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The Development of Photoredox-Mediated Methods for the Aminofunctionalisation of Alkenes

A thesis submitted to The University of Nottingham for the degree of Doctor of Philosophy

By

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Declaration

I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification. I confirm that the work submitted is my own, except work which has formed part of jointly authored publications. The contributions of myself and other authors to this work have been specifically indicated where relevant. I confirm that appropriate credit has been given with the thesis where references has been made to the work of others.

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Abstract

Nitrogen-centered radicals (NCRs), such as amidyl radicals, are a versatile reaction intermediate for the installation of C–N bonds by means of the functionalisation of alkenes. In this thesis, the development of photoredox-mediated methodologies for the aminofunctionalisation of alkenes by means of reductively generated amidyl radicals is described, and its application towards the synthesis of amino-substituted all-carbon quaternary centres and saturated heterocycles.

We disclose an efficient method for the synthesis of β-aminoketones containing all-carbon quaternary centres in a photoredox-mediated one-pot procedure utilizing semi-pinacol chemistry and reductively generated amidyl radical, achieving yields of up to 96%. Good functional group tolerance is observed in a variety of positions around the aryl ring. Application of this chemistry has also been demonstrated on unactivated alkene substrates and acylic substrates, which to the best of our knowledge has not been demonstrated in the literature using photoredox-based methodology.

In addition, we also disclose a robust method for the synthesis aminomethyl-substituted tetrahydrofurans, utilizing a photoredox-based radical-polar crossover methodology and reductively generated amidyl radicals. This chemistry has been demonstrated to attain yields of up to 82%, and be compatible to the synthesis of other saturated heterocycles such as pyrrodilines, morpholines and lactones.

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Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Ar	aryl
aq.	aqueous
BDE	bond dissociation energy
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
Cbz	benzyl chloroformate
Cu	copper
CV	cyclic voltammetry
d.r	diastereomeric ratio
DCE	1,2-dichloroethane
DIPEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDG	electron-donating group
eq.	equivalents
Et	ethyl
EWG	electron-withdrawing group
EY	eosin Y
FTIR	fourier transform infrared
h	hour
HAT	hydrogen atom transfer
HRMS	high-resolution mass spectrometry
HMBC	heteronuclear multiple-bond correlations
Hz	hertz
i-	*iso*-
IR	infrared

ISC	intersystem crossing
LED	light emitting diode
Lit.	literature value
M	molar
Me	methyl
MeCN	acetonitrile
MesAcr	9-methyl-10-mesitylacridinium
MHz	megahertz
MLCT	metal-to-ligand charge transfer
mp.	melting point
NBS	*N*-bromosuccinimide
NCR	nitrogen-centered radical
NMR	nuclear magnetic resonance
PC	photocatalyst
PCET	proton-coupled electron transfer
Ph	phenyl
PTOC	thiohydroximate
R_f	retention factor
rt	room temperature
SCE	standard calomel electrode
SET	single electron transfer
S_N	substitution nucleophillic
t-	*tert*-
^{t}Bu	*tert*-butyl
TBS	*tert*-butylsilyl ether
Tf	triflyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
Troc	trichloroethyl chloroformate
Ts	tosyl
UV	ultra-violet
XAT	halogen atom tranfer

Stereochemistry:

Throughout this work, “thick bonds/blocks” have been used to indicate new bonds formed, and “wedges and dashed bonds” have been used to indicate stereochemistry.

Introduction

Nitrogen-containing compounds are ubiquitous in nature and form the structural basis of many pharmaceuticals such as procyclidine (**1**) and mitomycin C (**2**), agrochemicals such as nitempyram (**3**) and propoxur (**4**), materials such as Kevlar (**5**) and bioactive natural products such as tryptophan (**6**).[1,2] Therefore, the development of methodologies to incorporate nitrogen *via* the formation of C–N bonds is of great interest within synthetic chemistry. As a result, C–N bond formations to form amines, commonly known as amination reactions, have been widely explored in chemistry in order to access these versatile compounds.[3]

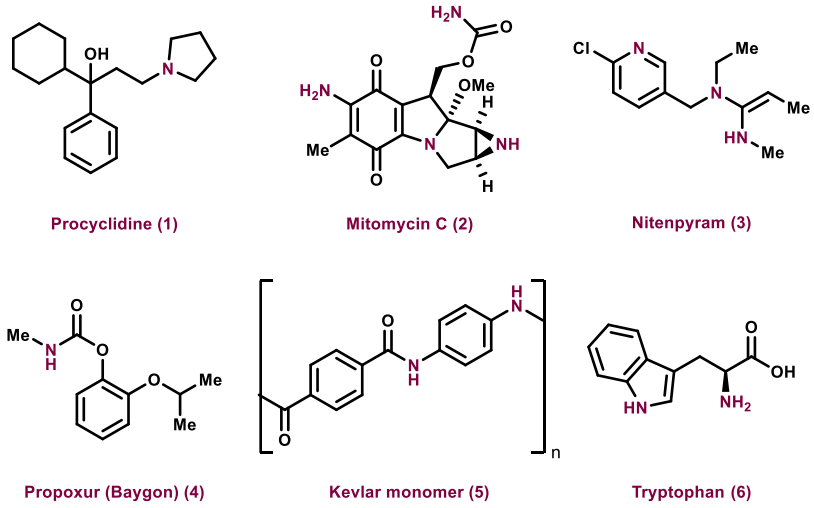
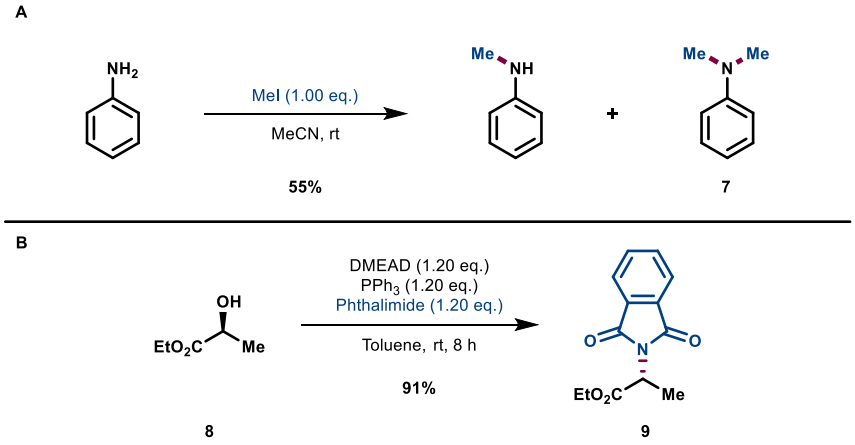


Figure 1: Structures of widely used nitrogen containing compounds

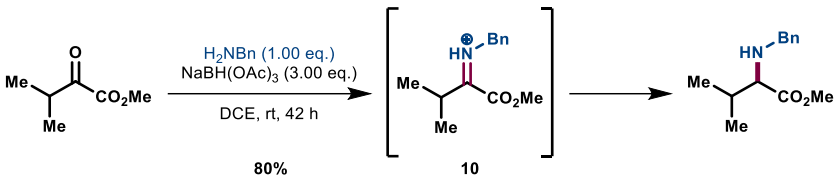
Classical Two Electron Approaches towards C–N Bond Formation

With global routes to nitrogen containing compounds such L-glutamic acid surpassing 650,000 ta^{-1},[4] routes to form C–N bonds have been extensively explored.[3,5–11] A well-known strategy is direct alkylation which is highlighted in an example by Cantat and coworkers (scheme 1A).[12] However, in addition to the inherent risk posed by the use of alkyl halides, this can often lead to overalkylation and the formation of side-products such as aniline **7**, which can reduce the practicality of this method. The Mitsunobu reaction is an analogous S_N2 approach to C–N bond formation which mitigates these drawbacks, as demonstrated by Taniguchi *et al.* (scheme 1B).[13] Although affording an excellent yield of phthalimide **9**, the requisite of stoichiometric amounts of triphenylphosphine, in turn providing a stoichiometric amount of triphenylphosphine oxide waste, render this approach costly and unsustainable.



Scheme 1: Synthetic approaches towards C–N bond formation: (A) direct alkylation[12] (B) Mitsunobu reaction[13]

Reductive amination (scheme 2) is a classical alternative method to form C–N bonds.[14] Like the Mitsunobu approach, this tactic generally affords good selectivity because of the generation of iminium **10** which is only able to form once on a given C=O bond. As a result, this approach is widely employed in industry.[8] The disadvantages of this approach however are that they typically employ stoichiometric amounts of a borohydride reagent, and can require the use of environmentally unfriendly solvents such as 1,2-dichloroethane (DCE).



Scheme 2: Reductive amination as an approach towards C–N bond formation reported by Shah et al[14]

It is noteworthy that because of the drawbacks of each of these routes, recent developments in this field have focussed on the development of catalytic methods for the formation of C–N bonds.[15] For a comprehensive overview of this area, see recent reviews by Chang[15] and Balaraman[16].

Nitrogen centered radicals (NCRs)

In addition to the two-electron strategies discussed in the previous section, single-electron processes using nitrogen centred radicals (NCRs) have also been used in the construction of C–N bonds.[17,18] NCRs offer a unique activity due to the umpolung nature of the typically nucleophilic nitrogen centre.[17,19,20] The main classes of NCRs are shown in figure 2. Iminyl radicals have a σ-configuration with the unpaired electron localised in the sp^2 orbital of the nitrogen atom, and are weakly nucleophilic.[21] Similarly, aminyl radicals are also nucleophilic but conversely have a π-configuration with the unpaired electron occupying the higher energy p-orbital. Protonation of aminyl radicals to form aminium radicals maintains the π-configuration, however, completely changes the electronic character from mildly nucleophilic to strongly electrophilic.[22] Likewise, amidyl radicals are π-configurated and are highly electrophilic because of the delocalisation of the unpaired electron across the neighbouring carbonyl, lowering the energy of the singularly occupied molecular orbital.[23]

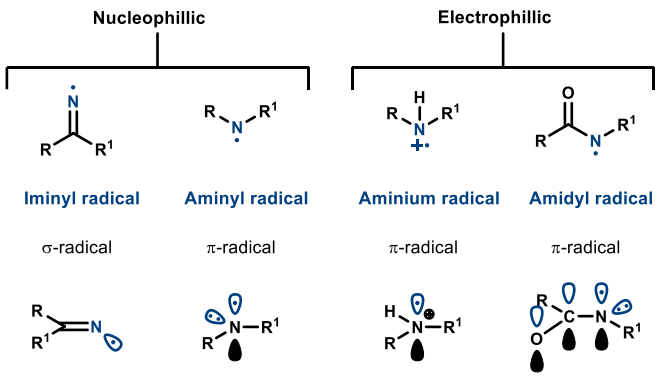
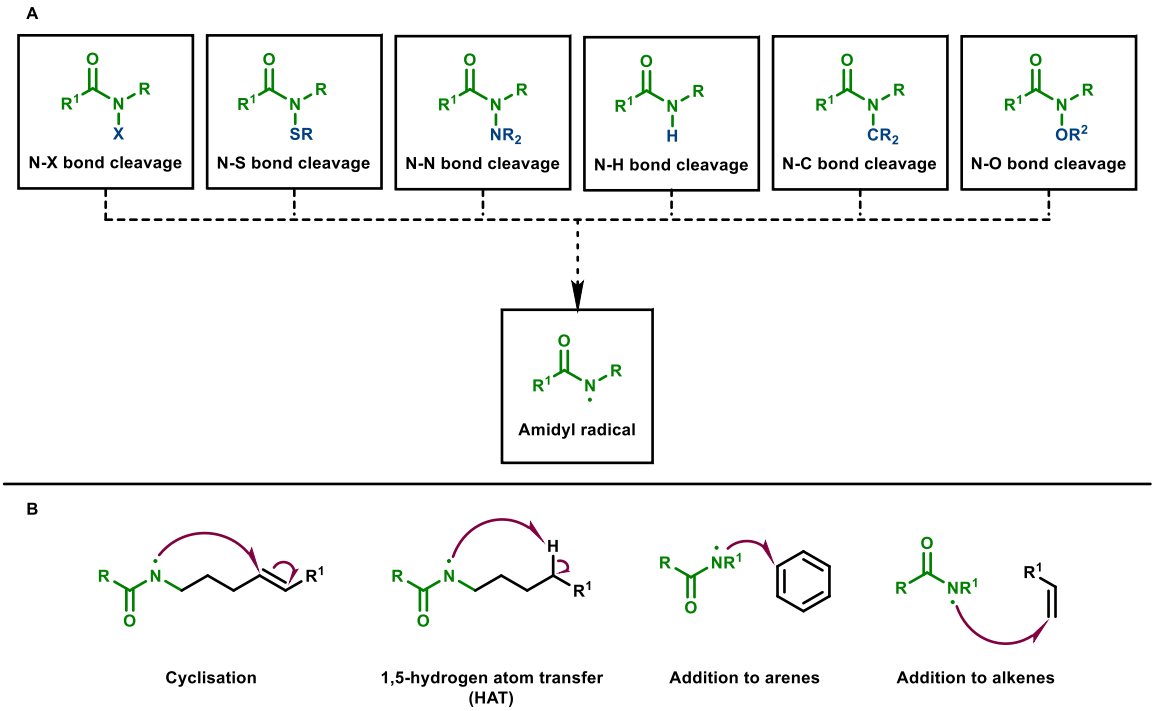


Figure 2: Shape and configuration of nitrogen centred radicals

Amidyl radicals



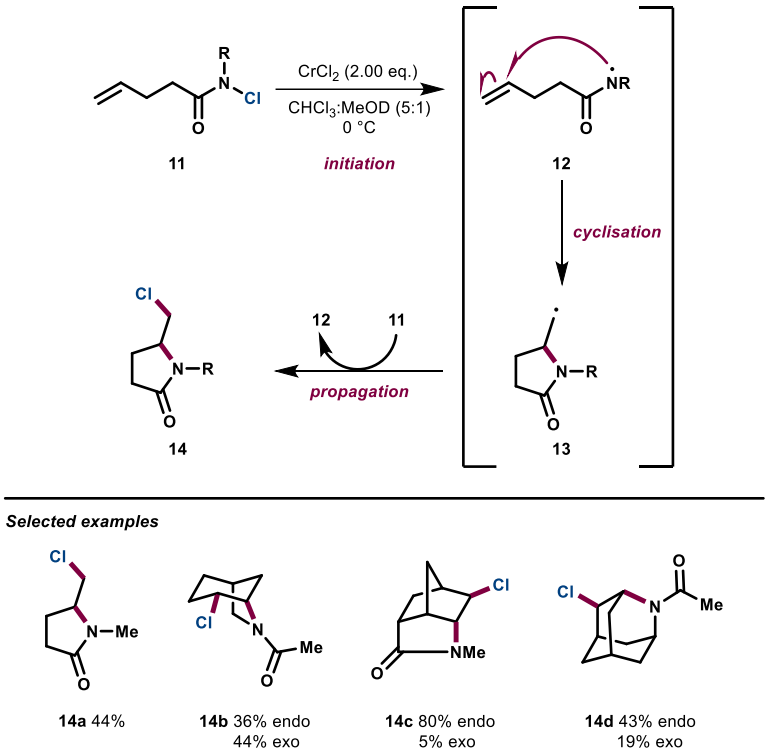
Scheme 3[18,19]*: (A) Classical bond cleavages to form amidyl radicals (B) Reactions of amidyl radicals*

Classical methods to generating amidyl radicals originate from the cleavage of N–X, N–S, N–N, N–H, N–C and N–O bonds using typically stoichiometric amounts of oxidant or high energy UV light (scheme 3A).[19] Once formed, amidyl radicals are able undergo cyclization reactions, 1,5-hydrogen atom transfer (HAT) and addition to arenes and alkenes (scheme 3B). This section will highlight some key examples of these bond cleavages to form amidyl radicals and their subsequent use in the addition to alkenes, however for a more comprehensive look see reviews by Zard,[19] Zhang,[24] Roizen[18] and Murphy.[25]

N–X bond cleavage

A seminal method for the generation of amidyl radical using nitrogen-halogen (N–X) bond cleavage and its subsequent addition into olefins was demonstrated by Lessard and coworkers (scheme 4).[26,27] This method proceeds *via* N–Cl bond cleavage facilitated by chromium(II) chloride to evolve amidyl radical **12**. 5-*exo-trig* cyclization of olefin **12** enables the formation of carbon-centred radical **13**. Propagation of radical **13** with haloamine **11** regenerates amidyl radical **12** and provides the β-halo-γ-lactam product **14**. Although poor yields of lactam **14a** and

β-halo amide **14b** were formed, Lessard found that products such as β-halo-γ-lactam **14c** provided excellent yields and selectivity towards the endo-product because of the favourable orbital overlap in the transition state for the 5-*exo-trig* cyclization step. Therefore, increasing the propensity of the amidyl radical to undergo cyclization, and circumvent any H-atom abstraction pathways. Additionally, Lessard and coworkers were also able to extend the utility of this procedure to form novel caged systems such as amide **14d** in a moderate yield.

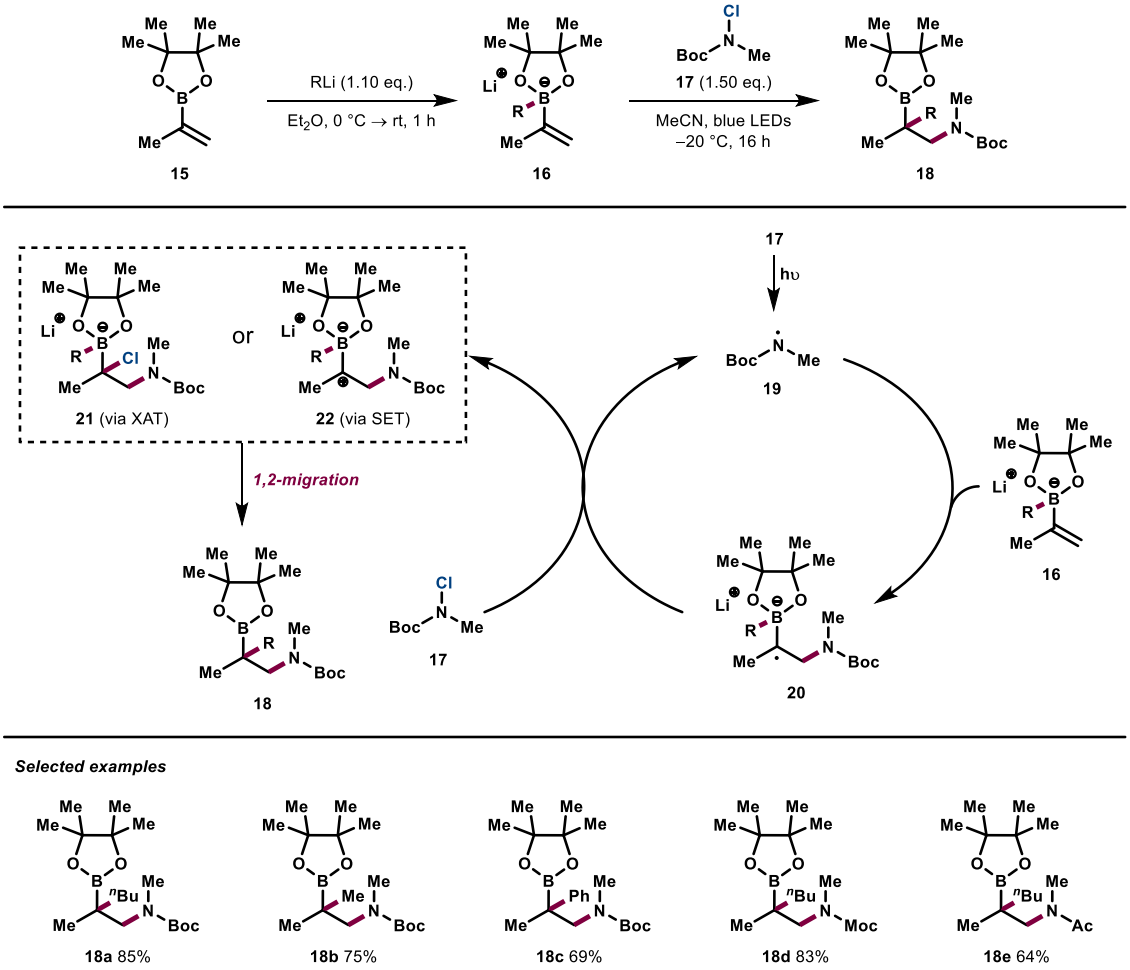


Scheme 4: Amidyl radical generation using N–X bond cleavage as reported by Lessard et al. [26,27]

Recent examples in this area have focussed on the use of lower energy visible light, as opposed to high energy UV or use of oxidants, to undergo homolytic cleavage of the N–X bond to form amidyl radicals. This strategy is highlighted in the three-component 1,2-carboamination of vinyl boronic esters by Studer and coworkers (scheme 5).[28] This methodology begins with the alkylation of boronate ester **15** to form boronate **16**. Following this, the homolytic cleavage of the N–Cl bond of substrate **17** to form amidyl radical **19**, which upon addition to the electron-rich vinylboronate complex **16** forms boronate radical **20**. Radical **20** is then able to propagate the chain by halogen atom transfer (XAT) with amidyl radical precursor **17** to form adduct **21**, or *via* a single electron transfer (SET) with radical precursor **17** to form adduct **22**.

Adducts **21** and **22** are able to undergo a boronate 1,2-migration to afford 1,2-aminoboronic ester **19**.

Studer was able to extend the scope of the methodology to include a range of boronic esters (**18a – 18e**) in good to excellent yields.



Scheme 5: Visible light mediated N–X bond cleavage to generate amidyl radicals reported by Studer et al.[28]

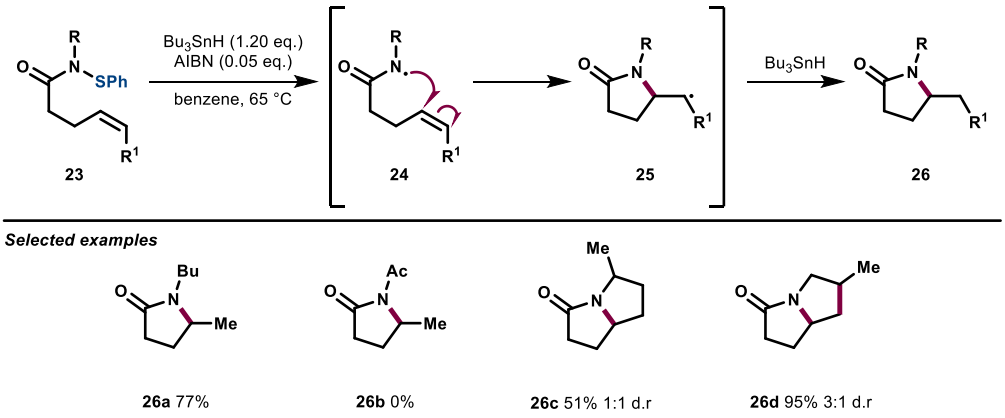
N–S bond cleavage

The formation of amidyl radicals *via* N–S bond cleavage has traditionally been carried out utilizing stannane chemistry. Pioneering work by Esker and Newcomb found conditions using AIBN and tributyltin hydride to facilitate the homolytic cleavage of the N–S bond in amide derivative **23** to afford secondary amidyl radical **24** (scheme 6).[29] Intramolecular cyclization of radical **24** in a 5-*exo*-*trig* manner provides carbon-centred radical **25**. Propagation with tributyltin hydride provides γ-lactam **26** and another stannyl radical to sustain the chain.

Interestingly, Esker and Newcomb found that although the use of a butyl group provided γ-lactam **26a** in a 77% yield, replacement of this butyl group with an acetyl group completely inhibited the reaction, leading to a no formation of product **26b**. This may have been a result of delocalisation of the radical into the carbonyl of the acetyl group.

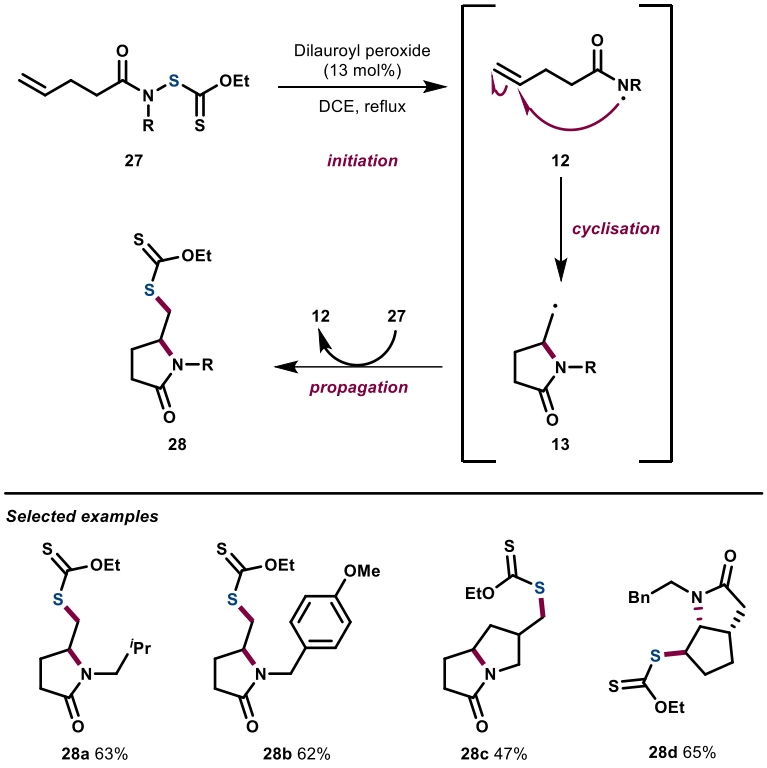
Furthermore, because of the required orbital orientation and transition state needed for this chemistry, Esker and Newcomb were able to selectively cyclize olefin bonds on substrates containing multiple alkene moieties, to yield fused γ-lactams **26c** and **26d** exclusively in moderate to excellent yields.

It is noteworthy that this approach was further advanced by Lessard and coworkers,[30] who demonstrated that this chemistry can be extended towards primary amidyl radicals.



Scheme 6: Formation of secondary amidyl radicals using N–S bond cleavage developed by Esker and Newcomb[29]

As a result of the toxicity and unsustainability in using stannane chemistry, a recent development by Zard has focussed on tin-free methods to generate amidyl radicals (scheme 7).[31] Zard's methodology utilized dilauroyl peroxide to mediate the homolytic cleavage of a N–S bond to form amidyl radical **12** and a xanthate radical. Radical **12** is then able to undergo a 5-*exo-trig* cyclization with the internal olefin to form cyclized radical **13**. Addition of radical **13** with substrate **27** affords xanthate-substituted pyrrolidinone product **28** and regenerating amidyl radical **12** to propagate the chain. Additionally, Zard was also able to extend the scope of this methodology to bicyclic pyrrolidinones such as **28c**, however the use of refluxing dichloroethane, a solvent which is now subject to REACH regulation by the European Union,[32] would deem this protocol unsuitable for industrial use.

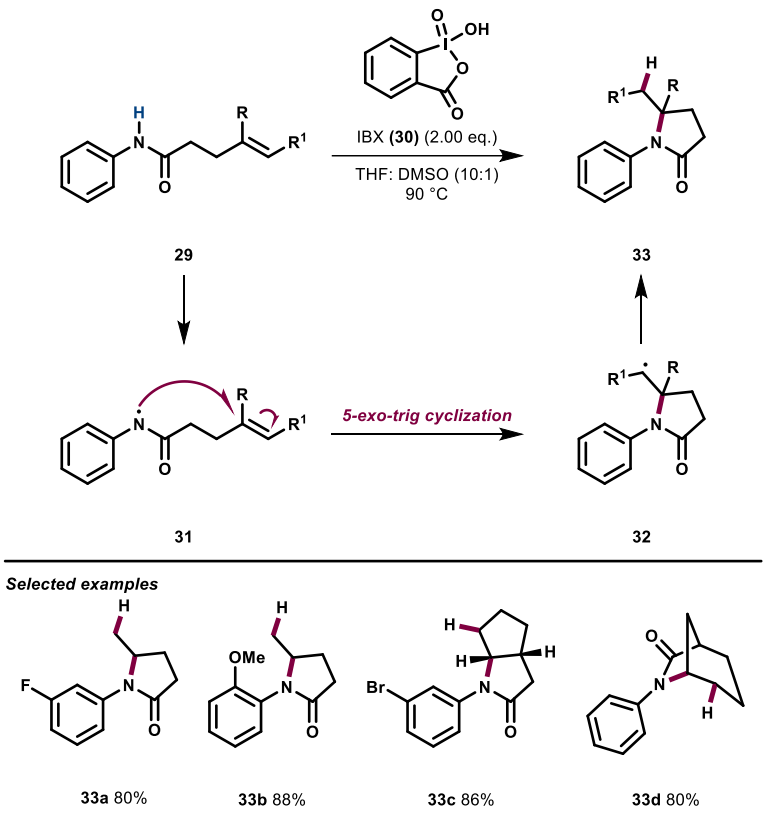


Scheme 7: Tin-free generation of amidyl radicals from N–S bond cleavage reported by Zard et al.[31]

N–H bond cleavage

As a result of the high bond dissociation energy of the N–H bond (BDE ~ 107 kcal/mol),[18,33] the generation of amidyl radicals from N–H bond cleavage is challenging. Seminal methods mainly explored formal hydrogen abstraction from the parent amide[18,34] utilizing stoichiometric amounts of oxidant and high temperatures. However, the harsh conditions required limited the generality of functional groups on the amide substrates.[18]

A notable development by Nicolaou in this area found 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) (**30**), a hypervalent iodine reagent, was able to generate amidyl radicals from *N*-aryl amide derivatives **29** (scheme 8).[35,36] Once formed, the evolved amidyl radical **31** could participate in a 5-*exo*-*trig* cyclization, followed by a subsequent H-atom abstraction to form pyrrolidinone **33**.[35] Nicolaou found this milder alternative to be tolerant of electron deficient arenes **33a** and electron rich arenes **33b** providing both in excellent yields. In addition, fused and bridged bicyclic compounds **33c** and **33d** respectively were also synthesised in comparable yields.

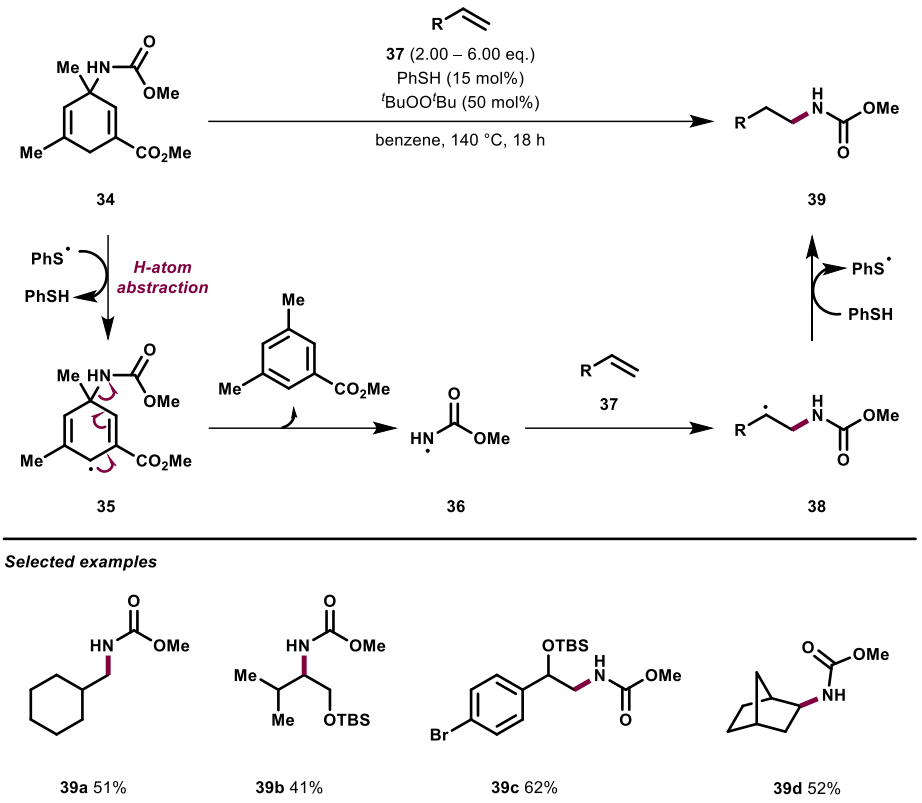


Scheme 8: Amidyl radical generation via N–H bond cleavage reported by Nicolaou and coworkers [35]

N–C bond cleavage

Similar to N–H bond cleavage, the strength of N–C bonds means this type of approach to form amidyl radicals is challenging and as a result, this type of approach is seldom reported. A rare example was reported by Studer to enable the radical transfer hydroamination of olefins using aminated 1,4-cyclohexadiene derivatives **34** as amidyl radical precursors (scheme 9).[37] Amidyl radical **36** is formed by means of a H-atom abstraction of 1,4-cyclohexadiene **34** by a thiyl radical, and subsequent fragmentation of radical **35**. Addition of amidyl radical **36** to olefin **37** provides carbon-centred radical **38**, which can undergo a final H-atom abstraction from thiophenol to afford hydroamination product **39**.

Studer was able to extend the generality of this methodology to cyclohexyl-substituted product **39a** and TBS protected product **39b**, in addition to aryl containing products **39c** and sterically hindered bridged product **39d**.

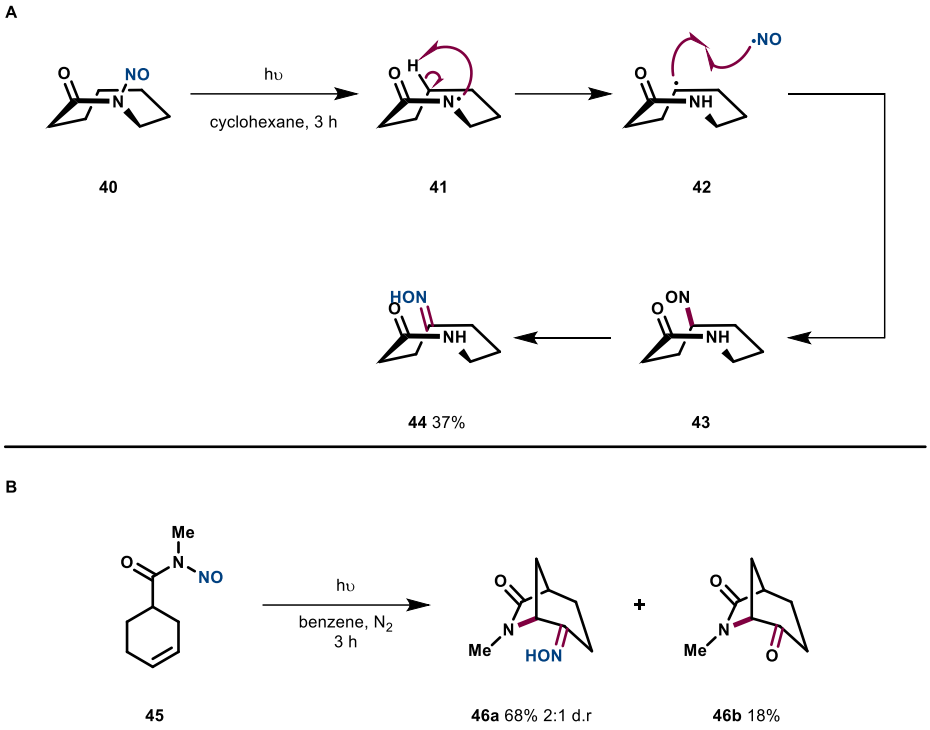


Scheme 9: Amidyl radical generation via N–C bond cleavage developed by Studer et al.[37]

N–N bond cleavage

Seminal methods to form amidyl radicals *via* the cleavage of N–N bonds focussed on the photolysis of *N*-nitrosoamide **40**, as demonstrated by Edwards and coworkers (scheme 10A).[38] Following photolysis of the N–N bond by UV light, the evolved amidyl radical **41** undergoes a 1,5-HAT to generate alkyl radical **42**. A subsequent termination reaction of alkyl radical **42** with a nitric oxide radical provides nitrosoamide **43**, which can then enable the formation of (hydroxyimino)azocanone product **44**.

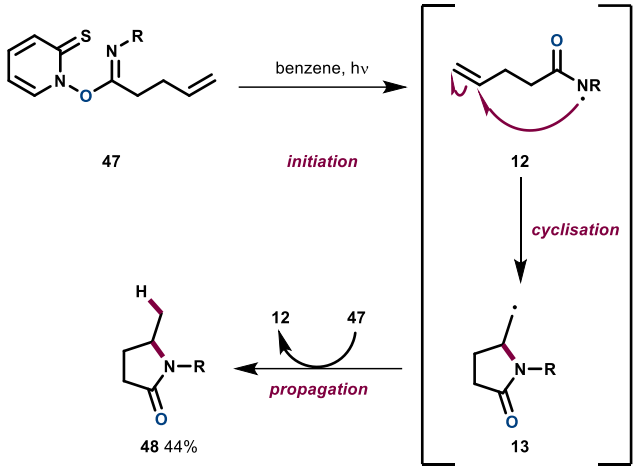
This approach was advanced further by Chow and Perry enabling an intramolecular cyclization by the coupling of an amidyl radical with an internal alkene **45** to provide bridged oxime **46a** in a 68% yield in a 2:1 d.r in addition to ketolactam **46b** in an 18% yield (scheme 10B).[39]



Scheme 10: Amidyl radical generation via N–N bond cleavage reported by (A) Edwards et al.[38] *(B) Chow and Perry.*[39]

N–O bond cleavage

Compared to the N–N bond, the N–O bond is weak and easily cleaved.[19] As a result, cleavage of this bond to evolve amidyl radicals has been widely explored within synthetic chemistry.[18,19] Early methods to produce amidyl radicals utilizing this approach involved the Barton Decarboxylation of thiohydroximate (PTOC) ester derivatives **47**.[40] An example of this was published by Esker and Newcomb towards the synthesis of γ-lactams (scheme 11).[41] This protocol mechanistically begins with the homolytic cleavage of the N–O bond using high energy UV light to form amidyl radical **12**. Addition of **12** to the internal olefin in a *5-exo-trig* manner enables the formation of carbon-centred radical **13**. Propagation of the chain with PTOC ester **47** enables the formation of γ-lactam **48** and regenerates amidyl radical **12**.



Scheme 11: Amidyl radical generation via N–O bond cleavage of PTOC esters developed by Esker and Newcomb.[41]

The key disadvantages of the early methods for generating amidyl radicals highlighted in this section consist of harsh conditions owing to the requirement of stoichiometric amounts of oxidant and high energy UV light, leading to a limited synthetic utility. Therefore, there is a need for milder conditions to generate amidyl radicals to form C–N bonds with good synthetic utility, and photoredox catalysis has emerged as a solution to this need.[18,42]

Photoredox Catalysis

Photoredox catalysis has evolved to become a valuable method of photochemistry within organic chemistry, because of its ability to carry out novel chemistry under milder conditions. [43–47] Figure 3 illustrates the variety of key inorganic iridium and ruthenium based photocatalysts such as **49**, **50** and **51**, in addition to organic based 4CzIPN (**52**).

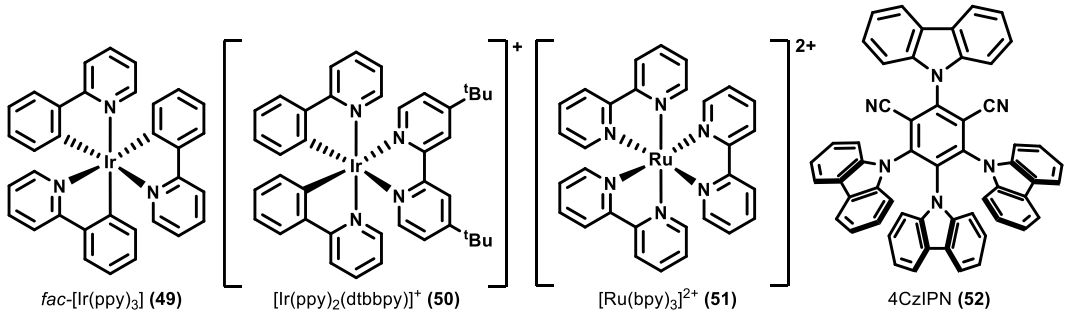
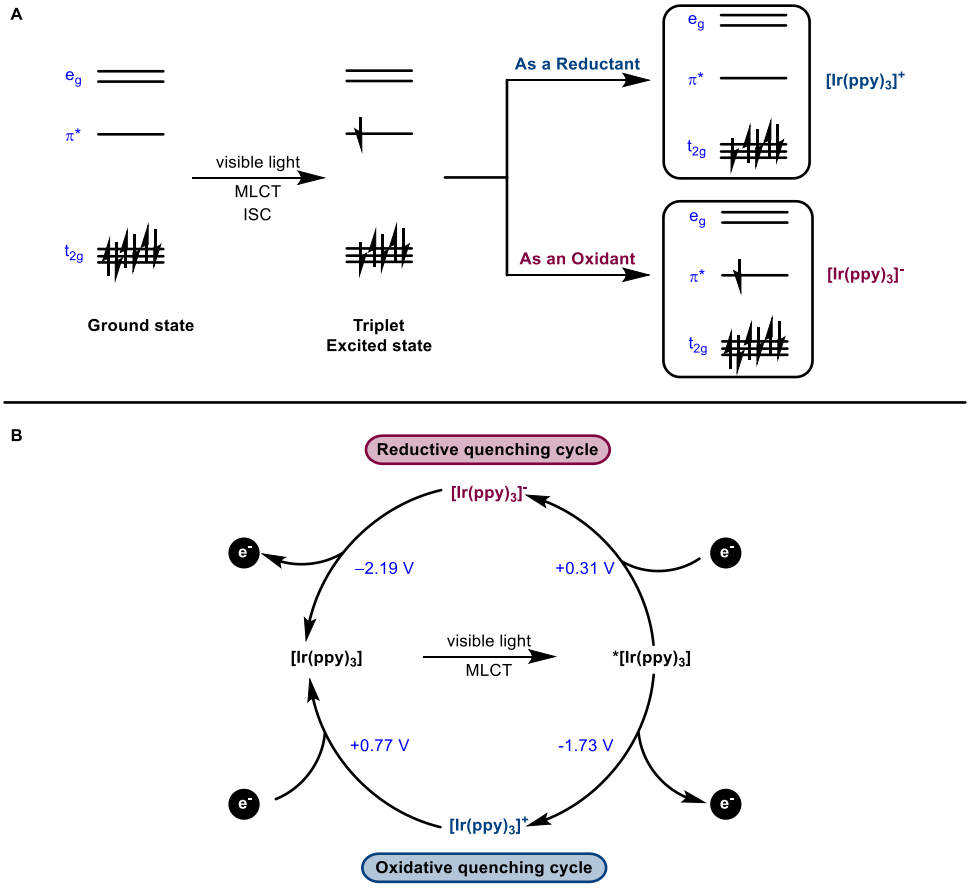


Figure 3: Typical photocatalysts used in photoredox catalysis

The mechanism of these photocatalysts follows a general pattern: a photocatalyst such as $Ir(ppy)_3$ (**49**) absorbs light of a specific wavelength, and photoexcitation of the ground state [$Ir(ppy)_3$] catalyst leads to a metal-to-ligand charge transfer (MLCT) from the highest occupied molecular orbital (HOMO) t_{2g} to the lowest unoccupied molecular orbital (LUMO) π^* anti-bonding orbital. Subsequent intersystem crossing (ISC) results in the formation of a triplet excited state [$Ir(ppy)_3$]* with a long lifetime (1.9 μs).[44] This long lifetime enables the excited state photocatalyst to carry out single electron transfer (SET) processes, either as a reductant or as an oxidant,[44] enabling novel chemical transformations to occur, as shown in scheme 12A. Following this SET, regeneration of the ground state photocatalyst is achieved *via* a reductive quenching or oxidative quenching cycle (scheme 12B).



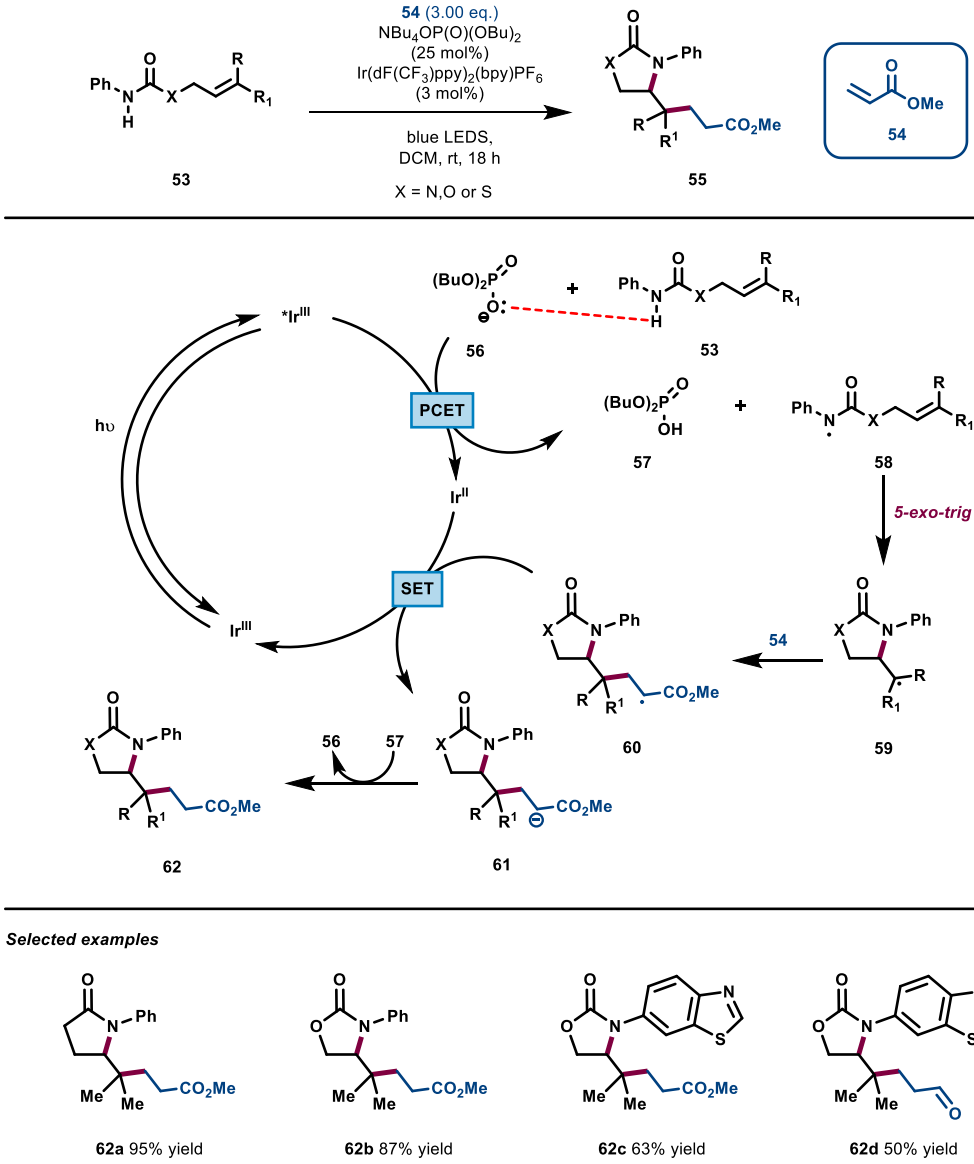
Scheme 12[48,49]: (A) Orbital diagram depicting general photoredox catalysis mechanism (B) Quenching cycles

The ability for photoexcitation to occur with mild low energy visible light is as a result of the presence of a ligand-centred π* orbital (LUMO) in the photocatalyst, which is of lower energy than the e_g molecular orbital. Thus, a lower wavelength of light would be required to promote an electron to the LUMO. This property, in addition to the long lifetime of the triplet excited state photocatalyst, collectively enables reactions to be conducted using milder conditions utilizing lower energy visible light compared to higher energy UV light.

This section will highlight notable and recent advances in amidyl radical generation using photoredox catalysis. For a more comprehensive overview of this area, see recent reviews by Zard,[19] Walton,[50] Chen,[51] Xiong,[24] Roizen[18] and Murphy.[25]

Oxidative Generation of Amidyl Radicals

The use of reductive quenching in photoredox-mediated amidyl radical generation has been widely explored.[18,19,25] A seminal paper in this field reporting amidyl radical generation was published by Knowles *et al.* (scheme 13).[52] This pioneering approach applied a proton-coupled-electron transfer (PCET), which is the concerted transfer of an electron and proton from the same source to a Brønsted-base and one-electron oxidant respectively leading to a lowering of the energy required.[52,53] Notably, it also involved the formal hydrogen abstraction of a secondary amide to generate amidyl radicals; an approach which previously required strong stochiometric oxidants and high temperatures as a result of the high N–H bond strength of amides (BDE = 107 kcal mol^{-1}).[2] This process begins with the formation of a hydrogen bonded complex between phosphate base **56** and amide **53**. A PCET event enables the formation of amidyl radical **58**, which undergoes a *5-exo-trig* cyclisation to form cyclic radical intermediate **59**. Radical addition to methyl acrylate (**54**) enables the formation of carbon-centred radical **60**, which is reduced *via* SET to form anion intermediate **61**, which can be protonated to form carboamination product **62**. In addition to forming buyrolactam **62a** in 95% yield, Knowles was able to extend this protocol to carbamidyl derived oxazolidinone products **62b**, **62c** and **62d** in moderate to good yields. This PCET approach has been further developed by Knowles,[53–57] Moon,[58] Tu[59] and Bhargava Reddy[60].

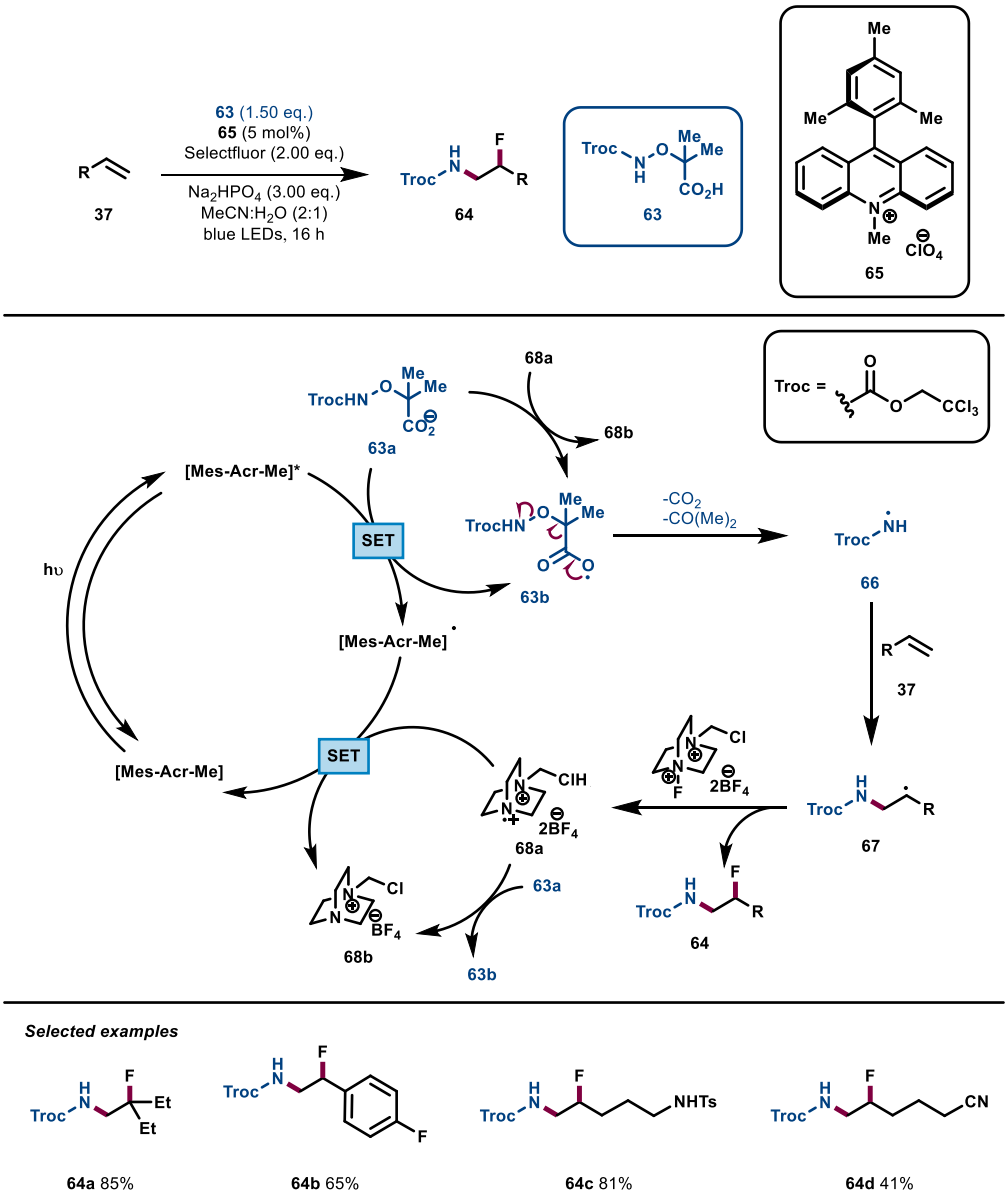


Scheme 13: Seminal example of the photoredox-mediated oxidative generation of amidyl radicals by Knowles.[52]

Another key example of the oxidative generation of amidyl radicals is described by Jiang and Studer in their amidofluorination of unactivated alkenes using amino-oxy-acids **63** as amidyl radical precursors (scheme 14).[61] This reaction proceeds *via* the oxidation of carboxylate **63a** by SET using the excited state photocatalyst [Mes-Acr-Me]* to form radical **63b**. Fragmentation of radical **63b** affords amidyl radical **66**, which upon addition to olefin **37** yields carbon-centred radical intermediate **67**. Sequential F-atom transfer from Selectfluor delivers amidofluorinated product **64** and amidyl radical cation **68a** as the by-product. The catalytic cycle is closed through SET reduction of radical cation **68a** by [Mes-Acr-Me] to provide **68b** and regenerate the ground state photocatalyst **65**.

In parallel to this, an alternative pathway investigated by Studer indicates that the radical cation **68a** may also react with carboxylate **63a** in a chain propagation step to provide by-product **68b** and intermediate **63b**, which could fragment to regenerate amidyl radical **66**.[61]

It is noteworthy that Studer attained good yields using electron-rich and electron-poor substrates to form products **64a** and **64b** respectively. The protocol was also tolerant of substrates containing protected amines, enabling the formation of product **64c** in 81% yield. However, the presence of a nitrile group had a detrimental effect on the yield, providing carbamate **64d** in a 41% yield.

