Synthesis and Reactivity of Allylic Fluorides under Transition Metal Catalysis

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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.

Elena Benedetto

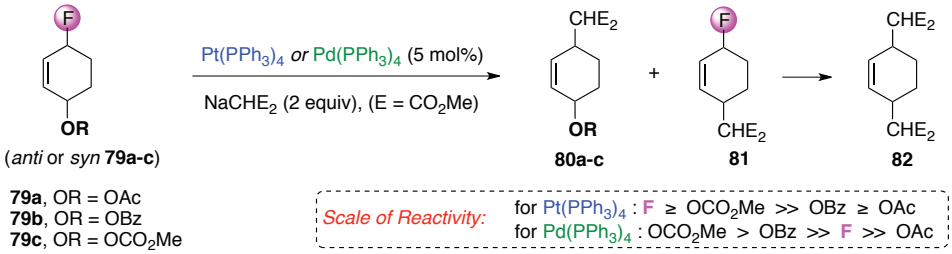
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In this thesis, C-F bond activation and C-F bond construction under platinum and iridium catalysis is described.

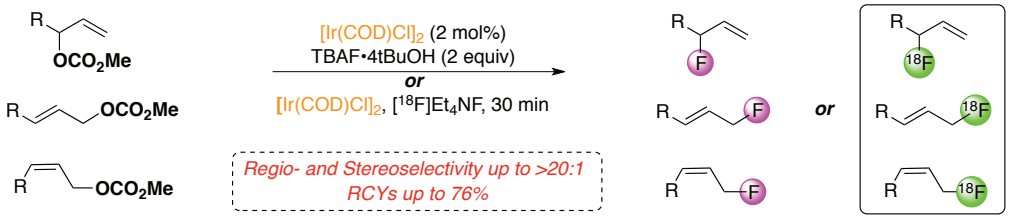
Chapter 1 provides a general introduction on the use of transition metal catalysis for the formation and activation of Csp^3-F bonds in organofluorine compounds.

In **Chapter 2**, an investigation on the reactivity of allylic fluorides, under platinum and palladium catalysed alkylation conditions, is presented. The relative reactivity of fluoride versus other commonly used leaving groups was compared *via* internal competition experiments. Fluoride showed a different reactivity profile, when subjected to Pt and Pd catalytic systems (Scheme i). Based on the observed reactivity trend, a Pd-catalysed fluorination reaction of allylic alcohol derivatives was successfully developed, within the group.



Scheme i Reactivity of Allylic Fluoride under Pt- and Pd-Catalysed Alkylation Conditions

In **Chapter 3**, a new iridium catalysed fluorination using branched, *E*- or *Z*-linear allylic carbonates is described. The catalyst $[Ir(COD)Cl]_2$ leads to an unexpected regio- and stereoretentive selectivity, affording fluorinated products not accessible *via* palladium catalysis. The effect of a fluoride additive on the selectivity of the Ir-catalysed alkylation reaction is also presented. A highly efficient ^{18}F-fluorination variant for this new catalytic transformation is reported (Scheme ii).



Scheme ii Iridium-Catalysed Regio- and Stereoretentive Fluorination of Allylic Carbonates

Chapter 4 gives full experimental procedures and characterisation data for all compounds.

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Abbreviations and Acronyms

[^{18}F]FDG	2-Deoxy-2-[^{18}F]fluoro-D-glucose
[^{18}F]FDOPA	6-[^{18}F]Fluoro-L-3,4-dihydroxyphenylalanine
Å	Ångström (10^{-10} metres)
Ac	Acetyl
Acac	Acetylacetone
Ar	Aryl
ax	Axial
b	Branched
BC	Bathocuproine
BINAP	1,1'-Binaphthalene-2,2'-diyl)bis(3,5-dimethyl-diphenylphosphine
biphep	2,2'-Bis(diphenylphosphanyl)biphenyl
Bn	Benzyl
Bq	Bequerel (s^{-1})
BQd	Benzoylquinidine
BSA	Bis(trimethylsilyl)acetamide
Bu	Butyl
Bz	Benzoyl
CFC	Chlorofluorocarbon
CI	Chemical Ionisation
COD	1,5-Cyclooctadiene
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAST	Diethylaminosulfur trifluoride
dba	Dibenzylideneacetone
DBFOX/Ph	4,6-Dibenzofurandiyl-2,2′-bis(4-phenyloxazoline)
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
dippp	1,3-Bis(diisopropylphosphino)propane
DMA	*N*,*N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide

DMSO	Dimethylsulfoxide
DPE-Phos	Bis[(2-diphenylphosphino)phenyl] ether
DPMED	*N*,*N*-Bis(phenylmethylene)-1,2-ethanediamine
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereoisomeric Ratio
DTBM-SEGPHOS	5,5'-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
ee	Enantiomeric Excess
eq	Equatorial
equiv	Equivalent(s)
ESI	Electrospray Ionisation
Et	Ethyl
eV	Electron Volt(s)
FI	Field Ionisation
FIR	Far Infrared Spectroscopy
g	Gram(s)
gem	Geminal
h	Hour(s)
HDF	Hydrodefluorination
HFIP	Hexafluoro-*iso*-propanol
HMQC	Heteronuclear Multiple Quantum Coherence
HOESY	Heteronuclear Overhauser Effect Spectroscopy
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
Josiphos (*R*,*S*)-ppf-P*t*Bu$_2$	(*(R*-1-[*(S)-2*-diphenylphos-phinoferrocenyl]ethyldi-*tert*-butyl-phosphine
IR	Infrared Spectroscopy
Kcal	Kilocalorie(s)
Kryptofix 222 (K_{222})	1,10-Diaza-4,7,13,16,21,24-hexaoxabicyclo[8.8.8]hexacosane
L	Neutral Ligand
l	Linear
M	Moles per cubic decimetre (moldm^{-3})
MM	Molecular Mechanical

M	Moles per cubic decimetre (moldm^{-3})
Me	Methyl
min	Minute(s)
mL	Millilitre(s)
mol	Mole(s)
Mp	Melting Point
n	Normal
NFSI	*N*-Fluorobenzenesulfonimide
NHPI	*N*-Hydroxyphthalimide
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
$^{n}J_{XY}$	Scalar coupling constant (in NMR Spectra) between nuclei X and Y through n bonds
NMR	Nuclear Magnetic Resonance Spectroscopy
o	Ortho
p	Para
PET	Positron Emission Tomography
Ph	Phenyl
PHOX	2-[2-(Diphenylphosphino)phenyl]-2-oxazoline
Ph-BOX	2,2-bis(4-phenyl-2-oxazolin-2-yl)propane
Pin	Pinacol
Piv	Dimethylpropanoyl (Pivaloyl)
PNB	*p*-Nitrobenzoyl
PNNP	(1*S*,2*S*)-*N*,*N*'-Bis[o-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine
PPFPz	1-{1-[2-Diphenylphosphanyl-ferrocenyl]ethyl}-1*H*-pyrazole
ppm	Parts per Million
QM	Quantum Mechanical
RCY	Radiochemical Yield
rt	Room Temperature
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	Bimolecular nucleophilic substitution
S_NAr	Nucleophilic aromatic substitution
t	*Tert*
TADDOL	2,2-Dimethyl-α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol

TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBME	*tert*-Butyl methyl ether
Tf	Trifluoromethanesulfonyl (Triflyl)
TFA	Trifluoroacetic Acid
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
T_R	Retention time
Triphos	Bis(2-diphenylphosphinoethyl)phenylphosphine
UV	Ultraviolet
V	Volt(s)
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Xylyl-phanephos	(S)-(−)-4,12-Bis[di(3,5-xylyl)-phosphine]-[2,2]-paracyclophane
β^+	Positron (Positive Beta Radiation)
δ	Chemical Shift
µL	Microlitre(s)
ν	Frequency
ºC	Degrees Celcius

Chapter 1

Organofluorine Compounds and Transition Metal Catalysis

1.1 Organofluorine Compounds

1.1.1 Properties and Applications of Fluorinated Compounds

The fluorine atom is characterised by unique properties, such as high electronegativity (χ = 4 in the Pauling scale), low polarizability (0.95 Å for free fluoride ion),[1] and small Van der Waals radius (1.47 Å). These characteristics render the C-F bond the strongest carbon-heteroatom single bond, with bond energies of 120-129 kcal/mol for aliphatic and vinyl C-F bonds, and up to 154 kcal/mol in C_6F_6.[2] The strength of the bond is in part due to a large electrostatic contribution to the covalent interaction. This is reinforced by the observation of progressive C-F bond shortening when comparing fluoromethane to tetrafluoromethane, due to an increasingly positive carbon centre. For these reasons, the insertion of a fluorine atom into an organic compound significantly changes its physical and chemical properties,[3] rendering fluorinated compounds valuable substrates for a wide range of applications.

Bond C-X	Bond Length (Å)	Bond Dissociation Energy (Kcal/mol)
C-H	1.09	98.8
C-F	1.35	105.4
C-O	1.43	84.0
C-N	1.47	69.7
C-C	1.54	83.1
C-Cl	1.77	78.5

Table 1. 1 Length and Dissociation Energy of Common Covalent Bonds[3]

The information, gained by the use of fluorinated analogues of biologically active molecules, makes these substrates useful tools for medicinal investigation and drug

discovery.[4] The high polarity of the C-F bond modifies the electronic distribution of nearby functional groups in a molecule, which may increase its lipophilicity and therefore bioavailability. Its ability to interact *via* hydrogen bonding and dipole-dipole interactions may improve protein-ligand binding. The relatively short half-life of the non-natural radioisotope ^{18}F (110 min) makes it ideal for the synthesis of radiotracers for Positron Emission Tomography (PET) imaging.[5] This is a non-invasive imaging technique, relying on the detection of coincident gamma rays, a result of positron annihilation. It is commonly used for the investigation of biological processes *in vivo*, as well as in the identification and monitoring of diseases at their early stage of development.[6] The use of perfluorinated solvents, which are immiscible with common organic solvents, is a useful tool for purification processes as well as a method for catalyst recovery.[7] Fluorocarbons have found wide applications as refrigerants, pesticides and non-adhesive polymers, as they are thermally stable, water repellent and resistant to chemical degradation.[8] Unfortunately, their robustness can also make organofluorines environmentally persistent, such as in the case of chlorofluorocarbons (CFCs), responsible for the ozone depletion, and of perfluoroakanes, the combustion of which generates greenhouse gases.[9]

1.1.2 Challenges Associated with C-F Bond Activation and Formation

The unique character of organofluorine compounds prompted synthetic chemists to investigate efficient methodologies for both the synthesis and the activation/derivatisation of fluorinated substrates.

The strength of the C-F bond makes fluoride a poor leaving group in organic chemistry, particularly in bimolecular nucleophilic substitution (S_N2) reactions, even under vigorous reaction conditions. The most common example of fluoride acting as a leaving group is in nucleophilic aromatic substitution (S_NAr) of fluoroarenes. Here, the rate-determining step is the nucleophilic attack on the aromatic ring, which generates a Meisenheimer adduct, that is highly stabilised by the inductive effect of the fluorine atom. Subsequent loss of fluoride

generates substituted aromatic products. Due to the harsh conditions required to activate the C-F bond, most of the existing procedures are not suitable for the derivatisation of complex organic molecules.

The insertion of a fluorine atom into an organic molecule is as much of a challenge, due to the forcing conditions typically required in the current methodologies. Whilst enormous progress has been accomplished in the synthesis of fluorinated compounds, the fluorination of a defined substitution pattern remains challenging.[10] Often synthetic chemists rely on readily accessible fluorinated building blocks to access more complex structures. The fluorination either of neutral, electron-rich or electron-poor substrates can be carried out by the use of nucleophilic or electrophonic fluorinating agents. The more easily accessible fluoride-based reagents are often solvated, due to the high electronegativity and small size of the F^-, and therefore show reduced nucleophilicity. On the other hand, when 'naked', their high Brönsted basicity competes with the nucleophilic character. For this reason, the fluoride source of choice should be the result of a compromise between solubility and nucleophilicity. Often harsh reaction conditions are required in nucleophilic fluorination methodologies. As an alternative to nucleophilic fluorinating agents, a series of electrophilic sources of fluorine has also been developed. The direct use of gaseous F_2 is not desirable due to its high reactivity, low selectivity and difficult handling. However, N-F^+ based reagents, such as Selectfluor® (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) and NFSI (*N*-fluorobenzenesulfonimide) have emerged as valuable electrophilic fluorinating reagents. They can be employed in mild reaction conditions, also allowing for the exploration of asymmetric fluorination variants. Even though a number of F^+ agents are commercially available, they are normally more expensive than F^- sources and generate more organic waste. Moreover, their use in the context of ^{18}F-radiosynthesis is highly disfavoured compared to ^{18}F-fluoride.

Despite the wide applications of organofluorine compounds, general methods for their selective derivatisation and synthesis are sparse. Both processes are thermodynamically favoured, but characterised by high energy barriers.[11] Therefore, the use of catalytic approaches, which are commonly employed to lower the barrier of activation, and accordingly employ mild conditions and increase the selectivity of reactions, was sought.[12]

1.2 Transition Metal Catalysis and Organofluorine Compounds

The valuable contribution of organometallic catalysis to the development of organic synthesis is widely recognised and exploited in both academia and industry. Organometallic catalysed processes can be characterised by the following aspects, such as activation of highly stable substrates, high selectivity and functional group tolerance, and use of mild reaction conditions, when compared to traditional transformations. These properties perfectly meet the requirements to overcome the limitations of existing methodologies for the synthesis and selective derivatisation of organofluorine compounds. However, the development of catalytic processes, for fluorination or defluorination, presents many challenges, such as the formation of a strong M-F bond, which might interfere with the turn-over of the catalytic cycle. For this reason, most of the catalysed C-F bond construction and activation reactions employ late transition metal complexes, which form weaker bonds to fluorine, due to both the π-donation from the fluoride ligand to the empty d orbitals of the metal, and the less polarised nature of the M-F σ-bond.

The use of transition metal catalysis for the activation of fluorocarbons and selective derivatisation of readily available and inexpensive perfluorocarbons, to access more valuable fluorinated building blocks, has increased exponentially in the past years. Even more interest has been shown for the organometallic catalysed insertion of a fluorine atom into an organic molecule, although it is still less explored when compared to C-C or C-X (O, N, S) bond construction. Enormous progress has already been made on aryl[13] and vinylic

derivatives,[14] but by contrast, literature on the formation of Csp^3-F bonds has appeared only recently. Fluorination methodologies are typically based on one of two different approaches, which employ either nucleophilic or electrophilic fluorinating reagents.

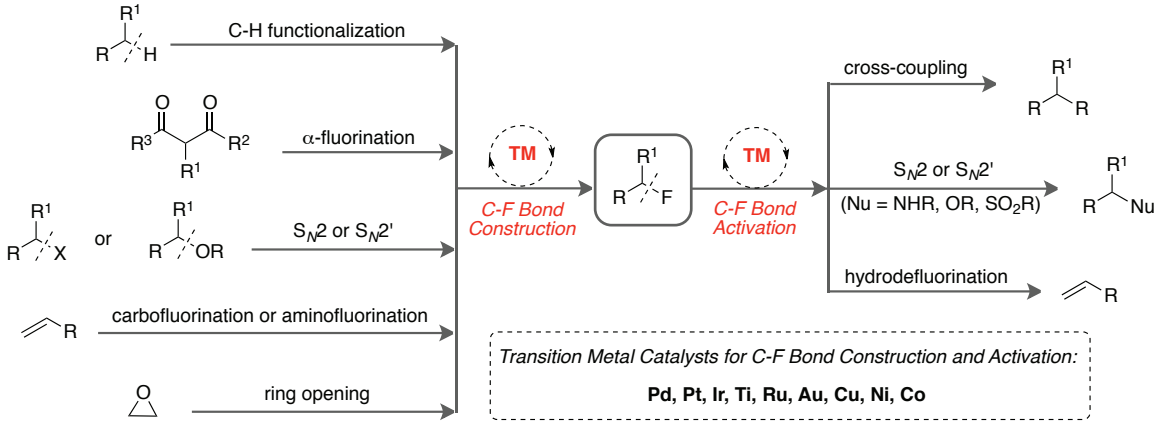


Figure 1. 1 Transition Metal Catalysed C-F Bond Formation and Activation

In the subsequent two sections of this chapter, the development of both Csp^3-F bond activation and formation *via* transition metal catalysed approaches will be discussed. A particular emphasis will be given to mechanistic considerations, which are useful information for a better understanding of this relatively new research area in the context of organometallic catalysis.

1.3 Transition Metal Catalysed Csp^3-F Bond Activation

The use of transition metal catalysis for the activation of organofluorine compounds is underdeveloped when compared to other halide derivatives, due to the thermodynamic stability and inherent kinetic inertness of the C-F bond towards oxidative addition to a metal centre. However, great advances have been made in recent years on the intra- and intermolecular activation of fluorocarbons by transition metal complexes, for the construction of new C-C/C-X bonds (*Cross-Coupling/Nucleophilic Substitution*) or conversion into C-H bonds (*Hydrodefluorination*). The development of catalytic methods is highly desirable, not only for a complete degradation of perfluorinated compounds, but also

to selectively modify them, and access more valuable fluorinated motifs. Despite this, existing examples are relatively rare for non (hetero)aromatic or vinylic functionalities.

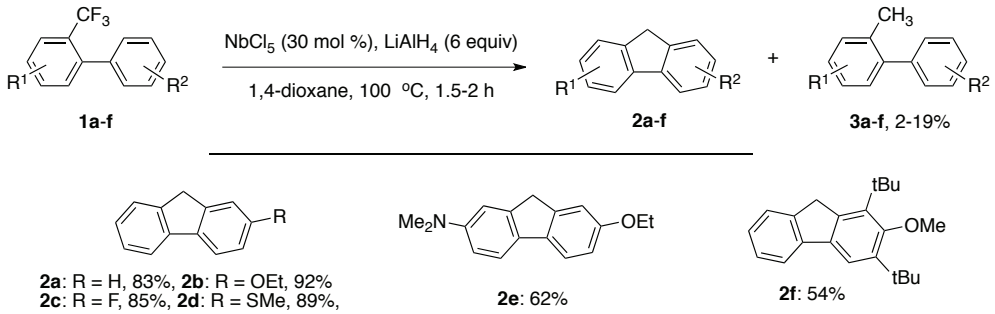
1.3.1 Hydrodefluorination (HDF)

The reduction of a C-F bond into a C-H bond is the easier and more commonly used method to decompose monofluoro- or perfluorinated compounds. The reduction of a Csp^3-F bond is underrepresented when compared to the literature on the hydrodefluorination of fluoroaromatic and fluoroalkene derivatives.[15,16]

The first examples of selective defluorination of perfluorocarbons, to yield fluoroaromatic and fluoroalkene derivatives, were reported by Richmond[17] and Crabtree,[18] respectively. In the first report, early transition metallocenes, such as Cp_2TiF_2 (Cp = cyclopentadienyl), were employed as catalysts in combination with an excess of the reducing agent $Al/HgCl_2$. The authors suggested that the reaction proceeded *via* an electron-transfer mechanism, where the metallocene worked as an "electron shuttle" by transferring electrons from the aluminium to the fluorinated compound. A similar approach was employed by Crabtree and co-workers, however the key feature of this procedure was a photoinduced electron transfer from the Cp*Fe (Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl) catalyst. The presence of a Li^+ salt was also necessary to capture the liberated fluorides. Both methods required long reaction times and high catalyst loadings, neither of which are ideal. In 2000, Jones and co-workers reported a metal mediated reduction of a variety of fluorinated functionalities into hydrogenated products, employing the 16-electron complex $Cp^*_2ZrH_2$.[19] The reaction was carried out under an atmosphere of hydrogen and in this example, the possibility of a radical abstraction of the fluorine was ruled out. The mechanism was believed to involve a bond metathesis pathway, yielding a Zr-F species (Cp^*_2ZrHF) and a new C-H bond. The driving force of the reaction was suggested to be the formation of the strong Zr-F bond, which hindered the development of a catalytic variant of the transformation. Indeed, the development of an effective catalytic HDF was only possible by

employing late transition metal hydride complexes, in combination with strong electrophiles. These electrophiles are able to form highly favoured bonds, such as Si-F, Al-F and B-F, which act as the driving force of the reaction and allow the regeneration of the initial M-H complex.

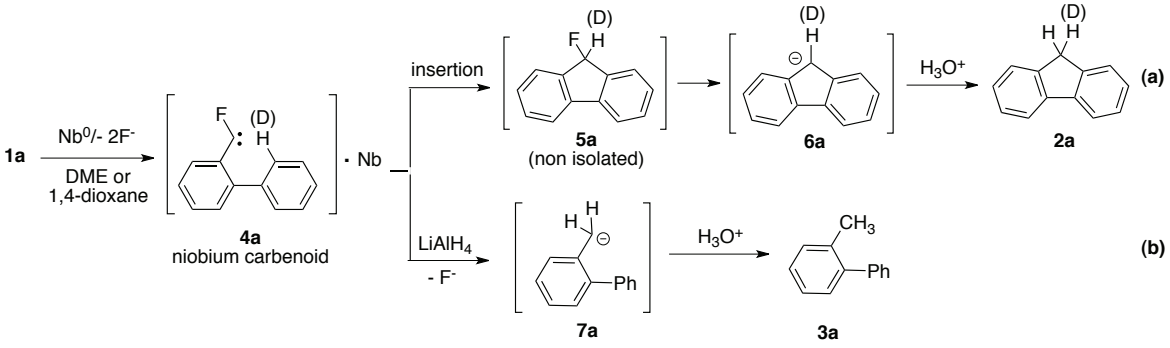
In the literature, the majority of reports related to the HDF of Csp^3-F bonds employ trifluoromethyl aryl derivatives as starting materials, despite the fact the trifluoromethyl group is normally considered an inert functionality. Akiyama and co-workers developed a hydrodefluorination of formal benzylic fluorides, by adapting their previous methodology on the reduction of fluoroarenes into the corresponding arenes.[20] Starting from *o*-arylated α,α,α-trifluorotoluene derivatives **1a**-**f** and employing $LiAlH_4$ as the hydride source, the synthesis of fluorenes **2a**-**f** was achieved, *via* a Nb-catalysed double activation of C-F and C-H bonds.[21] The new C-C coupling reaction was accomplished by employing 30 mol% of $NbCl_5$ catalyst and an excess of $LiAlH_4$ in refluxing 1,4-dioxane. Under these conditions formation of by-products **3a**-**f** was minimised to 2-19%. The CF_3 group was activated in preference to C-O (**2b**, **2e**-**f**), C-S (**2d**), C-N (**2e**) and C-F (**2c**) aromatic bonds, allowing the isolation of heteroatom-substituted fluorenes in good yields (Scheme 1.1).



Scheme 1. 1 Synthesis of Fluorenes from *o*-Arylated α,α,α-Trifluorotoluene Precursors

In an attempt to gain some mechanistic insights of the process, deuterium-labeling experiments were performed.[22] These studies suggested that insertion of the CF_3 carbon atom into the aromatic C-H bond did take place and $LiAlH_4$ was not directly involved in the

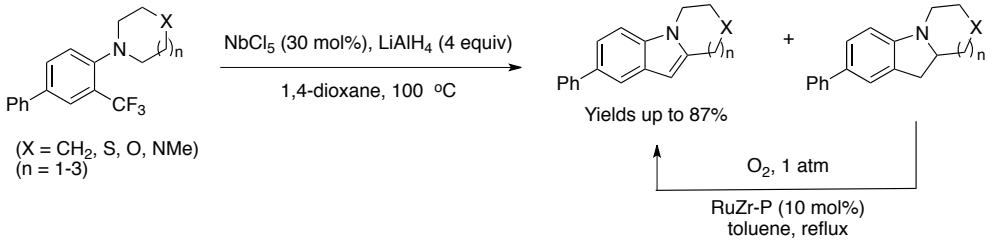
formation of **2a-f**, when solvents with poor Lewis basicity, such as DME (1,2-dimethoxyethane) and 1,4-dioxane, were employed. It was instead proposed that $Nb(V)Cl_5$ is reduced by $LiAlH_4$ *in situ* to form a Nb(0) complex, which interacts with starting material **1a**, leading to the fluorocarbenoid species **4a**, upon elimination of two fluoride anions. This active intermediate undergoes carbenoid insertion into the *ortho* C-H bond, affording fluorofluorene **5a**. This is further reduced under the reaction conditions to give anion **6a**, which yields the final product **2a** after protonation, as was shown in the deuterium-labeling experiments (Scheme 1.2a). The formation of the reduced product **3a** arose from the $LiAlH_4$-induced decomposition of intermediate **4a** into benzyl anion **7a**, which undergoes protonation after a water-quench (Scheme 1.2b). This side reaction was minimised by the slow addition of reducing agent over time. Independent investigations were also undertaken for this side-reaction, and after optimisation of the reaction conditions, the HDF of trifluorotoluene derivatives was successfully reported, yielding products **3** in excellent yields and with good selectivity.[23]



Scheme 1. 2 Proposed Mechanism for the Synthesis of Fluorene **2a**

The C-F/C-H bond activation reaction was also carried out under similar conditions for the synthesis of indene derivatives, starting from *o*-alkenyl-α,α,α-trifluorotoluenes[24] or 3-aryl trifluoropropenes,[25] *via* an intramolecular coupling reaction of the CF_3 group with alkene or an *o*-aryl C-H bond, respectively. More recently, the same strategy was combined with a Pd-catalysed aryl amination for the synthesis of a variety of *N*-fused indoles. The starting *o*-

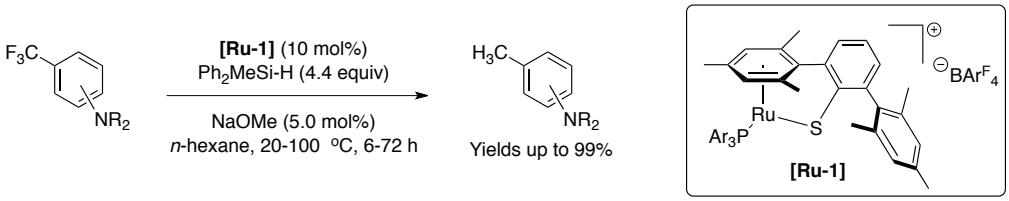
(trifluoromethyl)bromobenzene was subjected to a Pd-catalysed amination with cyclic amines to yield a library of precursors, which were next subjected to Nb-catalysed intramolecular C-H insertion.[26] The indole derivatives were obtained as a mixture with the corresponding indolines, which were subsequently isolated and oxidised using a Ru catalyst and atmospheric oxygen, to yield the desired products with very good overall yields.



Scheme 1. 3 Nb-Catalysed Synthesis of Indoles *via* C-H/C-F Bond Activation

Cao et al reported an alternative system to carry out the HDF of both fluoro- and trifluoromethylbenzene derivatives, based on the use of $NiCl_2$ catalyst and the selective superhydride reagent, $LiEt_3BH$.[27]

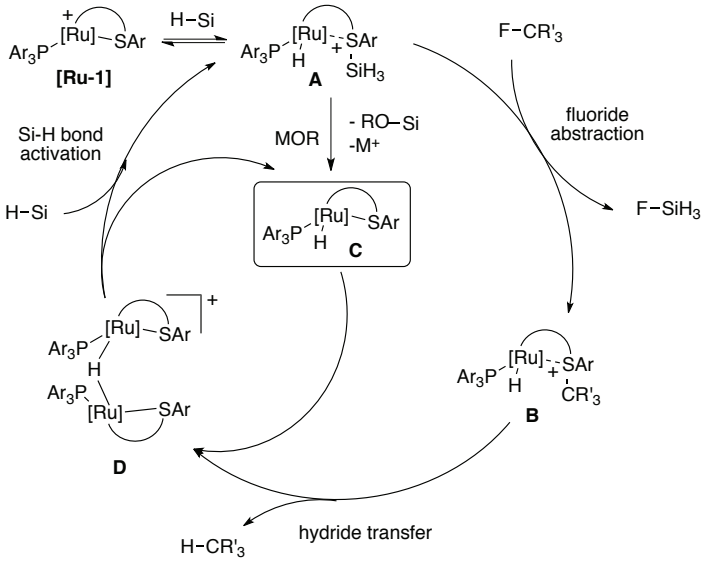
Oestreich and co-workers developed a unique method to activate the C-F bond of CF_3-substituted anilines, based on the use of the Ru-S complex **[Ru-1]** as the catalyst and an excess of Ph_2MeSiH as the hydride source (Scheme 1.4).[28]



Scheme 1. 4 Ru-Catalysed HDF of CF_3 Substituted Anilines

The addition of a sub-stoichiometric amount of alkoxide salt significantly accelerated the reaction, even with electronically and sterically disfavoured substrates. The optimised conditions were applied to a range of CF_3-substituted anilines to yield the hydrogenated products in excellent yields, under mild to harsh conditions.

A catalytic cycle was proposed for this transformation, with and without the auxiliary NaOMe salt (Scheme 1.5). The Si-H bond activation mediated by complex **[Ru-1]** generates intermediate **A**, where the silicon cation is stabilised by interaction with the sulfur ligand. Fluoride abstraction follows to give fluorosilane and the 18e Ru-H complex **B**, which transfers hydride intramolecularly to the carbocation to afford the hydrocarbon product and regenerate the 16e Ru-S complex **[Ru-1]**. The ability of the Ru-H complex **A** to transfer the hydride to the intermediate carbenium ion was found to be dependent on the electronic nature of the phosphine ligand.



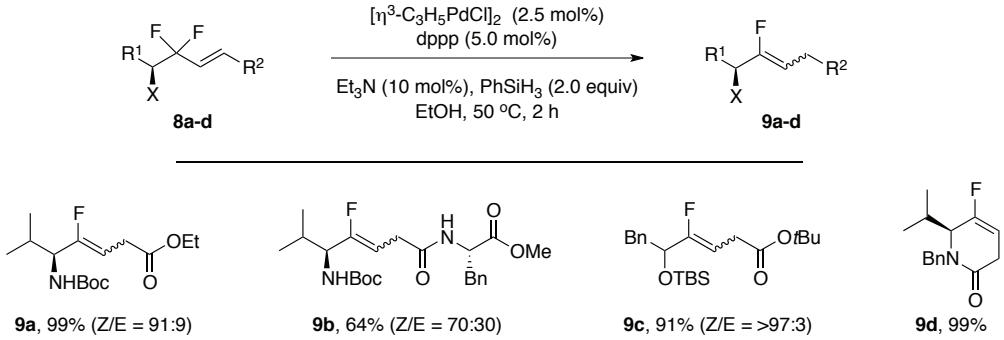
Scheme 1. 5 Proposed Mechanism for Ru-Catalysed HDF of CF_3 Substituted Anilines

In particular, electron-rich phosphine ligands facilitate the reductive elimination of the hydrogenated product from the cationic thioether complex **B**, which will instead be highly stabilised by electron-poor phosphine ligands. However, when electron-withdrawing phosphine ligands are used in combination with an alkoxide additive, the reactivity of the system is increased. Here, the authors proposed that the silicon cation would transfer from intermediate **A** to the alkoxide, yielding an unreactive silyl ether along with Ru-H complex **C**. After consumption of the alkoxide, complex **A** can undergo fluoride abstraction to generate the cationic thioether complex **B**. The hydride transfer step is facilitated by the

presence of complex **C**, which cooperates with **B** in the formation of the hydride-bridged dimer **D**, after the release of the hydrocarbon. The dimeric complex **D** undergoes Si-H bond activation to regenerate the active intermediates **A** and **C**.

In independent reports, Holland[29] and Lentz[30] developed the HDF of fluorinated aromatic rings and alkenes, employing silane as the hydride source and Fe(II)fluoride complexes, stabilised by diketiminate ligands, or $[Cp_2TiF_2]$ as catalysts, respectively. Under these reducing conditions, formal allylic C-F bond activation was observed when 3,3,3-trifluoropropene was employed as the substrate. However harsh reaction conditions were required to afford 1,1-difluoropropene in poor yields, and in general the HDF proceeded less smoothly than vinylic C-F bond activation. Cao et al reported a hydrodefluorination of *gem*-difluoromethylene derivatives with lithium aluminum hydride, employing the readily available and inexpensive $ZnCl_2$ as a catalyst.[31]

Based on the first example of Pd-catalysed hydrogenolysis of allylic fluorides in the presence of Pd/C,[32] Fujii et al developed a chemo- and stereoselective Pd-catalysed reductive defluorination of allylic *gem*-difluorides with phenylsilane (Scheme 1.6).[33]

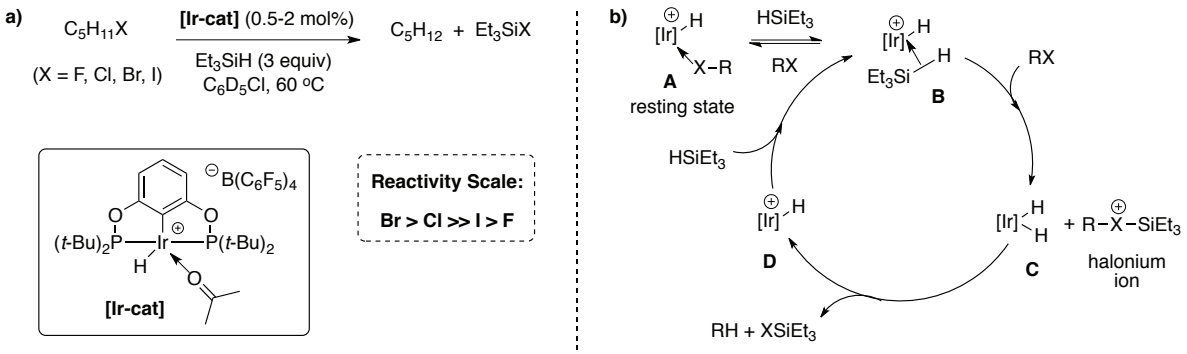


Scheme 1. 6 Pd-Catalysed Reductive Defluorination of Allylic *gem*-Difluorides

Starting from a series of substituted allylic *gem*-difluorides **8a**-**d** and employing $(allylPdCl)_2$/dppp (dppp = 1,3-bis(diphenylphosphino)propane) as the catalyst, the reactions allowed the synthesis of a variety of fluoroalkene peptidomimetics **9a**-**d** in good to excellent yields and with moderate to good *E*:*Z* selectivity. A catalytic amount of Et_3N was required,

in order to promote the dehydrogenative coupling between $PhSiH_3$ and EtOH and generate *in situ* active species, such as $Ph(OEt)SiH_2$ or $Ph(OEt)_2SiH$. The latter were responsible for the reduction of the catalyst to Pd(0) and worked as hydride sources for the reaction. This report is the first example, reported in the literature, which highlights the activation of allylic fluorides.

Only recently, Brookhart and co-workers developed the reduction of an alkyl monofluoride, employing triethylsilane as the reducing agent and the cationic iridium(III) bis(phosphinite) pincer catalyst **[Ir-cat]**.[34] The reduction was carried out with a series of alkyl halides and full conversion into the corresponding hydrocarbons could be achieved with a catalyst loading as low as 0.5 mol% and an excess of Et_3SiH. A reactivity study identified RBr > RCl >> RI > RF, moreover the primary halides were found to be much more reactive than the corresponding secondary derivatives (Scheme 1.7a).



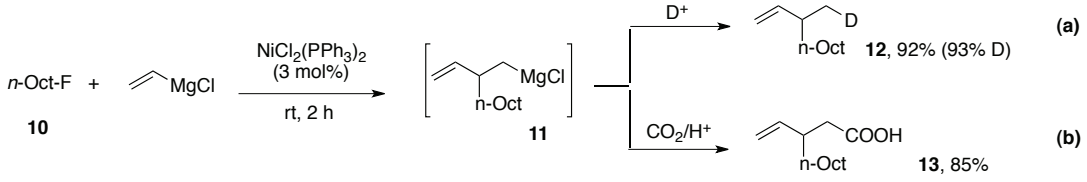
Scheme 1. 7 Iridium-Catalysed Reduction of Alkyl Halides with Triethylsilane

The catalytic cycle suggested by the authors is based on a unique process. The cationic Ir-H complex activates the H-Si bond (**B**) to generate an IrH_2 complex **C** and a $^+SiEt_3$ cation, which is subsequently transferred to the halide of the substrate, generating a highly reactive halonium ion. This is promptly reduced by the iridium dihydride **C** and silyl transfer ends the cycle, yielding the regenerated cationic Ir-H complex **D**.

1.3.2 Nucleophilic Substitution and Cross-Coupling Reactions

The heterolytic cleavage of the C-F bond can be performed by the use of either a C- or heteroatom nucleophile. The selective functionalisation of CF_3 and CHF_2 groups has been employed to afford highly valuable difluoro- or monofluoroderivatives, respectively. Monofluorinated alkyl, allylic and benzylic derivatives have also been shown to be versatile starting materials for nucleophilic substitution under metal catalysis, and their leaving group ability has been investigated *via* competition studies. Although fluoride is considered a poor leaving group with respect to other halides and commonly used leaving groups, the high polarity of the C-F bond increases the electrophilicity of the α-carbon, making the nucleophilic attack more favourable.

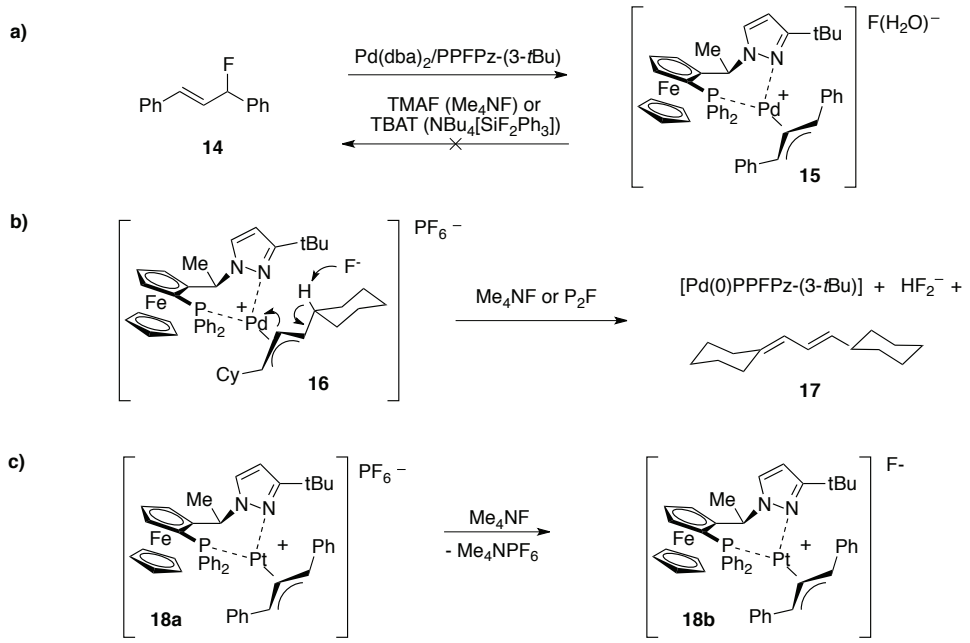
Although the first transition metal-catalysed cross-coupling of aryl fluorides was reported in 1973,[35] Kambe and co-workers reported the first example of a Ni- or Cu-catalysed cross-coupling of non-activated alkyl fluorides with Grignard reagents in 2003.[36] Here the reaction could be carried out with primary, secondary or tertiary alkyl and aryl Grignard reagents employing $CuCl_2$ or $NiCl_2$ catalysts, under mild conditions and in moderate yields. A comparative study between alkyl halides showed the following reactivity order towards the cross-coupling reaction: Br > F > Cl. Further optimisation of the reaction followed, in order to stabilise the catalyst[37] and expand the substrate scope of the transformation.[38] Interestingly, it was noticed that when vinyl Grignard reagents were used under the same reaction conditions in combination with fluoroalkanes, such as **10**, the butenyl Grignard reagent **11** was exclusively formed (Scheme 1.8).[39]



Scheme 1. 8 Ni-Catalyzed Alkylative Dimerisation of Vinyl Grignard Reagent with Alkyl Fluorides

Deuteration of the highly versatile intermediate **11** yielded 3-methyl-1-undecene **12** (Scheme 1.8a), and treatment with a combination of CO_2 and H^+ led to the formation of the carboxylic acid **13** (Scheme 1.8b). An interesting feature of this reaction is that under the same reaction conditions neither bromo or chloro alkanes are active substrates, yielding mainly reduction, elimination, or cross-coupling products. The authors suggested that the activation of the C-F bond might be partially due to the strong Mg-F interaction, however, the reaction has been shown not to proceed in the absence of the Ni-catalyst.

In pioneering work, Togni and co-workers reported that allylic fluoride **14** could be activated by a stoichiometric amount of the Pd(0) complex, $Pd(dba)_2$/PPFPz-(3-*t*Bu) (3-*tert*-butyl-1-{1-[2-diphenylphosphanyl-ferrocenyl]ethyl}-1*H*-pyrazole), to yield the cationic complex **15** with F^- as counterion. However, under these conditions the reverse reaction to form an allylic C-F bond was not successful (Scheme 1.9a).

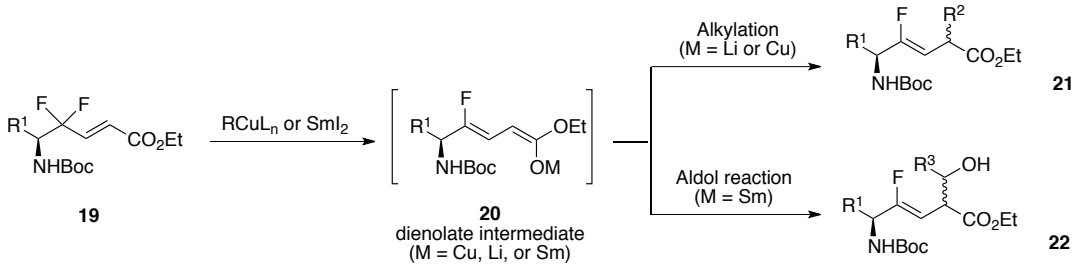


Scheme 1. 9 Interactions of Cationic Pd(II)- and Pt(II)-η^3-Allyl Complexes with Fluoride

When allyl-Pd(II) complex **16** was subjected to fluorination conditions, F^- acted as base and led to elimination of the ligand to form diene **17** (Scheme 1.9b). Exchange of the counterion was instead observed for the allyl-Pt(II) complex **18a**, under the same conditions (Scheme

1.9c). On the basis of these findings, the authors concluded that allylic fluorides readily undergo oxidative addition with Pt(0) or Pd(0) complexes, but the reverse reaction of fluorination is thermodynamically disfavoured.[40]

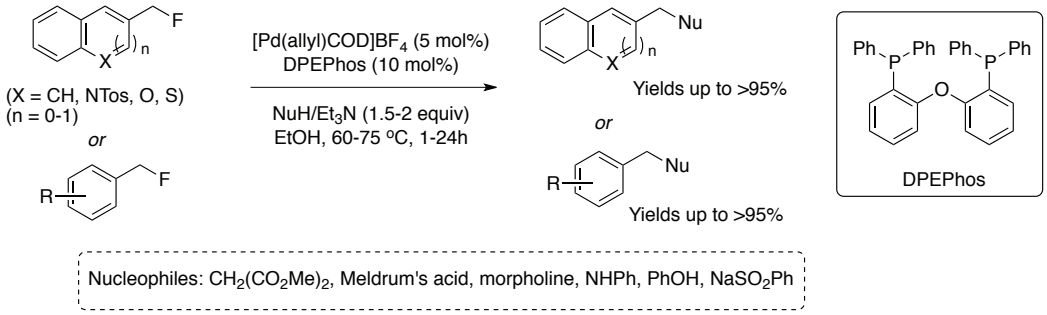
The leaving group ability of allylic fluorides under Pd-catalysis was previously demonstrated through the reduction of allylic bisfluorides **8a**-**d** (Scheme 1.6).[33] In a closely related reaction, the same authors reported a methodology based on a reductive organocopper or SmI_2-mediated defluorination of allylic bisfluoride derivatives **19**. Subsequent trapping of intermediate **20** by carbon electrophiles afforded fluoroalkene dipeptide isosteres **21** and **22** (Scheme 1.10).[41]



Scheme 1. 10 Reductive Defluorination/Enolate Trapping Methodology

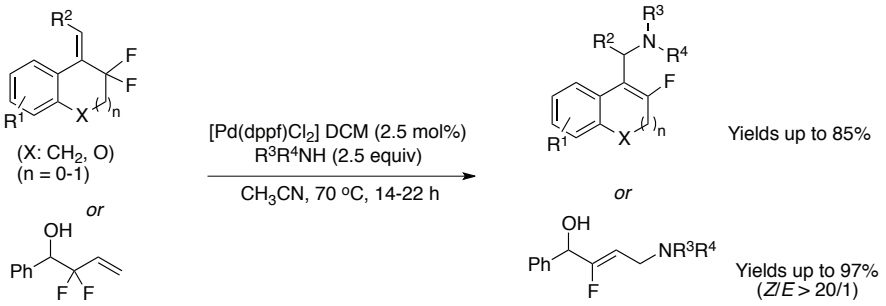
Based on these literature precedents, Gouverneur and Brown embarked on an investigation of the reactivity of allylic fluorides under Pd-catalysed alkylation conditions.[42] Preliminary results showed that both linear and cyclic allylic fluorides are suitable substrates to undergo substitution with a malonate nucleophile and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2/PPh_3$ as the catalytic system. For a direct comparison of the reactivity and stereoselectivity in the substitution of fluoride versus other commonly used leaving groups, an internal comparative study was undertaken. Under Pd-catalysed alkylation conditions, it was found that fluoride is displaced in preference to acetate, but is an inferior leaving group compared to carbonate and benzoate (OCO_2Me > OBz >> F >> OAc) - This study will be discussed in detail in Chapter 2. These findings gave the authors essential information to develop the reverse reaction of allylic fluorination, discussed in Section 1.4.1 of this Chapter.

The investigation on the displacement of fluoride under Pd-catalysis was extended only recently to benzylic C-F bonds, when the Tsuji-Trost substitution and cross-coupling of benzylic and naphthalene fluoride derivatives was reported (Scheme 1.11).[43] The initial screening of the reaction conditions identified Pd(η^3-C_3H_5)(COD)BF_4/DPE-Phos (COD = 1,5-cyclooctadiene, DPE-Phos = bis[(2-diphenylphosphino)phenyl] ether) in EtOH at 60 °C for 24 h, as the best catalytic system. Under these conditions, the bicyclic benzylic fluorides underwent nucleophilic substitution with C-nucleophiles, such as dimethyl malonate and Meldrum's acid, in addition to morpholine, aniline, phenol and sodium benzenesulfinate, leading to the desired substituted products with yields from 41% to >95%. The monocyclic benzylic fluorides required a higher temperature and extended reaction times to yield the corresponding substitution products. Competition experiments were carried out to determine the reactivity of fluoride towards other commonly used leaving groups and the reactivity order found was CF_3CO_2 ≈ *p*-$NO_2C_6H_4CO_2$ ≈ OCO_2CH_3 > F > CH_3CO_2. The reactivity scale is similar to that found for allylic derivatives under Pd catalysis.[42] Stereochemical investigations, carried out by subjecting enantioenriched (*S*)-1-(1-fluoroethyl)naphthalene to the standard conditions, suggested a double inversion mechanism for the replacement of fluoride, although with partial loss of stereochemical information.



Scheme 1. 11 Pd-Catalysed Substitution of Benzylic Fluorides

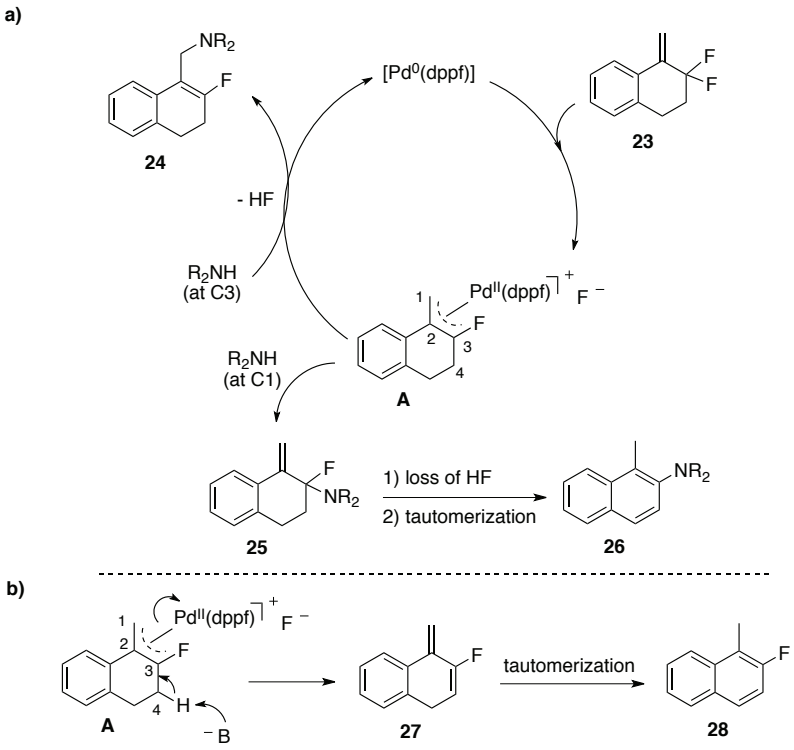
Given the great interest in the synthesis of fluorinated compounds, Paquin et al decided to exploit the reactivity of allyl fluorides under Pd-catalysis to develop a synthetic procedure to access functionalised fluoroalkenes (Scheme 1.12).[44] A series of 3,3-difluoropropene derivatives were exposed to amine nucleophiles in the presence of 2.5 mol% of [Pd(dppf)Cl_2]·DCM (dppf = 1,1'-bis(diphenylphosphino)ferrocene) catalyst, to afford selectively the β-aminofluoroalkenes in good yields. The substrate scope was further expanded by the use of the linear 3,3-difluoropropanes, which let to the formation of the corresponding (*Z*)-fluoroalkenes with excellent *Z*/*E* ratio and yields.



Scheme 1. 12 Palladium-Catalysed Allylic Amination of 3,3-Difluoropropenes

A mechanism for this transformation was also postulated (Scheme 1.13a). Oxidative addition to the allylic C-F bond in **23** by the Pd(0) catalyst could afford irreversibly the Pd π-allyl cationic complex **A**, with F^- as the counterion; subsequent nucleophilic attack of the amine on the less electron-rich and less hindered carbon C1 might selectively lead to the monofluoroalkene product **24**. In the initial screening, trace formation of byproducts **26** and **28** were also observed (Scheme 1.13b).

The authors proposed that the aromatic amine **26** could derive from the nucleophilic attack at C3 of intermediate **A**, with formation of *gem*-fluoroamine **25**, and subsequent amine-assisted elimination of HF, followed by tautomerisation. Alternatively, the base-elimination (with a fluoride ion or an amine) of a proton at C4 of complex **A** could lead to **27**, and the following tautomerisation of the latter would afford 2-fluoro-1-methylnaphthalene **28**.

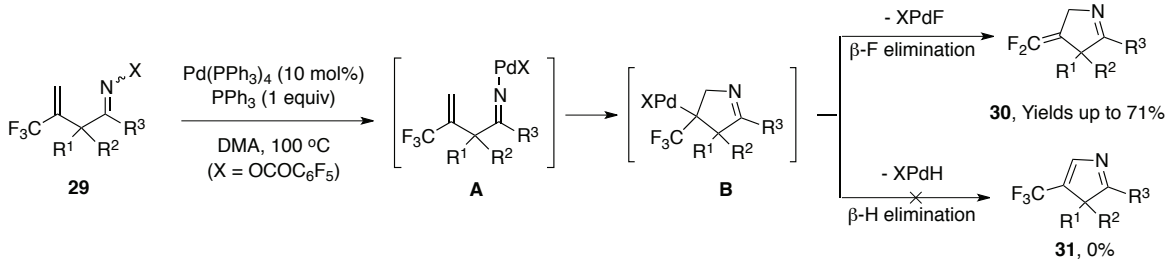


Scheme 1. 13 Postulated Mechanism for Palladium-Catalysed Allylic Amination of 3,3-Difluoropropenes

Taguchi et al adopted a similar approach, in order to synthesise highly functionalised fluoroalkene dipeptide isosteres, *via* a copper-catalysed alkylation of allylic *gem*-difluorides with Grignard reagents.[45]

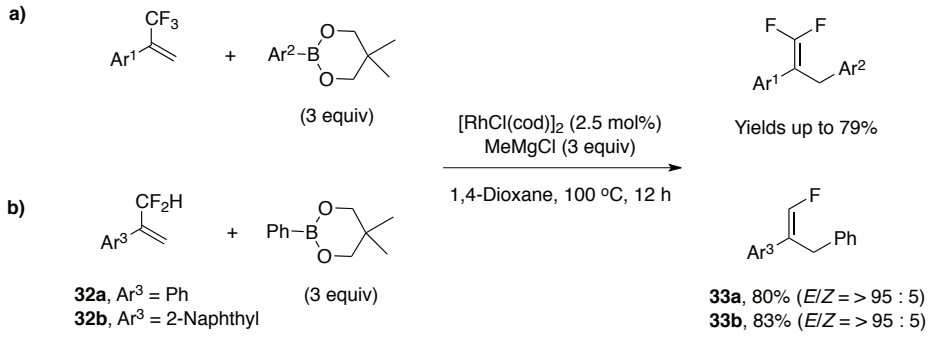
Based on a previous report on the synthesis of fluorinated pyrrolidines,[46] Ichikawa and co-workers developed a similar route to access 4-difluoromethylene-substituted 1-pyrrolines **30** (Scheme 1.14).[47] The use of $Pd(PPh_3)_4$ catalyst allowed the non-favoured 5-*endo* Heck-type cyclisation of 2-(trifluoromethyl)allyl ketone oximes **29** to proceed, in a similar fashion to the corresponding chemistry developed for difluorinated olefins.[48] The Pd-catalysed alkene insertion *via* oxidative addition of the N-O bond afforded the intermediate **A**, which underwent cyclisation to yield **B**. While there were two possible pathways, namely β-fluorine and β-hydrogen elimination after ring formation, surprisingly, the former elimination took place exclusively to yield a range of different 4-difluoromethylene-1-pyrrolines **30** (**31** was not detected). It was observed that *gem*-dialkylsubstituents in the starting material **29**

are required to promote the reaction, as they prevent the protonation of the aminopalladium intermediate **A** and thereafter facilitate the cyclisation process. The CF_3 group was shown to have a crucial role both in the vinylic terminal carbon activation and in the stabilisation of the cyclic Pd-intermediate **B**.



Scheme 1. 14 Pd-Catalysed 5-*endo* Heck-Type Cyclisation of 2-(Trifluoromethyl)allyl Ketone Oximes

Murakami et al developed a different approach for the activation of a CF_3 group at a vinylic position, based on a Rh-catalysed addition of arylboronic esters to α-(trifluoromethyl)styrenes to afford *gem*-difluoroalkenes (Scheme 1.15).[49] The reaction proceeds through the addition of arylrhodium(I) species across the electron-deficient carbon–carbon double bond. Subsequent β-fluoride elimination, based on a sequential carborhodation/β-fluoride elimination pathway, leads to the arylated product.[50]



Scheme 1. 15 Rh-Catalysed Synthesis of *gem*-Difluoroalkenes

The optimal conditions required an arylboronic ester and also MeMgCl as an additive, which was thought to promote the C-F bond activation step *via* a Mg-F interaction. The substrate scope was investigated by varying both aryl substituents at the vinylic and

boronic position, yielding the correspondent *gem*-difluoroalkenes in good yields (Scheme 1.15a). The substitution of α-(difluoromethyl)styrenes **32a**-**b** was also carried out under the same reaction conditions to afford the fluoroalkenes **33a**-**b** with complete regiocontrol (Scheme 1.15b).

1.4 Transition Metal Catalysed Csp^3-F Bond Formation

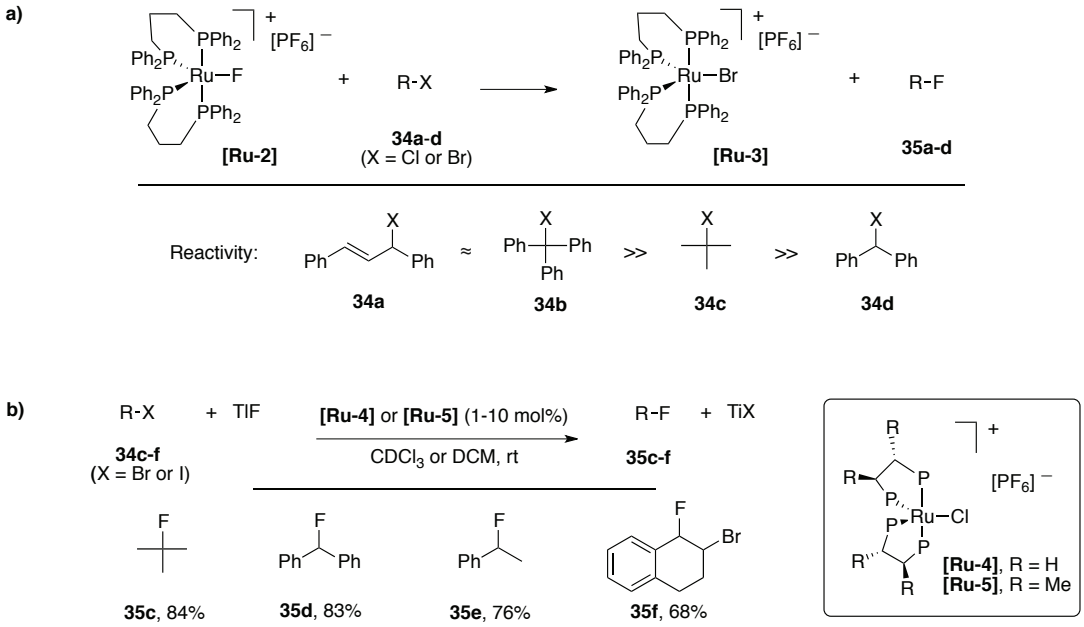
Huge breakthroughs have been made in the palladium catalysed fluorination of aromatic or heteroaromatic derivatives.[13] Most of these procedures rely on the formation of a high-valent ArPd(IV)F intermediate, generated by oxidative addition of a F^+ source to a Pd(II) complex, and subsequent reductive elimination to yield the fluorinated product. In contrast, C-F bond formation by reductive elimination from Pd(II)ArF intermediates, generated from Pd(II) precursors with nucleophilic "F^-" reagents, is more challenging.[51] To date, only one successful example of a Pd(0)-catalysed fluorination of aryl triflates with CsF at elevated temperature (80-120 °C) has been reported.[13e]

Less well explored is the synthesis of vinylic or aliphatic fluorides, with existing methodologies being sparse and limited in scope and selectivity. These reactions tend to be highly sensitive to the substrate, catalyst and fluorinating reagent.[52] The use of nucleophilic sources of fluorine has been successfully employed for the nucleophilic substitution of allylic halide or alcohol derivatives. Nucleophilic fluorinations have also been employed for the ring-opening of epoxides to yield fluorohydrins with good selectivity. F^+ reagents have been used for the α-fluorination of β-keto esters and carboxylic acid derivatives or for the oxidative fluorination of C-H bonds under Pd-catalysis.

1.4.1 Nucleophilic Substitution

In 1999, Togni and co-workers reported the first example of a transition metal-mediated fluorination of bromides and chlorides, employing the 16-electron pentacoordinated ruthenium fluoride complex $[RuF(dppp)_2]PF_6$ **[Ru-2]**, obtained from the chloro analogue[53]

and thallium fluoride (TlF).[54] The fluorination was proposed to proceed *via* a halide metathesis between the fluorinated complex **[Ru-2]** and bromide (chloride) derivatives **34a-d** (Scheme 1.16a). The substrates tested showed a clear reactivity trend. Both tertiary alkyl (**34b**) and allyl halides (**34a**) were highly reactive towards fluorination. This may suggest that substrates able to stabilise positive charge are beneficial. The scope of the transformation is limited, and unselective for less reactive substrates, giving an ether byproduct for bromodiphenylmethane **34d** and diene formation with *tert*-butyl bromide **34c**. However, this work represents the first systematic study on the use of low-valent fluoro complexes of a transition metal for selective C-F bond formation under mild conditions. Only one other example was reported previously by Grushin and co-workers, where the fluorination of CH_2Cl_2 by $[PdF(Ph)(PPh_3)_2]$ occurred within hours to yield CH_2ClF and CH_2F_2.[55]

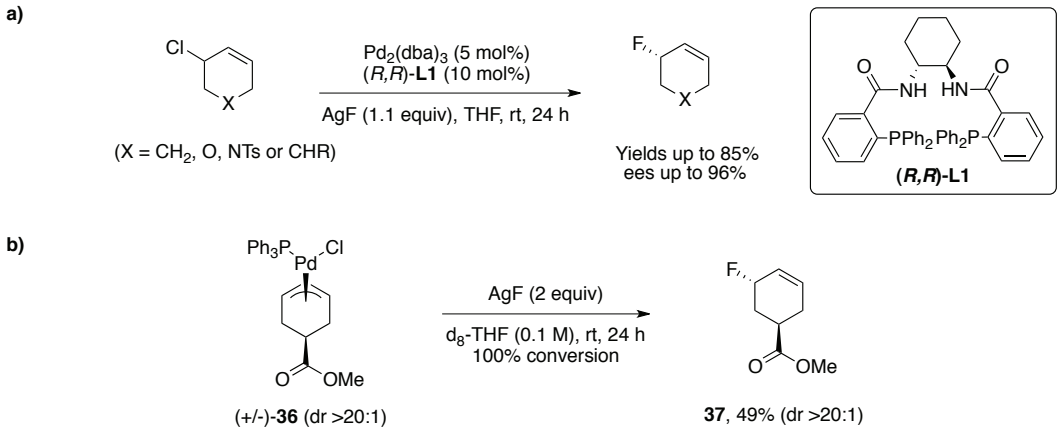


Scheme 1. 16 Ru-Mediated and Catalysed Fluorination of Halides

Based on these preliminary results, a catalytic variant for the fluorination of alkyl and benzyl halides was next developed (Scheme 1.16b).[56] The complex $[RhCl(dppe)_2]PF_6$ **[Ru-4]** (dppe = 1,2-bis(diphenylphosphino)ethane) showed reactivity towards the fluorination of

tert-butyl iodide **34c** and dibenzylic bromide **34d** (providing **35c** in 84% and **35d** in 83% yields, respectively), when employing the inorganic salt TlF as the fluorinating source, and carrying out the reaction at room temperature. The intermediacy of difluorobridged thallium adduct $[Tl(\mu\text{-}F)_2Ru(dppe)_2]PF_6$ was proved by comparing the ^{31}P NMR signals recorded during catalysis with that of an authentic sample independently synthesised.

In 2010, Doyle and co-workers reported the first example of an enantioselective Pd-catalysed fluorination of cyclic allylic chlorides, employing AgF as fluorinating agent.[57] The combined used of the pre-catalyst $Pd_2(dba)_3$ (dba = dibenzylideneacetone) and Trost bidentate chiral ligand (*R,R*)-**L1**[58] allowed access to a variety of substituted cyclic allylic fluorides in good yields and with good to excellent enantioselectivity (Scheme 1.17a). Due to the inactivity of traditional leaving groups under the reaction conditions, it was suggested that the driving force of the fluorination reaction is the formation of the insoluble salt AgCl. Under the optimised conditions the elimination product could be reduced to < 10%.

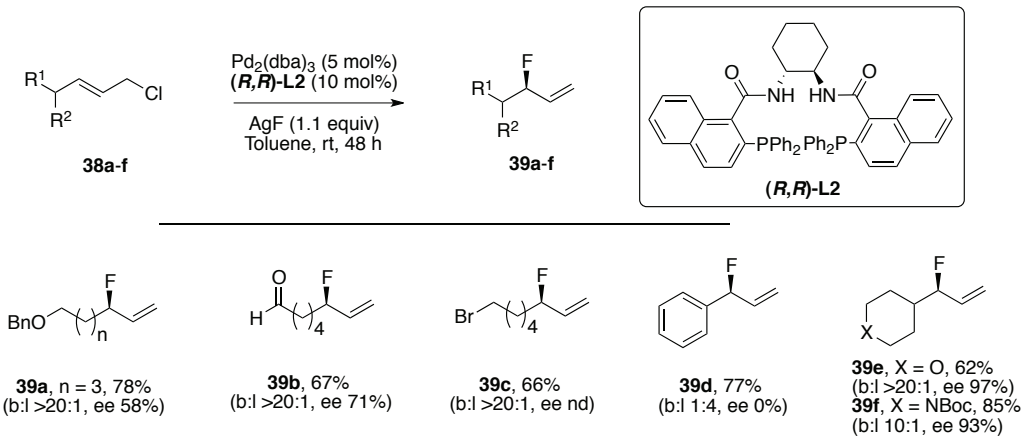


Scheme 1. 17 Pd-Catalysed Fluorination of Cyclic Allylic Chlorides with AgF

The authors suggested a mechanism similar to the one reported by Trost for the Pd-catalysed allylic substitution with various carbon- and heteroatom-nucleophiles.[59] The catalytic cycle starts with the oxidative addition of allyl chloride to the Pd(0) catalyst to generate an electrophilic Pd(II)-allyl intermediate, followed by nucleophilic attack of the

outer sphere fluoride anion on the allyl ligand to generate the fluoride product. This hypothesis was validated by carrying out a stoichiometric fluorination of the isolated (*syn*)-allyl-Pd intermediate **36**, synthesised from the corresponding allylic chloride,[60] which afforded exclusively the *anti*-allylic fluoride **37** (Scheme 1.17b). This result however is in disagreement with the classical inversion of configuration observed for hard nucleophiles, which the fluoride ion is often classified as.[61]

The Doyle group adapted their methodology to access regio- and enantioselectively non-cyclic branched allylic fluorides **39a-f**, starting from the corresponding linear chlorides **38a-f** (Scheme 1.18).[62] In this report, the use of Trost naphthyl ligand (*R,R*)-**L2** in toluene for longer reaction times was required in order to access the product with good regioselectivity (branched:linear ratio, b:l, up to >20:1) and conversion. The enantioselectivity of the process was increased by employing hindered or hereroatomic substituents on the allylic chloride. Good tolerance towards a range of different functionalities was observed, although competitive diene formation occurred with tertiary and exocyclic methylene-containing allylic fluorides.



Scheme 1. 18 Pd-Catalysed Fluorination of Linear Allylic Chlorides with AgF

Gouverneur and Brown, shortly after the initial publication of Doyle et al, reported an alternative methodology for the fluorination of linear alcohol derivatives under palladium catalysis,[63] basing their work on their previous studies on the reactivity of allylic fluorides,

under Pd-catalysis.[42] Employing *para*-nitrobenzoate as the leaving group and TBAF·4*t*BuOH (TBAF = tetra-*n*-butylammonium fluoride) as the fluorinating agent, allylic fluorination led to the selective synthesis of linear allylic fluorides in good to excellent yields. Competing β-hydride elimination could not be overcome under the reported conditions, preventing the use of substrates bearing protons in the β-position. This methodology will be described in more detail in Chapter 3. The use of cinnamyl phosphorothioate esters[64] in combination with AgF, to access linear allylic fluorides, has also been reported.[65]

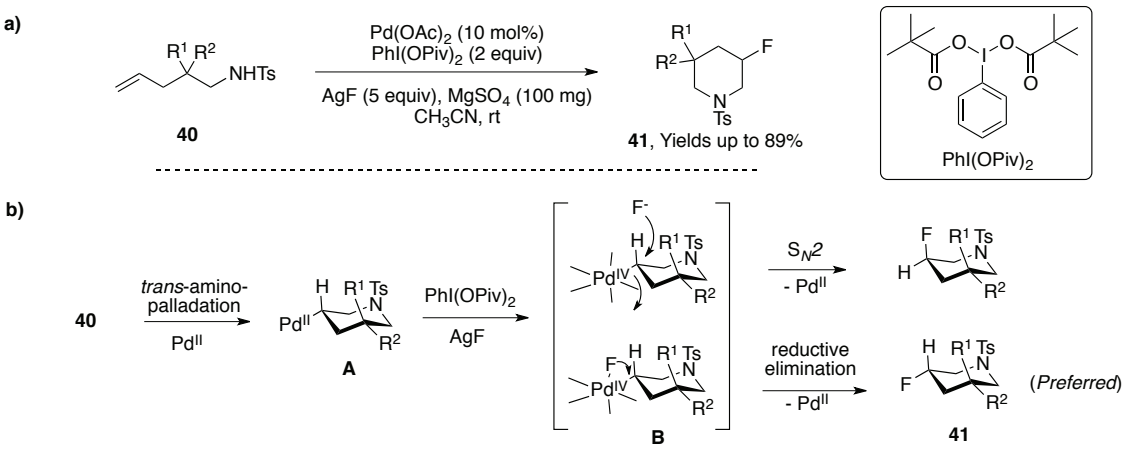
The first example of a transition metal other than palladium able to catalyse the synthesis of allylic fluorides was reported in 2011 by Nguyen and co-workers, who described a new Ir-catalysed fluorination of branched trichloroacetimidates with $Et_3N·3HF$.[66] The use of unligated $[Ir(COD)Cl]_2$ as the catalyst showed higher selectivity in terms of fluorination/β-H elimination ratio, with respect to a series of Rh-catalysts tested, and led to the formation of the product derived from the insertion of the fluoride at the same carbon bearing the leaving group. This report, published during the course of our research, will be discussed in more detail in Chapter 3.

1.4.2 Fluorination of Alkenes and C-H Functionalisation

The goal in the context of fluorine chemistry is the possibility to insert selectively a fluorine atom in a non-prefunctionalised position of complex organic molecules. Despite recent developments, this goal has jet to be realised. A limited number of examples of functionalisation of simple double bonds have been reported, with reactions being highly substrate dependent and limited in scope.

In 2009, Liu and co-workers reasoned that the treatment of an unactivated alkene with electrophilic fluorinating agents, such as $N\text{-}F^+$ based reagents, could lead to the formation of an aminofluorinated product, under Pd-catalysis. This approach was based on previous reports on the difunctionalisation of olefins *via* a Pd(II)/Pd(IV) cycle.[67] However, every

attempt in subjecting amino-alkene **40** to a series of F^+ sources, employing $Pd(OAc)_2$ as the catalyst, was unsuccessful. Surprisingly, when AgF was used as the fluorinating agent in combination with the oxidant $PhI(OPiv)_2$ (Piv = pivaloate), the intramolecular aminofluorination was achieved. The use of an excess of AgF and $MgSO_4$ as an additive proved to be the optimal conditions, providing the desired cyclic product **41** in very good yield (Scheme 1.19a).[68] Deuterium-labeling experiments helped to provide mechanistic insights. The authors proposed that the Pd(II)-catalyst mediates a *trans*-aminopalladiation of the alkene, generating the Pd(II) intermediate **A**, which undergoes oxidative fluorination with AgF and $PhI(OPiv)_2$. This combination may form $PhIF_2$ *in situ*, which acts as both the oxidant and fluorinating reagent, as was later proposed by Sandford.[69] The resulting Pd(IV) complex **B** could undergo C-F reductive elimination (preferred), when fluorine is bound to the metal centre. Alternatively, a S_N2 type fluorination of the ligand could occur with an outer sphere fluoride ion (Scheme 1.19b).



Scheme 1. 19 Pd-Catalysed Intramolecular Aminofluorination of Alkenes

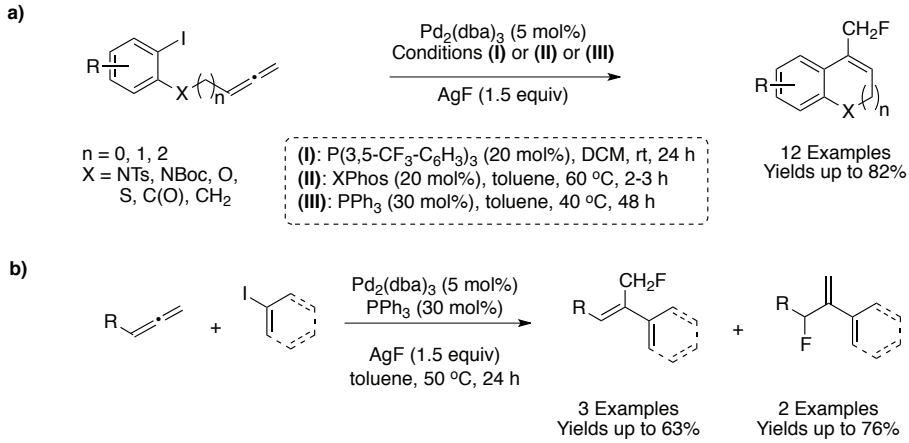
One year later, the authors disclosed a novel palladium-catalysed intermolecular aminofluorination, employing the electrophilic fluorine source NFSI, which also acts as an amination reagent.[70] The optimal conditions were based on the use of 5 mol% of $Pd(OAc)_2$ and bathocuproine (BC), as the only competent ligand, in dioxane. The aminofluorination of

a broad series of vinyl styrenes was performed with excellent regioselectivity and up to 80% yield. Although the mechanistic pathway still needs to be elucidated, the fluoropalladation of styrene was proposed as the key step for C-F bond formation. An intramolecular variant was also developed for the synthesis of fluorinated pyrrolidines.[71]

Building on these literature precedents, Gagné and co-workers developed a catalytic enantioselective cyclisation/fluorination cascade reaction of polyenes, to yield C3-fluorinated carbocycles.[72] The use of a (xylyl-phanephos)PtI_2 catalyst (xylyl-phanephos = (S)-(−)-4,12-bis[di(3,5-xylyl)-phosphine]-[2,2]-paracyclophane) in combination with XeF_2 allowed access to a series of fluorinated products in 60-69% yield with ees up to 87% (Chapter 2, Section 2.3). The proposed mechanism is based on a stereoretentive fluorination of a P_2Pt-alkyl cation intermediate, similar to that suggested by Liu, which occurs in preference to the competing β-H elimination reaction. This methodology represents a convenient approach for the selective fluorine-insertion in important precursors for the synthesis of fluorinated steroids.

Doyle et al reported an alternative approach for a palladium-catalysed intra- and intermolecular carbofluorination, employing AgF as the fluorine source, to yield monofluoromethylated heteroarenes and allylic fluorides, not accessible *via* previous methodologies.[73] On the basis of their first reports on Pd-catalysed allylic fluorination,[57,62] the Heck-fluorination cascade was first carried out with allenes substituted with a tethered aryl iodide, employing $Pd_2(dba)_3$ as the pre-catalyst in combination with a phosphine based ligand. The fluorinated heterocycles, such as indoles, benzofuran, benzothiophene, 6- and 7-membered ring products, isoquinolinone and 1,2-dihydroquinoline, were formed with excellent regioselectivity and in good yields (Scheme 1.20a). An intermolecular variant was also developed, *via* a three-component coupling of allenes, aryl, heteroaryl or vinyl iodides and AgF, which delivered 2-substituted allylic fluorides. The attack of fluoride to give linear or branched products was shown to be dependent on the structure of the allene (Scheme

1.20b). Mechanistic investigations suggested the intermediacy of a Pd(II)allyl complex, which is attacked by an external fluoride. The authors postulated that the competent fluorinating agent might be a Pd-F type species generated *in situ* by a second Pd centre.



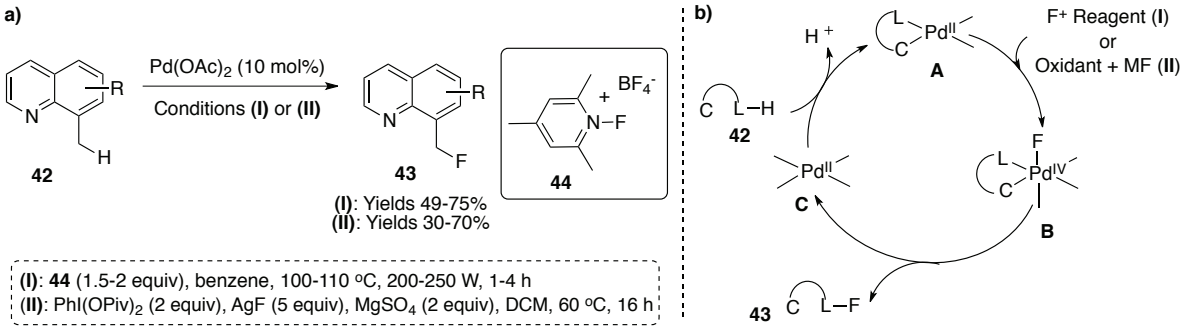
Scheme 1. 20 Pd-Catalysed Intra- and Intermolecular Carbofluorination

The substitution of hydrogen for fluorine is one of the more common approaches to improve metabolic stability, biological activity and lipophilicity in organic substances, however there are few synthetic methods currently available for a direct fluorination, starting from non pre-functionalised substrates.

In 2006, Sanford and co-workers developed a palladium-catalysed C-H activation/C-F bond formation reaction of aryl and benzylic derivatives, based on the use of an electrophilic fluorinating reagent and a Pd(II)/Pd(IV) catalytic system (Scheme 1.21).[74] Quinoline-directing groups derivatives **42** promoted the $Pd(OAc)_2$-catalysed C-H activation, to yield Pd(II) intermediate **A**, which could thereafter be subjected to oxidative fluorination. The use of an excess of *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**44**) as the F^+ source and forcing reaction conditions (condition **I**) led to increased yields (up to 75%) of the desired products **43**, almost completely avoiding byproduct formation.

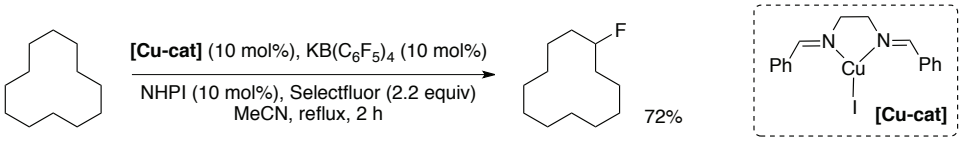
Six years later, the same authors reported a variant of this transformation, which employed the nucleophilic fluoride source AgF as the fluorinating agent, in combination with the

oxidant $PhI(OPiv)_2$.[69] The milder reaction conditions (**II**) allowed access to a broader substrate scope, although yields were not improved under these conditions (Scheme 1.21a). Mechanistically, both approaches rely on the formation of the Pd(IV)F species **B** from **A**, *via* an oxidation/fluorination step, which could be carried out by the use of an F^+ source or the combined use of F^- and an oxidant (Scheme 1.21b).



Scheme 1. 21 Pd-Catalysed Fluorination of C-H Bond

Lectka and co-workers, also employed an electrophilic approach for the fluorination of aliphatic, allylic and benzylic C-H bonds, *via* a polycomponent metal-catalytic system.[75] The radical based fluorination could be carried out successfully, employing a Cu(I) bisamine complex **[Cu-cat]** in combination with the anionic phase-transfer catalyst $KB(C_6H_5)_4$ and Selectfluor® as the fluorine source (Scheme 1.22). Running the reaction with 10 mol% of catalyst (BPMED)CuI (BPMED = *N*,*N*-bis(phenylmethylene)-1,2-ethanediamine) and 10 mol% of co-catalyst *N*-hydroxyphthalimide (NHPI) in refluxing MeCN, a variety of fluorinated products were formed in moderate yields.



Scheme 1. 22 Cu-Catalysed Radical Fluorination of C-H Bonds

This represents the first general method for a metal catalysed C-H activation/C-F bond

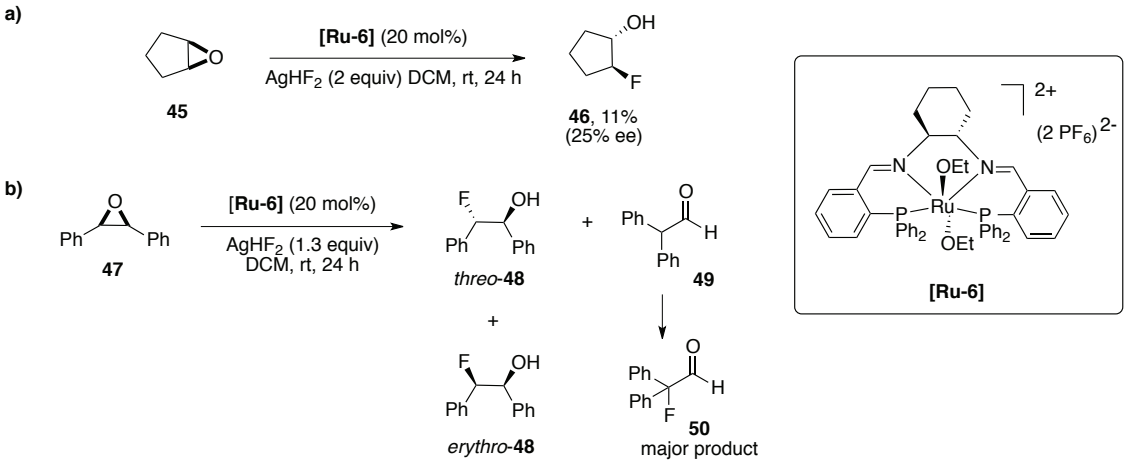
formation reaction, and shows potential applications for the fluorination of complex structures and natural products.

1.4.3 **Fluorohydrins**:

The synthesis of fluorohydrins *via* diastereo- and regioselective ring opening of epoxides by the use of hydrofluorinating reagents is widely reported in the literature.[76] Existing methodologies, however, are lacking in scope and selectivity, and often require harsh reaction conditions. To accomplish good enantioselectivity, the chiral non-racemic catalyst must compete with the proton of the hydrofluorinating reagent, and consequently a less acidic but more nucleophilic fluoride source should be used. In 2000, Haufe and co-workers reported the first example of asymmetric ring opening of epoxides catalysed by the (*S*,*S*)-(+)-(Salen)chromium chloride complex **[Cr-1]** to yield enantioenriched fluorohydrins.[77] The reaction of cyclohexane oxide with KHF_2/18-crown-6 in the presence of 10 mol % of **[Cr-1]**, at 100 °C for 80 h, gave 2-fluorocyclohexanol in 65% conversion and with 11% ee. Improved enantiomeric excess could be afforded by employing one equivalent of **[Cr-1]**. The methodology was successfully applied to a range of *meso*- and racemic epoxides, such as phenyl glycide ether. In all cases a small amount of the corresponding chlorohydrins was formed. When AgF was selected as alternative fluorinating agent, 2-fluorocyclohexanol was afforded in 90% yield and with 72% ee, under milder conditions. Here, the fluorinating agent functioned also as a trap for the competing chloride nucleophile, *via* AgCl precipitation.[78]

In an attempt to improve the efficiency of the Haufe sub-stoichiometric system, Togni and collaborators disclosed that the Lewis acid $[Ru(OEt_2)_2(PNNP)](PF_6)_2$ **[Ru-6]** (PNNP = (1*S*,2*S*)-*N*,*N*'-bis[o-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine), with the use of $AgHF_2$ as the fluoride source, was able to catalyse an asymmetric epoxide ring opening reaction (Scheme 1.23a).[79] Although the epoxides tested afforded the corresponding fluorohydrins in poor yields and selectivity (**46**, 11%, 25% ee), an interesting observation

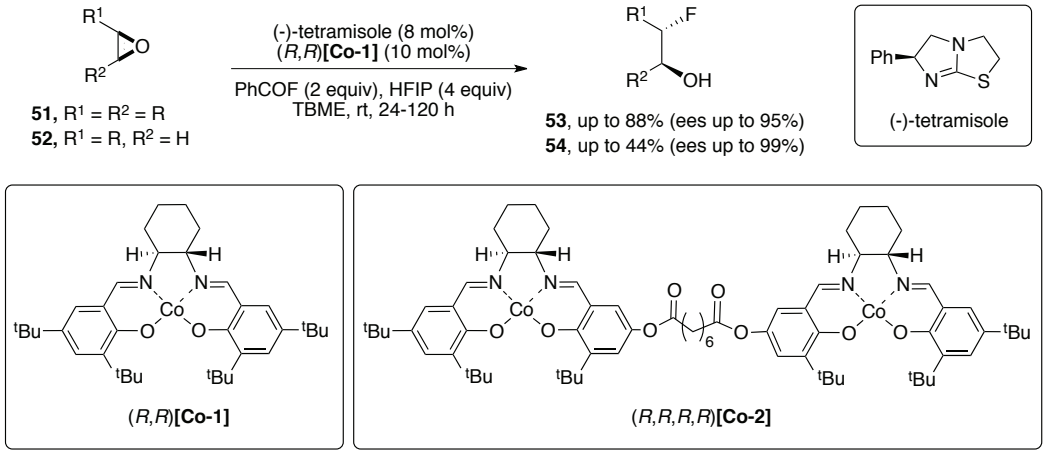
was made when *cis*-stilbene oxide **47** was used. Under the fluorination conditions the Ru Lewis acid catalyst **[Ru-6]** was found to promote the [1,2]-phenyl shift (Meinwald rearrangement) to give the corresponding diphenylacetaldehydes **49**, that subsequently underwent oxidative fluorination to yield **50** (Scheme 1.23b). This unexpected finding encouraged the authors to investigate the feasibility of a nucleophilic fluorination at the α-position of aldehydes. Further details of this new transformation will be discussed in the following section (Section 1.4.4, Scheme 1.29).



Scheme 1. 23 Ru-Catalysed Asymmetric Ring Opening of Epoxides

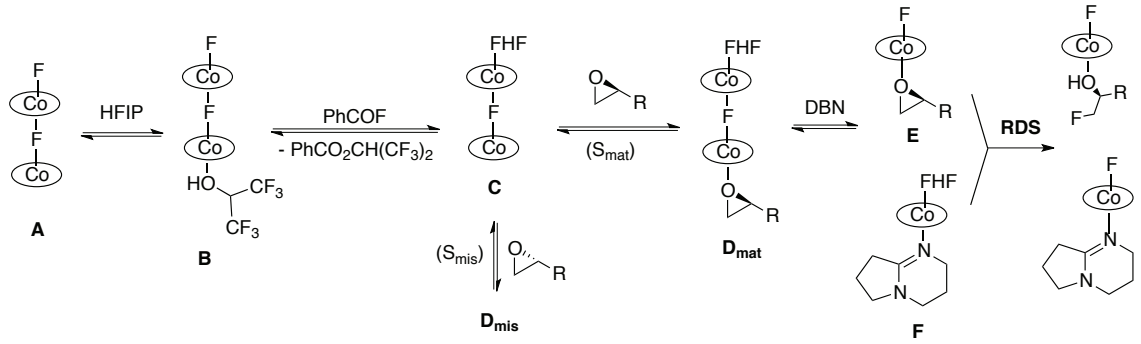
As the major drawback of this methodology in terms of selectivity arises from the use of highly reactive hydrofluorinating reagents, Doyle et al reasoned that the use of a latent source of fluoride could improve the process. The amine-HF reagent, generated *in situ* by an amine-catalysed activation of benzoyl fluoride and hexafluoro-*iso*-propanol (HFIP),[80] showed to be a convenient fluoride source for this purpose. The dual-catalyst system of a chiral amine, as (-)-tetramisole, and a Lewis acid, such as the chiral (Salen)Co complex **[Co-1]**, efficiently promoted the ring opening of *meso* **51** and the kinetic resolution of terminal epoxides **52** (Scheme 1.24).[81] The new methodology showed good functional group tolerance, yielding the desired products in up to 88% yield and with 99% ee for *meso* epoxides. A significant matched-mismatched effect on both yield and enantioselectivity was

observed between the two co-catalysts. The reaction in the absence of one of the catalysts proceeded only to a small extent, indicating the presence of a cooperative effect between the **[Co-1]** complex and the amine.



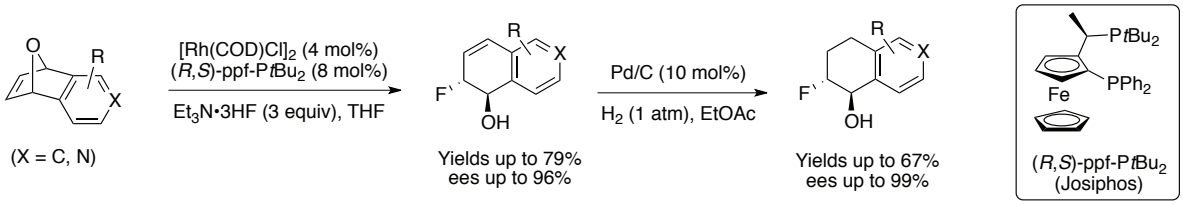
Scheme 1. 24 Cooperative Dual-Catalysis for Enantioselective Synthesis of Fluorohydrins

Some mechanistic insights were later elucidated through a combination of experiments, which allowed the authors to postulate a catalytic cycle, based on a series of equilibrating fluoride-bridged dimers of **[Co-1]** (Scheme 1.25).[82] The initial **[Co-1]**F dimer **A** is bound by HFIP to lead to adduct **B**, which interacts with PhCOF, providing the bifluoride-containing dimer **C**, *via* an alkoxide/fluoride exchange. Both matched (**Dmat**) and mismatched (**Dmis**) epoxide binding modes could occur with dimer **C**, but only the matched combination would lead to fluorinated product. Axial ligation of DBN (1,5-diazabicyclo[4.3.0]non-5-ene) to the **Dmat** complex facilitates the dimer dissociation to form adducts **E** and **F**, the latter being the suggested fluoride source. The ring-opening of the epoxide would then occur, as the rate-limiting step of the reaction. Based on this information, the authors designed a linked Co catalyst **[Co-2]**, which showed superior efficiency in terms of reactivity and selectivity (Scheme 1.24). A similar protocol for selective aziridine opening has been reported, employing a combination of (Salen)Co catalyst and an achiral Ti(IV) co-catalyst.[83]



Scheme 1. 25 Proposed Mechanism for Enantioselective Synthesis of Fluorohydrins

Recently, Lautens et al developed a rhodium-catalysed asymmetric ring opening of oxabicyclic alkenes[84] using $Et_3N{\cdot}3HF$ as the source of nucleophilic fluorine (Scheme 1.26).[85] The 1,2-trans products, containing both allylic fluoride and fluorohydrin moieties, were generated as single regio- and diastereoisomers. The combined use of $[Rh(COD)Cl]_2$ and chiral Josiphos ligand (*R*,*S*)-ppf-P*t*Bu$_2$ (*(R*-1-[*(S)-2*-diphenylphos-phinoferrocenyl]ethyldi-*tert*-butyl-phosphine), in THF at 50 °C within 1 h, allowed the fluorination of difluoro-, dimethyl-, and dibromo-substituted oxabicyclic alkenes in good yields and with excellent enantioselectivities. Substrates bearing electron-rich substituents on the aromatic ring gave unstable fluorohydrins, prone to elimination yielding 1-naphthol, upon silica gel chromatography. This problem was overcome by reduction of the double bond after ring opening, under mild reduction conditions (10 mol% Pd/C, 1 atm H_2, rt, 1 h), to afford stable alkyl fluorohydrin products. Although the nature of the fluoride species is unclear, the authors ruled out fluorometallation as a mechanistic pathway, due to the trans stereochemistry of the ring-opened products.



