Palladium Mediated Allylic Fluorination

Charlotte Hollingworth

A thesis submitted to the Board of the Faculty of Physical Sciences in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Oxford

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To My Sister,

For every laugh we have shared,
For every tear you wiped away,
For every memory we've made,
…. for everything.

Author's Declaration

The work presented in this thesis was conducted at the Chemistry Research Laboratory at the University of Oxford under the supervision of Professor Véronique Gouverneur. All the work is my own, except where otherwise stated, and has not been submitted for any other degree at this or any other university.

Charlotte Hollingworth

July 2013

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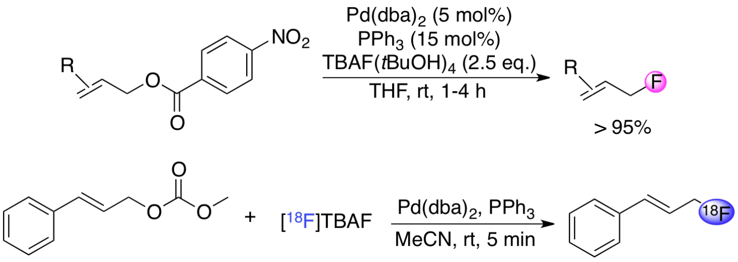
In this thesis, the construction of the allylic fluorides under palladium catalysis was investigated.

Chapter 1 provides a general introduction to organofluorine compounds and the use of palladium for the formation of both Csp^2- and Csp^3-F bonds. The aims of the thesis are presented.

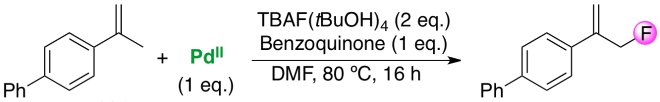
In **Chapter 2** the identification that a *p*-nitrobenzoate is the optimum leaving group under Pd-catalysis to give allyl fluorides is described. A range of allylic fluorides was synthesized in 35->95% yield using the nucleophilic fluorinating reagent, TBAF(*t*BuOH)$_4$. To further develop this transformation we have examined the effect of a variety of leaving groups and phosphine ligands. This methodology led to the development of the first transition metal-mediated C-^{18}F bond formation.



Scheme A. Pd-catalysed nucleophilic allylic fluorination

The development of Ir-catalysed fluorination of allylic carbonates to give allylic fluorides is also discussed. This system provided access to branched, *E*- and *Z*-linear allylic fluorides in a regioselective manner. This methodology was also translated to ^{18}F radiochemistry.

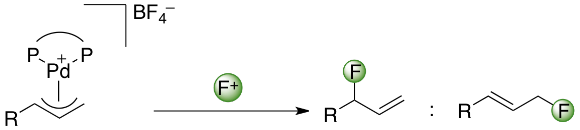
In **Chapter 3** the synthesis of allylic fluorides *via* a C-H functionalisation with Pd and nucleophilic source of fluorine was investigated. Comprehensive screening of Pd sources, fluoride reagents and additives was performed. The presence of a quinone was found to be crucial for this transformation.



294 **158c** ≤ 65%

Scheme B. Pd-mediated nucleophilic C-H fluorination

Chapter 4 describes the synthesis and characterization of a series of allylpalladium(II) complexes and their subsequent reactivity towards a range of electrophilic fluorination reagents.



Scheme C. Fluorination of isolated allylpalladium complexes

Chapter 5 gives full experimental procedures and characterization data for all compounds.

Acknowledgements

First and foremost I would like to thank my supervisor Professor Véronique Gouverneur for her constant support and guidance throughout my DPhil. I am grateful for the opportunity to have been involved in this exciting research. I would also like to thank Dr John Brown for his advice over the last few years and always seeing the positive even when the chemistry wasn't going well.

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I would like to thank all members of the VG for making life in the lab enjoyable. A special mention must go to Guy Giuffredi, who while will never realize I am not from Birmingham has been a fantastic source of advice in and out of the lab. Thank you to Jamie Wolstenhulme for answering all my questions and for all the 'Crazy Tuesdays'. Thanks also to Keary and Becky for being great desk mates over the years and to Sam for being a constant source of entertainment in the fumehood. A special thank you to Oscar (aka The Mexican) for always making me smile and for all the Froot Loops.

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Last, but certainy not least, I would like to thank my family for all their support and guidance through everything. Jay, I can't begin to say how grateful I am for your unwavering belief in me and for always providing an escape from the Oxford bubble. To Mamma, thank you for your letters and little treats, your coconut tarts will always be a welcome surprise. A special thank you to my Dad, who has made the last few months so much easier, I am so grateful for everything you have done for me over the years. To my sister, I can't begin to thank you for the love and encouragement you give me everyday, you are the best sister anyone could wish for and my best friend. You are an inspiration. Finally I would like to thank my Mum for everything she has done for me and hope that I can continue to make her proud.

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Abbreviations and Acronyms

[^{18}F]FDG	2-Deoxy-2-[^{18}F]fluoro-D-glucose
Å	Ångström (10^{-10} metres)
Ac	Acetyl
aq	Aqueous
Ar	Aryl
BC	Bathocuproine
BINAP	1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bn	Benzyl
Bq	Bequerel (s^{-1})
Bu	Butyl
Bz	Benzoyl
CI	Chemical Ionisation
COD	1,5-Cyclooctadiene
Cy	Cyclohexyl
DAST	Diethylaminosulfur trifluoride
dba	Dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DM-BINAP	1,1’-Binaphthalene-2,2’-dily)bis(3,5-dimethyl-diphenyl)phosphine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,2-Bis(diphenylphosphino)ferrocene
DTBM-SEGPHOS	((*R*)-(-)-5,5’-bis[di(3,3-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4’-bi-1,3-benzodioxole)
dr	Diastereoisomeric Ratio
ee	Enantiomeric Excess
eq	Equivalent(s)
ESI	Electrospray Ionisation
Et	Ethyl
FI	Field Ionisation
g	Gram(s)

gem	Geminal
h	Hour(s)
HFIP	Hexafluoro-*iso*-propanol
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
i	*Iso*
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	Infrared Spectroscopy
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
Kcal	Kilocalorie(s)
Kryptofix 222 (K222)	1,10-Diaza-4,7,13,16,21,24-hexaoxabicyclo[8.8.8]hexacosane
L	Neutral Ligand
LRMS	Low Resolution Mass Spectrometry
LUMO	Lowest Unoccupied Molecular Orbital
M	Moles per cubic decimetre (moldm^{-3})
m	Meta
Me	Methyl
Mes	1,3,5-Trimethylphenyl (Mesityl)
min	Minute(s)
mL	Millilitre(s)
mol	Mole(s)
Mp	Melting Point
n	Normal
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NFSI	*N*-Fluorobenzenesulfonimide
J	Scalar coupling constant (in NMR Spectra)
NMR	Nuclear Magnetic Resonance Spectroscopy
o	Ortho
p	Para
PET	Positron Emission Tomography
Ph	Phenyl
$PhI(OAc)_2$	(Diacetoxyiodo)benzene

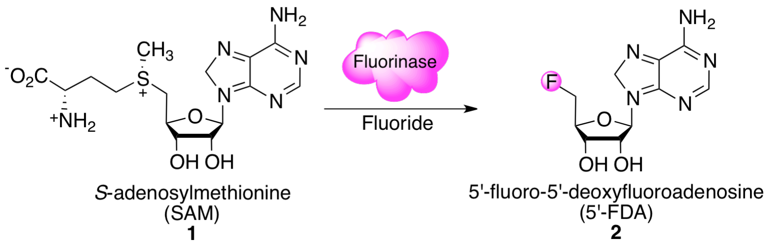
PHOX	2-[2-(Diphenylphosphino)phenyl]-2-oxazoline
PPFPz	1-{1-[2-Diphenylphosphanyl-ferrocenyl]ethyl}-1*H*-pyrazole
ppm	Parts per Million
QMA	Quaternary Methyl Ammonium
RCY	Radiochemical Yield
rt	Room Temperature
SA	Specific Activity
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SET	Single Electron Transfer
S_N1	Unimolecular nucleophilic substitution
S_N2	Bimoleculate nucleophilic substitution
S_NAr	Nucleophilic Aromatic Substitution
t	Tertiary (*tert*)
TADDOL	2,2-Dimethyl-α-α-α’-α’-tetraaryl-1,3-dioxolan-4,5-dimethanol
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
$t_{½}$	Half-Life
TBAF	Tetra-*n*-butylammonium fluoride
t-BuBrettphos	2-(Di(*tert*-butyl)phosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
TBDPS	*tert*-Butyldiphenylsilyl
TBME	*tert*-Butyl methyl ether
TFA	Trifluoroacetic Acid
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
Ts	*para*-Toluenesulfonyl (Tosyl)
UV	Ultraviolet
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
β^+	Positron (Positive Beta Radiation)
δ	Chemical Shift
μL	Microlitre(s)
ν	Frequency
ºC	Degrees Celcius

Chapter 1

Introduction to Transition Metal Mediated Fluorination

1.1 Fluorine and its applications

While fluorine is the 13th most abundant element in the Earth's crust, there is only a handful of naturally occurring organofluorine compounds compared to that of other organohalogens (nearly 5000).[1] This is often attributed to the low bioavailability of fluorine (found as the highly insoluble CaF_2 in nature) and its poor nucleophilicity in aqueous media. The redox potential of fluorine being much higher than that of the reduction of hydrogen peroxide also means it cannot be incorporated *via* haloperoxidase catalysed reaction. While the family of haloperoxidase enzymes are known to catalyse the incorporation of chlorine, bromine and iodine, to date only one fluorinase enzyme has been discovered. Isolated from the bacterium *Streptomyces cattleya* in 2002 by O'Hagan and co-workers, this enzyme was shown to catalyse the fluorination of *S*-adenosyl-L-methionine **1** with fluoride to give 5'-fluoro-5'-deoxyfluoroadenosine **2**.[2]



Scheme 1.1 Fluorinase enzyme isolated from *Streptomyces cattleya*

Despite its scarcity in nature, fluorine is ubiquitous in material, agrochemical, pharmaceutical and medicinal chemistry due to the profound effects the introduction of this small motif can have on both the physiochemical and biological properties of a compound.[3] Evidence of this is demonstrated by its use in 3 of the top selling pharmaceuticals in 2012, Crestor **3** and Lipitor **4** both used to lower the level of cholesterol and Advair **5** used for the treatment of asthma and chronic obstructive pulmonary disease.[4] The introduction of aryl fluorides has also given access to insecticides, an example is Diflubenzuron **8**. Furthermore the use of trifluoromethyl groups has provided agrochemicals such as Mefluidide **6** and polyfluorination of hydrocarbons afford valuable materials such as polytetrafluoroethylene (Teflon®, **7**) (Figure 1.1). There are several properties of fluorine that permit the dramatic effects it imparts onto a compound.

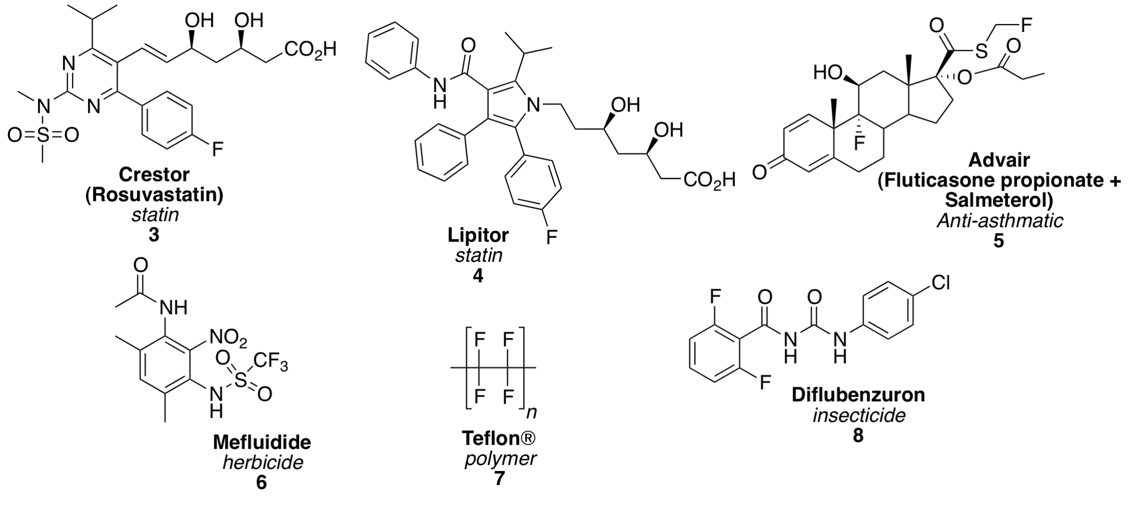
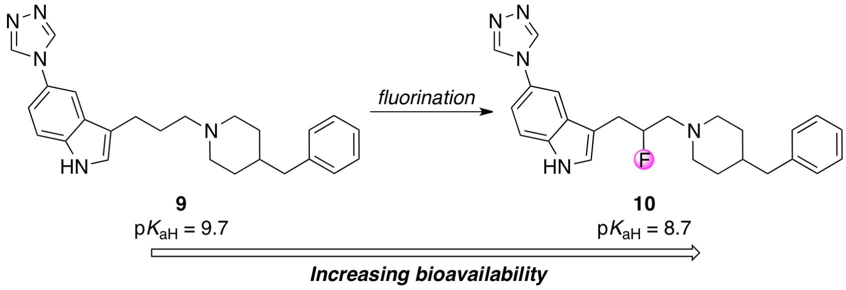


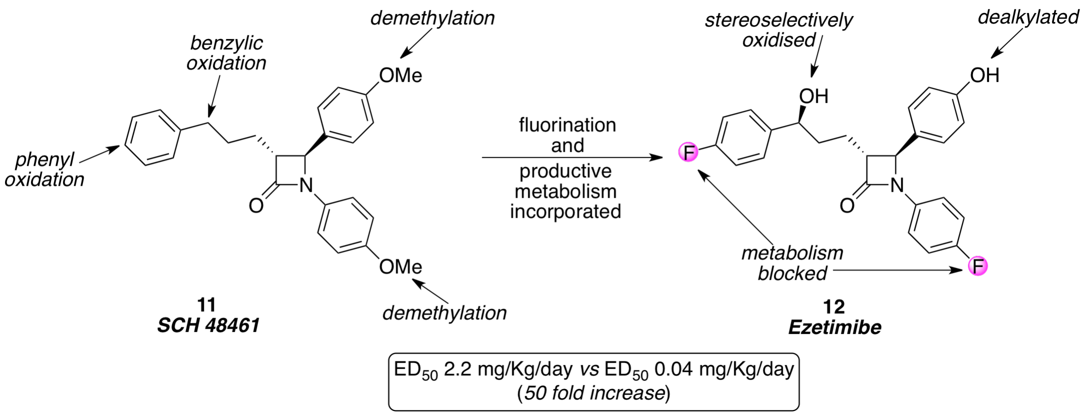
Figure 1.1 Applications of organofluorine compounds

As fluorine is the most electronegative element (χ = 3.98 on Pauling scale) this results in a highly polarised bond and the strongest single bond to carbon. Fluorination adjacent to a basic functionality, such as an amine or hydroxyl, decreases the p*K*a of the group due to the inductive effect of fluorine.[5] With the basicity of this functionality reduced the overall effect on the compound is increased hydrophobobicity and lipophilicity. The ability of fluorine to have such effects on the properties of a compound is of particular importance in pharmaceutical chemistry. While the mono- and trifluoromethylation of saturated alkyls decrease the lipophilicity of a compound such as a drug target, the introduction of aryl fluorides or per/polyfluorination can increase the bioavailability of this compound. An example of this effect is presented in Scheme 1.2, the pK_{aH} of **9** is lowered by the introduction of a fluorine adjacent to the nitrogen atom, **10**.[6]



Scheme 1.2 Fluorination to increase lipophilicity of compounds

The incorporation of fluorine is also used to enhance the metabolic stability of a compound against enzymes in the cytochrome P450 family that catalyse the oxidation of organic compounds. This can be achieved by the direct blocking of the site of metabolism or by inductive effects on neighbouring functionalities. This is demonstrated by the optimisation of the cholesterol-absorption inhibitor, SCH 48461, **11** (Scheme 1.3). The introduction of two aryl fluorides was successful in blocking detrimental oxidation sites and providing the lead compound Ezetimibe **12** with a substantially increased potency resulting in a much lower effective dose.[7]



11
SCH 48461

12
Ezetimibe

Scheme 1.3 Increased metabolic stability of organofluorine

Furthermore with a Van der Waals radius between that of hydrogen and carbon along with an *A* value (preference of a substituent on a cyclohexane ring to be equatorial over axial) of 0.25-0.42 *k*cal/mol fluorine is often used as an isostere for hydrogen in compounds (Figure 1.2).[8] However while the steric demands due to the introduction of fluorine are minimal, the electronic nature of the C-F bond itself is orthogonal to that of the C-H bond.

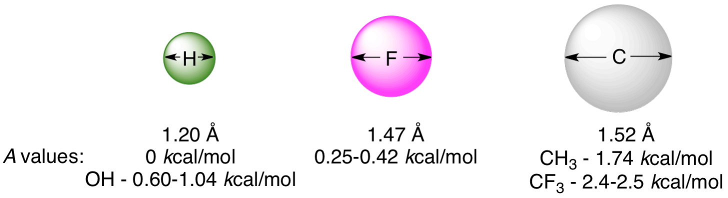
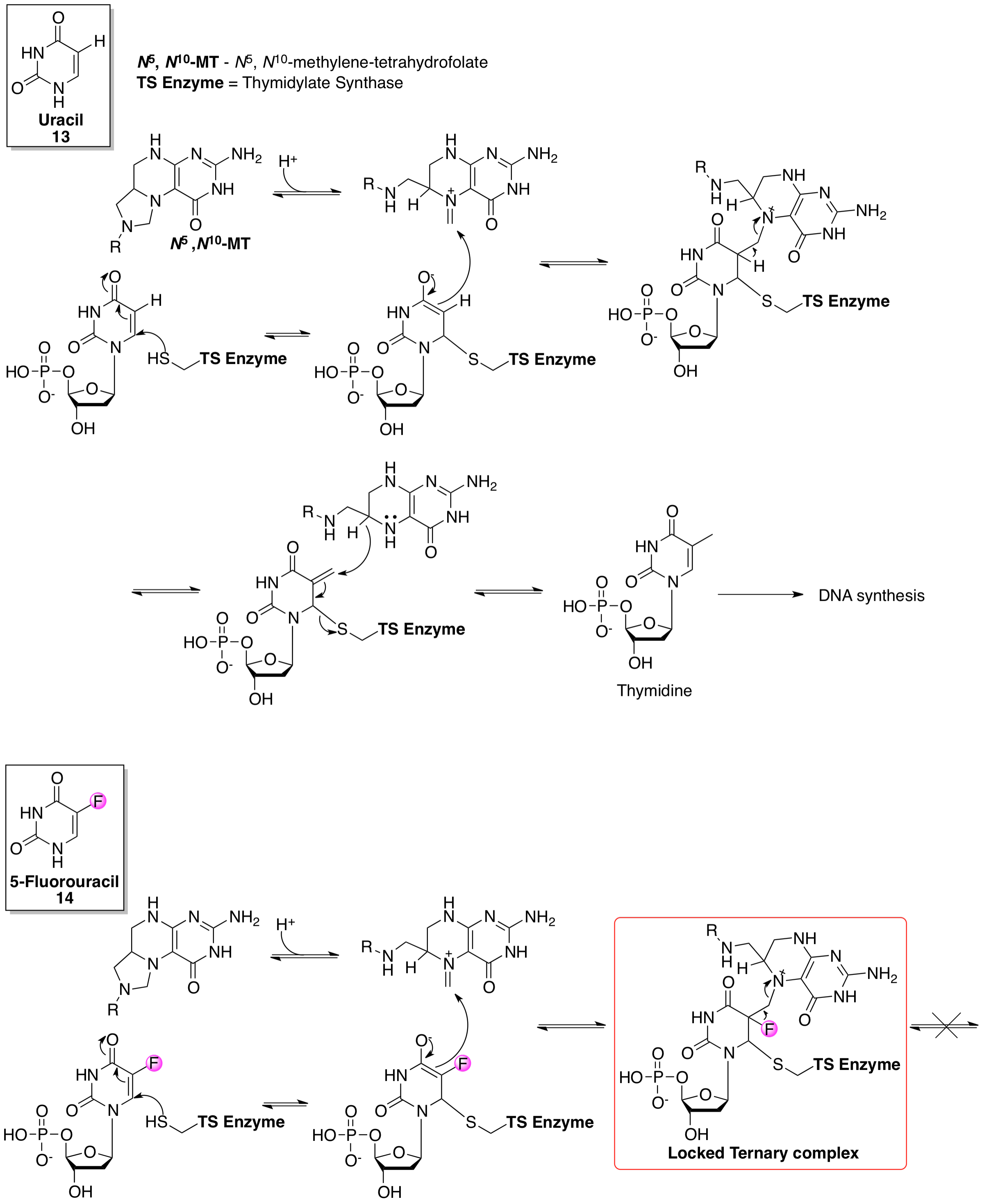


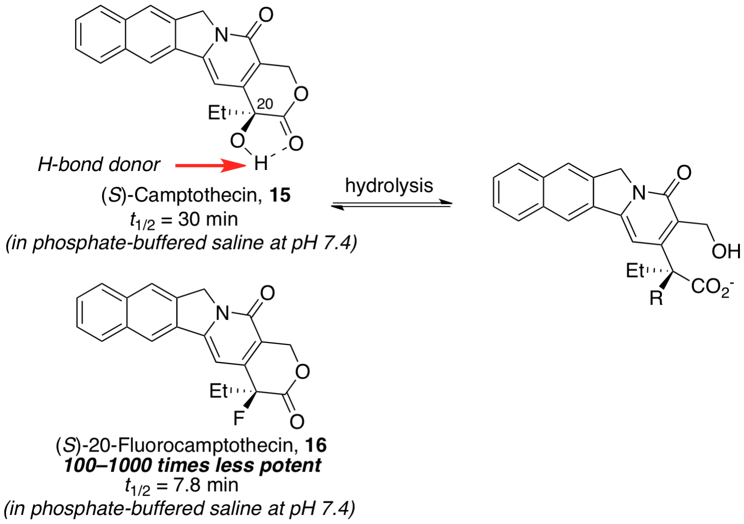
Figure 1.2 Comparison of fluorine to hydrogen and carbon

This property of the C-F bond is of particular use in the design of new drug targets as the introduction of fluorine can vastly improve the activity or stability of a compound. The fluorinated drug analogue of uracil **13**, 5-fluorouracil **14** is used as an antimetabolite agent in chemotherapy. The subtle substitution of hydrogen for fluorine provides a compound that can disrupt DNA and RNA function and inhibit essential biosynthetic processes.[9] 5-Fluorouracil **14** is used as an inhibitor of the thymidylate synthase enzyme, which is essential for the synthesis of thymidylate necessary for DNA synthesis (Scheme 1.4). The binding of 5-fluorouracil into the enzyme active site in place of uracil prevents breakdown of the ternary complex between the substrate, enzyme and *N*^{5}, *N*^{10}-methylene-tetrahydrofolate.



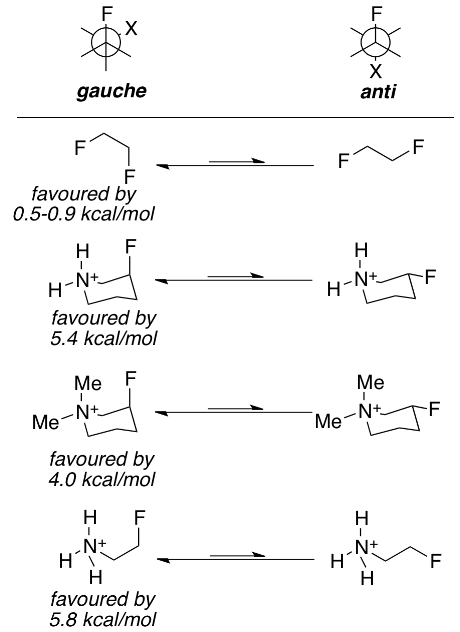
Scheme 1.4 Use of fluorine in anticancer agent 5-fluorouracil

The introduction of fluorine can be used to probe the effects of hydrogen bonding and molecular conformation. The use of a C-F bond in place of a C-OH provides a key tool to explore the contribution of hydrogen bonding while maintaining the steric and electronic effects of the bond. This is demonstrated well in the structure of collagen where hydroxyl groups were replaced with fluorine. Maintenance of the well-defined triple helix structure in the absence/reduction of the hydrogen bonding network established the intrinsic C-OH polarity as the determining factor.[10] (*S*)-Camptothecin **15**, a natural product shown to have activity against a variety of solid tumors, has been shown to interact with the topoisomerase/DNA cleavable complex and it is this that gives rise to its anticancer activity. Investigations have looked at accessing how crucial the hydrogen bonding of the 20-hydroxy group in (*S*)-Camptothecin is for this interaction.[11,12] The replacement of this group with fluorine showed that hydrogen bonding from the 20-hydroxyl group is essential in stabilizing the topoisomerase/DNA cleavable complex (Scheme 1.5). However the instability of the fluorinated analogue **16** has suggested that the inductive effect of the hydroxyl group is important in mediating lactone opening to the inactive hydroxy acid form.



Scheme 1.5 Effect of hydrogen bonding on anticancer activity if (*S*)-Camptothecin

The preference of fluorine to form *gauche* conformers has been used to probe protein:ligand interactions. The stereoelectronic *gauche* effect is demonstrated in the classical example with 1,2-difluoroethane where the two vicinal fluorine atoms result in the *gauche* conformer being lower in energy to the *anti* rotamer. One explanation for this effect is the stabilisation of the conformer as a result of donation of electron density from the C-H σ bonding orbital into the σ^* antibonding orbital of the C-F bond, which is not possible in the *anti* conformer. A secondary argument has been championed by Synder, Lankin and more recently O'Hagan that attributes this effect to the charged-dipole interactions that may occur between the C-F bond and charge moieties such as amines.[13] This reasoning was based on the much larger energy differences seen in the charged fluoropyridiniums compared to that of the neutral systems such as 1,2-difluoroethane.



Scheme 1.6 Preference for a *gauche* conformation

This sort of conformational effect has been used to investigate the exact conformation with which γ-aminobutyric acid (GABA) **17**, an inhibitory neurotransmitter of the central nervous system, binds to its receptor $GABA_A$. The synthesis of the two enantiomers of 3-

fluoroGABA **18/19** revealed that of the two allowed *gauche* conformations binding of the receptor occurs with the *anti*-zigzag conformation **18a/19a** depicted in Figure 1.3.[14]

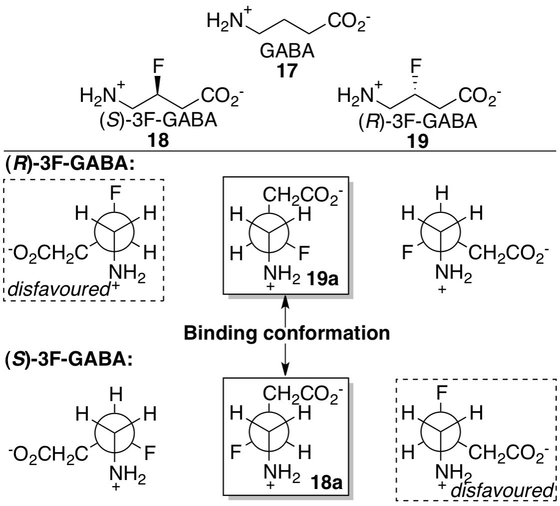


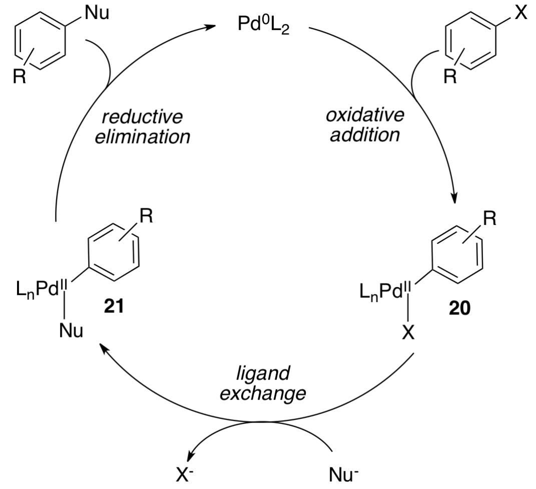
Figure 1.3 *Gauche* binding conformation of GABA to receptor

1.2 Palladium Mediated Fluorination

Due to the valuable properties of fluorine, access to a plethora of fluorinated compounds is well established with the use of both nucleophilic and electrophilic sources of fluorine. As such, a wide range of fluorinating reagents are now commercially available that are employed in a variety of different methodologies allowing for the fluorination of electron-rich, poor and neutral species that are often highly functionalised. Along with fluorine, the incorporation of other heteroatoms such as O, N, S and P is also essential across the chemical industries. However often electron rich substrates that are weak electrophiles are not particularly reactive towards these nucleophiles, as such they require the use of a catalyst. A vast amount of research has been focussed on the development of transition metal catalysed carbon-heteroatom bond formations, in particular with palladium, and in recent years transition metal catalysed fluorinations have also received a lot of attention. The remainder of this chapter will discuss the development of these transformations for the incorporation of fluorine at both sp^2 and sp^3 carbon centres.

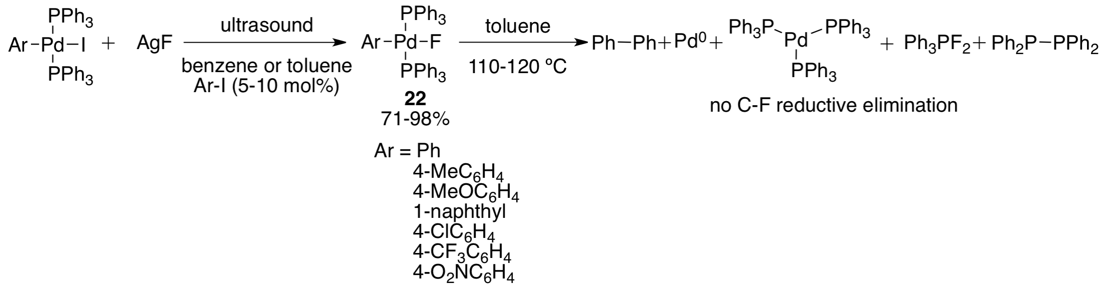
1.2.1 Aryl Fluorides

One of the most valuable fluorinated motifs is that of an aryl fluoride, of particular use in the pharmaceutical industry to modify the properties of a drug target. The formation of aryl-N, aryl-O and aryl-S bonds has provided valuable insight in the mechanism of the catalytic cross couplings that paved the way to the development of the challenging aryl fluorinations.[15] While other metals have received attention, the bulk of research has focussed on the use of palladium in these cross couplings. The proposed catalytic cycle for these reactions is shown in Scheme 1.7.



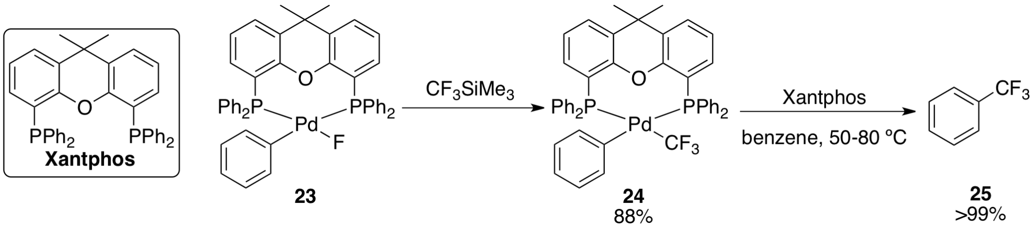
Scheme 1.7 Proposed catalytic cycle for Pd catalysed cross coupling with heteronucleophiles

The initial oxidative addition of Pd into a variety of aryl substrates (halides, triflates, boronic acids, stannanes) is well established. The attack of the arylpalladium complex **20** by an external nucleophile to form complex **21** has also been confirmed. In the case of fluoride Grushin *et al* confirmed that the formation of Pd-F complexes was possible in 1997 reporting the first isolable complex as [$(Ph_3P)_2Pd(Ph)F$], **22**.[16] The complex was found to be air stable and no sign of decomposition or dimerisation was observed in solution. Thermolysis of this complex gave no C-F bond formation, with only competitive F-P and C-P reductive elimination observed (Scheme 1.8).[17]



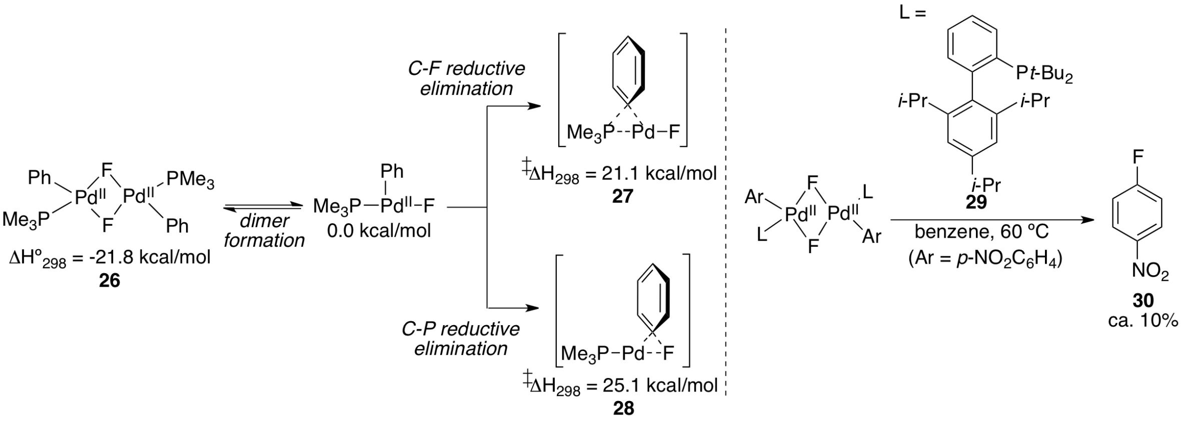
Scheme 1.8 Isolation and thermolysis of a Pd^{II}F complex

Interestingly the quantitative formation of trifluorotoluene **25** was seen when the bulky bidentate phosphine ligand, Xantphos was employed.[18] Synthesis of the complex [(Xantphos)Pd(Ph)CF$_3$] **24**, was possible from the corresponding fluoride complex **23** and Ruppert's reagent, CF$_3$SiMe$_3$. While complexes bearing other ligands such as ethylenebis(diphenylphosphine) (dppe) and 1,3-bis(diphenylphosphino)propane (dppp) were shown to be stable under rigorously dry conditions up to temperatures of 130-135 ºC in xylenes,[19] the [(Xantphos)Pd(Ph)CF$_3$] complex **24** gave a quantitative yield of trifluorotoluene **25** when heated to 50-80 ºC in benzene (Scheme 1.9).



Scheme 1.9 Synthesis of C-CF$_3$ *via* reductive elimination from [(Xantphos)Pd(Ph)CF$_3$]

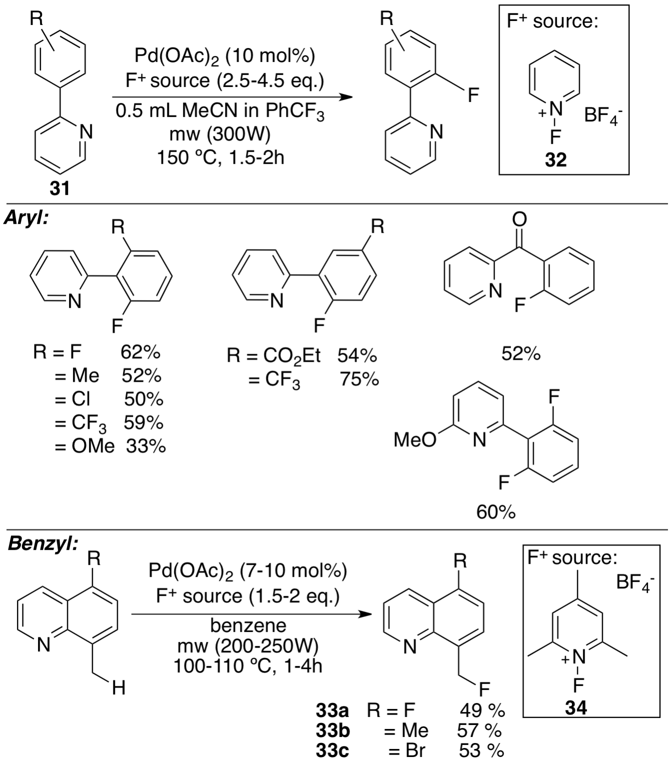
Hartwig and co-workers investigated the final reductive elimination step in the catalytic cycle to form a new C-X (heteroatom) bond. This work identified that the more nucleophilic the heteroatom the more rapid the reductive elimination from the palladium centre is, with the following order of reactivity established C-P > C-S > C-N > C-O.[20] A continuation of this work looked at the feasibility of formation of an aryl halide bond.[21] The findings here demonstrated that reductive elimination was disfavoured for iodine but the formation of aryl chlorides and aryl bromides was observed when an excess of the strongly electron donating phosphine ligand, P(*t*-Bu)$_3$ was used. This reactivity trend suggested that the formation of an aryl-F, while possible, could be challenging due to the high electronegativity of fluorine. Computational studies undertaken by Yandulov into the problematic C-F reductive elimination revealed that the activation enthalpies for C-F bond formation (**27**) are higher than that of the C-P reductive elimination (**28**).[22] Furthermore the formation of the dimeric species **26** is also shown to be more facile than the desired C-F bond formation (Scheme 1.10). The activation enthalpy of the C-F reductive elimination transition state could be lowered when electron withdrawing groups were present on the aryl substrate. This was demonstrated when an arene bearing a *para* nitro group along with the use of the bulky phosphine ligand, **29** developed in the Buchwald group[23] gave the desired aryl fluoride **30** in ~ 10%.



Scheme 1.10 Energies of transition states for C-F and C-P reductive elimination

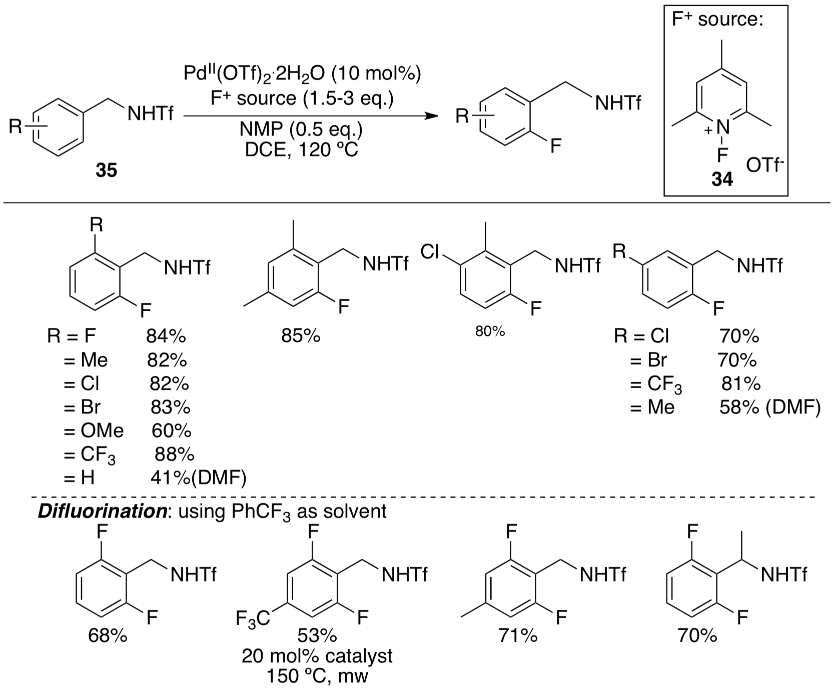
Although the reductive elimination of an aryl-F bond from a Pd^{II} species had been shown to be difficult, the hypothesis that this step maybe more facile with the use of a higher oxidation state Pd^{IV} complex led to the first Pd catalysed aryl-F bond formation in 2006 by Sanford and co workers. The Pd(OAc)$_2$ catalysed fluorination of 2-phenylpyridines **31** was achieved using the electrophilic fluorination reagent *N*-fluoropyridinium tetrafluoroborate

32 in a microwave reactor at 150 ºC.[24] The reaction was proposed to proceed *via* an initial cyclopalladation event that is directed by the nitrogen present in the substrate. This is followed by an oxidative fluorination mediated by oxidant **32**, acting as both the oxidant and fluorine source. Aryl fluorides were accessed in moderate yields with electron donating and withdrawing substitutions tolerated (Scheme 1.11). Examples of benzylic fluorination **33a-c** were also reported under slightly modified conditions using *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate **34** as the fluorinating reagent. The authors propose the formation of a Pd^{IV} intermediate that undergoes reductive elimination to give the desired aryl fluoride products. This type of intermediate had been proposed by Vigalok *et al* who observed ~10% of 4-difluorobenzene when the isolated complex Pd^{II}(*p*-FPhI)(dppp) was exposed to *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate.[25]



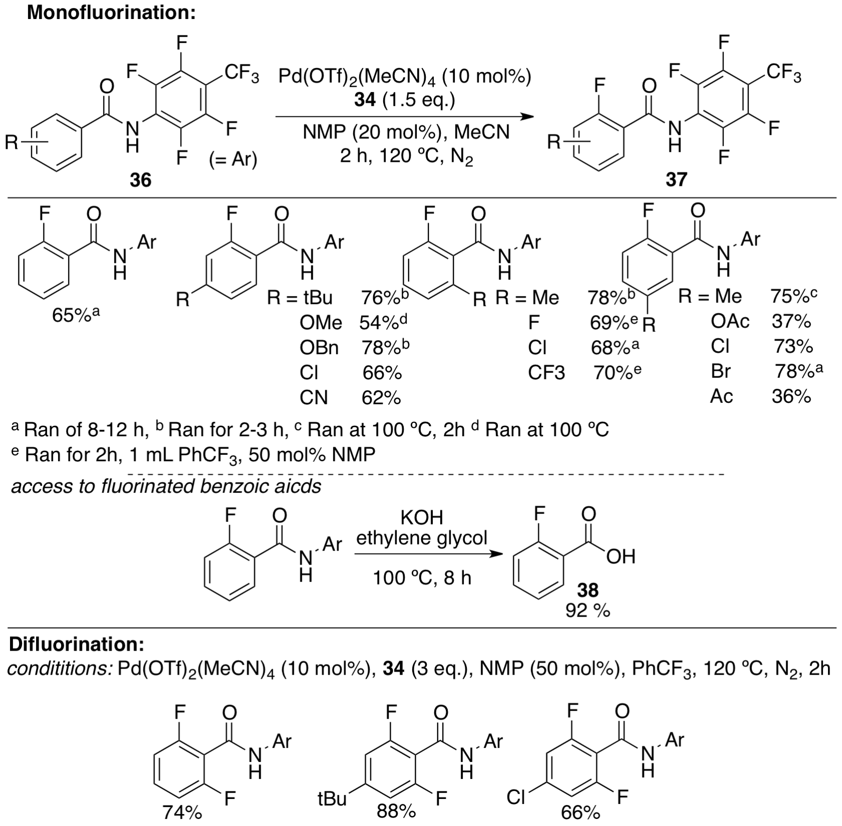
Scheme 1.11 Nitrogen directed Pd-catalysed aryl fluorination

The same principles were utilized by Yu *et al* to develop the *ortho*-aryl fluorination of benzylamines, **35** (Scheme 1.12).[26] The use of triflamide protected amines **35** allowed for selective *ortho*-fluorination catalysed by $Pd(OTf)_2{\cdot}2H_2O$ in the presence of *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, **34**. When $Pd(OAc)_2$ was used as the catalyst competitive C-OAc bond formation was observed. The addition of 0.5 equivalents of *N*-methyl-2-pyrrolidone (NMP) was found to improve yields. While the reaction was found to be tolerant of electron rich and poor functionalities, the problem of difluorination was observed when *meta*-substituted arenes were used, limiting the reaction to *ortho*-substituted substrates.



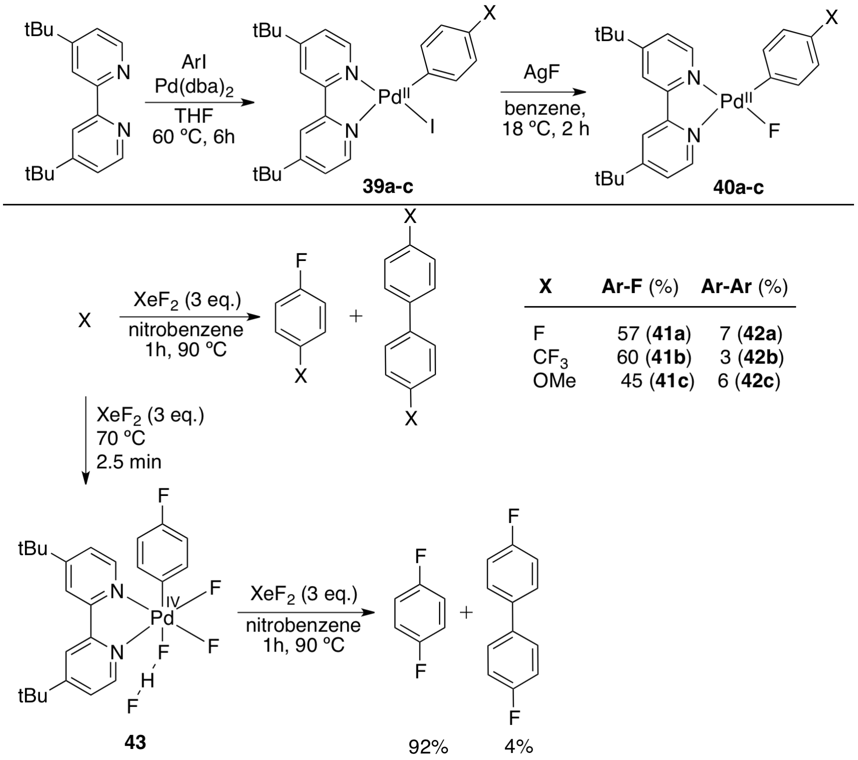
Scheme 1.12 Pd-catalysed *ortho*-fluorination of triflamide protectected benzylamines

Later work reported the undesired difluorination could be prevented if an alternative *ortho*-directing group was employed. The use of *N*-2,6-difluorophenylbenzamides **36** with a $[Pd(OTf)_2(MeCN)_4]$ catalyst in the presence of *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate **34** as the oxidizing and fluorinating reagent along with NMP gave the desired mono *ortho*-fluorinated arenes **37** in excellent yields and selectivity without the need for *ortho*-substituted substrates (Scheme 1.13).[27] Again the reaction was highly tolerant of substitution on the aryl, however arenes bearing electron-donating substitutents required extended reaction times. Interestingly, the reaction could be switched to favour the formation of the difluorinated product by solvent exchange to (trifluoromethyl)benzene. Access to valuable fluorinated benzoic acids (**38**) was possible after hydrolysis of the aryl fluorides under basic conditions. The reactions are proposed to proceed *via* a Pd^{IV} intermediate however the possibility of a redox-neutral Pd^{II}/Pd^{II} electrophilic cleavage pathway cannot be ruled out.



Scheme 1.13 Pd-catalysed mono and difluorination of aromatics

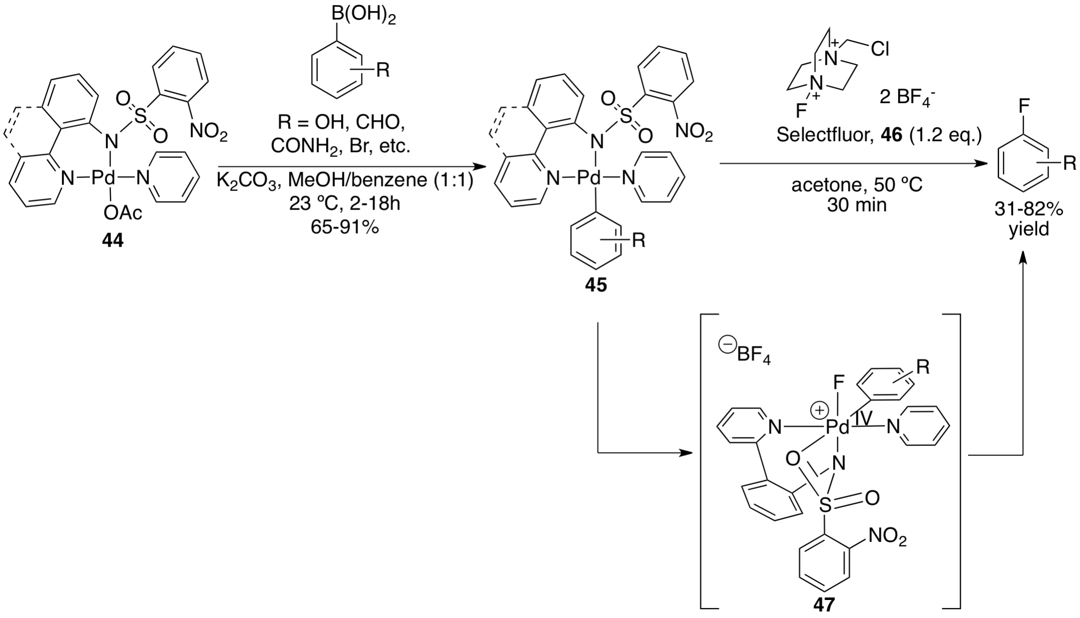
In 2008, Sanford *et al* validated aryl-F reductive elimination from isolated Pd^{IV}F complexes. The use of the rigid bidentate ligand 4,4'-di-*t*-butyl-2,2'bipyridine (*t*-Bu-bpy), selected based on its ability to stabilise Pd^{IV}, allowed for the isolation of Pd^{II}F complexes **40a-c** from the sonication of the corresponding Pd^{II} iodide **39a-c** with AgF (Scheme 1.14).[28] The reaction of these complexes with the electrophilic fluorinating reagent XeF_2 in nitrobenzene at 90 °C gave the corresponding aryl fluorides **41a-c** in moderate yields. When the reaction was conducted at 70 ºC for 2.5 minutes a new fluorinated species was observed by ^{19}F-NMR, isolation and analysis by X-ray crystallography allowed this complex to be unambiguously characterised as the Pd^{IV}F species **43**. While the thermolysis of this complex only gave trace amounts of aryl fluorides, excellent yields of aryl fluorides were possible in the presence of excess XeF_2. Along with C-F bond formation, products of C-C couplings, resulting from aryl exchange between metal centres, were also observed suggesting that the rate-limiting step of this transformation is the C-F reductive elimination.



X	Ar-F (%)	Ar-Ar (%)
F	57 (**41a**)	7 (**42a**)
CF_3	60 (**41b**)	3 (**42b**)
OMe	45 (**41c**)	6 (**42c**)

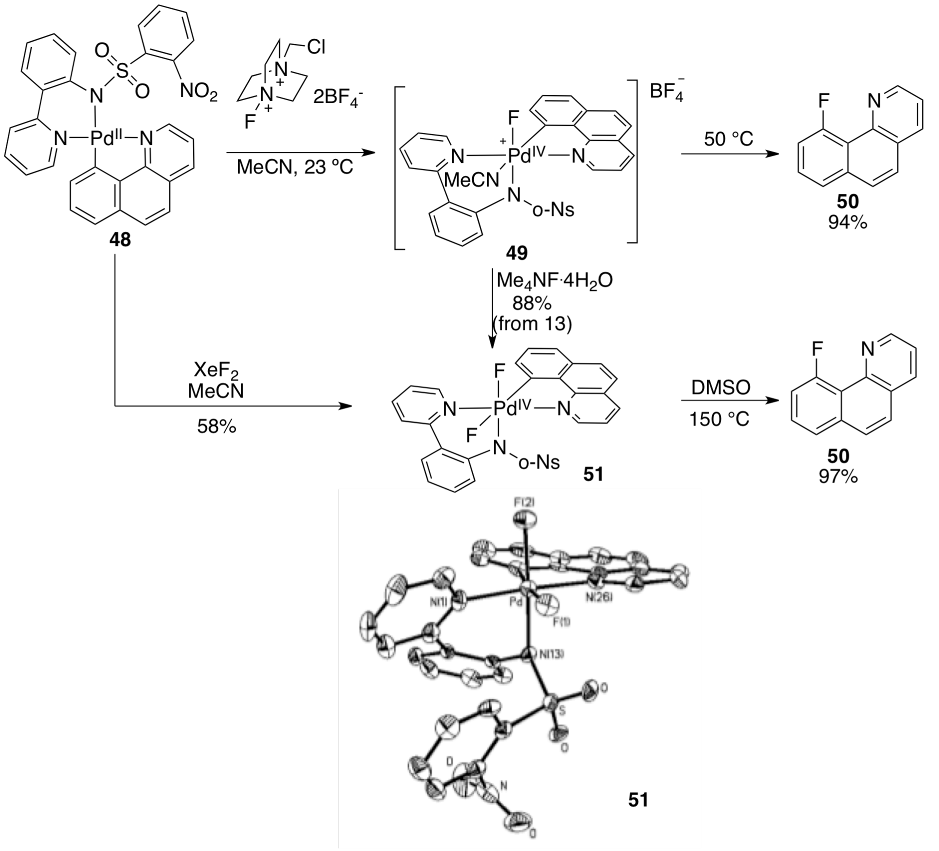
Scheme 1.14 Synthesis of aryl fluorides *via* a suggested Pd^{IV}F species

In 2008, Ritter reported the fluorination of arylboronic acids (Scheme 1.15). Transmetalation of a Pd^{II} species bearing a pyridyl-sulfonamide ligand **44** with a range of aryl boronic acids gave access to aryl Pd^{II} complexes **45**.[29] Aryl fluorides were obtained in moderate to excellent yields when these complexes were reacted with the oxidative electrophilic fluorinating reagent 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor, **46**). Though the Pd^{IV}F complex **47** was suspected as an intermediate of this reaction no evidence of this was found in ^{19}F-NMR analysis.



Scheme 1.15 Electrophilic fluorination of aryl Pd^{II} complexes bearing pyridyl-sulfonamide ligand

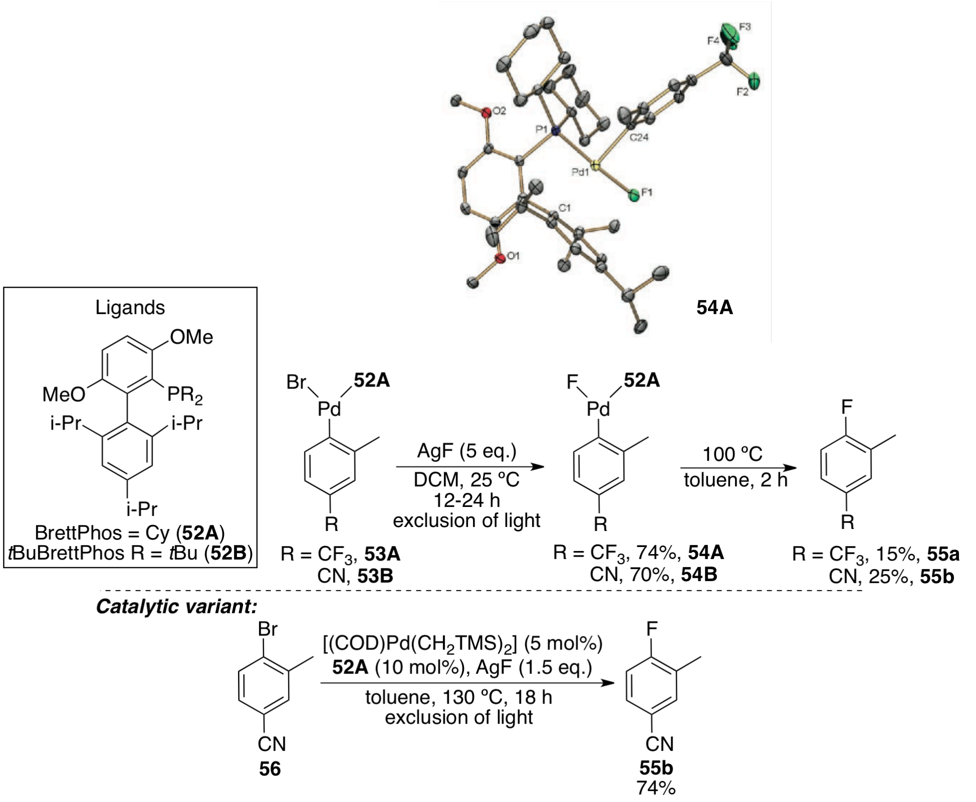
Based on previous work by Canty on ligands used to stabilise Pd^{IV} complexes,[30] Ritter reported the synthesis of Pd^{II} complex **48**, bearing a Pd^{IV} stabilising ligand, benzoquinolinyl to aid in isolation of the proposed intermediate (Scheme 1.16).[31] Fluorination of this complex with Selectfluor (**46**) gave aryl fluoride **50** in 94% yield. In this instance the presence of a Pd^{IV}F (**49**) was detected in the ^{19}F-NMR at δ -278ppm at room temperature, attempts to isolate this complex for further analysis were unsuccessful. However the thermolysis of this complex in solution did give the desired aryl fluoride in excellent yields. Exposure of complex **49** to TMAF·3H$_2$O allowed access to the Pd^{IV} difluoride complex **51** that could be isolated and fully characterised by X-ray crystallography. Thermolysis of this complex gave aryl fluoride **50** in quantitative yield after 10 minutes.



Scheme 1.16 Isolation of a $Pd^{IV}F$ and reductive elimination of a C-F bond

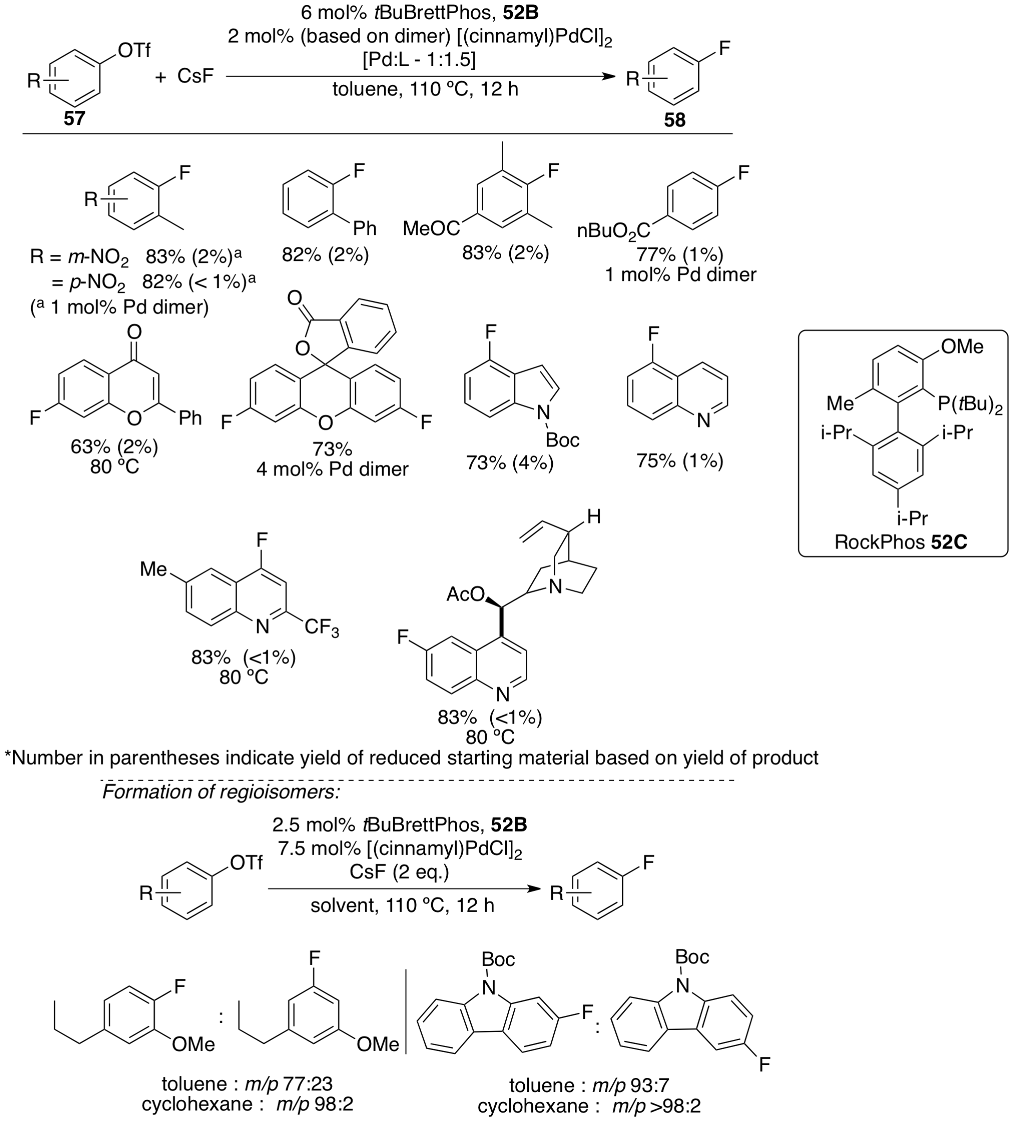
The pyridyl-sulfonamide ligand was found to be crucial for the correct positioning of ligands in the complex to allow for a C-F reductive elimination.[32] Although a catalytic variant has not been reported the scope of the reaction allows for the fluorination of both electron-rich and poor aryls and heterocycles along with protic functionalities that are not tolerated well in standard S_NAr reactions.

Buchwald reported the first reductive elimination of an aryl-F bond from Pd^{II} in 2009.[33] Having taken into account the observation of Yandulov that dimer formation would hinder C-F reductive elimination, the use of bulky phosphine ligands was investigated to aid this step. Previous work by this group has focussed on the development of new monophosphine ligands of which 2-(dicyclohexylphosphino)3,6-dimethyoxy-2',4',6'-triisopropyl-1,1'-biphenyl) (BrettPhos, **52A**) was shown to affect a C-N reductive elimination to access aryl amines.[34] The use of this ligand allowed access to complexes **53A** and **53B** that upon sonification with AgF gave the monomeric tricoordinated species [LPd^{II}(Ar)(F)] **54A/B**, which were unambiguously identified by X-ray crystallography and upon thermolysis in toluene gave low yields of aryl fluorides **55a/b** (Scheme 1.17). Pleasingly no dimer formation was identified. Further development of this reaction allowed for a catalytic variant to be developed utilising [(COD)Pd(CH$_2$TMS)$_2$] as the catalyst, along with 10 mol% BrettPhos (**52A**) and AgF as the fluoride source in toluene at 130 ºC. Using this conditions aryl fluoride **55b** could be accessed from the corresponding aryl bromide **56** in 73%.



Scheme 1.17 Isolation of an aryl Pd^{II}F complex and Pd-catalysed nucleophilic aromatic fluorination

Further optimisation led to the use of aryl triflates **57** with [(cinnamyl)PdCl]$_2$ (2 mol%) and the more bulky *t*BuBrettPhos **52B** as the optimal catalytic system, with an excess of CsF in toluene at 110 ºC (Scheme 1.18). The reaction scope included highly substituted aryls **58** along with various heterocycles such as quinolones and indoles and protic functionalities were tolerated. While both electron rich and poor aryls were compatible, higher temperatures were necessary for electron rich systems. An interesting observation was the presence of a mixture of regioisomers for some substrates, which could be suppressed by solvent exchange to the apolar solvent cyclohexane.

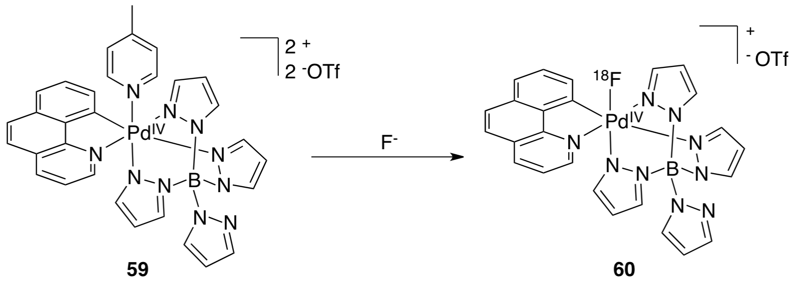


Scheme 1.18 Substrate scope of Pd-catalysed aromatic fluorination

The use of the RockPhos ligand **52C** was found to give comparable yields of fluorination; the complexes synthesised with this ligand proved easier to isolate and analyse in mechanistic investigations.[35] The mechanistic studies showed that in the case of electron rich aryl bromides, a modified arylated phosphine ligand where the aryl substrate is added to the phosphine ligand is formed, providing stable Pd complexes. It was suggested that the formation of these complexes maybe required for the C-F bond reductive elimination to occur.

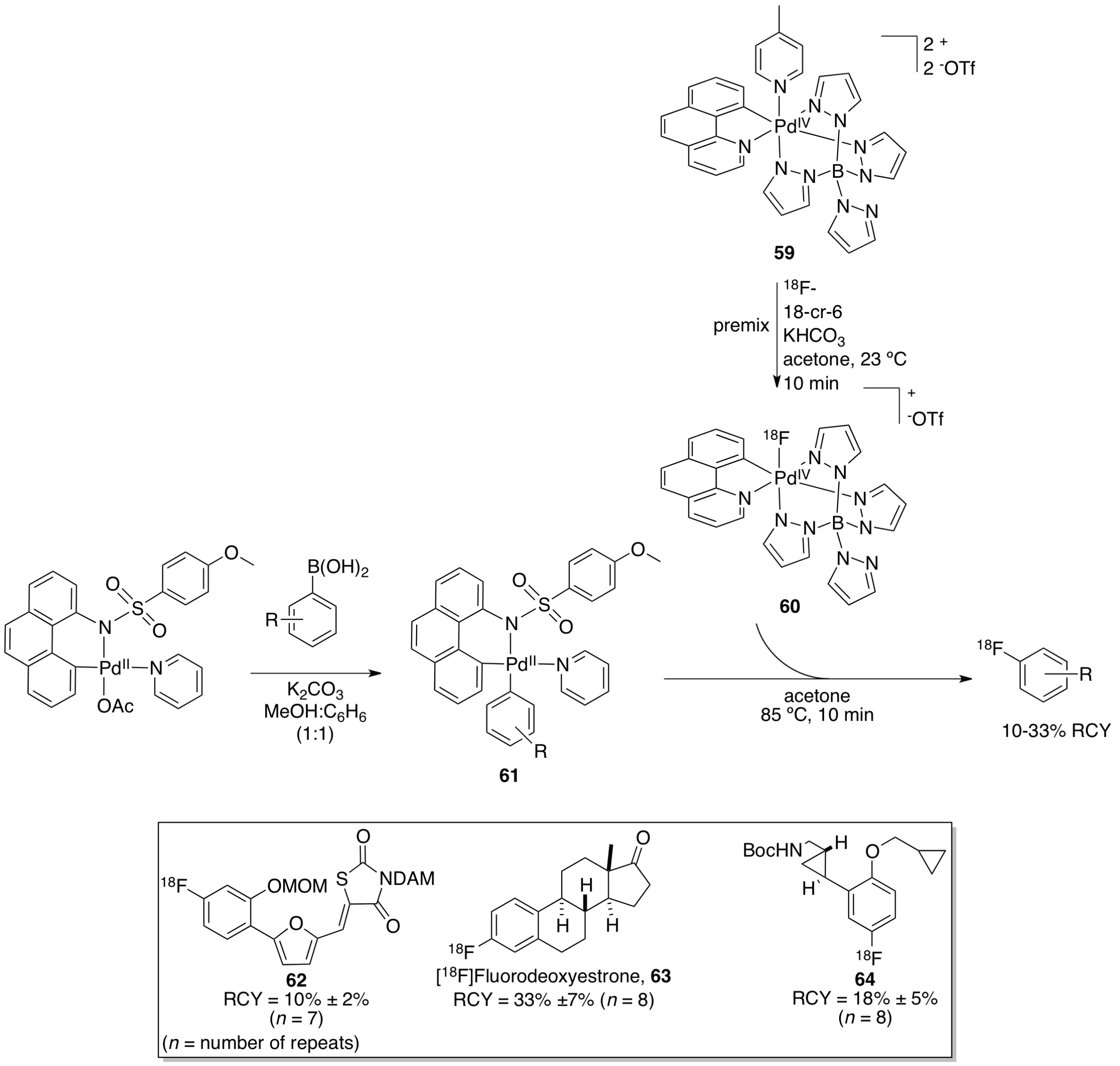
A key development of this reaction was the attempt to comply with the constraints of a [^{18}F]radiochemistry environment used in the imaging technique Positron Emission Tomography (PET) (a full discussion of this technique is available in Chapter 2). Due to the half life of the ^{18}F isotope ($t_{1/2}$ = 109.7 min)[36] radiofluorinations must occur in a short time and in this setting the stoichiometry of the reaction is reversed with fluoride becoming the limiting reagent. While reaction times could be shortened to ~30 minutes a large excess of CsF was still necessary which would suggest this reaction would be difficult to apply in a radiochemistry environment. However the recognition that a large excess of fluoride source is necessary for the reaction to occur lead Buchwald and co-workers to adapt this methodology to a microflow packed-bed reactor.[37] When the reaction was carried out at 120 ºC with a residence time of 20 minutes excellent yields of aryl fluorides were obtained. Pleasingly continuous mode production was possible allowing for 3 mmol of 1-naphthyl triflate to be converted to aryl fluoride with no depletion in yield or clogging of the reactor over 8 hours. In 2012 Coenen investigated the use of this reaction in a radiochemistry setting using carrier added Cs[^{18}F]fluoride. The synthesis of 1-[^{18}F]fluoronaphtalene was possible in a 33% radiochemical yield (RCY) using [Pd(COD)Cl_2] and *t*BuBrettPhos **52B** at 150 ºC. The use of a carrier could not be avoided so only low levels of specific activity were possible with this methodology.[38]

Recently, Ritter reported the synthesis of [^{18}F]aryl fluorides mediated by a novel [^{18}F]Pd^{IV}F complex **60** acting as the electrophilic fluorinating reagent that is derived from [^{18}F]fluoride (Scheme 1.19).[39] The elegant design of this [^{18}F]Pd^{IV}F complex **60** ensured the correct level of fluorophilicity (fluoride concentration 10^{-14}M for radiochemistry) and stability. The selection of the benzo(*h*)quinolyl and tetrapyrazole borate ligands was essential to ensure stability of the Pd^{IV} centre and avoid competing reductive eliminations. DFT calculations confirmed that only the LUMO energy levels of the fluorine in this complex would be susceptible to act, allowing Pd to behave as a leaving group in a traditional S_N2 reaction at the fluorine atom.



Scheme 1.19 Design of $Pd^{IV}F$ complex as an electrophilic fluorinating reagent

The reaction of complex **60** was initially validated with the ^{19}F variant. Reaction of the analogous $[^{19}F]Pd^{IV}F$ with Pd^{II}aryl precursors accessed from the corresponding boronic acids gave access to electron rich and neutral aryl fluorides within 10 minutes at 85 ºC. The radiochemical $[^{18}F]Pd^{IV}F$ complex **60** was synthesised *in situ* from complex **59** and $[^{18}F]$KF/[18]crown-6 in 10 minutes at room temperature and further reacted with Pd^{II}aryl precursors **61** to give decay-corrected radiochemical yields (RCY) from 10 to 33% (Scheme 1.20). Several aryl $[^{18}F]$fluorides (**62-64**) were accessed using this methodology that bear functionalities found in PET tracers with an overall reaction time of less than 60 minutes.

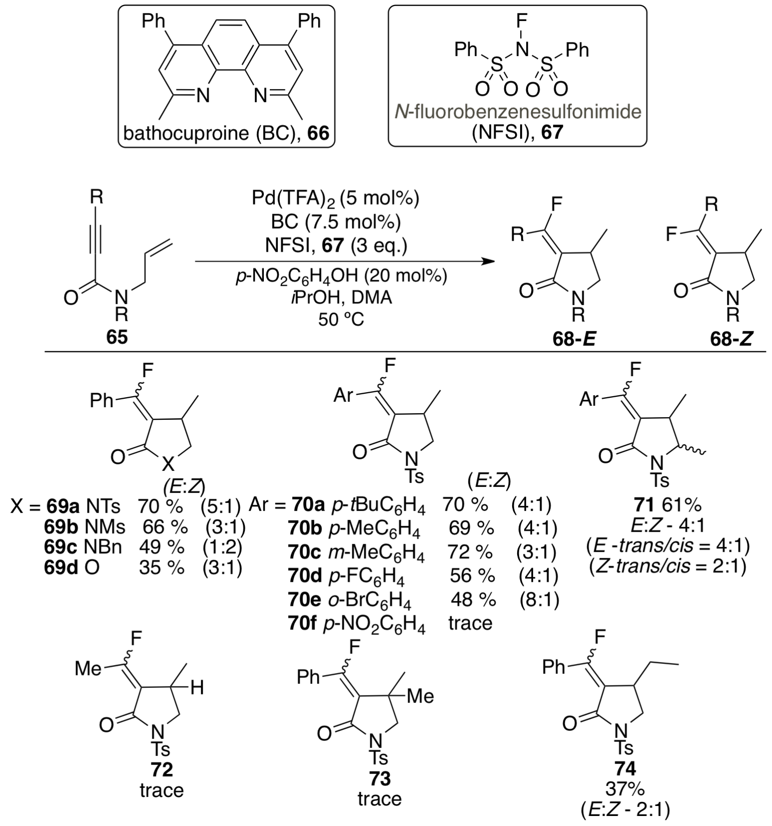


Scheme 1.20 Radiofluorination of aryl Pd complex with Pd^{IV}F source of ^{18}F

1.2.2 Alkenyl Fluorides

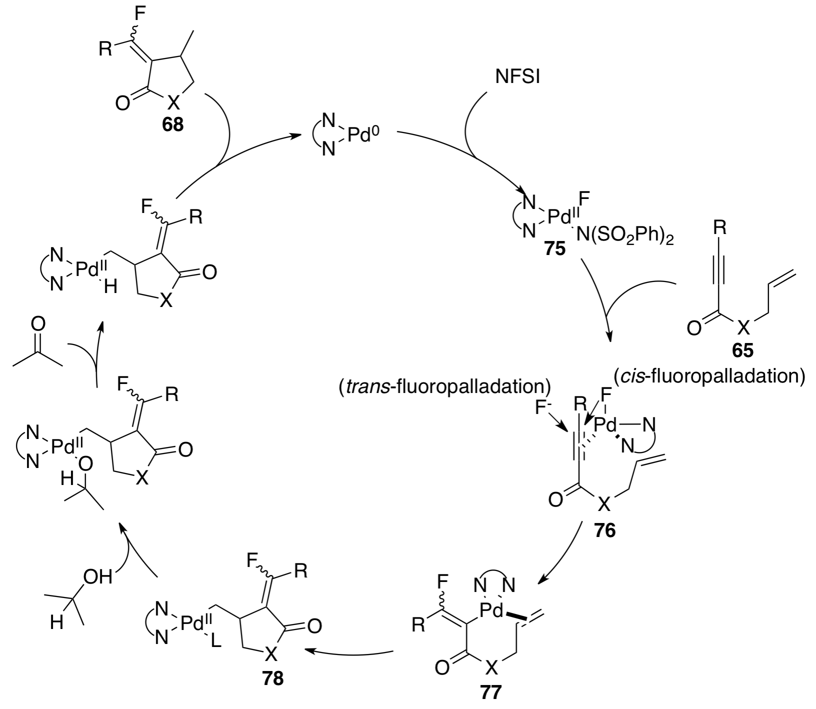
Although there are many synthetic routes to access fluoroalkenes there are challenges associated with control of regiochemistry and the geometry of the alkene. The production of alkenyl fluorides is also often complicated by over fluorination leading to the competitive formation of *gem*-difluoroalkanes. As such, methods for the selective preparation of these compounds are very desirable and the use of transition metals has been investigated to address these issues. The majority of this research has focussed on the use of Au^{I} catalysts on alkynes in the presence of both nucleophilic and electrophilic fluorinating reagents.[40] The use of substoichiometric silver salts has also allowed for the selective fluorination of vinylstannanes, alkenylboronic acids and allenes.[41]

Liu reported the synthesis of alkenyl fluorides via a Pd catalysed tandem fluorination-cyclisation of enynes **65** containing ester and amide functionalities in 2011.[42] The treatment of the enynes **65** with 5 mol% of Pd(TFA)$_2$ catalyst, 7.5 mol% of the bidentate ligand bathocuproine (BC, **66**) and *N*-fluorobenzenesulfonimide (NFSI, **67**) in *N,N*-dimethylacetamide at 50 ºC gave both geometrical isomers of the cyclic alkenyl fluorides **68*E*/*Z***. The selectivity and yield of the reaction was improved with the addition of 4-nitrophenol favouring the *E*-isomer. These optimised conditions allowed the fluorination of enynes bearing alkynes with electron rich and poor aryls with moderate to good *E* selectivity and yields, respectively. Furthermore the substitution of the amide for an ester gave the fluorinated lactone **69d** in a moderate yield of 35% (*E*:*Z* 3:1). While substitution at the nitrogen of the amide was predominantly tolerated, the use of a *N*-benzylated amide reversed the selectivity of the reaction giving the *Z* isomer as the major fluorinated product **69c**. In the case of alkyl-terminated alkynes **72** and disubstituted alkenes **73** only a trace amount of fluorinated product was obtained, however internal double alkenes did give a moderate level of fluorination, **74**.



Scheme 1.21 Pd-catalysed fluorination cyclisation of enynes

Mechanistic suggestions were aided by deuterium labelling experiments. The use of *i*PrOD was found to give no incorporation of deuterium in the alkenyl fluoride product, however when the reaction was run with *i*PrOH-d_8 the deuterium was incorporated into the product, even when H_2O was present. This observation led the authors to propose the initial formation of a $Pd^{II}F$ **75** that allows for a fluoropalladation of the alkyne to give vinyl fluoride intermediate **77** (Scheme 1.22). The presence of both *E* and *Z* products is assumed to result from an unselective *cis* and *trans* fluoropalladation. The *cis* fluoropalladation is suggested to occur due to the strong interaction between the Pd and fluorine, while the *trans* fluoropalladation is possible due to nucleophilic attack by free fluoride anion generated from the decomposition of NFSI. Indeed, when a fluoride trap in the form of Et_3SiH was used in the reaction only the *E* product was observed. The insertion of the alkene into the vinyl-Pd bond in species **77** gives **78**, which is reduced via hydride transfer with concomitant isopropyl alcohol oxidation, and subsequent reductive elimination affords the cyclic fluorinated product.

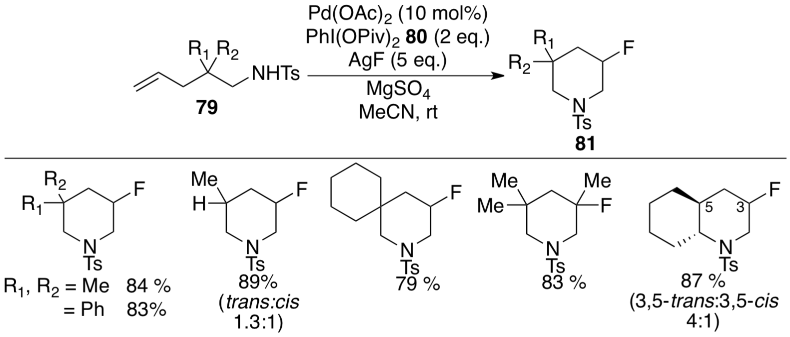


Scheme 1.22 Proposed mechanism for Pd-catalysed fluorination-cyclisation

1.2.3 Alkyl and Benzyl Fluorides

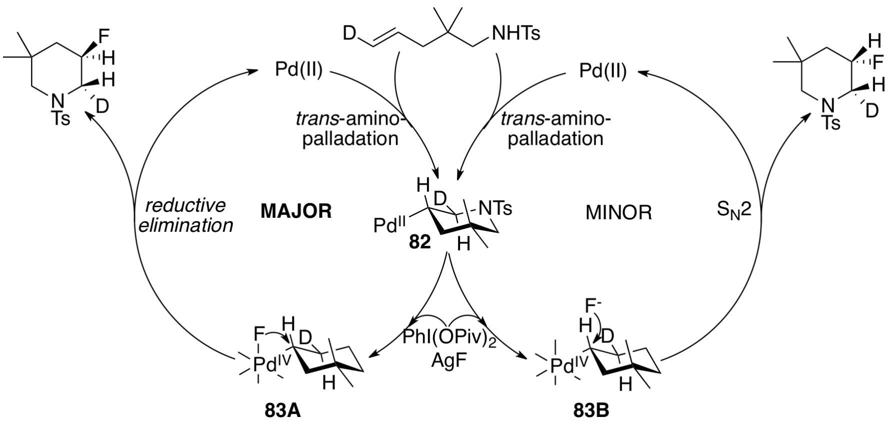
The use of high oxidation state metal fluorides (ReF_7, ReF_6, UF_6, IrF_6 and VF_5) to provide access to alkyl fluorides has been reported, however this method is often limited by harsh reaction conditions and extended reactions times of up to 5 days.[43] Grushin has also shown the use of [PdF(Ph)(PPh_3)$_2$] as a source of ‘naked’ fluoride in the halide metathesis with CH_2Cl_2 in the presence of bis(triphenylphosphine)iminium chloride ([PPN]Cl).[44] The use of RuF complexes has also been investigated by Togni and co-workers in the fluorination of alkyl, benzyl and allylic bromides.[45]

The use of Pd catalysis has also been demonstrated in the fluorination of unactivated alkenes. In 2009 Liu and co workers reported the first example of intramolecular oxidative fluoroamination of alkenes with a pending *N*-tosyl amino group, **79** (Scheme 1.23).[46] The reaction of these substrates with Pd(OAc)$_2$ as the catalyst gave no fluorination using the standard commercially available electrophilic fluorinating reagents NFSI (**67**) and Selectfluor (**46**). The use of AgF along with the hypervalent iodine reagent PhI(OPiv)$_2$ **80** provided access to a variety of fluorinated piperidine derivatives **81** in moderate to excellent yields and excellent regioselectivity. Substitutions of the alkene substrates were well tolerated however the use of a Boc protected nitrogen or a 1,2-disubstituted *Z*-alkene did not give any fluorinated products.



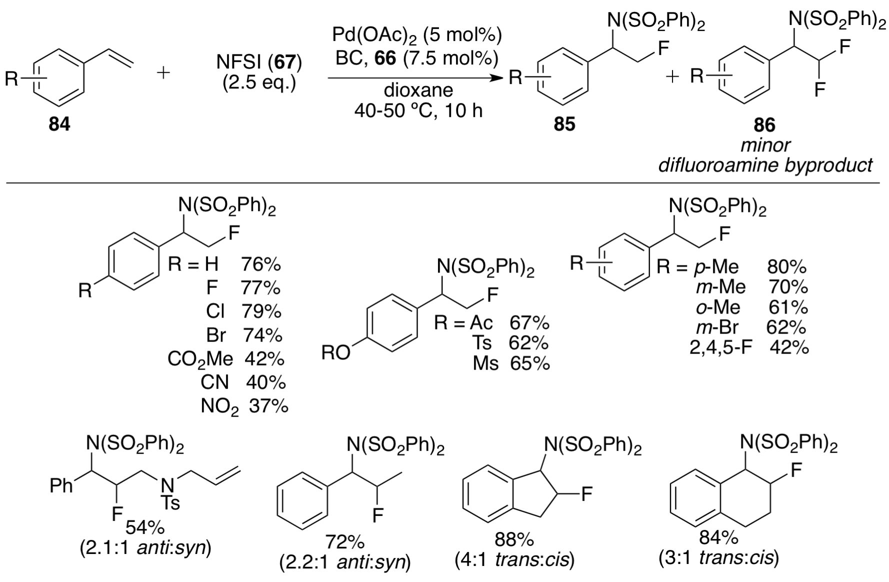
Scheme 1.23 Intramolecular fluoroamination of unactivated alkenes

Deuterium labelling studies provided insights into the reaction that led to the mechanism proposed in Scheme 1.24. An initial *trans*-aminopalladation of the alkene with Pd(OAc)$_2$ to give complex **82** followed by oxidation of this complex in the presence of PhI(OPiv)$_2$/AgF would give a Pd^{IV} complex, **83A/B**. The final step of the reaction is proposed to occur predominantly by reductive elimination of the C-F bond, however a minor competitive pathway is possible with the S$_N$2 attack of fluoride, which would provide the minor *cis*-fluorinated products observed.



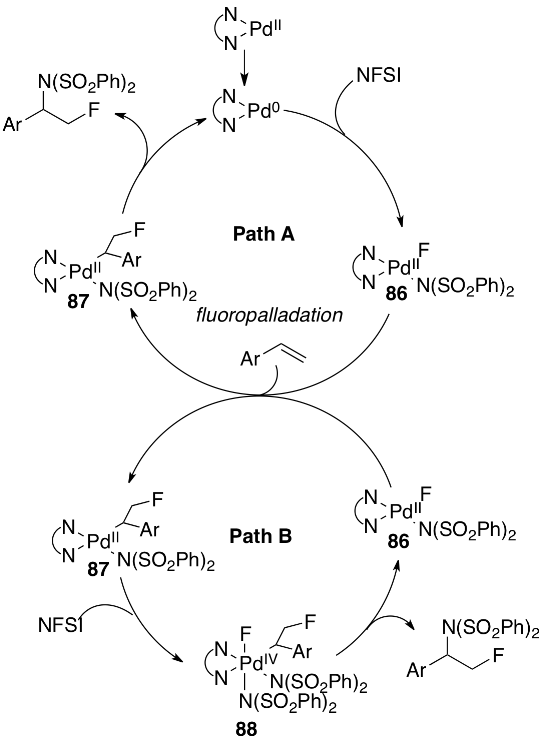
Scheme 1.24 Proposed mechanism based on deuterium labelling studies

The intermolecular variant of this reaction was developed with the use of styrenes **84** and the electrophilic fluorinating reagent NFSI (**67**) as both the fluorine and amine source.[47] The reaction of styrene with $Pd(OAc)_2$ (5 mol%) and the bidentate ligand BC **66** (5 mol%) in dioxane at 50 ºC gave the aminofluorinated product **85** with the difluoroamine **86** seen as a minor product (Scheme 1.25). The use of other bidentate nitrogen ligands resulted in a reduction of yield, with 7.5 mol% of BC found as the optimal loading. The reaction tolerates substitution of the styrene at all positions of the aryl, with electron withdrawing groups giving slightly reduced yields. However while the reaction shows good regio- and chemoselectivity, high levels of diastereoselectivity were not achieved.



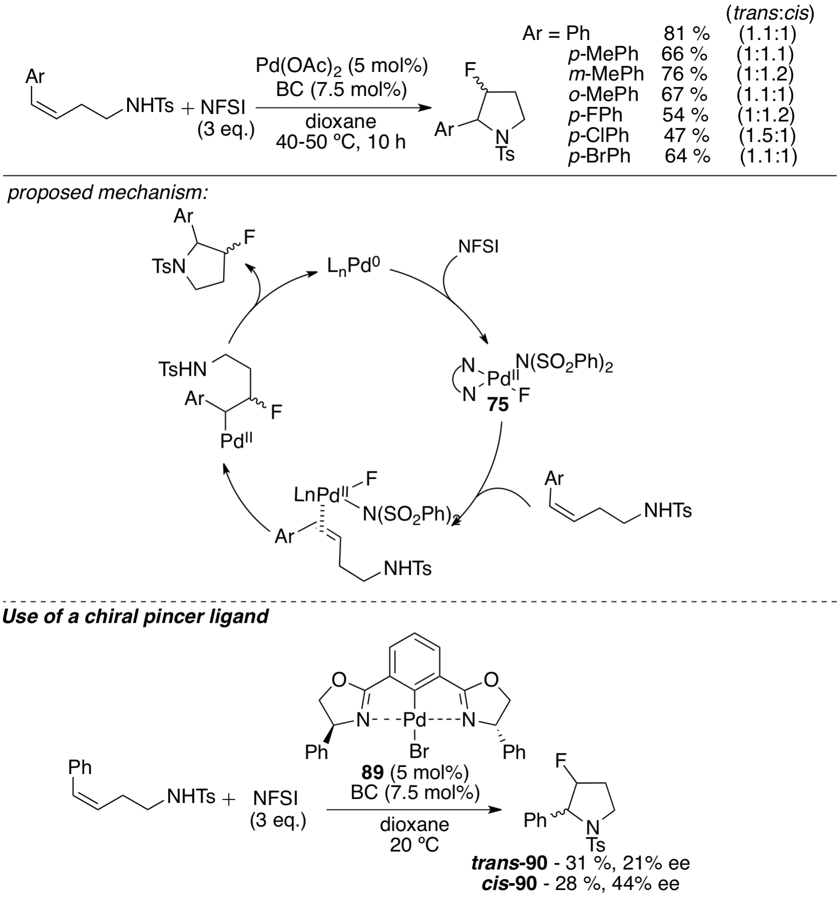
Scheme 1.25 Intermolecular Pd-catalysed aminofluorination of styrenes using NFSI

The authors proposed a mechanism based on the isolation of the Pd^{II}F complex **75** from the reaction of Pd(dba)$_2$ and BC with NFSI, which was characterized by ^{19}F-NMR (broad singlet -381ppm), ^{1}H-NMR (3.61ppm and 3.06ppm), and mass spectroscopy and its reaction with styrene to give the desired aminofluorination along with a vinylic fluoride. The initial formation of this complex *in situ* followed by fluoropalladation with styrene would give complex **87**. This can then undergo one of two pathways, **A**; nucleophilic attack by the amine or **B**; oxidation by NFSI to give a Pd^{IV} species **88** from which a C-N reductive elimination would yield the desired product (Scheme 1.26).



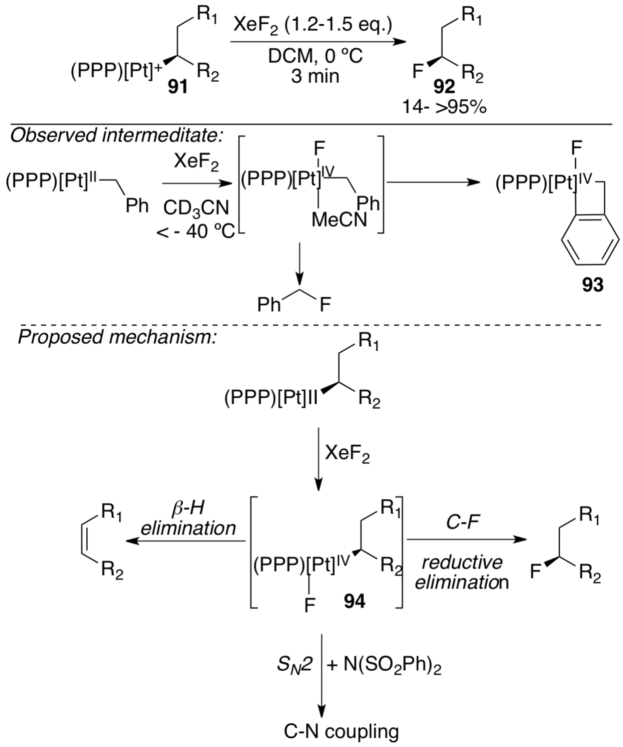
Scheme 1.26 Proposed mechanisms for aminofluorination of styrenes

The use of aryl alkenes in the intramolecular variant of this reaction has also been disclosed.[48] Utilising the same $Pd(OAc)_2$/BC catalytic system aryl alkenes underwent an aminofluorination cyclisation reaction in the presence of excess NFSI (**67**) (Scheme 1.27). Interestingly optimization of the reaction found *Z* alkenes to give superior yields and only aryl substituted alkenes were tolerated with alkyl groups giving no fluorinated product. The reaction was proposed to involve the same Pd complex **75** that takes part in an unselective *cis* or *trans*-fluoropalladation, suggested based on the low levels of diastereoselectivity seen in the product distribution. The use of a chiral Pd pincer ligand **89** allowed access to *trans* and *cis* 3-fluoro-2-phenyl-1-tosylpyrrolidine **90** in low to moderate levels of enantiomeric excess, respectively.



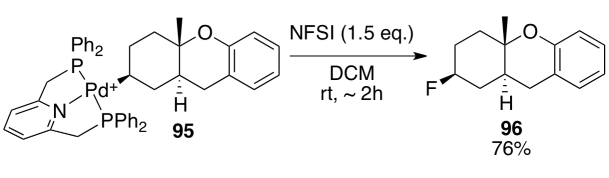
Scheme 1.27 Intramolecular Pd-catalysed aminofluorination of aryl-substituted alkenes

In 2011, Gagné reported the stereoretentive fluorination of alkyl Pt^{II} complexes **91** with XeF$_2$.[49] A variety of Pt complexes bearing a bis(2-diphenylphosphinoethyl)phenylphosphine (PPP) ligand reacted within 3 minutes to give alkyl fluorides **92** in varying yields from 14% to >95% (Scheme 1.28). It was found that bulky alkyl groups gave higher yields, with contending C-N bond formation and β-hydride elimination becoming competitive as the sterics were reduced. This reaction was proposed to involve a high oxidation state Pt^{IV} complex having observed characteristic peaks in the ^{19}F-NMR and ^{1}H-NMR spectra of complex **93**, that agree with similar structures prepared by Vigalok in 2010.[50] This observation along with the retentive nature of the reaction led to the tentative mechanism involving the proposed complex **94**, formed upon attack of F$^+$ on the Pt^{II} complex, followed by reductive elimination of a C-F bond. The catalytic variant of this reaction was later reported.[51]



Scheme 1.28 Pt mediated alkyl fluorination *via* a proposed $Pt^{IV}F$

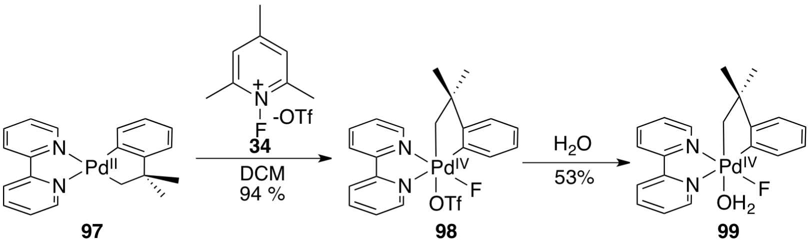
The analogous Pd complex **95** was prepared and reaction with NFSI gave the desired alkyl fluoride **96** in 76% within 2 hours at room temperature along with some alkene as a product of β-hydride elimination (Scheme 1.29). The use of other high oxidation state Pt and Au complexes to provide access to alkyl and benzyl fluorides have recently been reported.[52]



Scheme 1.29 Fluorination of an alkylPd complex with NFSI

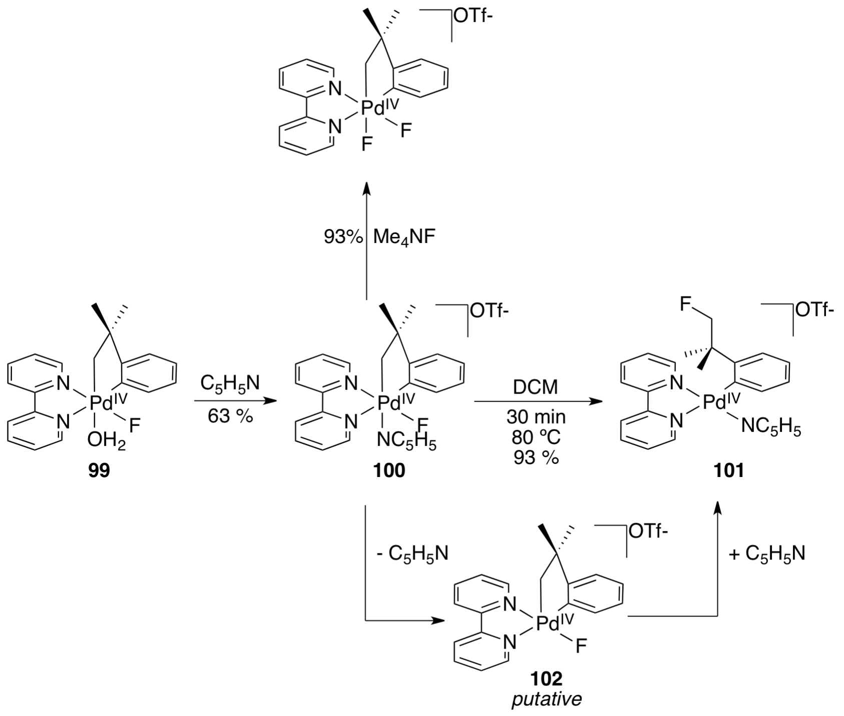
The same principles were employed by Sanford in 2012 in the isolation of an alkyl $Pd^{IV}F$ bearing a bipyridine ligand, [(CH_2CMe_2-*o*-C_6H_4)-$Pd^{IV}F(OH)(bpy)$], **99** (Scheme 1.30).[53] This complex was synthesized from the reaction of alkyl Pd^{II} complex **97** with *N*-fluoro-

2,4,6-trimethylpyridinium triflate (**34**) in dichloromethane after 15 minutes at room temperature. Exchange of the triflate ligand in **98** for a OH_2 ligand allowed for the isolation of complex **99** and characterisation by X-ray crystallography.



