Radical Hydrofunctionalisation of Alkenes

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Thesis submitted in partial fulfilment of the requirements for

the Degree of Doctor of Philosophy

University of Nottingham

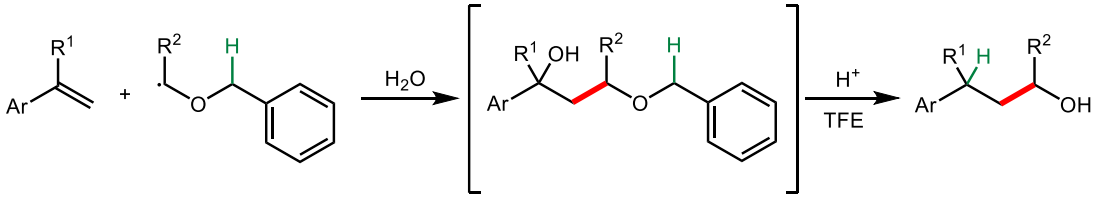
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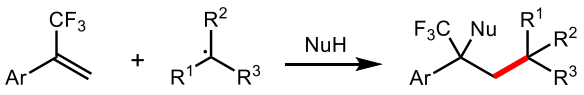
Abstract

A main objective in organic chemistry is the concise formation of C–C bonds, and the reaction between a carbon-centred radical and an alkene moiety has emerged as a reliable method to this end. In this Thesis, we describe the reaction of carbon-centred radicals with alkenes to form a new C–C bond, and different methods were explored to convert the resulting radical intermediate into potentially valuable products or building blocks for further operations.

In Chapter 2, the stepwise formal addition of simple alcohols to styrenes *via* an oxyalkylation intermediate is reported. The required alkyl radicals originate from *N*-hydroxyphthalimide esters and are generated using photoredox catalysis. The oxyalkylation intermediate fragments under mild Brønsted acidic conditions via a 1,5-hydride transfer process to give the target product. Mechanistic investigations were conducted to gain better understanding of the key 1,5-hydride transfer step.

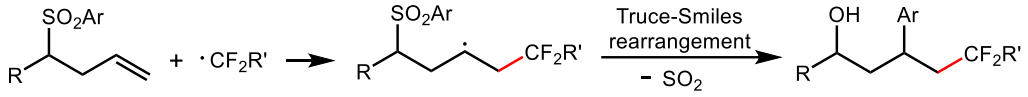


Fluorinated compounds have sparked great interest in organic chemistry due to their unique biological properties. In Chapter 3, we report several possibilities to synthesise such products through the carbofunctionalisation of alkenes via a radical polar crossover reaction. The reaction of α-trifluoromethyl styrenes with alkyl radicals in the presence of *O*- or *N*-based nucleophiles yields quaternary trifluoromethyl-functionalised products (Chapter 3.5).



Finally, we describe a carboarylation of unactivated alkenes via a radical Truce-Smiles rearrangement on β-arylsulfate alkenes in Chapter 4. Herein, the reaction commenced with the generation of a fluorinated carbon-centred radical, followed by its interaction

with an unactivated alkene. The migration ability of various aryl groups was analysed (Chapter 4.3).



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Finally, I would like to thank my wife for being at my side, especially throughout the last year. You give me hope. 我爱你

Declaration

The research presented in this Thesis was carried out at the University of Nottingham between October 2018 and March 2023. The work is, to the best of my knowledge, original except where due reference has been made to other workers.

Leonard Himmel

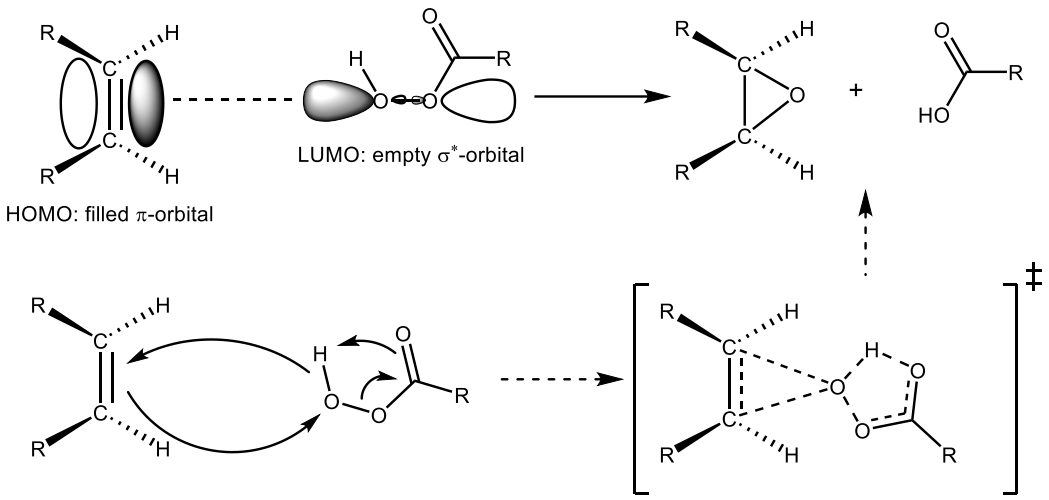
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Chapter 1. Introduction

1.1 The Reactivity of Alkenes

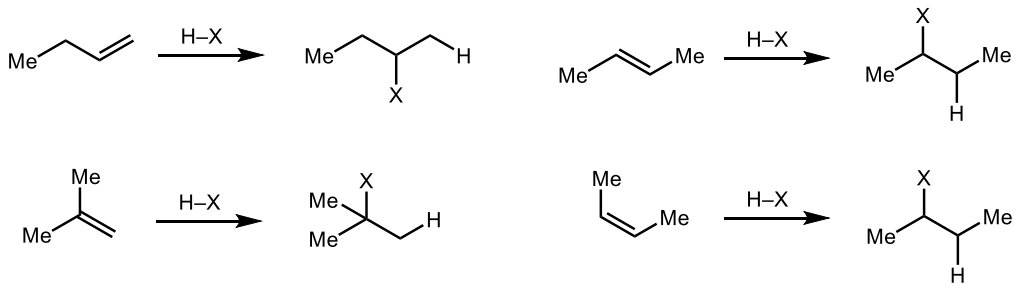
One of the most abundant functional groups in natural compounds and pharmaceutical products is the C=C bond. Therefore, the formation and functionalisation of C=C bonds has been a major focus in organic chemistry. Unlike other common groups as for instance C=O bonds or C–X bonds (X = halogen), alkene moieties are not inherently polarised. Instead, the reactivity of C=C bonds is very dependent on the substituents attached to the functional group due to their inductive and mesomeric effects on the electron density of the C=C bond as a whole as well as the two carbon atoms individually.[1]

Simple alkenes with alkyl groups or other non-conjugated, electron-donating groups as substituents often act as nucleophiles and react with electrophiles such as bromine in electrophilic additions.[2] In this simplified process, the π-orbital of the alkene interacts with the LUMO of the nucleophile (in the case of bromine the σ^*-orbital of the Br–Br bond). This step occurs faster if more electron-donating groups are present because every group raises the HOMO of the alkene by σ-donation and therefore increases its nucleophilicity.[3] As a result, the C=C bond is broken and new C–Br bonds are formed giving a bromonium ion as intermediate,[4] which is a good electrophile and reacts rapidly with other present nucleophiles (in this case bromide). The ring opening step can be seen as an S_n2-type mechanism resulting in trans-products.[5] Another related reaction, the epoxidation of alkenes with peracids for instance (Prilezhaev reaction),[6] stops after the initial addition. Herein, the cyclic epoxide is less electrophilic than the bromonium ion and the carboxylic acid by-product is less nucleophilic than bromide leading to no further reaction under standard conditions (Scheme 1.1).[7]



Scheme 1.1. Orbital interaction and simplified mechanism in a typical electrophilic addition.

Addition reactions with two different groups E–Nu (with E = H, BR_2, SiR_3, etc.; Nu = X, pseudohalogens, CHO, OR, CO_2R, NR_2, etc.) on asymmetrical alkenes result in the formation of regioisomers. Markovnikov's rule attempts to explain reaction patterns of electrophilic additions with alkenes and other unsaturated hydrocarbons and, although it originally only considers the number and not the nature of the substituents, still offers a reliable guideline to predict which isomer is predominantly formed. More precisely, Markovnikov suggested that in the reaction of an unsymmetrical hydrocarbon with halogen acids HX, the halide adds to the more substituted carbon atom (Scheme 1.2).



Scheme 1.2. Butene isomers and their reaction with H–X following Markovnikov's rule.

It has since been shown that the relative stabilities of the intermediates, or in other words, the activation energies to reach the possible transition states are more important than the number of hydrogen atoms attached to the C=C carbon atoms.[8] Nevertheless, Markovnikov's initial postulation, despite being not strictly correct in many cases, continues to be respected throughout the scientific community and his rule was merely modified rather than replaced.[9] Nowadays in a wider context, products that arise from additions of RH in which hydrogen adds to the less (hyper-)conjugated position are called Markovnikov products and the process is classified as a Markovnikov addition, whereas *anti*-Markovnikov products contain the added hydrogen at the more stabilised position.

Addition reactions proceeding via ionic mechanisms traditionally give Markovnikov products, meaning that the formation of *anti*-Markovnikov products requires other methods or pathways with more complex mechanisms. Notable exceptions are for instance hydroborations,[10] hydrostannations,[11] or hydrosilylations,[12] in which hydrogen (or hydride) is the nucleophile. Alongside these limited examples, radical chemistry has become a more widespread method to achieve *anti*-Markovnikov selectivity.[13]

1.1.1 Alkenes in Radical Addition Reactions

The addition of radicals into C=C bonds is one of the main reactions of radicals and is greatly influenced by the electronic nature of both reaction partners. Molecular orbital theory helps to understand radical addition processes and has proven consistent with experimental, kinetic investigations.[14] Generally, alkenes that contain alkyl groups as substituents can be classified as unactivated and tend to react with electron-deficient, electrophilic radicals. An unactivated alkene has a higher energy HOMO resulting from hyperconjugation by the substituents. Orbital overlap between the alkene HOMO and electrophilic radicals with low-energy SUMOs is increased and bond formation therefore favoured. Activated alkenes, on the other hand, possess one or more electron-withdrawing groups (such as carbonyl, nitrile or nitro groups, and to a lesser extent aromatic rings) and pair well with electron-rich, nucleophilic radicals. The electron-withdrawing group lowers the energy of the C=C π^* orbital to the point at which LUMO-SOMO interaction becomes dominant (Figure 1.1).[15,16]

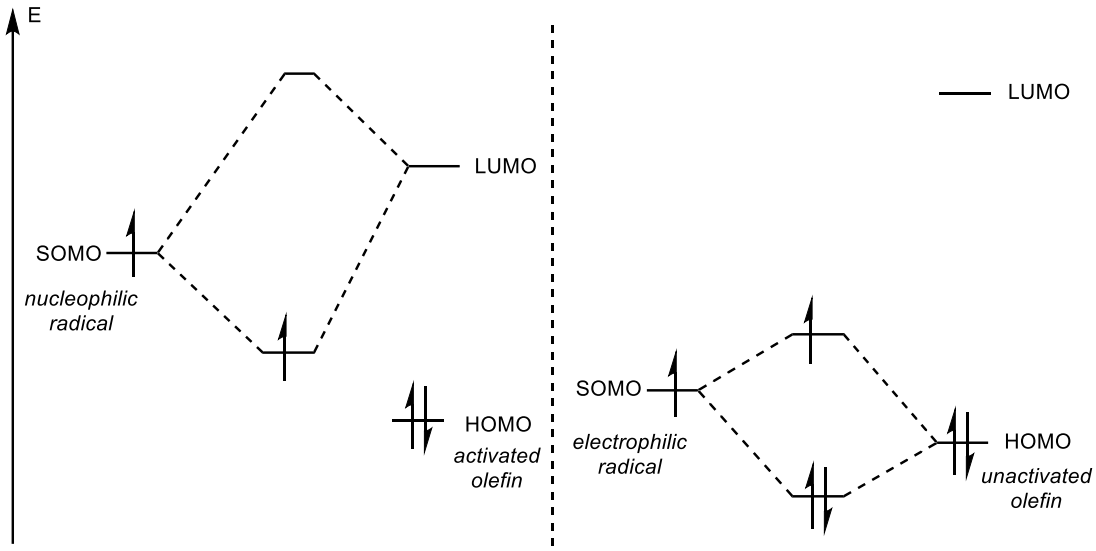
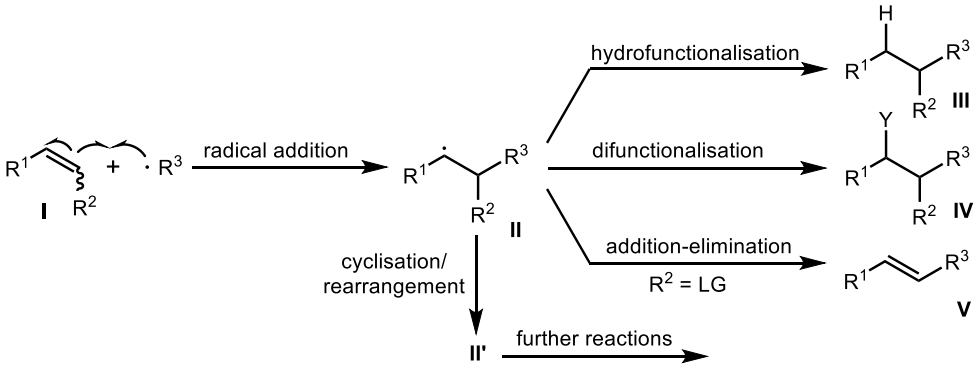


Figure 1.1. Molecular orbital diagrams of radical additions to C=C bonds.

The relative stabilities of the two possible radical intermediates determine the regioselectivity of the radical addition step similar to the stabilities of carbocations that control ionic electrophilic additions. Once the radical has reacted with the C=C bond, a new carbon-centred radical is formed, and various different reaction pathways are conceivable from here onwards. The acceptance of a hydrogen atom leads to hydrofunctionalised *anti*-Markovnikov products **III**, and difunctionalised products **IV** are obtained if the radical intermediate reacts with a second radical or a radical precursor (Scheme 1.3). Lastly, the radical can also reform the C=C double bond to alkenes **V** by elimination of small molecules like hydrogen, water or CO_2. Cyclisations and rearrangements of the carbon-centred radical to radical intermediates **II'** are common and generally take place before intermolecular radical quenching. It should be noted that novel methods like photoredox catalysis or electrochemical procedures open the door to further pathways via single electron transfers and will be discussed later.



Scheme 1.3. Reaction between an alkene and a radical and subsequent conversions of radical intermediate **II**.

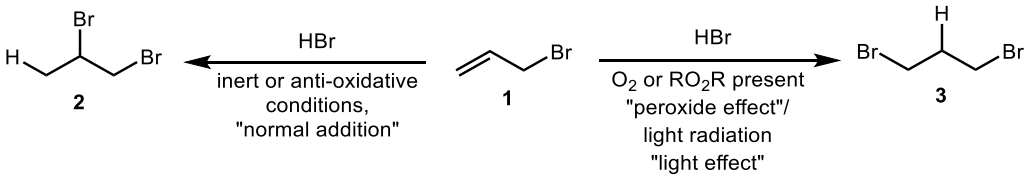
Styrenes are particularly popular alkene feedstocks due to their unique properties in reactions with radicals. The resulting carbon-centred radical is considerably stabilised due to conjugation with the adjacent phenyl group.[17] Although the unsubstituted phenyl group has a weakly electron-withdrawing effect on the C=C bond, its impact can be enhanced with electron-withdrawing groups, and the effect can readily be reversed with electron-donating substituents. The stabilisation effect enables styrenes to react with both nucleophilic and electrophilic radicals,[17] while unconjugated alkenes typically only react well with one class of radicals. The substituents, however, can have a detrimental effect on the final outcome of the reaction. Electron-rich styrenes are known to be prone to polymerisation under radical conditions, whereas electron-withdrawing groups on the aromatic ring often destabilise the benzylic carbocation formed in the latter course of the mechanism leading to lower product yields.[18]

1.2 Classical Radical Addition Reactions

1.2.1 Radical Chemistry with Halogens

The early beginnings of radical chemistry were laid in 1930, when Kharasch was the first to collect and evaluate scattered, reported examples that yielded *anti*-Markovnikov products.[19] In his review of addition reactions between halogen acids and C=C bonds, he suggested that the polarisation of the C=C bond constitutes a determinative factor in addition reactions and makes a clear distinction between ionic

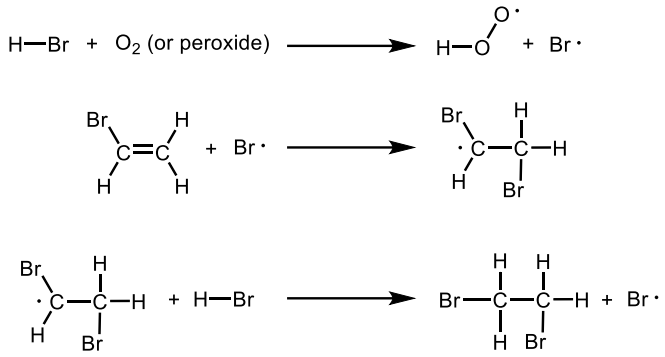
and molecular/atomic (radical) additions. He described the double bond as valence electrons, which were displaced away from the carbon atom with the more electronegative substituents, and thereby illustrated the polarisation without relying on orbital considerations that had not been well established at that time. Moreover, he added that a significant polarisation is required for high selectivities and that insufficient polarisation results in isomeric product mixtures. In extensive studies on allyl bromide **1**, he observed that the addition with hydrogen bromide is slow and selective towards 1,2-dibromopropane **2** under inert conditions or with antioxidants (Scheme 1.4). Contrary, in reactions under air or oxygen atmosphere, or in the presence of peroxides, the main product became 1,3-dibromopropane **3** and the reaction rate was significantly increased. Kharasch termed this observation the "peroxide effect", and noticed the same effect regarding product selectivities under radiation with light ("light effect"). However, the two explanations that he gave initially (a possible conversion of the alkene substrate or an enhanced peroxide effect based on miniscule peroxide or oxide quantities) were disproved in further studies.[20] Instead, his investigations led him to conclude that peroxides enable the formation of radical bromine atoms as reactive species as supposed to bromide ions, which lead to Markovnikov products.[21]



Scheme 1.4. Addition of hydrogen bromide under different conditions observed by Kharasch.

In one of the first proposed mechanisms for radical additions, Kharasch and co-workers presented the radical hydrobromination of vinyl bromide under oxidative conditions. The authors recapitulated the two possible pathways and the driving factors that led to the opposing outcomes utilising Kharasch's initial postulation: while under "normal" (ionic) conditions, the bromide ion is directed towards the carbon atom with lower electron-density, under "peroxide" conditions, bromine atoms are supplied

and preferably bind to the negatively polarised carbon atom. The radical addition leads to a new carbon-centred radical which then engages in a reaction with another hydrogen bromide molecule furnishing the *anti*-Markovnikov product while simultaneously providing a new bromine atom that is able to propagate the chain reaction (Scheme 1.5).[21] In the following years, it was shown that bromine atoms, and thus *anti*-Markovnikov selectivity in hydrobomination, can also be generated *in-situ* via photoinduced methods (photo addition).[22]



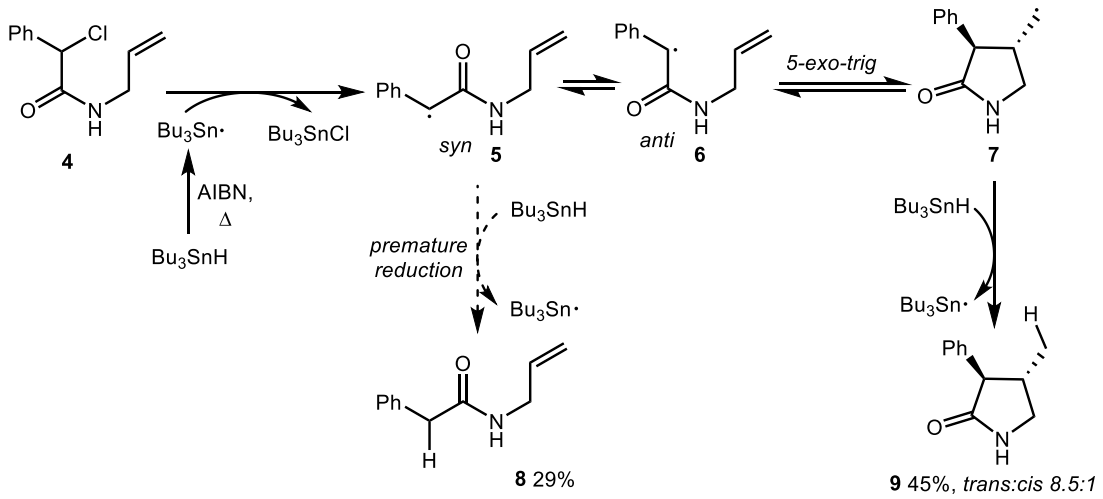
Scheme 1.5. Radical hydrobromination of vinyl bromide.

1.2.2 Radical Chemistry with Tin Hydrides

At first, radical reactions remained exclusive for hydrohalogenations or dihalogenations and were beyond such disparate applications widely considered uncontrollable and unpredictable due to the high reactivities of radicals and thus lowered reaction selectivities.[23] A major advancement in radical chemistry came with organotin hydrides and radical initiators.[24] The radical initiator enables facile radical formation and the weak Sn–H bond (BDE(Bu_3Sn–H) = 74 kcal·mol^{-1})[25] presents a clear target for homolytic cleavage. The resulting tin-centred radical is notoriously eager to attack C–X bonds, resulting in the formation of strong Sn–X bonds (BDE(Me_3Sn–X) = 127/107/91/77 kcal·mol^{-1} (with X=F/Cl/Br/I))[26,27] as driving force for the conversion. Consequently, an alkyl or aryl radical could be generated in good yield from the corresponding halide, which could undergo various further reactions such as cyclisations, in which the carbon-centred radical adds to a C=C or C≡C bond in the cyclisation step. Another documented variant involved the use of allyltin derivatives to introduce an allyl group, in which the Sn–C bond is broken to

generate an allyl radical.[28] Mercury-based methods were also developed at the time but never gained as much popularity as tin-mediated methods and will therefore not be discussed here.[29]

The generation of carbon-centred radicals using tin hydrides is illustrated in the radical cyclisation of amides published by Parson and co-workers.[30] The group observed that direct reduction to side product **8** was a problem, particularly, with smaller substituents attached to the nitrogen atom. However, larger groups led to higher yields, presumably as a result of a higher concentration of *anti*-conformer **6**, in which the C=C bond lies closer to the carbon-centred radical. Furthermore, it was found that the temperature had a big impact on the conformer population and elevated temperatures generally increased concentration of intermediate **6** by easing rotation around the N–CO bond leading to higher product yields. Interestingly, the group observed high *trans*-stereoselectivies when radical stabilising groups were attached to the initially formed radical, which let them to conclude that the *5-exo*-trig cyclisation might be reversible (Scheme 1.6).

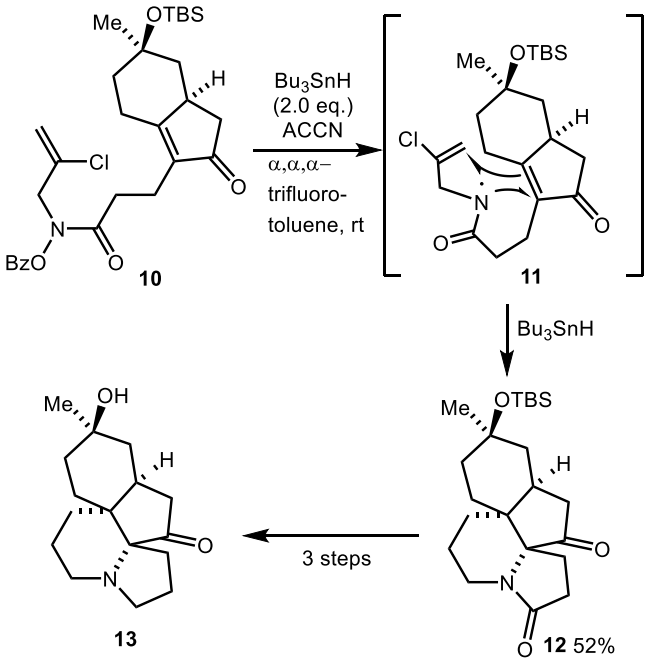


Scheme 1.6. Organotin hydride mediated cyclisation to pyrrolidinones.[31]

Many procedures using tin hydrides were developed far beyond the scope of homolytic C–X cleavage. Pioneers like Barton, for instance, substantially expanded the scope of radical chemistry and demonstrated that carbon-centred radicals could be accessed from (di-) thiocarbonyl-containing substrates among various other functional

groups.[32] Barton's initial work was heavily influenced by tin hydride chemistry and featured stannyl radicals as key intermediates in radical reactions, such as in the Barton-McCombie deoxygenation of alcohols or in the Barton decarboxylation of carboxylic acids.[33,34]

Zard, who was a student in the Barton group before starting his independent research, continued his mentor's work. In the total synthesis of (±)-13-deoxyserratine **13**, he employed tributyltin hydride in combination with a radical initiator to generate a nitrogen-centred radical **11** from its benzoate-protected precursor **10** (Scheme 1.7).[35] The formation of radical **11** triggered a cascade cyclisation and a further equivalent of tin hydride was employed to remove the chlorine atom reductively affording the tetracyclic intermediate **12**.

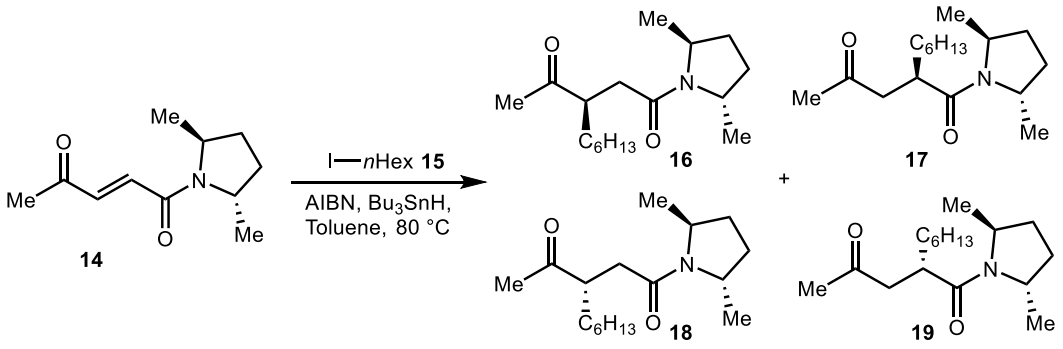


Scheme 1.7. Synthesis of (±)-13-deoxyserratine reported by Zard.[35]

Despite their huge impact on non-ionic reactions historically, radical chemistry based on tin hydrides has been associated with significant drawbacks, such as toxicity concerns, disposal and product isolation issues, or harsh activation conditions that could favour polymerisation of alkenes. Additionally, the scope of possible transformations was soon exhausted because all procedures had a fast, irreversible

hydrogen atom transfer in common, which prematurely occurred in many cases before desired steps could take place. This meant that additional functionality could not be introduced, and target conversions had to be quick in order to outcompete the final reduction step.[36]

Practically, cyclisation procedures were mostly confined to the formation of five-membered rings,[37,38] while intermolecular additions of radicals to alkenes were rarely reported and exclusive for strongly activated alkenes such as demonstrated in radical addition to amide-substituted alkenes by Giese.[39] In the addition of *n*-hexyl radical to enantiomerically pure 4-oxopentenoic amide **14**, Giese and co-workers obtained a complex mixture of four products **16-19** without disclosing exact yields for the individual products (Scheme 1.8). Two regioisomers arise from radical addition to the ketone- or the amide-substituted end of the C=C bond as a result of insufficient electronic differentiation between the two positions, and both regioisomers appear as a mixture of stereoisomers.



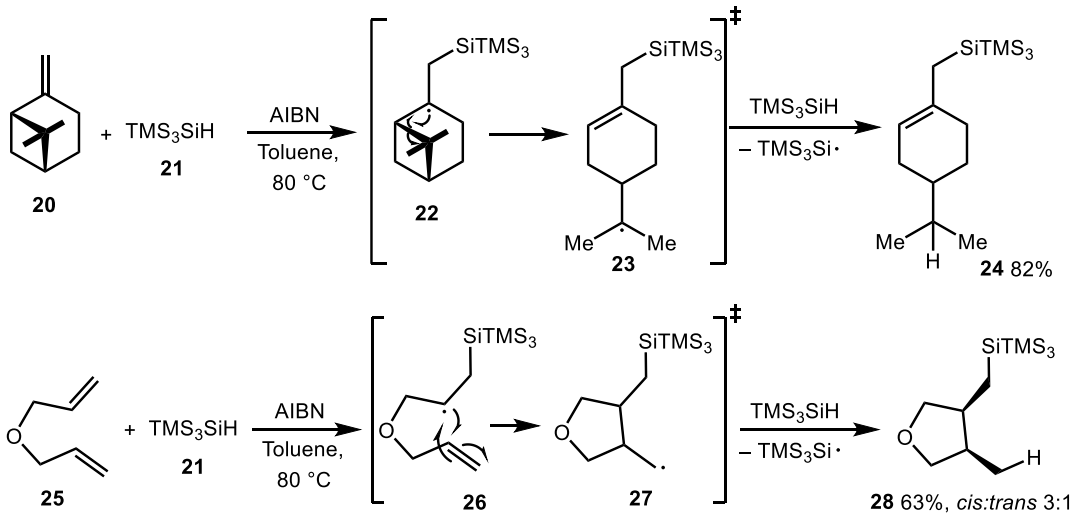
Scheme 1.8. Hydroalkylation of activated alkenes using tin hydride.

1.2.3 Radical Chemistry with Silanes

An obvious choice as substitute for tin hydrides are silanes. Silicon is in the same element group as tin and displays similar reactivities and trends in bond strengths, while being considered much more environmentally friendly.[40] Germanium-based hydrides have also been employed successfully but suffer from high prices of the rare element and never came to play a significant role in conventional organic chemistry.[41] Early radical chemistry with silanes is closely tied to research conducted by Chatgilialoglu. He was mainly faced with the challenge of silane activation due to the

stronger Si–H bond (BDE(Me_3Si–H) = 95 kcal·mol^{-1}).[42] Chatgilialoglu identified $(Me_3Si)_3SiH$ as a suitable candidate, in which the trimethylsilyl groups weaken the key Si–H bond (BDE$(Me_3Si)_3$Si–H = 79 kcal·mol^{-1}) by hyperconjugation towards the range of typical Sn–H bonds.[43] His group and others have reported numerous procedures in which tin hydrides could be replaced with this TMS-substituted silane such as radical dehalogenations C–X bonds followed by addition, cyclisation or rearrangement sequences.[44]

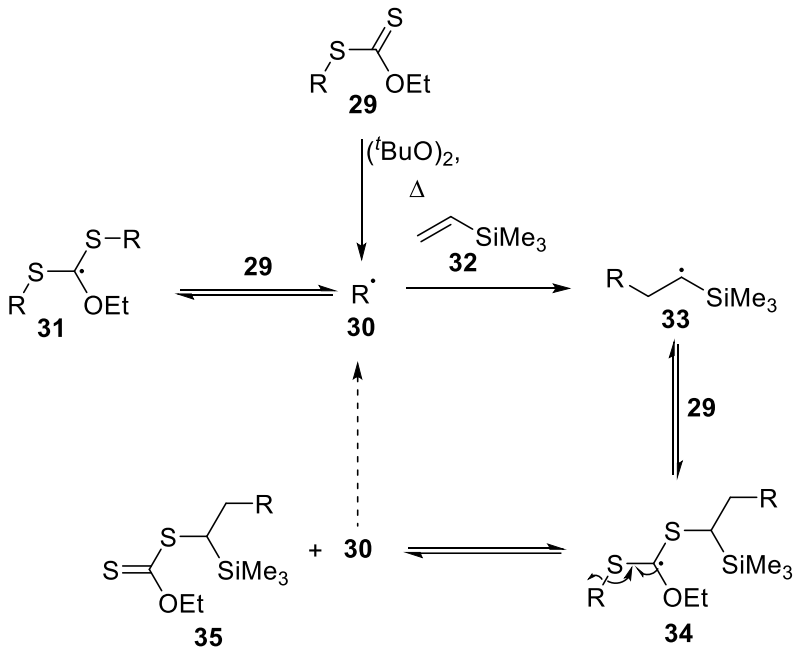
In a collaboration with Giese, he employed $(Me_3Si)_3SiH$ **21** as hydrosilylation agent of alkenes and alkynes.[45] The silane was activated using AIBN and the silicon-centred radical added to the carbon-carbon double/triple bond of a variety of alkenes and alkynes. The resulting carbon-centred radical could abstract a hydrogen atom from another silane molecule to give *anti*-Markovnikov products in accord with a radical chain mechanism. Moreover, the bulky silyl group led to high *anti*-stereoselectivity as the hydrogen atom was preferentially donated to the opposite side. The authors emphasized that the process is successful with unsaturated substrates that contain either electron-withdrawing or electron-donating substituents and attributed this remarkable behaviour to the rapid addition of $(Me_3Si)_3Si\cdot$ radicals to unsaturated compounds referring to previous kinetic investigations on radical additions with silanes.[46] Interestingly, the reaction of β-pinene **20** with $(Me_3Si)_3SiH$ **21** afforded a rearranged product **24**, in which the four-membered ring was opened, while diallyl ether **25** yielded a cyclised tetrahydrofuran derivative **28** (Scheme 1.9).



Scheme 1.9. *anti*-Markovnikov hydrosilylation of alkenes using $(Me_3Si)_3SiH$.[45]

1.2.4 Radical Chemistry with Xanthates

Zard, however, pursued another approach as he realised that xanthates are suitable precursors for carbon-centred radicals that do not require activation by stannyl or silyl radicals.[47] Indeed, he reported that xanthates **29** fragment to carbon-centred radicals **30** under thermal or photolytic conditions (Scheme 1.10). Crucially, radical species **30** and excess xanthate **29** were in equilibrium with species **31**, effectively lowering the concentration of the reactive radical. This led to an increased lifetime of radical **30**, which enabled Zard to perform radical additions with unactivated alkenes **32**. The resulting carbon-centred radical **33** could engage with xanthate **29** to form new xanthate products **35**, in which the xanthate group was transferred across the alkene, while recreating **30**. The stabilities of the initial radical **30** and the carbon-centred radical **33** after radical addition are determinative for the kinetics of the entire process, and it was proposed that the forward reaction would generally be favoured if intermediate **33** was less stable than radical **30**.[48]



Scheme 1.10. Xanthate group transfer with an unactivated alkene.

While the efforts by researchers like Giese, Chatgilialoglu or Zard marked a milestone in radical chemistry, reported transformations via radical processes remained limited and almost exclusively required stoichiometric additives to initiate the reaction. This has changed over the last two decades with the rise of photoredox catalysis.

1.3 Photoredox Catalysis

1.3.1 Principles of Photoredox Catalysis

Photoredox catalysis has surfaced as an innovative approach to initiate radical processes via photoinduced excitation of a photocatalyst.[49–51] In the excited state, an electron from the HOMO of the photocatalyst is elevated to the LUMO giving a single occupied molecular orbital (SOMO). In the case of metal-based photocatalysts, the electron is transferred from a metal-centred orbital to a ligand centred orbital (metal ligand charge transfer (MLCT)).[52] The unpaired electron undergoes quick intersystem crossing (ISC) to give the reactive triplet state (Figure 1.2).[53]

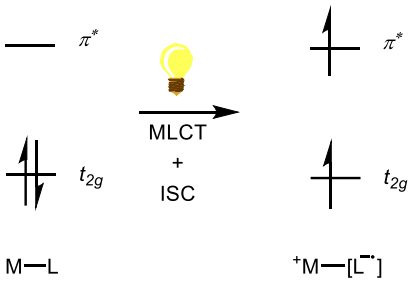


Figure 1.2. Activation of a metal-based photocatalyst.

Although formally a forbidden transition, the electron often falls back into its original state resulting in no reaction. However, the excited photocatalyst can also engage in one of three intermolecular transformations.

1.3.1.1 Single Electron Transfer

Most commonly, a single electron transfer (SET) between the excited photocatalyst and a substrate or radical precursor is exploited, wherein both directions of electron flow are possible (Figure 1.3). Upon SET, the substrate can participate in the successive step directly or undergoes mesolytic fragmentation to afford the productive radical (or ionic) species. In the case of SET from the catalyst to the radical precursor, the electron transfer process is called oxidative quenching, yielding a reduced and unstable radical anion precursor and the radical cation of the photocatalyst. Similarly, reductive quenching describes the donation of an electron from the radical precursor

under formation of the reduced photocatalyst. In both cases the photocatalyst is brought back to its original oxidation state in a second SET event, which often, but not necessarily, involves a radical species that is formed in the course of the reaction mechanism.

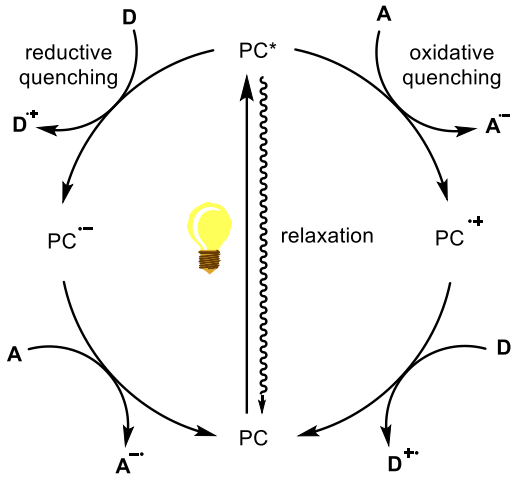


Figure 1.3. Principle of photoredox catalysis via single electron transfer.

1.3.1.2 Atom Transfer and Energy Transfer

As an alternative mechanistic scenario, the excited photocatalyst can also abstract a hydrogen atom (atom transfer) from a reaction partner, which is thus activated for further transformations. However, this photocatalysis mechanism requires different set-ups of photocatalysts that accept hydrogen atoms, such as decatungstate anion ($W_{10}O_{32}^{4-}$), and suitable hydrogen donors (often aldehydes or formic acid derivatives).[54] Thirdly, energy transfer from the excited triplet state photocatalyst to the substrate affords an excited, triplet state substrate while regenerating the ground state of the photocatalyst in one step.[51] This triplet-triplet energy transfer (TTET) depends on the triplet state energy of the excited photocatalyst rather than its redox potential. Only if the triplet state energy of the photocatalyst matches or surpasses the triplet state energy of the substrate, energy transfer between the two compounds can occur (Figure 1.4).

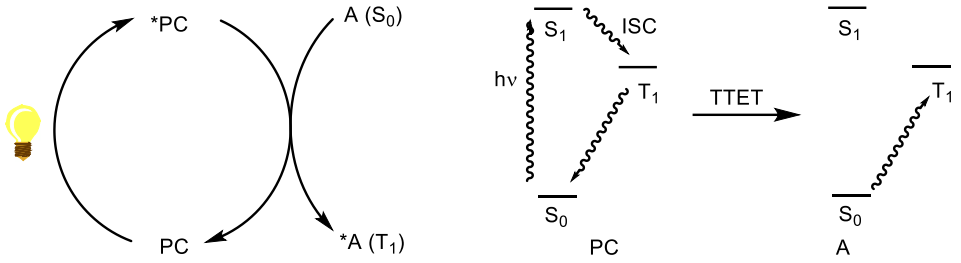


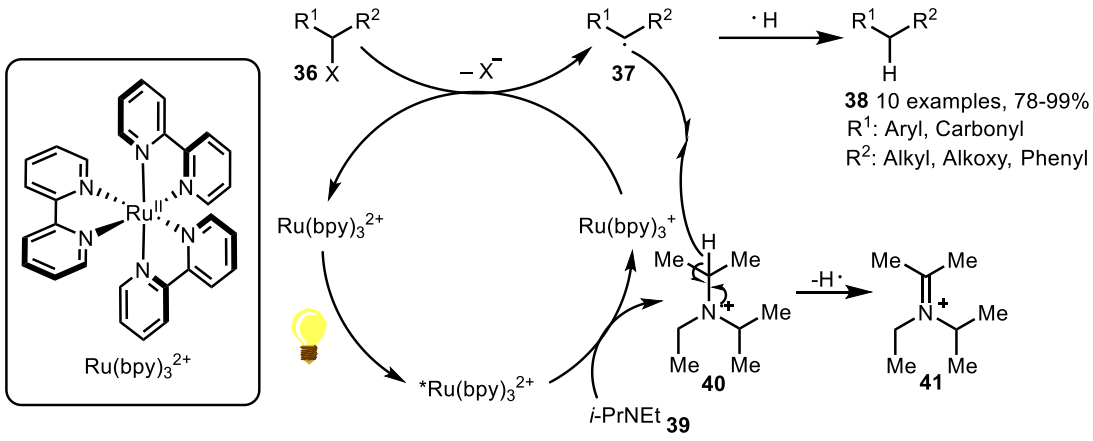
Figure 1.4. Principle of photoredox catalysis via energy transfer.

Energy and electron transfer can compete if both triplet state energy and redox potential are sufficiently high to induce reactivity. The operating mechanism in energy transfer and electron transfer conversions can be quite different leading to seemingly unrelated products.

1.3.2 Radical Chemistry via Photoredox Catalysis

Since the photocatalyst is constantly recovered in all three possible mechanisms, its required concentration can be as low as 0.1 mol% making the method more economically feasible and less wasteful. Moreover, an additional benefit is the possibility of redox neutral conversions whereas previous radical methodologies were net reductive or oxidative. Due to these advantages, more efficient and sustainable procedures operating via photoredox catalysis have been developed replacing older methods based on tin hydrides or silanes.

Stephenson, who was one of the early visionaries in this novel field, reported a reductive dehalogenation based on photoredox catalysis directly rivalling established methods (Scheme 1.11).[55] While under previous conditions stoichiometric amounts of radical precursor were necessary and the formed by-products often complicated product isolation, this method proceeded smoothly with low loadings of $Ru(bpy)_3^{2+}$ as photocatalyst (2.5 mol%), and the formed products **38** were easily separated from all by-products. The group employed Hünig's base **39**, which acted (1) as an electron donor to turn over the catalyst, (2) as a hydrogen source to furnish the reduced product (although this was significantly facilitated by formic acid), and (3) as a trap to remove formed halide from the mixture as salt. The procedure was successful on a variety of substrates.

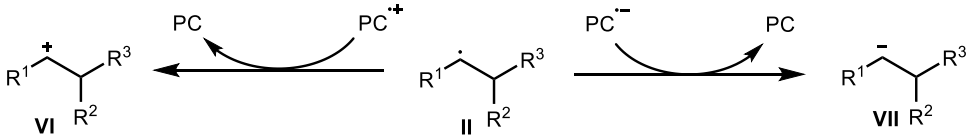


Scheme 1.11. Photoredox-mediated dehalogenation reported by Stephenson.[55]

1.4. Functionalisation of Alkenes Using Photoredox Catalysis

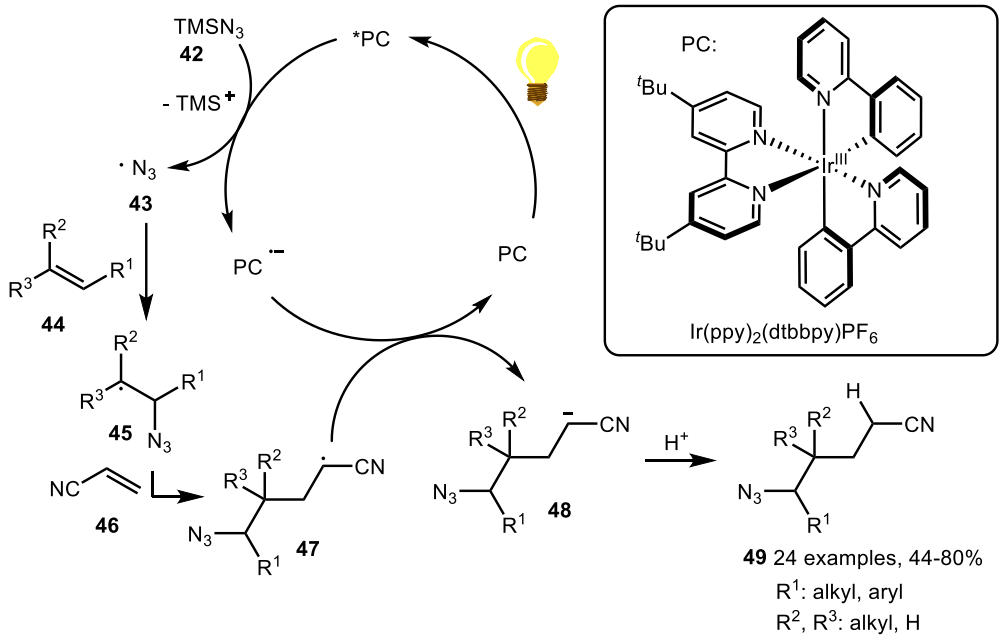
1.4.1 Radical Addition

Different strategies have been developed for the functionalisation of alkenes using photoredox catalysis. The addition of radicals is the most popular way to achieve such transformations. Herein, the photocatalyst is firstly involved in the initial fragmentation of the radical precursor. The fragmented radical adds to the alkene substrate if the electronic attributes of the two reaction partners match. The further course of the mechanism is different from case to case; however, in contrast to the previously mentioned radical methods (see Scheme 1.4), another SET must take place in order to close the catalytic cycle. In Stephenson's dehalogenation, this is accomplished by oxidation of the tertiary amine, but involvement of the carbon-centred radical **II** directly or after successive steps is arguably even more common. In this scenario, the second SET gives a carbanion **VI** or carbocation **VII** that can be trapped with wide range of possible electrophiles or nucleophiles, respectively (Scheme 1.12).



Scheme 1.12. Second SET event between photocatalyst and radical intermediate.

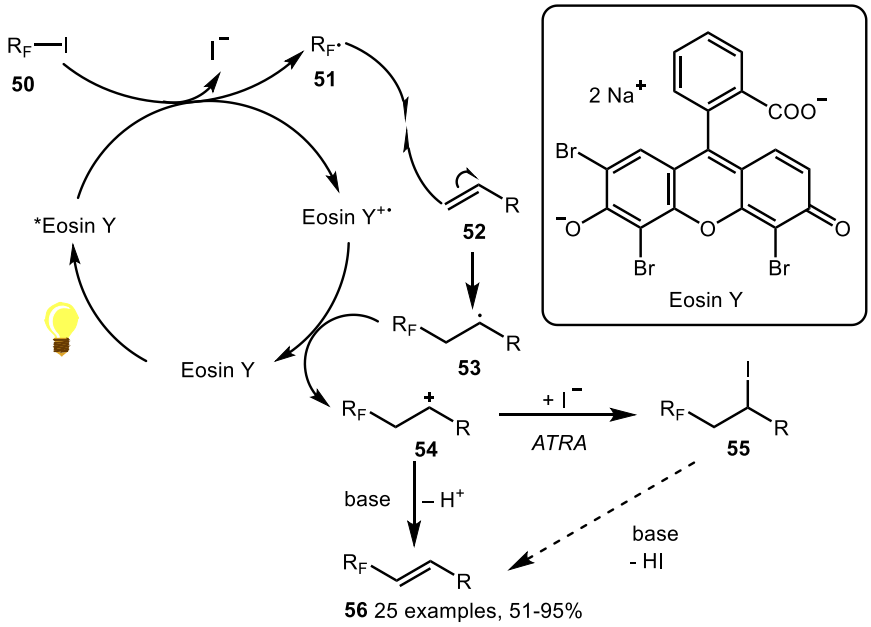
Carbanions are often simply protonated, and an exemplary procedure is given by Lu and co-workers (Scheme 1.13).[56] In their three-component carboazidation, azidyl radical N_3· **43** is generated from $TMSN_3$ **42** upon single electron oxidation. The electrophilic radical **43** reacts with an electron-rich, unactivated alkene **44**. The resulting carbon-centred radical **45** is now nucleophilic and reacts with the more electron-deficient alkene, in this case acrylonitrile **46**, highlighting the selectivity of radical-alkene interactions as described above. The α-cyano radical **47** can be reduced and the anion **48** finally protonated to afford the target product **49**, in which the two original C=C bonds are fully saturated; one of which formally oxidised, the other one formally reduced.



Scheme 1.13. Three-component carboazidation of unactivated alkenes reported by Lu.[56]

Carbocation intermediates that can be formed in oxidative quenching cycles, have been demonstrated to react with various oxygen-[57–61] or nitrogen-based nucleophiles,[62,63] halides,[64–66] pseudohalides[67,68] and electron-rich aromatics.[69,70] Alternatively, the ionic compound can recover the C=C bond via elimination if no trapping agents are present and an appropriate leaving group is attached. An interesting observation was made by the Bolm group, who reported switchable elimination

processes in photo-mediated radical additions of perfluoroalkyl halides to unactivated alkenes (Scheme 1.14).[71] Rather than atom transfer radical addition (ATRA) products **55**, in which the perfluoroalkyl halide would be formally added across the alkene C=C bond, elimination (ATRE) products **56** were obtained if the solvent was changed, and a base was added. Both possible products succeed a carbocation intermediate **54**; however, while under non-basic conditions the cation was attacked with iodide as the nucleophile, the presence of base led to deprotonation of the carbocation or rapid elimination of any iodide **55** present yielding perfluoroalkenyl products **56** in high yield.

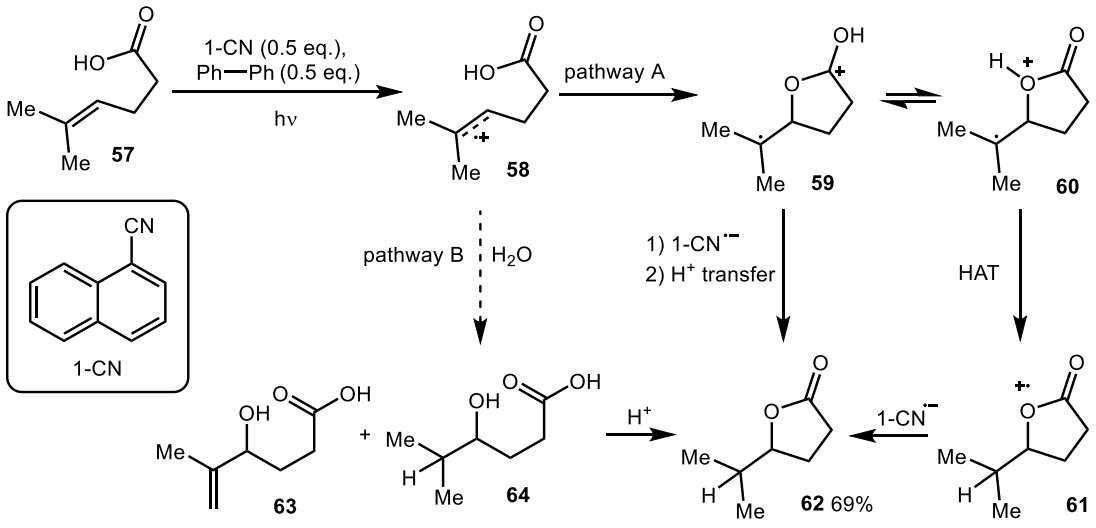


Scheme 1.14. Atom transfer radical addition-elimination for the synthesis of perfluoroalkenes.[71]

1.4.2 Single Electron Oxidations and Reductions

The single electron oxidation of unactivated alkenes to generate cation radicals under photolytic conditions was long known before photoredox catalysis became popular.[72,73] Early research is this field was based on intramolecular rearrangements, particularly of strained rings, that occurred after photolytic activation in the presence of a photosensitizer. Cyanoarenes served this purpose in many cases and were required in significant, sometimes even (super-)stoichiometric quantities. In the photoinduced

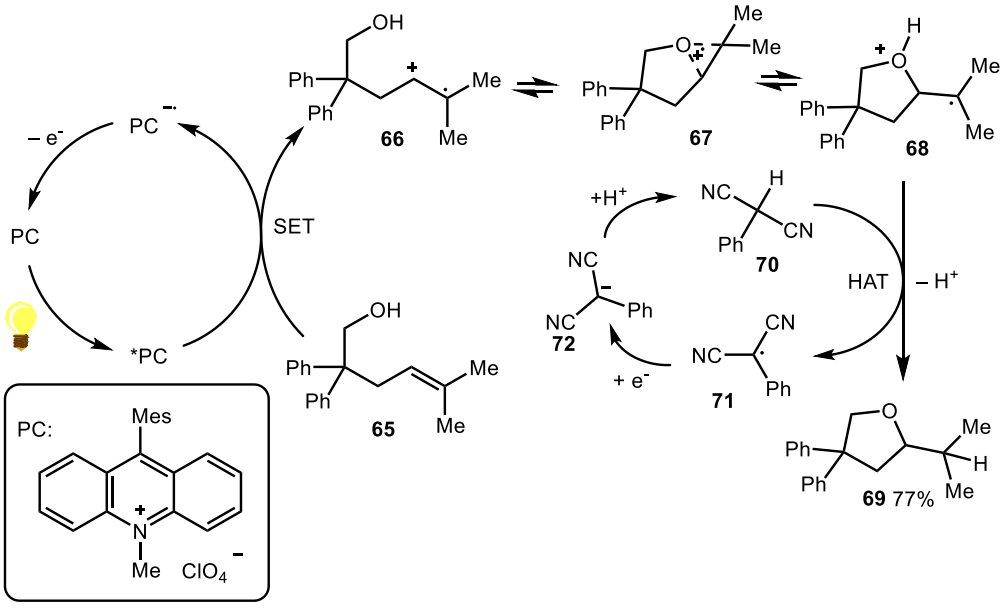
lactonization reported by Gassmann, 1-cyanonaphthalene (1-CN, 0.5 eq.) and biphenyl (0.5 eq.) were employed as a photosensitiser pair and interesting observations were made that prompted the group to propose a complex mechanistic framework (Scheme 1.15).[73] It was possible to isolate 1,4-dihydro-1-cyanonaphthalene as a reduced form of the photosensitiser, upon which the group concluded that its radical or anion precursor is formed in the course of the mechanism. In labelling experiments, it was proven that the added hydrogen in the fully saturated product **62** originates partially from the photosensitizer via radical cation intermediates **59**, **60**, and **61** (pathway A) and partially from conversion of hydrated (unsaturated) intermediates **63** and **64** (pathway B) after acidic aqueous work-up.



Scheme 1.15. Single electron oxidation in the synthesis of lactones.[73]

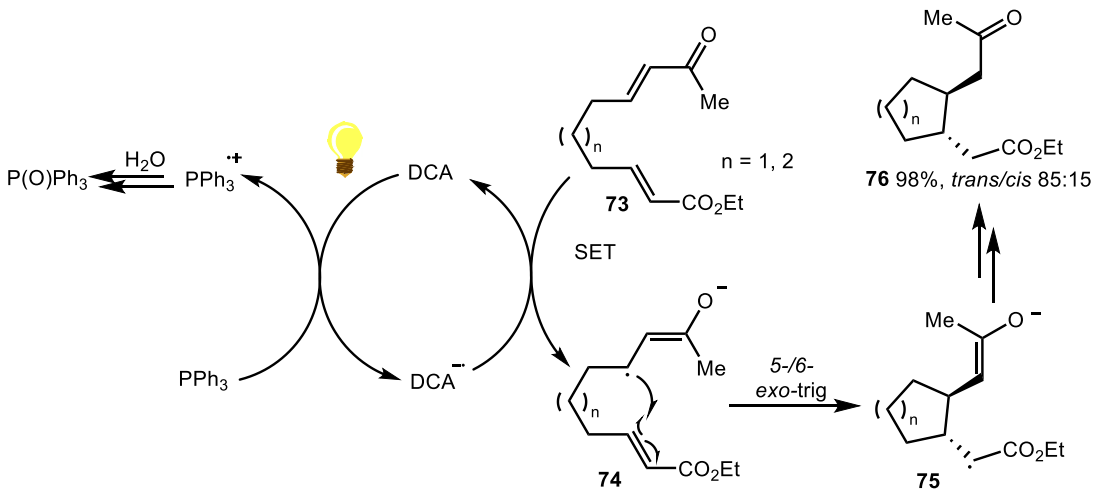
Direct oxidations of alkenes remained a niche phenomenon because catalytic procedures were limited to 1,1-diarylethylenes,[74,75] and non-catalytic procedures usually gave low product yields, especially if the reduced photosensitiser was not inert any longer or favoured reverse electron transfers.[76] Interest in single electron oxidations of alkenes grew immensely with the appearance of catalytic procedures, which can be largely contributed to the Nicewicz laboratory. The group hypothesised that in order for the process to require only catalytic amounts, the photosensitiser should exhibit complete redox reversibility, while still enabling alkene oxidation. It was proposed that positively charged photosensitisers could be suitable catalysts by

minimising unproductive backward electron transfer while remaining inert (apart from acting as single electron acceptor) in the reduced, neutral form. In the first of many publications using this alkene functionalisation strategy, the group presented the hydroetherification of alkenols using 9-mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$ ClO_4^-) as photocatalyst (5 mol%) (Scheme 1.16).[77] The acridinium salt was chosen due to its strong absorption in the visible region, its oxidising power in the excited state ($E_{1/2}^{red*}$ = +2.06 V vs. SCE) and the potential to act as reductant in its reduced form ($E_{1/2}^{ox}$ = −0.57 V vs. SCE).[78,79] The product yield increased significantly in the presence of 2-phenylmalononitrile **70** to facilitate the hydrogen atom transfer. The reaction was successful with styrene derivatives and trisubstituted alkenes **65** to yield exclusively *anti*-Markovnikov products **69** showcasing the effectiveness to oxidise electronically different C=C bonds with this novel concept. Furthermore, the reaction could be performed in an intermolecular fashion with alcohol additives as nucleophiles, or with terminal carboxylic acid moieties to furnish lactones, thus offering a catalytic alternative to Gassmann's procedure. The cyclisation step is believed to proceed via the three-membered ring cation radical **67** based on previous computational studies.[80] Rupture of this ring intermediate gives the more stable tertiary radical **68** in the regioselectivity-determining cyclisation step.



Scheme 1.16. Photoredox-catalysed *anti*-Markovnikov hydroetherification reported by Nicewicz.[77]

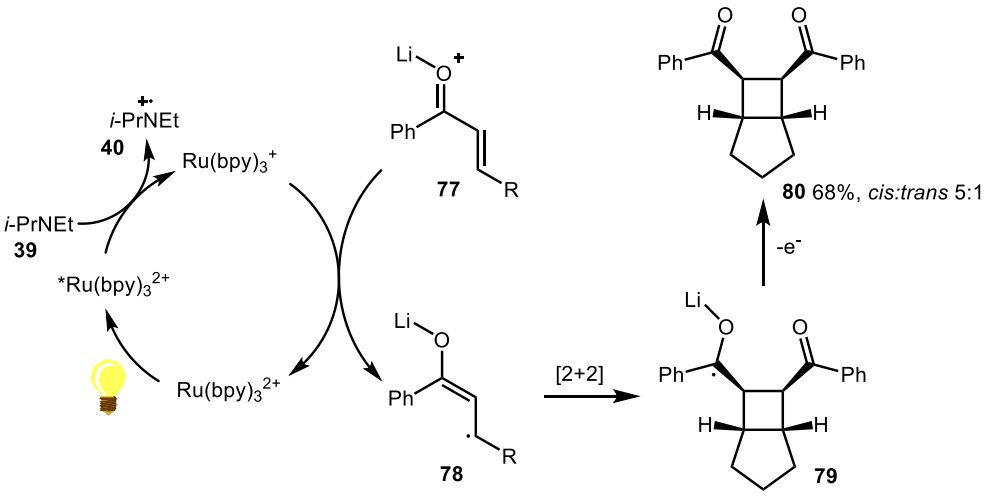
Similar to single electron oxidations of electron-rich alkenes, single electron reductions are possible with activated alkenes, although less common.[81–83] Pandey and Hajra used a photolytic reductive method to generate cyclopentanes and cyclohexanes **76** from functionalised α,β-unsaturated ketone substrates **73** (Scheme 1.17).[84] 9,10-Dicyanoanthracene (DCA, 40 mol%) was chosen as the photosensitizer, which upon excitation engaged in an electron transfer with PPh_3 as a sacrificial electron donor. The resulting radical anion species was able to reduce the substrate enone under neutral conditions ($E_{1/2}^{red}$ = −0.89 V vs. SCE). The nucleophilic enolate radical **74** underwent rapid and *trans*-selective *5-/6-exo*-trig cyclisation. Product yields were only high with substrates containing a second electron-deficient C=C bond. If this condition was not fulfilled (only terminal alkenes were reported), electronic mismatch between radical and alkene led to reduced yields as cyclisation was increasingly outcompeted by reduction of the enone to afford reduced ketone substrate, instead.



Scheme 1.17. Single electron reduction in the synthesis of cyclopentanes and cyclohexanes.[84]

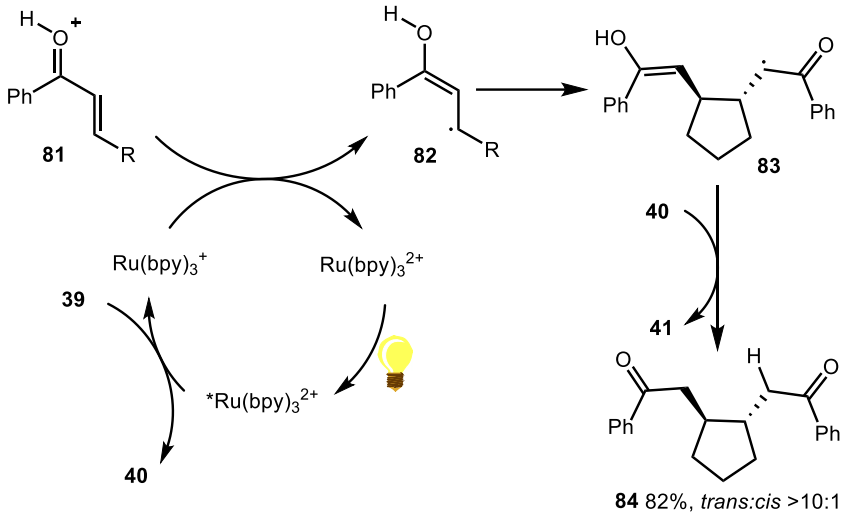
1.4.3 Photoredox-catalysed [2+2] and [4+2] Cycloadditions

In one of the ground-breaking publications in the field of photoredox chemistry, Yoon reported the Ruthenium-catalysed [2+2] cycloaddition of aryl (bis)enones (Scheme 1.18).[85] Although the substrates appeared very similar to those that Pandey and Hajra had tested, in this case cyclobutane-containing dione derivatives were formed via an entirely different mechanistic pathway. The first step, however, was comparable as the photoexcited catalyst was reduced with Hünig's base **39** and the reduced species transferred an electron to the activated enone **77**. In the proposed mechanism, the following [2+2] cyclisation occurred between reduced enone **78** and the second enone derivative under concerted formation of two new C–C bonds. The ketyl radical adduct **79** could be oxidised to furnish bicyclic product **80** in high *cis*-selectivity. Alkyl enones were recovered in the reaction, and only aryl enones underwent efficient single electron reduction with $Ru(bpy)_3^+$ ($E_{1/2}^{red}$ = +1.33 V vs. SCE) in the key electron transfer step.[86,87] However, the other α,β-unsaturated carbonyl compound could be substituted for aliphatic ketones, esters or amides. Furthermore, $LiBF_4$ was a crucial additive for the reaction to increase solubility of the photocatalyst and activate the enone for single electron reduction. The intermolecular reaction of aryl enones was also successfully demonstrated and resulted in monocyclic, rather than bicyclic products.



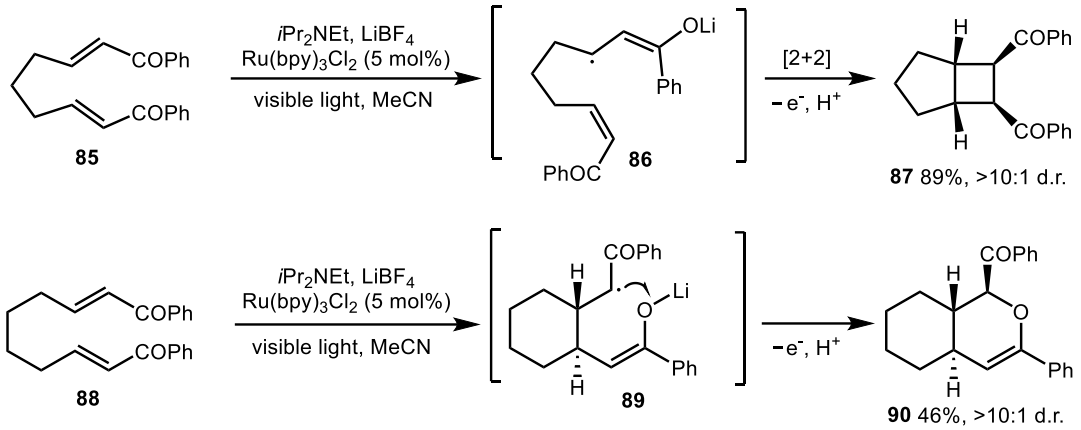
Scheme 1.18. Photoredox-catalysed [2+2] cylcoaddition of (bis)enones.[85]

The Yoon group developed their procedure much beyond the original scope. To address the limitation to aryl enones due to their lower reduction potentials, the group identified *N*-methyl protected imidazole as potential redox auxiliary, which can be easily cleaved and replaced with various nucleophiles.[88] When substituting the Lewis acid for a Brønsted acid, the group observed the reductive formation of cyclopentanes **84** in accordance with the report published by Pandey and Hajra. Yoon rationalised this divergent reactivity with the presence of neutral α-enol radical **83** as the reactive species that would favour the formation of five-membered rings (Scheme 1.19).[81]



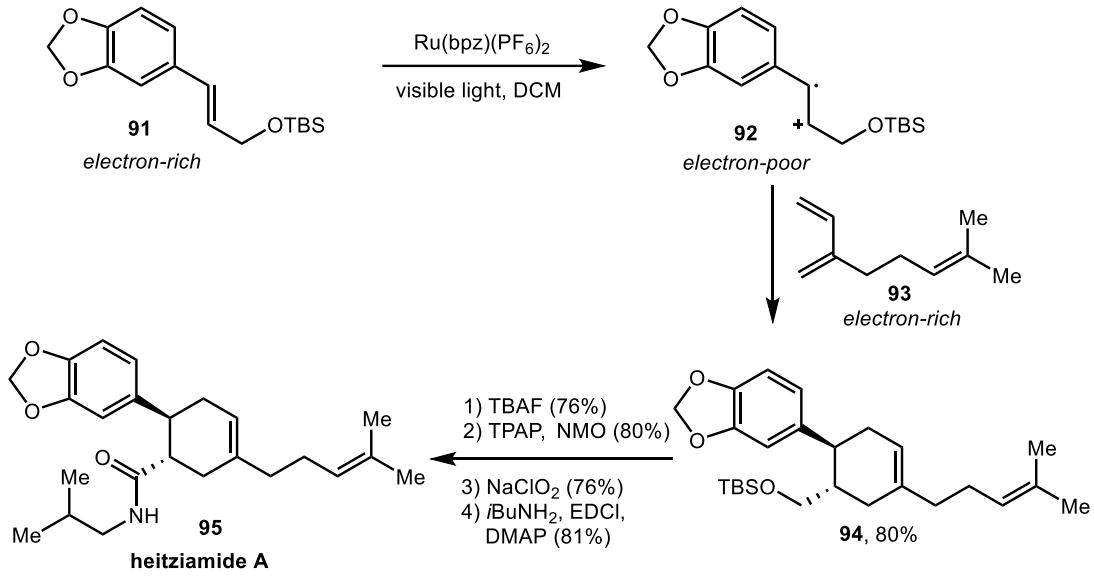
Scheme 1.19. Photoredox-catalysed reductive cyclisation of (bis)enones with Brønsted acid.[81]

Interesting observations were made with (bis)enones that contained another methylene unit in the chain (Scheme 1.20).[89] Herein, bicyclic products **90** were obtained that mirrored hetero Diels-Alder products. It was proposed that the anion radical firstly undergoes *trans*-selective *6-exo*-trig cyclisation to intermediate **89**. In this conformation, a [2+2] cycloaddition to cyclobutane derivatives was highly disfavoured, and instead a second six-membered ring was generated via C–O bond formation. The resulting ketyl radical was reduced to furnish the bicyclic product **90**.



Scheme 1.20. Photoredox-catalysed cyclisation of (bis)enones via different radical anion intermediates.[89]

The group extended this application to electron-rich styrenes and exemplified the utility in the total synthesis of Heitziamide A (Scheme 1.21).[90] The group had already established a method to functionalise electron-rich styrenes via [2+2] cycloadditions in intramolecular reactions using $Ru(bpz)_3^{2+}$ as catalyst.[91] However, in contrast to reactions with (bis)enones, the process was initiated by single electron oxidation to give radical cation intermediate **92**. Notably, this oxidation renders the originally electron-rich styrene **91** electron-poor, thus enabling the reaction with an otherwise mismatching electron-rich diene **93**. Employing this strategy, a precursor **94** of the target natural compound **95** could be prepared in one step with high stereo- and chemoselectivity.

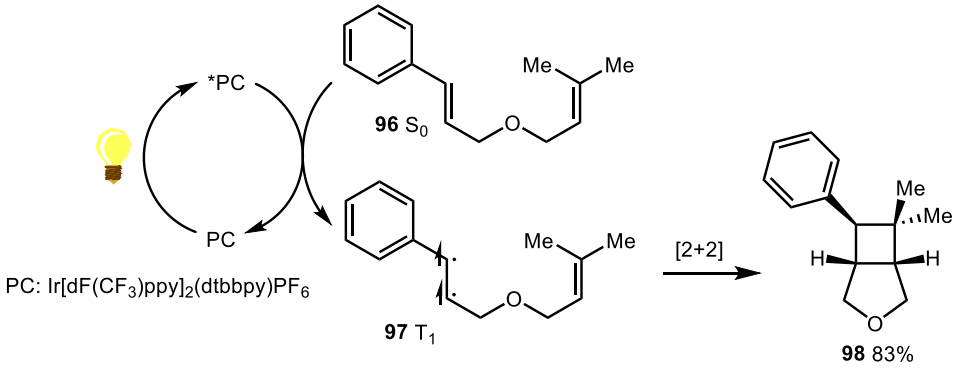


Scheme 1.21. Photoredox-catalysed Diels-Alder reaction in the total synthesis of heitziamide A.[90]

1.4.4 Energy Transfer Reactions

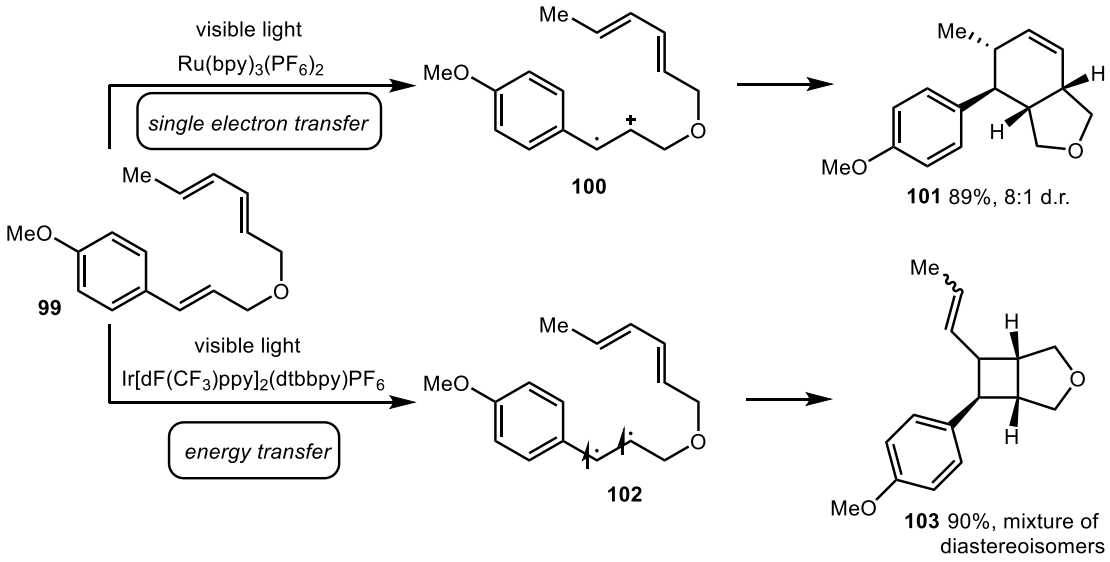
The idea of transferring energy as opposed to electrons was presented many decades before photoredox catalysis became popular.[92,93] As a matter of fact, attention was originally drawn to $Ru(bpy)_3^{2+}$ due to its ability to transfer energy in the photolytically excited state to various inorganic and organic compounds.[94,95] However, as early examples were built on electron transfer mechanisms, the concept of photolytic energy transfer slid out of the spotlight at first. During his research on [2+2] and [4+2] cycloadditions, Yoon encountered several reactions that could not be explained on the basis of single electron transfer.[96,97] An oxidative single electron transfer between two components can only take place if the oxidation potential of the excited photocatalyst is sufficient to remove an electron to the reaction partner. In the case of $Ir[dF(CF_3)ppy]_2(dtbbpy)^+$ as photocatalyst ($E_{1/2}^{*III/II}$ = +1.21 V vs. SCE)[98] and the shown styrene derivative **96** (($E_{1/2}^{red}$ = +1.42 V vs. SCE),[99] this fundamental prerequisite was not satisfied, yet the desired [2+2] cyclisation to **98** proceeded smoothly, even with highly electron-deficient styrene derivatives (Scheme 1.22). The redox potential could thus not be a decisive factor in the transformation, but the reported triplet energy of the excited photocatalyst (E_T = 61 kcal·mol^{-1})[98] matched those of typical styrene derivatives (E_T = 60±3 kcal·mol^{-1}).[97,99] Therefore, the group suggested that the excited photocatalyst triggers activation of the styrene via TTET.

Consequently, the π-bond was broken giving triplet-state 1,2-diradical **97** that was able to perform the observed reaction.



Scheme 1.22. Photoredox-catalysed [2+2] cycloaddition by energy transfer.[97]

In a striking example, Yoon and co-workers demonstrated that a diene-tethered styrene derivative **99** could give Diels-Alder product **101** under electron transfer conditions with a photocatalyst that is sufficiently oxidising after photoexcitation or, alternatively, undergo [2+2] cycloaddition to **103** via an energy transfer pathway (Scheme 1.23).[97] Energy transfer methods have witnessed an impressive revival as a direct consequence of Yoon's pioneering work.[100]



Scheme 1.23. Electron/energy transfer on styrene derivative with different photocatalysts.[97]

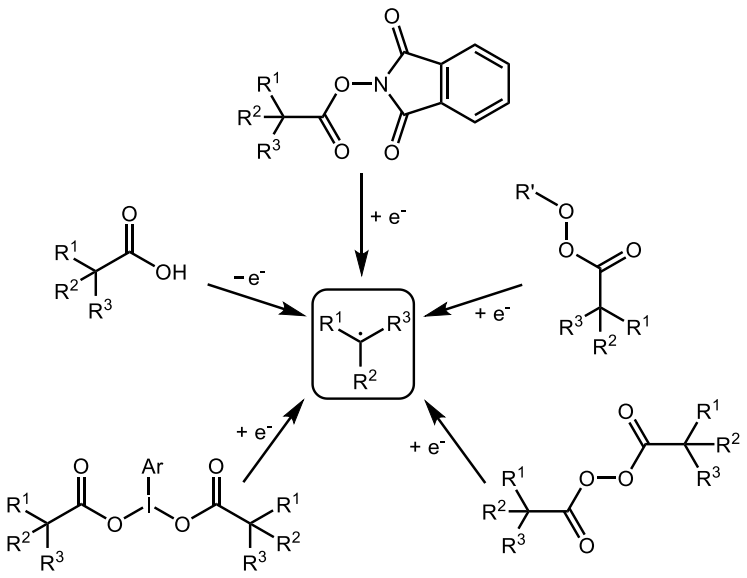
1.5 Formation and Reaction of Carbon-centred Radicals with Alkenes

The addition of carbon-centred radicals to alkenes enables the effective construction of new C–C bonds and is therefore a hot topic in modern organic chemistry. Following the guidelines presented in previous Chapters 1.1 and 1.2, the radical addition step is selective towards the formation of the more stable carbon-centred radical intermediate. The reaction can be quenched using an extensive array of techniques ranging from radical traps or ionic traps to elimination procedures. Photoredox catalysis has vastly expanded the scope of such transformations and intensive research efforts have been dedicated to finding radical precursors for carbon-centred radicals and establishing novel methodologies for the functionalisation of radical intermediate.

1.5.1 Carbon (sp^3)-centred Radicals

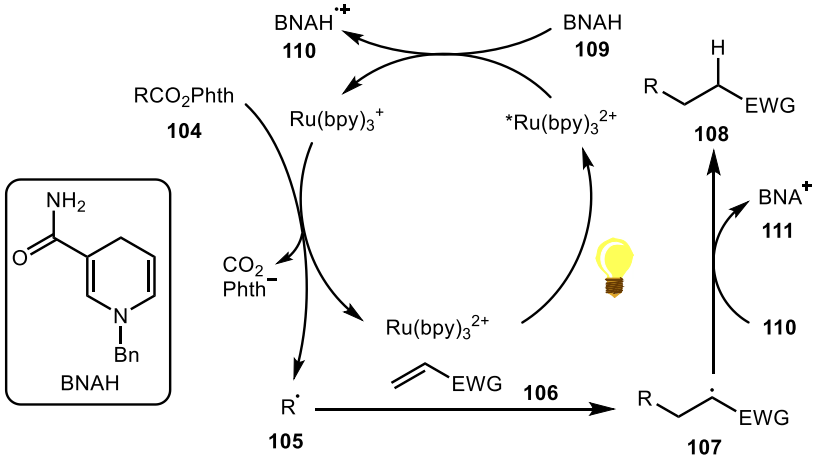
The electronic nature of a sp^3-hybridised carbon-centred radical depends on its substituents. Electron-withdrawing substituents render the radical electrophilic, while electron-rich groups such as alkyl chains make the radical more nucleophilic. It is important to make this clear distinction to recognise possible alkene coupling partners. Furthermore, the substituents greatly affect the bond dissociation energy, thus dictating which radical precursor might be required to generate the desired radical.

Electron-rich, nucleophilic, carbon-centred alkyl radicals are often obtained from carboxylic acids or activated forms, thereof. *N*-(acyloxy)phthalimides (NPI) are popular radical precursors and belong to the class of redox-active esters (RAEs).[101,102] Furthermore, alkyl diacyl peroxides, alkyl peresters and aryliodine(III) dicarboxylates have all been reported as alternative precursors (Scheme 1.24).[102] Generally, the radical generation occurs upon single electron reduction of the carboxylic acid derivative, while free carboxylic acids as radical precursors fragment upon single electron oxidation.



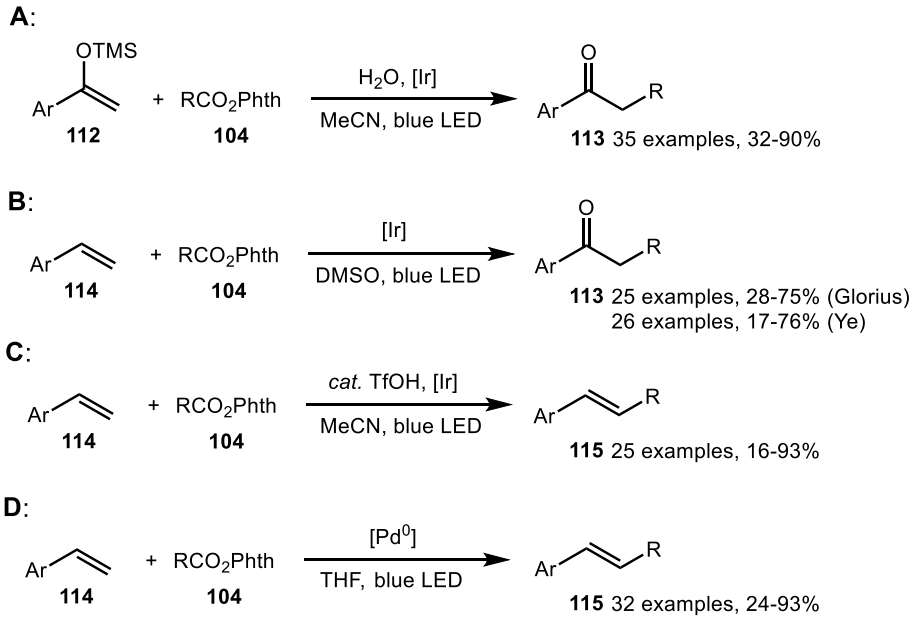
Scheme 1.24. Carboxylic acid derivatives as alkyl radical precursors.

A milestone in the photoredox-catalysed functionalisation of alkenes with alkyl radicals was made in 1991 when Okuda presented the decarboxylative Michael addition with *N*-(acyloxy)phthalimides **104** to activated alkenes **106** (Scheme 1.25).[103] The group suggested a reductive quenching cycle, in which the excited photocatalyst accepts an electron from 1-benzyl-1,4.dihydronicotinamide (BNAH) **109**. The reduced catalyst species could reduce the phthalimide ester **104** to initiate fragmentation. Radical addition of **105** to alkene **106** and hydrogen abstraction led to the conjugate addition product **108**.



Scheme 1.25. Photoredox-catalysed conjugate addition using alkyl radicals.[103]

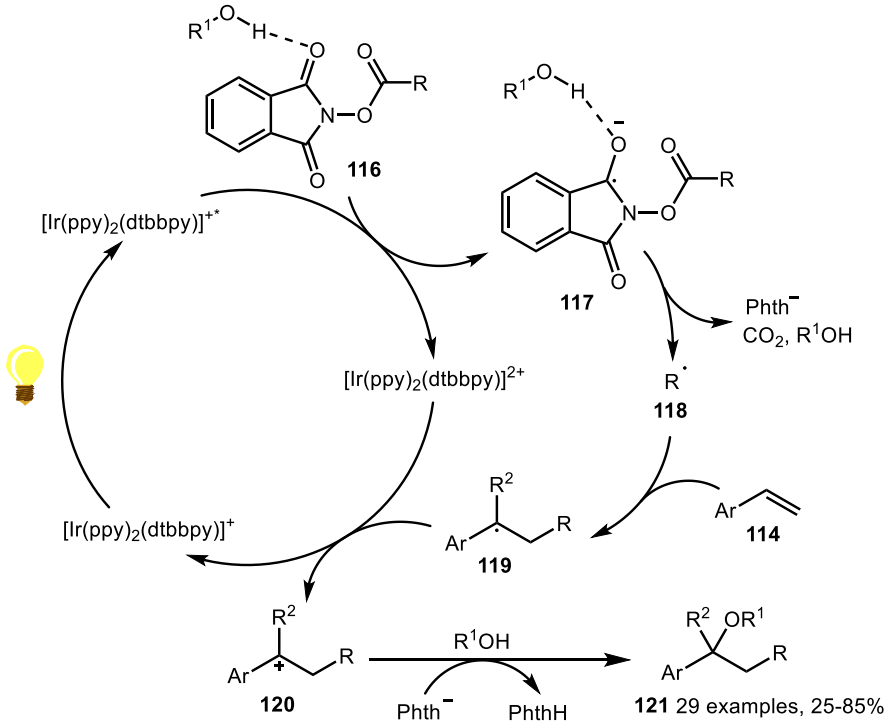
Okuda's work prompted other groups to employ NPIs as alkyl radical precursors. To illustrate this, a number of transformations from different styrenes derivatives are shown, all of which proceed via a radical addition-oxidation sequence (Scheme 1.26). The Song group presented the synthesis of acetophenones **113** from silyl enol ethers **112** exploiting the silyl group as leaving group after oxidation to the corresponding benzyl cation (Scheme 1.26A).[104] Ye and Glorius independently published the Kornblum-oxidation in DMSO synthesise acetophenone derivatives **113** from styrene substrates **114** (Scheme 1.26B).[105,106] Furthermore, Ye obtained elimination products **115** in the presence of Brønsted acids under otherwise identical conditions as shown in Scheme 1.26C.[106] Alternatively, Scheme 1.26D depicts the Heck-type reaction disclosed by the Glorius group exploiting palladium(0) as the photocatalyst, in which the final step was a β-hydride elimination.[107]



Scheme 1.26. Various photoredox-catalysed transformations of styrenes using alkyl radicals.

An impactful example is the photoredox-catalysed oxyalkylation of styrenes by Glorius (Scheme 1.27).[108] In this case, the quenching cycle is oxidative and fragmentation of species **116** occurs upon single electron reduction by the excited photocatalyst. The group suggested that the redox-active ester is further activated by

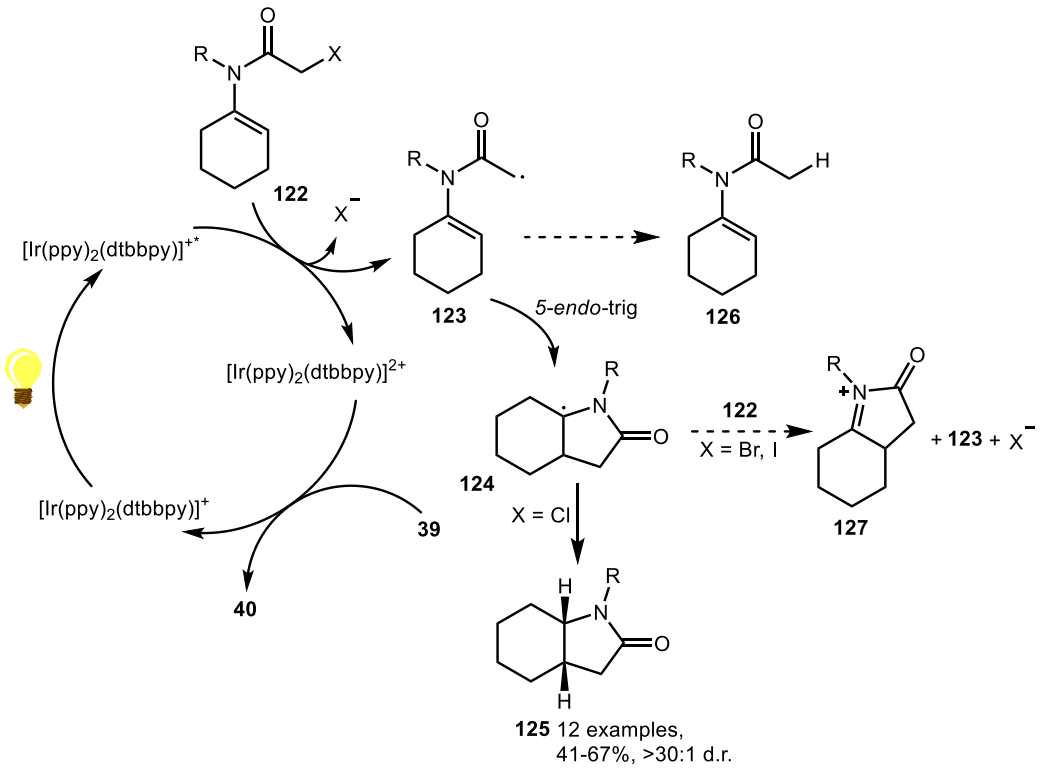
the nucleophile acting as Lewis acid. The benzylic radical intermediate **119** is oxidised in a second SET event thereby recovering the photocatalyst in its ground state. Oxygen-based nucleophiles like H_2O or simple alcohols were used to give benzyl alcohol or benzyl ether derivatives as products **121**. Low yields were observed with electron-deficient styrenes presumably due to destabilisation of the benzylic cation. On the other hand, particularly electron-rich examples were not reported and might have undergone significant polymerisation, instead.