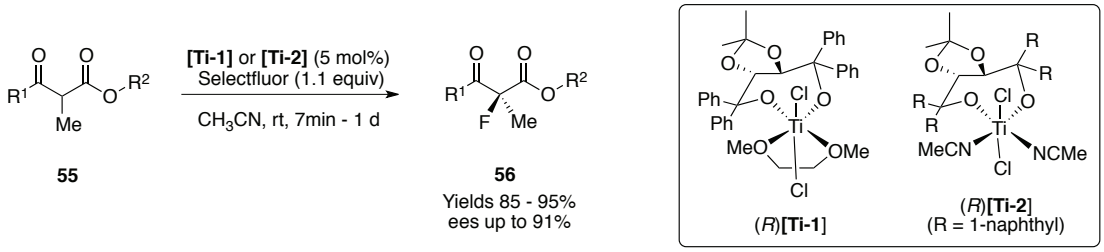
Scheme 1. 26 Rh-Catalysed Enantioselective Ring Opening of Oxabicyclic Alkenes

1.4.4 Synthesis of α-Fluoro-Carbonyl Derivatives

Stereoselective Csp^3-F bond formation is very desirable for the construction of biologically and pharmaceutically relevant compounds. Research has mainly focused on the use of chiral fluorinating reagents or chiral starting materials but has more recently redirected towards the development of catalytic asymmetric fluorinations.[86]

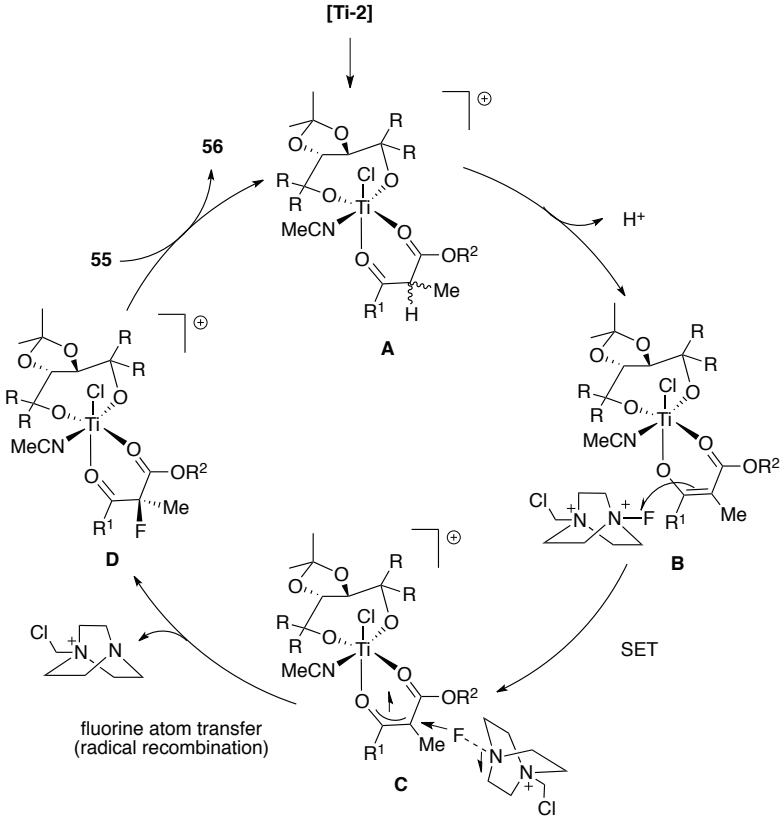
The most common catalytic approach is based on the enantioselective fluorination of β-ketoesters, to afford optically active and non-enolisable α-fluorocarbonyl derivatives.[87] In contrast to the synthesis of other fluorinated functionalities, an extensive study has been reported in the literature addressing selectivity and substrate scope for this transformation.

In pioneering work, Togni and co-workers disclosed the capability of a Ti-based Lewis acid to enolise β-ketoesters, and promote the α-fluorination with electrophilic fluorinating agents.[88] Selectfluor® was shown to be the favoured F^+ source for this reaction. The use of pre-synthesised chiral catalysts [$TiCl_2$(*R,R*)-TADDOLato)] (TADDOL = 2,2-dimethyl-α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol), **[Ti-1]** and **[Ti-2]**) allowed the asymmetric synthesis of α-fluoro-β-ketoesters. A quaternary stereogenic centre could be formed in products **56**, starting from a series of substrates bearing a α-methyl group (**55**). Generally, substrates afforded the desired products in good to excellent yields (Scheme 1.27). The steric environment of both the catalyst and the substrate was shown to be important with regard to the selectivity of the process. The best enantioselectivity (90% ee) was indeed achieved employing complex **[Ti-2]**, bearing 1-naphthyl groups, and the β-ketoester with a mesityl substituent (R^2 = mesityl).



Scheme 1. 27 Ti-Catalysed Enantioselective Fluorination of β-Ketoesters

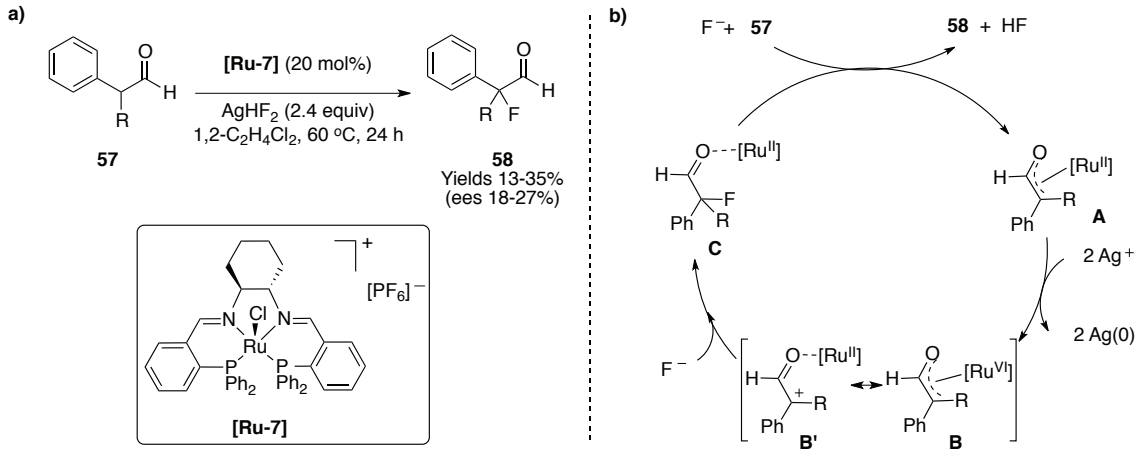
Quantum Mechanical/Molecular Mechanical (QM/MM) studies[89] and isolation of Ti (TADDOLato) complexes bearing two carbonylenolate units,[90] analogues of the intermediate **A**, provided an insight on the mechanism and the stereocontrol of the reaction. It was suggested that **55** coordinates the **[Ti-2]** complex, with subsequent loss of one chlorine and one acetonitrile ligand, to afford **A**. Upon deprotonation of the coordinated β-ketoester, the corresponding enolato complex **B** is formed, which eventually undergoes electrophilic fluorination. It was proposed that the C-F bond-forming step is based on a Single Electron Transfer (SET), in agreement with several reports on reactions employing N-F reagents, such as Selectfluor®. In complex **A**, the face-on naphthyl group of the (*S*,*S*)-TADDOL shields the *Si*-side of the coordinated enolate, forcing the fluorine radical to attack the *Re*-face of the complex. The proposed stereocontrol is consistent with the absolute configuration obtained in the α-fluoro-β-ketoester product **56** (Scheme 1.28).



Scheme 1. 28 Proposed Mechanism for Ti-Catalysed Fluorination of β-Ketoesters

The Ru-based catalyst **[Ru-6]** showed a higher efficiency than the **[Ti-2]** complex, allowing the use of less reactive fluorinating agents, such as NFSI, and therefore avoiding unselective background reactions with more reactive enolate derivatives.[91]

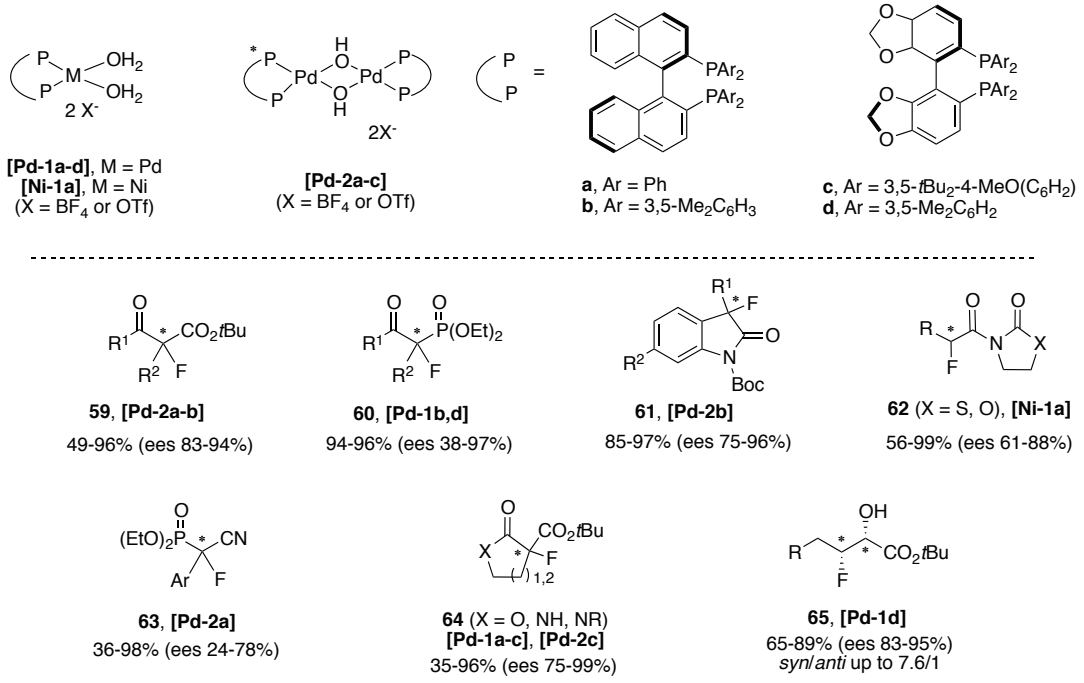
The same authors developed a unique example of nucleophilic α-fluorination of aldehydes, employing the catalyst **[Ru-6]**, under reaction conditions similar to these adopted for the ring-opening of epoxide fluorination.[79] Only secondary aldehydes bearing at least one aromatic substituent (**57**) were reactive, and best results (**58**, 35% yield, 25% ee) were obtained when 20 mol% of **[Ru-7]** catalyst was used, performing the reaction for 24 h at 60 °C (Scheme 1.29a). The transition metal-catalysed α-fluorination of aldehydes employing a nucleophilic fluorinating agent is unprecedented. This process is likely to proceed *via* the oxidation of the aldehyde by 2 Ag^+, leading to a Ru-stabilised carbocation intermediate **B**, followed by nucleophilic fluorination of the highly reactive species at the α-position of the carbonyl. This mechanism would also account for the limitation in substrate scope to 2-phenyl alkyl aldehyde species (Scheme 1.29b).



Scheme 1. 29 Ru-Catalysed Asymmetric α-Fluorination of 2-Alkylphenylacetaldehydes

Building on Togni's pioneering study, several authors have developed different variants for the fluorination of β-ketoesters, by making use of Lewis acid catalysts and N-F reagents. Based on their previous success in the enantioselective Pd-catalysed Michael addition to β-

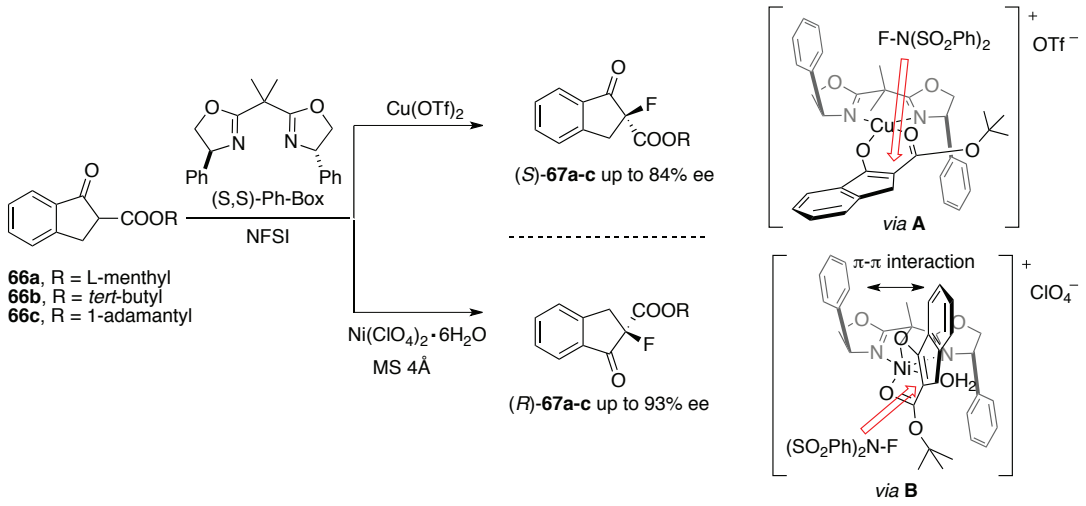
ketoesters,[92] Sodeoka et al reported an efficient selective synthesis of α-fluoro-β-ketoesters **59** with 83-94% ees. They employed Pd(II)hydroxo complexes **[Pd-1a,b]** and **[Pd-2a,b]** ligated to (*R*)-DM-BINAP (**a**, (*R*)-(+)-(1,1'-binaphthalene-2,2'-diyl)bis(3,5-dimethyl-diphenylphosphine)) or (*R*)–DTBM-SEGPHOS (**b**, (*R*)-(-)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole) with NFSI as the fluorinating reagent, in EtOH. The methodology was successfully expanded to the enantioselective synthesis of α-fluoro-β-ketophosphonates **60**,[93] α-fluoro-oxindoles **61**,[94] α-fluoro-(2-arylacetyl)thiazolidin-2-ones and α-fluoro-oxazolidin-2-ones **62**,[95] α-fluoro-α-cyanophosphonates **63**,[96] lactones and lactams **64**[97] and β-fluoro-α-hydroxy acid derivatives **65**, *via* mono-fluorination of α-keto esters (Scheme 1.30).[98] Following Sodeoka's work, the substrate scope was further expanded by Kim and co-workers.[99]



Scheme 1. 30 Pd- and Ni-Catalysed Electrophilic Fluorination of β-Keto Derivatives

In 2004, Shibata and co-workers reported the first example of an enantio-flexible fluorination reaction of β-ketoesters, using bis(oxazoline)-based ligand (Ph-BOX = 2,2-bis(4-phenyl-2-oxazolin-2-yl)propane) in combination with different metal catalysts and

NFSI as the fluorinating agent.[100] Extensive screening of the reaction conditions allowed access to both (*S*) and (*R*) cyclic α-fluoro-β-ketoesters **67a-c** with good stereocontrol, by changing the transition metal precursor from $Cu(OTf)_2$ to $Ni(ClO_4)_2{\cdot}6H_2O$ (Scheme 1.31). The opposite stereoinduction of the two complexes is thought to be due to a change in the metal centre geometry from square planar **A** to square pyramidal **B** in the transition state.

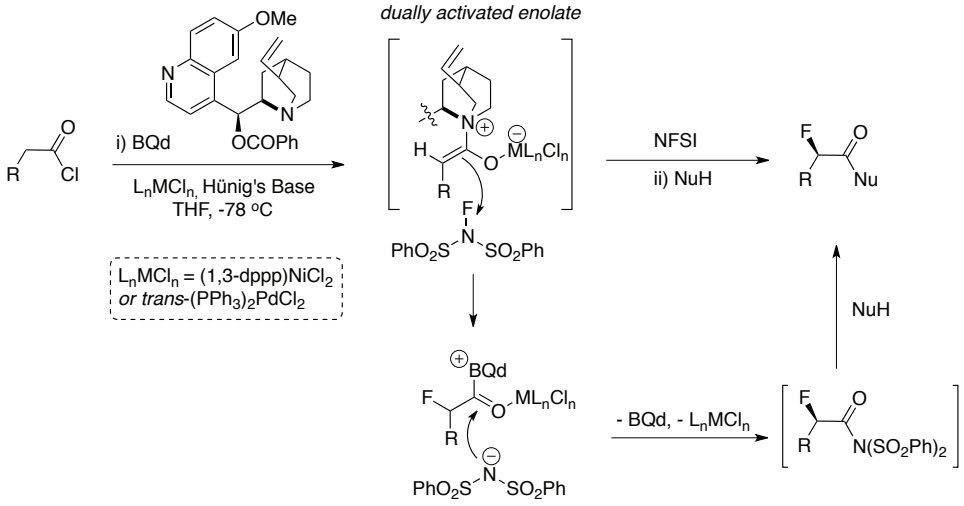


Scheme 1. 31 Reversible Stereoselective Fluorination of β-Ketoesters with Ni- and Cu-Catalysts

The selectivity and scope of the process was subsequently improved by employing a Ni(II) complex with a second generation Ph-BOX ligand, such as DBFOX/Ph (4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline)). Under these conditions, substrates capable of two-point binding, such as oxindoles were also fluorinated with enantiomeric excesses up to 99%. Furthermore, a significant example of asymmetric amplification in the halogenation of β-ketoesters was also reported.[101] Excellent selectivity was obtained for the enantioselective fluorination of racemic malonates *via* a desymmetrisation-like approach, with the best catalytic system being DBFOX/$Zn(OAc)_2$. The synthetic utility of the method was demonstrated by the conversion of enantiopure 2-fluoro malonates into chiral fluorinated hydroxyesters, ester-amides, β-amino acids and β-lactams.[102] Similar catalysts, such as Ph-DBFOX-$Zn(SbF_6)_2$ and Ph-DBFOX-$Zn(ClO_4)_2$, were also employed by

Jørgensen and co-workers for the fluorination and chlorination of cyclic and acyclic β-keto phosphonates, yielding the halogenated products with ees up to 92%.[103]

Based on a "dual activation" strategy of enolates,[104] Lectka and co-workers developed the enantioselective α-fluorination of acid chlorides to access a variety of fluorinated carboxylic acid derivatives with excellent selectivity.[105] The use of a transition metal co-catalyst, able to bind the ketene enolate oxygen, enhanced the reactivity of the ketene BQd-enolates (BQd = benzoylquinidine) towards fluorination, employing the commonly used reagent NFSI. Both *trans*-$(PPh_3)_2PdCl_2$ and the chelating complex (dppp)-$NiCl_2$ are active catalysts in the reaction, when used in combination with Hünig's base, 10 mol % of BQd, and 1 equiv of NFSI in THF at -78 °C. Fluorination of the dually activated enolate leads to an acyl ammonium salt that reacts with the liberated dibenzenesulfonimide anion to form the active amide intermediate (Scheme 1.32).

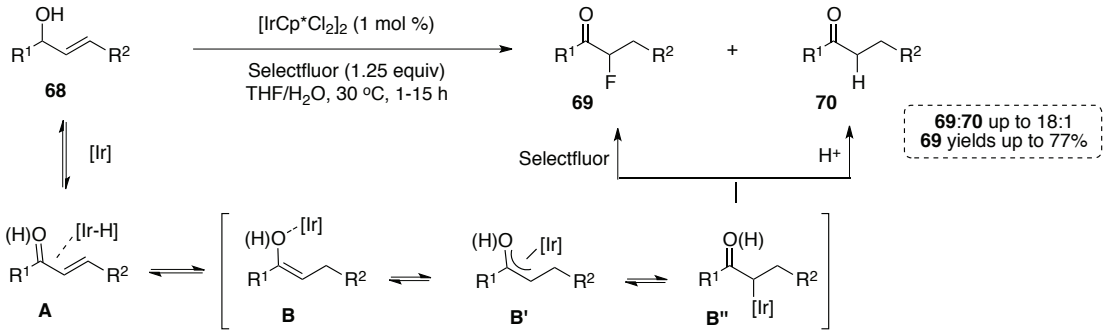


Scheme 1. 32 Asymmetric Bifunctional Catalytic α-Fluorination of Acid Chlorides

Simply by changing quenching conditions, a variety of α-fluorinated carboxylic acid derivatives could be accessed *via* transacylation of the amide, such as esters (MeOH), carboxylic acids (H_2O), amides (amine), and thioesters (thiol). Moreover, the reaction showed a good functional group tolerance, and was successfully carried out with acid

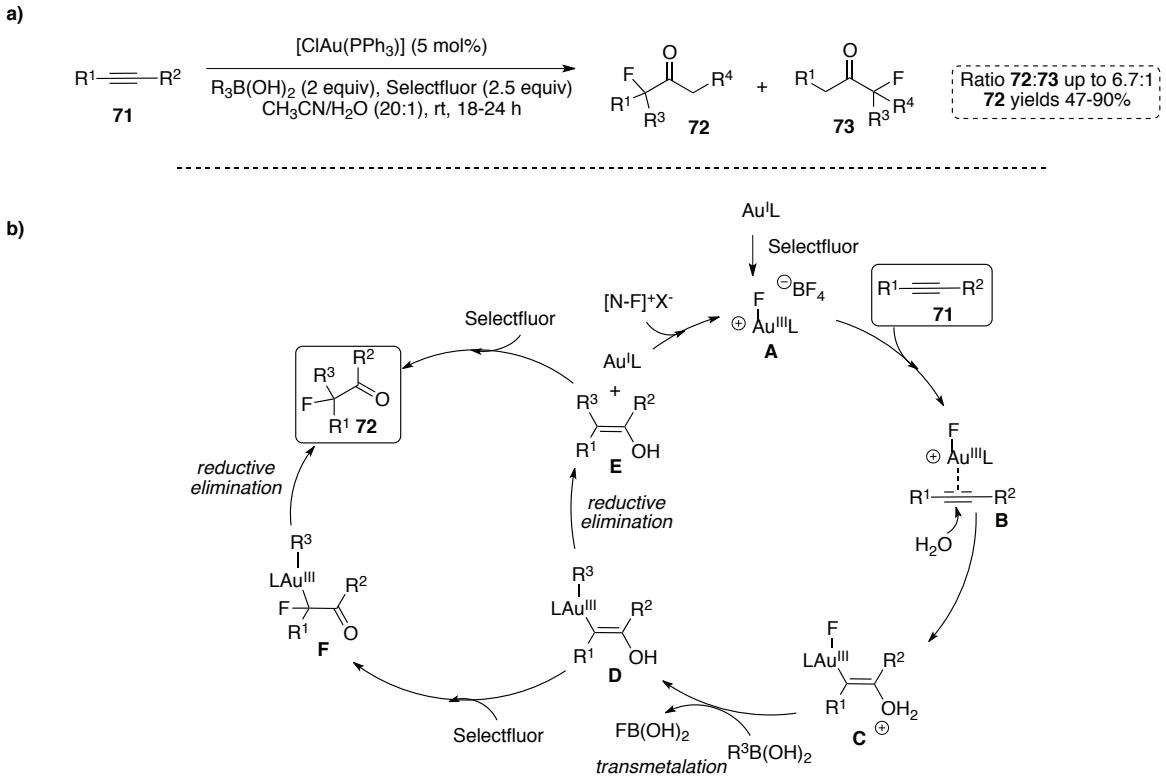
chlorides bearing aromatic, heterocyclic and protected aminoalkyl substituents, allowing access in a single step to enantiopure molecules of high complexity. Extensive investigations disclosed that the use of a third co-catalyst, a lithium salt, increased the reactivity of the fluorinating agent and allowed access to aliphatic products in excellent yields and ees, which are not accessible *via* the previous methodology.[106] A "tricomponent" catalytic system was also reported for the α,α-difluorination of acid chlorides.[107]

An approach based on a tandem allylic alcohol isomerisation/electrophilic fluorination led the research group of Martín-Matute to regioselectively afford α-fluoroketones.[108] The combination of $[IrCp^*Cl_2]_2$ as the catalyst and Selectfluor® as the fluorinating reagent led to the fluorinated ketones **69** as single regioisomer, with the C-F bond formed exclusively at the alkenyl carbon of the starting allylic alcohol **68** (Scheme 1.33). Both terminal and 1,2-disubstituted alkenes **68** (R_2=H and R_2=Me, Ph, respectively) could be fluorinated, carrying out the reaction in a co-solvent system (THF and deionised water) at 30 °C. The formation of the ketone byproduct **70** could not be completely suppressed under the reaction conditions. Deuterium-labeling experiments suggested a mechanism whereby oxidation of **68** to α,β-unsaturated ketone **A** occurs with concomitant formation of an [Ir-H] species. A hydride transfer to the double bond led to the Ir-enolate intermediate **B**, which could undergo fluorination upon reaction with Selectfluor®, or alternatively protonation to yield byproduct **70**.



Scheme 1. 33 Ir-Catalysed Tandem Isomerisation/C-F Bond Formation

Inspired by the pioneering work of Zhang and co-workers,[109] Xu and Hammond reported the first example of a Au-catalysed synthesis of α-fluoroketones, starting from alkyne derivatives and employing Selectfluor® in combination with a boronic acid. The process was based on a tandem addition/oxidative coupling/fluorination sequence.[110] Selectfluor® has been widely employed in gold catalysis as an oxidant of the pre-catalyst Au(I), to yield the highly Lewis acidic Au(III)-F cationic species, and therefore able to activate alkynes towards nucleophilic attack.[111] In this study, the authors made use of Selectfluor® not only as a catalyst oxidant, but also as a fluorinating reagent. During the course of the Au-catalysed hydroxylation of the alkyne **71**, activated by a stoichiometric amount of Selectfluor®, the vinyl-Au(III) hydration intermediate would undergo transmetallation with the organoboronic acid ($R^3B(OH)_2$). The subsequent electrophilic fluorination would yield the α,α-fluoroalkyl ketone derivative **72** (Scheme 1.34a).



Scheme 1. 34 Au-Catalysed "Functionalised Hydration" of Alkynes with Selectfluor®

The one pot reaction, carried out with both functionalised and unfunctionalised internal alkynes **71**, employing 5 mol% of pre-catalyst AuCl(PPh_3), and an excess of Selectfluor® with a variety of boronic acids, yielded fluorinated α-substituted ketones in very good yields and moderate regioselectivity (**72**:**73** ratio up to 6.7:1).

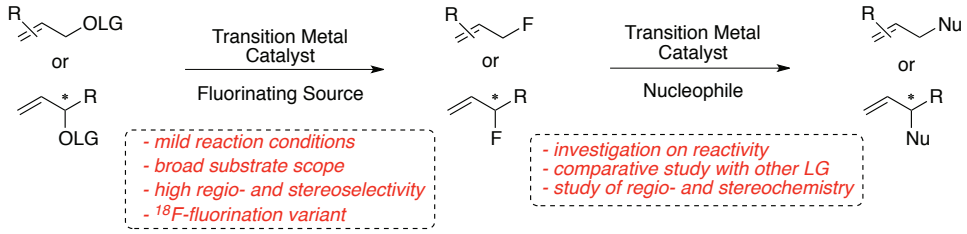
Preliminary mechanistic investigations suggested the formation of intermediate **C**, upon water attack on the vinyl-Au(III) complex **B**, which undergoes transmetallation with $R^3B(OH)_2$, with the driving force being the formation of the strong B-F bond. Complex **D** could either undergo electrophilic fluorination (**F**) and subsequent reductive elimination to yield **72**, or alternatively lead to the intermediate **E**, which can be subsequently fluorinated by Selectfluor® (Scheme 1.34b).

Nevado and co-workers reported an analogous method for the synthesis of α-fluoro acetals and α-fluoro ketones starting from alkynes, *via* an alkoxylation/hydration-fluorination protocol using alcohol as the solvent, Selectfluor® as the fluorinating agent and $Ph_3PAuNTf_2$ as the catalyst.[112] The selective formation of fluorinated acetals or ketones could be achieved by changing the reaction conditions, obtaining a good degree of chemo- and regioselectivity, for both internal and terminal alkynes.

1.5 Thesis Outline

On the basis of the great advantages that fluorine chemistry gained when combined with transition metal catalysis, and due to the longstanding interest of the Gouverneur and Brown groups in the synthesis of the highly versatile allylic fluoride motif, we embarked on a research program aimed at investigating the reactivity and construction of allylic C-F bonds under transition metal catalysis. Initial results from others and us showed that allylic fluorides are reactive towards nucleophilic substitution, under Pd-catalysis. Recently, the reverse reaction of fluorination of allylic derivatives was also disclosed, receiving considerable attention by the organic chemistry community. These outstanding results encouraged us to pursue the study of allylic fluorides in terms of reactivity and ease of

synthesis, employing catalysts other than palladium, in order to expand and overcome limitations of the existing methodologies. In Chapter 2, a comparative study on the reactivity and selectivity of Pd- and Pt-catalysed alkylation of allylic fluorides will be described. Despite the similarity between these two transition metals, interesting and unexpected differences were disclosed with regard to the C-F bond activation reaction. In Chapter 3, another commonly used transition metal catalyst for allylic transformation, iridium, was examined. Although the Ir-based catalyst was shown to be active towards allylic fluorination, similarly to palladium, significant differences were observed between the two catalytic systems. Moreover, the use of the Ir-catalyst enables us to overcome the limitations and expand the scope of existing methods, showing an unusual regioselectivity in the presence of a fluoride source.



Scheme 1. 35 Transition Metal Catalysed Synthesis and Substitution of Allylic Fluorides

Chapter 2

Platinum Catalysed Substitution of Allylic Fluorides

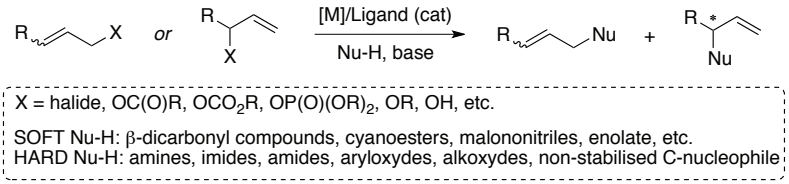
2.1 Introduction

The synthetic value of the Tsuji-Trost substitution of allylic derivatives with heteroatom nucleophiles is unquestionable. The application of this methodology to the synthesis of important fluorinated building blocks, such as allylic fluorides, is thus highly desirable. However, the reactivity of allylic fluorides under transition metal catalysis should be considered, on the basis of precedent examples involving allylic chlorides and bromides. In a pioneering study, Togni et al reported the feasibility of allylic C-F bond activation, to generate the corresponding allyl-Pd species, when the allylic fluoride was subjected to a stoichiometric amount of Pd(0) complex (Chapter 1, Scheme 1.9).[40] Unsuccessful attempts to perform the reverse reaction, by treating the allyl-Pd complex with a nucleophilic source of fluoride, prompted the authors to conclude that Pd-mediated allylic fluorination reaction is highly disfavoured. Building on these observations, the Gouverneur and Brown groups began an investigation on the reactivity of allylic fluorides under catalysed alkylation conditions. In addition, the relative reactivity of fluoride versus other commonly used leaving groups was examined by carrying out internal competition experiments. This information provides useful guidelines in the selection of highly reactive starting materials for the development of the reverse reaction, the allylic fluorination.

2.2 Background Work on Palladium Catalysed Substitution of Allylic Fluorides

2.2.1 Tsuji-Trost Substitution

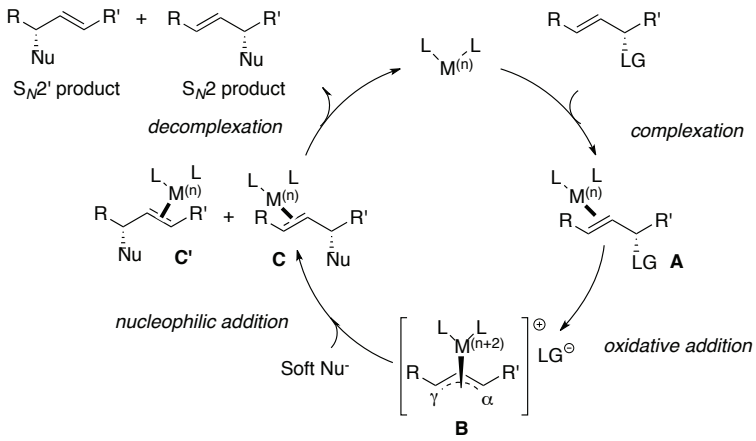
The Tsuji-Trost substitution is a transition metal catalysed reaction carried out with allylic chlorides, acetates, carbonates or other esters, derived from an allylic alcohol, and carbon or heteroatom nucleophiles to form the product of formal S_N2 or S_N2' substitution (Scheme 2.1).[59,113] Since the first reports,[114] this transformation has attracted a great deal of interest, due to the use of mild conditions, broad functional group tolerance and excellent control over regio- and stereoselectivity in the formation of new C-C, C-H, C-O, C-N and C-S bonds. The majority of the processes developed, inclusive of asymmetric variants, employ a Pd-complex as the catalyst of choice, due to their ease of accessibility. However, several studies have focused on transition metals other than Pd, such as nickel, platinum, rhodium, iron, iridium, ruthenium, molybdenum and tungsten. The availability of a variety of catalysts in combination with the broad library of ligands allowed selectivity and reactivity issues to be addressed, as well as the extension of the methodology scope.



Scheme 2. 1 General Scheme for Tsuji-Trost Substitution

Mechanistically, the process starts with the coordination of a low-valent metal to the double bond of the allylic derivative (**A**), which results in the activation of the latter towards ionisation. The allyl-metal intermediate **B** is generally afforded in a cationic form with the leaving group acting as counterion (Scheme 2.2). Typically, soft C-nucleophiles attack the allyl ligand from the face opposite to that of the metal centre, to yield the olefin complex **C** (or **C'**), which is the initial product of the reaction. Subsequent decomplexation releases the

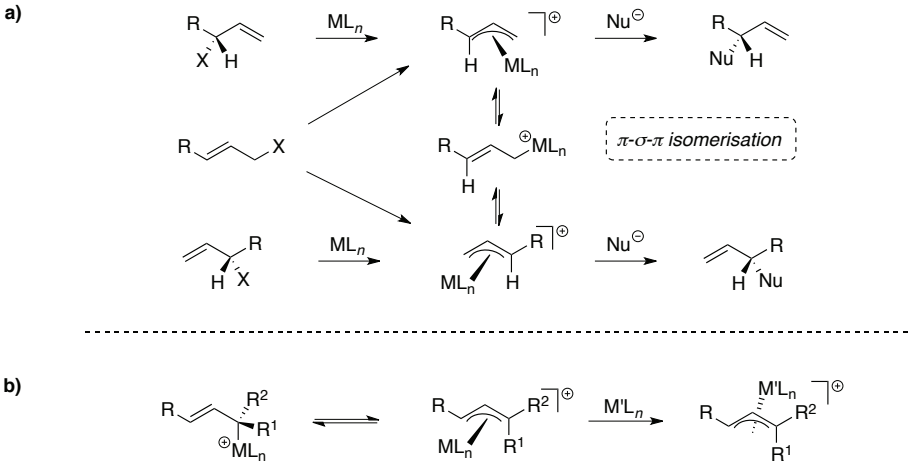
final product and regenerates the low-valent catalyst. When heteroatom or non-stabilised carbon nucleophiles are employed, the nucleophilic attack occurs at the metal centre, which will liberate the product *via* reductive elimination. With soft nucleophiles, overall retention of stereochemistry is observed due to the double inversion process, whereas hard nucleophiles tend to substitute with overall inversion of stereochemistry.



Scheme 2. 2 Mechanism for Tsuji-Trost Substitution with Soft Nucleophiles

The nature of the allyl metal intermediate can greatly affect the product distribution. When one of the termini of the allyl complex **B** is symmetrically substituted, the intramolecular exchange of the metal from one face to the other of the allyl ligand can occur *via* η^3-η^1-η^3 interconversion (Scheme 2.3a).[113] Alternatively, when both termini of the allyl complex contain two different substituents, the stereochemistry of the intermediate could be inverted by the external attack of a second metal centre, *via* an intermolecular exchange (Scheme 2.3b).[113] These rearrangements allow the racemisation of enantiomerically pure starting materials, but also the enantioselective substitution of non-symmetric racemic derivatives, when chiral ligands are coordinated to the metal centre. If nucleophilic attack is faster than the equilibration event, only retention of configuration product will be observed (Scheme 2.3). Several authors have shown that the use of additives, such as halide anions, phosphines or coordinating solvents, can increase the rate of both intra- and intermolecular rearrangements. The additive, by coordinating the metal centre, may favour the

interconversion from η^3- to η^1-allyl complex, or alternatively form a pentacoordinate intermediate, which is stereochemically non-rigid.

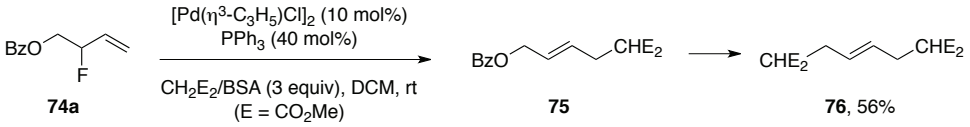


Scheme 2. 3 Intra- and Intermolecular Isomerisation of Allyl Metal Intermediate

For palladium-catalysed alkylation reactions, a general reactivity trend has been established for allylic alcohol derivatives, following the order: carbonate > phosphate > benzoate > acetate,[115] enabling chemoselective substitutions to be performed. In addition to common leaving groups, sulfonates, nitro compounds, protonated amines, ethers, acetals and geminal diacetates have been employed as active starting materials for this transformation.

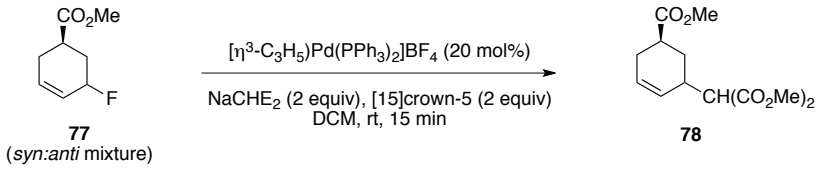
2.2.2 Pd-Catalysed C-F Bond Activation

Due to the longstanding interest of the groups of Gouverneur and Brown in the synthesis and chemistry of allylic fluorides, previously in the group, an investigation into the reactivity and stereoselectivity of Pd-catalysed alkylation of allylic fluorides was initiated.[42] In a preliminary study, allylic fluoride **74a** was subjected to an excess of malonate nucleophile, employing BSA (bis(trimethylsilyl)acetamide) as base, in the presence of 10 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and PPh_3 ligand (40 mol%). The doubly substituted derivative **76** was formed exclusively in 56% yield. The monosubstituted product **75** could be isolated by using < 1.5 equivalents of malonate (Scheme 2.4).



Scheme 2. 4 Pd-Catalysed Substitution of Branched Allylic Fluoride **74**

To gain an insight on the stereochemistry of the substitution, the reactivity of cyclic fluoride **77** was also investigated. Allylic fluoride **77** underwent smooth malonate substitution in the presence of 20 mol% of $[\eta^3$-allylPd$(PPh_3)_2]BF_4$; surprisingly, the product **78** was obtained with a similar diastereomeric ratio (*syn*:*anti* ~ 70:30), irrespective of the starting material *syn*/*anti* ratio (Table 2.1, entries 1-3). Variation of the solvent did not affect the outcome significantly. Interestingly an inversion of selectivity, in favour of the *anti*-product, was observed when 2,2'-bis(diphenylphosphanyl)biphenyl (biphep) was used in place of PPh_3 (Table 2.1, entry 4). The stereochemical outcome of these reactions indicated an unusual mechanistic pathway with respect to what is observed for more common leaving groups.[116]



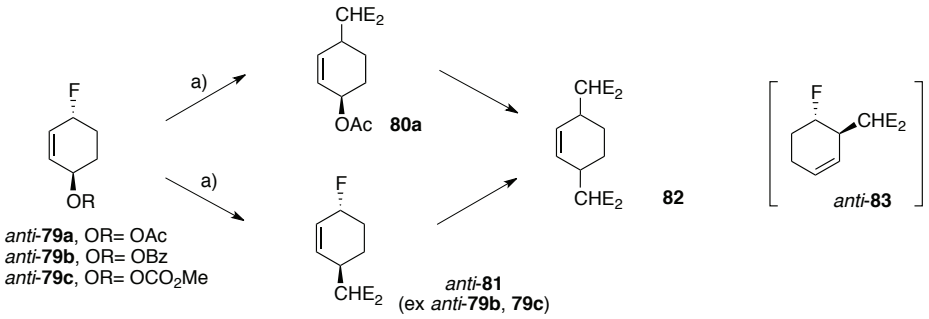
Entry	*Syn/anti* ratio in **77**	*Syn/anti* ratio in **78**
1	40:60	76:24
2	10:90	72:28
3	87:13	73:27
4[a]	40:60	37:63

a. Catalyst was $[(\eta^3$-$C_3H_5)PdCl]_2$, biphep.

Table 2. 1 Stereochemistry of Palladium-Catalysed Substitution of Allylic Fluoride **77**

In order to compare the relative reactivity of fluoride with respect to other common leaving groups, a series of internal competition experiments were carried out. Cyclohexenyl allyl fluorides *anti*-**79a-c**, bearing *anti*-disposed competing leaving groups (OAc, *anti*-**79a**; OBz,

anti-**79b**; OCO_2Me, *anti*-**79c**), were selected as model substrates. These substrates were accessed *via* fluorodesilylation of the corresponding cyclohexenyl silanes.[117]



a) $[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$ (20 mol%), $NaCHE_2$ (E= CO_2Me)/ [15]crown-5, DCM, rt.

Entry	Starting material	*Anti*:*syn* in SM	Nu equiv	Product ratio *anti*/*syn*-**80**	*anti*/*syn*-**81**	*anti*/*syn*-**82**
1	**79a**	92:8	3	40:0	--	9:51
2	**79a**	92:8	1.2	44:44	--	3:9
3	**79b**	98:2	3	--	--	11:89
4	**79c**[a]	98:2	1.1	--	91:0[b]	--
5	**81**[c]	>99:1	3	--	--	12:88

a $[\{Pd((\eta^3\text{-}C_3H_5)Cl\}_2]$ (2.5 mol%), 3 h. *b* 9% is *anti*-**83**. *c* CH_2E_2/BSA, 16 h.

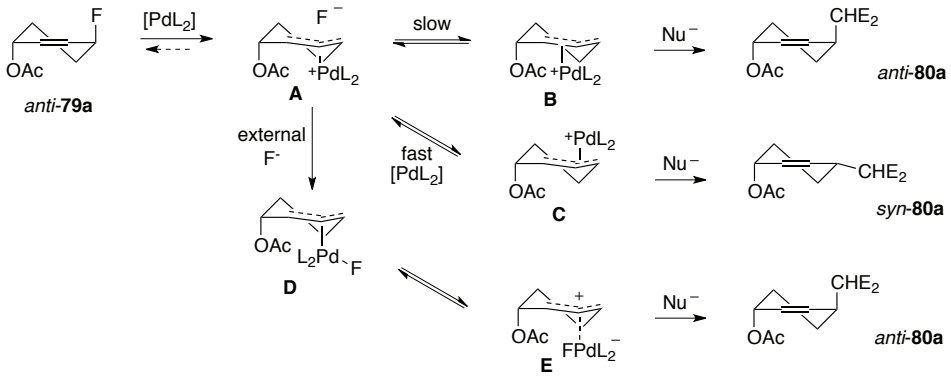
Table 2. 2 Pd-Catalysed Internal Competing Studies with Allylic Fluorides *anti*-**79**

The reaction of **79a** (*anti*:*syn* = 92:8) with 3 or 1.2 equivalents of sodium dimethyl malonate in the presence of 20 mol% of $[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$ afforded exclusively acetate **80a** and the disubstituted product **82**, indicating that fluoride is a better leaving group than acetate (Table 2.2, entries 1-2). In the presence of 1.2 equivalents of nucleophile a 50:50 ratio of *anti*/*syn* **80a** was formed. Based on the result with 3 equivalents of nucleophile, this suggests that *syn*-**80a** is much more reactive than *anti*-**80a** towards the second substitution. When **79b** (*anti*:*syn* = 98:2) was subjected to identical reaction conditions, full conversion into **82** (*syn*:*anti* = 89:11) indicated that both leaving groups were displaced, one with inversion and the other with retention of configuration (Table 2.2, entry 3). The order of substitution was determined by ^{1}H NMR experiments, which detected exclusively

81 (*anti*:*syn* = 87:13) as reaction intermediate, indicating the higher reactivity of benzoate with respect to fluoride. This experiment also confirmed that the benzoate leaving group was displaced with complete retention of configuration. A minor product *anti*-**83**, derived from S_N2' addition, was also detected.

The reaction of carbonate **79c** (*anti*:*syn* = 98:2), carried out with 2.5 mol% of [{Pd((η^3-C_3H_5)Cl}$_2$] and 1.1 equivalents of nucleophile, led, within 3 h, to the formation of derivative **81** (*anti*:*syn* >98:2) with complete retention of configuration (Table 2.2, entry 4). In this case, *anti*-**83** was detected in the crude reaction mixture (9%). Reaction of pure *anti*-**81** (Table 2.2, entry 5) led to the product **82** (*syn*:*anti* = 88:12), with almost complete inversion of configuration, in agreement with the results obtained for *anti*-**79b**.

These findings demonstrated that allylic fluorides are active substrates towards Pd-catalysed alkylation reaction, with a reactivity trend being OCO_2Me > OBz >> F >> OAc. The unusual stereochemical outcome for the substitution of fluoride was rationalised as a consequence of an intermolecular inversion mechanism. This isomerisation process of π-allyl Pd complexes was, first, elucidated by Bäckvall and co-workers, for Pd-catalysed allylic substitution reactions.[118] The ionised intermediate **A** could be attacked by a second neutral Pd(0)L_2 complex in preference to the malonate nucleophile, yielding intermediate **C**, which would lead to the overall inversion product, *syn*-**80a** (Scheme 2.5).

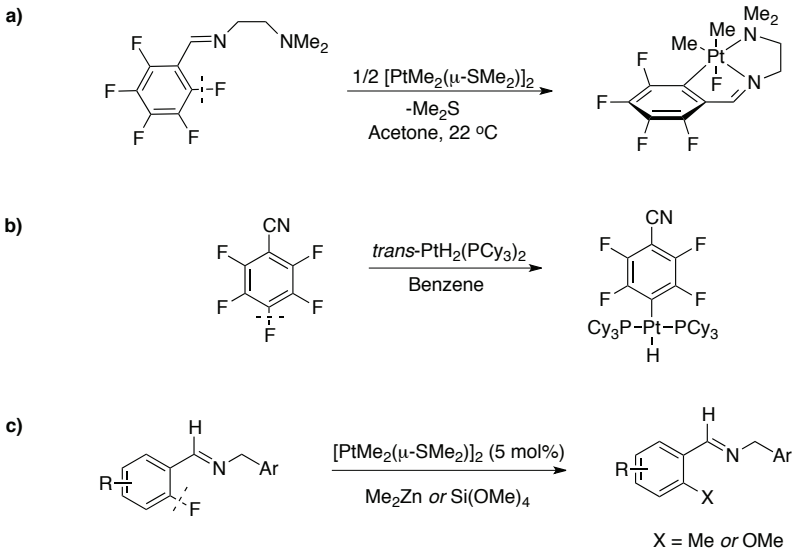


Scheme 2. 5 Postulated Mechanism for the Stereochemical Course of Alkylation of Allylic Fluoride

When the alkylation of *anti*-**79a** was performed in the presence of added TBAF, the reactivity of the system was significantly increased, and **80a** obtained with overall retention of configuration. This observation is in agreement with Togni's report on the enhanced enantioselectivity effect of coordinating ligands in the asymmetric allylic amination.[119] The fluoride could bind the Pd centre in the π-complex **A** to afford the neutral species **D**, which could undergo ionic dissociation yielding the intermediate **E**, amenable to the nucleophilic attack to give *anti*-**80a** (Scheme 2.5).

2.3 Platinum Catalysed C-F Bond Activation of Allylic Fluorides

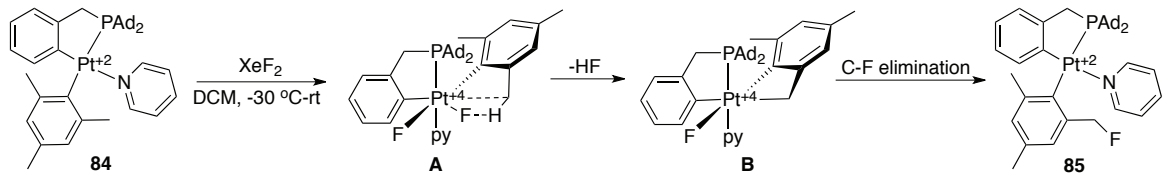
Platinum complexes have been widely employed as mediators for aryl C-F bond activation reactions.[120] Pioneering studies showed the feasibility of chelate-assisted intramolecular oxidative addition of Pt(II) complexes to aryl C-F bonds to afford isolable Pt(IV)-F species. The reaction was carried out with the pentafluorophenyl group linked to a bidentate ligand, which coordinates the Pt centre, rendering the C-F bond activation highly selective (Scheme 2.6a).[121]



Scheme 2. 6 Pt-Mediated Aryl C-F Bond Activation

Platinum-mediated activation of fluoroarenes was also developed *via* a Single Electron Transfer mechanism performed by a Pt hydride complex (Scheme 2.6b),[122] or *via* oxidative addition to a 14-electron Pt(0) complex.[123] Recently, Love and co-workers developed a catalytic variant to carry out Pt-catalysed cross coupling reactions of polyfluoroaryl imines with both C- and O-nucleophiles (Scheme 2.6c).[124]

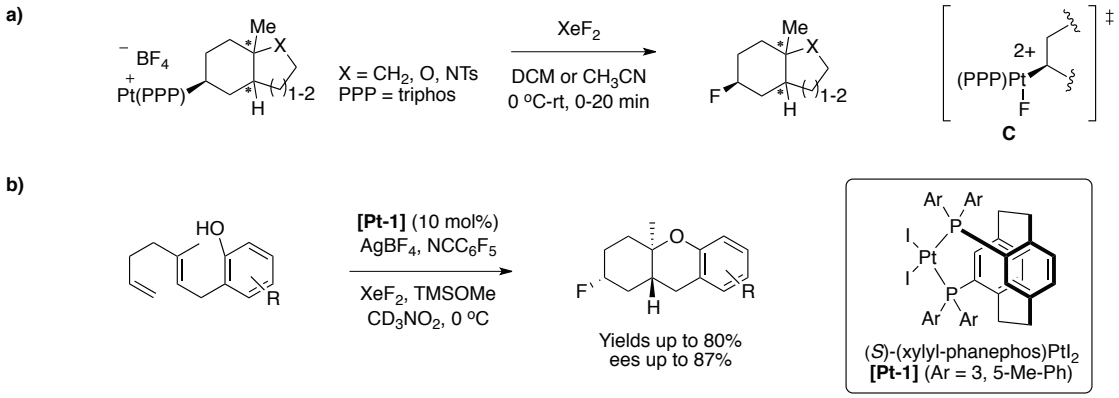
To the best of our knowledge, no example of Pt-mediated Csp^3-F bond activation has been reported in the literature. On the contrary, Pt-mediated benzylic and aliphatic fluorination reactions were disclosed by Vigalok and Gagné, respectively. In an initial work, Vigalok and co-workers reported a C-C coupling reaction of diaryl derivatives, by treating the chelating diphosphine complex $(P,P)Pt(Ar)_2$ ((P,P) = 1,3-bis(diisopropylphosphino)propane (dippp), dppp or 2 PPh_3) with XeF_2, with concomitant formation of the corresponding Pt(II) difluoride.[125] In order to elucidate the reaction mechanism and isolate the putative Pt(IV) complex intermediate, the stable cyclometalated Pt(II) complex **84** (bearing a mesityl group) was considered next. When **84** was treated with XeF_2, complex **85**, derived from a benzylic (C-H) fluorination of one of the *ortho*-methyl groups of the mesityl ligand, was observed (Scheme 2.7).[126] Mechanistically, the authors suggested a first oxidative addition, leading to difluoro Pt(IV) species **A**, followed by metalation of one of the methyl groups, along with elimination of HF, to give **B**. A benzylic C-F reductive elimination would afford the final product **85**.



Scheme 2. 7 Pt-Mediated Aryl C-F Bond Formation

A putative Pt(IV) fluoride intermediate was also postulated for the electrophilic fluorination reaction of (triphos)Pt-R^+ (triphos = bis(2-diphenylphosphinoethyl)phenylphosphine),

developed by Gagné and co-workers.[127] Here, the fluorination of cyclic aliphatic Pt(II) complexes was carried out with a series of F^+ sources, with XeF_2 yielding the fluorinated products within minutes (Scheme 2.8a). The stereoretentive fluorination suggested a mechanism based on C-F reductive elimination from the dicationic Pd(IV) fluoride intermediate **C**, with much more reactive systems for more hindered alkyl substituents in the starting Pt-complex (Scheme 2.8a). As previously discussed (Chapter 1, Section 1.4.2), a catalytic variant for an enantioselective cyclisation/fluorination cascade reaction of polyenes followed (Scheme 2.8b),[72] building on these preliminary studies.

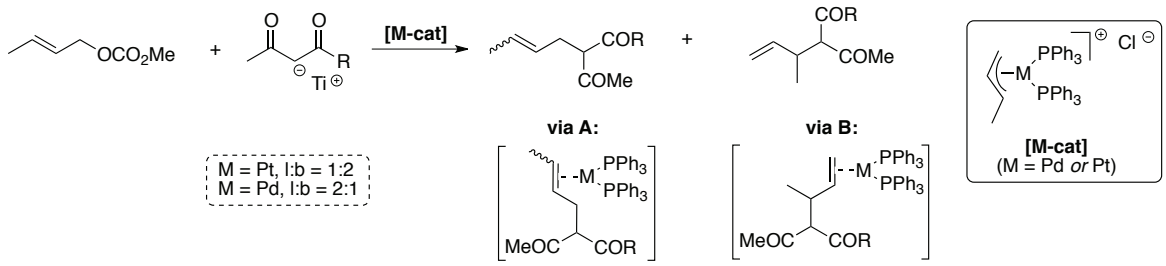


Scheme 2. 8 Pt-Mediated and Catalysed Aliphatic C-F Bond Formation

2.3.1 Pt-Catalysed Allylic Alkylation Reactions

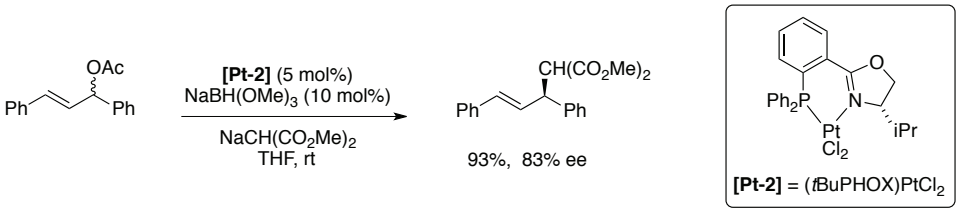
Despite the similarities in many aspects of Pd and Pt catalysis, literature on platinum catalysed allylic substitution reactions[128] is less comprehensive when compared to that of palladium. Nevertheless, platinum complexes have found applications in elucidating the mechanism of transition metal catalysed reactions. Indeed, the characterisation of platinum complexes can be achieved by NMR analysis, as ^{195}Pt is a NMR active isotope.[129] Moreover its high stability in both oxidative states Pt(II) and Pt(IV) permits the isolation and characterisation of intermediates that are not easily detectable with other comparable metal complexes.[130] The earliest investigations on Pt-catalysed allylic alkylation were provided by Kurosawa[131] and Brown.[132] Key differences in Pt-catalysis with respect to Pd-catalysis were

observed, such as the preference for η^1-coordination of the allyl ligand over the η^3-binding type. This implies a faster η^1-η^3-allyl interconversion, and therefore a quicker racemisation of chiral intermediates (Scheme 2.3a). Moreover, it was observed that under the same reaction conditions, with less hindered substrates, Pt-catalysts favoured branched alkylation products. This is a result of the higher propensity of Pt towards back π-donation than Pd, favouring electronically the terminal olefin-Pt complex **B**, derived from the substitution step (Scheme 2.9).



Scheme 2. 9 Regioselectivity of Pd- and Pt-Catalysed Allylic Alkylation Reaction

Williams and Clarke developed the first asymmetric Pt-catalysed alkylation of *rac*-1,3-diphenylallyl acetate, employing *t*Bu-PHOXPtCl$_2$ (PHOX = 2-[2-(diphenylphosphino)phenyl]-2-oxazoline, **[Pt-2]**) as catalyst and affording the enantioenriched substituted product with a selectivity comparable to that obtained under Pd-catalysis (Scheme 2.10).[133] More recently, a series of Pt-catalysed allylic amination reactions were reported,[134] inclusive of examples describing a direct amination of allylic alcohols.[135]

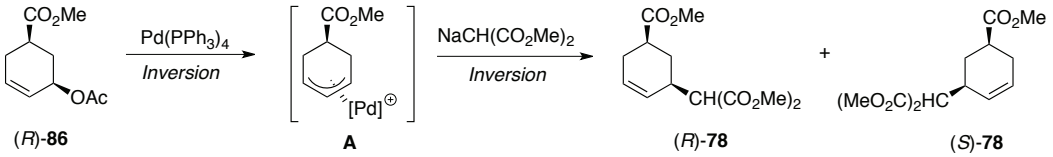


Scheme 2. 10 Enantioselective Pt-Catalysed Allylic Alkylation

Based on these literature precedents, we commenced our comparative study between Pd and Pt catalysis, in order to exploit the potential of platinum-catalysis and gain further mechanistic insights into allylic C-F bond activation.

2.3.2 Stereochemical Study on Pt- and Pd-Catalysed Allylic Alkylation

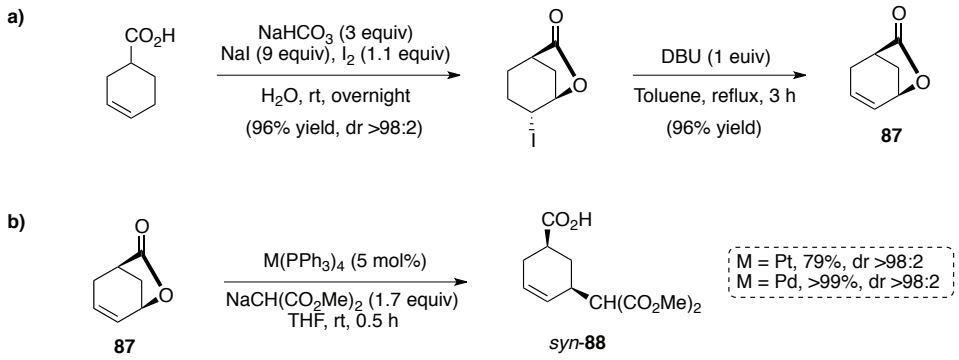
At the beginning of our investigation,[136] we noticed that no experimental study has been reported in the literature to validate the stereochemical outcome of Pt-catalysed substitution of commonly activated allylic derivatives, although several authors have suggested a mechanism of double inversion of configuration.[131,132] It has been reported that coordination of the complex $Pd(PPh_3)_4$ to the allyl acetate (*R*)-**86** occurs *anti* to the leaving group, yielding the allyl-Pd intermediate with inversion (**A**). Soft nucleophiles attack the allyl ligand of **A** from the opposite face of the Pd-centre, affording a second inversion of configuration, and therefore resulting in the formation of the product **78** with overall retention of configuration (Scheme 2.11).



Scheme 2. 11 Stereochemistry of Pd-Catalysed Allylic Alkylation

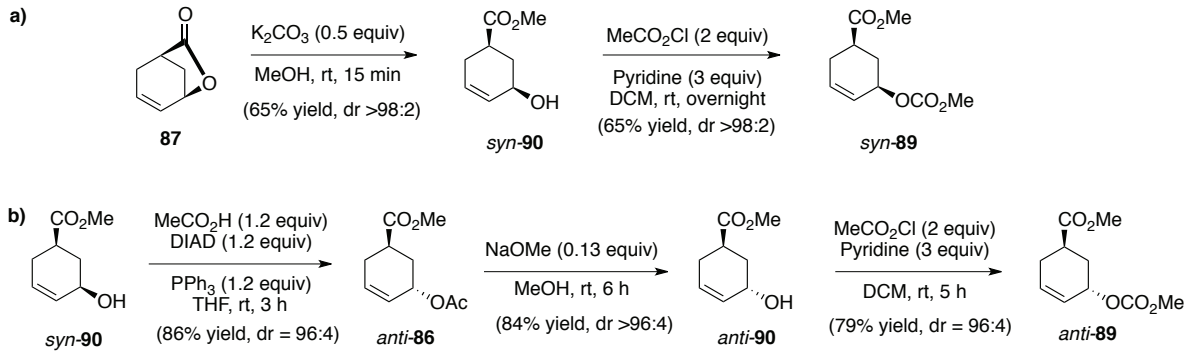
In order to experimentally validate the stereochemistry of Pt-catalysed allylic alkylation, the stereochemical probe lactone **87** was synthesised from the commercially available 3-cyclohexene-1-carboxylic acid (Scheme 2.12a).[116,137] The probe **87** was subjected to 5 mol% of catalyst $Pt(PPh_3)_4$ in the presence of an excess of sodium dimethyl malonate. For a direct comparison, the reaction was repeated with the corresponding Pd-catalyst, $Pd(PPh_3)_4$ (Scheme 2.12b). Performing the reaction at room temperature in THF, under both Pt and Pd catalytic systems, within 30 minutes product *syn*-**88** was afforded with complete retention of configuration, with the Pd-catalyst giving a higher yield than Pt (>99%

and 79%, respectively). This result confirmed the hypothesis of a double inversion mechanism for Pt-catalysed allylic alkylation.



Scheme 2. 12 Pt- and Pd-Catalysed Allylic Substitution of Lactone **87**

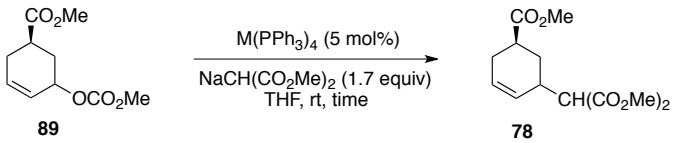
With the purpose of investigating the reactivity and selectivity of the process starting from different diastereomers, both *syn*- and *anti*-isomers of 5-(methoxycarbonyl)-2-cyclohexenyl methylcarbonate **89** were then tested. The synthesis of *syn*-**89** was carried out by methanolysis of the lactone **87**, followed by protection of the resulting alcohol *syn*-**90** with methyl chloroformate (Scheme 2.13a). For the formation of the isomer *anti*-**89,** a Mitsunobu reaction was carried out to invert the stereochemistry of alcohol *syn*-**90**, followed by deprotection of the product *anti*-**86** (Scheme 2.13b).



Scheme 2. 13 Synthesis of Stereochemical Probes *Syn*/*Anti*-**90**

In an analogous fashion to what was observed for lactone **87** (Scheme 2.12b), diastereomerically pure *syn*-**89** (dr >98:2) underwent substitution, under identical

conditions, yielding *syn*-**78** with comparable conversion and selectivity under Pd- and Pt-catalysis (Table 2.3, entries 1-2). Interestingly, when *anti*-**89** (dr 96:4) was subjected to the reaction conditions, the Pt-catalysed alkylation was significantly slower than Pd, affording 68% of *anti*-**78**, with unchanged diastereomeric ratio, after 16 h (Table 2.3, entry 3). Under Pd-catalysis *anti*-**89** showed similar reactivity to the *syn*-counterpart, however, *anti*-**78** was isolated with a lower diastereomeric ratio with respect to the starting material (dr 89:11, Table 2.3, entry 4). When TBAF was added to the reaction mixture in the attempt to increase the selectivity of the process, as previously observed for the Pd-catalysed alkylation reaction (Scheme 2.5),[42] no changes in diastereoselectivity was observed under Pt-catalysis. The only noticeable effect was a decreased reactivity of the system, which may be in part due to the deactivation of the malonate nucleophile by the presence of traces of water in the fluoride source. These observations suggested that both Pt- and Pd-catalysed substitutions are substrate-dependent, with Pt catalytic system being less reactive but more selective than Pd system for *anti* derivatives.



89 **78**

Entry	*Syn*:*anti*-**89**	Metal	Time (h)	Yield of **78**[a]	*Syn*:*anti*-**78**[b]
1	>98:2	Platinum	0.5	86%	>98:2
2	>98:2	Palladium	1	71%	97:3
3	4:96	Platinum	16	68%	4:96
4	4:96	Palladium	1	78%	11:89

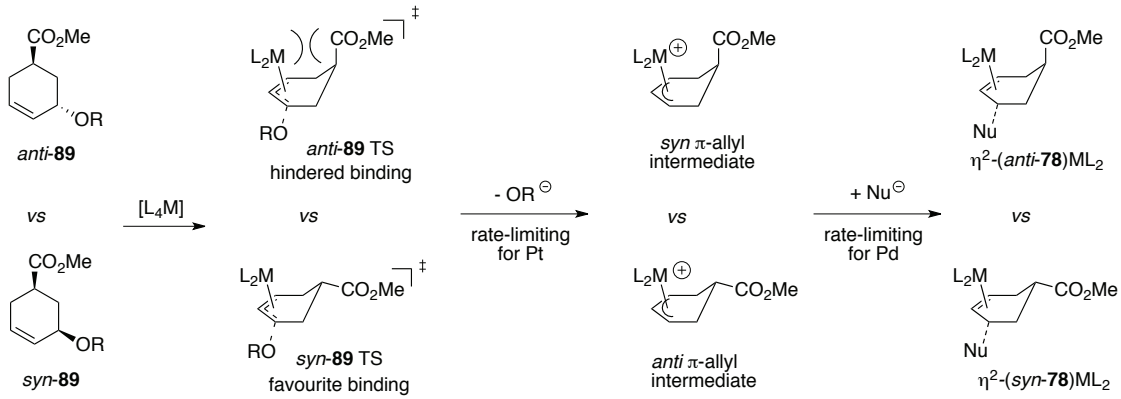
a.Isolated yields. *b*. *Syn/anti* ratio determined by ^{1}H NMR of the crude reaction mixture.

Table 2. 3 Pt- and Pd-Catalysed Allylic Substitution of *Syn*- and *Anti*-Carbonate **89**

2.3.3 Mechanistic Considerations

The contrasting behavior of the two transition metals under study was tentatively explained on the basis of different rate-limiting steps for the two catalytic mechanisms. Lloyd-Jones

and co-workers showed that with more reactive leaving groups, such as carbonate, the rate-limiting step for Pd-catalysis is normally the attack of the nucleophile to the π-allyl intermediate.[138] The partial loss of selectivity exhibited under Pd-catalysis may be due to epimerisation, promoted by a second Pd(0) centre, of the allyl intermediate.[118] The greater loss in stereochemical integrity for *anti*-**78** over *syn*-**78** may derive from the differing stability of the corresponding *syn*- and *anti*-allyl intermediates. The different lifetimes of the two π-allyl complexes may affect the ease of epimerisation, as reported by Bäckvall and co-workers.[118b] The different reactivity of *anti*-**89** and *syn*-**89** under Pt-catalysis suggests that the rate-limiting step for this transformation is the ionisation step, which leads to highly reactive π-allyl intermediates, inclined to undergo selective attack from the nucleophile, irrespective of their configuration.

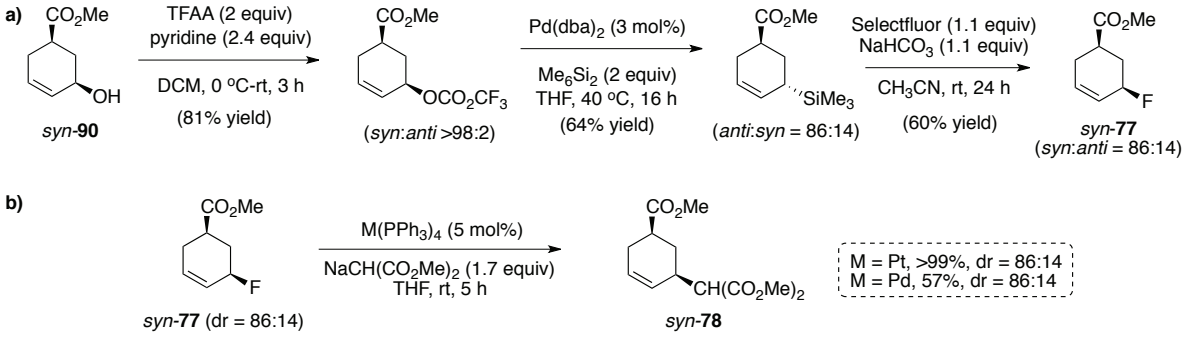


Scheme 2. 14 Postulated Rate Limiting Steps for Pt- and Pd-Catalysed Allylic Alkylation

2.3.4 Substitution of Allylic Fluoride *Syn*-77

The experimental work in this sub-section was conducted by M. Keita.[139] Having confirmed the double inversion pathway for Pt-catalysed allylic substitution of commonly used starting materials, we turned our attention to the reactivity and stereoselectivity of the model allylic fluoride *syn*-**77**, under both Pt and Pd catalysis. The synthesis of the cyclic allylic fluoride was carried out from *syn*-**90**, following the procedure previously reported within the group,[42] and affording **77** with good degree of diastereoselectivity (*syn*:*anti* = 86:14, Scheme 2.15a).

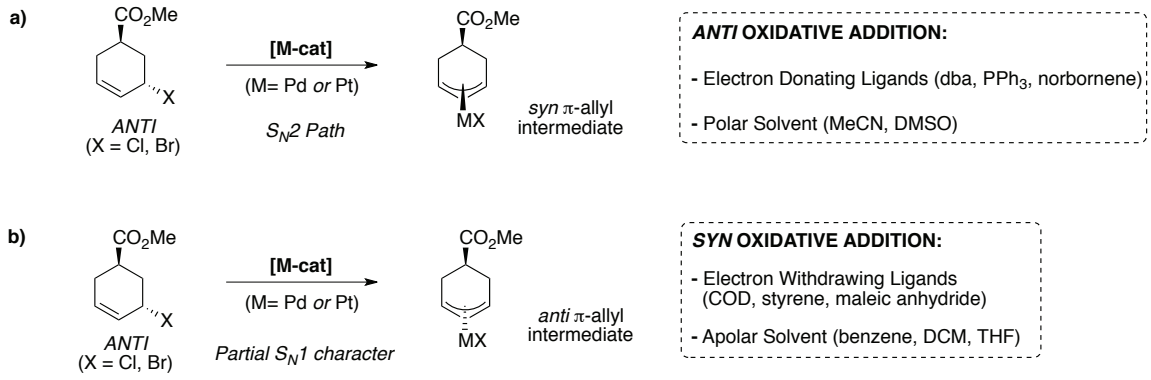
When the substrate was subjected to the conditions previously described for malonate substitution, full conversion into the product **78** (99%, *syn*:*anti* = 86:14) was observed under Pt-catalysis within 5 h (Scheme 2.15b). This result suggested that allylic fluorides are active substrates under Pt-catalysis, and that replacement of fluoride, with the soft nucleophile malonate, is occurring with overall retention of configuration, in line with other commonly used leaving groups. The lower conversion observed under Pd-catalysis (57%), when compared to that with Pt-catalyst (>99%), suggested a different reactivity of the allylic fluoride under the two catalytic systems. Starting material *syn*-**77** was recovered with unchanged diastereopurity, indicating it does not epimerise under palladium catalysis (Scheme 2.15b). The complete stereocontrol (**78**, *syn*:*anti* = 86:14) observed with $Pd(PPh_3)_4$ is unexpected, when compared to the results obtained with $[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$ as catalyst in DCM (Table 2.1, entries 1-3). There, product **78** was formed with a diastereomeric ratio of *ca.* 70:30, starting from different diastereomeric mixtures of fluoride **77**.[42] This difference in selectivity may depend on the solvent or on different electronic and steric properties of the ligands coordinated to the metal centre. This is in line with the preferred formation of the retention product *syn*-**78** starting from *syn*-**77**, when $[(\eta^3\text{-}C_3H_5)PdCl]_2$/biphep was employed as catalytic system (Table 2.1, entry 4).[42]



Scheme 2. 15 Pt- and Pd- Catalysed Allylic Substitution of Fluoride **77**

Kurosawa and co-workers observed a similar selectivity dependence of ligands and solvent, when they carried out an extensive study on Pd- and Pt-catalysed substitution of

the corresponding chloride and bromide derivatives of the model substrate **77**.[60a,140] Interestingly, they observed that electron-donating ligands increase the nucleophilicity of the metal centre, favouring an *anti*-attack to the allyl halide (Scheme 2.16a). The resulting ionic pair formed with inversion of configuration would be greatly stabilised/favoured by polar solvents. Conversely, electron-withdrawing ligands favour the coordination of the metal to the halide leaving group, inducing a *syn*-oxidative addition of the allylic derivative and hence the formation of the π-allyl intermediate with retention of configuration (Scheme 2.16b). Interestingly, it was observed that Pt complexes preferred the *anti*-addition to the allyl halides. Under Pt-catalysis the reaction was more sluggish when compared to the corresponding Pd-catalysis.



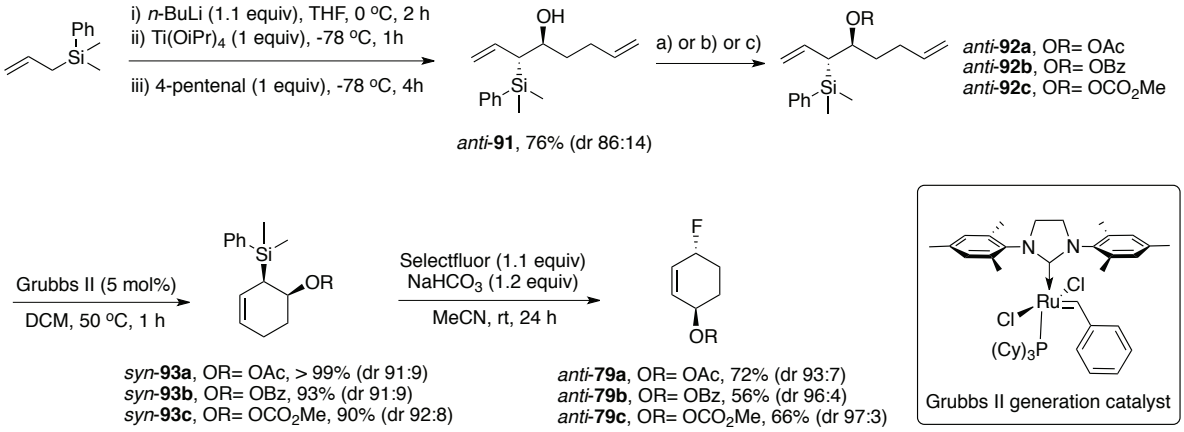
Scheme 2. 16 *Anti* and *Syn* Oxidative Addition of Pd and Pt Catalysts to Allylic Halides

2.4 Internal Competition Studies

The leaving group ability of fluoride *versus* other commonly used alternatives under Pt-catalysis was investigated, similarly to the earlier work involving Pd-catalysis. To this end, the previously described model substrates *anti*-**79a-c** (Table 2.2) were selected to carry out internal competition studies. To enable a direct comparison of reactivity and selectivity between the two catalytic systems, the substitution reactions were also performed with $Pd(PPh_3)_4$ under identical reaction conditions.

2.4.1 Synthesis of Cyclohexenyl Fluorides *Anti*-79a-c

The three model substrates *anti*-**79a-c** were synthesised *via* a method adapted from a procedure previously developed in the Gouverneur group (Scheme 2.17).[42,117] Treatment of dimethyl(phenyl) allylsilane with *n*BuLi, followed by Ti(O*i*Pr)$_4$ allowed the coupling with 4-pentenal to yield, with *anti*-selectivity, the β-hydroxyallylsilane **91**. The latter was isolated in 76% yield and with an *anti*/*syn* ratio equal to 86:14. Next, the alcohol *anti*-**91** was protected with the three competing leaving groups following standard procedures, yielding derivatives *anti*-**92a-c**, isolated with good diastreomeric ratio. A ring closing metathesis carried out with Grubbs second-generation catalyst in DCM for 1 h at 50 °C led to the formation of cyclic *syn*-β-alkoxyallylsilanes *syn*-**93a-c** in excellent yields and diastereocontrol. Fluorodesilylation of the cyclic allylsilanes was carried out in the presence of Selectfluor® and $NaHCO_3$ in MeCN for 24 h at room temperature, affording the corresponding fluorinated products *anti*-**79a-c** with inverted configuration in moderate yields and with excellent selectivity (dr up to 97:3).

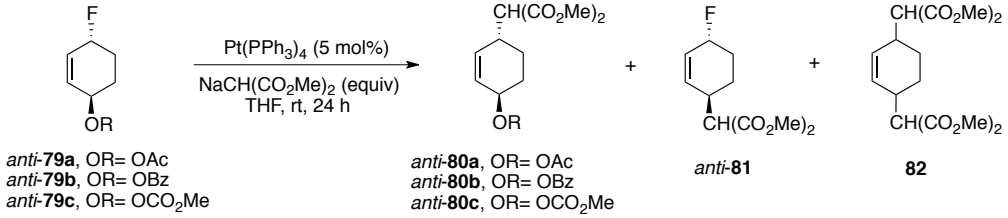


a) AcCl (2.5 equiv), pyridine (4 equiv), DCM, rt, 4 h (*anti*-**92a**, 79%, dr >98:2); b) BzCl (3 equiv), pyridine (4 equiv), DCM, rt, 24 h (*anti*-**92b**, 69%, dr > 98:2); c) methyl chloroformate (1.5 equiv), *n*BuLi (1.2 equiv), THF, -78 °C, 1 h (*anti*-**92c**, 62%, dr 94:6)

Scheme 2. 17 Synthesis of Model Substrates *Anti*-**79a-c**

2.4.2 Platinum Catalysis

The model substrates *anti*-**79a-c** were subjected to 5 mol% of $Pt(PPh_3)_4$ and an excess of sodium dimethyl malonate in THF at room temperature. The reactions were run until complete conversion of the starting material was observed (as determined by TLC), but no longer than 24 h (Table 2.4). In contrast to the studies carried out under Pd-catalysis, formation of both monosubstituted derivatives **80a-c** and **81**, in addition to the disubstituted derivative **82**, was observed for the substitution of all model substrates under Pt-catalysis.



Entry	SM	*Anti*:*syn* in **79**	Nu (eq)	Yield **80**[a]	*Anti*:*syn* in **80**[b]	Yield **81**[a]	*Anti*:*syn* in **81**[b]	Yield **82**[a]	*Anti*:*syn* in **82**[b]
1	**79a**	93:7	2	40%	86:14	5%	>98:2	9%	67:33
2	**79a**[c]	91:9	1.2	31%	91:9	14%	94:6	6%	33:67
3	**79b**	96:4	2	38%	75:25	11%	83:17	21%	91:9
4	**79b**	96:4	1.2	28%	83:17	13%	95:5	4%	67:33
5	**79c**	97:3	2	25%	83:17	11%	>98:2	64%	94:6
6	**79c**[d]	90:10	1.2	12%	86:14	8%	>98:2	12%	75:25
7	**79c**[e]	90:10	2	42%	87:13	15%	>98:2	43%	84:16

a.Isolated yields. *b*. *Anti:syn* ratio determined by ^{1}H NMR of isolated products. *c*. 4 h, *anti*-**79a** was recovered in 6% (*anti:syn* >98:2). *d*. 3 h, *anti*-**79c** was recovered in 25% (*anti:syn* = 75:25). *e*. Product distribution and *anti:syn* ratio ratios determined by quantitative ^{13}C NMR of the crude reaction mixture.

Table 2. 4 Platinum Catalysed Alkylation of *Anti*-**79a-c**

When acetate **79a** (*anti*:*syn* = 97:3) was subjected to 2 equivalents of sodium dimethyl malonate and the reaction mixture stirred for 24 h (Table 2.4, entry 1), *anti*-**80a** was isolated as major product (40%) with overall retention of configuration, but decreased diastereopurity (*anti*:*syn* = 86:14). *Anti*-**81** (5%), derived by displacement of acetate, was recovered as single diastereoisomer. These results proved the higher reactivity of fluoride over acetate under the described catalytic conditions. The disubstituted product **82** was

obtained in 9% yield with a significant leakage of stereoselectivity (*anti*:*syn* = 67:33). This may be due to the higher reactivity of the minor *syn*-isomers of intermediates **80a** and **81** towards the second substitution step. This discrepancy in reactivity between the two diastereoisomers is in accordance with our initial study carried out with model substrates *syn*- and *anti*-**89** under Pt-catalysis (Table 2.3, entries 1 and 3, respectively). The poor diastereopurity of **82** could also be partially due to an unselective displacement of the fluoride in both starting material *anti*-**79a** and intermediate *anti*-**81**.

In an attempt to avoid the formation of the second substitution product **82** and hence gain a better understanding of the diastereoselectivity of the C-F substitution process, the reaction with *anti*-**79a** was repeated employing 1.2 equivalents of nucleophile and quenched after 4 h (Table 2.4, entry 2). Unreacted **79a** was recovered in 6% yield as single diastereoisomer (*anti*:*syn* >98:2). Formation of **82** could not be avoided and was isolated in 6% yield, mainly as *syn* isomer (*syn*:*anti* = 67:33). This observation supported our hypothesis of the higher reactivity of minor *syn* isomers of intermediates **80** and **81** with respect to the major *anti* counterparts. As before, derivative **80a** (31%, *anti*:*syn* = 91:1) was formed in preference to **81** (14%, *anti*:*syn* = 94:6), and with unchanged diastereomeric ratio when compared to **79a** (*anti*:*syn* = 91:9).

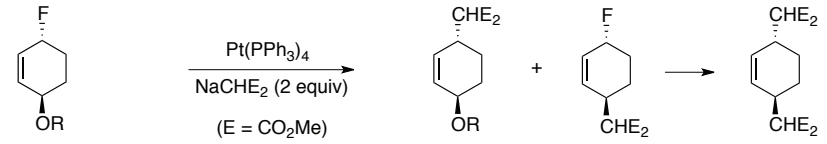
A comparable reactivity trend was also observed for benzoate **79b** (*anti*:*syn* = 96:4), when 2 equivalents of nucleophile were employed (Table 2.4, entry 3). Fluoride was displaced in preference to the competing leaving group, and all products isolated with overall retention of configuration, **80b** (38%, *anti*:*syn* = 75:25), **81** (11%, *anti*:*syn* = 83:17) and **82** (21%, *anti*:*syn* = 91:9). The higher conversion into disubstituted product **82**, obtained with *anti*-**79b** with respect to *anti*-**79a** (Table 2.4, entry 1), suggested that benzoate is more active than acetate towards substitution under Pt-catalysis, in agreement with reports on Pd-catalysis (Table 2.2).

When the reaction of *anti*-**79b** was repeated with 1.2 equivalents of sodium dimethyl malonate (Table 2.4, entry 4), lower conversion into **82** (4%, *anti*:*syn* = 67:33) was observed, which was isolated with a lower diastereomeric ratio, with respect to entry 3. The monosubstituted derivatives, **80b** (28%, *anti*:*syn* = 83:17) and **81** (13%, *anti*:*syn* = 95:5), were instead afforded with increased selectivity with respect to the reaction carried out with an excess of nucleophile (Table 2.4, entry 3).

Carbonate **79c** (*anti*:*syn* = 97:3) exhibited the highest reactivity among the substrates under study, yielding 64% of disubstituted derivative **82** (*anti*:*syn* = 94:6), when 2 equivalents of nucleophile were employed and the reaction left stirring for 24 h (Table 2.4, entry 5). Fluoride showed a slightly higher reactivity than carbonate, with **80c** isolated in 25% yield in comparison to 11% yield of **81**. Both substitutions occurred with overall retention of configuration, in particular for the formation of substrate **81** (*anti*:*syn* > 98:2). When 1.2 equivalents of nucleophile were employed and the reaction quenched after 3 h (Table 2.4, entry 6), 25% of **79c** was recovered with an eroded diastereomeric ratio (*anti*:*syn* = 75:25), with respect to the starting material (*anti*:*syn* = 90:10). This result, along with the lower diastereopurity of **82** (*anti*:*syn* = 75:25), with respect to that obtained in entry 5 (**82**, *anti*:*syn* = 94:6), are further evidence of the reactivity discrepancy between *syn* and *anti* diastereoisomers of **79c** and intermediates **80c** and **81**, respectively. Intermediates **80c** (12%, *anti*:*syn* = 86:14) and **81** (8%, *anti*:*syn* >98:2) were isolated in a ratio and selectivity comparable to that achieved in entry 5.

Due to the complexity of the crude reaction mixtures, the diastereomeric ratio of the products was determined after column chromatography. To validate the reliability of our analytical method, a quantitative ^{13}C NMR of the crude reaction mixture for the substitution of carbonate *anti*-**79c** was acquired (Table 2.4, entry 7). The result found was comparable with that obtained for the same reaction, after isolation of the products (Table 2.4, entry 6).

The product distribution observed for the substitution of the three model substrates, *anti*-**79a-c**, summarised in Scheme 2.18, allowed us to draw a reactivity trend under Pt-catalysis, as follows: F ≥ OCO_2Me >> OBz ≥ OAc, under the above described reaction conditions. In contrast to what was observed under Pd-catalysis (Table 2.2), the fluoride displayed the highest reactivity among the leaving groups tested. Moreover, higher stereocontrol in the displacement of fluoride was observed when Pt-catalyst was used in place of Pd-catalyst.

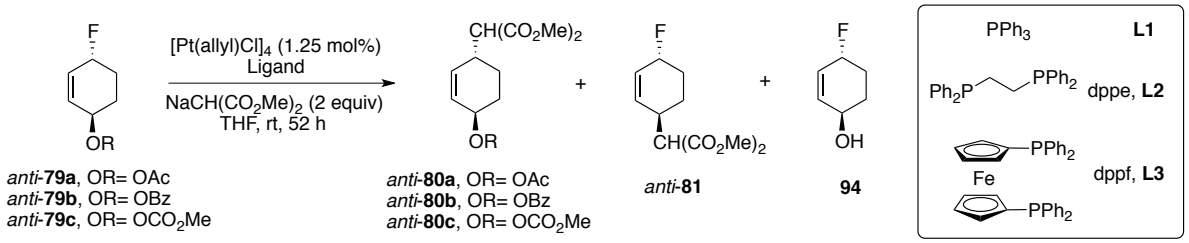


anti-**79a-c** **80a-c** **81** **82**

	Overall Yield:	Product Distribution (%):		
anti-**79a**, OR= OAc	54%	74	9	7
anti-**79b**, OR= OBz	70%	54	16	30
anti-**79c**, OR= OCO_2Me	>99%	25	11	64

Scheme 2. 18 Summary of Product Distribution in Pt-Catalysed Alkylation of *Anti*-**79a-c**

On the basis of the distinct selectivity afforded by different ligands under Pd-catalysis (Table 2.2, entries 3-4), a screening of Pt-catalysts was undertaken in an attempt to improve the reaction selectivity (Table 2.5). When the alkylation of substrates *anti*-**79a-c** was carried out with $[(allyl)PtCl]_4/PPh_3$, the resulting systems were less reactive when compared to the previous catalytic condition (Table 2.4), with no formation of the disubstituted product **82**, even after 52 h (Table 2.5, entries 1-3).



anti-**79a**, OR= OAc
anti-**79b**, OR= OBz
anti-**79c**, OR= OCO_2Me

anti-**80a**, OR= OAc
anti-**80b**, OR= OBz
anti-**80c**, OR= OCO_2Me

anti-**81**

94

Entry	SM	*Anti*:*syn* in **79**	**L**[a]	Recovered SM[b]	*Anti*:*syn* in **79**[c]	Yield **80**[b]	*Anti*:*syn* in **80**[c]	Yield **81**[b]	*Anti*:*syn* in **81**[c]
1	**79a**	93:7	**L1**	11%	>98:2	44%	89:11	4%	>98:2
2	**79b**	96:4	**L1**	66%	>98:2	--	--	--	--
3	**79c**	97:3	**L1**	63%[d]	91:9	4%	87:13	3%	>98:2
4[e]	**79a**	>98:2	**L2**	>99%	>98:2	--	--	--	--
5[e]	**79a**	>98:2	**L3**	>99%	>98:2	--	--	--	--

a. Pt:L ratio of 1:2 with **L1** and 1:1 with **L2** and **L3**. *b*. Isolated yields. *c*. *Anti*/*syn* ratio determined by ^{1}H NMR of isolated products. *d*. 14% of **94** (dr >98:2) was formed. *e*. 1.2 equiv of nucleophile and 24 h.