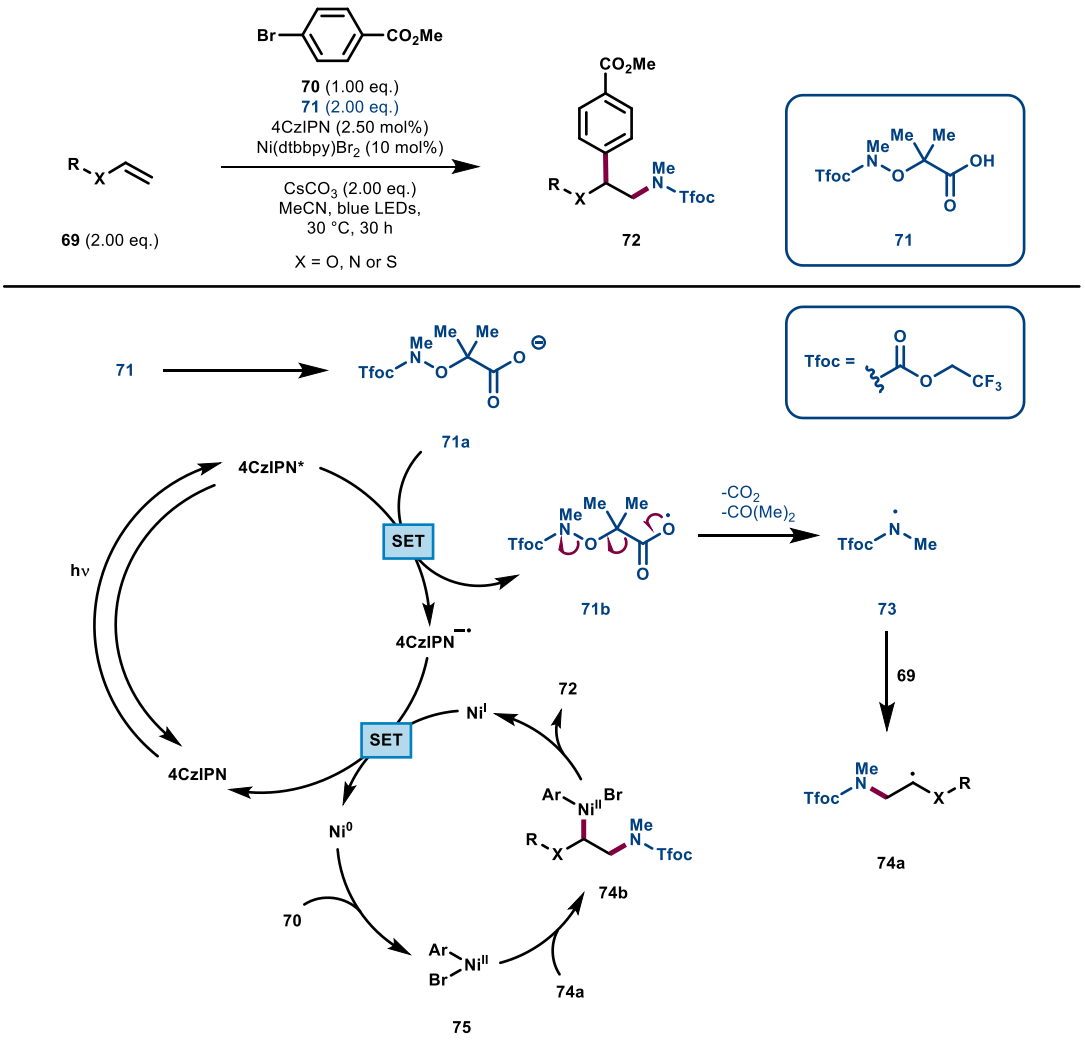


Scheme 14: Recent example of oxidative generation of amidyl radicals reported by Jiang and Studer.[61]

More recent developments have focussed on using metallophotoredox catalysis, or dual photoredox catalysis.[48,62–72] This approach typically involves the collaborative use of a photocatalyst and a transition metal co-catalyst.[73–76]

A key development in this area using reductive quenching was highlighted by Studer *et al.*[77] in the aminoarylation of alkenes using a dual photoredox and nickel catalysis-based method (scheme 15). This transformation begins with the formation of carboxylate **71a** from the deprotonation of **71**. A SET from excited state 4CzIPN* to anion **71a** forms $4CzIPN^{-\bullet}$ and radical **71b**, that upon fragmentation affords carbamidyl radical **73**. Addition of carbamidyl radical **73** to olefin **69** yields carbon-centred radical **74a**. Oxidative insertion of Ni^0 into aryl bromide **70** generates Ni^{II} species **75**, which is trapped by radical **74a** to produce **74b**. Reductive elimination of nickel species **74b** provides aminoarylation product **72** and Ni^I, which can undergo a subsequent SET to regenerate ground state 4CzIPN and Ni^0.

Studer found that this protocol was tolerant of aliphatic ethers, providing products **72a** and **72b** in 87% and 81% yields respectively, however the use of an aromatic ether had a negative effect on yield affording **72c** in 65% yield. The presence of nitrogen and sulfur heteroatoms was also tolerated, providing products **72e** and **72f** in 67% and 53% yields respectively.

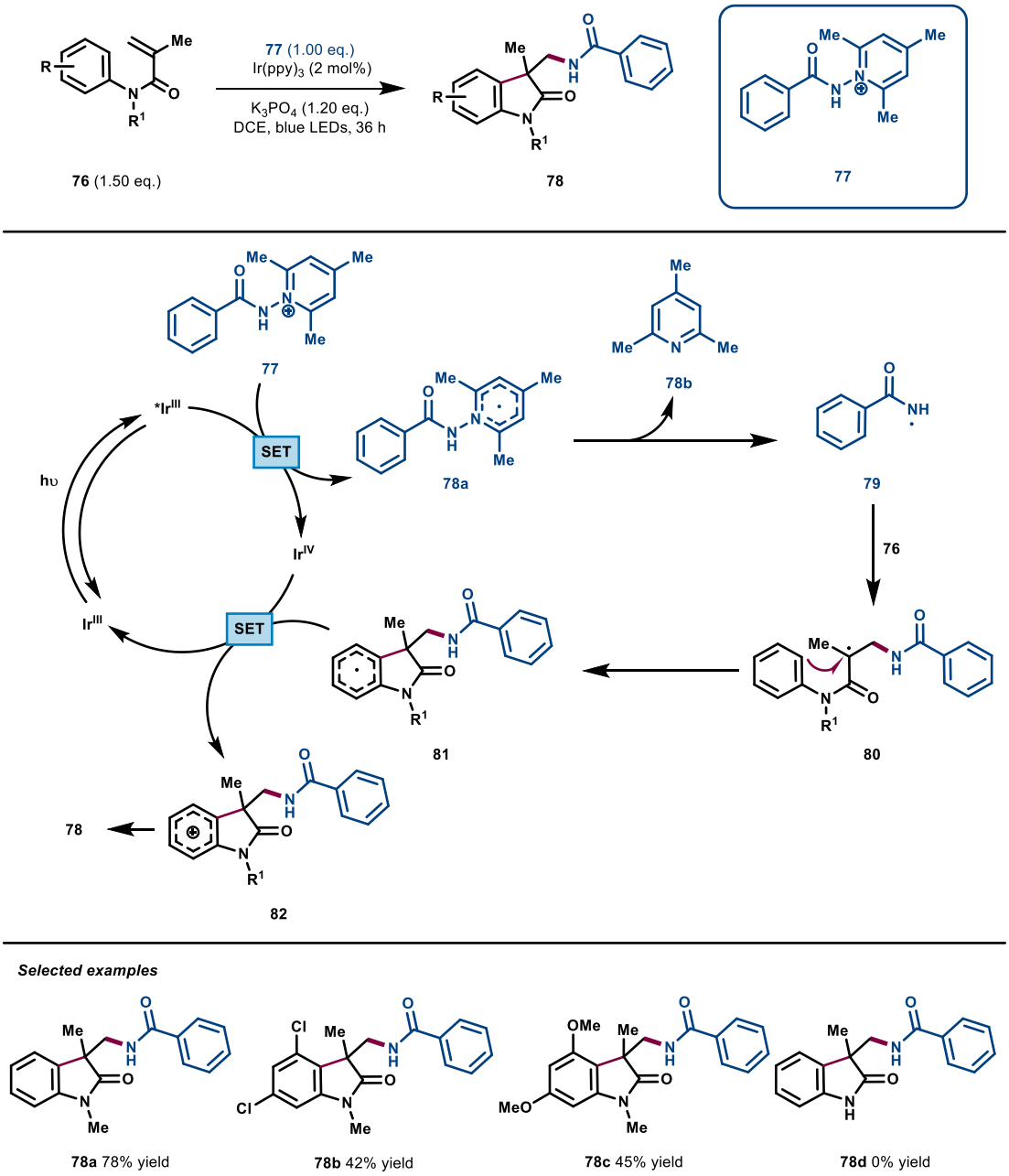


Scheme 15: Oxidative generation of amidyl radicals using dual photoredox catalysis developed by Studer et al.[77]

Reductive Generation of Amidyl Radicals

The reductive generation of amidyl radicals was pioneered by Studer using *N*-aminopyridinium salts as amidyl radical precursors.[78] Further advancement of the use of *N*-aminopyridinium salts as amidyl radical precursors was reported by Yu *et al.* towards the synthesis of aminated oxindoles (scheme 16).[79] Yu's protocol proceeded by the photoexcitation of ground state Ir^{III} to $*Ir^{III}$. Following this, a subsequent SET from this excited state iridium species to *N*-aminopyridinium salt **77** evolved Ir^{IV} and carbon-centred radical **78a**, which could fragment to yield pyridine derivative **78b** and amidyl radical **79**. Addition of amidyl radical **79** to alkene **76** afforded carbon-centred radical **80**. Cyclization of **80** provided radical adduct **81**. A second SET from adduct **81** to Ir^{IV} regenerated the ground state Ir^{III} species and produced cationic intermediate **82**, which enabled the formation of amidated oxindole product **78**.

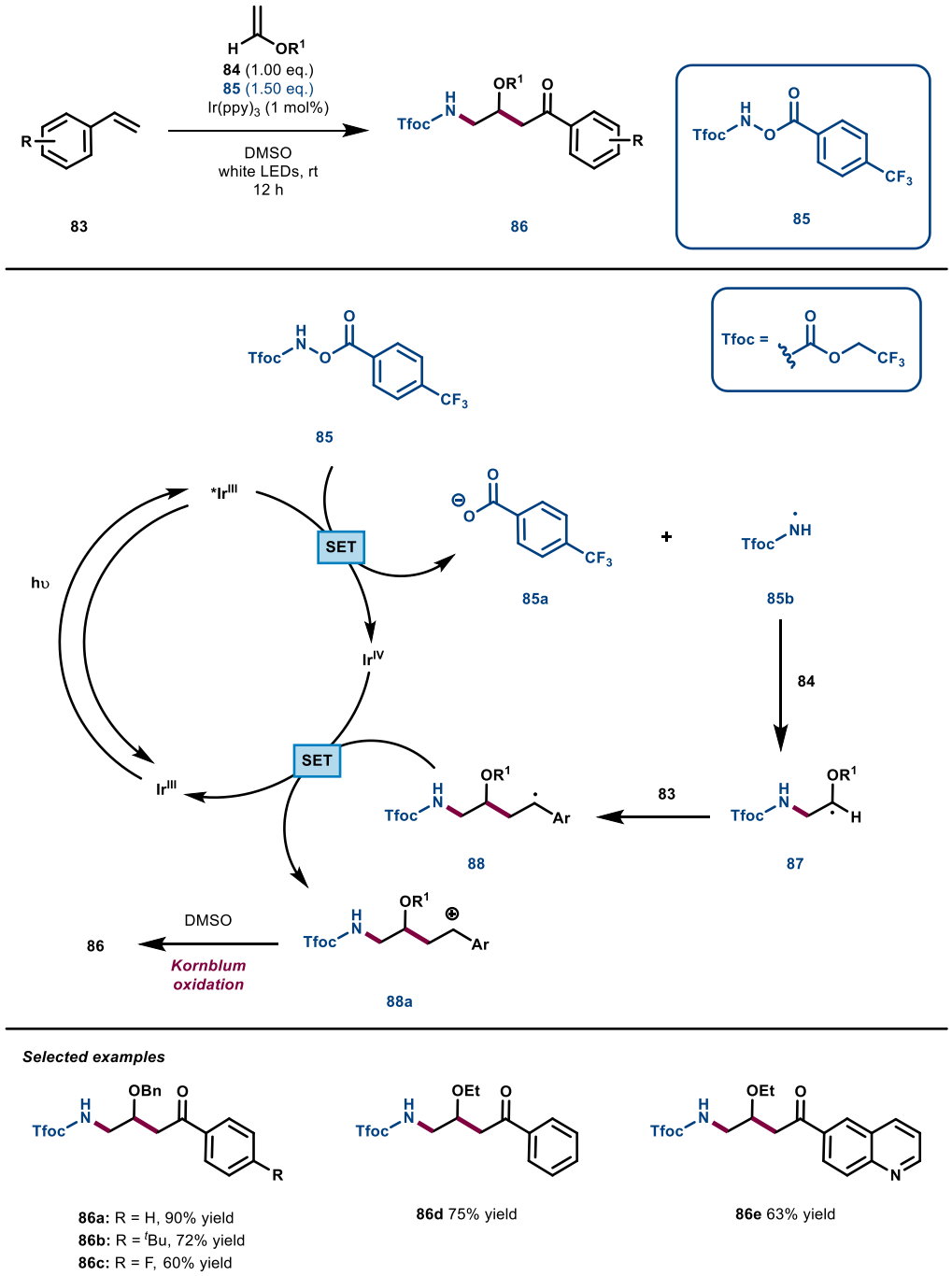
Interestingly, although the use of unsubstituted substrates provides the corresponding product **78a** in a moderate yield, the presence of electron-donating groups and electron-withdrawing groups on the aryl ring have a negative effect on yield providing oxindoles **78b** and **78c** in 42% and 45% yields respectively. Akin to Studer's protocol, Yu also observed detrimental effects on yield when using unsubstituted nitrogen atoms with no oxindole **78d** isolated.



Scheme 16: Recent example of the use of N-aminopyridinium salts as radical precursors for the reductive generation of amidyl radicals reported by Yu et al.[79]

Further developments by Yu in this area were made towards the synthesis of β-amino alcohols (scheme 17).[80] This methodology proceeds *via* homolytic N-O bond cleavage to form amidyl radical **85b** from carbamate **85.** Radical addition of **85b** to enol ether **84** enables the formation of radical adduct **87**. Succeeding addition of adduct **87** to styrene **83** affords intermediate **88**, which can be oxidised by photocatalytic SET to cationic intermediate **88a** and undergo subsequent Kornblum oxidation using DMSO to yield product **86**.

The selectivity of this reaction is driven by the polarity of the radical species generated, as the electrophilic amidyl radical **85b** will have a higher propensity to react with the most electron-rich substrate first, which is enol ether **84**.

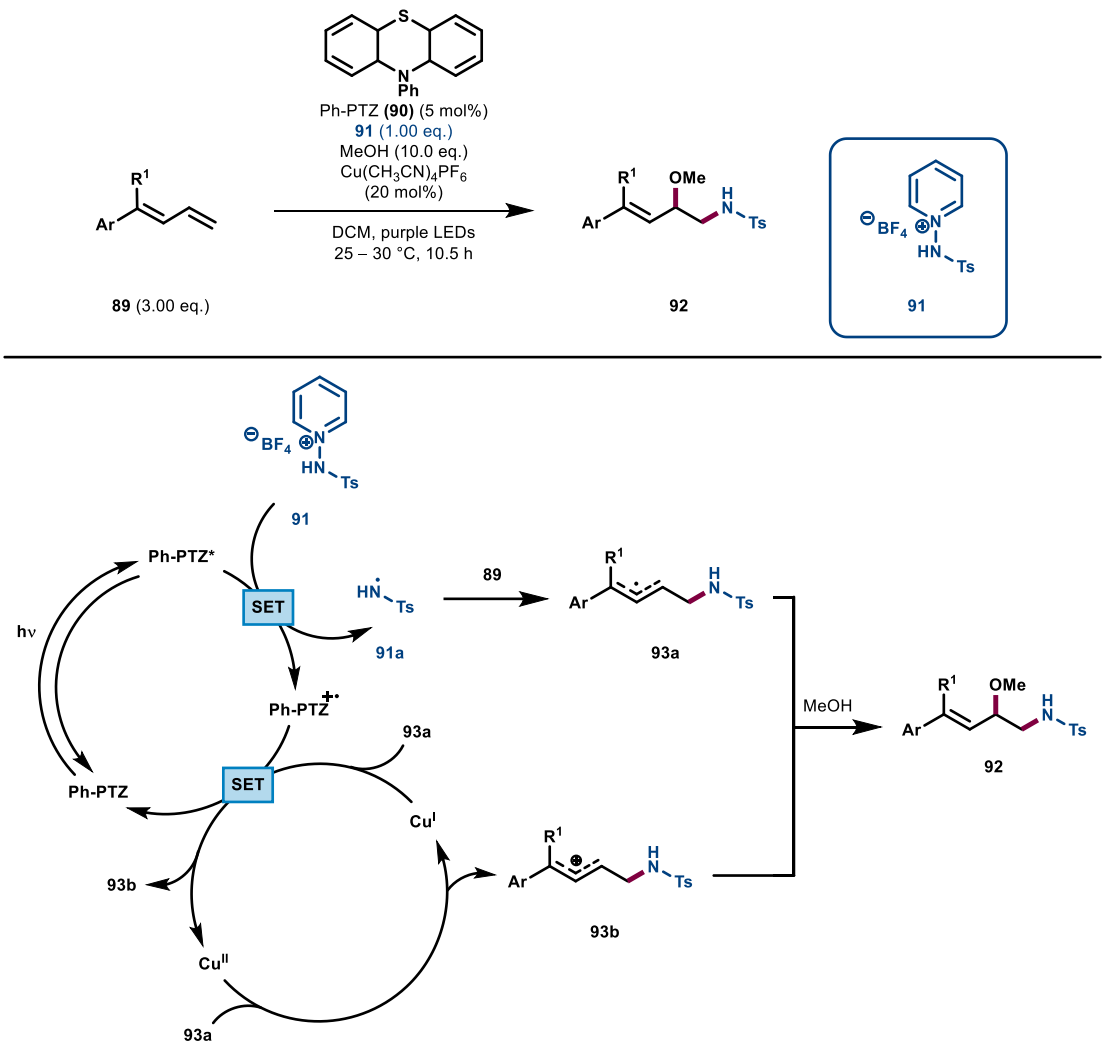


Scheme 17: Recent example of the reductive generation of amidyl radicals using carbamates precursors developed by Yu and coworkers.[80]

Recent developments in the use of reductive generation of amidyl radicals utilizes dual photoredox catalysis.[43,49] This is highlighted by methodology from Chen and coworkers towards the 1,2-aminoalkoxylation of 1-aryl-1,3-dienes (scheme 18).[81]

Proceeding with the photoexcitation of Ph-PTZ photocatalyst to Ph-PTZ*, and a subsequent SET to *N*-aminopyridinium salt **91** enabling the formation of amidyl radical **91a**. Addition of radical **91a** to olefin **89** leads to the formation of stabilised radical adduct **93a** which can react with methanol to provide the product **92**. Similarly, a SET from Ph-PTZ$^{\bullet+}$ to Cu^{I} can regenerate the ground state photocatalyst and Cu^{II}, which could oxidise **93a** to form cationic intermediate **93b** and recover the Cu^{I} catalyst. Cationic intermediate **93b** can also undergo nucleophilic addition by methanol to afford the product **92**.

Chen was able to attain moderate yields with unsubstituted arene (**92a**) and substituted arenes bearing electron-donating groups (**92b**) and electron-withdrawing groups (**92c**). This was similar when a substituted olefin was utilized, leading to the corresponding product **92d** in a 50% yield. This methodology was also able to be extended to heteroaromatics to form substituted thiophene **92e** in a comparable yield. Interestingly, utilizing sterically demanding 1,3-disubstituted substrates were also tolerated, generating product **92f** in a 55% yield.

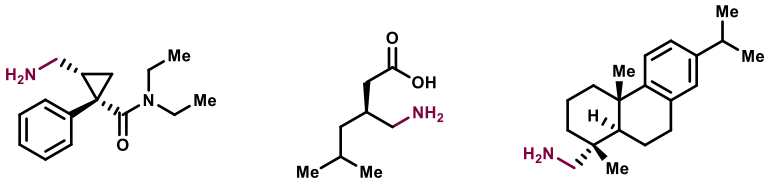


Scheme 18: Reductive generation of amidyl radicals using dual photoredox catalysis developed by Chen et al.[81]

It is noteworthy that alternative methods such as electrochemistry and photomediated charge transfer can be utilized for evolution of amidyl radicals.[82,83] These are outside the scope of these studies, and for a comprehensive overview of this area, see reviews by Knowles[84] and Chen.[85]

Semi-Pinacol Chemistry

As highlighted in the previous section, amidyl radicals can be generated and added into olefins to access a range of aminomethyl bearing compounds. This aminomethyl moiety is of great interest within medicinal chemistry due to its presence in a range of bioactive alkaloids (figure 4).[86] Most of the transformations highlighted in this section focus on the formation of secondary and tertiary carbon centres bearing an aminomethyl group. Although the formation of all-carbon quaternary centres bearing an aminomethyl group has been explored,[87–90] at the outset of this project, a photoredox-mediated variant was unexplored.



Milnacipran (94) Pregbalin (95) Leelamine (96)

Figure 4: Aminomethyl functionality in bioactive compounds

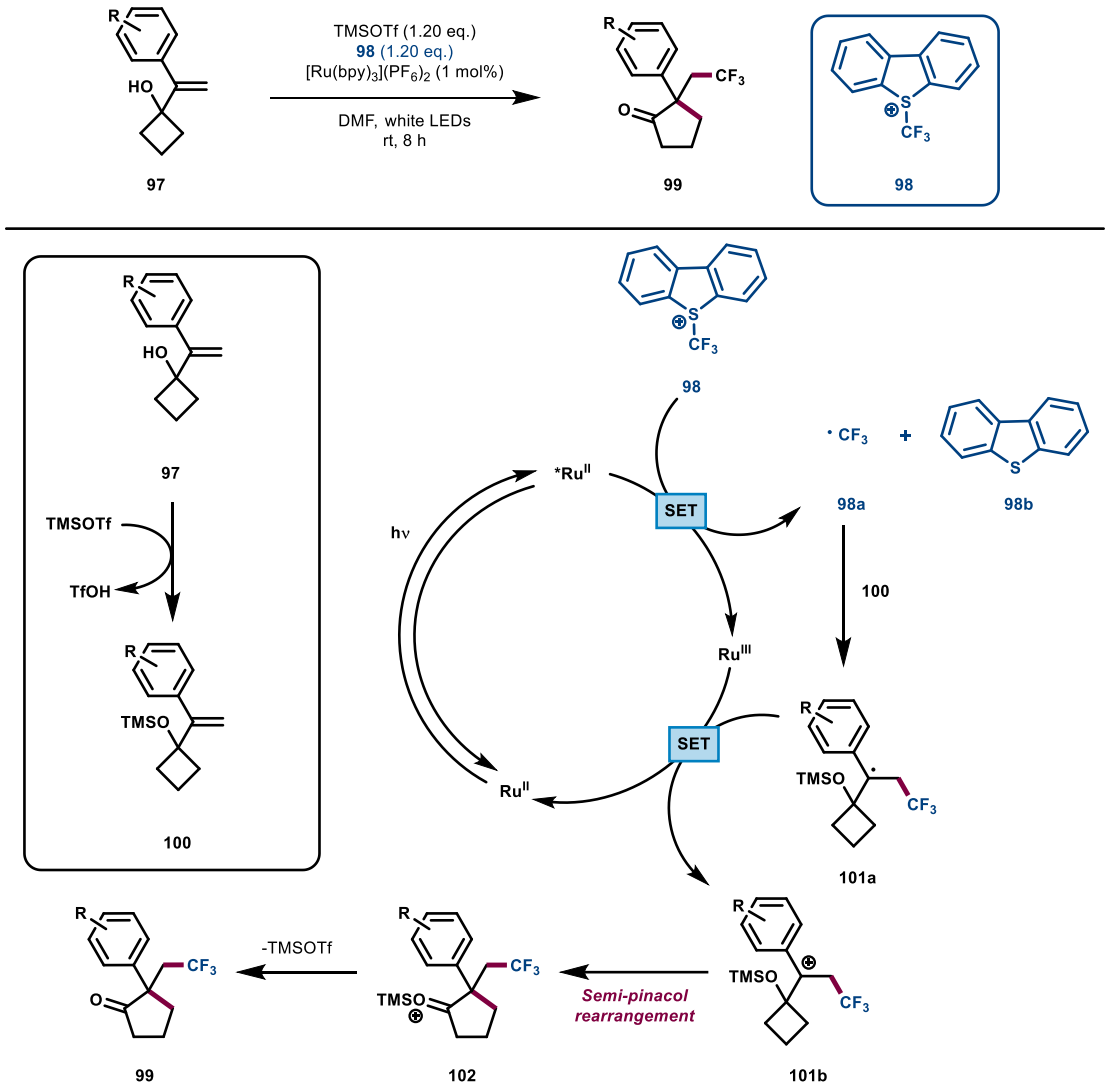
The semi-pinacol rearrangement has been demonstrated as an important strategy for the formation of all-carbon quaternary centres.[91,92] Discovered by Tiffeneau,[93] this rearrangement was used to describe the unique 1,2-migration of the tertiary-secondary alcohol towards the secondary centre as opposed to the tertiary one (scheme 19).[93,94] The key difference between the semi-pinacol rearrangement and pinacol rearrangements, are the leaving group which must be water in the case of pinacol rearrangements, but may be any other group in the case of semi-pinacol rearrangements.



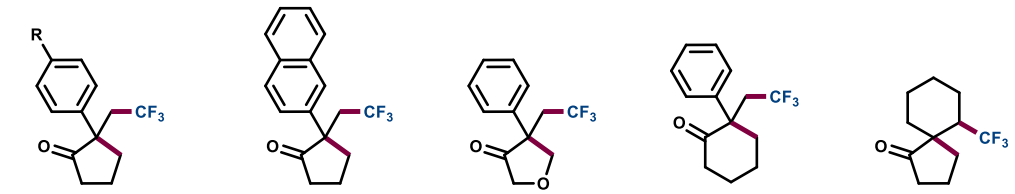
Scheme 19: General Semi-pinacol rearrangement [93]

More recently radicals generated using photoredox catalysis have been utilized to carry out semi-pinacol chemistry.[95,96] A key development in this area was made by Glorius towards trifluoromethylation/semi-pinacol ring expansion methodology using Umemoto's reagent for the formation of trifluoromethylated cycloalkanones with all-carbon quaternary centres (scheme 20).[97] This work was built upon pioneering work by Macmillan and coworkers who first discovered the use of Umemoto's reagent for the trifluoromethylation of arenes.[98] Under visible light irradiation, Ru^{II} is excited to triplet excited state $*Ru^{II}$. A SET from this species to Umemoto's reagent (**98**) affords Ru^{III}, trifluoromethyl radical **98a** and dibenzothiophene (**98b**). Addition of radical **98a** to TMS-protected olefin **100** provides carbon centred radical adduct **101a**, which can undergo a secondary SET to Ru^{III} to regenerate ground state photocatalyst Ru^{II} and cationic intermediate **101b**. A subsequent semi-pinacol ring expansion and subsequent removal of the TMS-protecting group yields product **99**.

Glorius found that this protocol was tolerant of simple aryl systems, affording **99a** in a good yield, in addition to electron-rich and electron-deficient aryl groups providing **99b** and **99c** in good to excellent yields. Furthermore, the extended aromatic systems were also compatible, providing product **99d** in a good yield. Interestingly, the presence of a heteroatom in the expanding ring (**99e**), and formation of a 6-membered ring (**99f**) were also tolerated, however in poor yields. Substrates which did not have an olefin in conjugation with an aryl ring were not compatible with this protocol, with no formation of product **99g** observed.



Selected examples



99a: R = H, 74% yield
99b: R = OMe, 90% yield
99c: R = Cl, 60% yield

99d 80% yield

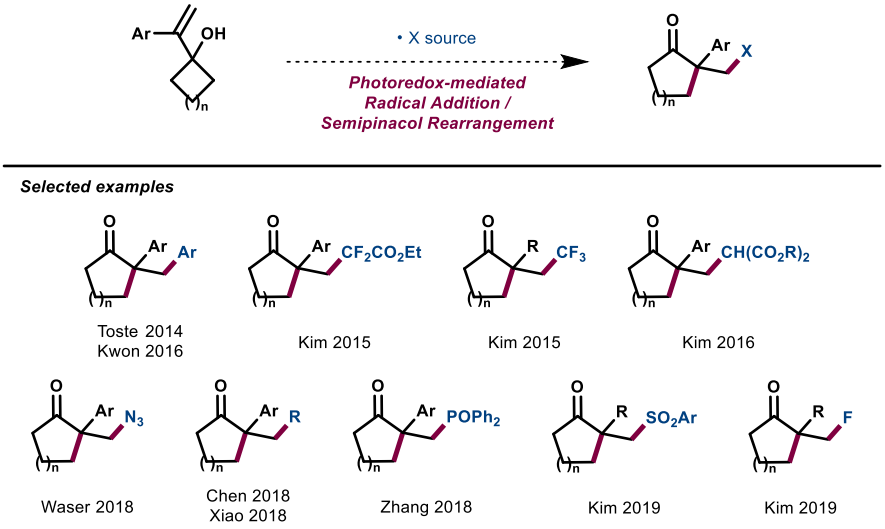
99e 27% yield

99f 33% yield

99g 0% yield

Scheme 20: Example of Semi-pinacol chemistry used in photoredox catalysis reported by Glorius et al.[97]

Since this initial report, other groups have used this tandem radical addition / semipinacol rearrangement strategy towards the construction of all-carbon quarternary centres using mild conditions (scheme 21),[99–110] however at the outset of this project, a photoredox-mediated semipinacol method initiated by a nitrogen centred amidyl radical had not been reported.

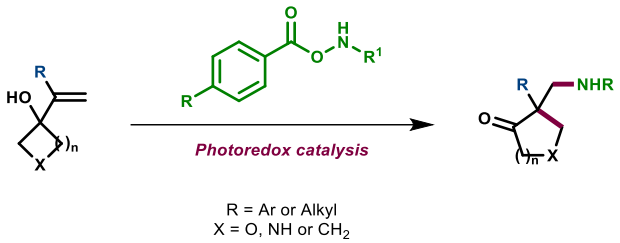


Scheme 21: Key examples utilizing semi-pinacol chemistry for the formation of all-carbon quaternary centres.[99–110]

Aims and Objectives

As summarised, the generation of amidyl radicals using mild photoredox conditions has been well explored, and the semi-pinacol rearrangement provides an important strategy for the formation of all-carbon quaternary centres. However, at the outset of our studies, the use of photoredox-mediated amidation-induced semi-pinacol rearrangements had not been reported.

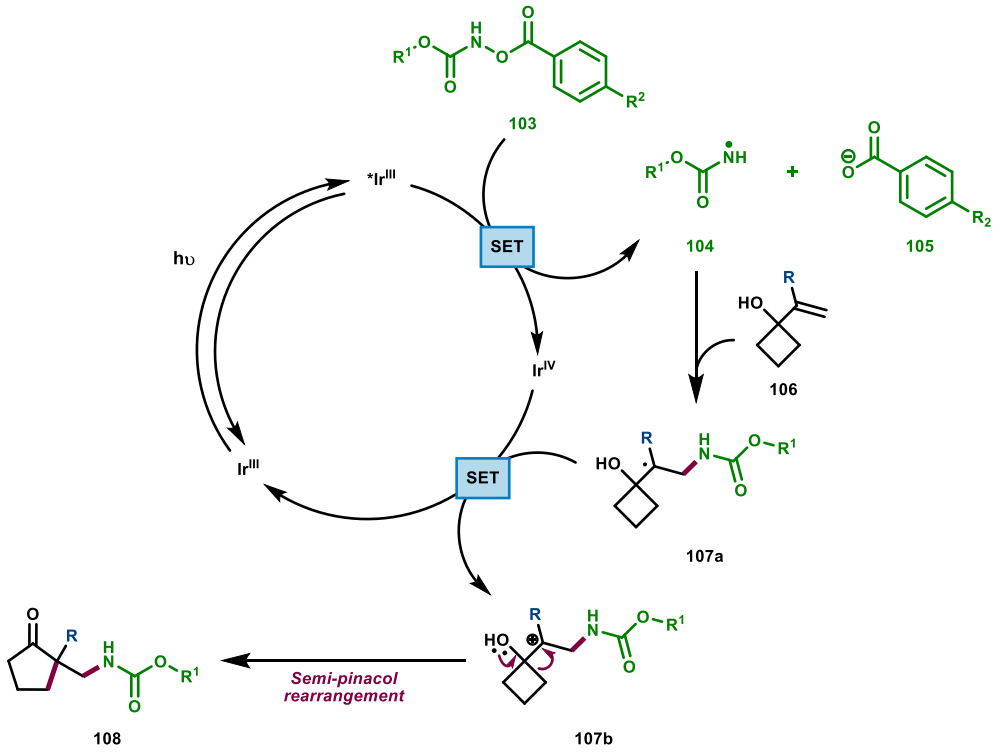
Our aim was also to demonstrate a one-pot photoredox-mediated amidation/semi-pinacol rearrangement to enable the formation of aminomethyl-substituted all-carbon quaternary centres (scheme 22). We envisaged this process to be carried out by a reductively generated amidyl radical. Importantly, we aspired to design our methodology to generate sp^3-rich amine derivatives from both activated and unactivated alkene systems to broaden its synthetic utility.



Scheme 22: Reaction principle

Proposed Mechanism

Based on literature precedent,[97] the proposed mechanism is shown in scheme 23. Under visible light irradiation, the ground state photocatalyst $[Ir^{3+}(ppy)_3]$ is excited to $*[Ir^{3+}(ppy)_3]$. An SET from $*[Ir^{3+}(ppy)_3]$ to amidyl radical precursor **103** would generate $[Ir^{4+}(ppy)_3]$, carboxylate **105** and amidyl radical **104**. Addition of amidyl radical **104** to olefin **106** would give the carbon centered radical **107a**. Subsequent SET from carbon-centered radical **107a** to $[Ir^{4+}(ppy)_3]$ would regenerate the ground state photocatalyst $[Ir^{3+}(ppy)_3]$ and yield cationic intermediate **107b**, which would undergo a semi-pinacol ring expansion *via* 1,2 – carbon shift to deliver β-aminoketone **108**.

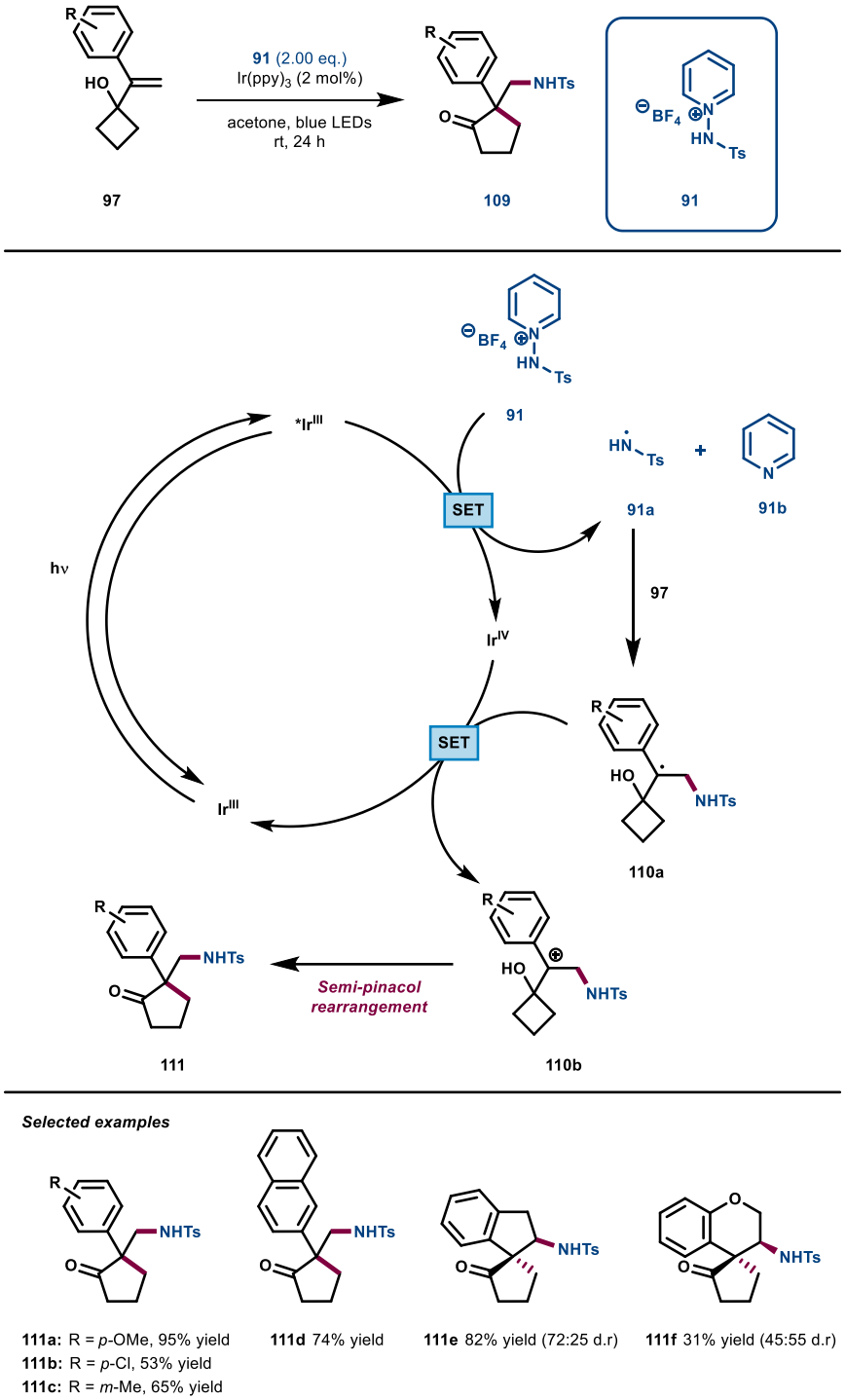


Scheme 23: Proposed mechanism for the radical amination semi-pinacol sequence

During the course of our studies, Shi and coworkers developed the use of the semipinacol rearrangement with amidyl radicals (scheme 24),[111] utilizing a similar mechanism to our work.

Shi found this protocol was able to provide excellent yields using electron-rich arenes such as **111a**, however the use of electron-poor arenes such as **111b** only attained a poor yield. A comparable yield was also attained when a *meta*-substituted arene such as **111c** was used, which may suggest that steric as well as electronic impacts of the substrate be a factor in this mechanism.

Interestingly, Shi extended the scope of this protocol to extended aromatic systems and β-amino (spiro)cyclic ketones and was able to attain products **111d** and **111e** in good yields. however poor diastereoselectivity was observed for the latter. Similar poor diastereoselectivity was also observed when a heteroatom was present in the expanding ring (**111f**). It is noteworthy that since this report, an electrochemical variant has also been reported.[112]

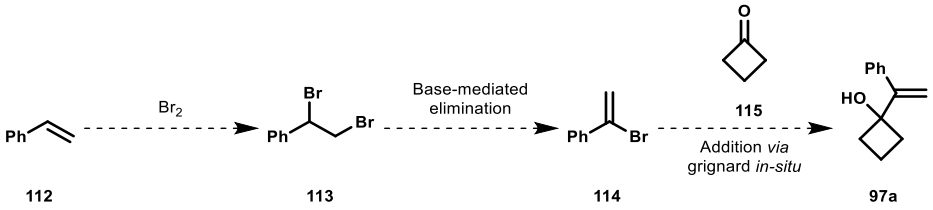


Scheme 24: Amidyl radical formation using photoredox-mediated Semi-pinacol rearrangements reported by Shi et al.[111]

Photoredox Mediated Ring Expansions for the Synthesis of sp^3-rich Amine Derivatives

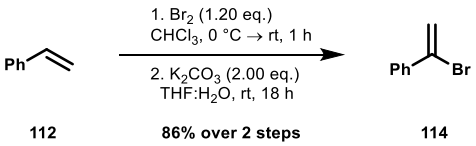
Synthesis of Model Substrate for Optimisation

The synthesis of the substrate **97a** was initially carried out in 3 steps involving the formation of the α-bromostyrene (**114**), which could be converted into a Grignard *in-situ* to add into cyclobutanone (**115**) (scheme 25).



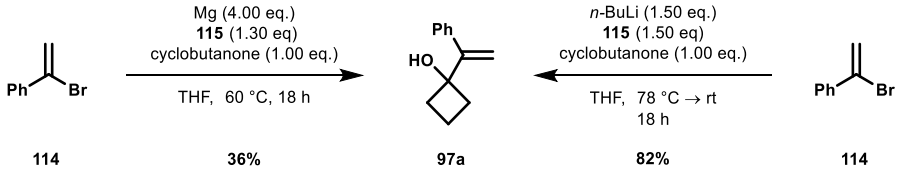
*Scheme 25: Synthetic route towards model substrate **97a***

Formation of vinyl bromide **114** proceeded *via* a bromination of styrene (**112**) and subsequent base-catalysed elimination reported by Cain *et al.*[113] to give bromide **114** in an excellent yield over 2 steps (scheme 26).



*Scheme 26: Formation of styrene derivative **114** reported by Cain et al.*[113]

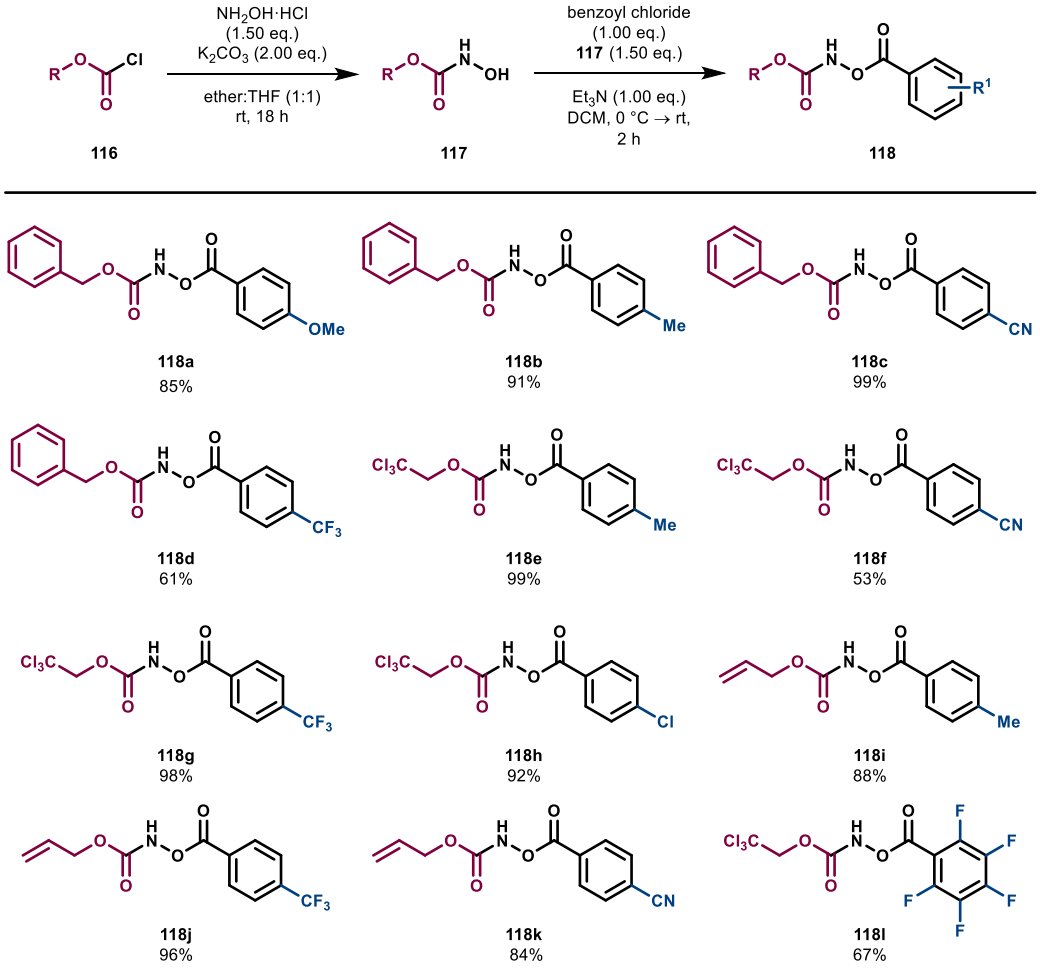
The final step in the formation of substrate **97a** involved the addition of vinyl bromide **114** into cyclobutanone (**115**) (scheme 27). However, initial attempts utilizing a Grignard approach led to a poor yield.[114] This was most likely due to the poor activation of magnesium to form the Grignard reagent *in-situ*. An alternative approach using a lithium-halogen exchange was employed,[115] which afforded a higher yield (82%). This approach was then scaled up using commercially available α-bromostyrene (**114**), which enabled a large quantity of alcohol **97a** (1.43 g) to be rapidly synthesised in a single step using the lithium-halogen exchange approach (scheme 27).



*Scheme 27: Synthesis of olefin **97a** using a Grignard approach*[114] *and lithium-halogen exchange approach*[115]

Amidyl radical precursor synthesis

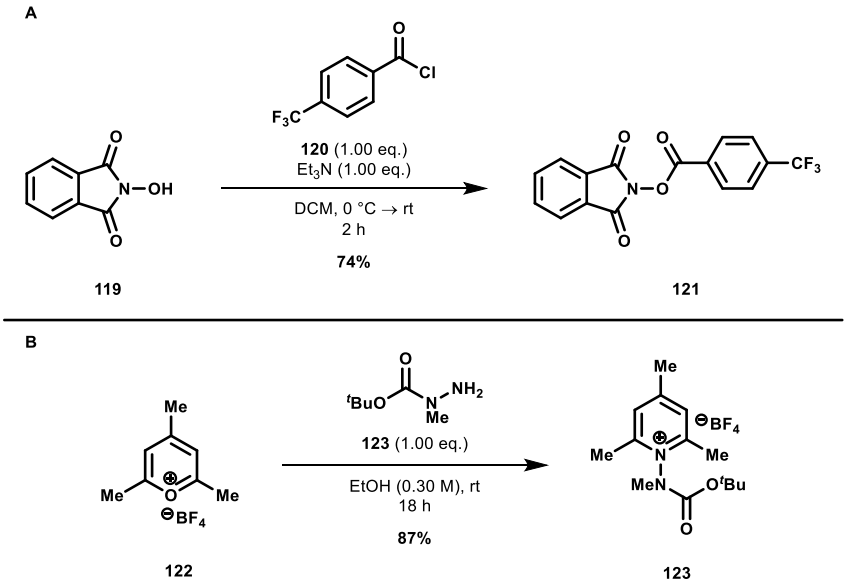
In order to reductively generate amidyl radicals, we proposed to synthesise a range of hydroxylamine based amidyl radical precursors which were precedented in the literature.[18] Typically, carbamate amidyl radical precursors were synthesised in two steps, [116] beginning with the formation of the hydroxycarbamate **117**, which could then be reacted with a benzoyl chloride to form the product precursors **118** (scheme 28). A range of precursors (**118a** – **118l**) were prepared in moderate to excellent yields with a range of protecting groups on the nitrogen atom, and varying functionality on the aryl ring. This was done to manipulate the electron density of the N–O bond and enable its cleavage to generate the amidyl radical.



Scheme 28: Synthesis of amidyl radical precursors; yields quoted are over 2 steps

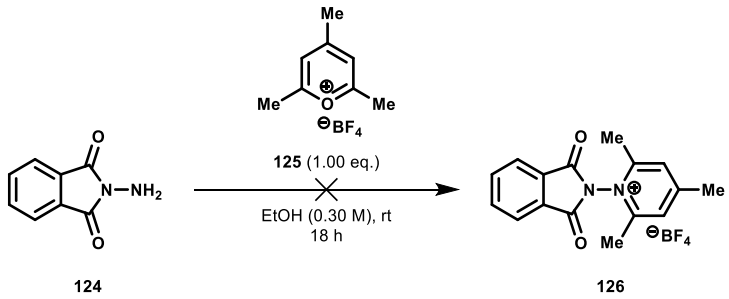
Alternative amidyl radical precursor synthesis

Using methodology developed by Studer[78] and Sanford,[117] phthalimide and *N*-aminopyridinium salt NCR precursors were also prepared using single step procedures from *N*-hydroxyphthalimide (**119**) (scheme 29A) and trimethylpyrylium tetrafluoroborate (**122**) (scheme 29B) in good yields. These alternative amidyl radicals were selected as they have been well reported in the literature,[78,117] and would enable a sufficiently thorough screen of NCRs to be undertaken.



*Scheme 29: (A) Synthesis of phthalimide **121**[78] (B) Synthesis of N-aminopyridinium salt **123**[117]*

As a result of their use as precursors for NCRs,[18,118] attempts were made to synthesise a phthalimide pyridinium salt **126**. However, this was found to be unsuccessful, and unreacted *N*-aminophthalimide (**124**) and pyrylium **125** were recovered at the end of the reaction.

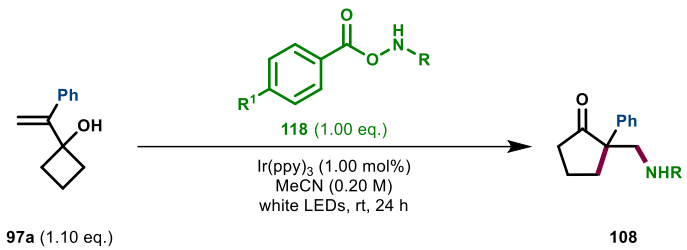


Scheme 30: Attempted formation of phthalimide derived pyridinium NCR precursor

Reaction Optimisation

Using conditions reported by Yu *et al.*[119] as a starting point, initial experiments were carried out using hydroxylamine based amidyl radical precursors **118a** – **118k**. All optimisation experiments were carried out on a 0.2 mmol scale with respect to olefin **97a** using a Hepatochem EvoluChem PhotoRedOx Box™. 1,3-Benzodioxole was identified as an internal standard for ^{1}H NMR spectroscopy as it had distinct peaks (6.81ppm and 5.90 ppm) which were distant from the diagnostic peaks of the expected product (~3.50 ppm).

Pleasingly, using troc protected precursor **118g** provided a 38% ^{1}H NMR yield in the first instance (table 1, entry 1). Changing the protecting group on the nitrogen atom to a Cbz or Alloc group had a detrimental effect on conversion (table 1, entries 2–3). A range of 'electron-neutral' and electron-rich moieties at the R^1 position were also tested (table 1, entry 4–7), and similarly no product was observed in these cases. It is also noteworthy that in these cases, only the corresponding amidyl radical precursors were recovered at the end of the reaction. Interestingly, no product was observed when using a different electron-withdrawing group at the R^1 position (table 1, entry 7–10).



Entry	R	R^1	Yield/ %	Unreacted 97a/ %
1	Troc	CF_3	38	9
2	Cbz	CF_3	0	54
3	Alloc	CF_3	0	0
4	Cbz	Me	0	0
5	Troc	Me	0	0
6	Alloc	Me	0	0
7	Cbz	OMe	0	0
8	Cbz	CN	0	0
9	Troc	CN	0	0
10	Troc	Cl	0	0

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard

Table 1: Hydroxylamine-based amidyl radical precursors screen

To rationalise these data, further analysis of precursors **118e**, **118f** and **118g** was carried out using cyclic voltammetry (figure 5). This indicated that *p*-CF_3 substituted precursor **118g** had a reduction potential (–1.70 V vs. SCE) within the range of the reduction potential of Ir(ppy)$_3$ [$E_{1/2}(*Ir^{III}/Ir^{IV})$ = −1.73 V vs. SCE],[2] whereas *p*-Me substituted precursor **118e** and *p*-CN substituted precursor **118f** fell outside this range. This also rationalises the recovery of only amidyl radical precursor in these cases and established a hypothesised requirement for an electron withdrawing CF_3 functionality on the aryl ring.

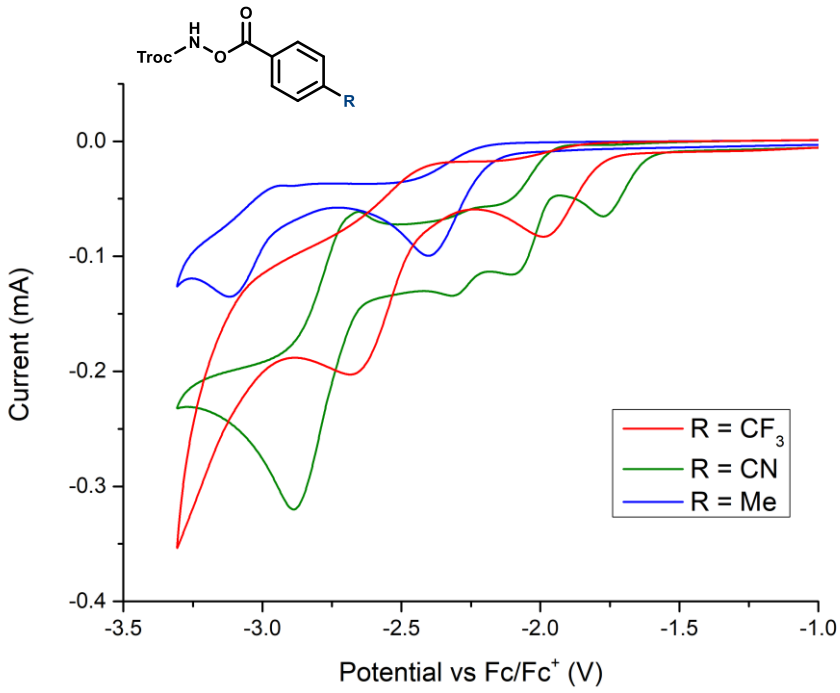
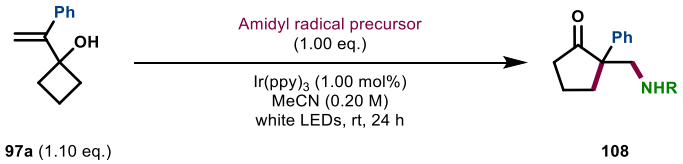


*Figure 5: Cyclic voltammograms of amidyl radical precursors **118e** – **118g** bearing different aryl substituents. A standard three electrode cell was utilized with a glassy carbon working electrode, a platinum counter-electrode, and a silver/silver nitrate non-aqueous reference electrode. A solution of hydroxylamine derivatives **118e** – **118g** (5.00 mM) and $TBAPF_6$ (0.10 M) in MeCN was degassed with Ar prior to any measurements taken.*

Alternative amidyl radical precursors **118l**, **121** and **123** were also screened (table 2), and a 20% yield was attained when using pentafluoro-substituted precursor **118l** (entry 1, table 2), however the use of phthalimide **121** and *N*-aminopyridinium **123** led to no product observed (entry 2 and 3, table 2). In these instances, ^{1}H NMR spectroscopy and thin-layer chromatography (TLC) indicated a complex mixture of products were present in the reaction mixture.



Entry	Amidyl radical precursor	Yield/ %	Unreacted 97a/ %
1	**118l**	20	52
2	**121**	0	47
3	**123**	0	44

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard

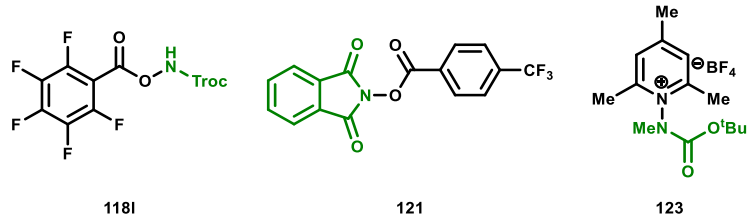
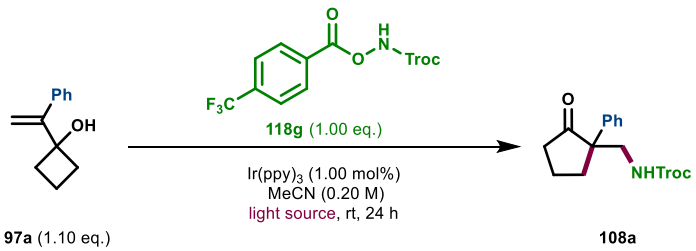


Table 2: Alternative amidyl radical precursor screen

Having established the feasibility of the desired process, certain reaction parameters were investigated with the aim of increasing the yield. Initially, light source was examined (table 3), and due to their use in the literature,[2,120] blue LEDs were investigated as an alternative to white LEDs. Pleasingly the reaction was found to be more efficient when irradiating with blue LEDs, providing an increased yield of 50% (entry 2, table 3).