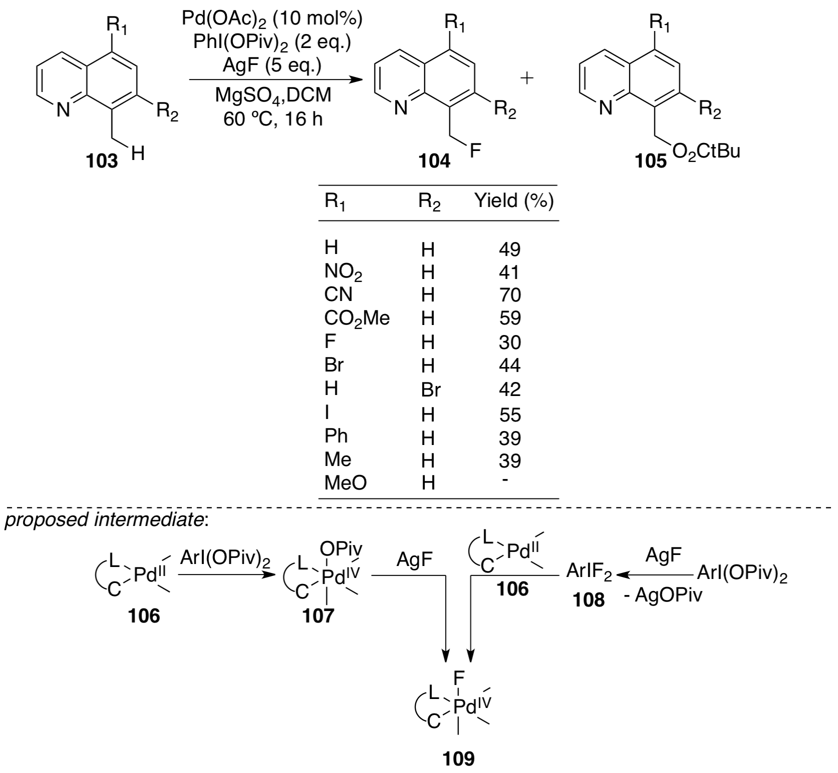
Scheme 1.30 Isolation of Pd^{IV}F complex

Further reaction of this complex with pyridine gave complex **100**, which allowed alkyl C-F bond formation when heated to 80 ºC in DCM for 30 minutes, giving the product **101** in 93% yield (Scheme 1.31). Investigation into this reaction showed that there was an inverse first-order dependence on the concentration of pyridine, with excess pyridine slowing down the reaction considerably. Based on this finding the authors proposed that dissociation of a pyridine ligand must occur before the rate-limiting C-F bond formation. Two routes are suggested for this formation, firstly by a reductive elimination from the putative complex **102** or secondly by the dissociation of fluoride ligand and S_N2 attack of the fluoride on the alkyl of the resulting Pd^{IV} dication. Due to the poor nucleophilicity of fluoride and unfavourable formation of a Pd^{IV} dication the authors propose the reductive elimination is more likely. Furthermore DFT calculations show that the C_{sp3}-F formation gives a lower energy transition state to that of a C_{sp2}-F formation to account for the outcome of this reaction.



Scheme 1.31 Alkyl fluorination of a Pd^{IV}F

Sanford has recently reported the use of Pd catalysis utilising nucleophilic fluorine for the synthesis of benzylic fluorides.[54] The previously discussed use of PhI(OPiv)$_2$ (**80**) with AgF allowed for the fluorination of 8-methylquinoline derivatives **103** using Pd(OAc)$_2$ as the catalyst in DCM at 60 ºC (Scheme 1.32). Along with benzylic fluorides **104** the oxygenation product **105** derived from the iodine reagent was seen as a minor byproduct. The authors proposed the reaction proceeds *via* a Pd^{II}/Pd^{IV} mechanism involving complex **109**. This complex is formed *in situ* either by oxidation of benzylic Pd^{II} species **106** with PhI(OPiv)$_2$ (**80**) to a Pd^{IV} intermediate **107** that undergoes ligand exchange with fluoride or by the formation of ArIF$_2$ **108**, from AgF and PhI(OPiv)$_2$, which then oxidatively fluorinates complex **106**. While a ^{19}F-NMR peak at -176ppm, corresponding to ArIF$_2$, was observed under the reaction conditions, the addition of independently synthesised *p*CH$_3$PhIF$_2$ in place of PhI(OPiv)$_2$/AgF only gave 7% of the benzylic fluoride suggesting this is not the primary fluorinating reagent in the reaction.



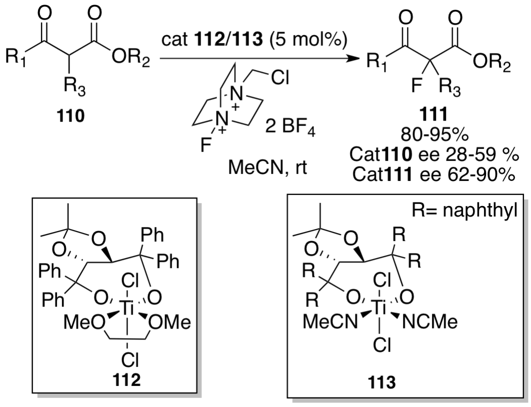
103 **104** **105** **106** **107** **106** **108** **109**

R_1	R_2	Yield (%)
H	H	49
NO_2	H	41
CN	H	70
CO_2Me	H	59
F	H	30
Br	H	44
H	Br	42
I	H	55
Ph	H	39
Me	H	39
MeO	H	-

Scheme 1.32 Pd-catalysed benzylic fluorination

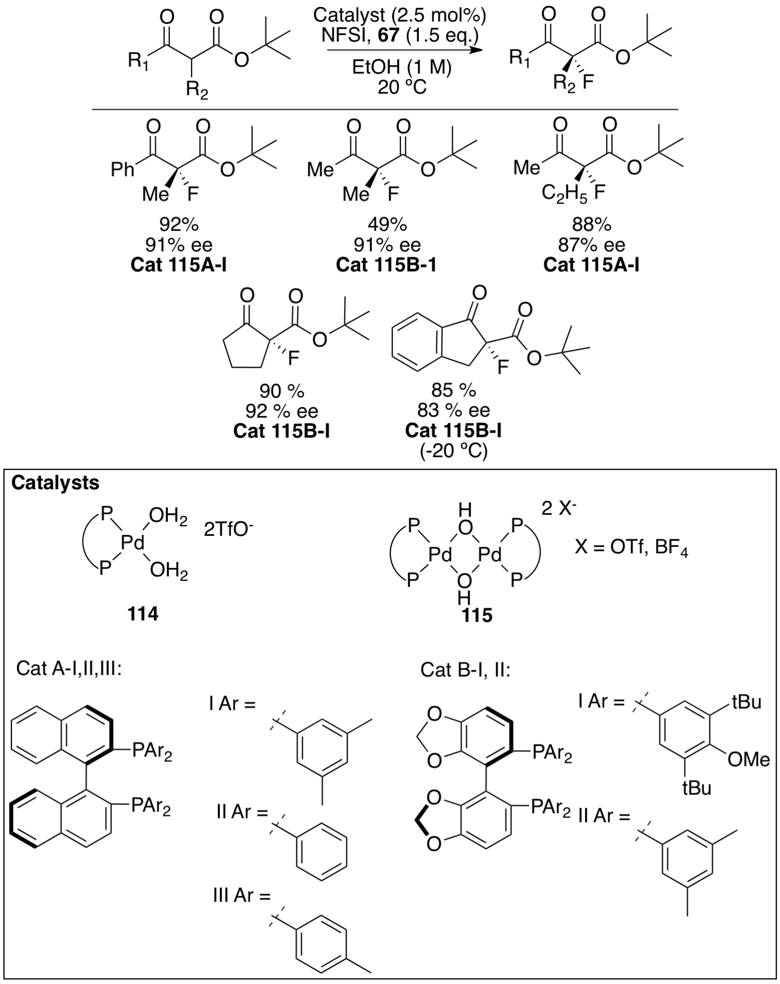
1.2.4 α-Fluorination of Carbonyls

The field of catalytic asymmetric fluorination for the construction of stereoselective C_{sp3}-F bonds, while highly challenging has received a lot of attention over recent years.[55] Substrates that allow the facile formation of enol intermediates are particularly attractive in this research with their ability to react with electrophilic fluorinating reagents. Togni and co-workers were the first to report an asymmetric fluorination of *β*-ketoesters using Ti-taddol based Lewis acids **112/113** in the presence of Selectfluor (**46**) to give α-fluoro-*β*-ketoesters **111** in excellent yields and enantiomeric excesses of 28-90% (Scheme 1.33).[56] The principle of using chiral metal-ligand complexes for enol formation in these transformations has been heavily researched in recent years by the groups of Togni, Cahard, and Shibata who have disclosed asymmetric fluorinations involving chiral Cu^{II}, Ni^{II} and Ru^{II} complexes.[57]



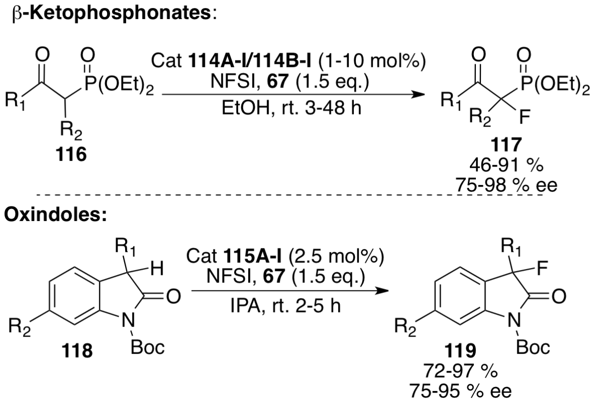
Scheme 1.33 Ti-catalysed enantioselective electrophilic fluorination of *ß*-ketoesters

In 2002, Sodeoka *et al* reported the use of Pd enolates in the catalytic asymmetric Michael reaction of 1,3-dicarbonyl compounds. On the basis of these results the authors developed the asymmetric fluorination of *β*-ketoesters using these same chiral Pd catalysts.[58] The initial optimisations found the use of Pd catalyst **114a-II** bearing a BINAP ligand ((*R*)-(+)-(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine) with NFSI as the fluorinating reagent gave α-fluoro-*β*-ketoesters with moderate enantioselectivities (Scheme 1.34). On changing the ligands to DM-BINAP (3,5-dimethylBINAP) or DTBM-SEGPHOS ((*R*)-(-)-5,5'-bis[di(3,3-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole) gave improved enantioselectivies. Exchanging the catalyst to the Pd μ-hydroxo complex **115** bearing the DTBM-SEGPHOS ligand (cat **115B-I**) was equally successful in this reaction. A substrate scope using these Pd μ-hydroxo complexes **115** gave cyclic and acylic α-fluoro-*β*-ketoesters in high yields and with excellent enantiocontrol (83-94% ee). No loss of reactivity or selectivity was observed on scaling up of the reaction. Furthermore the use of ionic liquids was shown to improved the reaction while allowing the catalyst to be recycled up to ten times in the reaction.[59]



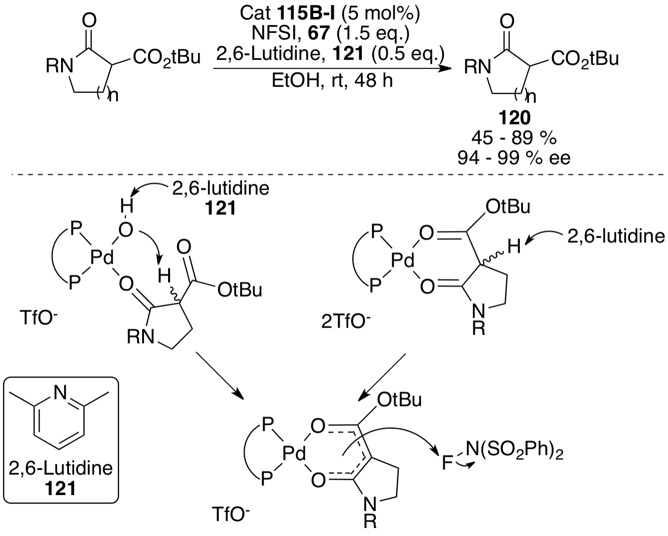
Scheme 1.34 Pd-catalysed α-fluorination of 1,3-dicarbonyl compounds with NFSI

The reaction has been extended to the asymmetric fluorination of *β*-ketophosphonates **116** using catalysts **114A-I/114B-I** with NFSI (**67**) in ethanol.[60] While high levels of enantioselectivity were obtained the yields of this reaction were reduced, proposed to occur due to a large steric repulsion upon fluorination. The reaction was tolerant of cyclic substrates such as tetralones and indanones and acyclic *β*-ketophosphonates, however these acyclic substrates required extended reactions times. The use of catalyst **114A-I** did not allow for the fluorination of *N*-Boc protected oxindoles **118** as deprotection became competitive. The use of catalyst **115A-I** was able to overcome this limitation and allowed access to these useful fluorinated compounds, **119** (Scheme 1.35).[61]



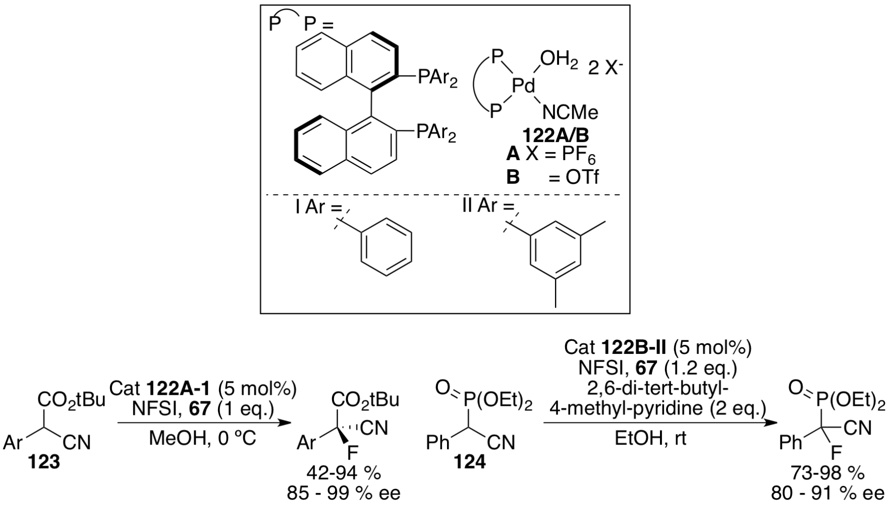
Scheme 1.35 Pd-catalysed fluorination of *ß*-ketophosphonates and oxindoles

Finally this methodology has provided a route to enantioenriched fluorinated lactones and lactams, **120** (Scheme 1.36).[62] In the case of the less acidic lactams the use of the mild base 2,6-lutidine, **121** was necessary as a co-catalyst to aid in enolisation of the substrate. This same system was employed in the asymmetric monofluorination of α-ketoesters.[63]



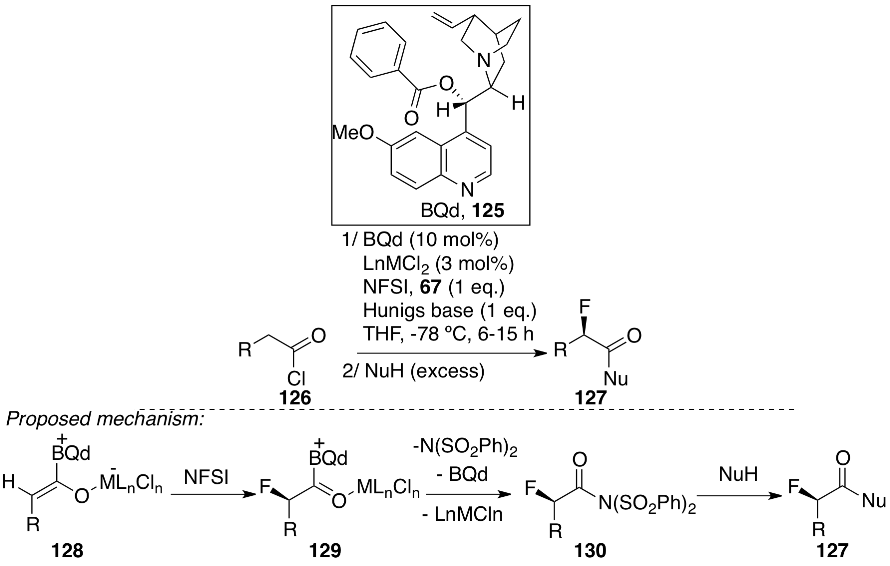
Scheme 1.36 Synthesis of fluorinated lactams using Pd-catalysis in the presence of 2,6-lutidine

Kim and co-workers reported how the fluorination of *β*-keto phosphonates could be further optimized applying new combinations of ligand, catalyst counter-ion and additives.[64] The DM-BINAP catalyst **115A-I** was slightly modified with the replacement of a hydroxyl ligand with acetonitrile and tetrafluoroborate as the counter ion; this system allowed for the efficient fluorination of cyclic and acyclic *β*-ketoesters with NFSI, **67**. The fluorination of arylated *α*-cyanoacetates **123** was best performed with catalyst **122A** ligated to (*R*)-BINAP.[65] The reaction could not be extended to alkyl substituents with the exception of *α*-cyanoalkylphosphonates[66] **124**; these substrates required the addition of 2,6-di-*tert*-butyl-4-methyl-pyridine, the use of the DM-BINAP ligand and catalyst **122B-II** with the triflate counterion (Scheme 1.37).



Scheme 1.37 Pd-catalysed fluorination of *α*-cyanoacetates and *α*-cyanoalkylphosphonates

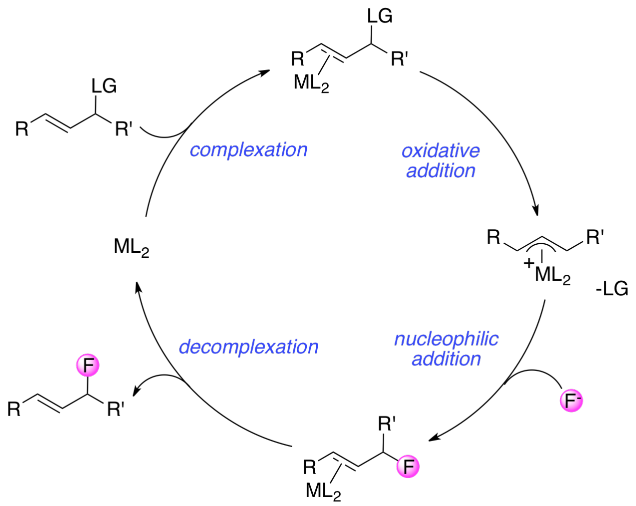
Leckta *et al* have reported the use of a Pd catalyst in conjunction with an organocatalyst.[67] The *α*-fluorination of acyl chlorides **126** was possible using either *trans*$(PPh_3)_2PdCl_2$ or (dppp)$NiCl_2$ and the organocatalyst benzoylquinidine (BQd, **125**) with Hunig's base in the presence of NFSI, **67**. The use of a variety of nucleophiles to quench the amide intermediate provides access to products difficult to reach by direct enolisation/fluorination (Scheme 1.38). The dual catalyst system is proposed to activate the acyl chloride providing a chiral enolate **128** that can then undergo fluorination. Once the fluorinated acyl ammonium salt **129** is formed, subsequent attack by the dibenzenesulfonimide anion gives the amide intermediate **130** that undergoes transacylation with an external nucleophile providing fluorinated products, **127**. Acyl chlorides bearing aryls, heterocycles and aminoalkyl substitutions were tolerated and access to fluorinated acids, amides, esters and thioesters were possible with the corresponding nucleophile. Further investigation of this reaction found the Lewis acid $LiClO_4$ acts as a co-catalyst to give improved yields of aliphatic products by activating the NFSI, **67**.[68]



Scheme 1.38 Dual metal and organocatalysed fluorination of acyl chlorides

1.3 Aims of this Thesis

The examples of Pd-mediated and catalysed fluorinations discussed here display the usefulness of this metal to allow access to a large range of valuable fluorinated compounds. The observation that the use of both electrophilic and nucleophilic sources of fluorine is applicable to this chemistry also adds value to this methodology. A useful fluorinated building block not discussed above is an allylic fluoride. This particular motif has been a focus in the Gouverneur group over the last decade. The formation of an allylic fluoride provides an interesting platform to investigate the development of a selective Pd-mediated fluorination (Scheme 1.39).



Scheme 1.39 Proposed mechanism for a Pd-catalysed nucleophilic allylic fluorination

In the subsequent three chapters the use of Pd in combination with both electrophilic and nucleophilic fluorine is investigated in an allylic system. Initial focus validated the feasibility of an allylic fluorination utilising the standard allylic substitution reaction with a nucleophilic source of fluoride. The development of this reaction to the first Pd mediated C-^{18}F bond formation is discussed. Chapter 3 presents the efforts towards the extension of this methodology to the C-H functionalisation reaction. Finally, Chapter 4 summarises our results in the synthesis of novel (π-allyl)Pd complexes and their reactivity with electrophilic fluorinating reagents leading to access to enantioenriched allylic fluorides.

Chapter 2

Metal Catalysed Allylic Fluorination

2.1 Introduction

The plethora of fluorinated building blocks in natural and non-natural product synthesis is ever increasing. The importance of these compounds is demonstrated in the introduction to this thesis. A valuable fluorinated motif is that of an allylic fluoride. The double bond functionality in this group allows for numerous chemical manipulations making this a particularly useful fluorinated building block.[69]

Fluorinations of allylic alcohols have been reported with various fluoride sources including the Yarovenko's reagent[70], Ishikawa's reagent[71] and 2,2-difluoro-1,3-dimethylimidazolidine depicted in Figure 2.1.

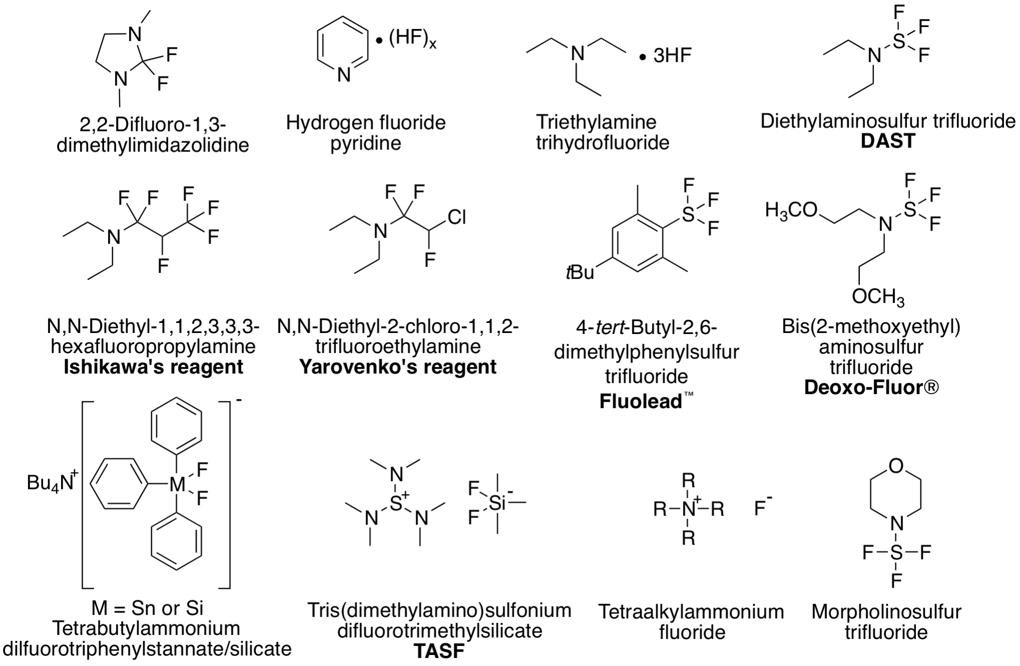
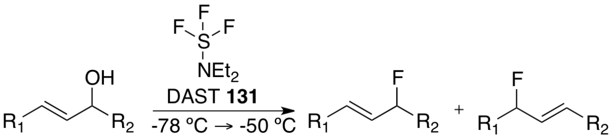


Figure 2.1 Common nucleophilic fluorinating reagents

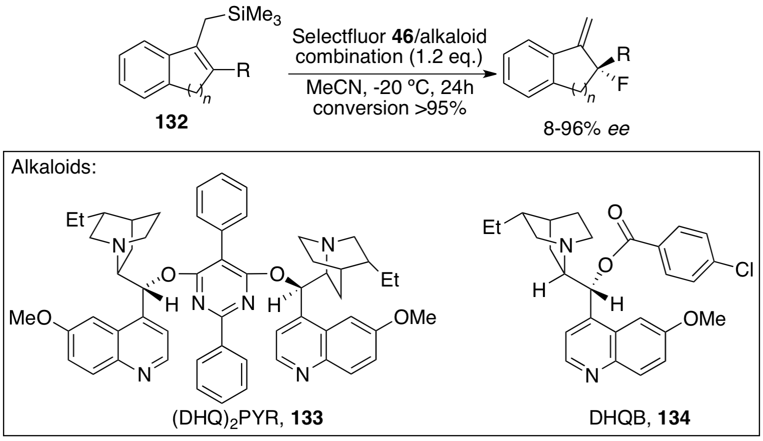
However, the uncatalysed reaction of unactivated allylic alcohols with the nucleophilic fluorinating reagent DAST (diethylaminosulfur trifluoride, **131**) is still the most commonly used synthesis of allylic fluorides since it was first reported by Middleton in 1975 (Scheme 2.1).[72]



Scheme 2.1 DAST fluorination of allylic alcohol giving mixture of regioisomers

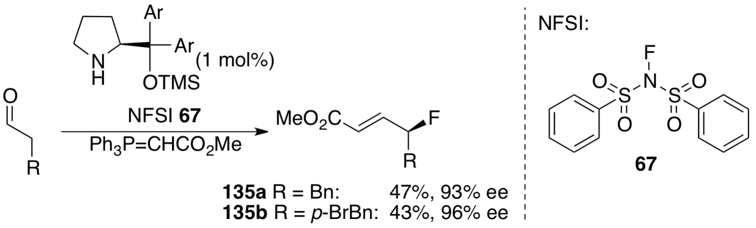
Other sulfur trifluoride derivatives have since been developed such as bis(2-methoxyethyl)-aminosulfur trifluoride (Deoxofluor)[73] and the more recently-reported 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead)[74] (Figure 2.1). Deoxyfluorination of aromatic and aliphatic alcohols has also been reported using 1,3-bis(2,6-diisopropylphenyl)-2,2-difluoro-2,3-dihydro-1*H*-imidazole (PhenoFluor)[75], a reagent developed by the Ritter group in 2011. This reagent was shown to increase functional group tolerance and avoid competing eliminations and side reactions often seen with other reagents.[76] The use of tetralkylammonium fluorides and metal fluorides have also been demonstrated in the fluorination of allylic halides and activated alcohols. However, with all these methodologies, limitations are evident in substrate scope and regio- and stereoselectivity.[77] To some extent, these issues have been addressed using electrophilic fluorinating reagents. Fluorination of unactivated alkenes with *N*-F fluorinating reagents including *N*-fluoropyridinium salts, *N*-fluorobenzenesulfonimide (NFSI, **67**) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate (Selectfluor, **46**) have been reported. In 2003, Gouverneur *et al* demonstrated the use of alkenes **132** temporarily activated at the allylic position with a trimethylsilyl substituent to undergo a regioselective fluorination either with Selectfluor

(**46**) or NFSI (**67**).[78] The use of a bis-cinchona alkaloids **133**/**134** lead to the asymmetric variant of this reaction, with the catalytic reaction later reported (Scheme 2.2). This approach allowed access to a wide range of allylic fluorides with the fluorine substituent on a stereogenic centre.



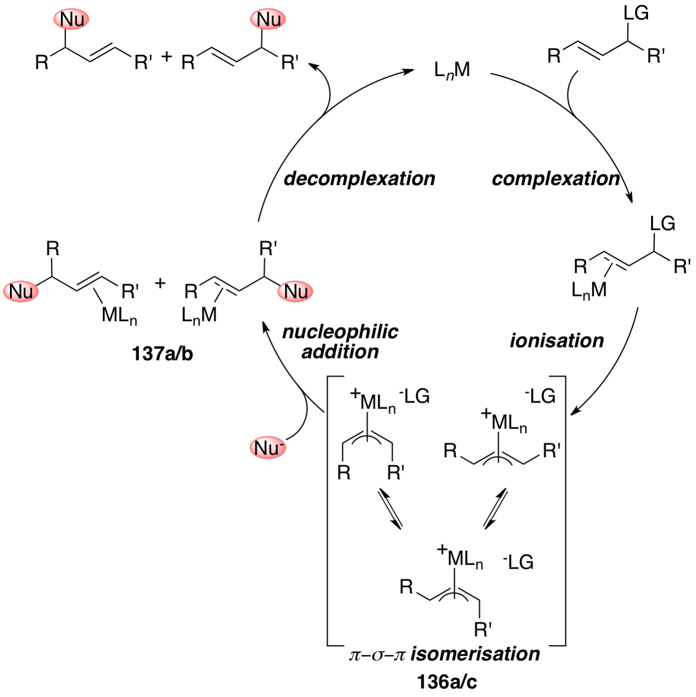
Scheme 2.2 Asymmetric allylic fluorodesilylation

In 2009, Jørgensen *et al* reported the synthesis of enantioenriched allylic fluorides by an α-fluorination/Wittig route. An organocatalytic asymmetric fluorination of an aldehyde with NFSI **67** followed by a Wittig reaction gave allylic fluorides **135a** and **135b** in 47-43% yield and 93-96% ee, respectively (Scheme 2.3).[79]



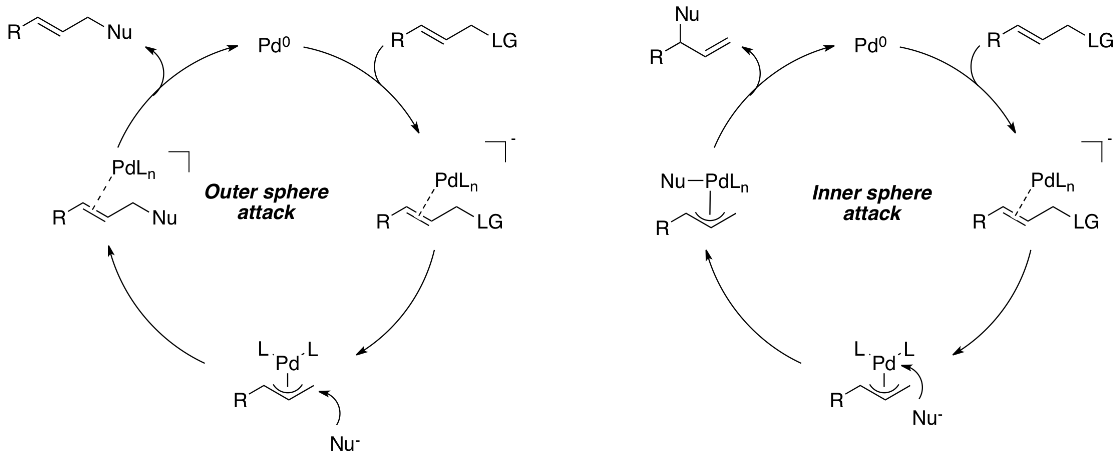
Scheme 2.3 Organocatalytic α-fluorination of aldehydes to give enantioenriched allylic fluorides

The use of late transition metals as catalysts to address these issues of reactivity and selectivity has been considered. In the case of allylic fluorination, the Tsuji-Trost reaction provides a possible alternative regio- and stereoselective nucleophilic route to access allylic fluorides. This reaction has allowed for the introduction of a variety of nucleophiles to allylic compounds in an asymmetric manner, finding applications in natural product synthesis.[80] The mechanism of the Tsuji-Trost reaction is presented in Scheme 2.4; initial coordination of Pd^0 to the allyl carbonate/halide followed by ionisation leads to a π-allylpalladium complex **136a/c**. This species then undergoes external attack of a nucleophile to form an olefin complex **137a**/**b** that releases the product either by a dissociative or associative process.



Scheme 2.4 Mechanism of a Tsuji-Trost allylic substitution

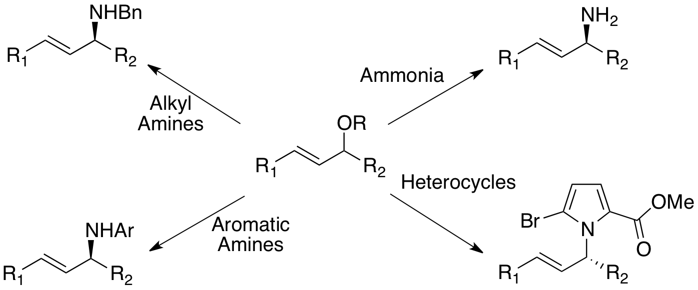
This reaction has been shown to be extremely tolerant providing a diverse substrate scope including acyclic, cyclic, aliphatic, aromatic and a vast array of substitutions at both termini of the allyl as well as the central carbon. These substitutions along with the use of metals other than Pd, such as Mo, W, Ru, Rh and Ir help to determine the regioselectivity of this reaction.[81] The regioselectivity of these reactions is a result of both electronic and steric effects on the allylpalladium intermediate and the type of nucleophile employed. When an unsymmetrical π-allylpalldium species is used where the electronics of both termini are similar soft nucleophiles prefer to attack the least hindered terminus in an outer sphere attack giving the linear products. However hard nucleophiles operate *via* an inner sphere attack forming a metal-nucleophile bond where if reductive elimination of the desired C-X (X = heteroatoms) is faster than the competing isomerisation branched products are formed (Scheme 2.5).[82]



Scheme 2.5 Mechanism of inner and outer nucleophilic attack

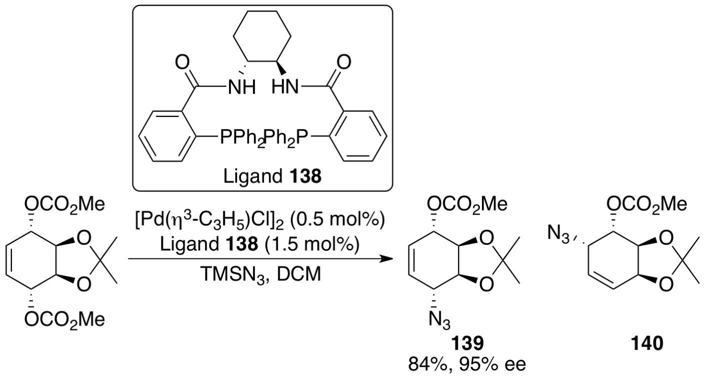
While Pd-catalysed allylic alkylations are well established in the literature when using ‘soft’ carbon nucleophiles, the formation of carbon–heteroatom bonds, such as fluorine, is less well precedented. There are several challenges associated with the use of heteroatoms in conjunction with Pd, in this case in the form of an allylpalladium species.[83] Firstly the ‘hard’ nature of heteroatom nucleophiles such as N, O and halides can often lead to significant affinities towards the metal centre which can inhibit the action of the catalyst or outcompete the olefin substrate for complexation. Futhermore the mismatch of a ‘hard’ nucleophile with a ‘softer’ electrophile such as the π-allylpalladium intermediates mean that productive nucleophilic attack can be difficult. The ample leaving group ability of heteroatom nucleophiles (*i.e.* carbonates, imides, halides) also introduce reversibility into the system and in the case of asymmetric reactions can lead to substantial erosion of the enantiomeric exccess. As a result of these issues halides are often deemed as unsuitable nucleophiles for allylic substitutions. As the formation of a C-N, C-O and C-S bond is essential for almost all pharmaceuticals available to date, substantial research has been carried out in this area.[84] In the case of nitrogen and oxygen nucleophiles, Tsuji-Trost systems have allowed for valuable allylic substitutions to be realised.

A wide range of nitrogen nucleophiles have been utilised in allylic substitutions. The use of ammonia as a nucleophile would be ideal, however problems of polyalkylation and poor nucleophilicity/good ligand availability have led to the use of alternative nucleophiles. Recently the use of aqueous ammonia was used to form a primary allylic amine, diphenyl allyl amine, using $[Pd(allyl)Cl]_2$ and the chiral phosphine ligand (*R*)-BINAP, in a 71% yield and 87% enantiomeric excess, however the scope of the reaction was not investigated.[85] Examples of alkyl, and to a lesser extent aromatic amines, have been reported from 1989 onwards.[86] Efforts to overcome these issues have been addressed with the use of more activated nitrogen centres (Scheme 2.6).



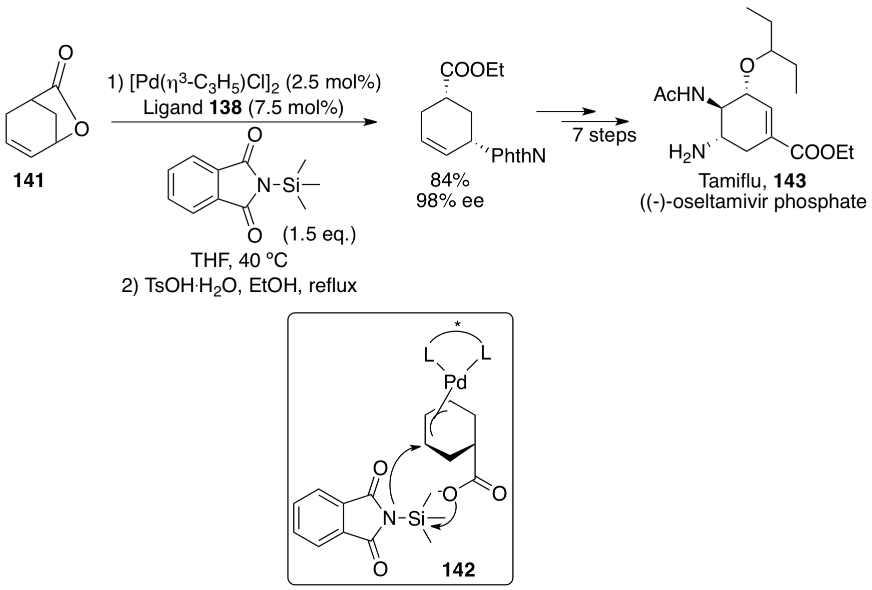
Scheme 2.6 Palladium catalysed allylic substitutions with N nucleophiles

Activated amides, such as *N*-methoxyamide have been used in intramolecular allylic aminations.[87] Furthermore isocyanates and carbodiimides have been used as nitrogen nucleophiles with vinyl epoxides and aziridines.[88] An alternative way to introduce the amino functionality was also reported with the use of azide nucleophiles which can be easily converted to valuable moieties. Trost and Pulley reported the use of trimethylsilyl azide to give 1,4 and 1,2-substituted allylic azides **139** and **140**, the 1,2 product **140** is proposed to form either by Pd catalysed isomerisation of **139** or due to a [3,3]-sigmatropic rearrangement, common in allylic azides. (Scheme 2.7).[89]



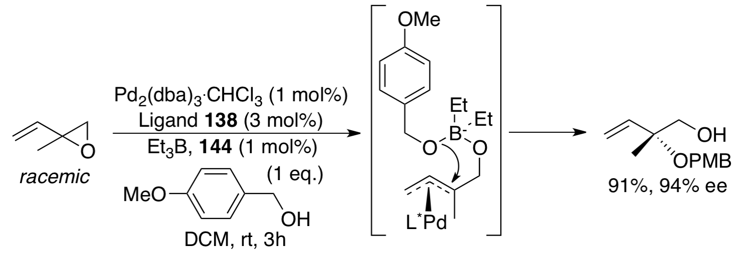
Scheme 2.7 Use of azides as nucleophiles

The introduction of a sulfonyl group to the nitrogen in alkyl substituted and unsubstituted sulfonamides results in the softening of the nitrogen making this a particular attractive nucleophilic for allylic substitutions. This nucleophile is widely used in Tsuji-Trost substitutions for key steps in natural product synthesis.[90] Another method to ‘soften’ the nature of the nitrogen nucleophile is in the case of imides, which allow for the delocalisation of the electron density on the nitrogen into the adjacent carbonyl group. One of the most commonly used nucelophiles in this class is phthalimide, which acts as a protected amino group thoroughout lengthy syntheses. A variety of substrates were shown to undergo allylic substitutions with this class of nucleophile.[91] The usefulness of this reaction was demonstrated in the total synthesis of Tamiflu (Scheme 2.8). The addition of the silyl group allows for the nucleophilic addition to occur as the carboxylate formed after ionisation is silylated *in situ* **142** so the large charge repulsion between the carboxylate and nucleophile is circumvented.[92]



Scheme 2.8 Synthesis of Tamiflu using Pd-catalysed asymmetric allylic alkylation reaction

The most commonly used oxygen nucelophiles are phenols. The high tolerance for substitution on the phenol have meant this reaction has become an extremely powerful tool in total synthesis.[93] Furthermore, allylic substitution with phenols followed by a Claisen rearrangement provides access to asymmetric C-C bonds, increasing the value of this reaction.[94] Efforts have been made to manipulate the nature of the oxygen nucleophiles to allow for the introduction of a wide range of functionalities. The use of other alcohols and alkoxides nucleophiles are demonstrated in the literature. Often the nucleophile must be 'softened' or activation of the substrate towards nucleophile attack is necessary. Intramolecular allylic substitutions have been demonstrated where the alcohol nucleophile is positioned in close proximity to the alkene, activating the substrate to attack by the oxygen.[95] The use of alkoxide nucleophiles in the presence of trialkylborane **144** as an additive was reported to give the desired allylic oxidation products. This additive 'softens' the alkoxide nucleophile by generating a borate species *in situ* that can now attack the π-allylpalladium intermediate, leading to branched products (Scheme 2.9).[96]



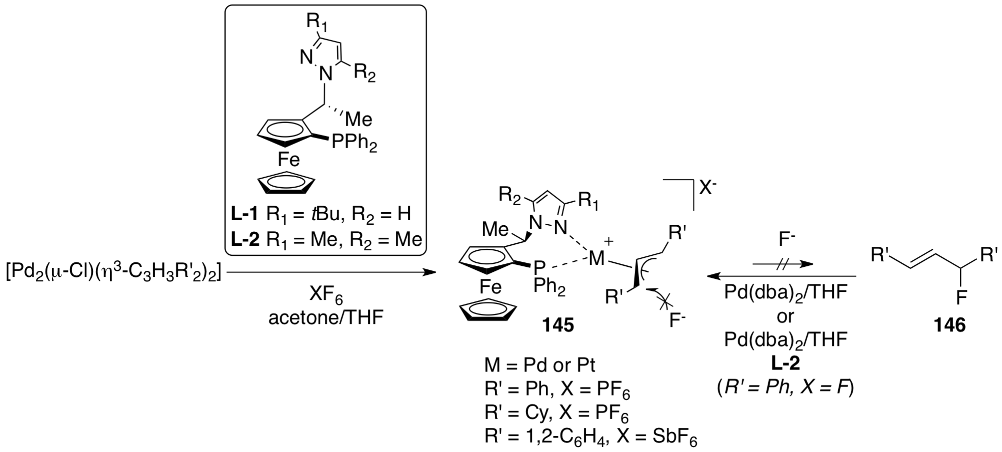
Scheme 2.9 Triethylborane as an additive to soften O nucleophiles in Tsuji-Trost reaction

Silanols or siloxides have also been reported to give allylic alcohols or silyl-protected alcohols.[97] Conjugated 1,2-diketones have been used successfully as nucleophiles in tandem Tsuji-Trost/Claisen sequences, the enol-like structure providing a useful nucleophile.[98] Modifications to nitronates, increasing sterics and conjugation of the substitutents results in increased nucleophilicity of the oxygen over the carbon centre, providing another source of oxygen nucleophile for allylic substitutions.[99] Carboxylates are also useful nucleophiles, leading to allylic alcohols after saponification of the resulting ester.[100] Problems can arise as the products can also act as substrates in the allylic substitution, as such electron-rich carboxylates are often used to ensure the starting allylic carbonate undergoes ionisation in preference to the formed product. Though more commonly used as a base, hydrogen carbonate has also been utilised as a nucleophile in this reaction. Either $NaHCO_3$ is used directly or hydrogen carbonate is generated *in situ* by saponification of the allyl leaving group with water.[101]

Some examples of sulfur as a nucleophile in the Tsuji-Trost reaction are reported using sulfones and thiocarboxylates, however this is far less developed than the analogous carbon, nitrogen and oxygen systems.[102] The use of P and Si nucleophiles has recently received attention.

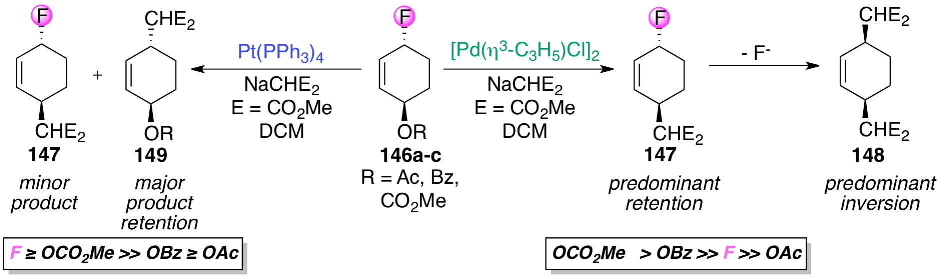
While the problems with these heteroatoms have been addressed, the use of halides in the Tsuji-Trost reaction had not been considered. In the case of fluoride, the numerous difficulties experienced with other heteroatoms persist and are often enhanced due to is small size and highly charged nature. The use of fluoride as a nucleophile in this system also presents its own set of challenges. Solvation of the fluoride ion can drastically decrease its reactivity as a nucleophile while forming a strong Brønsted base that favours elimination over the desired substitution. Furthermore the low nucleophilicity of fluoride in allylic substitution is evidenced by its use as an additive to enhance selectivity or modulate catalytic reactivity in Tsuji-Trost allylic alkyations, not as a competent nucleophile. In these systems, addition of fluoride is proposed to enhance the rate of π–σ–π isomerisation of the π-allylpalladium intermediates, seemingly by interacting with an available coordination site on Pd.[103] Finally the oxidative addition of various metals, including Pd and Pt, into allylic C–F bonds introduces the problem of potential reversibility into this system.[104]

Togni was the first to investigate the feasbility of a Pd-catalysed allylic nucleophilic fluorination.[105] Isolated cationic Pd^{II} and Pt^{II} allyl complexes **145** were prepared and exposed to a variety of fluoride sources at variable temperatures. No allylic fluorides were identified and where substrates were able to undergo eliminations, diene products were formed (Scheme 2.10). In the case of the Pt^{II} complexes anion exhange of PF_6^- for F^- was observed. When allylic fluoride **146** (synthesised from the corresponding bromide and a Ru-F complex[106]) was reacted with $[Pd_2(dba)_3]{\cdot}CHCl_3$ the formation of π-allylpalladium complex **145** (X = F) was observed. The author concluded that the fluorination was thermodynamically unfavourable due to facile oxidative addition of the allylic fluoride to Pd^0.



Scheme 2.10 Feasibility of a transition metal catalysed allylic fluorination

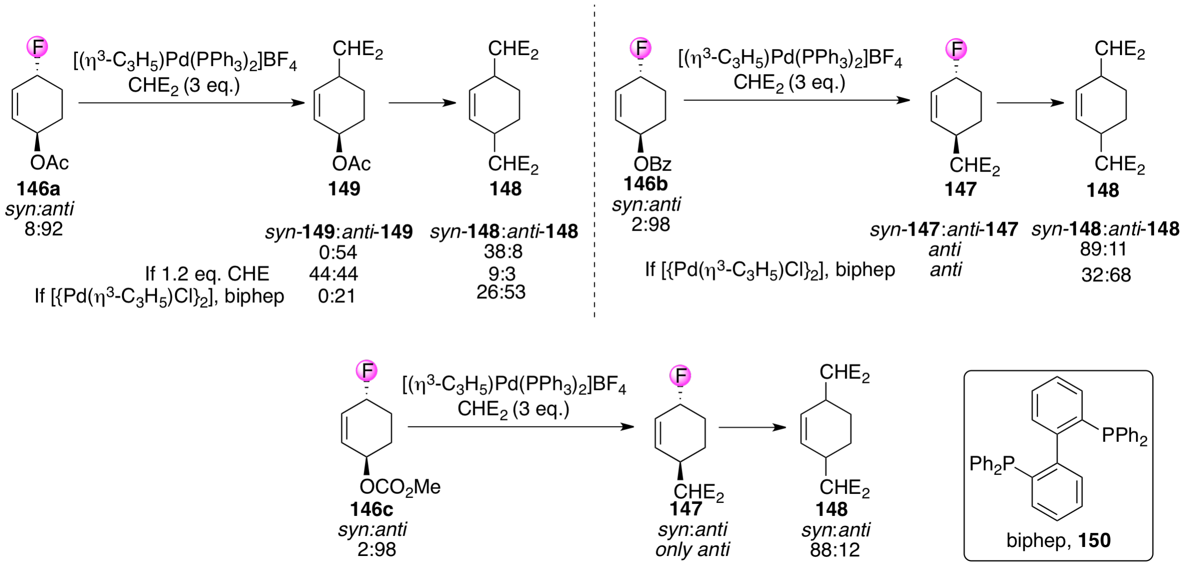
Based on these results, the Gouverneur and Brown groups considered the activation of allylic C–F bonds under Pd^0 and Pt^0 catalysis.[107] Using the model substrate **146a-c**, investigations of the leaving group propensity of the fluoride under traditional Pd/Pt-catalysed allylic alkylations with a malonate nucleophile were undertaken (Scheme 2.11).



Scheme 2.11 Leaving group propensities in metal-catalysed allyl fluoride alkylation

Importantly a different reactivity order was established for both systems. In the case of the Pt-catalysed substitutions fluoride is found to be the superior leaving group to carbonate, benzoate and acetate, suggesting Pt catalysis would not be suitable for an allylic fluorination. However in the case of Pd, while fluoride remains a better leaving group to acetate, benzoate and particularly carbonate are found to be superior.

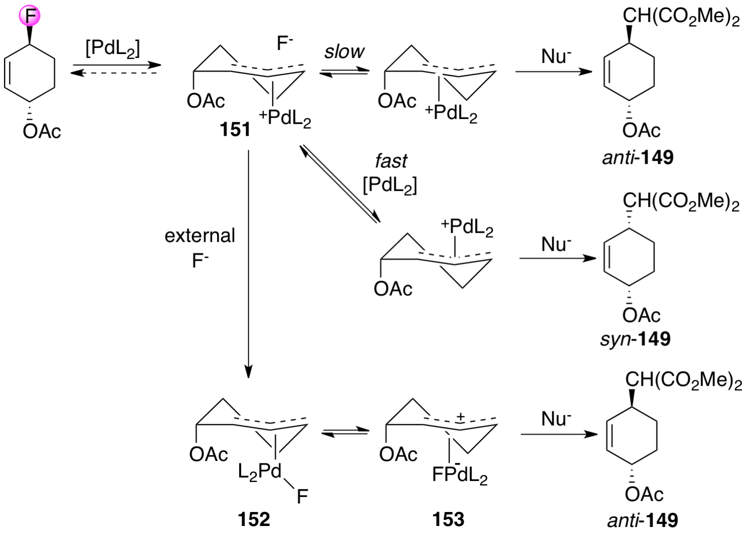
An interesting stereochemical outcome in the Pd-catalysed system was observed. In the case of acetate **146a** as the leaving group the reaction was found to be give both the *syn* and *anti* product **148**. In certain cases intermediate *anti*-**149** was detected, however the more reactive *syn*-**149** was only seen under reagent limited conditions. However when methyl carbonate **146c** or benzoate **146b** were used as the leaving group, the displacement of F$^-$ did not proceed *via* the normal double-inversion retention mechanism (Scheme 2.12).



Scheme 2.12 Stereochemical outcome of allyl fluoride substitution under Pd^0 catalysis

When allyl fluorides **146b**/**c** were reacted with malonate and $[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$ as the catalyst, selective formation of monoinverted product *syn*-**148** was observed. If PPh_3 was replaced with a bidentate ligand such as 2,2'-bis(diphenylphosphanyl)biphenyl (biphep, **150**) overall retention to give *anti*-**148** was preferred. The formation of intermediate **147** was also seen, with predominant retention of configuration in the case of a benzoate leaving group (87% *anti*). In the case of the carbonate leaving group (**146c**) only *anti*-**147** was observed. A preference for retention of configuration was identified with the carbonate leaving group. However in the second step where fluoride is the leaving group an inversion of configuration was observed.

The stereochemical outcome of this reaction was rationalised by the postulated mechanism represented in Scheme 2.13. The initial π-allylpalladium complex **151** formed is proposed to be a tight ion pair, with fluoride as a counterion. In the case of a typical double-inversion pathway this would react with the malonate nucleophile to give the product of overall retention. However if this species reacts reversibly and more rapidly with a Pd^0 nucleophile, due to coulombic repulsion between the fluoride and attacking nucleophile, this standard pathway can be outcompeted and the product of inversion obtained. This is based on the mechanism for stereochemical leakage disclosed by Backväll in 1991.[108] The use of *cis*-chelating diphosphines such as biphep **150** would disfavour this pathway based on the preferred geometry of isolable [P_2Pd] complexes reported to be near-linear, which while possible in the case of monophosphines such as PPh_3 is dsfavoured for *cis*-chelating ligands.

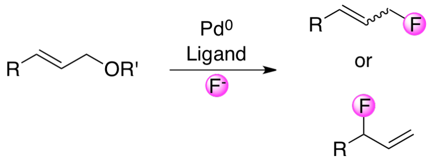


Scheme 2.13 Proposed mechanism for the stereochemical outcome of allyl fluoride alkylation

Experimental investigations into the effect of fluoride concentration revealed increasing the [F^-] favoured retention of stereochemistry. This was suggested to occur *via* the formation of a Pd–F bond, such as that in intermediate **152** that can then undergo ionic dissociation leading to complex **153** and an overall retentive allylic alkylation.

Analogous intermediates to **153** have been reported by Amatore and Jutand.[109] Togni had previously reported that the use of coordinating anions such as fluoride could increase the enantioselectivity of asymmetric allylic amination however the use of non-coordinating anions such as PF_6^-, were detrimental.[110] The effect of the fluoride at the tight-ion pair was supported by the degradation of reaction rate when increasing concentrations of sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate ($NaBAr^F$) were used, in agreement with the previous work.

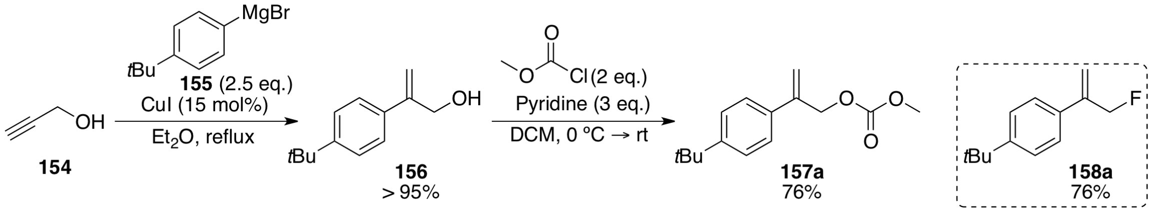
Based on these results we considered the use of a carbonate leaving group under Pd^0 catalysis with the correct choice of ligand, substrate and fluoride source could provide a route to the desired nucleophilic allylic fluorination. In the following chapter our results towards the development of this reaction are presented (Scheme 2.14).



Scheme 2.14 Palladium-catalysed allylic fluorination

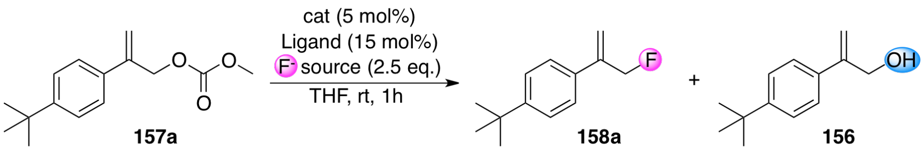
2.2 Preliminary Results

Initial studies focussed on the validation of an allylic fluorination under Pd catalysis.[111] The model substrate 2-(4-(*tert*-butyl)phenyl)allyl methyl carbonate **157** was selected for preliminary investigations based on its inability to undergo competitive elimination reactions. Furthermore the resulting allylic fluorides **158** stability and distinctive ^{1}H NMR (δ = 5.27 ppm, dd, $^2J_{H\text{-}F}$ = 47 Hz $^4J_{H\text{-}H}$ = 6 Hz, CH_2 in $CDCl_3$) and ^{19}F NMR spectra (δ = 212.7 ppm, td, $^2J_{H\text{-}F}$ = 47 Hz, $^4J_{H\text{-}F}$ = 3 Hz), was demonstrated by the previously reported synthesis of (1-fluoromethylvinyl)benzene *via* a fluorodesilylation.[112] A methyl carbonate leaving group was selected based on the established leaving group propensities demonstrating carbonate to be a superior leaving group to fluoride under Pd^0 catalysis, a crucial factor to avoid competing C-F displacement. This substrate was easily prepared by the reaction of 4-(*tert*-butyl)phenylmagnesium bromide **155** (2.5 eq.) with propargyl alcohol **154** in the presence of CuI (15 mol%) providing the allylic alcohol **156** isolated in quantitative yield. This alcohol **156** could be further reacted with methyl chloroformate to give the desired carbonate **157a** in a 76% yield (Scheme 2.15).



Scheme 2.15 Synthesis of model methyl carbonate **157a**

The allylic carbonate **157a** was reacted with various Pd^0/Pd^{II} precatalysts (5 mol%) and ligand (15 mol%) in the presence of 2.5 equivalents of the fluoride source. After stirring in THF for 1 hour at room temperature reactions were quenched with sat. NH_4Cl. ^{1}H-NMR and ^{19}F-NMR spectra of the crude reaction mixture were taken to confirm the presence of the allylic fluoride **158a**. In cases where a substantial conversion to the desired fluorinated product was observed, purification by silica gel column chromatography was performed allowing for isolated yields to be reported. These results are presented in Table 2.1.



Entry	Catalyst	Ligand	Fluoride source	**157a/158a/156**[a]			Yield **158a** [%][b]
1	Pd(dba)$_2$	PPh$_3$	CsF	70	2	28	---
2	Pd(dba)$_2$	PPh$_3$	KF/Kryptofix 222	72	6	22	---
3	Pd(dba)$_2$	PPh$_3$	TBAF$\cdot$3H$_2$O (**159**)	0	8	92	---
4	Pd(dba)$_2$	PPh$_3$	TBAF(*t*BuOH)$_4$ (**160**)	43	43	14	30 (1h)
5	Pd(OAc)$_2$	PPh$_3$	TBAF(*t*BuOH)$_4$ (**160**)	67	13	20	15 (1h)
6	Pd(PPh$_3$)$_4$	-	TBAF(*t*BuOH)$_4$ (**160**)	12	63	25	10 (1h)
7	[Pd(allyl)(PPh$_3$)$_2$][BF$_4$]	-	TBAF(*t*BuOH)$_4$ (**160**)	24	5	71	---
8	-	-	TBAF(*t*BuOH)$_4$ (**160**)	100	0	0	---
9[c]	Pd(dba)$_2$	PPh$_3$	TBAF(*t*BuOH)$_4$ (**160**)	0	100	0	---

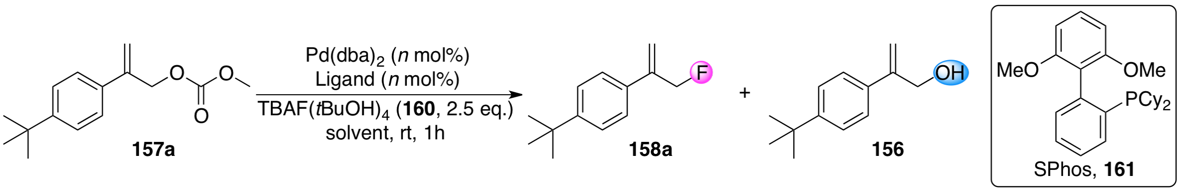
[a] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated product. [c] Control reaction with **158a** as substrate.

Table 2.1 Optimisation of catalyst and fluoride source

The use of the metal fluorides CsF and KF (with solubilising agent Kryptofix 222) as fluoride sources along with the well established Pd(dba)$_2$ (dba = dibenzylideneacetone) and PPh$_3$ catalyst system, only gave trace amounts of the desired allylic fluoride **158a**, along with the corresponding allylic alcohol (entries 1-2). When the more soluble tetralkylbutylammonium fluoride TBAF$\cdot$3H$_2$O (**159**) was employed, complete consumption of the starting material was observed, however the major product was disappointingly found to be the allylic alcohol **156** (entry 3). As the hygroscopic nature of tetraalkylammonium fluorides is well documented we investigated the tetrabutylammonium tetra(*tert*-butyl alcohol)-coordinated fluoride [TBAF(*t*BuOH)$_4$] **160**. This reagent was first reported by Kim and co-workers to be less basic and hygroscopic than standard TBAF and display good levels of nucleophilicity in traditional S_N2 substitution chemistry.[113] The TBAF(*t*BuOH)$_4$ **160** can be easily prepared in quantitative yield by refluxing commercially available TBAF·3H$_2$O **159** and *tert*-butanol in hexanes for 30 minutes and isolating the crystalline solid formed upon cooling. We were pleased to see a vast improvement with this reagent. The use of a Pd(dba)$_2$ and PPh$_3$ catalysis system (entry 4) gave allylic fluoride **158a** in an isolated yield of 30% after 1 hour at room temperature. The use of Pd(OAc)$_2$/PPh$_3$, Pd(PPh$_3$)$_4$ or the preformed allyl complex [Pd(allyl)(PPh$_3$)$_2$][BF$_4$] were found to give lower yields of allylic fluoride (entries 5-7). Attempts to improve the conversion of the fluorination by extending reaction times were unsuccessful. To confirm that the observed allylic fluorination was Pd catalysed, the control reaction was performed in the absence of any Pd catalyst or ligand (entry 8). No formation of allylic fluoride was detected under these conditions with only starting carbonate **157a** recovered, confirming the reaction is Pd-catalysed and not the result of a direct S_N2 mechanism. Furthermore as there is precedent for the activation of allylic C–F bonds by Pd catalysis we investigated the stability of the allylic fluoride **158a** under our reaction conditions. However after 24 hours at room temperature in the presence of Pd(dba)$_2$ and PPh$_3$ only the starting allylic fluoride **158a** was observed, confirming the stability of the C–F under these reaction conditions (entry 9).

2.3 Optimisation of Reaction

With the allylic fluorination of allyl carbonate **157a** validated, we sought to identify standard reaction conditions, which optimised both the yield of allylic fluoride **158a** and reduced formation of the undesired allylic alcohol **156**. Screening of reaction conditions including catalyst/ligand loading, solvent and concentration were carried out (Table 2.2). Varying the catalyst and ligand loadings failed to improved yields of allylic fluoride or reduce alcohol formation (entries 1-4), with the initial 5 mol% Pd(dba)$_2$ and PPh$_3$ found to be the optimum. Use of the bulky monophosphine ligand 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos, **161**) also failed to improved the fluorination. Due to the limited solubility of the TBAF(*t*BuOH)$_4$ **160**, a full solvent screen was not possible however the exchange of THF for DCM showed no improvement in the reaction (entry 6). Varying the equivalents of the fluoride source was shown to decrease the level of conversion in the reaction (entry 7). Furthermore the slow addition of allylic carbonate to a solution of Pd(dba)$_2$, PPh$_3$ and TBAF(*t*BuOH)$_4$ in THF were shown to hinder the fluorination (entry 8). As such the addition of 2.5 equivalents of the crystalline TBAF(*t*BuOH)$_4$ **160** in one portion was found to be the optimal procedure for the fluorination to occur. Reaction concentrations below 0.1 M were shown to not give any allylic fluoride product, as such all fluorinations have been carried out on at a 0.1 M concentration.

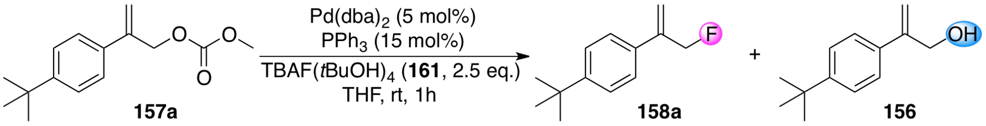


Entry	Pd (mol %)	Ligand (mol %)	Concentration (M)[a]	Solvent	Ratio of **157a**:**158**:**156**[b]		
1	1	PPh$_3$ (3 mol%)	0.1	THF	40	40	20
2	5	PPh$_3$ (15 mol%)	0.1	THF	6	29	65
3	10	PPh$_3$ (30 mol%)	0.1	THF	20	40	40
4	5	PPh$_3$ (15 mol%)	0.01	THF	100	-	-
5	5	SPhos **161**(15 mol%)	0.1	THF	91	0	9
6	5	PPh$_3$ (15 mol%)	0.1	DCM	33	33	33
7[c]	5	PPh$_3$ (15 mol%)	0.1	THF	25	25	50
8[d]	5	PPh$_3$ (15 mol%)	0.1	THF	77	15	8
9[e]	5	PPh$_3$ (15 mol%)	0.1	THF	0	33	67

[a] Concentration based on **157a**. [b] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [c] 1 equivalent of TBAF(*t*BuOH)$_4$ [d] Slow addition of allylic carbonate to reaction mixture over 15 mins. [e] Reaction run in the presence of 3Å molecular sieves.

Table 2.2 Optimisation of reaction conditions

These reactions were monitored over time to establish the optimal point at which conversion of starting material **157a** to the desired allylic fluoride **158a** was at a maximum. Aliquots of the crude reaction mixture were taken at various time points and the ratio of the three compounds determined by analysis of the ^{1}H NMR and ^{19}F NMR spectra; these results are presented in Table 2.3. In the presence of 1 mol% of Pd catalyst (Pd:Ligand 1:3), low levels of conversion were detected even after 24 hours (entry 3). When the catalyst loading was increased, conversion was improved with complete consumption of starting material found between 1-5 hours (entries 2-3). However, after 5 hours only the undesired allylic alcohol **156** was observed, the highest conversion to allylic fluoride **158a** was seen after 1 hour. Monitoring of these reactions at 5 and 15 minutes revealed the transient formation of an unidentified product that could not be detected after this time. Lowering the concentration of the reaction was shown to reduce the level of fluorination with only trace amounts of product detected after 5 hours (entry 4). In the presence of SPhos **161** as the ligand no fluorinated product was formed even after extended reaction times (entry 5). The reaction with slow addition of the carbonate **157a** was similarly unsuccessful, delivering **158a** in a trace amount. In the cases where fluorination was observed, loss of the allylic fluoride **158a** product was evident, with only allylic alcohol **156** remaining after 24 hours in most cases. With the combination of the Pd(dba)$_2$ and PPh$_3$ catalyst system, with 2.5 equivalents of fluoride source for 1 hour at room temperature identified as the optimal system for fluorination, our attention turned to reducing the formation of allylic alcohol **156**.

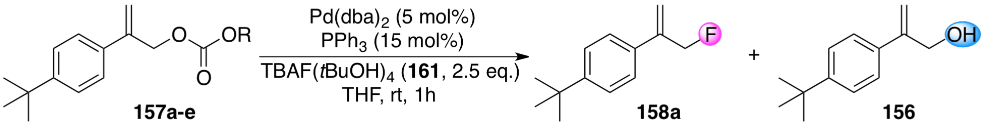


Entry	Pd mol%	PPh$_3$ mol%	Ratio **157a:158a:156**[a]			
			30 min	1h	5h	24h
1	1	3	48 : 33 : 19	48 : 33 : 19	19 : 34 : 47	11 : 23 : 66
2	5	15	17 : 41 : 41	2 : 6 : 92	0 : 0 : 100	0 : 0 : 100
3	10	30	21 : 32 : 47	22 : 33 : 45	17 : 50 : 33	-
4[b]	5	15	100: 0 : 0	100 : 0 : 0	38 : 24 : 38	-
5[c]	5	15	95 : 0 : 5	91 : 0 : 9	67 : 0 : 33	-
6[d]	5	15	50 : 30 : 20	33 : 33 : 33	11 : 9 : 80	0 : 0 : 100
8[e]	5	15	-	77 : 15 : 8	-	0 : 0 : 100

[a] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Reaction concentration 0.01M [c] SPhos **161** as ligand [d] Reaction run in DCM [e] Slow addition of allylic carbonate to reaction mixture over 15 mins.

Table 2.3 Monitoring of reaction over extending reaction times

At this point we were unsure of the mechanism by which the alcohol side product **156** was formed; direct hydrolysis of the methyl carbonate **157a** as well as a Pd mediated substitution with external hydroxide were possible. The use of dry solvents along with the addition of molecular sieves to the reaction to remove any remaining water failed to reduce formation of the allylic alcohol (Table 2.2, entry 9). To assess the extent to which the carbonate leaving group was responsible for the alcohol formation we investigated the use of alternative leaving groups in this reaction. These substrates could be easily prepared in an analogous way to the allylic carbonate **157a**. When the commonly used acetate **157b** and trifluoroacetate **157c** leaving groups were exposed to the standard fluorination conditions only starting material or the undesired allylic alcohol **156** were observed by ^{1}H NMR and ^{19}F NMR analysis of the crude reaction mixtures (Table 2.4, entries 2-3).



Entry	**157a-e**	R	**157/158a/156**[a]			Yield of **158a** [%][b]
1	**157a**	OMe	43	43	14	30
2	**157b**	Me	100	0	0	-
3	**157c**	CF_3	0	0	100	-
4	**157d**	Ph	80	20	0	-
5	**157e**	p-$NO_2C_6H_4$	0	100	0	> 95
6[c]	**157e**	p-$NO_2C_6H_4$	100	0	0	-

[a] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated product.
[c] Reaction run in the absence of Pd catalyst

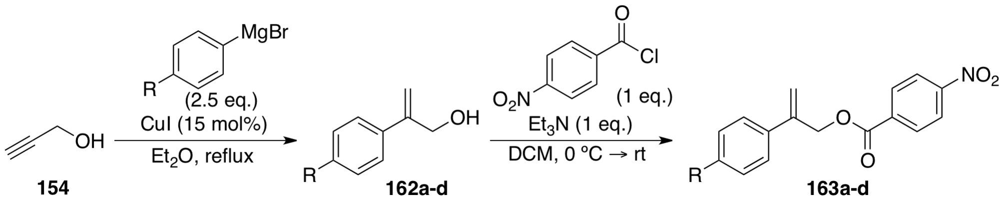
Table 2.4 Optimisation of leaving group

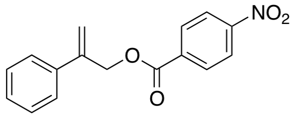
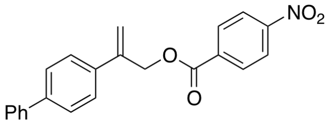
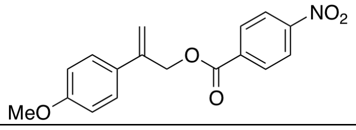
The use of benzoate **157d** gave some conversion to allylic fluoride **158a** and no alcohol formation was detected (entry 4). The *p*-nitrobenzoate leaving group was next investigated, for which there is little precedent in the literature. The Jutand group reported the use of this group to increase the rate of π–σ–π isomerisation in allylic transformations but its use as a leaving group as not been investigated.[114] Pleasingly, substrate **157e** gave a quantitative yield of the desired allylic fluoride **158a** in 1 hour at room temperature when using the optimised catalyst system of $Pd(dba)_2$ and PPh_3 along with 2.5 equivalents of $TBAF(tBuOH)_4$ as the fluoride source (entry 5). Furthermore no trace of the allylic alcohol side product could be detected. A control reaction in the absence of Pd and ligand showed no fluorination, confirming the reaction is Pd-catalysed (entry 6).

2.4 Preparation of Allylic *p*-Nitrobenzoates

The synthesis of substrates was conducted in collaboration with Dr. Matthew Tredwell (University of Oxford).[115]

Having optimised the reaction conditions, we next investigated the scope and limitations of the nucleophilic allylic fluorination with a range of different linear and *gem*-disubstituted allylic *p*-nitrobenzoates. The *gem*-disubstituted substrates **163a-c** were synthesised from the aryl Grignard and propargyl alcohol in an analogous procedure to that of substrate **157a**, originally reported by Zheng and co-workers[116], followed by reaction of the corresponding allylic alcohol **162a-c** with 4-nitrobenzoyl chloride (1 eq.) in the presence of triethylamine. Where necessary the Grignard was prepared *in situ* by the reaction of the corresponding aryl bromide and magnesium turnings (1.03 eq.) with a bead of iodine and used without titration (Table 2.6).

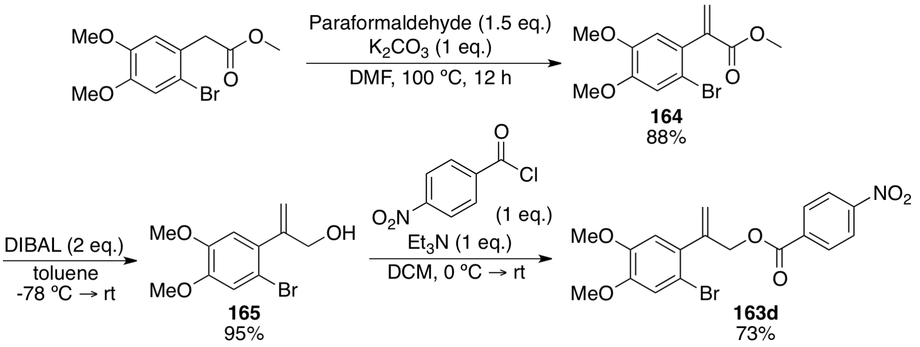


Entry	R	Yield of Alcohol	Final Product X	Yield[a]
1	H	90%		83% (**163a**)
2	Ph[b]	70 %		95% (**163b**)
3	OMe[b]	20 %		60% (**163c**)

[a] Isolated yield. [b] Grignard prepared *in situ*

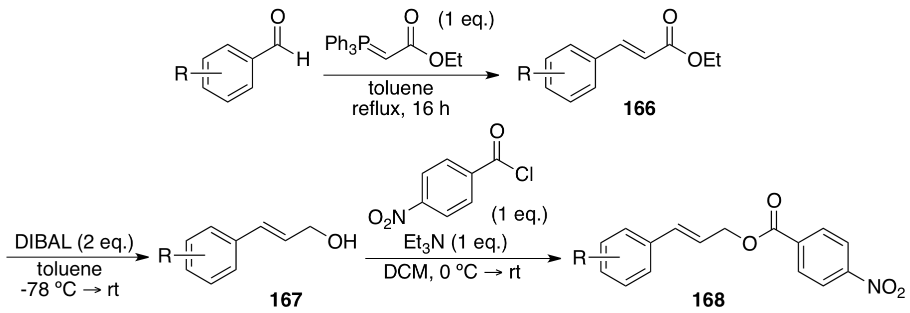
Table 2.5 Preparation of 2-substituted propenyl benzoates

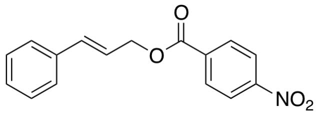
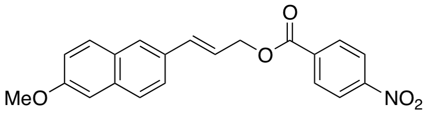
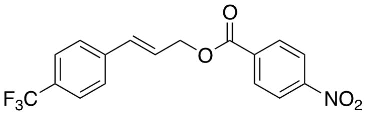
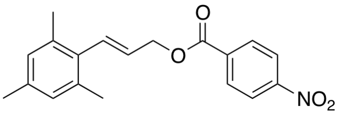
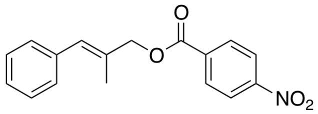
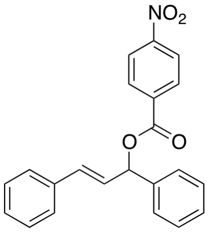
Under these conditions, allylic *p*-nitrobenzoates **163a-c**, bearing various substitutions at the *para* position of the phenyl group were delivered in good to excellent yields up to 95%. Substrate **163d** was also prepared from the reaction of methyl 2-(2-bromo-4,5-dimethoxyphenyl)acetate with paraformaldehyde (1.5 eq.) in the presence of K_2CO_3 as the base. Subsequent DIBAL reduction of the intermediate acrylate **164** gave the allylic alcohol **165** in excellent yield that could be easily functionalised to the corresponding *p*-nitrobenzoate **163d** (Scheme 2.16).



Scheme 2.16 Synthesis of *p*-nitrobenzoate **163d**

A series of linear cinnamyl *p*-nitrobenzoate derivatives were synthesised *via* two different synthetic routes where the allylic alcohol was not commercially available. Substrates **168b-d** were prepared by a Wittig reaction of the corresponding aryl aldehyde and (carbethoxymethylene)triphenylphosphorane to give the intermediate esters **166**. Subsequent DIBAL reduction gave the allylic alcohol products **167b-d**. Theses alcohols along with the commercially available alcohols were reacted with 4-nitrobenzoyl chloride affording allylic *p*-nitrobenzoates **168a-f**. This provided substrates with both electron-withdrawing and donating substitutents present on the phenyl group in good to excellent yields (Table 2.6). The ratio of geometrical isomers (*E* or *Z*) was obtained from analysis of the crude ^{1}H NMR spectra. The isomers were easily separated by silica gel column chromatograpy and the isolated yields reported are for the pure *E* isomers. The stereochemistry of the final product was assigned from the ^{1}H NMR spectra. The observed $^3J_{HH}$ alkene coupling constant of 16 Hz in the ^{1}H NMR spectra of each substrate is consistent with the proton-proton coupling across a *trans*-double bond. A smaller coupling constant of $^3J_{HH}$ of 12 Hz is observed for a *cis*-double bond. The branched allylic nitrobenzoate **168f** was synthesized, that had previously been investigated by Togni *et al* in a Pd-catalysed allylic fluorination and found to be unsuccessful.[105]

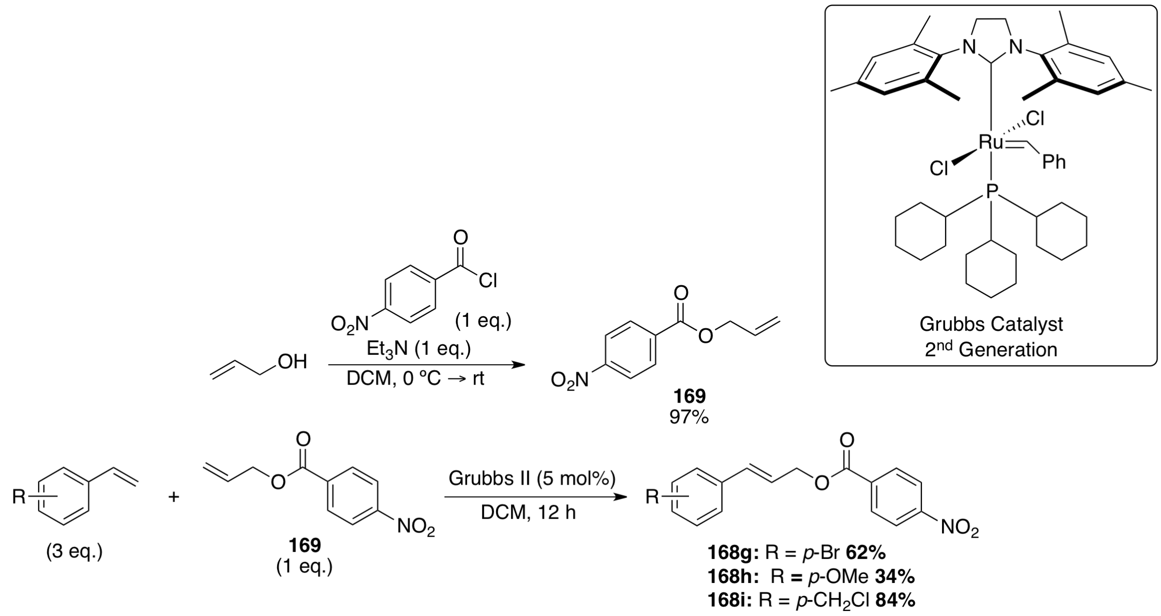


Entry	Yield of Acrylate	Yield of Alcohol	Final Product	Yield[a]
1	-	-[b]		**168a** 95% *E*:*Z* >20:1
2	75%	98%		**168b** 70% *E*:*Z* >20:1
3	50%	48%		**168c** 55% *E*:*Z* >20:1
4	94%	30%		**168d** 63% *E*:*Z* >20:1
5	-	-[b]		**168e** 72% *E*:*Z* >20:1
6	-	-[b]		**168f** 63% *E*:*Z* >20:1

[a] Isolated yield. [b] Allylic alcohol is commercially available

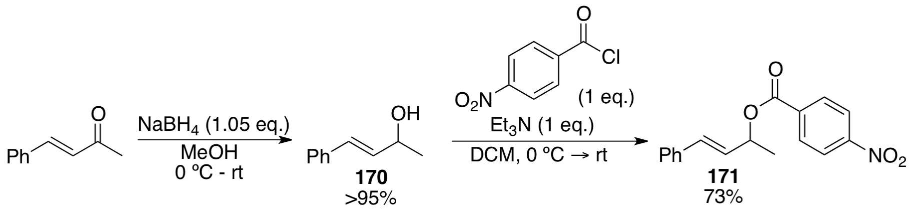
Table 2.6 Preparation of linear allylic *p*-nitrobenzoates Xza-d

The cross-metathesis of styrene derivatives with allyl 4-nitrobenzoate **169** (accessed from allyl alcohol) using Grubbs II catalyst provided linear allylic *p*-nitrobenzoates **168g-i** in yields up to 84% (Scheme 2.17)



Scheme 2.17 Preparation of linear allylic *p*-nitrobenzoates **168g-i**

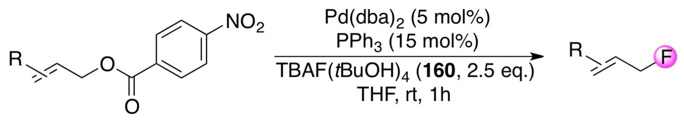
The branched substrate **171** was also synthesis by a sodium borohydride reduction of (3*E*)-4-phenyl-3-butene-2-one to afford alcohol **170**. The protection of this alcohol with 4-nitrobenzoyl chloride provided **171** in 73% isolated yield (Scheme 2.18).

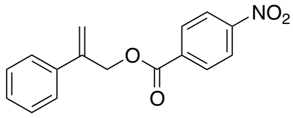
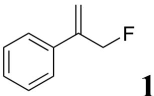
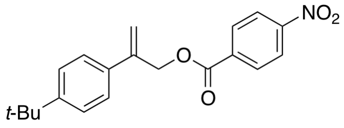
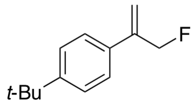
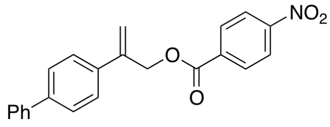
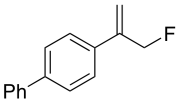
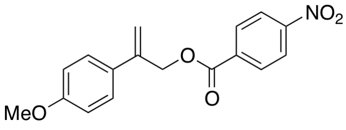
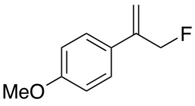
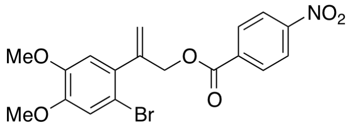
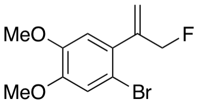
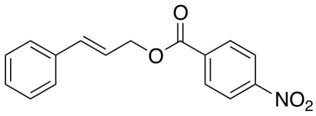
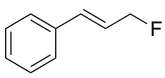
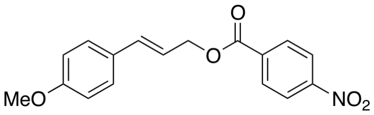
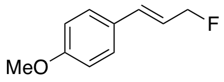
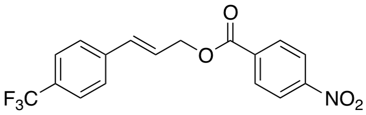
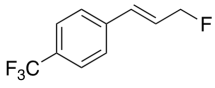
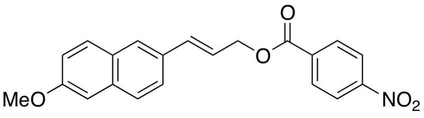
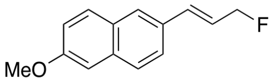
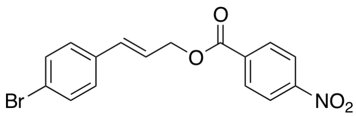
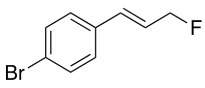
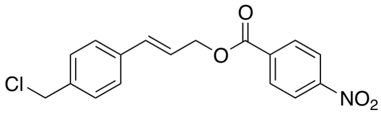
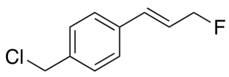
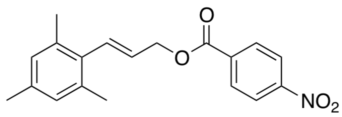
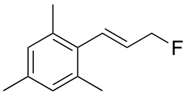


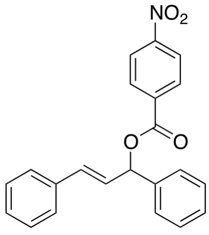
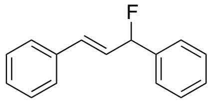
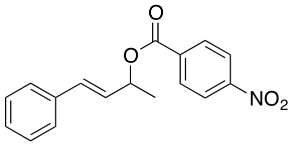
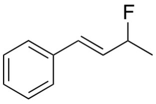
Scheme 2.18 Synthesis of branched allylic *p*-nitrobenzoate **171**

2.5 Scope and Limitations of the Allylic Fluorination

The allylic *p*-nitrobenzoates were subjected to the fluorination conditions with $Pd(dba)_2$ (5 mol%), PPh_3 (15 mol%) and TBAF(*t*BuOH)$_4$ (2.5 eq.) in THF (0.1M). The results are displayed in Table 2.7.



Entry	Allylic *p*-Nitrobenzoate	Allyl Fluoride	Yield [%][a]
1	 **163a**	 **158b**	66
2	 **157e**	 **158a**	> 95
3	 **163b**	 **158c**	95
4	 **163c**	 **158d**	85
5	 **163d**	 **158e**	84
6	 **168a**	 **172a**	> 95
7[b]	 **168h**	 **172b**	39
8[c]	 **168c**	 **172c**	35
9	 **168b**	 **172d**	46
10	 **168g**	 **172e**	53
11	 **168i**	 **172f**	60
12[c]	 **168d**	 **172g**	65

13[d]	 **168f**	 **172i**	0
14[d,e]	 **171**	 **172j**	5

[a] Isolated yield. [b] Reaction run for 1 h at rt and 20 min at 40 °C. [c] Reaction run at 40 °C for 4 h. [d] Determined by ^{1}H NMR of crude mixture as product unstable. [e] Major product identified as diene

Table 2.7 Nucelophilic allylic fluorination of allyl *p*-nitrobenzoates

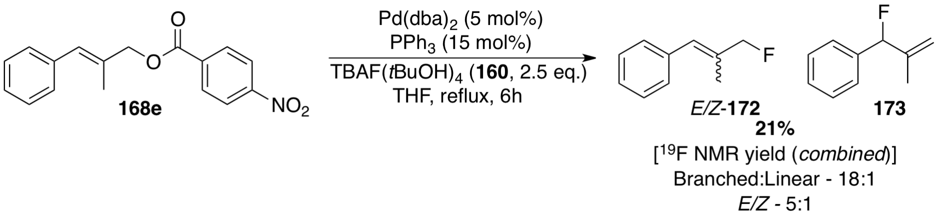
The reactions were monitored by thin layer chromatography (TLC) and quenched upon completion, in most cases this was found to be within 1 hour. The various 2-substituted propenyl *p*-nitrobenzoates have comparable reactivity to the model *t*-butyl substituted substrate **157e**. Removal of substitution on the phenyl group was found to yield a highly volatile fluoride product **158b** and so while reactivity remained as efficient the isolated yield in this case was lowered (Entry 1). The reaction was shown to tolerate electron-donating and withdrawing substituents on the phenyl group as well as multiple substitutions (entries 3-5) with yields of 95%, 85% and 84% possible for allyl fluorides bearing either *para* phenyl **158c**, *para* methoxy **158d** or 2-bromo-4,5-methoxy- **158e** groups.

We were pleased to see that cinnamyl fluoride **172a** could be accessed in a quantitative yield under these conditions (entry 6), a compound reported to be highly unstable and difficult to isolate. This demonstrates that the fluorination conditions were mild enough to prevent decomposition of sensitive products.[117] Furthermore the branched regioisomer was not detected in the ^{19}F NMR sprectra (distinctive peak at -169.6 ppm, linear isomer is found at -210.8 ppm), as is the case in the unselective DAST mediated fluorination of cinnamyl alcohol.[118] Other linear allyl fluorides were accessed using this procedure. Where electron rich allyl fluorides were formed yields were lower, as demonstrated by compounds **172b** and **172d** which were obtained in 39% and 46% yield, respectively. Monitoring of the reactions showed that the reaction is efficient when an electron-donating substituent is present however the products were sensitive to the work-up and purification. When an electron-withdrawing substituent was present on the (2*E*)-3-phenylprop-2-en-1-yl substrates the reaction was found to be less efficient. In the case of a *para* bromo substituent **168g** a moderate yield of 53% of allyl fluoride **172e** was possible (entry 10). With the *para* trifluoromethyl analogue **168c** heating of the reaction to 40 ºC for 4 hours was required to obtain a low yield of allyl fluoride **172c** (35%, entry 8). A sterically hindered mesityl nitrobenzoate **168d** was also tolerated in the reaction giving a yield of 65% of **172g** after heating at 40 ºC for 20 minutes in addition to the 1 hour at room temperature. Substitutions at both *ortho* positions of 2,6-disubstituted arylallyl esters have not previously been tolerated in other Pd coupling chemistry. The reaction was found to be chemoselective for the *p*-nitrobenzoate motif. Along with the formation of 1-bromo-4-[(1*E*)-3-fluoroprop-1-en-1-yl]benzene which contains an easily manipulated aryl halide functionality, the allyl fluoride **172f** was accessed that contains a chloromethyl group that may also undergo further functionalisation. The ability of this mild reaction to tolerate these functional groups improved the value of this methodology to access useful fluorinated building blocks.

Attempts to access allyl fluoride **172i** were unsuccessful, which is comparable to the results obtained by Togni *et al.*[105] A limitation of this methodology is the competing elimination reaction to form the corresponding diene product as demonstrated with substrate **171**. The allyl fluoride **172j** was only formed in conversions < 5%, whereas the corresponding diene was detected in a 45% conversion from the ^{1}H NMR spectra of the crude reaction mixture by the diagnostic peaks at 5.18 ppm and 5.34 ppm that correspond to the terminal protons of the alkene.

The reaction was found to highly regioretentive with only linear allylic fluorides observed from the starting linear *p*-nitrobenzoates. When branched allylic *p*-nitrobenzoates **168f** and **171** were utilised, poor reactivity was observed preventing the formation of branched allylic fluorides under these reactions conditions. The regioselectivity of Pd-catalysed allylic substitutions have been heavily investigated with a 'memory effect' often seen where the regioselectivity of the reaction is determined by the regiochemistry of the starting allylic precursor. Lloyd-Jones *et al* presented a mechanistic rationale for this in the generation of an unsymmetrical π-allylpalladium intermediate that results in the nucleophilic attack occurring *trans* to the π-accepting ligand (often phosphine).[119] These reactions therefore give regioretentive products as long as nucleophilic attack is faster than the competing isomerisation of the π-allylpalladium intermediate. The allylic fluorination discussed is shown to be regioretentive which would suggest that this memory effect could be operating and furthermore that the fluoride ion adopts the behaviour of a soft nucleophile with an outer sphere attack at the least hindered allyl terminus. Attempts to access branched allylic fluorides from branched starting benzoates resulted in fast isomerisation of the starting allylic *p*-nitrobenzoate to the linear isomer under the reaction conditions.

One substrate that did give a mixture of regioisomers was allylic *p*-nitrobenzoate **168e**. Fluorination of compound **168e** gave a mixture of branched **173** and linear fluorides *E*-**172** and *Z*-**172** (Scheme 2.19). By ^{19}F-NMR we observed that the ratio of **173**:**172** was 1:18 and that the allylic linear products *E*-**172** and *Z*-**172** are in a ratio of 5:1 (*E*:*Z*). This is the only example where we have observed any trace of the branched product. In comparison to other substrates compound **168e** was much less reactive requiring refluxing in THF for 6 h to show any conversion to the fluorinated products. Previous work has identified that changing the electronics of the termini on the allylpalladium intermediate or the nature of the ligands can reverse the regioselectivity of the reaction to favour the branched product over the linear product. The use of electron-withdrawing groups on allylic precursors results in nucleophilic attack at the terminus distant from the electron-withdrawing motif. Furthermore the use of tricyclohexylphosphine, PCy_3, has been shown to catalyse allylic alkylations of terminal allylic acetates with high regioselectivity toward branched products.[120] Other ligands, even those of similar basicity or bulkiness, did not show the same regioselectivity. However when we investigated this fluorination further with PCy_3 as the ligand no allylic fluoride products were detected.

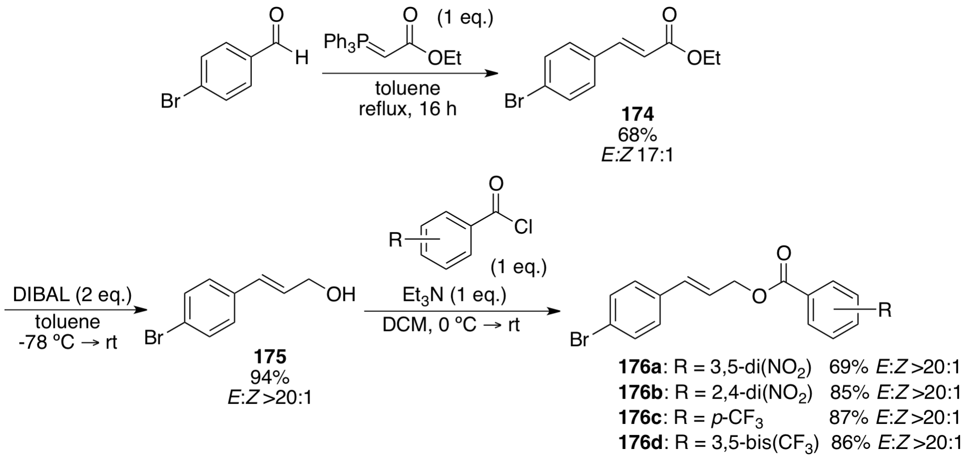


21%
[^{19}F NMR yield (*combined*)]
Branched:Linear - 18:1
E/Z - 5:1

Scheme 2.19 Synthesis of branched and linear allyl fluorides

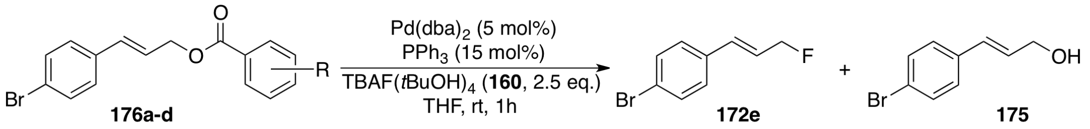
2.6 Investigation into leaving group effect

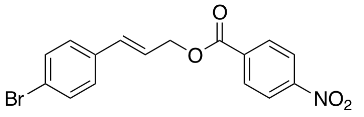
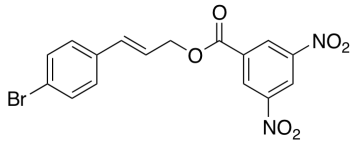
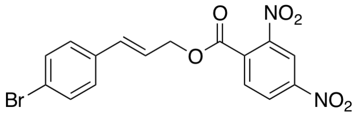
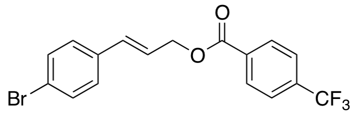
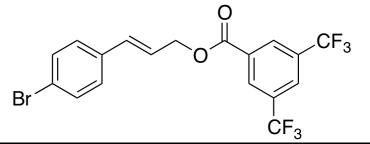
As the reason for the superior behaviour of the *p*-nitrobenzoate as a leaving group is not fully understood in this system further investigations focused on variation of this group, in the hope that the reactivity could be improved and competitive side reactions suppressed. Allyl benzoate **168g** was chosen as a model substrate to investigate as only a moderate yield of allyl fluoride **172e** (53%) was possible under our optimised fluorination conditions. A variety of leaving groups were screened with various electron-withdrawing substitutents on the benzoate. This study was conducted in collaboration with M. L. Ó Dúill (Part II).[128] These (2*E*)-3-(4-bromophenyl)prop-2-en-1-yl derivatives **176a-d** were easily accessed in excellent yields following the procedure in Scheme 2.20. Acid chlorides that were not commercially available were synthesized *in situ* from the reaction of the corresponding carboxylic acids with thionyl chloride.