Scheme 1.27. Photoredox-catalysed oxyalkylation of styrenes.[108]

Electron-withdrawing substituents allow the generation of sp^3-hybridised carbon-centred radicals from other types of precursors, most importantly alkyl halides. Stephenson, for instance, exploited alkyl bromides with electron-withdrawing substituents in his dehalogenation procedure,[55] and the group quickly realised that the same system can be employed to build higher complexity in intramolecular cyclisations.[109] More recently, the Rueping group presented a related method to prepare γ-lactams **125** from α-halo enamides **122** (Scheme 1.28).[110] Interestingly, the group obtained *5-endo*-trig products that are considered disfavoured.[111] When

examining methods to minimise direct reduction (to enamide **126**), it was noticed that the bromo- and iodo-based precursors **122** (X = Br, I) can react with the cyclised α-nitrogen radical **124** thus outcompeting hydrogen abstraction. The target products **125** were afforded in higher yields with α-chloro enamides **122** (X = Cl) that were inert to reactions with intermediate **124**.

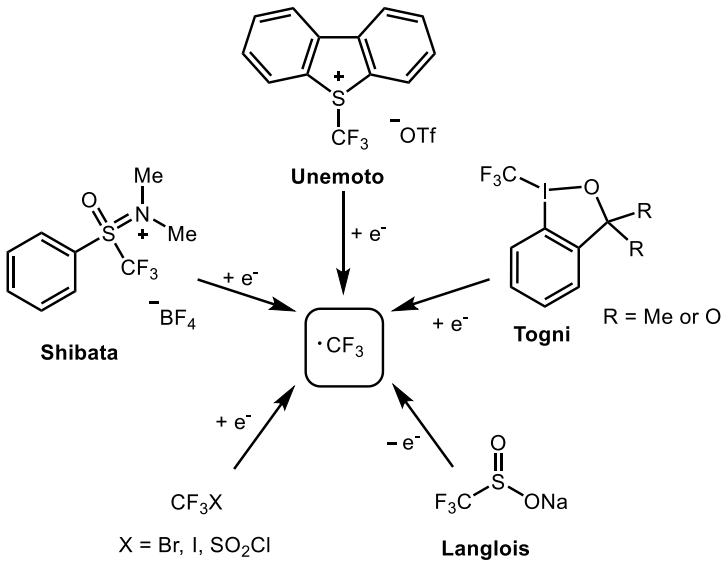


Scheme 1.28. Photoredox-catalysed 5-*endo*-trig cyclisation of α-halo enamides.[110]

Other procedures report the net addition of alkyl halides via photoredox catalysis.[64,112] These ATRA reactions are amenable to reactions with a range of different unactivated alkenes in the absence of basic additives. Notably, the C–X bond in the product is not susceptible to single electron reduction as a result of the adjacent electron-donating groups.

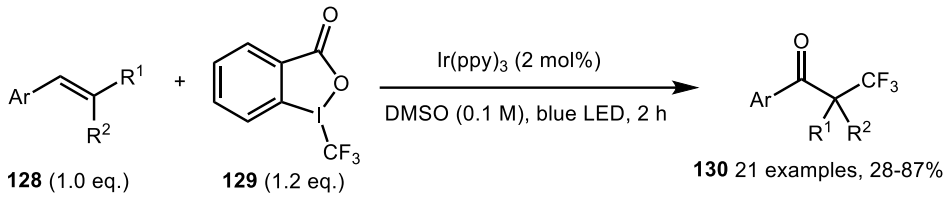
1.5.2 Fluorinated Carbon-centred Radicals

Fluorinated carbon-centred radicals are a special class of sp^3-hybridised carbon-centred radicals that deserve to be discussed separately. With the rising interest in fluorinated molecules based on their exceptional biology activities as pharmaceutical drugs, new methods to incorporate fluorinated moieties are highly desired.[113] The trifluoromethyl radical $\cdot CF_3$, perfluoroalkyl radicals $\cdot C_nF_{2n+1}$ as well as related, less fluorinated derivatives $\cdot CF_2R$ and $\cdot CFR_2$ have become routinely used tools in synthesising such products.[114–116] Typical precursors include the corresponding bromide or iodide compounds, which yield the desired radical by single electron reduction of C–Br and C–I bonds, respectively, along with the anionic halide. However, as mentioned above, the reaction outcome can be disappointing if radical intermediates, precursors and/or halides engage in unwelcome side-reactions. For this reason, many different precursors have been presented, especially for the trifluoromethyl radical $\cdot CF_3$ (Scheme 1.29). Typical precursors like Unemoto's reagent or Togni's reagents fragment to the target radical upon single electron reduction, while Langlois reagent requires single electron oxidation to initiate the precursor collapse.



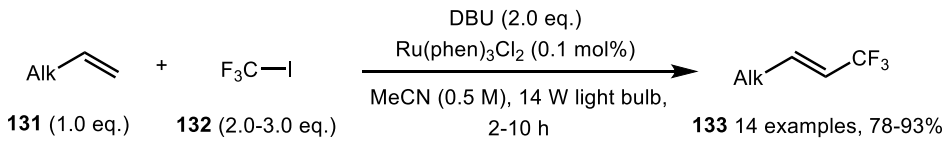
Scheme 1.29. Common precursors for the trifluoromethyl radical in photoredox catalysis.

Fluorinated carbon-centred radicals are highly electrophilic due to the strong σ-inductive effect exerted by the fluorine atoms, and therefore naturally add to unactivated alkenes or styrene derivatives. The carbon-centred radicals that arise after trifluoromethyl radical addition can undergo a variety of transformations. The Akita group presented a keto-trifluoromethylation procedure of styrene derivatives **128** using Togni reagent **129** (Scheme 1.30).[117] Similar to the conversions discussed above (Scheme 1.26B), the introduced oxygen atom stems from DMSO as solvent. Trifluorormethylated styrene-derivatives formed via a radical addition-elimination sequence were observed as the main by-products.



Scheme 1.30. Keto-trifluoromethylation of styrene derivatives.[117]

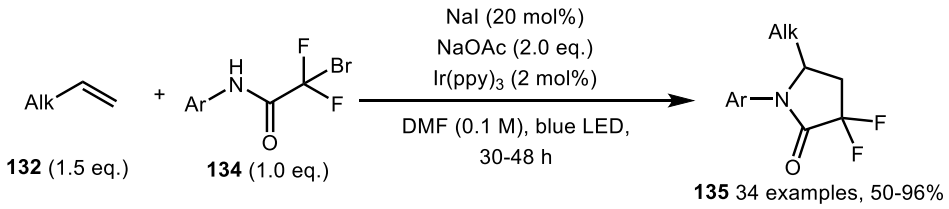
Cho and co-workers reported the trifluoromethylation of unactivated alkenes to synthesise trifluoromethylalkenes via an addition-elimination mechanism (Scheme 1.31).[118] However, ATRA products could also be prepared under slightly diverging conditions with a weaker base. Elimination products **133** were obtained with high *trans*-selectivity due to *anti*-periplanar elimination of HI assisted by the base. When exposing reaction products **133** to reaction conditions, no reaction was observed, thereby highlighting the selective reaction of the trifluoromethyl radical with unactivated alkenes **131**. It was also shown that cyclisations, ring openings or rearrangements to a more stable radical/cation can occur before final elimination takes place.



Scheme 1.31. Synthesis of trifluoromethylalkenes reported by Cho.[118]

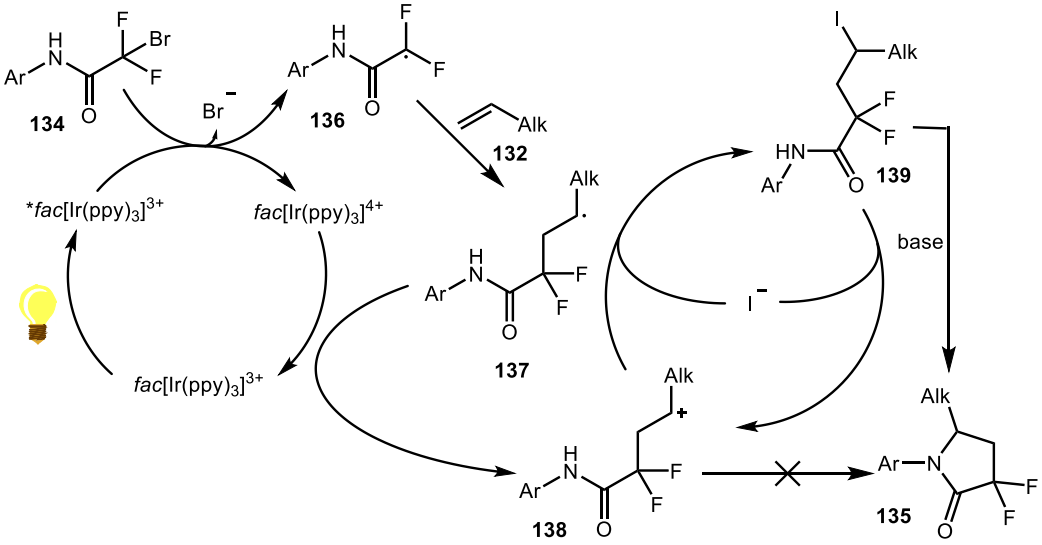
Difluoroalkylation with $\cdot CF_2R$ radicals is often accomplished by single electron reduction of bromo difluoroacetates (R = CO_2Et).[119] Procedures yielding ATRA products or the corresponding addition-elimination products are common due to the ability of bromide to act both as nucleophile and leaving group. Product mixtures can arise if the cation intermediate is to react with other nucleophiles. This process can be avoided if intramolecular nucleophiles are installed, or the radical is intercepted by a suitable trapping agent.

The Zhu group developed an elegant method to prepare difluoro-γ-lactams with styrene substrates **114** employing a bromodifluoroacetate **134** tethered with an unprotected nitrogen (Scheme 1.32).[120]



Scheme 1.32. Synthesis of difluoro-γ-lactams reported by Zhu.[120]

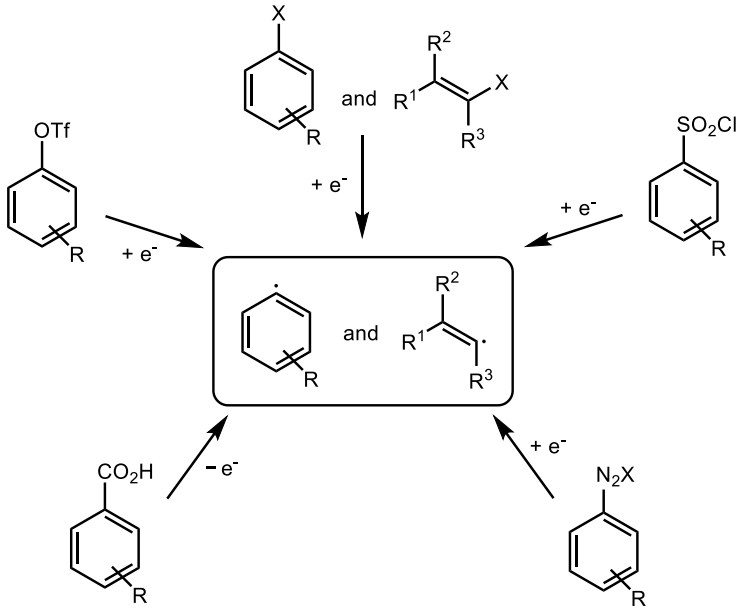
Nonetheless, the cyclised product was not formed directly, and an iodide source was required as nucleophilic catalyst, as shown in the suggested mechanism (Scheme 1.33). It was proposed that only the iodine-containing intermediate **139** could perform the crucial cyclisation step, not the benzylic cabocation **138**. The lack of iodide in the reaction mixture prevented product formation resulting in a complex mixture, in which no lactam product **135** could not be identified.



Scheme 1.33. Proposed mechanism of the synthesis of difluoro-γ-lactams reported by Zhu.[120]

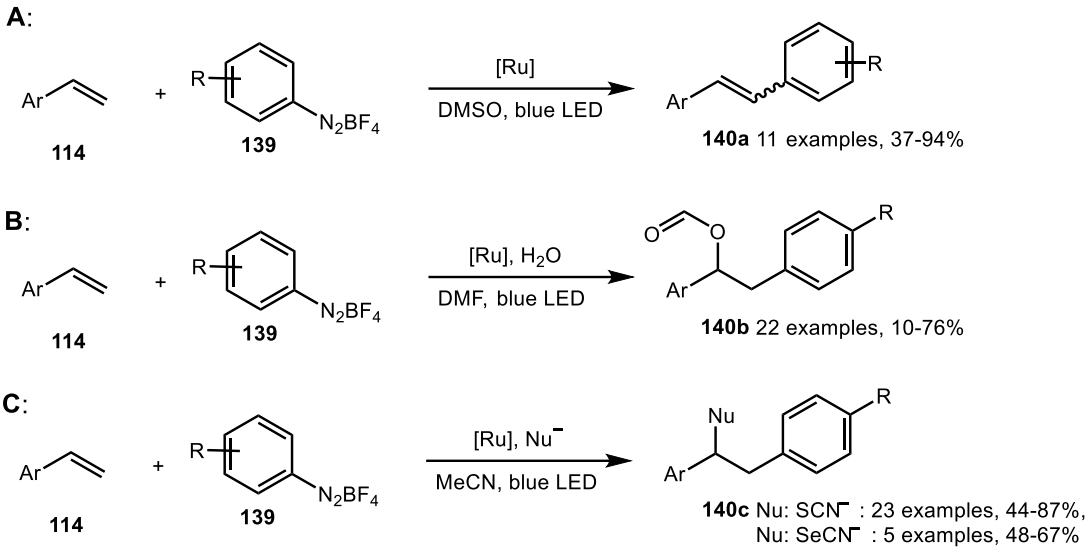
1.5.3 Carbon (sp^2)-centred Radicals

(Hetero-)Aryl radicals are popular building blocks to construct new C(sp^2)–C(sp^3) bonds in addition reactions to alkenes.[121] They can be accessed from diazonium salts,[121] aryl sulfonyl chlorides,[122] aryl halides,[123] aryl triflates,[124] and aryl carboxylic acids.[125] Vinyl radicals form the same type of bond and often stem from a vinyl halide precursor (Scheme 1.34).[126] In contrast to aryl radicals, vinyl radicals have proven more elusive in intermolecular additions to alkenes due to lower radical stabilities. They possess high reduction potentials, which makes direct reduction a common observation in bimolecular reactions.[127] Thus, only a few examples have been presented in which vinyl radicals added to alkenes outside the scope of intramolecular cyclisations.[128–130] Vinyl radicals, however, are relevant as they are the species formed upon radical addition reactions to alkynes.



Scheme 1.34. Precursors for (sp^2)-hybridised carbon-centred radicals.

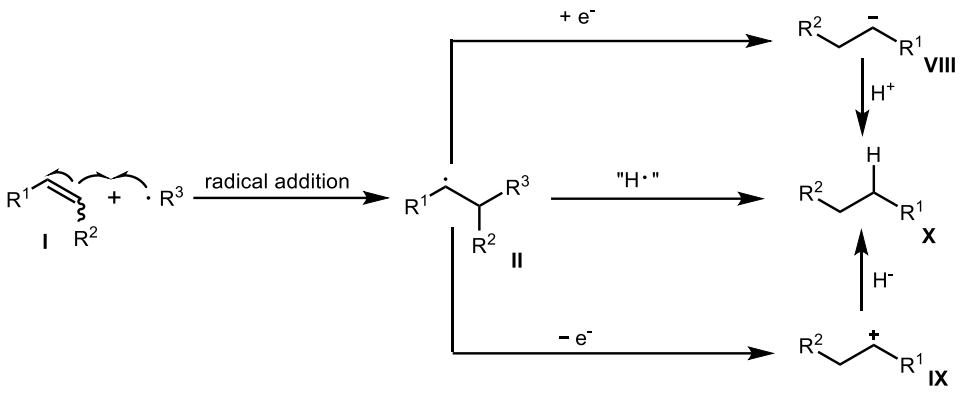
The C(sp^2)-hybridisation makes aryl and vinyl radicals electrophilic. In addition reactions to alkenes, aryl radicals have been shown to react with activated and non-activated alkenes. To illustrate this, König and co-workers developed the synthesis of stilbenes **140a** employing diazonium salts as aryl radical precursors **139** (Scheme 1.35A).[131] The mechanism proceeds via a benzylic carbocation that eliminates a proton to furnish the addition-elimination product in the absence of any nucleophile. Alternatively, the reaction led to formyloxylation products **140b** if a DMF/H_2O mixture was used as reaction medium (Scheme 1.35B).[132] The Maity lab independently explored further the possibility of trapping the benzylic cation with various nucleophiles such as thiocyanate and selenocyanate to generate difunctionalised products **140c** (Scheme 1.35C).[133] Lower yields were obtained with sterically more demanding *ortho*-substituted aryl radicals, which is in agreement with other reports using this class of radicals.[134,135]



Scheme 1.35. Aryl radical in various reactions with styrene substrates.[131–133]

1.6 Photoredox-catalysed *anti*-Markovnikov Hydrofunctionalisation of Alkenes Involving Carbon-centred Radicals

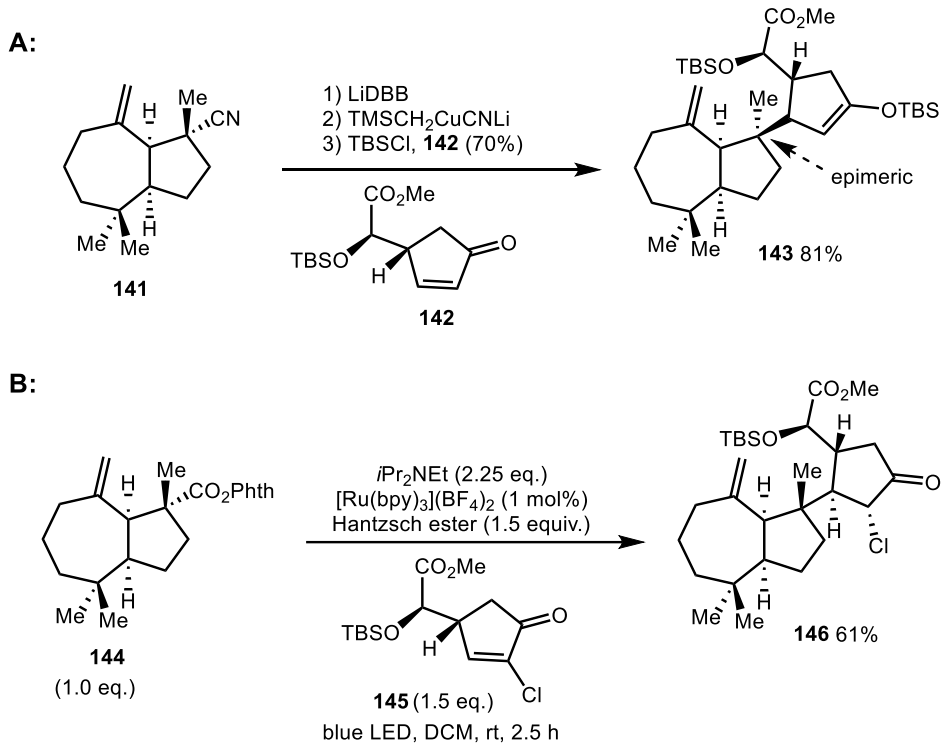
The hydrofunctionalisation of alkenes by means of initial radical addition of carbon-centred radicals affords *anti*-Markovnikov products. The reaction between electron-deficient alkenes and nucleophilic radicals is often called Giese reaction, after the chemist who spent much of his research studying radical additions to alkenes.[13]. Giese reactions were particularly common in the era of tin hydride chemistry as the terminal hydrogenation by tin hydride would be rapid. Due to the advances in photoredox catalysis, a manifold of procedures has been developed to achieve hydrofunctionalisation under mild conditions by (1) trapping the carbon-centred radical **II** with a hydrogen atom donor or (2) by trapping the ionic species after reduction or oxidation with a suitable proton or hydride source (Scheme 1.36). Notably, hydroalkylation methods promoted by transition metals that commence with hydrogen donation to the π-system give Markovnikov products and are equally important in modern organic chemistry but will not be discussed here any further.[136–138]



Scheme 1.36. Strategies to achieve radical hydrofunctionalisation.

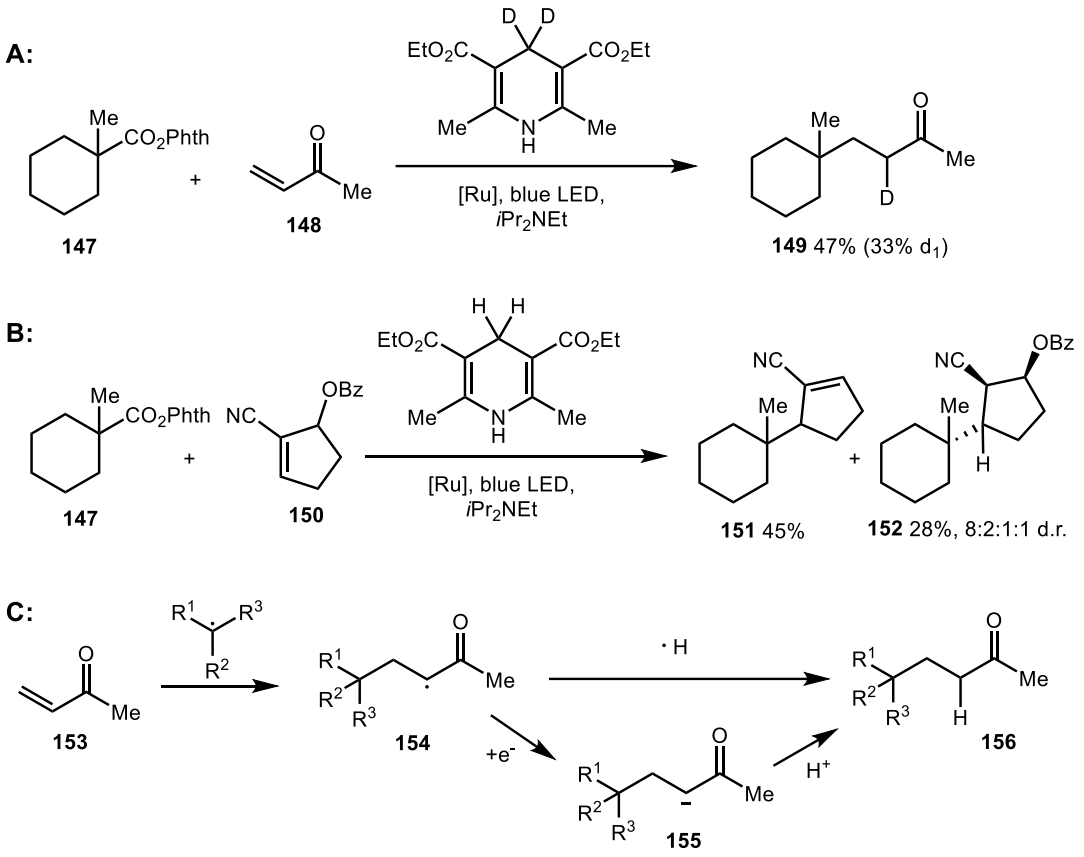
1.6.1 Radical *anti*-Markovnikov Hydroalkylation

In the previous section, the hydroalkylation reported by Okuda has already been presented as an important example. In this case, the radical adduct **II** was converted to the final product by hydrogen abstraction from BNAH. The Overman lab revisited Okuda's fundamental work after initial attempts for the total synthesis of (–)-aplyviolene disappointingly led to epimerisation at a quaternary centre of intermediate **143** (Scheme 1.37A).[139] Looking for alternative approaches to form the key C–C bond stereoselectively, the group considered a radical approach and identified the phthalimide ester adduct **144** as a potential precursor.[140] Indeed, by modifying the reaction conditions slightly, the reaction of the primarily formed tertiary radical and the enone coupling partner **145** proceeded in high stereoselectivity as the convex face of the bicyclic radical was considerably less hindered (Scheme 1.37B). Hantzsch ester was employed as a cheap, non-toxic hydrogen atom donor.



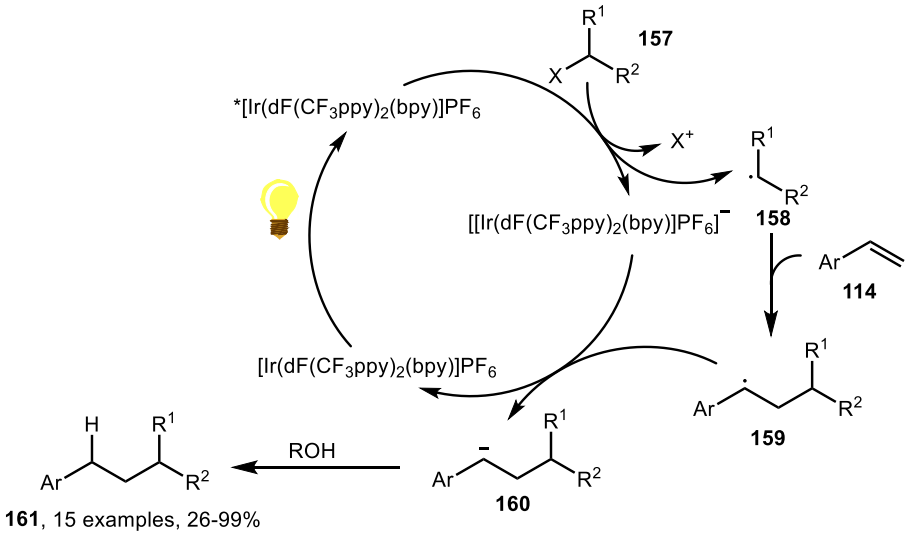
Scheme 1.37. Preparation of a key intermediate in the total synthesis of (–)-aplyviolene via photocatalysed hydroalkylation of an activated alkene.[140]

Inspired by his success and the general interest in photocatalysis at the time, Overman elaborated further on the reaction of alkyl radicals with activated alkenes.[141] The group proposed two possible mechanisms via direct trapping of the radical or alternatively a sequence consisting of a reduction followed by protonation of the anion. Labelling experiments revealed that neither pathway was exclusive as deuterium incorporation by the hydrogen donor was partial (Scheme 1.38A). Moreover, elimination products **151** were observed, which could only have been formed via a carbanion intermediate (Scheme 1.38B). The group therefore depicted reduction of the radical intermediate **154** followed by protonation of anion **155** *and* hydrogen donation from to intermediate **154** as simultaneous processes leading to the hydroalkylation product **156** (Scheme 1.38C).



Scheme 1.38. Mechanistic investigations and final proposal of the hydrogenation step in the hydroalkylation of activated alkenes by Overman.[141]

Many research groups capitalised on Overman's and Okuda's findings and developed other methods to realise radical hydrofunctionalisation. The Hull group accomplished *anti*-Markovnikov hydroalkylation of styrene derivatives via a slightly different approach (Scheme 1.39).[142] Instead of phthalimide ester precursors, the group utilised organotrifluoroborate salts and carboxylic acids **157** to access alkyl radicals **158** upon single electron oxidation with highly oxidising excited *[Ir(dF(CF$_3$ppy)$_2$(bpy)]PF$_6$ ($E^{*III/II}$ = +1.32 vs. SCE).[143] Consequently, the carbon-centred radical **159** was reduced in the second SET event, thereby recovering the original Ir^{III}-species. The formed benzylic carbanion **160** was protonated with a phenol derivative that was inert to electron transfers throughout the reaction.



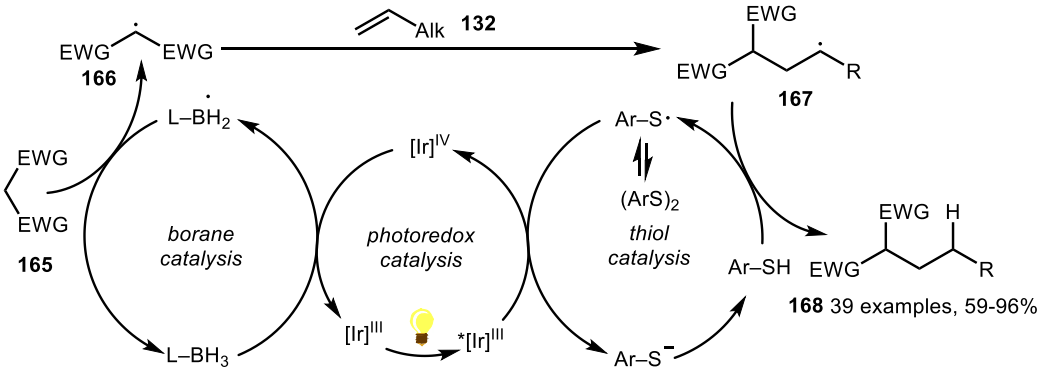
Scheme 1.39. Hydroalkylation of styrene derivatives reported by Hull.[142]

Interestingly, tertiary amines could also be oxidised under reaction conditions and afford α-amino radicals after deprotonation, yet the scope was restricted to tertiary amines and yields dropped as a result of over-oxidation of the products.[144] The group therefore employed α-TMS amines, which can be oxidised under milder conditions (arising from cation radical stabilisation by orbital overlap of the σ_{C-Si} and the half-filled p-orbital located at nitrogen)[145] in combination with a less oxidising photocatalyst. This procedure allowed Hull and co-workers to synthesise several pharmaceutical compounds containing a γ-aminoaryl substructure such as Phenpyramine in one step (Scheme 1.40).



Scheme 1.40. Hydroalkylation method to synthesis Phenpyramine.[142]

The Ye laboratory published a related hydroalkylation procedure with electron-rich sp^3-hybridised carbon-centred radicals.[146] The group was particularly interested in finding conditions that would favour HAT to the electron-rich carbon-centred radical and prevent oxidation to carbocations that would require terminal protonation. Furthermore, electron-rich carbon-centred radical was observed to react with thiols as hydrogen donors in undesired thiol-ene reactions.[147] A sophisticated mechanistic framework consisting of three intertwining catalytic cycles was presented to access target molecules **168** in high yields (Scheme 1.41).



Scheme 1.41. Hydroalkylation of unactivated alkenes reported by Ye.[146]

An amine-borane additive was employed to facilitate initial radical formation. A key feature was an attached hydroxy group on the borane, which held the reaction partner in proximity by hydrogen bonding to enable HAT. Density functional theory (DFT) calculations indicated that the same hydrogen bonding effect would play a pivotal role in activating the borane for oxidation by the photocatalyst (Figure 1.5).

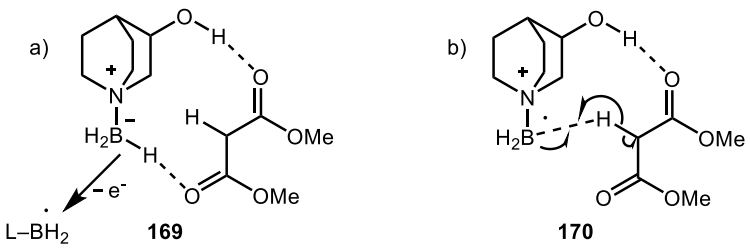
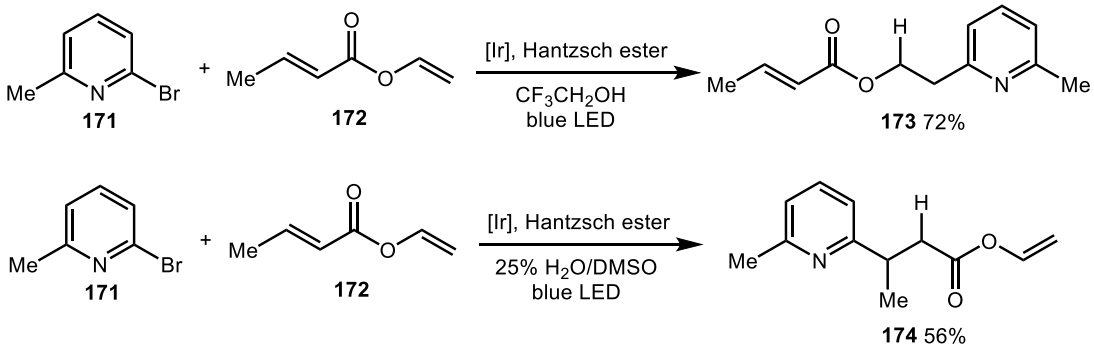


Figure 1.5. Key interactions between borane and substrate leading to mutual activation for a) oxidation and b) radical formation.[146]

1.6.2 Radical *anti*-Markovnikov Hydroarylation

The Jui group disclosed a hydroarylation procedure of unactivated alkenes using halopyridines **171** as radical precursors and Hantzsch ester as hydrogen atom source.[148] Interestingly, the group observed orthogonal chemoselectivity of the pyridyl radical depending on the reaction medium. The pyridyl radical preferably reacted with unactivated alkene moieties in 25% H_2O/DMSO as solvent, yet it selectively favoured the electron-deficient C=C bond of diene **172** in trifluoroethanol (TFE) as solvent (Scheme 1.42).



Scheme 1.42. Hydroarylation with pyridyl radicals and solvent-dependent electrophilicity.[149]

A supplement work was published seeking to gain a better understanding of this phenomenon.[149] Herein, the group employed substoichiometric amounts of cyclohexanethiol (CySH) in addition to Hantzsch ester (1.3 eq. relative to halopyridine) under revised conditions in order to increase the rate of HAT and minimise side-reactions of the radical intermediate with excess alkene substrate. The divergent reaction outcome was explained using a proton-coupled electron transfer (PCET) concept, thereby distinguishing between radical **175** and radical cation **176** (Figure 1.6).[150] TFE is a potent H-bond donor while also being poorly H-bond accepting;[151] however, meaningful protonation of the halopyridine (pK_a = 0.5 in DMSO) was not supported by a preliminary analysis of the pK_a values (TFE: pK_a = 12 in DMSO). On the basis of DFT calculations, the group proposed an intermediate lying between the neutral hydrogen-bonded substrate and fully protonated pyridinium salt

as reactive species that would collapse upon single electron reduction to an electrophilic, protonated pyridine radical.

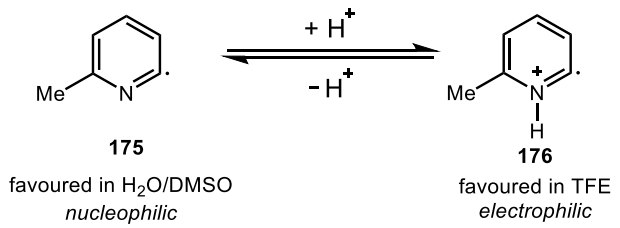
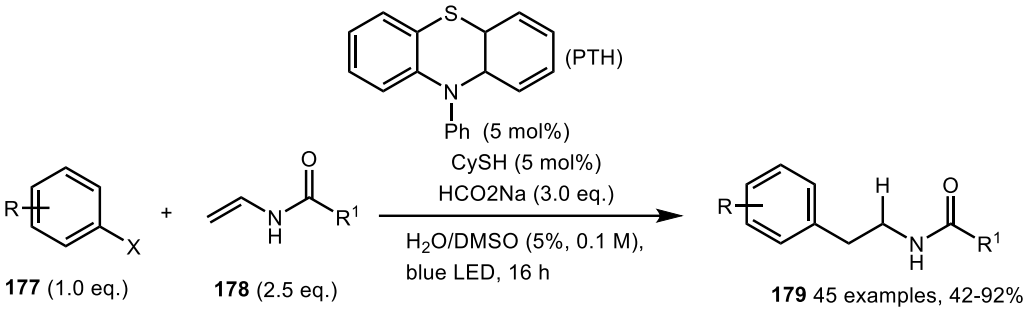


Figure 1.6. Solvent-dependent interconversion of pyridyl radical **175** and pyridyl radical cation **176**.

The effect of TFE could be overturned by addition of H_2O, which the group attributed to the possible dissociation of the proton form the pyridyl radical. When discussing the terminal hydrogen adoption step by the radical intermediate, Jui and co-workers outlined that hydrogen atom transfer is likely the predominant pathway referring to previous investigations by the group.[152,153] Further experimental support was given as deuterium incorporation by a deuterated hydrogen atom source was high, while side-products that would arise from carbocation intermediates were not observed.

Moreover, the group further developed the catalytic system to implement hydroarylations of enamine derivatives **178**.[154] *N*-Phenylphenothiazine (PTH) was employed as a strongly reducing photocatalyst and cyclohexanethiol as hydrogen atom source (no Hantzsch ester was added). It was crucial for the process to limit the hydrogen source to sub-stoichiometric amounts as otherwise direct hydrogenation of the (hetero-)aryl radical was problematic. Elegantly, a sacrificial formic acid salt was added to recover both the thiol via hydrogen donation and the photocatalyst in its original oxidation state by single electron reduction (Scheme 1.43).



Scheme 1.43. Hydroarylation of enamine derivatives.[154]

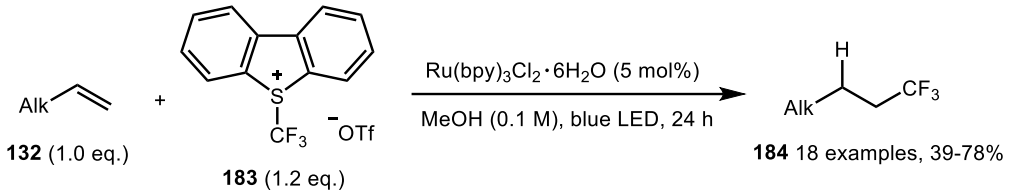
The utility of this hydroarylation method was proven in the two-step synthesis of Fluopyram, a fungicide whose patented route involves seven steps (Scheme 1.44).



Scheme 1.44. Synthesis of Fluopyram via radical *anti*-Markovnikov hydroarylation.[154]

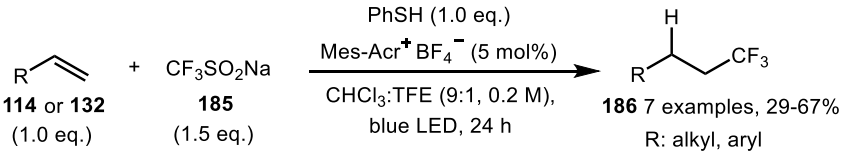
1.6.3 Radical *anti*-Markovnikov Hydroalkylation with Fluorinated Carbon-centred Radicals

The Gouverneur group presented a hydrotrifluoromethylation procedure of unactivated alkenes using Unemoto reagent **183** as trifluromethyl radical source (Scheme 1.45).[155] As hydrogen donor, the group firstly tested Hantzsch ester with limited success. Incomplete alkene conversions were observed and rationalised with premature radical trapping. The yield was significantly higher with methanol as solvent and weak hydrogen donor, which was confirmed in labelling experiments.



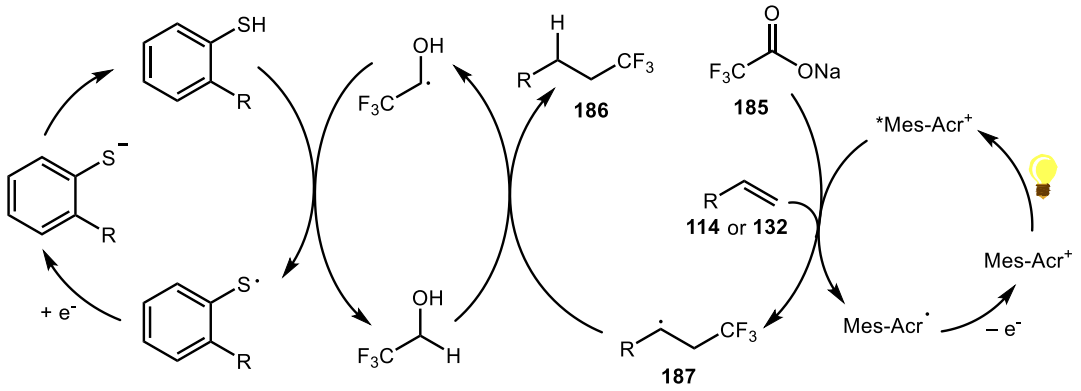
Scheme 1.45. *anti*-Markovnikov hydrotrifluoromethylation reported by Gouverneur.[155]

An alternative protocol to achieve hydrotrifluoromethylation of unactivated alkenes and styrene derivatives was reported by the Nicewicz group (Scheme 1.46).[156] The Langlois reagent **185** was used as radical precursor and its photochemical oxidation was facilitated by mesityl acridinium (Mes-Acr$^+$ BF_4^-).



Scheme 1.46. *anti*-Markovnikov hydrotrifluoromethylation reported by Nicewicz.[156]

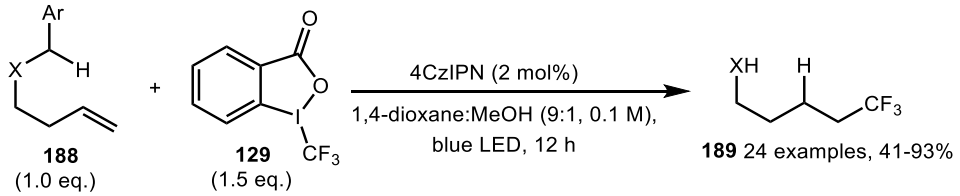
In contrast to the Gouverneur's procedure, in which hydrogen abstraction from methanol afforded the target product, Nicewicz and co-workers employed a thiol as hydrogen atom donor (Scheme 1.47). However, moderate product formation was observed in the absence of thiol hinting that it plays merely a supportive role. Meanwhile, the addition of TFE as co-solvent seemed essential as a lack thereof had detrimental impact on the product yield. The group therefore concluded, that TFE acted as hydrogen donor similar to methanol in the original Gouverneur protocol. The thiol could accelerate hydrogen donation in a separate HAT cycle as its S–H bond (BDE (thiophenol, S–H) = 79 kcal·mol^{-1}) undergoes homolytic cleavage quicker than TFE (BDE = 95 kcal·mol^{-1}).[157] The detection of trace amounts of oxidation products from TFE was described as circumstantial, supporting evidence for the formation of TFE radical, since the direct oxidation of TFE was ruled out.



Scheme 1.47. Proposed mechanistic framework in the hydrotrifluoromethylation reported by Nicewicz.[156]

1.6.4. Radical *anti*-Markovnikov Hydrofunctionalisation Using 1,5-HAT

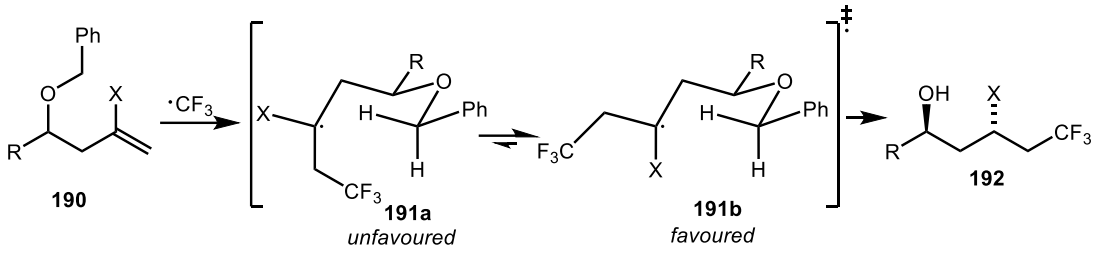
The trapping event of the carbon-centred radical intermediate can also occur in an intramolecular fashion via 1,5-HAT. This concept was applied to the hydrotrifluoromethylation of unactivated alkenes using photoredox-catalysis presented by Xu and Zhang.[158] The group employed Togni reagent **129** as precursor for the $\cdot CF_3$ radical and 4CzIPN as organic photocatalyst to obtain alcohol (X = O) and secondary amine (X = NR) products **189** (Scheme 1.48). Labelling experiments confirmed that the hydrogen originated form the alkyl tether.



Scheme 1.48. Hydrotrifluoromethylation of unactivated alkenes via 1,5-HAT reported by Xu and Zhang.[158]

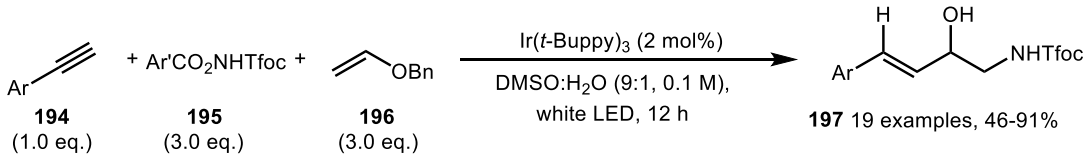
Interestingly, the researchers observed that the process is highly diastereoselective and rationalised this with the hydrogen transfer via a six-membered ring chair-like transition state (Scheme 1.49). The sterically more demanding group was thought to preferentially occupy pseudoequatorial position (**191b**) and the hydrogen shift would

thus take place via a well-defined radical intermediate. Reaction with methyl-substituted alkenes resulted in slight diastereomeric excess of the product (d.r. 3:2), presumably stemming from an insufficient difference in size between the methyl group and the 2,2,2-trifluoroethyl group. Oxidation to the oxonium ion followed by hydrolysis furnished the target product **192**.[159,160]



Scheme 1.49. Transition state model for 1,5-HAT with alkyl tether donors.

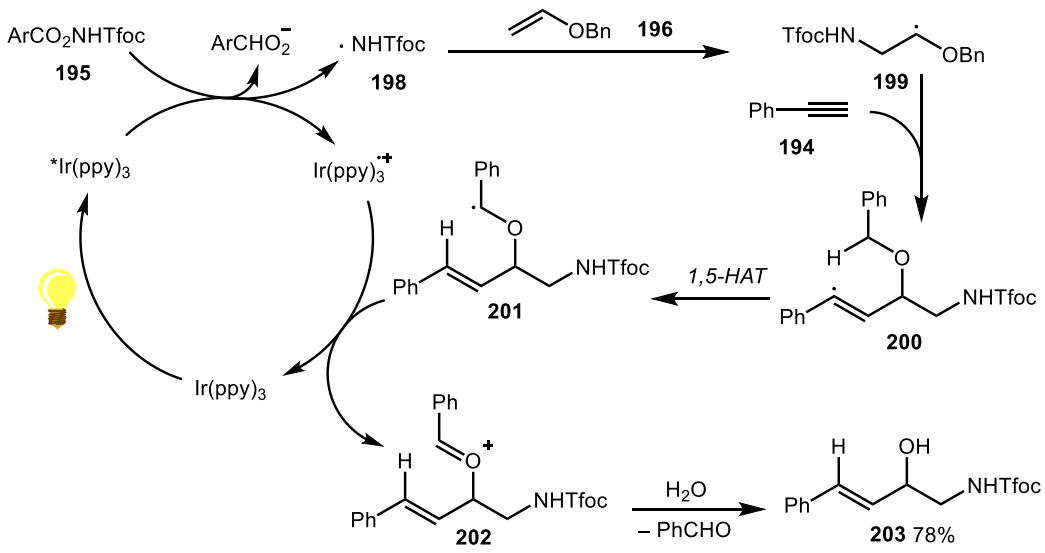
Yu and co-workers exploited the same sequence of radical addition-1,5 HAT to the *trans*-selective synthesis of styrene derivatives **197** from phenylacetylenes **194** (Scheme 1.50).[161] In this case, *O*-acyl hydroxy amines **195** were employed as precursors for nitrogen-centred radicals and benzyl vinyl ether **196** was added as a trap for the electrophilic radical.



Scheme 1.50. Synthesis of styrenes form phenylacetylenes via 1,5-HAT reported by Yu.[161]

It was proposed that the reaction of the nucleophilic radical intermediate **199** and the alkyne group of **194** brought forth a reactive vinyl radical **200** that underwent rapid 1,5-HAT to intermediate **201**. Single electron oxidation to oxonium ion **202** and final hydrolysis afforded β-aminoalcohols such as product **203** (Scheme 1.51). No further

hydrofunctionalisations with carbon-centred radicals based on 1,5-HAT are reported to date.

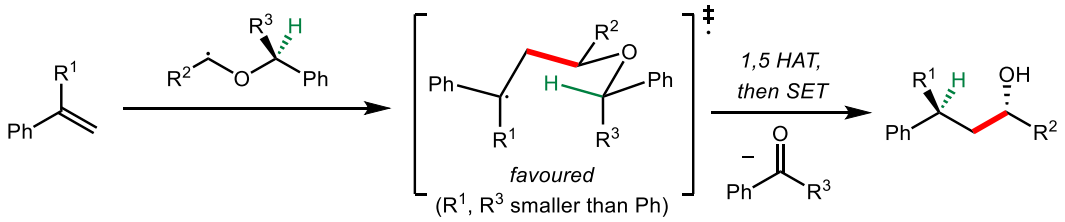


Scheme 1.51. Synthesis of styrenes form phenylacetylenes via 1,5-HAT by reported Yu.[161]

As the hydrofunctionalisation via 1,5-HAT represents an intriguing yet under-reported mechanistic scenario, and the concise formation of new C–C and C–H bonds from cheap and abundant chemical feedstocks represents one of the main goals in modern organic chemistry, we decided to develop a novel strategy to achieve hydroalkylations of styrene derivatives.

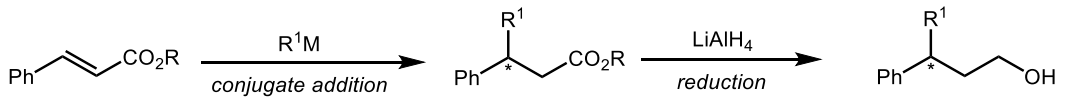
Chapter 2. Stereoselective Hydroalkylation of Styrenes

This work aimed to develop a one-pot hydroalkylation of styrenes using a 1,5-HAT pathway. We hypothesised that this process could be achieved by alkylation of a styrene with an alkyl radical generated from a redox-active phthalimide ester in a photoredox-catalysed reaction. The alkyl radical (as shown in Scheme 2.1) or the styrene would contain an ether protected alcohol which would act as a H-atom donor. Ultimately, this would lead to the stereoselective net addition of alcohols across a styrene C=C double bond with *anti*-Markovnikov regioselectivity. Furthermore, the influence of side chains attached to the alkyl group on product yield and stereoselectivity would be analysed.



Scheme 2.1 Proposed one-step hydrofunctionalisation.

This strategy represents a novel approach to obtain products with a 3-phenyl-1-propanol substructure. Alternative pathways to synthesise similar molecules generally proceed via conjugate additions to protected cinnamic acid derivatives. While these methods have been reported to give high product yields and excellent stereoselective control over the chiral centre at the benzylic position in the 1,4-addition step, the direct addition to the carbonyl group in order to install the substituent R^2 has not been reported yet (Scheme 2.2).[162,163] Instead, this technique has only been reported in the preparation of primary alcohols.



Scheme 2.2 Synthesis of products containing a 3-phenyl-1-propanol substructure via conjugate addition to cinnamic acid derivatives.

2.1 Attempts at a One-Pot Procedure

2.1.1 Preparation of a Suitable Styrene and Phthalimide Ester

The initial task was the preparation of a suitable pair of *N*-hydroxyphthalimide ester and a styrene substrate. At first, a reaction was designed in which the alkyl ether was attached to the styrene and not (as shown in Scheme 2.1) attached to the alkyl radical. 4-Benzyloxy-2-phenyl-1-butene **207** was chosen as a model substrate for the hydrofunctionalisation because the benzyl protecting group had been used as a hydrogen atom source in the literature.[164] The driving force facilitating this hydrogen atom transfer is the formation of a more stable C–H bond. While the benzylic C–H bond dissociation enthalpy in the substrate is approximately 86±1 kcal·mol^{-1}, the benzylic C–H bond in the product is slightly stronger at approximately 88±1 kcal·mol^{-1} (Figure 2.1).[165]

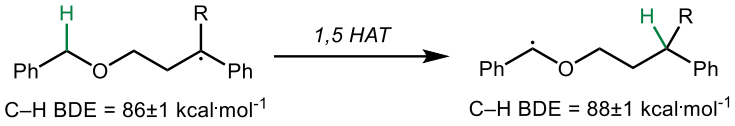
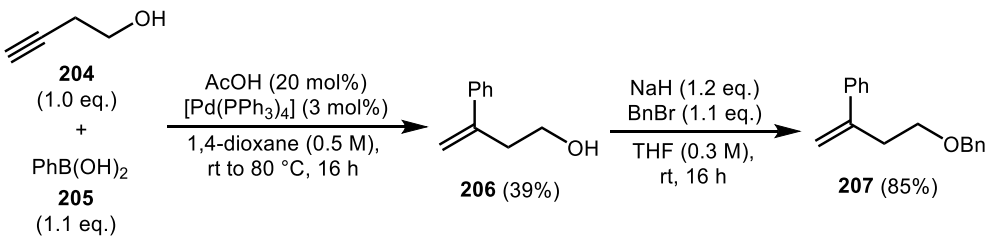


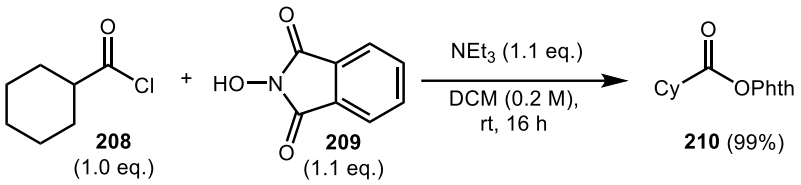
Figure 2.1. Formation of a more stable C–H bond as driving force.

The synthesis of 4-benzyloxy-2-phenyl-1-butene **207** was achieved in two steps. (Scheme 2.3). Following a procedure developed by Kim,[166] phenylboronic acid **205** was added to 3-butyn-1-ol **206** to obtain 3-phenyl-3-buten-1-ol **207** in moderate yield. The benzyl protecting group was then attached to the hydroxy group under standard *O*-alkylation conditions.



Scheme 2.3. Preparation of 4-benzyloxy-2-phenyl-1-butene **207**.

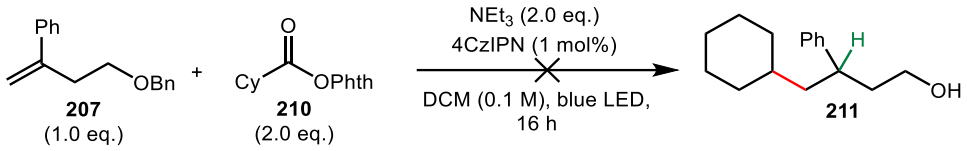
Meanwhile, a readily accessible phthalimide ester **210** was prepared from *N*-hydroxyphthalimide **209** and commercially available cyclohexanecarboxylic acid chloride **208** (Scheme 2.4).



Scheme 2.4. Preparation of 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate **210**.

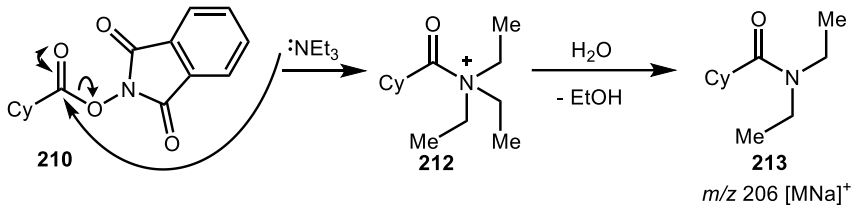
2.1.2 Initial Reactions

The one-pot hydrofunctionalisation of styrene **207** with phthalimide ester **210** was firstly attempted under conditions similar to those that had been used by Xu and Zhang in their hydrotrifluoromethylation procedure via 1,5-HAT using 4CzIPN as organic photocatalyst.[158] We choose NEt_3 as base, and DCM as a solvent since similar conditions were employed by the Overman group in a hydroalkylation procedure with alkyl radicals derived from phthalimide esters (Scheme 2.5).[141]



Scheme 2.5. Unsuccessful initial hydroalkylation.

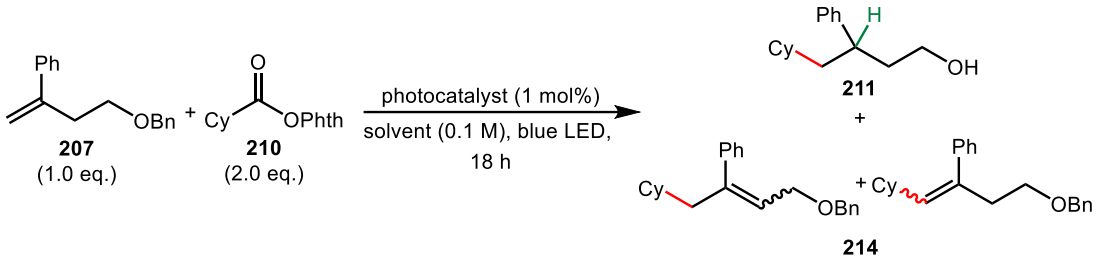
Unfortunately, no radical addition to the styrene C=C double bond was observed under these conditions. Instead, NEt_3 reacted with the phthalimide ester in a nucleophilic attack. The resulting amide product **213**, presumably formed after hydrolysis during the aqueous work-up,[167] was detected by NMR spectroscopy and mass spectrometry (Scheme 2.6). This was surprising because in the hydroalkylation of electron-deficient alkenes reported by Overman and co-workers, structurally similar Hünig's base (iPr$_2$NEt) was successfully used without attacking the phthalimide ester.[141] We did not test whether Hünig's base would behave differently than NEt_3 in our reaction.



Scheme 2.6. Formation of amide **213**.

The reaction was tested without base and with $Ir(ppy)_3$ as a photocatalyst; however, no reaction was observed in DCM.[168] We then commenced a solvent screening with 4CzIPN, $Ir(ppy)_3$, and $Ru(bpy)_3Cl_2$ photocatalysts in several solvents commonly used for radical reactions (Table 2.1).

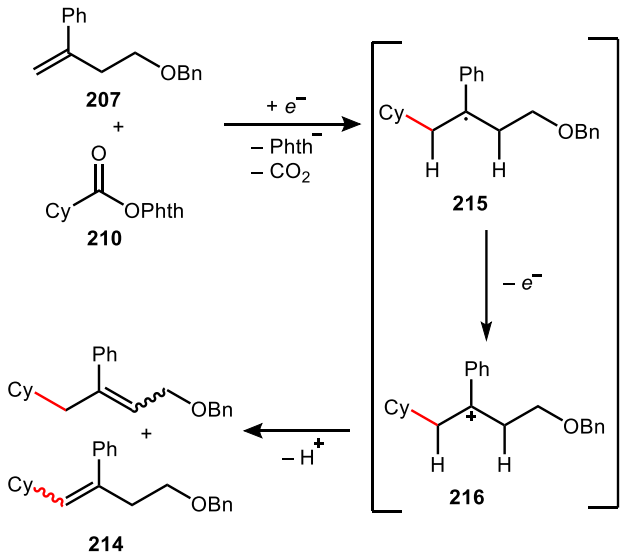
Table 2.1. One-pot hydrofunctionalisation (1): Photocatalyst and solvent.



Entry	Photocatalyst	Solvent	Product (Yield)
1	$Ir(ppy)_3$	DMSO	**214** (~10%)[a]
2	$Ir(ppy)_3$	DMF	**214** (~10%)[a]
3	$Ir(ppy)_3$	DMA	**214** (25%)[b]
4	4CzIPN	DMSO	No reaction
5	4CzIPN	DMF	No reaction
6	4CzIPN	DMA	**214** (~10%)[a]
7	$Ru(bpy)_3Cl_2$	DMSO	No reaction
8	$Ru(bpy)_3Cl_2$	DMF	No reaction
9	$Ru(bpy)_3Cl_2$	DMA	No reaction

[a]Yield determined by ^1H NMR spectroscopy using 1,3-benzodioxole as an internal standard. [b]Isolated yield.

The reactions with $Ir(ppy)_3$ (Table 2.1 entries 1-3) and the reaction with 4CzIPN in DMA (entry 6) afforded a mixture of elimination products **214**, albeit in low yield (Scheme 2.7). $Ru(bpy)_3Cl_2$ as photocatalyst seemed unsuited to reduce phthalimide ester **210**, and thus to generate the cyclohexyl radical (entries 7-9).

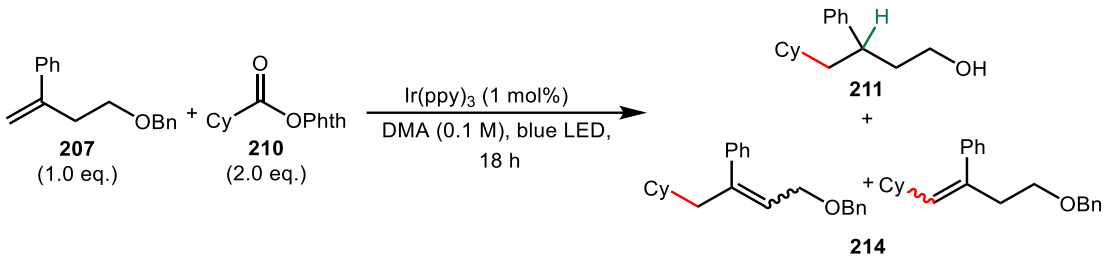


Scheme 2.7. Proposed mechanism for the formation of elimination products **214**.

In reactions with all three tested photocatalysts, activation of the phthalimide ester was clearly the main problem and unreacted substrates could mostly be recovered. This was again unexpected because the reaction of a phthalimide ester in DMSO with $Ir(ppy)_3$ (same conditions as in entry 1) had been demonstrated to give high yields of alkylation product.[169,170]

The addition of an acid to suppress elimination was then investigated. To test this hypothesis, *p*TSA was added to the reaction mixture in sub-stoichiometric and stoichiometric amounts (Table 2.2).

Table 2.2. One-pot hydrofunctionalisation (2): Influence of additive acid.



Entry	Additive	Eq. [Additive]	Product (Yield)
1	*p*TSA	0.02	**214** (25%)[a]
2	*p*TSA	1.00	**214** (35%)[a]

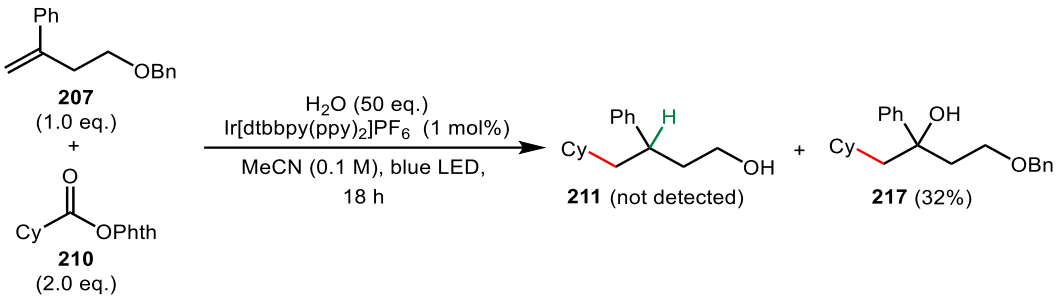
[a]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

The addition of *p*TSA (2 mol%) did not affect the reaction outcome significantly (Table 2.2, entry 1). Notably, the addition of stochiometric amounts of *p*TSA seemed to enhance both phthalimide activation (less unreacted phthalimide ester was seen in the ^{1}H NMR spectrum of the unpurified reaction mixture) and formation of elimination product (entry 2). This is in accordance with Ye's observations, who reported elimination reactions of benzylic cations in acidic medium (although this was seemingly not a requirement as elimination also took place in the absence of acid).[169]

2.1.3 Hydroalkylation via Oxyalkylation

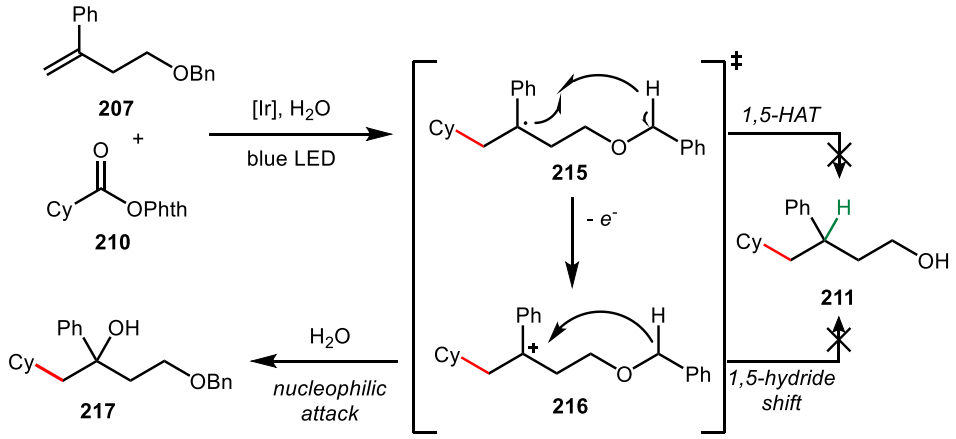
To solve the issue of incomplete fragmentation of radical precursor, our attention turned to the oxyalkylation reaction reported by Glorius and co-workers.[18] The group explored the activation mode of phthalimide esters in detail and postulated that slight electron-withdrawal, for instance by H-bonding with water or simple alcohols, is vital in order to activate phthalimide esters towards single electron reduction.

We initially attempted the model reaction using the conditions reported by Glorius anticipating that the intramolecular 1,5-HAT to target molecule **211** would outcompete intermolecular nucleophilic attack by water (Scheme 2.8).



Scheme 2.8. Oxyalkylation of 4-benzyloxy-2-phenyl-1-butene **207**.

Pleasingly, in the presence of water, phthalimide ester **210** fragmented completely and could not be detected in the unpurified reaction mixture. However, only oxyalkylation product **217** was isolated from the reaction, signalling oxidation of the benzylic radical intermediate and favoured nucleophilic attack of water rather than intramolecular hydride shift to the resulting carbocation (Scheme 2.9).

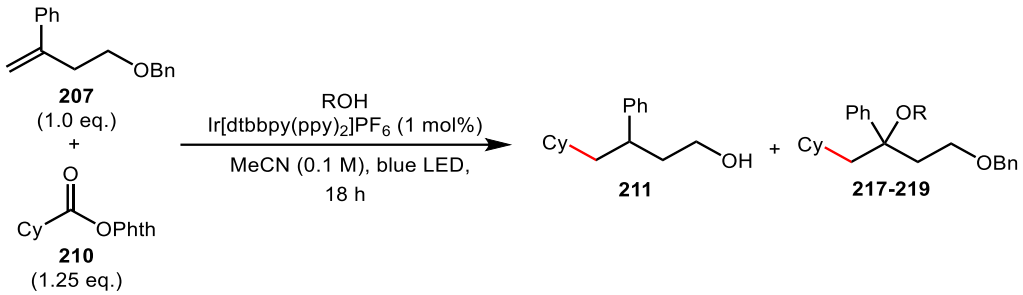


Scheme 2.9. Possible reactive pathway in the reaction of styrene **207** and phthalimide ester **210** in the presence of H_2O.

Further experiments were conducted with stochiometric and sub-stoichiometric amounts of water in an attempt to mitigate nucleophilic capture by water (Table 2.3). In the original protocol it was shown that simple alcohols can also be used but typically give lower product yields. Glorius and co-workers proposed that this would result from weaker H-bonds, and hence inadequate RAE activation. Additional steric hindrance was accredited for the low yield of the corresponding ether product with

i-PrOH (bulkier alcohols were not tested). In our desired hydrofunctionalisation this could be beneficial and enable hydride shift before nucleophilic attack by the bulky alcohol. We therefore set up two further reactions with methanol and *i*-PrOH as substitutes for water.

Table 2.3. One-pot hydrofunctionalisation (3): Modification of oxyalkylation procedure.



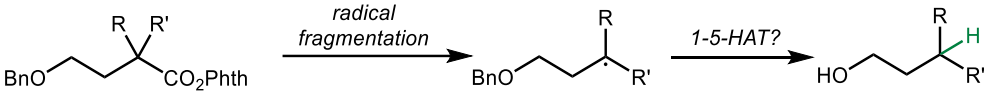
Entry	ROH	Eq. [ROH]	Product (Yield)[a]
1	H_2O	1	**217** (<5%)
2	H_2O	0.02	**217** (<5%)
3	MeOH	50	**218** (35%)
4	*i*-PrOH	50	**219** (<5%)

[a]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

Reactions with (sub-)stoichiometric water did not result in the formation of target molecule **211** (Table 2.3, entries 1, 2) and instead suffered from insufficient phthalimide ester activation. The reaction with MeOH (entry 3) led to the formation of methyl ether **218** but no deprotected alcohol **211** could be detected. In the reaction with *i*-PrOH (entry 4), only trace amounts of isopropyl ether **219** were observed by mass spectrometry (*m/z* 389 $[MNa]^+$) and unreacted phthalimide ester **210** could mainly be recovered.

2.2 Mechanistic Investigations of the 1,5-HAT step

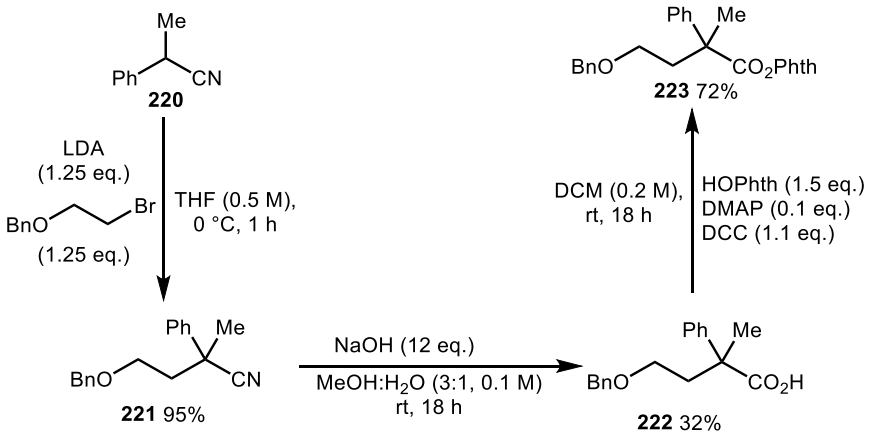
Intending to gain a better understanding of the proposed HAT step, we decided to access a carbon-centred radical as a suitable precursor for a 1,5-HAT process directly from a phthalimide ester rather than via addition of an alkyl radical to a styrene. This approach would allow the *in-situ* generation of non-benzylic carbon-centred radicals (R, R' ≠ Ph) and thus an appropriate comparison with benzylic carbon-centred radicals regarding consecutive reaction behaviour (Scheme 2.10).



Scheme 2.10. Intramolecular conversion of *O*-benzyl tethered phthalimide esters.

2.2.1 Synthesis of a Phthalimide Ester Precursor for a Benzylic Radical

Firstly, a precursor for a benzylic radical was prepared. This novel type of phthalimide ester required a new synthetic pathway. We chose α-methylphenylacetonitrile (**220**) as starting material and the initial instalment of the hydride/hydrogen donor tether was realised in the LDA-assisted alkylation with benzyl 2-bromo ethyl ether. The nitrile **221** was then hydrolysed and esterification of the resulting carboxylic acid **222** concluded the substrate preparation (Scheme 2.11).

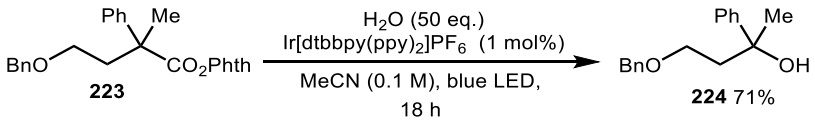


Scheme 2.11. Preparation of phthalimide ester **223**.

The initial alkylation proceeded well (95% yield); yet, the hydrolysis product was only obtained in low yield (32%). Nonetheless, an attempt at synthesising acid **222** via alkylation of the acid instead of the nitrile was incomplete, even with an excess of alkylating reagent (2.0 eq.) and led to an inseparable mixture of carboxylic acids. The hydrolysis of nitrile **221** under acidic conditions was likewise inferior to the shown conversion with hydroxide, and largely did not result in any conversion. As anticipated, the esterification of the acid substrate was successful in good yield (72%).

2.2.2 Reaction with Phthatlimide Ester 223

The phthalimide ester **223** was then subjected to identical conditions previously established as full fragmentation of the radical precursor herein was assured (Scheme 2.12). The presence of water required to activate the phthalimide ester, however, meant that the formation of a benzyl alcohol derivative was a possible scenario.



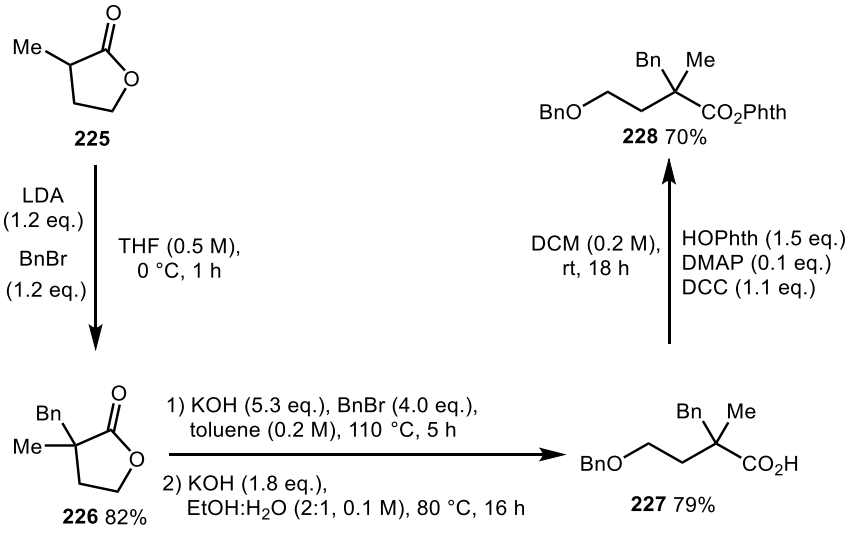
Scheme 2.12. Reaction of phthalimide ester **223** under the standard conditions.

The reaction of phthalimide ester **223** under the standard conditions afforded alcohol **224** in good yield (71%). Since trapping of the benzylic radical with water can be ruled out,[18] this product must be formed after single electron oxidation to the corresponding benzylic cation followed by nucleophilic attack of water.

2.2.3 Synthesis of a Phthalimide Ester Precursor for a *non*-Benzylic Radical

It was then tested if a non-benzylic radical intermediate would behave differently. To this end, phthalimide ester **231** was slightly modified by substituting the phenyl group for a benzyl group while keeping the rest of the molecule unchanged. We employed a new strategy to access the phthalimide ester with α-methyl-γ-butyrolactone (**225**) as starting material. The Petersen group reported the synthesis of benzyl-protected

γ-hydroxyacids from γ-butyrolactone in the presence of benzyl bromide under aqueous basic conditions.[171] We envisioned that lactone **225** could be alkylated with benzyl bromide to obtain the quaternary carbon-centre. Using Petersen's procedure, we then aimed to convert the cyclic lactone **226** into the open carboxylic acid **227** and successively into the phthalimide ester **228** in a three-step reaction sequence (Scheme 2.13).

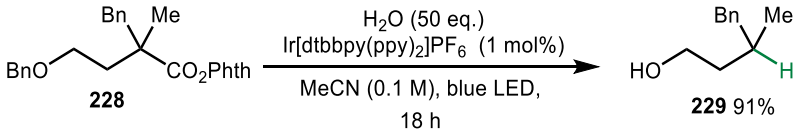


Scheme 2.13. Preparation of phthalimide ester **228**.

The preparation of phthalimide ester **228** proceeded well across all three steps with a yield of 45% over three steps.

2.2.4 Reaction with Phthatlimide Ester 228

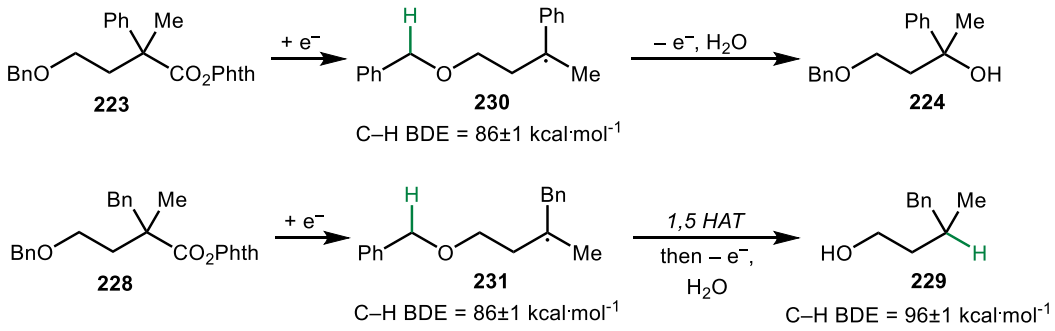
The phthalimide ester **228** was then examined as precursor for a non-benzylic carbon-centred radical under reaction conditions (Scheme 2.14).



Scheme 2.14. Reaction of phthalimide ester **228** under the standard conditions.

Interestingly, a non-benzylic phthalimide ester behaved differently and formed the primary alcohol **229** in excellent yield (91%). This process occurs presumably via 1,5-HAT, followed by oxidation of the benzylic radical and hydrolysis of the resulting oxonium ion. Labelling experiments with deuterium would help to provide further evidence for the benzyl group as the origin of the hydrogen at the tertiary centre.

The divergent reaction behaviour between phthalimide esters **223** and **228** can be rationalised with the difference of bond strengths in the products. Importantly, the fragmentation of phthalimide ester **228** leads to a non-benzylic, tertiary alkyl radical, while substrate **223** collapses to a benzylic, tertiary radical, instead. The C–H bond in product **229** is significantly stronger (96±1 kcal·mol^{-1}) and therefore a sufficient driving force to initiate the 1,5-HAT.[172] Phthalimide ester **223** on the other hand gives a benzylic radical similar to the radical species after radical addition to styrene substrate. Herein, the energy gain resulting from the 1,5-HAT step is not sufficient to initiate the target conversion and is subsequently outcompeted by oxidation and nucleophilic attack (Scheme 2.15).



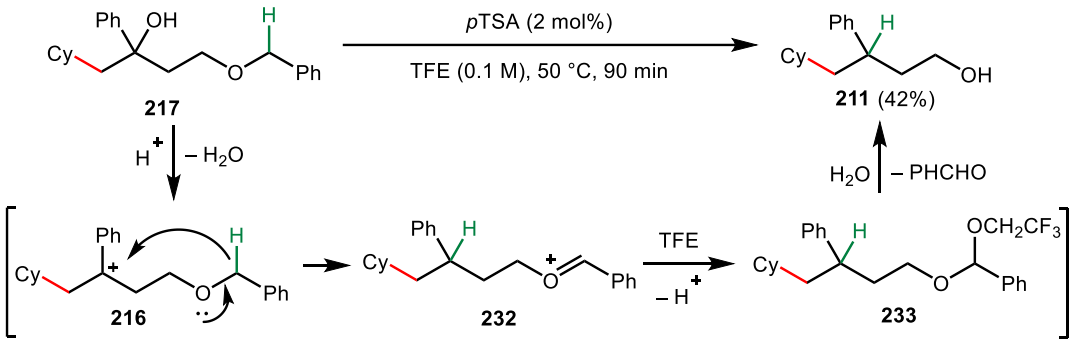
Scheme 2.15. Divergent reaction behaviour of alkyl radicals generated from phthalimide esters **223** and **228**.

At this stage we decided to focus on a two-step procedure by employing the obtained benzylic alcohol as a substrate hoping that a 1,5-hydride shift can be achieved under suitable conditions.

2.3 Two-Pot Hydrofunctionalisation

2.3.1 Initial Reactions

In an initial attempt, we tested alcohol **217** as precursors for an intramolecular 1,5-hydride transfer (Scheme 2.16). By employing this strategy, it would be possible to analyse both steps (radical addition and intramolecular 1,5-hydride transfer) individually and identify potential problems. We obtained the target molecule **211** in moderate yield (42%) after 90 min reaction time from the corresponding oxyalkylation product using conditions developed by Chiba and Gagosz.[160]



Scheme 2.16. Conversion of oxyalkylation product **217** into hydroalkylation product **211**.

In the reported protocol, complete conversions were achieved after 15 min, yet in the reaction with tertiary alcohol **217**, little conversion was shown by TLC after 15 min. This observation suggested that either protonation of the hydroxy group or 1,5-hydride transfer were hindered. Chiba and Gagosz conducted the screening only with methyl substituents at C-2 or linear alkyl chains, but no sterically demanding substituents such as -CH_2Cy were present in any of the reported examples. It seemed therefore likely that this group disfavoured the desired 1,5-HAT or 1,5-hydride transfer due to steric effects. The benzyl group could be prevented from approaching the reactive centre to the point where nucleophilic attack by water or MeOH molecules occurs at a much faster rate resulting in the formation of the oxyalkylation product (Figure 2.2).

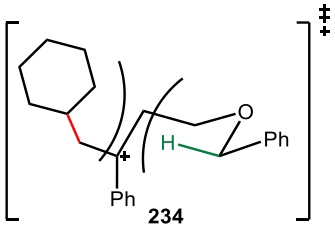
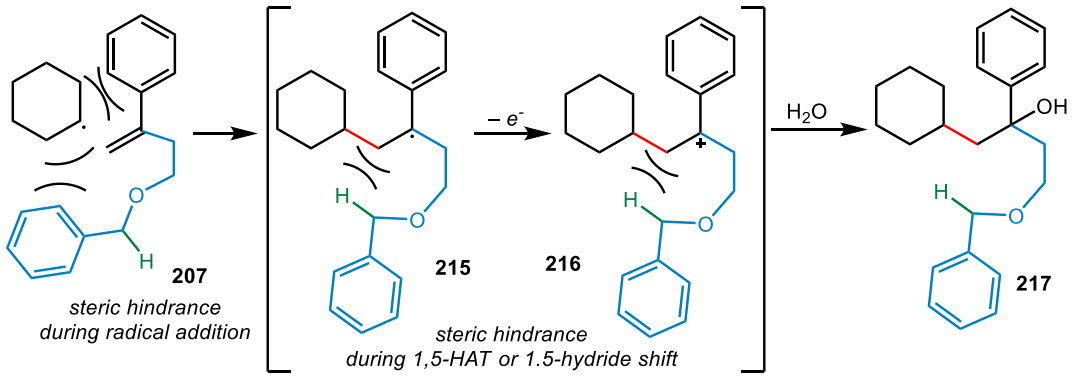


Figure 2.2. Proposed transition state of the 1,5-hydride transfer event.

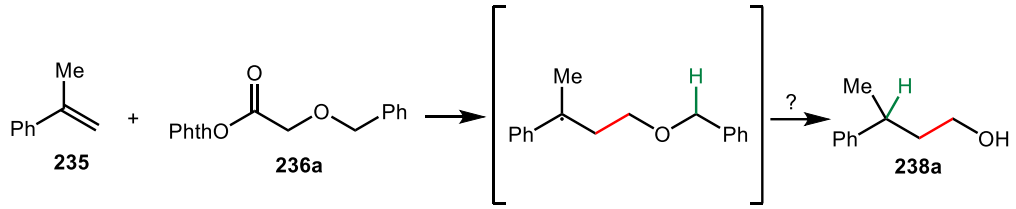
It should be noted that steric hindrance could also be a decisive factor in the radical addition step of the cyclohexyl radical to styrene **207**, thus giving a reasonable explanation for the low yields of oxyalkylation products even when full conversion of the radical precursor was achieved with 50.0 equivalents of water and methanol. Indeed, many known radical additions to styrenes are limited to α,β-unsubstituted styrenes, 1,1-diaryl styrenes or styrenes derivatives with methyl groups attached at the benzylic C-2 position and decreased yields are generally reported with bulkier substituents attached to the C=C double bond (highlighted in blue in Scheme 2.17).



Scheme 2.17. Possible steric hindrance preventing formation of hydroalkylation product.

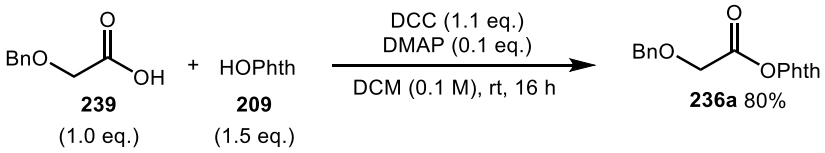
2.3.2 Reactions with an Alternate System

In order to circumvent these problems, we proposed an alternative model reaction, wherein the benzyl ether was incorporated into the radical and not into the styrene (Scheme 2.18). α-Methyl styrene **235** was chosen as substrate as it is known to undergo addition reactions with radicals and allows facile analysis by ^{1}H NMR spectroscopy.



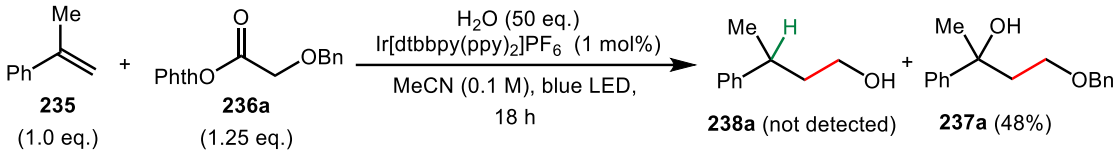
Scheme 2.18. Proposed hydroalkylation of α-methyl styrene **235**.

The corresponding phthalimide precursor **236a** has been used in several radical alkylation reactions,[173] and was prepared in one step from commercially available benzyloxyacetic acid (Scheme 2.19).



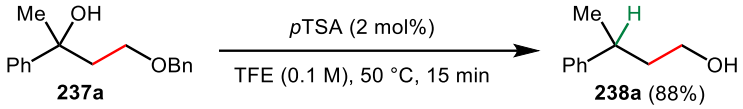
Scheme 2.19. Preparation of phthalimide ester **236a**.

