacetamide **495c** (53 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford *N*-phenylacetamide (13 mg, 33%) and *N*-allyl-*N*-phenylacetamide **495c** (31 mg, 59%). *N*-phenylacetamide **497c**[247] was a white solid; M.pt. 103-105 ^oC (lit.[247] 113-114 ^oC); ν_{max} (ATR)/cm^{-1} 3290, 1661, 1597, 1431, 1319, 1261, 750, 692; δ_H (400 MHz, $CDCl_3$) 2.18 (3H, s, C(O)CH_3), 7.12 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.31 (2H, dd, *J* = 7.6, 7.4 Hz, Ar*H*), 7.52 (2H, d, *J* = 7.6 Hz, Ar*H*); 7.68-7.78 (1H, bs, N*H*); δ_C (100 MHz, $CDCl_3$) 24.0, 119.5, 123.8, 128.5, 137.5, 168.0; *m*/*z* (MM-ES+APCI$^+$) 136.1 ($[M+H]^+$, 100%).

Reaction of *N*-allyl-*N*-phenylacetamide 495c with donor 250 in the absence of UV light



N-allyl-*N*-phenylacetamide **495c** (53 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F with the omission of photoactivation to afford recovery of *N*-allyl-*N*-phenylacetamide **495c** (53 mg, 100%).

Reaction of *N*-allyl-*N*-phenylpivalamide 495d with photoactivated donor 250



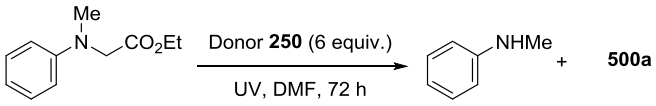
N-allyl-*N*-phenylpivalamide **495d** (65 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford *N*-phenylpivalamide **497d** as a white solid (44 mg, 83%) and recovery of *N*-allyl-*N*-phenylpivalamide **495d** (5 mg, 8%) with data matching those reported previously.

N-phenylpivalamide **497d**; M.pt. 122-124 ^{o}C (lit.[248] 121-124 ^{o}C); ν_{max} (ATR)/cm^{-1} 3311, 2964, 1653, 1595, 1529, 1435, 1315, 1240, 1168, 927, 902, 752, 694; δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, C(O)CC*H*$_3$), 7.12 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.34 (2H, dd, *J* = 7.4, 7.4 Hz, Ar*H*), overlapping with 7.32-7.40 (1H, bs, N*H*), 7.55 (2H, d, *J* = 7.4 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 27.1, 39.1, 119.5, 123.7, 128.4, 137.6, 176.1; *m*/*z* (MM-ES+APCI$^+$) 178.1 ([M+H]$^+$, 100%).

Reaction of ethyl allyl(phenyl)carbamate 495e with photoactivated donor 250

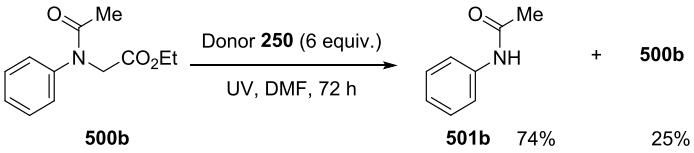
Ethyl allyl(phenyl)carbamate **495e** (62 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford ethyl phenylcarbamate **497e** as a colourless solid (39 mg, 58%) and recovered ethyl allyl(phenyl)carbamate **495e** as a colourless solid (23 mg, 37%) with data matching those reported previously.

Reaction of ethyl 2-(methyl(phenyl)amino)acetate 500a with photoactivated donor 250



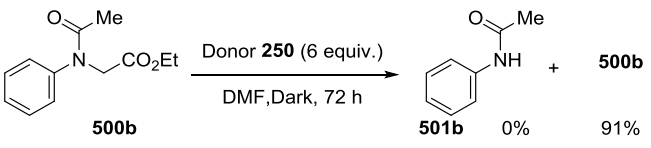
2-(Methyl(phenyl)amino)acetate **500a** (58 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford recovered 2-(methyl(phenyl)amino)acetate **500a** as a colourless oil (34 mg, 58%) and *N*-methylaniline **501a** as a pale yellow oil (11 mg, 34%)

Reaction of ethyl 2-(*N*-phenylacetamido)acetate 500b with photoactivated donor 250



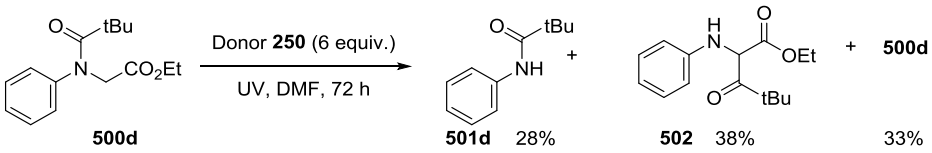
Ethyl 2-(*N*-phenylacetamido)acetate **500b** (66 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford *N*-phenylacetamide **501b** (30 mg, 74%) and recovered ethyl 2-(*N*-phenylacetamido)acetate **500b** (17 mg, 25%) with data as reported previously.

Reaction of ethyl 2-(*N*-phenylacetamido)acetate 500b with donor 250 in the absence of UV light



Ethyl 2-(*N*-phenylacetamido)acetate **500b** (66 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F with the omission of UV activation to afford recovery of ethyl 2-(*N*-phenylacetamido)acetate **500b** (60 mg, 91%).

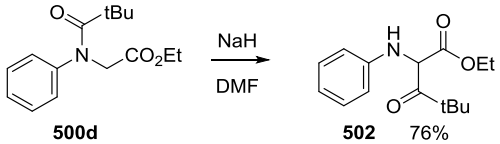
Reaction of ethyl 2-(*N*-phenylpivalamido)acetate 500d with photoactivated donor 250



Ethyl 2-(*N*-phenylpivalamido)acetate **500d** (79 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford ethyl 2-(*N*-phenylpivalamido)acetate **500d** (26 mg, 33%), *N*-phenylpivalamide **501d** (15 mg, 28%) and *ethyl 4,4-dimethyl-3-oxo-2-(phenylamino)pentanoate* **502** (31 mg, 38%) as an off-white solid.

Ethyl 4,4-dimethyl-3-oxo-2-(phenylamino)pentanoate **502**; M.pt. 44-46 ^{o}C; [Found: (HNESP^{+}) $(M+H)^{+}$, 264.1597. $C_{15}H_{22}NO_3^{+}$ (M+H), requires 264.1594]; ν_{max} (ATR)/cm^{-1} 3375, 2970, 2872, 1741, 1707, 1602, 1504, 1367, 1300, 1184, 999, 748, 690; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.28 (9H, s, $C(O)CCH_3$), 4.20 (2H, q, J = 7.1 Hz, OCH_2CH_3), 4.88 (1H, d, J = 8.4 Hz, ArN*H*CH), 5.18 (1H, d, J = 8.4 Hz, ArNHC*H*), 6.71-6.73 (2H, m, Ar*H*), 6.78-6.83 (1H, m, ArH), 7.20-7.24 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.5, 26.0, 44.3, 61.2, 61.5, 113.5, 118.6, 128.9, 145.3, 168.1, 207.3.

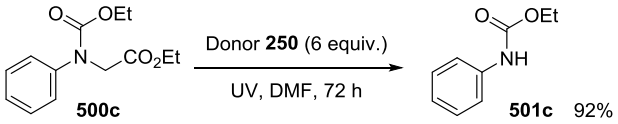
Reaction of ethyl 2-(*N*-phenylpivalamido)acetate 500d with sodium hydride



Sodium hydride (as a 60% suspension in mineral oil, 29 mg, 0.72 mmol, 1.2 equiv.) was rinsed with dry hexane (3 x 20 mL) and blown dry under argon. To this was added dry DMF (4 mL) followed by a solution of ethyl 2-(*N*-phenylpivalamido)acetate **500d** (158 mg, 0.6 mmol, 1 equiv.) in dry DMF (4 mL). The reaction mixture was stirred for 72 h at room temperature under an atmosphere of argon then poured into 2N aqueous HCl (40 mL) and

ethyl acetate (40 mL) and rinsed with further ethyl acetate (3 x 40 mL). This solution was then sequentially rinsed with water (3 x 40 mL) and brine (25 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure then purified over silica (ethyl acetate and petroleum ether) to afford *ethyl 4,4-dimethyl-3-oxo-2-(phenylamino)pentanoate* **502** (120 mg, 76%) as an off-white solid with data matching those reported above.

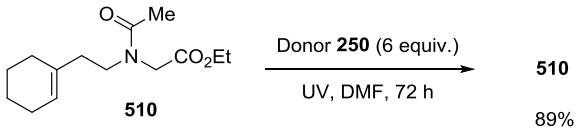
Reaction of ethyl 2-((ethoxycarbonyl)(phenyl)amino)acetate 500c with photoactivated donor 250



500c **501c** 92%

Ethyl 2-((ethoxycarbonyl)(phenyl)amino)acetate **500c** (75 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford ethyl phenylcarbamate **501c** as a colourless solid (46 mg, 92%) with data as reported previously.

Reaction of ethyl 2-(*N*-(2-(cyclohex-1-en-1-yl)ethyl)acetamido)acetate 510 with donor 250

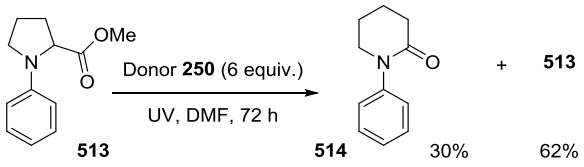


510 **510**

89%

Ethyl 2-(*N*-(2-(cyclohex-1-en-1-yl)ethyl)acetamido)acetate **510** (76 mg, 0.3 mmol), was reacted according to procedure F to afford recovered ethyl 2-(*N*-(2-(cyclohex-1-en-1-yl)ethyl)acetamido)acetate **510** as a pale yellow oil (68 mg, 89%) with data matching those reported previously.

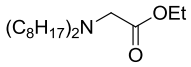
Reaction of methyl 1-phenylpyrrolidine-2-carboxylate 513 with donor 250



Methyl 1-phenylpyrrolidine-2-carboxylate **513** (62 mg, 0.3 mmol), was reacted according to procedure F to afford 1-phenylpiperidin-2-one **514** as a white solid (16 mg, 30%); M.pt. 100-101 °C (lit.[249] 100-101 °C); ν_{max} (ATR)/cm^{-1} 2956, 2916, 2851, 1638, 1487, 1427, 1304, 1161, 1069, 972, 825, 762; δ_H (400 MHz, $CDCl_3$) 1.92-2.04 (4H, m, $NCH_2(CH_2)_2CH_2$), 2.56-2.65 (2H, m, $NC(O)CH_2$), 3.65-3.71 (2H, m, NCH_2), 7.22-7.28 (3H, m, Ar*H*), 7.38-7.41 (2H, m Ar*H*); δ_C (100 MHz, $CDCl_3$); *m*/*z* (MM-ES+APCI$^+$) 176.2 ([M+H]$^+$, 100%), 124.1 (6), 100.2 (28).

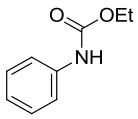
Also recovered was methyl 1-phenylpyrrolidine-2-carboxylate **513** as a pale yellow oil (38 mg, 62%) with data matching those reported previously.

Ethyl 2-(dioctylamino)acetate



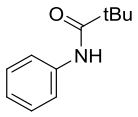
To a solution of dioctylamine (3.02 mL, 10 mmol, 1 equiv.) in chloroform (20 mL) was added potassium carbonate (2.07 g, 15 mmol, 1.5 equiv.) followed slowly by ethyl bromoacetate (1.11 mL, 10 mmol, 1 equiv.). The reaction mixture was stirred overnight at room temperature, then poured into water (40 mL) and rinsed with DCM (3 x 30 mL). This solution was then sequentially rinsed with water (30 mL) and brine (30 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was eluted over silica (10% diethyl ether in petroleum ether) to afford ethyl 2-(dioctylamino)acetate[250] as a colourless oil (2.55 g, 78%); [Found: (FTMS$^+$) (M+H)$^+$, 328.3207. $C_{20}H_{42}NO_2^+$ (M+H), requires 328.3210]; ν_{max} (ATR)/cm^{-1} 2922, 2855, 1732, 1466, 1377, 1176, 1103, 1030, 723; δ_H (400 MHz, $CDCl_3$) 0.90 (6H, t *J* = 6.8 Hz, $N(CH_2)_7CH_3$), 1.24-1.36 (20H, m, $NCH_2CH_2(CH_2)_5CH_3$), 1.29 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.42-1.50 (4H, m, NCH_2CH_2), 2.55-2.59 (4H, m, NCH_2CH_2), 3.33 (2H, s, NCH_2COOEt), 4.18 (2H, q, *J* = 7.1 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 13.6, 13.8, 22.2, 26.9, 27.0, 28.8, 29.0, 31.3, 54.1, 54.8, 59.7, 171.2.

Synthesis of ethyl phenylcarbamate 501c



To a solution of aniline (1.00 mL, 11 mmol, 1.1 equiv.) and ethyl chloroformate (952 μL, 10 mmol, 1 equiv.) in chloroform (20 mL) was added potassium carbonate (2.76 g, 20 mmol, 2 equiv.). The solution was then stirred at reflux overnight before allowing to cool and quenching with water (25 mL). The aqueous fraction was extracted with dichloromethane (3 x 20 mL) and the combined organic fractions washed with additional aqueous HCl (2 x 20 mL), water (20 mL) and brine (10 mL), and then dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The precipitate was recrystallized (hot ethanol) to yield ethyl phenylcarbamate **501c** as pale pink crystals (1.62 g, 98%); M.pt. 48-50 ^{o}C (lit.[239] 48-50 ^{o}C); [Found: (HNESP^{+}) $(M+H)^{+}$, 166.0858. $C_9H_{12}NO_2^{+}$ (M+H), requires 166.0863]; ν_{max} (ATR)/cm^{-1} 3315, 2981, 1701, 1597, 1529, 1440, 1226, 1058, 900, 740, 692; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, J = 7.1 Hz, OCH_2CH_3), 4.25 (2H, q, J = 7.1 Hz, OCH_2CH_3), 6.70-6.81 (1H, bs, N*H*), 7.05-7.10 (1H, m, Ar*H*), 7.29-7.35 (2H, m, Ar*H*), 7.40-7.43 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 60.7, 118.2, 122.8, 128.5, 137.5, 153.2; *m*/*z* (APCI) 165.2 ($[M+H]^{+}$, 100%).

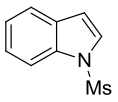
Synthesis of *N*-phenylpivalamide



To a solution of aniline (2.0 mL, 22 mmol, 1.1 eq) and pivaloyl chloride (2745 mL, 20 mmol, 1 eq) in chloroform (25 mL) was added potassium carbonate (4.15 g, 30 mmol, 1.5 eq). The resulting suspension was heated at reflux overnight with stirring. After allowing to cool, the reaction mixture was washed with water (3 x 50 mL) then dried over sodium sulfate and concentrated *in vacuo*. Recrystallization of the residue from hot ethanol yielded *N*-phenylpivalamide[248] (3.12 g, 88%) as white needles; M.pt. 122-124 ^{o}C (lit.[248] 121-124 ^{o}C); ν_{max} (ATR)/cm^{-1} 3311, 2964, 1653, 1595, 1529, 1435, 1315, 1240, 1168, 927, 902, 752, 694; δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, C(O)CCH_3), 7.12 (1H, t, J = 7.4 Hz, Ar*H*), 7.34 (2H, dd, J = 7.4, 7.4 Hz, Ar*H*), overlapping with 7.32-7.40 (1H, bs, N*H*), 7.55 (2H, d, J = 7.4 Hz,

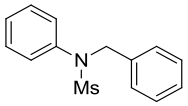
Ar*H*); δ_C (100 MHz, $CDCl_3$) 27.1, 39.1, 119.5, 123.7, 128.4, 137.6, 176.1; *m*/*z* (MM-ES+APCI$^+$) 178.1 ([M+H]$^+$, 100%).

Synthesis of 1-(methylsulfonyl)-1*H*-indole 554



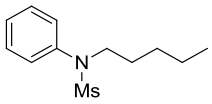
Indole **236** (1.17 g, 10 mmol), was reacted with methanesulfonyl chloride (1.72 g, 15 mmol) as per the procedure reported by Wang *et al.*[251] to yield 1-(methylsulfonyl)-1*H*-indole **554** as a colourless oil (1.87 g, 96%); [Found: (HASP$^+$) (M+H)$^+$, 196.0425. $C_9H_{10}NO_2S^+$ (M+H), requires 196.0427]; ν_{max} (ATR)/cm^{-1} 3018, 2929, 1446, 1355, 1163, 1120, 999, 954, 746; δ_H (400 MHz, $CDCl_3$) 3.12 (3H, s, SC*H*$_3$), 6.74 (1H, d, *J* = 3.6 Hz, Ar*H*), 7.35 (1H, dd, *J* = 7.8, 7.1 Hz, Ar*H*), 7.40 (1H, dd, *J* = 8.2, 7.1 Hz, Ar*H*), 7.65 (1H, d, *J* = 3.6 Hz, Ar*H*), 7.47 (1H, d, *J* = 7.8 Hz, Ar*H*), 7.94 (1H, d, *J* = 8.2 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 40.2, 108.4, 112.5, 121.2, 123.1, 124.4, 125.6, 130.2, 134.4.

Synthesis of *N*-benzyl-*N*-phenylmethanesulfonamide 555



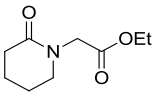
To a solution of *N*-phenylmethanesulfonamide **557** (1.71 g, 10 mmol, 1 equiv.) and benzyl bromide (1.07 mL, 9 mmol, 0.9 equiv.) in DMF (15 mL) was added potassium carbonate (2.07 g, 15 mmol, 1.5 eq). The reaction mixture left stirring at room temperature overnight, then quenched with 2N aqueous NaOH (50 mL). The aqueous fraction was extracted with diethyl ether (3 x 30 mL) and the combined organic fractions washed with additional aqueous NaOH (2 x 30 mL), water (30 mL) and brine (30 mL) then dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield *N*-benzyl-*N*-phenylmethanesulfonamide **555**[252] (2.14 g, 91%) as a white solid; M.pt. 121-123 ^{o}C (lit.[252] 122 ^{o}C); [Found: (HNESP$^+$) (M+Na)$^+$, 284.0718. $C_{14}H_{15}NNaO_2S^+$ (M+Na), requires 284.0716]; ν_{max} (ATR)/cm^{-1} 3020, 2922, 1492, 1452, 1321, 1149, 1062, 968, 869, 754, 696; δ_H (400 MHz, $CDCl_3$) 2.99 (3H, s, SO_2CH_3), 4.88 (2H, s, NCH_2), 7.23-7.40 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 38.2, 54.9, 127.8, 128.1, 128.5, 128.6, 128.8, 129.4, 136.2, 139.2.