Scheme 2.20 Synthesis of (2*E*)-3-(4-bromophenyl)prop-2-en-1-yl benzoate derivatives **176a-d**

These substrates were subjected to the optimised fluorination conditions and the ratio of products determined by analysis of the ^{1}H NMR spectra of the crude reaction mixture. Where appropriate isolated yields of the allyl fluoride **172e** were obtained after purification by silica gel column chromatography (Table 2.8).

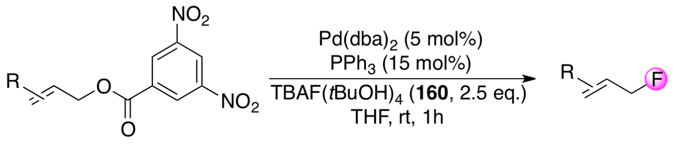


Entry	Allyl benzoate	Ratio of **176**:**172e**:**175**[a]	Yield of **172e**[b]
1		48:52:0	53
2		5:33:62	33
3		77:8:15	3
4		61:25:6	20
5		71:21:7	14[c]

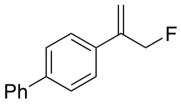
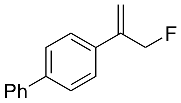
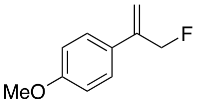
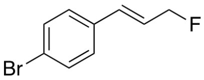
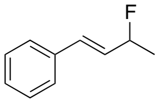
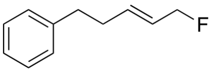
[a] Ratio determined by analysis of ^{1}H NMR of crude reaction mixture. [b] Isolated yield. [c] Yield determined from ^{1}H NMR

Table 2.8 Fluorination of (2*E*)-3-(4-bromophenyl)prop-2-en-1-yl benzoate derivatives

In all cases the yield of allyl fluoride **172e** was lower than the parent *p*-nitrobenzoate leaving group (53%). The use of *p*-trifluoromethylbenzoate **176c**, 3,5-bis(trifluoromethyl)benzoate **176d** and 2,4-dinitrobenzoate **176b** showed little reactivity under the fluorination conditions with the starting benzoate mainly recovered and low yields of allyl fluoride **172e** of 20%, 14% and 3%, respectively. In the case of the 3,5-dintrobenzoate **176a** leaving group a yield of 33% was possible however allylic alcohol **175** was the major product of this reaction. A plausible reason for this would be the direct hydrolysis of the substrates bearing superior leaving groups competing with the Pd-catalysed substitution. The reactivity of this leaving group was further screened on substrates **177**, **178**, **179** and **180** that were accessed *via* the protocol depicted in Table 2.5, giving good overall yields after the various steps. These 3,5-dintrobenzoates were then subjected to the standard fluorination conditions (Table 2.9).



177-180

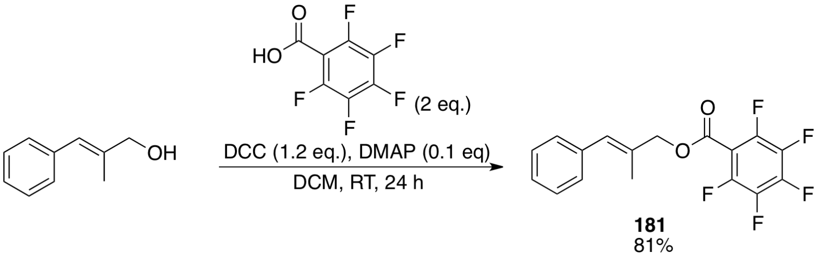
Entry	Product	Yield [R' = 3,5-di(NO_2)][a]	Yield [R' = *p*-NO_2][a]
1[b]	 **158c**	> 95%	95%
2[c]	 **158c**	0%[d]	0%
3	 **158d**	60%	85%
4	 **172e**	33%	53%
5	 **172j**	3%[e]	5%[f]
6	 **172h**	Trace[g]	Trace

[a] Isolated yield. [b] Reaction time of 30 minutes. [c] Reaction carried out in the absence of Pd. [d] 55% recovered starting material, 45% allylic alcohol by ^1H NMR. [e] 61% recovered starting material, 39% diene by ^1H NMR. [f] 45% diene by ^1H NMR. [g] 42% recovered starting material, 58% diene by ^1H NMR.

Table 2.9 Comparison of 3,5-dintrobenzoate and *p*-nitrobenzoate as leaving groups

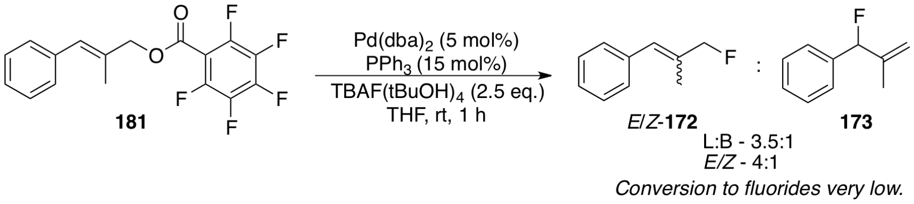
The use of the 3,5-dintrobenzoate as a leaving group was found to give diminished yields in comparison to the *p*-nitrobenzoate. Furthermore the formation of diene was still apparent in substrates where elimination was possible. A reaction run in the absence of Pd catalysis was found to give the allylic alcohol **156b** in a 45% ^1H NMR yield (entry 2) demonstrating that its formation is not, or at least not entirely, metal mediated in the case of the 3,5-dintrobenzoate.

Recent work investigating the development of the nucleophilic allylic florination reaction for FPSE purification has identified a pentafluorobenzoate as leaving group with comparable reactivity to the *p*-nitrobenzoate.[121] As such the substrates, which were not successful in the nitrobenzoate chemistry were synthesized with a pentafluorobenzoate leaving group. The reaction of (*E*)-2-methyl-3-phenylprop-2-en-1-ol (1 eq.) with pentafluorobenzoic acid (1.1 eq.) in the presence of *N*,*N'*-dicyclohexylcarbodiimide (1 eq.) and 4-(dimethylamino)pyridine (12 mol%) gave the desired pentafluorobenzoate **181** in excellent yield (Scheme 2.21).



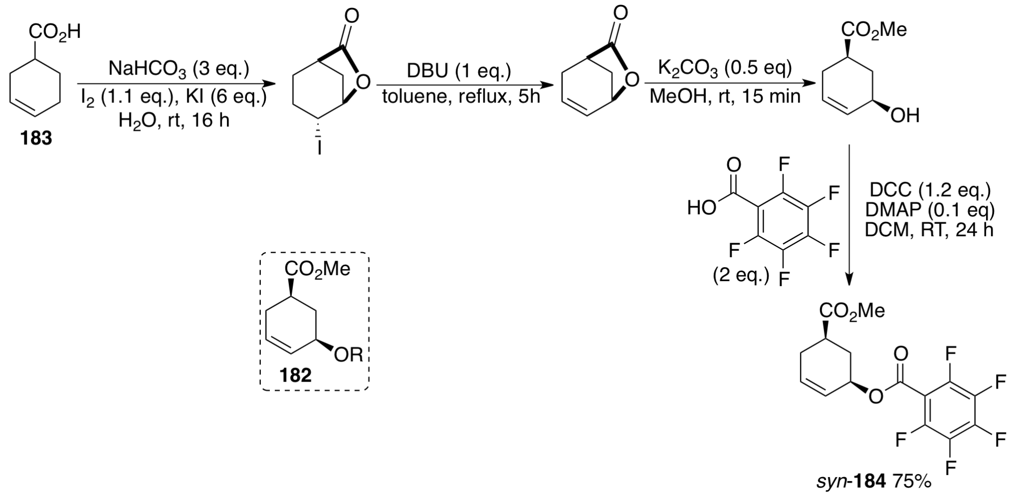
Scheme 2.21 Synthesis of pentafluorobenzoates

This substrate was then subjected to the conditions established for the allylic fluorination. Traces of linear **172** and branched fluoride **173** were detected for the reaction of (*E*)-2-methyl-3-phenylallyl 2,3,4,5,6-pentafluorobenzoate **181** in a ratio of 3.5:1 (linear:branched) however the conversions were very low not allowing for isolated yields to be obtained (Scheme 2.22).



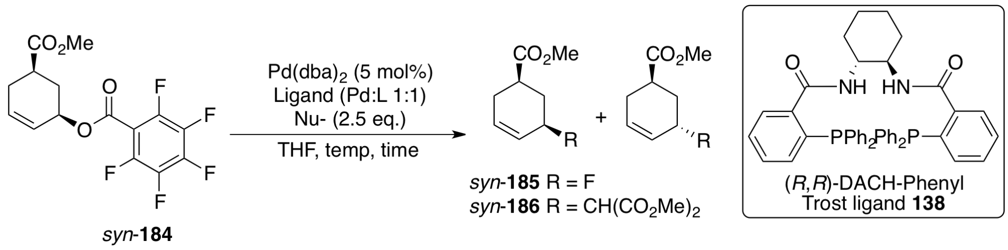
Scheme 2.22 Fluorination of pentafluorobenzoates

The cyclic substrate often used in allylic substitution reactions, (1*R*,5*R*)-5-(methoxycarbonyl)cyclohex-2-en-1-yl carbonate **182**, was synthesized bearing a pentafluorobenzoate *syn*-**184** to see if the use of this leaving group allowed for fluorination to occur as the *p*-nitrobenzoate was not successful on this system. The substrate was synthesized following the procedure of Watson from 3-cyclohexene-1-carboxylic acid **183** (Scheme 2.23).[122]



Scheme 2.23 Synthesis of cyclic pentafluorobenzoate

The screening of *syn*-**184** with different ligands, nucleophiles and temperature was carried out (Table 2.10). Extremely low conversions to the *syn*-fluoride **185** were seen when triphenylphosphine was used as a ligand with TBAF(*t*BuOH)$_4$. As no reaction was seen with the use of any other ligand in the presence of TBAF(*t*BuOH)$_4$ control reactions were carried out using a malonate nucleophile. We were surprised to find that in the case of the malonate no reaction was seen with triphenylphosphine, however with the use of the (*R,R*)-DACH-phenyl Trost ligand **138** full conversion to the *syn*-**186** was seen. In both the case of the fluorination and alkylation the stereochemistry is retained.



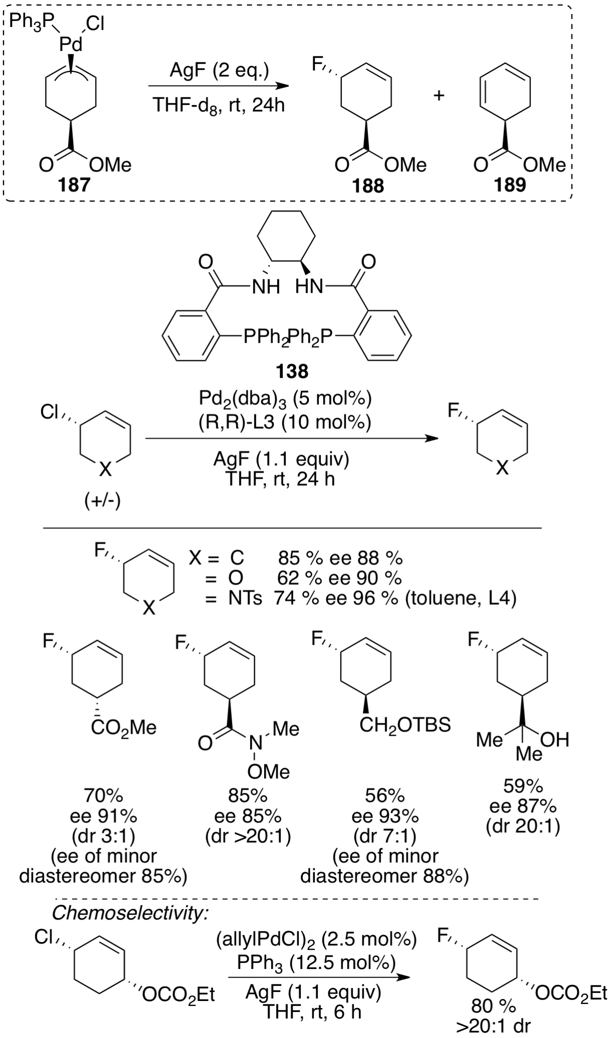
Entry	Ligand	Temperature	Nucleophile	Result
1	PPh_3	rt	F^-	Low conversion to *syn* fluoride
2	(R,R)-DACH-Phenyl Trost ligand **138**	rt	F^-	-
3	(R,R)-DACH-Phenyl Trost ligand **138**	60	F^-	-
4	XantPhos	60	F^-	-
5	PPh_3	rt	Malonate	-
6	(R,R)-DACH-Phenyl Trost ligand **138**	rt	Malonate	Full conversion to *syn* product

Table 2.10 Screening of cyclic substrate

As the yield of allylic fluorides could not be improved and alcohol formation became competitive, along with β-hydride elimination when using 3,5-dintrobenzoate or pentafluorobenzoate we concluded the optimal leaving group to still be *p*-nitrobenzoate and turned out attention to the investigation of ligands as a way to control the competing β-hydride elimination in the fluorination system.

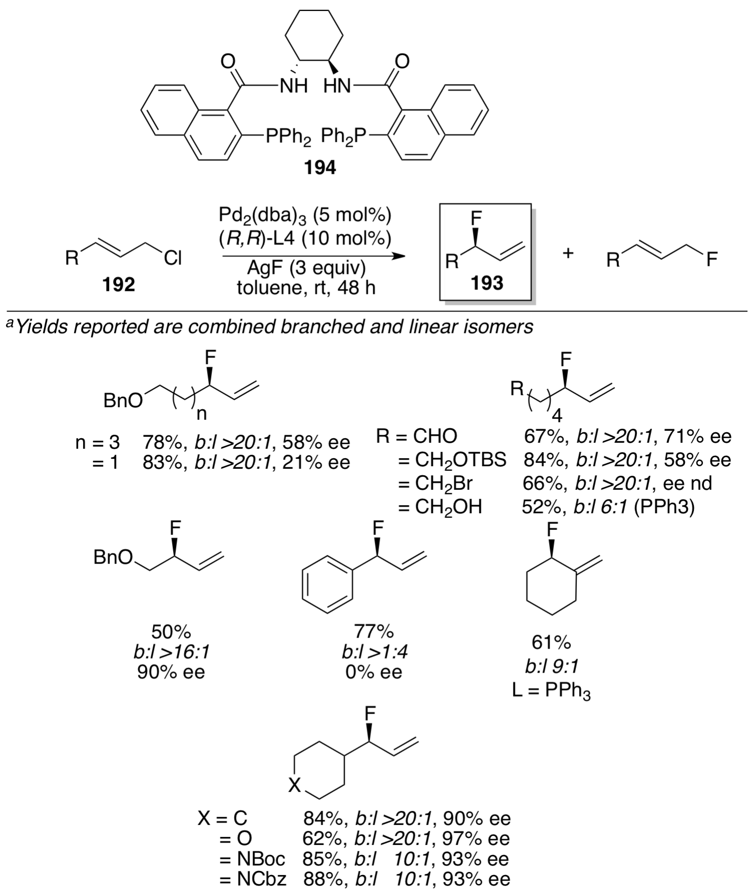
During the course of this project, Pd-catalysed asymmetric allylic fluorination was published by Doyle *et al.*[123] Initial stoichiometric reactions on a known palladium(II)allyl complex[124] **187** formed from the starting allyl chloride[125] found that AgF was the optimal source of fluoride giving allylic fluoride **188** with a 49% NMR yield and surprisingly only a 4% yield of the product of elimination **189**. The reason for the lack of elimination is not detailed. The catalytic variant of this reaction utilising allylic chlorides was developed. In contrast to the work presented here the conventional leaving groups in palladium catalysed allylic alkylations are found to be unreactive in this system, with only allylic chlorides giving good yields up to 88% of the desired allyl fluorides **191** using the commercially available Trost ligand, (1*R*,2*R*)-(+)-1,2-diaminocyclohexane-N,N′-bis(2-diphenylphosphinobenzoyl), **138** to impart high levels of enantioselectivity. Control reactions confirmed that the background S_N2 reaction can be suppressed at room temperature in non polar solvents so the enantiomeric excess is not diminished. The reaction was shown to be tolerant of a wide range of functional groups such as ethers, amines, esters, amides and even the silyl ethers and unprotected alcohols, functionalities known to be sensitive to fluoride. All allyl fluorides were obtained in good to excellent yields (56-85%) with enantiomeric excesses from 85 to 96% measured when the allylic fluorides were stabile to isolation, Scheme 2.24.

Furthermore this work provides a route to access allyl fluorides with easily functionalised motifs tolerated under the reaction conditions. The reaction is shown to be chemoselective for the allyl chlorides even in the presence of an allylic carbonate, which could be easily functionalised in subsequent Pd-catalysed reactions. Mechanistically, the authors proposed an initial inversion in the oxidative addition of Pd^0 into the allyl chloride followed by a second inversion due to S_N2-type outer-sphere attack of the fluoride on the allyl ligand, giving the product with overall retention of configuration. This stereochemical outcome fits with the expected result from the use of a soft nucleophile, not a hard nucleophile such as fluoride. The previous work on cyclic substrate *syn*-**184** that gave the product of retention suggests the allylic fluorination we have developed operates *via* the same mechanism.



Scheme 2.24 Pd catalysed asymmetric fluorination of allylic chlorides

The reaction was later extended to the fluorination of acyclic linear allylic chlorides using the naphtyl substituted Trost ligand (1*R*, 2*R*)-(+)-1,2-diaminocyclohexane-*N,N'*-bis(2-diphenylphosphino-1-naphthoyl) **194**. Linear chloride precursors **192** were shown to give predominantly branched allylic fluorides **193** in good yields, and poor to high levels of enantioselectivity (0-97%) (Scheme 2.25).[126]



Scheme 2.25 Formation of enantioenriched branched allylic fluorides

The preference for the formation of branched products still remains unclear however the authors proposed the small size of the fluoride and possible hydrogen bonding interaction with the chiral ligand could contribute. Work by Lloyd-Jones and Norrby has demonstrated the regiodirected delivery of nucleophiles (other than fluoride) is facilitated by hydrogen-bonding with the amide N−H in cationic Pd-η^3-allyl and Pd-η^3-cyclohexenyl bearing *trans*-cyclohexylenediamine-based Trost ‘Standard Ligand’ **138**.[127] Screening of solvents identified toluene as the optimum, giving the highest level of enantioselectivity. The authors propose this is due to the limited solubility of AgF in this solvent, surpressing the background S_N2 reaction. A wide range of functionalities were tolerated other than a free alcohol, which resulted in competitive intramolecular capture of the transiently formed Pd-η^3-allyl complex. Access to tertiary fluorides did not exceed

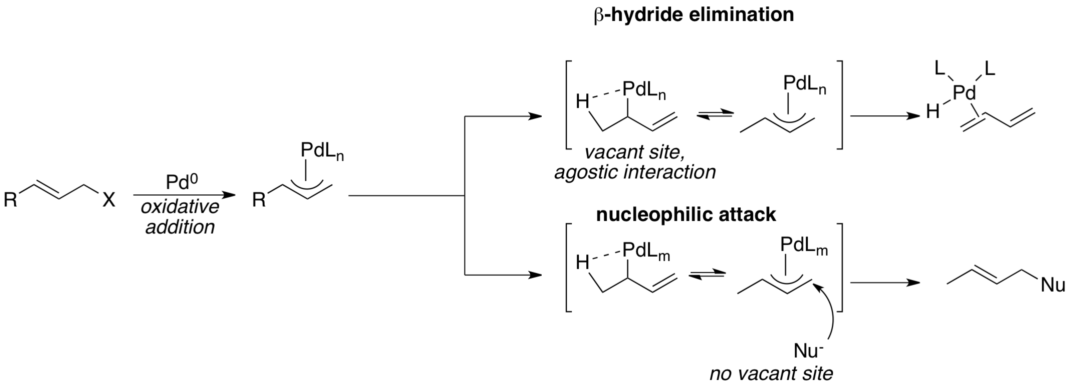
45% due to competitive elimination reactions leading to diene formation.

2.7 Attempts to Overcome β-Hydride Elimination

With the scope and limitations of the allylic fluorination methodology identifying the competitive β-hydride elimination as the major obstacle in expanding the process to allow access to branched allyl fluorides our attention turned to addressing this problem. This study was conducted with Miriam L. Ó Dúill (Part II, University of Oxford, 2011)[128] and this section provides a summary of the results.

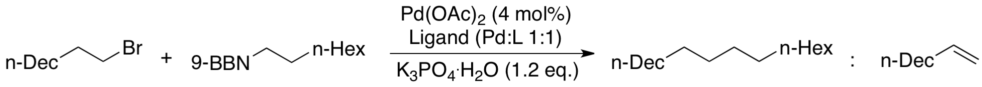
2.7.1 Investigation of ligands as a way to suppress β-hydride elimination

It is well known that to afford a β-hydride elimination the metal and hydride must adopt a conformation allowing for a *syn*-periplanar arrangement with a vacant site on the metal to allow for a concerted *syn*-elimination.[129] This agostic interaction is well documented and substantial efforts have been made to overcome this competitive side reaction in metal cross-coupling reactions (Scheme 2.26).



Scheme 2.26 Competitive β-hydride elimination in allylpalladium system

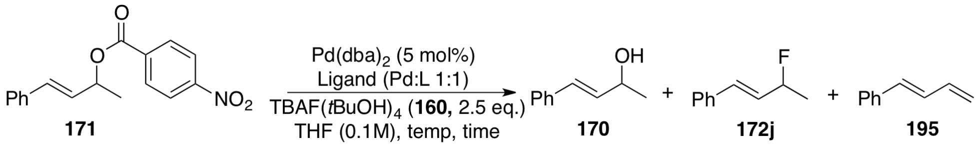
As detailed studies into overcoming β-hydride elimination have not been carried out on allylic substitutions we based our investigations on other systems. While mechanistically different, work has been carried out by Fu *et al* that demonstrated that sterically bulky phosphine ligands with wide bite angles and electron-donating ability have reduced the undesired β-hydride elimination in Suzuki cross-coupling reactions with alkyl halides possessing β-hydrogens (Scheme 2.27).[130]



Ligand	GC Ratios	
PPh_3	<2	<2
PCy_3	85	<2
$P(OPh)_2$	<2	<2
dppf (99 °)	<2	12
binap (93 °)	<2	12
$P(t\text{-}Bu)_3$	<2	21
$P(o\text{-}tol)_3$	<2	14
$P(n\text{-}Bu)_3$	9	27

Scheme 2.27 Effect of ligand on Suzuki coupling[131]

Furthermore Hartwig and Buchwald reported the use of sterically hindered bidendate ligands reduce the amount of β-hydride elimination in aryl aminations.[132] It is proposed that the higher coordination number of the metal along with increased bite angles of the ligand disfavour β-hydride elimination and favour reductive elimination to form the desired product. Encouraged by these findings ligand screens were carried out using a variety of common mono and bidentate phosphine ligands on (3*E*)-4-phenylbut-3-en-2-yl 4-nitrobenzoate **171**, which under our standard conditions gave 5% fluoride **172j** and 45% diene **195**. The ratio of products formed in this reaction could be easily distinguished by observation of the allylic proton in each product by ^{1}H NMR analysis of the crude mixture (**171**: 5.83, dq, *J* = 7.0 Hz, 6.5 Hz; **170**: 4.49 ddq, *J* = 6.5 Hz, 1.0 Hz (x2); **172j**: 5.21, ddq, *J* = 48.0 Hz, 6.5 Hz, 1.0 Hz; **195**: 6.52, ddd, *J* = 17.0 Hz, 11.0 Hz, 10.0 Hz.). In all cases a mixture of starting *p*-nitrobenzoate, allylic alcohol, allylic fluoride and diene were observed, these results are presented in Table 2.11.



Entry	Ligand	Time (h)	Temperature (° C)	Ratio of **171**:**170**:**172j**:**195**			
1	PPh3	24	rt	65	6	6	23
2	PPh3	24	40	8	7	21	64
3	JohnPhos **197**	24	rt	65	27	0	8
4	JohnPhos **197**	24	40	47	44	1	8
5	JohnPhos **197**	48	40	40	55	0	5
6	dppf (99 °) **198**	24	rt	63	17	0	20
7	dppf (99 °) **198**	24	40	41	25	5	29
8	Xantphos **199**	24	rt	4	7	23	66
9	Xantphos **199**	24	40	4	7	23	66
10	Xantphos **199**	48	40	0	18	0	82

Table 2.11 Effect of ligand on β-hydride elimination

Initial reactions were carried out at room temperature and showed poor conversions of the starting *p*-nitrobenzoate **171** with both mono and bidentate ligands.[1] In the case of dppf **198** and JohnPhos **197** low conversions were also observed with extended reaction times and increased temperatures. However when Xantphos **199**, a bidentate ligand reported to control both reactivity and selectivity of a reaction due to the bite angle and rigidity of the backbone was used levels of conversion were improved.[133] While higher levels of conversion were possible with this ligand at both room temperature and 40 ºC, there was no improvement in the selectivity of fluorination over β-hydride elimination when compared to triphenylphosphine at 40 ºC (entry 2). Control reactions in the absence of Pd only gave unreacted starting benzoate **171** and no formation of diene **198**. As TBAF(*t*BuOH)$_4$ can play

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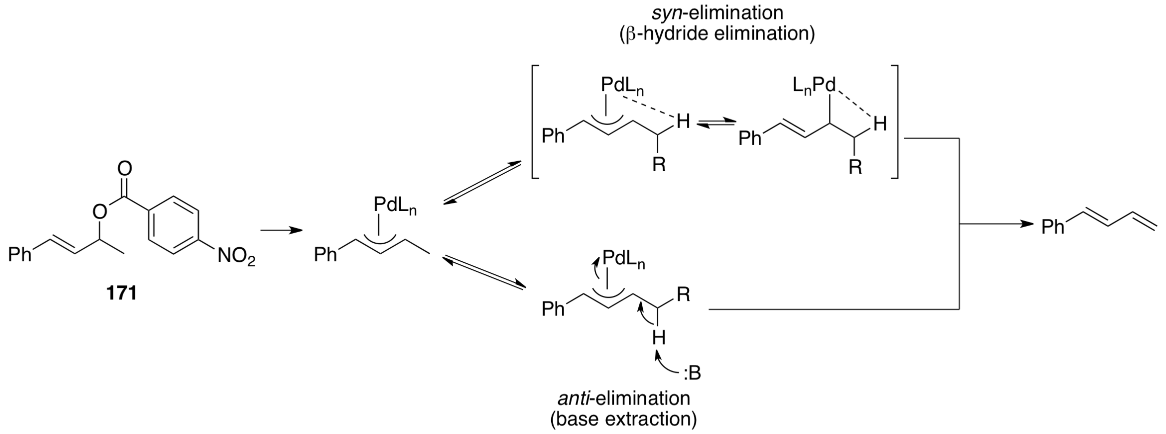
[1] A full table of screening results are presented in Appendix A1, the most informative results are discussed here.

the role of a base, diene formation by also be due to a base extraction of hydrogen by a direct E2 elimination giving an overall *anti*-elimination from the allylpalladium intermediate. This effect has been reported by Takacs and Lautens.[134] When the reactions were conducted without the addition of TBAF(*t*BuOH)$_4$ diene was still observed, suggesting that the formation of a π-allylpalladium intermediate is necessary for diene formation. However the elimination can occur *via* both *anti* and *syn*-elimination (Scheme 2.28).

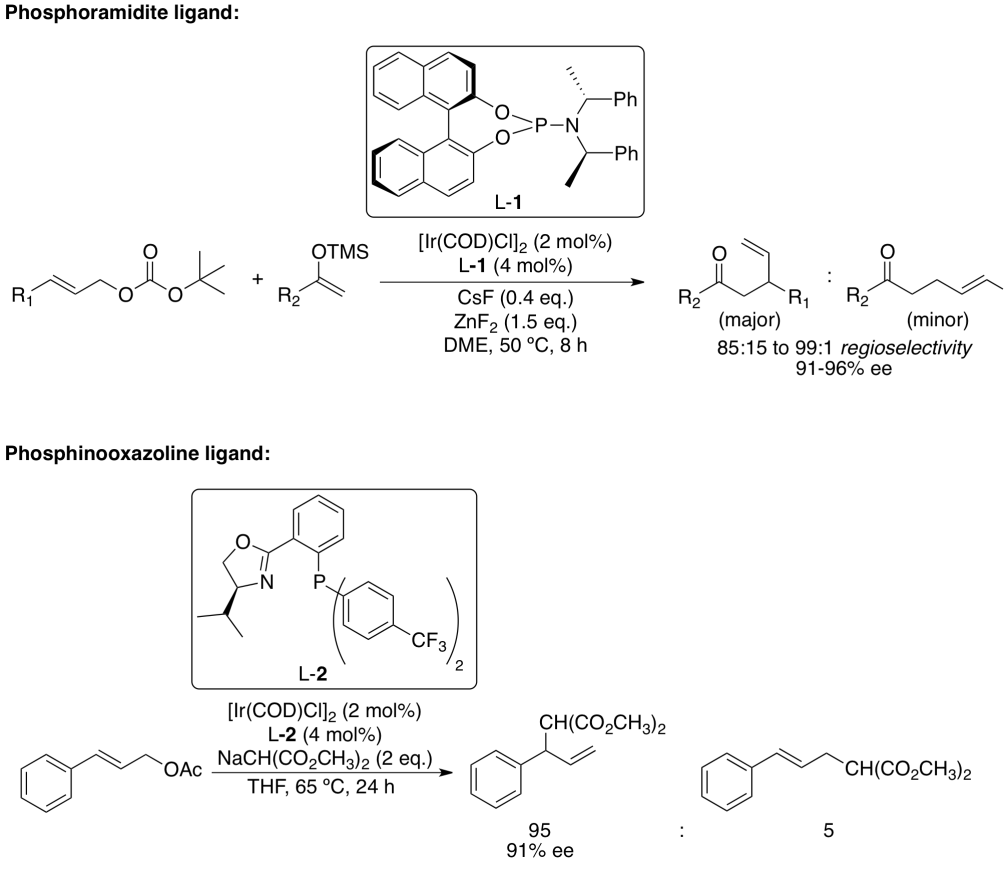


Scheme 2.28 Pd-mediated elimination of allylic *p*-nitrobenzoates for form dienes

In summary, the use of a *p*-nitrobenzoate leaving group, rarely used in Pd chemistry, gave quantitative yields of allyl fluorides when TBAF(*t*BuOH)$_4$ was employed as the fluoride source. A range of allylic fluorides was synthesized in good to excellent yield. The reaction was found to be regioselective for the least hindered allyl terminus. A limitation of this chemistry is the competing elimination reaction in substrates containing a β-hydrogen, attempts were made to overcome this through ligand screening however the elimination could not be suppressed. Therefore, with a desire to increase the substrate scope and access a different regioselectivity, variation of the metal was considered.

2.8 Overcoming limitations with Ir-Catalysed Allylic Fluorination

Iridium catalysis has become a powerful tool for the formation of carbon-carbon and carbon-heteroatom bonds in allylic substitutions. Traditional Ir catalysed allylic substitutions are known to be highly regioselective favouring the branched product over the linear regardless of the regioisomer of the substrate.[135] This selectivity is complementary to that of Pd, which often provides allylic substitution products at the least substituted carbon terminus as seen in the previously discussed allylic fluorination. The formation of branched products encouraged a vast amount of research into the ligands used in these reactions to develop an asymmetric variant (Scheme 2.29).



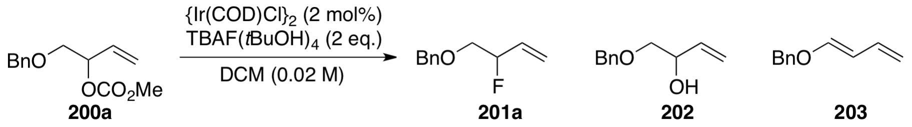
Scheme 2.29 Ir-catalysed asymmetric allylic subsitution

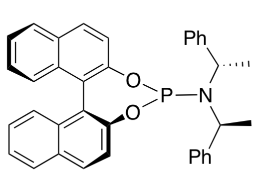
The phosphoramidite ligands were first prepared by Feringa and Alexakis[136] for Cu-mediated chemistry and utilised in asymmetric allylic aminations and etherifications by

Hartwig and co-workers.[137] The second family of ligands often used to achieve high levels of selectivity in these reactions are the phosphinooxazolines, often referred to as PHOX ligands developed independently by Pfaltz, Helmchen and Williams.[138] The contrasting selectivity seen between Ir and Pd encouraged us to explore the use of Ir catalysis in an allylic fluorination to gain access to branched allylic fluorides. Our studies towards the development of this reaction are presented here.

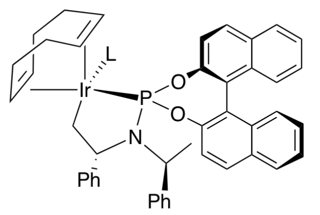
2.8.1 Optimisation of Reaction

A model substrate that under palladium catalysis gives predominantly diene, was selected to perform the initial validation of the reaction. Initial results were carried by Dr M. Tredwell[115] and E. Benedetto[139] on 1-(benzyloxy)but-3-en-2-yl methyl carbonate **200** establishing methyl carbonate as the optimal leaving group in an $[Ir(COD)Cl]_2$ catalysed fluorination in dichloromethane at 40 ºC. Again TBAF(*t*BuOH)$_4$[113] **160** was found to be the only competent fluoride source (Table 2.12).[140]





(*S*,*S*,*S*)-L, **204**



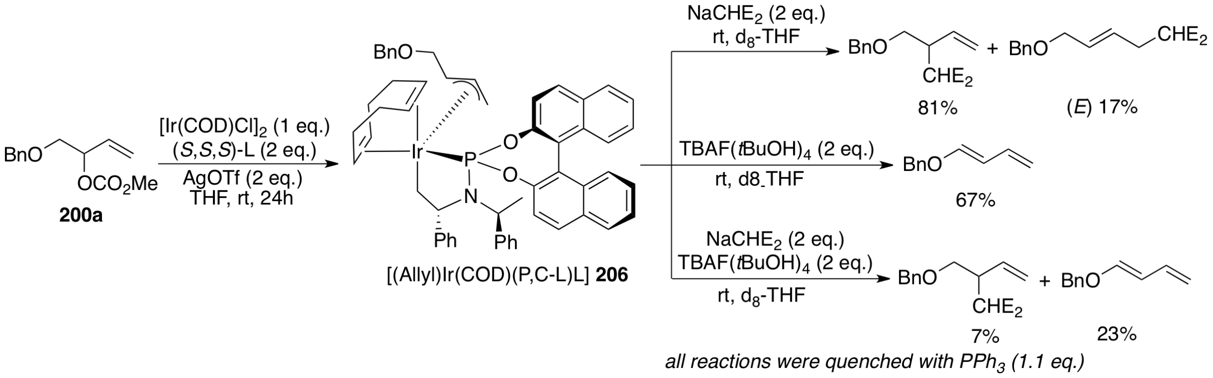
[Ir(COD)(P,C-L)L] **205**

Entry[a]	Catalyst	F^- source	Solvent	Time (h)	Ratio[b]			
					200a	**201a**	**202**	**203**
1	$[\text{Ir(COD)Cl}]_2/\text{P(OPh)}_3$	TBAF(*t*BuOH)$_4$ **160**	THF	24	50	0	25	25
2	$[\text{Ir(COD)Cl}]_2$/(*S,S,S*)-L **204**[c]	TBAF(*t*BuOH)$_4$ **160**	THF	24	38	25	25	12
3	[Ir(COD)(P,C-L(L] **205**	TBAF(*t*BuOH)$_4$ **160**	THF	24	-[d]			
4[e]	$[\text{Ir(COD)Cl}]_2$	TBAF(*t*BuOH)$_4$ **160**	THF	3	33	33	33	1
5[e]	$[\text{Ir(COD)Cl}]_2$	$\text{TBAF·3H}_2\text{O}$ **159**	THF	24	0	15	81	4
6[e]	$[\text{Ir(COD)Cl}]_2$	HF·Pyridine	THF	24	-[f]			
7[e]	$[\text{Ir(COD)Cl}]_2$	CsF	THF	24	82	0	9	9
8[e]	$[\text{Ir(COD)Cl}]_2$	AgF	THF	24	100	0	0	0
9[g][h]	$[\text{Ir(COD)Cl}]_2$	TBAF(*t*BuOH)$_4$ **160**	DCM	2	0	80	13	7
10[i]	$[\text{Ir(COD)Cl}]_2$	TBAF(*t*BuOH)$_4$ **160**	DCM	4	18	70	4	8

[a] Conditions: 4 mol %[Ir] cat, Ir:Ligand – 1:2. [b] Ratio determined by ^{1}H-NMR spectra of crude reaction mixture. [c] Addition of 0.1 eq. of 1,4-diazabicyclo[2.2.2]octane (DABCO). [d] Complex reaction mixture of which only **203** could be identified. [e] Reaction run at rt. [f] Complex reaction mixture. [g] Reaction run at 40 ºC. [h] Addition of crushed 3 Å molecular sieves to reaction. [i] Reaction run at 40 ºC and (0.02 M).

Table 2.12 Screening of Ir-catalysed allylic fluorination

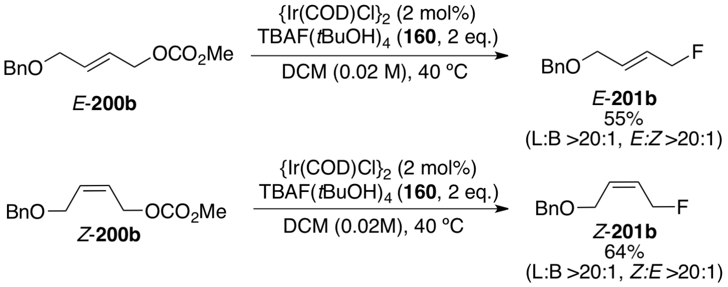
Interestingly the use of phosphoramidite ligands along with $[\text{Ir(COD)Cl}]_2$, which are now commonplace in Ir-catalysis, gave low levels of conversion to the desired allylic fluoride **201a** (25%). The use of the pre-formed catalyst [Ir(COD)(P,C-L)(L)] **205** also only gave trace amounts of fluorination. Investigations into this lack of reactivity found that the presence of fluoride was detrimental to the reaction with the phosphoramidite complex **206** even when malonate was used as a nucleophile. When phosphoramidite complex **206** was exposed to a malonate nucleophile in the absence of TBAF(*t*BuOH)$_4$ **160** the desired C-C coupled product was obtained in 81% yield (Scheme 2.30). However when the reaction was carried out in the presence of 2 equivalents of TBAF(*t*BuOH)$_4$ **160** only a trace amount of product was formed, along with diene **203**. Furthermore when complex **206** was reacted with TBAF(*t*BuOH)$_4$ **160**, no allylic fluoride products were observed, only diene **206** in a 67% yield. As such $[\text{Ir(COD)Cl}]_2$ was selected as the optimal catalyst for the allylic fluorination to carry out further investigations. Control reactions carried out with Ir showed no formation of allylic fluoride, confirming the reaction is Ir-catalysed.



all reactions were quenched with PPh3 (1.1 eq.)

Scheme 2.30 Synthesis and reactivity of the isolated complex **206**

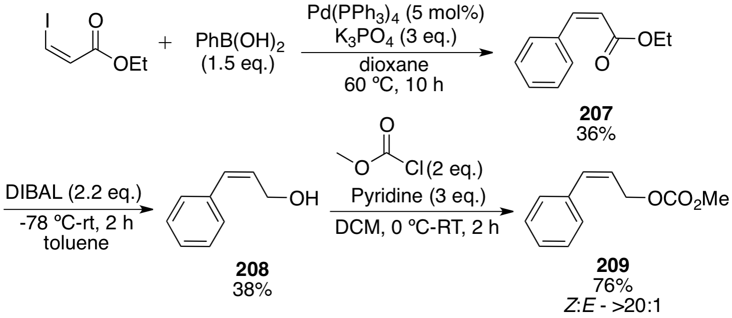
Further studies also identified the use of the *Z* allylic carbonate (*Z*)-4-(benzyloxy)but-2-en-1-yl methyl carbonate *Z*-**200b** to afford Z allylic fluoride *Z*-**201b** with excellent regio- and stereoselectivity (b:l 1: >20, *Z/E* 98/2), a transformation difficult to perform under Pd catalysis.[141] We were surprised to find that the reaction of *E*-linear substrate *E*-**200b** was selective for the *E*-linear allyl fluoride *E*-**201b**. Further optimization of the fluorination conditions by E. Benedetto found the optimal concentration of the reaction to be 0.02 M, allowing for higher conversions to allylic fluorides than the previously used 0.1 M (Scheme 2.31).[139140]



Scheme 2.31 Initial fluorination catalysed by $[Ir(COD)Cl]_2$

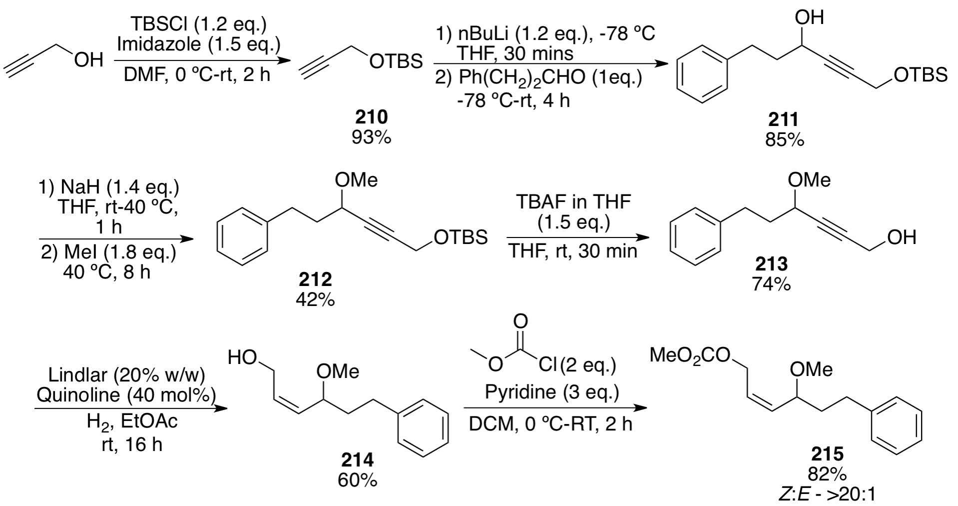
2.8.2 Preparation of Allylic Carbonates

Encouraged by the reactivity and selectivity of the initial screening reactions we further investigated the substrate scope of this reaction on various branched and *E* and *Z*-linear allylic carbonates. These substrates were synthesized using various literature procedures and are discussed here. As the cinnamyl benzoate had been successful in the Pd catalysed reaction we hoped that the use of (*Z*)-methyl (3-phenylallyl) carbonate **209** in the Ir reaction would allow for the synthesis of the (*Z*)-(3-fluoroprop-1-en-1-yl)benzene. This was accessed by a Suzuki reaction with phenyl boronic acid, subsequent reduction of the ester **207** with DIBAL and protection of the allylic alcohol **208** with methyl carbonate **209** in a disappointing overall yield of 10% (Scheme 2.32).



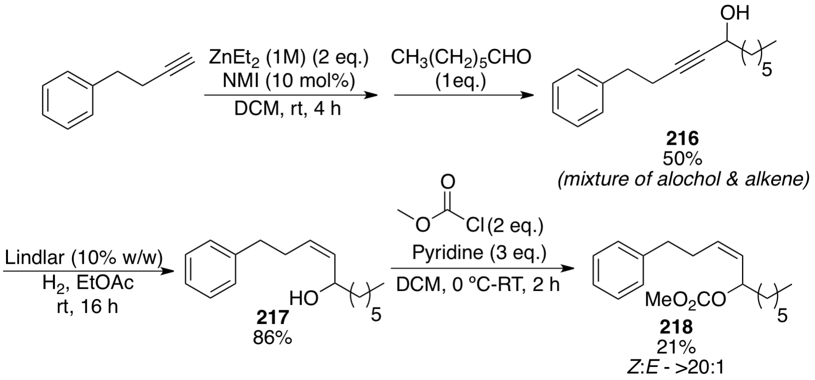
Scheme 2.32 Synthesis of (*Z*)-methyl (3-phenylallyl) carbonate

Substrate (*Z*)-4-methoxy-6-phenylhex-2-en-1-yl methyl carbonate **215** was accessed *via* a six step synthesis from hydrocinnamaldehyde and propargyl alcohol. The first step involves the protection of the propargyl alcohol with a *tert*-butyldimethylsilyl group. Reaction of the alkyne **210** with hydrocinnamaldehyde afforded product **211** in excellent yield. Further protection of the free alcohol with a methyl group **212** and deprotection of the TBS group gave product **213**, which was hydrogenated to the *Z*-allylic alcohol **214** and further protected to give the desired allylic carbonate **215** in 12% overall yield (Scheme 2.33).



Scheme 2.33 Synthesis of substrate **215**

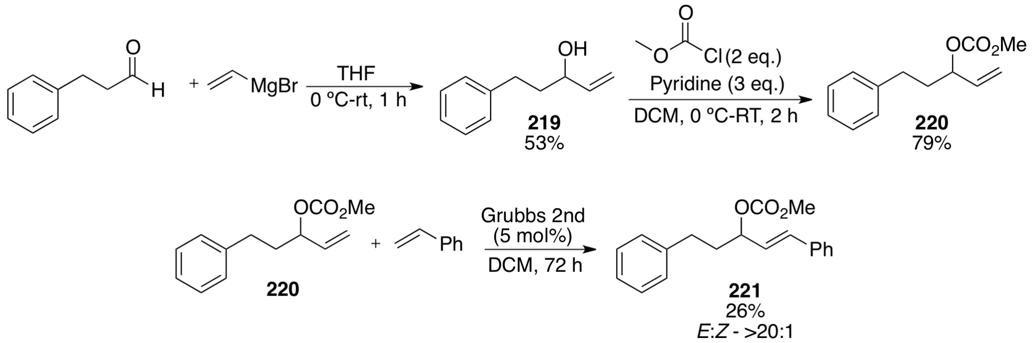
A branched *Z* allylic carbonate, (*Z*)-methyl (1-phenyldodec-3-en-5-yl) carbonate was synthesized following the procedure of Pu to give alcohol **216**.[142] Hydrogenation of **216** with Lindlar's catalyst gave allylic alcohol **217**. Protection of **217** with methyl carbonate afforded the desired product **218** in 21% isolated yield (Scheme 2.34).



Scheme 2.34 Synthesis of (*Z*)-methyl (1-phenyldodec-3-en-5-yl) carbonate **218**

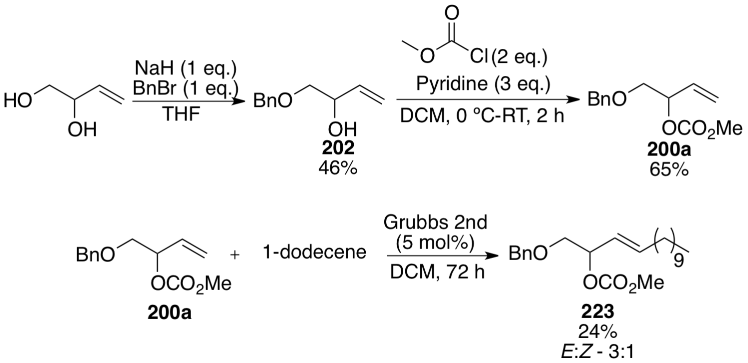
The branched alcohol **219**, 5-phenylpent-1-en-3-ol was synthesized by the Grignard coupling with hydrocinnamaldehyde. Subsequent protection **219** with methyl carbonate gave allylic carbonate **220**. This was also exposed to a cross metathesis with styrene using

Grubbs 2nd generation catalyst to afford (*E*)-1,5-diphenylpent-1-en-3-yl methyl carbonate **221**, in a 26% yield (Scheme 2.35).



Scheme 2.35 Synthesis of methyl carbonates **220** and **221**

A derivative of the model substrate, 1-(benzyloxy)but-3-en-2-yl methyl carbonate **200a**, was accessed via the selective mono benzyl protection of 3,4-dihyroxy-1-butene and protection of the secondary allylic alcohol **202** with methyl carbonate. The subsequent cross metathesis of **200a** with 1-dodecene afforded product **223** in a yield of 24% (Scheme 2.36).

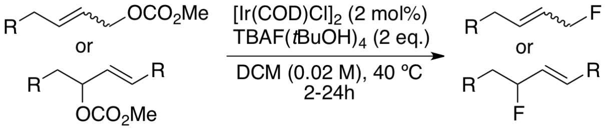


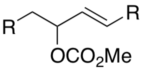
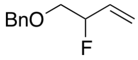
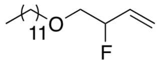
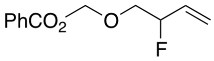
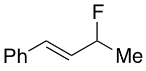
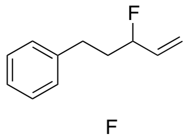
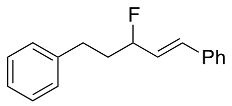
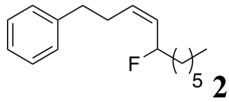
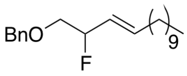
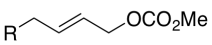
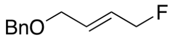
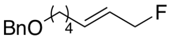
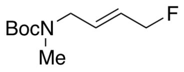
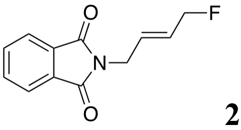
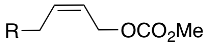
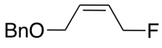
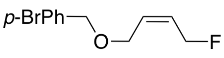
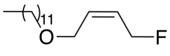
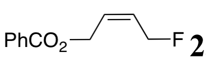
Scheme 2.36 Modified synthesis of branched methyl carbonates

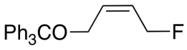
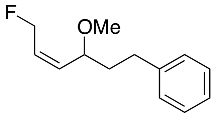
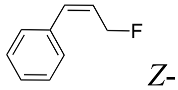
The following substrate scope was conducted in collaboration with Elena Benedetto[139], Dr Matthew Tredwell[115] and Tanatorn Khotavivattana.[143] The author of this thesis assisted with repeat reactions and fluorination of the substrates discussed above.

2.8.3 Scope and Limitations of the Ir-Catalysed Allylic Fluorination

Allylic methyl carbonates were subjected to the optimised fluorination conditions with {Ir(COD)Cl}$_2$ (2 mol%), and TBAF(tBuOH)$_4$ (2 eq.) in DCM (0.02M) at 40 ºC between 2-24 hours. The results of these experiments are presented in Table 2.13.[140]



Entry	Carbonate	Allylic Fluoride	Yield[a]	Selectivity[b]
1		 **201a**	57	>20:1 b/l ratio
2		 **224**	64	>20:1 b/l ratio
3		 **225**	32	>20:1 b/l ratio
4		 **172j**	66	>20:1 b/l ratio, *E*/*Z* >20:1
5		 **226**	14[c][d]	>20:1 b/l ratio
6		 **227**	65[d][e]	>20:1 b/l ratio
7		 **228**	Trace[d]	>20:1 b/l ratio
8		 **229**	-[d][f]	-
10		 **201b**	55	>20:1 l/b ratio, *E*/*Z* >20:1
11		 **230**	68	>20:1 l/b ratio, *E*/*Z* >20:1
12		 **231**	64	>20:1 l/b ratio, *E*/*Z* >20:1
13		 **232**	48	>20:1 l/b ratio, *E*/*Z* >20:1
14		 **201b**	64	>20:1 l/b ratio, *Z*/*E* >20:1
15		 **233**	52	>20:1 l/b ratio, *Z*/*E* >20:1
16		 **234**	65	>20:1 l/b ratio, *Z*/*E* >20:1
17		 **235**	65	>20:1 l/b ratio,

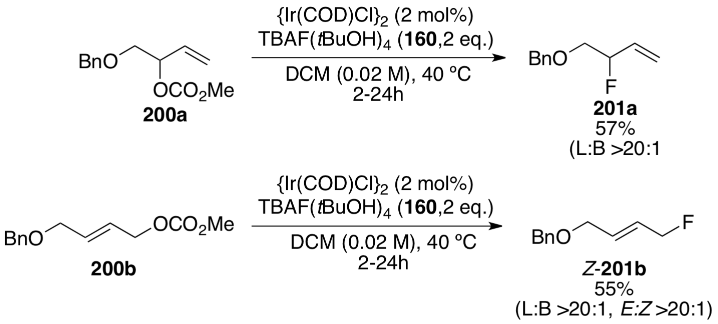
			Z/*E* >20:1
18	 **236**	50	>20:1 l/b ratio, *Z*/*E* 18:1
19	 **237**	Trace[d]	-
20	 *Z*-**172a**	1:20[d]	>20:1 l/b ratio, *Z*/*E* 8:1

[a] Isolated yield. [b] Ratio determined from ^{1}H NMR, ^{13}C NMR and ^{19}F NMR of crude reaction mixture. [c] ^{19}F NMR yield based on 1-fluoro-3-nitrobenzene as an internal reference. [d] Reaction concentration of 0.1M.[e] Additional 2 mol% {Ir(COD)Cl}$_2$ added to reaction after 6 h. [f] Additional 2 mol% {Ir(COD)Cl}$_2$ added to reaction after 24 h.

Table 2.13 Substrate scope of Ir-catalysed allylic fluorination

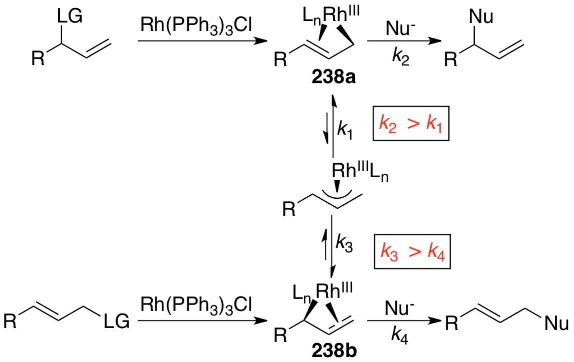
The same selectivity observed for the initial model substrates was also observed over a wide range of branched and linear (*E* and *Z*) allylic methyl carbonates. Entries 1-9 showed that branched methyl carbonates underwent fluorination with a high degree of selectivity for the branched allylic fluoride. Products were obtained in moderate to good yields when a terminal allyl motif was used however the formation of internal fluorides gave consistently lower yields and were found to be highly unstable. Both *E* and *Z* linear isomers were also obtained in an unusually high regioselectivity. Retention of the regiochemistry of the allylic carbonate was seen in the allylic fluoride product, providing access to both *E* and *Z* allylic fluorides. The reaction allowed for a series of allylic fluorides to be accessed in moderate to good yields and high selectivity with varying functionalities such as imide, ester, aryl halides and carbamates tolerated under reaction conditions. In all reactions allylic alcohol was observed as a side product that could be easily separated by silica gel column chromatography from the desired allylic fluoride.

The surprising selectivity seen in the reaction suggests that the reaction does not proceed through one common intermediate. This is demonstrated with substrates **200a** and **200b**. If the reaction proceeded through an allyl intermediate then the same product would be expected in both cases however this was not the case (Scheme 2.37).



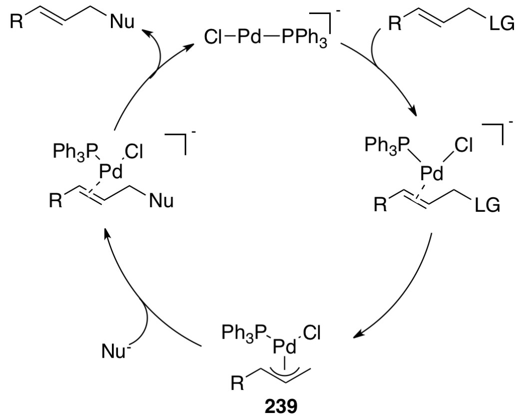
Scheme 2.37 Surprising regioselectivity observed in Ir-catalysed allylic fluorination

It is suggested that the reason for this regioretentive mechanism could be the result of the same memory effect as previously discussed for Pd-catalysed allylic alkylations. The regioselectivity seen in the fluorination reaction is similar to that observed for the Rh-catalysed allylic alkylation reported by Evans *et al.*[144] The 'memory effect' observed in these reactions is proposed to occur due to the formation of enyl organorhodium species **238a** and **238b**. In the presence of a nucleophile these intermediates undergo a rapid S_N2' displacement which is faster than the competing σ-π-σ isomerisation (Scheme 2.38).



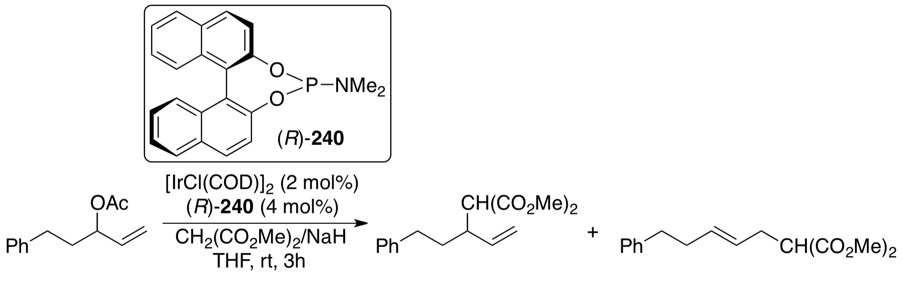
Scheme 2.38 Memory effect seen in Rh-catalysed allylic alkylations

The regioselectivity seen in the fluorination reaction could also be due halide effects. Previous work has proposed that when a halide additive was employed in Pd-catalysed allylic substitutions that an unequal '*trans*' effect is present in the unsymmetrical π-allylpalladium intermediate formed. Fristrup and Norrby observed that the addition of chloride ions increased the reactivity of the Pd^0 species in the oxidative addition of the substrate to give a neutral unsymmetrical π-allylpalladium intermediate **239**. The nucleophilic addition to this intermediate *trans* to the phosphorus ligand would explain the 'memory effects' observed in these experiments (Scheme 2.39).[145]



Scheme 2.39 Halide effect in Pd-catalysed allylic substitutions

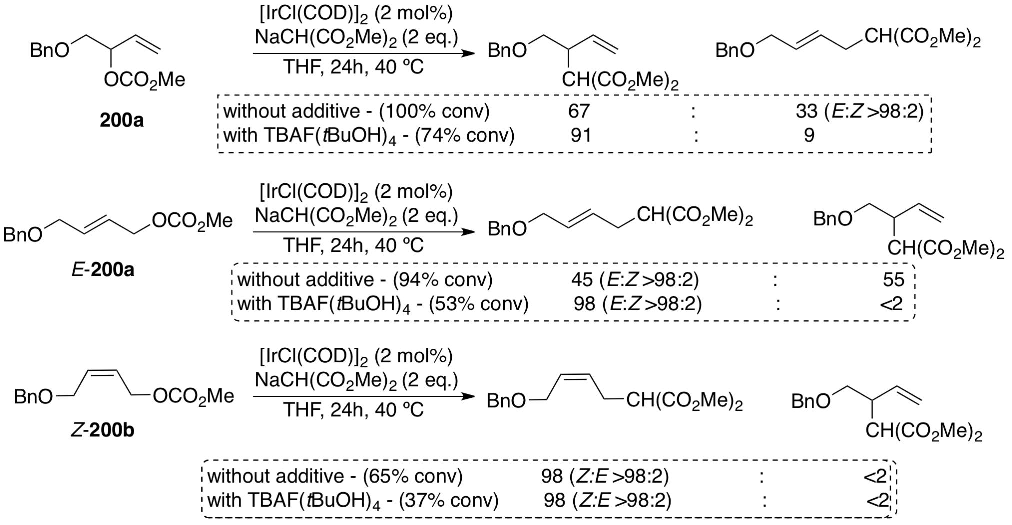
Furthermore Helmchen *et al* have reported a similar counterion effect on the regio- and stereocontrol in allylic substitutions under Ir catalysis. The branched to linear selectivity and enantioselectivity of the Ir-catalysed alkylation shown in Scheme 2.40 is increased in the presence of LiCl.[146]



Additive	Yield	B/L	ee of B
-	92%	98:2	69
LiCl (1 eq.)	83%	99:1	86

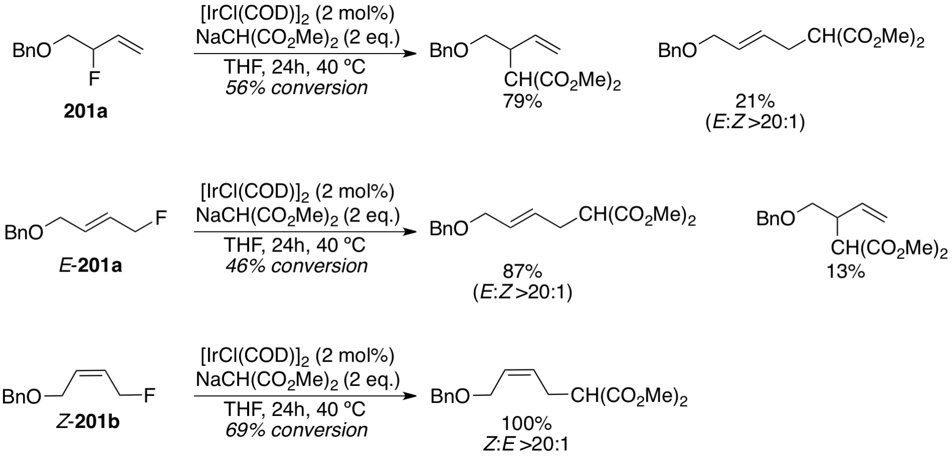
Scheme 2.40 Halide additive in Ir-catalysed allylic alkylations

To investigate this effect the Ir-catalysed allylic alkylation of substrates **200a**, *E*-**200b**, and *Z*-**200b** with and without a fluoride additive was carried out.[139] When an additive was not present the alkylation of branched carbonate **200a** and linear *E*-**200b** were found to be highly unselective, which is in agreement with previous reports in the literature. A higher degree of selectivity was observed for the *Z* carbonate *Z*-**200b** but with a severely reduced reactivity. This lack of selectivity in the alkylation would suggest it, unlike the allylic fluorination, proceeds *via* a common π-allyl-Ir intermediate. However when the same reactions were run in the presence of TBAF(tBuOH)$_4$ **160** as an additive (2 equivalents) a significant improvement in the selectivity of the alkylation reaction was observed. While selectivity was much improved in the presence of fluoride the rate of alkylation was reduced with starting carbonates still recovered after 24h. The same effect was observed when nBu$_4$NCl was used as an additive (Scheme 2.41).



Scheme 2.41 Ir-catalysed alkylation of allylic carbonates with and without fluoride as an additive

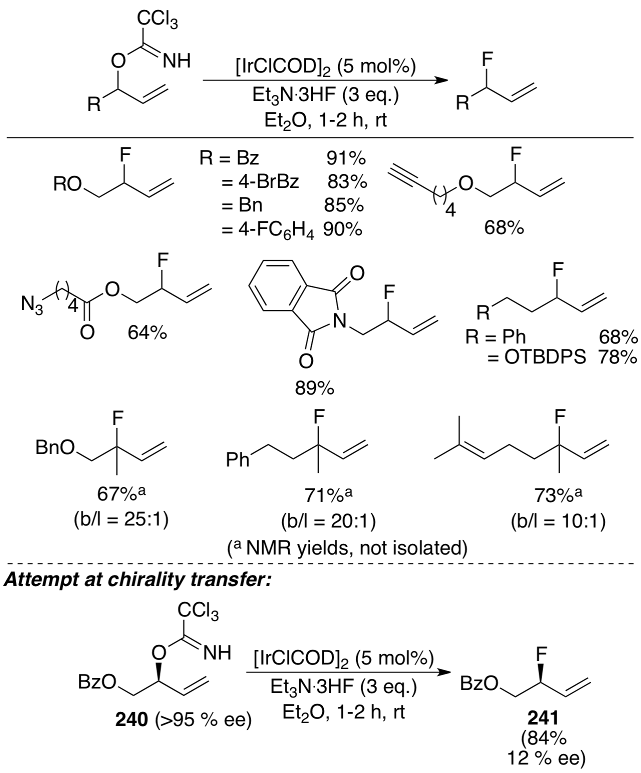
A possible reason for this improvement of selectivity was the formation of an allylic fluoride intermediate, which encouraged further investigations into the reactivity of allylic fluorides in an Ir-catalysed alkylation. Allylic fluorides **201a**, *E*-**201b** and *Z*-**201b** were all found to give regioretentive alkylation products under Ir catalysis however the selectivity was not as pronounced compared to the carbonates (Scheme 2.42).



Scheme 2.42 Ir-catalysed alkylation of allylic fluorides

The increase in the regiocontrol of the alkylation with the addition of fluoride to provide regioretentive products agrees with the product formation observed in the fluorination reaction. The regiocontrol of these two systems suggest that the reactions may involve a similar allyl-Ir intermediate that resembles the enyl organorhodium species **238a** and **238b** in the Rh-catalysed alkylations.

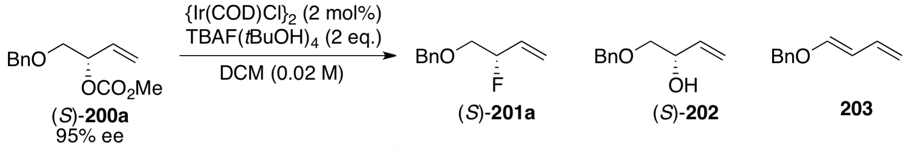
Concurrently with this work Nguyen reported the Ir catalysed fluorination of branched allylic trichloroacetimidates with triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$).[147] A wide substrate scope yielding secondary allylic fuorides in moderate to excellent yields was accessed bearing valuable functionalities such as imidates, azides and terminal alkynes. While tertiary fluorides could also be accessed, isolation was not possible due to the instability of the products. The use of a chiral starting material **240** under these reaction conditions led to almost complete racemisation in the allylic fluoride **245** product (Scheme 2.43).



Scheme 2.43 Ir-catalysed allylic fluorination of allyl trichloroacetimidates

2.8.4 Chirality Transfer

The fluorination of the enantioenriched allylic carbonate (*S*)-**200a** (95% ee) was investigated. The allylic fluoride (*S*)-**201a** and allylic alcohol (*S*)-**202** side product were isolated in 46% yield with 37% ee and 43% yield with 20% ee, respectively. When the reaction was carried out at room temperature for 24 hours 33% of starting carbonate (*S*)-**200a** was recovered with an ee of 93% and while the yield of fluoride (*S*)-**201a** was reduced (34%) it was obtained with a higher ee of 48% (Scheme 2.44).



A - 40 °C, 2h	(*S*)-**201a**	46%, 37% ee
	(*S*)-**202**	43%, 20% ee
B - rt, 24h	(*S*)-**201a**	34%, 48% ee
	(*S*)-**202**	20%, 65% ee
	(*S*)-**200a**	33%, 93% ee
C - No F$^-$	(*S*)-**200a**	77%, 87% ee
	203	23%

Scheme 2.44 Fluorination of chiral carbonate – stereochemical outcome

Though significant stereochemical leakage was observed, the isolated fluoride was found to be the *S* enantiomer by comparison with the independently synthesised product, demonstrating the reaction proceeds with overall retention. This result provides further support for a mechanism similar to the Rh-catalysis, suggesting the involvement of an enyl organoiridium intermediate. Furthermore the overall retention observed suggests that the fluoride is ‘softened’ in these systems and so behaviours as a ‘soft’ nucleophile, hence an outer sphere attack of the fluoride ion. In a control reaction in the absence of TBAF(tBuOH)$_4$ the starting allylic carbonate (*S*)-**200a** was recovered in 77% yield with a 87% ee, the remaining material was identified as diene **203**. The substantial level of racemisation seen in the reaction is proposed to be consistent with the rapid C-C bond rotation of a σ-species before fluorination takes place.

The development of the Ir-catalysed fluorination of allylic carbonates has allowed access to linear *E* and *Z* as well as branched allylic fluorides. The reaction was found to be highly regioselective giving the products of retention. Furthermore the competing β-hydride elimination seen in the case of the Pd-catalysed fluorination was overcome, allowing the substrate scope to be expanded. With these two new methodologies established the experience within the Gouverneur group in ^{18}F radiochemistry encouraged us to investigate whether these systems could be extended to the first metal mediated ^{18}F-C bond formation.

2.9 Translation of Transition Metal Catalysis to ^{18}F-Radiochemistry

2.9.1 Introduction to PET Imaging and ^{18}Fluorine

Positron emission tomography (PET) is a non-invasive imaging modality that allows for the monitoring of biological processes in patients.[148] A compound with biological relevance is labelled with a positron-emitting radioisotope and injected into a patient, after a period of time to allow the tracer to become concentrated in the tissues of interest, scans are taken. The 3D image that results from PET scans is built up by the detection of radioactivity emitted upon decay of the radioisotope in the labelled probe. When a radioisotope decays a positron is emitted that travels a short distance in the body until it collides with an electron. The result of this collision is the production of two annihilation gamma photons that are oriented approximately 180 ºC from each other. Millions of these annihilation events occur and are detected by a scintillator in the PET scanner and can then be computed to give an image such as that shown in Figure 2.2.

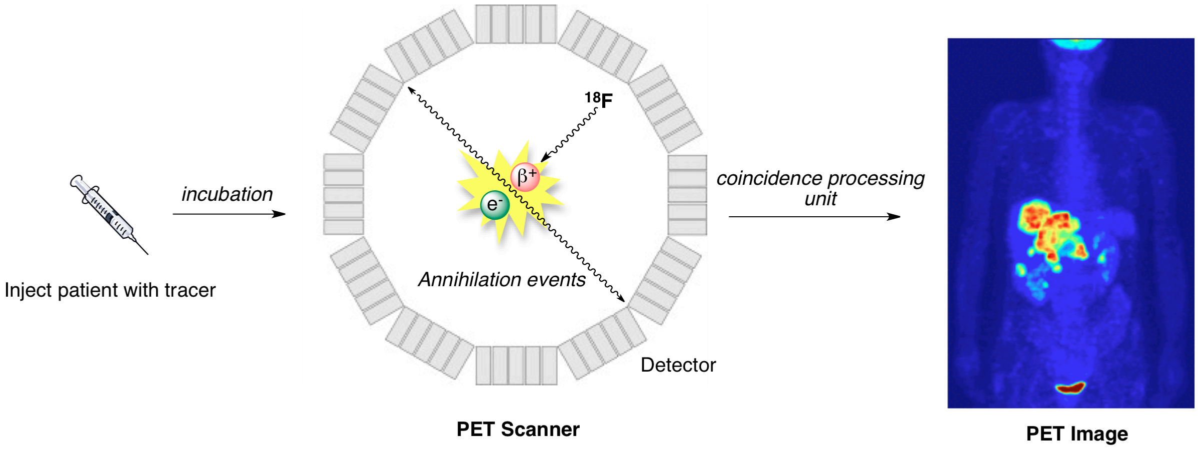


Figure 2.2 Schematic of Positron Emission Tomography (PET) to give image

This technique is used for diagnostics in neurological disorders such as Parkinson's and Alzheimer's[149] and diseases such as cancer[150]. It can also be used to determine the effectiveness of a given treatment and is finding more applications as a tool to aid the discovery of new drugs and personalized medicine.

The most commonly used positron-emitting radioisotopes are those of oxygen (^{15}O) nitrogen (^{13}N), carbon (^{11}C) and fluorine (^{18}F). The relatively short half-lives of these isotopes shown in Table 2.14.[148] Other isotopes are also employed, such as copper (Cu^{62}) and iodine (I^{123}) when longer timescales are required. The process under investigation will dictate the isotope used.

Radionuclide	Half-life ($t_{1/2}$, min)	Nuclear reaction	Decay Product	Maximum positron energy (MeV)	Distance travelled in H_2O (mm)
^{11}C	20.4	$^{14}N(p,\alpha)^{11}C$	^{11}B	0.96	4.1
^{13}N	9.97	$^{16}O(p,\alpha)^{13}N$	^{13}C	1.19	5.4
^{15}O	2.04	$^{15}N(p,n)^{15}O$	^{15}N	1.72	8.2
^{18}F	109.7	$^{18}O(p,n)^{18}F$	^{18}O	0.64	2.4

Table 2.14 Properties of commonly used short half-life PET radioisotopes

Of these positron emitters ^{18}F is the most widely used for which there are several reasons. Firstly the longer half-life of 109.7 minutes allows for tracers requiring post-label incorporation chemical manipulations to be synthesised. This half-life also allows for transport of the tracer after labelling with ^{18}F to the required facility removing the need for the synthesis of the isotope and tracer to be located at the same site. Finally the fluorine-18 emits low-energy positrons so the distance this can travel before an annihilation event is very small. This results in higher resolution PET images than with other isotopes, as there is less error between the site of decay and production of the gamma photons. The most commonly employed ^{18}F-tracer is [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), used to image the upregulation of glucose in cancers.[151]

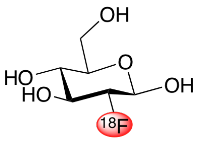


Figure 2.3 Structure of [^{18}F]FDG PET radiotracer

The labelling of compounds, such as [^{18}F]FDG with ^{18}F present additional challenges to standard fluorination reactions. As the half-life of the fluorine-18 isotope is 109.7 minutes the generation of the isotope, preparation of the radiofluorinating reagent, radiofluorination reaction, additional chemical manipulations, purification, delivery and administration of the final ^{18}F-labelled tracer to the patient must occur within three half-lives of the fluorine-18 (~ 6 hours). As such reactions to incorporate this motif must occur efficiently and selectivity and where possible at a late stage in the synthetic pathway.

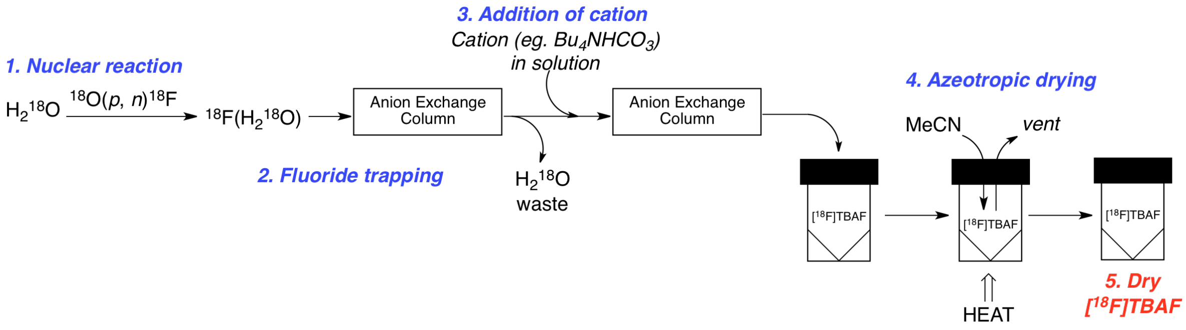
Furthermore the stoichiometry of a radiofluorination is often opposite to that of a ^{19}F-fluorination, where the fluorinating reagent is used in excess. In a radiochemistry environment this is now the limiting reagent typically only present in picomolar amounts with the target precursor now in a large excess. As such reactions requiring substoichiometric loadings of fluorinating reagent often require further optimization before they can be translated into a radiochemistry setting.

2.9.2 Production of ^{18}F: *nucleophilic and electrophilic*

The fluorine-18 isotope can be generated as nucleophilic [^{18}F]fluoride or electrophilic [^{18}F]F_2 depending on what radiofluorinating reagent is required for the synthesis of the desired tracer. The nuclear reaction $^{18}O(p,n)^{18}F$, involves the bombardment of oxygen-18 with a beam of protons which are accelerated by the cyclotron.[152] In the case of [^{18}F]fluoride the source of oxygen-18 is ^{18}O-labelled water which allows for the fluoride to be collected as a $H_2{}^{18}O$ solution. Where [^{18}F]F_2 is required, oxygen-18 gas is used to generate fluorine-18, that is then removed from the cyclotron by irradiation with inert gas containing $^{19}F_2$ gas. This 'carrier-added' source of [^{18}F] results in a lower specific activity (SA) due to contamination with fluorine-19.[153] Specific activity is defined as the activity of a given radioactive material per unit mass measured in GBq/μmol. High specific activity is desirable so that less radioactive material is administered to the patient and there is no competition for receptor binding by non-radioactive compounds. A maximum theoretical radiochemical yield of only 50% is possible when $[^{18}F]F_2$ is used. The high toxicity and reactivity of this reagent requires the use of specialised equipment and personal and can lead to undesired side reactions. This problem has been somewhat circumvented by the synthesis of the more selective ^{18}F-labeled fluorinating N–F reagents, such as Selectfluor[154] and NFSI[155] and umpolung strategies[39] as previously discussed in the Chapter 1. However due to the many drawbacks associated with $[^{18}F]F_2$ the use of high specific activity nucleophilic $[^{18}F]$fluoride is preferred.

2.9.3 Generation of $[^{18}F]$fluoride reagents

As the $[^{18}F]$fluoride is generated in a $H_2{}^{18}O$ solution and fluoride is highly solvated in aqueous media it is not a competent nucleophile in this form so further transformations must be performed to convert this to a useful organic soluble fluorinating reagent. The most commonly used source of $[^{18}F]$fluoride is potassium $[^{18}F]$fluoride, often used with the phase-transfer catalyst Kryptofix 222 to improve solubility. The use of cesium $[^{18}F]$fluoride has also been reported along with the more soluble tetraalkylammonium salt, such as tetrabutylammonium $[^{18}F]$fluoride, that do not require the addition of phase-transfer catalysts. The reagents are synthesised with the use of an anion exchange column. The $H_2{}^{18}O$ solution containing $[^{18}F]$fluoride is loaded onto the column and the $[^{18}F]$fluoride adheres to the surfaces. The fluoride is then eluted with an acetonitrile or acetonitrile/water eluent that contains the desired cation (i.e K, Cs or tetraalkylammonium). Acetonitrile is often the solvent of choice as its polarity allows the dissolution of most $[^{18}F]$fluoride sources. Water is then removed from the system by azeotropic drying with anhydrous acetonitrile yielding the desired [^{18}F]fluoride reagent ready for radiofluorination reactions (Scheme 2.45).



Scheme 2.45 Preparation and drying of [^{18}F]radiofluorinating reagents from ^{18}F($H_2{}^{18}O$)

2.10 Transition Metal Catalysis for Allylic ^{18}F-Radiofluorination

At present most ^{18}F-labelling methodology is focussed on the use of [^{18}F]fluoride in direct nucleophilic substitutions of aliphatic or aromatic leaving groups.[156] Often these reactions require harsh reaction conditions, have limited substrate scope and further manipulations are required to synthesise complex tracers *via* the coupling of a ^{18}F-labelled prosthetic group.[157] The use of transition metals to improve the reactivity and selectivity of a reaction is well established, however its application to radiochemistry has not been explored and the use of high specific activity [^{18}F]fluoride with transition metals has not been demonstrated. With the success of the two metal catalysed allylic fluorinations discussed here we were eager to investigate whether this chemistry could be translated to a radiochemistry environment to produce ^{18}F-labelled allylic fluorides. The next two sections discuss the development of both a Pd and Ir mediated allylic [^{18}F]radiofluorination using [^{18}F]fluoride. Dr Matthew Hopkinson[158] (Pd) and Dr Matthew Tredwell[115] (Ir) performed the experiments presented here.

2.10.1 Palladium-Mediated Allylic [^{18}F]Radiofluorination

Preliminary investigations were performed with the test substrate cinnamyl methyl carbonate **242**, synthesised from cinnamyl alcohol and methyl chloroformate in the presence of pyridine in DCM. The corresponding cinnamyl fluoride **172a** was synthesised *via* the previously discussed Pd-catalysed allylic fluorination to provide an authentic sample for HPLC analysis of the radiofluorinations.

As an initial experiment cinnamyl methyl carbonate **242** was reacted with $Pd(dba)_2$ and PPh_3 in the presence of the [^{18}F]fluoride reagent, [^{18}F]TBAF. [^{18}F]TBAF was prepared by the counter-ion exchange/azeotropic drying procedure detailed in Section 2.8.3 (Scheme 2.45) in a lead-shield hot cell. [^{18}F]$H_2{}^{18}O$ was loaded onto a quaternary methyl ammonium anion exchange cartridge and a solution of tetrabutylammonium bicarbonate (13 mg) in $MeCN/H_2O$ (4:1, 0.45 mL) passed through the cartridge. The resulting [^{18}F]TBAF was collected and azeotropically dried at 120 ºC by consecutive additions of anhydrous MeCN under a flow of nitrogen. The radioactivity after this process remained at > 98% (decay-corrected) based on the total radioactivity received from the cyclotron. This radiofluorinating reagent was selected based on the success of TBAF(tBuOH)$_4$ in the 'cold' reaction. In a separate borosilicate glass vial cinnamyl methyl carbonate **242** (5±1 mg), $Pd(dba)_2$ (2±1 mg) and triphenylphosphine (2±1 mg) were mixed in a solution of acetonitrile (450 μL). Then 50 μL of the [^{18}F]TBAF in acetonitrile was added to the vial by a lead-shielded syringe and the reaction stirred for 5 minutes at room temperature. After this time the reaction was quenched with water (0.5 mL) and the crude reaction mixture loaded onto the HPLC (Phenomenex NX 5μm C18 column, $MeCN/H_2O$, Gradient A, 1 mL/min) (Appendix). The radioactivity trace shown in Figure 2.4 revealed the presence of one [^{18}F]radioactive product that correlates with the retention time of the non-radioactive cinnamyl fluoride [^{18}F]-**172a** and when spiked with 'cold' cinnamyl fluoride was confirmed as the [^{18}F]allylic fluoride [^{18}F]-**172a**. Analysis of the reaction by radio-TLC (eluent: MeCN/H_2O, 95:5) showed the [^{18}F]allylic fluoride [^{18}F]-**172a** was produced in a 19% radiochemical yield ([RCY], decay corrected), based on the amount of [^{18}F]fluoride. As well as an extremely rapid process the reaction is exceptionally clean with only one radioactive organic material identified along with unreacted [^{18}F]TBAF present in the radioactivity trace. Control reactions is the absence of Pd and ligand did not give any of the [^{18}F]allylic fluoride [^{18}F]-**172a**, even when reaction times were extended and the temperature raised to 110 ºC, confirming the reaction to be Pd-mediated. To the best of our knowledge this is the first example of a transition metal mediated C-^{18}F bond formation.

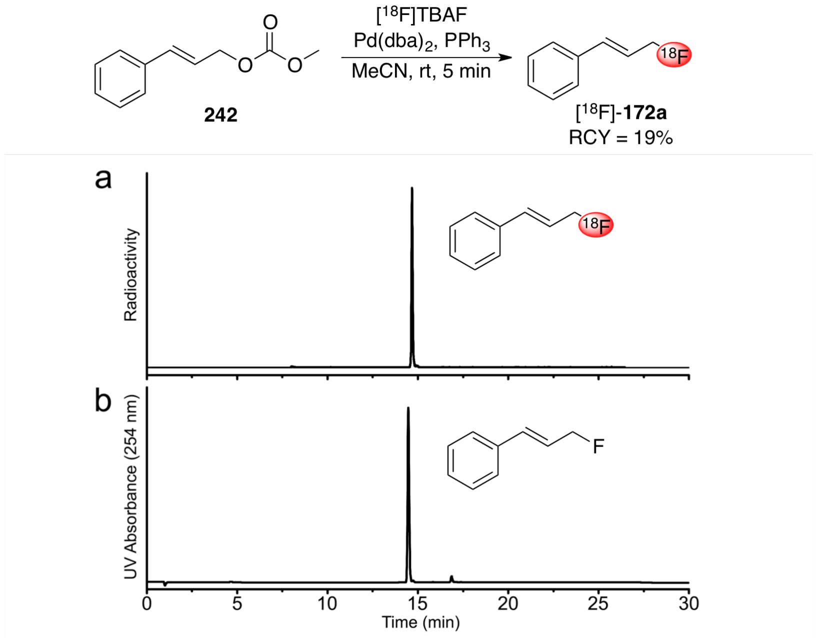
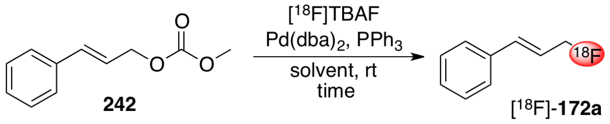


Figure 2.4 Comparison of radioactivity trace and UV trace identifying the presence of [^{18}F]allylic fluoride [^{18}F]-**172a**

After the initial validation of the Pd-mediated allylic [^{18}F]radiofluorination a full investigation of the reaction conditions was performed (Table 2.15). Reactions were conducted as previously described and radiochemical yields (decay-corrected) were determined by the analysis of radio-TLC of the crude reaction mixture or comparison of the radioactivity injected into the HPLC with that of the eluted product.



Entry[a]	Solvent	Time (min)	Radiochemical Yield of [^{18}F]-**172a** (RCY, %)[b]
1	MeCN	5	9-42 (*n* = 17)
2	MeCN/*t*BuOH (9:1)	5	7-32 (*n* = 7)
3[c]	MeCN/*t*BuOH (9:1)	5	-
4	MeCN/*t*BuOH (9:1)	10	9-46 (*n* = 5)
5	MeCN	10	11-13 (*n* = 2)
6	MeCN/*t*BuOH (9:1)	15	17-19 (*n* = 2)
7	MeCN/*t*BuOH (9:1)	30	10-22 (*n* = 2)
8	MeCN	30	10-52 (*n* = 7)
9	MeCN/*t*BuOH (9:1)	1	4-7 (*n* = 2)
10	MeCN/*t*BuOH (9:1)	2	6-20 (*n* = 2)
11[d]	MeCN/*t*BuOH (9:1)	5	6 (*n* = 1)
12	THF	5	-

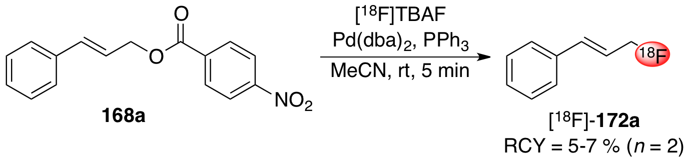
[a] Carbonate X (5±1 mg), Pd(dba)$_2$ (2±1 mg), PPh$_3$ (2±1 mg), [^{18}F]TBAF (activity = 10-50 MBq), solvent (0.5 mL). [b] Decay corrected RCY of X were determined by radio-TLC of the crude reaction mixture (MeCN/H$_2$O, 95:5) or by HPLC, *n* = the number of repeats. [c] Reaction performed in absence of Pd(dba)$_2$. [d] Reaction run at 100 ºC.

Table 2.15 Pd-mediated allylic [^{18}F]fluorination

The reproducibility of the reaction was first investigated by performing repeats of the initial reaction. As entry 1 shows, while [^{18}F]allylic fluoride [^{18}F]-**172a** was always observed the radiochemical yields varied significantly from 7 to 32% over 7 reactions. One reason for this irregularity in the RCY is proposed to occur from the instability of [^{18}F]allylic fluoride [^{18}F]-**172a**, which, as the corresponding [^{19}F]cinnamyl fluoride, has been reported to be a highly sensitive compound that can decompose when in contact with borosilicate glass.

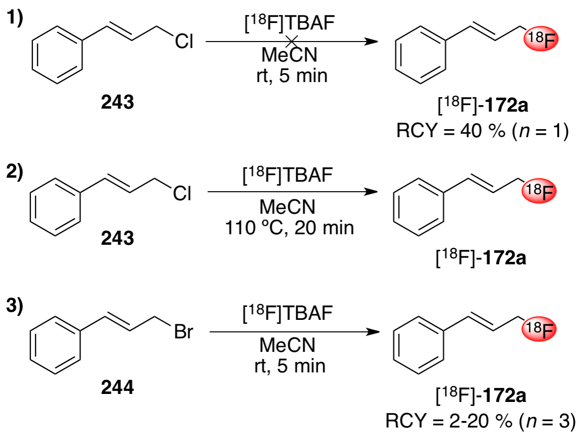
The use of *tert*-butanol in the radiofluorination was also investigated due to its presence in the optimised reaction conditions for the fluorination of the allylic *p*-nitrobenzoates as

TBAF(*t*BuOH)$_4$ **160**. When a solvent mixture of 9:1 MeCN:*t*BuOH was employed comparable radiochemical yields were possible. Repeat reactions showed the same variation in yield (Entry 2). No reaction was seen when this reaction was carried out in the absence of Pd(dba)$_2$. Extension of the reaction time gave no noticeable improvement to the radiochemical yield, except in one case giving a 52% RCY. Pleasingly, the formation of an allylic C-^{18}F bond was seen after just one minute and radiochemical yields reaching 20% were possible when the reaction was run for 2 minutes at room temperature (Entries 9-10). Increasing the reaction temperature to 100 ºC gave no improvement in yield (Entry 11). Screening of the radiofluorination reaction with THF as the solvent, the optimal solvent for the 'cold' fluorination, gave no formation of the [^{18}F]allylic fluoride [^{18}F]-**172a**. Furthermore when the *p*-nitrobenzoate **168a** was investigated in the radiofluorination lower yields were obtained compared to that of the cinnamyl methyl carbonate (Scheme 2.46).



Scheme 2.46 Radiofluorination of cinnamyl *p*-nitrobenzoate **168a**

The efficiency of this new methodology was assessed by the direct comparison with the standard S$_N$2-type synthesis pathway of [^{18}F]allylic fluoride [^{18}F]-**172a** from the corresponding allylic chloride and bromide (Scheme 2.47). In the case of the allylic chloride **243** no reaction was observed when the mild reaction conditions used in the Pd-mediated radiofluorination were employed. Only an extended reaction time of 20 minutes and elevated temperature of 110 ºC gave [^{18}F]allylic fluoride-**172a** in 40%.



Scheme 2.47 Comparison of S_N2 substitutions with Pd-mediated radiofluorination

With the more reactive allylic bromide **244** radiochemical yields between 2-20% were possible at room temperature for 5 minutes, comparable to those obtained in the Pd-mediated methodology. The success of the less reactive methyl carbonate in the Pd-mediated reaction could allow for the direct aliphatic ^{18}F-labelling of sensitive substrates where such active leaving groups as bromides are not tolerated. Furthermore this methodology may provide a direct route to tracers, avoiding the need for the use of prosthetic groups.

2.10.2 Iridium-Mediated Allylic [^{18}F]Radiofluorination

With the success of the Pd-mediated we sought to investigate whether the Ir-mediated allylic fluorination could be extended to the synthesis of branched and linear *E* and *Z* allylic fluorides in 30 minutes. In this case tetraethylammonium [^{18}F]fluoride ([^{18}F]TEAF) was the preferred source of fluorine-18[2], which was accessed *via* the same counter-ion exchange/azeotropic process described in section 2.8.2. To the glass vial containing [^{18}F]TEAF (30 MBq in 30 μL of MeCN) was added a mixture of allylic methyl carbonate (5 mg in 440 μL of MeCN) and [Ir(COD)Cl]$_2$ (60 μL of 1 mg/mL solution in DCM). The reaction was allowed to stir at 40 ºC for 30 minutes before cooling and analysis of the crude

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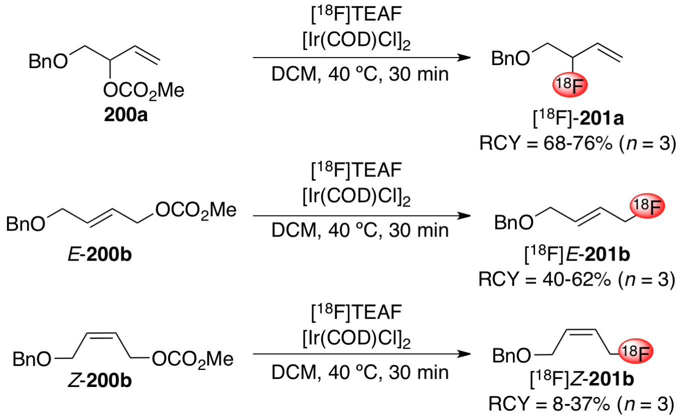
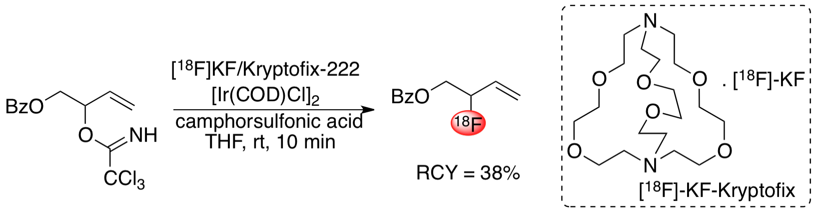
[2] The use of [^{18}F]KF/Kryptofix 222 was also successful in this reaction, however RCY were superior with [^{18}F]TEAF

reaction mixture by radio-TLC and HPLC (Nova-Pak C18 column, MeCN/H_2O, Gradient B, 1 mL/min) (Appendix). As depicted in Scheme 2.49 the parent branched **200a**, linear *E*-**200b** and *Z*-**200b** methyl carbonates used in the 'cold' Ir catalysed fluorination were all found to give the corresponding [^{18}F]allylic fluorides in good radiochemical yields (Scheme 2.48).[139140]



Scheme 2.48 Ir-mediated [^{18}F]radiofluorination for the synthesis of branched and linear *E* and *Z* [^{18}F] allylic fluorides

A higher RCY was possible with the branched allylic carbonate **200a** than that of the linear *E* and *Z* allylic carbonates *E*-**200b** and *Z*-**200b**. Furthermore the use of a higher loading of [Ir(COD)Cl]$_2$ was necessary in the case of the *Z* allylic carbonate *Z*-**200b** (120 µL of 1 mg/mL solution in DCM) to obtain comparable radiochemical yields. Control reaction in the absence of [Ir(COD)Cl]$_2$ confirmed the reaction to be Ir-mediated with no formation of C-^{18}F bonds observed. As with the Pd-mediated radiofluorination the reaction was found to be capricious giving variable yields over a number of repeats. Nguyen also reported the use of [Ir(COD)Cl]$_2$ in the [^{18}F]radiofluorination of allylic trichloroacetimidates with [^{18}F]KF/Kryptofix 222 (Scheme 2.49).[147]



Scheme 2.49 [18F]Radiofluorination of allylic trichloroacetimidates

2.11 Conclusions

In conclusion the development of two regioselective allylic fluorination reactions has been reported using the TBAF(tBuOH)$_4$ under Pd and Ir catalysis. This methodology has provided access to branched, linear *E* and *Z* allylic fluorides in synthetically useful yields. The functionalities tolerated in these reactions allow significant post-fluorination modifications that could provide access to valuable fluorinated building blocks. Furthermore both reactions have been extended to a radiochemical environment with the first transition metal mediated radiofluorination of cinnamyl methyl carbonate achieved with the high specific activity [^{18}F]fluoride.