The hydrofunctionalisation reaction with phthalimide ester **236a** was firstly attempted using original oxyalkylation conditions (Scheme 2.20).



Scheme 2.20. Oxyalkylation of α-methyl styrene **235**.

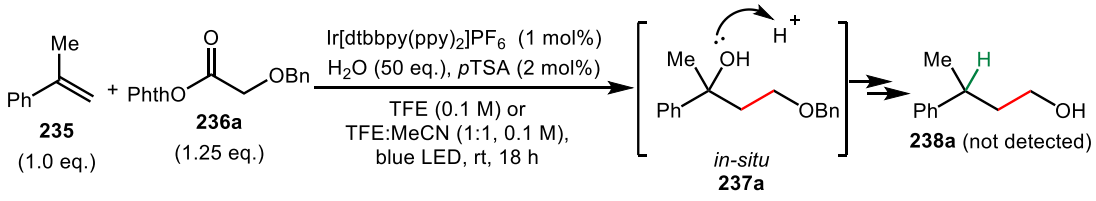
Unfortunately, the target molecule **238a** could not be detected. However, the oxyalkylation product **237a** was isolated in moderate yield (48%). Alcohol **237a** was then treated with *p*TSA in TFE in order to assess its ability to undergo 1,5-hydride shifts in the absence of water (Scheme 2.21).



Scheme 2.21. Conversion of oxyalkylation product **237a** to alcohol **238a**.

A high yield (88%) of target molecule **238a** could be obtained after 15 min reaction time suggesting that steric hindrance is not preventing the formation of a six-membered ring transition state.

In an attempt to achieve the target hydrofunctionalisation in one step, a reaction was designed, in which the required carbocation should be re-formed *in-situ*. Acid present in the reaction mixture should initiate protonation of the oxyalkylation intermediate and dehydration to the carbocation, which would then undergo the 1,5-hydride shift to give hydroalkylation product **238a**. Chiba and Gagosz reported that trifluoroethanol (TFE) plays a key role in the formation of the carbocation and stabilises the later-formed oxonium ion as the corresponding acetal. Therefore, pure TFE and a 1:1 mixture of MeCN:TFE were used as solvents (Scheme 2.22).



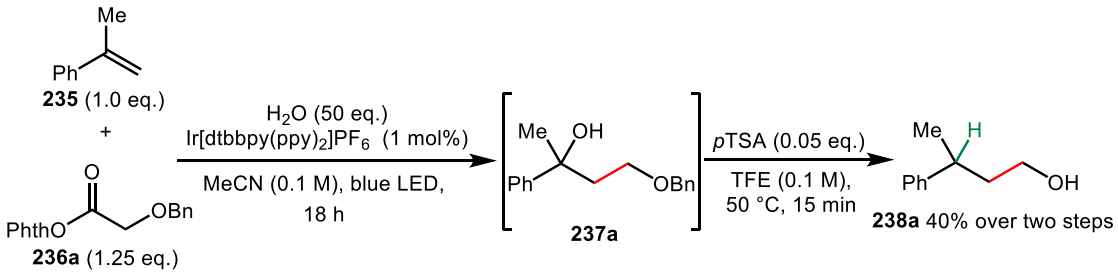
Scheme 2.22. Attempt to obtain alcohol **238a** *via in-situ* formation of oxyalkylation product **237a**.

Unfortunately, only complex mixtures were obtained in the test reactions, in which no target product could be detected.

2.3.3 A Simplified Purification Sequence

Since the reaction could not be realised in one step under any of the conditions tested, we sought to develop a two-step, one-pot sequence, as a complete purification of the intermediate would needlessly require a lot of time. Preliminary attempts at simply removing the solvent and exposing the unpurified reaction mixture to the second reaction step were feasible with regards to target product formation. However, the final hydroalkylation products could not be separated from the phthalimide by-product formed in the first reaction step via flash column chromatography.

Aiming to remove phthalimide from the oxyalkylation product without the need of chromatographic separation, we exploited the significant difference in polarities of phthalimide and the oxyalkylation intermediates. It was observed that evaporation of the reaction solvent (acetonitrile) followed by addition of (cyclo)hexane completely dissolved the oxyalkylation product. Trace amounts of phthalimide in this organic phase could be removed by extraction with water, 1 M aq. NaOH and brine. Analysis of the undissolved residue and the aqueous phase confirmed that no oxyalkylation product was lost in this purification sequence (Scheme 2.23). It is important to note that this purification process might not be applicable when working with more polar oxyalkylation products.



Scheme 2.23. Formation of oxyalkylation product and further reaction of crude product.

Using this technique, the hydroalkylation product could be obtained more rapidly and in similar yield (40% over two steps) compared to the two-pot process, in which the oxyalkylation intermediate was chromatographically purified (42% over two steps).

2.4 Hydrofunctionalisation via Diastereoselective 1,5-Hydride Transfer

With the established two-step, one-pot procedure in hand, our attention shifted towards exploring the possibilities of the hydroalkylation process. One of the key features of intramolecular 1,5-hydride shifts is the potential for control over the stereochemistry of the product arising from the six-membered ring transition state, as the bulkier substituents preferably occupy pseudoequatorial positions (Figure 2.3, only one disfavoured conformation shown). We envisioned that a suitable phthalimide ester could serve as a radical precursor that could be utilised to install a stereogenic centre into the oxyalkylation intermediate, and henceforth lead to diastereomeric products in the consecutive 1,5-hydride shift.

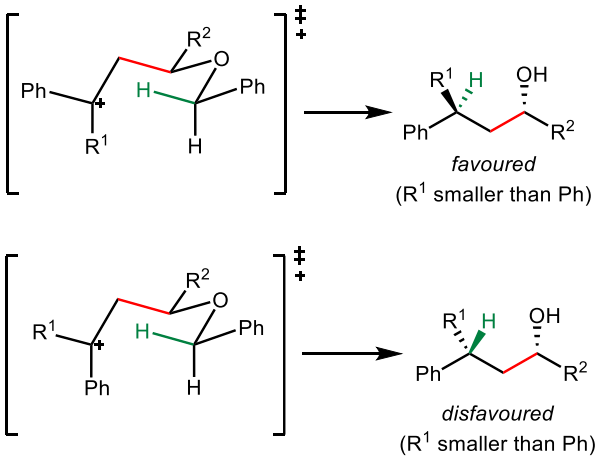
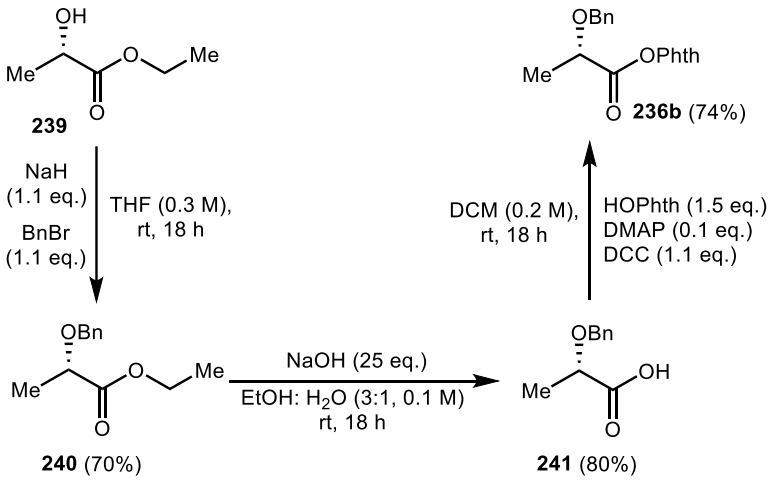


Figure 2.3. Diastereoselective 1,5-hydride shift.

2.4.1 Synthesis of a Phthalimide Ester Precursor for a Secondary Alkyl Radical

In the simplest case with R^2 = Me, we identified cheap and naturally abundant (*L*)-ethyl lactate (**239**) as a potential starting material that could be converted into the required phthalimide ester **236b** using the established reaction sequence consisting of *O*-alkylation, hydrolysis of the ester and DCC-promoted esterification with *N*-hydroxyphthalimide (Scheme 2.24).

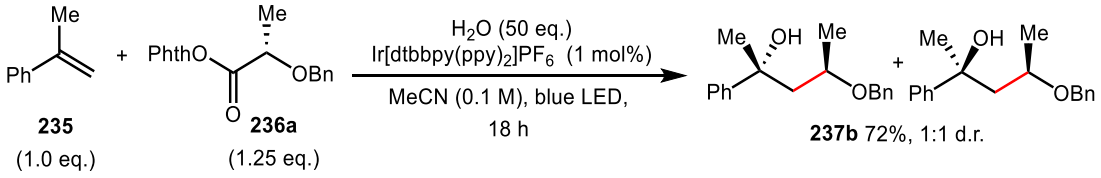


Scheme 2.24. Synthesis of phthalimide ester **236b**.

The preparation of phthalimide ester **236b** proceeded well in all three reaction steps (41% yield over three steps) and was then employed as radical precursor for a secondary alkyl radical.

2.4.2 Reaction with Phthalimide Ester 236b

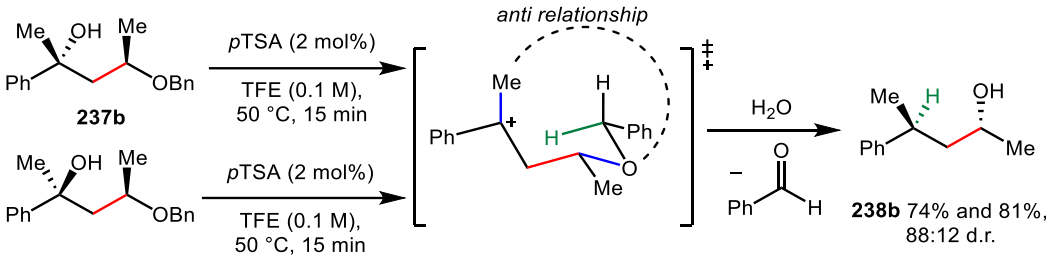
Phthalimide ester **236b** was initially tested in the oxyalkylation of α-methyl styrene **235** (Scheme 2.25). It was expected that the chiral information in radical precursor **236b** would not affect the radical addition and/or the 1,5-hydride transfer since the chiral centre is converted into a planar C-sp^2 free radical before reaction with the C=C bond occurs.



Scheme 2.25. Oxyalkylation with phthalimide ester **236b**.

The two possible diastereoisomers could be separated and were obtained in a 1:1 ratio (the same ratio was detected in the crude mixture of the unpurified reaction mixture). The isolated diastereoisomers were separately exposed to acidic conditions in TFE (Scheme 2.26). In this case, preferential formation of one diastereoisomers was

expected in the intramolecular transformation regardless of which diastereoisomer served as substrate. In the transition state, the methyl group at the carbocation was likely to occupy a pseudoaxial position, while the methyl group in α-position to the oxygen atom would prefer a pseudoequatorial position. As a result, a higher yield of the product displaying a 1,3-*anti*-relationship between the benzylic methyl group and the hydroxy group was anticipated.



Scheme 2.26. Diastereoselective 1,5-hydride transfer of substrates **237b**.

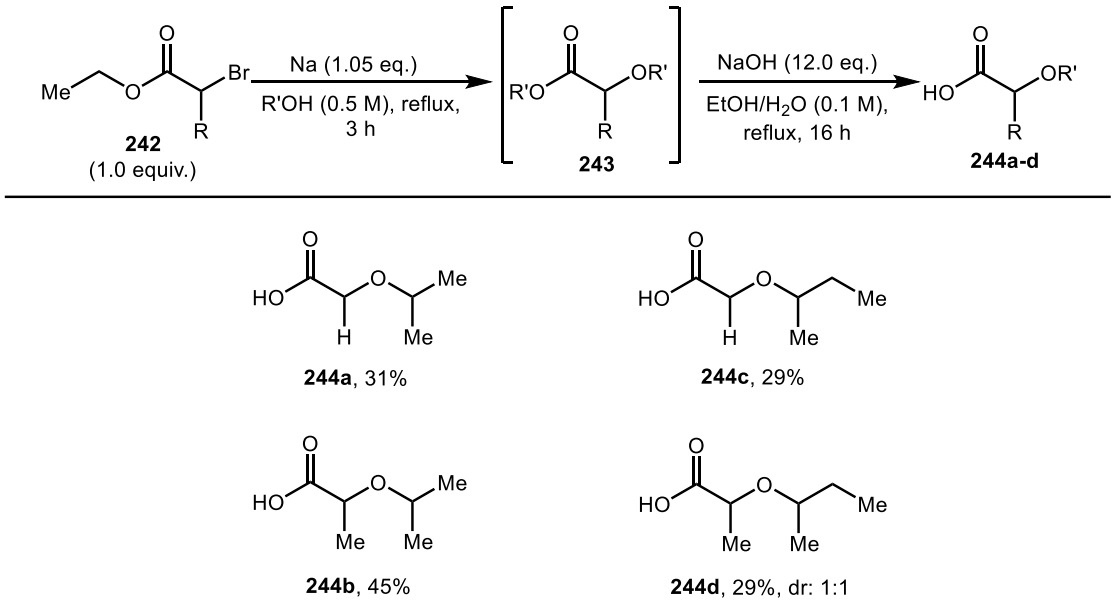
The target alcohol **238b** was obtained in high yield (74% and 81%) and 1,3-*anti*-diastereoselectivity. Both substrate diastereoisomers delivered identical diastereomeric ratios of 7:1 in the unpurified reaction mixture, yet the isolated yields varied slightly. Altogether, the products were isolated in 53% and 58% over two steps, respectively. The recorded data exactly match those reported in the literature thereby confirming the formation of the shown *anti*-diastereoisomer **238b**.[160] Moreover, the secondary alcohol product **238b** could be isolated in 60% yield by employing the purification sequence previously described to the crude mixture of diastereomeric oxyalkylation intermediates. It was encouraging to obtain significantly higher yields with secondary alkyl radical.

2.4.3 Screening of the Hydride Donor Moiety

It was obvious that the structure of the hydride donor unit would have a significant impact on the diastereoselectivity (see Scheme 2.26). In the publication by Chiba and Gagosz, various alkyl groups were reported to fulfil this role, although a benzyl group tended to perform best in terms of product yield and stereoselectivity.[174]

2.4.3.1 Synthesis of Different Phthalimide Ester

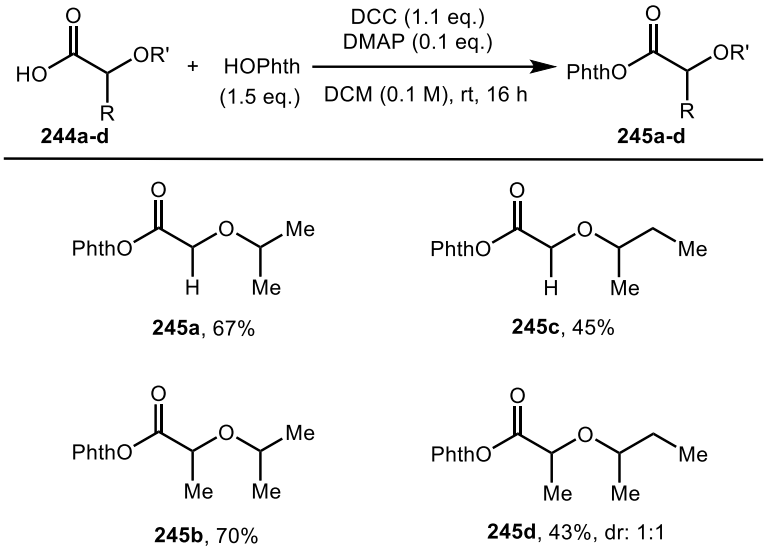
When contemplating a synthetic route towards potential phthalimide esters, we were forced to alter the established pathway (see Scheme 2.25) as non-benzylic/-α-keto alkyl halides are not electrophilic enough to engage with an alkoxide. Instead, we proposed the *O*-alkylation of bromoacetate derivatives (**242**) with simple alcohols. The Yeleswarapu group reported a two-step transformation of ethyl bromoacetate with sodium in isopropanol followed by hydrolysis of the ester to obtain the desired acid.[175] We envisioned that the reaction of ethyl-2-bromopropiante in different alcohols would yield the required acids **244b**,**d** with different hydride donor groups (Scheme 2.27). Furthermore, we decided to conduct *O*-alkylation of ethyl bromoacetate (leading to precursors for primary alkyl radicals) in order to compare the various hydride donors with the benzyl group in non-stereoselective reactions.



Scheme 2.27. Preparation of carboxylic acids **244a-d** with various hydride donor alkyl groups.

All target carboxylic acids could be obtained following this alkylation-hydrolysis strategy. However, yields of the isolated acids were low (29-45%) compared to Yeleswarapu's article, in which acid **244a** was obtained in 94% yield. The presence of two stereogenic centres in **244d** led to the formation of diastereoisomers in equal

proportions. The acids were then transformed to the respective phthalimide esters using standard conditions supported by DCC (Scheme 2.28).



Scheme 2.28. Preparation of phthalimide esters **245a-d** with various hydride donor alkyl groups.

The esterification of the *iso*-propyl-protected α-hydroxy acids proceeded well (67-70%), while the yields of phthalimide esters containing a *sec*-butyl group were consistently lower (43-45%). It should be noted that these phthalimide esters (and to a smaller extend the benzyl-substituted analogues) proved unstable even when stored in the freezer. This is illustrated with **245c**, which after purification (a) hydrolysed within 6 months completely (b) back to the original acid (c) and phthalimide (Figure 2.4). The lack of phthalimide peaks (at 8.0-7.8 ppm) in the shown sample results from the low solubility of phthalimide in chloroform.

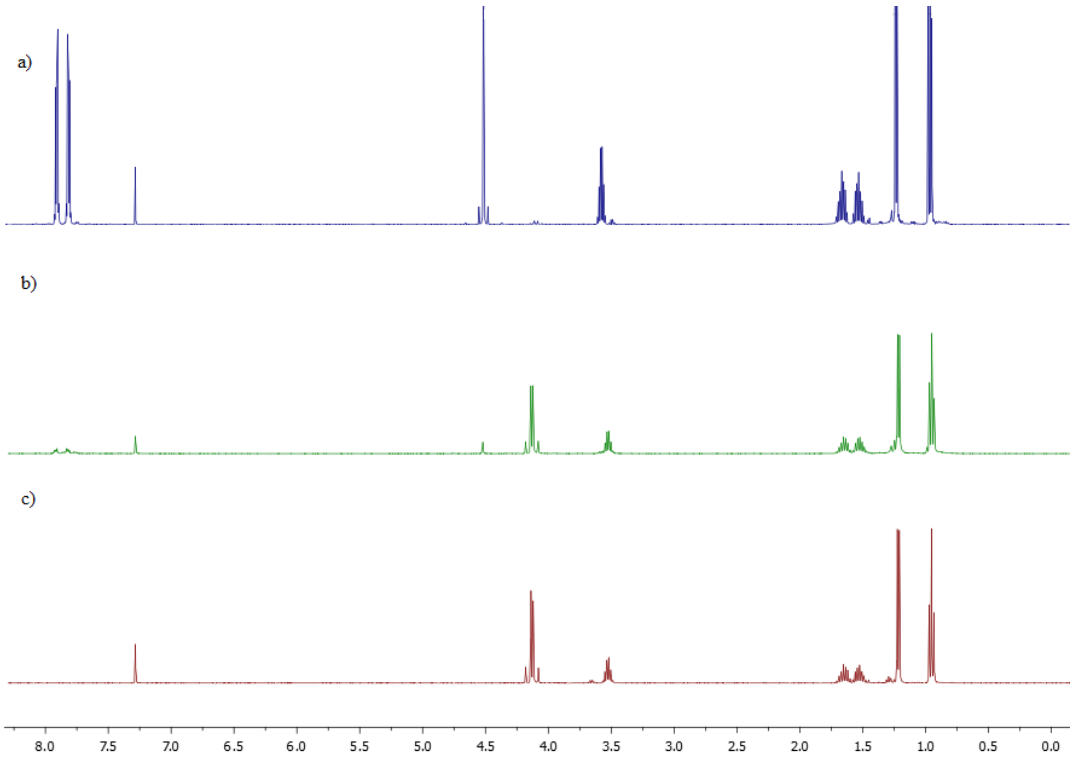


Figure 2.4. Fragmentation of **245c** (a) back to acid **244c** (c). ^{1}H NMR spectra (400 MHz) recorded in $CDCl_3$.

2.4.3.2 Reactions with Phthalimide Esters 245a-d

With the freshly prepared phthalimide esters in hand, the impact of the hydride donor group on product yield and stereoselectivity was examined. We decided to investigate hydroalkylations of 1-bromo-4-isopropenylbenzene (**246**) as this simplified evaluation of the ^{1}H NMR spectra of the unpurified reaction mixture and thus the assignment of diastereomeric ratios. All reactions were conducted using the developed purification sequence (see Chapter 2.3.3) and the performances of the alkyl groups in comparison to the benzyl group are summarised in Table 2.4.

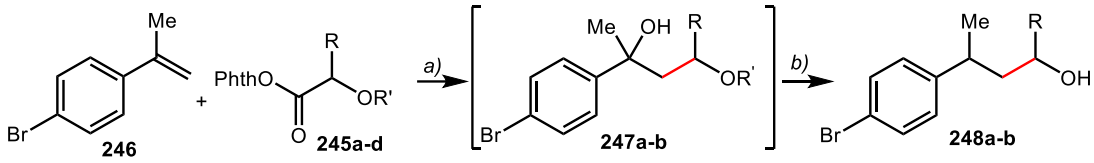


Table 2.4. Investigation of different alkyl groups as hydride donors. Conditions: a) **246** (1.0 eq.), **245a-d** (1.25 eq.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), MeCN (0.1 M), H_2O (50.0 eq.) blue LED, rt, 18 h; b) pTSA in TFE (0.06 M, 0.05 eq.), TFE (0.1 M), 50 °C, 45 min.

Entry	R'	R = H (248a)	R = Me (248b)
1	Bn	49%	67% (dr: 8:1)
2	*i*Pr	40%	45% (dr; 2:1)
3	*s*Bu	50%	52% (dr; 2.4:1)

As expected, the tethered alkyl group exhibits a great influence on the overall hydroalkylation process. With the three tested phthalimide esters that afforded primary radicals (R = H), similar yields were obtained for the benzyl and *sec*-butyl group (Table 2.4 entry 1 and 3), while the *iso*-propyl group (entry 2) led to a slightly lower yield (40%). Among phthalimide esters that led to the formation of product **248b** via fragmentation of a secondary radical, the product yield was highest with a benzyl group (67%). Additionally, a significantly better diastereoselectivity was obtained with a benzyl group as hydride donor (dr: 8:1) as opposed to the *iso*-propyl group (dr: 2:1) and the *sec*-butyl group (2.4:1). Given the superior results regarding product yield and stereoselectivity, the benzyl group was chosen as standard tether moiety.

2.4.4 Synthesis of Phthalimide Esters to Introduce Different Alkyl Groups

Now that the benzyl group had been established as a potent hydride donor group with good diastereoselectivity, the process was expanded to the radical addition with other alkyl groups. The preparation of suitable phthalimide ester precursors was inspired by the synthesis of lactic acid-derived phthalimide ester **236b**. Since several α-hydroxyacids **249a-d** were commercially available, a two-step sequence commencing with the *O*-benzylation of the alcohol followed by esterification of the carboxylic acid functional group with *N*-hydroxyphthalimide sufficed to afford the

alkyl radical precursors **251a-d**. It should be noticed that the carboxylic acids **250a-d** could not be separated completely from unreacted substrates **249a-d**. Therefore, the yields for the phthalimide esters over two steps are summarised in Table 2.5.

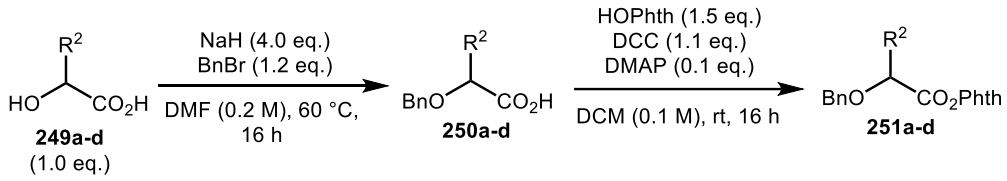


Table 2.5. Yields of phthalimide esters **251a-d**.

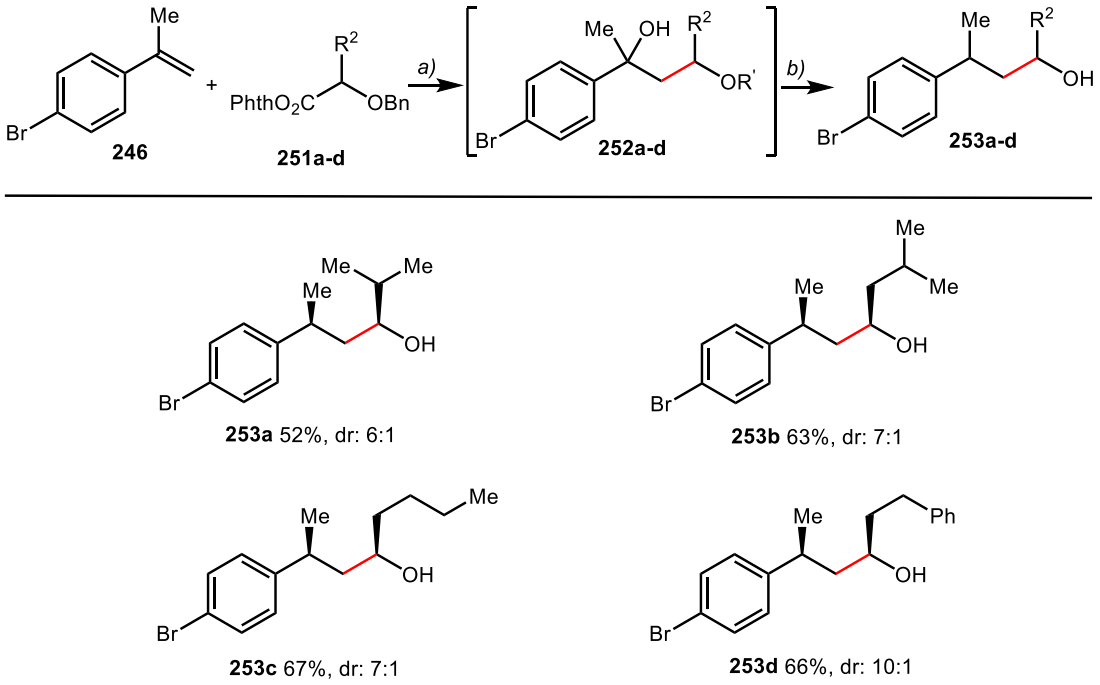
Entry	R^2	Product (Yield)[a]
1	*i*Pr	**251a** (42%)
2	*s*Bu	**251b** (16%)
3	*n*Bu	**251c** (16%)
4	Bn	**251d** (15%)

[a]Isolated yield over two steps given.

The phthalimide esters **251a-d** were formed in low yield using this two-step strategy. This can largely be attributed to lacklustre formation of the acid precursors **250a-d** based on analysis of the unpurified reaction mixtures by ^{1}H NMR spectroscopy and TLC analysis.

2.4.5 Reaction with Phthalimide Esters 251a-d to Introduce Different Alkyl Groups

The hydroalkylation of 1-bromo-4-isopropenylbenzene **246** was then conducted with the novel phthalimide esters **251a-d** in hand (Scheme 2.29). We were particularly interested in analysing the influence of the installed substituents on the stereoselectivity during the 1,5-hydride shift event, as such reactions with substituents at C-4 had not been discussed in the similar transformations reported by Chiba and Gagosz.[164]



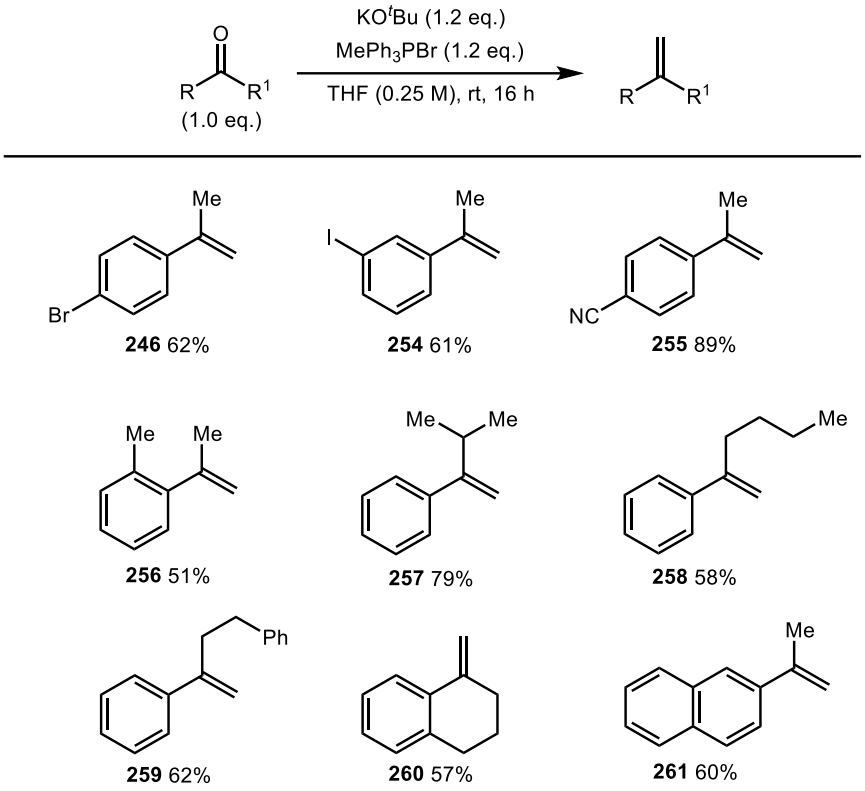
Scheme 2.29. Hydroalkyation of 1-bromo-4-isopropenylbenzene **246** with differently substituted phthalimide esters **251a-d**. Conditions: a) **246** (1.0 eq.), **251a-d** (1.25 eq.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), MeCN (0.1 M), H_2O (50.0 eq.) blue LED, rt, 18 h; b) *p*TSA in TFE (0.06 M, 0.05 eq.), TFE (0.1 M), 50 °C, 45 min.

Gratifyingly, all hydroalkylation products were obtained in good yield (52-67%) and high diastereoselectivity (dr: ≥6:1). Although a sterically demanding group such as the *iso*-propyl group in product **253a**, seems to reduce product yield and stereoselectivity (compared to **241** with a methyl substituent that was obtained in 67% yield and 8:1 d.r.), this effect wanes off with less bulky groups in products **253b-d**. All products are novel compounds; however, chemical shifts and coupling patterns suggest that the shown *anti*-diastereoisomers are preferably formed in accordance with a chair-like six-membered ring transition state, which will be discussed further in Chapter 2.5.3. The generally good results in this part of the discussion demonstrate that the developed process might be a viable strategy for the synthesis of highly complex molecules from readily accessible phthalimide ester and styrene substrates.

2.5 Scope of Stereoselective Hydroalkylation of Styrenes

2.5.1 Synthesis of Styrene Substrates

After a basic understanding of the hydroalkylation process had been established and various phthalimide ester had been employed successfully in the stereochemical studies, the feasibility of the process regarding different styrene substrates was investigated. An array of styrene derivatives was prepared from commercially available acetophenone derivatives via Wittig reaction with methyl triphenylphosphonium bromide (Scheme 2.30).

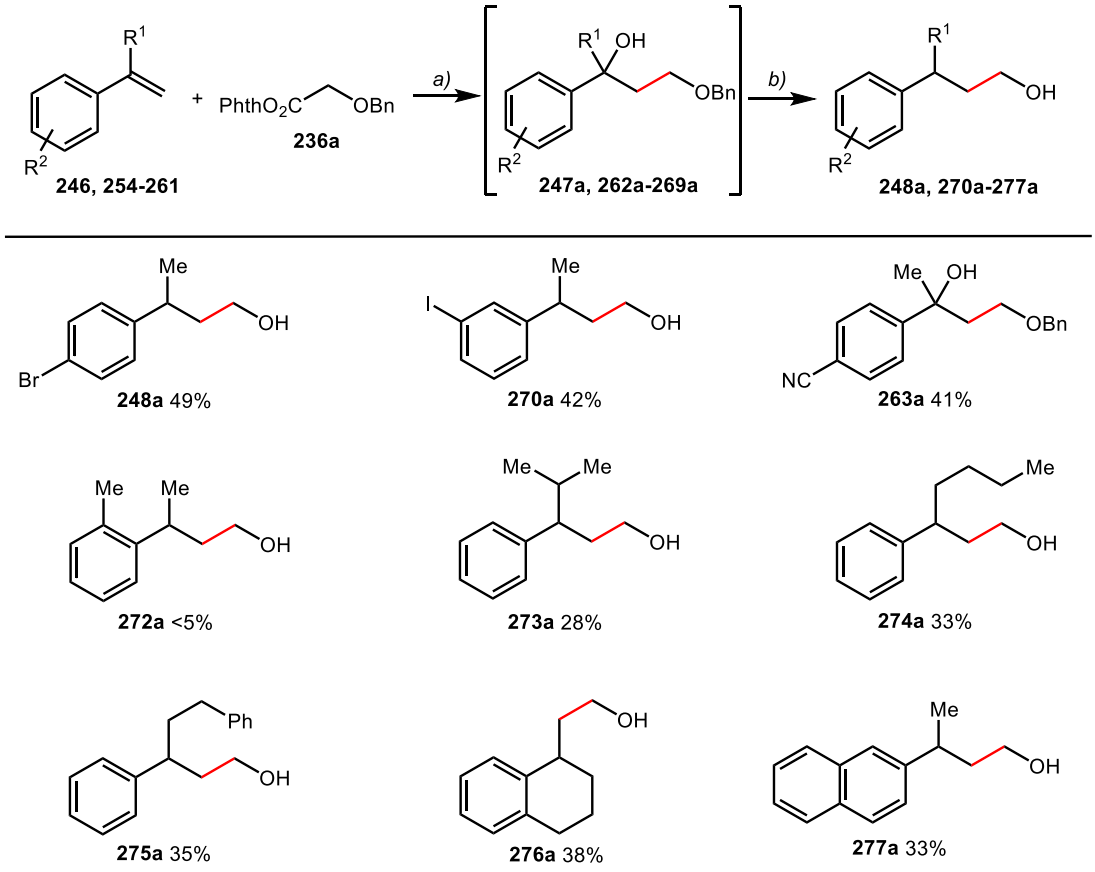


Scheme 2.30. Preparation of styrene derivatives via Wittig reaction.

Several α-methyl styrene derivatives with substituents on the aromatic ring (**246**, **254**-**256**) as well as examples in which the methyl group was substituted for other alkyl groups (**257**-**259**) and products stemming from 1-tetralone **260** and 2-naphthalene derivative **261** were synthesised in moderate to good yields.

2.5.2 Scope with Phthalimide Ester 236a

We firstly tested the various styrene substrates in the two-step, one-pot hydroalkylation with phthalimide ester **236a** (Scheme 2.31). The lack of substituents at the introduced alkyl group meant that no additional stereogenic centre was introduced to the molecule in the radical addition step, thus no control could be exhibited to the prochiral benzylic position.



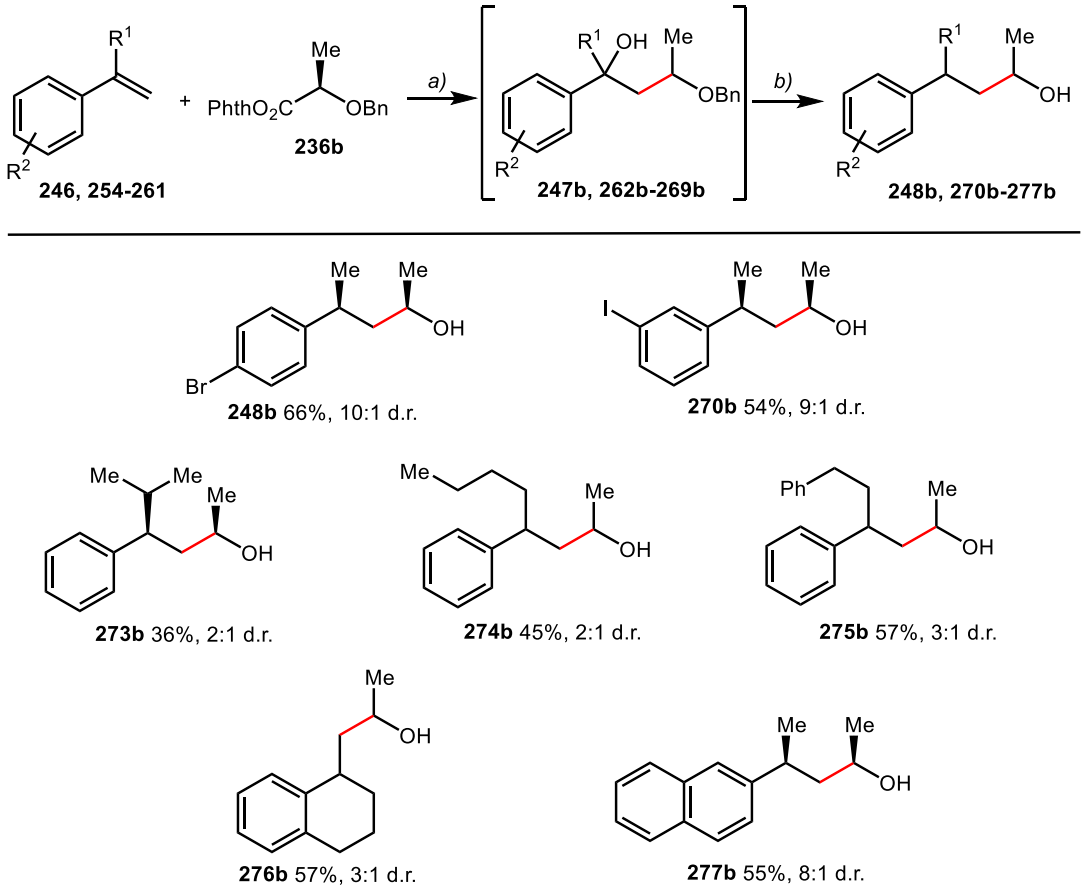
Scheme 2.31. Hydroalkylation styrene scope with phthalimide ester **236a**. Conditions: a) Styrene (1.0 eq.), **236a** (1.25 eq.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), MeCN (0.1 M), H_2O (50.0 eq.) blue LED, rt, 18 h; b) *p*TSA in TFE (0.06 M, 0.05 eq.), TFE (0.1 M), 50 °C, 45 min.

The hydroalkylation procedure was successfully applied to most of the tested styrene derivatives with phthalimide ester **236a**. Notable exceptions are the reactions with 2-(4-cyanophenyl)propene **255** and *ortho*-substituted 1-methyl-2-(prop-1-en-2-yl)benzene **256**. The electron-withdrawing nitrile group in styrene **255** shut down the

second reaction step completely (no hydroalkylation product could be detected) and the oxyalkylation product **263a** could be isolated from the reaction mixture in 41% yield. A similar observation was made in the hydroalkylation of (3,3,3-trifluoro-1-propen-2-yl)benzene **301**, which will be discussed in detail in Chapter 3. An *ortho*-substituent such as in product **272a** appears to have detrimental impact on the yield presumably due to distortion of the benzylic radical. Overall, TLC analysis showed that consumption of the starting materials was complete after 45 min and yields of the hydroalkylation products were low to moderate (28-49%). Compared to the unsubstituted α-methyl styrene that led to the respective hydroalkylation product **238a** in 40% yield, the implementation of halide group onto the aromatic ring in *para*- and *meta*-position slightly favoured product formation (products **248a**, **270a**, 42-49%). Meanwhile, displacing the methyl group with other alkyl substituents such as in products **273a**-**275a** or introducing a fused cyclohexane ring as demonstrated in product **276a** led to lower yields (28-38%). The hydroalkylation of 2-(1-propen-2-yl)naphthalene **261** led to a low yield of 33% presumably as a result of its poor performance in the initial oxyalkylation step (compare report by Glorius).[18]

2.5.3 Scope with Phthalimide Ester 236b

In the second part of the scope, we reacted the prepared styrene derivatives with phthalimide ester **259** (Scheme 2.32). Herein, the generated secondary alkyl radical would introduce a new stereocentre to the molecule, thus resulting in the formation of diastereoisomers. We were particularly interested how more bulky alkyl groups at the benzylic carbon would affect the diastereomeric ratio. Overall higher yields were expected in accordance with the significant increase in yield of hydroalkylation product **243** (60%) with the initially formed secondary alkyl radical.



Scheme 2.32. Hydroalkylation styrene scope with phthalimide ester **236b**. Conditions: a) Styrene (1.0 eq.), **236b** (1.25 eq.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), MeCN (0.1 M), H_2O (50.0 eq.) blue LED, rt, 18 h; b) *p*TSA in TFE (0.06 M, 0.05 eq.), TFE (0.1 M), 50 °C, 45 min.

Gratifyingly, the stepwise reaction of various styrene derivatives with phthalimide ester **236b** followed by exposure of the intermediate to Brønsted-acidic conditions led to the formation of hydroalkylation products in higher yields (36-66%) in comparison with the products arising from the initial addition of primary alkyl radicals (Scheme 2.31). This is likely due to higher yields of oxyalkylation intermediates in the first step (as described in Chapter 2.3), which can be seen in the ^1H NMR spectra of the unpurified reaction mixture Herein, the ratio of substrate styrene to oxyalkylation intermediate was higher (approximately 1:3) in the reaction with primary alkyl radical stemming from phthalimide ester **236a** compared to the reaction with phthalimide ester **236a** that led to an approximate substrate:product ratio of 1:5.

The increased formation of oxyalkylation products (and ultimately hydroalkylation products) in reactions with phthalimide ester **236b** can presumably be attributed to the increased nucleophilicity due to the inductive effect of the alkyl group (Figure 2.5). This hypothesis would also explain the good yields that were obtained in reaction with differently substituted phthalimide esters **251a-d**. Furthermore, the introduction of a substituent to generate secondary radicals enhances the stability compared to primary radicals that arise from fragmentation of phthalimide ester **236a**.

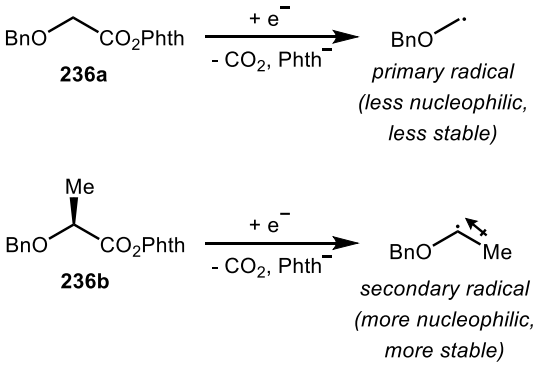


Figure 2.5. Fragmentation of phthalimide esters **236a** and **236b** and the resulting alkyl radicals.

Notably, benzyl alcohol (and 1-phenylethan-1-ol in the case of reactions with **236b**) was detected as a by-product in the unpurified reaction mixtures. The formation of benzyl alcohol via a sequence consisting of β-scission followed by oxidation of the benzylic radical and hydrolysis could account for the mass loss of alkyl radical (Figure 2.6)

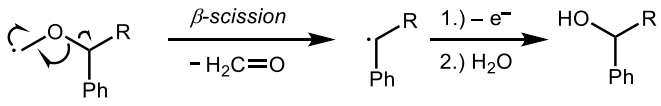


Figure 2.6. Potential β-scission in α-O alkyl radicals.

The scope revealed that the alkyl group attached to the benzylic C-2 position impacts the ratio of diastereoisomers considerably. While a methyl group rendered the overall reaction highly diastereoselective (dr: ≤8:1), significantly lower ratios of diastereoisomers were obtained with larger alkyl groups (dr: ≥3:1). The lowered diastereomeric ratios herein signify a lower energy difference in two opposing transition states. Eliel and Manoharan conducted conformational studies on 1-methyl-1-phenyl-cyclohexane and calculated a difference of only 0.34 kcal·mol^{-1} for the two possible conformations.[176] An increase in size of the substituent at C-2 can decrease this energy gain further. Allinger and Hu studied *iso*-propyl-substituted cyclohexane derivatives (as would be expected in the transition state in the formation of product **273b**) and reported the free energy of an axial *iso*-propyl-group of +2.10 kcal·mol^{-1}, while the free energy of an axial methyl-group (leading to product **236b**) was found to be +1.92 kcal·mol^{-1} (Figure 2.7).[177]

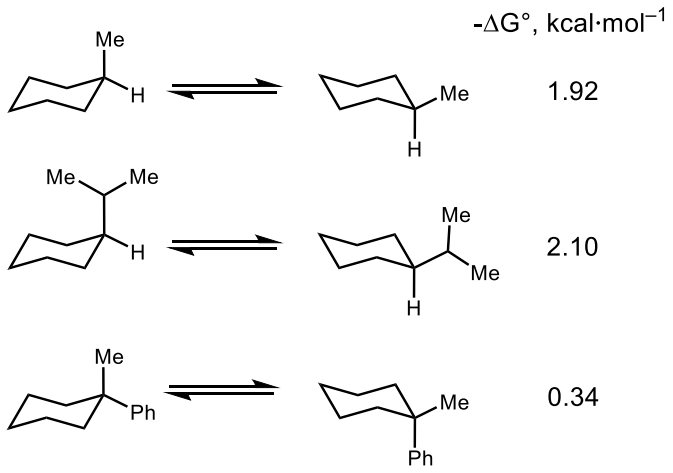


Figure 2.7. Reported energies of cyclohexane derivatives in different conformations.

The higher steric demand of the bulkier groups in comparison to the methyl group likely leads to a lower difference in energies of the opposing transition states. This insufficient energy difference can ultimately result in a decreased stereoselectivity between the *syn* and *anti*-products of products **273b**-**276b** compared to the methyl-substituted analogue **238b** (Figure 2.8).

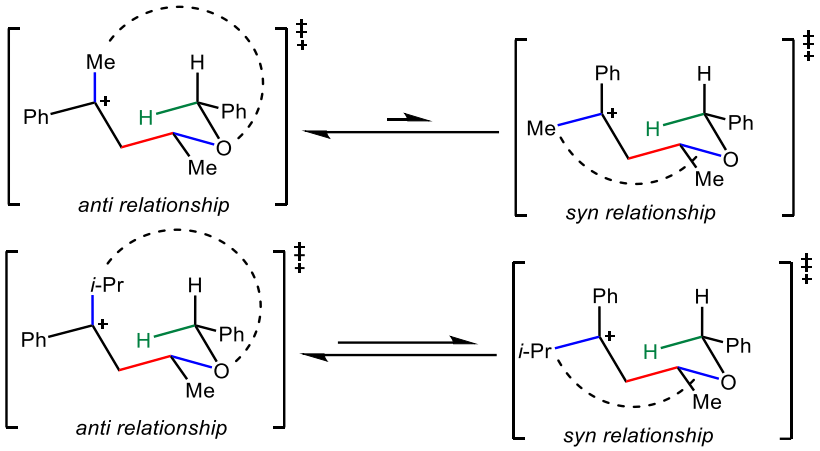
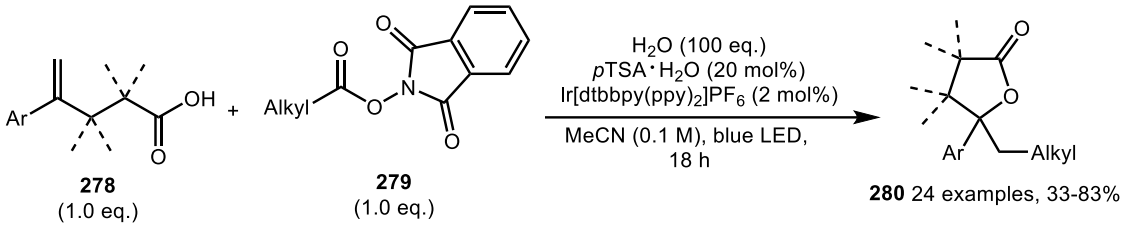


Figure 2.8. Transition states in the formation of products **238b** and **273b**.

Some of the products with a methyl group at C-2 are known compounds and can be assigned to the *anti*-diastereoisomer as the major component of the mixture.[174] The novel products **248b**, **270b** and **277b** only differ in the substitution at the aromatic group and can therefore be assumed to give predominately *anti*-diastereoisomers. This general assignment is not possible with other products that were obtained as inseparable diastereomeric mixtures of lower ratios. However, the chemical shifts and splitting pattern of the benzylic protons indicate that the *anti*-diastereoisomer is the major component in the product mixtures of **273b**-**276b**. Only product **273b** has been reported in the literature and the major component that was present in the product mixture matches the data given for the *anti*-diastereoisomer.[178]

2.6 A Novel Oxyalkylation Pathway to THF Derivatives

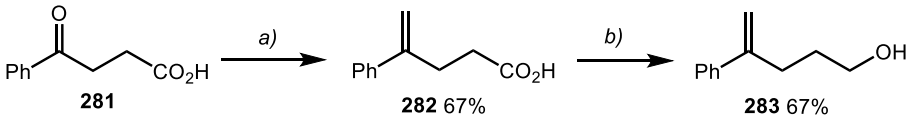
An intramolecular oxyalkylation constituted an intriguing reaction scenario. This would allow the unprecedented synthesis of cyclic ethers from alcohol-tethered styrene derivatives. A similar report has been made by the Pan group, who published the synthesis of lactones **280** from acid-tethered styrene substrates **278** (Scheme 2.33).[179] Higher yields were obtained in the presence of sub-stoichiometric amounts of *p*TSA (20 mol%), which assisted in dehydrating potential oxyalkylation products.



Scheme 2.33. Alkylation/lactonization of acid-tethered styrene derivatives reported by Pan.[179]

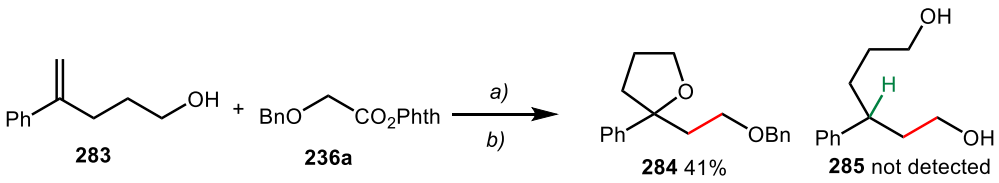
2.6.1 Synthesis of an Alcohol-tethered Styrene and Its Reaction with Alkyl Radicals

We envisioned that 4-phenylpent-4-en-1-ol (**281**) would be a suitable substrate leading to 2,2-difunctionalised THF products. As the Pd-supported coupling between alcohol tethered alkynes and aryl boronic acids had not resulted in good yields, we decided to pursue a different approach. The selective olefination of the ketone functional group in ketoacid **281** had been reported by the Wang group,[180] and we conducted the successive reduction of acid **282** with lithium aluminium hydride to afford the required starting material **283** in two steps (Scheme 2.34).



Scheme 2.34. Preparation of alcohol-tethered styrene derivative **283**. Conditions: a) **281** (1.0 eq.), KO^{t}Bu (1.2 eq.), $MePh_3PBr$ (1.2 eq.), THF (0.25 M), rt, 16 h; b) $LiAlH_4$ (2.1 eq.), THF (0.3 M), 0 °C, 1 h.

We decided to conduct the reaction with styrene **283** using the standard procedure developed previously (Chapter 2.3.3). It was expected that the THF derivative was already formed in the first reaction step (Scheme 2.35). However, reacting this product as well as potentially formed oxyalkylation product by external trapping with water would allow us to evaluate the relative reaction rates of two competing intramolecular nucleophilic attacks by the alcohol tether leading to cyclic ether products or 1,5-hydride transfer resulting in the hydroalkylation product.

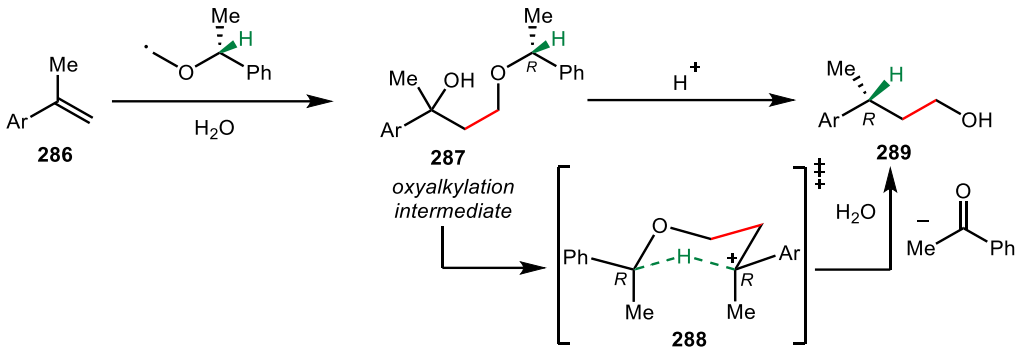


Scheme 2.35. Reaction of alcohol-tethered styrene **283** under standard hydroalkylation conditions with phthalimide ester **236a**. Conditions: a) **280** (1.0 eq.), **236a** (1.25 eq.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), MeCN (0.1 M), H_2O (50.0 eq.) blue LED, rt, 18 h; b) *p*TSA in TFE (0.06 M, 0.05 eq.), TFE (0.1 M), 50 °C, 45 min.

The THF derivative **284** was obtained as the only product, implying a high stability of the five-membered heterocycle. The ^1H NMR spectrum of the unpurified reaction mixture indicated that its formation occurred largely in this step. Unfortunately, no internal standard was added to allow a quantitative analysis. The formation of 2,2,2-trifluoroethyl ethers was not detected further indicating that the five-membered ring is not opened under reaction conditions. The reaction has not been tested yet on other substrates or with different phthalimide esters.

2.7 Hydrofunctionalisation via Enantioselective 1,5-Hydride Transfer

An enantioselective 1,5-hydride transfer was a long-term goal of this project. In Chapter 2.4, it was demonstrated that suitable phthalimide esters can fragment to secondary alkyl radicals that lead to hydroalkylation products in high diastereoselectivities as a result of a defined chair-like transition state.[164] We hypothesised that a hydride donor group with a stereogenic centre would similarly exert stereocontrol during the 1,5-hydride shift event. In this case, the chiral centre would not be affected by the precursor fragmentation, meaning that, in contrast to phthalimide esters that collapse to planar sp^2-carbon-centred radicals at the stereocentre, the chiral information can be retained throughout the reaction sequence. We therefore expected the preferential formation of one enantiomer with the stereocentre at the benzylic carbon atom (Scheme 2.36).

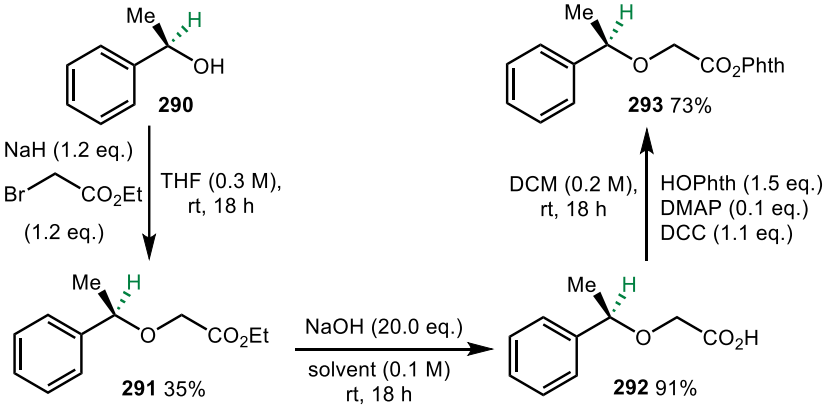


Scheme 2.36. Proposed two-step enantioselective hydroalkylation of styrene derivatives.

It should be noted that the proposed reaction is better classified as a diastereoselective reaction, as the two competing transition states (the favoured conformation **288** is shown in Scheme 2.36) are diastereomeric, not enantiomeric. However, as the chiral hydride donor moiety is cleaved during the transformation, an enantioenriched product with only one chiral centre is obtained.

2.7.1 Synthesis of a Phthalimide Ester with a Chiral Alkyl Tether

We chose to test the stereoselective hydroalkylation of α-methyl styrene **235** with a chiral enantioenriched variant of the standard *O*-benzyl-tethered phthalimide ester. Commercially available (*R*)-1-phenylethanol (**290**) (Sigma Aldrich, 97% *ee*) was used as starting material and converted into the target phthalimide ester in three steps via *O*-alkylation, hydrolysis and esterification (Scheme 2.37).



Scheme 2.37. Preparation of chiral enantioenriched phthalimide ester **293.**

The initial alkylation step of (*R*)-1-phenylethanol (**290**) afforded the desired ester **291** only in a low yield of 35%. Despite addition of excess base and alkylation reagent, it was not possible to obtain full conversion of the alcohol. The following hydrolysis and esterification steps proceeded well affording the final product **293** in 66% yield over two steps.

2.7.2 Analysis of Phthalimide Ester 293

It was crucial to ascertain full retention of the stereocentre in phthalimide ester **293** after the three reaction steps. Therefore, the phthalimide ester was analysed via chiral HPLC. Since it was a novel compound, no conditions for the separation of enantiomers via chiral HPLC had been reported. This meant that we had to prepare a racemic sample of radical precursor **293** in order to sufficiently differentiate between the minor enantiomer and potential impurities in the analysis of the enantioenriched compound. The HPLC measurement parameters are disclosed in the Experimentals (Chapter 6).

As expected, starting with racemic 1-phenylethanol led to the formation of racemic phthalimide ester **293**. The recorded *ee* value was 4%, which appeared within a reasonable margin of error considering the uneven baseline. Using the same measurement parameters, the enantioenriched sample of phthalimide ester **293** was then analysed (Figure 2.9).

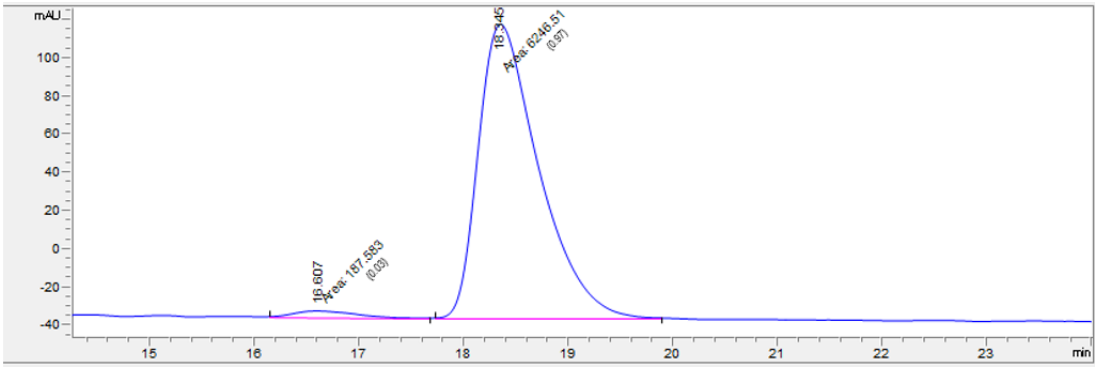
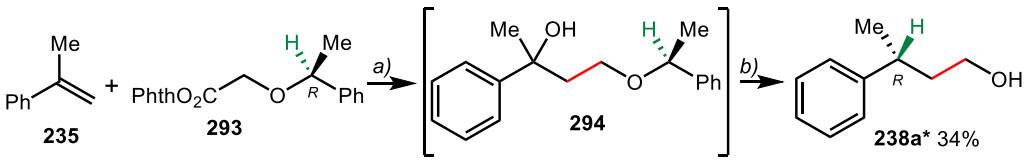


Figure 2.9. HPLC analysis of the enantioenriched sample of phthalimide ester **293**. HPLC conditions: ODH, hexane/isopropanol = 95/5, flow rate 0.5 mL/min.

An *ee*-value of 94% was recorded in the analysis of the enantioenriched sample. As inversion of chirality was unlikely, it was assumed that the target phthalimide ester **293** with *R*-configuration at the stereocentre stemming from the alcohol substrate was present in large excess.

2.7.3 Reaction with Phthalimide Ester 293

Having demonstrated the retention of chirality in radical precursor **293**, the phthalimide ester was employed in the hydroalkylation of α-methyl styrene **235** (Scheme 2.38). It was anticipated that the *R*-enantiomer was formed in excess if a transition state with chair-conformation was resembled during the chiral 1,5-hydride transfer as proposed in Scheme 2.36.



Scheme 2.38. Hydroalkyation of α-methyl styrene **235** with enantioenriched phthalimide ester **293**. Conditions: a) **235** (1.0 eq.), **293** (1.25 eq.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), MeCN (0.1 M), H_2O (50.0 eq.) blue LED, rt, 18 h; b) *p*TSA in TFE (0.06 M, 0.05 eq.), TFE (0.1 M), 50 °C, 60 min.

The primary alcohol product was obtained in a slightly lower yield of 34% over the reaction sequence compared to a yield of 40% when using achiral phthtalimide ester **236a**. TLC monitoring indicated that the conversion was complete after 60 min reaction time. The *ee*-value was then determined via chiral HPLC using literature conditions and the results are shown in Figure 2.10.[181]

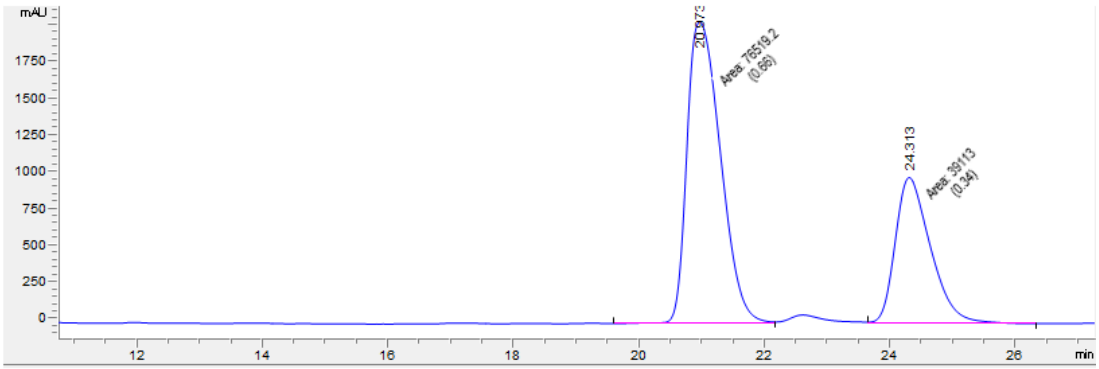
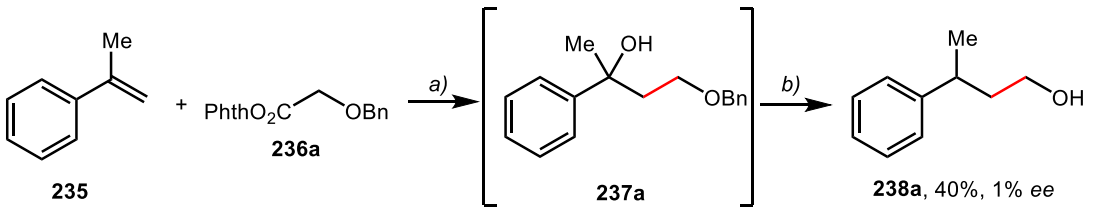


Figure 2.10. HPLC analysis of hydroalkylation product **238a*** with enantioenriched phthalimide ester **293**. HPLC conditions: ODH, hexane/isopropanol = 90/10, flow rate 0.5 mL/min.

The separation of product enantiomers via chiral HPLC revealed that the chirality transfer from the chiral auxiliary to the product was successful. The *ee*-value using phthalimide ester **293** was 32%. A comparison with literature data[181] revealed that the *R*-enantiomer was formed preferentially, indicating that a simplified chair-like transition state resembles the true transition state approximately. In order to prove that the enantiomeric excess of the *R*-enantiomer originates from the chiral auxiliary, the hydroalkylation product from *O*-benzyl-tethered phthalimide ester was also investigated by chiral HPLC (Scheme 2.39).



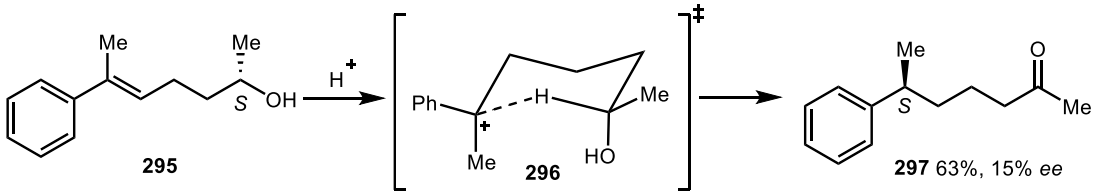
Scheme 2.39. Hydroalkylation of α-methyl styrene **235** with achiral phthalimide ester **236a**. Conditions: a) **235** (1.0 eq.), **236a** (1.25 eq.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), MeCN (0.1 M), H_2O (50.0 eq.) blue LED, rt, 18 h; b) *p*TSA in TFE (0.06 M, 0.05 eq.), TFE (0.1 M), 50 °C, 60 min.

A racemic mixture (1% *ee*) of hydroalkylation product **238a** was obtained if no chiral auxiliary was attached, thereby proving that the chiral auxiliary is responsible for the stereocontrol in the product.

The preferential formation of one enantiomer proves that the postulated concept reflects a viable method to introduce chirality at the benzylic C-2 position although the obtained enantiomeric excess was low. Importantly, the 1,5-hydride transfer takes place in a six-membered transition state that resembles a chair-like conformation, whose exact structure is largely governed by the substituents along the carbon skeleton and the chiral auxiliary. It seems therefore reasonable to assume that different or additional substituents along the alkyl group or at the chiral auxiliary can exhibit great impact on the optical purity of the product. In our model reaction, insufficient differentiation of the substituents can play a role and lead to insufficient energetic differences between the two opposing enantiomers. As mentioned above, conformational studies on 1-methyl-1-phenyl-cyclohexane revealed a difference of only 0.34 kcal·mol^{-1} for the two possible conformations.[176] In intermediate **294** this would apply to both the hydride donor centre as well as the carbocation and substitution at either centre could alter the final result greatly. Computational studies as well as test reactions with different styrenes and chiral auxiliaries should be undertaken to gain a better understanding of this under-reported chirality transfer.

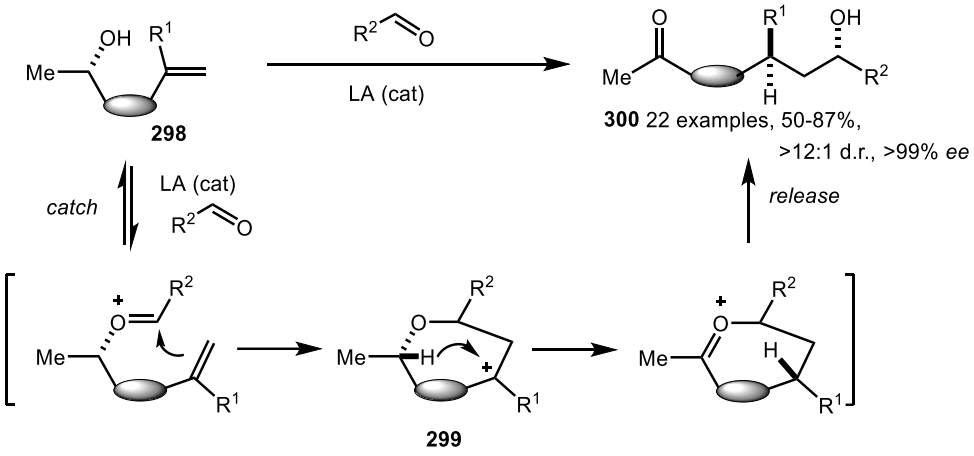
2.7.4 Chirality Transfers in the Literature

Despite the low degree of optical purity in the reaction mixture, this chirality transfer from a remote chiral centre constitutes a rare example of an enantioselective 1,5-hydride transfer to an *in-situ* generated carbocation. Hill and Carlson have reported a similar type of chirality transfer in the conversion of 6-phenyl-5-hepten-2-ol **295** to 6-phenyl-2-heptanone **297** under acidic conditions.[182] The researchers proposed a six-membered ring transition state that resembled chair conformation **296**, which sufficed to predict the correct stereochemical outcome of the reaction based on occupation of larger groups in pseudoequatorial positions. However, the optical purity of the isolated product was only 15% (Scheme 2.40).



Scheme 2.40. Chirality transfer reported by Hill and Carlson.[182]

An enantioselective 1,5-hydride transfer has recently been reported by the Maulide group using a "catch and release" approach.[183] This strategy is based on the formation of a cyclic ("caught") carbocation intermediate **299** in which the hydride transfer occurs. The ring can then open ("release") maintaining the chiral information in the ketohydroxy products **300** (Scheme 2.41).



Scheme 2.41. "Catch and release" approach to achieve enantioselective hydride transfer reported by Maulide.[183]

2.8 Summary and Future Work

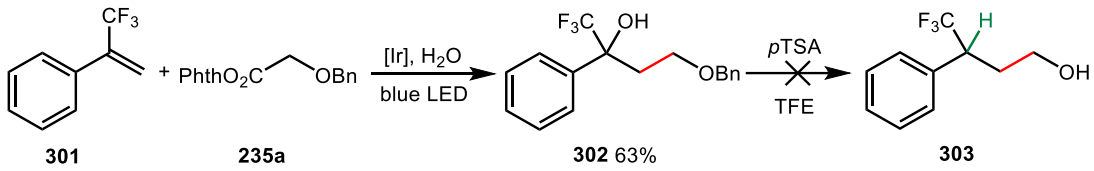
A two-step, one-pot procedure has been developed to achieve *anti*-Markovnikov hydroalkylation of styrene derivatives. Mechanistic investigations revealed that a 1,5-HAT was outcompeted by single electron oxidation and trapping with water preventing the formation of target products in one step. The reaction is successful on a range of styrene derivatives with various alkyl groups at C-2. However, no product was obtained with an *ortho*-substituted aromatic ring as starting material. Generally, higher yields were obtained originating from the addition of secondary radicals as a result of enhanced radical stability and nucleophilicity. The process is highly diastereoselective with α-methyl styrene-derivatives but the selectivity dropped rapidly with other alkyl groups attached at the benzylic position. Gratifyingly, it could be shown that chirality transfer from a chiral hydride donor group to the benzylic position is a viable strategy to achieve enantioselective hydroalkylation. Furthermore, the initial oxyalkylation step could be extended to the formation of THF-derivatives with alcohol-tethered styrene substrates.

The possibility to conduct this hydroalkylation in an enantioselective fashion is intriguing and deserves further investigations. Computational studies should be undertaken in order to gain a better understanding of the structure of the transition state. The results obtained in this work could then help to identify potential chiral auxiliaries that lead to a higher degree of stereocontrol.

Chapter 3. Oxyalkylation of α-Trifluoromethyl Styrenes

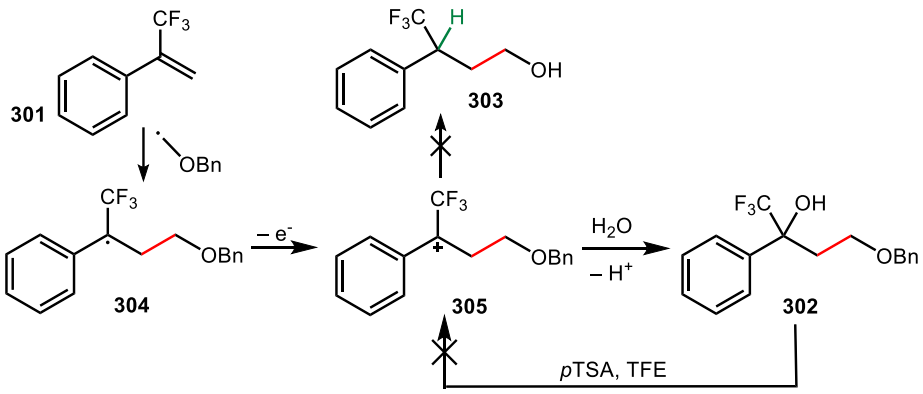
3.1 Anomaly of α-Trifluoromethyl Styrene

During the investigation of the hydrofunctionalisation of styrenes, an interesting observation was made in the reaction with α-trifluoromethyl styrene **301**. The oxyalkylation product **302** was formed in good yield, yet no further reaction took place when subjecting the unpurified compound to conditions that were used to initiate the 1,5-hydride shift with related intermediates (Scheme 3.1).



Scheme 3.1. Oxyalkylation of styrene **301** and unsuccessful 1,5-hydride shift.

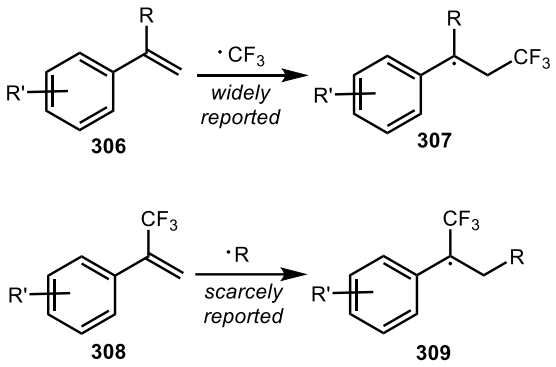
This behaviour, which mirrored that of 2-(4-cyanophenyl)propene **255**, was unexpected given that the oxyalkylation product could only be formed from the benzylic carbocation intermediate, which appears highly destabilised by the vicinal electron-withdrawing group at first glance. Additionally, despite the carbocation being a key intermediate, it could not be generated again via the standard protonation-dehydration sequence (Scheme 3.2).



Scheme 3.2. Key benzylic carbocation and unreactive oxyalkylation product.

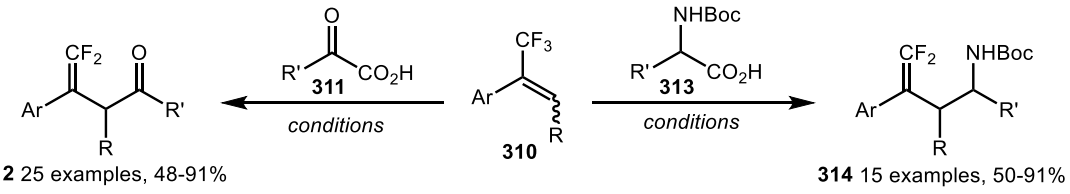
3.2 Review of Reactions with α-Trifluoromethyl Styrenes

A literature review revealed that only a limited number of publications on radical additions into α-trifluoromethyl styrenes substrates have been reported.[184] By contrast, procedures relying on the addition of CF_3· radicals into styrenes have been widely reported to access a related type of radical addition adduct (Scheme 3.3).[185]



Scheme 3.3. Approaches to generate trifluoromethylated benzylic radicals **306** or **308**.

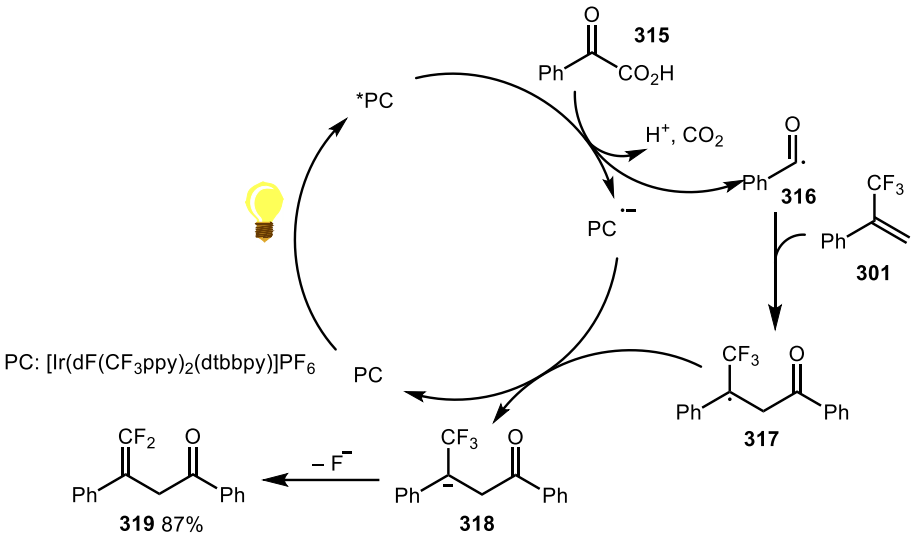
In 2016, Zhou and co-workers presented the first photoredox catalysed method to synthesise *gem*-difluorostyrenes from α-trifluoromethyl styrenes.[186] The group employed α-ketoacids **311** and α-aminoacids **313** as precursors for acyl and α-amino-radicals through an oxidative decarboxylative process, respectively (Scheme 3.4).



Scheme 3.4. Synthesis of *gem*-difluorostyrenes reported by Zhou. Conditions: **310** (1.0 eq.), carboxylic acid derivative (2.0 eq.), $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ (2 mol%), LiOH (2.0 eq.), DMSO (0.2 M), blue LED, 24 h.

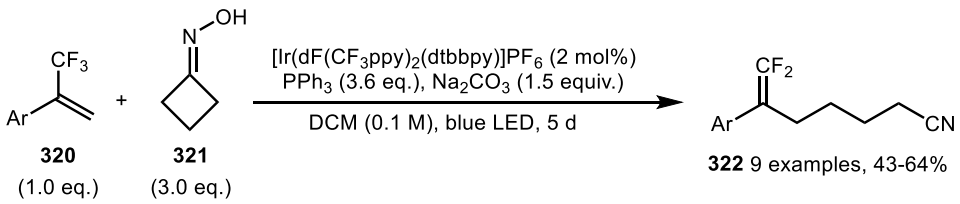
It was proposed that the benzylic radical intermediate **317** was reduced to the corresponding anion **318** and terminal fluoride elimination facilitated by a lithium base

recovered the C=C moiety in product **319** (Scheme 3.5). The reaction exhibited a wide range of substrate scope regarding different styrenes (including heterocycles) and radical coupling partners.



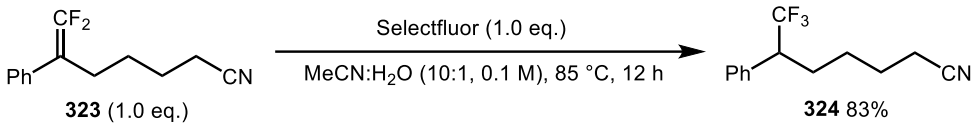
Scheme 3.5. Proposed mechanism for the synthesis of 1,1-difluorostyrenes reported by Zhou.[186]

This radical-polar crossover strategy to generate *gem*-difluorostyrenes is the most conventional reactivity of α-trifluoromethyl styrenes in radical reactions. The Yang group reported the *anti*-Markovnikov reaction of styrene derivatives using oxime-derived alkyl radicals.[187] However, when conducting the reaction with α-trifluoromethyl styrenes, final protonation of the anion was outcompeted by elimination of fluoride (Scheme 3.6).



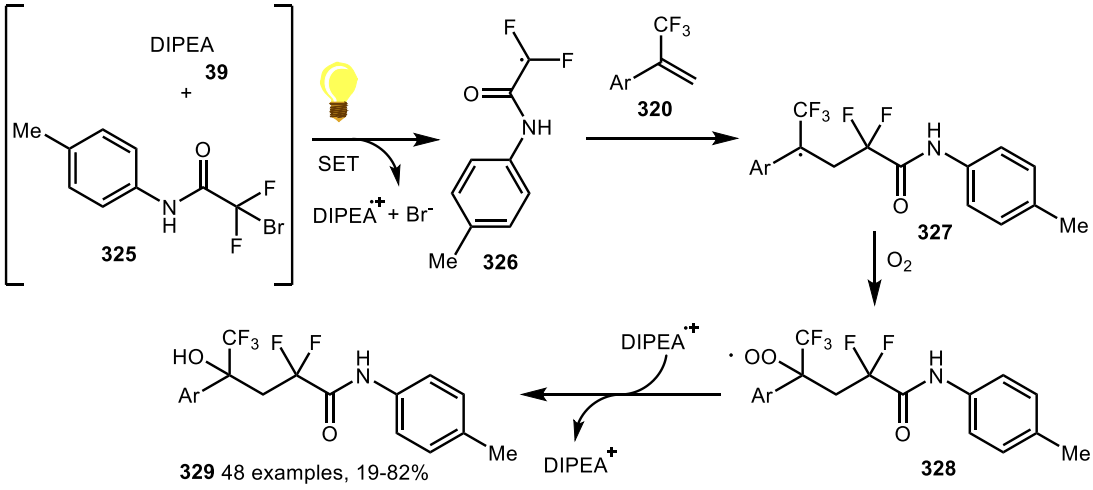
Scheme 3.6. Synthesis of *gem*-difluorostyrenes reported by Yang.[187]

The group highlighted the importance of the 1,1-difluoroalkene as carbonyl bioisostere but also presented a potential fluorination with Selectfluor to recover the trifluoromethyl group (Scheme 3.7).



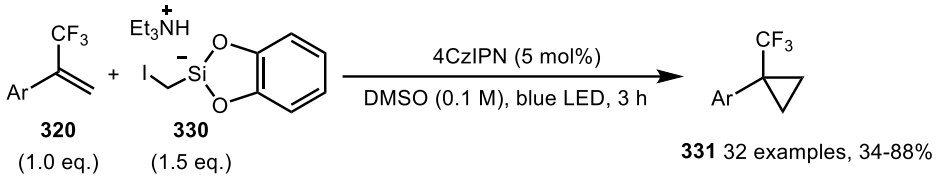
Scheme 3.7. Conversion of *gem*-difluorostyrene **323** to α-trifluromethyl styrene **324** using Selectfluor.[187]

Reactions, in which the trifluoromethyl group is retained, are less common. In a successive publication, the Yang group achieved the oxyalkylation of α-trifluoromethyl styrenes with electron-deficient radicals.[188] No photoredox catalyst was required, and instead, an electron donor-acceptor (EDA) system consisting of DIPEA **39** and alkyl bromide as radical precursor (possible involvement of α-trifluoromethyl styrene could not be ruled out) was suggested as the photolytically active complex. The benzylic radical **327** was trapped with oxygen from trace O_2-atmosphere before electron transfer could take place in the absence of a traditional photoredox catalyst. Instead, the base donated a second electron and homolysis of the O–O bond followed by hydrogen abstraction furnished target products **329** (Scheme 3.8).



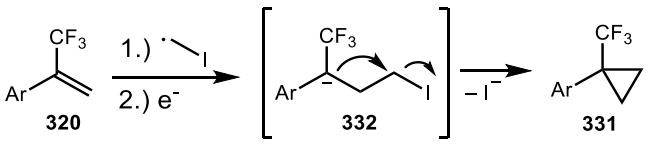
Scheme 3.8. Oxyalkylation of α-trifluoromethyl styrene reported by Yang.[188]

Other strategies to preserve the trifluoromethyl group exploit the benzylic anion as nucleophile, typically in cyclisation reactions. The Molander group developed the first procedure of this kind to synthesise trifluoromethylated cyclopropanes **331** (Scheme 3.9).[189]



Scheme 3.9. Synthesis of trifluoromethyl-substituted cyclopropanes reported by Molander.[188]

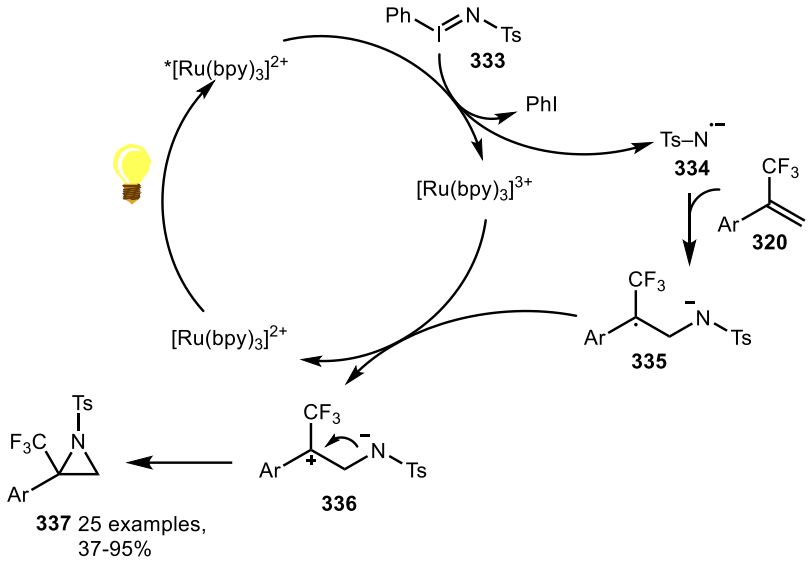
The group employed an iodomethyl-based silicate reagent **330** as radical precursor for iodomethylene radicals. Herein, the benzylic anion **332** performs an intramolecular *3-exo*-tet ring closure taking advantage of iodide as excellent leaving group (Scheme 3.10).



Scheme 3.10. Proposed mechanistic steps in the synthesis of trifluoromethylated cyclopropanes reported by Molander.[189]

The formation of benzylic carbocations is not often observed with α-trifluoromethyl styrene substrates. A recent example is given by the Koenigs laboratory who reported the synthesis of trifluoromethylated aziridines from α-trifluoromethyl styrenes.[190] A hypervalent iodine(III) reagent **333** was employed as precursor for nitrogen-centred nitrene radical anion **334**. Upon addition into styrene derivatives, a 1,3-radical anion **335** was generated that could perform single electron reduction. Zwitterion **336** rapidly cyclises to afford the aziridine ring product **337**. Computational studies on the basis

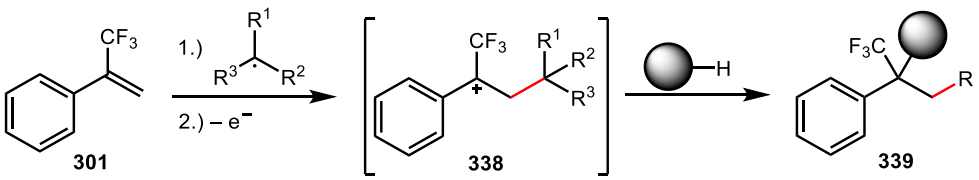
of DFT were disclosed to rationalise formation of the intermediates and were interpreted as supporting evidence for the proposed mechanism (Scheme 3.11).



Scheme 3.11. Synthesis of trifluoromethylated aziridines reported by Koenigs[190].

3.2.1 Difunctionalisation of α-trifluoromethyl styrenes

With the rising interested in fluorinated compounds for pharmaceutical use and the scarce reports of related transformations published thus far, we decided to investigate the oxyalkylation of α-trifluoromethyl styrenes further. We envisioned that the benzylic carbocation intermediate could be trapped with a broad array of nucleophiles. Following this strategy, a library of novel α-trifluoromethylarenes could be accessed in one step from cheap and readily available starting materials (Scheme 3.12).