Synthesis of *N*-pentyl-*N*-phenylmethanesulfonamide 556



To a solution of *N*-phenylmethanesulfonamide **557** (1.71 g, 10 mmol) and pentyl bromide (1.36 g, 9 mmol) in DMF (15 mL) was added potassium carbonate (2.07 g, 15 mmol). The suspension was stirred at room temperature for 72 h then quenched with sodium hydroxide (2N, aq., 25 mL) and extracted with ethyl acetate (4 x 25 mL). The organic fractions were washed with further sodium hydroxide (2N, aq., 25 mL) then water (3 x 20 mL) and brine (10 mL) then dried over sodium sulfate and concentrated *in vacuo* to yield *N-pentyl-N-phenylmethanesulfonamide* **556** as a white solid (1.99 g, 92%); M.pt. 65-67 ^{o}C; [Found: (HNESP^{+}) $(M+H)^{+}$, 242.1209. $C_{12}H_{20}NO_2S^{+}$ (M+H), requires 242.1209]; ν_{max} (ATR)/cm^{-1} 2926, 2854, 1492, 1328, 1145, 1066, 960, 761, 696; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J = 7.1Hz, CH_2CH_3), 1.29-1.34 (4H, m, $NCH_2CH_2CH_2CH_2CH_3$), 1.46-1.54 (2H, m, $NCH_2CH_2CH_2$), 2.88 (3H, s, SO_2CH_3), 3.68 (2H, t, J = 7.3 Hz, NCH_2), 7.34-7.38 (3H, m, Ar*H*), 7.41-7.45 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.4, 21.7, 27.7, 28.0, 36.4, 50.1, 127.5, 128.0, 128.9, 138.7.

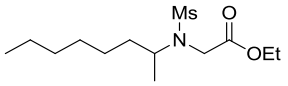
Ethyl 2-(2-oxopiperidin-1-yl)acetate



Sodium hydride (as a 60% suspension in mineral oil, 440 mg, 11 mmol, 1.1 equiv.) was rinsed with dry hexane (3 x 30 mL) and blown dry under argon. To this was added dry THF (20 mL) followed by a solution of piperidin-2-one (991 mg, 10 mmol, 1 equiv.) in dry THF (20 mL). Ethyl bromoacetate (995 μL, 9 mmol, 0.9 equiv.) was then added to the mixture which was stirred overnight at room temperature. The reaction mixture was poured into water (40 mL) and ethyl acetate (40 mL) and rinsed with further ethyl acetate (3 x 30 mL). This solution was then sequentially rinsed with water (30 mL) and brine (30 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was eluted over silica (ethyl acetate) to afford ethyl 2-(2-oxopiperidin-1-yl)acetate[253] as a colourless oil. ν_{max} (ATR)/cm^{-1} 2949, 2870, 1741, 1634, 1493, 1350, 1188, 1024, 742, 700, 657; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.82-1.92 (4H, m, CH_2CH_2), 2.43-2.46 (2H, m,

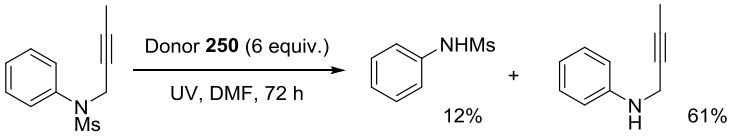
CH_2), 3.35-3.40 (2H, m, CH_2), 4.12 (2H, s, NCH_2), 4.21 (2H, q, J = 7.1 Hz, OCH_2CH$_3$); δ_C (100 MHz, $CDCl_3$) 13.7, 20.9, 22.7, 31.6, 48.1, 48.7, 60.6, 168.7, 170.0.

Ethyl 2-(*N*-(octan-2-yl)methylsulfonamido)acetate



Sodium hydride (as a 60% suspension in mineral oil, 96 mg, 2.4 mmol, 1.2 equiv.) was rinsed with dry hexane (3 x 20 mL) and blown dry under argon. To this was added dry THF (10 mL) followed by a solution of *N*-(octan-2-yl)methanesulfonamide (456 mg, 2.2 mmol, 1.1 equiv.) in dry THF (10 mL). Ethyl bromoacetate (221 µl, 2 mmol, 1 equiv.) was dissolved in dry THF (10 mL) and added to the mixture which was then stirred overnight at room temperature. The reaction mixture was poured into water (25 mL) and diethyl ether (25 mL) and extracted with further diethyl ether (2 x 25 mL). This solution was then sequentially washed with water (3 x 25 mL) and brine (25 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The resulting precipitate was eluted over silica in 5% ethyl acetate in petroleum ether to afford *ethyl 2-(N-(octan-2-yl)methylsulfonamido)acetate* (399 mg, 68%) as a colourless oil. ν_{max} (ATR)/cm^{-1} 2929, 2856, 1748, 1327, 1198, 1142, 1026, 960, 779, 727; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, J = 7.1 Hz, (CH$_2$)$_5$CH_3), 1.14 (3H, d, J = 6.8 Hz, CHCH_3), 1.25-1.56 (10H, m, NCH(CH_2)$_5$CH$_3$), 1.27 (3H, t, J = 7.0 Hz, OCH$_2$CH_3) 3.09 (3H, s, SO$_2$CH_3), 3.79-3.86 (1H, m, NCH), 3.87 (1H, d, J = 18.5 Hz, NCH_2), 4.03 (1H, d, J = 18.5 Hz, NCH_2), 4.17 (2H, q, J = 7.0 Hz, OCH_2CH$_3$); δ_C (100 MHz, $CDCl_3$) 14.0, 14.1, 19.1, 22.5, 26.4, 29.0, 31.6, 35.0, 41.3, 43.4, 53.8, 61.3, 170.7.

Reaction of *N*-(but-2-yn-1-yl)-*N*-phenylmethanesulfonamide with donor 250

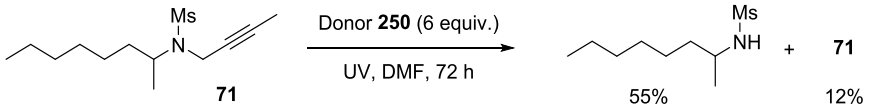


N-(but-2-yn-1-yl)-N-phenylmethanesulfonamide (67 mg, 0.3 mmol), was reacted according to procedure F to afford the mixture of products given below.

N-phenylmethanesulfonamide was isolated as a white solid (6 mg, 12%). Data were as reported previously.

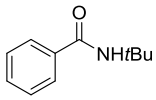
N-(but-2-yn-1-yl)aniline[254] was recovered as a pale yellow oil (26 mg, 61%); ν_{max} (ATR)/cm^{-1} 3402, 3051, 3020, 2918, 2852, 1600, 1500, 1429, 1350, 1311, 1251, 1180, 1132, 1089, 1059, 993, 871, 746, 690; δ_H (400 MHz, $CDCl_3$) 1.87 (3H, t, *J* = 2.3 Hz, CCC*H*$_3$), 3.82-4.00 (1H, bs, N*H*), 3.92 (2H, q, *J* = 2.3 Hz, NC*H*$_2$CC), 6.72 (2H, dd, *J* = 8.6, 1.0 Hz, Ar*H*), 6.83 (1H, tt, *J* = 7.4, 1.0 Hz, Ar*H*), 7.28 (2H, dd, *J* = 8.6, 7.4 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 3.09, 33.6, 75.7, 78.6, 113.0, 117.8, 128.7, 146.9; *m*/*z* (GC-CI$^+$) 146.1 ([M+H]$^+$, 100%).

Reaction of *N*-(but-2-yn-1-yl)-*N*-(octan-2-yl)methanesulfonamide with donor 250



N-(but-2-yn-1-yl)-*N*-octan-2-ylmethanesulfonamide (67 mg, 0.3 mmol, 1 equiv.), was reacted according to procedure F to afford *N*-octan-2-ylmethanesulfonamide (7.2 mg, 12%) and *N-(but-2-yn-1-yl)-N-octan-2-ylmethanesulfonamide* (42.6 mg, 55%) as a colourless oil. Data were as reported previously.

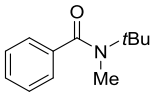
Synthesis of *N*-(*tert*-butyl)-benzamide



To a mixture of *tert*-butylamine (5.78 mL, 55 mmol, 1.1 equiv.) and triethylamine (8.37 mL, 60 mmol, 1.2 equiv.) was added benzoyl chloride (5.81 mL, 50 mmol, 1 equiv.) dropwise with stirring at 0 ^oC then the solution left stirring at room temperature overnight. Aqueous 2N HCl (50 mL) was then added, and extracted with ethyl acetate (3 x 50 mL). The organic fractions were then washed with further portions of aqueous 2N HCl (3 x 25 mL) and once with brine (25 mL) then dried over anhydrous sodium sulfate and the solvent evaporated. The crude organic residue was recrystallized from hot ethanol to yield *N*-(*tert*-butyl)-benzamide as a white solid (7.98 g, 90%); M.pt. 125-126 ^oC (lit.[255] 126-128 ^oC); ν_{max} (ATR)/cm^{-1} 3317, 2964, 1633, 1529, 1309, 1215, 875, 715, 692; δ_H (400 MHz, $CDCl_3$) 1.49

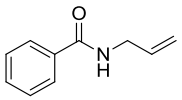
(9H, s, C(O)CCH_3), 7.41-7.46 (2H, m, Ar*H*), 7.47-7.52 (1H, m, Ar*H*), 7.73-7.76 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 28.3, 51.1, 126.2, 127.9, 130.5, 135.4, 166.4; *m*/*z* (MM-ES+APCI) 178.1 ($[M+H]^+$, 11%), 122.1 (100).

Synthesis of *N*-(*tert*-butyl)-*N*-methylbenzamide 521



Sodium hydride (as a 60% suspension in mineral oil, 480 mg, 12 mmol, 1.2 equiv.) was rinsed with dry hexane (3 x 30 mL) and blown dry under argon. To this was added dry THF (30 mL) followed by a solution of *N*-(*tert*-butyl)-benzamide (1.95 g, 11 mmol, 1.1 equiv.) in dry THF (20 mL). Iodomethane (620 µl, 10 mmol, 1 equiv.) was added to the mixture which was then stirred overnight at room temperature. The reaction mixture was poured into water (50 mL) and ethyl acetate (50 mL) and rinsed with further ethyl acetate (3 x 30 mL). This solution was then sequentially rinsed with water (3 x 30 mL) and brine (25 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The resulting precipitate recrystallized from hot ethanol to afford *N*-(*tert*-butyl)-*N*-methylbenzamide **521** as a white solid (1.74 g, 91%); M.pt. 72-74 ^oC (lit.[256] 78-80 ^oC); [Found: (HNESP) $(M+H)^+$, 192.1384. $C_{12}H_{18}NO^+$ (M+H), requires 192.1383]; ν_{max} (ATR)/cm^{-1} 2966, 1618, 1361, 1176, 1060, 796, 726, 698; δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C(O)CCH_3), 2.84 (3H, s, NCH_3), 7.37-7.40 (3H, m, Ar*H*), 7.40-7.46 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 27.2, 34.8, 56.0, 126.8, 127.8, 128.9, 138.6, 172.7.

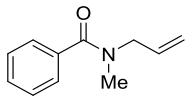
Synthesis of *N*-allyl-benzamide



To a mixture of allylamine (4.12 mL, 55 mmol, 1.1 equiv.) and triethylamine (8.37 mL, 60 mmol, 1.2 equiv.) was added benzoyl chloride (5.81 mL, 50 mmol, 1 equiv.) dropwise with stirring at 0 ^oC then the solution left stirring at room temperature overnight. Aqueous 2N HCl (50 mL) was then added, and extracted with ethyl acetate (3 x 50 mL). The organic fractions were then washed with further portions of aqueous 2N HCl (3 x 25 mL) and once

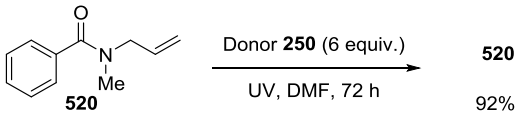
with brine (25 mL) then dried over anhydrous sodium sulfate and the solvent evaporated. The crude organic residue was purified over silica (30-50% ethyl acetate/ petroleum ether) to yield *N*-allyl-benzamide[257] as a pale yellow oil (7.66 g, 95%), ν_{max} (ATR)/cm^{-1} 3302, 3064, 1635, 1529, 1292, 916, 690; δ_H (400 MHz, $CDCl_3$) 4.00 (2H, ddd, *J* = 5.7, 1.5, 1.5, NC*H*$_2$), 5.08 (1H, ddt, *J* = 10.2, 1.5, 1.5, NCH$_2$CHC*H*), 5.16 (1H, ddt, *J* = 17.2, 1.5, 1.5, NCH$_2$CHC*H*), 5.85 (1H, ddt, *J* = 17.2, 10.2, 5.7 Hz, NCH$_2$C*H*), 7.31-7.35 (2H, m, Ar*H*), 7.40-7.45 (1H, m, Ar*H*) overlapping with 7.40-7.46 (1H, bs, N*H*), 7.80-7.83 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 41.9, 115.6, 126.7, 127.9, 130.9, 133.8, 133.9, 167.3; *m*/*z* (MM-ES+APCI) 162.2 ([M+H]$^+$, 79%), 105.2 (100).

Synthesis of *N*-allyl-*N*-methylbenzamide 520



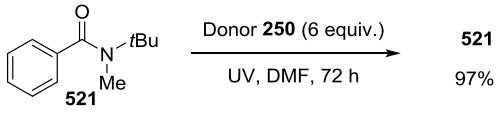
Sodium hydride (as a 60% suspension in mineral oil, 480 mg, 12 mmol, 1.2 equiv.) was rinsed with dry hexane (3 x 30 mL) and blown dry under argon. To this was added dry THF (30 mL) followed by a solution of *N*-allyl-benzamide (1.77 g, 11 mmol, 1.1 equiv.) in dry THF (20 mL). Iodomethane (620 µl, 10 mmol, 1 equiv.) was added to the mixture which was then stirred overnight at room temperature. The reaction mixture was poured into water (50 mL) and ethyl acetate (50 mL) and rinsed with further ethyl acetate (3 x 30 mL). This solution was then sequentially rinsed with water (3 x 30 mL) and brine (25 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The resulting organic residue was eluted over silica (30% ethyl acetate in petroleum ether) to afford *N*-allyl-*N*-methylbenzamide **520**[258] as a pale yellow oil (1.45 g, 83%); [Found: (HNESP) (M+H)$^+$, 176.1070. $C_{11}H_{14}NO^+$ (M+H), requires 176.1070]; ν_{max} (ATR)/cm^{-1} 2966, 1618, 1361, 1176, 1060, 796, 723, 698; δ_H (400 MHz, DMSO-d$_6$, 343 K) 2.90 (3H, s, NC*H*$_3$), 3.83-4.06 (2H, bs, NC*H*$_2$), 5.13-5.22 (2H, m, NCH$_2$CHC*H*$_2$), 5.78-5.90 (1H, m, NCH$_2$C*H*CH$_2$), 7.39-7.44 (5H, m, Ar*H*); δ_C (100 MHz, DMSO-d$_6$, 343 K) 34.9, 52.0, 117.4, 127.0, 128.7, 129.7, 134.0, 137.1, 170.8.

Reaction of *N*-allyl-*N*-methylbenzamide 520 with donor 250



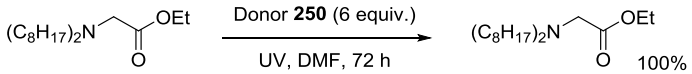
N-allyl-*N*-methylbenzamide **520** (53 mg, 0.3 mmol), was reacted according to procedure F to afford recovery of ethyl 2-(dioctylamino)acetate **520** (49 mg, 92%). Data were as reported previously.

Reaction of *N*-(*tert*-butyl)-*N*-methylbenzamide 521 with donor 250



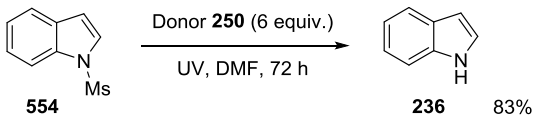
N-(*tert*-butyl)-*N*-methylbenzamide **521** (57 mg, 0.3 mmol), was reacted according to procedure F to afford complete recovery of ethyl 2-(dioctylamino)acetate **521** (55 mg, 97%). Data were as reported previously.

Reaction of ethyl 2-(dioctylamino)acetate with donor 250



Ethyl 2-(dioctylamino)acetate (98 mg, 0.3 mmol), was reacted according to procedure F to afford complete recovery of ethyl 2-(dioctylamino)acetate (98 mg, 100%).

Reaction of 1-(methylsulfonyl)-1*H*-indole 554 with photoactivated donor 250

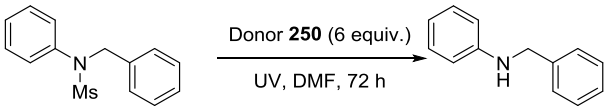


1-(Methylsulfonyl)-1*H*-indole **554** (59 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford indole **236** as a pale yellow solid (29 mg, 83%); M.pt. 51-52

°C (lit.[259] 49.5-50.5 °C); ν_{max} (ATR)/cm^{-1} 3396, 3049, 1454, 1413, 1334, 1246, 1089, 742, 721; δ_H (400 MHz, $CDCl_3$) 6.59-6.61 (1H, m, Ar*H*), 7.14-7.28 (3H, m, Ar*H*), 7.43 (1H, dd, *J* = 7.9, 0.8 Hz, Ar*H*), 7.69 (1H, d, *J* = 7.9 Hz, Ar*H*), 7.98-7.30 (1H, bs, N*H*); δ_C (100 MHz, $CDCl_3$) 102.1, 110.9, 119.5, 120.4, 121.6, 124.0, 127.5, 135.4; *m*/*z* (MM-ES+APCI$^+$) 165.0 (M+Li+MeCN]$^+$, 19%), 118.1 ([M+H]$^+$, 10), 124.0 ([M+Li]$^+$, 100).

A control reaction run in parallel in the absence of UV light at room temperature also delivered indole in high yield (30 mg, 85%) with data matching those reported previously.

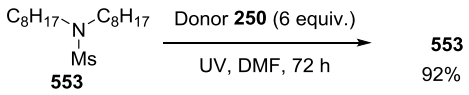
Reaction of *N*-benzyl-*N*-phenylmethanesulfonamide 555 with photoactivated donor 250



555 **536** 77%

N-benzyl-*N*-phenylmethanesulfonamide **555** (78 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford *N*-benzylaniline **536** as a pale yellow solid (42 mg, 77%); M.pt. 36-38 °C (lit.[260] 37-40 °C); ν_{max} (ATR)/cm^{-1} 3415, 3022, 2926, 1598, 1508, 1327, 1274, 1180, 983, 856, 732, 686; δ_H (400 MHz, $CDCl_3$) 4.04-4.23 (1H, bs, N*H*), 4.45 (2H, s, NCH_2), 6.77 (2H, d, *J* = 7.7 Hz, Ar*H*), 6.89 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.33 (2H, dd, *J* = 7.7, 7.3 Hz, Ar*H*), 7.41-7.53 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 48.4, 113.1, 117.7, 127.4, 127.7, 128.8, 129.4, 139.6, 148.3; *m*/*z* (MM-ES+APCI$^+$) 184.2 ([M+H]$^+$, 100%).