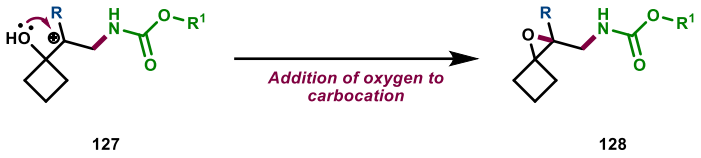


Entry	Light Source	Yield/ %	Unreacted 97a/ %
1	30 W white LED	38	15
2	30 W blue LED	50	9

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard

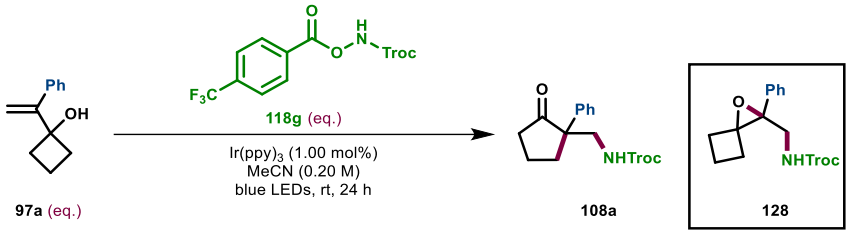
Table 3: Investigation of light source on reaction methodology

During our investigations, epoxide **128** was consistently observed as a side-product within most reactions. A similar side-product was also observed by Glorius and co-workers and was attributed to the intramolecular addition of the oxygen atom into the carbocation in intermediate **127** (scheme 31).[97]



*Scheme 31: Formation of epoxide-by product **128***

Having attributed some of the remaining mass balance to unreacted olefin **97a**, it was hypothesised that having an excess of radical precursor **118g** would ensure complete conversion and so the stoichiometry of the process was investigated. Varying the stoichiometry to an excess of amidyl radical precursor provided higher yields (entries 1 – 4), and satisfyingly, a comparable yield and complete consumption of olefin **97a** was achieved when using 1.00 equivalent of olefin **97a** and 1.20 equivalents of amidyl radical precursor **118g** (entry 5, table 3). Greater excesses of amidyl radical precursor **118g** had no effect on yield (entry 6, table 4). This enabled a lower stoichiometric ratio of substrate **97a** to be required per reaction, whilst minimizing any unreacted alkene **97a** at the end of the reaction.



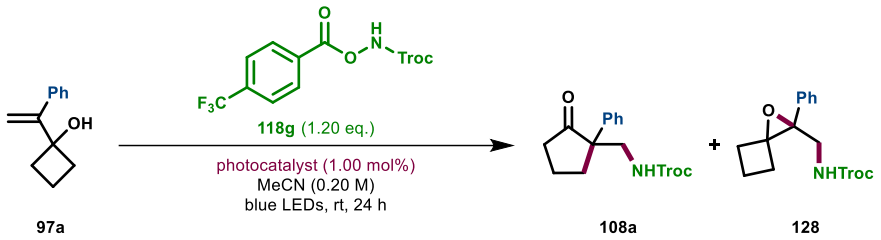
Entry	Olefin 97a/ eq.	Precursor 118g/ eq.	Yield/ %	Epoxide 128/ %
1	1.20	1.00	24	3
2	1.10	1.00	35	10
3	1.00	1.00	32	9
4	1.00	1.10	50	3
5	1.00	1.20	45	14
6	1.00	1.50	43	12
7[a]	1.00	1.20	59	0

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.
[a]Reaction mixture stirred with 1 M aq. HCl at the end of the reaction.

Table 4: Stoichiometry screen

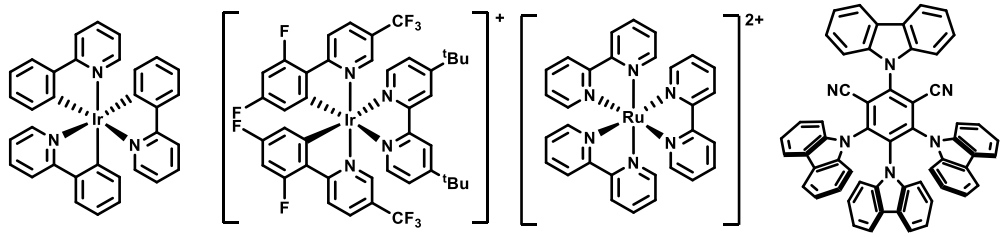
It was hypothesised that the epoxide by-product **128** could be converted into the desired product **108a** using an acid-stir in the work up procedure. This was precedented in a report by Jiao and coworkers which found that a similar epoxide can be activated and undergo a ring-opening and subsequent semi-pinacol ring expansion to deliver product.[99,121] Remarkably, this modification showed conversion of epoxide **128** into product **108a** by an increased yield of 59% with no epoxide **128** detected (entry 7, table 4). Having shown that epoxide **128** could be converted to product **108a** using this modification, ^{1}H NMR spectroscopic yields for further optimisations were taken as the sum of both components.

Having optimised the stoichiometry, a screen of photocatalysts was undertaken (table 5). Utilizing $Ir(ppy)_3$ as the photocatalyst provided a yield of 59% and complete consumption of NCR precursor **118g** (entry 1, table 5). Changing the photocatalyst had a detrimental effect on yield (entry 2 – 4, table 5) and unreacted NCR precursor **118g** and substrate **97a** was recovered in these instances. These yields were attributed to the lower reduction potential ranges of these photocatalysts which are highlighted in table 5.[49] In addition, the low recovery of substrate **97a** at the end of the reaction suggested that there may be some decomposition of this compound when subjected to the reaction conditions.



Entry	Photocatalyst	Yield/ %	Unreacted 97a/ %
1	$Ir(ppy)_3$	59	0
2	$[Ir[dF(CF_3)(ppy)]_2(dtbbpy)]PF_6$	0	58
3	$[Ru(bpy)_3]Cl_2$	0	67
4	4CzIPN	0	63

Yields were determined by ^1H NMR spectroscopy using 1,3-benzodioxole as an internal standard, and are the sum of both product **108a** and epoxide **128**.



fac-[Ir(ppy)$_3$] **(49)** E[*M^{III}/M^{IV}] vs. SCE = –1.73 V[49]

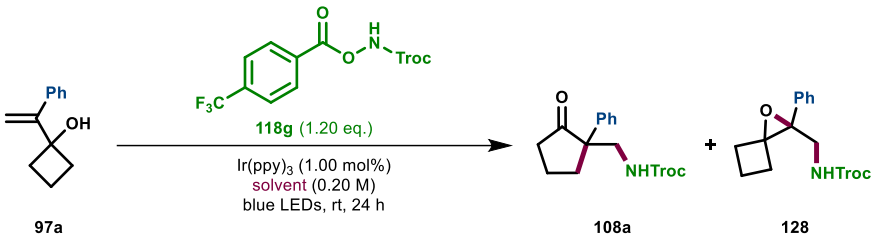
[Ir[dF(CF$_3$)(ppy)]$_2$(dtbbpy)]$^+$ **(50)** E[*M^{III}/M^{IV}] vs. SCE = –0.89 V[49]

[Ru(bpy)$_3$]$^{2+}$ **(51)** E[*M^{II}/M^{III}] vs. SCE = –0.81 V[49]

4CzIPN **(52)** E[*M^{II}/M^{III}] vs. SCE = –0.81 V[49]

Table 5: Screening of photocatalysts

The reaction was then carried out using these optimised conditions in a range of alternative solvents typically used in photoredox-catalysed methodology (table 6).[18,19] As product was observed when using MeCN, a polar aprotic solvent, we wanted to determine if other polar aprotic solvents could enhance the yield attained. Replacing MeCN with DMSO led to a reduced yield of 36% (entry 2, table 6). However, the use of other polar aprotic solvents such as DCM and acetone resulted in no conversion observed (entries 3 and 4, table 6). It was then hypothesised that this may be due to the high polarity of MeCN and DMSO, and as a result, DMA was also screened in the reaction conditions (entry 5, table 6), however this was also unsuccessful.

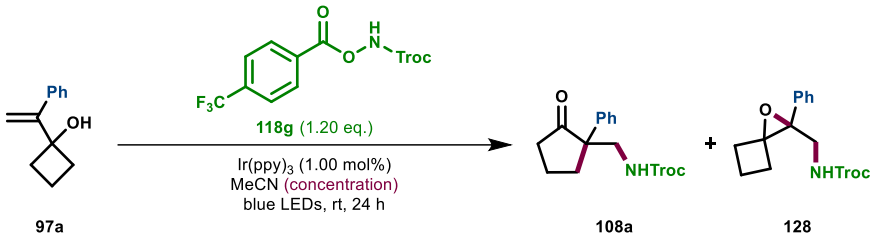


Entry	Solvent	Yield/ %
1	MeCN	59
2	DMSO	36
3	DCM	0
4	Acetone	0
5	DMA	0

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard, and are the sum of both product **108a** and epoxide **128**.

Table 6: Solvent screen experiments

MeCN remained the optimal solvent, and a subsequent investigation into concentration was undertaken (table 7). Reducing the concentration to 0.10 M led to a reduced yield of 45% (entry 1, table 7), whilst increasing the concentration to 0.30 M and 0.50 M similarly led to gradual reductions of yield to 48% and 34% respectively (entry 3 and 4, table 7).

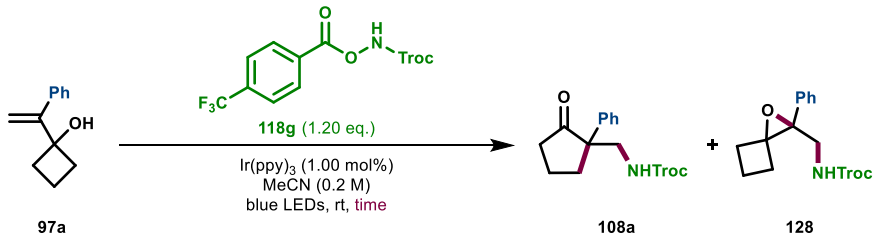


Entry	Concentration/ M	Yield/ %
1	0.10	45
2	0.20	59
3	0.30	48
4	0.50	34

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard, and are the sum of both product **108a** and epoxide **128**.

Table 7: Concentration screening

Encouraged by our findings, the reaction time was lastly examined (table 8). Within the first 3 hours, the reaction continued to progress (entries 1 – 2, table 8), and pleasingly at 3 hours, a comparable yield of 57% (entry 4, table 8) was attained. After 3 hours, the yield remained approximately constant (entries 5 – 6, table 8), and ^{1}H NMR data highlighted the complete consumption of amidyl radical precursor **118g** and olefin **97a**. Therefore, the reaction time could be reduced from 24 hours to 3 hours

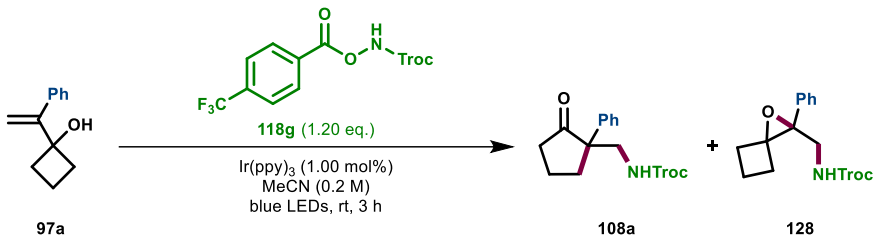


Entry	Reaction time/ h	Yield/ %
1	0.5	18
2	1	39
3	2	42
4	3	57
5	4	56
6	24	59

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard, and are the sum of both product **108a** and epoxide **128**.

Table 8: Reaction time screening

Having established the optimal conditions, a series of control reactions (table 9) were conducted to understand how deviations from these conditions affect reproducibility. When the reaction was run under an air atmosphere, a reduced yield of 10% was observed (entry 1, table 9). A reduced yield was also observed with the addition of 5.00 equivalents of water into the reaction mixture (entry 2, table 9). Finally, further control reactions confirmed the requirement for both light and a photocatalyst, with no product observed in their absence (entries 3 – 4, table 9).



Entry	Deviation from optimised conditions	Yield/ %
1	air atmosphere	10
2	with water	41
3	no light	0
4	no photocatalyst	0

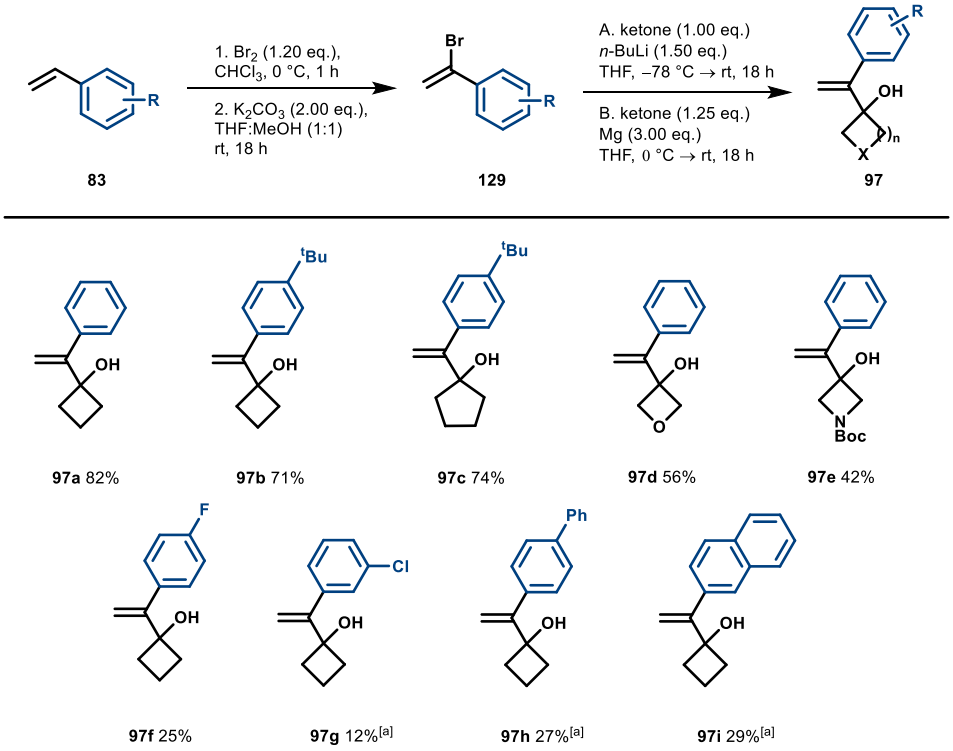
Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard, and are the sum of both product **108a** and epoxide **128**.

Table 9: Control reactions

Reaction Scope

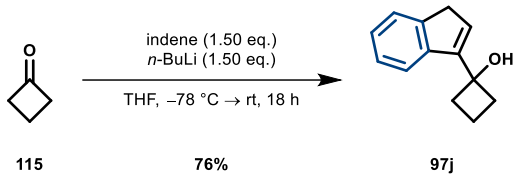
Styrene-derived Alkene Scope

Initially, a range of 1-(1-arylvinyl)alcohol derivatives **97a** – **97h** were synthesised over 3 steps (scheme 32). The first step involved the formation of the bromostyrene derivatives **129** using a procedure reported by Watson and co-workers,[122] and a subsequent lithium-halogen exchange according to Ngai *et al.*[115] which provided styrenyl bromides **129** in poor to moderate yields. The lithium-halogen exchange approach was utilized to form substrates **97g** – **97i**, however this frustratingly proved unsuccessful. Therefore, an alternative Grignard approach using conditions reported by Chen and co-workers[114] was employed for the final step to enable the formation of **97g**, **97h** and **97i** in 12%, 27% and 29% yields respectively.



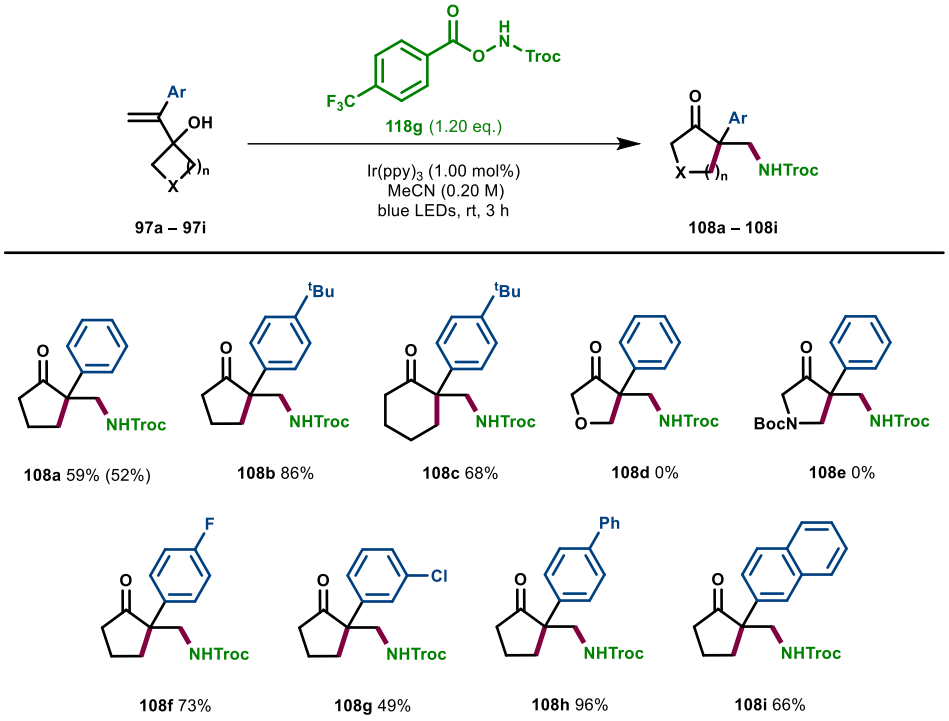
*Scheme 32: Synthesis of 1-(1-arylvinyl)cycloalcohol derivatives **97a** – **97i**. Final step carried out using conditions A. [a]Conditions B utilized for final step*

As all of the prepared substrates **97a** – **97i** contained terminal alkenes, an internal alkene substrate **97j** was prepared from indene (scheme 33) in a good yield using conditions reported by Ngai and coworkers.[115]



*Scheme 33: Synthesis of substrate **97j** using the conditions reported by Ngai and coworkers.*[115]

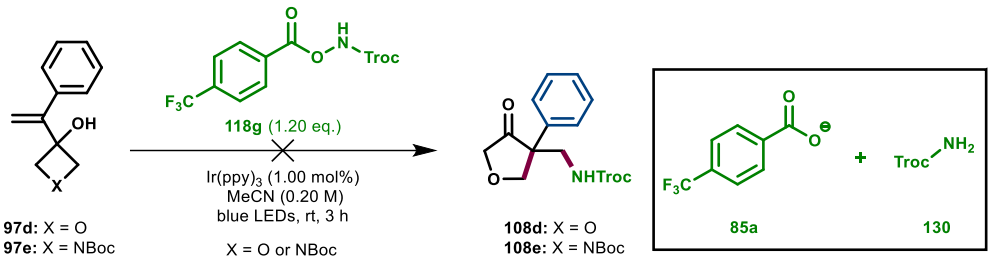
With the optimised conditions, and a range of functionalised 1-(1-arylvinyl)cycloalcohol substrates in hand, the reaction scope was explored (scheme 34).



Scheme 34: Activated alkene substrate scope

Using the unsubstituted styrene derivative **97a** used in the optimisation reactions provided **108a** in a 59% yield, and pleasingly the reaction could be conducted on a larger scale (2.00 mmol) giving ketone **108a** in a comparative yield. Increasing the electron density by inclusion of a *p*-*t*Bu group provided β-aminoketone **108b** in an excellent yield. Interestingly, increasing the size of the expanding ring using substrate **97c** yielded cyclohexanone derivative **108c** in a good yield.

Unfortunately, incorporating a heteroatom in the expanding ring provide unsuccessful with complete consumption of olefins **97d** and **97e** and no β-aminoketone **108d** and **108e** observed. This result was hypothesised as being due to the electronic effect of the heteroatom in the ring enabling the electrophilic amidyl radical formed to preferentially undergo hydrogen abstraction to form troc-protected amine **130** as opposed to add into olefin **97d** or **97e** (scheme 35).



*Scheme 35: The unsuccessful synthesis of β-aminoketone **108d** and **108e** resulting in the formation of carboxylate **85a** and Troc-protected amine **130***

The use of halides in the *meta* and *para* positions were also tolerated, providing **108f** and **108g** in 73% and 43% yields. The lower yield when using *meta*-substituted aromatic systems may be because of steric hinderance. The use of extended aromatic systems by means of a 4-biphenyl group and a naphthalene group afforded **108h** and **108i** in 96% and 66% yields respectively.

Gratifyingly, a single crystal of biphenyl derivative **108h** was submitted for X-ray crystallographic analysis, confirming the installation of the aminomethyl functionality, and the construction of the cyclopentanone ring (figure 6).

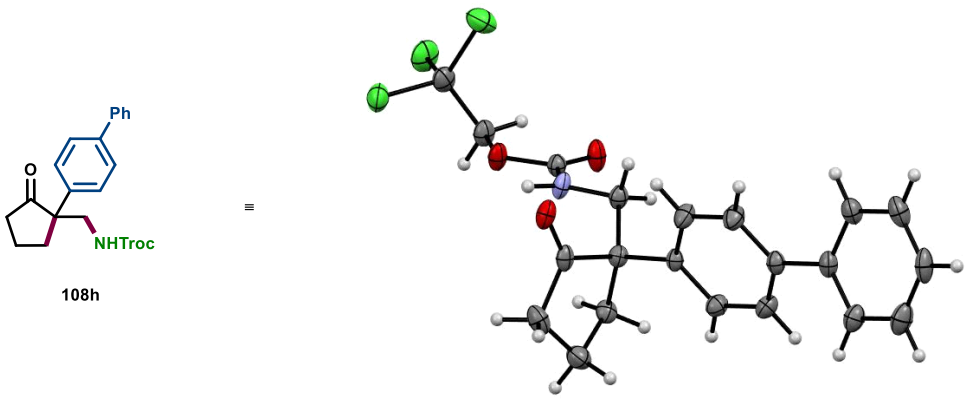
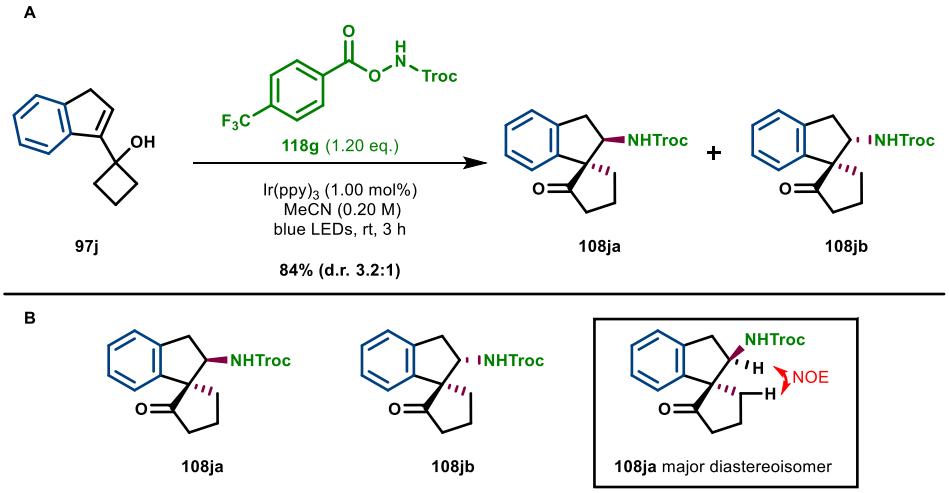


*Figure 6: X-ray crystal structure of diphenyl β-aminoketone **108h***

Interestingly, using cyclic alkene substrate **97j** provided diastereomeric products **108ja** and **108ja** in excellent yields in a 3.2:1 diastereomeric ratio (scheme 36A). In these instances, the stereochemistry was assigned based on the results of an NOE experiment (scheme 36B).

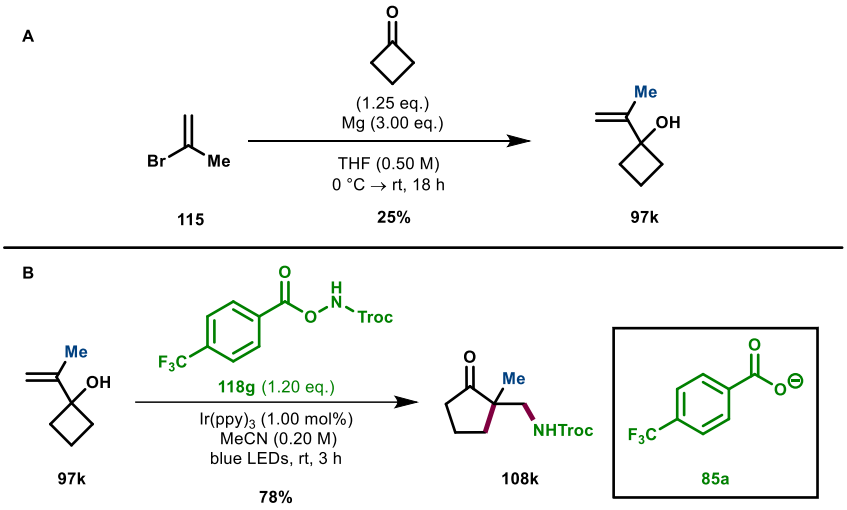


*Scheme 36: The formation of ketone **108ja** and **108ja** from olefin **97j** using the developed reaction conditions*

Aliphatic Alkene Scope

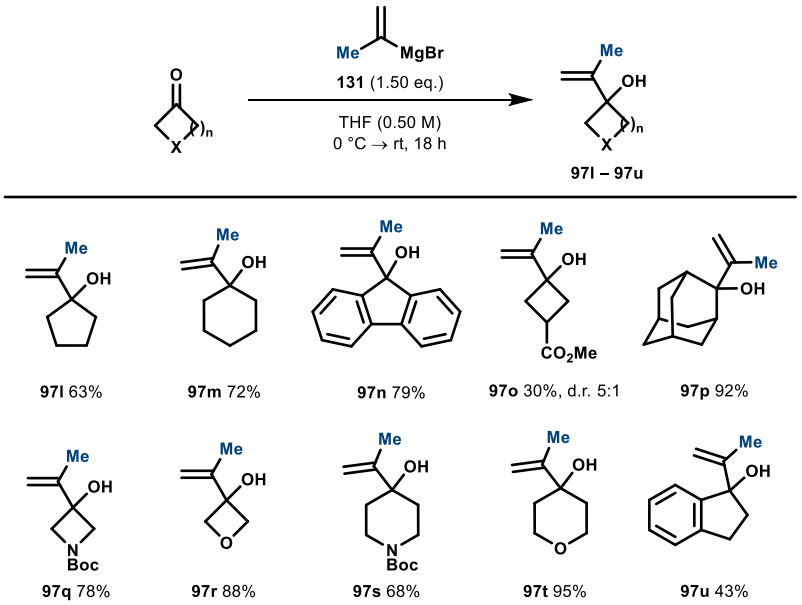
As amidyl radicals are known to add to aliphatic alkenes,[61] we questioned whether the optimised conditions could tolerate aliphatic alkene substrates. This would enable rapid access to sp^3-rich fragment building blocks, which are widely used in the pharmaceutical industry.[123,124]

To explore this, alkene **97k** was identified as a suitable substrate as it could be easily synthesised and its structural simplicity. Unactivated alkene **97k** was synthesised in a 25% yield using a Grignard approach with conditions reported by Gaunt and co-workers (scheme 37A).[125] Pleasingly, the use of propenyl substrate **97k** in our reaction conditions yielded β-aminoketone **108k** in a 78% yield (scheme 37B). In addition, the reaction profile highlighted the only by-product to be carboxylate **85a** derived from amidyl radical precursor **118g**, which could be easily separated in the workup.



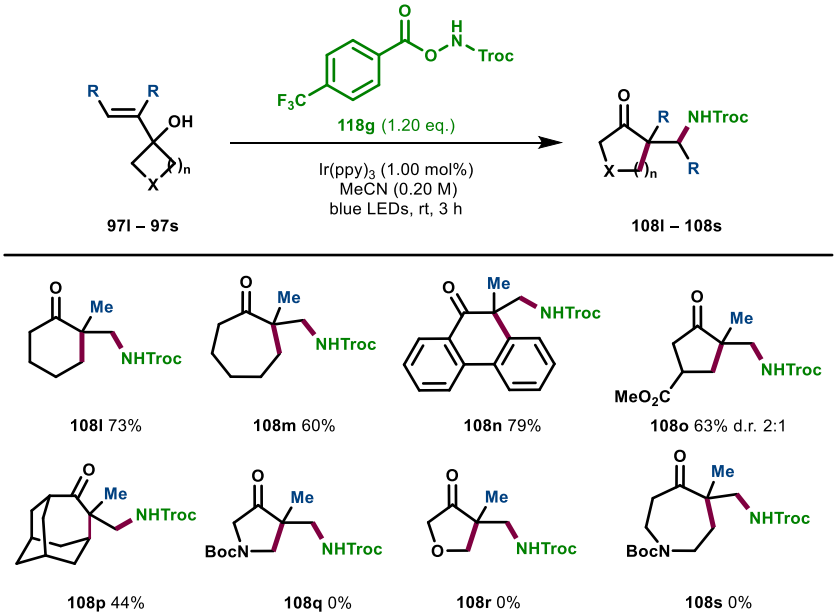
*Scheme 37: (A) Synthesis of substrate **97k** (B) Use of unactivated alkene **97k** in reaction conditions*

Encouraged by these results, additional unactivated alkene substrates **97l – 97u** were synthesised to determine the synthetic utility of this methodology. Simple propenyl-derived substrates were prepared according to the procedure reported by Wang and co-workers using commercially available isopropenylmagnesium bromide solution (**131**) (scheme 38).[126] To determine the effect of ring size, cyclopentanone-derived substrate **97l** and cyclohexanone-derived substrate **97m** was synthesised in good yields. Furthermore, on account of substrates **97d** and **97e** being unsuccessful in the aromatic scope, a range of heterocyclic substrates **97q** – **97t** were also synthesised in good yields to investigate if any product would form.



*Scheme 38: Synthesis of unactivated alkenes **97l** – **97u** using conditions reported by Wang et al.*[126]

With these unactivated alkene substrates and optimised conditions in hand, a reaction scope was explored (scheme 39).

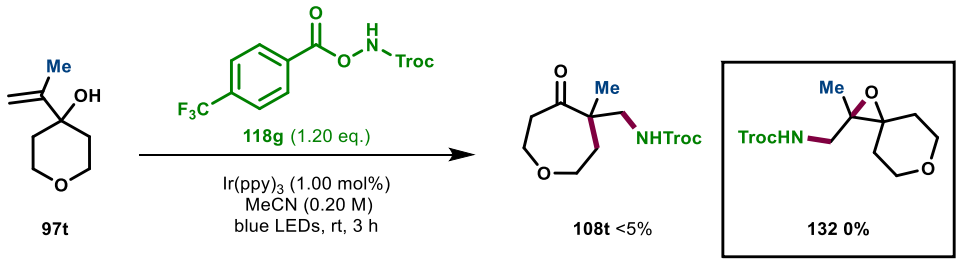


Scheme 39: Reaction scope of unactivated alkenes

Increasing the ring size pleasingly led to the formation of cyclohexanone derivative **108l** and cycloheptanone derivative **108m** in a 73% and 60% yield respectively. Fluorenone-derived product **108n** was attained in a 79% yield, and the presence of substitution on the expanding ring was tolerated, providing methyl ester **108o** in a 63% yield. Notably, the use of sterically hindered caged substrate **97p** delivered novel caged product **108p**.

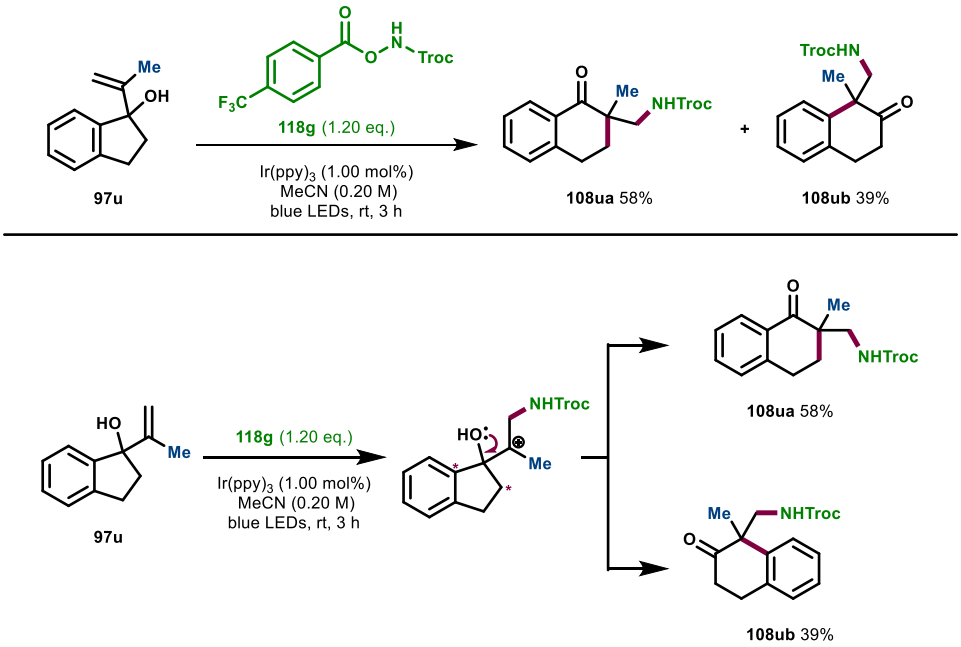
The tolerance of substitution on the expanding ring, in addition to the formation of sterically bulky caged product **97p** are interesting, as they suggest that this reaction could be utilized in late-stage development on sterically hindered compounds containing multiple functionalities. Heterocyclic substrates **97q**, **97r** and **97s** were unsuccessful in the formation of products **108q**,**108r** and **108s**.

Although heterocyclic substrates **97q**, **97r** and **97s** proved unsuccessful, diagnostic peaks in the ^{1}H NMR spectra (doublet of doublet peaks at 3.40 ppm) suggested traces (<5%) of oxepanone derivative **108t** were formed (scheme 40). This was confirmed to not be epoxide **132**, as after stirring the crude reaction mixture in 1 M HCl, the same peaks remained. Attempts to cleanly isolate oxepanone derivative **108t** using column chromatography proved unsuccessful, as the fraction containing oxepanone **108t** obtained from column chromatography contained an inseparable by-product.



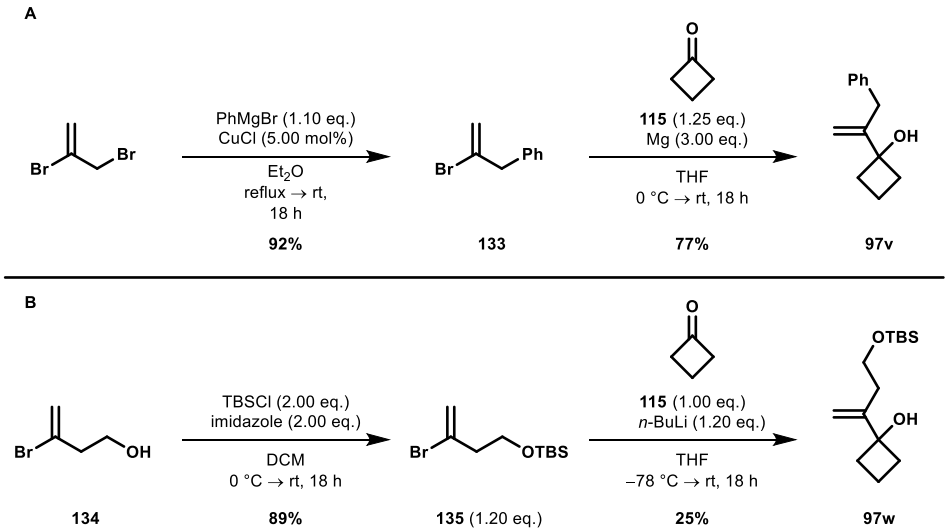
*Scheme 40: Synthesis of oxepanone derivative **108t***

Furthermore, indanone-derived substrate **97u** provided major product **108ua** in a 58% yield, in addition to a minor regioisomeric product **108ub** in a 39% yield, originating from the migration of the phenyl ring during the semi-pinacol rearrangement (scheme 41). The presence of both regioisomers in unequal quantities suggest that migratory group aptitude of the sp^3 carbon (leading to the formation of major regioisomer **108ua**) is greater than the sp^2-carbon. This is unusual as migratory group aptitude is focussed on the group which can stablise the carbocation,[127] and therefore the sp^2 carbon should be the dominant migratory group. A reason for this unusual result may be due the lowering of overall energy provided by conjugation of the newly formed carbonyl to the aromatic ring.



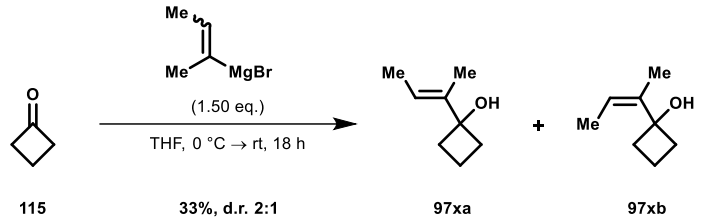
*Scheme 41: Synthesis of indanone derived product **108ua** and **108ub** and mechanistic reasoning behind regioisomer formation*

To further examine the scope, substrates bearing substituents on the olefin were also synthesised. Vinyl bromide intermediate **133** was prepared using conditions reported by Breit *et al.*,[128] and subsequently converted into substrate **97v** (scheme 42A).[114] Similarly, TBS protection of bromo-alcohol **134** using conditions reported by Liu and Yeung afforded vinyl bromide **135**,[129] which underwent a subsequent lithium-halogen exchange facilitated addition to yield substrate **97w** in a 25% yield (scheme 42B).



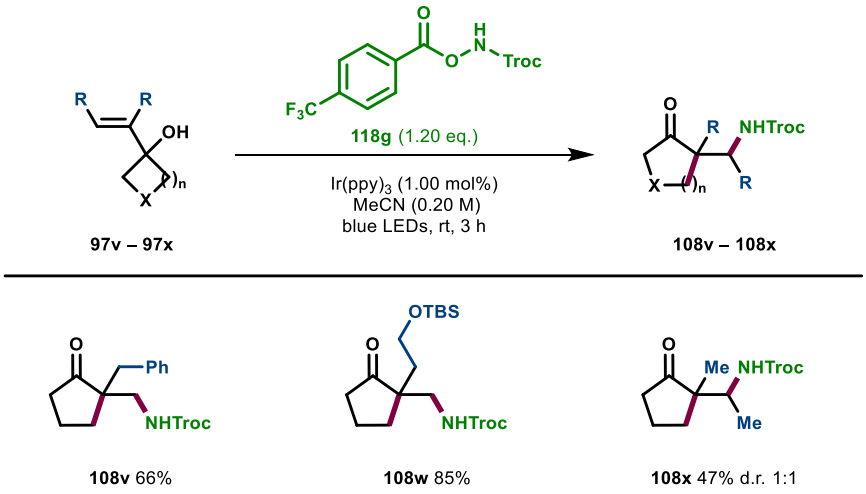
*Scheme 42: (A) Synthesis of benzyl substituted substrate **97v**[114,128] (B) Synthesis of TBS-protected substrate **97w**[129]*

Furthermore, to determine if the methodology was tolerant of non-terminal olefins as substrates. A trisubstituted alkene substrate was also prepared (scheme 43) in 33% yield as an inseparable mixture of cis-trans isomers (**97xa** and **97xb**) (d.r. 2:1) using a procedure reported by Wang and co-workers.[126]



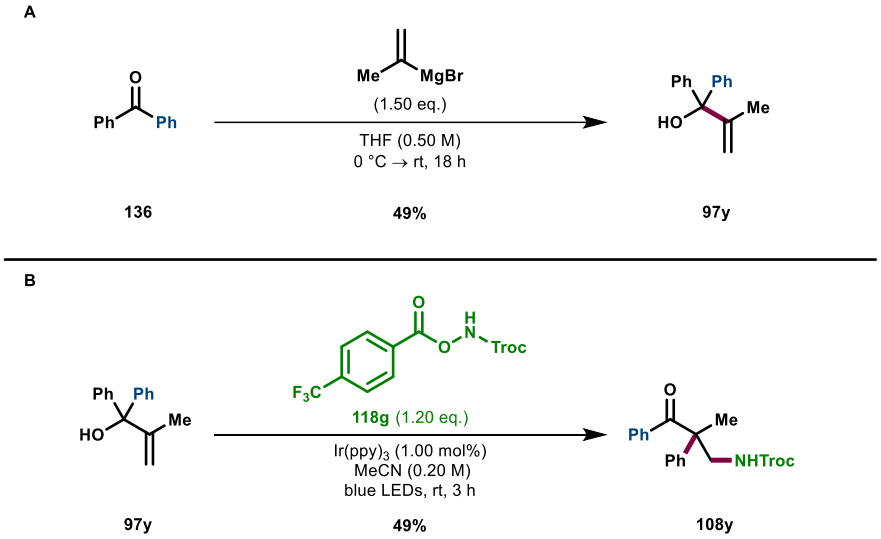
*Scheme 43: Synthesis of trisubstituted substrate **97xa** and **97xb** using conditions reported by Wang and coworkers.*[126]

Exploration of the reaction scope using substrates with substitution on the alkene gratifyingly exhibited that benzyl-substituted substrate **97v** and TBS-protected alcohol **97w** could be used, enabling the formation of **108v** and **108w** in yields of 66% and 85% respectively. Moreover, the use of trisubstituted olefin **97x** also led to the formation of **108x** in 47% yield as an inseparable mixture of diastereoisomers.



Scheme 44: Reaction scope using substituted alkene derivatives

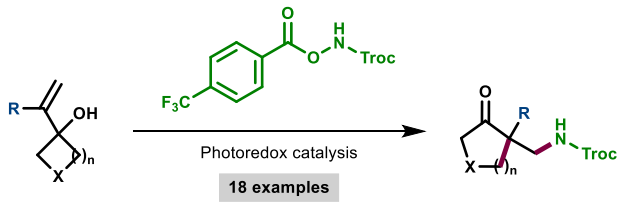
To further increase the generality of the chemistry to non-ring expansion processes, a benzophenone-derived substrate **97y** was prepared in a 49% yield from benzophenone (**136**) using a procedure reported by Wang and co-workers[126] (scheme 45A). Upon reaction of substrate **97y** under the standard conditions, substrate **97y** underwent a radical amination 1,2-aryl migration cascade to deliver ketone **108y** in 49% yield (scheme 45B).



*Scheme 45: (A) Synthesis of benzophenone-derived substrate **97y** (B) Reactionn of substrate **97y** under the standard conditions.*

Conclusion

In summary, the development of photoredox-mediated radical amidation methodology utilizing semi-pinacol chemistry has been achieved using reductively generated amidyl radicals, attaining yields up to 96% (scheme 46). This methodology provides access to a broad range of compounds with all carbon quaternary centres bearing an aminomethyl group.



Scheme 46: Photoredox-mediated radical amidation

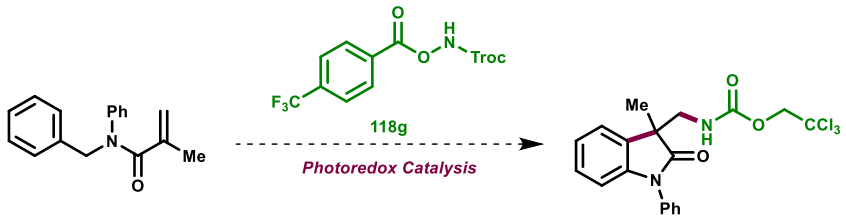
The methodology tolerates a wide range of activated alkene substrates containing various functional groups, including extended aromatic systems (**97h** and **97i**) and 6-membered expanding rings (**97c**). Aryl halide systems were also tolerated, enabling a platform for further transformations such as cross-couplings which are widely used in medicinal chemistry.[130] Products were successfully obtained when substituted in the *para*-position, and to a lesser extent when substituted in the *meta*-position, suggesting that steric hinderance has a detrimental effect on yield.

Expansion of the reaction scope towards non-styrene based olefins alkenes led to formation of product in most instances, in 5-,6- and 7-membered ring sized products **108k**, **108l** and **108m** respectively. This mode of reactivity, which to the best of our knowledge, has not been demonstrated using photoredox-based methodology applied to unactivated alkene substrates. Furthermore, to thoroughly explore the reaction scope, adamantanone-derivative **97o** and trisubstituted alkene **97x** were synthesised in one step using commercially available ketones.[126] Subjection of olefins **97p** and **97x** to the reaction conditions successfully led to the formation of β-aminoketones **108p** and **108x** in moderate yields.

Finally, efforts to broaden the synthetic utility of this methodology to non-ring expansion processes were investigated. Benzophenone-derived substrate **97y** was formed in a single step using commercially available isopropenylmagnesium bromide. Subjection of substrate **97y** to the reaction conditions pleasingly provided ketone **108y** in a moderate yield, highlighting the generality of the conditions.

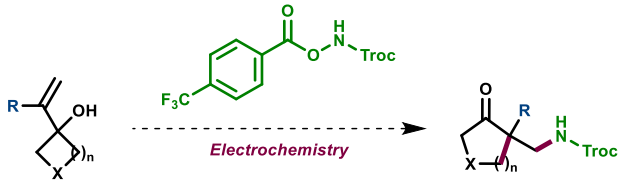
Future work

Initial studies have demonstrated the application of this photoredox-mediated methodology towards non-ring expansion processes. Therefore, a logical next step would be to further assess the application of these conditions to non-ring expansion processes and other cyclic systems such as towards the synthesis of oxindoles (scheme 47).



Scheme 47: Synthesis of oxindoles using amidyl radicals

Optimisation studies highlighted that the scope of amidyl radical precursors available for this chemistry was limited due to the reduction potential range of the photocatalyst. As a result, another area for further study would involve the development of an electrochemical-variant of this transformation (scheme 48). Replacement of a photocatalyst with a power source would enable greater control of potential and access to higher potentials which would broaden the scope of NCR precursors available.



Scheme 48: Electrochemically-mediated radical amidation reactions using semi-pinacol chemistry and amidyl radicals

Amino-Substituted THFs

Amino-substituted tetrahydrofurans (THFs) form the structural basis of many pharmaceutical APIs such as Telbivudine (**137**) and Vidarabine (**138**) (figure 7). (2-Aminomethyl)substituted THFs are especially interesting as an intermediate towards APIs such as Mefruside (**139**) and exhibit inherent potent antidepressant activity.[131] Therefore the development of methodologies to enable access towards these (2-aminomethyl)substituted THF scaffolds are of great importance within synthetic chemistry.

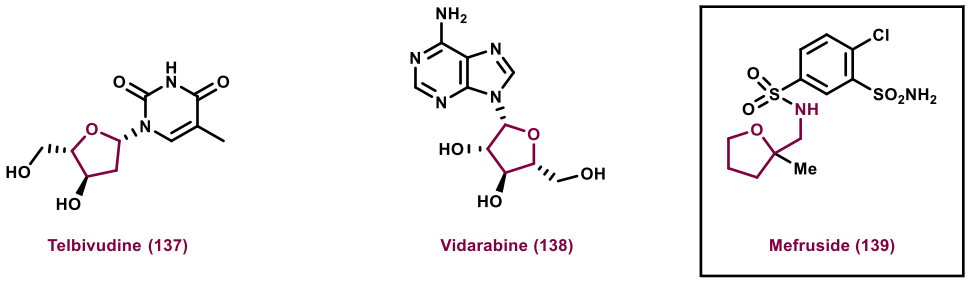
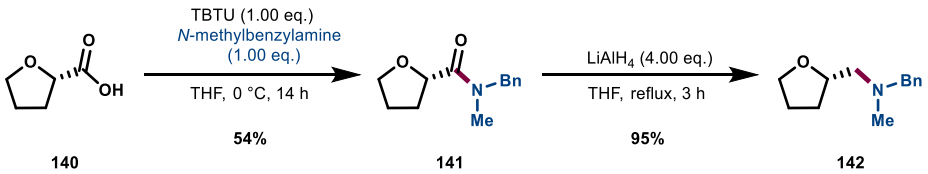


Figure 7: Amino-substituted THFs motifs in bioactive compounds

Routes to (2-aminomethyl)THFs

Two-Electron Routes

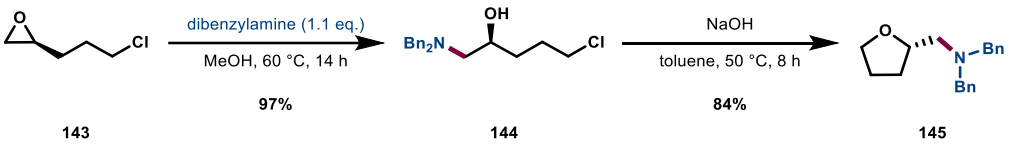
Although two-electron routes towards the formation of THF have been thoroughly explored,[ref] few routes towards (2-aminomethyl) THF derivatives have been developed. A typical strategy used to access this motif is highlighted in a protocol by Durham *et al.* (scheme 49),[132] and involved the amide coupling of carboxylic acid **140** with *N*-methylbenzylamine to amide **141**, followed by a subsequent reduction using lithium aluminium hydride to afford (2-aminomethyl)THF **142**. In addition to the use of stoichiometric amounts of $LiAlH_4$ to form **142**, another key disadvantage is this approach requires a pre-installed THF ring.



Scheme 49: Formation of (2-aminomethyl)THF using amide coupling and reduction approach reported by Durham.[132]

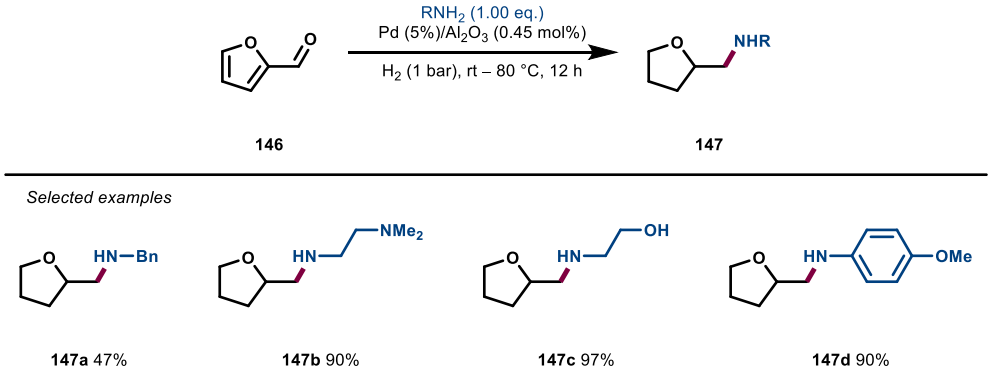
Another approach which mitigates the need for a pre-installed THF ring was demonstrated by Ge and co-workers for the synthesis of chiral 2-aminomethyl THFs (scheme 50).[133] This method involves the ring opening of epoxide **143** using dibenzylamine to generate amino-alcohol **144**, then a subsequent base-promoted cyclization to yield (2-aminomethyl)THF **145**.

This strategy by Ge enables the installation of the THF ring and the aminomethyl functional group, however is a multistep process, which consequently leads to inherently low yields attained of THF **145**.



Scheme 50: Formation of (2-aminomethyl)THF using epoxide ring-opening and cyclization approach by Ge et al.[133]

More recent routes towards the synthesis of this motif focus on sustainability and the use of biomass-derived furfural (**146**) as a starting material. An example of this was highlighted in the conversion of furfural to tetrahydrofurfurylamine derivatives used by Vigier and coworkers (scheme 51).[134] Vigier found that besides *N*-benzylamine **147a**, alkyl amines such as **147b** and **147c** were obtained in excellent yields, and comparable yields were also attained when using anilines (**147d**).

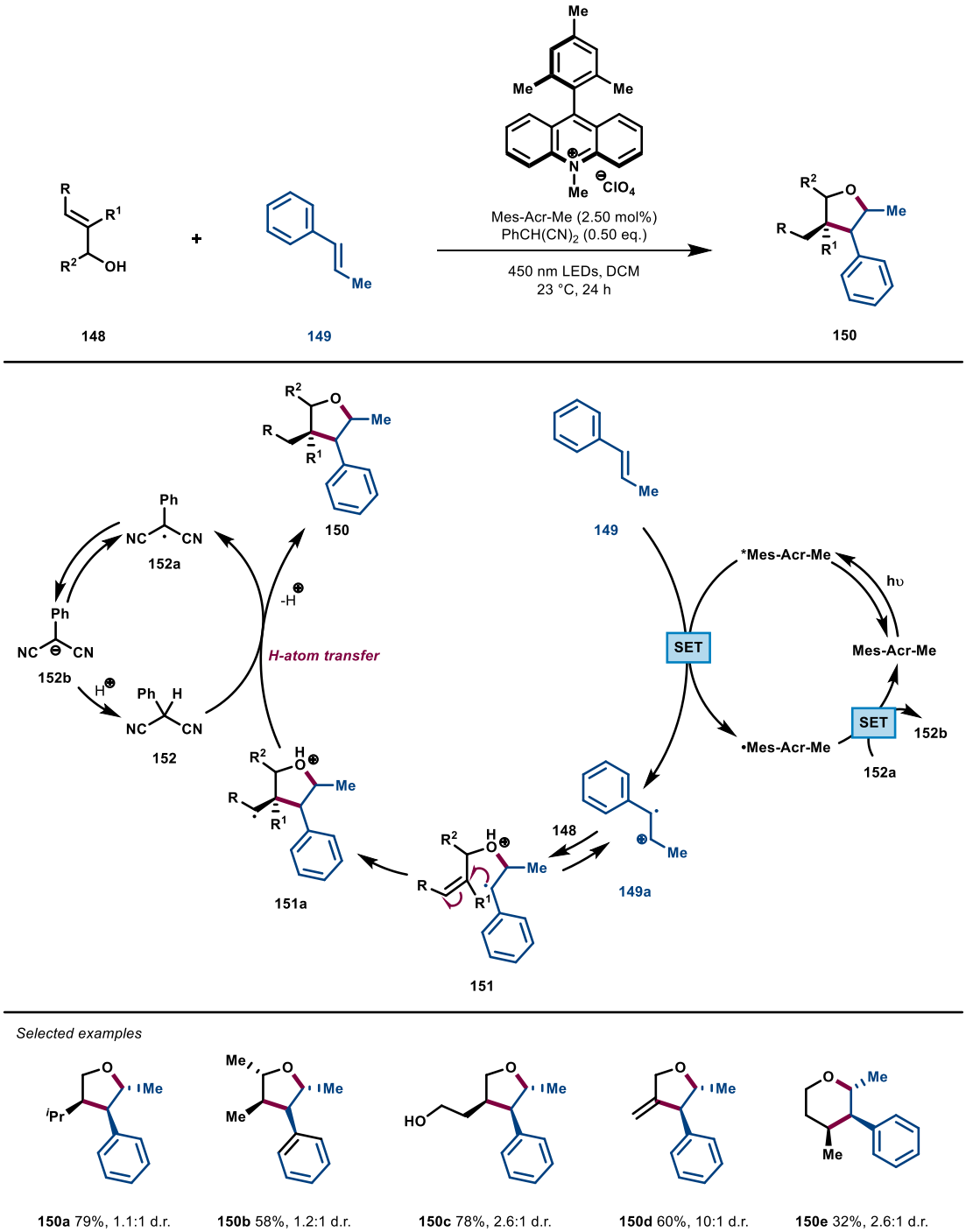


Scheme 51: Synthesis of (2-aminomethyl)THF motif using biomass-derived furfural developed by Vigier et al.[134]

One Electron Routes

One electron radical processes to synthesise (2-aminomethyl)THFs have been unexplored. However, recently there have been advances in the field of photoredox catalysis that have opened up new routes to heterocycles, and these have enabled the synthesis of 2-substituted THFs using alkyl radicals.[135,136] An example of this was reported by Nicewicz and coworkers (scheme 52).[137] Interestingly, Nicewicz utilized an oxidative approach whereby allylic alcohol **148** adds to radical cation **149a**, which was formed from a SET from excited state Mes-Acr-Me to styrene **149**, in an anti-Markovnikov manner to generate carbon centred radical cation **151**. Cyclization of radical cation **151** with the pendant olefin, and a subsequent hydrogen-atom abstraction mediated by malonitrile **152** generates radical **152a** and product **150**. A SET from

malonitrile radical **152a** to •Mes-Acr-Me regenerates the ground state photocatalyst, and forms malonitrile anion **152b**, which upon protonation reforms catalyst **152**.