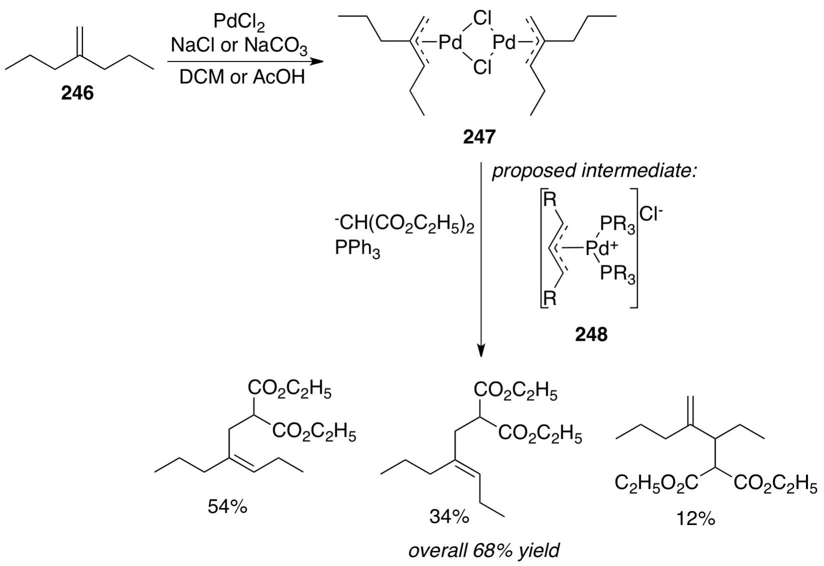
The ultimate goal is to create a catalogue of reactions that would enable one to label any organic molecule selectively at any position with either ^{19}F or radioactive ^{18}F. The methodology presented here along with the asymmetric variants make a significant step towards the goal. Though development is still needed to have methodologies that are tolerant of all functionalities and capable of imparting high levels of enantiomeric excess the progress so far has been vast.

Chapter 3

C-H Functionalisation-Fluorination

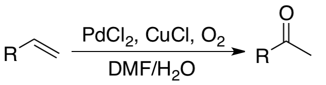
3.1 Introduction

While the development of a metal-catalysed nucleophilic fluorination at an sp^3-hybridised carbon is not insignificant, the need for prefunctionalisation of the starting material adds additional steps and reduces the atom economy of the reaction. A solution would be the direct functionalisation of a carbon-hydrogen bond. The use of Pd^{II} to form π-allyl palladium complexes is an area that has received substantial attention, particularly in recent years. Previous work has focused on C-H functionalisation of sp^3 and sp^2-hybridised[159] carbon centres to form carbon-carbon and carbon-heteroatom bonds (O,N,B).[160] In 1973 Trost investigated the use of an unactivated olefin substrate for C-C bond formation. The reaction of olefin **246** with $Pd^{II}Cl_2$ yielded an electrophilic π-allypalladium complex **247**.[161] It was envisioned that this activated intermediate could be further reacted to yield the products of C-C coupling. While no reaction was seen when this complex was exposed to a malonate nucleophile, the introduction of triphenylphosphine led to malonate addition at the less substituted end of the allyl intermediate. With the requirement of an additive necessary for the reaction to occur, the intermediate **248** was suggested.



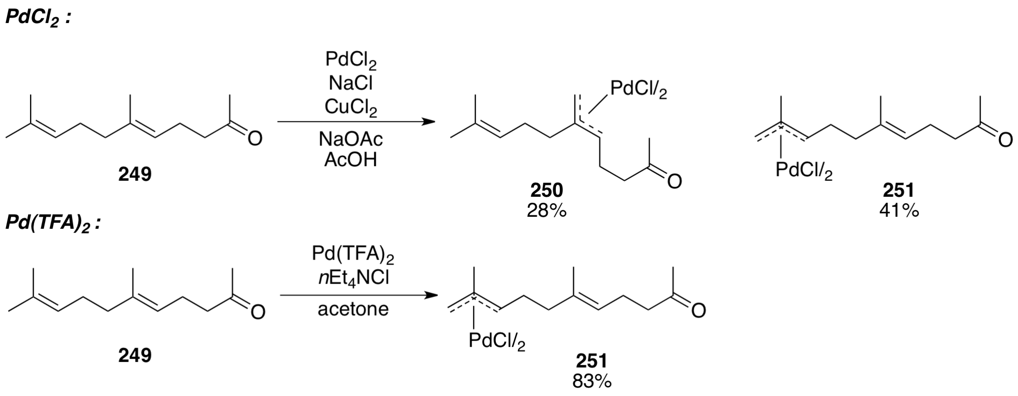
Scheme 3.1 Suggested intermediate for alkylation of allylpalladium complex

The product outcome observed by Trost implied different elementary steps than those observed in classical Wacker oxidation chemistry (Scheme 3.2). Further mechanistic studies on the above reaction focused on elucidating the preference for forming π-allypalladium complexes over Wacker oxidation products and developing a catalytic variant.



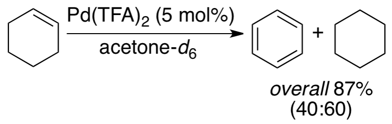
Scheme 3.2 Wacker oxidation of alkenes with $PdCl_2$

In 1965, Wilkinson reported the preparation of palladium trifluoroacetate, $Pd(TFA)_2$, a strongly electrophilic palladium source with a non-basic, non-nucleophilic counterion.[162] $Pd(TFA)_2$ provided more efficient access to π-allylpalladium complexes, enabling alkene loadings to be lowered to 1:1 (alkene to Pd) and giving better chemoselectivity than $PdCl_2$, as demonstrated in the formation of π-allylpalladium chloride complexes **250** and **251** from geranylacetone **249** (Scheme 3.3).[163] When $Pd(TFA)_2$ was used, the terminal π-allylpalladium chloride complex **251** was formed exclusively and isolated in 83% yield.



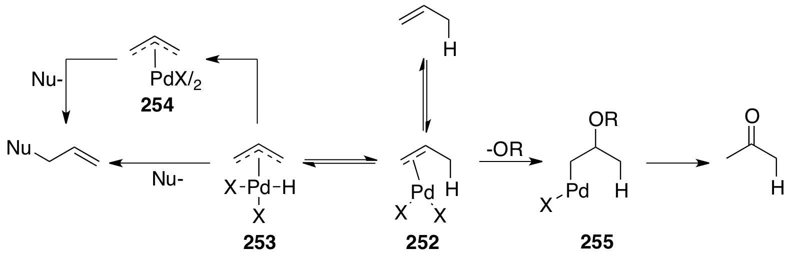
Scheme 3.3 Selective π-allypalladium formation with Pd(TFA)$_2$

Moreover, its use also led to new mechanistic insights. The formation of allyl dimers (assumed to be dimers based on analogous acetate complexes) was possible with acyclic alkenes and those exocyclic to polycyclic ring systems. In contrast, endocyclic alkenes and simple methylenecycloalkanes underwent a disproportionation reaction, which is catalytic in Pd(TFA)$_2$ (Scheme 3.4).



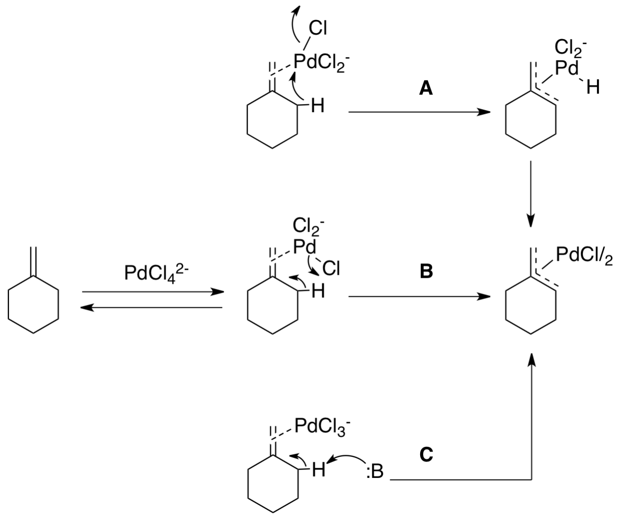
Scheme 3.4 Disproportionation of methylenecycloalkanes with Pd(TFA)$_2$

This experimental observation led to the suggestion of a Pd hydride intermediate, as shown in the mechanism presented in Scheme 3.5. Trost *et al.* proposed that the first step is initial coordination of the alkene to Pd.[164] Two possible outcomes are feasible from complex **252**. The first possibility is the attack of an external oxygen nucleophile on the complex leading to an oxidation. The second possibility is formation of a Pd-H species, **253**. This latter pathway requires a suitably electrophilic Pd species. Subsequent attack of a nucleophile onto this complex would give the product of an allylic substitution. This product could also be accessed from allylpalladium intermediate **254**, which is formed by loss of HX from **253**. Internal delivery of the X ligand to the allylic position is also possible. The isolation of intermediates such as **254** was possible with Pd(TFA)$_2$ in the absence of nucleophile. Trost *et al.* proposed that as Pd(TFA)$_2$ is highly electrophilic it is able to insert into the allylic C-H bond, and possesses weakly nucleophilic counteranions to allow access to a stable allyl intermediate that is susceptible to attack by an external nucleophile.[163]



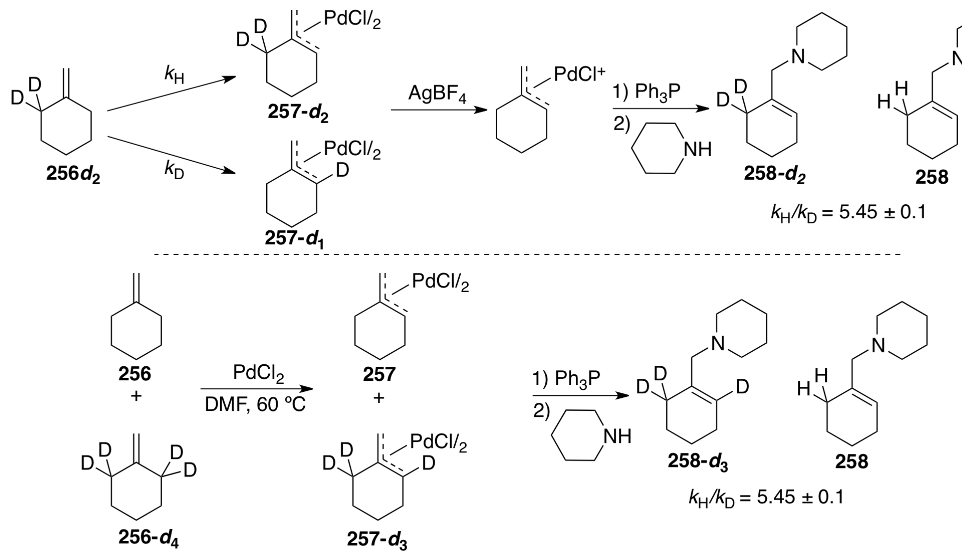
Scheme 3.5 Proposed mechanism involving a Pd-H intermediate

In 1988 Saunders *et al.* published work disagreeing with this conclusion.[165] While it is generally accepted that the reaction of alkenes with PdCl$_2$ gives π-allyl complexes via initial fast π-complexation of the olefin to Pd, the mechanism for the removal of the allylic hydrogen has not been confirmed. Three possible mechanisms for the removal of the allylic hydrogen in the insertion of Pd^{II}Cl$_2$ into methylenecyclohexene were suggested (Scheme 3.6). All routes involved the rapid, reversible formation of a π-bound alkene complex, proposed based on isolation of these structures[166], followed by: **A**, insertion of Pd into the C-H bond to give a Pd-hydride that reacts with an oxidant or base to give the π-allylpalladium complex; **B**, intramolecular removal of the allylic hydrogen by a chloride ligand; or **C**, removal of the proton by an external base.



Scheme 3.6 Proposed routes for removal of an allylic hydrogen atom

Ketley and Braatz had demonstrated in 1968 that treatment of π-alkene complexes with inorganic and organic bases gave π-allyl complexes.[167] However, Saunders found the kinetics of the reaction showed first-order dependence on the concentration of alkene and Pd but not on acetate, suggesting that an external base is not involved. This kinetic data suggests that route **C** is unlikely. Product isotope effects were measured for the reaction of methylenecyclohexane with $PdCl_2$ in DMF at 25 ºC, derivatisation of the Pd-olefin complex **257** was necessary to observed these effects. Animation gave products **258**, **258-*d*$_2$** and **258-*d*$_3$** (Scheme 3.7).



Scheme 3.7 Isotope effect studies on methylenecyclohexane

Both a kinetic and product isotope effect of k_H/k_D 5.45 ± 0.1 was found under these conditions using various deuterium labelled methylenecyclohexanes **256**, **256-*d*$_2$** and **256-*d*$_4$**. This value is inconsistent with a mechanism involving the insertion of Pd into the C-H bond which has been calculated to be in the range of k_H/k_D 1.7-2.3, which suggests route **A** is also not likely.[168] Finally calculations of deuterium isotope effect on the three transitions states of pathway **A**, **B** and **C** were found to be most consistent with intramolecular abstraction of the hydrogen by the chloride ligand. Furthermore previous studies of X-ray crystal structures of related Pt-alkene complexes[169] had shown close contacts between the chloride ligand and the allylic hydrogen atoms, less than the sum of Van der waals radii.[170] Despite this informative work, the mechanism of an allylic C–H activation/functionalisation is not yet fully understood.[3] However the vast developments of C-H functionalisations reported give informative insights into the requirements of the reaction, which have provided a platform for the design of our C-H

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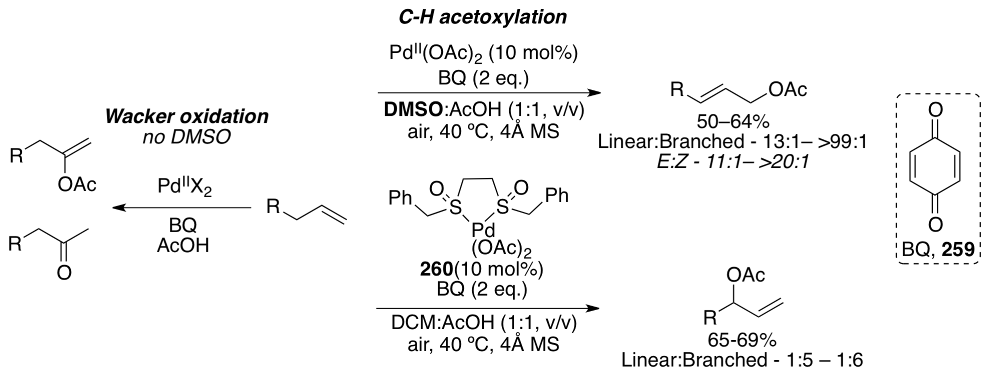
[3] In the literature there is widespread disagreement on the appropriate use of the term "C–H activation", with some researchers using it specifically to refer to an oxidative addition into a C–H bond and hence a change in oxidation state of the metal and others using it more broadly. To avoid confusion, throughout this thesis, we use the term "C–H functionalization," without any mechanistic implications."

fluorination reaction.

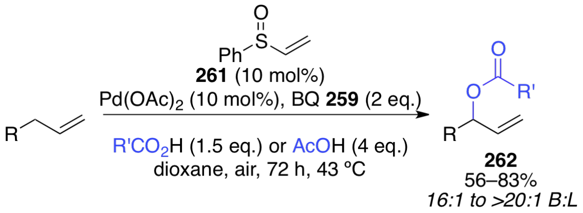
While the intermediates accessed from Pd^0 and a Pd^{II} are similar π-allylpalladium complexes, the two mechanistic manifolds require very different conditions to effect a nucleophilic attack. In the case of Pd^0, strong nucleophiles under basic conditions with σ-donating ligands are required to stabilised the Pd^{II} centre formed as an intermediate. In contrast, the Pd^{II} system favours acidic conditions and the presence of π-acceptor ligands to ensure a suitably electrophilic Pd centre that is able to undergo nucleophilic attack. Below, recent developments in allylic C–H functionalization are discussed.

The use of Pd^{II} salts in mild allylic substitutions of internal olefins had been previously reported but suffered from poor regioselectivity and limited substrate scope. In the case of monosubstituted olefins, competing Wacker oxidation was also observed.[171] Research over the last decade has yielded a collection of practically useful catalytic allylic C-H functionalisation reactions. Bäckvall first reported the use of a metal-quinone system for the Pd-catalysed aerobic oxidations of alkenes.[172] In 2004, White *et al.* reported the use of dimethyl sulfoxide (DMSO) in a $Pd(OAc)_2$-catalysed allylic acetoxylation in the presence of benzoquinone (BQ, **259**) as an oxidant (Scheme 3.8).[173]



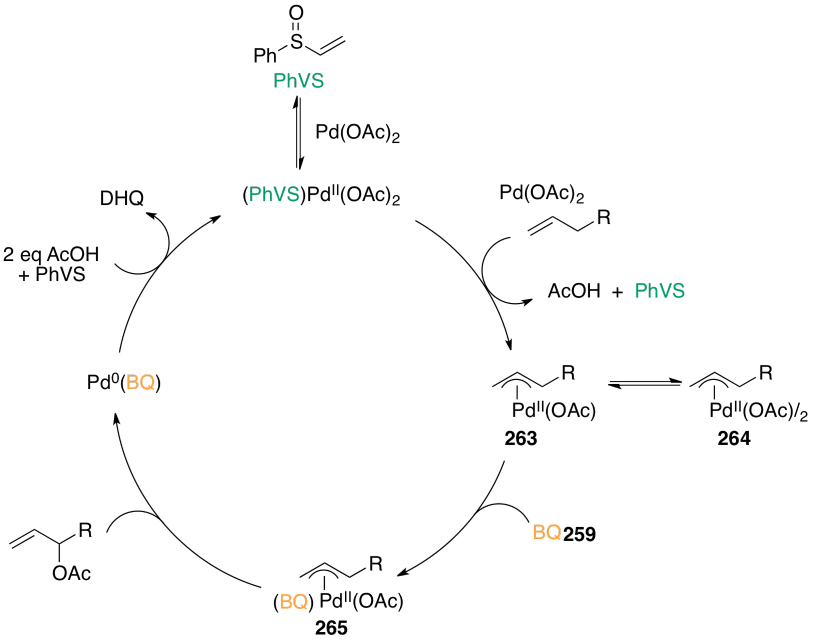
Scheme 3.8 Pd-catalysed regioselective allylic acetoxylation

The addition of DMSO was found to supress the competing Wacker oxidation and provide high regioselectivities and moderate to good yields of linear allylic acetates. The change in reactivity seen with DMSO was attributed to sulfoxide ligation to Pd. This was confirmed by examining the bis-sulfoxide palladium acetate complex **260**, which was also a competent catalyst for this system in the absence of DMSO. In this case, however, the regioselectivity of the reaction was reversed to give predominantly branched products. Further development of this reaction resulted in the finding that the sulfoxide ligand decomposed in the reaction to give phenyl vinyl sulfoxide **261**, which also proved to be a competent ligand for the reaction, leading to the formation of predominantly branched products **262** and tolerating a wide range of functionalites (Scheme 3.9).[174]



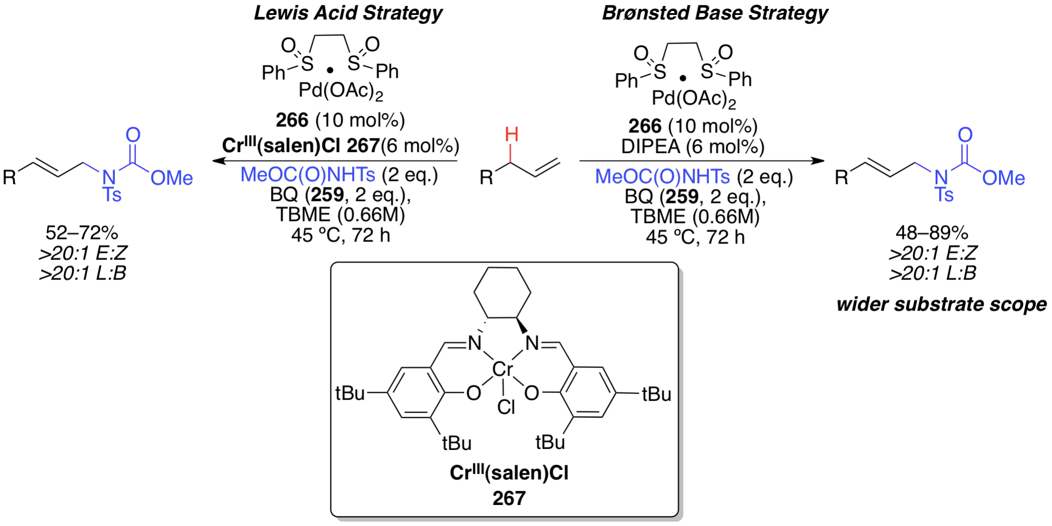
Scheme 3.9 Regioselective C-O bond formation of C–H bond using sulfoxide ligand

Mechanistic investigations have revealed the need for both the sulfoxide ligand and the benzoquinone to provide a successful catalytic reaction. This serial ligand mechanism was proposed to require the sulfoxide ligand in the initial C-H cleavage to form intermediate **263** and then benzoquinone to be involved in the formation of a reactive π-allylpalladium intermediate **265**, that was susceptible to attack by an acetate nucleophile followed by reoxidation of the Pd^0 to Pd^{II} (Scheme 3.10).[174] The branched selectivity is attributed to the unsymmetrical π-allylpalladium intermediate accessed from the use of the benzoquinone as a ligand. This hypothesis was supported by the use of PPh_3 or 1,2-bis(diphenylphosphino)ethane (dppe) to break up dimeric complex **264**. The use of these ligands provides access to electronically symmetric Pd-π-allyl intermediates, that under the reaction conidtions gave high yields of product but with no regioselectivity observed.



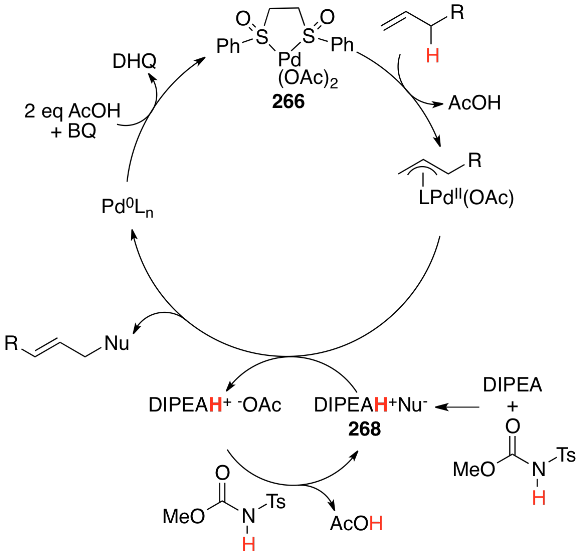
Scheme 3.10 Proposed serial ligand mechanism for formation of allylic acetates

This system was extended to the stereoselective intramolecular allylic C-H amination of chiral homoallylic *N*-tosyl carbamates with the use of a pre-formed Pd/bis-sulfoxide catalyst **266**.[175] The development of an intermolecular variant of this reaction was also possible with the addition of a Lewis acid Cr^{III}(salen) co-catalyst **267**, (*1S, 2S*)-(+)-[1,2-cyclohexanediamino-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)]Cr^{III}chloride, to the system.[176] Again, the Pd/bis-sulfoxide **266** is necessary for the initial C-H cleavage with the Cr catalyst, and BQ is proposed to promote nucleophilic attack to give linear (*E*)-allylic amines in good yields.



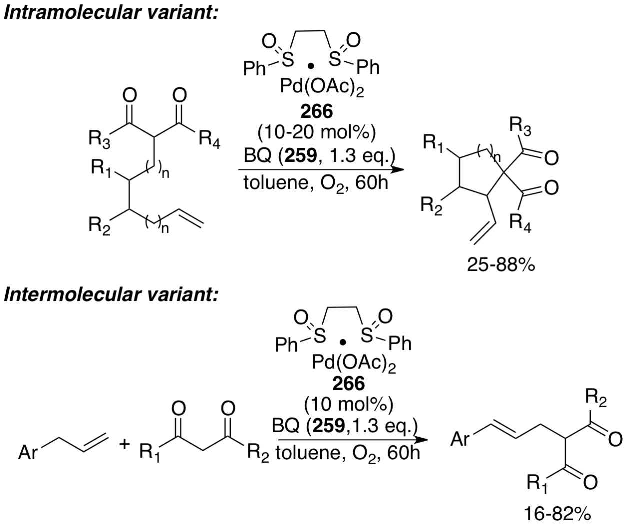
Scheme 3.11 Co-catalysed intermolecular amination

Improvement of the scope of the intermolecular system was also possible by changing to Brønsted base activation of the nucleophile by deprotonation with *N,N*-diisopropylethylamine (DIPEA). This deprotonated species **268** is then able to attack the π-allylpalladium intermediate to give the aminated product (Scheme 3.12). Under these mild conditions a wider range of functionalities are tolerated, such as unprotected alcohols and terminal epoxides, and the reaction is high yielding with good chemo- and regioselectivity.[177]



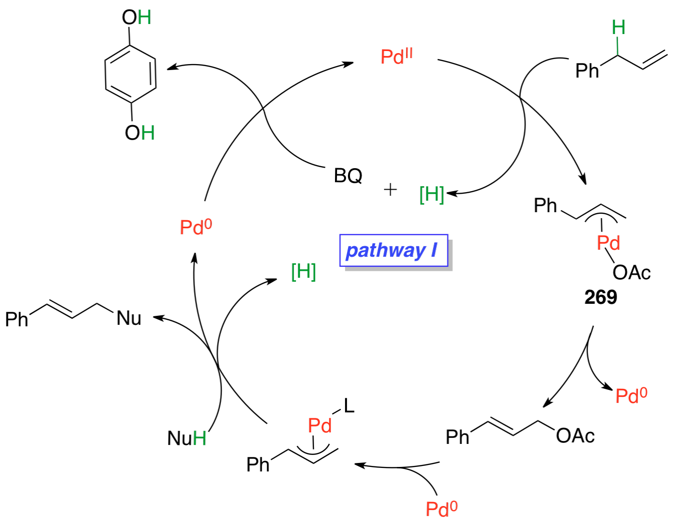
Scheme 3.12 Proposed mechanism for Brønsted base activation for allylic C-H amination

The intra/intermolecular allylic alkylation of terminal alkenes under an oxygen atmosphere was first reported by Shi using the Pd/bis-sulfoxide catalyst **266**. The presence of BQ was shown to be crucial for the reaction to occur (Scheme 3.13).[178]



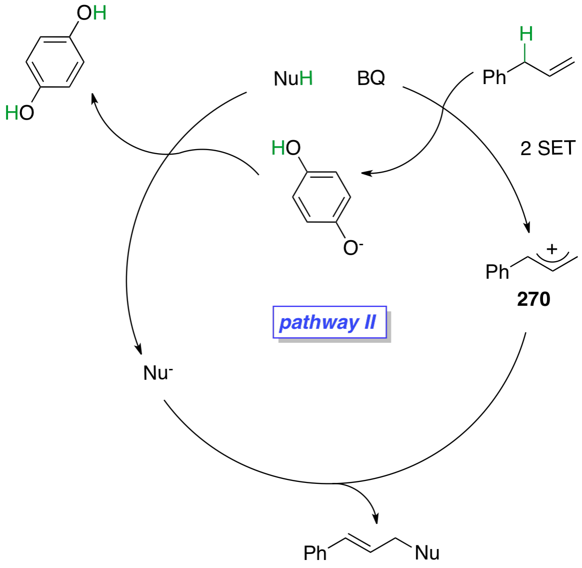
Scheme 3.13 Intra/Intermolecular Pd-catalysed allylic alkylation

Mechanistic investigations examined the possible pathways. As cinnamyl acetate was seen as a byproduct in some reactions, Pathway I was suggested (Scheme 3.14). It is proposed that this intermediate could first be formed by C-H acetoxylation from **269**, and subsequent Tsuji–Trost substituition gives the final product. However competing reactions of a substrate bearing both an allylic acetate and unsubstituted allyl group showed that only the allyl acetate remained intact after the reaction. Furthermore, the reaction of cinnamyl acetate under these conditions did not yield product.



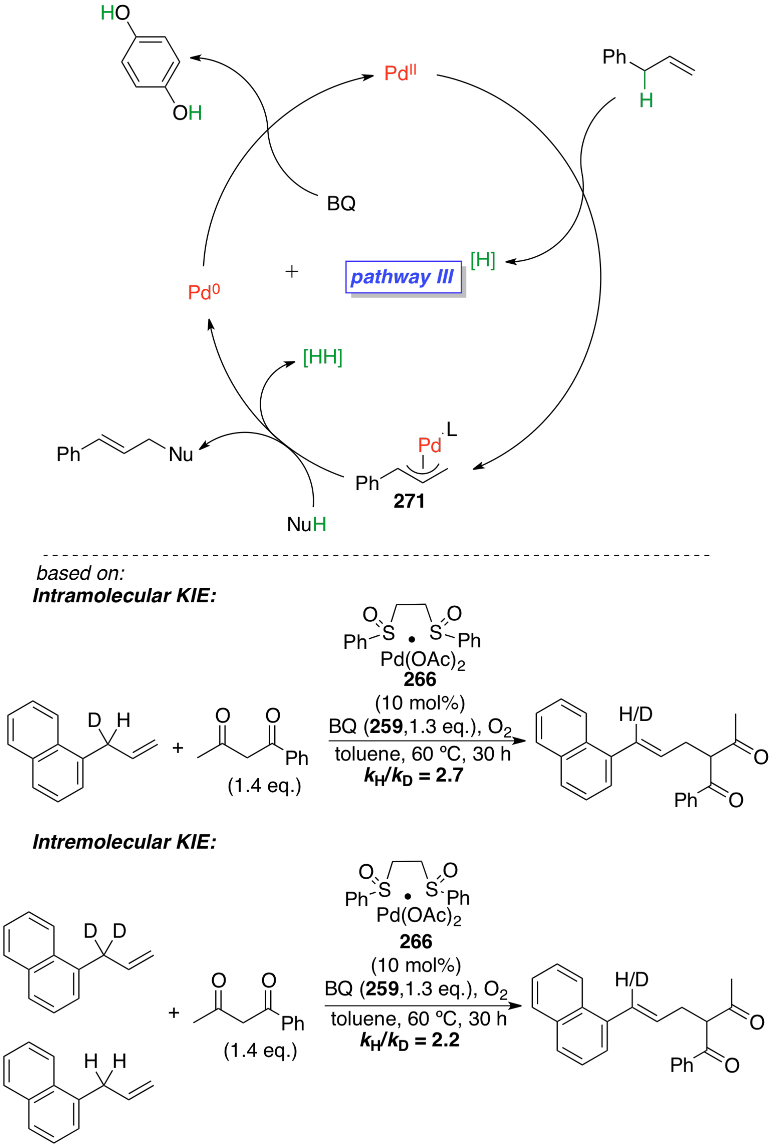
Scheme 3.14 Possible Pathway I – C-H Acetoxylation followed by Tsuji-Trost substitution

In 2008, Bao *et al.* reported the DDQ-mediated oxidative coupling of diarylallylic C-H bonds with activated methylenic C-H bonds.[179] This work proposed the oxidation of the alkene to an allyl cation, such as **270**, in the presence of a quinone followed by reaction with a nucleophile to give the product. As such, Pathway II was suggested; however, no reaction occurred in the absence of $Pd(OAc)_2$ in the presence of benzoquinone or DDQ (Scheme 3.15).



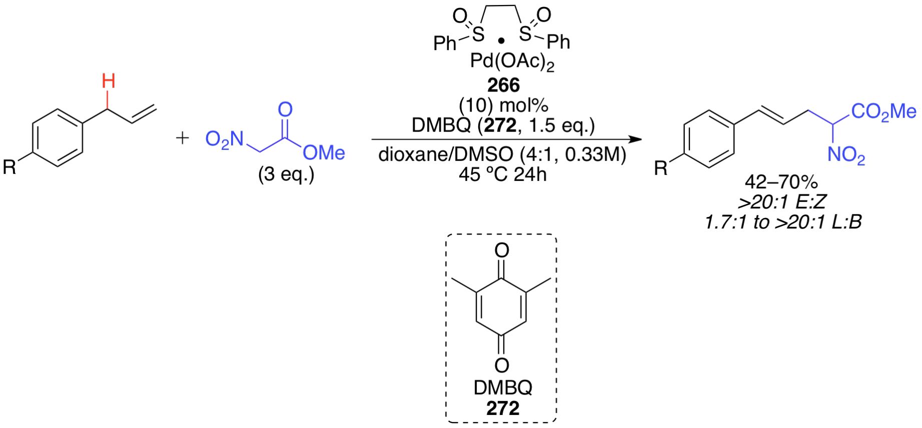
Scheme 3.15 Pathway II – Proposed single electron transfer to generate an allyl cation

The final proposed pathway was electrophilic C-H cleavage of the alkene by Pd^{II} to give a π-allylpalladium intermediate **271** that undergoes nucleophilic attack to give the product, and reoxidation of Pd by benzoquinone. The intra/intermolecular kinetic isotope effects of k_H/k_D = 2.7 and 2.2, respectively, support this mechanism by demonstrating the C-H cleavage step to be both the rate- and selectivity-determining step in the reaction (Scheme 3.16).



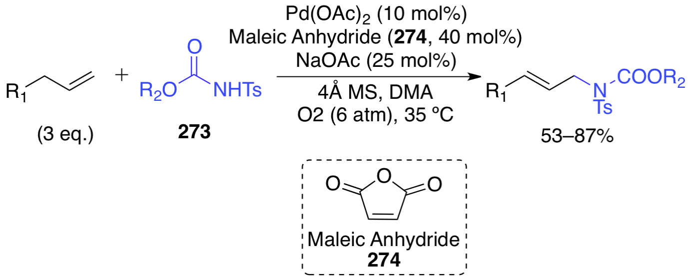
Scheme 3.16 Pathway III - Plausible mechanism for allylic C-H alkylation

White was able to use the same bis-sulfoxide/$Pd(OAc)_2$ (**266**) catalytic system to implement the first intermolecular allylic C-H alkylation of allyl arenes under Pd^{II} catalysis, this time using dimethylbenzoquinone **272** in place of benzoquinone (Scheme 3.17). Aliphatic substrates were found to be unreactive under these conditions with only ca. 10% yield observed.[180]



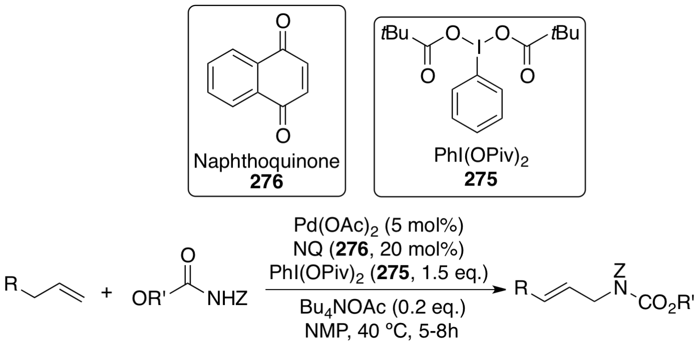
Scheme 3.17 Pd catalysed intermolecular allylic alkylation

Allylic C-H substitutions have also been reported that do not require benzoquinone or other quinones as additives. Previously Stahl reported the Pd-catalysed intermolecular aerobic oxidative amination of unactivated alkenes, proceeding by Markonikov aminopalladation across the alkene followed by *β*-hydride elimination.[181] Building on this, in 2008 Liu demonstrated intermolecular amination of terminal alkenes under aerobic conditions. Allylic C-H cleavage followed by attack of the *O*-methyl-*N*-tosylcarbamate **273** nucleophile was proposed as the mechanism. The optimal conditions employed maleic anhydride **274** and $Pd(OAc)_2$ as the catalyst under a 6 atm of O_2 pressure. Use of other Pd^{II} salts was found to give lower yields. The reaction was found to be highly regioselective for the linear product and tolerant of a wide range of functionalities (Scheme 3.18).[182]



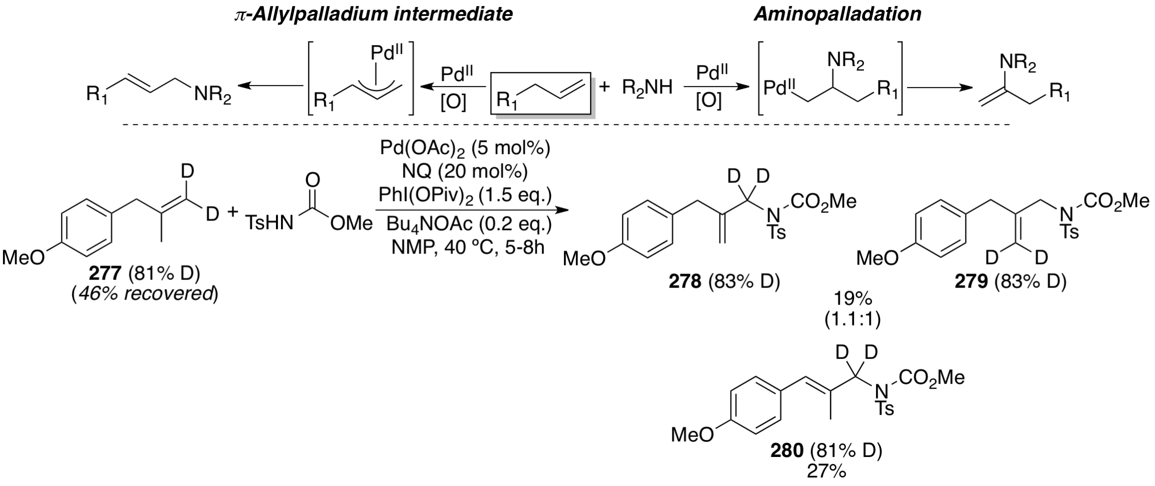
Scheme 3.18 Regioselective intermolecular amination of terminal alkenes

In 2010 it was shown that the reaction efficiency could be increased by the use of the stronger oxidant PhI(OPiv)$_2$ **275** to reoxidise the Pd^0 to Pd^{II}.[183] This work also investigated the role of a quinone, in this case naphthoquinone **276**, in the reaction (Scheme 3.19). Comprehensive analysis of the reaction kinetics and kinetic isotope effects were carried out.



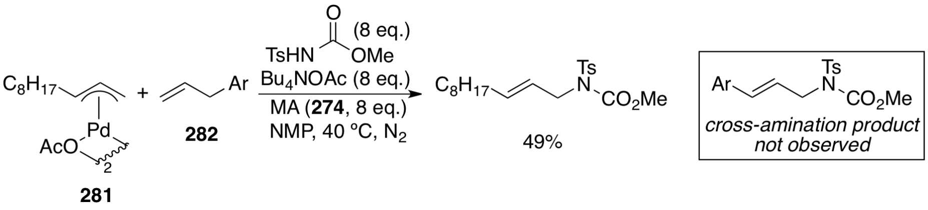
Scheme 3.21 Pd-catalysed allylic C-H amination using PhI(OPiv)$_2$ **275** and naphthoquinone **276**

Initial deuterium labelling of olefin **277** revealed a mixture of products, the presence of **279** suggested that the reaction involves a π-allylpalladium intermediate and does not proceed *via* an aminopalladation/*β*-hydride elimination which would not allow access to **279** (Scheme 3.20).



Scheme 3.20 Deuterium labelling to confirm the presence of a π-allylpalladium intermediate

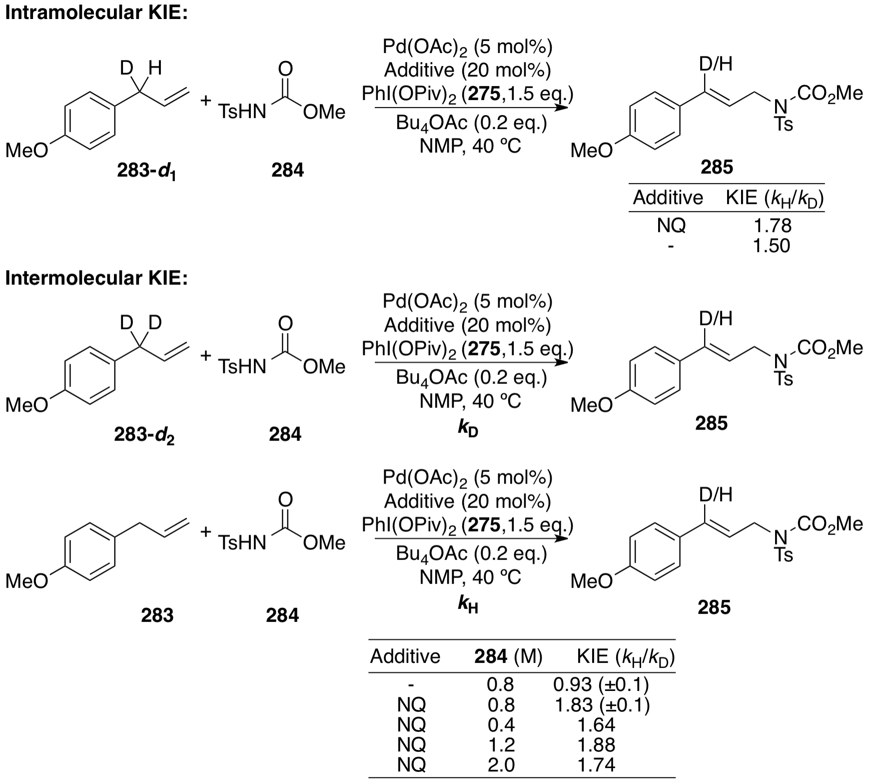
As previously discussed the possibility of an allylic acetate intermediate was also considered, however reactions of cinnamyl acetate under the reaction conditions did not see any amination or cross-amination in competition reactions. Competition reactions between pre-formed π-allylpalladium intermediate **281** and alkene **282** revealed that the formation of the (π-allyl)Pd complex was irreversible with no cross amination product observed (Scheme 3.21).



Scheme 3.21 Reaction of isolated π-allylpalladium intermediate **281**

Furthermore the reaction of complex **281** in the presence of various oxidants PhI(OAc)$_2$, PhI(OPiv)$_2$, benzoyl peroxide and NQ (**276**) provided the amination product in low to moderate yields with NQ (**276**) giving the highest yield. However no product was formed in the absence of oxidant. This observation is in contrast to the catalytic reaction which while superior in the presence of NQ (**276**) giving a 83% yield does also provide the product in 68% in the absence of NQ (**276**). The effect of varying the structure of the quinone on the initial rate of the reaction confirmed the fastest rate with NQ (**276**), a first-order dependence on [NQ] at low concentation and a zero-order dependence at high concentrations. As such, all kinetic studies were conducted under the standard conditions in the presence and absence of NQ (**276**). In both systems the reaction was zero order for [$PhI(OPiv)_2$]. When NQ (**276**) was present, a saturation rate dependence on the [olefin] and [nucleophile] along with a first-order dependence on [Pd] was observed. However when NQ (**276**) was removed the reaction was first-order in [olefin] and [Pd] but zero-order for [nucleophile].

Intramolecular and intermolecular kinetic isotope effects for the two systems were also measured using olefin **283-*d*₁** and a mixture of **283** and **283-*d*₂**, respectively (Scheme 3.22). The intramolecular KIE values were similar in the presence and absence of NQ, k_H/k_D = 1.78 (NQ) and 1.50 (no NQ). However while the intermolecular KIE value in the presence of NQ was k_H/k_D = 1.83 without NQ almost no KIE was observed k_H/k_D = 0.93. When the KIE values were measured at different nucleophile concentrations no significant dependence was observed. Finally no scrambling of the deuterium label was observed in product **285** in these systems indicating that the allylic C-H bond cleavage is irreversible.

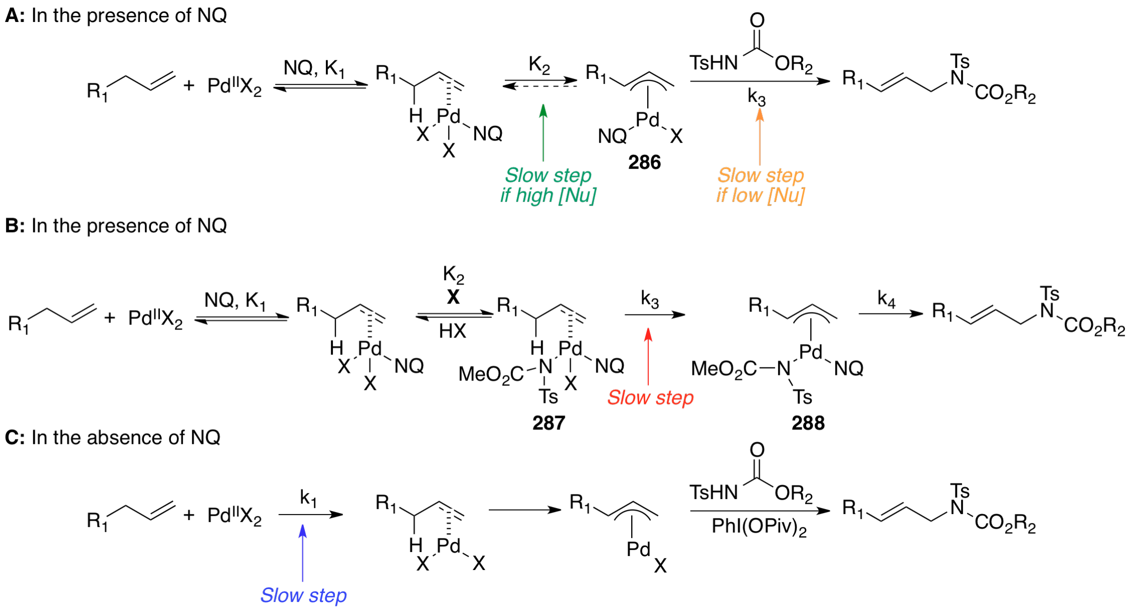


Additive	KIE (k_H/k_D)
NQ	1.78
-	1.50

Additive	**284** (M)	KIE (k_H/k_D)
-	0.8	0.93 (±0.1)
NQ	0.8	1.83 (±0.1)
NQ	0.4	1.64
NQ	1.2	1.88
NQ	2.0	1.74

Scheme 3.22 Intramolecular and intermolecular kinetic isotope effects

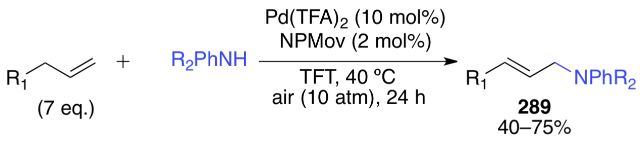
This data indicates that in the presence of NQ the C-H bond activation is involved in the rate-limiting step and not the coordination of the Pd and olefin based on the KIE values and a rate saturation dependence seen on the concentrations of olefin and nucleophile. This dependence can be reasoned by two hypotheses (Scheme 3.23). **A**; Firstly a kinetic competition between the reversal of a π-allylpalladium intermediate **286** and nucleophilic attack, where at low nucleophile concentrations reversal would out compete nucleophilic attack and at high concentrations the rate would level and π-allylpalladium formation would be rate limiting. **B**; Secondly the rapid formation of a nitrogen coordinated Pd complex **287** followed by rate limiting allylic C-H activation to give **288** may also explain this data. The KIE observed suggest that the second mechanism is more likely. The authors suggest the presence of NQ allows for a fast and reversible coordination of Pd to the olefin based on the π-acid ligands ability to increase the electron-deficiency at the Pd centre. In the absence of NQ the KIE value of $k_H/k_D = 0.93$ would suggest that coordination of the substrate to the Pd is rate-limiting, **C**.



Scheme 3.23 Possible mechanisms for C-H amination with and without NQ

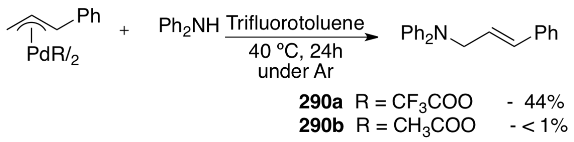
The final C-N formation is proposed to occur *via* nucleophilic attack of the π-allylpalladium **288** and reoxidation of the Pd^0 by $PhI(OPiv)_2$ (**275**) or by oxidation of the allylpalladium species **288** with $PhI(OPiv)_2$ (**275**) and reductive elimination to give the product and Pd^{II}. At this time neither mechanism can be ruled out.

Ishii has previously reported the use of a Pd^{II}/molybdovanadophosphate (NPMoV) system to catalyse the aza-Wacker type reaction of alkenes with simple amines to form enamines that were previously difficult to access.[184] In 2010, efficient intermolecular aerobic oxidative allylic amination to give (*E*)-allylamines **289** with high regio- and stereoselectivity was disclosed using a similar Pd^{II}/NPMoV system under an atmosphere of air (10 atm) (Scheme 3.24).[185]



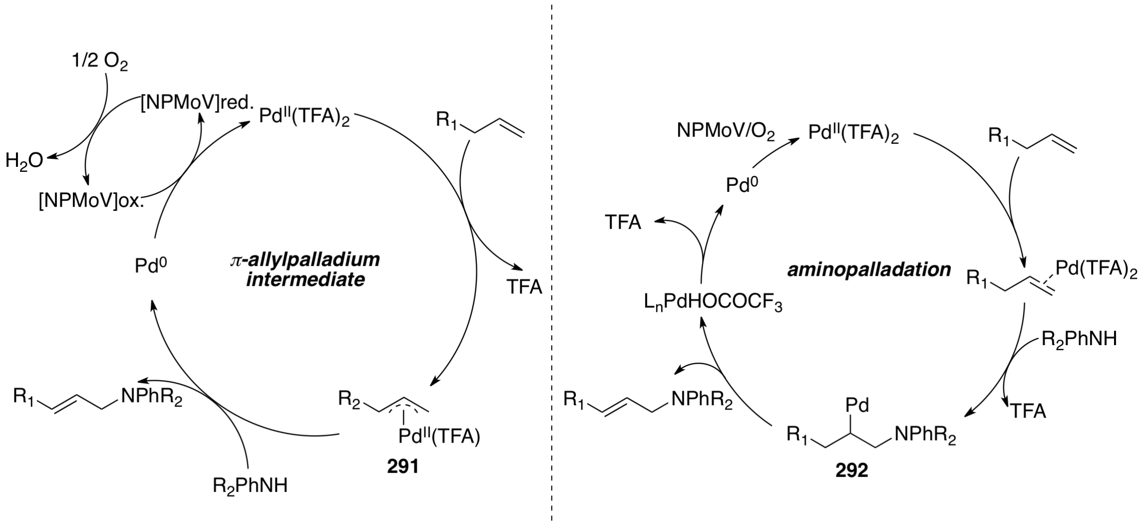
Scheme 3.24 Allylic amination using a Pd^{II}/NPMoV co-catalyst system

Whereas previously the catalyst was $PdCl_2(PhCN)_2$, this system utilised the more electrophilic $Pd(TFA)_2$ to provide an efficient reaction. Other Pd^{II} salts such as $Pd(OAc)_2$ and $Pd(acac)_2$ gave lower yields. The exposure of independently synthesised cinnamyl palladium acetate and trifluoroacetate dimers **290a/b** to the amine nucleophile only showed product formation in the case of the trifluoroacetate indicating the electrophilicity of the π-allylpalladium intermediate is key to the success of this reaction (Scheme 3.25).



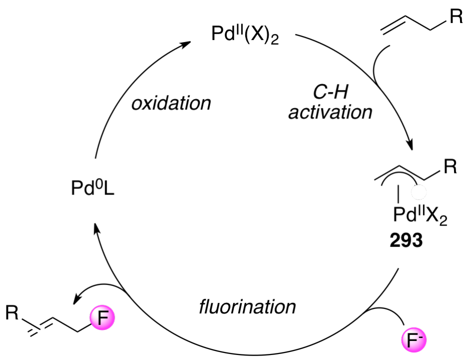
Scheme 3.25 Allylic amination of isolated π-allylpalladium complexes

Unlike previous reactions, this system does not require the use of non-basic nitrogen nucleophiles or an oxygen atmosphere. The authors propose a similar mechanism to previous studies, the formation of a π-allylpalladium intermediate **291** through allylic C-H cleavage, followed by attack of the amine nucleophile and finally reoxdiation of Pd^0 by the NPMoV/O_2 system as shown (Scheme 3.26). However at this time the possibility of aminopalladation to form **292** followed by *β*-hydride elimination cannot be ruled out. Again the NPMoV/O_2 system is proposed to reoxidise the Pd^0.



Scheme 3.26 Proposed mechanisms for Pd^{II}/NPMoV co-catalyst system

Following the successful validation of a Pd-catalysed nucleophilic allylic fluorination, we sought to investigate whether the reaction could be extended to C-H functionalisation which would obviate the need for a pre-activation of the substrate. With the previously discussed literature in mind, we sought to validate the feasibility of an allylic C-H functionalisation/fluorination. Considering the mechanistic proposals presented in the literature the following catalytic cycle was hypothesised; Pd^{II}-mediated allylic C-H cleavage forms the desired π-allyl palladium intermediate **293**, and subsequent attack by fluoride would yield allyl fluoride and Pd^0. An oxidant is thus required to close the catalytic cycle (Scheme 3.27). As demonstrated in the literature a variety of additives have also been used in C-H functionalisations which are proposed to either aid in the formation of a π-allyl palladium intermediate or activate this complex towards nucleophilic attack.



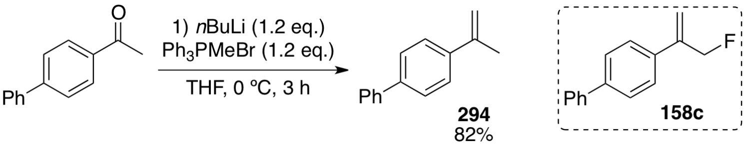
Scheme 3.27 Proposed allylic C-H fluorination catalytic cycle

As the literature demonstrates, there is not one set of general conditions that are applied to all C-H activation reactions. Each reaction requires a specific combination of catalyst, oxidant, solvent and temperature along with possible additives such as a base. Thus, we surmised that comprehensive screening of these components would be required to develop a catalytic C-H functionalisation-fluorination reaction. Consequently, we decided to validate the first two steps in the catalytic cycle separately, before using the knowledge gained from these studies to complete the catalytic cycle. In this chapter, our findings towards the development of this methodology, both stoichiometric and catalytic, are presented.

3.2 Preliminary studies

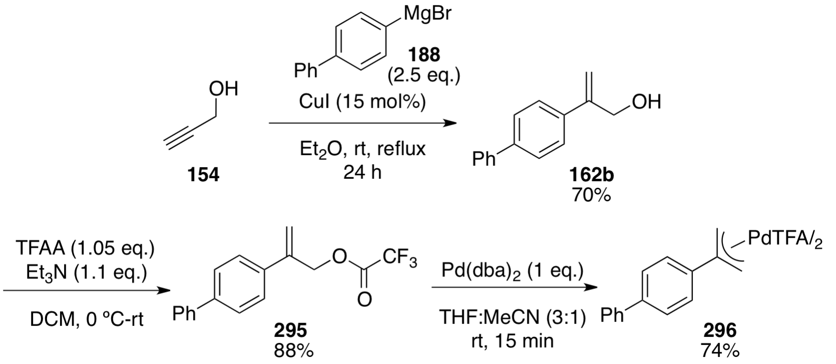
3.2.1 Formation of a π-allylpalladium intermediate

Initially we focussed on the first step in the cycle, formation of an π-allyl palladium intermediate *via* a C-H functionalisation. As previously discussed, Trost had demonstrated that stable allylpalladium dimers could be easily accessed from the insertion of Pd(TFA)$_2$ into a variety of unactivated alkene.[162] The proposed mechanism involves the electrophilic insertion of Pd^{II} into the allylic C-H bond and loss of F$_3$CCO$_2$H to give a dimeric product. Therefore, the insertion of the Pd(TFA)$_2$ into the standard substrate 4-(prop-1-en-2-yl)biphenyl, **294**, was investigated. This model substrate 4-(prop-1-en-2-yl)biphenyl **294** was selected for conceptual validation, as previous work on the Tsuji–Trost system proved the stability of the corresponding allylic fluoride **158c**.[186] Furthermore, no competitive elimination is possible and the product **158c** is distinctive in ^{1}H NMR (5.34 ppm, d, J = 47 Hz, CH$_2$ in CDCl$_3$) and ^{19}F NMR spectra (212.7 ppm, td, J = 47, 3 Hz), which allows easy idenitification. To obtain the substrate 4-(prop-1-en-2-yl)biphenyl **294**, methyltriphenylphosphonium bromide (1.2 eq. relative to 4-acetylbiphenyl) was first added to *n*BuLi (2. 2 M in hexane, 1.2 eq.) in tetrahydrofuran at 0 ºC and then allowed to react at room temperature for 1 hour. After this time, one equivalent of 4-acetylbiphenyl in tetrahydrofuran was added carefully and the solution allowed to stir at room temperature for 3 hours. Purification of the crude mixture by silica column chromatography delivered the desired product in an excellent yield of 82% (Scheme 3.28).



Scheme 3.28 Synthesis of model substrate

An authentic sample of the proposed dimeric species was synthesised as a reference from the allylic trifluoroacetate **295** using a literature procedure reported by Vitagliano.[187] Firstly, the allylic trifluoroacetate **295** was easily prepared by the reaction of 4-biphenylmagnesium bromide (2.5 eq.) with propargyl alcohol **154** in the presence of CuI (15 mol%) providing the allylic alcohol **162b** in 70% isolated yield. This was further reacted with trifluoroacetic anhydride in the presence of triethylamine to give the allylic trifluoroacetate **295** in a 81% yield (Scheme 3.29). Reaction of 2.5 equivalents of **295** with Pd(dba)$_2$ in a THF:MeCN solvent system for 15 minutes gave the desired {[allylPd(TFA)]$_2$} dimer complex **296** after extraction of the crude mixture with 10% MeCN:H_2O.



Scheme 3.29 Preparation of {[allyPd(TFA)]$_2$} **296**

The identify of this complex was confirmed by the presence of characteristic allylpalladium peaks in the ^{1}H-NMR as broad signals at 2.51-3.37 ppm (m, 2H) and 4.14-4.61 ppm(m, 2H). Corresponding signals are reported for the known allylpalladium complex **297** (Figure 3.1).[188]

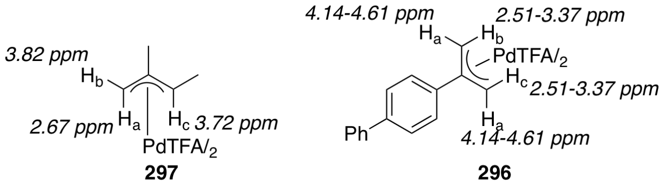


Figure 3.1 ^{1}H-NMR signals for {[allyPd(TFA)]$_2$} dimer complexes

Further analysis of the complex by mass spectrometry revealed a molecular ion corresponding to the monomeric species and the identity of the complex was unambiguously confirmed by X-ray crystallography (Figure 3.2). Both the dimer and monomeric complexes were observed indicating that the two species could be in equilibrium, however the exact nature of this complex in solution could not be determined from the NMR spectra.

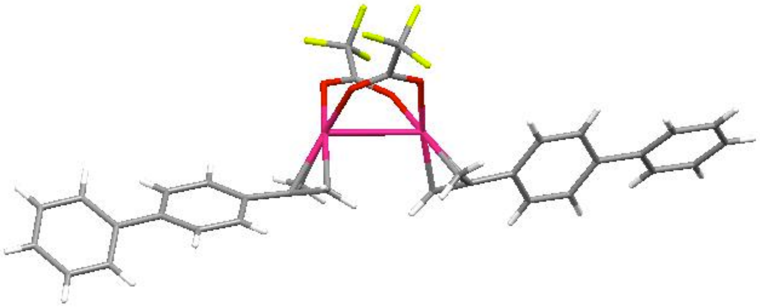
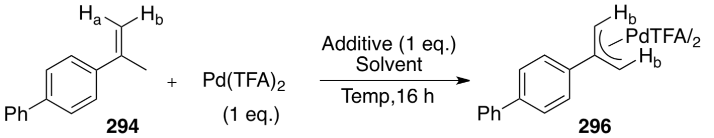


Figure 3.2 X-ray crystal of {[allylPd(TFA)]$_2$} dimer complex **296**

With the stability and characterisation of {[allylPd(TFA)]$_2$} dimer complex **296** confirmed the reaction of alkene **294** with Pd(TFA)$_2$ was performed under various conditions to observe the formation of **296**. All screening reactions with substrate **294** using a stoichiometric loading of Pd(TFA)$_2$ were performed in dried glassware under an argon atmosphere. Pd(TFA)$_2$ was dissolved in the appropriate solvent (0.1 M), and the alkene **294** was added, followed by benzoquinone (when used). Reactions were flushed with Ar, sealed and stirred at 80 ºC for 1 hour, after which time the reactions were filtered through a plug of celite to remove any Pd precipitates, and solvent was removed *in vacuo*. Conversion to the dimeric complex **296** was calculated from ^{1}H NMR analysis of the crude material by comparison with the authentic sample of allylpalladium trifluoroacetate dimer **296**. Ratio of alkene (**294**) to dimer (**296**) was determined by the intergration of the $H_{a/b}$ proton (5.15-5.11 ppm, m, 1H) of alkene **294** with protons H_b (2.51-3.37 ppm, m, 2H) of the allylpalladium complex **296**.



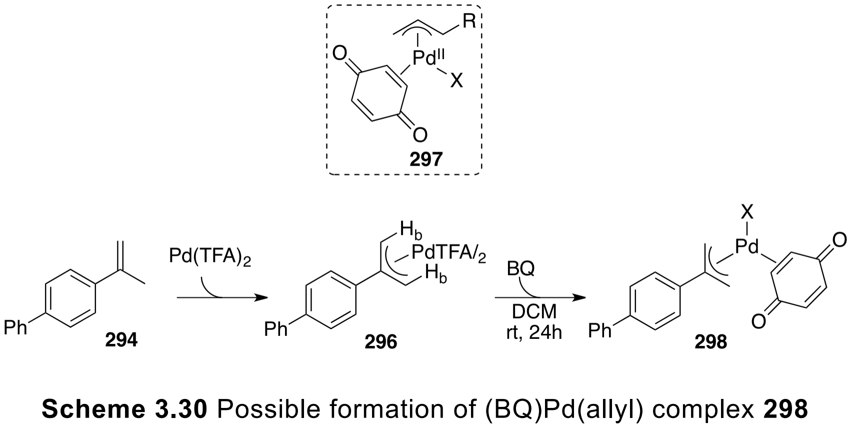
Entry	Solvent	Additive	Temperature (°C)	**294**:**296**	Conversion to Dimer **296**[a]
1	DCM	-	40	1:0	-
2	DCM	BQ	40	1:0	-
3	DCE	-	80	1:1.5	75%
4	DCE	BQ	80	1:1.1	69%
5	DMF	-	80	1:1	66%
6	DMF	BQ	80	2.5:1	46%
7	THF	-	60	1.4:1	59%
8	THF	BQ	60	2.5:1	43%

[a] Ratio of alkene (**294**) to dimer (**296**) was determined by the intergration of the $H_{a/b}$ proton (5.15-5.11 ppm, m, 1H) of alkene **294** with protons H_b (2.51-3.37 ppm, m, 2H) of the allylpalladium complex **296** taking into account that 2 alkene motifs are present in the dimer.

Table 3.1 Investigation of allylpalladium formation using $Pd(TFA)_2$

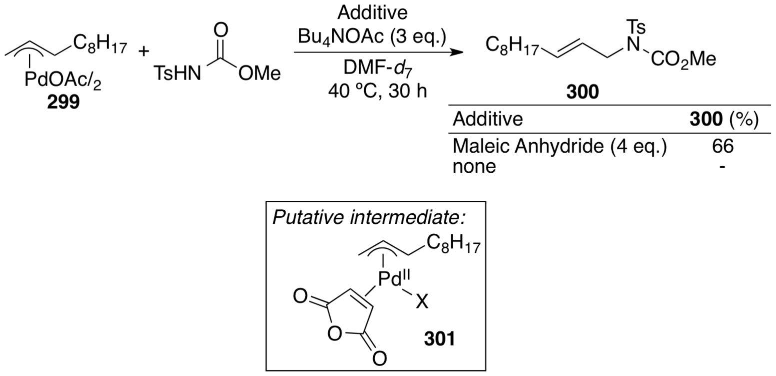
As Table 3.1 demonstrates, the formation of the desired dimeric complex was observed in moderate to high conversions in all solvents other than DCM where no diagnostic peaks for the allylpalladium complex **296** were observed. Most C-H functionalisations discussed in the literature for both sp^3 and sp^2 carbon centres required elevated temperatures, suggesting C-H cleavage is not observed in DCM as these high temperatures cannot be achieved. While the highest level of conversion was obtained when DCE was used as the solvent with a conversion of 75% observed, analysis of the ^{1}H-NMR of this reaction showed the formation of a complex mixture. Peaks corresponding to the alkene **294** and allylpalladium dimer **296** were observed along with new peaks throughout the spectra that were not identified. In the case of DMF and THF, the reactions were far more selective, with only alkene **294** and dimeric complex **296** identified in the ^{1}H NMR spectra in a 66% and 59% conversion, respectively.

As previously discussed the presence of an additive, often a quinone, is frequently required in many C-H functionalisations, with Liu demonstrating how NQ (**276**) aided in the allylic C-H cleavage to form a π-allylpalladium intermediate.[183] As such, we investigated the use of the commonly used additive benzoquinone in the formation of the π-allylpalladium trifluoroacetate dimer **296**. Reactions run in the presence of BQ (**259**) were found to reduce the conversion to the dimer compared to when BQ (**259**) was absent (Table 3.1, entries 2,4,6,8). Furthermore, the spectra of the crude reactions became far more complex, suggesting the formation of other products, which also explains the lower conversions. One possible product could be an intermediate allylpalladium complex such as **297**. C-H activation involving the use of additives such as benzoquinone and maleic anhydride are suggested to form intermediates such as **297** where the additive acts as a ligand for the Pd to aid in nucleophilic attack, however these complexes have yet to be characterised. A control reaction between trifluoroacetate dimer **296** and benzoquinone in DCM showed no formation of any other allyl species, such as **298**, by analysis of the ^{1}H-NMR spectra, even after 24 hours only the starting trifluoroacetate dimer **296** and BQ (**259**) were observed in the spectra. However this does not rule out the involvement of intermediate **298** in the fluorination reaction (Scheme 3.30).



Scheme 3.30 Possible formation of (BQ)Pd(allyl) complex **298**

With the formation of the π-allylpalladium intermediate validated under our reaction conditions, we continued to investigate the second step of the catalytic cyclic which is the nucleophilic attack of this intermediate. The previously discussed work by Trost *et al* had demonstrated the requirement of triphenylphosphine to allow for the attack of a malonate nucleophilic on isolated π-allylpalladium dimers. Liu also reported a similar observation in 2008 when investigating Pd-catalysed allylic C-H amination. When isolated π-allylpalladium complex **299** was reacted with an imide nucleophile no product **300** was observed unless the additive maleic anhydride was present. Again the formation of π-allylpalladium intermediate **301** was suggested to aid nucelophilic attack (Scheme 3.31).[182]

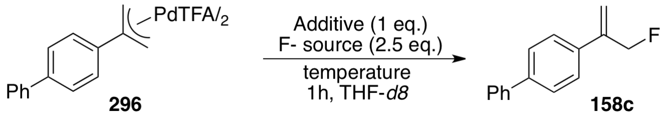


Additive	**300** (%)
Maleic Anhydride (4 eq.)	66
none	-

Scheme 3.31 Use of additives to allow nucleophilic attack of π-allylpalladium complexes

Taking these observations into consideration we investigated the use of a variety of additives along with fluoride sources in the fluorination of the isolated π-allylpalladium trifluoroacetate complex **296**. This complex was accessed by the previously discussed method (Scheme 3.29).

Initial investigations were carried out in deuterated THF at room temperature. Under an Ar atmosphere, the palladium complex was first dissolved in deuterated THF, and subsequently one equivalent of additive (where necessary) and 2.5 equivalents of the fluoride reagent were introduced. Reactions were flushed with Ar, sealed and stirred at the appropriate temperature for 1 hour. In each case, the yield was determined by ^{19}F-NMR analysis of the crude reaction mixture by comparing integration of the peak for the allylic fluoride **158c** with the signal corresponding to a known quantity of internal reference, 20 mol% (based on Pd) of 1-fluoro-3-nitrobenzene. The fluorinated product **158c** could be easily detected by the presence of a peak at 212.7 ppm (td, $^{2}J_{H\text{-}F}$ = 47 Hz, $^{4}J_{H\text{-}H}$ = 3 Hz) in the ^{19}F NMR spectra. These results are presented in Table 3.2.

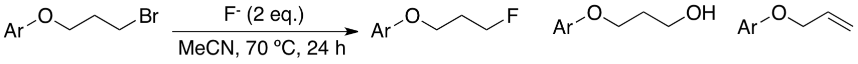


Entry	Additive	F^- source	Temperature (°C)	Yield of **158c**
1	-	TBAF(*t*BuOH)$_4$	25	-
2	BQ (**259**)	TBAF(*t*BuOH)$_4$	25	2%
3	-	TBAF(*t*BuOH)$_4$	60	-
4	-	TBAF(Pinacol)$_2$	25	-
5	BQ (**259**)	TBAF(Pinacol)$_2$	25	Trace
6	-	KHF$_2$	25	-
7	BQ (**259**)	KHF$_2$	25	-
8	-	TBA.HF$_2$	25	-

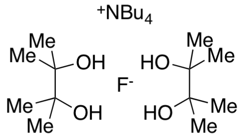
Table 3.2 Fluorination of isolated dimer **191**

Current research being undertaken in the Gouverneur group aims to produce a new set of fluoride sources, initially based on the tetraalkylammonium fluoride salts due to the success of TBAF(*t*BuOH)$_4$ reagent **160** in the Pd-catalysed allylic fluorination (Chapter 2).[189] Recent work has focused on the replacement of *t*-butanol in the complex with other alcohols which have shown superior reactivity in traditional S_N2 fluorinations (Scheme

3.32).



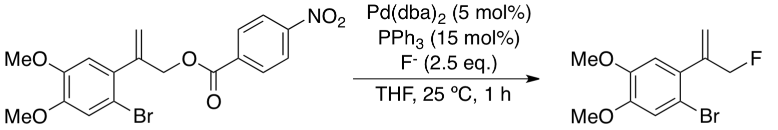
F^- reagent	Fluoride	Alkene	Alcohol	SM	F/O Ratio
TBAF(H_2O)$_3$	59	35	-	8	1.7
TBAF(*t*BuOH)$_4$ **160**	65	32	3	-	2.0
TBAF(Pinacol)$_2$ **302**	60	22	2	15	2.7



TBAF(Pinacol)$_2$
302

Scheme 3.34 Reactivity of TBAF(alcohol) complexes in S_N2 fluorination

Along with screening in simple S_N2 substitutions, these new complexes have been tested in the Tsuji-Trost palladium-catalysed systems. Initial results from use of TBAF(Pinacol)$_2$ **302** in the allylic fluorination of nitrobenzoates showed reasonable conversion to the desired allyl fluoride product, but this new reagent was less reactive than TBAF(*t*BuOH)$_4$ **160** (Scheme 3.33).



F^- reagent	Fluoride	Alcohol	SM
TBAF(*t*BuOH)$_4$ **160**	83	6	12
TBAF(Pinacol)$_2$ **302**	47	6	47

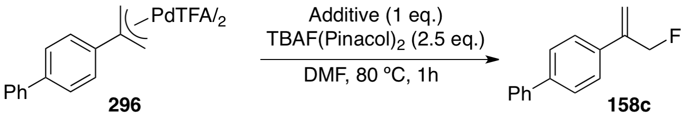
Scheme 3.33 Reactivity of TBAF(alcohol) complexes in Pd-catalysed allylic fluorination

Consequently, TBAF(Pinacol)$_2$ **302** was selected as a fluoride source to screen in these reactions as it showed superior properties to TBAF(*t*BuOH)$_4$ **160** in terms of stability in the air and ease of handling.

No fluorination was observed with various fluoride sources at room temperature or elevated temperatures in the absence of an additive (Table 3.2, entries 1, 3, 4, 6, and 8).

When the reactions were carried out in the presence of benzoquinone at room temperature with either TBAF(*t*BuOH)$_4$ (**160**) or TBAF(Pinacol)$_2$ (**302**), trace fluorination was observed (entries 2 and 5). However at elevated temperature (60 ºC), the desired product **158c** was not formed, or is unstable under these reaction conditions. Bifluoride reagents, were also tested. No fluorination was observed with or without an additive at room temperature. In all cases, the starting π-allylpalladium trifluoroacetate complex **296** could still be observed in the ^{1}H-NMR spectra as the major component of the reaction.

With trace conversions seen with the use of tetrabutyllammonium fluorides we next investigated the use of these with DMF as a solvent, based on its success in the initial step of the catalytic cycle. The reactions were carried out as above, using DMF as the solvent and stirring at 80 ºC for 1 hour (Table 3.3).



Entry	Additive	Yield of **158c**
1	Phenyl vinyl sulfoxide (**261**)	Trace
2	Methyl acrylate	2%
3	BQ (**259**)	4%
4	Phenylnaphthylquinone	-
5	PPh$_3$	-

Table 3.3 Screening of additives in fluorination of dimer **296**

The use of the phenyl vinyl sulfoxide ligand **261**, reported by White *et al* to aid allylic C-H substitution reactions, gave trace amounts of fluorination under these conditions (Table 3.3, Entry 1). The use of methyl acrylate led to 2% NMR yield of the allylic fluoride (Entry 2). When benzoquinone was used, fluorination was observed in 4% NMR yield, confirming that the formation of the allylic fluoride **158c** is possible at elevated temperatures (Entry 3). However the use of phenylnaphthylquinone did not give any allylic fluoride product (Entry 4).

These results indicate that the fluorination of the π-allylpalladium intermediate proposed to be involved in a C-H functionalisation/fluorination is problematic. As such attempts to find conditions suitable to allow for a C-H functionalisation-fluorination to occur required a comprehensive screen of all these variables. We embarked on this study to screen both C-H activation and fluorination steps *in situ* using a stoichiometric loading of Pd. Attempts to complete the catalytic cycle with the addition of an oxidant were also screened. The results of these two studies are presented in the following two sections.

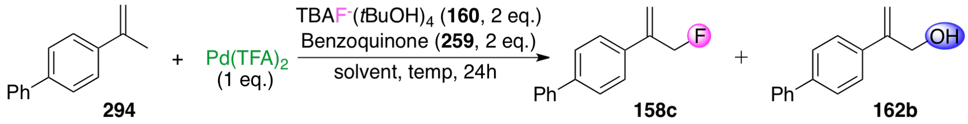
3.3 Screening of an *in situ* fluorination

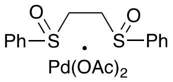
3.3.1 Initial optimisation of stoichiometric reaction

We sought to identify a standard set of reaction conditions through a thorough screening of catalyst, solvent, temperature and additives. $Pd(OAc)_2$, $Pd(TFA)_2$ and $PdCl_2$ are commonly used sources of Pd^{II} in C-H functionalisations. Screening of these along with the White catalyst (commercially available) used in C-H functionalisation-acetoxylations, and $Pd(OTs)_2$ (synthesised from $Pd(OAc)_2$ and *p*-toluenesulfonic acid)[190] was carried out using a stoichiometric loading of the palladium source in the presence of benzoquinone. $Pd(TFA)_2$ was either obtained from a commercial source or synthesized from $Pd(OAc)_2$ and trifluoroacetic acid following the procedure of Wilkinson in 1965[162].

Reactions were carried out with alkene **294** in the presence of BQ with $TBAF(tBuOH)_4$ **160** as the fluoride source. Screening of Pd^{II} sources revealed $Pd(TFA)_2$ to be the only complex to give the allylic fluoride **158c** in the presence of BQ (**259**) (Table 3.4, Entry

17). When the reaction was conducted without BQ (**259**) no allylic fluoride **158c** was observed indicating the need for an additive in this reaction (Entry 18). This result is in agreement with the results of Trost discussed previously, suggesting an electrophilic source of Pd facilitates the formation of a π-allylpalladium intermediate. While the presence of benzoquinone is shown to be necessary, its role, if any, in the initial C-H activation step or fluorination is not yet fully understood.

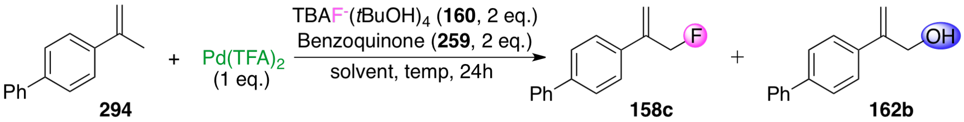


Entry	Pd source[a]	Solvent	Temp (°C)	Ratio of **158c**:**294**:**162b** [b]	Isolated Yield **158c**(%)
1	White Catalyst  	DMF	80	0:100:0	-
2	$Pd(OAc)_2$	DCE	80	0:100:0	-[c]
3	$Pd(OAc)_2$	MeCN	80	0:100:0	-[c]
4	$Pd(OAc)_2$	DMF	80	0:100:0	-[c]
5	$Pd(OAc)_2$	Toluene	80	0:100:0	-[c]
6	$Pd(OAc)_2$	AcOH	80	0:100:0	-[c]
7	$Pd(OAc)_2$	*t*BuOH	80	0:100:0	-[c]
8	$\{Pd(MeCN)(O_3STol)_2\}$	DCE	80	0:100:0	-
9	$PdCl_2$	DCE	80	0:100:0	-
10	$PdCl_2$	Toluene	80	0:100:0	-
11	$PdCl_2$	MeCN	80	0:100:0	-
12	$PdCl_2$	*t*BuOH	80	0:100:0	-
13	Pd((-)-sparteine)Cl_2	DMF	80	0:100:0	-
14	Pd((-)-sparteine)Cl_2	DCE	80	0:100:0	-
15	Pd((-)-sparteine)Cl_2	Toluene	80	0:100:0	-
16	Pd((-)-sparteine)Cl_2	*t*BuOH	80	0:100:0	-
17	$Pd(TFA)_2$	DCE	80	-	56
18	$Pd(TFA)_2$[d]	DCE	80	0:50:50	-
19	$Pd(hfacac)_2$	DMF	80	0:100:0	-

[a] Reaction conditions: 4-(prop-1-en-2-yl)biphenyl (1 eq.), catalyst (1 eq., based on Pd(II), benzoquinone (2 eq.), TBAF(*t*BuOH)$_4$ (2 eq.), solvent (0.1M); [b] Determined from ^{1}H NMR; [c] No fluorinated product identified in crude ^{1}H NMR/^{19}F NMR; [d] No BQ

Table 3.4 Catalyst screening

A screening of solvents was then carried out using Pd(TFA)$_2$. DMF was identified as the optimal solvent for the reaction giving allylic fluoride **158c** in up to 65% (Table 3.5, Entry 9). Although the yield of allylic fluoride **158c** did not increase significantly upon changing the solvent from DCE to DMF, the reaction suffered from far fewer side reactions. In the case of both chlorinated solvents DCM and DCE, a complex reaction mixture was obtained, with only fluoride **158c**, alcohol **162b** and starting alkene **294** recovered. A screen of concentrations identified 0.1M to be the optimal concentration for the reaction.



Entry	Solvent	Temp (°C)	Ratio of **158c**:**294**:**162b**[a]	Yield of **158c** (%)
1	Acetone	50	0:100:0	-
2	NMP	80	0:100:0	-
3	THF	rt	7:93:0	Not isolated
4	MeCN	80	7:90:3	Not isolated
5	DMA	80	10:90:0	Not isolated
6	DMSO	80	13:87:0	Not isolated
7	DCM	40	-	30
8	DCE	80	-	56
9	DMF	80	-	≤ 65[b]

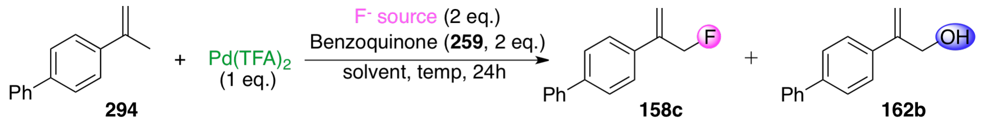
[a] Determined from ^{1}H-NMR. [b] Reaction repeated, yields range from 35-65%

Table 3.5 Initial solvent screening

It is demonstrated in the literature that the source of fluoride can have a profound effect on a reaction, in some cases dictating whether the fluorination can occur. As such, a screening of nucleophilic fluorinating reagents was undertaken. As Table 3.6 shows, the use of alkali metal fluoride (KF, entry 1), silver fluoride (entry 4,5 and 11) and

HF•pyridine (entry 3/10) as the fluoride source provided no fluorination. The need for a preformed complex of TBAF with a protic solvent, known to reduce the hygroscopicity and basicity of the fluoride, was necessary, as demonstrated by entry 8. When the reaction was performed with the commercially available trihydrate complex, alcohol formation becomes the predominant, with only low levels of fluorination detected.

The previously discussed TBAF(Pinacol)$_2$ reagent **302** was also screened and showed a comparable conversion to the desired allylic fluoride **158c** as the TBAF(*t*BuOH)$_4$ **160** (Entry 24). A recently reported asymmetric fluorination of *meso* epoxides utilizes a reactive form of HF formed *in situ* upon addition of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) to benzoyl fluoride in the presence of an amine catalyst.[191] This *in situ* HF formation method was unsuccessful in our C-H functionalisation. The use of KF with Kryptofix, TBAT and TMAF were also unsuccessful in this transformation. However when the less nucleophilic tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) reagent was used, a 30% conversion of starting material to fluoride was observed via HPLC analysis and NMR. Furthermore the use of the bifluoride reagents KHF$_2$ and tetrabutylammonium hydrogen difluoride (TBA.HF$_2$) showed even higher conversions to allylic fluoride **158c**. However preformed TBAF(*t*BuOH)$_4$ **160** and TBAF(Pinacol)$_2$ **302** reagents still remained the optimal fluoride sources.



Entry	F^- source	Solvent	Temp (°C)	**158c**:**294**:**162b**[a]	Yield of **158c** (%)
1	KF[b]	THF	rt	-	-
2	TBAF$(H_2O)_3$	DCM	40	-	-
3	HF.Pyridine	DMF	80	Complex mixture	-
4	AgF	DMF	80	SM decomposed	-
5	KF/Kryptofix222	DMF	80	0:100:0	-
6	KHF_2	DMF	80	40:60:0	-
7	BzF/HFIP	DMF	80	0:100:0	-
8	TBAF$(H_2O)_3$	DCE	80	7:7:86	-
9	TBAT	DMF	80	0:100:0	-
10	TMAF	DMF	80	0:100:0	-
11	TBA HF_2	DMF	80	53:47:0	-
12	TASF	DMF	80	24:76:0	-
13	TBAF(*t*BuOH)$_4$[b] (**160**)	DMF	80	33:67:0	12-66%
14	TBAF(*t*BuOH)$_4$ (**160**)	DMF	120	0:100:0	-
15	TBAF(Pinacol)$_2$ (**302**)	DMF	80	54:45:0	-

[a] Determined from ^{1}H-NMR; [b] 1 eq. of benzoquinone

Table 3.6 Fluoride source screening[4]

To ensure the stability of the allylic fluoride product, control reactions were run with the fluoride under the reaction conditions at various temperatures. This revealed the fluoride to be stable at temperatures below 80 ºC, however when the reactions were carried out at 120

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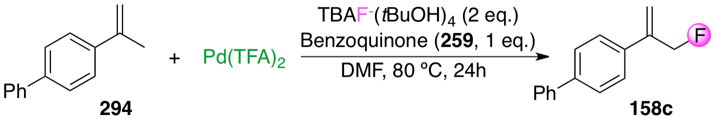
[4] A full set of screening tables are presented in Appendix A-2.

ºC complete lost of the allylic fluoride was observed. As such reaction temperatures were also maintained at 80 ºC or below.

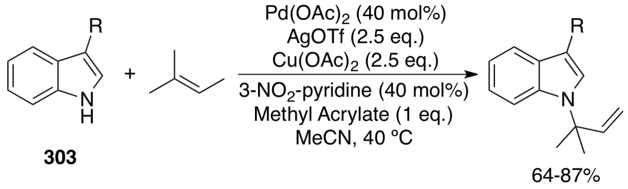
As a catalytic variant was desirable we next investigated the effect of Pd loading on the reaction. Table 3.7 shows that there is a decrease in conversion to fluoride from 100% Pd to 50% and complete lost of reactivity with Pd loadings below 50%.



Pd loading	Ratio F:SM
100 mol%	50:50
80 mol%	40:60
50 mol%	27:73
40 mol%	0:100
30 mol%	0:100

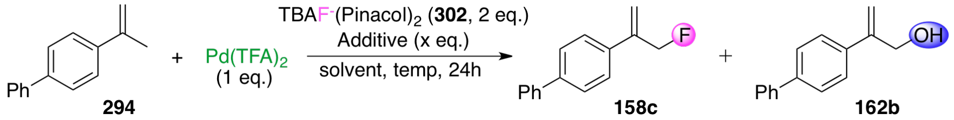
Table 3.7 Investigation of Pd loading

As the presence of benzoquinone was found to be essential for the reaction to occur, we investigated whether any other quinones or additives gave better conversion to product. Commonly used additives in C-H functionalisation reactions along with coordinating alkenes were examined. Based on work by Liu, maleic anhydride was investigated however no fluorinated products were observed (Table 3.8, Entry 6). The use of methyl acrylate and 3-NO$_2$-pyridine in Pd-catalysed C-H *N-tert*-prenylation of indoles **303** has also been reported by Baran *et al* (Scheme 3.34).[192] These conditions were investigated in the fluorination reaction, however only trace amounts of allylic fluoride **158c** were observed (Table 3.8, Entries 8-10).



Scheme 3.34 Pd-catalysed C-H *N*-*tert*-prenylation of indoles

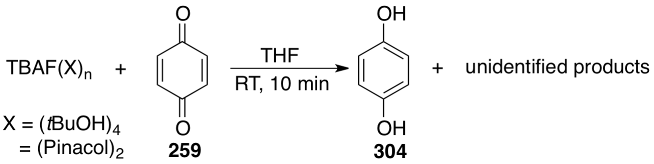
Similarly, trace fluorination was also observed when the conditions established by White *et al.* were screened.[193] Neither the phenyl sulfoxide ligand nor DMSO, used in allylic acetoxylation proved to be effective in C–H fluorination. These additives were screened in the presence of benzoquinone to test the hypothesis that more than one ligand is necessary, as is true in the case of the White acetoxylation reaction discussed previously. However, no increase in conversion to fluoride was seen when compared to benzoquinone used alone. Since Pd(TFA)$_2$ is synthesized from trifluoroacetic acid, we were interested to see the affect of adding trifluoroacetic acid to the reaction. The presence of the acid in the system was shown to completely suppress any fluorination in THF. As such the addition of a base to the system was investigated, however no fluorination was observed (Appendix A-3).



Entry	Additive	Solvent	Temp (°C)	158c:294:162b
1	PPh$_3$ (2 eq.)	DCE	80 °C	-
2	BQ (**259**, 20 mol%)	DCE	80 °C	17:75:8
3	BQ (**259**, 2 eq.)	DMF	80	33:67:0
4	BQ (**259**, 1 eq.)	DMF	80	33:67:0
5	BQ (**259**, 2 eq.)/TFA (1 eq.)	THF	RT	-
6	Maleic Anhydride (**274**, 1 eq.)	DMF	80	-
7	Pyridine (1 eq.)	DMF	80	-
8	Methyl acrylate (1 eq.)	DMF	80	2:98:0
9	Methyl acrylate (3 eq.)	DMF	80	Trace (decoupled ^{19}F-NMR)
10	3-Nitropyridine (1 eq.) and Methyl acrylate (1 eq.)	DMF	80	Trace (decoupled ^{19}F-NMR)
11	Methyl vinyl ketone (1 eq.)	DMF	80	Trace (decoupled ^{19}F-NMR)
12	DMSO (1 eq.)	DMF	80	2:94:4
13	Phenyl vinyl sulfoxide (**261**)	DMF	80	0:98:2
14	Phenyl vinyl sulfoxide (**261**)	Dioxane	80	1:99:0 (9%)
15	DMSO/BQ	DMF	80	7:93:0
16	MA/BQ	DMF	80	50:50:0
17	PhVS/BQ	DMF	80	17:83:0

Table 3.8 Screening of additives in the C-H functionalisation

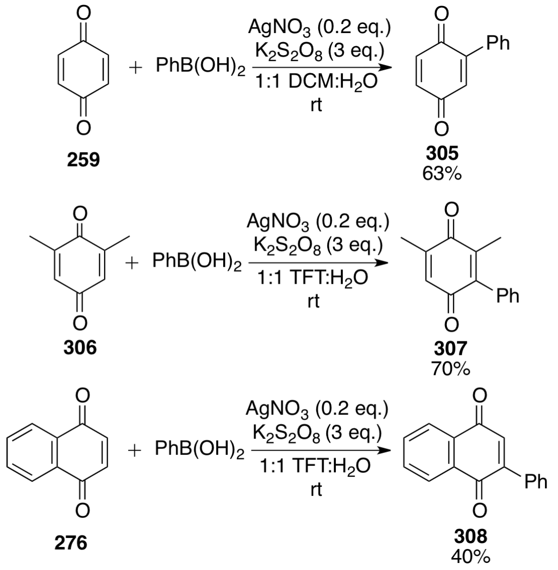
Though benzoquinone was identified as the only effective additive, we were nonetheless concerned that one reason the reaction did not proceed to completion was potentially due to the BQ (**259**) being consumed in competing side reactions with the TBAF(*t*BuOH)$_4$ (**160**). As entries 2–4 of Table 4 demonstrate, increasing the equivalents of BQ (**259**) did not improve yields, and one equivalent was shown to be the optimal loading. However a control reaction between BQ (**259**) and the fluoride source in THF at room temperature was carried out (Scheme 3.35).



Scheme 3.35 Reaction of TBAF complexes and benzoquinone

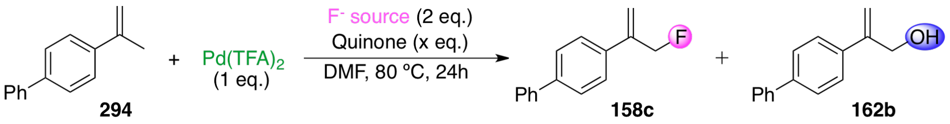
An instant colour change was seen, and the quinone was completely consumed within 10 minutes when monitored by thin layer chromatography, resulting in a complex reaction mixture of which only hydroquinone **304** could be identified.

Other more hindered quinones were then considered as they have been shown to be successful in other C-F functionalisations. Along with commercially available 2,6-dimethylquinone **306**, modified quinones were synthesized following the procedure recently reported by Baran *et al* for the C-H functionalisation of quinones with boronic acids.[194] The starting quinone, either benzoquinone **259**, 2,6-dimethylbenzoquinone (**306**, 1 eq) or naphthoquinone (**276**) was reacted with phenyl boronic acid (1.5 eq.) in the presence of silver nitrate (20 mol%), potassium persulfate (3 eq.) and H_2O (17 mol%) in DCM (0.2M) (Scheme 3.36). The desired products **305**, **307** and **308** were formed in moderate to good yields and were subsequently tested in the C-H functionalisations.



Scheme 3.34 Synthesis of modified quinones

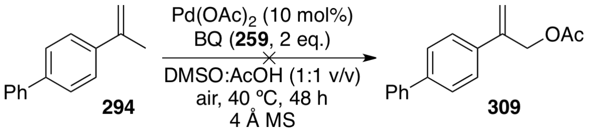
Pleasingly the use of 2-phenylbenzoquinone **305** gave allylic fluoride **158c** in 24% yield, however when the amount of equivalents were increased no improvement was found. Lower levels of fluorination were observed with 2,6-dimethylbenzoquinone **306** and 2,6-dimethyl-1,3-phenylbenzoquinone **307** (Table 3.10, Entries 3, 5). However the use of 2-phenylnaphthoquinone **308** was shown to give comparable levels of fluorination to benzoquinone **259** (Table 3.10, Entry 4). Control reactions between all quinones and TBAF(X)$_n$ in THF at room temperature were carried out. Again the quinone was consumed, resulting in a complex reaction mixture. Furthermore, increasing the equivalents of the 2-phenylbenzoquinone **305** did not lead to any improvement in conversion to fluoride.



Entry	Quinone	**158c**:**294**:**162b**
1	2-Phenylbenzoquinone (1 eq.)	7:93:0 (24%)
2	2-Phenylbenzoquinone (5 eq.)	7:93:0
3	2,6-Dimethylbenzoquinone (1 eq.)	3:97:0
4	2-Phenylnaphthoquinone (1 eq.)	25:75:0
5	2,6-Dimethyl-3-phenylbenzoquinone (2 eq.)	5:95:0

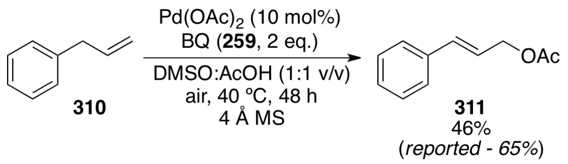
Table 3.10 Screening of modified quinones

As most C(sp^3)-H functionalisations are performed on substrates containing mono-substituted terminal alkenes, we investigated whether our model substrate **294**, which bears a 1,2-disubstituted alkene, was compatible with these methodologies. The conditions from the C-H acetoxylation reported by White were used on 4-(prop-1-en-2-yl)biphenyl **294** (Scheme 3.37).[173] No allylic acetate **309** was obtained from the reaction, with only the starting alkene **294** recovered.



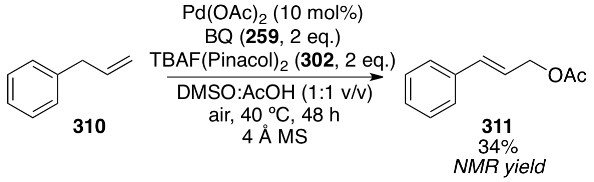
Scheme 3.37 Attempted White C-H acetoxylation on model substrate

To ensure that this was a competent catalytic system and that no experimental error had occurred, the literature reaction in Scheme 3.38 was run. Pleasingly, the desired cinnamyl acetate **311** was obtained in moderate yield, comparable to that reported.[5]



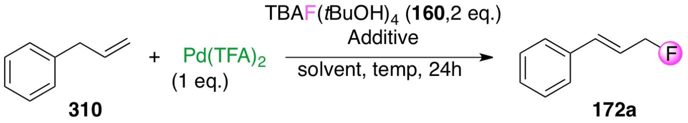
Scheme 3.36 Literature reported allylic acetoxylation

We were interested to see the effect of the addition of fluoride to this reaction. Therefore the reaction was repeated in the presence of 2 equivalents of TBAF(Pinacol)$_2$ **302**. After 48 hours a NMR yield (with 3-nitro-1-fluorobenzene as an internal reference) for **311** of 34% was obtained, this suggests that the presence of fluoride in the C-H functionalisation can have detrimental effects (Scheme 3.39). However as the reaction was still able to occur we continued to a investigate the possibility of a C-H functionalisation/fluorination.



Scheme 3.39 Literature C-H acetoxylation in the presence of fluoride

Having verified White's catalyst system to be viable, it confirmed that 4-(prop-1-en-2-yl)biphenyl **294** was not a suitable substrate for acetoxylation. We were thus concerned that this disubstituted motif may not be an optimal substrate for fluorination. Hence, we tested allylbenzene **310** under the reaction conditions to see if the level of fluorination could be improved (Table 3.11).