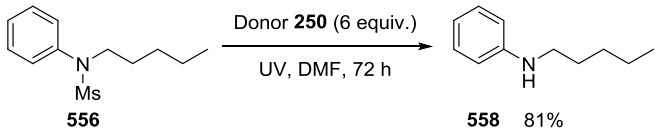
Reaction of *N*,*N*-dioctylmethanesulfonamide 553 with photoactivated donor 250



553 **553** 92%

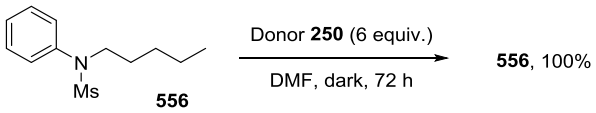
N,*N*-dioctylmethanesulfonamide **553** (96 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford *N*,*N*-dioctylmethanesulfonamide **553** as a pale yellow oil (88 mg, 92%) with data matching those reported previously.

Reaction of *N*-butyl-*N*-phenylmethanesulfonamide 556 with photoactivated donor 250



N-pentyl-*N*-phenylmethanesulfonamide **556** (68 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F to afford *N*-pentylaniline **558**[261] as a colourless oil (49 mg, 81%). ν_{max} (ATR)/cm^{-1} 3412, 2954, 2926, 2858, 1600, 1502, 1317, 1257, 1178, 1151, 1089, 991, 886, 744, 690; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.40-1.44 (4H, m, $NCH_2CH_2CH_2CH_2CH_3$), 1.62-1.68 (2H, m, $NCH_2CH_2CH_2$), 3.14 (2H, t, J = 7.0 Hz, NCH_2CH_2), 3.59.3.64 (1H, bs, N*H*), 6.61-6.66 (2H, m, Ar*H*), 6.72 (1H, tt, J = 7.4, 1.1 Hz, Ar*H*), 7.18-7.24 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.5, 22.0, 28.8, 28.9, 43.5, 112.2, 116.6, 128.7, 148.1; *m*/*z* (MM-ES+APCI$^+$) 164.2 ([M+H]$^+$, 100%).

Reaction of *N*-pentyl-*N*-phenylmethanesulfonamide 556 with donor 250 in the absence of UV light



N-pentyl-*N*-phenylmethanesulfonamide **556** (68 mg, 0.3 mmol, 1 equiv.) was reacted according to general procedure F with the omission of photoactivation to afford recovery of *N*-pentyl-*N*-phenylmethanesulfonamide **556** (53 mg, 100%). Data were as reported previously.

10.5. Experimental Details for Chapter 6

General Procedure for oxidation using *m*-chloroperbenzoic acid

To a solution of the substrate in dichloromethane at 0 ^{o}C was added *m*-chloroperbenzoic acid portion-wise with stirring. The reaction mixture was then stirred at room temperature for 16 h after which time the reaction was diluted with an additional DCM and quenched with saturated sodium thiosulfate solution. The organic fraction was then further extracted with 2N aqueous NaOH (2 x 30 mL) then brine (30 mL) before drying over sodium sulfate, filtration and concentration. Flash column chromatography then yielded the pure compounds in the yields stated.

General Procedure for reaction of substrate with photoactivated donor 250

In a nitrogen-filled glovebox, a solution of donor **250** (512 mg, 1.8 mmol, 6 equiv.) in dry DMF (4 mL) was added directly to the substrate (0.3 mmol, 1 equiv.) in a 5 mL round-bottom flask. The reaction flask was sealed and removed to a fumehood where it was stirred for 72 h under UV radiation (365 nm, 2 x 100W). The mixture was then poured into aqueous 2N aqueous HCl (30 mL) and diethyl ether (30 mL) before extracting with diethyl ether (2 x 30 mL). The combined organic layers were then washed with 2N aqueous HCl (3 x 30 mL) and dried over Na_2SO_4. The crude organic residue, obtained after evaporation under reduced pressure, was purified by flash column chromatography to obtain the pure products with yields as given.

General Procedure for reaction of substrate with donor 250 in the absence of photoactivation

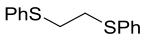
In a nitrogen-filled glovebox, a solution of donor **250** (512 mg, 1.8 mmol, 6 equiv.) in dry DMF (4 mL) was added directly to the substrate (0.3 mmol, 1 equiv.) in a 5 mL round-bottom flask. The reaction flask was sealed and removed to a fumehood where it was wrapped in aluminium foil and stirred for 72 h at room temperature. The mixture was then poured into aqueous 2N aqueous HCl (30 mL) and diethyl ether (30 mL) before extracting with diethyl ether (2 x 30 mL). The combined organic layers were then washed with 2N aqueous HCl (3 x 30 mL) and dried over Na_2SO_4. The crude organic residue, obtained after

evaporation under reduced pressure, was purified by flash column chromatography to obtain the pure products with yields as given.

General Procedure for reaction of substrate with photoactivation in the absence of donor

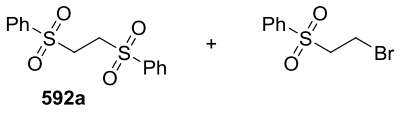
In a nitrogen-filled glovebox, dry DMF (4 mL) was added directly to the substrate (0.3 mmol, 1 equiv.) in a 5 mL round-bottom flask. The reaction flask was sealed and removed to a fumehood where it was stirred for 72 h under UV radiation (365 nm, 2 x 100W). The mixture was then poured into aqueous 2N aqueous HCl (30 mL) and diethyl ether (30 mL) before extracting with diethyl ether (2 x 30 mL). The combined organic layers were then washed with 2N aqueous HCl (3 x 30 mL) and dried over Na_2SO_4. The crude organic residue, obtained after evaporation under reduced pressure, was purified by flash column chromatography to obtain the pure products with yields as given.

Synthesis of 1,2-bis(phenylthio)ethane 587



A solution of thiophenol (1.10 g, 10 mmol, 2 equiv.), 1,2-dichloroethane (495 mg, 5 mmol, 1 equiv.) and DBU (3.04 g, 20 mmol, 4 equiv.) in tetrahydrofuran (2 mL) was heated under microwave radiation at 150 ^{o}C for 0.5 h. The reaction mixture was then diluted with diethyl ether (50 mL) and rinsed with 2N aqueous HCl (25 mL), 2N aqueous NaOH (25 mL), water (25 mL), brine (25 mL), then dried over sodium sulfate, filtered and concentrated under reduced pressure. Recrystallization from diethyl ether gave rise to 1,2-bis(phenylthio)ethane **587** as a white crystalline solid (2.14 g, 87%). M.pt. 58-60 ^{o}C (lit.[262] 63-64 ^{o}C); ν_{max} (ATR)/cm^{-1} 3076, 3055, 2936, 1580, 1476, 1427, 1082, 1022, 731, 685; δ_H (400 MHz, $CDCl_3$) 3.10 (4H, s, C*H*$_2$C*H*$_2$), 7.20-7.34 (10H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 33.4, 126.6, 129.1, 130.1, 135.1; *m*/*z* (GCMS CI$^+$) 245.9 (4%), 217.9 ([M]$^+$, 1), 165.0 (4), 136.9 (100).

Synthesis of 1,2-bis(phenylsulfonyl)ethane 592a and ((2-bromoethyl)sulfonyl)benzene



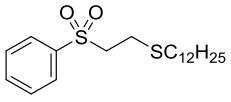
592a

A solution of 1,2-dibromoethane (3.76 g, 20 mmol, 1 equiv.) and sodium benzenesulfinate (3.28 g, 20 mmol, 1 equiv) in acetone (20 mL) and water (20 mL) stirred at reflux for 16 h. The mixture was allowed to cool then diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL) before rinsing with water (3 x 50 mL) and brine (10 mL). Concentration of the dried organic fraction yielded a white solid which upon recrystallization from ethanol/ethyl acetate gave 1,2-bis(phenylsulfonyl)ethane **592a** as a white crystalline solid (4.04 g, 65%). Chromatography of the mother liquor in 50% DCM/ petroleum ether yielded ((2-bromoethyl)sulfonyl)benzene (1.146 g, 23%)

1,2-Bis(phenylsulfonyl)ethane **592a**: M.pt. 178-180 ^{o}C (lit.[263] 183-184 ^{o}C); ν_{max} (ATR)/cm^{-1} 2995, 2941, 1449, 1300, 1144, 1082, 775, 743, 684; δ_H (400 MHz, $CDCl_3$) 3.45 (4H, s, C*H*$_2$C*H*$_2$), 7.58-7.63 (4H, m, Ar*H*), 7.69-7.74 (2H, m, Ar*H*) 7.87-7.89 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 49.5, 128.1, 129.7, 134.6, 138.0; *m*/*z* (GC-MS CI$^+$) 236.9 ([M+C_2H_3]$^+$, 3%), 209.0 (4), 168.9 (100).

((2-Bromoethyl)sulfonyl)benzene; M.pt. 59-61 ^{o}C (lit.[264] 55-56 ^{o}C); ν_{max} (ATR)/cm^{-1} 3067, 3038, 2995, 1447, 1306, 1281, 1146, 1074, 945, 785, 746, 685; δ_H (400 MHz, $CDCl_3$) 3.50-3.63 (4H, m, SO_2C*H*$_2$C*H*$_2$Br), 7.59-7.63 (2H, m, Ar*H*), 7.69-7.74 (1H, m, Ar*H*), 7.92-7.94 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 20.4, 57.8, 127.7, 129.1, 133.9, 137.8; *m*/*z* (GC-MS, CI$^+$) 208.9 (2%), 168.9 ([M-Br]$^+$, 100), 124.8 (2).

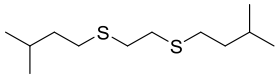
Synthesis of dodecyl(2-(phenylsulfonyl)ethyl)sulfane 594



To a suspension of sodium hydride (84 mg as a 60% suspension in mineral oil, 2.1 mmol, 1.2 equiv.) in THF (20 mL) was slowly added dodecanethiol (0.462 mL, 0.391 g, 1.93 mmol, 1.1 equiv.). After 0.25 h, ((2-bromoethyl)sulfonyl)benzene (0.436 g, 1.75 mmol, 1 equiv.) was added slowly with stirring, then the reaction mixture brought to reflux and left for 16 h. The

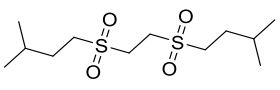
mixture was allowed to cool to room temperature then quenched with water (50 mL) and extracted with diethyl ether (2 x 30 mL). The combined organic fractions were extracted with water (3 x 30 mL) and brine (10 mL). Concentration of the dried organic fraction followed by flash column chromatography in 10-20% ethyl acetate/petroleum ether yielded a white solid identified as *dodecyl(2-(phenylsulfonyl)ethyl)sulfane* **594** (604 mg, 93%). M.pt. 28-30 ^{o}C; ν_{max} (ATR)/cm^{-1} 3061, 2918, 2849, 1447, 1309, 1290, 1147, 1088, 816, 762, 733, 687; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, J = 6.8 Hz, CH_2CH_3), 1.27-1.36 (18H, m, $(CH_2)_9$), 1.50-1.58 (2H, m, $SCH_2CH_2CH_2$), 2.49 (2H, dd, J = 7.5, 7.3 Hz, $SCH_2CH_2CH_2$), 2.79-2.83 (2H, m, $SO_2CH_2CH_2S$), 3.32-3.36 (2H, m, SO_2CH_2), 7.60-7.64 (2H, m, Ar*H*), 7.69-7.73 (1H, m, Ar*H*), 7.93-7.95 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 13.6, 22.2, 23.8, 28.3, 28.7, 28.8, 28.9, 29.0, 29.1, 29.1, 31.4, 31.7, 55.9, 127.6, 128.9, 133.5, 138.2; *m*/*z* (GC-MS, CI$^+$) 371.2 ([M+H]$^+$, 26%), 229.2 (100).

Synthesis of 1,2-bis(isopentylthio)ethane 588



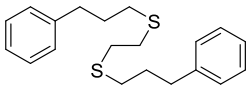
To a solution of 1,2-dithioethane (0.942 g, 10 mmol, 1 equiv.) and isopentyl bromide (3.17 g, 21 mmol, 2.1 equiv) in DMF (20 mL) was added potassium carbonate (3.46 g, 25 mmol, 2.5 equiv.)and the reaction mixture stirred at room temperature for 16 h. The mixture was diluted with water (50 mL) and extracted with diethyl ether (3 x 50 mL) before rinsing with water (50 mL), 2N NaOH (aq. 50 mL) and brine (10 mL). Concentration of the dried organic fraction yielded a white solid which upon distillation @ 1 mbar and 120 ^{o}C gave 1,2-bis(isopentylthio)ethane **588**[265] as a colourless oil. (1.80 g, 77%). ν_{max} (ATR)/cm^{-1} 2953, 2924, 2870, 1466, 1366, 1273, 1273, 1198, 920, 741, 696; δ_H (400 MHz, $CDCl_3$) 0.90 (12H, d, J = 6.6 Hz, $CH(CH_3)_2$), 1.46-1.50 (4H, m, $CHCH_2CH_2$), 1.64-1.71 (2H, m, C*H*), 2.53-2.57 (4H, m, SCH_2CH_2CH), 2.71 (4H, s, SCH_2CH_2S); δ_C (100 MHz, $CDCl_3$) 22.3, 27.4, 30.2, 32.1, 38.7; *m*/*z* (GC-MS CI$^+$) 234.1 ([M]$^+$, 5%), 177.0 (4), 131.0 (100).

Synthesis of 1,2-bis(isopentylsulfonyl)ethane 592c



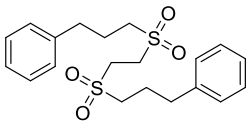
To a solution of 1,2-bis(isopentylthio)ethane (0.495 g, 2 mmol, 1 equiv.) in methanol (10 mL) was slowly added Oxone (3.074 g, 10 mmol, 5 equiv., as a solution in 10 mL water). After an initial exotherm, the resultant white suspension was stirred at room temperature for 16 h before dilution with ethyl acetate (50 mL) and extraction with water (2 x 25 mL) and brine (10 mL). Concentration of the dried organic fraction yielded a white solid which upon crystallization from chloroform gave *1,2-bis(isopentylsulfonyl)ethane* **592c** as a white crystalline solid (513 mg, 86%); M.pt. 174-176 ^{o}C; ν_{max} (ATR)/cm^{-1} 2957, 2870, 1468, 1302, 1273, 1111, 797, 741; δ_H (400 MHz, $CDCl_3$) 0.97 (12H, d, J = 6.4 Hz, $CH(CH_3)_2$), 1.72-1.80 (6H, m, $CHCH_2CH_2$), 3.07-3.11 (4H, m, $SO_2CH_2CH_2CH$), 3.45 (4H, s, $SO_2CH_2CH_2SO_2$); δ_C (100 MHz, $CDCl_3$) 22.0, 27.4, 30.4, 44.5, 52.6; *m*/*z* (GC-MS, CI$^+$) 299.1 ([M+H]$^+$, 100%), 211.0 (8), 163.0 (38).

Synthesis of 1,2-bis((3-phenylpropyl)thio)ethane 589



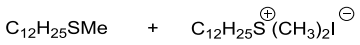
To a suspension of sodium hydride (2.94 g as a 60% suspension in mineral oil, 44 mmol, 2.2 equiv.) in THF (100 mL) was slowly added 1,2-ethanedithiol (1.68 mL, 1.88 g, 20 mmol, 1 equiv.). After 0.25 h, (3-bromopropyl)benzene (6.7 mL, 44 mmol, 2.2 equiv.) was added slowly with stirring, then the reaction mixture brought to reflux and left for 16 h. The mixture was allowed to cool to room temperature then quenched with 2N aqueous NaOH (50 mL) and extracted with diethyl ether (2 x 50 mL). The combined organic fractions were extracted with 2N aqueous NaOH (2 x 50 mL) water (25 mL) and brine (10 mL). Concentration of the dried organic fraction followed by flash column chromatography in 10-50% chloroform/petroleum ether yielded a colourless oil identified as *1,2-bis((3-phenylpropyl)thio)ethane* **589** (5.82 g, 88%); ν_{max} (ATR)/cm^{-1} 3024, 2926, 2852, 1494, 1452, 1200, 1074, 1030, 743, 696; δ_H (400 MHz, $CDCl_3$) 1.96 (4H, quintet, J = 7.5 Hz, $ArCH_2CH_2CH_2$), 2.59 (4H, t, J = 7.5 Hz, $ArCH_2CH_2CH_2$), 2.74 (4H, s, SCH_2CH_2S), 2.77 (4H, t, J = 7.5 Hz, $ArCH_2CH_2CH_2$), 7.22-7.27 (6H, m, Ar*H*), 7.31-7.35 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 31.2, 31.6, 32.2, 34.8, 126.0, 128.46, 128.52, 141.4; *m*/*z* (GC-MS, CI$^+$) 330.1 ([M]$^+$, 5%), 207.1 (4), 179.1 ([M+2CH_3^+]/2, 100), 151.0 (10), 119.0 (9), 91.0 (10).

Synthesis of 1,2-bis((3-phenylpropyl)sulfonyl)ethane 592b



1,2-Bis((3-phenylpropyl)thio)ethane (673 mg, 2 mmol, 1 equiv.) was reacted with mCPBA (~70% pure, 2.47 g, 10 mmol, 5 equiv.) as per the standard procedure followed by recrystallization from ethanol/methanol to yield *1,2-bis((3-phenylpropyl)sulfonyl)ethane* **592b** as a white solid (765 mg, 97%); M.pt. 178-180 ^{o}C; ν_{max} (ATR)/cm^{-1} 3030, 2992, 2941, 2866, 1454, 1231, 1109, 1022, 789, 745, 692; δ_H (400 MHz, $CDCl_3$) 2.17-2.25 (4H, m, $ArCH_2CH_2CH_2$), 2.81 (4H, dd, J = 7.2, 7.4 Hz, $ArCH_2CH_2CH_2$), 3.01-3.05 (4H, m, $ArCH_2CH_2CH_2$), 3.36 (4H, s, $SO_2CH_2CH_2SO_2$), 7.17-7.21 (4H, m, Ar*H*), 7.21-7.29 (2H, m, Ar*H*), 7.29-7.34 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 23.5, 34.1, 44.7, 53.2, 126.7, 128.4, 128.8, 139.3. *m*/*z* (GC-MS, CI$^+$) 239.1 (4%), 211.1 ([M+2CH_3^+]/2, 100), 119.0 (10), 91.0 (9).

Synthesis of dodecyl(methyl)sulfane 571 and dodecyldimethylsulfonium iodide 572

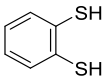


To a suspension of potassium carbonate (13.82 g, 100 mmol, 2 equiv.) in DMF (50 mL) was added dodecanethiol (10.12 g, 50 mmol, 1 equiv.) followed slowly by methyl iodide (10.65 g, 75 mmol, 1.5 equiv.). The mixture was stirred at room temperature for 72 h after which time the reaction was quenched by addition of water (150 mL). The aqueous mixture was extracted with diethyl ether (3 x 100 mL) and the resulting organic fraction rinsed with water (3 x 100 mL), dried over sodium sulfate and concentrated under reduced pressure. Tricheration of the resulting solid with small volumes of ether yielded dodecyldimethylsulfonium iodide (4.66 g, 40%) as an off white solid. Concentration of the washings yielded dodecyl(methyl)sulfane as a colourless oil (4.88 g, 45%).