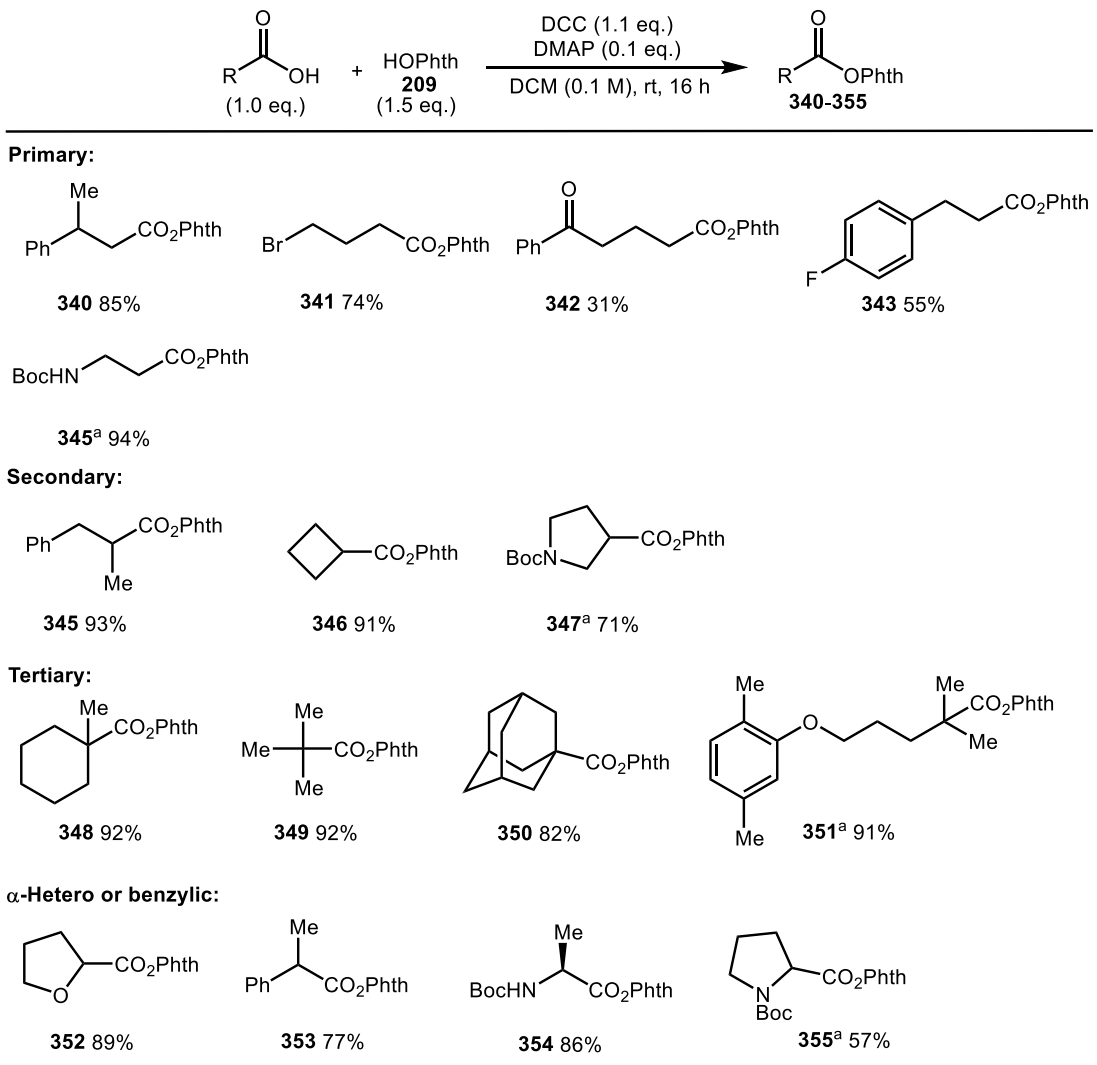


Scheme 3.12. Radical difunctionalisation of α-trifluoromethyl styrenes with various nucleophiles.

3.3 Phthalimide Ester Scope

3.3.1 Synthesis of Different Phthalimide Esters

As the initial oxyalkylation of α-trifluoromethyl styrene **301** afforded the product alcohol in good yield, we decided to investigate the process under unchanged conditions with other alkyl radicals. To this end, an array of different phthalimide esters was prepared as radical precursors for primary, secondary, tertiary, α-hetero and benzylic radicals. All phthalimide esters except for 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate (see Experimental section) were prepared from the corresponding carboxylic acid and *N*-hydroxy phthalimide in DCC-promoted couplings (Scheme 3.13). The reactions were generally conducted in DCM. However, in some cases esterifications in THF were cleaner and gave higher yields.

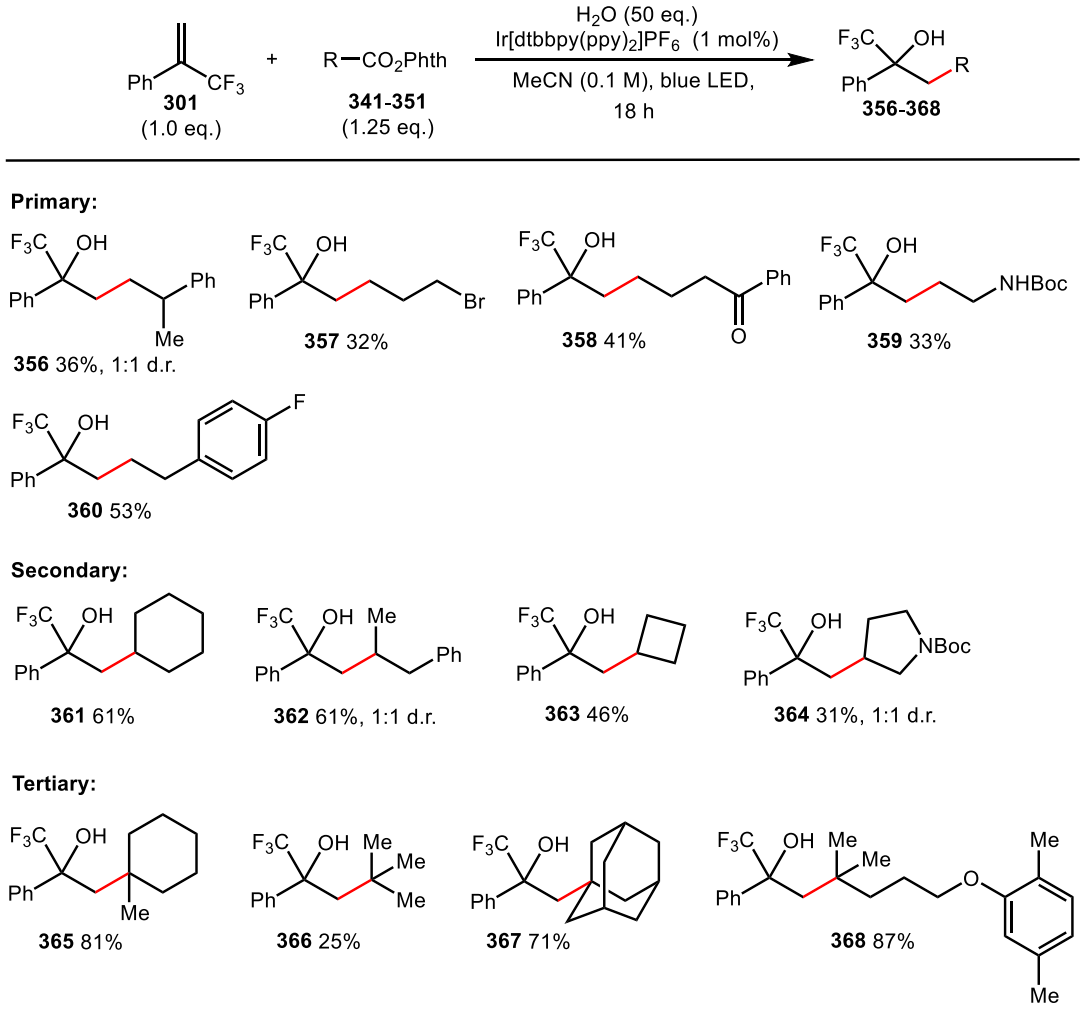


Scheme 3.13. Preparation of phthalimide esters. a: reaction in THF (0.15 M).

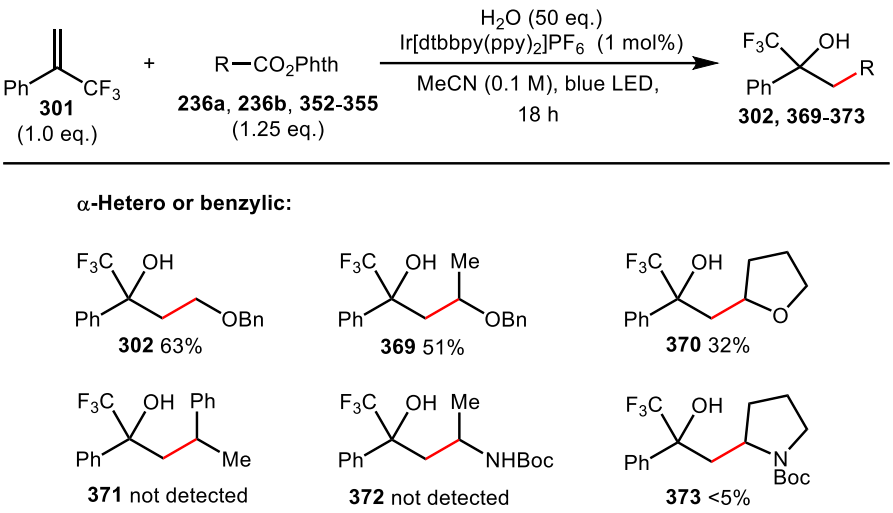
The yields for the phthalimide ester were typically high (75-95%) in alignment with reported yields. Only compound **342** containing a γ-carbonyl group was isolated in significantly lower yield (87% Lit. yield after 44.5 h).[191]

3.3.2 Oxyalkylation of Styrene 301 with Different Phthalimide Esters

With the phthalimide esters **340**-**355** as well as previously reported phthalimide esters **210**, **236a** and **236b** in hand, the first part of the scope was commenced. We chose α-trifluoromethyl styrene **301** as standard substrate as it is commercially available and water as nucleophile using the original conditions for radical oxyalkylation previously established (Scheme 3.14, Scheme 3.15)



Scheme 3.14. Phthalimide ester scope (1).



Scheme 3.15. Phthalimide ester scope (2).

Satisfyingly, the oxyalkylation of α-trifluoromethyl styrene **301** was successful with a wide range of alkyl radicals. The yields, however, varied significantly depending on the nature of the alkyl radical. While primary and secondary alkyl radicals afforded the corresponding products **356**-**364** in low to moderate yield (31-61%), high yields (71-87%) were obtained in reactions with tertiary carbon-centred radicals. An exception was the reaction with *tert*-butyl radical that formed the oxyalkylation product **366** in poor yield (25%). The reaction with α-oxygen radicals to oxyalkylation products **302**, **369** and **370** proceeded in moderate yield (32-63%), yet no product could be detected in reactions where radical precursors collapsed to α-nitrogen radicals. Reactions that led to the formation of diastereoisomers displayed no stereoselectivity and 1:1 product mixtures of isomers were detected in all cases. The addition of benzylic radical into α-trifluoromethyl styrene towards oxyalkylation product **371** failed.

The ^{1}H NMR spectrum of the unpurified reaction mixture of product **366** suggested a yield of 96%, but the pure compound was only isolated in poor yield. We assumed that the mass loss is due to the volatility of the product and occurs during product drying on the high vacuum. Although the formular weight of the compound (246.27 g·mol^{-1}) does not suggest high volatility, and a similar product (**363**) could be isolated in significantly better yield, no other explanation appeared likely, and the result was confirmed when the experiment was repeated.

Furthermore, it was remarkable that reactions with α-oxygen radicals were successful, whereas no products could be obtained in reactions involving α-nitrogen radicals. In these cases, oxidation of the α-amino radicals could potentially take place rather than radical addition into the C=C bond followed by oxidation. It has been described that α-amino radicals readily undergo oxidation ($E_{1/2}$ = –1.03 V vs SCE)[192] to imines or enamines in various instances and the oxidised photocatalyst $[Ir(IV)(dtbbpy)(ppy)_2]^{2+}PF_6$ would be sufficiently oxidising ($E_{1/2}^{IV/III}$ = +1.21 V vs SCE) to realise this electron transfer.[98] For this reason, photoredox-catalysed reactions with α-amino radicals are typically based on reductive quenching cycles.[144]

Evidence supporting this hypothesis can be seen in the ^{1}H NMR spectrum of the unpurified reaction mixture in the reaction with phthalimide ester **354.** Herein, a new quartet signal at 9.77 ppm (J = 2.9 Hz) and a doublet at 2.19 ppm (J = 2.9 Hz) appear that match literature data for acetaldehyde (Figure 3.1).[193] This could be formed via oxidation of the α-amino radical followed by hydrolysis. Although partial conversion of the styrene was suggested, no product could be isolated form the reaction mixture.

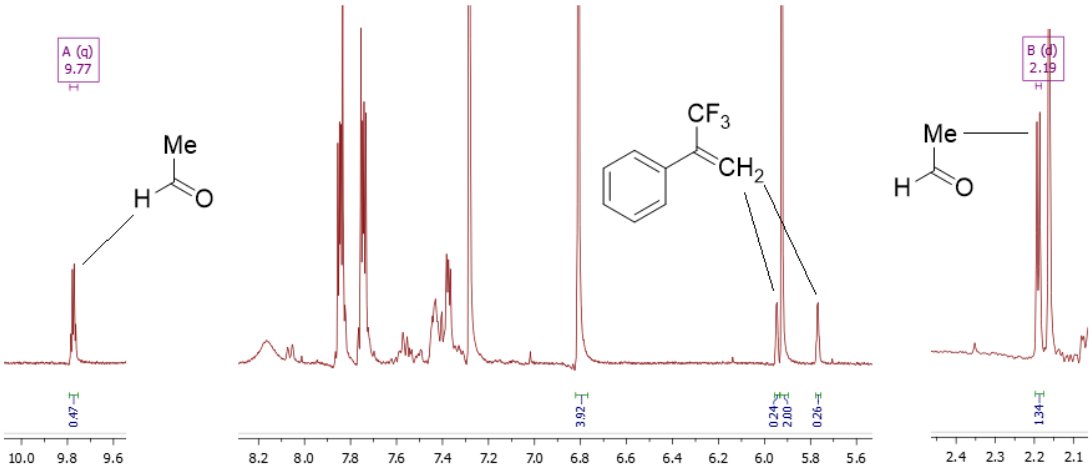
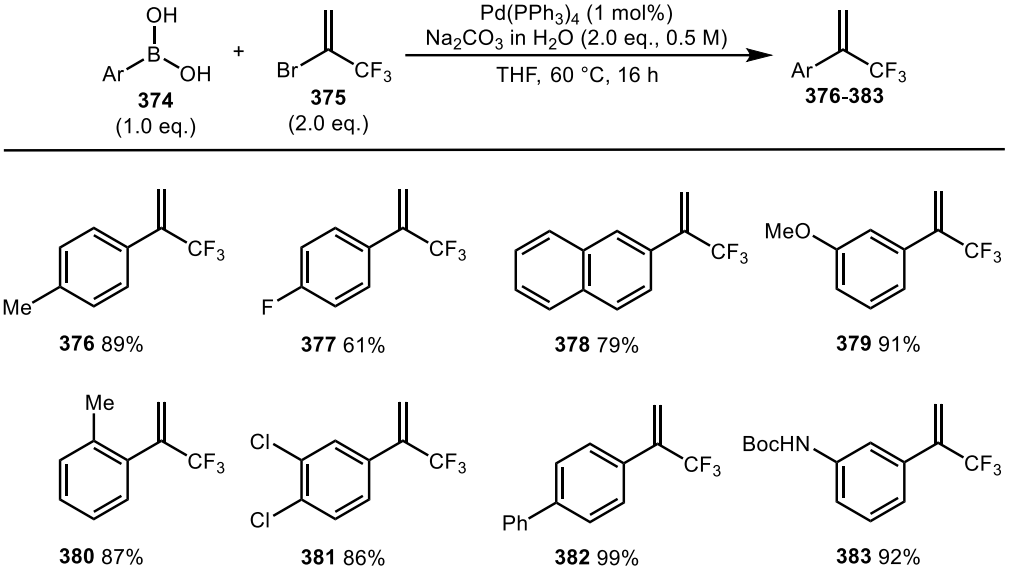


Figure 3.1. ^{1}H NMR spectrum of the unpurified reaction mixture in the reaction with phthalimide ester **354**.

3.4 Styrene Scope

3.4.1 Synthesis of Different α-Trifluoromethyl Styrenes

Next, we wanted to investigate the feasibility of the process towards different α-trifluoromethyl styrenes. We decided to employ a Suzuki-coupling between 2-bromo-3,3,3-trifluoropropene and aryl boronic acids to access the target substrates in one step using conditions reported by the Cheng group (Scheme 3.16).[194]

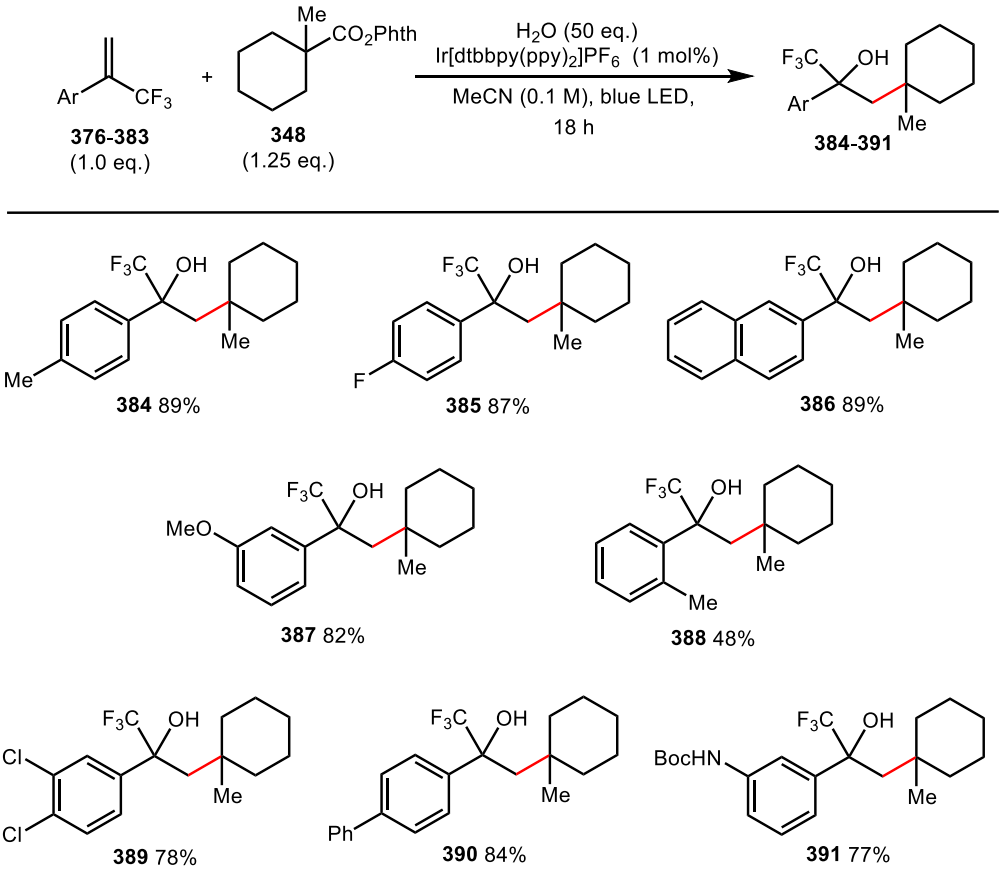


Scheme 3.16. Preparation of α-trifluoromethyl styrenes.

The Suzuki couplings proceeded smoothly in all cases affording the target α-trifluoromethyl styrene derivatives **376**-**383** in high yield (61-99%). It was suspected that the products could be volatile, particularly products **376**, **377** or **380**, and the lower yield for product **377** could be the result of mass loss by during drying. Hence, these samples were purified with volatile solvents (ether, hexane) and not dried on the high vacuum.

3.4.2 Oxyalkylation of Different α-Trifluoromethyl Styrenes with Phthalimide Ester 348

Once the styrenes had been prepared, their ability to participate in radical oxyalkylation was tested. As model reaction partner, we chose phthalimide ester **348** as it performed well in the first part of the scope and allowed facile analysis of the unpurified reaction mixture due to the characteristic signal of the methyl group in the ^{1}H NMR spectrum (Scheme 3.17).



Scheme 3.17. α-Trifluoromethyl styrene scope.

To our delight, the reaction gave high product yields (48-89%) for the tested α-trifluoromethyl styrene derivatives. Different functional groups such as halides (**385** and **389**) and alkyl- or aryl-substituents (**384**, **390**) were tolerated without having a significant impact on the reaction outcome. Substrates with electron-donating substituents were feasible reactants such as demonstrated in products **387** and **391**.

Furthermore, naphthalene derivative **386** was obtained in satisfying yield. Even product **388** with an *ortho*-substituent could be obtained, albeit in lower yield.

The decreased yield in the formation of compound **388** compared to other α-trifluoromethyl styrene derivatives is likely a result of destabilisation of the benzylic radical/carbocation intermediate. The *ortho*-substituent can cause additional steric hindrance and distort the planar sp^2-hybridised benzylic radical/carbocation leading to a lower yield. In the isolated product sample, the steric restraint arising from the *ortho*-substituent manifests in the hindrance of free rotation of the $C_{benz.}$–C_{aryl} bond. In fact, the appearance of rotamers at room temperature complicated the assessment of the ^{1}H and ^{13}C NMR spectroscopic data. Final confirmation proving that the target molecule **388** was indeed formed was provided by the HMBC NMR spectrum, which showed coupling between the one of the diastereotopic protons at C-3 (at 1.99 ppm) and the highly split quaternary benzylic carbon at 81.5 ppm (Figure 3.2).

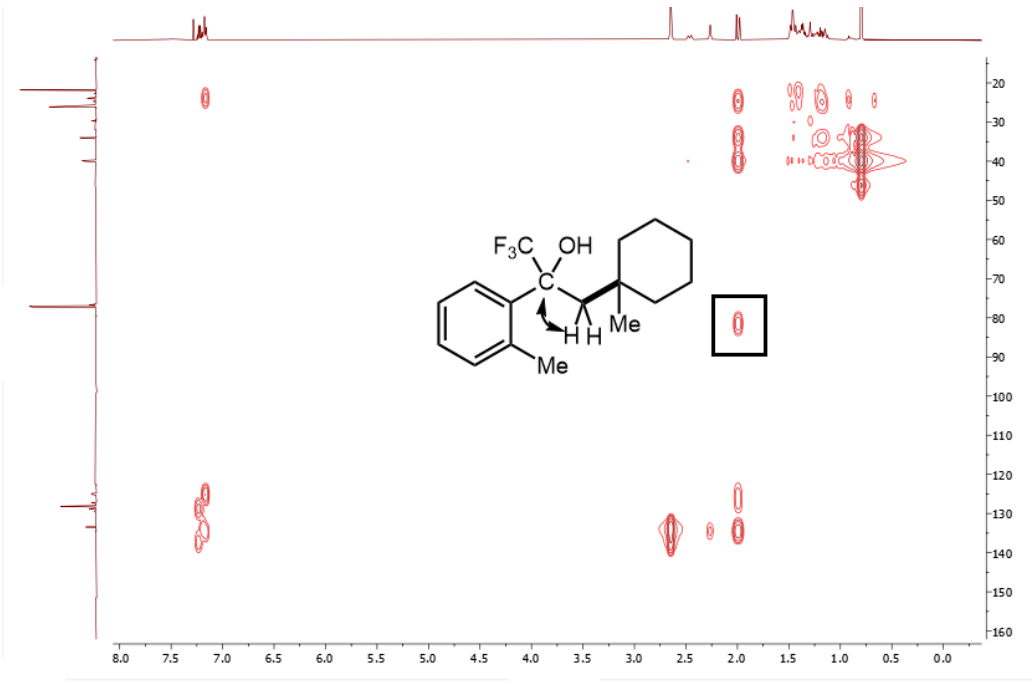
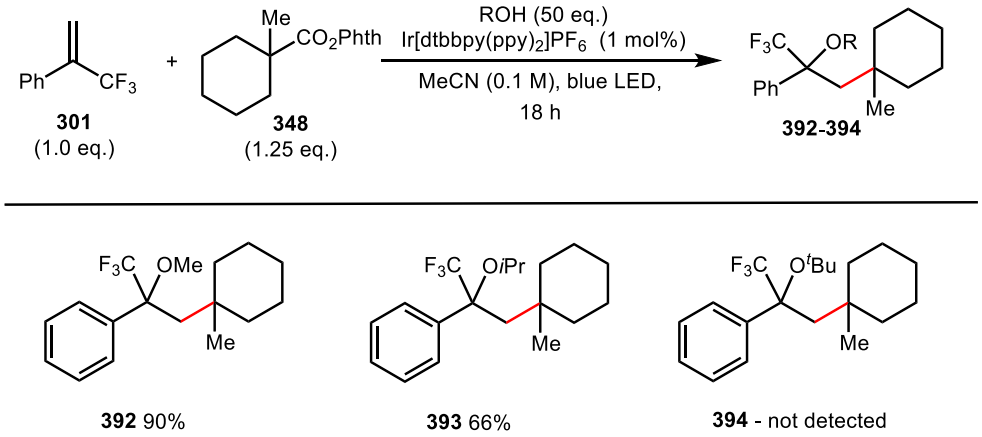


Figure 3.2. HMBC NMR spectrum of oxyalkylation product **388**.

3.5 Nucleophile Scope

3.5.1 Difunctionalisation with *O*-based Nucleophiles

The model reaction between α-trifluoromethyl styrene **301** and phthalimide ester **348** was conducted using different nucleophiles to trap the carbocation intermediate. From the original oxyalkylation procedure reported by Glorius and co-workers, it had been demonstrated that simple alcohols are feasible substitutes for water.[108] We therefore tested the reaction using 50.0 equivalents of methanol, *iso*-propanol and *tert*-butanol (Scheme 3.18).



Scheme 3.18. Nucleophile scope with alcohols.

The reaction with methanol as nucleophile afforded the target methyl ether **392** in high yield (90%), while product **393** trapped with *iso*propanol was obtained in lower yield (66%). Meanwhile, no product could be obtained in the reaction with *tert*-butanol. In this case, the ^{1}H NMR of the unpurified reaction mixture suggested approximately 76% recovered phthalimide ester, which could hint at insufficient activation of the phthalimide ester towards single electron reduction.

3.5.1 Difunctionalisation with *N*-based Nucleophiles

Our focus then shifted to nitrogen-based nucleophiles that could lead to highly valuable products or building blocks for pharmaceutical applications. However, it was not feasible to use nucleophiles in such excess (50.0 equivalents) as was standard for water or simple alcohols. We therefore commenced investigations on small scale with (a) 1.0 equivalent and (b) 3.0 equivalents of nucleophile in the absence of water.

Moreover, we conducted test reactions with (c) 3.0 equivalents of nucleophile *and* 50.0 equivalents of water hoping that the more potent nitrogen-based nucleophiles would outcompete water despite their relative scarcity. The results of the test reactions are summarised in Table 3.1. We were particularly looking for the diastereotopic protons that typically appear in the region between 2.0 and 3.0 ppm as they are the only characteristic signals that can be assigned to the potential products.

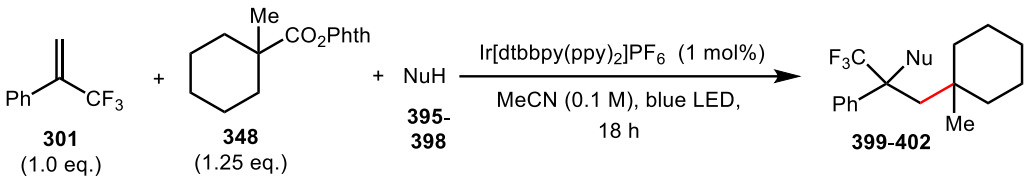


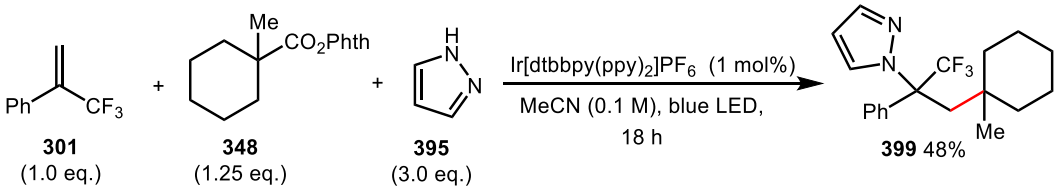
Table 3.1. Test reactions with styrene **301** and different nitrogen-based nucleophiles.

Entry	Nucleophile	Additive	Yield[a]
1	Pyrazole (1.0 eq.)	-	-
2	Pyrazole (3.0 eq.)	-	39%
3	Pyrazole (3.0 eq.)	H_2O (50.0 eq.)	6%
4	*p*-Toluenesulfonamide (1.0 eq.)	-	<5%
5	*p*-Toluenesulfonamide (3.0 eq.)	-	-
6	*p*-Toluenesulfonamide (3.0 eq.)	H_2O (50.0 eq.)	-
7	*p*-Toluidine (1.0 eq.)	-	-
8	*p*-Toluidine (3.0 eq.)	-	-
9	*p*-Toluidine (3.0 eq.)	H_2O (50.0 eq.)	-
10	*N*-Methylindole (1.0 eq.)	-	-
11	*N*-Methylindole (3.0 eq.)	-	-
12	*N*-Methylindole (3.0 eq.)	H_2O (50.0 eq.)	-

[a]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

The ^{1}H NMR spectra of the unpurified reaction mixtures of test reactions using *p*-toluenesulfonamide **396**, *p*-toluidine **397** and *N*-methylindole **398** as nucleophiles did not display any signals that could be assigned to diastereotopic protons in the target products. Generally, large amounts of unreacted styrene and phthalimide ester could

be seen in the ^{1}H NMR spectra and via TLC analysis. On the other hand, reactions with pyrazole **395** as nucleophile did lead to the appearance of promising signals at 2.8-2.9 ppm in the ^{1}H NMR spectrum that could indicate the diastereotopic protons of the product. The reaction with excess pyrazole (3.0 equivalents) without additive worked best and was therefore repeated on a larger scale (Scheme 3.19).



Scheme 3.19. Difunctionalisation of styrene **301** with an alkyl radical and pyrazole.

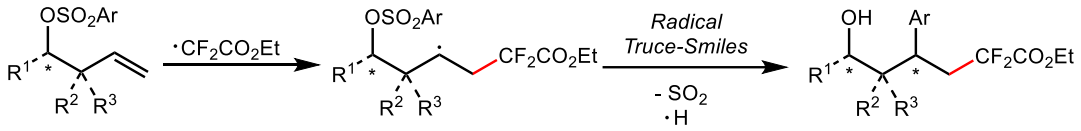
Using these un-optimised conditions, the desired α-trifluoromethylated pyrazole **399** was isolated in moderate yield (48%). This reaction constitutes the only reported alkene functionalisation by addition of an alkyl radical followed by terminal trapping with a pyrazole. Due to limited research time, no further experiments could be conducted to further explore this encouraging result.

3.6 Summary and Future Work

The oxyalkylation of α-trifluoromethyl styrenes was successful across a broad scope of styrene and alkyl radical coupling partners. However, no products could be obtained with α-amino radicals, presumably due to oxidation thereof under reaction conditions. Several alternatives to water as nucleophile were explored. While trapping of the benzylic cation with other *O*-based nucleophiles has already been reported on styrene derivatives, the addition of pyrazole led to the formation of a novel class of α-trifluoromethylated pyrazoles. Future research on this project will continue to screen different pyrazole derivatives in the reaction with α-trifluoromethyl styrenes. Various electron-deficient groups could be tested as substitutes for the trifluoromethyl group to expand the scope of this difunctionalisation method further. Moreover, it would be interesting to employ pyrazoles in other photoredox-catalysed transformations as nucleophiles to trap commonly generated carbocations.

Chapter 4. Alkene Difunctionalisation via Radical Truce-Smiles Rearrangement

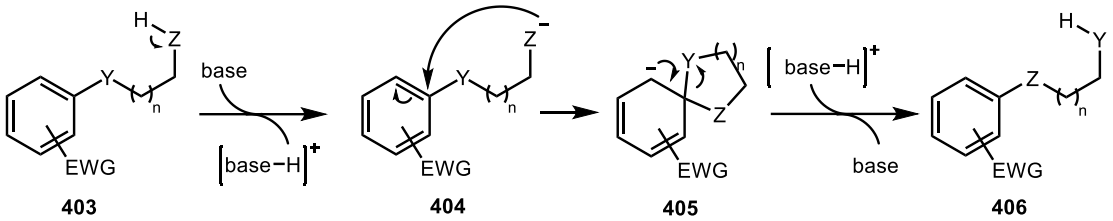
In a different part of this project, we were interested in achieving radical difunctionalisation of unactivated alkenes using fluorinated alkyl radicals. The intramolecular migration of a suitable aryl group is an intriguing method to generate a second new C–C bond at the higher substituted carbon of the original alkene moiety. Using this radical Truce-Smiles rearrangement strategy, it would be possible to synthesise γ-fluorinated arenes via an alternative pathway to the addition of fluorinated alkyl radicals into styrenes previously described. Moreover, the intramolecular nature of the aryl migration step renders this reaction (dia-)stereoselective as a result of a defined transition state similar to the stereoselective 1,5-hydride shift discussed in Chapter 2 (Scheme 4.1).



Scheme 4.1. Proposed preparation of γ-fluorinated arenes by radical Truce-Smiles rearrangements.

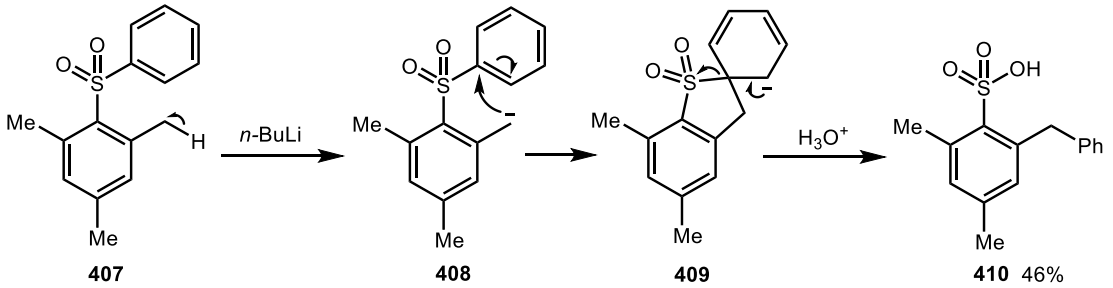
4.1 Review of Radical Truce Smiles Rearrangements

Smiles rearrangements are intramolecular migration events of aryl groups to nucleophilic centres.[195] Although originally defined as two electron process,[196] Smiles rearrangements with radicals have also been reported.[197] The key feature in the mechanism is an *ipso*-attack of an entering group Z onto the aromatic ring under formation of an ionic or radical cyclic intermediate **405**. Herein, the electron density in the aromatic ring is a decisive factor and electron withdrawing groups are often used to facilitate this cyclisation step as they stabilise a negative charge that is generated at the cost of the aromaticity. The bicyclic intermediate **405** opens by cleaving the C–Y bond thereby recovering aromaticity in the product (Scheme 4.2).[198]



Scheme 4.2. General mechanism of the ionic Smiles rearrangement.

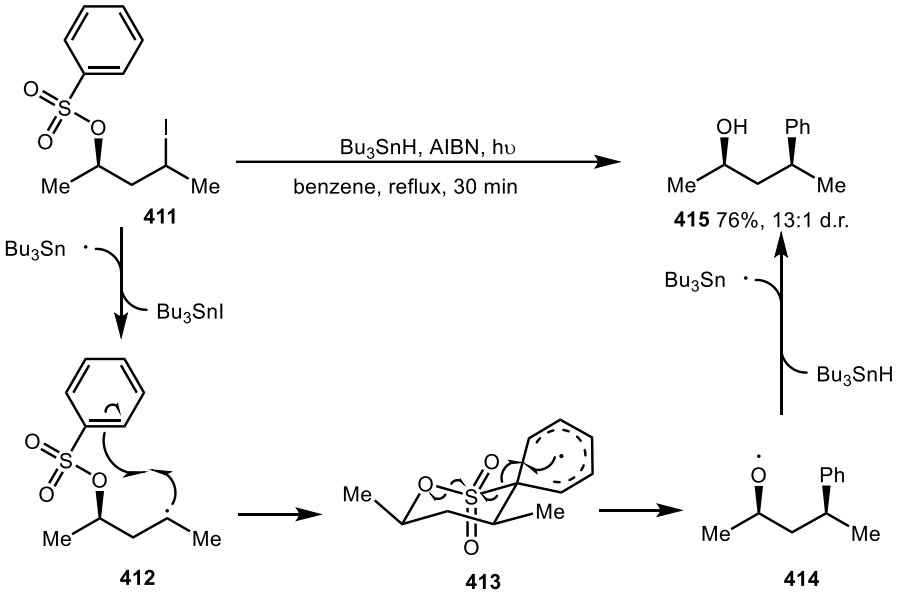
The Truce-Smiles rearrangement is a special modification in which a C–C bond is formed. In the first example of this reaction type, Truce and co-workers treated mesityl phenyl sulfone **407** with strong base to generate a benzylic carbanion **408** that was able to attack into the electron-deficient phenyl group. The resulting anionic Meisenheimer intermediate **409** profited from the stabilisation by the electron-withdrawing sulfone group and the five-membered ring opened accordingly. Subsequent treatment of anion **409** under aqueous acidic conditions yielded sulfonic acid product **410** (Scheme 4.3).[199]



Scheme 4.3. First Truce-Smiles rearrangement by Truce.[199]

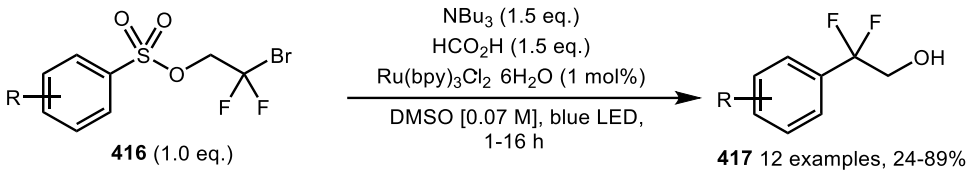
Aryl sulfonates are very common in (Truce-)Smiles rearrangements which can be attributed to the high nucleofugality of the sulfonyl group.[198] Moreover, the SO_2 bridge can be cleaved and its irreversible extrusion as gas creates a strong entropic driving force. The Studer group first studied the radical Truce-Smiles rearrangement on aryl sulfonates using traditional organo tin activation of an alkyl halide.[200] Unfortunately, the process suffered from the typical drawbacks associated with organostannane chemistry such as significant direct reduction as well as purification and toxicity issues. It was found that, if the stereocentre at C-4 was defined, products

like **415** could be obtained with high stereoselectivity. The group explained this phenomenon with a chair-like six-membered ring transition state **413** (Scheme 4.4).



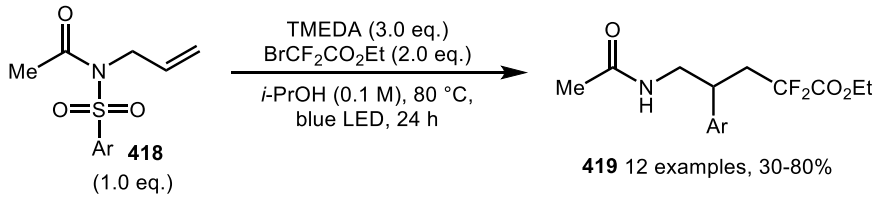
Scheme 4.4. Stereoselective radical Smiles-Truce rearrangement.[200]

Based on Studer's finding and equipped with many advancements in radical chemistry, the Stephenson group were the first to publish a photoredox-catalysed Truce-Smiles rearrangement (Scheme 4.5).[201] Similar to Studer's dehalogenation procedure, Stephenson and co-workers used sulfonates of bromo difluoroethylacetate to initiate a unimolecular transformation. It was shown that the process is viable to synthesise a broad range of difluoroarylethanol derivatives with electron-poor aryl groups including several pharmaceutically relevant heteroaromatics. Nonetheless, yields dropped sharply with *ortho*-substituted arenes.



Scheme 4.5. Photoredox-catalysed Truce-Smiles rearrangement by Stephenson.[201]

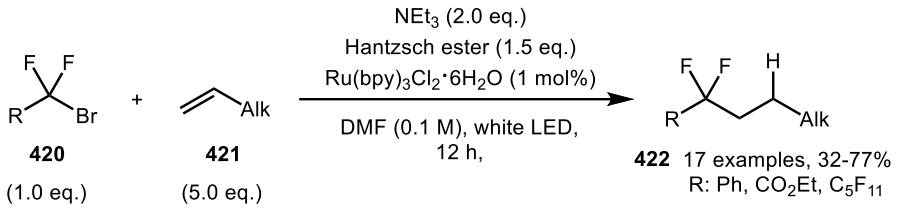
Other groups have presented bimolecular radical Truce-Smiles rearrangements. Generally, these protocols involve the addition of a radical to an alkene leading to an intermediate that is able to perform the key aryl migration step.[198] Greaney and co-workers have recently published a visible light-mediated Truce-Smiles rearrangement with arene sulfonyl-protected amides (Scheme 4.6).[202] Although the reaction is mediated by light, no photocatalyst is required. Based on UV/Vis spectroscopy, it was proposed that the base (TMEDA) and ethyl bromodifluoroacetate could form a reactive EDA complex that would provide ethyl difluoroacetate radicals under visible light irradiation. The group exclusively used protected amides **418** as substrates. Aryl groups are mostly limited to substituted benzene derivatives with 2-thiophene (Y = 56%) as the only reported heterocycle.



Scheme 4.6. Visible light-mediated Truce-Smiles rearrangement reported by Greaney.[202]

4.2 Optimisation for a Radical Truce-Smiles Rearrangement

We commenced this part of the project by employing reported conditions that were used to perform similar transformations to our system. Kishikawa and co-workers published a photoredox-catalysed hydrodifluoroalkylation of alkenes using difluorohaloalkyl compounds **420**.[203] The irradiation of the difluorohaloalkyl reagent generated an active difuoroalkyl radical that could attack the π-system of an alkene **421**. The resulting carbon-centred radical could be reduced by a hydrogen source, in this case Hantzsch ester, to furnish the target product (Scheme 4.7). Terminal and internal alkenes were successfully employed in the reaction, and the yields were typically higher with EWGs attached to the C=C double bond that could facilitate the radical attack. We envisioned that an intramolecular Truce-Smiles rearrangement could outcompete terminal hydrogen trapping by a hydrogen donor.



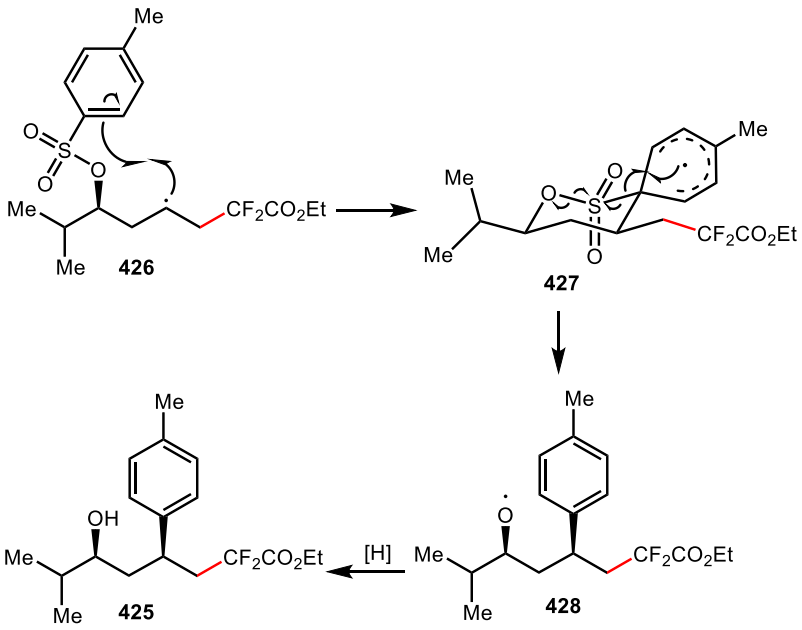
Scheme 4.7. Hydrodifluoroalkylation of alkenes by Kishikawa.[203]

The optimisation was conducted with ethyl bromodifluoroacetate (**424**) as a commercially available difluorohaloalkyl reagent and 2-methyl-5-hexen-3-4-methylbenzenesulfonate (**423**) as substrate (preparation thereof and related alkenes is covered in Chapter 4.3.1). Since the aryl sulfonate had to be prepared from the corresponding alcohol and was more valuable than the difuorohaloalkyl compound, the optimisation was started with 2.0 equivalents rather than 5.0 equivalents of alkene. In a test reaction under Kishikawa's conditions, no product was observed, and instead, reduced starting material and oxidised Hantzsch ester were found. The reaction was then repeated without Hantzsch ester (HE) and product **425** was isolated in 25% yield (same yield using blue or white LED) (Scheme 4.8).



Scheme 4.8. Initial hydrodifluoroalkylation test reactions.

The product was obtained as an inseparable mixture of diastereoisomers. A comparison with literature data revealed that predominately formed diastereoisomer had a *syn* relationship between the hydroxy group and the migrated aryl group (Scheme 4.9).[204] This observation is in agreement with the findings reported by Studer.[200] Throughout the optimisation of the reaction conditions, combined yields of the two product diastereoisomers are given.



Scheme 4.9. Origin of diastereoselectivity in the synthesis of product **425**.

According to Kishikawa, Hantzsch ester was involved both in the hydrogen donation of the radical adduct and in the catalyst cycle as electron source. However, it is well established that a tertiary amine can also fulfil the latter role,[49] while being a significantly less potent hydrogen donor. Encouraged by the first results, we continued the optimisation by screening several common solvents (Table 4.1).

The target product was not formed in THF and EtOAc (Table 4.1, entry 2 and 5). The yields in MeCN and DCM were determined by ^{19}F NMR spectroscopy using fluorobenzene as internal standard, and were high (entry 3 and 4), but purification by flash column chromatography revealed that the actual yield was far lower (entry 3 was not purified). Further studies showed that yields determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as internal standard were more accurate. The reactions proceeded equally well in acetone and EtOH (entry 6 and 7), the yield in DCM was slightly lower (entry 5).

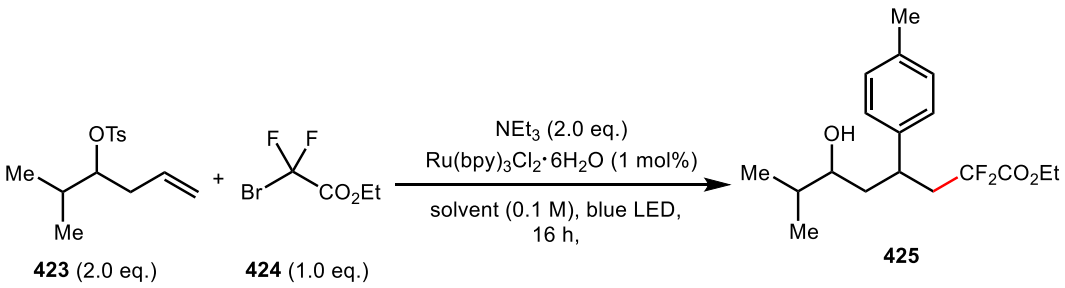


Table 4.1. Optimisation of difunctionalisation (1): solvent.

Entry	Solvent	Yield
1	DMF	25%
2	THF	-
3	MeCN	37%[b]
4[a]	DCM	54%[b] (27%)
5	EtOAc	-
6[a]	Acetone	35%[c] (33%)
7	EtOH	35%[c]

[a]Isolated yield in parenthesis, [b]Yield determined by ^{19}F NMR spectroscopy using fluorobenzene as internal standard, [c]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as internal standard.

Next, the base was optimised. This step of the optimisation was mainly conducted with DCM as solvent since the incorrect yields on the basis of ^{19}F NMR spectroscopy using fluorobenzene as internal standard were taken as reference. MeCN served as solvent for the inorganic bases CsF and K_2CO_3 that did not dissolve in DCM.

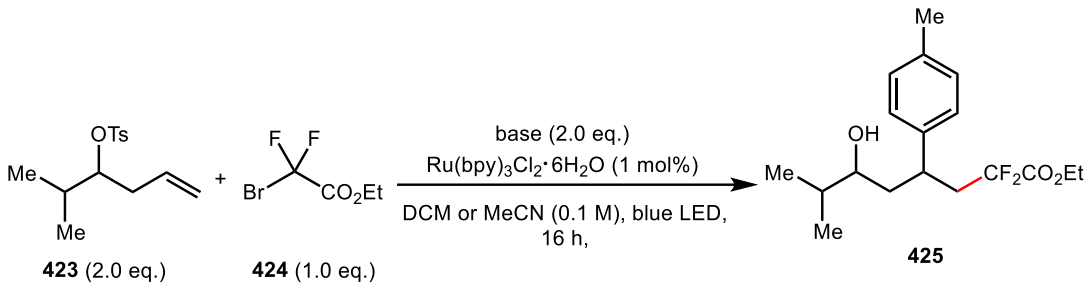


Table 4. 2. Optimisation of difunctionalisation (2): base.

Entry	Base	Solvent	Yield[a]
1	K_2CO_3	MeCN	-
2	Hantzsch ester	DCM	12%
3	DABCO	DCM	10%
4	DBU	DCM	5%
5	CsF	MeCN	-
6	DIPEA	DCM	22%

[a]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as internal standard.

Inorganic bases were not able to support product formation (Table 4.2, entry 1 and 5). Surprisingly, the reaction with Hantzsch ester as surrogate for NEt_3 did yield product, albeit in low yield (Table 7, entry 2). DABCO and DBU gave significantly lower yields (Table 7, entry 3 and 4), while DIPEA (Table 7, entry 6) was almost as effective as NEt_3.

The photocatalyst is a decisive factor in the reaction. The Kishikawa group reported that *fac*-Ir(ppy)$_3$ and eosin Y (an organic dye) did not catalyse the process as effectively as $Ru(bpy)_3Cl_2{\cdot}6H_2O$. We wanted to employ *fac*-Ir(ppy)$_3$ and 4CzIPN as photocatalysts in our reaction. The photocatalysts were tested in DCM, acetone and EtOH (Table 4.3).

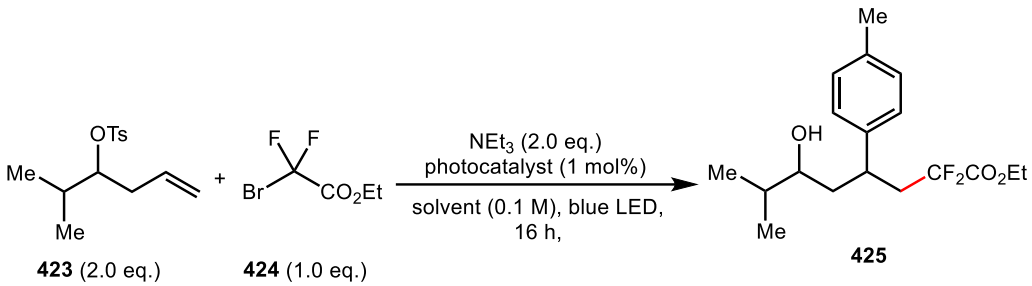


Table 4.3. Optimisation of difunctionalisation (3): photocatalyst.

Entry	Photocatalyst	Solvent	Yield[a]
1	*fac*-Ir(ppy)$_3$	DCM	36%
2	*fac*-Ir(ppy)$_3$	Acetone	36%
3	4CzIPN	DCM	33%
4	4CzIPN	Acetone	50%
5	4CzIPN	EtOH	50%

[a]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as internal standard.

Table 4.3 lists the results of the photocatalyst screening in the three best solvents. Test reactions with *fac*-Ir(ppy)$_3$ (entries 1 and 2) led to slightly higher yields in each of the solvents compared to reactions with Ru(bpy)$_3$Cl$_2$·6H$_2$O (Table 4.1, entries 5-7). Gratifyingly, the organic photocatalyst 4CzIPN gave even better results with yields of 50% in acetone and EtOH (Table 4.3, entry 4 and 5). EtOH is more environmentally friendly and was therefore used as standard solvent in the further course of the optimisation. Moreover, acetone and DCM evaporated partially during the degassing process thus distorting real reaction concentrations.

Lastly, different reactant ratios were screened. Additional parameters like concentration as well as amounts of base and photocatalyst were also varied.

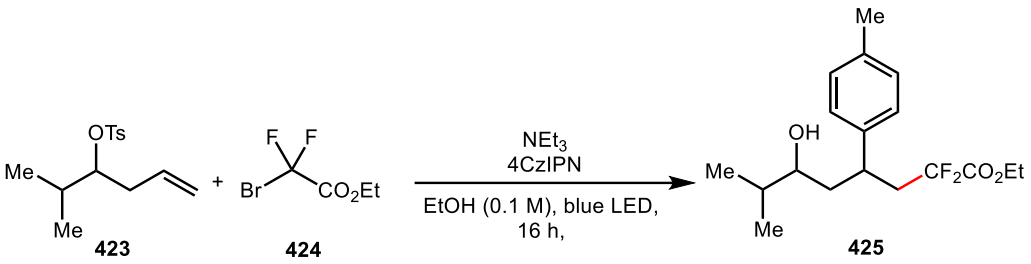


Table 4.4. Optimisation of difunctionalisation (4): stoichiometry and concentration.

Entry	Eq. (422)/ Eq. (424)	Eq. (4CzIPN)	Eq. (NEt_3)	Yield[a]
1[b]	**1/2**	**0.01**	**2**	**49% (44%)**
2	1/1	0.01	2	43%
3	2/1	0.01	2	50%
4	1/2	0.025	2	57%
5	1/2	0.01	1.05	44%
6	1/2	0.01	4	40%
7[b, c]	1/2	0.01	2	51% (45%)

[a]Yield determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as internal standard. [b]Isolated yield in parenthesis. [c]Reaction on 0.45 mmol scale.

To our delight, swapping the ratio of alkene to difluoroalkyl reagent from 2:1 (Table 4.4, entry 3) to 1:2 (entry 1) gave a marginally better yield whereas equivalent amounts of alkene substrate and radical precursor led to lower yield (entry 2). The yield with 2.5 mol% photocatalyst was higher (entry 4), yet the impact was not sufficient to justify an increased catalyst loading. Changing the base concentration did not result in higher yields (entries 5 and 6). When scaling up the reaction from 0.3 mmol of alkene substrate to 0.45 mmol, no significant change in yield was obtained (compare entry 1 and 7).

4.2.1 Discussion of By-products

In the ^{19}F NMR spectrum of the unpurified reaction mixture, there was always a signal at –123.4 ppm which can be assigned to debrominated ethyl 2,2-difluoroacetate **426** (Figure 4.1).[205] This species is not able to re-form an active radical due to the stronger C–H bond, and an excess of bromodifluoroalkyl reagent appears therefore favourable. Furthermore, hydrogen abstraction can also occur after radical addition into the alkene. The corresponding side-product **427** was confirmed by mass spectroscopy. The ATRA product (in this case side-product **428**), which is regularly observed in radical reactions with bromo difluoroethylacetate, was not detected.

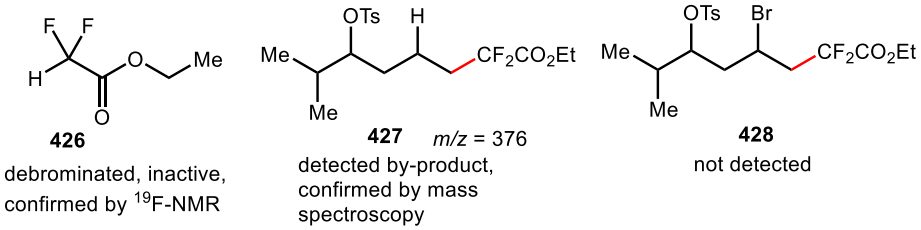


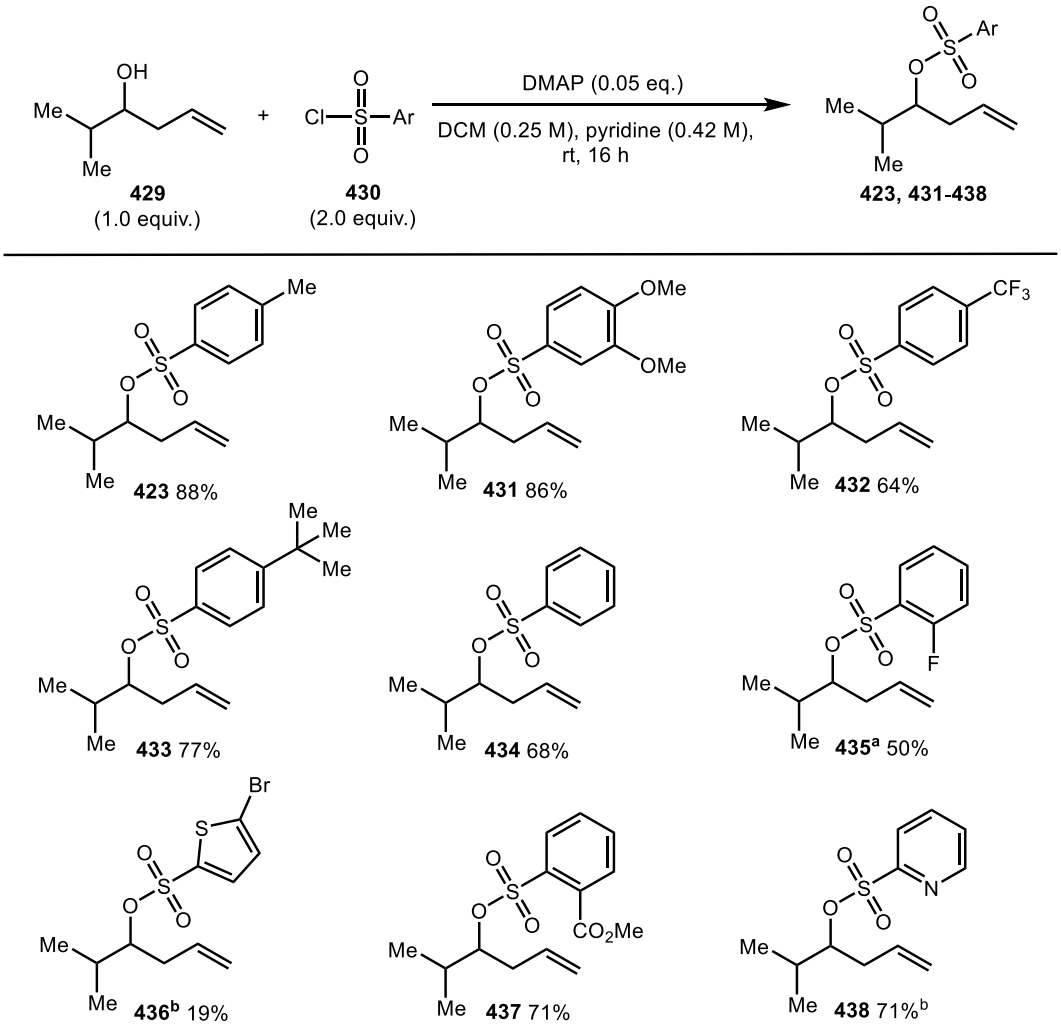
Figure 4.1. Detected side products in the radical Truce-Smiles rearrangement.

We concluded that the conditions with excess radical precursor and excess base (Table 4.4, entry 1), sufficed even though the product yield using these conditions was only moderate. This was rationalised as the tolyl migration group had not been reported to give particularly high yields compared to a similar reported radical Truce-Smiles rearrangement.[206] However, in hindsight, we should have tested if the employment of additional radical precursor beyond 2.0 equivalents relative to alkene would give better results, as unreacted alkene was commonly detected in the NMR spectrum of the unpurified reaction mixture.

4.3 Investigation of the Aryl Migration Group

4.3.1 Preparation of Aryl Sulfonates

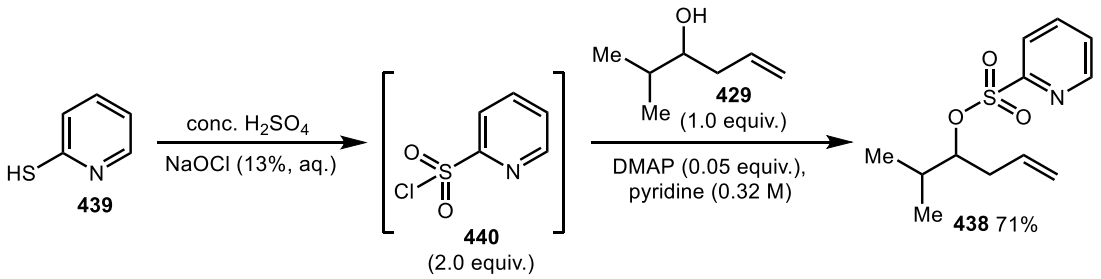
With optimised conditions in hand, the feasibility of the process was analysed on different substrates. In the first part of the scope, we decided to keep the alkyl framework unchanged while altering the aryl migration group. To this end, several aryl sulfonates were prepared in a nucleophilic substitution using the corresponding sulfonyl chloride and 2-methyl-5-hexen-3-ol **429** (Scheme 4.10). The reaction medium was a mixture of DCM and pyridine unless a related reaction with a particular sulfonyl chloride was reported to give higher yields using pyridine as the only solvent.



Scheme 4.10. Preparation of aryl sulfonates. a) with 1.0 eq. sulfonyl chloride; b) in pyridine (0.32 M).

Most of the aryl sulfonates could be isolated in good to high yields (64-88%), with the exception of sulfonate **436**, which was only obtained in poor yield (19%). A possible explanation is given by the Shenvi group who reported significant decomposition of the corresponding 5-bromothiophene sulfonate using (–)-isopulegol as alcohol coupling partner.[206] The yield of product **435** is lower because only 1.0 equivalent of sulfonyl chloride was added. Generally, transformations of alcohols into sulfonates are conducted with excess sulfonyl chloride to account for loss thereof via hydrolysis for instance.

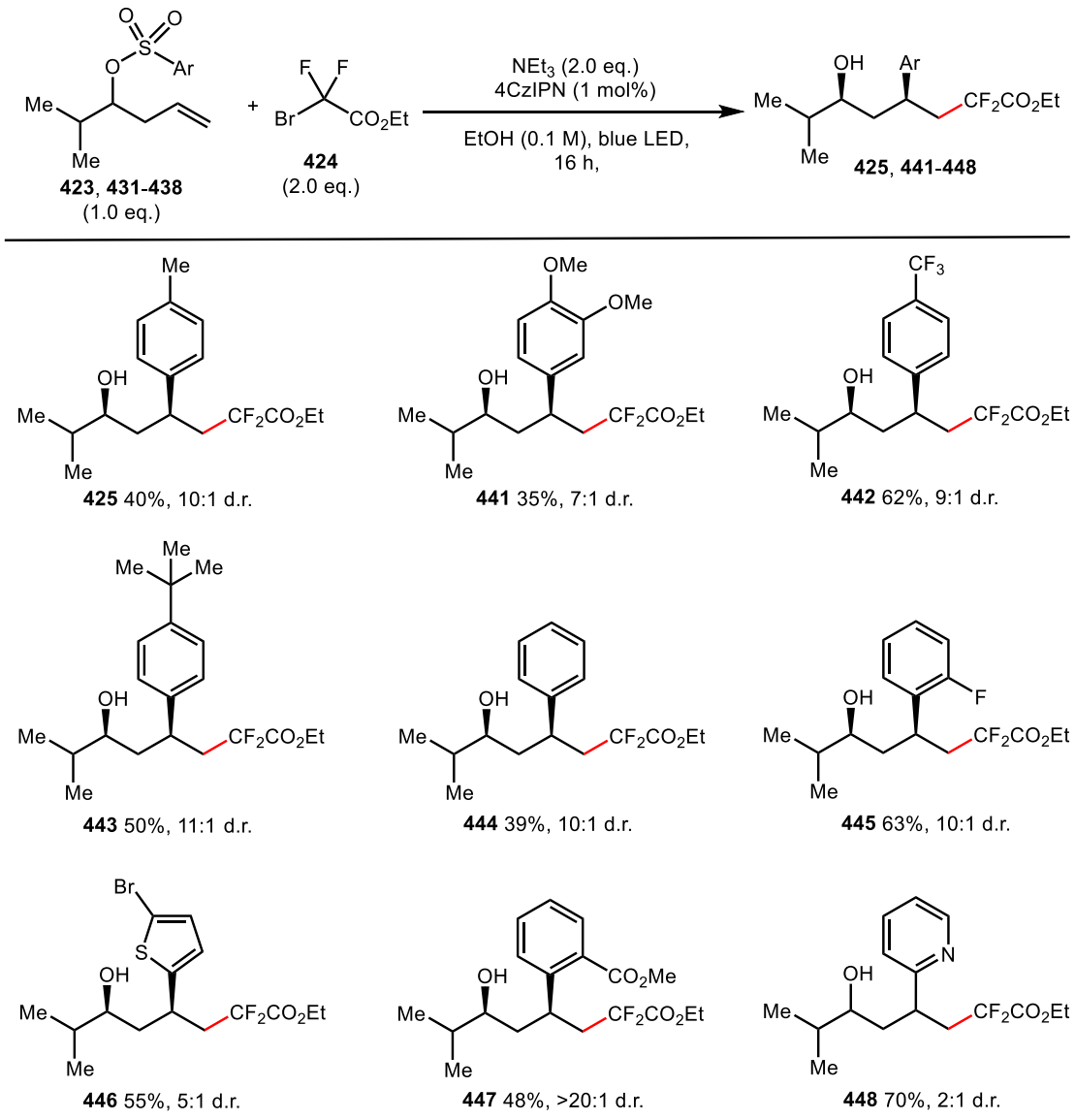
Sulfonate **438** with a 2-pyridyl group stemmed from pyridine-2-sulfonyl chloride, which had to be prepared beforehand from the respective thiol under strongly oxidising conditions. It should be noted that these *N*-heteroaryl sulfonyl chlorides are known to be unstable at room temperature, hence the crude sulfonyl chloride **440** (which was sufficiently clean aside from minor solvent residue of <5%) was used in the nucleophilic substitution without purification via chromatographic methods or prolonged exposure to reduced pressure (Scheme 4.11).



Scheme 4.11. Preparation of sulfonate **438**.

4.3.2 Radical Truce Smiles Rearrangement with Different Aryl Sulfonates

After the aryl sulfonates had been prepared, we turned to examining the aryl group migration ability using the standard conditions for radical Truce-Smiles rearrangements developed above (Scheme 4.12).

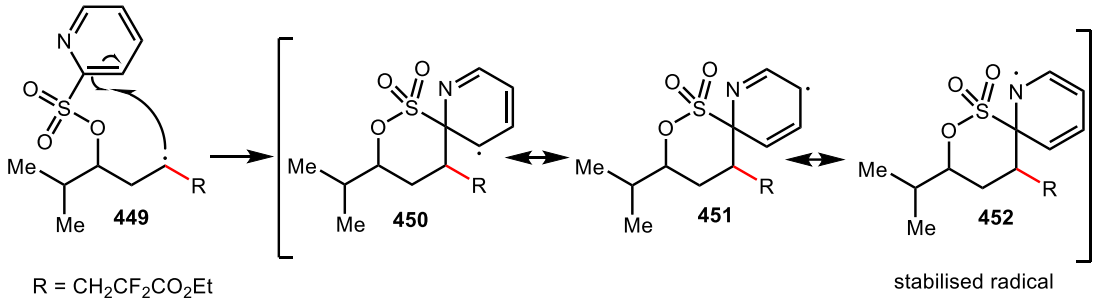


Scheme 4.12. Aryl migration group scope.

As expected, a wide range of aryl sulfonates successfully underwent radical Truce-Smiles rearrangements, wherein the aryl migration group displayed significant impact on the reaction outcome. Generally, the unsubstituted phenyl group in product **444** as

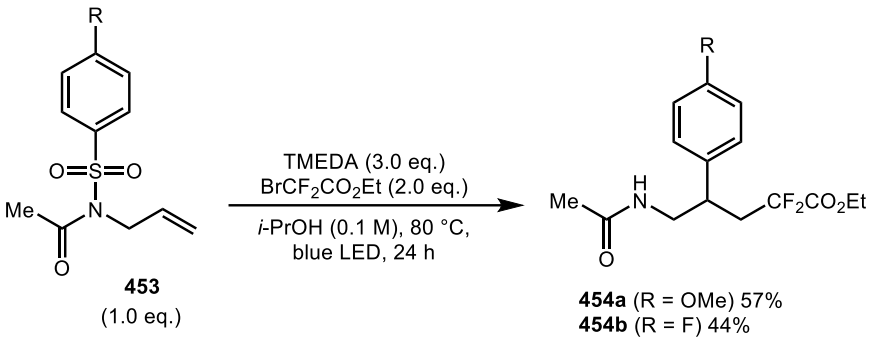
well as aryl groups with electron-donating substituents in products **425**, **441**, **443** and **447** led to lower product yields (35-55%) in comparison to products that arose from migration of more electron-deficient (hetero-)aromatics (**442**, **445** and **448** 62-70%). As the diastereoselectivity was high for products **441**-**447**, the predominant formation of *syn*-diastereoisomer can be assumed in these cases. The lower selectivity in the case of product **448** forbids this generalisation; however, chemical shifts and splitting patterns suggest that the major diastereoisomer also resembles the *syn*-configuration.

A good yield of 70% was obtained of product **448**, in which the 2-pyridine unit is transferred. A closer look on the mesomeric forms of the Meisenheimer adduct can aid to understand this result. In polar Truce-Smiles rearrangements, 2- and 4-pyridines are reported to generally afford higher product yields due to the stabilised resonance structure with the negative charge located on the nitrogen.[207,208] A similar effect could account for the higher yield of rearrangement product **448** via a radical process (Scheme 4.13).



Scheme 4.13. Possible mesomeric stabilisation in rearrangement of 2-pyridyl group.

It should be noted, however, that electronic nature of the migration groups appears considerably less impactful in contrast to anionic Truce-Smiles rearrangements, which are reportedly shut down completely with electron-rich aromatics.[207,208] Furthermore, in the very similar radical Truce-Smiles rearrangement reported by the Greaney group, this trend cannot be confirmed as higher product yields were obtained in several cases with electron-rich migration groups compared to aromatics that possess electron-withdrawing substituents (Scheme 4.14).



Scheme 4.14. Migration of electron-rich and electron-poor aryl group reported by Greaney.

Interestingly, the increased yield of pyridine derivative **448** is accompanied by a significant drop in diastereoselectivity (2:1 vs. typically 10:1) compared to higher ratios of diastereoisomers in the other reactions.

By contrast, a bulky *ortho*-substituent as in substrate **437**, led to a particularly high selectivity, which can be attributed to a larger energy difference in the transition state between two opposing conformations **455** and **456** significantly favouring the transition state with the alkyl chain in pseudoequatorial position (Figure 4.2).

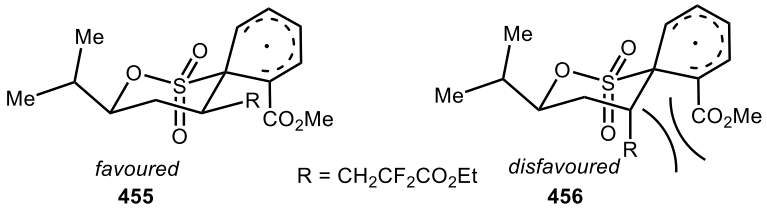


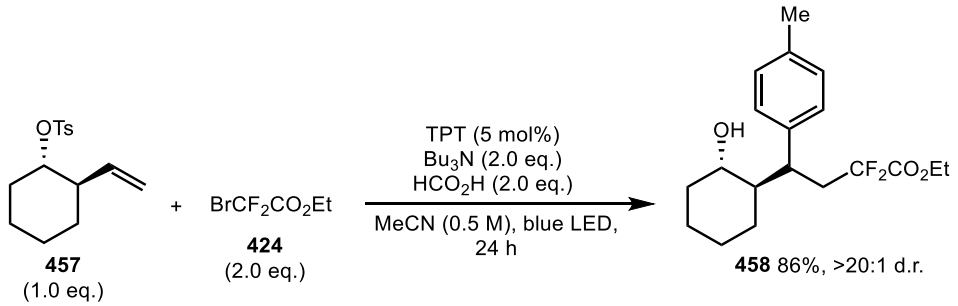
Figure 4.2. Possible conformations of transition state in the synthesis of **447**.

With the reaction scope of different aryl groups completed, our focus shifted towards the analysis of various alkyl frameworks and their impact on the reaction. A range of β-hydroxy alkenes would be prepared and subsequently converted into the corresponding aryl sulfonates. However, as we were planning out this part of the scope, a paper was published by the Liu group that demonstrated the same

transformation that we were investigating: the radical Truce-Smiles rearrangement of aryl sulfonates using bromo difluoroethylacetate as radical precursor (Chapter 4.4).[204] In light of Liu's work, we decided to pause this project before further looking into the scope or the mechanism (kinetics, transition state energies, etc.).

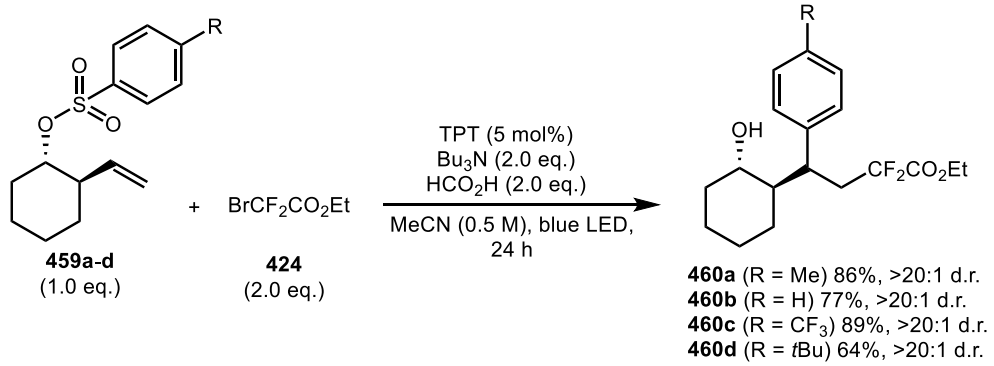
4.4 Radical Truce-Smiles Rearrangement of Aryl Sulfonates Reported by Liu

The Liu group used slightly different conditions in their visible-light-induced difunctionalisation of unactivated alkenes with bromo difluoroethylacetate (Scheme 4.15). Crucially, the group employed 2.0 equivalents of formic acid as hydrogen donor, which significantly increased the yield from 37% to 63% under otherwise same conditions. Moreover, the group observed that 2,4.6-triphenylpyrylium tetrafluoroborate (TPT) is a superior photocatalyst over several other tested metal-based and organic alternatives. 4CzIPN was also tested and afforded the standard product in the optimisation process in 66% yield while TPT yielded 82% target product (both reactions with 2 mol% of photocatalyst). It was decided to add 5 mol% photocatalyst to the reaction even though the increase from 2 mol% only led to a marginally higher yield (86%). The stoichiometric ratios of alkene, radical precursor and base were identical to our conditions (1:2:2). Optimal product yields were obtained in acetonitrile, but similar results were achieved in ethyl acetate and DMF (neither DCM, acetone nor ethanol were mentioned in the optimisation).



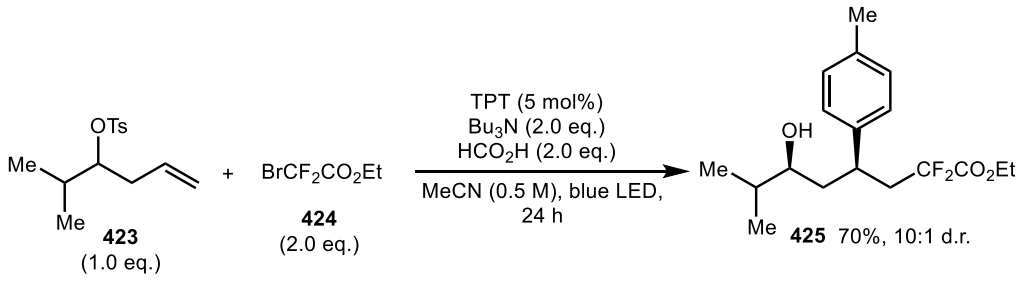
Scheme 4.15. Standard reaction under optimised conditions reported by Liu.[204]

In the first part of the scope, the group investigated the aryl group migration ability using different 2-vinylcyclohexanol-derived substrates **459** and report good yields across a broad spectrum of (hetero-)aryl groups (13 examples, 70-96%). Notably, the reported diastereoselectivities are exceptionally high throughout (typically >20:1, all ≥10:1) which could result from conformational restriction due to the underlying cyclohexane ring. Examples, in which the group explored the same aryl group as we tested are given below (Scheme 4.16). Unfortunately, the scope did not involve the migration of pyridyl groups.



Scheme 4.16. Scope of aryl sulfonates.[204]

Reactions with linear distal alkene tosylates in comparison afforded products in lower stereoselectivities (typically 10:1, all ≥7:1) but similar yields (7 examples, 62-95%). The reaction to obtain product **425** was the only given example, that contained the same carbon skeleton that our substrates had, and product **425** was obtained in better yield and similar diastereoselectivity (Scheme 4.17)



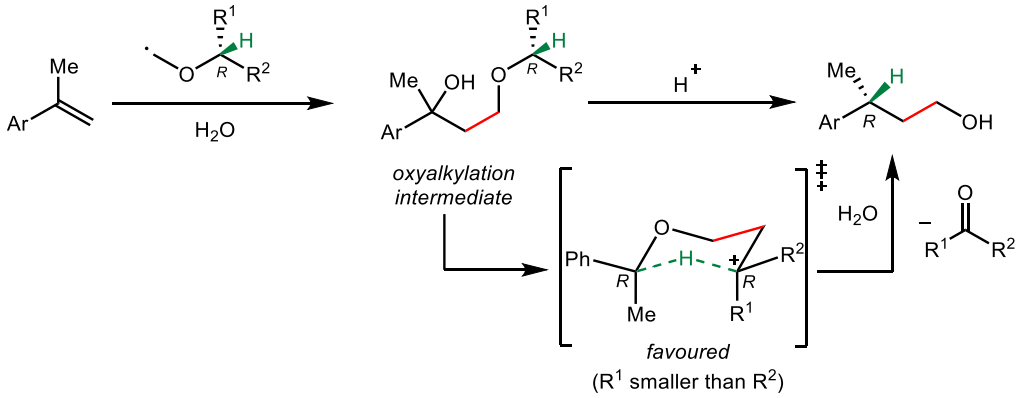
Scheme 4.17. Scope of different linear alkene tosylates.[204]

4.5 Summary

A procedure for the radical Truce-Smiles rearrangement with aryl sulfonate substrates and bromo difluoroethyl acetate as radical precursors was developed. The method proved useful in the conversion of several sulfonates with electronically different aryl migration groups. The migration of a 2-pyridyl group resulted in particularly high product formation, yet a particularly low diastereoselectivity at the same time. Unfortunately, a report by the Liu group describing the same process under different conditions was published before further investigations could be undertaken.

Chapter 5. Conclusion and Outlook

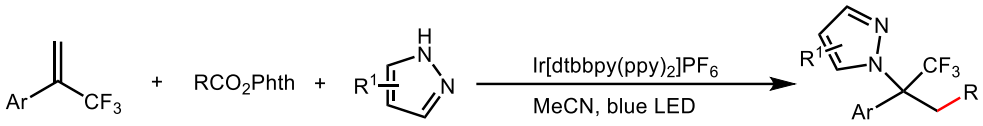
Several methods for the radical functionalisation of alkenes are reported in this Thesis. The radical hydroalkylation of styrene derivatives is presented as a two-step, one-pot process employing phthalimide esters as alkyl radical precursors. The oxyalkylation intermediate resulting from the initial photoredox-catalysed step is converted into the target molecule under Brønsted-acidic conditions. Mechanistic investigations suggest that a hydride transfer takes place in this second step and no 1,5-HAT occurs. Various substitution patterns on the phenyl ring (with the exception of *ortho*-substituents) and different alkyl groups attached to the benzylic carbon atom are tolerated in the overall transformation. Generally, higher product yields are obtained with secondary alkyl radicals than with primary alkyl radicals, presumably as a result of enhanced nucleophilicity and radical stability. In reactions with styrene derivatives bearing a substituent at C-2 and secondary alkyl radicals, the final products are obtained as diastereoisomers. The selectivity herein can be explained using a six-membered ring chair-like transition state for the hydride transfer, and the relative sizes of the substituents exhibit a great impact on the isomer ratios. A similar model can be applied in the hydride transfer step from a chiral enantioenriched alkyl tether. In this case, the stereoselective transfer ultimately leads to the preferential formation of one enantiomer of the product (Scheme 5.1).



Scheme 5.1 Remote chirality transfer in the hydroalkylation of α-methyl styrene derivatives.

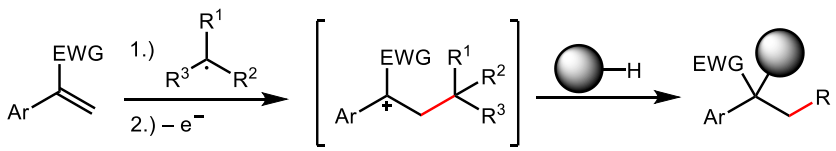
It is planned to investigate the stereoselectivity in the hydride transfer step further. To this end, the obtained results will serve as a basis for DFT calculations to gain further insight into the exact structure of the transition state. This could help develop more sophisticated systems operating via a remote chirality transfer.

Moreover, the difunctionalisation of α-trifluoromethyl styrenes is described. The product yields largely depend on the nature of the alkyl radical clearly favouring electron-rich tertiary radicals. Meanwhile, the electronic and steric attributes of the α-trifluoromethyl styrenes seem to play an inferior role. Alongside trapping the benzylic carbocation intermediate with water, limited examples utilising other nucleophiles are demonstrated. Most importantly, a test reaction with pyrazole under un-optimised conditions affords the corresponding product in moderate yield, potentially enabling synthesis of α-trifluoromethylated pyrazoles (Scheme 5.2).



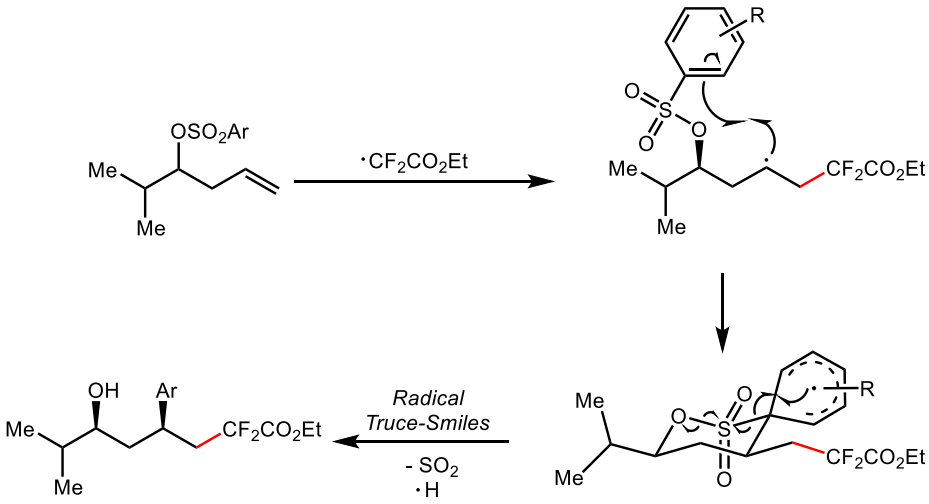
Scheme 5.2. Potential synthesis of α-trifluoromethylated pyrazoles,

This process is intriguing because radical addition reactions into electron-deficient alkenes followed by oxidation and trapping with a nucleophile are uncommon. Further research in the group is focusing on exploring substitutes for the trifluoromethyl group to evaluate, which other groups allow such transformations (Scheme 5.3). Secondly, no procedures are reported that employ pyrazole as a nucleophile in photoredox-catalysed reactions. Therefore, after testing various substituted pyrazoles in the reaction with α-trifluoromethyl styrenes, different reactions following literature procedures could be conducted with pyrazole as an alternative nucleophile.



Scheme 5.3 Difunctionalisation of electron-deficient styrene derivatives via benzylic carbocations.

Lastly, the radical Truce-Smiles rearrangement of aryl sulfonates is reported commencing with the addition of fluorinated alkyl radicals to unactivated alkenes. As in the presented hydroalkylation procedure discussed in Chapter 2, a six-membered ring chair-like transition state is a key aspect of the process and determinative for the stereoselective outcome of the reaction. The migration ability of different aryl groups is analysed, and electron-poor aromatics seem to favour product formation, although this trend cannot be confirmed by literature precedent. Unfortunately, a publication by the Liu group has been released before the process could be investigated further. Thus, no additional work is planned on this part of the project.



Scheme 5.4 Radical Truce-Smiles rearrangement of aryl sulfonates

Chapter 6. Experimental

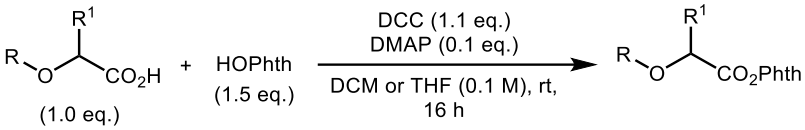
Starting materials were obtained from commercial sources and were used without further purification unless stated otherwise. Reactions were carried out under an atmosphere of argon (unless otherwise stated), and reactions requiring anhydrous conditions were performed in oven-dried apparatus using distilled solvents. Diethyl ether, *N*,*N*-dimethylformamide and tetrahydrofuran were taken from an Inert® PureSolv MD5 solvent purification system under nitrogen. All water used was previously deionised. 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. 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 ($CDCl_3$ δH 7.26, δC 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; pent, pentet; sext, sextet; hept, heptet; br, broad; app, apparent. J values are reported in Hertz (Hz) to the nearest decimal place. Structural assignment was aided by the use of DEPT, COSY, HSQC and HMBC spectroscopy. All numbering on the structures below is for the benefit of structure characterisation and does not conform to IUPAC rules. Diastereotopic protons are labelled with lower case a or b. Indistinguishable protons (such as in *iso*-propyl groups or in cyclohexane rings) are labelled with (A) or (B). Spectroscopic data for diastereoisomers are given separately if all protons can be assigned to the major and minor component, and signals are labelled major or minor if not all signals can clearly be assigned for the minor isomer.