Scheme 52: Early example of the formation of substituted THF scaffolds using a radical approach reported by Nicewicz and coworkers[137]

Nicewicz discovered that this methodology was able to generate highly substituted THF scaffolds such as **150a** and **150b** in moderate to good yields, in addition to being tolerant of substrates bearing multiple alcohol and alkene moieties, enabling the formation of corresponding products **150c** and **150d** in 78% and 60% yields respectively. Furthermore, the reaction scope was extended towards the construction of substituted 6-membered tetrahydropyran **150e** in a 32% yield. Since this development, Nicewicz has since extended the methods to enable the formation of pyrrolidines.[138]

Although the aminomethyl moiety is absent in these examples, they demonstrate alternative strategies that could be potentially used to access 2-aminomethyl THFs.

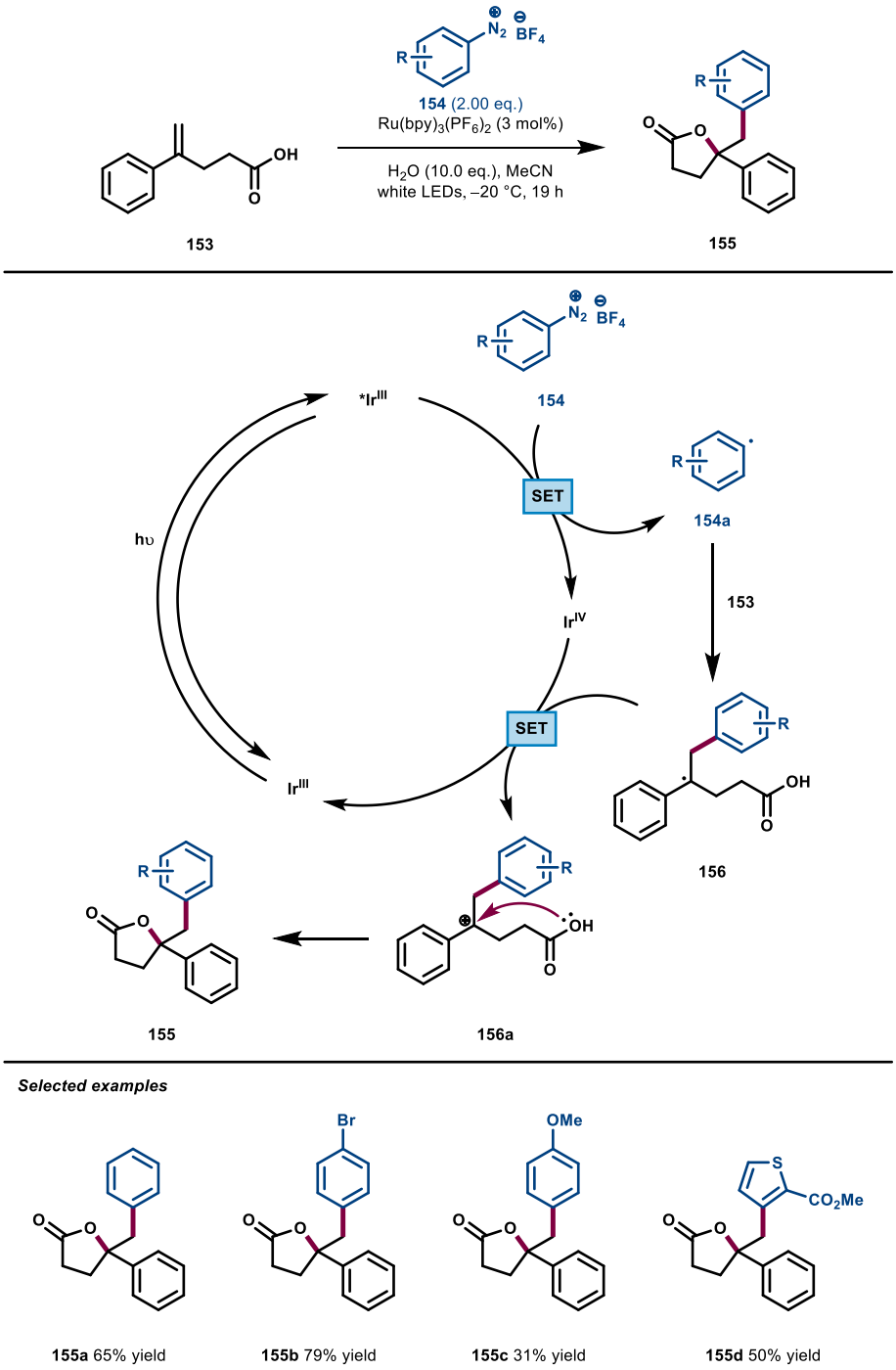
Radical Polar Crossover Reactions for the Synthesis of THFs

As highlighted in this section, a key drawback of two electron processes to produce (2-aminomethyl)substituted THFs are that they often require multiple steps or a pre-installed tetrahydrofuran ring. Furthermore, single electron processes predominantly focus on the formation of general heterocycles and 2-substituted THFs, however the formation of (2-aminomethyl)substituted THFs remains under explored.

Radical polar crossover reactions have been demonstrated as a valuable strategy for the formation of heterocycles.[139] Discovered by Murphy in 1993,[140] radical polar crossover reactions are processes whereby radical intermediates can undergo a single electron transfer with a reductant or oxidant to evolve anions or cations.[97]

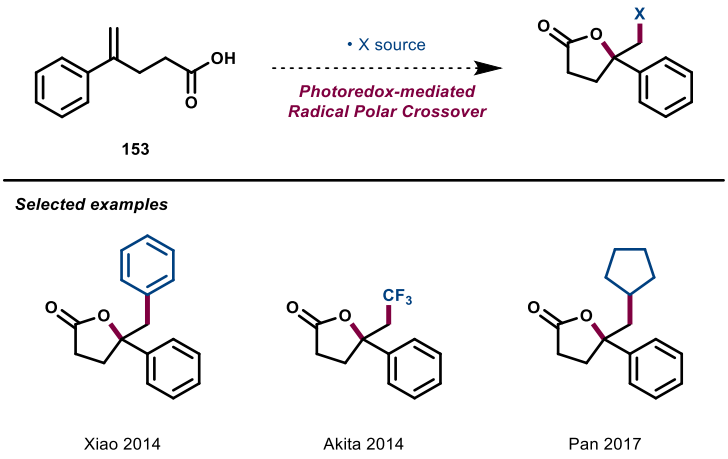
More recently, photoredox catalysis has been used to carry out radical polar crossover reactions as a result of a photocatalyst's ability to carry out two SET events,[139] however, current reports in this area predominantly focus on the synthesis of lactones. A key development in this area is highlighted in the synthesis of γ-disubstituted butyrolactones by Xiao and coworkers (scheme 53).[141] Interestingly, in this example an oxidative radical polar crossover strategy was employed using an alternative domino addition/cyclization approach. Under visible light irradiation, Ir^{III} is promoted to excited state $*Ir^{III}$, which can carry out a SET to aryldiazonium salt **154** to evolve aryl radical **154a** and Ir^{IV}. Addition of radical **154a** to alkene **153** affords carbon-centred radical **156**, which upon a second SET to Ir^{IV} produces cation **156a** and regenerates ground state Ir^{III}. Subsequent *5-exo-trig* cyclization of **156a** yields lactone **155**.

In addition to providing product **155a** in a moderate yield, this procedure was able to utilize electron-poor substrates, providing the corresponding product **155b** in a good yield. This was also observed with electron-rich substrates to a lesser extent, providing the corresponding product **155c** in a poor yield. Xiao was able to further extend the method to heteroaromatic group bearing substrates, such as thiophenes affording the corresponding product **155d** in a 50% yield.



Scheme 53: Seminal example of the use of photoredox catalysis in radical-polar crossover reactions reported by Xiao et al.[141]

Since this development, photoredox-mediated radical polar crossover reactions have been expanded to include a wide range of radical such as CF_3 [142] and alkyl,[143] however these oxidative radical-polar crossover examples predominantly focus on the formation of γ-lactones as opposed to 2-aminomethylTHFs, and the requirement of the nucleophile to be incorporated into the substrate.



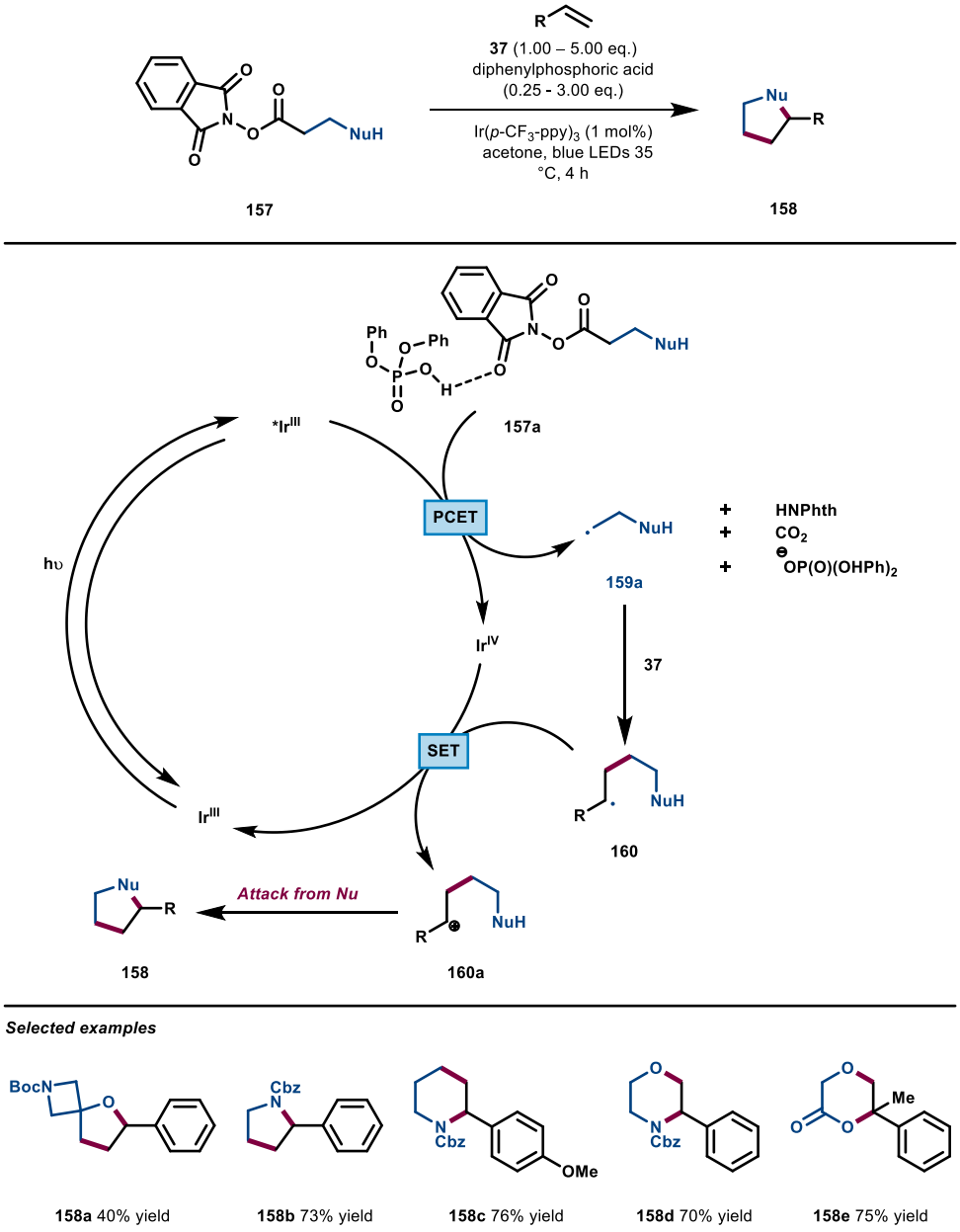
Scheme 54: Recent examples of the use of radical-polar crossover reactions using a variety of radicals [142,143]

More recent developments in the use of this strategy have been focussed towards alleviating the requirement of the nucleophile in the substrate. An example of this is highlighted in a report by Doyle and coworkers towards the synthesis of saturated heterocycles (scheme 55).[144] Under visible light irradiation, ground state photocatalyst Ir^{III} is promoted to excited state photocatalyst $*Ir^{III}$. A reductive proton coupled electron transfer (PCET) followed by fragmentation evolves Ir^{IV} and radical **159a**. Anti-markovnikov addition of **159a** into olefin **37** provides adduct **160** which upon a subsequent SET to Ir^{IV} from radical **160** furnishes cationic intermediate **160a**. Cyclization via attack from the tethered nucleophile converts **160a** to heterocycle **158**.

Doyle was able to attain azetidine-substituted THF **158a** in a 40% yield. It is noteworthy that Doyle was able to extend the generality of the scope to give moderate yields of pyrrolidine **158b**, piperidine **158c**, morpholine **158d** and dioxanone **158e**. This development reports the only example of the construction of nitrogen substituted THF derivatives using one electron processes.

In summary, methods to form (2-aminomethyl)THFs have been explored and carried out utilizing two well-known approaches: an amide coupling and subsequent reduction approach, which can requires a pre-installed THF ring, or an epoxide ring opening and subsequent cyclization, which would require multiple steps.

In contrast, single electron processes to form (2-aminomethyl)THFs are underdeveloped, and the only method to date is being currently developed by Doyle and coworkers.[144]

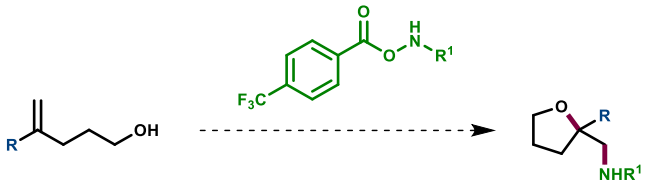


Scheme 55: Recent developments in the use of photoredox-mediated radical-polar crossover reactions utilizing nucleophiles untethered to the substrate developed by Doyle and coworkers[144]

Radical-polar crossover reactions have been demonstrated to be a key strategy towards the formation of heterocyclic scaffolds,[137–139] however current methods involving this approach focus on the formation of lactones. Furthermore, to the best of our knowledge, a radical-polar crossover processes initiated by the addition of an amidyl radical remains unexplored.

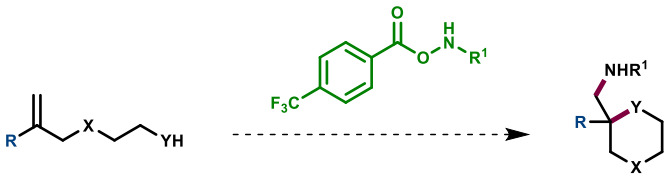
Aims And Objectives

As summarised, the use of photoredox-mediated radical-polar crossover reactions is a useful tool to access saturated heterocycles. Current approaches utilizing this strategy focus predominantly on the formation of lactones, however there are no robust methodologies for the synthesis of (2-aminomethyl)THFs using a photoredox-mediated radical polar crossover strategy. Our aim was to develop the first of this kind using amidyl radicals to enable access to (2-aminomethyl)THF motifs (scheme 56).



Scheme 56: Reaction principle

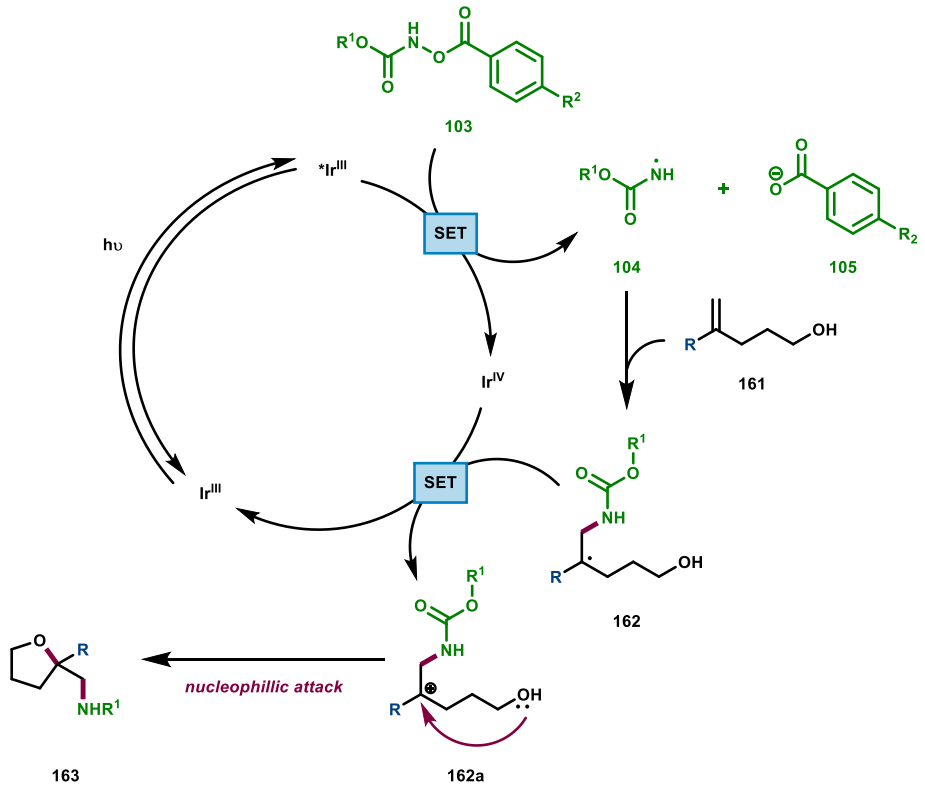
We were interested in using a reductive approach employing carbamates as amidyl radical precursors. Furthermore, we aspired to extend the protocol to other saturated heterocyclic motifs such as pyrrolidines, morpholines and lactones to increase the synthetic utility and generality of the method (scheme 57).



Scheme 57: Envisaged extension of reaction principle to saturated heterocycles

Proposed Mechanism

Based on literature precedent,[111] the proposed mechanism is shown in scheme 58. Under visible light irradiation, ground state Ir^{3+} is converted to its excited state $*Ir^{3+}$ .Single electron transfer (SET) from triplet excited state species to precursor **103** would generate Ir^{4+}, amidyl radical **104** and carboxylate **105**. Addition of radical **104** to olefin **161** would provide carbon-centered radical **162**. Subsequent SET from carbon-centered radical **162** to $[Ir^{4+}(ppy)_3]$ would regenerate ground state photocatalyst $[Ir^{3+}(ppy)_3]$ and form cationic intermediate **162a**, which can undergo nucleophilic attack by the OH group to deliver (2-aminomethyl)THF **163**.

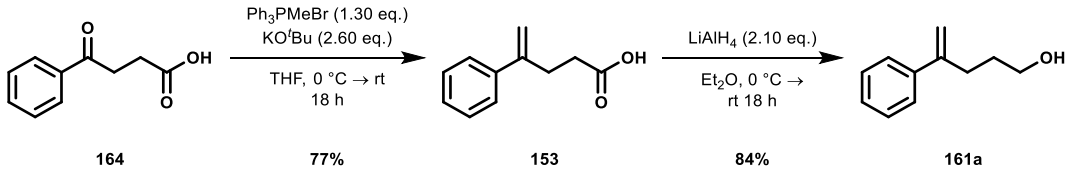


Scheme 58: Proposed mechanism for the photoredox-mediated radical polar crossover process for the synthesis of saturated heterocycles

Photoredox-Mediated Radical Polar Crossover Process for the Synthesis of Saturated Heterocycles

Synthesis of Model Substrate for Optimisation

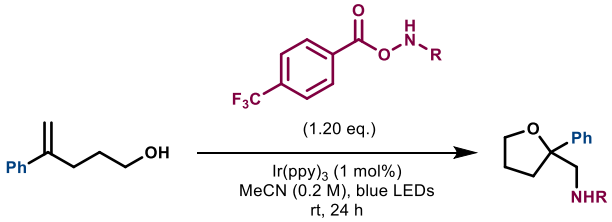
For the optimisation studies, the model substrate was required to be easy to synthesise, and structurally simple to limit the influence of steric and electronic effects on the photoredox reaction. As a result, olefin **161a** was identified as a suitable model compound for the optimisation studies. The synthesis of the model substrate **161a** required for the optimisation experiments was carried out in 2 steps from commercially available 3-benzoylpropionic acid (**164**) (scheme 59).[145,146] A Wittig reaction using **164** afforded carboxylic acid **153** in a 77% yield,[145] and a subsequent reduction with $LiAlH_4$ yielded olefin **161a** in 87% yield.[146] This synthesis could be scaled up providing sufficient material for optimisation studies.



*Scheme 59: Formation of model olefin **161a** for optimisation studies*[145,146]

Reaction Optimisation

Using a modification (24-hour reaction time) of the conditions found during the semi-pinacol project, initial optimisation experiments focussed on screening a carbamate-based amidyl radical precursors with varying amino-protecting groups (table 10). Pleasingly, the troc-protecting group provided the product **163a** in a good yield (entry 1, table 10). Changing the protecting group on the nitrogen had a detrimental effect on conversion (entries 2 – 5, table 10). Interestingly, the use of a Tosyl protecting group on the nitrogen atom exhibited a poor yield (entry 6, table 10). This was a surprising result, as amidyl radicals bearing this *N*-protecting group are highly reported in the literature.[25,80]



161a 163a

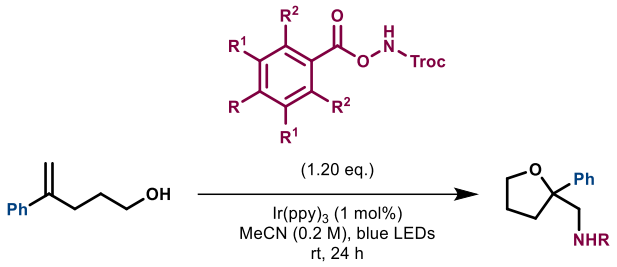
Entry	R group	Yield/ %
1	Troc	72
2	Boc[a]	59
3	Alloc	27
4	Cbz	40
5	Tfoc[a]	20
6	Tosyl[a]	<5%

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard; [a]Precursors synthesised by Dr Arunprasath Dhanarajan (Cuthbertson group)

Table 10: Amidyl radical precursor screen

As the previous project in this thesis had showed carbamates with electron deficient aryl rings as being the most potent efficient amidyl radical precursors, a further screening of electron withdrawing moieties was conducted (table 11). This screening further validated our findings of amidyl radical precursor **118g** being the optimal for this process (entry 1, table 11). Changing the position of the CF_3 functionality from the *para* position to the *meta* position had a negative effect on the yield (58%) (entry 2, table 11), and this trend was also observed upon changing the CF_3 functionality to a cyano group leading to a yield of 60% (entry 3, table 11).

Furthermore, the use of pentafluoro-aryl substituted amidyl radical precursor **118l** was investigated but, in this instance, a poor yield was attained (entry 4, table 11). As mentioned in the semi-pinacol project, this may be attributed to the reduction potential of amidyl precursor **118l** falling outside of the reduction potential range of $Ir(ppy)_3$ [$E_{1/2}(*Ir^{III}/Ir^{IV})$ = −1.73 V vs. SCE],[2] as a direct result of the electronic effect of pentafluoro-substituted aryl ring.



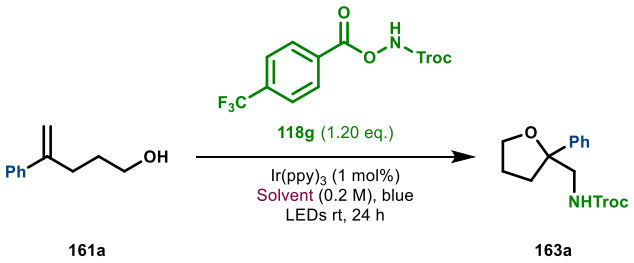
161a **163a**

Entry	Precursor	R	R^1	R^2	Yield/ %
1	**118g**	CF_3	H	H	72
2	**118m**[a]	H	CF_3	H	58
3	**118f**	CN	H	H	60
4	**118l**	F	F	F	55

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard; [a]Precursor synthesised by Dr Arunprasath Dhanarajan (Cuthbertson group)

Table 11: Further amidyl radical precursor screening experiments

Having established the feasibility of the process, a solvent screen was conducted using a range of polar aprotic solvents commonly utilized in photoredox catalysis (table 12).[19] It was found that utilizing acetonitrile provided a good yield (entry 1, table 12). Replacement of acetonitrile with DMSO, DMA or acetone led to poor yields (entry 2 – 4, table 12), and interestingly, the use of DCM in this reaction completely inhibited the formation of THF **163a** (entry 5, table 12). These results may be rationalised in terms of their dielectric constants, as less polar solvents such as DCM (dielectric constant = 9.08) are unable to solvate the transition state of the photoredox reaction compared to more polar solvents such as MeCN (dielectric constant = 38.30).[147]

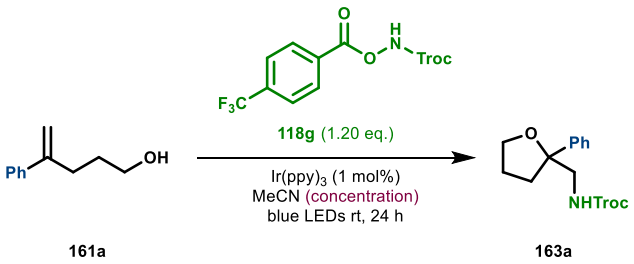


Entry	Solvent	Yield/ %
1	MeCN	70
2	DMSO	20
3	DMA	43
4	Acetone	37
5	DCM	0

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard

Table 12: Solvent screen

In addition to the solvent screen, the concentration of the reaction was also investigated (table 13). It was found that diluting the reaction mixture to 0.10 M reduced the yield of the reaction to 59% (entry 1, table 13) compared to standard concentration of 0.2 M (69% yield) (entry 2, table 13). A similar effect was observed when increasing the concentration to 0.3 M (48% yield) and 0.4 M (38% yield) (entries 3 – 4, table 13). It is worth noting, that at these higher concentrations, the reaction mixture appeared heterogeneous, and this may have contributed to the poor yield attained.

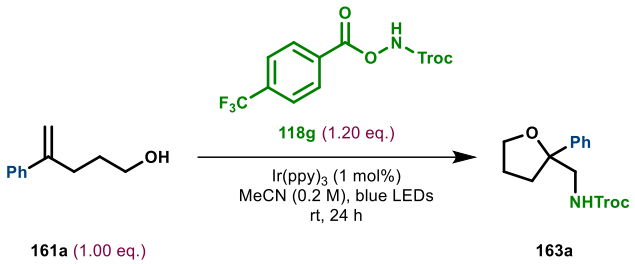


Entry	Concentration/ M	Yield/ %
1	0.10	59
2	0.20	69
3	0.30	48
4	0.40	38

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard

Table 13: Reaction mixture concentration screen

The stoichiometry of the reaction was also considered (table 14) to determine if the yield could be further enhanced whilst minimizing stoichiometry of reagents required. Utilizing an excess of the olefin provided a yield of 54% (entry 1, table 14), and a 1:1 ratio of olefin:precursor led to a 60% yield (entry 2, table 14). A similar yield of 59% was attained when using a slight excess of precursor **118g** (entry 3, table 14) which was significantly lower yield than the standard conditions (70% yield) (entry 4, table 14). Further increasing the stoichiometric excess of precursor **118g** to 0.30 and 0.40 equivalents proved futile and led to yields of 61% and 59% respectively (entries 5 – 6, table 14).

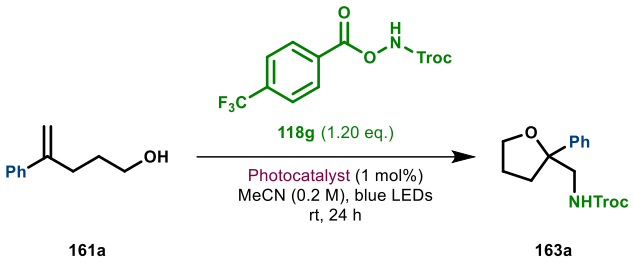


Entry	Olefin 161a/ eq.	Precursor 118g/ eq.	Yield/ %
1	1.10	1.00	54
2	1.00	1.00	60
3	1.00	1.10	59
4	1.00	1.20	70
5	1.00	1.30	61
6	1.00	1.40	59

Yields were determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard

Table 14: Stoichiometry screen

Following this, the reaction was tested using a variety of photocatalysts (table 15), which highlighted the requirement for strongly reducing $Ir(ppy)_3$ as a photocatalyst for this process, attaining a yield of 72% (entry 1, table 15). The use of a less strongly-reducing photocatalysts proved ineffective (entries 2 – 4, table 15), however it is noteworthy that there was some product observed in these instances, which differs from previous studies carried out in the semi-pinacol project when utilizing amidyl radical precursor **118g**. As a result of time constraints, further exploration of these results could not be carried out.



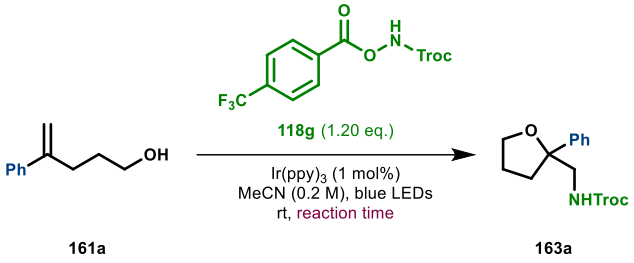
161a 163a

Entry	Photocatalyst	Yield/ %
1	$Ir(ppy)_3$	72
2	$[Ir[dF(CF_3)(ppy)]_2(dtbbpy)]PF_6$	6
3	$Ru(bpy)_3$	0
4	4CzIPN	8

Yields were determined by ^1H NMR spectroscopy using 1,3-benzodioxole as an internal standard

Table 15: Photocatalyst screen

With these optimised conditions in hand, the reaction time was monitored (table 16), to determine the optimum reaction time. Within the first 2 hours, the reaction proceeded at a high rate (entries 1 – 2, table 16), and gratifyingly at 3 hours, a comparative yield of 71% (entry 3, table 16) was attained. After 3 hours, the yield remained comparative (entries 4 – 5, table 16), and therefore the reaction time could be reduced from 24 hours to 3 hours.



161a 163a

Entry	Reaction time/ h	Yield/ %
1	1	32
2	2	58
3	3	71
4	4	71
5	24	72

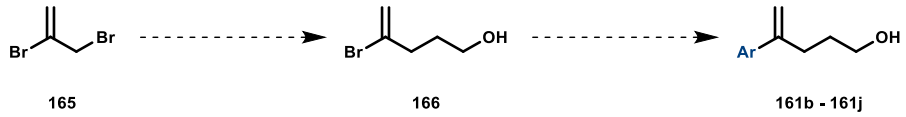
Yields were determined by ^1H NMR spectroscopy using 1,3-benzodioxole as an internal standard

Table 16: Reaction time study

Reaction Scope

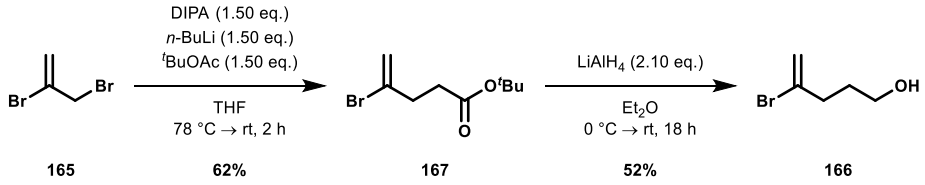
Aromatic Substrate Scope

The approach used for the synthesis of activated olefin substrates for the reaction scope focussed on employing a Suzuki-Miyaura coupling to rapidly access a range of styrene substrates (scheme 60).



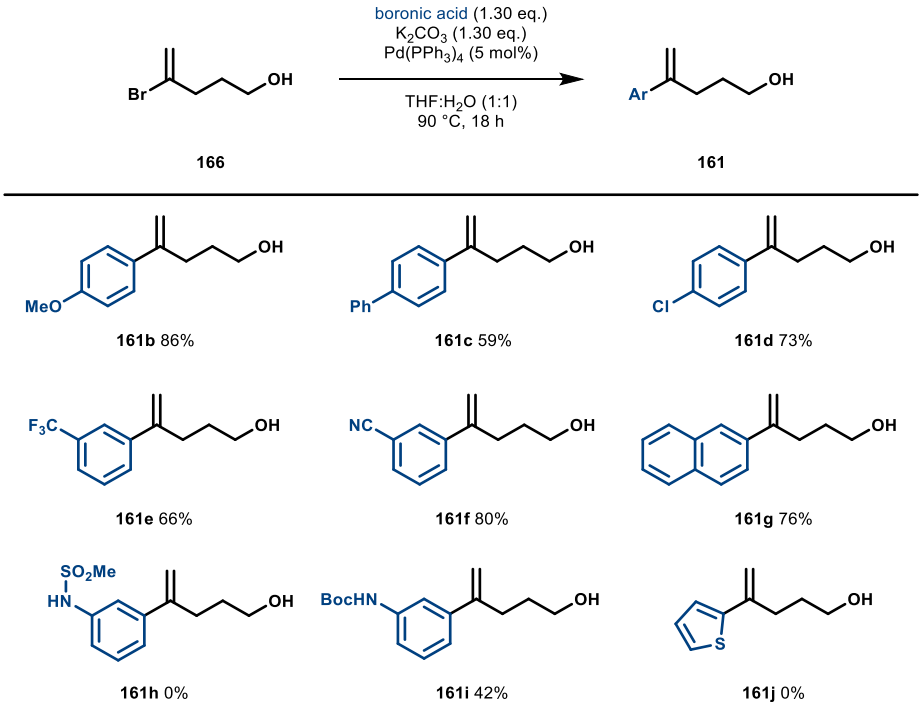
*Scheme 60: Synthetic route for the production of styrene substrates **161b** – **161j***

To generate precursor **166** required for the cross coupling, deprotonation of *tert*-butyl acetate with LDA and subsequent alkylation with bromide **165** gave ester **167** in a 62% yield.[146] Reduction of ester **167** using conditions reported by Campbell and co-workers, [146] provided vinyl bromide **166** in a 52% yield.



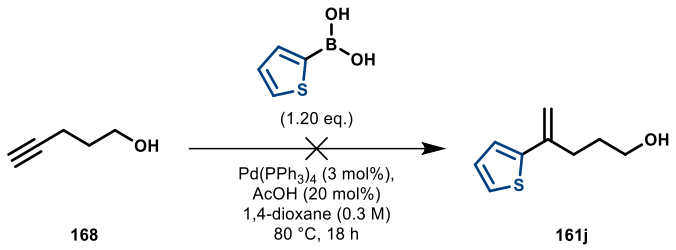
*Scheme 61: Formation of Suzuki-Miyaura cross coupling precursor **166** using conditions reported by Campbell et al.*[146]

Following this, a Suzuki-Miyaura cross coupling procedure reported by Truong *et al.*[148] using commercially available aryl boronic acids successfully provided olefin substrates **161b** – **161i** in moderate to good yields. Attempts were made to prepare sulfonamide **161h**, however these were unsuccessful, and as a result, Boc-protected aniline **161i** was synthesised in a 42% yield.



*Scheme 62: Synthesis of aromatic substrates **161b** – **161j** using Suzuki-Miyaura conditions reported by Truong et al.*[148]

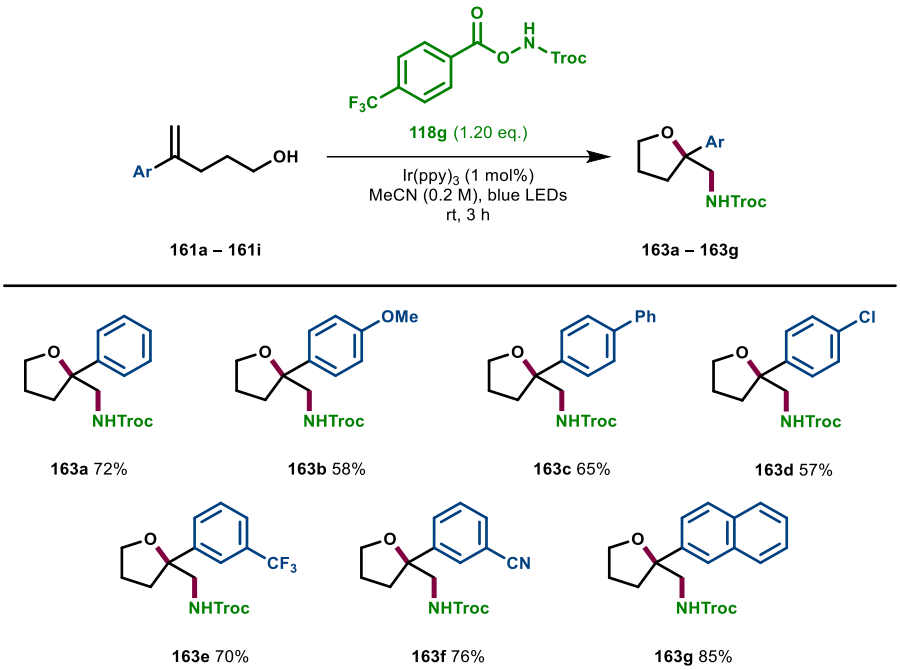
Attempts to synthesise thiophene **161j** using the Suzuki-Miyaura cross coupling were unfruitful, and an alternative palladium catalysed approach was attempted using terminal alkyne **168** and 2-thienylboronic acid.[149] This strategy however was also unsuccessful, and led to the formation of a complex mixture of regioisomers which were unable to be separated (scheme 63).



*Scheme 63: Attempt to synthesise thiophene substrate **161j** using conditions developed by Yasuda and coworkers*[149]

With the optimised conditions, and a range of styrene substrates **161a** – **161l** in hand, the scope of the reaction was explored (scheme 64). The unsubstituted styrene substrate **161a** used in the optimisation reactions provided **163a** in a 72% yield, and pleasingly the presence of an electron-donating groups (*p*-OMe group and 4-biphenyl) provided the corresponding products **161b** and **161c** in 58% and 65% yields respectively. A chloro-substituted aryl ring system was also well tolerated affording the corresponding product **161d** in a 57% yield.

Furthermore, substitution on the aryl ring was not limited to the *para*-position, and could be extended to the *meta*-position, such as with the generation of **163e** and **163f** in 70% and 76% yields respectively. The use of extended aromatic ring systems such as a naphthalene group were also compatible, enabling the formation of THF **163g** in an excellent yield.



Scheme 64: Aromatic olefin substrate scope

Gratifyingly, a single crystal of **163b** was submitted for X-ray crystallographic analysis, confirming the installation of the aminomethyl functionality, and the construction of the tetrahydrofuran ring (figure 8).

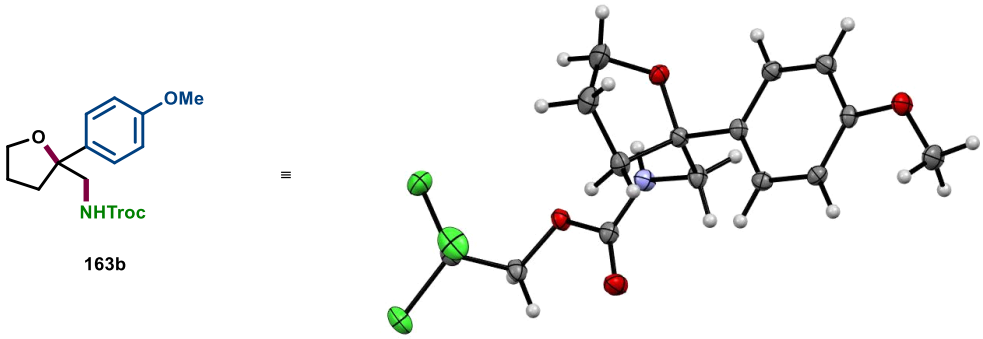
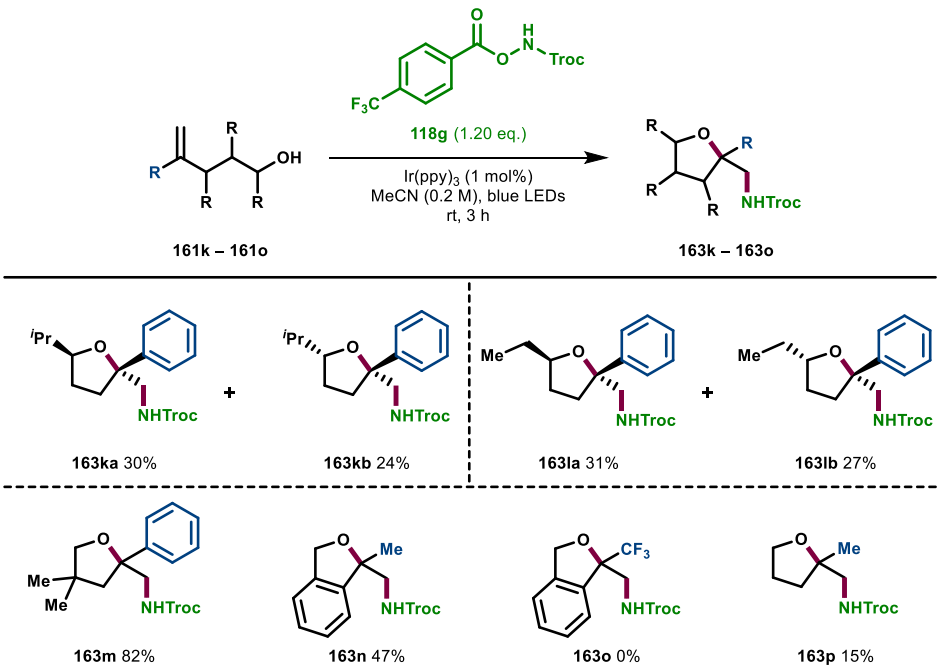


*Figure 8: X-ray crystal structure of para-methoxyphenyl product **163b** determined by Dr Stephen Argent (Chemistry Department, University of Nottingham)*

Encouraged by these results, a range of substituted olefin substrates (**161k** –**161p**) prepared by Dr Arunprasath Dhanarajan (Cuthbertson group), were subjected to the reaction conditions to examine the effect of the alcohol component on the reaction (scheme 65). Substitution in the 2 position by inclusion of an *iso*-propyl group provided diastereoisomers **163ka** and **163kb** in a 30% and 24% yield. Similarly, inclusion of an ethyl group in this position afforded diastereoisomers **163la** and **163lb** in a 31% and 27% yield. The identification of each diastereoisomer was based off the result of NOE experiments.

Geminal dimethyl substitution at the 4 position also enabled the generation of **3**in an 82% yield. This good yield was attributed to the Thorpe-Ingold effect, which could facilitate the cyclization process. Inclusion of a fused aromatic ring system led to the formation of benzofuran **163n** in a 47% yield. Notably, the substitution of the methyl group with a trifluoromethyl functionality inhibited the reaction, and led to no formation of benzofuran **163o**. This was rationalised as a result of the inductive withdrawal of electron density from the C=C bond to the CF_3 group, leading to an electron-deficient alkene which would be much less likely to be added into by an electron-deficient amidyl radical.

Interestingly, replacement of the phenyl group with a methyl group afforded THF **163p** in a 15% yield, illustrating that the reaction conditions could be extended to unactivated alkene substrates, which to our knowledge has not been demonstrated in the literature using a photoredox-mediated radical polar crossover strategy.



Scheme 65: Reaction scope of substrates bearing substitution on the alkyl chain

Gratifyingly, a single crystal of benzofuran **163n** was submitted for X-ray crystallographic analysis, confirming the identity of compound **163n** and the installation of the aminomethyl functionality, and the construction of the tetrahydrofuran ring (figure 9).

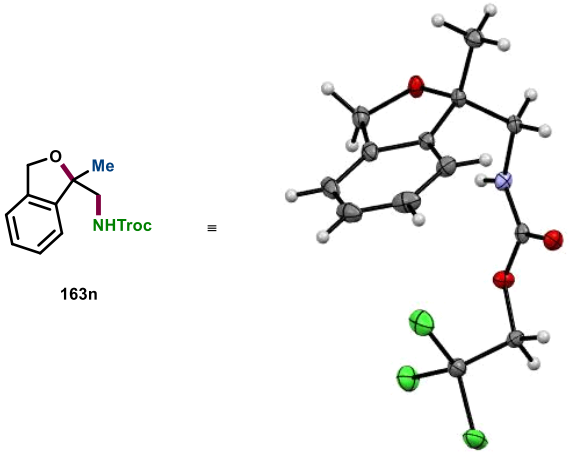
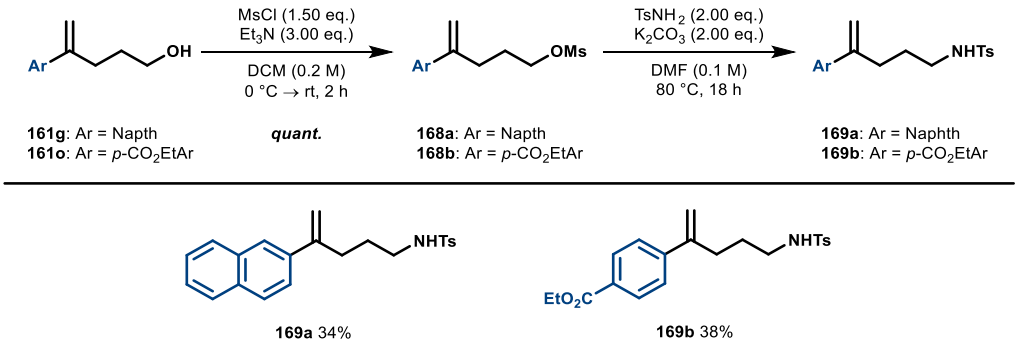


*Figure 9: X-ray crystal structure of benzofuran product **163n** determined by Dr Stephen Argent (Chemistry Department, University of Nottingham)*

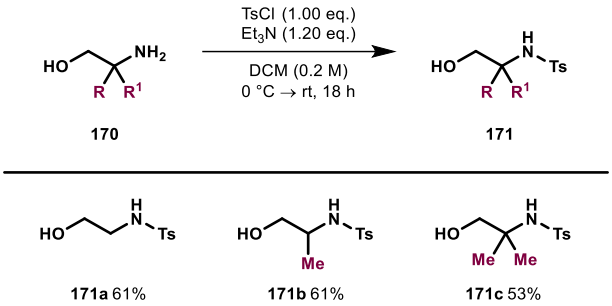
Saturated Heterocycle Scope

Encouraged by these results, we decided to synthesise a range of substrates to determine whether the reaction conditions could be extended to enable the synthesis of other saturated heterocycles. First, with the aim of generating pyrrolidine heterocyclic ring systems, *N*-tosyl substrates **169a** and **169b** were synthesised using a two-step procedure proceeding with the mesylation of the corresponding alkenols **161g** and **161o**, and a subsequent displacement of tosylamine onto mesylate **168a** and **168b**.[150] Although the mesylation step provided excellent yields of **169a** and **169b**, poor yields of *N*-tosyl substrates **168a** and **168b** were obtained during the displacement step.



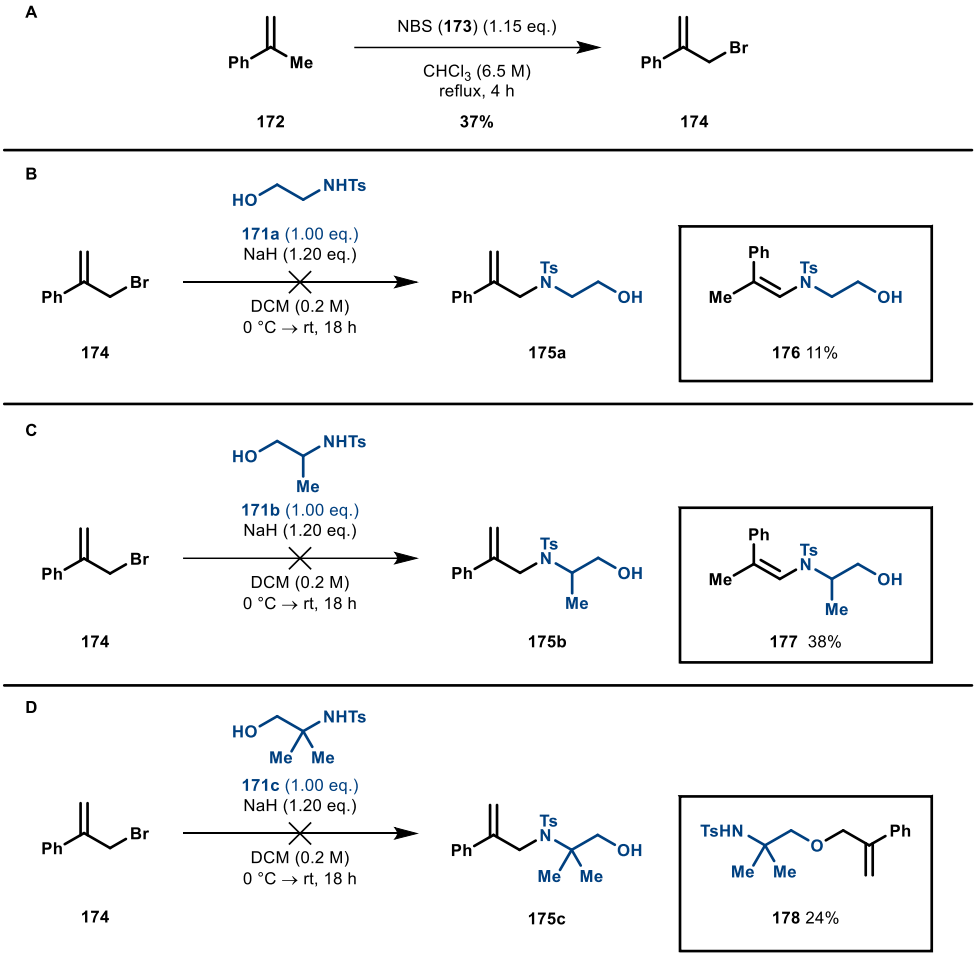
*Scheme 66: Synthesis of N-tosyl substrates **169a** and **169b***

With the aim of generating morpholine heterocycles, olefins **171a** – **171c** were targeted as substrates. The synthesis of these substrates was carried out using a 2-step route proceeding with the tosylation of the corresponding commercially available amino alcohol (scheme 67),[151,152] which enabled the formation of *N*-tosyl alcohol **171a** – **171c** in moderate yields.



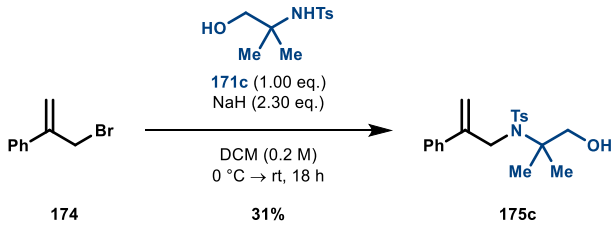
*Scheme 67: Synthesis of N-tosyl alcohol **171a** – **171c**[151,152]*

Following this, the second step utilized allyl bromide **174**, which was synthesised from α-methyl styrene (**172**) (scheme 68A) using methodology reported by Dong *et al.*,[153] which could be utilized to alkylate *N*-tosyl alcohol **171a** – **171c** (scheme 68) using conditions from Yar and coworkers.[151] Interestingly, initial attempts of the alkylation of *N*-tosylamine **171a** and **171b** led to the formation of enamine **176** (scheme 68B) and enamine **177** (scheme 68C), which may be as a result of the isomerisation of the desired products **175a** and **175b**. Furthermore, subjection of *N*-tosylamine **171c** to these alkylation conditions afforded *O*-alkylated product **178** in a 24% yield (scheme 68D).



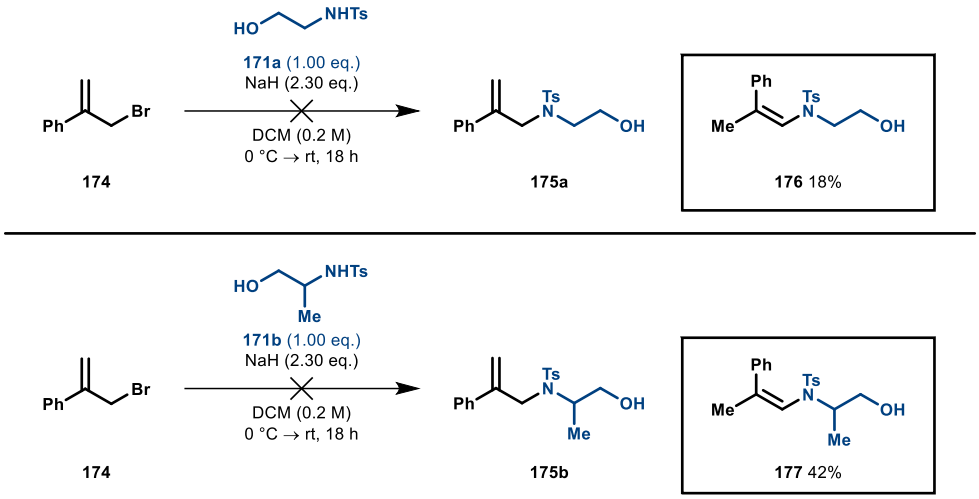
*Scheme 68: (A) Synthesis of allyl bromide **174**[153] Unsuccessful synthesis of: (B) **175a** (C) **175b** (D) Synthesis of O-alkylated product **178**[151]*

To promote the formation of substrate **175c**, 2.30 equivalents of NaH were used, as this would enable the deprotonation of both the alcohol and *N*-tosyl groups of N-tosyl alcohol **171c**, hopefully enabling the alkylation to occur at the more reactive N terminus. This proved fruitful and provided the *N*-alkylated product **175c** in a 31% yield (scheme 69).



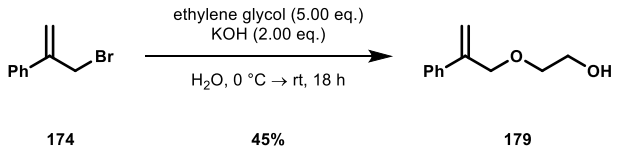
*Scheme 69: Synthesis of substrate **175c***

It is noteworthy that reaction of *N*-tosyl alcohol **171a** and **171b** under these conditions was unsuccessful in delivering substrates **175a** and **175b**. In these instances, enamine **176** and **177** were observed in increased yields of 18% and 42% yields respectively (scheme 70).



*Scheme 70: Unsuccessful synthesis of substrates **175a** and **175b***

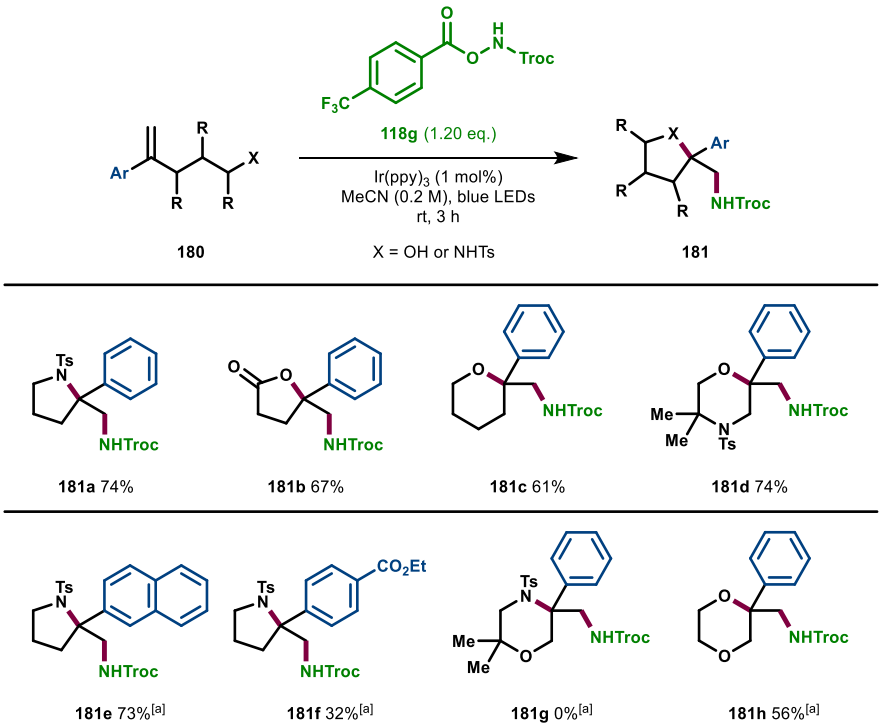
Pleasingly, ether **179** was synthesised with the aim of synthesising 1,4-dioxane ring systems, in a single step using a procedure developed by Glorius and coworkers,[154] affording substrate **179** in 45% yield (scheme 71).



*Scheme 71: Synthesis of ether **179**[154]*

The scope of the reaction with respect to the synthesis of saturated heterocycles was investigated (scheme 72). Generally, all heterocyclic ring systems were well tolerated, with five membered pyrrodoline **181a** and γ-lactone **181b** formed in yields of 74% and 67% respectively. This methodology was not limited to five membered ring systems only, and could be extended to six membered ring systems, as demonstrated in the formation of tetrahydropyran **181c** and morpholine **181d** in yields of 61% and 74% respectively.

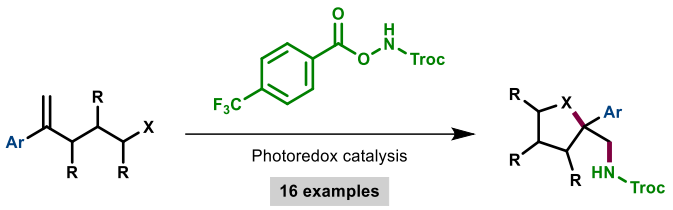
Unfortunately, due to time constraints, substrates **169a**, **169b**, **178** and **179** were not tested in the reaction by me. However, this project was continued by Dr Arunprasath Dhanarajan (Cuthbertson group), and *N*-tosyl substrate **169a** and **169b** were able to form pyrrolidine **181e** and **181f** in 73% and 32% yields, whilst no product **181g** was observed when *O*-alkylated substrate **178** was reacted under the standard conditions. Finally, use of ether substrate **179** provided 1,4-dioxane **181h** in a 56% yield.



Scheme 72: Saturated heterocycles substrate scope using tested substrates;[a]Reaction carried out by Dr Arunprasath Dhanarajan (Cuthbertson group)

Conclusions

In summary, the use of photoredox-generated amidyl radicals towards the generation of saturated heterocycles has been achieved, attaining yields of up to 82% (scheme 73).



Scheme 73: Photoredox-mediated radical-polar crossover utilizing amidyl radicals for the generation of saturated heterocycles

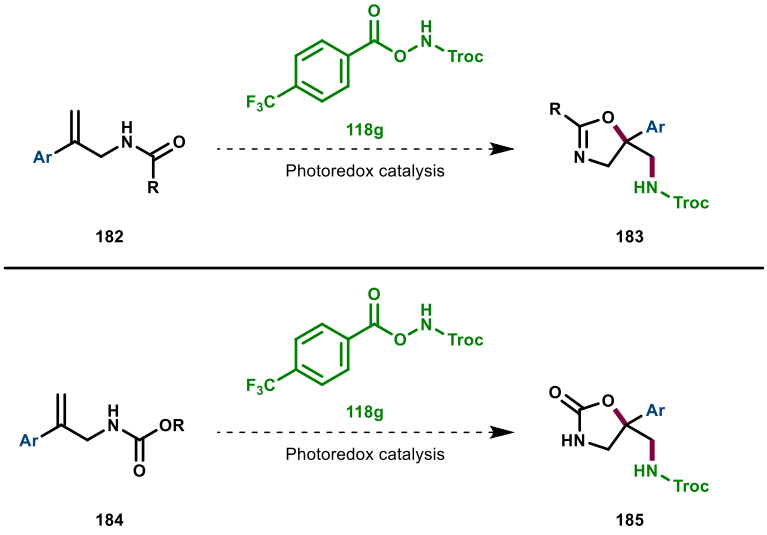
This methodology provides access to (2-aminomethyl)tetrahydrofuran derivatives in a one-pot procedure using radical-polar crossover chemistry and tolerates a range of activated alkene substrates containing numerous functional groups. Aryl halide substrates such as **161d** were also compatible, delivering product **163d** in moderate yield and giving rise to the potential of further transformations.

Furthermore, expansion of the reaction scope to substituted alcohol derivatives delivered substituted tetrahydrofuran derivatives in all cases, with the best yield being delivered by dimethyl substituted THF derivative **163m**. This was most likely because of the Thorpe-Ingold effect aiding the cyclization process and could be explored further to access THF derivatives which may not be tolerant of the reaction conditions.

Moreover, this mode of reactivity has been extended to enable the formation of other saturated heterocycles bearing an aminomethyl moiety, such as pyrrolidines **181a**, lactones **181b**, tetrahydropyrans **181c** and morpholines **181d** in moderate to good yields.

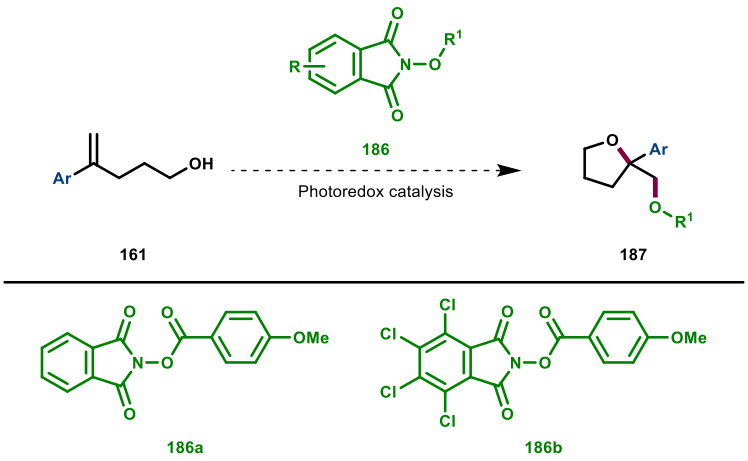
Future Work

Future work would comprise of expanding the substrate scope to include other saturated heterocycles. One such avenue to explore is oxazoles **183** and oxazolidinones **185** using amides **182** and carbamates **184** respectively and our reaction conditions (scheme 74) which would enable access to these pharmaceutically interesting motifs,[155,156] in addition to increasing the synthetic utility of the developed methodology.



*Scheme 74: Extension of current conditions for the formation of oxazoles **183** and oxazolidinones **185***

Other types of radicals, such as oxygen-centred radicals could also be explored (scheme 75). These may include *N*-alkoxyphthalimides *O*-centered radical precursors such as **186a** and **186b**, which are precedented in the literature.[157] This would enable access to all carbon quaternary centres bearing a protected alcohol (**187**).



Scheme 75: Application of current conditions to oxygen-centered radicals

General Experimental

Starting materials were obtained from commercial sources and were used without further purification unless stated otherwise. Reactions were carried out under an atmosphere of argon (unless otherwise stated), and reactions requiring anhydrous conditions were performed in oven-dried apparatus using distilled solvents. Acetonitrile and tetrahydrofuran were taken from an Inert® PureSolv MD5 solvent purification system under nitrogen. Photochemical reactions were carried out using an EvoluChem™ PhotoRedOx Box under irradiation at 450 nm using an EvoluChem™ LED (30 W) at room temperature. Standard borosilicate glass vessels were used. All water used was deionised, petrol refers to petroleum ether (b.p. 40-60 °C), and ether refers to diethyl ether. Thin layer chromatography was carried out using Merck silica gel precoated sheets SIL G/UV254, which were visualised under UV light then stained with basic potassium permanganate solution or vanillin-sulfuric acid solution. Flash column chromatography was performed using Merck silica gel 60, 35-70 μm particles as the packing agent.

NMR spectra were obtained as dilute solutions in the appropriate solvent at 298 K unless otherwise stated. Spectra were recorded on the δ scale in ppm referenced to the residual solvent peak ($CDCl_3$ δ_H 7.26, δ_C 77.16). Spectra were recorded on Bruker AV400 MHz, AV(III) 400 MHz or AV(III) 500 MHz. The multiplicity of each signal is denoted by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. J values are reported in Hertz (Hz) to the nearest decimal place. ^{1}H and ^{13}C NMR assignments were made using 2D data.

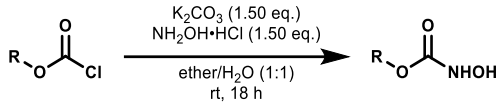
All IR experiments were carried out on a Bruker Tensor 27 FT-IR spectrometer. Mass spectra were recorded on a Micro TOF 61 spectrometer using electrospray ionisation techniques with positive ion detection. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. X-ray diffraction data were collected at 120 K on an Agilent SuperNova diffractometer using CuKα radiation by Dr Stephen Argent (Chemistry Department, University of Nottingham).

Determination of ^{1}H NMR Yields for Optimisation Experiments

To the heterogeneous end of reaction mixture, was added $CDCl_3$ (3 mL) and left to stir until homogenous. 1,3-Benzodioxole (1.00 eq.) was added to the homogenous crude solution, and an aliquot (0.2 mL) of this homogenous solution was diluted in $CDCl_3$ (0.7 mL) and submitted for ^{1}H NMR.

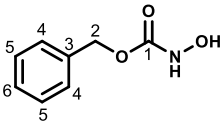
Preparation of Amidyl Radical Precursors

General procedure A: [158] Synthesis of hydroxylamine derivatives



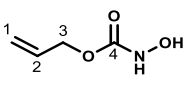
116 117

To a mixture of hydroxylamine hydrochloride (1.50 eq.) and K_2CO_3 (1.50 eq.) in ether:water (1:1) cooled to 0 °C, was added chloroformate (1.00 eq.) dropwise, and the reaction mixture was left to stir at room temperature for 18 h. The organic phase was then separated and the aqueous was extracted using ether (3 × 80 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product which was taken through to the next step without purification.



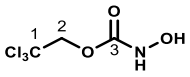
Benzyl hydroxycarbamate (117a): Prepared according to general procedure a using hydroxylamine hydrochloride (1.04 g, 15.0 mmol, 1.50 eq.), K_2CO_3 (2.08 g, 15.0 mmol, 1.50 eq.) and benzyl chloroformate (1.43 mL, 10.0 mmol, 1.00 eq.) in ether (40 mL) and water (40 mL) to afford the crude product as a white solid (1.65 g, 9.85 mmol, 99%); R_f = 0.53 (cyclohexane/EtOAc; 6:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.31 (5H, m, H-4, H-5 and H-6), 5.17 (2H, s, C-2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3 (C, C-1), 135.5 (ArC, C-3), 128.8 (ArCH), 128.7 (ArCH), 128.5 (ArCH), 68.1 (CH_2, C-2).

Data are consistent with those reported in the literature.[158]



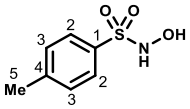
Allyl hydroxycarbamate (117b): Prepared according to general procedure A using hydroxylamine hydrochloride (1.04 g, 15.0 mmol, 1.50 eq.), K_2CO_3 (2.07 g, 15.0 mmol, 1.50 eq.) and allyl

chloroformate (1.09 mL, 10.0 mmol, 1.00 eq.) in ether (40 mL) and water (40 mL) to afford the crude product as a colourless oil (1.03 g, 8.83 mmol, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, br s, NH), 5.95-5.85 (1H, m, H-2), 5.40 – 5.19 (2H, m, H-1), 4.64 (2H, d, *J*= 5.7 Hz, H-3). ^{13}C NMR (101 MHz, $CDCl_3$) 159.3 (C, C-4), 131.9 (CH, C-2), 118.9 (CH_2, C-1), 66.9 (CH_2, C-3).
Data are consistent with those reported in the literature.[159]



2,2,2-Trichloroethyl hydroxycarbamate (117c): Prepared according to general procedure A using hydroxylamine hydrochloride (1.06 g, 15.0 mmol, 1.50 eq.), K_2CO_3 (2.08 g, 15.0 mmol, 1.50 eq.) and 2,2,2-trichloroethyl chloroformate (1.40 mL, 10.0 mmol, 1.00 eq.) in ether (40 mL) and water (40 mL) to afford the crude product as a colourless solid (2.17 g, 10.0 mmol, *quant.*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (1H, br s, OH), 6.16 (1H, br s, NH), 4.80 (2H, s, H-2). ^{13}C NMR (126 MHz, $CDCl_3$) 156.9 (C, C-3), 94.9 (C, C-1), 75.1 (CH_2, C-2).

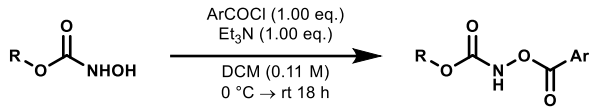
Data are consistent with those reported in the literature.[116]



***N*-hydroxy-4-methylbenzenesulfonamide**[160] **(117d):** To a mixture of hydroxylamine hydrochloride (1.09 g, 15.7 mmol) in pyridine (5 mL) cooled to 0 °C, was added DMAP (1.92 g, 15.7 mmol) then tosyl chloride (1.50 g, 7.90 mmol). After 2 h, the reaction mixture was quenched using aq. 1 M HCl solution (20 mL), and the aqueous layer was extracted using ethyl acetate (3 × 50 mL). The combined organic phase was acidified to pH 3 using aq. 1 M HCl solution (2 × 20 mL), and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide the crude. Washing of the crude with cold DCM (20 mL) provided the title compound as a pale yellow solid (791 mg, 4.23 mmol, 54%); mp. 158 – 160 °C (Lit.[160] 154 – 156 °C); ^{1}H NMR (500 MHz, MeOD) δ 7.81 (2H, d, *J* = 8.4 Hz, H-2), 7.40 (2H, d, *J* = 8.4 Hz, H-3), 2.46 (3H, s, H-5); ^{13}C NMR (126 MHz, MeOD) δ 145.5 (ArC, C-4), 135.7 (ArC, C-1), 130.4 (ArCH, C-3), 129.7 (ArCH, C-2), 21.5 (CH_3, C-5).

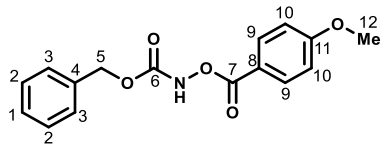
Data are consistent with those reported in the literature.[160]

General procedure B: [116] Synthesis of Amidyl Radical Precursors

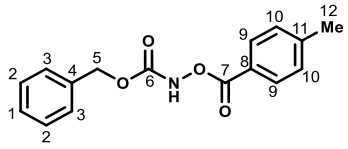


117 (1.50 eq.) **118**

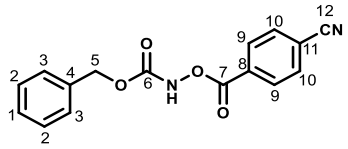
To a stirred solution of hydroxycarbamate (1.50 eq.) in DCM (0.11 M) at 0 °C, was added triethylamine (1.00 eq.). Benzoyl chloride (1.00 eq.) was added at 0 °C, then the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched using aq. 1 M HCl solution (30 mL). The organic phase was separated and washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.



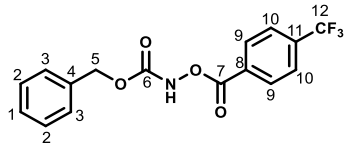
Benzyl [(4-methoxybenzoyl)oxy]carbamate (118a): Prepared according to general procedure B using crude benzyl hydroxycarbamate **117a** (814 mg, 4.78 mmol), triethylamine (440 μL, 3.19 mmol) and *para*-methoxybenzoyl chloride (430 μL, 3.19 mmol) in DCM (24 mL). Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 6:4) gave the title compound **118a** (802 mg, 2.13 mmol, 67%) as a colourless crystalline solid; R_f = 0.32 (cyclohexane/EtOAc; 6:4); mp. 69 – 71 °C; υ_{max}/cm^{-1} 3210, 2940, 1754, 1708, 1606, 1237, 1166, 1107, 757, 742; ^{1}H NMR (500 MHz, $CDCl_3$) 8.46 (1H, br s, NH), 8.09 – 8.01 (2H, m, H-9), 7.41 – 7.29 (5H, m, H-1, H-2 and H-3), 6.99 – 6.91 (2H, m, H-10), 5.24 (2H, s, H-5), 3.87 (3H, s, H-12); ^{13}C NMR (126 MHz, $CDCl_3$) 165.6 (C, C-7), 164.5 (C, C-6), 156.7 (ArC, C-11), 135.2 (ArC, C-4), 132.3 (ArCH, C-9), 128.7 (ArCH, C-2), 128.6 (ArCH, C-1), 128.4 (ArCH, C-3), 118.8 (ArC, C-8), 114.1 (ArCH, C-10), 68.4 (CH_2, C-5), 55.7 (CH_3, C-12); [HRMS (ESI+) Exact mass cald. for $C_{16}H_{19}N_2O_5$, 319.1288. Found $[MH_4N]^+$, 319.1287 (0.50 ppm error)].



Benzyl [(4-methylbenzoyl)oxy]carbamate (118b): Prepared according to general procedure B using crude benzyl hydroxycarbamate **117a** (790 mg, 4.72 mmol), triethylamine (330 μL, 2.36 mmol) and *para*-toluoyl chloride (310 μL, 2.36 mmol) in DCM (24 mL). Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 8:2) gave the title compound **118b** (605 mg, 2.15 mmol, 91%) as a colourless crystalline solid; R_f = 0.53 (cyclohexane/EtOAc; 6:4); mp. 99 – 100 °C; υ_{max}/cm^{-1} 1970, 1770, 1713, 1286, 745; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (1H, br s, NH), 7.98 (2H, d, *J*= 8.2 Hz, H-9), 7.44 – 7.26 (7H, m, H-1, H-2, H-3 and H-10), 5.25 (2H, s, H-5), 2.43 (3H, s, H-12); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0 (C, C-7), 156.6 (C, C-6), 145.4 (ArC, C-11), 135.2 (ArC, C-4), 130.2 (ArCH, C-9), 129.6 (ArCH, C-10), 128.8 (ArCH, C-2), 128.7 (ArCH, C-1), 128.4 (ArCH, C-3), 123.9 (ArC, C-8), 68.5 (CH_2, C-5), 22.0 (CH_3, C-12); [HRMS (ESI+) Exact mass cald. for $C_{16}H_{15}NNaO_4$, 308.0893. Found $[MNa]^+$, 308.0894 (0.10 ppm error)].

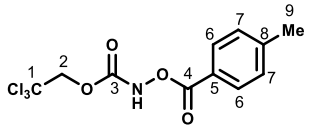


Benzyl [(4-cyanobenzoyl)oxy]carbamate (118c): Prepared according to general procedure B using crude benzyl hydroxycarbamate **117a** (1.65 g, 9.85 mmol), triethylamine (920 μL, 6.57 mmol) and *para*-cyanobenzoyl chloride (1.09 g, 6.57 mmol) in DCM (50 mL). Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 8:2) gave the title compound **118c** (1.92 g, 6.48 mmol, 99%) as a colourless crystalline solid; R_f = 0.39 (cyclohexane/EtOAc; 6:4); mp. 126 – 128 °C; υ_{max}/cm^{-1} 3218, 2188, 1777, 1707, 1492, 1238, 1109, 869, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (1H, br. s, NH), 8.20 (2H, d, *J*= 8.3 Hz, H-9), 7.79 (2H, d, *J*= 8.3 Hz, H-10), 7.39-7.35 (5H, m, H-1, H-2 and H-3), 5.26 (2H, s, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4 (C, C-7), 156.2 (C, C-6), 134.9 (ArC, C-4), 132.7 (ArCH, C-10), 130.6 (ArCH, C-9), 130.1 (ArC, C-8), 128.9 (ArCH, C-1), 128.9 (ArCH, C-3), 128.6 (ArCH, C-2), 117.9 (C, C-12), 117.7 (ArC, C-11), 68.9 (CH_2, C-5); [HRMS (ESI+) Exact mass cald. for $C_{16}H_{12}N_2NaO_4$, 319.0689. Found $[MNa]^+$, 319.0688 (0.30 ppm error)].

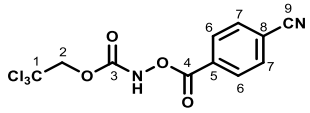


Benzyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (118d): Prepared according to general procedure B using crude benzyl hydroxycarbamate **117a** (797 mg, 4.78 mmol), triethylamine (440 μL, 3.19 mmol) and *para*-trifluoromethylbenzoyl chloride (480 μL, 3.19 mmol) in DCM (24 mL). Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 8:2) gave the title compound **118d** (661 mg, 1.95 mmol, 61%) as a colourless crystalline solid; R_f = 0.58 (petrol/EtOAc; 6:4); mp. 118 – 120 °C (Lit.[161] 115 – 117 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (1H, br s, NH), 8.19 (2H, d, *J*= 8.0 Hz, H-9), 7.74 (2H, d, *J*= 8.0 Hz, H-10), 7.37 – 7.33 (5H, m, H-1, H-2 and H-3), 5.25 (2H, s, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8 (C, C-7), 156.4 (C, C-6), 135.7 (ArC, q, *J*= 32.8 Hz, C-11), 135.0 (ArC, C-4), 130.5 (ArCH, C-9), 130.1 (ArC, C-8), 128.8 (ArCH, C-2), 128.8 (ArCH, C-1), 128.5 (ArCH, C-3), 125.9 (ArCH, q, *J*= 3.7 Hz, C-10), 123.5 (C, q, *J*= 272.9 Hz, C-12), 68.7 (CH_2, C-5); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.3 ppm [HRMS (ESI+) Exact mass cald. for $C_{16}H_{12}F_3NNaO_4$, 362.0611. Found $[MNa]^+$, 362.0607 (1.10 ppm error)].

Data are consistent with those reported in the literature.[161]

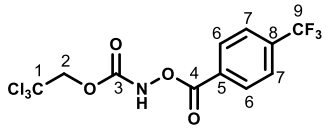


2,2,2-Trichloroethyl [(4-methylbenzoyl)oxy]carbamate (118e): Prepared according to general procedure B using crude 2,2,2-trichloroethyl hydroxycarbamate **117a** (1.05 g, 5.05 mmol), triethylamine (470 μL, 3.37 mmol) and *para*-toluoyl chloride (460 μL, 3.37 mmol) in DCM (32 mL). Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 8:2) gave the title compound **117a** (1.09 g, 3.34 mmol, 99%) as a colourless crystalline solid; R_f = 0.50 (petrol/EtOAc; 6:4); mp. 81 – 83 °C; υ_{max}/cm^{-1} 3253, 1757, 1735, 1233, 1127, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (1H, s, NH), 8.00 (2H, d, *J*= 8.3 Hz, H-6), 7.30 (2H, d, *J*= 8.3 Hz, H-7), 4.84 (2H, s, H-2), 2.44 (3H, s, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (C, C-4), 154.8 (C, C-3), 145.7 (ArC, C-8), 130.2 (ArCH, C-6), 129.7 (ArCH, C-7), 123.6 (ArC, C-5), 94.6 (C, C-1), 75.3 (CH_2, C-2), 22.0 (CH_3, C-9); [HRMS (ESI+) Exact mass cald. for $C_{11}H_{14}{}^{35}Cl_3N_2O_4$, 343.0014. Found $[MH_4N]^+$, 343.0013 (0.20 ppm error)].



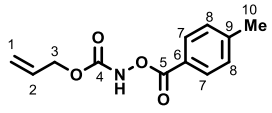
2,2,2-Trichloroethyl [(4-cyanobenzoyl)oxy]carbamate (118f): Prepared according to general procedure B using crude 2,2,2-trichloroethyl hydroxycarbamate **117c** (2.17 g, 10.4 mmol), triethylamine (970 μL, 6.94 mmol) and *para*-cyanobenzoyl chloride (1.15 g, 6.94 mmol) in DCM (65 mL). Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 8:2) gave the title compound **118f** (1.90 g, 5.62 mmol, 81%) as a colourless crystalline solid; R_f = 0.46 (cyclohexane/EtOAc; 6:4); mp. 71 – 73 °C; υ_{max}/cm^{-1} 3203, 2192, 1783, 1730, 1492, 1228, 1132, 755; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (1H, s, NH), 8.21 (2H, d, *J*= 8.5 Hz, H-6), 7.81 (2H, d, *J*= 8.5 Hz, H-7), 4.85 (2 H, s, H-2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1 (C, C-4), 154.5 (C, C-3), 132.7 (ArCH, C-7), 130.7 (ArCH, C-6), 130.3 (ArC, C-5), 118.1 (C, C-9), 117.6 (ArC, C-8), 94.4 (C, C-1), 75.4 (CH_2, C-2); [HRMS (ESI+) Exact mass cald. for $C_{11}H_7{}^{35}Cl_3NaN_2O_4$, 358.9364. Found $[MNa]^+$, 358.9358 (1.70 ppm error)].

Data are consistent with those reported in the literature.[116]

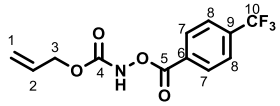


2,2,2-Trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (118g): Prepared according to general procedure B using crude 2,2,2-trichloroethyl hydroxycarbamate **117c** (2.10 g, 10.1 mmol), triethylamine (940 μL, 6.70 mmol) and *para*-trifluoromethylbenzoyl chloride (1.00 mL, 6.70 mmol) in DCM (64 mL). Purification by column chromatography (SiO_2, cyclohexane:EtOAc – 8:2) provided the title compound **118g** as a colourless crystalline solid (2.49 g, 6.55 mmol, 98%); R_f = 0.32 (cyclohexane/EtOAc; 8:2); υ_{max}/cm^{-1} 3224, 1772, 1728, 1487, 1128; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (1H, br s, NH), 8.24 (2H, d, *J*= 8.3 Hz, H-6), 7.78 (2H, d, *J*= 8.3 Hz, H-7), 4.86 (2H, s, H-2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5 (C, C-4), 154.5 (C, C-3), 136.0 (ArC, q, *J*= 32.9 Hz, C-8), 130.6 (ArCH, C-6), 129.7 (ArC, C-5), 126.0 (ArCH, q, *J*= 3.7 Hz, C-7), 125.1 (C, q, *J*= 273 Hz, C-9), 94.5 (C, C-1), 75.4 (CH_2, C-2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.4 ppm [HRMS (ESI+) Exact mass calcd for $C_{11}H_7{}^{35}Cl_3F_3N_2NaO_4$, 401.9285. Found $[MNa]^+$, 401.9283 (0.60 ppm error)].

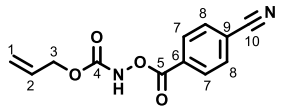
Data are consistent with those reported in the literature.[116]



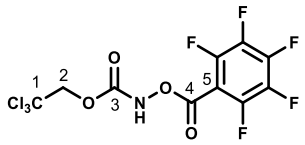
Allyl [(4-methylbenzoyl)oxy]carbamate (118i): Prepared according to general procedure B using crude allyl hydroxycarbamate **117b** (226 mg, 1.93 mmol), triethylamine (180 μL, 1.28 mmol) and *para*-toluoyl chloride (170 μL, 1.28 mmol) in DCM (10 mL). Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 9:1) gave the title compound **118i** (268 mg, 1.13 mmol, 89%) as a yellow oil; R_f = 0.38 (cyclohexane/EtOAc; 8:2); υ_{max}/cm^{-1} 1757, 1735, 1233, 1127, 703; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 8.3 Hz, H-7), 7.30 (2H, d, *J* = 8.3 Hz, H-8), 5.81 – 5.71 (1H, m, H-2), 5.41 – 5.26 (1H, m, H-1A), 5.24 – 5.16 (1H, m, H-1B), 4.76 – 4.63 (2H, m, H-3), 2.48 – 2.42 (3H, m, H-10; ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1 (C, C-5), 156.5 (C, C-4), 143.4 (ArC, C-9), 131.5 (ArC, C-6), 130.5 (CH, C-2), 129.6 (ArCH, C-7), 129.0 (ArCH, C-8), 119.3 (CH_2, C-1), 68.4 (CH_2, C-3), 22.01 (CH_3, C-10); HRMS (ESI+) Exact mass cald. for $C_{12}H_{14}NO_4$, 236.0917. Found $[MNa]^+$, 236.0917 (0.10 ppm error)].



Allyl [(4-(trifluoromethyl)benzoyl)oxy]carbamate (118j): Prepared according to general procedure B using crude allyl hydroxycarbamate **117b** (1.03 g, 8.83 mmol), triethylamine (820 μL, 5.89 mmol) and *para*-trifluoromethylbenzoyl chloride (880 μL, 5.89 mmol) in DCM (32 mL). Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 8:2) gave the title compound **118j** (1.64 g, 5.66 mmol, 96%) as a colourless solid; R_f = 0.46 (cyclohexane/EtOAc; 6:4); mp. 65 – 68 °C; υ_{max}/cm^{-1} 1775, 1727, 1325, 1232, 1158, 1115, 1009, 860; ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (1H, br. s, NH), 8.22 (2H, d, *J*= 8.2 Hz, H-7), 7.77 (2H, d, *J*= 8.2 Hz, H-8), 5.98 – 5.88 (1H, m, H-2), 5.38 (1H, dd, *J*= 17.2, 1.4 Hz, H-1_A), 5.30 (1H, dd, *J*= 10.5, 1.4 Hz, H-1_B), 4.73 (2H, d, *J*= 5.7 Hz, H-3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9 (C, C-5) 156.2 (C, C-4), 136.0 (ArC, q, *J*= 33.0 Hz, C-9), 135.7 (ArC, C-6), 131.4 (CH, C-2), 130.6 (ArCH, C-7), 130.1 (C, q, *J*= 273.0 Hz, C-10), 126.0 (ArCH, C-8), 119.4 (CH_2, C-1), 67.6 (CH_2, C-3). [HRMS (ESI+) Exact mass cald. for $C_{12}H_{10}F_3NNaO_4$, 312.0454. Found $[MNa]^+$, 312.0456 (0.50 ppm error)].



Allyl [(4-cyanobenzoyl)oxy]carbamate (118k): Prepared according to general procedure B using crude allyl hydroxycarbamate **117b** (330 mg, 2.78 mmol), triethylamine (260 μL, 1.85 mmol) and *para*-cyanobenzoyl chloride (310 mg, 1.85 mmol) in DCM (10 mL). Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 8:2) gave the title compound **118k** (376 mg, 1.54 mmol, 84%) as a colourless solid; R_f = 0.41 (cyclohexane/EtOAc; 6:4); mp. 81 – 82 °C; υ_{max}/cm^{-1} 3220, 2197, 1738, 1455, 1423, 1250, 1223, 1181, 1122, 1110, 994, 962; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (1H, br s, NH), 8.21 (2H, d, *J*= 8.4 Hz, H-7), 7.80 (2H, d, *J*= 8.4 Hz, H-8), 5.98 – 5.89 (1H, m, H-2), 5.38 (1H, dd, *J*= 17.2, 1.4 Hz, H-1_A), 5.30 (1H, dd, *J*= 10.4, 1.4 Hz, H-1_B), 4.73 (2H, d, *J*= 5.7 Hz, H-3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4 (C, C-5), 156.1 (C, C-4), 132.7 (ArCH, C-7), 131.3 (CH, C-2), 130.7 (ArC, C-6), 130.6 (ArCH, C-8), 119.5 (ArC, C-9), 117.9 (CN, C-10), 117.7 (CH_2, C-1), 67.7 (CH_2, C-3); [HRMS (ESI+) Exact mass cald. for $C_{12}H_{10}N_2NaO_4$, 269.0533. Found $[MNa]^+$, 269.0526 (2.40 ppm error)].

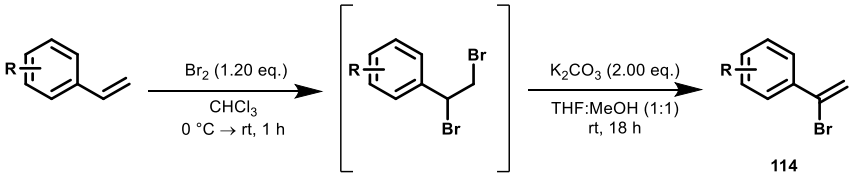


2,2,2-Trichloroethyl ((perfluorobenzoyl)oxy)carbamate (118l): To a suspension of pentafluorobenzoic acid (2.12 g, 10.0 mmol) in DCM (12 mL), was added DMF (3 drops) then oxalyl chloride (169 μL, 20.0 mmol). The reaction mixture was heated at reflux for 2 h then concentrated *in vacuo*. The residue was diluted in DCM (10 mL) and further concentrated *in vacuo* to provide the crude pentafluorobenzoyl chloride. The title compound was prepared according to general procedure B using crude 2,2,2-trichloroethyl hydroxycarbamate **117c** (1.83 g, 8.79 mmol), triethylamine (820 μL, 5.86 mmol) and crude pentafluorobenzoyl chloride (1.35 g, 5.86 mmol) in DCM (40 mL). Purification using column chromatography afforded 2,2,2-trichloroethyl ((perfluorobenzoyl)oxy)carbamate (**118l**) as a white solid (1.57 g, 3.91 mmol, 67%); R_f = 0.35 (cyclohexane/EtOAc; 8:2); m.p 65-66 °C; υ_{max}/cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (1H, s, NH), 4.86 (3H, s, H-2).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (C-4), 154.3 (C-3), 147.5 (m, ArC), 146.2 – 145.7 (m, ArC), 145.1 – 144.7 (m, ArC), 143.6 – 143.0 (m, ArC), 139.7 – 138.9 (m, ArC), 137.1 – 136.5 (m, ArC), 104.6 – 104.4 (m, ArC), 94.3 (C-1), 75.6 (C-2); ^{19}F NMR (376 MHz, $CDCl_3$) δ -134.8 − -134.6 (m), -144.5 − -144.2 (m),

-159.7 – -158.7 (m); [HRMS (ESI+) Exact mass cald. for $C_{10}H_2{}^{35}Cl_3{}^{19}F_5NO_4$, 399.8975. Found $[MH]^+$, 399.8985 (2.40 ppm error)].

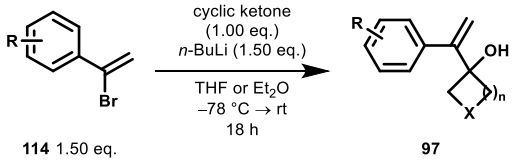
Synthesis of Substrates for Semi-pinacol Project

General procedure C:[113] Synthesis of Bromostyrene Intermediates



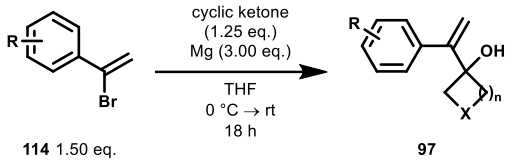
To a solution of styrene derivative (1.00 eq.) in chloroform (0.38 M) cooled to 0 °C, was added bromine (1.20 eq.). The reaction mixture was left to stir at rt for 1 h, then was quenched using sat. aq. $Na_2S_2O_3$ solution (12 mL) and diluted with chloroform (20 mL). The organic phase was separated and washed with brine (2 × 20 mL) then concentrated *in vacuo* to provide the crude dibrominated intermediate. To a solution of the crude dibrominated intermediate (1.00 eq.) in THF: MeOH (1:1, 0.2 M) was added K_2CO_3 (2.00 eq.) and left to stir at rt for 18 h. The reaction mixture was diluted in ethyl acetate (20 mL) and water (20 mL), then the aqueous layer was separated and extracted using ethyl acetate (2 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude product.

General procedure D:[115] Synthesis of Activated Photoredox Substrates – Organolithium approach



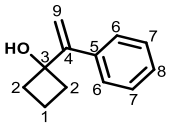
To a solution of α-bromostyrene (1.50 eq.) in THF (0.5 M) cooled to −78 °C, was added *n*-BuLi (1.50 eq.) dropwise, then the reaction mixture was left to stir at −78 °C for 1 h. A solution of cyclic ketone (1.00 eq.) in THF (0.5 M) was then added dropwise, before the reaction mixture was warmed to room temperature and left to stir for a further 18 h. The reaction mixture was quenched using sat. aq. NH_4Cl solution (12 mL), then the reaction mixture was separated and extracted using ethyl acetate (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

General procedure E:[162] Synthesis of activated photoredox substrates – Grignard approach



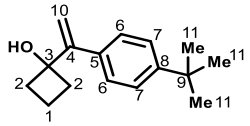
114 1.50 eq. **97**

To a suspension of Mg (3.00 eq.) in THF (1.2 M), was added α-bromostyrene (1.00 eq.) dropwise as a solution in THF (1.2 M), then the suspension was left to stir at room temperature for 1 h. The suspension was cooled to 0 °C, then a solution of cyclic ketone (1.25 eq.) in THF (1.2 M) was added dropwise. The reaction mixture was warmed to room temperature and left to stir for a further 18 h. The reaction mixture was quenched using sat. aq. NH_4Cl solution (12 mL) then the aqueous phase was separated and extracted using DCM (3 × 30 mL). The combined organic phases were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.



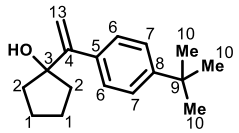
1-(1-Phenylvinyl)cyclobutanol (97a): Prepared according to general procedure D using α-bromostyrene (1.95 mL, 15.0 mmol) in THF (30 mL), *n*-BuLi (2.5 M in hexanes, 6.00 mL, 15.0 mmol) and cyclobutanone (750 μL, 10.0 mmol) in THF (20 mL) to afford the crude product. Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 4:1) gave 1-(1-phenylvinyl)cyclobutanol (**97a**) (1.43 g, 8.20 mmol, 82%) as a yellow oil; R_f = 0.30 (cyclohexane/ethyl acetate, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.46 (2H, m, H-7), 7.35 – 7.28 (3H, m, H-6 and H-8), 5.38 (1H, br. s, H-9_A), 5.36 (1H, br. s, H-9_B), 2.51 – 2.44 (2H, m, H-2_A), 2.29 – 2.21 (2H, m, H-2_B), 2.04 – 1.94 (2H, m, H-1_A and OH), 1.67 – 1.60 (1H, m, H-1_B); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5 (C, C-4), 139.2 (ArC, C-5), 128.3 (ArCH, C-7), 127.8 (ArCH, C-8), 127.7 (ArCH, C-6), 113.0 (CH_2, C-9), 78.2 (C, C-3) 35.8 (CH_2, C-2), 13.5 (CH_2, C-1).

Data are consistent with those reported in the literature.[163]



1-{1-[4-(*tert*-Butyl)phenyl]vinyl}cyclobutan-1-ol (97b): Prepared using general procedure C using 4-*tert*-butylstyrene (2.72 mL, 15.0 mmol), bromine (920 μL, 18.0 mmol) and chloroform (40 mL) to form the dibrominated intermediate. Then K_2CO_3 (4.15 g, 30.0 mmol) and THF:MeOH (1:1, 70 mL) to yield crude 1-(1-bromovinyl)-4-(*tert*-butyl)benzene (2.94 g, 12.3 mmol, 82%). The title compound was prepared according to general procedure D using crude 1-(1-bromovinyl)-4-(*tert*-butyl)benzene (2.94 g, 12.3 mmol) in THF (25 mL), *n*-BuLi (2.5 M in hexanes, 7.70 mL, 12.3 mmol) and cyclobutanone (620 μL, 8.19 mmol) in THF (27 mL) to afford the crude product. Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 20:1) gave the title compound **97b** (1.35 g, 5.85 mmol, 71%) as a colourless oil; R_f = 0.38 (cyclohexane/ethyl acetate, 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.40 (2H, m, H-7), 7.37 – 7.32 (2H, m, H-6), 5.36 (1H, br s, H-10_A), 5.35 (1H, br s, H-10_B), 2.55 – 2.45 (2H, m, H-2_A), 2.31 – 2.22 (2H, m, H-2_B), 2.03 – 1.93 (2H, m, H-1_A and OH), 1.70 – 1.58 (1H, m, H-1_B), 1.33 (9H, s, H-11); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (C, C-4), 150.7 (ArC, C-8), 136.0 (ArC, C-5), 127.3 (ArCH, C-6), 125.3 (ArCH, C-7), 112.2 (CH_2, C-10), 78.3 (C, C-3), 35.9 (CH_2, C-2), 34.65 (C, C-9), 31.5 (CH_3, C-11), 13.5 (CH_2, C-1).

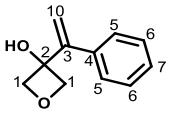
Data are consistent with those reported in the literature.[163]



1-{1-[4-(*tert*-Butyl)phenyl]vinyl}cyclopentan-1-ol (97c): Prepared using general procedure C using 4-*tert*-butylstyrene (2.72 mL, 15.0 mmol), bromine (920 μL, 18.0 mmol) and chloroform (40 mL) to form the dibrominated intermediate. Then K_2CO_3 (4.15 g, 30.0 mmol) and THF:MeOH (1:1, 70 mL) to yield crude 1-(1-bromovinyl)-4-(*tert*-butyl)benzene (2.77 g, 11.6 mmol, 77%). The title compound was prepared according to general procedure D using crude 1-(1-bromovinyl)-4-(*tert*-butyl)benzene (2.77 g, 11.6 mmol) in THF (23 mL), *n*-BuLi (2.5 M in hexanes, 4.64 mL, 11.6 mmol) and cyclopentanone (690 μL, 7.70 mmol) in THF (15 mL) to afford the crude product. Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 20:1) gave the title compound **97c** (1.39 g, 5.69 mmol, 74%) as a colourless crystalline solid; mp. 101 – 103 °C; R_f = 0.20 (cyclohexane/ethyl acetate, 20:1); ^{1}H

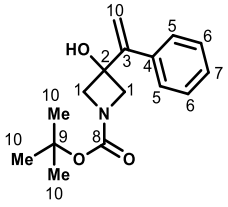
NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (4H, m, H-6 and H-7), 5.40 (1H, d, *J*= 1.4 Hz, H-11_A), 5.08 (1H, d, *J*= 1.4 Hz, H-11_B), 1.94 – 1.84 (4H, m, H-1_A, H-2_A), 1.83 – 1.76 (2H, m, H-2_B) 1.72 – 1.62 (2H, m, H-1_B), 1.33 (9H, s, H-10); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8 (C, C-4), 150.0 (ArC, C-8), 138.7 (ArC, C-5), 128.2 (ArCH, C-6), 124.9 (ArCH, C-7), 113.0 (CH_2, C-11), 84.3 (CH_2, C-3), 39.4 (CH_2, C-2), 34.6 (C, C-9), 31.5 (CH_3, C-10), 23.5 (CH_2, C-1).

All data, except melting point, are consistent with those reported in the literature.[164]



3-(1-Phenylvinyl)oxetan-3-ol (97d): The title compound was prepared according to general procedure D using α-bromostyrene (200 µL, 1.50 mmol) in THF (3 mL), *n*-BuLi (2.5 M in hexanes, 600 µL, 1.50 mmol) and 3-oxetanone (65.0 µL, 1.00 mmol) in THF (200 µL). Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 10:1) gave the title compound **97d** (100 mg, 567 µmol, 56%) as a yellow oil; R_f = 0.17 (cyclohexane/ethyl acetate, 6:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.31 (5H, m, H-5, H-6 and H-7), 5.59 (1H, s, H-10_A), 5.40 (1H, s, H-10_B), 4.91 (2H, dd, *J* = 7.0, 0.8 Hz, H-1_A), 4.79 (2H, dd, *J* = 7.0, 0.8 Hz, H-1_B); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1 (C, C-3), 137.4 (ArC, C-4), 128.8 (ArCH, C-6), 128.3 (ArCH, C-7), 126.9 (ArCH, C-5), 114.8 (CH_2, C-10), 83.4 (C, C-2), 77.2 (CH_2, C-1).

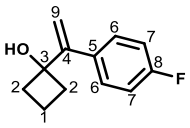
Data are consistent with those reported in the literature.[110]



***tert*-Butyl 3-hydroxy-3-(1-phenylvinyl)azetidine-1-carboxylate (97e):** Prepared according to general procedure D using α-bromostyrene (200 µL, 1.50 mmol) in THF (3 mL), *n*-BuLi (2.5 M in hexanes, 600 µL, 1.50 mmol) and 1-Boc-3-azetidinone (172 mg, 1.00 mmol) in THF (200 µL). Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 10:1) gave the title compound **97e** (116 mg, 421 µmol, 42%) as a colourless crystalline solid; mp. 97 – 99 °C (lit.[110] 95 – 110 °C); R_f = 0.22 (cyclohexane/ethyl acetate, 8:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.35 (2H, m, H-6), 7.35 – 7.23 (3H, m, H-5 and H-7), 5.50 (1H, s, H-10_A), 5.38 (1H, s, H-10_B), 4.21 (2H, d, *J* = 9.1 Hz, H-1_A), 4.03 (2H, d, *J* = 9.1 Hz, H-1_B), 1.40 (9H, s, H-10); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4 (C, C-8), 149.5 (C-3), 137.7 (ArC, C-4),

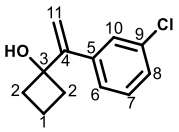
128.5 (ArCH, C-6), 128.0 (ArCH, C-7), 127.0 (ArCH, C-5), 114.8 (CH_2, C-10), 79.8 (C, C-9), 72.4 (C, C-2), 69.8 (CH_2, C-1), 28.2 (CH_3, C-10).

Data are consistent with those reported in the literature.[110]



1-[1-(4-Fluorophenyl)vinyl]cyclobutan-1-ol (97f): Prepared using general procedure C using 4-fluorostyrene (1.20 mL, 10.0 mmol), bromine (620 μL, 12.0 mmol) and chloroform (20 mL) to form the dibrominated intermediate. Then K_2CO_3 (2.77 g, 20.0 mmol) and THF:MeOH (1:1, 44 mL) to yield crude 1-(1-bromovinyl)-4-fluorobenzene (1.79 g, 8.92 mmol, 89%). The title compound was prepared according to general procedure D using crude 1-(1-bromovinyl)-4-fluorobenzene (1.79 g, 8.92 mmol) in THF (18 mL), *n*-BuLi (2.5 M in hexanes, 3.60 mL, 8.92 mmol) and cyclobutanone (450 μL, 5.95 mmol) in THF (12 mL) to afford the crude product. Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 20:1) gave 1-[1-(4-fluorophenyl)vinyl]cyclobutan-1-ol (**97f**) (290 mg, 1.51 mmol, 25%) as a pale yellow oil; R_f = 0.30 (cyclohexane/ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.41 (2H, m, H-6), 7.05 – 6.95 (2H, m, H-7), 5.36 (1H, s, H-9_a), 5.32 (1H, s, H-9_B), 2.50 – 2.38 (2H, m, H-2_A), 2.27 – 2.16 (2H, m, H-2_B), 2.06 – 1.92 (1H, m, H-1_A), 1.85 (1H, br. s, OH), 1.68 – 1.58 (1H, m, H-1_B); ^{13}C NMR (126 MHz, $CDCl_3$) 162.5 (d, *J* = 246.1 Hz, ArC, C-8), 151.5 (C, C-4), 135.2 (d, *J* = 3.5 Hz, ArC, C-5), 129.4 (d, *J* = 7.8 Hz, ArCH, C-6), 115.2 (d, *J* = 21.0 Hz, ArCH, C-7), 113.0 (CH_2, C-9), 78.2 (C, C-3), 35.8 (CH_2, C-2), 13.5 (CH_2, C-1); ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.08 (tt).

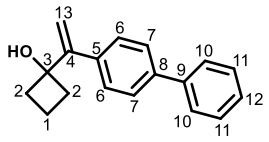
Data are consistent with those reported in the literature.[163]



1-[1-(3-Chlorophenyl)vinyl]cyclobutan-1-ol (97g): Prepared using general procedure C using 3-chlorostyrene (1.28 mL, 10.0 mmol), bromine (620 μL, 12.0 mmol) and chloroform (20 mL) to form the dibrominated intermediate. Then K_2CO_3 (2.77 g, 20.0 mmol) and THF:MeOH (1:1, 44 mL) to yield crude 1-(1-bromovinyl)-3-chlorobenzene (2.10 g, 9.64 mmol, 96%). The title compound was prepared according to general procedure E using crude 1-(1-bromovinyl)-3-chlorobenzene (2.10 g, 9.64 mmol) in THF (8 mL), Mg (703 mg, 28.9

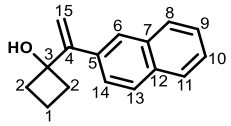
mmol) in THF (24 mL) and cyclobutanone (904 μL, 12.1 mmol) in THF (10 mL) to afford the crude product. Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 20:1) gave 1-[1-(3-chlorophenyl)vinyl]cyclobutan-1-ol (**97g**) (260 mg, 1.24 mmol, 12%) as a yellow oil; R_f = 0.48 (cyclohexane/ethyl acetate, 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.47 (1H, m, H-7), 7.44 – 7.36 (1H, m, H-8), 7.31 – 7.24 (2H, m, H-6 and H-10), 5.43 (1H, s, H-11_A), 5.40 (1H, s, H-11_B), 2.52 – 2.41 (2H, m, H-2_A), 2.29 – 2.18 (2H, m, H-2_B), 2.07 – 1.95 (1H, m, H-1_A), 1.92 (1H, br. s, OH), 1.71 – 1.58 (1H, m, H-1_B); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (C, C-4), 141.2 (ArC, C-5), 134.1 (ArC, C-9), 129.5 (ArCH, C-7), 127.9 (ArCH, C-8), 127.7 (ArCH, C-10), 125.9 (ArCH, C-6), 114.1 (CH_2, C-11), 78.1 (C, C-3), 35.8 (CH_2, C-2), 13.5 (CH_2, C-1).

Data are consistent with those reported in the literature.[162]



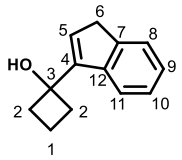
1-{1-[(1,1'-Biphenyl)-4-yl]vinyl}cyclobutan-1-ol (97h): Prepared using general procedure C using 4-vinylbiphenyl (1.81 g, 10.0 mmol), bromine (620 μL, 12.0 mmol) and chloroform (20 mL) to form the dibrominated intermediate. Then K_2CO_3 (2.77 g, 20.0 mmol) and THF:MeOH (1:1, 44 mL) to yield crude 4-(1-bromovinyl)-1,1'-biphenyl (2.54 g, 9.80 mmol, 98%). The title compound was prepared according to general procedure E using crude 4-(1-bromovinyl)-1,1'-biphenyl (2.54 g, 9.80 mmol) in THF (8 mL), Mg (712 mg, 29.3 mmol) in THF (24 mL) and cyclobutanone (920 μL, 12.2 mmol) in THF (10 mL) to afford the crude product. Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 20:1) afforded 1-{1-[(1,1'-biphenyl)-4-yl]vinyl}cyclobutan-1-ol (**97h**) (668 mg, 2.67 mmol, 27%) a yellow oil; R_f = 0.45 (cyclohexane/ethyl acetate, 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.55 (6H, m, H-6, H-7 and H-10), 7.51 – 7.43 (2H, m, H-11), 7.43 – 7.33 (1H, m, H-12), 5.43 (1H, s, H-13_A), 5.40 (1H, s, H-13_B), 2.60 – 2.46 (2H, m, H-2_A), 2.32 – 2.24 (2H, m, H-2_B), 2.11 – 1.99 (1H, m, H-1_A), 1.98 (1H, s, OH), 1.75 – 1.61 (1H, m, H-1_B); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (C, C-4), 140.9 (ArC, C-9), 140.5 (ArC, C-8), 138.1 (ArC, C-5), 128.9 (ArCH, C-11), 128.1 (ArCH, C-7), 127.5 (ArCH, C-12), 127.2 (ArCH, C-10), 127.0 (ArCH, C-6), 113.0 (CH_2, C-13), 78.3 (C, C-3), 35.9 (CH_2, C-2), 13.6 (CH_2, C-1).

Data are consistent with those reported in the literature.[163]



1-[1-(Naphthalen-2-yl)vinyl]cyclobutan-1-ol (97i): Prepared using general procedure C using 2-vinylnaphthalene (1.54 g, 10.0 mmol), bromine (620 μL, 12.0 mmol) and chloroform (20 mL) to form the dibrominated intermediate. Then K_2CO_3 (2.58 g, 18.7 mmol) and THF:MeOH (1:1, 44 mL) to yield crude 2-(1-bromovinyl)naphthalene (1.93 g, 8.29 mmol, 89%). The title compound was prepared according to general procedure E using crude 2-(1-bromovinyl)naphthalene (1.93 g, 8.29 mmol) in THF (7 mL), Mg (605 mg, 24.9 mmol) in THF (21 mL) and cyclobutanone (770 μL, 10.4 mmol) in THF (9 mL) to afford the crude product. Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 20:1) gave 1-[1-(naphthalen-2-yl)vinyl]cyclobutan-1-ol (**97i**) (530 mg, 2.37 mmol, 29%) as a yellow oil; R_f = 0.40 (cyclohexane/ethyl acetate, 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, s, H-6), 7.91 – 7.76 (3H, m, H-11, H-13 and H-14), 7.63 (1H, dd, *J*= 8.5, 1.8 Hz, H-8), 7.54 – 7.42 (2H, m, H-9 and H-10), 5.53 – 5.45 (2H, m, H-15), 2.61 – 2.46 (2H, m, H-2_A), 2.38 – 2.29 (2H, m, H-2_B), 2.12 – 1.94 (2H, m, H-1_A and OH), 1.75 – 1.56 (1H, m, H-1_B); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6 (C, C-4), 136.6 (ArC, C-5), 133.4 (ArC, C-7), 132.9 (ArC, C-12), 128.4 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 126.6 (ArCH), 126.2 (ArCH), 126.1 (ArCH), 126.0 (ArCH), 113.5 (CH_2, C-15), 78.4 (C, C-3), 35.9 (CH_2, C-2), 13.6 (CH_2, C-1).

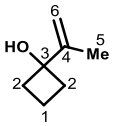
Data are consistent with those reported in the literature.[110]



1-(1*H*-Inden-3-yl)cyclobutan-1-ol (97i): The title compound was prepared according to general procedure D using indene (700 μL, 6.00 mmol), *n*-BuLi (2.5 M in hexanes, 2.40 mL, 6.00 mmol) and cyclobutanone (300 μL, 4.00 mmol) in diethyl ether (8 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 9:1 → 8:2) gave 1-(1*H*-inden-3-yl)cyclobutan-1-ol (**97i**) (570 mg, 3.05 mmol, 76%) as a colourless crystalline solid; mp. 105 – 107 °C (Lit.[7] 97 – 98 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (1H, d, *J*= 7.5 Hz, H-11), 7.49 (1H, d, *J*= 7.4 Hz, H-8), 7.30 (1H, dd, *J*= 7.5, 1.0 Hz, H-10), 7.23 (1H, app. dt, *J*= 7.4 Hz, H-9), 6.46 (1H, t, *J*= 2.0 Hz, H-5), 3.41 (2H, d, *J*= 2.0 Hz, H-6), 2.64 – 2.55 (2H, m, H-2_A), 2.45 – 2.32 (2H, m, H-2_B), 2.06 (1H, br. s, O-H), 1.98 – 1.88 (1H, m, H-1_A), 1.70 – 1.57 (1H, m, H-

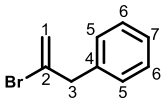
1_B); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4 (C, C-12), 145.2 (C, C-7), 142.8 (C, C-4) , 128.3 (CH, C-5), 126.1 (ArCH, C-10), 125.0 (ArCH, C-9), 124.2 (ArCH, C-8), 121.7 (ArCH, C-11), 74.1 (C, C-3), 37.7 (CH_2, C-6), 35.7 (CH_2, C-2), 13.4 (CH_2, C-1).

All data, except melting point, are consistent with those reported in the literature.[165]



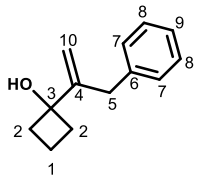
1-(Prop-1-en-2-yl)cyclobutan-1-ol (97j): The title compound was prepared according to general procedure E using 2-bromopropene (1.34 mL, 15.0 mmol) in THF (12.5 mL), Mg (1.10 g, 45.0 mmol) in THF (37.5 mL) and cyclobutanone (1.40 mL, 18.8 mmol) in THF (16 mL). Purification by column chromatography (SiO_2, petrol:diethyl ether – 8:2) gave 1-(prop-1-en-2-yl)cyclobutan-1-ol (**97j**) (420 mg, 3.74 mmol, 25%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 – 4.95 (1H, m, H-6_A), 4.86 (1H, t, *J* = 1.4 Hz, H-6_B), 2.40 – 2.28 (2H, m, H-2_A), 2.12 – 1.98 (2H, m, H-2_B), 1.96 – 1.82 (1H, m, H-1_A), 1.80 (3H, br. s, H-5), 1.66 (1H, br. s, OH), 1.63 – 1.47 (1H, m, H-1_B); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0 (C, C-4), 109.7 (CH_2, C-6), 78.1 (C, C-3), 34.5 (CH_2, C-2), 17.6 (CH_2, C-1), 13.0 (CH_3, C-5).