Dodecyl(methyl)sulfane **571**;[266] ν_{max} (ATR)/cm^{-1} 3554, 3286, 2934, 2853, 1655, 1422, 1080, 1026, 916, 739; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, J = 6.8 Hz, CH_3), 1.32-1.41 (19H, m, $(CH_2)_9$ overlapping with S*H*), 1.57-1.65 (2H, m, SCH_2CH_2), 2.11 (3H, s, SCH_3), 2.51 (2H, dd, J = 7.5, 7.3 Hz, SCH_2); δ_C (100 MHz, $CDCl_3$) 13.6, 22.2, 27.9, 28.6, 28.9, 29.0, 29.1, 29.1, 31.4, 33.6; *m*/*z* (GC-MS CI$^+$) 245.1 (45%), 217.2 ([M+H]$^+$, 100), 201.1 (7).

Dodecyldimethylsulfonium iodide **572**; M.pt. 69-70 °C (lit.[267] 68 °C) ; ν_{max} (ATR)/cm^{-1} 3586, 2973, 2853, 1669, 1474, 1332, 1045, 914, 722; δ_H (400 MHz, DMSO-d$_6$) 0.86 (3H, t, J = 6.9 Hz, CH_2CH_3), 1.24-1.38 (18H, m, $(CH_2)_9$), 1.65-1.72 (2H, m, SCH_2CH_2), 2.86 (6H, s, $S(CH_3)_2$), 3.23-3.26 (2H, m, SCH_2) ; δ_C (100 MHz, DMSO-d$_6$) 31.9, 22.0, 24.1, 27.7, 28.2, 28.7, 28.9, 29.0, 31.2, 41.8; *m*/*z* (ESI$^+$) 360.20 ([M+I+H]$^+$, 100%), 289.13 ([M]$^+$, 32), 255.13 (11).

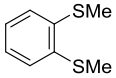
Synthesis of benzene-1,2-dithiol



Benzene-1,2-dithiol was prepared from thiophenol as per the procedure by Block *et al.*[268]

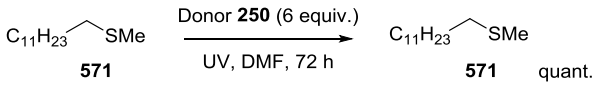
To a flame dried flask under argon was added dry cyclohexane (200 mL), TMEDA (24.5 mL, 2.2 equiv. 160 mmol) and *n*-BuLi (2.5 M in hexanes, 64 mL, 2.2 equiv, 160 mmol). and the mixture cooled to 0 °C. Thiophenol (7.43 mL, 1 equiv., 73 mmol) was slowly added and the resultant suspension stirred at room temperature overnight. To the reaction mixture was the added sublimed sulfur (5.0 g, 2.2 equiv., 160 mmol) and the suspension stirred for 12 h. The cyclohexane was distilled off under reduced pressure and dry THF (200 mL) added before cooling to 0 °C and the slow addition of lithium aluminium hydride (3.0 g, 1.1 equiv., 80 mmol). The reaction mixture was heated at reflux overnight before quenching in 2N HCl (aq. 400 mL) at 0 °C. Extraction of the aqueous suspension with diethyl ether (3 x 400 mL) was followed by rinsing of the organic fractions with water (3x250 mL) and brine (100 mL) and drying over sodium sulfate. The concentrated residue was distilled (75-80 °C @ 1 mmHg) to yield benzene-1,2-dithiol[268] as a pale yellow oil (5.7 g, 55%). ν_{max} (ATR)/cm^{-1} 3103, 2536, 1572, 1451, 1427, 1285, 1113, 1042, 926, 739, 658; δ_H (400 MHz, $CDCl_3$) 3.75 (2H, s, S*H*), 7.08-7.12 (2H, m, Ar*H*), 7.36-7.41 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 126.3, 130.6, 130.7; *m*/*z* (GC-MS CI$^+$) 348.9 (7%), 170.9 (13), 142.9 ([M+H]$^+$, 100), 108.9 (19).

Synthesis of 1,2-bis(methylthio)benzene 577



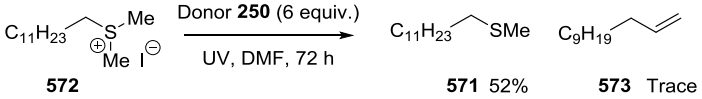
To a solution of benzene-1,2-dithiol (854 mg, 6 mmol, 1 equiv.) and iodomethane (0.822 mL,13.2 mmol, 2.2 equiv.) in DMF (5 mL) was added potassium carbonate (1.842 g, 13.2 mmol, 2.2 equiv.) and the mixture stirred at room temperature for16 h. Dilution of the reaction mixture with water and extraction with ethyl acetate (3 x 50 mL) was followed by rinsing of the organic fractions with 2N NaOH (2 x 50 mL), water (2 x 50 mL0, brine (10 mL), drying over sodium sulfate and concentration under reduced pressure to yield 1,2-bis(methylthio)benzene **577**[269] as a coloured oil (1.001 g, 98%); ν_{max} (ATR)/cm^{-1} 2916, 1568, 1429, 1252, 1111, 1043, 968, 953, 737, 660; δ_H (400 MHz, $CDCl_3$) 2.50 (6H, s, SC*H*$_3$), 7.18-7.21 (2H, m, Ar*H*), 7.22-7.26 (2H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 16.3, 125.9, 126.7, 137.5; *m*/*z* (GC-MS CI$^+$) 198.9 (28%), 170.9 ([M+H]$^+$, 100), 123.9 (16).

Reaction of dodecyl(methyl)sulfane 571 with donor 250 under photoactivation conditions



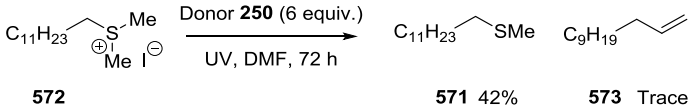
Dodecyl(methyl)sulfane **571** (65 mg , 0.3 mmol, 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield dodecyl(methyl)sulfane **571** as a colourless oil (quant.). Data were as reported previously.

Reaction of dodecyldimethylsulfonium iodide with donor 250 under photoactivation conditions



Dodecyldimethylsulfonium iodide **572** (108 mg, 0.3 mmol, 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield dodecyl(methyl)sulfane **571** as a colourless oil (34 mg, 52%) with data as reported previously and traces of a terminal alkene believed to be dodec-1-ene **573**.

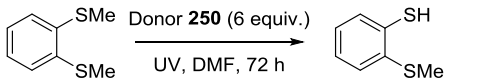
Reaction of dodecyldimethylsulfonium iodide with donor 250 in the absence of photoactivation



572 **571** 42% **573** Trace

Dodecyldimethylsulfonium iodide **572** (108 mg, 0.3 mmol, 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure but without UV activation to yield dodecyl(methyl)sulfane **571** as a colourless oil (27 mg, 42%) with data as reported previously and traces of a terminal alkene believed to be dodec-1-ene **573**.

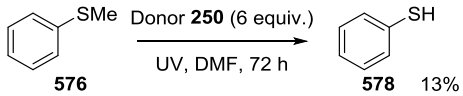
Reaction of 1,2-bis(methylthio)benzene 576 with donor 250 under photoactivation conditions



577 **579** 68%

1,2-Bis(methylthio)benzene **577** (51 mg, 0.3 mmol, 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield 2-(methylthio)benzenethiol **579**[270] (32 mg, 68%) as a colourless oil. ν_{max} (ATR)/cm^{-1} 3418, 3053, 2918, 2532, 1570, 1449, 1429, 1258, 1043, 739, 568; δ_H (400 MHz, $CDCl_3$) 2.50 (3H, s, SC*H*$_3$), 4.03 (1H, s, S*H*), 7.10 (1H, ddd, *J* = 7.7, 7.5, 1.5 Hz, Ar*H*), 7.16 (1H, ddd, *J* = 7.8, 7.5, 1.5 Hz, Ar*H*), 7.31 (dd, *J* = 7.8, 1.5 Hz, Ar*H*), 7.35 (1H, ddd, *J* = 7.7, 1.5 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 16.3, 125.7, 125.9, 127.7, 129.4, 131.7, 136.0; *m*/*z* (GC-MS CI$^+$) 184.9 (26%) , 156.9 ([M+H]$^+$, 100), 123.9 (16).

Reaction of thioanisole 576 with donor 250 under photoactivation conditions

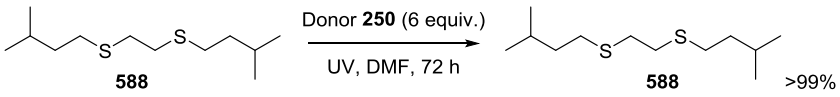


576 **578** 13%

Thioanisole (37 mg, 0.3 mmol, 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield thiophenol **578** (4.5 mg, 13%) as a colourless oil with data matching those reported in the literature:[271] δ_H (400 MHz, $CDCl_3$) 3.49 (1H, s, S*H*),

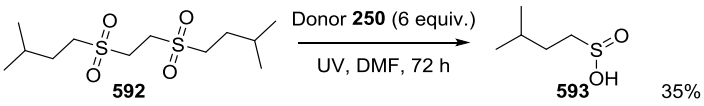
7.20 (1H, t, J = 7.0 Hz, Ar*H*), 7.30-7.36 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 125.2, 128.6, 128.9, 130.3; *m*/*z* (GC-MS CI^+) 138.9 (9%), 110.9 ($[M+H]^+$, 100).

Reaction of 1,2-bis(isopentylthio)ethane 588 with donor 250 under photoactivation conditions



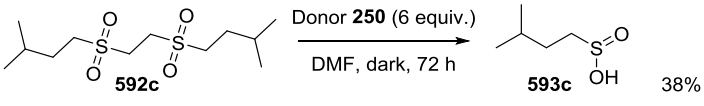
1,2-Bis(isopentylthio)ethane **588** (70 mg, 0.3 mmol, 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield quantitative recovery of 1,2-bis(isopentylthio)ethane **588** as a colourless oil. Data were as reported previously.

Reaction of 1,2-bis(isopentylsulfonyl)ethane 592 with donor 250 under photoactivation conditions



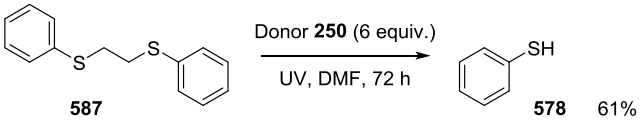
1,2-Bis(isopentylsulfonyl)ethane **592** (90 mg, 0.3 mmol, 1 equiv) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield isopentylsulfinic acid **593**[272] as a pale yellow oil. (29 mg, 35%); ν_{max} (ATR)/cm^{-1} 3030, 2992, 2941, 2866, 1454, 1231, 1109, 1022, 789, 745, 692; δ_H (400 MHz, $CDCl_3$) 0.96 (6H, d, J = 6.8 Hz, $CH(CH_3)_2$), 1.60-1.64 (2H, m, $CHCH_2$), 1.66-1.75 (1H, m, C*H*), 2.82-2.86 (2H, m, SO_2CH_2), 8.80-8.98 (1H, bs, SO_2H); δ_C (100 MHz, $CDCl_3$) 21.7, 26.9, 29.4, 55.2; *m*/*z* (GC-MS, CI^+) 239.0 (100%), 168.8 ($[M+C_2H_7]^+$, 8), 102.8 (3), 71.0 (32), 57.0 (27).

Reaction of 1,2-bis(isopentylsulfonyl)ethane 592c with donor 250 without photoactivation



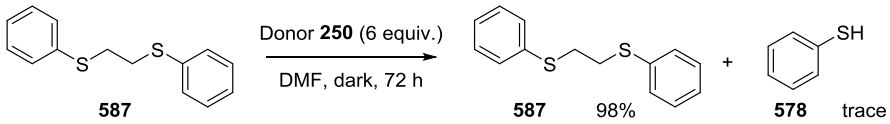
1,2-Bis(isopentylsulfonyl)ethane **592c** (90 mg, 0.3 mmol. 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield isopentylsulfinic acid **593c** as a pale yellow oil (31 mg, 38%) with data as reported above.

Reaction of 1,2-bis(phenylthio)ethane 587 with donor 250 under photoactivation conditions



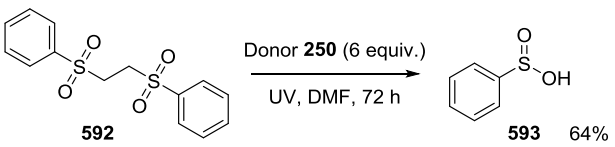
1,2-Bis(phenylthio)ethane **587** (74 mg, 0.3 mmol, 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield thiophenol **578** as a colourless oil (40 mg, 61%). Data were as reported previously.

Reaction of 1,2-bis(phenylthio)ethane 587 with donor 250 but without photoactivation



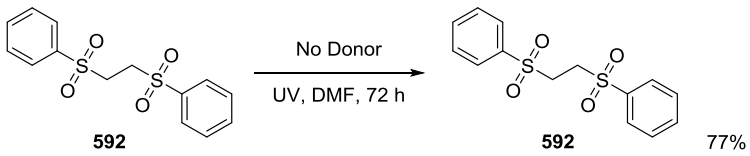
1,2-Bis(phenylthio)ethane **587** (74 mg, 0.3 mmol, 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield recovery of 1,2-bis(phenylthio)ethane **587** (73 mg, 98%) plus a trace of thiophenol. Data were as reported previously

Reaction of 1,2-bis(phenylsulfonyl)ethane 592a with donor 250 under photoactivation conditions



1,2-Bis(phenylsulfonyl)ethane **592a** (93 mg, 0.3 mmol, 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield benzenesulfinic acid **593a** as a white solid; (20 mg, 46%); M.pt. 80-83 ^{o}C (lit.[273] 83-84 ^{o}C); ν_{max} (ATR)/cm^{-1} 3373, 2739, 1661, 1474, 1445, 1287, 1086, 1051, 1011, 993, 841, 754, 698, 687; δ_H (400 MHz, DMSO-d_6) 5.20-5.95 (bs, O*H*), 7.56-7.59 (3H, m, Ar*H*), 7.66-7.69 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 124.5, 128.6, 131.6, 145.7; *m*/*z* (GC-MS, CI$^+$) 250.9 (100%), 140.8 ([M-H]$^+$, 45), 111.0 (35).

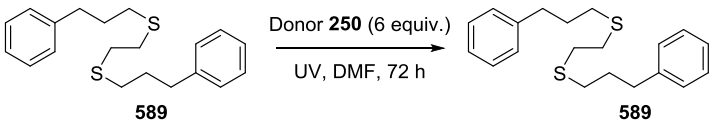
Reaction of 1,2-bis(phenylsulfonyl)ethane 592a in the absence of donor 250 but under photoactivation conditions



592 **592** 77%

1,2-Bis(phenylsulfonyl)ethane **592a** (93 mg, 0.3 mmol, 1 equiv.) was reacted in the absence of donor **250** as per the general procedure to yield 1,2-bis(phenylsulfonyl)ethane **592a** (72 mg, 77%) as a white solid. Data were as reported previously.

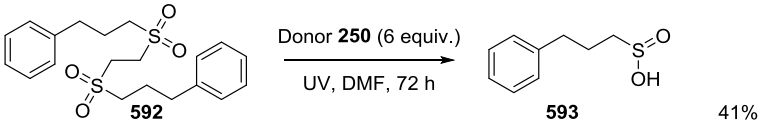
Reaction of 1,2-bis((3-phenylpropyl)thio)ethane 589 with donor 250 under photoactivation conditions



589 **589** 92%

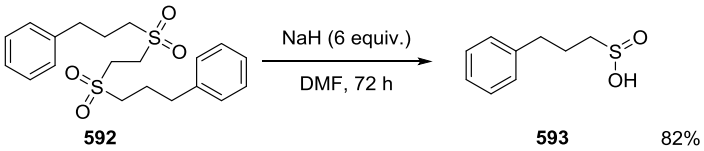
1,2-Bis((3-phenylpropyl)thio)ethane **589** (99 mg, 0.3 mmol, 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield recovered 1,2-bis((3-phenylpropyl)thio)ethane **589** as a colourless oil (91 mg, 92%) with data as previously reported.

Reaction of 1,2-bis((3-phenylpropyl)sulfonyl)ethane 592b with donor 250 under photoactivation conditions



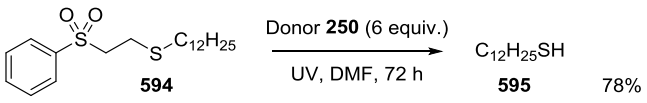
1,2-Bis((3-phenylpropyl)sulfonyl)ethane **592b** was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield 3-phenylpropane-1-sulfinic acid **593b**[274] (45 mg, 41%); ν_{max} (ATR)/cm^{-1} 3393, 3025, 2945, 2926, 2859, 1684, 1497, 1454, 1117, 1030, 746, 698; δ_H (400 MHz, $CDCl_3$) 2.03-2.10 (2H, m, $PhCH_2CH_2$), 2.77 (2H, t, J = 7.5 Hz, $PhCH_2$), 2.80-2.85 (2H, m, CH_2SO_2), 7.19-7.26 (3H, m, Ar*H*), 7.29-7.34 (2H, m, Ar*H*), 9.65-9.85 (1H, bs, SO_2H); δ_C (100 MHz, $CDCl_3$) 22.5, 34.0, 56.1, 125.9, 128.0, 128.1, 139.9. *m*/*z* (ESI$^+$) 124.9 (100%), 184.7 ([M-H]$^+$, 38).

Reaction of 1,2-bis((3-phenylpropyl)sulfonyl)ethane 592b with sodium hydride



1,2-Bis((3-phenylpropyl)sulfonyl)ethane **592b** (118 mg, 0.3 mmol, 1 equiv.) was reacted with sodium hydride (43 mg, 1.8 mmol, 6 equiv.) at room temperature for 72 h under an atmosphere of argon. Aqueous work-up as per the general procedure yielded 3-phenylpropane-1-sulfinic acid **593b** (91 mg, 82%) with data as reported previously.

Reaction of dodecyl(2-(phenylsulfonyl)ethyl)sulfane 594 with donor 250 under photoactivation conditions



Dodecyl(2-(phenylsulfonyl)ethyl)sulfane **594** (110 mg, 0.3 mmol, 1 equiv.) was reacted with donor **250** (512 mg, 1.8 mmol, 6 equiv.) as per the general procedure to yield dodecanethiol **595** (47 mg, 78%) with data matching those reported in the literature:[275] δ_H (400 MHz,

$CDCl_3$) 0.90 (3H, t, J = 6.8 Hz, CH_3), 1.28-1.40 (19H, m, (CH_2)$_9$ overlapping with S*H*), 1.58-1.66 (2H, m, SCH_2CH_2), 2.55 (2H, quartet, J = 7.4 Hz, SCH_2); δ_C (100 MHz, $CDCl_3$) 13.6, 22.2, 27.9, 28.6, 28.9, 29.0, 29.1, 29.1, 31.4, 33.6.