All IR experiments were carried out on a Bruker Tensor 27 FT-IR spectrometer. Mass spectra were recorded on a Bruker MicroTOF spectrometer using electrospray ionisation (ESI) and electron impact ionisation (EI) techniques with positive or negative ion detection. Melting points were recorded on a Stuart SMP20 instrument and optical activity was measured using an Anton Paar MCP 100.

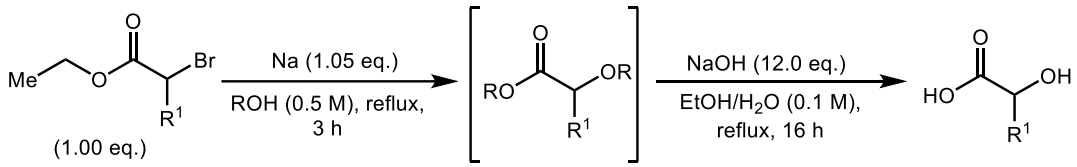
6.1 General Procedures

6.1.1 General Procedure for the Synthesis of Phthalimide Esters from Carboxylic Acids (General Procedure A):



The carboxylic acid (1.0 eq.) was dissolved in DCM or THF (0.1-0.15 M) at rt, then hydroxy phthalimide (1.1–1.5 eq.), DCC (1.1 eq.) and DMAP (0.1 eq.) were added. The reaction was stirred for 16 h at rt, then the precipitate was filtered off and the filtrate was concentrated *in vacuo* to afford the crude product which was purified by FCC.

6.1.2 General Procedure for the Synthesis of Carboxylic Acids Containing Non-Benzylic Hydride Donors (General Procedure B):



Alkylation:

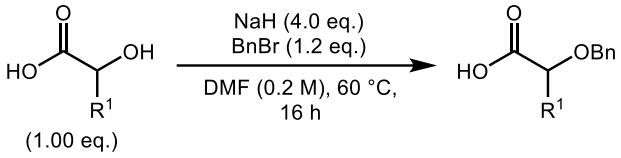
Sodium (1.05 eq.) was added carefully to the respective alcohol (0.5 M) under inert atmosphere and heated to reflux for 30 min. To the solution of sodium alkoxide, alkyl bromide (1.0 eq.) was added over a period of 30 min, then the resulting mixture was heated to reflux. After 3 h, the solvent was removed, the residue redissolved in water and Et_2O, then the aqueous layer was separated and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), then concentrated *in vacuo*.

Acid hydrolysis:

The residue was redissolved in EtOH (0.2 M) and a solution of NaOH (12.0 eq.) in water (0.2 M) was added. The resulting mixture was then heated at reflux for 16 h.

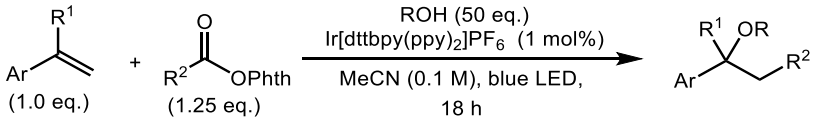
After cooling to rt, the solvent was removed, and the residue redissolved in water and Et_2O. The organic layer was extracted with water, then the combined aqueous layers were acidified with 1 M aq. HCl to pH = 1. The aqueous layer was then extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting acid was used in the next step without further purification.

6.1.3 General Procedure for the Synthesis of Carboxylic Acids Containing Benzylic Hydride Donors (General Procedure C):



α-Hydroxy acid (1.0 eq.) was dissolved in DMF (0.2 M) and NaH (60 wt% in mineral oil, 4.0 eq.) was added at 0 °C. The reaction was stirred at 0 °C for 30 min, then benzyl bromide (1.2 eq.) was added dropwise. The resulting mixture was stirred at 60 °C for 16 h. After cooling to rt, the mixture was diluted with Et_2O and 1 M aq. HCl. The organic layer was separated, then washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was flushed through a small filter column to afford the crude carboxylic acid, which was sufficiently pure to use without further purification.

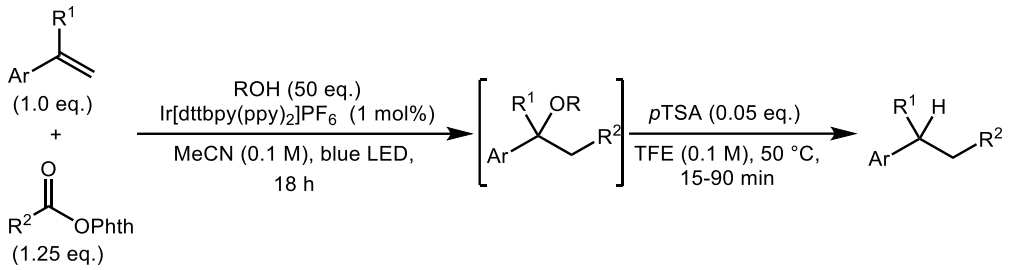
6.1.4 General Procedure for the Oxyalkylation of Styrene Derivatives (General Procedure D):



Following the procedure developed by reported Glorius,[108] styrene (1.0 eq.) and phthalimide ester (1.0-1.25 eq.) were dissolved in MeCN (0.1 M). $Ir[dtbbpy(ppy)_2]PF_6$ (1 mol%) and water (50 eq.) were added and the solution was degassed with argon for

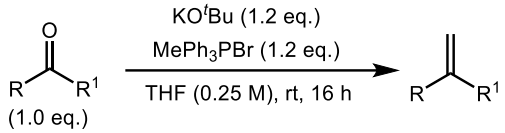
5-10 min. The mixture was stirred for 18 h at rt under irradiation of blue LED (455 nm). The volatiles were then evaporated, and the residue was purified by FCC.

6.1.5 General Procedure for the Hydroalkylation of Styrene Derivatives (General Procedure E):



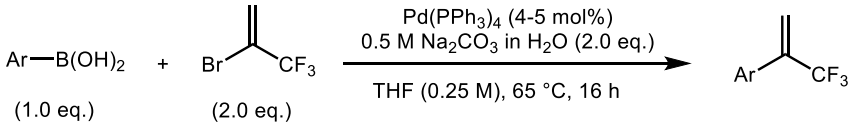
Styrene (1.0 eq.), phthalimide ester (1.25 eq.) and $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%) were dissolved in MeCN (0.1 M). H_2O (50.0 eq.) was added, and the mixture was sparged with argon for 5-10 min. The reaction was then stirred under irradiation with blue LED (456 nm) at rt for 16 h. The solvent was removed, and the residue redissolved in cyclohexane (or hexane), filtered and the filtrate washed with H_2O, 1M aq. NaOH, and brine. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude oxyalkylation product, which was used in the next step without further purification. The residue was redissolved in TFE (0.1 M) and a solution of *p*TSA in TFE (0.06 M, 0.05 eq.) was added. The mixture was stirred at 50 °C for 45 min. After cooling to rt, the reaction was quenched with an aq. NH_3 solution (pH = 9). The aqueous layer was then extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FCC.

6.1.6 General Procedure for the Wittig Reaction of Benzylic Ketones (General Procedure F):



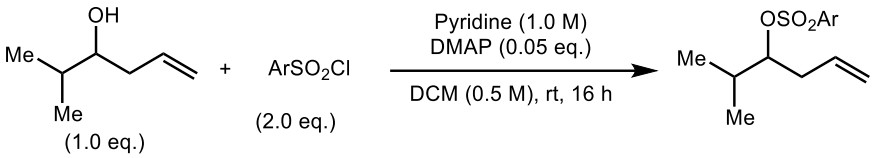
In an oven-dried flask, methyl triphenylphosphonium bromide (1.2 eq.) and potassium *tert*-butoxide (1.2 eq.) were dissolved in dry THF (0.3 M) at 0 °C and the solution was stirred for 30 min. Ketone (1.0 eq.) in THF (0.2 M) was added slowly and the reaction was stirred at rt for 16 h. The reaction was quenched with sat. aq. NH_4Cl, then the aqueous phase was separated and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), then concentrated in *vacuo* to afford the crude product which was purified by FCC.

6.1.7 General Procedure for the Synthesis of α-Trifluoromethyl Styrene Derivatives via Suzuki Coupling (General Procedure G):



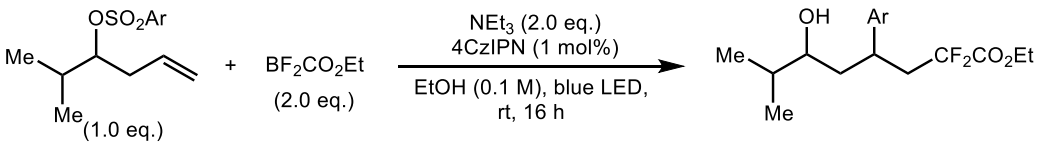
The aryl boronic acid (1.0 eq.) was dissolved in THF (0.25 M) at rt and 2-bromo-3,3,3-trifluoropropene (2.0 eq.), $Pd(PPh_3)_4$ (4-5 mol%) and Na_2CO_3 (0.5 M in H_2O, 2.0 eq.) were added. The mixture was degassed for 5 min with Ar and then stirred at 65 °C for 16 h. After cooling to rt, the mixture was quenched with sat. aq. NH_4Cl and extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and carefully concentrated *in vacuo*. The residue was purified by FCC.

6.1.8 General Procedure for the Synthesis of Aryl Sulfonates (General Procedure H):



In an oven-dried flask, 2-methylhex-5-en-3-ol (1.0 eq.) was dissolved in DCM (0.5 M) and pyridine (1.0 M). Arylsulfonyl chloride (1.0-2.0 eq.) and DMAP (0.05 eq.) were added, and the resulting mixture stirred at rt for 16 h. The reaction was quenched with cold water and the aqueous layer was extracted with DCM (3 × 30 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was then purified by FCC.

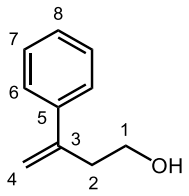
6.1.9 General Procedure for the Radical Truce-Smiles Rearrangement of Aryl Sulfonates (General Procedure I):



Aryl sulfonate (0.400 mmol, 1.0 eq.), bromo difluoroethyl acetate (102 µL, 0.800 mmol, 2.0 eq.), 4CzIPN (3.10 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and NEt_3 (112 µL, 0.800 mmol, 2.0 eq.) were dissolved in EtOH (4 mL). The mixture was degassed with Ar for 5 min and then stirred at rt under irradiation of blue LED for 16 h. The mixture was then diluted with EtOAc and H_2O. The aqueous phase was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacou*. The residue was purified by FCC.

6.2 Experimental Procedures and Compound Data

3-Phenyl-3-buten-1-ol (206)

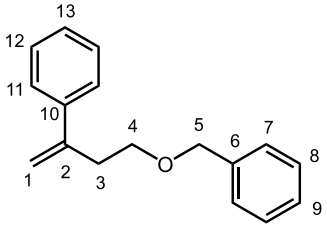


In a flame-dried flask under argon atmosphere, 3-butyn-1-ol (0.380 mL, 5.00 mmol, 1.0 eq.), phenylboronic acid (730 mg, 6.0 mmol, 1.2 eq.), and [$Pd(PPh_3)_4$] (173 mg, 0.150 mmol, 3 mol%) were dissolved in 1,4-dioxane (10 mL). AcOH (57.0 μL, 1.00 mmol, 0.2 eq.) was added and firstly stirred for 10 min at rt and then stirred at 80 °C for 16 h. After cooling to rt, MeOH (20 ml) was added, the resulting mixture stirred for 5 min and then the solvent was removed under reduced pressure. The residue was filtered through a plug of silica (SiO_2, cyclohexane:EtOAc, 1:1). Purification of the yellow oil by FCC (cyclohexane:EtOAc, 3:1) gave the title compound **206** as a colourless oil (290 mg, 1.96 mmol, 39%); R_f 0.20 (cyclohexane:EtOAc, 3:1); δ_H (400 MHz, $CDCl_3$) 7.45–7.27 (5H, m, ArH), 5.42 (1H, d, *J* = 1.3 Hz, H-4a), 5.17 (1H, d, *J* = 1.3 Hz, H-4b), 3.74 (2H, t, *J* = 6.3 Hz, H-1), 2.80 (2H, t, *J* = 6.3 Hz, H-2); δ_C (101 MHz, $CDCl_3$) 145.0 (C, C-3), 140.5 (C, C-5), 128.5 (CH, ArCH), 127.9 (CH, ArCH), 126.3 (CH, ArCH), 114.8 (CH_2, C-4), 61.1 (CH_2, C-1), 38.7 (CH_2, C-2).

Lab. Book. Ref.: LH147

Data are consistent with those previously reported.[209]

4-Benzyloxy-2-phenyl-1-buten (207)

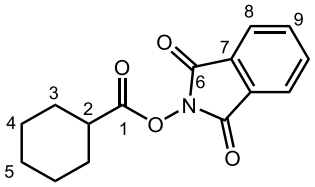


In a flame-dried flask under an argon atmosphere, 3-phenyl-3-buten-1-ol **206** (290 mg, 1.96 mmol, 1.0 eq.) was dissolved in THF (15 mL). The solution was cooled to 0 °C, sodium hydride (60 *wt.*% in mineral oil, 56.0 mg, 2.35 mmol, 1.2 eq.) was added

carefully and the resulting reaction was stirred until bubbling ceased (30-60 min). Then, benzyl bromide (0.26 mL, 2.15 mmol, 1.1 eq.) was added slowly at 0 °C and the mixture was stirred at rt for 16 h. The reaction was quenched with water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Purification by FCC (SiO_2, cyclohexane:EtOAc 20:1) gave the title compound **207** as a colourless oil (394 mg, 1.66 mmol, 85%); δ_H (400 MHz, $CDCl_3$) 7.44–7.27 (10H, m, ArH), 5.38 (1H, d, *J* = 1.3 Hz, H-1a), 5.16 (1H, d, *J* = 1.3 Hz, H-1b), 4.52 (2H, s, H-5), 3.60 (2H, t, *J* = 7.1 Hz, H-4), 2.85 (2H, t, *J* = 7.1 Hz, H-3).

Lab. Book. Ref.: LH160

1,3-Dioxoisoindolin-2-yl cyclohexanecarboxylate (210):

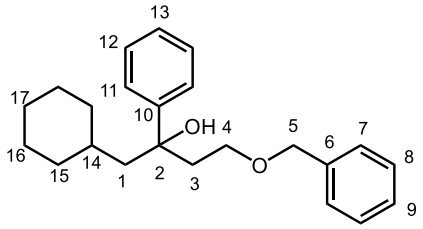


To a stirred solution of hydroxy phthalimide (2.15 g, 13.2 mmol, 1.1 eq.) in DCM (70 mL) was added cyclohexanecarboxlic acid chloride (1.60 mL, 12.0 mmol, 1.0 eq.). Triethylamine (1.84 mL, 13.2 mmol, 1.1 eq.) was added dropwise over a period of 10 min and the resulting orange mixture was stirred at rt for 16 h. The solvent was removed, and the residue redissolved in EtOAc. The suspension was filtered, the filtrate concentrated *in vacuo* and purified by FCC (SiO_2, cyclohexane:EtOAc, 6:1) to give the title compound **210** as a colourless, crystalline solid (3.27 g, 12.0 mmol, 99%); mp. 73-75 °C (Lit.[210] 69-71 °C); δ_H (500 MHz, $CDCl_3$) 7.92–7.82 (2H, m, ArH), 7.82–7.74 (2H, m, ArH), 2.73 (1H, tt, *J* = 10.9, 3.7 Hz, H-2), 2.14–2.03 (2H, m, CyH), 1.88–1.76 (2H, m, CyH), 1.73–1.58 (3H, m, CyH), 1.44–1.23 (3H, m, CyH); δ_C (126 MHz, $CDCl_3$) 171.9 (C, C-1), 162.2 (C-C-6), 134.8 (CH, ArCH), 129.1 (C, C-7), 124.0 (CH, ArCH), 40.6 (CH, C-2), 28.9 (CH_2, $CyCH_2$), 25.6 (CH_2, $CyCH_2$), 25.1 (CH_2, $CyCH_2$).

Lab Book Ref.: LH681

Data are consistent with those previously reported.[210]

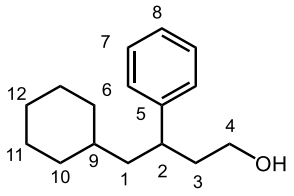
4-Benzyloxy-1-cyclohexyl-2-phenyl-2-butanol (217)



Following General Procedure D, 4-benzyloxy-1-cyclohexyl-2-phenyl-2-butanol was prepared from 4-benzyloxy-2-phenyl-1-buten **207** (95.3 mg, 0.400 mmol, 1.00 eq.) and 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate **210** (137 mg, 0.500 mmol, 1.00 eq.) with Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, $4\cdot10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) in MeCN (4 mL). Purification by FCC (SiO_2, cyclohexane:EtOAc 25:1) gave the title compound **217** as a colourless oil (43.1 mg, 0.127 mmol, 32%); δ_H (400 MHz, $CDCl_3$) 7.48–7.14 (10H, m, ArH), 4.32 (1H, d, *J* = 11.7 Hz, H-5a), 4.29 (1H, d, *J* = 11.7 Hz, H-5b), 4.18 (1H, s, OH), 3.54 (1H, app dt, *J* = 10.1, 4.2 Hz, H-4a), 3.26 (1H, ddd, *J* = 10.6 Hz, 9.5 Hz, 3.0 Hz, H-4b), 2.28 (1H, ddd, *J* = 14.7, 10.6, 4.2 Hz, H-3a), 1.97 (1H, app dt, *J* = 14.7, 3.5 Hz, H-3b), 1.83–1.75 (1H, m, H-14), 1.72–1.68 (2H, m, CyH), 1.53–1.32 (4H, m, CyH), 1.22–0.88 (5H, m, CyH), 0.78–0.67 (1H, m, CyH); *m/z* (ESI) 361 $[MNa]^+$; [HRMS (ESI): calc. for $C_{23}H_{30}NaO_2^+$, 361.2138. Found $[MH]^+$, 361.2136 (0.6 ppm error)].

Lab Book Ref.: LH154

4-Cyclohexyl-3-phenyl-1-butanol (211)

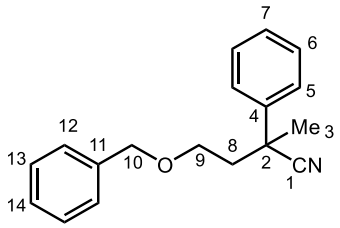


To a solution of 4-benzyloxy-1-cyclohexyl-2-phenyl-2-butanol **217** (40 mg, 0.12 mmol, 1.0 eq.) in TFE (1.2 mL) was added a solution of *p*TSA in TFE (39.0 µL, 0.06 M, $2.4\cdot10^{-3}$ mmol, 2 mol%) and the resulting mixture stirred for 90 min at 50 °C.

After cooling to rt, the reaction was quenched with an aq. NH_3 solution (pH = 9). The aqueous layer was then extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by FCC (SiO_2, cyclohexane:EtOAc 8:1) gave the title compound **211** as a colourless to yellowish oil (11.5 mg, 0.050 mmol, 42%); R_f 0.20 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3331, 2920, 2850, 1449, 1047, 759, 700; δ_H (400 MHz, $CDCl_3$) 7.33–7.26 (2H, m, ArH), 7.23–7.12 (3H, m, ArH), 3.51 (1H, ddd, *J* = 10.7, 7.0, 5.4 Hz, H-4a), 3.48 (1H, ddd, *J* = 10.7, 7.4, 6.7 Hz, H-4b), 2.89–2.77 (1H, m, H-2), 1.96–1.84 (1H, m, H-9), 1.83–1.69 (2H, m, H-3), 1.70–1.52 (5H, m, H-1, CyH), 1.50–1.39 (1H, m, CyH), 1.19–0.98 (4H, m, CyH), 0.96–0.82 (2H, m, CyH); δ_C (100 MHz, $CDCl_3$) 145.7 (C, C-5), 128.8 (CH, ArCH), 127.9 (CH, ArCH), 126.4 (CH, ArCH), 61.6 (CH_2, C-4), 45.2 (CH_2, C-3), 40.4 (CH_2, C-1), 39.6 (CH, C-2), 35.1 (CH, C-9), 34.4 (CH_2, $CyCH_2$ (A)), 33.1 (CH_2, $CyCH_2$ (B)), 26.9 (CH_2, $CyCH_2$), 26.5 (CH_2, $CyCH_2$ (A)), 26.4 (CH_2, $CyCH_2$ (B)); *m/z* (ESI) 255 $[MNa]^+$; [HRMS (ESI): calc. for $C_{16}H_{24}NaO^+$, 255.1725. Found: $[MNa]^+$, 255.1721 (1.6 ppm error)].

Lab Book Ref.: LH169

4-(Benzyloxy)-2-methyl-2-phenylbutanenitrile (221)

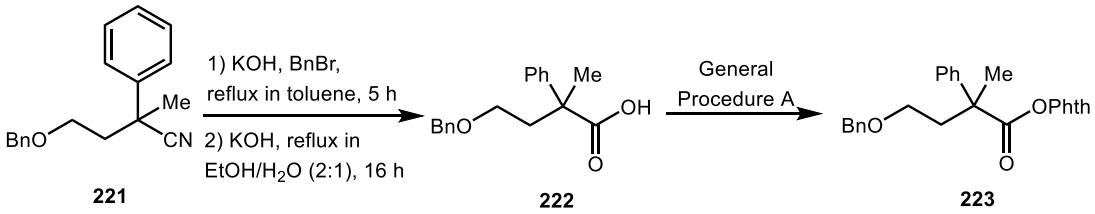


Diisopropylamine (1.23 mL, 8.75 mmol, 1.25 eq.) in THF (15 mL) was cooled down to 0 °C and *n*BuLi (2.5 M in hexanes, 3.5 mL, 8.75 mmol, 1.25 eq.) was added, then the mixture was stirred at 0 °C for 30 min. α-Methylphenylacetonitrile (0.93 mL, 7.00 mmol, 1.0 eq.) was added and the mixture stirred for 1 h at 0 °C. Benzyl 2-bromo ethyl ether (1.38 mL, 8.75 mmol, 1.25 eq.) in THF (10 mL) was added, then the resulting mixture was stirred at rt for 16 h. The reaction was quenched with water and the aqueous layer was extracted with Et_2O (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FCC (SiO_2, Cyclohexane:EtOAc, 20:1) to afford the title compound **221**

as a colourless oil (1.76 g, 6.63 mmol, 95%); R_f 0.30 (Cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 2869, 1495, 1448, 1365, 1099, 1028, 760, 736, 696; δ_H (500 MHz, $CDCl_3$) 7.48–7.44 (2H, m, ArH), 7.43–7.36 (2H, m, ArH), 7.35–7.26 (6H, m, ArH), 4.46 (1H, d, *J* = 11.8 Hz, H-10a), 4.42 (1H, d, *J* = 11.8 Hz, H-10b), 3.62 (1H, ddd, *J* = 9.7, 7.6, 6.5 Hz, H-9a), 3.46 (1H, ddd, *J* = 9.7, 7.7, 5.6 Hz, H-9b), 2.33 (1H, ddd, *J* = 14.1, 7.7, 6.5 Hz, H-8a), 2.26 (1H, ddd, *J* = 14., 7.6, 5.6 Hz, H-8b), 1.79 (3H, s, H-3); δ_C (126 MHz, $CDCl_3$) 140.0 (C, ArC), 138.1 (C, ArC), 129.1 (CH, ArCH), 128.5 (CH, ArCH), 128.0 (CH, ArCH), 127.8 (CH, ArCH), 127.7 (CH, ArCH), 125.5 (CH, ArCH), 123.3 (C, C-1), 73.3 (CH_2, C-10), 67.1 (CH_2, C-9), 41.4 (CH_2, C-8), 40.7 (C, C-2), 28.3 (CH_3, C-3); *m/z* (ESI) 266 $[MH]^+$; [HRMS (ESI): calc. for $C_{18}H_{20}NO^+$, 266.1539. Found: $[MH]^+$, 266.1538 (0.4 ppm error)].

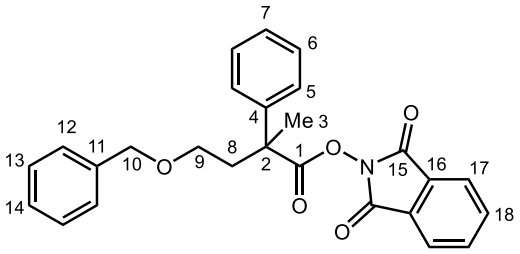
Lab Book Ref.: LH576

1,3-Dioxoisoindolin-2-yl 4-(benzyloxy)-2-methyl-2-phenylbutanoate (223)



221 **222** **223**

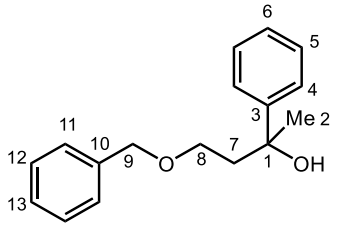
4-(Benzyloxy)-2-methyl-2-phenylbutanenitrile **221** (530 mg, 2.00 mmol, 1.0 eq.) was hydrolysed with NaOH (960 mg, 24.0 mmol, 12.0 eq.) in MeOH/H_2O (3:1, 20 mL) and stirred at 80 °C for 16 h. The solvent was removed, and the residue redissolved in Et_2O and H_2O. The aqueous layer was acidified 1 M aq. HCl to pH=1, and then extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. to afford the crude carboxylic acid **222** as a viscous yellow oil (183 mg, 0.644 mmol, 32%), which was sufficiently pure to be used without further purification; δ_H (500 MHz, $CDCl_3$) 7.48–7.23 (10H, m), 4.45–4.40 (2H, m), 3.51–3.46 (2H, m), 2.48 (1H, dt, *J* = 14.0, 7.2 Hz), 2.43–2.21 (1H, m), 1.63 (3H, s).



Carboxylic acid **222** (150 mg, 0.530 mmol) was used in the successive esterification following General Procedure A. The title compound **223** was obtained after purification by FCC (SiO_2, Cyclohexane:EtOAc, 6:1) as a viscous colourless oil (163 mg, 0.379 mmol, 72%); R_f 0.25 (Cyclohexane:EtOAc, 5:1); υ_{max}/cm^{-1} (neat) 2857, 1780, 1739, 1365, 1164, 1052, 1021, 965, 877, 736, 699; δ_H (500 MHz, $CDCl_3$) 7.89–7.85 (2H, m, ArH), 7.80–7.76 (2H, m, ArH), 7.49–7.45 (2H, m, ArH), 7.44–7.39 (2H, m, ArH), 7.35–7.24 (6H, m, ArH), 4.51 (1H, d, *J* = 11.8Hz, H-10a), 4.48 (1H, d, *J* = 11.8Hz, H-10b), 3.78–3.71 (2H, m, H-9), 2.60 (1H, ddd, *J* = 14.1, 7.7, 6.5 Hz, H-8a), 2.42 (1H, ddd, *J* = 14.1, 7.5, 6.2 Hz, H-8b), 1.85 (3H, s, H-3); δ_C (126 MHz, $CDCl_3$) 172.7 (C, C-1), 162.1 (C, C-15), 141.6 (C, ArC), 138.4 (C, ArC), 134.9 (CH, ArCH), 129.2 (C, ArC), 128.8 (CH, ArCH), 128.6 (CH, ArCH), 127.9 (CH, ArCH), 127.7 (CH, ArCH), 127.7 (CH, ArCH), 126.2 (CH, ArCH), 124.0 (CH, ArCH), 73.2 (CH_2, C-10), 66.9 (CH_2, C-9), 49.2 (C, C-2), 38.9 (CH_2, C-8), 24.3 (CH_3, C-3); *m/z* (ESI) 430 $[MH]^+$; [HRMS (ESI): calc. for $C_{26}H_{24}NO_5^+$, 430.1649. Found: $[MH]^+$, 430.1645 (1.0 ppm error)].

Lab Book Ref.: LH580

4-(Benzyloxy)-2-phenylbutan-2-ol (224)



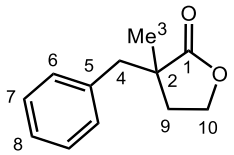
4-(Benzyloxy)-2-phenylbutan-2-ol **224** was prepared using General Procedure D with 1,3-dioxoisoindolin-2-yl 4-(benzyloxy)-2-methyl-2-phenylbutanoate **223** (86.0 mg, 0.200 mmol), Ir[dtbbpy(ppy)$_2$]PF_6 (1.80 mg, $2 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.180 mL, 10.0 mmol, 50.0 eq.) in MeCN (2 mL). Purification by FCC (SiO_2,

Cyclohexane:Et_2O, 6:1) gave the title compound **224** as a pale yellow oil (36.6 mg, 0.142 mmol, 71%); δ_H (400 MHz, $CDCl_3$) 7.89–7.85 (2H, m, ArH), 7.80–7.76 (2H, m, ArH), 7.49–7.45 (2H, m, ArH), 7.47–7.39 (2H, m, ArH), 7.39–7.20 (8H, m, ArH), 4.43–4.35 (2H, m, H-9), 3.61 (1H, ddd, *J* = 9.3, 4.9, 4.2 Hz, H-8a), 3.37 (1H, ddd, *J* = 9.7, 9.3, 3.5 Hz, H-8b), 2.24 (1H, ddd, *J* = 14.5, 9.7, 4.2 Hz, H-7a), 2.09 (1H, ddd, *J* = 14.5, 4.9, 3.5 Hz, H-7b), 1.55 (3H, s, H-2); δ_C (101 MHz, $CDCl_3$) 147.9 (C, C-3), 137.6 (C, C-10), 128.6 (CH, ArCH), 128.2 (CH, ArCH), 127.9 (CH, ArCH), 127.8 (CH, ArCH), 126.4 (CH, ArCH), 125.0 (CH, ArCH), 75.1 (C, C-1), 73.6 (CH_2, C-9), 68.2 (CH_2, C-8), 42.1 (CH_2, C-7), 31.1 (CH_3, C-2).

Lab Book Ref.: LH344

Data are consistent with those previously reported.[160]

3-Benzyl-3-methyldihydrofuran-2(3*H*)-one (226)



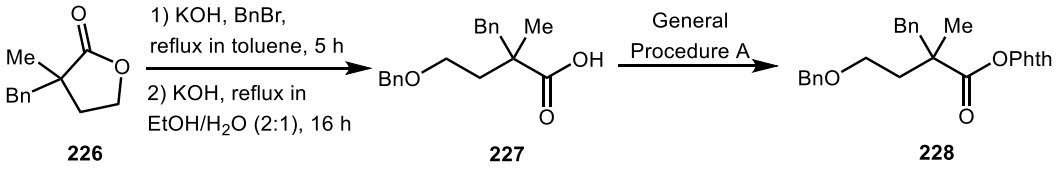
Diisopropylamine (1.69 mL, 12.0 mmol, 1.2 eq.) in THF (50 mL) was cooled to 0 °C and *n*BuLi (2.5 M in hexanes, 4.80 mL, 12.0 mmol, 1.2 eq.) was added, then the mixture was stirred at 0 °C for 30 min. α-Methyl-γ-butyrolactone (1.00 g, 10.0 mmol, 1.0 eq.) was added and the mixture stirred for 1 h at 0 °C. Then, benzyl bromide (1.43 mL, 12.0 mmol, 1.2 eq.) in THF (10 mL) was added and the resulting mixture was stirred at rt for 16 h. The reaction was quenched with water, then the aqueous layer was separated and extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FCC (SiO_2, Cyclohexane:EtOAc, 10:1) to afford the title compound **226** as a colourless oil (1.56 g, 8.20 mmol, 82%); δ_H (400 MHz, $CDCl_3$) 7.33–7.18 (5H, m, ArH), 4.11 (1H, ddd, *J* = 9.0, 8.0, 6.4 Hz, H-10a), 3.75 (1H, ddd, *J* = 9.0, 8.1, 6.0 Hz, H-10b), 3.04 (1H, d, *J* = 13.5 Hz, H-4a), 2.74 (1H, d, *J* = 13.5 Hz, H-4b), 2.29 (1H, ddd, *J* = 12.9, 8.1, 6.4 Hz, H-9a), 1.93 (1H, ddd, *J* = 12.9, 8.0, 6.0 Hz, H-9b), 1.30 (3H, s, H-3); δ_C (101 MHz, $CDCl_3$) 181.9 (C, C-1), 136.9 (C, C-5), 130.1 (CH,

ArCH), 128.6 (CH, ArCH), 127.2 (CH, ArCH), 65.1 (CH_2, C-10), 44.1 (C, C-2), 43.7 (CH_2, C-9), 33.6 (CH_3, C-3).

Lab Book Ref.: LH336

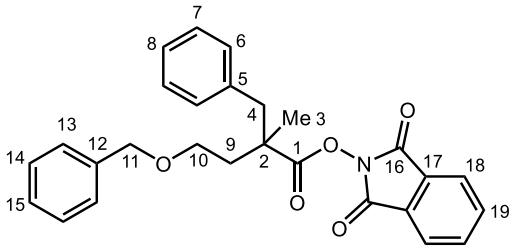
Data are consistent with those previously reported.[211]

1,3-Dioxoisoindolin-2-yl 2-benzyl-4-(benzyloxy)-2-methylbutanoate (228)



226 **227** **228**

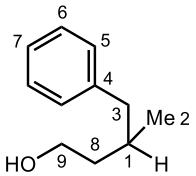
3-Benzyl-3-methyldihydrofuran-2(3*H*)-one **226** (1.33 g, 7.00 mmol, 1.0 eq.) was dissolved in toluene (35 mL). Crushed KOH (2.07 g, 36.9 mmol, 5.3 eq.) and benzyl bromide (3.30 mL, 27.9 mmol, 4.0 eq.) were added. The mixture was heated at 110 °C for 5 h. After cooling to rt, the mixture was extracted with H_2O, then the aqueous layer was acidified with 1 M aq. HCl to pH=1. The aqueous layer was extracted with Et_2O (×3) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was redissolved in EtOH/H_2O (2:1, 75 mL), crushed KOH (704 mg, 12.6 mmol, 1.8 eq.) was added and the reaction stirred at 80 °C for 16 h. The solvent was removed, and the residue redissolved in Et_2O and H_2O. The aqueous layer was acidified with 1 M aq. HCl, and then extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude carboxylic acid **227** as a viscous yellow oil (1.65 g, 5.70 mmol, 79%), which was sufficiently pure to be used without further purification; δ_H (500 MHz, $CDCl_3$) 7.43–7.10 (10H, m), 4.48 (2H, s), 3.58 (2H, app t, J = 6.7 Hz), 3.03 (1H, d, J = 13.3 Hz), 2.81 (1H, d, J = 13.3 Hz), 2.19 (1H, dt, J = 14.0, 7.2 Hz), 1.76 (1H, dt, 14.0, 6.3 Hz), 1.15 (3H, s).



Carboxylic acid (1.57 g, 5.27 mmol) was used in the successive esterification following General Procedure D. The title compound **228** was obtained after purification by FCC (SiO_2, Cyclohexane:EtOAc, 8:1) as a viscous colourless oil (1.63 g, 3.67 mmol, 70%); R_f 0.25 (Cyclohexane:EtOAc, 8:1); υ_{max}/cm^{-1} (neat) 2910, 1781, 1749, 1050, 750, 695; δ_H (500 MHz, $CDCl_3$) 7.95–7.85 (2H, m, ArH), 7.82–7.78 (2H, m, ArH), 7.40–7.15 (10H, m, ArH), 4.57 (2H, s, H-11), 3.74 (1H, ddd, *J* = 9.6, 7.9, 6.0 Hz, H-10a), 3.72 (1H, ddd, *J* = 9.6, 7.8, 6.2 Hz, H-10b), 3.24 (1H, d, *J* = 13.6 Hz, H-4a), 3.02 (1H, d, *J* = 13.6 Hz, H-4b), 2.32 (1H, ddd, *J* = 14.0, 7.8, 6.0 Hz, H-9a), 1.95 (1H, ddd, *J* = 14.0, 7.9, 6.2 Hz, H-9b), 1.31 (3H, s, H-2); δ_C (126 MHz, $CDCl_3$) 173.0 (C, C-1), 162.1 (C, C-16), 138.5 (C, C-12), 136.0 (C, C-5), 134.8 (CH, ArCH), 130.8 (CH, ArCH), 129.1 (CH, ArCH), 128.5 (CH, ArCH), 128.3 (CH, ArCH), 128.0 (CH, ArCH), 127.7 (CH, ArCH), 127.0 (C, C-17), 124.0 (CH, ArCH), 73.3 (CH_2, C-11), 66.8 (CH_2, C-10), 45.8 (C, C-2), 45.5 (CH_2, C-4), 38.4 (CH_2, C-9), 21.4 (CH_3, C-3); *m/z* (ESI) 466 $[MNa]^+$; [HRMS (ESI): calc. for $C_{27}H_{25}NNaO_5^+$, 466.1625. Found: $[MNa]^+$, 466.1624 (0.1 ppm error)].

Lab Book Ref.: LH342

3-Methyl-4-phenylbutan-1-ol (229)



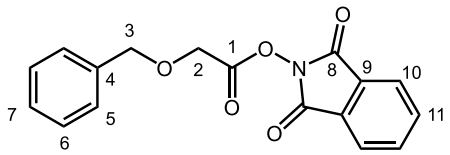
3-Methyl-4-phenylbutan-1-ol **229** was prepared using General Procedure D with 1,3-dioxoisoindolin-2-yl 2-benzyl-4-(benzyloxy)-2-methylbutanoate **228** (86.0 mg, 0.200 mmol), $Ir[dtbbpy(ppy)_2]PF_6$ (1.80 mg, $2{\cdot}10^{-3}$ mmol, 1 mol%) and water (0.180 mL, 10.0 mmol, 50.0 eq.) in MeCN (2 mL). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 6:1) gave the title compound **229** as a pale yellow oil (29.8 mg, 0.182 mmol, 91%); δ_H

(500 MHz, $CDCl_3$) 7.30–7.27 (2H, m, ArH), 7.23–7.12 (3H, m, ArH), 3.78–3.61 (2H, m, H-9), 2.64 (1H, d, *J* = 13.4, 6.5 Hz, H-3a), 2.45 (1H, dd, *J* = 13.4, 7.9 Hz, H-3b), 2.00–1.83 (1H, m, H-1), 1.66 (1H, app dtd, *J* = 12.6, 7.3, 5.1 Hz, H-8a), 1.53–1.36 (1H, m, H-8b), 0.90 (3H, d, *J* = 6.7 Hz, H-2); δ_C (126 MHz, $CDCl_3$) 141.2 (C, C-4), 129.3 (CH, ArCH), 128.3 (CH, ArCH), 125.9 (CH, ArCH), 61.3 (CH2, C-9), 43.9 (CH2, C-3), 39.6 (CH2, C-8), 31.8 (CH, C-1), 19.6 (CH3, C-2).

Lab Book Ref.: LH356

Data are consistent with those previously reported.[160]

1,3-Dioxoisoindolin-2-yl 2-(benzyloxy)acetate (236a)

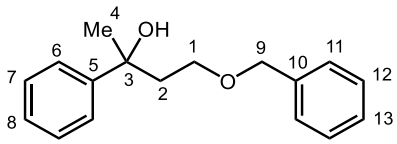


1,3-Dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** was prepared using General Procedure A with benzyloxy acetic acid (590 mg, 3.55 mmol). Purification by FCC (SiO_2, Cyclohexane:EtOAc, 4:1) gave the title compound **236a** as a colourless, crystalline solid (884 mg, 2.84 mmol, 80%); mp. 85-88 °C (Lit. 85-86 °C); δ_H (500 MHz, $CDCl_3$) 7.94–7.89 (2H, m, ArH), 7.84–7.77 (2H, m, ArH), 7.43–7.30 (5H, m, ArH), 4.75 (2H, s, H-3), 4.53 (2H, s, H-2); δ_C (126 MHz, $CDCl_3$) 166.9 (C, C-1), 161.7 (C, C-8), 136.4 (C, C-4), 135.0 (CH, ArCH), 129.0 (C, C-9), 128.8 (CH, ArCH), 128.5 (CH, ArCH), 128.4 (CH, ArCH), 124.2 (CH, ArCH), 73.8 (CH_2, C-3), 65.0 (CH_2, C-2).

Lab Book Ref.: LH577

Data are consistent with those previously reported.[212]

4-Benzyloxy-2-phenyl-2-butanol (237a)

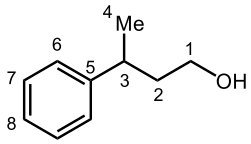


Following General Procedure D, 4-benzyloxy-2-phenyl-2-butanol **237a** was prepared from α-methyl styrene **235** (26.0 μL, 0.200 mmol, 1.00 eq.) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (77.8 mg, 0.25 mmol, 1.25 eq.) with $Ir[dtbbpy(ppy)_2]PF_6$ (1.80 mg, $2 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.180 mL, 10.0 mmol, 50.0 eq.) in MeCN (2 mL). Purification by FCC (SiO_2, cyclohexane:EtOAc 8:1) gave the title compound **237a** as a colourless oil (24.3 mg, 0.095 mmol, 54%); δ_H (400 MHz, $CDCl_3$) 7.42–7.20 (10H, m, ArH), 4.40 (1H, d, *J* = 11.8 Hz, H-9a), 4.37 (1H, d, *J* = 11.8 Hz, H-9b), 4.21 (1H, s, OH), 3.60 (1H, ddd, *J* = 9.7, 9.3, 4.8 Hz, H-1a), 3.36 (1H, ddd, *J* = 9.5, 4.3, 3.4 Hz, H-1b), 2.23 (1H, ddd, *J* = 14.5, 4.8, 3.4 Hz, H-2a), 2.08 (1H, ddd, *J* = 14.5, 9.7, 4.3 Hz, H-2b), 1.53 (3H, s, H-4); δ_C (101 MHz, $CDCl_3$) 147.9 (C, C-5), 137.6 (C, C-10), 128.6 (CH, ArCH), 128.2 (CH, ArCH), 128.0 (CH, ArCH), 127.8 (CH, ArCH), 126.4 (CH, ArCH), 125.0 (CH, ArCH), 75.2 (C, C-3), 73.6 (CH_2, C-9), 68.2 (CH_2, C-1), 42.2 (CH_2, C-2), 31.1 (CH_3, C-4).

Lab Book Ref.: LH171b

Data are consistent with those previously reported.[160]

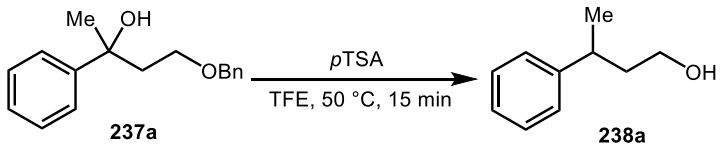
3-Phenyl-1-butanol (238a)



a) 3-Phenyl-1-butanol **238a** was prepared using General Procedure E with isopropenylbenzene **235** (47.2 mg, 0.400 mmol), 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (156 mg, 0.500 mmol), $Ir[dtbbpy(ppy)_2]PF_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) in MeCN (4 mL). The crude oxyalkylation product was dissolved in TFE (4 mL) and treated with a solution of *p*TSA in TFE (0.32 mL, 0.06 M, 0.020 mmol, 0.05 eq.). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 6:1) gave the title compound **238a** as a pale yellow oil

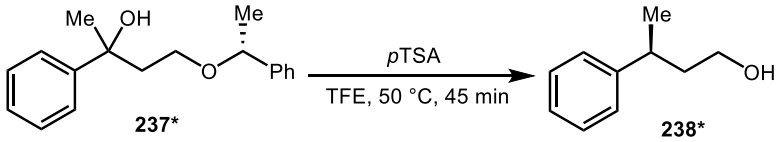
(24.0 mg, 0.160 mmol, 40%); δ_H (500 MHz, $CDCl_3$) 7.33–7.27 (2H, m, ArH), 7.23–7.16 (3H, m, ArH), 3.62–3.51 (2H, m, H-1), 2.88 (1H, qt, *J* = 7.0, 6.5 Hz, H-3), 1.92–1.81 (2H, m, H-2), 1.28 (3H, d, *J* = 7.0 Hz, H-4); δ_C (126 MHz, $CDCl_3$) 147.0 (C, C-5), 128.7 (CH, ArCH), 127.1 (CH, ArCH), 126.3 (CH, ArCH), 61.4 (CH_2, C-1), 41.1 (CH, C-3), 36.6 (CH_2, C-2), 22.6 (CH_3, C-4).

Lab Book Ref.: LH464



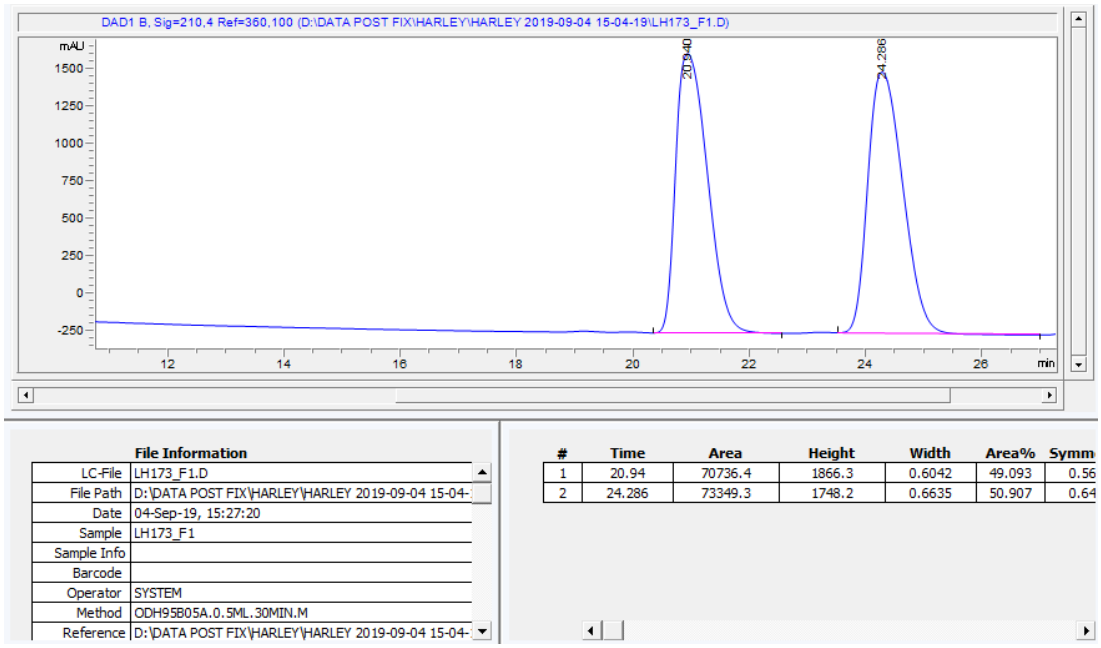
b) 4-Benzyloxy-2-phenyl-2-butanol **237a** (23.0 mg, 0.090 mmol, 1.0 eq.) was treated with a solution of *p*TSA in TFE (31.0 µL, 0.06 M, $1.9 \cdot 10^{-3}$ mmol, 2 mol%) in TFE (1.0 mL) at 50 °C for 15 min. After cooling to rt, the reaction was quenched with an aq. NH_3 solution (pH = 9). The aqueous layer was then extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by FCC (SiO_2, Cyclohexane:Et_2O, 6:1) gave the title compound **238a** as a pale yellow oil (11.8 mg, 0.079 mmol, 88%).

Lab Book Ref.: LH173



c) 2-Phenyl-4-(*R*)-1-phenylethoxy-2-butanol **237*** (18.5 mg, 0.068 mmol, 1.00 eq.) was reacted with a solution of *p*TSA in TFE (22.5 µL, 0.06 M, $1.4 \cdot 10^{-3}$ mmol, 2 mol%) in TFE (0.7 mL) for 45 min. After cooling to rt, the reaction was quenched with an aq. NH_3 solution (pH = 9). The aqueous layer was then extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by FCC (SiO_2, Cyclohexane:Et_2O, 6:1) gave the title compound **238a** as a pale yellow oil (7.1 mg, 0.05 mmol, 69%). Enantiomeric excess: 32%, determined by HPLC (ODH, hexane/isopropanol = 90/10, flow rate 0.5 mL/min, t_R (major) 20.97 min, t_R (minor) 24.31 min.

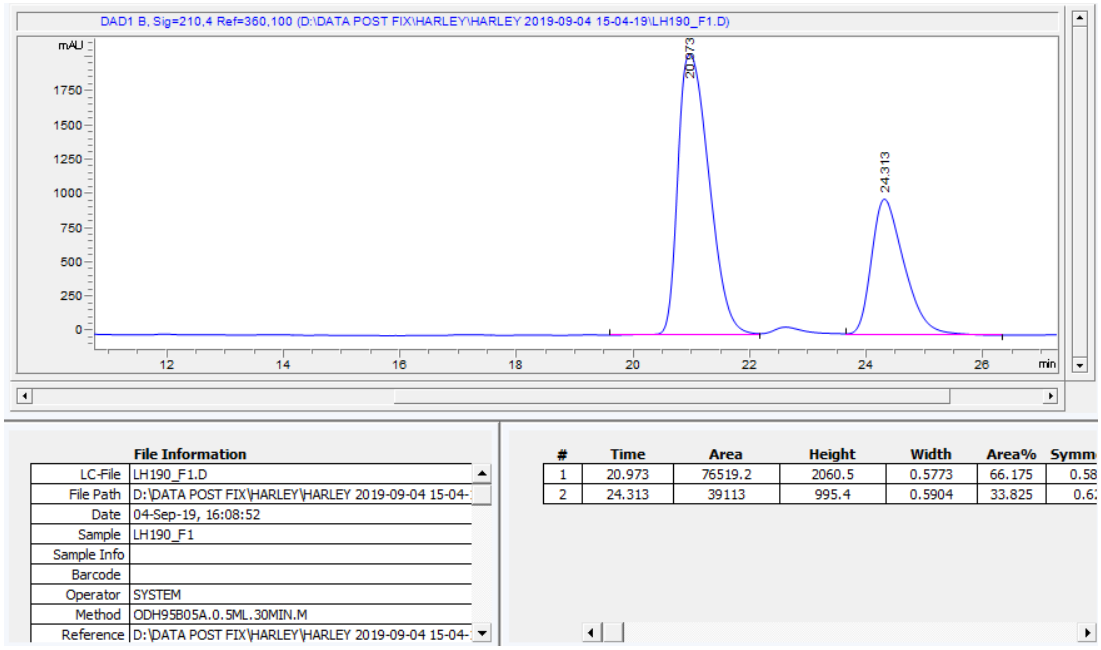
Lab Book Ref.: LH190



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Sample Info	
Barcode	
Operator	SYSTEM
Method	ODH95B05A.0.5ML.30MIN.M
Reference	D:\DATA POST FIX\HARLEY\HARLEY 2019-09-04 15-04-

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1	20.94	70736.4	1866.3	0.6042	49.093	0.56
2	24.286	73349.3	1748.2	0.6635	50.907	0.64

Figure 5.1. HPLC measurement for racemic sample of product **238a**.



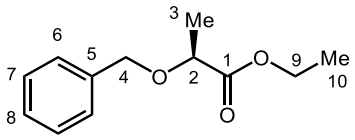
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Reference	D:\DATA POST FIX\HARLEY\HARLEY 2019-09-04 15-04-

#	Time	Area	Height	Width	Area%	Symm
1	20.973	76519.2	2060.5	0.5773	66.175	0.58
2	24.313	39113	995.4	0.5904	33.825	0.6

Figure 5.2. HPLC measurement for enantioenriched sample of product **238a**.

Data are consistent with those previously reported.[213]

Ethyl (*S*)-2-(benzyloxy)propanoate (240)

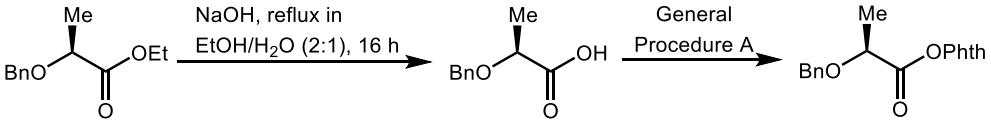


Ethyl-(*L*)-lactate (1.71 mL, 15.0 mmol, 1.0 eq.) was dissolved in DMF (45 mL). The mixture was cooled to 0 °C and NaH (60 wt%, 720 mg, 18.0 mmol, 1.2 eq.) was added, then the reaction was stirred at 0 °C for 30 min. Benzyl bromide (1.96 mL, 16.5 mmol, 1.1 eq.) in THF (15 mL) was added slowly at 0 °C and the reaction stirred at rt for 16 h. The reaction was quenched with ice water and extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FCC (SiO_2, Cyclohexane:EtOAc, 25:1) to afford the title compound **240** as a yellow oil (2.19 g, 10.5 mmol, 70%); δ_H (400 MHz, $CDCl_3$) 7.40–7.27 (5H, m, ArH), 4.69 (1H, d, *J* = 11.7 Hz, H-4a), 4.46 (1H, d, *J* = 11.7 Hz, H-4b), 4.30–4.14 (2H, m, H-2, H-9a), 4.06 (1H, q, *J* = 6.9 Hz, H-2), 1.44 (3H, d, *J* = 6.9 Hz, H-3), 1.30 (3H, t, *J* = 7.2 Hz, H-10); δ_C (101 MHz, $CDCl_3$) 173.4 (C, C-1), 137.7 (C, C-5), 128.5 (CH, ArCH), 128.1 (CH, ArCH), 128.0 (CH, ArCH), 74.2 (CH_2, C-4), 72.1 (CH, C-2), 61.0 (CH_2, C-9), 18.8 (CH_3, C-3), 14.4 (CH_3, C-10).

Lab Book Ref.: LH527

Data are consistent with those previously reported.[214]

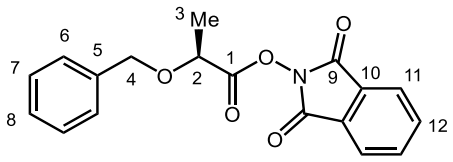
2,3-Dihydro-1*H*-inden-2-yl (*S*)-2-benzyloxy-propanoate (236b)



240 **241** **236b**

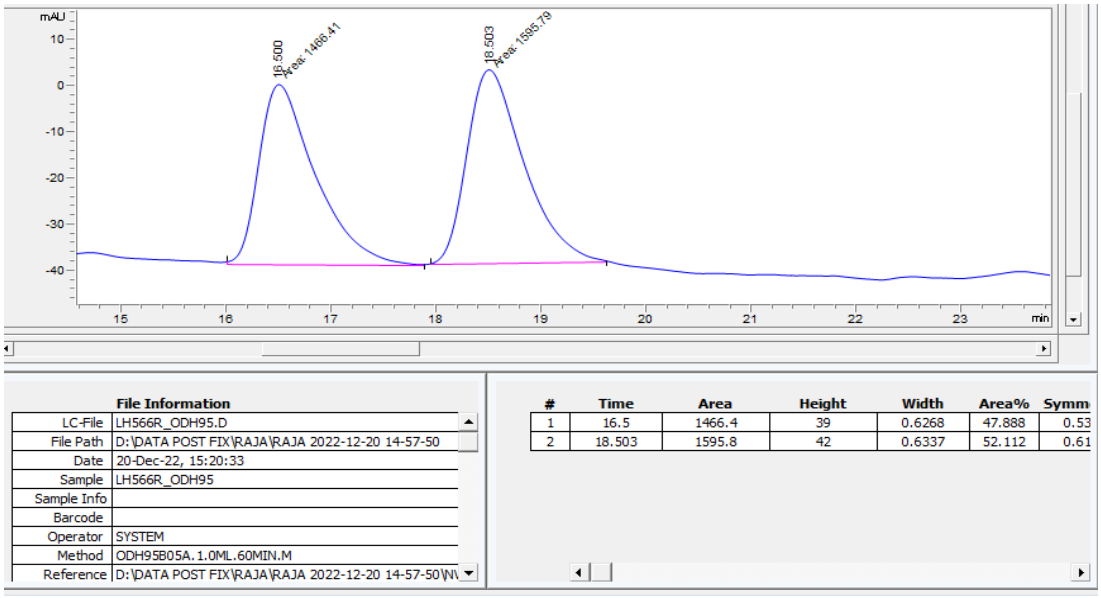
The ethyl ester **240** (2.19 g, 10.5 mmol, 1.0 eq.) was hydrolysed using NaOH (2.94 g, 73.5 mmol, 7.0 eq.) in EtOH/H_2O (2/1, 75 mL). After cooling to rt, the solvent was removed, and the residue redissolved in water and Et_2O. The organic layer was extracted with water, then the combined aqueous layers were acidified with 1 M aq. HCl to pH = 1. The aqueous layer was then extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*.

The resulting acid **241** was used in the next step without further purification (1.52 g, 8.41 mmol, 80%); δ_H (500 MHz, $CDCl_3$) 7.40–7.29 (5H, m), 4.70 (1H, d, *J* = 11.6 Hz), 4.56 (1H, d, *J* = 11.6 Hz), 4.12 (1H, q, *J* = 6.9 Hz), 1.50 (3H, d, *J* = 6.9 Hz).



Carboxylic acid **241** (1.50 g, 8.30 mmol, 1.0 eq.), was then reacted with *N*-hydroxyphthalimide (2.04 g, 12.5 mmol, 1.5 eq.), DCC (1.12 g, 9.10 mmol, 1.1 eq.) and DMAP (86.0 mg, 0.42 mmol, 0.05 eq.) in DCM (50 mL) following General Procedure A. Purification by FCC (SiO_2, Cyclohexane:EtOAc, 4:1) gave the title compound **236b** as a colourless, crystalline solid (1.99 g, 6.12 mmol, 74%); mp. 85-87 °C; R_f 0.20 (Cyclohexane:EtOAc, 4:1); $[\alpha]^{20}_D$ –6.71 (*c* 0.055, DCM); υ_{max}/cm^{-1} (neat) 2921, 1787, 1730, 1460, 1355, 1184, 1079, 1051, 873; δ_H (500 MHz, $CDCl_3$) 7.96–7.87 (2H, m, ArH), 7.85–7.78 (2H, m, ArH), 7.47–7.28 (5H, m, ArH), 4.85 (1H, d, *J* = 11.4 Hz, H-4a), 4.57 (1H, d, *J* = 11.4 Hz, H-4b), 4.45 (1H, q, *J* = 6.9 Hz, H-2), 1.69 (3H, d, *J* = 6.9 Hz, H-3); δ_C (126 MHz, $CDCl_3$) 169.8 (C, C-1), 161.9 (C, C-9), 136.9 (C, C-5), 135.0 (CH, ArCH), 129.1 (C, C-10), 128.7 (CH, ArCH), 128.4 (CH, ArCH), 128.3 (CH, ArCH), 124.2 (CH, ArCH), 72.6 (CH_2, C-4), 72.4 (CH, C-2), 19.3 (CH_3, C-3); *m/z* (ESI) 326 $[MH]^+$; [HRMS (ESI): calc. for $C_{18}H_{16}NO_5^+$, 326.1023. Found: $[MH]^+$, 326.1021 (0.5 ppm error)]. Enantiomeric excess: 94%, determined by HPLC (ODH, hexane/isopropanol = 95/5, flow rate 0.5 mL/min, t_R (major) 18.35 min, t_R (minor) 16.61 min.

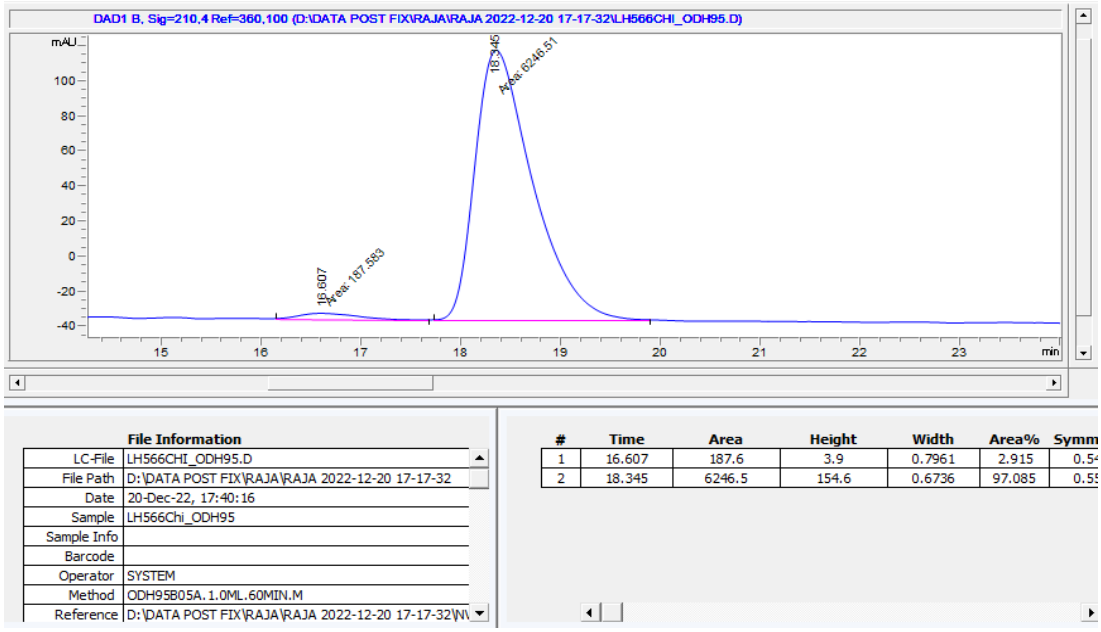
Lab Book Ref.: LH531



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Operator	SYSTEM
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Reference	D:\DATA POST FIX\RAJA\RAJA 2022-12-20 14-57-50\N

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1	16.5	1466.4	39	0.6268	47.888	0.53
2	18.503	1595.8	42	0.6337	52.112	0.61

Figure 5.3. HPLC measurement for a racemic sample of product **236b**.

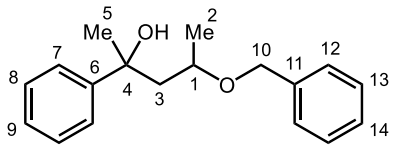


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Reference	D:\DATA POST FIX\RAJA\RAJA 2022-12-20 17-17-32\N

#	Time	Area	Height	Width	Area%	Symm
1	16.607	187.6	3.9	0.7961	2.915	0.54
2	18.345	6246.5	154.6	0.6736	97.085	0.55

Figure 5.4. HPLC measurement for the enantioenriched sample of product **236b**.

4-Benzyloxy-2-phenyl-2-pentanol (237b)



Following General Procedure D, α-methyl styrene **235** (26.0 µL, 0.200 mmol, 1.00 eq.) and 2,3-dihydro-1*H*-inden-2-yl (*S*)-2-benzyloxy-propanoate **236b** (65.1 mg, 0.200 mmol, 1.25 eq.) were reacted with Ir[dtbbpy(ppy)$_2$]PF$_6$ (1.80 mg, $2 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.180 mL, 10.0 mmol, 50.0 eq.) in MeCN (2 mL). Purification by FCC (SiO_2, cyclohexane:EtOAc 8:1) afforded the title compound **237b** as a colourless oil (38.7 mg, 0.143 mmol, 72%, dr: 1:1). The diastereomers could be separated; the relative configuration was not determined.

Diastereomer A (20.1 mg, 0.074 mmol, 37%): δ_H (400 MHz, $CDCl_3$) 7.42–7.19 (10H, m, ArH), 4.95 (1H, s, OH), 4.44 (1H, d, *J* = 10.9 Hz, H-10a), 4.01 (1H, *J* = 10.9 Hz, H-10b), 3.38 (1H, dqd, *J* = 10.2, 6.0, 3.0 Hz, H-1), 2.12 (1H, dd, *J* = 14.9, 10.2 Hz, H-3a), 2.06 (1H, dd, *J* = 14.9, 3.0 Hz, H-3b), 1.46 (3H, s, H-5), 1.15 (3H, d, *J* = 6.0 Hz, H-2); δ_C (101 MHz, $CDCl_3$) 148.3 (C, C-6), 137.7 (C, C-11), 128.7 (CH, ArCH), 128.2 (CH, ArCH), 128.1 (CH, ArCH), 128.0 (CH, ArCH), 126.3 (CH, ArCH), 125.1 (CH, ArCH), 75.0 (C, C-4), 74.5 (CH, C-1), 70.6 (CH_2, C-10), 49.4 (CH_2, C-3), 32.3 (CH_3, C-5), 19.7 (CH_3, C-2). *m/z* 293 $[MNa]^+$; [HRMS (ESI+): Found: 293.1519 $C_{18}H_{22}NaO_2$ $[MNa]^+$ Requires: 293.1512 (2.3 ppm error)].

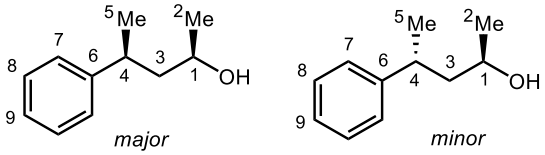
Lab Book Ref.: LH219_F1

Diastereomer B (18.6 mg, 0.068 mmol, 34%): δ_H (400 MHz, $CDCl_3$) 7.51–7.45 (2H, m, ArH), 7.40–7.19 (8H, m, ArH), 4.70 (1H, d, *J* = 11.1 Hz, H-10a), 4.64 (1H, s, OH), 4.46 (1H, d, *J* = 11.1 Hz, H-10b), 4.08 (1H, dqd, *J* = 10.3, 6.0, 2.8 Hz, H-1), 2.02 (1H, dd, *J* = 14.9, 10.3 Hz, H-3a), 1.86 (1H, dd, *J* = 14.9, 2.8 Hz, H-3b), 1.56 (3H, s, H-5), 1.25 (3H, d, *J* = 6.0 Hz, H-2); δ_C (101 MHz, $CDCl_3$) 149.5 (C, C-6), 137.7 (C, C-11), 128.7 (CH, ArCH), 128.3 (CH, ArCH), 128.2 (CH, ArCH), 128.1 (CH, ArCH), 126.4 (CH, ArCH), 124.6 (CH, ArCH), 73.9 (C, C-4), 73.6 (CH, C-1), 70.6 (CH_2, C-10), 50.3 (CH_2, C-3), 28.5 (CH_3, C-5), 19.9 (CH_3, C-2). *m/z* 293 $[MNa]^+$; [HRMS (ESI+): Found: 293.1519 $C_{18}H_{22}NaO_2$ $[MNa]^+$ Requires: 293.1512 (2.3 ppm error)].

Lab Book Ref.: LH219_F2

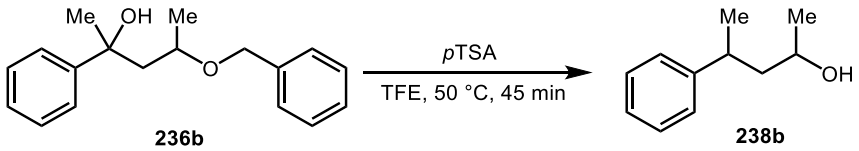
Data are consistent with those previously reported.[160]

4-Phenyl-2-pentanol (238b)



a) 4-Phenyl-2-pentanol **238b** was prepared using General Procedure E with isopropenylbenzene **235** (47.2 mg, 0.400 mmol), 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236b** (156 mg, 0.500 mmol), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, 4·10^{-3} mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) in MeCN (4 mL). The crude oxyalkylation product was dissolved in TFE (4 mL) and treated with a solution of *p*TSA in TFE (0.32 mL, 0.06 M, 0.020 mmol, 0.05 eq.). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 6:1) gave the title compound **238b** as a pale yellow oil (39.6 mg, 0.240 mmol, 60%); δ_H (400 MHz, $CDCl_3$) 7.34–7.26 (2H, m, ArH), 7.24–7.16 (3H, m, ArH), 3.78 (1H, dqd, *J* = 8.3, 6.9, 5.3 Hz, H-1, major), 3.61–3.52 (1H, m, H-1, minor), 3.02–2.93 (1H, m, H-4, minor), 2.87 (1H, app tq, *J* = 7.3, 6.2 Hz, H-4, major), 1.83 (1H, ddd, *J* = 13.7, 8.1, 7.3 Hz, H-3a), 1.65 (1H, ddd, *J* = 13.7, 7.3, 5.3 Hz, H-3b), 1.27 (3H, d, *J* = 6.9 Hz, H-2, major), 1.26 (3H, d, *J* = 7.0 Hz, H-2, minor), 1.19 (3H, d, *J* = 6.2 Hz, H-5, major), 1.13 (3H, d, *J* = 6.2 Hz, H-5, minor); δ_C (101 MHz, $CDCl_3$) 147.4 (C, C-6, major), 146.9 (C, C-6, minor), 128.7 (CH, ArCH, major), 128.6 (CH, ArCH, minor), 127.2 (CH, ArCh, minor), 127.0 (CH, ArCH, major), 126.3 (CH, ArCH, major), 126.2 (CH, ArCH, minor), 66.5 (CH, C-1, major), 66.0 (CH, C-1, minor), 48.0 (CH_2, C-3, major), 47.8 (CH_2, C-3, minor), 37.1 (CH, C-4, major), 36.7 (CH, C-4, minor), 24.3 (CH_3, C-5, minor), 23.8 (CH_3, C-5, major), 23.2 (CH_3, C-2, minor), 22.5 (CH_3, C-2, major).

Lab Book Ref.: LH518



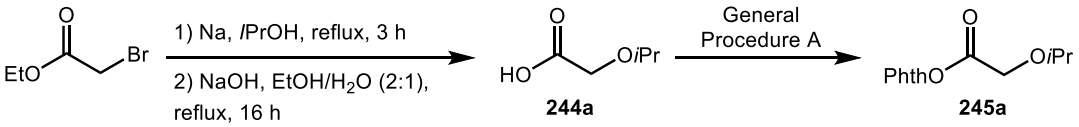
236b **238b**

b) 4-Benzyloxy-2-phenyl-2-pentanol **237b** (15.2 mg, 0.056 mmol, 1.0 eq.) was treated with a solution of *p*TSA in TFE (18.0 µL, 0.06 M, $1.1 \cdot 10^{-3}$ mmol, 2 mol%) in TFE (1.0 mL) at 50 °C for 15 min. After cooling to rt, the reaction was quenched with an aq. NH_3 solution (pH = 9). The aqueous layer was then extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by FCC (SiO_2, Cyclohexane:Et_2O, 6:1) gave the title compound **238b** as a pale yellow oil (11.8 mg, 0.072 mmol, 88%).

Lab Book Ref.: LH223

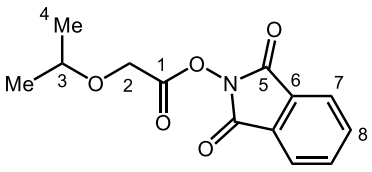
Data are consistent with those previously reported.[174]

1,3-Dioxoisoindolin-2-yl 2-isopropoxyacetate (245a)



244a **245a**

The acid precursor of 1,3-dioxoisoindolin-2-yl 2-isopropoxyacetate **245a** was prepared using General Procedure B with ethyl bromoacetate (6.65 mL, 60.0 mmol) in *i*PrOH (108 mL) followed by hydrolysis and acid work-up as described (2.19 g, 18.6 mmol, 31%); δ_H (500 MHz, $CDCl_3$) 4.12–4.08 (2H, m), 3.78–3.70 (1H, m), 1.25–1.21 (6H, m).

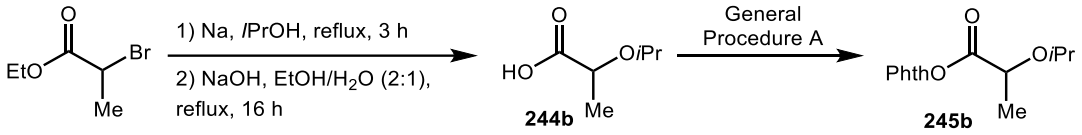


The crude acid **244a** (472 mg, 4.00 mmol, 1.0 eq.) was then reacted with *N*-hydroxyphthalimide (979 mg, 6.00 mmol, 1.5 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.400 mmol, 0.1 eq.) in DCM (30 mL) following General Procedure A. The title compound **245a** was obtained after purification by FCC (SiO_2, Cyclohexane:EtOAc, 4:1) as a colourless, crystalline solid (732 mg, 2.78 mmol, 70%);

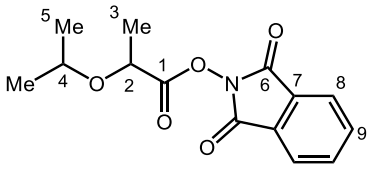
mp. 85-87 °C; R_f 0.30 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2917, 1789, 1737, 1186, 1060, 875, 692, 621; δ_H (500 MHz, $CDCl_3$) 7.90–7.84 (2H, m, ArH), 7.81–7.74 (2H, m, ArH), 4.46 (2H, s, H-2), 3.77 (1H, hept, *J* = 6.1 Hz, H-3), 1.23 (6H, d, *J* = 6.1 Hz, H-4); δ_C (126 MHz, $CDCl_3$) 167.5 (C, C-1), 161.7 (C, C-5), 135.0 (CH, ArCH), 128.9 (C, C-6), 124.1 (CH, ArCH), 73.7 (CH, C-3), 63.7 (CH_2, C-2), 21.8 (CH_3, C-4); *m/z* (ESI) 264 $[MH]^+$; [HRMS (ESI): calc. for $C_{13}H_{14}NO_5^+$, 264.0866. Found: $[MH]^+$, 264.0867 (0.1 ppm error)].

Lab Book Ref.: LH669

1,3-Dioxoisoindolin-2-yl 2-isopropoxypropanoate (245b)



The acid precursor of 1,3-dioxoisoindolin-2-yl 2-isopropoxypropanoate **245b** was prepared using General Procedure B with ethyl 2-bromopropionate (1.95 mL, 15.0 mmol) in *i*PrOH (27 mL) followed by hydrolysis and acid work-up as described. (887 mg, 3.21 mmol, 21%); δ_H (500 MHz, $CDCl_3$) 4.08 (1H, q, *J* = 6.9 Hz), 3.79–3.68 (1H, m), 1.43 (1H, d, *J* = 6.9 Hz), 1.25–1.18 (6H, m).

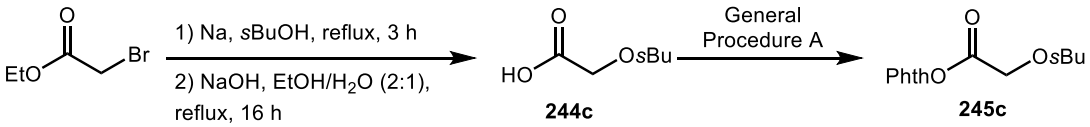


The crude acid **244b** (870 mg, 6.58 mmol, 1.0 eq.) was then reacted with *N*-hydroxyphthalimide (1.61 g, 9.87 mmol, 1.5 eq.), DCC (1.49 g, 7.24 mmol, 1.1 eq.) and DMAP (80.0 mg, 0.658 mmol, 0.1 eq.) in DCM (50 mL) following General Procedure A. The title compound **245b** was obtained after purification by FCC (SiO_2, Cyclohexane:EtOAc, 4:1) as a colourless, crystalline solid (1.22 g, 4.39 mmol, 67%); mp. 78-79 °C; R_f 0.30 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2979, 2197, 1965, 1785, 1736, 1467, 1362, 1076, 1026, 966, 875, 692, 610; δ_H (500 MHz, $CDCl_3$) 7.92–7.84 (2H, m, ArH), 7.82–7.75 (2H, m, ArH), 4.43 (1H, q, *J* = 6.9 Hz, H-2), 3.80 (1H, hept, *J* = 6.1 Hz, H-4), 1.61 (3H, d, *J* = 6.9 Hz, H-2), 1.26 (3H, d, *J* = 6.1 Hz, H-5 (A)),

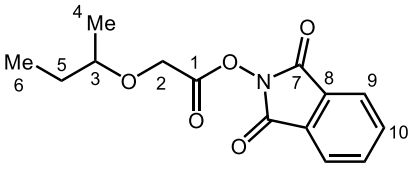
1.22 (3H, d, J = 6.1 Hz, H-5 (B)); δ_C (126 MHz, $CDCl_3$) 170.5 (C, C-1), 161.9 (C, C-6), 134.9 (CH, ArCH), 129.1 (C, C-6), 124.1 (CH, ArCH), 72.7 (CH, C-4), 71.0 (CH, C-2), 22.9 (CH_3, C-5 (A)), 21.5 (CH_3, C-5 (B)), 19.7 (CH_3, C-3); *m/z* (ESI) 278 $[MH]^+$; [HRMS (ESI): calc. for $C_{14}H_{16}NO_5^+$, 278.1023. Found: $[MH]^+$, 278.1018 (1.7 ppm error)].

Lab Book Ref.: LH671

1,3-Dioxoisoindolin-2-yl 2-(*sec*-butoxy)propanoate (245c)



The acid precursor of 1,3-dioxoisoindolin-2-yl 2-(*sec*-butoxy)propanoate **245c** was prepared using General Procedure B with ethyl bromoacetate (2.22 mL, 20.0 mmol) in *s*BuOH (40 mL) followed by hydrolysis and acid work-up as described. (773 mg, 5.80 mmol, 29%); δ_H (500 MHz, $CDCl_3$) 4.13 (1H, d, J = 16.5 Hz), 4.08 (1H, d, J = 16.5 Hz), 3.50 (1H, app sext, J = 6.1 Hz), 1.72–1.44 (2H, m), 1.19 (3H, d, J = 6.1 Hz), 0.93 (3H, t, J = 7.5 Hz).

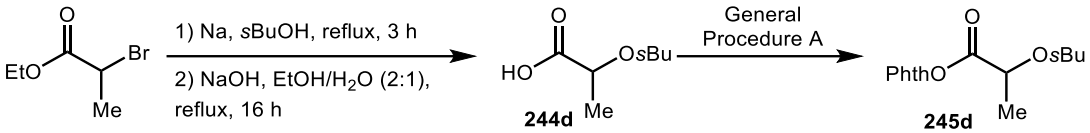


The crude acid (687 mg, 5.20 mmol, 1.0 eq.) was then reacted with *N*-hydroxyphthalimide (1.27 g, 7.80 mmol, 1.5 eq.), DCC (699 mg, 3.38 mmol, 0.65 eq.) and DMAP (107 mg, 0.877 mmol, 0.17 eq.) in DCM (40 mL) following General Procedure A. The title compound **245c** was obtained after purification by FCC (SiO_2, Cyclohexane:EtOAc, 4:1) as a colourless, crystalline solid (645 mg, 2.33 mmol, 70%); mp. 48-49 °C; R_f 0.35 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2969, 1789, 1730, 1184, 1124, 1054, 962, 873, 698; δ_H (500 MHz, $CDCl_3$) 7.92–7.85 (2H, m, ArH), 7.83–7.75 (2H, m, ArH), 4.54–4.44 (2H, m, H-2), 3.55 (1H, app sext, J = 6.1 Hz, H-3), 1.64 (1H, dqd, J = 14.2, 7.5, 6.1 Hz, H-5a), 1.51 (1H, dqd, J = 14.2, 7.5, 6.1 Hz, H-5b), 1.21 (3H, d, J = 6.1 Hz, H-4), 0.94 (3H, t, J = 7.5 Hz, H-6); δ_C (126 MHz, $CDCl_3$) 167.5 (C, C-1), 161.8 (C, C-7), 135.0 (CH, ArCH), 129.0 (C, C-8), 124.2 (CH,

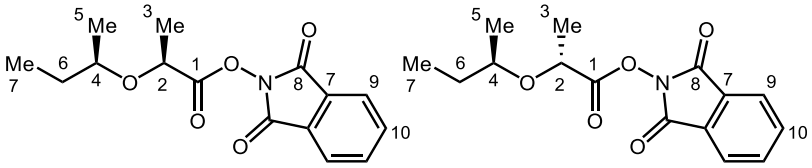
ArCH), 78.8 (CH, C-3), 64.0 (CH_2, C-2), 29.1 (CH_2, C-5), 18.9 (CH_3, C-4), 9.7 (CH_3, C-6); *m/z* (ESI) 278 $[MH]^+$; [HRMS (ESI): calc. for $C_{14}H_{16}NO_5^+$, 278.1023. Found: $[MH]^+$, 278.1024 (0.3 ppm error)].

Lab Book Ref.: LH511

2,3-Dihydro-1*H*-inden-2-yl-2-*iso*-butyloxy-propanoate (245d)



The acid precursor of 2,3-dihydro-1*H*-inden-2-yl-2-*iso*-butyloxy-propanoate **245d** was prepared using General Procedure B with ethyl 2-bromopropionate (2.60 mL, 20.0 mmol) in *s*BuOH (40 mL) followed by hydrolysis and acid work-up as described. (841 mg, 5.80 mmol, 29%); δ_H (500 MHz, $CDCl_3$) 4.09 (1H, q, *J* = 7.0 Hz), 4.08 (1H, q, *J* = 7.0 Hz), 3.80–3.35 (2H, m), 1.67–1.45 (4H, m), 1.44 (3H, d, *J* = 7.0 Hz), 1.43 (3H, d, *J* = 7.0 Hz), 1.19 (3H, d, *J* = 6.1 Hz), 1.18 (3H, d, *J* = 6.1 Hz), 0.93 (3H, t, *J* = 7.5 Hz), 0.91 (3H, t, *J* = 7.5 Hz).

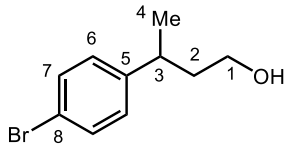


The crude acid (700 mg, 4.79 mmol, 1.0 eq.) was then reacted with *N*-hydroxyphthalimide (1.17 g, 7.18 mmol, 1.5 eq.), DCC (644 mg, 3.12 mmol, 0.65 eq.) and DMAP (99.0 mg, 0.480 mmol, 0.17 eq.) in DCM (30 mL) following General Procedure A. Purification by FCC (SiO_2, Cyclohexane:EtOAc, 4:1) gave an inseparable mixture of diastereoisomers of the title compound **245d** as a colourless, crystalline solid (676 mg, 2.32 mmol, 74%, dr: 1:1); mp. 46-48 °C; R_f 0.35 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 2977, 1789, 1742, 1358, 1071, 1022, 874, 694; δ_H (500 MHz, $CDCl_3$) 7.93–7.84 (4H, m, ArH (A+B)), 7.82–7.75 (4H, m, ArH (A+B)), 4.46 (1H, q, *J* = 6.9 Hz, H-2 (A)), 4.41 (1H, q, *J* = 6.9 Hz, H-2 (B)), 3.61–3.51 (2H, m, H-4 (A+B)), 1.67–1.58 (2H, m, H-6a (A+B)), 1.62 (3H, d, *J* = 6.9 Hz, H-3 (A)), 1.61 (3H, d, *J* = 6.9 Hz, H-3 (B)), 1.54–1.46 (2H, m, H-6b (A+B)), 1.24 (3H, d, *J* = 6.2 Hz, H-3 (A)), 1.19 (3H, d, *J* = 6.2 Hz, H-3 (B)), 0.95 (3H, t, *J* = 7.5 Hz,

H-7 (A)), 0.93 (3H, t, *J* = 7.5 Hz, H-7 (B)); δ_C (126 MHz, $CDCl_3$) 170.6 (C, C-1 (A)), 170.3 (C, C-1 (B)), 161.9 (C, C-8 (A+B)), 134.9 (CH, ArCH, (A+B)), 129.1 (C, C-6 (A+B)), 124.1 (CH, ArCH (A+B)), 78.4 (CH, C-4 (A)), 77.4 (CH, C-4 (B)), 71.8 (CH, C-2 (A)), 70.7 (CH, C-2 (B)), 30.0 (CH_2, C-6 (A)), 28.7 (CH_2, C-6 (B)), 19.9 (CH_3 (A)), 19.7 (CH_3 (B)), 19.6 (CH_3 (A)), 18.8 (CH_3 (B)), 10.0 (CH_3, C-7 (A)), 9.6 (CH_3, C-7 (B)); *m/z* (ESI) 292 $[MH]^+$; [HRMS (ESI): calc. for $C_{15}H_{18}NO_5^+$, 292.1179. Found: $[MH]^+$, 292.1182 (1.4 ppm error)].

Lab Book Ref.: LH512

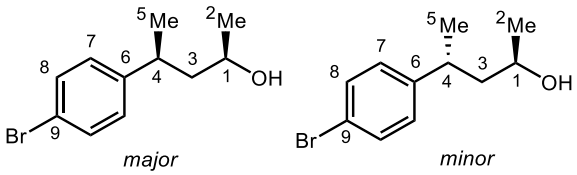
3-(4-Bromophenyl)-1-butanol (248a)



3-(4-Bromophenyl)-1-butanol **248a** was prepared using General Procedure E with 1-bromo-4-isopropenylbenzene **246** (79.0 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (156 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 5:1) afforded the title compound **248a** as a pale yellow oil (44.8 mg, 0.196 mmol, 49%); R_f 0.20 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3332, 2958, 2872, 1486, 1071, 1041, 1008, 829; δ_H (400 MHz, $CDCl_3$) 7.44–7.38 (2H, m, ArH), 7.09–7.05 (2H, m), 3.57 (1H, app dt, *J* = 10.6, 6.3 Hz, H-1a), 3.51 (1H, app dt, *J* = 10.6, 6.8, Hz, H-1b), 2.87 (1H, dqd, *J* = 7.8, 7.0, 6.9 Hz, H-3), 1.91–1.72 (2H, m, H-2), 1.25 (3H, d, *J* = 7.0 Hz, H-4); δ_C (101 MHz, $CDCl_3$) 146.0 (C, C-5), 131.6 (CH, ArCH), 128.9 (CH, ArCH), 119.8 (C, C-8), 61.0 (CH_2, C-1), 40.9 (CH_2, C-2), 36.0 (CH, C-3), 22.4 (CH_3, C-4); *m/z* (ESI) 251 $[MNa]^+$; [HRMS (ESI): calc. for $C_{10}H_{13}BrNaO^+$, 251.0042. Found: $[MH]^+$, 251.0047 (2.1 ppm error)].