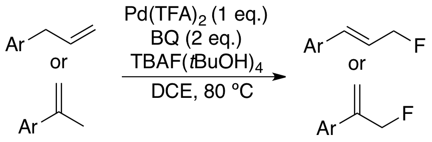


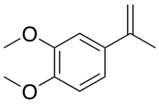
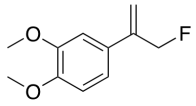
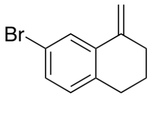
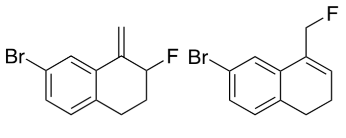
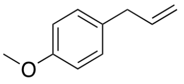
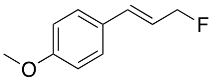
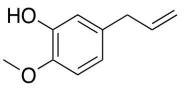
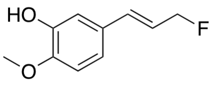
Entry	Additive	F^- Source	Solvent	Temp (°C)	Conversion to **172a**
1	Pyridine (1 eq.)	TBAF(*t*BuOH)$_4$	DMF	80	-
2	Methyl acrylate (1 eq.)	TBAF(*t*BuOH)$_4$	DMF	80	Trace (decoupled ^{19}F-NMR)
3	Methyl acrylate (3 eq.)	TBAF(*t*BuOH)$_4$	DMF	80	Trace (decoupled ^{19}F-NMR)
4	Methyl vinyl ketone (1 eq.)	TBAF(*t*BuOH)$_4$	DMF	80	Trace (decoupled ^{19}F-NMR)
5	DMSO(1 eq.)	TBAF(*t*BuOH)$_4$	DMF	80	-
6	3-Nitropyridine (1 eq.) and Methyl acrylate (1 eq.)	TBAF(*t*BuOH)$_4$	DMF	80	Trace (decoupled ^{19}F-NMR)
7	Benzoquinone (2 eq.)	TBAF(*t*BuOH)$_4$	DCE	80	Trace (decoupled ^{19}F-NMR)
8	Phenyl vinyl sulfoxide	TBAF(*t*BuOH)$_4$	Dioxane	80	-
9	4,5-Diazafluoren-9-one	TBAF(*t*BuOH)$_4$	Dioxane	80	-
10	-	HF•Pyridine	DCM	40	-
11	PhVS/BQ	TBAF(Pinacol)$_2$	DMF	80	12%[a]
12	MA/BQ	TBAF(Pinacol)$_2$	DMF	80	10%[a]
13	DMSO/BQ	TBAF(Pinacol)$_2$	DMF	80	20%[a]

[a] NMR yield of allylic fluoride **172a**

Table 3.11 Additive screening with allylbenzene

The results are consistent with those from the previous screens in that only TBAF derivatives appear to be effective sources of fluoride (entry 10, no fluorination). However overall, the conversions to fluoride are much lower, with only trace amounts of the cinnamyl fluoride present in the decoupled ^{19}F-NMR spectra. Variations of solvents and additives had little effect on the outcome of the reaction. These result show substrates known to be compatible with allylic C-H functionalization appear to be unreactive in allylic C-H fluorination. The scope of the reaction was further investigated as shown in Table 3.12, to see how general the initial successful reaction was. In the case of the allyl benzene derivatives the substrates were commercially available. The *gem*-disubstituted alkenes were accessed from the Wittig reaction of the commercially available ketones with methyltriphenylphosphonium bromide in the presence of *n*BuLi to give **312** and **313**.



Entry	Substrate	Product	Ratio of F:SM[a]
1	 **312**		41% conversion[b] 37:63[c]
2	 **313**		Trace (decoupled ^{19}F-NMR) *B:L* - 1.8:1
3			-[c]
4			-[c]

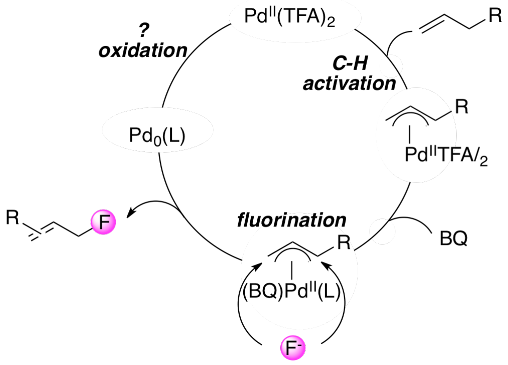
[a] Ratio of fluorinated product to starting alkene determined from crude ^{1}H NMR; [b] Conversion based on recovered starting material. [c] Compound decomposed when isolation was attempted; [c] No fluorinated product observed.

Table 3.12 Substrate scope

Although Table 3.12 shows that the reaction is not yet applicable to other substrates, two interesting observations can be made. Firstly, allylbenzene derivatives are consistently less reactive under these reaction conditions compared to the disubstituted alkenes. The reaction of 1,2-dimethoxy-4-(prop-1-en-2-yl)benzene gives the corresponding allylic fluoride in moderate conversion; however, the instability of this fluoride led to decomposition upon attempts to purify. Thus, an isolated yield could not be obtained. In the case of 7-bromo-1-methylene-1,2,3,4-tetrahydronaphthalene, an interesting product distribution was seen, with the branched fluoride favoured over the linear. This result is particular interesting as the expected product with a Tsuji–Trost system would be the linear fluoride. Further development of the reaction could potentially provide access to branched allylic fluorides with the correct choice of ligand and substitution on the allyl precursors. Additional insights into the mechanism of this reaction and the observed regioselectivity are currently under investigation in the Gouverneur group.

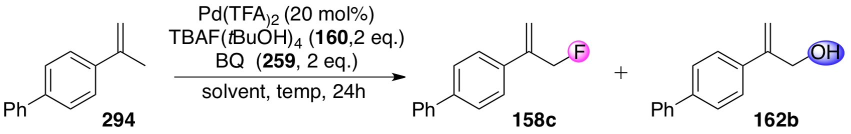
3.4 Preliminary Results – Catalytic Variant

Along with investigations of the stoichiometric reaction, some initial experiments have been carried out to test if fluorination is possible in a catalytic variant. The matter of how to turn over the catalyst by reoxidising the Pd^0 back to Pd^{II} was now considered.



Scheme 3.38 Proposed catalytic cycle for C-H functionalisation/fluorination

The loading of $Pd(TFA)_2$ was reduced to 20 mol% based on 4-(prop-1-en-2-yl)biphenyl **294**, and a comprehensive screen of all commercially available, commonly used oxidants was performed, varying solvent and temperature. Transitioning from the stoichiometric version, we anticipated a loss in yield. However, to our surprise, fluorination was completely suppressed in most cases, and at best only trace fluorination was observed in reactions with 50 mol% or less loading of palladium. The only oxidants that allowed for trace fluorination were CuCl in the presence of O_2 (entry 19) and oxone (entry 21), however, not to isolable amounts.



Entry	Additive	Oxidant (2 eq.)	Solvent	Temp (°C)	**158c**:**294**:**162b**
1	DDQ (2 eq.)	-	DCM	40	-
2	DDQ (2 eq.)	-	DCE	80	-
3	BQ (2 eq.)	-	DCM	40	-
4	BQ (2 eq.)	O_2	DCM	40	-
5	BQ (2 eq.)	PIFA	DCM	40	-
6	BQ (2 eq.)	PIFA	DCE	60[a]	0:8:1
7	BQ (1 eq.)	PIFA	DMF	80	-
8	BQ (1 eq.)	PIDA	DMF	80	-
9	BQ (2 eq.)	AgOAc	DCE	80	-
10	BQ (1 eq.)	Ag_2O	DMF	80	-
11	BQ (1 eq.)	Ag_2CO_3	DMF	80	-
12	BQ (2 eq.)	Ag_2CO_3	*t*BuOH	80	-
13	BQ (2 eq.)	$Cu(OAc)_2$	DCE	80	Decomposed
14	BQ (1 eq.)	$Cu(OAC)_2$	DMF	80	-
15	BQ (1 eq.)	$Cu(OTFA)_2$	DMF	80	-
16	BQ (2 eq.)	$Cu(OTFA)_2$	MeCN	60	-
17	BQ (2 eq.)	$Cu(OTFA)_2$	MeCN	80	-
18	BQ (2 eq.)	$Cu(OTFA)_2$	DCM	40	-
19	BQ (2 eq.)	CuCl[b], O_2	DCE	80	Trace[c]
20	BQ (2 eq.)	$Cu(CF_3SO_3)_2$	DCE	80	-
21	BQ (2 eq.)	Oxone	DCE	80	Trace[c]
22	BQ (1 eq.)	Oxone	DMF	80	-
23	BQ (1 eq.)	tBuO_2H	DMF	80	-
24	BQ (1 eq.)	tBuO_2H	DCM	40	-
25	BQ (1 eq.)	tBuO_2H	MeCN	80	-

[a] Decomposition of 294 at 80 ºC. [b] 40 mol% CuCl with O_2 balloon. [c] Only observed in decoupled ^{19}F-NMR.

Table 3.13 Initial screening of oxidants in catalytic variant

At this point, the loading of Pd(TFA)$_2$ was increased to 30 mol% based on 4-(prop-1-en-2-yl)biphenyl, and screening of commercially available, commonly used oxidants was performed, with varying additives and fluoride source (Appendix **A-4**). Both sources of TBAF were screened to see if any difference in reactivity was seen with catalytic palladium. However, all screens gave negative results; no fluorination was seen with or without benzoquinone in the presence of TBAF(*t*BuOH)$_4$. No reactivity was seen using TBAF(Pinacol)$_2$ with any of the additives. Maleic anhyride and 3-nitropyridine were screened, as previous work has shown these to be viable alternatives to benzoquinone in C-H functionalisation. Dibenzylideneacetone was also used in place of benzoquinone and showed no reactivity.

Unfortunately a catalytic variant of this reaction was not possible under the reaction conditions examined. Further work is needed on the fluorination of possible isolated intermediates of this reaction to gain deeper insights into the exact requirements for a fluorination to occur.

3.5 Conclusions

Though there have been vast developments in the field of metal-catalysed allylic fluorination over the last decade, successful translation of this approach towards C-H fluorination has yet to be realized. This chapter discloses preliminary results in our attempts to reach this goal.

In summary, success was seen in the stoichiometric reaction of alkene **294** with 1 equivalent of Pd(TFA)$_2$ in the presence of benzoquinone **259** as an additive. Under these conditions allylic fluoride **158c** was afforded in 60% isolated yield. While further studies are required to investigate the substrate scope of this reaction and move towards a catalytic variant, valuable insights have nonetheless been made through this effort. Interestingly the use of substrate **294** under established C-H acetoxylation conditions did not give the desired allylic acetate as a product. This would suggest that the disclosed C-H fluorination proceeds *via* a different mechanism to previously reported C-H functionalisations of terminal alkenes.

Investigations of the commonly used terminal alkenes, such as allylbenzene, only gave the desired cinnamyl fluoride in trace amounts. This demonstrates the different reactivity seen with the use of fluoride as a nucleophile when compared to other heteratoms such as oxygen and nitrogen. Established C-H acetoxylation and amination conditions applicable to O- and N- nucleophiles were unsuccessful when the nucleophile was changed to fluoride.

The screening of fluoride sources in the reaction also highlights the importance of the choice of fluoride, with TBAF(*t*BuOH)$_4$ and TBAF(Pinacol)$_4$ found as the optimal fluorinating reagents. The choice of fluoride source appears to be critical for each transition metal catalyzed fluorination discussed in this thesis, highlighting the need for a wider range of fluoride reagents. Furthermore a better understanding of the precise properties (nucleophilicity/basicity) of these fluoride reagents and mechanistic insights into a transition metal fluorination will accelerate the development of synthetically useful catalytic nucleophilic fluorinations.

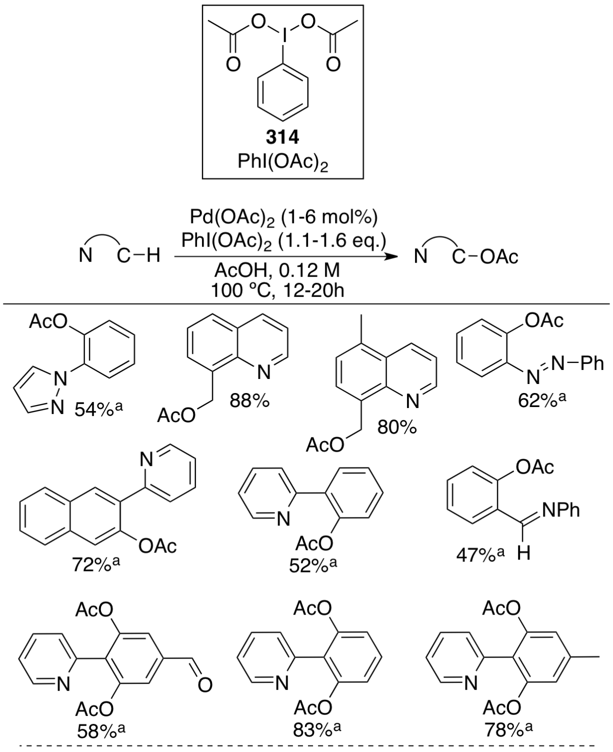
Chapter 4

Fluorination via Pd^{II}/Pd^{IV}

4.1 Introduction

Along with research into the use of Pd^{II} to affect an allylic fluorination event, work into the use of high oxidation state Pd^{IV} intermediates is also being increasingly investigated. As discussed in Chapter 1 of this thesis, reductive elimination of C-F from a Pd^{II} complex to form an aryl C-F bond is known to be a challenging process. The realization that the use of a Pd^{IV} intermediate would provide a more facile route to these valuable products has resulted in a vast amount of research in this area.

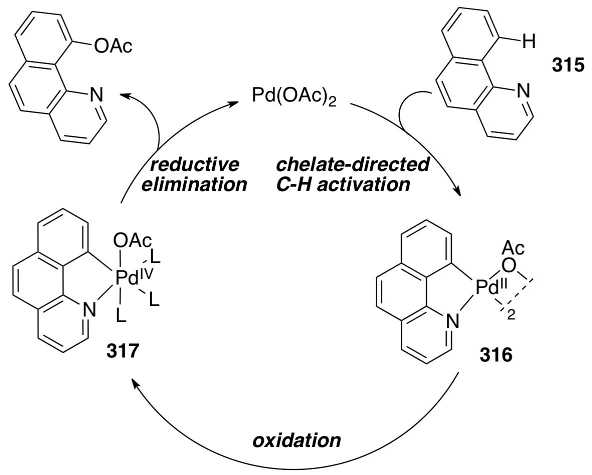
The Sanford group has reported a plethora of research into the use of high oxidation Pd at both sp^2 and sp^3 carbon centres. In 2004 the oxidative functionalisation of C-H bonds was described.[195] Using substrates containing a nitrogen directing group the regioselective acetoxylation was possible using $Pd(OAc)_2$ and phenyl iododiacetate ($PhI(OAc)_2$) **314** as the oxidant. Initial work looked at the reactivity of benzo[*h*]quinoline (**315**), the presence of the nitrogen in the substrate is used as a directing group to allow cyclopalladation, ensuring the reaction is regioselective for only one C-H bond. The reaction of this substrate with $Pd(OAc)_2$ and $PhI(OAc)_2$, **314** allowed access to a variety of alkyl-aryl ethers depending on the alcohol solvent used. The substrate scope was extended to those bearing other chelate-directing groups such as azobenzene, pyrazole, imine and pyridine. The selective acetoxylation products were accessible at both sp^2 and sp^3 carbon centres in moderate to excellent yields (Scheme 4.1).



[a] $Pd(OAc)_2$ 6-8 mol%, $PhI(OAc)_2$ **314** 2.3-2.5 eq.

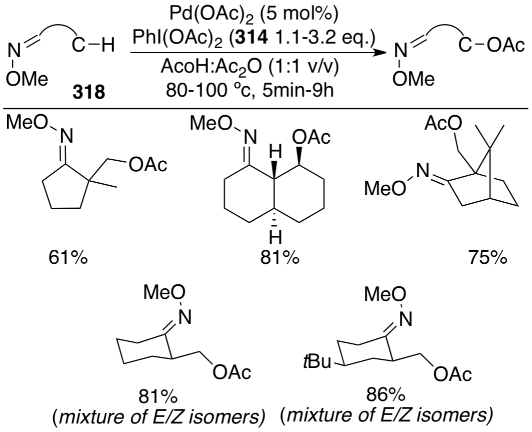
Scheme 4.1 Selective catalytic oxidative functionalisation of C-H bonds

Increasing the equivalents of $PhI(OAc)_2$ **314** to 2.3-2.5 equivalents led to the formation of the diacetoxylated products. The authors suggest a mechanism involving a Pd^{IV} intermediate **317** as shown in Scheme 4.2. Initial C-H bond cleavage is directed by the chelating group and allows for formation of a five-membered palladocycle intermediate, **316**. This complex is then oxidised with $PhI(OAc)_2$ **314** to form a Pd^{IV} species **317** that can undergo reductive elimination to give the desired product or external attack of the nucleophile. Screening of common oxidants used for Pd^0/Pd^{II} transformations, such as $Cu(OAc)_2$ and BQ **259**, did not give any formation of the desired products. Interestingly the use of *N*-chlorosuccinimide/*N*-bromosuccinimide in place of $PhI(OAc)_2$ (**314**) as the oxidant also gave trace amounts of the corresponding halogenated product.



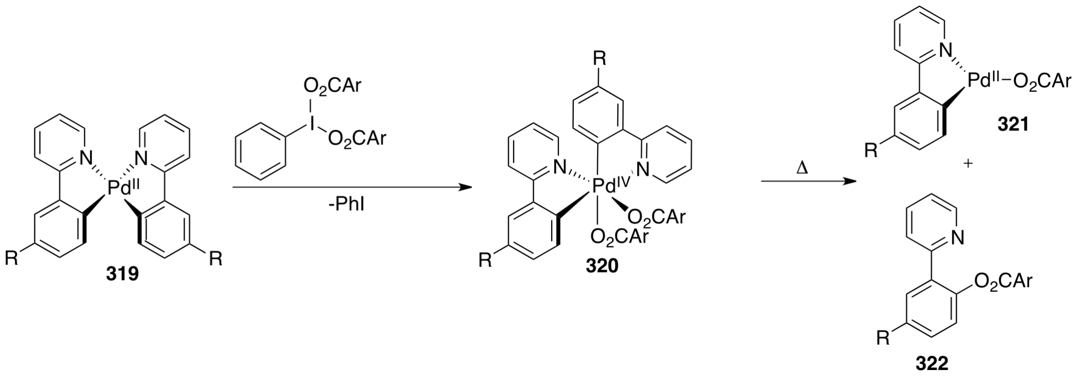
Scheme 4.2 Suggested mechanism of C-H oxidation via a Pd^{IV} intermediate

This system has also been used for the oxidation of unactivated sp^3 C-H bonds using *O*-methyl oximes **318** as the directing group, again the reaction was found to be highly regioselective (Scheme 4.3).[196] Later work identified the use of oxone in place of the $PhI(OAc)_2$ **314** as an effective oxidant for this system.[197]



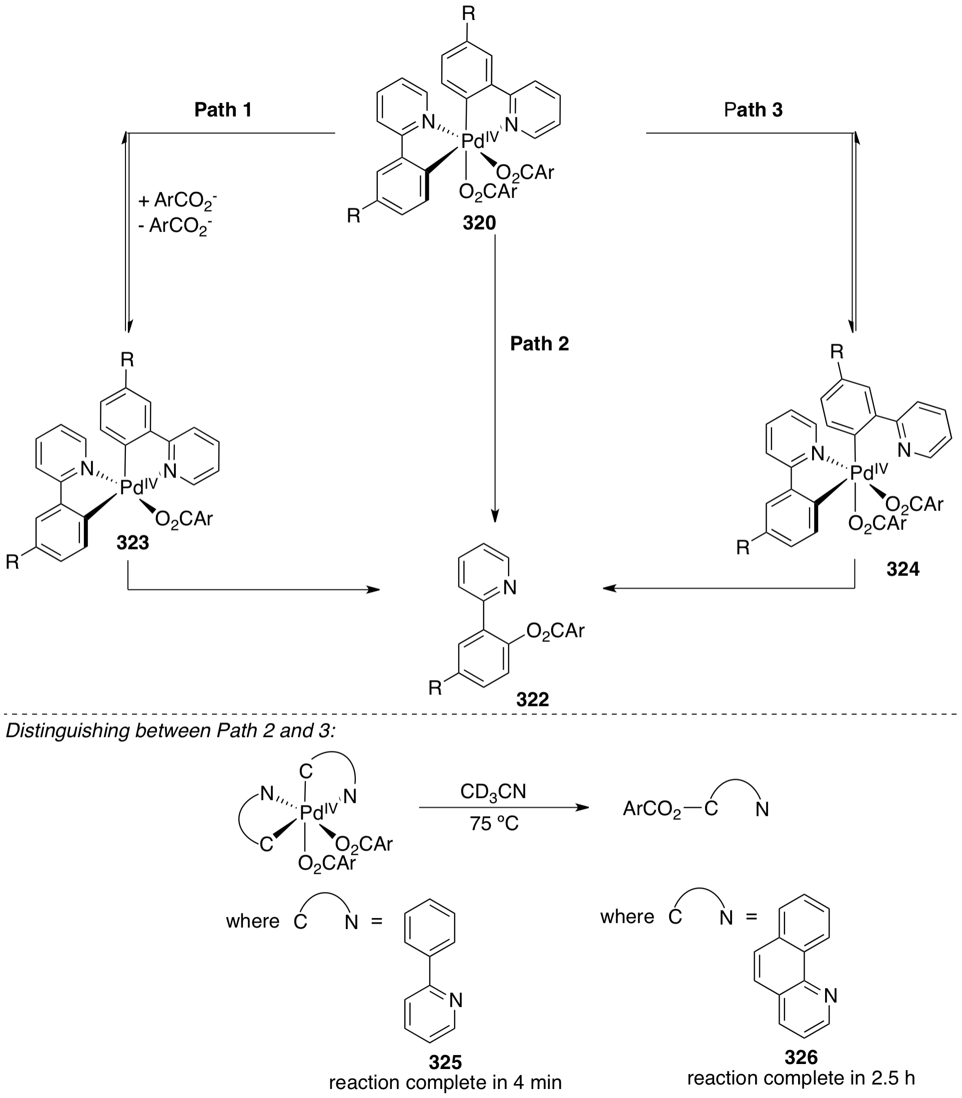
Scheme 4.3 *O*-Methyl oxime directed Pd-catalysed C-H acetoxylation

Mechanistic investigations by the Sanford group into the acetoxylation reaction led to the formation and isolation of a Pd^{IV} complex **320** using aryl pyridine ligands that was identified by ^{1}H-NMR.[198] Where *R* is a nitro group the structure could be unambiguously characterised by X-ray crystallography and upon thermoylsis gave the oxidation products **322**, as well as Pd^{II} species **321** (Scheme 4.4).



Scheme 4.4 Isolation of a Pd^{IV} complex

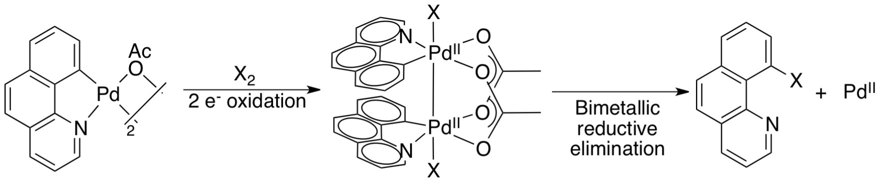
The authors proposed three possible mechanisms of reductive elimination of the product; 1) a pre- equilibrium dissociation of the benzoate ligand to form intermediate **323** with subsequent external or intramolecular nucleophilic attack, 2) reductive elimination from the Pd^{IV} complex **320**, or 3) the dissociation of the pyridine of one of the phenylpyridine ligand to give **324** followed by reductive elimination (Scheme 4.5). While the Pathway **2** and **3** are kinetically indistinguishable, the rigidity of the complex was expected to decrease the rate of nitrogen dissociation and lead to an overall decrease in the rate of reductive elimination. Therefore the reaction of compounds **325** and **326**, bearing a fused ring to provide more rigidity to the complex was carried out. A 40-fold difference in rate was observed between the two complexes, with **326** having severely reduced reactivity. This led the authors to suggest that Pathway **3** is the preferred mechanism of this reaction.



Scheme 4.5 Possible mechanisms for reductive elimination

Sanford has also reported the formation of sp^2 and sp^3 C-F bonds with the use of electrophilic fluorination reagents as the oxidants (Chapter 1).[24,28] Furthermore the use of NCS or PhICl$_2$ as the oxidant has provided access to chlorinated products.[199] Again the proposed Pd^{IV} intermediates were isolated and upon heating gave the desired product indicating Pd^{IV} is a possible reactive intermediate.

Ritter *et al* reported an interesting observation into the mechanism of these reactions in 2009.[200] The oxidation of benzo[*h*]quinoline bimetallic palladium acetate dimer **327** by two electrons from various oxidants delivered bimetallic Pd^{III} complexes, **328** featuring a Pd-Pd bond. When 1 equivalent of $PhICl_2$ was used as the oxidant and the resulting complex warmed to 23 ºC 10-chlorobenzo[*h*]quinoline **329a** was obtained in 94% yield (Scheme 4.6).

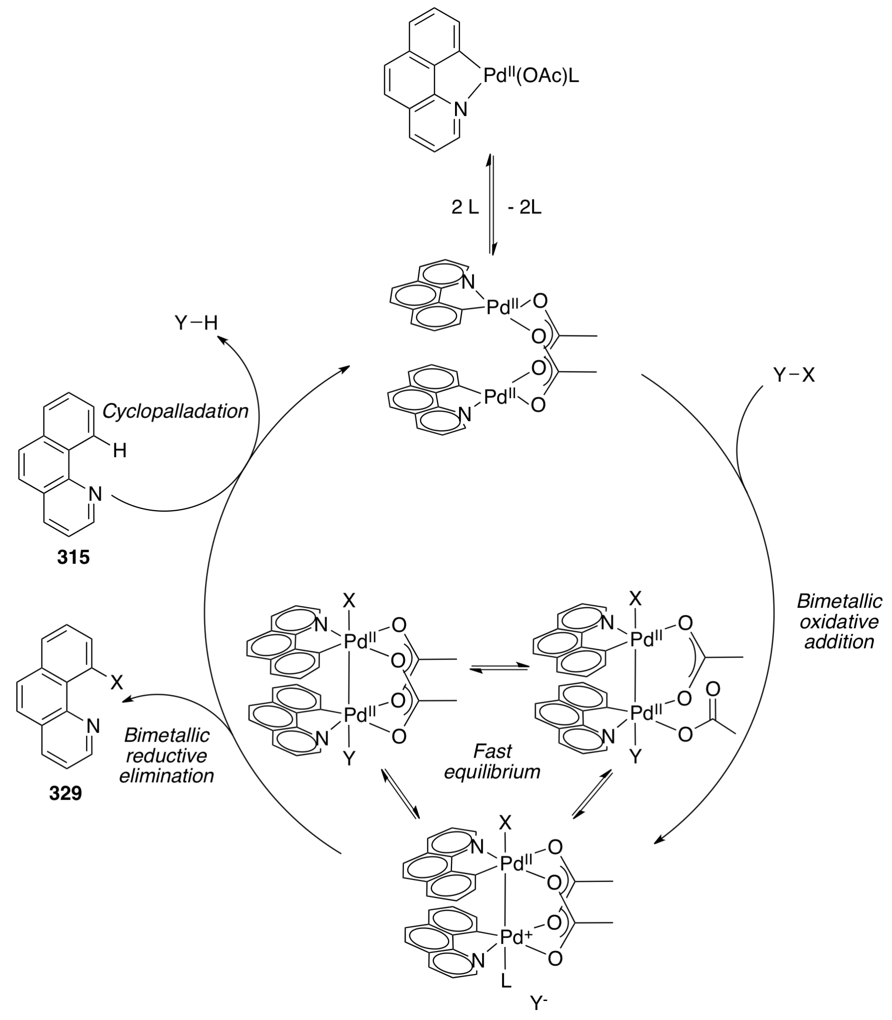


327 **328** **329**

X_2 = $PhICl_2$, X = Cl 94% (**329a**)

Scheme 4.6 Synthesis and reductive elimination of a bimetallic Pd^{III} species **328**

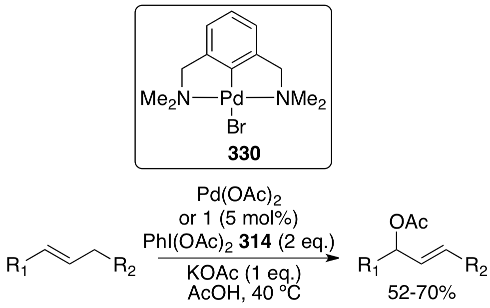
Several possible pathways to deliver the C-X reductive elimination products **329** were considered, with a concerted 1,1-reductive elimination from a Pd^{III} species proposed as a feasible mechanism. As substrates are present in excess in the catalytic reactions further investigations were carried out in the presence of excess benzo[*h*]quinoline (**315**). These revealed that acetate/chloride ligand dissociation from the Pd^{III} occurs at a much faster rate than the reductive elimination in support of a concerted 1,1-reductive elimination from a bimetallic Pd^{III} intermediate and the suggestion that the previously discussed Pd^{II}/Pd^{IV} systems may in fact proceed by bimetallic Pd^{III} species (Scheme 4.7).



Scheme 4.7 Bimetallic Pd^{III}-Pd^{III}C-H functionalisation mechanism

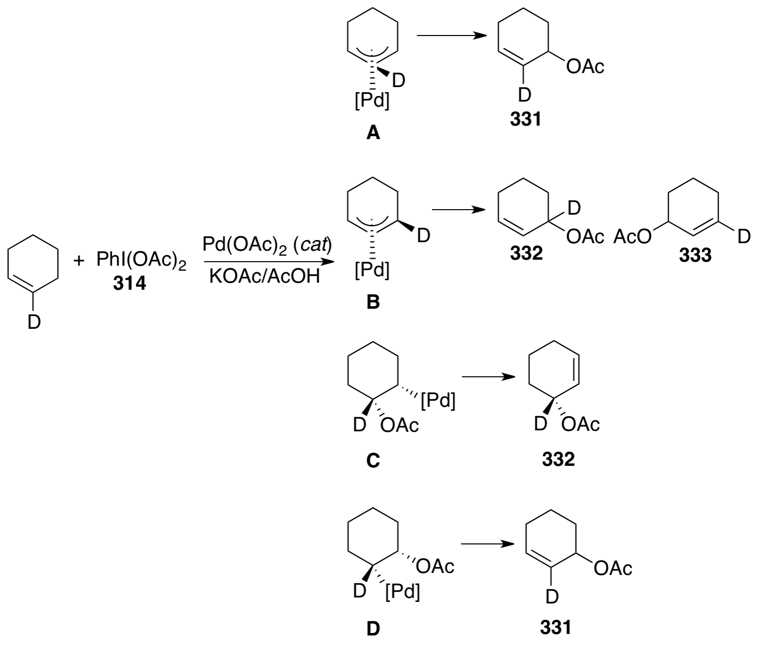
Further investigation into this mechanism has looked at the formation of C-CF_3 bonds via Pd^{II} complexes and electrophilic trifluoromethylating reagents.[201] This work suggested the initial oxidation of a Pd^{II} species to a Pd^{III} and not a Pd^{IV} as the formation of a Pd-Pd could lower the activation barrier for oxidation. However the ligands present on these bimetallic species determine whether the reductive elimination of C-X occurs from either a bimetallic Pd^{III} centre or if the Pd-Pd bond cleavage, to give a Pd^{IV} and Pd^{II}, becomes competitive with subsequent reductive elimination from Pd^{IV}.

In addition to the suggestion of a Pd^{IV} or Pd^{III} intermediate in the previously discussed systems, the presence of a (η^3-allyl)Pd^{IV} species has been proposed in Pd catalysed allylic substitution reactions. In 2009 Szabó reported the catalytic allylic C-H acetoxylation and benzoyloxylation via proposed (η^3-allyl)Pd^{IV} intermediates generated by hypervalent iodine salts. The use of these oxidizing reagents was shown to relieve the need for further additives such as benzoquinone, (BQ) (Scheme 4.8).[202]



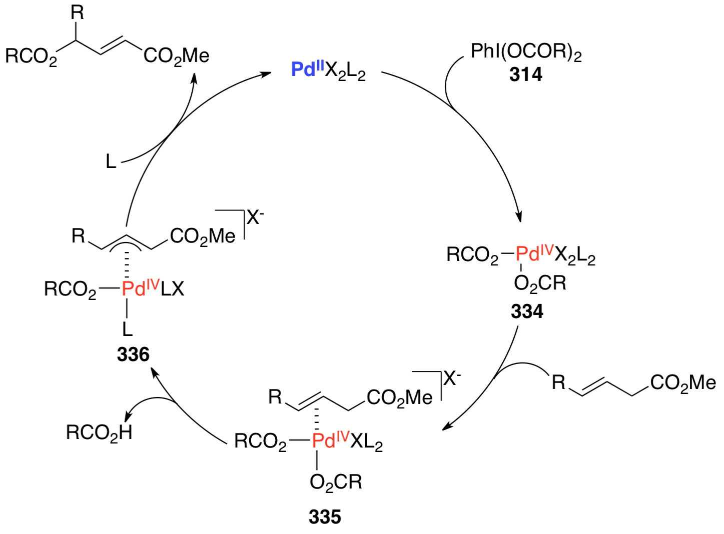
Scheme 4.8 Catalytic allylic C-H acetoxylation

To investigate the mechanism of this reaction deuterium labelling studies were carried out. Monodeuterated cyclohexene was treated with $Pd(OAc)_2$ and $PhI(OAc)_2$ to observe the products formed (Scheme 4.9). If the reaction proceeds via a (η^3-allyl)palladium complex then either species **A** or **B** are possible and would lead to the products shown. However the acetoxy-palladation of the $Pd(OAc)_2$ is also plausible and would give distinct products. Products **331**, **332** and **333** were obtained in a ratio of 1:2:1, revealing the presence of an allylpalladium intermediate in the reaction.



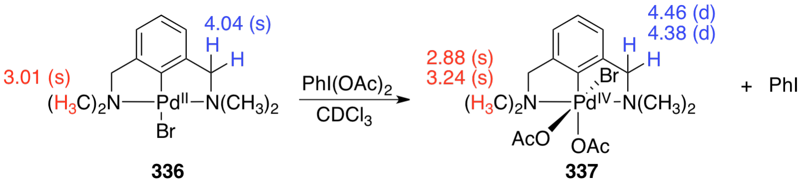
Scheme 4.9 Deuterium labelling showing formation of a (η^3-allyl)palladium intermediate

This observation, along with previous work by Sanford[198][203] showing the use of benzoyloxy iodonium salts to oxidize Pd^{II} to Pd^{IV}, and von Koten who showed that NCN pincer complex **336** reacts with PhCl$_2$ to form a Pd^{IV} species, led the authors to propose the mechanism shown in Scheme 4.10.[204]



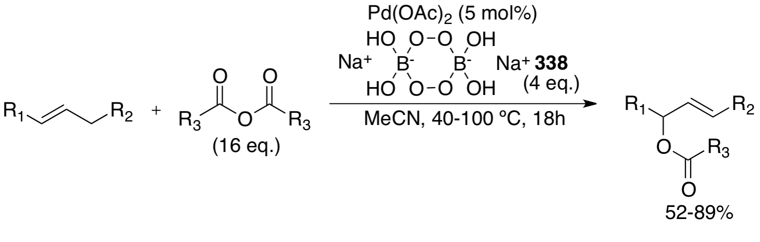
Scheme 4.10 Proposed Pd^{II}/Pd^{IV} mechanism of allylic C-H acetoxylation

The initial oxidation of the Pd^{II} catalyst by the iodonium salt gives Pd^{IV} complex **334** that coordinates the alkene substrate to give **335**. The deprotonation of this complex, driven by the stabilization of the Pd^{IV} by a π-donor allyl ligand, gives the Pd^{IV} allyl intermediate **336**, which upon reductive elimination provides the desired product and regenerates the Pd^{II} catalyst. The formation of the (π-allyl)Pd^{II} complex with the alkene first with subsequent oxidation to a Pd^{IV} intermediate cannot be ruled out. The oxidation of the pincer complex **330** by $PhI(OAc)_2$ **314** was monitored by ^{1}H-NMR spectroscopy, the presence of signals corresponding to the Pd^{IV} complex **337** were identified to further support this mechanism (Scheme 4.11).



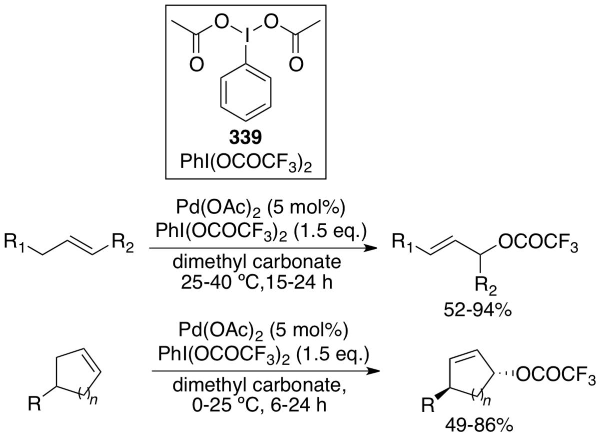
Scheme 4.11 Observation of a Pd^{IV} complex in ^{1}H-NMR spectra

The allylic C-H acetoxylation has also been reported using sodium perborate **338** as the oxidant with anhydrides used as the acyloxy sources (Scheme 4.12).[205] The reaction was shown to have a large substrate scope allowing terminal and internal alkenes to undergo oxidation.



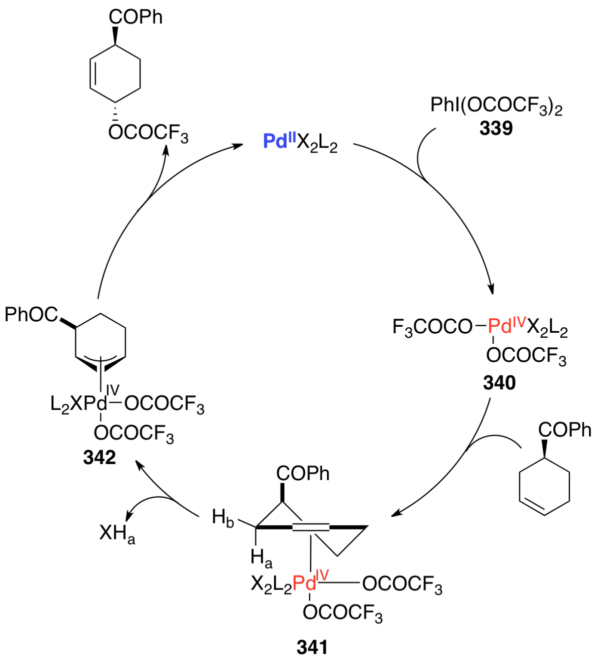
Scheme 4.12 Sodium perborate **338** as oxidant in C-H acetoxylation

In 2012 the regio- and diastereoselective allylic C-H trifluoroacetoxylation of functionalized acyclic and cyclic alkenes was disclosed using $PhI(OCOCF_3)_2$ **339** as the oxidant and the acyloxy source (Scheme 4.13).[206] The isolation of a cyclic allylpalladium(II)trifluoroacetate dimer and exposure to $PhI(TFA)_2$ gave trace amounts of the desired product leading the authors to suggest the reaction proceeds through a π-allylpalladium(IV) intermediate.



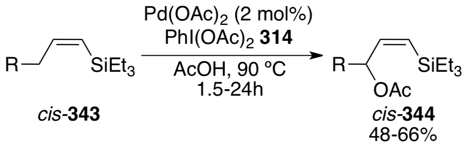
Scheme 4.13 Synthesis of allylic trifluoroacetates *via* a proposed Pd^{II}/Pd^{IV} mechanism

This intermediate **341** was proposed to form by a *trans* selective C-H activation of the alkene with the *in situ* genereated Pd^{IV} species **340** formed by oxidation of the Pd^{II} catalyst with $PhI(OCOCF_3)_2$ **339**. The subsequent formation of (π-allyl)Pd complex **342** is proposed to be due to the π-donation of the allyl into the Pd centre, the electron-deficiency of this complex allows for rapid reductive elimination with the trifluoroacetate ligand. This step occurs with a *trans* stereoselectivity and a 1,4 as opposed to a 1,2 regioselectivity, attributed to the hyperconjugation between the σ-bond of the β-substitutent and the π-allyl moiety (Scheme 4.14). This effect has been extensively studied by Sazbo and co-workers demonstrating the nature of the β-substitutent to influence not only the regioselectivity of the reaction but also the structure, and kinetic and thermodynamic stability of the (π-allyl)Pd intermediates.[207] However this mechanism was not confirmed and the possibility of a *cis* C-H activation followed by external attack of a trifluoroacetate ligand could not be ruled out. Furthermore the involvement of a bimetallic Pd^{III} intermediate is also possible.



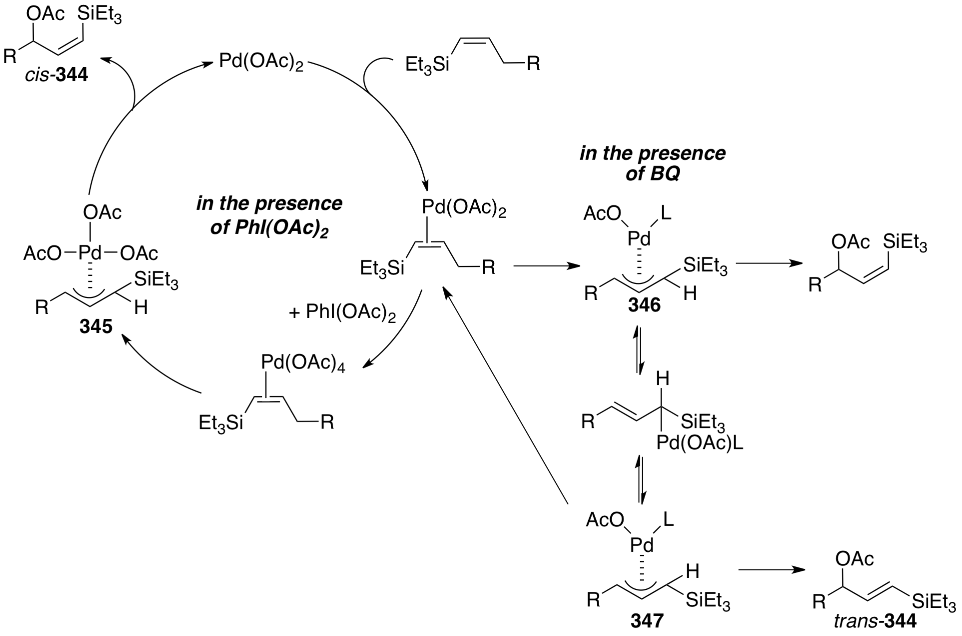
Scheme 4.14 Proposed mechanism of C-H trifluoroacetoxylation

Stambuli reported the use of $PhI(OAc)_2$ **314** in the stereoselective Pd-catalysed allylic oxidation of *cis*-vinylsilanes *cis*-**343**, a Pd^{II}/Pd^{IV} mechanism was proposed.[208] When $PhI(OAc)_2$ **314** was used as the oxidant the branched allylic acetate *cis*-vinylsilanes **344** were obtained (Scheme 4.15), however when $PhI(OAc)_2$ **314** is replaced with BQ **259** the major products became the *trans*-vinylsilanes *trans*-**344** (Scheme 4.16).



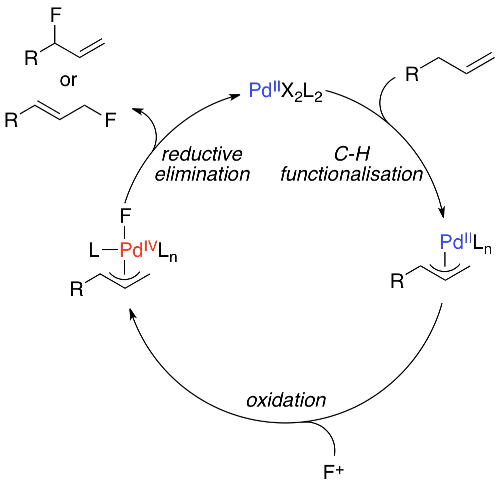
Scheme 4.15 Stereoselective Pd-catalysed allylic oxidation of cis-vinylsilanes

The *cis* stereoselectivity is proposed to occur from the facile reductive elimination possible from the Pd^{IV} intermediate **345** formed when $PhI(OAc)_2$ is used as the oxidant (Scheme 4.16). If the oxidant is not present and BQ **259** is used then the allylpalladium intermediate **346** is proposed to undergo *π*-*σ*-*π* isomerisation to give the allylPd^{II} **347** that can reductive eliminate to give the *trans*-vinylsilanes. The reaction was also extended to the first intramolecular allylic C–H etherification of *cis*-vinylsilanes.



Scheme 4.16 Proposed mechanism for C-H acetoxylation with BQ versus PIDA

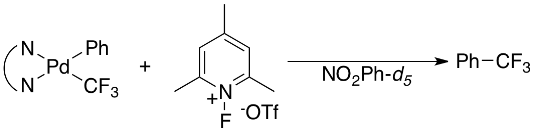
The use of high valent Pd^{IV} species has also provided a route to the formation of C-F bonds. The majority of work has focused on the reductive elimination of C_{sp2}-F from isolated $\{Pd^{IV}F\}$ intermediates (Chapter 1). We envisaged an oxidative allylic C-H functionalisation-fluorination could also provide access to allylic fluorides. We wished to validate the two steps of the proposed catalytic cycle, the oxidation of a π-allyl palladium species and formation of a C-F bond (Scheme 4.17). Firstly we investigated the oxidation of an isolated π-allyl palladium species by an electrophilic fluorinating reagent acting as both oxidant and fluorine source to give the desired allylic fluoride. Later work attempted to investigate the mechanism of this reaction by observation of the reactions with NMR spectroscopy to reveal possible reactive intermediates. The results of these investigations are presented in the subsequent sections.



Scheme 4.17 Proposed oxidative Pd^{II}/Pd^{IV} fluorination

4.2 Preliminary Results

Recent work by Sanford in 2011 demonstrated the effect that the ligand on the Pd complex can have on the reductive elimination of a C-CF$_3$ bond. The reductive elimination of an aryl C-CF$_3$ from a (aryl)Pd^{IV} species is reported to proceed at 80 ºC using di-*tert*-butylbipyridine (dtbpy) **348** as the ligand, however on changing the ligand to *N,N,N’,N’*-tetramethylethylenediamine (TMEDA) **349** the reaction was possible at room temperature (**Table 4.1**).[209]



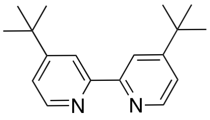
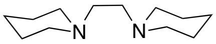
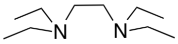
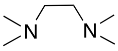
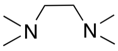
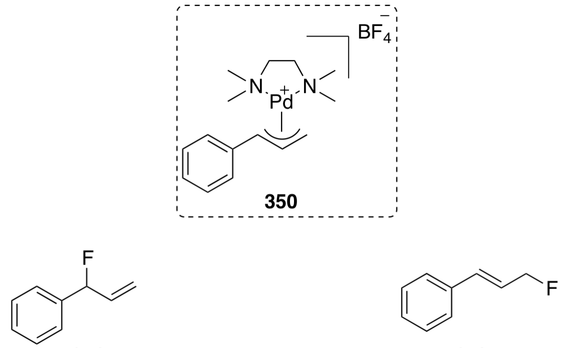
Entry	Ligand (N-N)	Temperature (° C)	Yield of Ph-CF$_3$ (%)
1	 **348**	80	66
2		80	99
3		80	40
4		80	90
5	 **349**	23	83

Table 4.1 Ligand effect in C–CF$_3$ reductive elimination

As there is precedent in the literature for the synthesis and isolation of π-allyl palladium species {[(η-1-Ph-C_3H_4)Pd(tmeda)]BF_4} **350** as a stable complex, with known crystal structure, this was chosen as the model substrate.[210] Furthermore the fluorinated products expected, cinnamyl fluoride **172a** and (1-fluoroprop-2-en-1-yl)benzene **351**, have been reported and have distinct ^{19}F-NMR spectra (cinnamyl fluoride δ_F -212 ppm, (1-fluoroprop-2-en-1-yl)benzene δ_F -168 ppm) enabling easy identification of the expected fluorinated products (Figure 4.1).[118]



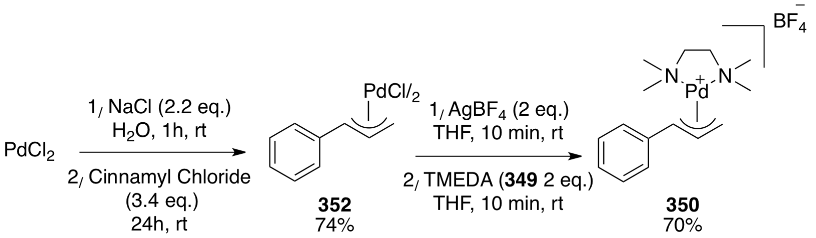
350

351
(1-fluoroprop-2-en-1-yl)benzene

172a
(*E*)-(3-fluoroprop-1-en-1-yl)benzene
(*cinnamyl fluoride*)

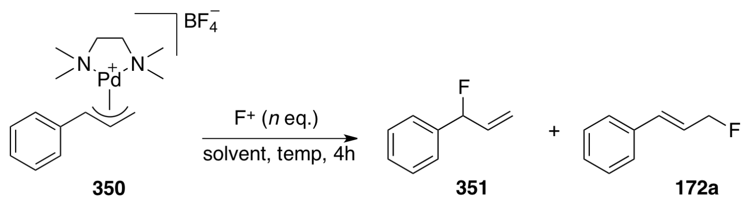
Figure 4.1 Branched and linear allylic fluoride products

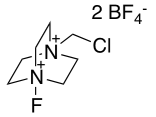
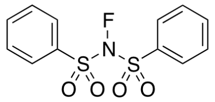
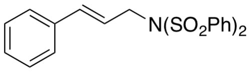
The synthesis of the {[(η-1-Ph-C_3H_4)Pd(tmeda)]BF_4} **350** was possible via a two step process from cinnamyl chloride and $PdCl_2$ following the procedures of Nolan[211] and Hegedus (Scheme 4.18).[212] $PdCl_2$ (1 eq.) was first added to a solution of NaCl (2.2 eq.) in water and allowed to react at room temperature for 30 minutes. After this time, cinnamyl chloride (3.4 eq.) was added and the solution allowed to stir at room temperature overnight. After extraction of the reaction with chloroform the product was crystallised from dichloromethane by the slow addition of pentane. This delivered the desired product **352** in 74% yield, which was in agreement with literature data. The dimer complex **352** (1 eq.) was then treated with $AgBF_4$ (2 eq.) in THF (0.01M) by stirring at room temperature for 10 minutes. A precipitate of AgCl was removed by filtration and TMEDA **349** (2 eq.) added to the filtrate and stirred for 30 minutes at room temperature. Product **350** was obtained in a 70% yield after crystallisation from dichloromethane by the slow addition of pentane. The structure of **350** was unambiguously determined by X-ray crystallography. The synthesis of analogous complexes bearing hexafluorophosphate or triflate counterions were carried out however decomposed on attempts to isolate.



Scheme 4.18 Synthesis of tmeda complex **350**

The reaction of complex **350** with common electrophilic fluorinating reagents was then screened in deuterated solvent due to the instability of the allylic fluoride products. Complex **350** (1 eq.) was treated with electrophilic fluorinating agent (2.5 eq.) in CD_3CN (0.1M) with stirring at 50 ºC for either 4h or overnight. Direct analysis of the reaction mixture by ^{1}H-NMR and ^{19}F-NMR was carried out and the results presented in **Table 4.2**.

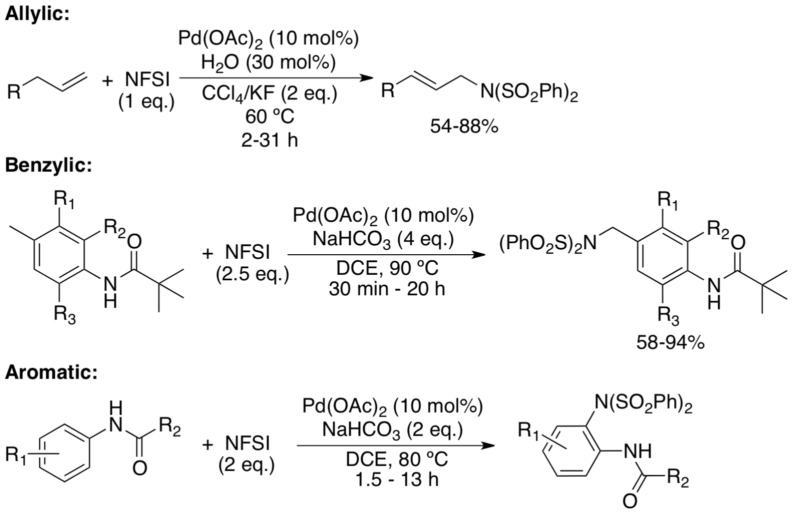


Entry	F^+ source	Time (h)	Conversion to Fluorides **351**:**172a**
1	 Selectfluor® (1.2 eq.)	16	Decomposed **350**
2	 NFSI (1.2 eq.)	16	100% conversion[a] 
3	XeF_2 (2.5 eq.)	4	100% conversion 3.4:1 (**351**:**172a**)
4	AgF/PhI(OPiv)$_2$ (5 eq.)/(2 eq.)	1	-[b]

[a] Conversion based on remaining starting material **350** in ^{1}H-NMR spectra. [b] No reaction observed, recovered **350**

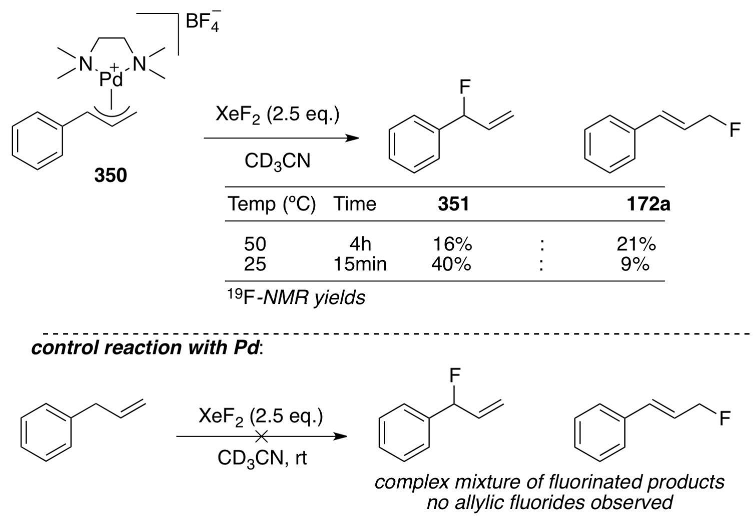
Table 4.2 Screening of oxidative electrophilic fluorinating reagent

The use of Selectfluor **46** and NFSI **67** did not afford either allylic fluoride as product. However, in the case of NFSI **67** complex **350** was completely consumed with the only observed product amine **353**. Indeed palladium catalysed allylic,[213] benzylic[214] and aromatic[215] animation reactions utilizing NFSI **67** have been reported in the literature (Scheme 4.19).



Scheme 4.19 Use of NFSI in Pd-catalysed C-H aminations

Conversely when reactions were carried out in the presence of XeF_2, complete conversion to fluorinated products in a 3.4:1 ratio of branched **351** to linear **172a** fluoride was observed, determined by ^{1}H-NMR/^{19}F-NMR on the crude reaction mixture (Scheme 4.20). Due to the instability of the products, ^{19}F-NMR was used to determine yields using 3-nitro-1-fluorobenzene as an internal reference.[216] We were pleased to see that the reaction of complex **350** with XeF_2 for 4 hours at 50 ºC gave both products **351** and **172a** in ~20% yield, in a 1:1 ratio. As the stability of the branched fluoride **351** is poor and the reaction conditions are relatively harsh we were concerned that the low yields could be a result of decomposition. As such the reactions were carried out at room temperature and reaction times decreased to 15 minutes to see if the yields were improved. Pleasingly it was possible to form the branched fluoride **351** in a 40% yield (^{19}F-NMR, 3-nitro-1-fluorobenzene as internal reference) with a moderate branched to linear selectivity of allylic fluorides. The control reaction of allylbenzene in the presence of XeF_2 (2 equivalents) under the same reaction conditions gave neither allylic fluoride as product, only unselective fluorination leading to a complex mixture of alkyl and aryl fluorides, confirming the process was indeed Pd-mediated.

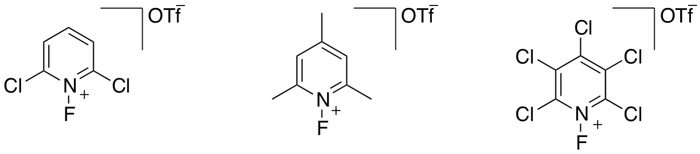


Temp (°C)	Time	**351**		**172a**
50	4h	16%	:	21%
25	15min	40%	:	9%

^{19}F-*NMR yields*

Scheme 4.20 Electrophilic fluorination of isolated Pd complex

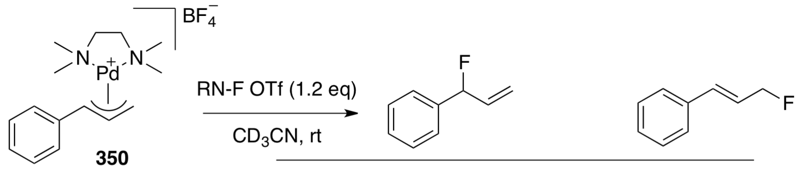
Sanford had demonstrated the use of *N*-fluoropyridinium salts (Figure 4.3) for both the fluorination and oxidation of C-H bonds *via* proposed Pd^{IV} intermediates, consequently these reagents were also investigated for the allylic system.[24] A variety of *N*-fluoropyridinium salts are available with various substitutions on the pyridine and counterions that allow for different levels of reactivity.[217] As the triflate salts have better solubility to the BF_4 analogues, the series of reagents in Figure 4.3 were screened.



353 **354** **355**

Figure 4.3 *N*-Fluoropyridinium salts as F^+ reagents

Reactions of the TMEDA complex **350** with the 2,6-dichloro-1-fluoropyridinium triflate **353** and 1-fluoro-2,4,6-trimethylpyridinium triflate **354** reagents showed no conversion to fluoride, however low levels of conversion were seen with the more reactive 1-fluoro-2,3,4,5,6-pentachloropyridinium triflate **355**. (Scheme 4.21). No fluorinated products could be detected when the reaction temperature was increased.



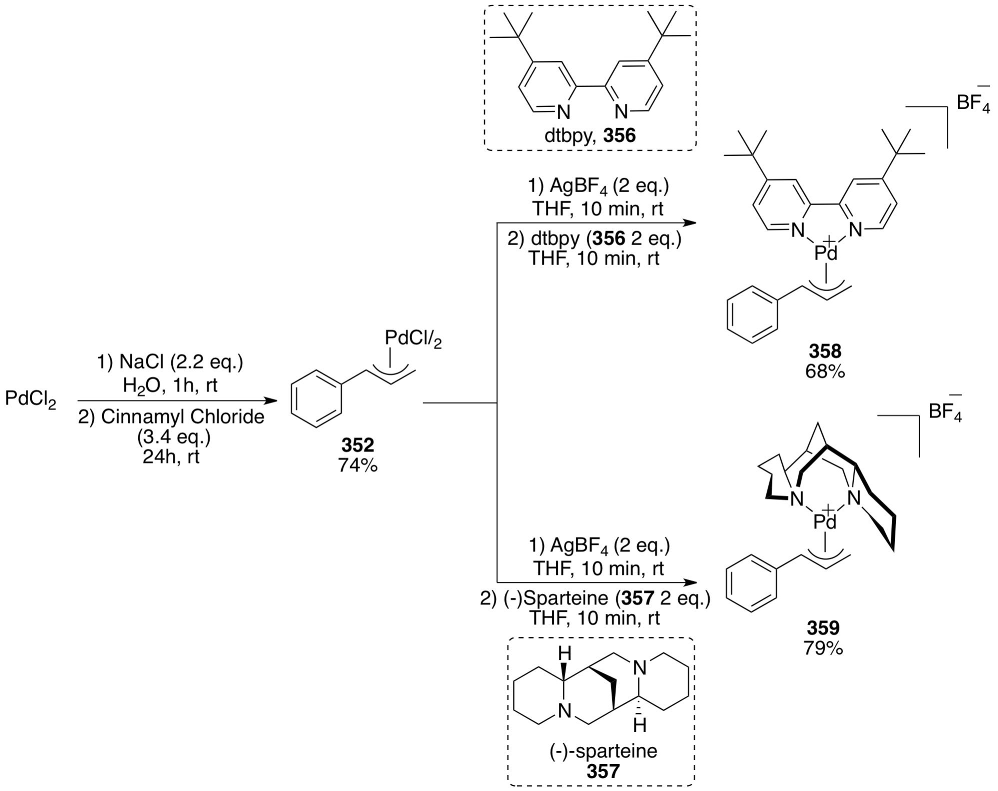
N-F reagent	351		172a
353	-	:	-
354	-		-
355	8%		3%
555/50 °C	-		-

^{19}F-*NMR yields*

Scheme 4.21 Reaction of TMEDA Pd allyl complex **350** with N-F reagents

4.3 Variation of ligand in fluorination

With this initial pleasing result on the cinnamyl system we wished to investigate the effect substitution of the ligand would have on the yield and selectivity of the fluorination reaction. Previous work by Stille and Milstein had suggested the presence of a Pd^{IV} intermediate in the reaction of dimethylbis(phosphine)palladium(II) with iodomethane to give ethane, however a stable Pd^{IV} complex containing phosphine ligands could not be isolated.[218] In 1986 Canty and co-workers reported the first isolable (alkyl)Pd^{IV} complex, bearing the stabilising bidentate nitrogen ligand, 2,2′-bipyridyl.[219] Since this initial report a variety of stable aryl, alkyl and benzyl Pd^{IV} complexes have been synthesised with a diverse set of bidentate and tridentate nitrogen ligands. As this type of ligand had shown to be successful, the bidentate ligands 4,4’-di-*tert*-butyl-2,2’-dipyridyl (dtbpy) **356** and (−)-sparteine **357** were selected to screen in this reaction. Both complexes **358** and **359** were synthesized from the cinnamyl palladium chloride dimer **352** using the same preparation as the TMEDA complex **350** in good yields (Scheme 4.22). The allyl motif could be easily identified in the ^{1}H-NMR with diagnostic peaks between 4-5 ppm that are in agreement with the allyl peaks for the known complex **350**. In both cases we were pleased to see only one allylpalladium species in the ^{1}H-NMR spectra and not a mixture of *cis* and *trans* isomers.



Scheme 4.22 Synthesis of Pd complexes

These novel complexes were crystalline solids and thus allowed for the unambiguous assignment of the structures by X-ray crystallographic analysis (Figure 4.4). While the complexes could be crystallised they were substantially less stable than the TMEDA analogue **350**. As such the complexes were kept at 15 ºC under argon and handled under an argon atmosphere where possible.

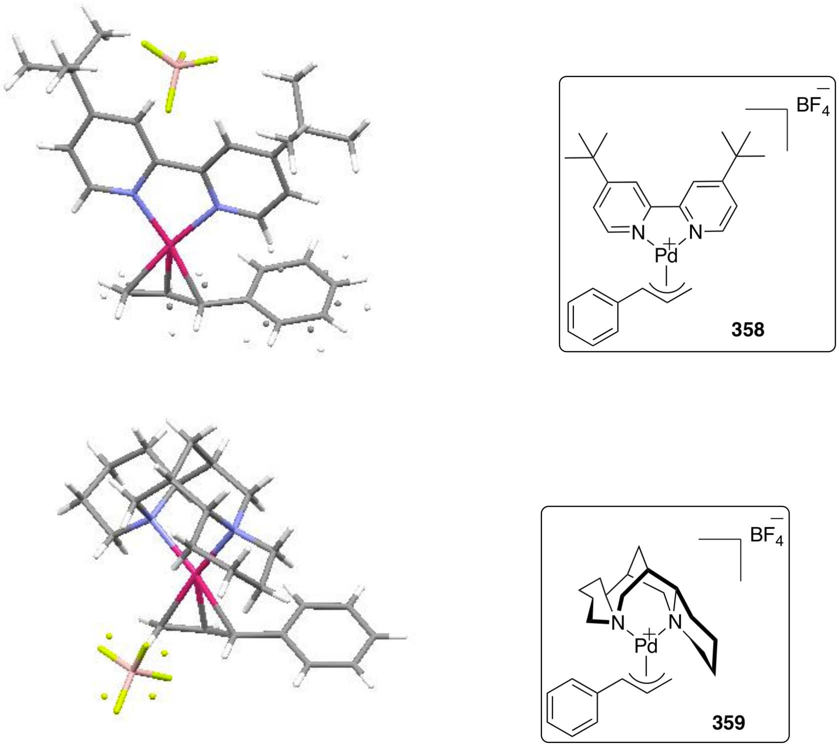
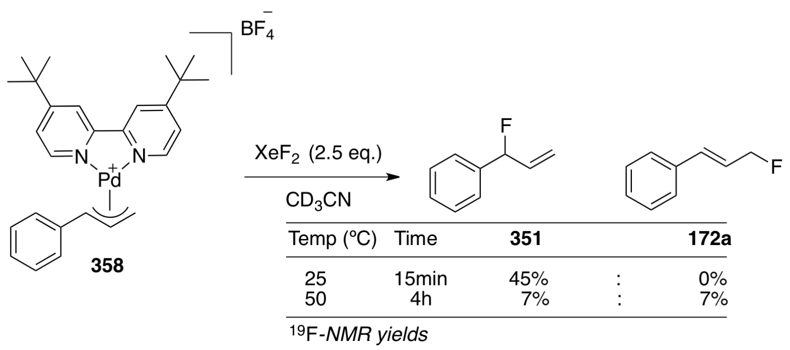


Figure 4.4 Structure of Pd complexes **358** and **359**

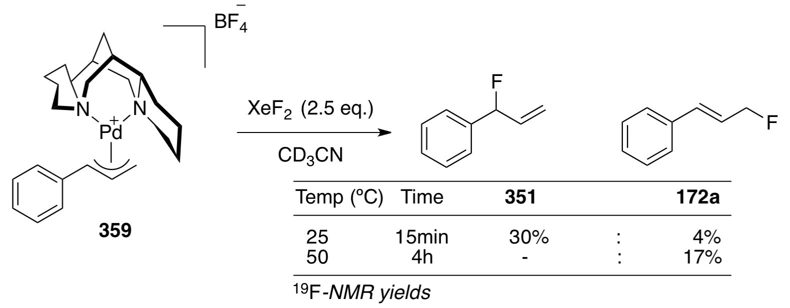
The fluorination reactions were then carried out at room temperature for 15 minutes. In both cases the reactions showed an excellent level of selectivity for the branched product. The 4,4′-di-*tert*-butyl-2,2′-dipyridyl complex **358** gave a 45% yield of branched fluoride **351** with no linear fluoride **172a** observed (Scheme 4.23). The yield of branched fluoride **351** for (-)-sparteine complex **359** was slightly reduced (30%) and a trace amount of linear product **172a** was identified (Scheme 4.24). Conducting the reactions at an elevated temperature of 50 ºC was detrimental to the yield and selectivity of the fluorination reactions. The regioselectivity for the branched allylic fluoride **351** shows the same selectivity as the C-H acetoxylations and trifluoroacetoxylation previously reported by Szabó that are proposed to proceed *via* a (π-allyl)Pd^{IV} intermediate.[202,206]



Temp (ºC)	Time	**351**		**172a**
25	15min	45%	:	0%
50	4h	7%	:	7%

^{19}F-*NMR yields*

Scheme 4.23 Fluorination of isolated Pd allyl complexes at room temperature

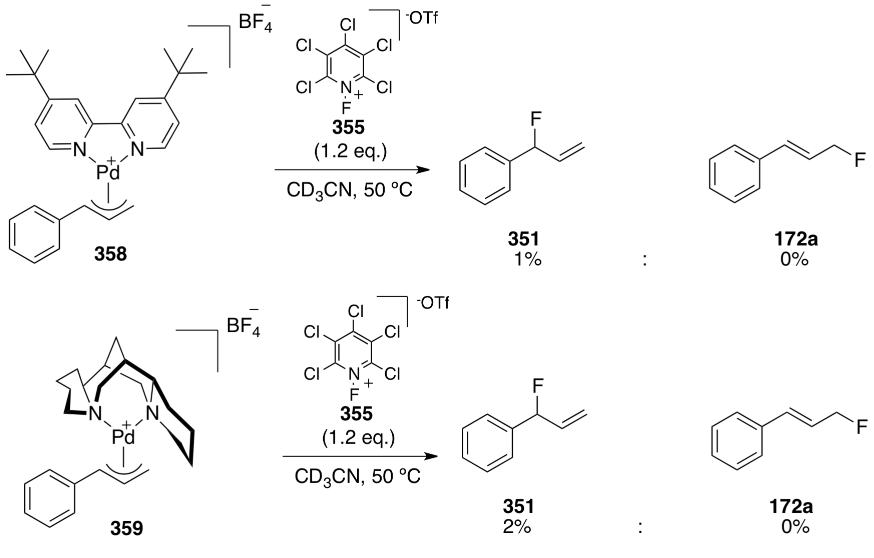


Temp (ºC)	Time	**351**		**172a**
25	15min	30%	:	4%
50	4h	-	:	17%

^{19}F-*NMR yields*

Scheme 4.24 Fluorination of isolated Pd allyl complexes at room temperature

As some reactivity was seen with the 1-fluoro-2,3,4,5,6-pentachloropyridinium triflate **355** for the TMEDA complex **350** at 50 ºC this reagent was also screened with complexes **358** and **359** (Scheme 4.25). When the N-F reagent **355** is used with these complexes only trace levels of branched fluorinated products **351** and **172a** were observed.

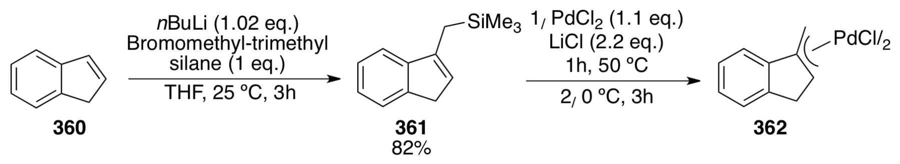


Scheme 4.25 Screening of ligand effects with N-F reagents

As previously discussed this reaction is proposed to proceed *via* a (π-allyl)$Pd^{IV}F$. Reported $Pd^{IV}F$ complexes have been observed as broad signals between 250-350 ppm in the ^{19}F-NMR spectra.[49] Therefore we monitored the fluorination of these complexes in the ^{1}H-NMR and ^{19}F-NMR spectra from -40 ºC to 35 ºC to see if any such intermediate could be identified during the course of the reaction. A sample of Pd complex **350** was dissolved in CD_3CN and ^{1}H-NMR and ^{19}F-NMR were recorded at -40 ºC. While maintaining the solution at -40 ºC in the NMR tube 2 equivalents of solid XeF_2 were added and spectra continuously recorded while the reaction was slowly warmed (by 10 ºC every 30 mins) to 25 ºC. The ^{19}F-NMR region between -150ppm and -400ppm was monitored during the warming of the solution as based on previous literature Pd^{IV}-F complexes. During the reaction no peaks indicative of Pd^{IV}-F were identified in the NMR spectra. While we did not observe an intermediate this does not rule out the possibility of a Pd^{IV} mechanism. Monitoring of the ratio of branched to linear fluoride in the ^{19}F-NMR spectra showed that this is diminished as the temperature increases, changing from 8:1 (**351**:**172a**) at -40 ºC to 5:1 (**351**:**172a**) at 25 ºC. Based on the instability of these allylic fluorides (discussed in Chapter 2), other allylpalladium complexes were synthesised in order to further investigate this reaction.

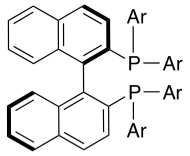
4.4 Asymmetric Variant

Access to the palladium complex **362** was possible by the formation of (3*H*-inden-1-ylmethyl)-trimethyl-silane **361** from the reaction of indene **360** with bromomethyltrimethylsilane (1 eq.) in excellent yield. The subsequent reaction of this with Li_2PdCl_4, following the procedure of Hayashi and Kumada gave the final palladium chloride dimer **362** (Scheme 4.26) that was used directly in the subsequent step.[220]



Scheme 4.26 Formation of indene complex **362**

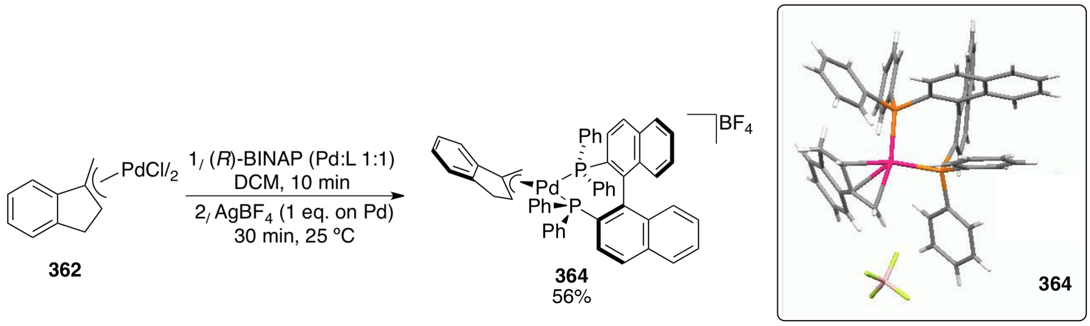
Attempts to substitute the ligands for the previously used bidentate nitrogen ligands were unsuccessful only leading to decomposition of the starting chloride dimer. However at this time other work on-going in the Gouverneur group had identified chiral bidentate phosphine ligands, in particular (±)-(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine) (BINAP)[221] **363A** as suitable ligands for the enantioselective fluorination in palladium mediated reactions.[222]



(*R*)-**363A** Ar = Ph [(*R*)-BINAP]
(*R*)-**363B** Ar = Tol [(*R*)-T-BINAP]

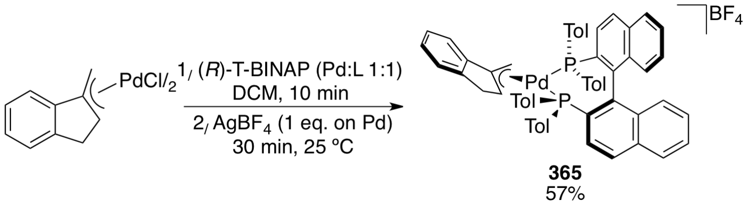
Figure 4.5 Structure of BINAP phosphine ligand

The synthesis of phosphine complex **364** was accomplished by reacting chloride dimer **362** with enantiopure (*R*)-(+)-(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine) (*R*)-BINAP (*R*)-**363A** (1 eq. based on Pd) at room temperature for 10 minutes followed by the addition of $AgBF_4$ (1 eq.) and stirring for a further 30 minutes. The complex **364** was isolated after recrystallisation as a yellow solid that was found to be unstable and as such was stored at -15 ºC under an Ar atmosphere. The structure of complex **57** was confirmed by X-ray crystallography, showing a square planar allyl complex (Scheme 4.27). Only one allylpalladium species was identified in the ^{1}H-NMR spectra that was assigned as **364** with diagnostic peaks in the allyl region (4.33-4.24 (d, 1H, *J* = 9.0 Hz, *H2*), 4.05 (bs, 1H, *H3'*), 4.00-3.90 (d, 1H, *J* = 9.0 Hz, *H3*)).



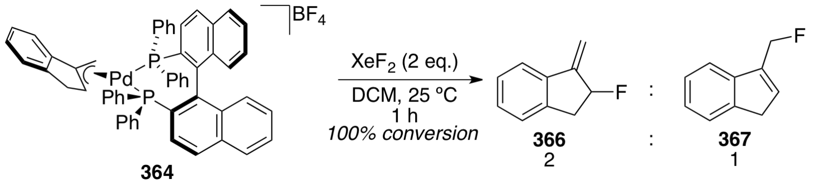
Scheme 4.27 Synthesis of (*R*)-BINAP complex **364**

The same protocol was used to synthesis the (*R*)-(+)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl ((*R*)-T-BINAP) complex **365** where the phenyl groups of the BINAP ligand are replaced with tolyl groups (Scheme 4.28). The complex was isolated in 57% yield after recrystallisation from DCM:Pentane. Again only one allylpalladium species was identified in the ^{1}H-NMR spectra that was assigned as **365** with a diagnostic peaks in the allyl region in agreement with complex **364.**



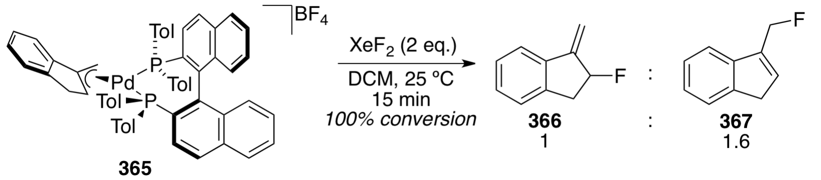
Scheme 4.28 Synthesis of (*R*)-T-BINAP complex **365**

The reaction of complex **364** with XeF_2 was screened in both acetonitrile (MeCN) and dichloromethane (DCM). No fluorination was observed in MeCN unlike the previously discussed nitrogen systems, even with prolonged reaction times. However allylic fluoride products **366** and **367** were observed when the reaction was carried out in DCM with a 2:1 selectivity in favour of the branched product. Monitoring this reaction over the period of 1 hour showed complete consumption of the XeF_2 complex **364** (Scheme 4.29). The ratio of branched to linear fluoride was reversed during this time, with a 1:2 branched:linear ratio after 1 hour. When the reaction was carried out at an elevated temperature (35 ºC) no fluorinated product could be observed by TLC.



Scheme 4.29 Fluorination of complex **364**

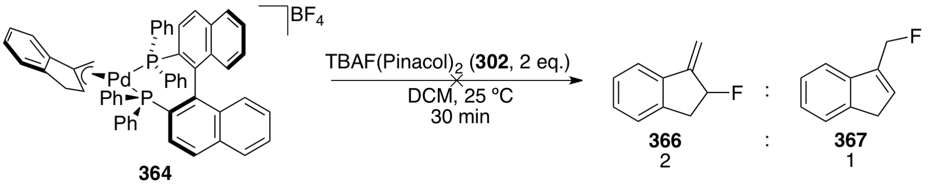
When complex **365** was submitted to these reaction conditions we were pleased to see full conversion of the starting complex after 20 minutes when the reaction was carried out in DCM (Scheme 4.30). However the selectivity was in favour of the linear product **367**, 1.6:1 linear:branched. Monitoring of the reaction by ^{1}H-NMR and ^{19}F-NMR showed that decomposition of both products occurred at reaction times exceeding 30 mins.



Scheme 4.30 Fluorination of complex **365**

A sample of Pd complex **364** was dissolved in DCM-*d2* and ^{1}H-NMR and ^{19}F-NMR were recorded at -60 ºC. While maintaining the solution at -60 ºC in the NMR tube 2 equivalents of solid XeF_2 was added and spectra continuously recorded as the reaction was slowly warmed (by 10 ºC every 30 mins). The ^{19}F-NMR region between -150ppm and -400ppm was observed during the warming of the solution. No peaks corresponding to a Pd^{IV}-F or the allylic fluoride products were observed from -60 ºC to 0 ºC, with NMR spectra only showing unreactived complex **364** and XeF_2. When the solution was warmed to room temperature peaks corresponding to the two fluorinated products **366** and **367** were observed but still no obvious Pd^{IV}-F intermediate could be detected.

We next investigated the reactivity of complex **364** with a fluoride source, TBAF(Pinaol)$_2$ **302**. Monitoring of this reaction in the ^{1}H-NMR and ^{19}F-NMR spectra showed the decomposition of complex **364** after 30 minutes at room temperature, however no formation of allylic fluorides **366** and **367** was observed (Scheme 4.32).

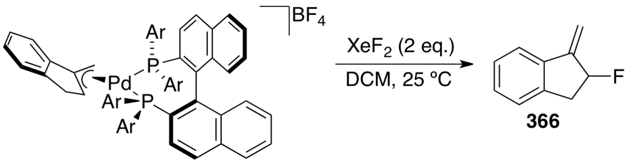


Scheme 4.32 Reaction of **364** with TBAF(Pinacol)$_2$ **302**

This result would suggest that the reaction does not involve fluoride and hence does not operate *via* a nucleophilic attack on the π-allylpalladium species. While no (π-allyl)Pd^{IV}F intermediate could be observed during the reactions with XeF$_2$ the lack of reactivity with fluoride suggests that Pd^{II}/Pd^{IV} mechanism could still be possible.

As an enantiopure source of (*R*)-BINAP was used to synthesise complexes **364** and **365** we were intrigued to if this induced any asymmetric induction. A racemic sample of the branched fluoride **366** was synthesised by a fluorodesilylation reaction to establish HPLC conditions for the separation of enantiomers (Chiralcel OJ-H, Hexane/IPA, Gradient A, 1.3 mL/min).[78]

To carry out the reactions a solution of palladium complex (0.02 mmol) was dissolved in DCM under an Ar atmosphere and solid XeF$_2$ (2 eq.) was added and the reaction stirred at room temperature for 15 minutes. The reaction was then concentrated under a flow of N$_2$ and residue dissolved in the minimal amount of DCM (0.5 mL) to load onto a preparative TLC plate with a reference of the branched fluoride **366** (Hexane eleunt). The corresponding silica gel containing the fluoride product was removed and washed with DCM and solvent removed *in vacuo* to yield isolated branched fluoride **366**. The fluoride was dissolved in the appropriate amount of hexane (1 mg/1 mL) and HPLC analysis performed. These results are presented in Table 4.3.

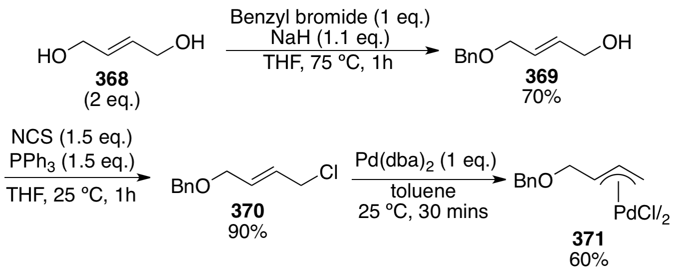


Entry	Complex	Time (min)	*ee* (%) of **366**
1	(*R*)-BINAP (**364**)	15	58%
2	(*R*)-T-BINAP (**365**)	15	57%
3	(*R*)-BINAP (**364**)	30	24%

Table 4.3 Enantiomeric excess of branched fluoride

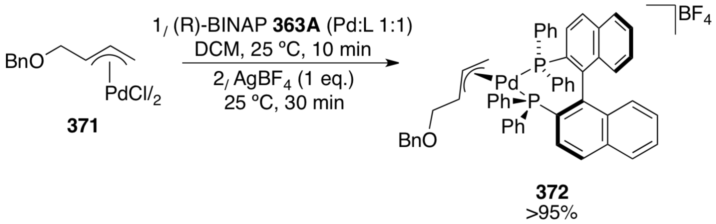
Complexes **364** and **365** provided the same sense of asymmetric induction, yielding the branched fluoride **366** in 58% and 57%, respectively. Attempts to improve this result by changing the reaction temperature or addition of a solution of XeF_2 did not improve the enantiomeric excess. When the reaction of complex **364** was extended to 30 minutes the *ee* was eroded to 24%. No absolute configuration was determined for the product. The formation of branched fluoride was seen in all reactions, however the ratio of **366**:**367** was not determined.

The scope of this reaction was next investigated. We selected the previously discussed benzyl 2-fluorobut-3-en-1-yl ether that could be isolated from the Ir-catalysed allylic fluorination (Chapter 2)[139,140]. The allyl chloride dimer **371** was synthesized from the corresponding allyl chloride **370** and $Pd(dba)_2$ at room temperature in a 60% yield. This chloride was produced via the benzyl bromide monosubstitution of (*E*)-but-2-ene-1,4-diol **368** which was converted to the allylic chloride **369** in the presence of triphenylphosphine and NCS in THF in 90% (Scheme 4.32).



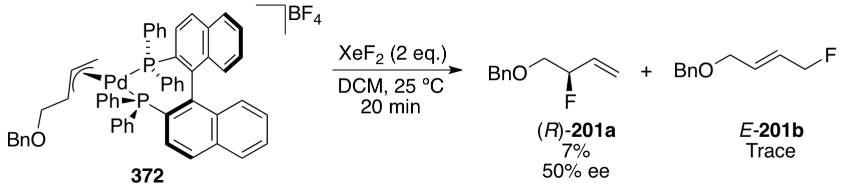
Scheme 4.32 Formation of Pd chloride dimer **371**

The synthesis of complex **372** was achieved by the reaction of chloride dimer **371** with enantiopure (*R*)-(+)-(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine) (*R*)-**363A** (1 eq. based on Pd) as for the indene substrate (Scheme 4.33). The complex was isolated after recrystallisation as a yellow solid that was found to be unstable and as such was stored at -15 ºC under an Ar atmosphere. We were pleased to see the presence of only one geometrical and regio- isomer in the ^{1}H-NMR spectra. This complex was assigned as novel complex **372.**



Scheme 4.33 Synthesis of (*R*)-BINAP Pd complex **372**

Reaction of complex **372** under the fluorination conditions provided the two allyl fluoride regioisomers **201a** and *E*-**201b**, favouring the branched fluoride **201a**. However the ^{1}H-NMR revealed that the reaction does not go to complete conversion and even after 24h the starting complex could still be identified in the NMR. The racemic sample of fluoride **201a** had been previously synthesised via Ir-catalysis and HPLC conditions determined (Chiralcel IA, Hexane/IPA, Gradient A, 1.3 mL/min). The fluorination of the complex **372** was carried out as for the indene complex for 20 minutes at room temperature (Scheme 4.34). The HPLC analysis of the fluorinated products obtained from this reaction revealed the branched fluoride **201a** was obtained in a 7% yield and a 50% *ee*. The absolute configuration of the product was determined to be (*R*)-**201a** based on an independently synthesised sample of (*S*)-**201a** by the procedure of Doyle *et al.*[123]



Scheme 4.34 Asymmetric fluorination of complex **66**

4.5 Conclusion and Future work

In conclusion, the combination of isolated allylpalladium complexes and electrophilic fluorinating reagents allows for the formation of a variety of allylic fluorides. Treatment of the Pd complexes with 2.5 equivalents of XeF_2 led to the formation of both branched and linear allylic fluorides. The reaction is shown to tolerate both nitrogen and phosphorus ligands with a range of success. The preference to form branched fluorides was demonstrated in the case of the bidentate nitrogen ligands and this could be extended to the asymmetric synthesis of stable branched fluorides **366** and **201a** when chiral (*R*)-BINAP ligands were employed.

While a Pd^{IV} intermediate was not directly observed the mechanism of this reaction remains under question. The synthesis of a large library of divergent π-allylpalladium complexes bearing a selection of ligands is necessary to further investigate this system. Attempts to access the Pt analogue of complex **364** have been unsuccessful, however the synthesis of this complex could aid in visualisation of the high oxidation state metal fluoride, proposed as a possible intermediate, in the NMR spectra.

Chapter 5

Experimental Procedures and Data

5.1 General Experimental Information

All solvents and chemicals were used as purchased unless otherwise stated. ^{1}H-NMR spectra were recorded in deuterated solvents using a Bruker DPX200, DPX250, AV400, DRX500, AVIII400 or AVII500 spectrometer. ^{13}C-NMR spectra were recorded in deuterated solvents using a Bruker AV400, AVIII400 or AVII500 equipped with a ^{13}C cryoprobe or DRX500 spectrometer. ^{19}F-NMR spectra (both with and without proton decoupling) were recorded on a Bruker DPX250, AV400, AVIII400 or AVII500 spectrometer, referenced externally to $CFCl_3$. ^{31}P-NMR spectra were recorded on a Bruker AV400 or DRX500 spectrometer and are referenced relative to phosphoric acid in D_2O. NMR data were processed using MESTRE-Nova or TOPSPIN software. Chemical shifts (δ) are quoted in parts per million (ppm) relative to the residual undeuterated solvent peak using the Bruker internal referencing procedure (edlock). Coupling constants (J) are reported to the nearest 0.5 Hz in ^{1}H-NMR and to the nearest hertz in ^{13}C- and ^{19}F-NMR. The following abbreviations are used to describe multiplicities – s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Multiplicities are reported as observed in the spectra. High-resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTof spectrometer using positive electrospray ionisation (EI+) or field ionisation (FI) and on a Micromass GCT using chemical ionization (CI+). Infrared spectra were recorded neat or in solvent using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}), and only peaks of interest are reported. Melting points of solids were measured on a Griffin apparatus and were uncorrected. HPLC was performed on a Dionex

Ulitmate3000 and chrial HPLC was performed on a Dionex UVD340D using a CHIRALCEL OJ-H or CHIRALCEL IA column.

IUPAC names were given using the ACD/I-Lab. Full characterisation data is provided for novel compounds. For known compounds two pieces of data are provided including ^{1}H-NMR data that are in agreement with literature values. All X-ray crystallography data is provided in the Appendix (**A5-8**).

All reactions requiring anhydrous conditions were conducted in dried apparatus under an inert atmosphere of argon or nitrogen with magnetic stirring. All solvents were dried on a column of alumina prior to use. Thin layer chromatography (TLC) was performed using Merck aluminium-foil backed plates precoated with Kieselgel 60 F_{254}. The products were visualized using UV fluorescence (254 nm) or potassium permanganate stain. Flash column chromatography was performed over silica gel using eluent systems as described for each experiment.

5.2 Experimental Data for Chapter 2

5.2.1 General Procedures

General Procedure A for the synthesis of allylic alcohols

To a solution of Grignard (12.5 mmol, 2.5 eq) in Et_2O (30 mL, 0.17 M) was added CuI (0.75 mmol, 15 mol%). The reaction mixture was allowed to stir at rt for 0.5 h. Propargyl alcohol (5 mmol, 1 eq) in Et_2O (5 mL, 1 M) was added dropwise at rt. The reaction was then heated to reflux for 24 h. After cooling to rt, $NH_4Cl_{(aq)}$ was added dropwise. The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 50 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Crude products were purified by flash column chromatography.

Where the Grignard was not commercially available it was synthesized *via* the following procedure:

To Mg (5.15 mmol, 1.03 eq) in dry THF (5 mL, 1 M) was added alkyl/arylbromide (5 mmol, 1.0 eq) and a bead of I_2 to activate the Mg. The reaction mixture was refluxed for 1h, after which the reaction was allowed to cool to rt and taken through to the next reaction step without further purification or titration.

General Procedure B for the synthesis of allylic *p*-nitrobenzoates

To a solution of allylic alcohol (1 mmol) and triethylamine (1 mmol) in DCM (10 mL) was added 4-nitrobenzoyl chloride (1 mmol) portion wise at 0°C. The reaction was allowed to warm to rt and stirred until complete by TLC. The reaction mixture was diluted with DCM and then washed successively with $NaHCO_{3(aq)}$, H_2O and brine. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. Crude products were purified by silica gel column chromatography where necessary.

General Procedure C for the synthesis of allylic acrylates

A solution of aldehyde (3 mmol, 1 eq.) and (carbethyoxymethylene)triphenylphosphorane (3 mmol) were stirred in toluene (0.1 M) at reflux for 16 h, after which the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo* to yield a residue that was purified by silica gel column chromatography to yield the acrylate product.

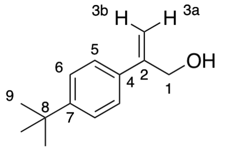
General Procedure D for the synthesis of linear *E*-allylic alcohols

To a suspension of allylic acrylate (4 mmol) in toluene (13 mL, 0.3 M) at -78 ºC was added dropwise DIBAL (1 M solution in toluene, 2.2 equiv.) over 30 mins. The reaction was allowed to warm to rt and then stirred for 2 h. After this time the reaction was quenched with ice and dilute HCl, extracted with EtOAc (3 x 25 mL), washed with brine (25 mL) and

H_2O (25 mL). The organics were then dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a residue that was purified by column chromatograph to yield the corresponding alcohol.

5.2.2 Synthesis of Allylic *p*-Nitrobenzoates for Pd-catalysed fluorination

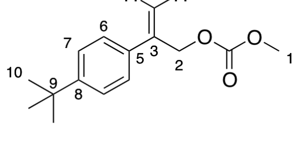
2-(4-*tert*-Butylphenyl)prop-2-en-1-ol (156)



General procedure A was followed using 4-(*tert*-butyl)phenylmagnesium bromide (12.5 mL, 25 mmol, 2 M solution in Et_2O, 2.5 eq.), CuI (286 mg, 1.5 mmol, 15 mol%), and propargyl alcohol (0.85 mL, 10 mmol) in Et_2O (70 mL (60 mL and 10 mL)). The mixture was stirred at reflux for 24 h. The resulting crude mixture was purified by silica gel column chromatography (EtOAc:hexane, 10:1) to afford the product **156** as a yellow oil (1.89g, > 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 9H, *H9*), 1.88 (bs, 1H, *H10*), 4.55 (s, 2H, *H1*), 5.33 (s, 1H, *H3a*/*H3b*), 5.48 (s, 1H, *H3a*/*H3b*), 7.39-7.44 (m, 4H, *H5/6*); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 31.3, 34.5, 65.0, 111.9, 125.4, 125.7, 135.5, 147.0, 151.0; **IR** (neat) ν 3383, 2965, 2246, 1631; **HRMS** calc for $C_{13}H_{19}O$ $[M+H]^+$ 191.1436, found 191.1443.

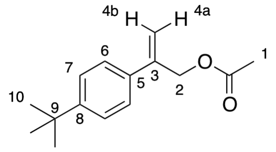
2-(4-*tert*-Butylphenyl)prop-2-en-1-yl methyl carbonate (157a)



To a solution of 2-(4-*tert*-butylphenyl)prop-2-en-1-ol **156** (248 mg, 1 mmol) and pyridine (0.24 mL, 3 mmol, 3 eq.) in THF (5 mL) at 0°C was added methyl chloroformate (0.15 mL, 2 mmol, 2 eq.) dropwise. The reaction was then allowed to warm to rt and stirred for 16 h. The reaction was quenched by the addition of $NH_4Cl_{(aq)}$, the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. Purification by silica gel column chromatography (Et_2O:hexane, 10:1) afforded allylic carbonate **157a** as a colourless oil (2g, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 9H, *H10*), 3.81 (s, 3H, *H1*), 5.05 (s, 2H, *H2*), 5.39 (s, 1H, *H4a*/*H4b*), 5.58 (s, 1H, *H4a*/*H4b*), 7.40 (s, 4H, *H5/6*); **^{13}C NMR** (100 MHz) δ: 31.3, 34.5, 54.8, 69.1, 114.9, 125.5, 125.6, 134.8, 141.6, 151.6, 155.6; **IR** (neat) ν 2962, 1751, 1268; **HRMS** calc for $C_{15}H_{20}O_3$ $[M]^+$ 248.1412, found 248.1409.

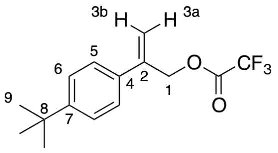
2-(4-*tert*-Butylphenyl)prop-2-en-1-yl acetate (157b)



To a solution of 2-(4-*tert*-butylphenyl)prop-2-en-1-ol **156** (250 mg, 1.31 mmol) and triethylamine (220 µL, 1.57 mmol, 1.2 eq.) in DCM (4 mL) at 0°C was added acetic anhydride (120 µL, 1.31 mmol, 1 eq.) dropwise. The reaction was allowed to stir at rt until complete by TLC. The reaction mixture was diluted with DCM and then washed successively by $NaHCO_{3(aq)}$, H_2O and brine. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (Et_2O:hexane, 10:1) to afforded allylic acetate **157b** (32 mg, 46%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 9H, *H10*), 2.10 (s, 3H, *H1*), 4.99 (s, 2H, *H2*), 5.34 (m, 1H, *H4a*/*H4b*), 5.57 (s, 1H, *H4a*/*H4b*), 7.40 (s, 4H, *H6/7*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 21.0, 31.3, 34.5, 65.8, 114.5, 125.4, 125.6, 135.0, 142.0, 151.1, 170.8; **IR** (neat) ν 2963, 1742, 1633, 1227; **HRMS** calc for $C_{15}H_{20}O_2$ $[M]^+$ 232.1463 found 232.1469.