Table 2. 5 $[Pt(allyl)Cl]_4$ Catalysed Alkylation of *Anti*-**79a-c** with Alternative Ligands

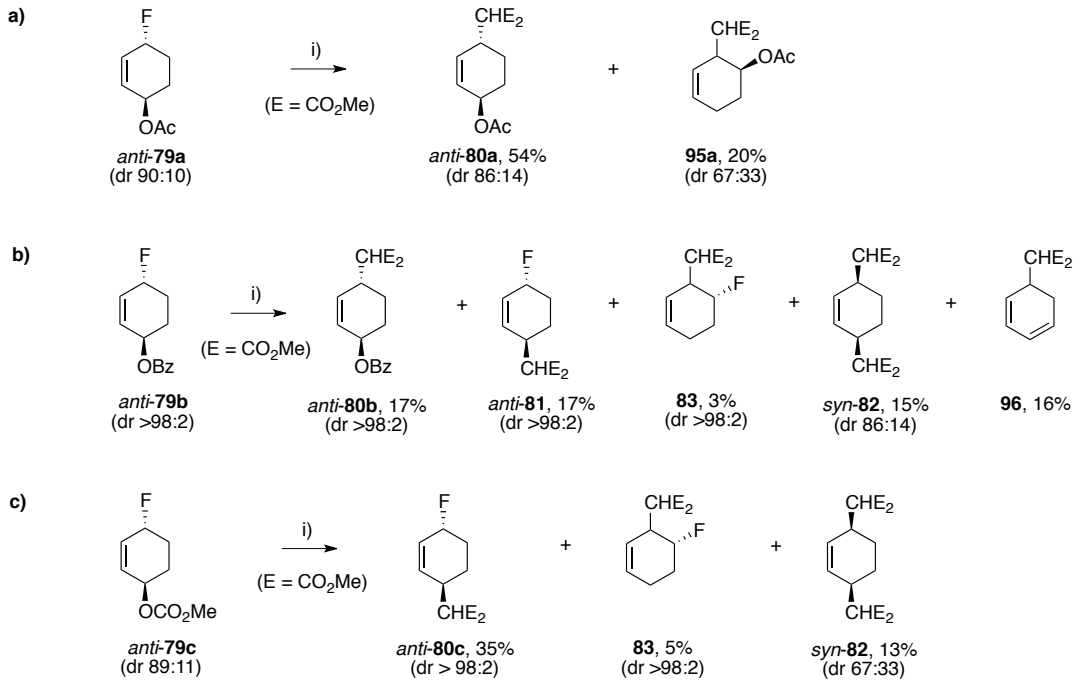
Starting from *anti*-**79a**, the major product formed was **80** (44%, *anti*:*syn* = 89:11), derived by displacement of the fluoride leaving group, with overall retention of configuration (Table 2.5, entry 1). This result was in line with that obtained employing $Pt(PPh_3)_4$ catalyst (Table 2.4, entry 1). For the reactions of *anti*-**79b** and *anti*-**79c**, mainly unreacted starting material was instead recovered (Table 2.5, entries 2-3).

Interestingly, formation of the alcohol derivative **94** (14%) was detected under the described conditions starting from carbonate *anti*-**79c**, which was tentatively assigned as the *anti* isomer (Table 2.5, entry 3). The low conversion into the monosubstituted products **80** and **81** discouraged further investigation with this catalytic system.

No reactivity was observed when the precatalyst $[(allyl)PtCl]_4$ was used in combination with bidentate ligands dppe and dppf (Table 2.5, entries 4-5). The unreacted starting material *anti*-**79c** was recovered with unchanged diastereomeric ratio. Therefore, $Pt(PPh_3)_4$, appeared to be optimal for this transformation.

2.4.3 Palladium Catalysis

In the previous report involving Pd-catalysis, the substitutions of *anti*-**79a-c** were carried out in DCM, employing 20 mol% of $[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$ as catalyst (Table 2.2). Due to the difference in the reaction conditions selected for Pt catalysis, the study under Pd catalysis was repeated, employing the optimised conditions for Pt-catalysis. When the reactions of the model substrates *anti*-**79a-c** were carried out with 5 mol% of $Pd(PPh_3)_4$ and 2 equivalents of sodium dimethyl malonate in THF, full conversion was observed after 1.5 h for the three systems (Scheme 2.19a-c).



i) $Pd(PPh_3)_4$ (5 mol%), $NaCH(CO_2Me)_2$ (2 equiv), THF, rt, 1.5 h.

Scheme 2. 19 Palladium Catalysed Alkylation of *Anti*-**9a-c**

The reactivity trend of the four leaving groups was consistent with the previous report (Table 2.2).[42] The fluoride was displaced in preference to acetate, but was less reactive than benzoate and carbonate (OCO_2Me > OBz ≥ F >> OAc). Interestingly, products *anti*-**80a-c** were isolated with almost complete retention of configuration, in contrast to what was found for the precedent Pd catalytic system (Table 2.2), and similarly to the results

obtained with $Pt(PPh_3)_4$ catalyst (Table 2.4). This observation confirmed that both solvent and ligands may play a role in the stereochemical outcome of the transformation, as previously reported for the substitution of allylic chlorides (Scheme 2.16).[60a,140]

The Pd-catalysed substitution of *anti*-**79a** and *anti*-**79c** is more chemoselective than in the analogous Pt-catalysed system (Table 2.4, entries 1 and 5). In the first case, exclusive displacement of fluoride was observed, yielding S_N2 and S_N2' products, **80a** and **95a**, respectively (Scheme 2.19a). Carbonate was instead substituted in preference, starting from *anti*-**79c**, to afford monosubstituted derivatives **80c** and **83** (Scheme 2.19c). Both monosubstituted products **80b** and **81** were isolated, when the reaction was performed with benzoate *anti*-**79b** (Scheme 2.18b). The substitution of both fluoride and competing leaving groups occurred with a lower level of regioselectivity with respect to the corresponding reactions under Pt-catalysis (Table 2.4), affording both S_N2 (**80** and **81**) and S_N2' products (**95** and **83**). Only the more reactive systems *anti*-**79b** and *anti*-**79c** led to formation of a small amount of disubstituted product **82** (15% and 13%, respectively), which was isolated mainly as *syn* isomer.

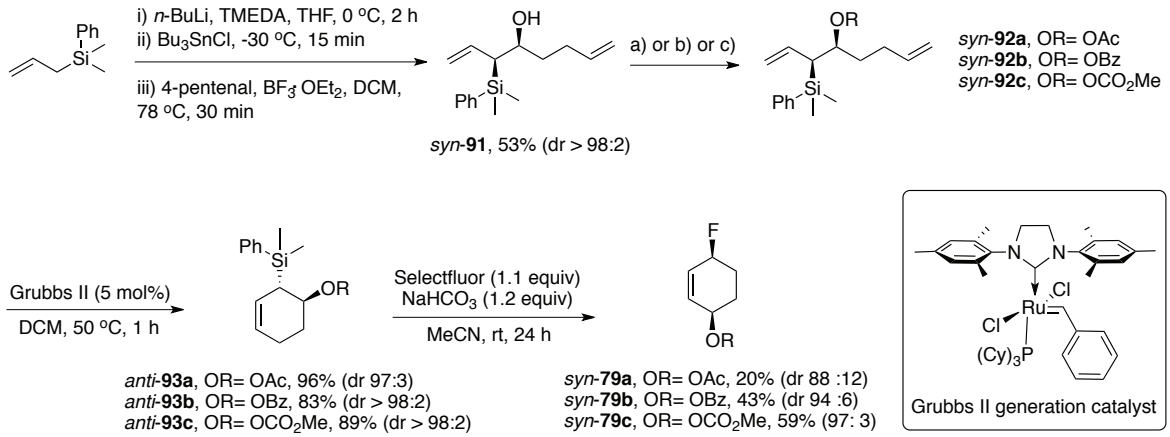
Reaction of derivative *anti*-**79b** led to the formation of 13% of diene **96**, likely derived from Pd-mediated β-hydride elimination of either intermediates **80b** or **81**. The origin of the differing reactivity profile of allylic fluorides under the two transition metal catalysis examined is still unclear.

2.5 Reactivity Comparison with *Syn*-Diastereoisomers

The diverse degree of reactivity observed for major *anti* isomers and *syn* counterparts in substrates **79a-c**, encouraged us to perform an analogous investigation with derivatives *syn*-**79a-c**. This new set of reactions will allow us to collect a comprehensive series of data, for a better understanding of the systems under study.

2.5.1 Synthesis of Cyclohexenyl Fluorides *Syn*-79a-c

The synthetic strategy for the preparation of *syn*-**79a-c** was identical with that developed for their *anti* counterparts (*anti*-**79a-c**, Scheme 2.17),[42] starting from the *syn*-γ-hydroxyallylsilane (*syn*-**91**) precursor. The latter was accessed employing as additive Bu_3SnCl in place of $Ti(OiPr)_4$, affording upon addition of 4-pentenal, **91** (53%, *syn*:*anti* >98:2), in moderate yield but excellent stereoselectivity.[141] Electrophilic fluorodesilylation of *anti*-allylsilanes **93a-c** was significantly less stereroselective than for the corresponding *syn*-**93a-c** derivatives, requiring careful silica gel column chromatography to isolate the corresponding fluorides *syn*-**79a-c** with good diastereopurity but poor yields.

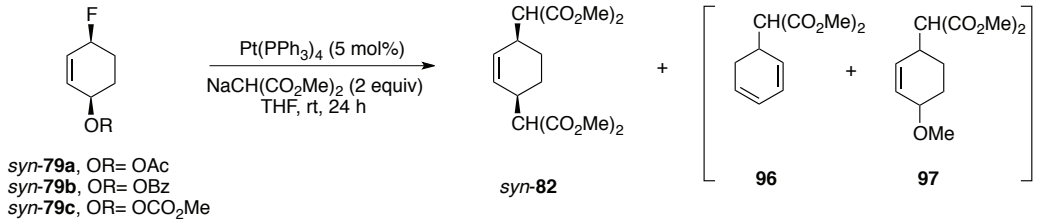


a) AcCl (2.5 equiv), pyridine (4 equiv), DCM, rt, 4 h (*syn*-**92a**, 71%, dr 98:2); b) BzCl (3 equiv), pyridine (4 equiv), DCM, rt, 24 h (*syn*-**92b**, 76%, dr > 98:2); c) methyl chloroformate (6 equiv), pyridine (6 equiv), DCM, rt, 48 h (*syn*-**92c**, 27%, dr 86:14)

Scheme 2. 20 Synthesis of Model Substrates *Syn*-**79a-c**

2.5.2 Platinum Catalysis

The outcome of the standard reactions under Pt-catalysis, with an excess of sodium dimethyl malonate (2 equiv), for isomers *syn*-**79a-c** are reported in Table 2.6. The disubstituted derivative **82** was the major product and isolated as single *syn*-isomer, suggesting a complete retention of configuration in the displacement of both fluoride and competing leaving groups.



syn-**79a**, OR= OAc
syn-**79b**, OR= OBz
syn-**79c**, OR= OCO_2Me

syn-**82**

Entry	SM	*Syn*:*anti* in **79**	Nu (eq)	Time (h)	SM **79**[a]	*Syn*:*anti* in **79**[b]	Yield **82**[c]	*Syn*:*anti* in **82**[d]	Yield[a] (**96**:**97**)[e]
1	**79a**	88:12	2	24	6%	88:12	39%	>98:2	7%
2	**79b**	94:6	2	24	19%	80:20	38%	>98:2	9%
3	**79c**	97:3	2	10	19%	>98:2	69%	98:2	6%
4	**79b**	67:33	1.2	3	34%	33:67	27%	>98:2	4%

a. Recovered starting material after reaction. *b*. *Syn*:*anti* ratios determined by ^{1}H NMR of recovered starting material. *c.* Isolated yields. *d*. *Syn:anti* ratios determined by ^{1}H NMR of isolated products. *e*. **96**:**97** ratio equal to 1:1 for all entries.

Table 2. 6 Platinum Catalysed Alkylation of *Syn*-**79a-c**

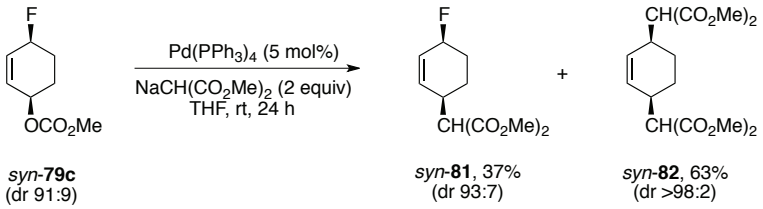
Here, conservation of stereochemistry is more pronounced than in the substitution of the corresponding isomers *anti*-**79a-c** (Table 2.4, entries 1, 3, 5). Unreacted starting material was recovered with unchanged diastereopurity for **79a** and **79c**, and with slightly decreased diastereomeric excess for **79b**. Interestingly, no monosubstituted derivatives **80a-c** or **81** were isolated, indicating their higher reactivity with respect to the *anti*-counterparts as well as to the corresponding starting materials, *syn*-**79a-c**. Two inseparable byproducts were also isolated from the crude reaction mixture in a ratio equal to 1:1, and tentatively assigned as diene **96** and ether **97**.

In an attempt to detect derivatives **80** and **81**, the reaction with benzoate **79b** (*syn*:*anti* = 67:33) was repeated with 1.2 equivalents of nucleophile and quenched after 3 h (Table 2.6, entry 4). A similar outcome to the previous reaction of entry 3 was, however, obtained. Starting material was recovered in 34% yield, mainly as *anti* diastereoisomer (*anti*:*syn* = 67:33), confirming the higher reactivity of *syn*-isomer towards substitution. Derivative **82** was isolated in 27% yield as single *syn* isomer, along with 4% of byproducts **96** and **97**

mixture. The impossibility to detect monosubstituted derivatives **80a-c** and **81** prevented us from determining a scale of reactivity between the competing leaving groups for *syn*-**79a-c**.

2.5.3 Palladium Catalysis

The reactivity of the *syn*-**79** derivatives was not investigated in the previous study under palladium catalysis, carried out within the group,[42] therefore the reaction of carbonate *syn*-**79c** was performed under our standard conditions with $Pd(PPh_3)_4$ catalyst. In contrast to platinum catalysis (Table 2.4, entry 3), complete conversion of the starting material was observed after 24 h, with **82** being the major derivative formed (63%). Only the *syn* diastereoisomer of **82** was formed, in contrast to the stereochemical erosion observed for the formation of *anti*-**82**, starting from *anti*-**79c**, under identical reaction conditions (Scheme 2.19c). This may suggest that the higher reactivity of *syn*-**79c** over *anti*-**79c**, towards addition of the malonate nucleophile, leads to a lower level of epimerisation.



Scheme 2. 21 Palladium Catalysed Alkylation of *Syn*-**79c**

Monosubstituted product **81** was isolated in 37% yield, demonstrating the higher reactivity of carbonate with respect to fluoride under palladium catalysis, irrespective of the relative stereochemistry of **79c**. These results also suggested that *syn*-**79a-c** model substrates are more reactive and selective systems than their *anti*-counterparts.

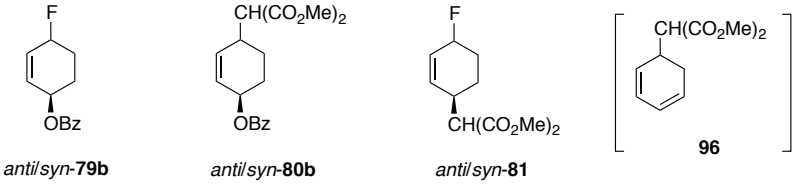
2.6 Further Competition Experiments and Kinetic Studies

Due to the complexity of the product distribution in the Pt-catalysed reaction of *anti*-**79a-c**, and the inconclusive results, in terms of leaving group reactivity, obtained for the

investigation with *syn*-**79a-c**, a series of additional competition studies were carried out. These experiments would provide a clearer picture of the selectivity and reactivity of the process.

2.6.1 Tests for Competing Epimerisation

Both *anti*- and *syn*-isomers of the starting material **79b** and monosubstituted products **80b** and **81** were subjected to 5 mol% of $Pt(PPh_3)_4$ in the absence of sodium dimethyl malonate. The reaction mixtures were left stirring for 24 h, in an attempt to verify whether epimerisation of these derivatives occur under the reaction conditions (Table 2.7).



anti/*syn*-**79b** *anti*/*syn*-**80b** *anti*/*syn*-**81**

Entry	Substrate	Substrate *anti*:*syn* ratio	Recovered substrate[a]	Recovered substrate *anti*:*syn* ratio[a]	Diene **96** yield
1	**79b**	96:4	>99%	96:4	0%
2	**79b**	20:80	>99%	25:75	0%
3	**80b**	>98:2	>99%	>98:2	0%
4	**80b**	<2:98	86%	17:83	14%
5	**81**	>98:2	>99%	>98:2	0%
6	**81**	8:92	0%	--	>99%

Reaction conditions: Substrate, $Pt(PPh_3)_4$ (5 mol%), THF, rt, 24 h. *a*. Conversion and dr determined by ^1H NMR of the crude reaction mixture.

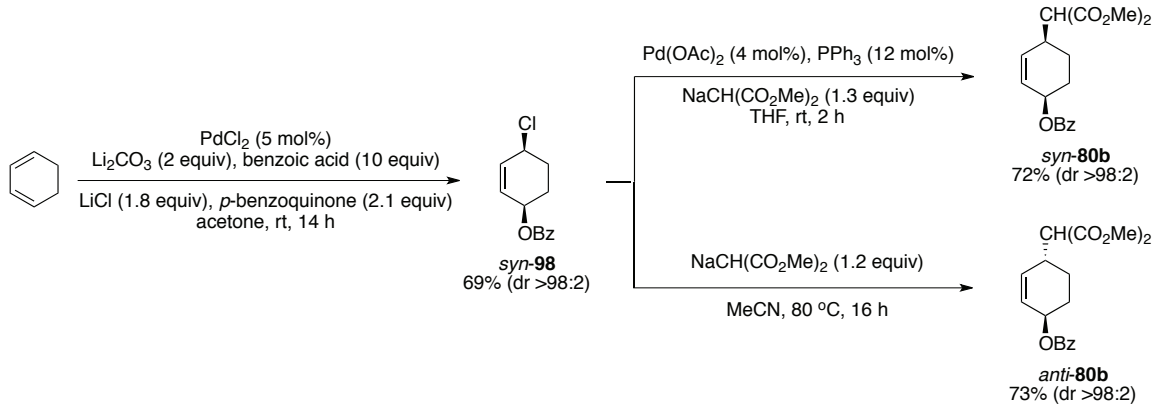
Table 2. 7 Competing Epimerisation Test under Pt-Catalysis

Interestingly, whilst derivative *anti*-**79b** was recovered with unchanged diastereomeric ratio, *syn*-**79b** showed partial epimerisation under identical conditions (Table 2.7, entries 1-2). A similar trend was also observed for derivatives **80b** and **81**, with the *anti*-isomers recovered with complete retention of diastereomeric ratio (Table 2.7, entries 3-6). Substrate *syn*-**80b** (dr >98:2) was partially degraded into diene **96**, and recovered in 86% yield with significant erosion of its diastereomeric ratio (*syn*:*anti* = 83:17, Table 2.7, entry 4). *Syn*-**81** showed to

be far more reactive towards the side reaction into diene **96**, which was the only product detected for this reaction (Table 2.7, entry 6). The latter results suggest that the formation of diene **96**, in the reactions carried out with substrates *syn*-**79a-c**, derives from a Pt-mediated β-hydride elimination of intermediates **80b** and **81** (Table 2.5).

2.6.2 Reactivity of *Syn* and *Anti* Isomers of Intermediate 80b

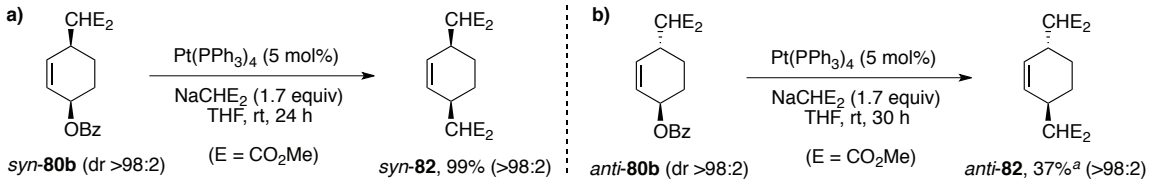
In order to verify the relative reactivities towards Pt-catalysed alkylation of the two epimers of intermediate **80b**, both were synthesised independently following a literature procedure (Scheme 2.22).[142] The two diastereomers were accessed from the common intermediate chloride *syn*-**98**, which was afforded, with excellent selectivity, *via* palladium(II)-catalysed *cis*-1,4-chlorobenzyloxylation of 1,3-cyclohexadiene. Dimethyl malonate substitution of *syn*-**98**, *via* either Pd-catalysed alkylation or S_N2 displacement, afforded *syn*-**80b** and *anti*-**80b** products, respectively, in good yields and with excellent diastereoselectivity.



Scheme 2. 22 Synthesis of Diastereoisomers *Syn*-**80b** and *Anti*-**80b**

Isomers *syn*-**80b** and *anti*-**80b** were subjected to 1.7 equivalents of malonate nucleophile in the presence of 5 mol% of $Pt(PPh_3)_4$ in THF at room temperature (Scheme 2.23). As expected, *syn*-**80b** was more reactive than the *anti* counterpart, as it was fully converted within 24 h into *syn*-**82**. After 30 h, only 37% of *anti*-**82** was formed, starting from *anti*-**80b**, with the unreacted starting material recovered with unchanged diastereomeric ratio. Both products *syn*- and *anti*-**82** were formed with complete retention of configuration, in line with

our previous investigation on the stereocontrol of Pt-catalysed alkylation of alcohol derivatives (Table 2.3).

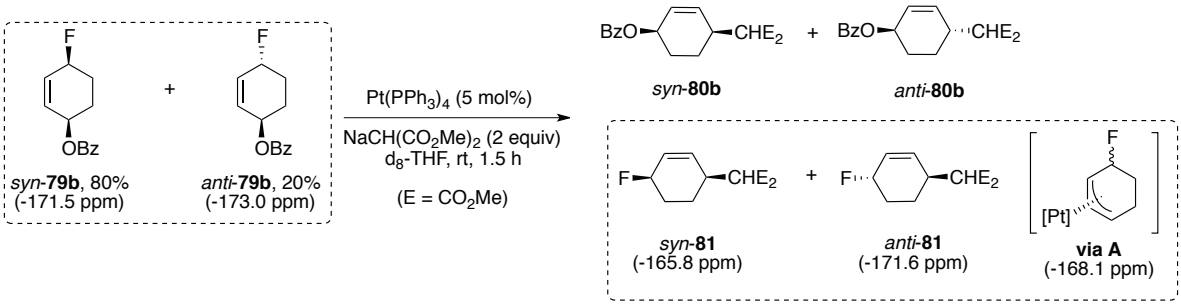


a. Anti-**80b** was recovered in 63% (dr >98:2).

Scheme 2. 23 Reactivity and Stereoselectivity Investigation on Alkylation of Intermediate **80b**

2.6.3 Kinetic Studies

With the aim of obtaining more information on the reactivity of intermediate *syn*-**81** in the Pt-catalysed substitution of *syn*-**79** derivatives, the alkylation of **79b** (*syn*:*anti* = 80:20) was monitored over time by ^{19}F NMR spectroscopy. To this end, the reaction was carried out in d_8-THF in a NMR tube and ^{19}F NMR spectra recorded every 5 minutes over 1.5 h (Scheme 2.24).



Scheme 2. 24 Pt-Catalysed Substitution of **79b** Monitored by ^{19}F NMR

The peak of *syn*-**79b** (-171.5 ppm) disappeared more rapidly than the minor *anti* isomer peak at -173.0 ppm (Chart 2.1), consistent with the experimental observations described previously (Table 2.4, entry 2 and Table 2.3, entry 3, respectively). Formation of *syn*-**81** (-165.8 ppm) was detected only after 50 min and it was never more intense than 1% of the total integral. This observation confirms the high propensity of this intermediate towards

conversion into the disubstituted product **82**, in line with previous results (Table 2.6, entry 2). The peak of *anti*-**81** at -171.6 ppm was detected from the onset of the reaction with a slightly increasing concentration over time (from 0.5% to 2.1%). An additional weak signal at -168.1 ppm was also observed, not accountable for any of the known intermediates. We postulated that this transient species may be attributed to the platinum allyl-intermediate **A**, generated by displacement of the benzoate group in **79b**.

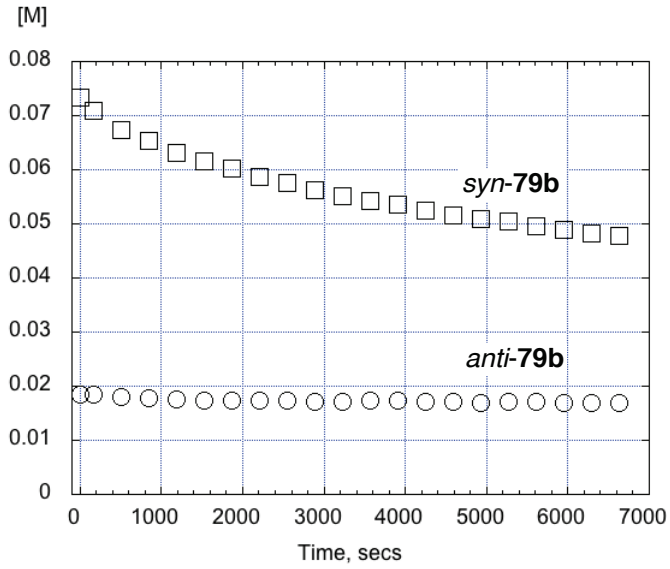


Chart 2. 1 Relative Concentrations of *Syn*-**79b** and *Anti*-**79b** Determined by ^{19}F NMR

This experiment confirmed our hypothesis on the higher reactivity of intermediate *syn*-**81** with respect to its *anti* counterpart under Pt-catalysis, explaining the difficulty in its isolation. However, the absence of fluorine in derivative **80b** prevents us from assigning the relative reactivity between those two competing intermediates, in this reaction. As previously stated, the ^{1}H NMR spectra of the reaction mixtures were too complex to gather any useful information.

2.7 Configuration Assignment and Conformational Analysis

In order to determine the preferred conformation and validate the configuration of new cyclohexenyl compounds, a series of 1D and 2D NMR spectroscopic analysis was undertaken.

NOE (Nuclear Overhauser Effect) and HOESY (Heteronuclear Overhauser Effect Spectroscopy) experiments were performed on acetate *syn*-**79a** and benzoate *syn*-**79b**, in a similar fashion to what has previously been done with the carbonate analogue *syn*-**79c**.[42] In both cases, NOE data showed a diaxial relationship between H_1 and H'_3, that are consistent with the equatorial position of fluoride. Further support came from the HOESY between the F and H'_2, which indicates the F and H'_2 *syn*-relationship. The axial-equatorial relationship between H'_3 and H_4, strongly suggested that substituents acetate and benzoate are *syn* with respect to fluoride, preferring the axial position (Figure 2.1).



Figure 2. 1 Conformational Analysis of Starting Materials *Syn*-**79a** and *Syn*-**79b**

NOESY (Nuclear Overhauser Effect Spectroscopy) data for *anti*-**80c** suggested that malonate substitution has taken place *anti* to the carbonate functionality, as expected. The NOESY between H_1 and H'_3 and between H'_2 and H_4 were consistent with a diaxial relationship between the pairs. Further validation was provided by the large coupling constant of 13.9 Hz observed between H'_2 and H_1 and between H'_2 and H'_3. From these studies, the conformation, where malonate and carbonate are disposed *anti*, both in equatorial positions, was proposed for *anti*-**80c** (Figure 2.2).

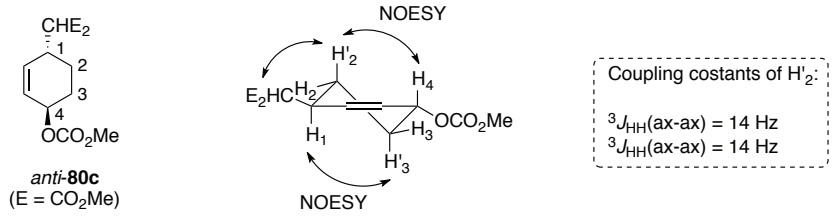


Figure 2. 2 Conformational Analysis of Product *Anti*-**80c**

The configuration of intermediate *anti*-**93c** was determined by NOE analysis, to assign unambiguously the sense of diastereoselectivity in the synthesis of allylic fluordes *syn*-**79a-c**. NOE between H'_3 and the substituents at the silicon centre suggested a Si-H_3' diaxial relationship. The NOE data also showed that H_1 and H_2 occupy *trans* equatorial positions. These observation suggested that the carbonate substituent is in axial position, and therefore *anti* with respect to $SiMe_2Ph$ (Figure 2.3).

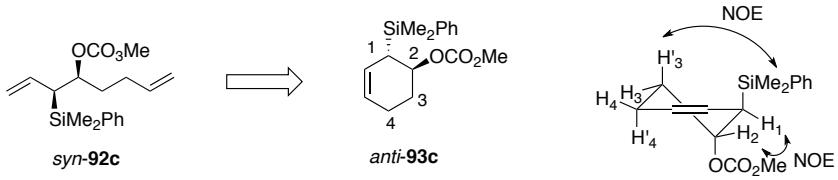


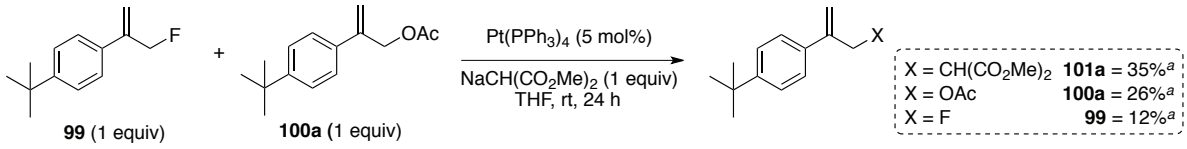
Figure 2. 3 Conformational Analysis of Intermediate *Anti*-**93c**

2.8 Survey of the Scope of Pt-Catalysed Substitution of Allylic Fluoride

2.8.1 External Competition Experiment under Pt-Catalysis

In order to validate the scale of reactivity under platinum catalysis determined for substrates *anti*-**79a-c**, an external competition experiment was performed between allylic fluoride **99** and the allyl acetate **100a**. This particular allylic moiety was selected, as the absence of protons in the β-position would avoid any byproduct derived from β-hydride elimination. In addition no regioisomers can be formed. Moreover, fluoride **99** has been proven to be a non-volatile and stable substrate under purification procedures.[63] The experiment was performed under $Pt(PPh_3)_4$ catalysis, employing 1 equivalent of a 1:1

mixture of **99** and **100a** and 1 equivalent of sodium dimethyl malonate, respectively (Scheme 2.25). After 24 h, the substituted product **101a** was isolated in 35% yield, along with unreacted **99** (12%) and **100a** (26%). The relative percentage of recovered starting materials indicated the preferential substitution of allylic fluoride with respect to the corresponding acetate, in line with the results on the internal competition carried out with substrate *anti*-**79a** (Table 2.4, entries 1-2).

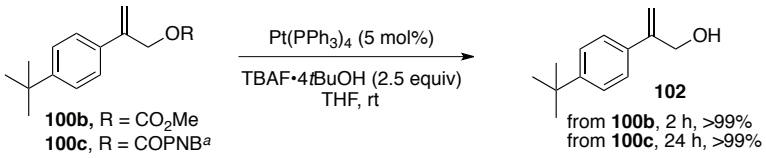


a. Isolated product and unreacted starting materials.

Scheme 2. 25 External Competition Experiment under Pt-Catalysis

2.8.2 Attempt of Pt-Catalysed Allylic Fluorination

From the previous work within the group, based on the significant difference in reactivity between allylic carbonates and fluorides, a Pd-catalysed fluorination was developed using allylic carbonates as starting materials. By contrast, from our data on the leaving group propensity under Pt-catalysis, no leaving group is clearly more reactive than fluoride. Unsurprisingly, attempts to synthesise allylic fluoride **99** from both carbonate **100b** and *p*-nitrobenzoate **100c** under $Pt(PPh_3)_4$ catalysis were unsuccessful. Full conversion into the corresponding alcohol byproduct **102** was instead achieved within 2 h for **100b** and 24 h for **100c** (Scheme 2.26). We concluded that Pt-catalysed allylic fluorination is highly disfavoured under the selected reaction conditions.

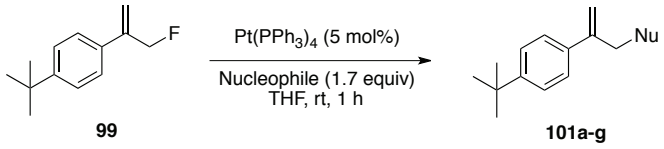


a. Compound kindly provided by C. Hollingworth.[143]

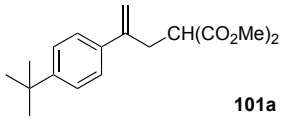
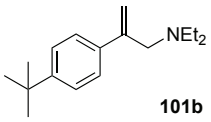
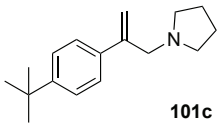
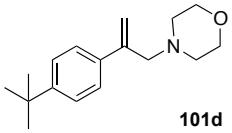
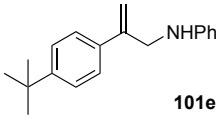
Scheme 2. 26 Attempts for Pt-Catalysed Fluorination of Allylic Carbonate

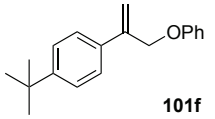
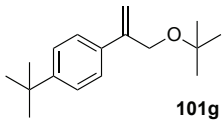
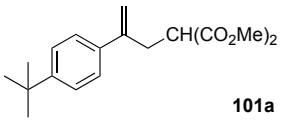
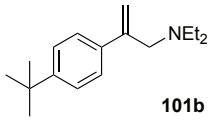
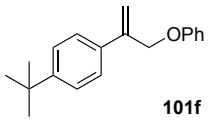
2.8.3 Substrate Scope for Pt-Catalysed Substitution of Allylic Fluoride 99

The experimental work in this sub-section was conducted by M. Keita.[139] Given the extraordinary reactivity that allylic fluorides showed under Pt-catalysis, we decided to investigate their potential in Tsuji-Trost reactions. As a test of generality, the reactivity of allylic fluoride **99** under Pt-catalysis was tested with a variety of nucleophiles (Table 2.8). Interestingly, not only malonate but also N- and O-nucleophiles were effective, affording the corresponding products **101a-g** in excellent yields within 1h at room temperature (Table 2.8, entries 1-7). The reaction of primary amines and O-nucleophiles required a higher temperature (50 °C) and longer reaction times to achieve the corresponding products **101e-g** in moderate to excellent yields (Table 2.8, entries 5-7).



99 **101a-g**

Entry	Nucleophile	T (°C)	Time (h)	Product **101a-f**	**101** yield%[a]
1	$NaCH(CO_2Me)_2$	rt	1	 **101a**	91
2	Et_2NH	rt	1	 **101b**	92
3	pyrrolidine	rt	1	 **101c**	90
4	morpholine	rt	1	 **101d**	83
5	$PhNH_2$	50	16	 **101e**	72

6	PhONa	50	4	 **101f**	99
7	*t*BuONa	50	16	 **101g**	38
8[b]	$NaCH(CO_2Me)_2$	rt	1	 **101a**	>99[c]
9[b]	Et_2NH	rt	1	 **101b**	>99[c]
10[b]	PhONa	50	4	 **101f**	>99[c]

a. Isolated yields. *b.* Reaction run with $Pd(PPh_3)_4$ (5 mol%). *c*. Conversion determined by ^1H NMR of the crude reaction mixture.

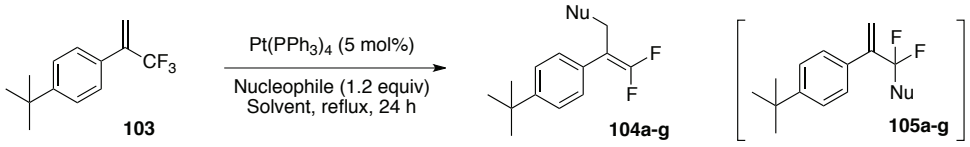
Table 2. 8 Substrate Scope of Pt-Catalysed Substitution of Allylic Fluoride **99**

A control reaction was conducted in the absence of catalyst with sodium dimethyl malonate, diethyl amine and phenoxide as test nucleophiles. Leaving the reaction stirring at room temperature for 16 h in the first two cases and at reflux for 7 h in the latter, only unreacted starting material **99** was recovered, proving that the transformation proceeds only through Pt catalysis. When allylic fluoride **99** was subjected to the standard conditions with the three test nucleophiles, employing $Pd(PPh_3)_4$ as catalyst in place of $Pt(PPh_3)_4$, similar conversions into the expected products **101a-b** and **101f** were observed (Table 2.8, entries 8-10).

2.8.4 Pt-Catalysed Substitution of α-(Trifluoromethyl)styrene 103

Inspired by Paquin's study on the Pd-catalysed amination of allylic difluoropropane derivatives to access the corresponding functionalised fluoroalkenes (Chapter 1, Section 1.3.2),[44] and based on the high reactivity that allylic fluorides exhibited under Pt-catalysis, we began an investigation on a Pt-catalysed functionalisation of α-(trifluoromethyl)styrene

derivative **103** (Table 2.9). The experimental work in this sub-section was conducted by M. Keita.[139] The displacement of one or two allylic C-F bonds would lead to the formation of difluoro- or monofluorinated derivatives, useful fluorinated building blocks.



Entry	Nucleophile	Solvent	Product	Conversion (%)[a]	**104** Yield (%)[b]
1	pyrrolidine	THF	**104a**	0	--
2	morpholine	THF	**104b**	0	--
3	$PhNH_2$	THF	**104c**	0	--
4	PhONa	THF	**104d**	0	--
5	PhC_2H_4ONa	THF	**104e**	0	--
6	$PhSO_2Na$	DMSO	**104f**	0	--
7	$NaCH(CO_2Me)_2$	THF	**104g**	50	30
8	$NaCH(CO_2Me)_2$[c]	THF	**104g**	50	30

a. Conversion determined by ^1H NMR of the crude reaction mixture. *b*. Isolated yield. *c*. Reaction run in the absence of the catalyst

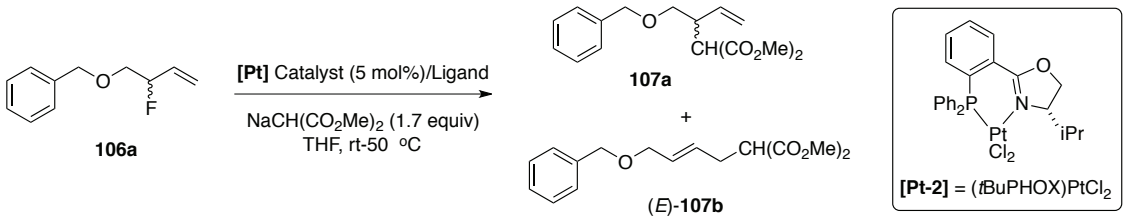
Table 2. 9 Pt-Catalysed C-F Bond Activation in α-(Trifluoromethyl)styrene Derivative

When substrate **103** was subjected to standard conditions with a variety of N- and O-nucleophiles in refluxing THF, after 24 h only starting material was recovered (Table 2.9, entries 1-5). No conversion of the starting material was observed with $PhSO_2Na$ as nucleophile, running the reaction at 70 °C in DMSO (Table 2.9, entry 6). These results are in line with the higher energy of the C-F bond in a trifluoromethyl group (114.6 kcal/mol in CHF_3) than in monofluoromethyl groups (107 kcal/mol in CH_3F). However, when the sodium salt of dimethyl malonate was tested as nucleophile in THF, 50% of conversion into the S_N2' product **104g** was observed, which was isolated in 30% yield (Table 2.9, entry 7). No traces of the S_N2 product **105g** were detected. Interestingly, when the control reaction in the absence of catalyst was performed, product **104g** was formed with an identical conversion, proving that the substitution does not occur through Pt-catalysis. These results

discouraged us to proceed in the investigation of the derivatisation of α-(trifluoromethyl)styrene derivatives.

2.8.5 Kinetic Resolution of Branched Allylic Fluoride 106a

The experimental work in this sub-section was conducted by M. Keita.[139] The synthesis of enantiopure allylic fluorides is highly desirable, however, to date only one method, based on a Pd-catalysed asymmetric fluorination of allylic derivatives, has been reported.[57,62] Driven by this lack in the literature, we reasoned that, by employing a chiral ligand at the Pt-centre, kinetic resolution of racemic branched allylic fluorides may afford enantiomerically enriched allylic fluorides.



Entry	Pt Catalyst	Ligand[a]	T (°C)	Time (h)	Ratio **107a**:**107b**[b]	**107** Yield[c]
1	$Pt(PPh_3)_4$	--	rt	1	< 2:98	89%
2	$[(C_3H_5)PtCl]_4$	*t*Bu-PHOX	50	24	--[d]	--
3	**[Pt-2]**	*t*Bu-PHOX	50	24	--[d]	--

a. Ratio Pt:L = 1:1. *b*. Ratio determined by ^{1}H NMR of the crude reaction mixture. c. Isolated yield. *d*. Fully recovered **106a**.

Table 2. 10 Pt-Catalysed Kinetic Resolution of Non Cyclic Branched Fluoride

Firstly, allylic fluoride **106a**[144] was subjected to the standard reaction conditions with sodium dimethyl malonate as nucleophile, to assess its suitability as a substrate (Table 2.10, entry 1). Full conversion into linear isomer (*E*)-**107b**, isolated in 89% yield, was observed within 1 h at room temperature. No traces of branched product **107a** or byproduct diene, derived from β-hydride elimination, were detected in the crude reaction mixture. The use of chiral PHOX ligands for the asymmetric allylic alkylation, under both Pd- and Pt-catalysis, is well established in the literature.[145] Based on these precedents, the alkylation

of fluoride **106a** was repeated employing the pre-catalyst $[(C_3H_5)PtCl]_4$ in combination with chiral ligand *t*Bu-PHOX. Under these conditions, the reaction did not proceed and **106a** was fully recovered after 24 h at 50 °C. An identical outcome was also observed, when the preformed complex **[Pt-2]** was employed, with addition of *t*Bu-PHOX ligand to stabilise the catalyst. These results confirmed that the activation of the substrate is highly dependent on the nature of the ligand at the metal centre. None of the (P,P)- or (P,N)-bidentate ligands tested for Pt-catalysis showed reactivity under the selected reaction conditions.

2.9 Conclusions

In conclusion, an extensive comparative study on the reactivity and selectivity of platinum and palladium catalysed allylic substitution indicated important differences in their behavior, under comparable reaction conditions. We have experimentally confirmed that Pt-catalysed alkylation of conventional allylic derivatives occurs with overall retention of configuration, with slightly higher stereochemical integrity than for palladium. Under Pt-catalysis *syn*- and *anti*-isomers of carbonate **89** showed a significant difference in reactivity, suggesting that the rate-limiting step for this transformation may be the formation of the π-(allyl)Pt intermediate, rather than the nucleophilic attack on the allyl species. Based on a previous report on the investigation of reactivity of allylic fluoride among other commonly used leaving groups under Pd-catalysis,[42] a similar investigation was undertaken under Pt-catalysis. Employing model substrates *anti*-**79a-c**, we found the relative reactivity to be F ≥ OCO_2Me >> OBz ≥ OAc. This stands in contrast to the results obtained under Pd-catalysis, where carbonate and benzoate exhibited superior reactivity to fluoride. The favoured stereochemical outcome in the displacement of the fluoride is an overall retention of configuration for both Pt- and Pd-catalysts. This result is in contrast to the leakage of stereochemistry observed in the prior report, when the reaction under Pd-catalysis was carried out in DCM. Reactions with the corresponding *syn*-isomers of the model substrates,

syn-**79a-c**, showed higher reactivity and an increased level of stereoselectivity in the substitution of the allylic C-F bond, under both Pt- and Pd-catalysis, in agreement with previous data obtained for the Pt-catalysed substitution of carbonate *syn*-**89**.

On the basis of the high reactivity of allylic fluorides under Pt catalysis, we concluded that the reverse reaction of allylic fluorination under Pt-catalysis will be highly challenging, in contrast to what has been achieved with palladium catalysis.[42] Some preliminary experiments with allylic carbonate **100b** and *p*-nitrobenzoate **100c** under Pt-catalysed fluorination conditions reinforced this view, and the desired fluoride **99** was not detected. The high reactivity of allylic C-F bond was further investigated by M. Keita,[139] by carrying out the substitution with a variety of N- and O-nucleophiles, affording the corresponding products in excellent yield.

Chapter 3

Iridium Catalysed Allylic Fluorination

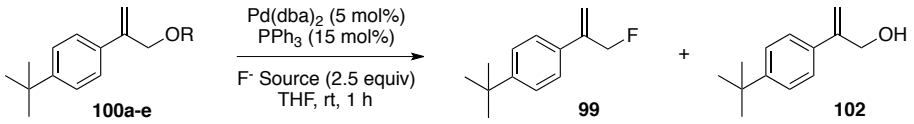
3.1 Introduction

The longstanding interest of the Gouverneur group in the synthesis of allylic fluorides encouraged us to expand the synthetic strategies to access this important class of fluorinated building blocks. The possibility to use a transition metal catalysed fluorination reaction, starting from readily accessible precursors, in a similar fashion to a Tsuji-Trost substitution, was highly desirable. Indeed, the use of a catalytic process would allow direct access to highly functionalised allylic fluorides, under mild reaction conditions and with excellent regio- and stereoselectivity. However, the use of nucleophilic sources of fluorine presents several challenges to be overcome, such as the high degree of solvation and the Brönsted basicity, which competes with the nucleophilic character. In a preliminary report, Togni and co-workers suggested that the allylic fluorination reaction is thermodynamically disfavoured, based on their unsuccessful attempts.[40] Building on this study, previous work within the group showed that allylic fluorides are suitable substrates for Pd- and Pt-catalysed alkylation reactions (Chapter 2). Critically, a scale of leaving group ability was established by internal competition experiments under the two catalytic systems. Fluoride showed the highest reactivity under Pt-catalysed substitution conditions, discouraging to proceed with the investigation on the reverse reaction of allylic fluorination. By contrast, the results obtained under Pd-catalysis indicated that carbonate and benzoate are more reactive leaving groups than fluoride, suggesting the feasibility of a Pd-catalysed fluorination reaction. Encouraged by these observations, an investigation on the nucleophilic fluorination of allylic alcohol derivatives under palladium catalysis was initiated within the group.

3.2 Background Work on Pd-Catalysed Allylic Fluorination

3.2.1 Optimisation and Scope

This section provides a summary of the results carried out previously within the group.[63,143,42b] Building on previous investigations, a highly activated starting material, such as allylic methyl carbonate, was selected for the initial study. The use of 2-(4-(*tert*-butyl)phenyl)allyl methyl carbonate **100b** as model substrate, due to the absence of hydrogen in β-position, would avoid competitive side reactions, promoted by fluorinating agents with marked Brønsted basicity. A screening of fluorinating agents was carried out with carbonate **100b**, employing 5 mol% of $Pd_2(dba)_3$ as pre-catalyst with 15 mol% of PPh_3 ligand, in THF at room temperature (Table 3.1).



100a-e **99** **102**

Entry	Substrate **100**	OR	F^- Source	Ratio **100**:**99**:**102**	Yield **99** (%)[b]
1	**100b**	OCO_2Me	CsF	70:**2**:28	--
2	**100b**	OCO_2Me	TBAF	0:**8**:92	--
3	**100b**	OCO_2Me	TBAF·4*t*BuOH	11:**45**:44	30
4	**100b**[c]	OCO_2Me	TBAF·4*t*BuOH	100:**0**:0	--
5	**100a**	OAc	TBAF·4*t*BuOH	100:**0**:0	--
6	**100c**	OCF_3	TBAF·4*t*BuOH	0:**0**:100	--
7	**100d**	OBz	TBAF·4*t*BuOH	80:**20**:0	--
8	**100e**	OPNB	TBAF·4*t*BuOH	0:**100**:0	> 95
9	**100e**[c]	OPNB	TBAF·4*t*BuOH	100:**0**:0	--

a. Analysis by ^{1}H NMR of the crude reaction mixture. *b*. Yields of the isolated product. *c*. Reaction run in the absence of Pd catalyst.

Table 3. 1 Palladium-Catalysed Allylic Fluorination-Optimisation Screening

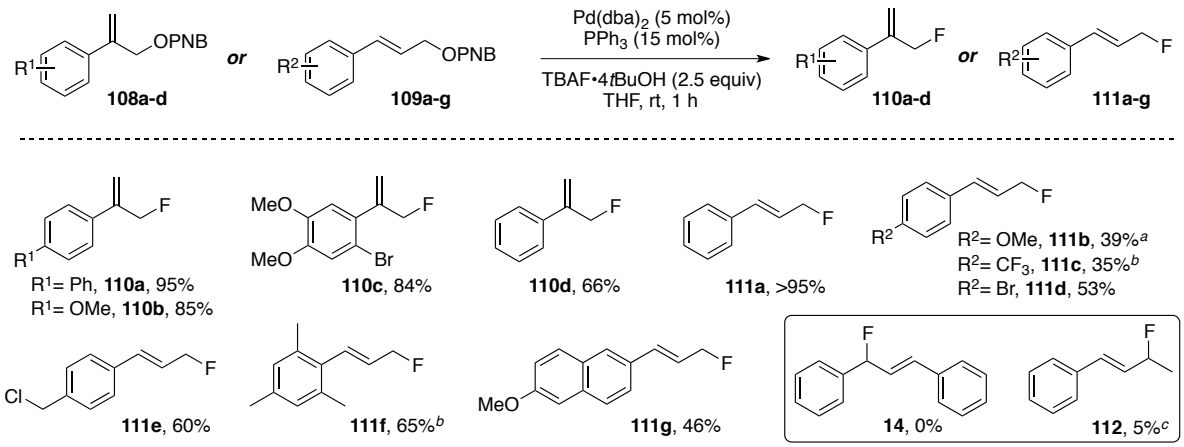
With CsF only traces of the fluorinated product **99** were detected after 1 h, along with 28% formation of the corresponding alcohol by-product **102**, and 70% of recovered starting material (Table 3.1, entry 1). The use of a solution of TBAF in THF resulted in almost

complete conversion of **100b** into the undesired alcohol **102** (Table 3.1, entry 2). Reasoning that the formation of **102** may partially derive from the presence of H_2O in the reaction system, TBAF·4*t*BuOH was tested as a dry fluoride source. The synthesis of the tetra-coordinated fluoride complex, starting from the commercially available TBAF·$3H_2O$, was performed following the procedure of Kim and co-workers, yielding a crystalline reagent.[146] Pleasingly, the new fluorinating agent led to 45% of desired product **99**, which was isolated in 30% yield. Formation of alcohol **102** could not be completely suppressed under these reaction conditions (Table 3.1, entry 3). A test reaction, run in the absence of Pd catalyst, afforded exclusively unreacted **100b**, indicating the fluorination reaction occurs exclusively through Pd-catalysis (Table 3.1, entry 4).

In an attempt to decrease the alcohol formation, a screening of alternative leaving groups was undertaken (Table, entries 5-8).[147] Reactions with acetate **100a** and trifluoroacetate **100c** were fruitless and afforded entirely unreacted starting material and alcohol by-product, respectively. When benzoate **100d** was tested, only 20% of conversion into the desired product was observed. Pleasingly, *para*-nitrobenzoate (PNB) derivative **100e** showed excellent reactivity, leading to 100% formation of fluoride **99**, isolated in >95% yield. A control reaction confirmed that the presence of the catalyst is essential for the reaction to proceed (Table, entry 8-9). The origin of the superior reactivity of the *p*-nitrobenzoate leaving group is still unclear.[115d,e,148] The reactivity trend observed does not have an obvious correlation to the p*K*a values of the released corresponding carboxylic acids (p*K*a (H_2O) = -0.25 for CF_3COOH, 4.20 for PhCOOH, 3.44 for $pNO_2C_6H_4COOH$ and 3.18 for HF).

With the optimised conditions in hand, the scope of the new allylic fluorination was subsequently examined. A variety of 2-substituted propenyl fluorides **108a-d** were obtained with high yields, except for substrate **108d**, which was isolated in 66% yield due its high volatility. Under the optimised conditions, 3-substituted propenyl derivatives **109a-g** also

afforded the corresponding linear fluorides with excellent regioselectivity and in moderate yields. Substrates bearing electron-withdrawing groups (**109c-d**) and highly hindered substrates (**109f**) required heating to 40 °C and gave lower conversion to the desired product. Isolation of the 4-bromo and 4-chloromethyl derivatives (**111d**,**e**) highlight the functional group tolerance of the reaction. As anticipated,[40] the fluorination of (*E*)-1,3-diphenylprop-2-en-1-ol derivative did not proceed (**14**, 0%). When the synthesis of **112** was attempted, mainly diene formation was observed, as product of β-hydride elimination. The decreased reactivity of electron deficient substrates may suggest that the rate limiting step of the transformation is the formation of the π-allylpalladium intermediate.



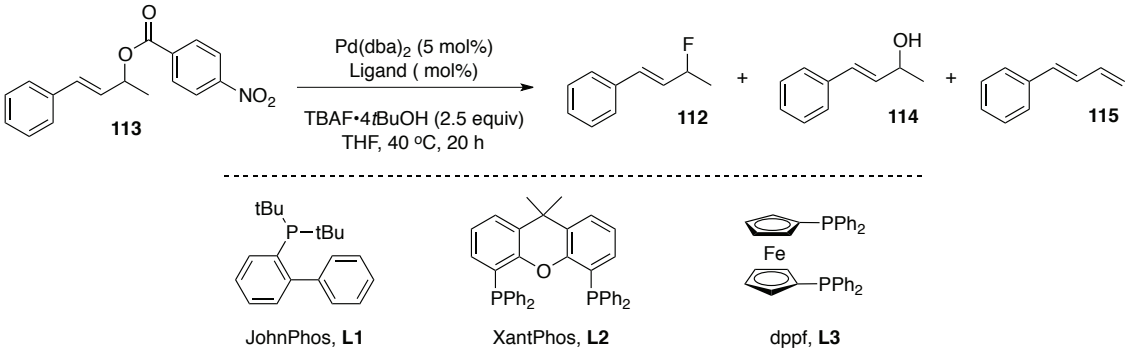
a. Reaction run for 1 h at rt and 20 min at 40 °C. *b*. Reaction run for 4 h at 40 °C. *c*. 95% of diene was formed.

Scheme 3. 1 Substrate Scope of Pd-Catalysed Allylic Fluorination

3.2.2 Limitations

The main drawback of this fluorination reaction is the significant percentage of competing elimination reaction observed with substrates bearing a hydrogen in the β-position, which highly limits the scope of the methodology. This side-reaction presumably occurs at the π-allylpalladium intermediate stage, *via* palladium-hydride formation, and hence requires a vacant site on the metal.[149] Two main approaches have been adopted in an attempt to minimise this event. The results discussed in this section were obtained by M. O'Duill.[150] A screening of a variety of leaving groups was carried out (3,5-dinitrobenzoate, 2,4-

dinitrobenzoate, *p*-trifluoromethylbenzoate and pentafluorobenzoate) in order to increase the rate of fluorination versus competing elimination reaction. However, among the derivatives tested, *p*-nitrobenzoate showed superior performance in terms of reactivity and selectivity towards the formation of the desired product.



Entry	Ligand **L**	Pd:L Ratio	Ratio[a] **113**:**112**:**114**:**115**
1	PPh_3	1:2	8:**21**:7:64
2	**L1**	1:2	47:**1**:44:8
3	**L2**	1:1	4:**23**:7:66
4	**L3**	1:1	41:**5**:25:29

a. Analysis by ^{1}H NMR of the crude reaction mixture.

Table 3. 2 β-Hydride Elimination-Ligand Screening

The variation of the ligand was then considered. The use of multidentate ligands would coordinatively saturate the metal centre, blocking the vacant site necessary for this process to occur.[151] For the ligand screening tests, derivative **113** was selected as the model substrate, $Pd(dba)_2$ as the pre-catalyst and the reaction run in THF at 40 °C for 20 h. When the reaction was performed with the standard ligand PPh_3, only 21% of fluorinated product **112** was detected, in addition to alcohol **114** (7%) and 64% of diene **115** (Table 3.2, entry 1). The use of a more bulky monodentate ligand, such as (2-biphenyl)di-*tert*-butylphosphine (JohnPhos, **L1**), reduced the diene formation to 8%, but resulted in an overall decreased reactivity of the system, with 47% of recovered starting material and 44% of undesired alcohol **114** (Table 3.2, entry 2). An unchanged product distribution, with respect to the first

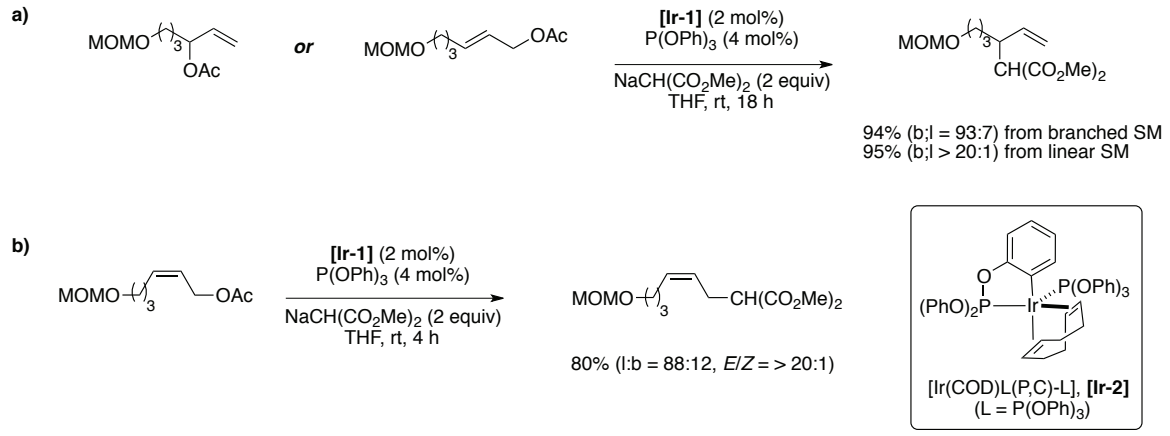
entry, was observed, when the bidentate ligand 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos, **L2**, bite angle = 108°) was tested. Lower conversion to fluoride **112** was detected with dppf, **L3** (bite angle = 99°, Table 3.2, entry 4).

A further limitation of this reaction is the regioselectivity towards linear products, which prevented the possibility to develop an asymmetric variant of the transformation.[152] It is well documented that under Pd-catalysis, when electronic properties of the π-allyl termini are similar, soft-nucleophiles prefer to attack the less hindered terminus yielding in preference the linear substituted product. Conversely, hard nucleophiles favour the branched kinetic product formation, when the isomerisation of the π-allylpalladium intermediate is slower than reductive elimination of the C-X (X = N, O, hard C) bond.[153] The regiochemical outcome of the Pd-catalysed fluorination reaction confirmed that the attack of the fluoride nucleophile is occurring from an outer sphere of the π-allyl complex,[57] in a similar fashion to a soft nucleophile. The regiochemical outcome of Pd-catalysed allylic substitution reactions with soft nucleophiles can be affected by the electronic properties of the substituents of the allyl group, with the addition occurring at the allylic terminus remote from the electron-withdrawing group.[154] Also the ligands coordinated to the metal may influence the regioselectivity of the nucleophilic attack to the π-allyl Pd intermediate. This was observed for ligands unsymmetrically bounded to the metal, or alternatively if the leaving group is still attached to the π-allyl Pd species.[155] However, the high tendency of branched allylic *p*-nitrobenzoates to isomerise to the linear derivatives under the reaction conditions discouraged further investigation in that direction.[156]

3.3 Iridium Catalysed Allylic Substitution

Due to the unsuccessful attempts in tuning selectivity and stereocontrol of the fluorination reaction under Pd-catalysis, our attention moved to iridium. The distinctive characteristics

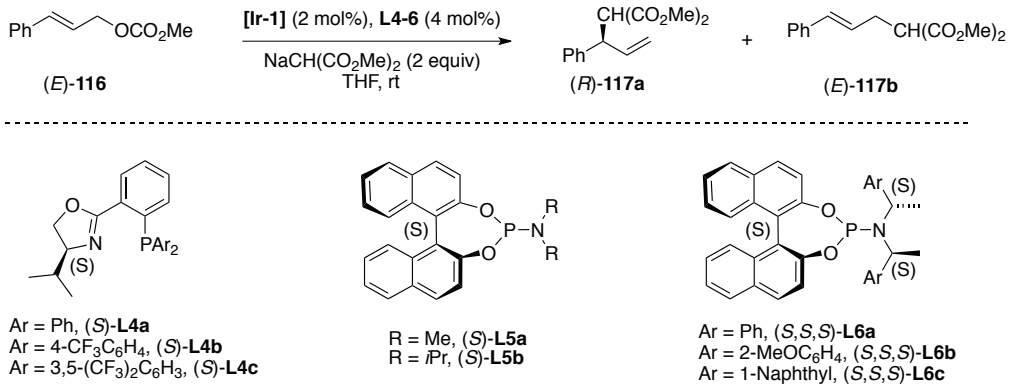
of Ir in allylic substitution reactions were reported in the initial investigations, carried out by Takeuchi and co-workers.[157] In these original papers, two distinct features emerged that contrasted with palladium chemistry: a) the kinetic branched product is favoured starting either from linear or branched allylic alcohol derivatives (Scheme 3.2a) and b) the stereochemical integrity was maintained, when *Z*-allylic substrates were employed (Scheme 3.2b). The more efficient catalytic system, in terms of reactivity and selectivity, was found to be $[Ir(COD)Cl]_2$ **[Ir-1]** as pre-catalyst and $P(OPh)_3$ as ligand.[158] Interestingly, it was noticed that the active catalyst was formed after addition of typically strongly basic nucleophiles (e.g. malonate or amine). Thus, in the case of the achiral ligand $P(OPh)_3$, the Ir-mediated *ortho* C-H activation led to the active intermediate **[Ir-2]** (Scheme 3.2).



Scheme 3. 2 Regioselectivity in Ir-Catalysed Allylic Substitution

The preference for the branched over the linear product encouraged further investigations towards asymmetric variants. Helmchen and co-workers reported the first example of Ir-catalysed asymmetric alkylation of linear allylic carbonates, with up to 95% ees, by employing chiral PHOX ligands ((*S*)-**L4a-c**, Table 3.3, entry 1).[159] The same group reported the efficiency of phosphoramidite ligands in Ir catalysed allylic alkylations ((*S*)-**L5a**, Table 3.3, entry 2),[160] which has been further developed by Hartwig and co-workers for its application in an asymmetric allylic amination[161] ((*S*)-**L5b**, (*S*,*S*,*S*)-**L6a**, Table 3.3, entry 3).

With further improvements in the ligand design contributed by Alexakis' group ((*S*,*S*,*S*)-**L6b-c**, Table 3.3, entry 4),[162] the phosphoramidite family has become established as the dominant ligand in Ir catalysis.

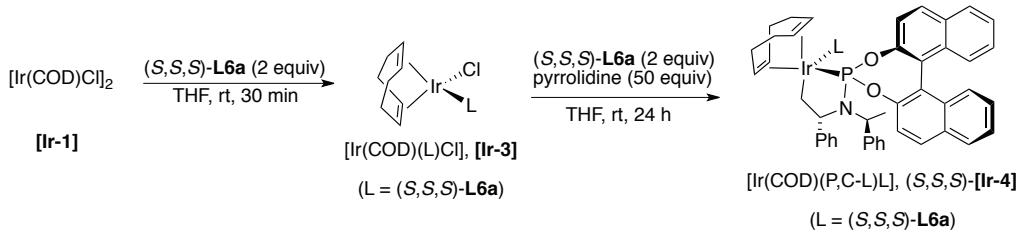


Entry	Catalytic System[a]	Temp	Time (h)	Yield **117**[b]	Ratio **117a**:**117b**[c]	ee **117a**
1	(*S*)-**L4b**[d]	65 °C	24	99%	95:5	91%
2	(*S*)-**L5a**[d]	rt	3	99%	98:2	37%
3	(*S*,*S*,*S*)-**L6a**	rt	1.5	92%	98:2	96%
4	(*S*,*S*,*S*)-**L6b**	rt	22	79%	99:1	97%

a. **[Ir-1]** in combination with **L4-6**. *b*. Isolated yield of the mixture **117a**+**117b**. *c*. Ratio determined by ^{1}H NMR of isolated mixture. *d*. Reaction run with corresponding acetate of (*E*)-**116b**.

Table 3. 3 Selectivity of Chiral Ligands for Enantioselective Ir-Catalysed Allylic Substitution

Mechanistic insights have been elucidated by both Helmchen and Hartwig,[163] a key feature being the identification of an isolable reactive intermediate **[Ir-4]**. This species is formed by a stereospecific internal C-H activation of the phosphoramidite methyl side-chain (Scheme 3.3). The cycloocta-1,5-diene ligand remains coordinated to the Ir centre in the metalacycle **[Ir-4]**. The complex **[Ir-4]** was shown to be catalytically active in asymmetric allylic substitution reactions, with a reactivity comparable to that of the catalyst generated *in situ* from **[Ir-1]** and ligand (*S*,*S*,*S*)-**L6a**. Among the variety of reactants screened, allylic carbonates and acetates are the preferred ones. In recognition of its current synthetic importance, Ir-catalysed allylic substitution has been extensively reviewed.[164]



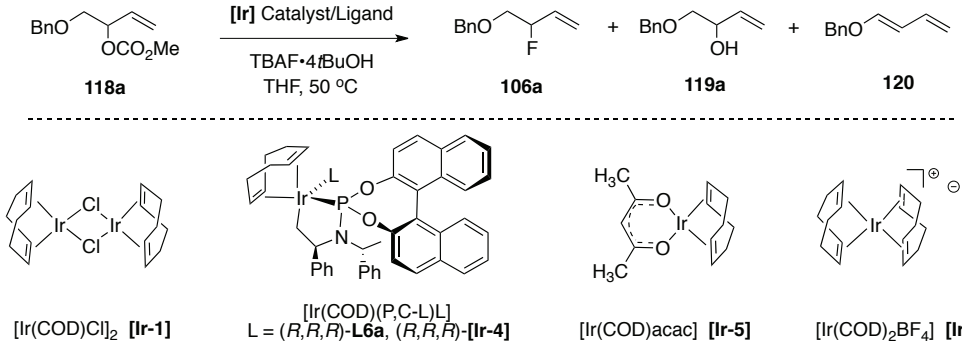
Scheme 3. 3 Synthesis of Reactive Intermediate (*S,S,S*)-**[Ir-4]** *via* Ir-Mediated C-H Activation

Iridium catalysis has been particulary exploited for the substitution of allylic derivatives with heteroatom nucleophiles, in a highly selective fashion. Hartwig and others reported several asymmetric methods for the synthesis of allylic amines,[161,165] sulfonamides,[166] imides[167] and ethers,[168] accomplished by the use of phosphoramidite ligands. Carreira has developed the enantioselective synthesis of allylic alcohols from primary allylic carbonates, employing a phosphoramidite ligand. The reaction was based on an etherification with $KOSiEt_3$, followed by a silyl deprotection to give the desired alcohol.[169]

3.4 Ir-Catalysed Allylic Fluorination

3.4.1 Screening of the Reaction Conditions

For our initial investigation of Ir-catalysed allylic fluorination reaction,[170] branched carbonate **118a** was selected as model substrate, as the corresponding fluorinated product **106a** is a stable compound.[144] The reactions were run in THF (0.1 M), under N_2 atmosphere, at 50 °C with 2 equivalents of TBAF·4*t*BuOH as the fluorinating agent, due to its success under Pd-catalysis. The $[Ir(COD)Cl]_2$ **[Ir-1]** (2 mol%) was used as the pre-catalyst in combination with a variety of commonly used ligands in Ir-catalysed allylic substitutions (Table 3.4). The reaction mixture was stirred until complete conversion of the starting material, as indicated by TLC, however no longer than 24 h. The product distribution was determined by ^1H and ^{19}F NMR spectroscopy of the crude reaction mixture.



Entry	Catalyst **[Ir]**	Ligand	**[Ir]** (mol%)	F^- equiv	Time (h)	Ratio[a] **118a**:**106a**:**119a**:**120**
1	**[Ir-1]**[b]	$P(OPh)_3$	2	2	24	--[c]
2	**[Ir-1]**	$P(OPh)_3$	2	2	24	50:**0**:25:25
3	**[Ir-1]**	(*S*,*S*,*S*)-**L6a**[d]	2	2	24	38:**25**:25:12
4	(*R*,*R*,*R*)-**[Ir-4]**	--	4	2	24	--[c]
5	**[Ir-1]**	--	2	2	5	0:**55**:41:4
6	**[Ir-5]**	--	4	2	2	7:**48**:41:4
7	**[Ir-6]**[e]	--	4	2	4	7:**56**:31:6
8	**--**	--	--	2	5	86:**0**:14:0
9	**[Ir-1]**	--	4	2	2	4:**25**:64:7
10	**[Ir-1]**	--	1	2	24	25:**38**:31:6
11	**[Ir-1]**	--	2	1.2	3	16:**25**:57:2
12	**[Ir-1]**	--	2	4	5	0:**7**:88:5

a. Analysis by ^{1}H NMR of the crude reaction mixture. *b*. Reaction run at rt. *c*. Traces of **106a** in a complex reaction mixture. *d*. Addition of 0.1 equiv of DABCO. *e*. Reaction run in DCM at 40 °C.

Table 3. 4 Screening of Iridium Catalyst

When the π-acceptor ligand $P(OPh)_3$ was used at room temperature, after 24 h, only traces of fluoride **106a** were detected in a complex reaction mixture. Increasing the temperature to 50 °C did not lead to any formation of **106a**, and **118a** was recovered in 50%, along with 25% of alcohol **119a** and 25% of elimination product **120** (Table 3.4, entries 1-2).

The use of the chiral phosphoramidite ligand (*S*,*S*,*S*)-**L6a** required the addition of 0.1 equivalents of DABCO (1,4-diazabicyclo[2.2.2]octane) to promote the C-H activation at the ligand position and generate the active species (*S*,*S*,*S*)-**[Ir-4]** *in situ*.[163] Under these conditions, we were pleased to observe, after 24 h, 25% of fluorinated product **106a**, in

addition to 38% of recovered allylic carbonate **118a**. However, the presence of a significant amount of by-products **119a** and **120** was still observed (Table 3.4, entry 3).

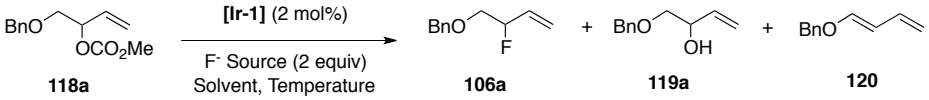
Surprisingly, the pre-formed complex (*R*,*R*,*R*)-**[Ir-4]**, prepared from (*R*,*R*,*R*)-**L6a**,[163a] afforded only traces of fluoride **106a** (Table 3.4, entry 4). This unexpected result led us to verify whether the precursor complex **[Ir-1]** was active under the fluorination conditions. Indeed, this was found to be a superior catalyst, leading to full conversion of carbonate **118a** within 5h, and yielding 55% of branched product **106a**, formed as single regioisomer. The formation of product **120** was minimised to 4%, but 41% of alcohol **119a** was still observed (Table 3.4, entry 5). A similar product distribution was observed with the pre-synthesised monomer complexes bearing one or two COD ligands, [Ir(COD)acac] **[Ir-5]**[171](acac = acetylacetone) and $[Ir(COD)_2BF_4]$ **[Ir-6]**,[172] respectively (Table 3.4, entries 6-7). A control reaction showed that the fluorination does not proceed without catalyst, however 14% of alcohol **119a** was still formed in the absence of **[Ir-1]** (Table 3.4, entry 8).

Both higher and lower catalyst loadings did not increase the conversion into **106a**, resulting in either greater alcohol formation or in an overall decreased reactivity, respectively (Table 3.4, entries 9-10). The product distribution of the reaction could not be improved, even when the amount of the fluorinating agent was varied (Table 3.4, entries 11-12). As expected, when carbonate **118a** was subjected to Pd-catalysed fluorination under the previously optimised conditions, only diene **120** was isolated.

With the optimal catalyst in hand, we turned our attention to screening different fluorinating agents and reaction conditions, carring out the reaction with carbonate **118a** and **[Ir-1]** (2 mol%), in an attempt to improve the product distribution.

When the reaction with TBAF·4*t*BuOH was repeated at room temperature, within 3 h an equal percentage of carbonate **118a**, fluoride **106a** and alcohol **119a** was observed (Table 3.5, entry 1). The use of the commercially available $TBAF·3H_2O$ led mainly to alcohol **119a**, after 24 h at room temperature (Table 3.5, entry 2). When HF·pyridine was employed only a

trace of **106a** was detected, and $Et_3N{\cdot}3HF$ led mainly to recovered carbonate **118a** and 30% of the corresponding methyl ether (Table 3.5, entries 3-4). Fluoride salts, such as CsF and AgF led mainly to recovered starting material **118a** after 24 h, probably due to their low solubility, while KF/16-crown-8 afforded mainly **119a** (Table 3.5, 5-7).



Entry	F^- source	Temp (°C)	Solvent	Time (h)	Ratio[a] **118a**:**106a**:**119a**:**120**
1	TBAF·4*t*BuOH	rt	THF	3	33:**33**:33:1
2	$TBAF{\cdot}3H_2O$	rt	THF	24	0:**15**:81:4
3	HF·pyridine	rt	THF	24	--[b]
4	$Et_3N{\cdot}3HF$	rt	THF	24	63:**0**:6:1[c]
5	CsF	rt	THF	24	82:**0**:9:9
6	AgF	rt	THF	24	100:**0**:0:0
7	KF/16-crown-8	rt	CH_3CN	24	44:**trace**:56:0
8	TBAF·4*t*BuOH	50[d]	THF	5	0:**69**:29:2
9	TBAF·4*t*BuOH	50	DMF	2	24:**12**:62:2
10	TBAF·4*t*BuOH	50	*t*BuOH	1	31:**0**:69:0
11	TBAF·4*t*BuOH	50	Toluene	2	0:**61**:35:4
12	TBAF·4*t*BuOH	40	DCM	2	0:**80**:13:7
13	TBAF·4*t*BuOH	40[d]	DCM	2	0:**84**:6:10

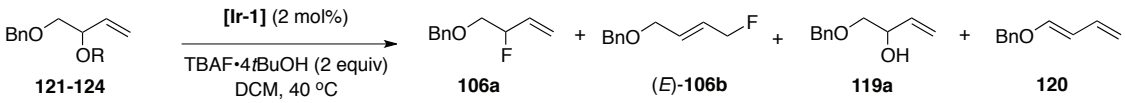
a. Analysis by ^1H NMR of the crude reaction mixture. *b.* Traces of **106a** in a complex reaction mixture. *c*. 30% of methyl ether detected. *d*. Addition of crushed 3Å sieves.

Table 3. 5 Optimisation of the Reaction Conditions

We concluded that TBAF·4*t*BuOH was the best fluorinating agent for our reaction, and that anhydrous conditions could prevent the competing alcohol formation. To this end, the reaction with TBAF·4*t*BuOH (**106a**, 55%, Table 3.4, entry 5) was repeated with the addition of 3 Å molecular sieves, affording after 5 h fluoride **106a** in an increased yield of 69% (Table 3.5, entry 8).

A brief screening of solvents (Table 3.5, entries 8-12) identified DCM as the optimal solvent for this reaction, yielding, within 2 h at 40 °C, 80% of **106a** along with 13% of alcohol **119a** and 7% of diene **120** (Table 3.5, entry 12). The yield was slightly improved in the presence of molecular sieves, although more diene **120** was formed (Table 3.5, entry 13), therefore the conditions of entry 12 were identified as optimal.

On the basis of the previous study on Pd-catalysed allylic fluorination, where the reactivity was greatly improved by changing the leaving group from carbonate to *p*-nitrobenzoate (Table 3.1), a similar investigation was also carried out for Ir-catalysis.



Entry	Leaving group (OR)	Substrate	Time (h)	Ratio[a] **121-124**:**106a**:**119a**:**120**
1	OAc	**121**	24	94:**6**:0:0
2	OBz	**122**	24	90:**10**:0:0
3	OPNB	**123**	24	56:**31**:10:3
4	$OCOC_6F_5$	**124**[b]	1	14:**43**[c]:14:28

a. Analysis by ^{1}H NMR of the crude reaction mixture. *b*. At rt. *c*. Fluorinated product formed in a mixture of branched and linear (**106a**:(*E*)-**106b**/20:80).

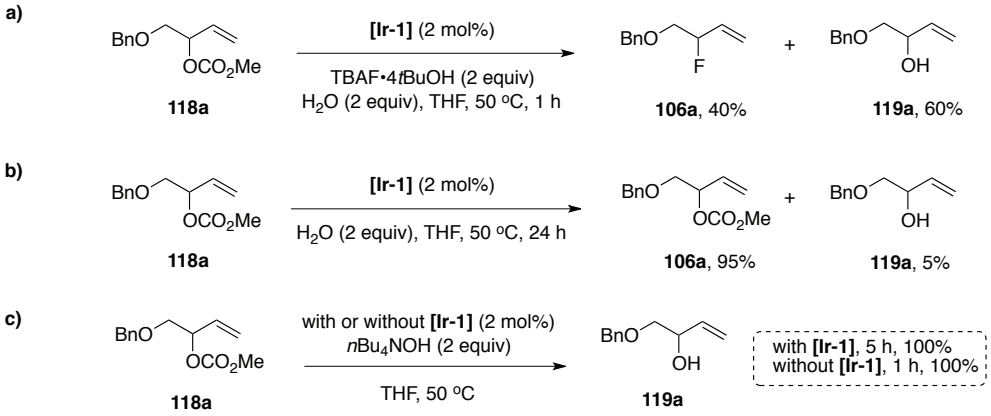
Table 3. 6 Screening of Leaving Groups

Acetate **121** and benzoate **122** derivatives showed lower reactivity than carbonate **118a**, after 24 h mainly unreacted starting material was recovered. *p*-Nitrobenzoate **123** yielded only 31% of **106a** after 24 h (Table 3.6, entries 1-3). When the pentafluorobenzoate **124** was tested, the reaction was carried out at room temperature, obtaining almost full conversion of the starting material within 1 h. The fluorinated product was formed in 43% yield, as a mixture of branched **106a** and linear (*E*)-**106b** regioisomers (Table 3.6, entry 4).

These results clearly showed that carbonate **118a** is the best substrate for this transformation, allowing complete conversion within 2 h to yield **106a** in a highly selective fashion (Table 3.5, entry 12).

3.4.2 Attempts to Decrease the Alcohol Formation

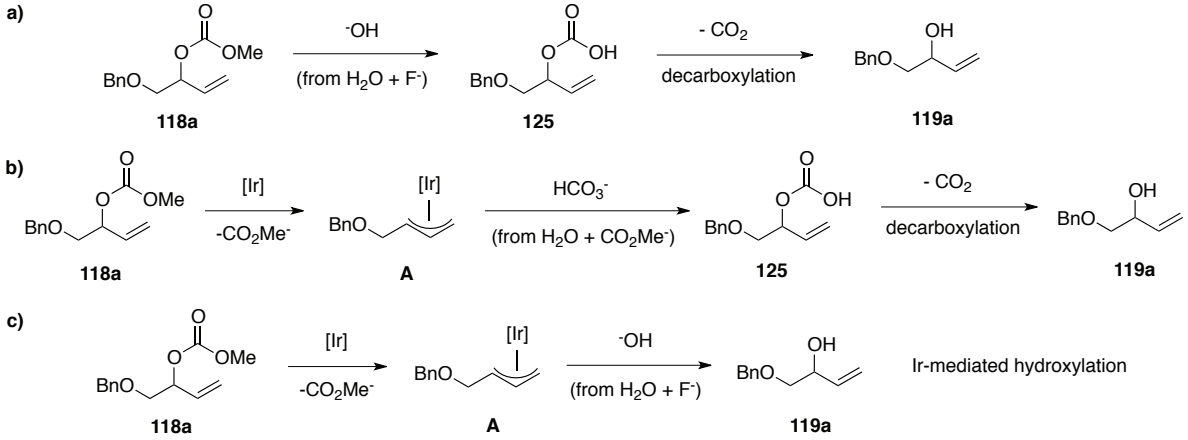
Based on our preliminary observations, it was reasoned that the formation of by-product **119a** may derive from the presence of hydroxide ion in the reaction, which acts as a competing nucleophile with fluoride. A partial decrease of alcohol formation was achieved by employing more anhydrous reaction conditions, indicating that the presence of water may be responsible for this side reaction. Indeed, when the fluorination of carbonate **118a** in THF at 50 °C (conditions in entry 5 of Table 3.5) was performed in the presence of 2 equivalents of H_2O, alcohol **119a** was formed in 60% yield within 1 h (Scheme 3.4a). This is in contrast to 41% of **119a** yielded within 5 h in the previous observation. This result indicated that traces of water in the reaction mixture may act as the source of hydroxide, under fluorination conditions, as confirmed by the test reaction carried out with addition of H_2O, in the absence of TBAF·4*t*BuOH (Scheme 3.4b).



Scheme 3. 4 Study on the Competing Nucleophile Hydroxide Ion

During the optimisation of the fluorination reaction, it was found that the amount of alcohol formed variated slightly between batches of TBAF·4*t*BuOH. This observation suggested that the commercial precursor TBAF·3H_2O may contain somewhat traces of hydroxide, as there are no reported analytical methods to measure the percentage of fluoride in the ammonium salt. To validate our hypothesis, carbonate **118a** was subjected to 2 equivalents of *n*Bu_4NOH, either in the presence or absence of catalyst **[Ir-1]** in THF at 50 °C (Scheme

3.4c). In both cases, full conversion into **119a** was observed within 1 h, confirming that the carbonate leaving group could be replaced by a hydroxyde source, such as nBu$_4$NOH, without Ir-mediation. The latter observation is in agreement with the outcome of the test reaction carried out in the absence of **[Ir-1]** in THF, where **119a** was formed in 14% yield (Table 3.4, entry 8). The exclusive formation of the branched alcohol suggests that an S_N2 pathway is not operating as traces of the S_N2' product (*E*)-**119b** were not observed.

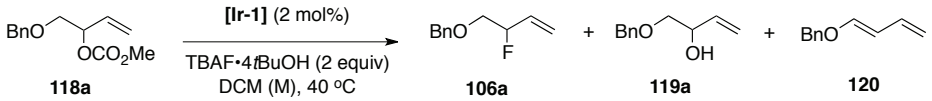


Scheme 3. 5 Plausible Mechanisms for Alcohol By-Product Formation

A plausible mechanism could involve the hydrolysis of the carbonate **118a**, followed by decarboxylation of the resulting carboxylic acid **125** (Scheme 3.5a). However, the possibility of an Ir-mediated alcohol formation reaction can not be ruled out, on the basis of the results obtained in Scheme 3.4a. In addition, an example of Ir-catalysed enantioselective synthesis of branched allylic alcohols, starting from the corresponding linear carbonates, has been reported.[173] This work was developed from the observation of alcohol by-product formation during an Ir-catalysed intramolecular amination of allylic carbonate derivatives. Based on the hypothesis of a decarboxylative-step of the carboxylic acid, generated *via* Ir-mediated activation of the starting material, potassium bicarbonate was identified as the best nucleophile. In line with this transformation, we could assume a similar mechanism occured under our reaction conditions (Scheme 3.5b). Alternatively, an

Ir-catalysed hydroxylation of the carbonate leaving group could occur, *via* the π-allyl iridium intermediate **A**, with hydroxide acting as nucleophile (Scheme 3.5c).

In order to suppress the competing hydroxide attack, the molarity of the reaction was varied (Table 3.7). At high dilution (0.02 M), the formation of by-product **119a** and **120** was almost completely overcome, although the system was slightly less reactive, requiring a longer reaction time and affording incomplete conversion of **118a** (Table 3.7, entry 3). A 0.02 M concentration in DCM for 4 h was optimal, as further dilution of the reaction mixture led to low conversion into product (Table 3.7, 4-5).



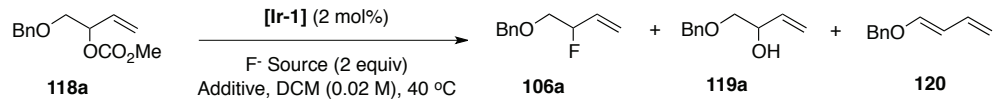
Entry	Conc. (M)	Time (h)	Ratio[a] **118**:**106a**:**119a**:**120**
1	0.1	2	0:**80**:13:7
2	0.04	6	9:**58**:23:10
3	0.02	4	18:**70**:4:8
4	0.01	24	30:**46**:18:6
5	0.005	24	81:**trace**:19:0

a. Analysis by ^{1}H NMR of the crude reaction mixture.

Table 3. 7 Screening of Dilution Conditions

As any attempt to decrease trace water in our reaction environment were unsuccessful, additives, such as trifluoroacetic anhydride (Table 3.8, entry 2) or carboxylic acids (Table 3.8, entries 3-4) were employed in order to neutralise the hydroxide generated under the reaction conditions. However, improved product distribution was not obtained. Even the addition of thiourea, an anion chelator, was not effective, and no fluorinated product was observed (Table 3.8, entry 5). Addition of fluoride ions, such as CsF and KF, to increase the concentration of fluoride over the competing hydroxide nucleophile in the reaction environment, had little effect (Table 3.8, entries 6-7). Under the optimised reaction

conditions, a screening of less hygroscopic fluorinating agents was undertaken. Although all of them were active agents, except for KHF_2, they all afforded less of the desired product (Table 3.8, entries 8-11).



Entry	F^- source	Additive	Equiv	Time (h)	Ratio[a] **118a**:**106a**:**119a**:**120**
1	TBAF·4*t*BuOH	--	--	4	18:**70**:4:8
2	TBAF·4*t*BuOH	TFAA[b]	0.5	12	2:**67**:14:17
3	TBAF·4*t*BuOH	*p*-nitrobenzoic acid	0.5	12	0:**73**:21:6
4	TBAF·4*t*BuOH	TFA	0.5	12	0:**39**:37:24
5	TBAF·4*t*BuOH	Thiourea	0.5	12	70:**0**:0:30
6	TBAF·4*t*BuOH	CsF[c]	2	24	0:**73**:21:6
7	TBAF·4*t*BuOH	KF/18-crown-6	0.5	12	0:**89**:11:0
8	TBAF·2pin	--	--	18	0:**44**:44:12
9	TBAF[d]	--	--	18	0:**47**:33:20
10	TASF	--	--	18	30:**55**:10:5
11	KHF_2	--	--	18	43:**0**:0:57
12	$TBAHF_2$	--	--	18	8:**67**:22:3

a. Analysis by ^{1}H NMR of the crude reaction mixture. *b*. 0.1 M concentration. *c*. Reaction run in THF. *d*. 1 M THF solution.

(Pin = pinacol, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, TBA = tetra-*n*-butyl amonium)

Table 3. 8 Screening of Additives and Dry Fluorinating Agents

A kinetic study of the fluorination reaction under the optimised conditions, employing 2 mol% of **[Ir-1]** catalyst and 2 equivalents of TBAF·4*t*BuOH in DCM at 40 °C, was carried out to monitor the rate of fluorination over hydroxylation reaction. The relative ratio in percentage of the starting material **118a** and products **106a** and **119a** over time were determined by ^{1}H NMR analysis on the crude reaction mixture and reported in Chart 3.1.

After 1 h, around 65% of carbonate **118a** was converted into the desired fluoride product **106a**, however the reaction did not proceed further and after 18 h 45% of **106a** remained. The rate of alcohol formation was significantly slower with 30% of **119a** formed within 18 h,

suggesting that it could partially derive from hydrolysis of fluoride **106a**. A test reaction, subjecting the fluoride to the standard reaction conditions for 3 h at 40 °C, showed no decomposition of the product, confirming its stability over the reaction time.

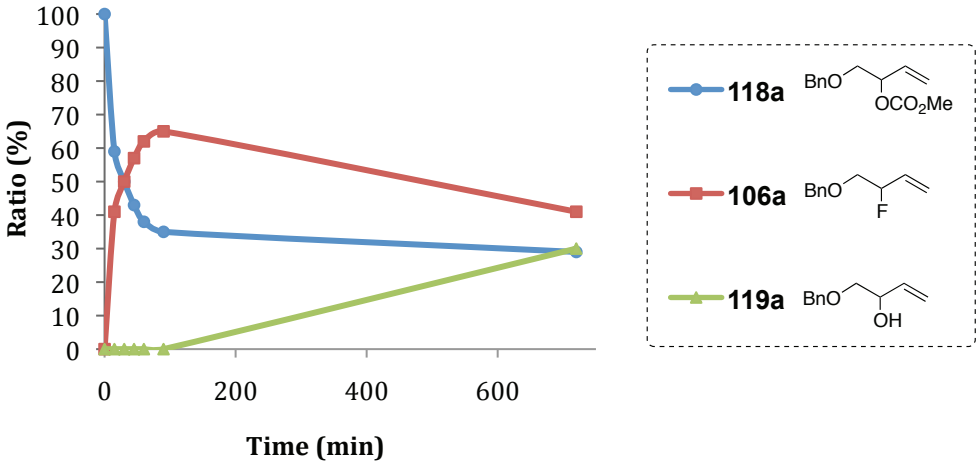


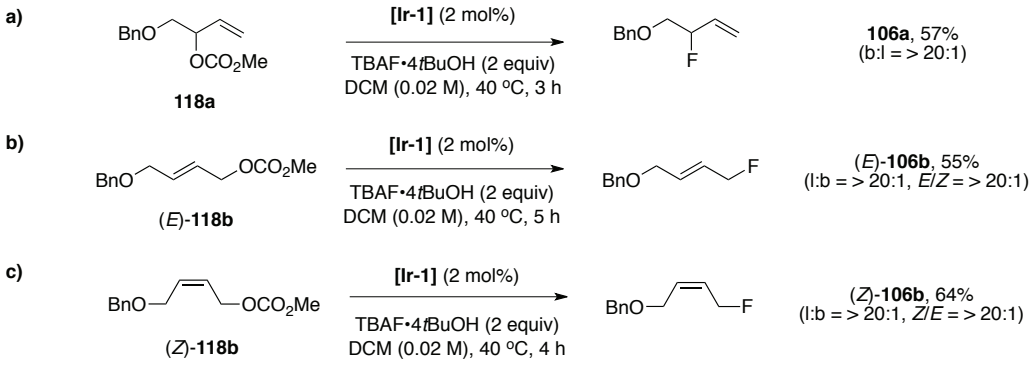
Chart 3. 1 ^{1}H NMR Ratios of **118a**, **106a** and **119a** over Time

The observation that the reaction stopped after 1 h questions the stability of the catalyst in the presence of our fluorinating agent. To this end, the reaction was performed employing 2 mol% of **[Ir-1]** pre-treated with 10 mol% of TBAF·4*t*BuOH at room temperature for 30 minutes. The unchanged product distribution obtained indicated that **[Ir-1]** is not deactivated by the presence of the fluorinating agent. However, when the portionwise addition of catalyst **[Ir-1]** was attempted over 1 h, 83% of **106a** was formed within 3 h, and only 5% of alcohol **119a** and 6% of diene **120** observed. The latter were identified as optimal conditions for the reaction, allowing the isolation of fluoride **106a** in 57% yield as single regioisomer (Scheme 3.6a).