Lab Book Ref.: LH449

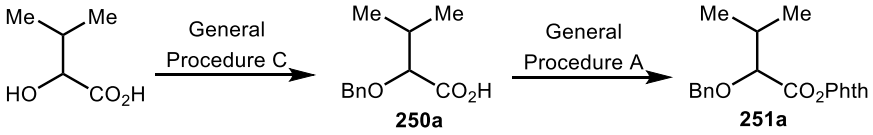
4-(4-Bromophenyl)-2-pentanol (248b)



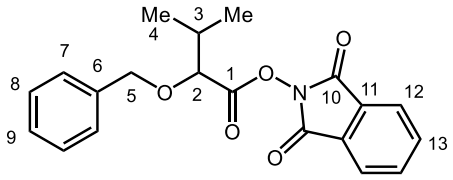
4-(4-Bromophenyl)-2-pentanol **248b** was prepared using General Procedure E with 1-bromo-4-isopropenylbenzene **246** (79.0 mg, 0.400 mmol, 1.0 eq.) and 2,3-dihydro-1*H*-inden-2-yl (*S*)-2-benzyloxy-propanoate **236b** (165 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:EtOAc, 7:1) gave an inseparable mixture of isomers of the title compound **248b** as a pale yellow oil (65.0 mg, 0.267 mmol, 67%, dr: 8:1); R_f 0.25 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3343, 2962, 2926, 1481, 1406, 1375, 1073, 1008, 908, 819, 728, 637; δ_H (400 MHz, $CDCl_3$) 7.40 (2H, d, *J* = 8.4 Hz, ArH), 7.08 (2H, d, *J* = 8.4 Hz, ArH), 3.74 (1H, dqd, *J* = 7.5, 7.0, 5.4 Hz, H-1, major), 3.50 (1H, dqd, *J* = 12.5, 6.1, 3.7 Hz, H-1, minor), 3.00–2.90 (1H, m, H-4, minor), 2.84 (1H, ddq, *J* = 7.7, 7.5, 6.2 Hz, H-4, major), 1.77 (1H, app dt, *J* = 13.6, 7.5 Hz, H-3a), 1.60 (1H, ddd, *J* = 13.6, 7.7, 5.4 Hz, H-3b), 1.23 (3H, d, *J* = 7.0 Hz, H-2), 1.18 (3H, d, *J* = 6.2 Hz, H-1, major), 1.12 (3H, d, *J* = 6.2 Hz, H-1, minor); δ_C (101 MHz, $CDCl_3$) 146.5 (C, C-6, major), 145.9 (C, C-6, minor), 131.7 (CH, ArCH, major), 131.6 (CH, ArCH, minor), 129.0 (CH, ArCH, minor), 128.8 (CH, ArCH, major), 119.8 (C, C-9), 66.2 (CH, C-1, major), 65.8 (CH, C-1, minor), 47.7 (CH_2, C-3, major), 47.6 (CH_2, C-3, minor), 36.3 (CH, C-4, major), 36.2 (CH, C-4, minor), 24.4 (CH_3, C-5, minor), 23.9 (CH_3, C-5, major), 23.0 (CH_3, C-2, minor), 22.2 (CH_3, C-2, major); *m/z* (ESI) 265 $[MNa]^+$; [HRMS (ESI): calc. for $C_{11}H_{15}BrNaO^+$, 265.0198. Found: $[MNa]^+$, 265.0202 (1.5 ppm error)].

Lab Book Ref.: LH515

1,3-Dioxoisoindolin-2-yl 2-(benzyloxy)-3-methylbutanoate (251a)



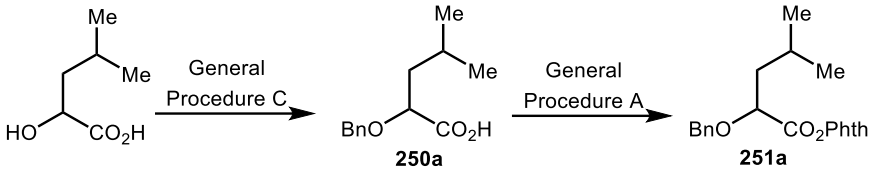
The carboxylic acid of 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)-3-methylbutanoate **251a** was prepared from 2-hydroxy-3-methylbutyric acid (780 mg, 6.60 mmol) using General Procedure C. Purification by FCC (SiO_2, Cyclohexane:EtOAc, 6:1) gave the crude carboxylic acid as a pale yellow oil (715 mg, 3.43 mmol, 52%); δ_H (500 MHz, $CDCl_3$) 7.41–7.28 (5H, m), 4.76–4.68 (1H, m), 4.56–4.47 (1H, m), 3.85–3.79 (1H, m), 2.22–2.13 (1H, m), 1.03 (3H, d, *J* = 7.0 Hz), 1.01 (3H, d, *J* = 7.0 Hz).



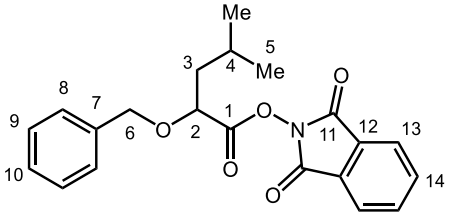
The phthalimide ester was prepared following the instructions given in General Procedure A using carboxylic acid precursor **250a** (700 mg, 3.36 mmol, 1.0 eq.), *N*-hydroxyphthalimide (823 mg, 5.04 mmol, 1.5 eq.), DCC (763 mg, 3.70 mmol, 1.1 eq.) and DMAP (41.0 mg, 0.336 mmol, 0.10 eq.) in DCM (20 mL). The title compound **251a** was obtained after purification by FCC (SiO_2, Cyclohexane:EtOAc, 6:1) as a colourless, crystalline solid (971 mg, 2.75 mmol, 82%); mp. 59-61 °C; R_f 0.35 (Cyclohexane:EtOAc, 6:1); υ_{max}/cm^{-1} (neat) 2978, 1786, 1723, 1067, 873, 739, 691; δ_H (500 MHz, $CDCl_3$) 7.94–7.86 (2H, m, ArH), 7.83–7.77 (2H, m, ArH), 7.47–7.41 (2H, m, ArH), 7.39–7.34 (2H, m, ArH), 7.34–7.29 (1H, m, ArH), 4.89 (1H, d, *J* = 11.6 Hz, H-5a), 4.53 (1H, d, *J* = 11.6 Hz, H-5b), 4.07 (1H, d, *J* = 5.9 Hz, H-2), 2.30 (1H, heptd, *J* = 6.9, 5.9 Hz, H-3), 1.14 (3H, d, *J* = 6.9 Hz, H-4 (A)), 1.12 (3H, d, *J* = 6.9 Hz, H-4 (B)); δ_C (126 MHz, $CDCl_3$) 168.9 (C, C-1), 161.9 (C, C-10), 137.1 (C, C-6), 135.0 (CH, ArCH), 129.1 (C, C-11), 128.6 (CH, ArCH), 128.4 (CH, ArCH), 128.2 (CH, ArCH), 124.1 (CH, ArCH), 81.6 (CH, C-2), 72.8 (CH_2, C-5), 32.1 (CH, C-3), 18.5 (CH_3, C-4 (A)), 17.9 (CH_3, C-4 (B)); *m/z* (ESI) 354 $[MH]^+$; [HRMS (ESI): calc. for $C_{20}H_{20}NO_5^+$, 354.1336. Found: $[MH]^+$, 354.1333 (0.7 ppm error)].

Lab Book Ref.: LH547

1,3-Dioxoisoindolin-2-yl 2-(benzyloxy)-4-methylpentanoate (251b)



The carboxylic acid of 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)-4-methylpentanoate **251b** was prepared from 2-hydroxy-4-methylvaleric acid (793 mg, 6.00 mmol) using General Procedure C. Purification by FCC (SiO_2, Cyclohexane:Et_2O, 6:1) gave the crude carboxylic acid as a pale yellow oil (287 mg, 1.29 mmol, 21%); δ_H (500 MHz, $CDCl_3$) 7.39–7.29 (5H, m), 4.73 (1H, d, *J* = 11.4 Hz), 4.47 (1H, d, *J* = 11.4 Hz), 4.03 (1H, dd, *J* = 9.2, 4.1 Hz), 1.8 (1H, dddd, *J* = 13.2, 11.7, 8.7, 6.6 Hz), 1.78 (1H, ddd, *J* = 14.2, 9.2, 5.1 Hz), 1.59 (1H, ddd, *J* = 14.2, 8.9, 4.1 Hz), 0.94 (3H, d, *J* = 6.7 Hz), 0.86 (3H, d, *J* = 6.6 Hz).

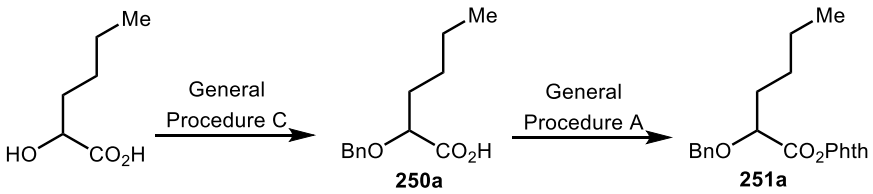


The phthalimide ester was prepared following the instructions given in General Procedure A using carboxylic acid precursor (271 mg, 1.22 mmol, 1.0 eq.), *N*-hydroxyphthalimide (299 mg, 1.83 mmol, 1.5 eq.), DCC (277 mg, 1.34 mmol, 1.1 eq.) and DMAP (15.0 mg, 0.122 mmol, 0.10 eq.) in DCM (15 mL). The title compound **251b** was obtained after purification by FCC (SiO_2, Cyclohexane:EtOAc, 8:1) as a colourless, crystalline solid (348 mg, 0.95 mmol, 78%); mp. 83-84 °C; R_f 0.30 (Cyclohexane:EtOAc, 8:1); υ_{max}/cm^{-1} (neat) 2960, 1785, 1740, 1075, 874, 697; δ_H (500 MHz, $CDCl_3$) 7.94–7.86 (2H, m, ArH), 7.84–7.77 (2H, m, ArH), 7.47–7.29 (5H, m, ArH), 4.86 (1H, d, *J* = 11.4 Hz, H-6a), 4.53 (1H, d, *J* = 11.4 Hz, H-6b), 4.35 (1H, dd, *J* = 9.1, 4.3 Hz, H-2), 2.03–1.91 (2H, m, H-3a, H-4), 1.80–1.71 (1H, m, H-3b), 0.99 (3H, d, *J* = 6.4 Hz, H-5 (A)), 0.89 (3H, d, *J* = 6.4 Hz, H-5 (B)); δ_C (126 MHz, $CDCl_3$) 169.8 (C, C-1), 161.9 (C, C-11), 136.9 (C, C-7), 135.0 (CH, ArCH), 129.1 (C, C-12), 128.7 (CH, ArCH), 128.6 (CH, ArCH), 128.3 (CH, ArCH), 124.2 (CH, ArCH), 75.0 (CH, C-2), 72.8 (CH_2, C-6), 41.9 (CH_2, C-3), 24.6 (CH, C-4), 23.2 (CH_3, C-5

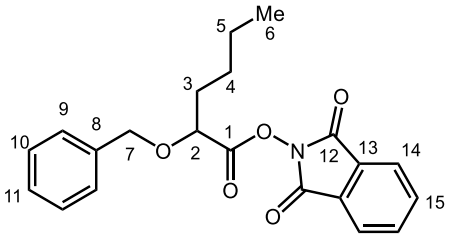
(A)), 21.6 (CH_3, C-5 (B)); *m/z* (ESI) 368 $[MH]^+$; [HRMS (ESI): calc. for $C_{21}H_{22}NO_5^+$, 368.1492. Found: $[MH]^+$, 368.1499 (1.7 ppm error)].

Lab Book Ref.: LH555

1,3-Dioxoisoindolin-2-yl 2-(benzyloxy)hexanoate (251c)



The carboxylic acid of 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)hexanoate **251c** was prepared from 2-hydroxyhexanoic acid (793 mg, 6.00 mmol) using General Procedure C. Purification by FCC (SiO_2, Cyclohexane:Et_2O, 6:1) gave the crude carboxylic acid as a pale yellow oil (285 mg, 1.28 mmol, 21%); δ_H (500 MHz, $CDCl_3$) 7.39–7.30 (5H, m), 4.71 (1H, d, *J* = 11.5 Hz), 4.52 (1H, d, *J* = 11.5 Hz), 4.01 (1H, t, *J* = 6.0 Hz), 1.90–1.75 (2H, m), 1.47–1.38 (2H, m), 1.37–1.25 (2H, m), 0.90 (3H, t, *J* = 7.2 Hz).

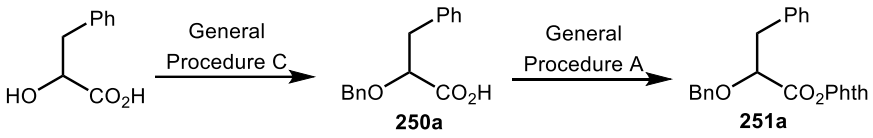


The phthalimide ester was prepared following the instructions given in General Procedure A using carboxylic acid precursor (255 mg, 1.15 mmol, 1.0 eq.), *N*-hydroxyphthalimide (281 mg, 1.72 mmol, 1.5 eq.), DCC (261 mg, 1.27 mmol, 1.1 eq.) and DMAP (14.0 mg, 0.115 mmol, 0.10 eq.) in DCM (15 mL). The title compound **251c** was obtained after purification by FCC (SiO_2, Cyclohexane:EtOAc, 8:1) as a colourless, crystalline solid (324 mg, 0.89 mmol, 77%); mp. 41-43 °C; R_f 0.30 (Cyclohexane:EtOAc, 8:1); υ_{max}/cm^{-1} (neat) 2956, 1795, 1739, 1355, 1184, 1124, 1060, 964, 873, 735, 694; δ_H (500 MHz, $CDCl_3$) 7.94–7.86 (2H, m, ArH), 7.85–7.76 (2H, m, ArH), 7.45–7.40 (5H, m, ArH), 4.86 (1H, d, *J* = 11.5 Hz, H-7a), 4.54 (1H, d, *J* = 11.5 Hz, H-7b), 4.31 (1H, dd, *J* = 6.9, 6.0 Hz, H-2), 2.04–1.93 (2H, m, H-3), 1.63–1.45 (2H, m, H-4), 1.37 (2H, app sext, *J* = 7.4 Hz, H-5), 0.93 (3H, d, *J* = 7.4

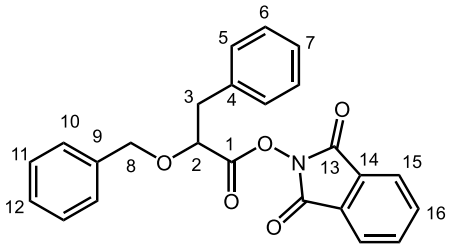
Hz, H-6); δ_C (126 MHz, $CDCl_3$) 169.5 (C, C-1), 161.9 (C, C-12), 137.0 (C, C-8), 135.0 (CH, ArCH), 129.1 (C, C-13), 128.7 (CH, ArCH), 128.5 (CH, ArCH), 128.3 (CH, ArCH), 124.2 (CH, ArCH), 76.4 (CH, C-2), 72.7 (CH_2, C-7), 33.0 (CH_2, C-3), 27.1 (CH_2, C-4), 22.4 (CH_2, C-5), 14.0 (CH_3, C-6); *m/z* (ESI) 368 $[MH]^+$; [HRMS (ESI): calc. for $C_{21}H_{22}NO_5^+$, 368.1492. Found: $[MH]^+$, 368.1488 (1.2 ppm error)].

Lab Book Ref.: LH556

1,3-Dioxoisoindolin-2-yl 2-(benzyloxy)-3-phenylpropanoate (251d)



The carboxylic acid of 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)-3-phenylpropanoate **251d** was prepared from 3-phenyllactic acid (997 mg, 6.00 mmol) using General Procedure C. Purification by FCC (SiO_2, Cyclohexane:EtOAc, 6:1) gave the crude carboxylic acid as a pale yellow oil (350 mg, 1.37 mmol, 23%); δ_H (500 MHz, $CDCl_3$) 7.30–7.23 (5H, m), 4.67 (1H, d, *J* = 11.7 Hz), 4.43 (1H, d, *J* = 11.7 Hz), 4.20 (1H, dd, *J* = 8.5, 4.1 Hz), 3.18 (1H, dd, *J* = 14.1, 4.1 Hz), 3.06 (1H, 14.1, 8.5 Hz).

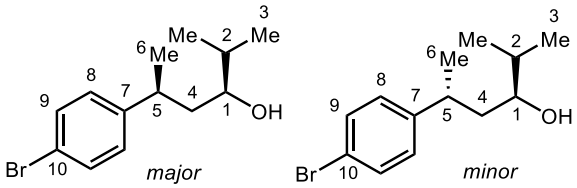


The phthalimide ester was prepared following the instructions given in General Procedure A with the carboxylic acid (340 mg, 1.33 mmol, 1.0 eq.), *N*-hydroxyphthalimide (325 mg, 1.99 mmol, 1.5 eq.), DCC (301 mg, 1.46 mmol, 1.1 eq.) and DMAP (16.0 mg, 0.133 mmol, 0.10 eq.) in DCM (15 mL). The title compound **251d** was obtained after purification by FCC (SiO_2, Cyclohexane:EtOAc, 8:1) as a colourless, crystalline solid (267 mg, 0.67 mmol, 66%); mp. 84-85 °C; R_f 0.25 (Cyclohexane:EtOAc, 6:1); υ_{max}/cm^{-1} (neat) 3030, 1785, 1737, 1455, 1332, 1183, 1071, 1040, 976, 875, 737, 694; δ_H (500 MHz, $CDCl_3$) 7.96–7.88 (2H, m, ArH), 7.85–7.77 (2H, m, ArH), 7.37–7.21 (10H, m, ArH), 4.84 (1H, d, *J* = 11.7 Hz, H-8a), 4.50

(1H, d, *J* = 11.7 Hz, H-8b), 4.48 (1H, dd, *J* = 8.4, 4.9 Hz, H-2), 3.31 (1H, dd, *J* = 14.1, 4.9 Hz, H-3a), 3.25 (1H, dd, *J* = 14.1, 8.4 Hz, H-3b); δ_C (126 MHz, $CDCl_3$) 168.7 (C, C-1), 161.8 (C, C-13), 136.7 (C, ArC), 136.0 (C, ArC), 135.0 (CH, ArCH), 129.8 (CH, ArCH), 129.1 (C, C-14), 128.6 (CH, ArCH), 128.6 (CH, ArCH), 128.3 (CH, ArCH), 128.1 (CH, ArCH), 127.2 (CH, ArCH), 124.2 (CH, ArCH), 77.5 (CH, C-2), 72.8 (CH_2, C-8), 39.5 (CH_2, C-3); *m/z* (ESI) 402 $[MH]^+$; [HRMS (ESI): calc. for $C_{24}H_{20}NO_5^+$, 402.1336. Found: $[MH]^+$, 402.1341 (1.2 ppm error)].

Lab Book Ref.: LH583

5-(4-Bromophenyl)-2-methyl-3-hexanol (253a)

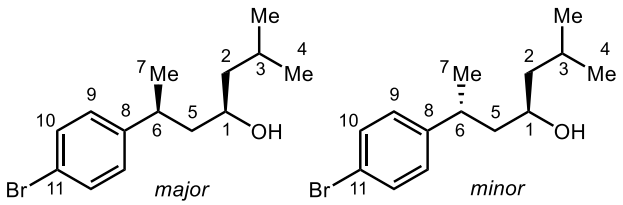


5-(4-Bromophenyl)-2-methyl-3-hexanol **253a** was prepared using General Procedure E with 1-bromo-4-isopropenylbenzene **246** (79.0 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)-3-methylbutanoate **251a** (177 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 7:1) gave an inseparable mixture of isomer of the title compound **253a** as a yellow oil (56.0 mg, 0.220 mmol, 52%, dr:7:1); R_f 0.25 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3366, 2959, 2930, 1487, 1072, 1009, 982, 817, 676; δ_H (500 MHz, $CDCl_3$) 7.43–7.40 (2H, m, ArH), 7.11–7.08 (2H, m, ArH), 3.63–3.51 (1H, m, H-1, minor), 3.46 (1H, app dt, *J* = 7.4, 4.9 Hz, H-1, major), 3.05–2.96 (1H, m, H=5, minor), 2.92 (1H, app sext, *J* = 7.0 Hz, H-5, major), 1.68–1.62 (3H, m, H-4, H-2), 1.24 (3H, d, *J* = 7.0 Hz, H-6), 0.90 (6H, d, *J* = 6.9 Hz, H-3, major), 0.84 (3H, d, *J* = 6.8 Hz, H-3 (A), minor), 0.83 (3H, d, *J* = 6.8 Hz, H-3 (B), minor); δ_C (126 MHz, $CDCl_3$) 147.2 (C, C-7, major), 145.9 (C, C-7, minor), 131.7 (CH, ArCH, major), 131.6 (CH, ArCH, minor), 129.1 (CH, ArCH, minor), 128.8 (CH, ArCH, major), 119.7 (C, C-10), 74.6 (CH, C-1, major), 74.2 (CH, C-1, minor), 42.9 (CH, C-2, major), 42.3 (CH, C-2, minor), 36.2 (CH, C-5, minor), 36.2 (CH, C-5, major), 34.2 (CH_2, C-4, minor), 33.9 (CH_2, C-4, major), 23.6 (CH_3, C6, minor), 21.4 (CH_3, C-6, major), 18.9 (CH_3, C-3 (A), major), 18.7 (CH_3, C-3 (A), minor), 17.3 (CH_3,

C-3 (B), minor), 17.0 (CH_3, C-3 (B), major); *m/z* (ESI) 288 $[MNH_4]^+$; [HRMS (ESI): calc. for $C_{13}H_{23}{}^{79}BrNO^+$, 288.0958. Found: $[MNH_4]^+$, 288.0959 (0.6 ppm error)].

Lab Book Ref.: LH548

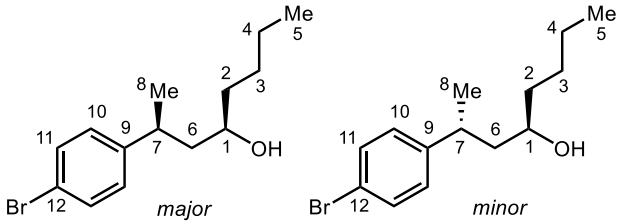
2-(4-Bromophenyl)-6-methyl-4-heptanol (253b)



2-(4-Bromophenyl)-6-methyl-4-heptanol **253b** was prepared using General Procedure E with 1-bromo-4-isopropenylbenzene **246** (79.0 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)-4-methylpentanoate **251b** (184 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 7:1) gave an inseparable mixture of isomers of the title compound **253b** as a pale yellow oil (71.5 mg, 0.251 mmol, 63%, dr: 7:1); R_f 0.25 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3344, 2955, 2926, 1488, 1073, 1008, 908, 821, 738; δ_H (400 MHz, $CDCl_3$) 7.44–7.33 (2H, m, ArH), 7.13–7.05 (2H, m, ArH), 3.67 (1H, app tt, *J* = 8.7, 4.4 Hz, H-1, major), 3.37 (1H, app tt, *J* = 8.6, 4.4 Hz, H-1, minor), 3.04–2.95 (1H, m, H-6, minor) 2.90 (1H, app sext, *J* = 7.0 Hz, H-6, major), 1.81–1.51 (3H, m, H-5, H-3), 1.37 (1H, ddd, *J* = 13.9, 8.7, 5.2 Hz, H-2a), 1.29–1.22 (1H, m, H-2b), 1.24 (3H, d, *J* = 7.0 Hz, H-7), 0.92 (3H, d, *J* = 6.7 Hz, H-4 (A), major)), 0.86 (3H, d, *J* = 6.6 Hz, H-4 (B), major), 0.81 (3H, d, *J* = 6.7 Hz, H-4 (A), minor)), 0.81 (3H, d, *J* = 6.6 Hz, H-4 (B), minor); δ_C (101 MHz, $CDCl_3$) 146.8 (C, C-8, major), 144.9 (C, C-8, minor), 131.7 (CH, ArCH, major), 131.6 (CH, ArCH, minor), 129.0 (CH, ArCH, minor), 128.8 (CH, ArCH, major), 119.7 (C, C-11), 68.1 (CH, C-1, major), 67.8 (CH, C-1, minor), 47.6 (CH_2, C-2, minor), 47.3 (CH_2, C-2, major), 46.7 (CH_2, C-5, major), 46.2 (CH_2, C-5, minor), 36.1 (CH, C-6, major), 36.0 (CH, C-6, major), 24.7 (CH, C-3, minor), 24.7 (CH, C-3, major), 23.6 (CH_3, C-7, major), 23.3 (CH_3, C-7, minor), 22.4 (CH_3, C-4 (A), minor), 22.2 (CH_3, C-4 (A), major), 21.8 (CH_3, C-4 (B)); *m/z* (ESI) 307 $[MNa]^+$; [HRMS (ESI): calc. for $C_{14}H_{21}{}^{79}BrNaO^+$, 307.0668. Found: $[MNa]^+$, 307.0669 (0.3 ppm error)].

Lab Book Ref.: LH560

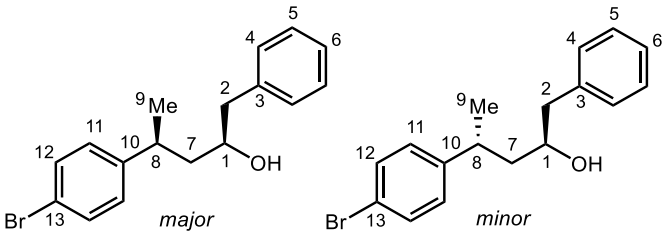
2-(4-Bromophenyl)-4-octanol (253c)



2-(4-Bromophenyl)-4-octanol **253c** was prepared using General Procedure E with 1-bromo-4-isopropenylbenzene **246** (79.0 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)hexanoate **251c** (184 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 7:1) gave an inseparable mixture of isomers of the title compound **253c** as a yellow oil (79.4 mg, 0.278 mmol, 67%, dr: 8:1); R_f 0.30 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3358, 2957, 2928, 1488, 1073, 1009, 907, 820, 732; δ_H (400 MHz, $CDCl_3$) 7.41 (2H, d, *J* = 8.4 Hz, ArH), 7.09 (2H, d, *J* = 8.4 Hz, ArH), 3.60 (1H, app ddt, *J* = 12.5, 8.4, 4.5 Hz, H-1, major), 3.26 (1H, app pent, *J* = 6.1 Hz, H-1, minor), 3.03–2.94 (1H, m, H-7, minor), 2.90 (1H, app sext, *J* = 6.9 Hz, H-6, major), 1.76–1.58 (2H, m), 1.50–1.18 (6H, m), 1.24 (3H, d, *J* = 6.9 Hz, H-8), 0.90 (3H, t, *J* = 7.0 Hz, H-5); δ_C (100 MHz, $CDCl_3$) 146.8 (C, C-9, major), 145.9 (C, C-9, minor), 131.6 (CH, ArCH, major), 131.6 (CH, ArCH, minor), 129.1 (CH, ArCH, minor), 128.8 (CH, ArCH, major), 119.7 (C, C-12), 70.0 (CH, C-1, major), 69.7 (CH, C-1, minor), 46.1 (CH_2, C-6, major), 45.7 (CH_2, C-6, minor), 38.1 (CH_2, C-2, minor), 37.6 (CH_2, C-2, major), 36.1 (CH, C-7, major), 36.0 (CH, C-7, minor), 27.8 (CH_2, major), 27.8 (CH_2, minor), 23.3 (CH_2, minor), 22.8 (CH_2, major), 21.8 (CH_3, C-8), 14.2 (CH_3, C5); *m/z* (ESI) 307 $[MNa]^+$; [HRMS (ESI): calc. for $C_{14}H_{21}{}^{79}BrNaO^+$, 307.0668. Found: $[MNa]^+$, 307.0667 (0.3 ppm error)].

Lab Book Ref.: LH561

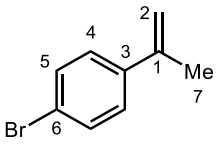
4-(4-Bromophenyl)-1-phenyl-2-pentanol (253d)



4-(4-Bromophenyl)-1-phenyl-2-pentanol **253d** was prepared using General Procedure E with 1-bromo-4-isopropenylbenzene **246** (79.0 mg, 0.400 mmol) and 11,3-dioxoisoindolin-2-yl 2-(benzyloxy)-3-phenylpropanoate **251d** (201 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 7:1) gave an inseparable mixture of isomers of the title compound **253d** as a pale yellow oil (84.2 mg, 0.264 mmol, 66%, dr: 10:1); R_f 0.25 (Cyclohexane:EtOAc, 6:1); υ_{max}/cm^{-1} (neat) 3407, 2959, 2926, 1488, 1453, 1074, 1008, 908, 821, 731, 699; δ_H (500 MHz, $CDCl_3$) 7.47–7.39 (2H, m, ArH), 7.36–7.32 (2H, m, ArH), 7.29–7.24 (1H, m), 7.21–7.15 (2H, m), 7.13–7.08 (2H, m), 3.82 (1H, dddd, *J* = 8.5, 8.3, 4.7, 4.0 Hz, H-1, major), 3.50 (1H, app tt, *J* = 8.5, 4.7 Hz, H-1, minor), 3.11–3.01 (1H, m, H-8, minor), 2.96 (1H, dqd, *J* = 8.3, 6.9, 6.7 Hz, H-8, major), 2.85 (1H, dd, *J* = 13.6, 4.0 Hz, H-2a, major), 2.72 (1H, dd, *J* = 13.5, 4.6 Hz, H-2a, minor), 2.64 (1H, dd, *J* = 13.6, 8.5 Hz, H-2b, major), 2.64–2.59 (1H, m, H-2b, minor), 1.83 (1H, ddd, *J* = 13.8, 8.3, 6.7 Hz, H-7a), 1.72 (1H, ddd, *J* = 13.8, 8.2, 4.7 Hz, H-7b), 1.26 (3H, d, *J* = 6.9 Hz, H-9); δ_C (126 MHz, $CDCl_3$) 146.6 (C, C-10, major), 145.7 (C, C-10, minor), 138.3 (C, C-3, major), 138.3 (C, C-3, minor), 131.7 (CH, ArCH, major), 131.6 (CH, ArCH, minor), 129.5 (CH, ArCH, major), 129.4 (CH, ArCH, minor), 129.1 (CH, ArCH, minor), 128.8 (CH, ArCH, major), 128.7 (CH, ArCH, major), 128.6 (CH, ArCH, minor), 126.7 (CH, ArCH, major), 126.6 (CH, ArCH, minor), 119.7 (C, C-13), 70.7 (CH, C-1, major), 70.2 (CH, C-1, minor), 45.3 (CH_2, C-7, major), 45.0 (CH_2, C-7, minor), 44.8 (CH_2, C-2, minor), 44.3 (CH_2, C-2, major), 36.0 (CH, C-8), 23.3 (CH_3, C-9, minor), 21.7 (CH_3, C-9, major); *m/z* (ESI) 341 $[MNa]^+$; [HRMS (ESI): calc. for $C_{17}H_{19}{}^{79}BrNaO^+$, 341.0511. Found: $[MNa]^+$, 341.0514 (0.7 ppm error)].

Lab Book Ref.: LH584

1-Bromo-4-isopropenylbenzene (246)

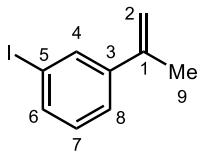


1-Bromo-4-isopropenylbenzene **246** was prepared using General Procedure F with 4-bromoacetophenone (1.99 g, 10.0 mmol). Purification by FCC (SiO_2, pentane) gave the title compound **246** as a colourless oil (1.23 g, 6.24 mmol, 62%); δ_H (400 MHz, $CDCl_3$) 7.47–7.42 (2H, m, ArH), 7.35–7.30 (2H, m, ArH), 5.37–5.35 (1H, m, H-2a), 5.10 (1H, app p, *J* = 1.5 Hz, H-2b), 2.15–2.10 (3H, m, H-7); δ_C (100 MHz, $CDCl_3$) 142.4 (C, C-3), 140.3 (C, C-1), 131.4 (CH, ArCH), 127.3 (CH, ArCH), 121.5 (C, C-6), 113.2 (CH_2, C-2), 21.8 (CH_3, C-7).

Lab Book Ref.: LH422

Data are consistent with those previously reported.[215]

1-Iodo-3-isopropenylbenzene (254)

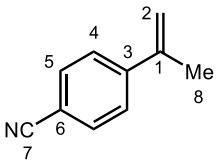


1-Iodo-3-isopropenylbenzene **254** was prepared using General Procedure F with 3-iodoacetophenone (984 mg, 4.00 mmol). Purification by FCC (SiO_2, pentane) gave the title compound **254** as a colourless oil (635 mg, 2.61 mmol, 65%); δ_H (400 MHz, $CDCl_3$) 7.80 (1H, app t, *J* = 1.8 Hz, H-4), 7.59 (1H, ddd, *J* = 7.8, 1.8, 1.1 Hz, ArH), 7.42 (1H, ddd, *J* = 7.8, 1.8, 1.1 Hz, ArH), 7.08 (1H, app t, *J* = 7.8 Hz, H-8), 5.36–5.34 (1H, m, H-2a), 5.14–5.12 (1H, app p, *J* = 1.5 Hz, H-2b), 2.12 (3H, dd, *J* = 1.5, 0.8 Hz); δ_C (100 MHz, $CDCl_3$) 143.7, 142.1, 136.4, 134.8, 130.1, 124.9, 113.8, 94.6, 21.8.

Lab Book Ref.: LH525

Data are consistent with those previously reported.[216]

2-(4-Cyanophenyl)propene (255)

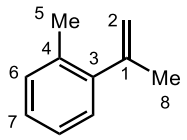


2-(4-Cyanophenyl)propene **255** was prepared using General Procedure F with 4-cyanoacetophenone (290 mg, 2.00 mmol). Purification by FCC (SiO_2, pentane:EtOAc, 4:1) gave the title compound **255** as a colourless oil (152 mg, 1.06 mmol, 53%); δ_H (400 MHz, $CDCl_3$) 7.63–7.59 (2H, m), 7.56–7.52 (2H, m), 5.48–5.46 (1H, m, H-2a), 5.26–5.23 (1H, m, H-2b), 2.16 (3H, dd, *J* = 1.6, 0.8 Hz, H-8); δ_C (100 MHz, $CDCl_3$) 145.8 (C, C-3), 142.0 (C, C-1), 132.2 (CH, ArCH), 126.3 (CH, ArCH), 119.1 (C, C-6), 115.8 (CH_2, C-2), 111.0 (C, C-7), 21.6 (CH_3, C-8).

Lab Book Ref.: LH764

Data are consistent with those previously reported.[217]

1-Methyl-2-(1-propen-2-yl)benzene (256)

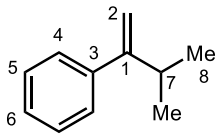


1-Methyl-2-(prop-1-en-2-yl)benzene **256** was prepared using General Procedure F with 1-(o-tolyl)ethan-1-one (537 mg, 4.00 mmol). Purification by FCC (SiO_2, pentane) gave the title compound **256** as a colourless oil (268 mg, 2.02 mmol, 51%); δ_H (400 MHz, $CDCl_3$) 7.19–7.09 (4H, m, ArH), 5.19 (1H, dq, *J* = 3.0, 1.5 Hz, H-2a), 4.87–4.82 (1H, m, H-2b), 2.32 (3H, s, H-5), 2.04 (3H, t, *J* = 1.5 Hz, H-8); δ_C (100 MHz, $CDCl_3$) 146.0 (C), 144.0 (C), 134.6 (C), 130.2 (CH, ArCH), 128.0 (CH, ArCH), 126.9 (CH, ArCH), 125.7 (CH, ArCH), 114.8 (CH_2, C-2), 24.5 (CH_3), 19.9 (CH_3).

Lab Book Ref.: LH541

Data are consistent with those previously reported.[218]

(3-Methyl-1-buten-2-yl)benzene (257)

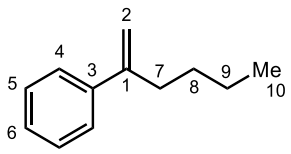


(3-Methyl-1-buten-2-yl)benzene **257** was prepared using General Procedure F with 2-methyl-1-phenylpropan-1-one (445 mg, 3.00 mmol). Purification by FCC (SiO_2, pentane) gave the title compound **257** as a colourless oil (345 mg, 2.36 mmol, 78%); δ_H (400 MHz, $CDCl_3$) 7.38–7.24 (5H, m, ArH), 5.17–5.13 (1H, m, H-2a), 5.04 (1H, t, *J* = 1.3 Hz, H-2b), 2.84 (1H, sext, *J* = 6.8 Hz, H-7), 1.10 (6H, d, *J* = 6.8 Hz, H-8); δ_C (100 MHz, $CDCl_3$) 156.0 (C), 143.0 (C), 128.3 (CH, ArCH), 127.2 (CH, ArCH), 126.8 (CH, ArCH), 110.1 (CH_2, C-2), 32.5 (CH, C-7), 19.9 (CH_3, C-8).

Lab Book Ref.: LH521

Data are consistent with those previously reported.[219]

2-Phenyl-1-hexene (258)

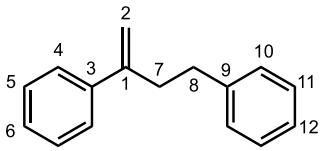


2-Phenyl-1-hexene **258** was prepared using General Procedure F with valerophenone (0.670 mL, 4.00 mmol). Purification by FCC (SiO_2, pentane) gave the title compound **258** as a colourless oil (406 mg, 2.52 mmol, 63%); δ_H (400 MHz, $CDCl_3$) 7.44–7.37 (2H, m, ArH), 7.36–7.30 (2H, m, ArH), 7.29–7.24 (1H, m, ArH), 5.26 (1H, d, *J* = 1.6 Hz, H-2a), 5.03 (1H, app p, *J* = 1.6 Hz, H-2b), 2.55–2.46 (2H, m, H-7), 1.53–1.22 (4H, m), 0.93 (3H, t, *J* = 7.2 Hz, H-10); δ_C (100 MHz, $CDCl_3$) 148.9 (C), 141.7 (C), 128.4 (CH, ArCH), 127.4 (CH, ArCH), 126.3 (CH, ArCH), 112.1 (CH_2, C-2), 35.2 (CH_2, C-7), 30.6 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

Lab Book Ref.: LH433

Data are consistent with those previously reported.[220]

2,4-Diphenyl-1-butene (259)

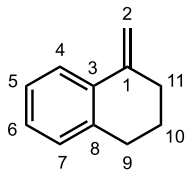


2,4-Diphenyl-1-butene **259** was prepared using General Procedure F with 3-phenylpropiophenone (841 mg, 4.00 mmol). Purification by FCC (SiO_2, pentane) gave the title compound **259** as a colourless oil (514 mg, 2.47 mmol, 62%); δ_H (400 MHz, $CDCl_3$) 7.48–7.41 (2H, m, ArH), 7.39–7.31 (2H, m, ArH), 7.32–7.27 (3H, m, ArH), 7.24–7.16 (3H, m, ArH), 5.30 (1H, d, *J* = 1.3 Hz, H-2a), 5.07 (1H, q, *J* = 1.3 Hz), 2.88–2.74 (4H, m); δ_C (100 MHz, $CDCl_3$) 148.0 (C), 142.1 (C), 141.2 (C), 128.6 (CH, ArCH), 128.5 (CH, ArCH), 128.5 (CH, ArCH), 127.6 (CH, ArCH), 126.3 (CH, ArCH), 126.0 (CH, ArCH), 112.8 (CH_2, C-2), 37.4 (CH_2), 34.9 (CH_2).

Lab Book Ref.: LH537

Data are consistent with those previously reported.[221]

1-Methylene-1,2,3,4-tetrahydronaphthalene (260)

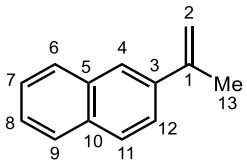


1-Methylene-1,2,3,4-tetrahydronaphthalene **260** was prepared using General Procedure F with 1-tetralone (0.530 mL, 4.00 mmol). Purification by FCC (SiO_2, pentane) gave the title compound **260** as a colourless oil (330 mg, 2.29 mmol, 57%); δ_H (400 MHz, $CDCl_3$) 7.70–7.61 (1H, m, ArH), 7.22–7.07 (3H, m, ArH), 5.51–5.46 (1H, m, H-2a), 4.96 (1H, dt, *J* = 3.2, 1.6 Hz, H-2b), 2.86 (2H, td, *J* = 6.3, 2.0 Hz, H-9), 2.60–2.52 (2H, m, H-11), 1.95–1.84 (2H, m, H-10); δ_C (100 MHz, $CDCl_3$) 143.6 (C), 137.5 (C), 135.1 (C), 129.4 (CH, ArCH), 127.7 (CH, ArCH), 126.0 (CH, ArCH), 124.4 (CH, ArCH), 108.0 (CH_2, C-2), 33.4 (CH_2), 30.6 (CH_2), 24.0 (CH_2).

Lab Book Ref.: LH534

Data are consistent with those previously reported.[222]

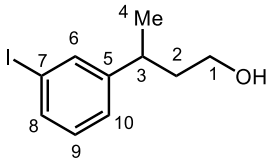
2-Isopropenylnaphthalene (261)



2-Isopropenylnaphthalene **261** was prepared using General Procedure F with 2-acetonaphthalone (340 mg, 2.00 mmol). Purification by FCC (SiO_2, pentane) gave the title compound **261** as a colourless, crystalline solid (204 mg, 1.21 mmol, 60%); mp. 55-57 °C (Lit. 53-55 °C); δ_H (400 MHz, $CDCl_3$) 7.89–7.75 (4H, m, ArH), 7.68 (1H, dd, *J* = 8.6, 1.9 Hz, ArH), 7.52–7.41 (2H, m, ArH), 5.56–5.52 (1H, m, H-2a), 5.20 (1H, app p, *J* = 1.5 Hz, H-2b), 2.28 (3H, dd, *J* = 1.5, 0.8 Hz, H-13); δ_C (100 MHz, $CDCl_3$) 143.2 (C), 138.5 (C), 133.5 (C), 132.9 (C), 128.4 (CH, ArCH), 127.8 (CH, ArCH), 127.7 (CH, ArCH), 126.2 (CH, ArCH), 126.0 (CH, ArCH), 124.4 (CH, ArCH), 124.0 (CH, ArCH), 113.2 (CH_2, C-2), 22.0 (CH_3, C-13).

Data are consistent with those previously reported.[223]

3-(3-Iodophenyl)-1-butanol (270a)

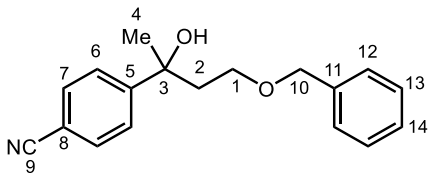


3-(3-Iodophenyl)-1-butanol **270a** was prepared using General Procedure E with 1-iodo-3-isopropenylbenzene **254** (97.6 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (156 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 5:1) gave the title compound **270a** as a yellow oil (46.0 mg, 0.167 mmol, 42%); R_f 0.20 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3315, 2958, 2926, 1588, 1561, 1472, 1421, 1040, 993, 781, 695, 654; δ_H (400 MHz, $CDCl_3$) 7.58–7.49 (2H, m, ArH), 7.17 (1H, app dt, *J* = 7.7, 1.4 Hz, ArH), 7.03 (1H, app t, *J* = 7.7 Hz, H-9), 3.58 (1H, app dt, *J* = 10.6, 6.4 Hz, H-1a), 3.55 (1H, app dt, *J* = 10.6, 6.7, Hz, H-

1b), 2.83 (1H, dqd, *J* = 7.5, 7.0, 6.9 Hz, H-3), 1.90–1.73 (2H, m, H-2), 1.25 (3H, d, *J* = 7.0 Hz, H-4); δ_C (101 MHz, $CDCl_3$) 149.5 (C, C-5), 136.2 (CH, ArCH), 135.3 (CH, ArCH), 130.4 (CH, C-9), 126.5 (CH, ArCH), 94.8 (C, C-7), 61.0 (CH2, C-1), 40.8 (CH_2, C-2), 36.2 (CH, C-3), 22.3 (CH_3, C-4); *m/z* (ESI) 299 $[MNa]^+$; [HRMS (ESI): calc. for $C_{10}H_{13}INaO^+$, 298.9903. Found: $[MH]^+$, 298.9903 (0.3 ppm error)].

Lab Book Ref.: LH532

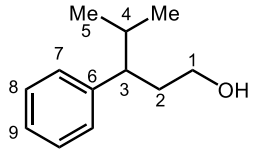
4-(4-(Benzyloxy)-2-hydroxybutan-2-yl)benzonitrile (263a)



4-(4-(benzyloxy)-2-hydroxybutan-2-yl)benzonitrile **263a** was prepared using General Procedure E with 2-(4-cyanophenyl)propene **255** (57.3 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (156 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 5:1) gave the title compound **263a** as a yellow oil (46.0 mg, 0.163 mmol, 41%); R_f 0.15 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3315, 2958, 2926, 1588, 1561, 1472, 1421, 1040, 993, 781, 695, 654; δ_H (500 MHz, $CDCl_3$) 7.62–7.57 (2H, m, H-6), 7.53–7.47 (2H, m, H-7), 7.35–7.28 (3H, m, ArH), 7.24–7.20 (2H, m, ArH), 4.43 (1H, br s, OH), 4.42 (1H, d, *J* = 11.7 Hz, H-10a), 4.34 (1H, d, *J* = 11.7 Hz, H-10b), 3.61 (1H, ddd, *J* = 9.3, 5.0, 4.0 Hz, H-1a), 3.29 (1H, ddd, *J* = 9.9, 9.3, 3.1 Hz, H-1b), 2.23 (1H, ddd, *J* = 15.0, 9.9, 4.0, H-2a), 2.06 (1H, ddd, *J* = 15.0, 5.0, 3.1 Hz, H-2b), 1.51 (3H, s, H-4); δ_C (126 MHz, $CDCl_3$) 153.5 (C, ArC), 137.2 (C, ArC), 132.1 (CH, C-6), 128.6 (CH, ArCH), 128.2 (CH, ArCH), 127.9 (CH, ArCH), 126.0 (CH, C-7), 119.1 (C, ArC), 110.3 (C, C-9), 75.1 (C, C-3), 73.7 (CH_2, C-10), 67.7 (CH_2, C-1), 41.6 (CH_2, C-2), 30.8 (CH_3, C-4); *m/z* (ESI) 304 $[MNa]^+$; [HRMS (ESI): calc. for $C_{18}H_{19}NaO_2^+$, 304.1308. Found: $[MNa]^+$, 304.1308 (0.2 ppm error)].

Lab Book Ref.: LH767

4-Methyl-3-phenyl-1-pentanol (273a)

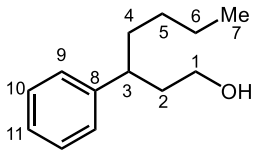


4-Methyl-3-phenyl-1-pentanol **273a** was prepared using General Procedure E with 3-methyl-2-phenyl-1-butene **256** (59.0 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (156 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 5:1) gave the title compound **273a** as a pale yellow oil (19.6 mg, 0.110 mmol, 28%); δ_H (500 MHz, $CDCl_3$) 7.31–7.26 (2H, m, ArH), 7.23–7.15 (1H, m, ArH), 7.15–7.11 (2H, m, ArH), 3.53–3.44 (1H, m, H-1a), 3.38 (1H, ddd, *J* = 10.5, 7.4, 4.9 Hz, H-1b), 2.41 (1H, ddd, *J* = 11.6, 7.8, 3.9 Hz, H-3), 2.08 (1H, app dtd, *J* = 13.6, 7.8, 3.9 Hz, H-2a), 1.89–1.75 (2H, m, H-2b, H-4), 0.97 (3H, t, *J* = 6.7 Hz, H-5 (A)), 0.73 (3H, t, *J* = 6.7 Hz, H-5 (B)); δ_C (126 MHz, $CDCl_3$) 143.9 (C, C-6), 128.5 (CH, ArCH), 128.3 (CH, ArCH), 126.2 (CH, ArCH), 61.8 (CH_2, C-1), 49.7 (CH, C-3), 36.0 (CH, C-4), 33.7 (CH_2, C-2), 21.0 (CH_3, C-5 (A)), 20.8 (CH_3, C-5 (B)).

Lab Book Ref.: LH575

Data are consistent with those previously reported.[224]

3-Phenyl-1-heptanol (274a)



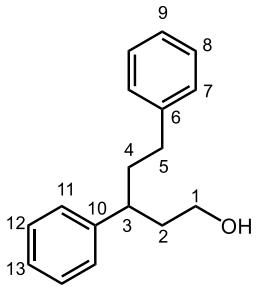
3-Phenyl-1-heptanol **274a** was prepared using General Procedure E with 2-phenyl-1-hexene **258** (64.0 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (156 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 10:1) gave the title compound **274a** as a pale yellow oil (25.2 mg, 0.131 mmol, 33%); δ_H (400 MHz, $CDCl_3$) 7.36–7.27 (2H, m, ArH), 7.22–7.16 (3H, m, ArH), 3.53 (1H, ddd, *J* = 10.6, 7.0, 5.4 Hz, H-1a), 3.46 (1H, ddd, *J* = 10.6, 7.6, 6.6 Hz, H-1b), 2.67 (1H, dddd, *J* = 9.7, 9.5, 5.0, 4.8 Hz, H-3), 1.94 (1H, app dtd, *J* = 14.0, 7.3, 4.9 Hz, H-2a), 1.82 (1H, dddd, *J* = 14.0, 10.0, 6.5, 5.4 Hz, H-2b), 1.71–1.52 (2H, m, H-4), 1.30–1.04

(4H, m, H-5, H-6), 0.83 (3H, t, *J* = 7.2 Hz, H-7); δ_C (100 MHz, $CDCl_3$) 145.4 (C, C-8), 128.6 (CH, ArCH), 127.8 (CH, ArCH), 126.3 (CH, ArCH), 61.4 (CH2, C-1), 42.6 (CH, C-3), 39.8 (CH_2, C-2), 36.9 (CH_2, C-4), 36.9 (CH_2, C-5), 22.9 (CH_2, C-6), 14.1 (CH_3, C-7).

Lab Book Ref.: LH471

Data are consistent with those previously reported.[225]

3,5-Diphenyl-1-pentanol (275a)

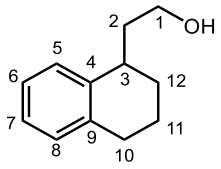


3,5-Diphenyl-1-pentanol **275a** was prepared using General Procedure E with 2,4-diphenyl-1-butene **259** (83.0 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (156 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 5:1) gave the title compound **275a** as a pale yellow oil (33.4 mg, 0.139 mmol, 36%); δ_H (400 MHz, $CDCl_3$) 7.38–7.32 (2H, m, ArH), 7.30–7.16 (6H, m, ArH), 7.14–7.11 (2H, m, ArH), 3.53 (1H, ddd, *J* = 10.6, 6.9, 5.4 Hz, H-1a), 3.46 (1H, ddd, *J* = 10.6, 7.5, 6.4 Hz, H-1b), 2.75 (1H, app tt, *J* = 9.9, 5.2 Hz, H-3), 2.48 (2H, t, *J* = 8.0 Hz, H-5), 2.05–1.90 (3H, m, H-2, H-4a), 1.86 (1H, app ddt, *J* = 13.7, 9.9, 5.9 Hz, H-4b); δ_C (101 MHz, $CDCl_3$) 144.7 (C, ArC), 142.5 (C, ArC), 128.7 (CH, ArCH), 128.5 (CH, ArCH), 128.4 (CH, ArCH), 127.9 (CH, ArCH), 126.5 (CH, ArCH), 125.8 (CH, ArCH), 61.2 (CH_2, C-1), 42.2 (CH, C-3), 39.9 (CH_2), 39.8 (CH_2), 33.9 (CH_2, C-5).

Lab Book Ref.: LH540

Data are consistent with those previously reported.[174]

2-(1,2,3,4-Tetrahydronaphthalen-1-yl)-1-ethanol (276a)

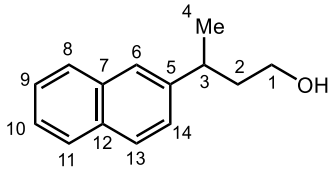


2-(1,2,3,4-Tetrahydronaphthalen-1-yl)-1-ethanol **276a** was prepared using General Procedure E with 1-methylene-1,2,3,4-tetrahydronaphthalene **260** (58.0 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (156 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 5:1) gave the title compound **276a** as a pale yellow oil (26.8 mg, 0.152 mmol, 38%); δ_H (400 MHz, $CDCl_3$) 7.22–7.04 (4H, m, ArH), 3.83–3.76 (2H, m, H-1), 2.98 (1H, app dq, *J* = 10.2, 5.0 Hz, H-3), 2.86–2.29 (2H, m, H-10), 2.01 (1H, app dtd, *J* = 14.4, 7.4, 5.0 Hz, H-2a), 1.97–1.68 (5H, m, H-2b, H11, H-12); δ_C (100 MHz, $CDCl_3$) 140.8 (C, ArC), 137.2 (C, ArC), 129.3 (CH, ArCH), 128.7 (CH, ArCH), 125.7 (CH, ArCH), 125.7 (CH, ArCH), 61.2 (CH_2, C-1), 39.9 (CH_2, C-2), 34.2 (CH, C-3), 29.7 (CH_2, C-10), 27.8 (CH_2, C-12), 19.8 (CH_2, C-11).

Lab Book Ref.: LH478

Data are consistent with those previously reported.[226]

3-(Naphthalen-2-yl)-1-butanol (277a)

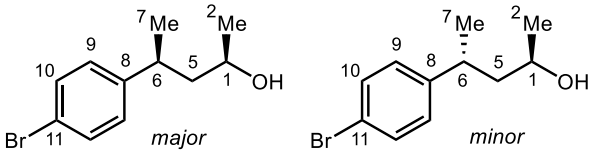


3-(Naphthalen-2-yl)-1-butanol **277a** was prepared using General Procedure E with 2-(1-propen-2-yl)naphthalene **261** (67.3 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (156 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 5:1) gave the title compound **277a** as a pale yellow oil (26.5 mg, 0.132 mmol, 33%); R_f 0.20 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3420, 2925, 2856, 1600, 1452, 1040, 907, 855, 818, 744, 731; δ_H (500 MHz, $CDCl_3$) 7.88–7.78 (3H, m), 7.67 (1H, d, *J* = 1.7 Hz), 7.52–7.44 (2H, m), 7.40 (1H, dd, *J* = 8.5, 1.7 Hz),

3.63 (1H, ddd, *J* = 10.6, 6.6, 4.2 Hz, H-1a), 3.59 (1H, app td, *J* = 10.6, 6.6 Hz, H-2a), 3.10 (1H, qdd, *J* = 7.0, 6.9, 6.5 Hz, H-3), 2.04–1.94 (2H, m, H-2), 1.40 (3H, d, *J* = 7.0 Hz, H-4); δ_C (126 MHz, $CDCl_3$) 144.4 (C, C-5), 133.8 (C, ArC), 132.4 (C, ArC), 128.3 (CH, ArCH), 127.7 (CH, ArCH), 127.7 (CH, ArCH), 126.1 (CH, ArCH), 125.7 (CH, ArCH), 125.4 (CH, ArCH), 125.4 (CH, ArCH), 61.4 (CH_2, C-1), 40.0 (CH_2, C-2), 36.7 (CH, C-3), 22.6 (CH_3, C-4); *m/z* (ESI) 201 $[MH]^+$; [HRMS (ESI): calc. for $C_{14}H_{17}O^+$, 201.1274. Found: $[MH]^+$, 201.1267 (3.6 ppm error)].

Lab Book Ref.: LH582

4-(4-bromophenyl)pentan-2-ol (248b)

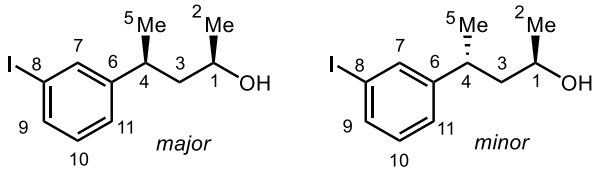


4-(4-bromophenyl)pentan-2-ol **248b** was prepared using General Procedure E with 1-bromo-4-isopropenylbenzene **246** (79.0 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)-4-methylpentanoate **236b** (184 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 7:1) gave an inseparable mixture of isomers of the title compound **248b** as a pale yellow oil (65.0 mg, 0.267 mmol, 67%, dr: 8:1); R_f 0.25 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3343, 2962, 2926, 1481, 1406, 1375, 1073, 1008, 908, 819, 728, 637; δ_H (400 MHz, $CDCl_3$) 7.44–7.36 (2H, m, ArH), 7.13–7.02 (2H, m, ArH), 3.74 (1H, dqd, *J* = 7.5, 7.0, 5.4 Hz, H-1, major), 3.50 (1H, dqd, *J* = 12.5, 6.1, 3.7 Hz, H-1, minor), 3.02–2.90 (1H, m, H-6, minor), 2.84 (1H, ddq, *J* = 7.7, 7.5, 6.2 Hz, H-6, major), 1.77 (1H, app dt, *J* = 13.6, 7.5 Hz, H-5a), 1.60 (1H, ddd, *J* = 13.6, 7.7, 5.4 Hz, H-5b), 1.23 (3H, d, *J* = 7.0 Hz), 1.18 (3H, d, *J* = 6.2 Hz, major), 1.12 (3H, d, *J* = 6.1 Hz, H-7, minor); δ_C (101 MHz, $CDCl_3$) 146.5 (C, C-8, major), 145.9 (C, C-8, minor), 131.7 (CH, ArCH, major), 131.6 (CH, ArCH, minor), 129.1 (CH, ArCH, minor), 128.8 (CH, ArCH, major), 119.7 (C, C-11), 66.2 (CH, C-1, major), 65.8 (CH, C-1, minor), 47.7 (CH_2, C-5, major), 47.6 (CH_2, C-5, minor), 36.3 (CH, C-6, major), 36.2 (CH, C6, minor), 24.4 (CH_3, C-2, minor), 23.9 (CH_3, C-2, major), 23.0 (CH_3, C-7, minor), 22.2 (CH_3, C-7, major); *m/z* (ESI) 265 $[MNa]^+$;

[HRMS (ESI): calc. for $C_{11}H_{15}{}^{79}BrNaO^+$, 265.0198. Found: $[MNa]^+$, 265.0202 (1.5 ppm error)].

Lab Book Ref.: LH515

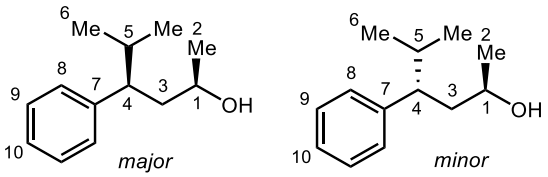
4-(3-Iodophenyl)-2-pentanol (270b)



4-(3-Iodophenyl)-2-pentanol **270b** was prepared using General Procedure E with 1-iodo-3-isopropenylbenzene **254** (97.6 mg, 0.400 mmol) and 2,3-dihydro-1*H*-inden-2-yl (*S*)-2-benzyloxy-propanoate **236b** (165 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:EtOAc, 7:1) gave an inseparable mixture of isomers of the title compound **270b** as a pale yellow oil (62.6 mg, 0.215 mmol, 54%, dr: 10:1); R_f 0.20 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3331, 2961, 2925, 1562, 1421, 1128, 1064, 994, 778, 695; δ_H (400 MHz, $CDCl_3$) 7.56–7.50 (2H, m, ArH), 7.17 (1H, app dt, *J* = 7.8, 1.4 Hz, ArH), 7.02 (1H, app t, *J* = 7.8 Hz, H-12), 3.82–3.70 (1H, m, H-1, major), 3.58–3.46 (1H, m, H-1, minor), 3.00–2.87 (1H, m, H-4, minor), 2.87–2.74 (1H, m, H-4, major), 1.85–1.70 (1H, m, H-3a), 1.60 (1H, ddd, *J* = 13.5, 7.9, 5.3 Hz, H-3b), 1.24 (3H, d, *J* = 7.0 Hz, H-2), 1.19 (3H, d, *J* = 6.2 Hz, H-5, major), 1.13 (3H, d, *J* = 6.1 Hz, H-5, minor); δ_C (101 MHz, $CDCl_3$) 150.1 (C, C-6, major), 149.6 (C, C-6, minor), 136.3 (CH, ArCH, minor), 136.1 (CH, ArCH, major), 135.3 (CH, ArCH, minor), 135.3 (CH, ArCH, major), 130.4 (CH, ArCH, major), 130.4 (CH, ArCH, minor), 126.8 (CH, ArCH, minor), 126.3 (CH, ArCH, major), 94.8 (C, C-8, major), 94.8 (C, C-8, minor), 66.1 (CH, C-1, major), 65.8 (CH, C-1, minor), 47.7 (CH, C-4, major), 47.5 (CH, C-4, minor), 36.5 (CH_2, C-3, major), 36.4 (CH_2, C-3, minor), 24.4 (CH_3, C-2, minor), 24.0 (CH_3, C-2, major), 23.0 (CH_3, C-5, minor), 22.1 (CH_3, C-5, major); *m/z* (ESI) 313 $[MNa]^+$; [HRMS (ESI): calc. for $C_{11}H_{15}INaO^+$, 313.0060. Found: $[MNa]^+$, 313.0055 (1.6 ppm error)].

Lab Book Ref.: LH517

5-Methyl-4-phenyl-2-hexanol (273b)



5-Methyl-4-phenyl-2-hexanol **273b** was prepared using General Procedure E with 3-methyl-2-phenyl-1-butene **257** (59.0 mg, 0.400 mmol) and 2,3-dihydro-1*H*-inden-2-yl (*S*)-2-benzyloxy-propanoate **236b** (165 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:EtOAc, 6:1) gave an inseparable mixture of isomers of the title compound **273b** as a pale yellow oil (23.5 mg, 0.120 mmol, 30%, dr: 2:1);

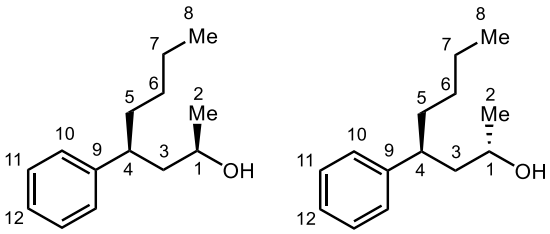
Major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 7.31–7.26 (2H, m, ArH), 7.22–7.17 (1H, m, ArH), 7.16–7.11 (2H, m, ArH), 3.55 (1H, app dp, *J* = 7.5, 6.1 Hz, H-1), 2.30 (1H, ddd, *J* = 13.4, 6.9, 3.2 Hz, H-4), 1.92 (1H, ddd, *J* = 13.5, 11.0, 5.6 Hz, H-3a), 1.87–1.75 (2H, m, H-3b, H-5), 1.14 (3H, d, *J* = 6.1 Hz, H-2), 0.95 (3H, d, *J* = 6.7 Hz, H-6 (A), 0.71 (3H, d, *J* = 6.7 Hz, H-5 (B)); δ_C (101 MHz, $CDCl_3$) 143.9 (C, C-7), 128.6 (CH, ArCH), 128.4 (CH, ArCH), 126.4 (CH, ArCH), 67.4 (CH, C-1), 50.6 (CH, C-4), 42.9 (CH_2, C-3), 33.9 (CH, C-5), 23.0 (CH_3, C-2), 21.1 (CH_3, C-6 (A)), 20.6 (CH_3, C-6 (B)).

Minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 7.30–7.27 (2H, m, ArH), 7.21–7.17 (1H, m, ArH), 7.15–7.13 (2H, m, ArH), 3.41 (1H, dqd, *J* = 9.9, 6.2, 2.7 Hz, H-1), 2.55 (1H, ddd, *J* = 11.8, 7.9, 3.7 Hz, H-4), 1.88–1.74 (2H, m, H-3a, H-5), 1.70 (1H, ddd, *J* = 14.1, 11.8, 2.7 Hz, H-3b), 1.11 (3H, d, *J* = 6.2 Hz, H-2), 0.96 (3H, d, *J* = 6.6 Hz, H-6 (A), 0.72 (3H, d, *J* = 6.7 Hz, H-5 (B)); δ_C (101 MHz, $CDCl_3$) 144.2 (C, C-7), 128.7 (CH, ArCH), 128.3 (CH, ArCH), 126.2 (CH, ArCH), 65.9 (CH, C-1), 49.4 (CH, C-4), 42.7 (CH_2, C-3), 33.9 (CH, C-5), 24.6 (CH_3, C-2), 21.1 (CH_3, C-6 (A)), 21.0 (CH_3, C-6 (B)).

Lab Book Ref.: LH529

Data are consistent with those previously reported.[178]

4-Phenyl-2-octanol (274b)



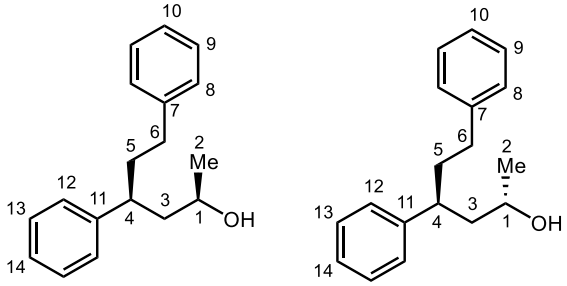
4-Phenyl-2-octanol **274b** was prepared using General Procedure E with 2-phenyl-1-hexene **258** (64.0 mg, 0.400 mmol) and 2,3-dihydro-1*H*-inden-2-yl (*S*)-2-benzyloxy-propanoate **236b** (165 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:EtOAc, 8:1) gave an inseparable mixture of isomers of the title compound **274b** as a pale yellow oil (40.6 mg, 0.196 mmol, 48%, dr: 2:1); R_f 0.25 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3341, 2958, 2925, 1453, 1375, 1065, 938, 759, 690; *m/z* (ESI) 229 $[MNa]^+$; [HRMS (ESI): calc. for $C_{14}H_{22}NaO^+$, 229.1563. Found: $[MNa]^+$, 229.1559 (1.7 ppm error)].

Major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 7.33–7.28 (2H, m, ArH), 7.23–7.13 (3H, m, ArH), 3.68 (1H, app sext, *J* = 6.3 Hz, H-1), 2.60 (1H, app tt, *J* = 9.3, 5.5 Hz, H-4), 1.90–1.78 (1H, m, H-3a), 1.76–1.49 (3H, H-3b, H-5), 1.30–1.01 (4H, m, H-6, H-7), 1.16 (3H, d, *J* = 6.3 Hz, H-2), 0.82 (3H, t, *J* = 7.3 Hz, H-8); δ_C (101 MHz, $CDCl_3$) 145.6 (C, C-9), 128.7 (CH, ArCH), 127.7 (CH, ArCH), 126.3 (CH, ArCH), 66.9 (CH, C-1), 46.7 (CH_2, C-3), 43.4 (CH, C-4), 37.0 (CH_2, C-5), 29.8 (CH_3, C-2), 23.5 (CH_2), 22.9 (CH_2), 14.1 (CH_3, C-8).

Minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 7.32–7.27 (2H, m, ArH), 7.22–7.15 (3H, m, ArH), 3.48 (1H, dqd, *J* = 9.4, 6.2, 3.2 Hz, H-1), 2.79 (1H, dddd, *J* = 10.8, 8.5, 6.3, 4.4 Hz, H-4), 1.74 (1H, ddd, *J* = 14.0, 9.4, 4.4 Hz, H-3a), 1.62–1.55 (2H, m, H-5), 1.33–1.01 (4H, m, H-6, H-7), 1.10 (3H, d, *J* = 6.2 Hz, H-2), 0.82 (3H, t, *J* = 7.2 Hz, H-8); δ_C (101 MHz, $CDCl_3$) 145.5 (C, C-9), 128.5 (CH, ArCH), 127.9 (CH, ArCH), 126.2 (CH, ArCH), 65.8 (CH, C-1), 46.5 (CH_2, C-3), 42.5 (CH, C-4), 37.3 (CH_2, C-5), 29.9 (CH_3, C-2), 24.5 (CH_2), 22.9 (CH_2), 14.2 (CH_3, C-8).

Lab Book Ref.: LH516

4,6-Diphenyl-2-hexanol (275b)



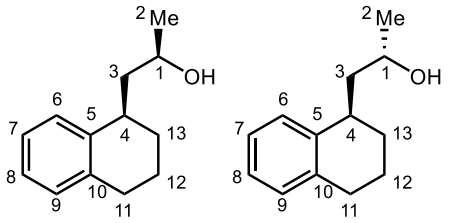
4,6-Diphenyl-2-hexanol **275b** was prepared using General Procedure E with 2,4-diphenyl-1-butene **259** (83.0 mg, 0.400 mmol) and 2,3-dihydro-1*H*-inden-2-yl (*S*)-2-benzyloxy-propanoate **236b** (165 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:EtOAc, 7:1) gave an inseparable mixture of isomers of the title compound **275b** as a pale yellow oil (62.0 mg, 0.244 mmol, 61%, dr: 3:1); R_f(major) 0.20 (Cyclohexane:EtOAc, 4:1) R_f(minor) 0.30 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3356, 2924, 2856, 1494, 1453, 1128, 758, *m/z* (ESI) 277 $[MNa]^+$; [HRMS (ESI): calc. for $C_{18}H_{22}NaO^+$, 277.1563. Found: $[MNa]^+$, 277.1564 (0.3 ppm error)].

Major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 7.38–7.31 (2H, m, ArH), 7.30–7.14 (6H, m, ArH), 7.14–7.08 (2H, m, ArH), 3.69 (1H, app sext, *J* = 6.2 Hz, H-1), 2.68 (1H, app tt, *J* = 9.3, 5.4 Hz, H-4), 2.46 (2H, app t, *J* = 8.1 Hz, H-6a, H-6b), 2.02 (1H, dtd, *J* = 13.2, 8.1, 4.9 Hz, H-5a), 1.96–1.83 (2H, m, H-5b, H-3a), 1.76 (1H, app dt, *J* = 13.7, 6.2 Hz, H-3b), 1.16 (3H, d, *J* = 6.2 Hz, H-2); δ_C (101 MHz, $CDCl_3$) 145.0 (C, ArC), 142.5 (C, ArC), 128.8 (CH, ArCH), 128.5 (CH, ArCH), 128.4 (CH, ArCH), 127.8 (CH, ArCH), 126.6 (CH, ArCH), 125.8 (CH, ArCH), 66.6 (CH, C-1), 46.7 (CH_2, C-3), 42.9 (CH, C-4), 38.8 (CH_2, C-5), 33.8 (CH_2, C-6), 23.5 (CH_3, C-2).

Minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 7.37–7.30 (2H, m, ArH), 7.29–7.08 (8H, m, ArH), 3.49 (1H, dqd, *J* = 9.6, 6.1, 3.4 Hz, H-1), 2.86 (1H, app ddt, *J* = 15.0, 6.5, 4.7 Hz, H-4), 2.46 (1H, t, *J* = 7.3 Hz, H-6a), 2.45 (1H, t, *J* = 7.3 Hz, H-6b), 1.97–1.88 (2H, m, H-5a, H-5b), 1.82–1.64 (2H, m, H-3a, H-3b), 1.10 (3H, d, *J* = 6.2 Hz, H-2); δ_C (100 MHz, $CDCl_3$) 144.9 (C, ArC), 142.6 (C, ArC), 128.7 (CH, ArCH), 128.5 (CH, ArCH), 128.4 (CH, ArCH), 128.0 (CH, ArCH), 126.4 (CH, ArCH), 125.8 (CH, ArCH), 65.8 (CH, C-1), 46.5 (CH_2, C-3), 42.3 (CH, C-4), 39.3 (CH_2, C-5), 34.0 (CH_2, C-6), 24.5 (CH_3, C-2).

Lab Book Ref.: LH539

1-(1,2,3,4-Tetrahydronaphthalen-1-yl)-2-propanol (277b)



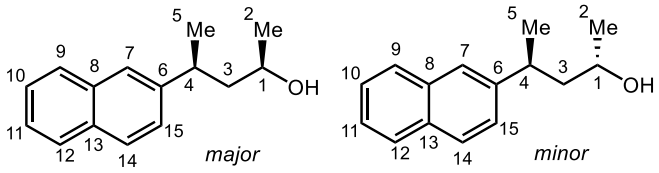
1-(1,2,3,4-Tetrahydronaphthalen-1-yl)-2-propanol **277b** was prepared using General Procedure E with 1-methylene-1,2,3,4-tetrahydronaphthalene **260** (58.0 mg, 0.400 mmol) and 2,3-dihydro-1*H*-inden-2-yl (*S*)-2-benzyloxy-propanoate **236b** (165 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 7:1) gave an inseparable mixture of isomers of the title compound **277b** as a yellow oil (43.0 mg, 0.226 mmol, 57%, dr: 3:1); R_f 0.25 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3354, 2927, 1490, 1450, 1127, 754, 731; *m/z* (ESI) 213 $[MNa]^+$; [HRMS (ESI): calc. for $C_{13}H_{18}NaO^+$, 213.1250. Found: $[MNa]^+$, 213.1243 (3.2 ppm error)].

Major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 7.24–7.05 (4H, m, ArH), 4.08–3.93 (1H, m, H-1), 3.06 (1H, app dq, *J* = 9.8, 4.8 Hz, H-4), 2.85–2.72 (2H, m, H-11), 2.00–1.58 (6H, m, H-3, H-12, H-13), 1.26 (3H, d, *J* = 6.2 Hz, H-2); δ_C (100 MHz, $CDCl_3$) 141.4 (C, ArC), 137.2 (C, ArC), 129.2 (CH, ArCH), 128.7 (CH, ArCH), 125.8 (CH, ArCH), 125.6 (CH, ArCH), 65.6 (CH, C-1), 46.9 (CH_2, C-3), 34.0 (CH, C-4), 29.8 (CH_2, C-11), 27.2 (CH_2, C-12), 24.7 (CH_3, C-2), 19.6 (CH_3, C-2).

Minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 7.24–7.05 (4H, m, ArH), 4.08–3.93 (1H, m, H-1), 2.95 (1H, app tt, *J* = 7.4, 4.4 Hz, H-4), 2.85–2.72 (2H, m, H-11), 2.00–1.58 (6H, m, H-3, H-12, H-13), 1.21 (3H, d, *J* = 6.2 Hz, H-2); δ_C (100 MHz, $CDCl_3$) 140.8 (C, ArC), 137.0 (C, ArC), 129.4 (CH, ArCH), 129.0 (CH, ArCH), 125.8 (CH, ArCH), 125.6 (CH, ArCH), 66.5 (CH, C-1), 46.8 (CH_2, C-3), 34.8 (CH, C-4), 29.5 (CH_2, C-11), 28.6 (CH_2, C-12), 23.9 (CH_3, C-2), 19.4 (CH_3, C-2).

Lab Book Ref.: LH520

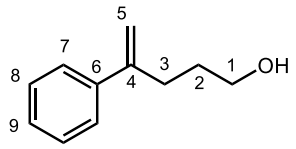
4-(Naphthalen-2-yl)-2-pentanol (277b)



4-(Naphthalen-2-yl)-2-pentanol **277b** was prepared using General Procedure E with 2-(1-propen-2-yl)naphthalene **261** (67.3 mg, 0.400 mmol) and 2,3-dihydro-1*H*-inden-2-yl (*S*)-2-benzyloxy-propanoate **236b** (165 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:EtOAc, 7:1) gave an inseparable mixture of isomers of the title compound **277b** as a pale yellow oil (47.6 mg, 0.222 mmol, 56%, dr: 9:1); R_f 0.20 (Cyclohexane:EtOAc, 4:1); υ_{max}/cm^{-1} (neat) 3354, 2962, 2925, 1454, 1376, 1125, 907, 855, 816, 739; δ_H (500 MHz, $CDCl_3$) 7.84–7.75 (3H, m, ArH), 7.65 (1H, d, *J* = 1.7 Hz, H-7), 7.51–7.34 (3H, m, ArH), 3.81 (1H, app dpent, *J* = 7.6, 6.1 Hz, H-1, major), 3.63–3.52 (1H, m, H-1, minor), 3.22–3.11 (1H, m, H-4, minor), 3.05 (1H, app hept, *J* = 7.1 Hz, H-4, major), 1.95 (1H, ddd, *J* = 13.8, 7.9, 7.5 Hz, H-3a), 1.76 (1H, ddd, *J* = 13.8, 7.5, 5.2 Hz, H-3b), 1.37 (3H, d, *J* = 6.9 Hz, H-2), 1.22 (3H, d, *J* = 6.1 Hz, major), 1.14 (3H, d, *J* = 6.1 Hz, minor); δ_C (126 MHz, $CDCl_3$) 144.8 (C, ArC, major), 144.4 (C, ArC, minor), 133.8 (C, ArC), 132.4 (C, ArC), 128.4 (CH, ArCH, major), 128.3 (CH, ArCH, minor), 127.7 (CH, ArCH), 127.7 (CH, ArCH), 126.1 (CH, ArCH, major), 126.1 (CH, ArCH, minor), 125.7 (CH, ArCH, minor), 125.7 (CH, ArCH, major), 125.6 (CH, ArCH, minor), 125.4 (CH, ArCH, major), 125.4 (CH, ArCH, minor), 125.2 (CH, ArCH, major), 66.6 (CH, C-1, major), 66.1 (CH, C-1, minor), 44.8 (CH, C-4, major), 47.7 (CH, C-4, minor), 37.2 (CH_2, C-3, major), 36.9 (CH_2, C-3, minor), 24.4 (CH_3, C-2, minor), 23.9 (CH_3, C-2, major), 23.2 (CH_3, C-5, minor), 22.5 (CH_3, C-5, major); *m/z* (ESI) 237 $[MNa]^+$; [HRMS (ESI): calc. for $C_{15}H_{18}NaO^+$, 237.1250. Found: $[MNa]^+$, 237.1249 (0.2 ppm error)].

Lab Book Ref.: LH519

4-Phenyl-4-pentenol (283)



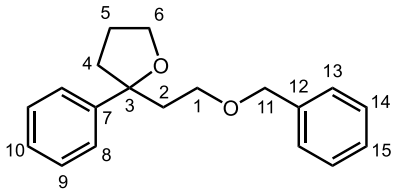
4-Phenyl-4-pentenol **283** was prepared using General Procedure F starting with 3-benzylpropionic acid (1.43 g, 8.00 mmol). After the reaction was completed, the solvent was removed under reduced pressure and the residue diluted with DCM and 1 M aq. NaOH. The aqueous layer was separated, washed with DCM, and acidified with 1 M aq. HCl to give a pale orange precipitate. The crude acid was obtained after filtration and used in the following step without further purification; δ_H (400 MHz, $CDCl_3$) 7.43–7.37 (2H, m), 7.37–7.26 (3H, m), 5.33 (1H, d, *J* = 1.0 Hz), 5.14–5.09 (1H, m), 2.85 (2H, td, *J* = 7.8, 1.4 Hz), 2.58–2.50 (2H, m).

The acid (626 mg, 3.50 mmol, 1.0 eq.) was added to a suspension of $LiAlH_4$ (280 mg, 7.40 mmol, 2.1 eq.) in dry THF (10 mL) under inert atmosphere, then stirred at rt for 2 h. The reaction was quenched with 1 M aq. NaOH, and the resulting precipitate filtered off. The aqueous layer was extracted with Et_2O (3×), then the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by FCC (SiO_2, Cyclohexane:EtOAc, 5:1) gave the title compound **283** as a colourless oil (380 mg, 2.34 mmol, 45% over two steps); δ_H (400 MHz, $CDCl_3$) 7.45–7.38 (2H, m, ArH), 7.36–7.31 (2H, m, ArH), 7.29–7.24 (1H, m, ArH), 5.30 (1H, app q, *J* = 1.4 Hz, H-5a), 5.10 (1H, dt, *J* = 1.4, 1.2 Hz, H-5b), 3.71–3.63 (2H, m, H-1), 2.61 (2H, td, *J* = 7.5, 1.4 Hz, H-3), 1.74 (2H, tt, *J* = 7.5, 6.0 Hz, H-2); δ_C (100 MHz, $CDCl_3$) 148.2 (C), 141.2 (C), 128.5 (CH, ArCH), 127.6 (CH, ArCH), 126.3 (CH, ArCH), 112.7 (CH_2, C-5), 62.6 (CH_2, C-1), 31.7 (CH_2), 31.3 (CH_2).

Lab Book Ref.: LH570

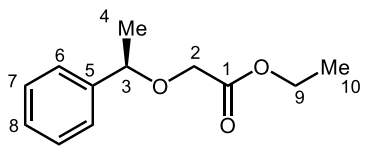
Data are consistent with those previously reported.[227]

2-(2-(Benzyloxy)ethyl)-2-phenyltetrahydrofuran (284)



2-(2-(Benzyloxy)ethyl)-2-phenyltetrahydrofuran **284** was prepared using General Procedure E with 4-phenyl-4-pentenol **283** (65.0 mg, 0.400 mmol) and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (156 mg, 0.500 mmol). Purification by FCC (SiO_2, Cyclohexane:Et_2O, 20:1) gave the title compound **284** as a pale yellow oil (44.2 mg, 0.157 mmol, 39%); R_f 0.60 (Cyclohexane:EtOAc, 3:1); υ_{max}/cm^{-1} (neat) 2925, 2867, 1447, 1385, 1097, 1051, 1028, 909, 733, 698; δ_H (500 MHz, $CDCl_3$) 7.40–7.36 (2H, m, ArH), 7.35–7.30 (4H, m, ArH), 7.29–7.21 (4H, m, ArH), 4.43–4.36 (2H, m, H-11), 3.99 (1H, app td, *J* = 7.9, 6.7 Hz, H-6a), 3.90 (1H, app td, *J* = 7.9, 5.5 Hz, H-6b), 3.59 (1H, app td, *J* = 9.0, 5.5 Hz, H-1a), 3.27 (1H, app td, *J* = 9.0, 5.9 Hz, H-1b), 2.31–2.14 (4H, m, H-2, H-4), 1.96 (1H, app dtt, *J* = 13.1, 7.9, 5.5 Hz, H-5a), 1.79 (1H, app dqd, *J* = 12.2, 7.9, 6.7 Hz, H-5b); δ_C (126 MHz, $CDCl_3$) 146.3 (C, ArC), 138.6 (C, ArC), 128.4 (CH, ArCH), 128.2 (CH, ArCH), 127.7 (CH, ArCH), 127.5 (CH, ArCH), 126.5 (CH, ArCH), 125.2 (CH, ArCH), 85.5 (C, C-3), 73.1 (CH2, C-11), 67.7 (CH_2, C-6), 67.3 (CH_2, C-1), 41.9 (CH_2), 39.0 (CH_2), 25.6 (CH_2, C-5); *m/z* (ESI) 283 $[MH]^+$; [HRMS (ESI): calc. for $C_{19}H_{23}O_2^+$, 283.1693. Found: $[MH]^+$, 283.1687 (1.9 ppm error)].

Ethyl (*R*)-2-(1-phenylethoxy)acetate (291)



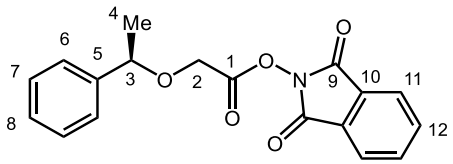
(*R*)-Phenylethanol (2.40 mL, 20.0 mmol, 1.0 eq.) was dissolved in DMF (50 mL). The mixture was cooled to 0 °C and NaH (60 wt%, 960 mg, 24.0 mmol, 1.2 eq.) was added, then the reaction was stirred at 0 °C for 30 min. Ethyl bromoacetate (2.68 mL, 24.0 mmol, 1.2 eq.) in THF (20 mL) was added slowly at 0 °C and the reaction stirred at rt for 16 h. The reaction was quenched with ice water and extracted with Et_2O (×3). The

combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FCC (SiO_2, Cyclohexane:EtOAc, 40:1) to afford the title compound **291** as a yellow-orange oil (1.46 g, 7.01 mmol, 35%); δ_H (500 MHz, $CDCl_3$) 7.38–7.26 (5H, m, ArH), 4.56 (1H, q, *J* = 6.5 Hz, H-3), 4.19 (1H, dq, *J* = 10.8, 7.1 Hz, H-9a), 4.18 (1H, dq, *J* = 10.8, 7.1 Hz, H-9b), 3.99 (1H, d, *J* = 16.4 Hz, H-2a), 3.87 (1H, d, *J* = 16.4 Hz, H-2b), 1.53 (3H, d, *J* = 6.5 Hz, H-4), 1.25 (3H, t, *J* = 7.1 Hz, H-10); δ_C (126 MHz, $CDCl_3$) 170.7 (C, C-1), 142.6 (C, C-5), 128.7 (CH, ArCH), 128.0 (CH, ArCH), 126.5 (CH, ArCH), 78.6 (CH, C-3), 66.0 (CH_2, C-9), 60.9 (CH_2, C-2), 23.9 (CH_3, C-4), 14.3 (CH_3, C-10).

Lab Book Ref.: LH549

Data are consistent with those previously reported.[228]

1,3-Dioxoisoindolin-2-yl-(*R*)-2-(1-phenylethoxy)acetate (293)



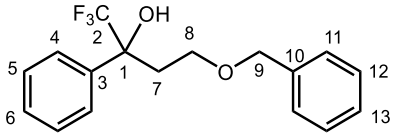
The ethyl ester **291** (700 mg, 3.36 mmol, 1.0 eq.) was reacted with NaOH (1.61 g, 40.0 mmol, 12.0 eq.) in EtOH/H_2O (2/1, 45 mL) at 60 °C for 16 h. After cooling to rt, the solvent was removed, and the residue redissolved in water and Et_2O. The organic layer was extracted with water, then the combined aqueous layers were acidified with 1 M aq. HCl to pH = 1. The aqueous layer was then extracted with Et_2O (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting acid was used in the next step without further purification (550 mg, 3.05 mmol, 91%); δ_H (500 MHz, $CDCl_3$) 7.40–7.27 (5H, m), 4.57 (1H, q, *J* = 6.5 Hz), 4.01 (1H, d, *J* = 16.8 Hz), 3.94 (1H, d, *J* = 16.8 Hz), 1.54 (1H, d, *J* = 6.5 Hz).

The phthalimide ester was prepared following the instructions given in General Procedure A with the carboxylic acid (370 mg, 2.05 mmol, 1.0 eq.), *N*-hydroxyphthalimide (512 mg, 3.08 mmol, 1.5 eq.), DCC (466 mg, 2.26 mmol, 1.1 eq.) and DMAP (25.0 mg, 0.210 mmol, 0.10 eq.) in DCM (30 mL). Purification by FCC (SiO_2, Cyclohexane:EtOAc, 4:1) gave the title compound **293** as a colourless, crystalline solid (484 mg, 1.49 mmol, 73%); mp. 85-87 °C; R_f 0.20

(Cyclohexane:EtOAc, 4:1); $[\alpha]^{20}_D$ +19.1 (*c* 0.055, DCM); υ_{max}/cm^{-1} (neat) 2979, 1780, 1736, 1176, 1076, 967, 853, 692; δ_H (500 MHz, $CDCl_3$) 7.93–7.86 (2H, m, ArH), 7.85–7.76 (2H, m, ArH), 7.43–7.28 (5H, m, ArH), 4.67 (1H, q, *J* = 6.4 Hz, H-3), 4.42 (1H, d, *J* = 17.1 Hz, H-2a), 4.24 (1H, d, *J* = 17.1 Hz, H-2b), 1.55 (3H, d, *J* = 6.4 Hz, H-4); δ_C (126 MHz, $CDCl_3$) 167.1 (C, C-1), 161.8 (C, C-9), 141.6 (C, C-5), 135.0 (CH, ArCH), 129.0 (C, C-10), 128.9 (CH, ArCH), 128.4 (CH, ArCH), 126.7 (CH, ArCH), 124.2 (CH, ArCH), 79.2 (CH, C-3), 63.7 (CH_2, C-2), 23.7 (CH_3, C-4); *m/z* (ESI) 348 $[MNa]^+$; [HRMS (ESI): calc. for $C_{18}H_{15}NNaO_5^+$, 348.0842. Found: $[MNa]^+$, 348.0838 (0.8 ppm error)].

Lab Book Ref.: LH566

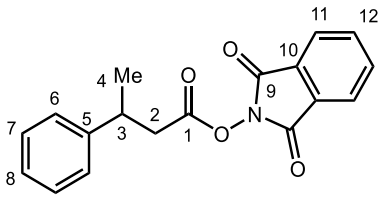
4-(Benzyloxy)-1,1,1-trifluoro-2-phenylbutan-2-ol (302)



Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **236a** (156 mg, 0.50 mmol, 1.25 eq.), $Ir[dtbbpy(ppy)_2]PF_6$ (3.60 mg, $4{\cdot}10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 10:1) gave the title compound **302** as a colourless oil (77.6 mg, 0.250 mmol, 63%); R_f 0.35 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3424, 2875, 1239, 1154, 1140, 1093, 1072, 732, 697; δ_H (500 MHz, $CDCl_3$) 7.61 (2H, d, *J* = 7.5 Hz, ArH), 7.44–7.29 (6H, m, ArH), 7.25–7.21 (2H, m, ArH), 5.14 (1H, s, OH), 4.43 (1H, d, *J* = 11.7 Hz, H-9a), 4.37 (1H, d, *J* = 11.7 Hz, H-9b), 3.76 (1H, ddd, *J* = 9.8, 4.6, 3.8 Hz, H-8a), 3.48 (1H, ddd, *J* = 10.1, 9.8, 2.9 Hz, H-8b), 2.58 (1H, ddd, *J* = 15.1, 10.1, 3.8 Hz, H-7a), 2.35 (1H, ddd, *J* = 15.1, 4.6, 2.9 Hz, H-7b); δ_C (126 MHz, $CDCl_3$) 137.7 (C, ArC), 136.8 (C, ArC), 128.7 (CH, ArCH), 128.5 (CH, ArCH), 128.4 (CH, ArCH), 128.2 (CH, ArCH), 127.9 (CH, ArCH), 126.8 (CH, ArCH), 125.4 (C, q, *J* = 285.1 Hz, C-2), 77.8 (C, q, *J* = 28.5 Hz, C-1), 73.8 (CH_2, C-9) 67.0 (CH_2, C-8), 33.9 (CH_2, C-7); δ_F (376 MHz, $CDCl_3$) –80.0 (CF_3); *m/z* (ESI) 311 $[MH]^+$; [HRMS (ESI): calc. for $C_{17}H_{17}F_3O_2^+$, 311.1253. Found: $[MH]^+$, 311.1261 (2.3 ppm error)].

Lab Book Ref.: LH684

1,3-Dioxoisoindolin-2-yl 3-phenylbutanoate (340)

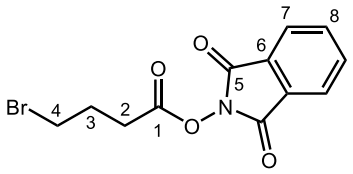


Following General Procedure A, 3-phenylbutyric acid (657 mg, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (979 mg, 6.00 mmol, 1.5 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:1) gave the title compound **340** as a colourless, crystalline solid (1.05 g, 3.39 mmol, 85%); mp. 112-115 °C; δ_H (500 MHz, $CDCl_3$) 7.90–7.84 (2H, m, ArH), 7.81–7.77 (2H, m, ArH), 7.38–7.31 (2H, m, ArH), 7.29–7.21 (3H, m, ArH), 3.41 (1H, qdd, *J* = 7.0, 6.1, 5.9 Hz, H-3), 2.98 (1H, dd, *J* = 15.4, 6.1 Hz, H-2a), 2.88 (1H, dd, *J* = 15.4, 5.9 Hz, H-2b), 1.46 (3H, d, *J* = 7.0 Hz, H-4); δ_C (126 MHz, $CDCl_3$) 168.4 (C, C-1), 162.0 (C, C-9), 144.7 (C, C-5), 134.9 (CH, ArCH), 129.0 (C, C-10), 128.8 (CH, ArCH), 127.0 (CH, ArCH), 126.8 (CH, ArCH), 124.1 (CH, ArCH), 39.7 (CH, C-3), 36.6 (CH_2, C-2), 21.5 (CH_3, C-4).

Lab Book Ref.: LH694

Data are consistent with those previously reported.[229]

1,3-Dioxoisoindolin-2-yl 4-bromobutanoate (341)



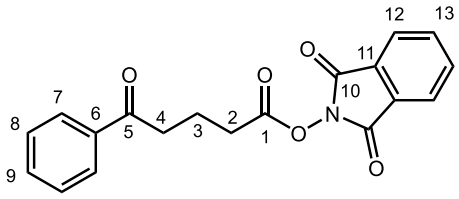
Following General Procedure A, 4-bromobutyric acid (668 mg, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (979 mg, 6.00 mmol, 1.5 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 5:1) gave the title compound **341** as a colourless oil (927 mg, 2.97 mmol, 74%); δ_H (500 MHz, $CDCl_3$) 7.91–7.86 (2H, m,

ArH), 7.83–7.77 (2H, m, ArH), 3.54 (2H, t, *J* = 6.4 Hz, H-4), 2.89 (2H, t, *J* = 7.2 Hz, H-2), 2.33 (2H, tt, *J* = 7.2, 6.4 Hz, H-3); δ_C (126 MHz, $CDCl_3$) 168.9 (C, C-1), 162.0 (C, C-1), 135.0 (CH, ArCH), 129.0 (C, C-6), 124.2 (CH, ArCH), 31.7 (CH_2, C-4), 29.7 (CH_2, C-2), 27.7 (CH_2, C-3).

Lab Book Ref.: LH695

Data are consistent with those previously reported.[230]

1,3-Dioxoisoindolin-2-yl 5-oxo-5-phenylpentanoate (342)

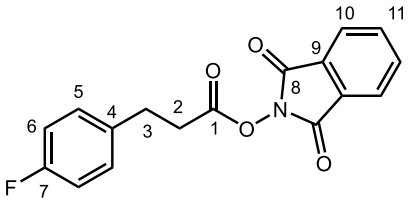


Following General Procedure A, 4-benzoylbutyric acid (769 mg, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (979 mg, 6.00 mmol, 1.5 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 4:1) gave the title compound **342** as a colourless, crystalline solid (420 mg, 1.25 mmol, 41%); mp. 89-92 °C; δ_H (500 MHz, $CDCl_3$) 8.01–7.98 (2H, m), 7.91–7.85 (2H, m), 7.83–7.76 (2H, m), 7.59–7.54 (1H, m), 7.50–7.42 (2H, m), 3.20 (2H, t, *J* = 7.1 Hz, H-4), 2.82 (2H, t, *J* = 7.0 Hz, H-2), 2.24 (2H, tt, *J* = 7.1, 7.0 Hz, H-3); δ_C (126 MHz, $CDCl_3$) 199.0 (C, C-5), 169.5 (C, C-1), 162.1 (C, C-10), 136.8 (C, C-11), 134.9 (CH, ArCH), 133.3 (CH, ArCH), 129.0 (C, C-6), 128.8 (CH, ArCH), 128.2 (CH, ArCH), 124.1 (CH, ArCH), 36.9 (CH_2, C-4), 30.4 (CH_2, C-2), 19.3 (CH_2, C-3).

Lab Book Ref.: LH699

Data are consistent with those previously reported.[191]

1,3-Dioxoisoindolin-2-yl 5-oxo-5-phenylpentanoate (343)

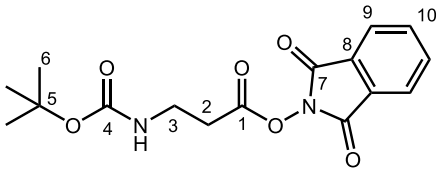


Following General Procedure A, 3-(4-fluorophenyl)propionic acid (673 mg, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (783 mg, 4.80 mmol, 1.2 eq.), DCC (990 mg, 4.80 mmol, 1.2 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:1) gave the title compound **343** as a colourless, crystalline solid (683 mg, 2.18 mmol, 55%); mp. 76-77 °C (Lit.[231] 74-75 °C); δ_H (500 MHz, $CDCl_3$) 7.94–7.85 (2H, m, ArH), 7.83–7.76 (2H, m, ArH), 7.25–7.19 (2H, m, H-5), 7.05–6.97 (2H, m, H-6), 3.08 (2H, t, *J* = 7.6 Hz), 2.99–2.93 (2H, m); δ_C (126 MHz, $CDCl_3$) 168.8 (C, C-1), 162.0 (C, C-8), 161.9 (d, *J* = 244.7 Hz, C-7), 134.9 (CH, ArCH), 130.0 (d, *J* = 8.1 Hz, CH, C-5), 129.0 (C, C-8), 124.1 (CH, ArCH), 115.6 (d, *J* = 21.2 Hz, CH, C-6), 33.2 (CH_2), 30.1 (CH_2); δ_F (376 MHz, $CDCl_3$) –116.3 (ArF).

Lab Book Ref.: LH707

Data are consistent with those previously reported.[231]

1,3-Dioxoisoindolin-2-yl 3-((*tert*-butoxycarbonyl)amino)propanoate (344)



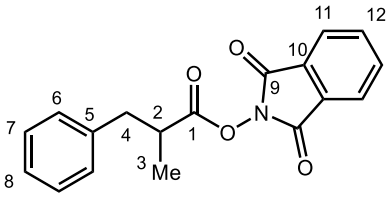
Following General Procedure A, boc-β-alanine (757 mg, 4.00 mmol, 1.0 eq.) in THF (30 mL) was stirred with hydroxy phthalimide (718 mg, 4.40 mmol, 1.1 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 3:1) gave the title compound **344** as a colourless, crystalline solid (1.26 g, 3.26 mmol, 94%); mp. 115-118 °C; δ_H (500 MHz, $CDCl_3$) 7.91–7.87 (2H, m, ArH), 7.82–7.77 (2H, m, ArH), 5.13 (1H, br s, NH), 3.55 (2H, dt, *J* = 6.2, 6.0 Hz, H-3), 2.90 (2H, t, *J* = 6.0 Hz, H-2), 1.44 (9H, s, H-6); δ_C (126 MHz,

$CDCl_3$) 168.8 (C, C-1), 162.0 (C, C-7), 155.9 (C, C-4), 135.0 (CH, ArCH), 129.1 (C, C-8), 124.2 (CH, ArCH), 79.9 (C, C-5), 36.3 (CH_2), 32.3 (CH_2), 28.4 (CH_3, C-6).

Lab Book Ref.: LH705

Data are consistent with those previously reported.[232]

1,3-Dioxoisoindolin-2-yl 2-methyl-3-phenylpropanoate (345)

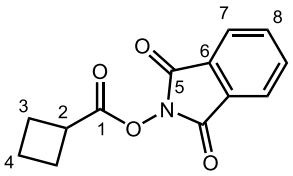


Following General Procedure A, α-methylhydrocinnamic acid (657 mg, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (979 mg, 6.00 mmol, 1.5 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:1) gave the title compound **345** as a colourless, crystalline solid (1.15 g, 3.73 mmol, 93%); mp. 52-55 °C; δ_H (500 MHz, $CDCl_3$) 7.91–7.85 (2H, m, ArH), 7.82–7.75 (2H, m, ArH), 7.37–7.31 (2H, m, ArH), 7.29–7.23 (3H, m, ArH), 3.27 (1 dd, *J* = 13.7, 6.2 Hz, H-4a), 3.12 (1H, dqd, *J* = 8.1, 7.0, 6.2 Hz, H-2), 2.84 (1H, dd, *J* = 13.7, 8.1 Hz, H-4b), 1.34 (3H, d, *J* = 7.0 Hz, H-3); δ_C (126 MHz, $CDCl_3$) 172.3 (C, C-1), 162.1 (C, C-9), 138.0 (C, C-5), 134.9 (CH, ArCH), 129.3 (CH, ArCH), 129.1 (C, C-10), 128.7 (CH, ArCH), 126.9 (CH, ArCH), 124.0 (CH, ArCH), 39.3 (CH_2, C-4), 39.0 (CH, C-3), 16.5 (CH_3, C-3).

Lab Book Ref.: LH689

Data are consistent with those previously reported.[230]

1,3-Dioxoisoindolin-2-yl cyclobutanecarboxylate (346)

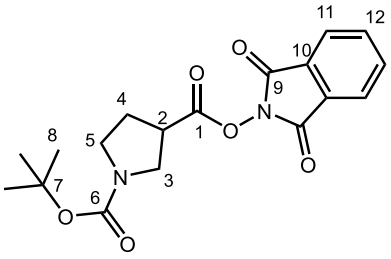


Following General Procedure A, cyclobutene carboxylic acid (400 mg, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (718 mg, 4.40 mmol, 1.1 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:1) gave the title compound **346** as a colourless, crystalline solid (890 mg, 3.63 mmol, 91%); mp. 74-76 °C; δ_H (500 MHz, $CDCl_3$) 7.90–7.85 (2H, m, ArH), 7.80–7.76 (2H, m, ArH), 3.56–3.45 (1H, m), 2.56–2.46 (2H, m), 2.44–2.36 (2H, m), 2.15–2.00 (2H, m); δ_C (126 MHz, $CDCl_3$) 171.5 (C, C-1), 162.2 (C, C-5), 134.8 (CH, ArCH), 129.1 (C, C-6), 126.1 (CH, ArCH), 35.2 (CH, C-2), 25.2 (CH_2, C-3), 18.5 (CH_2, C-4).

Lab Book Ref.: LH721

Data are consistent with those previously reported.[173]

1-(*tert*-Butyl) 3-(1,3-dioxoisoindolin-2-yl) pyrrolidine-1,3-dicarboxylate (347)



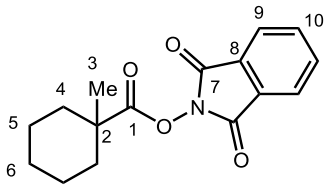
Following General Procedure A, *N*-boc-pyrrolidine-3-carboxylic acid (861 mg, 4.00 mmol, 1.0 eq.) in THF (20 mL) was stirred with hydroxy phthalimide (718 mg, 4.40 mmol, 1.1 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 3:1) gave the title compound **347** as a colourless, crystalline solid containing traces of a minor rotamer (1.02 g, 2.82 mmol, 71%); mp. 74-76 °C; δ_H (500 MHz, $CDCl_3$) 7.90–7.86 (2H, m, ArH), 7.82–7.76 (2H, m, ArH), 3.83–3.39 (5H, m, H-2, H-4, H-5), 2.35 (2H, s, H-3), 1.48 (9H, s, H-8); δ_C (126 MHz, $CDCl_3$) 169.8 (C, C-1), 161.9 (C, C-9), 154.3 (C, C-6), 135.0

(CH, ArCH, major), 134.3 (CH, ArCH, minor), 129.0 (C, C-10, major), 128.3 (C, C-10, minor), 124.2 (CH, ArCH, major), 123.4 (CH, ArCH, minor), 80.0 (C, C-7, major), 79.9 (C, C-7, minor), 48.0 (CH_2, major), 47.6 (CH_2, minor), 45.2 (CH_2, minor), 45.0 (CH_2, major), 40.7 (CH, C-2, major), 39.9 (CH, C-2, minor), 28.6 (CH_3, C-8).

Lab Book Ref.: LH733

Data are consistent with those previously reported.[233]

1,3-Dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate (348)

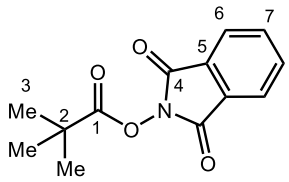


Following General Procedure A, 1-methyl-1-cyclohexanecarboxylic acid (569 mg, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (979 mg, 6.00 mmol, 1.5 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:1) gave the title compound **348** as a colourless, viscous oil (1.06 g, 3.67 mmol, 92%); δ_H (500 MHz, $CDCl_3$) 7.90–7.85 (2H, m, ArH), 7.81–7.75 (2H, m, ArH), 2.26–2.20 (2H, m), 1.72–1.52 (6H, m), 1.43 (3H, s, H-3), 1.44–1.22 (4H, m); δ_C (126 MHz, $CDCl_3$) 173.8 (C, C-1), 162.4 (C, C-7), 134.8 (CH, ArCH), 129.3 (C, C-8), 124.0 (CH, ArCH), 43.3 (C, C-2), 35.7 (CH_2), 26.8 (CH_3, C-3), 25.7 (CH_2), 23.3 (CH_2).

Lab Book Ref.: LH692

Data are consistent with those previously reported.[218]

1,3-Dioxoisoindolin-2-yl pivalate (349)

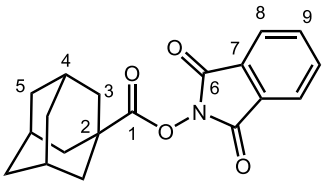


Following General Procedure A, pivalic acid (0.45 mL, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (979 mg, 6.00 mmol, 1.5 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:1) gave the title compound **349** as a colourless, crystalline solid (914 mg, 3.70 mmol, 92%); mp. 46-48 °C (Lit.[210] 78-79 °C); δ_H (500 MHz, $CDCl_3$) 7.89–7.85 (2H, m, ArH), 7.80–7.75 (2H, m, ArH), 1.43 (9H, s, H-3); δ_C (126 MHz, $CDCl_3$) 174.7 (C, C-1), 162.4 (C, C-4), 135.0 (CH, ArCH), 129.4 (C, C-5), 124.2(CH, ArCH), 38.7 (C-2), 27.4 (C-3).

Lab Book Ref.: LH697

All data except melting point are consistent with those previously reported.[210]

1,3-Dioxoisoindolin-2-yl (3*r*,5*r*,7*r*)-adamantane-1-carboxylate (350)

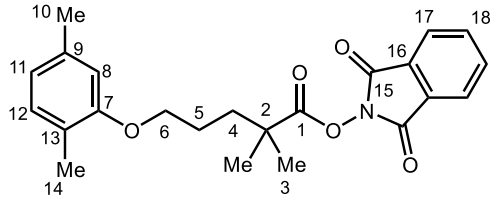


Following General Procedure A, 1-adamantylcarboxylic acid (721 mg, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (783 mg, 6.00 mmol, 1.5 eq.), DCC (990 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:1) gave the title compound **350** as a colourless, crystalline solid (1.07 g, 3.28 mmol, 82%); mp. 118-120 °C (Lit.[141] 143-144); δ_H (500 MHz, $CDCl_3$) 7.89–7.85 (2H, m, ArH), 7.79–7.75 (2H, m, ArH), 2.14 (6H, app d, J = 2.9 H), 2.12–2.08 (3H, m), 1.80–1.76 (6H, m); δ_C (126 MHz, $CDCl_3$) 173.4 (C, C-1), 162.3 (C, C-6), 134.8 (CH, ArCH), 129.3 (C, C-7), 124.0 (CH, ArCH), 40.7 (C, C-2), 38.6 (CH_2), 36.3 (CH_2), 27.8 (CH, C-4).

Lab Book Ref.: LH708

All data except melting point are consistent with those previously reported.[141]

1,3-Dioxoisoindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (351)

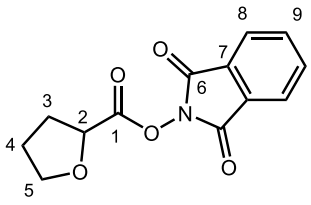


Following General Procedure A, gemfibrozil (501 mg, 2.00 mmol, 1.0 eq.) in THF (15 mL) was stirred with hydroxy phthalimide (359 mg, 2.20 mmol, 1.1 eq.), DCC (454 mg, 2.20 mmol, 1.1 eq.) and DMAP (24.5 mg, 0.20 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:1) gave the title compound **351** as a colourless, crystalline solid (717 mg, 1.81 mmol, 91%); mp. 62-64 °C (Lit.[234] 62-64 °C); δ_H (500 MHz, $CDCl_3$) 7.90–7.86 (2H, m, ArH), 7.81–7.76 (2H, m, ArH), 7.01 (1H, d, *J* = 7.5 Hz, ArH), 6.66 (1H, d, *J* = 7.5 Hz, ArH), 6.65 (1H, s, H-8), 4.05–3.99 (2H, m, H-6), 2.31 (3H, s, ArMe), 2.19 (3H, s, ArMe), 1.98–1.94 (4H, m, H-4, H-5), 1.46 (6H, s, H-3); δ_C (126 MHz, $CDCl_3$) 173.9, 162.2, 157.1, 136.6, 134.8, 130.4, 129.2, 124.0, 123.7, 120.8, 112.1, 67.9, 42.1, 37.5, 25.3, 25.1, 21.5, 15.9.

Lab Book Ref.: LH722

Data are consistent with those previously reported.[234]

1,3-Dioxoisoindolin-2-yl tetrahydrofuran-2-carboxylate (352)



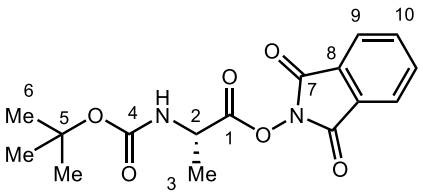
Following General Procedure A, tetrahydrofuran-2-furoic acid (0.387 mL, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (718 mg, 4.40 mmol, 1.1 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:2) gave the title compound **352** as a colourless, crystalline solid containing traces of a minor rotamer (962 mg, 3.68

mmol, 92%); mp. 69-73 °C; δ_H (500 MHz, $CDCl_3$) 7.92–7.85 (2H, m, ArH), 7.81–7.77 (2H, m, ArH), 4.87 (1H, dd, *J* = 8.5, 5.0 Hz, H-2), 4.09 (1H, app dd, *J* = 14.5, 7.5 Hz, H-5a), 4.00 (1H, app dd, *J* = 14.5, 7.5 Hz, H-5b), 2.51–2.33 (2H, m), 2.14–1.97 (2H, m); δ_C (126 MHz, $CDCl_3$) 169.9 (C, C-1), 161.8 (C, C-6), 134.9 (CH, ArCH, major), 134.8 (CH, ArCH, minor), 129.0 (C, C-7), 124.2 (CH, ArCH, major), 123.6 (CH, ArCH, minor), 75.1 (CH, C-2), 70.1 (CH_2, C-5, minor), 70.0 (CH_2, C-5, major), 31.0 (CH_2, major), 30.2 (CH_2, minor), 25.7 (CH_2, minor), 25.2 (CH_2, major).

Lab Book Ref.: LH713

Data are consistent with those previously reported.[232]

1,3-Dioxoisoindolin-2-yl (tert-butoxycarbonyl)-*L*-alaninate (353)

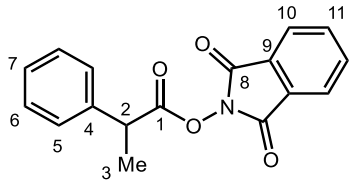


Following General Procedure A, *N*-boc-*L*-alanine (757 mg, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (718 mg, 4.40 mmol, 1.1 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:2) gave the title compound **353** as a colourless, crystalline solid containing traces of a minor rotamer (1.15 g, 3.45 mmol, 86%); mp. 72-74 °C; δ_H (500 MHz, $CDCl_3$) 7.90–7.84 (2H, m, ArH), 7.80–7.76 (2H, m, ArH), 5.08 (1H, br s, NH), 4.81–4.71 (1H, m, H-2), 1.62 (3H, d, *J* = 7.2 Hz, H-3), 1.46 (9H, s, H-6); δ_C (126 MHz, $CDCl_3$) 170.1 (C, C-1), 162.5 (C, C-4, minor), 161.6 (C, C-4, major), 135.0 (CH, ArCH, major), 134.9 (CH, ArCH. minor), 129.2 (C, C-8, minor), 129.0 (C, C-8, major), 124.2 (CH, ArCH, major), 124.1 (CH, ArCH, minor), 82.0 (C, C-5, minor), 80.6 (C, C-5, major), 49.2 (CH, C-2, minor), 47.8 (CH, C-2, major), 28.4 (CH_3, C-6, major), 28.1 (CH_3, C-6, minor), 19.0 (CH_3, C-3, major), 18.3 (CH_3, C-3, minor).

Lab Book Ref.: LH714

Data are consistent with those previously reported.[235]

1,3-Dioxoisoindolin-2-yl tetrahydrofuran-2-carboxylate (354)

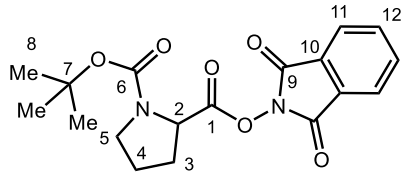


Following General Procedure A, 2-phenylpropionic acid (0.546 mL, 4.00 mmol, 1.0 eq.) in DCM (30 mL) was stirred with hydroxy phthalimide (979 mg, 6.00 mmol, 1.5 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 13:2) gave the title compound **354** as a colourless oil (905 mg, 3.07 mmol, 77%); δ_H (500 MHz, $CDCl_3$) 7.89–7.83 (2H, m, ArH), 7.79–7.74 (2H, m, ArH), 7.44–7.37 (4H, m, ArH), 7.35–7.30 (1H, m, ArH), 4.13 (1H, q, *J* = 7.2 Hz, H-2), 1.68 (3H, d, *J* = 7.2 Hz, H-3); δ_C (126 MHz, $CDCl_3$) 170.9 (C, C-1), 162.0 (C, C-8), 138.5 (C, C-4), 134.8 (CH, ArCH), 129.0 (CH, ArCH), 129.0(C, C-9), 127.9 (CH, ArCH), 127.7 (CH, ArCH), 124.0 (CH, ArCH), 43.1 (CH, C-2), 19.1 (CH_3, C-3).

Lab Book Ref.: LH698

Data are consistent with those previously reported.[236]

1-(*tert*-Butyl) 2-(1,3-dioxoisoindolin-2-yl) pyrrolidine-1,2-dicarboxylate (355)



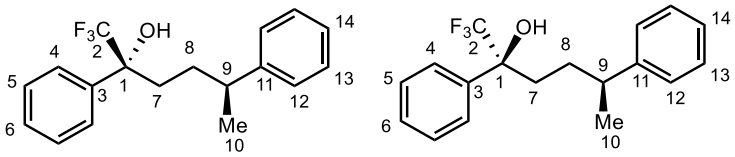
Following General Procedure A, *N*-boc-proline (861 mg, 4.00 mmol, 1.0 eq.) in THF (30 mL) was stirred with hydroxy phthalimide (718 mg, 4.40 mmol, 1.1 eq.), DCC (908 mg, 4.40 mmol, 1.1 eq.) and DMAP (49.0 mg, 0.40 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:1) gave the title compound **355** as a colourless, crystalline solid containing traces of a minor rotamer (820 mg, 2.28 mmol, 57%); mp. 71-73 °C (Lit.[210] 71-73 °C); δ_H (500 MHz, $CDCl_3$) 7.90–7.82 (2H, m, ArH), 7.82–7.75 (2H, m, ArH), 4.73–4.67 (1H, m, H-2, minor), 4.60 (1H, dd, *J* = 8.8, 3.7 Hz, H-2, major), 3.62 (1H, ddd, *J* = 10.5, 7.9, 4.5 Hz, major), 3.58–3.51 (1H, m, minor), 3.48

(1H, app dt, *J* = 10.5, 7.6 Hz, major), 3.44–3.40 (1H, m, minor), 2.50–2.30 (2H, m), 2.13–1.93 (2H, m), 1.51 (9H, s, H-8, major), 1.47 (9H, s, H-8, minor); δ_C (126 MHz, $CDCl_3$) 166.8 (C, C-1, major), 169.5 (C, C-1, minor), 161.8 (C, C-6, major), 161.7 (C, C-6, minor), 154.2 (minor), 153.6 (major), 134.9 (major), 134.8 (minor), 129.1 (minor), 129.0 (major), 124.1 (major), 124.0 (minor), 81.2 (major), 80.5 (minor), 57.4 (major), 57.2 (minor), 46.6 (minor), 46.4 (major), 31.5 (major), 30.4 (minor), 28.5 (minor), 28.2 (major), 24.5 (minor), 23.7 (major).

Lab Book Ref.: LH706

Data are consistent with those previously reported.[210]

1,1,1-Trifluoro-2,5-diphenylhexan-2-ol (356)

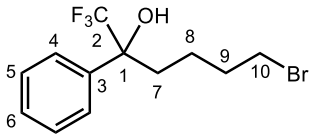


Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 3-phenylbutanoate **340** (155 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF_6 (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 40:1) gave the title compound **356** as a colourless oil as an inseparable mixture of diastereoisomers (44.2 mg, 0.143 mmol, 36%, dr: 1:1); R_f 0.30 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3547, 2961, 1494, 1451, 1257, 1150, 1073, 730, 699, 531; δ_H (500 MHz, $CDCl_3$) 7.51 (2H, d, *J* = 7.5 Hz, ArH), 7.43–7.34 (8H, m, ArH), 7.33–7.28 (4H, m, ArH), 7.24–7.19 (2H, m, ArH), 7.14 (2H, d, *J* = 7.1 Hz, ArH), 7.08 (2H, d, *J* = 7.1 Hz, ArH), 2.71–2.59 (2H, m, H-9), 2.33 (1H, br s, OH), 2.21 (1H, ddd, *J* = 13.9, 8.3, 4.5 Hz, H-7a), 2.21 (1H, br s, OH), 2.09–1.90 (2H, m, H-7a, H-7b), 1.82 (1H, ddd, *J* = 14.3, 12.2, 4.2 Hz, H-7b), 1.73–1.60 (2H, m, H-8), 1.37–1.25 (2H, m, H-8), 1.21 (3H, d, *J* = 7.0 Hz, H-10), 1.20 (3H, d, *J* = 7.0 Hz, H-10); δ_C (126 MHz, $CDCl_3$) 146.7 (C, C-11), 146.4 (C, C-11), 136.4 (C, C-3), 136.2 (C, C-3), 128.7 (CH, ArCH), 128.6 (CH, ArCH), 128.5 (C, ArCH), 128.5 (C, ArCH), 128.4 (CH, ArCH), 128.4 (CH, ArCH), 127.1 (CH, ArCH), 127.1 (CH, ArCH), 126.5 (CH, ArCH), 126.5

(CH, ArCH), 126.5 (CH, ArCH), 126.4 (CH, ArCH), 125.7 (C, q, J = 285.6 Hz, C-2), 125.6 (C, q, J = 285.6 Hz, C-2), 77.4 (C, q, J = 27.7 Hz, C-1), 77.3 (C, q, J = 27.7 Hz, C-1), 40.1 (CH, C-9), 40.0 (CH, C-9), 33.3 (CH_2, C-7), 33.1 (CH_2, C-7), 30.8 (CH_2, C-8), 30.5 (CH_2, C-8), 23.0 (CH_3, C-10), 22.4 (CH_3, C-10); δ_F (376 MHz, $CDCl_3$) –80.2 (CF_3 (B)), –80.4 (CF_3 (A)); *m/z* (ESI) 307 $[MH]^+$; [HRMS (ESI): calc. for $C_{18}H_{19}F_3O^+$, 307.1315. Found: $[MH]^+$, 307.1316 (0.3 ppm error)].

Lab Book Ref.: LH741

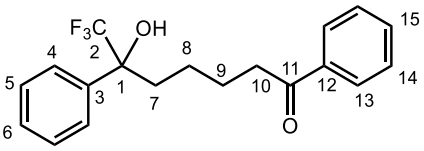
6-Bromo-1,1,1-trifluoro-2-phenylhexan-2-ol (357)



Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 4-bromobutanoate **341** (156 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF_6 (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 30:1) gave the title compound **357** as a colourless oil (42.7 mg, 0.127 mmol, 32%), R_f 0.20 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3507, 2960, 1450, 1260, 1147, 1073, 764, 701; δ_H (500 MHz, $CDCl_3$) 7.53 (2H, d, J = 7.7 Hz, H-4), 7.45–7.34 (3H, m, ArH), 3.38–3.29 (2H, m, H-10), 2.39 (1H, br s, OH), 2.23 (1H, ddd, J = 14.3, 10.7, 3.0 Hz, H-7a), 2.01 (1H, ddd, J = 14.3, 11.9, 4.7 Hz, H-7b), 1.91–1.78 (2H, m, H-9), 1.53 (1H, dddd, J = 14.0, 11.6, 5.3, 3.9 Hz, H-8a), 1.17 (1H, dddd, J = 11.6, 8.9, 7.7, 3.8 Hz, H-8b); δ_C (126 MHz, $CDCl_3$) 136.2 (C, C-3), 128.7 (CH, ArCH), 128.6 (CH, ArCH), 126.3 (CH, ArCH), 125.7 (C, q, J = 285.7 Hz, C-2), 77.5 (C, q, J = 28.0 Hz, C-1), 34.4 (CH_2, C-10), 33.1 (CH_2, C-7), 32.6 (CH_2, C-8), 21.1 (CH_2, C-9); δ_F (376 MHz, $CDCl_3$) –80.1 (CF_3); *m/z* (EI) 241 $[M–CF_3H]^+$; [HRMS (EI): calc. for $C_{11}H_{14}{}^{79}BrO^+$, 241.0223. Found: $[M–CF_3H]^+$, 241.0221 (0.8 ppm error)].

Lab Book Ref.: LH704

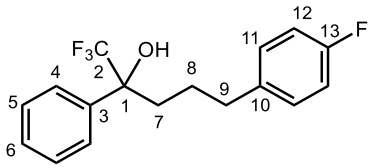
7,7,7-Trifluoro-6-hydroxy-1,6-diphenylheptan-1-one (358)



Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 5-oxo-5-phenylpentanoate **342** (169 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 10:1) gave the title compound **358** as a colourless oil (55.8 mg, 0.166 mmol, 41%), R_f 0.15 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3543, 2953, 1679, 1449, 1182, 1132, 965, 764, 689; δ_H (500 MHz, $CDCl_3$) 7.93–7.87 (2H, m, ArH), 7.60–7.51 (3H, m, ArH), 7.46–7.31 (5H, m, ArH), 2.97 (1H, br s, OH), 2.92 (2H, td, *J* = 7.4, 1.1 Hz, H-10), 2.28 (1H, ddd, *J* = 14.3, 11.9, 4.9 Hz, H-7a), 2.09 (1H, ddd, *J* = 14.3, 11.5, 4.7 Hz, H-7b), 1.83–1.67 (2H, m, H-9), 1.50–1.40 (1H, m, H-8a), 1.12 (1H, app dtt, *J* = 14.6, 11.3, 4.5 Hz, H-8b); δ_C (126 MHz, $CDCl_3$) 200.4 (C, C-11), 136.9 (C, ArC), 136.6 (C, ArC), 133.2 (CH, ArCH), 128.7 (CH, ArCH), 128.5 (CH, ArCH), 128.4 (CH, ArCH), 128.2 (CH, ArCH), 126.5 (CH, ArCH), 125.8 (C, q, *J* = 285.8 Hz, C-2), 77.5 (C, q, *J* = 27.9 Hz, C-1), 38.2 (CH_2, C-10), 35.0 (CH_2, C-7), 24.1 (CH_2, C-9), 22.2 (CH_2, C-8); δ_F (376 MHz, $CDCl_3$) –80.1 (CF_3); *m/z* (ESI) 337 $[MH]^+$; [HRMS (ESI): calc. for $C_{19}H_{19}F_3O_2^+$, 337.1410. Found: $[MH]^+$, 337.1412 (0.6 ppm error)].

Lab Book Ref.: LH709

1,1,1-Trifluoro-5-(4-fluorophenyl)-2-phenylpentan-2-ol (359)

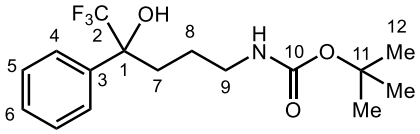


Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 5-oxo-5-phenylpentanoate **343** (157 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and

water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 40:1) gave the title compound **359** as a colourless oil (66.7 mg, 0.214 mmol, 53%), R_f 0.10 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3443, 2953, 1681, 1510, 1235, 1142, 1073, 762, 696; δ_H (500 MHz, $CDCl_3$) 7.49 (2H, d, *J* = 7.5 Hz, ArH), 7.43–7.34 (3H, m, ArH), 7.07–7.01 (2H, m, ArH), 6.98–6.92 (2H, m, ArH), 2.64–2.50 (2H, m, H-9), 2.36 (1H, s, OH), 2.22 (1H, ddd, *J* = 14.2, 6.6, 4.2 Hz, H-7a), 2.01 (1H, ddd, *J* = 14.2, 12.0, 4.6 Hz, H-7b), 1.75–1.63 (1H, m, H-8a), 1.39–1.27 (1H, m, H-8b); δ_C (126 MHz, $CDCl_3$) 161.5 (C, d, *J* = 243.6 Hz, C-13), 137.2 (C, d, *J* = 3.8 Hz, C-10), 136.3 (C, C-3), 129.8 (CH, d, *J* = 7.6 Hz, C-11)), 128.6 (CH, ArCH), 128.5 (CH, ArCH), 126.3 (CH, ArCH), 125.8 (C, q, *J* = 285.9 Hz, C-2), 115.3 (CH, d, *J* = 21.1 Hz, C-12), 77.5 (C, q, *J* = 27.8 Hz, C-1), 34.9 (CH_2, C-9), 34.6 (CH_2, C-7), 24.2 (CH_2, C-8); δ_F (376 MHz, $CDCl_3$) –80.1 (CF_3), –117.4 (ArF); *m/z* (ESI) 311 $[M-H]^-$; [HRMS (ESI): calc. for $C_{17}H_{16}F_4O^-$, 311.1065. Found: $[M-H]^-$, 311.1060 (1.3 ppm error)].

Lab Book Ref.: LH711

***tert*-Butyl (5,5,5-trifluoro-4-hydroxy-4-phenylpentyl)carbamate (360)**

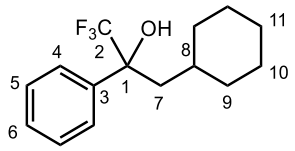


Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 3-((*tert*-butoxycarbonyl)amino)propanoate **344** (167 mg, 0.50 mmol, 1.25 eq.), $Ir[dtbbpy(ppy)_2]PF_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 10:1) gave the title compound **360** as a colourless oil containing traces of a minor rotamer (44.2 mg, 0.133 mmol, 33%), R_f 0.10 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3344, 2924, 1651, 1529, 1277, 1249, 1145, 996, 704; δ_H (500 MHz, $CDCl_3$) 7.58 (2H, d, *J* = 7.5 Hz, ArH), 7.42–7.36 (2H, m, ArH), 7.35–7.31 (1H, m, ArH), 4.95 (1H, br s), 4.67 (1H, br s), 3.46–3.43 (1H, m, H-9a), 2.99–2.92 (1H, m, H-9b), 2.19 (1H, app dt, *J* = 15.0, 6.6 Hz, H-7a), 2.10 (1H, app dt, *J* = 15.0, 8.3 Hz, H-7b), 1.46–1.28 (2H, m, H-8), 1.44 (9H, s, H-12); δ_C (126

MHz, $CDCl_3$) 157.5 (C, C-10, major), 151.7 (C, C-10, minor), 137.0 (C, C-3, major), 135.9 (C, C-3, minor), 129.3 (CH, ArC, minor), 128.3 (CH, ArC, major), 128.3 (CH, ArC), 126.6 (CH, ArC, major), 125.9 (C, q, *J* = 286.5 Hz, C-2), 125.7 (CH, ArC, minor), 80.3 (C, C-11), 77.3 (C, q, *J* = 27.7 Hz, C-1), 39.9 (CH_2, C-9), 29.8 (CH_2, C-7), 29.8 (CH_2, C-8), 28.4 (CH_3, C-12); δ_F (376 MHz, $CDCl_3$) –80.5 (CF_3); *m/z* (ESI) 334 $[MH]^+$; [HRMS (ESI): calc. for $C_{16}H_{22}F_3NO_5^+$, 334.1625. Found: $[MH]^+$, 334.1624 (0.3 ppm error)].

Lab Book Ref.: LH715

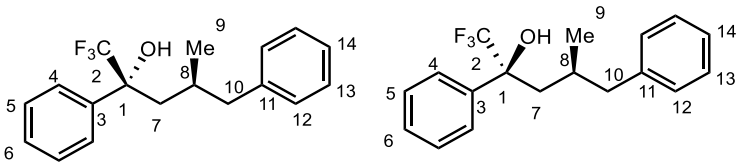
3-Cyclohexyl-1,1,1-trifluoro-2-phenylpropan-2-ol (361)



Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate **210** (137 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF_6 (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 25:1) gave the title compound **361** as a colourless oil (66.8 mg, 0.245 mmol, 61%), R_f 0.40 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3543, 2924, 1679, 1449, 1265, 1143, 1072, 965, 763, 709; δ_H (500 MHz, $CDCl_3$) 7.56 (2H, d, *J* = 7.6 Hz, H-4), 7.43–7.33 (3H, m, ArH), 2.32 (1H, s, OH), 2.17 (1H, dd, *J* = 14.9, 4.6 Hz, H-7a), 1.88 (1H, dd, *J* = 14.9, 6.8 Hz, H-7b), 1.85–1.80 (1H, m, H-8), 1.66–1.58 (1H, m, CyH), 1.57–1.50 (2H, m, CyH), 1.36–1.27 (2H, m, CyH), 1.12–0.96 (4H, m, CyH), 0.91–0.82 (1H, m, CyH); δ_C (126 MHz, $CDCl_3$) 136.8 (C, C-3), 128.4 (CH, ArCH), 128.3 (CH, ArCH), 126.5 (CH, ArCH), 125.8 (C, q, *J* = 286.2 Hz, C-2), 78.1 (C, q, *J* = 27.5 Hz, C-1), 42.1 (CH_2, C-7), 34.8 (CH_2, $CyCH_2$), 32.7 (CH, C-8), 26.2 (CH_2, $CyCH_2$), 26.1 (CH_2, $CyCH_2$); δ_F (376 MHz, $CDCl_3$) –80.7 (CF_3); *m/z* (EI) 203 $[M–CF_3H]^+$; [HRMS (EI): calc. for $C_{14}H_{19}O^+$, 203.1430. Found: $[M–CF_3H]^+$, 203.1422 (3.9 ppm error)].

Lab Book Ref.: LH685

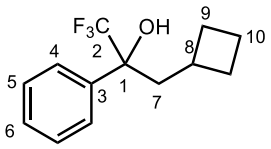
1,1,1-Trifluoro-4-methyl-2,5-diphenylpentan-2-ol (362)



Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 2-methyl-3-phenylpropanoate **345** (155 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 25:1) gave the title compound **362** as a colourless oil as an inseparable mixture of diastereoisomers (74.9 mg, 0.243 mmol, 61%, dr: 1:1), R_f 0.35 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3553, 2928, 1451, 1266, 1148, 744, 699; δ_H (500 MHz, $CDCl_3$) 7.56 (2H, d, *J* = 7.6 Hz, ArH), 7.44–7.36 (3H, m, ArH), 7.34–7.33 (5H, m, ArH), 7.30–7.17 (6H, m, ArH), 7.05 (2H, d, *J* = 7.9 Hz, ArH), 6.95 (2H, d, *J* = 7.9 Hz, ArH), 2.74 (1H, dd, *J* = 13.3, 6.7 Hz, H-10a), 2.44–2.31 (3H, m, H-10b, H-10a, H-10b), 2.28 (1H, br s, OH), 2.16 (1H, dd, *J* = 14.8, 5.6 Hz, H-7a), 2.08 (1H, dd, *J* = 14.8, 5.5 Hz, H-7b), 1.97 (1H, br s OH), 1.77 (1H, dd, *J* = 14.6, 8.6 Hz, H-7a), 1.71–1.64 (1H, m, H-7b), 0.99 (3H, t, *J* = 6.9 Hz, H-9), 0.64 (3H, t, *J* = 6.7 Hz,H-9); δ_C (126 MHz, $CDCl_3$) 140.8 (C, ArC), 140.4 (C, ArC), 136.7 (C, ArC), 136.2 (C, ArC), 129.4 (CH, ArCH), 129.3 (CH, ArCH), 128.5 (CH, ArCH), 128.5 (CH, ArCH), 128.4 (CH, ArCH), 128.4 (CH, ArCH), 128.4 (CH, ArCH), 128.4 (CH, ArCH), 126.5 (CH, ArCH), 126.5 (CH, ArCH), 126.3 (CH, ArCH), 126.2 (CH, ArCH), 125.8 (C, q, *J* = 286.1 Hz, C-2), 125.7 (C, q, *J* = 286.1 Hz, C-2), 78.4 (C, q, *J* = 27.5 Hz, C-1), 77.6 (C, q, *J* = 27.5 Hz, C-1), 45.0 (CH_2, C-10), 44.4 (CH_2, C-10), 41.0 (CH_2, C-7), 40.4 (CH_2, C-7), 30.6 ((CH, C-8), 30.3 (CH, C-8), 21.7 (CH_3, C-9), 21.6 (CH_3, C-9); δ_F (376 MHz, $CDCl_3$) –80.5 (CF_3), –80.9 (CF_3); *m/z* (ESI) 326 $[MH]^+$; [HRMS (ESI): calc. for $C_{19}H_{19}F_3O^+$, 326.1726. Found: $[MH]^+$, 326.1736 (3.0 ppm error)].

Lab Book Ref.: LH690

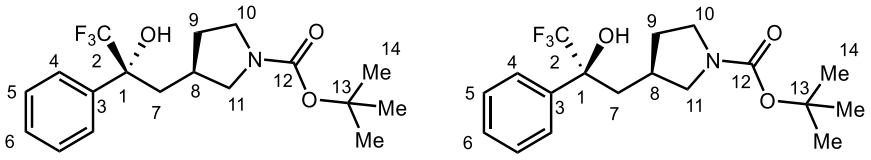
3-Cyclobutyl-1,1,1-trifluoro-2-phenylpropan-2-ol (363)



Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate **346** (123 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, $4\cdot10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 25:1) gave the title compound **363** as a colourless oil (45.2 mg, 0.185 mmol, 46%), R_f 0.35 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3497, 2961, 1273, 1152, 1073, 762, 701; δ_H (500 MHz, $CDCl_3$) 7.54 (2H, d, J = 7.6 Hz, H-4), 7.42–7.33 (3H, m, ArH), 2.33–2.23 (3H, m, H-7a, H-8, OH), 2.17–2.08 (1H, m, H-7b), 2.07–1.98 (1H, m), 1.80–1.66 (3H, m), 1.67–1.58 (1H, m), 1.54–1.44 (1H, m); δ_C (126 MHz, $CDCl_3$) 136.9 (C, C-3), 128.4 (CH, ArCH), 128.3 (CH, ArCH), 126.3 (CH, ArCH), 125.7 (C, q, J = 285.8 Hz, C-2), 77.8 (C, q, J = 28.0 Hz, C-1), 42.3 (CH_2, C-7), 30.8 (CH, C-8), 30.1 (CH_2), 19.7 (CH_2); δ_F (376 MHz, $CDCl_3$) –80.1 (CF_3); *m/z* (EI) 175 [M–CF_3H]$^+$; [HRMS (EI): calc. for $C_{12}H_{15}O^+$, 175.1117. Found: [M–CF_3H]$^+$, 175.1119 (0.2 ppm error)].

Lab Book Ref.: LH723

***tert*-Butyl 3-(3,3,3-trifluoro-2-hydroxy-2-phenylpropyl)pyrrolidine-1-carboxylate (364)**

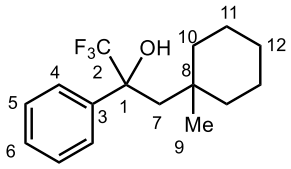


Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1-(*tert*-butyl) 3-(1,3-dioxoisoindolin-2-yl) pyrrolidine-1,3-dicarboxylate **347** (180 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, $4\cdot10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 7:1) gave the title compound **364** as a colourless oil as an

inseparable mixture of diastereoisomers (45.1 mg, 0.125 mmol, 31%, dr: 1:1), R_f 0.15 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3323, 2924, 1653, 1421, 1261, 1193, 1000, 769, 704; δ_H (500 MHz, $CDCl_3$) 7.54 (2H, d, *J* = 7.2 Hz, H-4), 7.45–7.35 (3H, m, ArH), 3.38 (1H, app t, *J* = 9.1 Hz), 3.07 (1H, app td, *J* = 10.6, 6.4 Hz), 2.93 (1H, br s), 2.57 (1H, br s), 2.40–2.21 (1H, m), 2.15–1.95 (3H, m), 1.64–1.45 (2H, m), 1.38 (9H, s, H-14), 0.91–0.81 (1H, m); δ_C (126 MHz, $CDCl_3$) 154.5 (C, C-12), 154.5 (C, C-12), 136.4 (C, C-3), 135.9 (C, C-3), 128.8 (CH, ArCH), 128.8 (CH, ArCH), 128.6 (CH, ArCH), 128.6 (CH, ArCH), 126.2 (CH, ArCH) 125.8 (CH, ArCH), 125.7 (C, q, *J* = 286.2 Hz, C-2), 125.7 (C, q, *J* = 286.2 Hz, C-2), 79.3 (C, C-13), 79.2 (C, C-13), 77.5 (C, q, *J* = 27.8 Hz, C-1), 77.5 (C, q, *J* = 27.8 Hz, C-1), 51.8 (CH_2), 51.6 (CH_2), 45.7 (CH_2), 45.1 (CH_2), 38.2 (CH_2, C-7), 38.2 (CH_2, C-7), 33.8 (CH, C-8), 33.8 (CH, C-8), 32.5 (CH_2, C-9), 32.5 (CH_2, C-9), 28.6 (CH_3, C-14), 28.6 (CH_3, C-14); δ_F (376 MHz, $CDCl_3$) –80.1 (CF_3 (A)), –80.2 (CF_3 (B)); *m/z* (ESI) 360 $[MH]^+$; [HRMS (ESI): calc. for $C_{18}H_{24}F_3NO^+$, 360.1781. Found: $[M-H]^-$, 360.1783 (0.5 ppm error)].

Lab Book Ref.: LH736

1,1,1-Trifluoro-3-(1-methylcyclohexyl)-2-phenylpropan-2-ol (365)

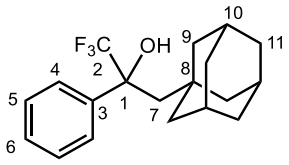


Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), $Ir[dtbbpy(ppy)_2]PF_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 40:1) gave the title compound **365** as a colourless oil (92.9 mg, 0.324 mmol, 81%); R_f 0.50 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3618, 2926, 1449, 1251, 1116, 1049, 762, 704; δ_H (500 MHz, $CDCl_3$) 7.61 (2H, d, *J* = 7.6 Hz, H-4), 7.40–7.32 (3H, m, ArH), 2.36 (1H, s, OH), 2.25 (1H, d, *J* = 15.1 Hz, H-7a), 2.04 (1H, d, *J* = 15.1 Hz, H-7b), 1.46–1.16 (8H, m, CyH), 1.07–0.97 (2H, m, CyH), 0.73 (3H, s, H-9); δ_C (126 MHz, $CDCl_3$) 137.5 (C, C-3), 128.3 (CH, ArCH), 128.1 (CH, ArCH), 126.5 (CH,

ArCH), 125.5 (C, q, *J* = 287.1 Hz, C-2), 78.5 (C, q, *J* = 26.9 Hz, C-1), 45.5 (CH_2, C-7), 40.0 (CH_2, $CyCH_2$ (A)), 39.6 (CH_2, $CyCH_2$ (B)), 34.2 (C, C-8), 26.2 (CH_2, $CyCH_2$), 25.1 (CH_3, C-9), 22.0 (CH_2, $CyCH_2$ (A)), 21.9 (CH_2, $CyCH_2$ (B)); δ_F (376 MHz, $CDCl_3$) –81.3(CF_3); *m/z* (ESI) 309 $[MNa]^+$; [HRMS (ESI): calc. for $C_{16}H_{21}F_4NaO^+$, 309.1437. Found: $[MNa]^+$, 309.1453 (4.3 ppm error)].

Lab Book Ref.: LH702

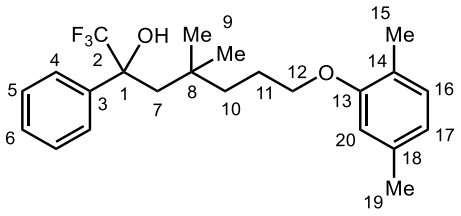
3-((3*r*,5*r*,7*r*)-Adamantanyl)-1,1,1-trifluoro-2-phenylpropan-2-ol (367)



Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl (3*r*,5*r*,7*r*)-adamantane-1-carboxylate **350** (163 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF_6 (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 50:1) gave the title compound **367** as a colourless oil (92.5 mg, 0.285 mmol, 71%); R_f 0.45 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3594, 2902, 2847, 1447, 1243, 1154, 1105, 1071, 762, 700; δ_H (500 MHz, $CDCl_3$) 7.60 (2H, d, *J* = 7.5 Hz, H-4), 7.40–7.32 (3H, m, ArH), 2.35 (1H, s, OH), 2.15 (1H, d, *J* = 15.2 Hz, H-7a), 1.85 (1H, d, *J* = 15.2 Hz, H-7b), 1.83–1.79 (3H, m), 1.59 (3H, dt, *J* = 12.3, 2.5 Hz), 1.50 (6H, ddd, *J* = 12.2, 2.5, 1.8 Hz), 1.33 (3H, ddd, *J* = 12.2, 4.8, 2.5 Hz); δ_C (126 MHz, $CDCl_3$) 137.3 (C, C-3), 128.3 (CH, ArCH), 128.1 (CH, ArCH), 126.6 (CH, ArCH), 125.7 (C, q, *J* = 287.0 Hz, C-2), 78.3 (C, q, *J* = 26.9 Hz, C-1), 47.3 (CH_2, C-7), 44.1 (CH_2), 36.8 (CH_2), 33.8 (C, C-8), 28.7 (CH, C-10); δ_F (376 MHz, $CDCl_3$) –81.5 (CF_3); *m/z* (ESI) 255 $[M–CF_3H]^+$; [HRMS (ESI): calc. for $C_{18}H_{23}O^+$, 255.1743. Found: $[M–CF_3H]^+$, 255.1746 (0.9 ppm error)].

Lab Book Ref.: LH712

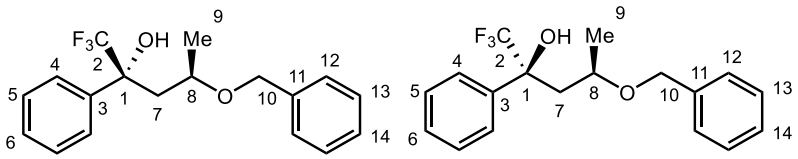
7-(2,5-Dimethylphenoxy)-1,1,1-trifluoro-4,4-dimethyl-2-phenylheptan-2-ol (368)



Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate **351** (198 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 40:1) gave the title compound **368** as a colourless oil (137 mg, 0.347 mmol, 87%); R_f 0.40 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3515, 2954, 1509, 1260, 1149, 1129, 804, 705; δ_H (500 MHz, $CDCl_3$) 7.62 (2H, d, *J* = 7.0 Hz, H-4), 7.42–7.32 (3H, m, ArH), 7.03 (1H, dd, *J* = 7.3, 2.3 Hz, H-17), 6.71 (1H, d, *J* = 7.3 Hz, H-16), 6.61 (1H, d, *J* = 2.3 Hz, H-20), 3.82 (2H, t, *J* = 6.2 Hz, H-12), 2.48–2.45 (1H, br s, OH), 2.33 (3H, d, *J* = 2.2 Hz, ArMe), 2.26 (1H, dd, *J* = 15.0, 2.2 Hz, H-7a), 2.20 (3H, d, *J* = 2.8 Hz, ArMe), 2.10 (1H, dd, *J* = 15.0, 2.2 Hz, H-7b), 1.84–1.64 (2H, m, H-11), 1.47 (1H, ddd, *J* = 11.9, 6.5, 3.2 Hz, H-10a), 1.32–1.22 (1H, m, H-10b), 0.87 (3H, d, *J* = 2.2 Hz, H-9 (A)), 0.76 (3H, d, *J* = 2.2 Hz, H-9 (B)); δ_C (126 MHz, $CDCl_3$) 157.1 (C, C-13), 137.4 (C, ArC), 136.6 (C, ArC), 130.5 (CH, C-17), 128.4 (CH, ArCH), 128.2 (CH, ArCH), 126.5 (CH, ArCH), 125.8 (C, q, *J* = 287.1 Hz, C-2), 123.8 (C, ArC), 120.9 (CH, C-16), 112.3 (CH, C-20), 78.4 (C, q, *J* = 27.0 Hz, C-1), 68.5 (CH_2, C-12), 43.3 (CH_2, C-7), 40.4 (CH_2, C-10), 33.8 (C, C-8), 29.0 (CH_3, ArMe), 28.8 (CH_3, ArMe), 24.4 (CH_2, C-11), 21.5 (CH_3, C-9 (A)), 16.0 (CH_3, C-9 (B)); δ_F (376 MHz, $CDCl_3$) –81.2 (CF_3); *m/z* (ESI) 395 $[MH]^+$; [HRMS (ESI): calc. for $C_{23}H_{29}F_3O_2^+$, 395.2954. Found: $[MH]^+$, 395.2183 (2.3 ppm error)].

Lab Book Ref.: LH724

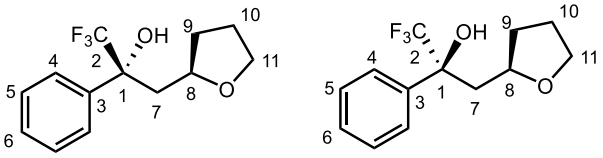
4-(Benzyloxy)-1,1,1-trifluoro-2-phenylpentan-2-ol (369)



Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)propanoate **236b** (155 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 40:1) gave the title compound **369** as a colourless oil as an inseparable mixture of diastereoisomers (65.7 mg, 0.203 mmol, 51%, dr: 1:1); R_f 0.40 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3380, 2976, 1258, 1145, 1129, 1074, 737, 697; δ_H (500 MHz, $CDCl_3$) 7.60 (2H, d, *J* = 7.9 Hz), 7.58 (2H, d *J* = 7.6 Hz), 7.46–7.29 (14H, m), 7.22–7.18 (2H, m) 6.06 (1H, s, OH), 5.53 (1H, s, OH), 4.68 (1H, d, *J* = 10.8 Hz, H-10a), 4.48 (1H, d, *J* = 10.8 Hz, H-10b), 4.46 (1H, d, *J* = 10.8 Hz, H-10b), 4.34–4.26 (1H, m, H-8), 4.01 (1H, d, *J* = 10.8 Hz, H-10b), 3.56 (1H, dqd, *J* = 12.1, 6.0, 3.9 Hz, H-8), 2.42 (1H, dd, *J* = 15.5, 2.6 Hz, H-7a), 2.39–2.31 (2H, m, H-7a, H-7b), 2.06 (1H, ddd, *J* = 15.5, 11.0, 2.2 Hz, H-7b), 1.29 (3H, d, *J* = 6.0 Hz, H-9), 1.25 (3H, d, *J* = 6.0 Hz, H-9, H-9); δ_C (126 MHz, $CDCl_3$) 139.9 (C, C-3), 137.9 (C, C-3), 137.2 (C, C-11), 136.9 (C, C-11), 128.8 (CH, ArCH), 128.7 (CH, ArCH), 128.4 (CH, ArCH), 128.4 (CH, ArCH), 128.3 (CH, ArCH), 128.3 (CH, ArCH), 128.3 (CH, ArCH), 128.3 (CH, ArCH), 128.2 (CH, ArCH), 128.2 (CH, ArCH), 127.1 (CH, ArCH), 126.2 (C, q, *J* = 287.4 Hz, C-2), 125.6 (CH, ArCH), 125.1 (C, q, *J* = 284.3 Hz, C-2), 77.5 (C, q, *J* = 32.5 Hz, C-1), 77.0 (C, q, *J* = 28.0 Hz, C-1), 74.4 (CH_2, C-10), 73.2 (CH_2, C-10), 71.1 (CH_2, C-8), 70.7 (CH_2, C-8), 43.5 (CH_2, C-7), 40.2 (CH, C-7), 20.2 (CH_3, C-9), 19.7 (CH_3, C-9); δ_F (376 MHz, $CDCl_3$) –75.7 (CF_3), –81.2 (CF_3); *m/z* (ESI) 325 $[MH]^+$; [HRMS (ESI): calc. for $C_{18}H_{19}F_3O_2^+$, 325.1410. Found: $[MH]^+$, 325.1407 (0.7 ppm error)].

Lab Book Ref.: LH742

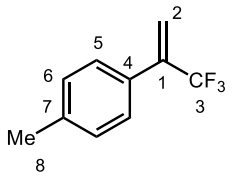
1,1,1-Trifluoro-2-phenyl-3-(tetrahydrofuran-2-yl)propan-2-ol (370)



Following General Procedure D, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl tetrahydrofuran-2-carboxylate **352** (131 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 35:1) gave the title compound **370** as a colourless oil as an inseparable mixture of diastereoisomers (33.6 mg, 0.129 mmol, 32%, dr: 1:1); R_f 0.40 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3403, 2970, 1460, 1260, 1153, 1140, 1060, 765, 701; δ_H (500 MHz, $CDCl_3$) 7.64–7.54 (4H, m, ArH), 7.44–7.31 (6H, m, ArH), 5.94 (1H, s, OH), 5.52 (1H, s, OH), 4.46 (1H, app dtd, *J* = 9.4, 7.9, 0.9 Hz, H-8), 3.98–3.86 (3H, m, H-11a, H-11a, H-11b), 3.78–3.72 (1H, m, H-11b), 3.73 (1H, app td, *J* = 7.9, 5.6 Hz, H-8), 2.53 (1H, dd, *J* = 15.1, 2.3 Hz, H-7a), 2.43 (1H, dd, *J* = 14.4, 1.6 Hz, H-7a), 2.18 (1H, dd, *J* = 14.4, 11.0 Hz, H-7b), 2.19–2.13 (1H, m, H-7b), 2.01 (1H, dddd, *J* = 10.8, 6.8, 5.6, 3.5 Hz), 1.94–1.81 (4H, m), 1.81–1.70 (1H, m), 1.57 (1H, dddd, *J* = 12.2, 8.8, 7.7, 6.8 Hz), 1.48 (1H, dddd, *J* = 12.2, 10.6, 10.3, 6.4 Hz); δ_C (126 MHz, $CDCl_3$) 140.0 (C, C-3), 137.9 (C, C-3), 128.4 (CH, ArCH), 128.4 (CH, ArCH), 128.3 (CH, ArCH), 128.3 (CH, ArCH), 127.2 (CH, ArCH), 126.1 (C, q, *J* = 287.2 Hz, C-2), 125.7 (CH, ArCH), 125.2 (C, q, *J* = 284.4 Hz, C-2), 77.5 (C, q, *J* = 31.5 Hz, C-1), 76.8 (C, q, *J* = 29.2 Hz, C-1), 76.0 (CH, C-8), 76.0 (CH, C-8), 68.5 (CH_2, C-11), 68.5 (CH_2, C-11), 42.0 (CH_2), 38.8 (CH_2), 32.9 (CH_2), 32.5 (CH_2), 25.2 (CH_2), 25.1 (CH_2); δ_F (376 MHz, $CDCl_3$) –75.7(CF_3), –81.0 (CF_3); *m/z* (ESI) 261 $[MH]^+$; [HRMS (ESI): calc. for $C_{13}H_{15}F_3O_2^+$, 261.1097. Found: $[MH]^+$, 261.1102 (1.8 ppm error)].

Lab Book Ref.: LH717

1-Methyl-4-(3,3,3-trifluoropropen-2-yl)benzene (376)

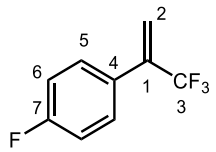


Following General Procedure G, 4-tolylboronic acid (544 mg, 4.00 mmol, 1.0 eq.) in THF (16 mL) and 0.5 M aq. Na_2CO_3 (16 mL, 8.00 mmol, 2.0 eq.) was reacted with 2-bromo-3,3,3-trifluoropropene (0.850 mL, 8.00 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (231 mg, 0.20 mmol, 5 mol%). Purification by FCC (SiO_2, pentane) gave the title compound **376** as a colourless oil (667 mg, 3.58 mmol, 89%); δ_H (400 MHz, $CDCl_3$) 7.36 (2H, d, *J* = 8.0 Hz, ArH), 7.20 (2H, d, *J* = 8.0 Hz, ArH), 5.91 (1H, d, *J* = 1.3 Hz, H-2a), 5.74 (1H, d, *J* = 1.3 Hz, H-2b), 2.38 (3H, s, H-8); δ_C (101 MHz, $CDCl_3$) 139.1 (C, C-4), 139.0 (C, q, *J* = 31.1 Hz, C-1), 130.9 (C, C-7), 129.4 (CH, ArCH), 127.4 (CH, ArCH), 123.5 (C, q, *J* = 274.0 Hz, C-3), 119.8 (CH_2, q, *J* = 5.8 Hz, C-2), 21.3 (CH_3, C-8); δ_F (377 MHz, $CDCl_3$) –64.8 (CF_3).

Lab Book Ref.: LH688

Data are consistent with those previously reported.[237]

1-Fluoro-4-(3,3,3-trifluoropropen-2-yl)benzene (377)



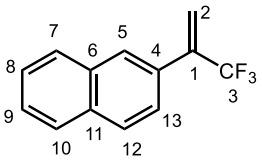
Following General Procedure G, 4-fluorobenzene boronic acid (420 mg, 3.00 mmol, 1.0 eq.) in THF (12 mL) and 0.5 M aq. Na_2CO_3 (12 mL, 6.00 mmol, 2.0 eq.) was reacted with 2-bromo-3,3,3-trifluoropropene (0.640 mL, 6.00 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (173 mg, 0.15 mmol, 5 mol%). Purification by FCC (SiO_2, pentane) gave the title compound **377** as a colourless oil (340 mg, 1.79 mmol, 60%); δ_H (400 MHz, $CDCl_3$) 7.43 (2H, dd, *J* = 8.4, 5.5 Hz, ArH), 7.12–7.04 (2H, m, ArH), 5.92 (1H, m, H-2a), 5.73 (1H, d, *J* = 1.4 Hz, H-2b); δ_C (101 MHz, $CDCl_3$) 163.3 (d, *J* = 248.8 Hz, C-7), 138.2 (C, q, *J* = 30.2 Hz, C-1), 129.9 (C, d, *J* = 3.5 Hz, C-4), 129.5 (CH, d, *J* = 8.3

Hz, C-5), 123.3 (C, q, J = 273.9 Hz, C-3), 120.3 (CH_2, q, J = 5.6 Hz, C-2), 115.3 (CH, d, J = 21.6 Hz, C-6); δ_F (377 MHz, $CDCl_3$) –65.1 (CF_3), –112.6 (ArF).

Lab Book Ref.: LH730

Data are consistent with those previously reported.[237]

2-(3,3,3-Trifluoropropen-2-yl)naphthalene (378)

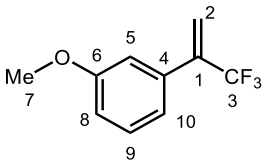


Following General Procedure G, 2-naphtylboronic acid (430 mg, 2.5 mmol, 1.0 eq.) in THF (10 mL) and 0.5 M aq. Na_2CO_3 (10 mL, 5.00 mmol, 2.0 eq.) was reacted with 2-bromo-3,3,3-trifluoropropene (0.530 mL, 5.00 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol, 4 mol%). Purification by FCC (SiO_2, pentane) gave the title compound **378** as a colourless oil (496 mg, 2.23 mmol, 89%); δ_H (400 MHz, $CDCl_3$) 7.96 (1H, s, ArH), 7.90–7.83 (2H, m, ArH), 7.62–7.56 (1H, m, ArH), 7.54 (2H, app dt, J = 6.2, 3.2 Hz, ArH), 6.07 (1H, m, H-2a), 5.92 (1H, m, H-2b); δ_C (101 MHz, $CDCl_3$) 139.1 (C, q, J = 29.9 Hz, C-1), 133.4 (C, ArC), 133.2 (C, ArC), 131.0 (C, ArC), 128.6 (CH, ArCH), 128.4 (CH, ArCH), 127.8 (CH, ArCH), 127.1 (CH, ArCH), 127.0 (CH, ArCH), 126.7 (CH, ArCH), 124.9 (CH, ArCH), 123.6 (C, q, J = 275.4 Hz, C-3), 120.8 (CH_2, q, J = 5.8 Hz, C-2); δ_F (377 MHz, $CDCl_3$) –64.4 (CF_3).

Lab Book Ref.: LH738

Data are consistent with those previously reported.[238]

1-Methoxy-3-(3,3,3-trifluoropropen-2-yl)benzenene (379)

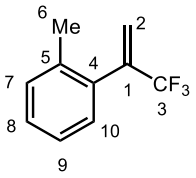


Following General Procedure G, 3-methoxybenzene boronic acid (380 mg, 2.5 mmol, 1.0 eq.) in THF (10 mL) and 0.5 M aq. Na_2CO_3 (10 mL, 5.00 mmol, 2.0 eq.) was reacted with 2-bromo-3,3,3-trifluoropropene (0.530 mL, 5.00 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol, 4 mol%). Purification by FCC (SiO_2, pentane) gave the title compound **379** as a colourless oil (461 mg, 2.28 mmol, 91%); δ_H (400 MHz, $CDCl_3$) 7.31 (1H, dd, *J* = 8.3, 7.7 Hz, H-9), 7.05 (1H, d, *J* = 7.7 Hz, ArH), 6.99 (1H, s, H-5), 6.93 (1H, dd, *J* = 8.3, 2.4 Hz, ArH), 5.97–5.95 (1H, m), 5.79–5.77 (1H, m), 3.83 (3H, s, H-7); δ_C (101 MHz, $CDCl_3$) 159.8 (C, C-6), 139.0 (C, q, *J* = 30.1 Hz, C-1), 135.1 (C, C4), 129.8 (CH, ArCH), 123.4 (C, q, *J* = 273.9 Hz, C-3), 120.8 (CH_2, q, *J* = 5.7 Hz, C-2), 120.0 (CH, ArCH), 114.5 (CH, ArCH), 113.5 (CH, ArCH), 55.4 (CH_3, C-7); δ_F (377 MHz, $CDCl_3$) –64.8 (CF_3).

Lab Book Ref.: LH739

Data are consistent with those previously reported.[237]

1-Methyl-2-(3,3,3-trifluoropropen-2-yl)benzene (380)



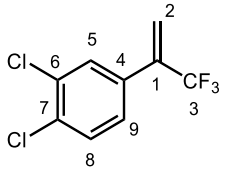
Following General Procedure G, α-tolylboronic acid (340 mg, 2.5 mmol, 1.0 eq.) in THF (10 mL) and 0.5 M aq. Na_2CO_3 (10 mL, 5.00 mmol, 2.0 eq.) was reacted with 2-bromo-3,3,3-trifluoropropene (0.530 mL, 5.00 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol, 4 mol%). Purification by FCC (SiO_2, pentane) gave the title compound **380** as a colourless oil (405 mg, 2.18 mmol, 87%); δ_H (400 MHz, $CDCl_3$) 7.31–7.27 (2H, m, ArH), 7.22–7.18 (2H, m, ArH), 6.12–6.10 (1H, m, H-2a), 5.50 (1H, s, H-2b), 2.30 (3H, s, H-6); δ_C (101 MHz, $CDCl_3$) 138.4 (C, q, *J* = 31.3 Hz, C-1), 137.0 (C,

ArC), 133.8 (C, ArC), 130.5 (CH, ArCH), 130.0 (CH, ArCH), 128.9 (CH, ArCH), 125.6 (CH, ArCH), 123.2 (C, q, J = 273.7 Hz, C-3), 122.8 (CH_2, q, J = 5.3 Hz, C-2), 20.0 (CH_3, C-6); δ_F (377 MHz, $CDCl_3$) –67.2 (CF_3).

Lab Book Ref.: LH743

Data are consistent with those previously reported.[237]

1,2-Dichloro-4-(3,3,3-trifluoropropen-2-yl)benzene (381)

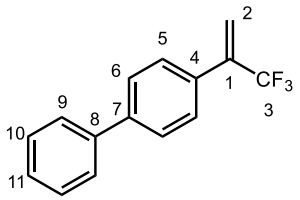


Following General Procedure G, 3,4-dichlorobenzene boronic acid (477 mg, 2.5 mmol, 1.0 eq.) in THF (10 mL) and 0.5 M aq. Na_2CO_3 (10 mL, 5.00 mmol, 2.0 eq.) was reacted with 2-bromo-3,3,3-trifluoropropene (0.530 mL, 5.00 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol, 4 mol%). Purification by FCC (SiO_2, pentane) gave the title compound **381** as a colourless oil (520 mg, 2.157 mmol, 86%); δ_H (400 MHz, $CDCl_3$) 7.55 (1H, d, J = 1.7 Hz, H-5), 7.47 (1H, d, J = 8.4 Hz, H-8), 7.29 (1H, dd, J = 8.4, 1.7 Hz, H-9), 6.02 (1H, d, J = 1.2 Hz, H-2a), 5.80 (1H, d, J = 1.2 Hz, H-2b); δ_C (101 MHz, $CDCl_3$) 137.2 (C, q, J = 30.8 Hz, C-1), 133.6 (C, C-4), 133.6 (C, ArC), 133.1 (C, ArC), 130.7 (CH, ArCH), 129.6 (CH, ArCH), 126.8 (CH, ArCH), 123.0 (C, q, J = 273.9 Hz, C-3), 122.0 (CH_2, q, J = 5.6 Hz, C-2); δ_F (377 MHz, $CDCl_3$) –65.0 (CF_3).

Lab Book Ref.: LH735

Data are consistent with those previously reported.[123]

4-(3,3,3-Trifluoropropen-2-yl)-1,1'-biphenyl (382)

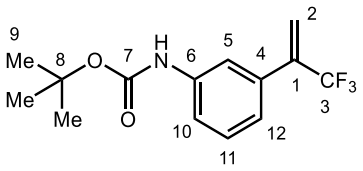


Following General Procedure G, 4-biphenyl boronic acid (495 mg, 2.5 mmol, 1.0 eq.) in THF (10 mL) and 0.5 M aq. Na_2CO_3 (10 mL, 5.00 mmol, 2.0 eq.) was reacted with 2-bromo-3,3,3-trifluoropropene (0.530 mL, 5.00 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol, 4 mol%). Purification by FCC (SiO_2, pentane) gave the title compound **382** as a colourless oil (617 mg, 2.49 mmol, 99%); δ_H (400 MHz, $CDCl_3$) 7.68–7.53 (6H, m, ArH), 7.50–7.35 (3H, m, ArH), 6.01–5.99 (1H, m, H-2a), 5.87–5.85 (1H, m, H-2b); δ_C (101 MHz, $CDCl_3$) 142.0 (C, ArC), 140.4 (C, ArC), 138.7 (C, q, *J* = 30.1 Hz, C-1), 132.6 (C, ArC), 129.0 (CH, ArCH), 127.9 (CH, ArCH), 127.8 (CH, ArCH), 127.4 (CH, ArCH), 127.2 (CH, ArCH), 123.5 (C, q, *J* = 274.0 Hz, C-3), 120.4 (CH_2, q, *J* = 5.8 Hz, C-2); δ_F (377 MHz, $CDCl_3$) –64.6 (CF_3).

Lab Book Ref.: LH745

Data are consistent with those previously reported.[237]

***tert*-Butyl (3-(3,3,3-trifluoropropen-2-yl)phenyl)carbamate (383)**



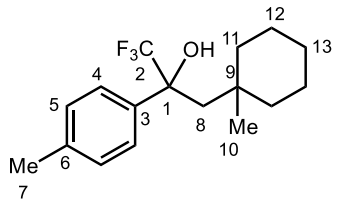
Following General Procedure G, 3-(*N*-boc-amino)phenylboronic acid (593 mg, 2.5 mmol, 1.0 eq.) in THF (10 mL) and 0.5 M aq. Na_2CO_3 (10 mL, 5.00 mmol, 2.0 eq.) was reacted with 2-bromo-3,3,3-trifluoropropene (0.530 mL, 5.00 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol, 4 mol%). Purification by FCC (SiO_2, pentane) gave the title compound **383** as a colourless, crystalline solid (660 mg, 2.30 mmol, 92%); mp. 61-63 °C; δ_H (400 MHz, $CDCl_3$) 7.47 (1H, s, H-5), 7.39 (1H, d, *J* = 7.9 Hz, ArH), 7.30 (1H, dd, *J* = 7.9, 7,7 Hz, H-11), 7.12 (1H, d, *J* = 7.7 Hz, ArH), 5.96–5.94 (1H, m, H-2a), 5.79–5.77 (1H, m, H-2b); δ_C (101 MHz, $CDCl_3$) 152.8 (C, C-7), 138.8 (C, q, J

= 30.0 Hz, C-1), 134.6 (C, ArC), 129.3 (CH, ArCH), 123.4 (C, q, *J* = 273.9 Hz, C-3), 122.1 (CH, ArCH), 120.9 (CH_2, q, *J* = 5.7 Hz, C-2), 119.2 (CH, ArCH), 117.7 (C, ArC), 81.0 (C, C-8), 28.5 (CH_3, C-9); δ_F (377 MHz, $CDCl_3$) –64.7 (CF_3).

Lab Book Ref.: LH750

Data are consistent with those previously reported.[189]

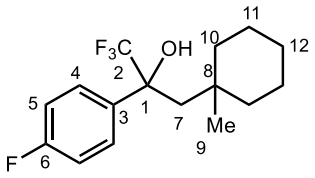
1,1,1-Trifluoro-3-(1-methylcyclohexyl)-2-(*p*-tolyl)propan-2-ol (384)



Following General Procedure D, 1-methyl-4-(3,3,3-trifluoropropen-2-yl)benzene **376** (75.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF_6 (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 35:1) gave the title compound **384** as a colourless oil (107 mg, 0.356 mmol, 89%); R_f 0.50 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3619, 2925, 1250, 1146, 1109, 811, 732; δ_H (500 MHz, $CDCl_3$) 7.47 (2H, d, *J* = 8.1 Hz, H-4), 7.18 (2H, d, *J* = 8.1 Hz, H-5), 2.36 (3H, s, H-7), 2.33 (1H, s, OH), 2.21 (1H, d, *J* = 15.0 Hz, H-8a), 2.01 (1H, d, *J* = 15.0 Hz, H-8b), 1.45–1.17 (8H, m, CyH), 1.09–0.96 (2H, m, CyH), 0.74 (3H, s, H-10); δ_C (126 MHz, $CDCl_3$) 138.0 (C, C-6), 134.5 (C, C-3), 128.9 (CH, C-5), 126.4 (CH, C-4), 125.9 (C, q, *J* = 287.1 Hz, C-2), 78.4 (C, q, *J* = 26.6 Hz, C-1), 45.3 (CH_2, C-8), 40.0 (CH_2, $CyCH_2$ (A)), 39.6 (CH_2, $CyCH_2$ (B)), 34.2 (C, C-9), 26.3 (CH_2, $CyCH_2$), 22.0 (CH_2, $CyCH_2$ (A)), 22.1 (CH_2, $CyCH_2$ (B)), 21.2 (CH_3, C-7); δ_F (376 MHz, $CDCl_3$) –81.5 (CF_3); *m/z* (ESI) 322 $[MNa]^+$; [HRMS (ESI): calc. for $C_{17}H_{23}F_3NaO^+$, 323.1593. Found: $[MNa]^+$, 323.1601 (2.5 ppm error)].

Lab Book Ref.: LH731

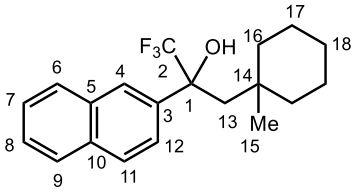
1,1,1-Trifluoro-2-(4-fluorophenyl)-3-(1-methylcyclohexyl)propan-2-ol (385)



Following General Procedure D, 1-fluoro-4-(3,3,3-trifluoropropen-2-yl)benzene **377** (76.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, 4·10^{-3} mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 35:1) gave the title compound **385** as a colourless oil (106 mg, 0.349 mmol, 87%); R_f 0.50 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3617, 2928, 1512, 1238, 1149, 1096, 831, 735; δ_H (500 MHz, $CDCl_3$) 7.55 (2H, dd, *J* = 8.6, 5.3 Hz, H-4), 7.10–7.02 (2H, m, H-5), 2.35 (1H, s, OH), 2.20 (1H, d, *J* = 15.1 Hz, H-7a), 2.01 (1H, d, *J* = 15.1 Hz, H-7b), 1.45–1.15 (8H, m, CyH), 1.05–0.95 (2H, m, CyH), 0.73 (3H, s, H-9); δ_C (126 MHz, $CDCl_3$) 162.8 (C, d, *J* = 247.2 Hz, C-6), 133.3 (C, d, *J* = 3.3 Hz, C-3), 128.4 (CH, d, *J* = 8.2 Hz, C-4), 125.7 (C, q, *J* = 287.1 Hz, C-2), 115.1 (CH, d, *J* = 21.3 Hz, C-5), 78.2 (C, q, *J* = 27.0 Hz, C-1), 45.6 (CH_2, C-7), 40.0 (CH_2, $CyCH_2$ (A)), 39.6 (CH_2, $CyCH_2$ (B)), 34.2 (C, C-8), 26.4 (CH_2, $CyCH_2$), 25.1 (CH_3, C-9), 21.9 (CH_2, $CyCH_2$ (A)), 21.8 (CH_2, $CyCH_2$ (B)); δ_F (376 MHz, $CDCl_3$) –81.6 (CF_3), –114.4 (CF); *m/z* (ESI) 305 $[MH]^+$; [HRMS (ESI): calc. for $C_{16}H_{20}F_4O^+$, 305.1523. Found: $[MH]^+$, 305.1513 (3.4 ppm error)].

Lab Book Ref.: LH734

1,1,1-Trifluoro-3-(1-methylcyclohexyl)-2-(naphthalen-2-yl)propan-2-ol (386)

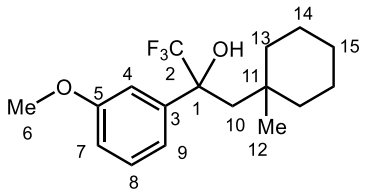


Following General Procedure D, 2-(3,3,3-trifluoropropen-2-yl)naphthalene **378** (89.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-

carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, 4·10^{-3} mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 40:1) gave the title compound **386** as a colourless oil (119 mg, 0.354 mmol, 89%); R_f 0.45 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3616, 2925, 1250, 1174, 1146, 1118, 815, 746, 476; δ_H (500 MHz, $CDCl_3$) 8.14–8.12 (1H, m, ArH), 7.93–7.82 (3H, m, ArH), 7.67 (1H, d, *J* = 8.7 Hz, ArH), 7.55–7.50 (2H, m, ArH), 2.49 (1H, s, OH), 2.38 (1H, d, *J* = 15.2 Hz, H-13a), 2.11 (1H, d, *J* = 15.2 Hz, H-13b), 1.49–1.13 (8H, m, CyH), 1.10–0.96 (2H, m, CyH), 0.74 (3H, s, H-15); δ_C (126 MHz, $CDCl_3$) 135.0 (C, C-3), 133.1 (C, ArC), 133.0 (C, ArC), 128.6 (CH, ArCH), 127.7 (CH, ArCH), 127.7 (CH, ArCH), 126.6 (CH, ArCH), 126.4 (CH, ArCH), 126.0 (CH, ArCH), 125.9 (C, q, *J* = 287.3 Hz, C-2), 124.3 (CH, ArCH), 78.7 (C, q, *J* = 26.6 Hz, C-1), 45.4 (CH_2, C-13), 40.0 (CH_2, $CyCH_2$ (A)), 39.6 (CH_2, $CyCH_2$ (B)), 34.3 (C, C-14), 26.2 (CH_2, $CyCH_2$), 25.1 (CH_3, C-15), 21.9 ((CH_2, $CyCH_2$ (A)), 21.8 (CH_2, $CyCH_2$ (B)); δ_F (376 MHz, $CDCl_3$) –81.0 (CF_3); *m/z* (ESI) 359 [MNa]$^+$; [HRMS (ESI): calc. for $C_{20}H_{23}F_3NaO^+$, 359.1593. Found: [MNa]$^+$, 359.1607 (3.5 ppm error)].

Lab Book Ref.: LH740

1,1,1-Trifluoro-2-(3-methoxyphenyl)-3-(1-methylcyclohexyl)propan-2-ol (387)

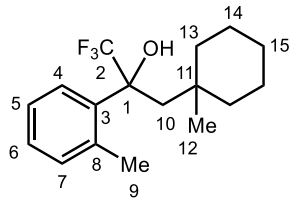


Following General Procedure D, 1-methoxy-3-(3,3,3-trifluoropropen-2-yl)benzenene **379** (81.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, 4·10^{-3} mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 20:1) gave the title compound **387** as a colourless oil (104 mg, 0.327 mmol, 82%); R_f 0.45 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3474, 2925,

1453, 1248, 1145, 1046, 750, 712; δ_H (500 MHz, $CDCl_3$) 7.28 (1H, t, *J* = 8.0 Hz, H-8), 7.21–7.13 (2H, m, ArH), 6.88 (1H, dd, *J* = 8.0, 0.7 Hz, ArH), 3.83 (3H, s, H-8), 2.38 (1H, s, OH), 2.21 (1H, d, *J* = 15.1, H-10a), 2.01 (1H, d, *J* = 15.1, H-10b), 1.46–1.15 (8H, m, CyH), 1.09–0.97 (2H, m, CyH), 0.76 (3H, s, H-12); δ_C (126 MHz, $CDCl_3$) 159.5 (C, C-5), 139.2 (C, C-3), 129.1 (CH, C-8), 125.8 (C, q, *J* = 287.2 Hz, C-2), 119.0 (CH, ArCH), 113.4 (CH, ArCH), 112.9 (CH, ArCH), 78.4 (C, q, *J* = 26.8 Hz, C-1), 55.4 (CH_3, C-6), 45.5 (CH_2, C-10), 40.0 (CH_2, $CyCH_2$ (A)), 39.5 (CH_2, $CyCH_2$ (B)), 34.2 (C, C-11), 26.2 (CH_2, $CyCH_2$), 25.1 (CH_3, C-12), 22.0 (CH_2, $CyCH_2$ (A)), 21.9 (CH_2, $CyCH_2$ (B)); δ_F (376 MHz, $CDCl_3$) –81.2 (CF_3); *m/z* (ESI) 334 $[MNH_4]^+$; [HRMS (ESI): calc. for $C_{17}H_{27}F_3NO_2^+$, 334.1988. Found: $[MNH_4]^+$, 334.1982 (2.0 ppm error)].

Lab Book Ref.: LH744

1,1,1-Trifluoro-3-(1-methylcyclohexyl)-2-(*o*-tolyl)propan-2-ol (388)

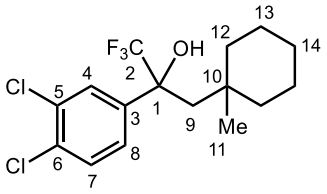


Following General Procedure D, 1-methyl-2-(3,3,3-trifluoropropen-2-yl)benzene **380** (74.5 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF_6 (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 40:1) gave the title compound **388** as a colourless oil (57.1 mg, 0.190 mmol, 48%); R_f 0.55 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3613, 2925, 1248, 1175, 1154, 1100, 759, 732; δ_H (500 MHz, $CDCl_3$) 7.63–7.29 (1H, m, ArH), 7.18 (1H, ddd, *J* = 14.5, 7.3, 1.3 Hz, ArH), 7.15–7.11 (2H, m, ArH), 2.62 (3H, s, H-9), 2.44 (1H, d, *J* = 15.2 Hz, H-10a), 2.24 (1H, s, OH), 1.97 (1H, d, *J* = 15.2 Hz, H-10b), 1.51–1.07 (8H, m, CyH), 0.93–0.83 (2H, m, CyH), 0.77 (3H, s, H-12); δ_C (126 MHz, $CDCl_3$) 137.6 (C, C-3), 134.6 (C, C-8), 133.6 (CH, ArCH), 128.9 (CH, ArCH), 128.3 (CH, ArCH), 126.2 (C, q, *J* = 287.9 Hz, C-2), 125.3 (CH, ArCH), 81.5 (C, C-1), 46.3 (CH_2, C-10), 40.2 (CH_2, $CyCH_2$ (A)), 40.0 (CH_2, $CyCH_2$ (B)), 34.1 (C, C-11),

26.3 (CH_2, $CyCH_2$), 24.8 (CH_3, C-12), 24.1 (CH_3, C-9), 22.0 (CH_2, $CyCH_2$); δ_F (376 MHz, $CDCl_3$) –64.5 (CF_3), –81.3 (CF_3); *m/z* (ESI) 318 $[MNH_4]^+$; [HRMS (ESI): calc. for $C_{17}H_{27}F_3NO^+$, 318.2039. Found: $[MNH_4]^+$, 318.2057 (4.6 ppm error)].

Lab Book Ref.: LH747

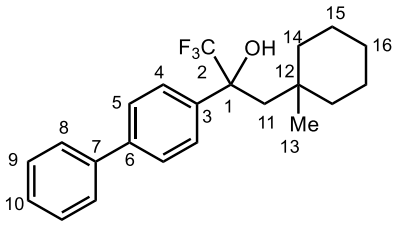
2-(3,4-Dichlorophenyl)-1,1,1-trifluoro-3-(1-methylcyclohexyl)propan-2-ol (389)



Following General Procedure D, 1,2-dichloro-4-(3,3,3-trifluoropropen-2-yl)benzene **381** (96.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), $Ir[dtbbpy(ppy)_2]PF_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 40:1) gave the title compound **389** as a colourless oil (111 mg, 0.314 ol, 78%); R_f 0.45 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3617, 2928, 1474, 1248, 1156, 1021, 819, 681; δ_H (500 MHz, $CDCl_3$) 7.73 (1H, d, *J* = 1.6 Hz, H-4), 7.44 (1H, d, *J* = 8.5 Hz, H-7), 7.41 (1H, dd, *J* = 8.5, 1.6 Hz, H-8), 2.38 (1H, s, OH), 2.17 (1H, d, *J* = 15.2 Hz, H-9a), 2.02 (1H, d, *J* = 15.2 Hz, H-9b), 1.48–1.17 (8H, m, CyH), 1.08–0.98 (2H, m, CyH), 0.76 (3H, s, H-11); δ_C (126 MHz, $CDCl_3$) 137.9 (C, C-3), 132.7 (C, ArC), 132.6 (C, ArC), 130.1 (CH, C-7), 128.9 (CH, C-4), 126.2 (CH, C-8), 125.3 (C, q, *J* = 287.2 Hz, C-2), 78.0 (C, q, *J* = 27.2 Hz, C-1), 45.6 (CH_2, C-9), 40.0 (CH_2, $CyCH_2$ (A)), 39.7 (CH_2, $CyCH_2$ (B)), 34.3 (C, C-10), 26.1 (CH_2, $CyCH_2$), 25.2 (CH_3, C-11), 21.9 (CH_2, $CyCH_2$ (A)), 21.8 (CH_2, $CyCH_2$ (B)); δ_F (376 MHz, $CDCl_3$) –81.4 (CF_3); *m/z* (EI) 285 $[M–CF_3H]^+$; [HRMS (EI): calc. for $C_{15}H_{19}OCl_2^+$, 285.0808. Found: $[M–CF_3H]^+$, 285.0804 (1.3 ppm error)].

Lab Book Ref.: LH748

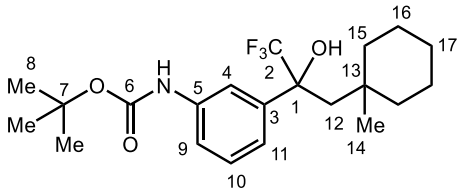
2-([1,1'-Biphenyl]-4-yl)-1,1,1-trifluoro-3-(1-methylcyclohexyl)propan-2-ol (390)



Following General Procedure D, 4-(3,3,3-trifluoropropen-2-yl)-1,1'-biphenyl **382** (99.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 40:1) gave the title compound **390** as a colourless oil (122 mg, 0.336 mmol, 84%); R_f 0.45 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3617, 2925, 1248, 1149, 1106, 1007, 834, 764, 736, 696; δ_H (500 MHz, $CDCl_3$) 7.70–7.59 (6H, m, ArH), 7.48–7.43 (2H, m, ArH), 7.38–7.34 (1H, m, ArH), 2.39 (1H, s, OH), 2.27 (1H, d, *J* = 15.1 Hz, H-11a), 2.07 (1H, d, *J* = 15.1 Hz, H-11b), 1.49–1.15 (8H, m, CyH), 1.13–0.98 (2H, m, CyH), 0.78 (3H, s, H-13); δ_C (126 MHz, $CDCl_3$) 141.0 (C, ArC), 140.5 (C, ArC), 136.6 (C, C-3), 128.9 (CH, ArCH), 127.6 (CH, ArCH), 127.2 (CH, ArCH), 127.0 (CH, ArCH), 126.7 (CH, ArCH), 125.8 (C, q, *J* = 287.3 Hz, C-2), 78.5 (C, q, *J* = 26.7 Hz, C-1), 45.5 (CH_2, C-11), 40.0 (CH_2, $CyCH_2$ (A)), 39.6 (CH_2, $CyCH_2$ (B)), 34.2 (C, C-12), 26.2 (CH_2, $CyCH_2$), 25.2 (CH_3, C-13), 22.0 (CH_2, $CyCH_2$ (A)), 21.9 (CH_2, $CyCH_2$ (B)); δ_F (376 MHz, $CDCl_3$) –81.2 (CF_3); *m/z* (ESI) 385 $[MNa]^+$; [HRMS (ESI): calc. for $C_{22}H_{25}F_3NaO^+$, 385.1750. Found: $[MNa]^+$, 385.1744 (1.6 ppm error)].

Lab Book Ref.: LH749

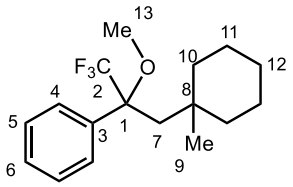
***tert*-Butyl (3-(1,1,1-trifluoro-2-hydroxy-3-(1-methylcyclohexyl)propan-2-yl) phenyl)-carbamate (391)**



Following General Procedure D, *tert*-butyl (3-(3,3,3-trifluoropropen-2-yl)phenyl)carbamate **383** (115 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and water (0.360 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 15:1) gave the title compound **391** as a colourless oil (123 mg, 0.307 mmol, 77%); R_f 0.25 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 3605, 3333, 2930, 1697, 1594, 1542, 1437, 1240, 1149, 1138, 1065, 788, 713; δ_H (500 MHz, $CDCl_3$) 7.55–7.48 (2H, m, ArH), 7.28 (1H, t, *J* = 8.0 Hz, H-10), 7.22 (1H, d, *J* = 8.0 Hz, ArH), 6.58 (1H, s, NH), 2.48 (1H, br s, OH), 2.20 (1H, d, *J* = 15.1 Hz, H-12a), 2.01 (1H, d, *J* = 15.1 Hz, H-12b), 1.52 (9H, s, H-8), 1.46–1.15 (8H, m, CyH), 1.07–0.98 (2H, m, CyH), 0.74 (3H, s, H-14); δ_C (126 MHz, $CDCl_3$) 152.8 (C, C-6), 138.6 (C, ArC), 138.5 (C, ArC), 128.8 (CH, ArCH), 125.7 (C, q, *J* = 287.2 Hz, C-2), 121.2 (CH, ArCH), 118.2 (CH, ArCH), 116.6 (CH, ArCH), 80.8 (C, C-7), 78.4 (C, q, *J* = 26.8 Hz, C-1), 45.4 (CH_2, C-12), 39.9 (CH_2, $CyCH_2$ (A)), 39.5 (CH_2, $CyCH_2$ (B)), 34.2 (C, C-13), 28.5 (CH_3, C-8), 26.2 (CH_2, $CyCH_2$), 25.1 (CH_3, C-14), 21.9 (CH_2, $CyCH_2$ (A)), 21.9 (CH_2, $CyCH_2$ (B)); δ_F (376 MHz, $CDCl_3$) –81.2 (CF_3); *m/z* (ESI) 402 $[MH]^+$; [HRMS (ESI): calc. for $C_{21}H_{30}F_3NO_3^+$, 402.2251. Found: $[MH]^+$, 402.2254 (0.9 ppm error)].

Lab Book Ref.: LH751

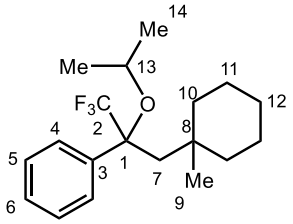
(1,1,1-Trifluoro-2-methoxy-3-(1-methylcyclohexyl)propan-2-yl)benzene (392)



Following General Procedure D with a slight modification, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), $Ir[dtbbpy(ppy)_2]PF_6$ (3.60 mg, $4 \cdot 10^{-3}$ mmol, 1 mol%) and MeOH (0.800 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, pentane) gave the title compound **392** as a colourless oil (108 mg, 0.359 mmol, 90%); R_f 0.60 (cyclohexane); υ_{max}/cm^{-1} (neat) 2925, 1449, 1251, 1146, 1114, 1081, 761, 703; δ_H (500 MHz, $CDCl_3$) 7.59 (2H, d, *J* = 7.9 Hz, H-4), 7.39–7.31 (3H, m, ArH), 3.55 (3H, q, *J* = 2.3 Hz, H-13), 2.16 (1H, d, *J* = 15.3 Hz, H-7a), 2.03 (1H, d, *J* = 15.3 Hz, H-7b), 1.46–1.18 (8H, m, CyH), 1.10–0.93 (2H, m, CyH), 0.76 (3H, s, H-9); δ_C (126 MHz, $CDCl_3$) 137.5 (C, C-3), 128.1 (CH, ArCH), 128.0 (CH, ArCH), 127.4 (CH, ArCH), 126.0 (C, q, *J* = 292.9 Hz, C-2), 82.9 (C, q, *J* = 24.1 Hz, C-1), 53.6 (CH_3, q, *J* = 8.4 Hz, C-13), 43.5 (CH_2, C-7), 40.1 (CH_2, $CyCH_2$ (A)), 39.5 (CH_2, $CyCH_2$ (B)), 34.0 (C, C-8), 26.3 (CH_2, $CyCH_2$), 24.5 (CH_3, C-9), 22.1 (CH_2, $CyCH_2$ (A)), 22.0 (CH_2, $CyCH_2$ (B)); δ_F (376 MHz, $CDCl_3$) –71.1 (CF_3); *m/z* (EI) 231 $[M–CF_3H]^+$; [HRMS (EI): calc. for $C_{16}H_{23}O^+$, 231.1743. Found: $[M–CF_3H]^+$, 231.1752 (3.7 ppm error)].

Lab Book Ref.: LH754

(1,1,1-Trifluoro-2-isopropoxy-3-(1-methylcyclohexyl)propan-2-yl)benzene (393)

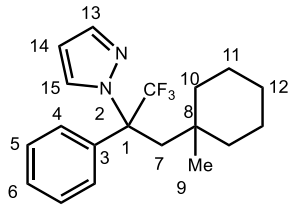


Following General Procedure D with a slight modification, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-

methylcyclohexane-1-carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, 4·10^{-3} mmol, 1 mol%) and IPA (1.50 mL, 20.0 mmol, 50.0 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, pentane) gave the title compound **393** as a colourless oil (87.2 mg, 0.266 mmol, 66%); R_f 0.65 (cyclohexane); υ_{max}/cm^{-1} (neat) 2925, 1251, 1151, 1103, 1029, 908, 761, 735, 701; δ_H (500 MHz, $CDCl_3$) 7.60 (2H, d, *J* = 8.2 Hz), 7.39–7.28 (3H, m, ArH), 3.95 (1H, hept, *J* = 6.1 Hz, H-13), 2.02 (2H, s, H-7), 1.44–1.12 (10H, m, CyH), 1.23 (3H, d, *J* = 6.1 Hz, H-14 (A)), 1.22 (3H, d, *J* = 6.1 Hz, H-14 (B)), 0.82 (3H, s, H-9); δ_C (126 MHz, $CDCl_3$) 139.0 (C, C-3), 128.0 (CH, ArCH), 127.9 (CH, ArCH), 127.7 (CH, ArCH), 126.6 (C, q, *J* = 288. Hz, C-2), 83.9 (C, q, *J* = 25.3 Hz, C-1), 68.9 (CH, C-13), 49.6 (CH_2, C-7), 40.1 (CH_2, $CyCH_2$ (A)), 39.7 (CH_2, $CyCH_2$ (B)), 34.1 (C, C-8), 27.1 (CH_2, $CyCH_2$), 26.4 (CH_3, C-14 (A)), 25.1 (CH_3, C-14 (B)), 23.7 (q, CH_3, *J* = 2.3 Hz, C-9), 22.2 (CH_2, $CyCH_2$ (A)), 22.1 (CH_2, $CyCH_2$ (B)); δ_F (376 MHz, $CDCl_3$) –68.4 (CF_3); *m/z* (ESI) 346 [MNH_4]$^+$; [HRMS (ESI): calc. for $C_{19}H_{31}F_3NO^+$, 346.2352. Found: [MNH_4]$^+$, 346.2371 (5.5 ppm error)].

Lab Book Ref.: LH756

1-(1,1,1-Trifluoro-3-(1-methylcyclohexyl)-2-phenylpropan-2-yl)-1H-pyrazole (399)

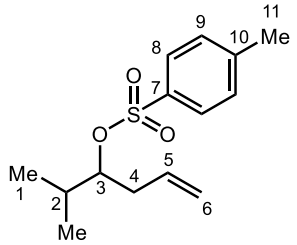


Following General Procedure D with a slight modification, (3,3,3-trifluoropropen-2-yl)benzene **301** (69.0 mg, 0.40 mmol, 1.00 eq.), 1,3-dioxoisoindolin-2-yl 1-methylcyclohexane-1-carboxylate **348** (144 mg, 0.50 mmol, 1.25 eq.), Ir[dtbbpy(ppy)$_2$]PF$_6$ (3.60 mg, 4·10^{-3} mmol, 1 mol%) and pyrazole (82.0 mg, 1.20 mmol, 3.00 eq.) were stirred in MeCN (4 mL) for 16 h under irradiation of blue LED. Purification by FCC (SiO_2, cyclohexane:EtOAc, 20:1) gave the title compound **399** as a colourless oil (64.9 mg, 0.193 mmol, 48%); R_f 0.60 (cyclohexane:EtOAc, 10:1); υ_{max}/cm^{-1} (neat) 2924, 2855, 1449, 1208, 1157, 1087, 917, 754, 707; δ_H (500 MHz, $CDCl_3$) 7.65 (1H, d, *J* = 1.5 Hz, ArH), 7.57–7.50 (1H, m, ArH), 7.40–7.30 (3H, m,

ArH), 7.29–7.21 (2H, m, ArH), 6.35 (1H, dd, *J* = 2.5, 1.5 Hz, ArH), 2.93 (1H, d, *J* = 15.5 Hz, H-7a), 2.84 (1H, d, *J* = 15.5 Hz, H7b), 1.49–1.05 (10H, m, CyH), 0.70 (3H, s, H-9); δ_C (126 MHz, $CDCl_3$) 139.0 (CH, ArCH), 137.5 (C, C-3), 131.8 (CH, q, *J* = 2.3 Hz, ArCH), 128.9 (CH, ArCH), 128.3 (CH, ArCH), 128.1 (CH, q, *J* = 2.1 Hz, ArCH), 125.4 (C, q, *J* = 287.0 Hz, C-2), 106.2 (CH, ArCH), 73.2 (C, q, *J* = 27.0 Hz, C-1), 46.4 (CH_2, C-7), 39.3 (CH_2, $CyCH_2$ (A)), 39.2 (CH_2, $CyCH_2$ (B)), 34.0 (C, C-8), 26.2 (CH_2, $CyCH_2$), 22.8 (CH_3, C-9), 22.0 (CH_2, $CyCH_2$ (A)), 22.0 (CH_2, $CyCH_2$ (B)); δ_F (376 MHz, $CDCl_3$) –64.6 (CF_3); *m/z* (ESI) 337 $[MH]^+$; [HRMS (ESI): calc. for $C_{19}H_{24}F_3N_2^+$, 337.1886. Found: $[MH]^+$, 337.1885 (1.0 ppm error)].

Lab Book Ref.: LH772

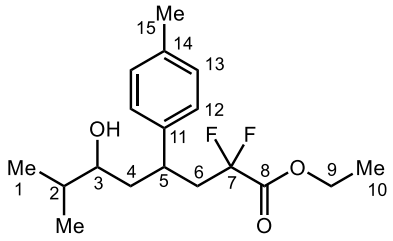
2-Methylhex-5-en-3-yl 4-methylbenzenesulfonate (423)



Following general Procedure H, to a solution of 2-methylhex-5-en-3-ol (144 mg, 1.25 mmol, 1.0 eq.) in DCM (5 mL) and pyridine (3 mL) was added tosyl chloride (477 mg, 2.50 mmol, 2.0 eq.) and DMAP (15.0 mg, 0.125 mmol, 0.10 eq.). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 25:1) gave the title compound **423** as a colourless oil (293 mg, 0.109 mmol, 88%); R_f 0.50 (cyclohexane:EtOAc, 4:1); ν_{max}/cm-1 (neat) 2967, 1359, 1339, 1173, 899, 814, 667, 564; δ_H (500 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.3 Hz, ArH), 7.31 (2H, d, *J* = 8.3 Hz, ArH), 5.62 (1H, ddt, *J* = 17.1, 10.1, 7.1 Hz, H-5), 5.06–4.97 (2H, m, H-6), 4.44 (1H, dt, *J* = 6.0, 5.3 Hz, H-3), 2.44 (3H, s, H-11), 2.39–2.35 (2H, m, H-4), 1.93 (1H, heptd, *J* = 7.0, 5.3 Hz, H-2), 0.86 (3H, d, *J* = 7.0 Hz, H-1 (A)), 0.85 (3H, d, *J* = 7.0 Hz, H-1 (B)); δ_C (126 MHz, $CDCl_3$) 144.5 (C, C-10), 134.8 (C, C-7), 132.8 (CH, C-5), 129.8 (CH, ArCH), 127.9 (CH, ArCH), 118.4 (CH_2, C-6), 87.7 (CH, C-3), 35.9 (CH_2, C-4), 30.9 (CH, C-2), 21.8 (CH_3, C-11), 18.2 (CH_3, C-1 (A)), 17.4 (CH_3, C-1 (B)); *m/z* (ESI) 269 $[MH]^+$; [HRMS (ESI): calc. for $C_{14}H_{21}O_3S^+$, 269.1206. Found $[MH]^+$, 269.1207 (0.2 ppm error)].

Lab Book Ref.: LH626

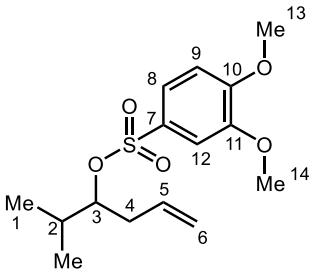
Ethyl 2,2-difluoro-6-hydroxy-7-methyl-4-(*p*-tolyl)octanoate (425)



Following General Procedure I, ethyl 2,2-difluoro-6-hydroxy-7-methyl-4-(*p*-tolyl)octanoate **425** was prepared using 2-methylhex-5-en-3-yl 4-methylbenzenesulfonate **423** (107 mg, 0.400 mmol). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 8:1) gave the title compound **425** as a yellow oil as an inseparable mixture of diastereoisomers (47.7 mg, 0.152 mmol, 40%, dr: 10:1); R_f 0.20 (cyclohexane:Et_2O, 5:1); ν_{max}/cm-1 (neat) 3426, 2961, 1760, 1220, 1188, 1085, 1021, 816, 776; δ_H (500 MHz, $CDCl_3$) 7.14–7.04 (4H, ArH), 3.97 (1H, dq, *J* = 10.7, 7.2 Hz, H-9a), 3.93 (1H, dq, *J* = 10.7, 7.2 Hz, H-9b), 3.38 (1H, dt, *J* = 8.5, 4.2 Hz, H-3), 3.03 (1H, qd, *J* = 7.7, 5.1 Hz, H-5), 2.55–2.39 (2H, m, H-6), 2.31 (3H, s, H-15), 1.83 (1H, ddd, *J* = 14.1, 7.2, 3.8 Hz, H-4a), 1.73–1.60 (2H, m, H-4b, H-2), 1.20 (3H, t, *J* = 7.2 Hz, H-10), 0.88 (3H, d, *J* = 6.8 Hz, H-1 (A), major), 0.87 (3H, d, *J* = 6.8 Hz, H-1 (B), major), 0.81 (6H, d, *J* = 6.8 Hz, H-1 (A+B), minor); δ_C (126 MHz, $CDCl_3$) 164.2 (C, t, *J* = 32.7 Hz, C-8, minor), 164.1 (C, t, *J* = 32.7 Hz, C-8, major), 140.4 (C, ArC, major), 139.6 (C, ArC, minor), 136.6 (C, ArC, major), 136.4 (C, ArC, minor), 129.5 (CH, ArCH, major), 129.3 (CH, ArCH, minor), 128.0 (CH, ArCH, minor), 127.7 (CH, ArCH, major), 116.0 (C, dd, *J* = 252.1, 249.1 Hz, C-7), 116.0 (C, dd, *J* = 252.1, 249.1 Hz, C-7), 74.5 (CH, C-3, major), 73.6 (CH, C-3, minor), 62.8 (CH_2, C-9, major), 62.7 (CH_2, C-9, minor), 42.1 (CH_2, C-4, major), 42.0 (CH_2, t, *J* = 22.6 Hz, C-6, minor), 41.2 (CH_2, C-4, minor), 40.7 (CH_2, t, *J* = 22.5 Hz, C-6, major), 36.7 (CH_2, dd, *J* = 5.2, 2.8 Hz, C-5, major), 36.0 (CH, dd, *J* = 5.5, 2.5 Hz, C-5, minor), 34.3 (CH, C-2, minor), 33.3 (CH, C-2, major), 22.8 (CH_3, C-15, minor), 21.1 (CH_3, C-15, major), 19.0 (CH_3, C-1 (A), major), 18.6 (CH_3, C-1 (A), minor), 17.5 (CH_3, C-1 (B), minor), 16.6 (CH_3, C-1 (B), major), 14.3 (CH_3, C-10, minor), 13.8 (CH_3, C-10, major); δ_F (376 MHz, $CDCl_3$) –100.1 (CF_2, dd, *J* = 260.1, 5.2 Hz, minor), –100.7 (CF_2, dd, *J* = 260.6, 6.2 Hz, major), –105.9 (CF_2, d, *J* = 260.6 Hz, major), –106.1 (CF_2, d, *J* = 260.1 Hz, minor); *m/z* (ESI) 351 $[MNa]^+$; [HRMS (ESI): calc. for $C_{18}H_{26}NaF_2O_3^+$, 351.1742. Found $[MNa]^+$, 351.1740 (0.5 ppm error)].

Lab Book Ref.: LH598

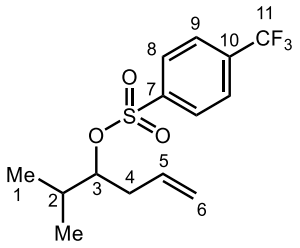
2-Methylhex-5-en-3-yl 3,4-dimethoxybenzenesulfonate (431)



Following general Procedure H, to a solution of 2-methylhex-5-en-3-ol (144 mg, 1.25 mmol, 1.0 eq.) in DCM (5 mL) and pyridine (3 mL) was added 3,4-dimethoxybenzensulfonylchloride (592 mg, 2.50 mmol, 2.0 eq.) and DMAP (15.0 mg, 0.125 mmol, 0.10 eq.). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 7:1) gave the title compound **431** as a colourless oil (293 mg, 0.107 mmol, 86%); R_f 0.40 (cyclohexane: Et_2O, 10:1); ν_{max}/cm-1 (neat) 2959, 1509, 1351, 1260, 1168, 1143, 1015, 905, 900, 670, 587; δ_H (500 MHz, $CDCl_3$) 7.53 (1H, dd, *J* = 8.5, 2.2 Hz, H-8), 7.34 (1H, d, *J* = 2.2 Hz, H-12), 6.94 (1H, d, *J* = 8.5 Hz, H-9), 5.63 (1H, ddt, *J* = 17.2, 10.1, 7.1 Hz, H-5), 5.07–4.97 (2H, m, H-6), 4.42 (1H, app td, *J* = 6.3, 5.1 Hz, H-3), 3.95 (3H, s, OMe), 3.93 (3H, s, OMe), 2.40–2.32 (2H, m, H-4), 1.94 (1H, heptd, *J* = 6.9, 5.1 Hz, H-2), 0.89 (3H, d, *J* = 6.9 Hz, H-1 (A)), 0.87 (3H, d, *J* = 6.9 Hz, H-1 (B)); δ_C (126 MHz, $CDCl_3$) 153.4 (C, ArC), 149.3 (C, ArC), 132.9 (CH, C-5), 129.3 (C, ArC), 122.0 (CH, ArC), 118.4 (CH_2, C-6), 110.5 (C, ArC), 110.3 (C, ArC), 87.8 (CH, C-3), 56.4 (CH_3, OMe), 56.3 (CH_3, OMe), 35.8 (CH_2, C-4), 31.0 (CH, C-2), 18.2 (CH_3, C-1 (A)), 17.5 (CH_3, C-1 (B)); *m/z* (ESI) 337 $[MNa]^+$; [HRMS (ESI): calc. for $C_{15}H_{22}NaO_5S^+$, 337.1080. Found $[MNa]^+$, 337.1072 (2.4 ppm error)].

Lab Book Ref.: LH627

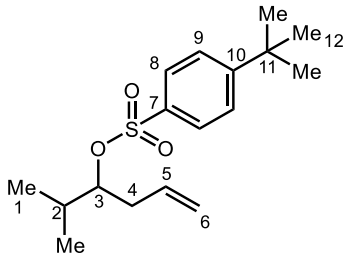
2-Methylhex-5-en-3-yl 4-(trifluoromethyl)benzenesulfonate (432)



Following general Procedure H, to a solution of 2-methylhex-5-en-3-ol (144 mg, 1.25 mmol, 1.0 eq.) in DCM (5 mL) and pyridine (3 mL) was added 4-trifluoromethylbenzenesulfonyl chloride (612 mg, 2.50 mmol, 2.0 eq.) and DMAP (15.0 mg, 0.125 mmol, 0.10 eq.). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 50:1) gave the title compound **432** as a colourless oil (258 mg, 0.800 mmol, 64%); R_f 0.37 (cyclohexane: Et_2O, 20:1); ν_{max}/cm-1 (neat) 2970, 1321, 1170, 1135, 1062, 997, 841, 713, 603; δ_H (500 MHz, $CDCl_3$) 8.04 (2H, d, *J* = 8.2 Hz, H-8), 7.80 (2H, d, *J* = 8.2 Hz, H-9), 5.59 (1H, ddt, *J* = 17.2, 10.2, 7.1 Hz, H-5), 5.05–4.95 (2H, m, H-6), 4.56 (1H, app td, *J* = 6.0, 4.9 Hz, H-3), 2.43–2.35 (2H, m, H-4), 1.98 (1H, heptd, *J* = 6.8, 4.9 Hz, H-2), 0.89 (6H, app dd, *J* = 6.8, 1.0 Hz, H-1 (A+B)); δ_C (126 MHz, $CDCl_3$) 141.4 (C, C-7), 135.3 (C, q, *J* = 33.2 Hz, C-10), 132.5 (CH, C-5), 128.4 (CH, C-8), 126.4 (CH, q, *J* = 3.7 Hz, C-9), 123.3 (C. q, *J* = 273.4 Hz, C-11), 118.8 (CH_2, C-6), 89.3 (CH, C-3), 35.9 (CH_2, C-4), 31.3 (CH, C-2), 18.2 (CH_3, C-1 (A)), 17.5 (CH_3, C-1 (B)); δF (376 MHz, $CDCl_3$) –63.2 (CF_3); *m/z* (ESI) 345 $[MNa]^+$; [HRMS (ESI): calc. for $C_{14}H_{17}F_3NaO_3S^+$, 345.0743. Found $[MNa]^+$, 345.0740 (0.8 ppm error)].

Lab Book Ref.: LH628

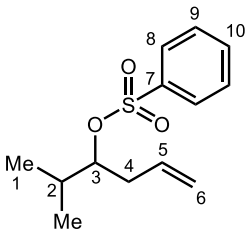
2-Methylhex-5-en-3-yl 4-(*tert*-butyl)benzenesulfonate (433)



Following general Procedure H, to a solution of 2-methylhex-5-en-3-ol (144 mg, 1.25 mmol, 1.0 eq.) in DCM (5 mL) and pyridine (3 mL) was added 4-*tert*butylbenzenesulfonyl chloride (582 mg, 2.50 mmol, 2.0 eq.) and DMAP (15.0 mg, 0.125 mmol, 0.10 eq.). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 50:1) gave the title compound **433** as a colourless oil (297 mg, 0.957 mmol, 77%); R_f 0.22 (cyclohexane:Et_2O, 20:1); ν_{max}/cm-1 (neat) 2965, 1361, 1339, 1178, 890, 832, 631, 580, 563; δ_H (500 MHz, $CDCl_3$) 7.83 (2H, d, *J* = 8.3 Hz, ArH), 7.53 (2H, d, *J* = 8.3 Hz, ArH), 5.59 (1H, ddt, *J* = 17.1, 10.1, 7.1 Hz, H-5), 5.03–4.92 (2H, m, H-6), 4.45 (1H, dt, *J* = 6.0, 5.3 Hz, H-3), 2.41–2.31 (2H, m, H-4), 1.95 (1H, heptd, *J* = 7.0, 5.3 Hz, H-2), 1.34 (9H, s, H-12), 0.87 (3H, d, *J* = 7.0 Hz, H-1 (A)), 0.85 (3H, d, *J* = 7.0 Hz, H-1 (B)); δ_C (126 MHz, $CDCl_3$) 157.7 (C, C-10), 134.6 (C, C-7), 132.8 (CH, C-5), 127.8 (CH, ArCH), 126.1 (CH, ArCH), 118.3 (CH_2, C-6), 87.7 (CH, C-3), 35.9 (CH_2, C-4), 35.4 (C, C-11), 31.1 (CH_3, C-12), 31.0 (CH, C-2), 21.5 (CH_3, C-11), 18.1 (CH_3, C-1 (A)), 17.4 (CH_3, C-1 (B)); *m/z* (ESI) 311 $[MH]^+$; [HRMS (ESI): calc. for $C_{17}H_{27}O_3S^+$, 311.1675. Found $[MH]^+$, 311.1675 (0.3 ppm error)].

Lab Book Ref.: LH630

2-Methylhex-5-en-3-yl benzenesulfonate (434)

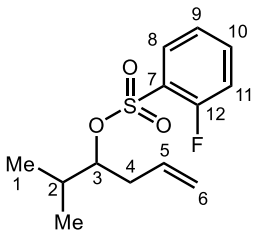


Following general Procedure H, to a solution of 2-methylhex-5-en-3-ol (144 mg, 1.25 mmol, 1.0 eq.) in DCM (5 mL) and pyridine (3 mL) was added benzenesulfonyl

chloride (0.320 mL, 2.50 mmol, 2.0 eq.) and DMAP (15.0 mg, 0.125 mmol, 0.10 eq.). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 30:1) gave the title compound **434** as a colourless oil (217 mg, 0.853 mmol, 68%); R_f 0.55 (cyclohexane:Et_2O, 20:1); ν_{max}/cm-1 (neat) 2968, 1448, 1360, 1338, 1183, 1175, 889, 753, 658, 591; δ_H (500 MHz, $CDCl_3$) 7.94–7.89 (2H, m, ArH), 7.66–7.58 (1H, m, ArH), 7.55–7.50 (2H, m, ArH), 5.60 (1H, ddt, *J* = 17.2, 10.1, 7.1 Hz, H-5), 5.04–4.95 2H, m, H-6), 4.48–4.44 (1H, m, H-3), 2.40–2.30 (2H, m, H-4), 1.94 (1H, heptd, *J* = 6.7, 5.5 Hz, H-2), 0.86 (3H, d, *J* = 6.7 Hz, H-1 (A)), 0.85 (3H, d, *J* = 6.7 Hz, H-1 (B)); δ_C (126 MHz, $CDCl_3$) 137.7 (C-7), 133.6 (CH, ArCH), 132.7 (CH, C-5), 129.1 (CH, ArCH), 127.9 (CH, ArCH), 118.5 (CH_2, C-6), 88.1 (CH, C-3), 35.9 (CH_2, C-4), 31.0 (CH, C-2), 18.2 (CH_3, C-1 (A)), 17.4 (CH_3, C-1 (B)); *m/z* (ESI) 277 $[MNa]^+$; [HRMS (ESI): calc. for $C_{13}H_{18}NaO_3S^+$, 277.0869. Found $[MNa]^+$, 277.0864 (1.7 ppm error)].

Lab Book Ref.: LH629

2-Methylhex-5-en-3-yl 2-fluorobenzenesulfonate (435)

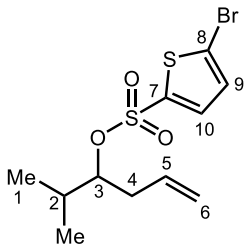


Following general Procedure H, to a solution of 2-methylhex-5-en-3-ol (149 mg, 1.31 mmol, 1.0 eq.) in DCM (5 mL) and pyridine (3 mL) was added 2-fluorobenzenesulfonyl chloride (255 mg, 1.31 mmol, 1.0 eq.) and DMAP (7.50 mg, 0.063 mmol, 0.05 eq.). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 15:1) gave the title compound **435** as a colourless oil (177 mg, 0.650 mmol, 50%); R_f 0.35 (cyclohexane:Et_2O, 10:1); ν_{max}/cm-1 (neat) 2969, 1477, 1366, 1183, 891, 762, 595; δ_H (500 MHz, $CDCl_3$) 7.91 (1H, ddd, *J* = 7.5, 6.7, 1.4 Hz, ArH), 7.66–7.60 (1H, m, ArH), 7.29 (1H, td, *J* = 7.5, 0.9 Hz, H-9), 7.22 (1H, ddd, *J* = 8.3, 7.5, 1.5 Hz, H-11), 5.64 (1 H, ddt, *J* = 17.2, 10.1, 7.1 Hz, H-5), 5.03 (1H, dd, *J* = 17.1, 1.0 Hz, H-6a), 4.97 (1H, dd, *J* = 10.1, 1.0 Hz, H-6b), 4.62–4.53 (1 H, m, H-3), 2.44–2.39 (2H, m, H-4), 2.04–1.93 (1H, m, H-2), 0.94–0.88 (6H, m, H-1); δ_C (126 MHz, $CDCl_3$) 159.4 (C, d, *J* = 258.7 Hz, C-12), 136.0 (CH, d, *J* = 8.4 Hz, ArCH), 132.5 (CH, C-5), 130.6 (CH,

ArCH), 126.0 (C, d, *J* = 13.9 Hz, C-7), 124.4 (CH, d, *J* = 4.0 Hz, C-9), 118.6 (CH_2, C-6), 117.4 (CH, *J* = 21.0 Hz, C-11), 89.4 (CH, C-3), 35.9 (CH_2, C-4), 31.1 (CH, C-2), 18.1 (CH_3, C-1 (A)), 17.4 (CH_3, C-1 (B)); δ_F (376 MHz, $CDCl_3$) –107.0 (CF); *m/z* (ESI) 295 $[MNa]^+$; [HRMS (ESI): calc. for $C_{13}H_{17}FNaO_3S^+$, 295.0775. Found $[MNa]^+$, 295.0770 (1.6 ppm error)].

Lab Book Ref.: LH634

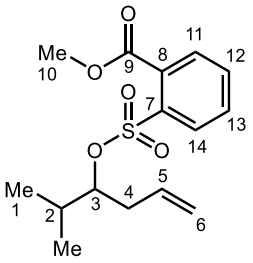
2-Methylhex-5-en-3-yl 5-bromothiophene-2-sulfonate (436)



Following general Procedure H, to a solution of 2-methylhex-5-en-3-ol (171 mg, 1.50 mmol, 1.0 eq.) in pyridine (4 mL) was added 5-bromothiophene-2-sulfonyl chloride (785 mg, 3.00 mmol, 2.0 eq.) and DMAP (18.0 mg, 0.150 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 30:1) gave the title compound **436** as a colourless oil (97.7 mg, 0.288 mmol, 19%); R_f 0.25 (cyclohexane:Et_2O, 10:1); ν_{max}/cm-1 (neat) 3327, 2972, 1375, 1178, 1087, 1048, 880, 608; δ_H (500 MHz, $CDCl_3$) 7.44 (1H, d, *J* = 4.2 Hz, ArH), 7.09 (1H, d, *J* – 4.2 Hz, ArH), 5.64 (1 H, ddt, *J* = 17.2, 10.1, 7.1 Hz, H-5), 5.09–5.01 (2H, m, H-6), 4.52–4.46 (1 H, m, H-3), 2.45–2.35 (2H, m, H-4), 1.98 (1H, heptd, *J* = 6.8, 5.2 Hz, H-2), 0.91 (6H, d, *J* = 6.8 Hz, H-1); δ_C (126 MHz, $CDCl_3$) 138.5 (C, ArC), 133.8 (CH, ArCH), 132.3 (CH, C-5), 130.5 (CH, ArCH), 121.3 (C, ArC), 118.8 (CH_2, C-6), 89.7 (CH, C-3), 35.8 (CH_2, C-4), 31.1 (CH, C-2), 18.1 (CH_3, C-1 (A)), 17.4 (CH_3, C-1 (B)); *m/z* (ESI) 360 $[MNa]^+$; [HRMS (ESI): calc. for $C_{11}H_{15}{}^{79}BrNaO_3S^+$, 360.9538. Found $[MNa]^+$, 360.9534 (1.2 ppm error)].

Lab Book Ref.: LH631

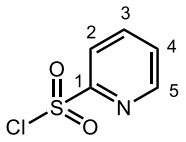
Methyl 2-(((2-methylhex-5-en-3-yl)oxy)sulfonyl)benzoate (437)



Following general Procedure H, to a solution of 2-methylhex-5-en-3-ol (144 mg, 1.25 mmol, 1.0 eq.) in DCM (5 mL) and pyridine (3 mL) was added methyl-2-chlorosulfonylbenzoate (585 mg, 2.50 mmol, 2.0 eq.) and DMAP (15.0 mg, 0.125 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 8:1) gave the title compound **437** as a colourless oil (278 mg, 0.889 mmol, 71%); R_f 0.25 (cyclohexane:Et_2O, 4:1); ν_{max}/cm-1 (neat) 2966, 1737, 1363, 1293, 1258, 1181, 1121, 1062, 896, 757, 584; δ_H (500 MHz, $CDCl_3$) 7.99 (1H, dd, *J* = 6.8, 2.5 Hz, ArH), 7.67–7.55 (3H, m, ArH), 5.65 (1 H, ddt, *J* = 17.2, 10.1, 7.1 Hz, H-5), 5.05–4.92 (2H, m, H-6), 4.63–4.57 (1H, m, H-3), 3.94 (3H, s, H-10), 2.41–2.36 (2H, m, H-4), 1.94 (1H, heptd, *J* = 6.8, 5.1 Hz, H-2), 0.92–0.85 (6H, m, H-1); δ_C (126 MHz, $CDCl_3$) 167.6 (C, C-9), 135.6 (C, ArC), 133.3 (CH, ArC), 133.2 (C, ArC), 132.7 (CH, C-5), 130.7 (CH, ArC), 129.6 (CH, ArC), 129.2 (CH, ArC), 118.4 (CH_2, C-6), 89.0 (CH, C-3), 53.2 (CH_3, C-10), 36.0 (CH_2, C-4), 31.0 (CH, C-2), 17.9 (CH_3, C-1 (A)), 17.2 (CH_3, C-1 (B)); *m/z* (ESI) 335 $[MNa]^+$; [HRMS (ESI): calc. for $C_{15}H_{20}NaO_3S^+$, 335.0924. Found $[MNa]^+$, 335.0919 (1.5 ppm error)].

Lab Book Ref.: LH633

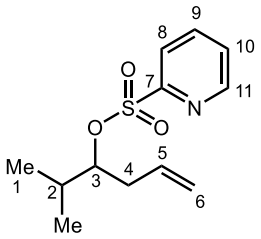
Pyridine-2-sulfonyl chloride (440)



To a solution of 2-mercaptopyridine (586 mg, 5.00 mmol) in concentrated H_2SO_4 (14 mL) was added slowly aq. NaOCl (13%, 21 mL) at 0 °C under formation of chlorine gas and the resulting mixture was stirred at 0 °C for 4 h. The reaction was quenched with H_2O and the product extracted with DCM (×3). The combined organic extracts

were dried ($MgSO_4$), filtered and carefully concentrated *in vacuo* to give the crude sulfonyl chloride **440**, which was used in the next step without further purification. δ_H (500 MHz, $CDCl_3$) 8.82 (1H, ddd, *J* = 4.6, 1.7, 0.9 Hz), 8.11 (1H, ddd, *J* = 7.9, 1.1, 0.9 Hz), 8.06 (1H, ddd, *J* = 7.9, 7.5, 1.7 Hz), 7.70 (1H, ddd, *J* = 7.5, 4.6, 1.1 Hz).

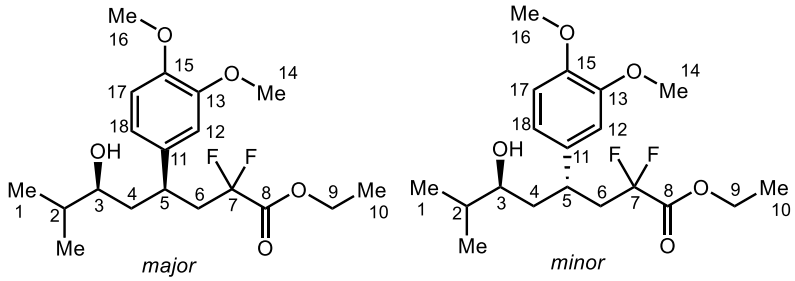
2-Methylhex-5-en-3-yl pyridine-2-sulfonate (438)



Following general Procedure H, to a solution of 2-methylhex-5-en-3-ol (144 mg, 1.25 mmol, 1.0 eq.) in pyridine (4 mL) was added pyridine-2-sulfonyl chloride **440** (448 mg, 2.50 mmol, 2.0 eq.) and DMAP (15.0 mg, 0.125 mmol, 0.1 eq.). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 8:1) gave the title compound **438** as a colourless oil (278 mg, 0.889 mmol, 71%); R_f 0.25 (cyclohexane:Et_2O, 4:1); ν_{max}/cm-1 (neat) 2966, 1737, 1363, 1293, 1258, 1181, 1121, 1062, 896, 757, 584; δ_H (500 MHz, $CDCl_3$) 8.74 (1H, ddd, *J* = 4.7, 1.7, 1.0 Hz, H-11), 8.03 (1H, ddd, *J* = 7.9, 7.7, 1.0 Hz, H-8), 7.93 (1H, ddd, *J* = 7.9, 7.7, 1.7 Hz, H-9), 7.54 (1H, ddd, *J* = 7.7, 4.7, 1.0 Hz, H-10), 5.61 (1 H, ddt, *J* = 17.2, 10.1, 7.1 Hz, H-5), 4.99 (1H, dd, *J* = 17.1, 1.1 Hz, H-6a), 4.92 (1H, dd, *J* = 10.1, 1.2 Hz, H-6b), 4.77–4.72 (1H, m, H-3), 2.45–2.39 (2H, m, H-4), 1.98 (1H, heptd, *J* = 6.8, 5.1 Hz, H-2), 0.88 (3H, d, *J* = 6.8 Hz, H-1 (A)), 0.87 (3H, d, *J* = 6.8 Hz, H-1 (B)); δ_C (126 MHz, $CDCl_3$) 155.5 (C, C-7), 150.3 (CH, C-11), 138.2 (CH, C-9), 132.7 (CH, C-5), 127.5 (CH, C-10), 123.2 (CH, C-8), 118.4 (CH_2, C-6), 90.0 (CH, C-3), 36.0 (CH_2, C-4), 31.2 (CH, C-2), 18.1 (CH_3, C-1 (A)), 17.4 (CH_3, C-1 (B)); *m/z* (ESI) 256 $[MH]^+$; [HRMS (ESI): calc. for $C_{12}H_{18}NO_3S^+$, 256.1002. Found $[MH]^+$, 256.0999 (1.0 ppm error)].

Lab Book Ref.: LH623

Ethyl 4-(3,4-dimethoxyphenyl)-2,2-difluoro-6-hydroxy-7-methyloctanoate (441)

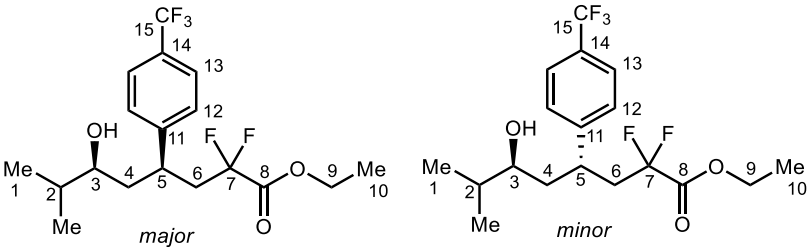


Following General Procedure I, ethyl 4-(3,4-dimethoxyphenyl)-2,2-difluoro-6-hydroxy-7-methyloctanoate **441** was prepared using 2-methylhex-5-en-3-yl 3,4-dimethoxybenzenesulfonate **431** (126 mg, 0.400 mmol). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 1:1) gave the title compound **441** as a yellow oil as an inseparable mixture of diastereoisomers (52.6 mg, 0.140 mmol, 35%, dr: 7:1); R_f 0.20 (cyclohexane:Et_2O, 3:1); ν_{max}/cm-1 (neat) 3545, 2961, 1760, 1513, 1260, 1220, 1142, 1087, 1025, 765, 731; δ_H (500 MHz, $CDCl_3$) 6.79 (1H, d, *J* = 8.2 Hz, H-17), 6.74 (1H, dd, *J* = 8.2, 2.0 Hz, H-18), 6.69 (1H, d, *J* = 2.0 Hz, H-12), 3.98 (1H, dq, *J* = 10.8, 7.2 Hz, H-9a), 3.94 (1H, dq, *J* = 10.8, 7.2 Hz, H-9b), 3.87 (3H, s, OMe), 3.83 (3H, s, OMe), 3.38 (1H, dt, *J* = 8.5, 4.2 Hz, H-3), 3.04–2.97 (1H, m, H-5), 2.53–2.32 (2H, m, H-6), 1.81 (1H, ddd, *J* = 14.0, 7.3, 3.9 Hz, H-4a), 1.74–1.60 (3H, m, H-4b, H-2, OH), 1.18 (3H, t, *J* = 7.2 Hz, H-10), 0.88 (3H, d, *J* = 6.8 Hz, H-1 (A), major), 0.87 (3H, d, *J* = 6.8 Hz, H-1 (B), major), 0.81 (6H, d, *J* = 6.8 Hz, H-1 (A+B), minor); δ_C (126 MHz, $CDCl_3$) 164.1 (C, t, *J* = 32.6 Hz, C-8, minor), 164.1 (C, t, *J* = 32.6 Hz, C-8, major), 149.1 (C, ArC, major), 149.0 (C, ArC, minor), 148.0 (C, ArC, major), 147.8 (C, ArC, minor), 136.0 (C, ArC, major), 135.1 (C, ArC, minor), 120.2 (CH, C-18, minor), 119.7 (CH, C-18, major), 115.9 (C, dd, *J* = 252.3, 248.9 Hz, C-7), 111.4 (CH, C-17, major), 111.2 (CH, C-17, minor), 111.2 (CH, C-12, minor), 111.0 (CH, C-12, major), 74.5 (CH, C-3, major), 73.7 (CH, C-3, minor), 62.8 (CH_2, C-9, major), 62.8 (CH_2, C-9, minor), 56.0 (CH_3, C-14, C-16), 42.0 (CH_2, t, *J* = 22.5 Hz, C-6, minor), 42.0 (CH_2, C-4, major), 41.2 (CH_2, C-4, minor), 40.7 (CH_2, t, *J* = 22.6 Hz, C-6, major), 36.7 (CH, dd, *J* = 5.2, 2.7 Hz, C-5, major), 36.0 (CH, dd, *J* = 5.4, 2.1 Hz, C-5, minor), 34.1 (CH, C-2, minor), 33.3 (CH, C-2, major), 19.0 (CH_3, C-1 (A), major), 18.5 (CH_3, C-1 (A), minor), 17.5 (CH_3, C-1 (B), minor), 16.6 (CH_3, C-1 (B), major), 13.8 (CH_3, C-10, minor), 13.8 (CH_3, C-10, major); δ_F (376 MHz, $CDCl_3$) –99.4 (CF_2, d, *J* = 260.0 Hz, minor), –100.1 (CF_2, d, *J* = 260.4 Hz, major), –106.6 (CF_2, d, *J* = 260.4 Hz, major), –

106.8 (CF2, d, *J* = 260.0 Hz, minor); *m/z* (ESI) 375 $[MH]^+$; [HRMS (ESI): calc. for $C_{19}H_{28}F_2O_5^+$, 375.1978. Found $[MH]^+$, 375.1979 (0.2 ppm error)].

Lab Book Ref.: LH603

Ethyl 2,2-difluoro-6-hydroxy-7-methyl-4-(4-(trifluoromethyl)phenyl)octanoate (442)

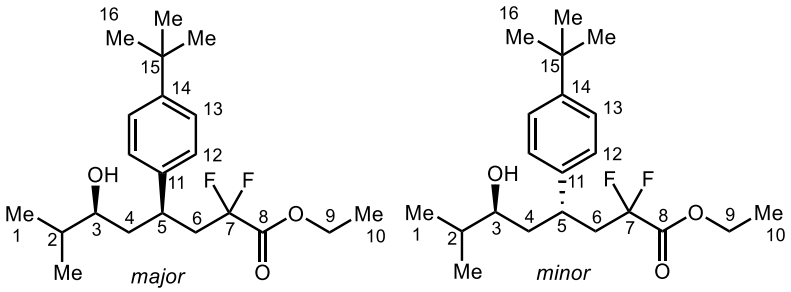


Following General Procedure I, ethyl 2,2-difluoro-6-hydroxy-7-methyl-4-(4-(trifluoromethyl)phenyl)octanoate **442** was prepared using 2-methylhex-5-en-3-yl 4-(trifluoromethyl)benzenesulfonate **432** (129 mg, 0.400 mmol). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 4:1) gave the title compound **442** as a yellow oil as an inseparable mixture of diastereoisomers (94.4 mg, 0.247 mmol, 62%, dr: 9:1); R_f 0.15 (cyclohexane:Et_2O, 5:1); ν_{max}/cm-1 (neat) 3418, 2964, 1760, 1321, 1164, 1122, 1085, 1068, 1017, 841, 734; δ_H (500 MHz, $CDCl_3$) 7.55 (2H, d, *J* = 8.2 Hz, H-13), 7.33 (2H, d, *J* = 8.2 Hz, H-12), 4.00 (1H, dq, *J* = 10.7, 7.2 Hz, H-9a), 3.97 (1H, dq, *J* = 10.7, 7.2 Hz, H-9b), 3.40 (1H, dt, *J* = 8.8, 4.2 Hz, H-3), 3.20 (1H, qd, *J* = 8.4, 5.7 Hz, H-5), 2.57 (1H, br s, OH), 2.56–2.40 (2H, m, H-6), 1.83 (1H, ddd, *J* = 14.0, 8.2, 3.9 Hz, H-4a), 1.73–1.59 (2H, m, H-4b, H-2), 1.19 (3H, t, *J* = 7.2 Hz, H-10), 0.88 (3H, d, *J* = 6.8 Hz, H-1 (A)), 0.87 (3H, d, *J* = 6.8 Hz, H-1 (B)); δ_C (126 MHz, $CDCl_3$) 164.1 (C, t, *J* = 32.5 Hz, C-8, major+minor), 148.7 (C, C-11, minor), 148.2 (C, C-11, major), 129.2 (C, q, *J* = 32.4 Hz, C-14, major+minor), 128.2 (CH, C-12, major), 128.0 (CH, C-12, minor), 125.6 (CH, q, *J* = 7.4 Hz, C-13, major+minor), 124.3 (C, q, *J* = 272.1 Hz, C-15, major+minor), 115.8 (C, t, *J* = 251.2 Hz, C-7, major+minor), 74.1 (CH, C-3, major), 73.6 (CH, C-3, minor), 63.0 (CH_2, C-9, major), 63.0 (CH_2, C-9, minor), 41.8 (CH_2, C-4, major), 41.5 (CH_2, t, *J* = 28.0 Hz, C-6, minor), 41.0 (CH_2, C-4, minor), 39.9 (CH_2, t, *J* = 22.7 Hz, C-6, major), 36.5–36.4 (CH, m, C-5, major), 36.4–36.3 (CH, m, C-5, minor), 34.3 (CH, C-2, minor), 33.5 (CH, C-2, major), 19.0 (CH_3, C-1 (A), major), 18.5 (CH_3, C-1 (A), minor), 16.8 (CH_3, C-1 (B), minor), 16.7 (CH_3, C-1 (B),

major), 13.8 (CH_3, C-10, major+minor); δ_F (376 MHz, $CDCl_3$) –62.4 (CF_3, minor), –62.5 (CF_3, major), –100.9 (CF_2, d, J = 261.3 Hz, minor), –101.5 (CF_2, d, J = 262.0 Hz, major), –105.2 (CF_2, d, J = 262.0 Hz, major), –105.7 (CF_2, d, J = 261.3 Hz, minor); *m/z* (ESI) 383 $[MH]^+$; [HRMS (ESI): calc. for $C_{18}H_{23}NaF_5O_3^+$, 383.1640. Found $[MH]^+$, 383.1655 (3.8 ppm error)].

Lab Book Ref.: LH609

Ethyl 4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-6-hydroxy-7-methyloctanoate (443)

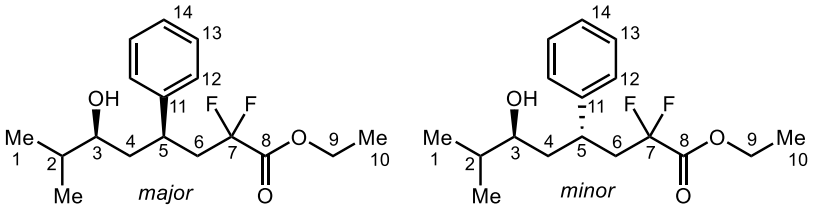


Following General Procedure I, ethyl 4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-6-hydroxy-7-methyloctanoate **443** was prepared using 2-methylhex-5-en-3-yl 4-(*tert*-butyl)benzenesulfonate **433** (124 mg, 0.400 mmol). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 11:1) gave the title compound as a yellow oil as an inseparable mixture of diastereoisomers (73.7 mg, 0.199 mmol, 50%, dr: 11:1); R_f 0.20 (cyclohexane:Et_2O, 5:1); ν_{max}/cm-1 (neat) 3398, 2961, 1760, 1220, 1191, 1110, 1085, 1019, 832, 775; δ_H (500 MHz, $CDCl_3$) 7.31 (2H, d, J = 8.3 Hz, ArH), 7.13 (2H, d, J = 8.3 Hz, ArH), 3.89 (1H, dq, J = 10.8, 7.2 Hz, H-9a), 3.81 (1H, dq, J = 10.8, 7.2 Hz, H-9b), 3.40 (1H, dt, J = 8.3, 4.0 Hz, H-3), 3.03 (1H, qd, J = 7.7, 4.8 Hz, H-5), 2.56–2.36 (2H, m, H-6), 1.83 (1H, ddd, J = 14.1, 7.3, 3.6 Hz, H-4a), 1.75–1.58 (2H, m, H-4b, H-2), 1.29 (9H, s, H-16), 1.15 (3H, t, J = 7.2 Hz, H-10), 0.89 (3H, d, J = 6.8 Hz, H-1 (A), major), 0.89 (3H, d, J = 6.8 Hz, H-1 (B), major), 0.82 (6H, m, H-1 (A+B), minor); δ_C (126 MHz, $CDCl_3$) 164.1 (C, t, J = 32.7 Hz, C-8, major+minor), 149.9 (C, ArC, major), 149.6 (C, ArC, minor), 140.2 (C, ArC, major), 139.4 (C, ArC, minor), 127.7 (CH, ArCH, minor), 127.5 (CH, ArCH, major), 125.7 (CH, ArCH, major), 125.4 (CH, ArCH, minor), 116.0 (C, dd, J = 252.1, 248.6 Hz, C-7, major+minor), 74.6 (CH, C-3, major), 73.6 (CH, C-3, minor), 62.7 (CH_2, C-9, major), 62.6 (CH_2, C-9, minor), 42.1 (CH_2, C-4, major), 42.0 (CH_2, t, J = 22.6 Hz, C-6, minor),

41.2 (CH_2, C-4, minor), 40.7 (CH_2, t, *J* = 22.7 Hz, C-6, major), 36.7 (CH, dd, *J* = 5.7, 2.5 Hz, C-5, major), 35.9 (CH, dd, *J* = 6.5, 2.5 Hz, C-5, minor), 34.6 (CH, C-2, major), 34.2 (CH, C-2, minor), 33.5 (C, C-15, minor), 33.5 (C, C-15, major), 31.5 (CH_3, C-18, minor), 31.5 (CH_3, C-18, major), 19.0 (CH_3, C-1 (A), major), 18.6 (CH_3, C-1 (A), minor), 17.4 (CH_3, C-1 (B), minor), 16.7 (CH_3, C-1 (B), major), 14.3 (CH_3, C-10, minor), 13.8 (CH_3, C-10, major); δ_F (376 MHz, $CDCl_3$) –99.4 (CF_2, d, *J* = 260.0 Hz, minor), –100.1 (CF_2, d, *J* = 260.4 Hz, major), –106.6 (CF_2, d, *J* = 260.4 Hz, major), –106.8 (CF_2, d, *J* = 260.0 Hz, minor); *m/z* (ESI) 393 $[MNa]^+$; [HRMS (ESI): calc. for $C_{21}H_{32}NaF_2O_3^+$, 393.2212. Found $[MNa]^+$, 393.2209 (0.9 ppm error)].

Lab Book Ref.: LH602

Ethyl 2,2-difluoro-6-hydroxy-7-methyl-4-phenyloctanoate (444)

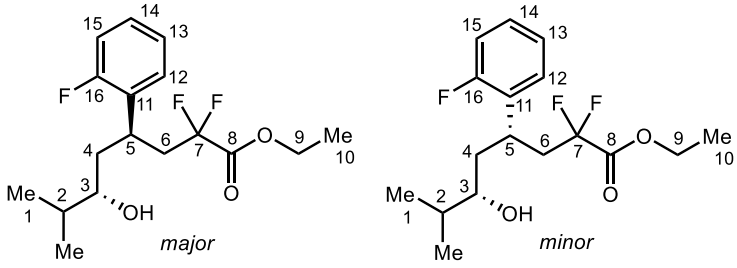


Following General Procedure I, ethyl 2,2-difluoro-6-hydroxy-7-methyl-4-phenyloctanoate **444** was prepared using 2-methylhex-5-en-3-yl benzenesulfonate **434** (102 mg, 0.400 mmol). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 9:1) gave the title compound **444** as a yellow oil as an inseparable mixture of diastereoisomers (48.9 mg, 0.156 mmol, 39%, dr: 10:1); R_f 0.15 (cyclohexane:Et_2O, 5:1); ν_{max}/cm-1 (neat) 3447, 2962, 1759, 1219, 1189, 1092, 1068, 1030, 764, 733, 700; δ_H (500 MHz, $CDCl_3$) 7.32–7.27 (2H, m, ArH), 7.23–7.16 (3H, m, ArH), 3.95 (1H, dq, *J* = 10.7, 7.2 Hz, H-9a), 3.91 (1H, dq, *J* = 10.7, 7.2 Hz, H-9b), 3.39 (1H, dt, *J* = 8.6, 4.2 Hz, H-3), 3.07 (1H, qd, *J* = 7.6, 4.9 Hz, H-5), 2.58–2.34 (2H, m, H-6), 2.05 (1H, br s, OH), 1.84 (1H, ddd, *J* = 14.1, 7.5 4.0 Hz, H-4a), 1.77–1.60 (2H, m, H-4b, H-2), 1.19 (3H, t, *J* = 7.2 Hz, H-10), 0.89 (3H, d, *J* = 6.8 Hz, H-1 (A)), 0.88 (3H, d, *J* = 6.8 Hz, H-1 (B)); δ_C (126 MHz, $CDCl_3$) 164.1 (C, t, *J* = 32.7 Hz, C-8, major+minor), 143.6 (C, C-11, major), 142.7 (C, C-11, minor), 128.8 (CH, ArCH, major) 128.6 (CH, ArCH, minor), 128.1 (CH, ArCH, minor), 127.9 (CH, ArCH, major), 127.0 (CH, ArCH, major), 126.9 (CH, ArCH, minor), 115.9 (C, dd, *J* = 252.1, 249.2 Hz, C-7,

major), 114.9 (C, t, *J* = 252.5 Hz, C-7, minor), 74.5 (CH, C-3, major), 73.7 (CH, C-3, minor), 62.8 (CH_2, C-9, major), 62.8 (CH_2, C-9, minor), 42.0 (CH_2, C-4, major), 41.8 (CH_2, t, *J* = 22.6 Hz, C-6, minor), 41.2 (CH_2, C-4, minor), 40.5 (CH_2, t, *J* = 22.6 Hz, C-6, major), 37.0 (CH, dd, *J* = 5.3, 2.8 Hz, C-5, major), 36.4 (CH, dd, *J* = 5.5, 2.4 Hz, C-5, minor), 34.2 (CH, C-2, minor), 33.3 (CH, C-2, major), 19.0 (CH_3, C-1 (A), major), 18.5 (CH_3, C-1 (A), minor), 17.4 (CH_3, C-1 (B), minor), 16.7 (CH_3, C-1 (B), major), 14.0 (CH_3, C-10, minor), 13.8 (CH_3, C-10, major); δ_F (376 MHz, $CDCl_3$) –100.0 (CF_2, d, *J* = 260.2 Hz, minor), –100.6 (CF_2, d, *J* = 260.7 Hz, major), –106.0 (CF_2, d, *J* = 260.7 Hz, major), –106.3 (CF_2, d, *J* = 260.2 Hz, minor); *m/z* (ESI) 337 $[MNa]^+$; [HRMS (ESI): calc. for $C_{17}H_{24}NaF_2O_3^+$, 337.1586. Found $[MNa]^+$, 337.1587 (0.3 ppm error)].

Lab Book Ref.: LH604

Ethyl 2,2-difluoro-4-(2-fluorophenyl)-6-hydroxy-7-methyloctanoate (445)

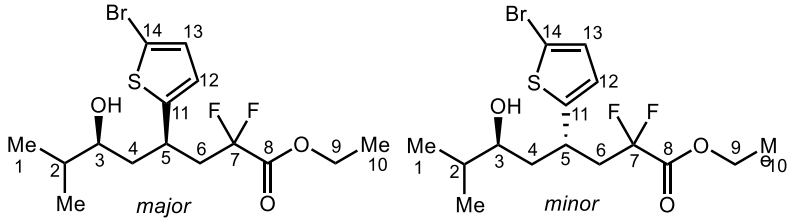


Following General Procedure I, ethyl 2,2-difluoro-4-(2-fluorophenyl)-6-hydroxy-7-methyloctanoate **445** was prepared using 2-methylhex-5-en-3-yl 2-fluorobenzenesulfonate **435** (109 mg, 0.400 mmol). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 5:1) gave the title compound **445** as a yellow oil as an inseparable mixture of diastereoisomers (83.4 mg, 0.251 mmol, 63%, dr: 10:1); R_f 0.20 (cyclohexane:Et_2O, 5:1); ν_{max}/cm-1 (neat) 3439, 2962, 1760, 1492, 1221, 1190, 1090, 1034, 757, 735; δ_H (500 MHz, $CDCl_3$) 7.23–7.15 (2H, m, ArH), 7.07 (1H, ddd, *J* = 8.2, 7.6, 1.0 Hz, H-14), 7.00 (1H, dd, *J* = 10.8, 8.2 Hz, H-13), 4.02 (1H, dq, *J* = 10.8, 7.2 Hz, H-9a), 4.01 (1H, dq, *J* = 10.8, 7.2 Hz, H-9b), 3.39 (1H, dt, *J* = 8.8, 4.3 Hz, H-3), 3.36–3.30 (1H, m, H-5), 2.66–2.42 (2H, m, H-6), 2.07 (1H, br s, OH), 1.83 (1H, ddd, *J* = 14.0, 7.9, 4.1 Hz, H-4a), 1.75 (1H, ddd, *J* = 14.0, 8.3, 6.8 Hz, H-4b), 1.66 (1H, heptd, *J* = 6.8, 4.8 Hz, H-2), 1.23 (3H, t, *J* = 7.2 Hz, H-10), 0.89 (3H, d, *J* =

6.8 Hz, H-1a), 0.88 (3H, d, *J* = 6.8 Hz, H-1b); δ_C (126 MHz, $CDCl_3$) 164.1 (C, t, *J* = 32.7 Hz, C-8, major+minor), 161.4 (C, d, *J* = 245.7 Hz, C-16, minor), 161.1 (C, d, *J* =245.9 Hz, C-16, major), 131.0 (C, d, *J* = 13.7 Hz, C-11, minor), 130.4 (C, d, *J* = 13.6 Hz, C-11, major), 129.8 (CH, d, *J* = 5.1 Hz, ArCH, major), 129.7 (CH, d, *J* = 5.4 Hz, ArCH, minor), 128.5 (CH, d, *J* = 8.6 Hz, ArCH, major), 128.4 (CH, d, *J* = 8.6 Hz, ArCH, minor), 124.3 (CH, d, *J* = 3.5 Hz, C-14, major+minor), 116.0 (C, t, *J* = 250.9 Hz, C-7, major+minor), 115.8 (CH, C-13, major+minor), 74.4 (CH, C-3, major), 74.0 (CH, C-3, minor), 62.9 (CH_2, C-9, major), 62.8 (CH_2, C-9, minor), 40.3 (CH_2, C-4, major+minor), 38.8 (CH_2, td, *J* = 22.6, 2.1 Hz, C-6, major+minor), 33.4 (CH, C-2, major+minor), 31.4 (CH, t, *J* = 4.2 Hz, C-5, major+minor), 19.0 (CH_3, C-1 (A), major), 18.5 (CH_3, C-1 (A), minor), 17.4 (CH_3, C-1 (B), minor), 16.7 (CH_3, C-1 (B), major), 13.8 (CH_3, C-10, major+minor); δ_F (376 MHz, $CDCl_3$) –101.5 (CF_2, d, *J* = 261.0 Hz, minor), –102.0 (CF_2, d, *J* = 261.6 Hz, major), –105.4 (CF_2, d, *J* = 261.6 Hz, major), –105.9 (CF_2, d, *J* = 261.0 Hz, minor), –116.7 (CF); *m/z* (ESI) 355 $[MNa]^+$; [HRMS (ESI): calc. for $C_{17}H_{23}NaF_3O_3^+$, 355.1491. Found $[MH]^+$, 355.1486 (1.6 ppm error)].

Lab Book Ref.: LH610

Ethyl 4-(5-bromothiophen-2-yl)-2,2-difluoro-6-hydroxy-7-methyloctanoate (446)

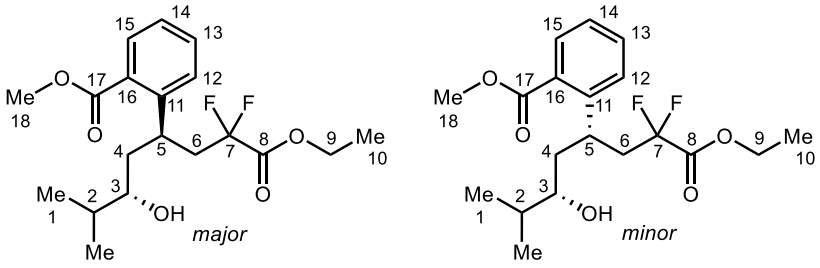


Following General Procedure I, ethyl 4-(5-bromothiophen-2-yl)-2,2-difluoro-6-hydroxy-7-methyloctanoate **446** was prepared using 2-methylhex-5-en-3-yl 5-bromothiophene-2-sulfonate **436** (135 mg, 0.400 mmol). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 8:1) gave the title compound **446** as a yellow oil as an inseparable mixture of diastereoisomers (87.8 mg, 0.220 mmol, 55%, dr: 5:1); R_f 0.20 (cyclohexane:Et_2O, 5:1); ν_{max}/cm-1 (neat) 3435, 2961, 2930, 1759, 1212, 1191, 1093, 1046, 967, 795, 763, 732; δ_H (500 MHz, $CDCl_3$) 6.84 (1H, d, *J* = 3.7 Hz, ArH), 6.60 (1H, d, *J* = 3.7 Hz, ArH), 4.14 (1H, dq, *J* = 10.8, 7.2 Hz, H-9a), 4.10 (1H, dq, *J* = 10.8, 7.2 Hz, H-9b), 3.46–3.37 (2H, m, H-3, H-5), 2.54–2.38 (2H, m, H-6), 2.03 (1H, br s,

OH), 1.82 (1H, ddd, *J* = 14.0, 7.9, 4.1 Hz, H-4a), 1.78–1.62 (2H, m, H-4b, H-2), 1.28 (3H, t, *J* = 7.2 Hz, H-10), 0.91 (3H, d, *J* = 6.9 Hz, H-1 (A)), 0.90 (3H, d, *J* = 6.9 Hz, H-1 (B)); δ_C (126 MHz, $CDCl_3$) 164.0 (C, t, *J* = 32.6 Hz, C-8, major+minor), 149.5 (C, C-11, major), 148.4 (C, C-11, minor), 129.5 (CH, C-13, minor), 129.4 (CH, C-13, major), 126.2 (CH, C-12, minor), 125.3 (CH, C-12, major), 115.6 (dd, *J* = 252.0, 250.1 Hz, C-7, major+minor), 110.3 (C, C-14, minor), 110.3 (C, C-14, major), 74.0 (CH, C-3, major), 73.5 (CH, C-3, minor), 63.2 (CH_2, C-9, major), 63.1 (CH_2, C-9, minor), 42.7 (CH_2, t, *J* = 22.9 Hz, C-6, minor), 42.6 (CH_2, C-4, major), 42.1 (CH_2, C-4, minor), 41.0 (CH_2, t, *J* = 22.8 Hz, C-6, major), 34.3 (CH, C-2, minor), 33.5 (CH, C-2, major), 32.7 (CH, dd, *J* = 5.5, 3.6 Hz, C-5, major), 32.1–32.0 (CH, m, C-5, minor), 18.9 (CH_3, C-1 (A), major), 18.5 (CH_3, C-1 (A), minor), 17.5 (CH_3, C-1 (B), minor), 16.7 (CH_3, C-1 (B), major), 14.3 (CH_3, C-10, minor), 13.9 (CH_3, C-10, major); δ_F (376 MHz, $CDCl_3$) –100.9 (CF_2, d, *J* = 262.6 Hz, minor), –100.6 (CF_2, d, *J* = 263.0 Hz, major), –105.7 (CF_2, d, *J* = 263.0 Hz, major), –106.3 (CF_2, d, *J* = 262.6 Hz, minor); *m/z* (ESI) 421 $[MNa]^+$; [HRMS (ESI): calc. for $C_{15}H_{21}{}^{79}BrF_2O_3S^+$, 421.0255. Found $[MNa]^+$, 421.0251 (1.1 ppm error)].

Lab Book Ref.: LH621

Methyl 2-(1-ethoxy-2,2-difluoro-6-hydroxy-7-methyl-1-oxooctan-4-yl)benzoate (447)

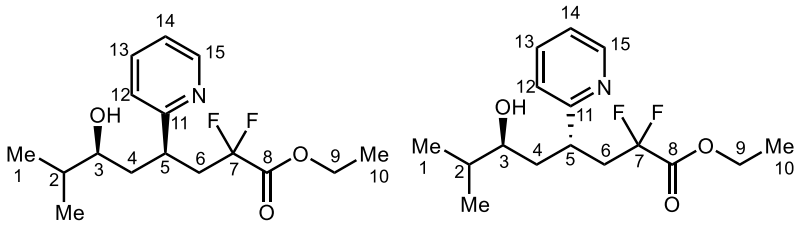


Following General Procedure I, methyl 2-(1-ethoxy-2,2-difluoro-6-hydroxy-7-methyl-1-oxooctan-4-yl)benzoate **447** was prepared using methyl 2-(((2-methylhex-5-en-3-yl)oxy)sulfonyl) benzoate **437** (125 mg, 0.400 mmol). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 6:1) gave the title compound **447** as a yellow oil as an inseparable mixture of diastereoisomers (71.4 mg, 0.192 mmol, 48%, dr: >20:1); R_f 0.10 (cyclohexane:Et_2O, 5:1); ν_{max}/cm-1 (neat) 3525, 2959, 1762, 1710, 1296,

1263, 1221, 1191, 1073, 1044, 911, 762, 730; δ_H (400 MHz, $CDCl_3$) 7.76 (1H, d, *J* = 7.8 Hz, H-15), 7.47 (1H, dd, *J* = 7.8, 7.5 Hz, ArH), 7.38 (1H, d, *J* = 7.8 Hz, H-12), 7.24 (1H, dd, *J* = 7.8, 7.5 Hz, ArH), 4.12–3.99 (2H, m, H-9), 3.90 (3H, s, H-18), 3.51–3.41 (1H, m, H-3), 2.62–2.40 (2H, m, H-6), 2.34 (1H, br s, OH), 1.85 (1H, ddd, *J* = 14.1, 7.7, 3.8 Hz, H-4a), 1.74 (1H, ddd, *J* = 14.1, 9.1, 5.5 Hz, H-4b), 1.67–1.54 (1H, m, H-2), 1.23 (3H, t, *J* = 7.2 Hz, H-10), 0.89 (3H, d, *J* = 7.1 Hz, H-1 (A)), 0.87 (3H, d, *J* = 7.1 Hz, H-1 (B)); δ_C (101 MHz, $CDCl_3$) 168.8 (C, C-17), 164.1 (C, t, *J* = 32.6 Hz, C-8), 145.5 (C, ArC), 132.1 (CH, ArCH), 130.4 (CH, C-15), 130.0 (CH, ArCH), 127.8 (CH, C-12), 126.4 (CH, ArCH), 115.9 (C, t, *J* = 251.2 Hz, C-7), 74.7 (CH, C-3), 62.9 (CH_2, C-9), 52.5 (CH_3, C-18), 42.5 (CH_2, C-4), 40.2 (CH_2, t, *J* = 22.4 Hz, C-6), 33.7 (CH, C-2), 31.4–31.3 (CH, m, C-5), 18.9 CH_3, C-1 (A)), 17.3 (CH_3, C-1 (B)), 13.8 (CH_3, C-10); δ_F (376 MHz, $CDCl_3$) –102.2 (CF_2, d, *J* = 260.7 Hz), –104.2 (CF_2, d, *J* = 260.7 Hz); *m/z* (ESI) 373 $[MH]^+$; [HRMS (ESI): calc. for $C_{19}H_{26}F_2O_5^+$, 373.1821. Found $[MH]^+$, 373.1822 (0.3 ppm error)].

Lab Book Ref.: LH776

Ethyl 2,2-difluoro-6-hydroxy-7-methyl-4-(2-pyridin)octanoate (448)



Following General Procedure I, ethyl 2,2-difluoro-6-hydroxy-7-methyl-4-(2-pyridin)octanoate **448** was prepared 2-methyl-5-hexen-3-pyridine-2-sulfonate **438** (102 mg, 0.400 mmol). Purification by FCC (SiO_2, cyclohexane:diethyl ether, 4:1) gave the title compound **448** as a yellow oil as an inseparable mixture of diastereoisomers (88.9 mg, 0.282 mmol, 70%, dr: 2:1);

Diastereomer A (28.0 mg, 0.089 mmol, 22%):

R_f 0.25 (cyclohexane:EtOAc, 3:1); ν_{max}/cm^{-1} (neat) 3421, 2960, 1762, 1439, 1190, 1080, 782; δ_H (500 MHz, $CDCl_3$) 8.54 (1H, ddd, *J* = 4.9, 1.9, 1.0 Hz, H-15), 7.62 (1H, td, *J* = 7.7, 1.9 Hz, H-13), 7.21 (1H, dt, *J* = 7.7, 1.0 Hz, H-12), 7.15 (1H, ddd, *J* = 7.7,

4.9, 1.0 Hz, H-14), 4.11 (1H, dq, *J* = 10.8, 7.2 Hz, H-9a), 4.11 (1H, dq, *J* = 10.8, 7.2 Hz, H-9b), 3.52–3.42 (1H, m, H-3), 2.95 (1H, ddd, *J* = 10.7, 5.4, 2.2 Hz, H-5), 2.85–2.71 (1H, m, H-6a), 2.51–2.35 (1H, m, H-6b), 1.96 (1H, ddd, *J* = 14.1, 10.6, 2.2 Hz, H-4a), 1.73 (1H, ddd, *J* = 14.1, 10.7, 3.7 Hz, H-4b), 1.62–1.49 (1H, m, H-2), 1.26 (3H, t, *J* = 7.2 Hz, H-10), 0.86 (3H, d, *J* = 6.5 Hz, H-1a), 0.85 (3 H, d, *J* = 6.5 Hz, H-1b); δ_c (126 MHz, $CDCl_3$) 164.2 (C, t, *J* = 34.2 Hz, C-8), 162.4 (C, C-11), 149.2 (CH, C-15), 136.9 (CH, C-13), 124.0 (CH, C-12), 122.0 (CH, C-14), 116.0 (C, t, *J* = 250.9 Hz, CF_2, C-7) 73.2 (CH, C-3), 62.9 (CH_2, C-9), 40.2 (CH_2, C-4), 39.6 (CH_2, t, *J* = 22.5 Hz, C-6), 38.0 (CH, app t, *J* = 5.1 Hz, C-5), 34.3 (CH, C-2), 18.7 (CH_3, C-1 (A)), 17.4 (CH_3, C-1 (B)), 14.0 (CH_3, C-10); δ_F (376 MHz, $CDCl_3$) –102.8 (CF_2, d, *J* = 259.3 Hz), –105.1 (CF_2, d, *J* = 259.3 Hz); *m/z* (ESI) 338 $[MNa]^+$; [HRMS (ESI): calc. for $C_{16}H_{23}F_2NNaO_3^+$, 338.1538. Found $[MH]^+$, 338.1537 (0.3 ppm error)].

Lab Book Ref.: LH625_F2

Diastereomer B (60.8 mg, 0.193 mmol, 48%):

R_f 0.20 (cyclohexane:EtOAc, 3:1); ν_{max}/cm^{-1} (neat) 3394, 2960, 1762, 1438, 1190, 1082, 781; δ_H (500 MHz, $CDCl_3$) 8.53 (1H, ddd, *J* = 4.9, 1.9, 0.9 Hz, H-15), 7.60 (1H, td, *J* = 7.7, 1.9 Hz, H-13), 7.17 (1H, dd, *J* = 7.7, 1.1 Hz, H-12), 7.13 (1H, ddd, *J* = 7.7, 4.9, 1.1 Hz, H-14), 4.13 (1H, dq, *J* = 10.7, 7.2 Hz, H-9a), 4.09 (1H, dq, *J* = 10.7, 7.2 Hz, H-9b), 3.37 (1H, ddd, *J* = 9.0, 5.1, 3.4 Hz, H-3), 3.34–3.26 (1H, m, H-5), 2.93–2.78 (1H, m, H-6a), 2.44 (1H, ddt, *J* = 14.3, 6.9, 3.4 Hz, H-6b), 2.18 (1H, br s, OH), 1.88 (1H, ddd, *J* = 14.2, 7.7, 3.4 Hz, H-4a), 1.78 (1H, ddd, *J* = 14.2, 9.0, 6.0 Hz, H-4b), 1.68–1.56 (1H, m, H-2), 1.25 (3 H, t, *J* = 7.2 Hz, H-10), 0.88 (3H, d, *J* = 6.9 Hz, H-1a), 0.87 (3H, d, *J* = 6.9 Hz, H-1b); δ_c (126 MHz, $CDCl_3$) 164.3 (C, t, *J* = 32.8 Hz, C-8), 163.2 (C, C-11), 149.3 (CH, C-15), 136.9 (CH, C-13), 123.5 (CH, C-12), 121.9 (CH, C-14), 116.1 (C, t, *J* = 250.8 Hz, CF_2, C-7), 74.4 (CH, C-3), 62.9 (CH_2, C-9), 40.8 (CH_2, C-4), 38.9 (CH_2, t, *J* = 22.5 Hz, C-6), 38.1 (CH, t, *J* = 3.2 Hz, C-5), 33.9 (CH, C-2), 18.9 (CH_3, C-1 (A)), 17.2 (CH_3, C-1 (B)), 14.0 (CH_3, C-10); δ_F (376 MHz, $CDCl_3$) –103.3 (CF_2, d, *J* = 260.0 Hz), –104.9 (CF_2, d, *J* = 260.0 Hz); *m/z* (ESI) 316 $[MH]^+$; [HRMS (ESI): calc. for $C_{16}H_{24}F_2NO_3^+$, 316.1719. Found $[MH]^+$, 316.1721 (0.8 ppm error)].

Lab Book Ref.: LH625_F3

Abbreviations

4CzIPN	2,4,5,6-Tetra(9*H*-carbazol-9-yl)-isophthalonitrile
1-CN	1-Cyanonaphthalene
A	Acceptor
ACCN	1,1'-Azobis(cyanocyclohexane)
AIBN	2,2-Azobis-2-methylpropionitrile
app.	Apparent
aq.	Aqueous
Ar	Aryl
ATRA	Atom transfer radical addition
ATRE	Atom transfer radical elimination
BDE	Bond dissociation energy
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bpy	2,2’-Bipyridine
bpz	2,2′-Bipyrazine
br	broad
Cy	Cyclohexyl
COSY	Correlation spectroscopy
d	Doublet
D	Donator
DEPT	Distortionless enhancement by polarisation transfer
dap	2,6-Diacetylpyridine

DBB	4,4-Di-*tert*-butylbiphenyl
DCA	9,10-Dicyanoanthracene
DCC	Dicyclohexylcarbodiimide
DCM	Dichlormethane
DFT	Density functional theory
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dtbbpy	4,4'-*Bis*(1,1-dimethylethyl)-2,2'-bipyridine-*N*1,*N*1
E	Electrophile
EDA	Electron donor-acceptor
EI	Electron impact ionisation
eq.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
ether	Diethyl ether
EtOAc	Ethyl acetate
EWG	Electron withdrawing group
FCC	Flash column chromatography
g	Gram(s)
h	Hour(s)
HAT	Hydrogen atom transfer
HMBC	Heteronuclear multiple bond correlation

HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
HRMS	High Resolution Mass Spectroscopy
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
i	*Iso*
IR	Infra-red
*i*PrOH	Isopropanol
ISC	Intersystem crossing
KO^{t}Bu	Potassium *tert*-butoxide
L	Ligand
LDA	Lithium di*iso*prpylamine
LUMO	Lowest unoccupied molecular orbital
LED	Light emitting diode
m	Multiplet
M	Molar
m/z	Mass to charge ratio
M^+/M^-	Molecular ion
Me	Methyl
MeCN	Acetonitrile
min.	Minutes
mL	Millilitre
mp.	Melting point
MLCT	Metal ligand charge transfer

MS	Mass spectroscopy
NEt_3	Triethylamine
*n*Hex	*n*-Hexyl
NPHI/Phth	Phthalimide
Nuc	Nucleophile
NMR	Nuclear magnetic resonance
PC	Photocatalyst
PCET	Proton-coupled electron transfer
Ph	Phenyl
ppy	2-Penylpyridinato
ppm	Parts per million
PTH	*N*-Phenylphenothiazine
q	Quartet
RAE	Redox-active ester
rt	Room temperature
s	Singlet
SCE	Saturated calomel electrode
SET	Single electron transfer
SOMO	Singly occupied molecular orbital
t	Triplet
TBS	*tert*-Butyldimehtylsilyl
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TMS	Trimethylsilyl

TLC	Thin-layer chromatography
TTET	Triplet-triplet energy transfer
δ	Chemical shift

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