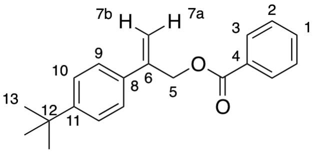
2-(4-*tert*-Butylphenyl)prop-2-en-1-yl trifluoroacetate (157c)



To a solution of 2-(4-*tert*-butylphenyl)prop-2-en-1-ol **156** (74 mg, 0.3 mmol) and triethylamine (50 μL, 0.36 mmol, 1.2 eq.) in DCM (3 mL) at 0°C was added trifluoroacetic anhydride dropwise (42 μL, 0.3 mmol, 1 eq.). The reaction was allowed to stir at rt until complete by TLC. The reaction mixture was diluted with DCM and then washed successively by $NaHCO_{3(aq)}$, H_2O and brine. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (Et_2O:hexane, 10:1) to afford **157c** (37 mg, 43%) as a colourless oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 1.37 (s, 9H, *H9*), 5.28 (s, 2H, *H1*), 5.46 (s, 1H, *H3a*/*H3b*), 5.70 (s, 1H, *H3a*/*H3b*), 7.42 (m, *J* = 9.0 Hz, 2H, *H5*), 7.46 (m, *J* = 9.0 Hz, 2H, *H6*); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 31.3, 34.9, 69.5, 115.2 (q, *J* = 285 Hz), 116.7, 125.9, 126.2, 134.5, 140.7, 152.1, 157.7 (q, *J* = 42 Hz); **^{19}F NMR** (376.5 Hz, CD_2Cl_2) δ: -75.4 (s); **IR** (neat) ν 2965, 1680, 1265, 738; **HRMS** calc for $C_{15}H_{17}O_2F_3$ $[M]^+$ 286.1181 found 286.1184.

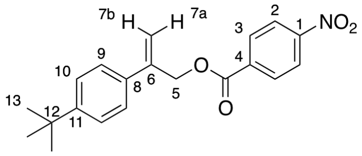
2-(4-*tert*-Butylphenyl)prop-2-en-1-yl benzoate (157d)



To a solution of 2-(4-*tert*-butylphenyl)prop-2-en-1-ol **156** (74 mg, 0.3 mmol) and triethylamine (50 μL, 0.36 mmol, 1.2 eq.) in DCM (3 mL) at 0°C was added benzoyl chloride (35 μL, 0.3 mmol, 1 eq.) dropwise. The reaction was allowed to stir at rt until complete by TLC. The reaction mixture was diluted with DCM and then washed successively by $NaHCO_{3(aq)}$, H_2O and brine. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (Et_2O:hexane, 10:1) to afford allylic benzoate **157d** (39 mg, 44%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.35 (s, 9H, *H13*), 5.24 (s, 2H, *H5*), 5.45 (s, 1H, *H7a*/*H7b*), 5.63 (s, 1H, *H7a*/*H7b*), 7.40-7.49 (m, 6H, *H2/9/10*), 7.57 (dd, *J* = 7.0, 1.0 Hz, 1H, *H1*), 8.08 (dm, *J* = 8.0 Hz, 2H, *H3*); **^{13}C NMR** (101MHz, $CDCl_3$): δ: 31.3, 34.6, 66.2, 114.5, 125.4, 125.6, 128.4, 129.7, 130.1, 133.0, 135.1, 142.1, 151.2, 166.3; **IR** (neat) ν 2963, 1720, 1268, 1110; **HRMS** calc for $C_{20}H_{22}O_2$ $[M]^+$ 294.1620, found 294.1621.

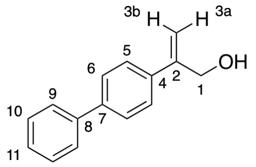
2-(4-*tert*-Butylphenyl)prop-2-en-1-yl 4-nitrobenzoate (157e)



General procedure B was followed using 2-(4-*tert*-butylphenyl)prop-2-en-1-ol **156** (250 mg, 1.31 mmol), triethylamine (200 μL, 1.44 mmol, 1.1 eq.) and 4-nitrobenzoyl chloride (243 mg, 1.31 mmol, 1 eq.) in DCM (4 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (EtOAc:hexane, 10:1) to afford the product **157e** (380 mg, 85%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 9H, *H13*), 5.28 (s, 2H, *H5*), 5.45 (s, 1H, *H7a*/*H7b*), 5.66 (s, 1H, *H7a*/*H7b*), 7.38-7.48 (m, 4H, *H9/10*) 8.20-8.29 (m, 4H, *H2/3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 31.7, 35.0, 67.6, 115.7, 124.0, 126.0, 126.0, 131.2, 135.2, 135.9, 142.0, 151.0, 151.9, 164.9; **IR** (KBr) ν 1726, 1530, 1265; **HRMS** calc for $C_{20}H_{21}NO_4$ $[M]^+$ 339.1471 found 339.1466; **Mp** 72-74°C

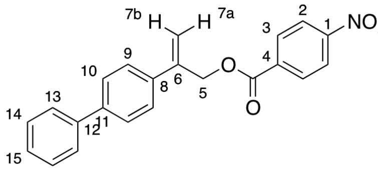
2-(Biphenyl-4-yl)prop-2-en-1-ol (162b)



General procedure A was followed using 4-biphenylmagnesium bromide (25 mL, 12.5 mmol, 0.5 M solution in THF, 2.5 eq.), CuI (142 mg, 0.75 mmol, 15 mol%), and propargyl alcohol (0.43 mL, 5 mmol) in Et_2O (35 mL). The mixture was stirred at reflux for 24 h. The resulting crude mixture was purified by silica gel column chromatography (EtOAc:hexane, 5:1) to afford the product **162b** (740 mg, 70%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.61 (s, 2H, *H1*), 5.40 (d, *J* = 1.0 Hz, 1H, *H3a/H3b*), 5.56 (s, 1H, *H3a/H3b*), 7.35-7.40 (m, 1H, *H11*), 7.44-7.49 (m, 2H, *H5*), 7.54-7.58 (m, 2H, *H6*), 7.59-7.65 (m, 4H, *H9/10*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 65.5, 113.2, 126.9, 127.5, 127.7, 127.4, 129.3, 137.8, 141.1, 141.2, 147.2; **IR** (neat) ν 3356, 1487, 1404, 840, 739; **HRMS** calc for $C_{15}H_{18}ON$ $[M+NH_4]^+$ 228.1387 found 228.1388; **Mp** 115-118°C.

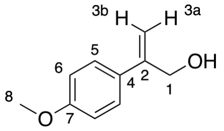
2-(Biphenyl-4-yl)prop-2-en-1-yl 4-nitrobenzoate (163b)



General procedure B was followed using 2-(biphenyl-4-yl)prop-2-en-1-ol **156** (250 mg, 1 mmol), triethylamine (139 μL, 1.2 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (186 mg, 1 mmol, 1 eq.) in DCM (3 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (DCM) to afford the product **163b** (360 mg, > 95%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.33 (s, 2H, *H5*), 5.52 (s, 1H, *H7a*/*H7b*), 5.73 (s, 1H, *H7a*/*H7b*), 7.35-7.40 (m, 1H, *H15*), 7.44-7.49 (m, 2H, *H10*), 7.56-7.66 (m, 2H, *H9*), 8.18-8.30 (m, 4H, *H2/3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 67.1, 116.1, 123.6, 126.3, 127.0, 127.3, 127.6, 128.9, 130.8, 135.4, 136.5, 140.4, 141.1, 141.5, 150.6, 164.4; **IR** (KBr) ν 1719, 1525, 1281, 1129; **HRMS** calc for $C_{22}H_{17}NO_4$ $[M]^+$ 359.1158 found 359.1159; **Mp** 167-168°C.

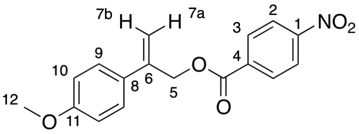
2-(4-Methoxyphenyl)prop-2-en-1-ol (162c)[223]



General procedure A was followed using 4-methoxyphenylmagnesium bromide (20 mL, 10 mmol, 0.5 M solution in THF, 2.5 eq.), CuI (114 mg, 0.6 mmol, 15 mol%), and propargyl alcohol (0.23 mL, 4 mmol) in Et_2O (35 mL). The mixture was stirred at reflux for 24 h. The resulting crude mixture was purified by silica gel column chromatography (EtOAc:hexane, 10:1) to afford the product **162c** (131 mg, 20%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.27 (s, 3H, *H8*), 4.53 (s, 2H, *H1*), 5.31 (d, *J* = 1.0 Hz, 1H, *H3a*/*H3b*), 5.44 (s, 1H, *H3a*/*H3b*), 6.94 (d, *J* = 8.0 Hz, 2H, *H5*), 7.44 (d, *J* = 6.0 Hz, 2H, *H6*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 55.7, 65.3, 111.4, 114.3, 127.6, 131.5, 147.0, 159.8.

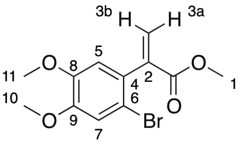
2-(4-Methoxyphenyl)prop-2-en-1-yl 4nitrobenzoate (163c)



General procedure B was followed using 2-(4-methoxyphenyl)prop-2-en-1-ol **162c** (92 mg, 0.56 mmol), triethylamine (86 μL, 0.62 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (115 mg, 1 mmol, 1 eq.) in DCM (3 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (DCM) to afford the product **163c** (105 mg, 60 %) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.88 (s, 3H, *H12*), 5.31 (s, 2H, *H5*), 5.43 (s, 1H, *H7a*/*H7b*), 5.62 (s, 1H, *H7a*/*H7b*), 6.95 (d, *J* = 9.0 Hz, 2H, *H10*), 7.48 (d, *J* = 9.0 Hz, 2H, *H9*), 8.20-8.35 (m, 4H, *H2/3*); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 55.7, 67.7, 123.9, 124.0, 127.6, 128.2, 130.6, 131.2, 135.9, 141.8, 151.0, 160.1, 164.9; **IR** (KBr) ν 1719, 1519, 1280, 832, 716; **HRMS** calc for $C_{17}H_{15}NO_5$ $[M]^+$ 313.0950 found 313.0949; **Mp** 72-73°C.

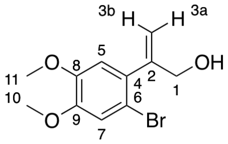
Methyl 2-(2-bromo-4,5-dimethoxyphenyl)acrylate (164)



A suspension of methyl (2-bromo-4,5-dimethoxyphenyl)acetate (0.89 mL, 4.3 mmol), K_2CO_3 (594 mg, 4.3 mmol) and paraformaldehyde (220 μL, 6.5 mmol, 1.5 eq.) was heated to 100 °C in DMF (30 mL) for 12 h. After cooling to rt, H_2O (50 mL) was added and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent remoned *in vacuo*. The crude product was purified by silica gel column chromatography (Et_2O:hexane, 10:1) and afforded acrylate **164** (1.140g, 88%) as a yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.80 (s, 3H, *H1/10/11*), 3.88 (s, 3H, *H1/10/11*), 3.90 (s, 3H, *H1/10*), 5.77 (d, *J* = 1.0 Hz, 1H, *H3a*/*H3b*), 6.51 (d, *J* = 1.0 Hz, 1H, *H3a*/*H3b*), 6.77 (s, 1H, *H5*), 7.05 (s, 1H, *H7*); **^{13}C NMR** (62 MHz, $CDCl_3$) δ: 52.8, 56.5, 56.6, 113.9, 114.0, 115.6, 129.4, 130.8, 141.9, 148.6, 149.8, 166.9; **IR** (neat) ν 2950, 1725, 1505, 1250; **HRMS** calc for $C_{12}H_{13}O_4Br$ $[M]^+$ 299.9997 found 299.9995.

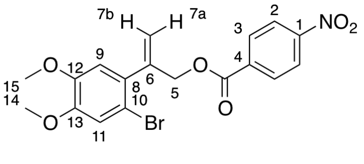
2-(2-Bromo-4,5-dimethoxyphenyl)prop-2-en-1-ol (165)



To a solution of methyl 2-(2-bromo-4,5-dimethoxyphenyl) acrylate (**164**) (993 mg, 3.3 mmol) in toluene (10 mL) at -78°C was added DIBAL-H (6.9 mL, 1M in toluene, 6.9 mmol, 2 eq.) dropwise over 15 minutes. The reaction mixture was then allowed to warm to rt and stirred for a further 30 minutes at rt. The reaction was quenched by addition of dilute $HCl_{(aq)}$ in ice. The aqueous phase was extracted with EtOAc (3 x 50 mL), the combined organic phases were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc:hexane, 10:1) and afforded alcohol **165** (884 mg, 95%) as a clear oil.

^{1}**H NMR** (400 MHz, $CDCl_3$) δ: 3.80 (s, 3H, *H10/11*), 3.81 (s, 3H, *H10/11*), 4.32 (s, 2H, *H1*), 5.08 (s, 1H, *H3a*/*H3b*), 5.47 (s, 1H, *H3a*/*H3b*), 6.68 (s, 1H, *H5*), 6.97 (s, 1H, *H7*); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ: 56.0, 56.1, 65.2, 112.1, 113.4, 115.0, 115.4, 133.0, 148.1, 148.8, 148.9; **IR** (neat) ν 3493, 2936, 1714, 1502, 1030; **HRMS** calc for $C_{11}H_{13}O_3Br$ $[M]^+$ 272.0048 found 272.0046.

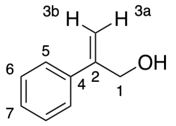
2-(2-Bromo-4,5-dimethoxyphenyl)prop-2-en-1-yl 4-nitrobenzoate (163d)



General procedure B was followed using 2-(2-bromo-4,5-dimethoxyphenyl)prop-2-en-1-ol **165** (754 mg, 2.76 mmol), triethylamine (462 μL, 3.3 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (512 mg, 2.76 mmol, 1 eq.) in DCM (10 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (EtOAc:hexane, 5:1) to afford the product **163d** (851 mg, 73%) as a yellow solid.

^{1}**H NMR** (400 MHz, $CDCl_3$) δ: 3.84 (s, 3H, *H14/15*), 3.88 (s, 3H, *H14/15*), 5.15 (s, 2H, *H5*), 5.30 (s, 1H, *H7a/H7b*), 5.61 (s, 1H, *H7a/H7b*), 6.75 (s, 1H, *H9*), 7.05 (s, 1H, *H11*), 8.14-8.29 (m, 4H, *H2/3*); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ: 56.6, 56.6, 67.9, 112.8, 113.7, 116.0, 119.1, 124.0, 131.2, 132.5, 135.9, 143.8, 148.7, 149.7, 151.0, 164.6; **IR** (KBr) ν 2932, 1731, 1600, 1529; **HRMS** calc for $C_{18}H_{16}NO_6Br$ $[M]^+$ 421.0161, found 421.0165; **Mp** 82-84°C.

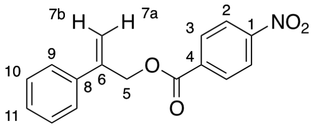
2-Phenylprop-2-en-1-ol (162a)[224]



General procedure A was followed using phenylmagnesium bromide (8.3 mL, 25 mmol, 3 M solution in Et_2O, 2.5 eq.), CuI (286 mg, 1.5 mmol. 15 mol%), and propargyl alcohol (0.85 mL, 10 mmol) in Et_2O (35 mL). The mixture was stirred at reflux for 24 h. The resulting crude mixture was purified by silica gel column chromatography (EtOAc:hexane 5:1) to afford the alcohol product **162a** (1.2 g, 90%) as a colourless oil.

^{1}**H NMR** (400 MHz, $CDCl_3$) δ: 2.11 (t, *J* = 6.0 Hz, 1H, *OH*), 4.54 (d, *J* = 5.0 Hz, 2H, *H1*), 5.36-5.38 (m, 1H, *H3a/H3b*), 5.49 (d, *J* = 1.0 Hz, 1H, *H3a/H3b*), 7.30-7.40 (m, 3H, *H6/7*), 7.45-7.50 (m, 2H, *H5*); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ: 64.9, 112.6, 126.1, 127.9, 128.5, 138.5, 147.3.

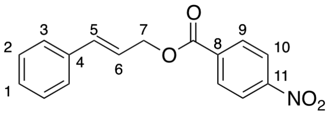
2-Phenylprop-2-en-1-yl 4-nitrobenzoate (163a)



General procedure B was followed using 2-phenylprop-2-en-1-ol **162a** (496 mg, 3.7 mmol), triethylamine (619 µL, 4.4 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (687 mg, 3.7 mmol, 1 eq.) in DCM (10 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (EtOAc: hexane, 5:1) to afford the product **163a** (870 mg, 83%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.29 (s, 2H, *H5*), 5.49 (s, 1H, *H7a*/*H7b*), 5.66 (s, 1H, *H7a*/*H7b*), 7.31-7.42 (m, 3H, *H10/11*), 7.48-7.52 (m, 2H, *H9*), 8.17-8.29 (m, 4H, *H2/3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 67.1, 116.0, 123.6, 126.0, 128.3, 128.6, 130.8, 135.4, 137.7, 142.0, 150.6, 164.4; **IR** (KBr) ν 1720, 1604, 1527; **HRMS** calc for $C_{16}H_{13}NO_4$ $[M]^+$ 283.0845 found 283.0846; **Mp** 79-81°C.

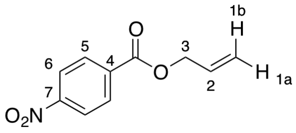
(2*E*)-3-Phenylprop-2-en-1-yl 4-nitrobenzoate (168a)



General procedure B was followed using 3-phenyl-2-propen-1-ol (129 µL, 1 mmol), triethylamine (139 µL, 1.2 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (186 mg, 1 mmol, 1 eq.) in DCM (5 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (EtOAc:hexane, 10:1) to afford the product **168a** (283 mg, 95%) as a yellow solid.

^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.07 (dd, *J* = 7.0, 1.0 Hz, 2H, *H7*), 6.44 (dt, *J* = 16.0, 7.0 Hz, 1H, *H6*), 6.82 (d, *J* = 16.0 Hz, 1H, *H5*), 7.28-7.50 (m, 5H, *H1/2/3*), 8.25-8.36 (m, 4H, *H9/10*); **^{13}C NMR** (63 MHz, $CDCl_3$) δ: 66.9, 122.7, 124.0, 127.1, 128.8, 129.1, 131.2, 135.7, 136.0, 136.3, 151.0, 164.9; **IR** (KBr) ν 3112, 1714, 1607, 1528, 1117; **HRMS** calc for $C_{16}H_{13}NO_4$ $[M]^+$ 283.0845 found 283.0846; **Mp** 73-75°C.

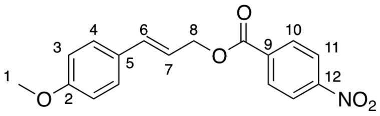
Allyl 4-nitrobenzoate (169)[225]



General procedure B was followed using 2-propen-1-ol (0.34 mL, 5 mmol), triethylamine (0.84 mL, 6 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (928 mg, 5 mmol, 1 eq.) in DCM (50 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (Et_2O:hexane, 10:1) to afford the product **169** (1.0 g, 97%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.82 (dt, *J* = 6.0, 1.0 Hz, 2H, *H3*), 5.28 (dq, *J* = 10.0, 1.0 Hz, 1H, *H1a/H1b*), 5.39 (dq, *J* = 1.0, 17.0 Hz, 1H, *H1a/H1b*), 5.96-6.06 (m, 1H, *H2*), 8.15-8.25 (m, 4H, *H5/6*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 66.3, 119.0, 123.5, 130.7, 131.5, 135.5, 150.5, 164.3.

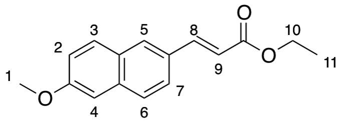
(2*E*)-3-(4-Methoxyphenyl)prop-2-en-1-yl 4-nitrobenzoate (168h)



To a solution of allyl 4-nitrobenzoate (**169**) (104 mg, 0.5 mmol) and 4-vinylanisole (200 µL, 1.5 mmol, 3 eq.) in DCM (4 mL) was added Grubbs' second generation catalyst (21 mg, 0.025 mmol, 5 mol%). The reaction was heated to reflux for 12 h. Upon cooling the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography to afford *p*-nitrobenzoate **168h** (63 mg, 34%) as a yellow solid.

^{1}H NMR (500MHz, CD_2Cl_2) δ: 3.86 (s, 3H, *H1*), 5.05 (d, *J* = 7.0 Hz, 2H, *H8*), 6.32 (dt, *J* = 7.0, 16.0 Hz, 1H, *H7*), 6.76 (d, *J* = 16.0 Hz, 1H, *H6*), 6.92 (d, *J* = 8.0 Hz, 2H, *H3*), 7.40 (d, *J* = 9.0 Hz, 2H, *H4*), 8.26-8.34 (m, 4H, *H10/11*); **^{13}C NMR** (125MHz) δ: 55.7, 67.2, 114.5, 120.4, 124.0, 128.4, 129.1, 131.2, 135.5, 136.1, 151.0, 160.3, 165.0; **IR** (KBr) ν 3112, 1714, 1607, 1528, 1117; **HRMS** calc for $C_{17}H_{15}NO_5$ $[M]^+$ 313.0950 found 313.0959; **Mp** 120-122°C.

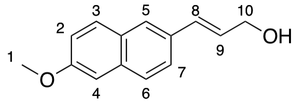
Ethyl (2*E*)-3-(6-methoxy-2-naphthyl)acrylate (166b)



General procedure **C** was followed using 6-methoxy-2-naphthaldehyde (559 mg, 3 mmol, 1.5 eq.) and (carbethoxymethylene)triphenylphosphorane (697 mg, 2 mmol) in toluene (30 mL). The reaction mixture was allowed to cool to rt and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (Et_2O:hexane, 10:1) to afford the acrylate product **166b** (530 mg, 75%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37 (t, *J* = 8.0 Hz, 3H, *H11*), 3.92 (s, 3H, *H1*), 4.30 (q, *J* = 8.0 Hz, 2H, *H10*), 6.50 (d, *J* = 16.0 Hz, 1H, *H9*), 7.11 (d, *J* = 16.0 Hz, 1H, *H8*), 7.16 (dd, *J* = 2.0, 9.0 Hz, 1H, *Ar-H*), 7.62 (dd, *J* = 1.0, 9.0 Hz, 1H, *Ar-H*) 7.70 (d, *J* = 9.0 Hz, 1H, *Ar-H*), 7.73 (d, *J* = 9.0 Hz, 1H, *Ar-H*), 7.79-7.84 (m, 2H, *Ar-H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 14.4, 55.3, 60.4, 105.9, 117.2, 119.4, 124.2, 127.5, 128.7, 129.7, 129.8, 130.1, 135.6, 144.8, 158.8, 167.2; **IR** ($CDCl_3$) ν 1708, 1624, 1170, 853, 815; **HRMS** calc for $C_{16}H_{16}O_3Na$ $[M+Na]^+$ 279.0997 found 279.0994; **Mp** 90-91°C.

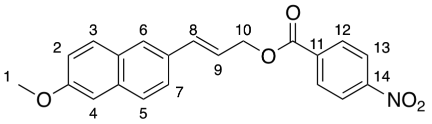
(2*E*)-3-(6-Methoxy-2-naphthyl)prop-2-en-1-ol (167b)



General procedure **D** was followed using ethyl (2*E*)-3-(6-methoxy-2-naphthyl)acrylate (**166b**) (769 mg, 4 mmol) and DIBAL-H (9.2 mL, 1M in toluene, 9.2 mmol, 2.3 eq.) in toluene (13 mL) at -78°C. The crude product was purified by silica gel column chromatography (EtOAc:hexane, 5:1) to afford allylic alcohol **167b** (857 mg, 98%) as a white solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.93 (s, 3H, *H1*), 4.37 (d, *J* = 4.0 Hz, 2H, *H10*), 6.45 (dt, *J* = 16.0, 4.0 Hz, 1H, *H9*), 6.75 (d, *J* = 16.0 Hz, 1H, *H8*), 7.10-7.17 (m, 2H, *Ar-H*), 7.57 (dd, *J* = 8.0, 4.0 Hz, 1H, *Ar-H*), 7.66-7.72 (m, 3H, *Ar-H*); **^{13}C NMR** (100 MHz, CDCl$_3$) δ: 55.3, 63.9, 105.9, 119.0, 124.1, 126.3, 127.1, 127.8, 129.0, 129.5, 131.5, 132.0, 134.2, 157.8; **IR** (CDCl$_3$) ν 3501, 1600; **HRMS** calc for $C_{14}H_{14}O_2$ $[M]^+$ 214.0994 found 214.0994; **Mp** 125-127°C.

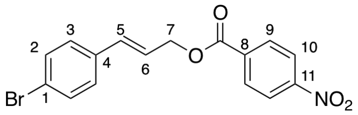
(2*E*)-3-(6-Methoxy-2-naphthyl)prop-2-en-1-yl 4-nitrobenzoate (168b)



General procedure **B** was followed using (2*E*)-3-(6-methoxy-2-naphthyl)prop-2-en-1-ol **167b** (64 mg, 0.3 mmol), triethylamine (50 µL, 0.36 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (56 mg, 0.3 mmol, 1 eq.) in DCM (2 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (EtOAc:hexane, 10:1) to afford the product **168b** (75 mg, 70%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.93 (s, 3H, *H1*), 5.08 (d, *J* = 8.0 Hz, 2H, *H10*), 6.48 (dt, *J* = 16.0, 8.0 Hz, 1H, *H9*), 6.90 (d, *J* = 16.0 Hz, 1H, *H8*), 7.12-7.18 (m, 2H, *Ar-H*), 7.60 (dd, *J* = 8.0, 1.0 Hz, 1H, *Ar-H*), 7.68-7.74 (m, 3H, *Ar-H*), 8.25-8.33 (m, 4H, *H12/13*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 55.3, 66.7, 105.9, 119.2, 121.5, 123.5, 124.0, 126.9, 127.2, 128.9, 129.6, 130.8, 131.2, 134.5, 135.6, 135.6, 150.6, 158.1, 164.6; **IR** ($CDCl_3$) ν 1631, 1550, 1271; **HRMS** calc for $C_{21}H_{17}NO_5$ $[M]^+$ 363.1107 found 363.1104; **Mp** 145-146°C.

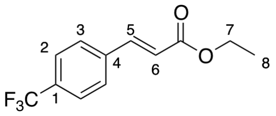
(2*E*)-3-(4-Bromophenyl)prop-2-en-1-yl 4-nitrobenzoate (168g)



To a solution of allyl 4-nitrobenzoate (**169**) (104 mg, 0.5 mmol) and 4-bromostyrene (0.2 mL, 1.5 mmol, 3 eq.) in DCM (4 mL) was added Grubbs' second generation catalyst (21 mg, 0.025 mmol, 5 mol%). The reaction was heated to reflux for 12 h. Upon cooling the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc:hexane, 5:1) to afford the *p*-nitrobenzoate **168g** (113 mg, 62%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.04 (dd, *J* = 1.0, 7.0 Hz, 2H, *H7*), 6.40 (dt, *J* = 7.0, 16.0 Hz, 1H, *H6*), 6.70 (d, *J* = 16.0 Hz, 1H, *H5*), 7.29 (d, *J* = 8.0 Hz, 2H, *H3*), 7.47 (d, *J* = 8.0 Hz, 2H, *H2*), 8.24-8.32 (m, 4H, *H9/10*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 66.2, 122.2, 123.2, 123.6, 128.2, 130.8, 131.8, 133.9, 134.8, 135.5, 150.6, 164.5; **IR** (KBr) ν 1751, 1525, 1270, 1099; **HRMS** calc for $C_{16}H_{12}NO_4Br$ $[M]^+$ 360.9950 found 360.9947; **Mp** 119-120°C

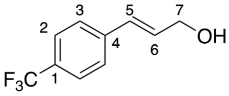
(2*E*)-3-[4-(Trifluoromethyl)phenyl]2-propenoate (166c)[226]



General procedure **C** was followed using 4-(trifluoromethyl)benzaldehyde (0.41 mL, 3 mmol, 1 eq.) and (carbethoxymethylene)triphenylphosphorane (1.05 g, 3 mmol) in toluene (25 mL). The reaction mixture was allowed to cool to rt and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (Et_2O:hexane, 1:10) to afford the acrylate product **166c** (366 mg, 50%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (t, *J* = 7.0 Hz, 3H, *H8*), 4.28 (q, *J* = 7.0 Hz, 2H, *H7*), 6.51 (d, *J* = 16.0 Hz, 1H, *H6*), 7.60-7.65 (m, 4H, *H2/3*), 7.69 (d, *J* = 16.0 Hz, 1H, *H5*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 60.8, 120.8, 125.8 (q, *J* = 4 Hz), 128.1, 129.9, 131.8, 137.8, 142.6, 166.4.

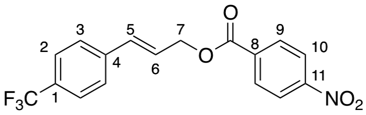
(2*E*)-3-[4-(Trifluoromethyl)phenyl]prop-2-en-1-ol (167c)[227]



General procedure **D** was followed using (2*E*)-3-[4-(trifluoromethyl)phenyl]2-propenoate (**166c**) (366 mg, 1.5 mmol) and DIBAL-H (3.3 mL, 1M in toluene, 3.3 mmol, 2.2 eq.) in toluene (4 mL) at -78°C. The crude product was purified by silica gel column chromatography (EtOAc:hexane, 1:5) afforded allylic alcohol **167c** (145 mg, 48%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (bs, 1H, *OH*), 4.35 (m, 2H, *H7*), 6.44 (dt, *J* = 16.0 Hz, 4Hz, 1H, *H6*), 6.64 (d, *J* = 16.0 Hz, 1H, *H5*), 7.44 (d, *J* = 8.0 Hz, 2H, *H3*), 7.55 (d, *J* = 8.0 Hz, 2H, *H2*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.2, 122.8, 125.5, 126.5, 129.2, 129.5, 131.2, 140.2.

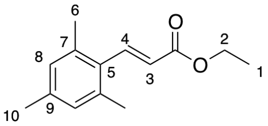
(2*E*)-3-[4-(Trifluoromethyl)phenyl]prop-2-en-1-yl 4-nitrobenzoate (168c)



General procedure **B** was followed using (2*E*)-3-[4-(trifluoromethyl)phenyl]prop-2-en-1-ol **167c** (392 mg, 1.9 mmol), triethylamine (0.32 mL, 2.3 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (353 mg, 1.9 mmol, 1 eq.) in DCM (20 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (DCM) to afford the product **168c** (375 mg, 55%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.11 (d, *J* = 6.0 Hz, 2H, *H7*), 6.56 (dt, *J* = 6.0, 16.0 Hz, 1H, *H6*), 6.84 (d, *J* = 16.0 Hz, 1H, *H5*), 7.54-7.64 (m, 4H, *H2/3*), 8.26-8.35 (m, 4H, *H9/10*); **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 65.9, 123.5, 124.0 (q, *J* = 272 Hz), 125.2, 125.5 (q, *J* = 4 Hz), 126.8, 129.9 (q, *J* = 32 Hz), 130.7, 133.2, 135.3, 139.4, 150.5, 164.3; **IR** (KBr) ν 1720, 1526, 1328, 1124, 785; **HRMS** calc for $C_{17}H_{12}NO_4F_3$ $[M]^+$ 351.0718 found 351.0714; **Mp** 70-72°C.

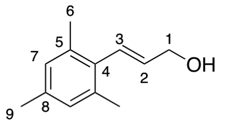
(*E*)-Ethyl 3-mesitylacrylate (166d)[228]



General procedure **C** was followed using mesitaldehyde (0.29 mL, 2 mmol, 1.5 eq.) and (carbethoxy methylene)triphenylphosphorane (697 mg, 2 mmol) in toluene (30 mL). The reaction mixture was allowed to cool to rt and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (Et_2O:hexane, 1:10) afforded acrylate **166d** (452 mg, 94%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.39 (t, *J* = 8.0 Hz, 3H, *H1*), 2.31 (s, 3H, *H10*), 2.36 (s, 6H, *H6*), 4.31 (q, *J* = 8.0 Hz, 2H, *H2*), 6.09 (d, *J* = 16.0 Hz, 1H, *H3*), 6.91 (s, 2H, *H8*), 7.89 (d, *J* = 16.0 Hz, 1H, *H4*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 14.3, 21.0, 21.1, 60.4, 123.2 (2C), 129.1, 136.8, 138.2, 143.1, 166.9.

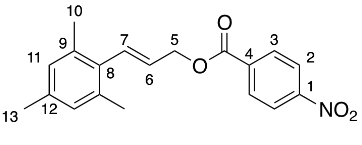
(*E*)-3-Mesitylprop-2-en-1-ol (167d)[228]



General procedure **D** was followed using ethyl (2*E*)-3-(6-methoxy-2-naphthyl)acrylate (**166d**) (310 mg, 1.4 mmol, 1 eq) and DIBAL-H (3 mL, 1M in toluene, 3 mmol, 2.2 eq) in toluene (4 mL) at -78°C. The crude product was purified by silica gel column chromatography (EtOAc:hexane, 1:5) and afforded allylic alcohol **167d** (75 mg, 30%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.06 (s, 3H, *H9*), 2.29 (s, 6H, *H6*), 4.35 (dd, *J* = 6.0 Hz, 2Hz, 2H, *H1*), 5.88 (dt, *J* = 16.0, 6.0 Hz, 1H, *H2*), 6.58 (s, 2H, *H7*), 6.89 (s, 1H, *H3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 20.9, 21.0, 64.0, 128.6, 128.6, 133.4, 133.5, 135.8, 136.2.

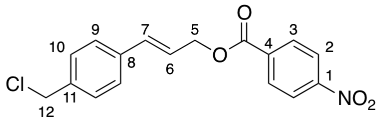
(2*E*)-3-Mesitylprop-2-en-1-yl 4-nitrobenzoate (168d)



General procedure **B** was followed using (*E*)-3-mesitylprop-2-en-1-ol **167d** (264 mg, 1.5 mmol), triethylamine (0.25 mL, 1.8 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (278 mg, 1.5 mmol, 1 eq.) in DCM (15 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (EtOAc:hexane, 1:5) to afford the product **168d** (312 mg, 63%) as a yellow solid.

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 2.36 (s, 3H, *H13*), 2.38 (s, 6H, *H10*), 5.14 (d, *J* = 6.0 Hz, 2H, *H5*), 6.01 (dt, *J* = 6.0, 16.0 Hz, 1H, *H6*), 6.86 (d, *J* = 16.0 Hz, 1H, *H7*), 6.95 (s, 2H, *H11*), 8.30-8.37 (m, 4H, *H2/3*); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ: 21.3, 21.4, 67.3, 124.0, 127.9, 129.2, 131.2, 133.1, 133.7, 136.3, 137.2, 151.0, 164.9; **IR** (KBr) ν 1720, 1607, 1523, 1345, 1101; **HRMS** calc for $C_{19}H_{19}NO_4$ $[M]^+$ 325.1314 found 325.1307; **Mp** 109-112°C.

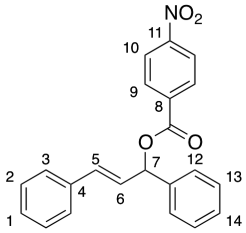
(2*E*)-3-[4-(Chloromethyl)phenyl]prop-2-en-1-yl 4-nitrobenzoate (168i)



To a solution of allyl 4-nitrobenzoate (**169**) (104 mg, 0.5 mmol) and 4-vinylbenzyl chloride (0.21 mL, 1.5 mmol, 3 eq.) in DCM (4 mL) was added Grubbs' second generation catalyst (21 mg, 0.025 mmol, 5 mol%). The reaction was heated to reflux for 12 hours. Upon cooling, the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc:hexane, 1:5) and afforded product **168i** (140 mg, 84%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.59 (s, 2H, *H12*), 5.05 (dd, *J* = 1.0, 7.0 Hz, 1H, *H5*), 6.43 (dt, *J* = 7.0, 16.0 Hz, 1H, *H6*), 6.77 (d, *J* = 16.0 Hz, 1H, *H7*), 7.36-7.44 (m, 4H, *H9/10*), 8.25-8.33 (m, 4H, *H2/3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 46.3, 66.8, 123.6, 124.0, 127.5, 129.4, 131.2, 134.9, 136.0, 136.6, 138.0, 151.0, 164.9; **IR** (KBr) ν 1718, 1521, 1268, 1100, 717; **HRMS** calc for $C_{17}H_{14}ClNO_4$ $[M]^+$ 331.0611 found 331.0611; **Mp** 110-111°C.

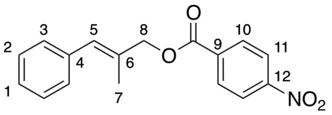
(2*E*)-1,3-Diphenylprop-2-en-1-yl 4-nitrobenzoate (168f)



General procedure **B** was followed using (*E*)-1,3-diphenylprop-2-en-1-ol (1 g, 5 mmol), triethylamine (0.84 mL, 6 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (928 mg, 5 mmol, 1 eq.) in DCM (50 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (DCM) to afford the product **168f** (1.13 g, 63%) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ: 6.55 (dd, *J* = 16.0, 8.0 Hz, 1H, *H7*), 6.76-6.84 (m, 2H, *H5/6*), 7.27-7.51 (m, 8H, *H2/3/12/13*), 7.57-7.61 (m, 2H, *H1/14*), 8.31 (s, 4H, *H9/10*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 78.0, 123.6, 126.8, 126.8, 127.1, 128.4, 128.6, 128.7, 128.9, 130.9, 133.7, 135.7, 136.0, 138.7, 150.6, 163.8; **HRMS** calc for $C_{22}H_{17}NO_4$ $[M]^+$ 359.1158 found 358.1161.

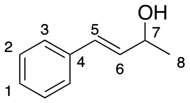
(2*E*)-2-Methyl-3-phenylprop-2-en-1-yl 4-nitrobenzoate (168e)



General procedure **B** was followed using *trans*-2-methyl-3-phenyl-2-propen-1-ol (0.43 mL, 3 mmol), triethylamine (0.5 mL, 3.6 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (557 mg, 3 mmol, 1 eq.) in DCM (30 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (DCM) to afford the product **168e** (641 mg, 72%) as a yellow solid.

^{1}H NMR (400MHz, $CDCl_3$) δ: 2.01 (s, 3H, *H7*), 4.96 (s, 2H, *H8*), 6.66 (s, 1H, *H5*), 7.25-7.39 (m, 5H, *H1/2/3*), 8.26-8.33 (m, 4H, *H10/11*); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 15.7, 71.6, 123.6, 127.0, 128.2, 128.9, 129.3, 130.8, 132.1, 135.6, 136.7, 150.6, 164.5; **IR** (KBr) ν 1709, 1605, 1524, 1283; **HRMS** calc for $C_{17}H_{15}NO_4$ $[M]^+$ 297.1001 found 297.1006; **Mp** 106-107°C.

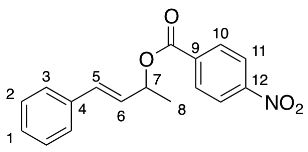
(3*E*)-4-phenylbut-3-en-2-ol[3] (170)



To a solution of (3*E*)-4-phenyl-3-butene-2-one (1 g, 7 mmol, 1 eq) in methanol (4 mL, 1.75 M) was added sodium borohydride (278 mg, 7.35 mmol, 1.05 eq) and the reaction stirred for 2 h at 0-10 °C. After this time dilute HCl (5%) was added and the aqueous and organic layers separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and organics combined. The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (EtOAc:hexane, 1:5) affording allylic alcohol **170** (964 mg, 93%) as a yellow oil.[4]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (d, *J* = 6.5 Hz, 3H, *H8*), 2.11 (br s, 1H, O*H*), 4.49 (ddq, *J* = 6.5 Hz, 1.0 Hz, 1H, *H7*), 6.27 (dd, *J* = 16.0 Hz, 6.5 Hz, 1H, *H6*), 6.57 (d, *J* = 16.0 Hz, 1H, *H5*), 7.24 (tt, *J* = 7.0, 1.5 Hz, 1H, *H1*), 7.32 (td, *J* = 7.0, 1.5 Hz, 2H, *H3*), 7.39 (dt, *J* = 7.0, 1.5 Hz, 2H, *H2*). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 23.4, 68.8, 126.4, 127.6, 128.6, 129.3, 133.6, 136.7.

(3*E*)-4-Phenylbut-3-en-2-yl 4-nitrobenzoate (171)



General procedure **B** was followed using (3*E*)-4-phenylbut-3-en-2-ol **170** (296 mg, 2 mmol), triethylamine (0.33 mL, 2.4 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (371 mg, 2 mmol, 1 eq.) in DCM (20 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (DCM) to afford the product **171** (434 mg, 73%) as a yellow solid.

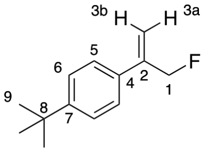
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60 (d, *J* = 6.0 Hz, 3H, *H8*), 5.83 (q, *J* = 6.0 Hz, 1H, *H7*), 6.32 (dd, *J* = 16.0, 7.0 Hz, 1H, *H6*), 6.74 (d, *J* = 16.0 Hz, 1H, *H5*), 7.24-7.44 (m, 5H, *H1/2/3*), 8.23-8.34 (m, 4H, *H10/11*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 20.4, 73.0, 123.5, 126.7, 128.0, 128.2, 128.6, 130.7, 132.6, 136.0, 150.5, 164.0, 167.7; **IR** (KBr) ν 2982, 1721, 1607; **HRMS** calc for $C_{17}H_{15}NO_4Na$ $[M+Na]^+$ 320.0889 found 320.0893; **Mp** 57-59°C.

5.2.3 Allylic Fluorides from Pd-catalysed fluorination

General Procedure E for the synthesis of allylic fluorides

To a solution of allylic benzoate (0.2 mmol) in THF (2 mL) was added $Pd(dba)_2$ (5 mol%) and PPh_3 (15 mol%). TBAF(*t*-BuOH)$_4$ (**160**) (2.5 eq, 0.5 mmol) was then added in one portion. The reaction was allowed to stir at rt for 1 hr. The reaction was quenched by the addition of NH_4Cl(aq). The aqueous layer was extracted with Et_2O (2 x 5 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. Crude products were purified by silica gel column chromatography. Addition of 5% triethylamine to the column eluent was necessary for unstable substrates.

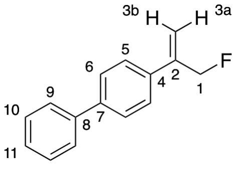
1-*tert*-Butyl-4-(3-fluoroprop-1-en-2-yl)benzene (158a)



General procedure **E** was followed using 2-(4-*tert*-butylphenyl)prop-2-en-1-yl 4-nitrobenzoate **157e** (68 mg, 0.2 mmol), Pd(dba)$_2$ (6 mg, 0.01 mmol, 5 mol%), PPh$_3$ (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **158a** (37 mg, 95%) as a colourless oil.

^{1}H NMR (500 MHz, CD$_2$Cl$_2$) δ: 1.41 (s, 9H, *H9*), 5.31 (dd, *J* = 47.0, 1.0 Hz, 2H, *H1*), 5.45-5.47 (m, 1H, *H3a/H3b*), 5.67 (s, 1H, *H3a/H3b*), 7.47 (s, 4H, *H5/6*); **^{13}C NMR** (125 MHz, CD$_2$Cl$_2$) δ: 31.3, 34.6, 84.4 (d, *J* = 175 Hz), 114.5 (d, *J* = 10 Hz), 125.5, 125.6, 134.3 (d, *J* = 3 Hz), 142.8 (d, *J* = 15 Hz), 151.3; **^{19}F NMR** (471 MHz, CD$_2$Cl$_2$) δ: -212.8 (td, *J* = 47.0, 3.0 Hz); **IR** (CD$_2$Cl$_2$) ν 1632, 1268, 838; **HRMS** calc for $C_{13}H_{17}F$ [M]$^+$ 192.1314 found 192.1310.

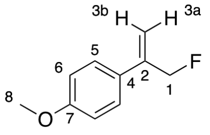
4-(3-Fluoroprop-1-en-2-yl)biphenyl (158c)



General procedure **E** was followed using 2-(biphenyl-4-yl)prop-2-en-1-yl 4-nitrobenzoate **163b** (72 mg, 0.2 mmol), Pd(dba)$_2$ (6 mg, 0.01 mmol, 5 mol%), PPh$_3$ (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **158c** (40 mg, 95%) as a white solid.

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 5.34 (d, *J* = 47.0 Hz, 2H, *H1*), 5.49-5.51 (m, 1H, *H3a/H3b*), 5.74 (s, 1H, *H3a/H3b*), 7.40-7.72 (m, 9H, *H5/6/9/10/11*); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ: 84.9 (d, *J* = 167 Hz), 115.8 (d, *J* = 11 Hz), 126.7, 127.3, 127.5, 127.9, 129.2, 136.6 (d, *J* = 2 Hz), 140.8, 141.3, 143.1 (d, *J* = 15 Hz); **^{19}F NMR** (471 MHz, CD_2Cl_2) δ: -212.5 (td, *J* = 47.0, 3.0 Hz); **IR** (CD_2Cl_2) ν 1487, 1261, 1104, 1033; **HRMS** calc for $C_{15}H_{13}F$ $[M]^+$ 212.1001 found 212.1005; **Mp** 86-88°C.

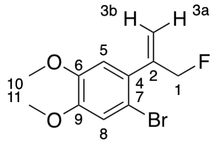
1-(3-Fluoroprop-1-en-2-yl)-4-methoxybenzene (158d)



General procedure **E** was followed using 2-(4-methoxyphenyl)prop-2-en-1-yl 4-nitrobenzoate **163c** (63 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol, 5 mol%), PPh_3 (8 mg, 0.03 mmol, 15 mol%), and $TBAF(tBuOH)_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **158d** (28 mg, 85%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.83 (s, 3H, *H8*), 5.23 (dm, *J* = 47.0 Hz, 2H, *H1*), 5.33-5.35 (m, 1H, *H3a/H3b*), 5.53 (s, 1H, *H3a/H3b*), 6.90 (m, *J* = 9.0 Hz, 2H, *H5*), 7.41 (m, *J* = 9.0 Hz, 2H, *H6*); **^{13}C NMR** (100 MHz, $CDCl_3$) 55.3, 84.6 (d, *J* = 170 Hz), 113.7 (d, *J* = 11 Hz), 113.9, 127.1, 129.7, 142.3 (d, *J* = 12 Hz), 159.6; **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ: -212.2 (dt, *J* = 47.0, 3.0 Hz); **IR** (CD_2Cl_2) ν 1609, 1514, 1251, 1182, 1029; **HRMS** calc for $C_{10}H_{11}OF$ $[M]^+$ 166.0794 found 166.0799.

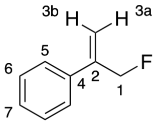
1-Bromo-2-(3-fluoroprop-1-en-2-yl)-4,5-dimethoxybenzene (158e)



General procedure **E** was followed using 2-(2-bromo-4,5-dimethoxyphenyl)prop-2-en-1-yl 4-nitrobenzoate **163d** (84 mg, 0.2 mmol), Pd(dba)$_2$ (6 mg, 0.01 mmol, 5 mol%), PPh$_3$ (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **158e** (46 mg, 84%) as a colourless oil.

^{1}H NMR (400 MHz, CD$_2$Cl$_2$) δ: 3.84 (s, 3H, *H10/11*), 3.86 (s, 3H, *H10/11*), 5.12 (d, *J* = 47.0 Hz, 2H, *H1*), 5.29 (s, 1H, *H3a/H3b*), 5.60 (s, 1H, *H3a/H3b*), 6.78 (s, 1H, *H5*), 7.08 (s, 1H, *H8*); **^{13}C NMR** (100 MHz, CD$_2$Cl$_2$) δ: 56.4, 56.5, 84.6 (d, *J* = 171 Hz), 112.3, 114.2, 116.1, 118.1 (d, *J* = 9 Hz), 131.7 (d, *J* = 4 Hz), 145.2 (d, *J* = 16 Hz), 148.9, 149.8; **^{19}F NMR** (376.5 MHz, CD$_2$Cl$_2$) δ: -213.9 (tm, *J* = 49.0 Hz); **IR** (CD$_2$Cl$_2$) ν 1505, 1248, 1130, 1032; **HRMS** calc for $C_{11}H_{12}O_2FBr$ [M]$^+$ 274.0005 found 274.0009.

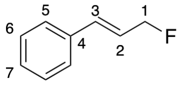
(3-Fluoroprop-1-en-2-yl)benzene (158b)[229]



General procedure **E** was followed using 2-phenylprop-2-en-1-yl 4-nitrobenzoate **163a** (57 mg, 0.2 mmol), Pd(dba)$_2$ (6 mg, 0.01 mmol, 5 mol%), PPh$_3$ (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography to afford allylic fluoride **158b** (18 mg, 66%) as a colourless oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 5.28 (dd, *J* = 47.0, 1.0 Hz, 2H, *H1*), 5.44-5.46 (m, 1H, *H3a/H3b*), 5.66 (s, 1H, *H3a/H3b*), 7.34-7.52 (m, 5H, *H5/6/7*); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 84.9 (d, *J* = 171 Hz), 115.6 (d, *J* = 10 Hz), 126.3, 128.6, 128.9, 137.7, 143.5 (d, *J* = 10 Hz); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ: -212.7 (td, *J* = 47.0, 3.0 Hz).

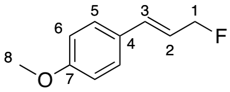
[(1*E*)-3-Fluoroprop-1-en-1-yl]benzene (172a)[230]



General procedure **E** was followed using (2*E*)-3-phenylprop-2-en-1-yl 4-nitrobenzoate **168a** (57 mg, 0.2 mmol), Pd(dba)$_2$ (6 mg, 0.01 mmol, 5 mol%), PPh_3 (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **172a** (26 mg, 95%) as a colourless oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 5.06 (ddd, *J* = 2.0, 6.0, 47.0 Hz, 2H, *H1*), 6.45 (ddt, *J* = 6.0, 12.0, 16.0 Hz, 1H, *H2*), 6.75 (dd, *J* = 5.0, 16.0 Hz, 1H, *H3*), 7.33 (t, *J* = 7.0 Hz, 2H, *H6*), 7.39 (t, *J* = 7.0 Hz, 1H, *H7*), 7.47 (d, *J* = 7.0 Hz, 2H, *H5*); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 83.9, (d, *J* = 162 Hz), 124.1, 127.1, (d, *J* = 2 Hz), 128.7, 129.0, 134.5 (d, *J* = 12 Hz), 136.4 (d, *J* = 2 Hz), **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ: -210.8 (ttd, *J* = 47.0, 12.0, 5.0 Hz); **HRMS** calc for C_9H_9F $[M]^+$ 136.0688 found 136.0691.

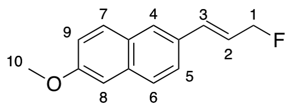
1-[(1*E*)-3-Fluoroprop-1-en-1-yl]-4-methoxybenzene (172b)



General procedure **E** was followed using (2*E*)-3-(4-methoxyphenyl)prop-2-en-1-yl 4-nitrobenzoate **168h** (63 mg, 0.2 mmol), Pd(dba)$_2$ (6 mg, 0.01 mmol, 5 mol%), PPh_3 (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **172b** (13 mg, 39%) as a colourless oil.

^{1}H NMR (500 MHz, CD$_2$Cl$_2$) δ: 3.84 (s, 3H, *H8*), 5.02 (ddd, *J* = 1.0, 6.0, 47.0 Hz, 2H, *H1*), 6.41 (ddt, *J* = 16.0, 13.0, 6.0 Hz, 1H, *H2*), 6.69 (dd, *J* = 16.0, 6.0 Hz, 1H, *H3*), 6.91 (d, *J* = 9.0 Hz, 2H, *H5*), 7.41 (d, *J* = 9.0 Hz, 2H, *H6*); **^{13}C NMR** (125 MHz, CD$_2$Cl$_2$) δ: 55.6, 84.2 (d, *J* = 160 Hz), 114.4, 121.6, 128.4, 129.1, 134.7 (d, *J* = 13 Hz), 160.3; **^{19}F NMR** (470 MHz, CD$_2$Cl$_2$) δ: -208.2 (tm, *J* = 47.0 Hz); **IR** (CD$_2$Cl$_2$) ν 1655, 1606, 1512, 1253, 952; **HRMS** calc for $C_{10}H_{11}OF$ [M]$^+$ 166.0794 found 166.0796.

2-[(1*E*)-3-Fluoroprop-1-en-1-yl]-6-methoxynaphthalene (172d)

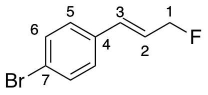


General procedure **E** was followed using (2*E*)-3-(6-methoxy-2-naphthyl)prop-2-en-1-yl 4-nitrobenzoate **168b** (73 mg, 0.2 mmol), Pd(dba)$_2$ (6 mg, 0.01 mmol, 5 mol%), PPh$_3$ (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **172d** (20 mg, 46%) as a white solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.95 (s, 3H, *H10*), 5.09 (dd, *J* = 44.0, 8.0 Hz, 2H, *H1*), 6.43-6.55 (m, 1H, *H2*), 6.86 (dd, *J* = 16.0, 4.0 Hz, 1H, *H3*), 7.15-7.20 (m, 2H, *Ar-H*), 7.61-7.65 (m, 1H, *Ar-H*), 7.73-7.78 (m, 3H, *Ar-H*); **^{13}C NMR** (125 MHz CDCl$_3$) δ: 55.3, 84.1 (d, *J* = 160 Hz), 105.8, 119.1, 123.4 (d, *J* = 15 Hz), 124.0, 126.9 (d, *J* = 3 Hz), 127.1, 128.8, 129.5, 131.3 (d, *J* = 2 Hz), 134.5 (d, *J* = 12 Hz), 134.6, 158.1; **^{19}F NMR** (376.5 MHz, CDCl$_3$) δ: -

209.4 (tdd, *J* = 45.0, 11.0, 8.0 Hz); **IR** (KBr) ν 1625, 1264, 1109, 950; **HRMS** calc for $C_{14}H_{13}OF$ $[M]^+$ 216.0950 found 216.0949; **Mp** 94-96°C.

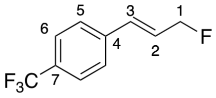
1-Bromo-4-[(1*E*)-3-fluoroprop-1-en-1-yl]benzene (172e)



General procedure **E** was followed using (2*E*)-3-(4-bromophenyl)prop-2-en-1-yl 4-nitrobenzoate **168g** (72 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol, 5 mol%), PPh_3 (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **172e** (23 mg, 53%) as a white solid.

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 5.04 (ddd, *J* = 1.0, 6.0, 47.0 Hz, 2H, *H1*), 6.41 (ddt, *J* = 6.0, 16.0, 28.0 Hz, 1H, *H2*), 6.68 (dd, *J* = 5.0, 16.0 Hz, 1H, *H3*), 7.34 (d, *J* = 8.0 Hz, 2H, *H5*), 7.51 (d, *J* = 8.0 Hz, *H6*); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 83.7 (d, *J* = 163 Hz), 122.4, 125.0 (d, *J* = 16 Hz), 128.7 (d, *J* = 2 Hz), 132.1, 133.0 (d, *J* = 12 Hz), 135.0; **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ: -212.0 (tdd, *J* = 47.0, 13.0, 5.0 Hz); **IR** (CD_2Cl_2) ν 1487, 1116, 964; **HRMS** calc for C_9H_8BrF $[M]^+$ 213.9793 found 213.9794; **Mp** 44-46 °C.

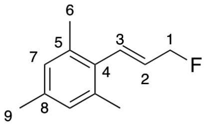
1-[(1*E*)-3-Fluoroprop-1-en-1-yl]-4-(trifluoromethyl)benzene (172c)



General procedure **E** was followed using (2*E*)-3-[4-(trifluoromethyl)phenyl]prop-2-en-1-yl 4-nitrobenzoate **168c** (70 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol, 5 mol%), PPh_3 (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **172c** (14 mg, 35%) as a colourless oil.

^{1}H NMR (500 MHz, CD_2Cl_2) δ: 5.09 (ddd, *J* = 47.0, 6.0, 1.0 Hz, 2H, *H1*), 6.52 (ddt, *J* = 16.0, 14.0, 6.0 Hz, 1H, *H2*), 6.78 (dd, *J* = 16.0, 4.0 Hz, 1H, *H3*), 7.58 (d, *J* = 8.0 Hz, 2H, *H6*), 7.65 (d, *J* = 8.0 Hz, 2H, *H5*); **^{13}C NMR** (125MHz, CD_2Cl_2) δ: 83.6 (d, *J* = 164 Hz), 124.8 (q, *J* = 272 Hz), 126.1 (q, *J* = 4 Hz), 127.1 (d, *J* = 13 Hz), 127.5, 130.2 (q, *J* = 32 Hz), 132.4 (d, 12 Hz), 140.3; **^{19}F NMR** (471 MHz, CD_2Cl_2) δ: -213.9 (td, *J* = 47.0, 13.0 Hz), -62.9; **HRMS** calc for $C_{10}H_8F_4$ $[M]^+$ 204.0562 found 204.0565.

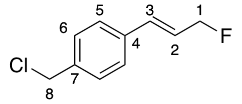
2-[(1*E*)-3-Fluoroprop-1-en-1-yl]-1,3,5-trimethylbenzene (172g)



General procedure **E** was followed using (2*E*)-3-mesitylprop-2-en-1-yl 4-nitrobenzoate **168d** (65 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol, 5 mol%), PPh_3 (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **172g** (23 mg, 65%) as a colourless oil.

^{1}H NMR (500 MHz, CD_2Cl_2) δ: 2.30 (s, 6H, *H6*), 2.31 (s, 3H, *H9*), 5.06 (dd, *J* = 6.0, 47.0 Hz, 2H, *H1*), 5.89-5.98 (m, 1H, *H2*), 6.63-6.80 (m, 1H, *H3*), 6.82-6.89 (m, 2H, *H7*); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ: 20.5, 20.6, 83.7 (d, *J* = 161 Hz), 128.6, 128.7 (d, *J* = 16 Hz), 132.5 (d, *J* = 13 Hz), 132.6, 135.8, 136.6; **^{19}F NMR** (470 MHz, CD_2Cl_2) δ: -209.78 (tdd, *J* = 47.0, 14.0, 9.0 Hz); **IR** (CD_2Cl_2) ν 1612, 1460, 1116, 976; **HRMS** calc for $C_{12}H_{15}F$ $[M]^+$ 178.1158 found 178.1159.

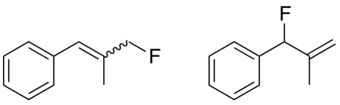
1-(Chloromethyl)-4-[(1*E*)-3-fluoroprop-1-en-1-yl]benzene (172f)



General procedure **E** was followed using (2*E*)-3-[4-(chloromethyl)phenyl]prop-2-en-1-yl 4-nitrobenzoate **168i** (66 mg, 0.2 mmol), Pd(dba)$_2$ (6 mg, 0.01 mmol, 5 mol%), PPh$_3$ (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **172f** (22 mg, 60%) as a colourless oil.

^{1}H NMR (400 MHz, CD$_2$Cl$_2$) δ: 4.64 (s, 2H, *H8*), 5.04 (ddd, *J* = 47.0, 6.0, 1.0 Hz, 2H, *H1*), 6.44 (ddt, *J* = 16.0, 12.0, 6.0 Hz, 1H, *H2*), 6.73 (dd, *J* = 16.0, 5.0 Hz, 1H, *H3*), 7.39-7.48 (m, 4H, *H5/6*); **^{13}C NMR** (100 MHz, CD$_2$Cl$_2$) δ: 46.4, 83.8 (d, *J* = 162 Hz), 124.8 (d, *J* = 16 Hz), 127.4 (d, *J* = 2 Hz), 129.4, 133.6 (d, *J* = 13 Hz), 136.6 (d, *J* = 2 Hz), 138.0; **^{19}F NMR** (376.5 MHz, CD$_2$Cl$_2$) δ: -211.6 (tdd, *J* = 47.0, 12.0, 5.0 Hz); I**R** (CD$_2$Cl$_2$) ν 2957, 1657, 1266, 968; **HRMS** calc for $C_{10}H_{10}FCl$ $[M]^+$ 184.0455 found 184.0448.

[3-Fluoro-2-methylprop-1-en-1-yl]benzene (*E/Z*-172) and [1-fluoro-2-methylprop-1-en-1-yl]benzene (173)

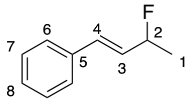


General procedure **E** was followed using (2*E*)-3-[4-(chloromethyl)phenyl]prop-2-en-1-yl 4-nitrobenzoate **168e** (66 mg, 0.2 mmol), Pd(dba)$_2$ (6 mg, 0.01 mmol, 5 mol%), PPh$_3$ (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. To the resulting crude mixture was added 20 mol% of 3-nitro-1-fluorobenzene as an internal reference and the mixture analysed by ^{19}F NMR.

Products were tentatively assigned as ***E*-172:*Z*-172:173** based on the ^{19}F NMR spectra in a combined ^{19}F NMR yield of 21%.

^{19}F NMR (376.5 MHz, CD_2Cl_2) δ: -173.68 (d, *J* = 47.0 Hz) (*benzylic fluoride-**45***); -212.72 (td, *J* = 48.0, 4.0 Hz) (*allylic fluoride-**44a***); -214.17 (t, *J* = 47.0 Hz) (*allylic fluoride-**44b***). Ratio of fluorinated products: ***E*-172:*Z*-172:173** = 4.6:1.2:1

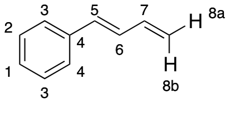
[(1*E*)-3-Fluorobut-1-en-1-yl]benzene[47] (172)



General procedure **E** was followed using (3*E*)-4-phenylbut-3-en-2-yl 4-nitrobenzoate **171** (66 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol, 5 mol%), PPh_3 (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. To the resulting crude mixture was added 20 mol% of 3-nitro-1-fluorobenzene as an internal reference and the mixture analysed by ^{19}F NMR.

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 1.48 (dd, *J* = 23.5, 6.5 Hz, 3H, *H1*), 5.21 (ddq, *J* = 48.0, 6.5 Hz, 1.0 Hz, 1H, *H2*), 6.26 (ddd, *J* = 16.0, 12.0, 6.5 Hz, 1H, *H3*), 6.53 (dd, *J* = 16.0, 6.0 Hz, 1H, *H4*), 7.17-7.43 (m, 5H, *H6/7/8*). **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ: -163.47 (s); **LRMS** calculated for $C_{10}H_{11}F$ $[M]^+$ 150.0845, found 150.0844.

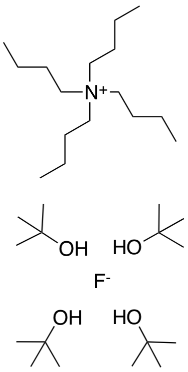
(1*E*)-Buta-1,3-dien-1-yl benzene[98] (195)



Diene **195** was observed as a side product in the allylic fluorination reactions using general procedure **E**. It was isolated as a yellow oil.

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 5.18 (dd, *J* = 10.0, 0,5 Hz, 1H, *H8a*), 5.34 (dd, *J* = 17.0, 0.5 Hz, 1H, *H8b*), 6.52 (ddd, *J* = 17.0, 11.0, 10.0 Hz, 1H, *H7*), 6.58 (d, *J* = 16.0 Hz, 1H, *H5*), 6.80 (dd, *J* = 16.0, 11.0 Hz, 1H, *H6*), 7.22-7.60 (m, 5H, *H1/2/3*); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 117.7, 126.6, 127.8, 128.5, 128.7, 129.8, 133.0, 137.3.

TBAF(*t*BuOH)$_4$ (160)[44,45]



TBAF hydrate (5.0 g, 15 mmol) was added to *t*BuOH (440 mL) and hexane (110 mL). The mixture was stirred for 30 min at 90° C, after which the solution was cooled to room temperature, and a white crystalline solid precipitated, which was filtered and washed rapidly with 200 mL of 70% *t*BuOH/hexane. The filtrate was kept in vacuum for 15–20 min to remove residual solvent, and TBAF(*t*BuOH)$_4$ (8.33 g, >95%) was obtained as a white crystalline solid.

^{1}H NMR (400 MHz, CD_3CN); δ 1.08 (t, *J* = 7.5 Hz, 12H), 1.17 (s, 36H), 1.32-1.42 (m, 8H), 1.58-1.66 (m, 8H), 1.95-1.99 (m, 4H, *OH*), 3.10-3.14 (m, 8H); **^{13}C NMR** (100 MHz, CD_3CN); δ 13.3, 19.7, 23.8, 31.1, 58.7 (t, *J* = 3 Hz), 67.3.

Fluorination of cinnamyl bromide and cinnamyl chloride

To a solution of cinnamyl halide (0.2 mmol) in THF (2 mL) was added Pd(dba)$_2$ (5 mol%) and PPh_3 (15 mol%). TBAF(*t*-BuOH)$_4$ (2.5 eq, 0.5 mmol) was then added in one portion. The reaction was allowed to stir at rt for 1 hr. The reaction was quenched by the addition of

$NH_4Cl_{(aq)}$. The aqueous layer was extracted with Et_2O (2 x 5 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. Conversion to product was taken from crude ^1H NMR.

Cinnamyl chloride – Product: Starting material – 1:6

Cinnamyl bromide - Product: Starting material – 1:3

To a solution of cinnamyl halide (0.2 mmol) in THF (2 mL) was added TBAF(*t*-BuOH)$_4$ (2.5 eq, 0.5 mmol) in one portion. The reaction was allowed to stir at rt for 1 hr. The reaction was quenched by the addition of $NH_4Cl_{(aq)}$. The aqueous layer was extracted with Et_2O (2 x 5 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. Crude products were purified by silica gel column chromatography. Addition of 5% triethylamine to the column eluent was necessary. Conversion to product was taken from crude ^1H NMR.

Cinnamyl chloride - Product: Starting material – 1:81

Cinnamyl bromide - Product: Starting material – 1:2

To a solution of cinnamyl halide (0.2 mmol) in MeCN (2 mL) was added TBAF$(H_2O)_3$ (2.5 eq, 0.5 mmol) in one portion. The reaction was allowed to stir at rt for 1 hr. The reaction was quenched by the addition of $NH_4Cl_{(aq)}$. The aqueous layer was extracted with Et_2O (2 x 5 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. Crude products were purified by silica gel column chromatography. Addition of 5% triethylamine to the column eluent was necessary. Conversion to product was taken from crude ^1H NMR.

Cinnamyl chloride - Product: Starting material – 1:26

Cinnamyl bromide - Product: Starting material – 1:3

5.2.4 Characterisation of β-hydride elimination studies

The experimental data detailed in this section was obtained by Miriam O Duill (Chemistry Part II, University of Oxford, 2011).

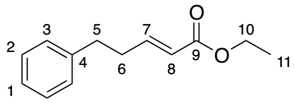
General Procedure F for the synthesis of allylic *3,5*-dinitrobenzoates

To a solution of allylic alcohol (1 mmol) and triethylamine (1 mmol) in DCM (10 mL) was added 3,5-nitrobenzoyl chloride (1 mmol) portion wise at 0°C. The reaction was allowed to warm at rt and stirred until complete by TLC. The reaction mixture was diluted with DCM and then washed successively by $NaHCO_3$(aq), H_2O and brine. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. Crude products were purified by silica gel column chromatography where necessary.

General Procedure G for the synthesis of allylic pentafluorobenzoates

Allylic alcohol (1 mmol, 1eq.), pentafluorobenzoic acid (1.1 mmol. 1.1 eq), DCC (1.1 mmol, 1.1 eq.) and DMAP (0.12 mmol, 0.12 eq.) were dissolved in DCM (0.1M) and stirred at rt for 24 h. Reactions were filtered through silica, concentrated and purified by flash chromatography to afford the desired product.

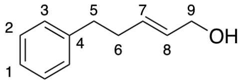
Ethyl (3*E*)-5-phenylpent-2-enoate[231] (166g)



General procedure **C** was followed using 3-phenylpropionaldehyde (0.4 mL, 3 mmol, 1 eq.) and (carbethoxymethylene)triphenylphosphorane (1.05 g, 3 mmol) in toluene (25 mL). The reaction mixture was allowed to cool rt and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (Et_2O:hexane, 1:10) to afford the acrylate product **166g** (542 mg, 88%) as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.50 (t, *J* = 7.0 Hz, 3H, *H11*), 2.54 (ddt, *J* = 7.0 Hz, 6.0 Hz, 1.5 Hz, 2H, *H6*), 2.79 (dt, *J* = 7.0, 3.0 Hz, 2H, *H5*), 4.20 (q, *J* = 7.0 Hz, 2H, *H10*), 5.87 (dt, *J* = 15.5, 1.5 Hz, 1H, *H8*), 7.02 (dt, *J* = 15.5, 6.0 Hz, 1H, *H7*), 7.19-7.24 (m, 3H, *H1/3*), 7.31 (dt, *J* = 7.5, 1.5 Hz, 2H, *H2*); **^{13}C NMR** (100 MHz, CDCl$_3$) δ: 14.3, 33.9, 34.3, 60.2, 121.8, 126.2, 128.3, 128.5, 140.8, 148.0, 166.6.

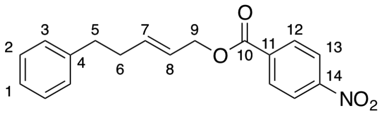
(2*E*)-5-phenylpent-2-en-1-ol[231] (167g)



General procedure **D** was followed using ethyl (3*E*)-5-phenylpent-2-enoate **166g** (2.44 mmol, 1 eq) and DIBAL-H (5.1 mL, 1M in toluene, 5.12 mmol, 2.1 eq.) in toluene (8 mL) at -78°C. The crude product was purified by silica gel column chromatography (EtOAc:hexane, 1:5) afforded allylic alcohol **167g (**190 mg, 73%) as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.89 (br s, 1H, O*H*), 2.46-2.57 (m, 2H, *H5*), 2.74 (dt, *J* = 9.5, 7.5 Hz, 2H, *H6*), 4.09 (d, *J* = 5.5 Hz, 2H, *H9*), 5.61-5.80 (m, 2H, *H7/8*), 7.21-7.34 (m, 5H, *H1/2/3*); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 34.0, 35.6, 63.6, 125.9, 128.4, 128.4, 139.6, 132.1, 141.7.

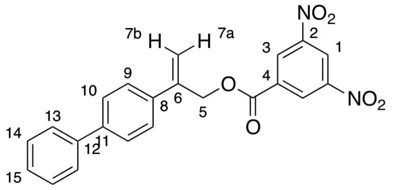
(2*E*)-5-Phenylpent-2-en-1-yl 4-nitrobenzoate (168g)



General procedure **B** was followed using (2*E*)-5-phenylpent-2-en-1-ol **167g** (341 mg, 2.1 mmol), triethylamine (0.35 mL, 2.5 mmol, 1.2 eq.) and 4-nitrobenzoyl chloride (390 mg, 2.1 mmol, 1 eq.) in DCM (20 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (DCM) to afford the product **168g** (529 mg, 81%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (ddt, *J* = 8.0, 5.0, 1.0 Hz, 2H, *H6*), 2.76 (dt, *J* = 8.0, 1.0 Hz, 2H, *H5*), 4.82 (dd, *J* = 6.5, 1.0 Hz, 2H, *H9*), 5.74 (dtt, *J* = 15.5, 6.5, 1.0 Hz, 1H, *H8*), 5.95 (dtt, *J* = 15.5, 5.0, 1.0 Hz, 1H, *H7*), 7.18-7.32 (m, 5H, *H1/2/3*), 8.20-8.31 (m, 4H, *H12/13*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 34.0, 35.2, 66.5, 123.5, 123.9, 126.0, 128.4, 128.4, 130.7, 135.7, 136.4, 141.3, 150.5, 164.5; **IR** (neat) ν 1714, 1520, 1271, 1102; **HRMS** calc for $C_{18}H_{17}NNaO_4$ $[M+Na]^+$ 334.1050, found: 334.1049; **Mp** 54-59° C.

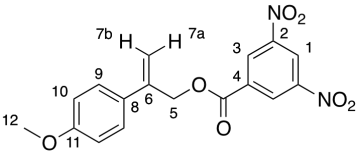
2-(Biphenyl-4-yl)prop-2-en-1-yl 3,5-dinitrobenzoate (177)



General procedure **F** was followed using 2-(biphenyl-4-yl)prop-2-en-1-ol **162b** (231 mg, 1.1 mmol), triethylamine (0.18 mL, 1.3 mmol, 1.2 eq.) and 3,5-dinitrobenzoyl chloride (254 mg, 1.1 mmol, 1 eq.) in DCM (11 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (DCM) to afford the product **177** (352 mg, 79%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.41 (s, 2H, *H5*), 5.55 (s, 1H, *H7a/7b*), 5.77 (s, 1H, *H7a/7b*), 7.36 (tt, *J* = 7.5, 2.0 Hz, 1H, *H15*), 7.43-7.47 (m, 2H, *H14*), 7.57-7.64 (m, 6H, *H9/10/13*), 9.13 (d, *J* = 2.0 Hz, 2H, *H3*), 9.20 (dd, *J* = 2.5, 2.0 Hz, 1H, *H1*). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 67.9, 116.8, 122.5, 126.4, 127.0, 127.3, 127.6, 129.0, 129.5, 133.7, 136.2, 140.2, 141.2, 141.3, 148.7, 162.3; **IR** (KBr) ν 3097, 1628, 1726, 1548, 1346, 1169; **HRMS** calc for $C_{22}H_{16}N_2O_6$ $[M]^+$ 404.1008, found 404.1009; **Mp** 133-137 ° C.

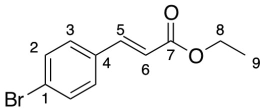
2-(4-Methoxyphenyl)prop-2-en-1-yl 3,5-dinitrobenzoate (178)



General procedure **F** was followed using 2-(4-methoxyphenyl)prop-2-en-1-ol **162c** (99 mg, 0.6 mmol), triethylamine (0.10 mL, 0.7 mmol, 1.2 eq.) and 3,5-dinitrobenzoyl chloride (138 mg, 0.6 mmol, 1 eq.) in DCM (6 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (DCM) to afford the product **178** (397 mg, 95%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.82 (s, 3H, *H12*), 5.34 (s, 2H, *H5*), 5.41 (s, 1H, *H7a/7b*), 5.60 (s, 1H, *H7a/7b*), 6.87-6.91 (m, 2H, *H10*), 7.40-7.44 (m, 2H, *H9*), 9.10 (dd, *J* = 2.0, 0.5 Hz, 2H, *H3*), 9.19 (dd, *J* = 2.0, 2.0 Hz, 1H, *H1*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 55.3, 68.0, 114.0, 115.1, 122.4, 127.1, 129.4, 129.8, 133.7, 140.9, 148.6, 159.8, 162.3; **IR** (KBr) ν 3092, 1734, 1629, 1545, 1458, 1387, 1344, 1167; **HRMS** calc for $C_{17}H_{14}N_2O_7$ $[M]^+$ 358.0801, found 358.0809; **Mp** 123-125 °C.

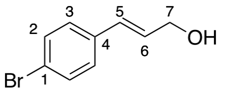
Ethyl (2*E*)-3-(4-bromophenyl)acrylate[232] (174)



General procedure **C** was followed using 4-bromobenzaldehyde (537 mg, 2.9 mmol, 1 eq.) and (carbethoxymethylene)triphenylphosphorane (1.0 g, 2.9 mmol) in toluene (25 mL). The reaction mixture was allowed to cool RT and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc:hexane, 1:10) to afford the acrylate product **174** (698 mg, 94%) as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.34 (t, *J* = 7.0 Hz, 3H, *H9*), 4.27 (q, *J* = 7.0 Hz, 2H, *H8*), 6.42 (d, *J* = 16.0 Hz, 1H, *H6*), 7.38 (ddd, *J* = 8.5, 2.5, 2.0 Hz, 2 H, *H3*), 7.52 (ddd, *J* = 8.5, 2.5, 2.0 Hz, 2H, *H2*), 7.62 (d, *J* = 16.0 Hz, 1H, *H5*). **^{13}C NMR** (100 MHz, CDCl$_3$) δ: 14.3, 60.6, 119.0, 124.4, 129.4, 132.1, 133.4, 143.2, 166.7.

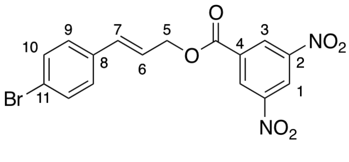
(2*E*)-3-(4-bromophenyl)prop-2-en-1-ol[233] (175)



General procedure **D** was followed using ethyl (2*E*)-3-(4-bromophenyl)acrylate **174** (2.58 mmol, 1 eq) and DIBAL-H (1.2M in toluene, 5.42 mmol, 2.1 eq) in toluene (9 mL) at -78°C. The crude product was purified by silica gel column chromatography (gradient = EtOAc:hexane, 1:3 to EtOAc:hexane, 1:1) and afforded allylic alcohol **175 (**490 mg, 90%) as a white solid.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.76 (br s, 1H, O*H*), 4.32 (d, *J* = 5.0 Hz, 2H, *H7*), 6.36 (dt, *J* = 16.0, 5.0 Hz, 1H, *H6*), 6.56 (d, *J* = 16.0 Hz, 1H, *H5*), 7.24 (dt, *J* = 8.5, 2.5, 2.0 Hz, 2H, *H3*), 7.44 (ddd, *J* = 8.5, 2.5, 2.0 Hz, 2H, *H2*). **^{13}C NMR** (100 MHz, CDCl$_3$) δ: 63.5, 121.4, 128.0, 129.3, 129.7, 131.7, 135.6.

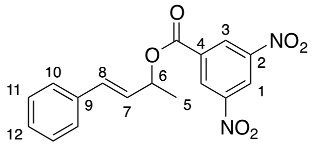
(2*E*)-3-(4-Bromophenyl)prop-2-en-1-yl 3,5-dinitrobenzoate (176a)



General procedure **F** was followed using (2*E*)-3-(4-bromophenyl)prop-2-en-1-ol **175** (149 mg, 0.7 mmol), triethylamine (0.12 mL, 0.8 mmol, 1.2 eq.) and 3,5-dinitrobenzoyl chloride (161 mg, 0.7 mmol, 1 eq.) in DCM (7 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (gradient = hexane to Et_2O:hexane, 1:1) to afford the product **176a** (70 mg, 17%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.10 (dd, *J* = 6.5, 1.0 Hz, 2H, *H5*), 6.42 (dt, *J* = 16.0, 6.5 Hz, 1H, *H6*), 6.74 (d, *J* = 16.0 Hz, 1H, *H7*), 7.27-7.31 (m, 2H, *H9*), 7.44-7.48 (m, 2H, *H10*), 9.19 (dd, *J* = 2.0, 1.5 Hz, 2H, *H3*), 9.22 (dd, *J* = 2.0, 1.5 Hz, 1H, *H1*). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 67.2, 122.4, 122.5, 122.5, 128.3, 129.5, 131.9, 133.8, 134.6, 135.0, 148.7, 162.3; **IR** (KBr) ν 3099, 1737, 1628, 1543, 1340, 1274, 1170; **HRMS** calc for $C_{16}H_{11}BrN_2O_6$ $[M]^+$ 405.9800, found 405.9799; **Mp** 101 °C.

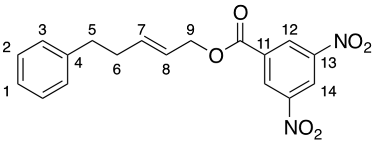
(3*E*)-4-Phenylbut-3-en-2-yl 3,5-dinitrobenzoate (179)



General procedure **F** was followed using (3*E*)-4-phenylbut-3-en-2-ol **170** (148 mg, 1 mmol), triethylamine (0.17 mL, 1.2 mmol, 1.2 eq.) and 3,5-dinitrobenzoyl chloride (231 mg, 1 mmol, 1 eq.) in DCM (10 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (eluent: DCM:hexane, 5:1) to afford the product **179** (222 mg, 65%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$); δ 1.65 (d, *J* = 6.5 Hz, 3H, *H5*), 5.88 (dq, *J* = 6.5, 6.0 Hz, 1H, *H6*), 6.32 (dd, *J* = 16.0, 6.0 Hz, 1H, *H7*), 6.76 (d, *J* = 16.0 Hz, 1H, *H8*), 7.26-7.43 (m, 5H, *H10/11/12*), 9.18 (d, *J* = 2.0 Hz, 2H, *H3*), 9.21 (t, *J* = 2.0 Hz, 1H, *H1*). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 20.4, 74.5, 122.3, 126.7, 127.2, 128.4, 128.7, 129.5, 133.6, 134.4, 135.7, 148.6, 161.8; **IR** (DCM) ν 3001, 1727, 1629, 1543, 1344, 1274, 1169; **HRMS** calc for $C_{17}H_{14}N_2O_6$ $[M]^+$ 342.0852, found 342.0850; **Mp** 27-29° C.

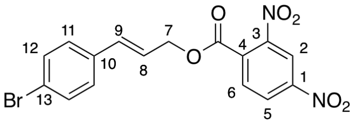
(2*E*)-5-Phenylpent-2-en-1-yl 3,5-dinitrobenzoate (180)



General procedure **F** was followed using (2*E*)-5-phenylpent-2-en-1-ol **167g** (162 mg, 1 mmol), triethylamine (0.17 mL, 1.2 mmol, 1.2 eq.) and 3,5-dinitrobenzoyl chloride (231 mg, 1 mmol, 1 eq.) in DCM (10 mL) at 0°C. The reaction was allowed to stir at rt until complete by TLC. The resulting crude mixture was purified by silica gel column chromatography (DCM) to afford the product **180** (268 mg, 75%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (q, *J* = 7.5, Hz, 2H, *H6*), 2.73-2.79 (m, 2H, *H5*), 4.86-4.90 (m, 2H, *H9*), 5.71-5.78 (m, 1H, *H8*), 5.96-6.03 (m, 1H, *H7*), 7.16-7.30 (m, 5H, *H1/2/3*), 9.12-9.17 (m, 2H, *H12*), 9.20-9.23 (m, 1H, *H14*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 34.0, 35.1, 67.5, 122.3, 123.3, 126.0, 128.4, 128.4, 129.5, 134.1, 137.6, 141.2, 148.6, 162.3; **IR** (KBr) ν 1723, 1629, 1543, 1343, 1270, 1162; **HRMS** calc for $C_{18}H_{16}N_2O_6$ $[M]^+$ 356.1008, found 356.1014; **Mp** 84-88 °C.

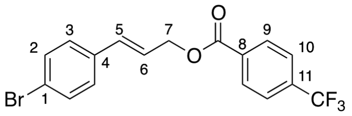
(2*E*)-3-(4-Bromophenyl)prop-2-en-1-yl 2,4-dinitrobenzoate (176b)



2,4-Dinitrobenzoyl chloride was prepared *in situ* by refluxing 2,4-dinitrobenzoic acid (212 mg, 1 mmol, 1.0 eq) at 80° C for 2 h in thionyl chloride (0.15 mL, 2 mmol, 2.0 eq), after which excess solvent was removed *in vacuo*. The crude product was used without purification. To a solution of (2*E*)-3-(4-bromophenyl)prop-2-en-1-ol (213 mg, 1 mmol) and triethylamine (0.17 mL, 1.2 mmol, 1.2 eq.) in DCM (10 mL) at 0°C was the solution of 2,4-dinitrobenzoyl chloride at 0°C. The reaction was allowed to warm to rt and stirred until complete by TLC. The reaction mixture was diluted with DCM and then washed successively by $NaHCO_3$(aq), H_2O and brine. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting crude mixture was purified by silica gel column chromatography (gradient: Petroleum Ether (30:40) to DCM:Petroleum Ether (30:40), 1:1) to afford the product **176b** (348 mg, 85%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.03 (dd, *J* = 6.5, 1.0 Hz, 2H, *H7*), 6.33 (dt, *J* = 16.0, 7.0 Hz, 1H, *H8*), 6.69 (d, *J* = 16.0 Hz, 1H, *H9*), 7.28 (ddd, *J* = 8.5, 2.5, 2.0 Hz, 2H, *H11*), 7.47 (ddd, *J* = 8.5, 2.5, 2.0 Hz, 2H, *H12*), 7.97 (d, *J* = 8.5 Hz, 1H, *H6*), 8.54 (dd, *J* = 8.5, 2.0 Hz, 1H, *H5*), 8.81 (d, *J* = 2.0 Hz, 1H, *H2*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 67.6, 119.7, 121.9, 122.4, 127.6, 128.3, 131.2, 131.8, 132.8, 134.7, 134.9, 148.1, 149.0, 163.5; **IR** (neat) ν 1722, 1548, 1353, 1281; **HRMS** calc for $C_{16}H_{11}N_2O_6Br$ $[M]^+$ 405.9800, found 405.9804; **Mp** 119-122 °C.

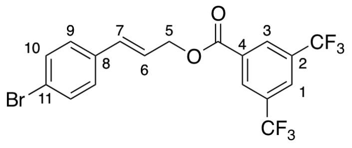
(2*E*)-3-(4-Bromophenyl)prop-2-en-1-yl 4-(trifluoromethyl)benzoate (176c)



4-(Trifluoromethyl)benzoyl chloride was prepared *in situ* by refluxing 4-(trifluoromethyl)benzoic acid (190 mg, 1 mmol, 1.0 eq) at 80° C for 2 h in thionyl chloride (0.15 mL, 2 mmol, 2.0 eq), after which excess solvent was removed *in vacuo*. The crude product was carried through to the next step without further purification. To a solution of (2*E*)-3-(4-bromophenyl)prop-2-en-1-ol (213 mg, 1 mmol) and triethylamine (0.17 mL, 1.2 mmol, 1.2 eq.) in DCM (10 mL) at 0°C was added 4-(trifluoromethyl)benzoyl chloride from the first step (1 mmol, 1 eq.). The reaction was allowed to warm to rt and stirred until complete by TLC. The reaction mixture was diluted with DCM and then washed successively by $NaHCO_3$(aq), H_2O and brine. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting crude mixture was purified by silica gel column chromatography (gradient = hexane to Et_2O:hexane, 1:10) to afford the product **176c** (280 mg, 87%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.02 (dd, *J* = 6.5, 1.0 Hz, 2H, *H7*), 6.40 (dt, *J* = 16.0, 6.5 Hz, 1H, *H6*), 6.70 (d, *J* = 16.0 Hz, 1H, *H5*), 7.29 (ddd, *J* = 8.5, 2.5, 2.0 Hz, 2H, *H3*), 7.46 (dd, *J* = 8.5, 2.5, 2.0 Hz, 2H, *H2*), 7.72 (ddd, *J* = 8.0, 1.0, 0.5 Hz, 2H, *H10*), 8.20 (ddd, *J* = 8.5, 1.0, 0.5 Hz, 2H, *H9*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 65.8, 122.1, 123.6, 123.6 (q, *J* = 273 Hz), 125.4 (q, *J* = 4 Hz), 128.2, 130.1, 131.8, 133.3, 133.5, 134.5 (q, *J* = 34 Hz), 135.0, 165.1; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ: -63.06 (s); **IR** (neat) ν 1722, 1267, 1094, 702; **HRMS** calc for $C_{17}H_{12}O_2BrF_3$ $[M]^+$ 383.9973, found 383.9979; **Mp** 71-73 °C.

(2*E*)-3-(4-Bromophenyl)prop-2-en-1-yl 3,5-*bis*(trifluoromethyl)benzoate (176d)

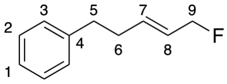


3,5-Bis(trifluoromethyl)benzoyl chloride was prepared *in situ* by refluxing 3,5-bis(trifluoromethyl)benzoic acid (258 mg, 1 mmol, 1.0 eq) at 80° C for 2 h in thionyl chloride (0.15 mL, 2 mmol, 2.0 eq), after which excess solvent was removed *in vacuo*. The crude product was carried through to the next step without further purification.

To a solution of (2*E*)-3-(4-bromophenyl)prop-2-en-1-ol (213 mg, 1 mmol) and triethylamine (0.17 mL, 1.2 mmol, 1.2 eq.) in DCM (10 mL) at 0°C was added 3,5-bis(trifluoromethyl)benzoyl chloride from the first step (1 mmol, 1 eq.). The reaction was allowed to warm to rt and stirred until complete by TLC. The reaction mixture was diluted with DCM and then washed successively by $NaHCO_3$(aq), H_2O and brine. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting crude mixture was purified by silica gel column chromatography (EtOAc:hexane, 1:10) to afford the product **176d** (388 mg, 86%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.06 (dd, *J* = 6.5, 1.0 Hz, 2H, *H5*), 6.42 (dt, *J* = 16.0, 6.5 Hz, 1H, *H6*), 6.72 (d, *J* = 16.0 Hz, 1H, *H7*), 7.28-7.31 (m, 2H, *H9*), 7.45-7.49 (m, 2H, *H10*), 8.09 (s, 1H, *H1*), 8.53 (s, 2H, *H3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 66.5, 122.3, 122.9 (q, *J* = 273 Hz), 123.0, 126.4 (s, *J* = 4 Hz), 129.8 (q, *J* = 3 Hz), 128.2, 131.8, 132.2 (q, *J* = 34 Hz), 132.3, 134.4, 134.8, 163.7; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ: -63.01 (s); **IR** (DCM) ν 3055, 1730, 1265, 1143, 239; **HRMS** calc for $C_{18}H_{11}BrF_6O_2$ $[M]^+$ 451.9847, found 451.9841.

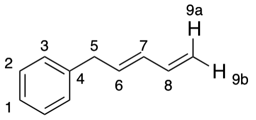
[(3*E*)-5-Fluoropent-3-en-1-yl]benzene (172h)



General procedure **E** was followed using (2*E*)-5-phenylpent-2-en-1-yl 3,5-dinitrobenzoate **180** (71 mg, 0.2 mmol), $Pd(dba)_2$ (6 mg, 0.01 mmol, 5 mol%), PPh_3 (8 mg, 0.03 mmol, 15 mol%), and TBAF(*t*BuOH)$_4$ (279 mg, 2.5 eq, 0.5 mmol) in THF (2 mL). The reaction was allowed to stir at rt for 1 hr. The resulting crude mixture was purified by silica gel column chromatography (Petroleum Ether 30:40) to afford allylic fluoride **172h** in a trace amount detected by ^{19}F-NMR.

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 2.44 (dt, *J* = 7.0, 6.0 Hz, 2H, *H6*), 2.76 (t, *J* = 7.0 Hz, 2H, *H5*), 4.80 (ddd, *J* = 47.0, 6.0 Hz, 1.0 Hz, 2H, *H9*), 5.70-5.80 (m, 1H, *H7*), 5.91 (ddd, *J* = 21.0, 6.5 Hz, 5Hz, *H8*), 7.20-7.33 (m, 5H, *H1/2/3*); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ: 34.3 (d, *J* = 2 Hz), 35.5 (d, *J* = 2 Hz), 84.0 (d, *J* = 160 Hz), 125.6 (d, *J* = 17 Hz), 126.2, 128.7, 128.8, 136.7 (d, *J* = 12 Hz), 142.0; **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ: -208.4 (m); **IR** (neat) ν 1455, 1379, 1078, 969; **HRMS** calc for $C_{11}H_{13}F$ $[M]^+$ 164.1001, found 164.1006.

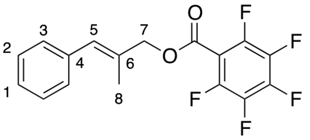
(1*E*)-Buta-1,3-dien-1-ylbenzene (*E*-172-D)



Diene ***E*-172-D** was observed as a side product in the allylic fluorination reactions using general procedure **E**.

^{1}**H NMR** (400 MHz, CD_2Cl_2); δ 3.45 (d, *J* = 10.0 Hz, 2H, *H3*), 5.03 (dd, *J* = 10.0 Hz, 0.5 Hz, 1H, *H9b*), 5.17 (dd, *J* = 17.0 Hz, 0.5 Hz, 1H, *H9a*), 5.84-5.93 (m, 1H, *H7*), 6.16 (ddd, *J* = 17.0 Hz, 10.0 Hz, 9.0 Hz, 1H, *H8*), 6.39 (dt, *J* = 17.0 Hz, 10.0 Hz, 1H, *H6*), 7.45-7.53 (m, 5H, *H1/2/3*); **LRMS** calculated for $C_{11}H_{12}$ $[M]^+$ 144.0939, found 144.0937.

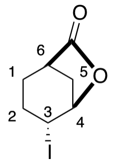
(2*E*)-2-Methyl-3-phenylprop-2-en-1-yl pentafluorobenzoate (181)



General procedure **G** was followed using 2-methyl-3-phenyl-1,2-propen-1-ol (0.14 mL, 1 mmol), DCC (227 mg, 1.1 mmol, 1.1 eq.), DMAP (15 mg, 0.12 mmol, 12 mol%) and pentafluorobenzoic acid (233 mg, 1.1 mmol, 1.1 eq.) in DCM (10 mL). The resulting crude mixture was purified by column chromatography (Et_2O:hexane, 1:5) to afford the product **181** (276 mg, 81%) as a colourless oil .

^{1}**H NMR** (400 MHz, $CDCl_3$) δ: 1.99 (s, 3H, *H8*), 4.96 (s, 2H, *H7*), 6.66 (s, 1H, *H5*), 7.25-7.32 (m, 3H, *H1/2*), 7.35-7.39 (m, 2H, *H3*); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ: 15.4, 72.6, 127.0, 128.2, 128.9, 129. 8, 131.4, 136.3-136.5 (m), 136.7, 138.7-139.2 (m), 141.7-142.1 (m), 143.8-144.6 (m), 146.6-147.0 (m), 158.9; ^{19}**F NMR** (376.5 MHz, $CDCl_3$) δ: -138.2 (dq, *J* = 12.5, 5.0 Hz), -143.7 (tt, *J* = 21.0, 4.5 Hz), -160.5 (m); **IR** (CH_2Cl_2) ν 1737, 1652, 1214; **HRMS** calc for $C_{17}H_{11}F_5O_2$ $[M+Na]^+$ 365.0577, found 365.0571.

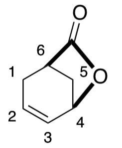
(4*R*)-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one (183a)[234]



To a solution of $NaHCO_3$ (5.04 g, 59.4 mmol, 3 eq.) in H_2O (50 mL) at rt was added 3-cyclohexene-1-carboxylic acid (2.3 mL, 19.8 mmol) dropwise. After solution became homogeneous a solution of NaI (27.0 g, 178.2 mmol, 9 eq.) and I_2 (5.59g, 22 mmol, 1.1 eq.) in H_2O (50 mL) was added and reaction stirred at rt excluding light for 16 h. The solution was extracted with DCM (3 x 50 mL) and the organic layers washed with $Na_2S_2O_3.5H_2O$ (aq, 10%), $NaHCO_3$ (aq, 10%), brine, dried over Na_2SO_4 and the solvent removed *in vacuo* to give crude product **183a** as a white solid (4.57 g, 18 mmol) which was used without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.81-1.95 (m, 2H, *H1*), 2.12 (dd, *J* = 16.0, 5.0 Hz, 1H, *H2/5*), 2.36-2.50 (m, 2H, *H2/5*), 2.67-2.68 (m, 1H, *H2/5*), 2.80 (d, *J* = 12.0 Hz, 1H, *H6*), 4.51 (t, *J* = 5.0 Hz, 1H, *H4*), 4.83 (t, *J* = 5.0 Hz, 1H, *H3*); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 23.1, 23.8, 29.7, 34.5, 38.6, 80.2, 177.8.

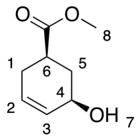
6-oxabicyclo[3.2.1]oct-3-en-7-one (183b)[19]



To (4*R*)-4-iodo-6-oxabicyclo[3.2.1]octan-7-one **183a** (4.57 g, 18 mmol) in toluene (55 mL) was added DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (2.7 mL, 18 mmol, 1 eq.) under N_2 and reaction stirred at reflux for 4h. After cooling, the solution was filtered and the solvent removed *in vacuo* to give crude product **183b** as a yellow oil (2.35 g, 18.9 mmol), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.09 (d, *J* = 11.0 Hz, 1H, *H1/5*), 2.44-2.52 (m, 3H, *H1/5*), 2.89-2.92 (m, 1H, *H6*), 4.75 (t, *J* = 5.0 Hz, 1H, *H4*), 5.82-5.86 (m, 1H, *H2/3*), 6.21-6.25 (d, *J* = 11.0 Hz, 1H, *H2/3*); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 29.1, 34.5, 38.0, 73.3, 129.3, 130.1, 179.4.