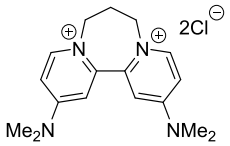
10.6. Experimental Details for Chapter 7

General procedure A – Reaction of substrates with donor 250 with recovery of donor-derived compounds

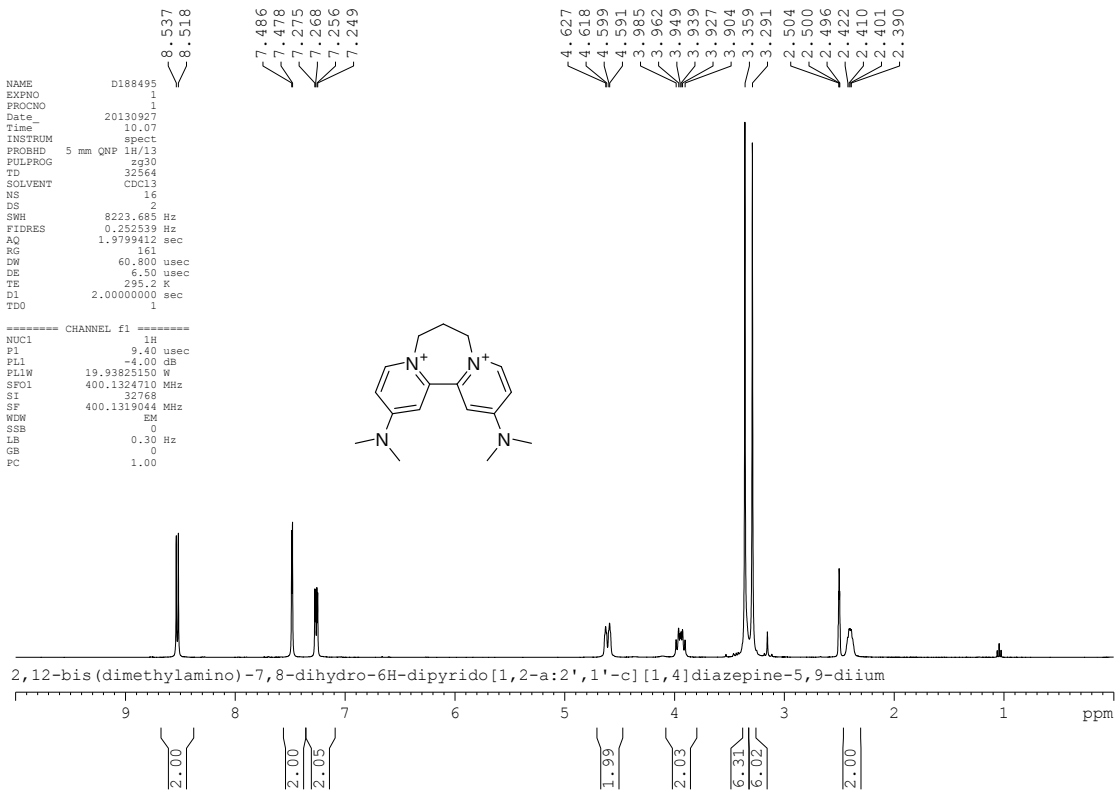
Donor **250** (512 mg, 1.8 mmol, 6 equiv.) was dissolved in degassed DMF (4 mL) in a glovebox. This solution was directly pipetted into the substrate (0.3 mmol, 1.0 equiv.). The solution was removed to a fumehood and stirred at room temperature for 72 h under UV radiation (365 nm). The mixture was poured into aqueous 2N HCl (25 mL) and ethyl acetate (25 mL) before extracting with ethyl acetate (4 x 15 mL). The combined organic layers were then washed with water (3 x 20 mL) and brine (10 mL) and dried over Na_2SO_4. The crude organic residue, obtained after evaporation under reduced pressure, was eluted with ethyl acetate on silica gel, to afford the pure corresponding products as reported.

The aqueous layers were concentrated *in vacuo* and purified by trituration with ether or chloroform followed by recrystallization first in acetonitrile, then ethanol, methanol and finally chloroform where possible. Recovery was poor in general but sufficient material was purified from the complex mixtures to characterize the species below and assign structures.

***N*,*N*,*N*',*N*'-tetramethyl-7,8-dihydro-6H-dipyrido[1,2a-2,1c]-[1,4]-didiazepinium-2,12-diamine chloride 252**



The crude aqueous washings from multiple photo-activated donor reactions were recrystallized from acetonitrile to yield *N*,*N*,*N*',*N*'-tetramethyl-7,8- dihydro-6H-dipyrido[1,2a-2,1c]-[1,4]-didiazepinium-2,12-diamine chloride **252** as a beige powder. M.pt. 183-185 ^{o}C (lit.[122] 182-186 ^{o}C); λ_{max} = 246 nm (MeCN); ν_{max} (Powder)/cm^{-1} 3458, 3389, 3023, 2986, 1639,1571, 1531, 1428, 1404, 1371, 1319, 1260, 1180; δ_H (400 MHz, DMSO-d_6) 2.37-2.41 (2H, m, $N^+CH_2CH_2$), 3.28 (6H, s, NCH_3), 3.32 (6H, s, NCH_3), 3.90-3.98 (2H, m, N^+CHH), 4.58-4.63 (2H, m, N^+CHH), 7.23 (2H, dd, *J* = 7.0. 3.0 Hz, Ar*H*), 7.40 (2H, d, *J* = 3.0 Hz, Ar*H*), 8.44 (2H, d, *J* = 7.0 Hz, Ar*H*); δ_C (100 MHz, DMSO-d_6) 28.6, 40.2, 40.5, 51.1, 108.0, 111.6, 142.8, 143.3, 156.1; *m/z* (ESI$^+$) 142.0 ([M/2]$^+$).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8.518
7.486
7.478
7.275
7.268
7.256
7.249
4.627
4.618
4.599
4.591
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3.962
3.949
3.939
3.927
3.904
3.359
3.291
2.504
2.500
2.496
2.422
2.410
2.401
2.390
NAME D188495
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PROCNO 1
Date_ 20130927
Time 10.07
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PULPROG zg30
TD 32564
SOLVENT CDCl3
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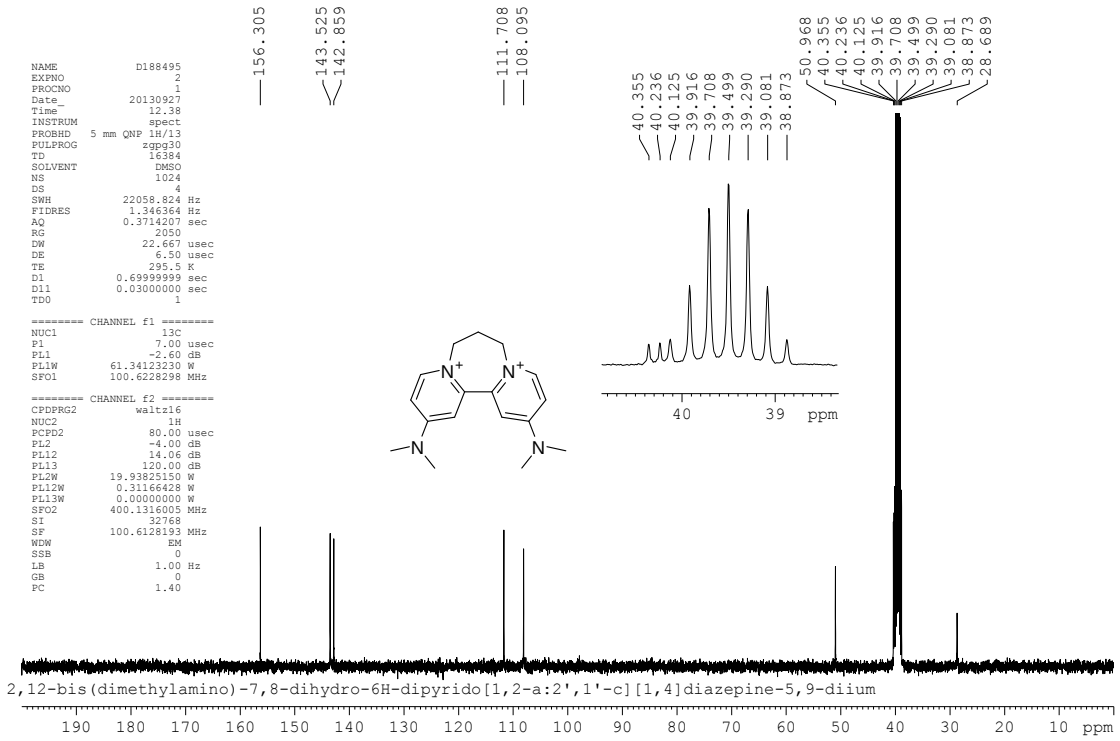
DS 2
SWH 8223.685 Hz
FIDRES 0.252539 Hz
AQ 1.9799412 sec
RG 161
DW 60.800 usec
DE 6.50 usec
TE 295.2 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.40 usec
PL1 -4.00 dB
PL1W 19.93825150 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1319044 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
2,12-bis(dimethylamino)-7,8-dihydro-6H-dipyrido[1,2-a:2',1'-c][1,4]diazepine-5,9-diium
9 8 7 6 5 4 3 2 1 ppm
2.00
2.00
2.05
1.99
2.03
6.31
6.02
2.00


156.305
143.525
142.859
111.708
108.095
50.968
40.355
40.236
40.125
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39.708
39.499
39.290
39.081
38.873
28.689
NAME D188495
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PROCNO 1
Date_ 20130927
Time 12.38
INSTRUM spect
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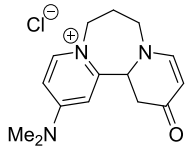
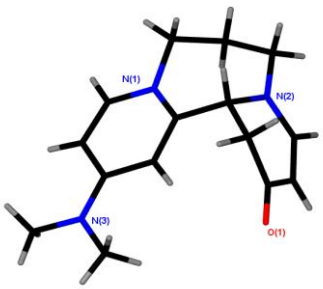
NS 1024
DS 4
SWH 22058.824 Hz
FIDRES 1.346364 Hz
AQ 0.3714207 sec
RG 2050
DW 22.667 usec
DE 6.50 usec
TE 295.5 K
D1 0.69999999 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 7.00 usec
PL1 -2.60 dB
PL1W 61.34123230 W
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -4.00 dB
PL12 14.06 dB
PL13 120.00 dB
PL2W 19.93825150 W
PL12W 0.31166428 W
PL13W 0.00000000 W
SFO2 400.1316005 MHz
SI 32768
SF 100.6128193 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
40 39 ppm
2,12-bis(dimethylamino)-7,8-dihydro-6H-dipyrido[1,2-a:2',1'-c][1,4]diazepine-5,9-diium
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

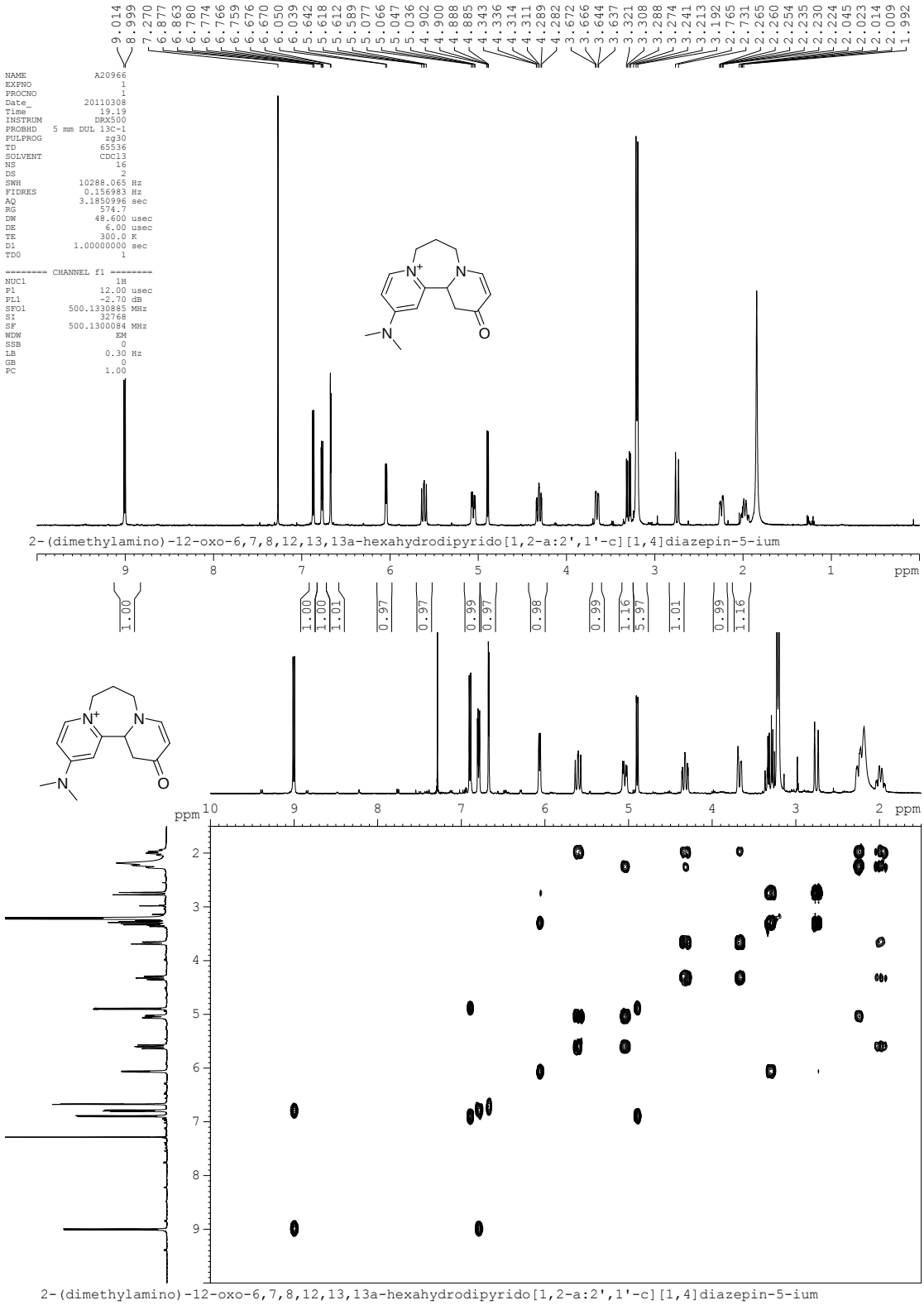
2-(Dimethylamino)-12-oxo-6,7,8,12,13,13a-hexahydrodipyrido-[1,2-a:2',1'-c][1,4]diazepin-5-ium chloride 602



The crude aqueous washings from multiple photo-activated donor reactions were recrystallized from ethanol to isolate *2-(dimethylamino)-12-oxo-6,7,8,12,13,13a-hexahydrodipyrido[1,2-a:2',1'-c][1,4]diazepin-5-ium chloride* **602** as an off-white solid. M.pt. 265-267 ^{o}C; [Found: $(M)^{+}$, 258.1598. $C_{15}H_{20}N_3O$ (M), requires 258.1601]; λ_{max} = 286 nm (MeCN); ν_{max} (KBr)/cm^{-1} 3648, 3049, 2945, 1728, 1599, 1476, 1276, 1111, 875, 760, 713; δ_H (400 MHz, $CDCl_3$) 1.99-1.2.04 (1H, m, $NCH_2CH\mathit{H}$), 2.22-2.27 (1H, m, $NCH_2C\mathit{H}H$), 2.75 (1H, d, *J* = 17.0, C(O)CH*H*), 3.19 (3H, s, $NC\mathit{H}_3$), 3.21 (3H, s, $NC\mathit{H}_3$), 3.29 (1H, dd, *J* = 17.0, 6.4 Hz, C(O)C*H*H), 3.65 (1H, dd, *J* = 14.1, 3.3 Hz, NC*H*H), 4.28-4.34 (1H, m, NCH*H*), 4.89 (1H, dd, *J* = 7.5, 1.1 Hz, NCH=C*H*), 5.06 (1H, dd, *J* = 14.7, 5.6, $N^{+}C\mathit{H}H$), 5.62 (1H, dd, *J* = 14.8, 11.8 Hz, $N^{+}CH\mathit{H}$), 6.04 (1H, d, *J* = 6.4 Hz, $NC\mathit{H}CH_2C(O)$), 6.67 (1H, d, *J* = 3.1 Hz, Ar*H*), 6.76 (1H, dd, *J* = 7.5, 3.1 Hz, Ar*H*), 6.86 (1H, d, *J* = 7.5 Hz, NC*H*=CH), 9.00 (1H, d, *J* = 7.5 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 28.8, 37.7, 39.7, 39.9, 54.8, 55.4, 56.4, 96.8, 106.1, 107.0, 145.7, 149.8, 151.0, 155.6, 189.3.

Shown below is a crude crystal structure. The crystal sample was badly twinned and so poorly resolved, but agrees with the other analytical data on the structure of the species. Thanks to Dr. Alan. Kennedy for his efforts to resolve the structure.




9.014
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6.863
6.780
6.774
6.766
6.759
6.676
6.670
6.050
6.039
5.642
5.618
5.612
5.589
5.077
5.066
5.047
5.036
4.902
4.900
4.888
4.885
4.343
4.336
4.314
4.311
4.289
4.282
3.672
3.666
3.644
3.637
3.321
3.308
3.288
3.274
3.241
3.213
3.192
2.765
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2.260
2.254
2.235
2.230
2.224
2.045
2.023
2.014
2.009
1.992
NAME A20966
EXPNO 1
PROCNO 1
Date_ 20110308
Time_ 19.19
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PULPROG zg30
TD 65536
SOLVENT CDCl3
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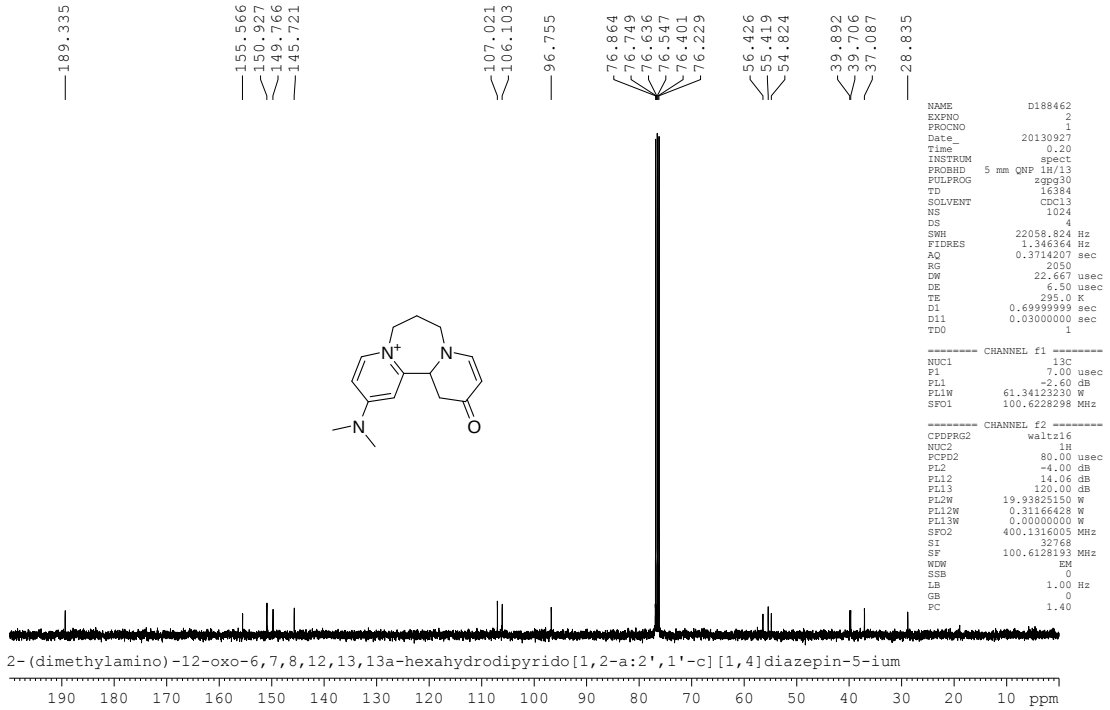
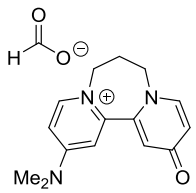
DS 2
SWH 10288.065 Hz
FIDRES 0.156983 Hz
AQ 3.1850996 sec
RG 574.7
DW 48.600 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -2.70 dB
SFO1 500.1330885 MHz
SI 32768
SF 500.1300084 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
2-(dimethylamino)-12-oxo-6,7,8,12,13,13a-hexahydrodipyrido[1,2-a:2',1'-c][1,4]diazepin-5-ium
ppm
1.00
1.00
1.00
1.01
0.97
0.97
0.99
0.97
0.98
0.99
1.16
5.97
1.01
0.99
1.16
2-(dimethylamino)-12-oxo-6,7,8,12,13,13a-hexahydrodipyrido[1,2-a:2',1'-c][1,4]diazepin-5-ium



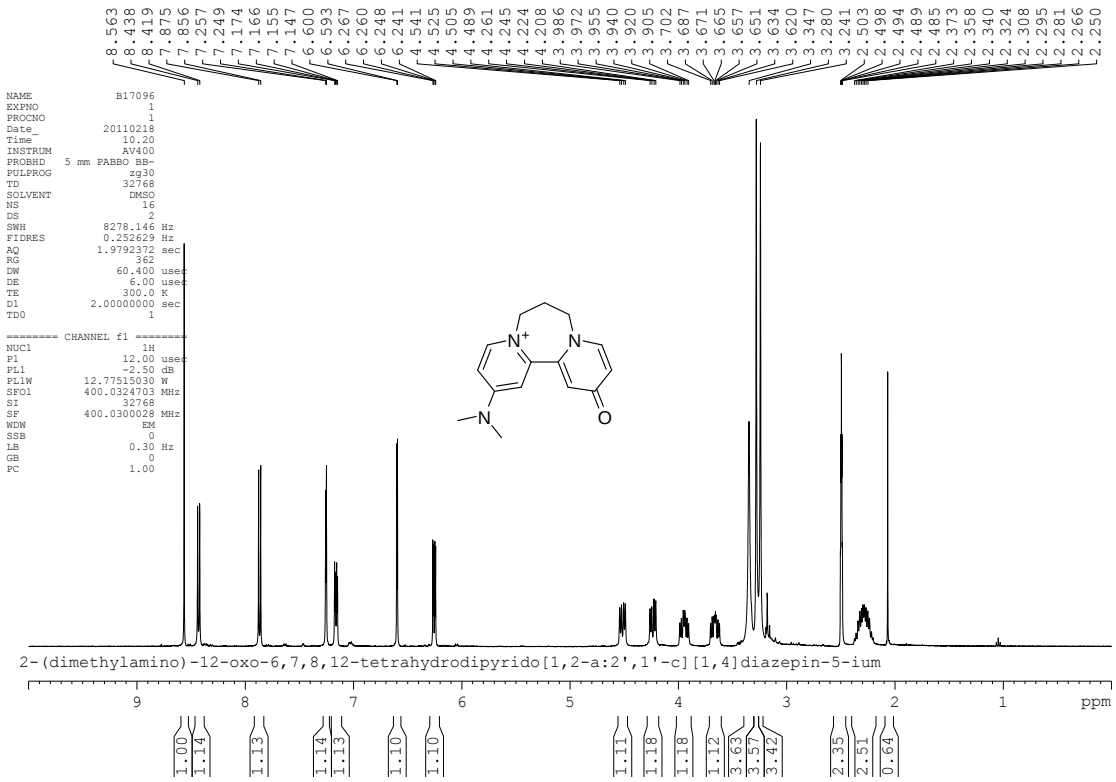
2-(Dimethylamino)-12-oxo-6,7,8,12-tetrahydro-dipyrido[1,2-a:2',1'-c][1,4]diazepin-5-ium formate 604

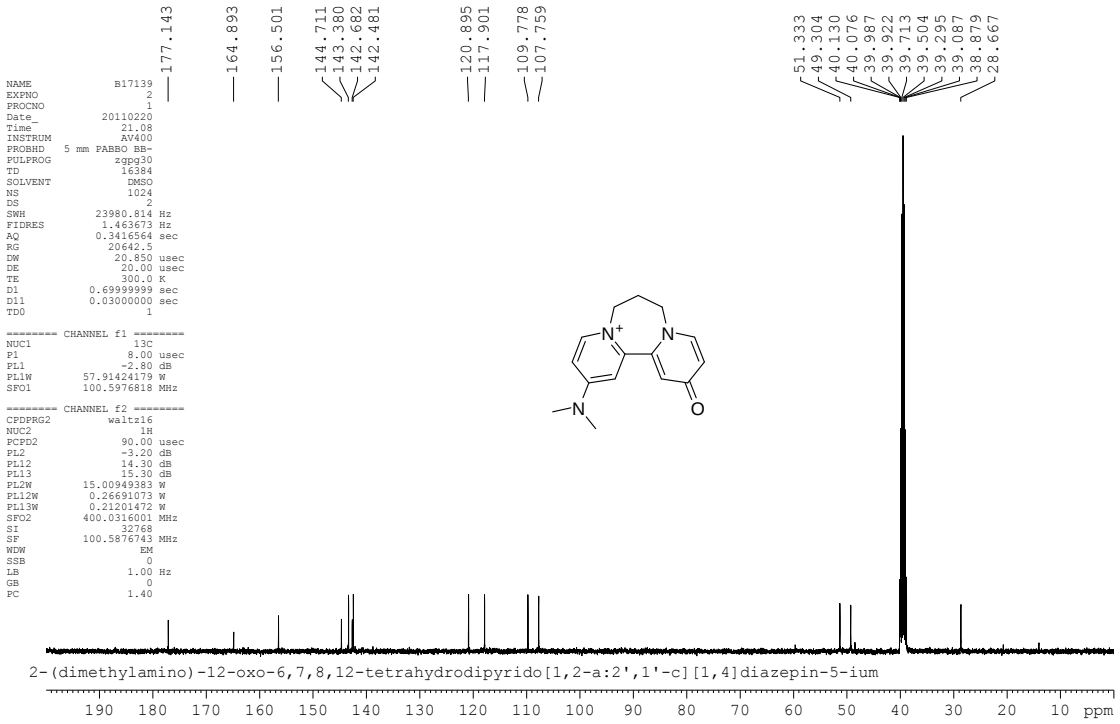


The crude aqueous washings from multiple photo-activated donor reactions were recrystallized from ethanol to yield *2-(dimethylamino)-12-oxo-6,7,8,12-tetrahydrodipyrido[1,2-a:2',1'-c][1,4]diazepin-5-ium formate* **604** as a yellow crystalline solid. [Found: $(M)^+$, 256.1446. $C_{15}H_{18}N_3O$ (M), requires 256.1444]; λ_{max} = 238 nm (MeCN); ν_{max} (ATR)/cm^{-1} 3377, 3034, 2967, 2928, 1622, 1568, 1473, 1402, 1314, 1186, 1163, 1022, 854, 831, 806, 727; δ_H (400 MHz, DMSO-d_6) 2.25-2.37 (2H, m, $N^+CH_2CH_2CH_2N$), 3.24 (3H, s, NCH_3), 3.28 (3H, s, NCH_3), 3.62-3.70 (1H, m, NCHH), 3.91-3.99 (1H, m, NCHH), 4.24 (1H, dd, *J* = 14.5, 6.5 Hz, N^+CHH), 4.51 (1H, dd, *J* = 14.5, 6.2 Hz, 1H, N^+CHH), 6.25 (1H, dd, *J* = 7.7, 2.7 Hz, C(O)C*H*), 6.60 (1H, d, *J* = 2.7 Hz, C(O)C*H*), 7.16 (1H, dd, *J* = 7.6, 3.2 Hz, Ar*H*), 7.25 (1H, d, *J* = 3.2 Hz, Ar*H*), 7.86 (1H, d, *J* = 7.7 Hz, NC*H*), 8.42 (1H, d, *J* = 7.6 Hz, Ar*H*), 8.56 (1H, s, C(O)*H*); δ_C (100 MHz, DMSO-d_6) 28.7, 40.0, 40.1, 49.3, 51.3,

107.8, 109.8, 117.9, 120.9, 142.5, 142.7, 143.4, 144.7, 156.5, 164.9, 177.1; *m/z* (ESI^+) 256.20 ($[M]^+$, 100%).

A peak of *m/z* 45.5 was observed in nano-electrospray MS corresponding to the formate anion 45.0. The error of 0.5 Daltons is outwith the normal error range of ± 0.4 Daltons because the low mass is outwith the normal calibration range. Also observed by this method was *m/z* 346.1 corresponding to [M + 2 formates]$^+$ and *m/z* 647.3 corresponding to [2M + 3 formates]$^+$. Many thanks to Gareth at EPSRC NMSSC Swansea for his efforts on our behalf.




177.143
164.893
156.501
144.711
143.380
142.682
142.481
120.895
117.901
109.778
107.759
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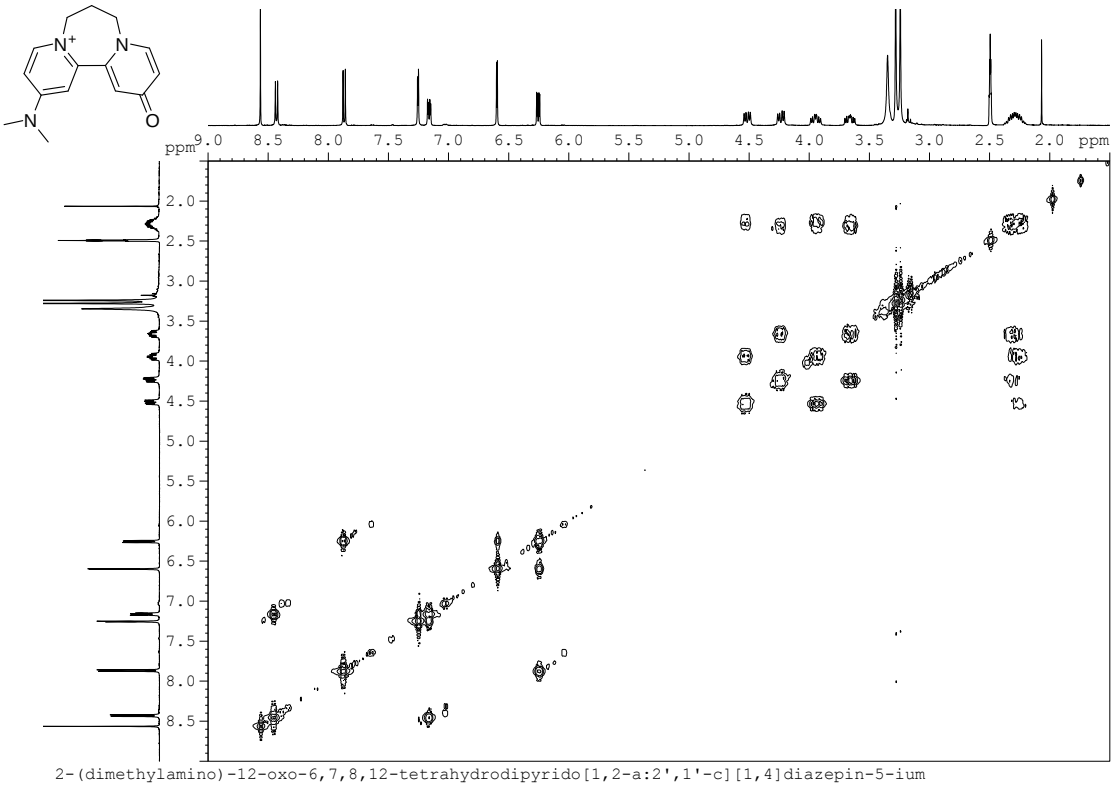
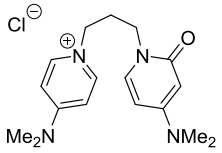
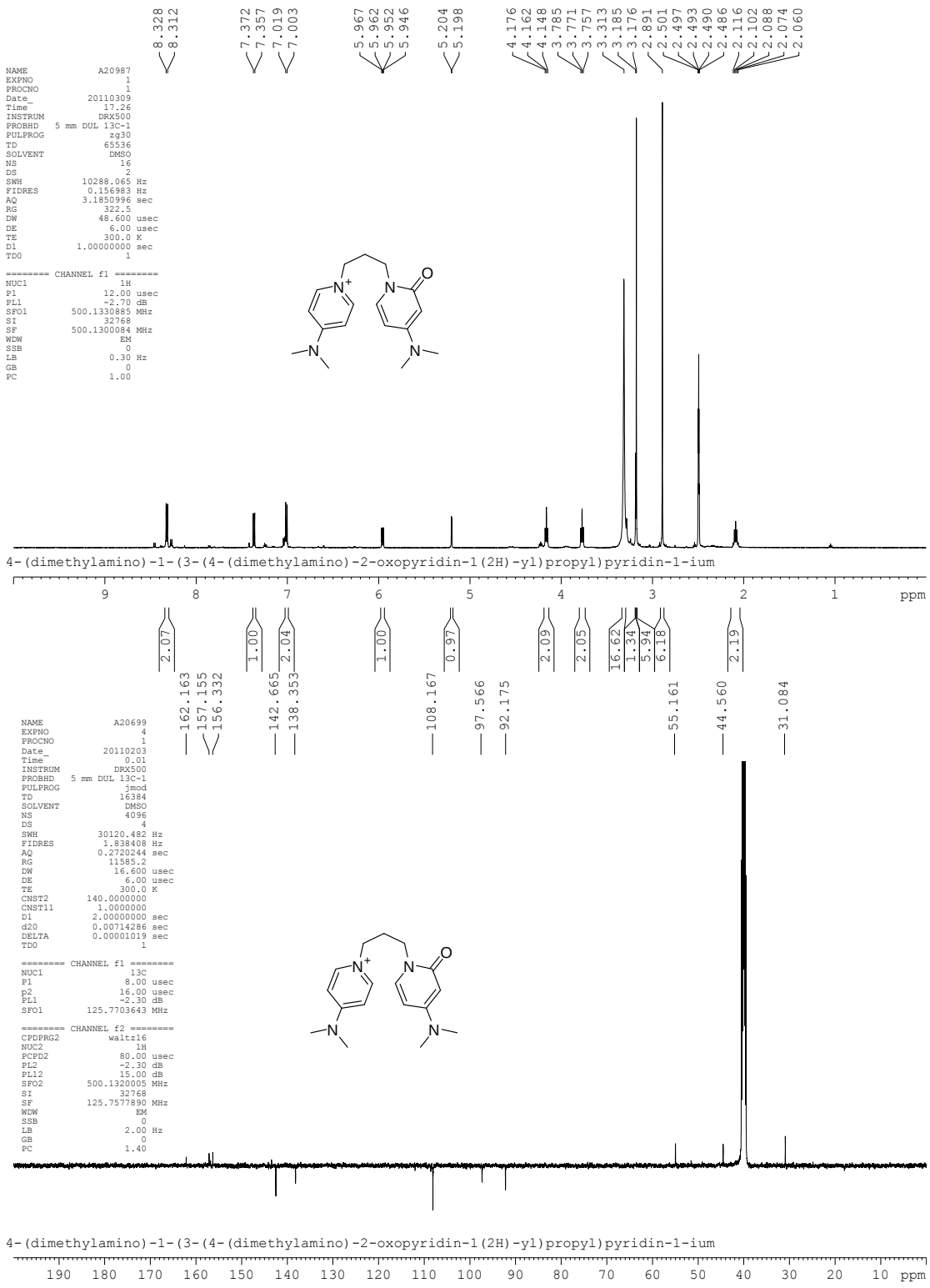
49.304
40.130
40.076
39.987
39.922
39.713
39.504
39.295
39.087
38.879
28.667
NAME B17139
EXPNO 2
PROCNO 1
Date_ 20110220
Time 21.08
INSTRUM AV400
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 16384
SOLVENT DMSO
NS 1024
DS 2
SWH 23980.814 Hz
FIDRES 1.463673 Hz
AQ 0.3416564 sec
RG 20642.5
DW 20.850 usec
DE 20.00 usec
TE 300.0 K
D1 0.69999999 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.00 usec
PL1 -2.80 dB
PL1W 57.91424179 W
SFO1 100.5976818 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 -3.20 dB
PL12 14.30 dB
PL13 15.30 dB
PL2W 15.00949383 W
PL12W 0.26691073 W
PL13W 0.21201472 W
SFO2 400.0316001 MHz
SI 32768
SF 100.5876743 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
2-(dimethylamino)-12-oxo-6,7,8,12-tetrahydrodipyrido[1,2-a:2',1'-c][1,4]diazepin-5-ium
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


ppm
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 ppm
2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5
2-(dimethylamino)-12-oxo-6,7,8,12-tetrahydrodipyrido[1,2-a:2',1'-c][1,4]diazepin-5-ium

4-(Dimethylamino)-1-(3-(4-(dimethylamino)-2-oxopyridin-1(2H)-yl)propyl)pyridin-1-ium chloride 603



The crude aqueous washings from multiple photo-activated donor reactions were recrystallized from chloroform to yield *4-(dimethylamino)-1-(3-(4-(dimethylamino)-2-oxopyridin-1(2H)-yl)propyl)pyridin-1-ium chloride* **603** as a hygroscopic light brown solid. λ_{max} = 286 nm (MeCN); ν_{max} (KBr)/cm^{-1} 3368, 3254, 3072, 2938, 2773, 2678, 1627, 1551, 1482, 1342, 1191, 1027, 809, 723, 615; δ_H (500 MHz, DMSO-d$_6$) 2.10 (2H, dt, *J* = 6.8, 6.8 Hz, NCH$_2$C*H*$_2$), 2.89 (6H, s, NC*H*$_3$), 3.18 (6H, s, NC*H*$_3$), 3.77 (2H, t, *J* = 6.8 Hz, NC*H*$_2$), 4.16 (2H, t, *J* = 6.8 Hz, N$^+$C*H*$_2$), 5.20 (1H, d, *J* = 2.7 Hz, Pyridone-*H*), 5.95 (1H, dd, *J* = 8.0, 2.7 Hz, Pyridone-*H*), 7.00 (2H, d, *J* = 7.5 Hz, Pyridinium-*H*), 7.36 (1H, d, *J* = 8.0 Hz, Pyridone-*H*), 8.31 (2H, d, *J* = 7.5 Hz, Pyridinium-*H*); δ_C (125 MHz, DMSO-d$_6$) 30.9, *two more aliphatic signals are expected which are thought to lie beneath the large DMSO septet at 40.0*, 44.5, 55.0, 92.2, 97.4, 108.1, 138.3, 142.5, 156.3, 157.1, 162.2; *m/z* (ESI$^+$) 301.0 ([M]$^+$, 100%).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5.946
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4.162
4.148
3.785
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2.493
2.490
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2.074
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PROCNO 1
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SOLVENT DMSO
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FIDRES 0.156983 Hz
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RG 322.5
DW 48.600 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -2.70 dB
SFO1 500.1330885 MHz
SI 32768
SF 500.1300084 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
4-(dimethylamino)-1-(3-(4-(dimethylamino)-2-oxopyridin-1(2H)-yl)propyl)pyridin-1-ium
9 8 7 6 5 4 3 2 1 ppm
2.07
1.00
2.04
1.00
0.97
2.09
2.05
16.62
1.34
5.94
6.18
2.19
162.163
157.155
156.332
142.665
138.353
108.167
97.566
92.175
55.161
44.560
31.084
NAME A20699
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PROCNO 1
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Time_ 0.01
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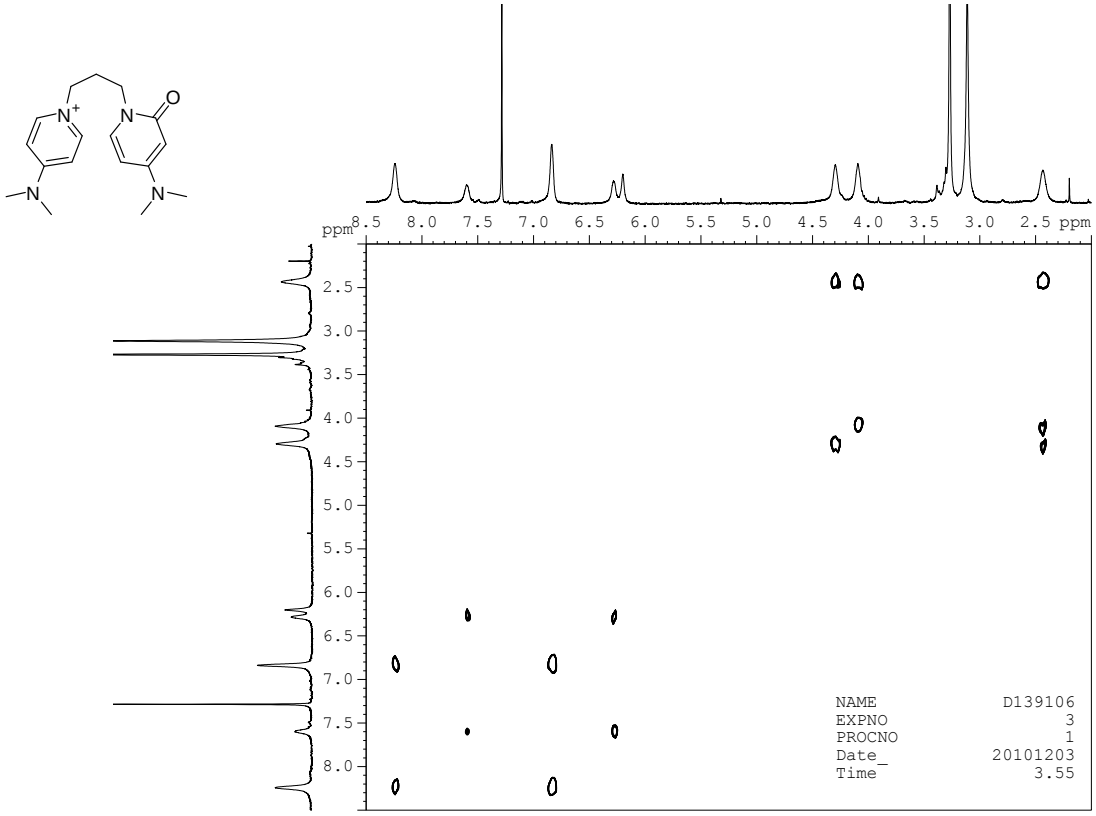
NS 4096
DS 4
SWH 30120.482 Hz
FIDRES 1.838408 Hz
AQ 0.2720244 sec
RG 11585.2
DW 16.600 usec
DE 6.00 usec
TE 300.0 K
CNST2 140.0000000
CNST11 1.0000000
D1 2.00000000 sec
d20 0.00714286 sec
DELTA 0.00001019 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.00 usec
p2 16.00 usec
PL1 -2.30 dB
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.30 dB
PL12 15.00 dB
SFO2 500.1320005 MHz
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40
4-(dimethylamino)-1-(3-(4-(dimethylamino)-2-oxopyridin-1(2H)-yl)propyl)pyridin-1-ium
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



4-(dimethylamino)-1-(3-(4-(dimethylamino)-2-oxopyridin-1(2H)-yl)propyl)pyridin-1-ium

References

References

(1) Taube, H.; Myers, H.; Rich, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 4118.
(2) Marcus, R. A. *J. Phys. Chem.* **1956**, *24*, 966.
(3) Heinze, J. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 831.
(4) Pavlishchuk, V. V.; Addison, A. W. *Inorg. Chim. Acta*, **2000**, *298*, 97.
(5) Shalev, H.; Evans, D. H. *J. Am. Chem. Soc.* **1989**, *111*, 2667.
(6) Svith, H.; Jensen, H.; Almstedt, J.; Andersson, P.; Lundbäck, T.; Daasbjerg, K.; Jonsson, M. *J. Phys. Chem. A*, **2004**, *108*, 4805.
(7) Birch, A. J. *J. Chem. Soc.* **1944**, 430.
(8) Birch, A. J. *J. Chem. Soc.* **1945**, 809.
(9) Birch, A. J. *J. Chem. Soc.* **1946**, 593.
(10) Birch, A. J. *J. Chem. Soc.* **1947**, 102.
(11) Birch, A. J. *J. Chem. Soc.* **1947**, 1642.
(12) Birch, A. J.; Dastur, K. P. *Aust. J. Chem.* **1973**, *26*, 1363.
(13) Birch, A. J.; Mukherji, S. M. *J. Chem. Soc.* **1949**, 2531.
(14) Harvey, R. G. *Synthesis*, **1970**, *1970*, 161.
(15) Zurek, E.; Edwards, P. P.; Hoffmann, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 8198.
(16) Gibson, G. E.; Argo, W. L. *J. Am. Chem. Soc.* **1918**, *40*, 1327.
(17) Bunnett, J. F.; Jenvey, J. *J. Org. Chem.* **1996**, *61*, 8069.
(18) Kim, J. T.; Gevorgyan, V. *J. Org. Chem.* **2005**, *70*, 2054.
(19) Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 1280.
(20) Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 2205.
(21) Zimmerman, H. E. *Acc. Chem. Res.* **2011**, *45*, 164.
(22) Vorndran, K.; Linker, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2489.
(23) Krüger, T.; Vorndran, K.; Linker, T. *Chem. Eur. J.* **2009**, *15*, 12082.
(24) Ankner, T.; Hilmersson, G. *Tetrahedron*, **2009**, *65*, 10856.
(25) Garst, M. E.; Dolby, L. J.; Esfandiari, S.; Fedoruk, N. A.; Chamberlain, N. C.; Avey, A. A. *J. Org. Chem.* **2000**, *65*, 7098.
(26) Benkeser, R. A.; Robinson, R. E.; Sauve, D. M.; Thomas, O. H. *J. Am. Chem. Soc.* **1955**, *77*, 3230.
(27) Benkeser, R. A.; Schroll, G.; Sauve, D. M. *J. Am. Chem. Soc.* **1955**, *77*, 3378.
(28) Benkeser, R.; Hazdra, J.; Lambert, R.; Ryan, P. *J. Org. Chem.* **1959**, *24*, 854.
(29) Benkeser, R. A.; Burrous, M. L.; Hazdra, J. J.; Kaiser, E. M. *J. Org. Chem.* **1963**, *28*, 1094.
(30) Benkeser, R. A.; Agnihotri, R. K.; Burrous, M. L.; Kaiser, E. M.; Mallan, J. M.; Ryan, P. W. *J. Org. Chem.* **1964**, *29*, 1313.
(31) Benkeser, R. A.; Kang, J. *J. Org. Chem.* **1979**, *44*, 3737.
(32) Benkeser, R. A.; Belmonte, F. G.; Kang, J. *J. Org. Chem.* **1983**, *48*, 2796.
(33) Benkeser, R. A.; Laugal, J. A.; Rappa, A. *Tetrahedron Lett.* **1984**, *25*, 2089.
(34) Donohoe, T. J.; Thomas, R. E. *Nat. Protocols*, **2007**, *2*, 1888.
(35) Donohoe, T. J.; Johnson, D. J.; Mace, L. H.; Bamford, M. J.; Ichihara, O. *Org. Lett.* **2005**, *7*, 435.
(36) Donohoe, T. J.; Guyo, P. M.; Helliwell, M. *Tetrahedron Lett.* **1999**, *40*, 435.
(37) Donohoe, T. J.; Guyo, P. M. *J. Org. Chem.* **1996**, *61*, 7664.
(38) Donohoe, T. J.; Guyo, P. M.; Harji, R. R.; Helliwell, M.; Cousins, R. P. C. *Tetrahedron Lett.* **1998**, *39*, 3075.
(39) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1331.

(40) Dye, J. L.; Cram, K. D.; Urbin, S. A.; Redko, M. Y.; Jackson, J. E.; Lefenfeld, M. *J. Am. Chem. Soc.* **2005**, *127*, 9338.
(41) Bouveault, L.; Blanc, G. *Compt. Rend.* **1903**, *136*, 1676.
(42) Bouveault, L.; Blanc, G. *Bull. Soc. Chim. France*, **1904**, *31*, 666.
(43) Bodnar, B. S.; Vogt, P. F. *J. Org. Chem.* **2009**, *74*, 2598.
(44) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833.
(45) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1*, **1978**, *8*, 829.
(46) Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194.
(47) Saleh, F. S.; Rahman, M. R.; Okajima, T.; Mao, L.; Ohsaka, T. *Bioelectrochemistry*, **2011**, *80*, 121.
(48) Belenky, P.; Bogan, K. L.; Brenner, C. *Trends Biochem. Sci.* **2007**, *32*, 12.
(49) Sancar, A. *Chem. Rev.* **2003**, *103*, 2203.
(50) Thauer, R. K. *Microbiology*, **1998**, *144*, 2377.
(51) Chen, S.-L.; Blomberg, M. R. A.; Siegbahn, P. E. M. *Chem. Eur. J.* **2012**, *18*, 6309.
(52) Pelmenschikov, V.; Blomberg, M. R. A.; Siegbahn, P. E. M.; Crabtree, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 4039.
(53) Pelmenschikov, V.; Siegbahn, P. M. *J. Biol. Inorg. Chem.* **2003**, *8*, 653.
(54) Scheller, S.; Goenrich, M.; Thauer, R. K.; Jaun, B. *J. Am. Chem. Soc.* **2013**, *135*, 14975.
(55) Scheller, S.; Goenrich, M.; Boecher, R.; Thauer, R. K.; Jaun, B. *Nature*, **2010**, *465*, 606.
(56) Lin, S.-K.; Jaun, B. *Helv. Chim. Acta*, **1992**, *75*, 1478.
(57) Harmer, J.; Finazzo, C.; Piskorski, R.; Ebner, S.; Duin, E. C.; Goenrich, M.; Thauer, R. K.; Reiher, M.; Schweiger, A.; Hinderberger, D.; Jaun, B. *J. Am. Chem. Soc.* **2008**, *130*, 10907.
(58) Färber, G.; Keller, W.; Kratky, C.; Jaun, B.; Pfaltz, A.; Spinner, C.; Kobelt, A.; Eschenmoser, A. *Helv. Chim. Acta*, **1991**, *74*, 697.
(59) Cedervall, P. E.; Dey, M.; Li, X.; Sarangi, R.; Hedman, B.; Ragsdale, S. W.; Wilmot, C. M. *J. Am. Chem. Soc.* **2011**, *133*, 5626.
(60) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617.
(61) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.
(62) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nature Chem.* **2012**, *4*, 854.
(63) Nguyen, J. D.; Matsuura, B. S.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2013**.
(64) Cho, D. W.; Parthasarathi, R.; Pimentel, A. S.; Maestas, G. D.; Park, H. J.; Yoon, U. C.; Dunaway-Mariano, D.; Gnanakaran, S.; Langan, P.; Mariano, P. S. *J. Org. Chem.* **2010**, *75*, 6549.
(65) Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600.
(66) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science*, **2011**, *334*, 1114.
(67) Manley, D. W.; McBurney, R. T.; Miller, P.; Howe, R. F.; Rhydderch, S.; Walton, J. C. *J. Am. Chem. Soc.* **2012**, *134*, 13580.
(68) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.
(69) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.
(70) Molander, G. A. In *Organic Reactions*; John Wiley & Sons, Inc.: 2004.
(71) Dahlén, A.; Nilsson, Å.; Hilmersson, G. *J. Org. Chem.* **2006**, *71*, 1576.
(72) Szostak, M.; Spain, M.; Parmar, D.; Procter, D. J. *Chem. Commun.* **2012**, *48*, 330.
(73) Girard, P.; Namy, J. L.; Kagan, H. B. *Nouv. J. Chem.* **1977**, *1*, 5.
(74) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron*, **1981**, *37, Supplement 1*, 175.
(75) Souppe, J.; Namy, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1982**, *23*, 3497.

(76) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
(77) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, *32*, 1699.
(78) Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron*, **1999**, *55*, 11755.
(79) Chopade, P. R.; Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2003**, *126*, 44.
(80) Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 18093.
(81) Flowers II, R. A. *Synlett*, **2008**, *10*, 1427.
(82) Shabangi, M.; Flowers, R. A. *Tetrahedron Lett.* **1997**, *38*, 1137.
(83) Choquette, K. A.; Sadasivam, D. V.; Flowers, R. A. *J. Am. Chem. Soc.* **2011**, *133*, 10655.
(84) Helm, M. D.; Da Silva, M.; Sucunza, D.; Helliwell, M.; Procter, D. J. *Tetrahedron*, **2009**, *65*, 10816.
(85) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811.
(86) Szostak, M.; Sautier, B.; Spain, M.; Procter, D. J. *Org. Lett.* **2014**.
(87) Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 2268.
(88) Brown, H. C.; Kim, S. C. *Synthesis*, **1977**, *1977*, 635.
(89) Shirai, A.; Miyata, O.; Tohnai, N.; Miyata, M.; Procter, D. J.; Sucunza, D.; Naito, T. *J. Org. Chem.* **2008**, *73*, 4464.
(90) Sloan, L. A.; Baker, T. M.; Macdonald, S. J. F.; Procter, D. J. *Synlett*, **2007**, *2007*, 3155.
(91) Baker, T. M.; Sloan, L. A.; Choudhury, L. H.; Murai, M.; Procter, D. J. *Tetrahedron: Asymmetry*, **2010**, *21*, 1246.
(92) Helm, M. D.; Da Silva, M.; Sucunza, D.; Findley, T. J. K.; Procter, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9315.
(93) Pinho, V. D.; Procter, D. J.; Burtoloso, A. C. B. *Org. Lett.* **2013**, *15*, 2434.
(94) Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* **2002**, *43*, 7197.
(95) Ankner, T.; Hilmersson, G. *Org. Lett.* **2009**, *11*, 503.
(96) Dahlén, A.; Sundgren, A.; Lahmann, M.; Oscarson, S.; Hilmersson, G. *Org. Lett.* **2003**, *5*, 4085.
(97) SmI_2 powder £95.50/g; SmI_2 0.1 M solution in THF £46.80/100 mL. Sigma Aldrich 28/01/2014
(98) Broggi, J.; Terme, T.; Vanelle, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 384.
(99) Doni, E.; Murphy, J. A. *Chem. Commun.* **2014**, *50*, 6073
(100) Wudl, F.; Wobschall, D.; Hufnagel, E. J. *J. Am. Chem. Soc.* **1972**, *94*, 670.
(101) Bendikov, M.; Wudl, F.; Perepichka, D. F. *Chem. Rev.* **2004**, *104*, 4891.
(102) Andrieux, C. P.; Pinson, J. *J. Am. Chem. Soc.* **2003**, *125*, 14801.
(103) Lampard, C.; Murphy, J. A.; Lewis, N. *J. Chem. Soc., Chem. Commun.* **1993**, *3*, 295.
(104) Fletcher, R.; Kizil, M.; Lampard, C.; Murphy, J. A.; Roome, S. J. *J. Chem. Soc., Perkin Trans. 1*, **1998**, *15*, 2341.
(105) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1*, **1999**, *8*, 995.
(106) Patro, B.; Merrett, M.; Murphy, J. A.; Sherrington, D. C.; Morrison, M. G. J. T. *Tetrahedron Lett.* **1999**, *40*, 7857.
(107) Burkholder, C.; Dolbier, W. R.; Médebielle, M. *J. Org. Chem.* **1998**, *63*, 5385.
(108) Pause, L.; Robert, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **1999**, *121*, 7158.
(109) Mahesh, M.; Murphy, J. A.; LeStrat, F.; Wessel, H. P. *Beilstein J. Org. Chem.* **2009**, *5*, 1.
(110) Ames, J. R.; Houghtaling, M. A.; Terrian, D. L.; Mitchell, T. P. *Can. J. Chem.* **1997**, *75*, 28.
(111) Murphy, J. A.; Khan, T. A.; Zhou, S.-z.; Thomson, D. W.; Mahesh, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1356.

(112) Thummel, R. P.; Goulle, V.; Chen, B. *J. Org. Chem.* **1989**, *54*, 3057.
(113) Taton, T. A.; Chen, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1011.
(114) Jolly, P. I.; Zhou, S.; Thomson, D. W.; Garnier, J.; Parkinson, J. A.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2012**, *3*, 1675.
(115) Murphy, J. A.; Zhou, S.-z.; Thomson, D. W.; Schoenebeck, F.; Mahesh, M.; Park, S. R.; Tuttle, T.; Berlouis, L. E. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5178.
(116) Lund, H. In *Organic Electrochemistry*; 4th ed.; Hammerich, O., Ed.; Marcel Dekker: New York, 2001.
(117) Schoenebeck, F.; Murphy, J. A.; Zhou, S.-z.; Uenoyama, Y.; Miclo, Y.; Tuttle, T. *J. Am. Chem. Soc.* **2007**, *129*, 13368.
(118) Findlay, N. J.; Park, S. R.; Schoenebeck, F.; Cahard, E.; Zhou, S.-z.; Berlouis, L. E. A.; Spicer, M. D.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 15462.
(119) Park, S. R.; Findlay, N. J.; Garnier, J.; Zhou, S.; Spicer, M. D.; Murphy, J. A. *Tetrahedron*, **2009**, *65*, 10756.
(120) Corr, M. J.; Roydhouse, M. D.; Gibson, K. F.; Zhou, S.-z.; Kennedy, A. R.; Murphy, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 17980.
(121) Kovacevic, L. S.; Idziak, C.; Markevicius, A.; Scullion, C.; Corr, M. J.; Kennedy, A. R.; Tuttle, T.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8516.
(122) Murphy, J. A.; Garnier, J.; Park, S. R.; Schoenebeck, F.; Zhou, S.-z.; Turner, A. T. *Org. Lett.* **2008**, *10*, 1227.
(123) Cutulic, S. P. Y.; Findlay, N. J.; Zhou, S.-Z.; Chrystal, E. J. T.; Murphy, J. A. *J. Org. Chem.* **2009**, *74*, 8713.
(124) Jolly, P. I.; Fleary-Roberts, N.; O'Sullivan, S.; Doni, E.; Zhou, S.; Murphy, J. A. *Org. Biomol. Chem.* **2012**, *10*, 5807.
(125) Cahard, E.; Schoenebeck, F.; Garnier, J.; Cutulic, S. P. Y.; Zhou, S.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3673.
(126) Doni, E.; O'Sullivan, S.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2239.
(127) Doni, E.; Mondal, B.; O'Sullivan, S.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 10934.
(128) O'Sullivan, S.; Doni, E.; Tuttle, T.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 474.
(129) Sword, R.; Baldwin, L. A.; Murphy, J. A. *Org. Biomol. Chem.* **2011**, *9*, 3560.
(130) Cutulic, S. P. Y.; Murphy, J. A.; Farwaha, H.; Zhou, S.-Z.; Chrystal, E. *Synlett*, **2008**, *14*, 2132.
(131) Stubbe, J.; Nocera, D. G.; Yee, C. S.; Chang, M. C. Y. *Chem. Rev.* **2003**, *103*, 2167.
(132) Giese, B. *Bioorganic & Medicinal Chemistry*, **2006**, *14*, 6139.
(133) Garnier, J.; Thomson, D. W.; Zhou, S.; Jolly, P. I.; Berlouis, L. E. A.; Murphy, J. A. *Beilstein J. Org. Chem.* **2012**, *8*, 994.
(134) Porter, W. W.; Vaid, T. P.; Rheingold, A. L. *J. Am. Chem. Soc.* **2005**, *127*, 16559.
(135) Han, Z.; Vaid, T. P.; Rheingold, A. L. *J. Org. Chem.* **2008**, *73*, 445.
(136) Vaid, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 15838.
(137) Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877.
(138) Staab, H. A.; Kirsch, A.; Barth, T.; Krieger, C.; Neugebauer, F. A. *Eur. J. Org. Chem.* **2000**, 1617.
(139) Vitske, V.; König, C.; Hübner, O.; Kaifer, E.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2010**, *2010*, 115.
(140) Farwaha, H. S.; Bucher, G.; Murphy, J. A. *Org. Biomol. Chem.* **2013**, *11*, 8073.
(141) Closson, W. D.; Wriede, P.; Bank, S. *J. Am. Chem. Soc.* **1966**, *88*, 1581.
(142) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A. J.; Bank, S.; Closson, W. D.; Wriede, P. A. *J. Am. Chem. Soc.* **1967**, *89*, 5311.
(143) Zhang, D.-H.; Yao, L.-F.; Wei, Y.; Shi, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2583.

(144) Yus, M.; Radivoy, G.; Alonso, F. *Synthesis*, **2001**, *2001*, 914.
(145) Donohoe, T. J.; House, D. *J. Org. Chem.* **2002**, *67*, 5015.
(146) Sword, R.; O'Sullivan, S.; Murphy, J. A. *Aust. J. Chem.* **2013**, *66*, 314.
(147) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673.
(148) Mousseau, J. J.; Charette, A. B. *Acc. Chem. Res.* **2012**, *46*, 412.
(149) Guastavino, J. F.; Rossi, R. A. *J. Org. Chem.* **2011**, *77*, 460.
(150) Foray, G. S.; Peñéñory, A. B.; Rossi, R. A. *Can. J. Chem.* **1999**, *77*, 676.
(151) Baars, H.; Beyer, A.; Kohlhepp, S. V.; Bolm, C. *Org. Lett.* **2013**, *16*, 536.
(152) Thomé, I.; Bolm, C. *Org. Lett.* **2012**, *14*, 1892.
(153) Beyer, A.; Buendia, J.; Bolm, C. *Org. Lett.* **2012**, *14*, 3948.
(154) Chen, Y.-y.; Zhang, X.-j.; Yuan, H.-m.; Wei, W.-t.; Yan, M. *Chem. Commun.* **2013**, *49*, 10974.
(155) Shirakawa, E.; Hayashi, Y.; Itoh, K.-i.; Watabe, R.; Uchiyama, N.; Konagaya, W.; Masui, S.; Hayashi, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 218.
(156) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nature Chem.* **2010**, *2*, 1044.
(157) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018.
(158) Leadbeater, N. E. *Nature Chem.* **2010**, *2*, 1007.
(159) Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2014**, *5*, 476.
(160) Cuthbertson, J.; Gray, V. J.; Wilden, J. D. *Chem. Commun.* **2014**, *50*, 2575.
(161) Swanson, R. M. *Science*, **2009**, *324*, 891.
(162) Yanilkin, V. V.; Gubskaya, V. P.; Morozov, V. I.; Nastapova, N. V.; Zverev, V. V.; Berdnikov, E. A.; Nuretdinov, I. A. *Russ. J. Electrochem.* **2003**, *39*, 1147.
(163) Sasabe, H.; Kido, J. *J. Mater. Chem. C*, **2013**, *1*, 1699.
(164) Zaumseil, J.; Sirringhaus, H. *Chem. Rev.* **2007**, *107*, 1296.
(165) Doctor Jens Sutter and Prof. David Birch of the Department of Physics, University of Strathclyde Glasgow assisted in these investigations.
(166) Barone, V.; Cossi, M. *J. Phys. Chem. A*, **1998**, *102*, 1995.
(167) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669.
(168) Jutand, A.; Mosleh, A. *J. Org. Chem.* **1997**, *62*, 261.
(169) Farrar, C. R.; Williams, A. *J. Am. Chem. Soc.* **1977**, *99*, 1912.
(170) Shirini, F.; Ali Zolfigol, M.; Mohammadi, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 1617.
(171) Rao Koganty, R.; Digenis, G. A. *J. Labelled Compd.* **1974**, *10*, 419.
(172) Stutz, A. E. *Glycoscience: Epimerisation, Isomerisation and Rearrangement Reactions of Carbohydrates* 1st ed.; Springer-Verlag: Heidelberg, 2001; Vol. 215.
(173) Doni, E. PhD Thesis, University of Strathclyde, 2013.
(174) Mortensen, J.; Heinze, J. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 84.
(175) Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299.
(176) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327.
(177) Greene, T. W. W., P. G. M. *Protective Groups in Organic Synthesis*; 2nd ed.; John Wiley & Sons, Inc.: New York, 1991.
(178) Angle, S. R.; Arnaiz, D. O. *Tetrahedron Lett.* **1989**, *30*, 515.
(179) Hanessian, S.; Masse, R. *Carbohydr. Res.* **1977**, *54*, 142.
(180) Mairanovsky, V. G. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 281.
(181) Szostak, M.; Spain, M.; Procter, D. J. *Angew. Chem.* **2013**, *125*, 7378.
(182) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3765.
(183) Laguzza, B. C.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 1483.
(184) Gigg, R.; Conant, R. *J. Carbohydr. Chem.* **1982**, *1*, 331.

(185) Gigg, R.; Conant, R. *Carbohydr. Res.* **1982**, *100*, C5.
(186) Chandrasekhar, S.; Raji Reddy, C.; Jagadeeshwar Rao, R. *Tetrahedron*, **2001**, *57*, 3435.
(187) Nandi, P.; Dye, J. L.; Jackson, J. E. *Tetrahedron Lett.* **2009**, *50*, 3864.
(188) Slebocka-Tilk, H.; Brown, R. S. *J. Org. Chem.* **1987**, *52*, 805.
(189) Merlin, P.; Braekman, J. C.; Daloze, D. *Tetrahedron Lett.* **1988**, *29*, 1691.
(190) Nandi, P.; Redko, M. Y.; Petersen, K.; Dye, J. L.; Lefenfeld, M.; Vogt, P. F.; Jackson, J. E. *Org. Lett.* **2008**, *10*, 5441.
(191) Naito, H.; Hata, T.; Urabe, H. *Org. Lett.* **2010**, *12*, 1228.
(192) Ritter, T.; Stanek, K.; Larrosa, I.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1513.
(193) Beak, P.; Sullivan, T. A. *J. Am. Chem. Soc.* **1982**, *104*, 4450.
(194) Azzena, U.; Dessanti, F.; Melloni, G.; Pisano, L. *Tetrahedron Lett.* **1999**, *40*, 8291.
(195) Francisco, M. A.; Kurs, A.; Katritzky, A. R.; Rasala, D. *J. Org. Chem.* **1988**, *53*, 596.
(196) Zhang, H.; Hay, E. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2013**, *135*, 16610.
(197) Garnier, J.; Kennedy, A. R.; Berlouis, L. E. A.; Turner, A. T.; Murphy, J. A. *Beilstein J. Org. Chem.* **2010**, *6*, 73.
(198) Hemström, P.; Irgum, K. *J. Sep. Science.* **2006**, *29*, 1784.
(199) Alpert, A. J. *J. Chromatogr. A.* **1990**, *499*, 177.
(200) Hu, J.; Hirao, H.; Li, Y.; Zhou, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 8676.
(201) Cacchi, S.; Lupi, A. *Tetrahedron Lett.* **1992**, *33*, 3939.
(202) Uchiyama, M.; Furuyama, T.; Kobayashi, M.; Matsumoto, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 8404.
(203) King, J. F.; Lee, T. M.-L. *Can. J. Chem.* **1981**, *59*, 362.
(204) Toepfer, A.; Kretzschmar, G.; Schuth, S.; Sonnentag, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1317.
(205) Mills, W. H.; Nixon, I. G. *J. Chem. Soc.* **1930**, *332*, 2510.
(206) Oberhauser, T. *J. Org. Chem.* **1997**, *62*, 4504.
(207) Nithyanandhan, J.; Jayaraman, N. *Tetrahedron*, **2005**, *61*, 11184.
(208) Creary, X. *J. Org. Chem.* **1980**, *45*, 2727.
(209) Murphy, J. A.; Schoenebeck, F.; Findlay, N. J.; Thomson, D. W.; Zhou, S.-z.; Garnier, J. *J. Am. Chem. Soc.* **2009**, *131*, 6475.
(210) Tancini, F.; Gottschalk, T.; Schweizer, W. B.; Diederich, F.; Dalcanale, E. *Chem. Eur. J.* **2010**, *16*, 7813.
(211) Machin, P. J.; Hurst, D. N.; Bradshaw, R. M.; Blaber, L. C.; Burden, D. T.; Fryer, A. D.; Melarange, R. A.; Shivdasani, C. *J. Med. Chem.* **1983**, *26*, 1570.
(212) Astrazeneca AB (2007) *Phenethanolamine derivatives as beta2 adrenoreceptor agonist*, WO 2007102771 A1.
(213) Molander, G. A.; Cavalcanti, L. N. *J. Org. Chem.* **2010**, *76*, 623.
(214) Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron*, **2005**, *61*, 9319.
(215) Bohnsack, H. *Riechstoffe und Aromen*, **1971**, *21*, 163.
(216) Hoi, K. H.; Çalimsiz, S.; Froese, R. D. J.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2012**, *18*, 145.
(217) Tang, Y.; Wei, Z.; Zhong, W.; Liu, X. *Eur. J. Inorg. Chem.* **2011**, *2011*, 1112.
(218) Ramachary, D. B.; Reddy, G. B. *Org. Biomol. Chem.* **2006**, *4*, 4463.
(219) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565.
(220) Sun, H.; Ye, D.; Jiang, H.; Chen, K.; Liu, H. *Synthesis*, **2010**, *2010*, 2577.
(221) Hoffmann, H.; Platz, G.; Ulbricht, W. *J. Phys. Chem.* **1981**, *85*, 1418.

(222) Pelah, Z.; Wilson, J. M.; Ohashi, M.; Budzikiewicz, H.; Djerassi, C. *Tetrahedron*, **1963**, *19*, 2233.
(223) Al-Hiari, Y. M.; Bennett, S. J.; Davies, R. J.; Khalaf, A. I.; Waigh, R. D.; Worsley, A. J.; Cox, B. *J. Heterocyclic Chem.* **2005**, *42*, 647.
(224) Sridhar, R.; Srinivas, B.; Kumar, V. P.; Narender, M.; Rao, K. R. *Adv. Synth. Catal.* **2007**, *349*, 1873.
(225) White, E. H.; Lim, H. M. *J. Org. Chem.* **1987**, *52*, 2162.
(226) Torimoto, N.; Shingaki, T.; Nagai, T. *J. Org. Chem.* **1978**, *43*, 631.
(227) De Luca, L.; Giacomelli, G. *J. Org. Chem.* **2008**, *73*, 3967.
(228) Wang, S.-F.; Chuang, C.-P.; Lee, J.-H.; Liu, S.-T. *Tetrahedron*, **1999**, *55*, 2273.
(229) Gellert, B. A.; Kahlcke, N.; Feurer, M.; Roth, S. *Chem. Eur. J.* **2011**, *17*, 12203.
(230) Fleming, P.; O'Shea, D. F. *J. Am. Chem. Soc.* **2011**, *133*, 1698.
(231) Shingaki, T.; Inagaki, M.; Torimoto, N.; Takebayashi, M. *Chem. Lett.* **1972**, *1*, 1181.
(232) Chantarasriwong, O.; Jang, D. O.; Chavasiri, W. *Tetrahedron Lett.* **2006**, *47*, 7489.
(233) Ankner, T.; Hilmersson, G. *Org. Lett.* **2009**, *11*, 503.
(234) Zhao, X.; Liu, D.; Guo, H.; Liu, Y.; Zhang, W. *J. Am. Chem. Soc.* **2011**, *133*, 19354.
(235) Barros, M. T.; Dey, S. S.; Maycock, C. D. *Eur. J. Org. Chem.* **2013**, *2013*, 742.
(236) Schmidt, B.; Krehl, S.; Jablowski, E. *Org. Biomol. Chem.* **2012**, *10*, 5119.
(237) Kim, H.; Lee, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 12303.
(238) Zacuto, M. J.; Xu, F. *J. Org. Chem.* **2007**, *72*, 6298.
(239) Herweh, J. E.; Hoyle, C. E. *J. Org. Chem.* **1980**, *45*, 2195.
(240) Wakita, Y.; Noma, S.-Y.; Maeda, M.; Kojima, M. *J. Organomet. Chem.* **1985**, *297*, 379.
(241) Tayama, E.; Yanaki, T.; Iwamoto, H.; Hasegawa, E. *Eur. J. Org. Chem.* **2010**, *2010*, 6719.
(242) Pace, V.; Holzer, W.; Verniest, G.; Alcántara, A. R.; De Kimpe, N. *Adv. Synth. Catal.* **2013**, *355*, 919.
(243) Gillis, B. T.; Dain, J. G. *J. Heterocyclic Chem.* **1971**, *8*, 339.
(244) Anderson, W. K.; Bhattacharjee, D.; Houston, D. M. *J. Med. Chem.* **1989**, *32*, 119.
(245) Jiang, B.; Huang, Z.-G.; Cheng, K.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 942.
(246) Zhao, Y.; Foo, S. W.; Saito, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3006.
(247) Zhang , M.; Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3905.
(248) Kamiński, Z. J. *Tetrahedron Lett.* **1985**, *26*, 2901.
(249) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101.
(250) Cleij, M. C.; Scrimin, P.; Tecilla, P.; Tonellato, U. *J. Org. Chem.* **1997**, *62*, 5592.
(251) Wang, K.; Liu, Z. *Synth. Commun.* **2009**, *40*, 144.
(252) Marvel, C. S.; Helfrick, M. D.; Belsley, J. P. *J. Am. Chem. Soc.* **1929**, *51*, 1272.
(253) Chung, J. Y. L.; Hughes, D. L.; Zhao, D.; Song, Z.; Mathre, D. J.; Ho, G.-J.; McNamara, J. M.; Douglas, A. W.; Reamer, R. A.; Tsay, F.-R.; Varsolona, R.; McCauley, J.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 215.
(254) Joe, C. L.; Tan, K. L. *J. Org. Chem.* **2011**, *76*, 7590.
(255) Saito, Y.; Ouchi, H.; Takahata, H. *Tetrahedron*, **2008**, *64*, 11129.
(256) Catt, J. D.; Matier, W. L. *J. Org. Chem.* **1974**, *39*, 566.
(257) Soulé, J.-F.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2011**, *133*, 18550.
(258) Ohmura, N.; Nakamura, A.; Hamasaki, A.; Tokunaga, M. *Eur. J. Org. Chem.* **2008**, *2008*, 5042.
(259) Gassman, P. G.; Van Bergen, T. J.; Gilbert, D. P.; Cue, B. W. *J. Am. Chem. Soc.* **1974**, *96*, 5495.
(260) Jolly, P. I.; Fleary-Roberts, N.; O'Sullivan, S.; Doni, E.; Zhou, S.; Murphy, J. A. *Org. Biomol. Chem.* **2012**.

(261) Barluenga, J.; Fananas, F. J.; Villamana, J.; Yus, M. *J. Org. Chem.* **1982**, *47*, 1560.
(262) Salbeck, G. *Phosphorous Sulfur Silicon Relat. Elem.* **1982**, *13*, 165.
(263) Bordwell, F. G.; Chapman, R. D.; McKellin, W. H. *J. Am. Chem. Soc.* **1954**, *76*, 3637.
(264) Fiandanese, V.; Marchese, G.; Naso, F. *J. Chem. Soc., Perkin Trans. 2*, **1973**, 1538.
(265) Tschugaeff, L. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 2222.
(266) Irvine, S.; Kerr, W. J.; McPherson, A. R.; Pearson, C. M. *Tetrahedron*, **2008**, *64*, 926.
(267) Paulsson, H.; Hagfeldt, A.; Kloo, L. *J. Phys. Chem. B*, **2003**, *107*, 13665.
(268) Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *J. Am. Chem. Soc.* **1989**, *111*, 658.
(269) Maiolo, F.; Testaferri, L.; Tiecco, M.; Tingoli, M. *J. Org. Chem.* **1981**, *46*, 3070.
(270) Sellmann, D.; Frank, P.; Knoch, F. *J. Organomet. Chem.* **1988**, *339*, 345.
(271) Xu, H.-J.; Liang, Y.-F.; Cai, Z.-Y.; Qi, H.-X.; Yang, C.-Y.; Feng, Y.-S. *J. Org. Chem.* **2011**, *76*, 2296.
(272) Fenton, G. W.; Ingold, C. K. *J. Chem. Soc.* **1929**, 2342.
(273) Taylor, E. C.; Berchtold, G. A.; Goeckner, N. A.; Stroehmann, F. G. *J. Org. Chem.* **1961**, *26*, 2715.
(274) Farng, L.-P. O.; Kice, J. L. *J. Org. Chem.* **1981**, *46*, 2599.
(275) Iimura, S.; Manabe, K.; Kobayashi, S. *Org. Lett.* **2002**, *5*, 101.