Data are consistent with those reported in the literature.[125]



(2-Bromoallyl)benzene[110] **(133)**: To a suspension of CuCl (500 µg, 0.50 mmol) in diethyl ether (10 mL), was added 2,3-dibromopropene (980 µL, 10.0 mmol) then phenylmagnesium bromide solution (3 M in hexanes, 3.70 mL, 11.0 mmol). The reaction mixture was heated at reflux for 4 h, before being left to stir at rt for a further 18 h. The reaction mixture was cooled to 0 °C and quenched with sat. aq. NH_4Cl solution (12 mL). The aqueous layer was extracted using diethyl ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide the crude product. Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 9:1) gave (2-bromoallyl)benzene (**133**) (1.81 g, 9.17 mmol, 92%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (5H, m, H-5, H-6 and H-7), 5.61 (1H, d, *J* = 1.6 Hz, H-1_A), 5.56 (1H, d, *J* = 1.6 Hz, H-1_B), 3.79 (2H, s, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3 (ArC, C-4), 132.9 (C, C-2), 129.2 (ArCH, C-5), 128.8 (ArCH, C-7), 128.6 (ArCH, C-6), 118.2 (CH_2, C-1), 47.9 (CH_2, C-3).

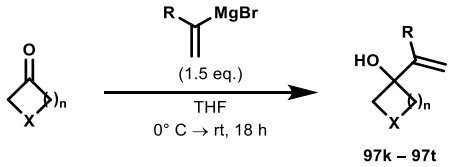
Data are consistent with those reported in the literature.[110]



1-(3-Phenylprop-1-en-2-yl)cyclobutan-1-ol (97v): The title compound was prepared according to general procedure E using (2-bromoallyl)benzene (900 mg, 4.57 mmol) in THF (4 mL), Mg (333 mg, 13.7 mmol) in THF (11 mL) and cyclobutanone (430 µL, 5.71 mmol) in THF (20 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 9:1 → 6:4) gave 1-(3-phenylprop-1-en-2-yl)cyclobutan-1-ol (**97v**) (662 mg, 3.52 mmol, 77%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (2H, m, H-8), 7.25 – 7.16 (3H, m, H-7 and H-9), 5.16 (1H, d, *J* = 1.0 Hz, H-10_A), 4.70 (1H, d, *J* = 1.0 Hz, H-10_B), 3.46 (2H, s, H-5), 2.40 – 2.29 (2H, m, H-2_A), 2.12 – 2.00 (2H, m, H-2_B), 1.99 – 1.85 (1H, m, H-1_A), 1.67 – 1.50 (1H, m, H-1_B); ^{13}C NMR (101 MHz, $CDCl_3$) 152.0 (C, C-4), 140.2 (ArC, C-6), 129.5 (ArCH, C-7) 128.5 (ArCH, C-8), 126.2 (ArCH, C-9), 111.2 (CH_2, C-10), 78.7 (C, C-3), 37.5 (CH_2, C-5), 35.0 (CH_2, C-2), 13.3 (CH_2, C-1).

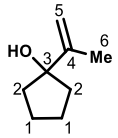
Data are consistent with those reported in the literature.[166]

General procedure F:[167] Synthesis of Unactivated Photoredox Substrates – Grignard Approach



97k – 97t

To a solution of alkenyl magnesium bromide (1.50 eq.) cooled to 0 °C, was added a solution of ketone (1.00 eq.) in THF (0.5 M) dropwise, then the reaction mixture was warmed to room temperature and left to stir for a further 18 h. The reaction mixture was quenched using sat. aq. NH_4Cl (10 mL) and the aqueous phase was extracted using ethyl acetate (3 × 30 mL). The combined organic phases were concentrated *in vacuo*.

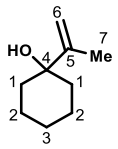


1-(Prop-1-en-2-yl)cyclopentan-1-ol (97l): The title compound was prepared according to general procedure F using isopropenylmagnesium bromide solution (0.5 M in THF, 9 mL, 4.50

mmol) and cyclopentanone (270 µL, 3.00 mmol) in THF (6 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 9:1) gave 1-(prop-1-en-2-yl)cyclopentan-1-ol (**97l**) (240 mg, 1.90 mmol, 63%) as a yellow oil; ν_{max}/cm^{-1} 3386, 2960, 2872, 1186, 1003, 897; ^1H NMR (400 MHz, $CDCl_3$) δ 5.02 (1H, d, J = 1.6 Hz, H-5_A), 4.80 (1H, d, J = 1.6 Hz, H-5_B), 1.93 – 1.75 (7H, m, H-1_A, H2_A and H-6), 1.75 – 1.58 (4H, m, H-1_B and H-2_B); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9 (C, C-4), 109.3 (CH_2, C-5), 84.5 (C, C-3), 38.6 (CH_2, C-2), 23.9 (CH_2, C-1), 19.6 (CH_3, C-6). [HRMS (GC-EIMS) Exact mass cald. for $C_8H_{14}O$, 126.1039. Found $[MH]^+$, 126.1032 (5.89 ppm error)].

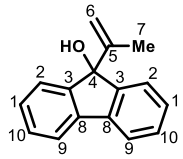
Note: Multiple HRMS techniques failed to give an accurate mass within 5 ppm.

Data are consistent with those reported in the literature.[164]



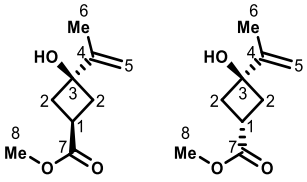
1-(Prop-1-en-2-yl)cyclohexan-1-ol (97l): The title compound was prepared according to general procedure F using isopropenylmagnesium bromide solution (0.5 M in THF, 9.00 mL, 4.50 mmol) and cyclohexanone (310 µL, 3.00 mmol) in THF (6 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 9:1) gave 1-(prop-1-en-2-yl)cyclohexan-1-ol (**97l**) (301 mg, 2.15 mmol, 72%) as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.01 (1H, s, H-6_A), 4.81 (1H, s, H-6_B), 1.80 (3H, s, H-7), 1.71 – 1.48 (10H, m, H-1, H-2 and H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1 (C, C-5), 109.4 (CH_2, C-6), 73.8 (C, C-4), 36.0 (CH_2, C-1), 25.8 (CH_2, C-3), 22.2 (CH_2, C-2), 19.1 (CH_3, C-7).

Data are consistent with those reported in the literature.[129]



9-(Prop-1-en-2-yl)-9*H*-fluoren-9-ol (97m): The title compound was prepared according to general procedure F using isopropenylmagnesium bromide solution (0.5 M in THF, 9.00 mL, 4.50 mmol) and 9-fluorenone (542 mg, 3.00 mmol) in THF (6 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 9:1) gave 9-(prop-1-en-2-yl)-9*H*-fluoren-9-ol (**97m**) (527 mg, 2.37 mmol, 79%) as a yellow oil; R_f = 0.22 (cyclohexane/ethyl acetate;

9:1); ν_{max}/cm^{-1} 3531, 3405, 1447, 1255, 1055, 986, 901, 753, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, ddd, *J*= 7.5, 1.0, 1.0 Hz, H-2), 7.45 – 7.35 (4H, m, H-1 and H-9), 7.30 (2H, ddd, *J*= 7.5, 1.0, 1.0 Hz, H-10), 5.71 (1H, s, H-6$_A$), 5.13 (1H, s, H-6$_B$), 2.20 (1H, br. s, O-H), 1.24 (3H, s, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4 (C, C-5), 145.5 (C, C-3), 140.3 (C, C-8), 129.3 (ArCH, C-1), 128.4 (ArCH, C-10), 123.9 (ArCH, C-9), 120.2 (ArCH, C-2), 111.0 (CH_2, C-6), 84.8 (C, C-4), 18.7 (CH_3, C-7). [HRMS (ESI+) Exact mass cald. for $C_{16}H_{14}NaO$, 245.0937. Found $[MNa]^+$, 245.0936 (0.60 ppm error)].

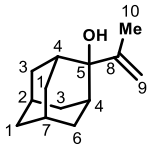


97n 97n'

Methyl 3-hydroxy-3-(prop-1-en-2-yl)cyclobutane-1-carboxylate (97n and 97n'): To a stirred solution of methyl 3-oxocyclobutanecarboxylate (340 µL, 3.15 mmol) in THF (6 mL) cooled to 0 °C, was added isopropenylmagnesium bromide solution (0.5 M in THF, 6 mL, 3.00 mmol) then the reaction mixture was warmed to rt and stirred for 18 h. The reaction was quenched using sat. aq. NH_4Cl solution (10 mL), then the aqueous phase was separated and extracted with diethyl ether (3 × 30 mL). The combined organic phases were concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 6:4) gave an inseparable mixture of the title compounds **97n** and **97n'** (151 mg, 887 µmol, 30%, d.r. 5:1) as a colourless oil; R_f = 0.11 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} 3441, 2971, 2935, 1700, 1240, 1182, 1107, 891; **Major diastereoisomer 97n**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (1H, s, H-5$_A$), 4.92 (1H, s, H-5$_B$), 3.71 (3H, s, H-8), 2.76 – 2.54 (3H, m, H-1 and H-2$_A$), 2.48 (1H, br. s, O-H), 2.39 – 2.23 (2H, m, H-2$_B$), 1.81 (3H, s, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (C, C-7), 146.7 (C, C-4), 110.6 (CH_2, C-5), 74.3 (C, C-3), 52.2 (CH_3, C-8), 38.5 (CH_2, C-2), 29.7 (CH, C-1), 17.6 (CH_3, C-6); **Minor diastereoisomer (resolved signals) 97n'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (1H, s, H-5$_A$), 3.68 (3H, s, H-8), 3.34 (1H, tt, *J* = 8.7, 4.1 Hz, H-1), 1.76 (3H, s, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9 (C, C-7), 148.4 (C, C-4), 110.5 (CH_2, C-5), 76.3 (C, C-3), 51.9 (CH_3, C-8), 37.0 (CH_2, C-2), 31.2 (CH, C-1), 17.3 (CH_3, C-6); HRMS (ESI+) Exact mass calcd for $C_9H_{14}NaO_3$, 193.0835. Found $[MNa]^+$, 193.0832 (1.90 ppm error).

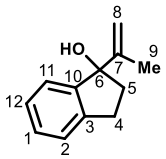
Note: Attempts to establish the relative stereochemistry of the major and minor diastereoisomers proved unsuccessful. The major diastereoisomer is tentatively assigned as

compound **97n** based on addition of the Grignard reagent to the least hindered face of the ketone in analogy with similar reactions reported in the literature.



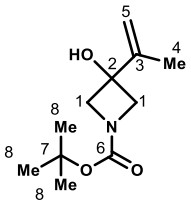
2-(Prop-1-en-2-yl)adamantan-2-ol (97o): Prepared according to general procedure F using isopropenylmagnesium bromide solution (0.5 M in THF, 15.0 mL, 7.50 mmol) and adamantanone (751 mg, 5.00 mmol) in THF (10 mL). Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 8:2) gave the title compound **97o** (880 mg, 4.58 mmol, 92%) as a colourless crystalline solid; mp. 49 – 51 °C (Lit.[168] 50 – 51 °C); R_f = 0.53 (cyclohexane/diethyl ether; 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (1H, s, H-9_A), 5.00 (1H, s, H-9_B), 2.33 – 2.23 (2H, m, H-4), 2.14 (1H, br. s, OH), 1.86 – 1.80 (5H, m, H-1_A, H-3_A and H-7), 1.80 – 1.58 (9H, m, H-1_B, H-3_B, H-6, H-10), 1.20 (1H, s, H-8); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7 (C, C-8), 112.1 (CH_2, C-9), 76.2 (C, C-5), 37.8 (CH, C-4), 35.1 (CH_2, C-3), 34.7 (CH_2, C-6), 33.0 (CH, C-2), 27.3 (CH_2, C-1), 27.1 (CH, C-7), 18.7 (CH_3, C-10).

Data are consistent with those reported in the literature.[168]



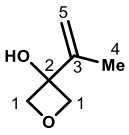
1-(Prop-1-en-2-yl)-2,3-dihydro-1*H*-inden-1-ol (97t): The title compound was prepared according to general procedure F using isopropenylmagnesium bromide solution (0.5 M in THF, 9.00 mL, 4.50 mmol) and 1-indanone (397 mg, 3.00 mmol) in THF (6 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 8:2) gave 1-(prop-1-en-2-yl)-2,3-dihydro-1*H*-inden-1-ol (**97t**) (225 mg, 1.29 mmol, 43%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.18 (4H, m, H-1, H-2, H-11 and H-12), 5.06 (1H, s, H-8_A), 4.96 (1H, s, H-8_B), 3.10 (1H, ddd, *J*= 16.0, 8.3, 5.8 Hz, H-4_A), 2.88 (1H, ddd, *J*= 16.0, 8.4, 5.3 Hz, H-4_B), 2.48 (1H, ddd, *J*= 13.5, 8.4, 5.8 Hz, H-5_A), 2.13 (1H, ddd, *J*= 13.5, 8.4, 5.3 Hz, H-5_B), 1.82 (1H, br. s, O-H), 1.74 (3H, s, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0 (C, C-10), 146.4 (C, C-7), 143.9 (C, C-3), 128.4 (ArCH, C-2), 126.8 (ArCH, C-1), 125.0 (ArCH, C-12), 123.3 (ArCH, C-11), 110.8 (CH_2, C-8), 86.5 (C, C-6), 39.9 (CH_2, C-5), 30.0 (CH_2, C-4), 19.5 (CH_3, C-9).

Data are consistent with those reported in the literature.[169]



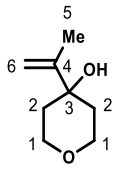
***tert*-Butyl 3-hydroxy-3-(prop-1-en-2-yl)azetidine-1-carboxylate (97p)**: The title compound was prepared according to general procedure F using isopropenylmagnesium bromide solution (0.5 M in THF, 6.00 mL, 3.00 mmol) and 1-Boc-3-azetidinone (342 mg, 2.00 mmol) in THF (4 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 6:4) gave the title compound **97p** (332 mg, 1.56 mmol, 78%) as a colourless crystalline solid; mp. 75 – 77 (Lit.[170] 76 – 78 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (1H, s, H-5_A), 4.95 (1H, s, H-5_B), 4.09 (2H, d, *J* = 8.5 Hz, H-1_A), 3.87 (2H, d, *J* = 8.5 Hz, H-1_B), 1.84 (3H, s, H-4), 1.41 (9H, s, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (C, C-6), 144.9 (C, C-3), 111.7 (CH_2, C-5), 80.0 (C, C-7), 73.4 (C, C-2), 61.2 (C, C-1), 28.8 (CH_3, C-4), 17.9 (CH_3, C-8).

Data are consistent with those reported in the literature.[170]



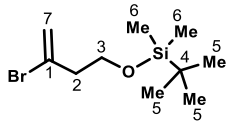
3-(Prop-1-en-2-yl)oxetan-3-ol (97o): The title compound was prepared according to general procedure F using isopropenylmagnesium bromide solution (0.5 M in THF, 6.00 mL, 3.00 mmol) and 3-oxetanone (130 µL, 2.00 mmol) in THF (4 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 6:4) gave 3-(prop-1-en-2-yl)oxetan-3-ol (**97o**) (201 mg, 1.76 mmol, 88%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (1H, s, H-5_A), 5.01 (1H, s, H-5_B), 4.78 (2H, d, *J* = 7.5 Hz, H-1_A), 4.63 (2H, d, *J* = 7.5 Hz, H-1_B), 2.61 (1H, br. s, OH), 1.90 (3H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4 (C, C-3), 111.8 (CH_2, C-5), 82.5 (C, C-1), 77.1 (C, C-2), 18.0 (CH_3, C-4).

Data are consistent with those reported in the literature.[170]



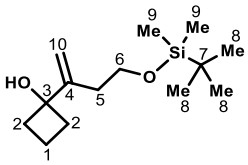
4-Isopropenyltetrahydropyran-4-ol (97s): Prepared according to general procedure F using isopropenylmagnesium bromide solution (0.5 M in THF, 9.00 mL, 4.50 mmol) and 4-oxotetrahydropyran (280 µL, 3.00 mmol) in THF (6 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 6:4) gave the title compound **97s** (400 mg, 2.83 mmol, 95%) as a colourless oil; R_f = 0.19 (cyclohexane/diethyl ether, 6:4); δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (1H, s, H-6_A), 4.87 (1H, s, H-6_B), 3.90 – 3.74 (4H, m, H-1_A and H-2_A), 2.00 – 1.90 (2H, m, H-1_B), 1.82 (3H, s, H-5), 1.53 – 1.45 (2H, m, H-2_B), 1.23 (1H, br. s, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0 (C, C-4), 110.0 (CH_2, C-6), 71.3 (C, C-3), 63.9 (CH_2, C-1), 36.2 (CH_2, C-2), 18.6 (CH_3, C-5).

Data are consistent with those reported in the literature.[168]

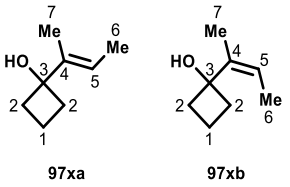


[(3-bromobut-3-en-1-yl)oxy](*tert*-butyl)dimethylsilane[129] **(135)**: To a stirring solution of 3-bromo-3-butenol (500 µL, 5.00 mmol) in DCM (10 mL) cooled to 0 °C, was added imidazole (681 mg, 10.0 mmol). A solution of TBDMSCl (1.51 g, 10.0 mmol) in DCM (5 mL) was then added at 0 °C, and the reaction mixture left to stir at rt. After 18 h, the reaction mixture was quenched using water (10 mL) and the aqueous phase was separated and extracted using DCM (3 × 30 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 20:1) gave the title compound (1.18 g, 4.46 mmol, 89%) as a colourless oil; R_f = 0.57 (cyclohexane/diethyl ether; 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (1H, d, *J*= 1.4 Hz, H-7_A), 5.46 (1H, d, *J*= 1.5 Hz, H-7_B), 3.79 (2H, t, *J*= 6.3 Hz, H-3), 2.62 (2H, td, *J*= 6.3, 1.0 Hz, H-2), 0.89 (9H, s, H-5), 0.07 (6H, s, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) 131.0 (C, C-1), 118.5 (CH_2, C-7), 61.0 (CH_2, C-3), 45.0 (CH_2, C-2), 26.0 (CH_3, C-5), 18.5 (C, C-4), -5.17 (CH_3, C-6).

Data are consistent with those reported in the literature.[171]



1-{4-[(*tert*-Butyldimethylsilyl)oxy]but-1-en-2-yl}cyclobutan-1-ol (97w): Prepared according to a modification of general procedure D (1.20 eq. of *n*-BuLi and 1.20 eq. of **135**) using [(3-bromobut-3-en-1-yl)oxy](tert-butyl)dimethylsilane (**135**) (956 mg, 3.60 mmol) *n*-BuLi (2.5 M in hexanes, 1.44 mL, 3.60 mmol) and cyclobutanone (230 µL, 3.00 mmol) in THF (6 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 20:1 → 9:1) gave the title compound **97w** (196 mg, 764 µmol, 25%) as a colourless oil; R_f = 0.10 (cyclohexane/diethyl ether; 20:1); ν_{max}/cm^{-1} 3428, 2952, 2930, 1249, 1088, 832, 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (1H, d, *J* = 1.2 Hz, H-10_A), 4.94 (1H, d, *J* = 1.2 Hz, H-10_B), 4.22 (1H, s, O-H), 3.77 (2H, t, *J* = 5.8 Hz, H-6), 2.35 (2H, t, *J* = 5.8 Hz, H-5), 2.30 – 2.19 (2H, m, H-2_A), 2.19 – 2.07 (2H, m, H-2_B), 1.84 – 1.75 (1H, m, H-1_A), 1.56 – 1.41 (1H, m, H-1_B), 0.89 (9H, s, H-8), 0.07 (6H, s, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5 (C, C-4), 110.9 (CH_2, C-10), 77.4 (C, C-3), 65.0 (CH_2, C-6), 35.3 (CH_2, C-2), 34.7 (CH_2, C-5), 26.1 (CH_3, C-8), 18.5 (C, C-7), 12.8 (CH_2, C-1), −5.37 (CH_3, C-9). [HRMS (ESI+) Exact mass cald. for $C_{14}H_{28}NaO_2Si$, 279.1745. Found $[MNa]^+$, 279.1751 (2.00 ppm error)].

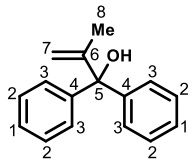


(*Z*)-1-(But-2-en-2-yl)cyclobutan-1-ol (97xa) and **(*E*)-1-(But-2-en-2-yl)cyclobutan-1-ol (97xb):** The title compound was prepared according to general procedure F using 1-methyl-1-propenylmagnesium bromide solution (0.5 M in THF, 9.00 mL, 4.50 mmol) and cyclobutanone (220 µL, 3.00 mmol) in THF (6 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 8:2) gave the title compound **97x** (124 mg, 982 µmol, 33%) as a colourless oil and as an inseparable mixture of E:Z isomers (1:2 E:Z ratio); R_f = 0.23 (cyclohexane/ethyl acetate; 9:1); ν_{max}/cm^{-1} 3331, 2935, 1137, 1102, 910; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (1H, dd, *J* = 6.5, 1.2 Hz, H-5'), 5.30 (1H, dd, *J* = 7.2, 1.5 Hz, H-5), 2.47 – 2.34 (2H, m, H-2_A), 2.33 – 2.26 (2H, m, H-2_A'), 2.20 – 2.07 (3H, m, H-2_B and H-1_A), 2.08 – 1.96 (2H, m, H-2_B'), 1.92 – 1.80 (1H, m, H-1_A'), 1.75 – 1.58 (13H, m, H-1_B, H-6, H-6', H-7 and H-7'), 1.56 – 1.46 (1H, m, H-1_B'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2 (C, C-4), 138.5 (C, C-

4’), 122.8 (CH, C-5), 118.3 (CH, C-5’), 79.3 (C, C-4’), 78.4 (C, C-4), 36.4 (CH_2, C-2), 34.2 (CH_2, C-2’), 20.4 (CH_3, C-7), 15.2 (CH_2, C-1), 14.6 (CH_3, C-6), 13.4 (CH_3, C-7’), 13.2 (CH_2, C-1’), 11.2 (CH_3, C-6’). [HRMS (GC-EIMS) Exact mass cald. for $C_8H_{14}O$, 126.1039. Found $[MH]^+$, 126.1039 (0.53 ppm error)].

NMR signals originating from E-isomer **97xb** are represented with a prime (‘) label.

Data are consistent with those reported in the literature.[173]

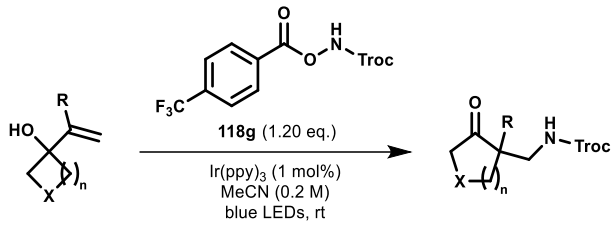


2-Methyl-1,1-diphenylprop-2-en-1-ol (97y): The title compound was prepared according to general procedure F using isopropenylmagnesium bromide solution (0.5 M in THF, 9.00 mL, 4.50 mmol) and benzophenone (547 mg, 3.00 mmol) in THF (6 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 9:1) gave the title compound **97y** (333 mg, 1.48 mmol, 49%) as a colourless oil; R_f = 0.22 (cyclohexane/diethyl ether; 9:1); ν_{max}/cm^{-1} 3473, 1445, 1162, 1022, 904, 756, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.24 (10H, m, H-1, H-2 and H-3), 5.14 (1-H, s, H-7_A), 4.73 (1H, s, H-7_B), 2.44 (1H, br. s, O-H), 1.80 (3H, s, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2 (C, C-6), 145.0 (ArC, C-4), 128.1 (ArCH, C-3), 127.8 (ArCH, C-2), 127.4 (ArCH, C-1), 115.7 (CH_2, C-7), 83.1 (C, C-5), 20.2 (CH_3, C-8).

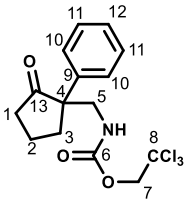
Data are consistent with those reported in the literature.[172]

Photoredox Mediated Amination / Semi-Pinacol Ring Expansion

General procedure G - Photoredox Mediated Amidation/Semi-pinacol Ring Expansion:



To a mixture of olefin substrate (1.00 eq.), amidyl radical precursor **118g** (1.20 eq.) and $Ir(ppy)_3$ (1 mol%), was added MeCN (0.2 M). The reaction mixture was sparged with argon for 10 minutes, then stirred at rt whilst irradiating with blue LEDs. After 3 h, 1 M aq. HCl solution (4 mL) was added, then the reaction was stirred at rt for a further 18 h. The aqueous layer was separated and extracted with ethyl acetate (3 × 20 mL), then the combined organic phases were washed with 1 M aq. NaOH solution (30 mL) and brine (30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

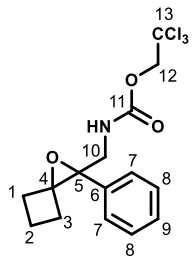


(±)-2,2,2-Trichloroethyl [(2-oxo-1-phenylcyclopentyl)methyl]carbamate (108a): The title compound was prepared according to general procedure G using 1-(1-phenylvinyl)cyclobutanol (**97a**) (71.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [$Ir(ppy)_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 30:1) gave 2,2,2-trichloroethyl [(2-oxo-1-phenylcyclopentyl)methyl]carbamate (**108a**) (86.0 mg, 236 μmol, 59%) as a colourless oil; R_f = 0.55 (cyclohexane/ethyl acetate; 1:1); ν_{max}/cm^{-1} 3331, 2959, 1724, 1513, 1229, 1139, 803, 722, 699, 566; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.27 (5H, m, H-10, H-11 and H-12), 5.33 – 5.25 (1H, m, NH), 4.68 (1H, d, *J*= 12.1 Hz, H-7_A), 4.67 (1H, d, *J*= 12.1 Hz, H-7_B), 3.65 (1H, dd, *J*= 14.0, 7.0 Hz, H-5_A), 3.52 (1H, dd, *J*= 14.0, 7.0 Hz, H-5_B), 2.60 – 2.50 (1H, m, H-3_A), 2.44 – 2.22 (2H, m, H-1), 2.18 – 2.08 (1H, m, H-3_B), 2.00 – 1.91 (1H, m, H-2_A), 1.84 – 1.72 (1H, m, H-2_B); ^{13}C NMR (126 MHz, $CDCl_3$) δ 220.0 (C, C-13), 155.0 (C, C-6), 137.5 (ArC, C-9), 129.2 (ArCH, C-11), 127.8 (ArCH, C-12), 126.9 (ArCH, C-10), 95.7 (C, C-8), 74.6 (CH_2,

C-7), 58.5 (C, C-4), 47.4 (CH_2, C-5), 37.8 (CH_2, C-1), 32.9 (CH_2, C-3), 18.6 (CH_2, C-2). [HRMS (ESI+) Exact mass cald. for $C_{15}H_{16}{}^{35}Cl_3NNaO_3$, 386.0088. Found $[MNa]^+$, 386.0087 (0.20 ppm error)].

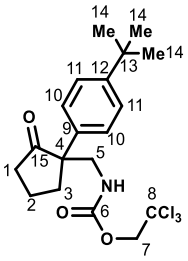
Scale up reaction (2.0 mmol):

Prepared according to general procedure G using 1-(1-phenylvinyl)cyclobutanol (**97a**) (349 mg, 2.00 mmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (913 mg, 2.40 mmol), [Ir(ppy)$_3$] (14.0 mg, 20.0 μmol) and acetonitrile (10 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether 30:1) gave the title compound **108a** (380 mg, 1.04 mmol, 52%) as a colourless oil.

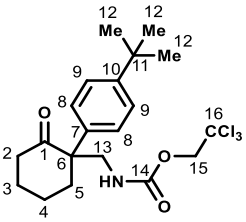


2,2,2-Trichloroethyl ((2-phenyl-1-oxaspiro[2.3]hexan-2-yl)methyl)carbamate (128): Prepared using a modification of general procedure G (no stir with 1 M aq. HCl solution) using 4-phenylpent-4-en-1-ol (**97a**) (33.0 mg, 200 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (92 mg, 240 μmol), [Ir(ppy)$_3$] (1.30 mg, 2.00 μmol, 1 mol%) and acetonitrile (1 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 9:1) gave the title compound **128** (4.0 mg, 13.7 μmol, 7%) as a colourless oil; R_f = 0.54 (cyclohexane/ethyl acetate; 8:2); (resolved signals) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (2H, m, H-8), 7.31 – 7.27 (3H, m, H-7 and H-9), 5.08 (1H, t, J = 5.6 Hz, NH), 4.70 – 4.66 (2H, m, H-12), 4.21 – 4.12 (1H, dd, J = 14.4, 5.1 Hz, H-10$_A$), 3.47 (1H, dd, J = 14.4, 5.1 Hz, H-10$_B$), 2.59 – 2.46 (2H, m, H-1$_A$ and H-3$_A$), 2.35 – 2.25 (1H, m, H-1$_B$), 1.95 – 1.78 (2H, m, H-3$_B$ and H-2$_A$), 1.76 – 1.65 (1H, m, H-2$_B$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5 (C, C-11), 136.1 (ArC, C-6), 128.5 (ArCH, C-8), 128.0 (ArCH, C-9), 126.5 (ArCH, C-7), 95.6 (C, C-13), 74.8 (C, C-5), 74.7 (CH_2, C-12), 65.2 (C, C-4), 44.1 (CH_2, C-10), 29.5 (CH_2, C-1), 29.3 (CH_2, C-3), 12.9 (CH_2, C-2).

Note: Attempts to isolate the product **128** in high purity proved unsuccessful

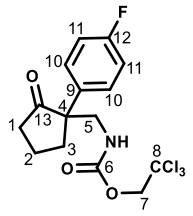


2,2,2-Trichloroethyl {1-[4-(*tert*-butyl)phenyl]-2-oxocyclopentyl}methylcarbamate (108b): The title compound was prepared according to general procedure G using 1-{1-[4-(*tert*-butyl)phenyl]vinyl}cyclobutan-1-ol (**97b**) (92.0 mg, 400 μmol), {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 20:1) gave 2,2,2-trichloroethyl {1-[4-(*tert*-butyl)phenyl]-2-oxocyclopentyl}methylcarbamate (**108b**) (144 mg, 342 μmol, 86%) as a colourless oil; R_f = 0.31 (cyclohexane/ethyl acetate; 8:2); ν_{max}/cm^{-1} 1732, 1512, 904, 723, 649; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (2H, d, *J* = 8.6 Hz, H-11), 7.25 (2H, d, *J* = 8.6 Hz, H-10), 5.25 (1H, t, *J* = 6.9 Hz, NH), 4.72 – 4.60 (2H, m, H-7), 3.63 (1H, dd, *J* = 14.0, 6.9 Hz, H-5$_A$), 3.51 (1H, dd, *J* = 14.0, 6.9 Hz, H-5$_B$), 2.61 – 2.47 (1H, m, H-3$_A$), 2.44 – 2.32 (1H, m, H-1$_A$), 2.31 – 2.18 (1H, m, H-1$_B$), 2.16 – 2.05 (1H, m, H-3$_B$), 2.01 – 1.89 (1H, m, H-2$_A$), 1.85 – 1.72 (1H, m, H-2$_B$), 1.30 (9H, s, H-14); ^{13}C NMR (126 MHz, $CDCl_3$) δ 220.0 (C, C-15), 155.0 (C, C-6), 150.6 (ArC, C-12), 134.3 (ArC, C-9), 126.6 (ArCH, C-10), 126.0 (ArCH, C-11), 95.7 (C, C-8), 74.6 (CH_2, C-7), 58.1 (C, C-4), 47.3 (CH_2, C-5), 37.8 (CH_2, C-1), 34.6 (C, C-13), 32.8 (CH_2, C-3), 31.4 (CH_3, C-14), 18.6 (CH_2, C-2); [HRMS (ESI+) Exact mass cald. for $C_{19}H_{28}{}^{35}Cl_3N_2O_3$, 437.1161. Found $[MNH_4]^+$, 437.1160 (0.30 ppm error)].

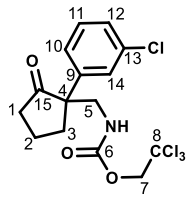


2,2,2-Trichloroethyl [1-{4-(*tert*-butyl)phenyl}-2-oxocyclohexyl]methylcarbamate (108c): Prepared according to general procedure G using 1-{1-[4-(*tert*-butyl)phenyl]vinyl}cyclopentan-1-ol (**97c**) (98.0 mg, 400 μmol), {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 20:1) gave the title compound **108c** (118 mg, 271 μmol, 68%) as

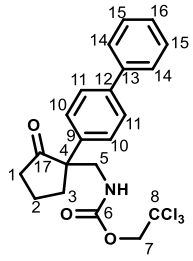
a colourless oil; R_f = 0.10 (cyclohexane/diethyl ether; 20:1); υ_{max}/cm^{-1} (thin film) 3356, 2948, 2867, 1740, 1701, 1506, 1212, 1142, 1127, 810, 727, 568; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, d, *J* = 8.5 Hz, H-8), 7.09 (2H, d, *J* = 8.4 Hz, H-9), 5.47 (1H, t, *J* = 6.6 Hz, NH), 4.62 (2H, s, H-15), 3.45 (1H, dd, *J* = 13.9, 6.1 Hz, H-13$_A$), 3.33 (1H, dd, *J* = 13.9, 6.1 Hz, H-13$_B$), 2.68 – 2.62 (1H, m, H-2$_A$), 2.48 – 2.36 (1H, m, H-2$_B$), 2.33 – 2.27 (1H, H-5$_A$), 2.01 – 1.82 (2H, m, H-3$_A$ and H-5$_B$), 1.78 – 1.61 (3H, m, H-3$_B$ and H-4), 1.31 (9H, s, H-12); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.8 (C, C-1), 155.0 (C, C-14), 150.6 (ArC, C-10), 135.2 (ArC, C-7), 126.7 (ArCH, C-8), 126.2 (ArCH, C-9), 95.8 (C, C-16), 74.5 (CH_2, C-15), 59.0 (C, C-6), 49.6 (CH_2, C-13), 40.3 (CH_2, C-2), 34.6 (C, C-11), 32.9 (CH_2, C-5), 31.4 (CH_3, C-12), 28.3 (CH_2, C-3), 21.2 (CH_2, C-4); HRMS (ESI+) Exact mass calcd for $C_{20}H_{27}{}^{35}Cl_3NO_3$, 434.1051. Found $[MH]^+$, 434.1050 (0.30 ppm error).



2,2,2-Trichloroethyl {[1-(4-fluorophenyl)-2-oxocyclopentyl]methyl}carbamate (108f): The title compound was prepared according to general procedure G using 1-[1-(4-fluorophenyl)vinyl]cyclobutan-1-ol (**97f**) (77.0 mg, 400 μmol), {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 20:1 → 9:1) gave 2,2,2-trichloroethyl {[1-(4-fluorophenyl)-2-oxocyclopentyl]methyl}carbamate (**108f**) (123 mg, 321 μmol, 73%) as a colourless oil; R_f = 0.34 (cyclohexane/ethyl acetate; 6:4); ν_{max}/cm^{-1} 3326, 2961, 1724, 1507, 1226, 1141, 815, 721; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (2H, m, H-10), 7.08 – 7.00 (2H, m, H-11), 5.26 (1H, t, *J* = 6.3 Hz, NH), 4.69 – 4.60 (2H, m, H-7), 3.62 (1H, dd, *J* = 14.1, 7.1 Hz, H-5$_A$), 3.48 (1H, dd, *J* = 14.1, 6.0 Hz, H-5$_B$), 2.56 – 2.45 (1H, m, H-3$_A$), 2.43 – 2.23 (2H, m, H-1), 2.20 – 2.08 (1H, m, H-3$_B$), 2.02 – 1.92 (1H, m, H-2$_A$), 1.83 – 1.69 (1H, m, H-2$_B$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.6 (C, C-13), 162.3 (d, *J* = 243.0 Hz, ArC, C-12), 155.0 (C, C-6), 133.2 (d, *J* = 3.2 Hz, ArC, C-9), 128.7 (d, *J* = 8.0 Hz, ArCH, C-10), 116.0 (d, *J* = 21.4 Hz, ArCH, C-11) 95.7 (C, C-8), 74.6 (CH_2, C-7), 57.8 (C, C-4), 47.4 (CH_2, C-5), 37.8 (CH_2, C-1), 33.0 (CH_2, C-3), 18.5 (CH_2, C-2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.6 ppm (tt); [HRMS (ESI+) Exact mass cald. for $C_{15}H_{16}{}^{35}Cl_3{}^{19}FNO_3$, 382.0174. Found $[MH]^+$, 382.0174 (0.10 ppm error)].



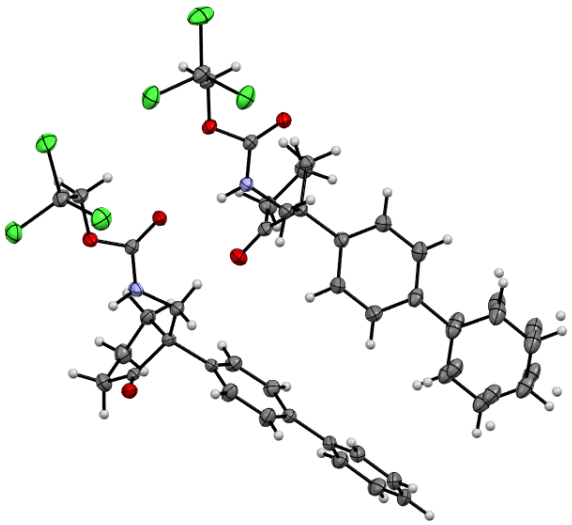
2,2,2-Trichloroethyl {[1-(3-chlorophenyl)-2-oxocyclopentyl]methyl}carbamate (108g): The title compound was prepared according to general procedure G using 1-[1-(3-chlorophenyl)vinyl]cyclobutan-1-ol (**97g**) (84.0 mg, 400 μmol), {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.70 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 9:1 → 6:4) gave 2,2,2-trichloroethyl {[1-(3-chlorophenyl)-2-oxocyclopentyl]methyl}carbamate (**108g**) (78.0 mg, 195 μmol, 49%) as a colourless oil; R_f = 0.44 (cyclohexane/ethyl acetate; 6:4); ν_{max}/cm^{-1} 3337, 2954, 1724, 1514, 1230, 1142, 723, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.21 (4H, m, H-10, H-11, H-12 and H-14), 5.28 (1H, t, *J* = 6.2 Hz, NH), 4.77 – 4.61 (2H, m, H-7), 3.62 (1H, dd, *J* = 14.1, 7.0 Hz, H-5$_A$), 3.49 (1H, dd, *J* = 14.1, 6.0 Hz, H-5$_B$), 2.54 – 2.44 (1H, m, H-3$_A$), 2.45 – 2.22 (2H, m, H-1), 2.20 – 2.09 (1H, m, H-3$_B$), 2.04 – 1.92 (1H, m, H-2$_A$), 1.85 – 1.71 (1H, m, H-2$_B$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.1 (C, C-15), 155.0 (C, C-6), 139.8 (ArC, C-9), 135.1 (ArC, C-13), 130.3 (ArCH, C-11), 128.0 (ArCH, C-14), 127.3 (ArCH, C-10), 125.2 (ArCH, C-12), 95.6 (C, C-8), 74.6 (CH_2, C-7), 58.2 (C, C-4), 47.3 (CH_2, C-5), 37.9 (CH_2, C-1), 32.9 (CH_2, C-3), 18.6 (CH_2, C-2); [HRMS (ESI+) Exact mass cald. for $C_{15}H_{19}{}^{35}Cl_4N_2O_3$, 415.0144. Found $[MNH_4]^+$, 415.0142 (0.50 ppm error)].

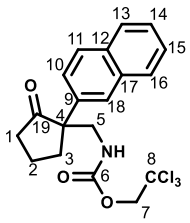


2,2,2-Trichloroethyl {1-[(1,1'-biphenyl)-4-yl]-2-oxocyclopentyl}methylcarbamate (108h): The title compound was prepared according to general procedure G using 1-{1-[(1,1'-biphenyl)-4-yl]vinyl}cyclobutan-1-ol (**97g**) (100 mg, 400 μmol), {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 9:1) gave 2,2,2-trichloroethyl {1-[(1,1'-biphenyl)-4-yl]-2-

oxocyclopentyl}methylcarbamate (**108h**) (169 mg, 383 μmol, 96%) as a colourless oil; R_f = 0.43 (cyclohexane/ethyl acetate; 6:4); ν_{max}/cm^{-1} 3336, 2953, 1724, 1512, 1229, 1142, 765, 726, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.57 (4H, m, H-10 and H-14), 7.49 – 7.42 (4H, m, H-11 and H-15), 7.41 – 7.34 (1H, m, H-16), 5.36 (1H, t, *J* = 6.1 Hz, NH), 4.78 – 4.65 (2H, m, H-7), 3.72 (1H, dd, *J* = 14.1, 7.1 Hz, H-5_A), 3.59 (1H, dd, *J* = 14.1, 6.0 Hz, H-5_B), 2.62 – 2.52 (1H, m, H-3_A), 2.50 – 2.39 (1H, m, H-1_A), 2.36 – 2.24 (1H, m, H-1_B), 2.22 – 2.12 (1H, m, H-3_B), 2.05 – 1.94 (1H, m, H-2_A), 1.88 – 1.79 (1H, m, H-2_B); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.8 (C, C-17), 155.0 (C, C-6), 140.6 (ArC, C-13), 140.4 (ArC, C-12), 136.5 (ArC, C-9), 128.9 (ArCH, C-15), 127.7 (ArCH, C-10), 127.6 (ArCH, C-16), 127.4 (ArCH, C-14), 127.1 (ArCH, C-11), 95.7 (C, C-8), 74.5 (CH_2, C-7), 58.3 (C, C-4), 47.3 (CH_2, C-5), 37.8 (CH_2, C-1), 32.8 (CH_2, C-3), 18.6 (CH_2, C-2); [HRMS (ESI+) Exact mass cald. for $C_{21}H_{21}{}^{35}Cl_3NO_3$, 440.0582. Found $[MH]^+$, 440.0582 (0.00 ppm error)].

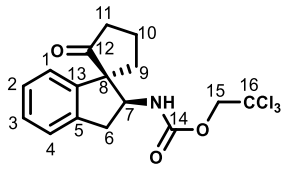
Crystals suitable for X-ray analysis were prepared by slow diffusion of *n*-heptane into a solution of **108h** in $CHCl_2$.



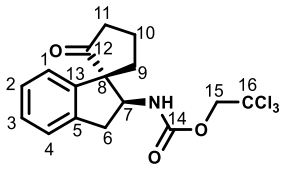


2,2,2-Trichloroethyl {[1-(naphthalen-2-yl)-2-oxocyclopentyl]methyl}carbamate (108i): The title compound was prepared according to general procedure G using 1-(1-(naphthalen-2-yl)vinyl)cyclobutan-1-ol (**97i**) (90.0 mg, 400 μmol), {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00

μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 15:1) gave 2,2,2-trichloroethyl {[1-(naphthalen-2-yl)-2-oxocyclopentyl]methyl}carbamate (**108i**) (109 mg, 263 μmol, 66%) as a colourless oil; R_f = 0.42 (cyclohexane/ethyl acetate; 8:2); ν_{max}/cm^{-1} 3334, 2962, 1725, 1508, 1230, 1140, 815, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, d, *J* = 8.7 Hz, H-10), 7.84 – 7.78 (2H, m, H-13 and H-16), 7.73 – 7.69 (1H, m, H-11), 7.54 – 7.46 (m, 3H, H-18, H-14 and H-15), 5.31 (1H, t, *J* = 6.1 Hz, NH), 4.64 – 4.58 (2H, m, H-7), 3.75 (1H, dd, *J* = 14.1, 5.8 Hz, H-5_A), 3.60 (1H, dd, *J* = 14.1, 6.4 Hz, H-5_B), 2.73 – 2.61 (1H, m, H-3_A), 2.52 – 2.38 (1H, m, H-1_A), 2.38 – 2.26 (1H, m, H-1_B), 2.26 – 2.16 (1H, m, H-3_B), 2.07 – 1.94 (1H, m, H-2_A), 1.88 – 1.71 (1H, m, H-2_B); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.0 (C, C-19), 155.0 (C, C-6), 134.8 (C, C-9), 133.3 (C, C-17), 132.7 (C, C-12), 129.2 (ArCH, C-10), 128.2 (ArCH, C-16), 127.7 (ArCH, C-13), 126.6 (ArCH, C-18), 126.6 (ArCH, C-15), 126.4 (ArCH, C-11), 124.4 (ArCH, C-14), 95.6 (C, C-8), 74.3 (CH_2, C-7), 58.7 (C, C-4), 47.3 (CH_2, C-5), 37.9 (CH_2, C-1), 33.0 (CH_2, C-3), 18.7 (CH_2, C-2). [HRMS (ESI+) Exact mass cald. for $C_{19}H_{18}{}^{35}Cl_3NNaO_3$, 436.0244. Found $[MNa]^+$, 436.0241 (0.80 ppm error)].



108ja



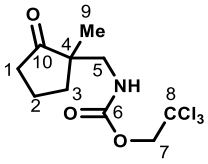
108jb

2,2,2-Trichloroethyl {(1*R,2'*S**)-2-oxo-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2'-yl}carbamate (108ja) and 2,2,2-trichloroethyl {(1*S**,2'*S**)-2-oxo-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2'-yl}carbamate (108jb):** The title compound was prepared according to general procedure G using 1-(1*H*-inden-3-yl)cyclobutan-1-ol (75.0 mg, 400 μmol) (**97j**), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether 8:2 → 6:4) provided 2,2,2-trichloroethyl {(1*R**,2'*S**)-2-oxo-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2'-yl}carbamate (**108ia**) (97.0 mg, 258 μmol, 64%) as a colourless oil and 2,2,2-trichloroethyl {(1*S**,2'*S**)-2-oxo-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2'-yl}carbamate (**108ib**) (30 mg, 80.0 μmol, 20%) as a colourless oil.

2,2,2-Trichloroethyl {(1*R,2'*S**)-2-oxo-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2'-yl}carbamate (108ja):** R_f = 0.43 (cyclohexane/diethyl ether; 6:4); ν_{max}/cm^{-1} 3319, 2954, 1718,

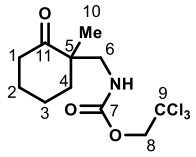
1510, 1238, 724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (3H, m, H-1, H-2 and H-4), 7.14 – 7.07 (1H, m, H-3), 5.51 (1H, d, *J* = 9.9 Hz, NH), 4.75 (1H, d, *J* = 12.0 Hz, H-15$_A$), 4.69 (1H, d, *J* = 12.0 Hz, H-15$_B$), 4.62 (1H, ddd, *J* = 9.9, 7.8, 2.2 Hz, H-7), 3.27 (1H, dd, *J* = 15.6, 7.8 Hz, H-6$_A$), 3.15 (1H, dd, *J* = 15.6, 7.8 Hz, H-6$_B$), 2.51 – 2.27 (4H, m, H-9 and H-11), 2.24 – 2.09 (2H, m, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.7 (C, C-12), 154.6 (C, C-14), 144.0 (ArC, C-13), 141.0 (ArC, C-5), 128.1 (ArCH, C-4), 127.6 (ArCH, C-2), 125.2 (ArCH, C-3), 123.2 (ArCH, C-1), 95.6 (C, C-16), 74.7 (CH_2, C-15), 64.5 (C, C-8), 60.1 (CH, C-7), 38.7 (CH_2, C-11), 38.2 (CH_2, C-6), 35.6 (CH_2, C-9), 20.2 (CH_2, C-10). [HRMS (ESI+) Exact mass cald. for $C_{16}H_{16}{}^{35}Cl_3NNaO_3$, 398.0088. Found $[M\text{-}Na]^+$, 398.0089 (0.30 ppm error)].

2,2,2-Trichloroethyl {(1*S,2'*S**)-2-oxo-2',3'-dihydrospiro[cyclopentane-1,1'-inden]-2'-yl}carbamate (108jb)**: R_f = 0.40 (cyclohexane/diethyl ether; 6:4); ν_{max}/cm^{-1} 3332, 2958, 1729, 1531, 1256, 1238, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.19 (4H, m, H-1, H-2 and H-4), 7.12 – 7.03 (1H, m, H-3), 5.19 (1H, d, *J* = 8.5 Hz, NH), 4.86 (1H, d, *J* = 12.0 Hz, H-15$_A$), 4.70 – 4.59 (2H, m, H-7 and H-15$_B$), 3.62 (1H, dd, *J* = 16.0, 7.0 Hz, H-6$_A$), 2.82 (1H, dd, *J* = 16.0, 4.0 Hz, H-6$_B$), 2.59 – 2.34 (3H, m, H-9$_A$ and H-11), 2.26 – 2.05 (3H, m, H-9$_B$ and H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.1 (C, C-12), 154.4 (C, C-14), 143.9 (ArC, C-13), 140.9 (ArC, C-5), 128.2 (ArCH, C-4), 127.6 (ArCH, C-1), 125.3 (ArCH, C-3), 123.4 (ArCH, C-2), 95.7 (C, C-16), 74.7 (CH_2, C-15), 65.3 (C, C-8), 58.1 (CH, C-7), 38.7 (CH_2, C-6), 37.7 (CH_2, C-11), 30.9 (CH_2, C-9), 19.7 (CH_2, C-10). [HRMS (ESI+) Exact mass cald. for $C_{16}H_{16}{}^{35}Cl_3NNaO_3$, 398.0088. Found $[MNa]^+$, 398.0088 (0.10 ppm error)].

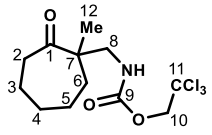


2,2,2-Trichloroethyl [(1-methyl-2-oxocyclopentyl)methyl]carbamate (108k): The title compound was prepared according to general procedure G using 1-(prop-1-en-2-yl)cyclobutan-1-ol (**97k**) (45.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 20:1) gave 2,2,2-trichloroethyl [(1-methyl-2-oxocyclopentyl)methyl]carbamate (**108k**) (94.0 mg, 310 μmol, 78%) as a colourless oil; R_f = 0.51 (cyclohexane/ethyl acetate; 6:4); ν_{max}/cm^{-1} 3348, 2964, 1727, 1519, 1236, 1147, 907, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, br. s, NH), 4.76 – 4.69 (2H, m, H-7), 3.35 (1H, dd, *J*

= 13.9, 7.0 Hz, H-5$_A$), 3.23 (1H, dd, *J* = 13.9, 7.0 Hz, H-5$_B$), 2.44 – 2.29 (1H, m, H-1$_A$), 2.29 – 2.13 (1H, m, H-1$_B$), 2.02 – 1.85 (3H, m, H-2 and H-3$_A$), 1.84 – 1.74 (1H, m, H-3$_B$), 1.06 (3H, s, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 223.1 (C, C-10), 155.3 (C, C-6), 95.7 (C, C-8), 74.7 (C, C-7), 49.2 (CH_2, C-5), 46.3 (C, C-4), 37.7 (CH_2, C-1), 34.2 (CH_2, C-3), 20.0 (CH_2, C-2), 18.7 (CH_3, C-9). [HRMS (ESI+) Exact mass cald. for $C_{10}H_{18}{}^{35}Cl_3N_2O_3$, 319.0378. Found $[MNH_4]^+$, 319.0377 (0.20 ppm error)].

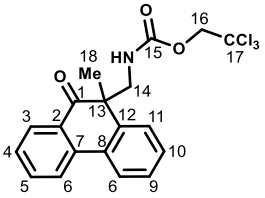


2,2,2-Trichloroethyl [(1-methyl-2-oxocyclohexyl)methyl]carbamate (108l): The title compound was prepared according to general procedure G using 1-(prop-1-en-2-yl)cyclopentan-1-ol (**97l**) (51.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 8:2 → 6:4) gave 2,2,2-trichloroethyl [(1-methyl-2-oxocyclohexyl)methyl]carbamate (**108l**) (93.0 mg, 294 μmol, 73%) as a colourless oil; R_f = 0.28 (cyclohexane/diethyl ether; 6:4); ν_{max}/cm^{-1} 3336, 2937, 1733, 1699, 1509, 1218, 1144, 810, 723, 567; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (1H, br. s, N-H), 4.77 – 4.65 (2H, m, H-8), 3.31 – 3.17 (2H, m, H-6), 2.57 – 2.45 (1H, m, H-1$_a$), 2.34 – 2.24 (1H, m, H-1$_b$), 2.08 – 1.99 (1H, m, H-4$_a$), 1.89 – 1.56 (5H, m, H-2, H-3 and H-4$_b$), 1.19 (3H, s, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.5 (C, C-11), 155.1 (C, C-7), 95.7 (C, C-9), 74.5 (CH_2, C-8), 49.9 (C, C-5), 48.0 (CH_2, C-6), 38.7 (CH_2, C-1), 36.6 (CH_2, C-4), 27.5 (CH_2, C-2), 20.9 (CH_2, C-3), 20.7 (CH_3, C-10); [HRMS (ESI+) Exact mass cald. for $C_{11}H_{20}{}^{35}Cl_3N_2O_3$, 333.0534. Found $[MNH_4]^+$, 333.0536 (0.70 ppm error)].

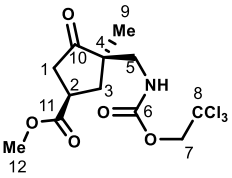


2,2,2-Trichloroethyl [(1-methyl-2-oxocycloheptyl)methyl]carbamate (108m): The title compound was prepared according to general procedure G using 1-(prop-1-en-2-yl)cyclohexan-1-ol (**97m**) (56.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2,

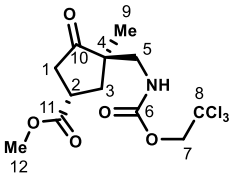
cyclohexane:diethyl ether – 8:2) gave 2,2,2-trichloroethyl [(1-methyl-2-oxocycloheptyl)methyl]carbamate (**108m**) (80.0 mg, 242 μmol, 60%) as a colourless oil; R_f = 0.25 (cyclohexane/diethyl ether; 6:4); ν_{max}/cm^{-1} 3348, 2931, 1731, 1696, 1514, 1235, 1146, 812, 724; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (1H, t, *J* = 5.6 Hz, N-H), 4.76 – 4.65 (2H, m, H-10), 3.34 (1H, dd, *J* = 13.8, 5.6 Hz, H-8$_A$), 3.26 (1H, dd, *J* = 13.8, 5.6 Hz, H-8$_B$), 2.68 – 2.58 (1H, m, H-2$_A$), 2.47 – 2.38 (1H, m, H-2$_B$), 1.81 – 1.72 (2H, m, H-6$_A$ and H3$_A$), 1.70 – 1.50 (5H, m, H-3$_B$, H-4, H-5$_A$ and H-6$_B$), 1.43 – 1.34 (1H, m, H-5$_B$), 1.13 (3H, s, H-12); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.8 (C, C-1), 155.2 (C, C-9), 95.8 (C, C-11), 74.6 (CH_2, C-10), 51.7 (C, C-7), 48.4 (CH_2, C-8), 40.5 (CH_2, C-2), 36.2 (CH_2, C-6), 30.6 (CH_2, H-4), 26.6 (CH_2, C-3), 24.8 (CH_2, C-5), 21.8 (CH_3, C-12). [HRMS (ESI+) Exact mass cald. for $C_{12}H_{22}{}^{35}Cl_3N_2O_3$, 347.0691. Found $[MH_4N]^+$, 347.0689 (0.60 ppm error)].



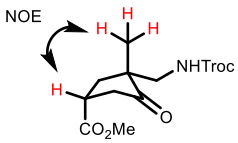
2,2,2-Trichloroethyl [(9-methyl-10-oxo-9,10-dihydrophenanthren-9-yl)methyl]carbamate (108n): Prepared according to a modification of general procedure G (reaction time: 48 h) using 9-(prop-1-en-2-yl)-9*H*-fluoren-9-ol (**97n**) (89.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether 9:1) gave the title compound **108n** (130 mg, 316 μmol, 79%) as a colourless oil; R_f = 0.38 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 1732, 1676, 1514, 1219, 905, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.96 (3H, m, H-6 and H-11), 7.69 (1H, td, *J* = 7.7, 1.5 Hz, H-3), 7.63 – 7.53 (1H, m, H-11), 7.47 – 7.33 (3H, m, H-4, H-5 and H-9), 5.24 (1H, br. t, *J* = 6.0 Hz, NH), 4.71 – 4.52 (2H, m, H-16), 3.95 (1H, dd, *J* = 13.8, 6.0 Hz, H-14$_A$), 3.79 (1H, dd, *J* = 13.8, 6.9 Hz, H-14$_B$), 1.50 (3H, s, H-18); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6 (C, C-1), 154.7 (C, C-15), 139.5 (ArC, C-12), 137.3 (ArC, C-7), 135.0 (ArC, C-2), 130.3 (ArC, C-8), 129.6 (ArCH, C-3), 128.8 (ArCH, C-5), 128.5 (ArCH, C-9), 127.9 (ArCH, C-6), 126.9 (ArCH, C-4), 124.5 (ArCH, C-11), 123.2 (ArCH, C-10), 95.6 (C, C-17), 74.5 (CH_2, C-16), 52.5 (C, C-13), 47.7 (CH_2, C-14), 24.8 (CH_3, C-18); HRMS (ESI+) Exact mass calcd For $C_{19}H_{17}{}^{35}Cl_3NO_3$, 412.0269. Found $[MH]^+$, 412.0262 (1.60 ppm error).



108



108n'

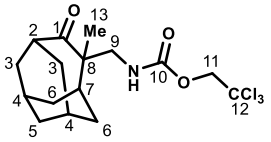


Major Diastereoisomer **108**

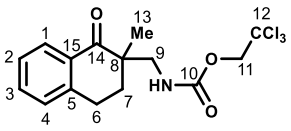
Methyl (1*R,3*R**)-3-methyl-4-oxo-3-{[(2,2,2-trichloroethoxy)carbonyl]aminomethyl}cyclopentane-1-carboxylate (108o) and methyl (1*S**,3*R**)-3-methyl-4-oxo-3-{[(2,2,2-trichloroethoxy)carbonyl]aminomethyl}cyclopentane-1-carboxylate (108o'):** Prepared according to a modification of general procedure G (no stir with 1 M aq. HCl solution) using methyl 3-hydroxy-3-(prop-1-en-2-yl)cyclobutane-1-carboxylate (**97o**) (68.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 440 μmol) and [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 95:5 → 6:4) gave the title compounds **108o** and **108o'** (91.0 mg, 252 μmol, 63%) as a colourless oil and as an inseparable mixture of diastereoisomers (2:1 d.r); R_f = 0.23 (cyclohexane/diethyl ether; 6:4); ν_{max}/cm^{-1} 3348, 2955, 1721, 1529, 1229, 1145, 811, 721, 566; [HRMS (ESI+) Exact mass cald. for $C_{12}H_{17}{}^{35}Cl_3NO_5$, 360.0167. Found $[MH]^+$, 360.0169 (0.60 ppm error)].

Methyl (1*R,3*R**)-3-methyl-4-oxo-3-{[(2,2,2-trichloroethoxy)carbonyl]aminomethyl}cyclopentane-1-carboxylate (108o):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (1H, t, *J* = 6.1 Hz, N-H), 4.80 – 4.67 (2H, m, H-7), 3.73 (3H, s, H-12), 3.42 – 3.28 (2H, m, H-5), 3.25 – 3.10 (1H, m, H-2), 2.81 – 2.52 (2H, m, H-1), 2.17 – 1.98 (2H, m, H-3), 1.09 (3H, s, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.2 (C, C-10), 174.5 (C, C-11), 155.3 (C, C-6), 95.7 (C, C-8), 74.6 (CH_2, C-7), 52.4 (CH_3, C-12), 50.7 (C, C-4), 46.1 (CH_2, C-5), 40.6 (CH_2, C-1), 37.3 (CH_2, C-3), 37.2 (CH, C-2), 20.2 (CH_3, C-9).

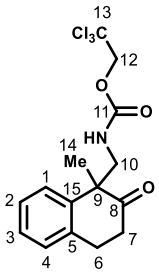
Methyl (1*S,3*R**)-3-methyl-4-oxo-3-{[(2,2,2-trichloroethoxy)carbonyl]aminomethyl}cyclopentane-1-carboxylate (108o'):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (1H, t, *J* = 5.5 Hz, N-H), 4.80 – 4.67 (2H, m, H-7), 3.74 (3H, s, H-12), 3.42 – 3.28 (2H, m, H-5), 3.25 – 3.10 (1H, m, H-2), 2.81 – 2.52 (2H, m, H-1), 2.40 – 2.31 (1H, m, H-3$_a$), 2.09 – 1.98 (1H, m, H-3$_b$), 1.12 (3H, s, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.0 (C, C-10), 174.9 (C, C-11), 155.3 (C, C-6), 95.6 (C, C-8), 74.7 (CH_2, C-7), 52.4 (CH_3, C-12), 49.8 (C, C-4), 46.4 (CH_2, C-5), 40.5 (CH_2, C-1), 37.7 (CH_2, C-3), 37.2 (CH, C-2), 20.9 (CH_3, C-9).



2,2,2-Trichloroethyl{[(1R,3s,6r,8S)-4-methyl-5-oxotricyclo[4.3.1.13,8]undecan-4-yl]methyl}carbamatee (108p): Prepared according to a modification of general procedure D (reaction time: 48 h) using 2-(prop-1-en-2-yl)adamantan-2-ol (**97p**) (90.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether 8:2) gave the title compound **108p** (68.0 mg, 178 μmol, 44%) as a colourless crystalline solid; mp. 79 – 81 °C, R_f = 0.40 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 2915, 2856, 1739, 1240, 1150, 724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 – 4.71 (1H, br. s, NH), 4.67 (2H, s, H-11), 3.57 (2H, app. d, *J* = 5.8 Hz, H-9), 2.21 (2H, m, H-2 and H-7), 2.19 (3H, s, H-13), 2.06 – 1.94 (2H, m, H-6$_A$), 1.86 (2H, m, H-4), 1.76 – 1.60 (9H, m, H-5, H-3 and H-6$_B$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.2 (C, C-1), 154.8 (C, C-10), 95.6 (C, C-12), 74.7 (CH_2, C-11), 57.3 (C, C-8), 43.7 (CH_2, C-9), 38.0 (CH_2, C-6), 35.0 (CH_2, C-3), 32.5 (CH_2, C-5), 30.4 (CH, C-2), 27.5 (CH, C-7), 26.9 (CH, C-4), 24.9 (CH_3, C-13); HRMS (ESI+) Exact mass calcd For $C_{16}H_{26}{}^{35}Cl_3N_2O_3$, 339.1004. Found $[MNH_4]^+$, 339.1005 (0.30 ppm error).



108ua



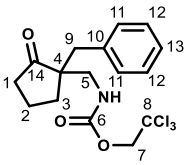
108ub

2,2,2-Trichloroethyl [(2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl]carbamate (108ua) and 2,2,2-Trichloroethyl [(1-methyl-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]carbamate (108ub): The title compound was prepared according to general procedure G using 1-(prop-1-en-2-yl)-2,3-dihydro-1*H*-inden-1-ol (**97u**) (70.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether 9:1 → 6:4) gave the

regioisomer **108ua** (84.0 mg, 230 μmol, 58%) as a colourless oil and regioisomer **108ub** (57.0 mg, 156 μmol, 39%) as a colourless oil.

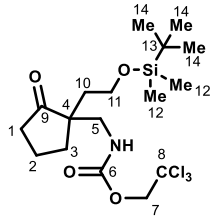
2,2,2-Trichloroethyl [(2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl]carbamate (108ua): R_f = 0.51 (cyclohexane/diethyl ether; 6:4); ν_{max}/cm^{-1} 3336, 2948, 1707, 1513, 1225, 1147, 761, 722; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, d, *J* = 7.5 Hz, H-1), 7.50 (1H, dd, *J* = 7.5, 1.0 Hz, H-3), 7.32 (1H, dd, *J* = 7.5, 1.0 Hz, H-2), 7.28 – 7.21 (1H, m, H-4), 5.65 (1H, t, *J* = 6.1 Hz, NH), 4.77 (1H, d, *J* = 12.0 Hz, H-11$_A$), 4.71 (1H, d, *J* = 12.0 Hz, H-11$_B$) (2H, q, *J* = 12.1 Hz, H-11), 3.57 (1H, dd, *J* = 13.8, 6.6 Hz, H-9$_A$), 3.36 (1H, dd, *J* = 13.8, 6.6 Hz, H-9$_B$), 3.22 – 3.10 (1H, m, H-7$_A$), 3.01 – 2.89 (1H, m, H-7$_B$), 2.25 – 2.11 (1H, m, H-6$_A$), 1.95 – 1.84 (1H, m, H-6$_B$), 1.21 (3H, s, H-13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.8 (C, C-14), 155.3 (C, C-10), 143.3 (ArC, C-15), 133.9 (ArCH, C-3), 131.4 (ArC, C-5) , 129.0 (ArCH, C-4), 128.0 (ArCH, C-1), 127.0 (ArCH, C-2), 95.8 (C, C-12), 74.7 (CH_2, C-11), 48.1 (CH_2, C-9), 46.3 (C, C-8), 32.1 (CH_2, C-6), 25.3 (CH_2, C-7), 19.2 (CH_3, C-13). [HRMS (ESI+) Exact mass cald. for $C_{15}H_{17}{}^{35}Cl_3NO_3$, 364.0269. Found $[MH]^+$, 364.0264 (1.30 ppm error)].

2,2,2-Trichloroethyl [(1-methyl-2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)methyl]carbamate (108ub): R_f = 0.48 (cyclohexane/diethyl ether; 6:4); ν_{max}/cm^{-1} 3350, 2929, 1731, 1674, 1510, 1223, 1143, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (1H, d, *J* = 7.6 Hz, H-1), 7.30 (dd, *J* = 7.5, 1.3 Hz, H-3), 7.27 – 7.14 (2H, m, H-2 and H-4), 5.22 (1H, t, *J* = 5.3 Hz, NH), 4.70 – 4.57 (2H, m, H-12), 3.80 (1H, dd, *J* = 13.9, 6.5 Hz, H-10$_A$), 3.62 (1H, dd, *J* = 13.9, 6.5 Hz, H-10$_B$), 3.17 – 3.07 (2H, m, H-6), 2.85 – 2.75 (1H, m, H-7$_A$), 2.70 – 2.60 (1H, m, H-7$_B$), 1.45 (3H, s, H-14); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.3 (C, C-8), 154.7 (C, C-11), 139.4 (ArC, C-5), 136.2 (ArC, C-15), 128.5 (ArCH, C-4), 127.5 (ArCH, C-3), 127.3 (ArCH, C-2), 126.9 (ArCH, C-1), 95.7 (C, C-13), 74.5 (CH_2, C-12), 52.5 (C, C-9), 48.1 (CH_2, C-10), 37.7 (CH_2, C-7), 27.0 (CH_2, C-6), 24.2 (CH_3, C-14). [HRMS (ESI+) Exact mass cald. for $C_{15}H_{16}{}^{35}Cl_3NNaO_3$, 386.0088. Found $[MNa]^+$, 386.0089 (0.30 ppm error)].



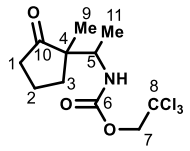
2,2,2-Trichloroethyl ((1-benzyl-2-oxocyclopentyl)methyl)carbamate (108v): The title compound was prepared according to general procedure G using 1-(3-phenylprop-1-en-2-yl)cyclobutan-1-ol (**97v**) (76.0 mg, 400 μmol), {[4-(trifluoromethyl)benzoyl]oxy}carbamate

(**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 20:1 → 9:1) gave 2,2,2-trichloroethyl [(1-benzyl-2-oxocyclopentyl)methyl]carbamate (**108v**) (100 mg, 264 μmol, 66%) as a colourless oil; R_f = 0.48 (cyclohexane/ethyl acetate; 6:4); ν_{max}/cm^{-1} 2927, 1726, 1515, 1230, 1148, 905, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.20 (3H, m, H-11 and H-13), 7.15 – 7.07 (2H, m, H-12), 5.45 (1H, t, *J* = 6.1 Hz, NH), 4.80 – 4.67 (2H, m, H-7), 3.41 (1H, dd, *J* = 13.9, 5.2 Hz, H-5$_A$), 3.22 (1H, dd, *J* = 13.9, 5.2 Hz, H-5$_B$), 2.89 (1H, d, *J* = 13.5 Hz, H-9$_A$), 2.67 (1H, d, *J* = 13.5 Hz, H-9$_B$), 2.31 – 2.20 (1H, m, H-1$_A$), 2.17 – 2.06 (1H, m, H-1$_B$), 2.05 – 1.95 (1H, m, H-3$_A$), 1.88 – 1.72 (2H, m, H-2$_A$ and H-3$_B$), 1.72 – 1.52 (1H, m, H-2$_B$); ^{13}C NMR (101 MHz, $CDCl_3$) 223.0 (C, C-14), 155.1 (C, C-6), 136.5 (ArC, C-10), 130.2 (ArCH, C-12), 128.7 (ArCH, C-11), 127.1 (ArCH, C-13), 95.7 (C, C-8), 74.7 (CH_2, C-7), 53.5 (C, C-4), 45.5 (CH_2, C-5), 39.3 (CH_2, C-9), 38.8 (CH_2, C-1), 30.9 (CH_2, C-3), 18.8 (CH_2, C-2). [HRMS (ESI+) Exact mass cald. for $C_{16}H_{19}{}^{35}Cl_3NO_3$, 378.0425. Found [MH]$^+$, 378.0414 (2.90 ppm error)].



2,2,2-Trichloroethyl {1-[2-(*tert*-butyldimethylsilyl)oxyethyl]-2-oxocyclopentyl}methylcarbamate (108w): Prepared according to a modification of general procedure G (no stir with 1 M aq. HCl solution) using 1-{4-[(*tert*-butyldimethylsilyl)oxy]but-1-en-2-yl}cyclobutan-1-ol (**97w**) (103 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 440 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether – 8:2) gave the title compound **108w** (151 mg, 338 μmol, 85%) as a colourless oil; R_f = 0.31 (cyclohexane/diethyl ether; 6:4); ν_{max}/cm^{-1} 2953, 2930, 1727, 1144, 1093, 833, 775, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (1H, t, *J* = 5.9 Hz, NH), 4.72 – 4.65 (2H, m, H-7), 3.82 – 3.73 (1H, m, H-11$_A$), 3.67 – 3.60 (1H, m, H-11$_B$), 3.38 (1H, dd, *J* = 14.0, 7.8 Hz, H-5$_A$), 3.19 (1H, dd, *J* = 14.0, 7.8 Hz, H-5$_B$), 2.34 – 2.24 (2H, m, H-1), 1.97 – 1.85 (4H, m, H-10 and H-2), 1.77 – 1.62 (2H, m, H-3), 0.87 (9H, s, H-14), 0.05 (6H, s, H-12); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.5 (C, C-9), 155.1 (C, C-6), 95.8 (C, C-8), 74.6 (CH_2, C-7), 59.4 (CH_2, C-11), 51.4 (C, C-4), 44.6 (CH_2, C-5), 37.9 (CH_2, C-1), 36.4 (CH_2, C-3), 32.4 (CH_2, C-

10), 26.0 (CH_3, C-14), 18.8 (CH_2, C-2), 18.3 (C, C-13), −5.44 (CH_3, C-12). [HRMS (ESI+) Exact mass cald. for $C_{17}H_{31}{}^{35}Cl_3NO_4Si$, 446.1082. Found $[MH]^+$, 446.1081 (0.40 ppm error)].

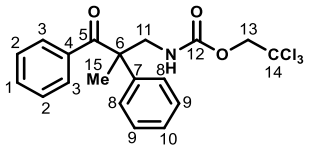


2,2,2-Trichloroethyl [1-(1-methyl-2-oxocyclopentyl)ethyl]carbamate (108x): Prepared according to general procedure G using 1-(but-2-en-2-yl)cyclobutan-1-ol (**97x**) (51 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether 9:1 → 6:4) gave the major diastereoisomer of the title compound **108x** (32.0 mg, 101 μmol, 25%) as a colourless oil and the minor diastereoisomer **108x'** (29.0 mg, 92.0 μmol, 23%, 1.1:1 d.r) as a colourless oil.

Major Diastereoisomer 108x: R_f = 0.28 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3339, 2964, 1721, 1509, 1230, 1114, 735; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, d, *J* = 9.1 Hz, NH), 4.80 – 4.67 (2H, m, H-7), 3.91 – 3.79 (1H, dq, *J* = 9.9, 6.8 Hz, H-5), 2.45 – 2.34 (1H, m, H-1_A), 2.25 – 2.11 (1H, m, H-1_B), 2.09 – 1.83 (3H, m, H-2 and H-3_A), 1.82 – 1.71 (1H, m, H-3_B), 1.20 – 1.09 (6H, m, H-9 and H-11); ^{13}C NMR (101 MHz, $CDCl_3$) δ 223.8 (C, C-10), 154.5 (C, C-6), 95.9 (C, C-8), 74.6 (CH_2, C-7), 51.9 (C, C-4), 51.5 (CH, C-5), 39.1 (CH_2, C-1), 34.3 (CH_2, C-3), 20.8 (CH_2, C-2), 19.0 (CH_3, C-11), 17.3 (CH_3, C-9). [HRMS (ESI+) Exact mass cald. for $C_{11}H_{20}{}^{35}Cl_3N_2O_3$, 333.0534. Found $[MNH_4]^+$, 333.0539 (1.50 ppm error)].

Minor Diastereoisomer 108x': R_f = 0.26 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} 3330, 2966, 1729, 1535, 1237, 1154, 736; ^1H NMR (400 MHz, $CDCl_3$) δ 4.91 (1H, d, *J* = 7.3 Hz, NH), 4.80 – 4.67 (2H, m, H-7), 4.02 – 3.89 (1H, m, H-5), 2.41 – 2.31 (1H, m, H-1_A), 2.30 – 2.15 (1H, m, H-1_B), 2.08 – 1.81 (3H, m, H-2 and H-3_A), 1.77 – 1.65 (1H, m, H-3_B), 1.18 (3H, d, *J* = 6.8 Hz, H-11), 1.07 (3H, s, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.6 (C, C-10), 154.5 (C, C-6), 95.8 (C, C-8), 74.7 (CH_2, C-7), 52.2 (C, C-4), 51.2 (CH, C-5), 38.4 (CH_2, C-1), 33.1 (CH_2 ,C-3), 19.6 (CH_2, C-1), 18.6 (CH_3, C-11), 16.8 (CH_3, C-9). [HRMS (ESI+) Exact mass cald. for $C_{11}H_{17}{}^{35}Cl_3NO_3$, 316.0269. Found $[MH]^+$, 316.0268 (0.10 ppm error)].

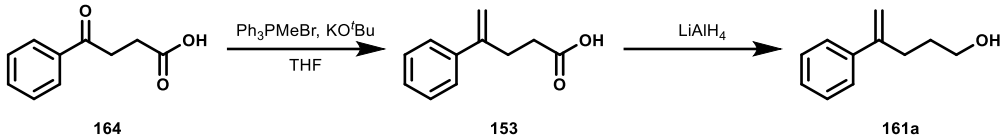
Note: It was not possible to establish the relative stereochemistry of the major and minor diastereoisomer.



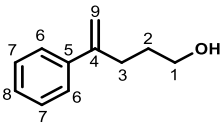
2,2,2-Trichloroethyl (2-methyl-3-oxo-2,3-diphenylpropyl)carbamate (108y): The title compound was prepared according to general procedure G using 2-methyl-1,1-diphenylprop-2-en-1-ol (**97y**) (90.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by column chromatography (SiO_2, cyclohexane:diethyl ether 95:5 → 6:4) gave the title compound **108y** (82.0 mg, 198 μmol, 49%) as a colourless oil; R_f = 0.43 (cyclohexane/diethyl ether; 6:4); ν_{max}/cm^{-1} 2948, 1744, 1670, 1506, 1216, 1151, 715, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.47 (2H, m, H-3), 7.44 – 7.21 (8H, m, H-1, H-2, H-8, H-9 and H-10), 5.65 (1H, app. t, *J* = 6.4 Hz, NH), 4.73 – 4.60 (2H, m, H-13), 3.70 (1H, dd, *J* = 13.8, 5.6 Hz, H-11$_A$), 3.56 (1H, dd, *J* = 13.8, 7.9 Hz, H-11$_B$), 1.75 (3H, s, H-15); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6 (C, C-5), 155.1 (C, C-12), 140.9 (ArC, C-7), 135.3 (ArC, C-4), 132.7 (ArCH, C-1), 130.2 (ArCH, C-3), 129.4 (ArCH, C-2), 128.3 (ArCH, C-8), 127.9 (ArCH, C-10), 126.5 (ArCH, C-2), 95.8 (C, C-14), 74.6 (CH_2, C-13), 56.2 (C, C-6), 51.4 (CH_2, C-15), 20.5 (CH_3, C-11). [HRMS (ESI+) Exact mass cald. For $C_{19}H_{19}{}^{35}Cl_3NO_3$, 414.0425. Found $[MH]^+$, 414.0421 (1.00 ppm error)].

Synthesis of Substrates for THF project

Formation of Alcohol Substrate **161a** for Optimisation using a Wittig[145] and reduction[146]



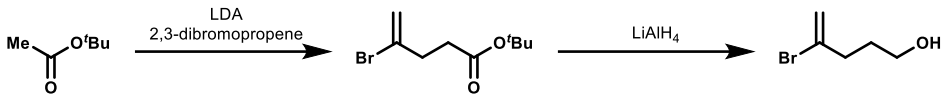
164 153 161a

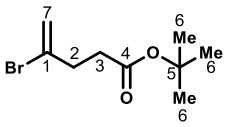


4-Phenylpent-4-en-1-ol (161a): To a solution of 3-benzoylpropionic acid (2.67 g, 15.0 mmol) and methyltriphenylphosphonium bromide (6.97 g, 19.5 mmol) in THF (0.2 M, 75 mL), was added potassium *tert*-butoxide (4.38 g, 39.0 mmol) and left to stir at rt. After 18 h, the reaction mixture was concentrated *in vacuo* and the residue was diluted with DCM (50 mL) and aq. 1 M NaOH solution (50 mL). The phases were separated, and aqueous layer extracted with DCM (3 × 100 mL), and the aqueous layer acidified with aq. 1 M HCl solution to pH 1. Buchner filtration provided the crude 4-phenylpent-4-enoic acid (2.05 g, 11.6 mmol, 77%) which was taken without further purification. To a solution of $LiAlH_4$ (925 mg, 24.4 mmol) in diethyl ether (29 mL) at 0 °C, was added crude 4-phenylpent-4-enoic acid (2.05 g, 11.6 mmol). After stirring at rt for 18 h, the reaction mixture was quenched using sodium sulfate decahydrate, then left to stir for 1.5 h. The reaction mixture was filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 6:4) gave the title compound **161a** (1.57 g, 9.66 mmol, 87%) as a yellow oil; R_f = 0.11 (pentane/diethyl ether; 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (2H, m, H-6), 7.33 (2H, app. t, *J* = 7.3 Hz, H-7), 7.28 (1H, d, *J* = 7.3 Hz, H-8), 5.30 (1H, s, H-9$_A$), 5.10 (1H, s, H-9$_B$), 3.67 (2H, t, *J* = 6.5 Hz, H-1), 2.61 (2H, t, *J* = 7.6 Hz, H-3), 1.78 – 1.68 (2H, m, H-2), 1.37 (1H, br. s, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1 (C, C-4), 141.2 (ArC, C-5), 128.5 (ArCH, C-7), 127.6 (ArCH, C-8), 126.3 (ArCH, C-6), 112.7 (CH_2, C-9), 62.6 (CH_2, C-1), 31.7 (CH_2, C-3), 31.3 (CH_2, C-2).

Data are consistent with those reported in the literature.[174]

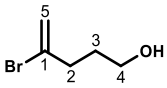
Formation of alcohol **166**:[146]





***tert*-Butyl 4-bromopent-4-enoate**[146] **(167):** To a freshly prepared 1 M solution of LDA at 0 °C (40 mL, 40.0 mmol) prepared from the addition of *n*-BuLi (2.5 M in hexanes, 16 mL, 40.0 mmol) to a solution of diisopropylamine (5.61 mL, 40.0 mmol) in THF (18.4 mL) at 0 °C, was added a solution of *tert*-butyl acetate (5.40 mL, 40.0 mmol) in THF (72 mL) dropwise. The reaction mixture was left to stir for 0.5 h at 0 °C, then 2,3-dibromopropene (1.56 mL, 26.7 mmol) was added dropwise, and the reaction mixture allowed to stir at 0 °C for 2 h. The reaction mixture was quenched using sat. aq. NH_4Cl solution (15 mL) and extracted using ether (3 × 100 mL). Combined organic phases dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane:ethyl acetate – 20:1) gave the title compound **167** (3.89 g, 17.0 mmol, 62%) as a yellow oil; R_f = 0.45 (cyclohexane/ethyl acetate; 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (1H, d, *J* = 1.6 Hz, H-7_A), 5.42 (1H, d, *J* = 1.6 Hz, H-7_B), 2.75 – 2.65 (2H, m, H-3), 2.49 (2H, td, *J* = 8.0 Hz, H-2), 1.45 (9H, s, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C, C-4), 132.7 (C, C-1), 117.5 (CH_2, C-7), 80.9 (C, C-5), 37.0 (CH_2, C-3), 34.3 (CH_2, C-2), 28.2 (CH_3, C-6).

Data are consistent with those reported in the literature.[146]

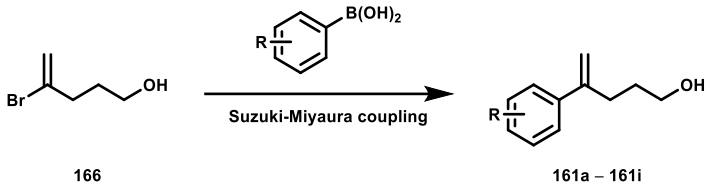


4-Bromopent-4-en-1-ol [146] **(166):** To a solution of $LiAlH_4$ (803 g, 21.7 mmol) in diethyl ether (25 mL) at 0 °C, was added *tert*-butyl 4-bromopent-4-enoate (2.37 g, 10.1 mmol) dropwise. After stirring at rt for 18 h, the reaction mixture was quenched using sodium sulfate decahydrate, then left to stir for 1.5 h. The reaction mixture was filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 1:1) gave the title compound **166** (862 mg, 5.22 mmol mmol, 52%) as a pale yellow oil; R_f = 0.22 (cyclohexane/diethyl ether; 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (1H, d, *J* = 1.5 Hz, H-5_A), 5.42 (1H, d, *J* = 1.6 Hz, H-5_B), 3.68 (2H, t, *J* = 6.1 Hz, H-4), 2.54 (2H, t, J = 7.3 Hz. H-2), 1.87

– 1.79 (2H, m, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.1 (C, C-1), 117.1 (CH_2, C-5), 61.5 (CH_2, C-4), 37.9 (CH_2, C-2), 31.0 (CH_2, C-3).

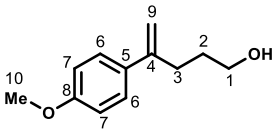
Data are consistent with those reported in the literature.[146]

General Procedure H – Preparation of alcohols **161a – 161i** using Suzuki-Miyaura Coupling[148]



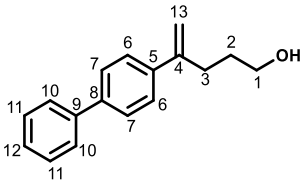
166 161a – 161i

To a mixture of vinyl bromide (1.00 eq.), boronic acid (1.30 eq.) and K_2CO_3 (1.30 eq.) in 1,2-dimethoxyethane (0.4 M) and water (0.4 M), was added $Pd(PPh_3)_4$ (5 mol%). The reaction mixture was sparged with argon for 10 minutes, then stirred at 90 °C for 18 h. The reaction mixture was filtered through celite and washed with water (10 mL), and the filtrate was extracted with diethyl ether (3 × 25 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentration *in vacuo*.

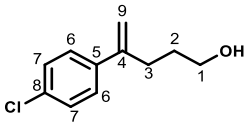


4-(4-Methoxyphenyl)pent-4-en-1-ol (161b): Prepared according to general procedure H using (4-methoxyphenyl)boronic acid (239 mg, 1.57 mmol), 4-bromopent-4-en-1-ol (**166**) (200 mg, 1.21 mmol), $Pd(PPh_3)_4$ (70.0 mg, 61.0 μmol, 5 mol%), K_2CO_3 (217 mg, 1.57 mmol), 1,2-dimethoxyethane (6 mL) and water (6 mL). Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 1:1) gave the title compound **161b** (199 mg, 1.04 mmol, 86%) as a colourless crystalline solid; mp. 48 – 50 °C (Lit.[175] 46 °C); R_f = 0.18 (cyclohexane/diethyl ether; 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (2H, d, *J* = 8.8 Hz, H-6), 6.87 (2H, d, *J* = 8.8 Hz, H-7), 5.23 (1H, d, *J* = 1.4 Hz, H-9_A), 5.02 (1H, d, *J* = 1.4 Hz, H-9_B), 3.81 (3H, s, H-10), 3.67 (2H, t, *J* = 6.5 Hz, H-1), 2.58 (2H, td, *J* = 7.4 Hz, H-3), 1.78 – 1.68 (2H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C, C-8), 147.4 (C, C-4), 127.3 (ArCH, C-6), 113.8 (ArCH, C-7), 111.2 (CH_2, C-9), 62.7 (CH_2, C-1), 55.4 (CH_3, C-10), 31.8 (CH_2, C-3), 31.4 (CH_2, C-2).

Data are consistent with those reported in the literature.[176]

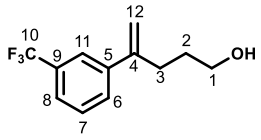


4-[(1,1'-biphenyl)-4-yl]pent-4-en-1-ol (161c): Prepared according to general procedure H using (4-biphenyl)boronic acid (311 mg, 1.57 mmol), 4-bromopent-4-en-1-ol (**166**) (200 mg, 1.21 mmol), $Pd(PPh_3)_4$ (70.0 mg, 61.0 μmol, 5 mol%), K_2CO_3 (217 mg, 1.57 mmol), 1,2-dimethoxyethane (6 mL) and water (6 mL). Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 6:4) gave the title compound **161c** (169 mg, 707 μmol, 59%) as a colourless crystalline solid; mp. 61 – 63 °C; R_f = 0.21 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3316, 3035, 2933, 2871, 1621, 1485, 1404, 1057, 1004, 843, 771, 735, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.55 (4H, m, H-10 and H-11), 7.51 (2H, d, *J* = 8.3 Hz, H-6), 7.45 (2H, t, *J* = 8.3 Hz, H-7), 7.39 – 7.32 (1H, m, H-12), 5.38 (1H, s, H-13_A), 5.14 (1H, s, H-13_B), 3.70 (2H, t, *J* = 6.4 Hz, H-1), 2.66 (2H, t, *J* = 7.6 Hz, H-3), 1.84 – 1.72 (2H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6 (C, C-4), 140.8 (ArC, C-9), 140.4 (ArC, C-5), 140.0 (ArC, C-8), 128.9 (ArCH, C-7), 127.4 (ArCH, C-12), 127.2 (ArCH, C-11), 127.1 (ArCH, C-10), 126.6 (ArCH, C-6), 112.7 (CH_2, C-13), 62.6 (CH_2, C-1), 31.6 (CH_2, C-3), 31.3 (CH_2, C-2); [HRMS (ESI+) Exact mass calcd for $C_{17}H_{22}NO$, 256.1696. Found $[MH_4N]^+$, 256.1693 (1.10 ppm error)].

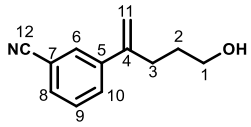


4-(4-Chlorophenyl)pent-4-en-1-ol (161d): Prepared according to general procedure H using (4-chlorophenyl)boronic acid (246 mg, 1.57 mmol), 4-bromopent-4-en-1-ol (**166**) (200 mg, 1.21 mmol), $Pd(PPh_3)_4$ (70.0 mg, 61.0 μmol, 5 mol%), K_2CO_3 (217 mg, 1.57 mmol), 1,2-dimethoxyethane (6 mL) and water (6 mL). Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 6:4) gave the title compound **161d** (174 mg, 884 μmol, 73%) as a yellow oil; R_f = 0.16 (cyclohexane/diethyl ether; 6:4); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (4H, m. H-6 and H-7), 5.28 (1H, s, H-9_A), 5.11 (1H, s, H-9_B), 3.66 (2H, t, *J* = 6.5 Hz, H-1), 2.62 – 2.52 (2H, m, H-3), 1.77 – 1.65 (2H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0 (C, C-4), 139.6 (ArCH, C-5), 133.4 (ArCH, C-8), 128.6 (ArCH, C-7), 127.6 (ArCH, C-6), 113.2 (CH_2, C-9), 62.5 (CH_2, C-1), 31.6 (CH_2, C-3), 31.2 (CH_2, C-2).

Data are consistent with those reported in the literature.[177]

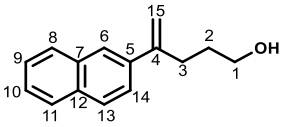


4-[3-(Trifluoromethyl)phenyl]pent-4-en-1-ol (161e): Prepared according to general procedure H using (3-trifluoromethylphenyl)boronic acid (298 mg, 1.57 mmol), 4-bromopent-4-en-1-ol (**166**) (200 mg, 1.21 mmol), $Pd(PPh_3)_4$ (70.0 mg, 61.0 μmol, 5 mol%), K_2CO_3 (217 mg, 1.57 mmol), 1,2-dimethoxyethane (6 mL) and water (6 mL). Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 8:2 → 4:6) gave the title compound **161e** (183 mg, 795 μmol, 66%) as a yellow oil; R_f = 0.28 (pentane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3321, 2942, 2874, 1330, 1163, 1117, 1071, 898, 805, 696, 656; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, d, *J* = 1.8 Hz, H-11), 7.65 – 7.60 (1H, m, H-8), 7.58 – 7.51 (1H, m, H-6), 7.50 – 7.41 (1H, m, H-7), 5.33 (1H, s, H-12_A), 5.20 (1H, s, H-12_B), 3.66 (2H, t, *J* = 6.4 Hz, H-1), 2.89 – 2.13 (2H, m, H-3), 2.24 – 0.80 (2H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8 (C, C-4), 141.9 (ArC, C-5), 130.8 (q, *J* = 32.1 Hz, ArC, C-9), 128.8 (ArCH, C-7), 124.2 (q, *J* = 273.4 Hz, C, C-10), 124.1 (q, *J* = 3.9 Hz, ArCH, C-11) 122.9 (q, *J* = 3.9 Hz, ArCH, C-8), 114.1 (CH_2, C-12), 62.3 (CH_2, C-1), 31.4 (CH_2, C-3), 31.0 (CH_2, C-2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6 ppm (s); [HRMS (EIMS+) Exact mass calcd for $C_{12}H_{13}OF_3$, 230.0913. Found $[MH]^+$, 230.0914 (0.56 ppm error)].



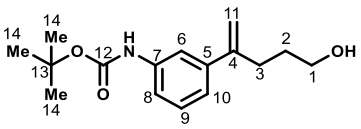
3-(5-Hydroxypent-1-en-2-yl)benzonitrile (161f): Prepared according to general procedure H using 3-cyanophenylboronic acid (230 mg, 1.57 mmol), 4-bromopent-4-en-1-ol (**166**) (200 mg, 1.21 mmol), $Pd(PPh_3)_4$ (70.0 mg, 61.0 μmol, 5 mol%), K_2CO_3 (217 mg, 1.57 mmol), 1,2-dimethoxyethane (6 mL) and water (6 mL). Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 1:1) gave the title compound **161f** (180 mg, 961 μmol, 80%) as a colourless oil; R_f = 0.10 (cyclohexane/diethyl ether; 1:1); υ_{max}/cm^{-1} (thin film) 3376, 2940, 2873, 2230, 1628, 1480, 1054, 897, 802, 651; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.66 (1H, m, H-6), 7.66 – 7.61 (1H, m, H-8), 7.57 – 7.53 (1H, m, H-10), 7.43 (1H, app. t, *J* = 7.8 Hz, H-9), 5.34 (1H, s, H-11_A), 5.21 (1H, s, H-11_B), 3.68 (2H, t, *J* = 6.4 Hz, H-1), 2.59 (2H, t, *J* = 7.6 Hz, H-3), 1.79 – 1.62 (2H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2 (C, C-4), 142.5 (ArC, C-5), 131.0 (ArCH, C-10), 130.6 (ArCH, C-8), 129.9 (ArCH, C-6), 129.3 (ArCH, C-9), 119.0 (C, C-9), 114.8 (CH_2, C-11), 112.7 (ArC, C-7), 62.2 (CH_2, C-1), 31.4 (CH_2, C-3), 31.0 (CH_2,

C-2); [HRMS (ESI+) Exact mass calcd for $C_{12}H_{17}N_2O$, 205.1335. Found $[MH_4N]^+$, 205.1335 (0.00 ppm error)].



4-(Naphthalen-2-yl)pent-4-en-1-ol (161g): Prepared according to general procedure H using 2-naphthylboronic acid (270 mg, 1.57 mmol), 4-bromopent-4-en-1-ol (**166**) (200 mg, 1.21 mmol), $Pd(PPh_3)_4$ (70.0 mg, 61.0 μmol, 5 mol%), K_2CO_3 (217 mg, 1.57 mmol), 1,2-dimethoxyethane (6 mL) and water (6 mL). Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 8:2 → 6:4) gave the title compound **161g** (195 mg, 919 μmol, 76%) as a colourless oil; R_f = 0.20 (pentane/diethyl ether; 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.73 (4H, m, H-6, H-8, H-11 and H-13), 7.59 (1H, dd, *J* = 8.6, 1.8 Hz, H-14), 7.52 – 7.42 (2H, m, H-9 and H-10), 5.50 – 5.40 (1H, m, H-15$_A$), 5.21 (1H, d, *J* = 1.3 Hz. H-15$_B$), 3.76 – 3.64 (2H, m, H-1), 2.73 (2H, td, *J* = 7.5, 1.3 Hz, H-3), 1.85 – 1.71 (2H, m, H-2), 1.31 (1H, br. s., OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9 (C, C-4), 138.4 (ArC, C-5), 133.5 (ArC, C-7), 133.0 (ArC, C-12), 128.3 (ArCH, C-13), 128.0 (ArCH, C-8), 127.7 (ArCH, C-11), 126.3 (ArCH, C-9), 126.0 (ArCH, C-10), 124.9 (ArCH, C-6), 124.8 (ArCH, C-14), 113.3 (CH_2, C-15), 62.6 (CH_2, C-1), 31.7 (CH_2, C-3), 31.4 (CH_2, C-2).

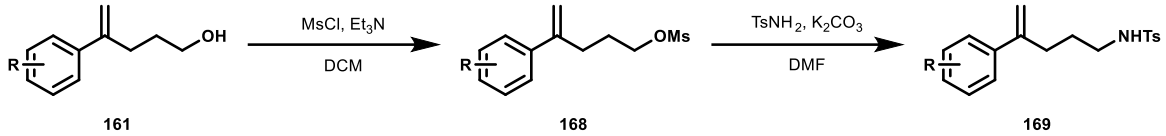
Data are consistent with those reported in the literature.[150]



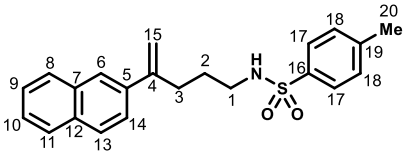
***tert*-Butyl [3-(5-hydroxypent-1-en-2-yl)phenyl]carbamate (161i):** Prepared according to general procedure H using 3-(*N*-Boc-amino)phenylboronic acid (372 mg, 1.57 mmol), 4-bromopent-4-en-1-ol (**166**) (200 mg, 1.21 mmol), $Pd(PPh_3)_4$ (70.0 mg, 61.0 μmol, 5 mol%), K_2CO_3 (217 mg, 1.57 mmol), 1,2-dimethoxyethane (6 mL) and water (6 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 6:4) gave the title compound **161i** (142 mg, 512 μmol, 42%) as a colourless oil; R_f = 0.13 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3320, 2925, 1697, 1541, 1367, 1155, 1055, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (1H, d, *J* = 1.8 Hz, H-6), 7.26 – 7.20 (2H, m, H-8 and H-9), 7.09 (1H, d, *J* = 3.9 Hz. H-10), 6.51 (1H, br. s, NH), 5.30 (1H, s, H-11$_A$), 5.09 (1H, s, H-11$_B$), 3.66 (2H, t, *J* = 6.4 Hz, H-1), 2.59 (2H, t, *J* = 7.5, H-3), 1.77 – 1.67 (2H, m, H-2), 1.52 (9H, s, H-14); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 152.8 (C, C-12), 147.7 (C, C-4), 141.9 (ArC, C-7), 138.4 (ArC, C-5), 128.9 (ArCH, C-9), 121.0 (ArCH, C-10), 117.7 (ArCH, C-8), 116.5 (ArCH, C-6), 112.9 (CH_2, C-11), 80.6 (C, C-13), 62.4 (CH_2, C-1), 31.5 (CH_2, C-3), 31.2 (CH_2, C-2), 28.4 (CH_3, C-14); [HRMS (ESI+) Exact mass calcd for $C_{16}H_{27}N_2O_3$, 295.2016. Found $[MH_4N]^+$, 295.2012 (1.50 ppm error)].

General Procedure I – Preparation of *N*-Tosyl substrates **169a** – **169b**:[150]

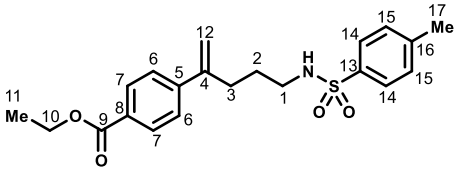


To a mixture of alcohol **161** (1.00 eq.) in DCM (0.2 M) at 0 °C, was added triethylamine (3.00 eq.) then MsCl (1.50 eq.) and reaction mixture allowed to stir at rt. After 2 h, the reaction mixture was quenched using water (5 mL) and extracted using DCM (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentration *in vacuo* to provide the crude mesylated product **168**. To a solution of **168** in DMF (0.1 M), was added tosylamine (2.00 eq.) and K_2CO_3 (2.00 eq.) and stirred at 80 °C for 18 h. The reaction mixture was cooled to rt, and diluted in ethyl acetate (10 mL), then washed with water (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentration *in vacuo.*



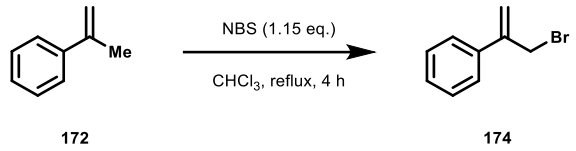
4-Methyl-*N*-[4-(naphthalen-2-yl)pent-4-en-1-yl]benzenesulfonamide (169a): Prepared according to general procedure I using 4-(naphthalen-2-yl)pent-4-en-1-ol (**161g**) (308 mg, 1.45 mmol), Et_3N (610 µL, 4.35 mmol), MsCl (170 µL, 2.17 mmol) and DCM (7.3 mL) to generate crude mesylated intermediate **168a** (421 mg, *quant.*). Then using mesylated intermediate (421 mg, 1.45 mmol), $TsNH_2$ (497 mg, 2.90 mmol) and K_2CO_3 (401 mg, 2.90 mmol) in DMF (15 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 8:2) gave the title compound **169a** (181 mg, 495 µmol, 34%) as a colourless oil; R_f = 0.21 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3277, 3055, 2925, 1597, 1320, 1305, 1154, 1092, 813, 659, 549; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.81 (2H, m, H-8 and H-13), 7.81 – 7.75 (2H, m, H-6 and H-14), 7.70 (2H, d, *J* = 8.0 Hz, H-17), 7.56 – 7.44 (3H, m, H-9, H-10 and H-11), 7.20 (2H, d, *J* = 8.0 Hz, H-18), 5.42 (1H, s, H-15_A), 5.14 (1H, s, H-15_B), 4.79

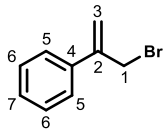
(1H, br. s, NH), 3.01 (2H, q, *J* = 6.8 Hz, H-1), 2.70 – 2.58 (2H, m, H-3), 2.37 (3H, s, H-20), 1.71 – 1.59 (2H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0 (C, C-4), 143.4 (ArC, C-5), 137.9 (ArC, C-19), 137.0 (ArC, C-16), 133.5 (ArC, C-5), 132.9 (ArC, C-12), 129.7 (ArCH, C-18), 128.3 (ArCH, C-13), 128.1 (ArCH, C-8), 127.6 (ArCH, C-14), 127.1 (ArCH, C-17), 126.3 (ArCH, C-11), 126.0 (ArCH, C-9), 124.8 (ArCH, C-10), 124.6 (ArCH, C-6), 113.8 (CH_2, C-15), 42.9 (CH_2, C-1), 32.4 (CH_2, C-3), 28.1 (CH_2, C-2), 21.5 (CH_3, C-20); [HRMS (ESI+) Exact mass calcd for $C_{22}H_{23}NNaO_2S$, 388.1342. Found $[MNa]^+$, 388.1341 (0.30 ppm error)].



Ethyl 4-{5-[(4-methylphenyl)sulfonamido]pent-1-en-2-yl}benzoate (161b): Prepared according to general procedure I using ethyl 4-(5-hydroxypent-1-en-2-yl)benzoate (**161q**) (288 mg, 1.16 mmol), Et_3N (490 µL, 3.48 mmol), MsCl (130 µL, 1.74 mmol) and DCM (5.8 mL) to generate crude mesylated intermediate **168b** (362 mg, *quant.*). Then using mesylated intermediate (362 mg, 1.16 mmol), $TsNH_2$ (397 mg, 2.32 mmol) and K_2CO_3 (321 mg, 2.32 mmol) in DMF (12 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 8:2 → 6:4) gave the title compound **161b** (173 mg, 446 µmol, 38%) as a colourless oil; R_f = 0.17 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3278, 2924, 2853, 1712, 1607, 1323, 1272, 1156, 1094, 660, 549; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (2H, d, *J* = 8.4 Hz, H-7), 7.70 (2H, d, *J* = 8.4 Hz, H-14), 7.36 (2H, d, *J* = 8.4 Hz, H-6), 7.27 (2H, d, *J* = 8.4 Hz, H-15), 5.33 (1H, s, H-12$_A$), 5.10 (1H, s, H-12$_B$), 4.73 (1H, t, *J* = 6.4, NH), 4.43 – 4.31 (2H, m, H-10), 2.95 (2H, q, *J* = 6.7 Hz, H-1), 2.52 (2H, d, *J* = 7.5 Hz, H-3), 2.41 (3H, s, H-17), 1.66 – 1.52 (2H, m, H-2), 1.43 (3H, t, J = 7.2 Hz, H-11); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C, C-9), 146.5 (C, C-4), 145.2 (ArC, C-5), 143.5 (ArC, C-16), 137.0 (ArC, C-13), 129.8 (ArCH, C-7), 129.8 (ArC, C-8), 128.7 (ArCH, C-15), 127.2 (ArCH, C-14), 126.1 (ArCH, C-6), 115.0 (CH_2, C-12), 61.1 (CH_2, C-10), 42.8 (CH_2, C-1), 32.2 (CH_2, C-3), 28.0 (CH_2, C-2), 21.6 (CH_3, C-17), 14.5 (CH_3, C-11); [HRMS (ESI+) Exact mass calcd for $C_{21}H_{29}N_2O_4S$, 405.1843. Found $[MH_4N]^+$, 405.1842 (0.20 ppm error)].

Preparation of allyl bromide **173** for morpholine substrates:[153]

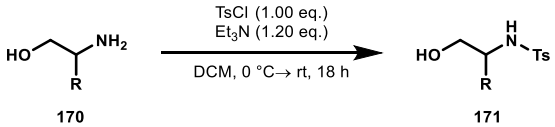




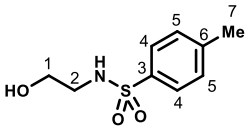
3-Bromo-2-phenylprop-1-ene [153] **(174):** To a stirring solution of α-methylstyrene (**172**) (2.60 mL, 20.0 mmol) in chloroform (4 mL), was added *N*-bromosuccinimide (4.09 g, 23.0 mmol). The reaction mixture was heated under reflux. After 4 h, the reaction mixture was concentrated *in vacuo* and diluted with petrol (40 mL). The insoluble precipitate was filtered and the organic mixture dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane) afforded the title compound **174** (1.47 g, 7.44 mmol, 37%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (2H, m, H-5), 7.41 – 7.31 (3H, m, H-6 and H-7), 5.56 (1H, s, H-3$_A$), 5.50 (1H, s, H-3$_B$), 4.39 (2H, s, H-1); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5 (C, C-2), 137.9 (ArC, C-4), 128.8 (ArCH, C-6), 128.6 (ArCH, C-7), 126.4 (ArCH, C-5), 117.5 (CH_2, C-3), 34.5 (CH_2, C-1).

Data are consistent with those reported in the literature.[153]

General procedure L – Preparation of *N*-tosylamino alcohols **171**:[151]

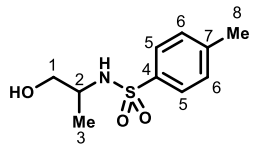


To a stirring solution of amino alcohol **170** (1.00 eq.) in DCM (0.2 M) at 0 °C, was added triethylamine (1.20 eq.). After 5 minutes, a solution of TsCl (1.00 eq.) in DCM (10 mL) was added and the reaction mixture was left to stir at rt. After 18 h, the reaction mixture was quenched using water (25 mL), and the aqueous phase was separated and extracted with DCM (3 × 100 mL). The combined organic phase was washed with aq. 1 M HCl solution (150 mL), water (150 mL), sat. aq. $NaHCO_3$ solution (150 mL) then brine (150 mL). The resultant organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*.



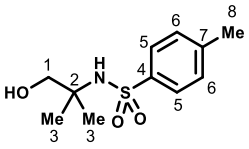
***N*-(2-Hydroxyethyl)-4-methylbenzenesulfonamide (171a):** Prepared according to general procedure L using (±)-2-aminoethanol (610 µL, 10.0 mmol), triethylamine (1.67 mL, 12.0 mmol), TsCl (1.91 g, 10.0 mmol) and DCM (50 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 6:4) gave the title compound **171a** (1.40 g, 6.10 mmol, 61%) as a colourless crystalline solid; mp. 54 – 55 °C (Lit.[178] 50 – 52°C); R_f = 0.23 (cyclohexane/EtOAc; 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.1 Hz, H-4), 7.32 (2H, d, *J* = 8.1 Hz, H-5), 3.74 – 3.63 (2H, m, H-2), 3.14 – 3.04 (2H, m, H-1), 2.43 (3H, s, H-7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (ArC, C-3), 136.4 (ArC, C-6), 129.7 (ArCH, C-5), 127.0 (ArCH, C-4), 61.0 (CH_2, C-1), 45.1 (CH_2, C-2), 21.4 (CH_3, C-7).

Data are consistent with those reported in the literature.[178]



(±)-*N*-(2-Hydroxy-1-methylethyl)-4-methylbenzenesulfonamide (171b): Prepared according to general procedure L using (±)-2-aminopropanol (800 µL, 10.0 mmol), triethylamine (1.67 mL, 12.0 mmol), TsCl (1.91 g, 10.0 mmol) and DCM (50 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 6:4) gave the title compound **171b** (1.40 g, 6.10 mmol, 61%) as a colourless crystalline solid; mp. 62 – 64 °C (Lit.[151] 60 – 61°C); R_f = 0.29 (cyclohexane/EtOAc; 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 8.1 Hz, H-5), 7.33 (2H, d, *J* = 8.1 Hz, H-6), 5.22 (1H, br. s, NH), 3.92 – 3.88 (1H, m, H-2), 3.05 (1H, dd, *J* = 13.0, 3.1 Hz, H-1$_A$), 2.79 (1H, dd, *J* = 13.0, 8.1 Hz, H-1$_B$), 2.45 (3H, s, H-8), 2.28 (1H, br. s, OH), 1.17 (3H, d, *J* = 6.3 Hz, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (ArC, C-4), 137.5 (ArC, C-7), 129.8 (ArCH, C-6), 127.2 (ArCH, C-5), 66.2 (CH_2, C-1), 51.5 (C, C-2), 21.5 (CH_3, C-8), 17.5 (CH_3, C-3).

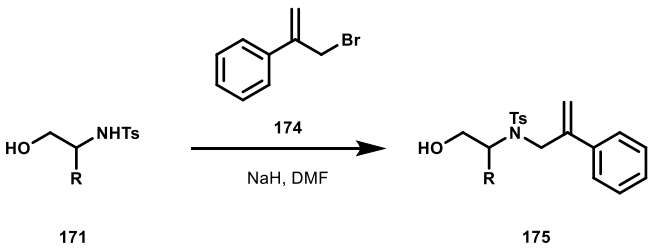
Data are consistent with those reported in the literature.[151]



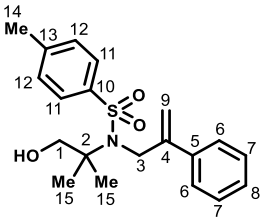
***N*-(2-Hydroxy-1,1-dimethylethyl)-4-methylbenzenesulfonamide (171c):** Prepared according to general procedure L using 2-amino-2-methylpropanol (960 µL, 10.0 mmol), triethylamine (1.67 mL, 12.0 mmol), TsCl (1.91 g, 10.0 mmol) and DCM (50 mL). Purification by column chromatography (SiO_2, cyclohexane:ethyl acetate – 6:4) gave the title compound **171c** (1.30 g, 5.30 mmol, 53%) as a colourless crystalline solid; mp. 95 – 96 °C (Lit.[151] 94 – 95°C); R_f = 0.31 (cyclohexane/EtOAc; 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.1 Hz, H-5), 7.30 (2H, d, *J* = 8.1 Hz, H-6), 4.86 (1H, br. s, NH), 3.46 (2H, s, H-1), 2.43 (3H, s, H-8), 2.13 (1H, br. s, OH), 1.13 (6H, s, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (ArC, C-4), 139.9 (ArC, C-7), 129.8 (ArCH, C-6), 127.2 (ArCH, C-5), 70.2 (CH_2, C-1), 58.1 (C, C-2), 24.8 (CH_3, C-3), 21.7 (CH_3, C-8).

Data are consistent with those reported in the literature.[151]

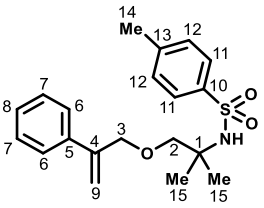
General Procedure M – Preparation of morpholine precursor substrates **175**[152]



To a mixture of *N*-tosyl amino alcohol **171** (1.00 eq.) in DMF (0.2 M) at 0 °C, was added NaH in mineral oil (2.30 eq.). A solution of allyl bromide **174** (1.00 eq.) in DMF (1 mL) was added and reaction mixture left to stir at rt. After 18 h, the reaction mixture was quenched using brine (10 mL), and aqueous layer was extracted using ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (3 × 30 mL), dried ($MgSO_4$), filtered and concentration *in vacuo*.

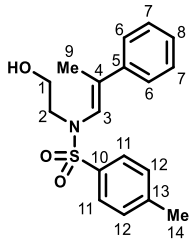


***N*-(1-Hydroxy-2-methylpropan-2-yl)-4-methyl-N-(2-phenylallyl)benzenesulfonamide (175c):** Prepared according to general procedure M using *N*-(1-hydroxy-2-methylpropan-2-yl)-4-methylbenzenesulfonamide (**171c**) (463 mg, 1.90 mmol), 3-bromo-2-phenylprop-1-ene (**174**) (375 mg, 1.90 mg) and NaH in mineral oil (105 mg, 4.37 mmol) in DMF (9.5 mL). Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 6:4) gave the title compound **175c** (212 mg, 590 µmol, 31%) as a colourless crystalline solid; mp. 85 – 86 °C; R_f = 0.12 (pentane/diethyl ether; 1:1); υ_{max}/cm^{-1} (thin film) 3479, 2921, 2853, 1596, 1312, 1289, 1145, 1066, 900, 806, 707, 651, 540; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.4 Hz, H-11), 7.40 – 7.30 (7H, m, H-6, H-7, H-8 and H-12), 5.61 (1H, s, H-9_A), 5.52 (1H, s, H-9_B), 4.39 (2H, s, H-3), 3.73 (2H, d, *J* = 7.5 Hz, H-1), 3.13 (1H, t, *J* = 7.5 Hz, OH), 2.45 (3H, s, H-14), 1.18 (6H, s, H-15); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8 (C, C-4), 143.8 (ArC, C-5), 139.8 (ArC, C-13), 139.3 (ArC, C-10), 129.9 (ArCH, C-12), 128.6 (ArCH, C-7), 128.0 (ArCH, C-8), 127.6 (ArCH, C-11), 126.2 (ArCH, C-6), 114.2 (CH_2, C-9), 69.8 (CH_2, C-1), 64.4 (C, C-2), 50.6 (CH_2, C-3), 24.5 (CH_3, C-15), 21.7 (CH_3, C-14); [HRMS (ESI+) Exact mass calcd for $C_{20}H_{25}NNaO_3S$, 382.1447. Found $[MNa]^+$, 382.1446 (0.40 ppm error)].

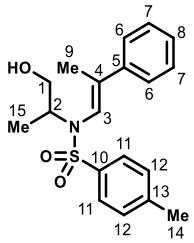


4-Methyl-*N*-{2-methyl-1-[(2-phenylallyl)oxy]propan-2-yl}benzenesulfonamide (178): Prepared using a modification of general procedure M (1.20 eq. of NaH) using *N*-(1-hydroxy-2-methylpropan-2-yl)-4-methylbenzenesulfonamide (**171c**) (453 mg, 1.86 mmol), 3-bromo-2-phenylprop-1-ene (**174**) (367 mg, 1.86 mg) and NaH in mineral oil (90 mg, 2.23 mmol) in DMF (9.3 mL). Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 6:4) gave the title compound **178** (163 mg, 453 µmol, 24%) as a colourless crystalline solid; mp. 95 – 97 °C; R_f = 0.21 (pentane/diethyl ether; 1:1); υ_{max}/cm^{-1} (thin film) 3279, 2979, 2866, 1320, 1149, 1005, 664, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 8.0 Hz, H-11), 7.47 – 7.42 (2H, m, H-6), 7.39 – 7.28 (3H, m, H-7 and H-8), 7.23 (2H, d, *J* = 8.0 Hz, H-12), 5.52 (1H,

s, H-9A), 5.26 (1H, s, H-9B), 4.87 (1H, s, NH), 4.31 (2H, s, H-3), 3.18 (2H, s, H-2), 2.40 (3H, s, H-14), 1.14 (6H, s, H-15); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (C, C-4), 142.9 (ArC, C-10), 140.5 (ArC, C-5), 138.5 (ArC, C-13), 129.5 (ArCH, C-12), 128.6 (ArCH, C-7), 128.1 (ArCH, C-8), 127.1 (ArCH, C-11), 126.2 (ArCH, C-6), 114.6 (CH_2, C-9), 77.4 (CH_2, C-2), 73.1 (CH_2, C-3), 56.6 (C, C-1), 24.8 (CH_3, C-15), 21.6 (CH_3, C-14); [HRMS (ESI+) Exact mass calcd for $C_{20}H_{25}NNaO_3S$, 382.1447. Found $[MNa]^+$, 382.1447 (0.10 ppm error)].



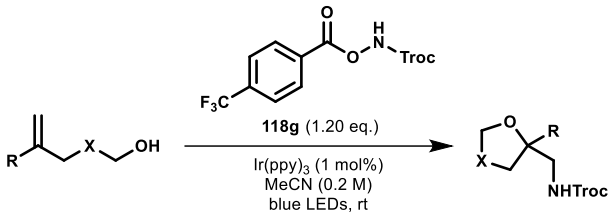
(*E*)-*N*-(2-Hydroxyethyl)-4-methyl-*N*-(2-phenylprop-1-en-1-yl)benzenesulfonamide (176): Prepared using a modification of general procedure M (1.20 eq. of NaH) using *N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (**171a**) (400 mg, 1.86 mmol), 3-bromo-2-phenylprop-1-ene (**174**) (367 mg, 1.86 mg) and NaH (90 mg, 2.23 mmol) in DMF (9.3 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 1:1) gave the title compound **176** (284 mg, 856 μmol, 46%) as a colourless oil; R_f = 0.10 (cyclohexane/diethyl ether; 1:1); υ_{max}/cm^{-1} (thin film) 3315, 2920, 1598, 1337, 1155, 1063, 747, 658, 548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, d, *J* = 8.4 Hz, H-11), 7.40 – 7.29 (7H, m, H-6, H-7, H-8 and H-12), 5.58 (1H, q, *J* = 1.5 Hz, H-3), 3.73 (2H, app. q, *J* = 5.4 Hz, H-1), 3.31 (2H, t, *J* = 5.4 Hz, H-2), 2.44 (3H, s, H-14), 2.22 (3H, d, *J* = 1.5 Hz, H-9), 1.98 (1H, t, *J* = 5.9 Hz, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4 (ArC, C-5), 140.0 (ArC, C-13), 134.9 (ArC, C-10), 129.9 (ArCH, C-12), 128.6 (ArCH, C-7), 128.4 (ArCH, C-8), 127.7 (ArCH, C-11), 126.3 (ArCH, C-6), 123.3 (CH, C-3), 60.7 (CH_2, C-1), 53.5 (CH_2, C-2), 21.7 (CH_3, C-14), 17.0 (CH_3, C-9); [HRMS (ESI+) Exact mass calcd for $C_{18}H_{22}NO_3S$, 332.1315. Found $[MH]^+$, 332.1314 (0.40 ppm error)].



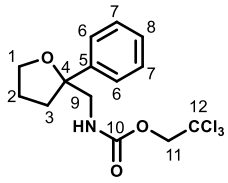
(*E*)-*N*-(1-Hydroxypropan-2-yl)-4-methyl-*N*-(2-phenylprop-1-en-1-yl)benzenesulfonamide (177): Prepared using a modification of general procedure M (1.20 eq. of NaH) using (±)-*N*-(2-hydroxy-1-methylethyl)-4-methylbenzenesulfonamide (**171b**) (426 mg, 1.86 mmol), 3-bromo-2-phenylprop-1-ene (**174**) (367 mg, 1.86 mg) and NaH (90 mg, 2.23 mmol) in DMF (9.3 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 6:4 → 1:1) gave the title compound **177** (242 mg, 700 µmol, 38%) as a colourless oil; R_f = 0.17 (cyclohexane/diethyl ether; 1:1); υ_{max}/cm^{-1} (thin film) 3520, 2973, 2921, 1598, 1339, 1158, 1089, 1023, 747, 548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (2H, d, *J* = 8.3 Hz, H-11), 7.39 – 7.29 (7H, m, H-6, H-7, H-8 and H-12), 5.55 (1H, s, H-3), 3.96 – 3.85 (1H, m, H-2), 3.26 (1H, dd, *J* = 13.4, 8.3 Hz, H-1_A), 2.91 (1H, dd, *J* = 13.5, 3.5 Hz, H-1_B), 2.44 (3H, s, H-14), 2.24 (3H, s, H-9), 1.21 (3H, d, *J* = 6.3 Hz, H-15); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (ArC, C-5), 140.0 (ArC, C-13), 134.9 (ArCH, C-10), 129.9 (ArCH, C-12), 128.6 (ArCH, C-7), 128.4 (ArCH, C-8), 127.7 (ArCH, C-11), 126.3 (ArCH, C-6), 123.9 (CH, C-3), 66.0 (CH_2, C-1), 58.7 (CH, C-2), 21.7 (CH_3, C-14), 20.5 (CH_3, C-9), 17.2 (CH_3, C-15); [HRMS (ESI+) Exact mass calcd for $C_{19}H_{24}NO_3S$, 346.1471. Found $[MH]^+$, 346.1465 (1.70 ppm error)].

Photoredox Mediated Amination / Cyclization

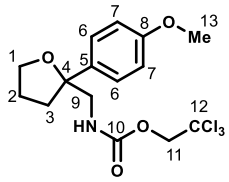
General Procedure N – Photoredox Mediated Amidation / cyclization:



To a mixture of olefin substrate (1.00 eq.), amidyl radical precursor **118g** (1.20 eq.) and $Ir(ppy)_3$ (1 mol%), was added acetonitrile (0.2 M). The reaction mixture was sparged with argon for 10 minutes, then stirred at rt whilst irradiating with blue LEDs. After 3 h, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with 1 M aq. NaOH solution (30 mL) and brine (30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentration *in vacuo*.

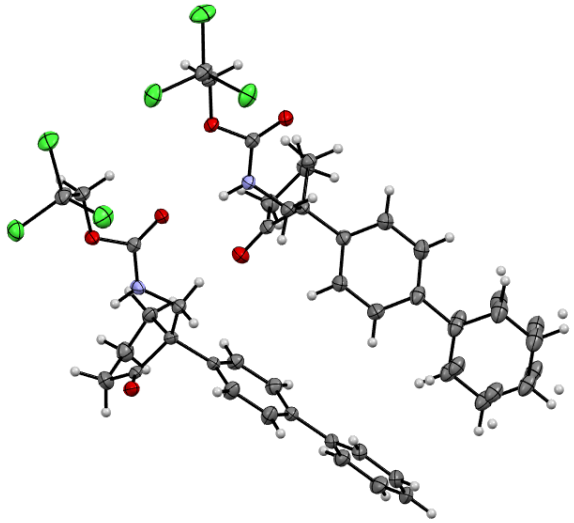


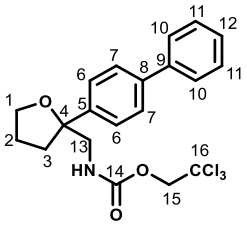
2,2,2-Trichloroethyl ((2-phenyltetrahydrofuran-2-yl)methyl)carbamate (168a): Prepared according to general procedure N using 4-phenylpent-4-en-1-ol (**161a**) (65.0 mg, 400 µmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 µmol), [$Ir(ppy)_3$] (2.7 mg, 4.00 µmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 9:1) gave the title compound **168a** (102 mg, 289 µmol, 72%) as a colourless oil; R_f = 0.23 (cyclohexane/diethyl ether; 8:2); υ_{max}/cm^{-1} (thin film) 3315, 2950, 1739, 1536, 1517, 1237, 1139, 1065, 725, 703; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.31 (4H, m, H-6 and H-7), 7.26 – 7.22 (1H, m, H-8), 5.23 (1H, s, NH), 4.76 – 4.60 (2H, m, H-11), 4.02 (1H, dt, *J* = 8.3, 6.0 Hz, H-1_a), 3.94 (1H, app. dt, *J* = 8.3, 6.0 Hz, H-1_b), 3.61 (1H, dd, *J* = 13.8, 6.9 Hz, H-9_a), 3.47 (dd, *J* = 13.8, 6.9 Hz, H-9_b), 2.22 – 2.09 (2H, m, H-3), 2.03 – 1.92 (1H, m, H-2_a), 1.92 – 1.79 (1H, m, H-2_b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0 (C, C-10), 144.3 (ArC, C-5), 128.5 (ArCH, C-7), 127.3 (ArCH, C-8), 125.4 (ArCH, C-6), 95.8 (C, C-12), 86.3 (C, C-4), 74.6 (CH_2, C-11), 68.4 (CH_2, C-1), 50.0 (CH_2, C-9), 35.6 (CH_2, C-3), 26.1 (CH_2, C-2); [HRMS (ESI+) Exact mass calcd for $C_{14}H_{20}{}^{35}Cl_3N_2O_3$, 369.0534. Found $[MH_4N]^+$, 369.0531 (0.90 ppm error)].



2,2,2-Trichloroethyl {[2-(4-methoxyphenyl)tetrahydrofuran-2-yl]methyl}carbamate (163b): Prepared according to general procedure N using 4-(4-methoxyphenyl)pent-4-en-1-ol (**161b**) (77.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 9:1) gave the title compound **163b** (89 mg, 233 μmol, 58%) as a colourless crystalline solid; mp. 94 – 96 °C; R_f = 0.10 (cyclohexane/diethyl ether; 9:1); υ_{max}/cm^{-1} (thin film) 3320, 2952, 1732, 1509, 1240, 1138, 1029, 810, 722; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 8.8 Hz, H-6), 6.87 (2H, d, *J* = 8.8 Hz, H-7), 5.25 (1H, t, *J* = 6.2 Hz, NH), 4.79 – 4.58 (2H, m, H-11), 4.03 – 3.95 (1H, m, H-1_a), 3.95 – 3.86 (1H, m, H-1_b), 3.80 (3H, s, H-13), 3.57 (1H, dd, *J* = 13.8, 6.8 Hz, H-9_a), 3.43 (1H, dd, *J* = 13.8, 6.8 Hz, H-9_b), 2.17 – 2.08 (2H, m, H-3), 2.02 – 1.90 (1H, m, H-2_a), 1.90 – 1.79 (1H, m, H-2_b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8 (ArC, C-8), 155.0 (C, C-10), 136.2 (ArC, C-5), 126.6 (ArCH, C-6), 113.8 (ArCH, C-7), 95.8 (C, C-12), 86.0 (C, C-4), 74.6 (CH_2, C-11), 68.2 (CH_2, C-1), 55.4 (CH_3, C-13), 50.1 (CH_2, C-9), 35.6 (CH_2, C-3), 26.0 (CH_2, C-2); [HRMS (ESI+) Exact mass calcd for $C_{15}H_{19}{}^{35}Cl_3NO_4$, 382.0374. Found $[MH]^+$, 382.0375 (0.20 ppm error)].

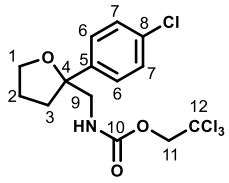
Crystals suitable for X-ray analysis were prepared by slow diffusion of *n*-heptane into a solution of **163b** in $CHCl_2$.



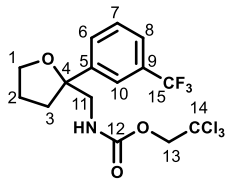


2,2,2-Trichloroethyl {2-[(1,1'-biphenyl)-4-yl]tetrahydrofuran-2-yl}methylcarbamate (163c): Prepared according to general procedure N using 4-[(1,1'-biphenyl)-4-yl]pent-4-en-1-ol (**161c**) (95.0 mg, 400 µmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 µmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 µmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 9:1) gave the title compound **163c** (111 mg, 259 µmol, 65%) as a colourless oil; R_f = 0.11 (cyclohexane/diethyl ether; 9:1); υ_{max}/cm^{-1} (thin film) 3321, 2950, 1737, 1548, 1486, 1235, 1139, 1032, 765, 727; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.52 (4H, m, H-7 and H-10), 7.52 – 7.39 (4H, m, H-6 and H-11), 7.39 – 7.31 (1H, m, H-12), 5.28 (1H, t, *J* = 6.2 Hz, NH), 4.80 – 4.59 (2H, m, H-15), 4.08 – 4.01 (1H, m, H-1_a), 4.00 – 3.93 (1H, m, H-1_b), 3.64 (1H, dd, *J* = 13.8, 6.7 Hz, H-13_a), 3.52 (1H, dd, *J* = 13.8, 6.7 Hz, H-13_b), 2.28 – 2.13 (2H, m, H-3), 2.07 – 1.95 (1H, m, H-2_a), 1.95 – 1.81 (1H, m, H-2_b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1 (C, C-14), 143.3 (ArC, C-5), 140.8 (ArC, C-9), 140.2 (ArC, C-8), 128.9 (ArCH, C-11), 127.4 (ArCH, C-12), 127.2 (ArCH, C-10), 127.2 (ArCH, C-7), 125.9 (ArCH, C-6), 95.8 (C, C-16), 86.2 (C, C-4), 74.6 (CH2, C-15), 68.4 (CH2, C-

1), 50.0 (CH2, C-13), 35.7 (CH2, C-3), 26.1 (CH2, C-2); [HRMS (ESI+) Exact mass calcd for $C_{20}H_{24}{}^{35}Cl_3N_2O_3$, 445.0847. Found $[MH_4N]^+$, 445.0846 (0.30 ppm error)].

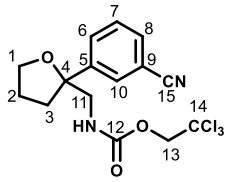


2,2,2-Trichloroethyl {[2-(4-chlorophenyl)tetrahydrofuran-2-yl]methyl}carbamate (163d): Prepared according to general procedure N using 4-(4-chlorophenyl)pent-4-en-1-ol (**161d**) (79.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 8:2) gave the title compound **163d** (88.0 mg, 227 μmol, 57%) as a colourless crystalline solid; mp. 90 – 92 °C; R_f = 0.37 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3328, 2952, 1739, 1537, 1518, 1490, 1237, 1140, 1091, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (4H, m, H-6 and H-7), 5.22 (1H, t, *J* = 5.0 Hz, NH), 4.76 – 4.60 (2H, m, H-11), 4.04 – 3.95 (1H, m, H-1$_a$), 3.95 – 3.87 (1H, m, H-1$_b$), 3.56 (1H, dd, *J* = 13.8, 6.5 Hz, H-9$_a$), 3.47 (1H, dd, *J* = 13.8, 6.5 Hz, H-9$_b$), 2.22 – 2.05 (2H, m, H-3), 2.05 – 1.91 (1H, m, H-2$_a$), 1.90 – 1.76 (1H, m, H-2$_b$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0 (C, C-10), 142.9 (ArC, C-5), 133.2 (ArC, C-8), 128.6 (ArCH, C-6), 127.0 (ArCH, C-7), 95.8 (C, C-12), 86.0 (C, C-4), 74.6 (CH_2, C-11), 68.4 (CH_2, C-1), 49.9 (CH_2, C-9), 35.7 (CH_2, C-3), 26.0 (CH_2, C-2); [HRMS (ESI+) Exact mass calcd for $C_{14}H_{15}{}^{35}Cl_4NNaO_3$, 407.9698. Found $[MNa]^+$, 407.9692 (1.60 ppm error)].



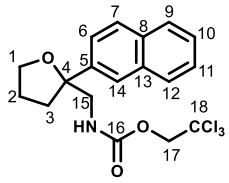
2,2,2-Trichloroethyl {[2-(3-(trifluoromethyl)phenyl]tetrahydrofuran-2-yl}methylcarbamate (163e): Prepared according to general procedure N using 4-[3-(trifluoromethyl)phenyl]pent-4-en-1-ol (**161e**) (92.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, pentane:diethyl ether – 8:2) gave the title

compound **163e** (118 mg, 281 μmol, 70%) as a colourless oil; R_f = 0.38 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3321, 2954, 1735, 1518, 1332, 1236, 1162, 1123, 1073, 726, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, d, *J* = 2.3 Hz, H-10), 7.56 (1H, dt, *J* = 7.6, 2.3 Hz, H-6), 7.52 (1H, d, *J* = 7.6 Hz, H-8), 7.46 (1H, t, *J* = 7.7 Hz, H-7), 5.28 (1H, t, *J* = 6.3 Hz, NH), 4.81 – 4.56 (2H, m, H-13), 4.07 – 3.99 (1H, m, H-1_a), 3.99 – 3.90 (1H, m, H-1_b), 3.60 (1H, dd, *J* = 13.9, 5.8 Hz, H-11_a), 3.50 (1H, dd, *J* = 13.9, 5.8 Hz, H-11_b), 2.28 – 2.17 (1H, m, H-3_a), 2.17 – 2.08 (1H, m, H-3_b), 2.07 – 1.94 (1H, m, H-2_a), 1.94 – 1.77 (1H, m, H-2_b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0 (C, C-12), 145.6 (ArC, C-5), 130.86 (q, *J* = 32.1 Hz, ArC, C-9), 129.0 (ArCH, C-6), 128.9 (ArCH, C-7), 124.28 (q, *J* = 272.4 Hz, C, C-15), 124.24 (q, *J* = 3.9 Hz, ArCH, C-10), 122.35 (q, *J* = 3.9 Hz, ArCH, C-8), 95.7 (C, C-14), 86.1 (C, C-4), 74.6 (CH_2, C-13), 68.6 (CH_2, C-1), 49.9 (CH_2, C-11), 35.8 (CH_2, C-3), 26.1 (CH_2, C-1); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.50 ppm; [HRMS (ESI+) Exact mass calcd for $C_{15}H_{15}{}^{35}Cl_3{}^{19}F_3NNaO_3$, 441.9962. Found $[MNa]^+$, 441.9962 (0.00 ppm error)].

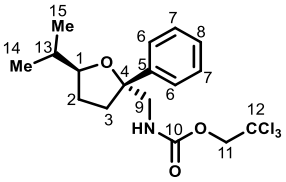


2,2,2-Trichloroethyl {[2-(3-cyanophenyl)tetrahydrofuran-2-yl]methyl}carbamate (163f): Prepared according to general procedure N using 3-(5-hydroxypent-1-en-2-yl)benzonitrile (**161f**) (75.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 6:4) gave the title compound **163f** (114 mg, 302 μmol, 76%) as a colourless oil; R_f = 0.32 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3323, 2952, 2230, 1731, 1531, 1234, 1152, 1111, 1030, 802, 724, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, d, *J* = 1.6 Hz, H-10), 7.56 (1H, app. dt, *J* = 7.6, 1.6 Hz, H-6), 7.52 (1H, app. dt, *J* = 7.6, 1.6 Hz, H-8), 7.46 (app. t, *J* = 7.6 Hz, H-7), 5.28 (1H, t, *J* = 6.3 Hz, NH), 4.73 – 4.60 (2H, m, H-13), 4.04 (1H, ddd, *J* = 8.3, 5.9, 1.3 Hz, H-1_a), 3.95 (1H, ddd, *J* = 8.3, 5.9, 1.3 Hz, H-1_b), 3.60 (1H, dd, *J* = 13.9, 5.8 Hz, H-11_a), 3.50 (1H, dd, *J* = 13.9, 5.8 Hz, H-11_b), 2.26 – 2.15 (1H, m, H-3_a), 2.14 – 2.04 (1H, m, H-3_b), 2.07 – 1.94 (1H, m, H-2_a), 1.94 – 1.77 (1H, m, H-2_b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8 (C, C-12), 146.0 (ArC, C-5), 130.9

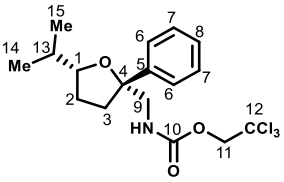
(ArCH, H-8), 129.9 (ArCH, C-6), 129.3 (ArCH, C-8), 129.2 (ArCH, C-7), 118.8 (C, C-15), 112.5 (ArC, C-9), 95.5 (C, C-14), 85.8 (C, C-4), 74.5 (CH_2, C-13), 68.5 (CH_2, C-1), 49.7 (CH_2, C-11), 35.7 (CH_2, C-3), 26.0 (CH_2, C-2); [HRMS (ESI+) Exact mass calcd for $C_{15}H_{19}{}^{35}Cl_3N_3O_3$, 394.0487. Found $[MH_4N]^+$, 394.0488 (0.30 ppm error)].



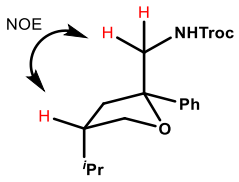
2,2,2-Trichloroethyl {[2-(naphthalen-2-yl)tetrahydrofuran-2-yl]methyl}carbamate (163g): Prepared according to general procedure N using 4-(naphthalen-2-yl)pent-4-en-1-ol (**161g**) (85.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 8:2) gave the title compound **163g** (111 mg, 276 μmol, 69%) as a colourless oil; R_f = 0.28 (cyclohexane/diethyl ether; 8:2); υ_{max}/cm^{-1} (thin film) 3312, 2951, 1730, 1509, 1232, 1138, 1101, 1063, 906, 815, 724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.90 (1H, m, H-14), 7.97 – 7.78 (3H, m, H-7, H-9 and H-12), 7.54 – 7.44 (3H, m, H-6, H-10 and H-11), 5.42 (1H, t, J = 6.0 Hz, NH), 4.84 – 4.56 (2H, m, H-17), 4.12 – 3.98 (2H, m, H-1), 3.72 (1H, dd, J = 13.9, 6.7 Hz, H-15_A), 3.59 (1H, dd, J = 13.8, 5.5 Hz, H-15_B), 2.33 – 2.21 (2H, m, H-3), 2.08 – 1.95 (1H, m, H-2_A), 1.95 – 1.82 (1H, m, H-2_B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0 (C, C-16), 141.5 (ArC, C-5), 133.2 (ArC, C-13), 132.6 (ArC, C-8), 128.3 (ArCH, C-9), 128.2 (ArCH, C-12), 127.7 (ArCH, C-7), 126.3 (ArCH, C-11), 126.0 (ArCH, C-10), 124.2 (ArCH, C-14), 123.7 (ArCH, C-6), 95.7 (C, C-18), 86.5 (C, C-4), 74.5 (CH_2, C-17), 68.4 (CH_2, C-1), 49.9 (CH_2, C-15), 35.6 (CH_2, C-3), 26.0 (CH_2, C-2); [HRMS (ESI+) Exact mass calcd for $C_{18}H_{18}{}^{35}Cl_3NNaO_3$, 424.0244. Found $[MNa]^+$, 424.0242 (0.60 ppm error)].



163ka



163kb



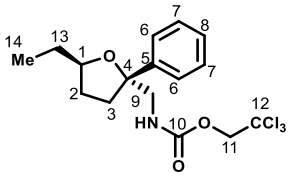
Minor Diastereoisomer **163kb**

2,2,2-Trichloroethyl [(5-isopropyl-2-phenyltetrahydrofuran-2-yl)methyl]carbamate (163ka): Prepared according to general procedure N using 2-methyl-6-phenylhept-6-en-3-ol (**161k**) (82.0 mg, 400 µmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 µmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 µmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 15:1) gave the major diastereoisomer of the title compound **163ka** (48 mg, 122 µmol, 30%) as a colourless oil and the minor diastereoisomer of the title compound **163kb** (38 mg, 9.63 µmol, 24%) as a colourless oil in a 1.20:1 d.r

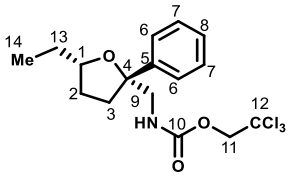
Major diastereoisomer 163ka: R_f = 0.59 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3348, 2958, 1733, 1510, 1213, 1145, 1061, 1030, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.31 (4H, m, H-6 and H-7), 7.26 – 7.22 (1H, m, H-8), 5.24 (1H, t, *J* = 6.1 Hz, NH), 4.75 (1H, dd, *J* = 12.1 Hz, H-11$_A$), 4.63 (1H, dd, *J* = 12.1 Hz, H-11$_B$), 3.71 – 3.61 (1H, m, H-1), 3.56 (1H, dd, *J* = 13.7, 5.2 Hz, H-9$_A$), 3.41 (1H, dd, *J* = 13.7, 5.2 Hz, H-9$_B$), 2.26 – 2.18 (1H, m, H-3$_A$), 2.18 – 2.10 (1H, m, H-3$_B$), 1.90 – 1.83 (1H, m, H-2$_A$), 1.83 – 1.76 (1H, m, H-13), 1.70 – 1.61 (1H, m, H-2$_B$), 1.06 (3H, d, *J* = 6.6 Hz, H-15), 0.93 (3H, d, *J* = 6.8 Hz, H-14); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0 (C, C-10), 145.0 (ArC, C-5), 128.5 (ArCH, C-7), 127.2 (ArCH, C-8), 125.3 (ArCH, C-6), 95.9 (C, C-12), 85.8 (C, C-4), 84.8 (CH, C-1), 74.5 (CH_2, C-11), 50.9 (CH_2, C-9), 35.7 (CH_2, C-3), 33.1 (CH, C-13), 29.5 (CH_2, C-2), 19.5 (CH_3, C-14), 18.6 (CH_3, C-15); [HRMS (ESI+) Exact mass calcd for $C_{17}H_{23}{}^{35}Cl_3NO_3$, 394.0738. Found $[MH]^+$, 394.0739 (0.30 ppm error)].

Minor diastereoisomer 163kb: R_f = 0.57 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3449, 2957, 1733, 1511, 1213, 1145, 1061, 1030, 762, 724, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.40 (2H, m, H-6), 7.34 – 7.30 (2H, m, H-7), 7.26 – 7.20 (1H, m, H-8), 5.16 (1H, t, *J* = 5.8 Hz, NH), 4.77 – 4.56 (2H, m, H-11), 3.78 – 3.71 (1H, m, H-1), 3.56 (1H, dd, *J* = 13.7, 6.3 Hz, 1H), 3.47 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.22 – 2.10 (2H, m, H-3), 2.05 – 1.94 (1H, m, H-2$_A$), 1.80 – 1.68 (1H, m, H-13), 1.55 –

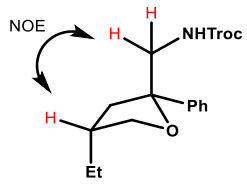
1.46 (1H, m, H-2_B), 1.09 (3H, d, *J* = 6.6 Hz, H-15), 0.86 (3H, d, *J* = 6.6 Hz, H-14); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0 (C, C-10), 145.0 (ArC, C-5), 128.3 (ArCH, C-7), 127.1 (ArCH, C-8), 125.6 (ArCH, C-6), 95.8 (C, C-12), 86.3 (CH, C-1), 86.0 (C, C-4), 74.5 (CH_2, C-11), 50.0 (CH_2, C-9), 36.3 (CH_2, C-3), 34.0 (CH, C-13), 29.5 (CH_2, C-2), 20.1 (CH_3, C-14), 18.8 (CH_3, C-15); [HRMS (ESI+) Exact mass calcd for $C_{17}H_{23}{}^{35}Cl_3NO_3$, 394.0738. Found $[MH]^+$, 394.0740 (0.50 ppm error)].



163la



163lb

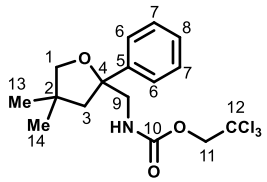


Minor Diastereoisomer **163lb**

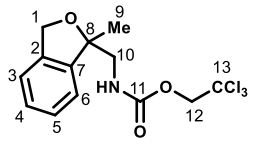
2,2,2-Trichloroethyl [(5-ethyl-2-phenyltetrahydrofuran-2-yl)methyl]carbamate (163l): Prepared according to general procedure N using 6-phenylhept-6-en-3-ol (**161l**) (76.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 15:1) gave the major diastereoisomer of the title compound **163la** (47.0 mg, 123 μmol, 31%) as a colourless oil and the minor diastereoisomer of the title compound **163lb** (41.0 mg, 108 μmol, 27%) as a colourless oil in a 1.16:1 d.r

Major diastereoisomer 163la: R_f = 0.59 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3344, 2962, 1738, 1512, 1229, 1144, 1105, 762, 724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.30 (4H, m, H-6 and H-7), 7.25 – 7.21 (1H, m, H-8), 5.26 (1H, t, *J* = 6.2 Hz, NH), 4.80 – 4.69 (1H, m, H-11_A), 4.69 – 4.54 (1H, m, H-11_B), 3.98 – 3.89 (1H, m, H-1), 3.57 (1H, dd, *J* = 13.7, 7.0 Hz, H-9_A), 3.41 (1H, dd, *J* = 13.7, 7.0 Hz, H-9_B), 2.28 – 2.19 (1H, m, H-3_A), 2.19 – 2.09 (1H, m, H-3_B), 1.97 – 1.86 (1H, m, H-2_A), 1.80 – 1.66 (1H, m, H-13_A), 1.64 – 1.56 (2H, m, H-2_B and H-13_B), 1.00 (3H, t, *J* = 7.5 Hz, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0 (C, C-10), 144.9 (ArC, C-5), 128.5 (ArCH, C-7), 127.2 (ArCH, C-8), 125.3 (ArCH,C-6), 95.9 (C, C-12), 86.1 (C, C-4), 80.8 (C-H, C-1), 74.5 (CH_2, C-11), 50.7 (CH_2, C-9), 35.3 (CH_2, C-3), 31.3 (CH_2, C-2), 28.8 (CH_2, C-13), 10.4 (CH_3, C-14); [HRMS (ESI+) Exact mass calcd for $C_{16}H_{20}{}^{35}Cl_3NNaO_3$, 402.0401. Found $[MNa]^+$, 402.0403 (0.40 ppm error)].

Minor diastereoisomer 163lb: R_f = 0.57 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3345, 2962, 1738, 1512, 1229, 1144, 1105, 724, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (2H, m, H-6), 7.37 – 7.28 (2H, m, H-7), 7.26 – 7.20 (1H, m, H-8), 5.20 (1H, t, *J* = 6.0 Hz, NH), 4.79 – 4.56 (2H, m, H-11), 4.12 – 3.99 (1H, m, H-1), 3.57 (1H, dd, *J* = 13.7, 6.3 Hz, H-9_A), 3.48 (1H, dd, *J* = 13.7, 6.3 Hz, H-9_B), 2.24 – 2.13 (2H, m, H-3), 2.08 – 1.97 (1H, m, H-2_A), 1.80 – 1.68 (1H, m, H-13_A), 1.57 – 1.42 (2H, m, H-2_B and H-13_B), 0.98 (3H, t, *J* = 7.5 Hz, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0 (C, C-10), 145.1 (ArC, C-5), 128.3 (ArCH, C-7), 127.1 (ArCH, C-8), 125.6 (ArCH, C-6), 95.8 (C, C-12), 86.1 (C, C-4), 82.2 (CH, C-1), 74.5 (CH_2, C-11), 50.1 (CH_2, C-9), 36.3 (CH_2, C-3), 31.2 (CH_2, C-2), 29.1 (CH_2, C-13), 10.7 (CH_3, C-14); [HRMS (ESI+) Exact mass calcd for $C_{16}H_{21}{}^{35}Cl_3NO_3$, 380.0582. Found $[MH]^+$, 380.0582 (0.10 ppm error)].

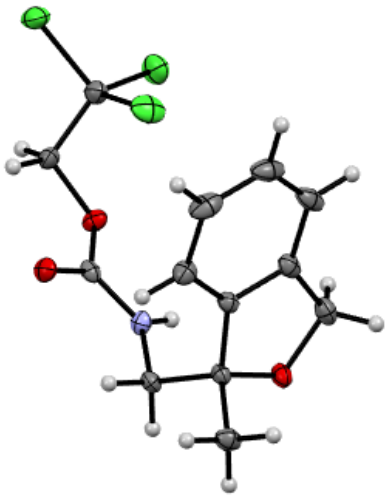


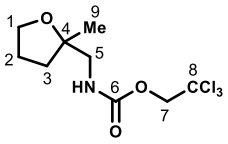
2,2,2-Trichloroethyl [(4,4-dimethyl-2-phenyltetrahydrofuran-2-yl)methyl]carbamate (163m): Prepared according to general procedure N using 2,2-dimethyl-4-phenylpent-4-en-1-ol (**161m**) (76.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 8:2) gave the title compound **163m** (125 mg, 328 μmol, 82%) as a colourless oil; R_f = 0.28 (cyclohexane/diethyl ether; 8:2); υ_{max}/cm^{-1} (thin film) 3319, 2957, 1733, 1514, 1231, 1143, 1030, 723, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.36 (2H, m, H-6), 7.33 (2H, dd, *J* = 8.5, 7.3 Hz, H-7), 7.23 (1H, t, *J* = 7.3 Hz, H-8), 5.29 (1H, t, *J* = 7.2 Hz, NH), 4.77 – 4.49 (2H, m, H-11), 3.67 (1H, d, *J* = 8.4 Hz, H-1_A), 3.60 (1H, d, *J* = 8.4 Hz, H-1_B), 3.58 – 3.53 (1H, m, H-9_A), 3.42 (1H, dd, *J* = 13.8, 5.8 Hz, H-9_B), 2.14 – 2.01 (2H, m, H-3), 1.15 (3H, s, H-13), 0.90 (3H, s, H-14); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9 (C, C-10), 144.9 (ArC, C-5), 128.4 (ArCH, C-7), 127.1 (ArCH, C-8), 125.4 (ArCH, C-6), 95.8 (C, C-12), 86.9 (C, C-4), 79.9 (CH_2, C-1), 74.5 (CH_2, C-11), 50.9 (CH_2, C-9), 50.5 (CH_2, C-3), 40.6 (C, C-2), 27.6 (CH_3, C-13), 27.2 (CH_3, C-14); [HRMS (ESI+) Exact mass calcd for $C_{16}H_{20}{}^{35}Cl_3NNaO_3$, 402.0401. Found $[MNa]^+$, 402.0392 (2.30 ppm error)].



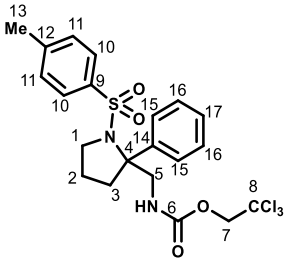
2,2,2-Trichloroethyl [(1-methyl-1,3-dihydroisobenzofuran-1-yl)methyl]carbamate (163n): Prepared according to general procedure N using [2-(prop-1-en-2-yl)phenyl]methanol (**161n**) (59.0 mg, 400 µmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 µmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 µmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 8:2) gave the title compound **163n** (63 mg, 186 µmol, 47%) as a colourless crystalline solid; mp. 91 – 93 °C; R_f = 0.31 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3318, 2924, 1727, 1534, 1237, 1148, 1026, 1018, 760, 721; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (2H, m, H-3 and H-5), 7.22 – 7.14 (2H, m, H-4 and H-6), 5.24 (1H, t, *J* = 6.4 Hz, NH), 5.14 – 5.07 (2H, m, H-1), 4.71 – 4.58 (2H, m, H-12), 3.64 – 3.49 (2H, m, H-10), 1.48 (3H, s, H-9); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9 (C, C-11), 142.5 (ArC, C-7), 139.3 (ArC, C-2), 128.2 (ArCH, C-3), 127.8 (ArCH, C-5), 121.4 (ArCH, C-4), 121.2 (ArCH, C-6), 95.7 (C, C-13), 88.0 (C, C-8), 74.5 (CH_2, C-12), 72.0 (CH_2, C-1), 49.6 (CH_2, C-10), 24.5 (CH_3, C-9); [HRMS (ESI+) Exact mass calcd for $C_{13}H_{14}{}^{35}Cl_3NNaO_3$, 359.9931. Found $[MNa]^+$, 359.9929 (0.60 ppm error)].

Crystals suitable for X-ray analysis were prepared by slow diffusion of *n*-heptane into a solution of **163n** in $CHCl_2$.



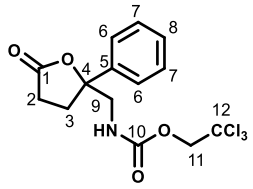


2,2,2-Trichloroethyl [(2-methyltetrahydrofuran-2-yl)methyl]carbamate (163p): Prepared according to general procedure N using 4-methylpent-4-en-1-ol (**161p**) (40.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 6:4) gave the title compound **163p** (19.8 mg, 68.0 μmol, 17%) as a colourless oil; R_f = 0.21 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3308, 2972, 1737, 1538, 1238, 1147, 1043, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (1H, br. s, NH), 4.74 (2H, s, H-7), 3.93 – 3.75 (2H, m, H-1), 3.28 (2H, app. d, *J* = 6.1 Hz, H-5), 2.05 – 1.86 (2H, m, H-2), 1.86 – 1.75 (1H, m, H-3$_A$), 1.75 – 1.63 (1H, m, H-3$_B$), 1.21 (3H, s, H-9). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (C, C-6), 81.9 (C, C-4), 74.5 (CH_2, C-7), 67.8 (CH_2, C-1), 49.1 (CH_2, C-5), 34.6 (CH_2, C-3), 26.3 (CH_2, C-2), 24.1 (CH_3, C-9); [HRMS (ESI+) Exact mass calcd for $C_9H_{14}{}^{35}Cl_3NNaO_3$, 311.9931. Found $[MNa]^+$, 311.9934 (0.70 ppm error)].

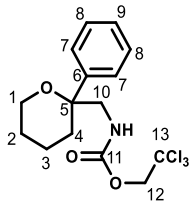


2,2,2-Trichloroethyl [(2-phenyl-1-tosylpyrrolidin-2-yl)methyl]carbamate (181a): Prepared according to general procedure N using 4-methyl-N-(4-phenylpent-4-en-1-yl)benzenesulfonamide (126 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 8:2 → 7:3) gave the title compound **181a** (150 mg, 297 μmol, 74%) as a colourless oil; R_f = 0.23 (cyclohexane/diethyl ether; 7:3); υ_{max}/cm^{-1} (thin film) 3426, 2955, 1737, 1536, 1334, 1224, 1153, 1119, 1090, 700, 591; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 8.3 Hz, H-10), 7.24 – 7.20 (7H, m, H-11, H-15, H-16 and H-17), 5.78 (1H, t, *J* = 6.4 Hz,

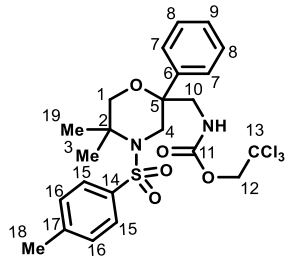
NH), 4.79 – 4.68 (2H, m, H-7), 4.23 (1H, dd, J = 14.3, 5.5 Hz, H-5_A), 4.13 (1H, dd, J = 14.3, 5.5 Hz, H-5_B), 3.71 – 3.50 (2H, m, H-1), 2.41 (3H, s, H-13), 2.34 – 2.24 (1H, m, H-3_A), 2.12 – 2.03 (1H, m, H-3_B), 1.91 – 1.75 (2H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (C, C-6), 143.6 (ArC, C-12), 142.7 (ArC, C-9), 137.2 (ArC, C-14), 129.7 (ArCH, C-11), 128.4 (ArCH, C-16), 127.4 (ArCH, C-17), 127.2 (ArCH, C-10), 126.2 (ArCH, C-15), 95.8 (C, C-8), 74.6 (CH_2, C-7), 73.8 (C, C-4), 50.6 (CH_2, C-1), 47.5 (CH_2, C-5), 41.5 (CH_2, C-3), 22.2 (CH_2, C-2), 21.7 (CH_3, C-13); [HRMS (ESI+) Exact mass calcd for $C_{21}H_{23}{}^{35}Cl_3N_2NaO_4S$, 527.0336. Found $[MNa]^+$, 527.0328 (1.50 ppm error)].



2,2,2-Trichloroethyl [(5-oxo-2-phenyltetrahydrofuran-2-yl)methyl]carbamate (181b): Prepared according to general procedure N using 4-phenylpent-4-enoic acid (70.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), $[Ir(ppy)_3]$ (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 6:4) gave the title compound **181b** (99 mg, 270 μmol, 67%) as a colourless oil; R_f = 0.17 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3324, 2923, 1776, 1724, 1531, 1233, 1154, 1095, 725, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (5H, m, H-6, H-7 and H-8), 5.40 (1H, t, J = 7.2 Hz, NH), 4.84 – 4.51 (2H, m, H-11), 3.77 (1H, dd, J = 14.6, 7.0 Hz, H-9_A), 3.65 (1H, dd, J = 14.6, 7.0 Hz, H-9_B), 2.73 – 2.35 (4H, m, H-2 and H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1 (C, C-1), 155.2 (C, C-10), 140.5 (ArC, C-5), 129.0 (ArCH, C-7), 128.5 (ArCH, C-8), 124.9 (ArCH, C-6), 95.5 (C, C-12), 88.5 (C, C-4), 74.7 (CH2, C-11), 45.0 (CH2, C-9), 31.6 (CH2, C-3), 28.6 (CH2, C-2); [HRMS (ESI+) Exact mass calcd for $C_{14}H_{15}{}^{35}Cl_3NO_4$, 366.0061. Found $[MH]^+$, 366.0063 (0.60 ppm error)].



2,2,2-Trichloroethyl [(2-phenyltetrahydro-2H-pyran-2-yl)methyl]carbamate (181c): Prepared according to general procedure N using 5-phenylhex-5-en-1-ol ((71.0 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl ether – 8:2) gave the title compound **181c** (90.0 mg, 245 μmol, 61%) as a colourless oil; R_f = 0.31 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3327, 2941, 1731, 1513, 1226, 1207, 1137, 1077, 723, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (4H, m, H-7 and H-8), 7.32 – 7.27 (1H, m, H-9), 5.30 (1H, t, *J* = 6.3 Hz, NH), 4.76 – 4.62 (2H, m, H-12), 3.78 – 3.69 (1H, m, H-1$_A$), 3.58 – 3.49 (1H, m, H-1$_B$), 3.43 (1H, dd, *J* = 13.7, 7.1 Hz. H-10$_A$), 3.26 (1H, dd, *J* =13.7, 7.1 Hz, H-10$_B$), 2.30 – 2.20 (1H, m, H-4$_A$), 1.92 – 1.79 (1H, m, H-4$_B$), 1.73 – 1.57 (2H, m, H-2), 1.53 – 1.37 (2H, m, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9 (C, C-11), 140.9 (ArC, C-6), 128.8 (ArCH, C-8), 127.5 (ArCH, C-9), 126.9 (ArCH, C-7), 95.8 (C, C-13), 78.1 (C, C-5), 74.6 (CH_2, C-11), 62.9 (CH_2, C-1), 52.5 (CH_2, C-10), 30.0 (CH_2, C-4), 25.9 (CH_2, C-2), 19.5 (CH_2, C-3); [HRMS (ESI+) Exact mass calcd for $C_{15}H_{18}{}^{35}Cl_3NNaO_3$, 388.0244. Found $[MNa]^+$, 388.0244 (0.00 ppm error)].



2,2,2-Trichloroethyl [(5,5-dimethyl-2-phenyl-4-tosyltetrahydro-2H-pyran-2-yl)methyl]carbamate (181d): Prepared according to general procedure N using *N*-(1-hydroxy-2-methylpropan-2-yl)-4-methyl-*N*-(2-phenylallyl)benzenesulfonamide (144 mg, 400 μmol), 2,2,2-trichloroethyl {[4-(trifluoromethyl)benzoyl]oxy}carbamate (**118g**) (183 mg, 480 μmol), [Ir(ppy)$_3$] (2.7 mg, 4.00 μmol, 1 mol%) and acetonitrile (2 mL). Purification by flash column chromatography (SiO_2, cyclohexane:diethyl

ether – 6:4) gave the title compound **181d** (163 mg, 296 μmol, 74%) as a colourless oil; R_f = 0.29 (cyclohexane/diethyl ether; 6:4); υ_{max}/cm^{-1} (thin film) 3355, 2952, 2924, 1739, 1236, 1159, 1090, 672; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (2H, d, *J* = 8.0 Hz, H-15), 7.44 – 7.31 (5H, m, H-7, H-8 and H-9), 7.23 (2H, d, *J* = 8.0 Hz, H-16), 5.14 (1H, t, *J* = 6.4 Hz, NH), 4.73 (1H, d, *J* = 12.1 Hz, H-12$_A$), 4.64 (1H, d, *J* = 12.1 Hz, H-12$_B$), 4.10 (1H, d, *J* = 13.6 Hz, H-4$_A$), 3.63 (1H, dd, *J* = 14.2, 7.0 Hz, H-10$_A$), 3.54 (1H, d, *J* = 13.6 Hz, H-4$_B$), 3.45 – 3.39 (1H, m, H-10$_B$), 3.38 (1H, d, *J* = 11.5 Hz, H-1$_A$), 3.27 (1H, d, *J* = 11.5 Hz, H-1$_B$), 2.41 (3H, s, H-18), 1.28 (3H, s, H-19), 1.15 (3H, s, H-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8 (C, C-11), 143.5 (ArC, C-6), 138.9 (ArC, C-17), 138.5 (ArC, C-14), 129.8 (ArCH, C-16), 129.0 (ArCH, C-8), 128.2 (ArCH, C-9), 127.6 (ArCH, C-15), 126.6 (ArCH, C-7), 95.7 (C, C-13), 78.4 (C, C-5), 74.6 (CH_2, C-12), 72.5 (CH_2, C-1), 57.1 (C, C-2), 49.0 (CH_2, C-10), 45.8 (CH_2, C-4), 23.6 (CH_3, C-19), 21.6 (CH_3, C-18), 21.3 (CH_3, C-3); [HRMS (ESI+) Exact mass calcd for $C_{23}H_{31}{}^{35}Cl_3N_3O_5S$, 566.1045. Found $[MH_4N]^+$, 566.1044 (0.00 ppm error)].

Crystallographic Data

Single Crystal X-ray Diffraction Method

Single crystals were selected and mounted using Fomblin® (YR-1800 perfluoropolyether oil) on a polymer-tipped MiTeGen MicroMountTM and cooled rapidly to 120 K in a stream of cold N_2 using an Oxford Cryosystems open flow cryostat. Single crystal X-ray diffraction data were collected on an Oxford Diffraction GV1000 (TitanS2 CCD area detector, mirror-monochromated Cu-Kα radiation source; λ = 1.54184 Å, ω scans). Cell parameters were refined from the observed positions of all strong reflections and absorption corrections were applied using a Gaussian numerical method with beam profile correction (CrysAlisPro). Structures were solved within Olex2[3] by dual space iterative methods (SHELXT)[4] and all non-hydrogen atoms refined by full-matrix least-squares on all unique F2 values with anisotropic displacement parameters (SHELXL). Structures were checked with checkCIF. CCDC-2237285 contains the supplementary data for compound **108h**. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

_refine_special_details for Compound 108h

Conformational disorder is observed in phenyl ring moiety C23B/C-C28B/C with the occupancies of two disorder components refined and constrained to sum to unity resulting in values of 0.82(1) and 0.18(1) respectively. The geometries of the two disorder components were restrained to be similar and planar (SADI, FLAT) and their pivot atoms C23B/C coplanar with the adjacent phenyl ring (FLAT). Rigid bond and similarity restraints were applied to the anisotropic displacement parameters of all the disordered atoms (RIGU, SIMU). Additionally, the anisotropic displacement parameters of each adjacent pair of disordered carbon atoms were constrained to be identical (EADP). All hydrogen atoms in the structure were observed in the electron density map. Amide hydrogen atoms H9A and H9B were refined with their N-H distances restrained to target values of 0.88 Å (DFIX, esd 0.02 Å). All other hydrogen atoms were geometrically placed and refined with a riding model.

Crystal Structure of Compound **108h**

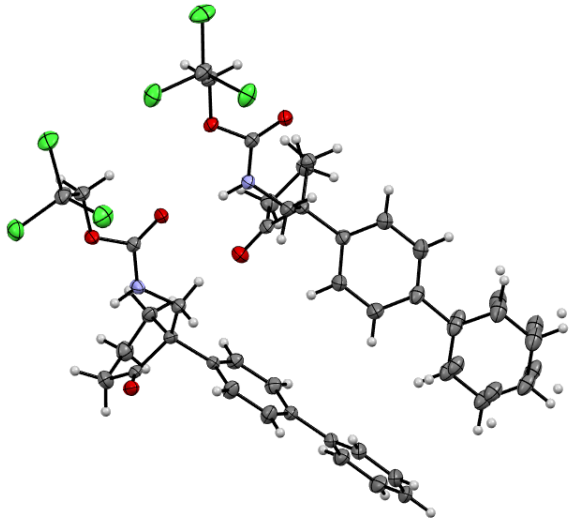


Table 1 Crystal data and structure refinement for MDJCCB (CCDC No. 2237285)

Identification code	MDJCCB
Empirical formula	$C_{21}H_{20}Cl_3NO_3$
Formula weight	440.73
Temperature/K	120(2)
Crystal system	triclinic
Space group	P-1
a/Å	11.0267(4)
b/Å	11.9294(5)
c/Å	18.1545(6)
α/°	77.691(3)
β/°	76.621(3)
γ/°	62.808(4)
Volume/Å^3	2050.51(15)
Z	4
ρ_{calc}g/cm^3	1.428
μ/mm^{-1}	4.234
F(000)	912.0
Crystal size/mm^3	0.116 × 0.053 × 0.034
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.398 to 145.638
Index ranges	$-13 \le h \le 13$, $-14 \le k \le 14$, $-20 \le l \le 22$
Reflections collected	31072
Independent reflections	7873 [R_{int} = 0.0385, R_{sigma} = 0.0343]
Data/restraints/parameters	7873/297/524
Goodness-of-fit on F^2	1.058
Final R indexes [I>=2σ (I)]	R_1 = 0.0375, wR_2 = 0.0930
Final R indexes [all data]	R_1 = 0.0456, wR_2 = 0.0970
Largest diff. peak/hole / e Å^{-3}	0.31/-0.42

Crystal Structure of Compound **161b**

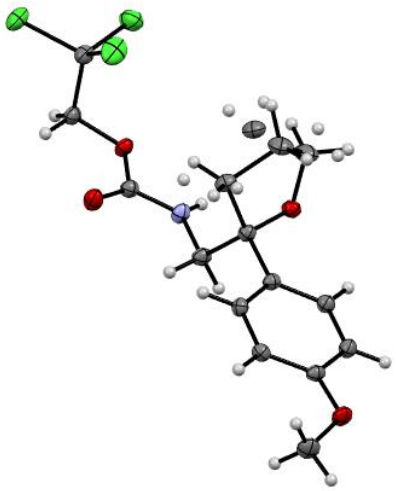


Table 1 Crystal data and structure refinement for MDJCCA.

Identification code	MDJCCA
Empirical formula	$C_{15}H_{18}Cl_3NO_4$
Formula weight	382.65
Temperature/K	120(2)
Crystal system	triclinic
Space group	P-1
a/Å	9.3347(4)
b/Å	9.6247(4)
c/Å	11.6183(3)
α/°	84.699(3)
β/°	66.926(4)
γ/°	64.497(4)
Volume/Å^3	863.08(7)
Z	2
ρ_{calc}g/cm^3	1.472
μ/mm^{-1}	4.975
F(000)	396.0
Crystal size/mm^3	0.181 × 0.106 × 0.052
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.308 to 151.308
Index ranges	-11 ≤ h ≤ 11, -11 ≤ k ≤ 11, -14 ≤ l ≤ 14
Reflections collected	17690
Independent reflections	3511 [R_{int} = 0.0343, R_{sigma} = 0.0227]
Data/restraints/parameters	3511/22/222
Goodness-of-fit on F^2	1.070
Final R indexes [I>=2σ (I)]	R_1 = 0.0321, wR_2 = 0.0852
Final R indexes [all data]	R_1 = 0.0371, wR_2 = 0.0878
Largest diff. peak/hole / e Å^{-3}	0.36/-0.42

Crystal Structure of Compound **161n**

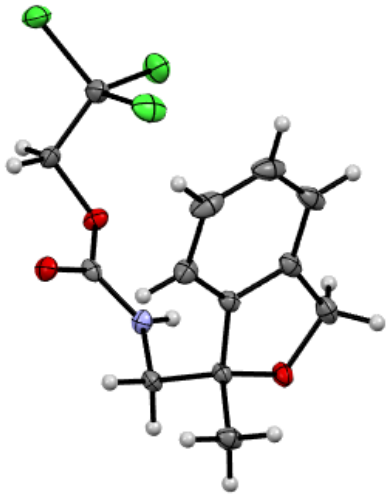


Table 1 Crystal data and structure refinement for MDJCCC.

Identification code	MDJCCC
Empirical formula	$C_{13}H_{14}NO_3Cl_3$
Formula weight	338.60
Temperature/K	120(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.21290(10)
b/Å	9.67390(10)
c/Å	18.6245(2)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1479.73(3)
Z	4
ρ_{calc}g/cm^3	1.520
μ/mm^{-1}	5.672
F(000)	696.0
Crystal size/mm^3	0.132 × 0.058 × 0.044
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	9.498 to 158.662
Index ranges	$-10 \leq h \leq 10$, $-12 \leq k \leq 12$, $-23 \leq l \leq 23$
Reflections collected	34467
Independent reflections	3199 [R_{int} = 0.0787, R_{sigma} = 0.0308]
Data/restraints/parameters	3199/1/185
Goodness-of-fit on F^2	1.051
Final R indexes [I>=2σ (I)]	R_1 = 0.0289, wR_2 = 0.0726
Final R indexes [all data]	R_1 = 0.0294, wR_2 = 0.0729
Largest diff. peak/hole / e Å^{-3}	0.20/-0.33
Flack parameter	0.038(7)

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