3.5 Regio- and Stereoselectivity of the Fluorination Reaction

3.5.1 Model Substrates

Encouraged by the high degree of regioselectivity reported for Ir-catalysed allylc substitution reactions,[158] our next objective was to examine the reactivity of *E*- and *Z*-linear carbonates under the optimised fluorination conditions. We were pleased to find that fluorination of the linear regioisomer (*E*)-**118b** proceeded smoothly affording the corresponding fluorinated product (*E*)-**106b** in 55% isolated yield (*E*/*Z* > 20/1), within 5 h (Scheme 3.6b). More interestingly, ^{19}F NMR spectroscopy of the crude reaction mixture showed no traces of the branched fluoride **106a**. This result was unexpected, as in disagreement with literature reports on C- and heteroatom nucleophilic substitution, where starting from *E*-linear substrates the favoured product is the branched isomer (Scheme 3.2a). When carbonate (*Z*)-**118b** was subjected to fluorination conditions, in a comparable time fluoride (*Z*)-**106b** was afforded in 64% isolated yield and as single regio- and stereoisomer (l/b >20/1, *Z*/*E* >20/1, Scheme 3.6c), as expected from literature precedents (Scheme 3.2b). The application to a large reaction scale was also explored, utilising 1 g of carbonate (*Z*)-**118b**. Allylic fluoride (*Z*)-**106b** was obtained in 47% isolated yield as single isomer, along with 31% of unreacted starting material recovered.



Scheme 3. 6 Regio- and Stereoretentive Ir-Catalysed Allylic Fluorination

The structure of *E*- and *Z*-linear stereoisomers for both carbonate **118b** and fluoride **106b** were unambiguously assigned by examining the chemical shifts of the carbons in α and α' position in their ^{13}C NMR spectra (Figure 3.1). For (*E*)-**118b** and (*E*)-**106b** the chemical shifts of Cα and Cα' are consistently higher than the corresponding *Z*-isomers. This is due to the fact that Cα and Cα' are more deshielded in *E*-isomers than in their *Z*-counterparts.

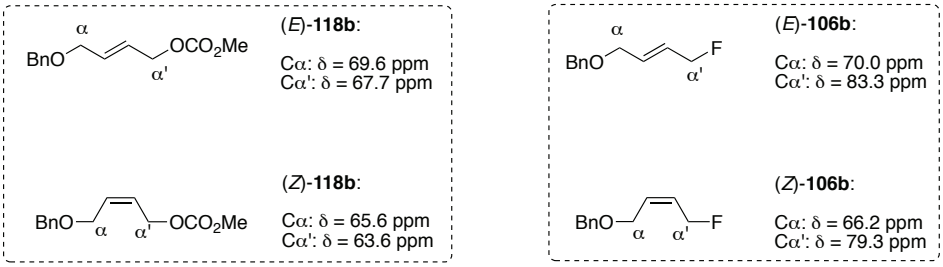
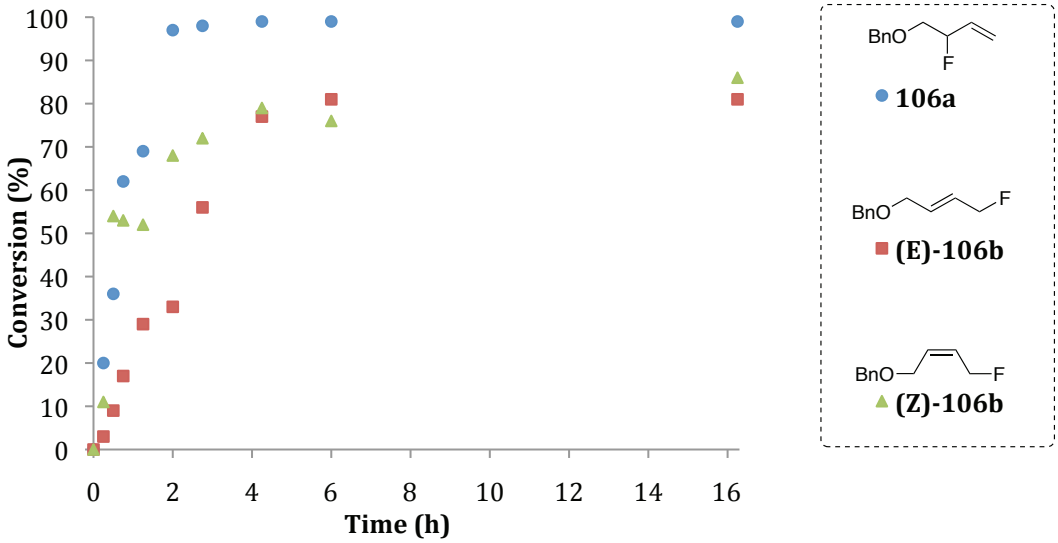


Figure 3. 1 Assignement of *E*- and *Z*-Geometry of Double Bond in **118b** and **106b**

A kinetic investigation of the reaction with the three carbonate isomers (Scheme 3.6a-c), suggested that the rate of fluorination followed the order: **118a** > (*Z*)-**118b** ≈ (*E*)-**118b** (Chart 3.2). This result is in line with what reported by Helmchen et al for the Ir-catalysed allylic alkylation of allyl acetates with malonate nucleophile.[158]



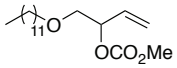
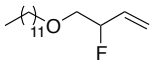
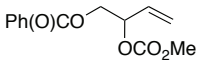
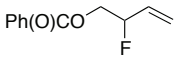
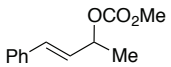
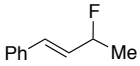
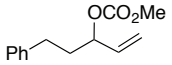
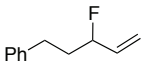
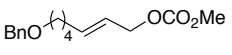
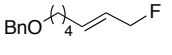
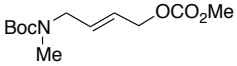
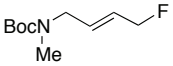
Reaction conditions: allylic carbonate (0.1 mmol), TBAF·4*t*BuOH (0.2 mmol), **[Ir-1]** (2 mol% in 4 portions), d_2-DCM (5 mL), 40 °C. 10 aliquotes of 0.5 mL collected over 16.5 h and analysed by ^1H NMR over 16.5 h.

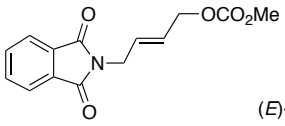
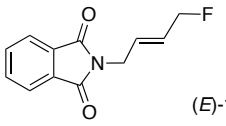
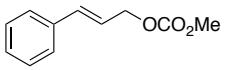
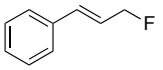
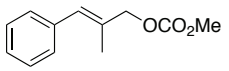
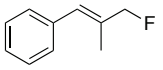
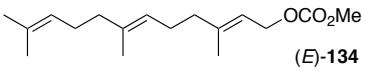
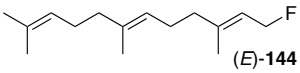
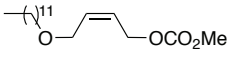
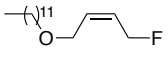
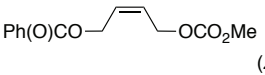
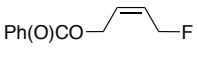
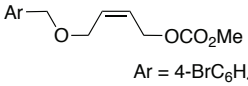
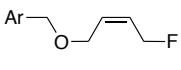
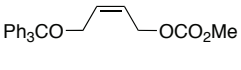
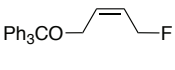
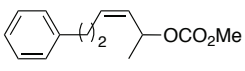
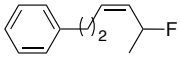
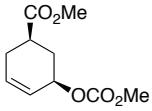
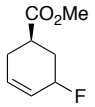
Chart 3. 2 Kinetic Study on Fluorination of **118a**, (*E*)-**118b** and (*E*)-**118b**

3.5.2 Substrate Scope

With the optimal conditions identified, the substrate scope of this reaction was examined. The work described in this section was carried out in collaboration with T. Khotavivattana[174] and Dr. M. Tredwell.[175]

The branched allylic carbonates **126**-**127a** and **128** underwent fluorination under the optimised conditions, affording products **138a, 74a** and **112**, as single branched isomers in moderate to good yields (Table 3.9, entries 1-3). Longer reaction times and higher catalyst loading (4 mol%) was required for less reactive substrates (Table 3.9, entries 1-3). The non-terminal branched allylic carbonate **128** gave (*E*)-4-fluoropent-2-en-1-ylbenzene **112** as a single regio- and *E*-isomer in 66% yield (based on ^{19}F NMR) (entry 3). This result is in contrast to what observed under Pd-catalysis, where diene **115** was the main product, starting from the corresponding *p*-nitrobenzoate **113** (Table 3.2). The fluorination of **129** was not successful, and only unreacted starting material remained after 24 h (Table 3.9, entry 4).

Entry	Allyl Carbonate (SM)		Product (P)		Time (h)	SM:P[a]	Yield (%)[b]
1[c]		**126a**		**138a**	3	5:95	64
2[c]		**127a**		**74a**	40[d]	42:58	32
3[e]		**128**		**112**	24[d]	12:88	66[f]
4[e]		**129**		**139**	24[d]	100:0	--
5		(*E*)-**130**		(*E*)-**140**	18	30:70	68
6		(*E*)-**131**		(*E*)-**141**	18	15:85	64

7	 (*E*)-**132**	 (*E*)-**142b**	18	34:66	48[g]
8	 (*E*)-**116**	 (*E*)-**111a**	24	100:0	--
9	 (*E*)-**133**	 (*E*)-**143**	18	100:0	--
10[e]	 (*E*)-**134**	 (*E*)-**144**	18[d]	100:0	--
11[c]	 (*Z*)-**126b**	 (*Z*)-**138b**	3	19:81	65
12[c]	 (*Z*)-**127b**	 (*Z*)-**74b**	24	29:71	65
13	 Ar = 4-BrC_6H_4, (*Z*)-**135**	 (*Z*)-**145**	18	13:87	52
14[e]	 (*Z*)-**136**	 (*Z*)-**146**	5[d]	0:100	50[h]
15[c]	 (*Z*)-**137**	 (*Z*)-**147**	18	100:0[i]	--
16	 *syn*-**89**	 **77**	24	100:0	--

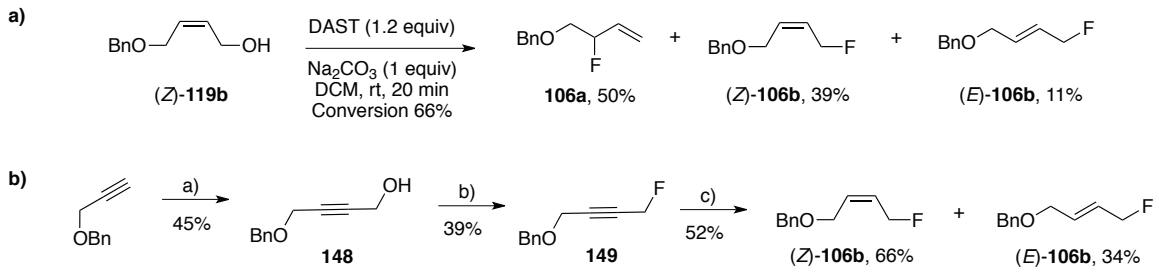
Reaction conditions: *a*. Analysis by ^{1}H NMR of the crude reaction mixture. *b*. Yield of isolated product. *c*. Starting material kindly provided by T. Khotavivattana.[174] *d*. 4 mol% of **[Ir-1]**. *e*. Starting material kindly provided by Dr. M. Tredwell.[175] *f*. NMR yield. *g*. l/b ratio = 15:1. *h*. *Z*/*E* ratio = 18:1. *i*. Trace of (*Z*)-**147** detected by ^{19}F NMR of the crude reaction mixture.

Table 3. 9 Ir-Catalysed Fluorination of Branched and Linear Allylic Carbonates

Linear allylic carbonates (*E*)-**130**-**132** reacted within 18 h, affording the fluorinated products (*E*)-**140**-**142** with excellent *E*-stereoselectivity and in good yields (48-68%, Table 3.9, entries 5-7). For this series, carbamate ((*E*)-**141**) and imide ((*E*)-**142b**) in addition to ether ((*E*)-**106b**) functional groups could be accommodated within the substrate. Cinnamyl carbonate (*E*)-**116** was unreactive under the optimised reaction conditions (Table 3.9, entry 8), in contrast to the results achieved under Pd-catalysis (Scheme 3.1). Also 2-methyl

cinnamyl carbonate (*E*)-**133** was inert to fluorination, and after 18 h only unreacted starting material was recovered (Table 3.9, entry 9). This is in line with the complete absence in literature of examples on the enantioselective Ir-catalysed substitutions of highly substituted allylic derivatives. The highly conjugated carbonate (*E*)-**134** led to complete recovery of starting material after 24 h (Table 3.9, entry 10).

Pleasingly, allylic fluorides (*Z*)-**138b**, (*Z*)-**74b** and (*Z*)-**145**-**146** were obtained in a highly regio- and stereoretentive fashion from the corresponding allylic carbonates (*Z*)-**126**-**127b** and (*Z*)-**135**-**136**, respectively (Table 3.9, entries 11-14). The latter were easily accessed by protection of the commercial available (*Z*)-but-2-ene-1,4-diol. The fluorination of (*Z*)-**135**, bearing a halogenated aryl substituent, was highly chemoselective, with the aryl bromide remaining intact (Table 3.9, entry 13). Derivative (*Z*)-**137**, bearing an aliphatic chain as substituent, gave only a trace of a fluorinated product, detected by ^{19}F NMR of the crude reaction mixture and tentatively identified as (*Z*)-**147** (Table 3.9, entry 15). Cyclic carbonate **89** was also an unsuitable substrate for the Ir-catalysed fluorination (Table 3.9, entry 16).[157] This is the first general transition metal catalysed method to synthesise both branched and linear fluorides with excellent selectivity, and starting from commonly used alcohol derivatives. Indeed, the highly selective synthesis of *Z* linear fluorides has no precedent in transition metal catalysis. Alternative methodologies to access this valuable building block are sparse and characterised by poor selectivity and multi-steps approaches.

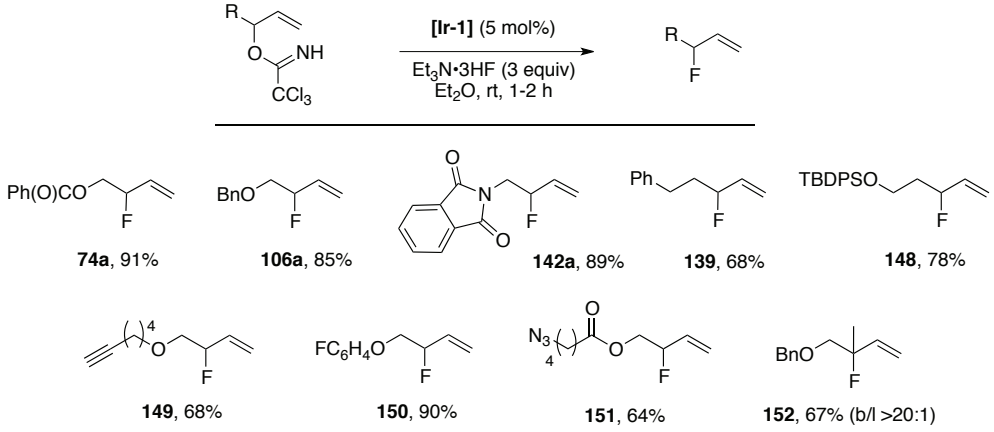


Reaction conditions: a) *n*BuLi (1.1 equiv), *p*-formaldehyde (1 equiv), THF, 0 °C, 4 h; b) DAST (1.1 equiv), DCM, -78 °C to rt, 2 h; c) H_2, Pd/$CaCO_3$, hexane, 0 °C, 2 h.

Scheme 3. 7 Alternative Synthesis for *Z*-Linear Allylic Fluoride (*Z*)-**106b**

When the more commonly used method of deoxyfluorination of alcohol (*Z*)-**119b** using DAST (diethylaminosulfur trifluoride) was attempted, a mixture of the three isomers **106a**, (*Z*)-**106b** and (*E*)-**106b** was afforded within 20 minutes at room temperature. The branched product was favoured, being formed in 50% of conversion (Scheme 3.7a). The *Z*-selective hydrogenation with $Pd/CaCO_3$ of the corresponding alkyne fluoride **149** was carried out as synthetic alternative. However, under these conditions the fluoroalkene (*Z*)-**106b** was afforded in 52% yield and with poor *Z*-stereoselectivity (*Z*/*E* = 66/34, Scheme 3.7b).

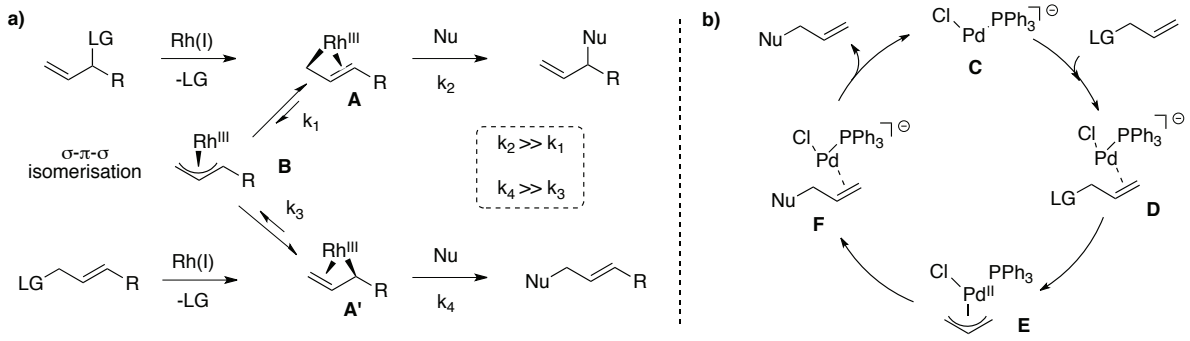
During the course of our research, Nguyen and co-workers reported an Ir-catalysed fluorination reaction of branched allylic trichloroacetimidates with $Et_3N{\cdot}3HF$.[66] They also found that unligated **[Ir-1]** was the best catalyst, leading to a variety of secondary and tertiary branched allylic fluorides with good yields and excellent selectivity (Scheme 3.8). A good functional group tolerance was also shown, and the use of imides (**142a**), silyl ether (**148**), terminal alkynes (**149**) and azide (**151**) substituents were tolerated. Starting from different derivatives, such as esters or carbonate, fluorination in the presence of **[Ir-1]** catalyst did not occur. This suggested a crucial role of the trichloroacetamidite,[176] acting not only as leaving group. Moreover, under these conditions the fluorination of *E*- and *Z*-linear trichloroacetamidate derivatives was unsuccessful, yielding less than 10% of the corresponding branched fluorinated product after 12 h at room temperature.



Scheme 3. 8 Ir-Catalysed Fluorination of Branched Allylic Trichloroacetamidates with $Et_3N{\cdot}3HF$

3.6 Probing the Origin of Regio- and Stereoselectivity

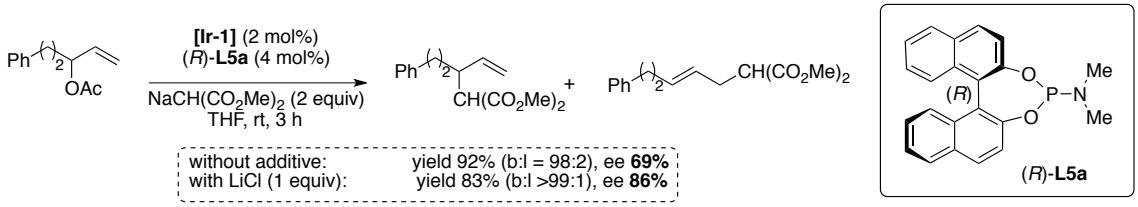
The regioselectivity observed upon fluorination of branched and *E*-linear carbonates implies that their transformations are not proceeding through similar η^3-allyl-Ir intermediates, as in the case of Ir-catalysed alkylation and heteroatom substitution reactions (Scheme 3.2). The sense of regioselectivity observed resembles that reported by Evans and co-workers for Rh-catalysed allylic alkylation reactions.[177] The authors suggested that the "memory effect" in the product formation was due to the intermediacy of an enyl organorhodium species (**A** and **A'**), providing mechanistic evidence of its formation. Intermediates **A** and **A'**, starting from branched and linear derivatives, respectively, in the presence of the nucleophile would undergo a rapid S_N2' displacement, faster than isomerisation ($k_2>>k_1$ and $k_4>>k_3$, Scheme 3.9a). A similar selectivity was also found for the corresponding Fe-catalysis, where a σ-allyl intermediate was instead postulated.[178]



Scheme 3. 9 Memory Effect in Rh- and Pd-Catalysed Allylic Alkylation

The Ir-catalysed allylic fluorination may operate *via* a similar mechanism. Another plausible reason behind a regioretentive mechanism in allylic alkylation is an unequal "*trans*" effect arising from unsymmetrical ligations, which are obtained when halide additives are employed (Scheme 3.9b). It has been proposed that, under Pd-catalysed allylic alkylation, the presence of a chloride ion increases the reactivity of monochlorinated-Pd(0) complex **C** towards oxidative addition of the allyl precursor yielding a neutral unsymmetrical π-allyl-Pd

intermediate **E**, with the phosphorus ligand occupying a position *trans* to the departing group. The subsequent nucleophilic addition "*trans*" to the P-ligand would explain the memory effect on the regioselectivity outcome.[179] The increased reactivity of the π-allyl-Pd intermediate coordinated to a halide was also beneficial for the σ-π-σ allylic isomerisation in the asymmetric amination reaction and hence increasement of the enantioselectivity of the process.[119]



Scheme 3. 10 Ir-Catalysed Enantioselective Allylic Alkylation with Halide Additive

Helmchen et al reported a similar influence of the counterion on regio- and stereocontrol of Ir-catalysed alkylation reactions.[158] The addition of 1 equivalent of LiCl increased the branched over linear selectivity and enantioselectivity in the substitution of branched allylic acetates with sodium dimethyl malonate nucleophile, when **[Ir-1]** catalyst is used with (*R*)-**L5a** (Scheme 3.10).

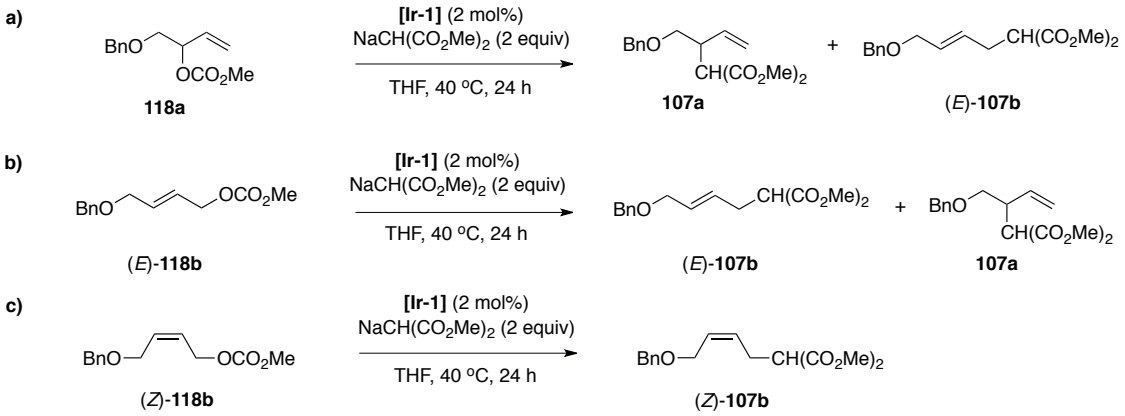
3.6.1 Ir-Catalysed Alkylation of Allylic Carbonates

In order to obtain a direct comparison in terms of reactivity and selectivity between fluorination and alkylation reactions, the **[Ir-1]** catalysed alkylation with sodium dimethyl malonate of the three isomeric carbonates **118a**, (*E*)-**118b** and (*Z*)-**118b** was run in THF at 40 °C for 24 h (Table 3.10, entries 1-3).

In line with what was previously reported by Helmchen and co-workers (Scheme 3.1),[158] the substitution of branched **118a** and linear (*E*)-**118b** were highly unselective, yielding a mixture of branched **107a** and linear (*E*)-**107b** products (Table 3.10, entries 1-2). The similar product distribution obtained for these two systems suggested both reactions

proceed *via* a similar η^3-allyl-Ir intermediate, in contrast to the corresponding fluorination reactions (Scheme 3.6a-b).

An excellent degree of regio- and *Z*-selectivity was instead observed for the alkylation of (*Z*)-**118b** (Table 3.10, entry 3), although characterised by a significantly lower reactivity when compared to the corresponding fluorination reaction (Scheme 3.6c).



Entry	Substrate	Conversion of **118a**/**b** (%)[a]	Ratio **107a**:**107b**[a]	*E*/*Z* in **107b**[a]
1	**118a**	100	67:33	>98:2
2	(*E*)-**118b**	94	55:45	>98:2
3	(*Z*)-**118b**	65	<2:98	<2:98

a. Analysis by ^{1}H NMR of the crude reaction mixture.

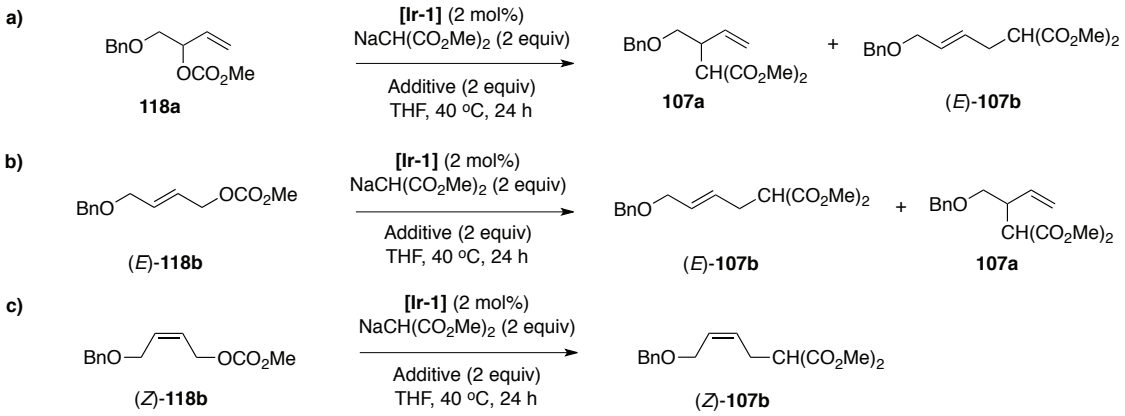
Table 3. 10 Ir-Catalysed Alkylayion of Allylic Carbonates **118a**, (*E*)-**118b** and (*Z*)-**118b**

In order to gain more insights into the unusual stereoselective outcome of the Ir-catalysed allylic fluorination, we decided to examine the influence of TBAF·4*t*BuOH as an additive in the Ir-catalysed allylic alkylation of **118a** and **118b** with sodium dimethyl malonate (Table 3.11, entries 1-3).

The addition of 2 equivalents of TBAF·4*t*BuOH led to a significant increase of regioselectivity for the alkylation of **118a** and (*E*)-**118b**, favouring a much higher degree of structural conservation (Table 3.11, entries 1-2). The results were particularly striking for (*E*)-**118b**, which led exclusively to (*E*)-**119b** (l/b ratio > 20:1). No trace of allylic fluoride was

detected in all three reactions, however a detrimental effect on the alkylation rate was observed, with recovery of unreacted carbonate after 24 h in all cases.

Interestingly, when nBu$_4$NCl was employed as alternative additive in the reaction with (*E*)-**118b** an identical effect of the regioselectivity of the process was observed (Table 3.11, entry 4), confirming the analogous influence of the two halides.



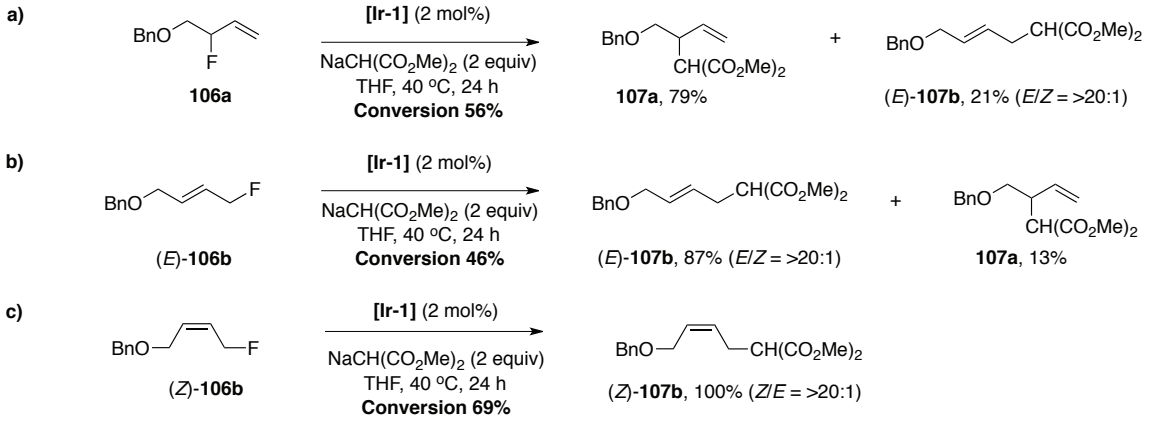
Entry	Substrate	Additive	Conversion of **118a**/**b** (%)[a]	Ratio **107a**:**107b**[a]	*E*/*Z* in **107b**[a]
1	**118a**	TBAF·4*t*BuOH	74	91:9	>98:2
2	(*E*)-**118b**	TBAF·4*t*BuOH	53	<2:98	>98:2
3	(*Z*)-**118b**	TBAF·4*t*BuOH	37	<2:98	<2:98
4	(*E*)-**118b**	nBu$_4$NCl	31	<2:98	>98:2

a. Analysis by ^{1}H NMR of the crude reaction mixture.

Table 3. 11 Ir-Catalysed Alkylayion of Allylic Carbonates in the Presence of External Additives

3.6.2 Ir-Catalysed Alkylation of Allylic Fluorides

To rationalise the role of the TBAF·4*t*BuOH additive, the possible transient formation of an allyl fluoride was considered. This intermediate would then undergo alkylation with malonate, as previously observed under Pd- and Pt-catalysis (Chapter 2). As control experiments allylic fluorides **106a**, (*E*)-**106b** and (*Z*)-**106b** were subjected to alkylation with sodium dimethyl malonate under **[Ir-1]** catalysis for 24 h (Scheme 3.11a-c).



Scheme 3. 11 Ir-Catalysed Alkylation of Branched and Linear Allylic Fluorides

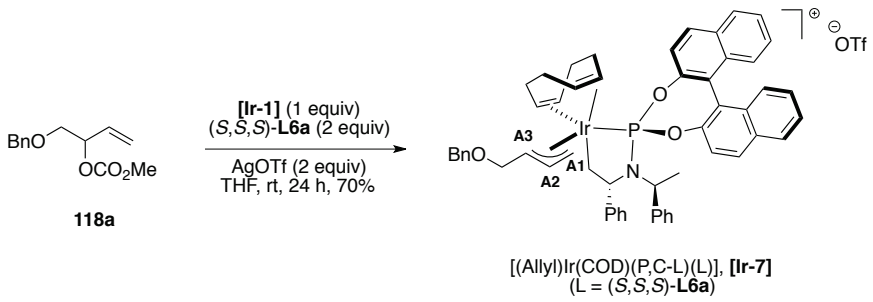
Both branched **106a** and linear **106b** fluorides were reactive towards alkylation, yielding mainly regioretentive products, **107a**, (*E*)-**107b** and (*Z*)-**107b**, respectively. The selectivity in the alkylation products formation was, however, less pronounced than that observed with allyl carbonates/ TBAF·4*t*BuOH systems (Table 3.11, entries 4-6). The lower degree of conversion of fluorides **106a** and **106b**, with respect to carbonates **118a** and **118b**, confirmed the superior leaving group ability of allylic carbonate over fluoride towards alkylation reactions, alike under Pd-catalysis. In an attempt to increase the regiocontrol of the alkylation reaction of allylic fluoride, the addition of 2 equivalent of TBAF·4*t*BuOH was tested in the reaction of linear fluoride (*E*)-**106b**. However, only 5% of conversion of the starting material was observed under these conditions.

The presence of a fluoride ion source, in allylic alkylation with unligated **[Ir-1]**, significantly increases the stereocontrol of the transformation in favour of the regio- and stereoretentive products, in a similar fashion to the corresponding fluorination. These observations may imply the formation of a similar allyl-Ir intermediate for the two transformations, which may resemble those described for Rh- and Fe-catalysed alkylation reactions, based on the high structural conservation observed in the product formation.

3.7 Mechanistic Investigations

3.7.1 Synthesis and Reactivity of [(Allyl)Ir(COD)(P,C-L)L] [Ir-7]

In order to investigate the inactivity of the commonly used complex **[Ir-4]** under our fluorination conditions (Table 3.4, entry 4), the corresponding allyl-Ir intermediate **[Ir-7]** was prepared from the model branched carbonate **118a**, applying a literature protocol (Scheme 3.12).[163i] The new complex **[Ir-7]** was isolated in 70% yield (isomeric ratio 94:6) and fully characterised by one- and two-dimensional NMR spectroscopy (Figure 3.2).



Scheme 3. 12 Synthesis of Allyl-Ir Intermediate **[Ir-7]**

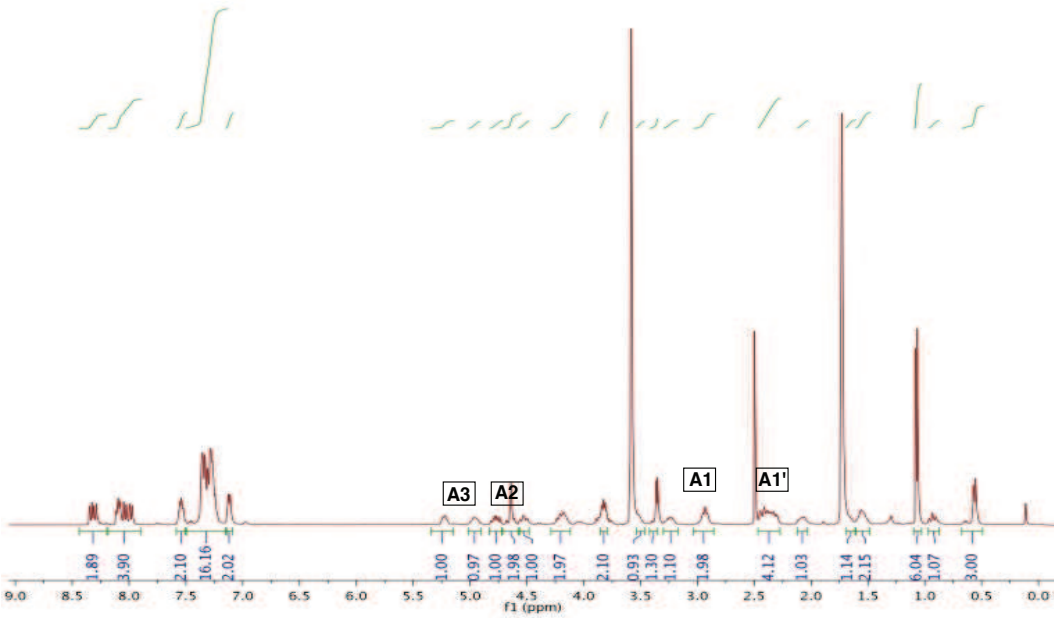
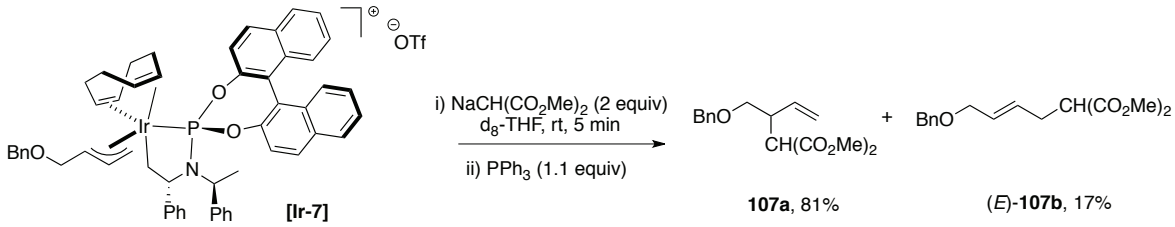


Figure 3. 2 ^{1}H NMR Spectrum of Complex **[Ir-7]** in d_8-THF

The intermediancy of allyl-Ir complexes of **[Ir-7]** type, in asymmetric substitutions catalysed by the pre-catalyst **[Ir-1]** in combination with phosphoramidite-based ligand **L6**, was

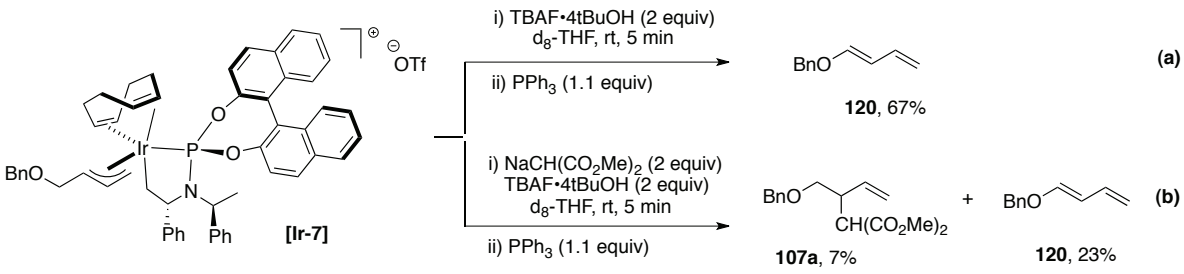
demonstrated independently by Hartwig and Helmchen.[163] To this end, Hartwig et al treated the pre-isolated allyl-Ir complex with a series of nucleophiles, obtaining the substituted products with yields and selectivity similar to that achieved under catalytic conditions.[163h] Employing a similar procedure, the reactivity of intermediate **[Ir-7]** was examined towards alkylation, by treating it with an excess of sodium dimethyl malonate in d_8-THF at room temperature (Scheme 3.13). After 5 minutes the reaction mixture was quenched by addition of 1.1 equivalents of PPh_3, to enable the release of the substituted product from the coordinative sphere of the metal. Full conversion into the substituted products **107a** and (*E*)-**107b** was obtained in a ~ 4:1 ratio, in line with the selectivity observed in catalytic mode (Table 3.10, entry 1).



Scheme 3. 13 Alkylation of Intermediate **[Ir-7]**

When complex **[Ir-7]** was exposed to 2 equivalents of TBAF·4*t*BuOH, following the same procedure, diene **120** was formed as the only detectable product, along with full decomposition of the unreacted starting material (Scheme 3.14a). The origin of the decomposition of the complex **[Ir-7]** under these conditions is unclear, and neither ^{19}F NMR or ^{31}P NMR analysis of the reaction mixture showed any signal attributable to new Ir-F or P-F bonds. The instability of **[Ir-7]** in the presence of TBAF·4*t*BuOH was further proved, by repeating the alkylation reaction, employing TBAF·4*t*BuOH as additive (Scheme 3.14b). In this case, derivative **107a** was obtained in 7% yield, and only traces of (*E*)-**107b** were detected, along with 23% of diene **120**, and full decomposition of **[Ir-7]**. Collectively, these

data, along with the unsuccessful catalytic attempts, demonstrate that the allyl Ir-intermediate **[Ir-7]** is deactivated by TBAF·4*t*BuOH in d_8-THF.



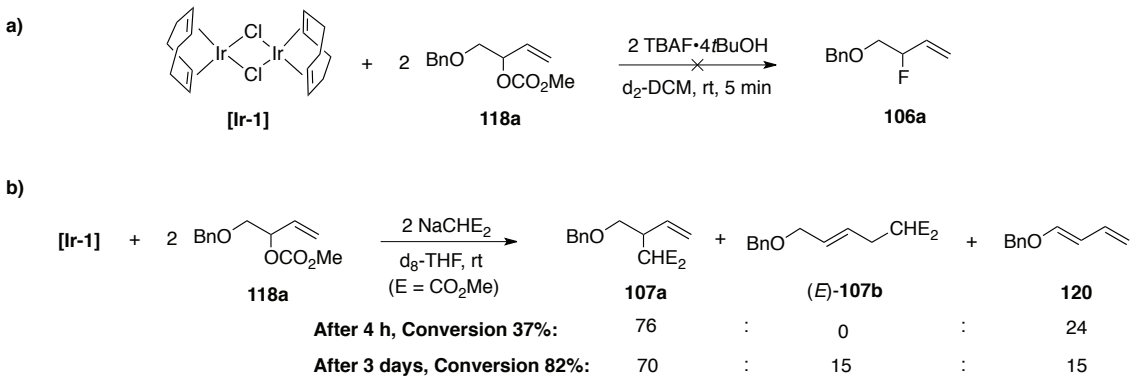
Scheme 3. 14 Interaction of Intermediate **[Ir-7]** with TBAF·4*t*BuOH

Further stoichiometric studies carried out in d_2-DCM indicated that **[Ir-7]** is stable in the presence of TBAF·4*t*BuOH at room temperature over 18 h, but decomposed into diene **120** after 30 minutes at 40 °C. This change in reactivity of **[Ir-7]** was unexpected, and we decided to further investigate the solvent dependency, by subjecting **[Ir-7]** to alkylation conditions in d_2-DCM, employing diethyl malonate (with BSA as base) as nucleophile. Surprisingly, the allyl-Ir complex was inert and fully recovered even after leaving the mixture over extended time at 40 °C (see Chapter 4 for further details). These results, although inconclusive in the origin of the inability of **[Ir-4]** to catalyse the allylic fluorination reaction, discouraged further work with phosphine-Ir catalysts and encouraged us to focus on the active complex **[Ir-1]**.

3.7.2 Stoichiometric Studies with [Ir-1]

In an attempt to identify the intermediate in the fluorination reaction of allylic carbonates, a series of stoichiometric studies was undertaken, employing **[Ir-1]** as catalyst, and TBAF·4*t*BuOH as fluorinating agent. First, a stoichiometric reaction, monitored by ^{1}H and ^{19}F NMR, was carried out in d_2-DCM at room temperature, employing 1 equivalent of dimer **[Ir-1]**, 2 equivalents of branched carbonate **118a** and 2 equivalents of TBAF·4*t*BuOH. After 5 minutes, the signals related to **[Ir-1]** and **118a** disappeared, but no fluorinated product

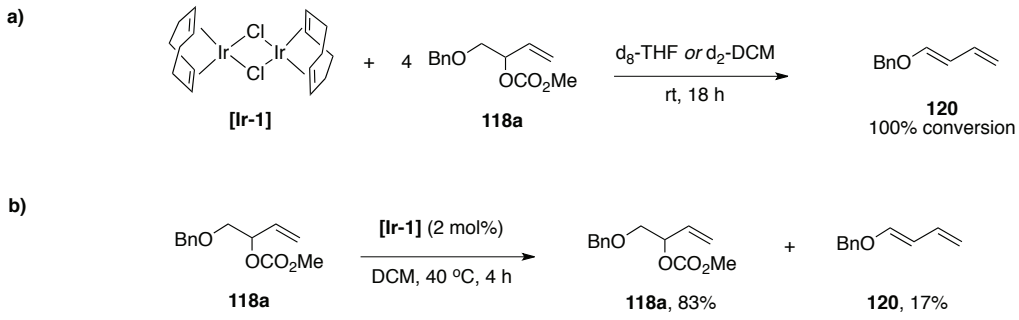
106a was formed (Scheme 3.15a). The addition of 2 extra equivalents of TBAF·4*t*BuOH and COD in order to push the fluorination reaction were unsuccessful. No apparent changes occurred in the ^{1}H NMR of the mixture after extended time. To validate the reactivity of the stoichiometric system, carbonate **118a** (2 equiv) was subjected to **[Ir-1]** (1 equiv) and sodium dimethyl malonate (2 equiv) in d_8-THF and monitored over time (Scheme 3.15b). After 5 minutes, only unreacted starting materials were detected by ^{1}H NMR, indicating a difference in reactivity between the two systems under study. After 4 h, 37% of carbonate **118a** was converted into branched substituted **107a** and diene **120**, in a ratio of 76% to 24%, respectively. Almost full conversion of **118a** was obtained after 3 days at room temperature, to yield mainly derivative **107a**, in line with the results obtained under catalytic conditions (Table 3.10, entry 1).



Scheme 3. 15 Stoichiometric Fluorination and Alkylation Reaction with **[Ir-1]** and Carbonate **118a**

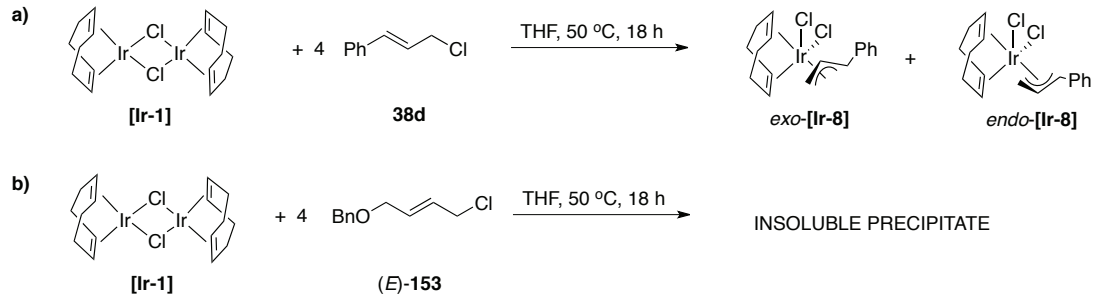
Based on the high reactivity of the stoichiometric system in the presence of TBAF·4*t*BuOH, we attempted to pre-form the Ir-allyl intermediate. To this end, **[Ir-1]** was treated with an excess carbonate **118a** (4 equiv) in THF at 50 °C for 18 h. The yellow precipitate formed was filtered off, but it could not be analysed due to poor solubility in most deuterated organic solvents. When the same reaction was performed in either d_8-THF or d_2-DCM at room temperature and monitored by ^{1}H NMR, no reactivity was observed within one hour, but after 18 h, carbonate **118a** was fully converted into diene **120** (Scheme 3.16a). This

result is in line with the results obtained subjecting **118a** to standard catalytic conditions in the absence of TBAF·4*t*BuOH (Scheme 3.16b). Indeed, after 4 h at 40 °C, 17% of diene **120** was afforded, along with 83% of recovered starting material.



Scheme 3. 16 Stoichiometric and Catalytic Interaction of **[Ir-1]** with Carbonate **118a**

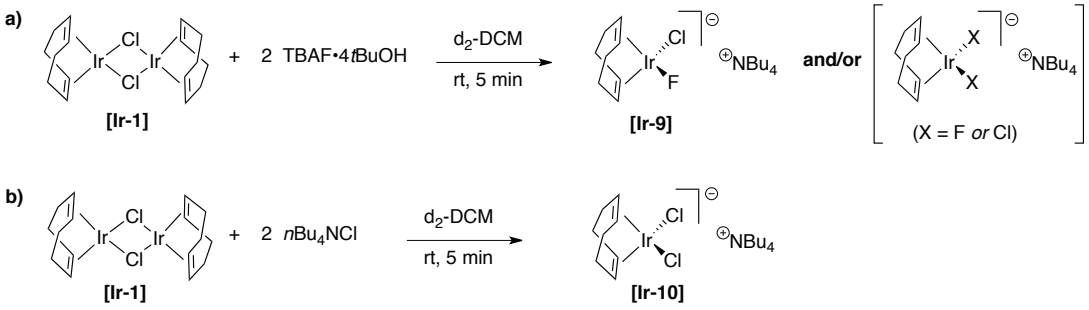
In a previous study, Helmchen et al found that the oxidative addition of an allyl acetate with precursor **[Ir-1]** did not take place in the absence of a nucleophile.[158] The same authors were able to isolate the η^3-allyl-Ir intermediate **[Ir-8]** starting from the corresponding allylic chloride **38d** (Scheme 3.17a). However, attempts to reproduce this method with allylic chloride (*E*)-**153** were unsuccessful (Scheme 3.17b).



Scheme 3. 17 Synthesis of Allyl-Ir Intermediate

A careful analysis of the ^{1}H NMR spectra of the reaction mixture in Scheme 3.15a, showed new distinctive signals related to COD ligand, which could be attributed to a monomeric Ir complex. Based on this observation, the interaction between **[Ir-1]** and TBAF·4*t*BuOH was then investigated. To this end, dimer **[Ir-1]** was mixed with 2 equivalents of TBAF·4*t*BuOH

in d_2-DCM at room temperature, and an instantaneous change in color was observed, from orange to deep green (Scheme 3.18a). The ^{1}H NMR spectra showed full consumption of dimer **[Ir-1]** and the formation of a new complex, tentatively assigned to the ionic monomeric species [Ir(COD)(Cl)(F)]NBu_4 **[Ir-9]** (Scheme 3.18a). The possibility of more than one fluoride coordinated to the metal was considered, and hence the stoichiometry of TBAF·4*t*BuOH versus **[Ir-1]** was increased from 2 to 4 and 6 equivalents. The ^{1}H NMR of the reactions gave a complex mixture of products, in addition to **[Ir-9]**. Although, there are no reports in the literature related to complex **[Ir-9]**, the corresponding chloride complex [Ir(COD)Cl_2]NBu_4 **[Ir-10]** was achieved, by treatment of **[Ir-1]** with *n*Bu_4NCl (Scheme 3.18b).[180]



Scheme 3. 18 Synthesis of Cationic Complexes **[Ir-9]** and **[Ir-10]**

Following the same procedure, we repeated the *in situ* preparation of complex **[Ir-10]**, which gave ^{1}H and ^{13}C NMR spectra comparable to that obtained for complex **[Ir-9]** (Figure 3.3b-c). The ^{19}F NMR of **[Ir-9]** showed a broad peak at -151.5 ppm, which may correspond to the fluorine atom coordinated to Ir. However, this signal may be attributed to a free fluoride species in solution (^{19}F NMR δ of $^-BF_4$ = -150.4 ppm). No trace of the TBAF reagent (broad peak at -119.0 ppm) was detected, suggesting full consumption of the reagent. The formation of the Ir-F bond could not be unambiguously confirmed by NMR analysis, due to the absence of any interaction between the ligand COD and the fluoride coordinated to the metal, as determined by a 2D HOESY experiment.

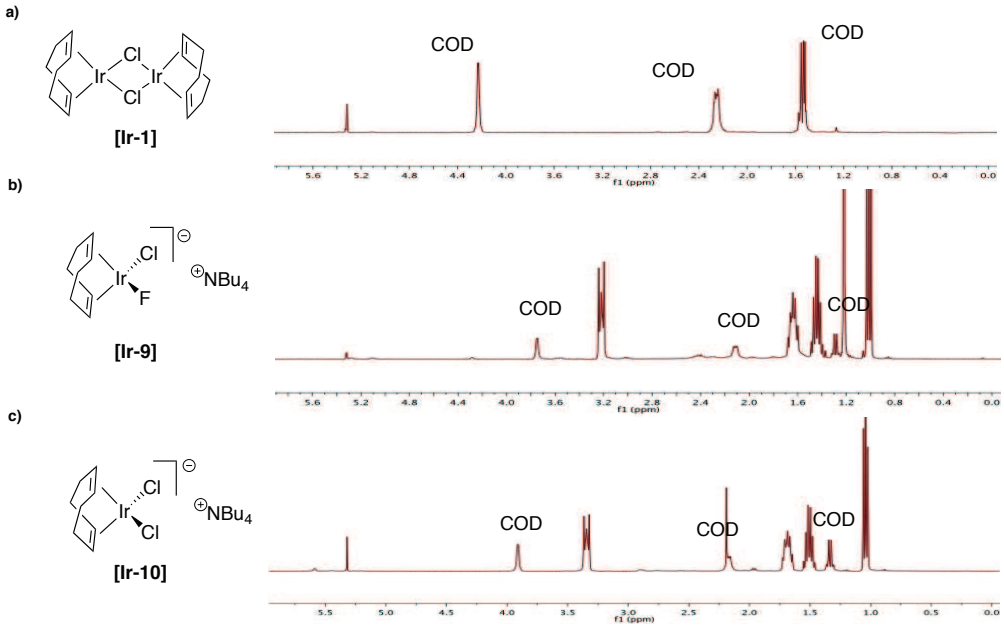
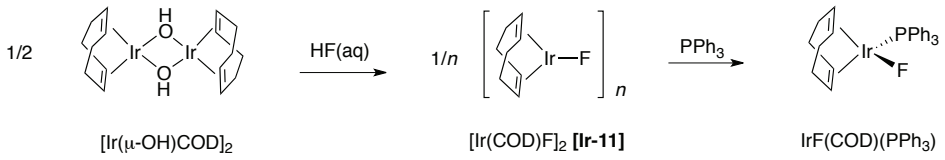


Figure 3. 3 ^{1}H NMR Spectra of Complexes **[Ir-1]**, **[Ir-9]** and **[Ir-10]**

Roesky et al reported the synthesis of complex $[Ir(COD)F]_n$ **[Ir-11]**, by treating dimer $[Ir(\mu\text{-}OH)COD]_2$ with 73% aqueous HF (Scheme 3.19).[181] The insolubility of the resulting product prevented the authors from characterising the complex, and a polymeric structure was proposed. However, the FIR spectrum of **[Ir-11]** exhibited an ν_{IrF} stretching mode at 478 cm^{-1}, similar to that of $IrF(CO)(PPh_3)_2$, ν_{IrF} = 451 cm^{-1}.[182] Treatment of **[Ir-11]** with PPh_3 allowed the isolation of the mono-phosphine complex $IrF(COD)(PPh_3)$, which showed a singlet at -219.3 ppm in the ^{19}F NMR spectrum, assigned to the Ir-bounded fluorine atom.

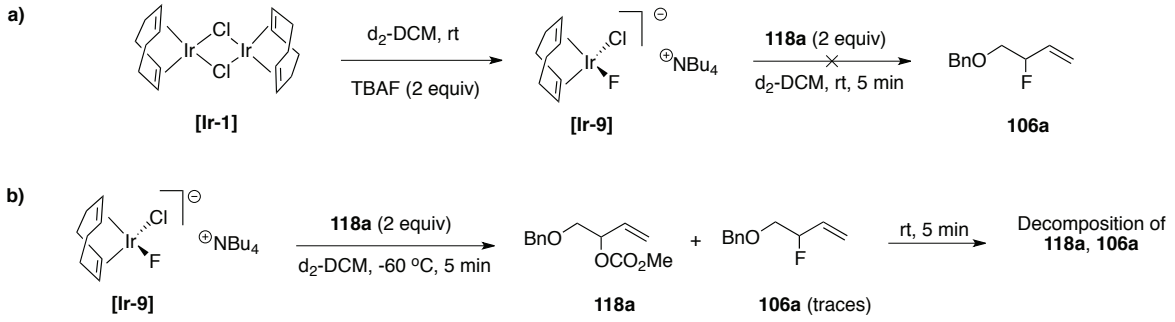


Scheme 3. 19 Synthesis of Ir-F Complex **[Ir-11]** by Roesky

The difference in chemical shift between the signal of **[Ir-9]** (-128.0 ppm) and **[Ir-11]** (-219.3 ppm) in their ^{19}F NMR spectrum may be due to the different electronic distribution on the metal, as the first is an anionic species and the latter is neutral. The FIR spectrum of

[Ir-9] showed a ν stretching at 455 cm^{-1}, which could be attributed to the Ir-F bond, by analogy with literature reports. Any attempt to isolate the complex **[Ir-9]** was unsuccessful, although it showed high stability in solution also after extended time. Mass spectroscopy analysis were inconclusive.

In order to validate the reactivity of complex **[Ir-9]** in the fluorination reaction, the allylic carbonate **118a** (2 equiv) was added to a pre-mixed solution of **[Ir-1]** (1 equiv) and fluorinating agent (2 equiv) in d_2-DCM (Scheme 3.20a). For this experiment TBAF, from a 1 M solution in THF, was employed as fluoride source as it is easier to handle than TBAF·4*t*BuOH (Table 3.8, entry 9). Within 5 minutes at room temperature full conversion of carbonate **118a** was observed, but the formation of the corresponding fluoride **106a** was not detected. The resulting ^{1}H NMR spectrum was very similar to that obtained for the reaction in Scheme 3.15a.



Scheme 3. 20 NMR Studies on **[Ir-1]**-Mediated Fluorination of Carbonate **118a**

Due to the high reactivity of the system, the addition of **118a** was carried out and monitored at -60 °C (Scheme 20b). The complex **[Ir-9]** was first formed by addition of **[Ir-1]** (1 equiv) and TBAF (2 equiv) at room temperature in d_2-DCM. The mixture was then cooled down at -60 °C and a ^{1}H and ^{19}F NMR were recorded, which did not differ from the one obtained for the mixture at room temperature. Carbonate **118a** (2 equiv) was added at -60 °C, and a ^{19}F NMR spectra acquired shortafter showed the appearance of a new distinct signal, related to the branched fluorinated product **106a** (singlet at -185.3 ppm). After 15 minutes a double

of doublet peak at -144.2 ppm (J = 15, 34 Hz) was detected in addition to that of the product **106a** and of the complex **[Ir-9]**. The ^{1}H NMR showed mainly starting material **118a** and complex **[Ir-9]**, along with a mixture of products that were not identified. As soon as the reaction was warmed to room temperature full decomposition of carbonate **118a** and fluoride **106a** was observed.

This preliminary result suggested that under the catalytic conditions the cationic species **[Ir-9]** is formed, and it may act as an active catalyst for the fluorination reaction. Further investigations are, however, required to fully understand the mechanism of the reaction and the high selectivity observed in the product distribution. The possibility to use an Ir catalyst other than **[Ir-1]** for mechanistic investigations, with at least one phosphine ligand, would enable an easier monitoring of the eventual Ir-intermediates formation.

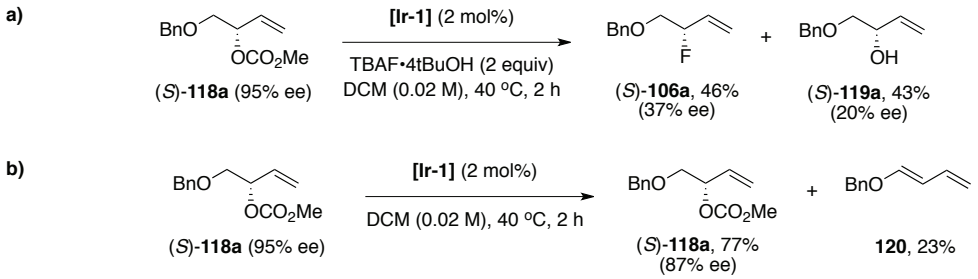
3.7.3 Stereochemistry

From initial studies by Takeuchi et al, it was demonstrated that the mechanism involved in the Ir-catalysed substitution with soft nucleophiles occurs *via* a double inversion pathway.[157] The highest degree of conservation of enantiopurity was achieved when **[Ir-1]** was used without ancillary ligands, such as phosphite.[158]

In an investigation of the stereoselectivity of the newly developed Ir-catalysed fluorination, the branched enantioenriched allylic carbonate (*S*)-**118a** (95 % ee) was synthesized by Dr. M. Tredwell.[175] The preparation was carried out from the commercial available butadiene monoxide, *via* enantioselective epoxide opening reported by Jørgensen.[183]

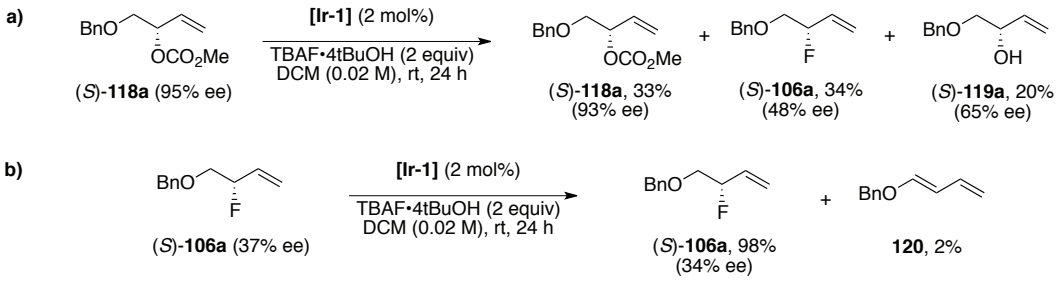
When (*S*)-**118a** was subjected to standard fluorination conditions, within 2 h the allylic fluoride (*S*)-**106a** was isolated in 46% yield and with significantly eroded enantiomeric excess (37% ee) with respect to the starting material (95% ee, Scheme 3.21a). The absolute configuration was assigned by preparing independently the allylic fluoride (*S*)-**106a** using a literature protocol.[62] The by-product alcohol (*S*)-**119a** was also afforded with overall retention of configuration and even lower stereocontrol (43%, 20% ee). Control

experiments, conducted in the absence of TBAF·4*t*BuOH (Scheme 3.21b), showed that starting material isomerised only to a small extent (77%, ee = 87%) and was partially converted into the elimination product **120** (23%).



Scheme 3. 21 Ir-Catalysed Fluorination of (*S*)-**1a** at 40 °C

When the reaction was run at room temperature for 24 h (Scheme 3.22a), both allylic fluoride (*S*)-**106a** (48% ee) and alcohol (*S*)-**119a** (65% ee) were obtained with higher enantiopurity. Under these milder conditions, it was possible to recover unreacted starting material in 93% ee. The isomerisation of the allylic fluoride (*S*)-**106a** (37% ee) was also investigated under the reaction conditions (Scheme 3.22b), taking into account its reactivity towards **[Ir-1]** catalysed substitution reactions. After 2 h, allylic fluoride (*S*)-**106a** was recovered with almost unchanged enantiomeric excess (34% ee).



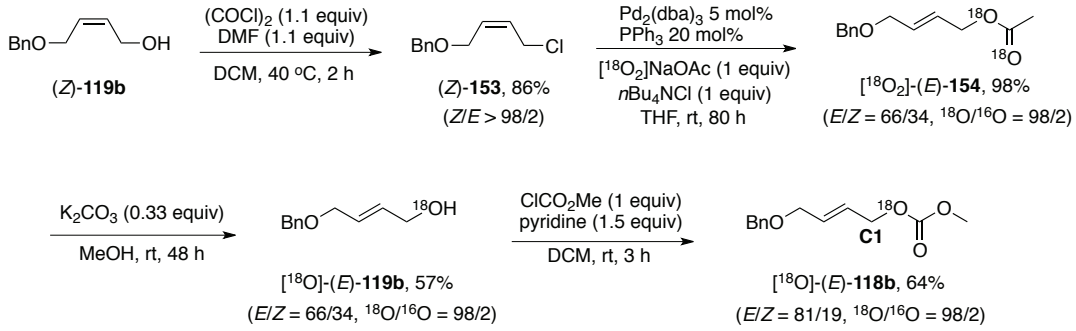
Scheme 3. 22 Ir-Catalysed Fluorination of (*S*)-**118a** at Room Temperature

Although the leakage of stereochemical integrity in the fluorination reaction is significant, overall retention is the predominant pathway. This observation may further account for the intermediancy of an enyl organoiridium intermediate, as suggested for the Rh-catalysed

allylic alkylation reaction (Scheme 3.9a).[177] In addition, this result is consistent with that reported by Doyle et al for the palladium catalysed enantioselective fluorination of cyclic allylic chlorides (Chapter 1, Section 1.4.1).[57] There, the authors showed that the fluoride ion attacks the allyl-Pd intermediate from an outer sphere, in a similar fashion to a soft nucleophile, yielding the overall retention product with excellent selectivity. A completely unselective pathway was instead observed by Nguyen and co-workers for their process of Ir-catalysed fluorination of trichloroacetimidate derivatives.[66] The significant degree of racemisation may derive from a rapid C-C bond rotation of a putative σ-allyl-Ir intermediate prior to fluoride trapping.

3.7.4 [^{18}O]-Labeling Experiments

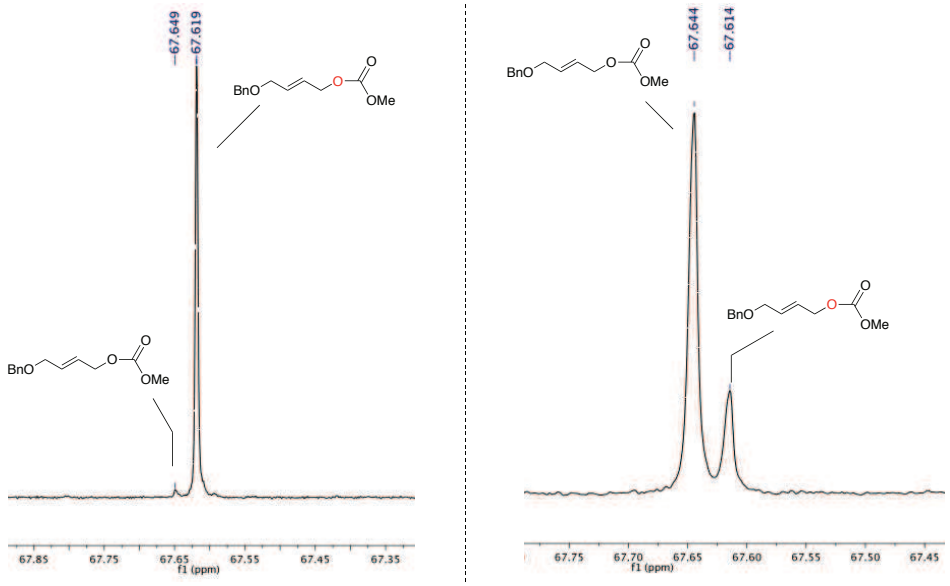
In order to investigate the origin of alcohol side product **119a** under our fluorination conditions, a series of [^{18}O]-labeling studies were designed. To this end, the ^{18}O-isotopomer of allylic methylcarbonate (*E*)-**118b** ([^{18}O]-(*E*)-**118b**) was synthesised from allylic chloride **153**, according to a literature procedure (Scheme 3.23).[184]



Scheme 3. 23 Synthesis of Labelled Carbonates [^{18}O]-**118b**

The Pd-catalysed acetylation of allylic chloride (*Z*)-**153** with [^{18}O]$_2$NaOAc led to formation of doubly labeled acetate [^{18}O]$_2$-**154** as a mixture of stereoisomers (*E*/*Z* = 66/34) and with 98% of ^{18}O incorporation. Subsequent hydrolysis of the acetate and protection of the resulting alcohol [^{18}O]-**119b** with methyl chloroformate yielded mono-labeled carbonate

[^{18}O]-(*E*)-**118b**, isolated in 64% yield (*E*/*Z* = 81/19) and with unchanged ^{18}O incorporation at **C1**. The ^{18}O/^{16}O ratio was assigned by integration of the distinctive **C1** (CH_2O) signal of the two isotopomers in the ^{13}C NMR, being the upfield ^{18}O isotope chemical shift of *ca.* 0.03 ppm (Figure 3.4a). A spiked sample with non labeled (*E*)-**118b** confirmed the assignment (Figure 3.4b).



a) **C1** Signal in the ^{13}C NMR of Carbonate [^{18}O]-(*E*)-**118b** (Scheme 3.23)

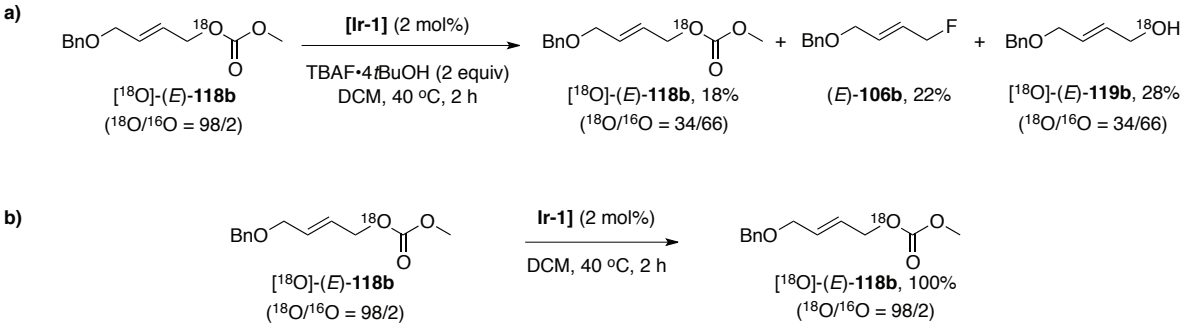
b) ^{13}C NMR of Carbonate [^{18}O]-(*E*)-**118b** spiked with (*E*)-**118b**

Figure 3. 4 Signal of **C1** in ^{13}C NMR of Labeled [^{18}O]-(*E*)-**118b**

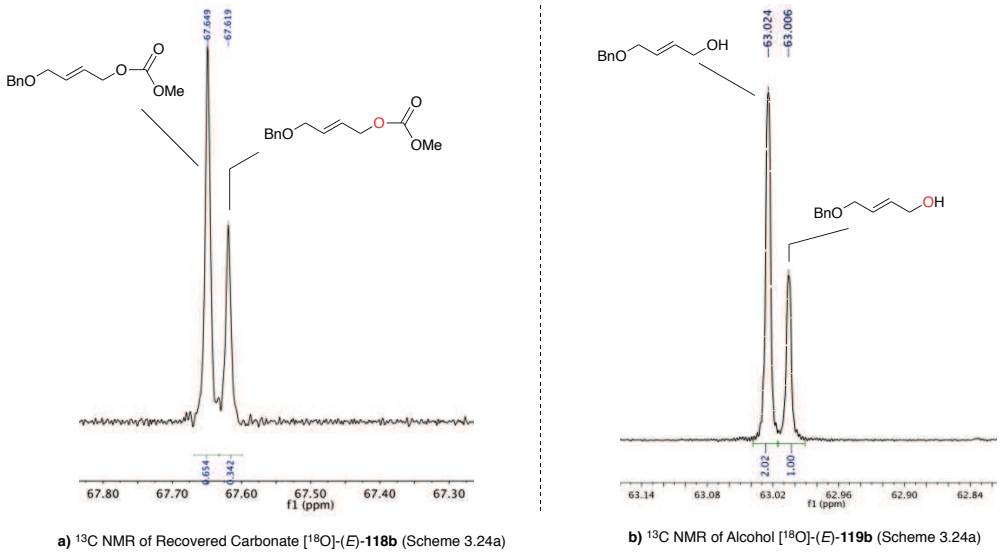
When labeled [^{18}O]-(*E*)-**118b** was subjected to the fluorination conditions (Scheme 3.24a), after 2 h fluoride (*E*)-**106b** (22%) was accompanied by recovered but isotope-depleted carbonate [^{18}O]-(*E*)-**118b** (18%, 34% ^{18}O at **C1**, similar *E*/*Z* ratio, Figure 3.5a). Alcohol (*E*)-**119b** was formed in 28% yield and with a percentage of ^{18}O incorporation identical to that found for the unreacted starting material (34% ^{18}O at **C1,** Figure 3.5b). This result suggested that formation of the alcohol (*Z*)-**119b** may derive from hydrolysis of carbonate [^{18}O]-(*E*)-**118b**.

A test reaction with labeled [^{18}O]-(*E*)-**118b**, under the reaction conditions and in the absence of TBAF·4*t*BuOH, indicated that the carbonate does not scramble in the absence

of the fluoride source within the reaction time, as the starting material remained intact after 2 h (Scheme 3.24b).



Scheme 3. 24 Ir-Catalysed Fluorination of Labelled Carbonate [^{18}O]-(*E*)-**118b**



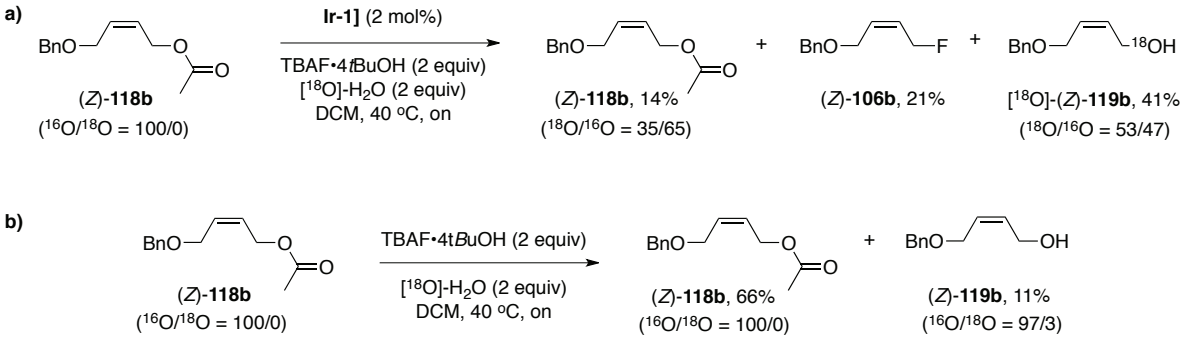
a) ^{13}C NMR of Recovered Carbonate [^{18}O]-(*E*)-**118b** (Scheme 3.24a)

b) ^{13}C NMR of Alcohol [^{18}O]-(*E*)-**119b** (Scheme 3.24a)

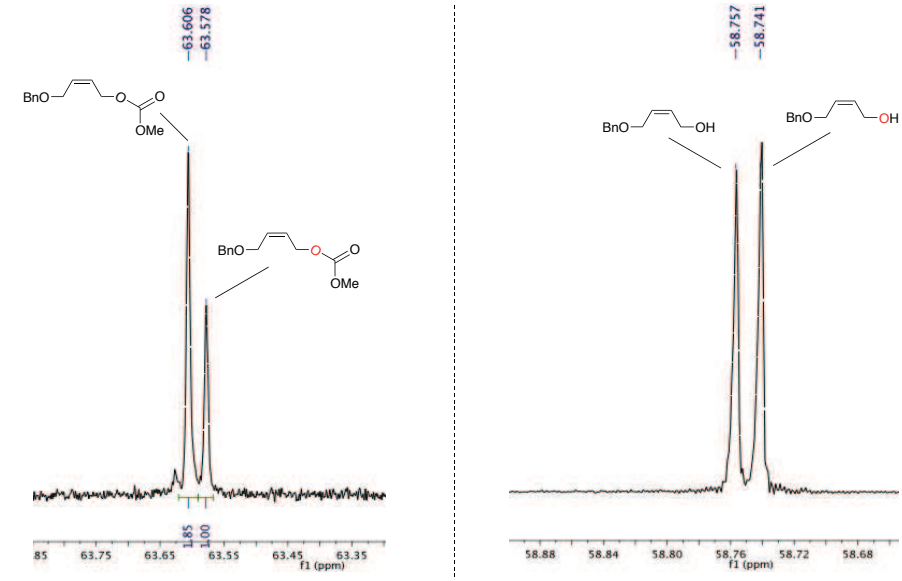
Figure 3. 5 Signal of **C1** in ^{13}C NMR of Recovered [^{18}O]-(*E*)-**118b** and Fomed Alcohol [^{18}O]-(*E*)-**119b**

In order to validate our hypothesis on the origin of the competing hydroxide ion, the fluorination of unlabeled carbonate (*Z*)-**118b** was carried out with the addition of 2 equivalents of [^{18}O]-labeled H_2O overnight (Scheme 3.25a). The major product alcohol (*Z*)-**119b** was isolated in 41% yield and with over 50% of ^{18}O incorporation (Figure 3.6b), along with 21% of allylic fluoride (*Z*)-**106b** and 18% of unreacted (*Z*)-**118b** (35% ^{18}O at **C1**, Figure 3.6a). The higher percentage of ^{18}O-isotopomer of alcohol (*Z*)-**119b**, with respect to that of

labeled carbonate [^{18}O]-(*Z*)-**118b**, suggests more than one pathway is involved in the alcohol formation. When the reaction with [^{18}O]H_2O was repeated in the absence of catalyst **[Ir-1]** (Scheme 3.25b), mainly intact starting material was recovered, and only 11% of alcohol (*Z*)-**119b** isolated (3% ^{18}O at **C1**). This low level of ^{18}O incorporation in (*Z*)-**119b** excluded the hypothesis of a non-catalysed S_N2 displacement of the carbonate by a hydroxide ion for the alcohol formation. In addition, this indicated that a plausible mechanism might involve the hydroxide attack to the carbonate, and subsequent decarboxylation of the resulting acid, as shown in Scheme 3.4a.



Scheme 3. 25 Ir-Catalysed Fluorination of Carbonate (*Z*)-**118b** with [^{18}O]-H_2O

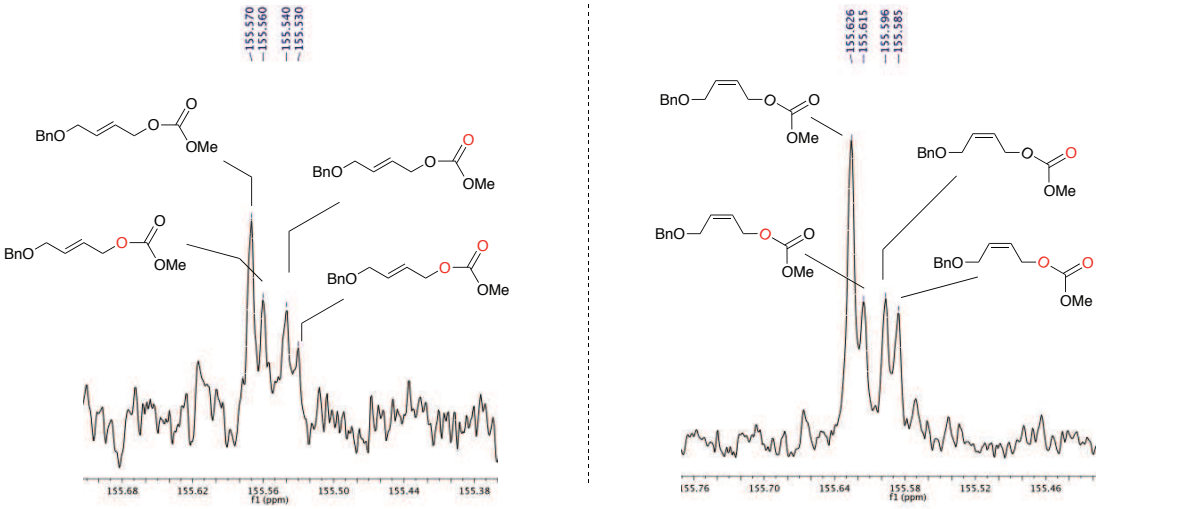


a) ^{13}C NMR of Recovered Carbonate [^{18}O]-(*E*)-**118b** (Scheme 3.25a)

b) ^{13}C NMR of Alcohol [^{18}O]-(*E*)-**119b** (Scheme 3.25a)

Figure 3. 6 Signal of **C1** in ^{13}C NMR of Recovered [^{18}O]-(*Z*)-**118b** and Fomed Alcohol [^{18}O]-(*Z*)-**119b**

Although these labeling experiments could not undoubtedly account for elucidating the origin of the by-product alcohol under these fluorination conditions, they revealed an unexpected result in the recovered carbonates (*E*)-**118b** and (*Z*)-**118b** under catalytic turnover experiments of Schemes 3.24a and 3.25a, respectively. Moreover, a closer analysis of the C=O region in their ^{13}C NMR spectrum showed that all four possible oxygen isotopomers of the CH_2O-C=O component were formed in both experiments, including significant amounts of the doubly labeled [$^{18}O]_2$-**118b**. The signals of the four carbonyls were assigned with an upfield ^{13}C chemical isotope shift of *ca.* 0.01 ppm for ^{18}O-C=O and *ca.* 0.03 ppm for O-C=^{18}O (Figure 3.7).[185]



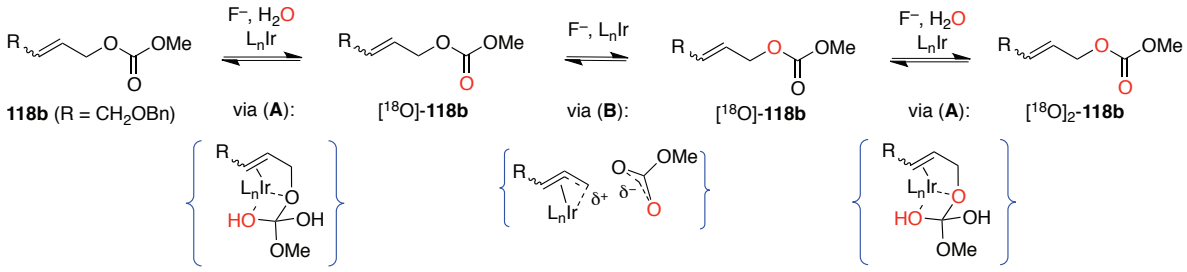
a) Ir-Catalysed Allylic Fluorination of Labelled [^{18}O]-(*E*)-**118b** (Scheme 3.24a)

b) Ir-Catalysed Allylic Fluorination of (*Z*)-**118b** with [^{18}O]-H_2O Additive (Scheme 3.25a)

Figure 3. 7 The ^{13}C NMR Region of Recovered [^{18}O]-(*E*)-**118b** and (*Z*)-**118b**

This observation indicated that an ion-pair intermediate, such as **B** (Scheme 3.26), may scramble the ^{18}O-label by internal return under the reaction conditions, as has been previously observed for ^{18}O-labeled sulfonates and carboxylates in S_N1 reactions.[186] A similar pathway was also suggested by Lloyd-Jones et al for the Pd-catalysed label equilibration between $^{13}CO_2$ and diallyl carbonate.[187] In addition, this labeling result supported the hypothesis of an unsymmetrical enyl σ-allyl intermediate rather than a η^3-allyl species for the Ir-catalysed fluorination, based on the high degree of regio- and

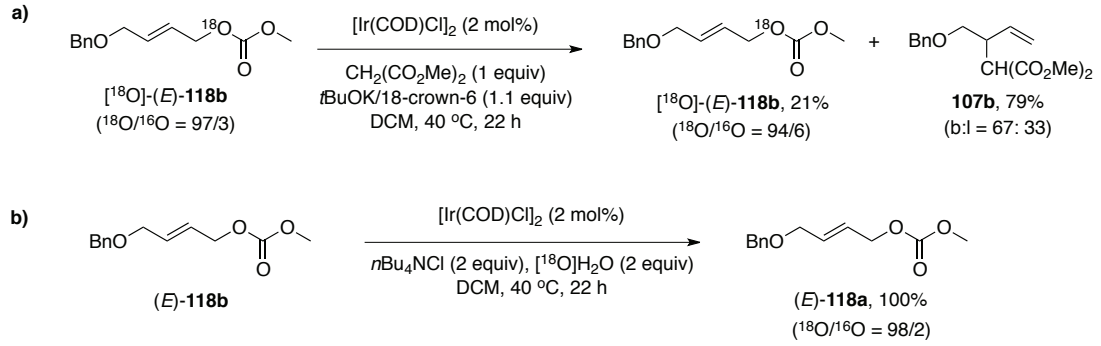
stereoselectivity of the process, similarly to Rh-catalysis.[177] For the recovery of doubly labeled [^{18}O]$_2$-**118b** and label depleted **118b** carbonates, a further ^{18}O label exchange between carbonate and external water present in the reaction environment is required. This process occurs only in the presence of both **[Ir-1]** and TBAF·4*t*BuOH, and it likely involves a reversible Ir-promoted addition of water to the carbonyl carbon of **118b**, *via* intermediate **A**, followed by dehydration (Scheme 3.26). This could be a common intermediate for the formation of alcohol by-product, if a molecule of methanol is released instead, to form the corresponding carboxylic acid, which leads to alcohol **119b** *via* decarboxylation (Scheme 3.5b). This intermolecular isotope exchange pathway is supported by a similar example in the literature reported by Mosey and Brown detailing a Pd-catalysed thioamide methanolysis reaction.[188]



Scheme 3. 26 Inter- and Intramolecular Isotopic Exchange under Ir-Catalysis

Preliminary studies, carried out by L. Pfeifer,[189] showed that ^{18}O isotope exchange is not occurring when the reaction with labeled [^{18}O]-(*E*)-**118b** is run with sodium dimethyl malonate as nucleophile, in place of TBAF·4*t*BuOH (Scheme 3.27a). In order to investigate the intra- and intermolecular isotopic scrambling in the recovered carbonate in more detail, the unlabeled (*E*)-**118b** was subjected to 2 mol% of **[Ir-1]** in the presence of [^{18}O]-H_2O (2 equiv) and *n*Bu_4Cl (2 equiv) as additive (Scheme 3.27b). After 22 h (*E*)-**118b** was fully recovered with no incorporation of ^{18}O-label, suggesting that the formation of intermediate **A** is exclusively promoted by the fluoride source. Further studies are ongoing in the group

to investigate this unusual isotopic exchange under Ir-catalysis, in the presence of fluoride ion.



Scheme 3. 27 Ir-Catalysed Substitution of Labeled Carbonate [^{18}O]-(*E*)-**118b**

3.8 Iridium Mediated [^{18}F]-Radiolabeling

3.8.1 Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is a non-invasive molecular imaging technique, commonly used to investigate biological processes *in vivo* and detect anomalies in the body at an early stage of a disease.[190] Recently, this methodology has also been employed as a powerful tool for drug discovery and development.[191] The technique is based on the detection of coincident gamma rays emitted by a radiotracer injected in the patient's body, and designed to be receptor or tissue specific, in order to gain information on the targeted tissue or biological process under study. PET imaging agents are radiolabeled with positron-emitting radionuclides, which decay by the emission of a positron (β+). This positron is not directly detected, but it travels for a short distance, which depends on the energy of the specific radionuclide, before colliding with an electron present in the surrounding tissue. This collision, named annihilation, generates two 511 keV γ-rays, that are emitted in opposite directions. By the use of a surrounding detector it is possible to collect a large number of annihilation events and elaborate a three-dimensional image that measures the spatial distribution of radioactivity in the organ under study.

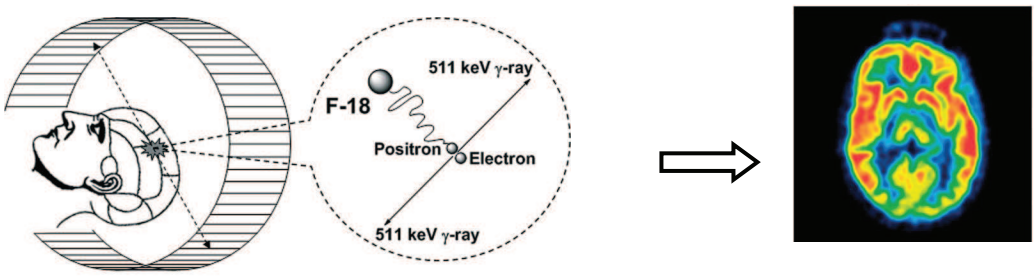


Figure 3. 8 Principle of Positron Emission Tomography (PET) Imaging

Among the radionuclides commonly used for the synthesis of PET radiotracers, ^{18}F represents the most convenient choice, due to its unique imaging physical properties, with respect to other β-emitting nuclides (Table 3.12).[190a] The non-natural radioisotope ^{18}F is characterised by a relatively long half-life of *ca.* 110 minutes and low positron energy ($E^{+}_{\beta+}$ = 0.64 MeV), providing high-resolution images. The long half-life allows for multi-step synthesis of desired radiotracers, long *in vivo* investigation, and makes transport and use of the radiotracers off site possible.[5]

Radionuclide	Nuclear Reaction[a]	Half-life	$E^{+}_{\beta+}$ max (MeV)	Average β^{+} range (mm)
^{11}C	$^{14}N(p,\alpha)^{11}C$	20.4 min	0.97	0.85
^{13}N	$^{16}O(p,\alpha)^{13}N$	10 min	1.20	1.15
^{15}O	$^{15}N(p,n)^{15}O$	2 min	1.74	1.80
^{18}F	$^{18}O(p,n)^{18}F$	110 min	0.64	0.46

a. Nuclear reaction is of the form: [Bombarded nuclide](cyclotron beam, side-product of nuclear reaction)[Product nuclide]; *p* = positron, *n* = neutron, α = alpha particle.

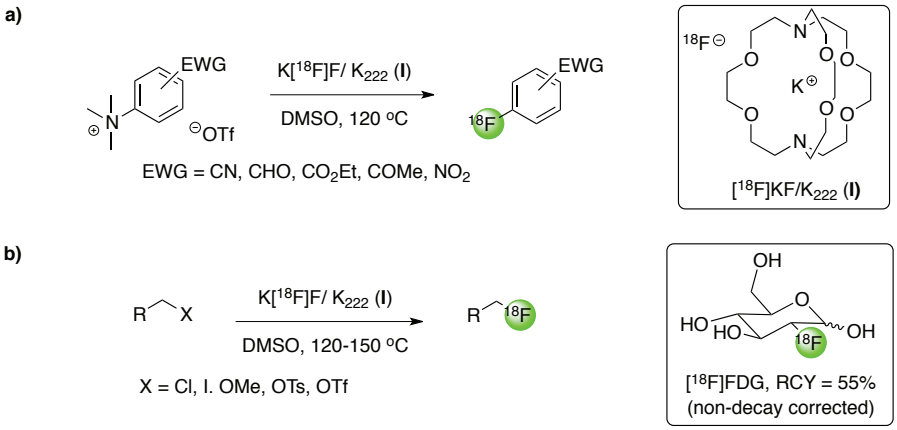
Table 3. 12 Properties of Common Radionuclides for PET Tracers Synthesis

The relatively short half-lives of positron-emitting nuclides require the use of highly efficient and selective radiosynthesis, in order to keep the reaction and purification time as short as possible. As such, late introduction of the radiolabel in the synthetic sequence is desired.

3.8.2 Radiosynthesis of ^{18}F-Radiotracers for PET

Both electrophilic and nucleophilic approaches are currently available for the synthesis of ^{18}F-radiopharmaceuticals. The reagent typically involved in the electrophilic fluorination is the molecular [^{18}F]F_2. This agent is obtained by the bombardment of a target gas consisting of neon or enriched oxygen (^{20}Ne(*d*,α)^{18}F or ^{18}O(*p*,*n*)^{18}F) and due its high reactivity, it is generally converted into less reactive derivatives, such as acetyl hypofluorite (CH_3COO[^{18}F]F),[192] xenon difluoride ([^{18}F]XeF_2)[193] and N-fluoro reagents.[194] The radiolabeling reactions involving [^{18}F]F_2 are not desirable, due to the low specific activity of the reagent, a result of the carrier-added method required for its production. In addition, the maximum achievable radiochemical yield is 50%, as only one of the fluorine atoms in [^{18}F]F_2 carries the ^{18}F label. Nevertheless, electrophilic ^{18}F-fluorinating agents are often employed to carry out S_EAr of non-activated aromatic rings, for example in the synthesis of [^{18}F]FDOPA (L-3,4-dihydroxy-6-[^{18}F]fluoro-phenylalanine).[195]

The preparation of ^{18}F-fluoride is based on the nuclear reaction ^{18}O(*p*,*n*)^{18}F, using enriched water, [^{18}O]H_2O, as target; the ^{18}F-fluoride generated is then dried by a ion-exchange column and eluted using potassium carbonate/kryptofix-222 (K_{222}) or tetra-*n*-butylammonium cation in a water/acetonitile solution. The majority of radiotracers are synthesised from ^{18}F-fluoride *via* either S_N2 or S_{NAr} transformations (Scheme 3.28), such as for the synthesis of [^{18}F]FDG ([^{18}F]2-fluoro-2-deoxy-*D*-glucosio), used in the imaging of cancer.[196] However, most of the direct nucleophilic [^{18}F] fluorination reactions require the use of starting material bearing suitable leaving groups, and in the case of aromatic rings, activation by electron-withdrawing groups.



Scheme 3. 28 Nucleophilic [^{18}F]-Radiofluorination Methodologies

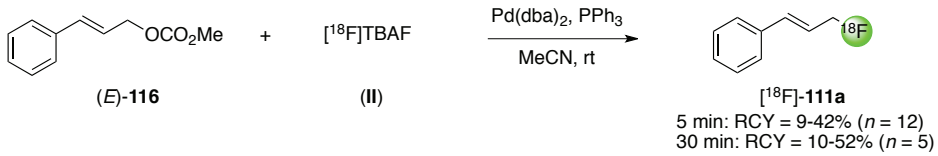
Due to the required harsh reaction conditions, direct nucleophilic fluorination is often not a suitable methodology for the radiosynthesis of complex molecular targets. A common way to overcome such limitation is the use of ^{18}F-labeled prosthetic groups, which are small building blocks employed in an indirect radiosynthetic strategy.[197] This solution, however, is not ideal, as it extends the radiosynthetic sequence, resulting in a decreased radioactivity of the labeled product. For these reasons, the development of general [^{18}F]-radiosynthetic methods that overcome the limitations of the existing techniques are of great interest.

3.8.3 Transition Metal Mediated [^{18}F]-Radiolabeling

Based on the extraordinary importance transition metal catalysis has recently gained in the context of fluorine chemistry, it shows great potential for the ^{18}F-labeling reactions. The mild reaction conditions and high efficiency, which characterise transition metal mediated transformations, perfectly fulfil the requirements for an efficient radiosynthetic sequence, potentially with the fluorination being the final step. Recently, new methodologies employing transition metal-mediated synthesis of ^{18}F-labeled aryl derivatives have been reported by Ritter[198] and our group.[199] The first example, based on an ^{18}F-fluoride umpolung strategy, employed a [^{18}F]F-Pd(IV) species, obtained by treatment of a highly fluorophilic Pd(IV) complex with [^{18}F]KF, as the electrophilic fluorinating source in

combination with Pd(II)Ar substrates. The contribution from our group was based on the electrophilic fluorination of silver aryl derivatives with [^{18}F]Selectfluor®, which was successfully applied to the radiosynthesis of [^{18}F]FDOPA.

The mild reaction conditions required for the previous work within the group on Pd-catalysed fluorination of allylic alcohol derivatives and the advantageous use of a nucleophilic source of fluorine encouraged the authors to investigate a ^{18}F-fluorination variant.[63] The fact that ^{18}F-agent is the limiting reagent (pico or nanomolar concentrations) in 'hot' synthesis required an optimisation of the 'cold' reaction, departing from the initial catalytic conditions (Scheme 3.29).

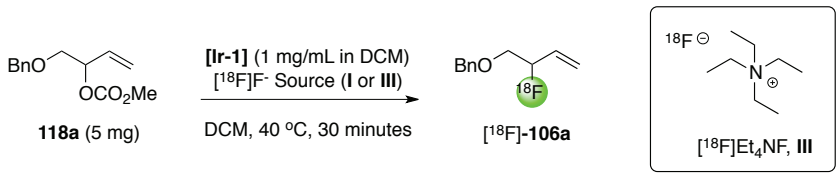


Scheme 3. 29 Pd-Mediated [^{18}F]-Radiofluorination of Cinnamyl Carbonate

The use of [^{18}F]TBAF as ^{18}F-fluoride source in combination with an excess of cinnamyl carbonate (*E*)-**116**, $Pd(dba)_2$ and triphenylphosphine in anhydrous acetonitrile at room temperature led, within 5 minutes, to [^{18}F]-cinnamyl fluoride [^{18}F]-**111a** with a decay corrected radiochemical yield (RCY) of 42% (*n*=12). No significant improvement was observed with longer reaction time (30 minutes, RCY=10-51%, *n*=5), and lower RCY was achieved starting from the corresponding cinnamyl *p*-nitrobenzoate **109a**.

3.8.4 Ir-Mediated [^{18}F]-Radiolabeling of Allylic Carbonates

Based on these precedents and on the mild conditions of our Ir-catalysed fluorination reaction of allylic carbonates, the investigation of the reaction conditions for an Ir-mediated radiosynthesis of allylic ^{18}F-fluorides was performed. These reactions were carried out by Dr. M. Tredwell.[175]



Entry	**[Ir-1]** Loading (μL)	[^{18}F]F$^-$ Source	RCY (TLC)
1	500	**I**	7%
2	250	**I**	8%
3	125	**I**	23%
4	60	**I**	44%
5	10	**I**	14%
6	0	**I**	0%
7	500	**III**	4%
8	250	**III**	21%
9	125	**III**	61%
10	60	**III**	68-76% (*n*=3)
11	60	**III**	44%[a]
12	0	**III**	0%

a. Reaction time of 15 minutes

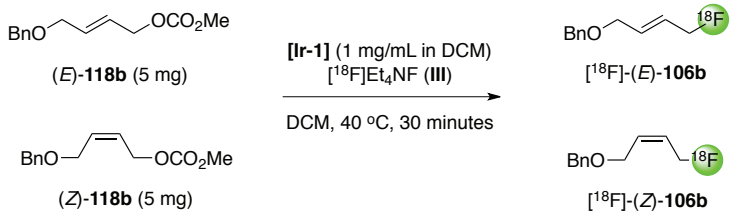
Table 3. 13 Radiochemical Optimisation

Initial screening was carried out with branched carbonate **118a** (5 mg in 440 μL DCM) and **[Ir-1]**, added varying quantities by the use of a 1mg/mL stock solution in DCM. [^{18}F]KF·Kryptofix [2.2.2] (**I**) or [^{18}F]Et$_4$NF (**III**)[200] were used as fluorinating agents (Table 3.13). Running the reaction in DCM at 40 °C for 30 minutes, both reagents (**I**) and (**III**) showed reactivity, with the latter giving superior and more reproducible results. A lower loading of the complex **[Ir-1]** resulted in higher conversion into the desired product [^{18}F]-**106a** (Table 3.13, entries 4 and 10) and test reactions, run in the absence of **[Ir-1]**, confirmed that the fluorination is mediated by the iridium complex (Table 3.13, entries 6 and 12).

The optimal conditions were, therefore, found to be: **118a** (5 mg in 440 μL DCM), **[Ir-1]** (60 μl of a 1mg/mL solution in DCM) and [^{18}F]Et$_4$NF (~ 30 MBq in 30 μl MeCN) in DCM at 40 °C

for 30 minutes. Running the ^{18}F-labeling under these conditions afforded [^{18}F]-**106a** in 68-79% (*n* = 3) RCYs (Table 3.13, entry 10). Shortening the reaction time to 15 minutes resulted in a consist decrease of RCY (44%, Table 3.13, entry 12).

The ^{18}F-fluorination was successfully extended to linear carbonates (*E*)-**118b** and (*Z*)-**118b**, when the **[Ir-1]** loading was increased (125 µl of a 1mg/mL solution in DCM) and the corresponding ^{18}F-labeled products [^{18}F]-(*E*)-**106b** and [^{18}F]-(*Z*)-**106b** were isolated in lower RCYs, especially for the latter (Table 3.14, entries 2 and 5, respectively).



Entry	Substrate	**[Ir-1]** Loading (µL)	RCY (TLC)
1	[^{18}F]-(*E*)-**106b**	60	30-74% (*n*=3)
2	[^{18}F]-(*E*)-**106b**	125	40-62% (*n*=3)
3	[^{18}F]-(*E*)-**106b**	0	0%
4	[^{18}F]-(*Z*)-**106b**	60	0-14% (*n*=3)
5	[^{18}F]-(*Z*)-**106b**	125	8-37% (*n*=3)

a. Analysis by ^{1}H NMR of the crude reaction mixture. *b*. Yield of isolated product. *c*. 4 mol% of **[Ir-1]**. *d*. NMR yield. e. l/b ratio = 15:1. *f*. *Z*/*E* ratio = 18:1

Table 3. 14 [^{18}F]Fluorination of (*E*)-**118b** and (*Z*)-**118b** with **[Ir-1]** and [^{18}F]Et$_4$NF

A control experiment with (*E*)-**118b** confirmed that no [^{18}F]fluorination took place in the absence of **[Ir-1]** also for linear carbonates (Table 3.14, entry 3). HPLC (High Performance Liquid Chromatography) analysis confirmed that the retention time of the [^{18}F]labeled product corresponds to the cold unlabeled material. The retention times of **106a**, (*E*)-**106b** and (*Z*)-**106b** are too similar (6.9 min, 6.8 min and 6.4 min, respectively) to differentiate unambiguously between the three possible [^{18}F]labeled allyl fluoride products. Branched versus linear and *E*/*Z* selectivity for the radiolabeling experiments was therefore assigned

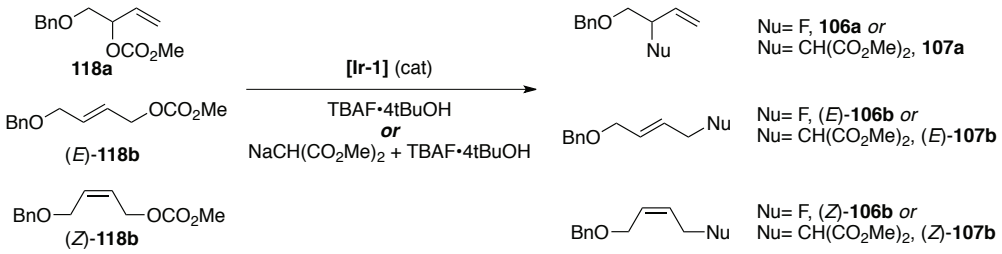
by analogy with the fluorinations performed using the unlabeled reagent TBAF·4*t*BuOH (Scheme 3.5).

Nguyen et al reported an example of Ir-mediated ^{18}F-fluorination of branched trichloroacetamidates, employing [^{18}F]KF·Kryptofix [2.2.2] (**I**) as ^{18}F-fluoride source and yielding labeled [^{18}F]-fluoride [^{18}F]-**74a** in 38% (*n*=1) of RCY within 10 minutes at room temperature.[66]

3.9 Conclusions

In conclusion, we have developed a new Ir-catalysed fluorination reaction of easily accessible allylic carbonates using TBAF·4*t*BuOH as the fluoride source. Unligated $[Ir(COD)Cl]_2$, **[Ir-1]**, was found to be the superior catalyst for this transformation, and either branched or *E*- and *Z*-linear allylic carbonates were suitable substrates towards fluorination. Under these catalytic conditions, the β-hydride elimination side reaction was completely suppressed, allowing an expansion of the substrate scope of the previously developed Pd-catalysis. The formation of branched, *E*- and *Z*-allylic fluorides was obtained with an excellent degree of regio- and stereoselectivity, with the fluoride insertion occurring at the same carbon bearing the leaving group. This unexpected stereochemical outcome was further investigated by carring out, under comparable conditions, the **[Ir-1]** catalysed alkylation of the three model isomeric carbonates **118a**, (*E*)-**118b** and (*Z*)-**118b** with sodium dimethyl malonate nucleophile. The alkylation of branched **118a** and linear (*E*)-**118b** carbonates was highly unselective, with the branched product **107a** being the favoured one. The use of TBAF·4*t*BuOH as additive in the alkylation reactions with **[Ir-1]** catalyst afforded a significantly increased conservation of stereochemistry. These results may suggest that in the presence of a fluoride ion, the catalyst **[Ir-1]** forms a σ-allyl-Ir

intermediate rather than a η^3-allyl species, as suggested by following ^{18}O-labeling experiments and preliminary investigations on the reaction mechanism.



Scheme 3. 30 Ir-Catalysed Allylic Substitution with TBAF·4*t*BuOH as Nucleophile or Additive

A study on the stereochemistry of the process, carrying out the fluorination of enantioenriched carbonate (*S*)-**118a**, suggested a double inversion mechanism, although with partial leakage of stereochemical integrity. The fluorination was highly sensitive to the presence of tracers of water in the reaction environment, being the major competing reaction the formation of the by-product alcohol. The inability of the commonly used $[Ir(COD)Cl]_2$/(*S*,*S*,*S*)-**L6a** catalytic system to induce fluorination was investigated by stoichiometric studies on the corresponding allyl-Ir intermediate **[Ir-7]**. The complex **[Ir-7]** was found to be highly instable in the presence of TBAF·4*t*BuOH, yielding exclusively the elimination product **120**. The [^{18}F]radiolabeling of representative branched and linear *E*- and *Z*-allyl carbonates was successfully validated with excellent RCYs, by Dr. M. Tredwell.[175]

Chapter 4

Experimental Data

4.1 General Experimental Information

All proton NMR spectra were recorded on either a Bruker AV400, DPX400 or AVC500 spectrometer. Carbon-13 NMR spectra were recorded on either a Bruker AV400 or a Bruker AVC500 spectrometer with a carbon-13 cryoprobe. Fluorine-19 and phosphorus-31 spectra were recorded on a Bruker AV400 or AVC500 spectrometer. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). Fluorine-19 NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Phosphorus-31 NMR spectra are referenced relative to phosphoric acid in D_2O. Coupling constants (*J*) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet). Multiplicities are reported as observed in the spectra. Assignments were aided by the use of COSY (correlation spectroscopy), HMQC (Heteronuclear Multiple Quantum Coherence), NOE, HOESY and NOESY experiments as required. High resolution mass spectra (HRMS, *m*/*z*) were recorded on a Bruker MicroTOF spectrometer using positive (ESI^+) or negative electrospray ionisation (ESI^-) or on a Micromass GCT spectrometer using either chemical ionisation (CI^+) or field ionisation (FI^+). Infrared spectra (IR) were recorded on NaCl discs either as the neat compound or in a solution using a Bruker Tensor 27 FT-IR spectrometer. Far infrared spectra (FIR) was recorded with a Varian FTS7000 spectrometer equipped with a DTGS detector. Absorptions are reported in wavenumbers (cm^{-1}) and only diagnostic peaks are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. Enantiomeric excesses were measured using High Performance Liquid

Chromatography (HPLC) on a machine supplied by the Waters Corporation using CHIRALCEL OD and IA columns. IUPAC names were obtained using the ACD/I-Lab service. All reported compounds are racemic mixtures unless otherwise indicated.

The following characterisation data are provided for each novel compound: proton NMR spectra (^{1}H NMR), carbon-13 NMR spectra (^{13}C NMR), infrared spectra (IR) and high resolution mass spectra (HRMS). Fluorine-19 or phosphorus-31 NMR spectra (^{19}F NMR, ^{31}P NMR) are also provided for compounds containing these heteroatoms whilst melting points (Mp) are provided for solids. For known compounds, a minimum of two pieces of characterisation data are provided.

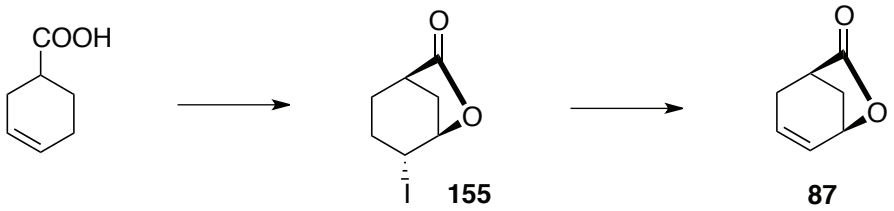
All reactions were performed in dried apparatus with magnetic stirring under an inert atmosphere unless otherwise stated. All solvents were dried on a column of alumina prior to use. Thin layer chromatography (TLC) was performed using Merck aluminium-foil backed plates precoated with Kieselgel 60 F_{254}. The products were visualised using UV fluorescence (254 nm), potassium permanganate or ceric ammonium molybdate stains. Flash column chromatography was performed over Merck silica gel C60 (40-60 μm).

All compounds used during the study for which a preparation does not appear in this chapter were commercially available.

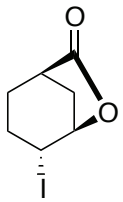
Complexes $[(C_3H_5)PtCl]_4$,[201] **[Pt-2]**,[133c] **[Ir-4]**,[163a] **[Ir-5]**[171] and **[Ir-6]**[172] were prepared according to literature procedures. TBAF·4*t*BuOH was prepared according to the procedure reported by Kim.[146]

4.2 Experimental Data for Chapter 2

4.2.1 Synthesis of Substrate 87

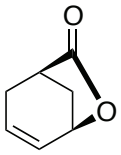


***exo*-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one (155)**



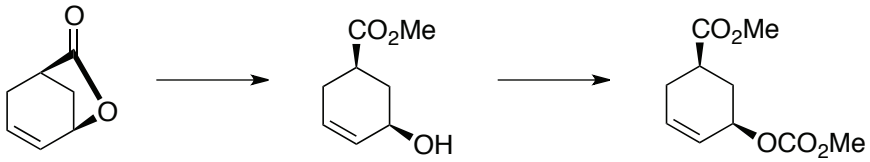
To a stirring solution of $NaHCO_3$ (9 g, 107.1 mmol) in water (90 ml) was added 3-cyclohexene-1-carboxylic acid (4.2 mL, 35.7 mmol) at room temperature causing evolution of CO_2. After the solution had become homogeneous and clear, a solution of NaI (48 g, 320.9 mmol) and I_2 (10 g, 39.3 mmol) in water (90 mL) was added in a single portion to the solution. The flask was covered with tin foil, and allowed to stir at room temperature overnight. The foil was then removed to reveal a white precipitate in a deep brown solution. The solution was extracted with DCM (4 x 45 mL) and the combined organic layers were washed with 10% $Na_2S_2O_8$ (2 x 50 mL), 10% $NaHCO_3$ (1 x 50 mL), brine (1 x 50 mL), dried over Na_2SO_4 and concentrated to yield the title compound (8.62 g, 96%, dr >98:2) as a white solid (mp = 136-137°C, lit.[202] = 134.5-135°C), that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.84 (dd, *J* = 6Hz, 4 Hz, 1H), 4.52 (dd, *J* = 5Hz, 4Hz, 1H), 2.84 (d, *J* = 12Hz, 1H), 2.68 (t, *J* = 4Hz, 1H), 2.50-2.37 (m, 2H), 2.13 (dd, *J* = 16Hz, 5Hz, 1H), 1.96-1.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.8, 80.2, 38.6, 34.5, 29.7, 23.7, 23.1. Data are in agreement with literature.[203]

6-Oxabicyclo[3.2.1]oct-3-en-7-one (87)



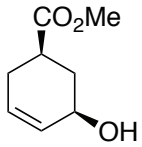
DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (5.1 mL, 34.2 mmol) was added via syringe to a solution of **155** (8.62 g, 34.2 mmol) in dry toluene (100 mL) and the reaction mixture was heated to reflux under nitrogen. After 3 h at reflux TLC indicated that the reaction was complete and the flask was cooled to room temperature. Solid DBU-HI was removed by vacuum filtration and the resultant yellow solution was concentrated *in vacuo* to yield a clear brown liquid. The crude product was purified by silica gel column chromatography (hexane: Et_2O, 50:50) to yield the title compound (4.01 g, 96%) as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (m, 1H), 5.86 (m, 1H), 4.77 (t, *J* = 5Hz, 1H), 2.92 (m, 1H), 2.57-2.43 (m, 3H), 2.12 (d, *J* = 11Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 130.3, 129.3, 73.3, 38.0, 34.4, 29.1. Data are in agreement with literature.[203]

4.2.2 Synthesis of Substrate *syn*-89a



87 *syn*-**90** *syn*-**89**

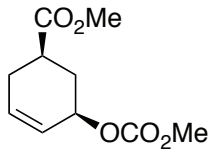
Methyl (*syn*)-5-hydroxycyclohex-3-ene-1-carboxylate (*syn*-90)



To a solution of **87** (868 mg, 7 mmol) in dry MeOH (7 mL) was added K_2CO_3 (484 mg, 3.5 mmol). The resulting heterogeneous solution was allowed to stir at room temperature for 15

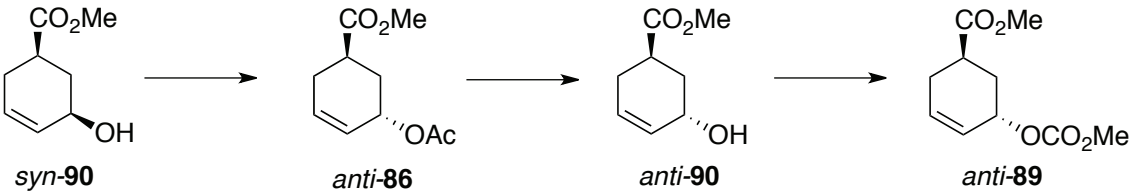
min, when TLC showed that the reaction was complete. The reaction was filtered through cotton wool to remove solid K_2CO_3, poured into DCM (10 mL) and washed with distilled water (1 x 10 mL). The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo* to yield the title compound (705 mg, 65%, *syn:anti* >98:2) as a clear oil that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80-5.74 (m, 2H), 4.30 (m, 1H), 3.71 (s, 3H), 3.42-3.32 (m, 1H), 2.77-2.69 (m, 1H), 2.33-2.27 (m, 3H), 2.11-2.08 (m, 1H), 1.79-1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 130.8, 126.9, 65.9, 51.9, 37.7, 34.2, 27.4. Data are in agreement with literature.[203]

Methyl (*syn*)-5-[(methoxycarbonyl)oxy]cyclohex-3-ene-1-carboxylate (*syn*-89)



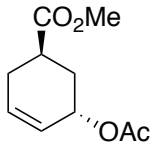
To a solution of *syn*-**90** (234 mg, 1.56 mmol, *syn:anti*, 96:4) and pyridine (0.36 mL, 4.68 mmol) in DCM (3.5 mL) was added dropwise methyl chloroformate (0.23 mL, 3.12 mmol) at 0°C. The reaction mixture was allowed to stir at room temperature until TLC showed that the reaction was complete. A saturated aqueous solution of NH_4Cl was added and the aqueous layer extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane: Et_2O, 90:10) to yield the title compound (217 mg, 65%, *syn:anti* >98:2) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91-5.88 (m, 1H), 5.71 (dm, *J* = 10Hz, 1H), 5.29-5.24 (m, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 2.77-2.69 (m, 1H), 2.47-2.42 (m, 1H), 2.34-2.30 (m, 2H), 1.88-1.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 155.4, 129.7, 126.1, 73.0, 54.7, 51.9, 37.6, 30.4, 27.1. Data are in agreement with literature.[203]

4.2.3 Synthesis of Substrate *anti*-89



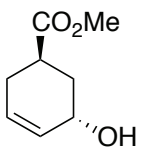
syn-**90** *anti*-**86** *anti*-**90** *anti*-**89**

Methyl (*anti*)-5-acetylcyclohex-3-ene-1-carboxylate (*anti*-86)



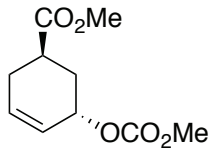
To a solution of methyl *syn*-**90** (1.38 g, 8.8 mmol, *syn:anti*, >98:2) in THF (35 mL) was added PPh_3 (2.76 g, 10.5 mmol) and acetic acid (0.6 mL, 10.5 mmol). The solution was cooled down to 0°C and DIAD (2.1 mL, 10.5 mmol) was added dropwise. The resultant orange solution was allowed to stir for 3 h at room temperature. MeOH (0.8 mL) was added to quench the reaction and the solvent was removed *in vacuo*. The oil was treated with a mixture of pentane and Et_2O (1:1, 20 mL), the solution was filtered and solvent evaporated. The crude product was purified by silica gel column chromatography (hexane: EtOAc, 90:10) to yield the title compound (1.50 g, 86%, *anti:syn*, 96:4) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04-5.99 (m, 1H), 5.85-5.82 (m, 1H), 5.31-5.26 (m, 1H), 3.72 (s, 3H), 2.82-2.75 (m, 1H), 2.42 (dt, *J* = 18Hz, 5Hz, 1H), 2.27-2.15 (m, 2H), 2.06 (s, 3H), 1.89-1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 170.4, 131.5, 124.3, 65.8, 51.8, 35.0, 30.7, 27.5, 21.3. Data are in agreement with literature.[116,118c]

Methyl (*anti*)-5-hydroxycyclohex-3-ene-1-carboxylate (*anti*-90)



Sodium methoxide (22 mg, 0.4 mmol) was added to a solution of *anti*-**86** (0.59 g, 3 mmol, *anti:syn*, 96:4) in MeOH (18 mL) and stirred at room temperature for 6 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between Et_2O and a 5% aqueous solution of $NaHCO_3$ (4.5 mmol). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo.* The crude product was purified by silica gel column chromatography (hexane: Et_2O, 50:50) to yield the title compound (393 mg, 84%, *anti:syn*, 96:4) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (dm, *J* = 10Hz, 1H), 5.87-5.84 (m, 1H), 4.31-4.25 (m, 1H), 3.71 (s, 3H), 2.85-2.77 (m, 1H), 2.37 (dt, *J* = 18Hz, 5Hz, 1H), 2.26-2.18 (m, 1H), 2.13 (dt, *J* = 14Hz, 3Hz, 1H), 1.87-1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 129.5, 127.9, 63.3, 51.8, 34.5, 33.8, 27.7. Data are in agreement with literature.[116,118c]

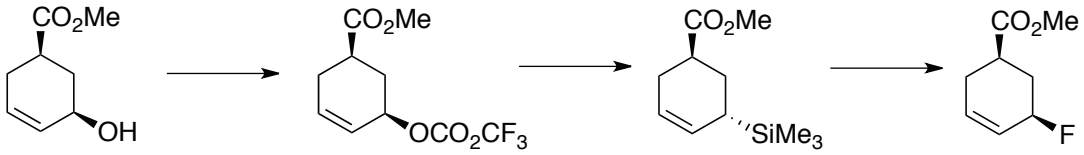
Methyl (*anti*)-5-[(methoxycarbonyl)oxy]cyclohex-3-ene-1-carboxylate (*anti*-89)



To a solution of *anti*-**90** (234 mg, 1.5 mmol, *anti:syn*, 96:4) and pyridine (0.38 mL, 4.7 mmol) in DCM (8 mL) was added methyl chloroformate (0.35 mL, 4.5 mmol) portion-wise over 4 h at room temperature. After the last addition, the solution was allowed to stir for 5 h. The reaction was quenched with distilled H_2O, extracted with Et_2O, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (255 mg, 79%, *anti:syn*, 96:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.07-6.03 (m, 1H), 5.91-5.85 (m, 1H), 5.18-5.14 (m, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 2.86-2.78 (m, 1H), 2.43 (dt, *J*= 18Hz, 5Hz, 1H), 2.31-2.18 (m, 2H), 1.92-1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 155.2, 132.2, 123.6, 69.6, 54.6, 51.8, 34.7, 30.5, 27.5. Data are in agreement with literature.[116,118c]

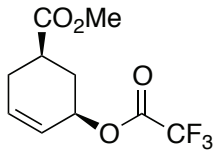
4.2.4 Synthesis of Substrate *syn*-77

The synthesis of substrate *syn*-**77** was carried out by M. Keita.[139]



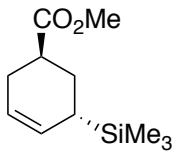
syn-**90** *syn*-**156** *anti*-**157** *syn*-**77**

Methyl (*syn*)-5-[(trifluoroacetyl)oxy]cyclohex-3-ene-1-carboxylate (*syn*-156)



To a solution of *syn*-**90** (500 mg, 3.2 mmol, *syn:anti* >20:1) and pyridine (0.62 mL, 7.7 mmol) in DCM (6 mL) was added dropwise trifluoroacetic anhydride (0.90 mL, 6.4 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over a period of 2 h. The reaction was quenched with distilled H_2O, extracted with Et_2O, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (653 mg, 81%, *syn:anti* >20:1) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03-6.00 (m, 1H), 5.70 (dm, *J* = 10Hz, 1H), 5.60-5.52 (m, 1H), 3.70 (s, 3H), 2.80-2.73 (m, 1H), 2.47-2.34 (m, 3H), 2.04-1.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 157.1 (q, J_{CF} = 42Hz), 131.7, 123.9, 114.4 (q, J_{CF} = 284Hz), 73.4, 51.9, 37.0, 29.7, 26.8. Data are in agreement with literature.[118c]

Methyl (*anti*)-5-(trimethylsilyl)cyclohex-3-ene-1-carboxylate (*anti*-157)

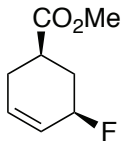


$Pd(dba)_2$ (20 mg, 0.035 mmol) was dissolved in THF (7 ml) and acetonitrile under an atmosphere of argon. A deep purple solution formed. *Syn*-**156** (300 mg, 1.2 mmol, *syn:anti* >20:1) and hexamethyldisilane (487 mg, 2.4 mmol) were then added. The reaction mixture gradually turned pale yellow and was stirred at 40 °C for 16 h. The reaction mixture was then cooled to room temperature, diluted with Et_2O (20 ml), washed with saturated $NaHCO_3$ (20 ml), dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: EtOAc, 90:10) to afford the title product as a colourless oil (162 mg, 64%, *anti:syn*, 84:16).

Anti-**157:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.68-5.58 (m, 2H), 3.68 (s, 3H), 2.67-2.61 (m, 1H), 2.37-2.12 (m, 2H), 2.03-1.97 (m, 1H), 1.91-1.85 (m, 1H), 1.65-1.56 (m, 1H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 127.9, 122.6, 51.6, 37.7, 26.9, 25,7, 25.2, -2.8.

Syn-**157:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.68-5.58 (m, 2H), 3.69 (s, 3H), 2.51-2.43 (m, 1H), 2.37-2.12 (m, 2H), 2.08-2.00 (m, 1H), 1.65-1.56 (m, 1H), 1.46 (q, *J* = 13Hz, 1H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 127.5, 123.7, 51.6, 40.2, 27.8, 27.1, 26.0, -3.7. Data are in agreement with literature.[204]

Methyl (*syn*)-5-fluorocyclohex-3-ene-1-carboxylate (*syn*-77)



A solution of *syn*-**156** (150 mg, 0.7 mmol, *anti:syn*, 84:16) and sodium bicarbonate (69 mg, 0.8 mmol) in acetonitrile (7 mL) was treated with Selectfluor® (269 mg, 0.8 mmol) and the mixture stirred at room temperature for 24 h. Water was added and the aqueous layer extracted 3 times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: EtOAc, 90:10) to afford the title product as a colourless oil (66 mg, 60%, *syn:anti*, 86:14). *Syn*-**77**: ^{1}H NMR (500 MHz,

$CDCl_3$) δ 5.95-5.87 (m, 1H), 5.86-5.77 (m, 1H), 5.16 (dm, J_{HF} = 49Hz, 1H), 3.72 (s, 3H), 2.65-2.63 (m, 1H), 2.46-2.24 (m, 3H), 2.02-1.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.3, 129.9 (d, J_{CF} = 10Hz) 126.8 (d, J_{CF} = 21Hz), 87.2 (d, J_{CF} = 163Hz), 51.9, 37.2 (d, J_{CF} = 5Hz), 31.5 (d, J_{CF} = 20Hz), 27.1; ^{19}F {^1H} NMR (376.5 MHz, $CDCl_3$) δ- 172.51. *Anti*-**77*:*** ^{19}F {^1H} NMR (376.5 MHz, $CDCl_3$) δ- 162.05. Data are in agreement with literature.[42]

4.2.5 Pt- and Pd-Catalysed Allylic Alkylation of 87, *Syn*/*Anti*-89 and *Syn*-77

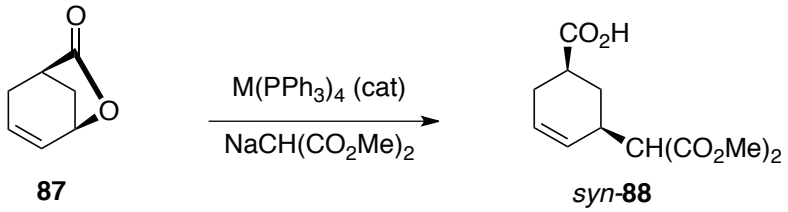
General procedure A: Platinum catalysed allylic alkylation

A solution of sodium dimethyl malonate (0.34 mmol) in THF (1 mL), prepared from dimethyl malonate (51.6 mL, 0.34 mmol) and NaH (60% in mineral oil, 13.6 mg, 0.34 mmol), was added to a stirring solution of $Pt(PPh_3)_4$ (0.01 mmol, 5 mol%) in THF (1 mL), followed by the addition of the allylic substrate (0.2 mmol). The reaction was stirred at room temperature and monitored by TLC. The reaction was quenched by addition of distilled water and the aqueous layer extracted 2 times with Et_2O. The combined organic layers were dried over $MgSO_4$, and solvent removed *in vacuo.*

General procedure B: Palladium catalysed allylic alkylation

A solution of sodium dimethyl malonate (0.34 mmol) in THF (1 mL), prepared from dimethyl malonate (51.6 mL, 0.34 mmol) and NaH (60% in mineral oil, 13.6 mg, 0.34 mmol), was added to a stirring solution of $Pd(PPh_3)_4$ (0.01 mmol, 5 mol%) in THF (1 mL), followed by the addition of the allylic substrate (0.2 mmol). The reaction was stirred at room temperature and monitored by TLC. The reaction was quenched by addition of distilled water and the aqueous layer extracted 2 times with Et_2O. The combined organic layers were dried over $MgSO_4$, and solvent removed *in vacuo.*

Results of Scheme 2.12b:

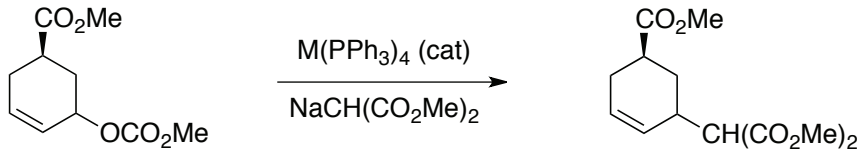


87 *syn*-**88**

Following the general procedure A, the reaction was carried out on 25 mg of **87** for 0.5 h. Silica gel column chromatography (hexane: Et_2O, 80:20) yielded *syn*-**88** (31 mg, 79%, *syn*:*anti* >98:2) as a colourless oil.

Following the general procedure B, the reaction carried out on 25 mg of **87** for 0.5 h. Silica gel column chromatography (hexane: Et_2O, 80:20) yielded *syn*-**88** (40 mg, 99%, >98:2) as a colourless oil.

Results of Table 2.3:



89 **78**

Entry 1: Following the general procedure A, the reaction was carried out on 43 mg of *syn*-**89** (*syn*:*anti*, >98:2) for 0.5 h. Silica gel column chromatography (hexane: Et_2O, 60:40) yielded *syn*-**78** (46 mg, 86%, >98:2) as a colourless oil.

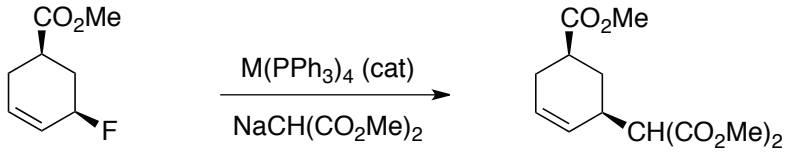
Entry 2: Following the general procedure B, the reaction carried out on 43 mg of *syn*-**89** (*syn:anti*, >98:2) for 1 h. Silica gel column chromatography (hexane: Et_2O, 60:40) yielded *syn*-**78** (38 mg, 71%, 97:3).

Entry 3: Following the general procedure A, the reaction was carried out on 43 mg of *anti*-**89** (*anti:syn*, 96:4) for 16 h. Silica gel column chromatography (hexane: Et_2O, 80:20) yielded *anti*-**78** (36 mg, 82%, *anti:syn*, 96:4) as a colourless oil.

Entry 4: Following the general procedure B, the reaction carried out on 43 mg of *anti*-**89** (*anti:syn*, 96:4) for 1 h. Silica gel column chromatography (hexane: Et_2O, 80:20) yielded *anti*-**78** (41 mg, 78%, *anti:syn*, 89:11).

Results of Scheme 2.15b:

The results of Scheme 2.15b were obtained by M. Keita.[139]

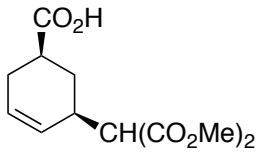


syn-**77** *syn*-**78**

Following the general procedure A, the reaction was carried out on 32 mg of *syn*-**77** (*syn:anti*, 86:14) for 5 h. Silica gel column chromatography (hexane: Et_2O, 80:20) yielded *syn*-**78** (54 mg, >99%, *syn:anti*, 86:14) as a colourless oil.

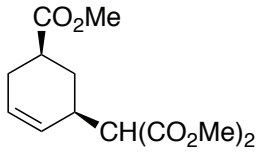
Following the general procedure A, the reaction was carried out on 32 mg of *syn*-**77** (*syn:anti*, 80:20) for 5 h. Silica gel column chromatography (hexane: Et_2O, 80:20) yielded *syn*-**78** (31 mg, 57%, *syn:anti*, 86:14) as a colourless oil.

(*syn*)-5-(1,3-Dimethoxy-1,3-dioxopropan-2-yl)cyclohex-3-ene-1-carboxylic acid (*syn*-88)



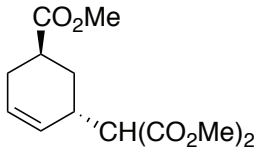
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81-5.76 (m, 1H), 5.55 (dm, *J* = 10 Hz, 1H), 3.75 (s, 6H), 3.30 (d, *J* = 9 Hz, 1H), 3.06-3.00 (m, 1H), 2.71-2.63 (m, 1H), 2.35 (dm, *J* = 18Hz, 1H), 2.26-2.19 (m, 2H), 2.16 (dm, *J* = 12Hz, 1H), 1.49 (dd *J* = 12Hz, 24Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.9, 168.5, 127.4, 127.1, 56.3, 52.5, 39.2, 35.9, 29.1, 27.4; IR (CH_2Cl_2) ν 2955, 1732, 1254, 1158; HRMS calc for $C_{12}H_{16}O_6$ $[M+Na]^+$ 279.0839 found 279.0843.

Dimethyl (*syn*)-[5-(methoxycarbonyl)cyclohex-2-en-1-yl]malonate (*syn*-78)



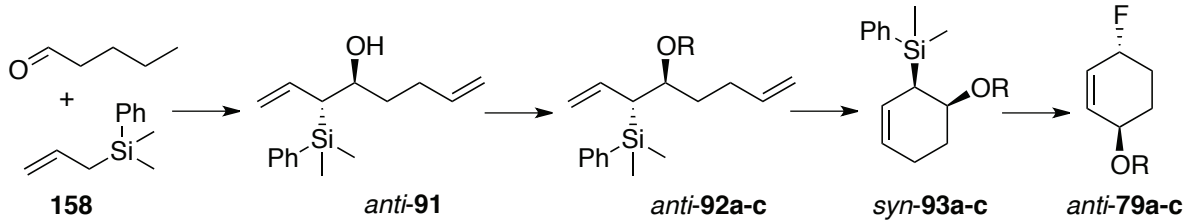
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79-5.74 (m, 1H), 5.53 (dm, *J* = 10Hz, 1H), 3.74 (s, 6H), 3.68 (s, 3H), 3.28 (d, *J* = 6Hz, 1H), 3.04-2.96 (m, 1H), 2.29 (dm, *J* = 16Hz, 1H), 2.23-2.14 (m, 1H), 2.10 (dm, *J* = 13Hz, 1H), 1.46 (dd, *J* = 24Hz, 13Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 168.5, 127.4, 127.3, 56.4, 52.5, 51.7, 39.3, 36.0, 29.3, 27.6. Data are in agreement with literature.[116,118c]

Dimethyl (*anti*)-[5-(methoxycarbonyl)cyclohex-2-en-1-yl]malonate (*anti*-78)



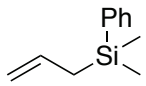
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80-5.75 (m, 1H), 5.58 (dm, *J* = 10Hz, 1H), 3.73 (s, 6H), 3.67 (s, 3H), 3.32 (d, *J* = 10Hz, 1H), 3.04-2.96 (m, 1H), 2.65-2.58 (m, 1H), 2.27-2.25 (m, 2H), 1.97-1.89 (m, 1H), 1.77 (dm, *J* = 14Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 168.4, 127.9, 126.7, 56.3, 52.5, 51.8, 35.7, 33.2, 28.0, 27.1. Data are in agreement with literature.[116,118c]

4.2.6 Synthesis of Substrate *Anti*-79a-c



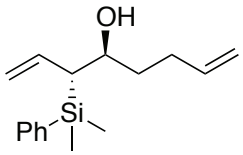
158 *anti*-**91** *anti*-**92a-c** *syn*-**93a-c** *anti*-**79a-c**

Dimethyl(phenyl)allylsilane (158)



Chlorodimethylphenylsilane (2 mL, 12 mmol) was added dropwise to a solution of allylmagnesium bromide (1 M in Et_2O, 18 mL, 18 mmol) in Et_2O (20 mL) at 0°C. The mixture was stirred vigourosly at room temperature for 24 h. A saturated solution of NH_4Cl was added and the aqueous layer extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The yellow oil afforded (2.09 g, > 99%) did not require further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.51 (m, 2H), 7.38-7.35 (m, 3H), 5.84-5.73 (m, 1H), 4.90-4.84 (m, 2H), 1.77 (d, *J* = 8Hz, 2H), 0.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 134.6, 133.6, 129.0, 127.7, 113.4, 23.7, -3.5. Data are in agreement with literature.[205]

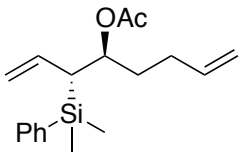
(*anti*)-3-(Dimethyl(phenyl)silyl)octa-1,7-dien-4-ol (*anti*-91)



To a solution of **158** (11.4 mmol, 2.01 g) in dry THF (50 mL) was added a solution of *n*-butyllithium (1.6 M in hexane, 12.5 mmol, 7.8 mL) at 0°C. The resulting pale-yellow solution was stirred at 0°C for 2h, turning reddish brown, then cooled to -78°C. Titanium(IV) isopropoxide (11.4 mmol, 3.3 mL) was added at -78°C and the mixture was stirred for 1h at this temperature. Finally, a solution of 4-pentenal (11.4 mmol, 1.1 mL) in dry THF (7 mL) was added at -78°C, and the reaction mixture was then stirred for 4 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl at -78°C. The organic layer was decanted and the aqueous layer extracted with Et_2O. The combined organic layers were then washed with H_2O, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude product was purified by silica gel column chromatography (100% hexane) to yield the

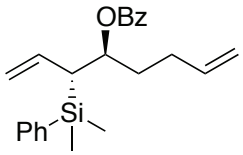
title compound (2.24 g, 76%, *anti:syn*, 86:14). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.52 (m, 2H), 7.37-7.35 (m, 3H), 5.84 (dt, *J* = 17Hz, 10Hz, 1H), 5.79-5.69 (m, 1H), 5.07 (dd, *J* = 10Hz, 2Hz, 1H), 4.98-4.90 (m, 3H), 3.79-3.74 (m, 1H), 2.07-2.02 (m, 2H), 1.92 (dd, *J* = 11Hz, 4Hz, 1H), 1.50 (q, *J* = 7Hz, 2H), 1.43 (d, *J* = 5Hz, 1H), 0.36 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 137.9, 135.0, 134.0, 129.1, 127.8, 115.6, 114.6, 71.0, 42.1, 36.2, 30.2, -3.4, -4.0. Data are in agreement with literature.[117]

(*anti*)-{1-[Dimethyl(phenyl)silyl]prop-2-en-1-yl}pent-4-en-1-yl acetate (*anti*-92a)



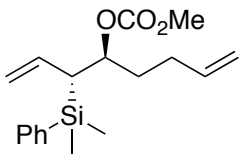
Acetyl chloride (0.8 ml, 11 mmol) was added dropwise to a solution of *anti*-**91** (1.15 g, 4.4 mmol, *anti:syn*, 86:14) and pyridine (1.4 mL, 17.6 mmol) in DCM (12 mL) at 0°C. The reaction mixture was stirred at room temperature for 4 h. Et_2O (10 ml) was added and the resulting suspension filtered through Celite® and concentrated *in vacuo*. The residue was extracted with Et_2O and the organic phase washed with 1 M HCl and saturated aqueous Na_2CO_3 solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica gel column chromatography (hexane: Et_2O, 95:5) to yield the title compound (1.05 g, 79%, *anti:syn* >98:2) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.45 (m, 2H), 7.36-7.32 (m, 3H), 5.84 (dt, *J* = 17Hz, 11Hz, 1H), 5.70 (ddt, *J* = 17Hz, 10Hz, 7Hz, 1H), 5.07-5.01 (m, 2H), 4.97-4.88 (m, 3H), 2.05-1.99 (m, 1H), 1.99-1.85 (m, 2H), 1.81 (s, 3H), 1.67-1.47 (m, 2H), 0.32 (s, 3H), 0.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 137.7, 137.4, 134.6, 134.0, 129.1, 127.7, 115.7, 114.8, 73.5, 39.4, 33.1, 29.6, 21.1, -3.9, -4.0. Data are in agreement with literature.[117]

***(anti)*-{1 Dimethyl(phenyl)silyl]prop-2-en-1-yl}pent-4-en-1-yl benzoate (*anti*-92b)**



Benzoyl chloride (2.96 mL, 25.5 mmol) was added dropwise to a solution of *anti*-**91** (2.21 g, 8.5 mmol, *anti:syn*, 86:14) and pyridine (2.7 mL, 34 mmol) in DCM (20 ml) at 0 °C. The reaction mixture was stirred at room temperature for 24 h. Et_2O was added and the resulting suspension filtered through Celite® and concentrated *in vacuo*. The residue was extracted with Et_2O and the organic phase washed with 1 M HCl and saturated aqueous Na_2CO_3 solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (2.13 g, 69%, *anti:syn* >98:2) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.86 (m, 2H), 7.57-7.20 (m, 8H), 5.94 (dt, *J* = 17Hz, 10Hz, 1H), 5.74 (ddt, *J* = 17Hz, 10Hz, 7Hz, 1H), 5.35-5.24 (m, 1H), 5.09 (dd, *J*= 10Hz, 2Hz, 1H), 4.99-4.89 (m, 3H), 2.17 (dd, *J* = 11Hz, 4Hz, 1H), 2.10-1.91 (m, 2H), 1.83-1.61 (m, 2H), 0.33 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 137.7, 137.1, 134.6, 133.9, 132.7, 130.5, 129.6, 129.0, 128.2, 127.6, 115.9, 114.8, 74.2, 39.5, 33.2, 29.6, -3.9, -4.0. Data are in agreement with literature.[117]

***(anti)*-{1 Dimethyl(phenyl)silyl]prop-2-en-1-yl}pent-4-en-1-yl methyl carbonate (*anti*-92c)**



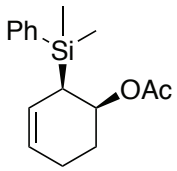
A solution of *n*BuLi (2.5 M in hexane, 1.4 mL, 3.6 mmol) was added dropwise to a solution of *anti*-**91** (780 mg, 3 mmol, *anti:syn*, 86:14) in THF (6 mL) at -78°C, and the reaction mixture was stirred for 30 min. Methyl chloroformate (0.35 mL, 4.5 mmol) was added

dropwise and the resulting yellow solution left stirring for 1 h. The reaction was quenched with 1N HCl and extracted 3 times with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (587 mg, 62%, *anti:syn*, 94:6) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.47 (m, 2H), 7.39-7.33 (m, 3H), 5.83 (dt, *J* = 17Hz, 10Hz, 1H), 5.74 (ddt, *J* = 17Hz, 10Hz, 7Hz, 1H), 5.05 (dd, *J* = 10Hz, 2Hz, 1H), 4.96-4.86 (m, 3H), 4.84-4.81 (m, 1H), 3.69 (s, 3H), 2.07 (dd, *J* = 11Hz, 4Hz, 1H), 2.02-1.89 (m, 2H), 1.73-1.66 (m, 1H), 1.66-1.56 (m, 1H), 0.34 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 137.5, 137.1, 134.1, 133.9, 129.2, 127.7, 116.0, 114.9, 78.3, 54.5, 39.5, 32.9, 29.3, -3.8, -4.3; IR ($CDCl_3$) ν 3055, 2987, 1744, 1422, 1265; HRMS calc for $C_{18}H_{26}O_3Si$ $[M]^+$ 318.1651, found 318.1653.

General procedure C: Ring closing metathesis

A solution of the allylsilane (1 eq) in DCM (c = 0.01 M) was treated with Grubbs "second generation" catalyst (5 mol%) and stirred for 1 h at 50 °C. The mixture was cooled to room temperature and the solvent removed *in vacuo*.

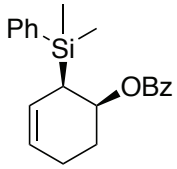
(*syn*)-2-[Dimethyl(phenyl)silyl]cyclohex-3-en-1-yl acetate (*syn*-93a)



Following the general procedure C, the reaction was carried out on 785 mg (2.6 mmol) of *anti*-**92a** (*anti:syn* >98:2). Silica gel column chromatography (petroleum ether 30-40 °C) yielded the title compound (713 mg, > 99%, *syn:anti*, 91:9) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.49 (m, 2H), 7.37-7.32 (m, 3H), 5.68-5.62 (m, 1H), 5.59-5.53

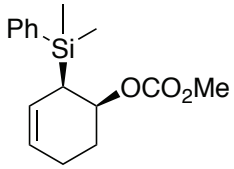
(m, 1H), 5.22 (ddd, *J* = 11Hz, 6Hz, 3Hz, 1H), 2.29-2.24 (m, 1H), 2.09-2.03 (m, 2H), 1.88-1.81 (m, 1H), 1.80 (s, 3H), 1.67-1.58 (m, 1H), 0.36 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 138.4, 133.7, 129.0, 127.7, 125.1, 124.6, 71.9, 31.6, 26.4, 22.1, 21.1, -3.0, -3.2. Data are in agreement with literature.[117]

(*syn*)-2-[Dimethyl(phenyl)silyl]cyclohex-3-en-1-yl benzoate (*syn*-93b)



Following the general procedure C, the reaction was carried out on 2.13 g (5.85 mmol) of *anti*-**92b** (*anti:syn* >98:2). Silica gel column chromatography (petroleum ether 30-40 °C) yielded the title compound (1.83 g, 93%, *syn:anti*, 91:9) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.86 (m, 2H), 7.57-7.24 (m, 8H), 5.75 (ddd, *J*= 10Hz, 7Hz, 3Hz, 1H), 5.66 (m, 1H), 5.54 (ddd, *J*= 7Hz, 5Hz, 3Hz, 1H), 2.39 (ddd, *J* = 8Hz, 6Hz, 3Hz, 1H), 2.25-2.09 (m, 2H), 2.07-1.97 (m, 1H), 1.78-1.68 (m, 1H), 0.36 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 138.0, 138.0, 132.7, 130.7, 129.6, 129.0, 128.2, 127.7, 125.0, 124.8, 72.1, 31.7, 26.7, 21.7, -3.2, -3.4. Data are in agreement with literature.[117]

(*syn*)-2-[Dimethyl(phenyl)silyl]cyclohex-3-en-1-yl methyl carbonate (*syn*-93c)



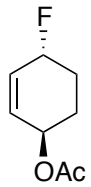
Following the general procedure C, the reaction was carried out on 1.66 g (5.2 mmol) of *anti*-**92c** (*anti:syn*, 94:6). Silica gel column chromatography (petroleum ether 30-40 °C) yielded the title compound (1.36 g, 90%, *syn:anti*, 92:8) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.53 (m, 2H), 7.37-7.33 (m, 3H), 5.65 (ddd, *J*= 10Hz, 6Hz, 4Hz, 1H),

5.53 (dm, *J* = 10Hz, 1H), 5.06 (ddd, *J* = 8Hz, 6Hz, 3Hz, 1H), 3.67 (s, 3H), 2.35-2.31 (m, 1H), 2.12-2.06 (m, 2H), 1.90-1.83 (m, 1H), 1.70-1.65 (m, 1H), 0.38 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 138.0, 133.9, 129.0, 127.7, 124.7, 124.5, 76.1, 54.3, 31.9, 26.4, 21.9, -3.2, -3.4; IR (CH_2Cl_2) ν 3055, 2987, 1742, 1422, 1266; HRMS calc for $C_{16}H_{22}O_3Si$ $[M]^+$ 290.1338, found 290.1341.

General procedure D: Electrophilic fluorodesilylation of allylsilanes

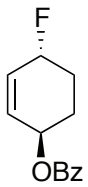
A solution of the allylsilane (1 equiv) and sodium bicarbonate (1.2 equiv) in acetonitrile (c = 0.1 M) was treated with Selectfluor® (1.1 equiv) and the mixture stirred at room temperature for 24 h. Water was added and the aqueous layer extracted 3 times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*.

(*anti*)-4-Fluorocyclohex-2-en-1-yl acetate (*anti*-79a)



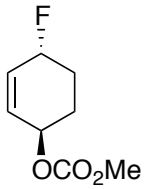
Following the general procedure D, the reaction was carried out on 676 mg (2.5 mmol) of *syn*-**93a** (*syn:anti*, 91:9). Silica gel column chromatography (hexane: Et_2O, 95:5) yielded the title compound (283 mg, 72%, *anti:syn*, 93:7) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.05-6.00 (m, 1H), 5.94 (dm, *J* = 10Hz, 1H), 5.34-5.30 (m, 1H), 5.08 (dm, *J* = 49Hz, 1H), 2.22-2.09 (m, 2H), 2.05 (s, 3H), 1.93-1.81 (m, 1H), 1.72-1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 130.9 (d, *J* = 10Hz), 130.1 (d, *J* = 19Hz), 85.4 (d, *J* = 165Hz), 67.3 (d, *J* = 2Hz), 26.5 (d, *J* = 20Hz), 25.1 (d, *J* = 5Hz), 21.2; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -172.1. Data are in agreement with literature.[42]

(*anti*)-4-Fluorocyclohex-2-en-1-yl benzoate (*anti*-79b)



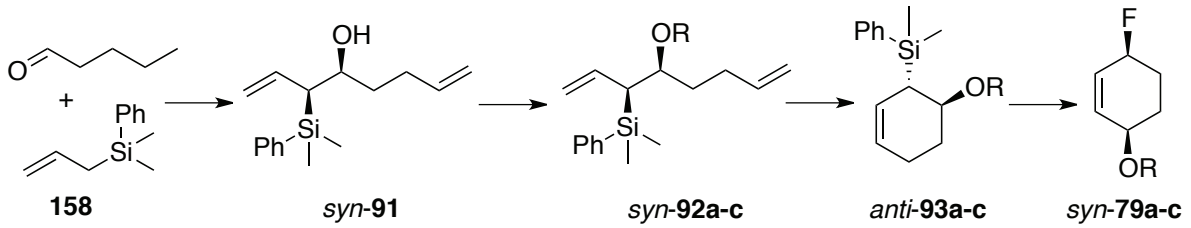
Following the general procedure D, the reaction was carried out on 1.8 g (5.4 mmol) of *syn*-**93b** (*syn:anti*, 91:9). Silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 95:5) yielded the title compound (670 mg, 56%, *anti:syn*, 96:4) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.03 (m, 2H), 7.59-7.55 (m, 1H), 7.48-7.41 (m, 2H), 6.12-6.06 (m, 2H), 5.61-5.56 (m, 1H), 5.15 (dm, *J* = 49Hz, 1H), 2.33-2.19 (m, 2H), 2.04-1.91 (m, 1H), 1.88-1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 133.0, 131.0 (d, *J* = 10Hz), 130.2 (d, *J* = 19Hz), 130.2, 129.6, 128.4, 85.5 (d, *J* = 165Hz), 67.8 (d, *J* = 20Hz), 26.6 (d, *J* = 5Hz), 25.2 (d, *J* = 10Hz); ^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$): δ - 172.2. Data are in agreement with literature.[42]

(*anti*)-4-Fluorocyclohex-2-en-1-yl methyl carbonate (*anti*-79c)



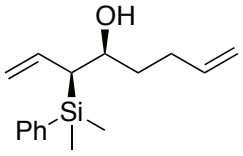
Following the general procedure D, the reaction was carried out on 1.36 g (4.7 mmol) of *syn*-**93c** (*syn:anti*, 92:8). Silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 80:20) yielded the title compound (536 mg, 66%, *anti:syn*, 97:3) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.08-5.98 (m, 2H), 5.22-5.16 (1H, m), 5.06 (dm, *J* = 48Hz, 1H), 3.79 (s, 3H), 2.23-2.10 (m, 2H), 1.95-1.82 (m, 1H), 1.80-1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 130.5 (d, *J* = 19Hz), 130.1 (d, *J* = 10Hz), 85.1 (d, *J* = 165Hz), 71.0 (d, *J* = 2Hz), 54.8, 26.3 (d, *J* = 21Hz) 25.0 (d, *J* = 5Hz); ^{19}F {^{1}H} NMR (376.5 MHz, $CDCl_3$): δ - 172.5. Data are in agreement with literature.[42]

4.2.7 Synthesis of Substrate *Syn*-79a-c



158 *syn*-**91** *syn*-**92a-c** *anti*-**93a-c** *syn*-**79a-c**

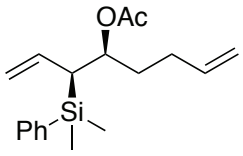
(*syn*)-3-(Dimethyl(phenyl)silyl)octa-1,7-dien-4-ol (*syn*-91)[206]



To a stirred solution of **158** (871 mg, 5 mmol) and TMEDA (0.75 mL, 5 mmol) in THF (8 mL), at 0°C was added a solution of *n*-BuLi (2.5 M in hexane, 2.4 mL, 6 mmol). The mixture was stirred for 2 h then Bu_3SnCl (1.8 mL, 6.6 mmol) was added dropwise at -30°C and stirred for additional 15 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer extracted with Et_2O. The combined organic layers were then washed with H_2O, dried over $MgSO_4$ and the solvents were removed *in vacuo*. To a solution of 4-pentenal (0.49 mL, 5 mmol) and crude vinylsilane in DCM (14 mL) at -78°C was added $BF_3.OEt_2$ (0.62 mL, 5 mmol) dropwise. After stirring at -78°C for 30 min, the reaction mixture was carefully quenched with saturated aqueous $NaHCO_3$ at this temperature, followed by removal of the cold bath and warming to room temperature. The organic layer was recovered and the aqueous layer extracted with Et_2O. The combined organic layers were then washed with H_2O, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane) to yield the title compound (692 mg, 53%, *syn:anti* >98:2) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.53 (m, 2H), 7.38-7.35 (m, 3H), 5.82-5.72 (m, 1H), 5.67 (dt, *J* = 17Hz, 10Hz, 1H), 5.02-4.96 (m, 2H), 4.95-4.94 (m, 1H), 4.92-4.90 (m, 1H), 3.76-

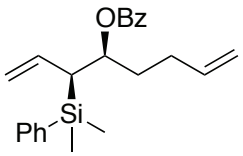
3.68 (m, 1H), 2.24-2.16 (m, 1H), 2.10-1.99 (m, 2H), 1.67-1.59 (m, 1H), 1.44-1.34 (m, 1H), 1.31 (d, *J* = 6Hz, 1H), 0.36 (s, 3H), 0.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 138.0, 135.8, 134.1, 129.1, 127.8, 115.4, 114.7, 72.2, 44.3, 35.9, 30.3, -3.0, -3.8; IR (CH_2Cl_2) ν 3346, 2945, 1450, 1029; HRMS calc for $C_{16}H_{24}NaOSi$ $[M+Na]^+$ 283.1489, found 283.1489.

(*syn*)-{1-[Dimethyl(phenyl)silyl]prop-2-en-1-yl}pent-4-en-1-yl acetate (*syn*-92a)



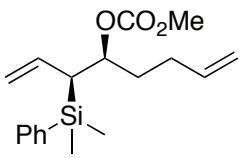
Acetyl chloride (0.43 ml, 6 mmol) was added dropwise to a solution of *syn*-**91** (624 mg, 2.4 mmol, *syn:anti* >98:2) and pyridine (0.78 mL, 9.6 mmol) in DCM (7 mL) at 0°C. The reaction mixture was stirred at room temperature for 4 h. Et_2O was added and the resulting suspension filtered through Celite® and concentrated *in vacuo*. The residue was extracted with Et_2O and the organic phase washed with 1 M HCl and saturated aqueous Na_2CO_3 solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica gel column chromatography (DCM) to yield the title compound (512 mg, 71%, *syn:anti*, 98:2) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.49 (m, 2H), 7.38-7.34 (m, 3H), 5.74-5.63 (m, 2H), 5.06-4.87 (m, 5H), 2.35 (dd, *J*= 10Hz, 7Hz, 1H), 2.05-1.89 (m, 2H), 1.79 (s, 3H), 1.68-1.55 (m, 2H), 0.35 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 137.8, 137.6, 135.0, 134.0, 129.1, 127.7, 115.3, 114.8, 74.4, 40.1, 32.5, 29.5, 21.0, -3.1, -4.2; IR (CH_2Cl_2) ν 3055, 2987, 1725, 1422, 1265, 1115, 896; HRMS calc for $C_{18}H_{26}NaO_2Si$ $[M+Na]^+$ 325.1594, found 325.1595.

(*syn*)-{1 Dimethyl(phenyl)silyl]prop-2-en-1-yl}pent-4-en-1-yl benzoate (*syn*-92b)



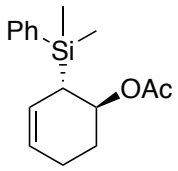
Benzoyl chloride (0.87 mL, 7.5 mmol) was added dropwise to a solution of *syn*-**91** (650 mg, 2.5 mmol, *syn:anti* >98:2) and pyridine (0.8 mL, 10 mmol) in DCM (6 ml) at 0 °C. The reaction mixture was stirred at room temperature for 24 h. Et_2O was added and the resulting suspension filtered through Celite® and concentrated *in vacuo*. The residue was extracted with Et_2O and the organic phase washed with 1 M HCl and saturated aqueous Na_2CO_3 solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C with 5% Et_3N) to yield the title compound (693 mg, 76%, *syn:anti*, >98:2) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.87 (m, 2H), 7.54-7.48 (m, 3H), 7.40-7.36 (m, 2H), 7.32-7.28 (m, 3H), 5.79 (dt, *J* = 17Hz, 10Hz, 1H), 5.74-5.63 (m, 1H), 5.31-5.27 (m, 1H), 5.02 (dd, *J* = 10Hz, 2Hz, 1H), 4.94-4.88 (3H, m), 2.52 (dd, *J* = 11Hz, 7Hz, 1H), 2.12-2.05 (m, 1H), 2.02-1.92 (m, 1H), 1.86-1.77 (m, 1H), 1.71-1.62 (m, 1H), 0.36 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 137.7, 137.3, 137.7, 134.0, 132.6, 130.6, 129.5, 129.1, 128.2, 127.7, 115.6, 115.0, 75.1, 40.3, 32.3, 29.6, -3.2, -4.0; IR ($CDCl_3$) ν 3073, 2929, 1708, 1641, 1428, 1277, 1112, 1026; *m/z* $[M+Na]^+$ 387.19.

(*syn*)-{1 Dimethyl(phenyl)silyl]prop-2-en-1-yl}pent-4-en-1-yl methyl carbonate (*syn*-92c)



To a solution of *syn*-**91** (642 mg, 2.4 mmol, *syn:anti* >98:2) and pyridine (1.2 mL, 15 mmol) in DCM (13 mL) was added methyl chloroformate (1.12 mL, 14.4 mmol) portion-wise over 4 h at room temperature. After last addition, the solution was allowed to stir for 48 h. The reaction was quenched with distilled H_2O, extracted with Et_2O, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (378 mg, 50%, *syn:anti*, 98:2) and recovered *syn*-**91** (171 mg, 27%, *syn:anti*, 86:14). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.55 (m, 2H), 7.39-7.34 (m, 3H), 5.77-5.62 (m, 2H), 5.02 (dd, *J* = 10Hz, 2Hz, 1H), 4.93 (m, 3H), 4.85-4.80 (m, 1H), 3.70 (s, 3H), 2.43-2.38 (m, 1H), 2.00-1.91 (m, 1H), 1.76-1.64 (m, 1H), 1.59-1.51 (m, 1H), 1.45-1.35 (m, 1H), 0.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 139.8, 137.6, 134.3, 133.0, 129.2, 127.7, 115.7, 115.1, 79.1, 54.4, 40.5, 32.3, 29.6, -3.5, -3.8; IR ($CDCl_3$) ν 2960, 1740, 1428, 1258, 1119, 1066; *m/z* $[M+Na]^+$ 341.15.

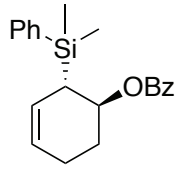
(*anti*)-2-[Dimethyl(phenyl)silyl]cyclohex-3-en-1-yl acetate (*anti*-93a)



Following the general procedure C, the reaction was carried out on 483 mg (1.6 mmol) of *syn*-**92a** (*syn:anti*, 98:2). Silica gel column chromatography (petroleum ether 30-40 °C) yielded the title compound (420 mg, 96%, *anti:syn*, 97:3) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.51 (m, 2H), 7.39-7.34 (m, 3H), 5.67-5.63 (m, 1H), 5.57-5.53 (m, 1H), 5.11-5.08 (m, 1H), 2.17-2.07 (m, 1H), 2.07-2.01 (m, 1H), 2.01-1.95 (m, 1H), 1.91 (s, 3H), 1.72-1.65 (m, 1H), 1.62-1.54 (m, 1H), 0.36 (s, 3H), 0.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 137.1, 133.9, 129.2, 127.8, 124.7, 124.6, 70.5, 32.6, 26.2, 21.5, 21.4, -4.2,

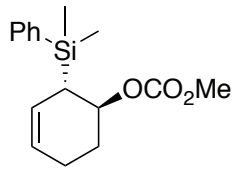
-4.3; IR (CH_2Cl_2) ν 3055, 2987, 1725, 1423, 1265, 1112, 1027, 896; HRMS calc for $C_{16}H_{22}NaO_2Si$ $[M+Na]^+$ 279.1281, found 279.1282.

(*anti*)-2-[Dimethyl(phenyl)silyl]cyclohex-3-en-1-yl benzoate (*anti*-93b)



Following the general procedure C, the reaction was carried out on 655 mg (1.8 mmol) of *syn*-**92b** (*syn:anti* >98:2). Silica gel column chromatography (petroleum ether 30-40 °C) yielded the title compound (501 mg, 83%, *anti:syn* >98:2) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00-7.97 (m, 2H), 7.57-7.52 (m, 3H), 7.43-7.40 (m, 2H), 7.36-7.34 (m, 3H), 5.73-5.70 (m, 1H), 5.62-5.59 (m, 1H), 5.41-5.39 (m, 1H), 2.30-2.23 (m, 2H), 2.08-2.01 (m, 1H), 1.87-1.82 (m, 1H), 1.70-1.62 (m, 1H), 0.42 (s, 3H), 0.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 136.9, 134.0, 132.6, 131.0, 129.5, 129.2, 128.2, 127.8, 124.7, 124.4, 71.1, 33.0, 26.0, 21.3, -3.9, -4.3; IR (CH_2Cl_2) ν 3055, 2987, 1709, 1602, 1265, 1114, 1026; *m/z* $[M+Na]^+$ 359.17.

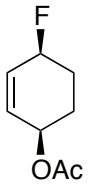
(*anti*)-2-[Dimethyl(phenyl)silyl]cyclohex-3-en-1-yl methyl carbonate (*anti*-93c)



Following the general procedure C, the reaction was carried out on 378 mg (1.2 mmol) of *syn*-**92c** (*syn:anti*, 86:14). Silica gel column chromatography (petroleum ether 30-40 °C) yielded the title compound (309 mg, 89%, *anti:syn* >98:2) as a colourless oil. The configuration of *anti*-**93c** has been determined by NOE studies. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.52 (m, 2H), 7.40-7.35 (m, 3H), 5.68-5.64 (m, 1H), 5.56-5.52 (m, 1H), 5.01-4.98 (m,

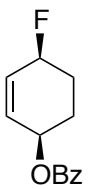
1H), 3.73 (s, 3H), 2.21-2.13 (m, 2H), 2.00-1.92 (m, 1H), 1.85-1.77 (m, 1H), 1.59-1.51 (m, 1H), 0.39 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 136.7, 134.0, 129.3, 127.8, 124.4, 124.2, 74.7, 54.3, 32.8, 25.7, 20.9, -4.0, -4.4; IR (CH_2Cl_2) ν 3054, 2978, 1740, 1443, 1265, 1113, 1027, 834; HRMS calc for $C_{16}H_{22}NaO_3Si$ $[M+Na]^+$ 313.1230, found 313.1231.

(*syn*)-4-Fluorocyclohex-2-en-1-yl acetate (*syn*-79a)



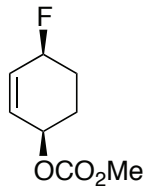
Following the general procedure D, the reaction was carried out on 383 mg (1.4 mmol) of *anti*-**93a** (*anti:syn*, 97:3). Silica gel column chromatography (hexane: Et_2O, 90:10) allowed the separation of the major isomer *syn*-**79a** (39 mg, 20%, *syn*:*anti*, 88:12) as a colourless oil. The relative stereochemistry of *syn*-**79a** has been determined by NOE and HOESY studies. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03-5.98 (m, 1H), 5.95-5.91 (m, 1H), 5.24-5.19 (m, 1H), 4.96 (dm, *J* = 52Hz, 1H), 2.07 (s, 3H), 2.04-1.92 (s, 1H), 1.90-1.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 131.7 (d, *J* = 10Hz), 129.3 (d, *J* = 19Hz), 84.8 (d, *J* = 165Hz), 67.7 (d, *J* = 3Hz), 25.9 (d, *J* = 22Hz), 24.0 (d, *J* = 4Hz), 21.2; ^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$): δ -170.5; IR (CH_2Cl_2) ν 3055, 2987, 1732, 1422, 1265; HRMS calc for $C_8H_{15}FNO_2$ $[M+NH_4]^+$ 176.1087, found 176.1087.

(*syn*)-4-Fluorocyclohex-2-en-1-yl benzoate (*syn*-79b)



Following the general procedure D, the reaction was carried out on 383 mg (1.4 mmol) of *anti*-**93b** (*anti:syn* >98:2). Silica gel column chromatography (hexane: Et_2O, 90:10) allowed the separation of the major diastereoisomer *syn*-**79b** (76 mg, 43%, *syn:anti*, 94:6). The relative stereochemistry of *syn*-**79b** has been determined by NOE and HOESY studies. ^1H NMR (400 MHz, $CDCl_3$): δ 8.08-8.05 (m, 2H), 7.60-7.56 (m, 1H), 7.47-7.44 (m, 2H) 6.10-6.05 (m, 2H), 5.52-5.48 (m, 1H), 5.03 (dm, *J* = 47Hz, 1H), 2.19-2.11 (m, 1H), 2.06-1.94 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 133.1, 131.8 (d, *J* = 10Hz), 130.2, 129.7, 129.5 (d, *J* = 19Hz), 128.4, 84.9 (d, *J* = 164Hz), 68.1 (d, *J* = 2Hz), 26.0 (d, *J* = 21Hz), 24.2 (d, *J* = 4Hz); $^{19}F\{^1H\}$ NMR (376.5 MHz, $CDCl_3$): δ - 170.4; IR (CH_2Cl_2) ν 3055, 2987, 1715, 1421, 1265; HRMS calc for $C_{13}H_{13}FNaO_2$ $[M+Na]^+$ 243.0792, found 243.0792.

(*syn*)-4-Fluorocyclohex-2-en-1-yl methyl carbonate (*syn*-79c)



Following the general procedure D, the reaction was carried out on 261 mg (0.9 mmol) of *anti*-**83c** (*anti:syn* >98:2). Silica gel column chromatography (hexane: Et_2O, 90:10) allowed the separation of the major diastereoisomer *syn*-**79c** (93 mg, 59%, *syn:anti*, 97:3) as a colourless oil. The relative stereochemistry of *syn*-**79c** is in agreement with literature.[6] ^1H NMR (400 MHz, $CDCl_3$): δ 6.05-5.97 (m, 2H), 5.11-5.06 (m, 1H), 4.97 (dm, *J* = 48Hz, 1H), 3.80 (s, 3H), 2.11-2.02 (m, 1H), 1.98-1.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 130.8 (d, *J* = 10Hz), 129.9 (d, *J* = 20Hz), 84.7 (d, *J* = 165Hz), 71.4 (d, *J* = 2Hz), 54.8, 25.7 (d, *J* = 21Hz) 24.0 (d, *J* = 5Hz); $^{19}F\{^1H\}$ NMR (376.5 MHz, $CDCl_3$): δ - 171.2; IR (CH_2Cl_2) ν 3055, 2987, 1746, 1422, 1265; HRMS calc for $C_8H_{11}FNaO_3$ $[M+Na]^+$ 197.0584, found 197.0589.

4.2.8 Pt-Catalysed Allylic Alkylation of *Anti*-79a-c

General procedure E: Pt-catalysed allylic alkylation with 2 equiv of $NaCH(CO_2Me)_2$

A solution of sodium dimethyl malonate (2 equiv) in THF (0.1 M), prepared from dimethyl malonate (2 equiv) and NaH (2 equiv), was added to a stirring solution of $Pt(PPh_3)_4$ (5 mol%) in THF (0.1 M), followed by the addition of the allylic substrate (1 equiv). The reaction was stirred at room temperature for 24 h. The reaction was quenched by addition of distilled water and the aqueous layer extracted 2 times with Et_2O. The combined organic layers were dried over $MgSO_4$, and solvent removed *in vacuo.*

General procedure F: Pt-catalysed allylic alkylation with 1.2 equiv of $NaCH(CO_2Me)_2$

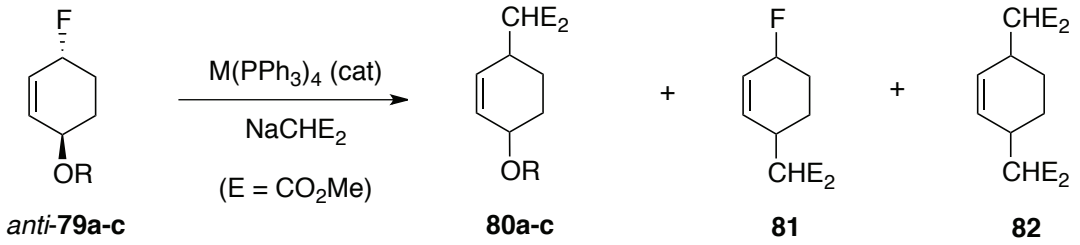
A solution of sodium dimethyl malonate (1.2 equiv) in THF (0.1 M), prepared from dimethyl malonate (1.2 equiv) and NaH (1.2 equiv), was added to a stirring solution of $Pt(PPh_3)_4$ (5 mol%) in THF (0.1 M), followed by the addition of the allylic substrate (1 equiv). The reaction was stirred at room temperature, until TLC indicated complete conversion of the starting material. The reaction was quenched by addition of distilled water and the aqueous layer extracted 2 times with Et_2O. The combined organic layers were dried over $MgSO_4$, and solvent removed *in vacuo.*

General procedure G: Pt-catalysed allylic alkylation with alternative ligands

A solution of sodium dimethyl malonate (2 or 1.2 equiv) in THF (0.1 M), prepared from dimethyl malonate (2 or 1.2 equiv) and NaH (2 or 1.2 equiv), was added to a stirring solution of $[Pt(allyl)Cl]_4$ (1.25 mol%) and phosphine ligand (**L1**, 5 mol% or **L2-3**, 10 mol%) in THF (0.1 M), followed by the addition of the allylic substrate (1 equiv). The reaction was stirred at room temperature, until TLC indicated complete conversion of the starting material and not longer than 52 h. The reaction was quenched by addition of distilled water

and the aqueous layer extracted 2 times with Et_2O. The combined organic layers were dried over $MgSO_4$, and solvent removed *in vacuo.*

Results of Table 2.4



anti-**79a-c** **80a-c** **81** **82**

Entry 1: Following the general procedure E, the reaction was carried out on 47 mg (0.3 mmol) of *anti*-**79a** (*anti:syn*, 93:7). Silica gel column chromatography (hexane: Et_2O, 90:10) yielded **80a** (32 mg, 40%, *anti:syn*, 86:14), **81** (4 mg, 5%, *anti:syn* >98:2) and **82** (9 mg, 9%, *anti:syn*, 67:33).

Entry 2: Following the general procedure F, the reaction was carried out on 47 mg (0.3 mmol) of *anti*-**79a** (*anti:syn*, 91:9) for 4 h. Silica gel column chromatography (hexane: Et_2O, 90:10) yielded **80a** (25 mg, 31%, *anti:syn*, 91:9), **81** (11 mg, 14%, *anti:syn*, 94:6) and **82** (6 mg, 6%, *anti:syn*, 33:67).

Entry 3: Following the general procedure E, the reaction was carried out on 66 mg (0.3 mmol) of *anti*-**79b** (*anti:syn*, 96:4). Silica gel column chromatography (hexane: Et_2O, 90:10) yielded **80b** (38 mg, 38%, *anti:syn*, 75:25), **81** (9 mg, 11%, *anti:syn*, 83:17), **82** (21 mg, 21%, *anti:syn*, 91:9) and recovered *anti*-**79b** (4 mg, 6%, *anti:syn* >98:2).

Entry 4: Following the general procedure F, the reaction was carried out on 66 mg (0.3 mmol) of *anti*-**79b** (*anti:syn*, 96:4) for 24 h. Silica gel column chromatography (hexane: Et_2O, 90:10) yielded **80b** (28 mg, 28%, *anti:syn*, 83:17), **81** (11 mg, 13%, *anti:syn*, 95:5), **82** (4 mg, 4%, *anti:syn*, 67:33).

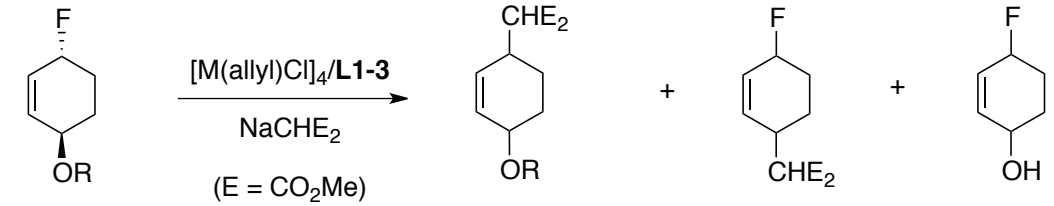
Entry 5: Following the general procedure E, the reaction was carried out on 52 mg (0.3 mmol) of *anti*-**79c** (*anti:syn*, 97:3). Silica gel column chromatography (hexane) yielded **80c**

(22 mg, 25%, *anti:syn*, 83:17), **81** (8 mg, 11%, *anti:syn* >98:2) and **82** (66 mg, 64%, *anti:syn*, 94:6).

Entry 6: Following the general procedure F, the reaction was carried out on 52 mg (0.3 mmol) of *anti*-**79c** (*anti:syn*, 90:10) for 3 h. Silica gel column chromatography (hexane) yielded **80c** (11 mg, 12%, *anti:syn*, 86:14), **81** (6 mg, 8%, *anti:syn* >98:2), **82** (12 mg, 12%, *anti:syn*, 75:25) and recovered *anti*-**79c** (13 mg, 25%, *anti:syn*, 75:25).

Entry 7: Following the general procedure E, the reaction was carried out on 52 mg (0.3 mmol) of *anti*-**79c** (*anti:syn*, 90:10) for 24 h. A quantitative ^{13}C NMR spectra was recorded on the crude reaction mixture, and the product distribution determined as follow: 42% of *anti*-**79c** (*anti*:*syn*, 87:13), 15% of **81c** (*anti*:*syn* >98:2) and 43% of **82** (*anti*:*syn*, 84:16).

Results of Table 2.5



anti-**79a-c** **80a-c** **81** **94**

Entry 1: Following the general procedure G, the reaction was carried out on 47 mg (0.3 mmol) of *anti*-**79a** (*anti:syn*, 93:7), 2 equiv of $NaCH(CO_2Me)_2$ and PPh_3 (**L1**) for 52 h. Silica gel column chromatography (hexane: Et_2O, 90:10) yielded **80a** (36 mg, 44%, *anti:syn*, 89:11), **81** (3 mg, 4%, *anti:syn* >98:2) and recovered *anti*-**79a** (5 mg, 11%, *anti:syn* > 98:2).

Entry 2: Following the general procedure G, the reaction was carried out on 66 mg (0.3 mmol) of *anti*-**79b** (*anti:syn*, 96:4), 2 equiv of $NaCH(CO_2Me)_2$ and PPh_3 (**L1**) for 52 h. Silica gel column chromatography (hexane: Et_2O, 90:10) yielded only recovered *anti*-**79b** (44 mg, 66%, *anti:syn* >98:2).

Entry 3: Following the general procedure G, the reaction was carried out on 52 mg (0.3 mmol) of *anti*-**79c** (*anti:syn*, 97:3), 2 equiv of $NaCH(CO_2Me)_2$ and PPh_3 (**L1**) for 52 h. Silica

gel column chromatography (hexane) yielded **80c** (3 mg, 4%, *anti:syn*, 87:13), **81** (2 mg, 3%, *anti:syn* >98:2), **94** (5 mg, 14%, *anti:syn* >98:2) and recovered **79c** (33 mg, 63%, *anti:syn*, 94:6).

Entry 4: Following the general procedure G, the reaction was carried out on 52 mg (0.3 mmol) of *anti*-**79c** (*anti:syn* > 98:2), 1.2 equiv of $NaCH(CO_2Me)_2$ and dppe (**L2**) for 24 h. A quantitative ^{13}C NMR spectra was recorded on the crude reaction mixture, showing the presence of >99% of *anti*-**79c** (*anti:syn* > 98:2).

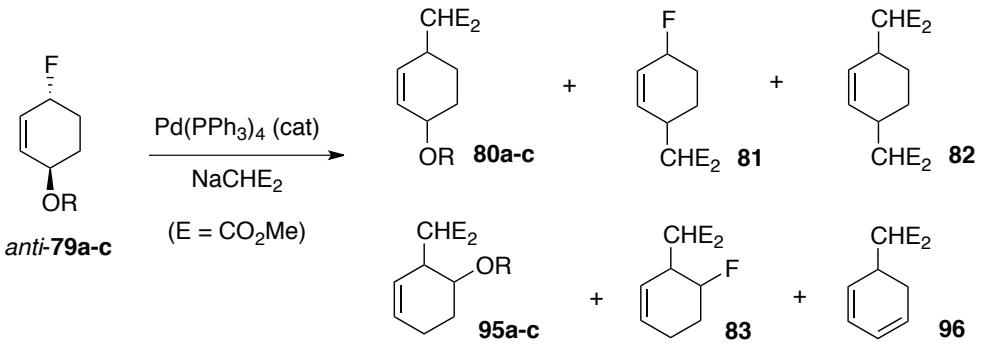
Entry 5: Following the general procedure G, the reaction was carried out on 52 mg (0.3 mmol) of *anti*-**79c** (*anti:syn* > 98:2), 1.2 equiv of $NaCH(CO_2Me)_2$ and dppf (**L3**) for 24 h. A quantitative ^{13}C NMR spectra was recorded on the crude reaction mixture, showing the presence of >99% of *anti*-**79c** (*anti:syn* > 98:2).

4.2.9 Pd-Catalysed Allylic Alkylation of *anti*-79a-c

General procedure H: Pd-catalysed allylic alkylation with 2 equiv of $NaCH(CO_2Me)_2$

A solution of sodium dimethyl malonate (2 equiv) in THF (0.1 M), prepared from dimethyl malonate (2 equiv) and NaH (2 equiv), was added to a stirring solution of $Pd(PPh_3)_4$ (5 mol%) in THF (0.1 M), followed by the addition of the allylic substrate (1 equiv). The reaction was stirred at room temperature. The reaction was quenched by addition of distilled water and the aqueous layer extracted 2 times with Et_2O. The combined organic layers were dried over $MgSO_4$, and solvent removed *in vacuo.*

Results of Scheme 2.19:



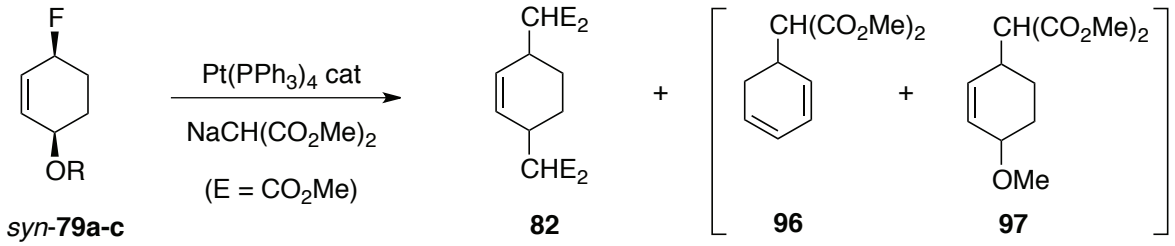
Scheme 2.19a: Following the general procedure G, the reaction was carried out on 47 mg (0.3 mmol) of *anti*-**79a** (*anti:syn*, 90:10) for 1.5 h. Silica gel column chromatography (hexane: Et_2O, 90:10) yielded a mixture of **80a** (44 mg, 54%, *anti:syn*, 86:14), **95a** (16 mg, 20%, *anti:syn*, 67:33).

Scheme 2.19b: Following the general procedure G, the reaction was carried out on 66 mg (0.3 mmol) of *anti*-**79b** (*anti:syn*, >98:2) for 1.5 h. Silica gel column chromatography (hexane: Et_2O, 90:10) yielded a mixture of **96**+**83** (13 mg, 16% and 3% (*anti*:*syn* >98:2), respectively), **80b**+**81** (29 mg, 17% (*anti:syn* >98:2) and 17% (*anti:syn* >98:2), respectively), and **82** (16 mg, 15%, *syn:anti*, 86:14).

Scheme 2.19c: Following the general procedure G, the reaction was carried out on 52 mg (0.3 mmol) of *anti*-**79c** (*anti:syn*, 89:11) for 1.5 h. Silica gel column chromatography (hexane) yielded *anti*-**80c** (24 mg, 35%, *anti:syn* > 98:2), **83** (4 mg, 5%, >98:2) and **82** (13 mg, 13%, *syn:anti*, 67:33).

4.2.10 Pt- and Pd-Catalysed Allylic Alkylation of *syn*-79a-c

Results of Table 2.6:



syn-**79a-c** **82** **96** **97**

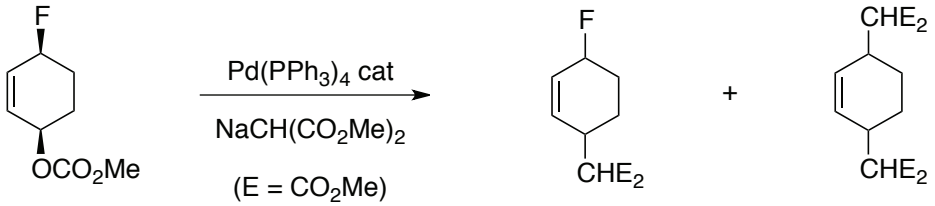
Entry 1: Following the general procedure E, the reaction was carried out on 32 mg (0.2 mmol) of *syn*-**79a** (*syn:anti*, 88:12) for 24 h. Silica gel column chromatography (hexane) yielded **82** (27 mg, 39%, *syn:anti* >98:2), recovered *syn*-**79a** (2 mg, 6%, *syn:anti*, 88:12) and an inseparable mixture of **96**:**97** (9 mg, 7%, 1:1). **97** was tentatively assigned by MS-GCT (m/z $[M+NH_4]^+$ 260.15).

Entry 2: Following the general procedure E, the reaction was carried out on 69 mg (0.3 mmol) of *syn*-**79b** (*syn:anti*, 94:6) for 24 h. Silica gel column chromatography (hexane) yielded **82** (38 mg, 38%, *syn:anti* >98:2), recovered *syn*-**79b** (13 mg, 19%, *syn:anti*, 80:20) and an inseparable mixture of **96**:**97** (12 mg, 9%, 1:1).

Entry 3: Following the general procedure E, the reaction was carried out on 52 mg (0.3 mmol) of *syn*-**79c** (*syn:anti*, 97:3) for 10 h. Silica gel column chromatography (hexane: Et_2O, 95:5) yielded **82** (47 mg, 69%, *syn:anti*, 98:2), recovered *syn*-**79c** (10 mg, 19%, *syn:anti* >98:2) and an inseparable mixture of **96**:**97** (8 mg, 6%, 1:1).

Entry 4: Following the general procedure F, the reaction was carried out on 69 mg (0.3 mmol) of *syn*-**79b** (*syn:anti*, 67:33) for 3 h. Silica gel column chromatography (hexane) yielded **82** (28 mg, 27%, *syn:anti* >98:2), recovered *syn*-**79b** (24 mg, 34%, *syn:anti*, 33:67) and an inseparable mixture of **96**:**97** (5 mg, 4%, 1:1).

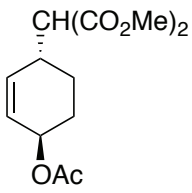
Results of Scheme 2.21:



syn-**79c** **81** **82**

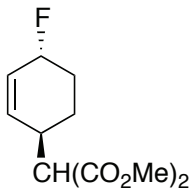
Following the general procedure H, the reaction was carried out on 52 mg (0.3 mmol) of *syn*-**79c** (*syn:anti*, 91:9) for 24 h. Silica gel column chromatography (hexane: Et_2O, 95:5) yielded **81** (26 mg, 37%, *syn:anti*, 93:7) and **82** (66 mg, 63%, *syn:anti* > 98:2).

Dimethyl [(*anti*)-4-acetoxycyclohex-2-en-1-yl]malonate14 (*anti*-80a)



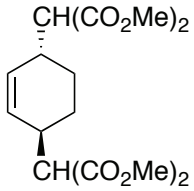
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78-5.70 (m, 2H), 5.27 (m, 1H) 3.74 (s, 6H) 3.28 (d, *J* = 9Hz, 1H), 2.97 (m, 1H), 2.08-2.04 (m, 1H) 2.04 (s, 3H), 1.89 (m, 1H), 1.66-1.57 (m, 1H) 1.50-1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 168.5, 168.4, 131.6, 128.7, 68.7, 56.0, 52.5, 52.4, 35.1, 27.2, 24.2, 21.3. Data are in agreement with literature.[42]

(*anti*)-Dimethyl(4-fluorocyclohex-2-en-1-yl) malonate (*anti*-81)



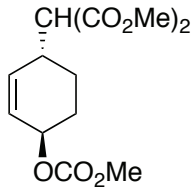
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92-5.87 (m, 1H), 5.83-5.81 (m, 1H), 5.04 (dm, *J* = 49Hz, 1H), 3.75 (s, 6H), 3.30 (d, *J* = 9Hz, 1H), 2.99 (m, 1H), 2.13-2.06 (m, 1H), 1.94 (m, 1H), 1.85-1.74 (m, 1H), 1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (d, *J* = 4Hz), 132.3 (d, *J* = 9Hz), 128.6 (d, *J* = 21Hz), 86.5 (d, *J* = 164Hz), 55.7 (d, *J* = 2Hz), 52.6 (d, *J* = 2Hz), 35.1 (d, *J* = 3Hz), 27.9 (d, *J* = 19Hz), 23.4 (d, *J* = 6Hz); ^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$): δ - 170.6. Data are in agreement with literature.[42]

(*anti*) -1,4-Bis(dicarboxymethyl)cyclohex-2-ene (*anti*-82)



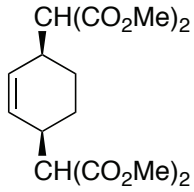
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.62 (s, 2H), 3.74 (s, 6H), 3.73 (s, 6H), 3.27 (d, *J* = 9Hz, 2H), 2.92-2.89 (m, 2H), 1.87-1.85 (m, 2H), 1.43-1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 130.1, 56.9, 52.9, 36.1, 26.5. Data are in agreement with literature.[42]

Dimethyl {(*anti*)-4-[(methoxycarbonyl)oxy]cyclohex-2-en-1-yl}malonate (*anti*-80c)



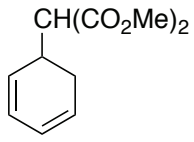
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.80 (s, 2H), 5.17-5.13 (m, 1H) 3.78 (s, 3H), 3.75 (s, 6H), 3.30 (d, *J* = 9Hz, 1H), 2.99-2.97 (m, 1H), 2.14-2.10 (m, 1H) 1.95-1.92 (m, 1H), 1.75-1.69 (q, *J* = 12Hz, 1H), 1.52-1.44 (q, *J* = 14Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 155.4, 132.1, 128.0, 72.5, 55.9, 54.7, 52.6, 35.0, 27.1, 24.0; IR (CH_2Cl_2) ν 3055, 2987, 1742, 1265; HRMS calc for $C_{13}H_{18}NaO_7$ $[M+Na]^+$ 309.0945, found 309.0944. The configuration of *anti*-**80c** has been determined by NOESY studies.

(*syn*) -1,4-Bis(dicarbomethoxymethyl)cyclohex-2-ene (*syn*-82)



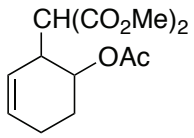
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.67 (s, 2H), 3.72 (s, 12H), 3.31 (d, *J* = 10Hz, 2H), 2.91-2.86 (m, 2H), 1.75-1.69 (m, 2H), 1.51-1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 129.8, 56.2, 52.4, 34.6, 23.6. Data are in agreement with literature.[42]

Dimethyl(2,4-cyclohexadien-1-yl) malonate (96)



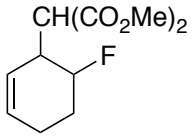
Tentative assignment based on the signals in the ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97-5.89 (m, 2H), 5.76-5.69 (m, 2H), 3.72 (s, 6H), 3.51 (d, *J* = 10Hz, 1H), 3.05-2.97 (m, 1H), 2.37-2.29 (m, 1H), 2.11-2.03 (m, 1H). Data are in agreement with literature.[207]

Dimethyl [(*anti*)-6-acetoxycyclohex-2-en-1-yl]malonate (95a)



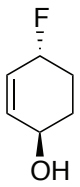
Tentative assignment based on the signals in the ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93-5.80 (m, 2H), 5.13-5.09 (m, 1H), 3.76 (s, 6H) 3.30 (d, *J* = 9Hz, 1H), 3.04-2.94 (m, 1H), 2.16-2.03 (m, 2H), 2.08 (s, 3H), 1.99-1.89 (m, 1H), 1.85-1.74 (m, 1H).

Dimethyl [(*anti*)-6-fluorocyclohex-2-en-1-yl] malonate (83)



Tentative assignment based on diagnostic signals in the NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81-5.72 (m, 1H), 5.54-5.50 (m, 1H), 4.74 (dm, *J* = 52Hz, 1H), 3.64 (d, *J* = 6Hz, 1H), 3.18-2.99 (m, 1H); ^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$): δ - 177.5. Data are in agreement with the literature.[42]

(*syn*)-4-Fluorocyclohex-2-en-1-yl (94)



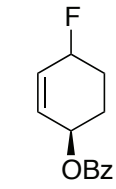
Tentative assignment based on the signals in the NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.95-5.86 (m, 2H), 5.04 (dm, *J* = 48Hz, 1H), 4.31-4.22 (m, 1H), 2.21-2.09 (m, 2H), 1.82-1.69 (m, 1H), 1.57-1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3 (d, *J* = 10Hz), 128.8 (d, *J* = 20Hz), 86.0 (d, *J* = 163Hz), 65.8 (d, *J* = 3Hz), 29.6 (d, *J* = 6Hz) 27.3 (d, *J* = 19Hz); ^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$): δ -171.3.

4.2.11 Isomerisation, Competition Expriment and Kinetic Study

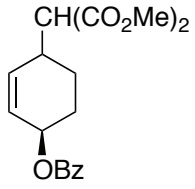
General procedure I: Epimerization test

To a solution of $Pt(PPh_3)_4$ (6 mg, 5 mol%) in THF (1 mL) was added the substrate (0.1 mmol) and the mixture was allowed to stir at room temperature for 24 h. The solution was diluted with Et_2O and filtered through Celite®. The combined organic layers were removed *in vacuo*.

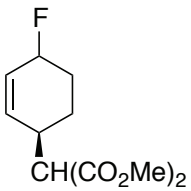
Results of Table 2.7:



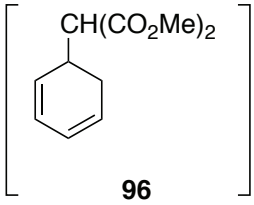
anti/*syn*-**79b**



anti/*syn*-**80b**



anti/*syn*-**81**



96

Entry 1: Following the general procedure I, the reaction was carried out on 22 mg of *anti*-**79b** (*anti:syn*, 96:4). By crude ^{1}H NMR detected was *anti*-**79b** (100%, *anti:syn*, 96:4).

Entry 2: Following the general procedure F, the reaction was carried out on 22 mg of *syn*-**79b** (*syn:anti*, 80:20). By crude ^{1}H NMR detected was *syn*-**79b** (100%, *syn:anti*, 75:25).

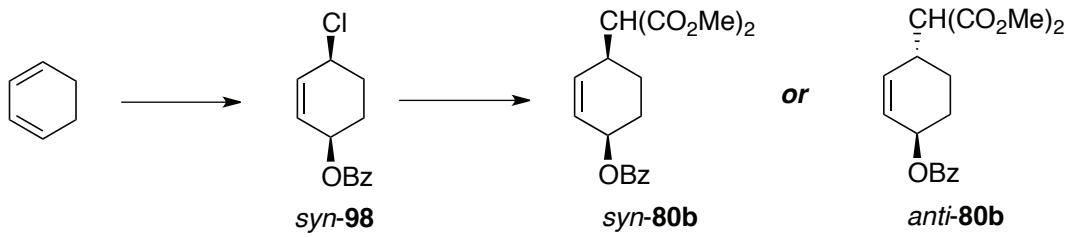
Entry 3: Following the general procedure F, the reaction was carried out on 33 mg of *anti*-**80b** (*anti:syn*, >98:2). By crude ^{1}H NMR detected was *anti*-**80b** (100%, *anti:syn*, 96:4).

Entry 4: Following the general procedure F, the reaction was carried out on 33 mg of *syn*-**80b** (*syn:anti*, >98:2). By crude ^{1}H NMR detected was *syn*-**80b** (86%, *syn:anti*, 83:17) and diene **96** (14%).

Entry 5: Following the general procedure F, the reaction was carried out on 23 mg of *anti*-**81** (*anti:syn*, >98:2). By crude ^{1}H NMR detected was *anti*-**81** (*anti:syn*, >98:2).

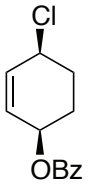
Entry 6: Following the general procedure F, the reaction was carried out on 23 mg of *syn*-**81** (*syn:anti*, 92:8). By crude ^{1}H NMR detected was **96** (100%).

Synthesis of *Anti*/*Syn*-80b:



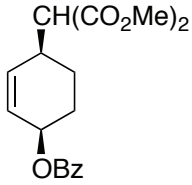
syn-**98** *syn*-**80b** *anti*-**80b**

(*syn*)-4-Chlorocyclohex-2-en-1-yl benzoate (*syn*-98)



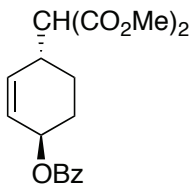
To a mixture of $PdCl_2$ (35.5 mg, 0.2 mmol), Li_2CO_3 (591 mg, 8 mmol), benzoic acid (4.88 g, 40 mmol), LiCl (297 mg, 7 mmol) and *p*-benzoquinone (908 mg, 8.4 mmol) in acetone (12 mL), was added 1,3-cyclohexadiene (0.38 mL, 4 mmol) *via* syringe over 4 h. After an additional 14 h, the acetone was removed *in vacuo* and Et_2O was added. The organic layer was washed with 2 M NaOH (2 x 20 mL) and $NaBH_4$ (30 mg) was added. The combined basic layers were back-extracted with Et_2O (2 x 10 mL) whereupon the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent afforded the crude product, which was purified by silica gel column chromatography (hexane: EtOAc, 95:5) to yield the title compound (650 mg, 69%, *syn*:*anti* >98:2) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08-8.06 (m, 2H), 7.60-7.56 (m, 1H), 7.47-7.44 (m, 2H), 6.05 (ddd, *J* = 10Hz, 4Hz, 2Hz, 1H), 5.95 (dd, *J* = 10Hz, 3Hz, 1H), 5.56-5.54 (m, 1H), 4.63-4.60 (m, 1H), 2.23-2.06 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 133.1, 131.9, 130.1, 129.7, 129.4, 128.4, 68.2, 53.6, 29.7, 24.6. Data are in agreement with literature.[142]

Dimethyl [(*syn*)-4-(benzoyloxy)cyclohex-2-en-1-yl]malonate (*syn*-80b)



To a solution of dimethyl malonate (0.19 mL, 1.7 mmol) in THF (6.5 mL) was added NaH (60% in mineral oil, 68 mg, 1.7 mmol) and the mixture was stirred for 10 min. To this mixture was added $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and PPh_3 (42 mg, 0.16 mmol) followed by *syn*-**98** (307 mg, 1.3 mmol, *syn*:*anti* >98:2). The resulting mixture was stirred for 2 h at room temperature and partitioned between Et_2O and H_2O. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over Na_2SO_4 and solvent removed *in vacuo.* The crude product was purified by silica gel column chromatography (hexane: Et_2O, 90:10) to yield the title compound (309 mg, 72%, *syn:anti* >98:2) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7Hz, 2H), 7.56 (t, *J* = 7Hz, 1H), 7.44 (t, *J* = 8Hz, 2H), 6.00-5.97 (m, 1H), 5.92-5.90 (m, 1H), 5.45 (m, 1H), 3.77 (s, 6H), 3.40 (d, *J* = 9Hz, 1H), 2.95 (m, 1H), 2.05-2.00 (m, 1H), 1.96-1.87 (m, 1H), 1.83-1.79 (m, 1H), 1.72-1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 168.5, 166.0, 133.6, 132.9, 130.5, 129.6, 128.3, 126.9, 66.7, 56.1 52.5, 41.1, 35.5, 27.2, 22.4. Data are in agreement with literature.[142]

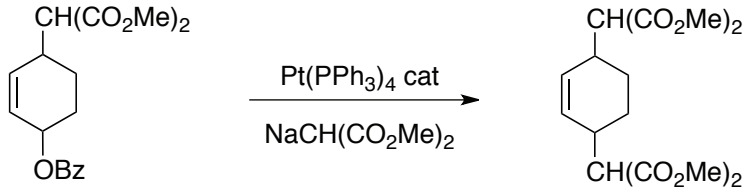
Dimethyl [(*anti*)-4-(benzoyloxy)cyclohex-2-en-1-yl]malnate (*anti*-80b)



Substrate *syn*-**98** (328 mg, 1.4 mmol, *syn*:*anti* >98:2) was added under nitrogen to a solution of sodium dimethyl malonate (1.7 mmol) in dry acetonitrile (6 mL) (prepared from dimethyl malonate and NaH (60% in mineral oil) as described in the preparation of *syn*-**80b**

above, followed by removal of the THF *in vacuo* and replacing it with acetonitrile. The resulting mixture was refluxed for 16 h and partitioned between Et_2O and H_2O. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases dried over Na_2SO_4 and solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (pentane: Et_2O, 90:10) to yield the title compound (341 mg, 73%, *anti:syn* >98:2) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7Hz, 2H), 7.55 (t, *J* = 7Hz, 1H), 7.43 (t, *J* = 8Hz, 2H), 5.88-5.81 (m, 2H), 5.54 (m, 1H), 3.76 (s, 6H), 3.33 (d, *J* = 9Hz, 1H), 3.04 (m, 1H), 2.23-2.17 (m, 1H), 2.01-1.97 (m, 1H), 1.83-1.74 (m, 1H), 1.60-1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 166.2, 132.9, 131.8, 130.4, 129.6, 128.8, 128.3, 69.2, 56.0, 52.5, 35.2, 27.3, 24.3; IR (CH_2Cl_2) ν 3055, 2987, 1735, 1265; HRMS calc for $C_{18}H_{20}NaO_6$ $[M+Na]^+$ 355.1152, found 355.1153.

Results of Scheme Scheme 2.23:



80b **82**

Scheme 2.23a: Following the general procedure A, the reaction was carried out on 66 mg (0.2 mmol) of *syn*-**80b** (*syn:anti*, >98:2) for 24 h at room temperature, until TLC indicated complete conversion of the starting material. By crude ^{1}H NMR detected was only *syn*-**82** (*syn:anti*, >98:2).

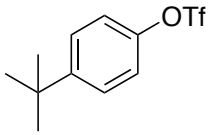
Scheme 2.23b: Following the general procedure A, the reaction was carried out on 66 mg (0.2 mmol) of *anti*-**8b** (*anti:syn*, >98:2) for 30 h at room temperature. By crude ^{1}H NMR detected were *anti*-**82** (*anti:syn*, >98:2) and *anti*-**80b** (*anti:syn*, >98:2) in a ratio 63:37 respectively.

Results of Scheme 2.24 and Chart 2.1:Kinetic Study

Following the general procedure E, the reaction was carried out in an NMR tube in d^8-THF on 16 mg (0.1 mmol) of **79a** (*syn:anti*, 80:20) for 24 h. ^{19}F NMR spectra were recorded every 5 minutes over 1.5 h, and ^1H NMR recorded early and late in the sequence. Relative concentrations of *syn*-**79b** and *anti*-**79b,** calculated by the relative integration of their fluorine peaks (at -171.6 ppm and -173.0 ppm, respectively) against time are reported in chart 1.

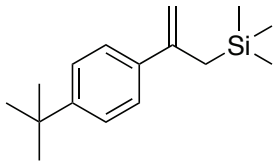
4.2.12 Synthesis of 99, 100a-c and 104

4-*tert*-Butylphenyl trifluoromethanesulfonate (159)[208]



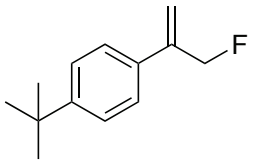
To 4-*tert*-butylphenol (1.2 g, 8 mmol) in dry DCM (40 mL) was added pyridine (1.3 mL, 16 mmol) and the solution was cooled to 0 °C. Trifluoromethanesulfonic anhydride (1.9 mL, 11.5 mmol) was added dropwise and the mixture was warmed to room temperature. The reaction was complete within 10 min as shown by TLC. The mixture was diluted with Et_2O, quenched with 10% aqueous HCl and washed successively with sat. $NaHCO_3$ and brine. The combined organic layers were dried over $MgSO_4$ and solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (2.16 g, 96%) as a yellow clear oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 9Hz, 2H), 7.20 (d, *J* = 9Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 147.4, 127.1, 120.7, 117.2, 34.7, 31.2; IR (CH_2Cl_2) ν 3055, 2987, 1422, 1265, 1143; *m/z* $[M]^+$ 282.05.

[2-(4-*tert*-Butylphenyl)prop-2-en-1-yl](trimethyl)silane (160)[209]



A mixture of **159** (1.7 g, 6 mmol), palladium acetate (40.4 mg, 0.18 mmol), 1,1'-bis(diphenylphosphino)ferrocene (444 mg, 0.8 mmol), allyltrimethylsilane (4.8 mL, 30 mmol), triethylamine (1.67 mL, 12 mmol), and dry acetonitrile (24 mL) was placed in a pressure tube. The tube was sealed and the reaction mixture was heated, with stirring, to 60°C for 20 hours. After allowing the resulting black solution to cool to room temperature, the reaction mixture was quenched with water (60 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane) to yield the title compound (1.07 g, 73%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.33 (m, 4H), 5.17-5.16 (m, 1H), 4.87-4.84 (m, 1H), 2.06-2.03 (m, 2H), 1.35 (s, 9H), -0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 146.2, 139.7, 125.9, 124.9, 109.3, 34.4, 31.3, 25.9, -1.4; IR (CH_2Cl_2) ν 3055, 2987, 1265; HRMS calc for $C_{16}H_{27}Si$ $[M+H]^+$ 247.1877, found 247.1885.

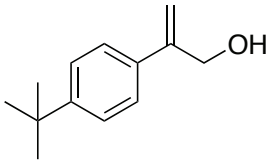
1-*tert*-Butyl-4-(3-fluoroprop-1-en-2-yl)benzene (99)



A solution of **160** (1.1 g, 4.5 mmol) in anhydrous acetonitrile (30 mL) was treated with Selectfluor® (1.91 g, 5.4 mmol). The reaction mixture was stirred at room temperature for 2.5 h, when the TLC shown the complete conversion of the starting material. Distilled water was added and the aqueous layer extracted 3 times with Et_2O. The combined organic

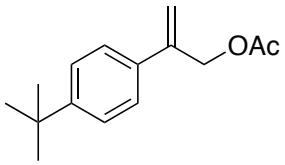
layers were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane) to yield the title compound (590 mg, 68%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 4H), 5.60 (s, 1H), 5.39 (s, 1H), 5.25 (d, *J* = 47Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 142.7 (d, *J* = 14Hz), 134.3, 128.2, 125.5 (4H, d, *J* = 8Hz), 114.5 (d, *J* = 10Hz), 84.4 (d, *J* = 169Hz), 34.6, 31.2; ^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$): δ - 212.8; IR (CD_2Cl_2) ν 1632, 1268, 838; HRMS calc for $C_{13}H_{17}F$ $[M]^+$ 192.1314 found 192.1310.

2-(4-*tert*-Butylphenyl)prop-2-en-1-ol (102)



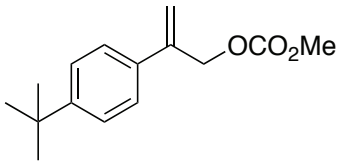
To a solution of (4-(*tert*-butyl)phenyl)magnesium bromide (1.3 mL of 2 M solution in THF, 2.5 mmol) in Et_2O (6 mL) was added CuI (29 mg, 0.15 mmol). The reaction mixture was allowed to stir at room temperature for 0.5 h. Propargyl alcohol (58 mL, 1 mmol) in Et_2O (1 mL) was added dropwise at room temperature. The reaction was then heated to reflux for 24 h. After cooling to room temperature, NH_4Cl saturated aqueous solution was added dropwise carefully. The organic phase was separated and the aqueous phase extracted with Et_2O, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane) to yield the title compound (188 mg, 99%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.44 (m, 4H), 5.48 (s, 1H), 5.33 (s, 1H), 4.55 (s, 2H), 1.88 (bs, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 147.0, 135.5, 125.7, 125.4, 111.9, 65.0, 34.5, 31.3; 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 acetate (100a)



To a solution of **102** (57 mg, 0.3 mmol) and triethylamine (50 μL, 0.36 mmol) in DCM (3 mL) at 0°C was added acetic anhydride (28 μL, 0.3 mmol) dropwise. The reaction was allowed to stir at room temperature overnight. The reaction mixture was diluted with DCM and then washed successively by $NaHCO_3$ saturated aqueous solution, H_2O and brine. The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane: Et_2O, 90:10) to yield the title compound (32 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 4H), 5.57 (s, 1H), 5.34 (m, 1H), 4.99 (s, 2H), 2.10 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 151.1, 142.0, 135.0, 125.6, 125.4, 114.5, 65.8, 34.5, 31.3, 21.0; IR (neat) ν 2963, 1742, 1633, 1227; HRMS calc for $C_{15}H_{20}O_2$ $[M]^+$ 232.1463 found 232.1469.

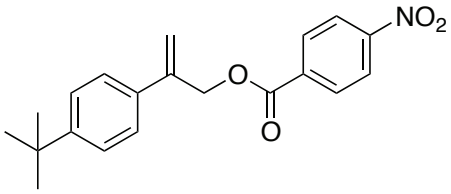
2-(4-*tert*-Butylphenyl)prop-2-en-1-yl methyl carbonate (100b)



To a solution of **102** (190 mg, 1 mmol) and pyridine (0.24 mL, 3 mmol) in THF (5 mL) at 0°C was added methyl chloroformate (0.15 mL, 2 mmol) dropwise. The reaction was then allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by the addition of NH_4Cl saturated aqueous solution, the aqueous phase was extracted 3 times with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane: Et_2O, 90:10) to yield the title compound (188 mg, 76%)**;** ^{1}H NMR

(400 MHz, $CDCl_3$): δ 7.40 (s, 4H), 5.58 (s, 1H), 5.39 (s, 1H), 5.05 (s, 2H), 3.81 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 151.2, 141.6, 134.8, 125.6, 125.5, 114.9, 69.1, 54.8, 34.5, 31.3; IR (neat) ν 2962, 1751, 1268.

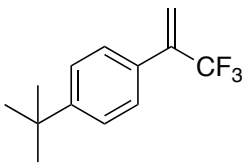
2-(4-*tert*-Butylphenyl)prop-2-en-1-yl 4-nitrobenzoate (100c)



The synthesis of substrate **100c** was carried out by C. Hollingworth.[143]

To a solution of **102** (190 mg, 1 mmol) and triethylamine (140 μL, 1 mmol) in DCM (10 mL) was added 4-nitrobenzoyl chloride (186 mg, 1 mmol) portion wise at 0°C. The reaction was allowed to warm at room temperature and stirred overnight. The reaction mixture was diluted with DCM and then washed successively by $NaHCO_3$ saturated aqueous solution, H_2O and brine. The organic phase was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane: Et_2O, 90:10) to yield the title compound (380 mg, 85%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.20-8.29 (m, 4H), 7.38-7.48 (m, 4H), 5.66 (s, 1H), 5.45 (s, 1H), 5.36 (s, 2H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 151.9, 151.0, 142.0, 135.9, 135.2, 131.2, 126.0, 126.0, 124.0, 115.7, 67.6, 35.0, 31.7; IR (KBr) ν 1726, 1530, 1265; HRMS calc for $C_{20}H_{21}NO_4$ $[M]^+$ 339.1466 found 339.1471. Mp 72-74°C.

4-tert-Butyl-1-(trifluoromethyl)vinylbenzene (103)



The synthesis of substrate **103** was carried out by M. Keita.[139]

To a solution of $PdCl_2$(dppm) (160 mg, 0.286 mmol) in 1,4-dioxane (10 mL) was added 2-bromo-3,3,3-trifluoroprop-1-ene (1 g, 5.72 mmol). A 0.5 M solution of ArMgBr in THF (16 mL, 8 mmol) was added at a rate of 100 µL/min using a syringe pump at 50 °C. The reaction mixture was stirred for 30 min at the same temperature. After cooling to room temperature, the reaction mixture was passed through a silica gel column chromatography (pentane), and the eluted solution was concentrated *in vacuo* to yield the title compound (1.03 g, 79%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.45 (m, 4H), 5.97-96 (m, 1H), 5.82-5.80 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8 (q, *J* = 30Hz), 130.7, 128.1, 127.0, 125.5, 123.5 (q, *J* = 272Hz), 119.6 (q, *J* = 6Hz), 34.9, 31.4; ^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$): δ -64.6. Data are in agreement with literature.[210]

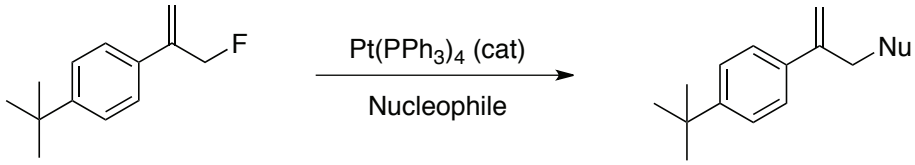
4.2.13 Pt-Catalysed Substitution of Allylic Fluoride

Results of Scheme 2.25: External Competition Experiment

A solution of sodium dimethyl malonate (0.2 mmol) in THF (1 mL), prepared from dimethyl malonate (22 µL, 0.2 mmol) and NaH (60% in mineral oil, 8 mg, 0.2 mmol), was added to a stirring solution of $Pt(PPh_3)_4$ (12 mg, 5 mol%), **99** (38 mg, 0.2 mmol) and **100a** (46 mg, 0.2 mmol) in THF (1 mL). The reaction was stirred at room temperature for 24 h. The reaction was quenched by addition of distilled water and the aqueous layer extracted 2 times with Et_2O. The combined organic layers were dried over $MgSO_4$, and solvent removed *in vacuo.* The crude mixture was purified by silica gel column chromatography (hexane) to afford **101** (42 mg, 35%), **100a** (24 mg, 26%) and **99** (9 mg, 12%).

Results of Table 2.8:

The results of Table 2.8 were obtained by M. Keita.[139]

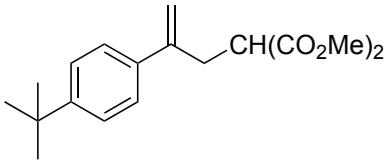


99 **101a-g**

General procedure J: Platinum catalysed allylic amination of 99

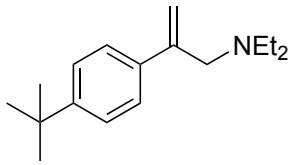
A solution of amine (0.34 mmol) and **99** (38 mg, 0.2 mmol) in THF (1 mL) was added to a stirring solution of $Pt(PPh_3)_4$ (0.01 mmol, 5%) in THF (1 mL). The reaction was stirred at rt for 1h. Distilled water was added and the aqueous layer extracted 2 times with Et_2O. The combined layers were dried over $MgSO_4$, and solvent removed *in vacuo*.

Dimethyl [2-(4-*tert*-butylphenyl)prop-2-en-1-yl]malonate (101a)



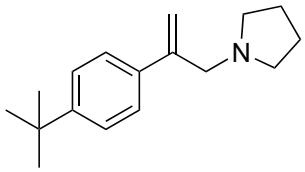
Following the general procedure A, the reaction was carried out on 38 mg of **99**. Silica gel column chromatography (hexane: Et_2O, 70:30) yielded the title compound (56 mg, 92%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.31 (m, 4H), 5.31 (d, *J* = 1Hz, 1H), 5.10 (d, *J* = 1Hz, 1H), 3.70 (s, 6H), 3.57 (t, *J* = 8Hz, 1H), 3.13 (dd, *J* = 8Hz, 1Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 153.7, 150.8, 144.4, 136.8, 125.9, 125.4, 114.1, 52.5, 50.8, 34.6, 31.3; IR (CH_2Cl_2) ν 3055, 2966, 1736, 1266; HRMS calc for $C_{18}H_{24}NaO_4$ $[M+Na]^+$ 327.1567, found 327.1567.

2-(2(4-*tert*-buthylphenyl)-*N,N*-diethylprop-2-en-1-amine (101b)



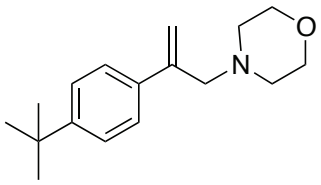
Following the general procedure J, the reaction was carried out on 35 mL of diethyl amine. Silica gel column chromatography (hexane: Et_2O, 1:1) yielded the title compound (45 mg, 91%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 9Hz, 2H), 7.36 (d, *J* = 9Hz, 2H), 5.44 (s, 1H), 5.26 (s, 1H), 3.42 (s, 2H), 2.56 (q, *J* = 7Hz, 4H), 1.35 (s, 9H), 1.02 (t, *J* = 7Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 145.5, 137.7, 125.9, 125.1, 114.1, 57.6, 46.8, 34.5, 31.3, 11.5; IR (CH_2Cl_2) ν 1265; HRMS calc for $C_{17}H_{27}N$ $[M+H]^+$ 246.2216 found 246.2215.

1-(2-(4-*tert*-butylphenyl)allyl)pyrrolidine (101c)



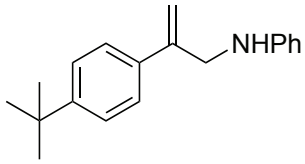
Following the general procedure J, the reaction was carried out on 28 mL of pyrrolidine. Silica gel column chromatography (hexane: Et_2O, 50:50) yielded the title compound (44 mg, 90%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 9Hz, 2H), 7.32 (d, *J* = 9Hz, 2H), 5.42 (s, 1H), 5.26 (s, 1H), 3.48 (s, 2H), 2.56 (m, 4H), 1.78 (m, 4H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 145.2, 137.6, 125.8, 125.1, 113.7, 60.7, 54.2, 34.5, 31.3, 23.6; IR (CH_2Cl_2) ν 1265; HRMS calc for $[M+H]^+$ 244.2060 found 244.2062.

4-(2-(4-*tert*-butylphenyl)allyl)morpholine (101d)



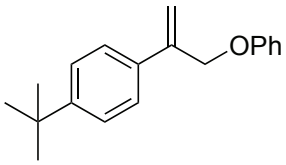
Following the general procedure J, the reaction was carried out on 30 mL of morpholine. Silica gel column chromatography (hexane: Et_2O, 60:40) yielded the title compound (43 mg, 82%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8Hz, 2H), 7.37 (d, *J* = 8Hz, 2H), 5.31 (s, 1H), 5.24 (s, 1H), 3.72 (t, *J* = 5Hz, 4H), 3.33 (s, 2H), 2.51 (m, 4H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 143.0, 137.3, 125.8, 125.0, 114.9, 67.1, 63.6, 53.6, 34.5, 31.3; IR (CH_2Cl_2) ν 1266, 1116; HRMS calc for $[M+H]^+$ 260.2009 found 260.2006.

N-(2-(4-*tert*-butylphenyl)allyl)benzenamine (101e)



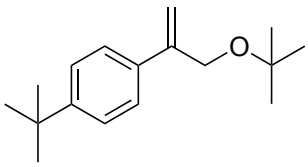
Following the general procedure J, the reaction was carried out on 32 mg of aniline for 16 h at reflux. Silica gel column chromatography (hexane) yielded the title compound (38 mg, 72%) as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7Hz, 2H), 7.41 (d, *J* = 7Hz, 2H), 7.03 (m, 2H), 6.74 (t, *J* = 7Hz, 1H), 6.67 (d, *J* = 9Hz, 2H), 5.53 (s, 1H), 5.33 (s, 1H), 4.19 (s, 2H), 3.95 (br s, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 148.1, 144.3, 136.2, 129.2, 125.7, 125.4, 117.5, 113.0, 112.9, 48.0, 34.6, 31.3; IR (CH_2Cl_2) ν 1603, 1265; HRMS calc for $[M+Na]^+$ 288.1723 found 288.1723.

1-tert-butyl-4(3-phenoxyprop-1-en-2-yl)benzene (101f)



A solution of sodium phenoxyde (0.34 mmol) in THF (1 mL), prepared from phenol (30 mL, 0.34 mmol) and NaH (60% in mineral oil, 13.6 mg, 0.34 mmol) was added to a stirring solution of $Pt(PPh_3)_4$ (0.01 mmol, 5%) in THF (1 mL), followed by the addition of **99** (38 mg, 0.2 mmol). The reaction was stirred for 4h at reflux. Distilled water was added and the aqueous layer extracted 2 times with Et_2O. The combined layers were dried over $MgSO_4$, and solvent removed *in vacuo*. Silica gel column chromatography (hexane) yielded the title compound (54 mg, 99%) as colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8Hz, 2H), 7.43 (d, *J* = 8Hz, 2H), 7.34 (m, 2H), 7.02 (td, *J* = 7Hz, 2Hz, 3H), 5.67 (s, 1H), 5.46 (s, 1H), 4.95 (s, 2H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 151.1, 142.6, 135.4, 129.5, 128.5, 125.4, 121.0, 114.8, 114.0, 69.8, 34.6, 31.3; IR (CH_2Cl_2) ν 1599, 1240, 1015; HRMS calc for $C_{19}H_{22}O$ $[M+Na]^+$ 289.1563 found 289.1563.

1-(3-*t*ert-Butoxyprop-1en-2-yl)-4-tert-butylbenzene (101g)

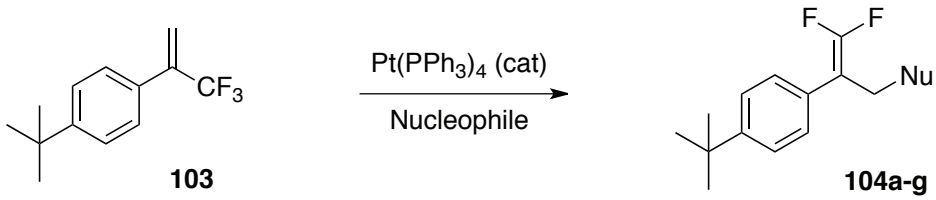


A solution of sodium *tert*-butoxyde (0.34 mmol) in THF (1 mL), prepared from *tert*-butanol (25 mg, 0.34 mmol) and NaH (60% in mineral oil, 13.6 mg, 0.34 mmol) was added to a stirring solution of $Pt(PPh_3)_4$ (0.01 mmol, 5%) in THF (1 mL), followed by the addition of **99** (38 mg, 0.2 mmol). The reaction was stirred for 16 h at reflux. Distilled water was added and the aqueous layer extracted 2 times with Et_2O. The combined layers were dried over $MgSO_4$, and solvent removed *in vacuo*. Silica gel column chromatography (hexane) yielded

the title compound (19 mg, 38%) as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8Hz, 2H), 7.35 (d, *J* = 8Hz, 2H), 5.55 (s, 1H), 5.35 (s, 1H), 4.44 (s, 2H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 143.8, 135.8, 125.8, 125.2, 113.9, 111.7, 71.9, 34.5, 31.30; IR (CH_2Cl_2) ν 1264; HRMS calc for $C_{17}H_{26}O$ $[M]^+$ 246.1984 found 246.1980.

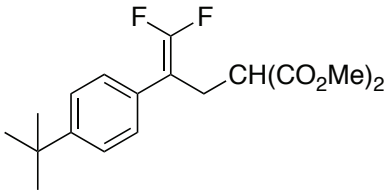
Results of Table 2.9:

The results of Table 2.9 were obtained by M. Keita.[139]



103 **104a-g**

Dimethyl 2-(2-(4-tert-buthylphenyl)-3,3-difluoroallyl)malonate (104g)



Following the general procedure F, the reaction was carried out on 46 mg of **103**. Silica gel column chromatography (hexane: Et_2O, 80:20) yielded the title compound (21 mg, 30%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.37 (m, 2H), 7.28-7.20 (m, 2H), 3.67 (s, 6H), 3.42-3.37 (m, 1H), 3.05-3.02 (m, 2H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 153.9, 150.7, 128.9, 128.0, 125.5, 89.1 (dd, *J* = 17Hz, 21Hz), 52.5, 49.9, 34.5, 31.2, 27.4; ^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$): δ - 89.5 (d, J_{FF} = 38Hz), - 89.8 (d, J_{FF} = 38Hz); IR (CH_2Cl_2) ν 1735, 1437, 1243; HRMS calc for $[M-H]^-$ 339.15 found 339.16.

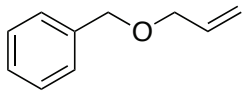
4.2.14 Pt-Catalysed Allylic Fluorination of 100b-c (Scheme 2.26)

To a solution of allylic carbonate **100b** (0.2 mmol) or *p*-nitrobenzoate **100c** (0.2 mmol) and $Pt(PPh_3)_4$ (5 mol%) THF (1 mL) was added TBAF·4*t*BuOH (2 eq, 0.4 mmol). The reaction was allowed at room temperature until TLC indicated complete conversion of the starting material and no longer than 24 h. The reaction was quenched by addition of saturated aqueous solution of NH_4Cl and the aqueous layer extracted 2 times with Et_2O. The combined organic layers were dried over $MgSO_4$, and solvent removed *in vacuo.* By ^1H NMR of the crude mixture, detected was alcohol **102** (> 99%). No traces of fluoride **99** were detected by ^{19}F NMR spectroscopy.

4.2.15 Kinetic Resolution of Allylic Fluoride 106a

Synthesis of 106:

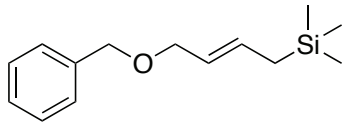
Allyl benzyl ether (161)



To a solution of allyl alcohol (0.6 mL, 10.3 mmol) and pyridine (1.9 mL, 23.2 mmol) in DCM (17 mL) at 0 °C was added benzyl chloride (2.0 mL, 17.4 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 5 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (1.29 g, 78%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 4Hz, 4H), 7.34-7.28 (m, 1H), 6.02-5.93 (ddt, *J* = 17Hz, 10Hz, 6Hz, 1H), 5.33 (ddt, *J* = 17Hz, 3Hz, 1Hz, 1H), 5.22 (ddt, *J* = 10Hz, 3Hz, 1Hz,

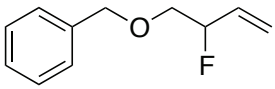
1H), 4.54 (s, 2H) (dt, *J* = 6Hz, 1Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 134.7, 128.4, 127.7, 127.6, 117.1, 72.1, 71.1. Data are in agreement with literature.[144]

[[[(2*E*)-4-(trimethylsilyl)-2-buten-1-yl]oxy]methyl]-benzene (162)



To a solution of **161** (1.00 g, 6.7 mmol) and trimethyl allylsilane (3.2 mL, 20.2 mol) in DCM (22 mL) at 50 °C was added Grubbs-Hoveyda 2nd generation catalyst (211 mg, 0.3 mmol) in 3 portions over 24 h. The reaction mixture was stirred for further 48 h at 50 °C. The mixture was cooled to room temperature and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (379 mg, 27%, *E:Z* = 5.8:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 4Hz, 4H), 7.32-7.28 (m, 1H), 5.77-5.63 (m, 1H), 5.57-5.44 (m, 1H), 4.51 (s, 2H), 3.99 (d, *J* = 7Hz, 2H), 1.53 (d, *J* = 8Hz, 2H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 131.9, 130.0, 128.3, 127.8, 127.5, 124.7, 123.6, 71.4, 71.2, 22.9, -1.9. Data are in agreement with literature.[144]

Benzyl 2-fluorobut-3-en-1-yl ether (106a)



Following the general procedure B, the reaction was carried out on 370 mg (1.6 mmol) of **162** (*E:Z* = 5.8:1). Silica gel column chromatography (hexane: Et_2O, 95:5) yielded the title compound (207 mg, 72%, b:l >20:1) as a colourless oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.42-7.36 (m, 4H), 7.35-7.31 (m, 1H), 5.95 (dddd, *J* = 18Hz, 15Hz, 11Hz, 6Hz, 1H), 5.45 (dq, *J* = 17Hz, 1Hz, 1H) 5.34 (dt, *J* = 11Hz, 1Hz, 1H) 5.05 (dm, *J* = 49Hz, 1H), 4.64 (s, 2H), 3.68 (dd, *J* = 2Hz, 5Hz, 1H), 3.62 (dd, *J* = 5Hz, 1Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ

138.5, 133.5 (d, *J* = 20Hz), 128.7, 128.1, 128.0, 118.5 (d, *J* = 11Hz), 92.3 (d, *J* = 171Hz), 73.7, 72.5 (d, *J* = 23Hz); ^{19}F {^{1}H}NMR (376.5 MHz, CD_2Cl_2): δ -184.76. Data are in agreement with literature.[144]

General procedure K: Pt-catalysed allylic alkylation of branched allylic fluoride 106a

A solution of sodium dimethyl malonate (0.34 mmol) in THF (0.1 M), prepared from dimethyl malonate (0.34 mmol) and NaH (0.34 mmol) was added to a stirring solution of pre-catalyst (1.25 mol%, $[Pt(allyl)Cl]_4$ and 5 mol%, **[Pt-2]**) and *t*Bu-PHOX (5 mol%) in THF (0.1 M), followed by the addition of the **106a** (0.2 mmol). The reaction was stirred at 50 °C for 24 h. The reaction was quenched by addition of distilled water and the aqueous layer extracted 2 times with Et_2O. The combined organic layers were dried over $MgSO_4$, and solvent removed *in vacuo.*

Results of Table 2.10:

The results of Table 2.10 were obtained by M. Keita.[139]



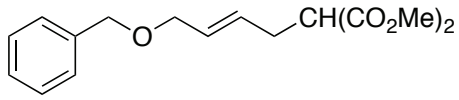
106a (*E*)-**107b**

Entry 1: Following the general procedure A, the reaction was carried out on 36 mg of **106a** for 1 h. Silica gel chromatography (hexane/Ether: 6/4) yielded (*E*)-**107b** (52 mg, 30%, *E*:*Z* > 20:1) as a colourless oil.

Entry 2: Following the general procedure K, the reaction was carried out on 36 mg of **106a**, and $[Pt(allyl)Cl]_4$. By crude ^{1}H NMR detected was **106a** (>99%, branched:linear ratio >98:2).

Entry 3: Following the general procedure K, the reaction was carried out on 36 mg of **106a** and **[Pt-2]**. By crude ^{1}H NMR detected was **106a** (>99%, branched:linear ratio >98:2).

(*E*)-Dimethyl 2-(4-(benzyolxy)but-2-enyl)malonate ((*E*)-107b)



^{1}H NMR (400 MHz, CD_3Cl): δ 7.37-7.29 (m, 5H), 5.76-5.64 (m, 2H), 4.48 (s, 2H), 3.97 (d, *J* = 4Hz, 2H), 3.74 (s, 6H), 3.47 (t, *J* = 7Hz, 1H), 2.67 (dd, *J* = 7Hz, 6Hz, 2H); ^{13}C NMR (100 MHz, CD_3Cl): δ 169.2, 138.2, 129.8, 129.1, 128.4, 127.7, 127.6, 71.9, 70.3, 52.5, 51.5, 31.5. IR (CD_2Cl_2) ν 1735, 1437, 1273; HRMS calc for $C_{16}H_{20}NaO_5$ $[M+Na]^+$ 315.1203, found 315.1197.

4.3 Experimental Data for Chapter 3

4.3.1 Preliminary Investigations on Allylic Carbonate 118a

General Procedure L: Table 3.4

To a solution of [Ir]/Ligand (4 mol%, Ir/Ligand: 1/2), in dry solvent THF (1 mL), **118a** (0.1 mmol) was added, followed by addition of TBAF·4*t*BuOH (2 eq, 0.2 mmol). The reaction was allowed to stir at 50 °C, if not differently stated, until TLC indicated complete conversion of the starting material and no longer then 24 h. The solvent was removed *in vacuo* and ^{1}H NMR and ^{19}F NMR of the crude mixture were recorded to determine the conversion of the starting material and the product distribution.

General Procedure M: Table 3.5

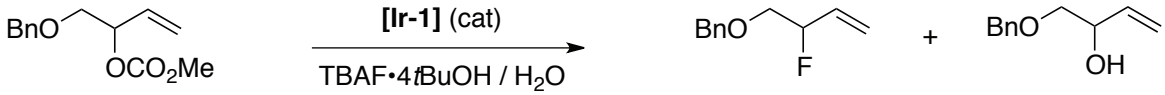
To a solution of **[Ir-1]** (2 mol%) in dry solvent (THF, CH_3CN, DMF, *t*BuOH, Toluene or DCM, 1 mL) **118a** (0.1 mmol) was added, followed by addition of the fluorinating source (TBAF·4*t*BuOH, TBAF·3H_2O, HF·pyridine, Et_3N·3HF, CsF, AgF or KF/16-crown-8, 0.2 mmol). The reaction was allowed to stir at the indicated temperature until TLC indicated complete conversion of the starting material and no longer then 24 h. The solvent was removed *in vacuo* and ^{1}H NMR and ^{19}F NMR of the crude mixture were recorded to determine the conversion of the starting material and the product distribution.

General Procedure N: Table 3.6

To a solution of allylic derivative **121-124a** (0.1 mmol) in dry DCM (1 mL) was added **[Ir-1]** (2 mol%), followed by addition of TBAF·4*t*BuOH (2 eq, 0.2 mmol). The reaction was allowed to stir at 40 °C, or room temperature, until TLC indicated complete conversion of the starting material and no longer than 24 h. The solvent was removed *in vacuo* and ^{1}H NMR and ^{19}F NMR of the crude mixture recorded to determine the conversion of the starting material and the product distribution.

4.3.2 Investigation on Alcohol Formation

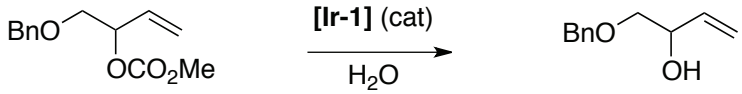
Ir-Catalysed Fluorination in the presence of H_2O



118a **106a** **119a**

To a solution of allylic derivative **118a** (24 mg, 0.1 mmol) and **[Ir-1]** (2 mg, 2 mol%) in dry THF (1 mL) were added TBAF·4*t*BuOH (2 eq, 0.2 mmol) and H_2O (4 μL, 0.2 mmol). The reaction was allowed to stir at 50 °C for 1 h. The solvent was removed *in vacuo.* By ^1H NMR of the crude reaction mixture, there were detected **119a** (b: l >98:2) and **106a** (b: l >98:2) in a ratio equal to 60:40.

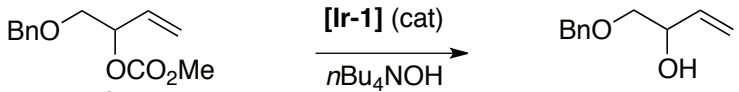
Ir-Catalysed Hydroxylation with H_2O



118a **119a**

To a solution of allylic derivative **118a** (24 mg, 0.1 mmol) and **[Ir-1]** (2 mg, 2 mol%) in dry THF (1 mL) was added H_2O (4 μL, 0.2 mmol). The reaction was allowed to stir at 50 °C for 24 h. The solvent was removed *in vacuo.* By ^1H NMR of the crude reaction mixture, there were detected **118a** (b: l >98:2) and **119a** (b: l >98:2) in a ratio equal to 95:5.

Ir-Catalysed Hydroxylation with *n*Bu_4NOH

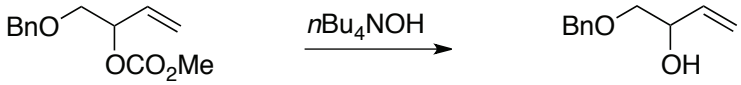


118a **119a**

To a solution of allylic derivative **118a** (24 mg, 0.1 mmol) and **[Ir-1]** (2 mg, 2 mol%) in dry THF (1 mL) was added a 1 M solution of *n*Bu_4NOH (0.2 mL, 0.2 mmol). The reaction was

allowed to stir at 50 °C for 5 h. The solvent was removed *in vacuo.* By ^{1}H NMR of the crude reaction mixture, **119a** (>99%, branched: linear >98:2) was detected.

Hydroxylation with *n*Bu$_4$NOH



118a **119a**

To a solution of allylic derivative **118a** (24 mg, 0.1 mmol) in dry THF (1 mL) was added a 1 M solution of *n*Bu$_4$NOH (0.2 mL, 0.2 mmol). The reaction was allowed to stir at 50 °C for 1 h. The solvent was removed *in vacuo.* By ^{1}H NMR of the crude reaction mixture, **119a** (>99%, branched: linear >98:2) was detected.

General Procedure O: Table 3.8

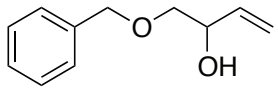
To a solution of **118a** (0.1 mmol) in dry DCM (5 mL) was added **[Ir-1]** (2 mol%), followed by addition of TBAF·4*t*BuOH (2 eq, 0.2 mmol) and additive or the alternative fluorinating agent (2 equiv, 0.2 mmol). The reaction was allowed to stir at 40 °C until TLC indicated complete conversion of the starting material and no longer than 24 h. The solvent was removed *in vacuo* and ^{1}H NMR and ^{19}F NMR of the crude mixture recorded to determine the conversion of the starting material and the product distribution.

Kinetic Study of Fluorination of 118a

To a solution of **118a** (0.1 mmol) in dry DCM (5 mL) was added **[Ir-1]** (2 mol%), followed by addition of TBAF·4*t*BuOH (2 eq, 0.2 mmol). The reaction was allowed to stir at 40 °C, and 5 aliquotes of 0.5 mL of the reaction mixture were collected over the first 1.5 h and one after 18 h. The solvent of the 6 aliquotes was removed *in vacuo* and ^{1}H NMR and ^{19}F NMR of the crude mixture recorded to determine the conversion of the starting material and the product distribution.

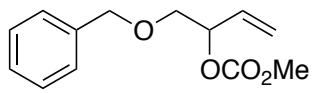
4.3.3 Synthesis of Substrates

1-(Benzyloxy)but-3-en-2-ol (119a)



To a solution of benzyloxyacetaldehyde (5.0 g, 33.3 mmol) in THF (150 mL) at 0 °C was added vinylmagnesium bromide solution (1M in THF, 50 mL, 50 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 5 h at room temperature. The reaction was quenched by addition of water. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (4.52 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H), 5.85 (ddd, *J* = 17Hz, 11Hz, 6Hz, 1H), 5.38 (dt, *J* = 17Hz, 2Hz, 1H), 5.21 (dt, *J* = 11Hz, 2Hz, 1H), 4.59 (s, 2H), 4.40-4.34 (m, 1H), 3.57 (dd, *J* = 10Hz, 3Hz, 1H), 3.57 (dd, *J* = 10Hz, 8Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 136.5, 128.5, 127.8, 127.7, 116.5, 74.0, 73.4, 71.5. Data are in agreement with literature.[211]

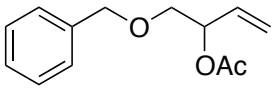
1-(Benzyloxy)but-3-en-2-yl methyl carbonate, 118a



To a solution of **119a** (2.67 g, 15.0 mmol) and pyridine (3.60 mL, 45 mmol) in DCM (65 mL) at 0^o C was added methyl chloroformate (2.31 mL, 30 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 8 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the

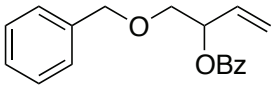
solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (3.04 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5H), 5.85 (ddd, *J* = 17Hz, 11Hz, 6Hz, 1H), 5.41 (d, *J* = 17Hz, 1H), 5.35-5.31 (m, 1H), 5.30 (d, *J* = 11Hz, 1H), 4.59 (s, 2H), 3.80 (s, 3H), 3.65-3.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 137.8, 132.7, 128.4, 127.7, 127.6, 118.7, 77.0, 73.3, 71.2, 54.8. Data are in agreement with literature.[212]

1-(Benzyloxy)but-3-en-2-yl acetate (121)



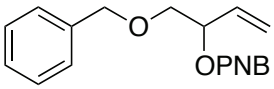
To a solution of **119a** (0.10 g, 0.56 mmol) and triethylamine (86 mL, 0.62 mmol) in DCM (4 mL) at 0 °C was added acetyl chloride (44 mL, 0.62 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 8 h at room temperature. The reaction was quenched by addition of sat. aqueous $NaHCO_3$ solution. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (DCM) to yield the title compound (0.11 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.24 (m, 5H), 5.83 (ddd, *J* = 17Hz, 11Hz, 6Hz, 1H), 5.49 (tdt, *J* = 6Hz, 5Hz, 1Hz, 1H), 5.31 (dt, *J* = 11Hz, 1Hz, 1H), 5.23 (dt, *J* = 11Hz, 1Hz, 1H), 4.55 (d, *J* = 3Hz, 2H), 3.57-3.54 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 137.9, 133.3, 128.4, 127.7, 127.6, 117.9, 73.2, 73.1, 71.2, 21.2; IR *v* 2863, 1739, 1233, 1094; HRMS calc for $C_{13}H_{16}NaO_3$ $[M+Na]^+$ 243.0997 found 243.0992.

1-(Benzyloxy)but-3-en-2-yl benzoate (122)



To a solution of **119a** (0.18 g, 1 mmol) and pyridine (0.08 mL, 1 mmol) in DCM (6 mL) at 0 °C was added benzoyl chloride (0.12 mL, 1 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (0.26 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 9Hz, 2H), 7.58 (t, *J* = 7Hz, 1H), 7.46 (t, *J* = 8Hz, 2H), 7.35-7.28 (m, 5H), 5.98 (ddd, *J* = 17Hz, 11Hz, 6Hz, 1H), 5.76 (dd, *J* = 10Hz, 5Hz, 1H), 5.44 (d, *J* = 17Hz, 1H), 5.31 (d, *J* = 11Hz, 1H), 4.63 (q, *J* = 12Hz, 2H), 3.76 (dd, *J* = 11Hz, 7Hz, 1H), 3.72 (dd, *J* = 11Hz, 5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 138.0, 133.4, 133.0, 130.3, 129.7, 128.4, 128.3, 127.7, 127.6, 118.0, 73.7, 73.2, 71.3. Data are in agreement with literature.[213]

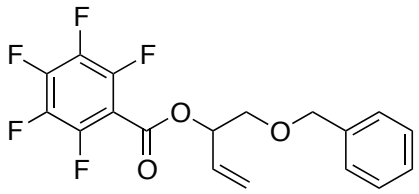
1-(Benzyloxy)but-3-en-2-yl 4-nitrobenzoate (123)



To a solution of **119a** (0.18 g, 1 mmol) and triethylamine (0.14 mL, 1 mmol) in DCM (6 mL) at 0 °C was added *p*-nitrobenzoyl chloride (0.19 mL, 1 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the

solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (0.27 g, 82%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.32-8.23 (m, 4H), 7.32-7.25 (m, 5H), 5.96 (ddd, *J* = 17Hz, 11Hz, 6Hz, 1H), 5.79-5.76 (m, 1H), 5.46-5.32 (m, 2H), 4.61 (d, *J* = 5Hz, 2H), 3.73 (dd, *J* = 5Hz, 2Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 151.0, 137.7, 135.7, 132.6, 130.8, 128.4, 127.8, 127.6, 123.5, 118.9, 74.9, 73.2, 71.1; IR (DCM) *v* 1724, 1525, 1267, 1100; HRMS calc for $C_{18}H_{17}NNaO_5$ $[M+Na]^+$ 350.0999 found 350.1003.

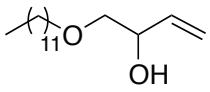
1-(Benzyloxy)but-3-en-2-yl-2,3,4,5,6-pentafluorobenzoate (124)



To a solution of **119a** (0.14 g, 0.8 mmol) and pyridine (0.2 mL, 2.4 mmol) in DCM (10 mL) at 0 °C was added 2,3,4,5,6-pentafluorobenzoyl chloride (0.23 mL, 1.6 mmol, 2.0 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 3 h at room temperature. The reaction was quenched by addition of NH_4Cl saturated aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (0.22 g, 72%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.20 (m, 5H), 5.83 (ddd, *J* = 17Hz, 10Hz, 6Hz, 1H), 5.70 (q, *J* = 6Hz, 1H), 5.38 (d, *J* = 17Hz, 1H), 5.28 (d, *J* = 10Hz, 1H), 4.51 (d, *J* = 6Hz, 2H), 3.60 (d, *J* = 6Hz, 2H); ^{13}C NMR (CD_3Cl, 100 MHz): δ 158.5, 140.3, 137.7, 134.0, 131.9, 128.4, 128.3, 127.8, 127.7, 127.6, 119.4, 76.0, 73.3, 71.1; $^{19}F\{^1H\}$ NMR ($CDCl_3$, 400 MHz), δ = -137.9 (m, 2F), -148.6 (m, 1F), -160.4 (m, 2F); IR

(neat): ν 1739, 1652, 1325, 1225, 995; HRMS calc for $C_{18}H_{13}F_5NaO_3$ $[M+Na]^+$ 395.0677 found 395.0674.

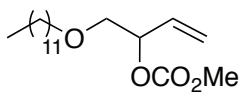
1-(Dodecyloxy)but-3-en-2-ol (163a)



The synthesis of substrate **163a** was carried out by T. Khotavivattana.[174]

To a solution of but-3-ene-1,2-diol (0.84 mL, 10.0 mmol) in THF (15 mL) and DMF (4 mL) at 0 °C was carefully added sodium hydride (0.30 g, 7.5 mmol). After being stirred for 20 min at 0 °C, 1-bromododecane (0.85 mL, 5.0 mmol) was added at 0 °C, and the resulting mixture was allowed to warm to room temperature and stirred for 24 h at room temperature. The reaction was quenched by addition of sat. aqueous NH_4Cl solution. The aqueous phase was extracted 3 times with EtOAc, the combined organic phases were washed with water and dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane : Et_2O, 90:10) to yield the title compound (0.26 g, 20%). ^1H NMR (400 MHz, $CDCl_3$): δ 5.82 (ddd, *J* = 17Hz, 11Hz, 6Hz, 1H), 5.34 (dt, *J* = 17Hz, 2Hz, 1H), 5.16 (dt, *J* = 11Hz, 2Hz, 1H), 4.32-4.26 (m, 1H), 3.46-3.40 (m, 3H), 3.29 (dd, *J* = 10Hz, 8Hz, 1H), 1.57-1.51 (m, 2H), 1.30-1.22 (m, 18H), 0.84 (t, *J* = 7Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 116.4, 74.7, 71.7, 71.6, 29.8, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 26.3, 22.8, 14.3. IR ($CDCl_3$) ν 3441, 1116; HRMS calc for $C_{16}H_{32}NaO_2$ $[M+Na]^+$ 279.2295, found 279.2300.

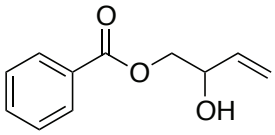
1-(Dodecyloxy)but-3-en-2-yl methyl carbonate (126a)



The synthesis of substrate **126a** was carried out by T. Khotavivattana.[174]

To a solution of **163a** (0.26 g, 1.0 mmol) and pyridine (0.24 mL, 3 mmol) in DCM (20 ml) at 0 °C was added dropwise methyl chloroformate (0.15 mL, 2 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40°C : Et_2O, 90:10) to yield the title compound (0.28 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (ddd, *J* = 17Hz, 11Hz, 6Hz, 1H), 5.36 (dt, *J* = 17Hz, 1Hz, 1H), 5.27-5.24 (m, 2H), 3.77 (s, 3H), 3.51-3.38 (m, 4H), 1.55-1.50 (m, 2H), 1.28-1.20 (m, 18H), 0.86 (t, *J* = 7Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4, 133.1, 118.8, 77.6, 72.1, 71.9, 54.9, 32.1, 29.9, 29.9, 29.8, 29.8, 29.7, 29.6, 26.2, 22.9, 14.3; IR ($CDCl_3$) ν 1752, 1264; HRMS calc for $C_{18}H_{34}NaO_4$ $[M+Na]^+$ 337.2349, found 337.2346.

2-Hydroxybut-3-en-1-yl benzoate (164a)

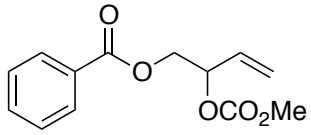


The synthesis of substrate **164a** was carried out by T. Khotavivattana.[174]

To a solution of butene-1,2-diol (0.33 mL, 4.0 mmol) in pyridine (2 mL) at -35 °C was added a solution of benzoyl chloride (0.56 mL, 4.8 mmol) in pyridine (1 mL). The reaction mixture was stirred for 12 h at -35 °C. The reaction was quenched by addition of water. The aqueous phase was extracted 3 times with DCM, the combined organic phases were washed with 2M HCl aqueous solution and $NaHCO_3$ saturated aqueous solution, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title

compound (0.66 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04-8.01 (m, 2H), 7.56-7.52 (m, 1H), 7.43-7.39 (m, 2H), 5.92 (ddd, *J* = 17Hz, 10Hz, 6Hz, 1H), 5.42 (d, *J* = 17Hz, 1H), 5.26 (d, *J* = 10Hz, 1H), 4.53-4.49 (m, 1H), 4.39 (dd, *J* = 11Hz, 4Hz, 1H), 4.27 (dd, *J* = 11Hz, 6Hz, 1H), 2.58 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 136.2, 133.2, 129.8, 129.7, 128.4, 117.2, 71.1, 68.3. Data are in agreement with literature.[214]

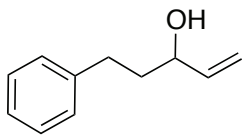
2-[(Methoxycarbonyl)oxy]but-3-en-1-yl benzoate (127a)



The synthesis of substrate **127a** was carried out by T. Khotavivattana.[174]

To a solution of **164a** (0.20 g, 1.04 mmol) and pyridine (0.25 mL, 3.12 mmol) in DCM (5 mL) at 0 °C was added methyl chloroformate (0.16 mL, 2.08 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 8 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (0.23 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8Hz, 2H), 7.55 (t, *J* = 8Hz, 1H), 7.44-7.40 (m, 2H), 5.89 (ddd, *J* = 17Hz, 11Hz, 6Hz, 1H), 5.50-5.45 (m, 2H), 5.35 (d, *J* = 11Hz, 1H), 4.49 (dd, *J* = 12Hz, 4Hz, 1H), 4.37 (dd, *J* = 12Hz, 7Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 155.1, 133.2, 131.7, 129.7, 129.6, 128.4, 119.7, 76.2, 65.1, 55.0; IR (CH_2Cl_2) ν 1752, 1735, 1264; HRMS calc for $C_{13}H_{14}O_5^+$ $[M]^+$ 250.0841, found 250.0841.

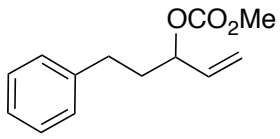
5-phenylpent-1-en-3-ol (165)



The synthesis of substrate **165** was carried out by Dr. M. Tredwell.[175]

To a solution of hydrocinnamaldehyde (0.13 mL, 1 mmol) in THF (5 mL) vinyl magnesium bromide (1 mL of 1 M solution in THF, 1 mmol) was added dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched by addition of NH_4Cl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (86 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.23 (m, 5H), 5.96 (ddd, *J* = 17Hz, 11Hz, 6Hz, 1H), 5.30 (ddd, *J* = 17Hz, 2Hz, 1Hz, 1H), 5.19 (ddd, *J* = 11Hz, 2Hz, 1Hz, 1H), 4.21-4.15 (m, 1H), 2.85-2.71 (m, 2H), 2.28 (br s, 1H), 1.99-1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 141.1, 128.5, 128.4, 125.9, 114.9, 72.4, 38.6, 31.7. Data are in agreement with literature.[215]

Methyl 1-(2-phenylethyl)-2-propen-1-yl carbonate (129)

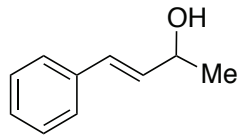


The synthesis of substrate **129** was carried out by Dr. M. Tredwell.[175]

To a solution of **165** (81 mg, 0.5 mmol) and pyridine (0.12 mL, 1.5 mmol) in DCM (2.5 mL) at 0 °C was added methyl chloroformate (80 μL, 1.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O,

the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (98 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.19 (m, 5H), 5.86 (ddd, *J* = 17Hz, 10Hz, 6Hz, 1H), 5.35 (d, *J* = 17Hz, 1H), 5.27 (d, *J* = 10Hz, 1H), 5.11 (dd, *J* = 13Hz, 7Hz, 1H), 3.81 (s, 3H), 2.78-2.65 (m, 2H), 2.12-2.03 (m, 1H), 2.00-1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 141.1, 135.7, 128.5, 128.4, 126.1, 117.8, 78.5, 54.7, 35.9, 31.3; IR (CH_2Cl_2) ν 1747, 1442, 1263; HRMS calc for $C_{13}H_{16}NaO_3$ $[M]^+$ 220.1099, found 220.1095.

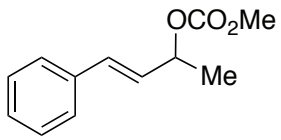
(3*E*)-4-Phenylbut-3-en-2-ol (166)



The synthesis of substrate **166** was carried out by Dr. M. Tredwell.[175]

To a solution of (3*E*)-4-phenyl-3-butene-2-one (1.02 mL, 7 mmol) in MeOH (4 mL) at 0 °C was added sodium borohydride (0.28 g, 7.35 mmol). The reaction mixture was stirred for 2 h at 0 °C. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with EtOAc, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane : EtOAc/ 5:5) to yield the title compound (0.96 g, 93%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (dt, *J* = 7Hz, 2Hz, 2H), 7.32 (dt, *J* = 7Hz, 2Hz, 2H), 7.24 (tt, *J* = 7Hz, 2Hz, 1H), 6.57 (d, *J* = 16Hz, 1H), 6.27 (dd, *J* = 16Hz, 7Hz, 1H), 4.55-4.43 (m, 1H), 2.11 (br s, 1H), 1.38 (d, *J* = 7Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7, 133.6, 129.3, 128.6, 127.6, 126.4, 68.8, 23.4. Data are in agreement with literature.[216]

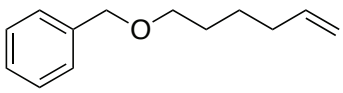
Methyl (3*E*)-4-phenylbut-3-en-2-yl carbonate (128)



The synthesis of substrate **128** was carried out by Dr. M. Tredwell.[175]

To a solution of **166** (0.15 g, 1.01 mmol) and pyridine (0.25 mL, 3.03 mmol) in DCM (5 mL) at 0 °C was added methyl chloroformate (0.16 mL, 2.02 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 8 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (0.19 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.39 (m, 2H), 7.35-7.31 (m, 2H), 7.28-7.25 (m, 1H), 6.67 (d, *J* = 16Hz, 1H), 6.22 (dd, *J* = 16Hz, 7Hz, 1H), 5.42-5.35 (m, 1H), 3.80 (s, 3H), 1.49 (d, *J* = 7Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 136.1, 132.3, 128.6, 128.1, 128.0, 126.6, 75.3, 54.6, 20.5. Data are in agreement with literature.[217]

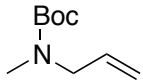
Benzyl hex-5-en-1-yl ether (167)



To a solution of NaH (0.7 g, 17.4 mmol) in DMF (12 mL) at 0 °C was added hex-5-en-1-ol (1.4 mL, 11.6 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 20 min. Benzyl bromide (2.1 mL, 17.4 mmol) was added and the mixture was allowed to stir for 1.5 h. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic

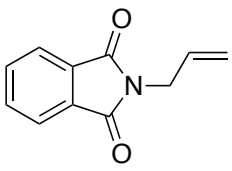
phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (1.04 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 4Hz, 4H), 7.33-7.28 (m, 1H), 5.87-5.77 (m, 1H), 5.02 (dd, *J* = 17Hz, 2Hz, 1H), 4.96 (dd, *J* = 10Hz, 1Hz, 1H), 4.52 (s, 2H), 3.49 (t, *J* = 7Hz, 2H), 2.11-2.06 (m, 2H), 1.69-1.62 (m, 2H), 1.53-1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 138.7, 128.3, 127.6, 127.5, 114.5, 72.9, 70.2, 33.6, 29.2, 25.5. Data are in agreement with literature.[218]

tert-Butyl allyl(methyl)carbamate (168)



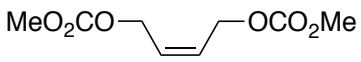
To a solution of *N*-methylprop-2-en-1-amine (0.5 mL, 5.0 mmol) and triethylamine (1.5 mL, 11.0 mmol) in anhydrous DCM (6 mL) at 0 °C was added di-*tert*-butyl malonate (1.3 mL, 5.5 mmol) in 2 portions. The reaction mixture was allowed to warm to room temperature and stirred overnight at room temperature. The solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (0.58 g, 68%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81-5.71 (m, 1H), 5.14-5.10 (m, 2H), 3.81 (br s, 2H), 2.82 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 133.6, 116.1, 79.3, 51.4, 33.6, 28.3. Data are in agreement with literature.[219]

2-Allyl-1*H*-isoindole-1,3(2*H*)-dione (169)



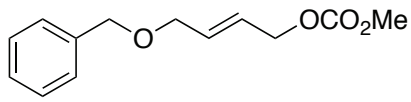
To a suspension of potassium phthalimide (1.9 g, 10.0 mmol) and tetrabutylammonium bromide (64 mg, 0.2 mmol) in anhydrous DMF (10 mL) at room temperature was added dropwise allylbromide (0.9 mL, 10.0 mmol). The reaction mixture was stirred overnight at room temperature and then poured into 10 mL of water. The solid was filtered and washed with water. The crude product is purified by recrystallization from hexane to yield the title compound (1.3 g, 70%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.85 (m, 2H), 7.75-7.71 (m, 2H), 5.95-5.85 (m, 1H), 5.26 (dd, *J* = 17Hz, 1Hz, 1H), 5.21 (dd, *J* = 10Hz, 1Hz, 1H), 4.31 (d, *J* = 6Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 134.0, 132.1, 131.5, 123.3, 117.7, 40.0. Data are in agreement with literature.[220]

(2*Z*)-But-2-ene-1,4-diyl dimethyl biscarbonate (170)



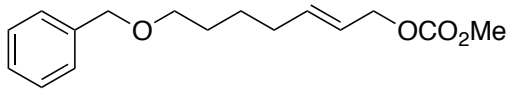
To a solution of *cis*-2-butene-1,4-diol (4.1 mL, 0.05 mol) and pyridine (24.3 mL, 0.3 mol) in DCM (220 mL) at 0 °C was added methyl chloroformate (15.4 mL, 0.2 mol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h at room temperature. The reaction was quenched by addition of HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 80:20) to yield the title compound (9.82 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (t, *J* = 4Hz, 2H), 4.76 (d, *J* = 4Hz, 4H), 3.79 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 128.0, 63.2, 54.9. Data are in agreement with literature.[221]

(2*E*)-4-(Benzyloxy)but-2-en-1-yl methyl carbonate ((*E*)-118b)



To a solution of **161** (1.48 g, 10 mmol) and **170** (4.08 g, 20 mol) in DCM (35 mL) at 50 °C was added Grubbs-Hoveyda 2nd generation catalyst (0.3 g, 0.5 mmol) in 3 portions over 24 h. The reaction mixture was stirred for further 48 h at 50 °C. The mixture was cooled to room temperature and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (1.02 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 5H), 5.98-5.85 (m, 2H), 4.66 (d, *J* = 5Hz, 2H), 4.53 (s, 2H), 4.06 (dd, *J* = 5Hz, 1Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 138.0, 131.7, 128.4, 127.7, 127.6, 125.8, 72.4, 69.6, 67.7, 54.8. Data are in agreement with literature.[222]

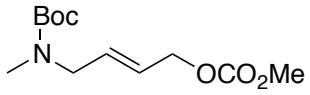
(2*E*)-7-(Benzyloxy)hept-2-en-1-yl methyl carbonate ((*E*)-130)



To a solution of **167** (0.95 g, 5 mmol) and **170** (2.04 g, 10 mol) in DCM (18 mL) at 50 °C was added Grubbs-Hoveyda 2nd generation catalyst (0.16 g, 0.3 mmol) in 3 portions over 24 h. The reaction mixture was stirred for further 48 h at 50 °C. The mixture was cooled to room temperature and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (1.06 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.29 (m, 5H), 5.85-5.78 (m, 1H), 5.63-5.56 (m, 1H), 4.57 (d, *J* = 7Hz, 2H), 4.51 (s, 2H), 3.79 (s, 3H), 3.48 (t, *J* = 6 Hz, 2H), 2.12-2.06 (m, 2H), 1.67-1.60 (m, 2H), 1.53-1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7,

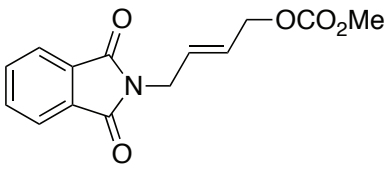
138.6, 137.0, 128.3, 127.6, 127.5, 123.5, 72.9, 70.1, 68.6, 54.7, 32.0, 29.2, 25.4; IR (CH_2Cl_2) ν 1750, 1264; HRMS calc for $C_{16}H_{22}NaO_4$ $[M+Na]^+$ 301.1410, found 301.1407.

(2*E*)-4-[(*tert*-Butoxycarbonyl)(methyl)amino]but-2-en-1-yl methyl carbonate ((*E*)-131)



To a solution of **168** (0.43 g, 2.5 mmol) and **170** (1.02 g, 5.0 mol) in DCM (9 mL) at 50 °C was added Grubbs-Hoveyda 2nd generation catalyst (78 mg, 0.13 mmol) in 3 portions over 24 h. The reaction mixture was stirred for further 48 h at 50 °C. The mixture was cooled to room temperature and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (190 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.73 (dt, *J* = 16Hz, 5Hz, 1H), 5.65 (dt, *J* = 16Hz, 6Hz, 1H), 4.60 (dd, *J* = 6Hz, 1Hz, 2H), 3.80 (br s, 2H), 3.76 (s, 3H), 2.78 (br s, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 131,1, 127.9, 125.3, 79.6, 67.6, 67.0, 54.8, 33.8, 28.4; IR (CH_2Cl_2) ν 1749, 1687, 1264, 1152, 907; HRMS calc for $C_{12}H_{21}NNaO_5$ $[M+Na]^+$ 282.1312, found 282.1316.

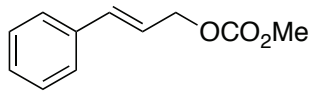
(2*E*)-4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)but-2-en-1-yl methyl carbonate ((*E*)-132)



To a solution of **169** (0.94 g, 5.0 mmol) and **170** (2.04 g, 10 mol) in DCM (18 mL) at 50 °C was added Grubbs-Hoveyda 2nd generation catalyst (0.16 g, 0.3 mmol) in 3 portions over 24 h. The reaction mixture was stirred for further 48 h at 50 °C. The mixture was cooled to

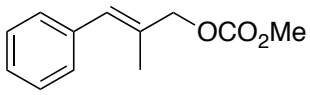
room temperature and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (0.51 g, 37%) as a grey solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79-7.78 (m, 2H), 7.72-7.67 (m, 2H), 5.84 (dt, *J* = 16Hz, 6Hz, 1H), 5.77 (dt, *J* = 16Hz, 5Hz, 1H), 4.57 (d, *J* = 5Hz, 2H), 4.27 (d, *J* = 6Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 155.6, 134.2, 132.2, 128.5, 127.2, 123.6, 67.3, 55.0, 38.9; IR (CH_2Cl_2) ν 1749, 1715, 1395, 1264, 907; HRMS calc for $C_{14}H_{13}NO_5$ $[M]^+$ 275.0794, found 275.0797. Mp 91-93 °C.

Methyl (2*E*)-3-Phenyl-2-propen-1-yl carbonate ((*E*)-116)



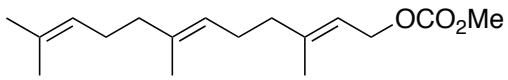
To a solution of cinnamyl alcohol (0.13 mL, 1 mmol) and pyridine (0.24 mL, 3 mmol) in DCM (5 mL) at 0 °C was added methyl chloroformate (0.16 mL, 2 mmol). The reaction mixture was allowed to warm to room temperature and stirred over night at room temperature. The reaction was quenched by addition of HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (167 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.22 (m, 5 H), 6.70 (d, *J* = 16 Hz, 1 H), 6.31 (dt, *J* = 16Hz, 7Hz, 1 H), 4.80 (d, *J* = 7Hz, 2 H), 3.82 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 136.0, 134.8, 128.6, 128.2, 126.7, 122.4, 68.4, 54.8. Data are in agreement with literature.[223]

Methyl (2*E*)-2-methyl-3-phenyl-2-propen-1-yl carbonate ((*E*)-133)



To a solution of (*E*)-2-methyl-3-phenylprop-2-en-1-ol (0.29 mL, 2.0 mmol) and pyridine (0.49 mL, 6 mmol) in DCM (9 mL) at 0°C was added methyl chloroformate (0.31 mL, 4 mmol). The reaction mixture was allowed to warm to room temperature and stirred over night at room temperature. The reaction was quenched by addition of HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (0.42 g, >99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.23 (m, 5H), 6.58 (s, 1H), 4.72 (s, 2H), 3.83 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz): δ 155.7, 136.9, 132.1, 128.9, 128.8, 128.2, 126.9, 73.7, 54.8, 15.4. Data are in agreement with literature.[224]

Methyl [(2*E*,6*E*)-3,7,11-trimethyl-2,6,10-dodecatrien-1-yl] carbonate ((*E*)-134)

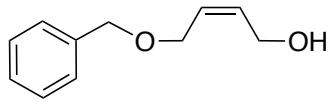


The synthesis of substrate (*E*)-**134** was carried out by Dr. M. Tredwell.[175]

To a solution of (2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol (0.63 mL, 2.5 mmol) and pyridine (0.61 mL, 7.5 mmol) in DCM (10 mL) at 0 °C was added methyl chloroformate (0.39 mL, 5 mmol). The reaction mixture was allowed to warm to room temperature and stirred over night at room temperature. The reaction was quenched by addition of HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The

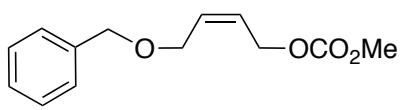
crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (686 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35-5.32 (m, 1H), 5.10-5.05 (m, 2H), 4.62-4.57 (m, 2H), 3.72 (s, 3H), 2.08-1.91 (m, 8H), 1.72-1.55 (m, 12H); ^{13}C NMR (100 MHz): δ 155.9, 143.3, 135.6, 131.3, 124.4, 123.7, 117.9, 64.8, 54.7, 39.8, 26.8, 26.3, 25.8, 17.8, 16.6, 16.1. Data are in agreement with literature.[224]

(2*Z*)-4-(Benzyloxy)but-2-en-1-ol ((*Z*)-119b)



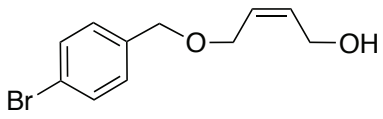
To a solution of (*Z*)-but-2-ene-1,4-diol (2.46 mL, 30 mmol) in THF (35 mL) at 0 °C was carefully added sodium hydride (421 mg, 10.5 mmol). After being stirred for 1 h at room temperature, benzyl bromide (1.18 mL, 10 mmol) was added, and the resulting mixture was stirred at 75 °C for 1 h. The reaction was then quenched at room temperature by addition of sat. aqueous NH_4Cl solution. The aqueous phase was extracted 3 times with DCM, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane : EtOAc, 90:10) to yield the title compound (1.25 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 5.87-5.80 (m, 1H), 5.79-5.72 (m, 1H), 4.54 (s, 2H), 4.18 (t, *J* = 6Hz, 2H), 4.11 (d, *J* = 6Hz, 2H), 1.95 (t, *J* = 6Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 132.4, 128.5, 128.3, 127.9, 127.8, 72.5, 65.7, 58.8. Data are in agreement with literature.[225]

(2*Z*)-4-(Benzyloxy)but-2-en-1-yl methyl carbonate ((*Z*)-118b)



To a solution of (*Z*)-**119b** (1.25 g, 7.0 mmol) and pyridine (1.70 mL, 21 mmol) in DCM (20 ml) at 0 °C was added dropwise methyl chloroformate (1.08 mL, 14 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (1.5 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 5.89-5.83 (m, 1H), 5.78-5.71 (m, 1H), 4.71 (d, *J* = 7Hz, 2H), 4.53 (s, 2H), 4.15 (dt, *J* = 6Hz, 1Hz , 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 137.9, 131.4, 128.4, 127.8, 127.7, 126.0, 72.5, 65.6, 63.6, 54.8. Data are in agreement with literature.[226]

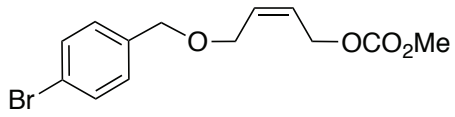
(2*Z*)-4-[(4-Bromobenzyl)oxy]but-2-en-1-ol ((*Z*)-171)



To a solution of (*Z*)-but-2-ene-1,4-diol (1.25 mL, 15 mmol) in THF (15 mL) at 0 °C was carefully added sodium hydride (0.21 g, 5.3 mmol). After being stirred for 1.5 h at room temperature, 4-bromobenzyl bromide (1.25 mL, 5 mmol) was added, and the resulting mixture was stirred at 90 °C for 1 h. The reaction was then cooled to room temperature and quenched by addition of sat. aqueous NH_4Cl solution and extracted 3 times with DCM. The combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (0.88 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8Hz, 2H), 7.21 (d, *J* = 8Hz, 2H), 5.81 (ddd, *J* = 6Hz, 6Hz, 11Hz, 1H), 5.71 (ddd, *J* = 6Hz, 6Hz, 11Hz, 1H), 4.46 (s, 2H), 4.16 (d, *J* = 6Hz, 2H), 4.08 (d, *J* = 6Hz, 2H); ^{13}C

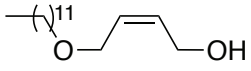
NMR (100 MHz, $CDCl_3$): δ 136.9, 132.5, 131.6, 129.4, 127.9, 121.6, 71.6, 65.8, 58.6. Data are in agreement with literature.[227]

(2*Z*)-4-[(4-Bromobenzyl)oxy]but-2-en-1-yl methyl carbonate ((*Z*)-135)



To a solution of (*Z*)-**171** (0.74 g, 3.0 mmol) and pyridine (0.73 mL, 9.0 mmol) in DCM (10 mL) at 0 °C was added dropwise methyl chloroformate (0.46 mL, 6.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (0.81 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8Hz, 2H), 7.22 (d, *J* = 8Hz, 2H), 5.79 (ddd, *J* = 6Hz, 6Hz, 11Hz, 1H), 5.71 (ddd, *J* = 11Hz, 7Hz, 6Hz, 1H), 4.67 (d, *J* = 7Hz, 2H), 4.44 (s, 2H), 4.11 (d, *J* = 6Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 137.0, 131.5, 131.1, 129.4, 126.2, 121.6, 71.6, 65.8, 63.5, 54.8; IR ($CDCl_3$) ν 1749, 1265; HRMS calc for $C_{13}H_{15}{}^{79}BrNaO_4$ $[M+Na]^+$ 337.0046, found 337.0051.

(2*Z*)-4-(Dodecyloxy)but-2-en-1-ol ((*Z*)-163b)

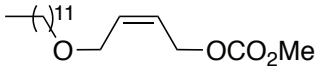


The synthesis of substrate (*Z*)-**163b** was carried out by T. Khotavivattana.[174]

To a solution of (*Z*)-butene-1,4-diol (2.18 mL, 26.5 mmol) in THF (40 mL) and DMF (10 mL) at 0 °C was carefully added sodium hydride (792 mg, 19.8 mmol). After being stirred for 20

min at 0 °C, 1-bromododecane (2.25 mL, 13.2 mmol) was added at 0 °C, and the resulting mixture was allowed to warm to room temperature and stirred for 24 h at room temperature. The reaction was quenched by addition of sat. aqueous NH_4Cl solution. The aqueous phase was extracted 3 times with EtOAc, the combined organic phases were washed with water and dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane : Et_2O, 90:10) to yield the title compound (1.67 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85-5.79 (m, 1H), 5.74-5.68 (m, 1H), 4.20 (d, *J* = 6Hz, 2H), 4.04 (d, *J* = 6Hz, 2H), 3.44 (t, *J* = 7Hz, 2H), 2.10 (s, 1H), 1.62-1.55 (m, 2H), 1.35-1.25 (m, 18H), 0.88 (t, *J* = 7Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.1, 128.6, 70.9, 66.5, 58.8, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.3, 26.2, 22.7, 14.1; IR ($CDCl_3$) ν 3379, 1108, 1030; HRMS calc for $C_{16}H_{32}NaO_2$ $[M+Na]^+$ 279.2295, found 279.2294.

(2*Z*)-4-(Dodecyloxy)but-2-en-1-yl methyl carbonate ((*Z*)-126b)

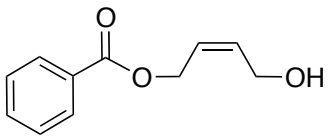


The synthesis of substrate (*Z*)-**126b** was carried out by T. Khotavivattana.[174]

To a solution of (*Z*)-**163b** (1.63 g, 6.36 mmol) and pyridine (1.6 mL, 20 mmol) in DCM (20 ml) at 0 °C was added dropwise methyl chloroformate (1.0 mL, 13 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane : Et_2O, 90:10) to yield the title compound (1.88 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84-5.78 (m, 1H), 5.74-5.68 (m, 1H), 4.73 (d, *J* = 7Hz, 2H), 4.08 (dt, *J* = 6Hz, 1Hz, 2H), 3.79 (s, 3H), 3.42 (t, *J* = 7Hz, 2H), 1.61-1.54 (m, 2H), 1.35-1.25

(m, 18H), 0.89 (t, *J* = 7Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 131.8, 125.6, 70.8, 66.4, 63.7, 54.8, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 26.2, 22.7, 14.1; IR ($CDCl_3$) ν 1751, 1262; HRMS calc for $C_{18}H_{34}NaO_4$ $[M+Na]^+$ 337.2349, found 337.2353.

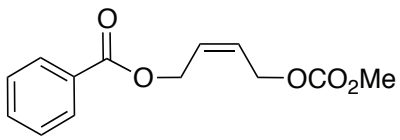
(*Z*)-4-Hydroxybut-2-en-1-yl benzoate ((*Z*)-164b)



The synthesis of substrate (*Z*)-**164b** was carried out by T. Khotavivattana.[174]

To a solution of (*Z*)-but-2-ene-1,4-diol (0.82 mL, 10.0 mmol) and pyridine (0.49 mL, 6.0 mmol) in DCM (20 ml) at 0 °C was added dropwise benzoyl chloride (0.58 mL, 5.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 2 times with DCM, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane : Et_2O, 90:10) to yield the title compound (0.78 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): d 8.07-8.04 (m, 2H), 7.60-7.55 (m, 1H), 7.47-7.43 (m, 2H), 5.93 (dtt, J = 11Hz, 7Hz, 1Hz, 1H), 5.78 (dtt, J = 11Hz, 7Hz, 1Hz, 1H), 4.95 (d, J = 7Hz, 2H), 4.36 (d, J = 7Hz, 2H), 1.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): d 166.7, 133.6, 133.1, 130.0, 129.6, 128.4, 125.6, 60.6, 58.5. Data are in agreement with literature.[228]

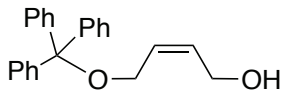
(*Z*)-4-((Methoxycarbonyl)oxy)but-2-en-1-yl benzoate ((*Z*)-127b)



The synthesis of substrate (*Z*)-**127b** was carried out by T. Khotavivattana.[174]

To a solution of (*Z*)-**164b** (0.16 g, 0.83 mmol) and pyridine (0.20 mL, 2.5 mmol) in DCM (3 ml) at 0 °C was added dropwise methyl chloroformate (0.13 mL, 1.7 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane : Et_2O, 90:10) to yield the title compound (0.20 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.03 (m, 2H), 7.58-7.54 (m, 1H), 7.46-7.42 (m, 2H), 5.95-5.89 (m, 1H), 5.86-5.80 (m, 1H), 4.94 (d, *J* = 6Hz, 2H), 4.82 (d, *J* = 6Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 155.6, 133.1, 129.9, 129.6, 128.7, 128.4, 127.6, 63.3, 60.4, 54.9. IR ($CDCl_3$) ν 1748, 1718, 1445, 1258; HRMS calc for $C_{13}H_{14}NaO_5$ $[M+Na]^+$ 273.0733, found 273.0732.

(2*Z*)-4-(Trityloxy)but-2-en-1-ol ((*Z*)-165)

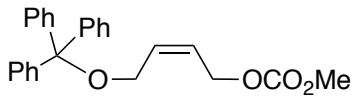


The synthesis of substrate (*Z*)-**165** was carried out by Dr. M. Tredwell.[175]

To a solution of (*Z*)-2-butene-1,4-diol (0.16 mL, 2 mmol) in pyridine (4 mL) was added dropwise trityl chloride (0.56 g, 2 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was quenched by addition of water. The aqueous phase was extracted 3 times with DCM, the combined organic phases were washed with 2M HCl aqueous solution and $NaHCO_3$ solution, dried (Na_2SO4), filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (0.40 g, 60%). ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.52-7.49 (m, 6H), 7.37-7.32 (m, 6H), 7.29-7.25 (m, 3H), 5.85-5.79 (m, 1H), 5.77-5.71 (m, 1H), 4.03 (d, *J* = 6Hz, 2H), 3.74 (d *J* = 6Hz, 2H), 1.86 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 131.2, 128.8, 128.6, 127.9, 127.1, 87.2, 60.2, 58.7. Data are in agreement with literature.[229]

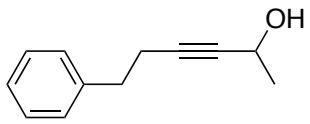
Methyl (2*Z*)-4-(trityloxy)but-2-en-1-yl carbonate ((*Z*)-136)



The synthesis of substrate (*Z*)-**136** was carried out by Dr. M. Tredwell.[175]

To a solution of (*Z*)-**165** (0.32 g, 0.97 mmol) and pyridine (0.24 mL, 2.91 mmol) in DCM (5 mL) at 0 °C was added dropwise methyl chloroformate (0.15 mL, 1.94 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 8 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (0.31 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.46 (m, 6H), 7.36-7.32 (m, 6H), 7.29-7.25 (m, 3H), 5.91 (dddt, *J* = 12 Hz, 11Hz, 5Hz, 1Hz, 1H), 5.68 (dddt, *J* = 13 Hz, 11Hz, 7Hz, 2Hz, 1H), 4.59 (dt, *J* = 7Hz, 1Hz, 2H), 3.78 (s, 3H), 3.79-3.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 143.9, 131.6, 128.6, 127.9, 127.1, 124.9, 87.1, 63.9, 60.3, 54.8; IR (CH_2Cl_2) ν 1749, 1448, 1264; HRMS calc for $C_{25}H_{24}NaO_4$ $[M+Na]^+$ 411.1567, found 441.1565.

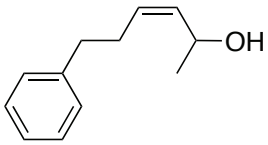
6-Phenyl-3-hexyn-2-ol (166)



The synthesis of substrate **166** was carried out by T. Khotavivattana.[174]

To a solution of 4-phenylbut-1-yne (961 mg, 6.0 mmol) in THF (10 mL) was added *n*BuLi (3.2 mL of 2.2 M solution in hexane, 7.0 mmol) at -78 °C. After stirring for 1 h, a solution of CH_3CHO (0.34 mL, 6.0 mmol) in THF (2.5 mL) was slowly added to the reaction mixture at -78 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by addition of sat. aqueous NH_4Cl solution and extracted with 3 times with Et_2O. The extract was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane:Et_2O, 90:10) to yield the title compound (369 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.32 (m, 5H), 4.51 (qt, *J* = 7Hz, 2Hz, 1H), 2.83 (t, *J* = 8Hz, 2H), 2.50 (td, *J* = 8Hz, 2Hz, 2H), 1.69 (s, 1H), 1.42 (d, *J* = 7Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.5, 128.4, 127.4, 126.3, 83.9, 83.0, 58.6, 35.0, 24.6, 20.9. Data are in agreement with literature.[230]

(3*Z*)-6-Phenyl-3-hexen-2-ol ((*Z*)-167)

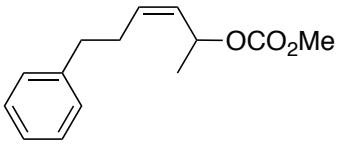


The synthesis of substrate (*Z*)-**167** was carried out by T. Khotavivattana.[174]

To a round-bottomed flask was added Lindlar catalyst (Pd, 5 wt % on $CaCO_3$ poisoned with 3.5% Pb, 21 mg) under N_2, then **166** (365 mg, 2.1 mmol) in distilled *n*-hexane (17 mL) was added to the catalyst. The flask was cooled to 0 °C and filled with H_2. After stirring for 6 h at 0 °C, the product was filtered through silica gel to remove the catalyst and then

concentrated to give the title compound (317 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.17 (m, 5H), 5.49-5.38 (m, 2H), 4.47-4.40 (m, 1H), 2.78-2.62 (m, 2H), 2.51-2.37 (m, 2H), 1.11 (d, *J* = 6Hz, 3H), 0.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 134.7, 129.7, 128.7, 128.3, 126.1, 63.6, 35.7, 29.5, 23.1. Data are in agreement with literature.[231]

Methyl (2*Z*)-1-methyl-5-phenyl-2-penten-1-yl carbonate ((*Z*)-137)



The synthesis of substrate (*Z*)-**137** was carried out by T. Khotavivattana.[174]

To a solution of (*Z*)-**167** (295 mg, 1.67 mmol) and pyridine (0.41 mL, 5.0 mmol) in DCM (5 ml) was added methyl chloroformate (0.26 mL, 3.35 mmol) dropwise at 0 ^{0}C. The resulting mixture was stirred at room temperature for 2 h. The reaction was then quenched with 1M HCl solution and washed with sat. aqueous NH_4Cl solution and H_2O, then dried over $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane:Et_2O, 90:10) to yield the title compound (355 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.17 (m, 5H), 5.61-5.44 (m, 1H), 5.46-5.38 (m, 2H), 3.76 (s, 3H), 2.81-2.61 (m, 2H), 2.57-2.44 (m, 2H), 1.20 (d, *J* = 6Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 141.4, 132.3, 129.4, 128.5, 128.3, 125.9, 71.1, 54.5, 35.6, 29.6, 20.6; IR ($CDCl_3$) ν 1743, 1261; HRMS calc for $C_{14}H_{18}NaO_3$ $[M+Na]^+$ 257.1148, found 257.1150.

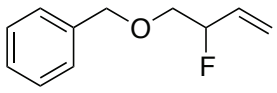
4.3.4 Ir-Catalysed Allylic Fluorination

General Procedure P: Ir-Catalysed Fluorination-Substrate Scope

To a solution of allylic carbonate (0.2 mmol) and TBAF·4*t*BuOH (2 eq, 0.4 mmol) in dry DCM (8 mL) was added a solution of **[Ir-1]** (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

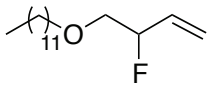
of the starting material and no longer than 24 h. Additional portions of catalyst (up to 4 mol%) were added to reactions which did not show completion after few hours. The solvent was removed *in vacuo* and ^{1}H NMR and ^{19}F NMR of the crude mixture recorded. Crude products were purified by silica gel column chromatography.

Benzyl 2-fluorobut-3-en-1-yl ether (106a)



Following the general procedure A, the reaction was carried out on 47 mg of **118a** and 2 mol% of **[Ir-1]** for 3 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 83% of conversion into **106a** (b/l: >20/1). Silica gel column chromatography (hexane) yielded **106a** (21 mg, 57%, b/l: >20/1) as a colourless oil. The NMR data are consistent with those reported previously.

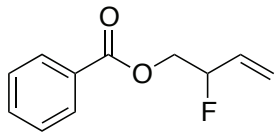
Dodecyl 2-fluorobut-3-en-1-yl ether (138a)



Following the general procedure A, the reaction was carried out on 63 mg of **126a** and 2 mol% of **[Ir-1]** for 3 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 95% of conversion into **138a** (b/l: >20/1). Silica gel column chromatography (hexane) yielded **138a** (33 mg, 64%, b/l: >20/1) as a colourless oil. %). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 5.90 (dddd, *J* = 14Hz, 12Hz, 9Hz, 5Hz, 1H), 5.40 (dq, *J* = 14Hz, 1Hz, 1H), 5.29 (dt, J = 9Hz, 1Hz, 1H), 5.02 (dm, *J* = 40Hz 1H), 3.57 (d, *J* = 4Hz, 1H), 3.52-3.51 (m, 1H), 3,47 (t, *J* = 5Hz, 2H), 1.60-1.54 (m, 2H), 1.31-1.22 (m, 18H), 0.89 (t, *J* = 6Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2):δ 133.7 (d, *J* = 15Hz), 118.3 (d, *J* = 9Hz), 92.8 (d, *J* = 136Hz), 73.0 (d, *J* =

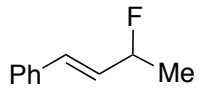
18Hz), 72.1, 32.3, 30.1, 30.0, 30.0, 29.9, 29.8, 26.5, 23.1, 14.3; ^{19}F {^{1}H}NMR (376.5 MHz, CD_2Cl_2): δ -184.72; IR (CH_2Cl_2) ν 1265, 1125; HRMS calc for $C_{16}H_{35}FNO^+$ $[M+NH_4]^+$ 276.2697, found 276.2700.

2-Fluorobut-3-en-1-yl benzoate (74a)



Following the general procedure A, the reaction was carried out on 50 mg of **127a** and 4 mol% of **[Ir-1]** for 24 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 58% of conversion into **74a** (b/l: >20/1). Silica gel column chromatography (hexane) yielded **74a** (13 mg, 32%, b/l: >20/1) as a colourless oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.06-8.04 (m, 2H), 7.60 (t, *J* = 8Hz, 1H), 7.49-7.45 (m, 2H), 6.05-5.93 (m, 1H), 5.52 (dt, *J* = 17Hz, 2Hz, 1H), 5.40 (dd, *J* = 11Hz, 2Hz, 1H), 5.25 (dm, *J* = 49Hz, 1H), 4.55-4.36 (m, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 166.4, 133.6, 132.7 (d, *J* = 19Hz), 130.4, 130.1, 129.0, 119.8 (d, *J* = 11Hz), 91.4 (d, *J* = 171Hz), 66.3 (d, *J* = 23Hz); ^{19}F {^{1}H}NMR (376.5 MHz, CD_2Cl_2): δ -186.01. Data are in agreement with literature.[144]

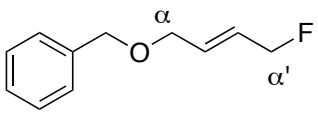
[(2*E*)-4-Fluoropent-2-en-1-yl]benzene (112)



Following the general procedure A, the reaction was carried out on 41 mg of **128** and 4 mol% of **[Ir-1]** for 24 h. A NMR yield of the crude mixture showed the formation of 66% of **112** as single regioisomer (*E*/*Z*: >20/1), employing 1-fluoro-3-nitrobenzene as internal standard (21 mL, 0.2 mmol). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.43-7.17 (m, 5H), 6.53 (dd, *J* = 16Hz, 6Hz, 1H), 6.26 (ddd, *J* = 16Hz, 12Hz, 7Hz, 1H), 5.21 (dm, *J* = 48Hz, 1H), 1.48 (dd, *J*

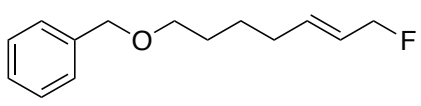
= 24Hz, 7Hz, 3H); ^{19}F {^{1}H}NMR (376.5 MHz, $CDCl_3$): δ -163.47; HRMS calc for $C_{10}H_{11}F$ $[M]^+$ 150.0845, found 150.0844. Data are in agreement with literature.[65]

Benzyl (2*E*)-4-fluorobut-2-en-1-yl ether ((*E*)-106b)



Following the general procedure A, the reaction was carried out on 47 mg of (*E*)-**118b** and 2 mol% of **[Ir-1]** for 5 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 86% of conversion into (*E*)-**106b** (l/b: >20/1, *E*/*Z*: >20/1). Silica gel column chromatography (hexane) yielded (*E*)-**106b** (20 mg, 55%, l/b: >20/1, *E*/*Z*: >20/1) as a colourless oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.35-7.33 (m, 4H), 7.31-7.27 (m, 1H), 5.95-5.93 (m, 2H), 4.87 (dd, *J* = 47Hz, 4Hz, 2H), 4.52 (s, 2H), 4.07-4.05 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 138.8, 132.0 (d, *J* = 9Hz), 128.7, 128.0, 127.9, 127.0 (d, *J* = 13Hz), 83.3 (d, *J* = 129Hz, **Cα'**), 72.7, 70.0 (d, *J* = 1Hz, **Cα**); ^{19}F {^{1}H}NMR (376.5 MHz, $CDCl_3$): δ -212.73. IR (CD_2Cl_2) ν 1216, 952. HRMS calc for $C_{11}H_{13}FNaO$ $[M+Na]^+$ 203.0843, found 203.0841. The geometry of the alkene was assigned by examining the chemical shift of the carbons in α and α' position of (*E*)-**106b** and (*Z*)-**106b**. For the (*E*)-allyl fluorides the chemical shifts of α and α' are consistently higher.

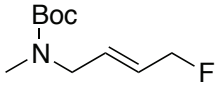
Benzyl (5*E*)-7-fluorohept-5-en-1-yl ether ((*E*)-140)



Following the general procedure A, the reaction was carried out on 56 mg of (*E*)-**130** and 2 mol% of **[Ir-1]** for 16 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 70% of conversion into (*E*)-**140** (l/b: >20/1, *E*/*Z*: >20/1). Silica gel column chromatography (hexane)

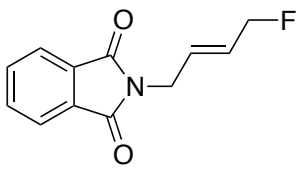
yielded (*E*)-**140** (30 mg, 68%, l/b: >20/1, *E*/*Z*: >20/1) as a colourless oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.35-7.33 (m, 4H), 7.30-7.25 (m, 1H), 5.89-5.81 (m, 1H), 5.74-5.65 (m, 1H), 4.78 (dd, *J* = 47Hz, 6Hz, 2H), 4.48 (s, 2H), 3.48 (t, *J* = 6Hz, 2H), 2.11 (dt, *J* = 14Hz, 6Hz, 2H), 1.66-1.59 (m, 2H), 1.53-1.46 (m, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 139.4, 137.7 (d, *J* = 12Hz), 128.6, 127.9, 127.7, 125.2 (d, *J* = 16Hz), 84.1 (d, *J* = 158Hz), 73.1, 70.6, 32.3, 29.6, 25.9; ^{19}F {^{1}H}NMR (376.5 MHz, CD_2Cl_2): δ -207.74; IR (CH_2Cl_2) ν 1265, 1108; HRMS calc for $C_{14}H_{19}OF$ $[M]^+$ 222.1420, found 222.1420.

tert-Butyl [(2*E*)-4-fluorobut-2-en-1-yl]methylcarbamate ((*E*)-141)



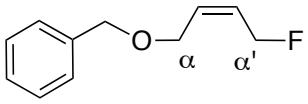
Following the general procedure A, the reaction was carried out on 63 mg of (*E*)-**131** and 2 mol% of **[Ir-1]** for 16 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 85% of conversion into (*E*)-**141** (l/b: >20/1, *E*/*Z*: >20/1). Silica gel column chromatography (hexane) yielded (*E*)-**141** (26 mg, 64%, l/b: >20/1, *E*/*Z*: >20/1) as a yellow oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 5.76-5.74 (m, 2H), 4.84 (dm, *J* = 47Hz, 2H), 3.83 (br s, 2H), 2.80 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 156.0, 131.7, 126.9 (d, *J* = 17Hz), 83.2 (d, *J* = 161Hz), 79.8, 50.7, 50.0 (rotamer), 34.3, 28.7; ^{19}F {^{1}H}NMR (376.5 MHz, CD_2Cl_2): δ -211.68, -211.81 (rotamer). IR (CH_2Cl_2) ν 1696, 1454, 1248, 1151; HRMS calc for $C_{10}H_{22}FN_2O_2^+$ $[M+NH_4]^+$ 221.1660, found 221.1664.

2-[(2*E*)-4-Fluorobut-2-en-1-yl]-1*H*-isoindole-1,3(2*H*)-dione, ((*E*)-142b)



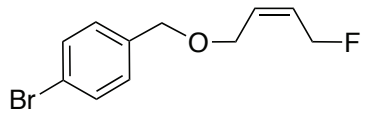
Following the general procedure A, the reaction was carried out on 58 mg of (*E*)-**132** and 2 mol% of **[Ir-1]** for 16 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 66% of conversion into (*E*)-**142b** (l/b: 15/1, *E*/*Z*: >20/1). Silica gel column chromatography (hexane) yielded (*E*)-**142b** (21 mg, 48%, l/b: >20/1, *E*/*Z*: >20/1) as a yellow oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.86-7.83 (m, 2H), 7.75-7.73 (m, 2H), 5.91-5.81 (m, 2H), 4.82 (dd, *J* = 46Hz, 4Hz, 2H), 4.30 (d, *J* = 5Hz, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 168.1, 134.5, 132.5, 128.7 (d, *J* = 12Hz), 128.1 (d, *J* = 17Hz), 123.6, 83.9 (d, *J* = 162Hz), 39.0; ^{19}F {^{1}H}NMR (376.5 MHz, CD_2Cl_2): δ -214.14; IR (CH_2Cl_2) ν 1709, 1427, 1393, 1061; HRMS calc for $C_{12}H_{10}NO_2F$ $[M]^+$ 219.0696, found 219.0702.

Benzyl (2*Z*)-4-fluorobut-2-en-1-yl ether ((*Z*)-106b)



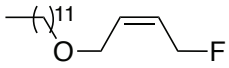
Following the general procedure A, the reaction was carried out on 47 mg of (*Z*)-**118b** and 2 mol% of **[Ir-1]** for 4 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 87% of conversion into (*Z*)-**106b** (l/b: >20/1, *Z*/*E*: >20/1). Silica gel column chromatography (hexane) yielded (*Z*)-**106b** (23 mg, 64%, l/b: >20/1, *Z*/*E*: >20/1) as a colourless oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.41-7.32 (m, 5H), 5.92-5.79 (m, 2H), 5.00 (dd, *J* = 5Hz, 46Hz, 2H), 4.53 (s, 2H), 4.15-4.13 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 138.7, 131.5 (d, *J* = 10Hz), 128.7, 128.1, 128.0, 127.3 (d, *J* = 20Hz), 79.3 (d, *J* = 158Hz, **Cα**'), 72.7, 66.2 (**Cα**); ^{19}F {^{1}H}NMR (376.5 MHz, $CDCl_3$): δ -213.10. IR (CD_2Cl_2) ν 1092, 1008; HRMS calc for $C_{11}H_{13}FO$ $[M]^+$ 180.0950, found 180.0947. The geometry of the alkene was assigned by examining the chemical shift of the carbons in α and α' position of (*E*)-**106b** and (*Z*)-**106b**. For the (*Z*)-allyl fluorides the chemical shifts of α and α' are consistently lower.

4-Bromobenzyl (2*Z*)-4-fluorobut-2-en-1-yl ether ((*Z*)-145)



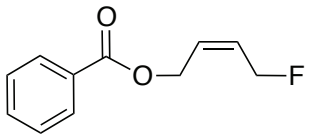
Following the general procedure A, the reaction was carried out on 63 mg of (*Z*)-**135** and 2 mol% of **[Ir-1]** for 16 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 87% of conversion into (*Z*)-**145** (l/b: >20/1, *Z*/*E*: >20/1). Silica gel column chromatography (hexane) yielded (*Z*)-**145** (27 mg, 52%, l/b: >20/1, *Z*/*E*: >20/1) as a colourless oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.52 (d, *J* = 9Hz, 2H), 7.26 (d, *J* = 9Hz, 2H), 5.89-5.79 (m, 2H), 4.99 (dd, *J* = 5Hz, 47Hz, 2H), 4.48 (s, 2H), 4.14-4.12 (m, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 137.8, 131.8, 131.3 (d, *J* = 10Hz), 129.7, 127.4 (d, *J* = 19Hz), 121.7, 79.3 (d, *J* = 157Hz), 71.9, 66.3; ^{19}F {^{1}H}NMR (376.5 MHz, $CDCl_3$): δ -213.14. IR (CD_2Cl_2) ν 1217, 1011; HRMS calc for $C_{11}H_{12}{}^{79}BrFO$ $[M]^+$ 258.0056, found 258.0051.

Dodecyl (2*Z*)-4-fluorobut-2-en-1-yl ether ((*Z*)-138b)



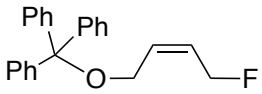
Following the general procedure A, the reaction was carried out on 63 mg of (*Z*)-**126b** and 2 mol% of **[Ir-1]** for 3 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 81% of conversion into (*Z*)-**138b** (l/b: >20/1, *Z*/*E*: >20/1). Silica gel column chromatography (hexane) yielded (*Z*)-**138b** (34 mg, 65%, l/b: >20/1, *Z*/*E*: >20/1) as a colourless oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 5.83-5.76 (m, 2H), 5.01 (dd, *J* = 47Hz, 5Hz, 2H), 4.05 (t, *J* = 5Hz, 2H), 3.42 (t, *J* = 7Hz, 2H), 1.58 (m, 2H), 1.30 (s, 18H), 0.92 (t, *J* = 7Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 132.0 (d, *J* = 10Hz), 126.8 (d, *J* = 19Hz), 79.4 (d, *J* = 158Hz), 71.1, 66.8, 32.3, 30.1, 30.0, 30.0, 29.9, 29.9, 29.8, 29.7, 26.6, 23.1, 14.2; ^{19}F {^{1}H}NMR (376.5 MHz, $CDCl_3$): δ -212.98. IR (CD_2Cl_2) ν 1109, 1011; HRMS calc for $C_{16}H_{31}FNaO$ $[M+Na]^+$ 281.2251, found 281.2249.

(2*Z*)-4-Fluorobut-2-en-1-yl benzoate ((*Z*)-74b)



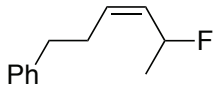
Following the general procedure A, the reaction was carried out on 66 mg of (*Z*)-**127b** and 2 mol% of **[Ir-1]** for 24 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 71% of conversion into (*Z*)-**74b** (l/b: >20/1, *Z*/*E*: >20/1). Silica gel column chromatography (hexane) yielded (*Z*)-**74b** (25 mg, 65%, l/b: >20/1, *Z*/*E*: >20/1) as a colourless oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.04-8.02 (m, 2H), 7.59 (t, *J* = 8Hz, 1H), 7.48-7.44 (m, 2H), 5.94-5.89 (m, 2H), 5.09 (dd, *J* = 47Hz, 5Hz, 2H), 4.90 (dd, *J* = 5Hz, 3Hz, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 166.6, 133.6, 130.6, 130.0, 129.1, 129.0, 128.9 (d, *J* = 10Hz), 79.4 (d, *J* = 159Hz), 61.0; ^{19}F {^{1}H}NMR (376.5 MHz, CD_2Cl_2): δ -214.52. IR (CD_2Cl_2) ν 1735, 1471, 1268, 1105; HRMS calc for $C_{11}H_{15}FNO_2^+$ $[M+NH_4]^+$ 212.1081, found 212.1086.

(2*Z*)-4-Fluorobut-2-en-1-yl trityl ether ((*Z*)-146)



Following the general procedure A, the reaction was carried out on 78 mg of (*Z*)-**136** and 4 mol% of **[Ir-1]** for 5 h. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 99% of conversion into (*Z*)-**146** (l/b: >20/1, *Z*/*E*: >20/1). Silica gel column chromatography (hexane) yielded (*Z*)-**146** (33 mg, 50%, l/b: >20/1, *Z*/*E*: 18/1) as a colourless oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.46-7.44 (m, 6H), 7.35-7.31 (m, 6H), 7.28-7.24 (m, 3H), 5.92-5.85 (m, 1H), 5.80-5.70 (m, 1H), 4.80 (dd, *J* = 47Hz, 6Hz, 2H), 3.70 (br s, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 144.4, 131.8 (d, *J* = 11Hz), 128.9, 128.3, 127.5, 126.5 (d, *J* = 19Hz), 87.5, 79.3 (d, *J* = 157Hz), 60.6; ^{19}F {^{1}H}NMR (376.5 MHz, CD_2Cl_2): δ -212.80; IR (CD_2Cl_2) ν 1490, 1448, 1264, 1059, 1010; HRMS calc for $C_{23}H_{25}FNO^+$ $[M+NH_4]^+$ 350.1920, found 350.1926.

[(3*Z*)-5-Fluoro-5-methylbut-3-en-1-yl]benzene ((*Z*)-147)



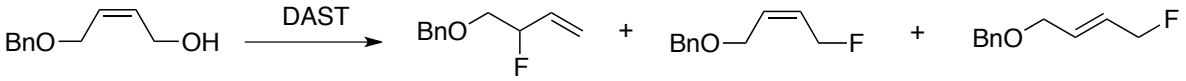
Following the general procedure A, the reaction was carried out on 47 mg of (*Z*)-**137** and 2 mol% of **[Ir-1]** for 18 h. ^{19}F NMR of the crude mixture showed a signal, which was tentatively assigned to (*Z*)-**147**. ^{19}F {^{1}H}NMR (376.5 MHz, CD_2Cl_2): δ -164.7.

Kinetic Study on Formation of 106a, (*E*)-106b and (*Z*)-106b:

To a solution of allylic carbonate (0.1 mmol) in d_2-DCM (5 mL) was added **[Ir-1]** (2 mol%), followed by addition of TBAF·4*t*BuOH (2 eq, 0.2 mmol). The reaction was allowed to stir at 40 °C, and 10 aliquotes of 0.5 mL of the reaction mixture were collected over the first 16.5 h. ^{1}H NMR and ^{19}F NMR of the crude mixture recorded to determine the conversion of the carbonate into the corresponding fluoride.

4.3.5 Alternative Synthetic Procedures of (Z)-106b

Fluorination of Alcohol (*Z*)-119b with DAST:

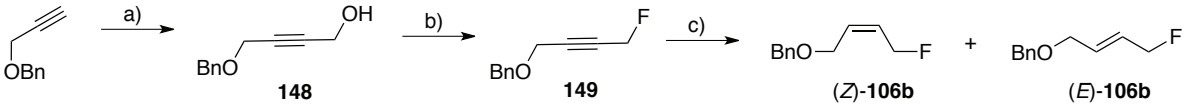


(*Z*)-**119b** **106a** (*Z*)-**106b** (*E*)-**106b**

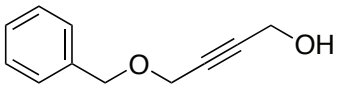
To a solution of DAST (0.95 mL, 0.72 mmol) in DCM (2.5 mL) was added a solution of (*Z*)-**119b** (107 mg, 0.6 mmol) in DCM (2.5 mL) at room temperature under N_2. After 20 minutes, Na_2CO_3 (64 mg, 0.6 mmol) was added and the organic phase washed twice with 1M Na_2CO_3 aqueous solution and once with H_2O. The combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. ^{1}H NMR and ^{19}F NMR of the crude mixture showed 66% of conversion into a mixture of fluorinated products (**106a** : (*Z*)-**106b :** (*E*)**-106b** = 50 : 39 : 11). The crude product was purified by silica gel column

chromatography (hexane) to yield **106a** (17 mg, 16 %, b:l >20:1) and (*Z*)-**106b** (25 mg, 23%, *Z*:*E*, 59:41). The NMR data are consistent with those reported previously.

Stereoselective Reduction of Alkyne Fluoride 149:

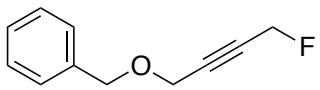


4-(Phenylmethoxy)-2-butyn-1-ol (148)



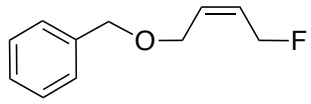
To a solution of ((prop-2-yn-1-yloxy)methyl)benzene (0.75 mL, 5.0 mmol) in THF (20 mL) was added dropwise *n*BuLi (4.6 mL of 1.2 M solution in hexane, 5.5 mmol) at -78 °C and the mixture stirred for 30 min at -78 °C. *p*-Formaldehyde (300 mg, 10 mmol) was added at -78 °C and the mixture allowed to warm to 0 °C and stirred for 2 h. The reaction was quenched by the addition of NH_4Cl aqueous solution. The aqueous layer was extracted 2 times with EtOAc, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (392 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.20 (m, 5H), 4.52 (s, 2H), 4.24 (t, *J* = 2Hz, 2H), 4.13 (t, *J* = 2Hz, 2H), 3.18 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 128.5, 128.1, 128.0, 84.8, 81.7, 71.8, 57.4, 51.0. Data are in agreement with literature.[232]

[[(4-Fluoro-2-butyn-1-yl)oxy]methyl]benzene (149)



To a solution of **148** (352 mg, 2 mmol) in DCM (6 mL) was added DAST (0.29 mL, 2.2 mmol) at -78 °C. The mixture was allowed to warm to room temperature over 2 h. The reaction was quenched by the addition of $NaHCO_3$ aqueous solution. The aqueous layer was extracted 2 times with DCM, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane) to yield the title compound (138 mg, 39%). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.41-7.31 (m, 5H), 5.06 (dt, *J* = 48Hz, 2Hz, 2H), 4.61 (s, 2H), 4.28 (dt, *J* = 8Hz, 2Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 128.8, 128.4, 128.2, 86.5, 80.9 (d, J_{CF} = 23Hz), 72.1, 71.2 (d, J_{CF} = 163Hz), 57.6 (d, J_{CF} = 3Hz); ^{19}F {^{1}H}NMR (376.5 MHz, CD_2Cl_2): δ -215.07. Data are in agreement with literature.[233]

Benzyl (2*Z*)-4-fluorobut-2-en-1-yl ether ((*Z*)-106b)



To a round-bottomed flask was added Lindlar catalyst (Pd, 5 wt % on $CaCO_3$ poisoned with 3.5% Pb, 5 mg) under N_2, then **149** (89 mg, 0.5 mmol) in distilled *n*-hexane (4 mL) was added to the catalyst. The flask was cooled to 0 °C and filled with H_2. After stirring for 3 h at 0 °C, the product was filtered through silica gel to remove the catalyst and then concentrated to give the title compound (47 mg, 52%, *Z*:*E*, 66:34). The NMR data are consistent with those reported previously.

4.3.6 Ir-Catalysed Allylic Alkylation Reactions

General Procedure Q: Alkylation of Carbonates 118a, (*E*)-118b and (*Z*)-118b

To a solution of allylic carbonate (0.2 mmol) in THF (1 mL) was added **[Ir-1]** (2 mol%). A solution of sodium dimethyl malonate (0.4 mmol) in THF (1 mL), prepared from dimethyl malonate (0.4 mmol) and NaH (0.4 mmol) was then added in one portion. The reaction was

allowed to stir at 40 °C for 24 h. The reaction was quenched by the addition of distilled water. The aqueous layer was extracted 2 times with Et_2O (2 x 5 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent removed *in vacuo*. ^1H NMR of the crude mixtures were recorded to determine the conversion of the starting material and the product distribution. Crude products were purified by silica gel column chromatography.

Results of Table 3.10:

Entry 1: Starting from **118a** (47 mg) and following the general procedure Q, ^1H NMR of the crude mixture showed 100% of conversion into **107a/**(*E*)-**107b** mixture (b/l: 67/33, *E*/*Z*: >20/1). Silica gel column chromatography (hexane: Et_2O, 90:10) yielded **107a** (25 mg, 42%) and (*E*)-**107b** (15 mg, 25%, *E*/*Z*: >20/1).

Entry 2: Starting from (*E*)-**118b** (47 mg) and following the general procedure B, ^1H NMR of the crude mixture showed 94% of conversion into **107a/**(*E*)-**107b** mixture (b/l: 55/45, *E*/*Z*: >20/1). Silica gel column chromatography (hexane: Et_2O, 90:10) yielded **107a** (25 mg, 42%) and (*E*)-**107b** (6 mg, 11 %, *E*/*Z*: >20/1).

Entry 3: Starting from (*Z*)-**118b** (47 mg) and following the general procedure B, ^1H NMR of the crude mixture showed 65% of conversion into (*Z*)-**107b** (l/b: >20/1, *Z*/*E*: >20/1). Silica gel column chromatography (hexane: Et_2O, 90:10) yielded (*Z*)-**107b** (29 mg, 50%, *Z*/*E*, >20/1).

General procedure R: Alkylation of Carbonates 118a, (*E*)-118b and (*Z*)-118b with Additive

To a solution of allylic carbonate (0.1 mmol) in THF (0.5 mL) was added a solution of sodium dimethyl malonate (0.2 mmol) in THF (0.5 mL), prepared from dimethyl malonate (0.2 mmol) and NaH (0.2 mmol). TBAF·4*t*BuOH or *n*Bu_4NCl (0.2 mmol) was then added, followed by the addition of **[Ir-1]** (2 mol%) in one portion. The reaction was allowed to stir at

40 °C for 24 h. The solvent was removed *in vacuo*. ^{1}H NMR and ^{19}F NMR of the crude mixtures were recorded to determine the conversion of the starting material and the product distribution.

Results of Table 3.11:

Entry 1: Starting from **118a** (24 mg) and following the general procedure R (TBAF·4*t*BuOH), ^{1}H NMR of the crude mixture showed 74% of conversion into **107a** (b/l: 91/9, *E*/*Z*: >20/1).

Entry 2: Starting from (*E*)-**118b** (24 mg) and following the general procedure R (TBAF·4*t*BuOH), ^{1}H NMR of the crude mixture showed 53% of conversion into (*E*)-**107b** (l/b: >20/1, *E*/*Z*: >20/1).

Entry 3: Starting from (*Z*)-**118b** (24 mg) and following the general procedure R (TBAF·4*t*BuOH), ^{1}H NMR of the crude mixture showed 37% of conversion into (*Z*)-**107b** (l/b: >20/1, *Z*/*E*: >20/1).

Entry 4: Starting from (*E*)-**118b** (24 mg) and following the general procedure R (nBu$_4$NCl), ^{1}H NMR of the crude mixture showed 25 % of conversion into (*E*)-**107b** (l/b: 16/, *E*/*Z*: >20/1).

General procedure S: Alkylation of Fluorides 106a, (*E*)-106b and (*Z*)-106b

To a solution of allylic fluoride (0.1 mmol) in THF (0.5 mL) was added **[Ir-1]** (2 mol%). A solution of sodium dimethyl malonate (0.2 mmol) in THF (0.5 mL), prepared from dimethyl malonate (0.2 mmol) and NaH (0.2 mmol) was then added in one portion. The reaction was allowed to stir at 40 °C for 24 h. The solvent was removed *in vacuo*. ^{1}H NMR and ^{19}F NMR of the crude mixtures were recorded to determine the conversion of the starting material and the product distribution.

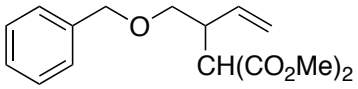
Results of Scheme 3.11:

Scheme 3.11a: Starting from **106a** (18 mg) and following the general procedure S, ^{1}H NMR of the crude mixture showed 56% of conversion into **107a** (b/l: 79/21, *E*/*Z*: >20/1).

Scheme 3.11b: Starting from (*E*)-**106b** (18 mg) and following the general procedure S, ^{1}H NMR of the crude mixture showed 46% of conversion into (*E*)-**107b** (l/b: 87/13, *E*/*Z*: >20/1).

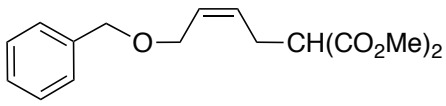
Scheme 3.11c: Starting from (*Z*)-**106b** (18 mg) and following the general procedure S, ^{1}H NMR of the crude mixture showed 69% of conversion into (*Z*)-**107b** (l/b: >20/1, *Z*/*E*: >20/1).

Dimethyl [1-(benzyloxy)but-3-en-2-yl]malonate (107a)



^{1}H NMR (400 MHz, CD_3Cl): δ 7.37-7.28 (m, 5H), 5.86 (ddd, *J* = 18Hz, 9Hz, 6Hz, 1H), 5.18 (d, *J* = 18Hz, 1H), 5.13 (d, *J* = 9Hz, 1H), 4.48 (s, 2H), 3.71 (d, *J* = 4Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.60-3.51 (m, 2H), 3.19-3.12 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 168.8, 168.6, 138.0, 135.4, 128.3, 127.7, 127.6, 118.2, 73.1, 71.0, 53.2, 52.4, 52.3, 44.0. IR (CD_2Cl_2) ν 1750, 1326, 1175; HRMS calc for $C_{16}H_{20}NaO_5$ $[M+Na]^+$ 315.1203, found 315.1202.

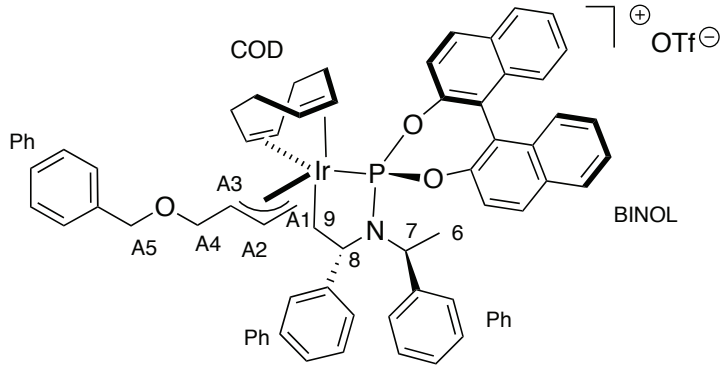
Dimethyl [(2*Z*)-4-(benzyloxy)but-2-en-1-yl]malonate ((*Z*)-107b)



^{1}H NMR (400 MHz, CD_3Cl): δ 7.36-7.28 (m, 5H), 5.73 (dddt, *J* = 11Hz, 6Hz, 4Hz, 2Hz, 1H), 5.53 (dddt, *J* = 11Hz, 8Hz, 5Hz, 1Hz, 1H), 4.52 (s, 2H), 4.12 (d, *J* = 6Hz, 2H), 3.74 (s, 6H), 3.43 (t, *J* = 8Hz, 1H), 2.67 (dd, *J* = 8Hz, 8Hz, 2H); ^{13}C NMR (100 MHz, CD_3Cl): δ 169.2, 138.2, 129.6, 128.4, 128.0, 127.8, 127.6, 72.4, 65.7, 52.6, 51.4, 27.1. IR (CH_2Cl_2) ν 1735, 1437, 1276. HRMS calc for $C_{16}H_{20}NaO_5$ $[M+Na]^+$ 315.1203, found 315.1208.

4.3.7 Mechanistic Investigation with [Ir-7]

Synthesis of [(Allyl)Ir(COD)(P,C-L)(L)] [Ir-7][161i]

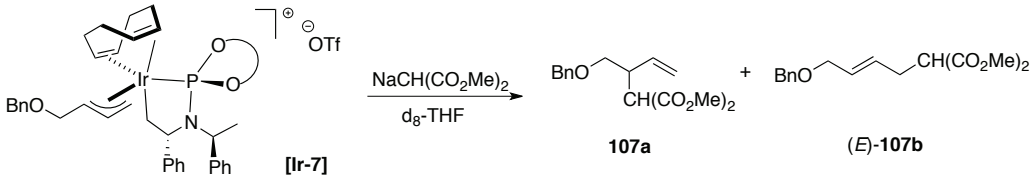


To a solution of **[Ir-1]** (0.17 g, 0.25 mmol) in THF (13 mL) was added (*S*,*S*,*S*)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)bis(1-phenylethyl)amine (*S*,*S*,*S*)-**L6a** (0.27 g, 0.5 mmol) at room temperature. After being stirred for 30 min at room temperature, carbonate **118a** (0.24 g, 1 mmol) and AgOTf (0.13 g, 0.5 mmol) were added, and the resulting mixture stirred for 20 h. The reaction was filtered trough Celite® and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (DCM: iPrOH/ 97:3) to yield the title complex **[Ir-7]** as a pale yellow powder (0.39 g, 70%). The product was isolated as a mixture of isomers 94:6 (ratio determined by ^{31}P NMR spectroscopy). ^{1}H NMR (500 MHz, d_8-THF): δ 8.34 (d, *J* = 9 Hz, 1H; BINOL), 8.30 (d, *J* = 9 Hz, 1H; BINOL), 8.09 (d, *J* = 8 Hz, 2H; 2 BINOL), 8.03 (d, *J* = 9Hz, 1H; BINOL), 7.99 (d, *J* = 9Hz, 1H; BINOL), 7.56–7.52 (m, 2H; 2 BINOL), 7.36–7.24 (m, 17H; 13 Ph, 4 BINOL), 7.12-7.10 (m, 2H, 2 Ph), 5.25–5.20 (m, 1H; cod-CH), 4.97–4.92 (m, 1H; 3A-H), 4.83–4.75 (m, 1H; 2A-H), 4.67–4.61 (m, 2H, A5-H), 4.56–4.49 (m, 1H; A4-H'), 4.24–4.16 (m, 2H; A4-H, cod-CH), 3.91–3.82 (m, 2H; 7-H, 8-H), 3.50–3.46 (m, 1H; cod-CH), 3.38–3.35 (m, 1H; cod-CH), 3.27–3.21 (m, 1H; cod-CH2), 2.96–2.93 (m, 2H ; 1A-H, cod-CH2), 2.43–2.33 (m, 3H; 1A-H', 2 cod-CH2), 2.32-2.30 (m, 1H, 9-H), 2.09–2.05 (m, 1H; cod- CH2), 1.73–1.71 (m, 1H; cod-CH2), 1.60-1.50 (m, 2H; 2 cod-CH2), 0.95 (t, *J* = 12 Hz, 1H; 9-H'), 0.57 (d, *J* = 7 Hz, 3H; 3 6-H); ^{13}C NMR (125 MHz, d_8-THF): δ 150.1 (d, J_{CP}=

16Hz; BINOL), 149.0 (d, J_{CP}= 8Hz; BINOL), 144.0 (d, J_{CP}= 12Hz; BINOL), 141.6 (s; BINOL), 139.5 (s; A-Ph), 134.2 (d, J_{CP}= 2Hz; BINOL), 133.7 (s; BINOL), 133.3, 133.1, 132.6 (s, 3xPh), 129.9, 129.8, 129.7, 129.4, 129.3, 129.2, 129.1, 129.0, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.6, 127.1 (s; 8xPh, 8xBINOL), 124.0 (s; BINOL), 123.8 (d, J_{CP}= 3Hz; BINOL), 123.3 (d, J_{CP}= 3Hz, BINOL), 122.6 (s; BINOL), 122.5 (d, J_{CP}= 1Hz; BINOL), 121.4 (s; BINOL), 101.5 (d, J_{CP}= 3Hz; CH-cod), 101.4 (d, J_{CP}= 4Hz, C2), 93.4 (d, J_{CP}= 3Hz; CH-cod), 89.0 (d, J_{CP}= 5Hz; CH-cod), 83.1 (d, J_{CP}= 6Hz; CH-cod), 76.0 (d, J_{CP}= 29Hz; C3), 73.9 (s; C5), 69.8 (d, J_{CP}= 3Hz; C4), 66.9 (d, J_{CP}= 33Hz; C8), 61.1 (d, J_{CP}= 5Hz; C7), 45.5 (s; C1), 37.8 (s; CH2-cod), 35.5 (s, CH2-cod), 28.8 (s; CH2-cod), 26.4 (s; CH2-cod), 19.2 (s; C6), 14.5 (d, J_{CP}= 7Hz; C9); ^{31}P NMR (97 MHz): δ 123.07 (minor isomer), 121.00 (major isomer); ^{19}F {^{1}H}NMR (376.5 MHz, d_8-THF): δ -80.59 (-OTf); m/z $[C_{55}H_{53}IrNO_3P]^+$: 999.34.

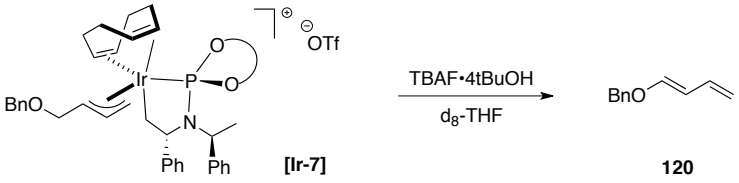
^{1}H NMR (500 MHz, CD_2Cl_2): δ 8.29 (d, *J* = 9 Hz, 1H; BINOL), 8.20 (d, *J* = 9 Hz, 1H; BINOL), 8.08 (t, *J* = 8 Hz, 2H; 2 BINOL), 7.81 (d, *J* = 9Hz, 1H; BINOL), 7.66 (d, *J* = 9Hz, 1H; BINOL), 7.61–7.55 (m, 2H; 2 BINOL), 7.40–7.31 (m, 15H; 11 Ph, 4 BINOL), 7.11-7.08 (m, 4H, 4 Ph), 5.13–5.09 (m, 1H; cod-CH), 4.65–4.59 (m, 4H; 3A-H, 2A-H, 2 5A-H), 4.54–4.48 (m, 1H; 4A-H), 4.22–4.16 (m, 1H, cod-CH), 4.11–4.07 (m, 1H; A4-H'), 3.87–3.79 (m, 1H; 7-H), 3.68–3.65 (m, 1H; 8-H), 3.37–3.32 (m, 1H; cod-CH), 3.29–3.26 (m, 1H; cod-CH2), 3.15–3.10 (m, 1H; cod-CH), 2.86–2.77 (m, 2H ; 1A-H, cod-CH2), 2.50–2.43 (m, 1H; cod-CH2), 2.35-2.27 (m, 2H; 9-H, cod-CH2), 2.15–2.11 (m, 1H; cod-CH2), 2.00–1.98 (m, 1H; 1A-H'), 1.68-1.55 (m, 3H; 3 cod-CH2), 0.95 (t, *J* = 12 Hz, 1H; 9-H'), 0.55 (d, *J* = 8 Hz, 3H; 3 6-H).

Procedure for the dimethyl malonate substitution of [Ir-7] in THF:[161h]



The complex **[Ir-7]** (12 mg, 0.01 mmol) was dissolved in d_8-THF (0.3 mL) in an NMR tube under N_2 atmosphere, and a ^{1}H NMR recorded. A solution of sodium dimethyl malonate (0.02 mmol) in d_8-THF (0.3 mL), prepared from dimethyl malonate (3 mL, 0.02 mmol) and NaH (1 mg, 0.02 mmol), was then added to the mixture and the reaction allowed to react at room temperature. After 5 min a second ^{1}H NMR showed completion, PPh_3 (3 mg, 0.01 mmol) was added and a ^{1}H NMR recorded. From the crude reaction mixture was observed the formation of the **107a** (81%) and (*E*)-**107b** (17%). The conversion was determined using an internal standard, *i*PrOH present in the complex **[Ir-7]**, deriving from the flash chromatography purification. When the reaction was repeated on 0.05 mmol scale of complex **[Ir-7]** (57 mg), the substituted product **107a** was isolated in 79% yield (12 mg).

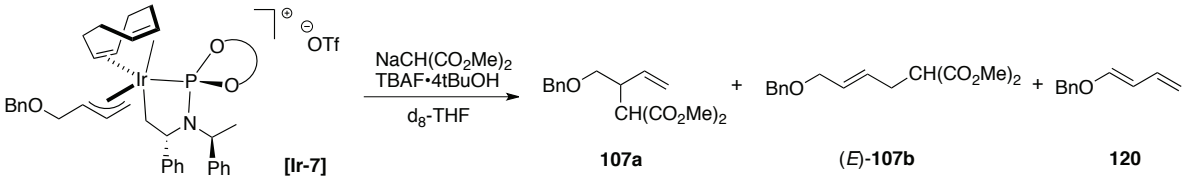
Procedure for fluorination of [Ir-7] in d_8-THF:



The complex **[Ir-7]** (12 mg, 0.01 mmol) was dissolved in d_8-THF (0.6 mL) in an NMR tube under N_2 atmosphere, and a ^{1}H NMR recorded. TBAF·4*t*BuOH, (6mg, 0.02 mmol) was added to the mixture and the reaction allowed to react at room temperature, and monitored by ^{1}H NMR and ^{19}F NMR spectroscopy. After 5 min, the ^{1}H NMR showed complete consumption of starting material, PPh_3 (3 mg, 0.01 mmol) was added and a second ^{1}H and ^{19}F NMR recorded. From the crude reaction mixture no formation of the fluorinated products **106a** or (*E*)-**106b** was detected, but formation of 67% of diene **120**, and

decomposition of the initial complex was observed. The conversion was determined using as internal standard Me_6Si_2 (3.9 mL, 0.019 mmol).

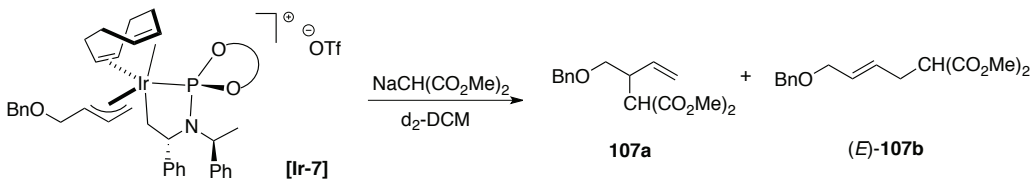
General Procedure for the dimethyl malonate substitution of [Ir-7] in the presence of TBAF·4*t*BuOH:



[Ir-7] **107a** (*E*)-**107b** **120**

The complex **[Ir-7]** (12 mg, 0.01 mmol) was dissolved in d_8-THF (0.3 mL) in an NMR tube under N_2 atmosphere, and a ^{1}H NMR recorded. A solution of sodium dimethyl malonate (0.02 mmol) in d_8-THF (0.3 mL), prepared from dimethyl malonate (3 mL, 0.02 mmol) and NaH (1 mg, 0.02 mmol) was then added to the mixture, followed by the addition of TBAF·4*t*BuOH, (6 mg, 0.02 mmol) and the reaction allowed to react at room temperature, and monitored by ^{1}H and ^{19}F NMR spectroscopy. After 5 min the ^{1}H NMR showed consumption of starting material, PPh_3 (3 mg, 0.01 mmol) was added and the second ^{1}H and ^{19}F NMR recorded. From the crude mixture no formation of the fluorinated products **106a** or (*E*)-**106b** was detected. Only 7% of **107a**, 3% of (*E*)-**107b** and 23% of **120** were observed, and complete decomposition of initial allyl-Ir complex. The conversion was determined using as internal standard, *i*PrOH present in the complex **[Ir-7]**, deriving from the flash chromatography purification.

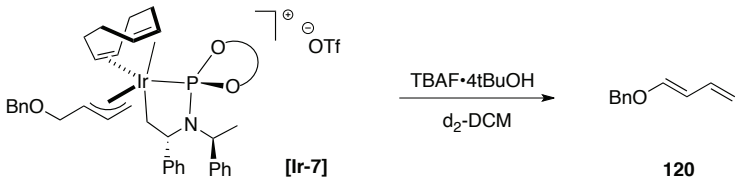
Procedure for the dimethyl malonate substitution of [Ir-7] in d_2-DCM:



[Ir-7] **107a** (*E*)-**107b**

The complex **[Ir-7]** (12 mg, 0.01 mmol) was dissolved in CD_2Cl_2 (0.3 mL) in an NMR tube under N_2 atmosphere, and a ^1H NMR recorded. A solution of dimethyl malonate (0.02 mmol) in CD_2Cl_2 (0.3 mL), prepared from dimethyl malonate (3 mL, 0.02 mmol) and BSA (5 mL, 0.02 mmol), was then added to the mixture and the reaction allowed to react at room temperature, and monitored by ^1H NMR spectroscopy. After 1h at rt still no product was observed in the crude reaction mixture by ^1H NMR. The mixture was subsequently warmed to 40 °C and monitored by ^1H NMR. After 18 h reacting at 40 °C, PPh_3 (3 mg, 0.01 mmol) was added and a last ^1H NMR recorded. From the crude reaction mixture was observed the formation of traces of the **107a** and (*E*)-**107b**, in addition to the un-reacted complex **[Ir-7]**.

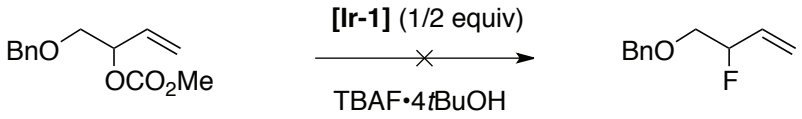
Procedure for fluorination of [Ir-7] in d_2-DCM:



The complex **[Ir-7]** (12 mg, 0.01 mmol) was dissolved in CD_2Cl_2 (0.6 mL) in an NMR tube under N_2 atmosphere, and a ^1H NMR recorded. TBAF·4*t*BuOH, (6 mg, 0.02 mmol) was added to the mixture and the reaction allowed to react at room temperature, and monitored by ^1H NMR and ^{19}F NMR spectroscopy. After 1 h at rt still no consumption of the starting material was observed in the crude reaction mixture by ^1H NMR. The mixture was subsequently warmed to 40 °C and monitored by ^1H NMR. After 30 min PPh_3 (3 mg, 0.01 mmol) was added and the last ^1H and ^{19}F NMR recorded. From the crude mixture no formation of the fluorinated products **106a** or (*E*)-**106b** was detected, but formation of 59% of diene **120**, and decomposition of the initial complex was observed. The conversion was determined using as internal standard, *i*PrOH present in the complex **[Ir-5]**, deriving from the flash chromatography purification.

4.3.8 Mechanistic Investigation with [Ir-1]:

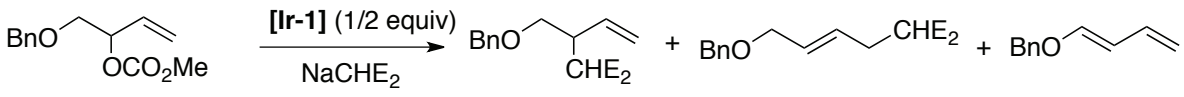
Ir-Mediated Fluorination Reaction:



118a **106a**

The complex **[Ir-1]** (7 mg, 0.01 mmol) was dissolved in CD_2Cl_2 (0.6 mL) in an NMR tube under N_2 atmosphere, and **118a** (5 mg, 0.02 mmol) was added at room temperature. After addition of TBAF·4*t*BuOH (11 mg, 0.02 mmol), a significant change in color of the solution, from orange to deep green was observed. ^{1}H NMR and ^{19}F NMR spectra were recorded short after and indicated full consumption of **[Ir-1]** and **118a**, and appearance of signals tentatively assigned to complex [Ir(COD)FCl]N*n*Bu$_4$ **[Ir-9]**. In the complex reaction mixture no traces of **106a** were detected. Additional TBAF·4*t*BuOH (11 mg, 0.02 mmol) was added and ^{1}H NMR and ^{19}F NMR spectra recorded. No significant changes in both spectra were observed. COD (3 μL, 0.02 mmol) was added to the mixture, and ^{1}H NMR and ^{19}F NMR spectra showed no trace of **106a**.

Ir-Mediated Alkylation Reaction:

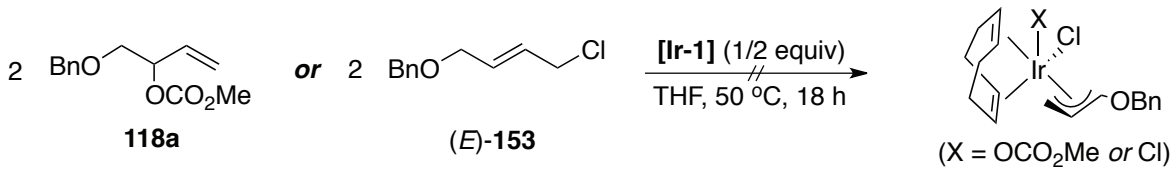


118a (E = CO_2Me) **107a** (*E*)-**107b** **120**

The complex **[Ir-1]** (7 mg, 0.01 mmol) was dissolved in d_8-THF (0.3 mL) in an NMR tube under N_2 atmosphere, and **118a** (5 mg, 0.02 mmol) was added at room temperature. A solution of NaCH(CO_2Me)$_2$ (0.02 mmol) in d_8-THF (0.4 mL), prepared from NaH (60% in mineral oil, 1 mg, 0.02 mmol) and $CH_2(CO_2Me)_2$ (3 μL, 0.02 mmol) was added. A significant change in color of the solution, from orange to brown was observed. A ^{1}H NMR spectra was recorded short after and showed only the signals of unreacted starting materials, **[Ir-1]**, **118a** and NaCH(CO_2Me)$_2$. After 4 h at room temperature, a ^{1}H NMR of the crude mixture

showed 37 % of conversion of **118a**, into **107a** (b/l: >20:1) and **120** in a ratio equal of 76:24, respectively. After 3 days at room temperature, a ^{1}H NMR of the crude mixture showed 82 % of conversion of **118a**, into **107a**, (*E*)-**107b** (*E*/*Z*: >20:1) and **120** in a ratio equal of 70:15:15, respectively.

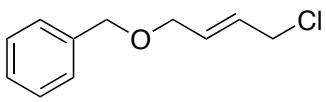
Procedure for the Synthesis of Ir-Allyl Intermediate:[158]



118a (*E*)-**153** (X = OCO_2Me *or* Cl)

The complex **[Ir-1]** (25 mg, 0.04 mmol) was dissolved in THF (0.5 mL) under N_2 atmosphere, and **118a** (36 mg, 0.16 mmol) or (*E*)-**153** (31 mg, 0.16 mmol) was added at room temperature. The reaction mixture was allowed to stir for 18 h at 50 °C. The yellow precipitate formed was filtered off and washed three times with hexane. NMR analysis could not be carried out, due to the poor solubility of the precipitate in CD_2Cl_2, d_8-THF, CD_3CN, d_6-DMSO or d_6-benzene.

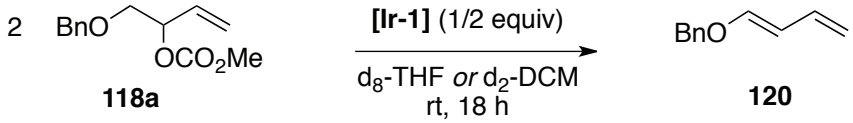
Benzyl (2*Z*)-4-chlorobut-2-en-1-yl ether (*E*)-153



To a solution of oxalyl chloride (76 μL, 0.88 mmol) in DCM, DMF (68 μL, 0.88 mmol) was added dropwise at 0 °C. The white suspension was allowed to warm to room temperature, and after 5 min cooled to 0 °C. Alcohol **119a** (142 mg, 0.8 mmol) was added and the reaction mixture stirred for 3 h at reflux. The reaction mixture was cooled to room temperature and poured into a NaCl saturated aqueous solution. The aqueous phase was extracted three times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel

column chromatography (hexane) to yield the title compound (45 mg, 29%, l/b > 20:1). ^{1}H NMR (400 MHz, CD_3Cl): δ 7.38-7.28 (m, 5H), 5.94-5.90 (m, 2H), 4.54 (s, 2H), 4.10-4.05 (m, 4H); ^{13}C NMR (100 MHz, CD_3Cl): δ 138.4, 131.7, 128.9, 128.8, 128.2, 128.1, 72.9, 69.9, 44.8. Data are in agreement with literature.[62]

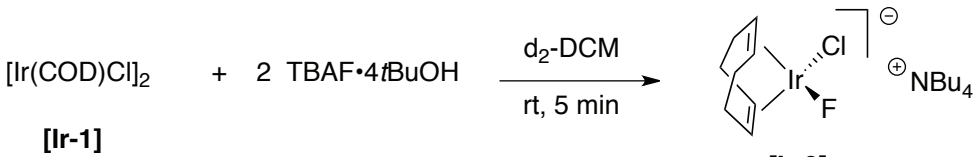
Procedure for Monitoring the Formation of Ir-Allyl Intermediate:



118a **120**

The complex **[Ir-1]** (7 mg, 0.01 mmol) was dissolved in CD_2Cl_2 (0.6 mL) or d_8-THF (0.6 mL) in an NMR tube under N_2 atmosphere, and **118a** (10 mg, 0.04 mmol) was added at room temperature. ^{1}H NMR spectra, recorded after 5 min and after 1 h, showed only the signals of unreacted starting materials, **[Ir-1]** and **118a**. After 18 h at room temperature, a ^{1}H NMR of the crude mixture showed >99% of conversion into diene **120**.

Synthesis of [Ir-9]:[180]

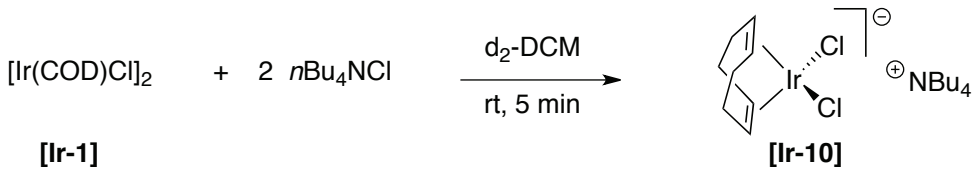


[Ir-1] **[Ir-9]**

The complex **[Ir-1]** (7 mg, 0.01 mmol) was dissolved in CD_2Cl_2 (0.6 mL) in an NMR tube under N_2 atmosphere, and TBAF·4*t*BuOH (11 mg, 0.02 mmol) was added. The tube was sealed and shaken well. A significant change in color of the solution, from orange to deep green was observed. NMR spectra were recorded short after and indicated full consumption of **[Ir-1]**, and appearance of signals tentatively assigned to complex [Ir(COD)FCl]N*n*Bu$_4$ **[Ir-9]**. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 3.75 (d, *J* = 3Hz, 4H; cod-CH), 3.24-3.20 (m, 8H), 2.13-2.10 (m, 4H; cod-CH_2), 1.68-1.60 (m, 8H), 1.50 (dt, *J* = 30Hz, 8Hz, 8H), 1.34 (q, J = 8Hz, 4H, cod-CH_2), 1.04 (t, *J* = 7Hz, 12H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ

59.3 (cod-CH), 59.2, 32.3 (2 x cod-CH_2), 24.4, 20.1, 13.8; ^{19}F {^1H}NMR (470MHz, CD_2Cl_2): δ -151.5 (br s); FIR(DCM) ν 532, 515, 455. HOESY did not show any interaction between the putative fluoride coordinated to Ir and the ligand COD.

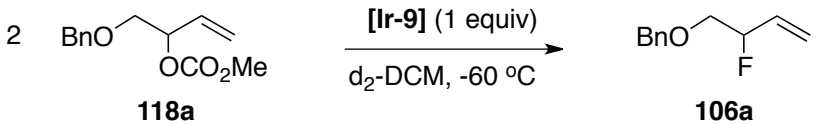
Synthesis of [Ir-10]:[180]



[Ir-1] **[Ir-10]**

The complex **[Ir-1]** (7 mg, 0.01 mmol) was dissolved in CD_2Cl_2 (0.6 mL) in an NMR tube under N_2 atmosphere, and *n*Bu_4NCl (6 mg, 0.02 mmol) was added. The tube was sealed and shaken well. A significant change in color of the solution, from orange to deep green was observed. NMR spectra were recorded short after and indicated full consumption of **[Ir-1]**, and appearance of signals assigned to complex [Ir(COD)Cl_2]N*n*Bu_4 **[Ir-10]**. ^1H NMR (400 MHz, CD_2Cl_2) δ 3.91 (d, *J* = 2Hz, 4H; cod-CH), 3.37-3.22 (m, 8H), 2.19-2.15 (m, 4H; cod-CH_2), 1.73-1.65 (m, 8H), 1.50 (dt, *J* = 22Hz, 8Hz, 8H), 1.34 (q, *J* = 8Hz, 4H, cod-CH_2), 1.04 (t, *J* = 7Hz, 12H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 59.5 (cod-CH), 59.2, 32.1 (2 x cod-CH_2), 24.3, 19.9, 13.8. Data are in agreement with literature.[180]

Ir-Mediated Fluorination at -60 °C:



118a **106a**

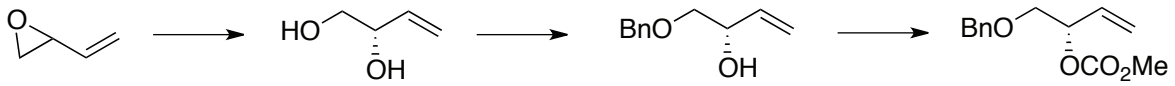
The complex **[Ir-1]** (14 mg, 0.02 mmol) was dissolved in CD_2Cl_2 (0.6 mL) in an NMR tube under N_2 atmosphere, and TBAF (40 L, 0.04 mmol, 1M solution in dry THF) was added. The tube was sealed and shaken well. A significant change in color of the solution, from orange to deep green was observed. ^1H NMR and ^{19}F NMR spectra were recorded short after and indicated full consumption of **[Ir-1]**, and appearance of signals tentatively

assigned to complex [Ir(COD)FCl]N*n*Bu$_4$ **[Ir-9]**. The solution was cooled to -60 °C and ^{1}H NMR and ^{19}F NMR spectra recorded at that temperature. The spectra obtained were identical to the ones acquired at room temperature. Carbonate **118a** (19 mg, 0.08 mmol) was added to the reaction mixture at -60 °C and ^{1}H NMR and ^{19}F NMR spectra recorded at that temperature. The appearance of a new signal at -185.3 ppm in the ^{19}F NMR spectra, corresponding to product **106a**, in addition to the signal of **[Ir-9]** (s, -128.0 ppm and br s, -151.5 ppm), was observed. After 15 minutes, the ^{19}F NMR spectra of the mixture showed the following species: **106a**, **[Ir-9]** and a new signal at -144.2 ppm (dd, *J* = 34Hz, 15Hz). The mixture was allowed to warm to room temperature, and ^{1}H and ^{19}F NMR spectra acquired at that temperature. Full decomposition of **118a** was observed by ^{1}H NMR spectrum, as the ^{19}F NMR spectrum showed only the signal related to **[Ir-9]** and no traces of allylic fluoride **106a**.

4.3.9 Investigation on the Stereochemistry of Fluorination

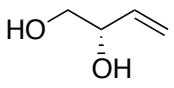
Synthesis of enantiopure allyl carbonate (*S*)-118a:

The synthesis of substrate (*S*)-**118a** was carried out by Dr. M. Tredwell.[175]



(*S*)-**168** (*S*)-**119a** (*S*)-**118a**

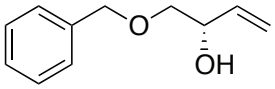
(*S*)-3-Butene-1,2-diol ((*S*)-168):



(*R*, *R*)-Jacobsen's catalyst (86 mg, 0.14 mmol) was added to a mixture of butadiene monoxide (2.3 mL, 28.52 mmol) and acetic acid (32 µL, 0.57 mmol) and cooled to 0 °C. H_2O (0.23 mL, 12.83 mmol) was added dropwise and the reaction mixture was stirred at 4 °C for 16 h. The crude reaction was purified directly by silica gel column chromatography

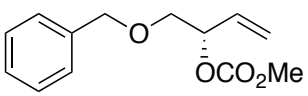
(petroleum ether 30-40 °C: EtOAc, 90:10) and the product afforded as a clear oil (1.0 g, 40 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.87-5.76 (ddd, *J* = 17Hz, 11Hz, 6Hz, 1H), 5.32 (d, *J* = 17Hz, 1H), 5.18 (d, *J* = 11Hz, 1H), 4.28-4.20 (m, 1H), 3.95 (br s, 2H), 3.75 (br s, 1H), 3.50 (dd, *J* = 11Hz, 8Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 116.6, 73.2, 66.1. Data are in agreement with literature.[183]

(2*S*)-1-(Benzyloxy)but-3-en-2-ol ((*S*)-119a)



To a solution of (*S*)-**168** (0.89 g, 10.1 mmol) in THF (30 mL) at 0 °C was added sodium hydride (0.25 g, 10.6 mmol) portionwise. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 h at room temperature. Benzyl bromide (1.24 mL, 10.6 mmol, 1.05 equiv) was subsequently added and the reaction mixture was stirred under reflux conditions for 1 h before being cooled to 0 °C. The mixture was carefully quenched by addition of 1M HCl aqueous solution. The aqueous phases were extracted 3 times with DCM, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane : Et_2O, 90:10) to yield the title compound (0.79 g, 44%, *ee* 97%). Chiral HPLC: (OD, Hexane/ *i*-PrOH= 95/5, 1.0 mL/ min, 259 nm) t_R (major-isomer)= 12.6 min, t_R (minor-isomer)= 14.4 min. The NMR data are consistent with those reported previously.

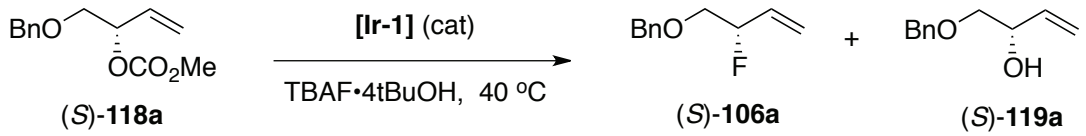
(2*S*)-1-(Benzyloxy)but-3-en-2-yl methyl carbonate ((*S*)-118a)



To a solution of (*S*)-**119a** (0.40 g, 2.21 mmol) and pyridine (0.53 mL, 6.57 mmol) in DCM (10 mL) at 0 °C was added dropwise methyl chloroformate (0.36 mL, 3.69 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h at room

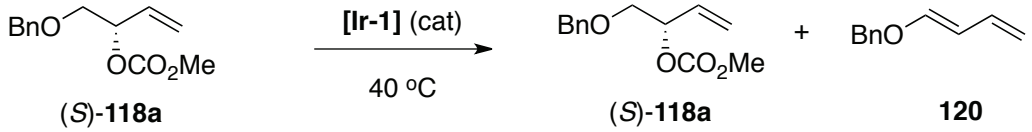
temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (hexane : Et_2O, 90:10) to yield the title compound (0.33 g, 62%, *ee* 95%). Chiral HPLC: (OD, Hexane/ *i*-PrOH= 95/5, 1.0 mL/ min, 259 nm) t_R (minor-isomer)= 6.9 min, t_R (major-isomer)= 9.4 min. The NMR data are consistent with those reported previously.

Results of Scheme 2.23a:



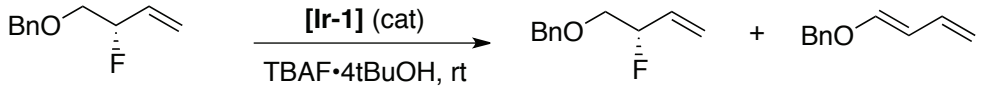
Following the general procedure P, the reaction was carried out on 48 mg of (*S*)-**118a** and 2 mol% of **[Ir-1]** for 2 h. Silica gel column chromatography (hexane) yielded (*S*)-**106a** (17 mg, 46%, *ee* 37%) and (*S*)-**119a** (15 mg, 43%, *ee* 20%).

Procedure for testing racemization of (*S*)-118a (Scheme 2.23b):



To a solution of (*S*)-**118a** (0.1 mmol, *ee* 95%) in DCM (5 mL) was added **[Ir-1]** (2 mol%). The reaction was allowed to stir at 40 °C for 2 h. The solvent was removed *in vacuo*. ^{1}H NMR of the crude mixture was recorded and showed 77% of (*S*)-**118a** (*ee* 87%) and 22% of diene **120**.

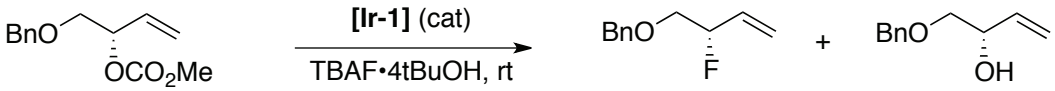
Procedure for testing racemization of (*S*)-106a (Scheme 2.24a):



(*S*)-**106a** (*S*)-**106a** **120**

To a solution of (*S*)-**106a** (0.1 mmol, *ee* 37%) in DCM (5 mL) was added **[Ir-1]** (2 mol%) and TBAF·4*t*BuOH (0.2 mmol). The reaction was allowed to stir at 40 °C for 2 h. The solvent was removed *in vacuo*. ^{1}H NMR of the crude mixture was recorded and showed 98% of (*S*)-**106a** (*ee* 35%) and 2% of **120**.

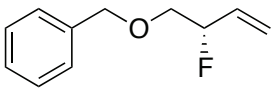
Results of Scheme 2.24b:



(*S*)-**118a** (*S*)-**106a** (*S*)-**119a**

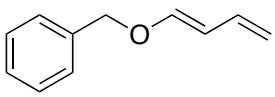
Following the general procedure P, the reaction was carried out on 48 mg of (*S*)-**118a** and 2 mol% of **[Ir-1]** at room temperature for 24 h. Silica gel column chromatography (hexane) yielded (*S*)-**118a** (16 mg, 33%, *ee* 93%), (*S*)-**106a** (12 mg, 34%, *ee* 48%) and (*S*)-**119a** (7 mg, 20%, *ee* 65%).

Benzyl (2*S*)-2-fluorobut-3-en-2-yl ether ((*S*)-106a)



Chiral HPLC for (*S*)-**106a**: (IA, Hexane/ *i*-PrOH= 99.5/0.5, 1.3 mL/ min, 210 nm) t_R (major-isomer)= 6.9 min, t_R (minor-isomer)= 8.1 min. The absolute configuration of (*S*)-**2a** was determined by synthesizing the title compound following a literature procedure.[62] Chiral HPLC traces were identical to those obtained from our iridium protocol). The NMR data are consistent with those reported previously.

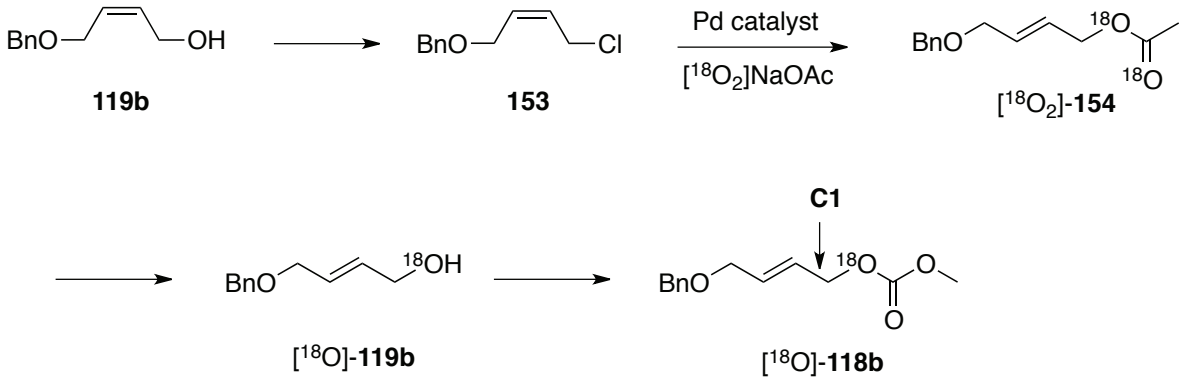
[[(1*E*)-1,3-Butadien-1-yloxy]methyl]benzene (120)



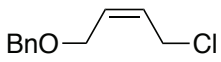
^{1}H NMR (400 MHz, d_8-THF): δ 7.35-7.24 (m, 5H), 6.71 (dddd, *J* = 17Hz, 11Hz, 10Hz, 1Hz, 1H), 6.11 (dd, *J* = 6Hz, 1Hz, 1H), 5.06 (dd, *J* = 11Hz, 6Hz, 1H), 4.97 (dd, *J* = 17Hz, 2Hz, 1H), 4.86 (s, 2H), 4.80 (dm, *J* = 10 Hz, 1H); HRMS calc for $C_{11}H_{12}O$ $[M]^+$ 160.0888, found 160.0890. Data are in agreement with literature.[62]

4.3.10 [^{18}O]-Labeling Experiments

Synthesis of [^{18}O]-(*E*)-118b:[184]



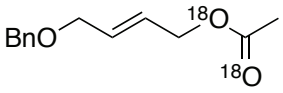
Benzyl (2*Z*)-4-chlorobut-2-en-1-yl ether ((*Z*)-153)



To a solution of oxalyl chloride (0.19 mL, 2.2 mmol) in DCM (8 mL) at 0 °C was added DMF (0.17 mL, 2.2 mmol) dropwise. The resulting white suspension was allowed to warm to room temperature, and after 10 min cooled again to 0 °C. Alcohol (*Z*)-**119b** (0.3 g, 2 mmol) was added and the reaction mixture stirred for 3 h at reflux. The reaction was cooled to room temperature and poured into a saturated solution of NaCl. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column

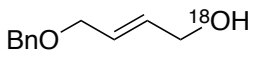
chromatography (petroleum ether 30-40 °C: Et_2O, 80:20) to yield the title compound (0.34 g, 86%, *Z*/*E* 99/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.24 (m, 5H), 5.84-5.75 (m, 2H), 4.52 (s, 2H), 4.16-4.14 (m, 2H), 4.12-4.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 130.8, 128.5, 128.5, 127.8, 127.8, 72.4, 65.1, 39.2. Data are in agreement with literature.[234]

(2*E*)-4-(Benzyloxy)but-2-en-1-yl [$^{18}O_2$]-acetate ([^{18}O]$_2$-154)



To a solution of benzyl (*Z*)-**153** (0.29 g, 1.5 mmol) in THF (4 mL) at room temperature was added $Pd_2(dba)_3$ (69 mg, 5 mol%), PPh_3 (81 mg, 20 mol%), *n*Bu_4NCl (0.48 g, 1.5 mmol) and [^{18}O]$_2$-NaOAc (129 mg, 1.5 mmol). The reaction mixture was stirred for 80 h at room temperature. The solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C) to yield the title compound (0.31 g, 98% yield, *E*/*Z* 66/34, 98% ^{18}O incorporation calculated from ^{13}C NMR). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.29 (m, 5H), 5.90-5.87 (m, 2H), 4.59 (d, *J* = 4Hz, 2H), 4.54 (s, 2H), 4.05 (d, *J* = 4Hz, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 138.1, 130.9, 128.4, 127.7, 127.6, 126.6, 72.4, 69.8, 64.2, 20.9. HRMS calc for $C_{13}H_{16}NaO^{18}O_2$ $[M+Na]^+$ 247.1077, found 247.1082.

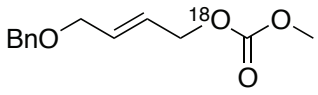
(2*E*)-4-(Benzyloxy)-[^{18}O]-but-2-en-1-ol ([^{18}O]-119b)



To a solution of allylic acetate [^{18}O]$_2$-**154** (0.25 mg, 1.2 mmol) in MeOH (4 mL) at room temperature was added K_2CO_3 (55 mg, 0.4 mmol). The reaction mixture was stirred for 3 days at room temperature. The reaction was filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 50:50) to yield the title compound (0.12 g, 57% yield, *E*/*Z* 66/34, 98% ^{18}O

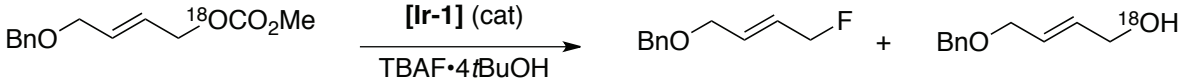
incorporation calculated from ^{13}C NMR). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.25 (m, 5H), 5.91 (dt, *J* = 16Hz, 5Hz, 1H), 5.83 (dt, *J* = 16Hz, 5Hz, 1H), 4.51 (s, 2H), 4.15 (dd, *J* = 5Hz, 1Hz, 2H), 4.03 (dd, *J* = 5Hz, 1Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 132.1, 128.4, 127.9, 127.7, 127.6, 72.3, 70.1, 63.0. HRMS calc for $C_{11}H_{14}NaO^{18}O$ $[M+Na]^+$ 203.0928, found 203.0921. Data are in agreement with literature.[235]

(2*E*)-4-(Benzyloxy)but-2-en-1-yl) [^{18}O]-methyl carbonate ([^{18}O]-118b)



To a solution of [^{18}O]-**119b** (90 mg, 0.5 mmol) and pyridine (0.12 mL, 1.5 mmol) in DCM (2 mL) at 0 °C was added methyl chloroformate (77 mL, 1 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 8 h at room temperature. The reaction was quenched by addition of 1M HCl aqueous solution. The aqueous phase was extracted 3 times with Et_2O, the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether 30-40 °C: Et_2O, 90:10) to yield the title compound (77 mg, 64% yield, *E*/*Z* 81/19, 98% ^{18}O incorporation calculated from ^{13}C NMR). The NMR data are consistent with those reported previously. HRMS calc for $C_{13}H_{16}NaO_3{}^{18}O$ $[M+Na]^+$ 261.0983, found 261.1011.

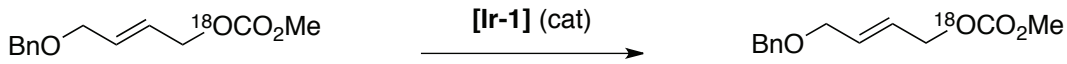
Procedure for fluorination of [^{18}O]-118b (Scheme 3.26a):



To a solution of [^{18}O]-**118b** (48 mg, 0.2 mmol, *E/Z*: 81/19, 98% ^{18}O incorporation) and TBAF·4*t*BuOH (2 eq, 0.4 mmol) in dry DCM (2 mL) was added **[Ir-1]** (2.7 mg, 0.004 mmol). The reaction was allowed to stir at 40 °C for 2 h and the solvent was removed *in vacuo.*

The crude reaction mixture was purified by silica gel column chromatography (hexane) to yield **106b** (8 mg, 22%), [^{18}O]-**119b** (10 mg, 28%, *E/Z*: 79/21, 33% ^{18}O incorporation calculated from ^{13}C NMR) and recovered [^{18}O]-**118b** (9 mg, 18%, *E/Z*: 74/26, 34% ^{18}O incorporation calculated from ^{13}C NMR).

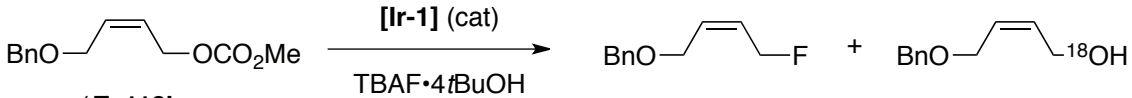
Procedure for scrambling test (Scheme 3.26b):



[^{18}O]-(*E*)-**118b** [^{18}O]-(*E*)-**118b**

To a solution of [^{18}O]-**118b** (12 mg, 0.05 mmol, *E/Z*: 81/19, ^{18}O/^{16}O: 98/2) in dry DCM (0.5 mL) was added **[Ir-1]** (0.7 mg, 0.001 mmol). The reaction was allowed to stir at 40 °C for 2 h. The crude reaction mixture was filtered and solvent was removed *in vacuo*. A ^{1}H NMR and a quantitative ^{13}C NMR of the crude mixture was recorded. 100% of recovered [^{18}O]-**118b** (*E/Z*: 79/21, 98% ^{18}O incorporation calculated from ^{13}C NMR) was detected.

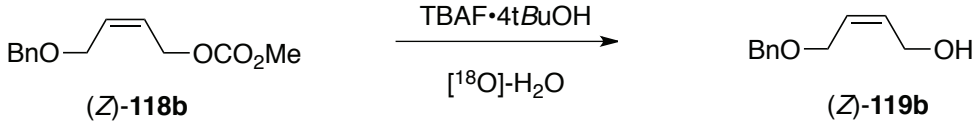
Procedure for fluorination of (Z)-118b in the presence of [^{18}O]-H_2O (Scheme 3.27a):



(*Z*)-**118b** (*Z*)-**106b** (*Z*)-[^{18}O]-**119b**

To a solution of (*Z*)-**118b** (47 mg, 0.2 mmol, *Z*/*E*: >20/1, 0% ^{18}O incorporation) and TBAF·4*t*BuOH (2 eq, 0.4 mmol) in dry DCM (2 mL) was added [^{18}O]-H_2O (8 mL, 0.4 mmol) and **[Ir-1]** (2.7 mg, 0.004 mmol). The reaction was allowed to stir at 40 °C overnight and the solvent was removed *in vacuo.* The crude reaction mixture was purified by silica gel column chromatography (hexane) to yield (*Z*)-**106b** (7 mg, 21%), (*Z*)-**119b** (15 mg, 41%, *Z/E*: >20/1, 53% ^{18}O incorporation calculated from ^{13}C NMR) and recovered (*Z*)-**118b** (7 mg, 15%, *Z/E*: 95/5, 35% ^{18}O incorporation calculated from ^{13}C NMR).

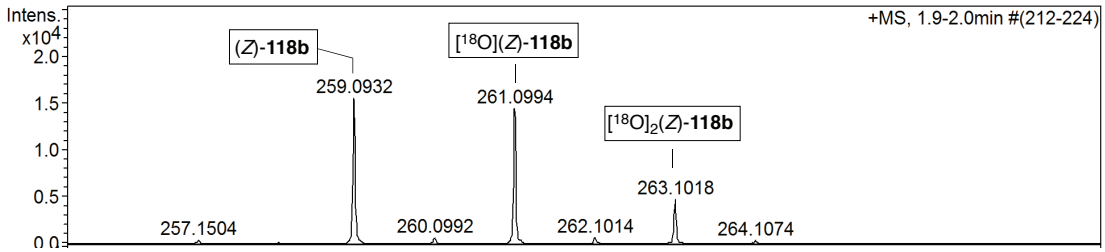
Procedure for test reaction in the presence of [^{18}O]-H_2O (Scheme 3.27b):



(*Z*)-**118b** (*Z*)-**119b**

To a solution of (*Z*)-**118b** (47 mg, 0.2 mmol, *Z*/*E*: >20/1, 0% ^{18}O incorporation) and TBAF·4*t*BuOH (2 eq, 0.4 mmol) in dry DCM (2 mL) was added [^{18}O]-H_2O (8 mL, 0.4 mmol) and **[Ir-1]** (2.7 mg, 0.004 mmol). The reaction was allowed to stir at 40 °C overnight and the solvent was removed *in vacuo.* The crude reaction mixture was purified by silica gel column chromatography (hexane) to yield (*Z*)-**119b** (4 mg, 11%, *Z*/*E*: >20/1, 2% ^{18}O incorporation calculated from ^{13}C NMR) and recovered (*Z*)-**118b** (31 mg, 66%, *Z*/*E*: >20/1, 0% ^{18}O incorporation calculated from ^{13}C NMR).

ES-MS of recovered (*Z*)-118b following experiment in Scheme 3.27a:



(*Z*)-**118b**: HRMS calc for $C_{13}H_{16}NaO_4$ $[M+Na]^+$ 259.0941, found 259.0932. Relative abundance determined by the intensity of the peak: 46%.

[^{18}O](*Z*)-**118b**: HRMS calc for $C_{13}H_{16}NaO_3{}^{18}O$ $[M+Na]^+$ 261.0983, found 261.0994. Relative abundance determined by the intensity of the peak: 41%.

[^{18}O]$_2$(*Z*)-**118b**: HRMS calc for $C_{13}H_{16}NaO_2{}^{18}O_2$ $[M+Na]^+$ 263.1026, found 263.1018. Relative abundance determined by the intensity of the peak: 13%.

4.3.11 [^{18}F]-RadioLabeling Experiments

The experimental results detailed in this section were obtained by Dr. M. Tredwell.[175]

Radiochemistry

[^{18}F]Fluoride was produced by PETNET Solutions at Mount Vernon Hospital (UK) via the ^{18}O(p,n)18F reaction and delivered as [^{18}F]fluoride in [^{18}O]water. Radiosynthesis and azeotropic drying was performed on a NanoTek® automated microfluidic device (Advion). [^{18}F]Fluoride was separated from ^{18}O-enriched water using an anion exchange cartridges (MP1, ORTG, Tennessee) and eluted with either a solution of tetraethylammonium bicarbonate (7 mg) in acetonitrile/water (9:1, 0.5 mL) or a solution of K_2CO_3 (3 mg)/K_{222} (15 mg) in acetonitrile/water (4:1, 0.5mL). The complex was dried with six cycles of azeotropic evaporation. The resultant [^{18}F]tetraethylammonium fluoride or [^{18}F]KF/K_{222} was dissolved in anhydrous acetonitrile for use in radiofluorination reactions. HPLC analysis was performed with a Dionex Ultimate 3000 system equipped with a LabLogic Flow-RAM NaI/PMT detector. Radio-TLC was performed on Merck Kiesegel 60 F254 plates. Analysis was performed using a plastic scintillator/PMT detector. TLC yields are calculated based on conversion of [^{18}F]fluoride to product.

General Radiochemical Procedure

To a glass V-vial containing a magnetic stirrer bar was added [^{18}F]Et_4NF (~ 30 MBq in 30 µL MeCN). To this vial was added a mixture of substrate (5 mg in 440 µL of DCM) with **[Ir-1]** (60 µL of a 1 mg/mL solution in DCM). The reaction mixture was then heated at 40 °C for 30 minutes. Upon cooling an aliquot was of the crude reaction mixture was taken and analysed by radio-TLC and radio-HPLC (equipped with Nova-Pak C18 column).

HPLC gradient (1 ml/min): 0-2 min 5 % MeCN 95 % H_2O isocratic

2-2.5 min 5 % MeCN to 40 % MeCN linear gradient

2.5-14 min 40 % MeCN to 95 % MeCN linear gradient

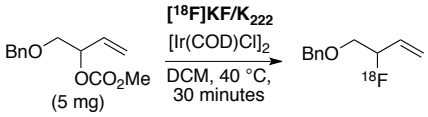
14-15 min 95 % MeCN to 5 % MeCN linear gradient

15-16 min 5 % MeCN 95 % H_2O isocratic.

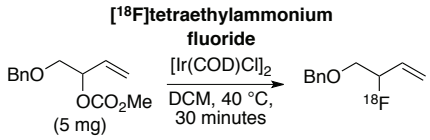
The radiofluorination of (*Z*)-**118b** was found to be rather capricious, giving variable yields. The specific activity was not measured for any of the products due to co-elution of the starting carbonate with the desired [^{18}F]products.

Radiochemical optimisation

All optimisation reactions were performed following the general procedure. For each reaction the total volume was made up to be 500 μL.

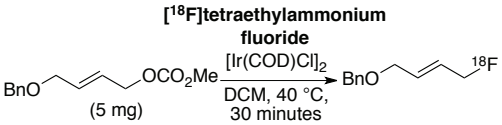


Ir loading (1mg/ml in DCM)	RCY (TLC)
500 μL	7 %
250 μL	8 %
125 μL	23 %
60 μL	44 %
10 μL	14 %
0	0 %

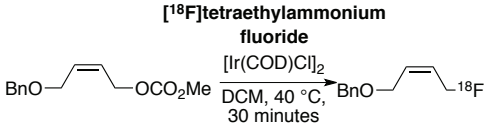


Ir loading (1mg/ml in DCM)	RCY (TLC)
500 μL	4 %
250 μL	21 %
125 μL	61 %
60 μL	68 %
0	0 %
60 μL	44 %[a]

a) reaction time of 15 minutes



Ir loading (1mg/ml in DCM)	RCY (TLC)
60 μL	30 %
60 μL	74 %
60 μL	65 %
125 μL	40 %
125 μL	62 %
125 μL	62 %



Ir loading (1mg/ml in DCM)	RCY (TLC)
60 μL	0 %
60 μL	14 %
60 μL	7 %
125 μL	11 %
125 μL	37 %
125 μL	8 %

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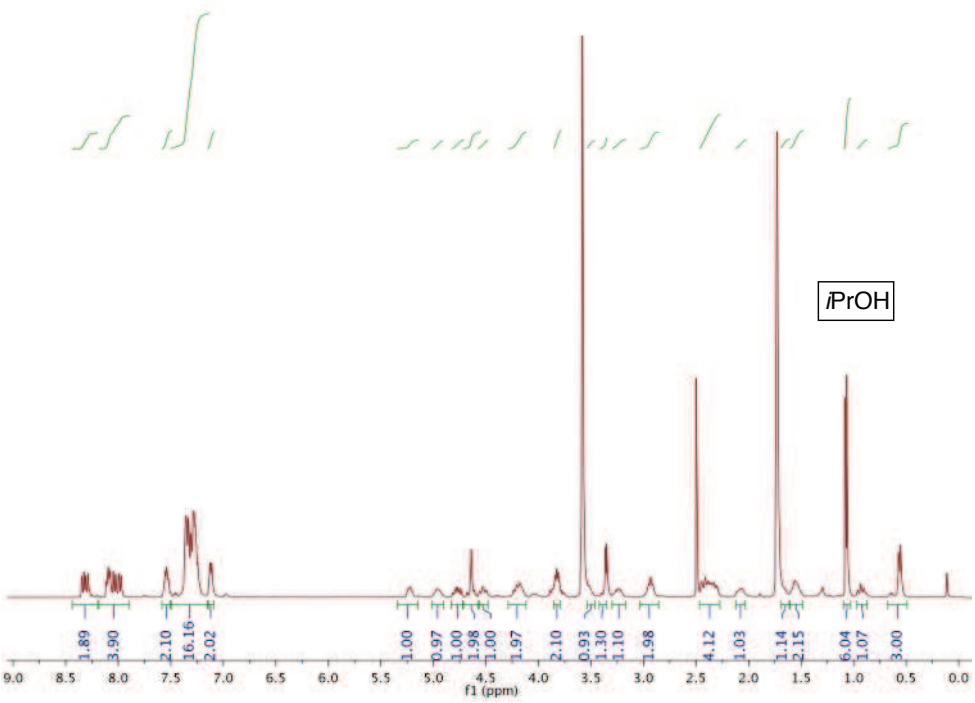
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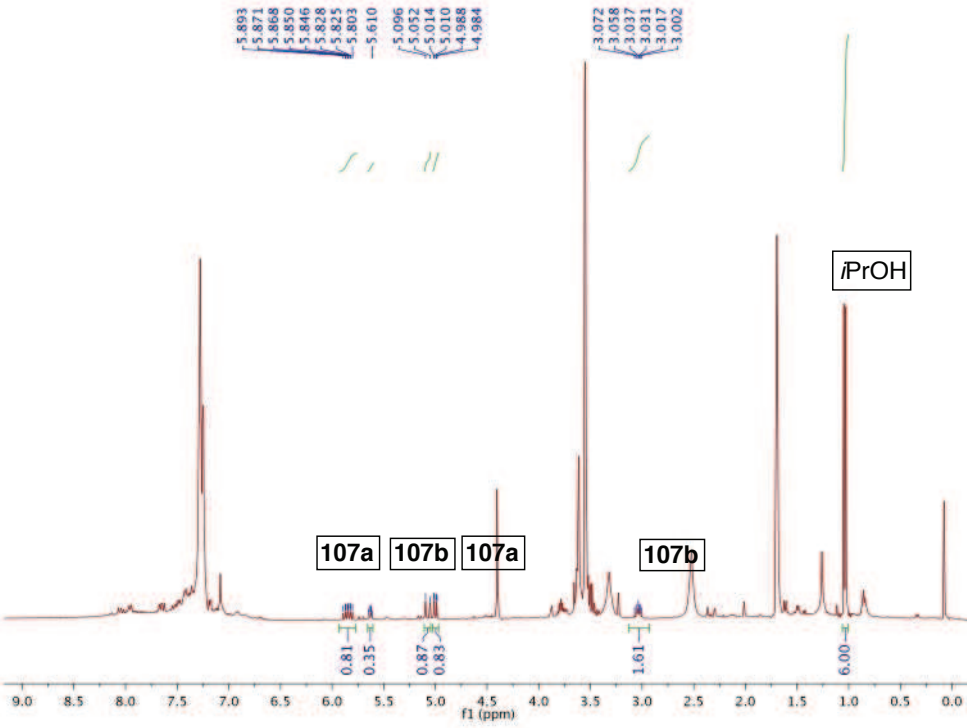
Stoichiometric Experiments Spectra

A-1 Malonate substitution of [Ir-7] in THF:

Complex [Ir-7] with internal standard *i*PrOH in d_8-THF:

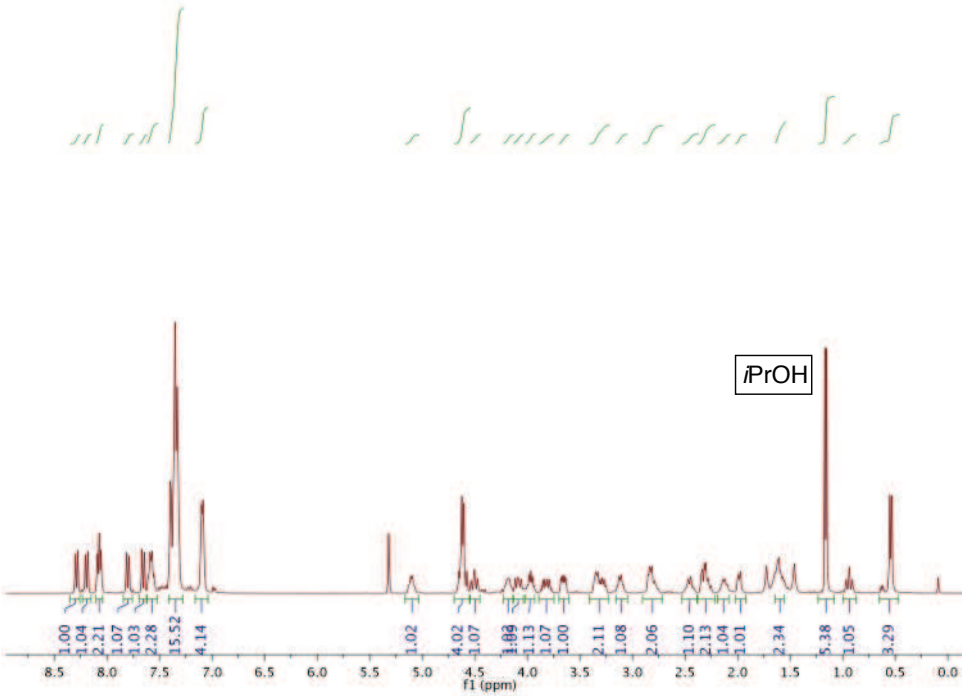


Reaction mixture in d_8-THF after addition of PPh_3:

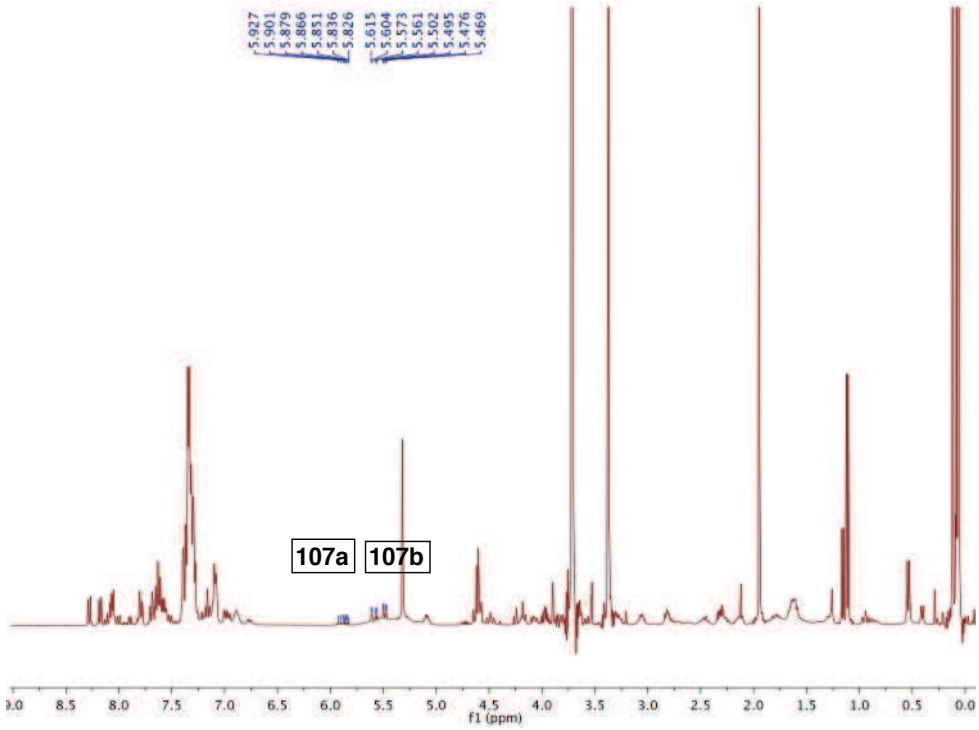


A-2 Malonate substitution of [Ir-7] in DCM:

Complex [Ir-7] with internal standard *i*PrOH in d_2-DCM:

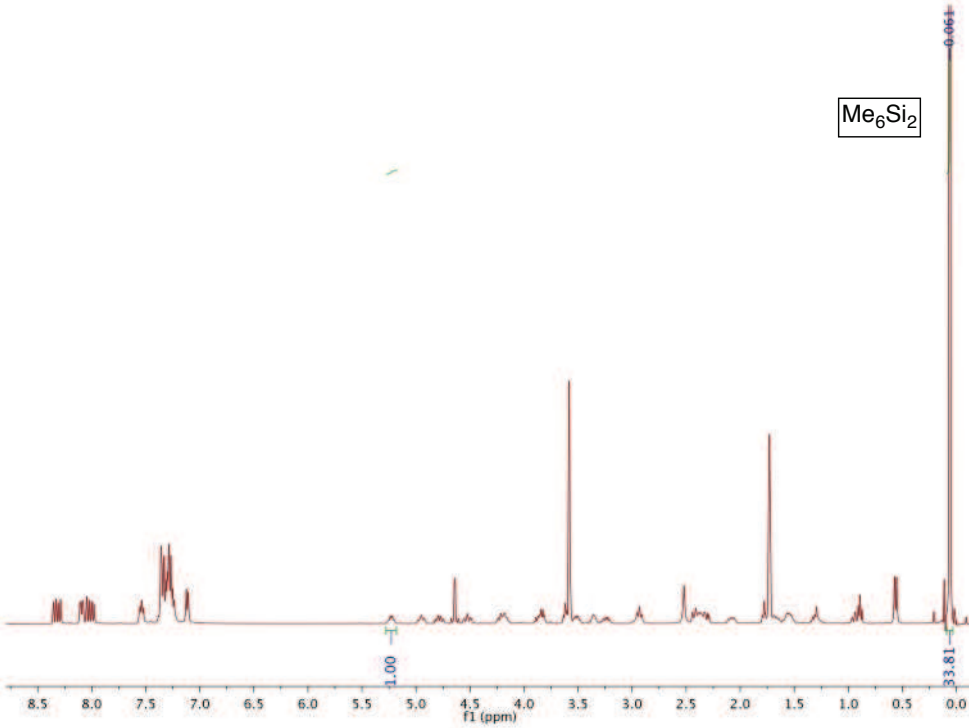


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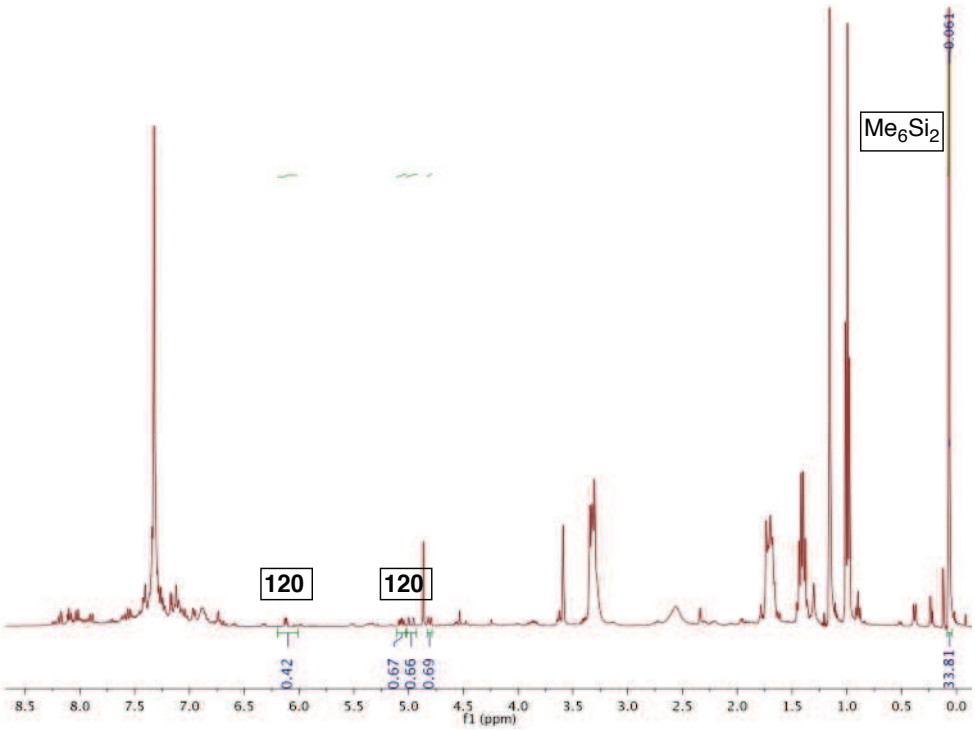


A-3 Fluorination of [Ir-7] in d_8-THF:

Complex [Ir-7] with internal standard Me_6Si_2 in d_8-THF:

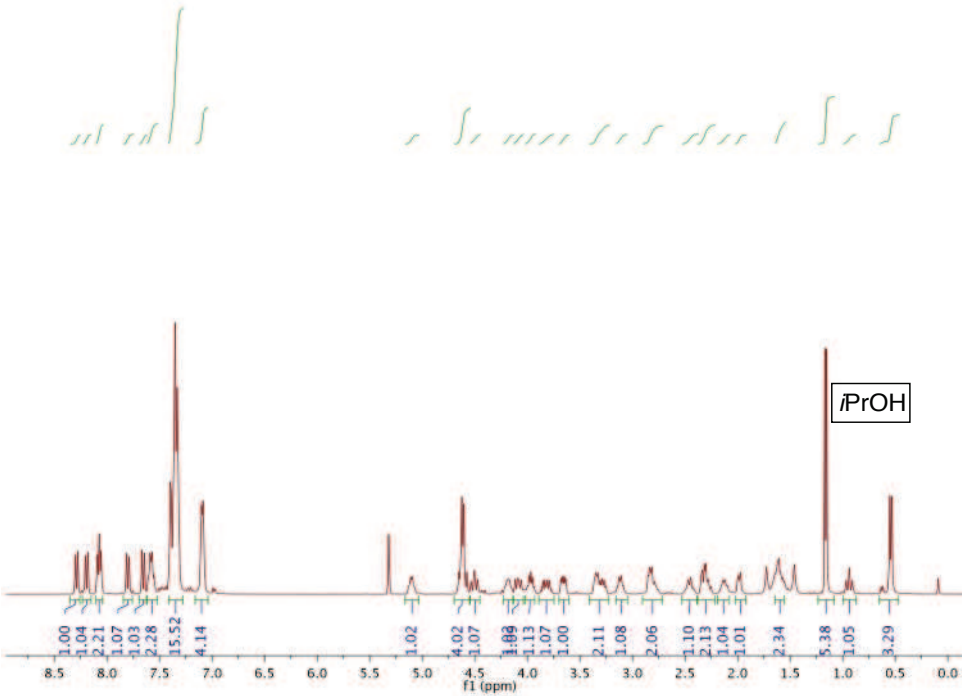


Reaction mixture in d_8-THF after addition of PPh_3:

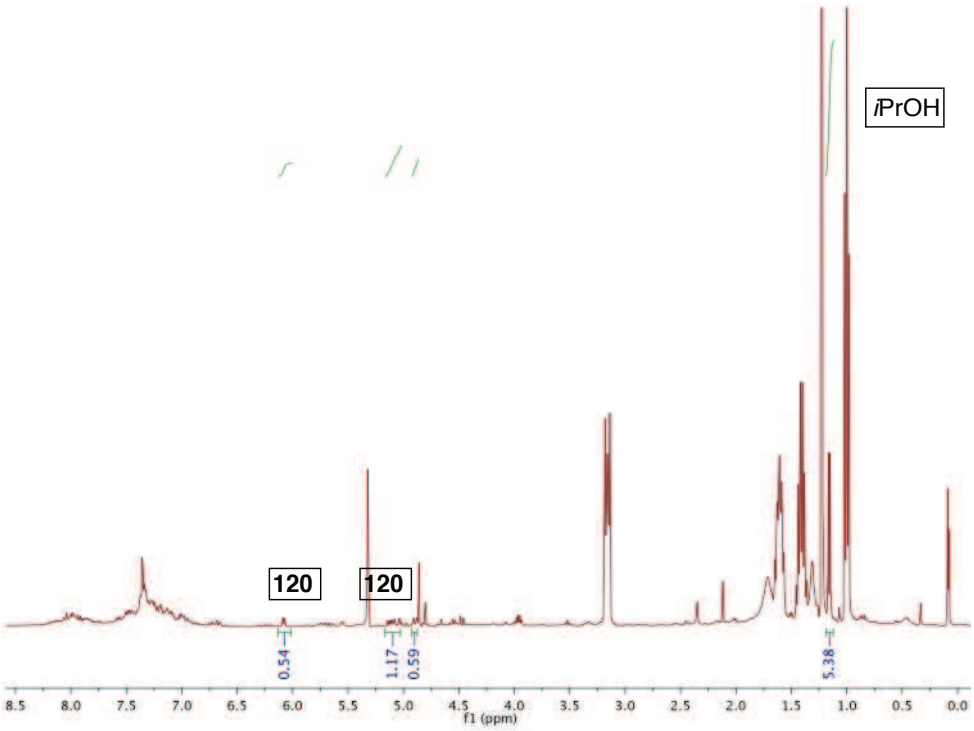


A-4 Fluorination of [Ir-7] in d_2-DCM:

Complex [Ir-7] with internal standard *i*PrOH in d_2-DCM:

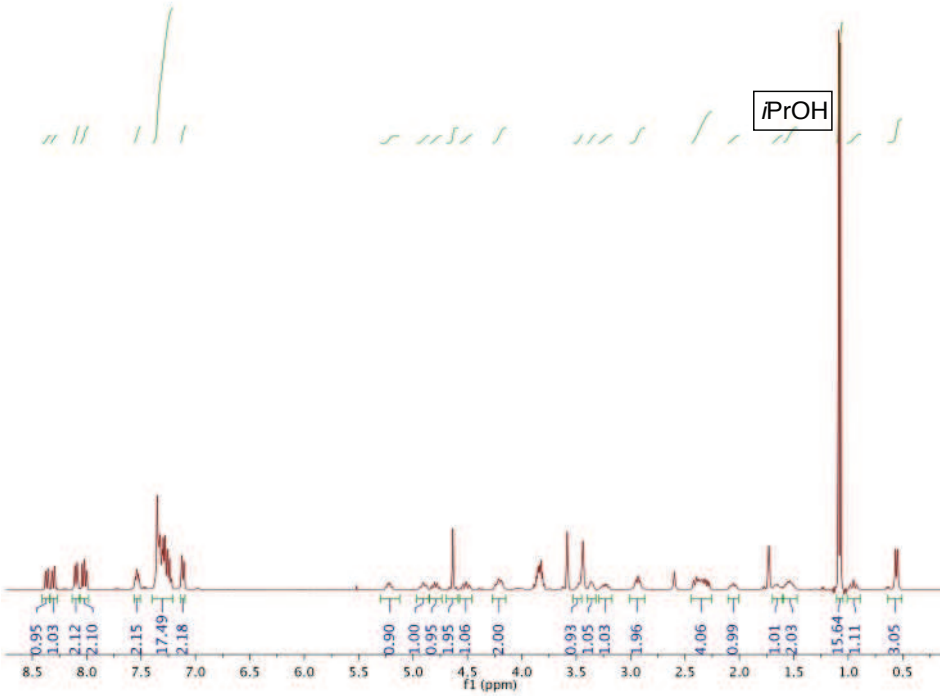


Reaction mixture in d_2-DCM after addition of PPh_3:

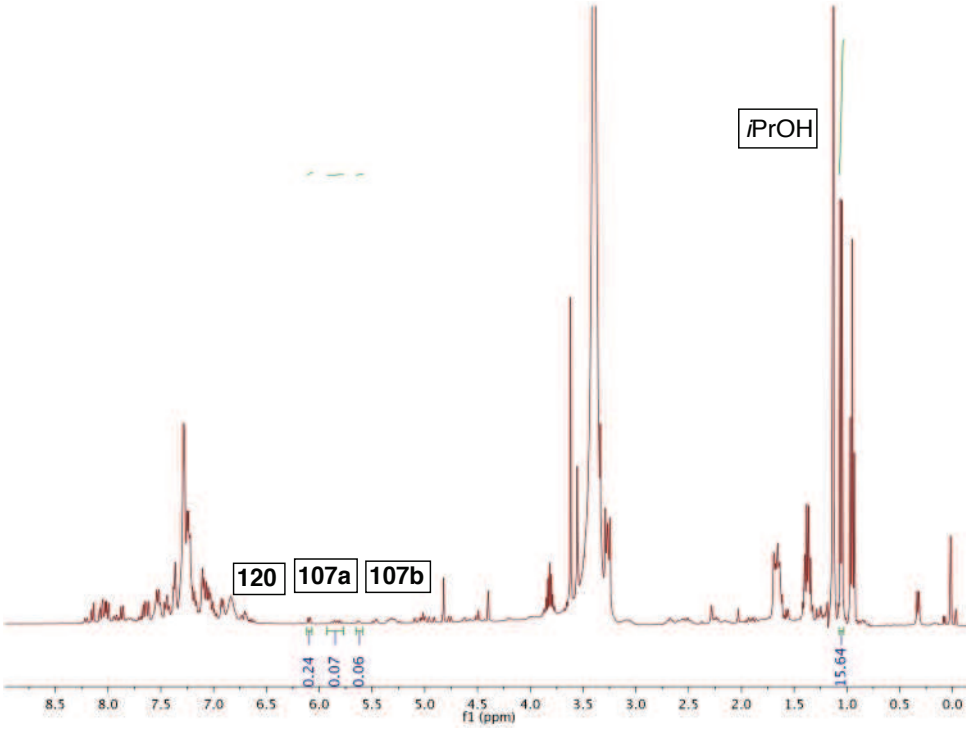


A-5 Malonate substitution of [Ir-7] with TBAF·4*t*BuOH additive:

Complex [Ir-7] with internal standard *i*PrOH in d_8-THF:



Reaction mixture after addition of PPh_3:

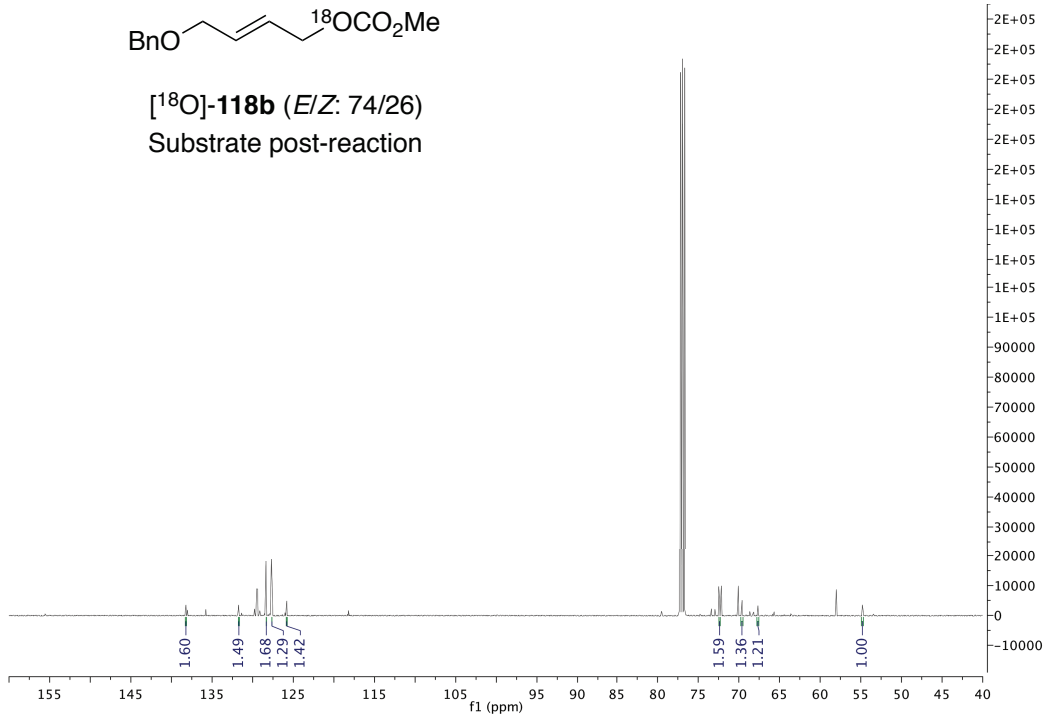


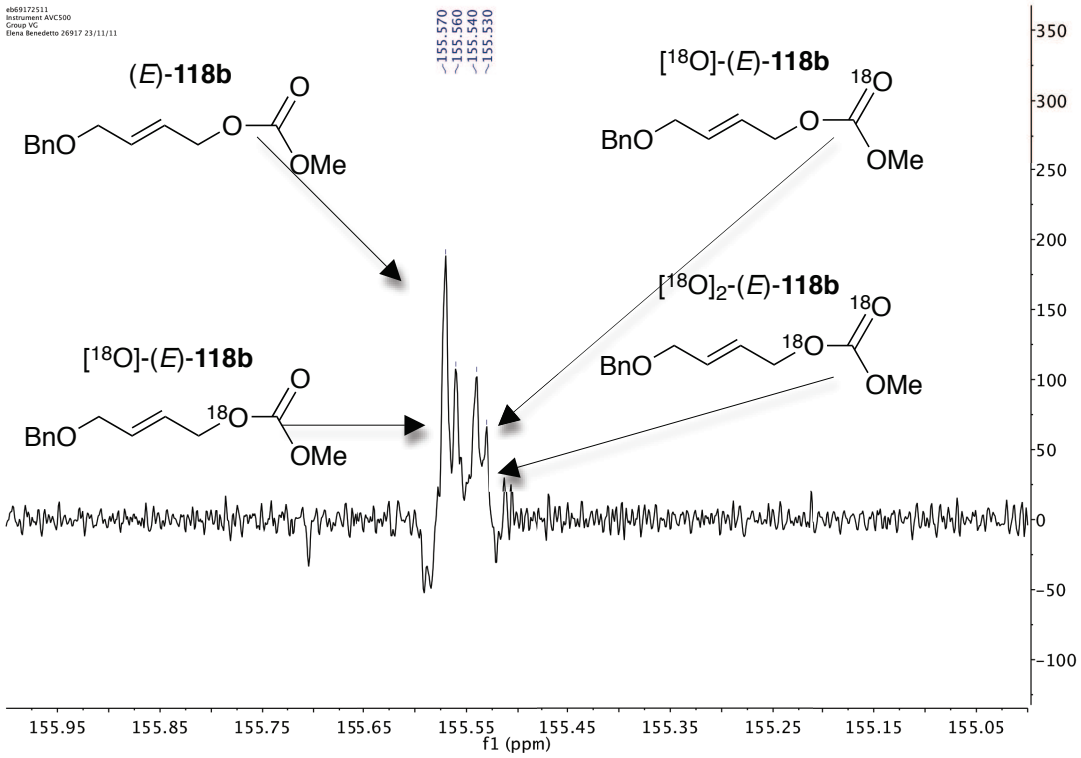
Appendix B

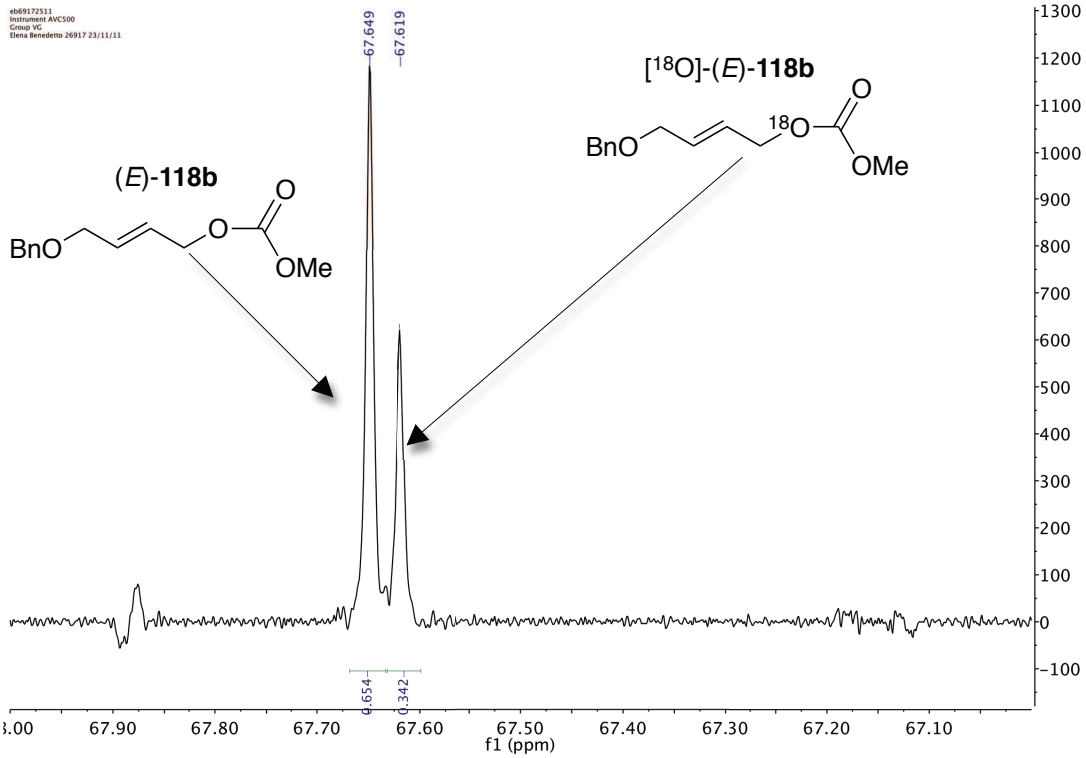
^{18}O-Labeling Experiments Spectra

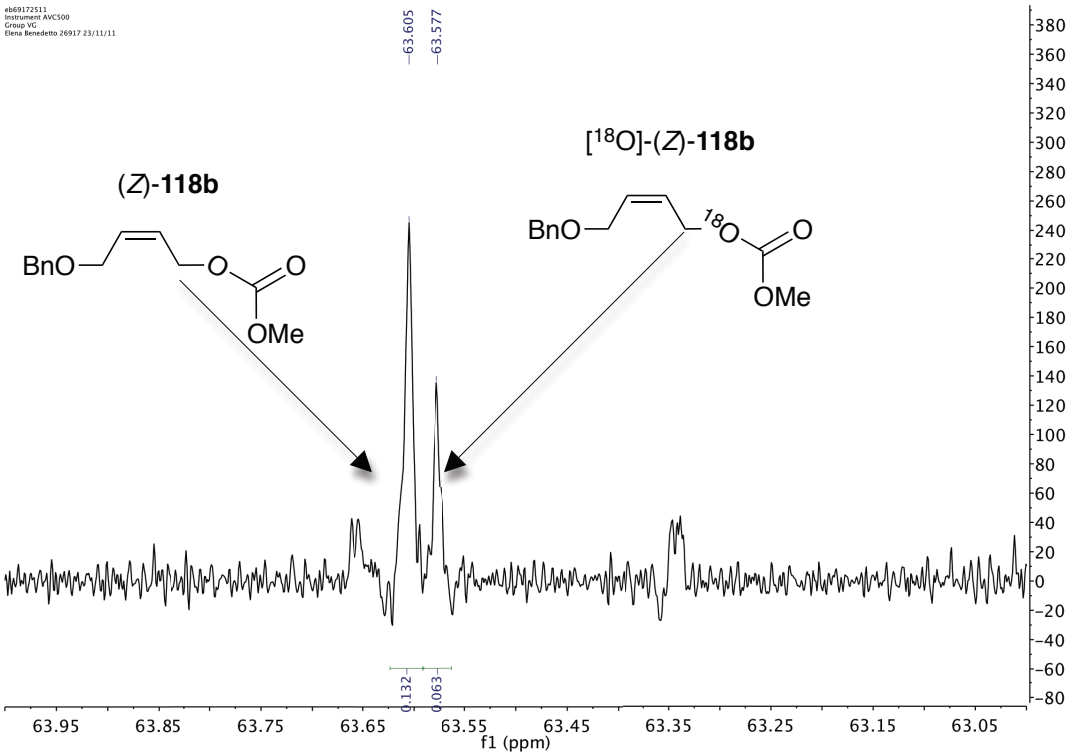
B-1 Fluorination of [^{18}O]-118b (Scheme 3.24a):

B-1.1 ^{13}C-NMR of recovered [^{18}O]-118b

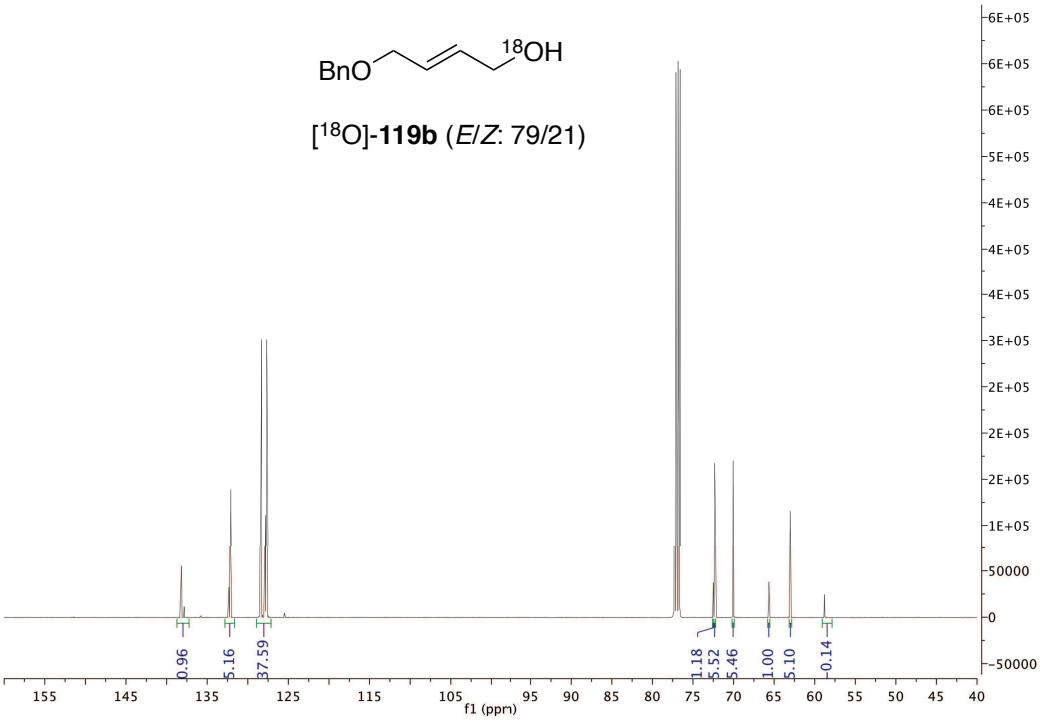


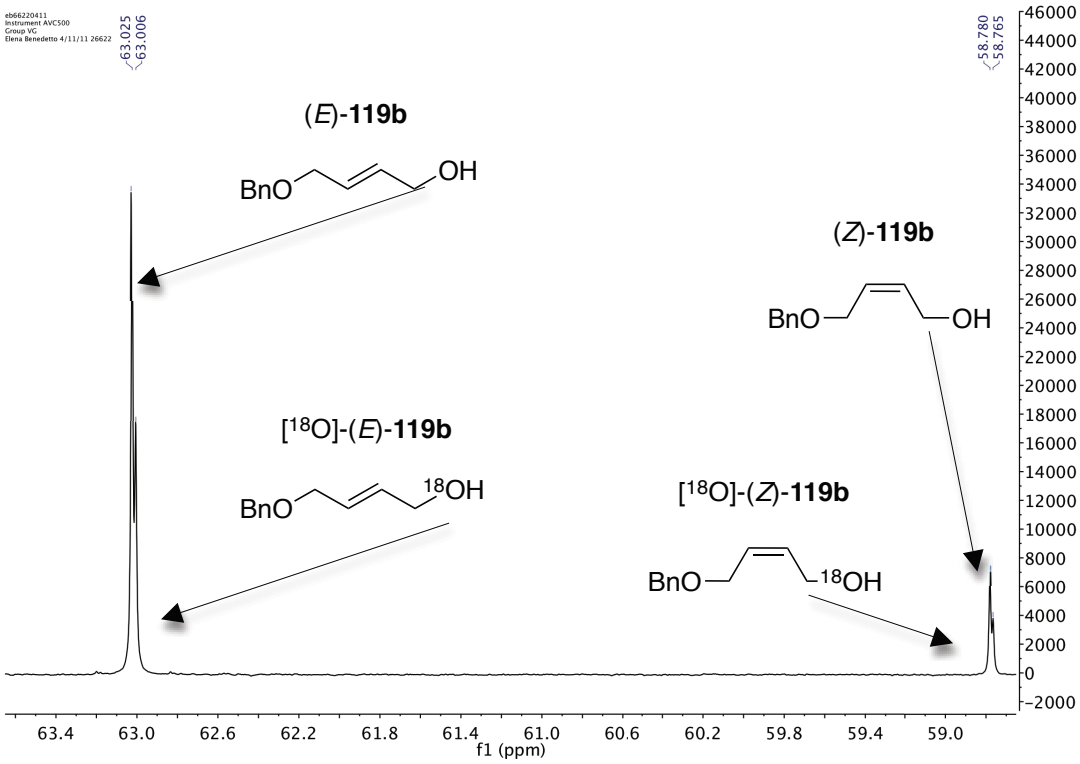

155.570
155.560
155.540
155.530
(E)-118b
[18O]-(E)-118b
[18O]2-(E)-118b
[18O]-(E)-118b
BnO
OMe
18O
155.95
155.85
155.75
155.65
155.55
155.45
155.35
155.25
155.15
155.05
f1 (ppm)


67.649
67.619
(E)-118b
[18O]-(E)-118b
BnO
OMe
18O
0.654
0.342
67.90
67.80
67.70
67.60
67.50
67.40
67.30
67.20
67.10
f1 (ppm)



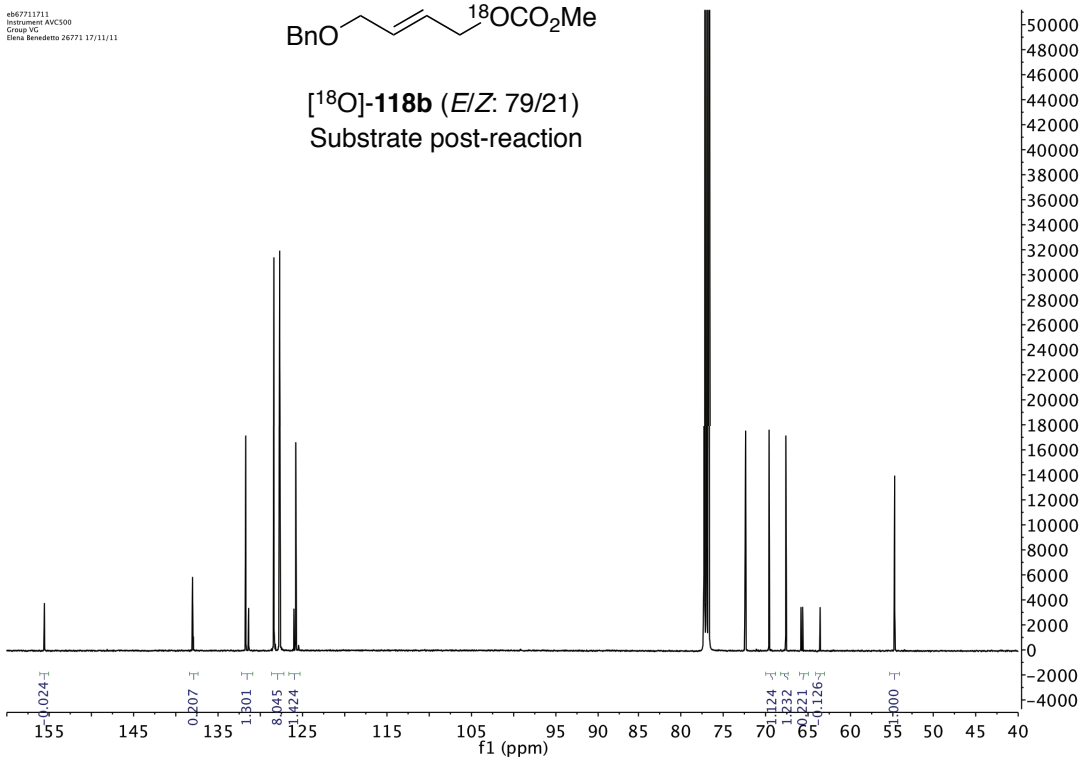
B-1.2 ^{13}C-NMR of [^{18}O]-119b

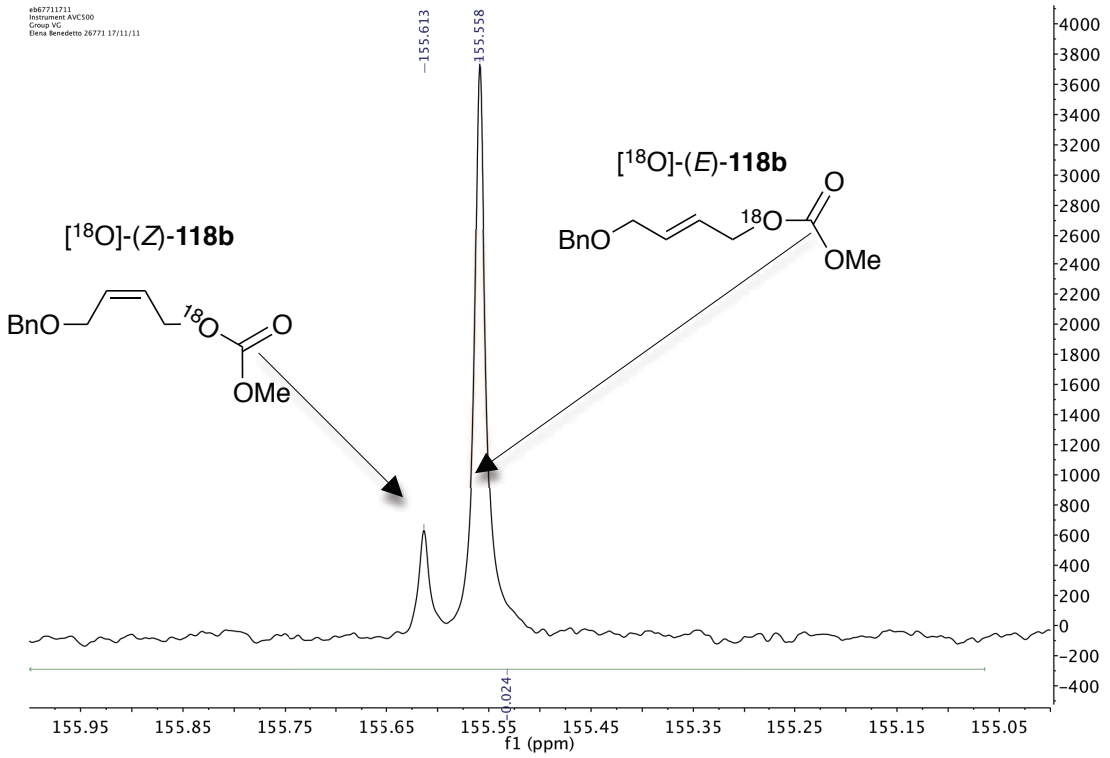


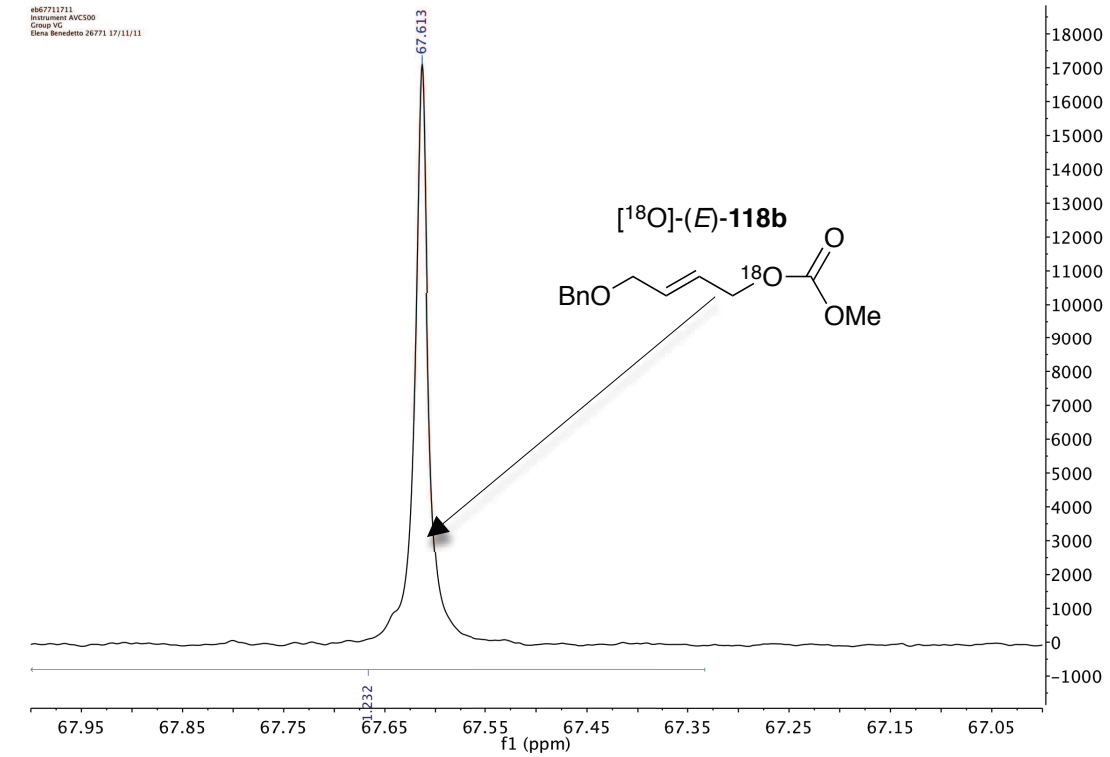


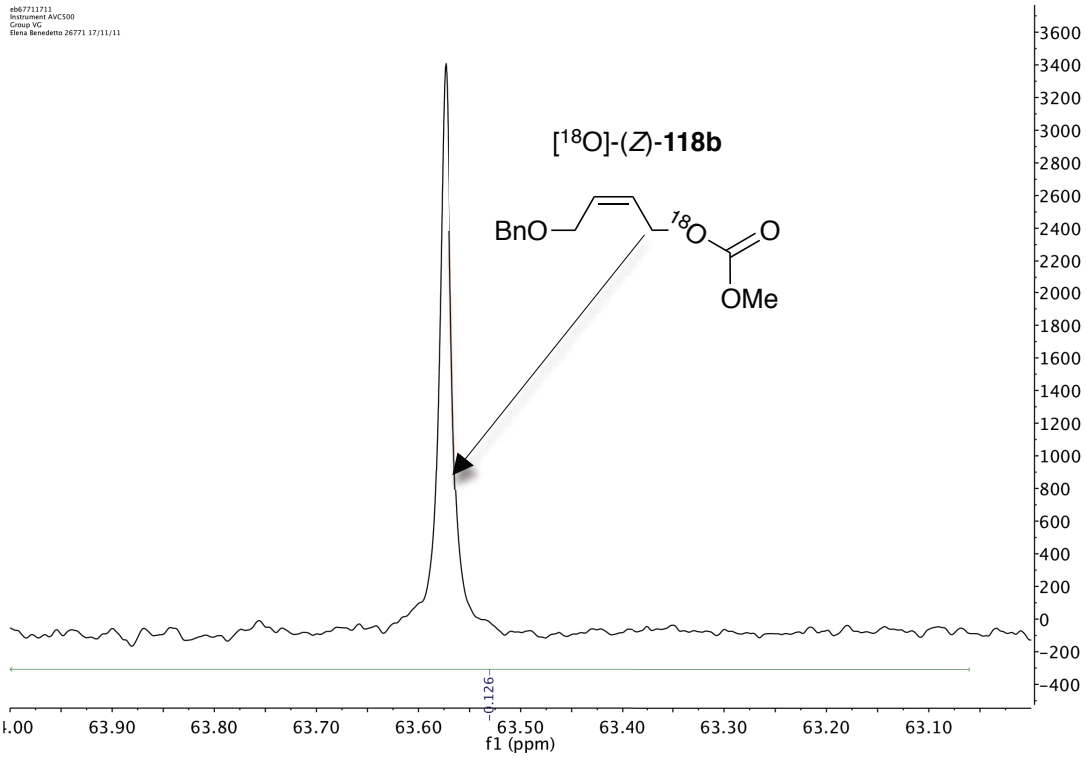
B-2 Scrambling test in [^{18}O]-(*E*)118b (Scheme 3.24b):

B-2.1 ^{13}C-NMR of recovered [^{18}O]-118b

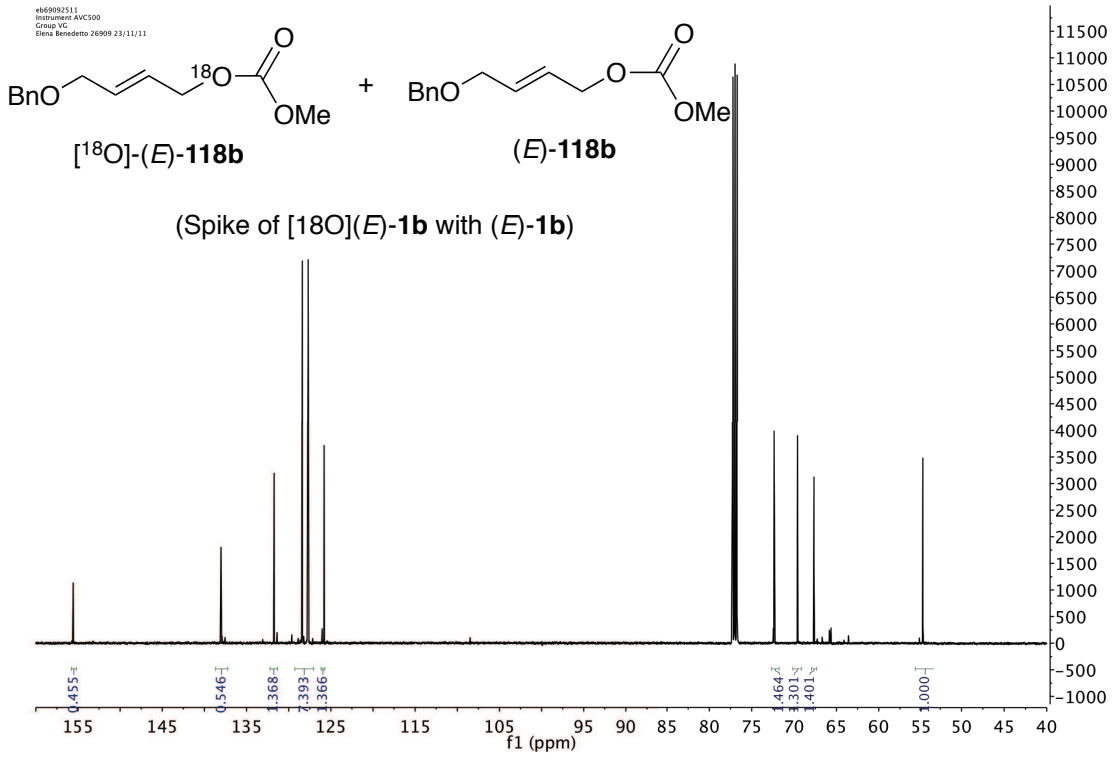


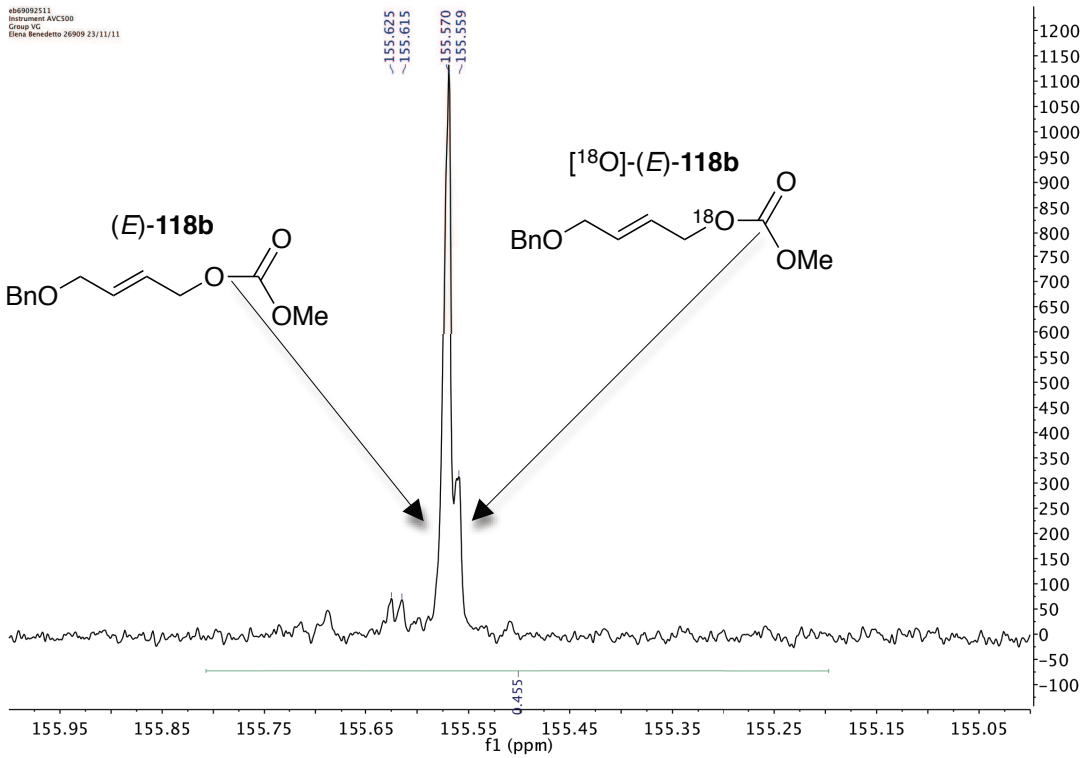

eb67711711
Instrument AVC500
Group VG
Elena Benedetto 26771 17/11/11
155.613
155.558
[18O]-(Z)-118b
BnO
18O
O
OMe
[18O]-(E)-118b
BnO
18O
O
OMe
0.024
155.95
155.85
155.75
155.65
155.55
155.45
155.35
155.25
155.15
155.05
f1 (ppm)

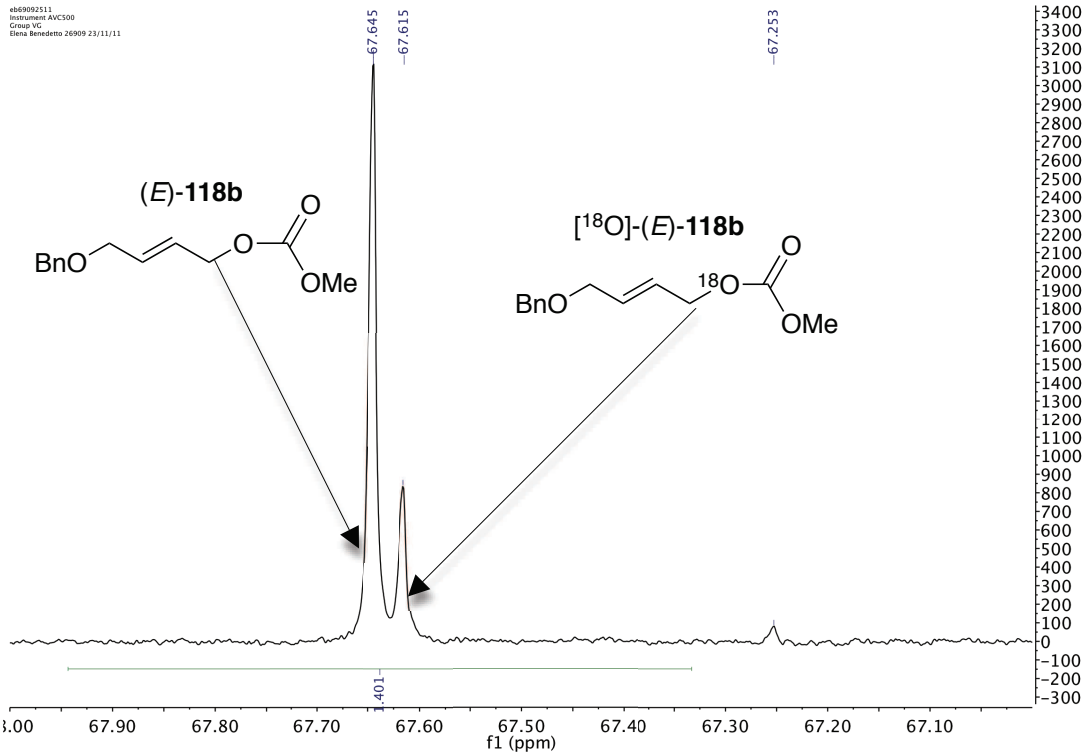

eb67711711
Instrument AVC500
Group VG
Elena Benedetto 26771 17/11/11
67.613
[18O]-(E)-118b
BnO
18O
O
OMe
1.232
67.95
67.85
67.75
67.65
67.55
67.45
67.35
67.25
67.15
67.05
f1 (ppm)



B-2.2 ^{13}C-NMR of recovered [^{18}O]-(*E*)-118b spiked with (*E*)-118b

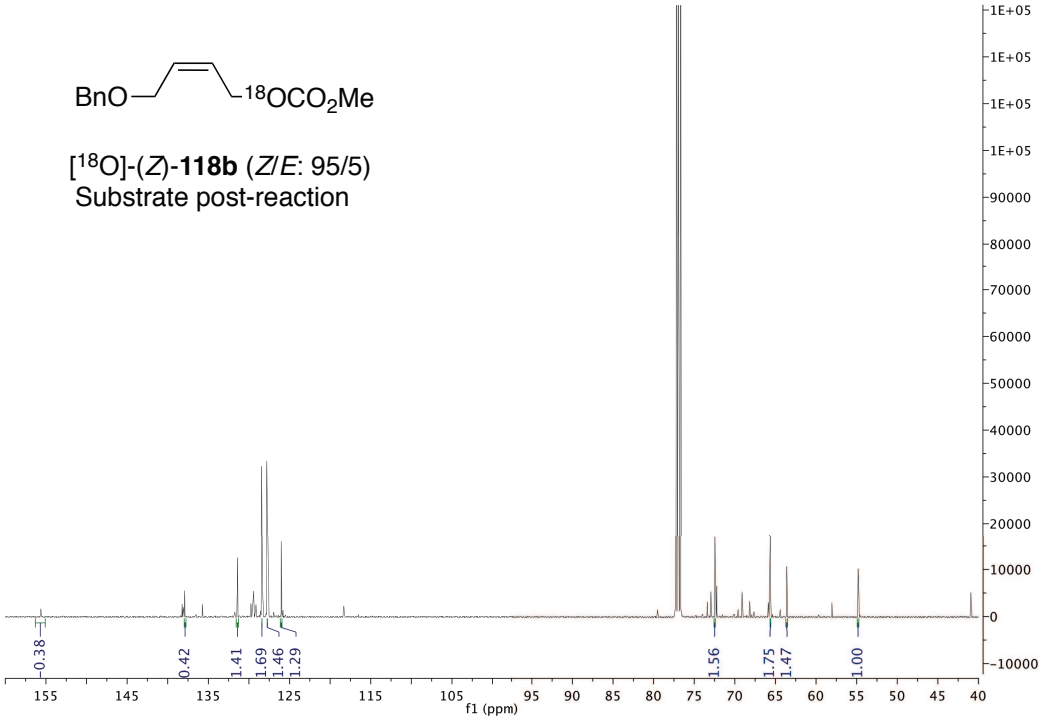


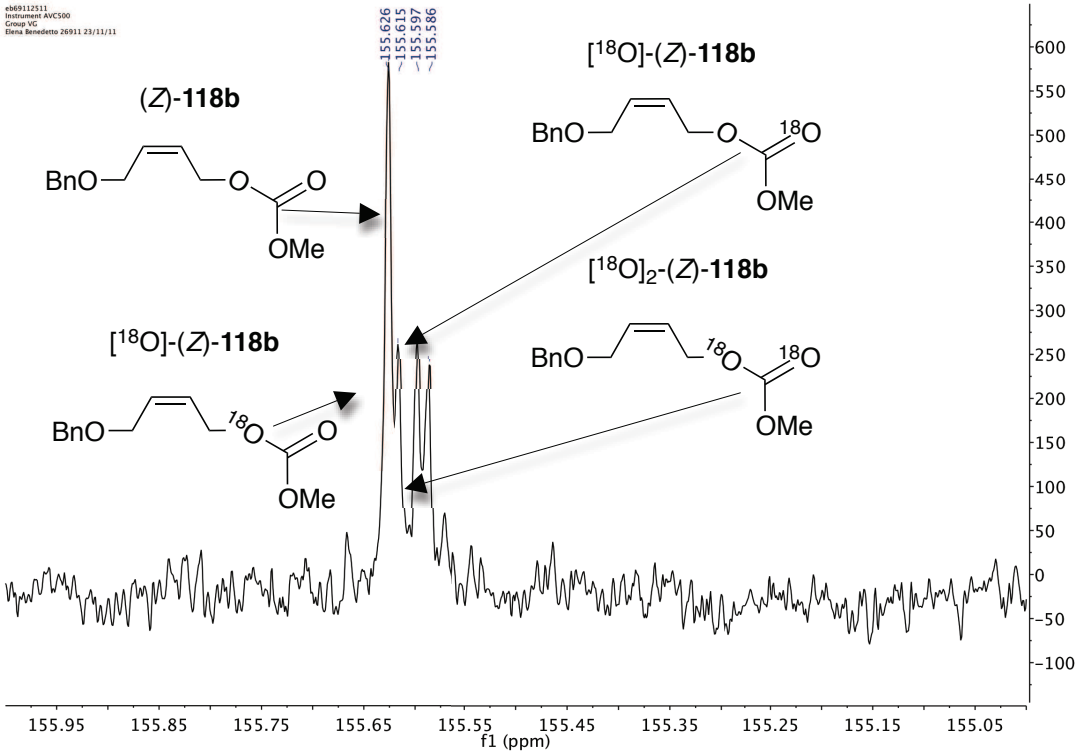

eb69092511
Instrument AVC500
Group VG
Elena Benedetto 26909 23/11/11
155.625
155.615
155.570
155.559
(E)-118b
BnO
O
O
OMe
[18O]-(E)-118b
BnO
18O
O
OMe
0.455
155.95
155.85
155.75
155.65
155.55
155.45
155.35
155.25
155.15
155.05
f1 (ppm)

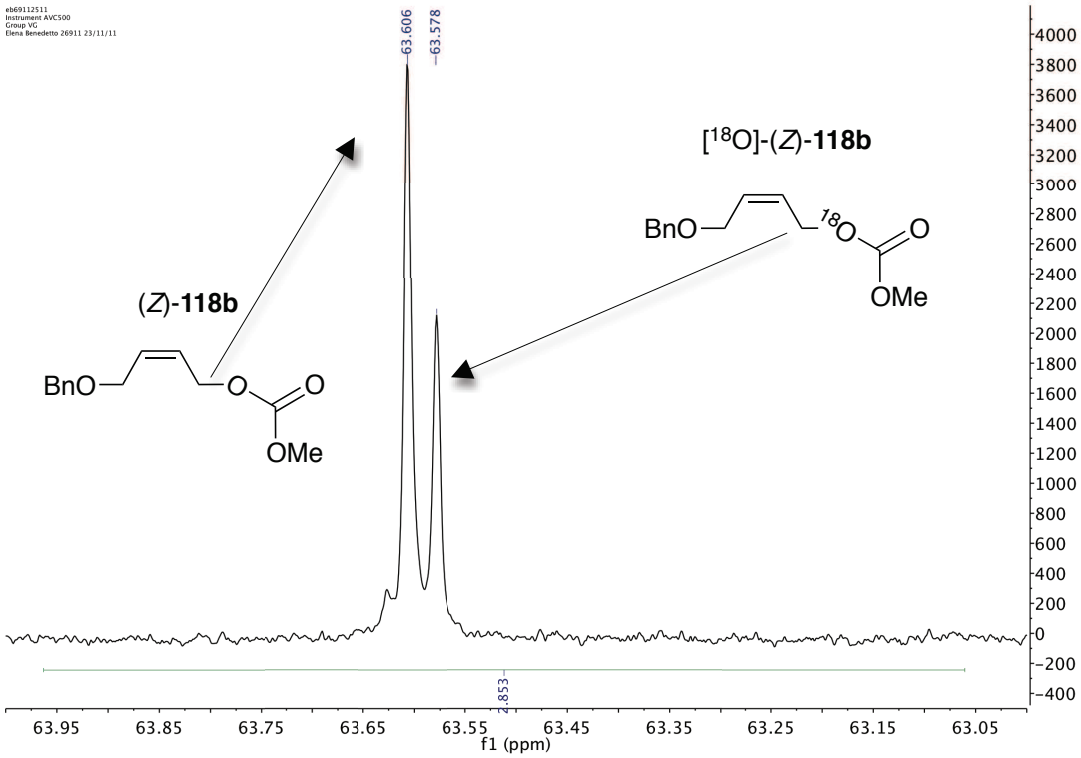

eb69092511
Instrument AVC500
Group VG
Elena Benedetto 26909 23/11/11
67.645
67.615
67.253
(E)-118b
BnO
O
O
OMe
[18O]-(E)-118b
BnO
18O
O
OMe
1.401
67.90
67.80
67.70
67.60
67.50
67.40
67.30
67.20
67.10
f1 (ppm)

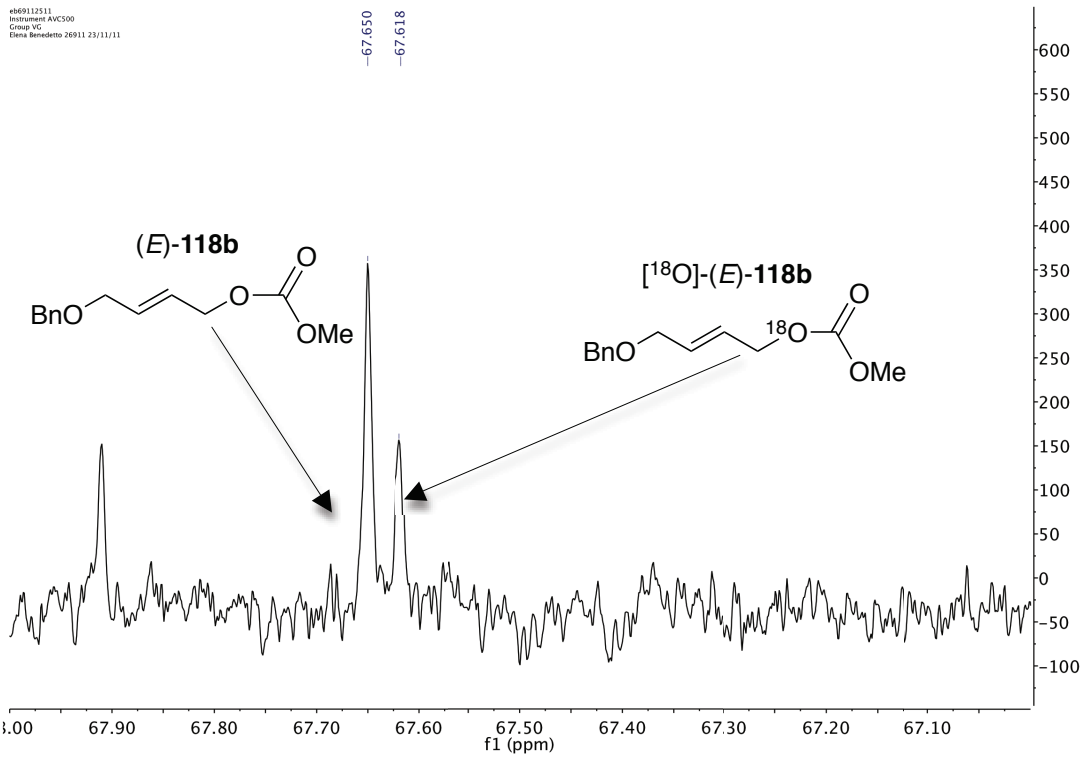
B-3 Fluorination of (*Z*)-118b with [^{18}O]-H_2O (Scheme 3.25a):

B-3.1 ^{13}C-NMR of recovered (*Z*)-118b

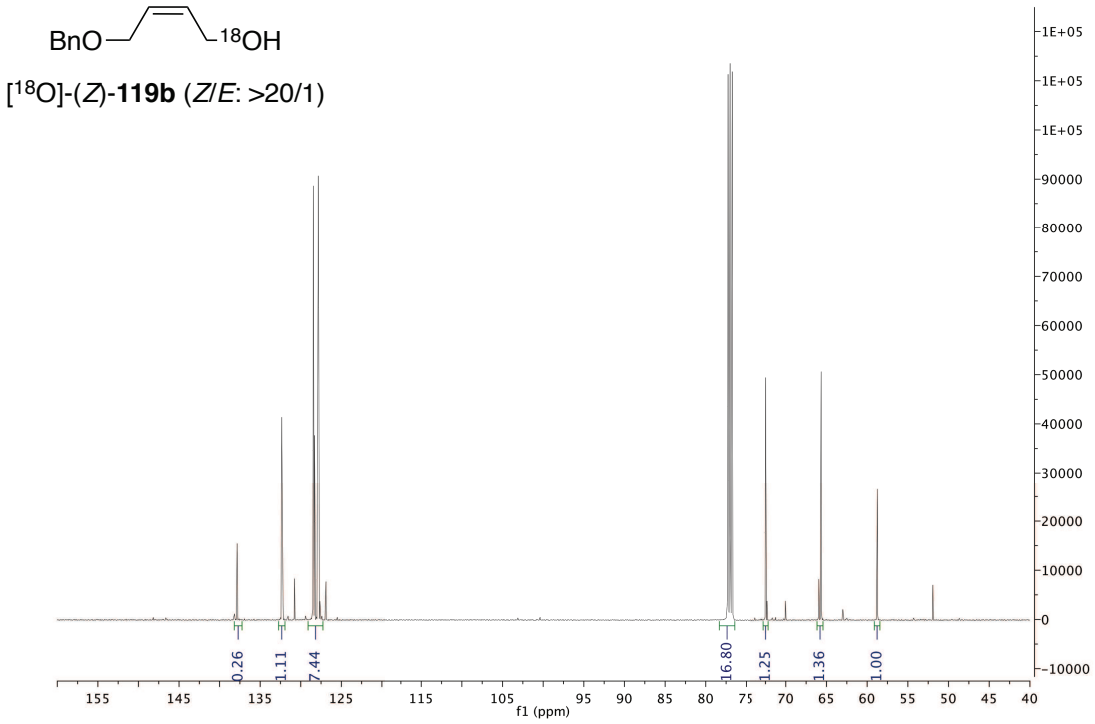


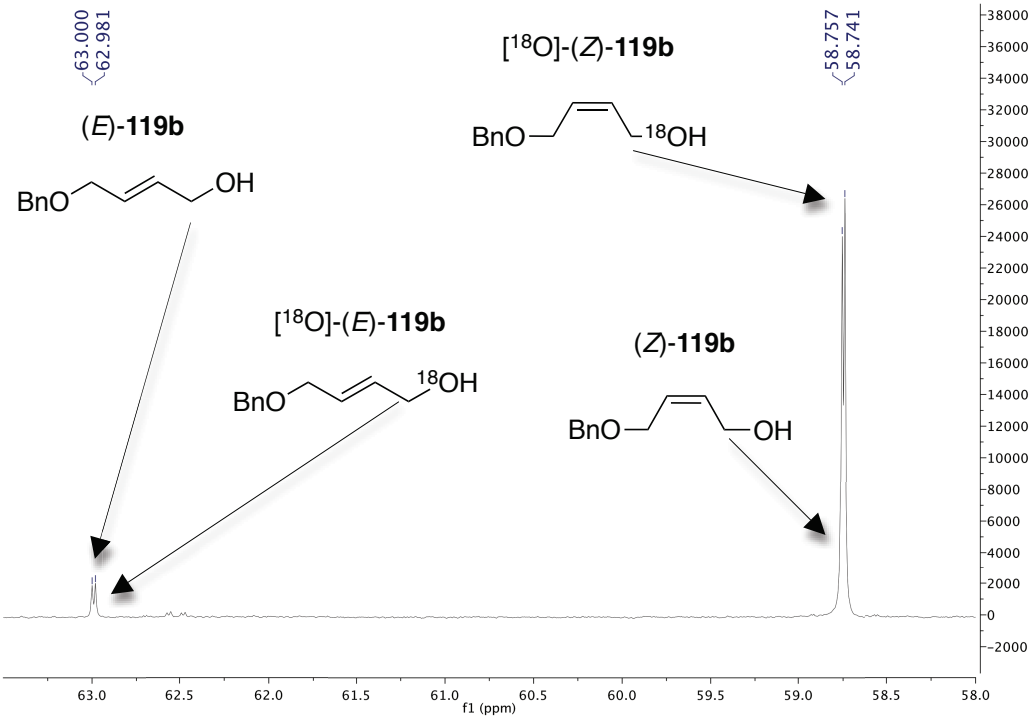



eb69112511
Instrument AVC500
Group VG
Elena Benedetto 26911 23/11/11
63.606
63.578
[18O]-(Z)-118b
BnO
18O
O
OMe
(Z)-118b
BnO
O
O
OMe
2.853
63.95
63.85
63.75
63.65
63.55
63.45
63.35
63.25
63.15
63.05
f1 (ppm)


eb69112511
Instrument AVC500
Group VG
Elena Benedetto 26911 23/11/11
67.650
67.618
(E)-118b
BnO
O
OMe
[18O]-(E)-118b
BnO
18O
O
OMe
67.90
67.80
67.70
67.60
67.50
67.40
67.30
67.20
67.10
f1 (ppm)

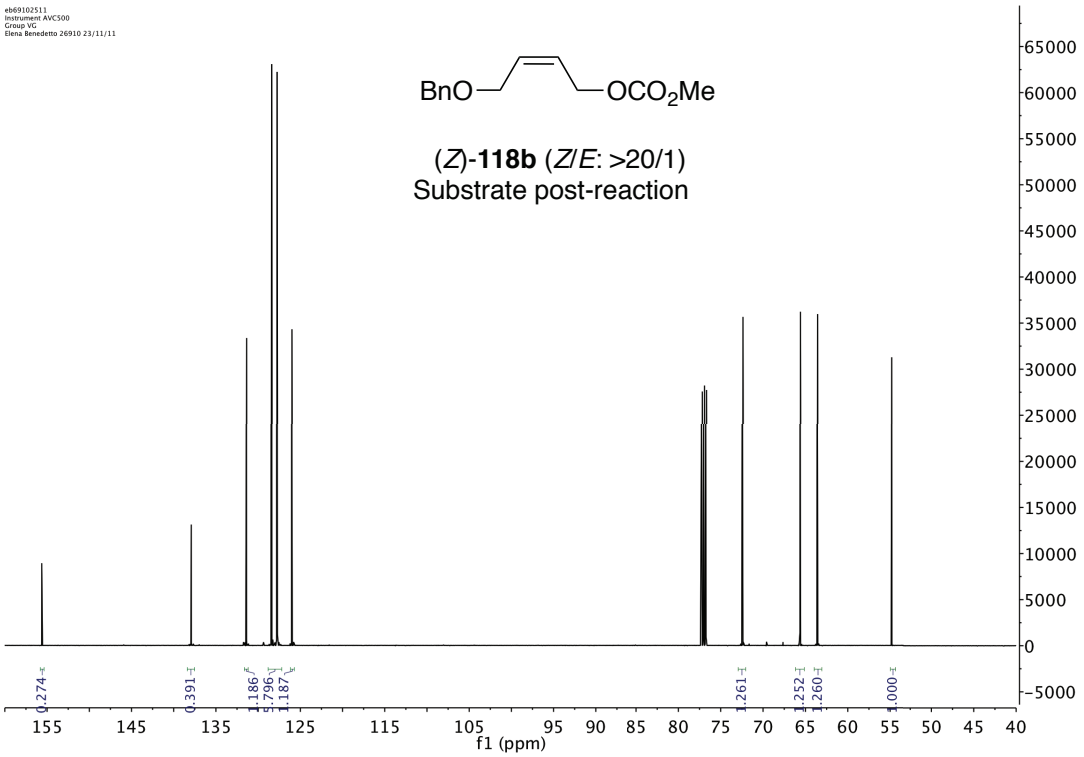
B-3.2 ^{13}C-NMR of [^{18}O]-(Z)-119b

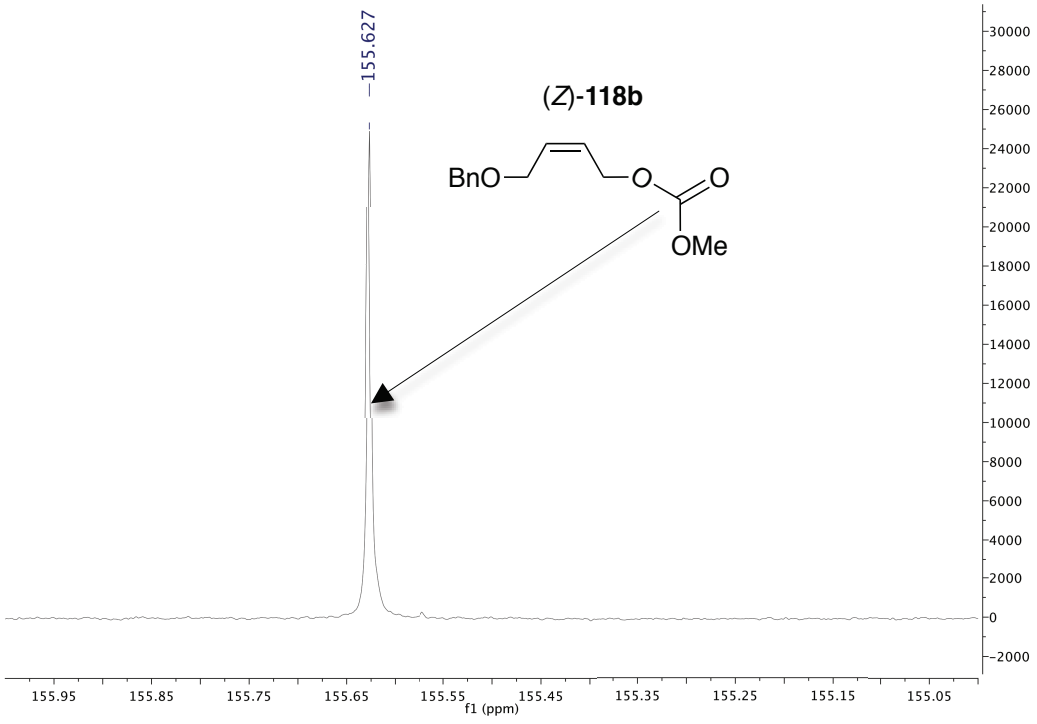


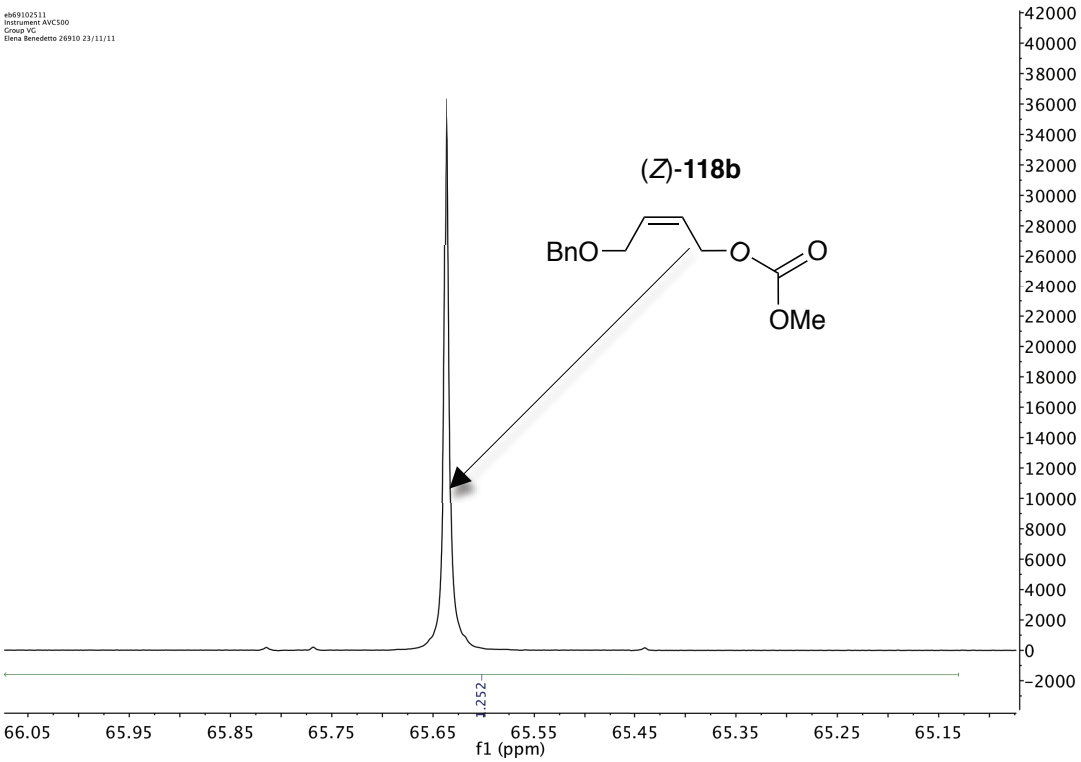


B-4 Test reaction with [^{18}O]-H_2O (Scheme 3.25b):

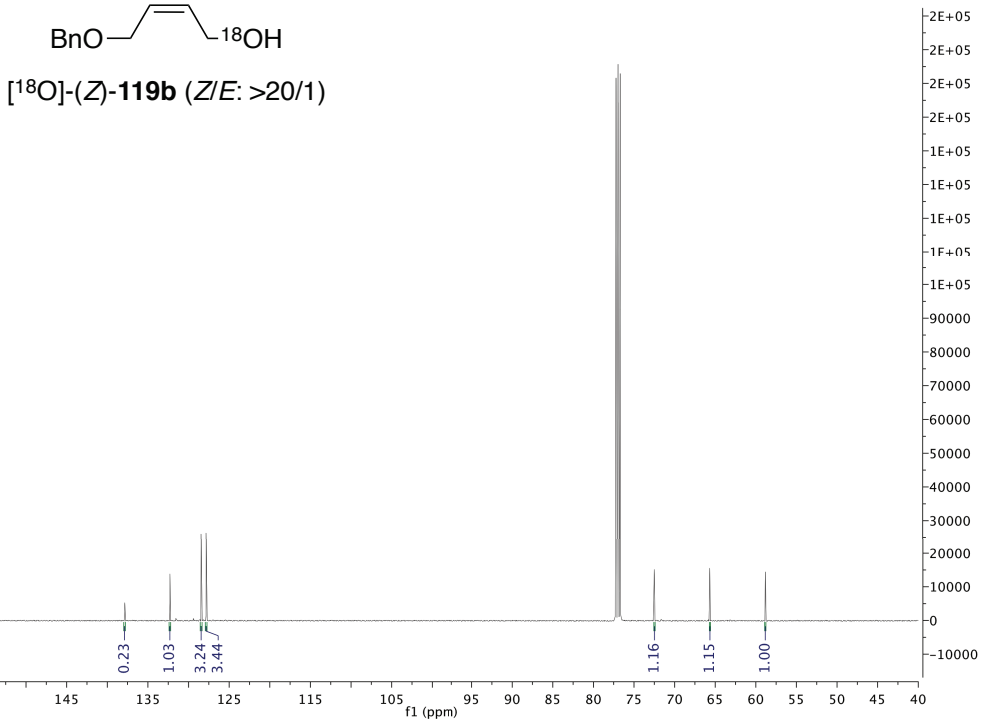
B-4.1 ^{13}C-NMR of recovered (*Z*)-118b

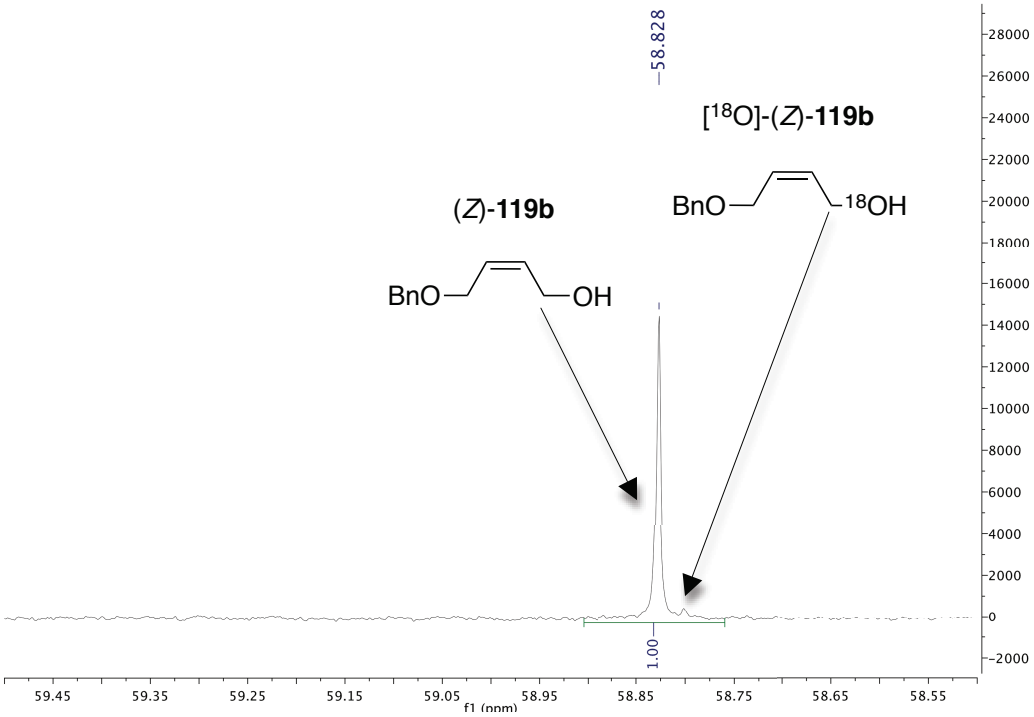






B-4.2 ^{13}C-NMR of (*Z*)-119b




58.828
[18O]-(Z)-119b
(Z)-119b
BnO
18OH
BnO
OH
1.00
59.45
59.35
59.25
59.15
59.05
58.95
58.85
58.75
58.65
58.55
f1 (ppm)