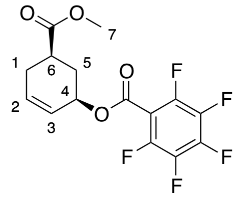
Methyl (1*R*,5*R*)-5-hydroxycyclohex-3-ene-1-carboxylate (183c)[235]



To a solution of 6-oxabicyclo[3.2.1]oct-3-en-7-one **183b** (2.35g, 18.9 mmol) in MeOH (18 mL) was added potassium carbonate (1.31 g, 9.5 mmol, 0.5 eq.) and the reaction was stirred at rt for 30 minutes. The solution was filtered, diluted with DCM and the organic phase extracted with H_2O (2 x 10 mL). The organics were combined, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resulting crude mixture was purified by column chromatography (1:1 Hexane:EtOAc) to afford product **183c** as a colourless oil (1.33 mg, 8.5 mmol, 47% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.70 (ddd, *J* = 13.0, 11.0, 8.0 Hz, 1H, *H1*), 2.22-2.32 (m, 3H, *H1/5*), 2.53 (s, 1H, *OH*), 2.69 (dtd, *J* = 11.0, 7.5, 3.0 Hz, 1H, *H6*), 4.27 (bs, 1H, *H4*), 3.68 (s, 3H, *H8*), 5.71-5.75 (m, 2H, *H2/3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 27.8, 34.6, 38.2, 52.4, 66.4, 127.2, 131.3, 176.1.

(1*R*,5*R*)-5-(Methoxycarbonyl)cyclohex-2-en-1-yl pentafluorobenzoate (*syn*-184)



General procedure **G** was followed using methyl (1*R*,5*R*)-5-hydroxycyclohex-3-ene-1-carboxylate **183c** (312 mg, 2 mmol), DCC (495 mg, 2.4 mmol, 1.2 eq), DMAP (24 mg, 0.2 mmol, 10 mol%) and pentafluorobenzoic acid (848 mg, 4 mmol, 2 eq.) in DCM (20 mL). The resulting crude mixture was purified by column chromatography (EtOAc:hexane, 1:5) to afford the product **33** (533 mg, 76%) as a colourless oil.

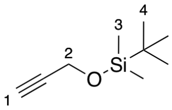
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.89 (td, *J* = 12.5, 9.0 Hz, 1H, *H5*), 2.33-2.38 (m, 2H, *H1*), 2.51-2.56 (m, 1H, *H5*), 2.79 (dddd, *J* = 12.0, 9.0, 7.0, 3.0 Hz, 1H, *H6*), 3.70 (s, 3H, *H7*), 5.67-5.76 (m, 2H, *H3/4*), 5.94-5.99 (m, 1H, *H2*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 27.1, 30.2, 37.7, 51.9, 72.3, 125.5, 130.4, 136.1-136.6 (m), 138.5-139.1 (m), 141.5-142.0 (m), 143.7-144.5 (m), 146.3-146.7 (m), 158.2, 174.17. ArC-F bonds identified but not reported due to complex splitting patterns; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ: -138.3 (ddt, *J* = 19.0, 12.0, 6.0 Hz, 2F), -148. 7 (tt, *J* = 21.0, 4.5 Hz, 1F), -160.4 (m, 2F); **IR** (CH_2Cl_2) ν 1732, 1653, 1226; **HRMS** calc for $C_{15}H_{11}F_5NaO_4$ $[M+Na]^+$ 373.0470, found 373.0468.

5.2.5 Synthesis of allylic carbonates for Ir-catalysed fluorination

General Procedure H for the synthesis of allylic carbonates

To a solution of allylic alcohol (2 mmol) and pyridine (6 mmol, 3 eq.) in DCM (0.5 M) at 0 °C was added methyl chloroformate (4 mmol, 2 eq.) dropwise. The reaction was then allowed to warm to rt and stirred until TLC shows completion. The reaction was quenched by the addition of saturated $NH_4Cl_{(aq)}$, the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography to afford the desired product.

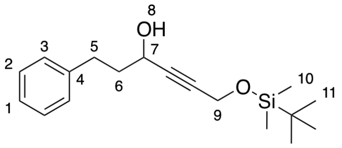
tert-Butyl(dimethyl)(prop-2-yn-1-yloxy)silane (210)[236]



Imidazole (1.02 g, 15 mmol, 1.5 eq.) was added to propargyl alcohol **154** (0.6 mL, 10 mmol) in DMF (20 ml) at 0 ºC. Tertbutyldimethylsilyl chloride (1.81g, 12 mmol, 1.2 eq.) was added and the reaction stirred for 2 h at rt. The reaction was then diluted with saturated $NaHCO_{3(aq)}$ and hexane. The organic layer was separated and aqueous layer extracted with hexane (20 mL x 3). The organics were combined, dried over $MgSO_4$, and the solvent removed was *in vacuo*. The residue was purified by flash silica gel column chromatography (Petroleum Ether(40:60): EtOAc, 95:5) to affored **210** (1.59 g, 93%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.14 (s, 6H, *H3*), 0.92 (s, 9H, *H4*), 2.40 (t, *J* = 2.5 Hz, 1H, *H1*), 4.32 (d, *J* = 2.5 Hz, 2H, *H2*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: –5.2, 18.3, 25.8, 51.5, 72.8, 82.4.

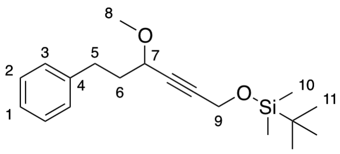
6-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-phenylhex-4-yn-3-ol (211)[237]



To a solution of *tert*-butyl(dimethyl)(prop-2-yn-1-yloxy)silane **210** (660mg, 3.9 mmol, 1.2 eq.) in THF (10 mL) was added *n*BuLi (1.7 mL, 2.3 M in hexane, 3.9 mmol, 1.2 eq.) at -78 ºC and reaction stirred for 30 min, after which hydrocinnamaldehyde (0.43 mL, 3.25 mmol) was added dropwise. The solution was allowed to warm to rt over 4 h and quenched with saturated $NH_4Cl_{(aq)}$. The organic layer was separated and the aqueous phase extracted with hexane (3 x 20 mL). The organics were combined, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was purified by flash silica gel column chromatography (95:5 hexane/EtOAc) to afforded product **211** (1g, 85%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.14 (s, 6H, *H10*), 0.93 (s, 9H, *H11*), 2.00-2.04 (m, 2H, *H6*), 2.81 (t, *J* = 8.0 Hz, 2H, *H5*), 4.38 (d, 2H, *J* = 2.0 Hz, *H9*), 4.39-4.44 (m, 1H, *H7*), 7.18-7.23 (m, 3H, *H1/H2*), 7.27-7.32 (m, 2H, *H3*); **^{13}C NMR** (100MHz, $CDCl_3$) δ: -5.1, 18.3, 25.8, 31.3, 39.1, 51.7, 61.8, 84.0, 85.4, 126.0, 128.4, 128.5, 141.3.

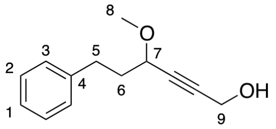
***tert*-Butyl[(4-methoxy-6-phenylhex-2-yn-1-yl)oxy]dimethylsilane (212)**



To a solution of 6-{[*tert*-butyl(dimethyl)silyl]oxy}-1-phenylhex-4-yn-3-ol **211** (500mg, 1.64 mmol) in THF (18 mL) was slowly added NaH (60% in oil, 92 mg, 2.3 mmol, 1.4 eq.) at 0 ºC. The mixture was stirred for 20 min at rt and then heated to 40 ºC and iodomethane (0.18 mL, 2.95 mmol, 1.8 eq.) was added. After stirring at 40 ºC for 8 h the reaction was quenched with saturated $NH_4Cl_{(aq)}$ at 0 ºC. The organic layer was separated and the aqueous phase extracd with Et_2O (3 x 20 mL). The organics were combined, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was purified by flash silica gel column chromatography (9:1 hexane:EtOAc) to afford **212** (219 mg, 42%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.15 (s, 6H, *H10*), 0.94 (s, 9H, *H11*), 1.96-2.11 (m, 2H, *H6*), 2.79 (t, *J* = 8.0 Hz, 2H, *H5*), 3.42 (s, 3H, *H8*), 3.94-3.98 (m, 1H, *H7*), 4.40 (d, 2H, *J* = 1.5 Hz, *H9*), 7.19-7.22 (m, 3H, *H1/H2*), 7.27-7.32 (m, 2H, *H3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: -5.1, 18.3, 25.8, 31.4, 37.1, 51.7, 56.4, 70.4, 83.2, 84.8, 125.9, 128.4, 128.5, 141.4; **IR** (CH_2Cl_2) ν 2361, 1128, 1089, 907; **HRMS** calc for $C_{19}H_{30}NaO_2Si$ $[M+Na]^+$ 341.1913, found 341.1907.

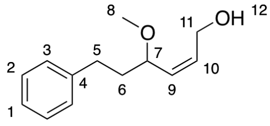
4-Methoxy-6-phenylhex-2-yn-1-ol (213)



To a solution of *tert*-butyl[(4-methoxy-6-phenylhex-2-yn-1-yl)oxy]dimethylsilane **212** (219 mg, 0.69 mmol) in THF (2 mL) was added Bu_4NF (1.03 mL, 1M in THF, 1.03 mmol, 1.5 eq.). The reaction was stirred at rt for 1 h and quenched with saturated $NH_4Cl_{(aq)}$. The organic layer was separated and the aqueous phase extracted with EtOAc (3 x 5 mL). The organics were combined, dried over $MgSO_4$, and solvent removed *in vacuo*. The residue was purified by flash silica gel column chromatography (9:1 hexane:EtOAc) to afford **213** (103 mg, 74%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.97-2.11 (m, 2H, *H6*), 2.14 (bs, 1H, *OH*), 2.74-2.85 (m, 2H, *H5*), 3.42 (s, 3H, *H8*), 3.95-3.99 (m, 1H, *H7*), 4.33 (s, 2H, *H9*), 7.19-7.22 (m, 3H, *H1/H2*), 7.27-7.32 (m, 2H, *H3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 31.4, 37.0, 51.0, 56.5, 70.4, 84.3, 84.5, 126.0, 128.4, 128.5, 141.3; **IR** (CH_2Cl_2) ν 2931, 2361, 1097; **HRMS** calc for $C_{13}H_{16}NaO_2$ $[M+Na]^+$ 227.1048, found 227.1043.

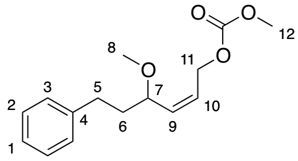
(2*Z*)-4-Methoxy-6-phenylhex-2-en-1-ol (214)[238]



To a solution of 4-methoxy-6-phenylhex-2-yn-1-ol **213** (103 mg, 0.5 mmol) in EtOAc (3 mL) was added Lindlar catalyst (21 mg, 20% w/w) and quinoline (0.02 mL, 0.2 mmol, 40 mol%) and the reaction was stirred for 16 h at rt under a H_2 atmosphere (balloon). The reaction was filtered through a short pad of Celite and the solvent was removed *in vacuo*. The residue was purified by flash silica gel column chromatography (9:1 hexane:EtOAc) to afford **214** (62 mg, 60%) as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.67-1.81 (m, 2H, *H6*), 1.94-2.07 (m, 1H, *H12*), 2.63-2.75 (m, 2H, *H5*), 3.30 (d, *J* = 1.0 Hz, 3H, *H8*), 3.89-3.95 (m, 1H, *H7*), 4.10-4.25 (m, 2H, *H11*), 5.45 (ddd, *J* = 11.5, 9.0, 1.0, 1H, *H9*), 5.83 (m, 1H, *H10*), 7.18-7.21 (m, 3H, *H1/H2*), 7.27-7.31 (m, 2H, *H3*); **^{13}C NMR** (100 MHz, CDCl$_3$) δ: 31.4, 36.8, 56.1, 58.8, 75.9, 125.9, 128.4, 132.1, 132.6, 141.7.

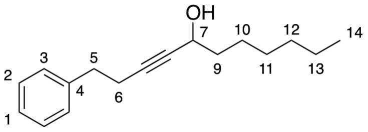
(2*Z*)-4-Methoxy-6-phenylhex-2-en-1-yl methyl carbonate (215)



General procedure **H** was followed using (2*Z*)-4-methoxy-6-phenylhex-2-en-1-ol **214** (62 mg, 0.3 mmol), pyridine (0.07 mL, 0.9 mmol, 3 eq.) and methyl chloroformate (0.05 mL, 0.6 mmol, 2 eq.) in DCM (1 mL) at 0°C. The reaction was then allowed to warm to rt and stirred for 2 h. The reaction was quenched by the addition of saturated NH$_4$Cl$_{(aq)}$ and the aqueous phase was extracted with Et$_2$O (3 x 5 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash silica gel column chromatography (9:1 hexane:EtOAc) to afford the product **215** (65mg, 82%) as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.70-1.79 (m, 1H, *H6*), 1.97 (ddt, *J* = 13.5, 9.5, 7.0 Hz, 1H, *H6*), 2.62-2.76 (m, 2H, *H5*), 3.29 (s, 3H, *H8*), 3.80 (s, 3H, *H12*), 3.90 (td, *J* = 8.0, 6.0 Hz, 1H, *H7*), 4.63 (ddd, *J* = 13.0, 6.0, 1.5 Hz, 1H, *H11*), 4.72 (ddd, *J* = 13.0, 7.0, 1.0 Hz, 1H, *H11*), 5.54-5.60 (m, 1H, *H9*), 5.79 (dt, *J* = 11.0, 7.0 Hz, 1H, *H10*), 7.15-7.21 (m, 3H, *H1/H2*), 7.28-7.34 (m, 2H, *H3*); **^{13}C NMR** (100 MHz, CDCl$_3$) δ: 31.4, 36.9, 54.9, 56.3, 63.5, 75.9, 125.9, 126.3, 128.4, 135.6, 141.7, 155.6.

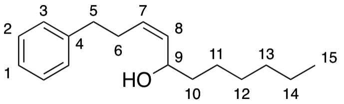
1-Phenylundec-3-yn-5-ol (216)[239,240]



To 4-phenyl-1-butyne (2.8 mL, 20 mmol, 2 eq.) dissolved in DCM (80 mL) was added $ZnEt_2$ (20 mL, 1M in hexane, 20 mmol, 2 eq.) and *N*-methylimidazole (0.08 mL, 1 mmol, 1 mol%) and the reaction was allowed to stir at rt for 4h, after which time heptanal (1.4 mL, 10 mmol) was added and the reaction was stirred overnight (16 h). The reaction was quenched with saturated $NH_4Cl_{(aq)}$, extracted with DCM (3 x 50 mL), dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was purified by flash silica gel column chromatography (9:1-5:1 hexane:EtOAc) to afford the product **216** (1.21 g, 50% mixture of alcohol and diene) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91-0.99 (m, 3H, *H14*), 1.27-1.46 (m, 8H, *H10/11/12/13*), 1.59-1.72 (m, 2H, *H9*), 1.90 (bs, 1H, *OH*), 2.51-2.55 (m, 2H, *H6*), 2.80 (t, *J* = 7.5 Hz, 2H, *H5*), 4.34 (ddd, *J* = 7.5, 6.0, 2.0 Hz, 1H, *H7*), 7.21-7.27 (m, 3H, *H1/2*), 7.30-7.43 (m, 2H, *H3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 14.1, 20.9, 22.6, 25.1, 29.0, 31.8, 35.0, 38.1, 62.7, 82.3, 84.6, 126.3, 128.4, 128.5, 140.6.

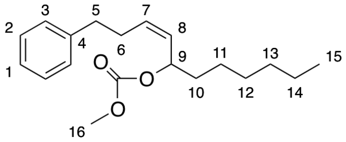
(3*Z*)-1-Phenylundec-3-en-5-ol (217)



To a solution of 1-phenylundec-3-yn-5-ol **216** (128 mg, 0.52 mmol) in hexane (5 mL) was added Lindlar catalyst (5.2 mg, 10% w/w) and the reaction was stirred for 16 h at rt under a H_2 atmosphere (balloon). The reaction was filtered through a short pad of Celite and the solvent removed *in vacuo*. The residue was purified by flash silica gel column chromatography (9:1 hexane:EtOAc) to afford **217** (103 mg, 80%) as a colourless oil.

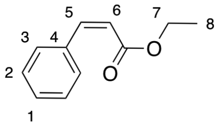
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, 3H, *J* = 6.5 Hz, *H15*), 1.18-1.40 (m, 9H, *H10/11/12/13/14*), 1.43-1.56 (m, 2H, *H10/OH*), 2.36-2.53- (m, 2H, *H6*), 2.64-2.79 (m, 2H, *H5*), 4.24-4.29 (m, 1H, *H7*), 5.39 (ddd, *J* = 10.5, 9.5, 1.0 Hz, 1H, *H9*), 5.50-5.56 (m, 1H, *H8*), 7.20-7.27 (m, 3H, *H1/2*), 7.29-7.34 (m, 2H, *H3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 14.1, 22.6, 25.3, 29.3, 29.7, 31.9, 35.8, 37.1, 67.5, 126.1, 128.3, 128.7, 130.5, 133.7, 140.6; **IR** (CH_2Cl_2) ν 2926, 697; **HRMS** calc for $C_{17}H_{26}NaO$ $[M+Na]^+$ 269.1881, found 269.1876.

Methyl (3*Z*)-1-phenylundec-3-en-5-yl carbonate (218)



General procedure **H** was followed using (3*Z*)-1-phenylundec-3-en-5-ol **217** (370 mg, 1.5 mmol), pyridine (0.36 mL, 4.5 mmol, 3 eq.) and methyl chloroformate (0.23 mL, 3 mmol, 2 eq.) in DCM (3 mL) at 0°C. The residue was purified by flash silica gel column chromatography (9:1 hexane:EtOAc) to afford product **218** (97mg, 21%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 0.89 (t, *J* = 7.0 Hz, 3H, *H15*), 1.17-1.70 (m, 10H, *H10/11/12/13/14*), 2.40-2.60 (m, 2H, *H6*), 2.61-2.70 (m, 1H, *H5*), 2.71-2.85 (m, 1H, *H5*), 3.77 (s, 3H, *H16*), 5.25-5.41 (m, 2H, *H7/8*), 5.58-5.71 (m, 1H, *H9*), 7.13-7.25 (m, 3H, *H1/2*), 7.25-7.40 (m, 2H, *H3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 14.1, 22.6, 24.9, 29.0, 29.8, 31.7, 34.6, 35.7, 54.5, 74.7, 125.9, 128.3, 128.5, 133.2, 133.2, 141.2, 155.3; **IR** (CH_2Cl_2) ν 1744, 1260, 699; **HRMS** calc for $C_{19}H_{28}NaO_3$ $[M+Na]^+$ 327.1936, found 327.1931.

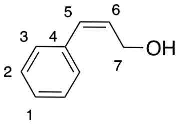
Ethyl (2*Z*)-3-phenylacrylate (207)[241]



To a solution of (*Z*)-ethyl 3-iodoacrylate (0.26 mL, 2 mmol) in dioxane (20 mL) was added $Pd(OAc)_2$ (22 mg, 0.1 mmol, 5 mol%), PPh_3 (52 mg, 0.2 mmol, 10 mol%), K_3PO_4 (1.27 g, 6 mmol, 3 eq.) and phenyl boronic acid (366 mg, 3 mmol, 1.5 eq.) and reaction was stirred at 60 ºC for 10 h. The reaction was filtered to remove solids and the solvent removed *in vacuo*. The crude residue was purified by flash silica gel column chromatography (9:1 hexane:Et_2O) to afford the product **207** (128mg, 36%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.0 Hz, 3H, *H8*), 4.19 (q, *J* = 7.0 Hz, 2H, *H7*), 5.96 (d, *J* = 12.5 Hz, 1H, *H6*), 7.00 (d, *J* = 12.5 Hz, 1H, *H5*), 7.57-7.60 (m, 2H, *H3*), 7.31-7.39 (m, 3H, *H1/2*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 14.1, 60.3, 119.9, 124.2, 128.0, 128.9, 129.7, 142.9, 166.2.

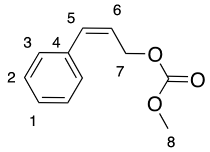
(2*Z*)-3-Phenylprop-2-en-1-ol (208)[242]



General procedure **D** was followed using ethyl (2*Z*)-3-phenylacrylate **207** (115 mg, 0.65 mmol) and DIBAL-H (1.43 mL, 1M in toluene, 1.43 mmol, 2.2 eq.) in toluene (2 mL) at -78°C. The residue was purified by flash silica gel column chromatography (9:1 hexane:EtOAc) to afford product **208** (33mg, 38%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.45 (d, *J* = 6.5 Hz, 2H, *H7*), 5.88 (dt, *J* = 12.0, 6.0 Hz, 1H, *H6*), 6.58 (d, *J* = 12.0 Hz, 1H, *H5*), 7.22 (d, *J* = 7.0 Hz, 2H, *H2*), 7.27-7.32 (m, 1H, *H1*), 7.34-7.38 (m, 2H, *H3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 59.7, 127.3, 128.3, 128.8, 130.9, 131.2, 136.5

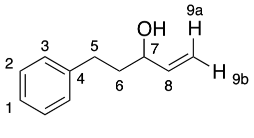
Methyl (2*Z*)-3-phenylprop-2-en-1-yl carbonate (209)[243]



General procedure **H** was followed using (2*Z*)-3-phenylprop-2-en-1-ol **208** (33 mg, 0.25 mmol), pyridine (60 μL, 0.75 mmol, 3 eq.) and methyl chloroformate (40 μL, 0.5 mmol, 2 eq.) in DCM (1 mL) at 0°C . The reaction was then allowed to warm to rt and stirred for 2 h. The reaction was quenched by the addition of saturated $NH_4Cl_{(aq)}$, the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The residue was purified by flash silica gel column chromatography (9:1 hexane:EtOAc) to afford product **209** (36mg, 76%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.81 (s, 3H, *H8*), 4.92 (dd, *J* = 6.5, 1.5 Hz, 2H, *H7*), 5.86 (dt, *J* = 12.0, 6.5 Hz, 1H, *H6*), 6.71 (d, *J* = 12.0 Hz, 1H, *H5*), 7.21-7.44 (m, 5H, *H3/2/1*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 59.7, 65.2, 125.6, 128.1, 128.9, 129.1, 134.0, 136.3, 156.1.

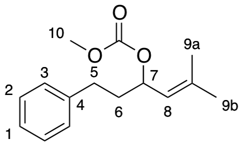
5-Phenylpent-1-en-3-ol (219)[244]



To a solution of hydrocinnamaldehyde (2 mL, 15 mmol) in THF (75 mL) was added dropwise vinyl magnesium bromide (15 mL, 1M in THF, 15 mmol, 1 eq.) at 0 ºC. The reaction was allowed to warm to rt and stirred for 1 h, after which the solution was quenched with saturated $NH_4Cl_{(aq)}$. The organic layer was separated and aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The residue was purified by flash silica gel column chromatography (9:1 hexane:EtOAc) to afford product **219** (1.30 g, 56%) as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.78-1.96 (m, 2H, *H*6), 2.62-2.85 (m, 2H, *H5*), 4.08-4.20 (m, 1H, *H7*), 5.12-5.18 (m, 1H, *H*9), 5.26 (dt, *J* = 17.0, 1.5 Hz, 1H, *H9*), 5.92 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H, *H8*), 7.15-7.40 (m, 5H, *H1/2/3*); **^{13}C NMR** (100MHz, CDCl$_3$) δ: 31.6, 38.6, 72.5, 114.8, 125.9, 128.4 (2C), 141.1, 142.0.

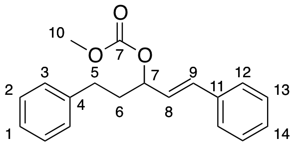
Methyl 5-phenylpent-1-en-3-yl carbonate (220)[245]



General procedure **H** was followed using 5-phenylpent-1-en-3-ol **219** (1g, 6.2 mmol), pyridine (1.5 mL, 18.5 mmol, 3 eq.) and methyl chloroformate (0.95 mL, 12.4 mmol, 2 eq.) in DCM (10 mL). The resulting crude mixture was purified by flash silica gel column chromatography (9:1-5:1 Hexane:Et$_2$O) to afford product **220** (1.07g, 79%) as a colourless oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.92-2.09 (m, 2H, *H*6), 2.58-2.82 (m, 2H, *H5*), 3.80 (s, 3H, *H10*), 5.05-5.15 (m, 1H, *H7*), 5.22-5.29 (m, 1H, *H9a/b*), 5.29-5.36 (m, 1H, *H9a/b*), 5.85 (ddd, *J* = 17.0, 10.5, 7.0 Hz, 1H, *H8*), 7.16-7.35 (m, 5H, *H1/2/3*); **^{13}C NMR** (100MHz, CDCl$_3$) δ: 30.2, 34.8, 53.6, 77.4, 116.7, 125.0, 127.3, 127.4, 134.8, 140.1, 154.2.

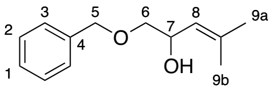
(1*E*)-1,5-Diphenylpent-1-en-3-yl methyl carbonate (221)



To a solution of methyl 5-phenylpent-1-en-3-yl carbonate **219** (300 mg, 1.36 mmol) and styrene (0.44 mL, 3.8 mmol, 2.8 eq.) in DCM (15 mL) was added Grubbs' second generation catalyst (58 mg, 0.07 mmol, 5 mol%). The reaction was heated to reflux for 72 h. Upon cooling, the solvent was removed *in vacuo*. The resulting crude mixture was purified by flash silica gel column chromatography (9:1-5:1 Hexane:Et_2O) to afford product **221** (104 mg, 26%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.04-2.13 (m, 1H, *H6*), 2.18-2.28 (m, 1H, *H*6), 2.72-2.86 (m, 2H, *H5*), 3.84 (s, 3H, *H10*), 5.27-5.37 (m, 1H, *H7*), 6.23 (dd, *J* = 16.0, 7.5 Hz, 1H, *H8*), 6.73 (d, *J* = 16.0 Hz, 1H, *H9*), 7.22-7.46 (m, 10H, *H/2/3/12/13/14*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 31.4, 36.2, 54.7, 78.6, 126.1, 126.7, 126.8, 128.2, 128.4, 128.5, 128.7, 133.6, 136.1, 141.1, 155.3; **IR** (CH_2Cl_2) ν 1743, 1256; **HRMS** calc for $C_{19}H_{20}NaO_3$ $[M+Na]^+$ 319.1310, found 319.1309.

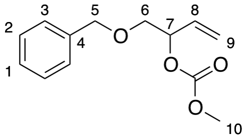
1-(Benzyloxy)but-3-en-2-ol (202)[246]



To a solution of 3,4-dihyroxy-1-butene (0.84 mL, 10 mmol) in THF (30 mL) was added sodium hydride (400 mg, 60% in oil, 10 mmol, 1 eq.) under an inert atmosphere. The reaction was cooled to -20 ºC and benzyl bromide (1.19 mL, 10 mmol, 1 eq.) in THF (6 mL) was added and the solution allowed to stir at rt for 5 h. The reaction was concentrated, diluted with DCM, washed with H_2O, dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The residue was purified by flash silica gel column chromatography (2:1 hexane:EtOAc) to afford product **202** (813 mg, 46%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.43 (m, 1H, *H10*), 3.39 (dd, *J* = 9.5, 8.0 Hz, 1H, *H6*), 3.56 (dd, *J* = 9.5, 3.5 Hz, 1H, *H6*), 4.30-4.43 (m, 1H, *H7*), 4.59 (s, 2H, *H5*), 5.17-5.25 (m, 1H, *H9*), 5.31-5.44 (m, 1H, *H9*), 5.85 (ddd, *J* = 17.0, 10.5, 5.5 Hz, 1H, *H8*), 7.29-7.43 (m, 5H, *H1/2/3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 72.0, 73.4, 74.5, 116.9, 127.4, 128.2, 128.9, 136.5, 138.3.

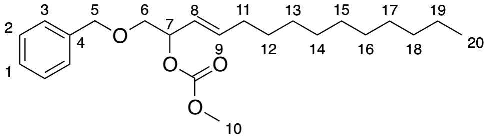
1-(Benzyloxy)but-3-en-2-yl methyl carbonate (200a)[247]



General procedure **H** was followed using 1-(benzyloxy)but-3-en-2-ol **202** (813 mg, 4.6 mmol), pyridine (1.12 mL, 13.8 mmol, 3 eq.) and methyl chloroformate (0.71 mL, 9.2 mmol, 2 eq.) in DCM (5 mL). The resulting crude mixture was purified by flash silica gel column chromatography (9:1-5:1 Hexane:Et_2O) to afford product **200a** (706 mg, 65%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.62-3.69 (m, 2H, *H6*), 3.80 (s, 3H, *H10*), 4.59 (s, 2H, *H5*), 5.26-5.45 (m, 3H, *H9/7*), 5.82 (dd, J = 10.5, 6.5 Hz, 1H, *H8*), 7.32-7.36 (m, 5H, *H1/2/3*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ: 54.5, 71.2, 73.3, 77.1, 118.7, 127.7, 127.7, 128.4, 132.7, 137.8, 155.3.

(3*E*)-1-(Benzyloxy)*tetra*dec-3-en-2-yl methyl carbonate (223)



To a solution of 1-(benzyloxy)but-3-en-2-yl methyl carbonate **200a** (100 mg, 0.42 mmol) and styrene (0.14 mL, 1.18 mmol, 2.8 eq.) in DCM (6 mL) was added Grubbs' second generation catalyst (18mg, 0.02 mmol, 5 mol%). The reaction was heated to reflux for 72 h. Upon cooling, the solvent was removed *in vacuo*. The resulting crude mixture was purified by flash silica gel column chromatography (9:1-5:1 Hexane:Et_2O) to afford product **223** (38 mg, 24%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, J = 6.0 Hz, 3H, *H18*), 1.22-1.46 (m, 12H, *H12-17*), 2.02-2.18 (m, 2H, *H11*), 3.50-3.66 (m, 2H, *H6*), 3.78 (s, 3H, *H10*), 5.25-5.35 (m, 1H, *H7*), 4.58 (s, 2H, *H5*), 5.36-5.50 (m, 3H, *H9*), 5.71-5.92 (m, 1H, *H8*), 7.26-7.38 (m, 5H, *H1/2/3*);

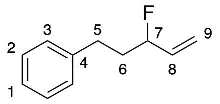
^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 28.7, 29.1, 29.2, 29.4, 29.5, 29.6, 31.9, 32.3, 54.6, 71.6, 73.2, 77.6, 124.2, 127.6, 127.6, 128.4, 136.8, 138.0, 155.2; **IR** (CH_2Cl_2) ν 1749, 1262; **HRMS** calc for $C_{23}H_{36}NaO_4^+$ ($[M+Na]^+$): 399.2511, found 399.2506.

5.2.6 Ir-catalysed fluorination

General procedure I for allylic fluorination with $[Ir(COD)Cl]_2$

To a solution of allylic carbonate (0.2 mmol) and TBAF(*t*BuOH)$_4$ (2 eq, 0.4 mmol) in dry DCM (8 mL) was added a solution of $[Ir(COD)Cl]_2$ (2 mol%) in dry DCM (2 mL) in 4 portions over 45 min. The reaction was allowed to stir at 40 °C until TLC indicated complete conversion of the starting material and no longer than 24 h. Additional portions of catalyst (up to 4 mol%) were added to reactions which did not show completion after 6 hours. To the resulting crude mixture was added 20 mol% of 3-nitro-1-fluorobenzene as an internal reference and the mixture analysed by ^{19}F NMR.

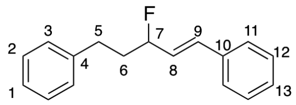
(3-fluoropent-4-en-1-yl)benzene (226)



General procedure **I** was followed using methyl 5-phenylpent-1-en-3-yl carbonate **220** (22 mg, 0.1 mmol), $[Ir(COD)Cl]_2$ (1.3 mg, 0.002 mmol, 2 mol%) and TBAF(*t*BuOH)$_4$ (112 mg, 0.2 mmol, 2 eq.) in DCM (1 mL) and reaction stirred for 1 h. To the resulting crude mixture was added 20 mol% of 3-nitro-1-fluorobenzene as an internal reference and the mixture analysed by ^{19}F NMR, giving a 14% ^{19}F-NMR yield of product that was tentatively assigned as **226** based on the reported data in the literature.[248]

^{19}F NMR (376.5 MHz, CD_2Cl_2) δ: -178.6.

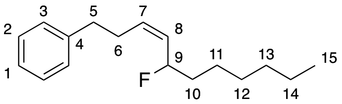
1,1'-[(1*E*)-3-fluoropent-1-ene-1,5-diyl]dibenzene (227)



General procedure **I** was followed using (1*E*)-1,5-diphenylpent-1-en-3-yl methyl carbonate **221** (29 mg, 0.1 mmol), $[Ir(COD)Cl]_2$ (1.3 mg, 0.002 mmol, 2 mol%) and TBAF(*t*BuOH)$_4$ (112 mg, 0.2 mmol, 2 eq.) in DCM (1 mL). A second portion of $[Ir(COD)Cl]_2$ (1.3 mg, 0.002 mmol, 2 mol%) was added after 6 h and the reaction was left to stir for 18 h. To the resulting crude mixture was added 20 mol% of 3-nitro-1-fluorobenzene as an internal reference and the mixture analysed by ^{19}F NMR giving a 14% ^{19}F-NMR yield of a product that was tentatively assigned as **227**.

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 2.00-2.11 (m, 2H, *H6*), 2.81-2.89 (m, 2H, *H5*), 5.10 (dq, *J* = 48.0, 8.0 Hz, 1H, *H7*), 6.27-6.36 (m, 1H, *H8*), 6.69 (d, *J* = 16.0 Hz, 1H, *H9*), 7.18-7.46 (m, Ar-H overlaid with starting carbonate); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ: -174.0.

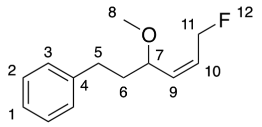
[(3*Z*)-5-fluoroundec-3-en-1-yl]benzene (228)



General procedure **I** was followed using methyl (3*Z*)-1-phenylundec-3-en-5-yl carbonate **218** (61 mg, 0.2 mmol), $[Ir(COD)Cl]_2$ (2.7 mg, 0.004 mmol, 2 mol%) and TBAF(*t*BuOH)$_4$ (224 mg, 0.4 mmol, 2 eq.) in DCM (2 mL). The reaction was left to stir for 24 h. To the resulting crude mixture was added 20 mol% of 3-nitro-1-fluorobenzene as an internal reference and the mixture was analysed by ^{19}F NMR, giving a trace amount of product that was tentatively assigned as **228**.

^{19}F NMR (376.5 MHz, CD_2Cl_2) δ: -171.4

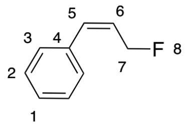
[(4*Z*)-6-fluoro-3-methoxyhex-4-en-1-yl]benzene (237)



General procedure **I** was followed using methyl (3*Z*)-1-phenylundec-3-en-5-yl carbonate **215** (61 mg, 0.2 mmol), $[Ir(COD)Cl]_2$ (2.7 mg, 0.004 mmol, 2 mol%) and $TBAF(tBuOH)_4$ (224 mg, 0.4 mmol, 2 eq.) in DCM (2 mL). The reaction was left to stir for 24 h. To the resulting crude mixture was added 20 mol% of 3-nitro-1-fluorobenzene as an internal reference and the mixture was analysed by ^{19}F NMR, giving a trace amount of product that was tentatively assigned as **237**.

^{19}F NMR (376.5 MHz, CD_2Cl_2) δ: -171.4

[(1*Z*)-3-fluoroprop-1-en-1-yl]benzene (*Z*-172a)



General procedure **I** was followed using methyl (2*Z*)-3-phenylprop-2-en-1-yl carbonate **209** (36 mg, 0.19 mmol), $[Ir(COD)Cl]_2$ (2.5 mg, 0.004 mmol, 2 mol%) and $TBAF(tBuOH)_4$ (212 mg, 0.38 mmol, 2 eq.) in DCM (2 mL) and the reaction was stirred for 1 h. To the resulting crude mixture was added 20 mol% of 3-nitro-1-fluorobenzene as an internal reference and the mixture analysed by ^{19}F NMR, giving a trace amount of product that was tentatively assigned as ***Z*-172a** based on the reported data in the literature.[249] A *Z*:*E* ratio of 8:1 was assigned from the ^{19}F NMR spectra

^{19}F NMR (376.5 MHz, CD_2Cl_2) δ: -208.2 (*Z*-**172a**), -210.8 (*E*-**172a**).

5.3 Experimental Data for Chapter 3

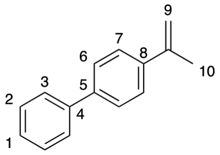
General Procedure J for the modification of quinones [17]

To a solution of quinone (0.25 mmol, 1.0 equiv) in dichloromethane (or trifluorotoluene where noted, 1.25 mL) was added the corresponding boronic acid (0.375 mmol, 1.5 equiv), water (0.75 mL), and silver(I) nitrate (0.1 M solution in water, 8.5 mg, 0.05 mmol, 0.2 equiv). Potassium persulfate (202 mg, 0.75 mmol, 3.0 equiv) was then added and the solution was stirred vigorously at rt and monitored by thin-layer chromatography analysis of the organic layer. The reaction was stirred for 24 h then diluted with DCM (3 mL) and washed with 5% sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 4 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography to afford the desired product.

General Procedure K for C-H functionalisation-fluorination

To a solution of solution of 4-(prop-1-en-2-yl)biphenyl (19 mg, 0.1 mmol) and $Pd(OTFA)_2$ (33 mg, 0.1 mmol) in solvent (0.1M) was added the required additive (0.1 mmol) and fluoride source (0.2 mmol) and reaction allowed to stir at 80 ºC for 24 h. The reaction was cooled to rt and filtered through a short pad of Celite. The organics were diluted with EtOAc and then washed with saturated $NH_4Cl_{(aq)}$. The combined organic extracts were dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The residue was analysed by HPLC: Phenomenex Gemini-NX 5u C18 110A 150 x 4.6 mm, CH_3CN/H_2O = 50/50 0-36 min, 95% CH_3CN 38-42 min, 50/50 45 min, 1.0 mL/ min, 259 nm) t_R (fluoride)= 17.2 min, t_R (starting alkene)= 30.9 min.

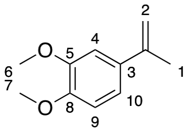
4-(Prop-1-en-2-yl)biphenyl (294)[250251]



To methyltriphenylphosphonium bromide (3.26 g, 9.12 mmol, 1.2 eq.) in THF (25 mL) at 0 ºC was added *n*BuLi (4 mL, 2.2M in hexane, 9.12 mmol, 1.2 eq.) dropwise and the reaction was allowed to stir at rt for 1 h. After this time, 4-acetylbiphenyl (1.5 g, 7.6 mmol) in THF (5 mL) was allowed to stir at rt for 3 h. The solution was quenched with saturated $NH_4Cl_{(aq)}$. The organic layer was separated and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash silica gel column chromatography (4:1 hexane:DCM) to afford product **294** as a white solid (1.21 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.20-2.23 (m, 3H, *H10*), 5.11-5.15 (m, 1H, *H9*), 5.40-5.46 (m, 1H, *H9*), 7.29-7.65 (m, 9H, *H1/2/3/6/7*); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 22.3, 112.9, 126.4, 127.4, 127.4, 127.7, 129.2, 139.5, 140.7, 141.2, 143.2.

1,2-Dimethoxy-4-(prop-1-en-2-yl)benzene (312)[252]

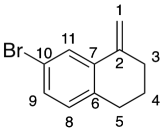


To methyltriphenylphosphonium bromide (1.29 g, 3.6 mmol, 1.2 eq.) in THF (10 mL) at 0 ºC was added *n*BuLi (1.6 mL, 2.3M in hexane, 3.6 mmol, 1.2 eq.) dropwise and the reaction was allowed to stir at rt for 1 h. After this time 3′,4′-dimethoxyacetophenone (541 mg, 3 mmol) in THF (5 mL) was added and the reaction allowed to stir at rt for 3 h. The solution was quenched with saturated $NH_4Cl_{(aq)}$. The organic layer was separated and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried

($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash silica gel column chromatography (4:1 hexane:DCM) to afford product **312** as a colourless oil (205 mg, 38%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15 (d, *J* = 1.0 Hz, 3H, *H1*), 3.89 (d, *J* = 1.0 Hz, 3H, *H6/7*), 3.91 (d, *J* = 1.0 Hz, 3H, *H6/7*), 5.02 (d, *J* = 1.0 Hz, 1H, *H2*), 5.30 (d, *J* = 1.0 Hz, 1H, *H2*), 6.83 (d, *J* = 8.0 Hz, 1H, *H10*), 6.98-7.05 (m, 2H, *H4/9*); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 21.9, 55.8, 55.9, 108.8, 110.8, 111.0, 118.0, 134.2, 142.8, 148.6, 148.7.

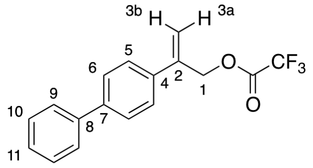
7-Bromo-1-methylidene-1,2,3,4-tetrahydronaphthalene (313)



To methyltriphenylphosphonium bromide (1.29 g, 3.6 mmol, 1.2 eq.) in THF (10 mL) at 0 ºC was added *n*BuLi (1.6 mL, 2.3M in hexane, 3.6 mmol, 1.2 eq.) dropwise and the reaction was allowed to stir at rt for 1 h. After this time 3′,4′-dimethoxyacetophenone (675 mg, 3 mmol) in THF (5 mL) was added and the reaction allowed to stir at rt for 3 h. The solution was quenched with saturated $NH_4Cl_{(aq)}$. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The residue was purified by flash silica gel column chromatography (4:1 hexane:DCM) to afford product **313** as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.85-1.91 (m, 2H, *H4*), 2.52-2.56 (m, 2H, *H3*), 2.79 (t, *J* = 6.0 Hz, 2H, *H5*), 5.02 (s, 1H, *H1*), 5.48 (s, 1H, *H1*), 7.00 (dd, *J* = 8.0, 0.5 Hz, 1H, *H8*), 7.29 (dd, *J* = 8.0 Hz, 2 Hz, 1H, *H9*), 7.78 (d, *J* = 1.5 Hz, 1H, *H11*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 23.5, 30.0, 32.8, 109.2, 119.7, 127.1, 130.4, 130.8, 136.1, 136.8, 142.3; **IR** (CH_2Cl_2) ν 2937, 1691, 1626, 638; **HRMS** calc for $C_{11}H_{11}Br$ $[M]^+$ 222.0044, found 222.0047.

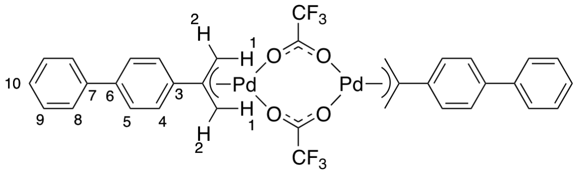
2-(Biphenyl-4-yl)prop-2-en-1-yl trifluoroacetate (295)



To a solution of **162b** (1.43 g, 6.8 mmol) in DCM (12 mL) at 0 ºC was added triethylamine (1 mL, 7.50 mmol, 1.1 eq.) and trifluoroacetic anhydride (1 mL, 7.15 mmol, 1.05 eq.) dropwise. The reaction was allowed to warm to rt and stirred until TLC showed completion. The reaction was quenched with H_2O and saturated aq. $NaHCO_{3(aq)}$. The organics were combined, dried ($MgSO_4$), filtered and the solvent was removed *in vacuo.* The resulting crude mixture was purified by flash silica gel column chromatography (5:1 Hexane:EtOAc) to afford the product **295** as a yellow solid (1.8 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.19 (s, 2H, *H1*), 5.41 (s, 1H, *H3a/b*), 5.65 (s, 1H, *H3a/b*), 7.24-7.33 (m, 1H, *H11*), 7.35-7.45 (m, 4H, *H9/10*), 7.50-7.58 (m, 4H, *H5/6*); **^{13}C NMR** (100MHz, $CDCl_3$) δ: 68.7, 117.2, 126.3, 127.0, 127.4, 127.6, 128.9, 135.9, 140.0, 140.3, 141.3, 157.5; **IR** (neat) ν 1720; **HRMS** calc for $C_{17}H_{13}O_2F_3$ $[M]^+$ 306.0868, found 306.0867; **Mp**: 81 ºC.

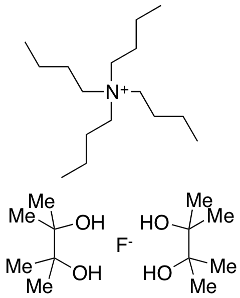
2-(Biphenyl-4-yl)prop-2-en-1-yl palladium trifluoroacetate dimer (296)



To a solution of $Pd(dba)_2$ (740 mg, 2.4 mmol) in THF:MeCN (3:1, 7.5 mL THF, 2.5 mL MeCN) at room temperature was added allylic trifluoroacetate **295** (1.8 g, 6 mmol). The reaction was allowed to stir until the deep red colour was lost and the reaction appeared green/yellow. The solvent was removed *in vacuo* and the residue was extracted with 10% MeCN:H_2O to afford **296** (734 mg, 74%) as a yellow solid. Product **296** was pure enough to use, crystals were grown from DCM:*t*BuOMe for analysis by x-ray crystallography.

^{1}H NMR (500 MHz, CD_2Cl_2) δ: 2.50-3.37 (bm, 2H, *H1/2*), 4.12-4.67 (bs, 2H, *H1/2*), 7.39-7.47 (m, 1H, *H10*), 7.48-7.56 (m, 2H, *H9*), 7.58-7.81 (m, 6H, *H8/5/4*); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ: 53.8, 116.6 (q, *J* = 289 Hz, *CF_3*), 127.4, 128.1, 128.4, 129.3, 140.1, 143.9, 165.3 (q, *J* = 38 Hz, *C=O*); **IR** (Solid): 1739, 1671; **HRMS** calc for $C_{34}H_{26}O_4F_6Pd_2$ ($[M]^+$): 823.9805, not found; **Mp**: 102 ºC (dec).

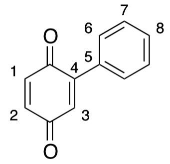
Tetra-*n*-butylammonium flouride bis(pinacol) (TBAF(Pin)$_2$) (302)



To an oven-dried 100 mL round bottom flask under a nitrogen atmosphere and equipped with a stir bar and reflux condenser, were added hexanes (50 mL), $TBAF(H_2O)_3$ (2.0 mmol, 630 mg) and pinacol (8.0 mmol, 473 mg). The resulting suspension was allowed to stir at vigorous reflux (80–85 °C) for 2 h. During the course of the reaction the persistent presence of a white solid precipitate was observed. The solution was allowed to cool to rt, rapidly filtered, washed with hexanes (×3), and dried under high vacuum, giving TBAF(Pin)$_2$ **302** as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (t, *J* = 7.0 Hz, 12H), 1.15 (s, 24 H), 1.40 (m, 8H), 1.64–1.56 (m, 8H), 3.28–3.24 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 13.6, 19.6, 24.0, 25.2, 58.4, 74.4; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ: –114.53; **IR** ($CDCl_3$) ν 3160, 2965, 2945, 2878, 1464, 1381, 1152, 951, 888.

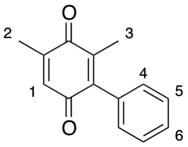
2-Phenyl-1,4-benzoquinone (305)[253254]



General procedure **J** was followed using benzoquinone (162 mg, 1.5 mmol), phenyl boronic acid (274 mg, 2.25 mmol), silver nitrate (51 mg, 0.3 mmol), potassium persulfate (1.22 g, 4.5 mmol) and H_2O (4.5 mL) in DCM (7.5 mL). The resulting crude mixture was purified by flash silica gel column chromatography (9:1-5:1 Hexane:Et_2O) to afford the product **305** as a yellow oil (174 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.73-6.82 (m, 3H, *H1/2/3*), 7.33-7.44 (m, 5H, *H6/7/8*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 128.5 (2C), 129.2, 130.1, 132.7, 136.2, 137.0, 145.9, 186.6, 187.6.

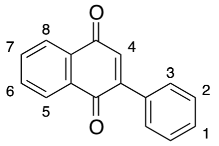
3,5-Dimethyl-2-phenyl-1,4-benzoquinone (307)[14]



General procedure **J** was followed using 2,6-dimethylbenzoquinone (204 mg, 1.5 mmol), phenyl boronic acid (274 mg, 2.25 mmol), silver nitrate (51 mg, 0.3 mmol), potassium persulfate (1.22 g, 4.5 mmol) and H_2O (4.5 mL) in DCM (7.5 mL). The resulting crude mixture was purified by flash silica gel column chromatography (9:1-5:1 Hexane:Et_2O) to afford product **307** as a yellow solid (223 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.98 (s, 3H, *H3*), 2.12 (d, J = 1.5 Hz, 3H, *H2*), 6.67 (q, J = 1.5 Hz, 1H, *H1*), 7.09-7.21 (m, 2H, Ar*H*), 7.35-7.49 (m, 3H, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 14.1, 15.9, 128.1, 128.5, 129.5, 132.9, 133.2, 141.6, 143.6, 145.5, 186.7, 188.6; **IR** (CH_2Cl_2) ν 1749; **HRMS** calc for $C_{14}H_{12}O_2$ $[M]^+$ 212.0837, found 212.0832.

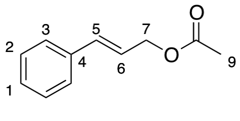
2-Phenyl-1,4-naphthoquinone (308)[255]



General procedure **J** was followed using 1,4-naphthoquinone (237 mg, 1.5 mmol), phenyl boronic acid (274 mg, 2.25 mmol), silver nitrate (51 mg, 0.3 mmol), potassium persulfate (1.22 g, 4.5 mmol) and H_2O (4.5 mL) in DCM (7.5 mL). The resulting crude mixture was purified by flash silica gel column chromatography (9:1-5:1 Hexane:Et_2O) to afford the product **308** as a yellow solid (141 mg, 40%).

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.10 (s, 1H, *H4*), 7.47-7.52 (m, 3H, *H1/2*), 7.56-7.62 (m, 2H, *H3*), 7.77-7.82 (m, 2H, *H5/8*), 8.12-8.23 (m, 2H, *H6/7*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 126.0, 127.0, 128.5 (2C), 129.4 (2C), 130.0, 132.1, 132.5, 133.4, 133.8, 133.9, 135.2, 148.1, 184.4, 185.1; **IR** (CH_2Cl_2) ν 1656; **HRMS** calc for $C_{16}H_{10}NaO_2$ $[M+Na]^+$ 257.0578, found 257.0573.

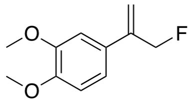
(2*E*)-3-Phenylprop-2-en-1-yl acetate (311)[256]



A borosilicate vial was charged with $Pd(OAc)_2$ (5 mg, 0.02 mmol, 10 mol%), benzoquinone (43 mg, 0.4 mmol, 2 eq.) and 4 Å molecular sieves (43 mg). A separate borosilicate vial was charged with DMSO (0.6 mL), acetic acid (0.6 mL) and allyl benzene (26 μL, 0.2 mmol) and then the liquids added to the vial containing the solids. The vial was then capped and allowed to stir at 40 ºC for 48 h. After this time the reaction was quenched with $NH_4Cl_{(aq)}$ (2 mL) and extracted with DCM (3 x 20 mL). The organic layers were combined and washed with H_2O (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude mixture was purified by flash silica gel column chromatography to afford product **311** (16 mg, 46%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.11 (s, 3H, *H9*), 4.74 (dd, *J* = 6.0, 1 Hz, 2H, *H7*), 6.30 (dt, *J* = 16.0, 6.0 Hz, 1H, *H6*), 6.63-6.71 (m, 1H, *H5*), 7.27-7.42 (m, 5H, *H1-3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 21.4, 65.5, 123.6, 127.1, 128.5, 129.1, 134.7, 136.7, 171.3.

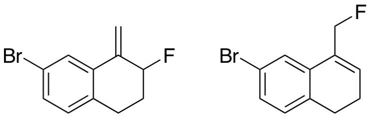
4-(3-Fluoroprop-1-en-2-yl)-1,2-dimethoxybenzene (158f)



General procedure **K** was followed using 1,2-dimethoxy-4-(prop-1-en-2-yl)benzene **312** (18 mg, 0.1 mmol), $Pd(TFA)_2$ (33 mg, 0.1 mmol, 1 eq.), benzoquinone (22 mg, 0.2 mmol, 2 eq.) and TBAF(*t*BuOH)$_4$ (112 mg, 0.2 mmol, 2 eq.) in DCE (1 mL). The reaction was stirred at 80 ºC for 24 h. To the resulting crude mixture was added 20 mol% of 3-nitro-1-fluorobenzene as an internal reference and the mixture analysed by ^{19}F NMR, giving a trace amount of product that was tentatively assigned as **158f**.

^{19}F NMR (376.5 MHz, $CDCl_3$) δ: -211.7 (td, *J* = 49.0, 3.0 Hz, 1F).

7-Bromo-2-fluoro-1-methylidene-1,2,3,4-tetrahydronaphthalene (158g) and 6-Bromo-4-(fluoromethyl)-1,2-dihydronaphthalene (172k)



General procedure **K** was followed using 7-bromo-1-methylene-1,2,3,4-tetrahydronaphthalene **313** (22 mg, 0.1 mmol), $Pd(TFA)_2$ (33 mg, 0.1 mmol, 1 eq.), benzoquinone (22 mg, 0.2 mmol, 2 eq.) and TBAF(*t*BuOH)$_4$ (112 mg, 0.2 mmol, 2 eq.) in DCE (1 mL). The reaction was stirred at 80 ºC for 24 h. To the resulting crude mixture was added 20 mol% of 3-nitro-1-fluorobenzene as an internal reference and the mixture analysed by ^{19}F NMR giving a trace amount of product that was tentatively assigned as **158g** and **172k** in a 2:1 ratio, respectively.

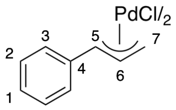
^{19}F NMR (376.5 MHz, $CDCl_3$) δ: -175.3 (**X**), -209.5.

5.4 Experimental Data for Chapter 4

General Procedure L for the fluorination of allylpalladium complexes

To a solution of allylpalladium complex (0.01 mmol) in DCM (1.5 mL) was added solid XeF_2 (0.02 mmol, 2 eq.) and the reaction was left to stir for the appropriate time. After this time, ferrocene was added to quench unreacted XeF_2. The solvent was then removed *in vacuo* and loaded onto a prep TLC plate to isolate fluoride for chiral HPLC analysis. To obtain conversions the reactions were conducted in the same way in CD_2Cl_2 and 20 mol% of 3-nitro-1-fluorobenzene was added as an internal reference. The reaction was then analysed by ^{19}F NMR.

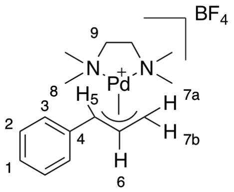
[Pd(1-phenylallyl)Cl]$_2$ (352)[257]



$PdCl_2$ (1 eq.) was added to a solution of NaCl (2.2 eq.) in water and allowed to react at rt for 30 minutes. After this time, cinnamyl chloride (3.4 eq.) was added and the solution was allowed to stir at rt overnight. After extraction of the reaction with chloroform the product was crystallised from dichloromethane by the slow addition of pentane. This delivered the desired product **352** in 74%.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.05 (dt, *J* = 12.0 Hz, 1H, *H7*), 3.98 (d, *J* = 6.0 Hz, 1H, *H7*), 4.63, (d, *J* = 12.0 Hz, 1H, *H5*), 5.81 (td, *J* = 11.7, 6.5 Hz, 1H, *H6*), 7.23-7.55 (m, 5H, *H1/2/3*); **IR** (CH$_2$Cl$_2$) ν 3059, 2360, 757, 691.

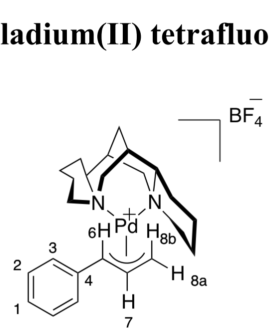
{[Pd(1-phenylallyl)tmeda]BF$_4$} (350)[258]



Dimer complex **352** (1 eq.) was reacted with AgBF$_4$ (2 eq.) in THF (0.01M) by stirring at rt for 10 minutes. A precipitate of AgCl was then removed by centrifugation at low rpm and the supernatant decanted and reacted further with tetramethylethylenediamine (TMEDA) (2 eq.) for 10 minutes at rt. Product **350** was obtained in a 70% yield by crystallisation from dichloromethane by the slow addition of pentane.

^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.46-2.67 (m, 12H, *H8*), 2.67-2.83 (m, 4H, *H9*), 3.29-3.35 (m, 1H, *H7a/b*), 3.81-3.87 (m, 1H, *H7a/b*), 4.56 (d, *J* = 12.0 Hz, 1H, *H5*), 6.16 (dtd, *J* = 12.0, 10.0, 2.0 Hz, 1H, *H6*), 7.39-7.56 (m, 5H, *H1/2/3*); **IR** (CH$_2$Cl$_2$) ν 2896, 1469, 1053, 766.

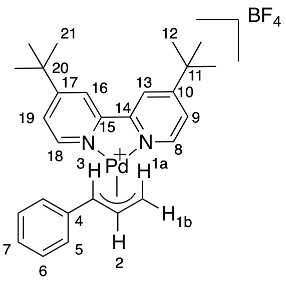
{(-(-)-sparteine)(1-phenylallyl)palladium(II) tetrafluoroborate} (359)



Dimer complex **352** (1 eq.) was reacted with AgBF$_4$ (2 eq.) in THF (0.01M) by stirring at rt for 10 minutes. A precipitate of AgCl was then removed by centrifugation at low rpm and the supernatant decanted and reacted further with (-)-sparteine (2 eq.) for 10 minutes at rt. Product **359** was obtained in a 79% yield by crystallisation from dichloromethane by the slow addition of pentane.

^{1}H NMR (500 MHz, CD_2Cl_2) δ: 1.31-3.21 (m, 26H, *Sparteine-H*), 3.76 (d, 1H, *J* = 13 Hz, *H8a/b*), 3.97 ((d, 1H, *J* = 7 Hz, *H8a/b*), 4.21 (d, 1H, *J* = 10 Hz, *H6*), 6.17-6.30 (m, 1H, *H7*), 7.36-7.42 (m, 2H, *H2*), 7.43-7.50 (m, 1H, *H1*), 7.53-7.59 (m, 2H, *H3*); **^{13}C NMR** (125MHz, CD_2Cl_2) δ: 24.1, 24.3, 26.4, 26.5, 26.6, 28.1, 31.6, 35.1, 61.1, 64.6, 66.3, 68.8, 71.3, 114.9, 128.1, 128.6, 130.0, 138.2, 139.2; **IR** (neat) ν 2970, 1614; **HRMS** calc for $C_{24}H_{35}N_2Pd_2$ $[M]^+$ 457.1830, found 457.1813; **Mp**: 185 ºC (dec).

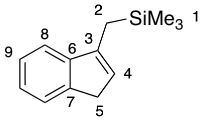
{(4,4′-di-*tert*-butyl-2,2′-dipyridyl)(1-phenylallyl)palladium(II) tetrafluoroborate} (358)



Dimer complex $[Pd(1\text{-phenylallyl})Cl]_2$ **352** (135mg, 0.26 mmol, 1 eq.) was reacted with $AgBF_4$ (101 mg, 0.52 mmol, 2 eq.) in THF (18 mL) by stirring at rt for 10 minutes. A precipitate of AgCl was then removed by centrifugation at low rpm and the supernatant decanted and reacted further with 4,4′-di-*tert*-butyl-2,2′-dipyridyl (140 mg, 0.52 mmol, 2 eq.) for 10 minutes at rt. Product **358** was obtained as a yellow solid (205 mg, 68%). Crystallisation from DCM:Pentane gave crystals suitable for x-ray crystallography.

^{1}H NMR (500 MHz, CD_2Cl_2) δ: 1.40 (s, 9H, *H12/21*), 1.49 (s, 9H, *H12/21*), 3.72 (d, *J* = 7.0 Hz, 1H, *H1a/b*), 4.39 (d, *J* = 7.0 Hz, 1H, *H1a/b*), 4.85 (d, *J* = 12.0 Hz, 1H, *H3*), 6.42 (dt, *J* = 12.0, 7 Hz, 1H, *H2*), 6.94 (d, *J* = 6.0 Hz, 1H, *H8*), 7.27 (dd, *J* = 6.0, 2 Hz, 1H, *H9*), 7.50-7.56 (m, 2H, *H5*), 7.57-7.62 (m, 1H, *H7*), 7.65-7.69 (m, 2H, *H6*), 7.70 (dd, *J* = 6.0 Hz, 1H, *H19*), 8.13 (d, *J* = 2.0 Hz, 1H, *H13/16*), 8.18 (d, *J* = 2.0 Hz, 1H, *H13/16*), 8.80 (d, *J* = 6.0 Hz, 1H, *H18*); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ: 30.3, 30.4, 36.1, 36.2, 61.8, 79.4, 114.4, 119.9, 120.0, 124.5, 125.3, 128.6, 129.7, 130.5, 136.5, 148.9, 154.4, 154.4, 155.4, 166.0, 166.2; **^{19}F NMR** (500 MHz, CD_2Cl_2) δ:: -151.4; **IR** (CH_2Cl_2) ν 2962, 1614; **HRMS** calc for $C_{27}H_{33}N_2Pd$ [M^+] 491.1673, found 491.1666; **Mp** 245 ºC decomposed.

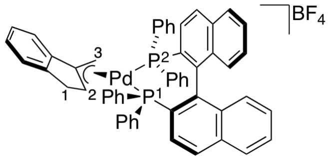
(1*H*-inden-3-ylmethyl)(trimethyl)silane (361)



To a solution of indene (1.8 mL, 15 mmol) in THF (17.5 mL) at 0 ºC was added dropwise *n*BuLi. The reaction mixture was then allowed to warm to rt and stirred for a further 3 h. This anion solution was then added dropwise to a solution of bromomethyltrimethylsilane in THF (8.5 mL) at -78 ºC. After addition the reaction was warmed to rt and stirred overnight. The reaction mixture was evaporated to dryness and the residue dissolved in DCM and filtered through Celite and the solvent removed *in vacuo*. The resulting residue was purified by flash column chromatograpy (100 % Pet Ether 30:40) affording **361** (2.49 g, 82%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.07 (s, 9H, *H1*), 2.09 (s, 2H, *H2*), 3.37 (s, 2H, *H5*), 6.08 (s, 1H, *H4*), 7.06-7.34 (m, 4H, *H8/9*); **^{13}C-NMR** (100 MHz, $CDCl_3$): -0.4, 17.6, 38.1, 119.4, 123.6, 124.1, 125.5, 125.8, 141.3, 144.5, 147.2.

{(*R*)-(+)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)((1*H*-inden-3-yl)methyl)palladium(II) tetrafluoroborate (364)

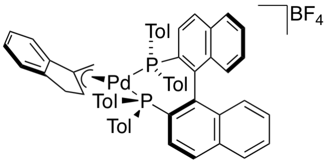


Into a vial was placed palladium chloride dimer **362** (27 mg, 0.05 mmol, 1 eq.) and (*R*)-BINAP (62 mg, 0.10 mmol, Pd:L 1:1). DCM (2.5 mL) was added and the solution stirred for 10 min. $AgBF_4$ (19 mg, 0.10 mmol, Pd:BF_4 1:1) was then added to the stirring solution and the resulting suspension stirred at rt for 30 mins. After this time the mixture was filtered through a syringe filter (Phenomenex, RC Membrane, pore size 0.45 μm, 4mm) to yield a clear yellow solution that was concentrated *in vacuo*. The residue was redissolved in the minimal amount of DCM and Et_2O was added until a solid precipitate was formed that was collect giving complex **364** as a yellow solid (53 mg, > 95%).

^{1}H NMR (500 MHz, CD_2Cl_2, 213K) δ: 2.21-2.31 (m, 1H, H_1'), 2.80-2.99 (m, 1H, *H1*), 3.90-4.00 (d, *J* = 9.0 Hz, 1H, *H3*), 4.05 (bs, 1H, *H3'*), 4.24-4.33(d, *J* = 9.0 Hz, 1H, *H2*), 5.62-5.70 (m, 1H, *Ar-H*, P_2), 6.32 (t, *J* = 7.0 Hz, 1H, *Ar-H*, P_2), 6.39 (t, *J* = 7.0 Hz, 1H, *Ar-H*, P_2), 6.46 (d, *J* = 8.5 Hz, 1H, *Ar-H*), 6.55 (d, *J* = 8.5 Hz, 1H, *Ar-H*), 6.74 (t, *J* = 7.0 Hz, 1H, *Ar-H*, P_2), 6.91 (t, *J* = 7.0 Hz, 1H, *Ar-H*, P_1), 6.96 (t, *J* = 8.0 Hz, 1H, *Ar-H*, P_2), 6.99-7.16 (m, 6H, *Ar-H*, P_2), 7.19 (d, *J* = 7.0 Hz, 1H, *Ar-H*), 7.32 (t, *J* = 7.0 Hz, 1H, *Ar-H*), 7.37-7.43 (m, 2H, *Ar-H*, P_1), 7.43-7.55 (m, 6H, *Ar-H*, $P_{1/2}$), 7.57-7.77 (m, 12H, *Ar-H*, $P_{1/2}$); **^{13}C NMR** (125 MHz, CD_2Cl_2, 213K) δ: 15.5, 21.5, 37.5, 66.2, 65.7, 65.9, 90.6 (dd, *J* = 31, 5 Hz), 121.0, 121.4, 123.5, 123.9, 125.4, 125.7, 126.3, 126.3, 126.4, 126.5, 126.9, 126.9, 127.0, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.7, 128.8, 128.9, 129.1, 129.1, 129.9, 130.5, 130.7, 131.5 (d, *J* = 9 Hz), 133.0, 133.1, 133.1, 133.2, 133.6, 133.8, 134.0, 134.1, 136.7, 136.8, 137.8, 138.2, 138.9, 138.1, 138.8, 138.7, 146.8; **^{19}F {1H}NMR** (376.5MHz, CD_2Cl_2, 213K): -152.71 (s, 4F, *BF_4*); **^{31}P NMR** (97 MHz, CD_2Cl_2, 213K) 26.4

(d, *J* = 49.0 Hz, 1P, *P1*), 25.8 (d, *J* = 49.0 Hz, 1P, *P2*); **IR** (CH_2Cl_2) ν 2361; **HRMS** calc for $C_{54}H_{41}P_2Pd$ $[M]^+$ 857.1713, found 857.1720; **Mp** decomposed 199 ºC.

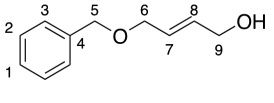
{(*R*)-(+)-(1,1′-Binaphthalene-2,2′-diyl)bis(ditolylphosphine)((1*H*-inden-3-yl)methyl))palladium(II) tetrafluoroborate (365)



Into a vial was placed palladium chloride dimer **362** (14 mg, 0.025 mmol, 1 eq.) and (*R*)-T-BINAP (34 mg, 0.05 mmol, Pd:L 1:1). DCM (1.25 mL) was added and the solution was stirred for 10 min. $AgBF_4$ (10 mg, 0.05 mmol, Pd:BF_4 1:1) was then added to the stirring solution and the resulting suspension stirred at rt for 30 mins. After this time the mixture was filtered through a syringe filter (Phenomenex, RC Membrane, pore size 0.45 μm, 4mm) to yield a clear yellow solution that was concentrated *in vacuo*. The residue was redissolved in the minimal amount of DCM and Et_2O added until a solid precipitate was formed that was collect giving complex **365** as a yellow solid (9 mg, > 18%)

^{1}H NMR (500 MHz, CD_2Cl_2, 213K) δ: 1.78 (s, 3H, *CH_3;Tol*), 1.94 (s, 3H, *CH_3;Tol*), 2.07 (s, 3H, *CH_3;Tol*), 2.34-2.45 (m, 1H, *H1'*), 2.51 (s, 3H, *CH_3;Tol*), 2.88-3.07 (m, 1H, *H1*), 3.94 (d, *J* = 9.0 Hz, 1H, *H3*), 4.07 (bs, 1H, *H3'*), 4.32 (d, *J* = 9.0 Hz, 1H, *H2*), 6.19 (d, *J* = 7.0 Hz, 2H, *Ar-H*; BINAP), 6.44-6.49 (m, 1H, *Ar-H*), 6.53-6.61 (m, 4H, *Ar-H*), 6.96-7.01 (m, 2H, *Ar-H*), 7.01-7.06 (m, 2H, *Ar-H*), 7.09-7.14 (m, 2H, *Ar-H*), 7.33-7.40 (m, 4H, *Ar-H*), 7.43-7.48 (m, 6H, *Ar-H*; BINAP), 7.58-7.70 (m, 9H, *Ar-H*; BINAP); **^{13}C NMR** (125 MHz, CD_2Cl_2, 213K) δ: 21.0, 21.2, 21.3, 21.6, 37.9 (d, *J* = 3 Hz), 64.7 (dd, *J* = 30, 5 Hz), 91.0 (dd, *J* = 32, 6 Hz), 121.3, 125.6, 125.9, 126.6, 126.7, 126.8, 126.9, 127.0, 127.0, 127.1, 127.2, 127.4, 127.5, 127.7, 127.8, 128.1, 128.3, 128.4, 128.5, 128.5, 128.7, 129.0, 129.1, 129.2, 129.3, 129.4, 129.6, 129.9 (d, *J* = 10 Hz), 130.0, 130.1, 130.2, 133.5, 133.7, 134.1, 134.2, 134.3, 134.4, 134.8, 134.9, 136.6, 137.0, 138.4, 138.8, 139.4, 140.1, 141.8, 141.9, 142.4, 142.5, 142.6, 147.2; **^{19}F {1H}NMR** (376.5 MHz, CD_2Cl_2, 213K) δ: -153.1 (s, 4F, *BF_4*); **^{31}P NMR** (97 MHz, CD_2Cl_2, 213K) δ: 24.0 (d, 1P, *J* = 49.0 Hz, *P1*), 24.8 (d, 1P, *J* = 49.0 Hz, *P2*); **IR** (CH_2Cl_2) ν 2361; **HRMS** calc for $C_{58}H_{49}P_2Pd$ $[M]^+$ 913.2339, found 913.2366; **Mp** decomposed 220 ºC.

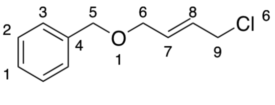
(2*E*)-4-(benzyloxy)but-2-en-1-ol (369)[259]



NaH (88 mg, 2.2 mmol, 60% in mineral oil, 1.1 eq.) was carefully added to a solution of diol (*E*)-but-2-ene-1,4-diol (352 mg, 4 mmol, 2 eq.) in THF (2 mL) at 0 ºC. The resulting suspension was stirred for 1 h at 0 ºC before benzyl bromide (0.24 mL, 2 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 75 ºC and subsequently cooled and quenched with sat. $NH_4Cl_{(aq)}$ solution. The aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (hexane/EtOAc) and afforded **369** (247 mg, 70%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.96-3.98 (m, 2H, *H6*), 4.08-4.10 (m, 2H, *H9*), 4.46 (s, 2H, *H5*), 5.74-5.89 (m, 2H, *H7/8*), 7.20-7.30 (m, 5H, *H1/2/3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 63.0, 70.1, 72.3, 127.7, 127.8, 127.9, 128.3, 132.3, 138.2.

({[(2*E*)-4-chlorobut-2-en-1-yl]oxy}methyl)benzene (370)[123]

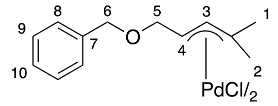


To a solution of allylic alcohol **369** (247 mg, 1.39 mmol) in THF (3 mL) at rt, triphenylphosphine (551 mg, 2.1 mmol, 1.5 eq.) was added, followed by *N*-

chlorosuccinimide (280 mg, 2.1 mmol, 1.5 eq.). The reaction mixture was allowed to stir at rt for 2 h. Pentane was then added to the mixture until a precipitate formed; the suspension was filtered through a cotton plug. The filtrate was then concentrated under reduced pressure and the residue was purified by column chromatography to afford allylic chloride **370** (166 mg, 61%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.97-3.99 (m, 2H, *H6*), 4.00-4.02 (m, 2H, *H9*), 4.46 (m, 2H, *H5*), 5.83-5.85 (m, 2H, *H7/8*), 7.20-7.31 (m, 5H, *H1/2/3*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 44.4, 69.5, 72.4, 127.8, 127.8, 128.4, 128.5, 131.2, 138.0.

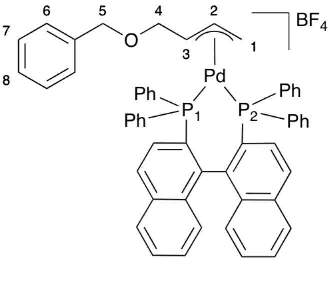
[(But-3-en-1-yloxy)methyl]benzene palladium chloride dimer (371)



To a solution of $Pd(dba)_2$ (332mg, 0.58 mmol) in toluene (6 mL) at rt was added allylic chloride **370** (227 mg, 1.15 mmol) and the reaction was stirred for 18 h. After this time the solvent was removed *in vacuo* and the residue purified by column chromatograpy (DCM:Et_2O, 100:0-50:50) to afford **371** (105 mg, 60%) as a yellow solid.

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 2.18 (d, J = 12.0 Hz, 1H, *H2*), 3.05-3.15 (m, 1H, *H4*), 3.17-3.27 (m, 2H, *H5*), 3.29 (d, J = 7.0 Hz, 1H, *H1*), 4.09-4.22 (AB, $\delta_{:A}$ = 4.11, $\delta_{:B}$ = 4.21, J_{AB} = 12.0 Hz, 2H, *H6*), 4.73 (td, J = 11.5, 7.0 Hz, 1H, *H3*), 6.86-6.94 (m, 5H, *H8/9/10*); **^{13}C NMR** (CD_2Cl_2, 100 MHz): 57.1, 67.0, 71.0, 77.2, 106.5, 125.6, 125.8, 126.4, 136.64; **IR** (CH_2Cl_2) ν 1739; **HRMS** calc for $C_{22}H_{26}Cl_2O_2Pd_2$ $[M]^+$ 602.9380, not found; **Mp** 105 ºC.

{(*R*)-(+)-(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)([(but-3-en-1-yloxy)methyl]benzene)palladium(II) tetrafluoroborate (372)

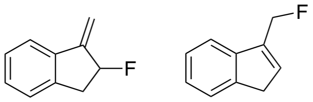


Into a vial was placed palladium chloride dimer **371** (27 mg, 0.05 mmol, 1 eq.) and (*R*)-BINAP **X** (64 mg, 0.10 mmol, Pd:L 1:1). DCM (2.5 mL) was added and the solution was stirred for 10 min. $AgBF_4$ (19 mg, 0.10 mmol, Pd:BF_4 1:1) was then added to the stirring solution and the resulting suspension stirred at rt for 30 mins. After this time the mixture was filtered through a syringe filter (Phenomenex, RC Membrane, pore size 0.45 µm, 4mm) to yield a clear yellow solution that was concentrated *in vacuo*. The residue was redissolved in the minimal amount of DCM and Et_2O added until a solid precipitate was formed that was collect giving complex **372** as a yellow solid (98 mg, > 95%)

^{1}H NMR (500 MHz, CD_2Cl_2, 213K) δ: 2.09-2.17 (m, 1H, *H4*), 3.11-3.23 (m, 1H, *H4*), 3.56-3.64 (m, 1H, *H3*), 3.66 (m, 1H, *H1*), 3.70-3.77 (m, 1H, *H1*), 3.85-3.99 (AB, $\delta{:}_A = 3.88$, $\delta{:}_B = 3.96$, $J_{AB} = 12.0$ Hz, 2H, *H5*), 5.90 (ddd, *J* = 13.0, 13.0, 7.5 Hz, 1H, *H2*), 6.38-6.44 (m, *Ar-H*, 2H; BINAP), 6.52 (d, *J* = 8.5 Hz, *Ar-H*, 1H; BINAP), 6.63-6.68 (m, 1H, *Ar-H*; BINAP), 6.72-6.78 (m, 1H, *Ar-H*; BINAP), 6.79-6.83 (m, 2H, *H6*), 6.91-6.99 (m, 3H, *Ar-H*; BINAP), 6.99-7.05 (m, 2H, *Ar-H*; BINAP), 7.07-7.13 (m, 2H, *H7*), 7.13-7.20 (m, 2H, *H8/Ar-H;* BINAP), 7.24-7.34 (m, 4H, *Ar-H*; BINAP), 7.41-7.46 (m, 5H, *Ar-H*; BINAP), 7.46-7.51 (m, 8H, *Ar-H*; BINAP), 7.51-7.57 (m, 4H, *Ar-H*; BINAP); **^{13}C NMR** (125 MHz, CD_2Cl_2, 213K) δ: 64.8, 73.2, 77.0-77.4 (m), 90.4-90.8 (m), 119.9, 125.7, 125.8, 125.9 (4C), 126.2 (2C), 126.8 (d, *J* = 9.0 Hz), 126.9 (2C), 127.1 (2C), 127.2, 127.2, 127.3 (d, *J* = 20

Hz), 127.4, 128.0, 129.5, 130.3, 133.0, 136.9, 137.6 (dt, 52.0, 7.0, 7.5 Hz, *qAr*); **^{19}F {1H}NMR** (376.5 MHz, CD_2Cl_2, 213K) δ: -152.6 (s, 4F, *BF_4*); **^{31}P NMR** (97 MHz, CD_2Cl_2, 213K) δ: 23.2 (bs, 2P); **IR** (CH_2Cl_2) ν 2360, 1310; **HRMS** calc for $C_{55}H_{45}P_2Pd$ $[M]^+$ 889.1975, found 889.1996; **Mp** 178-182 ºC (dec).

2-Fluoro-1-methylidene-2,3-dihydro-1*H*-indene (366)[78] and 3-(Fluoromethyl)-1*H*-indene (367)

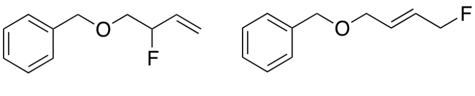


Fluorides **366** and **367** were obtained in reaction of complexes **364** and **365** with XeF_2 following general procedure **L**.

Fluoride 366: **^{1}H NMR** (500 MHz, CD_2Cl_2, 213K) δ: 3.08-3.50 (m, 2H), 5.51-5.57 (m, 1H), 5.58-5.66 (m, 1H), 5.79-5.90 (m, 1H), 7.14-7.42 (m, 3H), 7.51-7.65 (m, 1H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ: -166.7 (m).

Fluoride 367 (tentatively assigned)**:** **^{19}F NMR** (376.5 MHz, CD_2Cl_2, 213K) δ: - 216.43 (m)

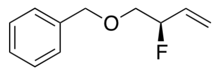
{[(2-fluorobut-3-en-1-yl)oxy]methyl}benzene (201a) and ({[(2*E*)-4-fluorobut-2-en-1-yl]oxy}methyl)benzene (172l)



Fluorides **201a** and **172l** were obtained in reaction of complex **372** with XeF_2 following general procedure **L**. Spectra data is consistent with literature values.[123,260]

Fluoride 201a: **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ: -184.7 (m).

Fluoride 172l: **^{19}F NMR** (376.5 MHz, CD_2Cl_2, 213K) δ: - 212.8 (m).



Chiral HPLC for (*R*)-**201a**: (IA, Hexane/ *i*-PrOH= 99.5/0.5, 1.3 mL/ min, 210 nm) tR (minor- isomer)= 7.8 min, tR (major-isomer)= 8.5 min. The absolute configuration of (*S*)-**201a** was determined by synthesizing the title compound following a literature procedure.[123] Chiral HPLC traces were identical to those obtained from the iridium protocol. The NMR data are consistent with those reported previously.

Chapter 6

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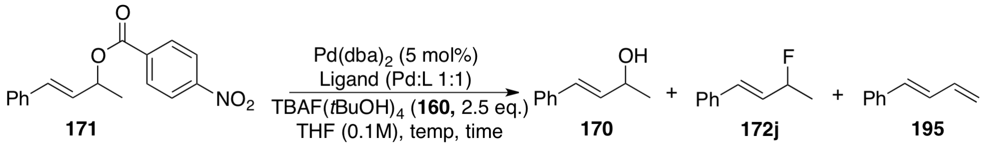
A-1 β-Hydride Elimination Ligand Screens

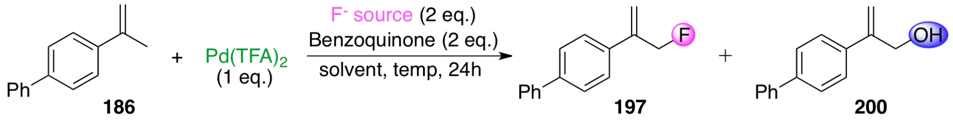


Entry	R	L[a]	t	T (°C)	**171:170:172j:195 (%)[b]**
1	*p*-$CF_3C_6H_4$	XantPhos	21 h	rt	37 : 2 : 23 : 38
2		dppf	21 h	rt	61 : 10 : 0 : 29
3		PPh_3	21 h	rt	81 : 2 : 0 : 17
4		JohnPhos	21 h	rt	77 : 16 : 1 : 6
5		XantPhos	6 h	40	10 : 13 : 27 : 50
6		XantPhos	21 h	40	10 : 30 : 20 : 40
7		dppf	21 h	40	52 : 4 : 1 : 43
8		PPh_3	21 h	40	61 : 28 : 0 : 11
9		JohnPhos	21 h	40	60 : 23 : 2 : 15
10	3,5-bis(CF_3)C_6H_3	XantPhos	20 h	rt	21 : 7 : 5 : 67
11		dppf	20 h	rt	3 : 23 : 0 : 74
12		PPh_3	20 h	rt	39 : 7 : 3 : 51
13		JohnPhos	20 h	rt	41 : 51 : 0.4 : 7
14		XantPhos	20 h	40	9 : 7 : 3 : 80
15		dppf	20 h	40	2 : 5 : 4 : 88
16		PPh_3	20 h	40	9 : 19 : 3 : 68
17		JohnPhos	20 h	40	21 : 70 : 0 : 8
18	*p*-$NO_2C_6H_4$	XantPhos	24 h	rt	4 : 7 : 22 : 66
19		dppf	24 h	rt	63 : 17 : 0 : 20
20		PPh_3	24 h	rt	65 : 6 : 6 : 23
21		JohnPhos	24 h	rt	65 : 27 : 0 : 8
22		XantPhos	24 h	40	4 : 7 : 23 : 66

23		XantPhos	48 h	40	0 : 18 : 0 : 82
24		dppf	24 h	40	41 : 25 : 5 : 29
25		PPh_3	24 h	40	8 : 7 : 21 : 64
26		JohnPhos	24 h	40	47 : 44 : 1 : 8
27		JohnPhos	48 h	40	40 : 55 : 0 : 5
28	3,5-di(NO_2)C_6H_3	XantPhos	22 h	rt	43 : 21 : 0 : 36
29		dppf	22 h	rt	43 : 48 : 0 : 9
30		PPh_3	22 h	rt	40 : 33 : 0 : 27
31		JohnPhos	22 h	rt	22 : 76 : 0.2 : 2
32		XantPhos	22 h	40	32 : 59 : 4 : 4
33		dppf	22 h	40	32 : 45 : 0 : 23
34		PPh_3	22 h	40	25 : 11 : 32 : 32
35		JohnPhos	22 h	40	18 : 81 : 0 : 0.1
36	OMe[c]	XantPhos	18 h	rt	12 : 46 : 12 : 29
37		dppf	18 h	rt	87 : 4 : 1 : 8
38		PPh_3	18 h	rt	58 : 22 : 0 : 20
39		JohnPhos	18 h	rt	96 : 3 : 0 : 1
40		XantPhos	18 h	40	52 : 13 : 10 : 26
41		dppf	18 h	40	75 : 11 : 0 : 14
42		PPh_3	18 h	40	80 : 5 : 0 : 15
43		JohnPhos	18 h	40	81 : 12 : 0 : 7

[a] XantPhos 5 mol%, dppf 5 mol%, PPh_3 10 mol%, JohnPhos 10 mol%. [b] From crude ^1H NMR. [c] Using the -OMe CH_3 as the diagnostic ^1H NMR peak.

A-2 C-H functionalisation screening tables

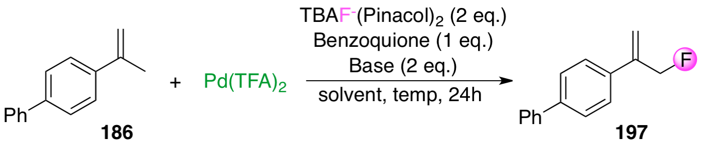


Entry	F$^-$ source	Solvent	Temp (^{o}C)	**197:186:200**[a]	Yield of **197** (%)
1	KF[b]	THF	rt	-	-
2	TBAF(H_2O)$_3$	DCM	40	-	-
3	HF.Pyridine[b]	DCM	40	SM decomposed	-
4	HF.Pyridine	DMF	80	Complex mixture	-
5	AgF	DCM	40	-	-
6	AgF	DCE	60	-	-
7	AgF	DMF	80	SM decomposed	-
8	KF/Kryptofix222	DMF	80	0:1:0	-
9	KHF$_2$	DMF	80	40:60:0	-
10	BzF/HFIP	DCE	80	0:1:0	-
11	BzF/HFIP	MeCN	80	0:1:0	-
12	BzF/HFIP	DMF	80	0:1:0	-
13	BzF/HFIP	Toluene	80	0:1:0	-
14	BzF/HFIP	AcOH	80	0:1:0	-
15	BzF/HFIP	*t*BuOH	80	0:1:0	-
16	TBAF(H_2O)$_3$	DCE	60	0:1:0	-
17	TBAF(H_2O)$_3$	DCE	80	1:1:13	-
18	TBAT	DMF	80	0:1:0	-
19	TMAF	DMF	80	0:1:0	-
20	TBA HF$_2$	DMF	80	53:47:0	-
21	TASF	DMF	80	24:76:0	-

22	TBAF(tBuOH)$_4$[b]	DMF	80	1:2:0	12-66%
23	TBAF(tBuOH)$_4$	DMF	120	0:1:0	-
24	TBAF(Pinacol)$_2$	DMF	80	54:46:0	-

[a] Determined from ^{1}H-NMR; [b] 1 eq. of benzoquinone

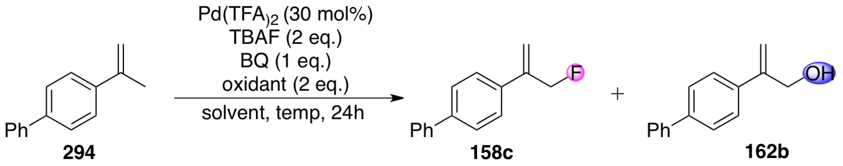
As acidic conditions suppress fluorination, we were concerned that any excess trifluoroacetic acid from the synthesis of the complex maybe hindering the reaction. We thus examined the effect of adding organic and inorganic base to the optimised reaction. As Table **A3** shows, the presence of a base actually suppresses the fluorination, as opposed to aiding it.



Entry	**Base**	**Solvent**	**Temp (°C)**	**Ratio of 186:197**[a]
1	K_2CO_3	DCM	40	1:0
2	Na_2CO_3	DCM	40	1:0
3	Cs_2CO_3	DCM	40	1:0
4	$NaHCO_3$	DMF	80	90:10
5	Na_2CO_3	DMF	80	86:14
6	Et_3N	DMF	80	1:0

Table A3 Screening of base in C-H functionalisation reaction

A-4 Catalytic C-H functionalisation screening tables



Entry	Oxidant	TBAF	Additive	Ratio of 294:158c
1	$AgOAc_2$	TBAF(*t*BuOH)$_4$	-	0:1
2	$Cu(OAc)_2$	“	-	0:1
3	PIFA	“	-	0:1
4	Oxone	“	-	0:1
5	Ag_2CO_3	“	-	0:1
6	PIDA	“	-	0:1
7	Ag_2O	“	-	0:1
8	$Ag(OTFA)_2$	“	-	0:1
9	$FeCl_3$	“	-	0:1
10	$Cu(CF_3SO_3)_2$	“	-	0:1
11	$AgOAc_2$	“	BQ (1 eq.)	0:1
12	$Cu(Oac)_2$	“	BQ (1 eq.)	0:1
13	PIFA	“	BQ (1 eq.)	0:1
14	Oxone	“	BQ (1 eq.)	0:1
15	Ag_2CO_3	“	BQ (1 eq.)	0:1
16	PIDA	“	BQ (1 eq.)	0:1
17	Ag_2O	“	BQ (1 eq.)	0:1
18	$Ag(OTFA)_2$	“	BQ (1 eq.)	0:1
19	$FeCl_3$	“	BQ (1 eq.)	0:1
20	$Cu(CF_3SO_3)_2$	“	BQ (1 eq.)	0:1
21	$Cu(Oac)_2$	TBAF(Pinacol)$_2$	dba (1 eq.)	0:1
22	Ag_2O	“	dba (1 eq.)	0:1
23	Oxone	“	dba (1 eq.)	0:1

24	Ag_2CO_3	“	dba (1 eq.)	0:1
25	$Cu(Oac)_2$	“	MA (1 eq.)	0:1
26	Ag_2O	“	MA (1 eq.)	0:1
27	Oxone	“	MA (1 eq.)	0:1
28	Ag_2CO_3	“	MA (1 eq.)	0:1
29	$Cu(OAc)_2$	“	3-NO_2Py (1 eq.)	0:1
30	Ag_2O	“	3-NO_2Py (1 eq.)	0:1
31	Oxone	“	3-NO_2Py (1 eq.)	0:1
32	Ag_2CO_3	“	3-NO_2Py (1 eq.)	0:1
33	-	TBAF(*t*BuOH)$_4$	2,2-Bipyridyl (1 eq.)	0:1
34	-	“	2-Picolinic acid (1 eq.)	0:1
35	-	“	Boc-Phe-OH (1 eq.)	0:1
36	-	“	1,1,3,3-Tetramethylguanidine (1 eq.)	0:1
37	BQ	TBAF(Pinacol)$_2$	Methyl Acrylate	0:1

X-Ray Crystallography Data

A-5 General Information

In each case, a typical crystal was chosen and mounted on a hair using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N_2 using an Oxford Cryosystems Cryostream N_2 open flow cooling device.[1] Diffraction data were measured using an Enraf-Nonius Kappa CCD diffractometer (graphite-monochromated MoKα radiation, $\lambda = 0.71073$ Å) to a maximum resolution of 0.77 Å. Intensity data were processed using the DENZO-SMN package and were corrected for absorption and other effects using SCALEPACK.[2] The systematic absences in the intensity data were examined to determine the space group. In each case, the structure was solved using the direct-methods program SIR92,[3] which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS[4] program suite to refine coordinates and anisotropic thermal parameters of all non-hydrogen atoms. Hydrogen atoms were located in the difference map and refined before being added to the model using a riding constraint.

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[1] J. Cosier, A. M. Glazer, *J. Appl. Cryst.*, **1986**, *19*, 105.

[2] Z. Otwinowski, W. Minor, "Processing of X-ray Diffraction Data Collected in Oscillation Mode" *Methods Enzymol.*, **1997**, *276*, Eds. C. W. Carter, R. M. Academic Press.

[3] A. Altamore, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli., *J. Appl. Cryst.,* **1994**, *27*, 435.

[4] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Cryst.*, **2003**, *36*, 1487.

Table 1. Crystal data and structure refinement for 002lp13.

Identification code	002lp13	
Empirical formula	C34 H26 F6 O4 Pd2	
Formula weight	825.37	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 17.0230(4) Å	α= 90°.
	b = 9.9456(2) Å	β= 111.233(3)°.
	c = 19.5918(5) Å	γ = 90°.
Volume	3091.80(14) Å^3	
Z	4	
Density (calculated)	1.773 Mg/m^3	
Absorption coefficient	10.050 mm^{-1}	
F(000)	1632	
Crystal size	0.43 x 0.28 x 0.03 mm^3	
Theta range for data collection	4.302 to 76.584°.	
Index ranges	-21<=h<=21, -11<=k<=12, -24<=l<=24	
Reflections collected	65847	
Independent reflections	6436 [R(int) = 0.059]	
Completeness to theta = 75.052°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.74 and 0.03	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6414 / 162 / 443	
Goodness-of-fit on F^2	1.0541	
Final R indices [I>2sigma(I)]	R1 = 0.0307, wR2 = 0.0889	
R indices (all data)	R1 = 0.0318, wR2 = 0.0899	
Largest diff. peak and hole	1.01 and -0.97 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 002lp13. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pd(1)	7280(1)	1505(1)	1721(1)	17
Pd(2)	5671(1)	2834(1)	1787(1)	19
C(1)	7220(2)	1881(4)	661(2)	26
C(2)	7986(2)	2446(3)	1140(2)	21
C(3)	7883(2)	3307(3)	1675(2)	27
C(4)	8840(2)	2027(3)	1163(2)	21
C(5)	8985(2)	809(3)	872(2)	23
C(6)	9774(2)	518(3)	849(2)	23
C(7)	10441(2)	1431(3)	1109(2)	20
C(8)	10296(2)	2635(4)	1406(2)	26
C(9)	9509(2)	2937(3)	1433(2)	26
C(10)	11282(2)	1139(3)	1065(2)	21
C(11)	11586(2)	-174(4)	1112(2)	24
C(12)	12386(2)	-422(4)	1093(2)	28
C(13)	12882(2)	629(4)	1018(2)	29
C(14)	12584(2)	1933(4)	963(2)	27
C(15)	11792(2)	2189(3)	987(2)	25
C(21)	5197(2)	3985(4)	823(2)	25
C(22)	5084(2)	4704(3)	1400(2)	21
C(23)	5832(2)	4867(4)	2021(2)	31
C(24)	4231(2)	4992(3)	1408(2)	19
C(25)	4027(2)	4844(4)	2031(2)	26
C(26)	3223(2)	5149(4)	2009(2)	28
C(27)	2606(2)	5661(3)	1376(2)	20
C(28)	2822(2)	5819(3)	759(2)	22
C(29)	3619(2)	5481(3)	774(2)	22
C(30)	1753(2)	6022(3)	1364(2)	21
C(31)	1624(2)	6299(4)	2013(2)	29
C(32)	825(3)	6646(4)	2002(2)	35
C(33)	155(2)	6736(4)	1347(2)	35
C(34)	275(2)	6464(4)	700(2)	33

C(35)	1065(2)	6101(4)	707(2)	26
O(41)	7499(2)	1478(3)	2860(1)	25
C(42)	7002(2)	1792(3)	3157(2)	22
O(43)	6258(2)	2169(3)	2886(2)	41
C(44)	7350(2)	1749(4)	4002(2)	31
F(45)	8112(1)	1202(3)	4276(1)	44
F(46)	6856(2)	1022(3)	4253(1)	53
F(47)	7405(3)	2983(3)	4269(2)	68
O(51)	6503(2)	-230(2)	1533(1)	26
C(52)	5727(2)	-117(3)	1363(2)	24
O(53)	5291(2)	874(3)	1359(2)	37
C(54)	5222(2)	-1423(2)	1137(2)	48
F(55)	5588(2)	-2367(4)	897(3)	55
F(56)	5088(4)	-1937(5)	1710(3)	81
F(57)	4483(3)	-1248(4)	634(3)	86
F(65)	5666(6)	-2506(7)	1321(8)	63
F(66)	4597(6)	-1574(10)	1361(8)	55
F(67)	4892(9)	-1420(12)	416(4)	71

Table 3. Bond lengths [Å] and angles [°] for 002lp13.

Pd(1)-C(1)	2.076(3)	C(13)-C(14)	1.383(5)
Pd(1)-C(2)	2.148(3)	C(13)-H(131)	0.919
Pd(1)-C(3)	2.085(3)	C(14)-C(15)	1.389(5)
Pd(1)-O(41)	2.126(2)	C(14)-H(141)	0.936
Pd(1)-O(51)	2.122(2)	C(15)-H(151)	0.925
Pd(2)-C(21)	2.103(3)	C(21)-C(22)	1.409(5)
Pd(2)-C(22)	2.117(3)	C(21)-H(211)	0.974
Pd(2)-C(23)	2.070(4)	C(21)-H(212)	0.971
Pd(2)-O(43)	2.125(3)	C(22)-C(23)	1.415(5)
Pd(2)-O(53)	2.128(3)	C(22)-C(24)	1.486(4)
C(1)-C(2)	1.418(5)	C(23)-H(232)	0.956
C(1)-H(12)	0.973	C(23)-H(231)	0.966
C(1)-H(11)	0.969	C(24)-C(25)	1.391(4)
C(2)-C(3)	1.414(5)	C(24)-C(29)	1.389(4)
C(2)-C(4)	1.497(4)	C(25)-C(26)	1.387(5)
C(3)-H(32)	0.962	C(25)-H(251)	0.934
C(3)-H(31)	0.970	C(26)-C(27)	1.399(5)
C(4)-C(5)	1.398(5)	C(26)-H(261)	0.935
C(4)-C(9)	1.400(5)	C(27)-C(28)	1.394(4)
C(5)-C(6)	1.391(4)	C(27)-C(30)	1.488(4)
C(5)-H(51)	0.928	C(28)-C(29)	1.388(4)
C(6)-C(7)	1.398(5)	C(28)-H(281)	0.932
C(6)-H(61)	0.925	C(29)-H(291)	0.928
C(7)-C(8)	1.393(5)	C(30)-C(31)	1.394(5)
C(7)-C(10)	1.492(4)	C(30)-C(35)	1.394(5)
C(8)-C(9)	1.392(5)	C(31)-C(32)	1.395(5)
C(8)-H(81)	0.930	C(31)-H(311)	0.933
C(9)-H(91)	0.943	C(32)-C(33)	1.377(6)
C(10)-C(11)	1.395(5)	C(32)-H(321)	0.930
C(10)-C(15)	1.401(5)	C(33)-C(34)	1.382(6)
C(11)-C(12)	1.398(5)	C(33)-H(331)	0.929
C(11)-H(111)	0.941	C(34)-C(35)	1.387(5)
C(12)-C(13)	1.384(5)	C(34)-H(341)	0.929
C(12)-H(121)	0.933	C(35)-H(351)	0.936

O(41)-C(42)	1.229(4)
C(42)-O(43)	1.240(4)
C(42)-C(44)	1.544(5)
C(44)-F(45)	1.327(4)
C(44)-F(46)	1.329(5)
C(44)-F(47)	1.324(5)
O(51)-C(52)	1.245(4)
C(52)-O(53)	1.232(4)
C(52)-C(54)	1.532(4)
C(54)-F(55)	1.306(4)
C(54)-F(56)	1.326(4)
C(54)-F(57)	1.299(4)
C(54)-F(65)	1.291(5)
C(54)-F(66)	1.298(5)
C(54)-F(67)	1.317(6)

C(1)-Pd(1)-C(2)	39.18(13)
C(1)-Pd(1)-C(3)	69.40(15)
C(2)-Pd(1)-C(3)	38.99(13)
C(1)-Pd(1)-O(41)	168.22(13)
C(2)-Pd(1)-O(41)	130.03(11)
C(3)-Pd(1)-O(41)	98.87(13)
C(1)-Pd(1)-O(51)	99.86(13)
C(2)-Pd(1)-O(51)	134.05(11)
C(3)-Pd(1)-O(51)	167.74(13)
O(41)-Pd(1)-O(51)	91.92(10)
C(21)-Pd(2)-C(22)	39.02(13)
C(21)-Pd(2)-C(23)	69.16(15)
C(22)-Pd(2)-C(23)	39.49(13)
C(21)-Pd(2)-O(43)	165.02(14)
C(22)-Pd(2)-O(43)	128.58(13)
C(23)-Pd(2)-O(43)	95.94(15)
C(21)-Pd(2)-O(53)	100.50(13)
C(22)-Pd(2)-O(53)	128.87(12)
C(23)-Pd(2)-O(53)	168.34(13)
O(43)-Pd(2)-O(53)	94.47(13)

Pd(1)-C(1)-C(2)	73.16(19)
Pd(1)-C(1)-H(12)	110.4
C(2)-C(1)-H(12)	119.8
Pd(1)-C(1)-H(11)	117.9
C(2)-C(1)-H(11)	118.7
H(12)-C(1)-H(11)	111.5
C(1)-C(2)-Pd(1)	67.66(18)
C(1)-C(2)-C(3)	113.5(3)
Pd(1)-C(2)-C(3)	68.08(18)
C(1)-C(2)-C(4)	124.1(3)
Pd(1)-C(2)-C(4)	125.9(2)
C(3)-C(2)-C(4)	121.8(3)
C(2)-C(3)-Pd(1)	72.93(19)
C(2)-C(3)-H(32)	120.4
Pd(1)-C(3)-H(32)	109.9
C(2)-C(3)-H(31)	118.5
Pd(1)-C(3)-H(31)	117.5
H(32)-C(3)-H(31)	111.8
C(2)-C(4)-C(5)	122.8(3)
C(2)-C(4)-C(9)	118.6(3)
C(5)-C(4)-C(9)	118.4(3)
C(4)-C(5)-C(6)	120.6(3)
C(4)-C(5)-H(51)	120.5
C(6)-C(5)-H(51)	118.9
C(5)-C(6)-C(7)	121.3(3)
C(5)-C(6)-H(61)	120.1
C(7)-C(6)-H(61)	118.6
C(6)-C(7)-C(8)	117.8(3)
C(6)-C(7)-C(10)	121.5(3)
C(8)-C(7)-C(10)	120.7(3)
C(7)-C(8)-C(9)	121.3(3)
C(7)-C(8)-H(81)	119.4
C(9)-C(8)-H(81)	119.3
C(4)-C(9)-C(8)	120.6(3)
C(4)-C(9)-H(91)	120.0
C(8)-C(9)-H(91)	119.4

C(7)-C(10)-C(11)	121.2(3)
C(7)-C(10)-C(15)	120.4(3)
C(11)-C(10)-C(15)	118.3(3)
C(10)-C(11)-C(12)	120.3(3)
C(10)-C(11)-H(111)	120.3
C(12)-C(11)-H(111)	119.4
C(11)-C(12)-C(13)	120.5(3)
C(11)-C(12)-H(121)	119.5
C(13)-C(12)-H(121)	120.0
C(12)-C(13)-C(14)	119.7(3)
C(12)-C(13)-H(131)	119.3
C(14)-C(13)-H(131)	120.9
C(13)-C(14)-C(15)	120.1(3)
C(13)-C(14)-H(141)	120.4
C(15)-C(14)-H(141)	119.5
C(10)-C(15)-C(14)	121.0(3)
C(10)-C(15)-H(151)	119.1
C(14)-C(15)-H(151)	119.9
Pd(2)-C(21)-C(22)	71.04(19)
Pd(2)-C(21)-H(211)	117.5
C(22)-C(21)-H(211)	118.1
Pd(2)-C(21)-H(212)	111.6
C(22)-C(21)-H(212)	119.2
H(211)-C(21)-H(212)	113.0
C(21)-C(22)-Pd(2)	69.94(19)
C(21)-C(22)-C(23)	114.0(3)
Pd(2)-C(22)-C(23)	68.5(2)
C(21)-C(22)-C(24)	121.6(3)
Pd(2)-C(22)-C(24)	120.1(2)
C(23)-C(22)-C(24)	123.2(3)
C(22)-C(23)-Pd(2)	72.0(2)
C(22)-C(23)-H(232)	117.5
Pd(2)-C(23)-H(232)	115.9
C(22)-C(23)-H(231)	118.5
Pd(2)-C(23)-H(231)	118.6
H(232)-C(23)-H(231)	110.0
C(22)-C(24)-C(25)	123.0(3)
C(22)-C(24)-C(29)	118.5(3)
C(25)-C(24)-C(29)	118.5(3)
C(24)-C(25)-C(26)	120.5(3)
C(24)-C(25)-H(251)	119.3
C(26)-C(25)-H(251)	120.2
C(25)-C(26)-C(27)	121.4(3)
C(25)-C(26)-H(261)	118.9
C(27)-C(26)-H(261)	119.6
C(26)-C(27)-C(28)	117.5(3)
C(26)-C(27)-C(30)	121.1(3)
C(28)-C(27)-C(30)	121.4(3)
C(27)-C(28)-C(29)	121.1(3)
C(27)-C(28)-H(281)	119.0
C(29)-C(28)-H(281)	119.9
C(24)-C(29)-C(28)	120.9(3)
C(24)-C(29)-H(291)	118.9
C(28)-C(29)-H(291)	120.1
C(27)-C(30)-C(31)	120.6(3)
C(27)-C(30)-C(35)	121.1(3)
C(31)-C(30)-C(35)	118.2(3)
C(30)-C(31)-C(32)	120.7(3)
C(30)-C(31)-H(311)	119.6
C(32)-C(31)-H(311)	119.7
C(31)-C(32)-C(33)	120.3(4)
C(31)-C(32)-H(321)	119.5
C(33)-C(32)-H(321)	120.3
C(32)-C(33)-C(34)	119.6(3)
C(32)-C(33)-H(331)	120.1
C(34)-C(33)-H(331)	120.3
C(33)-C(34)-C(35)	120.5(3)
C(33)-C(34)-H(341)	119.6
C(35)-C(34)-H(341)	119.9
C(30)-C(35)-C(34)	120.7(3)
C(30)-C(35)-H(351)	120.3
C(34)-C(35)-H(351)	119.0

Pd(1)-O(41)-C(42)	127.3(2)	O(53)-C(52)-C(54)	113.7(3)
O(41)-C(42)-O(43)	130.1(3)	Pd(2)-O(53)-C(52)	129.4(2)
O(41)-C(42)-C(44)	116.0(3)	C(52)-C(54)-F(55)	114.9(3)
O(43)-C(42)-C(44)	113.8(3)	C(52)-C(54)-F(56)	109.4(3)
Pd(2)-O(43)-C(42)	124.1(2)	F(55)-C(54)-F(56)	106.19(6)
C(42)-C(44)-F(45)	112.6(3)	C(52)-C(54)-F(57)	113.2(3)
C(42)-C(44)-F(46)	111.3(3)	F(55)-C(54)-F(57)	106.24(6)
F(45)-C(44)-F(46)	106.5(3)	F(56)-C(54)-F(57)	106.23(6)
C(42)-C(44)-F(47)	110.0(3)	C(52)-C(54)-F(65)	114.5(5)
F(45)-C(44)-F(47)	107.5(4)	C(52)-C(54)-F(66)	116.3(5)
F(46)-C(44)-F(47)	108.8(3)	F(65)-C(54)-F(66)	106.23(6)
Pd(1)-O(51)-C(52)	120.5(2)	C(52)-C(54)-F(67)	106.6(5)
O(51)-C(52)-O(53)	130.7(3)	F(65)-C(54)-F(67)	106.22(6)
O(51)-C(52)-C(54)	115.6(3)	F(66)-C(54)-F(67)	106.21(6)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for 002lp13. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	15(1)	19(1)	19(1)	0(1)	8(1)	1(1)
Pd(2)	15(1)	20(1)	21(1)	2(1)	6(1)	4(1)
C(1)	24(2)	36(2)	20(2)	7(1)	9(1)	3(1)
C(2)	21(2)	21(2)	25(2)	5(1)	12(1)	2(1)
C(3)	26(2)	14(2)	47(2)	-5(1)	21(2)	-2(1)
C(4)	20(2)	26(2)	20(1)	3(1)	11(1)	1(1)
C(5)	21(2)	25(2)	25(2)	-1(1)	10(1)	-4(1)
C(6)	24(2)	24(2)	24(2)	-4(1)	11(1)	0(1)
C(7)	20(2)	22(2)	19(1)	1(1)	9(1)	-1(1)
C(8)	20(2)	26(2)	34(2)	-6(1)	13(1)	-6(1)
C(9)	25(2)	22(2)	35(2)	-3(1)	16(1)	-1(1)
C(10)	18(1)	27(2)	17(1)	-1(1)	7(1)	0(1)
C(11)	24(2)	25(2)	26(2)	-3(1)	11(1)	-1(1)
C(12)	28(2)	28(2)	31(2)	-4(1)	13(1)	6(1)
C(13)	21(2)	42(2)	27(2)	-5(2)	12(1)	4(1)
C(14)	24(2)	33(2)	27(2)	0(1)	12(1)	-4(1)
C(15)	23(2)	25(2)	27(2)	1(1)	10(1)	1(1)
C(21)	25(2)	28(2)	26(2)	8(1)	13(1)	9(1)
C(22)	19(1)	17(1)	30(2)	2(1)	12(1)	-1(1)
C(23)	19(2)	31(2)	42(2)	-9(2)	10(1)	-3(1)
C(24)	17(1)	15(1)	25(2)	-2(1)	9(1)	0(1)
C(25)	21(2)	35(2)	19(1)	2(1)	5(1)	7(1)
C(26)	25(2)	42(2)	17(1)	2(1)	10(1)	6(2)
C(27)	18(1)	21(2)	21(1)	-1(1)	8(1)	1(1)
C(28)	21(2)	26(2)	19(1)	4(1)	7(1)	5(1)
C(29)	24(2)	25(2)	21(2)	3(1)	12(1)	3(1)
C(30)	19(1)	21(2)	24(2)	-1(1)	10(1)	1(1)
C(31)	24(2)	37(2)	26(2)	-1(1)	12(1)	5(1)
C(32)	32(2)	45(2)	39(2)	-4(2)	23(2)	4(2)
C(33)	21(2)	38(2)	50(2)	-4(2)	19(2)	2(2)
C(34)	20(2)	39(2)	36(2)	-1(2)	6(1)	0(1)

C(35)	22(2)	30(2)	26(2)	-2(1)	8(1)	2(1)
O(41)	20(1)	37(1)	19(1)	1(1)	9(1)	6(1)
C(42)	22(2)	24(2)	20(1)	5(1)	10(1)	6(1)
O(43)	29(1)	73(2)	27(1)	20(1)	16(1)	26(1)
C(44)	33(2)	37(2)	23(2)	3(1)	12(1)	10(2)
F(45)	29(1)	72(2)	24(1)	10(1)	2(1)	11(1)
F(46)	41(1)	90(2)	33(1)	27(1)	21(1)	13(1)
F(47)	118(3)	51(2)	31(1)	-8(1)	21(2)	19(2)
O(51)	21(1)	20(1)	38(1)	-2(1)	10(1)	-1(1)
C(52)	23(2)	18(2)	31(2)	0(1)	9(1)	-1(1)
O(53)	22(1)	22(1)	62(2)	0(1)	10(1)	4(1)
C(54)	35(2)	27(2)	81(2)	-12(2)	19(2)	-9(1)
F(55)	50(2)	31(2)	84(3)	-26(2)	25(2)	-7(2)
F(56)	99(4)	61(3)	91(3)	-8(2)	46(3)	-46(3)
F(57)	32(2)	45(2)	135(4)	-27(2)	-26(2)	-2(2)
F(65)	44(4)	23(4)	104(6)	-3(5)	3(5)	-9(3)
F(66)	35(4)	36(4)	96(5)	-16(4)	27(4)	-20(4)
F(67)	62(5)	52(5)	82(4)	-20(5)	6(5)	-22(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 002lp13.

	x	y	z	U(eq)
H(51)	8555	183	690	28
H(61)	9866	-290	656	28
H(81)	10736	3245	1598	31
H(91)	9430	3761	1637	31
H(111)	11255	-900	1159	29
H(121)	12586	-1303	1133	34
H(131)	13405	447	1004	35
H(141)	12912	2649	906	33
H(151)	11596	3063	953	30
H(251)	4436	4535	2463	31
H(261)	3093	5002	2427	33
H(281)	2422	6163	331	26
H(291)	3751	5584	357	27
H(311)	2076	6256	2458	34
H(321)	750	6821	2441	43
H(331)	-375	6976	1341	42
H(341)	-178	6519	259	39
H(351)	1129	5906	263	32
H(211)	4698	3649	432	30
H(32)	7479	4027	1534	32
H(212)	5642	4254	651	30
H(12)	6745	2465	407	31
H(31)	8377	3545	2096	33
H(232)	6302	5279	1948	37
H(231)	5786	5191	2470	37
H(11)	7244	1119	361	31

Table 6. Hydrogen bonds for 002lp13 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(33)-H(331)...O(43)#1	0.929	2.498	3.294(5)	143.82
C(23)-H(232)...O(41)#2	0.956	2.274	3.197(5)	161.93

Symmetry transformations used to generate equivalent atoms:

#1 -x+1/2,y+1/2,-z+1/2 #2 -x+3/2,y+1/2,-z+1/2

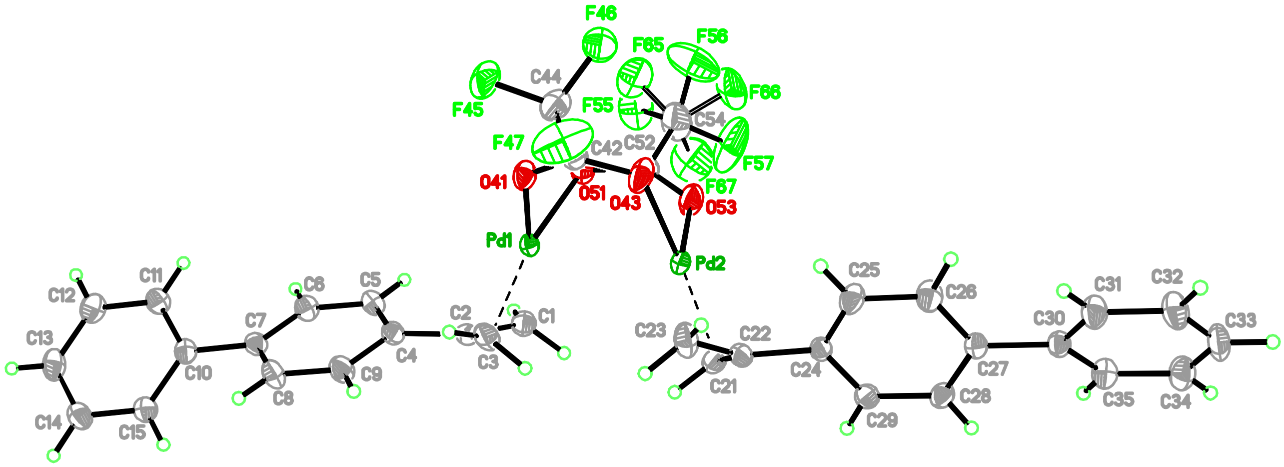

Table 1. Crystal data and structure refinement for 002ch11.

Identification code	002ch11	
Empirical formula	C24 H35 B1 F4 N2 Pd1	
Formula weight	544.76	
Temperature	150 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 9.5316(4) Å	α= 90°.
	b = 11.3545(5) Å	β= 107.1023(17)°.
	c = 10.9989(4) Å	γ = 90°.
Volume	1137.74(8) Å^3	
Z	2	
Density (calculated)	1.590 Mg/m^3	
Absorption coefficient	0.863 mm^{-1}	
F(000)	560	
Crystal size	0.30 x 0.30 x 0.30 mm^3	
Theta range for data collection	5.286 to 27.477°.	
Index ranges	-12<=h<=12, -14<=k<=12, -14<=l<=14	
Reflections collected	9195	
Independent reflections	4453 [R(int) = 0.045]	
Completeness to theta = 27.477°	97.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.77 and 0.70	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4451 / 153 / 327	
Goodness-of-fit on F^2	0.9416	
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0935	
R indices (all data)	R1 = 0.0381, wR2 = 0.0943	
Absolute structure parameter	0.07(4)	
Largest diff. peak and hole	1.36 and -0.87 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 002ch11. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pd(1)	1746(1)	2539(1)	1216(1)	18
C(2)	139(5)	3706(5)	42(4)	28
C(3)	-503(5)	3041(5)	805(5)	28
C(4)	136(4)	3128(4)	2154(4)	23
C(5)	-344(4)	2360(5)	3024(4)	23
C(6)	-701(5)	1179(5)	2773(5)	29
C(7)	-1176(5)	492(5)	3616(5)	35
C(8)	-1319(5)	979(6)	4732(5)	38
C(9)	-982(5)	2140(5)	4996(4)	33
C(10)	-494(5)	2846(5)	4172(5)	30
N(11)	2935(3)	1989(3)	-109(3)	17
C(12)	2197(4)	2574(7)	-1356(3)	23
C(13)	2675(5)	2090(5)	-2478(4)	27
C(14)	2357(5)	772(5)	-2619(5)	28
C(15)	3144(5)	160(4)	-1374(4)	24
C(16)	2761(4)	671(4)	-214(4)	20
C(17)	3639(4)	55(4)	1006(4)	21
C(18)	5279(5)	385(4)	1303(4)	24
C(19)	5367(4)	1695(4)	1544(4)	21
C(20)	4507(4)	2355(4)	349(4)	20
C(21)	4942(5)	1975(5)	2748(5)	22
C(22)	3180(4)	319(4)	2204(4)	21
N(23)	3395(4)	1562(3)	2638(3)	18
C(24)	3202(5)	1640(5)	3944(4)	23
C(25)	3432(5)	2882(4)	4464(5)	27
C(26)	4934(5)	3371(5)	4504(4)	28
C(27)	5135(6)	3245(5)	3168(5)	25
B(28)	2700(4)	6335(3)	2096(3)	43
F(29)	4026(12)	6042(11)	2980(10)	59
F(30)	1593(14)	5678(11)	2331(12)	54
F(31)	2417(14)	7524(7)	2211(9)	48

F(32)	2772(13)	6105(9)	884(8)	41
F(33)	3036(6)	5777(7)	1086(5)	54
F(34)	3516(8)	5836(4)	3224(5)	56
F(35)	3040(10)	7517(6)	2094(5)	73
F(36)	1224(5)	6205(7)	1969(6)	57

Table 3. Bond lengths [Å] and angles [°] for 002ch11.

Pd(1)-C(2)	2.146(4)	C(14)-H(142)	0.982
Pd(1)-C(3)	2.134(4)	C(15)-C(16)	1.540(6)
Pd(1)-C(4)	2.190(4)	C(15)-H(151)	0.969
Pd(1)-N(11)	2.184(3)	C(15)-H(152)	0.967
Pd(1)-N(23)	2.169(3)	C(16)-C(17)	1.526(6)
C(2)-C(3)	1.398(7)	C(16)-H(161)	0.985
C(2)-H(22)	0.966	C(17)-C(18)	1.546(6)
C(2)-H(21)	0.967	C(17)-C(22)	1.536(6)
C(3)-C(4)	1.432(6)	C(17)-H(171)	0.988
C(3)-H(31)	0.973	C(18)-C(19)	1.509(7)
C(4)-C(5)	1.463(7)	C(18)-H(181)	0.973
C(4)-H(41)	0.979	C(18)-H(182)	0.972
C(5)-C(6)	1.392(8)	C(19)-C(20)	1.525(6)
C(5)-C(10)	1.424(7)	C(19)-C(21)	1.528(7)
C(6)-C(7)	1.384(7)	C(19)-H(191)	1.002
C(6)-H(61)	0.943	C(20)-H(201)	0.967
C(7)-C(8)	1.389(8)	C(20)-H(202)	0.961
C(7)-H(71)	0.927	C(21)-N(23)	1.518(5)
C(8)-C(9)	1.368(8)	C(21)-C(27)	1.509(7)
C(8)-H(81)	0.930	C(21)-H(211)	0.991
C(9)-C(10)	1.388(7)	C(22)-N(23)	1.485(6)
C(9)-H(91)	0.950	C(22)-H(222)	0.966
C(10)-H(101)	0.929	C(22)-H(221)	0.967
N(11)-C(12)	1.500(5)	N(23)-C(24)	1.504(5)
N(11)-C(16)	1.506(5)	C(24)-C(25)	1.514(7)
N(11)-C(20)	1.493(5)	C(24)-H(242)	0.968
C(12)-C(13)	1.538(6)	C(24)-H(241)	0.956
C(12)-H(121)	0.961	C(25)-C(26)	1.524(6)
C(12)-H(122)	0.982	C(25)-H(252)	0.973
C(13)-C(14)	1.526(7)	C(25)-H(251)	0.958
C(13)-H(131)	0.977	C(26)-C(27)	1.543(7)
C(13)-H(132)	0.974	C(26)-H(262)	0.978
C(14)-C(15)	1.522(7)	C(26)-H(261)	0.968
C(14)-H(141)	0.972	C(27)-H(272)	0.971

C(27)-H(271)	0.960
B(28)-F(29)	1.390(7)
B(28)-F(30)	1.377(6)
B(28)-F(31)	1.390(7)
B(28)-F(32)	1.380(7)
B(28)-F(33)	1.396(5)
B(28)-F(34)	1.377(5)
B(28)-F(35)	1.381(6)
B(28)-F(36)	1.380(5)
C(2)-Pd(1)-C(3)	38.11(19)
C(2)-Pd(1)-C(4)	67.68(17)
C(3)-Pd(1)-C(4)	38.65(17)
C(2)-Pd(1)-N(11)	101.15(15)
C(3)-Pd(1)-N(11)	128.37(16)
C(4)-Pd(1)-N(11)	167.02(14)
C(2)-Pd(1)-N(23)	170.99(17)
C(3)-Pd(1)-N(23)	139.42(16)
C(4)-Pd(1)-N(23)	106.05(15)
N(11)-Pd(1)-N(23)	85.78(13)
Pd(1)-C(2)-C(3)	70.5(2)
Pd(1)-C(2)-H(22)	115.5
C(3)-C(2)-H(22)	120.9
Pd(1)-C(2)-H(21)	119.0
C(3)-C(2)-H(21)	116.5
H(22)-C(2)-H(21)	109.9
C(2)-C(3)-Pd(1)	71.4(2)
C(2)-C(3)-C(4)	117.2(5)
Pd(1)-C(3)-C(4)	72.8(2)
C(2)-C(3)-H(31)	122.0
Pd(1)-C(3)-H(31)	121.3
C(4)-C(3)-H(31)	120.6
C(3)-C(4)-Pd(1)	68.6(2)
C(3)-C(4)-C(5)	121.1(4)
Pd(1)-C(4)-C(5)	121.5(3)
C(3)-C(4)-H(41)	115.1
Pd(1)-C(4)-H(41)	108.6
C(5)-C(4)-H(41)	114.1
C(4)-C(5)-C(6)	123.4(4)
C(4)-C(5)-C(10)	118.8(5)
C(6)-C(5)-C(10)	117.8(4)
C(5)-C(6)-C(7)	121.3(5)
C(5)-C(6)-H(61)	119.1
C(7)-C(6)-H(61)	119.6
C(6)-C(7)-C(8)	120.3(5)
C(6)-C(7)-H(71)	119.7
C(8)-C(7)-H(71)	120.0
C(7)-C(8)-C(9)	119.5(5)
C(7)-C(8)-H(81)	120.3
C(9)-C(8)-H(81)	120.2
C(8)-C(9)-C(10)	121.4(5)
C(8)-C(9)-H(91)	118.9
C(10)-C(9)-H(91)	119.7
C(5)-C(10)-C(9)	119.7(5)
C(5)-C(10)-H(101)	121.5
C(9)-C(10)-H(101)	118.8
Pd(1)-N(11)-C(12)	106.7(3)
Pd(1)-N(11)-C(16)	105.6(2)
C(12)-N(11)-C(16)	111.0(4)
Pd(1)-N(11)-C(20)	111.2(3)
C(12)-N(11)-C(20)	109.8(3)
C(16)-N(11)-C(20)	112.3(3)
N(11)-C(12)-C(13)	113.9(5)
N(11)-C(12)-H(121)	108.0
C(13)-C(12)-H(121)	110.7
N(11)-C(12)-H(122)	106.9
C(13)-C(12)-H(122)	108.4
H(121)-C(12)-H(122)	108.8
C(12)-C(13)-C(14)	109.6(5)
C(12)-C(13)-H(131)	110.3
C(14)-C(13)-H(131)	112.3
C(12)-C(13)-H(132)	108.4

C(14)-C(13)-H(132)	107.8
H(131)-C(13)-H(132)	108.3
C(13)-C(14)-C(15)	109.0(4)
C(13)-C(14)-H(141)	109.3
C(15)-C(14)-H(141)	111.6
C(13)-C(14)-H(142)	108.7
C(15)-C(14)-H(142)	109.8
H(141)-C(14)-H(142)	108.4
C(14)-C(15)-C(16)	113.5(4)
C(14)-C(15)-H(151)	109.5
C(16)-C(15)-H(151)	109.2
C(14)-C(15)-H(152)	107.5
C(16)-C(15)-H(152)	109.5
H(151)-C(15)-H(152)	107.5
C(15)-C(16)-N(11)	113.0(3)
C(15)-C(16)-C(17)	110.7(3)
N(11)-C(16)-C(17)	111.6(3)
C(15)-C(16)-H(161)	107.1
N(11)-C(16)-H(161)	107.2
C(17)-C(16)-H(161)	106.9
C(16)-C(17)-C(18)	109.5(3)
C(16)-C(17)-C(22)	116.4(3)
C(18)-C(17)-C(22)	107.3(3)
C(16)-C(17)-H(171)	107.2
C(18)-C(17)-H(171)	108.5
C(22)-C(17)-H(171)	107.8
C(17)-C(18)-C(19)	106.1(3)
C(17)-C(18)-H(181)	109.8
C(19)-C(18)-H(181)	111.7
C(17)-C(18)-H(182)	111.1
C(19)-C(18)-H(182)	109.8
H(181)-C(18)-H(182)	108.4
C(18)-C(19)-C(20)	110.2(4)
C(18)-C(19)-C(21)	110.0(4)
C(20)-C(19)-C(21)	115.6(4)
C(18)-C(19)-H(191)	108.4
C(20)-C(19)-H(191)	106.1
C(21)-C(19)-H(191)	106.2
C(19)-C(20)-N(11)	112.7(3)
C(19)-C(20)-H(201)	108.6
N(11)-C(20)-H(201)	108.4
C(19)-C(20)-H(202)	110.1
N(11)-C(20)-H(202)	108.7
H(201)-C(20)-H(202)	108.3
C(19)-C(21)-N(23)	111.5(4)
C(19)-C(21)-C(27)	115.2(4)
N(23)-C(21)-C(27)	110.3(5)
C(19)-C(21)-H(211)	105.9
N(23)-C(21)-H(211)	108.3
C(27)-C(21)-H(211)	105.2
C(17)-C(22)-N(23)	114.4(3)
C(17)-C(22)-H(222)	108.3
N(23)-C(22)-H(222)	108.4
C(17)-C(22)-H(221)	108.7
N(23)-C(22)-H(221)	107.7
H(222)-C(22)-H(221)	109.2
C(21)-N(23)-C(22)	111.0(3)
C(21)-N(23)-Pd(1)	112.3(3)
C(22)-N(23)-Pd(1)	104.6(2)
C(21)-N(23)-C(24)	107.2(3)
C(22)-N(23)-C(24)	108.6(3)
Pd(1)-N(23)-C(24)	113.1(2)
N(23)-C(24)-C(25)	111.8(4)
N(23)-C(24)-H(242)	108.5
C(25)-C(24)-H(242)	108.8
N(23)-C(24)-H(241)	109.1
C(25)-C(24)-H(241)	107.8
H(242)-C(24)-H(241)	110.8
C(24)-C(25)-C(26)	112.4(4)
C(24)-C(25)-H(252)	110.2
C(26)-C(25)-H(252)	108.2
C(24)-C(25)-H(251)	108.0

C(26)-C(25)-H(251)	108.8	H(272)-C(27)-H(271)	108.5
H(252)-C(25)-H(251)	109.1	F(29)-B(28)-F(30)	109.24(6)
C(25)-C(26)-C(27)	108.5(4)	F(29)-B(28)-F(31)	109.22(6)
C(25)-C(26)-H(262)	110.3	F(30)-B(28)-F(31)	109.22(6)
C(27)-C(26)-H(262)	108.7	F(29)-B(28)-F(32)	109.71(6)
C(25)-C(26)-H(261)	108.5	F(30)-B(28)-F(32)	109.73(6)
C(27)-C(26)-H(261)	109.7	F(31)-B(28)-F(32)	109.71(6)
H(262)-C(26)-H(261)	111.1	F(33)-B(28)-F(34)	109.24(6)
C(26)-C(27)-C(21)	110.1(4)	F(33)-B(28)-F(35)	109.24(6)
C(26)-C(27)-H(272)	108.1	F(34)-B(28)-F(35)	109.26(6)
C(21)-C(27)-H(272)	110.1	F(33)-B(28)-F(36)	109.68(6)
C(26)-C(27)-H(271)	110.1	F(34)-B(28)-F(36)	109.69(6)
C(21)-C(27)-H(271)	109.9	F(35)-B(28)-F(36)	109.71(6)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for 002ch11. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	16(1)	17(1)	19(1)	2(1)	5(1)	2(1)
C(2)	29(2)	27(2)	26(2)	8(2)	6(2)	16(2)
C(3)	18(2)	34(2)	30(2)	1(2)	6(2)	13(2)
C(4)	18(2)	27(2)	28(2)	-4(2)	10(2)	5(2)
C(5)	16(1)	25(4)	28(2)	1(2)	5(1)	1(2)
C(6)	25(2)	30(3)	31(2)	2(2)	5(2)	3(2)
C(7)	23(2)	31(3)	47(3)	10(2)	6(2)	2(2)
C(8)	23(2)	52(4)	37(3)	19(2)	5(2)	-1(2)
C(9)	28(2)	49(3)	23(2)	7(2)	8(2)	2(2)
C(10)	23(2)	39(3)	31(2)	-2(2)	11(2)	-2(2)
N(11)	15(1)	17(2)	22(2)	2(1)	9(1)	0(1)
C(12)	21(1)	25(2)	22(2)	13(3)	7(1)	3(3)
C(13)	28(2)	33(2)	22(2)	3(2)	10(2)	5(2)
C(14)	31(2)	28(2)	27(2)	-8(2)	10(2)	0(2)
C(15)	24(2)	23(2)	27(2)	-8(2)	9(2)	-1(2)
C(16)	18(2)	16(2)	26(2)	-3(2)	9(2)	1(1)
C(17)	20(2)	15(2)	26(2)	2(2)	6(2)	1(1)
C(18)	17(2)	26(2)	28(2)	-1(2)	4(2)	5(2)
C(19)	15(2)	22(2)	25(2)	1(2)	4(1)	-1(1)
C(20)	16(1)	19(3)	25(2)	1(2)	6(1)	-3(1)
C(21)	14(2)	24(2)	26(3)	7(2)	4(2)	-2(2)
C(22)	19(2)	18(2)	23(2)	6(2)	4(1)	-2(1)
N(23)	15(1)	21(2)	20(2)	6(1)	5(1)	3(1)
C(24)	24(2)	25(2)	20(2)	6(2)	5(2)	1(2)
C(25)	31(2)	29(3)	21(2)	-3(2)	8(2)	-4(2)
C(26)	30(2)	31(3)	22(2)	-5(2)	5(2)	-7(2)
C(27)	30(2)	20(2)	26(3)	-2(2)	9(2)	-6(2)
B(28)	47(2)	42(2)	44(2)	9(2)	18(2)	2(2)
F(29)	62(5)	58(6)	52(6)	4(5)	10(5)	9(5)
F(30)	61(5)	48(6)	59(5)	4(5)	28(5)	-16(5)
F(31)	53(5)	34(4)	57(5)	12(6)	14(4)	2(6)

F(32)	41(5)	48(5)	42(4)	14(4)	22(4)	28(4)
F(33)	41(3)	77(4)	48(3)	-2(3)	19(2)	8(3)
F(34)	68(4)	56(3)	45(3)	20(2)	16(3)	21(3)
F(35)	84(4)	43(3)	82(3)	10(4)	11(3)	-13(4)
F(36)	40(3)	67(4)	71(4)	-5(3)	27(2)	3(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 002ch11.

	x	y	z	U(eq)
H(61)	-623	843	2012	35
H(71)	-1394	-296	3434	42
H(81)	-1627	517	5303	46
H(91)	-1117	2472	5746	39
H(101)	-286	3633	4382	37
H(121)	2386	3405	-1256	27
H(122)	1137	2441	-1533	26
H(131)	3709	2268	-2363	33
H(132)	2093	2475	-3254	33
H(141)	2671	468	-3323	34
H(142)	1293	651	-2816	34
H(151)	4195	209	-1230	29
H(152)	2876	-664	-1468	29
H(161)	1719	494	-328	24
H(171)	3537	-802	847	24
H(181)	5854	-54	2042	29
H(182)	5647	202	589	29
H(191)	6415	1948	1717	26
H(201)	4545	3188	537	24
H(202)	4947	2229	-322	24
H(211)	5634	1526	3441	26
H(222)	3746	-180	2884	26
H(221)	2150	135	2033	25
H(242)	3913	1127	4509	29
H(241)	2224	1408	3900	28
H(252)	3343	2903	5323	32
H(251)	2689	3374	3924	32
H(262)	4997	4206	4733	34
H(261)	5678	2918	5112	34
H(272)	6115	3514	3212	30

H(271)	4436	3730	2571	30
H(31)	-1292	2483	445	34
H(41)	392	3927	2476	29
H(22)	331	4537	199	33
H(21)	-212	3562	-864	33

Table 6. Hydrogen bonds for 002ch11 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(24)-H(241)...C(5)	0.956	2.588	3.332(7)	134.82

Symmetry transformations used to generate equivalent atoms:

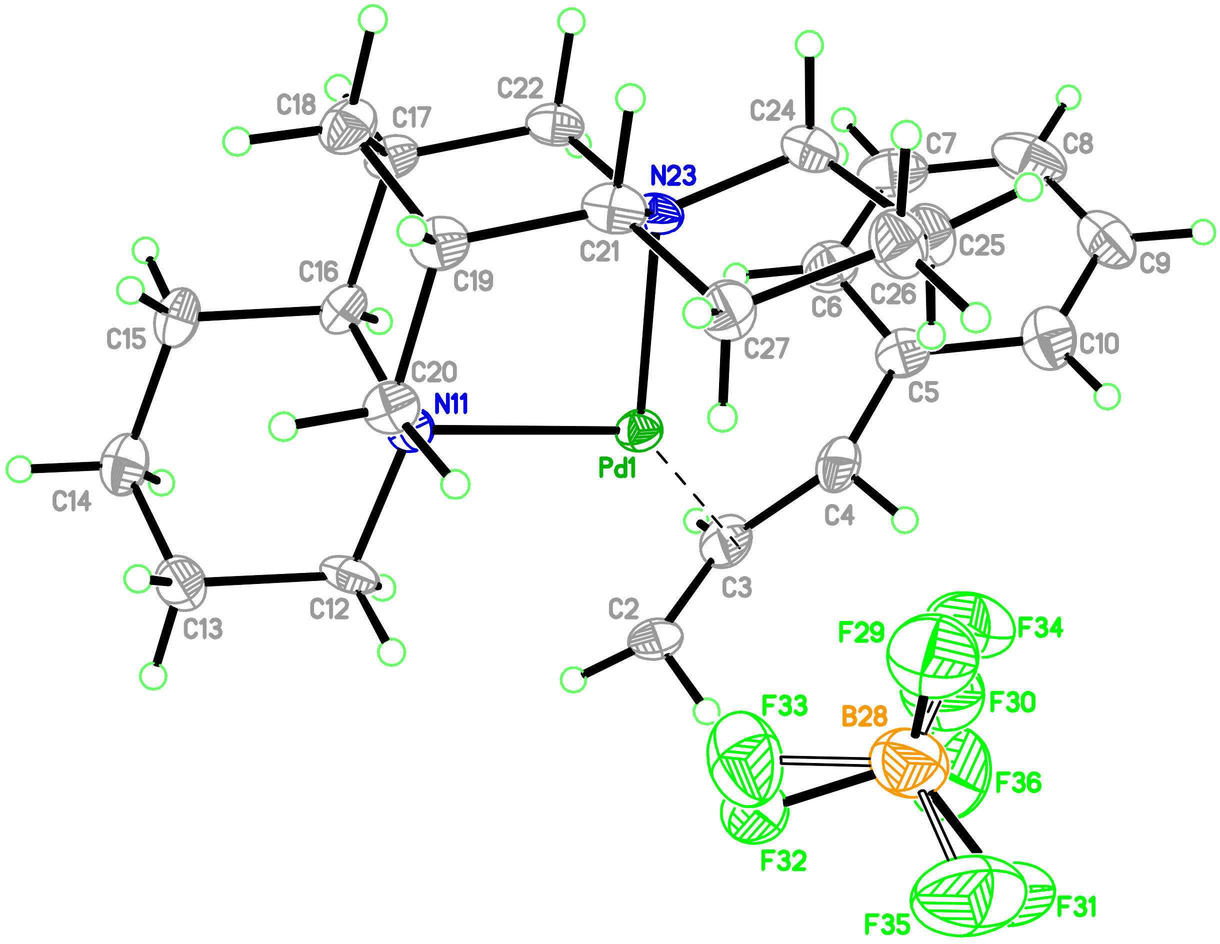

Table 1. Crystal data and structure refinement for 004ch11.

Identification code	004ch11	
Empirical formula	C27 H33 B1 F4 N2 Pd1	
Formula weight	578.78	
Temperature	150 K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	P 43 21 2	
Unit cell dimensions	a = 15.24790(10) Å	α= 90°.
	b = 15.24790(10) Å	β= 90°.
	c = 23.2036(3) Å	γ = 90°.
Volume	5394.80(9) Å^3	
Z	8	
Density (calculated)	1.425 Mg/m^3	
Absorption coefficient	0.733 mm^{-1}	
F(000)	2368.000	
Crystal size	0.330 x 0.320 x 0.310 mm^3	
Theta range for data collection	5.131 to 27.486°.	
Index ranges	-19<=h<=19, -14<=k<=13, -23<=l<=29	
Reflections collected	32003	
Independent reflections	6120 [R(int) = 0.039]	
Completeness to theta = 26.662°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.80 and 0.67	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6120 / 268 / 399	
Goodness-of-fit on F^2	0.9406	
Final R indices [I>2sigma(I)]	R1 = 0.0335, wR2 = 0.0729	
R indices (all data)	R1 = 0.0417, wR2 = 0.0826	
Absolute structure parameter	0.03(3)	
Largest diff. peak and hole	0.40 and -0.75 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 004ch11. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pd(1)	5969(1)	8309(1)	4503(1)	42
C(2)	7132(9)	9010(10)	4757(4)	44
C(3)	7085(4)	8923(5)	4144(3)	40
C(4)	6345(4)	9335(4)	3899(2)	36
C(5)	6018(7)	9202(7)	3311(3)	41
C(6)	6202(5)	8441(5)	3004(3)	48
C(7)	5821(6)	8268(5)	2471(3)	60
C(8)	5253(7)	8904(7)	2267(3)	57
C(9)	5049(6)	9681(6)	2537(4)	58
C(10)	5463(8)	9825(5)	3062(4)	53
N(11)	5638(2)	7462(2)	5177(1)	36
C(12)	6152(2)	7260(3)	5626(2)	43
C(13)	5966(3)	6576(3)	6002(1)	48
C(14)	5225(2)	6064(2)	5923(1)	40
C(15)	4664(2)	6311(2)	5474(1)	37
C(16)	4887(2)	6996(2)	5106(1)	33
C(17)	4344(2)	7260(2)	4606(1)	34
C(18)	3491(2)	6974(2)	4516(2)	36
C(19)	3013(2)	7246(2)	4035(2)	41
C(20)	3440(2)	7813(3)	3660(2)	46
C(21)	4287(2)	8089(3)	3775(2)	48
N(22)	4738(2)	7823(2)	4234(1)	41
C(23)	4997(3)	5287(3)	6307(2)	47
C(24)	5766(3)	5020(3)	6693(2)	64
C(25)	4745(3)	4500(3)	5933(2)	56
C(26)	4216(3)	5535(3)	6693(2)	52
C(27)	2062(3)	6959(3)	3947(2)	52
C(28)	1969(3)	5976(3)	4066(2)	60
C(29)	1497(3)	7479(4)	4375(2)	73
C(30)	1750(3)	7150(4)	3331(2)	75
B(31)	2050(3)	6039(3)	5844(2)	42

F(32)	2628(2)	5536(2)	5517(1)	60
F(33)	1957(2)	5694(2)	6381(1)	103
F(34)	1259(2)	6082(3)	5579(1)	93
F(35)	2394(2)	6858(2)	5879(2)	84
C(102)	7218(10)	8796(7)	4666(5)	50
C(103)	6832(6)	9284(4)	4207(3)	50
C(104)	6651(4)	8777(3)	3719(2)	44
C(105)	6101(7)	9045(6)	3231(3)	39
C(106)	5623(7)	9818(5)	3201(3)	43
C(107)	5083(5)	10013(4)	2734(3)	43
C(108)	5049(5)	9382(5)	2307(2)	50
C(109)	5480(6)	8590(5)	2310(3)	55
C(110)	6027(6)	8443(4)	2780(3)	49

Table 3. Bond lengths [Å] and angles [°] for 004ch11.

Pd(1)-C(2)	2.152(17)	C(14)-C(15)	1.400(5)
Pd(1)-C(3)	2.113(7)	C(14)-C(23)	1.523(5)
Pd(1)-C(4)	2.177(7)	C(15)-C(16)	1.390(5)
Pd(1)-N(11)	2.090(3)	C(15)-H(151)	0.935
Pd(1)-N(22)	2.112(3)	C(16)-C(17)	1.483(5)
Pd(1)-N(11)	2.090(3)	C(17)-C(18)	1.387(4)
Pd(1)-N(22)	2.112(3)	C(17)-N(22)	1.357(4)
Pd(1)-C(102)	2.080(16)	C(18)-C(19)	1.396(5)
Pd(1)-C(103)	2.101(8)	C(18)-H(181)	0.948
Pd(1)-C(104)	2.214(6)	C(19)-C(20)	1.388(5)
C(2)-C(3)	1.431(8)	C(19)-C(27)	1.528(5)
C(2)-H(21)	0.969	C(20)-C(21)	1.384(5)
C(2)-H(22)	0.960	C(20)-H(201)	0.923
C(3)-C(4)	1.410(7)	C(21)-N(22)	1.331(4)
C(3)-H(31)	0.976	C(21)-H(211)	0.938
C(4)-C(5)	1.468(6)	C(23)-C(24)	1.530(5)
C(4)-H(41)	0.977	C(23)-C(25)	1.529(6)
C(5)-C(6)	1.390(5)	C(23)-C(26)	1.538(5)
C(5)-C(10)	1.397(5)	C(24)-H(241)	0.972
C(6)-C(7)	1.391(5)	C(24)-H(243)	0.963
C(6)-H(61)	0.936	C(24)-H(242)	0.964
C(7)-C(8)	1.384(5)	C(25)-H(252)	0.958
C(7)-H(71)	0.942	C(25)-H(251)	0.968
C(8)-C(9)	1.376(5)	C(25)-H(253)	0.975
C(8)-H(81)	0.938	C(26)-H(261)	0.961
C(9)-C(10)	1.390(5)	C(26)-H(263)	0.966
C(9)-H(91)	0.928	C(26)-H(262)	0.962
C(10)-H(101)	0.921	C(27)-C(28)	1.531(6)
N(11)-C(12)	1.339(4)	C(27)-C(29)	1.536(6)
N(11)-C(16)	1.358(4)	C(27)-C(30)	1.535(6)
C(12)-C(13)	1.389(5)	C(28)-H(282)	0.960
C(12)-H(121)	0.935	C(28)-H(281)	0.976
C(13)-C(14)	1.385(5)	C(28)-H(283)	0.962
C(13)-H(131)	0.940	C(29)-H(293)	0.959

C(29)-H(291)	0.961
C(29)-H(292)	0.969
C(30)-H(301)	0.968
C(30)-H(302)	0.971
C(30)-H(303)	0.967
B(31)-F(32)	1.393(5)
B(31)-F(33)	1.361(5)
B(31)-F(34)	1.355(5)
B(31)-F(35)	1.356(5)
C(102)-C(103)	1.427(8)
C(102)-H(1021)	0.966
C(102)-H(1022)	0.964
C(103)-C(104)	1.400(7)
C(103)-H(1031)	0.971
C(104)-C(105)	1.465(6)
C(104)-H(1041)	0.975
C(105)-C(106)	1.388(5)
C(105)-C(110)	1.397(5)
C(106)-C(107)	1.393(5)
C(106)-H(1061)	0.923
C(107)-C(108)	1.381(5)
C(107)-H(1071)	0.935
C(108)-C(109)	1.376(5)
C(108)-H(1081)	0.921
C(109)-C(110)	1.391(5)
C(109)-H(1091)	0.937
C(110)-H(1101)	0.937

C(2)-Pd(1)-C(3)	39.2(3)
C(2)-Pd(1)-C(4)	66.5(3)
C(3)-Pd(1)-C(4)	38.3(2)
C(2)-Pd(1)-N(11)	107.5(3)
C(3)-Pd(1)-N(11)	139.8(2)
C(4)-Pd(1)-N(11)	171.51(16)
C(2)-Pd(1)-N(22)	170.7(3)
C(3)-Pd(1)-N(22)	139.0(2)
C(4)-Pd(1)-N(22)	107.25(18)
N(11)-Pd(1)-N(22)	77.85(11)
N(11)-Pd(1)-N(22)	77.85(11)
N(11)-Pd(1)-C(102)	107.8(3)
N(22)-Pd(1)-C(102)	173.4(3)
N(11)-Pd(1)-C(103)	146.4(2)
N(22)-Pd(1)-C(103)	135.1(2)
C(102)-Pd(1)-C(103)	39.9(3)
N(11)-Pd(1)-C(104)	158.09(15)
N(22)-Pd(1)-C(104)	106.72(18)
C(102)-Pd(1)-C(104)	66.7(4)
C(103)-Pd(1)-C(104)	37.8(2)
Pd(1)-C(2)-C(3)	68.9(7)
Pd(1)-C(2)-H(21)	116.4
C(3)-C(2)-H(21)	119.5
Pd(1)-C(2)-H(22)	116.4
C(3)-C(2)-H(22)	119.5
H(21)-C(2)-H(22)	110.6
C(2)-C(3)-Pd(1)	71.9(8)
C(2)-C(3)-C(4)	113.43(10)
Pd(1)-C(3)-C(4)	73.3(4)
C(2)-C(3)-H(31)	122.8
Pd(1)-C(3)-H(31)	119.0
C(4)-C(3)-H(31)	123.6
C(3)-C(4)-Pd(1)	68.4(4)
C(3)-C(4)-C(5)	125.68(10)
Pd(1)-C(4)-C(5)	114.1(7)
C(3)-C(4)-H(41)	114.2
Pd(1)-C(4)-H(41)	111.1
C(5)-C(4)-H(41)	114.1
C(4)-C(5)-C(6)	121.6(5)
C(4)-C(5)-C(10)	119.7(5)
C(6)-C(5)-C(10)	118.52(6)
C(5)-C(6)-C(7)	122.03(6)
C(5)-C(6)-H(61)	118.9
C(7)-C(6)-H(61)	119.1

C(6)-C(7)-C(8)	115.57(6)	C(18)-C(19)-C(20)	116.2(3)
C(6)-C(7)-H(71)	121.8	C(18)-C(19)-C(27)	121.1(3)
C(8)-C(7)-H(71)	122.7	C(20)-C(19)-C(27)	122.7(3)
C(7)-C(8)-C(9)	126.16(6)	C(19)-C(20)-C(21)	120.4(3)
C(7)-C(8)-H(81)	117.4	C(19)-C(20)-H(201)	120.2
C(9)-C(8)-H(81)	116.4	C(21)-C(20)-H(201)	119.3
C(8)-C(9)-C(10)	115.56(6)	C(20)-C(21)-N(22)	122.9(3)
C(8)-C(9)-H(91)	121.7	C(20)-C(21)-H(211)	119.0
C(10)-C(9)-H(91)	122.8	N(22)-C(21)-H(211)	118.1
C(5)-C(10)-C(9)	122.05(6)	C(17)-N(22)-C(21)	118.2(3)
C(5)-C(10)-H(101)	119.0	C(17)-N(22)-Pd(1)	115.3(2)
C(9)-C(10)-H(101)	119.0	C(21)-N(22)-Pd(1)	126.0(2)
Pd(1)-N(11)-C(12)	125.6(2)	C(14)-C(23)-C(24)	112.0(4)
Pd(1)-N(11)-C(16)	115.9(2)	C(14)-C(23)-C(25)	109.6(3)
C(12)-N(11)-C(16)	117.8(3)	C(24)-C(23)-C(25)	108.4(3)
N(11)-C(12)-C(13)	122.8(3)	C(14)-C(23)-C(26)	109.0(3)
N(11)-C(12)-H(121)	117.9	C(24)-C(23)-C(26)	108.6(3)
C(13)-C(12)-H(121)	119.3	C(25)-C(23)-C(26)	109.1(4)
C(12)-C(13)-C(14)	120.5(3)	C(23)-C(24)-H(241)	108.2
C(12)-C(13)-H(131)	119.7	C(23)-C(24)-H(243)	110.5
C(14)-C(13)-H(131)	119.8	H(241)-C(24)-H(243)	108.6
C(13)-C(14)-C(15)	116.3(3)	C(23)-C(24)-H(242)	110.4
C(13)-C(14)-C(23)	123.2(3)	H(241)-C(24)-H(242)	109.9
C(15)-C(14)-C(23)	120.4(3)	H(243)-C(24)-H(242)	109.2
C(14)-C(15)-C(16)	120.7(3)	C(23)-C(25)-H(252)	106.5
C(14)-C(15)-H(151)	120.0	C(23)-C(25)-H(251)	110.0
C(16)-C(15)-H(151)	119.3	H(252)-C(25)-H(251)	109.5
C(15)-C(16)-N(11)	121.7(3)	C(23)-C(25)-H(253)	109.8
C(15)-C(16)-C(17)	123.3(3)	H(252)-C(25)-H(253)	110.0
N(11)-C(16)-C(17)	115.0(3)	H(251)-C(25)-H(253)	110.9
C(16)-C(17)-C(18)	123.7(3)	C(23)-C(26)-H(261)	110.9
C(16)-C(17)-N(22)	115.0(3)	C(23)-C(26)-H(263)	109.0
C(18)-C(17)-N(22)	121.3(3)	H(261)-C(26)-H(263)	109.2
C(17)-C(18)-C(19)	121.0(3)	C(23)-C(26)-H(262)	110.3
C(17)-C(18)-H(181)	119.4	H(261)-C(26)-H(262)	108.8
C(19)-C(18)-H(181)	119.6	H(263)-C(26)-H(262)	108.6

C(19)-C(27)-C(28)	110.2(3)
C(19)-C(27)-C(29)	107.4(4)
C(28)-C(27)-C(29)	109.7(4)
C(19)-C(27)-C(30)	111.4(3)
C(28)-C(27)-C(30)	108.9(4)
C(29)-C(27)-C(30)	109.3(4)
C(27)-C(28)-H(282)	108.7
C(27)-C(28)-H(281)	109.6
H(282)-C(28)-H(281)	109.2
C(27)-C(28)-H(283)	108.8
H(282)-C(28)-H(283)	109.8
H(281)-C(28)-H(283)	110.7
C(27)-C(29)-H(293)	109.2
C(27)-C(29)-H(291)	109.2
H(293)-C(29)-H(291)	109.1
C(27)-C(29)-H(292)	109.2
H(293)-C(29)-H(292)	109.9
H(291)-C(29)-H(292)	110.1
C(27)-C(30)-H(301)	109.0
C(27)-C(30)-H(302)	110.3
H(301)-C(30)-H(302)	108.6
C(27)-C(30)-H(303)	110.0
H(301)-C(30)-H(303)	108.9
H(302)-C(30)-H(303)	110.0
F(32)-B(31)-F(33)	110.6(4)
F(32)-B(31)-F(34)	110.0(3)
F(33)-B(31)-F(34)	109.9(3)
F(32)-B(31)-F(35)	107.2(3)
F(33)-B(31)-F(35)	109.9(4)
F(34)-B(31)-F(35)	109.1(4)
Pd(1)-C(102)-C(103)	70.8(6)
Pd(1)-C(102)-H(1021)	116.2
C(103)-C(102)-H(1021)	118.1
Pd(1)-C(102)-H(1022)	116.2
C(103)-C(102)-H(1022)	118.7
H(1021)-C(102)-H(1022)	111.4
C(102)-C(103)-Pd(1)	69.2(7)
C(102)-C(103)-C(104)	113.43(10)
Pd(1)-C(103)-C(104)	75.5(4)
C(102)-C(103)-H(1031)	122.8
Pd(1)-C(103)-H(1031)	120.8
C(104)-C(103)-H(1031)	123.6
C(103)-C(104)-Pd(1)	66.8(4)
C(103)-C(104)-C(105)	125.67(10)
Pd(1)-C(104)-C(105)	117.1(6)
C(103)-C(104)-H(1041)	114.8
Pd(1)-C(104)-H(1041)	109.6
C(105)-C(104)-H(1041)	113.5
C(104)-C(105)-C(106)	125.2(4)
C(104)-C(105)-C(110)	116.2(4)
C(106)-C(105)-C(110)	118.54(6)
C(105)-C(106)-C(107)	122.04(6)
C(105)-C(106)-H(1061)	118.7
C(107)-C(106)-H(1061)	119.3
C(106)-C(107)-C(108)	115.58(6)
C(106)-C(107)-H(1071)	121.8
C(108)-C(107)-H(1071)	122.6
C(107)-C(108)-C(109)	126.16(6)
C(107)-C(108)-H(1081)	116.2
C(109)-C(108)-H(1081)	117.7
C(108)-C(109)-C(110)	115.57(6)
C(108)-C(109)-H(1091)	122.3
C(110)-C(109)-H(1091)	122.1
C(105)-C(110)-C(109)	122.06(6)
C(105)-C(110)-H(1101)	119.5
C(109)-C(110)-H(1101)	118.4

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for 004ch11. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	33(1)	49(1)	44(1)	7(1)	-2(1)	-9(1)
C(2)	36(5)	52(6)	45(4)	-5(4)	1(4)	-9(4)
C(3)	29(4)	47(4)	43(4)	3(3)	7(3)	-9(3)
C(4)	36(3)	27(3)	43(3)	0(3)	3(3)	-5(2)
C(5)	36(4)	40(4)	48(4)	8(3)	6(3)	-6(3)
C(6)	45(4)	55(4)	44(4)	-2(3)	6(3)	-8(3)
C(7)	57(4)	74(5)	48(4)	2(4)	-1(3)	-7(4)
C(8)	56(4)	70(5)	46(4)	0(4)	0(3)	-3(4)
C(9)	52(4)	60(5)	62(5)	11(4)	10(4)	5(4)
C(10)	42(4)	54(4)	62(4)	17(4)	9(4)	1(3)
N(11)	34(1)	38(2)	35(1)	-2(1)	2(1)	0(1)
C(12)	35(2)	56(2)	39(2)	-2(2)	-4(1)	-1(2)
C(13)	45(2)	65(2)	33(2)	3(2)	-6(2)	7(2)
C(14)	40(2)	48(2)	31(2)	2(1)	5(1)	9(2)
C(15)	36(2)	41(2)	33(2)	0(1)	5(1)	4(1)
C(16)	32(2)	34(2)	34(2)	-4(1)	4(1)	4(1)
C(17)	31(1)	37(2)	34(2)	2(1)	3(1)	0(1)
C(18)	30(2)	38(2)	40(2)	3(1)	2(1)	0(1)
C(19)	34(2)	46(2)	44(2)	4(2)	-2(1)	-1(1)
C(20)	37(2)	57(2)	44(2)	12(2)	-4(2)	-3(2)
C(21)	39(2)	58(2)	46(2)	20(2)	-3(2)	-9(2)
N(22)	32(1)	49(2)	42(2)	11(1)	-2(1)	-5(1)
C(23)	53(2)	51(2)	35(2)	8(2)	6(2)	15(2)
C(24)	65(3)	81(3)	46(2)	20(2)	2(2)	20(2)
C(25)	77(3)	42(2)	48(2)	5(2)	15(2)	11(2)
C(26)	60(3)	55(2)	40(2)	7(2)	15(2)	15(2)
C(27)	34(2)	70(3)	51(2)	10(2)	-4(2)	-7(2)
C(28)	45(2)	74(3)	60(2)	6(2)	-9(2)	-22(2)
C(29)	37(2)	95(4)	87(4)	2(3)	5(2)	2(2)
C(30)	45(2)	111(4)	70(3)	27(3)	-20(2)	-16(3)
B(31)	40(2)	45(2)	43(2)	-1(2)	9(2)	-7(2)

F(32)	61(1)	58(1)	60(1)	-1(1)	24(1)	5(1)
F(33)	119(3)	119(3)	69(2)	42(2)	52(2)	50(2)
F(34)	38(1)	160(3)	81(2)	-32(2)	2(1)	-6(2)
F(35)	82(2)	58(2)	113(2)	-32(2)	28(2)	-27(1)
C(102)	31(4)	45(5)	73(6)	-8(4)	0(4)	-6(4)
C(103)	41(4)	43(4)	66(5)	1(3)	5(4)	-10(3)
C(104)	40(3)	42(3)	51(3)	8(3)	12(3)	-4(3)
C(105)	41(3)	35(3)	41(3)	4(3)	13(3)	-1(3)
C(106)	48(4)	37(3)	43(3)	6(3)	11(3)	-1(3)
C(107)	46(3)	40(3)	44(3)	0(3)	8(3)	5(3)
C(108)	57(4)	44(4)	48(3)	0(3)	9(3)	4(3)
C(109)	63(5)	44(4)	58(4)	-5(3)	13(3)	8(3)
C(110)	55(4)	41(3)	52(4)	-8(3)	19(3)	-2(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10 ^{3}) for 004ch11.

	x	y	z	U(eq)
H(21)	7042	9580	4931	54
H(22)	7563	8682	4967	54
H(31)	7499	8570	3923	48
H(41)	6221	9916	4057	43
H(61)	6590	8031	3162	58
H(71)	5944	7749	2265	72
H(81)	4975	8797	1913	69
H(91)	4659	10079	2376	70
H(101)	5357	10341	3257	64
H(121)	6649	7607	5690	52
H(131)	6347	6459	6311	57
H(151)	4140	6007	5414	44
H(181)	3226	6595	4789	43
H(201)	3157	8018	3335	55
H(211)	4562	8473	3516	57
H(241)	5584	4518	6923	95
H(243)	5921	5492	6949	94
H(242)	6269	4866	6462	95
H(252)	4676	4013	6190	83
H(251)	5208	4375	5660	83
H(253)	4193	4619	5735	83
H(261)	4061	5059	6944	77
H(263)	4372	6041	6922	77
H(262)	3715	5682	6460	77
H(282)	1375	5805	3985	88
H(281)	2100	5857	4470	89
H(283)	2364	5661	3818	89
H(293)	892	7325	4321	111
H(291)	1569	8095	4304	111
H(292)	1677	7338	4765	111

H(301)	1151	6950	3290	114
H(302)	1770	7776	3254	114
H(303)	2115	6840	3057	114
H(1021)	7300	9087	5033	59
H(1022)	7701	8408	4580	59
H(1031)	6682	9901	4241	59
H(1041)	7110	8363	3613	53
H(1061)	5664	10213	3501	51
H(1071)	4769	10539	2712	51
H(1081)	4699	9508	1995	59
H(1091)	5410	8175	2016	65
H(1101)	6354	7923	2791	59

Table 6. Hydrogen bonds for 004ch11 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(21)-H(211)...C(5)	0.938	2.528	3.318(9)	142.03
C(21)-H(211)...C(105)	0.938	2.588	3.371(9)	141.20

Symmetry transformations used to generate equivalent atoms:

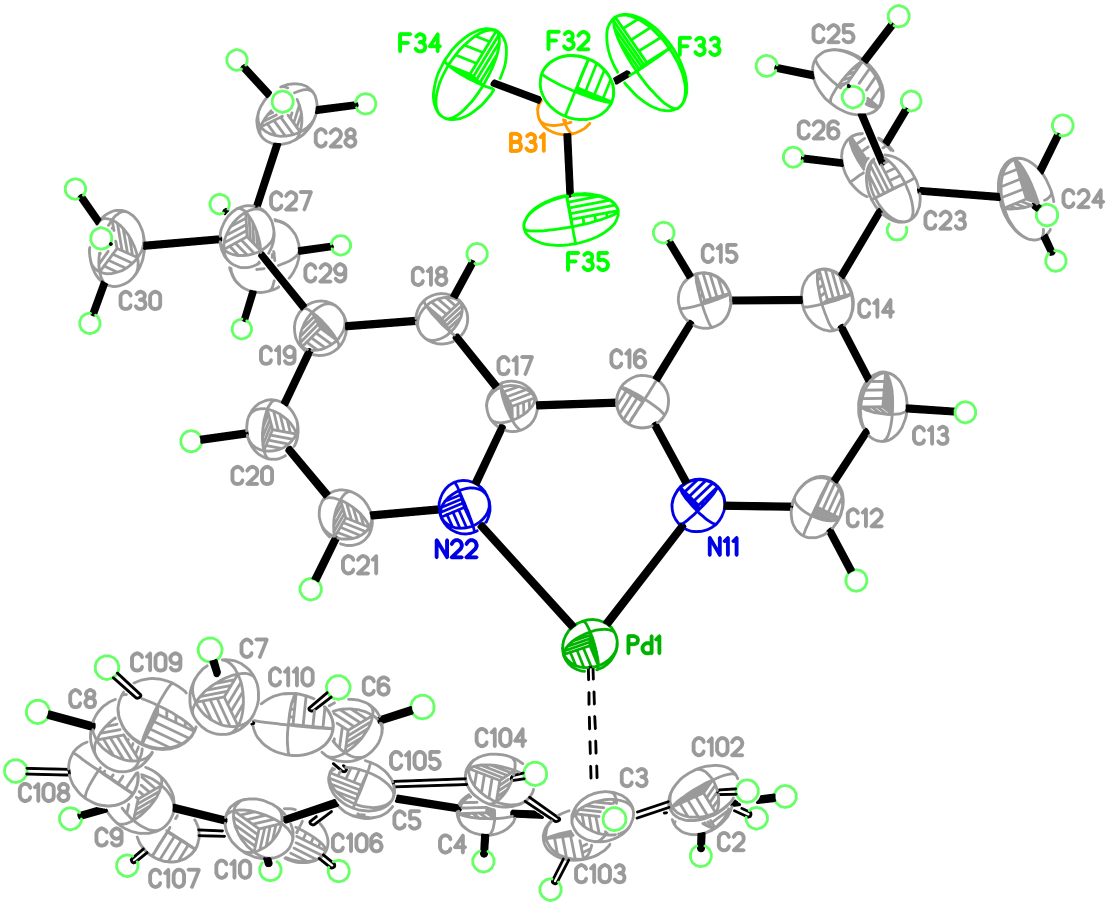

Table 1. Crystal data and structure refinement for 070gwp13.

Identification code	070gwp13	
Empirical formula	C55 H43 B1 Cl2 F4 P2 Pd1	
Formula weight	1030.00	
Temperature	150 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 13.9402(2) Å	α= 90°.
	b = 15.0450(2) Å	β= 90°.
	c = 23.0696(3) Å	γ = 90°.
Volume	4838.39(11) Å^3	
Z	4	
Density (calculated)	1.414 Mg/m^3	
Absorption coefficient	0.612 mm^{-1}	
F(000)	2096	
Crystal size	0.340 x 0.220 x 0.050 mm^3	
Theta range for data collection	5.126 to 27.470°.	
Index ranges	-18<=h<=18, -19<=k<=19, -29<=l<=29	
Reflections collected	76239	
Independent reflections	10975 [R(int) = 0.057]	
Completeness to theta = 26.646°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.97 and 0.77	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10974 / 971 / 645	
Goodness-of-fit on F^2	1.0037	
Final R indices [I>2sigma(I)]	R1 = 0.0466, wR2 = 0.1086	
R indices (all data)	R1 = 0.0609, wR2 = 0.1166	
Absolute structure parameter	-0.01(2)	
Extinction coefficient	230(50)	
Largest diff. peak and hole	0.82 and -0.63 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 070gwp13. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pd(1)	6595(1)	3559(1)	5920(1)	36
P(2)	5857(1)	4311(1)	6667(1)	35
C(3)	6416(3)	4040(3)	7359(2)	41
C(4)	5913(4)	3835(3)	7862(2)	50
C(5)	6431(4)	3593(3)	8356(2)	62
C(6)	7422(5)	3564(3)	8351(2)	65
C(7)	7909(4)	3768(3)	7854(2)	56
C(8)	7418(3)	3999(3)	7362(2)	47
C(9)	5961(3)	5525(2)	6618(2)	35
C(10)	5510(3)	5992(3)	6172(2)	35
C(11)	4783(3)	5569(2)	5786(2)	37
C(12)	5023(3)	5028(3)	5323(2)	39
P(13)	6250(1)	4606(1)	5223(1)	39
C(14)	7040(3)	5563(3)	5220(2)	45
C(15)	7855(3)	5548(3)	5575(2)	53
C(16)	8453(4)	6281(4)	5617(3)	70
C(17)	8218(4)	7035(4)	5292(3)	72
C(18)	7438(5)	7065(3)	4932(2)	65
C(19)	6827(4)	6323(3)	4901(2)	52
C(20)	6260(3)	4139(3)	4496(2)	47
C(21)	6731(4)	4521(3)	4041(2)	58
C(22)	6710(5)	4125(3)	3485(2)	73
C(23)	6250(5)	3363(4)	3406(2)	77
C(24)	5746(5)	2937(4)	3860(2)	68
C(25)	5783(4)	3335(3)	4400(2)	60
C(26)	4282(3)	4704(3)	4945(2)	51
C(27)	3347(4)	4882(3)	5066(2)	56
C(28)	3064(3)	5394(3)	5544(2)	49
C(29)	3790(3)	5766(2)	5910(2)	43
C(30)	3509(3)	6282(2)	6385(2)	48
C(31)	2554(3)	6399(3)	6517(2)	56

C(32)	1839(4)	6008(3)	6167(3)	64
C(33)	2082(4)	5524(3)	5694(3)	61
C(34)	5710(3)	6921(3)	6097(2)	36
C(35)	5298(3)	7420(3)	5646(2)	43
C(36)	5531(3)	8293(3)	5570(2)	48
C(37)	6174(3)	8723(2)	5933(2)	48
C(38)	6584(4)	8262(3)	6380(2)	50
C(39)	6364(3)	7352(3)	6473(2)	41
C(40)	6781(3)	6868(3)	6926(2)	47
C(41)	6600(4)	5979(3)	6999(2)	43
C(42)	4592(3)	4056(3)	6730(2)	39
C(43)	4211(3)	3375(3)	6396(2)	46
C(44)	3232(3)	3179(3)	6422(2)	56
C(45)	2640(3)	3646(4)	6777(2)	61
C(46)	3026(3)	4328(3)	7131(2)	58
C(47)	3980(3)	4527(3)	7107(2)	47
C(48)	6985(3)	2161(3)	5830(2)	45
C(49)	7039(3)	2398(3)	6429(2)	50
C(50)	6318(4)	1841(3)	6758(2)	59
C(51)	5736(3)	1390(3)	6290(2)	52
C(52)	6129(3)	1575(3)	5748(2)	44
C(53)	5725(4)	1249(3)	5247(2)	56
C(54)	4883(4)	748(3)	5296(3)	66
C(55)	4499(4)	578(3)	5828(3)	72
C(56)	4904(4)	894(3)	6340(3)	67
C(57)	7464(3)	2638(3)	5412(2)	52
B(60)	4697(5)	694(5)	3455(3)	72
F(61)	3969(2)	1222(2)	3682(2)	83
F(62)	5337(4)	576(5)	3892(2)	164
F(63)	4305(3)	-56(3)	3230(3)	121
F(64)	5164(4)	1153(3)	3028(2)	123
C(65)	4413(6)	5275(5)	3178(4)	105
Cl(66)	3428(2)	4636(2)	3406(1)	82
Cl(67)	4496(3)	6259(2)	3604(2)	137
C(68)	4948(17)	7994(12)	2957(7)	75
Cl(69)	5806(5)	8251(5)	2353(3)	62

Cl(70)	4317(7)	6926(6)	2810(5)	93
C(71)	4591(8)	7720(30)	3185(12)	110
Cl(72)	5554(11)	8113(11)	2699(7)	119
Cl(73)	5113(7)	7151(9)	3818(7)	103

Table 3. Bond lengths [Å] and angles [°] for 070gwp13.

Pd(1)-P(2)	2.3041(10)	C(16)-H(161)	0.938
Pd(1)-P(13)	2.3009(11)	C(17)-C(18)	1.368(9)
Pd(1)-C(48)	2.182(4)	C(17)-H(171)	0.950
Pd(1)-C(49)	2.194(4)	C(18)-C(19)	1.407(7)
Pd(1)-C(57)	2.182(4)	C(18)-H(181)	0.926
P(2)-C(3)	1.822(4)	C(19)-H(191)	0.924
P(2)-C(9)	1.835(4)	C(20)-C(21)	1.365(6)
P(2)-C(42)	1.811(4)	C(20)-C(25)	1.398(7)
C(3)-C(4)	1.390(6)	C(21)-C(22)	1.414(7)
C(3)-C(8)	1.399(6)	C(21)-H(211)	0.940
C(4)-C(5)	1.397(7)	C(22)-C(23)	1.326(9)
C(4)-H(41)	0.920	C(22)-H(221)	0.939
C(5)-C(6)	1.382(8)	C(23)-C(24)	1.415(9)
C(5)-H(51)	0.934	C(23)-H(231)	0.944
C(6)-C(7)	1.367(7)	C(24)-C(25)	1.384(7)
C(6)-H(61)	0.939	C(24)-H(241)	0.943
C(7)-C(8)	1.369(6)	C(25)-H(251)	0.935
C(7)-H(71)	0.937	C(26)-C(27)	1.360(7)
C(8)-H(81)	0.927	C(26)-H(261)	0.915
C(9)-C(10)	1.398(6)	C(27)-C(28)	1.402(7)
C(9)-C(41)	1.426(6)	C(27)-H(271)	0.928
C(10)-C(11)	1.491(5)	C(28)-C(29)	1.432(6)
C(10)-C(34)	1.435(5)	C(28)-C(33)	1.424(7)
C(11)-C(12)	1.384(6)	C(29)-C(30)	1.399(6)
C(11)-C(29)	1.444(6)	C(30)-C(31)	1.377(6)
C(12)-P(13)	1.839(4)	C(30)-H(301)	0.898
C(12)-C(26)	1.438(6)	C(31)-C(32)	1.411(7)
P(13)-C(14)	1.813(4)	C(31)-H(311)	0.924
P(13)-C(20)	1.818(4)	C(32)-C(33)	1.354(8)
C(14)-C(15)	1.402(7)	C(32)-H(321)	0.933
C(14)-C(19)	1.391(6)	C(33)-H(331)	0.951
C(15)-C(16)	1.385(7)	C(34)-C(35)	1.406(6)
C(15)-H(151)	0.926	C(34)-C(39)	1.416(5)
C(16)-C(17)	1.398(9)	C(35)-C(36)	1.365(6)

C(35)-H(351)	0.927
C(36)-C(37)	1.386(6)
C(36)-H(361)	0.919
C(37)-C(38)	1.368(7)
C(37)-H(371)	0.924
C(38)-C(39)	1.419(6)
C(38)-H(381)	0.955
C(39)-C(40)	1.400(6)
C(40)-C(41)	1.371(6)
C(40)-H(401)	0.928
C(41)-H(411)	0.941
C(42)-C(43)	1.387(6)
C(42)-C(47)	1.410(6)
C(43)-C(44)	1.398(6)
C(43)-H(431)	0.917
C(44)-C(45)	1.360(7)
C(44)-H(441)	0.927
C(45)-C(46)	1.418(8)
C(45)-H(451)	0.941
C(46)-C(47)	1.364(7)
C(46)-H(461)	0.925
C(47)-H(471)	0.945
C(48)-C(49)	1.427(6)
C(48)-C(52)	1.497(6)
C(48)-C(57)	1.376(6)
C(49)-C(50)	1.514(7)
C(49)-H(491)	0.962
C(50)-C(51)	1.511(7)
C(50)-H(501)	0.992
C(50)-H(502)	0.978
C(51)-C(52)	1.394(6)
C(51)-C(56)	1.383(7)
C(52)-C(53)	1.375(6)
C(53)-C(54)	1.399(7)
C(53)-H(531)	0.926
C(54)-C(55)	1.365(8)

C(54)-H(541)	0.941
C(55)-C(56)	1.392(9)
C(55)-H(551)	0.953
C(56)-H(561)	0.956
C(57)-H(26)	0.977
C(57)-H(30)	0.976
B(60)-F(61)	1.391(7)
B(60)-F(62)	1.358(8)
B(60)-F(63)	1.358(8)
B(60)-F(64)	1.367(9)
C(65)-Cl(66)	1.757(5)
C(65)-Cl(67)	1.782(5)
C(65)-H(651)	0.975
C(65)-H(652)	0.965
C(68)-Cl(69)	1.877(7)
C(68)-Cl(70)	1.865(7)
C(68)-H(681)	0.969
C(68)-H(682)	0.969
C(71)-Cl(72)	1.844(7)
C(71)-Cl(73)	1.846(7)
C(71)-H(711)	0.967
C(71)-H(712)	0.969

P(2)-Pd(1)-P(13)	95.35(4)
P(2)-Pd(1)-C(48)	130.92(12)
P(13)-Pd(1)-C(48)	130.24(12)
P(2)-Pd(1)-C(49)	96.68(13)
P(13)-Pd(1)-C(49)	167.90(13)
C(48)-Pd(1)-C(49)	38.07(17)
P(2)-Pd(1)-C(57)	164.01(14)
P(13)-Pd(1)-C(57)	100.14(14)
C(48)-Pd(1)-C(57)	36.75(17)
C(49)-Pd(1)-C(57)	67.97(18)
Pd(1)-P(2)-C(3)	110.77(13)
Pd(1)-P(2)-C(9)	114.05(12)
C(3)-P(2)-C(9)	104.05(18)

Pd(1)-P(2)-C(42)	112.99(14)	C(12)-P(13)-C(20)	104.8(2)
C(3)-P(2)-C(42)	107.36(19)	Pd(1)-P(13)-C(20)	112.22(15)
C(9)-P(2)-C(42)	107.04(17)	C(14)-P(13)-C(20)	107.3(2)
P(2)-C(3)-C(4)	124.5(4)	P(13)-C(14)-C(15)	118.4(3)
P(2)-C(3)-C(8)	116.2(3)	P(13)-C(14)-C(19)	121.7(4)
C(4)-C(3)-C(8)	119.3(4)	C(15)-C(14)-C(19)	119.8(4)
C(3)-C(4)-C(5)	118.6(5)	C(14)-C(15)-C(16)	121.0(5)
C(3)-C(4)-H(41)	119.0	C(14)-C(15)-H(151)	121.1
C(5)-C(4)-H(41)	122.4	C(16)-C(15)-H(151)	117.9
C(4)-C(5)-C(6)	121.2(4)	C(15)-C(16)-C(17)	117.9(5)
C(4)-C(5)-H(51)	118.6	C(15)-C(16)-H(161)	120.0
C(6)-C(5)-H(51)	120.3	C(17)-C(16)-H(161)	122.0
C(5)-C(6)-C(7)	119.8(4)	C(16)-C(17)-C(18)	122.5(5)
C(5)-C(6)-H(61)	120.3	C(16)-C(17)-H(171)	117.1
C(7)-C(6)-H(61)	119.9	C(18)-C(17)-H(171)	120.4
C(6)-C(7)-C(8)	120.2(5)	C(17)-C(18)-C(19)	119.1(5)
C(6)-C(7)-H(71)	119.1	C(17)-C(18)-H(181)	120.5
C(8)-C(7)-H(71)	120.7	C(19)-C(18)-H(181)	120.4
C(3)-C(8)-C(7)	121.0(4)	C(18)-C(19)-C(14)	119.7(5)
C(3)-C(8)-H(81)	120.4	C(18)-C(19)-H(191)	119.1
C(7)-C(8)-H(81)	118.5	C(14)-C(19)-H(191)	121.2
P(2)-C(9)-C(10)	120.7(3)	P(13)-C(20)-C(21)	123.5(4)
P(2)-C(9)-C(41)	119.3(3)	P(13)-C(20)-C(25)	118.5(4)
C(10)-C(9)-C(41)	119.6(3)	C(21)-C(20)-C(25)	118.1(4)
C(9)-C(10)-C(11)	122.1(3)	C(20)-C(21)-C(22)	120.7(5)
C(9)-C(10)-C(34)	119.4(4)	C(20)-C(21)-H(211)	119.9
C(11)-C(10)-C(34)	118.4(4)	C(22)-C(21)-H(211)	119.3
C(10)-C(11)-C(12)	123.2(4)	C(21)-C(22)-C(23)	120.0(5)
C(10)-C(11)-C(29)	116.4(3)	C(21)-C(22)-H(221)	120.6
C(12)-C(11)-C(29)	120.4(4)	C(23)-C(22)-H(221)	119.4
C(11)-C(12)-P(13)	121.7(3)	C(22)-C(23)-C(24)	121.9(5)
C(11)-C(12)-C(26)	119.6(4)	C(22)-C(23)-H(231)	118.7
P(13)-C(12)-C(26)	118.4(3)	C(24)-C(23)-H(231)	119.4
C(12)-P(13)-Pd(1)	110.08(13)	C(23)-C(24)-C(25)	116.9(5)
C(12)-P(13)-C(14)	106.93(19)	C(23)-C(24)-H(241)	123.3
Pd(1)-P(13)-C(14)	114.85(15)	C(25)-C(24)-H(241)	119.8

C(20)-C(25)-C(24)	122.4(5)
C(20)-C(25)-H(251)	118.7
C(24)-C(25)-H(251)	119.0
C(12)-C(26)-C(27)	119.8(4)
C(12)-C(26)-H(261)	120.7
C(27)-C(26)-H(261)	119.4
C(26)-C(27)-C(28)	122.7(4)
C(26)-C(27)-H(271)	117.8
C(28)-C(27)-H(271)	119.5
C(27)-C(28)-C(29)	118.6(4)
C(27)-C(28)-C(33)	122.5(5)
C(29)-C(28)-C(33)	118.8(5)
C(11)-C(29)-C(28)	118.7(4)
C(11)-C(29)-C(30)	122.5(4)
C(28)-C(29)-C(30)	118.7(4)
C(29)-C(30)-C(31)	120.9(4)
C(29)-C(30)-H(301)	118.6
C(31)-C(30)-H(301)	120.5
C(30)-C(31)-C(32)	120.3(5)
C(30)-C(31)-H(311)	118.5
C(32)-C(31)-H(311)	121.3
C(31)-C(32)-C(33)	120.5(5)
C(31)-C(32)-H(321)	118.5
C(33)-C(32)-H(321)	121.0
C(28)-C(33)-C(32)	120.7(5)
C(28)-C(33)-H(331)	119.7
C(32)-C(33)-H(331)	119.6
C(10)-C(34)-C(35)	121.9(4)
C(10)-C(34)-C(39)	119.9(4)
C(35)-C(34)-C(39)	118.1(4)
C(34)-C(35)-C(36)	120.8(4)
C(34)-C(35)-H(351)	120.0
C(36)-C(35)-H(351)	119.2
C(35)-C(36)-C(37)	121.7(4)
C(35)-C(36)-H(361)	119.4
C(37)-C(36)-H(361)	119.0
C(36)-C(37)-C(38)	119.3(4)
C(36)-C(37)-H(371)	120.0
C(38)-C(37)-H(371)	120.7
C(37)-C(38)-C(39)	120.8(4)
C(37)-C(38)-H(381)	119.5
C(39)-C(38)-H(381)	119.7
C(38)-C(39)-C(34)	119.3(4)
C(38)-C(39)-C(40)	121.7(4)
C(34)-C(39)-C(40)	119.1(4)
C(39)-C(40)-C(41)	121.6(4)
C(39)-C(40)-H(401)	118.2
C(41)-C(40)-H(401)	120.2
C(9)-C(41)-C(40)	120.4(4)
C(9)-C(41)-H(411)	119.7
C(40)-C(41)-H(411)	119.9
P(2)-C(42)-C(43)	119.0(3)
P(2)-C(42)-C(47)	122.1(3)
C(43)-C(42)-C(47)	118.9(4)
C(42)-C(43)-C(44)	120.4(4)
C(42)-C(43)-H(431)	119.3
C(44)-C(43)-H(431)	120.3
C(43)-C(44)-C(45)	120.7(5)
C(43)-C(44)-H(441)	119.7
C(45)-C(44)-H(441)	119.6
C(44)-C(45)-C(46)	119.3(4)
C(44)-C(45)-H(451)	121.4
C(46)-C(45)-H(451)	119.3
C(45)-C(46)-C(47)	120.4(5)
C(45)-C(46)-H(461)	121.0
C(47)-C(46)-H(461)	118.6
C(42)-C(47)-C(46)	120.3(5)
C(42)-C(47)-H(471)	120.1
C(46)-C(47)-H(471)	119.6
Pd(1)-C(48)-C(49)	71.4(2)
Pd(1)-C(48)-C(52)	112.5(3)
C(49)-C(48)-C(52)	108.2(4)

Pd(1)-C(48)-C(57)	71.6(2)
C(49)-C(48)-C(57)	121.5(4)
C(52)-C(48)-C(57)	127.3(4)
C(48)-C(49)-Pd(1)	70.5(2)
C(48)-C(49)-C(50)	108.2(4)
Pd(1)-C(49)-C(50)	121.5(3)
C(48)-C(49)-H(491)	121.4
Pd(1)-C(49)-H(491)	109.5
C(50)-C(49)-H(491)	117.7
C(49)-C(50)-C(51)	104.2(4)
C(49)-C(50)-H(501)	109.4
C(51)-C(50)-H(501)	111.3
C(49)-C(50)-H(502)	110.2
C(51)-C(50)-H(502)	112.4
H(501)-C(50)-H(502)	109.2
C(50)-C(51)-C(52)	110.0(4)
C(50)-C(51)-C(56)	129.3(5)
C(52)-C(51)-C(56)	120.7(5)
C(48)-C(52)-C(51)	108.4(4)
C(48)-C(52)-C(53)	130.1(4)
C(51)-C(52)-C(53)	121.5(4)
C(52)-C(53)-C(54)	117.9(5)
C(52)-C(53)-H(531)	121.5
C(54)-C(53)-H(531)	120.6
C(53)-C(54)-C(55)	120.1(6)
C(53)-C(54)-H(541)	119.3
C(55)-C(54)-H(541)	120.5
C(54)-C(55)-C(56)	122.7(5)
C(54)-C(55)-H(551)	118.8
C(56)-C(55)-H(551)	118.5
C(55)-C(56)-C(51)	117.1(5)
C(55)-C(56)-H(561)	121.5
C(51)-C(56)-H(561)	121.4
C(48)-C(57)-Pd(1)	71.6(2)
C(48)-C(57)-H(26)	118.9
Pd(1)-C(57)-H(26)	111.8
C(48)-C(57)-H(30)	119.3
Pd(1)-C(57)-H(30)	119.0
H(26)-C(57)-H(30)	111.1
F(61)-B(60)-F(62)	106.0(5)
F(61)-B(60)-F(63)	108.9(5)
F(62)-B(60)-F(63)	116.0(7)
F(61)-B(60)-F(64)	109.3(6)
F(62)-B(60)-F(64)	106.8(6)
F(63)-B(60)-F(64)	109.7(6)
Cl(66)-C(65)-Cl(67)	109.87(7)
Cl(66)-C(65)-H(651)	108.4
Cl(67)-C(65)-H(651)	111.7
Cl(66)-C(65)-H(652)	107.9
Cl(67)-C(65)-H(652)	109.6
H(651)-C(65)-H(652)	109.2
Cl(69)-C(68)-Cl(70)	110.04(7)
Cl(69)-C(68)-H(681)	109.2
Cl(70)-C(68)-H(681)	109.0
Cl(69)-C(68)-H(682)	109.8
Cl(70)-C(68)-H(682)	109.3
H(681)-C(68)-H(682)	109.5
Cl(72)-C(71)-Cl(73)	109.99(7)
Cl(72)-C(71)-H(711)	109.4
Cl(73)-C(71)-H(711)	109.6
Cl(72)-C(71)-H(712)	109.8
Cl(73)-C(71)-H(712)	108.9
H(711)-C(71)-H(712)	109.2

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for 070gwp13. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	38(1)	32(1)	37(1)	-1(1)	2(1)	0(1)
P(2)	38(1)	32(1)	36(1)	2(1)	2(1)	-1(1)
C(3)	59(3)	30(2)	35(2)	1(2)	1(2)	4(2)
C(4)	68(3)	36(2)	46(2)	2(2)	11(2)	3(2)
C(5)	113(4)	38(2)	34(2)	4(2)	11(2)	4(3)
C(6)	106(4)	42(2)	46(2)	3(2)	-23(2)	-2(3)
C(7)	69(3)	47(3)	51(3)	0(2)	-15(2)	4(2)
C(8)	51(2)	51(2)	39(2)	-2(2)	-4(2)	-2(2)
C(9)	41(2)	32(2)	33(2)	-2(2)	3(2)	-3(2)
C(10)	35(2)	33(2)	36(2)	-3(2)	3(2)	-2(2)
C(11)	42(2)	27(2)	41(2)	4(2)	-6(2)	-3(2)
C(12)	44(2)	33(2)	41(2)	4(2)	-1(2)	-4(2)
P(13)	49(1)	34(1)	34(1)	-1(1)	3(1)	-3(1)
C(14)	54(2)	40(2)	40(2)	-4(2)	18(2)	-4(2)
C(15)	49(2)	48(2)	62(3)	-6(2)	10(2)	-9(2)
C(16)	48(2)	74(3)	89(3)	-15(3)	11(3)	-20(3)
C(17)	75(3)	54(3)	89(4)	-7(3)	35(3)	-26(3)
C(18)	98(4)	41(2)	55(3)	-3(2)	35(3)	-11(3)
C(19)	76(3)	38(2)	41(2)	-2(2)	16(2)	-1(2)
C(20)	60(3)	41(2)	40(2)	-6(2)	-1(2)	4(2)
C(21)	86(3)	42(2)	46(2)	-3(2)	14(3)	5(2)
C(22)	113(4)	53(3)	54(3)	-5(2)	25(3)	13(3)
C(23)	116(4)	67(3)	48(3)	-19(2)	-7(3)	30(3)
C(24)	99(4)	53(3)	52(3)	-11(2)	-7(3)	-1(3)
C(25)	89(3)	43(3)	47(2)	-3(2)	5(2)	-2(2)
C(26)	55(3)	50(2)	47(2)	-2(2)	-10(2)	-10(2)
C(27)	58(3)	56(2)	54(2)	4(2)	-17(2)	-12(2)
C(28)	46(2)	37(2)	65(3)	11(2)	-8(2)	-5(2)
C(29)	44(2)	28(2)	58(2)	8(2)	-5(2)	-1(2)
C(30)	41(2)	32(2)	69(3)	1(2)	2(2)	2(2)
C(31)	47(2)	33(2)	89(3)	4(2)	13(2)	5(2)

C(32)	40(3)	45(2)	107(4)	14(3)	-2(2)	-1(2)
C(33)	45(2)	49(3)	90(4)	15(3)	-7(2)	-6(2)
C(34)	33(2)	34(2)	41(2)	-5(2)	6(2)	-2(2)
C(35)	43(2)	34(2)	52(2)	2(2)	-3(2)	-1(2)
C(36)	54(2)	37(2)	52(2)	6(2)	-1(2)	4(2)
C(37)	53(2)	30(2)	60(2)	0(2)	6(2)	-3(2)
C(38)	54(2)	36(2)	60(2)	-9(2)	6(2)	-5(2)
C(39)	41(2)	39(2)	42(2)	-7(2)	1(2)	-7(2)
C(40)	56(3)	43(2)	43(2)	-6(2)	-7(2)	-9(2)
C(41)	53(2)	39(2)	38(2)	0(2)	-4(2)	-3(2)
C(42)	37(2)	35(2)	44(2)	8(2)	6(2)	2(2)
C(43)	40(2)	43(2)	54(2)	2(2)	3(2)	-2(2)
C(44)	50(3)	51(2)	67(3)	1(2)	0(2)	-10(2)
C(45)	43(2)	58(3)	82(3)	13(3)	2(2)	-3(2)
C(46)	49(2)	48(3)	78(3)	15(2)	23(2)	12(2)
C(47)	49(2)	39(2)	54(2)	4(2)	11(2)	3(2)
C(48)	47(2)	35(2)	53(2)	-1(2)	2(2)	7(2)
C(49)	44(2)	46(2)	58(3)	5(2)	-8(2)	6(2)
C(50)	76(3)	46(2)	57(3)	8(2)	7(2)	16(2)
C(51)	57(2)	34(2)	64(3)	9(2)	10(2)	10(2)
C(52)	44(2)	31(2)	55(2)	-3(2)	-3(2)	7(2)
C(53)	66(3)	42(3)	59(3)	-8(2)	-1(2)	8(2)
C(54)	68(3)	33(2)	96(4)	0(2)	-13(3)	0(2)
C(55)	71(3)	39(2)	106(4)	1(3)	0(3)	-5(2)
C(56)	63(3)	47(3)	92(4)	16(3)	15(3)	2(2)
C(57)	46(2)	47(2)	64(3)	-14(2)	9(2)	9(2)
B(60)	49(3)	82(4)	86(4)	-9(4)	6(3)	8(3)
F(61)	49(2)	98(3)	101(2)	-25(2)	-7(2)	16(2)
F(62)	132(3)	247(5)	114(3)	-33(4)	-44(3)	120(4)
F(63)	98(3)	74(2)	191(4)	-43(3)	35(3)	-9(2)
F(64)	130(3)	128(3)	112(3)	-45(3)	44(3)	-47(3)
C(65)	94(3)	109(4)	112(4)	20(3)	13(4)	-21(3)
Cl(66)	80(1)	99(2)	66(1)	32(1)	-22(1)	-28(1)
Cl(67)	140(3)	110(2)	160(3)	-4(2)	70(2)	-5(2)
C(68)	59(4)	88(5)	80(5)	-26(5)	-22(4)	19(4)
Cl(69)	45(3)	77(4)	64(4)	-33(3)	-26(3)	19(3)

Cl(70)	77(4)	96(5)	107(5)	-21(4)	-14(4)	12(4)
C(71)	55(4)	101(6)	175(6)	-60(5)	-56(5)	28(5)
Cl(72)	73(5)	106(6)	179(6)	-64(6)	-54(5)	21(5)
Cl(73)	34(4)	97(5)	177(6)	-51(5)	-44(4)	30(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10 ^{3}) for 070gwp13.

	x	y	z	U(eq)
H(41)	5254	3863	7858	59
H(61)	7762	3402	8686	77
H(71)	8581	3745	7854	68
H(81)	7764	4114	7027	56
H(151)	8022	5042	5781	63
H(161)	9005	6255	5849	85
H(171)	8636	7531	5323	87
H(181)	7313	7568	4713	78
H(191)	6270	6362	4685	61
H(211)	7096	5039	4099	69
H(221)	7019	4396	3170	88
H(231)	6245	3109	3032	92
H(241)	5400	2403	3811	82
H(251)	5477	3059	4713	71
H(261)	4432	4374	4624	61
H(271)	2885	4658	4816	67
H(301)	3966	6521	6611	57
H(311)	2396	6734	6838	67
H(321)	1198	6074	6276	77
H(331)	1593	5276	5457	74
H(351)	4863	7156	5395	52
H(361)	5248	8609	5275	57
H(371)	6321	9314	5871	56
H(381)	7029	8555	6630	59
H(401)	7181	7166	7182	57
H(411)	6897	5666	7303	51
H(431)	4607	3059	6155	55
H(441)	2987	2716	6202	66
H(451)	1980	3516	6800	73
H(461)	2642	4640	7387	70

H(471)	4229	4985	7344	57
H(491)	7644	2518	6613	59
H(501)	6663	1400	7001	71
H(502)	5925	2219	7008	71
H(531)	5988	1368	4887	67
H(541)	4590	526	4958	79
H(551)	3919	243	5851	87
H(561)	4629	762	6710	81
H(651)	4990	4912	3210	126
H(652)	4312	5432	2777	127
H(681)	5302	7942	3317	90
H(682)	4480	8467	2992	90
H(711)	4217	8229	3315	132
H(712)	4176	7315	2980	132
H(51)	6093	3454	8693	74
H(26)	8149	2750	5462	63
H(30)	7305	2543	5005	62

Table 6. Hydrogen bonds for 070gwp13 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(26)-H(261)...C(25)	0.915	2.502	3.193(8)	132.66

Symmetry transformations used to generate equivalent atoms: