

Enantioselective Synthesis and Reactivity of Benzylic Fluorides

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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 and at GSK Stevenage between Michaelmas Term 2009 and Trinity Term 2013, under the supervision of Professor Veronique Gouverneur. All of the work is my own, except where stated otherwise, and has not been submitted for any other degree at this or any other university.

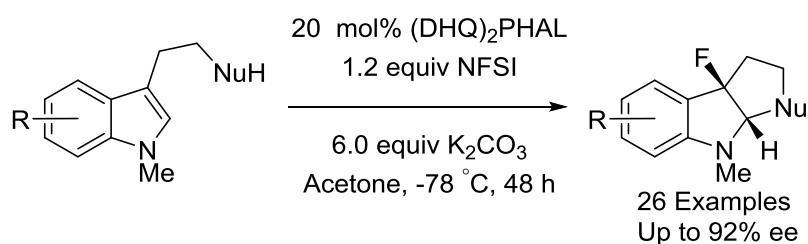
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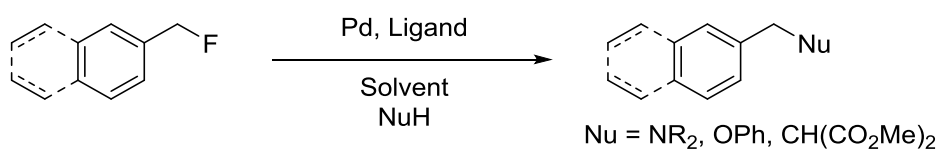
Enantioselective Synthesis and Reactivity of Benzylic Fluorides

Benzylic fluorides are attractive target molecules for medicinal chemistry, agrochemicals and materials chemistry. The enantioselective synthesis of benzylic fluorides is challenging and few general methods exist. This thesis describes several approaches to the synthesis of benzylic fluoride targets, including enantioselective processes

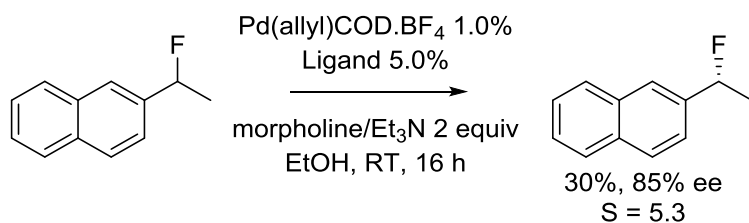
Chapter 1: Reviews the properties, uses and synthetic approaches to fluorinated molecules, with a particular focus on benzylic fluorides and enantioselective syntheses.



Chapter 2: Describes the fluorination cyclisation of prochiral indole precursors. The use of catalytic amounts of a *bis-cinchona* alkaloid gave good enantioselectivities for the cyclisation. Alcohol, tosylamine, amide and carbamate pendant nucleophiles all cyclised successfully to give quaternary benzylic fluorides in moderate yields and with enantioselectivities up to 92%. The substrate scope of the reaction is described, as well as methodology for deprotection of cyclised nitrogen nucleophiles.



Chapter 3: Details an investigation of the Pd catalysed substitution of polycyclic benzylic fluorides by a range of nucleophiles and their relative reactivity in comparison to oxygen leaving groups. Modification of the methodology to enable reaction of monocyclic substrate substitution was enabled by the use of a protic solvent. Chemoselective reaction conditions were identified for selective reaction of Bn-F or Ar-Cl bonds and comparative reactivity studies were undertaken. The feasibility of Pd(0)/(II) catalysed nucleophilic C-F bond formation was examined.



Chapter 4: The development of the defluorination methodology from Chapter 3 for secondary substrates is described. The stereochemical course of defluorination was probed, showing that displacement of fluoride is mechanistically similar to that of oxygen leaving groups. A kinetic resolution with a low selectivity was developed for access to enantioenriched benzylic fluorides.

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Contents

Author's Declaration.....	i
Abstract.....	iii
Acknowledgements.....	v
Abbreviations and acronyms.....	xii
Chapter 1: Benzylic Fluorine Substitution.....	1
1.1 Benzylic Fluorides: Properties and Uses	1
1.1.1 Physical Properties of Fluorinated Molecules.....	3
1.1.2 Biological Properties of Fluorinated Molecules	13
1.2 Synthesis of Benzylic Fluorides.....	22
1.2.1 Nucleophilic Fluorination	23
1.2.2 Electrophilic Fluorination	40
1.2.3 Building Block Approaches	48
1.2.4 Metal Catalysed Synthesis of Benzylic Fluorides.....	56
1.3 Reactivity of Benzylic Fluorides.....	62
1.3.1 Classical Benzyl Halide Reactivity.....	62
1.3.2 Solvolysis.....	63
1.3.3 Self Condensation	65
1.3.4 Reductive Defluorination.....	65
1.3.5 Electrochemical reduction.....	68
1.3.6 Lewis Acid Catalysed Defluorination.....	69
1.4 Aims of Thesis	72
Chapter 2: Organocatalysed Enantioselective Fluorocyclisation.....	74

2.1 Fluorination Cyclisation.....	74
2.1.1 Halogenation Cyclisation.....	74
2.1.2 Fluorination Cyclisation.....	77
2.1.3 Enantioselective Fluorination	82
2.2 Results and Discussion	87
2.3 Alcohol Nucleophile Substrate Synthesis	93
2.4 Alcohol Substrate Cyclisations	111
2.4.1 4- Position Substitution.....	112
2.4.2 5 - Position Substitution.....	113
2.4.3 6 - Position Substitution.....	114
2.4.4 7 - Position Substitution.....	114
2.4.5 Side Chain Substitution.....	116
2.5 Nitrogen Nucleophile Cyclisations in Electrophilic Fluorocyclisation.....	117
2.5.1 Substrate Synthesis	120
2.6 Nitrogen Nucleophile Cyclisations	123
2.6.1 Nitrogen Protecting Group Removal	124
2.7 Absolute Stereochemistry	128
2.8 Conclusions and Further Work	132
Chapter 3: Palladium Catalysed Benzylic Defluorination	134
3.1 Palladium Catalysed Allylic Defluorination and Fluorination.....	135
3.2 Benzylic Tsuji Trost Chemistry	139
3.2.1 Pd Catalysed Reactivity of Benzyl Halides	139
3.2.2 Less Activated Leaving Groups.....	140

3.2.3 Relative Reactivity of Pd-Benzyl Complexes.....	150
3.2.4 Regioselectivity.....	151
3.3 Results and Discussion	153
3.3.1 Reaction Development: Naphthalene Substrates	153
3.3.2 Reaction Development: Monocyclic Substrates	155
3.3.3 Reaction Scope.....	157
3.3.4 Substrate scope.....	163
3.3.5 Chemoselectivity.....	167
3.3.5 Fluorination of Benzylic Positions.....	168
3.4 Conclusions and Further Work	174
Chapter 4: Kinetic Resolution of Benzylic Fluorides	178
4.1 Palladium Mediated Enantioselective Chemistry	178
4.1.1 Enantioselective Alkylation	178
4.1.2 Tsuji Trost Kinetic Resolutions	182
4.2 Palladium Catalysed Substitution of Secondary Benzylic Fluorides	186
4.2.1 Synthesis of Secondary Benzylic Fluorides.....	186
4.2.2 Reaction Screening	188
4.3 Mechanistic Insights from Reaction with Enantioenriched Substrate	189
4.4 Reaction Screening with Enantiopure Chiral Ligands.....	195
4.4.1 Monitoring of Reaction Mixture by HPLC.....	196
4.4.2 Scaffold Based Ligand Screening.....	199
4.4.3 C ₂ Ligand Screening	201
4.4.4 C ₁ Ligand Screening	202

4.4.5 Solvent Screening	205
4.4.6 Temperature	208
4.4.7 Catalyst Precursor and Ligand Loading	209
4.4.8 Nucleophile	210
4.5 Substrate Scope	212
4.5.1 Substrate Synthesis	212
4.5.2 Steric Effects	213
4.5.3 Functional Group Tolerance	215
4.5.4 Aromatic Ring Electronic Effects	217
4.6 Conclusions and Further Work	219
Chapter 5: Experimental Procedures and Characterisation Data	221
5.2 Experimental Data for Chapter 2	222
5.2.1 Alcohol Substrate Synthesis for Fluorination-Cyclisation	222
5.2.2 Amine Substrate Synthesis for Fluorination Cyclisation	252
5.2.3 Procedures for Fluorination-Cyclisation	257
5.2.4 Fluorination-Cyclisation Products	259
5.3 Experimental Data for Chapter 3	266
5.3.1 Defluorination Substrates	266
5.3.2 Defluorination Products	275
5.3.3 Competition Reaction Substrates	292
5.3.4 Substrates for Benzylic Fluorination	298
5.4 Experimental Data for Chapter 4	301
5.4.1 Synthesis of Secondary and Tertiary Benzylic Fluorides	301

5.4.2 Secondary and Tertiary Fluoride Defluorination Products	313
5.4.3 Substrates for Stereochemical Investigation	318
5.5 References.....	320

Abbreviations and acronyms

Ac	Acetyl
ADME	Absorption, Distribution, Metabolism and Excretion
Ar	Aryl
atm	Multiple of Atmospheric Pressure
ATR	Attenuated Total Internal Reflection
Bn	Benzyl
bmim	1-butyl-3-methylimidazolium
BDE	Bond Dissociation Enthalpy
BSA	<i>bis</i> -trimethylsilylacetamide
COD	<i>cis, cis</i> -1,5-Cyclooctadiene
δ	chemical shift
DAST	Diethylaminosulfur trifluoride
DBDA	α, α -difluorobenzyl(dimethyl)amine
DBH	1,3-dibromo-5,5-dimethylhydantoin
DCM	Dichloromethane
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppbz	1,2- <i>bis</i> -(diphenylphosphino)benzene
dppe	1,2- <i>bis</i> -(diphenylphosphino)ethane
dppf	1,1'- <i>bis</i> -(diphenylphosphino)ferrocene
dppm	1,1- <i>bis</i> -(diphenylphosphino)methane
dpppr	1,3- <i>bis</i> -(diphenylphosphino)propane
ee	Enantiomeric excess
equiv	Reagent equivalents
GC	Gas Chromatography
GC-MS	Gas Chromatography – Time of Flight Mass Spectrometry
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared
L*	Chiral ligand
LRMS	Low Resolution Mass Spectrometry
MeCN	Acetonitrile
Mes	Mesityl
mp	Melting Point
m/z	Mass to charge ratio
NFSI	<i>N</i> -Fluorobenzenesulfonimide
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
ppm	Parts per million
RT	Room Temperature (25 °C)
S	Kinetic Resolution Parameter
TBAF	Tetrabutylammonium Fluoride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl

Tol Toly
Tr Trityl

Chapter 1: Benzylic Fluorine Substitution

1.1 Benzylic Fluorides: Properties and Uses

The effects of the introduction of fluorine into organic molecules are wide ranging and significant, with the perturbations in properties that can thus be realised allowing the development of better drugs, pesticides, liquid crystal display substrates, chemically resistant plastics and other high value materials.¹⁻⁴ Improvements in the selectivity, efficiency and safety of fluorination methodologies have led to fluorinated molecules becoming ubiquitous in fine chemical synthesis, with as many as 30% of blockbuster drugs⁵ and a large proportion of agrochemicals (>75% are halogenated, fluorine being the most common¹) bearing one or more fluorine atoms. The demands of these industries for robust methodologies for the efficient tonne scale preparation of complicated molecules, often as single enantiomers, drives the need for development of new routes to fluorinated molecules.

Benzylic fluorine substituents are relatively rare in the academic literature, with few examples of direct comparisons of fluorinated and non fluorinated skeletons available. The reasons for the lack of study of this motif are not clear, but it could be suggested that this is due to the poor availability of benzylic fluorides using current methodologies, or a perception that benzylic fluoride is labile under metabolic conditions, posing toxicity risks.⁶ Despite the paucity of information available on the utility of benzylic fluorides, they are relatively common in patent claims, where the use of fluorinated substituents could be for optimisation of binding potency, pharmacokinetics or a multitude of other drug properties. This demonstrates the potential importance of new routes to benzylic fluorides to medicinal and agricultural chemistry.

Pharmaceutical entities require both activity towards targets, physicochemical properties that enable the delivery of drug molecules to those targets, and safe properties in the body (*i.e.* the drug half life is acceptable and toxic metabolites are not formed). Fluorine substituents are used to help attain all of these objectives, with a slight bias towards their use for the modification of

ADME (absorption, distribution, metabolism and excretion) properties. These properties are those which affect the delivery of drug molecules to their sites of action, and depend on the lipophilicity, solubility, pKa and metabolic vulnerabilities of pharmaceutical entities.

The ultimate cause of the unique properties of fluorinated molecules is the extreme electronegativity of fluorine; this, combined with the small size of the fluorine atom, leads to large perturbations in electron densities relative to hydrogen substituted analogs, with implications for the properties of both fluorine substituents themselves and functional groups in close proximity to fluorine atoms. There is a large amount of literature which documents these effects of fluorination on molecular properties and in many cases it is possible to make good predictions as to the effects of fluorine substitution; this enables the strategic use of fluorine in the rational design of functional molecules. This chapter will review the origin and the application of these effects with a focus on examples of benzylic fluorine substitution, followed by an examination of the current synthetic routes to benzylic fluoride targets and the reactivity of benzylic fluorides.

1.1.1 Physical Properties of Fluorinated Molecules

1.1.1.1 Carbon – Fluorine Bonds

The high electronegativity of fluorine (Pauling 4.0 vs. 2.55 for carbon) leads to the C-F bond being highly polarised, with significant partial charges on carbon and fluorine. Due to this there is a significant contribution to bond enthalpy from electrostatic attraction, making this the strongest single bond to carbon;⁷ this effect is additive, with even higher bond strengths for perfluorinated molecules where the partial charge on carbon is larger (C-F BDE for fluoromethane: 107 kcal mol⁻¹; tetrafluoromethane: 116 kcal mol⁻¹).⁸

Bond / C-X	Element van der Waals Radius / Å	Average Bond Length / Å ^{*9}	Benzylic Bond Dissociation Energy / kcal mol ⁻¹
C-H	1.20	1.06	89.7
C-OH	1.52	1.43	82.6
C-CH ₃	1.70	1.51	77.6
C-Cl	1.75	1.79	74
C-F	1.47	1.40	98.7

Table 1: Element van der Waals Radii, C-X Bond Lengths, and Benzylic Dissociation Energies * unweighted mean of bond lengths from structures RCH₂X extracted from Cambridge Structural Database¹⁰

Due to the small Van der Waals radius of fluorine (1.47 Å, see Table 1 for comparison to other elements),¹⁰ bond lengths are short (approximately 1.40 Å) making fluorine one of the smallest substituents. Often comparison is made with C-O and C-H bonds: the C-F bond is the next smallest group to C-H, allowing for the smallest steric change possible by modifying a C-H to a C-F, but with a significant change in electron distribution; the C-OH group is very similar in steric effect (bond lengths and van der Waals radius) to a C-F bond, and as such is considered a good steric mimic, this effect will be considered in Section 1.1.2.3 in terms of the biological effects of fluorine substitution.

1.1.1.2 Chemical and Thermal Stability

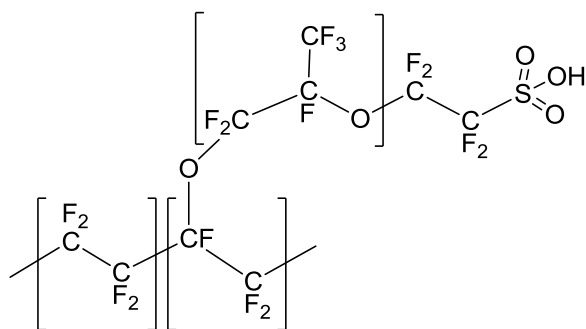


Figure 1: Fluorination for Stability: Nafion Fuel Cell Membrane Polymer⁴

In general fluorination leads to enhancements in the stability of molecules towards chemical attack or thermolysis. This inertness arises through both a thermodynamic component due to high bond strengths, as demonstrated by comparisons of the enthalpies of formation of polyfluorinated molecules and hydrocarbons;¹¹ and a kinetic component – due to the bond strength, the activation energy for uncatalysed reactions is very high. In addition the electron withdrawing effects and high charge densities of fluorinated moieties disfavour approach of and reaction with reactive species. This stability is one of the most common reasons for incorporation of fluorine in the design of functional molecules, examples of this are as diverse as specific C-F bonds introduced to prevent metabolism of drug molecules, and the use of highly fluorinated polymeric materials for fuel cell membranes which must resist high temperatures and acidic conditions (Figure 1).⁴

Closer inspection of the properties of the C-F bond requires further explanation of this stability; the separation of charge in fluorinated molecules gives the C-F bond some resemblance to a transition state for C-X bond cleavage. Combine this observation with the high stability of the fluoride ion (for HF, ΔH_f^0 273 kJ mol⁻¹)¹² and it suggests that S_N2 displacement of fluoride might be facile. In general C-F bonds are remarkably inert, the rationalisation of this is that reaction to eliminate fluoride must overcome a large electrostatic attraction. Elongation of the C-F bond requires the separation of large partial charges, thus the reaction coordinate for C-F cleavage will have a large activation energy.

1.1.1.3 Lipophilicity

Fluorine as a substituent can be viewed as a "polar hydrophobic" functional group.¹³ Similarly to their hydrocarbon parents, fluorocarbon compounds have negative entropies of solvation, driven by the formation of ordered hydrogen bonding networks around their surfaces to maintain hydrogen bond contacts. Solvation enthalpies for such molecules tend to be small, and the net effect of this is to cause phase separation and low solubility in water – the hydrophobic effect. Fluorinated molecules have larger apolar van der Waals surfaces relative to hydrocarbons and therefore the introduction of perfluorinated moieties in a molecule is expected to decrease aqueous solubility and increase the LogD value - the \log_{10} of the ratio of concentration of a compound in octanol to the concentration in water buffered at a specific pH (typically 7.4, physiological pH). LogD is an important property to modify in drugs or agrochemicals, if a molecule has too low a value (too water soluble) then it is unlikely to be able to cross lipid bilayers to reach intracellular targets, and will be excreted readily. If LogD is too high (very lipophilic molecules) then solubility may be too low for the molecule to be absorbed into the body, toxicity for these molecules also tends to be problematic as they are both retained longer by the body and are more likely to be subject to metabolism to create toxic metabolites.

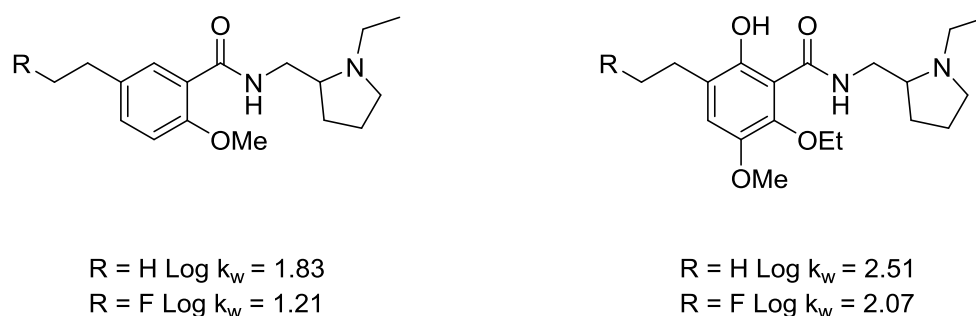


Figure 2: Fluorination of Apolar Positions to Decrease Lipophilicity¹⁴

The change in lipophilicity on introduction of fluorine into a molecule is more complicated than simply increasing lipophilicity with the introduction of each fluorine atom, in contrast to other halogens which invariably increase lipophilicity. For perfluorinated groups such as SF_5 , OCF_3 , SCF_3 , pentafluoroethyl and larger groups, the dramatic increase in hydrophobic surface area will always lead to an increase in hydrophobicity with their introduction, offsetting any other effects.

However, the introduction of smaller groups, even CF_3 , can increase polarity depending on the molecular environment in which they are introduced. Examples of the introduction of fluorine increasing polarity are found in environments where the polarity of the environment into which fluorine is introduced is low. By way of example the matched pairs of molecules in Figure 2 show a reduction in capacity factor $\log k_w$ (a proxy measurement for lipophilicity based on reverse phase HPLC retention times) from the addition of a single fluorine atom.¹⁴

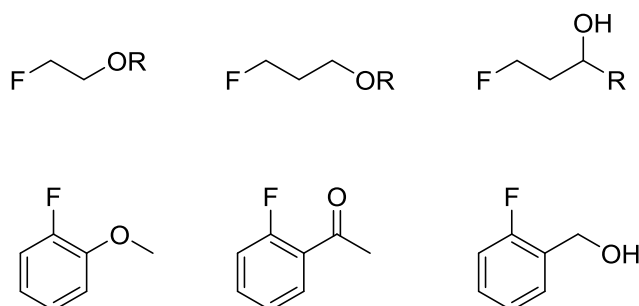
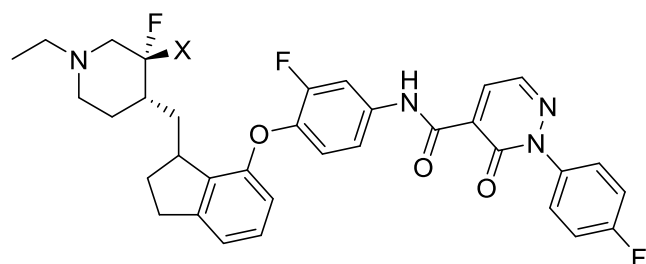


Figure 3: Substructures with Decreased Lipophilicity on Fluorination³

Fluorination of positions near to polar functional groups can also have the effect of reducing lipophilicity: the structures shown in Figure 3 are substructures which have shown a decrease in lipophilicity on moving from the hydrogen substituted analog to the fluorinated motif shown. In all these cases there is a polar functionality in close proximity to the fluorine atom. It is proposed that the introduction of fluorine can have effects on the conformation of these molecules, increasing the overall molecule polarity, thereby increasing interaction with polar solvents. An alternate explanation is that fluorine substituents tend to polarise the oxygen atoms, leading to greater polarity of these functional groups and stronger hydrogen bonding, increasing water solubility.³ The net effect of fluorination on lipophilicity is thus difficult to predict, and is strongly dependent on the molecular environment into which fluorine is introduced.

1.1.1.4 pKa Modification

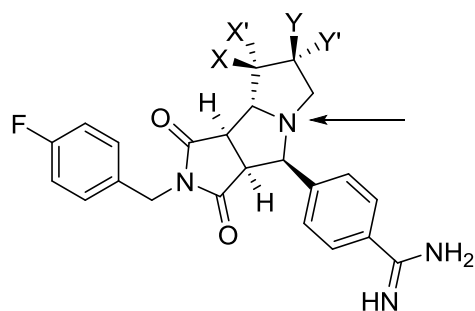


X = H; GEN-203, pK_{aH} 7.5, CLogP 4.3

X = F; GEN-890, pK_{aH} 5.9, CLogP 5.2

Figure 4: Effect of Fluorination on pKa: GEN-203 / GEN-890¹⁵

The large inductive effect of fluorinated substituents leads to significant pKa modification of proximal amines and alcohols. This effect can selectively modify the pKa of amines to give the best molecular properties for the application required. The reduction in pKa by β -fluorine substitution can be highly significant. For the pair shown in Figure 4 of GEN-203 (a Met inhibitor) and GEN-890 the pK_{aH} decreases from 7.5 for the monofluorinated compound to 5.9 for the difluorinated analog. GEN-890 was prepared as an analog with the intention to minimise tissue accumulation by pKa modification to increase drug plasma concentration and thus patient exposure. The decrease in pK_{aH} thus achieved also tends to increase the lipophilicity of the compound by disfavouring ionisation of the amine.



Entry	X, X'	Y, Y'	pKa ^a	CLogP	LogD
1	H, H	H, H	4.5	2.0	-1.2
2	F, H	H, H	3.4	2.1	-1.3
3	H, F	H, H	3.3	2.1	-1.2
4	F, F	H, H	< 2	2.3	-1.3
5	H, H	F, H	3.3	2.0	-1.6
6	H, H	H, F	3.3	2.3	-1.4
7	H, H	F, F	< 2	2.3	-1.0

Table 2: pKa Variation With Fluorine Scanning a) pKa_H for the basic nitrogen marked on structure, amidine pKa data are not shown.¹⁶

An increase in lipophilicity is not always observed with changes in pKa. In a study of a number of fluorinated analogs of a thrombin inhibitor it was noted that for molecules bearing more fluorine atoms the pKa followed the expected trends for the fluorination of small heterocycles (Table 2).¹⁶ Lipophilicity increased compared to the parent molecules when examined by CLogP. Examination of the LogD values showed the opposite effect, with the fluorinated molecules being less lipophilic. This underlines that the prediction of the effects of fluorination on lipophilicity is not always straightforward. The high polarity of this compound series leads to very polar molecules, and as such the differences in lipophilicity parameters for this system are small in comparison to other systems, even with the large differences in pKa recorded (an average of more than 1 pKa unit per fluorine).

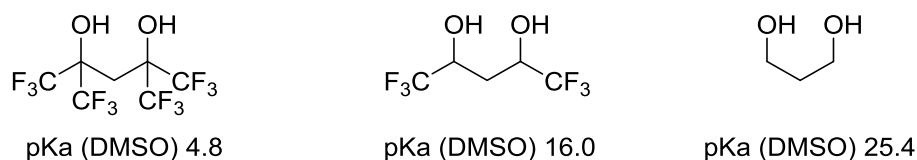


Figure 5: Effect of Fluorination on Alcohol pKa¹⁷

The pKa of a typical unfluorinated alcohol is >14 but multiple fluorine substitution can lead to significant changes in pKa, for example in trifluoroethanol (12.5 vs 15.9 for EtOH¹⁸ in water).

This also moderates the interactions of alcohols as H-bond donors and acceptors. A study of a range of oligofluoro polyols (Figure 5) shows the significant effects that can be realised by multiple fluorine substitution, providing a highly lipophilic acid which the authors proposed to be relevant to catalysis. The degree of fluorination required to achieve these large modifications of pKa is much larger for alcohols than for amines.¹⁷

1.1.1.5 Intermolecular Interactions

The presence of a high partial charge on fluorine would suggest that fluorine would be a good donor atom and acceptor of hydrogen bonds, and indeed fluoride ions form very strong hydrogen bonds. There is some evidence for fluorine-hydrogen bonding in the solid state, but due to the relative strengths of hydrogen bonds to fluorine versus those to oxygen or nitrogen (2-3 kcal mol⁻¹ to > 5 kcal mol⁻¹),¹⁹ competition between H-bond donors makes solution state fluorine-hydrogen bonding very rare. The poor H-bond acceptor ability is due to the lone pairs on fluorine being poor donors as they are contracted due to the electronegativity of fluorine.

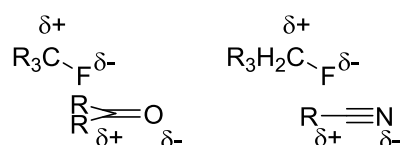


Figure 6: Dipolar Interactions of C-F Bonds²⁰

The dominant interactions of fluorine moieties for increasing binding energy are dipolar interactions; as previously mentioned, the C-F bond has a significant dipole moment, with a large δ^- on fluorine. There is evidence for interaction of C-F bonds with δ^+ centres in ligand binding; one of the most common interactions is that with a carbonyl group, with the C-F bond aligned roughly along the Burgi-Dunitz trajectory (Figure 6).

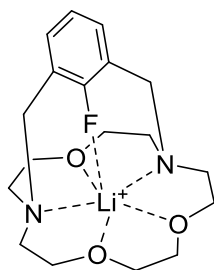
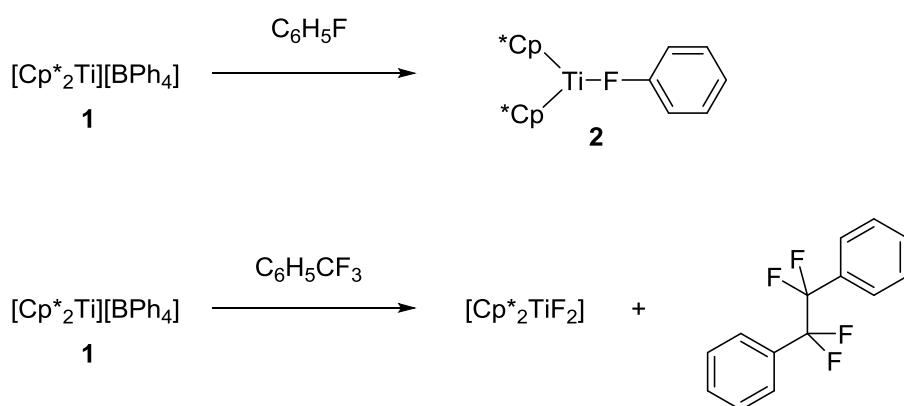


Figure 7: Fluorinated Crown Ether Lithium Complex²¹

In organometallic chemistry, fluorine can be a σ donor to metal centres; group I and II metals, transition metals and Lewis acidic complexes all coordinate to fluorine moieties. Lone pair donation as a σ donor ligand is rarely observed due to the contracted nature of the fluorine lone pairs, but it is common to see charge related interactions. For example, the fluorinated cryptand shown in Figure 7 shows a greater affinity for lithium ions than the non fluorinated parent molecule, due to the interaction between the high charge density on Li^+ and the δ^- on the fluorine.²¹



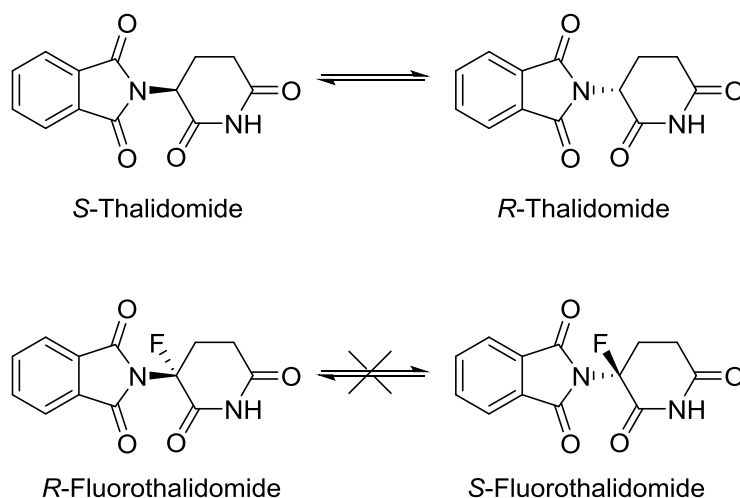
Scheme 1: Coordination of Organofluorine to Transition Metal²²

Fluorine can act as a weak donor to transition metal centres in some circumstances, but is readily displaced by superior donors. In benzene solution the cationic titanocene complex **1** will form a coordination complex with fluorobenzene (Scheme 1, eq. 1); showing a slight lengthening of the C-F bond in complex **2** relative to fluorobenzene. This complex is highly labile and will readily exchange fluorobenzene with THF. Of note for Section 1.3 on the reactivity of benzylic fluorides, reaction of complex **1** with trifluorotoluene (eq. 2) leads to complete consumption of the complex

to give the products shown, demonstrating the higher reactivity of benzylic fluorides relative to aryl fluorides.²²

1.1.1.6 Blocking of Racemisation

Racemisation by keto-enol tautomerisation of stereogenic acidic protons under physiological conditions is potentially problematic in medicinal chemistry, where one enantiomer of a racemic mixture may have drastically different biological activity. For the undesired isomer different rates of elimination and uptake may affect the ADME properties of the compound and differences in affinities for both the intended target and unintended targets can reduce the activity of the drug and increase the severity of side effects. The most often quoted example of this problem is the drug thalidomide, it was initially proposed that one enantiomer of this has sedative properties, but the other acts as a teratogen, causing severe birth defects (it has since been proposed that the toxic effects may instead be due to metabolic attack on the aromatic ring²³).



Scheme 2: Racemisation of Thalidomide²⁴

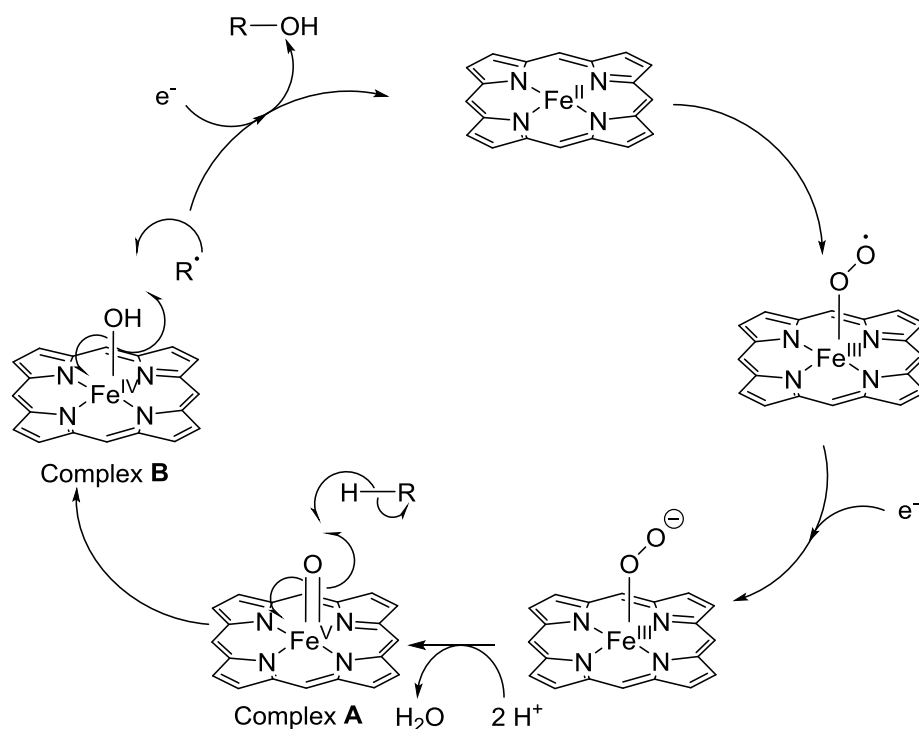
Fluorination of the α -position prevents the racemisation of chiral centres adjacent to enolates. The removal of F^+ is extremely unfavourable (in contrast to the relatively easy deprotonation under physiological conditions to remove H^+), so defluorination is only ever observed as the elimination of fluoride due to the high stability of the fluoride ion. Thus the fluorinated analog shown in Scheme 2 should be stereochemically stable. Unfortunately this molecule is hydrolytically

unstable compared to thalidomide and this made it impossible to study the differential biological activities of each enantiomer.²⁴

1.1.2 Biological Properties of Fluorinated Molecules

1.1.2.1 Alteration of Metabolic Fate

Benzylic C-H sites in drug molecules are frequently vulnerable to attack by P450 monooxidases and other enzymes. Oxidation generally gives a more polar metabolite product (which may or may not be pharmacologically active or toxic) that may either be cleared from the body as the metabolite, generally at a faster rate than the parent, or be subject to conjugation with biomolecules by other enzyme systems; conjugation invariably inhibits activity and leads to rapid clearance of drug from the blood. In order to increase drug exposure, and therefore effectiveness, it is often necessary to design structures that will have greater stability against such metabolic clearance, even at the expense of a decrease of binding affinity for drug targets.

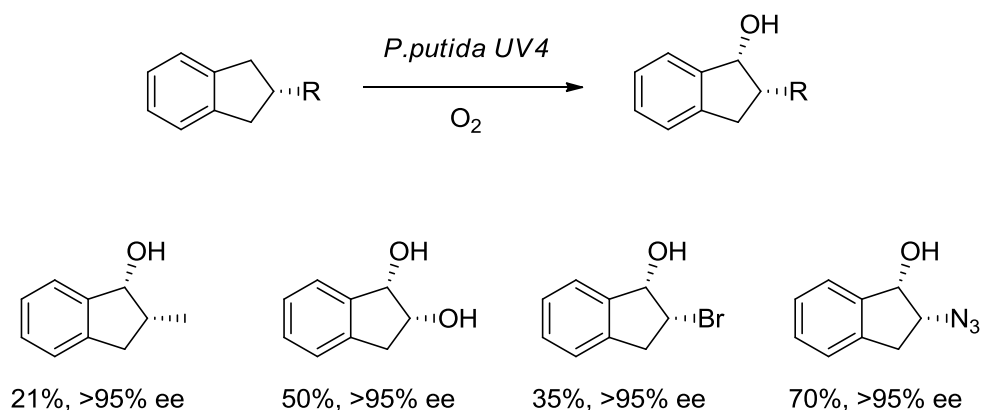


Scheme 3: Rebound Mechanism of Hydroxylation

The vulnerability of specific moieties to oxidation is explained by the mechanism of metabolism (Scheme 3). Fe(V) oxo species **A** abstracts a hydrogen atom from the site of metabolism, leaving a radical which rapidly recombines with the resulting Fe(IV) hydroxy species **B** to give net hydroxylation. The catalyst is then regenerated by the action of NADPH and oxygen. The

metabolic susceptibility of a position depends on the stability of the intermediate radical, any substituent such as an aromatic ring that stabilises radical species increases the metabolic susceptibility of a site.

Substitution of benzylic C-H bonds for C-D²⁵ or C-F bonds is a common strategy to block or attenuate this route of metabolic clearance. The increased bond strength in each case provides an increased barrier to the initial abstraction step, and for fluorine substitution the reaction is made particularly disfavoured by the requirement for the formation of an oxygen-fluorine bond, which would lead to a very high energy intermediate. Fluorinated sites are thus nearly invulnerable to oxidative metabolism, as is evidenced by the bioaccumulation of perfluorinated surfactants, which has necessitated their replacement with materials which are less persistent. In drug molecules however the introduction of smaller numbers of fluorine atoms is still very much an important strategy to improve stability, and this is particularly obvious with the exchange of benzylic methyl groups for trifluoromethyl moieties, though the resulting increase in lipophilicity and aforementioned extreme stability of this functionality are not always welcome in clinical candidates.

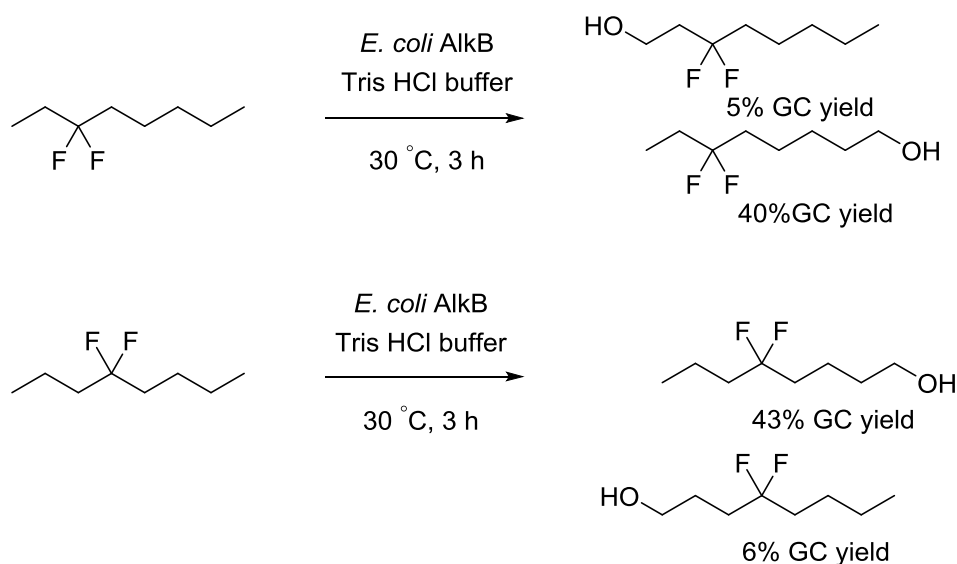


Scheme 4. Enantioselective hydroxylation of prochiral benzylic positions²⁶

As shown in Scheme 4, P450 enzymes frequently display enantioselectivity in the hydroxylation of prochiral C-H bonds due to substrate recognition.^{26, 27} Substitution of the enantiotopic C-H bond which is subject to metabolism with a C-F bond in a drug candidate might be expected to give the desired increase in resistance to metabolism but without changing drastically other

molecular properties. Conversely, the alternate enantiomer provides stabilisation through lone pair donation to a radical species at this site, so might be expected to be metabolised faster than the unsubstituted parent compound. This property could be exploited for introducing prodrug like properties to pharmaceutical entities, by directing productive oxidative metabolism.

Besides the blocking of positions liable to metabolic attack, fluorine substitution may, in molecules with multiple potential oxidation sites, change the regioselectivity of an enzymatic oxidation by perturbing the activation energy for the oxidation of neighbouring sites - generally disfavours oxidation near to fluorine relative to further away. An example of the preference of a hydroxylase for the site most distal from fluorine is shown in Scheme 5.

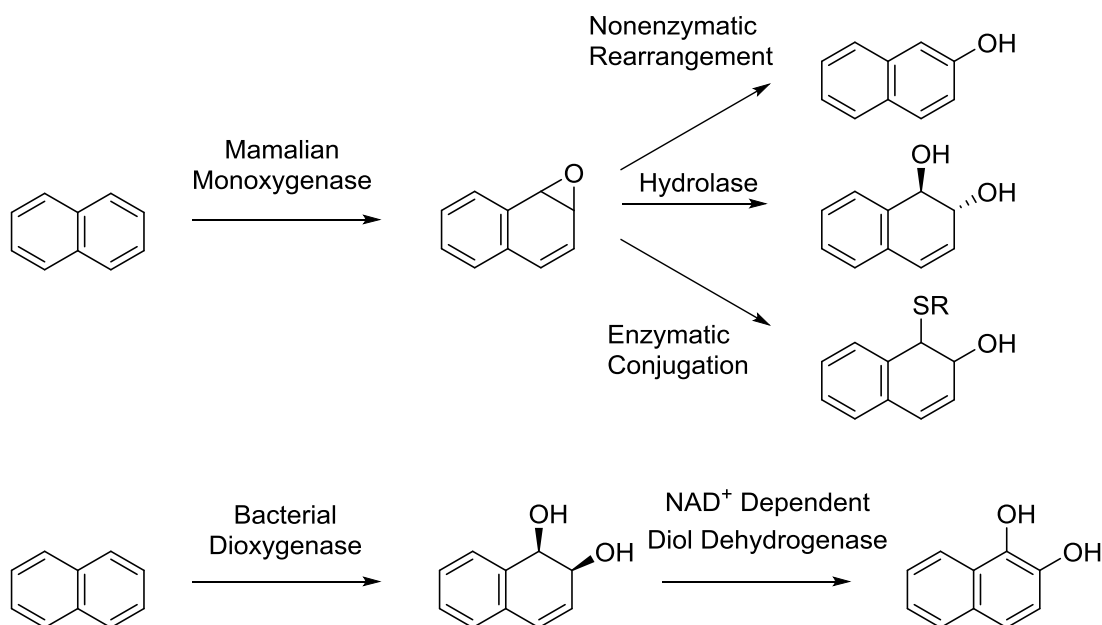


Scheme 5: Regioselective Hydroxylation Directed by Fluorine²⁸

The oxidation of a variety of difluorooctane regioisomers by a recombinant whole cell system expressing AlkB, a nonheme diiron monooxygenase which selectively oxidises unactivated terminal methyl groups, was investigated in order to provide a synthetic route to difluorinated 1-octanols.²⁸ The products observed were those of the oxidation of the methyl groups, and there was a strong preference in all cases for the methyl group most far removed from the difluoro centre. An interesting observation from this study was that the fluorinated molecule exhibited a much higher rate of hydroxylation than octane itself. The suggested reason for this is a higher K_M due to a polar hydrophobic interaction between the substrate and enzyme; the increased rate of

metabolism of molecules with greater hydrophobicity is a well known effect in medicinal chemistry.

1.1.2.2 Aromatic Ring Hydroxylation



Scheme 6: Metabolic Attack on Aromatic Rings²⁹

Metabolic attack on aromatic rings is not limited to the groups appended to rings, in fact direct attack on aromatic rings is more common and it is well known that these pathways are responsible for the toxicity and carcinogenicity of a variety of aromatic hydrocarbons e.g. benzene,³⁰ benzpyrene.³¹ The enzymes involved in these pathways are more numerous than P450 monooxidases, and a variety of different mechanisms operate, leading to a number of different possible products (Scheme 6).²⁹

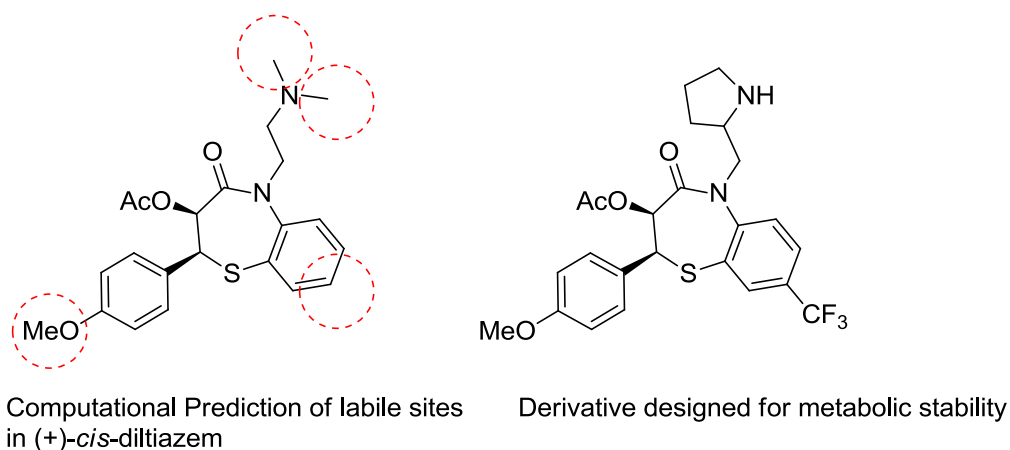


Figure 8: Designing molecules to prevent aromatic ring hydroxylation³²

Substitution of vulnerable positions by metabolically inert substituents, or remote substitution by deactivating groups are common strategies for reducing this class of metabolic processes. From the large amount of accumulated data on the metabolism of xenobiotics it is possible to make predictions about the metabolic susceptibilities of target molecules, based on the electronic and steric influences on a position in a molecule and the known substrate specificities of the members of the P450 superfamily of hydroxylases. The metabolism prediction of a compound is shown in Figure 8, along with the suggested structural modifications to prevent metabolism at vulnerable positions. The metabolic predictions are for the hydroxylation proximal to heteroatoms and the oxidation of an electron rich aromatic ring. Of note from the fluorine chemistry perspective is the use of a fluorinated substituent on the ring to prevent oxidation of the adjacent position – the CF_3 group is both metabolically inert and has some steric influence to inhibit the approach to enzyme active sites.³²

The vulnerability of aromatic rings to oxidative attack is due to the high electron density of aromatic rings, with electron withdrawing groups (CF_3 , CO_2Me , etc.) having protective effects on the metabolism of adjacent π -systems. Fluorine substituents are often favoured for this role as they are themselves generally inert (*c.f.* the potential enzymatic hydrolysis of an ester functionality or reduction of nitro groups).

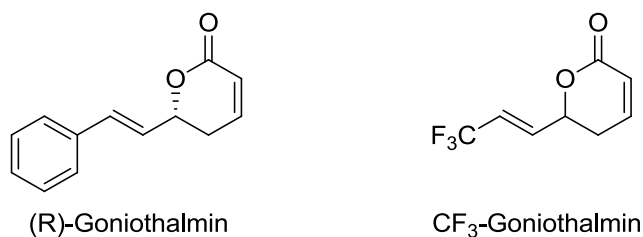
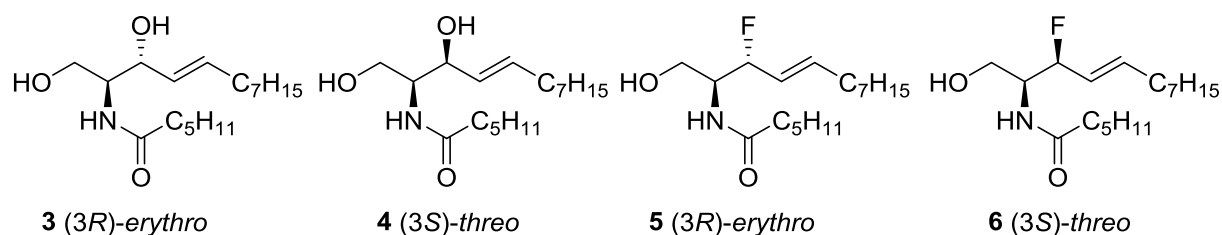


Figure 9: Deactivation of a π System Towards Epoxidation³³

Goniothalmin (Figure 9), a secondary metabolite from the *Goniothalamus* genus, shows antiproliferative activity against cancer cell lines *in vitro*, but in mouse studies proved to have genotoxic and embryotoxic effects. These effects were thought to be due to the metabolic epoxidation of the *trans* double bond to give a known natural product from a member of the same genus that shows abortifacient properties.³⁴ By replacement of the phenyl group with a trifluoromethyl group it was possible to protect the double bond from epoxidation under simulated metabolic degradation. This modification would appear to be a non conservative change from a steric and electronic effect, but the resulting compound maintained much of the cytotoxic activity of the parent against cancer cell lines.³³ This example is a demonstration of the use of fluorine to deactivate a π system towards metabolic attack, and this can be generalised to aromatic rings, both with ring and side chain fluorination.

1.1.2.3 Isosteric Motifs

The use of fluorine as an isosteric replacement for hydrogen or hydroxyl groups is based on the size similarity of the fluorine atom to these groups, with a good match to hydroxyl and slightly larger than hydrogen. This steric match enables the investigation of the effects of modifying polarity without significant changes of steric properties, or the effect of removing hydrogen bond donors whilst maintaining an electron withdrawing effect on the position substituted in the case of a switch with a hydroxyl group.



Compound	% apoptotic cells in MOLT Leukaemia cells	% apoptotic cells in K- 422 lymphoma cells
3 3R OH	3.5	12.5
4 3S OH	1	33
5 3R F	11	35
6 3S F	14	51

Table 3: Apoptogenic Activity of Fluorinated Ceramides³⁵

The replacement of the hydroxy group in ceramides by fluorine was attempted in a direct effort to determine the difference in biological activities on making an “isosteric” change.³⁵ The fluorinated compounds demonstrated increased apoptotic activity against a range of different cell lines, including cancer cell lines. This effect was observed in both *threo* and *erythro* series, with the observation that the difference between the apoptogenic activity of the diastereoisomers was decreased in the fluoro series; for both the hydroxyl and fluorine compounds the 3R compound is significantly less active, however for the fluorinated series the apoptogenic activity of the less active 3R isomer is better than the activity of the 3S OH isomer. This suggests that for ceramide apoptogenic activity, the hydrogen bonding capability of the hydroxy group is not critical, but the inductive effect of an electron withdrawing group does contribute to activity; the smaller difference in activity between *erythro* and *threo* in the fluorinated series can be explained by the larger inductive effect of fluorine relative to the hydroxyl.

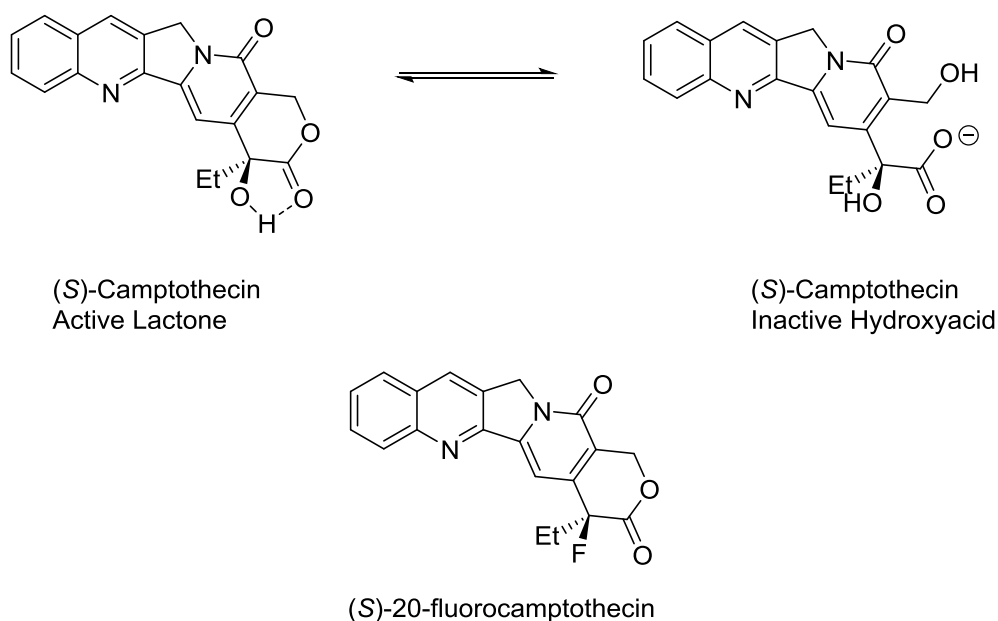
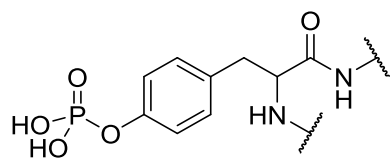
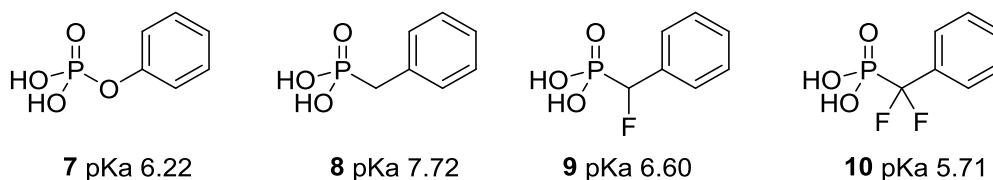


Figure 10: Replacement of 20-Hydroxyl Group in Camptothecin: Role of OH in Activity & Hydrolysis³⁶

The use of fluorine substitution for isosteric replacement of hydroxyl groups allows for the investigation of the role of the substituted group in the activity of a molecule under investigation. For example, camptothecin is a quinoline alkaloid inhibitor of topoisomerase I which was investigated as an anticancer agent leading to the development of several drugs based on the same quinoline core. The 20-hydroxy group was shown to be critical to activity in structure-activity relationships, but was hypothesised to accelerate the hydrolysis of the lactone ring by intramolecular hydrogen bonding. The synthesis of both isomers of the 20-fluoro derivative enabled the testing of this hypothesis. The *S* enantiomer gave essentially no activity, as was the case in the non fluorinated series, and the *R* enantiomer exhibited significantly lower activity (100-1000 fold less potent) towards topoisomerase I. Both compounds had significantly shorter half lives than the hydroxy analog. This allowed the confirmation of two design features of molecules of this drug class: firstly a hydrogen bond donor/hydroxyl was crucial for activity; secondly the hydrolytic instability of the lactone core is intrinsic and likely due to the inductive effect of the hydroxyl.



Phosphorylated Tyrosine Residue

**Figure 11: Phosphorylated Tyrosine Residue Mimics**³⁷

The replacement of an oxygen linkage by a carbon spacer is an isosteric strategy used to increase hydrolytic stability in molecules, particularly in highly labile molecules. The series of molecules in Figure 11 are tyrosine mimics. This class of molecules contains members that act as inhibitors of protein tyrosine kinases and phosphotyrosine phosphatases, and as such they are of significant interest in the study of biochemical pathways. The use of phosphonic acids instead of phosphate esters does however lead to lower affinity for the enzyme targets than the native substrates. The causes for this are suggested to be both the higher pKa of the acid, and the removal of a hydrogen bond acceptor in a position that may interact with the enzyme. The replacement of a CH₂ linker by a CF₂ linker to give **10** gives a molecule with a pKa similar to the parent phosphate **7**.³⁷ The monofluoro compound **9** gives a better match to the pKa of the original compound, but this introduces a stereocentre and thus tends to be avoided in medicinal chemistry to remove complexity from synthetic routes.

1.2 Synthesis of Benzylic Fluorides

The synthesis of benzylic fluorides suffers, as with all fluoroorganic chemistry, from the poor properties and difficulties of usage of fluorinating reagents; the difficulty of direct fluorination of complicated molecules leads to a variety of strategies being employed in their synthesis: early stage fluorination to allow for better selectivity, followed by elaboration; the construction of aromatic rings from fluorinated precursors; and the late stage selective fluorination of prefunctionalised precursors. Fluorination methods can be nucleophilic, electrophilic or radical in nature, though there is some overlap between electrophilic and radical reactivity.³⁸ An emerging area in fluorine chemistry is the metal catalysed fluorination of aromatic and aliphatic positions using a variety of different sources of fluorine, both electrophilic and nucleophilic. These will be considered separately from the other methodologies as it is informative to later chapters to address these as their own class of reactions. “Building Block” strategies, where a fluorinated precursor is elaborated to give a benzylic fluoride product, will also be considered separately from the direct fluorination methodologies. C-F cleavage reactions of benzylic fluorides are covered in the next section, although some of these methodologies produce fluorinated molecules they are not generally synthetically useful reactions and as such are not considered here.

For both fluorination and building block approaches, enantioselective synthesis of benzylic fluorides is challenging, with the few routes existing providing variable enantioselectivities or exhibiting poor substrate scopes. As mentioned in the previous section, the enantioselective synthesis of potential drug molecules is crucial for the approval of new drugs to ensure potency and to minimise the potential for side effects, and as such enantioselective syntheses of benzylic fluorides are potentially highly valuable reactions to pursue.

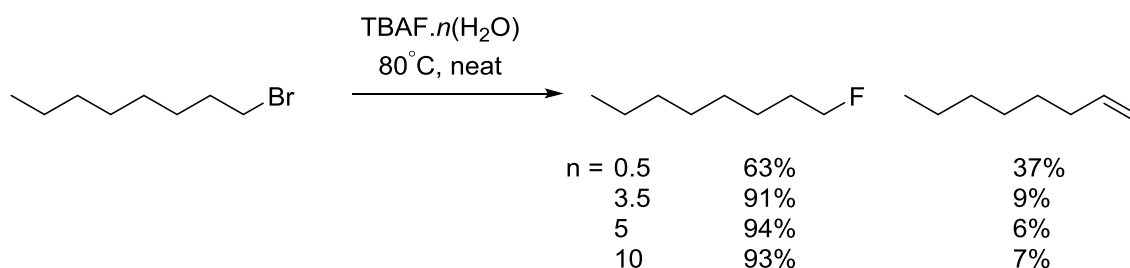
1.2.1 Nucleophilic Fluorination

Nucleophilic fluorination relies either on HF, a fluoride salt, or the *in situ* generation of fluoride by a parent reagent. The economic advantages of nucleophilic fluorination have led to a proliferation of methods and reagents for the introduction of fluoride. The use of hydrofluoric acid requires specialist equipment, can use very harsh conditions, and poses significant toxicity risks, so whilst this is the lowest cost source of fluoride ions, fluorine chemists have developed methodologies that either avoid the use of HF entirely, or use safer forms of it (e.g. triethylamine *tris* hydrogen fluoride, which can be used in normal glassware). Fluoride salts are another cost effective option for simple displacement reactions, but their poor solubility and reactivity means that they often require high temperatures to effect reactions. Reagents which generate fluoride *in situ* often give better reactivity as fluoride is generated in the absence of water and metal counterions, but these tend to be limited in their general applicability (*vide infra*).

Metal fluoride sources tend to be cheap and available, and have sufficiently good handling properties to not require specialist equipment. There are several problems with this class of reagents, most notably reactivity and solubility, though these are highly connected problems and solutions to one problem often solve the other. The small size and high charge density of fluoride are the root cause of both - the reactivity of fluoride as a nucleophile is poor due to its hardness, causing displacement reactions to proceed only slowly, despite the large enthalpic driving force for C-F formation, whilst the high charge density makes fluoride highly basic, leading to side reactions, most often E2 elimination to give an alkene. The high charge density of fluoride makes the lattice enthalpies of metal salts high, disavouring dissolution of fluoride, limiting the availability of the reagent for reaction.

The use of reagents that improve the solubility of fluoride can have dramatic effects on the reactivity of fluoride. To improve the solubility requires an additive to stabilise one or both components of the salt in solution. A lipophilic cation can be used or the metal cation can be stabilised by coordination/encapsulation. An alternate approach is to use hydrogen bonding

additives to solubilise the fluoride ion. A hydrogen bonding coordination environment around fluoride can support nucleophilic reactivity and reduce basicity.



Scheme 7: Fluorination of Alkyl Bromides - the Effect of Added Water³⁹

The most common fluoride reagent in synthetic chemistry is tetrabutylammonium fluoride (TBAF). This is supplied as either a hygroscopic solid or as a solution in THF, it is non toxic and easily used as a source of fluoride, mainly in the removal of silyl protecting groups. The usefulness of TBAF starts to reach its limit in the formation of C-F bonds, due to its moderate nucleophilicity and tendency to form alcohol byproducts due to the water that stabilises the reagent; the commercial material is a *tris*-hydrate, and any attempt to remove water from the TBAF leads to decomposition of the tetrabutylammonium cation by Hoffman elimination (drying of fluoride sources in general is difficult due to the high hydration enthalpy of fluoride ions $\Delta H_{\text{hydration}}$ is calculated at $\sim 480 \text{ kJ mol}^{-1}$). For some fluorination reactions the presence of water is not a problem and in fact, for the fluorination of alkyl bromides,³⁹ it has been shown that the hydration of fluoride can be beneficial to reactivity, with dried TBAF leading to significantly more elimination than TBAF with up to 10 equivalents of water (Scheme 7). These results would appear to suggest that water contamination is not problematic for TBAF fluorinations, however the alkene remains a persistent byproduct, and furthermore application of this methodology to different substrates, such as benzyl bromide, leads to significant alcohol formation (10%) along with the desired product (90%). Notably, this methodology also performs poorly for secondary substrates.

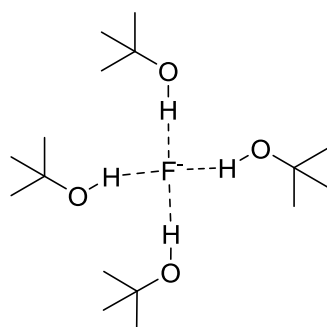


Figure 12: *Tert* butanol Coordinated Fluoride⁴⁰

Efforts to utilise TBAF in anhydrous conditions have provided several practical methods for reducing alcohol byproduct formation, as well as enabling reactions that were previously not possible with fluoride. Perhaps the most useful example is the *tert*-butanol coordinated fluoride developed by Kim *et al.*,⁴⁰ where commercially available TBAF.3.5 H₂O is refluxed in hexane/*tert*-butanol solution for 1h, on cooling the *tetrakis tert*-butanol complex of TBAF crystallises and can be easily collected and dried. This storable reagent acts as an anhydrous source of fluoride, and because of the hydrogen bonding provided by the alcohol (Figure 12) the reactivity of the fluoride is enhanced relative to its basicity. There is no detectable alcohol byproduct in fluorinations conducted with this reagent, though small amounts of ether may be formed in alcoholic solvents. Interestingly, this fluoride source appears to act to deprotect silyl protecting groups at a much reduced rate relative to TBAF hydrate, possibly due to the maintenance of a hydrogen bonding network in solution. The rate of consumption of starting material in a fluorination reaction is however very similar.

Insetad of the use of a lipophilic counterion, several options exist to enable the use of metal fluorides, either by making the cation more soluble in the organic phase or by using ionic liquids which can dissolve these salts better than traditional solvents. In a similar manner to the use of isolated *tert*-alcohol coordinated TBAF, *tert*-alcohol solvents can mediate fluorination with MF salts, but reactivity is generally lower.⁴¹

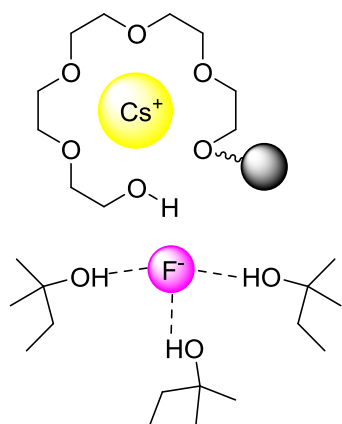


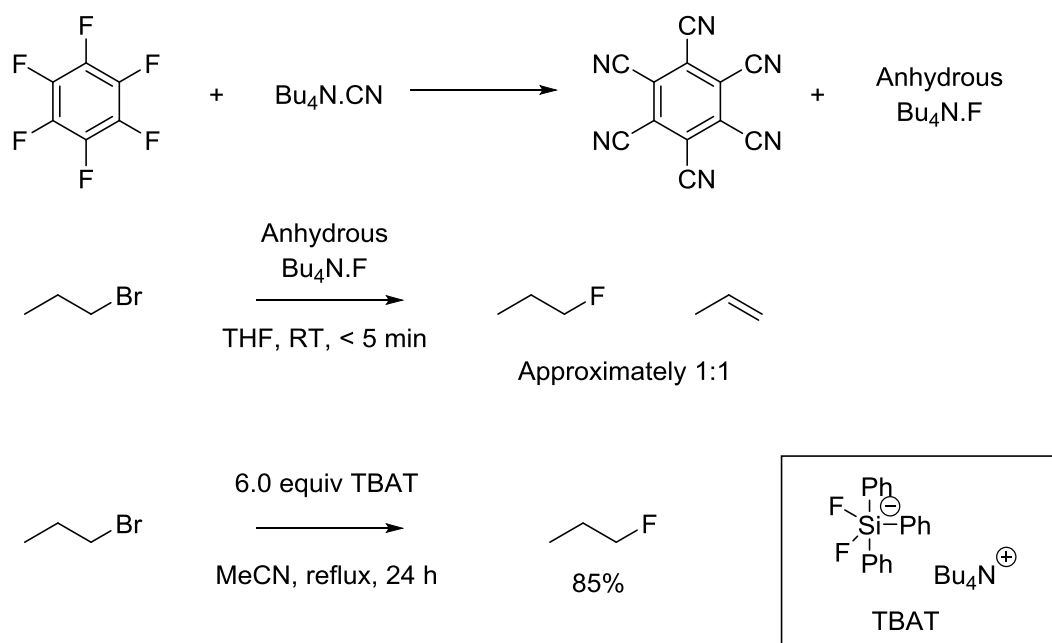
Figure 13: Solid Phase Ethylene Glycol Fluorination Catalyst⁴²

An interesting approach for the activation of metal fluorides is the use of heterogeneously supported pentaethylene glycol as an activator for CsF.⁴² The concept of "flexible fluoride" explains some of the reactivity differentials between various fluoride sources - this states that fluoride sources which are nucleophilic and non basic tend to have a flexible hydrogen bonding network surrounding the fluoride. This concept was applied to create a crown ether like catalyst with a terminal free hydroxyl group (Figure 13) - this was postulated to bind Cs⁺ and provide a hydrogen bond contact for F⁻, and indeed this catalyst is superior to that with a terminal methoxy group.

The demands of positron emission tomography (PET) for rapid and reliable synthesis of small molecules bearing an ¹⁸F label have led to development of highly effective methods for the displacement of leaving groups under radiochemical conditions employing picomolar quantities of ¹⁸F - the standard methodology is to use an ion exchange column to produce radioactive KF, which is then complexed by a cryptand ligand, Kryptofix. This encapsulates the potassium cation, solubilising the salt and providing highly reactive "naked" fluoride for rapid fluorination. The advantage of Kryptofix over the more common and cheaper 18-crown-6 is the higher affinity for the potassium cation, leading to better reactivity.

Reagents which generate fluoride *in situ* have been highly successful in the synthesis of fluorinated molecules. Due to the extreme properties of fluorine, molecules bearing multiple fluorine substituents can be highly electrophilic and will react with nucleophiles to liberate "free",

or unsolvated, fluoride which is highly reactive in comparison to the salts discussed above. Examples of this approach involve high valent sulfur fluorides such as the family of reagents based on aminosulfur trifluorides (covered in the section on deoxyfluorination), the S_NAr substitution of hexafluorobenzene with cyanide, hypervalent iodine difluoride reagents and amines bearing perfluoroalkene groups. These reagents are not without their own problems, frequently being moisture sensitive, and presenting explosive or toxicity hazards. However the high reactivities available and reliability of this approach has ensured that reagents of this class are widely used in the synthesis of organofluorine molecules.

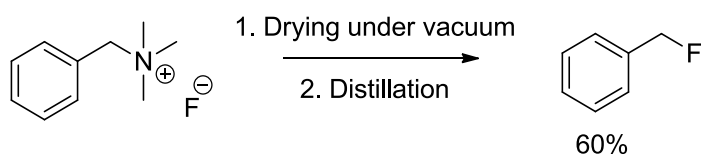


Scheme 8: S_NAr to Generate Anhydrous TBAF, Reactivity of Anhydrous TBAF⁴³

"Truly anhydrous TBAF" is an *in situ* generated reagent based on the substitution of hexafluorobenzene with tetrabutylammonium cyanide (Scheme 8).⁴³ The advantage of this reagent combination is that the starting reagents and solvents can be easily dried to ensure anhydrous conditions, and once the reaction to generate fluoride has reached completion the hexacyanobenzene product of this reaction is able to react with residual water, ensuring the reaction conditions remain strictly anhydrous. The absence of coordinating solvent means that this "naked" fluoride source is highly reactive, with fluorinations reaching full conversion very quickly in comparison to alternate reagents. For example, in the fluorination of benzyl bromide,

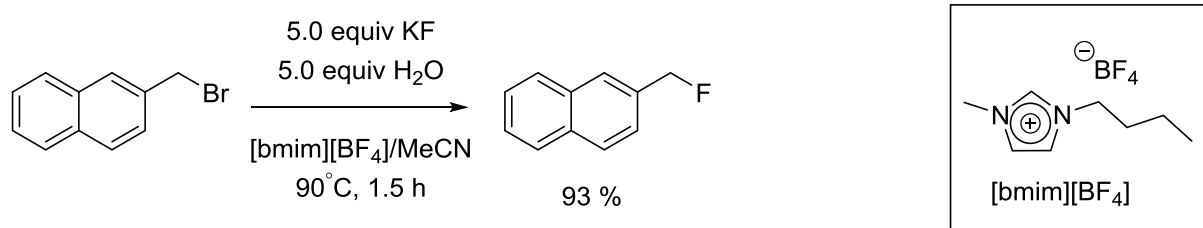
full conversion is achieved in < 5 min at -35 °C versus 8 h at RT (Scheme 8). This source of fluoride is however very basic, as demonstrated by the reaction of this reagent with propyl bromide – with tetrabutylammonium triphenyldifluorosilicate (TBAT) this reaction reaches 85% conversion to fluoride, but with anhydrous TBAF approximately half of the material is isolated as the alkene.

1.2.1.1 Displacement of Leaving Groups



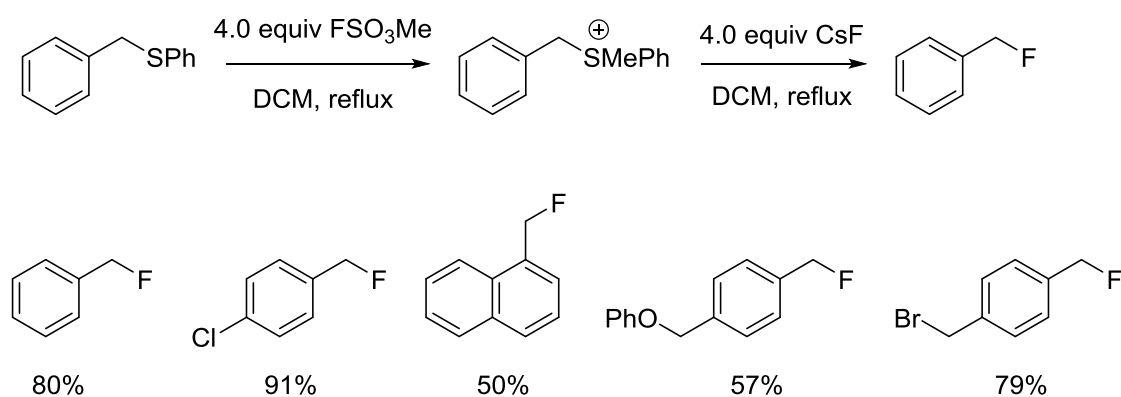
Scheme 9: First confirmed synthesis of benzyl fluoride⁴⁴

The pioneer synthesis of benzyl fluoride proved more difficult than those of the other benzyl halides (completed in: BnCl 1859, BnBr 1866, BnI 1875). The first unambiguous synthesis was successfully achieved by the thermolysis of benzyltrimethylammonium fluoride salts by Ingold and Ingold in 1928 (Scheme 9).⁴⁴ On heating of benzyltrimethylammonium fluoride the leaving group (either trimethylamine or dimethylbenzylamine) is displaced and the benzyl fluoride product could be isolated in good yield by distillation. The methodology developed proved to be limited to the synthesis of benzyl fluoride and, via nitration of this intermediate, isomeric mixtures of nitrobenzyl fluoride. A further more general historical procedure is the Br/F exchange of benzyl bromides with HgF₂ in chloroform.⁴⁵ The high toxicity of this reagent makes this a similarly undesirable method for the synthesis of benzylic fluorides. This reaction tolerated substituents at all ring positions; methyl, fluoro, chloro, bromo, iodo and nitro substituted substrates all reacted successfully to produce the corresponding fluorides, all of which were isolated in 40-60 % yields; the recovered yield could not be improved upon as the fluorides were unstable towards distillation.

Scheme 10: Ionic Liquid as Solvent for Fluorination⁴⁵

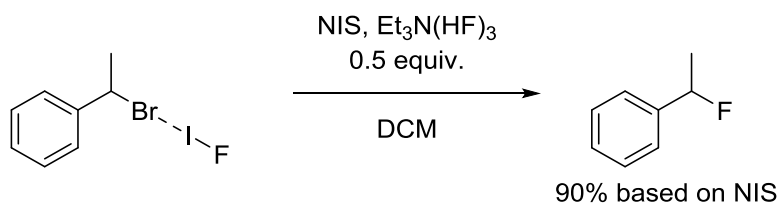
The difficulty of preparing benzylic fluorides by nucleophilic displacement is due to the poor nucleophilicity of fluoride, particularly in the presence of water, as mentioned in the previous section. TBAF *tert*-butanol is a convenient and safe reagent for the preparation of primary benzyl fluorides (*vide supra*). Alternatively, it is possible to use metal salts solubilised in an ionic liquid to effect this transformation (Scheme 10),⁴⁶ this methodology gives significant gains in reactivity, but the high cost of the ionic liquids dissuades greater use of this methodology.

1.2.1.2 Activation of Leaving Groups Under Reaction Conditions

Scheme 11: Activation of a Masked Phenylthio Leaving Group⁴⁶

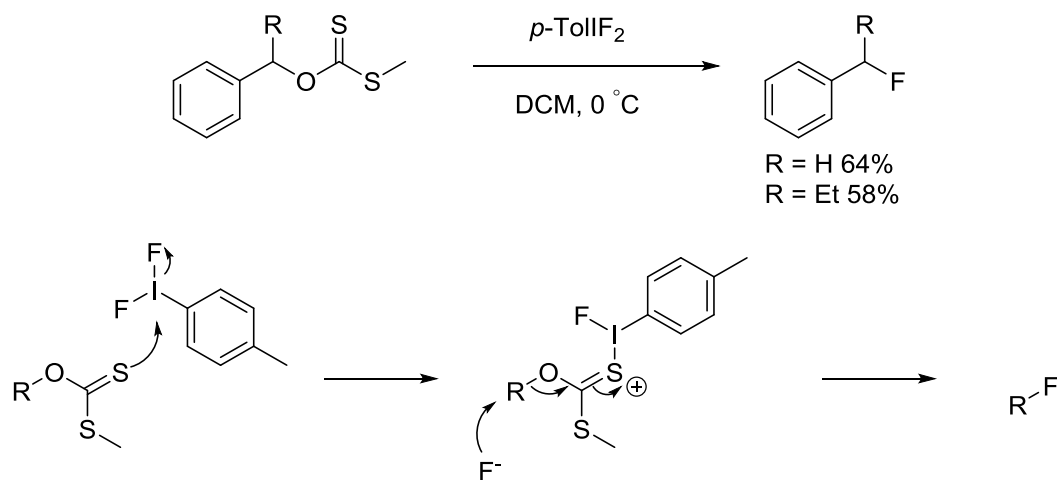
As mentioned previously, the poor reactivity of fluoride in nucleophilic fluorination requires highly activated precursors to ensure good yields of the desired product. This is problematic in that highly activated precursors are both likely to be unstable to prolonged storage and to synthetic manipulations, so that fluorine substitution has to be performed early in a synthesis, or with a step immediately prior to fluorination to introduce a leaving

group. The use of a masked leaving group gives some resolution to this dual problem - the installation of an unactivated group, stable to storage and tolerant of a range of reaction conditions allows the point of fluorination in a synthesis to be varied. One such method is the use of a phenylthio group;⁴⁷ on methylation of this group by a strong electrophile (FSO_3Me) the group becomes an excellent leaving group, yielding benzylic fluorides upon the addition of CsF in a one pot procedure (Scheme 11).

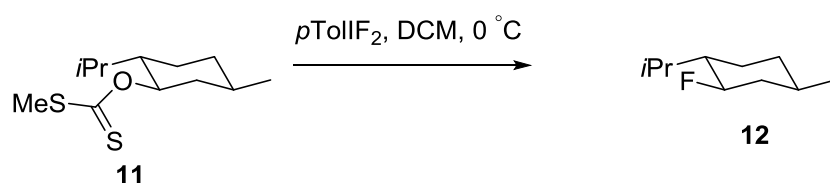


Scheme 12: NIS Promoted Substitution of Secondary Benzylic Bromides⁴⁸

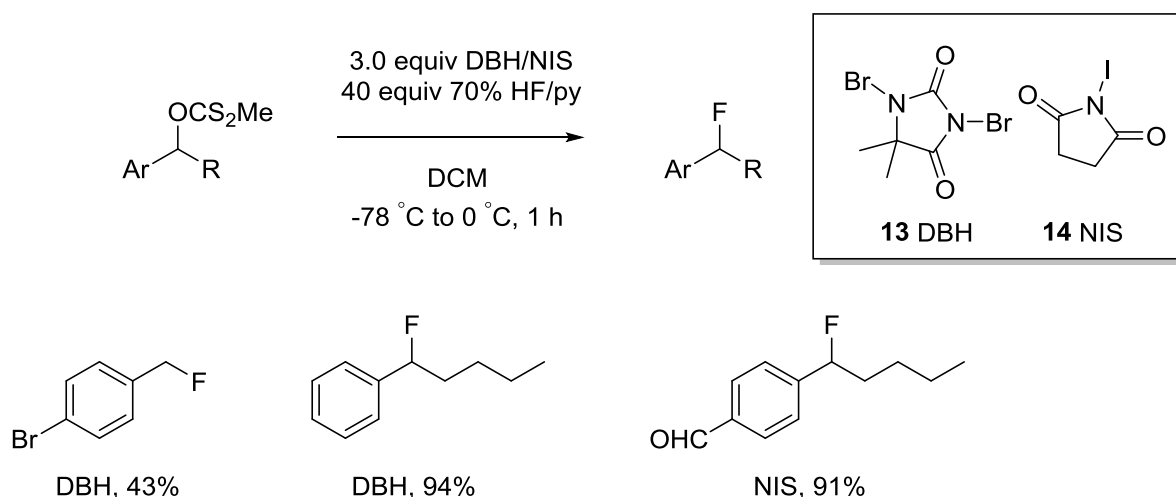
The use of leaving group activation is particularly useful in the synthesis of secondary benzylic fluorides. These are generally poorly accessible by nucleophilic exchange, due in large part to the propensity of fluoride to act as a base and promote elimination rather than fluorination. Iodine fluoride, generated *in situ* by the reaction of NIS and HF, serves to activate the leaving group as well as providing a nucleophilic source of fluorine (Scheme 12).⁴⁸ This approach gives no control of the enantiomeric purity of the product obtained, and it is difficult to imagine any enantioselective variant of this chemistry.

**Scheme 13: Fluorination of Xanthate Esters**⁴⁹

A conceptually related reaction is the reaction of xanthate esters with an oxidant and a fluoride source. The preliminary report of this chemistry utilises 4-methyl(difluoroiodo)benzene as both oxidant and fluoride source.⁴⁹ This reaction similarly relies on the activation of a leaving group by an electrophilic reagent, fluoride then attacks the activated intermediate species to give a fluoride product (Scheme 13). Moderate yields are achievable for even unactivated alkyl systems due to the mild nature of the reaction, with the main observable byproduct being the alkene; the reaction proceeds with predominant inversion of stereochemistry, albeit with significant erosion of stereochemical information.

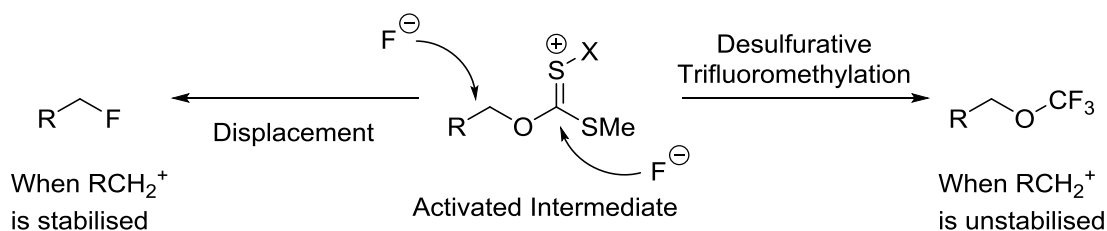
**Scheme 14: Stereochemical Outcome of Desulfurative Fluorination**⁴⁹

The adaptation of this reaction to the synthesis of benzylic fluorides is limited to two examples from the initial report, with both primary and secondary fluorides accessible in reasonable yield. Unfortunately there was no investigation into the stereospecificity of displacement at a benzylic centre. The reaction of menthol derivative **11** (Scheme 14) gives the product **12** corresponding to retention of configuration. DAST also gives retention of configuration with a $\text{S}_{\text{N}}1$ mechanism, so no conclusions about stereospecificity can be drawn from this observation.



Scheme 15: Benzylic Fluorination of Xanthates by Oxidant/HF⁵⁰

The fluorination of xanthate esters can also be achieved by the use of separate oxidant and fluoride sources. Reagent combinations have been reported with either 1,3-dibromo-5,5-dimethylhydantoin (**13**, DBH) or *N*-iodosuccinimide (**14**, NIS) as oxidant and 70% HF/pyridine solution as fluoride source (Scheme 15).⁵⁰ These reagent combinations have been demonstrated on more functionalised molecules and generally provide better yields than the iodotoluene difluoride reagent. For substrates which are less able to stabilise a positive charge at the position of fluorination, the predominant product is the trifluoromethyl ether resulting from desulfurative fluorination of the xanthate (Scheme 16).



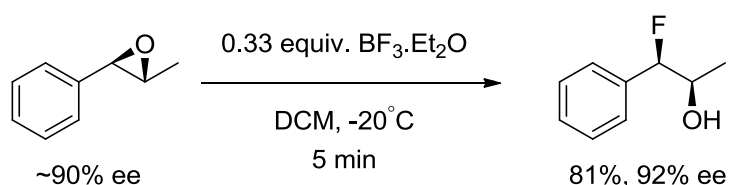
Scheme 16: Chemoselectivity in Fluorination of Xanthate Esters⁵⁰

This observation supports the authors' suggestion that the reaction proceeds via a cationic mechanism for fluorination, and thus substrates that can stabilise a positive charge, such as benzylic xanthate esters, will favour the fluoride over the trifluoromethyl ether. This suggests that

the use of this methodology is not suited to the preparation of enantiomerically pure benzylic fluorides.

Similarly to the use of pTolIF₂ (Scheme 14) the use of this reagent combination (70 % HF-py / NIS) on a menthol derivative gives the fluoride with retention of configuration. However, cationic dissociative mechanisms also favour the diastereomer formed in their reaction, so this does not constitute good evidence for a stereochemical pathway

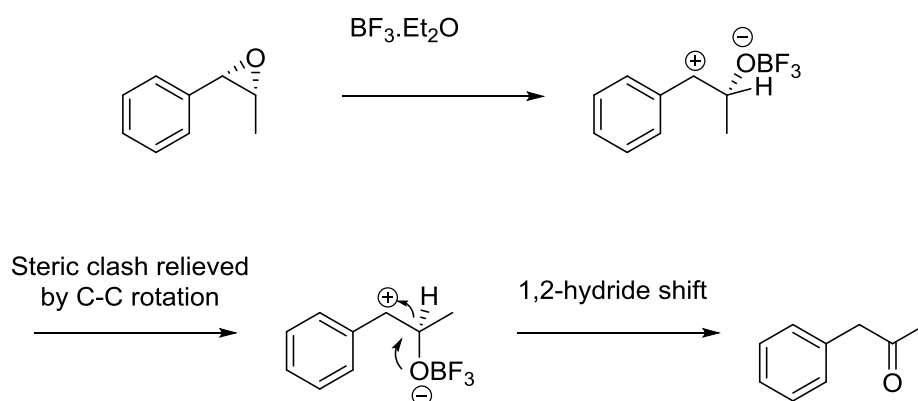
1.2.1.3 Nucleophilic Fluorination of Styrene Oxides



Scheme 17: Ring Opening Fluorination of Styrene Oxides with Boron Trifluoride⁵¹

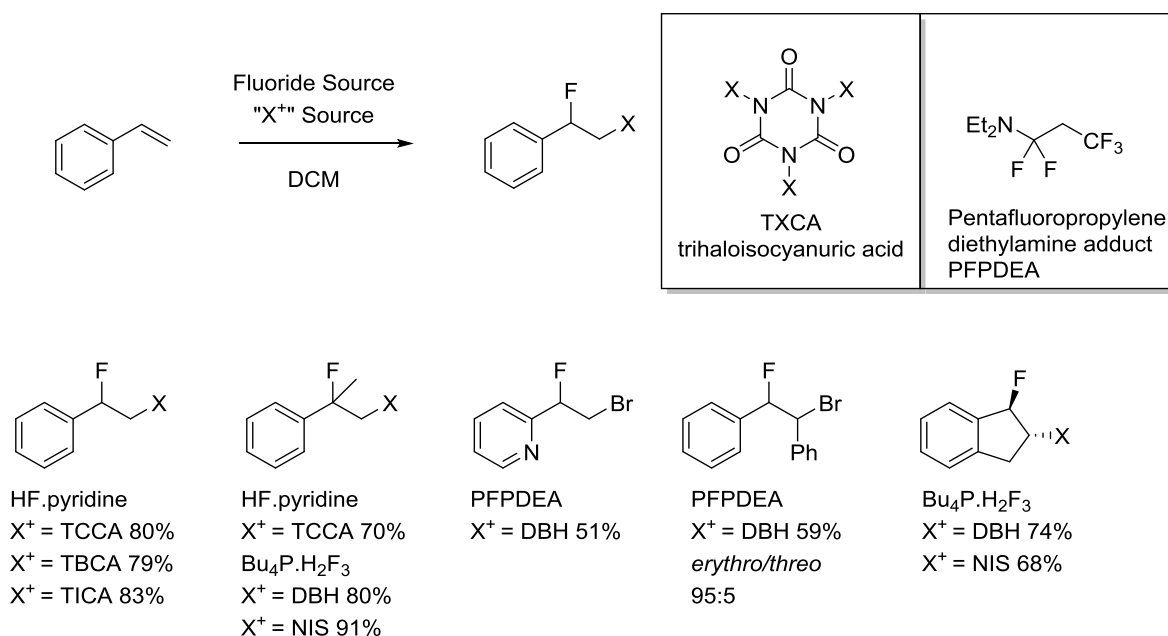
The stereoselective synthesis of benzylic fluorohydrins by treatment of the corresponding epoxides with BF₃.Et₂O is an efficient reaction, with full transfer of fluorine from the reagent to the substrate and complete stereocontrol (Scheme 17). The substrate scope is however limited, with only disubstituted *trans* epoxides proceeding to the desired product, and electron releasing substituents on the aryl ring favouring rearrangement rather than fluorination. Substitution other than alkyl on the epoxide is tolerated only for groups with a low propensity to migrate to a carbocation.

The stereochemistry of this reaction gives some information as to why the substrate scope is limited. The product isolated corresponds to that of *syn* delivery of fluoride to the same face of the epoxide as the oxygen. The postulated mechanism is that BF₃ first coordinates to the epoxide, acting as a Lewis acid to generate a benzylic carbocation, which is then attacked by a fluoride ion from the bound BF₃ molecule.

Scheme 18: Formation of Arylpropanone⁵¹

Epoxides with different substitution patterns do not maintain the reactive conformation for fluoride delivery and instead populate conformers which are reactive towards 1,2 hydride shift, leading to a 2-arylpropanone as a major product (see Scheme 18 for reaction of *cis* isomer). The ketone is similarly an observed product in the reaction of electron rich substrates, but multiple products are produced in these reactions. The balance between stability and reactivity of the carbocation intermediate to allow for successful fluorination amongst a number of competing pathways makes this methodology difficult to generalise.⁵¹

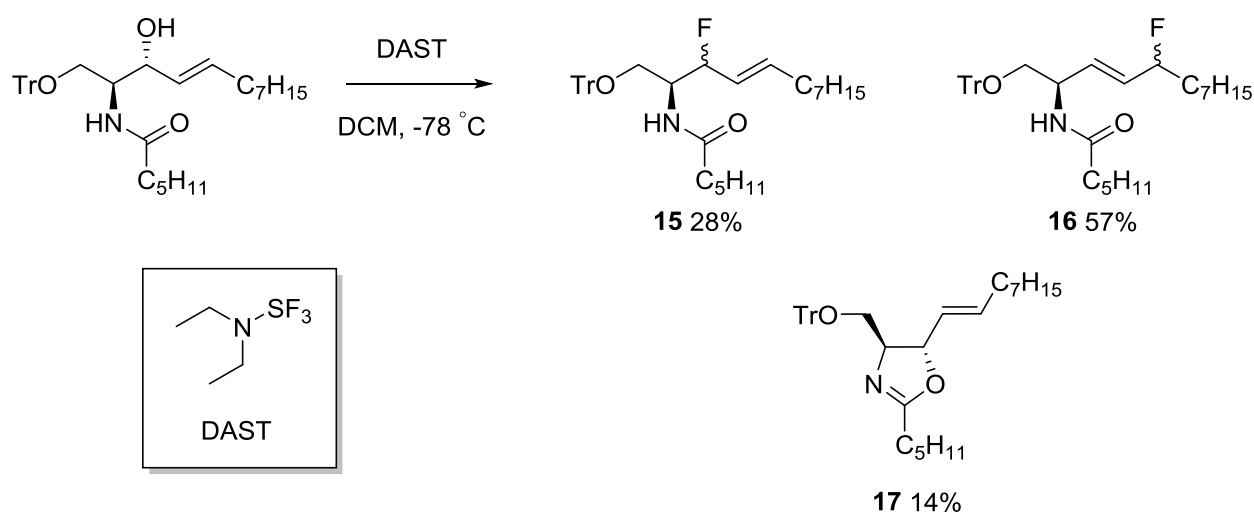
1.2.1.4 Halofluorination

Scheme 19: Halofluorination of styrene⁵²

The fluorination of alkenes with electrophilic fluorine sources is not facile due to the lack of reactivity of unactivated alkenes with fluorinating reagents: an umpolung strategy whereby reaction with an electrophilic source of another halogen generates a reactive intermediate and fluoride traps this intermediate is an alternative approach to the fluorination of double bonds (Scheme 19).⁵² A variety of sources of electrophilic halogens are suitable for the reaction, including dibromohydantoin, *N*-halosuccinimides and trihaloisocyanuric acids. Fluorine sources are similarly variable, with HF.pyridine, fluoroamine adducts, and phosphonium fluoride salts all giving fluorinated products. There is no data available for the comparison of the reactivity of different methods, so the reaction is reliant on the screening of different conditions to find the optimum for each substrate attempted.

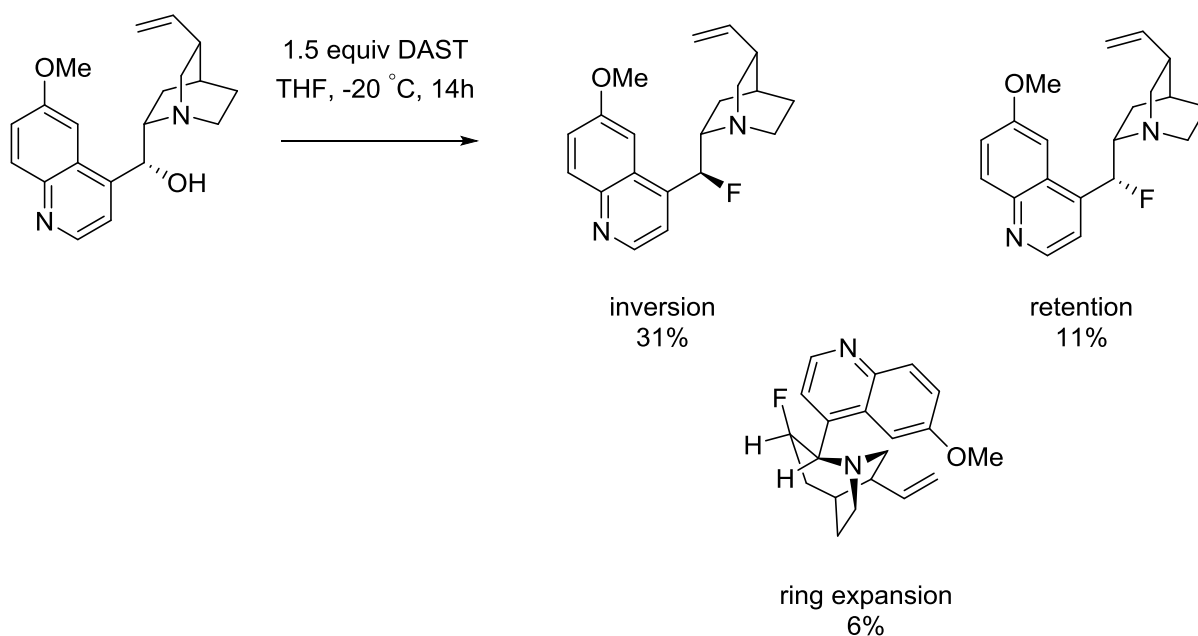
1.2.1.5 Deoxyfluorination

The most general synthetic route to secondary benzylic fluorides is the deoxyfluorination reaction of a benzylic alcohol by reaction with a sulfur trifluoride reagent. The highly electrophilic sulfur centre is attacked by the alcohol, liberating hydrogen fluoride; the OSF₂R moiety is a good leaving group and ideally the fluoride attacks in an S_N2 fashion, leading to inversion. The high reactivity of the SF₃ reagents can be problematic, leading to problems with functional group compatibility.



Scheme 20: Deoxyfluorination of Ceramide: Double Bond Transposition, Side Reaction³⁵

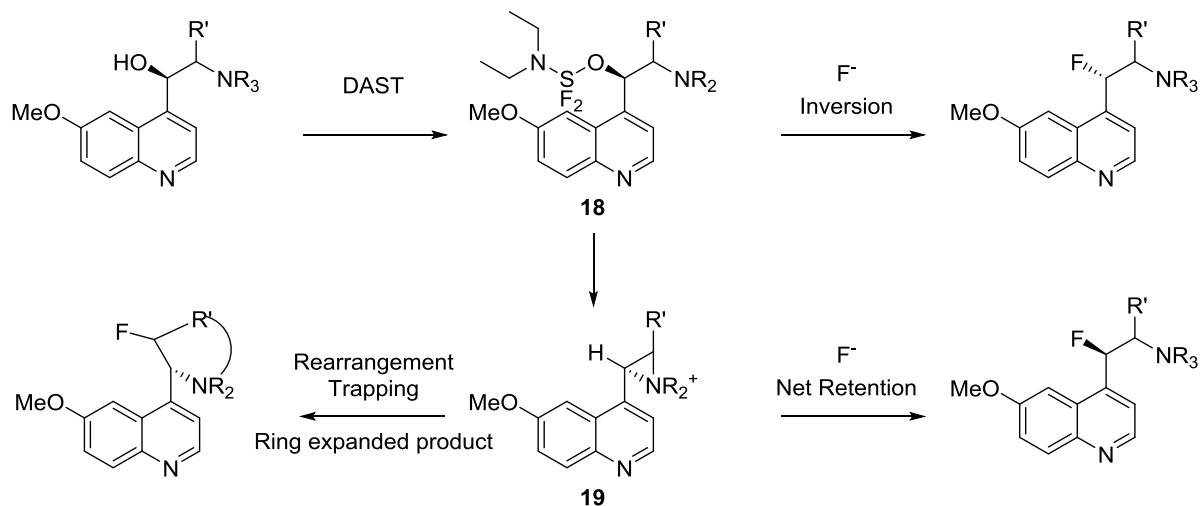
For example, in a non-benzylic reaction, the use of DAST on an allylic alcohol in the synthesis of an analogue of ceramide³⁵ led to the desired fluorinated product **15** as well as the product of double bond transposition **16** and cyclised product **17** (Scheme 20). The cyclic product is formed from the intramolecular attack of the neighbouring amide functional group on either the activated alcohol or the cation stabilised by the neighbouring π system. This demonstrates a problem common to allylic and benzylic systems - the stabilisation afforded to cationic species can be deleterious to reactions utilising aggressive reagents, with S_N1 pathways leading to loss of stereochemical information and rearrangements.



Scheme 21: Rearrangement in the Fluorination of *Cinchona* Alkaloids⁵³

Rearrangement can be problematic in deoxyfluorination, particularly with more active deoxyfluorination reagents. These tend to form intermediate adducts with the alcohol which are unstable with respect to dissociation, leading to S_N1 processes, as in the case where racemisation is observed. In the case where a heteroatom is present adjacent to the alcohol centre, nucleophilic trapping of the cation intermediate can occur to give a heterocyclic intermediate, which may then either be trapped by fluoride, leading to stereoretentive fluorination, or, in more complicated systems, it is also possible for rearrangement to occur. An example of both effects operating is found in the attempted synthesis of a library of fluorinated *cinchona* alkaloid analogs.⁵³ Under

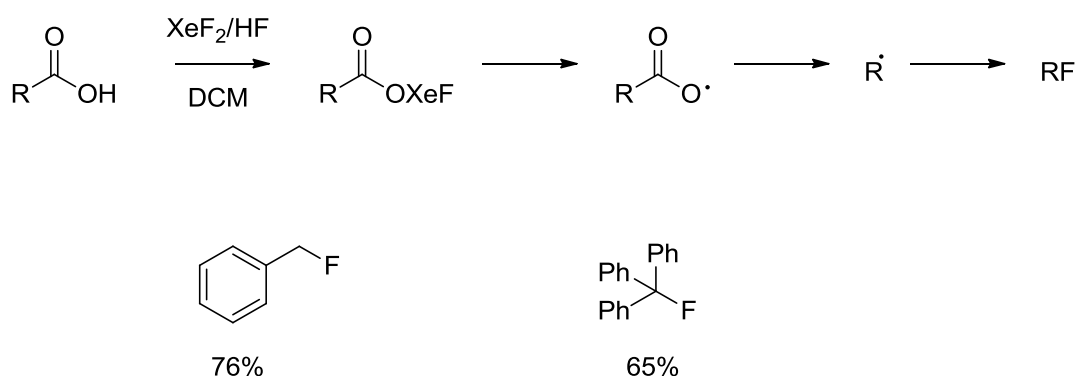
optimised reaction conditions, *cinchona* alkaloids reacted with DAST in THF to give a range of products, including in all cases the fluorinated product with inversion at the stereocentre, the fluorinated product with retention at the stereocentre and a ring-expanded product (Scheme 21).



Scheme 22: Rearrangement in Deoxyfluorination⁵³

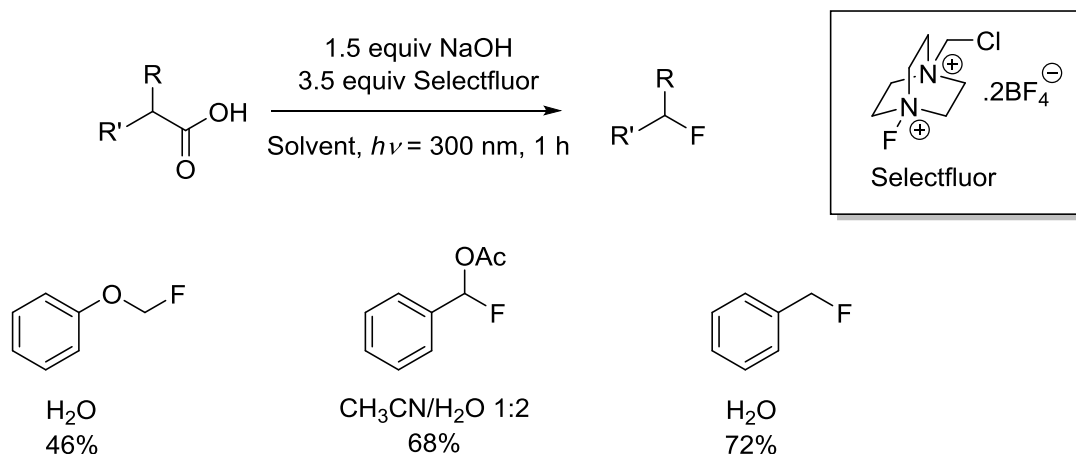
The retentive product arises by the intramolecular attack of the quinoline nitrogen on the reactive adduct **18**, giving the intermediate **19** which is then trapped by fluoride to give the fluoride product with retention of stereochemistry. Alternatively this intermediate may rearrange, giving a cation which can trap fluoride to afford the ring expanded product (Scheme 22). Both the configuration of the alcohol and the presence of a methoxy group on the quinoline ring have significant effects on the outcome of the reaction; the electronic properties of the ring determine the rate of S_N1 relative to S_N2 reaction, biasing the system to either inversion (the methoxy group increases the yield of inversion products) or the other products *via* the amine cyclised intermediate. The configuration of the alcohol has a less clear effect, this depends on the conformational effect on the rate of attack of the quinoline nitrogen towards the carbon centre. For the methoxyquinoline compounds, the *R* configuration at the alcohol (quinine) leads to the inversion isomer as the major product.

1.2.1.6 Fluorodecarboxylation

Scheme 23: Mechanism of Fluorodecarboxylation⁵⁴

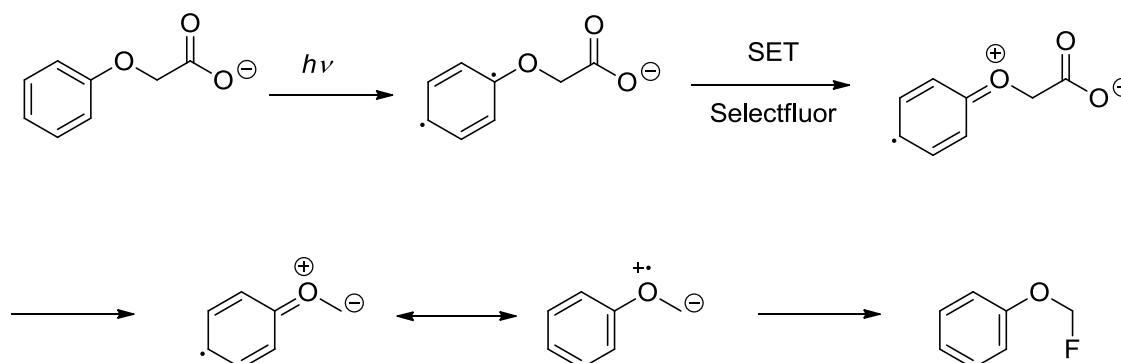
Halodecarboxylations are a classical route to haloorganic molecules, but the standard conditions of the Hunsdiecker reaction do not lead to any product when applied to fluorination-decarboxylation. The use of xenon difluoride instead of the more usual Ag salt and electrophilic source of halogen leads to clean reaction with a variety of carboxylic acids to give good yields of fluorinated product.⁵⁴ The reaction is thought to proceed *via* a xenon fluoride ester of the carboxylic acid, which can collapse to give a carbon radical, recombining with fluorine to give the intended product (Scheme 23).

Further developments of this methodology have dispensed with the need to use the highly aggressive and unstable XeF_2 . The use of catalytic silver salts in combination with Selectfluor (1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) in aqueous solution has been reported, but no examples of the synthesis of benzylic fluorides were provided, with the authors noting only that benzoic acids were unsuitable substrates. The radical mechanism of this fluorination would suggest that this may be a potential route to benzylic fluorides; unstabilised tertiary, secondary and primary substrates all provide products in acceptable yields.⁵⁵



Scheme 24: Fluorination of 2-Aryl and 2-Aryloxy Carboxylic Acids⁵⁶

In place of transition metal catalysis to generate a radical species, it is also possible to activate specific classes of substrates, namely 2-aryloxy and 2-aryl carboxylic acids, towards fluorodecarboxylation using irradiation with visible light (Scheme 24).⁵⁶



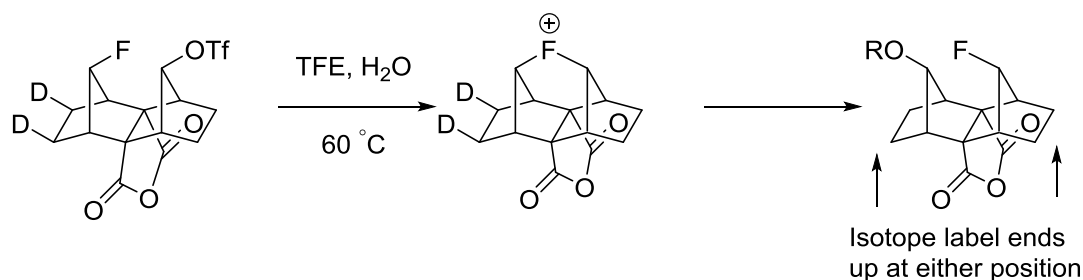
Scheme 25: Proposed Mechanism for Fluorodecarboxylation of 2-Aryloxy and 2-Aryl Carboxylic acids⁵⁶

The effectiveness of this transformation is dependent on the substrate chromophore being able to access an excited state on irradiation. The molecule in the excited state can then undergo single electron oxidation by Selectfluor, leading to decarboxylation and then transfer of a fluorine radical to the stabilised radical generated (Scheme 25).

1.2.2 Electrophilic Fluorination

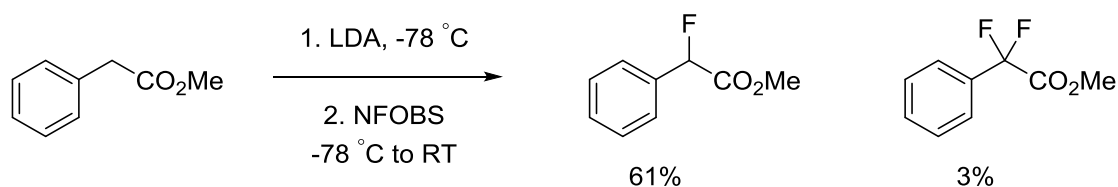
The use of electrophilic fluorinating reagents suffers from several problems; firstly the parent source of electrophilic fluorine, F_2 gas, is highly reactive and it can be difficult to achieve selective fluorination, though largely this problem has been circumvented by the use of milder reagents. Secondly, in contrast to the other halogens, there is no stabilisation of the intermediate for fluorination of a double bond by the formation of a halonium ion, thus for successful electrophilic fluorination an activating group is often required.

Moderation of the reactivity of fluorine gas can be achieved by dilution with nitrogen to give a mixture containing 5-10% fluorine. This can be used successfully in selective monofluorination, but due to the aggressive nature of fluorine gas careful control of stoichiometry is required to prevent overreaction. This inconvenience, combined with the fact that fluorine is dangerously reactive with common labware and requires passivated nickel equipment to handle safely, means that the use of fluorine gas is generally confined to specialist labs. Alternate reagents for electrophilic fluorine are either based on an O-F or N-F species, with O-F species generally requiring direct preparation from fluorine gas and thus maintaining many of the complications of use of F_2 . N-F reagents, however, have been successful replacements, with a number of reagents of varying degrees of reactivity commercially available. Their convenient handling properties (most are stable crystalline solids and may be used in standard glassware) allow their use by non specialists, and they have found use not only in fluorination chemistry but also as oxidants in other reactions. Further development of N-F reagents has provided some enantiopure fluorinating reagents which can enantioselectively fluorinate activated systems – these will be reviewed in Chapter 2.

**Scheme 26: Fluoronium Ion in Solution**⁵⁷

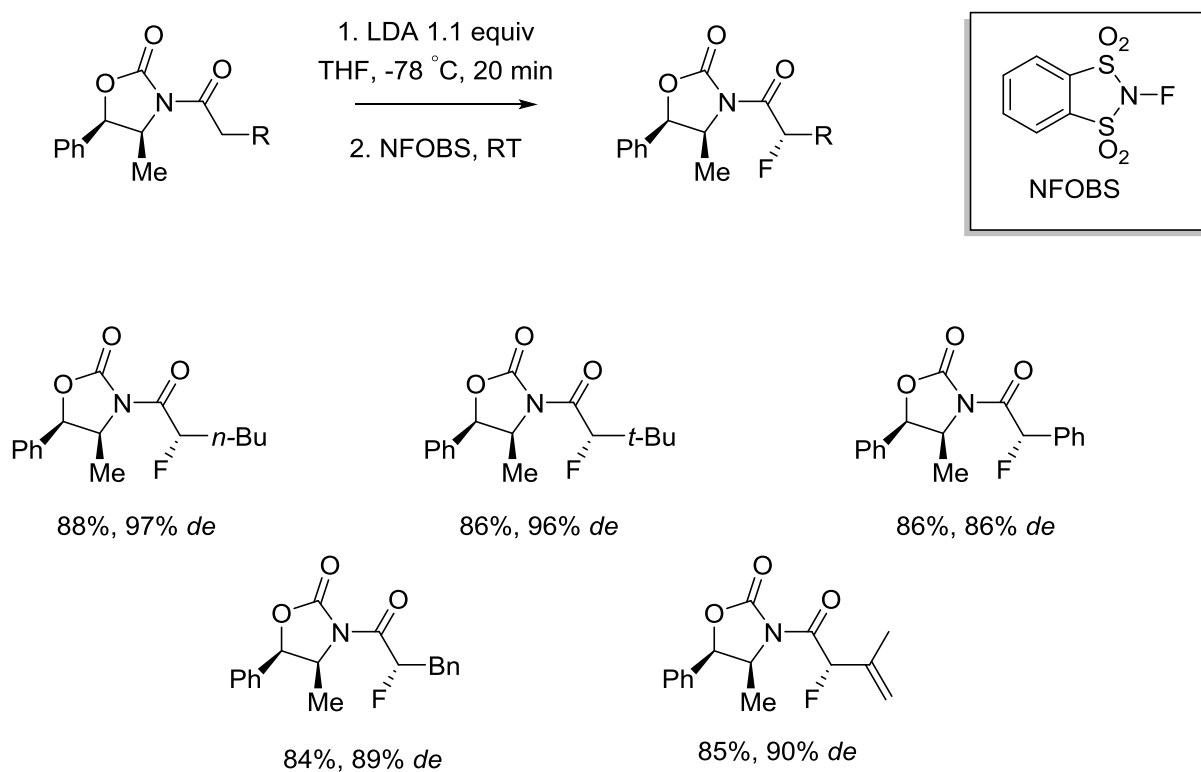
As mentioned previously, substrate activation is generally required for selective fluorination. This is due to the difficulty of formation of the fluoronium ion; in contrast to the commonly invoked bromonium and iodonium ions, chlorine and fluorine, due to their smaller size and higher electronegativity, do not readily form three membered rings as intermediates in halogenation, leading to higher activation energies for these reactions, particularly so for fluorine with the large inductive effect of the *alpha* C-F bond destabilising the carbocation intermediate formed. Chloronium ions have been invoked in several reactive systems; the fluoronium ion however probably plays no relevance to reactive systems: it has been observed in the gas phase⁵⁸ and in a highly constrained multicyclic system (Scheme 26).⁵⁷ Isotopic labelling of the carbon skeleton of the cage system proves that a symmetrical fluoronium ion exists in solution, and that the alcohol nucleophile can attack on either bridge carbon. This is demonstrated by the isotopic scrambling between the two positions.

1.2.2.1 Electrophilic Fluorination of Enolates and Enol Ethers

**Scheme 27: Electrophilic Fluorination of Enolates**⁵⁹

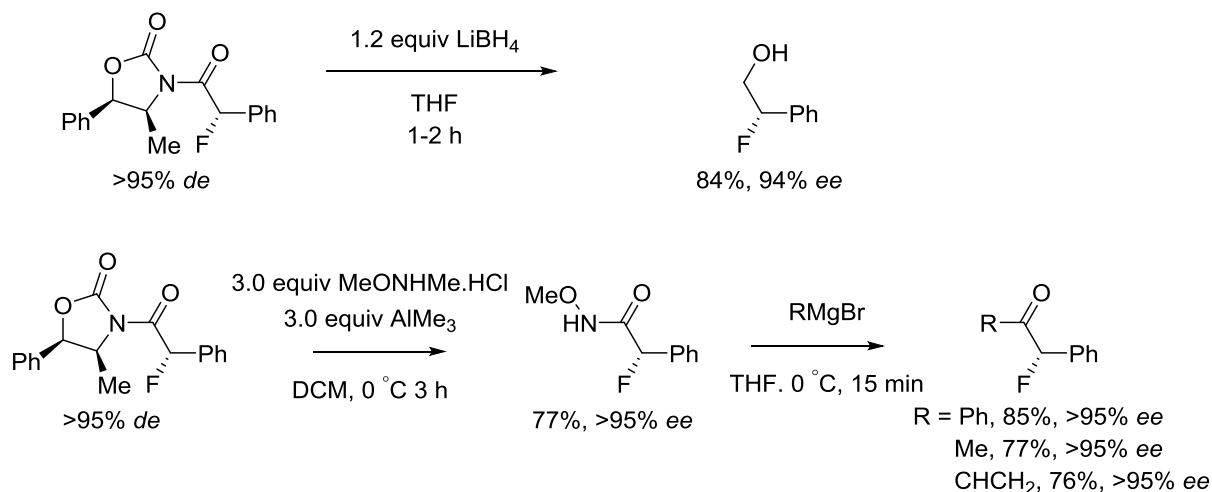
The most common activation provided for electrophilic fluorination is the formation of the corresponding enolate. Procedures for this are generally uncomplicated, comprising formation of the enolate using a strong base at low temperature followed by addition of the fluorine source and warming of the reaction mixture. A typical example is shown in Scheme 27.⁵⁹

There have been some moderately successful attempts to achieve enantioselective fluorination based on modifications of this methodology, utilising either catalyst or substrate control of enantioselectivity.



Scheme 28: Diastereoselective Fluorination of Enolates Bearing Enantiopure Auxiliary⁶⁰

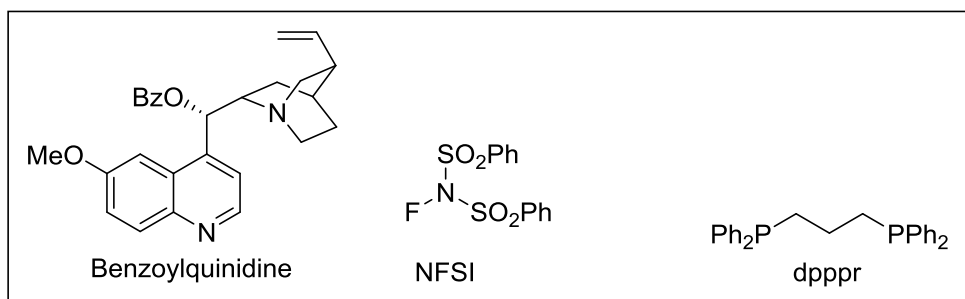
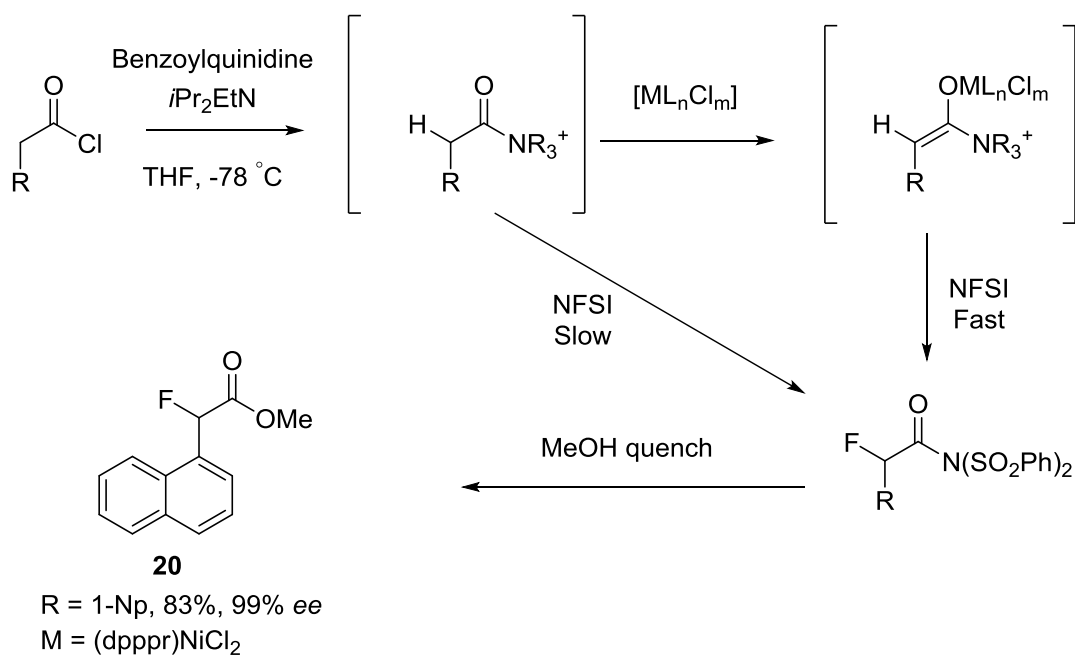
The fluorination of substrates bearing an enantiopure auxiliary suffers as a strategy from poor atom economy and the requirement for additional steps to remove the directing functionality post reaction. This strategy is however efficient for C-F formation by reaction of an enantiopure enolate with *N*-fluoro-*o*-benzenedisulfonimide, giving yields between 80 and 88%, and diastereoselectivities between 86 and 97%. The selectivity was slightly lower for a benzylic fluoride example, but this could be improved to >95% by crystallisation (Scheme 28).⁶⁰



Scheme 29: : Removal of Auxiliary to Access Benzylic Fluoride Products^{60, 61}

The removal of these auxiliaries proved straightforward, being achievable by either reduction with LiBH_4 to give the fluoro alcohol or, *via* the Weinreb amide, reaction with a Grignard reagent to give the fluoroketone. In both cases the enantiomeric excess of the fluorine substituted centre is maintained (Scheme 29).^{60, 61}

Catalytic enantioselective methodologies for the fluorination of enolates are preferable to minimise the use of expensive enantiopure reagents. Several such methodologies exist, these are either based on the formation of an enolate catalysed by an enantiopure catalyst or the catalytic generation of an enantiopure source of fluorine – these will be reviewed in the next chapter.



Scheme 30: Dual Catalyst Fluorination Acylation with Acyl Chlorides⁶²

Lectka and co-workers developed a dual catalyst system which mediates the fluorination-nucleophilic displacement of acyl chlorides to give an enantioenriched fluoroester, amide or thioester depending on the choice of terminal nucleophile (Scheme 30).⁶³ The proposed mechanism involves the attack of the quinuclidine nitrogen atom of benzoyl quinidine on the acyl chloride to produce an enantiopure species. Formation of a metal complex accelerates enolate formation. The enolate reacts with NFSI to produce the fluorinated ester **20** with excellent enantioselectivity after quenching with methanol (it is proposed that under reaction conditions the *bis*-sulfonyl amide anion may form an amide intermediate to enable turnover of the reaction). The addition of a metal cocatalyst increased the yields of the reaction dramatically, with Ni(dppr)Cl₂ or *trans*-(PPh₃)PdCl₂ giving the best results.

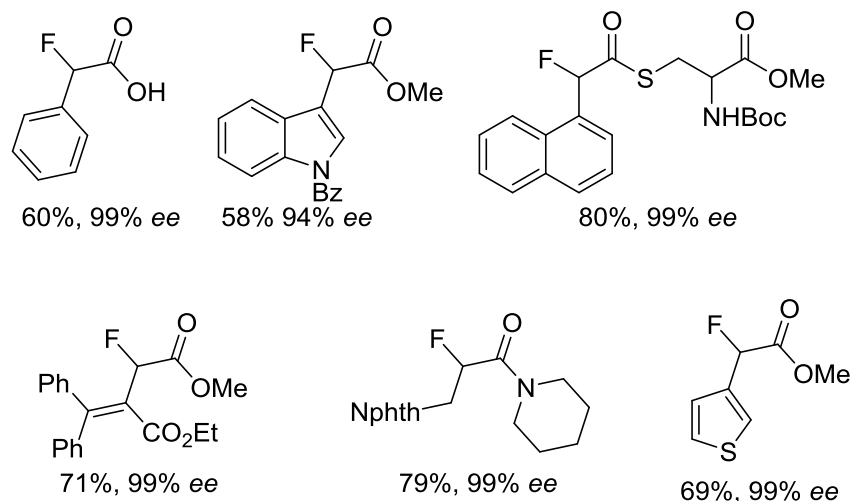
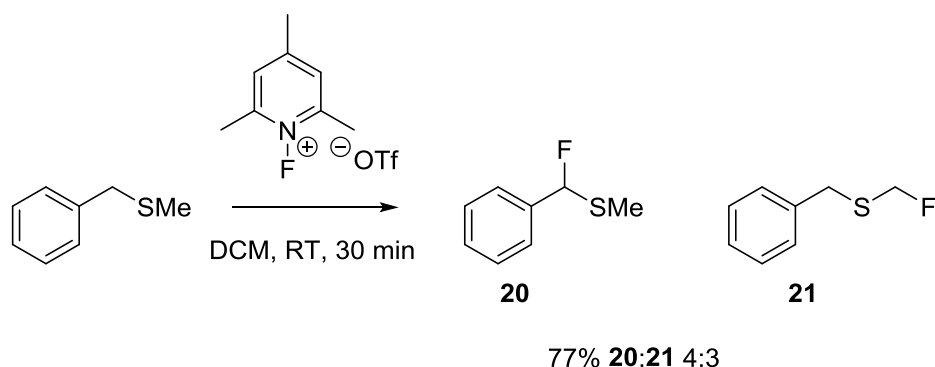


Figure 14: Substrate Scope for Fluorination-Acylation⁶²

This methodology has good scope for different substituents on the acyl chloride and nucleophiles, with enantiomeric excesses all exceeding 94% for a range of aryl, heteroaryl, alkene and heteroatom substituents and a range of nucleophiles, including complex natural products (Figure 14). The limitations of this methodology are the requirement for the preparation of the reactive acid chlorides and that the stereocentre produced must be *alpha* to an ester, amide or thioester.

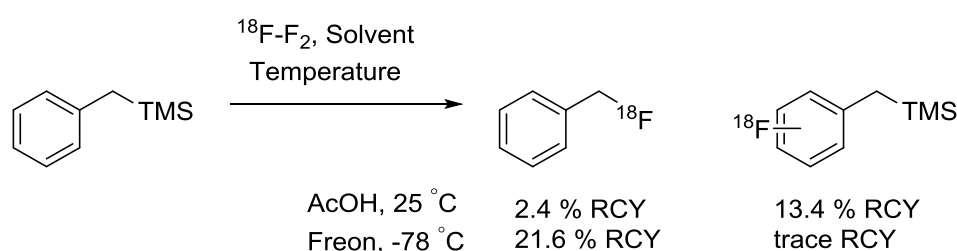
The use of the enolate fluorination methodology, whilst straightforward, does suffer from low levels of difluorination in some cases, and the constraint that substrates must bear a carbonyl group to enable activation, thus the range of structures accessible is somewhat constrained.

1.2.2.2 Alpha – Activation of Benzylic Positions



Scheme 31: Electrophilic Fluorination of Sulfides⁶⁴

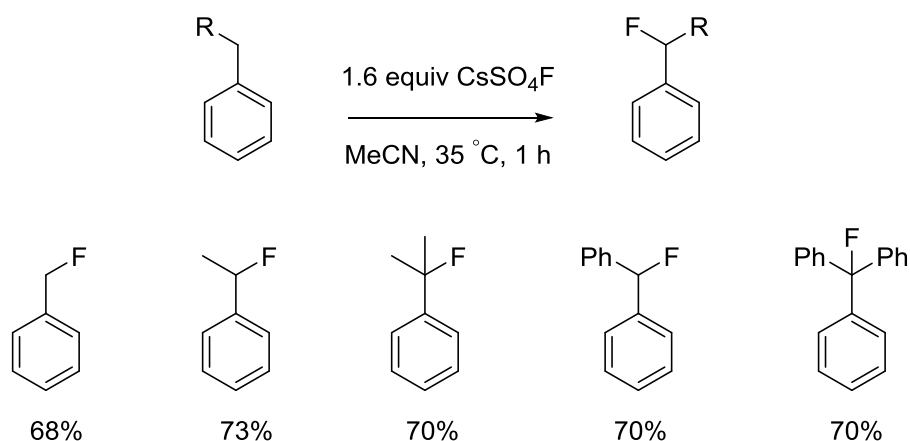
The α -fluorination of sulfides using N-F reagents has been reported to give an alternate access to α -fluoro sulfones by a fluorination-oxidation sequence. In this paper there was a single reported example of a benzylic substrate, from this reaction a mixture of products was isolated, with the benzylic fluoride **20** the major product in a 4:3 ratio with the fluoromethyl sulfide **21** in 77% yield (Scheme 31).⁶⁴ The reaction is proposed to proceed through a Pummerer-like mechanism, with S-fluorination followed by migration giving the product. The authors were able to provide evidence for S-fluorination by ^{19}F NMR of a substrate which could not undergo migration. This methodology is not a particularly practical route to benzylic fluorides as currently described due to the mixture of products obtained, but represents a different mechanism for activation of a molecule towards electrophilic fluorination.



Scheme 32: Radiofluorination of Benzyltrimethylsilane⁶⁵

An attempt to activate the benzylic position towards electrophilic radiochemical fluorination by substitution with a trimethylsilyl group gave a poor radiochemical yield of benzyl fluoride in Freon at -78 °C on reaction with $[^{18}\text{F}]\text{F}_2$ (Scheme 32).⁶⁵ At room temperature in acetic acid, where the active fluorinating reagent is AcOF, a milder reagent than F_2 , the main product was that of aryl fluorination and only trace benzyl fluoride was observed. Presumably the silyl group activates the aromatic ring in a manner similar to the allylsilane activation of alkenes towards electrophilic fluorination.⁶⁶ The authors did not report a preparative scale reaction to form benzyl fluoride, but the poor yields and purities encountered under radiochemical conditions (large excess of precursor relative to fluorinating reagent, short reaction times) suggest that this would not be an efficient route to benzylic fluorides.

1.2.2.3 Electrophilic Fluorination of Unactivated Positions

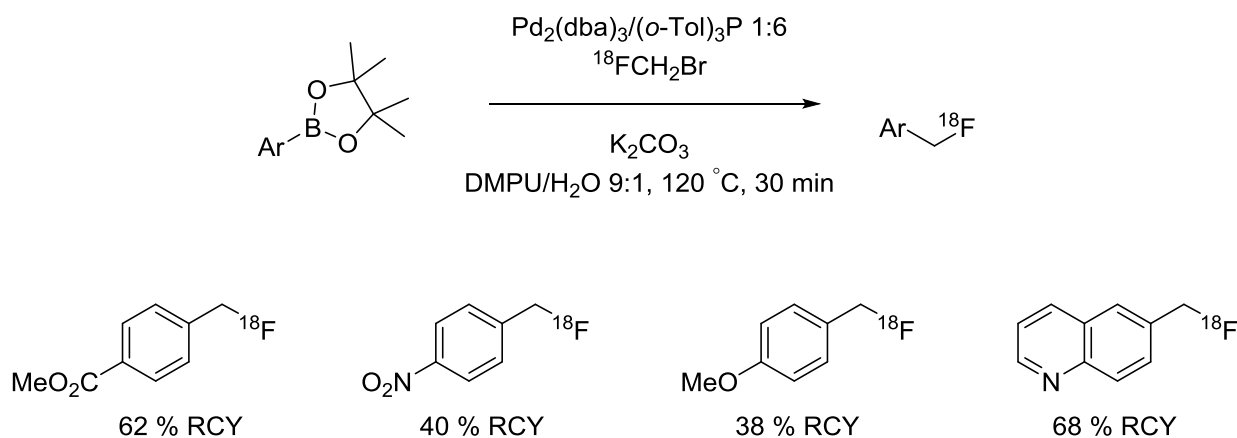


Scheme 33: Fluorination of Unactivated Benzylic Positions⁶⁷

Cesium fluoroxysulfate (CsSO₄F) is a more selective fluorinating reagent than elemental fluorine, and C-H fluorination of unactivated alkyl side chains attached to benzene rings has been reported (Scheme 33).⁶⁷ The fluorination of the aromatic ring is still problematic, as with F₂, but the ratio of benzyl to aryl fluorides is much improved (however if oxygen is present this can have a deleterious effect on the selectivity of the reaction, leading to more ring fluorination). A range of methyl substituted benzenes were also subjected to these reaction conditions, giving good yields for a range of substitution patterns. In most cases a mixture of chain and ring fluorinated products were observed.

1.2.3 Building Block Approaches

1.2.3.1 Cross Coupling with Monofluoro Precursors

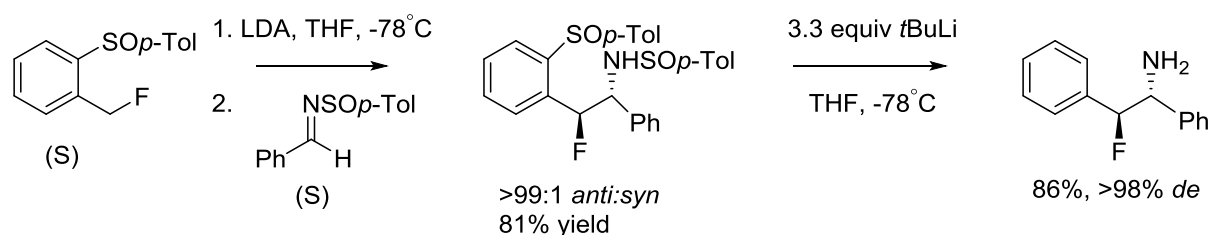


Scheme 34: Cross Coupling of Bromofluoromethane⁶⁸

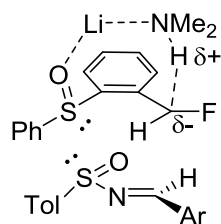
Cross coupling as a methodology has multiple advantages, including the ability to diversify structures at a chosen point in a synthetic sequence by the choice of a suitable coupling partner; generally mild and non toxic reagents and conditions; and the potential for late stage functionalisation of molecules. Crucial to the success of cross coupling reactions is the correct choice of precursors, in this case the fluoromethyl surrogate and the aryl component - this choice covers both which is the nucleophilic or organometallic reagent and which is the electrophilic partner. The use of ¹⁸F- fluoromethyl iodide or bromide has been documented⁶⁸ in cross coupling with an arylboronic acid partner to yield a radiolabelled benzylic fluoride (Scheme 34). This study was only performed on a radiochemical scale and this may not be appropriate for the preparation of larger quantities of benzylic fluorides (not least due to the fact that these compounds are regulated ozone depletors).

1.2.3.2 Enantioselective Nucleophilic Addition Mediated by Sulfoxide

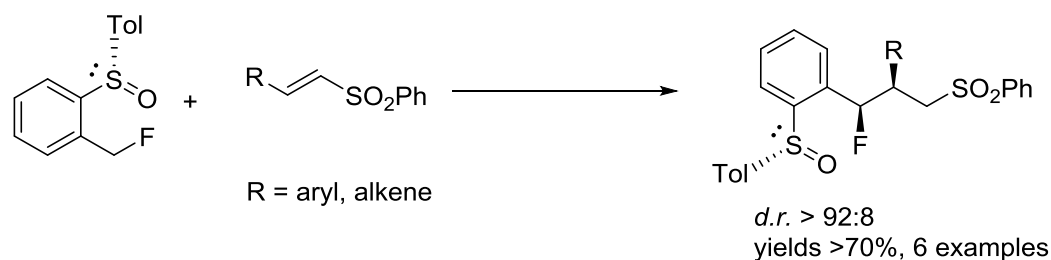
Auxiliary

Scheme 35: Diastereoselective Reaction of Benzylic Fluoride Anions⁶⁹

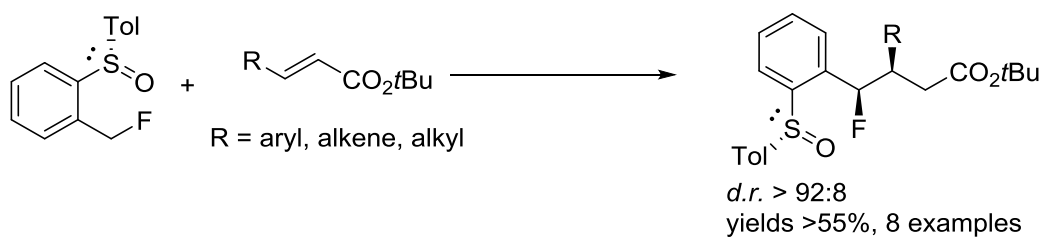
The use of a sulfonyl chiral auxiliary to direct the lithiation of a fluoromethyl group has been shown to give excellent diastereoselectivity when paired with a matched enantiomer of an imine electrophile (Scheme 35).⁶⁹

Figure 15: Transition State for Enantioselective Fluorobenylation⁶⁹

The suggested mechanism to explain the high diastereoselectivity is that the benzylic centre is controlled by a lithium amide chelate stabilising the fluorinated anion, and the tolyl substituent on the electrophile must point away from the reaction centre to prevent a clash (Figure 15). Global deprotection of the sulfinyl groups using *tert*-butyllithium gives the enantiopure fluorinated β -phenethylamine.

Scheme 36: Diastereoselective Fluorobenylation of Vinyl Sulfones⁷⁰

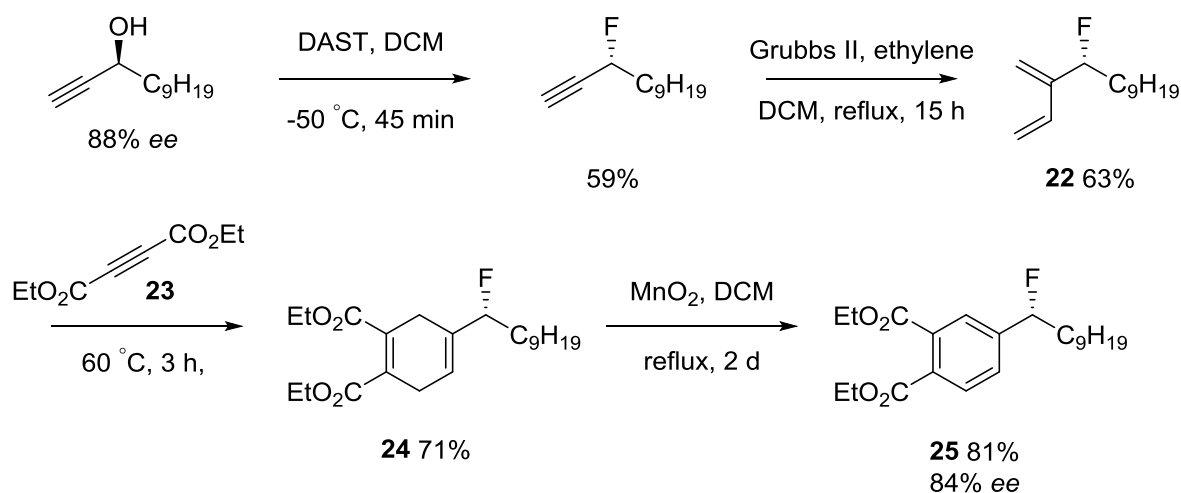
The scope of this reaction has been developed further to allow addition of the fluorobenzyl unit to carbon carbon double bonds (Scheme 36, Scheme 37).⁷⁰ The initial investigation relied on matched pairs of enantiopure reagents to access high enantioselectivities in the product, but for the vinyl acceptors in this further study the electrophiles are achiral, thus giving a test of the enantiocontrol provided by the sulfinyl group at remote positions. For vinylsulfones the enantiocontrol at the benzylic position was complete, giving a 92:8 ratio of two separable diastereomers with the same configuration at the fluorinated centre, with the *syn* diastereomer as the major product. Removal of the sulfinyl group was possible using *t*BuLi or Raney nickel to give the enantiopure benzylic fluoride which could then be further elaborated before removal of the sulfone group, giving access to a number of related enantiopure benzylic fluorides.



Scheme 37: Diastereoselective Fluorobenylation of Acrylates⁷⁰

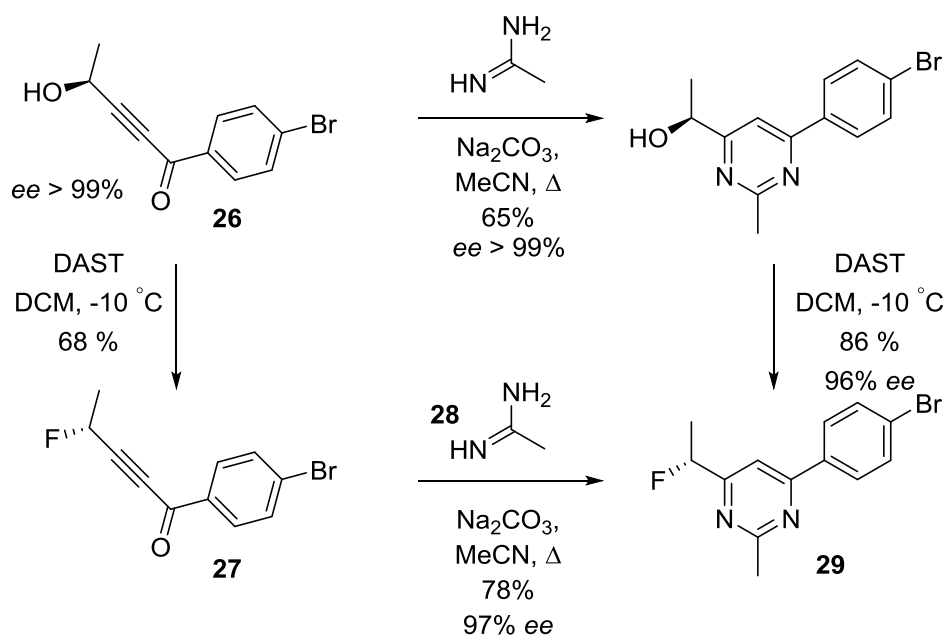
Application of the same methodology in the nucleophilic addition to acrylates was also possible by using a *tert*-butyl acrylate (Scheme 37); again complete control of the benzylic stereocentre was observed, and diastereomeric ratios were high, at greater than 92:8 for the *syn* isomer. Notably, the reaction also tolerates alkyl substitution on the vinyl position, which is not observed for the sulfone case. Similarly to the sulfone substrates, treatment with Raney nickel allowed for facile removal of the sulfinyl auxiliary.

1.2.3.3 Aromatic Ring Synthesis

Scheme 38: Diels-Alder/Aromatisation Route to Benzylic Fluorides⁷¹

The construction of an aromatic ring from an enantiopure fluorinated building block enables access to benzylic fluorides with the stereochemistry built in, avoiding the requirement for enantioselective benzylic fluorination (Scheme 38). Propargylic fluorides are readily accessible in enantiopure form by deoxyfluorination,⁷¹ in contrast to the special measures sometimes required for deoxyfluorination of benzylic alcohols. Reaction of propargylic fluorides with ethene in the presence of the second generation Grubbs catalyst gives the diene **22** in good yield.

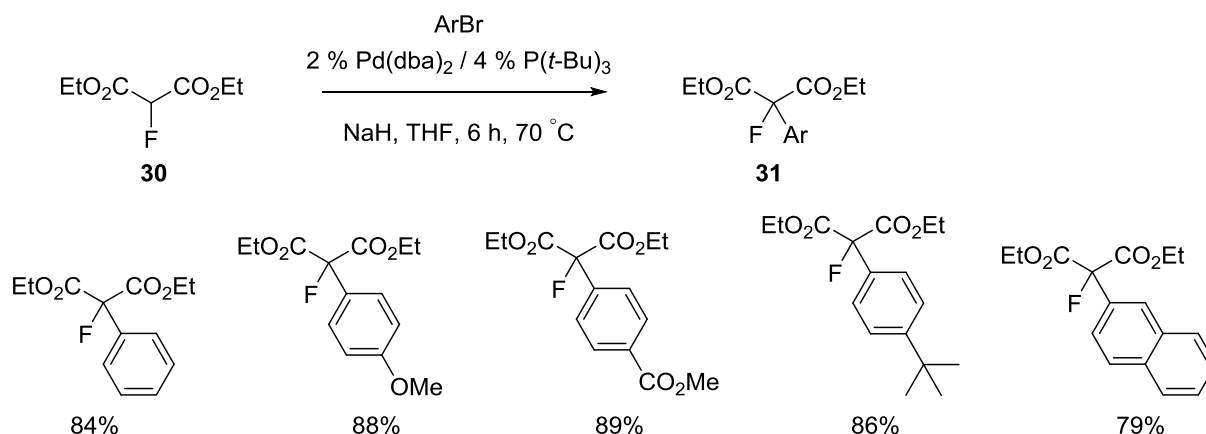
The diene **22** readily undergoes Diels-Alder reaction with acetylene **23** to give cyclic product **24**, which aromatises on treatment with MnO_2 to give the benzylic fluoride product **25**. The enantiomeric excess of the starting propargylic alcohol (88%) was largely maintained over the whole synthetic sequence, giving the final product with 84% *ee*. The ester groups could be removed by reduction to give the diol. Starting with the propargylic ketone, the same sequence of reactions led to the corresponding difluorinated compound.⁷²



Scheme 39: Enantioselective Synthesis of Pyrimidine Benzylic Fluoride from Alkyne Building Block⁷²

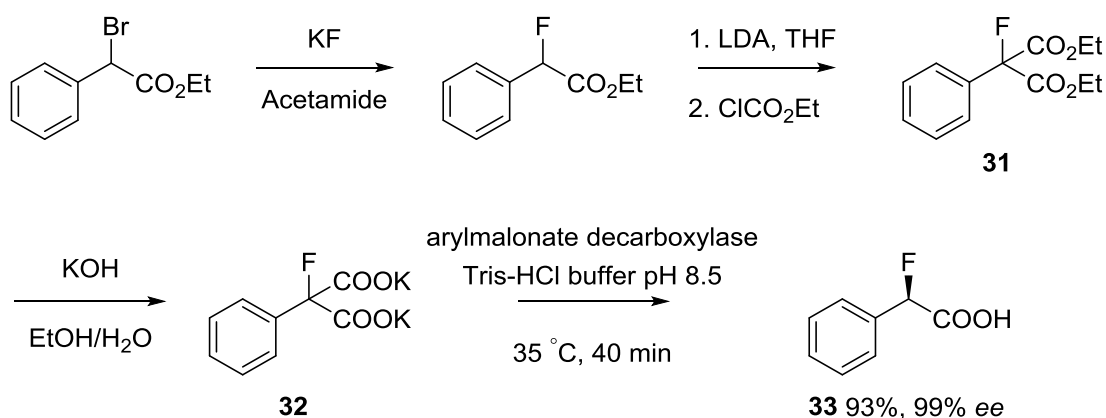
A similar strategy can be used to access aromatic heterocycles, again via a propargylic fluoride (Scheme 39). In this case the required propargylic fluoride would be too volatile to reliably isolate, so the authors performed the synthesis of the disubstituted alkyne **26** prior to the fluorination step. This was similarly successful to the fluorination of the unsubstituted alkyne in the previous example, and proceeded with excellent enantiocontrol to give the fluorinated alkyne **27**. Reaction with **28** gave the heterocycle **29** in good yield with the fluorinated stereocentre maintaining its enantiomeric purity. Interestingly, for this electron poor heterocycle it was also possible to reverse the order of steps, first performing the cyclisation followed by the enantiospecific fluorination, giving a slightly better overall yield. For electron poor heterocycles there is less stabilisation afforded the potential cationic intermediate, so the $\text{S}_{\text{N}}1$ reaction is slower, and therefore less racemisation occurs.

1.2.3.4 Arylation of Fluoromalonate

Scheme 40: Arylation of Fluoromalonate⁷³

The Pd catalysed reaction of diethyl fluoromalonate **30** with aryl bromides provides good yields with electron rich, neutral and electron poor substrates (Scheme 40).⁷³ The use of a very bulky phosphine is required, with a catalyst based on $\text{P}(t\text{-Bu})_3/\text{Pd}_2(\text{dba})_3$ being active for the transformation of aryl bromides; the use of aryl chlorides for the arylation of diethyl malonate required more specialised, non commercial ligands, negating the economic advantages of using aryl chlorides. As a result the reaction of diethyl fluoromalonate with aryl chlorides was not attempted. The substrate scope of this reaction has also been shown to allow reaction of aryl bromides with cyanoacetates and other activated carbon nucleophiles, but no other fluorinated synthons were examined; this route could thus potentially give access to a greater variety of benzylic fluorides.

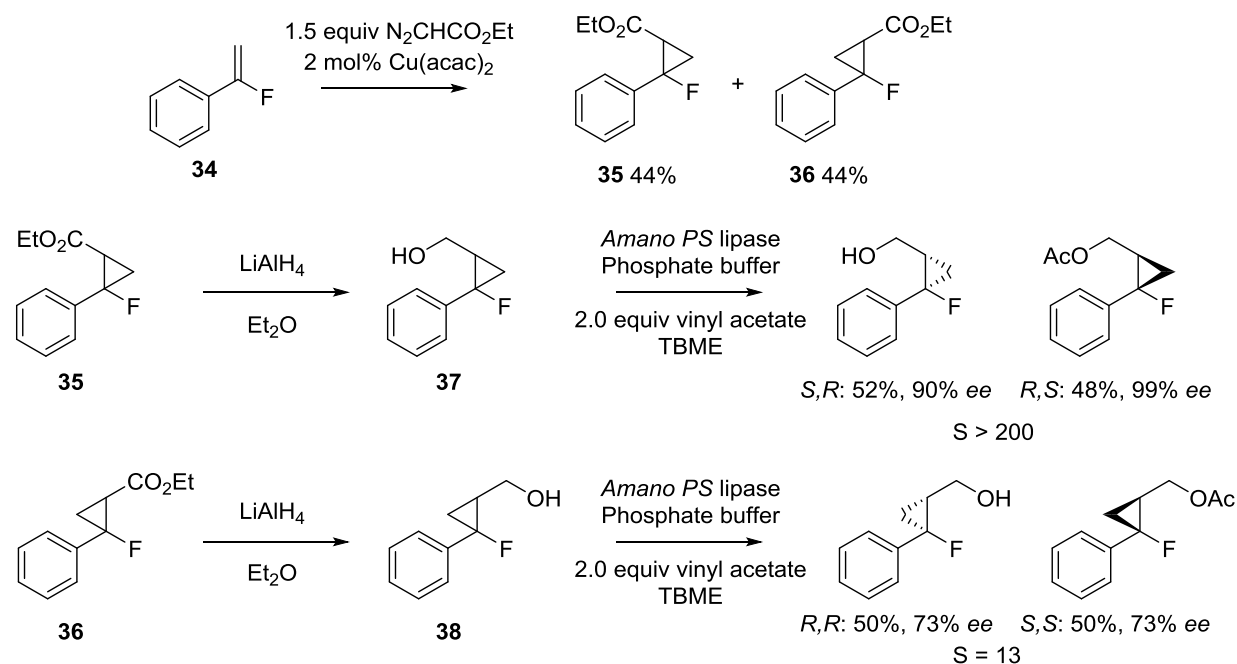
1.2.3.5 Decarboxylation

Scheme 41: Enzymatic Synthesis of *R*-2-fluoro-2-phenylacetic acid⁷⁴

The arylfluoromalonate derivatives **31** described in the previous section can be used to access the enantiomerically pure benzylic fluoride **31** by enzyme catalysed decarboxylation (Scheme 41).⁷⁴

The authors prepared the fluoromalonic acid **33** by the route shown in Scheme 40, using a nucleophilic displacement of a haloester to introduce the fluorine atom, then introducing the second carbonyl group by forming the enolate and trapping with chloroethyl carbonate. Hydrolysis of the esters gave the intermediate **32** which was subjected to decarboxylation with arylmalonate hydroxylase to give an excellent yield of **32** with an *ee* of > 95 %. The use of whole cell cultures to effect this transformation was not successful, giving a lower *ee* than the purified enzyme or a crude enzyme extract. This was proposed to be due to non catalysed spontaneous decarboxylation.

1.2.3.6 Cyclopropanation

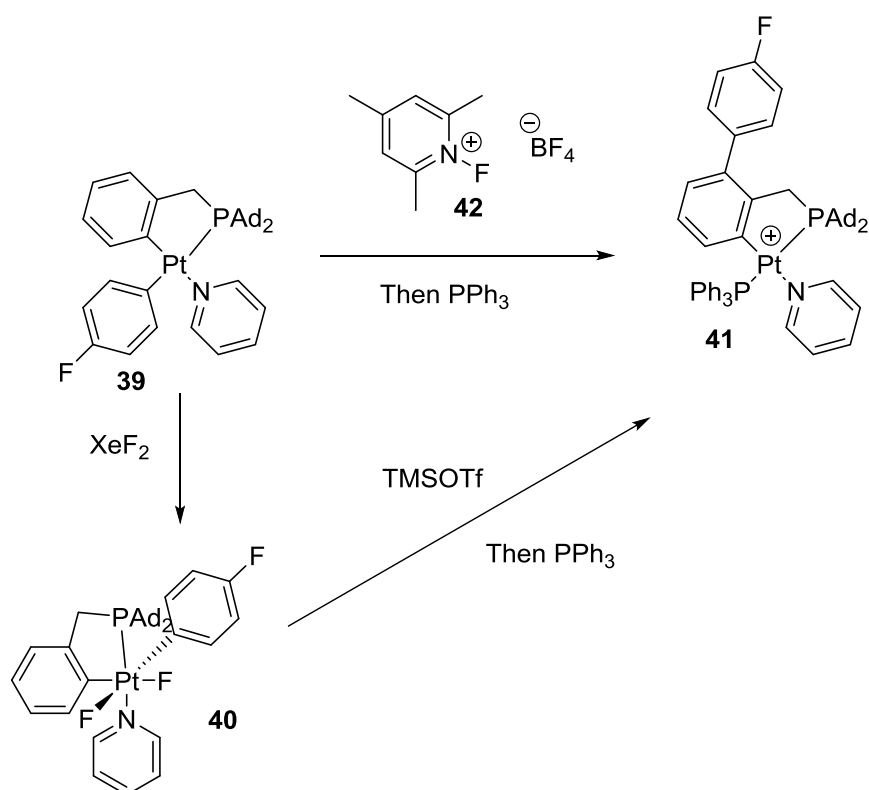
Scheme 42: Kinetic Resolution of Fluorinated Phenylcyclopropanes⁷⁵

Copper catalysed cyclopropanation of fluorostyrene **34** gives access to a mixture of benzylic fluoride esters **35** and **36**. Reduction of these esters gives alcohol substrates which are amenable to enzymatic kinetic resolution by enantioselective acylation (Scheme 42).⁷⁵ Resolution of the *cis* isomer **37** was successful, giving good enantiomeric excesses for both starting material and product in a short period of time using vinyl acetate as the acyl donor. The *trans* isomer **38** did not undergo the transformation with the same level of success: the maximum *S* value obtained for the transformation was 13, thus to access highly enantioenriched material it was necessary to perform two cycles of kinetic resolution. An alternate approach to kinetic resolution of these substrates is hydrolysis, using the racemic esters. This was again more successful for the *cis* isomer (chloroacetate ester, *S* = 97) but not for the *trans* (acetate ester, *S* = 12).

1.2.4 Metal Catalysed Synthesis of Benzylic Fluorides

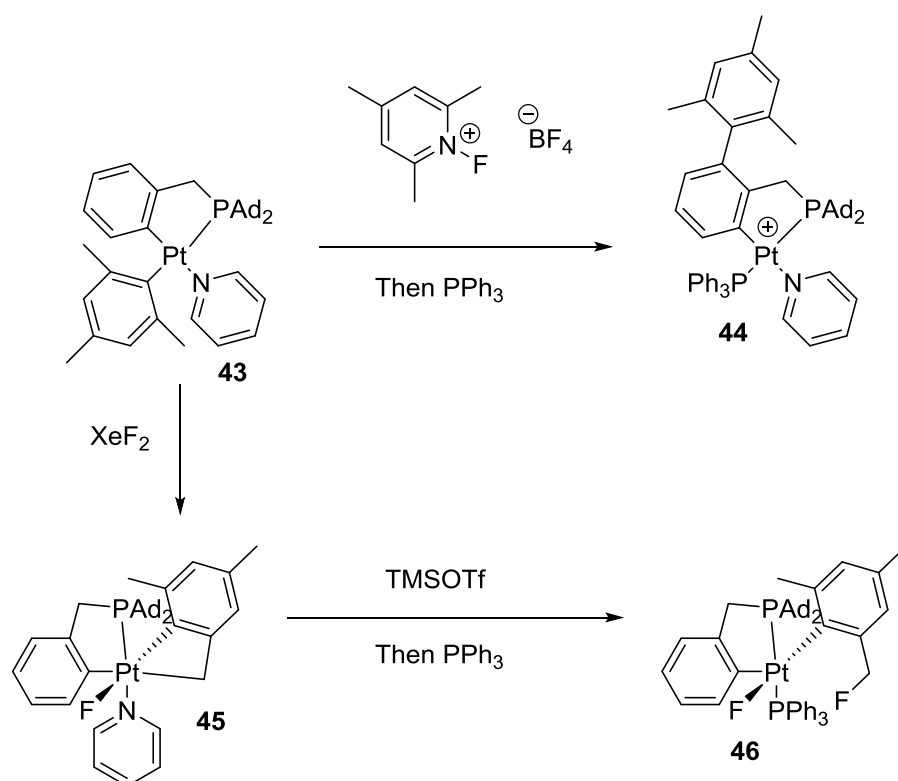
Metal catalysed fluorination is currently a very active research area, with significant progress having been made on allylic systems using a variety of metals, leaving groups and fluoride sources – these will be covered in more detail in Chapter 3.⁷⁶⁻⁷⁹ Some methods exist to selectively functionalise unactivated hydrocarbons oxidatively, but the regioselectivity of these methods is highly substrate dependent and generally fluorination is directed to the most electronically activated position.^{80, 81}

Reductive elimination of C-F bonds is challenging despite the large thermodynamic driving force, and this generally presents the biggest obstacle in the design of fluorination reactions. The use of high valent metal species can facilitate the C-F bond forming event, but this may require strongly oxidising reagents and consequently reduce the functional group compatibility of the methodology. The extension of these methods to benzylic centres is not trivial, and there are only a few examples of benzyl-F bond formation mediated by a metal catalyst.



Scheme 43: C-C Coupling of Ligands on Pt Enabled by Oxidative Fluorination⁸²

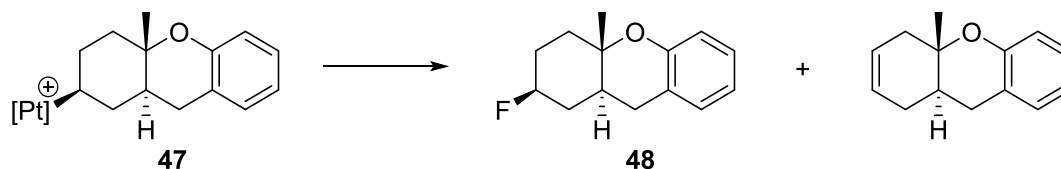
Amongst the examples of fluorination of benzylic centres mediated by metal catalysts there are both stoichiometric and catalytic methodologies. The synthetic utility of the stoichiometric reactivity is clearly limited, but these studies have provided valuable insights into the likely mechanisms of fluorination. In an attempt to study the XeF_2 mediated C-C coupling of the 2 aryl ligands of complexes of the type $(\text{bisphosphine})\text{Pt}(\text{Ar})_2$,⁸² complexes bearing an aryl group as a cyclometalated species **39** were synthesised (Scheme 43). The hypothesis was that C-C reductive elimination in these systems would be slower, allowing the isolation of the oxidation product of reaction with XeF_2 , **40**. This species, on abstraction of fluoride, underwent the expected reaction to produce a biaryl product **41** in the case where $\text{Ar} = p\text{-FPh}$. When **39** was reacted with a pyridinium fluoride reagent **42** the product **41** was produced. Presumably this reaction passes through a cationic species similar to that generated on abstraction of fluoride from **40**.



Scheme 44: Unexpected Fluorination of Mesityl Ligand on Pt(IV)⁸²

Unexpectedly, in the case where $\text{Ar} = 2,4,6\text{-trimethylphenyl}$ (Scheme 44), the reaction of cyclometallated complex **43** with XeF_2 did not afford the usual product, instead the benzylic fluoride complex **46** was observed. The authors propose that this complex arose from the

elimination of HF to generate a Pt(IV) benzyl species **45**, which could then undergo reductive elimination to generate the benzylic fluoride. Interestingly, treatment of the initial complex with the pyridinium reagent **42** led to the expected product of C-C coupling **44**.

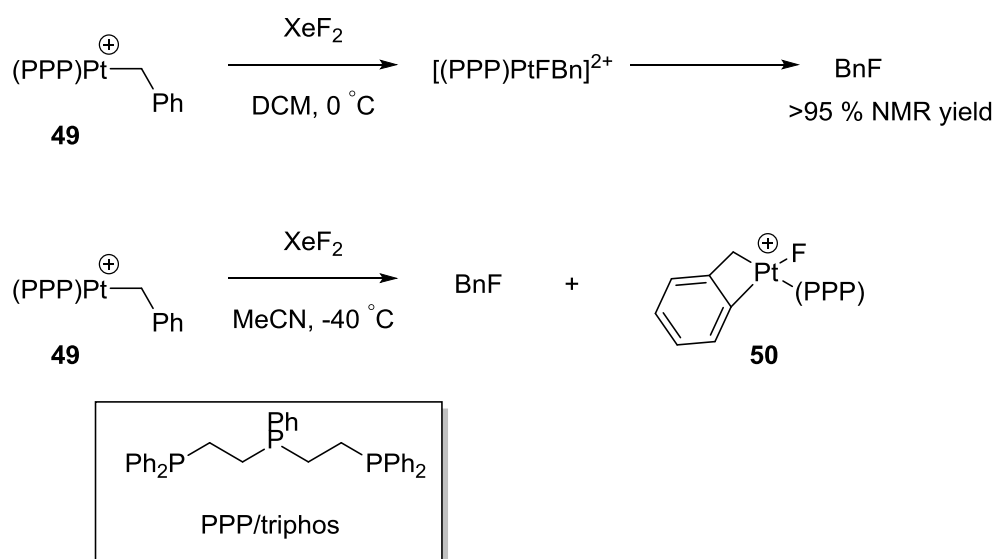


Scheme 45: C-F reductive elimination at Pt

Entry	F ⁺ Source	Temperature	Time	Yield of 48
1	Py-F.BF ₄	70°C	28 h	93%
2	2,4,6-MePy-F.BF ₄	70°C	3 d	NR
3	2,6-ClPy-F.BF ₄	25°C	35 h	91%
4	Selectfluor	25°C	6 h	88%
5	XeF ₂	0°C	< 3 min	87%
6	NFSI	70°C	17 h	81%

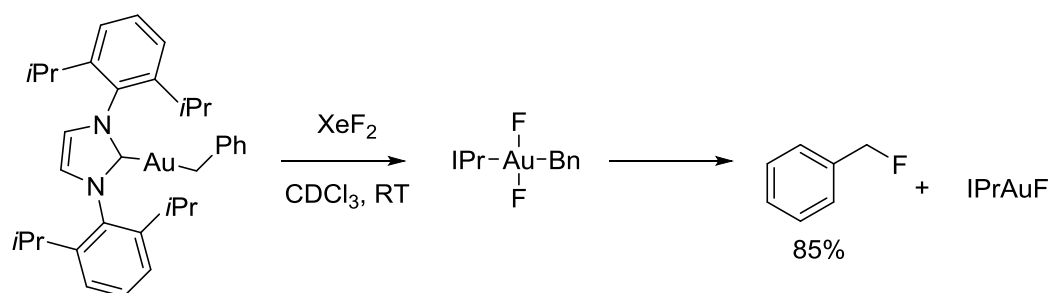
Table 4: C-F Reductive Elimination at Pt - Fluorine Sources⁸³

Further study of the reactivity of Pt complexes in the presence of electrophilic fluorinating reagents has provided the insight that steric encumbrance can favour C-F reductive elimination from Pt(IV) to give alkyl fluorides over C-N reductive elimination (in the case when the fluorine source is NFSI) or β -hydride elimination. The oxidation of a cationic Pt(II)triphos alkyl complex **47** by XeF₂ (Scheme 45) (or other electrophilic sources of fluorine of varying reactivity as in Table 4) leads to a doubly cationic Pt(IV) species which can undergo reductive elimination to give the alkyl fluoride. The reaction proceeds at secondary centres and is stereospecific for retention of stereochemistry from the Pt intermediate.⁸³



Scheme 46: Platinum Benzyl Complex Fluorination⁸³

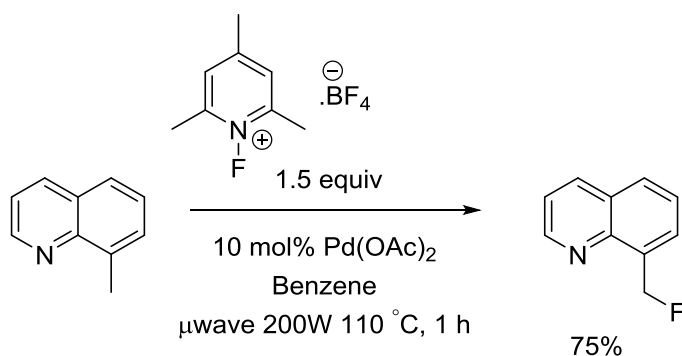
For the case where the alkyl group is benzyl, the potential for side reactions is greatly diminished and quantitative conversion to benzyl fluoride is observed (Scheme 46). When the Pt benzyl complex **49** was treated with XeF₂ in acetonitrile at -40 °C, it was observed that ~10 % of the complex did not form BnF, instead a cyclometallated complex identified as **50** was formed, which bears some similarity to the intermediates encountered in the previous report of Pt complex benzylic fluorination.



Scheme 47: C-F Reductive Elimination from Au (III)⁸⁴

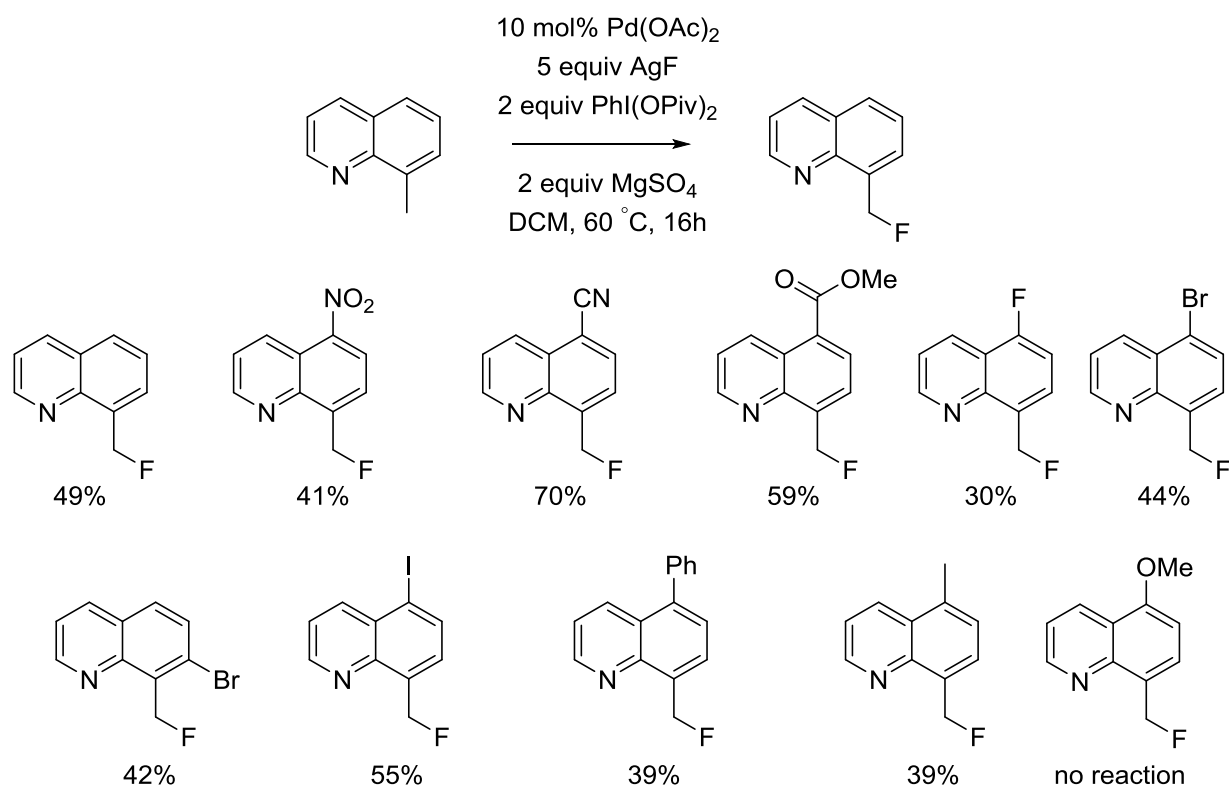
In a report by Toste, isolated alkylgold complexes supported by an NHC ligand were exposed to XeF₂ in an attempt to observe C-F formation by reductive elimination from a gold (III) difluoride species (Scheme 47).⁸⁴ Complexes bearing bulky alkyl groups produced some fluorinated products, and the use of cyclic alkyl groups to disfavour β-hydride elimination increased the conversion to fluorinated products. For some substrates alkyl migration was observed, with this

observation suggested as evidence of a cationic intermediate in C-F reductive elimination. A single example of IPr(benzyl)gold yielding benzyl fluoride in 85% yield was reported. More complicated benzyl systems were not investigated, but it might be expected from results with acyclic alkyl fragments that more complex secondary benzylic fluorides would not be accessible using this methodology, rather the expected products would be the corresponding styrenes.



Scheme 48: C-H Activation-Fluorination⁸⁵

These stoichiometric studies suggest that the C-F reductive elimination at benzylic centres is challenging but achievable, but do not provide practical methodologies for the synthesis of benzylic fluoride targets. A C-H functionalisation/fluorination reaction disclosed by Sanford *et al* provides a rare example of a catalytic benzylic fluorination (Scheme 48).⁸⁵ The main drawback to this methodology is the requirement for a directing group - in this case a quinoline ring nitrogen atom - to enable access to the Pd(II) alkyl complex. This methodology also makes use of an electrophilic source of fluorine, this makes it expensive and less applicable to late stage functionalisation, a key goal of metal catalysed reactions, due to the poor functional group compatibility of some of these reagents.



Scheme 49: C-H Oxidative Nucleophilic Fluorination of 8-methylquinolines⁸⁶

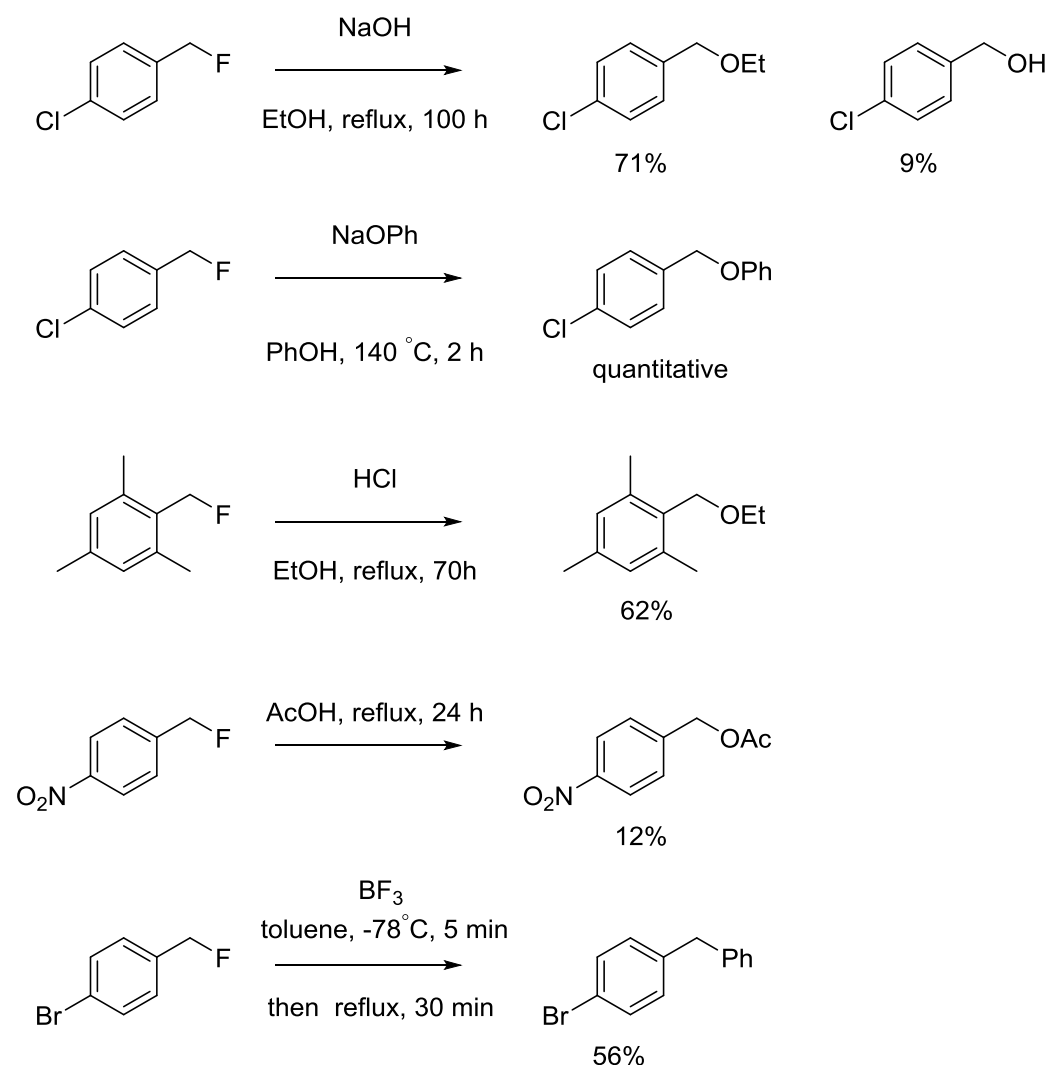
An improvement on this methodology that enables the use of a nucleophilic fluoride source is to separate the roles of oxidant to generate the high valent metal complex and fluoride source.⁸⁶ The use of a hypervalent iodine oxidant and silver(I) fluoride accomplished this reaction (Scheme 49).

The substrate scope for the fluorination reaction was again limited to quinolines, and there was no attempt to extend this to alternate scaffolds which might support sp^3 C-H activation. Encouragingly, a range of aryl substituents were amenable to reaction, with electron poor (NO_2 , CN, CO_2Me) and Pd labile (Br, I) groups providing reasonable yields (Scheme 49). Electron rich substrates did not react successfully.

1.3 Reactivity of Benzylic Fluorides

Despite the reputation of fluoroorganic molecules as unreactive there is a significant body of literature detailing the reactivity of benzylic fluorides under various conditions. Hydrogen fluoride is very stable, the solvation of fluoride ions is very favourable in protic solvents and many metal fluorides have very high enthalpies of formation; thus if it is possible to eliminate fluoride ions then many defluorination reactions are thermodynamically favoured, even though activation energies can be significant. This statement is true for much of organofluorine chemistry but generally kinetic barriers prevent reactivity.

1.3.1 Classical Benzyl Halide Reactivity

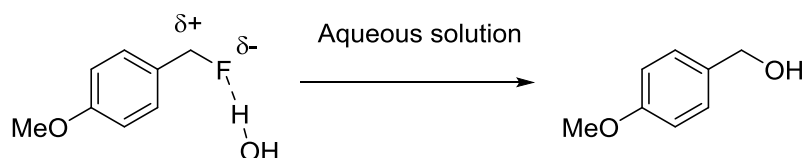


Scheme 50: Electrophilic Reactivity of Some Benzylic Fluorides⁴⁵

The reactivity of benzyl fluorides is significantly lower than that of the corresponding chlorides or bromides, however they will undergo some classical nucleophilic displacement reactions under forcing conditions (Scheme 50). Reaction is possible under basic conditions: treatment of *para*-chlorobenzyl fluoride with NaOH in ethanol under reflux for 100 h gave the ethyl ether in 71% yield, with 9% benzyl alcohol. Similarly, treatment of the same benzyl fluoride with sodium phenolate in molten phenol for 2 h at 140 °C gave a quantitative yield of the phenyl ether. The benzyl fluorides studied were less reactive under treatment with acidic reagents: treatment of 2,4,6-trimethylbenzyl fluoride with HCl in ethanol at reflux for 70 h gave the corresponding ether in 62% yield; 4-nitrobenzyl fluoride however gave only a 12% yield of the corresponding acetate after 24 h of heating under reflux in glacial acetic acid. In contrast to these nucleophilic displacements, the use of benzyl fluorides as precursors for Friedel-Crafts alkylation is facile: treatment of 4-bromobenzyl fluoride in toluene with BF₃ gas gave the product of alkylation in 56% yield after a 30 minute reflux.⁴⁵ In summary, benzyl fluorides are poor electrophiles in comparison to chlorides and bromides in simple displacement reactions, but will undergo reaction to give acceptable yields of displacement products under forcing conditions; the exception to this is Lewis acid catalysed alkylation, which is a facile reaction, presumably due to the strength of the B-F bond formed on abstraction of fluoride to create the active electrophile.

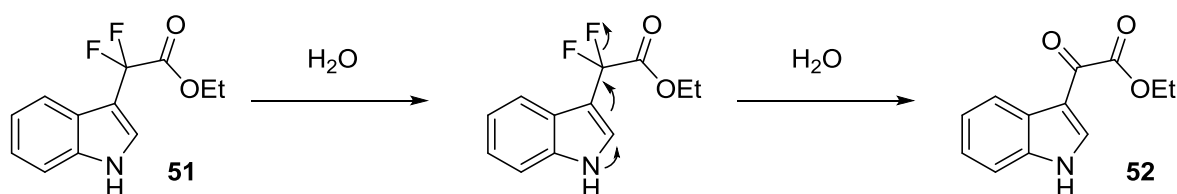
1.3.2 Solvolysis

Both activated (benzyl,⁸⁷ α -D-glucopyranosyl fluoride⁸⁸) and unactivated (alkyl⁸⁹) fluorides are vulnerable to specific acid catalysed solvolysis, which may be accelerated by the presence of acid catalysts. Some of these systems also suffer from autocatalytic decomposition due to the generation of HF in the solvolysis reaction, in contrast to organochlorine and bromine molecules, for which acid catalysis of solvolysis is relatively rare.



Scheme 51: Solvolysis of 4-Methoxybenzyl Fluoride⁹⁰

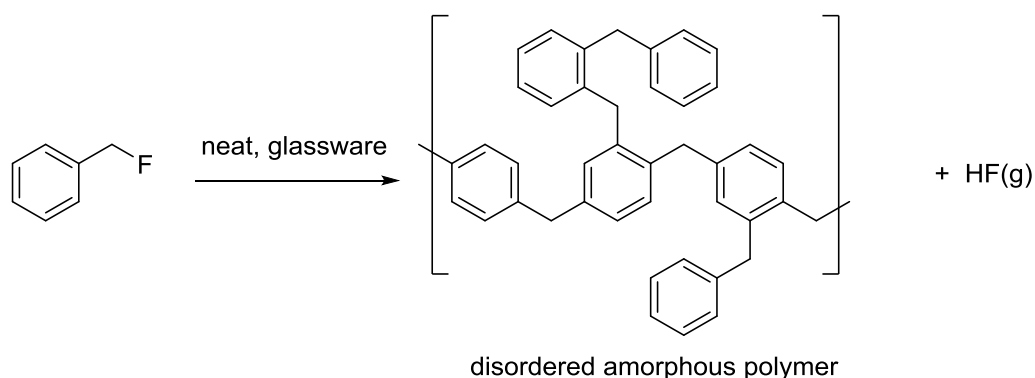
The high charge density of fluoride ion makes it a very good hydrogen bond acceptor, and this effect may serve to stabilise the developing negative charge on fluorine in a C-F bond cleavage step. If the electrofuge is also able to stabilise a developing positive charge then the reaction may become kinetically accessible, as in the case of 4-OMe benzyl fluoride (Scheme 51).⁹⁰



Scheme 52: Solvolysis of Difluoroindole Acetic Acid Ethyl Ester⁹¹

Most multiply fluorinated compounds are relatively inert to solvolysis, due to the increased bond strengths of a polyfluorinated molecule and the steric screening provided to the reacting centre by the fluorine atoms. α,α -Difluoroindoleacetic acid **51** however reacts readily with water to provide the carbonyl compound **52** (Scheme 52). In this case the indole nitrogen assists in this decomposition, presumably by stabilising the cationic intermediate. This is a fairly common theme in defluorination chemistry – the assistance provided by lone pairs or other interactions which stabilise a developing charge on fluorine lead to lowering of the activation energy for defluorination.⁹¹

1.3.3 Self Condensation



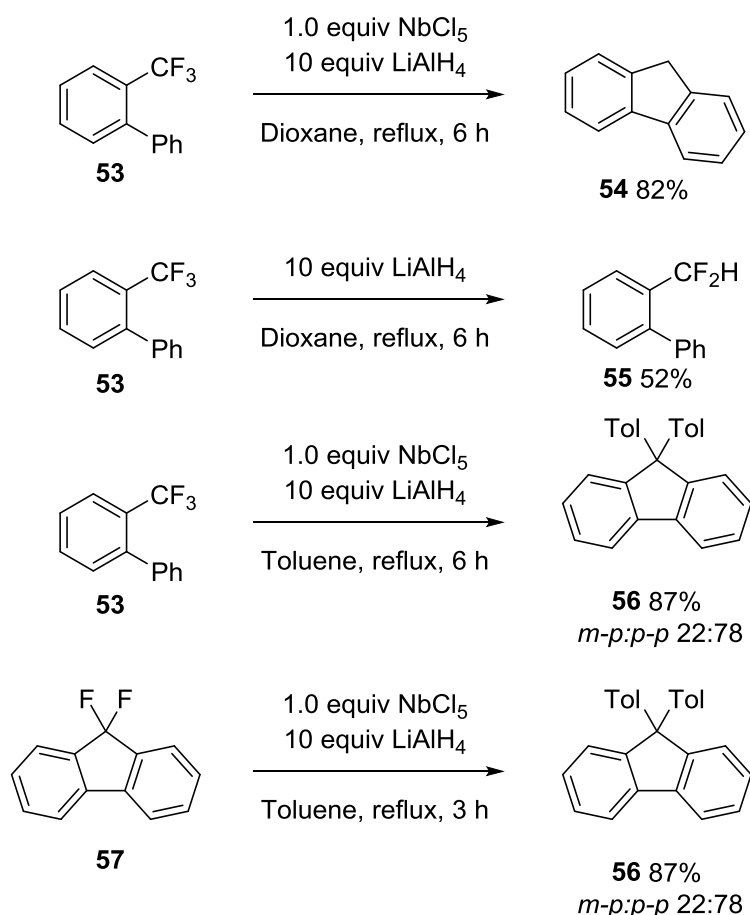
Scheme 53: Decomposition of Benzyl Fluorides⁴⁵

In a manner similar to the solvolysis of benzylic fluorides, some benzylic fluorides have the tendency to polymerise on storage to produce amorphous disordered polybenzyl material (Scheme 53); as mentioned in the previous section, this decomposition is autocatalytic with generation of HF.^{44, 45} This effect has been documented in some detail for the related allylic fluorides,⁹² and it is clear that the reaction is initiated by Lewis acid boron sites on the surface of standard laboratory glassware; it can also be initiated by traces of a strong acid such as H₂SO₄.⁹³ Silylation of glassware or use of different storage media (plastic, soda lime glass) can ameliorate this tendency. The decomposition is most problematic with electron rich aryl systems, due to both the greater stabilisation of the positive charge in the C-F cleavage step and the greater nucleophilic reactivity of the aromatic rings.

1.3.4 Reductive Defluorination

Hydrodefluorination has been proposed as a means to mediate organofluorine wastes which are otherwise persistent in the environment.⁹⁴ The uncontrolled reaction of alkali metals with perfluorinated materials is a highly exothermic reaction but generally leads to complete consumption of the organic material. Methods which selectively replace benzylic fluorine moieties with hydrogen are perhaps more synthetically useful, and may allow access to structures that would otherwise be difficult to synthesise, for example, whilst it is relatively facile to exhaustively fluorinate organic molecules, stopping this at an intermediate stage is essentially

impossible - selective defluorination might allow access to partially fluorinated materials which could not be produced directly.

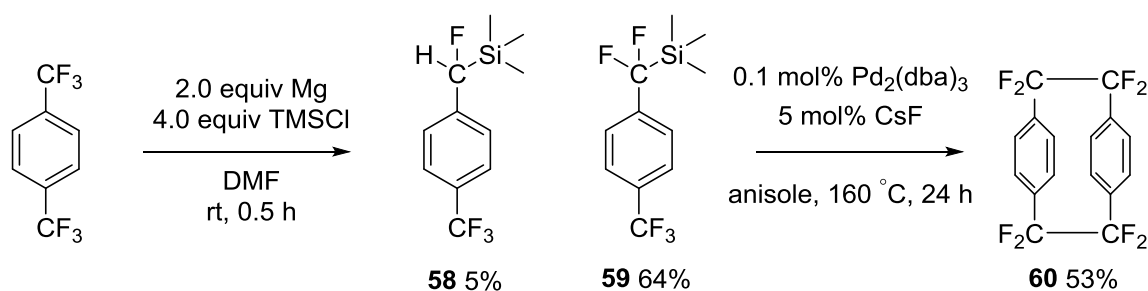


Scheme 54: Niobium Mediated Reductive Defluorination of Benzylic Positions⁹⁵

Niobium catalysts are capable of the reductive defluorination of vinylic, allylic and benzylic fluorides. This methodology is rare in that it will readily attack trifluoromethyl groups (Scheme 54), which are highly inert as discussed earlier. Due to the high activities of reactive systems able to activate multiply fluorinated centres, it is not generally possible to partially defluorinate molecules. This due to the lower C-F bond strengths encountered in partially fluorinated compounds, so in systems with multiple fluorine moieties multiple products will often be observed. An example of note of partial defluorination comes from the same publication as for the Nb mediated defluorination, where a control reaction of 2-trifluoromethylbiphenyl **53** in the absence of metal salts produces the difluoromethyl compound **55** as the major product. There was no mechanistic rationale for why this product is produced.

The synthetic utility of this transformation is low, but for *ortho* aryl trifluorotoluene substrates the main product observed after reaction is the fluorene **54** - this provides some insight into a possible reaction mechanism, proceeding via a carbene intermediate which can insert into the proximal C-H bond. Reaction in toluene rather than dioxane leads to the formation of a mixture of toluene adducts **56** through the *meta* and *para* positions. It is uncertain whether cyclisation occurs prior to formation of toluene adducts or *vice versa* but difluorofluorene **57** is also amenable to dehydrofluorination, producing similar but not identical yields of the same toluene adducts as for the reaction of 2-trifluoromethylbiphenyl, so presumably at least two pathways are operative under the reaction conditions.

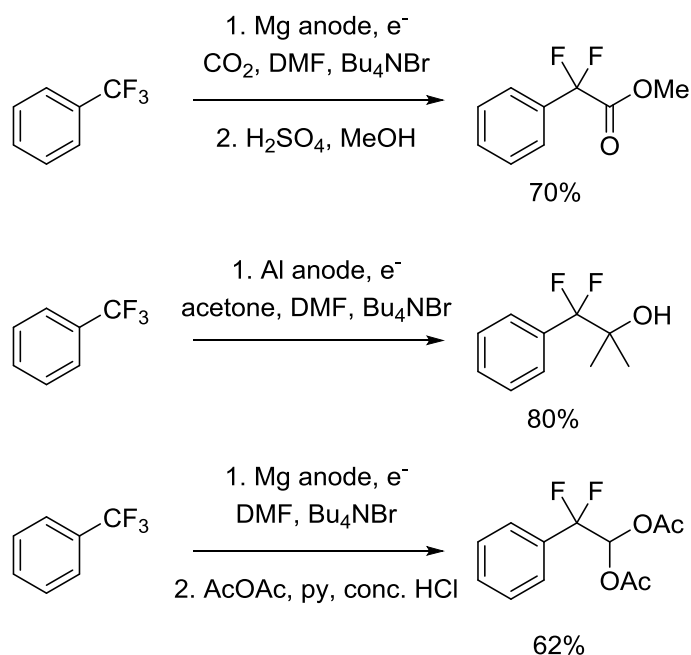
Despite the fact that benzyl fluorides do not form Grignard reagents, even under forcing conditions of reaction with activated magnesium at 100 °C for 10 days,⁴⁵ reaction of Mg(0) with a π -system adjacent to a trifluoromethyl group is relatively facile, presumably due to the lowering of the LUMO by the presence of the CF₃ group, generating an intermediate that can react with an electrophile to yield selectively a CF₂ unit (which may be either sp² or sp³ hybridised depending on the substrate).



Scheme 55: Reductive Defluorosilylation of Trifluoromethyl Groups⁹⁶

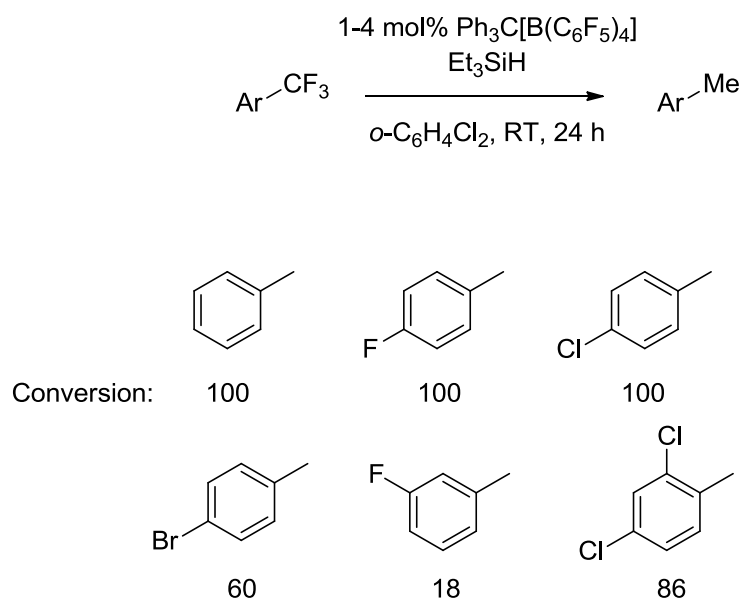
The selectivity possible in this reaction is demonstrated by the activation of a single C-F bond in 1,4-difluoromethylbenzene to replace a C-F moiety with C-SiMe₃ (Scheme 55).⁹⁶ There is generation of a small amount of a further hydrodefluorinated byproduct **58**, whose origin the authors could not explain. Compound **59** can undergo net elimination of TMS-F catalysed by CsF, followed by dimerisation to afford AF4 **60**, a precursor to a chemical vapour deposition (CVD) polymer used for to its high oxidative and chemical stability.

1.3.5 Electrochemical reduction

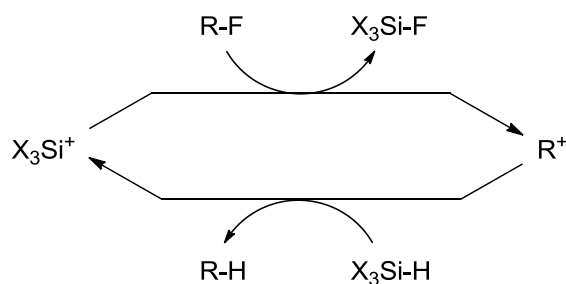
Scheme 56: Electroreductive Defluorination of PhCF₃⁹⁷

Electrochemical reduction is another methodology used to activate benzylic C-F bonds in CF₃ groups. Partial electrodefluorination of trifluoromethyl groups is possible in the presence of a sacrificial anode and appropriate electrophile (Scheme 56).⁹⁷ The anion generated on reduction of the CF₃ group reacts with the electrophile to generate a species PhCF₂E. The electrophile used may be CO₂, acetone or DMF, affording acid, dimethyl carbinol or aldehyde respectively after work up. The reaction appears to be completely selective for the CF₃ group, implying that the reactivity of the products towards defluorination is significantly reduced. This is unusual in defluorination chemistry, as the CF₃ group owes its high stability to the shielding and bond strengthening provided by multiple C-F bonds. Due to the partial loss of this stability, CF₂ groups are expected to be less stable, and monofluoromethyl less stable still.

1.3.6 Lewis Acid Catalysed Defluorination

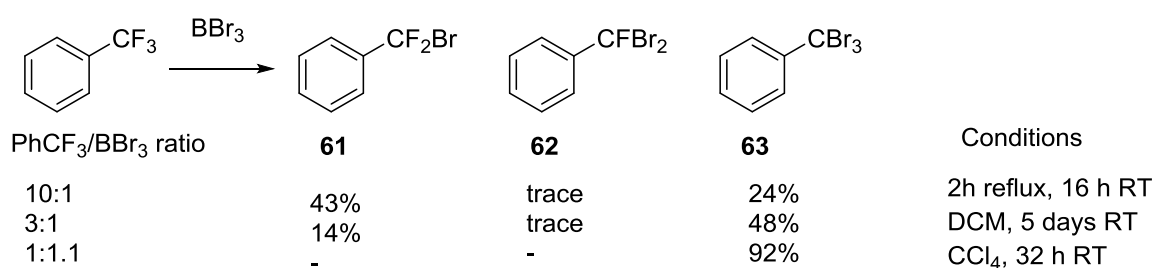
Scheme 57: Silylium Catalysed C-F Hydrodefluorination⁹⁸

Due to the exceptional stability of the Si-F bond (145 kcal mol⁻¹ in SiF₄⁹⁹) it might be expected that a Lewis acidic silicon centre would be a good choice of catalyst for the activation of C-F bonds. Defluorination of aryl trifluoromethyl groups using a cationic silicon catalyst (Scheme 57) is possible but has a relatively narrow substrate scope. Electron rich substrates produce better conversions of exhaustively defluorinated products under catalysis, presumably due to better stabilisation of R⁺. Aryl halide substituents are tolerated, including fluoride - the instability of a putative Ar⁺ intermediate relative to benzylic stabilisation explains this selectivity between substituents. It was not possible to observe partially fluorinated benzylic fluorides by NMR, reflecting the higher reactivity of monofluoro and difluoro species towards cleavage reactions.⁹⁸

Figure 16: Catalytic Cycle for X₃Si⁺ catalysis

The catalytic system is based on the catalytic cycle shown in Figure 16. Highly electrophilic X_3Si^+ abstracts a C-F bond to generate stable X_3SiF and a carbocation which regenerates X_3Si^+ by abstraction of hydride from X_3SiH (this is a known reaction for Et_3SiH and $[Ph_3C][B(C_6F_5)_4]$), and the substrates used bear less cation stabilisation than Ph_3C^+ , this is used to generate the active catalyst *in situ*).

Based on the same conceptual thinking as the silicon cation based catalysis, the same authors developed the alkylative defluorination of benzylic trifluoromethyl groups.¹⁰⁰ The greater polarity of the Al-C bond was postulated to lead to more facile alkyl transfer to the putative carbocation intermediate. The transfer of methyl groups from $AlMe_3$ was slow but proceeded cleanly to yield $ArCMe_3$ derivatives, but with higher alkyl groups such as Et and *i*Bu, there were product mixtures formed for all substrates tested. For the more sterically hindered intermediate products β -hydride abstraction from the aluminium reagent (by the carbocation product of C-F cleavage) is favoured over alkyl transfer. The hypothesis that steric influence is responsible is supported by the fact that no $ArCH_3$ products are observed for $AlEt_3$ or $Al*i*Bu_3$. This suggests that the first C-F cleavage step is always combined with alkyl transfer, but for more sterically encumbered cations this reaction becomes uncompetitive. It is worthy of note that the catalyst activation step involves the reaction of Ph_3C [carborane] with $AlEt_3$, which produces ethene by hydride elimination to produce the active catalyst – the transfer of an ethyl group does not occur with this bulky carbocation.



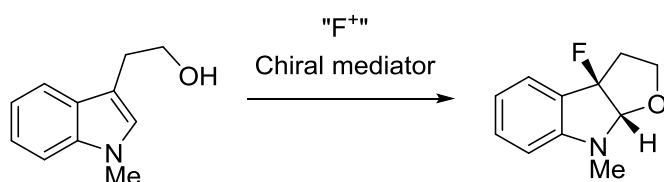
Scheme 58: Bromodefluorination of Trifluorotoluene¹⁰¹

To give access to halogenated benzylic fluorides, either radical halogenation or halodefluorination are viable routes. The reaction of trifluorotoluene with BBr_3 is unselective and slow despite the high stability of B-F bonds (Scheme 58).¹⁰¹ Under reagent limited conditions, whilst it is possible to isolate the monobrominated product **61**, in no case is it possible to isolate more than a trace of

the dibromo product **62**. The stability of the *gem*-difluoro unit is much higher than the monofluorinated compound, and thus the 3rd C-F cleavage must be a very rapid reaction. Even under conditions where the substrate is in vast excess, significant formation of the CBr₃ product **63** is observed, indicating the "downhill" nature of the C-F cleavage. In a ratio of 1:1.1 PhCF₃/BBr₃, 92% yield of PhCBr₃ is obtained after 32 h at room temperature in CCl₄, indicating that all of the bromine atoms of BBr₃ are transferrable (and that thus BFBBr₂ and BF₂Br must also be competent reagents for the transformation).

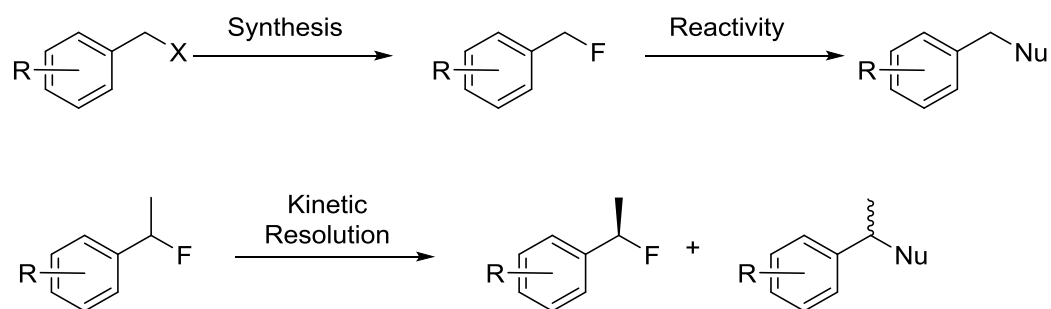
1.4 Aims of Thesis

The aim of this thesis is to investigate routes for the enantioselective preparation of benzylic fluorides. The research presented falls into two distinct themes: organocatalysis and metal catalysis. The enantioselective electrophilic fluorination-cyclisation of a prochiral precursor mediated by a *cinchona* based organocatalyst is described in Chapter 2 (Scheme 59). Chapters 3 & 4 concern metal catalysis: Chapter 3 details initial investigations of the chemistry of primary benzylic fluorides under palladium catalysis; and Chapter 4 describes attempts to adapt this defluorination methodology for the preparation of enantioenriched benzylic fluorides by kinetic resolution (both Chapters 3 & 4 are summarised in Scheme 60).



Scheme 59: Organocatalytic Cyclisation Strategy

The first strategy leads to heterocyclic benzylic fluoride compounds, which are high value targets in medicinal chemistry, due to both their potential bioactivity and the difficulty of enantioselective preparation of such compounds. Organocatalysts provide a powerful toolkit for the enantioselective optimisation of electrophilic fluorinations, and this has been extended in different cases to methods that use catalytic quantities of the *cinchona* alkaloid,¹⁰² to methods that provide enantioenriched cyclised material,¹⁰³ and to methods that provide benzylic fluoride products.^{104, 105} Our intention was to develop the methods described in the literature to enable enantioselective access to benzylic fluorides using a catalytic amount of the enantioselective reagent.

**Scheme 60: Catalytic Synthesis and Reactivity of Benzylic Fluorides**

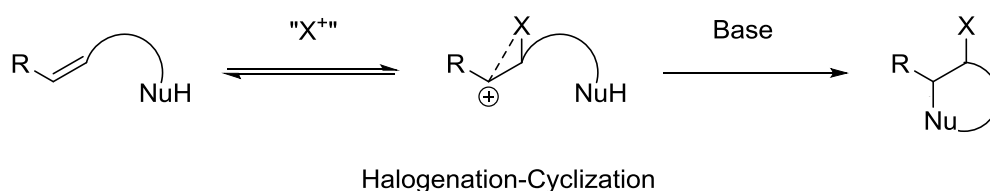
The second strategy builds on successful work within the Gouverneur group to adapt Tsuji-Trost methodology to fluorine chemistry. Development of the substitution of allylic fluoride substrates by carbon nucleophiles provided insights which enabled the development of a fluorination of allylic esters. The aim of our research was initially to examine the reactivity of benzylic fluorides in a similar fashion, to identify catalysts, leaving groups and conditions for fluorination of benzylic centres. This encompassed the investigation of the chemoselectivity and enantiospecificity of the defluorination reaction, the substrate scope and the nucleophilic partner scope. This investigation ultimately did not provide a successful nucleophilic benzylic fluorination reaction, but it was possible to develop the defluorination reaction to demonstrate a kinetic resolution of benzylic fluorides to access enantioenriched material.

Chapter 2: Organocatalysed Enantioselective Fluorocyclisation

The work described in this Chapter was performed in collaboration with Dr. Oscar Lozano and some of this data is described in a publication.¹⁰⁶

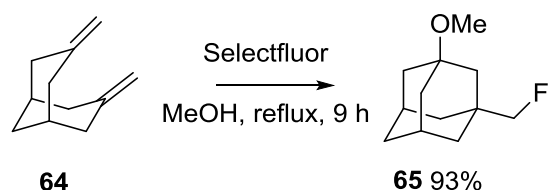
2.1 Fluorination Cyclisation

2.1.1 Halogenation Cyclisation



Scheme 61: Schematic Representations of Halocyclisation

Halogenation-cyclisation (Scheme 61) is a commonly used strategic step in synthetic chemistry, with accessible and reliable protocols for bromo- and iodo-cyclisations relying on cheap and readily available reagents. The substrate scope of these reactions is fairly general for small ring forming reactions, with little requirement for activation of alkenes due to the stabilisation afforded the transition state by the cyclic intermediate cations. Chloro-cyclisations and fluorocyclisations are less well developed, but there are still numerous examples of such reactions in the literature. The use of these reactions to construct benzylic halides is also precedented.

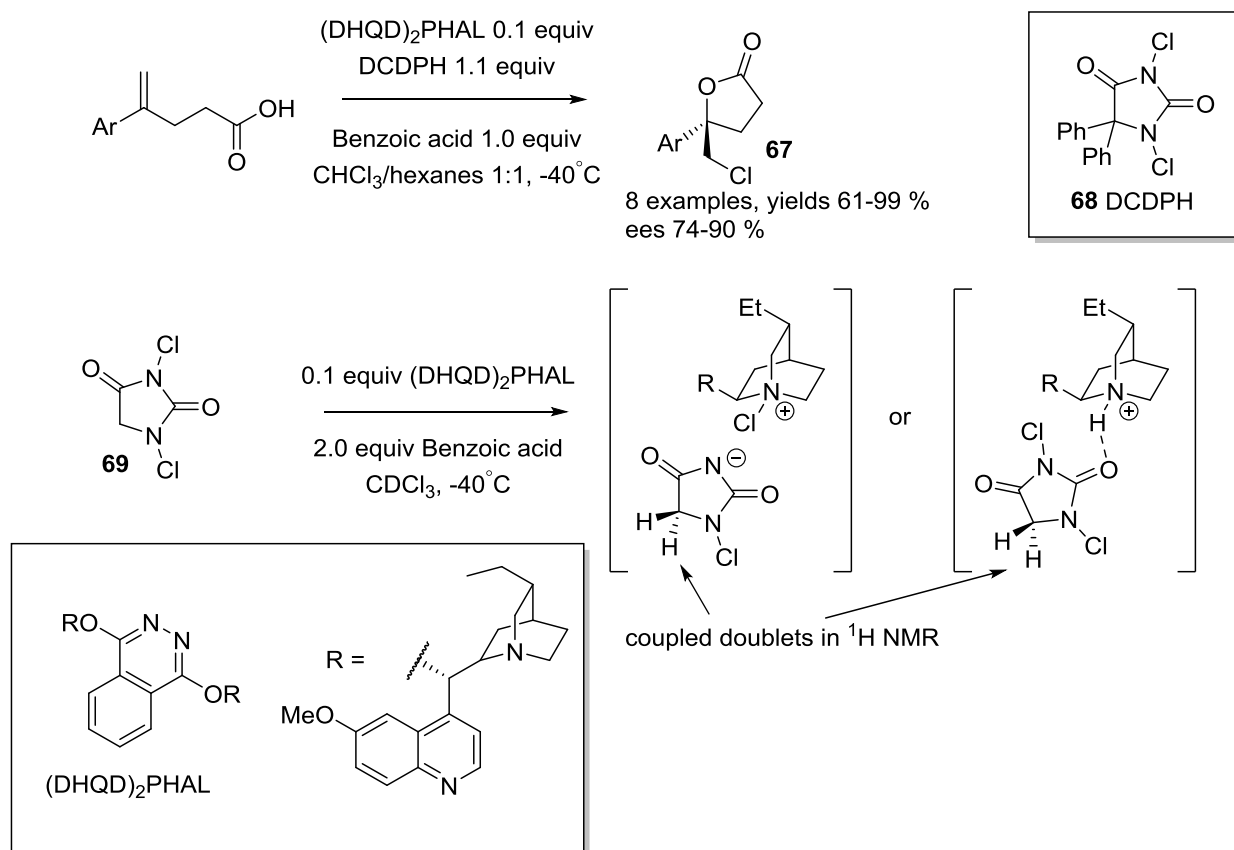


Scheme 62: Fluorination Cyclisation of Unactivated Olefins¹⁰⁷

Fluorination cyclisation typically requires a highly activated substrate, with a functionality capable of stabilising a carbocation adjacent to the carbon atom where C-F bond formation occurs. As mentioned in Chapter 1, this is due to the lack of stabilisation provided by the fluorine relative to the halonium ion stabilisation that is afforded by bromine and iodine (and as an equilibrium with the carbocation

species in chlorocyclisations). In fluorination cyclisation stabilisation of a positive charge may be achieved by silicon groups, benzylic positions or heteroatom lone pair donation. The nucleophilicity of a double bond and the power of the fluorinating reagent determine the rate of reaction, with examples of unactivated olefins requiring elongated heating under reflux to achieve reaction with Selectfluor (Scheme 62).¹⁰⁷

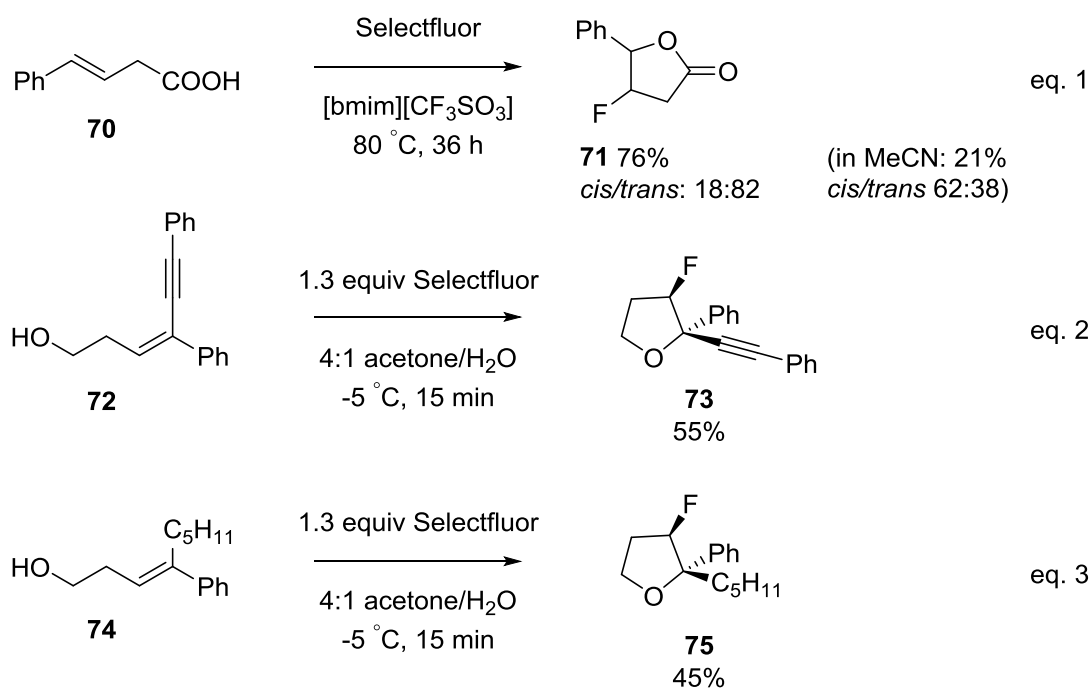
A major obstacle to the wider use of halocyclisations in synthesis is the difficulty of enantioselective halocyclisations. Schematically, these reactions must either start with an enantioselective C-X bond formation, followed by diastereoselective cyclisation, or a stereoselective cyclisation followed by a diastereoselective halogenation, with the first of these pathways being by far the more common mode of reaction. The initial C-X bond formation step thus sets the enantioselectivity of the reaction, and this enantioselective C-X formation can be achieved either by use of an enantiopure source of X⁺ or an enantiopure activating catalyst. For C-Br and C-I formation this is a reversible reaction step and can lead to loss of stereospecificity.¹⁰⁸ Both of these approaches have been demonstrated, but there are significant challenges in optimising the source of halide and chiral component, and matching the reactivity profiles to that of the precursor. The use of an enantiopure source of X⁺ can be achieved in a stoichiometric or catalytic sense. Stoichiometric reaction is clearly inefficient due to the generally high cost of enantiopure reagents, but catalytic generation of an enantiopure halogenating reagent which reacts preferentially with the substrate in the presence of a necessarily more reactive halogen source is a difficult problem to address. For the case of an enantiopure activating catalyst, background reactivity is a concern due to the unavoidable presence of the achiral halide source, which may itself be a competent reagent to effect the reaction in a racemic sense.

Scheme 63: Enantioselective Chlorocyclisation¹⁰⁹

Despite the conceptualisation of different asymmetric halocyclisation reactions as being separate, in practice it may be difficult to determine the exact role of catalyst and halogen source in the enantiodetermining step. The enantioselective chlorolactonisation shown in Scheme 63¹⁰⁹ is an example which may proceed through activation of the chlorohydantoin chlorination reagent or through chlorination of the cinchona alkaloid catalyst. When an equal ratio of dichlorohydantoin **69** and *cinchona* alkaloid dimer (DHQD)₂PHAL are mixed together it is possible to observe coupling between the enantiotopic protons in the hydantoin, evidence for the formation of a complex between the enantiopure catalyst and the chlorine source, though it is uncertain whether the hydantoin is a counterion to the chlorinated alkaloid which reacts with the alkene or whether this represents an activation of the hydantoin by the alkaloid to create an enantiopure complex reagent with higher reactivity than the uncoordinated hydantoin.

2.1.2 Fluorination Cyclisation

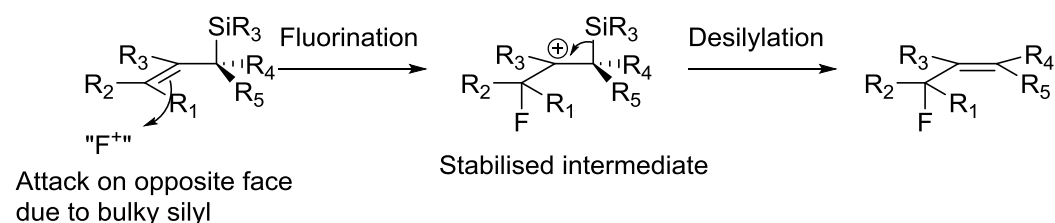
As mentioned in the previous section, fluorination cyclisation often tends to require highly activated substrates due to the difficulty of stabilisation of the fluorinated cationic intermediate. Reaction of unactivated substrates is possible under forcing conditions as shown in Scheme 62, but the requirement for highly active fluorinating reagents and high temperatures precludes the enantioselective development of these reactions – the reactivity of enantioselective reagents is addressed in the next section, but it is generally lower than the corresponding achiral reagents. To attempt enantioselective fluorination cyclisation it is thus necessary to design a substrate bearing an activating group.



Scheme 64: Benzylic Activation for Fluorination Cyclisation^{110, 111}

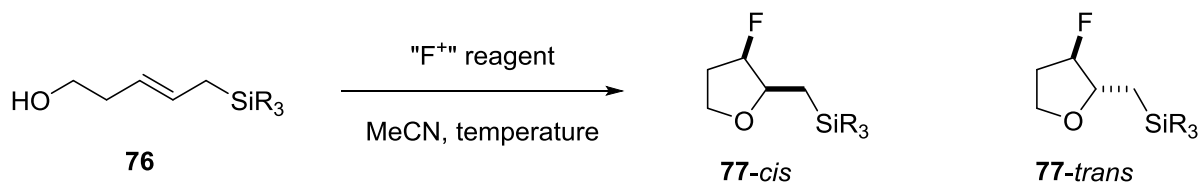
The simplest activating groups are aromatic rings, which can stabilise a benzylic cation, leading to fluorination at the homobenzylic position, with the cyclisation occurring at the benzylic position, as in Scheme 64. In the case where only benzylic activation is provided, an ionic liquid is required as solvent to increase the reactivity of Selectfluor (Scheme 64, eq 1), and even under these conditions the reaction requires 36 h at 80 °C to reach completion, giving 76% of a mixture of the *cis* and *trans* isomers of the cyclised product **71**. In acetonitrile only 21 % of the desired products are observed after

48 h at 80 °C. The remainder of the material undergoes side reaction with the solvent as opposed to cyclisation, reflecting the poorly stabilised nature of the cation.¹¹⁰ In contrast, substrate **72** bears an additional stabilising substituent – the alkyne; this substrate cyclises readily at -5 °C to give the product as a single diastereomer **73**. The corresponding substrate with an alkyl substituent at this position **74** also reacts under these conditions, giving a slightly lower yield, showing the additional stabilisation of a tertiary benzylic carbocation relative to the secondary cation intermediate for the cyclisation of **70**.¹¹¹



Scheme 65: Regiospecificity of Fluorodesilylation

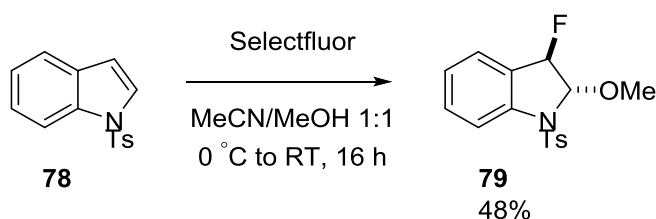
A reliable and efficient class of activating group for electrophilic reactions is a β -silyl group (Scheme 65). The C-Si bond is able to stabilise β carbocations and this reactivity has been developed to enable fluorodesilylation for the synthesis of allylic fluorides,⁶⁶ vinyl fluorides¹¹² and propargylic fluorides.⁷⁸ A representative example is shown below. The process is regiospecific due to the stereoelectronic demands of the stabilising interaction, and as such this reliably provides a specific isomer (Scheme 65). The silyl substituent acts as a leaving group to regenerate the double bond with transposition, leaving no trace of the activating group.



Entry	R ₃	Reagent	Temperature	Yield	Starting Material E / Z	cis / trans
1	(iPr) ₃	Selectfluor	RT	90%	2:1	2.5:1
2	(iPr) ₃	Selectfluor	RT	58%	1:10	1:8
3	(iPr) ₂ o-Tol	Selectfluor	RT	49%	1:18	1:6
4	(iPr) ₂ o-Tol	NFSI	reflux	60%	2:1	3:1

Table 5: Fluorocyclisation of Allylsilanes¹⁰³

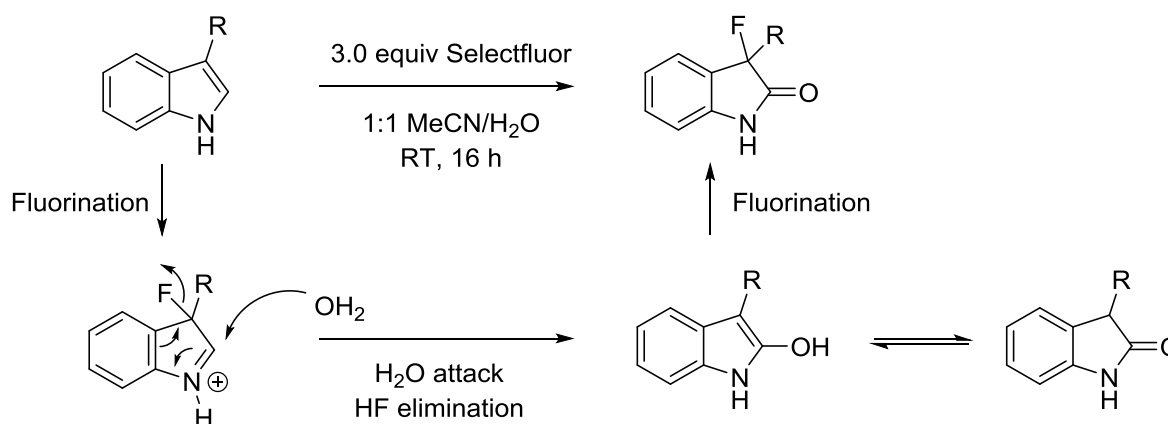
Modification of this methodology to enable fluorination cyclisation is possible, with the key challenge being the prevention of desilylation. The desilylation reaction with many silanes is fast relative to intramolecular nucleophilic attack, leading to fluorodesilylation rather than cyclisation.¹⁰³ A screen of different silyl groups identified the *triisopropylsilyl* group as the optimum group for cyclisation (Table 5), *diisopropylorthotolylsilane* was also an efficient group for cyclisation, with the advantage that it was possible to oxidatively cleave the activating group after reaction to give the alcohol. Dimethylbenzylsilane also provided the product in a poor yield but with many byproducts. The reaction could be performed in a short time at room temperature in MeCN with Selectfluor or in several hours at reflux in MeCN with NFSI. The reaction is stereospecific with some erosion of stereochemistry: *E* alkenes provide the *cis* product and *Z* alkenes the *trans* – stereochemical information is better conserved in the fluorination of *E* alkenes, which also provide higher yields of cyclised products. Allylsilanes as activating groups were also used in a fluorocyclisation mediated by a *cinchona* alkaloid which proceeded with a low enantioselectivity, but due to the low reactivity of the fluorinating agent this required 4 days at -20 °C to reach full conversion (see the next section for a discussion of enantioselective fluorination). This demonstrates one of the major problems with enantioselective fluorination – the limited reactivity of the enantiopure F⁺ sources.



Scheme 66: Fluorination - Methoxylation of *N*-Tosylindole¹¹³

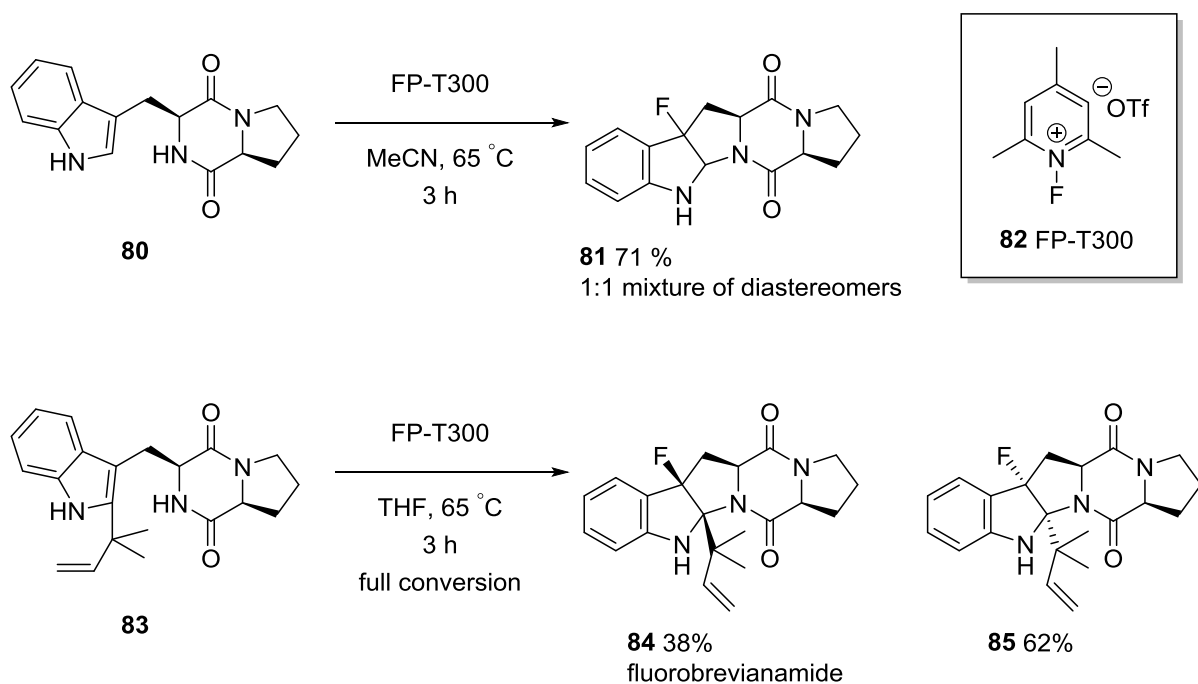
The indole nucleus is highly nucleophilic and will readily react with fluorinating reagents to give a range of products depending on the exact substitution pattern of the indole. Unsubstituted indole **78** bearing a deactivating tosyl group on nitrogen undergoes fluorination-nucleophilic addition on treatment with Selectfluor in the presence of methanol to give the benzylic fluoride *trans* product **79** (Scheme 66).¹¹³ The reaction of unprotected indoles is difficult to control and tends to be prone to side

reactions to give unfluorinated products - the inherent reactivity of the ring system towards F^+ reagents is high.



Scheme 67: Fluorination/Hydrolysis/Fluorination Synthesis of Oxindoles¹⁰⁵

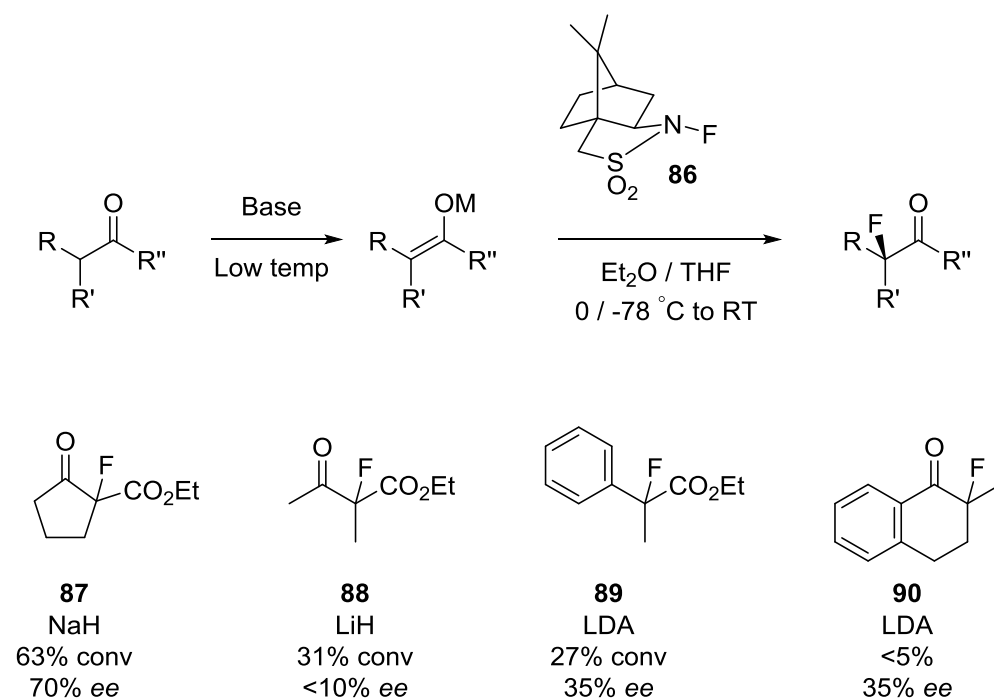
The reaction of 3-substituted indoles with fluorinating reagents is similarly facile (Scheme 67).¹⁰⁵ In the presence of three equivalents of Selectfluor in acetonitrile/water, the initially formed fluorindole reacts with water, eliminating HF to give 2-position hydroxylation. This intermediate reacts with Selectfluor to give the fluorooxindole product (this compound is a tautomer of the oxindole, oxindoles are also competent substrates for electrophilic fluorination without added base¹¹⁴). The elimination of HF to give net oxidation of the oxindole underlines a key problem with the fluorocyclisation of indoles – the attack of water gives an unstable intermediate which can eliminate HF and lead to side reaction.



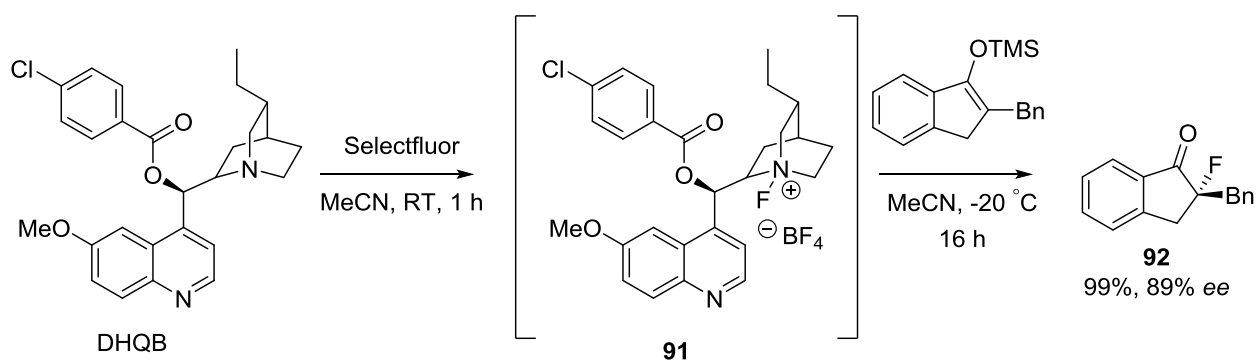
Scheme 68: Fluorination Cyclisation of Tryptophan-Proline Dimers¹⁰⁴

A fluorination cyclisation of an indole system has previously been reported for the synthesis of fluorinated analogs of brevianamide (Scheme 68).¹⁰⁴ Reaction of a series of cyclic dimers of tryptophan and other amino acids with Selectfluor at low temperature gave moderate yields of the cyclised products. Using the milder *N*-fluoropyridinium reagent FP-T300 **82** at 65 °C gave the same products in good yield. The reaction tolerated substitution on the 2-position with a bulky reverse prenyl group to give the natural product analog **84** as a minor product with the diastereoisomer **85** as the major product, in contrast to all reactions with indoles not bearing the reverse prenyl group where the products were observed as 1:1 mixtures of diastereomers.

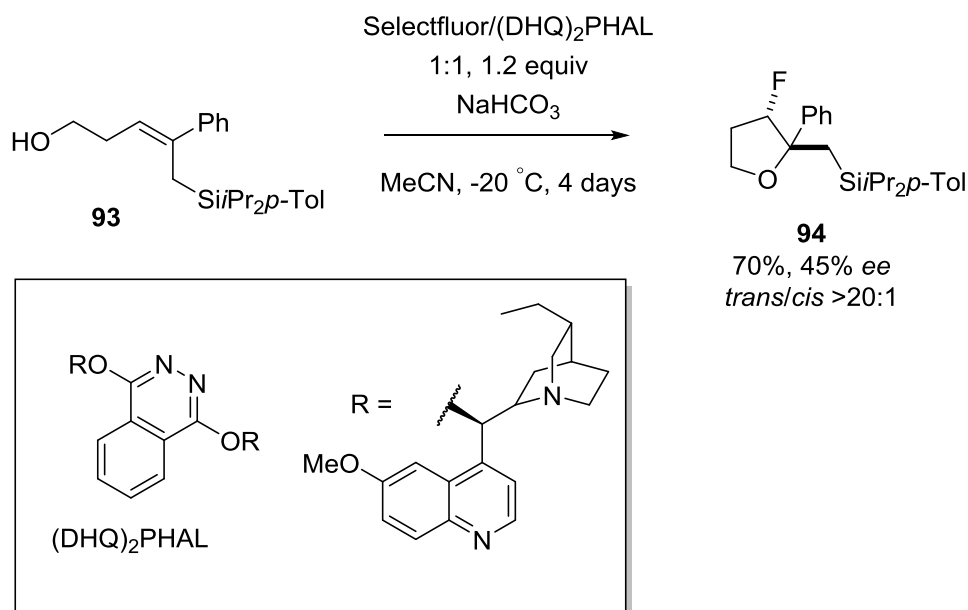
2.1.3 Enantioselective Fluorination

Scheme 69: Camphorsultam N-F Reagent as Enantiopure Fluorine Source¹¹⁵

The use of an enantiopure source of fluorine to effect an enantioselective fluorination was initially shown using a camphorsultam N-F reagent **86** (Scheme 69). Reaction with of a number of enolates gave variable yields of the corresponding fluorinated esters and ketones, with poor to good enantioselectivity depending on the substrate structure. This fluorinating reagent has not seen any further development due to the difficulty in its preparation, requiring F₂ gas, and the difficulty of derivatisation of the core to provide alternate reagents, but this introduced the concept of enantiopure N-F reagents which has since been developed to provide more user friendly methods and reagents.¹¹⁵

Scheme 70: Cinchona Alkaloid Mediated Enantioselective Fluorination¹¹⁶

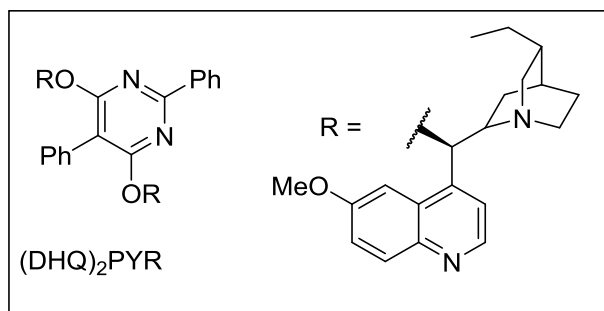
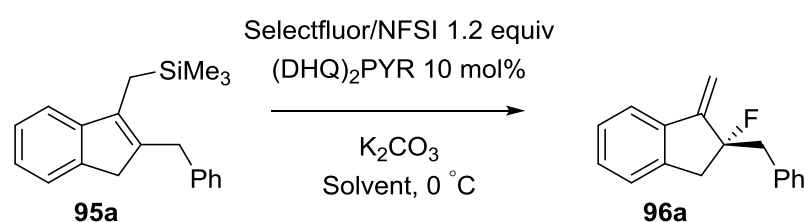
Currently the best method for enantioselective fluorination utilising an enantiopure fluorine source utilises a combination of a commercially available N-F reagent such as Selectfluor or NFSI and a *cinchona* alkaloid (Scheme 70).¹¹⁶ The N-F reagent that is generated from this combination can be used for electrophilic fluorination of enolates, enol ethers and allylsilanes with generally good enantioselectivities on a limited range of substrates. The availability of a range of *mono* and *bis-cinchona* alkaloids allows for rapid screening to find the appropriate reagent for maximum yield and enantioselectivity; conveniently the pseudoenantiomeric pairs of *cinchona* alkaloids give similar levels of enantioinduction in opposite directions, allowing for access to either enantiomer of a target compound. The operation of these reactions is simple; stirring equimolar amounts of Selectfluor and a *cinchona* alkaloid together for 1 h in MeCN at room temperature gives full conversion to the *cinchona* N-F reagent **91**, as monitored by ¹⁹F NMR; this reagent can either be isolated or used *in situ* for fluorination.¹¹⁷



Scheme 71: Enantioselective Fluorination Cyclisation of Allylsilanes¹⁰³

The use of this enantioselective fluorination methodology for enantioselective fluorination cyclisation has been performed within the Gouverneur group (Scheme 71). Treatment of the allylsilane substrate **93** (of the type discussed in the previous section on allylsilane activation) with a combination of (DHQ)₂PHAL and Selectfluor in MeCN at -20°C for 4 days gave a 70% yield of the fluorinated

product **94** in 45% *ee* with a diastereoselectivity of better than 20:1 in favour of the *trans* product (Scheme 71). This represents a good enantioselectivity for a reaction building two contiguous stereocentres from an open chain precursor, but the low reactivity of the substrate and resulting long reaction time is undesirable; it is clear that any attempt to fluorinate this substrate with a catalytically generated *cinchona* N-F reagent would have extreme difficulties with background reactivity with Selectfluor leading to racemic product.

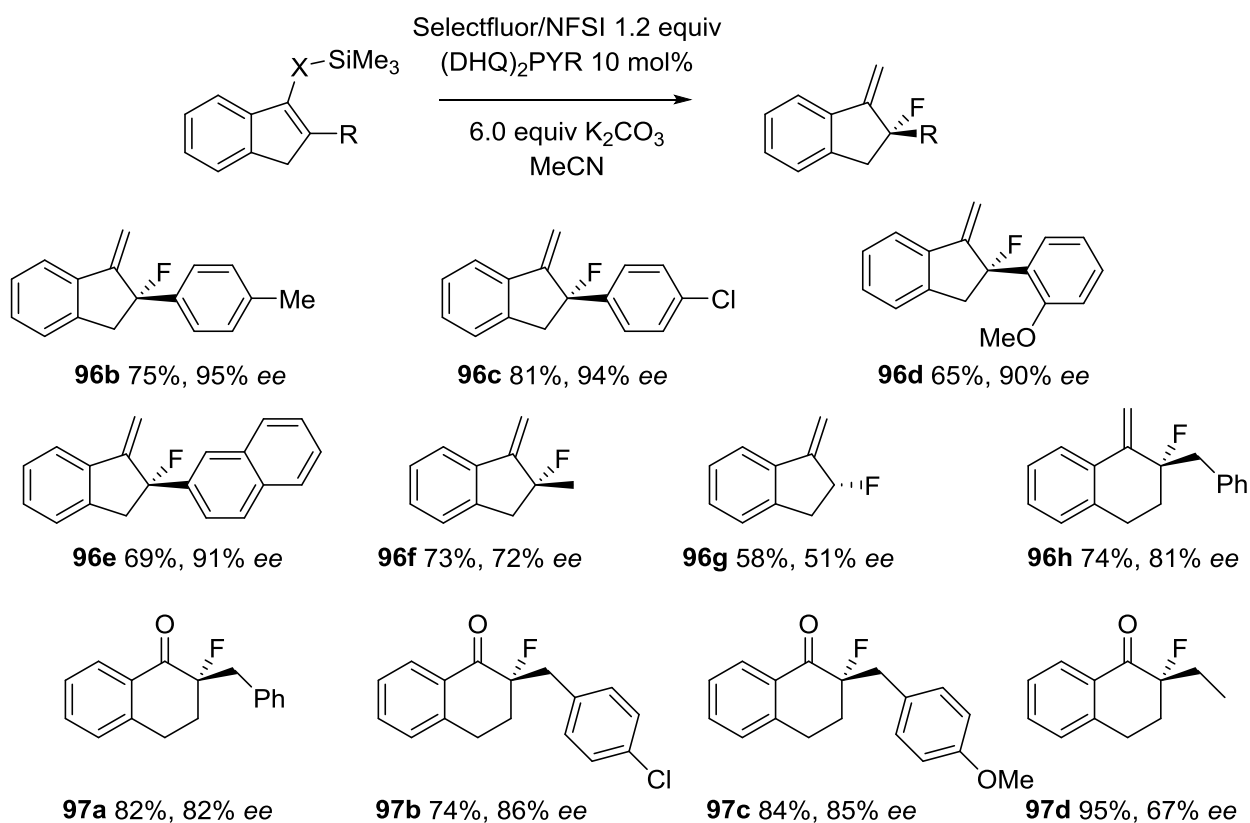


Entry	Fluorinating Reagent	K ₂ CO ₃ equiv	Solvent	Temperature, Time	Yield %	<i>ee</i> %
1	Selectfluor	0	MeCN	0 °C, 10 min	46	0
2	NFSI	0	MeCN	0 °C, 46 h	62	19
3	NFSI	1	MeCN	0 °C, 4 h	61	85
4	NFSI	3	MeCN	0 °C, 2 h	68	90
5	NFSI	6	MeCN	0 °C, 2 h	79	91
6	NFSI	6	MeCN	-20 °C, 9 h	63	94
7	NFSI	6	MeCN	-40 °C, 72 h	75	94
8	NFSI	6	MeCN	0 °C, 4 h	55	86
9	NFSI	6	THF	0 °C, 60 h	26	68
10	NFSI	6	Toluene	0 °C, 60 h	11	50

Table 6: Optimising the Catalytic Enantioselective Fluorination¹⁰²

The most recent application of this methodology for fluorodesilylation gave a significant improvement in the utility of the reagent combination as it allowed for the catalytic deployment of the *cinchona* alkaloid (Table 6).¹⁰² This is an important consideration given the high molecular weight and cost of these reagents (typically over 700 Daltons). Initial investigation of the use of 10 mol% alkaloid with Selectfluor showed no enantioselectivity (Table 6). Replacement of Selectfluor with

NFSI showed a promising 19% *ee* and this improved dramatically with the addition of 1 equivalent of potassium carbonate as a heterogeneous base, giving 85% *ee*. Reactivity was also much improved with added base, with the reaction reaching full completion in much reduced time. The use of a large excess of K_2CO_3 gave further improvement in enantioselectivity to 91%, as did reducing the temperature to $-20\text{ }^\circ\text{C}$, giving 94% *ee*. Reducing the temperature further to $-40\text{ }^\circ\text{C}$ did not increase enantioselectivity but did slightly increase the yield with prolonged reaction times. It is proposed that the addition of K_2CO_3 performs an anion exchange with the fluorinated alkaloid to give a more reactive enantioselective fluorinating agent.



Scheme 72: Substrate Scope for Catalytic Enantioselective Fluorination¹⁰²

The conditions developed for catalytic enantioselective fluorination was used in the fluorination of allylsilanes and oxindoles (Scheme 72). For the allylsilane substrates **95** the optimum alkaloid was $(DHQ)_2PYR$, but for enol ether substrates (giving fluoroketone products **97**) the highest enantioselectivity was observed with $(DHQ)_2PHAL$, again demonstrating the need for alkaloid screening in the development of enantioselective fluorination reactions. A variety of aromatic

substituents are tolerated - this reaction constitutes a route to difficult to access enantioenriched quaternary benzylic fluorides. 5 and 6 membered rings both give good enantioselectivity. Less sterically demanding groups on the alkene tended to give poorer reactivity and significantly lower enantioselectivity, suggesting that this motif has a role in enantiodiscrimination.

2.2 Results and Discussion

Racemic reaction optimisation was performed by Dr. Oscar Lozano. Screening of *cinchona* alkaloids was performed jointly with Dr. Oscar Lozano.

Based on the literature concerning fluorination cyclisation and the requirements for a catalytic enantioselective reaction (sufficient reactivity towards enantiopure fluorinating reagent to compete with achiral halide source), we recognised that the reactivity of the substrate towards electrophilic fluorine sources would have to be relatively high. Of the examples presented which can provide benzylic fluorides, allylsilanes are unsuitably unreactive but indole substrates are highly reactive towards "F⁺" reagents.

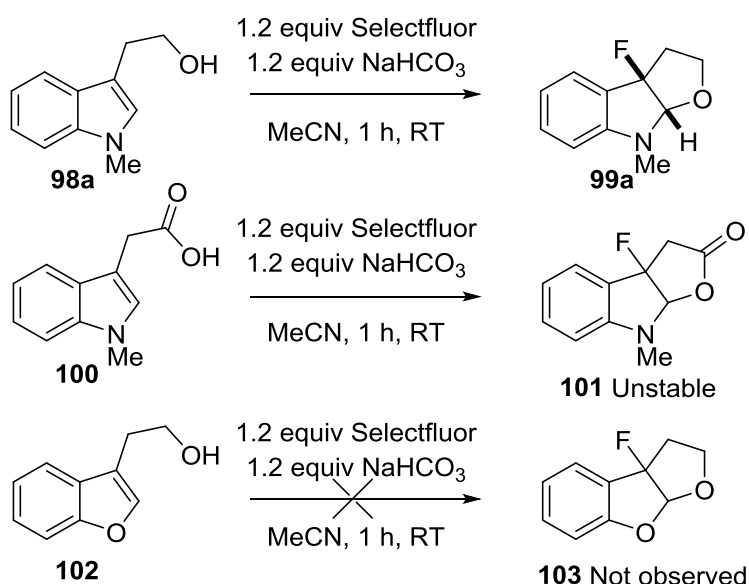
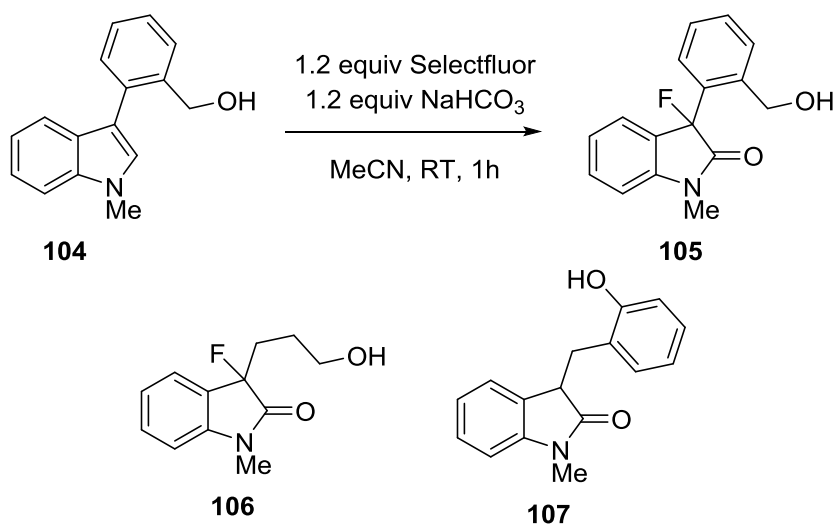


Figure 17: Initial Reaction Screening Substrates

Initial investigations focussed on the use of aromatic heterocycles as shown in Figure 17. On reacting these substrates with Selectfluor in the presence of NaHCO₃ in MeCN at RT, we were pleased to observe the product of fluorination-cyclisation **99a** in good yield for indole alcohol substrate **98a**. The 5-5 fused system ensures that only one diastereomer can be formed. This was confirmed by the observation of only one doublet at 5.49 ppm with a large *H-F* coupling of 19 Hz corresponding to the *cis* proton in the bicyclic system. This was confirmed by a heteronuclear Overhauser correlation between this proton and the fluorine atom. The acid substituted indole **100** cyclised successfully as

judged by ^1H NMR analysis of the crude reaction mixture but the product of cyclisation **101** was very unstable, to such a degree that it was not possible to isolate the pure product. The benzofuran substrate **102** was consumed to give no identifiable products of fluorination cyclisation in a complicated mixture.

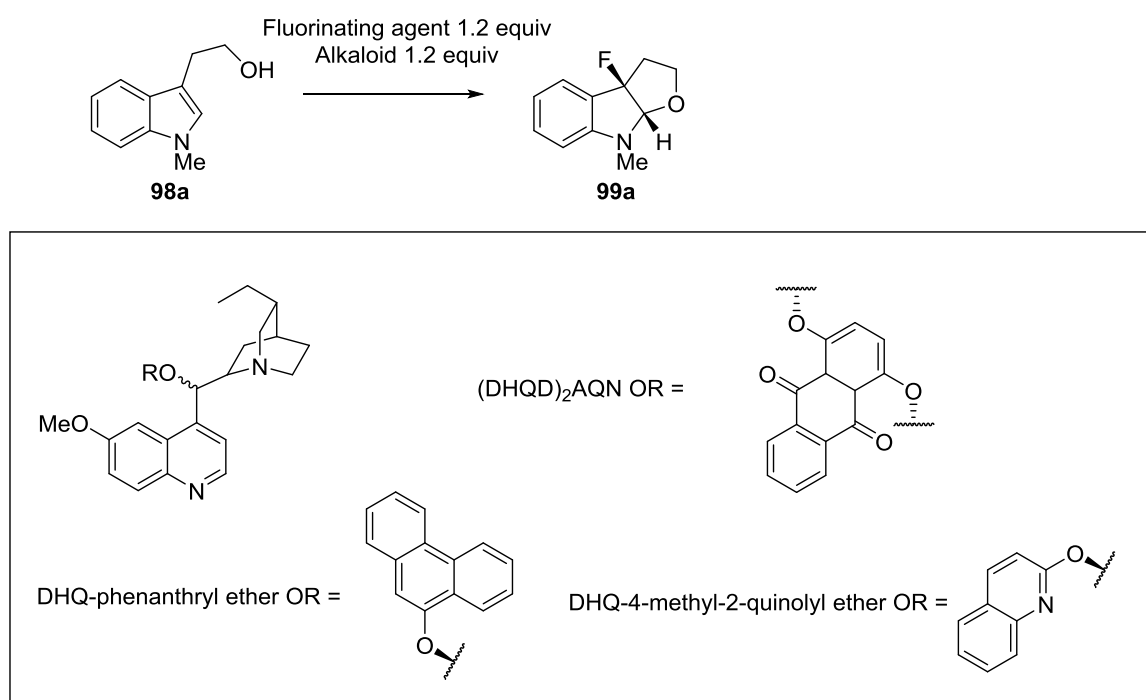


Scheme 73: Alternate Tether Lengths Lead to Non Cyclizing Substrates

We then attempted the cyclisation of substrates which would provide a 6-membered ring on cyclisation, shown in Scheme 73, these included a phenolic substrate which was of interest as it represented a different class of nucleophile to those that had been used in fluorocyclisation before. Generally 6-membered cyclisations occur more slowly than 5-membered cyclisations, and thus give lower yields and are more difficult to perform. This was true of these substrates; it was not possible to observe the products of cyclisation for substrates bearing longer tethers. Instead on exposing the requisite precursors to reaction conditions the fluorooxindole products **105** and **106** and the oxindole **107** were identified in the crude ^1H NMR of each reaction.

For the initial hit substrate **98a** the reactivity was examined under a range of different conditions to better understand the conditions that would be required for enantioselective reaction (Table 7, entries 1-4). **98a** reacted rapidly with Selectfluor and NFSI at room temperature (complete in 1h) and slowly with NFSI at $-78\text{ }^\circ\text{C}$ (complete in 16h). The reaction would operate in all solvent systems examined,

with acetone giving slightly poorer yields than MeCN but allowing the use of lower temperatures, which was considered a potentially important variable to increase enantioselectivity.



Entry	Fluorinating Agent	Alkaloid	Solvent	Temp	Yield	<i>ee</i>
1	Selectfluor	-	MeCN	RT	73	-
2	Selectfluor	-	acetone	RT	60	-
3	NFSI	-	MeCN	RT	76	-
4	NFSI	-	acetone	-78 °C	73	-
5	Selectfluor	DHQB	MeCN/DCM	-78 °C	30	30
6	Selectfluor	DHQ-phenanthryl ether	MeCN	RT	53	5
7	Selectfluor	DHQ-4-methyl-2-quinolyl ether	MeCN	RT	75	13
8	Selectfluor	(DHQ) ₂ PYR	MeCN	RT	50	20
9	Selectfluor	(DHQD) ₂ AQN	acetone	-78 °C	49	0
10	Selectfluor	(DHQ) ₂ PHAL	MeCN	RT	72	55
11	Selectfluor	(DHQ) ₂ PHAL	MeCN	-30 °C	55	59
12	Selectfluor	(DHQ) ₂ PHAL	acetone	-78 °C	56	74
13	Selectfluor	(DHQ) ₂ PHAL	THF	-78 °C	64	64
14	Selectfluor	(DHQ) ₂ PHAL	DCM	-78 °C	64	66
15	Selectfluor	(DHQ) ₂ PHAL	DCM/MeCN	-78 °C	50	68
16	Selectfluor	(DHQD) ₂ PHAL	acetone	-78 °C	65	-12

Table 7: Alkaloid Optimisation for Enantioselective Fluorination Cyclisation

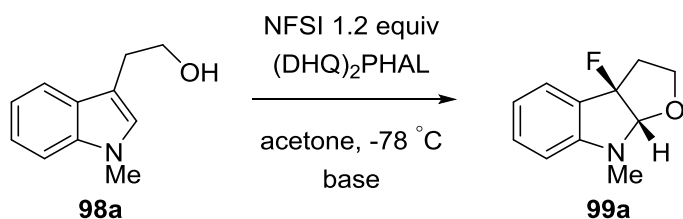
With an understanding of the potential range of successful conditions for fluorination-cyclisation, screening was performed using a range of *cinchona* alkaloid based organocatalysts in a stoichiometric fashion (Table 7). The reactions were performed by adding a solution of the substrate to the pre mixed

alkaloid and Selectfluor solution with NaHCO_3 , then stirring at $-78\text{ }^\circ\text{C}$. The enantioselectivity of reaction was assessed by chiral stationary phase HPLC against a sample of the racemic material prepared in the absence of any alkaloid. From this investigation it was clear that $(\text{DHQ})_2\text{PHAL}$ was the optimal ligand for enantioselectivity. Interestingly, the pseudoenantiomer $(\text{DHQD})_2\text{PHAL}$ gave a significantly worse result for the opposite enantiomer, so it is not necessarily possible to access the opposite enantiomer in high *ee*.

All other alkaloids tested amongst *mono* and *bis cinchona* alkaloids gave significantly worse enantioselectivities. This is somewhat surprising due to the similarities between the various *bis* alkaloids but reflects the non-predictive nature of this methodology. In an attempt to increase enantioselectivity the temperature was reduced, first to $-30\text{ }^\circ\text{C}$ in MeCN, then to $-78\text{ }^\circ\text{C}$ in a range of polar aprotic solvents. The reduction in temperature gave a very slight increase in enantioselectivity at $-30\text{ }^\circ\text{C}$, but gratifyingly reaction at $-78\text{ }^\circ\text{C}$ gave a significant increase in enantioselectivity to 74 % *ee*. The use of solvents other than acetone or MeCN gave similar yields but slightly lowered enantioselectivities, it was decided on the basis of this screening to continue efforts at catalytic optimisation at $-78\text{ }^\circ\text{C}$ using acetone as solvent.

2.2.2 Catalytic Reaction Development

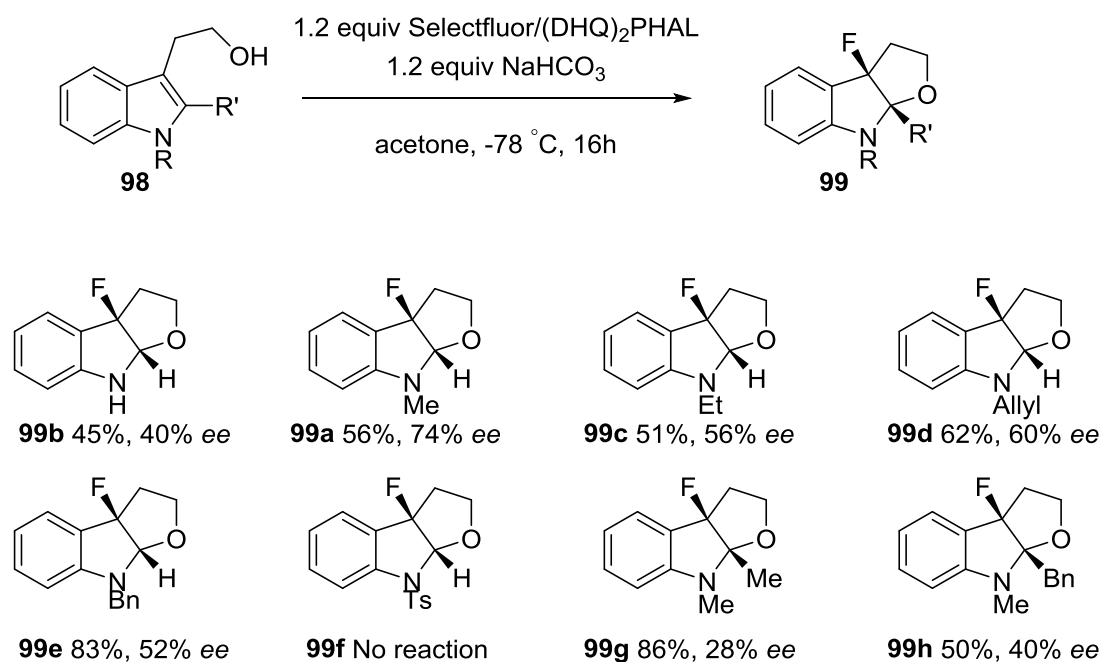
Catalytic reaction conditions were developed jointly with Dr. Oscar Lozano, as were cyclisations of 1- and 2- substituted substrates.



Entry	Equivalents of alkaloid	Base	Yield	<i>ee</i>
1	0.1	K ₂ CO ₃	50	50
2	0.2	K ₂ CO ₃	72	66
3	0.2	Cs ₂ CO ₃	58	66
4 ^a	0.2	K ₂ CO ₃	50	58
5	0.2	-	36	34
6 ^b	0.2	K ₂ CO ₃	47	32

Table 8: Catalytic Optimisation of Fluorination Cyclisation a) Reaction performed at RT b) Fluorine source was Selectfluor in place of NFSI

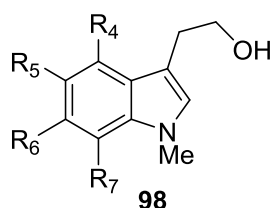
Direct application of the catalytic conditions as reported by Shibata *et al.*¹⁰² produced encouraging results, with only a modest deterioration in enantioselectivity with 20 mol% *cinchona* alkaloid in comparison to reaction with 120 mol% (66% vs. 74%) (Table 8). Reduction of the catalyst loading to 10 mol% lead to a significant decrease in enantioselectivity to 50% *ee*, so we continued screening with 20 mol%. Omitting the use of potassium carbonate gave a significantly poorer result, with only 36% isolated yield of the product with 34 % *ee*, demonstrating the importance of the base in the Shibata catalytic conditions. The use of caesium carbonate as an alternate base was also successful, with near identical results to potassium carbonate. Also noteworthy was the fact that the purification of catalytic reactions was much improved relative to stoichiometric reactions as the lower amount of alkaloid enabled better filtration of the reaction mixture, leading to a general increase in isolated yields of cyclised products for the catalytic reactions.



Scheme 74: 1- and 2- Substitution Effects on Fluorocyclisations

With these catalytic conditions in hand we tested the substrate scope of the reaction on the nitrogen atom in the stoichiometric reaction (Scheme 74). The unsubstituted substrate **98b** gave a poor yield of and enantioselectivity, whilst the tosyl substituted substrate **98f** failed to react with the fluorinating reagent due to its lower nucleophilicity. The methyl group proved optimal for enantioselectivity (**99a** 74% *ee*), with larger groups providing similar yields of cyclised products, but with poorer enantioselectivities (ethyl 56% *ee*, allyl 60% *ee*, benzyl 52% *ee*). The observation that steric demands at this position reduce the enantioselectivity of reaction was supported by the similarly poor performance of the 2-substituted substrates, 2-Me **98g** gave a good yield of cyclised product **99g** but with very poor *ee* (86%, 28% *ee*), whilst 2-Bn **98h** gave a moderate yield of **99h** and a slightly better *ee* (50%, 40% *ee*).

2.3 Alcohol Nucleophile Substrate Synthesis

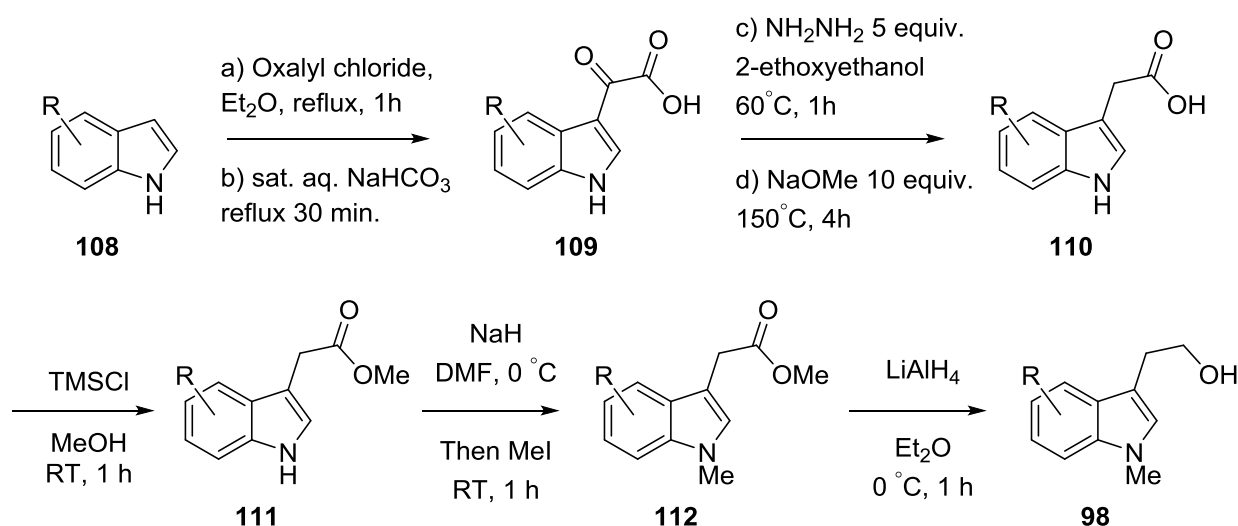


one of R groups = Ar, OR, Halide

Figure 18: Substrate Scope on “Benzene” Ring

With optimised conditions in hand we sought to probe further the substrate scope of the fluorination-cyclisation reaction, with a particular focus on the enantioselectivity of the reaction. To this end the synthesis of a range of substrates bearing the same pendant nucleophile was undertaken. Based on the initial investigations of substrate scope, demonstrating that 1- and 2- substitution were poorly tolerated, we aimed to synthesise a range of substrates with stepwise variation of substituents only on the "benzene" ring, maintaining an *N*-methyl group on the "pyrrole" ring (Figure 18).

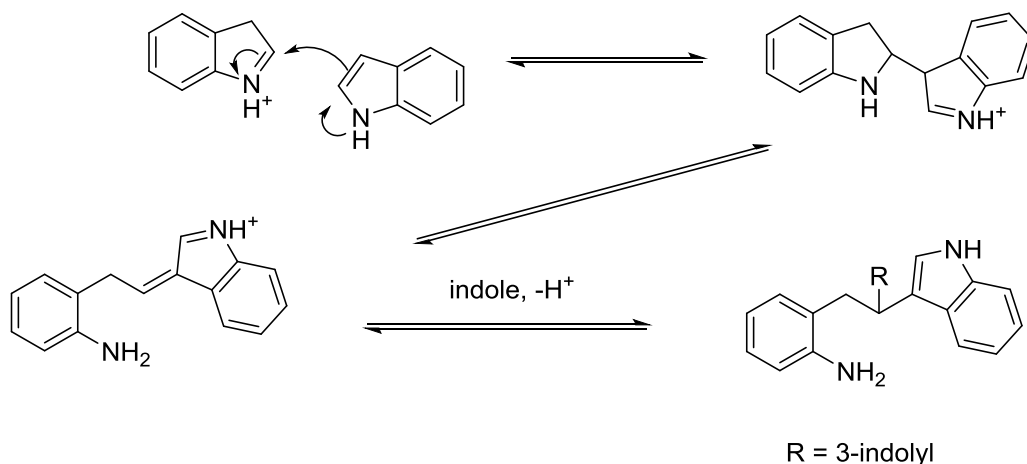
2.3.1 4-Substituted Indole Substrate Synthesis



Scheme 75: Synthetic Route to 3-indoleacetic Acids

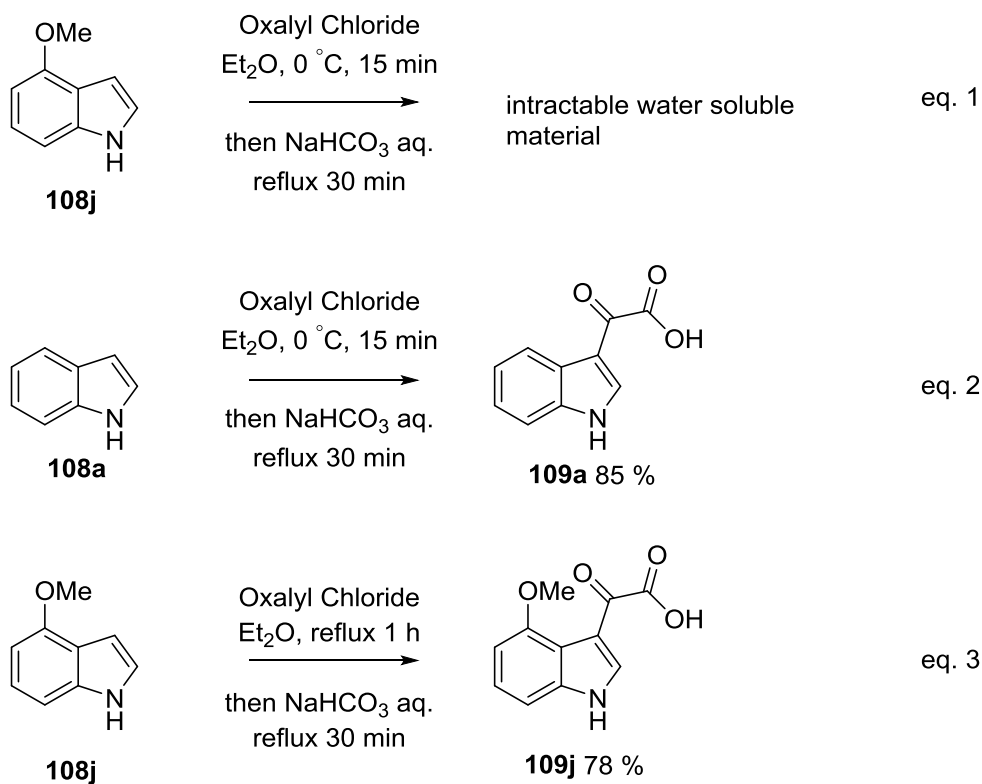
The routes to the cyclisation substrates proceeded via common indole-2-acetic acid intermediates **110** (Scheme 75), which were either commercially available or prepared from the indoles **108** by a modification of a reported two step sequence, acylation of the indole at the 3-position with oxalyl

chloride followed by Wolff-Kischner reduction (Scheme 75).¹¹⁸ Esterification, *N*-methylation and reduction provides the cyclisation precursors **98**.

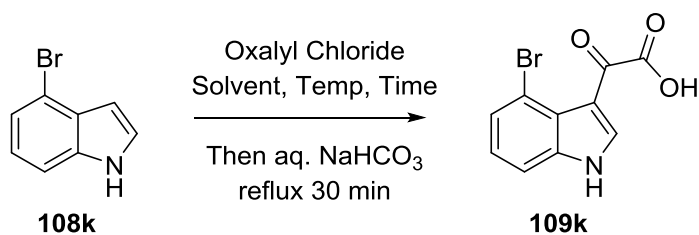


Scheme 76: Aqueous Acid Catalysed Oligomerisation of Indole

The reported procedure for acylation involves the reaction of the substituted indole with oxalyl chloride at 0°C or room temperature, followed by quenching of the reaction mixture with aqueous sodium bicarbonate solution to give the 2-oxoacetic acid product **109** after work up. On attempting the acylation procedure with 4-OMe indole **108j** and 4-Br indole **108k** it was only possible to isolate a small amount of the desired product in each case. In the case of the 4-OMe substrate the main product was highly coloured, highly water soluble and intractable (Scheme 77, eq. 1), possibly due to the acid catalysed dimerisation of the starting material under the reaction conditions or work up (Scheme 76).¹¹⁹

**Scheme 77: Acylation of 4-methoxyindole**

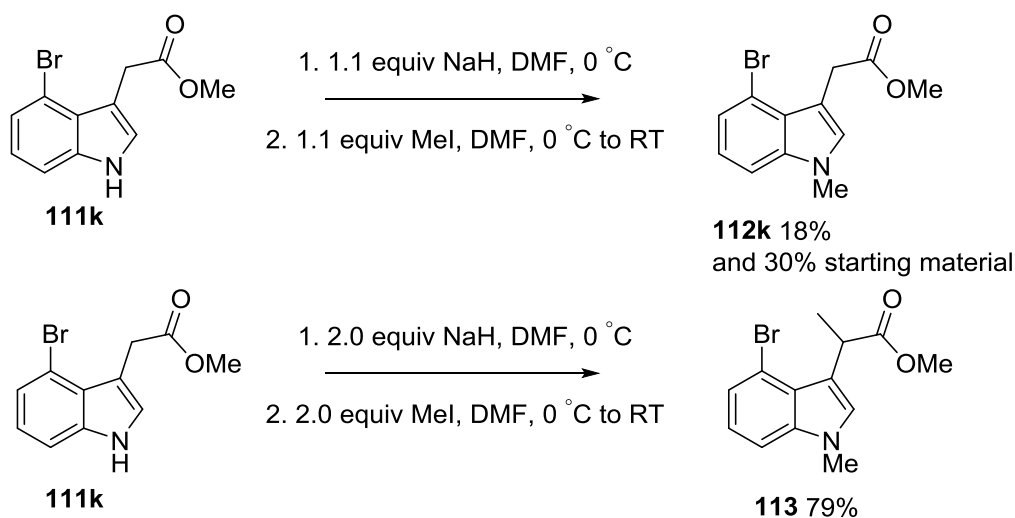
To verify that this procedure was effective the acylation of unsubstituted indole **108a** was attempted under identical conditions, yielding the desired product **109a** in 85% yield (Scheme 77, eq. 2). Based on this it was clear that the reagent quality and experimental details were appropriate for the reaction, but that the reactivity of the substrates selected was poor. Gratifyingly, when the initial reaction step was performed at reflux the product **109j** was isolated in good yield (78% to 98%, Scheme 77, eq. 3). Subsequent reduction, esterification (2 steps, **111j**, 57%), *N*-methylation (**112j**, 87%) and reduction (98%) gave cyclisation precursor **98j** with no further complications.



Entry	Solvent	Temperature	Time	Yield
1	Et ₂ O	0	15 min	traces
2	Et ₂ O	20	1 h	traces
3	Et ₂ O	45	2 h	22 %
4	Et ₂ O double concentration	45	2 h	41 %
5	THF	70	2 h	12 %
6	THF, pressure tube	80	3 h	decomposition

Table 9: Acylation of 4-Bromoindole

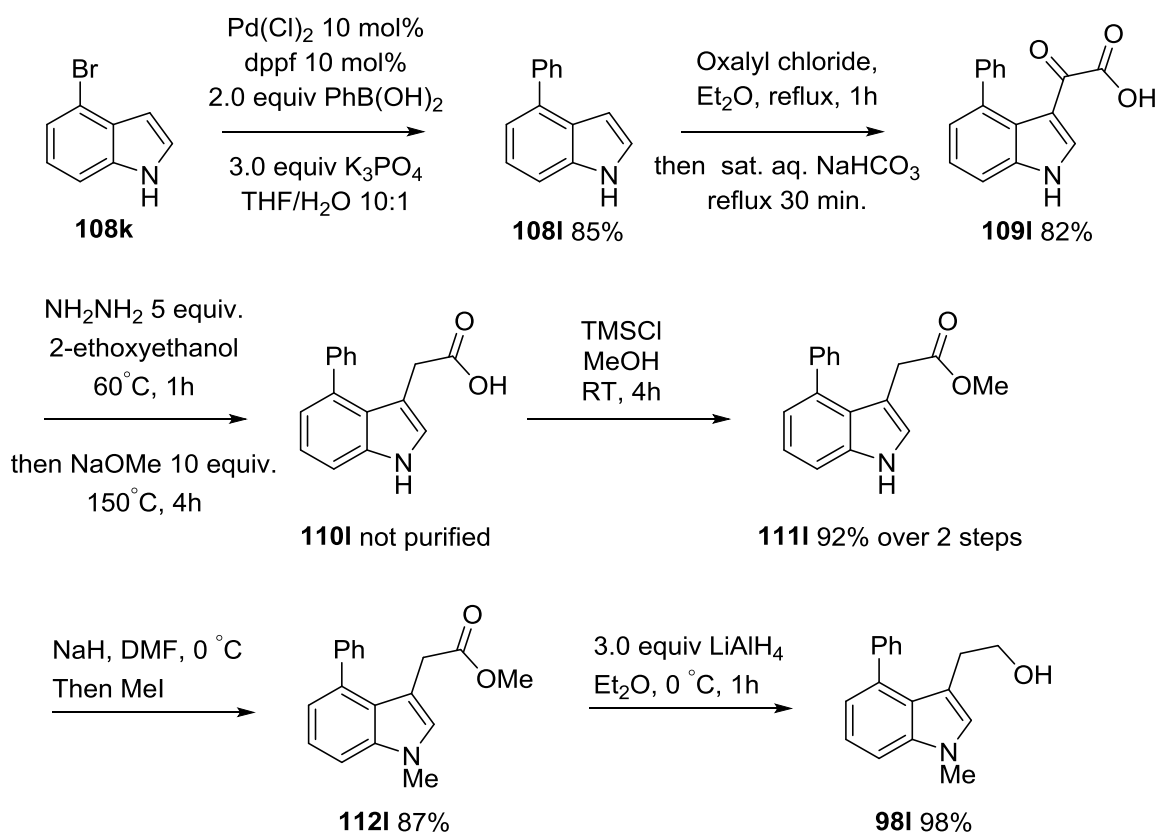
The reactivity of 4-bromoindole towards electrophiles is reported as being poor due to steric hindrance.¹²⁰ Attempts to increase the yield of the reaction by increasing the temperature and recycling unreacted starting material were moderately successful (Table 9), but at higher temperatures decomposition was observable, with the purity of the crude product being significantly poorer. Attempts to purify the material at this stage were not successful so the crude material was used unpurified in the Wolff-Kischner reduction.



Scheme 78: Methylation of 4-Bromoindole Ester 111k

Reduction and esterification of the 4-bromoindole oxoacid produced a low yield (44 %) of the ester **111k** over 2 steps. This poor yield may be due to either the instability of the molecule towards the forcing conditions of the reduction, or due to the impure nature of the starting material, as it was

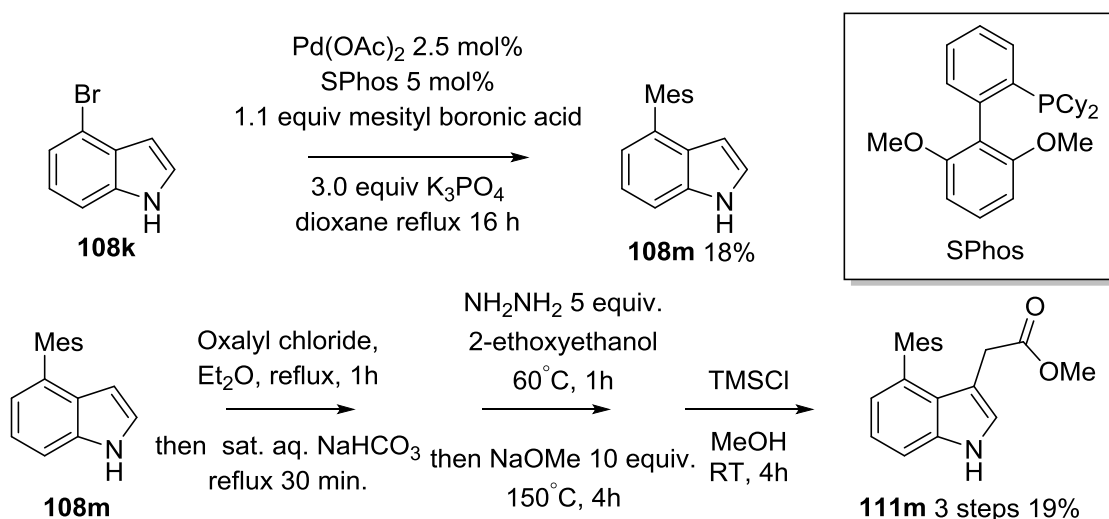
neither possible to determine the level of impurities accurately, nor identify them. Methylation of this ester using NaH/MeI was problematic (Scheme 78). The use of a 1:1.1:1.1 stoichiometry of starting material to each reagent did not enable the reaction to proceed to completion, providing only 18% of the desired product **112k** and 30% of the starting material, with the remaining material unaccounted for. On a slightly larger scale, using two equivalents of each reagent led to the main product being that of double methylation **113** in 79 % yield. This problem had also been encountered in the synthesis of 5-bromoindole substrates, and presumably arises from the deprotonation of the product by the excess base and the deprotonated starting material. Due to the difficulties in obtaining the desired product **112k** in sufficient quantities to enable onward synthetic steps we decided to reconsider our synthetic approach.



Scheme 79: Synthesis of Precursor **98l**

Due to the poor yields encountered at multiple points in the synthesis of the 4-bromo substrate an alternate sequence of reactions was used (Scheme 79), starting with cross coupling to afford 4-phenylindole **108l**, which we hoped would not suffer from the same lack of reactivity towards

electrophiles as 4-bromoindole. The reason for not initially using a route starting with cross coupling is that it lacks the option for late stage divergent cross coupling to access different substrates, however this did not appear feasible using the initial route selected. Suzuki coupling of 4-bromoindole **108k** with two equivalents of phenylboronic acid, using a catalyst prepared *in situ* from 10 mol% PdCl₂ and 10 mol% dppf, with potassium phosphate as base in 10% H₂O/THF gave the desired 4-phenylindole **108l** in 85% yield. Reaction with oxalyl chloride gave the oxo-acid **109l** in 82% yield. The rest of the synthesis was straightforward with good yields for reduction/esterification of the ketone (92%), N-methylation (87%) and reduction of the ester (98%) to afford precursor **98l**.



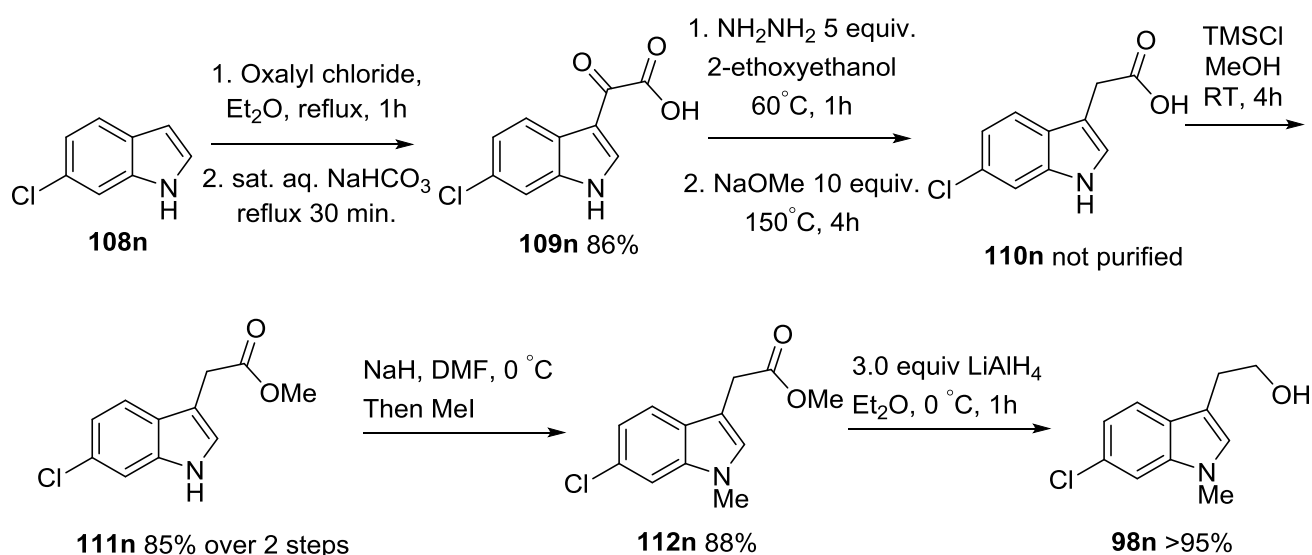
Scheme 80: Synthesis of 4-Mesitylindole Ester **111m**

In order to investigate a more sterically encumbered substrate, 4-mesityl substituted indole **108m** was synthesised by Suzuki coupling of 4-bromoindole with 2,4,6-trimethylphenylboronic acid (Scheme 80). This is a challenging coupling due to the ortho-ortho substitution pattern on the boronic acid and the electron rich nature of the indole ring, and we only obtained a low yield (18%) of the cross coupled product despite the use of SPhos, a highly general ligand for Suzuki-Miyaura coupling which is effective for hindered cross couplings.¹²¹ Reaction with oxalyl chloride provided a reasonable recovery of the oxoacid, but it was not possible to isolate this as pure material to determine the yield; instead the next two steps were performed without intermediate purification to give the reduced ester **111m** in a disappointing 19% yield over three steps. Preliminary results from the cyclisation of the 4-phenyl substrate demonstrated that 4-substitution was very poorly tolerated by the catalyst system,

giving poor enantioselectivity. Efforts to synthesise this substrate were abandoned due to the low yields encountered and the anticipated difficulty of producing sufficient material to investigate the cyclisation.

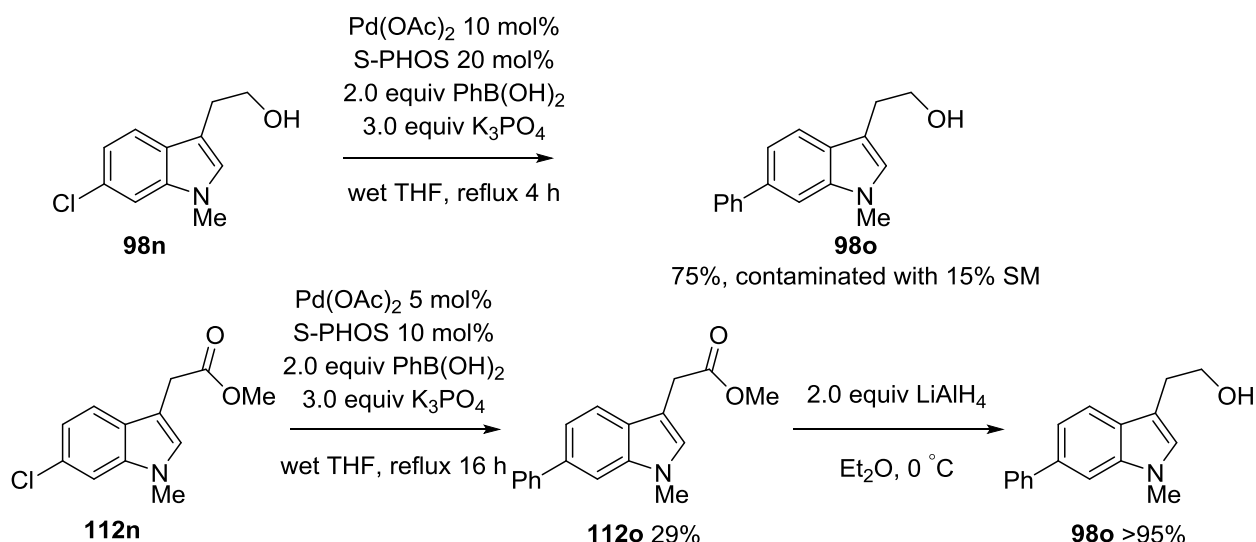
2.3.2 6-Substituted Indole Substrate Synthesis

We hypothesised that 6- substitution should be tolerated with nearly unchanged enantioselectivity from the unsubstituted parent, due to the remoteness of the substitution from the reactive centres. Thus the 5- and 6- positions could provide insights into the sensitivity of the reaction to the electronic properties of the indole nucleus.



Scheme 81: Synthesis of 6-Chloro Precursor 98n

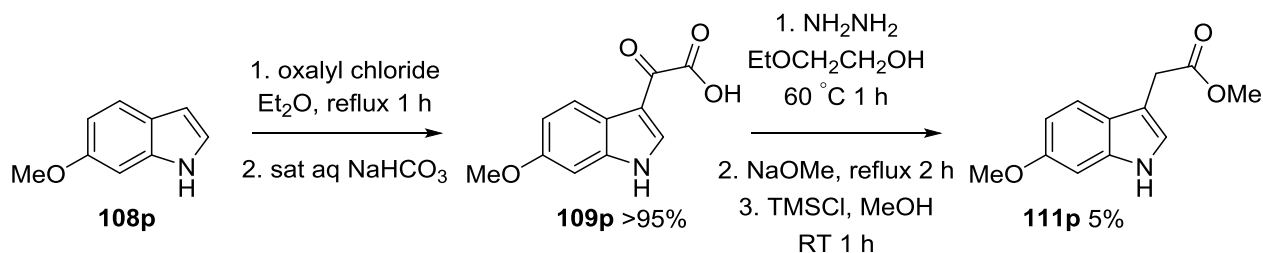
Starting with 6-chloroindole **108n** the alcohol cyclisation substrate **98n** was obtained without complication in good yields (acylation 86%, reduction and esterification 85%, methylation 88%, reduction >95% - Scheme 81).



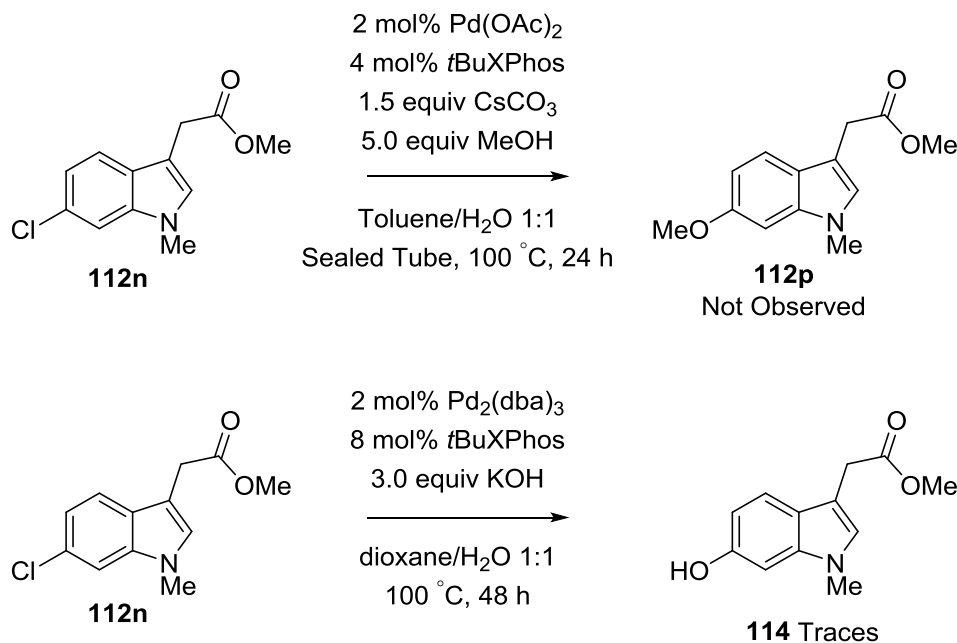
Scheme 82: Cross Coupling at Different Points in Synthetic Sequence on Route to 98o

Cross coupling to yield the 6-phenyl substrate was attempted with the 6-chloroalcohol **98n**, using a catalyst derived from Pd(OAc)_2 (10 mol%) and S-Phos (Scheme 82). The desired product **98o** was obtained in good yield, but was contaminated with the starting chlorinated material, which was inseparable by flash chromatography, giving material with the Ph:Cl ratio approximately 5:1 as measured by integration of the ^1H NMR spectrum, comparing the signals for the H2 protons. We reasoned that the separation of starting materials based on polarity would not be possible for this stage in the synthesis due to the chromatographic behaviour of the substrates being dominated by the alcohol functionality. Performing the cross coupling at the stage immediately prior to the ester reduction, at the point in the synthetic sequence with the lowest compound polarities, was attempted with the expectation that this would lead to an easier purification by flash chromatography.

Suzuki coupling of the alternate precursor **112n** similarly lead to a mixture of the Cl and Ph compounds in approximately a 1:2 ratio as determined by ^1H NMR integration of the H2 proton signals. Silica gel column chromatography only gave partial separation of the compounds but it was possible to isolate the 6-Ph substrate **112o** by recrystallisation from ethyl acetate/hexanes, albeit in low yield (29%). Reduction of **112o** gave **98o** in excellent yield.

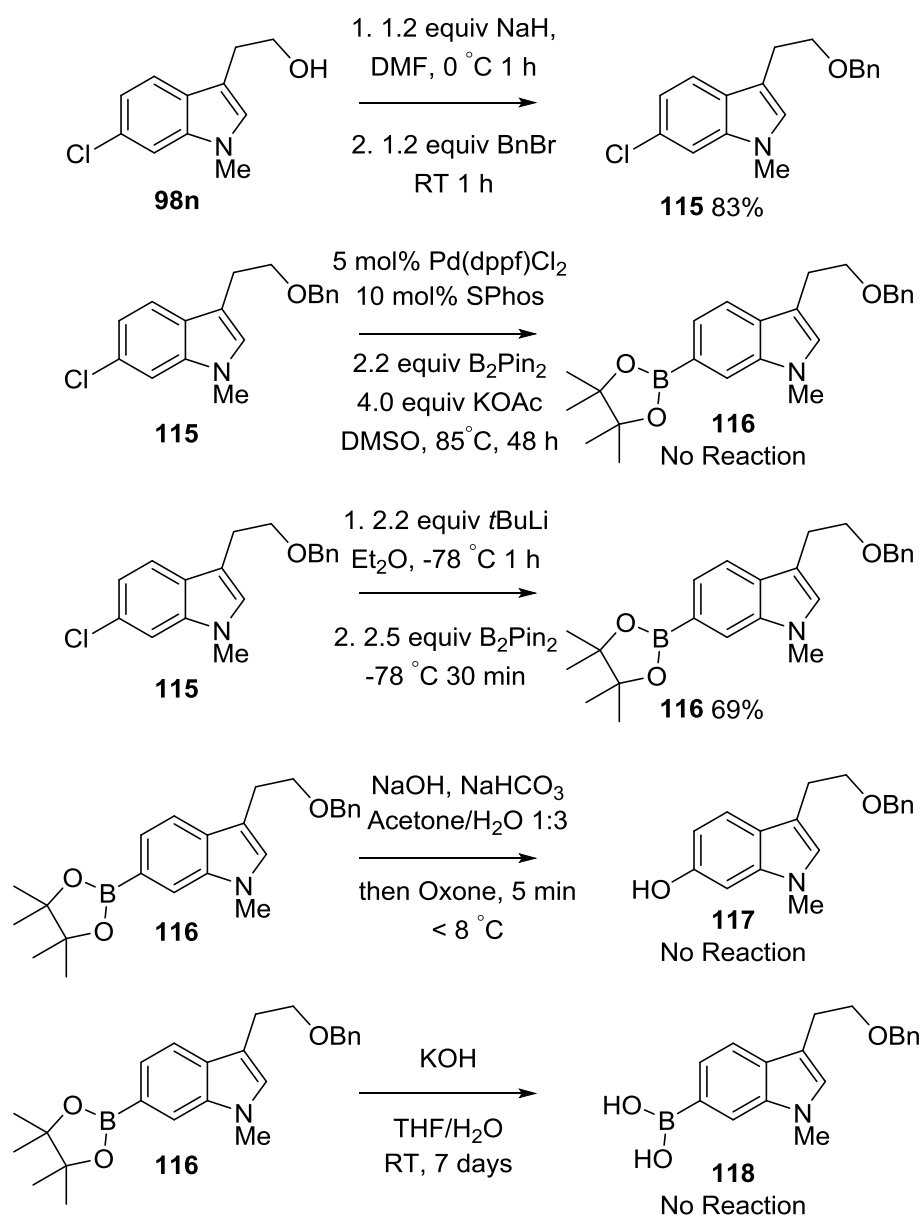
Scheme 83: Synthesis of 6-Methoxyindole Acetic Acid Methyl Ester **111p**

Due to promising results obtained with the 5-oxyalkyl series of substrates, the 6-OMe substrate was attempted to investigate whether this was an effect based on the electron rich nature of the aromatic ring. Standard reaction of 6-OMe indole **108p** with oxalyl chloride afforded the oxo-acid **109p** in quantitative yield, but subsequent attempts at Wolff-Kischner reduction provided only traces of the desired product, with no other identifiable products (Scheme 83). This result was perhaps unsurprising given the instability of the starting 6-OMe indole towards even mild conditions, and whilst the oxo-acids are in general more stable than the parent indoles towards storage the reaction conditions employed are harsh and might be expected to lead to decomposition of sensitive molecules.

Scheme 84: Pd Catalysed Oxygenation of **112n**

We sought to access this substrate by several alternate routes. Pd(0) catalysed reactions of aryl halides with either KOH¹²² or alkoxides¹²³ were attempted first (Scheme 84). Reaction using the optimised

conditions for aryl ether synthesis led to consumption of starting material **112n** to give a complicated mixture. It was only possible to isolate a small amount of the starting material by flash chromatography, with no other indole products identifiable. This may be due to the high electron density of the indole nucleus disfavours the oxidative addition into the poorly reactive C-Cl bond. This difficulty was also encountered in the synthesis of the 6-phenyl substrate by Suzuki-Miyaura cross coupling, where significant amounts of starting material were observed even on prolonged reaction times. The reaction with KOH was slightly more promising, but it was only possible to isolate traces of the product which was tentatively identified as the phenol and as such we did not continue with the synthesis through this route.

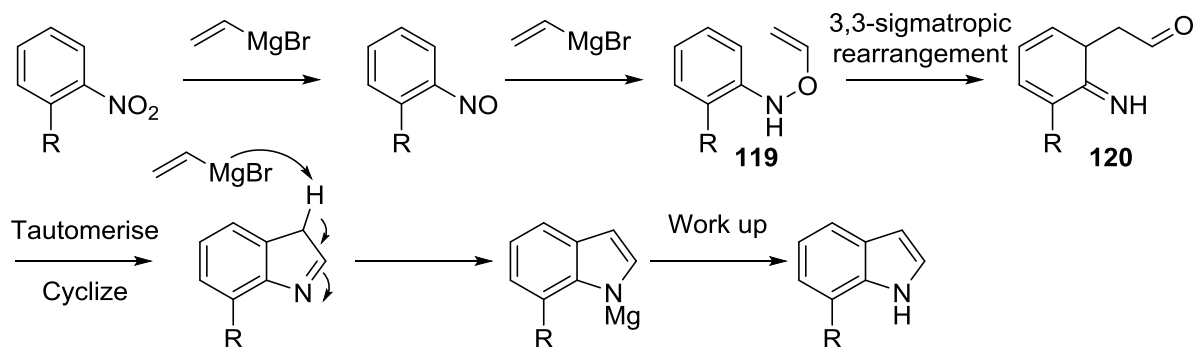


Scheme 85: Attempted Boron Oxidation Route to 6-Oxy Substrates

Due to the failure of the Pd catalysed reaction we sought to use an oxidative route to this substrate, *via* the boronate ester (Scheme 85).¹²⁴ Pd catalysed borylation was not successful, returning only starting material. Benzylation of the 6-Cl alcohol **98n** was performed by deprotonation with NaH followed by addition of BnBr, giving the protected derivative **115** in good yield (83%). Lithium halogen exchange with *t*-BuLi followed by quenching with *bis*-pinacolatodiboron (B₂Pin₂) gave the boronate ester **116** in 69% yield. This compound was not oxidised by treatment with oxone, returning the starting material unchanged. The unreactive nature of some boronic esters towards oxidation has been reported, so we attempted the hydrolysis of the pinacol ester by the use of KOH in THF/H₂O. This

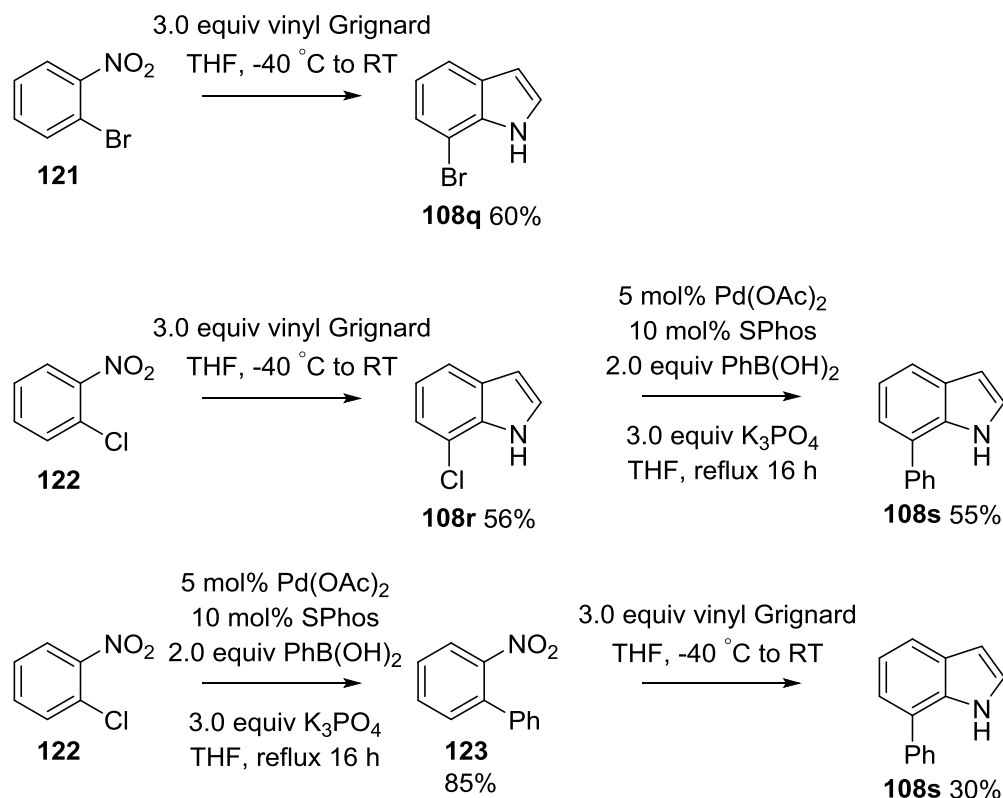
was unsuccessful, with starting material recovered even on extended reaction times. At this point we abandoned the synthesis of the 6-OMe substrate.

2.3.3 7-Substituted Indole Substrate Synthesis



Scheme 86: Bartoli Indole Synthesis

There are only a limited number of 7-substituted indoles commercially available, but for this particular substitution pattern it is possible to synthesise indoles in one step by using the Bartoli indole synthesis¹²⁵ from 2-substituted nitrobenzenes and 3 equivalents of vinylmagnesium bromide (Scheme 86). One equivalent of Grignard reagent reduces the nitro group to a nitroso group, which reacts with another equivalent of Grignard reagent to form species **119**. A 3,3-sigmatropic rearrangement occurs, promoted by steric crowding at the 2-position, to give an aldehyde product **120**. Intramolecular condensation and tautomerisation occurs to form the indole nucleus and the final equivalent of Grignard reagent acts as a base.

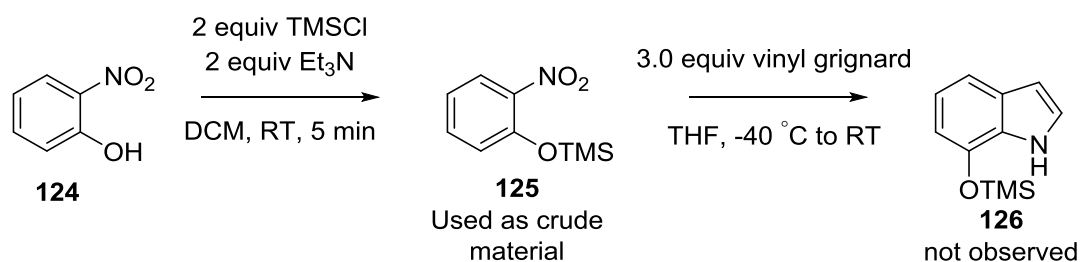


Scheme 87: Bartoli Indole Synthesis and Synthesis of 7-phenylindole

Using this reaction it was possible to synthesise 7-Cl and 7-Br indoles in good yield with no complications. Due to the problems of reactivity in subsequent steps that we had experienced with the synthesis of the 4-bromo substrate and problems with the purification of the late stage Suzuki coupling for the 6-phenyl substrate, the synthesis of 7-phenylindole was also performed using the same methodology (Scheme 87).

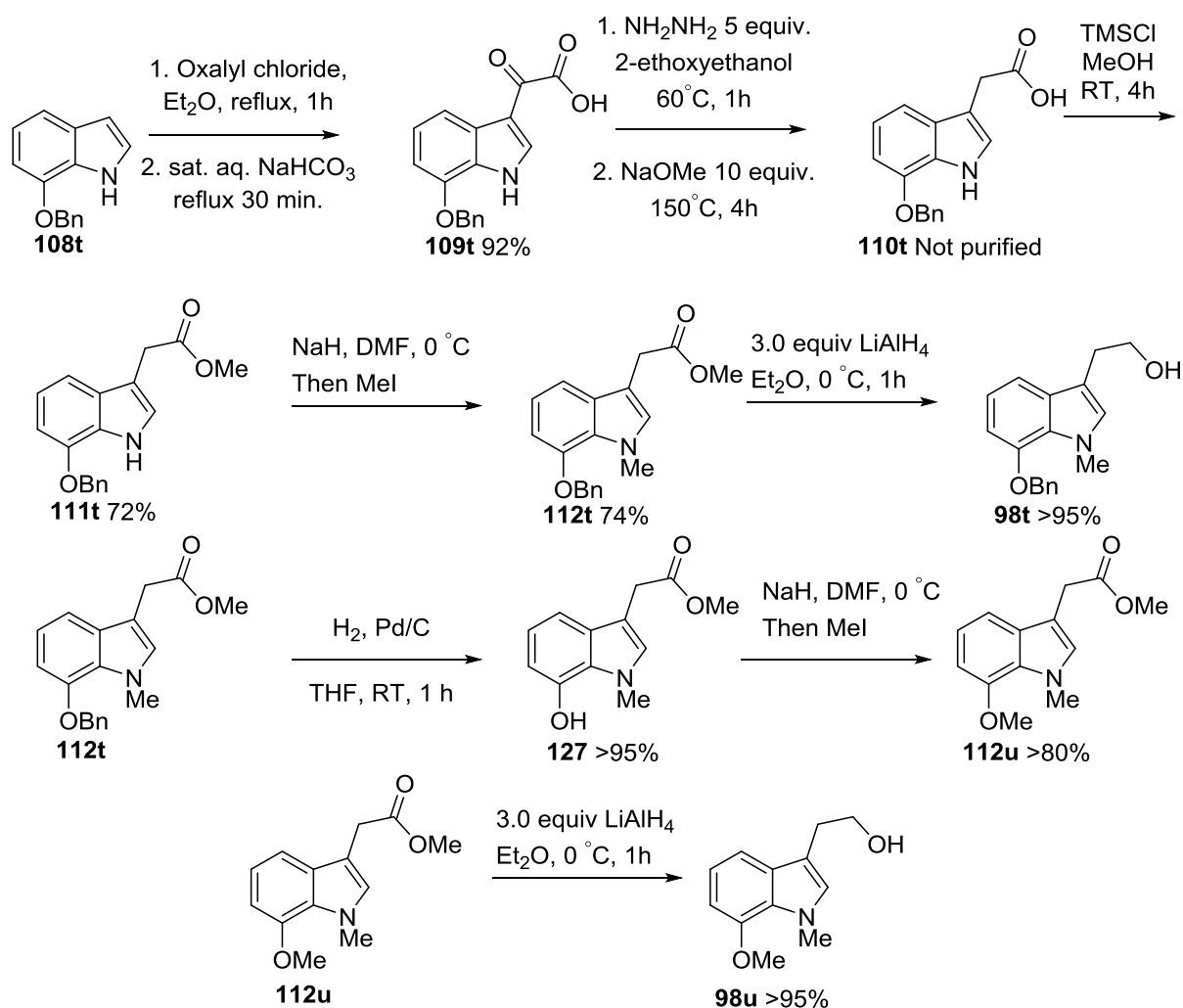
Suzuki coupling of 2-chloronitrobenzene **122** with phenylboronic acid proceeded to give 2-nitro-1,1'-biphenyl **123** in good yield (85%) and cyclisation of this precursor under the Bartoli conditions was successful, but in lower yield (30%) than for the halogenated substrates - presumably due to lower steric crowding of the cyclisation intermediate. Over the two steps it was marginally more efficient to perform the cyclisation prior to the cross coupling, as tested with the 7-chloroindole (26% for Suzuki then Bartoli versus 31%) - this would likely be improved by use of the 7-bromoindole due to higher reactivity for both cyclisation and cross coupling. We did not continue with the synthesis of the 7-phenyl substrate through this route as we were able to circumvent the problem which had caused us to

investigate this alternate route at a later stage in the synthesis, allowing a route to the substrate with better potential for variation of the substitution of the substrate (*vide infra*).



Scheme 88: Attempted Synthesis of 7-hydroxyindole

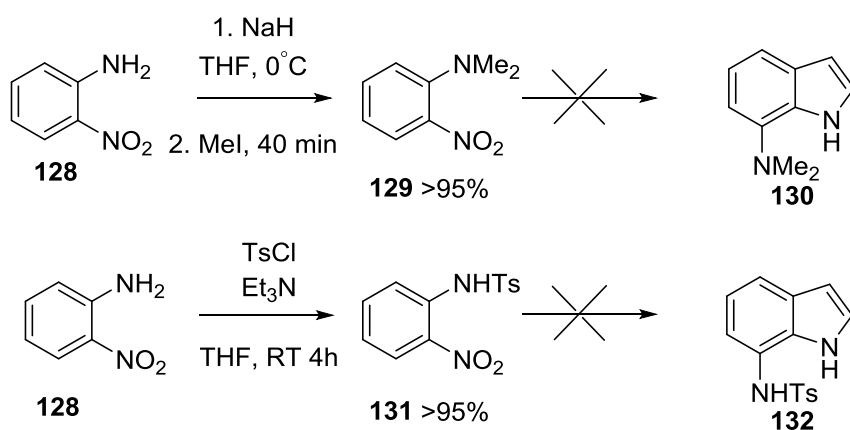
Cyclisation of 2-trimethylsilyloxynitrobenzene is reported in the original report of the Bartoli indole synthesis as a route to 7-hydroxyindole.¹²⁶ The cyclisation precursor was prepared by reaction of TMSCl with 2-nitrophenol in the presence of triethylamine and used for the indole synthesis as the crude product after filtration of the reaction mixture (Scheme 88). This was necessary in order to avoid rapid hydrolysis on contact with atmospheric moisture, as observed by the immediate reappearance of the yellow colour of the nitrophenol on exposure of the reaction mixture for silylation to the air. During cyclisation full consumption of starting material was observed. The crude ¹H NMR of the reaction mixture showed a complicated mixture of products, and whilst a signal in the ESI-mass spectrum was present corresponding to the [M-H]⁻ anion of 7-hydroxyindole, it was not possible to isolate either this product or the 7-OTMS product. The failure to obtain any product might be explained by the presence of excess TMSCl and Et₃N from the silylation reaction preceding the indole synthesis step interfering with the reaction by reacting with either Grignard reagent or the reaction intermediates.



Scheme 89: Synthesis of 7-OBn and 7-OMe substrates

As it was not possible to directly synthesise the 7-OH indole to perform alkylation and then build up the cyclisation substrates we sought to access this substrate through a 7-benzyloxy series of compounds (Scheme 89). Hydrogenolysis of the protecting group after N-methylation would give a 7-OH indole **127** which could provide a range of alkoxyindoles. This had the advantage of a readily available starting material and the possibility for substrate diversification at a late stage in the synthesis. Acylation (92%), Wolff-Kischner reduction and esterification (72%) and N-methylation (74%) proceeded without issue to give the intermediate **112t** in good yield. This intermediate could either provide the 7-benzyloxy substrate **98t** in quantitative yield by reduction, or the 7-hydroxy intermediate **127** by hydrogenolysis of the protecting group with a quantitative yield. Treatment of the phenol thus produced with NaH followed by MeI gave the immediate precursor to the 7-methoxy substrate **112u** in 80% yield, and reduction of this intermediate gave the cyclisation precursor **98u**.

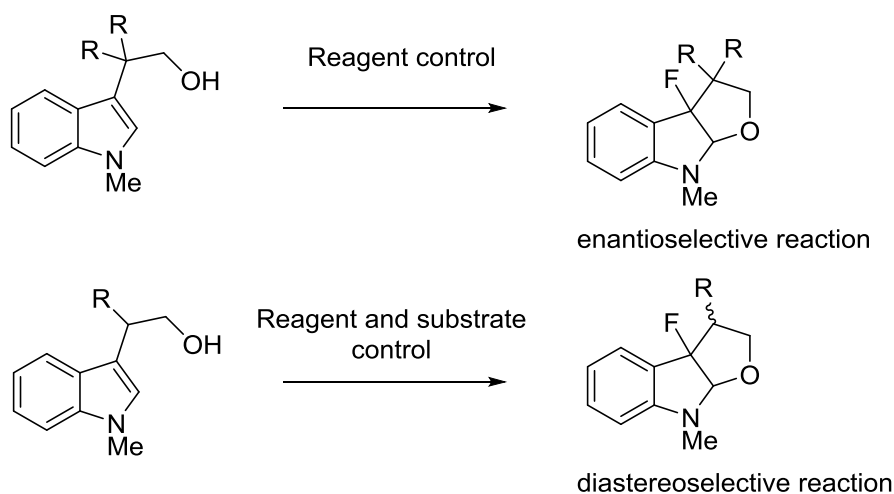
We were interested in the synthesis of aminoindoles to test the functional group tolerance of the fluorocyclisation and to determine whether the effects seen on introduction of alkoxy groups on the indole skeleton were maintained with another electron rich group. There are no reported Bartoli indole syntheses of aminoindoles but we could not find any compelling reasoning as to why this would not provide a 7-aminoindole product. We synthesised two precursors, 2-dimethylaminonitrobenzene and 2-tosylaminonitrobenzene from 2-nitroaniline, these substrates were chosen as they have steric bulk at the 2-position to favour the cyclisation step. It was noted that the tosyl group would potentially be labile under reaction conditions, but given the rapid nature of the Bartoli indole synthesis we hoped that indole formation would outcompete deprotection.



Scheme 90: Attempted Synthesis of 7-Aminoindoles

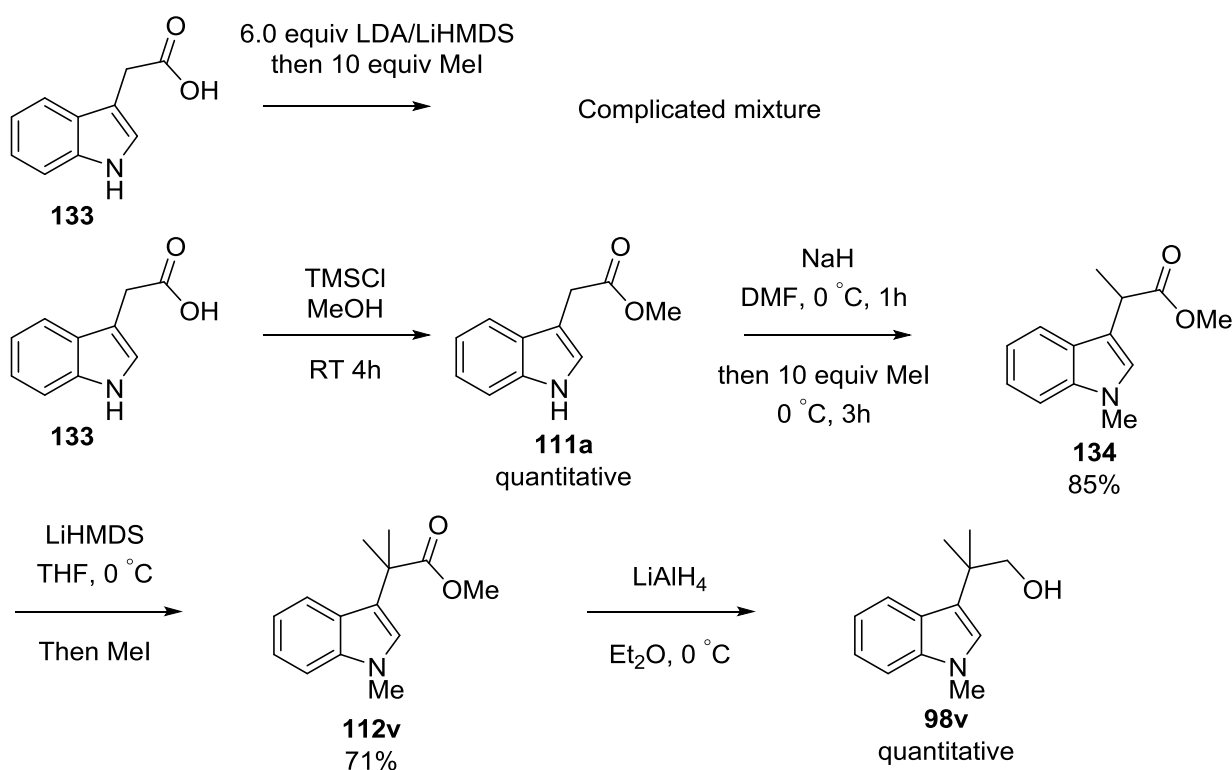
Attempted Bartoli indole synthesis on the aniline precursors was however not successful (Scheme 90). For the tosyl substrate **131** complete deprotection was observed to occur rapidly to yield the starting nitroaniline **128**. For the dimethylamino substrate **129** a complicated mixture was formed and it was not possible to observe any product.

2.3.4 Side Chain Substitution



Scheme 91: Enantioselective or Diastereoselective Cyclisation

Using the same logic which led us to prepare the 4-substituted substrates, it is possible that a substrate bearing steric bulk at the side chain position would have an effect on the immediately adjacent reacting centre at the 3-position. Installation of a *gem* dimethyl group is the most conservative substrate choice. The presence of two groups at this position accelerates cyclisation by the Thorpe-Ingold effect and avoids the potential issue of diastereoselectivity of fluorocyclisation of a racemic mixture of monosubstituted substrates (Scheme 91).

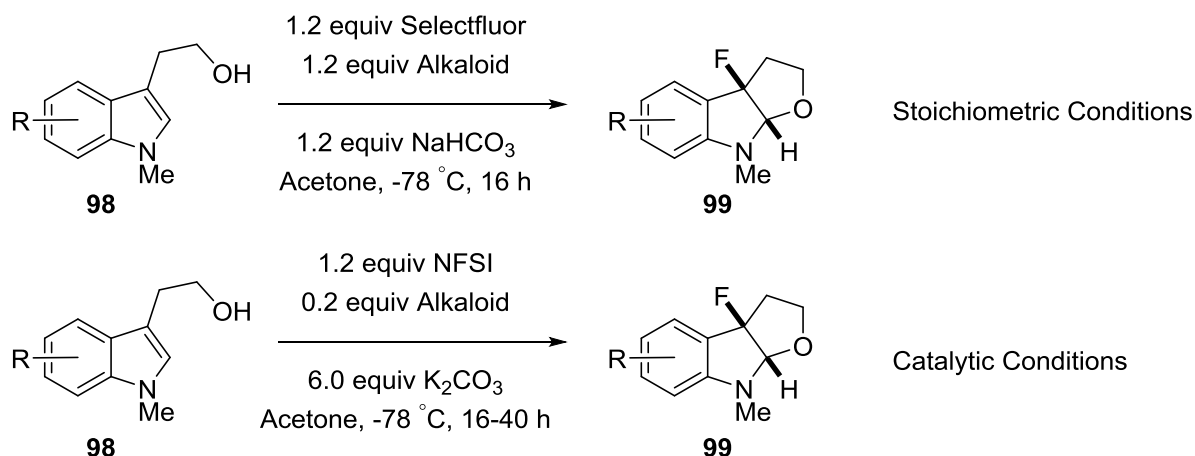


Scheme 92: Synthesis of Gem Dimethyl Substrate 98v

Attempted exhaustive methylation of 3-indoleacetic acid using either LDA or LiHMDS and methyl iodide (Scheme 92) was unsuccessful with multiple products and poor recovery of material, with a large exothermic reaction being observed on addition of the base and again on addition of methyl iodide. Stepwise reaction was required to obtain the ester **112v**, esterification of the acid using TMSCl in methanol proceeded in quantitative yield, methylation of **111a** using conditions similar to those employed for N-methylation of other substrates using excess sodium hydride (6.0 equiv) and methyl iodide (10 equiv) gave predominantly the monomethylated product **134** in 85% yield, with only traces of the desired dimethylated product **112v**.

As the monomethylated product was formed when sodium hydride was used as the base in alkylation, the use of an alternate base was required for production of the *gem*-dimethyl product. Reaction of the monomethylated material with first LiHMDS then MeI gave the intended product in good yield (71%). Reduction of **112v** with LiAlH₄ proceeded successfully to give the cyclisation precursor **98v** in quantitative yield.

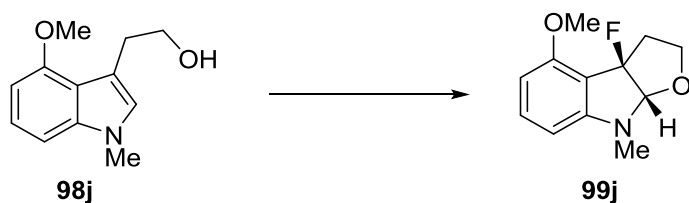
2.4 Alcohol Substrate Cyclisations



Scheme 93: Conditions for Cyclisations

Using the conditions optimised for the fluorination-cyclisation of the parent compound **98a** we attempted the cyclisation of each substrate under both catalytic (0.2 equiv alkaloid, 1.2 equiv NFSI, 6.0 equiv K₂CO₃) and stoichiometric (1.2 equiv alkaloid, 1.2 equiv Selectfluor, 1.2 equiv NaHCO₃) conditions (Scheme 93). Unless specified otherwise, the alkaloid used for all enantioselective cyclisations was (DHQ)₂PHAL. There was a marked dependence on enantioselectivity between the different substitution patterns, but no significant observations concerning the yields of different products, which were isolated in yields ranging from 20% to 90%. Stoichiometric reactions provided material with slightly higher enantiomeric excess, as on average catalytic enantioselectivities were about 5% lower, but for some substrates the difference was as much as 25%. Yields for catalytic reactions were higher by an average of 5% (stoi: 49%, cat: 54%). It is uncertain as to whether this is a finding of relevance to the reacting system as analysis of the crude mixture was not performed, and all reactions were run until completion, with catalytic reactions generally proceeding slightly slower. It is likely that the discrepancies here are due to the operational difficulties of using high loadings of cinchona alkaloids and Selectfluor; on dilution of reaction mixtures for stoichiometric reactions it was observed that a gum like mass formed. Maceration of this mass was performed as a part of the work up in an attempt to extract the product into solution, but the heterogeneous nature of the workup must be considered a complicating factor in the reported yields.

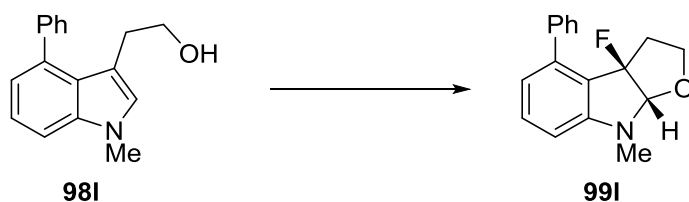
2.4.1 4- Position Substitution



Entry	Alkaloid	Conditions	Yield / %	<i>Ee</i> / %
1	(DHQ) ₂ PHAL	Stoichiometric	71	81
2	(DHQ) ₂ AQN	Stoichiometric	41	10
3	(DHQ) ₂ PYR	Stoichiometric	50	28

Scheme 94: Fluorocyclisation of 4-OMe Substrate

The enantiomeric excess of stoichiometric cyclisation was promising in the case of the 4-methoxy substrate at 81%. The increase in enantioselectivity for the electron rich substrate is consistent with the results for the 5-alkoxy substrates, but unfortunately we were unable to repeat this promising selectivity in catalytic reactions, despite multiple attempts.



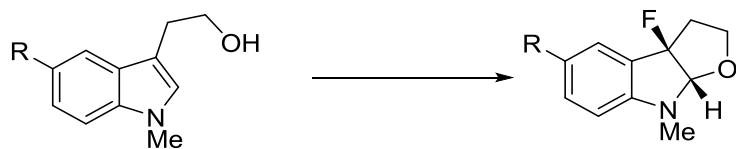
Entry	Alkaloid	Conditions	Yield / %	<i>Ee</i> / %
1	(DHQ) ₂ PHAL	Stoichiometric	35	38
2	(DHQ) ₂ AQN	Stoichiometric	84	18 ^a
3	(DHQ) ₂ PYR	Stoichiometric	66	6 ^a
4	(DHQ) ₂ PHAL	Catalytic	81	13

Scheme 95: Fluorocyclisation of 4-Phenyl Substrate a) Opposite enantiomer

Catalytic reaction on the 4-phenyl substrate lead to a significant decrease in enantioselectivity (81%, 13% ee) from an already low starting point from the stoichiometric reaction (35%, 38% ee). The low enantioselectivity of this substrate is presumably due to steric effects, as it is the adjacent ring position to the atom where the enantiodetermining C-F construction occurs. The natural preference for a biphenyl unit is for the aryl rings to lie orthogonal to each other,¹²⁷ thus the addition of the 4-aryl group turns the substrate from a flat aromatic plane to having a significant influence from the ring hydrogens pointing upwards. It is unfortunate that we were unable to prepare the mesityl analogue of this substrate, as it would be expected that any such effect would be amplified by the increase in bulk.

2.4.2 5 - Position Substitution

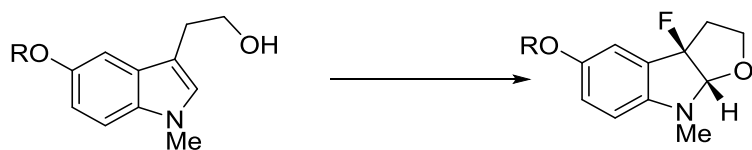
5-Substituted alcohol nucleophile substrates were prepared and cyclised by Dr. Oscar Lozano and are included for comparison purposes.



Entry	R	Conditions	Yield / %	<i>Ee</i> / %
1	Ph	Stoichiometric	55	72
2	Ph	Catalytic	61	62
3	Mes	Stoichiometric	57	90
4	Mes	Catalytic	55	84

Table 10: 5-Aryl Substrate Cyclisations

The presence of a phenyl group at the 5-position of the indole skeleton gave almost unchanged results for the fluorination cyclisation. Introduction of the more bulky mesityl group lead to a significant increase in enantioselectivity, with similar yields to the unsubstituted indoles.

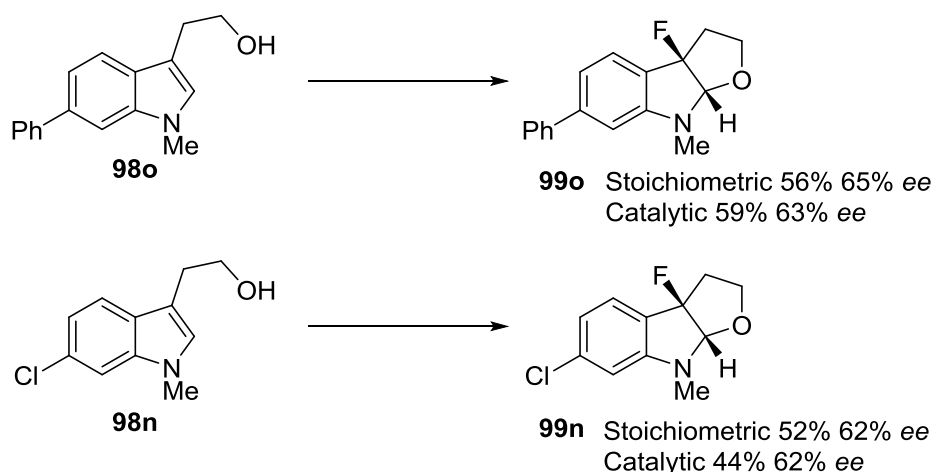


Entry	R	Conditions	Yield / %	<i>Ee</i> / %
1	Me	Stoichiometric	90	86
2	Me	Catalytic	65	74
3	Bn	Stoichiometric	69	84
4	Bn	Catalytic	78	74
5	Et	Stoichiometric	60	84
6	Et	Catalytic	78	72
7	Allyl	Stoichiometric	53	86
8	Allyl	Catalytic	65	78

Table 11: 5-Alkoxy Substrate Cyclisations

5-Alkoxy substrates all cyclised with good yields and good enantioselectivities. Relative to the unsubstituted indoles there was about a 10% increase in enantioselectivity in both stoichiometric and catalytic reactions. This increase in enantioselectivity was invariant with the alkoxy group, suggesting that the effect on the cyclisation is based on the electronic effect of the substituents. Catalytic reactions all gave approximately 10% lower enantioselectivities in all cases.

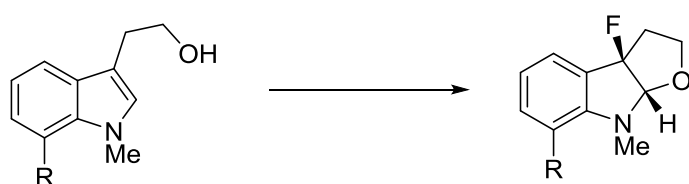
2.4.3 6 - Position Substitution



Scheme 96: 6- Position Substrate Cyclisation

6-Chloro and 6-Phenyl substituted substrates provided the cyclised products in good yields with enantioselectivities not significantly changed from the unsubstituted substrate **98a**. This was as expected from the results of cyclisation of the 5-substituted substrates. The enantiomeric excesses were the same for stoichiometric and catalytic reactions. The 6-chloro substrate is the only halogenated substrate which provided a good enantioselectivity, with the presence of the chloro giving the possibility for post cyclisation manipulations.

2.4.4 7 - Position Substitution

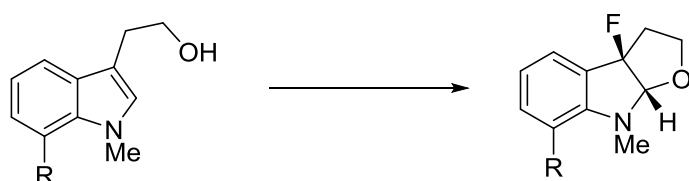


Entry	R	Alkaloid	Conditions	Yield / %	Ee / %
1	Cl	(DHQ) ₂ PHAL	Stoichiometric	37	14
2	Cl	(DHQ) ₂ AQN	Stoichiometric	64	0
3	Cl	(DHQ) ₂ PYR	Stoichiometric	65	14
4	Cl	(DHQ) ₂ PHAL	Catalytic	33	13
5	Br	(DHQ) ₂ PHAL	Stoichiometric	43	17
6	Ph	(DHQ) ₂ PHAL	Stoichiometric	48	20
7	Ph	(DHQ) ₂ PHAL	Catalytic	29	36

Table 12: Fluorocyclisation of 7-Cl, 7-Br and 7-Ph substrates

7-Br and 7-Cl substrates cyclised under stoichiometric conditions with poor yields and enantioselectivities (Br: 43%, 17% ee; Cl: 37%, 14% ee). The catalytic result for the 7-Cl substrate

(33%, 13% ee) was very similar to the stoichiometric, and for both substrates the use of alternate *cinchona* alkaloids gave no improvements. The 7-phenyl substrate has broadly similar results for cyclisation as the halogenated substrates (stoichiometric: 48%, 20% ee; catalytic: 29%, 36%), with the surprising result that the catalytic reaction operates with higher enantioselectivity - this cannot be explained by the current mechanistic rationalisation of enantioselective fluorination by *cinchona* alkaloids.

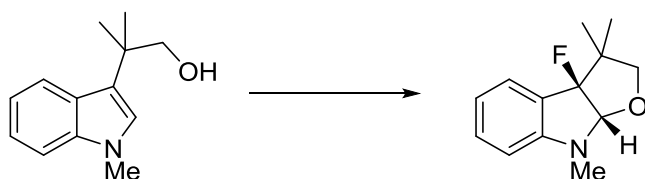


Entry	R	Alkaloid	Conditions	Yield / %	<i>Ee</i> / %
1	OBn	(DHQ) ₂ PHAL	Stoichiometric	20	31
2	OBn	(DHQ) ₂ PHAL	Catalytic	48	33
3	OMe	(DHQ) ₂ PHAL	Stoichiometric	98	24
4	OMe	(DHQ) ₂ PHAL	Catalytic	86	5

Table 13: Fluorination Cyclisation of 7-Alkoxy Substrates

For the other ring positions examined, alkoxy substrates have generally provided improvements in yield and enantioselectivity. For the cyclisation of the 7-halogen substituents it was clear that the absence of steric hindrance at the 7-position was crucial for good enantioselectivity, so we were interested to determine the interplay of the effects of electron rich substrates with some bulk at the 7-position. For both the OBn and OMe substrates the stoichiometric enantioselectivity was higher than for the halogen substituents, though not markedly (7-OBn: 20%, 31% ee; 7-OMe: 90%, 24% ee). The difference in enantioselectivity between these substrates is not enough to make firm conclusions about the impact of electron density on enantioselectivity, but it is clear that 7-position substitution is very poorly tolerated.

2.4.5 Side Chain Substitution

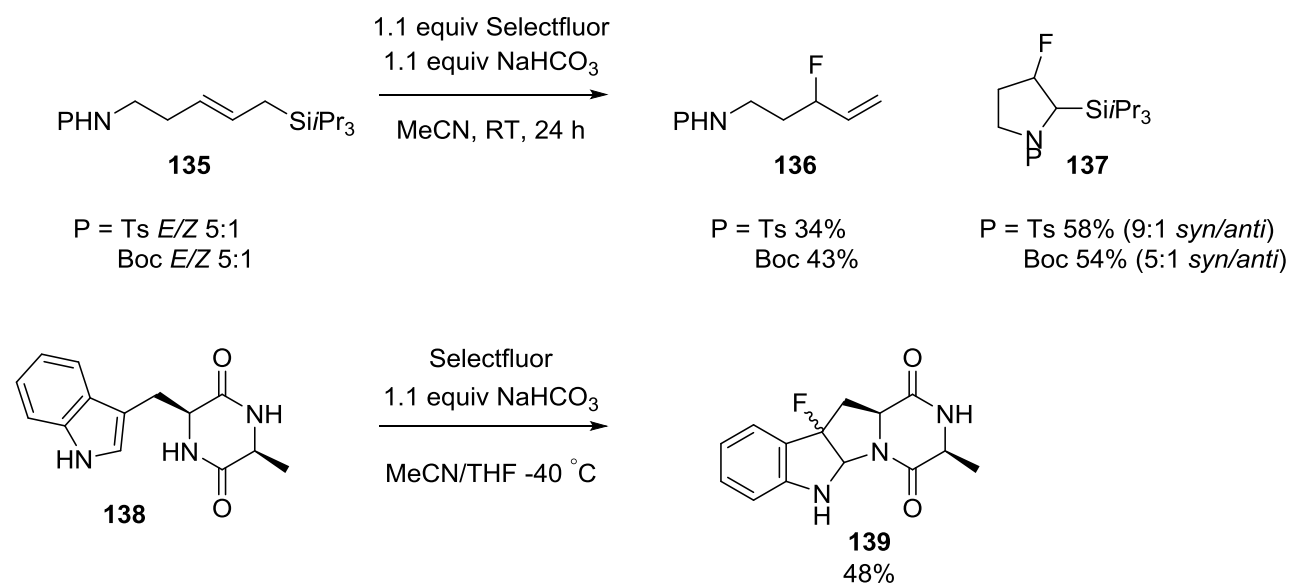


Entry	Alkaloid	Conditions	Yield / %	<i>ee</i> / %
1	(DHQ) ₂ PHAL	Stoichiometric	58	47
2	(DHQ) ₂ AQN	Stoichiometric	69	14 ^a
3	(DHQ) ₂ PYR	Stoichiometric	57	26 ^a

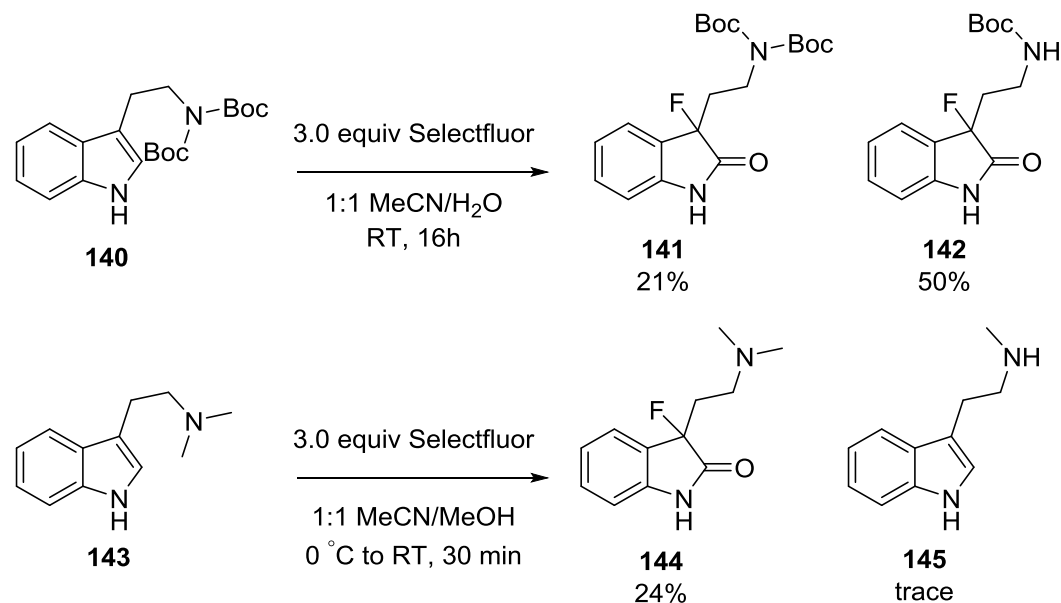
Table 14: Fluorocyclisation of *gem*-Dimethylated Sidechain Substrate a) opposite enantiomer

The cyclisation of **98v** bearing *gem*-dimethyl substituents on the pendant nucleophile proceeded smoothly giving moderate to good yields with all of the alkaloids tested. The enantioselectivity was significantly lower than for the unsubstituted parent, but was comparable to that for the cyclisation of the 4-Ph substrate (*vide supra*). This supports the hypothesis that steric bulk adjacent to the reacting centre leads to poorer substrate recognition in the enantiodetermining step. Again, the original alkaloid catalyst (DHQ)₂PHAL gave the best enantioselectivity, with the other *bis* alkaloids giving the opposite enantiomer.

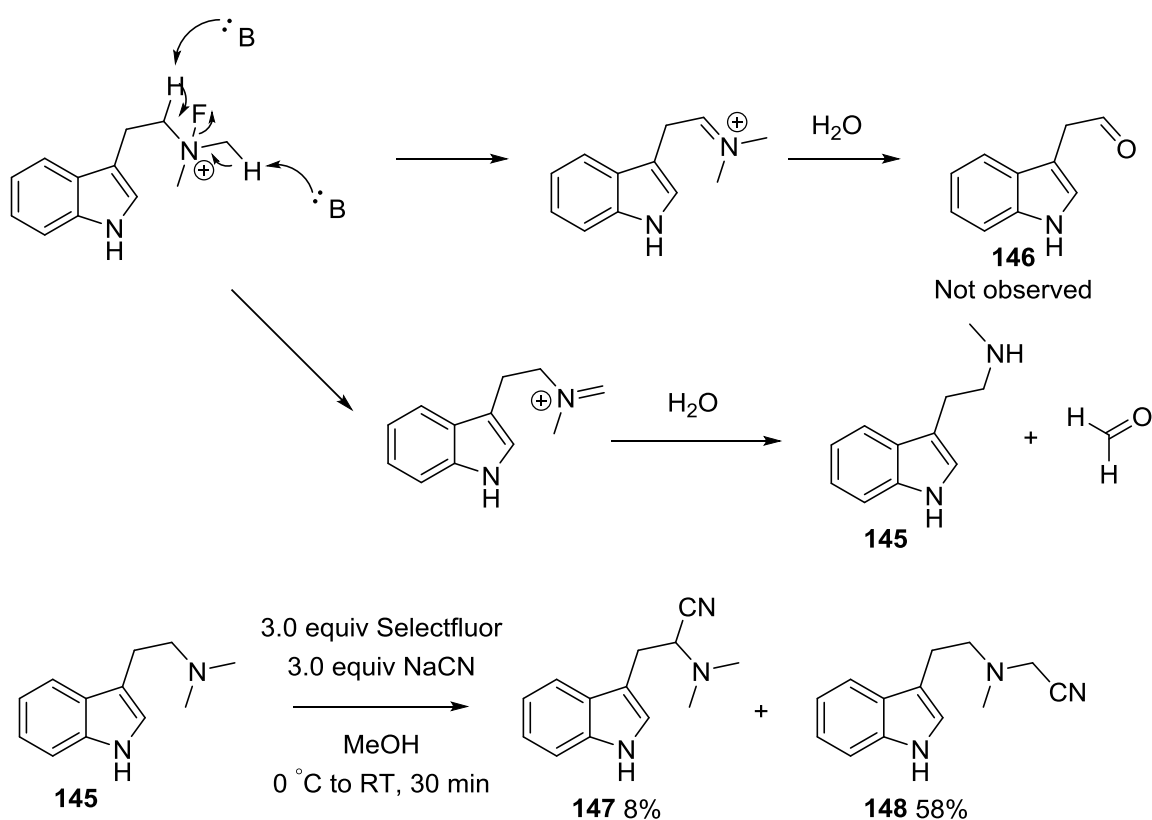
2.5 Nitrogen Nucleophile Cyclisations in Electrophilic Fluorocyclisation

Scheme 97: Fluorocyclisation with Nitrogen Nucleophiles^{104, 128}

In fluorination cyclisations, the large majority of reported reactions feature an alcohol pendant nucleophile. The use of carbon nucleophiles and non oxygen heteroatoms is also possible. With electrophilic fluorinating reagents there have been reports of the cyclisation with a nitrogen nucleophile bearing a deactivating protecting group¹²⁸ or within an amide bond (Scheme 97).¹⁰⁴

Scheme 98: Oxidative Demethylation of Dimethyltryptamine by Selectfluor¹²⁹

The requirement for electron withdrawing protecting groups can be explained by the tendency of unprotected amines to react with electrophilic fluorinating reagents to give *N*-fluoro species. Simple alkylamines will react with Selectfluor to give either monofluoro or difluoroamines, which are significantly less electrophilic than Selectfluor itself.¹³⁰ The reaction of dimethyltryptamine **143** with Selectfluor in an attempt to provide a 3-fluorooxindole product **144** gave a low yield of product, with many byproducts including a trace of monomethyltryptamine **145** (Scheme 98).¹²⁹ This is in contrast to the same reaction performed on a Boc-protected derivative **140**, which provided a good combined yield of monodeprotected and di-Boc 3-fluorooxindoles **142** and **141**.



Scheme 99: Trapping of Iminium Ion Products of Amine Oxidation¹²⁹

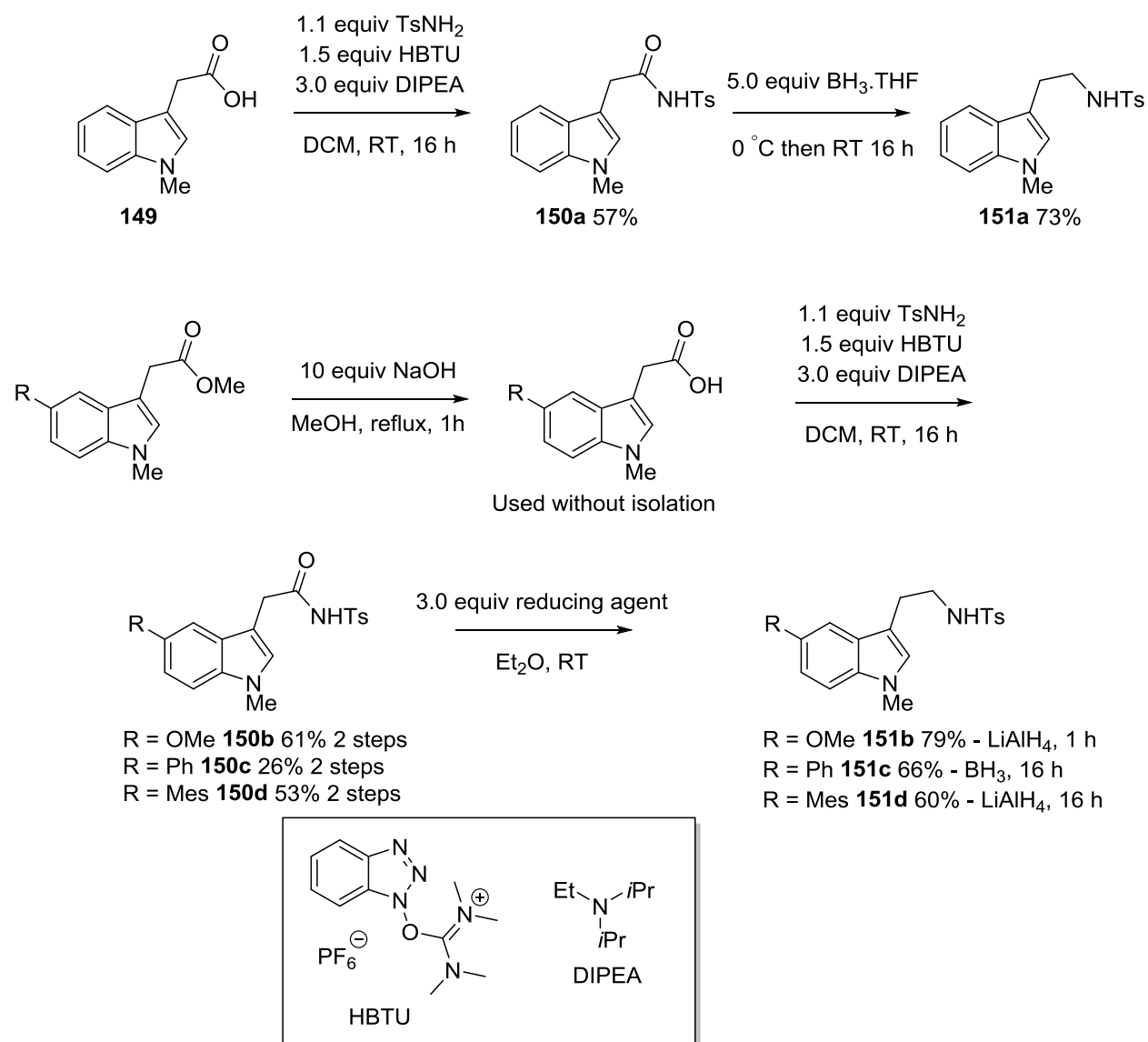
The observation of the demethylated byproduct **145** suggests an oxidative demethylation may be operating under reaction conditions. Fluorination of the electron rich NMe_2 unit provides a species which may be deprotonated to form two different iminium ions, which can be trapped by water to form 2 different α -aminoalcohols which may eliminate either formaldehyde or **146** in an analogous manner to enzymatic demethylation. Only one of the two possible products was observed after

reaction under the standard fluorination conditions, but in a trapping experiment in the presence of sodium cyanide it was possible to isolate products **147** and **148** which indicate the existence of both iminium ions (Scheme 99). This serves as proof that a significant side reaction is operating due to the reactivity of the side chain amine.

Those fluorination-cyclisations that have been successful with nitrogen nucleophiles use electron withdrawing protecting groups on nitrogen to avoid this problem. This tempers the reactivity of the amine towards N-fluorination, but also slows the cyclisation step, potentially allowing incidental nucleophiles to react with the carbocation intermediate, leading to side products. Typically the protecting group used is *para*-tolylsulfonamide. This has the advantage of good stability and good handling properties of the intermediates and cyclised products, but the removal of this group often requires harsh conditions that will readily decompose sensitive functionality in the product. We sought to use other protecting groups to expand the substrate scope for this class of reaction and ideally enable the deprotection of the amine functionality after fluorination-cyclisation to give the free amine product.

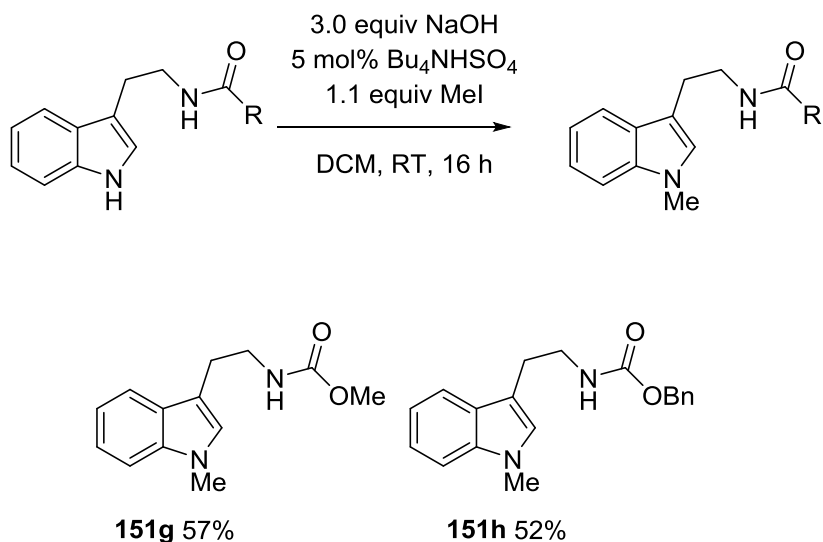
2.5.1 Substrate Synthesis

Nitrogen nucleophile substrate synthesis was performed jointly with Dr. Oscar Lozano.

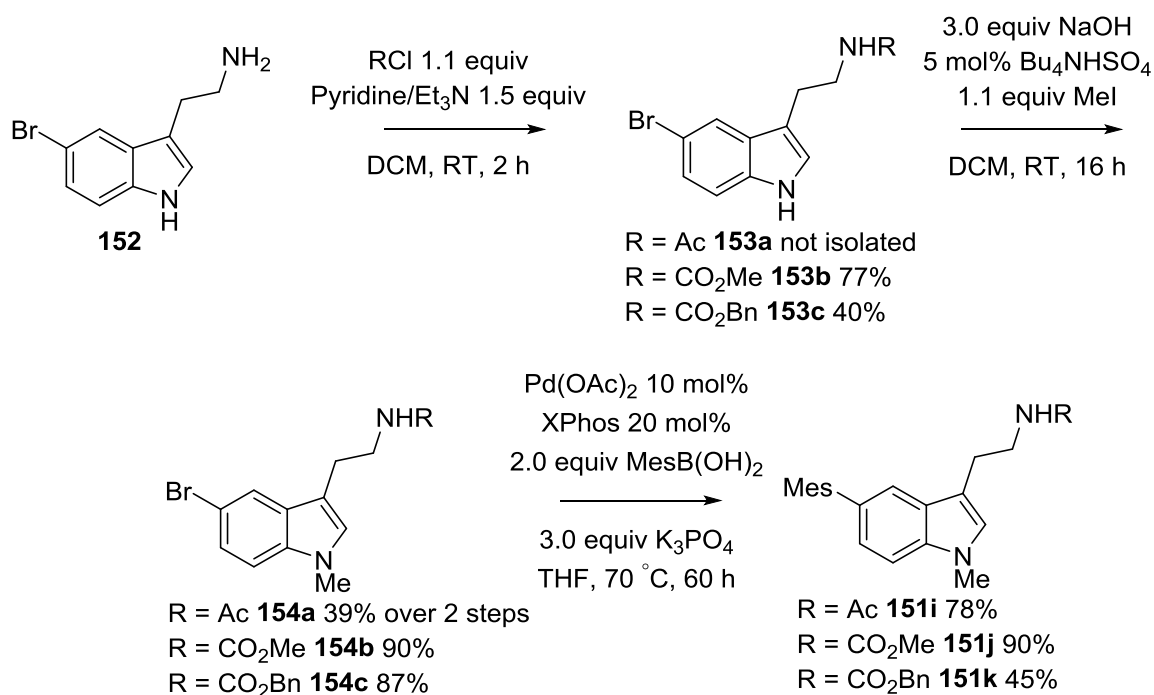


Scheme 100: Route to *N*-Tosyl Nucleophile Substrates

For *N*-tosyl substrates, the indole acetic acid intermediates were coupled with tosylamine using HBTU as a coupling agent in the presence of DIPEA. This gave moderate yields of the amide products shown. These were then reduced using either lithium aluminium hydride or borane tetrahydrofuran complex, again with moderate yields. Due to the poor combined yield for these steps it was only possible to access substrates for which the indole acetic acids were commercially available, namely the 5-substituted series (Scheme 100).

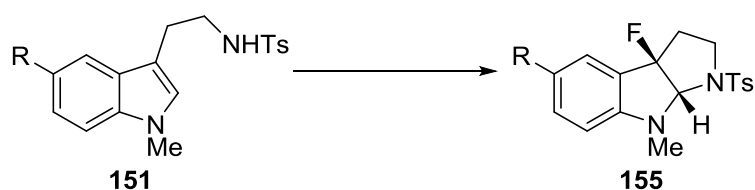
**Scheme 101: Synthesis of Unsubstituted *N*-Acyl Substrates**

Syntheses of cyclisation substrates bearing acyl protected nitrogens were performed *via* the corresponding acyl tryptamines. The acetyl and *tert*-butyl carbamate substrates **151e** and **151f** were available from literature procedures.¹³¹ The *NH* precursors to methyl carbamate¹³² and benzyl carbamate¹³³ substrates were synthesised by literature procedures, this was followed by phase transfer alkylation with methyl iodide to give the cyclisation precursors **151g** and **151h** (Scheme 101).

**Scheme 102: Synthesis of 5-Mes Acyl Protected Tryptamine Substrates**

Access to 5-aryl substituted substrates was possible starting with 5-bromotryptamine (Scheme 102). Acylation was facile with a range of acylating reagents. *N*-methylation was achieved using a phase transfer alkylation in good yields. The 5-bromo substrates were then cross coupled with mesityl boronic acid to give the cyclisation precursors **151i**, **151j** and **151k** in moderate to good yields.

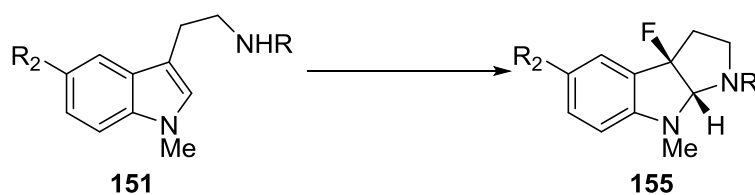
2.6 Nitrogen Nucleophile Cyclisations



Entry	R	Conditions	Yield / %	<i>ee</i> / %	Alcohol substrate <i>ee</i>
1	H	Stoichiometric	54	76	74
2	H	Catalytic	59	64	66
3	OMe	Stoichiometric	55	78	86
4	OMe	Catalytic	51	70	74
5	Ph	Stoichiometric	50	82	72
6	Ph	Catalytic	70	70	62
7	Mes	Stoichiometric	60	92	90
8	Mes	Catalytic	80	84	84

Table 15: Comparison of Alcohol and NTs Substrate Cyclisations

The cyclisation conditions used for amine nucleophile substrates were identical to those for the alcohol nucleophile cyclisations (Section 2.4). For cyclisations of the *N*-Tosyl protected substrates, the enantioselectivities were very similar to the alcohol substrates, following the same trends for 5-substitution. The unsubstituted substrate **151a** gave essentially identical enantioselectivity to the alcohol substrate **98a**. The 5-MeO substrate **151b** gave a slightly lower *ee* than the alcohol analog, but the 5-aryl substrates gave significantly higher *ees* in both catalytic and stoichiometric reactions.



Entry	R	R ₂	Conditions	Yield / %	<i>ee</i> / %
1	Ac	H	Stoichiometric	45	66
2	Ac	H	Catalytic	95	80
3	CO ₂ Me	H	Stoichiometric	56	78
4	CO ₂ Me	H	Catalytic	76	74
5	CO ₂ Bn	H	Stoichiometric	40	78
6	CO ₂ Bn	H	Catalytic	47	77
7	CO ₂ <i>t</i> Bu	H	Stoichiometric	67	86
8	CO ₂ <i>t</i> Bu	H	Catalytic	70	78
9	Ac	Mes	Stoichiometric	38	92
10	Ac	Mes	Catalytic	65	92

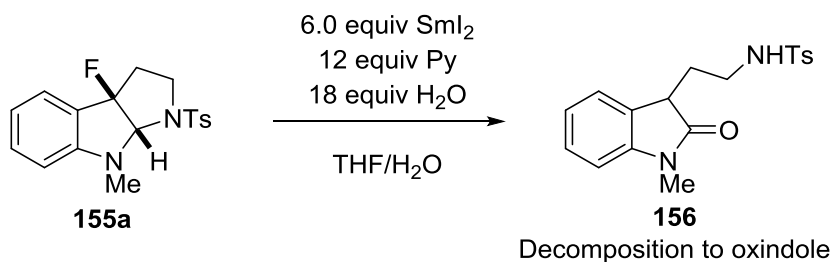
Table 16: Cyclisation of Acyl Protected Nitrogen Nucleophiles

The acyl protecting groups investigated (Table 16) gave slight increases in enantioselectivity in general, and especially in catalytic reactions, for which there were smaller decreases in enantioselectivity relative to the stoichiometric reactions of the alcohols. In the case of the acyl substrate **151e** (entries 1 & 2) the enantioselectivity increased significantly in the catalytic reaction from 66% (for the alcohol substrate **98a**) to 80%. The enantioselectivity of cyclisation was almost the same for all of the carbamate protecting groups investigated, with catalytic enantioselectivity exceeding that for the alcohol substrate in all cases. For all of these substrates it was possible to observe pairs of rotamers by NMR, with the interconversion slowing down and signals broadening in low temperature NMR, giving proof that only one compound was present in all samples. The nucleophile dependence of enantioselectivity may be evidence that the molecular recognition of the substrates by the enantiopure catalyst is not purely steric in nature and includes some interaction with the nucleophile in the enantiodetermining step. The introduction of a mesityl group in the 5-position for the N-acyl substrate **151i** led to an increase in enantioselectivity in the formation of **155i** as for the OH and NTs substrates. Attempted reaction of the 5-mesityl methyl carbamate **151j** substrate led to a complicated mixture containing several fluorinated compounds with no obvious cyclised product present. The 5-Mes benzyl carbamate substrate cyclised to give **155k** with a number of inseparable byproducts and it was not possible to determine the *ee* of the cyclised product due to overlap in HPLC of the rotamers.

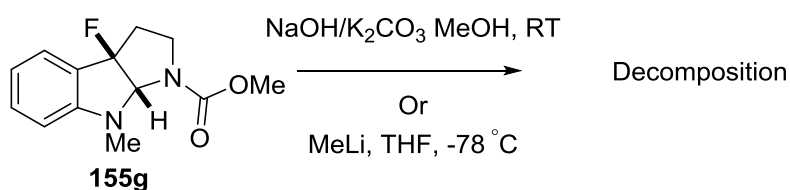
2.6.1 Nitrogen Protecting Group Removal

Nitrogen protecting group removal was performed jointly with Dr. Oscar Lozano.

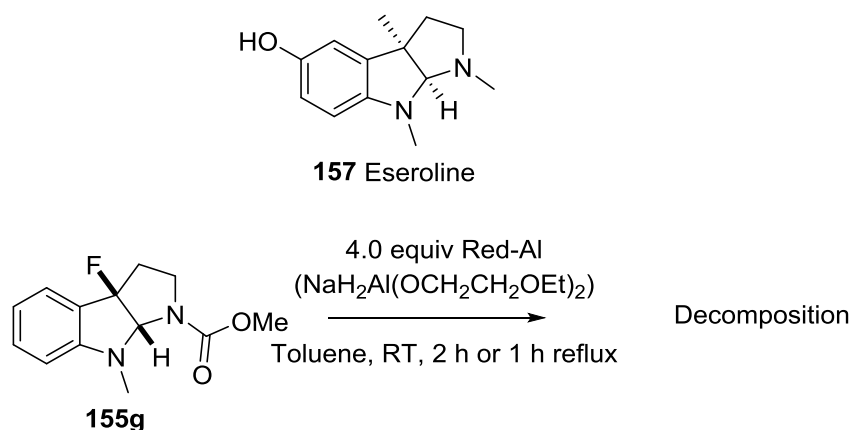
Despite the previous reports of fluorination-cyclisation with nitrogen nucleophiles there has been no description so far of a successful deprotection of a cyclised product. Indeed there is not even any mention of attempts to deprotect cyclised products in the literature concerning fluorination cyclisation with nitrogen nucleophiles. We sought to apply standard protecting group removal techniques to attempt to provide the free amine product of cyclisation, to allow further manipulation of our cyclised products.

**Scheme 103: Attempted Reductive Removal of NTs**

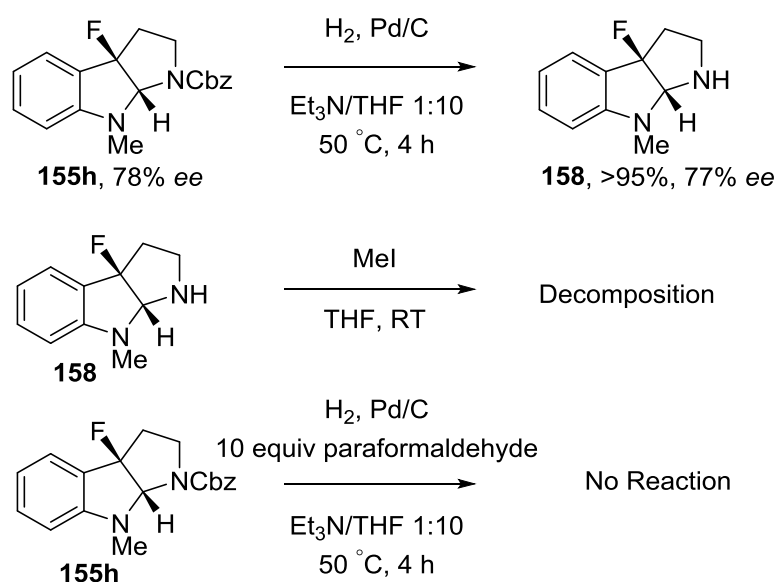
The removal of a tosyl group can be achieved under a number of different conditions, with the most common methods using reductive cleavage. Application of a SmI_2 protocol for deprotection (which is significantly milder than other methods) led to decomposition of the starting material to give the oxindole as the sole identifiable product (Scheme 103). We elected instead to develop the deprotection of acyl derivatives.

**Scheme 104: Attempted Cleavage of N-carbamate Protecting Group**

The deprotection of acyl and carbamate groups can generally be accomplished by hydrolysis or nucleophilic attack on the carbonyl carbon. A test reaction on the cyclised alcohol product **98a** showed stability towards Cs_2CO_3 in MeOH, suggesting that hydrolysis might be a useful route to the free amines. Reaction of the methyl carbamate product **155g** with NaOH or K_2CO_3 in MeOH led only to decomposition of the starting material (Scheme 104). Similarly, an attempt to cleave this group by reaction with methyl lithium was unsuccessful, giving only decomposition to a mixture of products.

**Scheme 105: Attempted Reduction of Methyl Carbamate Cyclised Product**

Due to the failure of deprotection of these protecting groups, we sought instead to attempt the conversion of the NCO_2Me group to an NMe group by reduction¹³⁴ as this in itself accomplishes the synthesis of near analogues of the tricyclic natural product eseroline **157** where the group on nitrogen is a methyl group (Scheme 105). Unfortunately despite multiple attempts we were unable to accomplish this reduction, with the starting material decomposing in all cases. The reaction with Red-Al (Sodium *bis*(2-methoxyethoxy)aluminium hydride) is known to be slow, so the decomposition of the starting material outcompetes reduction.

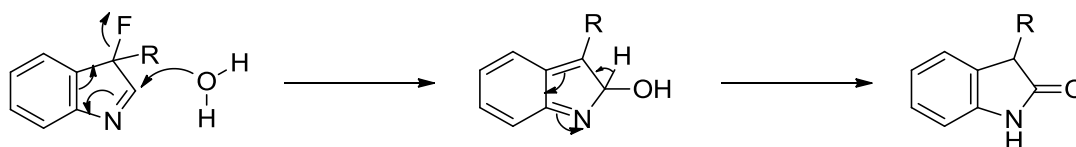
**Scheme 106: Hydrogenolysis of Benzyl Carbamate Protected Cyclised Product 155h**

For the benzyl carbamate substrate we attempted hydrogenation using Pd/C and 1 atmosphere of H_2 . In EtOAc decomposition was observed, but in THF in the presence of Et_3N the hydrogenolysis

proceeded cleanly to give the free amine **158** with unchanged enantiomeric excess (Scheme 106). Attempts to methylate this product were unsuccessful, with decomposition observed on treatment with MeI. An attempt at the one pot hydrogenolysis/reductive amination of **155h** with paraformaldehyde was also unsuccessful, with catalyst poisoning preventing hydrogenation.

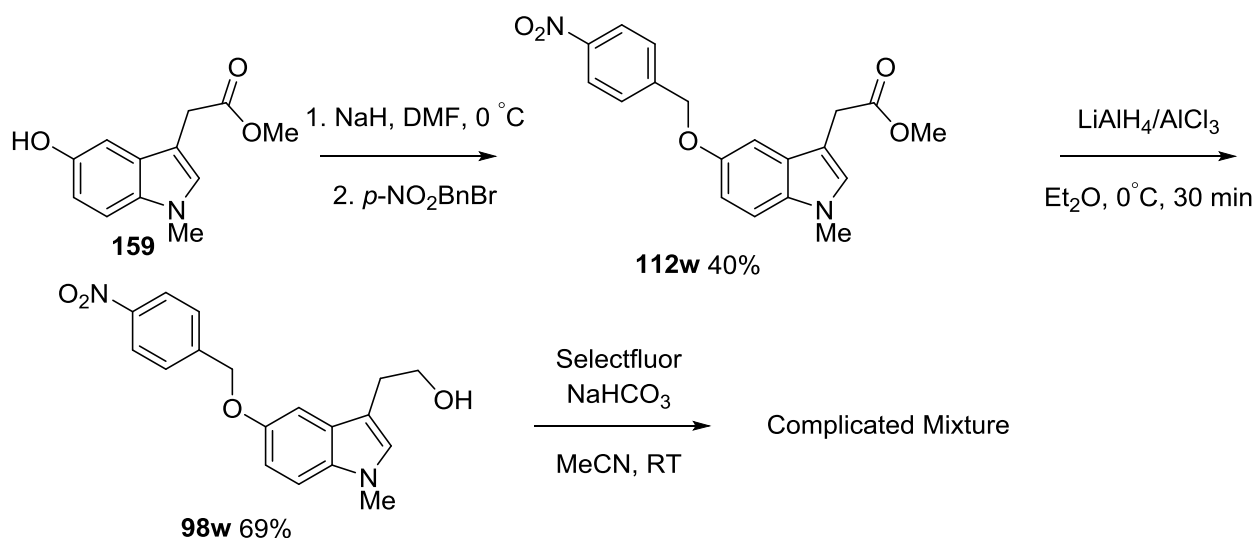
2.7 Absolute Stereochemistry

Due to the apolar nature of the cyclised products, initial attempts to prove the absolute stereochemistry of the reaction by single crystal X-ray diffraction were unsuccessful. This effort was further complicated by the instability of the products towards hydrolysis, as under ambient conditions solutions of the cyclised products underwent hydrolysis to afford the oxindole (Scheme 107). This is a known reaction in the fluorination of indoles to 3-fluorooxindoles.¹⁰⁵



Scheme 107: Hydrolysis of Fluorinated Indoles to Oxindoles

Initially we only attempted the crystallisation of those products which afforded the highest enantioselectivities, on the basis that for these substrates the crystals formed should represent the bulk material. For substrates with lower enantioselectivities, the outcome of the crystallisation depends on the behaviour of the material in the solid state - enantiomeric mixtures of compounds may exhibit multiple different crystallisation behaviours;¹³⁵ the 3 main categories of crystallisation behaviour are: pseudoracemates, in which there is random assortment of different enantiomers in solid solution; conglomerates, in which each enantiomer crystallises separately, and thus in a non enantiopure material there may be single crystals of the minor enantiomer; and racemates, where the most stable crystal form contains a 1:1 mixture of enantiomers in a well defined orientation. The behaviour of different compounds is rarely this simple, and it is not uncommon for different crystal forms to be favoured at different enantiomeric compositions, or there to be different kinetically or thermodynamically favoured polymorphs. Determination of the absolute stereochemistry of a non enantiopure sample must therefore be approached with caution, and we sought to gain multiple structures of different substrates in order to minimise the risk of misassignment.



Scheme 108: Synthesis of 98w to Determine Absolute Stereochemistry

It was not possible to isolate any crystals of any alcohol cyclised substrates. We attributed this both to the instability of this motif and the lack of polarity in the cyclised products –the cyclisation of precursor **98w** was attempted (Scheme 108), based on the reasoning that the 5-alkoxy substituent should give a high enantiomeric excess in the cyclised product, and the presence of a nitro group would provide a more polar cyclised product in an attempt to produce a crystal (Scheme 108). Alkylation of the 5-OH indole gave the product in poor yield (40%), chemoselective reduction of the ester in the presence of the nitro group was unsuccessful with LiEt₃BH, giving some product but inseparable from byproducts. The use of AlH₃, generated *in situ* from LiAlH₄ and AlCl₃ gave clean conversion to the cyclisation substrate in good yield (69%). The cyclisation gave some of the desired product but we were unable to isolate the pure cyclised product from a mixture of multiple species.

For some of the cyclised protected nitrogen nucleophile substrates crystals were grown by slow evaporation of hexane solutions of the purified product. These substrates benefit in stability from the electron withdrawing nature of the protecting group, and the tosyl protecting group provides polarity sufficient for some substrates to form stable crystals, as well as conveniently providing a heavy atom, which improves the accuracy of absolute stereochemistry determination.

The unsubstituted NHTs cyclised product **155a** provided crystals, however despite successful collection of diffraction data it was not possible to solve the crystal structure - this is because of an

effect called modulation. In addition to the long term order of the crystal lattice there is periodicity in the lattice spacing across the crystal. This phenomenon prevents the successful structure determination of such crystals, investigation of this is at the forefront of crystallography research and the structure is unsolvable using current processing methods. Chiral stationary phase HPLC of the crystal after X-ray diffraction showed the crystal to be composed of the major enantiomer.

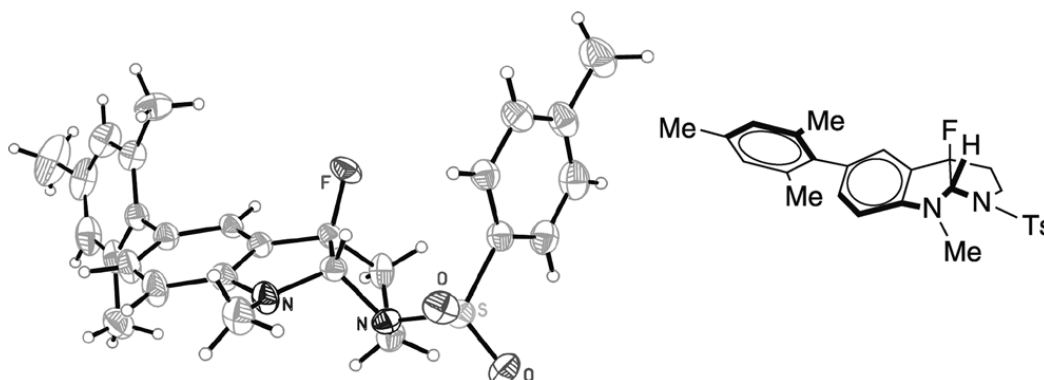
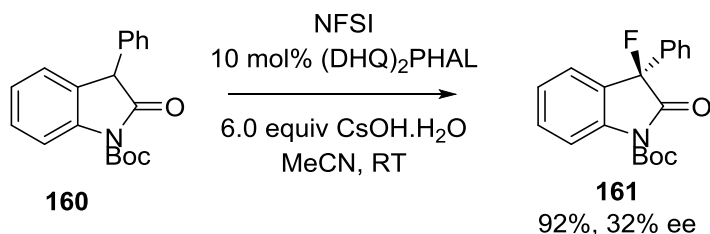


Figure 19: Crystal structure of 155d

We were able to obtain a crystal structure of the 5-mesityl substituted NTs substrate **155d** (Figure 19), proving the absolute configuration at the fluorinated centre as *R*. The enantiomeric excess of this sample was 92% so that the caveats aforementioned about the absolute configurations of enantioimpure samples must be applied here. It was not possible to perform HPLC of this crystal after diffraction data collection to verify that the crystal was of the major enantiomer. The assignment of absolute stereochemistry of all other substrates is tentatively assigned based on analogy with the absolute stereochemistry of this substrate.



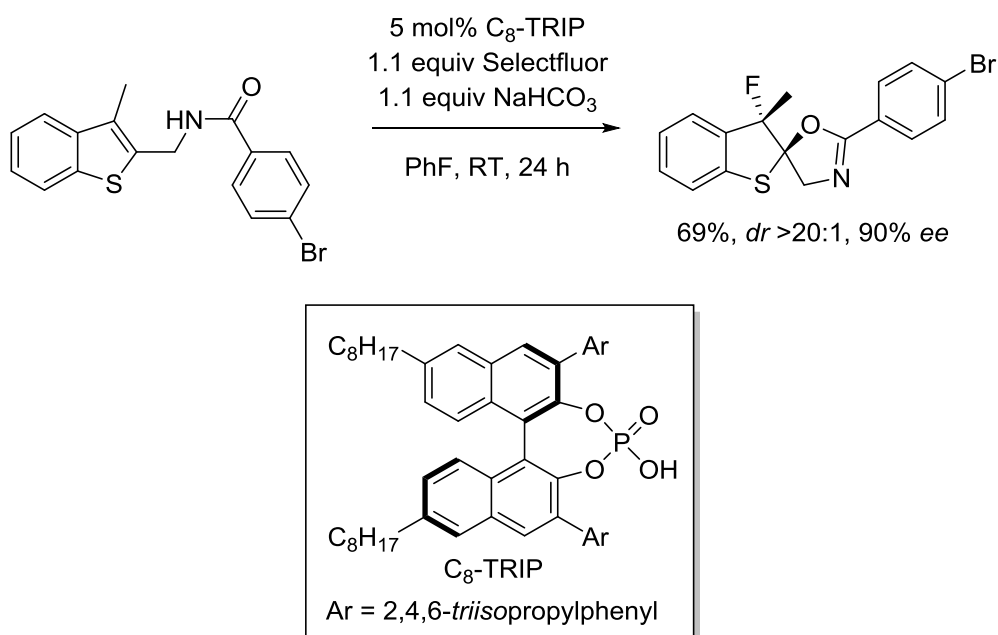
Scheme 109: Enantioselective Fluorination of Oxindoles

The absolute configuration observed for this system bears some similarities to the catalytic enantioselective fluorination of oxindoles as reported in the original paper on catalytic use of

cinchona alkaloids in fluorination (Scheme 109).¹⁰² The optimal alkaloid for this transformation is not (DHQ)₂PHAL, but all hydroquinine *bis* alkaloids give this enantiomer of the product with the same configuration at the fluorinated centre as in the fluorocyclisation system. This does not give any evidence for similarities in transition states for enantioselective fluorination but if the sense of enantiocontrol were different it would cast some doubt on the assignment of absolute stereochemistry of **155a**. These systems have some differences in structure, and substitution at the 5-position does not increase enantioselectivity for the oxindole system, so any comparison must be made with caution.

2.8 Conclusions and Further Work

This work represents the successful application of a catalytic enantioselective fluorination methodology to a novel system, extending the utility of the methodology to enable cyclisation concomitant with fluorination to access benzylic fluorides. This sequence of bond forming steps leads to greater molecular complexity and enables access to novel fluorinated heterocycles. We were able to demonstrate the limitations of the *cinchona* alkaloids in terms of substrate compatibility, of the substrate patterns investigated, those with substitution at the largest distance from the reacting centre were the best tolerated (the 5- and 6- substrates). The sense of enantioinduction was proved by single crystal X-ray diffraction of a cyclised product and was found to match that of a related system. Further development of this methodology enabled fluorination cyclisation with protected nitrogen nucleophiles other than the tosyl group used in most prior descriptions of fluorination cyclisation. Cyclisations of these nucleophiles resulted in the unusual finding that enantioselectivity had a modest nucleophile dependence, suggesting that substrate recognition by the organocatalyst may be more complicated than pure steric considerations. The use of carbonyl based protecting groups also enabled the development of a mild deprotection method which maintained the integrity of a sensitive benzylic fluoride heterocycle; this is of note as it has not to our knowledge been demonstrated that a fluorocyclised nitrogen nucleophile can be deprotected for further manipulations whilst retaining the ring structure introduced.

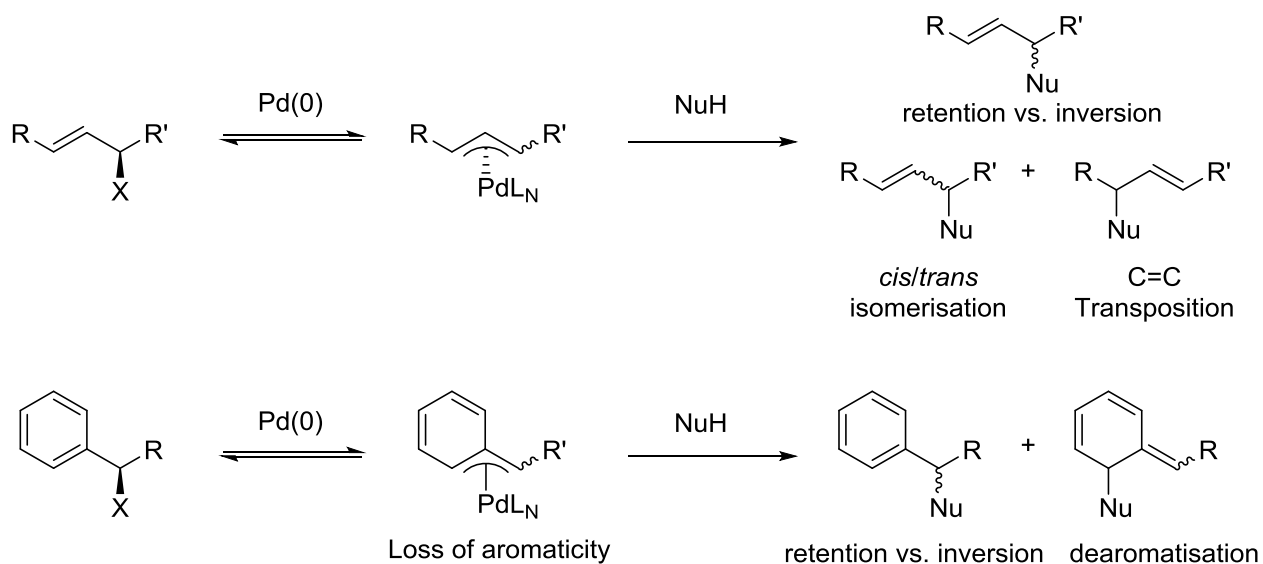
**Scheme 110: Phase Transfer Fluorination Cyclisation¹³⁶**

Since the completion of this project there have been several reports of the use of Selectfluor in combination with enantiopure phosphoric acid catalysts (Scheme 110). The use of these catalysts enables the use of a phase transfer regime to accomplish fluorination in an enantioselective manner.¹³⁶ This development removes background reactivity in the absence of the enantiopure catalyst, a problem which plagues the *cinchona* alkaloid catalysis approach.

The examples reported of enantioselective fluorination to date require a hydrogen bonding motif to direct interaction for high levels of enantioselectivity, and this limits the substrate scope of such fluorinations. The use of this reagent combination for the synthesis of benzylic fluorides has been demonstrated (Scheme 110). The efficiency of enantioselective induction is high, catalyst loadings are low and the reaction conditions mild, thus further development of this methodology for the synthesis of benzylic fluorides, particularly for substrates not bearing a directing motif, would be an attractive goal.

Chapter 3: Palladium Catalysed Benzylic Defluorination

The research described in this chapter was performed in collaboration with Patrick Holden, part II student 2010-11, and part of this work has been described in a publication.¹³⁷

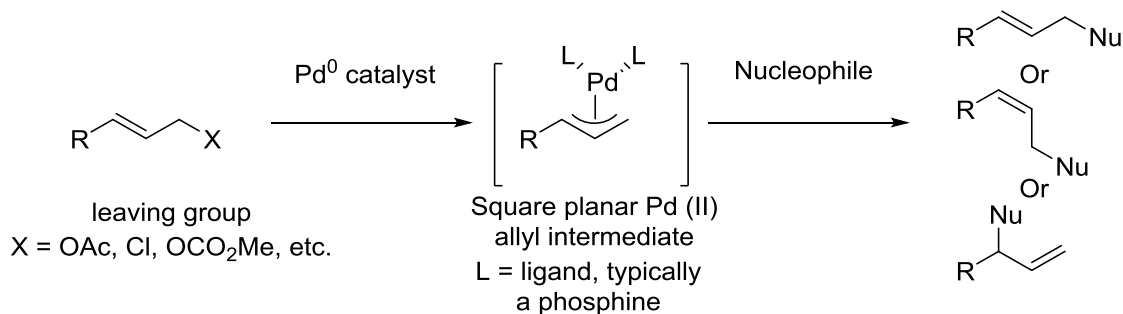


Scheme 111: Challenges in Allylic and Benzylic Catalysis

We were inspired to explore the potential of palladium catalysis for the synthesis of benzylic fluorides by a sequence of papers published concerning the reactivity of allylic fluorides under palladium catalysis,¹³⁸ and subsequent developments of this methodology to enable the synthesis of allylic fluorides.^{76, 78, 79} It was clear to us that the successful development of these fluorinations hinged on insights into allylic fluoride reactivity gained in the development of the defluorination reaction. This enabled the design of combinations of solvent, catalyst, leaving group and fluoride source to effect the C-F bond formation. There are multiple similarities between allylic and benzylic palladium allyl chemistry, using common catalysts and leaving groups and allowing functionalisations with a range of different nucleophiles. There are however significant differences in the reactivity of benzylic and allylic substrates towards metal catalysts, and between η-3 complexes of benzyl and allyl ligands. Arenes are poorer ligands for Pd(0) than alkenes for pre-association, and the ionisation of benzylic leaving groups is less favoured than for allylic systems due to loss of aromaticity. The reactivity and regioselectivity of attack on η-3 complexes is also complicated, with a range of products possible for

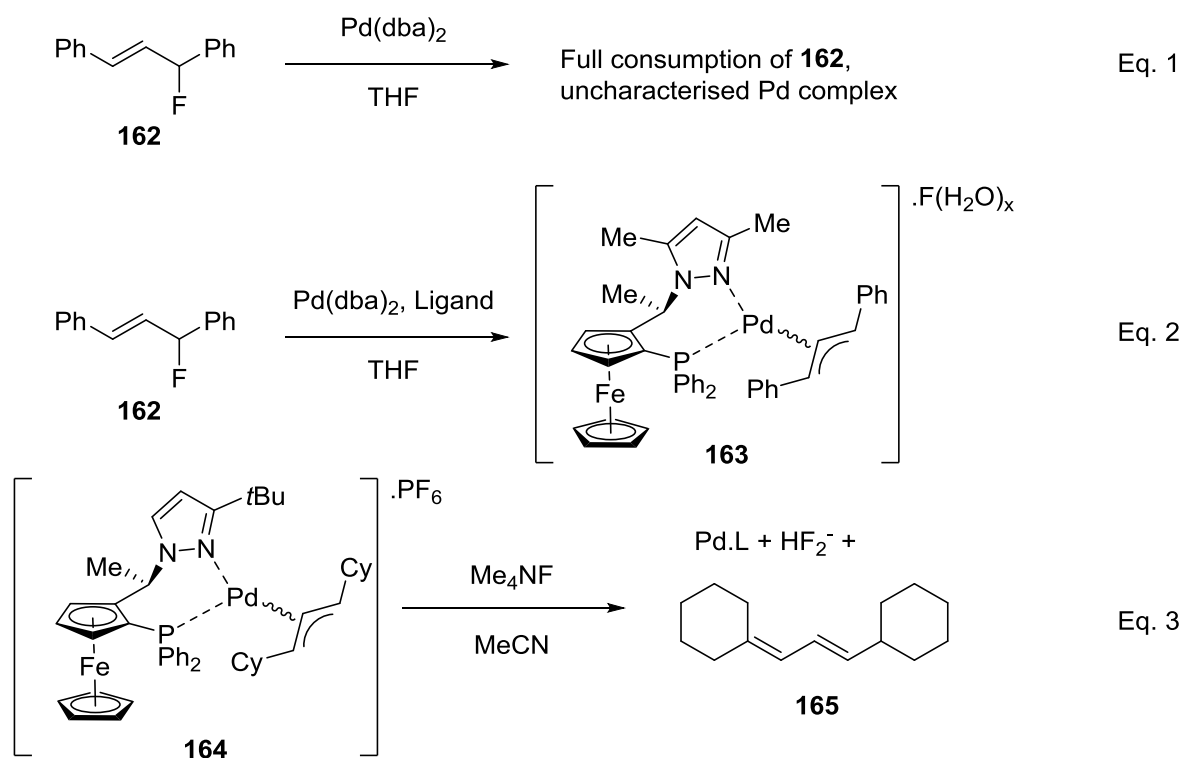
either system. Based on the literature precedents available, this project sought to develop knowledge of the reactivity of benzylic fluorides under metal catalysis to determine whether a catalytic benzylic fluorination was a feasible reaction (Scheme 111).

3.1 Palladium Catalysed Allylic Defluorination and Fluorination



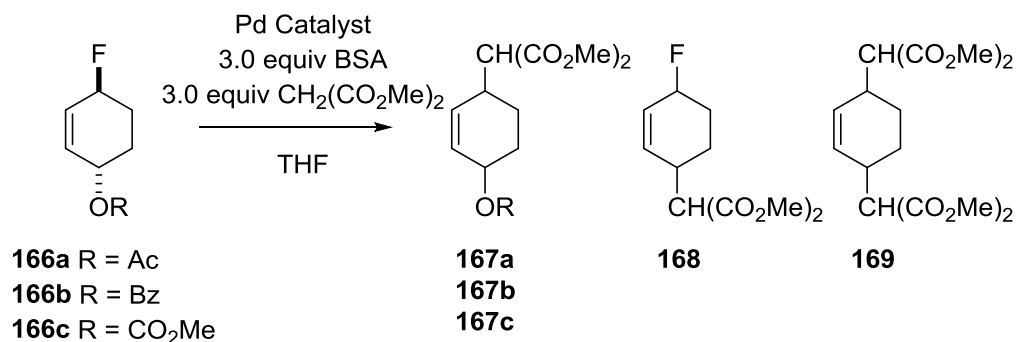
Scheme 112: C-X Displacement of a Terminal Allyl Substrate Under Pd (0) Catalysis - Tsuji Trost Reactivity

The Tsuji-Trost reaction, the substitution of a leaving group at an allylic position by a nucleophile (Scheme 112), proceeding through an η^3 Pd allyl intermediate has been investigated in much detail. It is sufficiently reliable and robust to have featured in numerous total syntheses since the first description of this transformation¹³⁹ and its subsequent development into a catalytic system.¹⁴⁰ Relatively unreactive allyl acetates are viable substrates, allowing for the reactive functionality to be carried through a synthetic sequence to allow late stage catalytic activation. Investigations of the reactivity of catalytic systems based on other metals have led to the discovery of reactions of allylic compounds with complementary selectivity, so that with the correct choice of catalyst the selectivity of a reaction may be altered. For example regioselectivity is typically altered from linear to branched by the use of iridium catalysts instead of palladium.¹⁴¹ Whilst the reaction was initially developed using carbon nucleophiles, subsequent developments have enabled a large range of functionalisations to be achieved including amination, etherification, thioetherification and sulfinylation.^{142, 143} The use of a variety of leaving groups is possible and this is a common parameter used in reaction optimisation. The recent development of this reaction to allow the use of fluoride as a leaving group or nucleophile has enabled the rapid development of useful fluorination methodologies.



Scheme 113: Palladium Catalysed Reactivity of Allylic Fluorides

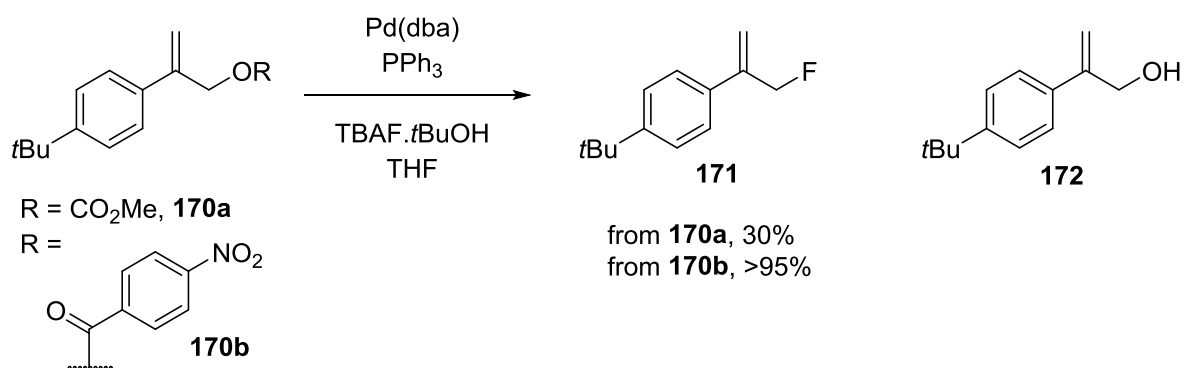
The oxidative addition of an allylic fluoride **162** to a $\text{Pd}(\text{dba})_2$ precatalyst was demonstrated to occur in THF to give an uncharacterised Pd allyl complex (Scheme 113, Eq. 1). In the presence of a P,N chelating ligand, the cationic allyl complex **163** is formed instead (Scheme 113, Eq. 2).¹⁴⁴ The same complex with Pt replacing Pd was prepared under strictly anhydrous conditions in order to prevent formation of less nucleophilic hydrated fluoride as the counterion. ^{19}F NMR provided no evidence of formation of the allylic fluoride by reductive elimination from either the Pd or Pt complex. The related Pd complex with a 1,3-dicyclohexyl allyl ligand **164** gave solely elimination product **165** on exposure to fluoride (Scheme 113, Eq. 3). The authors of this paper concluded from these results that the formation of allylic fluorides from solvated fluoride was not a feasible reaction due to the high enthalpy of solvation of fluoride, and the facile elimination in the presence of highly basic naked fluoride.



Entry	R	Catalyst (mol%)	167	168	169
1	Ac	(Pd(allyl)Cl) ₂ .2PPh ₃ (10)	40	-	60
2	Bz	(allyl)Pd(PPh ₃) ₂]BF ₄ (20)	-	-	>95
3 ^a	CO ₂ Me	(Pd(allyl)Cl) ₂ (2.5)	-	40	(10)

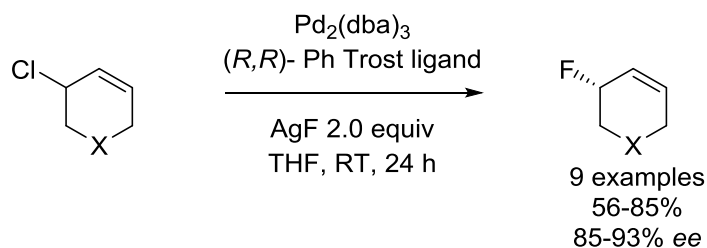
Table 17: Leaving Group Preferences for Allylic Substitution a) reaction with 3.0 equiv NaCH(CO₂Me)₂ / 15-crown-5

The reaction of a range of cyclic allylic substrates bearing both fluoride and carboxylate leaving groups enables calibration of the leaving group ability of fluoride relative to common leaving groups (Table 17).¹³⁸ It is found that fluoride is a superior leaving group to acetate, and it is possible to isolate the allylic acetate product **167a**. Benzoate gave full conversion of both leaving groups but ¹H NMR kinetic studies revealed preferential substitution of fluoride. The methyl carbonate was much more reactive than fluoride and it was possible to isolate allylic fluoride **168**. These results imply that benzoate or methyl carbonate groups might be suitable for allylic fluorination. The stereochemical course of fluoride displacement by malonate nucleophiles is unusual, giving products of net inversion of stereochemistry. The addition of TBAF increases the preference for inversion of stereochemistry in the alkylation of **166c**. These observations taken together suggest that fluoride coordinates to Pd(II) catalytic intermediates, which may have implications for Pd(0)/Pd(II) catalysis of allylic or benzylic fluorination.



Scheme 114: Palladium Catalysed Fluorination of Allylic Esters

The substitution of an oxygen leaving group by fluoride under Pd(0) catalysis has been developed based on the insights provided by the defluorination reaction (Scheme 114).⁷⁶ Reaction of the carbonate **170a** with a variety of fluoride sources in THF gave a lead result of 30% yield of the fluoride **171** when Pd(dba)₂/PPh₃ was used as catalyst and TBAF.(tBuOH)₄ as fluoride source. Other fluoride sources were ineffective, CsF gave only partial conversion (70% starting material remaining) and only traces of fluoride (< 2%), with the main product the alcohol **172** (28%). Commercially available TBAF.(H₂O)_{3.5} gave full conversion of the starting material, but the alcohol was the dominant product formed in 12:1 ratio with the fluoride. Other palladium catalysts gave similar conversions with TBAF. (tBuOH)₄ but in the absence of palladium the starting material was recovered unchanged. The use of different leaving groups was examined, demonstrating that indeed the acetate starting material was unsuitable, giving only starting material. The trifluoroacetate starting material gave full conversion to the alcohol, reflecting the hydrolytic instability of these esters. Benzoate, despite having a greater leaving group ability than fluoride, gave only a poor conversion to fluoride (20%) but the selectivity was promising, with no alcohol observed. The use of more reactive *para*-nitrobenzoate **170b** proved optimal, giving quantitative conversion to the allylic fluoride. This methodology enabled access to a range of 1- and 2-aryl substituted allylic fluorides in moderate to excellent yields.



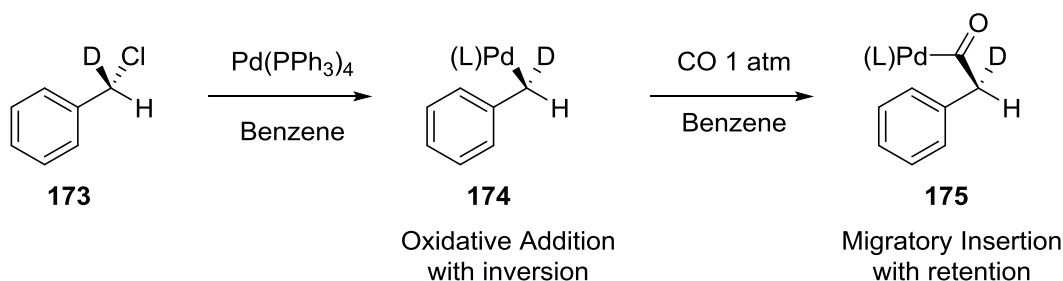
Scheme 115: Enantioselective Fluorination of Allylic Chlorides

Starting from more reactive cyclic allylic chlorides, Doyle *et al.* have demonstrated the enantioselective synthesis of allylic fluorides using AgF as the fluoride source (Scheme 115). There is a background uncatalysed fluorination in the absence of Pd catalyst, but the rate enhancement in the presence of the catalyst complex is sufficient to enable highly enantioselective reaction, outcompeting the background reaction. The authors have further developed this methodology to enable access to enantiopure acyclic allylic fluorides.⁷⁹

3.2 Benzylic Tsuji Trost Chemistry

The development of the benzylic variant of Tsuji-Trost reaction chemistry has been slower than for allylic substrates. This is attributable to the lower reactivity of benzylic relative to allylic substrates. Reactions of benzyl halides (BnCl & BnBr) under Pd catalysis have been known for a long time, but less activated esters and carbonates were only shown to be competent substrates after the development of the Tsuji-Trost reaction into a mature methodology. Consequently the chemistry of benzylic electrophiles in transition metal catalysis is currently a highly active research area.

3.2.1 Pd Catalysed Reactivity of Benzyl Halides

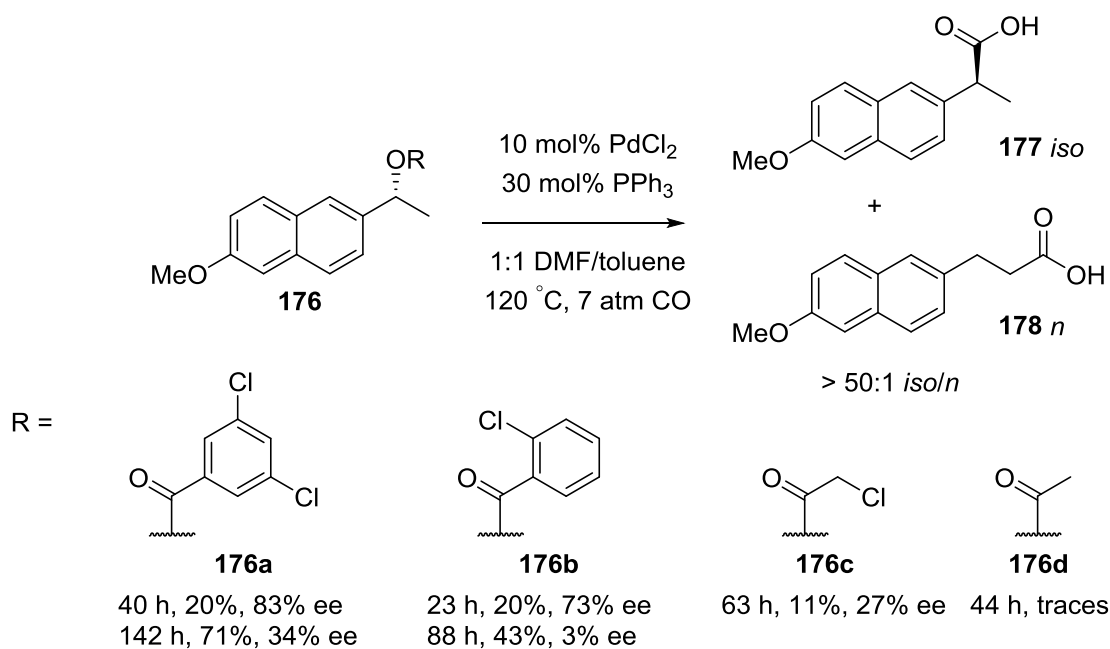


Scheme 116: Enantiospecific Benzylic Oxidative Addition¹⁴⁵

The stereochemistry of oxidative addition reactions of benzylic bromide and chloride substrates in palladium catalysed carbonylation was shown to proceed with inversion of configuration at the benzylic centre in the intermediate complex,^{145, 146} similarly to the Tsuji-Trost reaction (Scheme 116).¹⁴⁷ This requires the mechanism to be S_N2 attack at the reactive centre rather than a concerted oxidative addition. Carbonylation of enantiopure benzylic complex **174** is known to proceed with retention of stereochemistry, giving the product complex **175** with net inversion of stereochemistry. This is confirmed by transformation of the product complex into the corresponding deuterated phenyl ethanol and comparison to a sample of known stereochemical configuration. The measured optical rotation of the isolated material was lower than that of the standard, demonstrating that there is some stereochemical leakage during the synthetic sequence. The stereochemical course of benzylpalladium reductive elimination was not examined as a part of this study.

3.2.2 Less Activated Leaving Groups

The development of Pd benzyl chemistry towards less activated substrates was first demonstrated by the Pd(0) catalysed carbonylation of enantiopure 1-(6-methoxynaphth-2-yl)ethyl esters to the corresponding 2-arylpropanoic acids.¹⁴⁸ The rationale behind this development was to develop an alternative to carbonylation of enantiopure benzyl halides, due to the greater accessibility and chemical and configurational stability of benzyl alcohols and esters. It was found that relatively activated esters, such as the 3,5-dichlorobenzoate **176a**, were the only leaving groups which allowed for high conversions to be attained, with even these reactions requiring extended reaction times at high temperatures to reach good conversions (Scheme 117). 2-Chlorobenzoate ester **176b** was slightly less reactive, chloroacetate **176c** produced small amounts of product, but acetate ester **176d** showed only trace reactivity.

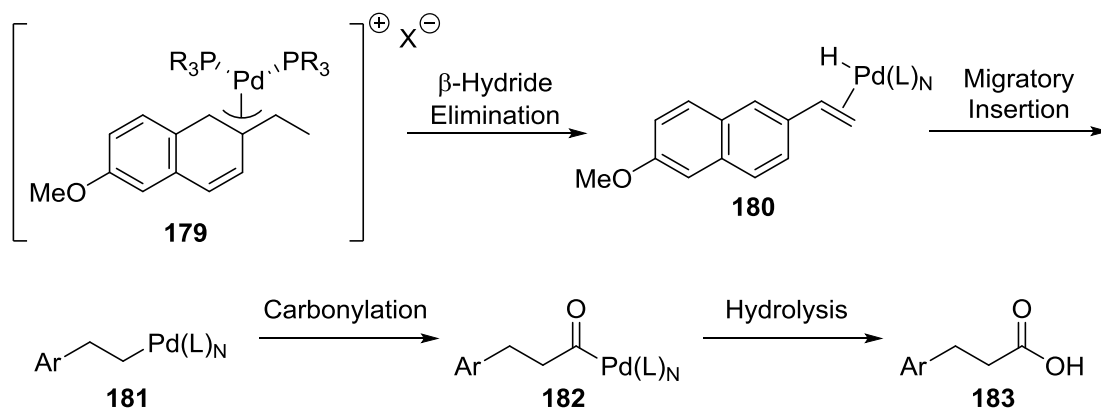


Scheme 117: Carbonylation of 1-(6-methoxynaphth-2-yl)ethyl esters - Leaving Group Propensity¹⁴⁸

Carbonylation was successful and highly selective for the branched product **177** over the linear **178** when the reaction was performed in a 1:1 mixture of DMF and either benzene or toluene (Scheme 117). Reactions performed in either solvent alone either failed to react, as in the case of benzene and toluene, or produced significant byproducts, as in DMF, MeCN, THF or DME, with the predominant byproduct being the linear 3-arylpropanoic acid isomer (up to 3:4 *iso/n* ratio in THF). The formation of this byproduct cannot be explained by a Tsuji-Trost mechanism, and probably occurs by β -hydride elimination of the alkene, followed by migratory insertion to produce the linear Pd complex **181** (Scheme 118), this undergoes carbonylation to give the linear complex **182**, hydrolysis then produces **183**. The presence of this byproduct thus suggests that under that catalyst/reaction conditions combination the intermediate benzyl complex undergoes elimination readily and that the preferred hydrocarbonylation product of the alkene thus produced is the linear product.

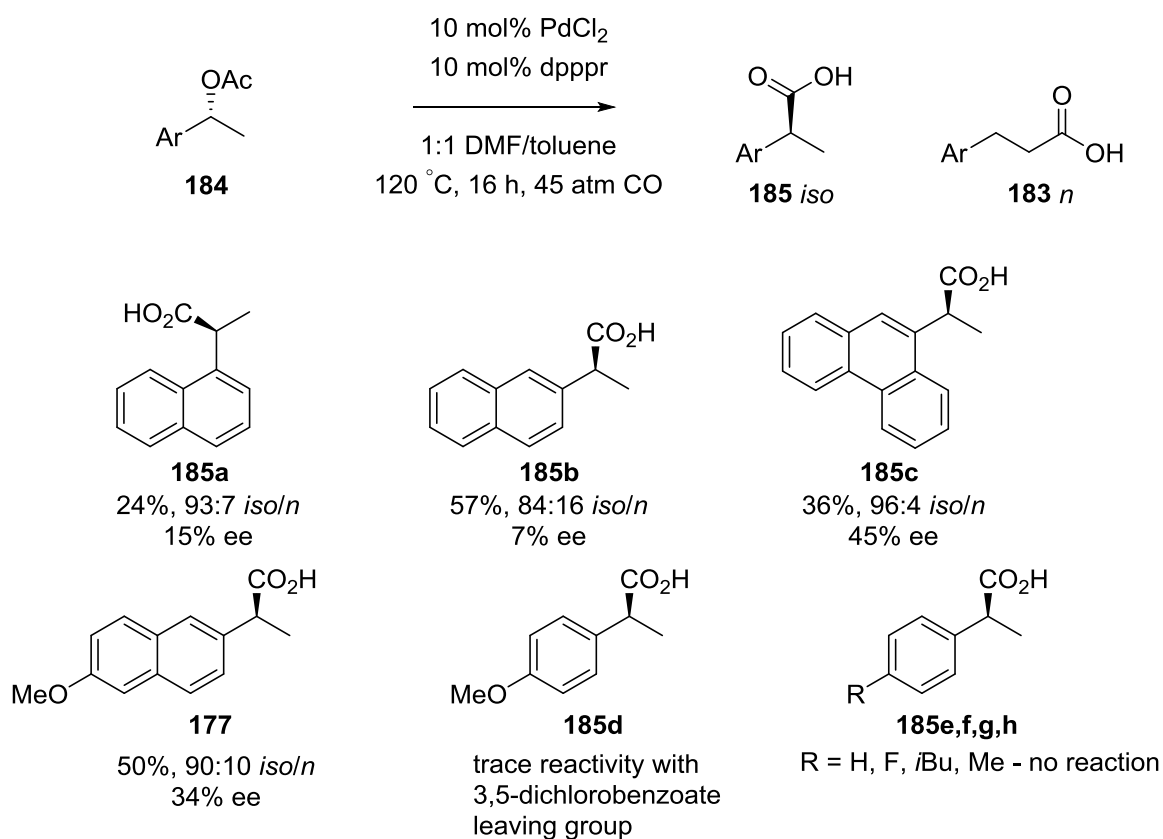
The reason for the low stereospecificity of carbonylation was suggested to be due to product racemisation, and indeed submission of enantiomerically pure 2-arylpropanoic acids to the reaction conditions led to slow racemisation. Supporting evidence for this is the time/conversion dependence of stereospecificity: at low conversions the reaction is more enantiospecific, suggesting that the oxidative addition and carbonylation steps are inherently stereospecific. The level of stereospecificity

was independent of Pd concentration, seemingly ruling out Pd-Pd interconversion as a racemisation mechanism (see chapter 4 for a full discussion of this effect).

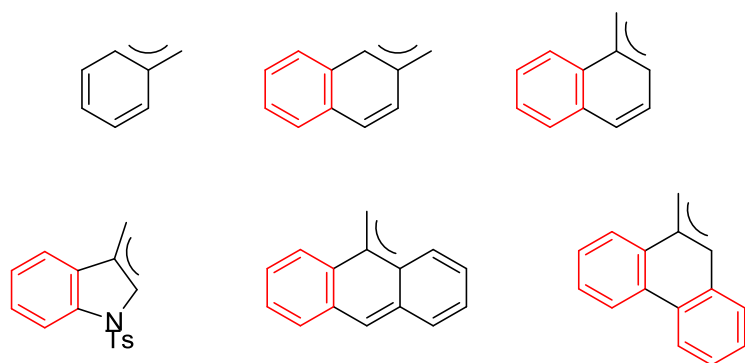


Scheme 118: Formation of Linear Arylpropanoic Acid Byproduct

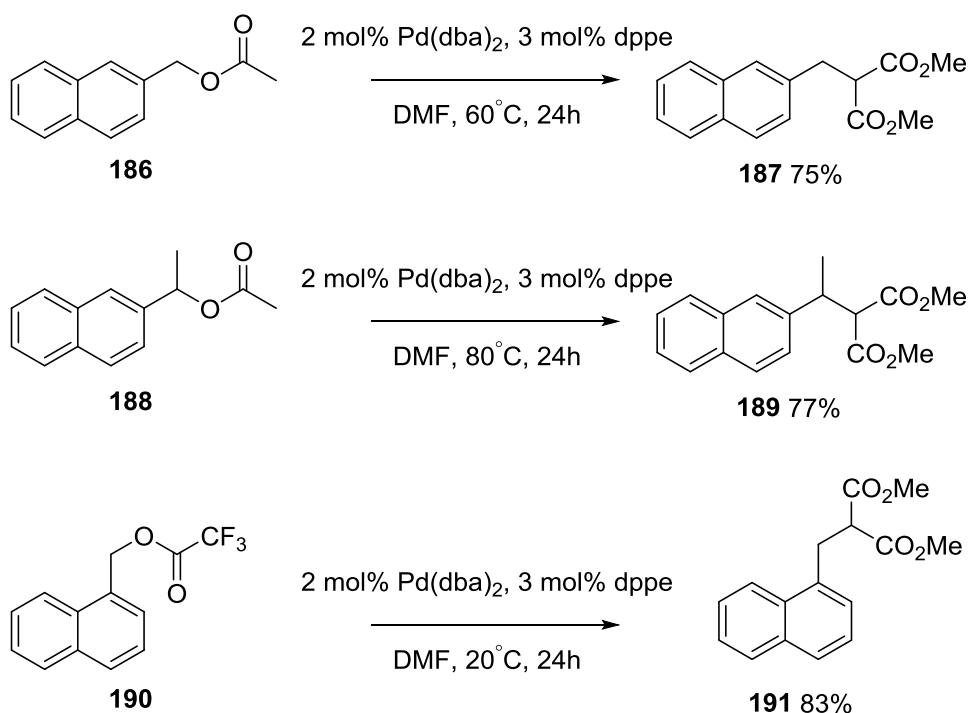
The use of alternate ligands to attempt to control regioselectivity and to maintain the stereochemical information in the starting material was unsuccessful. Reactivity was superior for the bidentate ligand *dpppr*, but regioselectivity under identical conditions was poorer at 4:3 *iso/n*. The more electron rich triaryl phosphine PAr_3 with $\text{Ar} = p\text{-OMePh}$ similarly produced the arylpropanoic acid in a 4:3 *iso/n* ratio. For the bidentate system, selectivity could be recovered to 9:1 by increasing the pressure of CO used to 45 atmospheres, but stereospecificity remained low. The unpredictable effects on selectivity of the variation of these parameters demonstrate the importance of screening of reaction conditions to determine optimal conditions for a transformation.

Scheme 119: Carbonylation Substrate Scope¹⁴⁸

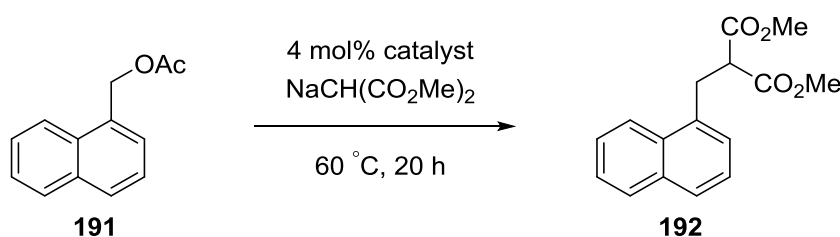
Other polycyclic substrates based on 1- and 2-naphthyl and 9-phenanthryl reacted similarly under dpppr/high pressure CO conditions to give the arylpropanoic acids in *iso/n* ratios from 84:16 to 93:7 (Scheme 119). The enantiospecificity for these substrates under these conditions was poor. The 1-naphthyl and 9-phenanthryl substrates **184a** and **184c** have more steric influences at the reactive centre, and as such are slightly less reactive (24% and 36% yield after 16-18h respectively, in comparison to 50% and 57% for 6-OMe 2-naphthyl and 2-naphthyl). The use of monocyclic substrates was not possible with this methodology, with electron poor (4-FPh), neutral and rich (4-OMePh) substrates tested. The esters of these substrates were recovered unchanged after the attempted reaction, with the exception of the doubly activated 3,5-dichlorobenzoate ester of 1-(4-methoxyphenyl)ethanol, where traces of the acid product were observed.

**Scheme 120: Aromaticity Maintained on Allyl Formation**

These results suggest that the problematic step for carbonylation of these substrates is C-O cleavage to create an η -3 intermediate. A complete treatment of the molecular orbitals involved is complicated but a simple argument explains the trend in reactivity. The reaction of a monocyclic substrate results in the complete loss of aromaticity in the intermediate complex, whilst for a polycyclic substrate the aromaticity of the ring which does not bear a leaving group is maintained (Scheme 120). The resonance stabilisation lost on formation of allyl complexes of polycyclic substrates is therefore less than that of benzene. The relative energy difference between the catalytic intermediate and the starting material is lower for polycyclic substrates, so they are more reactive.

**Scheme 121: Pd(0) Catalysed Substitution of Naphthylmethyl Esters¹⁴⁹**

The extension of Pd mediated transformation of oxygen leaving groups to Tsuji Trost chemistry followed shortly after the report of the carbonylation in a publication by Legros and Fiaud,¹⁴⁹ where they demonstrated that a catalyst derived from Pd(dba)₂ and dppe could mediate the substitution of naphthylmethyl acetate and trifluoroacetate esters by a malonate nucleophile (Scheme 121). The temperatures employed were lowered relative to the carbonylation reaction, but still higher than typical for Tsuji-Trost reactions, at 60 °C for primary and 80 °C for secondary substrates. Even with these high temperatures, long reaction times were required (24 h), reflecting the lower reactivity of benzylic substrates relative to allylic. The use of a trifluoroacetate leaving group enabled the reaction to proceed at room temperature. Under these conditions, monocyclic substrates were inert to substitution, similarly to results from the carbonylation reaction.

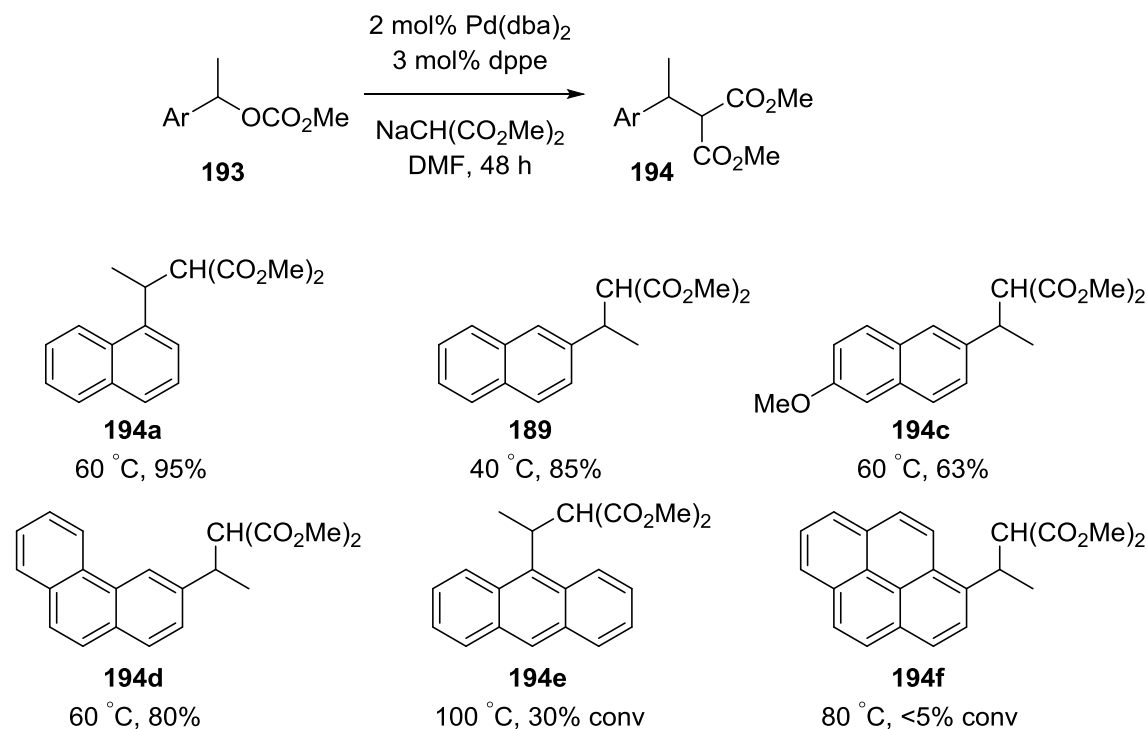


Entry	Solvent	Pd Precursor	Added Phosphine (equiv / Pd)	GC Yield
1	THF	Pd(OAc) ₂	dppe (1.0)	29
2	THF	Pd(dppe) ₂	-	25
3	THF	Pd(dba) ₂	dppe (1.0)	71
4	Dioxane	Pd(dba) ₂	dppe (1.5)	55
5	DMPU	Pd(dba) ₂	dppe (1.5)	58
6	MeCN	Pd(dba) ₂	dppe (1.5)	65
7	DMF	Pd(dba) ₂	dppe (1.5)	87

Table 18: Ligand and Solvent Optimisation for Displacement of Acetate¹⁵⁰

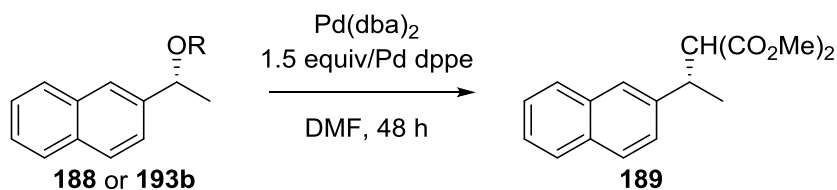
Further investigation of this methodology by the same authors provided better insight into the essential parameters for reactivity in these systems (Table 18).¹⁵⁰ The use of Pd(dba)₂ in conjunction with a bidentate ligand proved to give far superior reactivity compared to the use of either a Pd(0) phosphine catalyst or a Pd(II) precatalyst, suggesting that the dba ligand may have a role in supporting a catalytic cycle. The best yields of product were obtained with 4 mol% of Pd with between 0.75 and 1.5 equivalents of bidentate ligand to palladium; for further reactions a slight excess of phosphine relative to palladium was used to ensure catalyst stability. The bidentate ligands surveyed showed a

wide range in reactivity, with moderate length spacers (and thus mid range bite angle ligands) giving the catalysts with greatest activity. A range of polar aprotic solvents were employed, good reactivity was observed in most solvents, with DMF proving optimal.



Scheme 122: Substitution of Polycyclic Aromatic Benzylic Carbonates¹⁵⁰

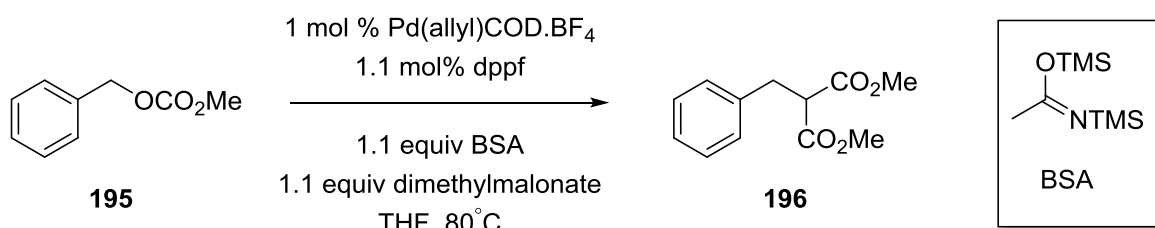
The use of carbonate leaving groups allowed the reaction to proceed at lower temperatures, but there was more elimination observed for secondary substrates than with acetate as leaving group, similarly to the use of more activated leaving groups in the carbonylation by Baird *et al.* The Tsuji-Trost substrate scope was examined for polycyclic aromatic hydrocarbons; for the same substrates as the carbonylation paper a different reactivity profile was observed (Scheme 122). 1- and 2-naphthyl substrates **193a** and **193b** reacted well, but it was found that the 6-methoxynaphthyl substrate **193c** was significantly less reactive than the unsubstituted naphthalenes, with the acetate unreactive even at 80 °C, and the carbonate leading to significant elimination at 60°C. The 2-phenanthryl carbonate **193d** exhibited good reactivity, but the 9-anthracenyl **193e** and 1-pyrenyl **193f** substrates gave poor yields of the desired product, with the majority of the material being converted to the corresponding alkenes (Scheme 122).



Entry	R	Temp / °C	Pd mol%	Yield	ee
1	Ac	80	2	78	31
2	CO ₂ Me	80	2	67	74
3	CO ₂ Me	60	0.5	80	97
4	CO ₂ Me	60	1	79	66
5	CO ₂ Me	60	2	92	72
6	CO ₂ Me	60	5	85	55
7	CO ₂ Me	60	20	80	62

Table 19: Stereochemical Outcome of Substitution of 2-Naphthyl Substrates

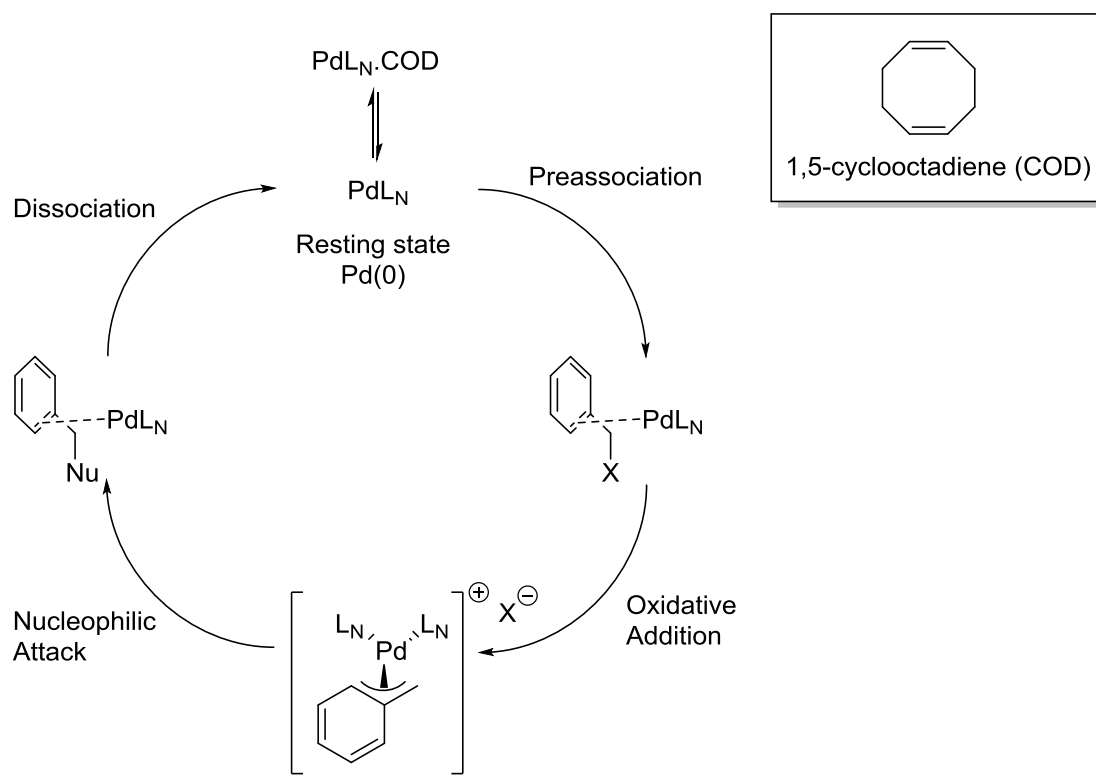
The stereochemistry of benzylic Tsuji-Trost substitution is similar to that for allylic reactions, with an inversion on formation of Pd η^3 complex followed by an inversion on nucleophile attack, leading to overall retention of stereochemistry. The enantiomer of product produced by malonate substitution of naphthylethyl esters is that of net retention of stereochemistry, albeit with significant erosion of stereochemistry depending on the conditions used (Table 19). In all cases more reactive carbonates give better transposition of stereochemistry - this is suggested to be because the free palladium concentration is maintained at a low level due to the high reactivity of these substrates. This acts to minimise the rate of Pd-Pd interconversion, whereas for acetate substrates it may be more favourable for free Pd to attack a Pd benzyl complex than the substrate. There is no significant effect of reaction temperature on the enantiospecificity of substitution.



Scheme 123: Substitution of Monocyclic Benzylic Carbonates¹⁵¹

The extension of this methodology to provide catalytic systems with high activity for the substitution of monocyclic aromatic substrates was performed by Kuwano *et al.*¹⁵¹ Optimising for palladium precursor, ligand and base they found that a catalyst based on Pd(allyl)COD.BF₄ and dppf would

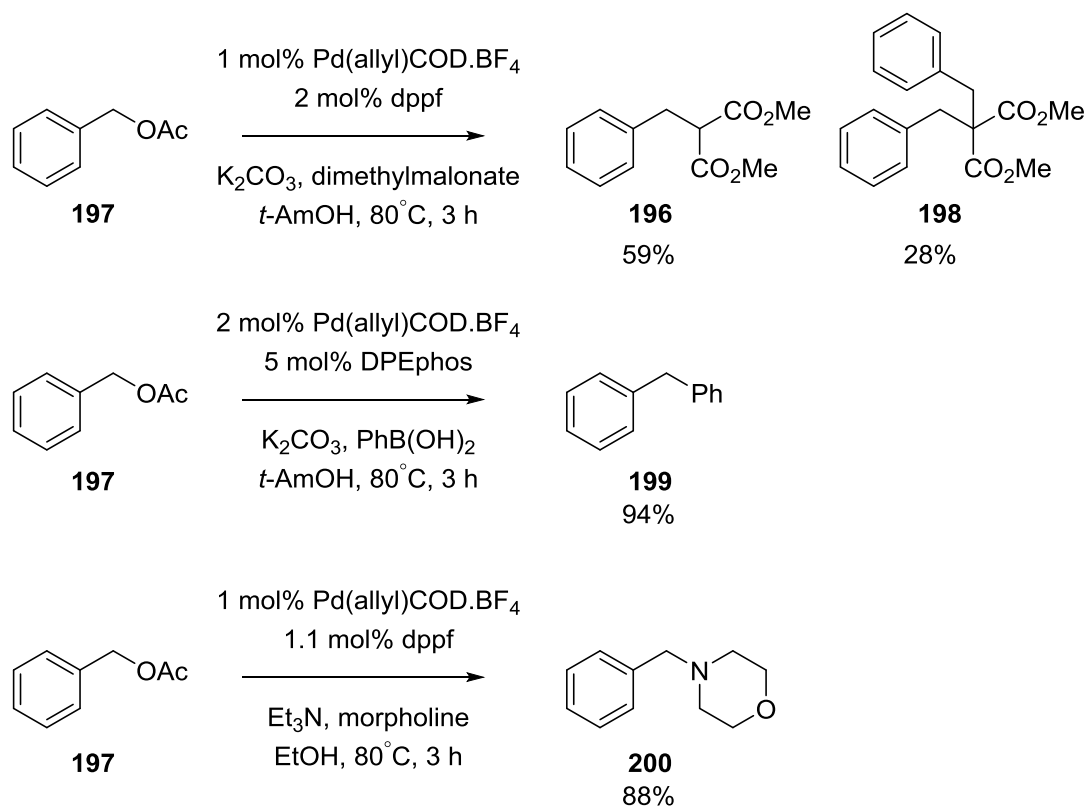
mediate the reaction between benzyl methyl carbonate **195** and a nucleophile generated *in situ* from dimethylmalonate and *bis*-trimethylsilyl acetamide (BSA) (Scheme 123).



Scheme 124: Catalytic Cycle: Stabilisation of Catalyst Resting State

The use of cationic Pd(II) precursor Pd(allyl)COD.BF₄ is superior both to Pd(dba)₂, a direct Pd(0) precursor, and (Pd(allyl)Cl)₂. This may be due to the presence of the labile 1,5-cyclooctadiene (COD) ligand which is readily substituted by a chelating ligand to give an active catalyst complex. There is also evidence that the use of COD in Tsuji-Trost benzylic chemistry serves to stabilise the resting state of the catalyst, preventing degradation (Scheme 124).¹⁵² The preference for bidentate ligands over monodentate was stronger for monocyclic systems than for polycyclic, with no observable product with triphenylphosphine as ligand. The yields provided by different ligands qualitatively suggest that the bite angle of the ligand is a key parameter, with ligands with smaller (dppe - 86°, 3% conv; dpppr - 91°, 16% conv; dppb - 95°, 39% conv) or larger bite angles (DPEphos - 102°, 74% conv; Xantphos - 112°, 71% conv) than dppf (99°, 99% conv) giving poorer conversions to product. It was found that for amination reactions of the same substrates studied, DPEphos was the optimal

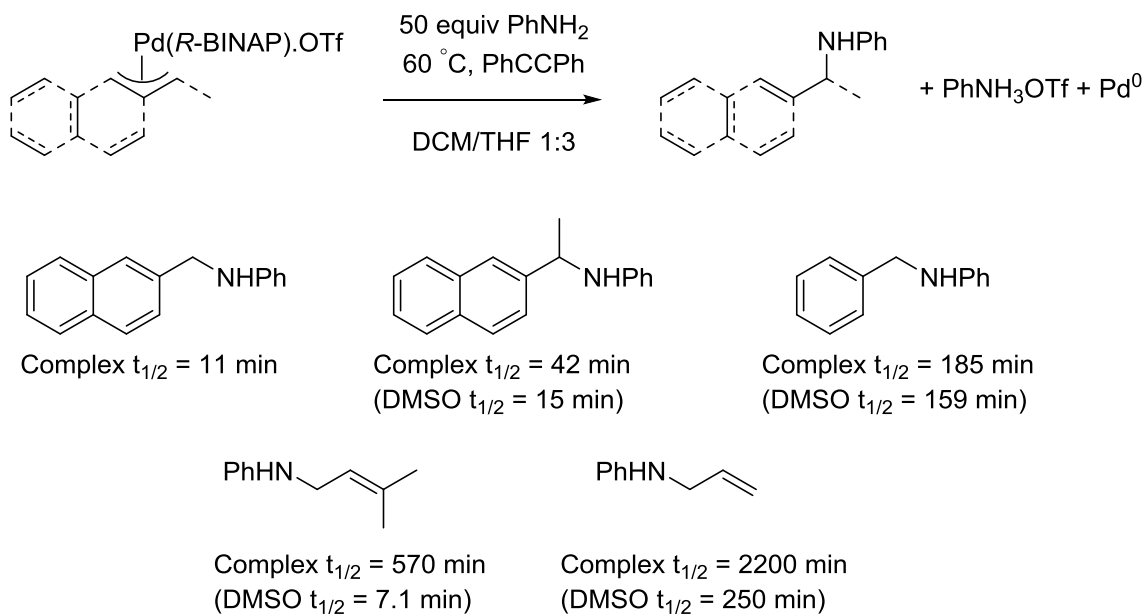
ligand, suggesting that the reactivities of the intermediate allyl complexes are very sensitive to the ligand employed.



Scheme 125: Use of Alcoholic Solvents to Activate Benzylic Acetates¹⁵³

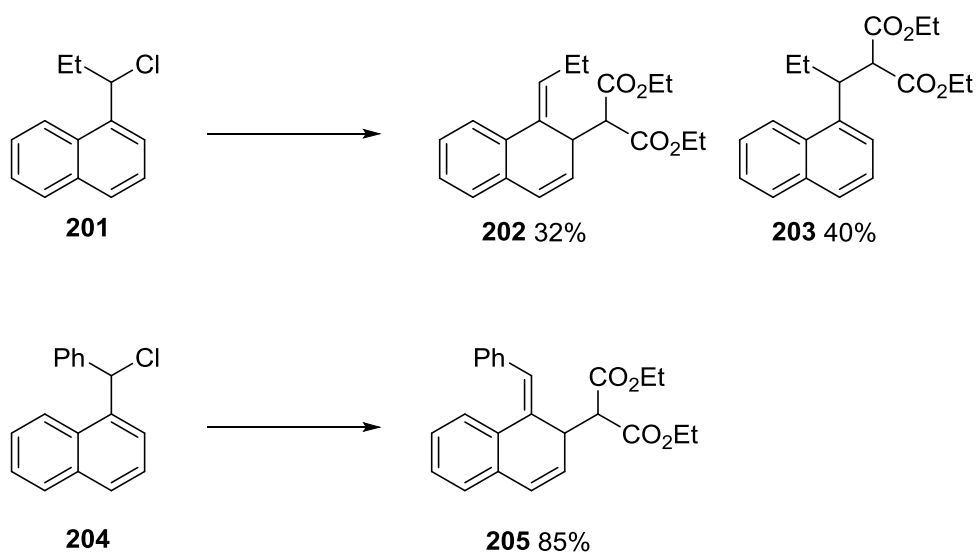
The further development of this methodology to enable substitution of monocyclic acetate substrates required the use of alcoholic solvents (Scheme 125).¹⁵³ Attempted reaction in polar aprotic solvents gave only poor conversions, the use of *tert*-amyl alcohol (*t*-AmOH) proved critical for reactivity. The use of ethanol led only to solvolysis of the acetate group, this side reaction was also problematic in *t*-AmOH with K₃PO₄ or Cs₂CO₃. Cross coupling of the same precursor proceeded under the same conditions with a slightly higher catalyst loading and an alternate ligand.¹⁵⁴ Amination was found to proceed most effectively in EtOH with the use of Et₃N as an additive to suppress solvolysis of the starting material.

3.2.3 Relative Reactivity of Pd-Benzyl Complexes

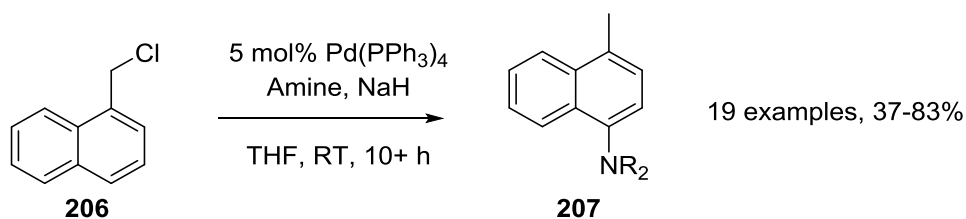
Scheme 126: Reaction of Pd π Complexes with Aniline¹⁵⁵

The putative intermediate complexes in benzylic alkylation have been shown to be significantly more reactive towards nucleophiles than the corresponding allylic intermediates based on a study of Pd(BINAP) π complexes.¹⁵⁵ Reaction of the isolated complexes with excess aniline (pseudo first order conditions) and determination of complex half life by ¹H NMR led to a ranking of the reactivity of various electrophiles. Bicyclic substrates were shown to be more reactive than monocyclic systems, with unhindered primary electrophiles more reactive than secondary (Scheme 126). In DMSO the reactivity of these complexes towards aniline was significantly increased relative to in DCM/THF, and the relative reactivities differed significantly, with larger enhancements in reactivity for allyl systems. These results imply that reactivity problems for benzylic substitution by nucleophilic attack are likely to be caused by the difficulty of formation of a Pd-benzyl complex, as the putative intermediate complexes formed are highly reactive towards nucleophilic attack.

3.2.4 Regioselectivity

Scheme 127: Nucleophilic Dearomatisation of Benzylic Chlorides¹⁵⁶

The regioselectivity of attack on palladium benzyl complexes is generally straightforward, with direct replacement of a leaving group at a benzylic position with a nucleophile, as demonstrated in all the previous examples. It is however possible in some systems for attack to occur at ring positions, leading to the formation of a dearomatised compound as shown in Scheme 127.¹⁵⁶ Substrates which form more stable benzyl complexes due to stabilisation of the partial positive charge of the allyl system show some reactivity towards nucleophiles at ring positions. Alkyl substituted 1-naphthalene substrate **201** reacts to give both dearomatisation (**202**) and benzylation (**203**) products, whilst the more stabilised phenyl substituted substrate **204** gives a good yield of the dearomatisation product **205** as the single reported product. Regioselectivity is strongly dependent on steric effects; substrates with some hindrance to attack at ring positions may provide mixtures of both products, whilst reaction with bulky nucleophiles can direct attack to the *para* position of the naphthalene ring.

Scheme 128: Non-Benzylic Amination of Benzyl Chlorides^{156, 157}

The regioselectivity of the reaction is not necessarily substrate dependent – by the use of the appropriate conditions and catalyst it is possible to change the site of nucleophile attack. There is no mechanistic rationale for why this should be the case, but the use of a $\text{Pd}(\text{PPh}_3)_4$ under highly basic conditions leads to direct attack of morpholine and other amines on the *para* position of the chloromethylnaphthalene substrate **206** (Scheme 128).^{157, 158} The conditions used are sufficiently basic for the amines used to exist as anions, so the anionic nature of the nucleophiles may be partially responsible for this change in regioselectivity.



Scheme 129: S_{N}' Intramolecular Aromatic Substitution of Benzylic Carbonates

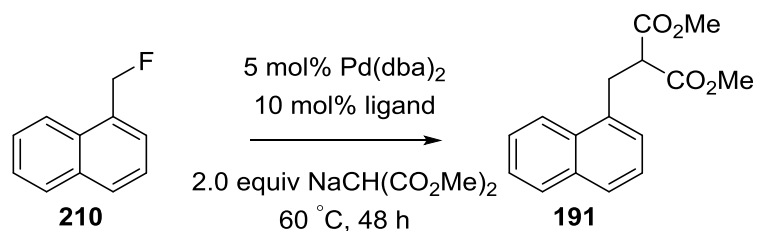
An alternate approach which can lead to attack at a ring position rather than the benzylic position is reaction of a substrate bearing a *meta* substituted internal nucleophile with an appropriate tether.¹⁵⁹ The system **208** was designed such that formation of the initial π complex would lead to internal attack, presumably at the *ortho* position due to the assumed structure of the π allyl complex, rearomatisation would then lead to the formation of a fused ring system. In actuality the products observed in all cases were those of cyclisation at the *para* position **209** (Scheme 129), suggesting that the palladium complex is able to move relatively freely around the ring by isomerisation, as with the naphthyl substrates previously mentioned. By choosing the correct ligand and reaction conditions the cyclisation can proceed in excellent yields, outcompeting the oligomerisation of the starting material by attack at the benzylic position. The pendant nucleophile can be modified with different electron withdrawing groups to give products of reaction with ketoesters and cyanoesters.

3.3 Results and Discussion

3.3.1 Reaction Development: Naphthalene Substrates

Reaction development and optimisation were performed jointly with Patrick Holden.

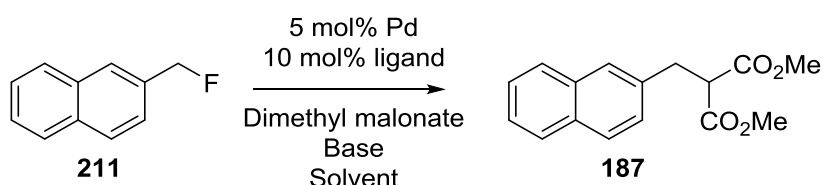
Benzylic Tsuji Trost reactions require more forcing conditions than the original allyl systems due to the loss of aromaticity on forming an η^3 intermediate, thus substrates for benzylic Tsuji-Trost chemistry which lose less stabilisation on ionisation are significantly more reactive. Due to the difficulty of substitution of monocyclic aromatic substrates we sought to first develop a C-F cleavage of a more active system. The energy penalty due to resonance stabilisation lost on formation of the intermediate complex is significantly lower for fused aromatic rings due to the maintenance of aromaticity in the neighbouring rings. We thus started our investigations on the defluorination of 1- and 2-fluoromethyl naphthalene with carbon nucleophiles.



Entry	Solvent	Ligand	Conversion
1	THF	dppe	95
2	DMF	dppe	95
3	DMSO	dppe	26
4	THF	DPEphos	81
5	THF	PPh ₃	0

Table 20: Substitution of 1-Fluoromethylnaphthalene

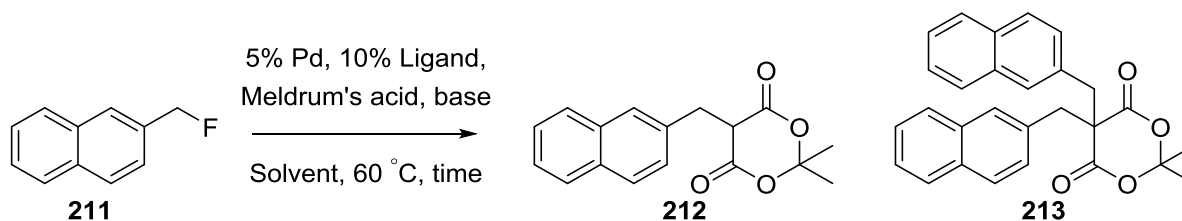
Use of the sodium salt of dimethylmalonate, the most common nucleophile encountered in Tsuji-Trost chemistry gave full conversion to the malonate product for the 1-fluoromethyl substrate **210** using a Pd/dppe catalyst in THF or DMF (Table 20).



Entry	Base	Solvent, Temp	Metal Precursor	Ligand	Conversion ^a
1	NaH	THF, 60 °C	Pd(dba) ₂	dppe	38
2	NaH	DMF, 60 °C	Pd(dba) ₂	dppe	0
3	K ₂ CO ₃	THF, 60 °C	Pd(allyl)COD.BF ₄	DPEphos	0
4	K ₂ CO ₃	DMF, 60 °C	Pd(allyl)COD.BF ₄	DPEphos	0
5	K ₂ CO ₃	DMSO, 60 °C	Pd(allyl)COD.BF ₄	DPEphos	0
6	NaH	THF, 50 °C	Ni(dpppr)Cl ₂	-	0
7	NaH	THF, 50 °C	Ni(dppe)Cl ₂	-	0
8	NaH	THF, 50 °C	(Ir(COD)Cl) ₂	(PhO) ₃ P	0
9	NaH	THF, 50 °C	Pt(PPh ₃) ₄	-	0

Table 21: Substitution of 2-Fluoromethylnaphthalene a) Conversion determined by comparison of ¹H NMR integrals of benzylic position

2-Fluoromethylnaphthalene **211** was less reactive under these conditions, with reactivity only observed in THF with the same catalyst system (Table 21). For this substrate the use of alternate metal catalysts based on platinum, nickel or iridium gave no reactivity. Due to the difficulty of optimisation of this system a more reactive nucleophilic component was investigated to enable further investigation of the effects of different variables on the defluorination reaction.



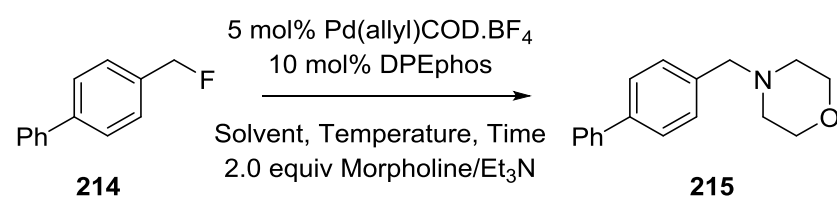
Entry	Pd Source	Ligand	Solvent	Base	Time	Monoalkylated conversion	Dialkylated conversion
1	Pd(dba) ₂	dppe	DMF	Et ₃ N	48	1	1
2	Pd(dba) ₂	dppe	DMSO	Et ₃ N	48	-	-
3	Pd(allyl)COD.BF ₄	dppe	DMSO	Et ₃ N	48	4	89
4	Pd(allyl)COD.BF ₄	DPEphos	DMSO	Et ₃ N	24	65 (65)	20
5	Pd(allyl)COD.BF ₄	DPEphos	DMF	Et ₃ N	24	30	28
6	Pd(allyl)COD.BF ₄	DPEphos	THF	Et ₃ N	24	2	3
7	Pd(allyl)COD.BF ₄	DPEphos	DMSO	NaH	8	-	>95 (81)
8	Pd(allyl)COD.BF ₄	DPEphos	EtOH	Et ₃ N	16	-	>95

Table 22: Substitution of 2-Fluoromethylnaphthalene by Meldrum's Acid

The use of Meldrum's acid (pK_a 5.0 vs 13 for dimethylmalonate) as a nucleophile provided further information for the optimisation of the substitution of 2-fluoromethylnaphthalene (Table 22). Pd(dba)₂

provided ineffective catalysts with dppe in DMF and DMSO. Pd(allyl)COD.BF₄ was a significantly more active catalyst precursor with the same ligand, giving 93% conversion to the products of *mono* and *bis* substitution **212** and **213** (Entry 3). DPEphos was also an effective ligand, and allowed reaction times to be reduced to 24 h. By variation of parameters the reaction could be biased towards either *mono* or *bis* substitution. The greater acidity of the nucleophilic carbon allowed for the use of Et₃N as the base, although inorganic bases were also effective.

3.3.2 Reaction Development: Monocyclic Substrates

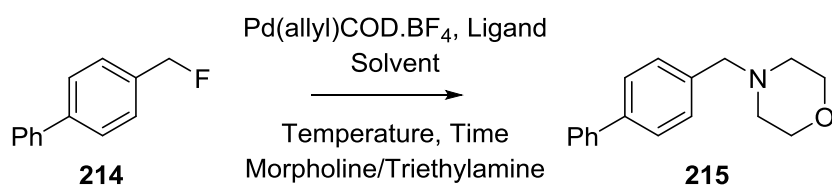


Entry	Solvent	Temperature	Time	Conversion
1	THF	70	24	0
2	DMSO	70	24	0
3	DMF	70	24	0
4	EtOH	70	24	>95 (79)
5	MeOH	70	24	89
6	<i>i</i> PrOH	70	24	31
7	<i>t</i> AmylOH	70	24	4
8	EtOH	70	2	43
9	EtOH ^a	75	1	0
10	EtOH ^b	75	1	0

Table 23: Monocyclic Reaction Development, Solvent Screen; a) reaction without Pd(allyl)COD.BF₄; b) reaction without Pd(allyl)COD.BF₄ or DPEphos

We sought to extend the initial results from bicyclic systems to enable substitution of monocyclic systems. The substitution of leaving groups in monocyclic systems requires more forcing conditions than those required for naphthyl substrates, so we anticipated that different conditions might be required. The optimisation of the reaction of monocyclic systems was performed for an amination reaction. On applying the optimised conditions for the naphthyl system (DMSO, DPEphos, 60 °C) no product formation was observed (Table 23, Entry 2), with the starting material **214** returned unchanged. This was also the case on increasing the temperature and increasing reaction time; this led only to some palladium black being formed due to catalyst degradation.

Based on the precedent for benzylic acetates discussed earlier, the use of alcoholic solvents was examined. Changing to a protic solvent was highly successful at promoting the C-F bond cleavage, presumably due to the high solvation enthalpy of fluoride ions and thus significant stabilisation of the transition state for C-F activation. Ethanol was the optimal protic solvent for the reaction (Table 23, Entry 4), but several other alcoholic solvents would allow some substitution, but with lower rates (*i*-PrOH, Entry 6) or obvious catalyst degradation (MeOH, Entry 5). All aprotic solvents tested gave poor reactivity. Since this work was undertaken it has been shown that amination can occur in uncatalysed conditions in water/ethanol mixtures¹⁶⁰ but in control reactions significantly slower reactivity was observed relative to the catalysed reaction (Entries 9 & 10).



Entry	Ligand	Solvent	Temperature	Time	Conversion
1	XantPhos	EtOH	70	1	0
2	XPhos	EtOH	70	2	3
3	<i>t</i> BuXPhos	EtOH	70	2	69
4	dppf	EtOH	75	4	71
5	SPhos	EtOH	70	4	17
6	dppe	EtOH	70	4	4
7	Ph ₃ P	EtOH	70	1	2
8	DPEphos	EtOH	75	1	>95
9	XPhos	EtOH	75	1	>95
10	<i>t</i> BuXPhos	EtOH	75	1	>95
11 ^a	<i>t</i> BuXPhos	EtOH	75	1	1
12 ^b	<i>t</i> BuXPhos	EtOH	75	1	11

Table 24: Reaction Development, Monocyclic Ligand Screen a) 0.5 mol% Pd loading b) Pd/L ratio 1:1

Optimisation of other parameters in the substitution was performed to broaden the range of conditions which could be employed for the reaction (Table 24). Temperature proved to be critical, with significantly faster rates at 75 °C than at 70 °C. The use of a Pd allyl precursor proved superior to either Pd(0) or Pd(II) salt sources, with Pd(allyl)COD.BF₄ being the preferred precursor due to its stability and activity. The bidentate ligands which were effective were in the middle of the bite angle range, with higher or lower bite angles being less successful, as observed in previous reports (*vide supra*). The square planar geometry of the allyl intermediate may be stabilised by chelating ligands

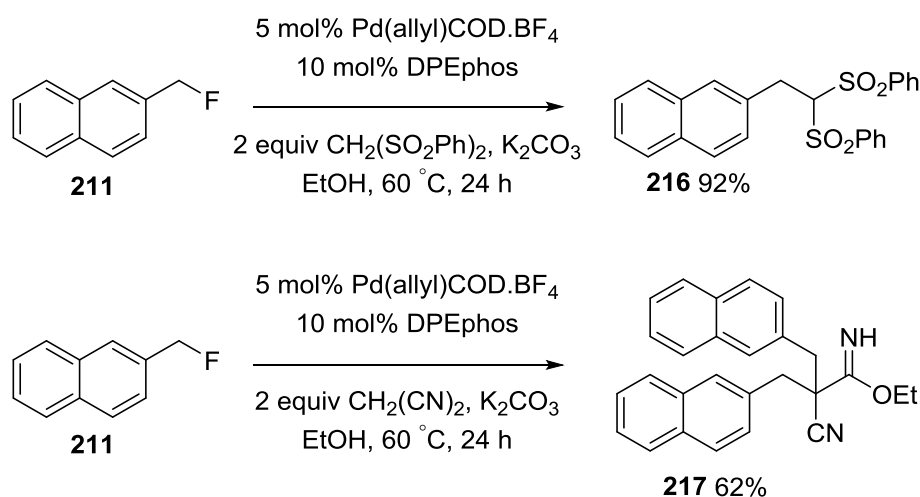
with a bite angle close to the preferred geometry. It was also found that a catalyst bearing XPhos or *t*Bu-XPhos as ligand was active for the transformation. The successful use of monodentate ligands in Pd catalysed benzylic substitution is unprecedented. The use of structurally related SPhos is known to generate coordinatively unsaturated Pd complexes due to the large steric demand at Pd and the existence of secondary interactions which stabilise such complexes.¹⁶¹ In this case it is not clear why XPhos gives reactivity similar to bidentate ligands.

The use of the conditions optimised for monocyclic systems on the original naphthalene substrates was highly successful, with reaction possible at much reduced temperatures and giving better conversions than in aprotic solvents (Table 25, Entry 2).

3.3.3 Reaction Scope

After validation of the C-F displacement with malonate and Meldrum's acid nucleophiles, the reaction scope of the procedure was investigated. The ability to displace a single C-F bond provides a novel route to functionalise molecules at a late stage in a synthesis, as a C-F group is inert towards many reaction conditions and purification manipulations.

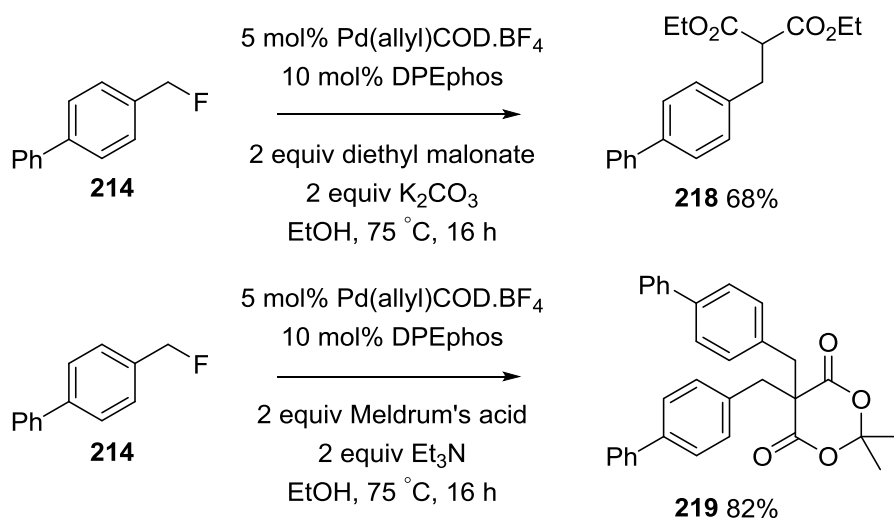
3.3.3.1 Carbon Nucleophiles



Scheme 130: Alternate Carbon Nucleophiles in Substitution of 2-Fluoromethylnaphthalene

Activated carbon nucleophiles other than malonates were similarly effective for the displacement of fluoride (Scheme 130). *Bis*-phenylsulfonyl methane provided a good yield of the monosubstituted

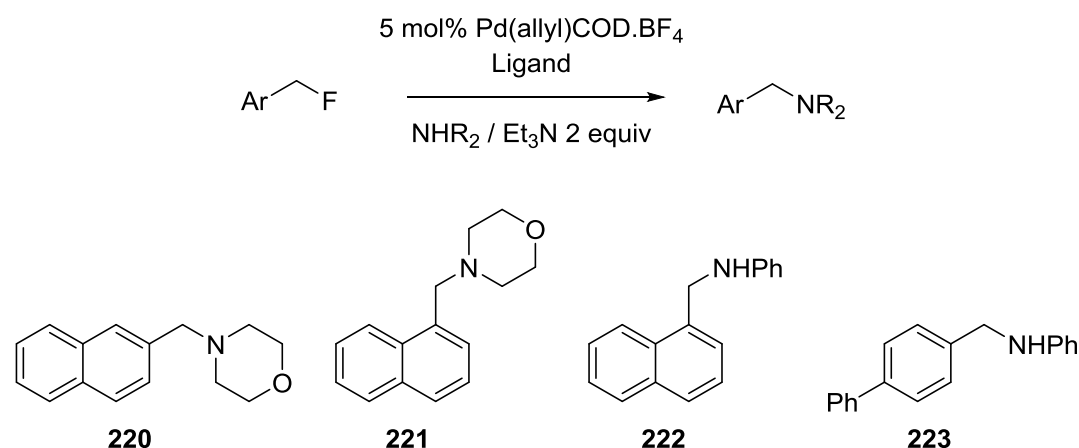
product **216** in the presence of K_2CO_3 in EtOH, but displayed no reactivity in DMSO (Scheme 130). Interestingly, reaction with malononitrile under the same conditions provided exclusively the ethanol adduct **217**. The reason that full solvolysis does not occur is unclear, and it is unknown whether attack by solvent occurs prior to nucleophilic attack. If the attack by ethanol occurs prior to attack of the allyl intermediate, then this may indicate preferential reactivity of this species over the unchanged malononitrile. The reaction of malononitrile with ethanol to form the mono adduct is known to be an efficient reaction under acidic conditions.¹⁶²



Scheme 131: Alkylation with 4-Fluoromethylbiphenyl

4-Fluoromethylbiphenyl reacted successfully with dimethylmalonate in ethanol with K_2CO_3 as base to give a good yield of **218**, or with Meldrum's acid in the presence of Et_3N to give the dialkylated product **219** (Scheme 131). With shorter reaction times (4 h) under the same conditions only 24% conversion to **219** was observed by 1H NMR, demonstrating the slower reactivity of the substrate/nucleophile system, as amination under similar conditions for this substrate was possible in one hour. For the malonate system this could be explained by the heterogeneous base limiting reactivity, but for the Meldrum's acid nucleophile the reaction mixture is homogenous thus the inherent reactivity of the catalytic intermediate towards the nucleophile must be relatively low.

3.3.3.2 Amination

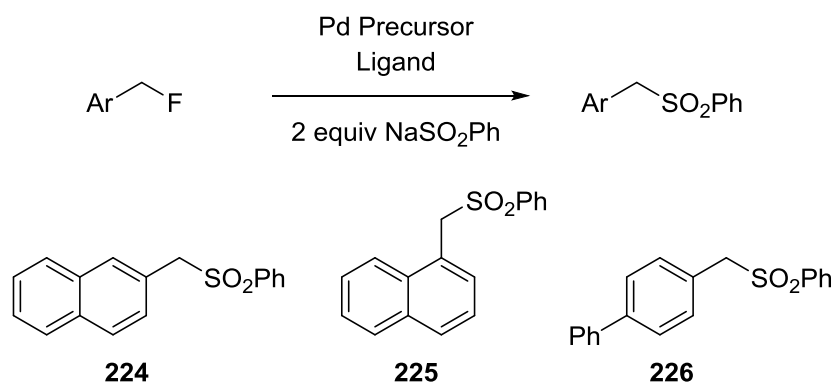


Entry	Substrate	Amine	Ligand	Solvent	Temperature	Time	Conversion (isolated yield)
1	2-Np	Morpholine	DPEphos	DMSO	60	24	> 95 (> 95)
2	2-Np	Morpholine	DPEphos	EtOH	RT	4	> 95 (70)
3	2-Np	Morpholine	Aq-Sphos	H ₂ O	70	4	56
4	1-Np	Morpholine	<i>t</i> BuXphos ^a	EtOH	75	1	> 95 (73)
5	1-Np	Morpholine	DPEphos ^b	DMSO	60	5	> 95
6	1-Np	Aniline	<i>t</i> BuXphos ^a	EtOH	75	4	> 95 (77)
7	4-Biphenyl	Aniline	DPEphos	EtOH	75	16	> 95 (87)

Table 25: Amination of Fluoromethylnaphthalenes a) 20 mol% ligand b) 10 mol% (Pd(allyl)Cl)₂ as Pd precursor

The optimisation of the monocyclic substrate defluorination demonstrated that the amination reaction could proceed smoothly on unactivated substrates. Amination of the 2-fluoromethylnaphthalene substrate could be performed with morpholine either at elevated temperatures in DMSO or at room temperature in EtOH to give good yields of amine **220**. It was also possible to perform the reaction in water with a catalyst based on a water soluble phosphine, giving a moderate conversion. 1-Fluoromethylnaphthalene was slightly less reactive towards morpholine, requiring a higher temperature in ethanol to reach full conversion to **221**. It was also possible to use aniline as a nucleophile but this was less reactive with either 1-fluoromethylnaphthalene or 4-fluoromethylbiphenyl (Table 25).

3.3.3.3 Sulfonylation

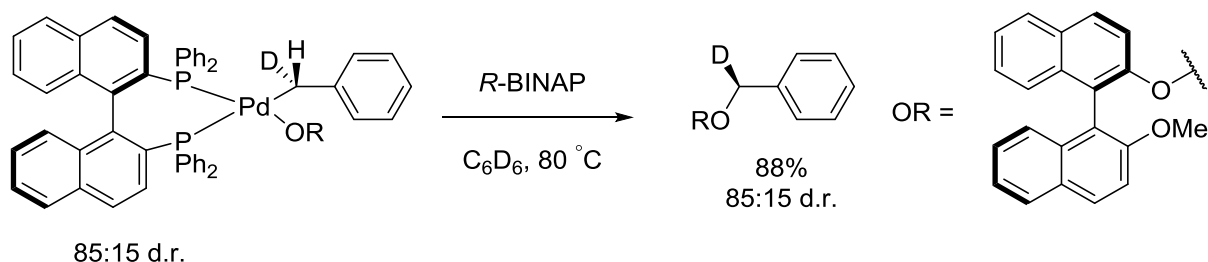


Entry	Substrate	Pd Source	Ligand	Solvent	Temperature	Time	Conversion (isolated yield)
1	1-Np	(Pd(allyl)Cl) ₂	DPEphos	EtOH	RT	20	> 95 (89)
2	1-Np	Pd(allyl)COD.BF ₄	DPEphos	EtOH	RT	24	84
3	1-Np	Pd(allyl)COD.BF ₄	DPEphos	DMSO	60	24	48
4	2-Np	(Pd(allyl)Cl) ₂	DPEphos	EtOH	RT	6	> 95 (82)
5	2-Np	Pd(allyl)COD.BF ₄	DPEphos	DMSO	60	24	> 95 (84)
6	4-Biphenyl	Pd(allyl)COD.BF ₄	<i>t</i> BuXphos	EtOH	75	4	15
7	4-Biphenyl	Pd(allyl)COD.BF ₄	<i>t</i> BuXphos	EtOH / H ₂ O 5:1	75	4	80 (66)

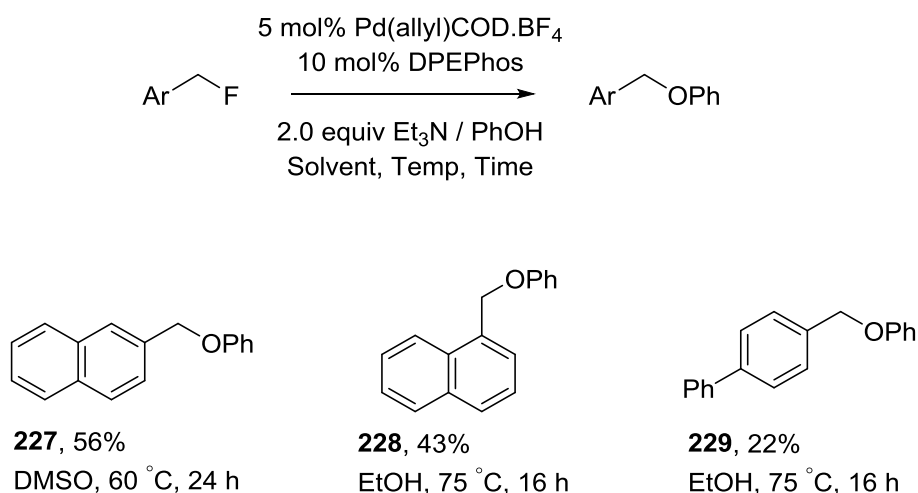
Table 26: Sulfonylation of Bicyclic and Monocyclic Substrates

Sulfonylation was similarly successful to amination, again using DMSO required the use of higher temperatures than ethanol and provided lower conversions (Table 26). An unexpected finding was that the use of (Pd(allyl)Cl)₂ was superior to Pd(allyl)COD.BF₄. This effect has not been observed for other nucleophiles tested. The sodium salt of the sulfonic acid is relatively insoluble in the reaction mixture so it is possible that anion exchange of Cl⁻ with PhSO₂⁻ may occur to form NaCl and a more soluble source of sulfinate anion may accelerate the reaction. Addition of water to the reaction mixture also improved reactivity, presumably by increasing the solubility of the nucleophile in the reaction mixture.

3.3.3.4 Oxygen nucleophiles

Scheme 132: Palladium Benzyl Alkoxide Complex Reactivity¹⁶³

Tusji Trost substitution with oxygen nucleophiles is challenging due to the hard nature of alkoxides. They are poorer nucleophiles in π -allyl chemistry than amines or stabilised carbon nucleophiles, but phenolic nucleophiles are competent in some cases.¹⁶⁴ It has been shown that from isolated Pd(benzyl)alkoxide complexes formation of C(sp³)-O bonds by reductive elimination from Pd(II) does not occur, rather dissociation of the alkoxide followed by the nucleophilic attack of the dissociated ligand occurs (demonstrated by inversion of stereochemistry at this centre, Scheme 132).¹⁶³

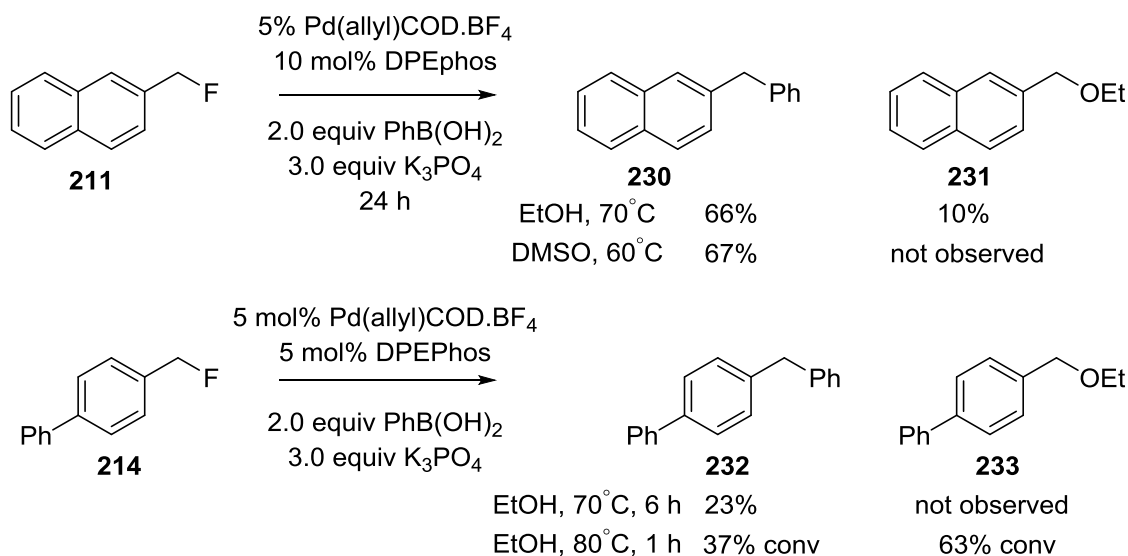


Scheme 133: Reaction of Fluoromethyl Electrophiles with Phenol

The absence of any products of reaction with alcohol solvents in previous reactions attests to the poor reactivity of alcohols towards Pd π -benzyl complexes. The use of phenol as a nucleophile was successful for both 1- and 2-fluoromethylnaphthalene substrates, giving high conversions to the products, though isolated yields were somewhat poor (Scheme 133). 4-Fluoromethylbiphenyl was much less reactive, giving only a small amount of product. The lower reactivity of both substrate and

nucleophile in this case represents the limit of this catalytic system to mediate the substitution of fluoride.

3.3.3.5 Cross coupling



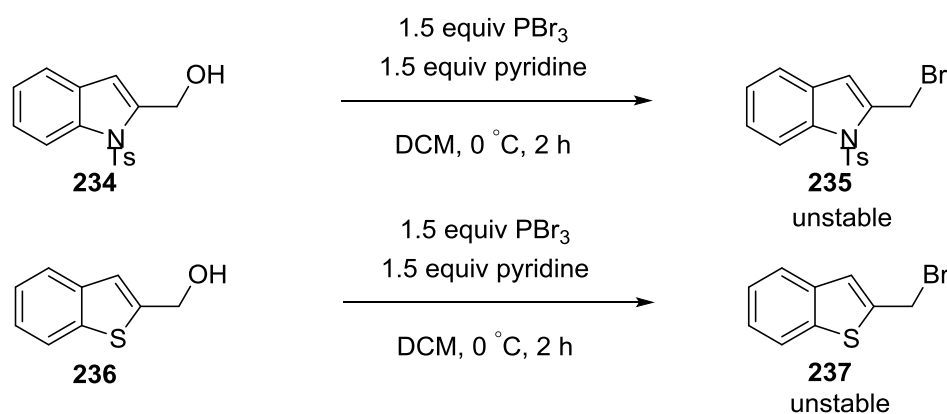
Scheme 134: Suzuki Coupling of Fluoromethyl Substrates

Diarylmethanes are ubiquitous motifs in medicinal chemistry, and due to the demand for efficient syntheses of this motif benzylic cross coupling has received much attention. Successful reactions have been achieved using a variety of different metals and cross coupling partners.^{154, 165} Many reactions use highly activated coupling partners such as Grignard reagents, and this gives the potential for side reactions to occur. The Suzuki-Miyaura reaction was selected for investigation as one of the most mild and general methods to synthesise this motif. The more activating conditions with ethanol as solvent were taken as the starting point for reaction development (Scheme 134). The use of 2.0 equivalents of PhB(OH)₂ and 3.0 equivalents of K₃PO₄ was moderately successful, providing the product **230** in 66% yield. It was also possible to isolate the ether product **231** in 10% yield, which was shown to form in an uncatalysed reaction in the presence of K₃PO₄ in ethanol. The use of DMSO alleviated this problem, giving clean conversion to the diarylmethane product, though the isolated yield was not improved. The biphenyl substrate was submitted to reaction in EtOH, giving only a 23% conversion at 70 °C. On increasing the temperature to 80 °C in a sealed tube the product **232** was observed as a minor component of the crude reaction mixture (37%) with the majority component

being the ethyl ether **233**. Reaction of this substrate in DMSO was not attempted due to the poor reactivity of the monocyclic system in the absence of protic solvents.

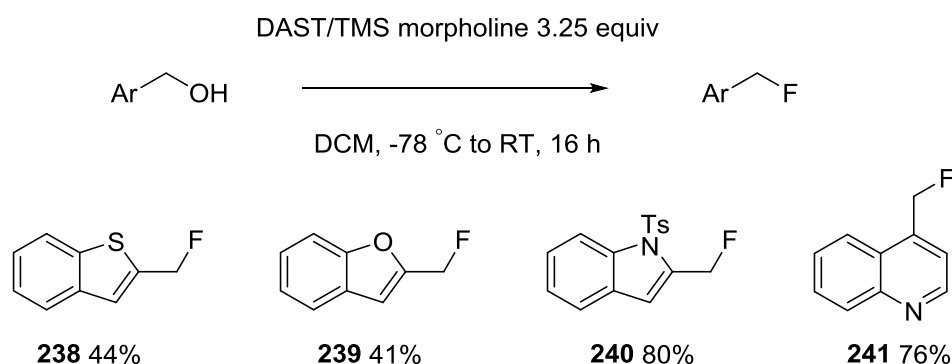
3.3.4 Substrate scope

3.3.4.1 Heteroaromatic Substrates



Scheme 135: Attempted Synthesis of Heteroaromatic Benzylic Fluorides

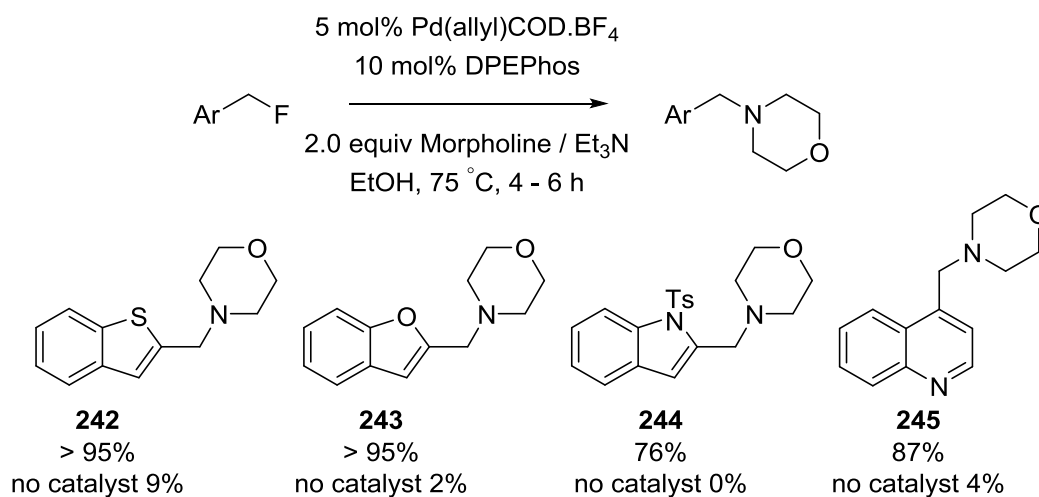
Heteroaromatic benzylic fluorides are of particular interest due to the abundance of heteroaromatic motifs in drug molecules. The preparation of several substrates was attempted by a nucleophilic fluorination route as for the fluoromethylnaphthalene substrates but it was found that indole and thiophene benzyl bromides **235** and **237** (shown in Scheme 135) were highly unstable to storage, making their use as precursors to the fluorides problematic.



Scheme 136: Synthesis of Heteroaromatic Benzylic Fluorides

Access to heteroaromatic benzylic fluorides was accomplished instead by deoxyfluorination. A small range of bicyclic heterocycle benzylic alcohols were synthesised by literature methods. The use of the

combination of TMS-morpholine and DAST or DAST alone was successful for the synthesis of the benzylic fluorides shown in Scheme 136 in moderate to excellent yields. The fluoride products were of moderate stability but could be stored in plastic containers in the freezer.

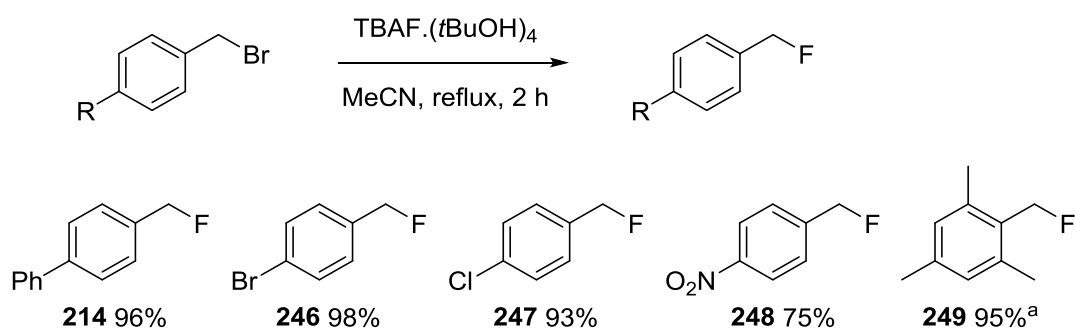


Scheme 137: Substitution of Fluoromethyl Heterocycles

Electron rich heterocyclic benzylic fluorides **238**, **239** and **240** all reacted readily with morpholine to give benzylamine products **242**, **243** and **244** (Scheme 137). The use of the optimised reaction conditions for monocyclic substrates was successful, with all reactions proceeding to full conversion within 6 h, and no attempt to optimise the conditions to allow lower temperatures was made. However it was noted that there was some background reactivity in the absence of palladium for these reactions, suggesting that these substrates are highly reactive electrophiles and thus that catalysis might operate at lower temperatures.

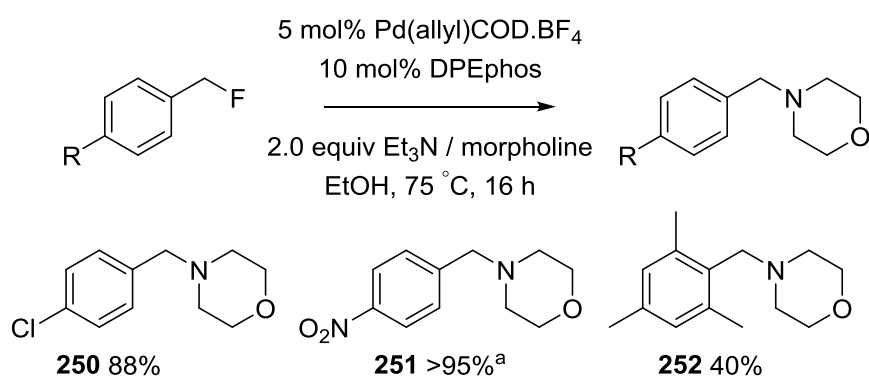
Quinoline substrates have been shown to be active under Pd(II)/Pd(IV) catalysis for fluorination, despite the potential for the nitrogen atom to coordinate to the Pd centre and sequester it as a non catalytic complex.¹⁶⁶ The amination of this electron poor heterocycle **241** proceeded as smoothly as the electron rich heterocycles to give an excellent yield of the amine product **245**.

3.3.4.2 Monocyclic Substrates



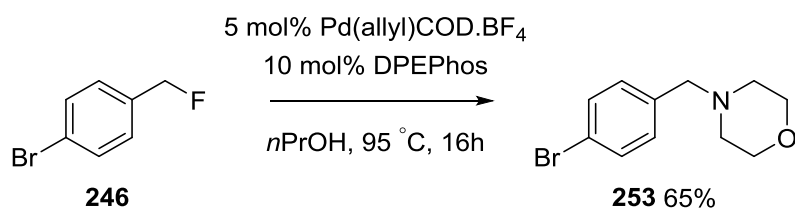
Scheme 138: Synthesis of Monocyclic Benzylic Fluorides a) From the Benzyl Chloride

The synthesis of a number of monocyclic benzylic fluorides was accomplished by reaction of TBAF.(*t*BuOH)₄ with the corresponding halides as shown in Scheme 138. We were also able to synthesise 4-methoxybenzyl fluoride and characterise it by ¹H NMR, but it was unstable to storage in plastic at room temperature so it was not possible to determine the yield or examine its Pd catalysed reactivity.

Scheme 139: Amination of 4-Chloro, 4-Nitro and Mesityl Benzyl Fluorides a) 4 h, 20 mol% *t*BuXphos

The reaction of 4-chloro and 4-nitrobenzyl fluorides with morpholine proceeded to give full conversions to the tertiary amine products in 16 h (Scheme 139). The use of *t*BuXphos gave better reactivity for the 4-nitro substrate **248**, but for all other substrates DPEphos was an effective ligand. It is also worthy of note that in the amination of the 4-chloro substrate **247** there is no observable reaction at the 4-position under these conditions. Reaction with the electron rich but hindered mesityl benzyl fluoride **249** did not proceed to full conversion (89%) and the isolated yield was low. As reviewed at the start of this chapter, Pd benzyl chemistry often displays significant reactivity variation

due to steric influences, with secondary positions reacting slower than primary, and ring substitution influencing the site of attack in the nucleophilic ring substitution cases in Section 3.2.4.

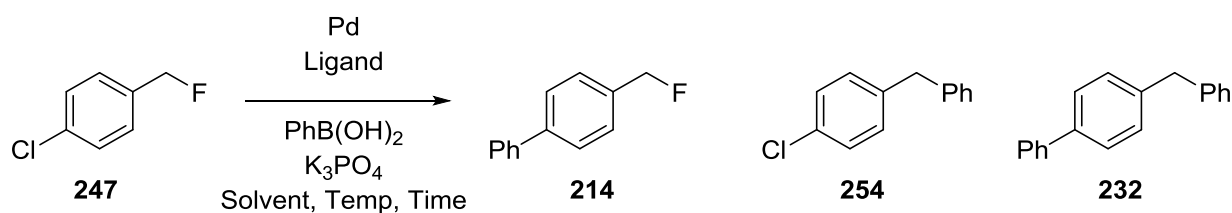


Scheme 140: Amination of 4-Bromobenzyl Fluoride

The 4-bromo substrate **246** is challenging due to the presence of the labile C-Br bond which can undergo oxidative addition with Pd(0). Amination of the less reactive chloro substrate was uncomplicated but on attempted amination of the 4-Br substrate the initial conversion to amine **253** as judged by ¹H NMR of the crude reaction mixture was low (13% in 4h at 75°C), with several unidentified byproducts present in the crude reaction mixture. Increasing the reaction time led to a complicated mixture of products. It was clear that the benzylic amination was the dominant reaction, so conditions were adapted in an attempt to increase the rate of this reaction in the hope of outcompeting the side reactions. The solvent was changed to *n*-PrOH in order to enable reaction at a higher temperature. This modification was successful and despite the presence of several byproducts it was possible to isolate the product in good yield (Scheme 140).

3.3.5 Chemoselectivity

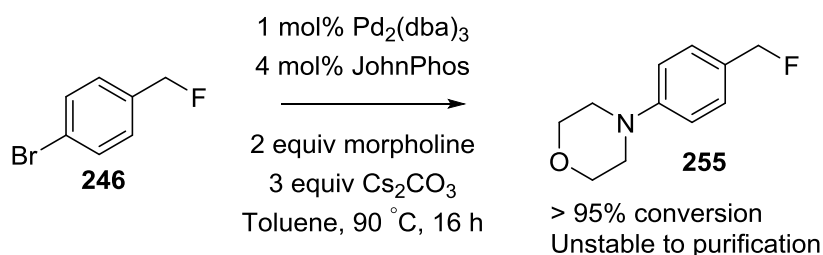
Due to the utility of cross coupling in synthesis, and the ability to discriminate between Pd labile functional groups C-Br and C-Cl and the benzylic C-F bond for the amination of 4-Br and 4-Cl benzyl fluorides, we sought to investigate whether we could develop conditions for the selective reaction of either functionality.



Entry	Ligand	Solvent	Temperature	214	254	232
1	Xphos	THF	60°C, 48h	78%	-	-
2	DPEphos	EtOH	75°C, 16h	-	32%	-
3	DPEphos	<i>n</i> PrOH	95°C, 16h	-	64%	-
4	Xphos	EtOH	75°C, 16h	-	-	>95%

Table 27: Modification of Chemoselectivity in Bifunctional Substrates

Suzuki-Miyaura cross coupling of the 4-Cl substrate **247** was readily accomplished in THF to leave the C-F bond intact (Table 27, Entry 1). The C-Cl bond is relatively unreactive, but the use of the hindered biaryl ligand Xphos enables efficient cross coupling of such substrates.¹⁶¹ Selective reaction at the C-F bond was achieved by reaction in EtOH using DPEphos, these conditions both have protic solvent activation of the C-F bond and the bidentate ligand which has been proposed to be crucial for benzylic substitution. Exhaustive substitution of both aryl and benzyl bonds was possible for both substrates by combination of the conditions for selective activation of either bond - a ligand able to activate relatively unreactive aryl-X bonds, and a protic solvent (Entry 4).



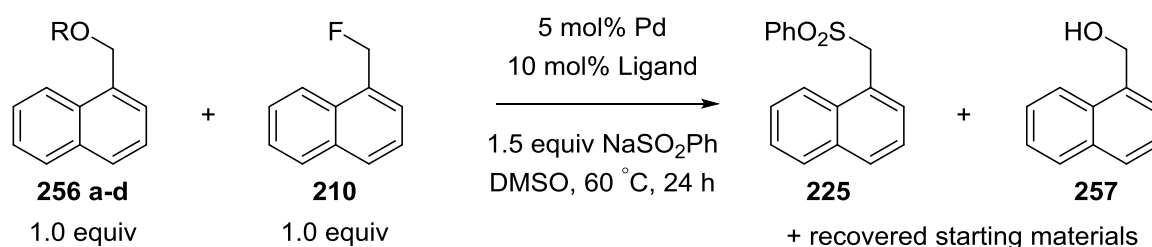
Scheme 141: Chemoselective Buchwald-Hartwig Amination

By attempting a Buchwald-Hartwig amination of the 4-Br substrate **246** using toluene as a non activating solvent we hypothesised that we should be able to selectively activate the C-Br bond without reaction at the C-F. As judged by the crude NMR of the reaction mixture, the reaction was successful and selective for the C-Br bond over the C-F, however it was not possible to isolate the products due to the instability of electron rich benzylic fluorides (*cf.* the 4-MeO substrate), exposure to silica led to rapid decomposition of the product (Scheme 141).

3.3.5 Fluorination of Benzylic Positions

3.3.5.1 Relative Reactivity of Benzylic Fluorides

A series of competition experiments were performed in order to produce a ranking of reactivity of various substrates under the reaction conditions employed. A 1:1 mixture of two substrates was added to a premixed solution of catalyst precursor and ligand, followed by the nucleophilic partner. The reaction was allowed to run for a period of time, then worked up and the ratio of the initial substrates to product determined by ^1H NMR integration of the signals corresponding to the benzylic positions.



Entry	R	Pd Source	OR ^a	F ^a	Product ^a	OH ^a
1	Ac	(Pd(allyl)Cl) ₂	32	3	63	2
2	<i>p</i> -NO ₂ Bz	(Pd(allyl)Cl) ₂	-	37	63	-
3	COCF ₃	(Pd(allyl)Cl) ₂	-	31	69	-
4	CO ₂ Me	(Pd(allyl)Cl) ₂	-	19	81	-
5	Ac	Pd(allyl)COD.BF ₄	29	-	71	-
6	<i>p</i> -NO ₂ Bz	Pd(allyl)COD.BF ₄	-	18	78	4
7	COCF ₃	Pd(allyl)COD.BF ₄	-	22	69	2
8	CO ₂ Me	Pd(allyl)COD.BF ₄	-	29	71	-

Table 28: Competition Reactions of 1-Naphthyl Benzylic Leaving Groups a) Normalised ratios determined by ^1H NMR

For substitution of substrates from the 1-naphthyl substrate series in DMSO the reactivity profile of fluoride relative to different leaving groups was the same as for the case of allylic fluorides (Table

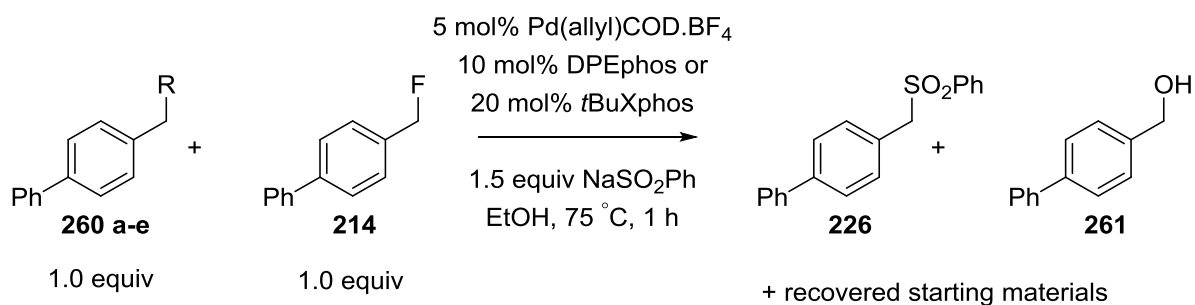
28). Acetate was less reactive than fluoride, and *para*-nitrobenzoate, trifluoroacetate and methyl carbonate were all more reactive. The choice of Pd precursor had no effect on the reactivity profile. Anhydrous conditions were essential to prevent hydrolysis of the most activated esters, when undried DMSO was used there was significant hydrolysis with the methyl carbonate substrate, giving approximately 30% conversion to the alcohol. These results are comparable to the reactivity order of allylic substrates: $\text{OCO}_2\text{Me} > \text{F} \sim \text{OBz} > \text{OAc}$. In allylic systems a *para*-nitrobenzoate leaving group is sufficiently reactive for fluorination reactions, despite similar reactivity between allylic fluorides and benzoates, so based on the reactivity ordering for benzylic systems any of the leaving groups examined here other than acetate would be potentially useful in fluorination reactions.



Entry	R	OR ^a	F ^a	Product ^a	OH ^a
1	<i>p</i> -NO ₂ Bz	10	8	82	trace
2	COCF ₃	-	18	82	trace
3	CO ₂ Me	-	21	79	trace

Table 29: Leaving Group Reactivity Comparison for 2-Naphthalene Substrates

In the 2-naphthyl substrate series under the same reaction conditions the trifluoroacetate and methyl carbonate leaving groups were clearly more reactive than the fluoride (Table 29), but the *para*-nitrobenzoate leaving group was of a comparable reactivity to fluoride. This result highlights that the optimum leaving group for a fluorination reaction of one substrate may not be optimum for another, potentially requiring the optimisation of leaving group for each individual substrate.

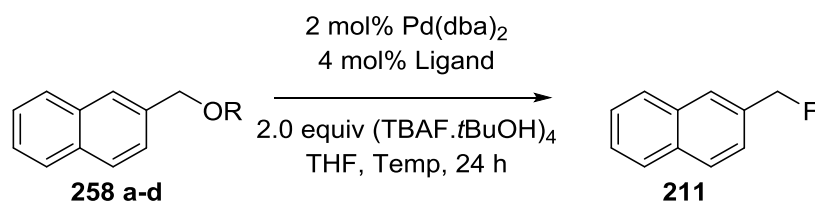


Entry	R	Ligand	R	F	Product	OH
1	OCOMe	<i>t</i> BuXphos	40	0	60	0
2	“	DPEphos	44	0	56	0
3	O-4-nitrobenzoate	<i>t</i> BuXphos	26	3	63	8
4	“	DPEphos	34	15	45	5
5 ^a	“	<i>t</i> BuXphos	23	35	39	3
6 ^a	“	DPEphos	38	44	13	4
7	OCOCF ₃	<i>t</i> BuXphos	0	0	51	49
8	“	DPEphos	0	0	52	48
9	OCO ₂ Me	<i>t</i> BuXphos	48	32	21	0
10	“	DPEphos	33	8	59	trace
11	Cl	<i>t</i> BuXphos	0	8	90	2
12	“	DPEphos	0	22	77	1

Table 30: Relative Reactivity of Biphenyl Benzylic Substrates a) Reaction in 1:1 THF / EtOH

The reactivity of the 4-biphenyl substrate series was examined under the optimised conditions for amination of the biphenyl substrate **214** (Table 30). A very different reactivity pattern was observed from the naphthalene substrates: OAc < OCO₂Me < *p*NO₂Bz < F < Cl. The relative reactivity of the trifluoroacetate substrate could not be determined due to rapid hydrolysis of the ester. The most likely explanation for the different reactivity order is the preferential activation of the fluoride over the oxygen leaving groups by the protic solvent. Interestingly, when the reaction of the partially insoluble *para*-nitrobenzoate substrate was attempted in a 1:1 mixture of THF and EtOH to increase the solubility of the substrate the relative reactivity of the two substrates was altered. The reaction slowed for both substrates, but the reactivity order swapped such that slightly more of the nitrobenzoate was consumed. This result underlines the sensitivity of the fluoride activation reaction to the exact solvent properties, though it is also possible that this reflects the hindering of a background reaction of morpholine with the fluoride in protic solvent. The use of a bidentate (DPEphos) or monodentate (*t*BuXphos) ligand gave only small differences in relative reactivity in this series of experiments, with no change in order of reactivity in any case.

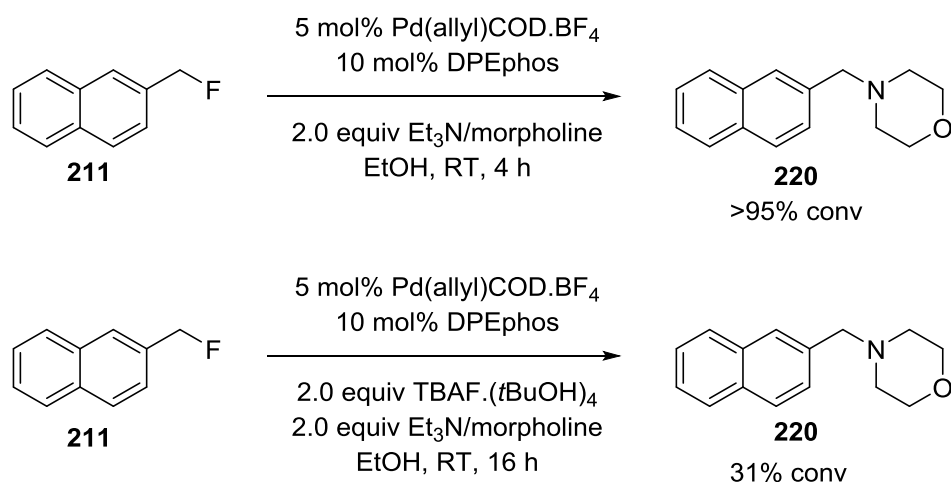
3.3.5.2 Attempted Fluorination Reactions



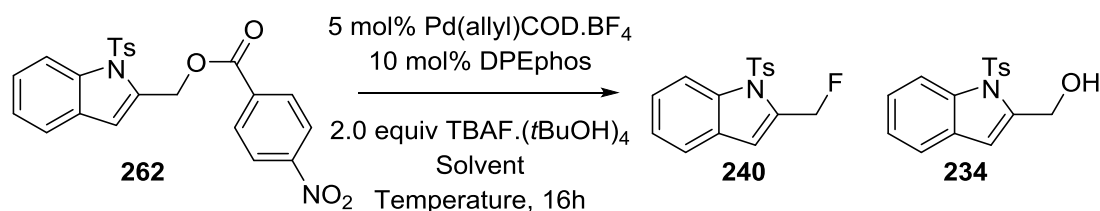
Entry	R	Ligand	Temp	Fluoride	OH	OR
1	CO ₂ Me	PPh ₃	20	0	0	100
2	4-nitrobenzoate	PPh ₃	20	0	43	57
3	COCF ₃	PPh ₃	20	0	99	1
4	CO ₂ Me	dppe	60	0	87	13
5	4-nitrobenzoate	dppe	60	0	100	0
6	COCF ₃	dppe	60	0	95	5
7	PO(OEt) ₂	dppe	60	10	5	85
8 ^a	PO(OEt) ₂	none	60	10	5	85

Table 31: Fluorination of 2-Naphthyl Esters a) reaction without Pd precursor

Initial experiments on the fluorination of benzylic ester substrates shown to be more reactive towards Pd (0) catalysed substitution than the respective fluorides gave no conversion of the starting material (Table 31, Entries 1-6). Hydrolysis was observed as a side reaction in all cases. A more activated diethyl phosphate leaving group gave some fluorinated product but a control reaction in the absence of a Pd catalyst gave the same level of fluorination. An analysis of the catalytic cycle suggests two points where the catalytic fluorination may fail. Oxidative addition, a known reaction, may be inhibited in the presence of fluoride, which is a reasonable proposition based on experiments that we later performed in an attempt to probe the mechanism (see Chapter 4). This is demonstrated by the pair of reactions in Scheme 142, where a reaction which reaches full conversion in 4 h in the absence of added fluoride only reaches 31% conversion in 16 h with added TBAF.tBuOH. Alternatively the palladium allyl formed as an intermediate is unreactive towards fluoride sources. In another project not reported here, test reactions using isolated Pd benzyl complexes showed no reactivity towards fluoride sources. Taken together these observations suggest that this reaction is not possible using current methodologies.

**Scheme 142: Effect of Added Fluoride on Turnover**

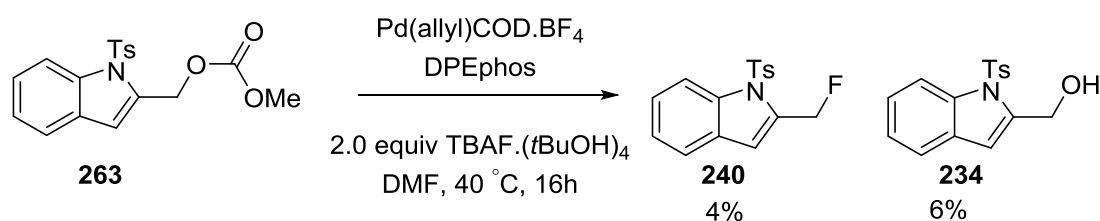
The naphthyl system examined shows good reactivity towards a range of nucleophiles with a variety of leaving groups but as it was not possible to observe any catalytic benzylic fluorination an alternate substrate was examined under fluorination conditions. In electron rich heteroaryl systems there is greater localisation of electron density, potentially giving different reactivity to the carbocyclic substrates examined previously. The *N*-tosyl indole substrate **262** was chosen for optimisation studies due to the stability of the benzyl fluoride product **240**.



Entry	Solvent	Temperature	OR	OH	Fluoride	Byproduct
1	THF	40	66	29	5	-
2	THF ^a	40	56	35	9	-
3	DMSO	40	65	4	15	16
4	DMF	40	55	4	27	14
5	DCM	RT	86	8	6	-
6	DMF	60	53	16	26	5
7	DMF ^a	60	50	2	7	41
8	DMF ^b	40	43	39	18	trace
9	DMF ^c	40	58	6	20	16
10	DMF	RT	71	2	18	9
11	DMF ^d	RT	73	5	22	-

Table 32: Fluorination of Indole Ester 262 a) Reaction without Pd or DPEphos b) ligand was dppf c) ligand was Xantphos d) 5x dilution relative to previous reactions

Initial reactions using THF as solvent showed low levels of fluorination both with and without catalyst, with significant hydrolysis in both cases (Table 32, Entries 1 and 2). A screen of different solvents was undertaken, with DMF proving optimal for fluorination. An unidentifiable byproduct was observed in both DMSO and DMF. On increasing the temperature to 60 °C in DMF the catalysed reaction gave very similar reactivity, but a control reaction showed increased levels of this byproduct (Entries 6 and 7). The use of different ligands gave small differences in product distribution but no enhancement of fluorination relative to DPEphos. Reaction at room temperature gave a very similar product distribution as at 40 °C, but using more dilute reaction conditions suppressed formation of the unknown byproduct.



Scheme 143: Fluorination of Indole Methyl Carbonate **263**

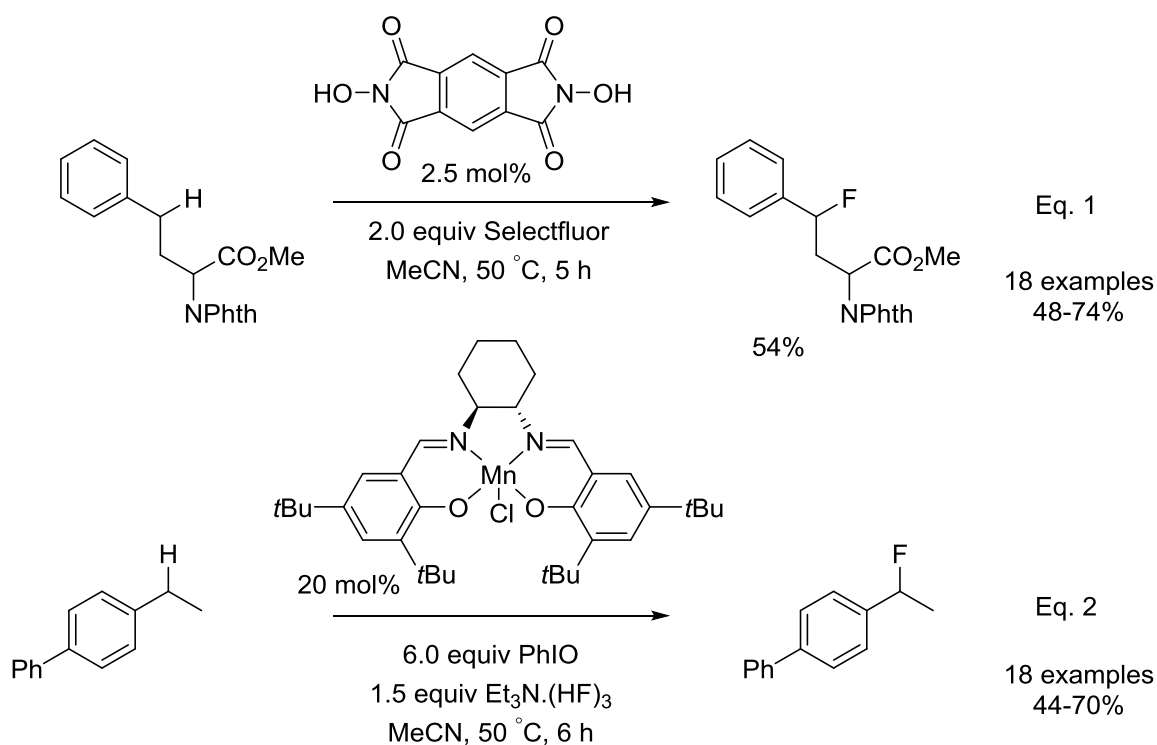
Attempts to increase the conversion to fluoride by using a more reactive leaving group were not successful. The methyl carbonate substrate **263** gave only low conversion to the fluoride and alcohol under the same conditions as the nitrobenzoate (Scheme 143). Substrates bearing trifluoroacetate and diphenylphosphate leaving groups were insufficiently stable to use as precursors, decomposing on purification.

3.4 Conclusions and Further Work

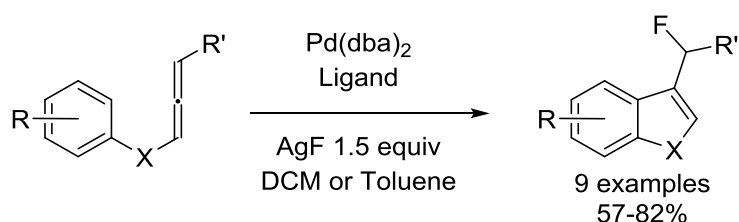
The reaction of benzylic fluorides with a variety of different nucleophiles was demonstrated, with fused aromatic and heterocyclic substrates giving good yields of products under mild conditions. For monocyclic substrates more forcing conditions were required, and a protic solvent was essential to promote reactivity. The reaction scope for benzylic fluorides was broad, with all nucleophiles tested showing reactivity towards the fluoride electrophiles. The least reactive nucleophiles required longer reaction times and higher temperatures and did not reach full conversion.

By modification of reaction conditions it was possible to extend the substrate scope of defluorination-amination to enable reaction on Pd-labile substrates as well as electron poor starting materials. Further development of these modified conditions allowed for the chemoselective cross coupling of 4-chlorobenzyl fluoride at either the C-Cl or C-F bond.

Investigation of the relative reactivity of benzylic fluorides under the two sets of conditions identified as suitable for the substitution of benzylic fluorides provided insights into the relative reactivity of benzylic fluorides compared to other benzylic electrophiles and how this is altered by the use of different ligands and solvents. These experiments led to the identification of several potential leaving groups for benzylic fluorination, namely *para*-nitrobenzoate and methyl carbonate. The attempted fluorination of substrates bearing these leaving groups was performed using conditions related to those for allylic fluorination, but it was not possible to observe any fluorination in carbocyclic systems. In an indole system there was some reactivity towards sources of fluoride, but it was not possible to optimise this reaction to make it significantly more effective than the background reaction. Taken with the difficulty of reaction of benzylic electrophiles with oxygen nucleophiles this suggests that catalytic nucleophilic fluorination may be a challenging reaction using current methodologies due to the hard nature of the nucleophile.

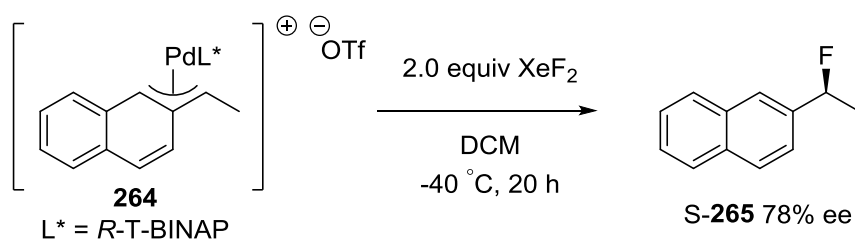
Scheme 144: Benzylic C-H Fluorination^{80, 167}

Based on this investigation, benzylic fluorination by Pd(0)-Pd(II) chemistry seems to be a challenging goal. C-H activation/fluorination has already been demonstrated using a Pd(II)-Pd(IV) system, and several benzylic C-H fluorinations have recently been described for systems without the use of directing groups (Scheme 144). Radical fluorinations¹⁶⁷ (eq. 1) and metal catalysed fluorinations⁸⁰ (eq. 2) both hold much promise for the future development of benzylic fluorination chemistry, but regioselectivity will always be a challenge for these systems, and the yields of such processes are currently quite low. The use of electron poor aromatic rings in such processes gives very poor yields.

Scheme 145: Pd(0) Catalysed Cyclisation-Fluorination¹⁶⁸

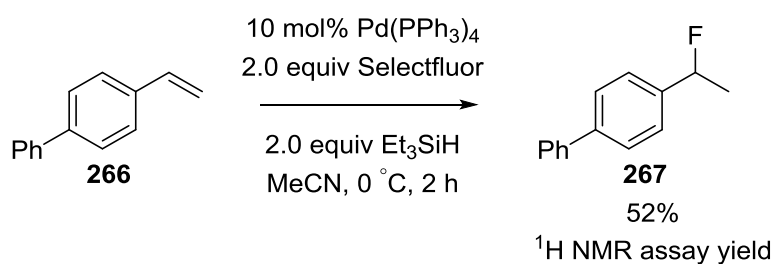
The development of a Pd(0)/Pd(II) catalytic system for cyclisation fluorination to yield benzylic fluorides has recently been accomplished by Doyle et al (Scheme 145).¹⁶⁸ Similarly to our

investigation of the reactivity of benzylic esters, those substrates which are successful are heterocyclic. C-I oxidative addition gives a Pd species which cyclises with an allene to give a benzylic Pd complex. Abstraction of I⁻ with AgF leads to fluorination. Electron poor ligands and aprotic solvents were optimal for reactivity - these conditions are significantly different to benzylic functionalisation reactions so the development of this methodology to enable Tsuji Trost benzylic fluorination may be a difficult goal.



Scheme 146: Stoichiometric Hydrofluorination

Preliminary experiments based on the work described in this thesis have shown that isolated Pd(II) benzyl complexes can react with electrophilic sources of fluorine (XeF₂, NFSI or Selectfluor) to generate benzylic fluorides (Scheme 146). For complexes bearing enantiopure ligands, the benzylic fluoride product was observed with up to 86% ee.



Scheme 147: Hydrofluorination of Styrene Precursors

The synthesis of the benzyl complexes used in the stoichiometric study was performed by exposing the styrene to a palladium precursor in the presence of a reducing agent. By changing the identity of reducing agent it proved possible to use a catalytic amount of palladium and generate the complex in the presence of a source of “F⁺”, closing the catalytic cycle and allowing for the catalytic synthesis of secondary benzylic fluorides from the alkene precursor (Scheme 147). Studies so far have shown good functional group tolerance and reactivity, but both the assay and isolated yields of benzylic

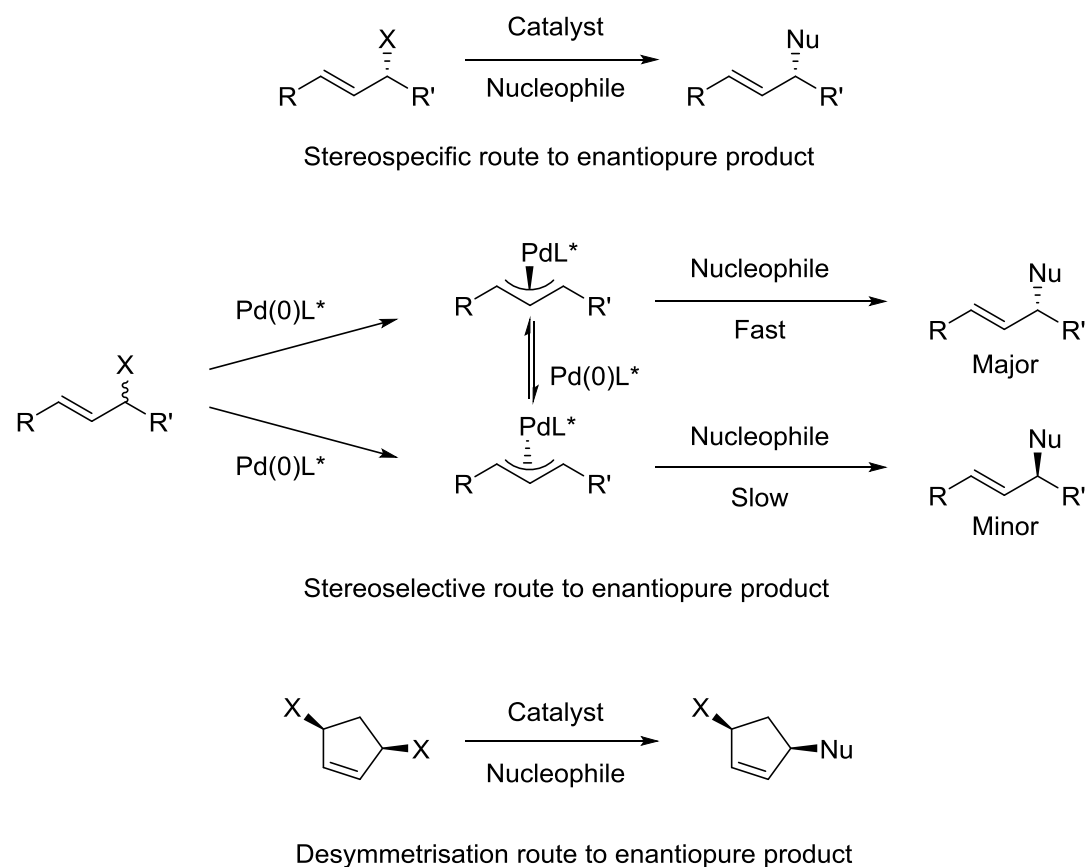
fluorides are low due to an unidentified side reaction. The use of enantiopure ligands does not give significant enantioinduction, in contrast to the stoichiometric study. Work is ongoing to improve the reaction conditions to give better isolated yields of products. This methodology circumvents the lack of reactivity of benzyl Pd complexes towards sources of fluoride, but does require the use of relatively expensive electrophilic fluorinating reagents. A further development of this methodology would be to use a source of nucleophilic fluoride in combination with an oxidising agent, as with the C-H fluorination of quinolines developed by Sanford *et al.*⁸⁶

Chapter 4: Kinetic Resolution of Benzylic Fluorides

As reviewed in Chapter 1, access to enantiopure benzylic fluorides is very challenging, and the available procedures suffer from poor substrate scope. We envisaged that the Pd catalysed C-F cleavage methodology described in the preceding chapter could be developed to effect a kinetic resolution of secondary benzylic fluorides by the action of a Pd catalyst system bearing enantiopure phosphine ligands. Investigations initially focussed on the reactivity of secondary benzylic fluorides under Pd catalysis, to understand the enantiospecificity of the reaction and possible mechanistic inferences that would inform the design of a kinetic resolution.

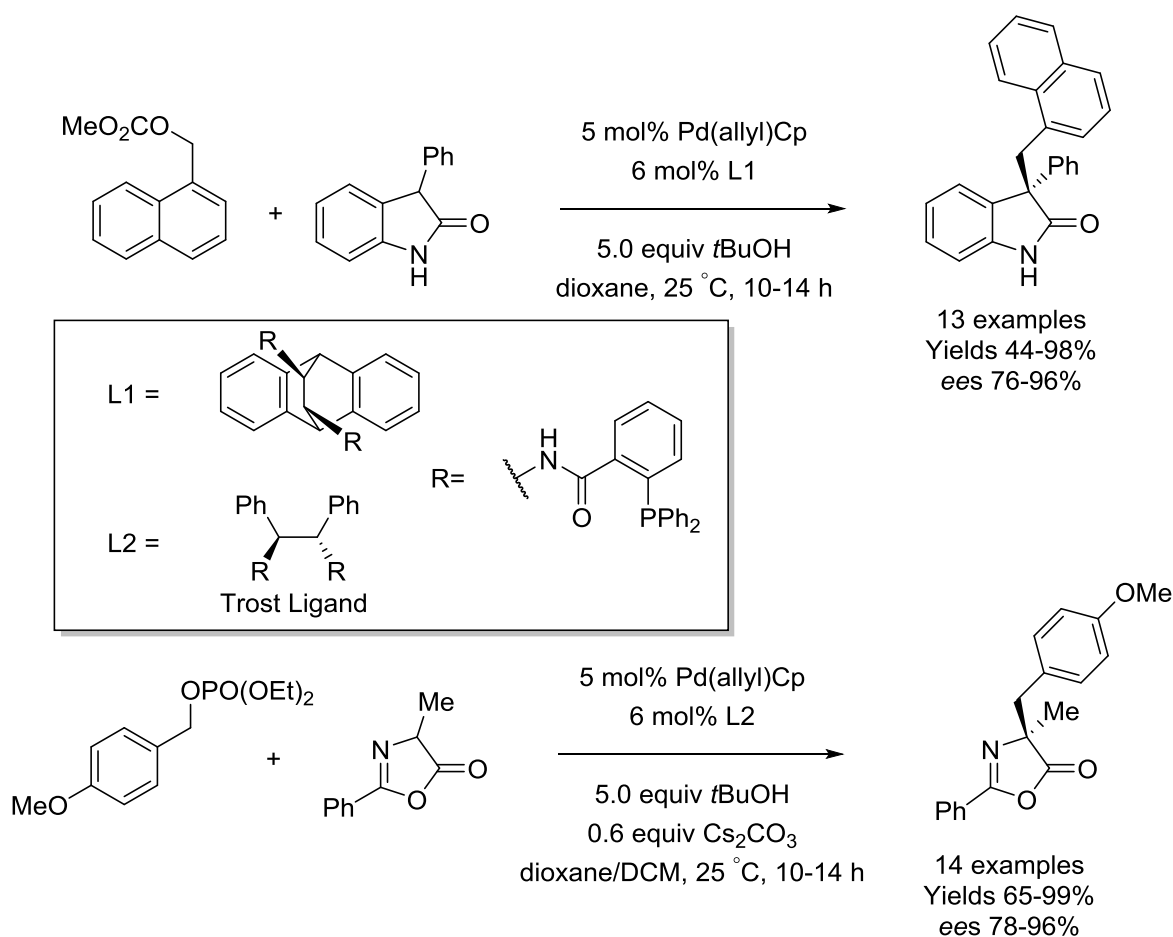
4.1 Palladium Mediated Enantioselective Chemistry

4.1.1 Enantioselective Alkylation



Scheme 148: Stereospecific vs. Stereoselective Tsuji-Trost Chemistry

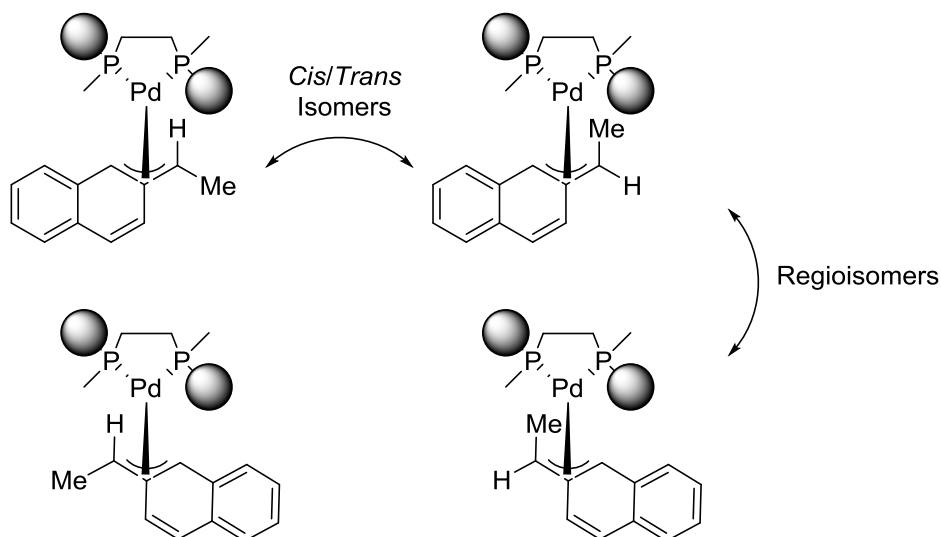
The Tsuji Trost reaction can be deployed to provide enantioenriched starting materials in multiple modes, either by the enantiospecific reaction of an enantiopure starting material, the enantioselective reaction of a racemic mixture, or the desymmetrisation of a *meso* compound (Scheme 148). The use of enantiospecific reactions is covered in the preceding chapter and does not require enantiopure catalyst complexes. Enantiospecific reactions require that interconversion of allyl intermediates does not occur under reaction conditions as this compromises stereochemical control of the reaction. For the development of enantioselective processes it is possible to garner information about the rate of interconversion from the enantiospecificity of substitution with achiral ligands. *Vide infra* for a discussion of the mechanism of interconversion.



Scheme 149: Benzylic Electrophiles with Prochiral Nucleophiles¹⁶⁹

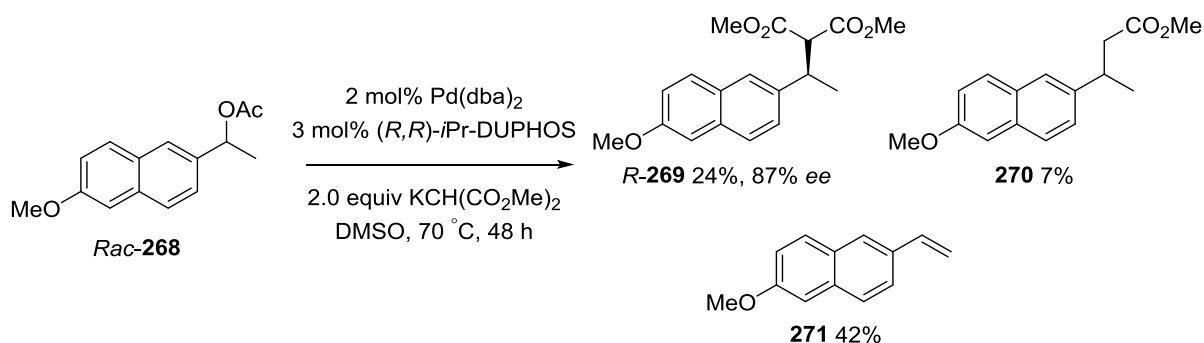
For the enantioselective Tsuji-Trost chemistry described the stereodefining step is the reaction of the nucleophile with the allyl complex. The stereocentre can be introduced either at a prochiral electrophile (as shown in Scheme 148) or a prochiral nucleophile. There are reports of examples of

both cases at benzylic centres. The reaction of highly activated benzylic electrophiles with either azlactones or oxindoles leads to enantioenriched protected amino acids or quarternary oxindoles (Scheme 149).¹⁶⁹ For both of these transformations the Pd / ligand combination is Pd(allyl)Cp with a C₂ symmetric bisphosphine.



Scheme 150: Isomerism in Enantioselective Alkylation Intermediates

The reaction of primary/achiral electrophiles with prochiral nucleophiles is mechanistically simple, it is only possible to form one enantiopure benzyl complex and this then reacts with the prochiral nucleophile on the face which has the lowest barrier for reaction. For enantioselective reactions where the chiral centre is on the electrophile the interactions are more complicated. The reaction of a racemic starting material with an enantiopure catalyst complex produces a mixture of complexes (Scheme 150). It is possible to form complexes with ligands in either *cis* or *trans* geometries, and the ligand may coordinate in multiple modes. For enantioselective synthesis, the reaction of one with the nucleophile must be favoured, but for full conversion of the racemic material it must be possible to interconvert between the diastereomers as shown in Scheme 148.

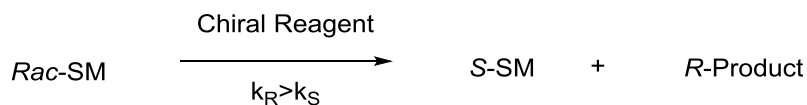


Scheme 151: Enantioselective Alkylation of Benzylic Electrophiles¹⁷⁰

For the reaction of benzylic systems, the only system reported to give good enantioselectivities gives poor yields of the product of substitution with large amounts of elimination byproducts (*vide infra* for a discussion of enantiodivergence in these systems) (Scheme 151).¹⁷⁰ The optimised conditions for the enantioselective alkylation of malonates used the C_2 symmetric ligand (*R,R*)-*iPr*-DUPHOS with Pd(dba)_2 in DMSO at 70°C, giving 24% of the intended product **269** in 87% *ee* (Scheme 151). There were two other products observed, the monoester **270** which presumably is produced by decarboxylation of the product under reaction conditions, and the alkene **271**. When the reaction was performed with a slow addition of nucleophile in an attempt to promote interconversion of the intermediate benzyl complexes and thus increase selectivity it was possible to increase the enantiomeric excess to 90%, but at the expense of the yield which fell precipitously to 11%, with 64% of the alkene byproduct.

The development of enantioselective benzylic chemistry is not as far advanced as for the allylic Tsuji Trost reaction but these precedents give some encouragement to the development of enantioselective chemistry for the preparation of benzylic fluorides.

4.1.2 Tsuji Trost Kinetic Resolutions



$$S = \frac{\ln((1 - \text{conversion})(1 - ee))}{\ln((1 - \text{conversion})(1 + ee))} = \frac{k_{Fast}}{k_{Slow}}$$

Scheme 152: Schematic Kinetic Resolution

Kinetic resolutions achieve the separation of enantiomers by differentials in reactivity. Reaction of an enantiomeric pair with a chiral non-racemic partner proceeds through diastereomeric transition states with different activation energies. The ratio of rates of reaction of the enantiomers, k_{fast}/k_{slow} is expressed as a value S ; the value of S is commonly used to predict the point at which to stop a kinetic resolution in order to maximise the yield and enantiomeric purity of the starting material and/or product, using the equation in Scheme 152.

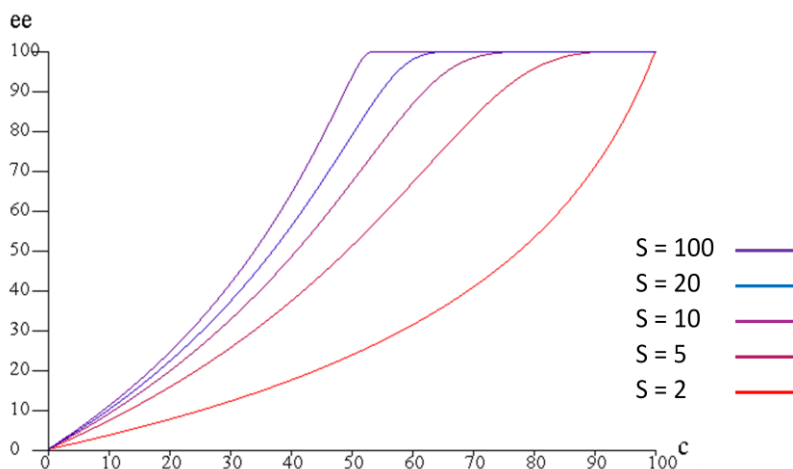
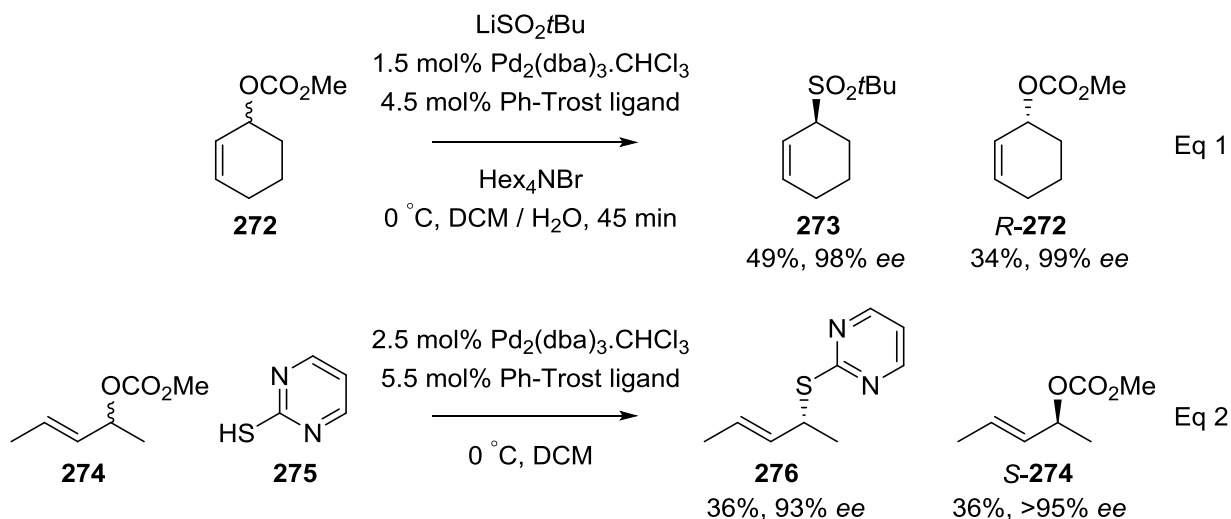


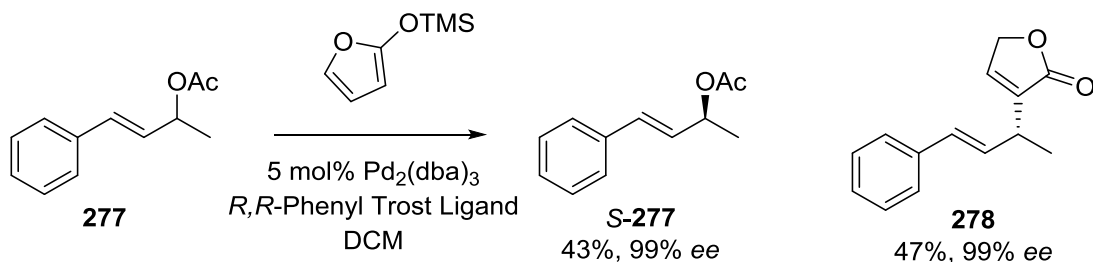
Figure 20: Kinetic Resolution ee vs. Conversion

Values of S in excess of 20 are considered viable for the preparation of enantiomerically pure material in reasonable yield; this equates, under standard conditions and assuming the pre-exponential factor in the Arrhenius equation to be equal for both enantiomers, to a difference in energy in the diastereomeric transition states of 9.9 kJmol^{-1} .

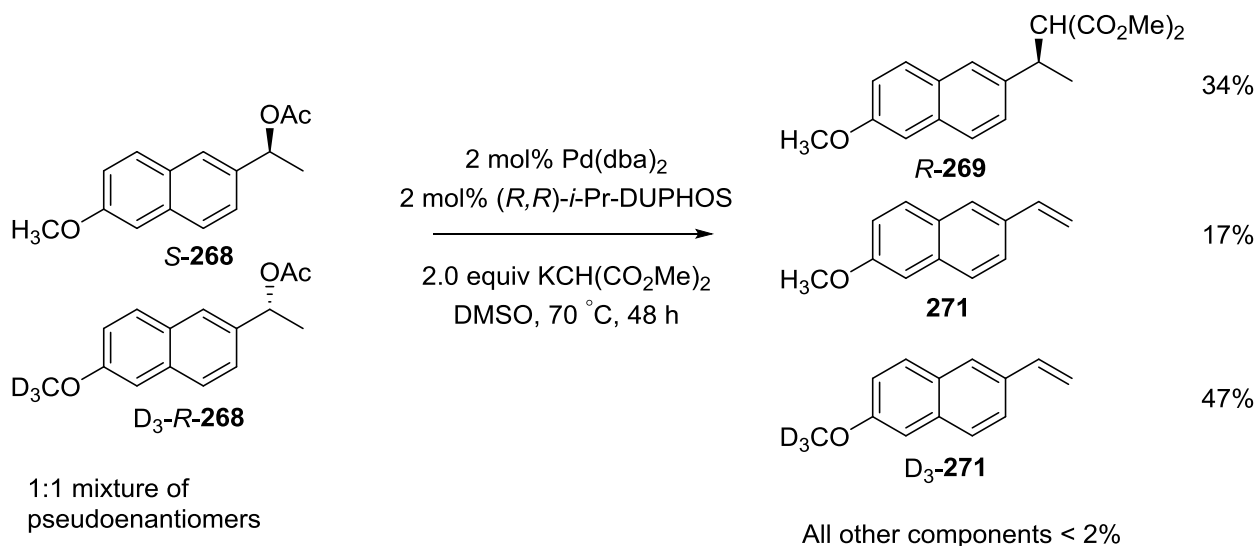


Scheme 153: Kinetic Resolution of Allylic Carbonates with Sulfur Nucleophiles¹⁷¹

The kinetic resolution of allylic carbonates¹⁷¹ can be achieved by palladium/Trost ligand catalysts with sulfur nucleophiles (Scheme 153). These reactions proceed at 0 °C in biphasic dichloromethane/water media and some examples give complete consumption of the fast reacting component in as little as 2h, with S values of 34 and above. Both the starting material **272** and the product **273** are provided with excellent enantioselectivities for the cyclic system in Eq. 1. If the reaction is run to full conversion the asymmetric synthesis of the sulfone can be accomplished readily; this observation suggests that the enantioselectivity of product formation is independent of the stereochemical preference for allyl ionisation, which is the critical step for kinetic resolution. The kinetic resolution of acyclic allyl systems is more challenging, but use of the same system on substrate **274** gave good selectivity. However, reactivity was very high leading to significant consumption of the enantioenriched starting material which limited the isolated yield. Notably the product of this reaction **276** was observed to have excellent enantiomeric purity at all conversions, demonstrating mechanistic divergence from classical kinetic resolutions due to asymmetric synthesis. In order to accomplish the kinetic resolution of acyclic systems, the transformation in Eq 2 was developed, using a pyrimidine thiol nucleophile **275**. The pyrimidine thiol is a potential ligand for Pd, requiring increased catalyst loadings for the optimised conditions, but this allowed the kinetic resolution of both cyclic and acyclic substrates with improved recovered yields.

Scheme 154: Kinetic Resolution of Allylic Acetates¹⁷²

The kinetic resolution of cinnamyl acetates¹⁷² uses the same catalyst with a silyl enol ether nucleophile (Scheme 154). For this system the attempted resolution of carbonates (either methyl or *tert*-butyl) gave full conversion to the product of alkylation in low enantioselectivity, hence the decision to use the less reactive acetate leaving group. With this less reactive leaving group it was necessary to reduce the temperature to 0 °C to improve the selectivity of kinetic resolution, as at room temperature the reaction proceeded to 80 % conversion. These reaction conditions are considerably milder than those required for the C-F activation of benzylic fluorides, as allylic substrates are much more reactive towards Pd(0) than benzylic substrates. The use of harsher conditions might be expected to reduce the enantioselectivity of the catalytic system.

Scheme 155: Enantiodivergence in Benzylic Alkylation¹⁷³

It has been demonstrated that in the presence of an enantiopure catalyst complex, the substitution of benzylic acetates exhibits enantiodivergence (Scheme 155).¹⁷³ The pseudoenantiomeric reactants *S*-

268 and *R*-D₃-**268** were reacted with KCH(CO₂Me)₂ in the presence of the catalyst system Pd(dba)₂/*i*Pr-DUPHOS and the products analysed by GC-MS, chiral stationary phase HPLC and ²H NMR to determine the relative product distributions of all deuterated and non deuterated products. The main products observed were those shown in Scheme 155, with > 95% of the *R*-D₃ substrate converted to the alkene D₃-**271**. For the *S* substrate, the product of retention of stereochemistry *R*-**269** was observed as the major product in a 2:1 ratio with the alkene **271**. This divergence in reactivity is due to a difference in reactivity for substitution and elimination between the two pseudodiastereomeric intermediate complexes. The authors however made no attempt to follow the course of the reaction kinetics so there is no data available on whether these diastereomeric complexes form at differential rates and thus whether at any point in the reaction duration there is a partial kinetic resolution of the substrate.

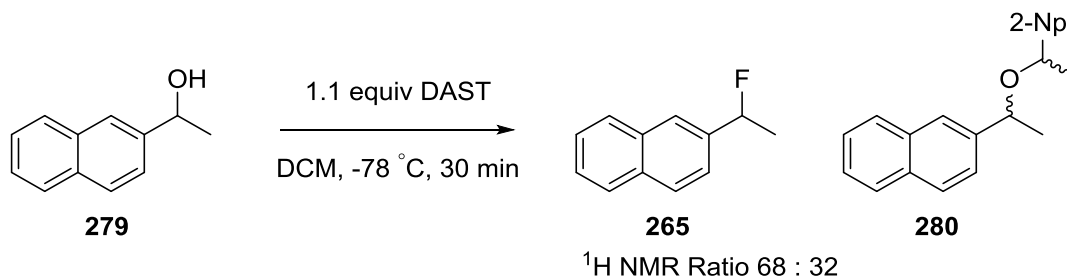
4.2 Palladium Catalysed Substitution of Secondary Benzylic Fluorides



Scheme 156: Kinetic Resolution of Benzylic Fluorides

The reactivity of secondary benzylic substrates under palladium catalysis is relatively well documented but there is no precedent for a preparative kinetic resolution. The initial aim of this project was first to develop effective conditions for the substitution of benzylic fluorides, and to gain mechanistic details about the course of the substitution reaction. The ultimate aim was the adaptation of this reaction by use of enantiopure ligands to enable the selective reaction of one enantiomer of a benzylic fluoride in a racemic mixture to enable access to the enantioenriched unreactive enantiomer and enantioenriched product (Scheme 156).

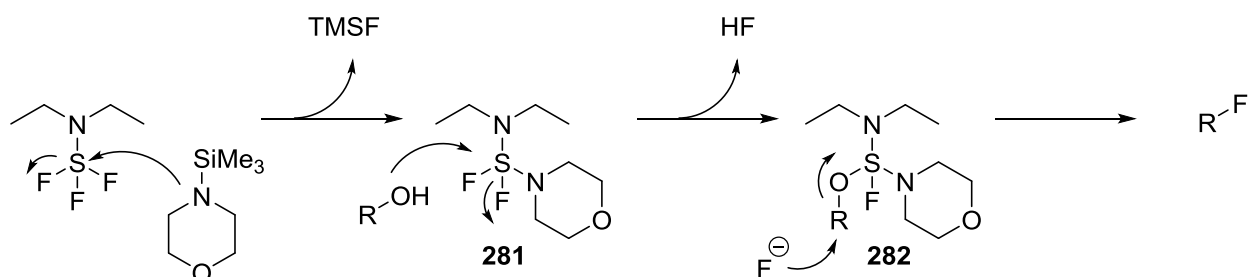
4.2.1 Synthesis of Secondary Benzylic Fluorides



Scheme 157: DAST Deoxyfluorination of Benzyl Alcohol 279

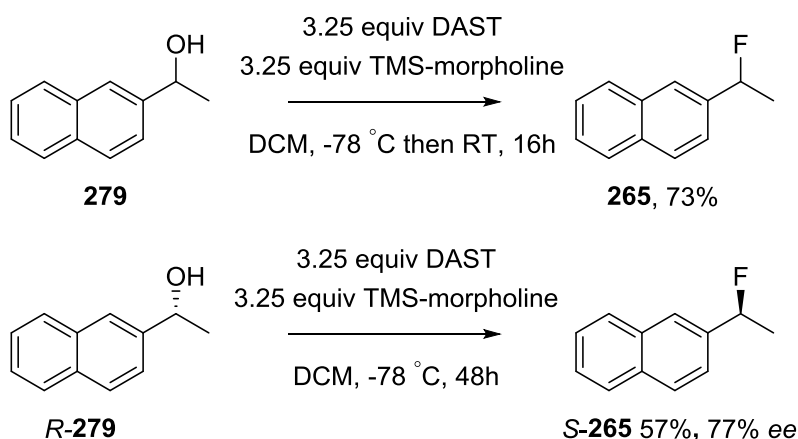
The synthesis of secondary benzylic fluorides is significantly more difficult than for primary substrates. Attempted deoxyfluorination of the alcohol **279** with DAST led to significant ether formation, even when the reaction was performed with a slow addition of starting material to excess DAST at low temperatures (Scheme 157). This side reaction is due to the dissociation of the activated alcohol intermediate as mentioned in Chapter 1. Due to the electron withdrawing fluorines bonded to sulfur in the intermediate the dissociation is favourable, giving a carbocation that can undergo attack by alcohol, elimination or fluorination with a loss of stereochemical integrity. Due to the difficulty of

separation of the ether from the fluoride by flash chromatography and the moderate conversion to fluoride it was necessary to use a modification of the deoxyfluorination methodology.



Scheme 158: DAST / TMS-morpholine Reagent Combination for Deoxyfluorination

Addition of one equivalent of TMS-morpholine to DAST in DCM leads to the formation of the modified reagent **281** (Scheme 158). This reacts with the alcohol to form a less activated intermediate **282** which is less likely to undergo dissociation and thus side reactions, giving better chemoselectivity and enantiospecificity for deoxyfluorination.^{174, 175} A threefold excess of the deoxyfluorinating reagent is used, one equivalent reacts with the alcohol to give the activated intermediate, a second equivalent releases fluoride to buffer the HF formed in this step and the third equivalent provides the fluoride for the displacement of the leaving group.

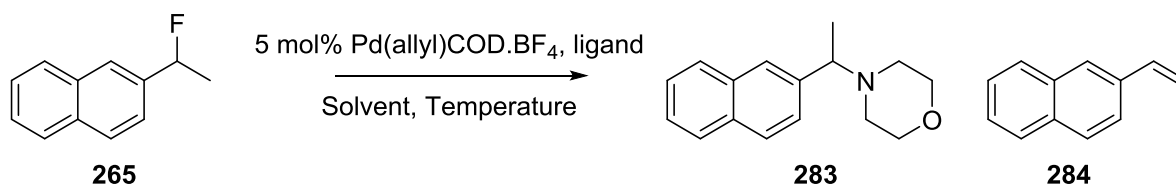


Scheme 159: Preparation of Secondary Benzylic Fluoride 265

The use of this modified methodology was successful. Initial results with the racemic alcohol were promising giving a 73% yield of the fluoride which was readily isolated by flash chromatography (Scheme 159). This compound was highly sensitive to glass, decomposing after several hours at room

temperature or on several occasions in a rotary evaporator flask, and needed to be stored in the freezer in a plastic vessel. The reaction of enantiopure **279** under the reported conditions (RT, 16h) for fluorination gave poor enantiospecificity (19% ee, measured by chiral stationary phase HPLC), but on decreasing the operating temperature for the reaction to $-78\text{ }^{\circ}\text{C}$ and increasing the reaction time we were able to improve the enantiospecificity to give products with 71-77% ee, though this is still far from the reported $>95\%$ enantiospecificities attainable with monocyclic substrates. The stereochemical outcome for all of these reactions is assumed to be inversion due to the mechanism of deoxyfluorination.

4.2.2 Reaction Screening

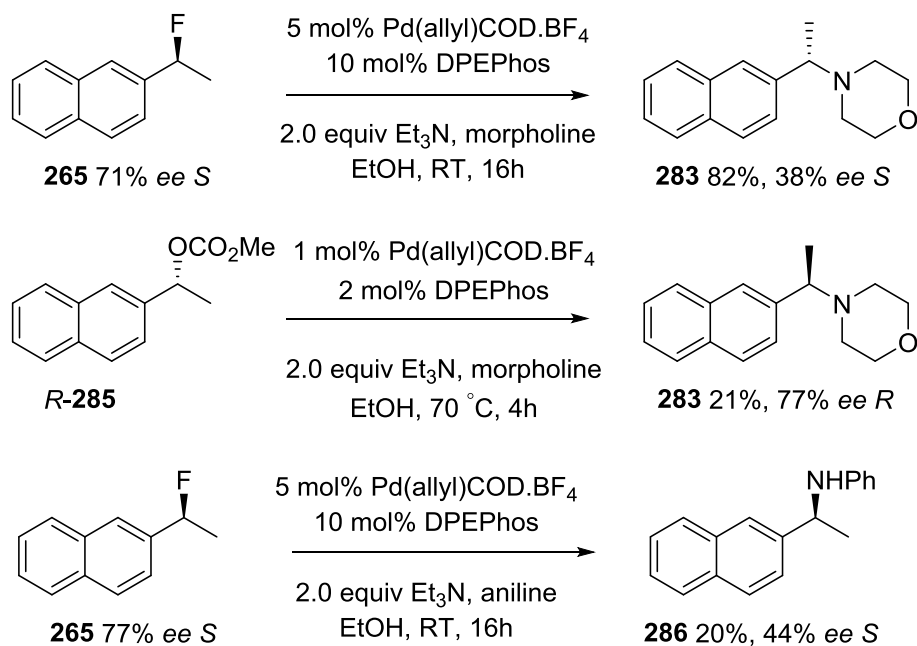


Entry	Ligand	Ligand loading	Solvent	Temperature $^{\circ}\text{C}$	Time h	Product	Alkene
1	tBuXPhos	20	EtOH	70	4	0	>95
2	DPEphos	10	EtOH	70	4	78	22
3	DPEphos	10	DMF	70 then 90	24, 6	0	0
4	DPEphos	10	DMSO	70 then 90	24, 6	0	0
5	dppf	10	EtOH	60	1.5	91	9
6	dppbz	10	EtOH	70	24	80	20

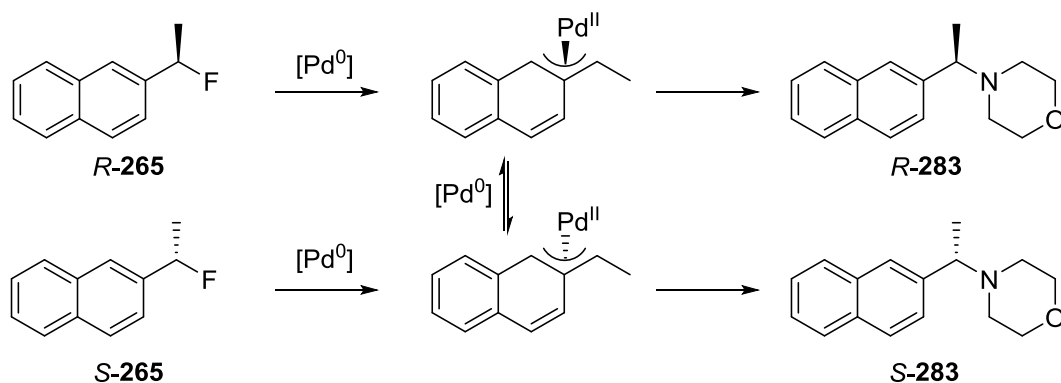
Table 33: Reaction Optimisation for Secondary Benzylic Fluorides

Based on previous work with benzylic fluoride substrates,¹³⁷ investigation of the palladium catalysed amination of **265** using broadly similar conditions to those described in the previous chapter was undertaken (Table 33). A protic solvent was found to be critical for reactivity, with reaction in DMF and DMSO not proceeding even on prolonged reaction at high temperatures. Bidentate ligands were essential for productive substitution, with a catalyst derived from *t*BuXPhos giving exclusively elimination. Otherwise a range of bidentate ligands were able to provide a competent catalyst, with dppf proving optimal. On reducing temperature slightly less alkene was formed, and with dppf the reaction went to completion at room temperature. These results place this secondary fluoride between fluoromethyl naphthalenes and fluoromethyl benzenes in reactivity.

4.3 Mechanistic Insights from Reaction with Enantioenriched Substrate

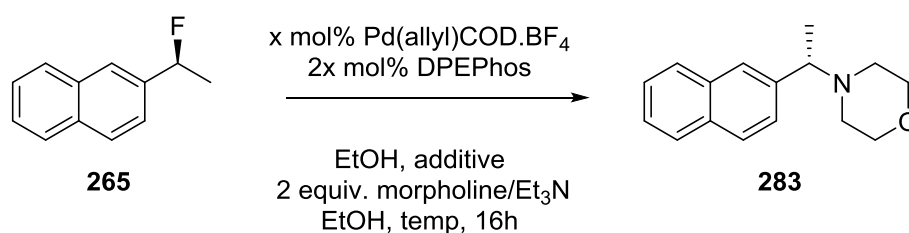
Scheme 160: Stereochemical Outcome of Amination of Benzylic Fluoride **265**

A preliminary reaction of enantioenriched fluoride **265** under the standard conditions gave the product **283** with overall retention of configuration but significant erosion of stereochemistry. This is the expected stereochemical outcome for a reaction operating with the double inversion mechanism as has been invoked in both allylic and benzylic Tsuji Trost chemistry. Assignment of the stereochemical outcome was performed by comparison to a sample of the same product produced from *R*-**285**, exploiting the known stereochemical outcome of benzylic substitution of carbonates. This was further confirmed by amination with aniline to give product **286** which was correlated with the known order of elution of the enantiomers from a Chiralcel OD column (Scheme 160).



Scheme 161: Pd(0) Mediated Racemisation of Pd(benzyl) Complexes

In palladium catalysed allylic Tsuji-Trost chemistry, the expected outcome of substitution of an enantiopure substrate with a soft nucleophile is for retention of configuration. Early mechanistic work by Bäckvall *et al.* suggested two potential mechanisms for racemisation;¹⁷⁶ both mechanisms involve the Pd(0) catalyst coordinating to the alkene, then displacing the leaving group with inversion of configuration to generate the palladium π -allyl intermediate. This intermediate is then attacked by the nucleophile with inversion of configuration to give overall retention of configuration in the product. In the first of the two racemisation pathways, the Pd-allyl intermediate can itself be attacked by Pd(0),¹⁷⁶ with inversion, to generate the Pd-allyl with the opposite configuration, which is then attacked by the nucleophile (Scheme 161). The alternate mechanism for stereochemical erosion is by isomerisation of the π -allyl to a σ -bonded species, which can then either undergo *syn* attack by a nucleophile with retention of configuration,¹⁷⁷ giving net inversion from the starting allyl. For certain substitution patterns, the σ intermediate may racemise due to rotation about C-C bonds (this is however not pertinent in benzylic Tsuji Trost chemistry). The first of these mechanisms (Scheme 161) shows a marked dependence on concentration of Pd in solution, as the rate of interconversion is second order in [Pd], and this can be used to probe the mechanism of racemisation. Any reaction where the ionisation of the allyl is slow in comparison to the attack by the nucleophile will tend to have a high concentration of Pd(0), and this might be expected to be the case for C-F activation, however the relative rates of attack by Pd(0) and nucleophile are also important parameters.

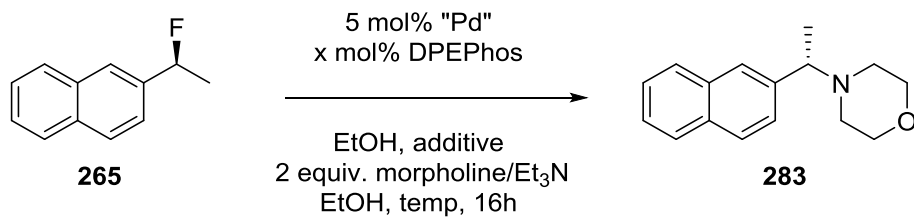


Entry	Pd %	[SM] mol l ⁻¹	[Pd] mmol l ⁻¹	Ligand	Temperature °C	Product conv	SM ee	Prod ee
1	5	0.11	5.7	DPEphos	RT	86 (82)	71	38
2	5	0.11	5.7	dppf	RT	98	77	20
3	5	0.11	5.7	dppbz	40	41	77	48
4	5	0.11	5.7	DPEphos	40	93	77	18
5	5	0.11	5.7	DPEphos	60	91	77	8
6	2.5	0.11	2.9	DPEphos	RT	52	77	69
7	20	0.11	23.0	DPEphos	RT	97	77	3
8	5	0.02	1.1	DPEphos	RT	92 (64)	77	66
9	5	0.01	0.6	DPEphos	RT	62 (14)	77	77

Table 34: Stereospecificity of Defluorination. Values in parentheses refer to isolated yields of product.

In order to probe the effect of Pd(0) concentration on enantiospecificity experiments were performed with higher and lower palladium loadings than the standard conditions (Table 34). On increasing to 20% catalyst loading, almost racemic product was formed (entry 7), whilst with a 2.5% loading the enantiomeric excess was largely conserved, decreasing from 77% to 69%, albeit with lower conversion to product (entry 6). Reactions run under higher dilution in substrate and palladium, whilst maintaining nucleophile concentration, starting from material with 77% *ee* gave the product with 66% *ee* (5 fold dilution, entry 8), or 77% *ee* (10 fold dilution, entry 9), though the conversion and isolated yield suffered in both cases due to the slower kinetics of reaction and the formation of emulsions on work up due to the volume of ethanol used.

The temperature dependence of enantiospecificity was significant (entries 1, 4 and 5) with higher temperatures giving more erosion of stereochemistry. The use of different ligands also affected the level of enantiospecificity (entries 1 vs. 2, and 3 vs. 4). This is not an unexpected result as the reactivity of the Pd(II) allyl and Pd(0) precatalyst will both be determined by the ligand bound to Pd, and the concentration of free Pd(0) will depend on the level of coordination of excess phosphine to the Pd(0)-phosphine complex. A combination of these effects leads to the order dppbz > DPEphos > dppf for the maintenance of enantiospecificity, with dppbz giving a significantly less reactive catalyst.



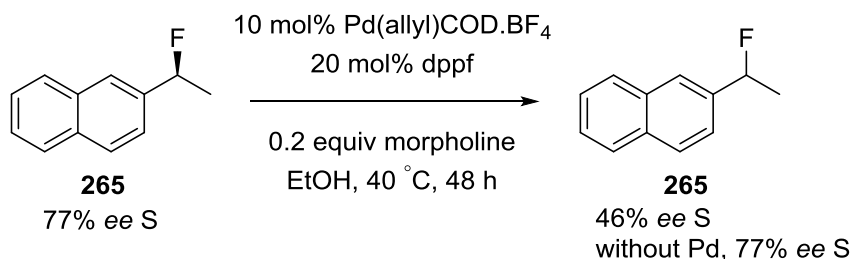
Entry	Pd source	mol% DPEphos	Additive	Temp	Product conv	SM ee	Prod ee
1	(Pd(allyl)Cl) ₂	10	-	40	90	77	12
2	Pd(allyl)COD.BF ₄	10	1.5 equiv TBAF.(<i>t</i> BuOH) ₄	RT	11	71	68
3	Pd(allyl)COD.BF ₄	10	0.5 equiv TBAF.(H ₂ O) _{3.5}	40	81	77	32
4	Pd(allyl)COD.BF ₄	10	0.1 equiv TBAF.(H ₂ O) _{3.5}	40	91	77	22
5	Pd(allyl)COD.BF ₄	5	-	RT	47	77	18
6	Pd(allyl)COD.BF ₄	10	-	RT	86 (82)	71	38

Table 35: Effect of Additives on Stereospecificity

The presence of coordinating anions, specifically chloride and fluoride was investigated as a potential variable affecting enantiospecificity (Table 35). In a previous reaction on racemic **265** an attempt to minimise elimination by the addition of 20 mol% LiCl, following literature precedents¹⁷⁸ found that LiCl significantly reduced the reactivity of the catalyst system, with only 30% conversion being achieved after 4h at 60 °C, with a colour change noted on addition of the salt from yellow to red. The use of (Pd(allyl)Cl)₂ as catalyst precursor gave much lower reactivity than Pd(allyl)COD.BF₄, with reaction only proceeding on heating the reaction to 40 °C to give a slightly worse enantiospecificity (entry 1) compared to the benchmark reaction (entry 6). Use of fluoride additives, either as TBAF.3H₂O or as the *tetrakis tert* butanol complex gave again lower reactivity, but better enantiospecificity, presumably by reversibly sequestering free Pd(0). It was however not possible to find conditions with both high conversion and a high degree of stereospecificity (entries 2, 3 and 4).

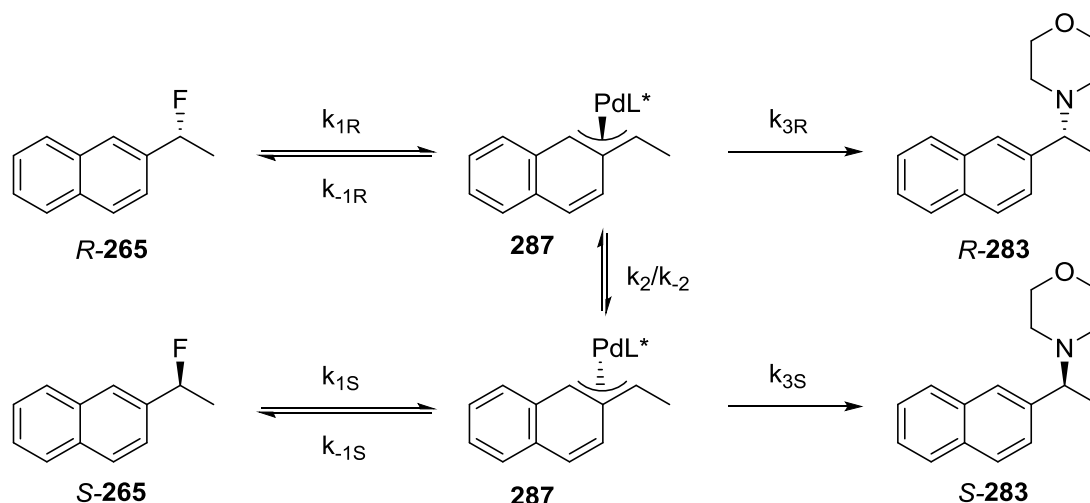
Another variable that is known to have an effect on the stereospecificity of substitution is the concentration of free phosphine ligand. In the work by Bäckvall it was postulated that attack of phosphine on the π -allyl frees Pd(0),¹⁷⁶ so that increasing concentration of phosphine can increase the free Pd concentration and thus increase the rate of racemisation via the Pd-Pd interconversion. As the benzylic fluorine displacements are typically run with ratios of P:Pd of 4:1 (*i.e.* a 2:1 ratio for bidentate phosphines and a 4:1 ratio for monodentate ligands) this might be expected to be an important factor in enantiocontrol. Reaction with a 1:1 mixture of DPEphos and Pd(allyl)COD.BF₄

gave a lower *ee* than with a 2:1 ratio, suggesting that the ligand does not attack the intermediate complex, but instead sequesters the active Pd(0) catalyst, decreasing the free Pd concentration and the rate of allyl interconversion (Table 35, entry 5). The conversion was also lower in the reaction with a 1:1 ratio, possibly because the catalyst is unstable when coordinatively unsaturated, as was observed in our previous studies on C-F activation of fluoromethyl benzenes.



Scheme 162: Test for Reversibility of C-F Cleavage

The formation of the intermediate π complex in Tsuji-Trost reactivity can be a reversible reaction.¹⁷⁹ If the allyl formed initially reacts with another Pd(0) complex, following the mechanism of loss of enantiospecificity as detailed previously, then the reversible cleavage and formation of the C-F bond leads to racemisation of the starting material. To test for potential racemisation, the enantioenriched fluoride **265** was exposed to palladium catalyst under reaction conditions with a limited amount of nucleophile (Scheme 162). Reaction with a limited amount of morpholine enables activation of the allylpalladium precatalyst by formation of *N*-allylmorpholine. Under these conditions the enantiopurity of the starting material decreases over the reaction period from 77% to 46%. Racemisation is therefore possible, though this experiment does not prove the mechanism of racemisation or whether it operates under the reaction conditions for kinetic resolution. The palladium loading is significantly higher and the reaction time longer for this experiment than for typical substitution experiments. A control reaction in the absence of precatalyst and ligand gave no racemisation.



Scheme 163: Mechanistic Model of Kinetic Resolution

This set of reactions taken together provides information about the relative rates of reaction in secondary benzylic fluoride amination. Ignoring the possible existence of *cis/trans* isomers of the intermediates, a simple model of the kinetic resolution of **265** is presented in Scheme 163. The reversibility of nucleophilic attack was not probed in our experiments but it is commonly assumed to be irreversible in allyl chemistry. The significant erosion in enantiomeric excess of the amine under the standard conditions shows that interconversion of the Pd π -species **287** is competitive with nucleophilic attack by morpholine ($k_2 \leq k_3$). This suggests that a kinetic resolution of benzylic fluorides would not follow classical kinetic resolution kinetics, as the enantiomer of product produced does not completely depend on the enantiomer of starting material due to a racemisation pathway. The finding that the starting material can racemise under reaction conditions also has implications for the kinetic resolution. The kinetic resolution parameter *S* is defined for a system where there is no racemisation, thus the calculation of *S* from starting material ee in this system must be treated with some caution, and the value of *S* calculated from the product ee is meaningless. To minimise racemisation, a low Pd loading and a high concentration of nucleophile may be required to minimise the concentration of allyl intermediates which are involved in the putative racemisation pathway. However, racemisation was slow in comparison to the amination reactions so this may not be a significant factor (if $k_1 \ll k_3$ and $[Pd(0)]$ is lower than $[morpholine]$ then racemisation will not be competitive).

4.4 Reaction Screening with Enantiopure Chiral Ligands

In our studies towards a kinetic resolution we first set out to survey the reactivity of different catalyst complexes, submitting racemic **265** to substitution with 2 equivalents of morpholine with a range of enantiopure phosphines. Catalyst loading for all reactions was 2.5% of Pd, with 1.5 equivalents of ligand to Pd. The use of a low loading of Pd limits any potential racemisation by Pd-Pd interconversion. Reactions were run at 60 °C for 16h with 2 equivalents of triethylamine and morpholine. These conditions are relatively harsh for enantioselective catalysis given that asymmetric Tsuji-Trost chemistry is typically performed at ambient or reduced temperatures. However, asymmetric induction at elevated temperatures is not unprecedented in metal catalysis¹⁸⁰ and we hoped that further screening of ligand hits would enable us to lower the temperature of reaction. After work up, all ligand screening reactions were assessed by proton NMR of the crude reaction mixtures to determine the conversion of starting material to alkene and amine.

The fluoride starting material could be separated from the products by careful flash chromatography and the enantiomeric excess measured by chiral stationary phase HPLC. The instability of the fluoride to isolation on glass meant that plastic containers were used – unfortunately this precluded obtaining an accurate isolated yield of fluoride, as plastic containers tend to swell in the presence of organic solvents, leading to erroneously high yields. Thus the conversions obtained by ¹H NMR of the crude mixtures, in addition to the enantiomeric excesses measured on the isolated material, were used to determine the parameter *S* for those ligands which were reactive but also had starting material remaining at the end of reaction. Those ligands which gave full conversion in the initial reaction screen were then used at lower temperatures and the reactions stopped after less time to allow isolation of the starting material.

4.4.1 Monitoring of Reaction Mixture by HPLC

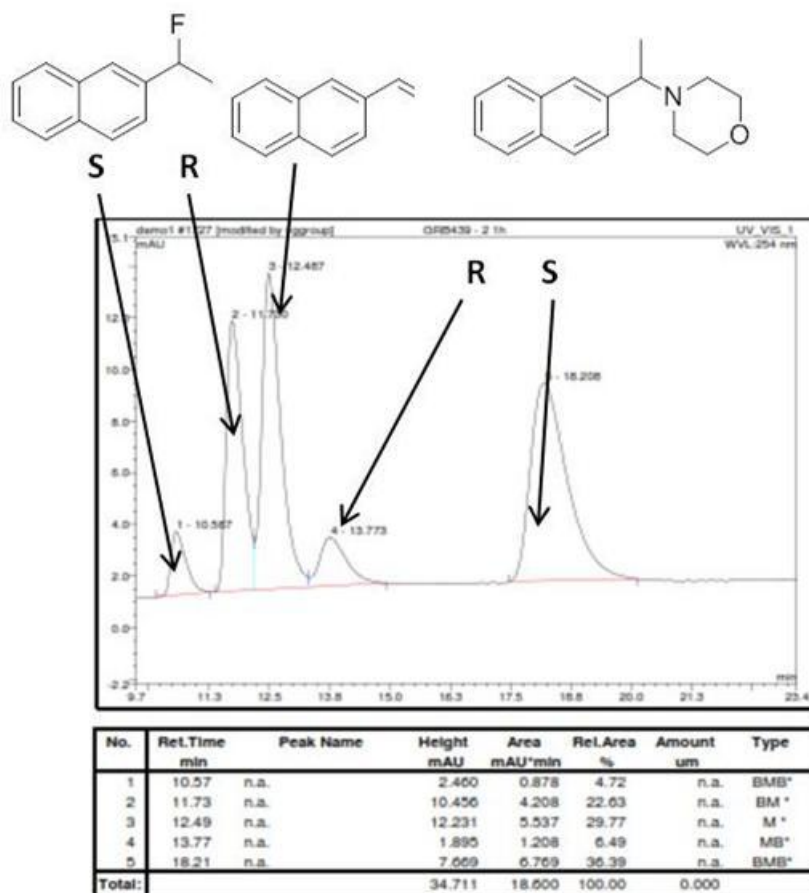
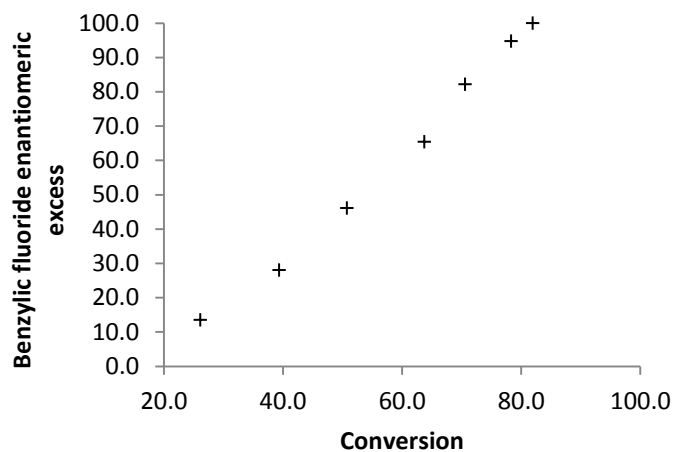
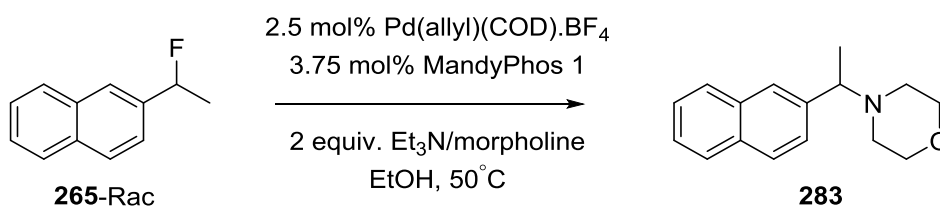


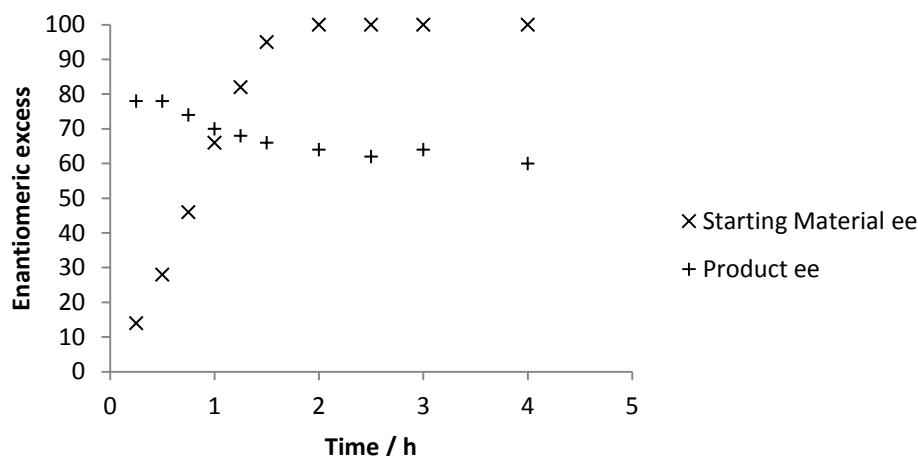
Figure 21: HPLC Trace of Crude Reaction Mixture

Using the same HPLC method and column as for the enantiomeric excess determination of the fluoride, it was possible to separate the fluoride, alkene and amine (Figure 21, first to elute are 2 fluoride peaks, then alkene, then 2 amine peaks). By calibration of the UV response of each component at a range of different concentrations, we were able to develop an assay for the relative concentrations of the different components in the reaction mixture. As it was not possible to perform a baseline separation of all of the components this method was not used for the routine determination of conversion and ee for S values. This methodology did however allow the comparison of a reactive system to the kinetic model illustrated in Scheme 163.



Graph 1: *ee* vs. Conversion for Kinetic Resolution

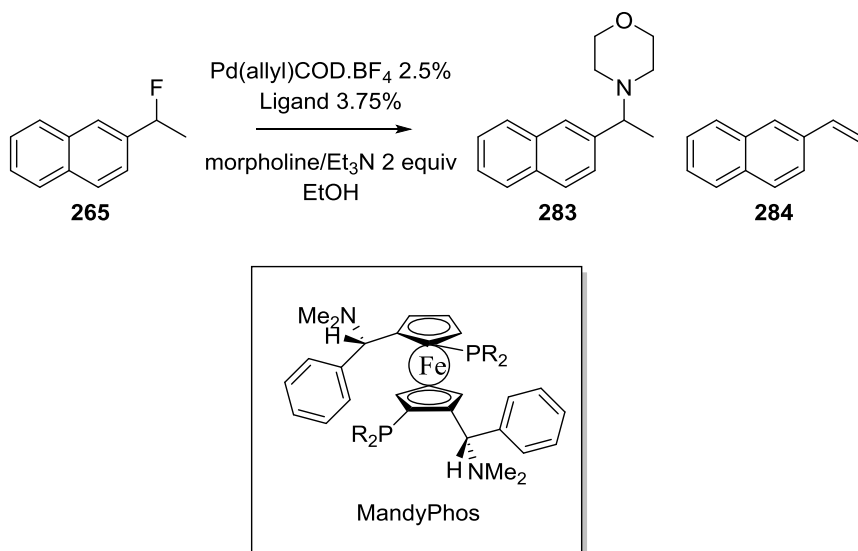
By sampling the kinetic resolution at a range of time points we could plot the *ee* against conversion for the reaction shown in Graph 1. The ability to measure the conversion and *ee* almost simultaneously to the reaction gives more confidence in the operation of a kinetic resolution as it enables quenching of reaction at a time to get the optimum result. The reaction course from the perspective of the starting material is uncomplicated, with the selectivity constant through the reaction and the *ee* vs. conversion in Graph 1 obeying theoretical predictions.



Graph 2: Starting Material and Product *ee* vs. Time

When the enantiomeric excess of the product is considered at the same time as the starting material it is clear that the enantiomeric excess of the product does not obey the predictions of the standard kinetic resolution (Graph 2). This is unsurprising in the light of the results of substitution experiments on the enantioenriched fluoride where significant erosion of enantiomeric excess was observed, implying that allyl interconversion is occurring. The enantiomeric excess of the product is at a maximum at low conversion as would be expected but does not decrease as rapidly as the standard kinetic resolution model predicts. Hence asymmetric synthesis of the amine product is occurring at the same time as kinetic resolution. This complicates the understanding of the kinetic resolution and renders modelling of the rates of reaction difficult; it also mandates the calculation of *S* based on the starting material *ee* as described earlier.

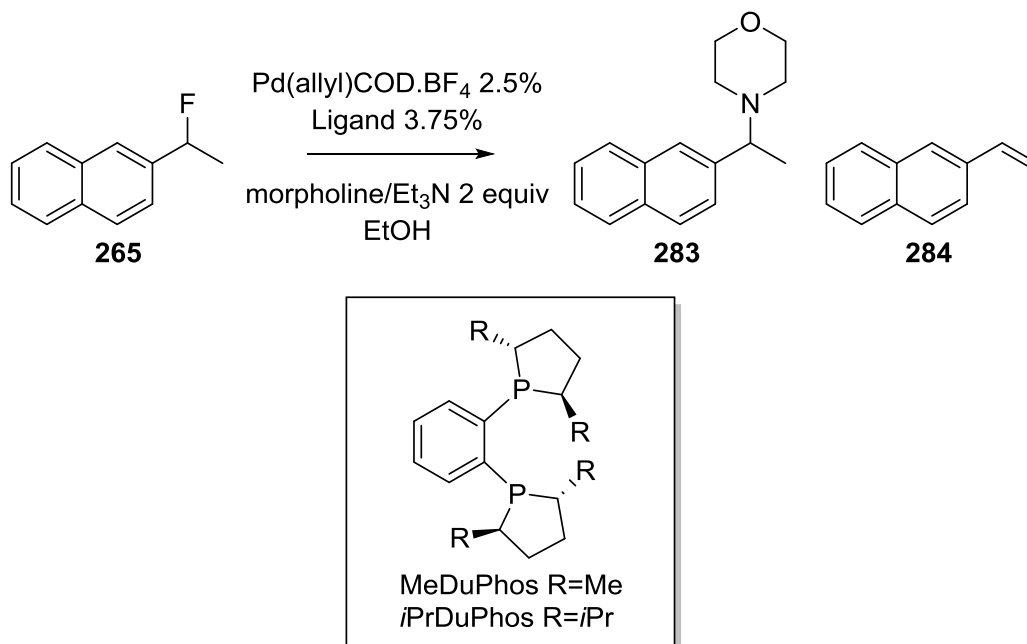
4.4.2 Scaffold Based Ligand Screening



Entry	R	Amine ^a	Alkene	Fluoride ee	S
1 ^b	Ph	81 ^b	5	86	R 2.9
2	Cy	43	3	18	R 1.8
3	3,5-CF ₃ Ph	-	2	nd	- -
4 ^b	3,5-Me-4-MeO-Ph	57 ^b	5	52	R 3.1
5 ^b	3,5-Me-Ph	75 ^b	4	80	R 3.3
6	2-Me-Ph	47	9	6	R 1.2

Table 36: MandyPhos Ligand Screening a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture, b) 40°C, 4h.

Based on the achiral ligand screen the most effective ligand for the substitution reaction was dppf, which is structurally related to the MandyPhos ligand family. Screening of all of the commercially available ligands based on this scaffold was undertaken (Table 36). The reactivity of the catalyst system depended largely on the substituents at phosphorus, with electron poor (entry 3) or alkyl (entry 2) substituted phosphines giving poor reactivity. Electron neutral and rich phosphines with little steric encumbrance showed higher reactivity, and essentially the same enantioselectivity, with S values of around 3. Somewhat surprisingly, a slightly more hindered electron neutral ligand, entry 6, showed both poor reactivity and selectivity. There was no clear optimal ligand within this class, with the most active ligands giving similar levels of enantioselectivity.

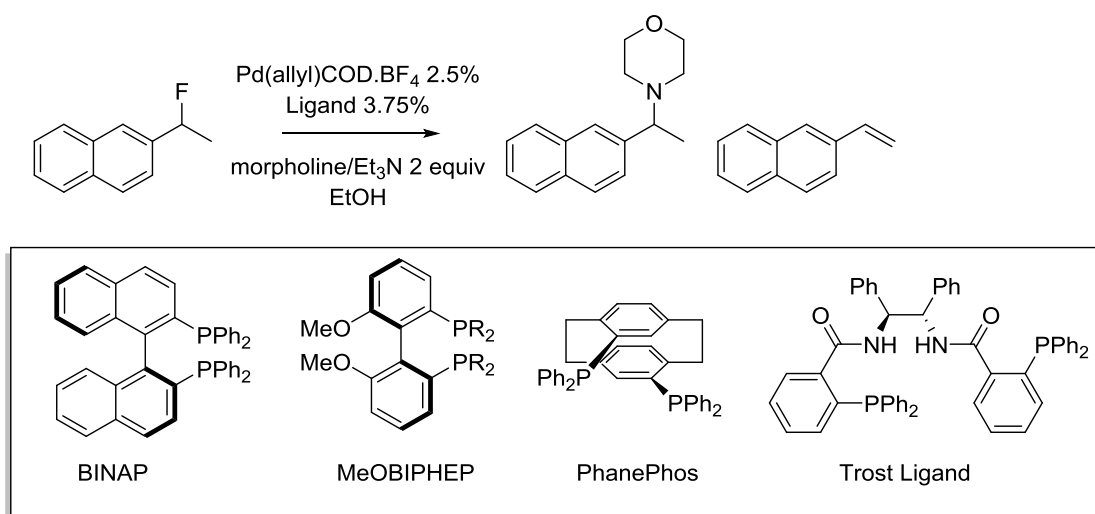


Entry	Ligand	Temperature, Time	Amine ^a	Alkene	Fluoride ee	S
1	MeDuPhos	70, 16h	-	trace	nd	- -
2	iPrDuPhos	70, 16h	4	2	nd	- -
3	MeDuPhos	80, 24h	trace	34	10	R 1.6
4	iPrDuPhos	80, 24h	trace	4	nd	- -

Table 37: DUPHOS Ligand Screening, a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

Of the other achiral ligands tested, *bis*-diphenylphosphinobenzene also has a C₂ symmetric chiral variant - the DuPhos ligands. These ligands gave catalyst complexes with very poor reactivity, similarly to the alkyl substituted MandyPhos ligand (Table 37). Under forcing conditions Me-DuPhos gave very low levels of selectivity, and we were unable to find any conditions under which these ligands would allow reactions to proceed to completion.

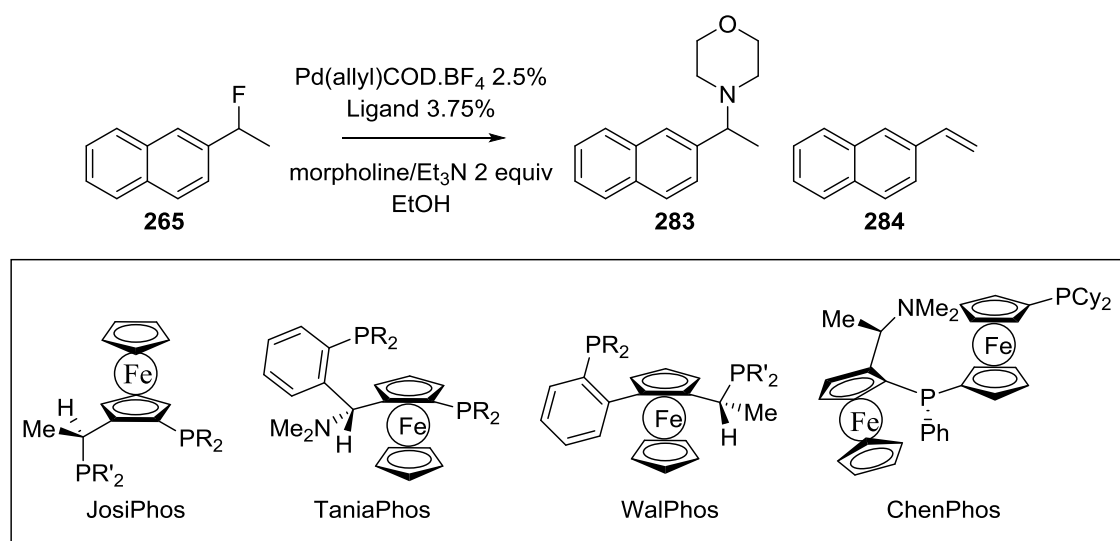
In addition to a rational design approach to screening chiral versions of achiral ligands, efforts were made to identify other ligand scaffolds that would give better selectivity for the desired transformation. These ligands can be divided into C₂ symmetric ligands, which are commonly used in catalysis, including allylic kinetic resolutions, and a range of less commonly used C₁ non symmetric ligands.

4.4.3 C₂ Ligand Screening

Entry	Ligand	Temperature, Time	Amine ^a	Alkene	Fluoride ee	S
1	<i>R</i> -BINAP	50°C, 4h	35	4	9	R 1.4
2	<i>R</i> -Ph-MeO-BIPHEP	60°C, 24h	82	6	13	R 1.1
3	<i>R</i> -3,5- <i>t</i> Bu-4-OMe-MeO-BIPHEP	40°C, 4h	22	2	1	nd 1.1
4	<i>S</i> -Phanephos	70°C, 60h	24	6	12	R 2.0
5	<i>R</i> -Ph Trost ligand	70°C, 16h	-	-	nd	nd -

Table 38: C₂ Ligand Screening, a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

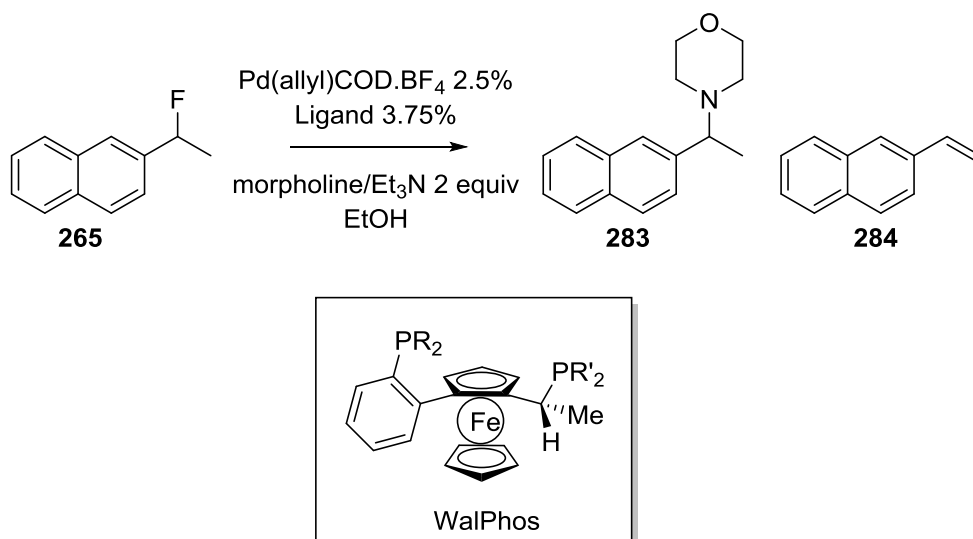
The C₂ ligand group provided catalysts with activity ranging from good to unreactive, but the fluoride **265** was returned with little enantioenrichment in all cases (Table 38). BINAP gave the best reactivity, but only slight enantioenrichment of the starting material. MeO-BIPHEP ligands gave slightly lower reactivity, and returned almost racemic starting material. PhanePhos provided only marginally reactive complexes, with a similarly low S value to BINAP. Ph-Trost ligand, commonly used in both allylic substitution and substitution of highly activated benzylic substrates, gave no conversion even under forcing conditions.

4.4.4 C₁ Ligand Screening

Entry	Ligand	PR ₂ , PR' ₂	Amine ^a	Alkene	Fluoride ee	S
1	JosiPhos 1	Ph, Cy	19	4	0	- 1
2	JosiPhos 2	Ph, <i>t</i> -Bu	14	12	nd	- -
3	JosiPhos 3	Cy, Cy	-	2	nd	- -
4	JosiPhos 5	Ph, 3,5-MePh	31	4	0	- 1
5	TaniaPhos 1	Ph, Ph	37	41	9	R 1.1
6	TaniaPhos 2	Cy, Cy	-	3	nd	- -
7	WalPhos 1	Ph, 3,5-CF ₃ Ph	-	2	nd	- -
8	WalPhos 2	Ph, Ph	57	17	76	R 3.5
9	ChenPhos	Ph/Fc, Cy	14	22	0	- 1

Table 39: C₁ Ligand Screening, a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

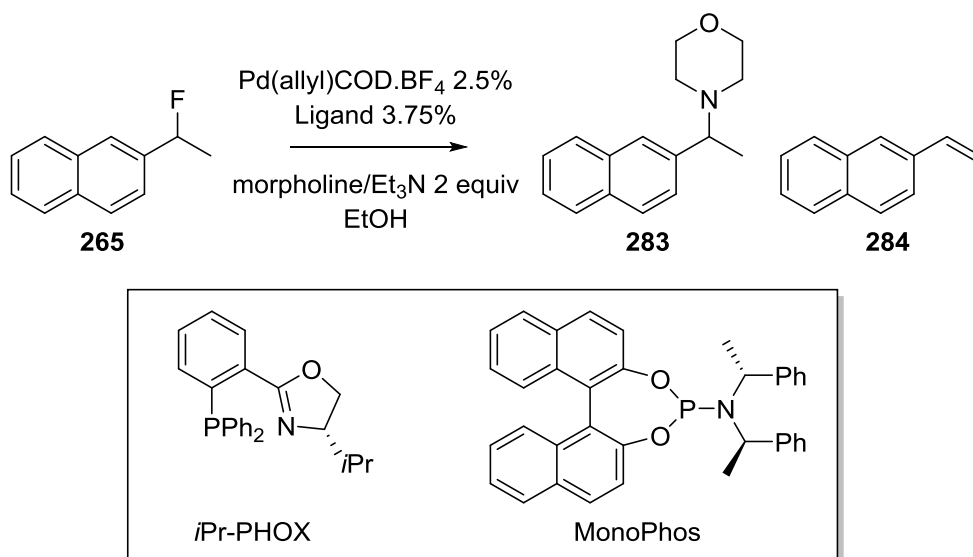
Within a structurally diverse C₁ bidentate ligand set similar phosphorus substituent preferences were observed for reactivity, with alkyl phosphines giving less reactive catalysts than aryl phosphine. This is most obvious in the JosiPhos series (Table 39, entries 1-4), where the most active member bears 2 aryl phosphines, the least active 2 alkyl phosphines. Of the ligands surveyed, only one based on the WalPhos scaffold proved to give any selectivity. The *P*-chiral ligand based on a 1,1'-ferrocene backbone, ChenPhos, gave poor reactivity and no selectivity. Viewed from the perspective of the similar MandyPhos ligands this may support that the origin of enantioselectivity in the MandyPhos series as being due to the C₂ steric environment around the phosphine substituents rather than due to secondary interactions with dimethylamino substituents, as there is a similar sidechain in the ChenPhos ligand.



Entry	PR ₂	PR' ₂	Amine ^d	Alkene	Fluoride ee	S
1 ^a	Ph	3,5-CF ₃ Ph	trace	3	nd	-
2 ^b	Ph	Ph	57	5	52	R 3.0
3 ^a	Ph	Cy	39	18	14	R 1.4
4 ^a	3,5-Me-4-MeO-Ph	3,5-CF ₃ Ph	trace	23	16	R 3.9
5 ^c	Ph	3,5-MePh	19	2	26	2.5
6 ^a	Cy	3,5-CF ₃ Ph	40	17	6	R 1.2
7 ^c	3,5-MePh	3,5-MePh	42	5	37	3.4
8 ^a	Ph	2-norbornyl	trace	50	9	R 1.2

Table 40: WalPhos Ligand Screening a) 80 °C, 24 h. b) 30 °C, 4 h. c) 30 °C, 7 h, d) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

Based on the hit with ligand WalPhos 2, screening of the other commercially available members of this family was performed (Table 40). The majority of these ligands bear one alkyl or electron poor substituent, and these are very unreactive, requiring prolonged reaction times at high temperatures to give partial conversion. A slight enhancement of S factor was observed in this ligand family for the *bis* aryl phosphines but the reactivity of these catalysts was poor, with very low conversions. The generally lower reactivity of this class of phosphines makes them less attractive as a ligand class than the MandyPhos ligand series.



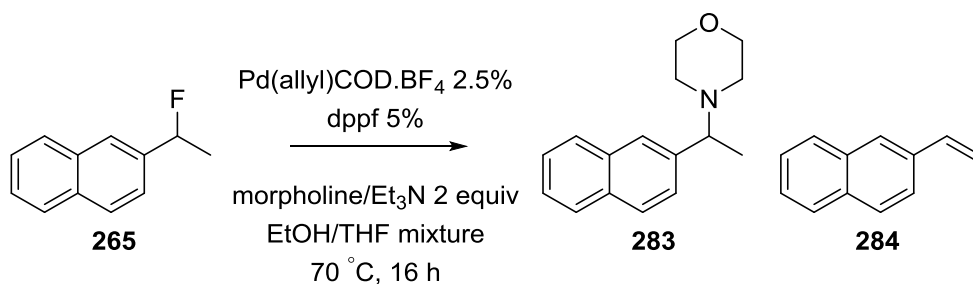
Entry	Ligand	Temperature, Time	Amine ^a	Alkene	Fluoride ee	S
1	<i>i</i> PrPhox	70°C, 16h	6	26	0	1
2	Monophos	70°C, 16h	trace	1	nd	-

Table 41: Monophosphine C1 Ligands, a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

There are relatively few chiral monophosphorus ligands available, but there are several reports of their use in asymmetric allylic substitutions.^{142, 181} The result for the defluorination of **265** by a Pd complex of tBuXPhos demonstrates that C-F activation of secondary substrates is possible with a monophosphine ligand, so presumably a chiral monophosphine might also be able to affect the kinetic resolution. In such a reaction it might be possible that the predominant product would be the alkene. Use of *i*Pr-Phox led as expected to reaction favouring the alkene product, but the starting material was returned with no enantioenrichment (Table 41, Entry 1). A phosphoramidite ligand was also tested for reactivity after a report detailed its use in a related Mizori-Heck reaction with a highly activated trifluoroacetate benzylic ester,¹⁸² but were unable to observe any reactivity in this less activated system (Entry 2).

Based on the ligand screening described, it was clear that the MandyPhos and WalPhos ligand families provide competent catalysts with a low selectivity for kinetic resolution. Electron rich phosphines give better reactivity but within these families the enantioselectivity differences between ligands were not significant.

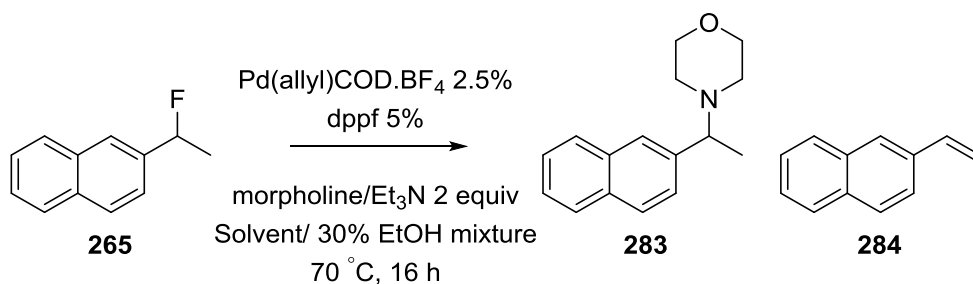
4.4.5 Solvent Screening



Entry	THF/EtOH ratio	Amine ^a	Alkene
1	1:1	82	8
2	3:1	7	<1
3	9:1	trace	trace
4	19:1	trace	trace

Table 42: Solvent Admixtures to Modulate Reactivity - Percentage of Ethanol, a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

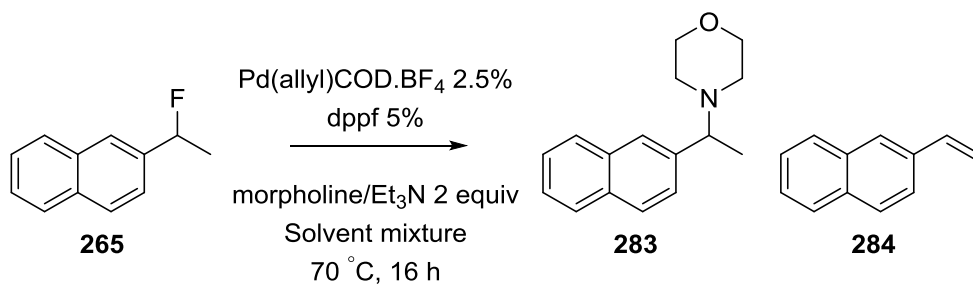
In the previous work on defluorination of benzylic fluorides the key parameters for successful reaction were identified as solvent and ligand. A protic solvent provides significant activation to the leaving group and a moderate bite angle bidentate ligand or hindered biaryl monodentate ligand was essential for reactivity. We sought to identify whether there was any solvent system in which we could improve the enantioselectivity of defluorination relative to the reaction in ethanol. Based on the initial reaction screen it was clear that a protic solvent was essential for reactivity, so in order to modify the solvent composition an investigation of cosolvent systems was undertaken. The Pd(allyl)COD.BF₄/dpf catalyst system proved to be reactive in a mixture of EtOH and THF (Table 42), but on decreasing the proportion of ethanol the reactivity dropped rapidly, with 25% ethanol in THF giving less than 10% conversion. At 10% EtOH and below there was only trace reactivity, indicating the important role that the protic solvent plays in assisting ionisation of the fluoride.



Entry	Solvent	Fluoride	Amine ^a	Alkene
1	THF	28	67	5
2	DMSO	84	16	trace
3	DMF	61	36	3
4	Dioxane	>95	-	trace
5	EtOAc	65	35	-
6	Acetone	40	53	7
7	MeCN	85	13	2

Table 43: Aprotic Cosolvent Screening for Secondary Fluoride Displacement, a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

Based on the level of reactivity observed with varying percentages of ethanol, a range of different solvents were tested as mixtures with 30% ethanol for the racemic reaction. These results are presented in Table 43. Most of the aprotic solvents investigated supported some reactivity, but noticeably better results were found with polar aprotic solvents: THF, DMF, ethyl acetate and acetone.

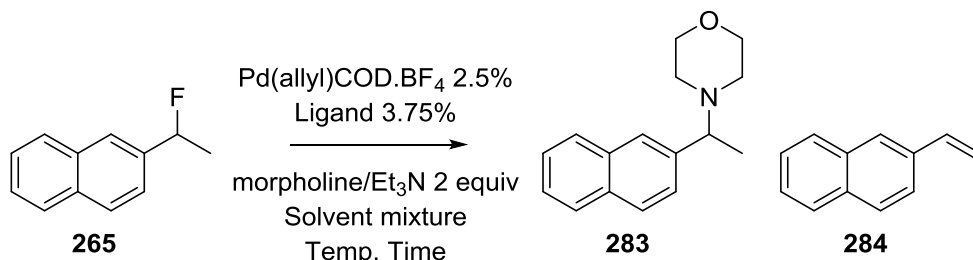


Entry	Solvent mixture	Temperature °C	Time h	Amine ^a	Alkene
1	10% fluoro tert butanol in THF	50	16	-	-
2	30% trifluoroethanol in THF	50	16	-	-
3	1:1 THF H ₂ O	70	16	81	19
4	30% Ethylene glycol in THF	70	16	39	7

Table 44: Alternative H-Bond Donor Screening, a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

The solvent compositions used can be viewed as "carrier" - the aprotic component - and "activator" - a protic solvent. After determining the variety of carrier solvents that were compatible with this

chemistry we sought to find alternate H-bonding solvents that might increase the reactivity or selectivity of the catalyst system. Fluorinated alcohols did not support reactivity. THF/H₂O 1:1 gave full conversion of the fluoride, and ethylene glycol gave a moderate conversion that was comparable to the result for EtOH/THF (Table 44).



Entry	Ligand	Solvent (1:1)	Temp, Time	Amine ^a	Alkene	Fluoride ee	S
1	MandyPhos 1	EtOAc/EtOH	50°C, 16h	50	9	46	2.9
2	MandyPhos 1	Acetone/EtOH	50°C, 16h	72	10	80	2.9
3	MandyPhos 1	DMSO/EtOH	50°C, 16h	15	0	10	4.0
4	MandyPhos 1	DMF/EtOH	50°C, 16h	7	1	nd	-
5	MandyPhos 1	THF/EtOH	50°C, 5h	28	2	33	10.6
6	MandyPhos 1	THF/EtOH	50°C, 5h	52	8	57	3.8
7	MandyPhos 4	THF/EtOH	50°C, 4h	32	4	17	2.2
8	WalPhos 2	THF/EtOH	50°C, 16h	-	-	nd	-

Table 45: Solvent Mixtures for Kinetic Resolution, a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

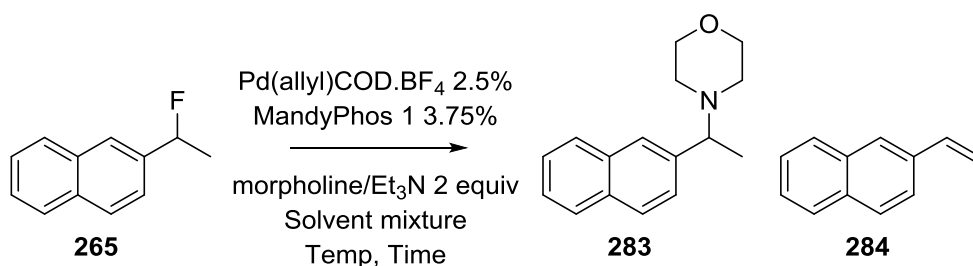
With this understanding of the solvent effects on the reactivity of this catalytic system the kinetic resolution of **265** was performed in a selection of 1:1 solvent mixtures with ethanol (Table 45). In all solvent systems tested the reactivity was significantly reduced. There was a slight improvement in enantioselectivity in THF/EtOH, with an S value of 10.6, though the reaction stopped at 30% conversion. A repeat of this reaction gave a slightly higher conversion but the S value fell. Repeatability was a problem for kinetic resolutions attempted in solvent mixtures, with reactions stalling at low conversions. An attempt to increase the number of turnovers of the catalyst by adding additional COD to stabilise the Pd(0) resting state was unsuccessful, with no reaction observed. For MandyPhos 4 the enantioselectivity did not improve in this solvent system and WalPhos 2 demonstrates no reactivity under the same conditions.

The investigation into solvent composition as a variable suggests that solvent composition is a highly sensitive variable for reactivity. For one system (1:1 THF/EtOH) there was a small increase in

enantioselectivity of defluorination, but this system gave unreliable catalytic performance. If this could be addressed by the use of an additive then it would provide a better result than for reaction in EtOH alone, but for reliable kinetic resolution reactions EtOH alone is the preferred solvent.

4.4.6 Temperature

The operating temperature of enantioselective processes can have a significant impact on the selectivity. A crude approximation is that lower temperatures will give better selectivity for a process where $\Delta\Delta G^\ddagger$ is invariant with temperature. Simplistically, the difference in activation energy for diastereomeric transition states compared to the thermal energy of reactants is relatively greater at lower temperatures. $\Delta\Delta G^\ddagger = \Delta\Delta H^\ddagger - T \Delta\Delta S^\ddagger$ so a more accurate description of this situation is that this will always be the case where $\Delta\Delta S^\ddagger$ is positive (*i.e.* there is higher activation entropy for the transition state for the disfavoured reaction). The situation where lowering of temperature increases enantioselectivity is viewed as the more common situation,¹⁸³ but examples are known where an increase in temperature may increase the enantioselectivity (*i.e.* $\Delta\Delta S^\ddagger$ is negative).¹⁸⁴ As a further complication, different mechanisms may operate at different temperatures, which is reflected in inflection points of the graph of ΔG^\ddagger vs. T.



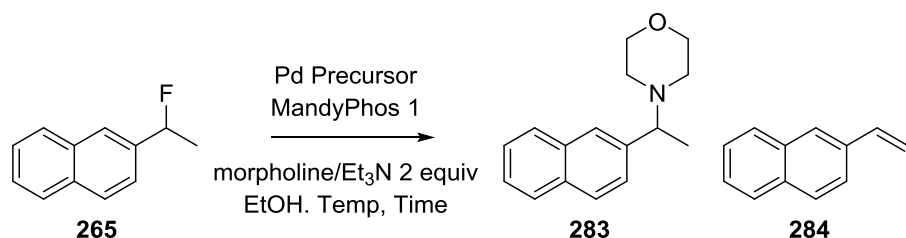
Entry	Temperature	Time	Amine ^a	Alkene	Fluoride ee	S
1	70	0.5	73	8	90	R 3.9
2	60	0.5	74	4	55	R 2.1
3	50	0.5	34	3	28	R 3.7

Table 46: Effect of Temperature on Enantioselectivity, a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

In order to test for the presence of temperature effects in the kinetic resolution reactions were performed at a range of temperatures (Table 46). The S value for the reactions was relatively constant. Given the slow kinetics of the reaction at lower temperatures it was not possible to measure a value

for *S* at below ambient temperature. The conclusion from these experiments is that the temperature is not a significant variable in the kinetic resolution under these conditions and that a temperature may be chosen to give the most convenient reaction time.

4.4.7 Catalyst Precursor and Ligand Loading

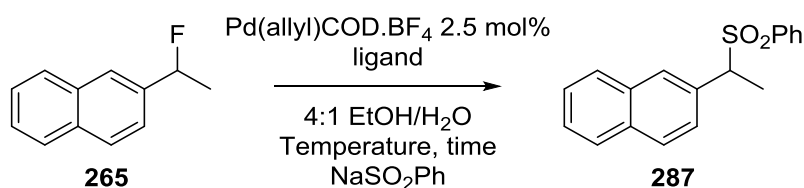


Entry	Pd Source	Pd Loading	Ligand Loading	Temp °C	Time h	Amine ^a	Alkene	Fluoride ee	<i>S</i>
1	(Pd(allyl)Cl) ₂	2.5	3.75	50	4	62	9	80	4.4
2	(Pd(allyl)Cl) ₂	2.5	3.75	40	16	82	6	87	2.8
3	Pd(allyl) COD.BF ₄	2.5	2	25	16	73	4	89	4.4
4	Pd(allyl) COD.BF ₄	5	2	40	2	16	3	8	2.2
5	Pd(allyl) COD.BF ₄	1	5	25	16	66	4	85	5.3

Table 47: Catalyst Parameter Investigation, a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

Other than solvent and ligand choice, the nature of the active catalyst may be influenced by the catalyst precursor and the ratio of Pd to ligand employed. The use of (Pd(allyl)Cl)₂ as precursor gave poorer reactivity in the racemic optimisation reactions and this was observed again in the kinetic resolution, with slower reaction at higher temperatures than the more active Pd(allyl)COD.BF₄ precursor (Table 47, Entries 2 & 3). Despite the decline in reactivity, the enantioselectivity of reaction was almost unchanged. The use of a Pd/phosphine ratio of close to 1:1 gave similar enantioselectivity to the standard conditions. A large excess of Pd relative to phosphine reduced the enantioselectivity. The use of a large excess of ligand relative to Pd gave a slight increase in selectivity, and allowed the loading of Pd to be reduced. This is however not an economically important change in reaction conditions as the ligand is significantly more expensive than the metal catalyst precursor.

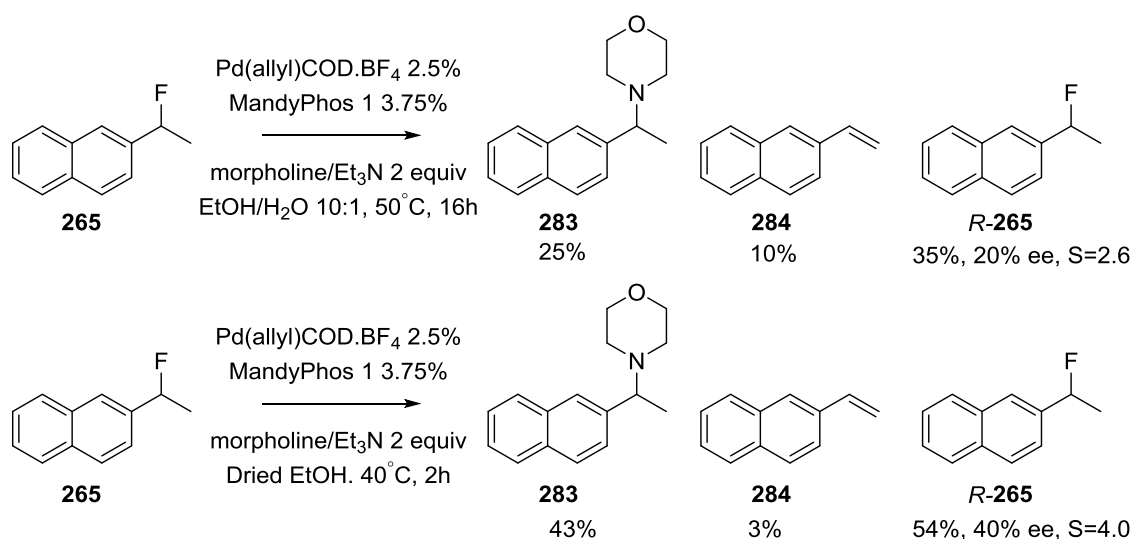
4.4.8 Nucleophile



Entry	Ligand	Ligand %	Temp	Time	Product	alkene ^b	Fluoride ee	S
1	dppf	5	25	16	43	trace		
2	dppf	5	60	16	>95% (86)	trace		
3	Mandy 1	3.75	25	16	71	trace	90	5.9
4 ^a	Mandy 1	3.75	25	16	57	trace	43	4.1

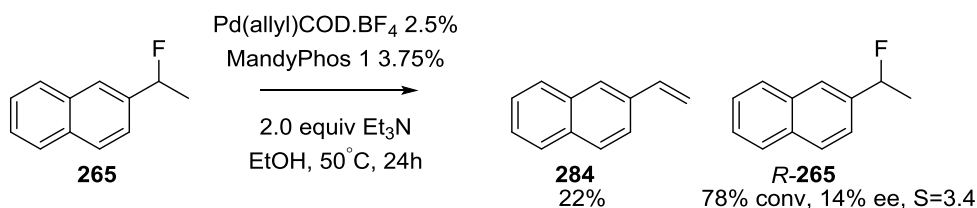
Table 48: Kinetic Resolution with Sodium Phenylsulfinate Nucleophile a) Reaction in EtOH without added H₂O, b) Conversion to alkene as determined by ¹H NMR of the crude mixture

Nucleophile effects on kinetic resolutions are rare but can have significant effects on selectivity as described in section 4.1.2. Kinetic resolution of **265** with sodium benzenesulfinate as nucleophile was attempted to probe for any nucleophile effects (Table 48). Reaction in 4:1 EtOH/H₂O was performed, giving 71% conversion to the sulfone **287**, with no observable alkene. The recovered starting material had an ee of 90%, corresponding to an S value of 5.9, similar to that for the amination reactions. This indicates that as expected the enantioselectivity depends on a step independent of the nucleophile, presumably the ionisation of the fluoride. This reaction typically requires the addition of water to solubilise the nucleophile, so an experiment in ethanol alone was also performed (entry 4), giving a similar S value as in the solvent mixture (4.1).



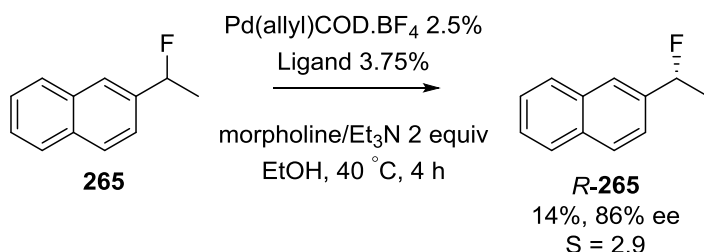
Scheme 164: Effect of Water on Kinetic Resolution

The observation that the presence of water is not highly important for the kinetic resolution was supported by two experiments for the kinetic resolution-amination reaction in either anhydrous ethanol (dried over molecular sieves prior to use) or a 10:1 ethanol/water mixture. Reaction under anhydrous conditions gave no enhancement in selectivity, but added water did decrease the reactivity and selectivity (Scheme 164).



Scheme 165: Kinetic Resolution by Elimination

Running the kinetic resolution reaction conditions with triethylamine but no morpholine in an attempt to perform an elimination of fluoride gave a value of 3.4 for S (Scheme 165), and the reaction did not proceed to completion. Again this is a similar level of selectivity and provides further support for the hypothesis that the effectiveness of the kinetic resolution is determined only by the C-F cleavage step, which does not involve the nucleophile.



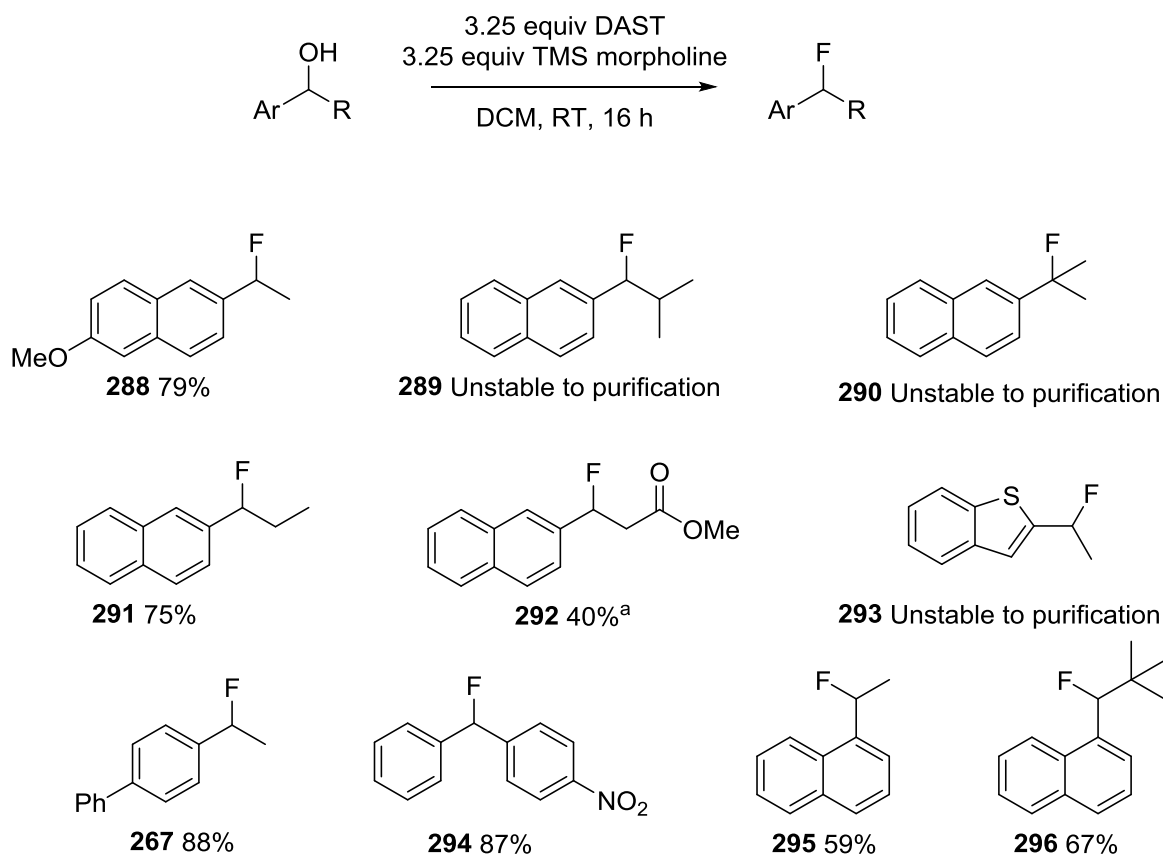
Scheme 166: Standard Kinetic Resolution Conditions

Despite significant efforts at optimisation, the selectivity of the kinetic resolution could not be improved upon significantly, with the MandyPhos ligands providing the most reliable reactivity and selectivity. The use of alternate solvents and nucleophiles and different ratios of Pd/L show some effects on the enantioselectivity of reaction, but within the range of experimental errors. Based on the optimisation studies performed the preferred kinetic resolution conditions were as shown in Scheme 166.

4.5 Substrate Scope

As it was not possible to significantly alter the reaction conditions to reliably enable kinetic resolution of our prototype substrate, the substrate scope of the kinetic resolution reaction was determined using the initial reaction conditions. The effects investigated were steric hindrance at the reactive centre, functional group tolerance and the nature of the aromatic ring.

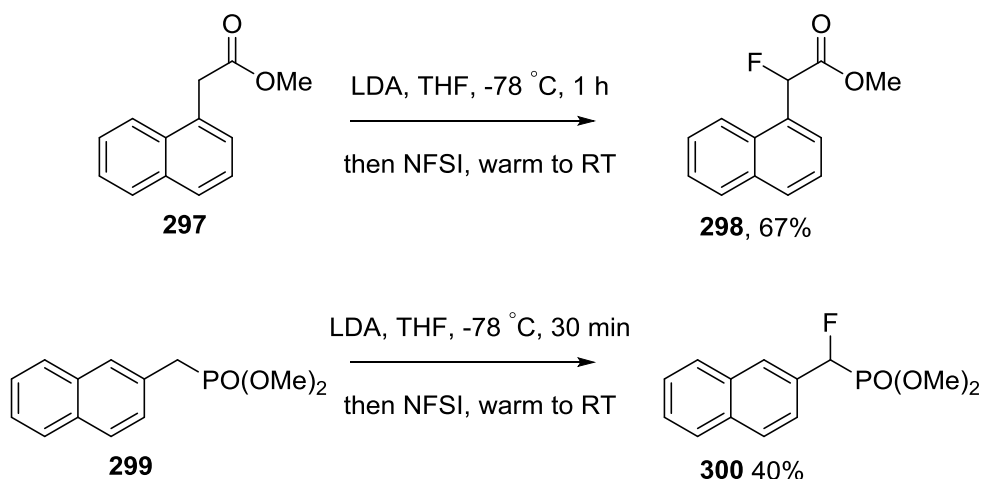
4.5.1 Substrate Synthesis



Scheme 167: Synthesis of Secondary Benzylic Fluorides by Deoxyfluorination a) reaction performed with 1.1 equiv DAST, no TMS-morpholine

Using the modified DAST methodology described earlier the deoxyfluorination of a number of benzylic alcohols was attempted (Scheme 167). The benzylic alcohols were all either commercially available or produced by literature procedures. This was successful for the synthesis of a range of benzylic fluorides (Scheme 167) but for several substrates fluorination was not the predominant reaction. The *i*Pr and tertiary substrates **289** and **290** were unstable to silica gel purification. Benzothiophene substrate **293** could not be isolated pure by chromatography, and when the impure

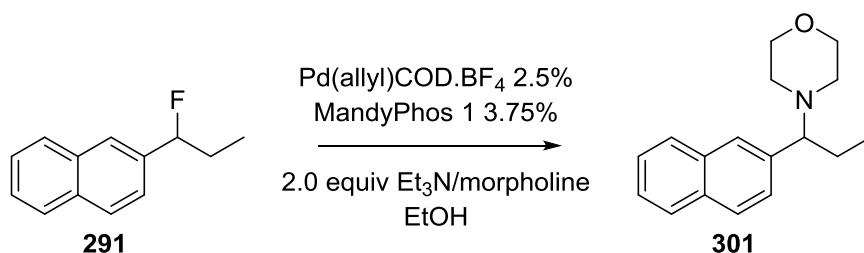
product was stored in plastic decomposed rapidly. The β -ester substrate **292** was not the major product when the TMS-morpholine conditions were used, with the alkene the most abundant molecule in the crude reaction mixture, but when standard DAST conditions were used (1.1 equiv, -78°C , 15 min) the product could be isolated in a low yield.



Scheme 168: Benzylic Fluoride Synthesis by Electrophilic Fluorination

For several other substrates the most direct synthetic route is the electrophilic fluorination of an unsubstituted precursor. This provided the benzylic fluorides **298** and **300** in moderate yields with no complications (Scheme 168).

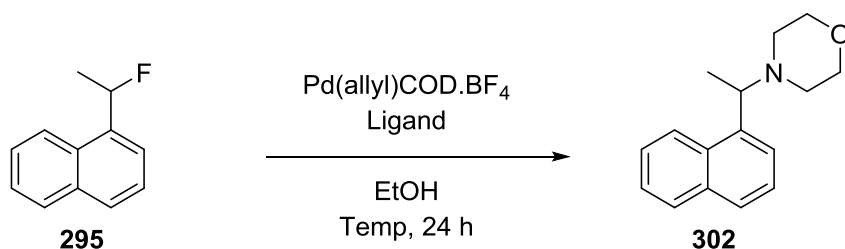
4.5.2 Steric Effects



Entry	Pd load	Ligand	Ligand load	Temp $^{\circ}\text{C}$	Time h	Product ^a	Alkene	Fluoride ee	S
1	2.5	MandyPhos 1	3.75	50	16	21	15	23	3
2	5	dppf	10	50	16	46 (45)	16	-	-
3	2.5	WalPhos 2	3.75	50	16	-	-	-	-
4	5	DPEphos	10	70	60	59	36	-	-

Table 49: Kinetic Resolution of 291, a) Conversion to alkene and amine product as determined by ^1H NMR of the crude mixture

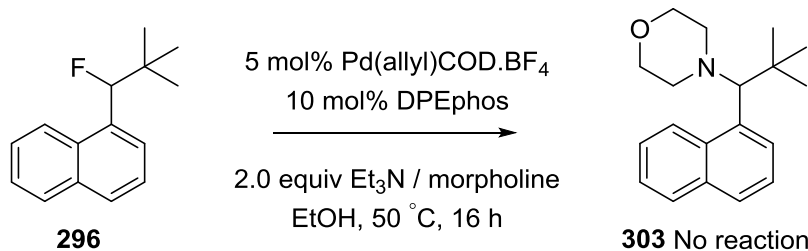
The one carbon homologue of the prototype substrate gave significantly lower reactivity, not reaching full conversion at 50 °C in EtOH in 16 h with dppf (Table 49, Entry 2). Attempted kinetic resolution with the optimum ligands also suffered from lower reactivity, Walphos 2 did not provide an active catalyst complex, and MandyPhos 1 only gave 36% conversion (Entries 1 & 3). The level of enantioselectivity for this reaction was maintained at a level similar to the optimisation substrate.



Entry	Pd loading	Ligand	Ligand loading	Temp	Product ^c	alkene	Fluoride ee	S
1	5	dppf	10	25	26	trace	-	-
2	5	dppf	10	60	75 (65) ^a	25	-	-
3	5	dppe	10	60	60	7	-	-
4	5	dpppr	10	60	64	3	-	-
5	5	DPEphos	10	60	77	23	-	-
6	5	dppbz	10	60	64	12	-	-
7	5	MandyPhos	10	25	26	trace	-	-
8 ^b	2.5	MandyPhos 1	3.75	60	25	17	6	1.2
9 ^b	2.5	Me-DuPhos	3.75	60	0	0	-	-
10 ^b	2.5	MeOBIPHE P	3.75	60	21	17	0	1
11 ^b	2.5	Walphos 2	3.75	60	18	8	9	1.8

Table 50: Kinetic Resolution of 1-Np Substrate 295 a) isolated yield b) 16 h reaction, c) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture

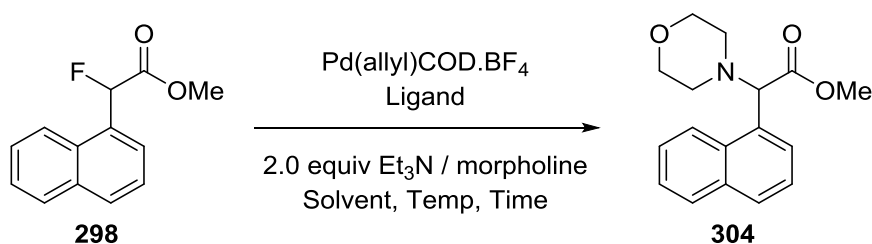
The 1-naphthyl secondary substrate **295** was significantly less reactive than the 2-naphthyl substrate, with reaction at room temperature giving only low conversion to product (Table 50, Entry 1). At 60 °C a range of ligands could catalyse the amination, with DPEphos and dppf again providing the most active catalysts (Entries 2 & 5). Attempts to perform the substitution in the presence of enantiopure ligands gave even slower reactions, and the enantioselectivity of the reaction was very low. These results are troubling for the development of a general kinetic resolution as the catalyst system is clearly highly sensitive to a change of substrate. Unsurprisingly, given the low reactivity of this substrate, the sterically encumbered substrate **296** was unreactive towards substitution (Scheme 169).



Scheme 169: Amination of Sterically Hindered Substrate 296

4.5.3 Functional Group Tolerance

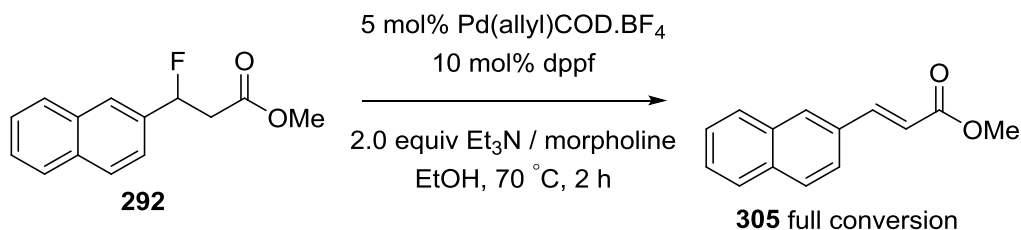
The utility of a reaction depends strongly on the functional group tolerance in the substrate. Given the solvent compatibility of the kinetic resolution as demonstrated in solvent screening, the presence of most remote substituents would not be expected to adversely affect reactivity. The modification of positions adjacent to the reactive centre is more challenging as it imposes greater constraints on the substrate/catalyst interaction.



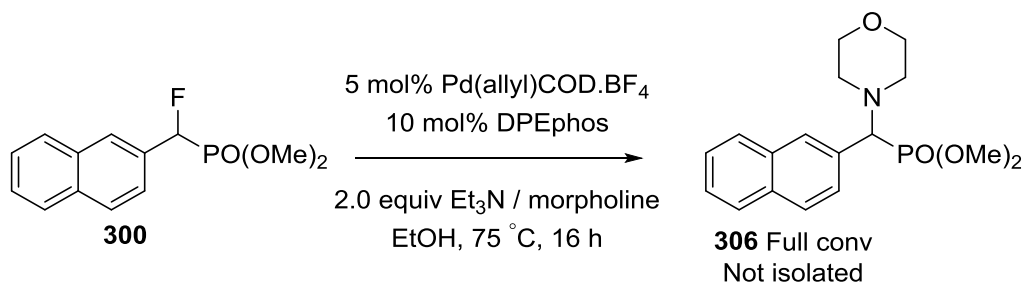
Entry	Pd %	Ligand	Ligand %	Solvent	Temp	Time	Product NMR assay
1	5	dppf	10	EtOH	75	16	19
2	5	dppf	10	MeOH	90	60	59 (54)
3	2.5	MandyPhos 1	3.75	MeOH	90	16	-
4	2.5	WalPhos 2	3.75	MeOH	90	16	-
5	2.5	MeOBIPHEP 1	3.75	MeOH	90	16	-
6	2.5	JosiPhos 5	3.75	MeOH	90	16	-

Table 51: Amination of Ester 298

Substrate **298** bearing an ester functionality is significantly less reactive than other substrates tested. Transesterification was observed on reaction in ethanol, necessitating a change to MeOH as solvent. In order to observe a reaction it was necessary to perform the reaction in a sealed tube at 90 °C. Testing of a range of chiral ligands gave no conversion of the fluoride under forcing conditions (Table 51).

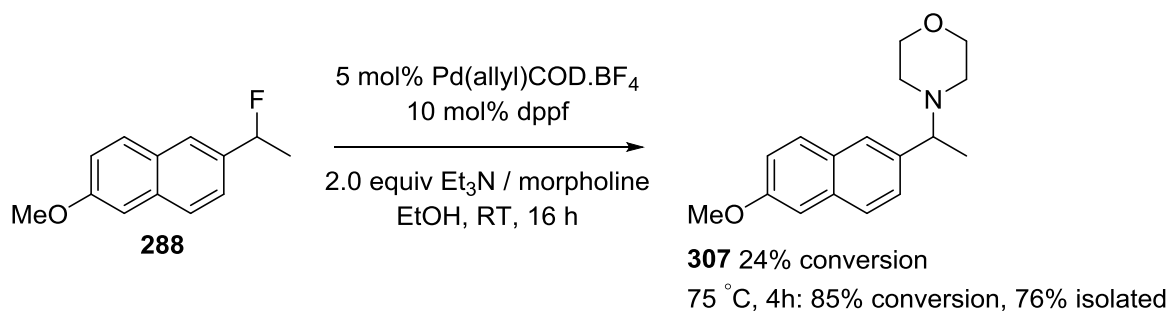
**Scheme 170: Amination of β -Fluoro Ester**

Whilst the α -fluoro ester is unreactive, the β -ester **292** reacts readily under Pd catalysis, giving elimination to give the alkene **305** (Scheme 170). It was not possible to develop a chiral stationary phase HPLC method for this substrate so a kinetic resolution was not attempted.

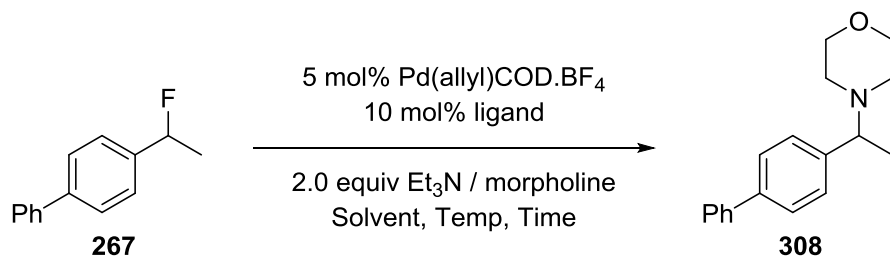
**Scheme 171: Amination of Fluorophosphonate 300**

The fluorophosphonate substrate **300** bears relevance to phosphate isosteric mimics as mentioned in Chapter 1. Substitution by morpholine in EtOH proceeded readily at 75°C, but it was not possible to purify and characterise the product (Scheme 171). At room temperature the substrate was unreactive. An attempt to perform a Suzuki-Miyaura reaction on this substrate was made to produce a less polar product which might be more amenable to purification, but there was no reactivity for this substrate under those conditions.

4.5.4 Aromatic Ring Electronic Effects

Scheme 172: Amination of **288**

Electron rich **288** proved to be less reactive than the unsubstituted naphthalene, requiring longer reaction times and higher temperatures to achieve similar conversions to the unsubstituted naphthalene (Scheme 172). The high electron density in the aromatic ring should favour the C-F activation step, so the reduction in reaction rate may be due to a more stable catalyst intermediate that is less reactive towards nucleophilic attack. The fluoride **288** could not be separated by chiral stationary phase HPLC so a kinetic resolution was not attempted.

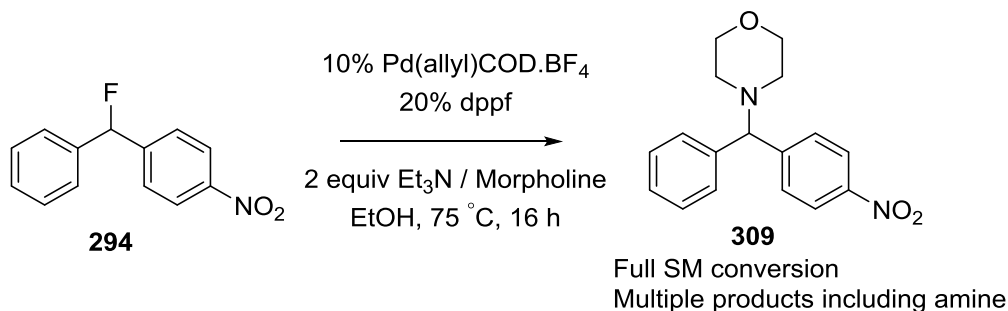


Entry	Ligand	Solvent	Temp °C	Time	Product ^a	Alkene	Fluoride ee	S
1	DPEphos	EtOH	75	4	10	39	-	-
2	dppf	EtOH	75	4	-	43	-	-
3	dppbz	EtOH	75	4	5	7	-	-
4	DPEphos	nPrOH	95	24	-	95 (>95) ^b	-	-
5	MandyPhos 1 ^c	EtOH	75	16	-	7	2	1.8

Table 52: Defluorination of **267**, a) Conversion to alkene and amine product as determined by ¹H NMR of the crude mixture. b) isolated yield. c) 2.5 mol% Pd, 3.75 mol% ligand

It was found that the biphenyl substrate **267** was almost inert to substitution without very forcing conditions (Table 52). Reaction at 95 °C gave the major product as the alkene. The use of an enantiopure ligand gave poor reactivity, so it was not possible to reliably measure an S value. The

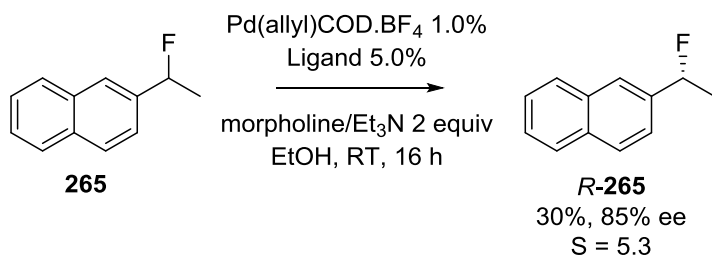
lack of reactivity of this substrate is somewhat unsurprising given the large difference in reactivity between the bicyclic and monocyclic substrates examined in chapter 3, and also the large difference in reactivity between primary and secondary substrates.



Scheme 173: Bisarylmethane Substrate 294

Substrate **294** bearing two monocyclic aromatic rings was more reactive. Reaction with an increased catalyst loading (10 mol% Pd) was required for the reaction to reach full conversion, with no starting material remaining after 16 h at 60 °C (Scheme 173). Multiple products were visible in the crude ¹H NMR, but the predominant peaks were indicative of the product **309** with peaks at 3.70 and 2.40 corresponding to morpholine CH₂O and CH₂N, low resolution mass spectrometry also confirmed the presence of a peak corresponding to [M+H]⁺ for this compound, but it was not possible to isolate the pure product despite multiple attempts. Due to the similarity between substituents at the stereogenic carbon this substrate did not separate on chiral stationary phase HPLC so a kinetic resolution was not attempted.

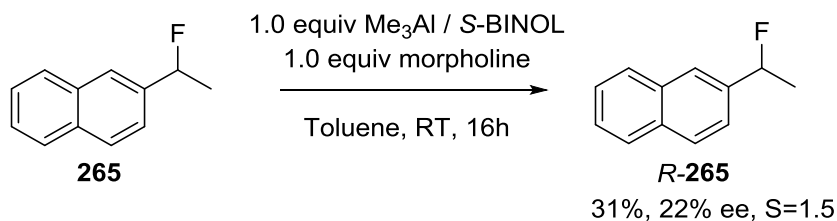
4.6 Conclusions and Further Work



Scheme 174: Kinetic Resolution of Benzyl Fluoride 265

Development of the Pd catalysed nucleophilic displacement of benzylic fluorides provided both mechanistic data supporting the expected mechanism for benzylic fluoride displacement and demonstrated the kinetic resolution of several benzylic fluorides with low selectivity (Scheme 174). As for the reaction of primary substrates, protic solvents were essential for reactivity, and a range of cosolvents were identified which could support the reaction. Ethanol was the optimal solvent for reactivity and reliability. Several ligand families were identified as competent ligands for this kinetic resolution, with the MandyPhos family providing the most active ligands. The kinetic resolution of the prototype substrate could be applied to closely related substrates but monocyclic and functionalised substrates were not competent substrates. The asymmetric synthesis of the amine product of kinetic resolution was achieved in moderate *ee* without optimisation, thus the ligands employed in this study may be useful for the development of enantioselective benzylic functionalisation.

For this methodology to provide useful access to enantiopure benzylic fluorides further optimisation studies are required to identify superior ligands for the kinetic resolution, both to increase selectivity for polycyclic substrates and reactivity for monocyclic substrates. The use of chiral at phosphorus C₂ symmetric ligands¹⁸⁵ might give better transfer of chirality from ligand to substrate given the requirement for a ligand to “reach around” to provide a chiral environment on the opposite side of the metal atom from the ligand itself.

**Scheme 175: Enantioenrichment in Lewis Acid Mediated Defluorination**

There were several attempts made to increase the reactivity of benzylic fluorides towards substitution by the use of Lewis acid complexes with the intention to develop a dual catalyst system. It was not possible to identify a Lewis acid which could promote Pd catalysed fluorination as the complexes investigated either had no effect or were more active for the defluorination than the Pd catalysts. It was possible to demonstrate a small enantioinduction in the Lewis acid mediated defluorination of **265** (Scheme 175) and this may be a productive area of investigation for further studies on the kinetic resolution of benzylic fluorides. There are significant challenges in controlling the reactivity of Lewis acids and in all reactions attempted there were multiple products, so the development of milder and more selective reagents would be required to enable facile access to enantioenriched benzylic fluorides.

Chapter 5: Experimental Procedures and Characterisation Data

5.1 General Information

^1H NMR spectra were recorded in deuterated solvents using Bruker DPX200, DPX400, AV400, AVIII 400 HD nanobay and AVC500 spectrometers, referenced internally to the undeuterated solvent peak. ^{13}C NMR spectra were recorded in deuterated solvents using Bruker DPX200, AV400, AVIII 400 HD nanobay and AVC500 spectrometers, referenced internally to the deuterated solvent peak. ^{19}F spectra were recorded on Bruker AV400, AVIII 400 HD nanobay and AVB500 spectrometers, referenced externally to CFCl_3 . Chemical shifts (δ) are quoted in parts per million (ppm) and coupling constants (J) are measured in hertz (Hz). The following abbreviations are used to describe multiplicities s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, b=broad, m=multiplet. NMR spectra were processed in ACD/SpecManager. Multiplicities are quoted as observed and assignment is given where possible.

High resolution mass spectra were recorded on Micromass GCT (CI) or Autospec-oaTof instruments. IR spectra were recorded as thin films on NaCl disks, as pressed KBr disks, or using a diamond cell ATR attachment, on a Bruker Tensor 27 spectrometer. Prominent absorptions are quoted in wavenumbers (cm^{-1}), and assigned for those identifiable. Melting points were measured on a Griffin melting point apparatus and are uncorrected.

All reactions requiring anhydrous conditions were conducted in oven dried apparatus under an inert atmosphere of argon or nitrogen. Dimethylformamide and dimethylsulfoxide were purchased as anhydrous grades, tetrahydrofuran, diethyl ether, pentane, dichloromethane, toluene and acetonitrile were dried over molecular sieves before eluting through an alumina column; acetone and alcoholic solvents were not dried. Water used in reactions was obtained from a Millipore Milli-Q unit. Small scale screening reactions were run in disposable screw-top vials equipped with conc. nitric acid cleaned Teflon magnetic stirrer bars, which were purged with argon from a balloon for ten seconds before sealing. Reactions were monitored by TLC using Merck Kieselgel 60 F254 plates.

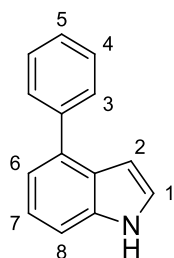
Visualisation of the reaction components was achieved using UV fluorescence (254 nm) and/or potassium permanganate stain. Column chromatography was carried out over Merck silica gel C60 (40-60 μm) or neutral alumina.

5.2 Experimental Data for Chapter 2

4-methyl-*N*-(2-nitrophenyl)benzenesulfonamide¹⁸⁶ and 2-methyl-2-(1-methyl-1*H*-indol-3-yl)propan-1-ol¹⁸⁷ were prepared by literature procedures.

5.2.1 Alcohol Substrate Synthesis for Fluorination-Cyclisation

4-Phenyl-1*H*-indole 108k

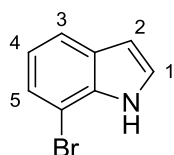


A flask was charged with 4-bromo-1*H*-indole (1.0 g, 5.1 mmol, 1.0 eq.), phenylboronic acid (1.24 g, 10.2 mmol, 2.0 eq.), 1,1'-Bis(diphenylphosphino)ferrocene (0.28 g, 0.5 mmol, 10 mol%), potassium phosphate tribasic (3.25 g, 15.3 mmol, 3.0 eq.), tetrahydrofuran (10 ml) and water (1 ml). The mixture was degassed by cycling the atmosphere between vacuum and argon (three cycles) prior to addition of palladium (II) chloride (89 mg, 0.5 mmol, 10 mol%). The reaction was then brought to reflux and stirred for 4h, at which point the reaction was complete by tlc and electrospray mass spectrometry showed complete consumption of the bromoindole. The reaction mixture was then cooled and filtered through a short plug of silica, eluting with ethyl acetate. The filtrate was concentrated *in vacuo* and then purified by flash column chromatography, eluting with a 4:1 ratio of petrol ether/ethyl acetate, to yield the title compound (0.82 g, 4.2 mmol, 83% yield) as a pale yellow oil.

¹H NMR (CHLOROFORM-*d*, 400MHz): δ = 8.28 (br. s., 1 H, NH), 7.70 - 7.78 (m, 2 H, H3), 7.48 - 7.54 (m, 2 H, H4), 7.37 - 7.45 (m, 2 H, H5 & H6/8), 7.31 (t, $J=7.6$ Hz, 1 H, H7), 7.28 (t, $J=2.9$ Hz, 1

H, *H2*), 7.23 (dd, $J=7.3, 1.0$ Hz, 1 H, *H6/8*), 6.77 ppm (ddd, $J=3.2, 2.0, 0.9$ Hz, 1 H, *H1*); ^{13}C NMR (CHLOROFORM-*d*, 101MHz): $\delta = 136.6, 134.9, 129.2, 128.9, 127.3, 126.5, 124.8, 122.7, 120.2, 110.6, 102.6, 100.0$ ppm.¹⁸⁸

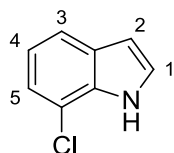
7-Bromo-1*H*-indole 108q



A flask was charged with a 1.0 M solution of vinylmagnesium bromide in tetrahydrofuran (29 ml, 29 mmol, 3.0 equiv) and cooled to -40°C . A solution of 1-bromo-2-nitrobenzene (2.0 g, 9.9 mmol, 1.0 equiv) in tetrahydrofuran (100 ml) was added rapidly with stirring, maintaining an acetone bath temperature of -40°C . The reaction mixture was stirred for 20 minutes at -40°C , then quenched by the addition of a saturated solution of ammonium chloride in water (CAUTION – if an excess of Grignard reagent remains, vigorous evolution of gas will occur) until precipitation was observed. The mixture was allowed to warm to room temperature. Tetrahydrofuran was removed *in vacuo*, the residue was diluted with 1M aqueous HCl, then extracted with 3 portions of diethyl ether. The combined organic extracts were extracted with water, then brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography, eluting with a 10:1 ratio of petrol ether/ethyl acetate, to give the title compound (1.16 g, 5.9 mmol, 60 % yield) as a waxy yellow solid.

^1H NMR (CHLOROFORM-*d*, 400MHz): $\delta = 8.35$ (br. s., 1 H, *NH*), 7.66 (d, $J=7.8$ Hz, 1 H, *H3/5*), 7.43 (d, $J=7.6$ Hz, 1 H, *H3/5*), 7.26 (t, $J=2.8$ Hz, 1 H, *H2*), 7.08 (t, $J=7.7$ Hz, 1 H, *H4*), 6.66 - 6.73 ppm (t, $J=2.5$ Hz, 1 H, *H1*); ^{13}C NMR (CHLOROFORM-*d*, 101MHz): $\delta = 134.5, 128.9, 124.7, 124.2, 120.9, 119.9, 104.6, 103.7$ ppm.¹⁸⁹

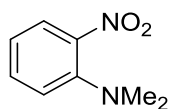
7-Chloro-1*H*-indole 108r



A flask was charged with a 0.7 M solution of vinylmagnesium bromide in tetrahydrofuran (27 ml, 19 mmol, 3.0 equiv) and cooled to $-40\text{ }^{\circ}\text{C}$. A solution of 1-chloro-2-nitrobenzene (1.0 g, 6.4 mmol, 1.0 equiv) in tetrahydrofuran (600 ml) was added rapidly with stirring, maintaining an acetone bath temperature of $-40\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 20 minutes at $-40\text{ }^{\circ}\text{C}$, then quenched by the addition of a saturated solution of ammonium chloride in water (CAUTION – if an excess of Grignard reagent remains, vigorous evolution of gas will occur) until precipitation is observed. The mixture was allowed to warm to room temperature. Tetrahydrofuran was removed *in vacuo*, the residue was diluted with 1M aqueous HCl, then extracted with 3 portions of diethyl ether. The combined organic extracts were extracted with water, then brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography, eluting with a 10:1 ratio of petrol ether/ethyl acetate, to give the title compound (0.54 g, 3.6 mmol, 56 % yield) as a waxy yellow solid.

$^1\text{H NMR}$ (CHLOROFORM- d ,400MHz): δ = 8.39 (br. s., 1 H, NH), 7.60 (d, $J=8.1$ Hz, 1 H, H3/5), 7.20 - 7.31 (m, 2 H, H2 & H3/5), 7.10 (t, $J=8.0$ Hz, 1 H, H4), 6.64 ppm (s., 1 H, H1); $^{13}\text{C NMR}$ (CHLOROFORM- d ,101MHz): δ = 133.1, 129.2, 124.8, 121.3, 120.5, 119.3, 116.5, 103.6 ppm.¹⁹⁰

***N,N*-dimethyl-2-nitroaniline 129**

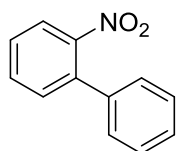


Sodium hydride (as 60% dispersion in mineral oil, 1.2 g, 30 mmol, 2.1 equiv) was placed in a flask and washed with pentane. THF (20 ml) was added and the suspension cooled to $0\text{ }^{\circ}\text{C}$. 2-nitroaniline (2.0 g, 15 mmol) was added slowly as a solution in THF (5 ml). Methyl iodide (1.9 ml, 30 mmol, 2.1 equiv) was added as a solution in THF (5 ml) and the mixture stirred at $0\text{ }^{\circ}\text{C}$ for 40 minutes. The

reaction was quenched by the addition of sat. aq. NH_4Cl solution, THF was removed *in vacuo* and the aqueous mixture extracted with Et_2O . The combined extracts were dried (Na_2SO_4) and the solvent removed to give the product as a brown liquid (2.4 g, quantitative).

$^1\text{H NMR}$ (CHLOROFORM- d ,400MHz): $\delta = 7.62$ (d, $J=8.3$ Hz, 1 H), 7.25 (t, $J=8.1$ Hz, 1 H), 6.88 (d, $J=8.6$ Hz, 1 H), 6.67 (t, $J=8.2$ Hz, 1 H), 2.74 ppm (s, 6 H); $^{13}\text{C NMR}$ (CHLOROFORM- d ,101MHz): $\delta = 162.5, 146.1, 133.2, 126.7, 118.1, 117.9, 42.4$ ppm.¹⁹¹

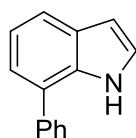
2-Nitro-1,1'-biphenyl 123



1-Chloro-2-nitrobenzene (160 mg, 1.0 mmol), $\text{Pd}(\text{OAc})_2$ (11 mg, 0.05 mmol, 5 mol%), SPhos (41 mg, 0.10 mmol, 10 mol%), $\text{PhB}(\text{OH})_2$ (240 mg, 2.0 mmol, 2.0 equiv) and K_3PO_4 (630 mg, 3.0 mmol, 3.0 equiv) were dissolved in THF (5 ml). The mixture was degassed by 3 vacuum/nitrogen cycles, then heated at reflux for 16 h. The mixture was cooled, filtered through a plug of silica, eluting with EtOAc, then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica, hexane/EtOAc 20:1) to give the product as a yellow solid (170 mg, 0.85 mmol, 85%).

$^1\text{H NMR}$ (CHLOROFORM- d ,400MHz): $\delta = 7.87$ (dd, $J=8.1, 1.0$ Hz, 1 H), 7.62 (dd, $J=7.6, 1.2$ Hz, 1 H), 7.38 - 7.54 (m, 6 H), 7.30 - 7.37 ppm (m, 2 H); $^{13}\text{C NMR}$ (CHLOROFORM- d ,101MHz): $\delta = 149.3, 137.3, 136.3, 132.2, 131.9, 128.7, 128.2, 128.1, 127.9, 124.0$ ppm¹⁹²

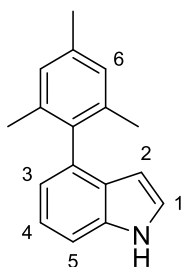
7-Phenyl-1H-indole 108s



7-Chloroindole (540 mg, 3.5 mmol), Pd(OAc)₂ (40 mg, 0.05 mmol, 5 mol%), SPhos (140 mg, 0.35 mmol, 10 mol%), PhB(OH)₂ (0.86 g, 7.1 mmol, 2.0 equiv) and K₃PO₄ (2.20 g, 10 mmol, 3.0 equiv) were dissolved in THF (20 ml). The mixture was degassed by 3 vacuum/nitrogen cycles, then heated at reflux for 20 h. The mixture was cooled, filtered through a plug of silica, eluting with EtOAc, then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica, pet ether/EtOAc 12:1) to give the product as a brown solid (370 mg, 1.9 mmol, 55%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 8.28 (br. s., 1 H), 7.49 - 7.59 (m, 3 H), 7.36 - 7.45 (m, 2 H), 7.26 - 7.34 (m, 1 H), 7.10 - 7.15 (m, 2 H), 7.04 - 7.10 (m, 1 H), 6.53 ppm (dd, *J*=3.2, 2.0 Hz, 1 H);
¹³C NMR (CHLOROFORM-d,101MHz): δ = 139.2, 133.7, 129.1, 128.2, 127.4, 125.6, 124.3, 121.9, 121.2, 120.3, 120.0, 103.0 ppm¹⁹³

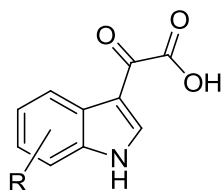
4-Mesityl-1H-indole 108m



4-Bromoindole (1.0 g, 5.1 mmol), mesitylboronic acid (0.92 g, 5.6 mmol, 1.1 equiv), Pd(OAc)₂ (29 mg, 0.013 mmol, 2.5 mol%), SPhos (110 mg, 0.26 mmol, 5 mol%), and K₃PO₄ (3.3g, 15 mmol, 3.0 equiv) were added to dioxane. The mixture was degassed by three vacuum/nitrogen cycles, then heated at reflux for 16 h. The mixture was cooled and passed through a plug of silica eluting with EtOAc. The solvent was removed and the residue purified by flash chromatography (silica, petrol ether/EtOAc 4:1) to give the product as a brown solid (210 mg, 0.91 mmol, 18% yield).

¹H NMR (CHLOROFORM-d ,400MHz): δ = 8.20 (br. s., 1 H, NH), 7.40 (d, *J*=8.1 Hz, 1 H, H3), 7.27 (t, *J*=7.5 Hz, 1 H, H4), 7.17 (t, *J*=2.5 Hz, 1 H, H1), 7.01 (s, 2 H, H6), 6.92 (d, *J*=7.1 Hz, 1 H), 6.15 (br. s., 1 H, H2), 2.40 (s, 3 H, ArCH₃), 2.00 ppm (s, 6 H, 2 x ArCH₃); ¹³C NMR (CHLOROFORM-d ,101MHz): δ = 137.3, 136.5, 136.3, 135.7, 133.6, 127.9, 127.2, 123.9, 122.0, 120.4, 109.5, 102.2,

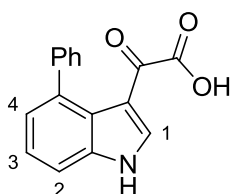
21.1, 20.3 ppm; **IR**: 3419 (N-H stretch), 3393 (N-H stretch), 1426, 1349 cm^{-1} ; **mp** 136 °C; **HRMS** (Probe EI+) m/z calc'd for $[\text{M}]^+$ $\text{C}_{17}\text{H}_{17}\text{N}$: 235.1361, found 235.1372.



General Procedure A: reaction of indole with oxalyl chloride to give 2-(1*H*-indol-3-yl)-2-oxoacetic acid

A solution of substituted indole (1 mmol, 1 equiv) in diethyl ether (4 ml) was cooled to 0 °C. Oxalyl chloride (0.10 ml, 1.2 mmol, 1.2 equiv) was added dropwise with stirring, and the reaction mixture was brought to reflux. The reaction was stirred at reflux for a time between 1 and 2 hours, then cooled to room temperature. Saturated aqueous sodium bicarbonate solution (2 ml) was then added (CAUTION – vigorous evolution of gas) and the mixture brought to reflux for a further 30 minutes. The mixture was then cooled, the aqueous layer was made basic by the addition of 1M aqueous sodium hydroxide solution and the organic layer was separated and discarded. The aqueous layer was then made acidic by the addition of 1M aqueous HCl, and extracted with three portions of ethyl acetate. The combined organic portions were then washed with brine, dried over anhydrous sodium sulfate, and dried *in vacuo* to yield the 2-(1*H*-indol-3-yl)-2-oxoacetic acid.

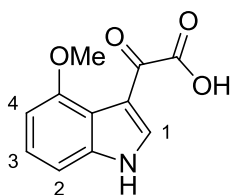
2-Oxo-2-(4-phenyl-1*H*-indol-3-yl)acetic acid 1091



The compound was prepared according to general procedure A, with a time for the first reflux of 2 h. The compound (220 mg, 0.82 mmol, 82 % yield) was isolated as a yellow-brown amorphous solid.

¹H NMR (MeOD ,400MHz): δ = 8.40 (s, 1 H, *H1*), 7.51 (d, $J=8.1$ Hz, 1 H, *H2/4*), 7.26 - 7.40 (m, 6 H, *Ph*, *H3*), 7.18 ppm (d, $J=7.3$ Hz, 1 H, *H2/4*); **¹³C NMR** (METHANOL-*d*₄ ,101MHz): δ = 179.5, 166.0, 143.3, 139.4, 138.6, 137.2, 128.8, 128.8, 128.8, 127.5, 126.6, 125.4, 124.2, 122.9, 111.4 ppm; **IR** (thin film): 3264 (O-H stretch), 1730 (C=O stretch) cm^{-1} ; **mp**: 98°C; **HRMS** (ESI-) *m/z* calc'd for $[\text{M-H}]^- \text{C}_{16}\text{H}_{10}\text{NO}_3$: 246.0666, found 246.0665.

2-Oxo-2-(4-methoxy-1*H*-indol-3-yl)acetic acid 109j

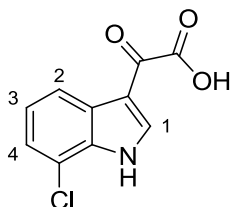


The compound was prepared according to general procedure A, with a time for the first reflux of 1 h.

The compound (220 mg, 0.98 mmol, 98 % yield) was isolated as a green crystalline solid.

¹H NMR (MeOD ,400MHz): δ = 8.15 (s, 1 H, *H1*), 7.22 (t, $J=8.0$ Hz, 1 H, *H3*), 7.11 (d, $J=8.1$ Hz, 1 H, *H2/4*), 6.75 (d, $J=7.8$ Hz, 1 H, *H2/4*), 3.91 ppm (s, 3 H, OCH_3); **¹³C NMR** (MeOD ,101MHz): δ = 183.8, 167.9, 154.3, 139.2, 135.5, 125.0, 115.3, 113.8, 105.6, 103.5, 54.5 ppm; **IR** (thin film): 3252 (O-H stretch), 1717 (C=O stretch) cm^{-1} ; **mp** 145°C; **HRMS** (ESI-) *m/z* calc'd for $[\text{M-H}]^- \text{C}_{11}\text{H}_8\text{NO}_4$: 218.0459, found 218.0460.

2-Oxo-2-(7-chloro-1*H*-indol-3-yl)acetic acid 109r

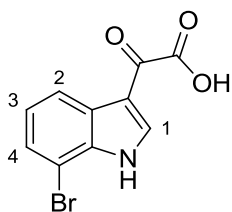


The compound was prepared according to general procedure A, with a time for the first reflux of 1 h.

The compound (210 mg, 0.95 mmol, 95 % yield) was isolated as a yellow crystalline solid.

¹H NMR (MeOD ,400MHz): δ = 8.58 (s, 1 H, *H1*), 8.24 (d, $J=7.6$ Hz, 1 H, *H2/4*), 7.32 (d, $J=7.3$ Hz, 1 H, *H2/4*), 7.26 ppm (t, $J=7.8$ Hz, 1 H, *H3*); **¹³C NMR** (MeOD ,101MHz): δ = 180.0, 164.4, 138.8, 134.2, 128.3, 123.9, 123.6, 120.6, 117.6, 114.1 ppm; **IR** (KBr Disk): 3247 (O-H stretch), 1740 (C=O stretch), 1717 (C=O stretch) cm^{-1} ; **mp** 195°C decomposed; **HRMS** (ESI-) m/z calc'd for $[\text{M-H}]^-$ $\text{C}_{10}\text{H}_5^{35}\text{ClNO}_3$: 221.9963, found 221.9961.

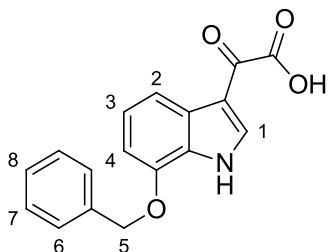
2-Oxo-2-(7-bromo-1*H*-indol-3-yl)acetic acid 109q



The compound was prepared according to general procedure A, with a time for the first reflux of 1 h. The compound (210 mg, 0.80 mmol, 80 % yield) was isolated as a yellow amorphous solid.

¹H NMR (MeOD ,400MHz): δ = 8.57 (s, 1 H, *H1*), 8.27 (d, $J=8.1$ Hz, 1 H, *H2/4*), 7.45 (d, $J=7.8$ Hz, 1 H, *H2/4*), 7.18 ppm (t, $J=8.0$ Hz, 1 H, *H3*); **¹³C NMR** (MeOD ,101MHz): δ = 180.2, 164.4, 138.7, 135.8, 128.1, 126.7, 124.3, 121.2, 114.2, 105.2 ppm; **IR** (KBr Disc): 3251 (O-H stretch), 1739 (C=O stretch), 1717 (C=O stretch) cm^{-1} ; **mp** 215°C decomposed; **HRMS** (ESI-) m/z calc'd for $[\text{M-H}]^-$ $\text{C}_{10}\text{H}_5^{79}\text{BrNO}_3$: 265.9458, found 265.9452.

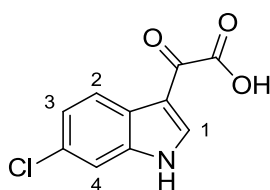
2-Oxo-2-(7-(benzyloxy)-1*H*-indol-3-yl)acetic acid 109t



The compound was prepared according to general procedure A, with a time for the first reflux of 1 h. The compound (270 mg, 0.92 mmol, 92 % yield) was isolated as a yellow amorphous solid.

¹H NMR (MeOD ,400MHz): δ = 8.44 (s, 1 H, *H1*), 7.87 (d, *J*=8.1 Hz, 1 H, *H2/4*), 7.54 (d, *J*=7.3 Hz, 2 H, *H6*), 7.36 - 7.44 (m, 2 H, *H7*), 7.34 (m 1 H, *H8*), 7.18 (t, *J*=8.0 Hz, 1 H, *H3*), 6.91 (d, *J*=7.8 Hz, 1 H, *H2/4*), 5.26 ppm (s, 2 H, *H5*); **¹³C NMR** (METHANOL-*d*₄ ,101MHz): δ = 180.1, 164.9, 146.1, 137.6, 137.4, 128.5, 128.3, 128.1, 127.9, 127.5, 123.9, 114.6, 113.8, 105.9, 70.3 ppm; **IR** (thin film) 3258 (O-H stretch), 1741 (C=O stretch) cm^{-1} ; **mp** 184°C decomposed; **HRMS** (ESI-) *m/z* calc'd for [M-H]⁻ C₁₇H₁₂NO₄: 294.0772, found 294.0774.

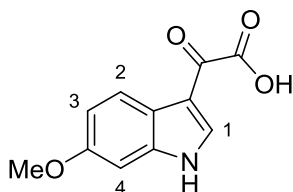
2-Oxo-2-(6-chloro-1*H*-indol-3-yl)acetic acid 109n



The compound was prepared according to general procedure A, with a time for the first reflux of 1 h. The compound (190 mg, 0.86 mmol, 86% yield) was isolated as a yellow crystalline solid.

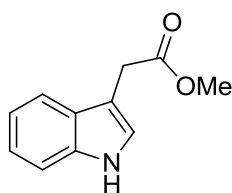
¹H NMR (MeOD ,400MHz): δ = 8.56 (s, 1 H, *H1*), 8.25 (d, *J*=8.6 Hz, 1 H, *H2*), 7.53 (d, *J*=1.8 Hz, 1 H, *H4*), 7.27 ppm (dd, *J*=8.6, 1.8 Hz, 1 H, *H3*); **¹³C NMR** (DMSO-*d*₆ ,101MHz): δ = 181.6, 165.8, 139.7, 138.0, 129.0, 125.2, 123.8, 123.3, 113.3, 113.1 ppm; **IR** (KBr Disc): 3226 (O-H stretch), 1713 (C=O stretch) cm^{-1} ; **mp** 260°C decomposed; **HRMS** (ESI-) *m/z* calc'd for [M-H]⁻ C₁₀H₅³⁵ClNO₃: 221.9963, found 221. 9961.

2-(6-Methoxy-1*H*-indol-3-yl)-2-oxoacetic acid 109p



The compound was according to general procedure A, with a time for the first reflux of 1 h. The compound (1.50 g, 6.8 mmol, 99% yield) was isolated as a yellow amorphous solid.

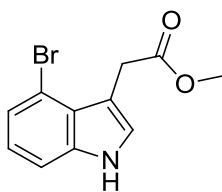
¹H NMR (DMSO-d₆, 400MHz): δ = 13.75 (br. s., 1 H, OH), 12.28 (br. s., 1 H, NH), 8.20 (d, $J=2.9$ Hz, 1 H, H1), 7.94 (d, $J=8.8$ Hz, 1 H, H2), 6.96 (d, $J=2.0$ Hz, 1 H, H4), 6.81 (dd, $J=8.8, 2.2$ Hz, 1 H, H3), 3.71 ppm (s, 3 H, OCH₃); **¹³C NMR** (DMSO-d₆, 101MHz): δ = 180.7, 165.3, 156.9, 137.7, 137.1, 121.7, 119.4, 112.4, 112.3, 95.8, 55.3 ppm; **IR**: 3168 (N-H stretch), 1733 (C=O stretch), 1610, 1397, 1143 cm⁻¹; **mp** 220 °C decomposed; **HRMS** (ESI -) m/z calc'd for [M-H]⁻ C₁₁H₈NO₄: 218.0459, found: 218.0459.



General Procedure B: reduction and esterification of 2-oxo-2-(1H-indol-3-yl)acetic acid

2-oxo-2-(1H-indol-3-yl)acetic acid (190 mg, 1.0 mmol, 1.0 equiv) was dissolved in 2-ethoxy-ethanol (2ml) and hydrazine monohydrate (0.24 ml, 5 mmol, 5.0 equiv) (CAUTION – carcinogen) was added. The solution was heated to 60 °C and stirred for 1 h, at which time sodium methoxide (540 mg, 10 mmol, 10 equiv) was added and the reaction mixture brought to reflux with an oil bath temperature of 150 °C (NOTE: use of an efficient condenser required). The reaction was stirred at reflux for 2 h, then cooled to room temperature. The mixture was poured into water, acidified with 1M aqueous HCl, and extracted with five portions of ethyl acetate. The combined organic portions were washed with three portions of water, then once with brine, before being dried over anhydrous sodium sulfate and the solvent removed *in vacuo*. The residue was dissolved in anhydrous methanol and cooled to 0 °C, chlorotrimethylsilane (0.38 ml, 3.0 mmol, 3.0 equiv) was added and the mixture stirred at room temperature for 4 h. The solvent and excess chlorotrimethylsilane was removed *in vacuo*, and the residue purified by flash column chromatography, eluting with a mixture of petrol ether and ethyl acetate, to yield the methyl 2-(1H-indol-3-yl)acetate.

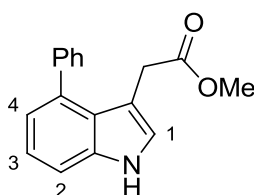
Methyl 2-(4-bromo-1H-indol-3-yl)acetate 111k



Following general procedure A, 4-bromoindole (1.0 g, 5.1 mmol) reacted with oxalyl chloride (0.80 g, 6.1 mmol, 1.2 equiv) to give the product as an impure purple solid (0.30 g, 1.1 mmol, 22%) which was used unpurified in the next step. Following general procedure B gave a tan solid (140 mg, 0.51 mmol, 3 steps, 10%). The eluent for chromatography was 4 parts petrol ether to 1 part ethyl acetate.

$^1\text{H NMR}$ (MeOD, 400MHz): δ = 7.35 (d, $J=8.1$ Hz, 1 H), 7.22 (s, 1 H), 7.16 (d, $J=7.6$ Hz, 1 H), 6.96 (t, $J=7.8$ Hz, 1 H), 4.02 (s, 2 H), 3.71 ppm (s, 3 H); **LRMS** (ESI+ MS) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{11}\text{H}_{11}^{79}\text{BrNO}_2$: 290.0, found 290.0.¹⁹⁴

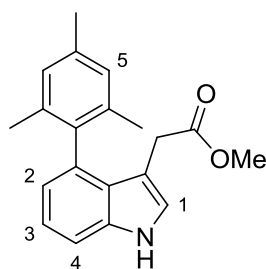
Methyl 2-(4-phenyl-1H-indol-3-yl)acetate 111l



The compound was prepared according to general procedure B to give a white crystalline solid (240 mg, 0.92 mmol, 92 % yield). The eluent for chromatography was 4 parts petrol ether to 1 part ethyl acetate.

$^1\text{H NMR}$ (400 MHz, CHLOROFORM- d) δ = 8.33 (br. s., 1 H, *NH*), 7.39 - 7.45 (m, 5 H, *Ph*), 7.31 (d, $J=8.1$ Hz, 1 H, *H2/4*), 7.23 (t, $J=7.6$ Hz, 1 H, *H3*), 6.95 - 7.03 (m, 2 H, *H1* & *H2/4*), 3.49 (s, 3 H, *OCH*₃), 3.40 (s, 2 H, *ArCH*₂*CO*₂*Me*) ppm; $^{13}\text{C NMR}$ (CHLOROFORM- d , 101MHz): δ = 172.8, 141.4, 136.7, 135.4, 129.6, 127.6, 126.9, 124.6, 124.4, 121.7, 121.4, 110.5, 108.4, 51.6, 32.3 ppm; **IR**: 3405 (N-H stretch), 1727 (C=O stretch) cm^{-1} ; **mp** 109°C; **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{17}\text{H}_{15}\text{NO}_2$: 288.0995, found 288.0994.

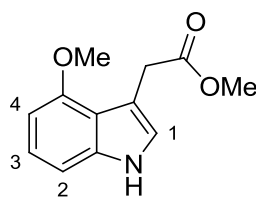
Methyl 2-(4-mesityl-1H-indol-3-yl)acetate 111m



The compound was prepared from 4-mesitylindole without isolating the oxo-acid, using general procedure A (2 h reflux) followed directly by general procedure B on the unpurified material to give a pale brown amorphous solid (94 mg, 0.31 mmol, 28% yield). The eluent for chromatography was 6 parts petrol ether to 1 part ethyl acetate.

¹H NMR (CHLOROFORM-*d*, 400MHz): δ = 8.17 (br. s., 1 H, NH), 7.34 (d, $J=8.1$ Hz, 1 H, H2/4), 7.23 (t, $J=7.6$ Hz, 1 H, H3), 7.08 (s, 1 H, H1), 6.95 (s, 2 H, H5), 6.82 (d, $J=7.1$ Hz, 1 H, H2/4), 3.49 (s, 3 H, OCH₃), 3.13 (s, 2 H, ArCH₂CO₂Me), 2.37 (s, 3 H, ArCH₃), 1.92 ppm (s, 6 H, 2 x ArCH₃); **¹³C NMR** (CHLOROFORM-*d*, 101MHz): δ = 172.4, 140.9, 137.0, 136.8, 136.6, 133.3, 127.6, 124.7, 123.8, 122.2, 120.8, 109.9, 108.9, 51.3, 30.8, 21.1, 20.4 ppm; **IR**: 3743 (N-H stretch), 1734 (C=O stretch), 1265 cm⁻¹; **mp** 146 °C; **HRMS** (ESI+) m/z calc'd for [M+Na]⁺ C₂₀H₂₁NO₂: 330.1465, found: 330.1456.

Methyl 2-(4-methoxy-1H-indol-3-yl)acetate 111j

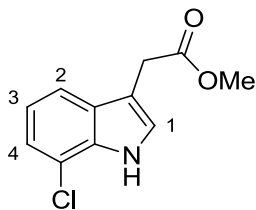


The compound was prepared according to general procedure B to give a white crystalline solid (130 mg, 0.57 mmol, 57% yield). The eluent for chromatography was 4 parts petrol ether to 1 part ethyl acetate.

¹H NMR (CHLOROFORM-*d*, 400MHz): δ = 8.14 (br. s., 1 H, NH), 7.08 (t, $J=8.1$ Hz, 1 H, H3), 6.92 (d, $J=8.3$ Hz, 1 H, H2/4), 6.90 (s, 1 H, H1), 6.49 (d, $J=7.6$ Hz, 1 H, H2/4), 3.97 (s, 2 H, ArCH₂CO₂Me), 3.80 (s, 3 H, OCH₃).

Me), 3.88 (s, 3 H, OCH₃), 3.74 ppm (s, 3 H, OCH₃); ¹³C NMR (CHLOROFORM-d ,101MHz): δ = 173.5, 154.6, 137.8, 123.0, 121.9, 117.4, 108.6, 104.7, 99.6, 55.1, 51.8, 32.5 ppm; **IR**: 3332 (N-H stretch), 1730 (C=O stretch) cm⁻¹; **mp** 82°C; **HRMS** (ESI+) m/z calc'd for [M+Na]⁺ C₁₂H₁₃NO₃: 242.0788, found 242.0788.

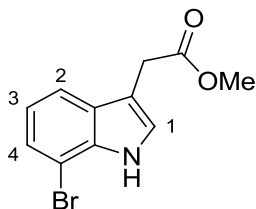
Methyl 2-(7-chloro-1H-indol-3-yl)acetate 111r



The compound was prepared according to general procedure B to give an off white crystalline solid (190 mg, 0.86 mmol, 86 % yield). The eluent for chromatography was 5 parts petrol ether to 1 part ethyl acetate.

¹H NMR (CHLOROFORM-d ,400MHz): δ = 8.33 (br. s., 1 H, NH), 7.53 (d, *J*=8.1 Hz, 1 H), 7.22 (d, *J*=7.6 Hz, 1 H, H_{2/4}), 7.18 (d, *J*=2.3 Hz, 1 H, H₁), 7.09 (t, *J*=7.8 Hz, 1 H, H₃), 3.79 (s, 2 H, ArCH₂CO₂Me), 3.72 ppm (s, 3 H, OCH₃); ¹³C NMR (CHLOROFORM-d ,101MHz): δ = 172.2, 133.4, 123.7, 121.6, 120.5, 117.6, 116.7, 109.7, 99.6, 52.1, 31.2 ppm; **IR**: 3359 (N-H stretch), 1730 (C=O stretch) cm⁻¹; **mp** 69°C; **HRMS** (ESI+) m/z calc'd for [M+Na]⁺ C₁₁H₁₀³⁵ClNO₂: 246.0292, found 246.0289.

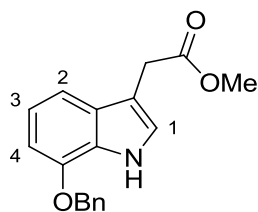
Methyl 2-(7-bromo-1H-indol-3-yl)acetate 111q



The compound was prepared according to general procedure B to give an off white crystalline solid (200 mg, 0.75 mmol, 75 % yield). The eluent for chromatography was 6 parts petrol ether to 1 part ethyl acetate.

¹H NMR (CHLOROFORM-d ,400MHz): δ = 8.33 (br. s., 1 H, NH), 7.57 (d, J =7.8 Hz, 1 H, H2/4), 7.37 (d, J =7.6 Hz, 1 H, H2/4), 7.22 (d, J =2.3 Hz, 1 H, H1), 7.01 - 7.06 (t, J =7.8 Hz, 1 H, H3), 3.78 (s, 2 H, ArCH₂CO₂Me), 3.72 ppm (s, 3 H, OCH₃); **¹³C NMR** (CHLOROFORM-d ,101MHz): δ = 172.2, 134.8, 128.4, 124.6, 123.7, 120.9, 118.2, 109.7, 104.8, 52.1, 31.2 ppm; **IR**: 3359 (N-H stretch), 1716 (C=O stretch) cm⁻¹; **mp** 75°C; **HRMS** (ESI+) m/z calc'd for [M+Na]⁺ C₁₁H₁₀⁷⁹BrNO₂: 289.9787, found 289.9786.

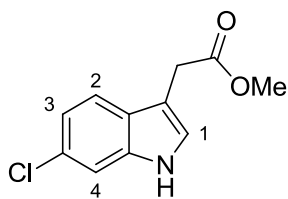
Methyl 2-(7-(benzyloxy)-1H-indol-3-yl)acetate 111t



The compound was prepared according to general procedure B to give an off white crystalline solid (210 mg, 0.72 mmol, 72 % yield). The eluent for chromatography was 6 parts petrol ether to 1 part ethyl acetate.

¹H NMR (CHLOROFORM-d ,400MHz): δ = 8.36 (br. s., 1 H, NH), 7.46 - 7.53 (m, 2 H, Ph), 7.34 - 7.46 (m, 3 H, Ph), 7.26 (d, J =7.6 Hz, 1 H, H2/4), 7.14 (d, J =2.0 Hz, 1 H, H1), 7.07 (t, J =7.8 Hz, 1 H, H3), 6.75 (d, J =7.8 Hz, 1 H, H2/4), 5.22 (s, 2 H, OCH₂Ph), 3.79 (s, 2 H, ArCH₂CO₂Me), 3.72 ppm (s, 3 H, OCH₃); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 172.5, 145.4, 137.0, 128.7, 128.6, 128.1, 127.8, 126.8, 122.6, 120.1, 111.8, 108.8, 103.3, 70.2, 51.9, 31.3 ppm; **IR**: 3583 (N-H stretch), 1731 (C=O stretch) cm⁻¹; **mp** 81°C; **HRMS** (ESI+) m/z calc'd for [M+Na]⁺ C₁₁H₁₀BrNO₂: 318.1101, found 318.1101.

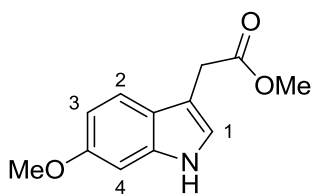
Methyl 2-(6-chloro-1H-indol-3-yl)acetate 111n



The compound was prepared according to general procedure B to give an orange crystalline solid (190 mg, 0.85 mmol, 85 % yield). The eluent for chromatography was 6 parts petrol ether to 1 part ethyl acetate.

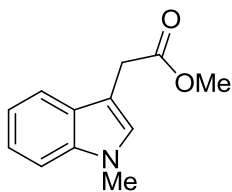
¹H NMR (CHLOROFORM-*d*, 400MHz): δ = 8.15 (br. s., 1 H, *NH*), 7.52 (d, $J=8.3$ Hz, 1 H, *H2/3*), 7.29 - 7.35 (d, $J=1.0$ Hz, 1 H, *H1/4*), 7.07 - 7.15 (m, 2 H, *H2/3* & *H1/4*), 3.77 (s, 2 H, ArCH₂CO₂Me), 3.72 ppm (s, 3 H, OCH₃); **¹³C NMR** (CHLOROFORM-*d*, 101MHz): δ = 172.4, 136.4, 128.2, 125.8, 123.7, 120.5, 119.8, 111.1, 108.6, 52.1, 31.0 ppm; **IR**: 3374 (N-H stretch), 1728 (C=O stretch) cm⁻¹; **mp** 80°C; **HRMS** (ESI+) *m/z* calc'd for [M+Na]⁺ C₁₁H₁₀³⁵ClNO₂: 246.0292, found 246.0292.

Methyl 2-(6-methoxy-1*H*-indol-3-yl)acetate 111p

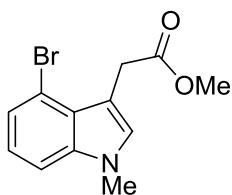


The compound was prepared according to general procedure B to give a green oil (70 mg, 0.32 mmol, 5 % yield). The eluent for chromatography was 4 parts hexane to 1 part ethyl acetate.

¹H NMR (CHLOROFORM-*d*, 400MHz): δ = 8.03 (br. s., 1 H, *NH*), 7.49 (d, $J=8.3$ Hz, 1 H, *H2*), 7.01 (d, $J=2.2$ Hz, 1 H, *H4*), 6.81 (s, 1 H, *H1*), 6.80 - 6.85 (m, 1 H, *H3*), 3.84 (s, 3 H, OCH₃), 3.76 (s, 2 H, ArCH₂CO₂Me), 3.72 ppm (s, 3 H, OCH₃); **¹³C NMR** (CHLOROFORM-*d*, 101MHz): δ = 172.6, 156.6, 136.8, 121.8, 121.6, 119.4, 109.7, 108.3, 94.6, 55.6, 51.9, 31.2 ppm; **IR**: 3404, 1730, 1630, 1261, 1158 cm⁻¹; **HRMS** (ESI+) *m/z* calc'd for [M+Na]⁺ C₁₂H₁₃NNaO₃: 242.0788 found: 242.0785.

**General procedure C: N-methylation of methyl 2-(1H-indol-3-yl)acetate**

A rigorously dried flask was charged with sodium hydride (60% suspension in mineral oil) (48 mg, 1.2 mmol, 1.2 equiv) and anhydrous N,N-dimethylformamide (2 ml) was added with care. The flask was cooled to 0°C and solution of the starting material (1.0 mmol, 1.0 equiv) in N,N-dimethylformamide (1 ml) was added dropwise. The reaction was stirred for 1h at 0°C and then a solution of iodomethane (0.07 ml, 1.2 mmol, 1.2 equiv) in N,N-dimethylformamide (1 ml) was added dropwise. The reaction was then stirred for a further 2 h, before being quenched by the addition of water. The mixture was then poured into water and extracted with 3 portions of ethyl acetate. The combined organic portions were washed with three portions of water, then brine, then dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography, eluting with a ratio of 6 parts petrol ether to one part ethyl acetate.

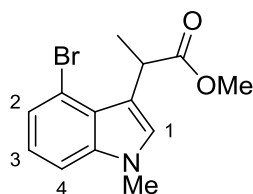
Methyl 2-(4-bromo-1-methyl-1H-indol-3-yl)acetate 112k

The title compound was prepared according to general procedure C to yield 27 mg (0.10 mmol, 18%) of product as a brown oil.

¹H NMR (CHLOROFORM-d,400MHZ): δ = 7.12 - 7.20 (m, 2 H, ArH), 6.93-6.97 (m, 2 H, ArH), 3.97 (s, 2 H, ArCH₂CO₂Me), 3.66 (s, 3 H, OCH₃), 3.66 ppm (s, 3 H, NCH₃); ¹³C NMR (CHLOROFORM-d,101MHZ): δ = 173.0, 138.2, 129.7, 125.7, 123.5, 122.5, 114.2, 108.7, 107.7,

52.0, 32.9, 31.7 ppm; **IR**: 1736 (C=O stretch), 1458, 1261 cm^{-1} ; **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+ \text{C}_{12}\text{H}_{12}^{79}\text{BrNO}_2$: 303.9944, found: 303.9944.

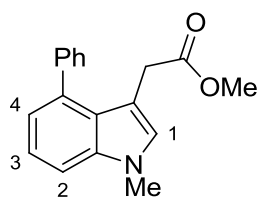
Methyl 2-(4-bromo-1-methyl-1H-indol-3-yl)propanoate 113



Observed as a byproduct in the alkylation of methyl 2-(4-bromo-1H-indol-3-yl)acetate following general procedure C with 2 equivalents of both NaH and MeI. Product was a brown oil (230 mg, 0.76 mmol, 79%).

^1H NMR (CHLOROFORM- d , 400MHz): δ = 7.29 (d, $J=7.3$ Hz, 1 H, $H_{2/4}$), 7.25 (d, $J=8.1$ Hz, 1 H, $H_{2/4}$), 7.10 (s, 1 H, H_1), 7.05 (t, $J=7.8$ Hz, 1 H, H_3), 4.77 (q, $J=7.2$ Hz, 1 H, ArCHCH $_3$), 3.76 (s, 3 H, OCH $_3$), 3.73 (s, 3 H, NCH $_3$), 1.63 ppm (d, $J=7.1$ Hz, 3 H, CHCH $_3$); **^{13}C NMR** (CHLOROFORM- d , 101MHz): δ = 176.3, 138.1, 127.9, 124.9, 123.8, 122.4, 114.9, 114.0, 108.7, 52.0, 36.4, 33.0, 19.7 ppm; **IR**: 1733 (C=O stretch) 1170, 1089 cm^{-1} ; **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+ \text{C}_{13}\text{H}_{14}^{79}\text{BrNO}_2$: 318.0100, found: 318.0090.

Methyl 2-(1-methyl-4-phenyl-indol-3-yl)acetate 112l

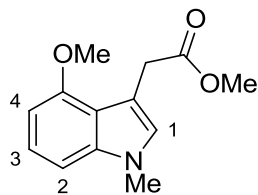


The title compound was prepared according to general procedure C to yield 240 mg (0.87 mmol, 87 %) of product as a crystalline white solid.

^1H NMR (CHLOROFORM- d , 400MHz): δ = 7.39 - 7.44 (m, 5 H, Ph), 7.34 (d, $J=8.1$ Hz, 1 H, $H_{2/4}$), 7.28 (m, 1 H, H_3), 7.04 (s, 1 H, H_1), 7.00 (d, $J=6.8$ Hz, 1 H, $H_{2/4}$), 3.82 (s, 3 H, OCH $_3$), 3.49 (s, 3 H,

NCH_3), 3.37 ppm (s, 2 H, $\text{ArCH}_2\text{CO}_2\text{Me}$); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 172.6, 141.4, 137.4, 135.5, 129.5, 129.0, 127.6, 126.9, 124.9, 121.4, 121.0, 108.5, 107.0, 51.5, 32.8, 32.1 ppm; IR: 1739 (C=O stretch) cm^{-1} ; mp 81°C; HRMS (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{18}\text{H}_{17}\text{NO}_2$: 302.1151, found 302.1149.

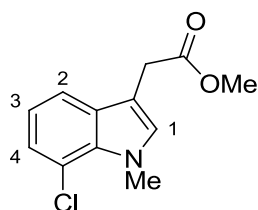
Methyl 2-(1-methyl-4-methoxy-indol-3-yl)acetate 112j



The title compound was prepared according to general procedure C to yield 240 mg (0.87 mmol, 87 %) of product as a pale yellow solid.

^1H NMR (CHLOROFORM- d , 400MHz): δ = 7.13 (t, $J=8.0$ Hz, 1 H, H_3), 6.84 - 6.95 (m, 2 H, H_1 & $H_{2/4}$), 6.49 (d, $J=7.8$ Hz, 1 H, $H_{2/4}$), 3.96 (s, 2 H, $\text{ArCH}_2\text{CO}_2\text{Me}$), 3.89 (s, 3 H, NCH_3), 3.73 ppm (m, 6 H, OCH_3); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 173.4, 154.7, 138.6, 126.4, 122.6, 117.7, 107.2, 102.7, 99.3, 55.1, 51.8, 32.9, 32.3 ppm; IR: 1738 (C=O stretch) cm^{-1} ; mp 82°C HRMS (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{15}\text{NO}_3$: 228.0995, found 228.0995.

Methyl 2-(1-methyl-7-chloro-indol-3-yl)acetate 112r

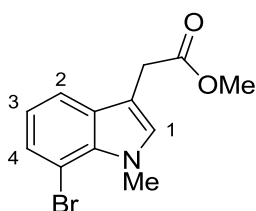


The title compound was prepared according to general procedure C to yield 200 mg (0.83 mmol, 83 %) of product as a yellow solid.

^1H NMR (CHLOROFORM- d , 400MHz): δ = 7.46 (dd, $J=8.0, 0.9$ Hz, 1 H, $H_{2/4}$), 7.16 (d, $J=7.6$ Hz, 1 H, $H_{2/4}$), 6.95 - 7.04 (m, 2 H, H_1 & H_3), 4.12 (s, 3 H, NCH_3), 3.74 (s, 2 H, $\text{ArCH}_2\text{CO}_2\text{Me}$), 3.71

ppm (s, 3 H, OCH₃); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 172.3, 130.5, 123.4, 123.3, 120.0, 119.9, 117.7, 117.0, 106.9, 52.0, 36.5, 30.8 ppm; **IR**: 1737 (C=O stretch) cm⁻¹; **mp** 66°C **HRMS** (ESI+) m/z calc'd for [M+Na]⁺ C₁₂H₁₂³⁵ClNO₂: 260.0449, found 260.0449.

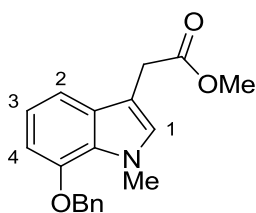
Methyl 2-(1-methyl-7-bromo-indol-3-yl)acetate 112q



The title compound was prepared according to general procedure C to yield 250 mg (0.88 mmol, 88 %) of product as a pale yellow oil.

¹H NMR (CHLOROFORM-d ,400MHz): δ = 7.52 (d, *J*=7.8 Hz, 1 H, *H*_{2/4}), 7.37 (d, *J*=7.6 Hz, 1 H, *H*_{2/4}), 7.00 (s, 1 H, *H*₁), 6.95 (t, *J*=7.7 Hz, 1 H, *H*₃), 4.13 (s, 3 H, NCH₃), 3.74 (s, 2 H, ArCH₂CO₂Me), 3.72 ppm (s, 3 H, OCH₃); ¹³C NMR (CHLOROFORM-d ,101MHz): δ = 172.2, 133.2, 130.8, 126.8, 126.7, 120.4, 118.3, 106.7, 104.0, 52.1, 36.7, 30.8 ppm; **IR**: 1737 (C=O stretch) cm⁻¹; **HRMS** (ESI+) m/z calc'd for [M+Na]⁺ C₁₂H₁₂⁷⁹BrNO₂: 303.9944, found 303.9944.

Methyl 2-(1-methyl-7-(benzyloxy)-indol-3-yl)acetate 112t

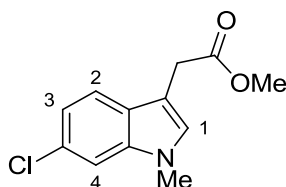


The title compound was prepared according to general procedure C to yield 230 mg (0.74 mmol, 74 %) of product as a colourless oil.

¹H NMR (CHLOROFORM-d ,400MHz): δ = 7.46 - 7.54 (m, 2 H, *Ph*), 7.33 - 7.46 (m, 3 H, *Ph*), 7.21 (d, *J*=8.1 Hz, 1 H, *H*_{2/4}), 7.02 (t, *J*=7.8 Hz, 1 H, *H*₃), 6.94 (s, 1 H, *H*₁), 6.72 (d, *J*=7.8 Hz, 1 H, *H*_{2/4}), 5.20 (s, 2 H, OCH₂Ph), 4.03 (s, 3 H, NCH₃), 3.76 (s, 2 H, ArCH₂CO₂Me), 3.72 ppm (s, 3 H, OCH₃);

^{13}C NMR (CHLOROFORM-d, 101MHz): $\delta = 172.6, 146.9, 137.2, 130.2, 128.9, 128.6, 127.9, 127.5, 126.7, 119.8, 112.0, 106.7, 103.8, 70.4, 52.0, 36.6, 31.1$ ppm; **IR**: 1738 (C=O stretch) cm^{-1} . **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+ \text{C}_{17}\text{H}_{19}\text{NO}_2$: 332.1257, found 332.1259.

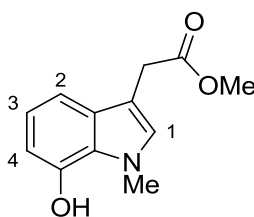
Methyl 2-(1-methyl-6-chloro-indol-3-yl)acetate 112n



The title compound was prepared according to general procedure C to yield 210 mg (0.88 mmol, 88 %) of product as a pale yellow oil.

^1H NMR (CHLOROFORM-d, 400MHz): $\delta = 7.50$ (d, $J=8.6$ Hz, 1 H, H_2), 7.30 (d, $J=1.8$ Hz, 1 H, H_4), 7.10 (dd, $J=8.5, 1.9$ Hz, 1 H, H_3), 7.03 (s, 1 H, H_1), 3.75 (s, 2 H, $\text{ArCH}_2\text{CO}_2\text{Me}$), 3.73 (s, 3 H, XCH_3), 3.71 ppm (s, 3 H, XCH_3); ^{13}C NMR (CHLOROFORM-d, 101MHz): $\delta = 172.3, 137.2, 128.4, 127.9, 126.2, 119.9, 119.8, 109.3, 107.1, 52.0, 32.7, 30.9$ ppm; **IR**: 1735 (C=O stretch) cm^{-1} ; **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+ \text{C}_{12}\text{H}_{12}^{35}\text{ClNO}_2$: 260.0449, found 260.0448.

Methyl 2-(1-methyl-7-hydroxy-indol-3-yl)acetate 127

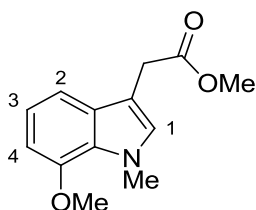


To a solution of methyl 2-(1-methyl-7-(benzyloxy)-indol-3-yl)acetate (1.0 g, 3.2 mmol, 1.0 equiv) in tetrahydrofuran was added palladium on carbon (10% dry weight) (100 mg). The atmosphere was exchanged to hydrogen (balloon pressure) by three vacuum/hydrogen cycles and the reaction was stirred for 14 h at room temperature under hydrogen. The atmosphere of hydrogen was then vented and the flask purged with nitrogen. The reaction mixture was filtered through Celite, eluting with

methanol (CAUTION: do not allow catalyst to dry out, risk of fire), and the solvent removed *in vacuo* to give the title compound as a brownish solid (710 mg, 3.2 mmol, quantitative yield).

¹H NMR (CHLOROFORM-d, 400MHz): δ = 7.14 (d, $J=8.1$ Hz, 1 H, *H2/4*), 6.92 (s, 1 H, *H1*), 6.88 (t, $J=7.8$ Hz, 1 H, *H3*), 6.46 (d, $J=7.6$ Hz, 1 H, *H2/4*), 5.51 (br. s., 1 H, *OH*), 4.02 (s, 3 H, *NCH₃*), 3.76 (s, 2 H *ArCH₂CO₂Me*), 3.73 ppm (s, 3 H, *OCH₃*); **¹³C NMR** (CHLOROFORM-d, 101MHz): δ = 173.1, 143.3, 130.6, 129.0, 125.9, 119.7, 111.5, 107.1, 106.6, 52.1, 36.0, 31.1 ppm; **IR**: 3396 (O-H stretch), 1716 (C=O stretch) cm^{-1} ; **mp** 78°C; **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{13}\text{NO}_3$: 242.0788, found 242.0786.

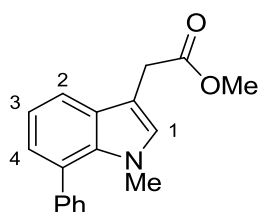
Methyl 2-(1-methyl-7-methoxy-indol-3-yl)acetate 112u



A flask was charged with sodium hydride (60wt% suspension in oil) (44 mg, 1.1 mmol, 1.2 equiv) and anhydrous N,N-dimethylformamide (1 ml) added. The flask was cooled to 0 °C and a solution of methyl 2-(1-methyl-7-hydroxy-indol-3-yl)acetate (200 mg, 0.91 mmol, 1.0 equiv) in N,N-dimethylformamide (1 ml) was added dropwise. The reaction mixture was stirred for one hour, and then a solution of iodomethane (0.07 ml, 1.1 mmol, 1.2 equiv) in N,N-dimethylformamide (1 ml) was added dropwise. The reaction was stirred for a further two hours at 0 °C, then quenched by the addition of a saturated aqueous solution of ammonium chloride (0.5 ml). Water was added and the aqueous layer extracted with three portions of ethyl acetate. The combined organic layers were then washed with three portions of water, one of brine, and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography, eluting with 6 parts petrol ether, 1 part ethyl acetate, to give the title compound as a pinkish solid (170 mg, 0.73 mmol, 80 % yield).

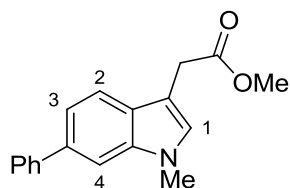
^1H NMR (CHLOROFORM- d , 400MHz): δ = 7.25 (d, J =7.8 Hz, 1 H, $H_{2/4}$), 7.08 (t, J =8.0 Hz, 1 H, H_3), 6.96 (s, 1 H, H_1), 6.68 (d, J =7.8 Hz, 1 H, $H_{2/4}$), 4.07 (s, 3 H, XCH_3), 3.97 (s, 3 H, XCH_3), 3.80 (s, 2 H, $\text{ArCH}_2\text{CO}_2\text{Me}$), 3.77 ppm (s, 3 H, XCH_3); **^{13}C NMR** (CHLOROFORM- d , 101MHz): δ = 172.6, 147.9, 130.0, 128.8, 126.6, 119.8, 111.8, 106.8, 102.6, 55.4, 51.9, 36.4, 31.1 ppm; **IR**: 1737 (C=O stretch) cm^{-1} ; **mp** 52°C; **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{15}\text{NO}_2$: 256.0944, found 256.0940.

Methyl 2-(1-methyl-7-phenyl-indol-3-yl)acetate 112s



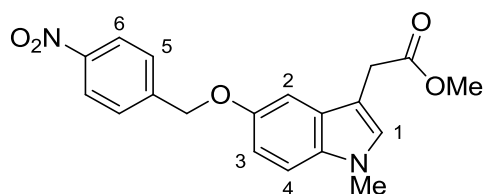
A solution of methyl 2-(1-methyl-7-bromo-indol-3-yl)acetate (400 mg, 1.4 mmol, 1.0 equiv), phenylboronic acid (350 mg, 2.8 mmol, 2.0 equiv), SPhos (2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl) (58 mg, 0.14 mmol, 0.1 equiv) and K_3PO_4 (900 mg, 4.3 mmol, 3.0 equiv) in tetrahydrofuran (15 ml) was degassed by three vacuum/argon cycles, and palladium acetate (16 mg, 0.07 mmol, 0.05 equiv) was added. The mixture was brought to reflux and stirred for 14 h, the reaction was then cooled and filtered through a short plug of silica, eluting with ethyl acetate. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography (10 parts petrol ether to 1 part ethyl acetate) to give the title compound as a yellow oil (310 mg, 1.1 mmol, 78 % yield).

^1H NMR (CHLOROFORM- d , 400MHz): δ = 7.61 (d, J =8.1 Hz, 1 H, $H_{2/4}$), 7.39 - 7.47 (m, 5 H, Ph), 7.16 (t, J =7.6 Hz, 1 H, H_3), 7.05 (d, J =7.1 Hz, 1 H, $H_{2/4}$), 6.98 (s, 1 H, H_1), 3.81 (s, 2 H, $\text{ArCH}_2\text{CO}_2\text{Me}$), 3.74 (s, 3 H, OCH_3), 3.28 ppm (s, 3 H, NCH_3); **^{13}C NMR** (CHLOROFORM- d , 101MHz): δ = 172.6, 140.3, 130.1, 129.9, 128.8, 127.6, 127.1, 126.9, 124.4, 119.0, 118.1, 118.1, 106.7, 52.0, 36.6, 31.0 ppm; **IR**: 1738 (C=O stretch) cm^{-1} . **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{18}\text{H}_{17}\text{NO}_2$: 302.1151, found 302.1151.

Methyl 2-(1-methyl-6-phenyl-indol-3-yl)acetate 112o

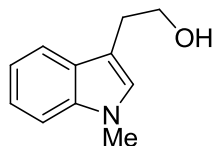
A solution of methyl 2-(1-methyl-6-chloro-indol-3-yl)acetate (400 mg, 1.7 mmol, 1.0 equiv), phenylboronic acid (410 mg, 3.4 mmol, 2.0 equiv), SPhos (2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl) (69 mg, 0.16 mmol, 0.1 equiv) and K_3PO_4 (1.1 g, 5.1 mmol, 3.0 equiv) in tetrahydrofuran (20 ml) was degassed by three vacuum/argon cycles, and palladium acetate (19 mg, 0.08 mmol, 0.05 equiv) was added. The mixture was brought to reflux and stirred for 20 h, the reaction was then cooled and filtered through a short plug of silica, eluting with ethyl acetate. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography (10 parts petrol ether to 1 part ethyl acetate) to give the desired compound as a yellow solid contaminated with the starting chloroarene. This solid was purified by recrystallisation from ethyl acetate/hexanes to afford the title compound as a white solid (140 mg, 0.50 mmol, 29 %).

1H NMR (CHLOROFORM- d , 400MHz): δ = 7.69 - 7.77 (m, 3 H, *Ph* & *H2/4*), 7.45 - 7.56 (m, 3 H, *Ph* & *H2/4*), 7.47 (dd, $J=8.1, 1.5$ Hz, 1 H, *H3*), 7.40 (t, $J=7.5$ Hz, 1 H, *Ph*), 7.10 (s, 1 H, *H1*), 3.85 (s, 2 H, $ArCH_2CO_2Me$), 3.82 (s, 3 H, NCH_3), 3.78 ppm (s, 3 H, OCH_3); ^{13}C NMR (CHLOROFORM- d , 101MHz): δ = 172.6, 142.5, 137.5, 135.5, 128.7, 128.5, 127.5, 127.1, 126.7, 119.3, 119.2, 108.0, 106.8, 52.0, 32.7, 31.1 ppm; **IR**: 1735 cm^{-1} ; **mp** 117°C; **HRMS** (ESI+) m/z calc'd for $[M+Na]^+$ $C_{18}H_{17}NO_2$: 302.1151, found 302.1154.

Methyl 2-(1-methyl-5-((4-nitrobenzyl)oxy)-1H-indol-3-yl)acetate 112w

methyl 2-(5-hydroxy-1-methyl-1H-indol-3-yl)acetate (0.25 g, 1.1 mmol) was dissolved in DMF (2 ml) and added to a slurry of NaH (50 mg of 60% dispersion in oil, 1.3 mmol, 1.1 equiv) in DMF (2 ml) at 0 °C. The mixture was stirred at this temperature for 1h, 4-nitrobenzyl bromide (0.49 g, 2.3 mmol, 2.0 equiv) was added and the mixture warmed to room temperature. The reaction was quenched by pouring into water and the aqueous mixture was extracted with Et₂O (3 portions). The combined organic fractions were washed with water and brine, then dried (Na₂SO₄) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, 4:1 hexane/EtOAc) to give the product as a brown solid (160 mg, 0.45 mmol, 40%).

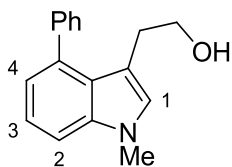
¹H NMR (CHLOROFORM-d ,400MHz): δ = 8.20 - 8.29 (m, 2 H, H6), 7.59 - 7.69 (m, J=8.6 Hz, 2 H, H5), 7.22 (d, J=8.8 Hz, 1 H, H4), 7.13 (d, J=2.5 Hz, 1 H, H2), 7.04 (s, 1 H, H1), 6.98 (dd, J=8.8, 2.3 Hz, 1 H, H3), 5.22 (s, 2H, ArCH₂OAr) 3.74 (s, 5 H, ArCH₂CO₂Me & NCH₃), 3.70 ppm (s, 3 H, OCH₃); ¹³C NMR (CHLOROFORM-d ,101MHz): δ = 172.4, 152.4, 147.3, 145.2, 132.6, 128.6, 127.8, 127.6, 123.6, 112.3, 110.2, 106.2, 102.5, 69.5, 51.9, 32.8, 31.0 ppm; IR: 1735 (C=O stretch), 1520 (NO₂ stretch), 1491, 1345 (NO₂ stretch) cm⁻¹; mp 115 °C; HRMS (ESI+) m/z calc'd for [M+Na]⁺ C₁₉H₁₈N₂NaO₅: 377.1108, found: 377.1112.



General Procedure D: reduction of methyl 2-(1H-indol-3-yl)acetate

Lithium aluminium hydride (76 mg, 2.0 mmol, 2.0 equiv) was added to a flask containing 5ml of diethyl ether. The flask was cooled to 0 °C and a solution of starting material (1.0 mmol, 1.0 equiv) in diethyl ether (5 ml) was added dropwise. The reaction mixture was stirred at 0 °C for one hour, at which point TLC showed complete consumption of the starting material. The reaction was quenched by the addition of water, then filtered through a short pad of Celite, eluting with diethyl ether. The solvent was removed *in vacuo* to yield the 2-(1-methyl-1H-indol-3-yl)ethanol product.

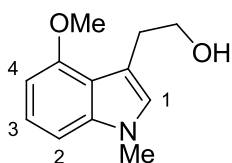
2-(1-Methyl-4-phenyl-indol-3-yl)ethanol 98k



The title compound was prepared according to general procedure D to give a white crystalline solid (250 mg, 0.98 mmol, 98 % yield).

¹H NMR (CHLOROFORM-d ,400MHz): δ = 7.38 - 7.51 (m, 5 H, *Ph*), 7.35 (d, $J=8.1$ Hz, 1 H, *H2/4*), 7.30 (t, $J=7.6$ Hz, 1 H, *H3*), 7.00 - 7.05 (dd, $J=7.1, 0.8$ Hz, 1 H, *H2/4*), 6.98 (s, 1 H, *H1*), 3.82 (s, 3 H, *NCH₃*), 3.28 (t, $J=6.4$ Hz, 2 H, *CH₂OH*), 2.61 ppm (t, $J=6.4$ Hz, 2 H, *ArCH₂*); **¹³C NMR** (CHLOROFORM-d ,101MHz): δ = 141.8, 137.8, 135.9, 129.7, 128.6, 127.6, 127.0, 124.9, 121.4, 120.9, 110.9, 108.5, 62.6, 32.8, 30.3 ppm; **IR**: 3423 (O-H stretch) cm^{-1} ; **mp** 114°C; **HRMS** (ESI+) m/z calc'd for $[M+Na]^+$ $C_{17}H_{17}NNaO$: 274.1202, found 274.1201.

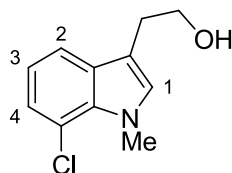
2-(1-Methyl-4-methoxy-indol-3-yl)ethanol 98j



The title compound was prepared according to general procedure D to give a white crystalline solid (250 mg, 0.98 mmol, 98 % yield).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.17 (t, $J=8.0$ Hz, 1 H, *H3*), 6.94 (d, $J=8.3$ Hz, 1 H, *H2/4*), 6.81 (s, 1 H), 6.53 (d, $J=7.8$ Hz, 1 H, *H2/4*), 3.95 (s, 3 H, *XCH₃*), 3.91 (t, $J=6.2$ Hz, 2 H, *CH₂OH*), 3.72 (s, 3 H, *XCH₃*), 3.16 ppm (t, $J=6.3$ Hz, 2 H, *ArCH₂*); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 154.6, 139.0, 126.4, 122.5, 117.6, 111.3, 102.8, 99.1, 63.8, 55.1, 32.8, 30.2 ppm; **IR**: 3396 (O-H stretch cm^{-1} ; **mp** 63°C; **HRMS** (ESI+) m/z calc'd for $[M+Na]^+$ $C_{12}H_{15}NO_2$: 228.0995, found 228.0995.

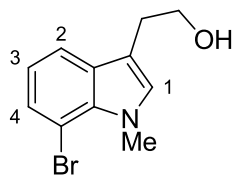
2-(1-Methyl-7-chloro-indol-3-yl)ethanol 98r



The title compound was prepared according to general procedure D to give a white crystalline solid (250 mg, 0.98 mmol, 98% yield).

¹H NMR (CHLOROFORM-d, 400MHz): δ = 7.47 (d, J =7.8 Hz, 1 H, $H_{2/4}$), 7.16 (d, J =7.6 Hz, 1 H, $H_{2/4}$), 6.99 (t, J =7.7 Hz, 1 H, H_3), 6.89 (s, 1 H, H_1), 4.12 (s, 3 H, NCH_3), 3.88 (t, J =6.3 Hz, 2 H, CH_2OH), 2.99 ppm (t, J =6.3 Hz, 2 H, $ArCH_2$); **¹³C NMR** (CHLOROFORM-d, 101MHz): δ = 132.4, 131.1, 130.0, 123.2, 119.7, 117.7, 117.1, 111.0, 62.6, 36.4, 28.5 ppm; **IR**: 3357 (O-H stretch) cm^{-1} ; **mp** 67°C **HRMS** (ESI+) m/z calc'd for $[M+Na]^+$ $C_{11}H_{12}^{35}ClNO$: 232.0500, found 232.0503.

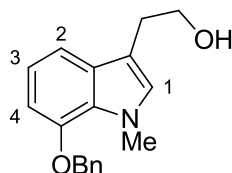
2-(1-Methyl-7-bromo-1H-indol-3-yl)ethanol 98q



The title compound was prepared according to general procedure D to give a brownish crystalline solid (250 mg, 1.0 mmol, quantitative yield).

¹H NMR (CHLOROFORM-d, 400MHz): δ = 7.53 (d, J =7.8, 0.8 Hz, 1 H, $H_{2/4}$), 7.36 (dd, J =7.6, 1.0 Hz, 1 H, $H_{2/4}$), 6.93 (t, J =7.7 Hz, 1 H, H_3), 6.89 (s, 1 H, H_1), 4.12 (s, 3 H, NCH_3), 3.87 (t, J =6.4 Hz, 2 H, CH_2OH), 2.98 ppm (t, J =6.3 Hz, 2 H, $ArCH_2$); **¹³C NMR** (CHLOROFORM-d, 101MHz): δ = 133.5, 131.0, 130.3, 126.7, 120.1, 118.3, 110.8, 104.0, 62.6, 36.6, 28.3 ppm; **IR**: 3375 (O-H stretch) cm^{-1} ; **mp** 54°C **HRMS** (ESI+) m/z calc'd for $[M+Na]^+$ $C_{11}H_{12}^{79}BrNO$: 275.9994, found 275.9995.

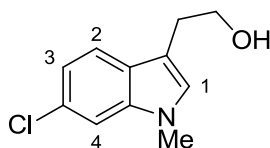
2-(1-Methyl-7-(benzyloxy)-1H-indol-3-yl)ethanol 98t



The title compound was prepared according to general procedure D to give a crystalline off white solid (250 mg, 0.98 mmol, 98% yield).

¹H NMR (CHLOROFORM-d ,400MHz): δ = 7.50 (d, J =7.3 Hz, 2 H, *o*-Ph), 7.43 (t, J =7.3 Hz, 2 H, *m*-Ph), 7.35 - 7.39 (m, 1 H, *p*-Ph), 7.22 (d, J =8.1 Hz, 1 H, *H*_{2/4}), 7.01 (t, J =8.0 Hz, 1 H, *H*₃), 6.84 (s, 1 H, *H*₁), 6.73 (d, J =7.6 Hz, 1 H, *H*_{2/4}), 5.20 (s, 2 H, PhCH₂), 4.03 (s, 3 H, NCH₃), 3.89 (t, J =6.3 Hz, 2 H, CH₂OH), 3.00 ppm (t, J =6.3 Hz, 2 H, ArCH₂); **¹³C NMR** (CHLOROFORM-d ,101MHz): δ = 147.0, 137.2, 130.4, 128.6, 128.6, 127.9, 127.5, 126.9, 119.5, 112.0, 110.6, 103.7, 70.4, 62.7, 36.5, 28.7 ppm; **IR**: 3385 (O-H stretch) cm⁻¹; **mp** 65°C; **HRMS** (ESI+) m/z calc'd for [M+Na]⁺ C₁₈H₁₉NO₂: 304.1308, found 304.1312.

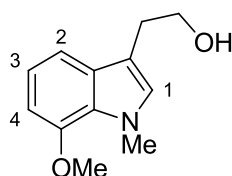
2-(1-Methyl-7-chloro-1H-indol-3-yl)ethanol 98r



The title compound was prepared according to general procedure D to give a yellow oil (250 mg, 0.98 mmol, 98 % yield).

¹H NMR (CHLOROFORM-d ,400MHz): δ = 7.51 (d, J =8.3 Hz, 1 H, *H*₂), 7.30 (d, J =1.8 Hz, 1 H, *H*₄), 7.08 (dd, J =8.5, 1.6 Hz, 1 H, *H*₃), 6.94 (s, 1 H, *H*₁), 3.88 (t, J =6.3 Hz, 2 H, CH₂OH), 3.73 (s, 3 H, NCH₃), 2.99 ppm (t, J =6.3 Hz, 2 H, ArCH₂); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 137.5, 127.9, 127.8, 126.5, 119.8, 119.5, 111.2, 109.3, 62.7, 32.7, 28.5 ppm; **IR**: 3357 (O-H stretch) cm⁻¹; **HRMS** (ESI+) m/z calc'd for [M+Na]⁺ C₁₁H₁₂³⁵ClNO: 232.0500, found 232.0500.

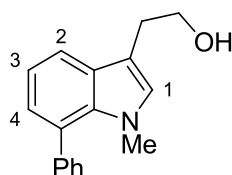
2-(1-Methyl-7-methoxy-1H-indol-3-yl)ethanol 98u



The title compound was prepared according to general procedure D to give an off white crystalline solid (85 mg, 0.41 mmol, 96% yield).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.20 (d, $J=7.8$ Hz, 1 H, $H_{2/4}$), 7.01 (t, $J=8.0$ Hz, 1 H, H_3), 6.82 (s, 1 H, H_1), 6.64 (d, $J=7.6$ Hz, 1 H, $H_{2/4}$), 4.03 (s, 3 H, XCH_3), 3.94 (s, 3 H, XCH_3), 3.88 (t, $J=6.3$ Hz, 2 H, CH_2OH), 2.99 ppm (t, $J=6.3$ Hz, 2 H, $ArCH_2$); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 147.9, 130.2, 128.4, 126.9, 119.5, 111.7, 110.6, 102.5, 62.7, 55.4, 36.3, 28.7 ppm; **IR**: 3357 (O-H stretch) cm^{-1} ; **mp** 66°C; **HRMS** (ESI+) m/z calc'd for $[M+Na]^+$ $C_{12}H_{15}NO_2$: 228.0995, found 228.0995.

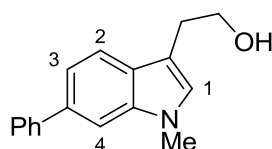
2-(1-Methyl-6-phenyl-1H-indol-3-yl)ethanol 98s



The title compound was prepared according to general procedure D to give a light brown oil (250 mg, 1.0 mmol, quantitative yield).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.65 (d, $J=7.8$ Hz, 1 H, $H_{2/4}$), 7.41 - 7.50 (m, 5 H, Ph), 7.17 (t, $J=7.5$ Hz, 1 H, H_3), 7.08 (d, $J=7.1$ Hz, 1 H, $H_{2/4}$), 6.90 (s, 1 H, H_1), 3.95 (t, $J=6.4$ Hz, 2 H, CH_2OH), 3.30 (s, 3 H, NCH_3), 3.08 (t, $J=6.3$ Hz, 2 H, $ArCH_2$), 1.71 ppm (s, 1 H, OH); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 140.4, 134.5, 130.1, 129.5, 129.1, 127.7, 127.2, 127.0, 124.4, 118.7, 118.1, 110.7, 62.7, 36.5, 28.6 ppm; **IR**: 3363 (O-H stretch) cm^{-1} . **HRMS** (ESI+) m/z calc'd for $[M+Na]^+$ $C_{17}H_{17}NO$: 274.1202, found 274.1203 .

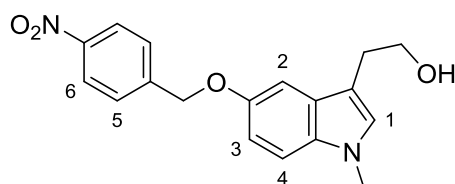
2-(1-Methyl-6-phenyl-1H-indol-3-yl)ethanol 98o



The title compound was prepared according to general procedure D to give a yellow oil (230 mg, 0.93 mmol, 93% yield).

^1H NMR (CHLOROFORM- d ,400MHz): δ = 7.67 - 7.76 (m, 3 H, H_2 & o -Ph), 7.54 (s, 1 H, H_4), 7.50 (t, J =7.7 Hz, 2 H, m -Ph), 7.43 (dd, J =8.3, 1.3 Hz, 1 H, H_3), 7.38 (t, J =7.3 Hz, 1 H, p -Ph), 6.99 (s, 1 H, H_1), 3.94 (t, J =6.4 Hz, 2 H, CH_2OH), 3.81 (s, 3 H, NCH_3), 3.07 ppm (t, J =6.3 Hz, 2 H, ArCH_2); **^{13}C NMR** (CHLOROFORM- d ,101MHz): δ = 142.5, 137.7, 135.4, 128.7, 128.0, 127.5, 127.3, 126.7, 119.2, 118.9, 110.8, 107.9, 62.8, 32.7, 28.7 ppm; **IR**: 3367 (O-H stretch) cm^{-1} . **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{17}\text{H}_{17}\text{NO}$: 274.1202, found 274.1203.

2-(1-Methyl-5-((4-nitrobenzyl)oxy)-1H-indol-3-yl)ethanol 98w

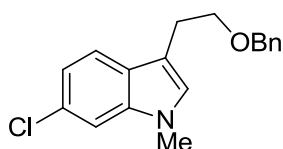


LiAlH_4 (78 mg, 2.1 mmol, 3.3 equiv) was suspended in Et_2O (10 ml) and AlCl_3 (90 mg, 0.68 mmol, 1.1 equiv) was added portionwise. The solution was stirred at RT for 10 minutes, then cooled to 0 °C. methyl 2-(1-methyl-5-((4-nitrobenzyl)oxy)-1H-indol-3-yl)acetate (0.22g, 0.62 mmol) was added as a solution in Et_2O (2 ml) and the reaction stirred for 30 min. Water was added to quench the reaction (1 ml), the reaction mixture was filtered through celite and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, Hexanes/ EtOAc 2:1) to give a yellow oil (140 mg, 0.43 mmol, 69%).

^1H NMR (CHLOROFORM- d ,400MHz): δ = 8.16 - 8.31 (m, J =8.6 Hz, 2 H, H_6), 7.59 - 7.70 (m, J =8.8 Hz, 2 H, H_5), 7.23 (d, J =9.0 Hz, 1 H, H_4), 7.13 (d, J =2.2 Hz, 1 H, H_2), 6.98 (dd, J =8.8, 2.4 Hz, 1 H, H_3), 6.94 (s, 1 H, H_1), 5.22 (s, 2 H, OCH_2Ar), 3.87 (t, J =6.4 Hz, 2 H, OCH_2CH_2), 3.75 (s, 3 H, NCH_3), 2.98 (t, J =6.4 Hz, 2 H, ArCH_2CH_2), 1.69 ppm (br. s., 1 H, OH); **^{13}C NMR** (CHLOROFORM-

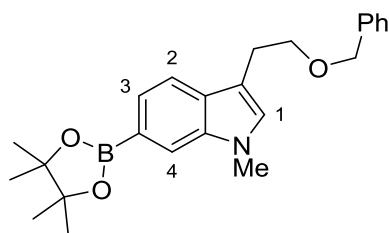
d,101MHz): $\delta = 152.3, 147.4, 145.2, 132.9, 129.8, 128.2, 128.1, 127.6, 123.7, 112.3, 110.2, 102.6, 69.7, 62.7, 32.8, 28.5$ ppm; **IR**: 1517, 1489, 1343 cm^{-1} ; **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{18}\text{H}_{18}\text{N}_2\text{NaO}_4$: 349.1159, found: 349.1151.

3-(2-(Benzyloxy)ethyl)-6-chloro-1-methyl-1H-indole 115



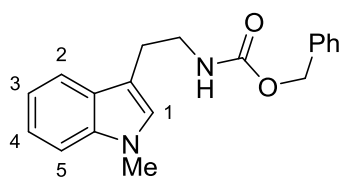
Sodium hydride (60 wt% dispersion in mineral oil, 140 mg, 3.6 mmol, 1.5 equiv) was placed in a flask and triturated with pentane to remove oil. THF (40 ml) was added and the slurry cooled to 0°C. 2-(1-methyl-7-chloro-1H-indol-3-yl)ethanol (0.50 g, 2.4 mmol) was added as a solution in THF (30 ml) and the mixture stirred for 1h. A solution of benzyl bromide (0.43 ml, 3.6 mmol, 1.5 equiv) in THF (20 ml) was added dropwise and the mixture stirred at RT for 1h. Sat. aq. NH_4Cl solution was added and the solvent removed *in vacuo*. The aqueous mixture was extracted with Et_2O (2 portions) and the combined extracts dried (MgSO_4) and the solvent evaporated. The crude mixture was purified by flash chromatography (silica, gradient 10:1 to 8:1 hexanes/ EtOAc) to give the product as a yellow oil (490 mg, 1.6 mmol, 69%).

^1H NMR (CHLOROFORM- d , 400MHz): $\delta = 7.50$ (d, $J=8.6$ Hz, 1 H), 7.30 - 7.41 (m, 5 H), 7.29 (d, $J=1.8$ Hz, 1 H), 7.08 (dd, $J=8.3, 1.8$ Hz, 1 H), 6.91 (s, 1 H), 4.58 (s, 2 H), 3.77 (t, $J=7.1$ Hz, 2 H), 3.71 (s, 3 H), 3.07 ppm (t, $J=7.1$ Hz, 2 H); **^{13}C NMR** (CHLOROFORM- d , 101MHz): $\delta = 138.4, 137.2, 128.3, 127.7, 127.7, 127.5, 127.4, 126.6, 119.9, 119.3, 111.9, 109.1, 73.0, 70.5, 32.6, 25.6$ ppm; **IR**: 1494, 1475 cm^{-1} ; **mp** 87 °C; **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{18}\text{H}_{18}^{35}\text{Cl}_1\text{NO}$: 322.0969, found 322.0963.

3-(2-(Benzyloxy)ethyl)-1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole 116

Tert-butyllithium (0.60 ml of 2.5 M solution in hexanes, 1.5 mmol, 2.2 equiv) was added to Et₂O (10 ml) and the solution cooled to -78°C. 3-(2-(benzyloxy)ethyl)-6-chloro-1-methyl-1H-indole (0.20 g, 0.67 mmol) was added dropwise as a solution in Et₂O (10 ml) and the mixture stirred for 1 h. B₂Pin₂ (0.42 g, 1.7 mmol, 2.5 equiv) was added as a solution in Et₂O (10 ml), the mixture was stirred at -78°C for a further 30 minutes then allowed to warm to room temperature. MeOH (1 ml) was added dropwise to quench the reaction and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (silica, gradient 0-10% EtOAc in hexane) to give the product as an off white semisolid (180 mg, 0.46 mmol, 69%).

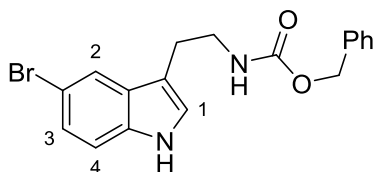
¹H NMR (CHLOROFORM-d ,400MHz): δ = 7.50 (d, *J*=8.3 Hz, 1 H, *H*₂), 7.34 - 7.38 (m, 4 H, *Ph*), 7.30 - 7.34 (m, 1 H, *Ph*), 7.28 (d, *J*=1.8 Hz, 1 H, *H*₄), 7.08 (dd, *J*=8.3, 1.8 Hz, 1 H, *H*₃), 6.89 (s, 1 H, *H*₁), 4.58 (s, 2 H, OCH₂Ph), 3.77 (t, *J*=7.1 Hz, 2 H, OCH₂CH₂), 3.69 (s, 3 H, NCH₃), 3.06 (t, *J*=7.1 Hz, 2 H, ArCH₂CH₂), 1.30 ppm (s, 12 H, 4 x CH₃); ¹³C NMR (CHLOROFORM-d ,101MHz): δ = 138.3, 137.1, 128.2, 127.6, 127.6, 127.4, 127.4, 126.5, 119.8, 119.2, 111.8, 109.0, 83.4, 72.9, 70.4, 32.5, 25.5, 24.9 ppm; IR: 1279, 1122 cm⁻¹; HRMS not found – attempted by ESI and probe EI.

5.2.2 Amine Substrate Synthesis for Fluorination Cyclisation**Benzyl (2-(1-methyl-1H-indol-3-yl)ethyl)carbamate 151h**

benzyl (2-(1H-indol-3-yl)ethyl)carbamate (0.50 g, 1.70 mmol),¹³³ NaOH (0.20 g, 5.1 mmol, 3.0 equiv) and Bu₄NHSO₄ (29 mg, 0.085 mmol, 5 mol%) were added to DCM (15 ml). MeI (0.12 ml, 1.87 mmol, 1.1 equiv) was added and the mixture stirred overnight. The reaction mixture was filtered and concentrated and the residue purified by flash chromatography (silica, hexane/EtOAc 2:1) to give the product as a yellow oil (0.34 g, 1.1 mmol, 65%).

¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.62 (d, J = 7.8 Hz, 1H, *H2/5*), 7.32-7.39 (m, 6H, *H2/5* & *Ph*), 7.27 (t, J = 6.8 Hz, 1H, *H3/4*), 7.14 (t, J = 7.3 Hz, 1H, *H3/4*), 6.88 (s, 1H, *H1*), 5.14 (s, 2H, PhCH₂O), 4.89 (br. s., 1H, NH), 3.76 (s, 3H, NCH₃), 3.55 (q, J = 6.3 Hz, 2H, NCH₂CH₂), 2.99 ppm (t, J = 6.6 Hz, 2H, ArCH₂CH₂); ¹³C NMR (101 MHz, CHLOROFORM-d) δ = 156.3, 137.1, 136.6, 128.5, 128.5, 128.0, 127.6, 126.8, 121.7, 118.9, 111.2, 109.2, 66.5, 41.4, 32.6, 25.5 ppm; IR: 3336 (N-H stretch), 1716 (C=O stretch), 1519, 1248 cm⁻¹; HRMS (ESI+) m/z calc'd for [M+Na]⁺ C₁₉H₂₀N₂O₂: 331.1417, found 331.1417.

Benzyl (2-(5-bromo-1H-indol-3-yl)ethyl)carbamate 153c

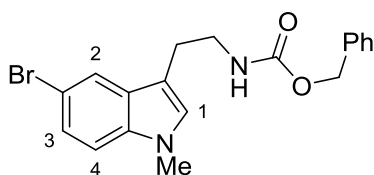


2-(5-Bromo-1H-indol-3-yl)ethanamine¹⁹⁵ (0.50 g, 2.1 mmol) and Et₃N (0.32 ml, 2.3 mmol, 1.1 equiv) were dissolved in DCM (20 ml) and the solution was cooled to 0°C. CbzCl (0.33 ml, 2.3 mmol, 1.1 equiv) in DCM (10 ml) was added dropwise and the mixture stirred at the same temperature for 4 h. NaHCO₃ (sat. aq.) was added, the mixture was stirred for 15 min, the organic fraction was separated, dried (MgSO₄) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc gradient 3:1 to 1:1) to yield the product as a pale brown solid (0.30 g, 0.81 mmol, 40%).

¹H NMR (CHLOROFORM-d, 400 MHz): δ = 8.61 (br. s., 1 H, *H2*), 7.74 (s, 1 H, *Ph*), 7.32 - 7.42 (m, 4 H, *Ph*), 7.29 (dd, J = 8.6, 1.8 Hz, 1 H, *H3*), 7.19 (d, J = 8.6 Hz, 1 H, *H4*), 6.91 (s, 1 H, *H1*), 5.15 (s, 2 H,

OCH₂Ph), 5.08 (br. s., 1 H, NH), 3.50 (q, *J*=6.3 Hz, 2 H, NCH₂CH₂), 2.90 ppm (t, *J*=6.8 Hz, 2 H, ArCH₂CH₂); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 156.4, 136.3, 134.8, 128.9, 128.4, 128.0, 127.9, 124.6, 123.3, 121.0, 112.7, 112.4, 112.1, 66.6, 41.2, 25.3 ppm; mp 90 °C; IR: 3315 (broad, N-H stretch), 1666 (C=O stretch), 1547, 1260 cm⁻¹; HRMS (ESI+) m/z calc'd for [M+Na]⁺ C₁₈H₁₇⁷⁹BrN₂O₂: 395.0366, found: 395.0364

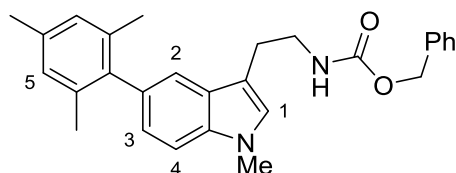
Benzyl (2-(5-bromo-1-methyl-1H-indol-3-yl)ethyl)carbamate 154c



Benzyl (2-(5-bromo-1H-indol-3-yl)ethyl)carbamate (0.75 g, 2.0 mmol), Bu₄NHSO₄ (34 mg, 0.10 mmol, 0.05 equiv), NaOH (0.24 g, 6.1 mmol, 3.0 equiv), MeI (0.14 ml, 2.2 mmol, 1.1 equiv) and DCM (20 ml) were charged in a flask and the mixture stirred at RT for 16 h. The mixture was poured into water, the organic fraction was separated and the organic layer extracted with DCM. The combined organic fractions were washed with brine, dried (MgSO₄) and the solvent removed. The residue was purified by flash chromatography (silica, 40% EtOAc in petrol ether) to give the product as a pale yellow oil (0.68 g, 1.8 mmol, 87%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.73 (s, 1 H, H₂), 7.33 - 7.45 (m, 5 H, Ph), 7.32 (dd, *J*=8.7, 1.6 Hz, 1 H, H₃), 7.15 (d, *J*=8.6 Hz, 1 H, H₄), 6.85 (s, 1 H, H₁), 5.13 (s, 2 H, OCH₂Ph), 4.95 (br. s., 1 H, NH), 3.70 (s, 3 H, NCH₃), 3.50 (q, *J*=6.2 Hz, 2 H, NCH₂CH₂), 2.91 ppm (t, *J*=6.7 Hz, 2 H, ArCH₂CH₂); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 156.2, 136.5, 135.6, 129.3, 128.4, 128.0, 128.0, 127.9, 124.4, 121.2, 112.2, 110.9, 110.7, 66.5, 41.2, 32.6, 25.3 ppm; IR 3333 (broad, N-H stretch), 1698 (C=O stretch), 1476, 1243 cm⁻¹; HRMS (ESI+) m/z calc'd for [M+Na]⁺ C₁₉H₁₉⁷⁹BrN₂O₂: 409.5022, found: 409.0508.

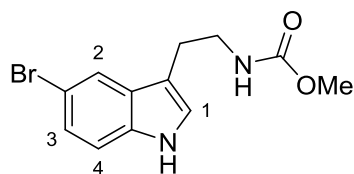
Benzyl (2-(5-mesityl-1-methyl-1H-indol-3-yl)ethyl)carbamate 151k



Benzyl (2-(5-bromo-1-methyl-1H-indol-3-yl)ethyl)carbamate (0.50 g, 1.3 mmol), mesitylboronic acid (0.42 g, 2.6 mmol, 2.0 equiv), Pd(OAc)₂ (29 mg, 0.13 mmol, 10 mol%), XPhos (120 mg, 0.26 mmol, 20 mol%), K₃PO₄ (0.82 g, 3.9 mmol, 3.0 equiv) and THF were degassed and then stirred in a sealed tube (Caution, internal pressure, use blast shield) at 70 °C for 36 h. The mixture was cooled, poured into water, and extracted with DCM. The combined organic fractions were dried and the solvent removed under reduced pressure. The residue was purified by flash chromatography (silica, hexanes/EtOAc gradient 3:1 to 1:1) to give the product as a pale brown solid (0.25 g, 0.59 mmol, 45%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.30 - 7.44 (m, 7 H, *Ph*, *H2* & *H4*), 7.05 (dd, *J*=8.3, 1.5 Hz, 1 H, *H3*), 6.99 (s, 2 H, *H5*), 6.92 (s, 1 H, *H1*), 5.10 (s, 2 H, OCH₂Ph), 4.89 (br. s., 1 H, *NH*), 3.80 (s, 3 H, NCH₃), 3.54 (q, *J*=6.3 Hz, 2 H, NCH₂CH₂), 2.98 (t, *J*=6.6 Hz, 2 H, ArCH₂CH₂), 2.39 (s, 3 H, ArCH₃), 2.05 ppm (s, 6 H, 2 x ArCH₃); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 156.3, 139.9, 139.6, 136.5, 136.1, 135.9, 131.7, 128.4, 128.1, 128.0, 127.9, 127.8, 127.0, 123.4, 119.1, 111.3, 109.1, 66.5, 41.5, 32.7, 25.5, 21.0, 20.9 ppm; IR: 1702 (C=O stretch), 1474, 1245 cm⁻¹; mp 92 °C; HRMS (ESI+) *m/z* calc'd for [M+Na]⁺ C₂₈H₃₀N₂O₂: 449.2199, found: 449.2202.

Methyl (2-(5-bromo-1H-indol-3-yl)ethyl)carbamate 153b

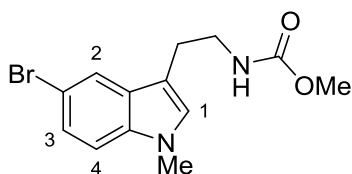


2-(5-Bromo-1H-indol-3-yl)ethanamine¹⁹⁵ (1.3 g, 5.3 mmol) was dissolved in DCM (40 ml). Et₃N (1.0 ml, 5.9 mmol, 1.1 equiv) was added and the mixture cooled to 0 °C. Methyl chloroformate (0.45 ml, 7.4 mmol, 1.4 equiv) was added and the mixture stirred at RT for 2 h. The reaction was quenched by

the addition of sat. aq. NaHCO₃ soln. (5 ml). The organic fraction was extracted with HCl (1M, 3 portions), dried (Na₂SO₄) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (Biotage 50g SNAP carriage, smooth gradient EtOAc in hexane 40% to 80%, giving the product as a yellow oil (1.3 g, 4.3 mmol, 77%).

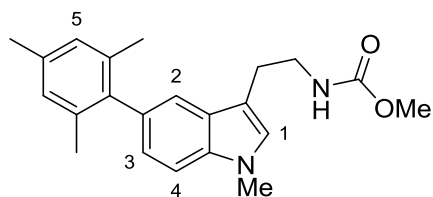
¹H NMR (CHLOROFORM-d,400MHz): δ = 8.57 (br. s., 1 H, NH), 7.70 (s, 1 H, H₂), 7.26 (dd, J =7.8, 1.8 Hz, 1 H, H₃), 7.21 (d, J =8.6 Hz, 1 H, H₄), 6.97 (s, 1 H, H₁), 4.91 (br. s., 1 H, NH), 3.68 (s, 3 H, OCH₃), 3.47 (q, J =6.2 Hz, 2 H, NCH₂CH₂), 2.90 ppm (t, J =6.8 Hz, 2 H, ArCH₂CH₂); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 157.2, 134.9, 129.0, 124.7, 123.3, 121.1, 112.7, 112.5, 112.3, 52.0, 41.2, 25.5 ppm.¹⁹⁶

Methyl (2-(5-bromo-1-methyl-1H-indol-3-yl)ethyl)carbamate 154b



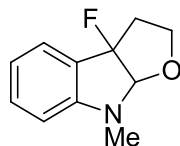
Methyl (2-(5-bromo-1H-indol-3-yl)ethyl)carbamate (1.3 g, 4.3 mmol), powdered NaOH (0.30 g, 13 mmol, 3.0 equiv) and Bu₄NHSO₄ (73 mg, 0.21 mmol, 5 mol%) were stirred in DCM (40 ml) for 10 min. MeI (0.30 ml, 4.7 mmol, 1.1 equiv) was added and the mixture stirred at RT for 16 h. The mixture was filtered through celite and the solvent removed. The residue was purified by flash chromatography (silica, gradient EtOAc in hexane 30% to 80%) to give the product as a yellow oil (1.20 g, 3.85 mmol, 90%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.69 (d, J =1.9 Hz, 1 H, H₂), 7.30 (dd, J =8.7, 1.7 Hz, 1 H, H₃), 7.16 (d, J =8.6 Hz, 1 H, H₄), 6.89 (s, 1 H, H₁), 3.73 (s, 3 H, OCH₃), 3.68 (s, 3 H, NCH₃), 3.47 (q, J =6.3 Hz, 2 H, NCH₂CH₂), 2.91 ppm (t, J =6.8 Hz, 2 H, ArCH₂CH₂); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 157.0, 135.7, 129.4, 128.0, 124.5, 121.4, 112.3, 111.1, 110.8, 52.0, 41.4, 32.8, 25.5 ppm; **IR**: 3333 (N-H stretch), 1699 (C=O stretch), 1524, 1477, 1249 cm⁻¹; **HRMS** (ESI+) m/z calc'd for [M+Na]⁺ C₁₃H₁₅⁷⁹BrN₂O₂: 333.0209, found: 333.0204.

Methyl (2-(5-mesityl-1-methyl-1H-indol-3-yl)ethyl)carbamate 151j

Methyl (2-(5-bromo-1-methyl-1H-indol-3-yl)ethyl)carbamate (1.2 g, 3.9 mmol), mesityl boronic acid (1.3 g, 7.7 mmol, 2.0 equiv), Pd(OAc)₂ (88 mg, 0.39 mmol, 10 mol%), XPhos (0.37 g, 0.77 mmol, 20 mol%) and K₃PO₄ (2.5 g, 12 mmol, 3.0 equiv) were dissolved in THF (40 ml) and the mixture degassed (3 x vacuum / N₂ cycles). The mixture was then heated at 70 °C in a sealed tube for 60 h, then cooled and filtered through a pad of silica eluting with EtOAc. The solvent was removed and the residue purified by flash chromatography (silica, EtOAc/hexane 3:1) to give the product as a yellow oil which solidified on standing (1.2 g, 3.5 mmol, 90%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.37 (d, *J*=8.6 Hz, 1 H, *H*₄), 7.35 (s, 1 H, *H*₂), 7.04 (dd, *J*=8.3, 1.5 Hz, 1 H, *H*₃), 6.99 (s, 2 H, *H*₅), 6.94 (s, 1 H, *H*₁), 4.81 (br. s., 1 H, *NH*), 3.81 (s, 3 H, OCH₃), 3.66 (s, 3 H, NCH₃), 3.51 (q, *J*=6.1 Hz, 2 H, NCH₂CH₂), 2.96 (t, *J*=6.7 Hz, 2 H, ArCH₂CH₂), 2.37 (s, 3 H, CH₃), 2.05 ppm (s, 6 H, 2 x CH₃); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 157.0, 139.9, 136.5, 136.1, 135.9, 131.7, 127.9, 127.9, 127.0, 123.4, 119.1, 111.4, 109.1, 51.9, 41.5, 32.7, 25.6, 21.0, 20.9 ppm; IR: 3299 (N-H stretch), 1686 (C=O stretch), 1541, 1474, 1249 cm⁻¹; mp 80 °C; HRMS (ESI+) *m/z* calc'd for [M+Na]⁺ C₂₂H₂₆N₂O₂: 373.1886, found: 373.1878.

5.2.3 Procedures for Fluorination-Cyclisation**General Procedure E: racemic fluorocyclisation of 2-(1-methyl-indol-3-yl)ethanol**

To a solution of substituted 2-(1-methyl-indol-3-yl)ethanol (18 mg, 100 μmol, 1.0 equiv.) in acetonitrile (1 ml) was added sodium bicarbonate (10 mg, 120 μmol, 1.2 equiv.) and Selectfluor (43

mg, 120 μmol , 1.2 equiv.). The reaction was stirred at room temperature for 2 h, or until full consumption of starting material was observed by tlc (Et_2O). The solvent was removed *in vacuo*, the residue dissolved in diethyl ether and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried (MgSO_4) and the solvent removed *in vacuo* to give the cyclised product, which could be purified if required by flash chromatography in a pipette using neutral alumina as the stationary phase (Et_2O /hexane). NOTE: products are unstable in CDCl_3 solution and when neat, NMR experiments were performed in C_6D_6 and products were stored in solution in benzene or diethyl ether/hexane.

General Procedure F: Stoichiometric cinchona alkaloid transfer fluorocyclisation of 2-(1-methyl-indol-3-yl)ethanol

To a flask containing a solution of bis-cinchona alkaloid (typically DHQ_2PHAL) (120 μmol , 1.2 equiv.) in acetone (1 ml) was added Selectfluor (43 mg, 120 μmol , 1.2 equiv.) and sodium bicarbonate (10 mg, 120 μmol , 1.2 equiv.). The mixture was stirred at room temperature for 1 h and then transferred to a cryostat at $-78\text{ }^\circ\text{C}$. A pre-cooled solution of the starting 2-(1-methyl-indol-3-yl)ethanol (100 μmol , 1.0 equiv.) in acetone (1 ml) was added rapidly and the reaction stirred for 16 h at $-78\text{ }^\circ\text{C}$. The reaction was allowed to warm to room temperature, the solvent was removed *in vacuo* and the residue dissolved in ethyl acetate. Hexane was added, and the precipitate of alkaloid and Selectfluor was removed by filtration. The solvent was removed *in vacuo* and the residue purified by column chromatography using neutral alumina as a stationary phase, eluting with 2 parts hexane to 1 part diethyl ether.

General Procedure G: Catalytic cinchona alkaloid transfer fluorocyclisation of 2-(1-methyl-indol-3-yl)ethanol

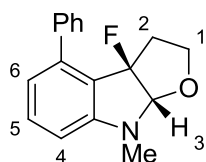
To a flask containing a solution of bis-cinchona alkaloid (typically DHQ_2PHAL) (20 μmol , 0.2 equiv.) in acetone (1 ml) was added N-fluorobenzenesulfonimide (38 mg, 120 μmol , 1.2 equiv.) and potassium carbonate (83 mg, 600 μmol , 6.0 equiv.). The mixture was stirred at room temperature for 1h and then transferred to a cryostat at -78°C . A pre-cooled solution of the starting 2-(1-methyl-

indol-3-yl)ethanol (100 μmol , 1.0 equiv.) in acetone (1 ml) was added rapidly and the reaction stirred for 20 h at $-78\text{ }^{\circ}\text{C}$. The reaction was allowed to warm to room temperature, the solvent was removed *in vacuo* and the residue dissolved in ethyl acetate. Hexane was added, and the precipitate of alkaloid was removed by filtration. The solvent was removed *in vacuo* and the residue purified by column chromatography using neutral alumina as a stationary phase, eluting with 2 parts hexane to 1 part diethyl ether.

5.2.4 Fluorination-Cyclisation Products

See Section 2.4 for yields and enantioselectivities.

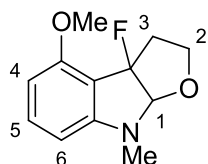
3a-Fluoro-8-methyl-4-phenyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole 99i



The title compound was a colourless oil.

^1H NMR (C_6D_6 , 400MHz): δ = 7.78 (d, $J=7.1$ Hz, 2 H, *o*-Ph), 7.30 - 7.39 (m, 2 H, *m*-Ph), 7.18 - 7.30 (m, 2 H, *p*-Ph & *H5*), 6.87 (d, $J=7.6$ Hz, 1 H, *H4/6*), 6.30 (d, $J=8.1$ Hz, 1 H, *H4/6*), 5.43 (d, $J=18.7$ Hz, 1 H, *H3*), 3.67 (m, 1 H, *H1*), 3.39 (m, 1 H, *H1*), 2.65 (s, 3 H, NCH_3), 2.11 - 2.28 (m, 1 H, *H2*), 1.92 ppm (m, 1 H, *H2*); **^{19}F NMR** (BENZENE- d_6 , 377MHz): δ = -133.6 ppm; **^{13}C NMR** (C_6D_6 , 101MHz): δ = 153.0, 142.0, 140.7, 132.1, 129.8 (d, $J=5$ Hz), 128.6, 128.3, 128.1, 120.3, 108.2 (d, $J=195$ Hz), 106.1, 103.0 (d, $J=34$ Hz), 67.5, 38.4 (d, $J=27$ Hz), 31.1 ppm; **IR**: 1595, 1476, 1261, 1018 (C-F stretch) cm^{-1} ; **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{16}\text{FNO}$: 270.1289, found: 270.1290; **HPLC**: Chiralcel OJ-H column, 90% hexane, 10% *i*-PrOH, 1 ml/min, retention times: 8.1 min, 14.0 min.

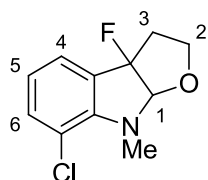
3a-Fluoro-4-methoxy-8-methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole 99j



Title compound was a colourless oil.

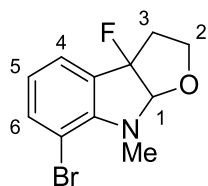
¹H NMR (BENZENE-*d*₆, 400MHz): δ = 7.19 (td, J =8.1, 1.9 Hz, 1 H, *H*5), 6.15 (d, J =8.3 Hz, 1 H, *H*4/6), 6.06 (dd, J =8.0, 1.4 Hz, 1 H, *H*4/6), 5.48 (d, J =18.4 Hz, 1 H, *H*1), 3.87 (m, 1 H, *H*2), 3.52 - 3.59 (m, 1 H, *H*2), 3.46 (s, 3 H, OCH₃), 2.62 - 2.68 (m, 2 H, *H*3), 2.61 ppm (s, 3 H, NCH₃); **¹³C NMR** (126 MHz, BENZENE-*d*₆) δ = 158.2, 154.4, 133.5, 112.2 (d, J =23 Hz), 107.8 (d, J =196 Hz), 103.8 (d, J =31 Hz), 101.6, 100.5, 67.9 (d, J =5 Hz), 55.2, 38.8 (d, J =30 Hz), 31.6 ppm; **¹⁹F NMR** (BENZENE-*d*₆, 377MHz): δ = -146.9 ppm; **IR**: 1610, 1483, 1261, 1068 (C-F stretch) cm⁻¹; **HRMS** (ESI+) *m/z* calc'd for [M+H]⁺ C₁₂H₁₄FNO₂: 224.1081, found: 224.1077; **HPLC** Chiralcel OD column, 95% hexane, 5% *i*PrOH, 1 ml/min, retention times: 8.1 min, 14.0 min.

7-chloro-3a-Fluoro-8-methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole 99r



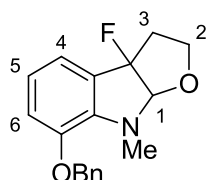
The title compound was a colourless oil.

¹H NMR (C₆D₆, 400MHz): δ = 7.03 (dt, J =7.9, 1.5 Hz, 1 H, *H*4/6), 6.95 (dt, J =7.5, 1.5 Hz, 1 H, *H*4/6), 6.38 (t, J =7.7 Hz, 1 H, *H*5), 5.21 (d, J =18.4 Hz, 1 H, *H*1), 3.70 - 3.83 (m, 1 H, *H*2), 3.40 (m, 1 H, *H*2), 3.05 (s, 3 H, NCH₃), 2.27 - 2.58 (m, 1 H, *H*3), 1.92 ppm (m, 1 H, *H*3); **¹⁹F NMR** (BENZENE-*d*₆, 377MHz): δ = -144.7; **¹³C NMR** (101 MHz, BENZENE-*d*₆) δ = 147.1, 133.2, 129.5, 123.4, 119.7, 114.5, 106.7 (d, J =196 Hz), 104.6 (d, J =29 Hz), 66.8, 40.0 (d, J =30 Hz), 34.9 ppm; **IR**: 1610, 1479, 1261, 1024 (C-F stretch) cm⁻¹; **HRMS** (Probe EI+) *m/z* calc'd for [M]⁺ C₁₁H₁₁³⁵ClFNO: 227.0508, found 227.0508; **HPLC**: Chiralcel OJ-H column, 99% hexane, 1% *i*-PrOH, 1 ml/min, retention times: 11.3 min, 14.2 min.

7-Bromo-3a-fluoro-8-methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole 99q

Title compound was a colourless oil.

¹H NMR (C₆D₆, 400MHz): δ = 7.34 (d, J =8.1 Hz, 1 H, *H4/6*), 7.08 (d, J =7.3 Hz, 1 H, *H4/6*), 6.41 (t, J =7.7 Hz, 1 H, *H5*), 5.30 (d, J =18.4 Hz, 1 H, *H1*), 3.69 - 3.78 (m, 1 H, *H2*), 3.36 (m, 1 H, *H2*), 3.05 (s, 3 H, NCH₃), 2.27 - 2.48 (m, 1 H, *H3*), 1.82 - 1.96 ppm (m, 1 H, *H3*); **¹³C NMR** (BENZENE-d₆, 126MHz): δ = 148.4, 136.7, 129.8 (d, J =24 Hz), 127.5, 124.0, 120.2, 106.4 (d, J =197 Hz), 104.8 (d, J =29 Hz), 66.8, 39.9 (d, J =30 Hz), 30.2 ppm **¹⁹F NMR** (C₆D₆, 377MHz): δ = -144.6; **IR**: 1609, 1476, 1417, 1058 (C-F stretch), 1022 cm⁻¹; **HRMS** (Probe EI+) *m/z* calc'd for [M]⁺ C₁₁H₁₁⁷⁹BrFNO: 271.0003, found 271.0010; **HPLC**: Chiralcel OJ-H column, 100% hexane, 1 ml/min, retention times: 23.7 min, 31.0 min.

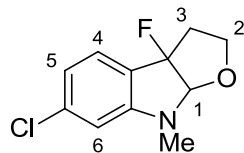
7-(Benzyloxy)-3a-fluoro-8-methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole 99t

Title compound was a colourless oil.

¹H NMR (C₆D₆, 400MHz): δ = 7.16 - 7.33 (m, 5 H, *Ph*), 7.08 - 7.13 (m, 1 H, *H4/H6*), 6.72 - 6.80 (m, 2 H, *H4/H6* & *H5*), 5.46 (d, J =18.9 Hz, 1 H, *H1*), 4.72 (s, 2 H, OCH₂Ph), 3.83 - 3.89 (m, 1 H, *H2*), 3.56 - 3.64 (m, 1 H, *H2*), 3.15 (s, 3 H, NCH₃), 2.42 - 2.59 (m, 1 H, *H3*), 2.02 - 2.15 (m, 1 H, *H3*) ppm; **¹³C NMR** (BENZENE-d₆, 126MHz): δ = 145.5, 141.6, 137.8, 129.1, 128.5, 128.3, 128.0, 120.2, 118.2, 116.1, 108.5 (d, J =196 Hz), 105.8 (d, J =29 Hz), 71.4, 67.5, 40.4 (d, J =31 Hz), 30.6 ppm; **¹⁹F NMR** (C₆D₆, 377MHz): δ = -142.8; **IR**: 1496, 1261, 1076, 1021 (C-F stretch) cm⁻¹; **HRMS** (ESI+)

m/z calc'd for $[M+Na]^+$ $C_{18}H_{18}FNO_2$: 274.1202, found 274.1197; **HPLC**: Chiralcel OD column, 99% hexane, 1% *i*PrOH, 1.0 ml/min, retention times: 22.5 min, 24.6 min.

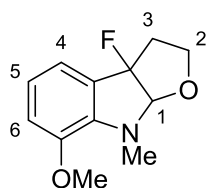
6-Chloro-3a-fluoro-8-methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole 99n



Title compound was a colourless oil.

1H NMR (BENZENE- d_6 , 400MHz): δ = 6.98 (d, $J=7.8$ Hz, 1 H, $H4/5$), 6.72 (d, $J=8.3$ Hz, 1 H, $H4/5$), 6.32 (s, 1 H, $H6$), 5.34 (d, $J=17.9$ Hz, 1 H, $H1$), 3.74 - 3.81 (m, 1 H, $H2$), 3.32 - 3.41 (m, 1 H, $H2$), 2.37 - 2.43 (m, 1 H, $H3$), 2.36 (s, 3 H, NCH_3), 1.89 - 1.97 ppm (m, 1 H, $H3$); **^{13}C NMR** (BENZENE- d_6 , 126 MHz) δ = 153.2, 138.0, 126.0, 124.9, 118.3, 107.4 (d, $J=196$ Hz), 107.2, 103.7, 67.5, 39.9 (d, $J=30$ Hz), 30.9 ppm; **^{19}F NMR** (C_6D_6 , 377MHz): δ = -146.4; **IR**: 1613, 1496, 1075 (C-F stretch), 1021 cm^{-1} ; **HRMS** (ESI+) m/z calc'd for $[M+H]^+$ $C_{11}H_{12}^{35}ClFNO$: 228.0586, found 228.0582; **HPLC**: Chiralcel OJ-H column, 99% hexane, 1% *i*-PrOH, 0.5 ml/min; retention times: 14.8 min, 18.2 min.

3a-Fluoro-7-methoxy-8-methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole 99u

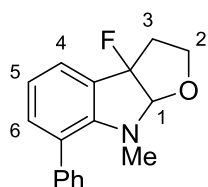


Title compound was a colourless oil.

1H NMR (BENZENE- d_6 , 500MHz): δ = 7.10 (d, $J=7.6$ Hz, 1 H, $H4/6$), 6.79 (t, $J=7.7$ Hz, 1 H, $H5$), 6.61 (d, $J=7.9$ Hz, 1 H, $H4/6$), 5.48 (d, $J=18.6$ Hz, 1 H, $H1$), 3.83 - 3.89 (m, 1 H, $H2$), 3.55 - 3.61 (m, 1 H, $H2$), 3.33 (s, 3 H, OCH_3), 3.16 (s, 3 H, NCH_3), 2.44 - 2.58 (m, 1 H, $H3$), 2.10 (m, 1 H, $H3$) ppm; **^{13}C NMR** (BENZENE- d_6 , 126MHz): δ = 146.4, 141.4, 128.4 ($J=26$ Hz), 120.3, 117.8, 114.6, 108.6 (d, $J=196$ Hz), 105.8 (d, $J=29$ Hz), 67.5, 55.7, 40.4 (d, $J=30$ Hz), 30.5 ppm; **^{19}F NMR** (C_6D_6

,377MHz): $\delta = -142.8$; **IR**: 1611, 1462, 1260, 1077 (C-F stretch), 1024 cm^{-1} ; **HRMS** (Probe EI+) m/z calc'd for $[\text{M}]^+ \text{C}_{12}\text{H}_{14}\text{FNO}_2$: 223.1009, found 223.1008; **HPLC** Chiralcel OD column, 99% hexane, 1% *i*PrOH, 1.0 ml/min, retention times 6.5 min, 8.0 min.

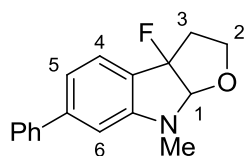
3a-Fluoro-8-methyl-7-phenyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole 99s



Title compound was a colourless oil.

^1H NMR (BENZENE- d_6 , 500MHz): $\delta = 7.43$ (m, 2 H, ArH), 7.35 (d, $J=7.3$ Hz, 1 H, ArH), 7.16 - 7.26 (m, 4 H, ArH), 6.86 (t, $J=7.6$ Hz, 1 H, ArH), 5.43 (d, $J=18.3$ Hz, 1 H, HI), 3.85 - 3.91 (m, 1 H, H2), 3.58 - 3.64 (m, 1 H, H2), 2.50 - 2.61 (m, 1 H, H3), 2.40 (s, 3 H, NCH₃), 2.10 - 2.16 ppm (m, 1 H, H3); **^{13}C NMR** (126 MHz, BENZENE- d_6) $\delta = 149.7$, 140.6, 134.4, 129.8, 128.8, 128.4 (d, $J=24$ Hz), 127.5, 125.2, 124.3, 120.0, 107.6 (d, $J=196$ Hz), 106.2 (d, $J=29$ Hz), 67.2, 40.4 (d, $J=30$ Hz), 37.4 ppm; **^{19}F NMR** (377 MHz, BENZENE- d_6) $\delta = -143.1$ ppm; **IR**: 1601, 1459, 1367, 1056 (C-F stretch), 1024 cm^{-1} ; **HRMS** (GCMS – ToF) m/z calc'd for $[\text{M}+\text{H}]^+ \text{C}_{17}\text{H}_{16}\text{FNO}$: 270.1289, not found 270.1306 (6.3 ppm); **HPLC** Chiralcel OJ-H column, 99% hexane, 1% *i*PrOH, 1.0 ml/min, retention times: 9.3 min, 12.1 min.

3a-Fluoro-8-methyl-6-phenyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole 99o

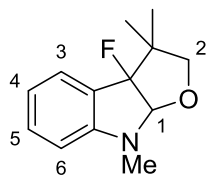


Title compound was a colourless oil.

^1H NMR (BENZENE- d_6 , 400MHz): $\delta = 7.63$ (d, $J=8.1$ Hz, 2 H, *o*-Ph), 7.35 (m, 3 H, *m*-Ph & *p*-Ph), 7.28 - 7.30 (m, 1 H, H4), 7.04 (d, $J=7.6$ Hz, 1 H, H5), 6.63 (s, 1 H, H6), 5.53 (d, $J=17.9$ Hz, 1 H, HI),

3.81 - 3.90 (m, 1 H, *H*2), 3.54 (m, 1 H, *H*2), 2.60 (s, 3 H, *NCH*3), 2.45 - 2.58 (m, 1 H, *H*3), 2.07 - 2.15 ppm (m, 1 H, *H*3); ¹³C NMR (BENZENE-*d*₆, 126MHz): δ = 152.9, 145.6, 142.6, 129.4, 129.0, 128.4 (d, *J*=24 Hz), 128.0, 128.0, 125.4, 118.1, 108.2 (d, *J*=196 Hz), 104.1 (d, *J*=30 Hz), 67.6, 40.2 (d, *J*=30 Hz), 31.4 ppm; ¹⁹F NMR (C₆D₆, 377MHz): δ = -145.5 ppm; **IR**: 2360, 1618, 1488, 1018 (C-F stretch) cm⁻¹; **HRMS** (Probe EI+) *m/z* calc'd for [M]⁺ C₁₇H₁₆FNO: 269.1210, found 269.1221; **HPLC**: Chiralcel OJ-H column, 99% Hexane, 1% *i*PrOH, 1.0 ml/min, retention times 10.2 min, 13.3 min.

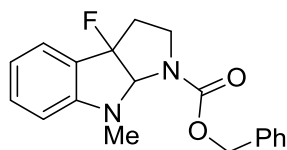
3a-Fluoro-3,3,8-trimethyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-*b*]indole 99v



Title compound was a colourless oil

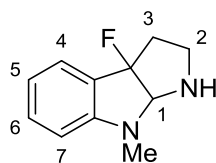
¹H NMR (C₆D₆, 400MHz): δ = 7.20 (d, *J*=7.3 Hz, 1 H, *H*3), 7.11 (t, *J*=7.7 Hz, 1 H, *H*5), 6.66 (t, *J*=7.5 Hz, 1 H, *H*4), 6.19 (d, *J*=7.8 Hz, 1 H, *H*6), 5.37 (d, *J*=20.0 Hz, 1 H, *H*1), 3.45 (dd, *J*=8.7, 1.9 Hz, 1 H, *H*2), 3.33 (d, *J*=8.8 Hz, 1 H, *H*2), 2.46 (s, 3 H, *NCH*3), 1.32 (d, *J*=4.3 Hz, 3 H, *CH*3), 0.79 ppm (s, 3 H, *CH*3); ¹³C NMR (BENZENE-*d*₆, 126MHz): δ = 153.2, 131.7, 126.6, 124.4 (d, *J*= 25 Hz), 118.0, 110.1 (d, *J*= 199 Hz), 106.9, 104.8 (d, *J*= 30 Hz), 79.6, 46.2 (d, *J*= 25 Hz), 31.8, 22.6 (d, *J*= 12 Hz), 21.8 ppm; ¹⁹F NMR (377 MHz, BENZENE-*d*₆) δ = -156.1 ppm (d, *J*=18 Hz); **IR**: 1613, 1493, 1469, 1016 (C-F stretch) cm⁻¹; **HRMS** (ESI+) *m/z* calc'd for [M+Na]⁺ C₁₃H₁₆FNO: 244.1108, found 244. 1104.

Benzyl 3a-fluoro-8-methyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2H)-carboxylate 155h



¹H NMR (400 MHz, C₆D₆) δ = 7.20 (m, 2H), 6.98-7.13 (m, 5H), 6.67 (bs, 1H), 6.22 (bs, 1H), 5.58-5.76 (m, 1H, major rotamer), 5.41 (d, J = 20.0 Hz, 1H, minor rotamer), 5.15 (t, J = 12.8 Hz, 2H, minor rotamer), 5.08 (bs, 2H, major rotamer), 3.85-4.02 (m, 1H, major rotamer), 3.58-3.78 (m, 1H, minor rotamer), 3.39-3.57 (m, 1H, major rotamer), 3.16-3.36 (m, 1H, minor rotamer), 2.92 (s, 3H, major rotamer), 2.83 (s, 3H, minor rotamer), 2.04-2.20 (m, 1H), 1.88 (d, J = 6.7 Hz, 1H) ppm; **¹³C NMR** (126 MHz, C₆D₆) δ = 152.5, 137.9, 137.2, 131.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 127.9, 126.6, 126.0, 125.8, 124.1, 122.0, 119.9, 119.3, 119.3, 118.7, 118.6, 109.4, 108.0, 67.4, 66.6, 46.0, 36.6 ppm; **¹⁹F NMR** (377 MHz, C₆D₆): δ = -135.5, -137.1 ppm; **IR**: 1713 (C=O stretch), 1460, 1070 (C-F stretch) cm⁻¹; **HRMS** (ESI+) m/z calc'd for [M+H]⁺ C₁₉H₂₀FN₂O₂: 327.1503, found: 327.1505; **HPLC** Chiralcel OD column, 99% hexane, 1% *i*PrOH, 1.0 ml/min, retention times 19.9 min, 21.7 min.

3a-Fluoro-8-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole 158



Benzyl 3a-fluoro-8-methyl-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (unisolated purified cyclisation product from 65 μ mol reaction) was dissolved in THF (3.0 ml) and Et₃N (0.3 ml). Pd/C (10 mg, 5 wt% on C) was added and the atmosphere exchanged first with nitrogen then with hydrogen. The mixture was stirred at 50 °C for 4 h, then cooled and filtered through celite, eluting with THF. The solvent was removed *in vacuo* to give the product as a colourless film (7.5 mg, 39 μ mol, 60%). The product was highly unstable and it was not possible to obtain a ¹³C NMR spectrum or IR spectrum.

¹H NMR (BENZENE-*d*₆, 400MHz): δ = 7.41 (d, J =7.1 Hz, 1 H, *H*_{4/7}), 7.22 (td, J =7.7, 0.8 Hz, 1 H, *H*_{5/6}), 6.79 (t, J =7.3 Hz, 1 H, *H*_{5/6}), 6.33 (d, J =7.8 Hz, 1 H, *H*_{4/7}), 4.69 (d, J =22.7 Hz, 1 H, *H*₁), 2.75 - 2.85 (m, 1 H, *H*₂), 2.62 - 2.71 (m, 1 H, *H*₂), 2.52 (s, 3 H, NCH₃), 2.19 - 2.37 (m, 1 H, *H*₃), 2.03 - 2.17 ppm (m, 1 H, *H*₃); **¹⁹F NMR** (377 MHz, BENZENE-*d*₆) δ = -138.6 ppm; **HRMS** (Probe EI+)

m/z calc'd for $[M+H]^+$ $C_{11}H_{13}FN_2$: 192.1063, found: 192.1063; **HPLC** Chiralcel OD column, 98% hexane, 2% *i*PrOH, 0.5 ml/min, retention times 11.9 min, 15.3 min.

5.3 Experimental Data for Chapter 3

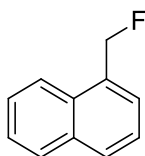
5.3.1 Defluorination Substrates

2-Fluoromethylnaphthalene,¹ benzofuran-2-carboxaldehyde¹⁹⁷ and *tert*-butanol coordinated tetrabutylammonium fluoride⁴⁰ were prepared by literature procedures.

General Procedure H: fluorination of benzylic bromides by *tert*-butanol coordinated tetrabutylammonium fluoride

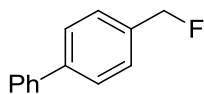
A solution of benzylic bromide and tetrabutylammonium fluoride (either as trihydrate or tetrakis *tert*-butanol coordinated) in acetonitrile (0.1 M substrate concentration) was heated at reflux for 2h, then cooled to room temperature. The solvent was removed *in vacuo* and the residue redissolved in DCM and filtered through a plug of silica eluting with diethyl ether. The solvent was removed *in vacuo* to give the benzylic fluoride product.

1-Fluoromethylnaphthalene 210



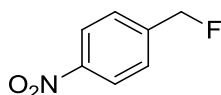
Following general procedure H, 1-bromomethylnaphthalene (500 mg, 2.3 mmol) and *tert*-butanol coordinated tetrabutylammonium fluoride (2.5 g, 4.5 mmol, 2.0 equiv) gave the product (340 mg, 2.1 mmol, 93%) as a colourless liquid.

¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 5.92 (d, $J=47.2$ Hz, 2 H, CH_2F) 7.38 - 7.79 (m, 4 H, ArH) 7.98 (t, $J=7.6$ Hz, 2 H, ArH) 8.18 (d, $J=8.08$ Hz, 1 H, ArH); **¹³C NMR** (101 MHz, CHLOROFORM-*d*) δ = 83.1 (d, $J=166$ Hz), 123.4, 125.0, 126.0, 126.6, 126.7, 126.8, 128.5, 129.7, 131.3, 131.6, 131.8 ppm; **¹⁹F NMR** (377 MHz, CHLOROFORM-*d*) δ ppm -205.8(d, $J=48$ Hz).¹⁹⁸

4-(Fluoromethyl)-1,1'-biphenyl 214

Following general procedure H, 4-bromomethyl)-1,1'-biphenyl (0.8 g, 3.2 mmol) and *tert*-butanol coordinated tetrabutylammonium fluoride (3.6 g, 6.5 mmol, 2.0 equiv) gave the product as a white solid (580 mg, 3.1 mmol, 96%).

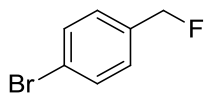
¹H NMR (CHLOROFORM-*d*, 400 MHz): δ = 7.58 - 7.70 (m, 4 H, ArH), 7.45 - 7.54 (m, 4 H, PhH), 7.40 (t, $J=7.3$ Hz, 1 H, PhH), 5.46 ppm (d, $J=47.5$ Hz, 2 H, CH₂F); **¹³C NMR** (101 MHz, CHLOROFORM-*d*) δ ppm 141.7, 140.6, 135.1 (d, $J=17$ Hz), 128.8, 128.0 (d, $J=6$ Hz), 127.5, 127.3, 127.1, 84.4 (d, $J=166$ Hz); **¹⁹F NMR** (377 MHz, CHLOROFORM-*d*) δ ppm -206.1 (t, $J=48.2$ Hz); **IR**: 978 (C-F stretch), 909, 762, 733 cm⁻¹; **mp** 72°C; **HRMS** (ESI+) m/z calc'd for [M+H]⁺ C₁₃H₁₂F: 187.0923, found: 187.0929.

4-Nitrobenzyl fluoride 248

Following general procedure H, 4-nitrobenzyl bromide (0.50 g, 2.3 mmol) and *tert*-butanol coordinated tetrabutylammonium fluoride (1.9 g, 3.5 mmol, 1.5 equiv) gave, after flash chromatography (dichloromethane) the product as a yellow solid (0.27 g, 1.7 mmol, 75%).

¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.2 (d, $J=8.3$ Hz, ArH), 7.5 (d, $J=8.1$ Hz, ArH), 5.5 (d, $J=46.7$ Hz, CH₂F); **¹³C NMR** (101 MHz, CHLOROFORM-*d*) δ ppm 147.7, 143.4 (d, $J=18$ Hz), 127.0, 123.7, 82.8 (d, $J=170$ Hz); **¹⁹F NMR** (377 MHz, CHLOROFORM-*d*) δ ppm -215.5 (t, $J=45.9$ Hz).¹⁹⁹

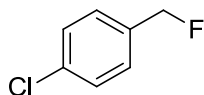
4-Bromobenzyl fluoride 246



Following general procedure H, 4-bromobenzyl bromide (0.50 g, 2.0 mmol) and tetrabutylammonium fluoride trihydrate (2.3 g, 4.1 mmol, 2.0 equiv) gave the product as a crystalline white solid (0.38 g, 2.0 mmol, 98%).

¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.54 (d, $J=8.3$ Hz, 2H, ArH), 7.26 (dd, $J=8.1, 1.5$ Hz, 2H, ArH), 5.34 (d, $J=47.0$ Hz, 2H, CH₂F); **¹³C NMR** (101 MHz, CHLOROFORM-*d*) δ ppm 135.1 (d, $J=18$ Hz), 131.8, 129.0, 122.8, 83.8 (d, $J=165$ Hz); **¹⁹F NMR** (377 MHz, CHLOROFORM-*d*) δ ppm -208.1 (t, $J=48.2$ Hz).²⁰⁰

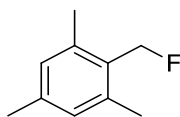
4-Chlorobenzyl fluoride 247



Following general procedure H, 4-chlorobenzyl bromide (0.30 g, 1.5 mmol) and *tert*-butanol coordinated tetrabutylammonium fluoride (1.7 g, 3.0 mmol, 2.0 equiv) gave the product as a low melting point white solid (0.20 g, 93%).

¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.38 (d, $J=8.6$ Hz, 2 H, ArH), 7.33 (dd, $J=8.5, 1.6$ Hz, 2 H, ArH), 5.36 (d, $J=47.5$ Hz, 2 H, CH₂F); **¹³C NMR** (101 MHz, CHLOROFORM-*d*) δ ppm 134.6 (d, $J=18$ Hz), 134.6, 128.8, 128.8, 83.7 (d, $J=167$ Hz); **¹⁹F NMR** (377 MHz, CHLOROFORM-*d*) δ ppm -207.3 (t, $J=47.0$ Hz).²⁰¹

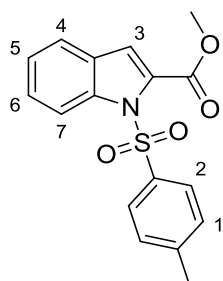
2-(Fluoromethyl)-1,3,5-trimethylbenzene 249



Following general procedure H, 2,4,6-trimethylbenzyl chloride (0.50 g, 3.0 mmol) and tetrabutylammonium fluoride trihydrate (2.0 g, 5.9 mmol, 2.0 equiv) gave the product as a pinkish oil that solidified on standing in the freezer (0.43 g, 2.8 mmol, 95%).

$^1\text{H NMR}$ (400 MHz, CHLOROFORM-*d*) δ ppm 7.01 (s, 2 H, ArH), 5.59 (d, $J=49.0$ Hz, 2 H, CH_2F), 2.52 (d, $J=2.3$ Hz, 6 H, *o*- CH_3), 2.41 (d, $J=3.3$ Hz, 3 H, *p*- CH_3); $^{13}\text{C NMR}$ (101 MHz, CHLOROFORM-*d*) δ ppm 139.0, 138.2, 129.3 (d, $J=14$ Hz), 129.0, 78.7 (d, $J=161$ Hz), 20.9, 19.1; $^{19}\text{F NMR}$ (377 MHz, CHLOROFORM-*d*) δ ppm -206.7 (t, $J=48.2$ Hz).²⁰²

Methyl 1-tosylindole-2-carboxylate

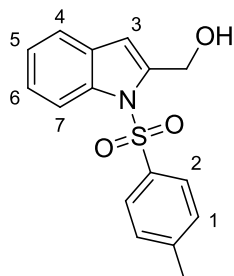


A solution of methyl 1H-indole-2-carboxylate (900 mg, 5.1 mmol) in dimethylformamide (2 ml) was added dropwise to a sodium hydride (250 mg, 6.2 mmol, 1.2 equiv) slurry in dimethylformamide (1 ml) at 0°C and the mixture stirred for 1 hour. A solution of *para*-toluenesulfonyl chloride (2.0 g, 10 mmol, 1.0 equiv) in dimethylformamide (2 ml) was added slowly and the mixture stirred at room temperature for 2 hours. The reaction mixture was poured into water and the aqueous mixture extracted with 3 portions of diethyl ether. The combined organic fractions were washed with water and then brine and dried over magnesium sulfate. The solution was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10 parts hexane to 1 part ethyl acetate) to give the product as a crystalline yellow solid (970 mg, 2.9 mmol, 57%).

$^1\text{H NMR}$ (CHLOROFORM-*d*, 400 MHz): δ = 8.14 (dd, $J=8.6, 0.8$ Hz, 1 H, $H_{4/7}$), 7.93 (d, $J=8.1$ Hz, 2 H, $H_{1/2}$), 7.57 (d, $J=7.8$ Hz, 1 H, $H_{4/7}$), 7.44 (ddd, $J=8.4, 7.3, 1.3$ Hz, 1 H, $H_{5/6}$), 7.24 - 7.31 (m, 3 H, $H_{1/2}$ & $H_{5/6}$), 7.17 (s, 1 H, H_3), 3.95 (s, 3 H, OCH_3), 2.37 ppm (s, 3 H, ArCH_3); $^{13}\text{C NMR}$

(CHLOROFORM-d,101MHz): $\delta = 161.7, 144.9, 138.2, 135.6, 131.4, 129.5, 128.1, 127.3, 127.0, 124.0, 122.5, 116.8, 115.3, 52.7, 21.6$ ppm.²⁰³

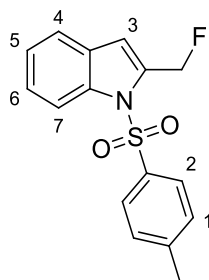
(1-Tosylindol-2-yl)methanol 234



A 1M toluene solution of di-*isobutyl*aluminium hydride in toluene (14 ml, 14 mmol, 3.0 equiv) was added to dichloromethane (20 ml) and the mixture cooled to -40°C . A solution of methyl 1-tosylindole-2-carboxylate (1.5 g, 4.6 mmol) in dichloromethane (10 ml) was added and the mixture stirred at this temperature for 4h. Methanol (1 ml) was added to quench the remaining reagent and the mixture poured into aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane and the combined organic fractions dried (MgSO_4). The solvent was removed *in vacuo* and the residue purified by flash chromatography (4:1 hexane/ethyl acetate) to give the product as an off white solid (1.3 g, 4.4 mmol, 96%).

$^1\text{H NMR}$ (CHLOROFORM-d,400MHz): $\delta = 8.07$ (dd, $J=8.3, 0.5$ Hz, 1 H, $H_{4/7}$), 7.74 (d, $J=8.6$ Hz, 2 H, $H_{1/2}$), 7.48 (d, $J=7.6$ Hz, 1 H, $H_{4/7}$), $7.28 - 7.34$ (m, 1 H, $H_{4/7}$), $7.21 - 7.26$ (m, 1 H, $H_{4/7}$), 7.19 (d, $J=8.1$ Hz, 2 H, $H_{1/2}$), 6.64 (s, 1 H, H_3), 4.92 (d, $J=6.3$ Hz, 2 H, CH_2OH), 3.21 (t, $J=6.9$ Hz, 1 H, OH), 2.33 ppm (s, 3 H, ArCH_3); $^{13}\text{C NMR}$ (CHLOROFORM-d,101MHz): $\delta = 145.1, 140.1, 136.9, 135.5, 129.9, 129.0, 126.4, 124.9, 123.7, 121.1, 114.3, 111.1, 58.5, 21.5$ ppm.²⁰⁴

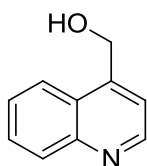
2-(Fluoromethyl)-1-tosylindole 240



Diethylaminosulfur trifluoride (0.14 ml, 1.1 mmol, 3.3 equiv) was added to dichloromethane (1 ml) and the mixture cooled to -78°C . 4-trimethylsilylmorpholine (0.19 ml, 1.1 mmol, 3.3 equiv) was added dropwise and the mixture stirred at room temperature for 2.5 hours. The mixture was cooled to -78°C and a solution of (1-tosylindol-2-yl)methanol (100 mg, 0.33 mmol) in dichloromethane (1.5 ml) was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 16h. Methanol (0.5 ml) was added dropwise, followed by saturated aqueous sodium bicarbonate solution (5 ml). The aqueous layer was extracted with 3 portions of dichloromethane and the combined organic fractions passed through a plug of silica eluting with dichloromethane, the solvent was removed *in vacuo* to give the product as a yellow oil that crystallised on standing (80 mg, 0.26 mmol, 80%).

^1H NMR (CHLOROFORM-*d*,400MHz): δ = 8.14 (d, $J=8.6$ Hz, 1 H, $H_{4/7}$), 7.83 (d, $J=8.1$ Hz, 2 H, $H_{1/2}$), 7.53 (d, $J=7.6$ Hz, 1 H, $H_{4/7}$), 7.37 (t, $J=7.8$ Hz, 1 H, $H_{5/6}$), 7.26 (t, $J=7.3$ Hz, 1 H, $H_{5/6}$), 7.21 (d, $J=8.1$ Hz, 2 H, $H_{1/2}$), 6.78 (d, $J=3.8$ Hz, 1 H, H_3), 5.77 (d, $J=42.2$ Hz, 2 H, CH_2F), 2.33 ppm (s, 3 H, ArCH_3); **^{13}C NMR** (CHLOROFORM-*d*,101MHz): δ = 145.0, 136.9, 135.4, 134.9 ($J = 18$ Hz), 129.7, 128.5, 126.9, 125.5, 123.6, 121.5, 114.4, 113.3, 77.1, 21.5 ($J = 165$ Hz) ppm; **^{19}F NMR** (377 MHz, CHLOROFORM-*d*) δ ppm -202.26 (td, $J=47.00, 3.40$ Hz); **IR**: 1367, 1172 (C-F stretch), 672 cm^{-1} ; **mp** 69°C ; **HRMS** (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{16}\text{H}_{14}\text{FNO}_2\text{S}$: 326.0621, found: 326.0621.

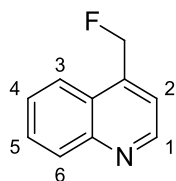
Quinolin-4-ylmethanol



4-Quinoline carboxaldehyde (2.7 g, 17 mmol) was added to a slurry of lithium aluminium hydride (0.71 g, 19 mmol, 1.1 equiv) in diethyl ether (150 ml) at 0°C and stirred at this temperature for 2 hours. Water was added slowly to quench and the solid residues removed by filtration. On evaporation of the solvent some decomposition was observed with the residue going dark in colour. The residue was purified by column chromatography (4:1 Hexane/ethyl acetate) to give the desired product as a pale yellow solid (930 mg, 5.9 mmol, 34%).

$^1\text{H NMR}$ (CHLOROFORM- d , 4000MHz): δ = 8.74 (d, $J=4.5$ Hz, 1 H, ArH), 7.92 (d, $J=8.6$ Hz, 1 H, ArH), 7.68 (ddd, $J=8.5, 6.9, 1.3$ Hz, 1 H, ArH), 7.45 - 7.58 (m, 2 H, ArH), 5.22 (d, $J=1.0$ Hz, 2 H, CH_2OH), 4.55 ppm (br. s, 1 H, OH); $^{13}\text{C NMR}$ (CHLOROFORM- d , 101MHz): δ = 150.1, 147.4, 147.0, 129.5, 129.3, 126.7, 125.8, 122.9, 118.1, 61.2 ppm.²⁰⁵

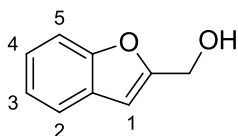
4-(Fluoromethyl)quinoline 241



Diethylaminosulfur trifluoride (0.54 ml, 4.1 mmol, 3.3 equiv) was added to dichloromethane (2 ml) and the mixture cooled to -78°C. 4-trimethylsilylmorpholine (0.72 ml, 4.1 mmol, 3.3 equiv) was added dropwise and the mixture stirred at room temperature for 2.5 hours. The mixture was cooled to -78°C and a solution of quinolin-4-ylmethanol (200 mg, 1.3 mmol) in dichloromethane (3 ml) was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 16h. Methanol (1 ml) was added dropwise, followed by saturated aqueous sodium bicarbonate solution (5 ml). Diethyl ether (20 ml) was added and the organic layer separated. The organic layer was extracted with 3 portions of dilute aqueous hydrochloric acid and then discarded. The acid extracts were combined, basified with aqueous sodium hydroxide solution and extracted with 3 portions of diethyl ether. The combined extracts were dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give the product as a brown oil (160 mg, 0.96 mmol, 76%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 8.92 (d, $J=4.3$ Hz, 1 H, *H1/2*), 8.16 (d, $J=8.3$ Hz, 1 H, *H3/6*), 7.83 (d, $J=8.3$ Hz, 1 H, *H3/6*), 7.74 (t, $J=7.7$ Hz, 1 H, *H4/5*), 7.58 (t, $J=8.0$ Hz, 1 H, *H4/5*), 7.45 (d, $J=4.3$ Hz, 1 H, *H1/2*), 5.82 ppm (d, $J=46.7$ Hz, 2 H, *CH₂F*); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 150.2, 147.9, 141.2 (d, $J = 16$ Hz), 130.2, 129.5, 127.0, 125.0, 122.6, 118.4 (d, $J = 10$ Hz), 81.3 (d, $J = 171$ Hz) ppm; **¹⁹F NMR** (377 MHz, CHLOROFORM-d) δ ppm -220.92 (t, $J=47.00$ Hz); **IR**: 1054 (C-F stretch), 986, 840, 759 cm^{-1} ; **HRMS** (ESI+) m/z calc'd for $[M+H]^+$ C₁₀H₉FN: 162.0714, found: 162.0714.

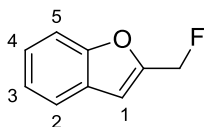
Benzofuran-2-methanol



Benzofuran-2-carboxaldehyde (500 mg, 3.4 mmol) was dissolved in EtOH (10 ml) and the mixture cooled to 0°C. NaBH₄ (130 mg, 3.4 mmol, 1.0 equiv) was added and the mixture was stirred at RT for 2h. Dilute aqueous HCl solution was added dropwise and the solvent was then removed *in vacuo*. Water was added and the mixture was extracted with 3 portions of DCM. The combined extracts were dried (MgSO₄) and the solvent removed *in vacuo* to give the product as a yellow oil (510 mg, 3.4 mmol, quantitative conversion).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.55 (d, $J=7.6$ Hz, 1 H, *H5*), 7.44 - 7.51 (d, $J=8.1$ Hz, 1 H, *H2*), 7.22 - 7.32 (m, 2 H, *H3 & H4*), 6.62 (d, $J=0.7$ Hz, 1 H, *H1*), 4.68 - 4.77 (m, 2 H, *CH₂OH*), 3.14 ppm (br. s., 1 H, *OH*); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 156.4, 154.9, 128.0, 124.2, 122.7, 121.0, 111.1, 104.0, 57.7 ppm.²⁰⁶

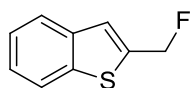
2-(Fluoromethyl)benzofuran 239



Diethylaminosulfur trifluoride (1.2 ml, 8.8 mmol, 3.3 equiv) was added to dichloromethane (4 ml) and the mixture cooled to -78°C . 4-trimethylsilylmorpholine (1.6 ml, 8.8 mmol, 3.3 equiv) was added dropwise and the mixture stirred at room temperature for 2.5 hours. The mixture was cooled to -78°C and a solution of benzofuran-2-methanol²⁰⁷ (400 mg, 2.7 mmol) in dichloromethane (9 ml) was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 16 h. Methanol (1 ml) was added dropwise, followed by 5% aqueous potassium carbonated solution (5 ml) and the mixture was stirred for 30 minutes. The organic fraction was separated and the aqueous layer extracted with 2 portions of dichloromethane. The combined organic fractions were concentrated *in vacuo* and then purified by passing through a short plug of silica, eluting with 4 parts petrol ether to 1 part dichloromethane. The solvent was removed to give a volatile straw coloured liquid (180 mg) containing approximately 9% hexanes by weight, determined by proton NMR (170 mg product, 1.1 mmol, 41%).

^1H NMR (CHLOROFORM-*d*, 400 MHz): δ = 7.62 (d, $J=7.6$ Hz, 1 H, $H_{2/5}$), 7.54 (d, $J=8.3$ Hz, 1 H, $H_{2/5}$), 7.37 (td, $J=7.7, 1.0$ Hz, 1 H, $H_{3/4}$), 7.28 (t, $J=8.1$ Hz, 1 H, $H_{3/4}$), 6.87 (d, $J=5.3$ Hz, 1 H, H_1), 5.45 ppm (d, $J=48.0$ Hz, 2 H, ArCH_2F); **^{13}C NMR** (101 MHz, CHLOROFORM-*d*) δ ppm 155.5, 151.6 (d, $J=17$ Hz), 127.6, 125.3, 123.0, 121.6, 111.6, 108.0 (d, $J=7$ Hz), 76.2 (d, $J=166$ Hz); **^{19}F NMR** (377 MHz, CHLOROFORM-*d*) δ ppm -207.4 (td, $J=48.2, 4.6$ Hz); **IR**: 1452.7, 1375.3, 1256.3, 1136 (C-F stretch, 974.4 cm^{-1}); **HRMS** (GC-MS CI) m/z calc'd for $[\text{M-F}]^+$ $\text{C}_9\text{H}_7\text{O}$: 131.0497 found: 131.0503.

2-(Fluoromethyl)benzothiophene 238



Diethylaminosulfur trifluoride (1.0 ml, 7.9 mmol, 3.3 equiv) was added to dichloromethane (4 ml) and the mixture cooled to -78°C . 4-trimethylsilylmorpholine (1.4 ml, 7.9 mmol, 3.3 equiv) was added dropwise and the mixture stirred at room temperature for 2.5 hours. The mixture was cooled to -78°C and a solution of benzothiophene-2-methanol²⁰⁸ (400 mg, 2.4 mmol) in dichloromethane (6 ml) was

added dropwise. The mixture was allowed to warm to room temperature and was stirred for 16h. Methanol (1 ml) was added dropwise, followed by 5% aqueous potassium carbonated solution (5 ml) and the mixture was stirred for 30 minutes. The organic fraction was separated and the aqueous layer extracted with 2 portions of dichloromethane. The combined organic fractions were concentrated *in vacuo* and then purified by column chromatography, eluting with 30-40 petroleum ether to give the product as a white solid (180 mg, 1.1 mmol, 44%).

¹H NMR (CHLOROFORM-*d*, 400 MHz): δ = 7.83 - 7.93 (m, 1 H, ArH), 7.75 - 7.83 (m, 1 H, ArH), 7.32 - 7.45 (m, 3 H, ArH), 5.60 ppm (d, $J=48.0$ Hz, 2 H, ArCH₂F); **¹³C NMR** (101 MHz, CHLOROFORM-*d*) δ ppm 140.7, 139.1, 138.5 (d, $J=18$ Hz), 125.0, 124.7, 124.5, 124.1, 122.5, 79.3 (d, $J=168$ Hz); **¹⁹F NMR** (377 MHz, CHLOROFORM-*d*) δ ppm -196.9 (td, $J=48.2, 4.6$ Hz); **IR**: 1459, 1435, 1139 (C-F stretch), 972 cm⁻¹; **mp** 45 °C; **HRMS** (GC-MS CI) m/z calc'd for [M-F]⁺ C₉H₇S: 147.0268 found: 147.0266.

5.3.2 Defluorination Products

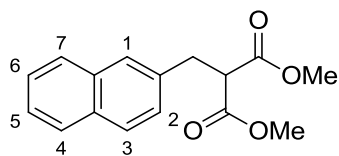
Pd(allyl)COD.BF₄ was prepared by a literature procedure.²⁰⁹

General Procedure I: Palladium catalysed defluorination of benzylic fluorides

Palladium precatalyst (Pd(dba)₂, Pd₂(dba)₃, (Pd(allyl)Cl)₂, Pd(allyl)COD.BF₄ or Pd(allyl)Cp) was added to screw top vial, then ligand and solvent. The suspension was stirred at room temperature for 30 minutes, at which time the solutions had generally clarified or become a homogenous suspension of catalyst complex. Benzylic fluoride was added, either as solid or by transferring catalyst solution to a vial containing the liquid starting material, and the mixture was stirred for a further 5 minutes. The nucleophile and base were added and the vial purged with N₂. The vial was placed in a preheated oil bath and stirred for the time indicated. The reaction mixture was then poured into water and extracted with DCM or Et₂O, depending on reaction solvent (Et₂O for DMF and DMSO). The combined organic extracts were dried (DCM/MgSO₄, Et₂O/Na₂SO₄) and the solvent removed *in vacuo*. The crude mixture was analysed by ¹H NMR (400 MHz) and the ratio of benzylic peaks was determined

by integration. The normalised ratio of peaks was used to express the conversion of the reactions. The crude mixture was purified by whatever means was most appropriate for the product of the reaction.

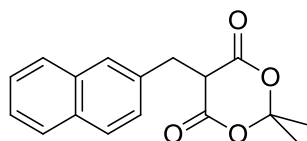
Dimethyl 2-(naphthalen-2-ylmethyl)malonate 187



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (2.1 mg, 5 mol%) and DPEphos (6.7 mg, 10 mol%), 2-fluoromethylnaphthalene (20 mg, 0.13 mmol) reacted with dimethyl malonate (0.03 ml, 0.25 mmol, 2.0 equiv) and triethylamine (0.04 ml, 0.25 mmol, 2.0 equiv) in ethanol at 75°C for 48h to give the product after flash chromatography (ethyl acetate/hexanes 1:5) as a colourless oil (6.7 mg, 25 μ mol, 20%).

$^1\text{H NMR}$ (CHLOROFORM-*d*,400MHz): δ = 7.74 - 7.84 (m, 3 H, ArH), 7.67 (s, 1 H, HI), 7.42 - 7.51 (m, 2 H, ArH), 7.34 (d, J =8.3 Hz, 1 H, ArH), 3.81 (t, J =7.8 Hz, 1 H, ArCH₂CHR₂), 3.71 (s, 6 H, OCH₃), 3.41 ppm (d, J =7.8 Hz, 2 H, ArCH₂CHR₂); $^{13}\text{C NMR}$ (CHLOROFORM-*d*,101MHz): δ = 169.2, 135.2, 133.4, 132.3, 128.2, 127.6, 127.3, 126.9, 126.0, 125.6, 53.5, 52.6, 34.9 ppm.²¹⁰

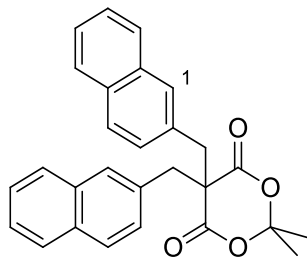
2,2-Dimethyl-5-(naphthalen-2-ylmethyl)-1,3-dioxane-4,6-dione 212



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (2.1 mg, 5 mol%) and DPEphos (6.7 mg, 10 mol%), 2-fluoromethylnaphthalene (20 mg, 0.13 mmol) reacted with Meldrum's acid (36 mg, 0.25 mmol, 2.0 equiv) and triethylamine (0.04 ml, 0.25 mmol, 2.0 equiv) in dimethylsulfoxide at 60°C for 48h to give the product after flash chromatography (dichloromethane) as a pale yellow solid (23 mg, 81 μ mol, 65%).

¹H NMR (CHLOROFORM-d,400MHz): $\delta = 7.70 - 7.88$ (m, 4 H, ArH), 7.37 - 7.56 (m, 3 H, ArH), 3.85 (t, $J=4.9$ Hz, 1 H, ArCH₂CH), 3.67 (d, $J=5.0$ Hz, 2 H, ArCH₂CH), 1.75 (s, 3 H, CH₃), 1.51 ppm (s, 3 H, CH₃); **¹³C NMR** (CHLOROFORM-d,101MHz): $\delta = 165.3, 134.7, 133.3, 132.4, 128.5, 128.2, 127.8, 127.8, 127.5, 126.1, 125.8, 105.2, 48.2, 32.1, 28.4, 27.1$ ppm.²¹¹

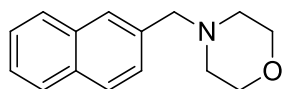
2,2-Dimethyl-5,5-bis(naphthalen-2-ylmethyl)-1,3-dioxane-4,6-dione 213



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (4.3 mg, 5 mol%) and DPEphos (14 mg, 10 mol%), 2-fluoromethylnaphthalene (40 mg, 0.25 mmol) reacted with the sodium salt of Meldrum's acid (formed by reaction of Meldrum's acid 72 mg, 0.50 mmol, 2.0 equiv and sodium hydride 60% dispersion in mineral oil 20 mg, 0.50 mmol, 2.0 equiv) in dimethylsulfoxide at 60°C for 8h to give the product after flash chromatography (dichloromethane) as a yellow solid (43 mg, 100 μ mol, 81%).

¹H NMR (CHLOROFORM-d,400MHz): $\delta = 7.76 - 7.87$ (m, 6 H, ArH), 7.73 (s, 2 H, HI), 7.42 - 7.53 (m, 4 H, ArH), 7.37 (dd, $J=8.5, 1.6$ Hz, 2 H, ArH), 3.70 (s, 4 H, 2 x ArCH₂), 0.44 ppm (s, 6 H, 2 x CH₃); **¹³C NMR** (CHLOROFORM-d,101MHz): $\delta = 168.3, 133.3, 132.6, 132.2, 129.2, 128.5, 127.9, 127.9, 127.5, 126.2, 126.1, 105.9, 59.9, 45.2, 28.6$ ppm; **IR**: 1728 (C=O stretch), 1350, 1270 cm⁻¹; **mp** 154 °C; **HRMS** (ESI) calc'd for [M+Na]⁺ C₂₈H₂₄NaO₄: 447.1567, found 447.1566.

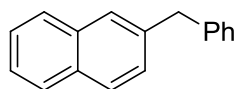
4-(Naphthalen-2-ylmethyl)morpholine 220



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (2.1 mg, 5 mol%) and *bis*-diphenylphosphinoferrocene (7.0 mg, 10 mol%), 2-fluoromethylnaphthalene (20 mg, 0.13 mmol) reacted with morpholine (0.02 ml, 0.25 mmol, 2.0 equiv) and triethylamine (0.04 ml, 0.25 mmol, 2.0 equiv) in ethanol at 25°C for 4h to give the product after acid/base extraction (1M HCl/Et₂O then NaOH/DCM) as a yellow oil (20 mg, 87 μmol, 70%).

¹H NMR (CHLOROFORM-d,200MHZ): δ = 7.71 - 7.95 (m, 4 H, ArH), 7.37 - 7.60 (m, 3 H, ArH), 3.74 (t, *J*=4.6 Hz, 4 H, 2 x OCH₂R), 3.67 (s, 2 H, ArCH₂NR₂), 2.51 ppm (t, *J*=4.6 Hz, 4 H, 2 x NCH₂R); ¹³C NMR (CHLOROFORM-d,50MHZ): δ = 135.3, 133.3, 132.8, 127.9, 127.7, 127.7, 127.6, 127.4, 126.0, 125.6, 67.0, 63.6, 53.7 ppm.²¹²

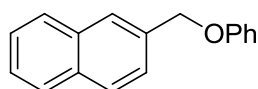
2-Benzyl-naphthalene 230



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (4.2 mg, 5 mol%) and DPEphos (13.4 mg, 10 mol%), 2-fluoromethylnaphthalene (40 mg, 0.25 mmol) reacted with phenylboronic acid (61 mg, 0.50 mmol, 2 equiv) and K₃PO₄ (100 mg, 0.50 mmol, 2.0 equiv) in DMSO at 60°C for 24 h to give the product after flash chromatography (silica, hexanes) as a colourless oil (36 mg, 170 μmol, 67%).

¹H NMR (CHLOROFORM-d,200MHZ): δ = 7.76 - 7.92 (m, 3 H, ArH), 7.69 (s, 1 H, ArH), 7.42 - 7.58 (m, 2 H, ArH), 7.20 - 7.42 (m, 6 H, ArH), 4.20 ppm (s, 2 H, ArCH₂Ph); ¹³C NMR (CHLOROFORM-d,50MHZ): δ = 140.9, 138.6, 133.6, 132.1, 129.0, 128.5, 128.0, 127.6, 127.5, 127.1, 126.1, 125.9, 125.3, 42.1 ppm.²¹³

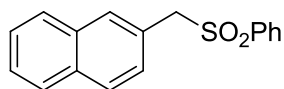
2-(Phenoxymethyl)naphthalene 227



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (4.2 mg, 5 mol%) and DPEphos (13 mg, 10 mol%), 2-fluoromethylnaphthalene (40 mg, 0.25 mmol) reacted with phenol (47 mg, 0.50 mmol, 2.0 equiv) and triethylamine (0.08 ml, 0.50 mmol, 2.0 equiv) in DMSO at 60°C for 24 h to give the product after flash chromatography (silica, 5:1 hexanes/dichloromethane) as a white solid (33 mg, 140 μ mol, 56%).

$^1\text{H NMR}$ (CHLOROFORM- d_3 , 200MHz): δ = 7.75 - 8.05 (m, 4 H, ArH), 7.45 - 7.66 (m, 3 H, ArH), 7.22 - 7.42 (m, 2 H, ArH), 6.91 - 7.13 (m, 3 H, ArH), 5.26 ppm (s, 2 H, ArCH₂OPh); $^{13}\text{C NMR}$ (CHLOROFORM- d_3 , 50MHz): δ = 158.8, 134.6, 133.3, 133.0, 129.5, 128.4, 127.9, 127.7, 126.3, 126.2, 126.0, 125.3, 121.0, 114.9, 70.0 ppm.²¹⁴

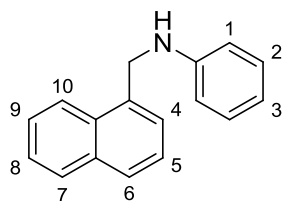
2-((Phenylsulfonyl)methyl)naphthalene 224



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (4.2 mg, 5 mol%) and DPEphos (13 mg, 10 mol%), 2-fluoromethylnaphthalene (40 mg, 0.25 mmol) reacted with sodium phenylsulfinate (70 mg, 0.50 mmol, 2.0 equiv) in DMSO at 60°C for 24 h to give the product after flash chromatography (silica, gradient 1:1 hexanes/dichloromethane to 100% dichloromethane) as a white solid (59 mg, 210 μ mol, 84%).

$^1\text{H NMR}$ (DICHLOROMETHANE- d_2 , 200MHz): δ = 7.68 - 7.91 (m, 3 H, ArH), 7.57 - 7.68 (m, 3 H, ArH), 7.50 - 7.57 (m, 2 H, ArH), 7.38 - 7.50 (m, 3 H, ArH), 7.22 (dd, $J=8.5, 1.7$ Hz, 1 H, ArH), 4.48 ppm (s, 2 H, ArCH₂SO₂Ph); $^{13}\text{C NMR}$ (DICHLOROMETHANE- d_2 , 50MHz): δ = 138.7, 134.3, 133.6, 133.6, 131.0, 129.5, 129.1, 128.7, 128.4, 128.4, 128.2, 127.2, 127.0, 126.4, 63.4 ppm.²¹⁵

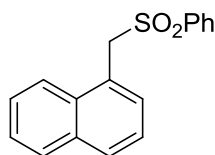
N-(Naphthalen-1-ylmethyl)aniline 222



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (2.1 mg, 5 mol%) and *t*BuXPhos (11 mg, 20 mol%), 1-fluoromethylnaphthalene (20 mg, 0.13 mmol) reacted with aniline (0.03 ml, 0.25 mmol, 2.0 equiv) and triethylamine (0.04 ml, 0.25 mmol, 2.0 equiv) in ethanol at 75°C for 4h to give the product after flash chromatography (silica, dichloromethane) as a brown oil (23 mg, 97 μ mol, 77%).

$^1\text{H NMR}$ (CHLOROFORM- d , 400MHz): δ = 8.07 - 8.14 (m, 1 H, *H*10/*H*7), 7.90 - 7.97 (m, 1 H, *H*10/*H*7), 7.85 (d, J =8.3 Hz, 1 H, *H*6), 7.51 - 7.60 (m, 3 H, *H*8, *H*9 & *H*4), 7.47 (t, J =8.1 Hz, 1 H, *H*5), 7.19 - 7.30 (m, 2 H, *H*2), 6.79 (m, J =7.3, 1.0 Hz, 1 H, *H*3), 6.72 (dd, J =8.7, 0.9 Hz, 2 H, *H*1), 4.77 (s, 2 H, ArCH₂NHPh), 4.02 ppm (br. s., 1 H, PhNH); $^{13}\text{C NMR}$ (CHLOROFORM- d , 101MHz): δ = 148.2, 134.3, 133.8, 131.5, 129.3, 128.7, 128.2, 126.3, 126.0, 125.8, 125.5, 123.6, 117.6, 112.7, 46.4 ppm.²¹⁶

1-((Phenylsulfonyl)methyl)naphthalene 225

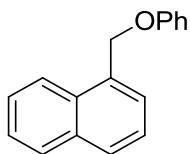


Following general procedure I, using a catalyst prepared *in situ* from palladium allyl chloride dimer (2.3 mg, 5 mol%) and DPEphos (7.4 mg, 11 mol%), 2-fluoromethylnaphthalene (20 mg, 130 μ mol) reacted with sodium phenylsulfinate (31 mg, 0.19 mmol, 1.5 equiv) in ethanol at 25°C for 24h to give the product after flash chromatography (silica, dichloromethane) as a white solid (32 mg, 110 μ mol, 89%).

$^1\text{H NMR}$ (CHLOROFORM- d , 400MHz) δ = 7.82 (m, 3 H, Ar*H*), 7.62 (m, 2 H, Ar*H*), 7.53 (m, 1 H, Ar*H*), 7.43 (m, 2 H, Ar*H*), 7.36 (t, J = 7.8 Hz, 3 H, Ar*H*), 7.22 (d, J =7.1 Hz, 1 H, Ar*H*), 4.84 ppm (s, 2

H, ArCH₂SO₂Ph); ¹³C NMR (CHLOROFORM-d, 101MHz) δ = 137.9, 133.7, 133.6, 132.1, 130.6, 129.7, 129.4, 128.8, 128.7, 126.6, 125.9, 125.0, 124.5, 123.5, 59.8 ppm.²¹⁷

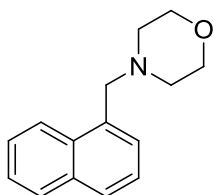
1-(Phenoxymethyl)naphthalene 228



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (2.1 mg, 5 mol%) and *t*BuXPhos (11 mg, 20 mol%), 1-fluoromethylnaphthalene (20 mg, 0.13 mmol) reacted with phenol (24 mg, 0.25 mmol, 2.0 equiv) and triethylamine (0.04 ml, 0.25 mmol, 2.0 equiv) in EtOH at 75°C for 4 h to give the product after flash chromatography (silica, 4:1 hexanes/dichloromethane) as a white solid (12 mg, 51 μmol, 41%).

¹H NMR (CHLOROFORM-d, 400MHz): δ = 8.04 - 8.12 (m, 1 H, ArH), 7.90 - 7.96 (m, 1 H, ArH), 7.88 (d, *J*=8.3 Hz, 1 H, ArH), 7.63 (d, *J*=6.8 Hz, 1 H, ArH), 7.52 - 7.60 (m, 2 H, ArH), 7.49 (t, *J*=7.2 Hz, 1 H, ArH), 7.36 (t, *J*=8.1 Hz, 2 H, ArH), 7.09 (d, *J*=8.6 Hz, 2 H, ArH), 7.03 (t, *J*=7.3 Hz, 1 H, ArH), 5.52 ppm (s, 2 H, ArCH₂OR); ¹³C NMR (CHLOROFORM-d, 101MHz): δ = 158.8, 133.8, 132.3, 131.5, 129.5, 129.0, 128.7, 126.6, 126.4, 125.9, 125.3, 123.7, 121.1, 114.9, 68.5 ppm.²¹⁸

4-(Naphthalen-1-ylmethyl)morpholine 221

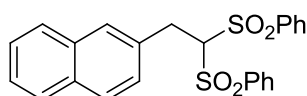


Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (2.1 mg, 5 mol%) and *t*BuXPhos (11 mg, 20 mol%), 1-fluoromethylnaphthalene (20 mg, 130 μmol) reacted with morpholine (0.03 ml, 0.25 mmol, 2.0 equiv) and triethylamine (0.04 ml, 0.25 mmol, 2.0 equiv) in ethanol at 75°C for 1h to give the product after acid/base extraction

(HCl/Et₂O then NaOH/DCM) as a yellow oil (21 mg, 92 μmol, 73%).

¹H NMR (CHLOROFORM-d,200MHz) δ = 8.38 - 8.27 (m, 1 H, ArH), 7.90 - 7.84 (m, 1 H, ArH), 7.80 (dd, J = 7.1, 2.7 Hz, 1 H, ArH), 7.56 - 7.49 (m, 2 H, ArH), 7.48 - 7.36 (m, 2 H, ArH), 3.93 (s, 2 H, ArCH₂NR₂), 3.71 (t, J = 4.5 Hz, 4 H, 2 x -CH₂O-), 2.53 (t, J = 4.6 Hz, 4 H, 2 x -CH₂NR-); ¹³C NMR (CHLOROFORM-d, 50MHz) δ = 134.3, 133.9, 133.0, 128.9, 128.6, 128.0, 126.2, 126.1, 125.5, 125.2, 67.5, 62.0, 54.2 ppm.²¹⁹

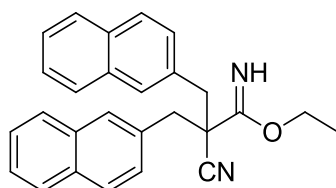
2-(2,2-Bis(phenylsulfonyl)ethyl)naphthalene 216



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (4.3 mg, 5 mol%) and DPEphos (14 mg, 10 mol%), 2-fluoromethylnaphthalene (20 mg, 0.13 mmol) reacted with *bis*(phenylsulfonyl)methane (74 mg, 2.0 equiv, 0.25 mmol) and potassium carbonate (35 mg, 2.0 equiv, 0.25 mmol) to give the product after flash chromatography (silica, 4:1 hexane/EtOAc) as a white solid (50 mg, 120 μmol, 92%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.88 (d, J=7.3 Hz, 4 H, ArH), 7.72 - 7.80 (m, 1 H, ArH), 7.57 - 7.69 (m, 4 H, ArH), 7.47 (t, J=8.0 Hz, 6 H, ArH), 7.39 (s, 1 H, ArH), 7.17 (dd, J=8.3, 1.5 Hz, 1 H, ArH), 4.86 (t, J=5.6 Hz, 1 H, (SO₂Ph)₂CHCH₂), 3.71 ppm (d, J=5.6 Hz, 2 H, ArCH₂CH); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 138.1, 134.5, 133.3, 133.1, 132.3, 129.4, 129.0, 128.5, 127.8, 127.6, 127.5, 126.3, 126.1, 126.0, 85.0, 31.5 ppm; IR: 1447, 1340, 1319, 1078 cm⁻¹; mp: 128 °C; HRMS (ESI) calc'd for [M+Na]⁺ C₂₄H₂₀NaO₄S₂: 459.0695, found 459.0689.

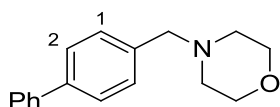
Ethyl 2-cyano-3-(naphthalen-2-yl)-2-(naphthalen-2-ylmethyl)propanimidate 217



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (4.3 mg, 5 mol%) and DPEphos (14 mg, 10 mol%), 2-fluoromethylnaphthalene (40 mg, 0.25 mmol) reacted with malononitrile (33 mg, 2.0 equiv, 0.50 mmol) and potassium carbonate (69 mg, 2.0 equiv, 0.50 mmol) to give the product after flash chromatography (silica, 4:1 hexane/EtOAc) as a pale brown oil (30 mg, 78 μ mol, 62%).

¹H NMR (CHLOROFORM-d, 400MHz): δ = 7.81 - 7.87 (m, 6 H, ArH), 7.79 (s, 2 H, ArH), 7.48 - 7.52 (m, 4 H, ArH), 7.44 (dd, J =8.6, 1.5 Hz, 2 H, ArH), 4.25 (q, J =6.5 Hz, 2 H, OCH₂CH₃), 3.55 (d, J =13.4 Hz, 2 H, NpCH₂), 3.35 (d, J =13.6 Hz, 2 H, NpCH₂), 1.49 ppm (t, J =7.1 Hz, 3 H, OCH₂CH₃); **¹³C NMR** (CHLOROFORM-d, 101MHz): δ = 164.7, 133.2, 132.8, 131.8, 129.1, 128.2, 127.8, 127.6, 126.2, 126.1, 119.4, 62.9, 55.4, 42.9, 14.2 ppm; **IR**: 2214 (C \equiv N stretch), 1739 (C=N stretch); **HRMS** (ESI+) m/z calc'd for [M+Na]⁺ C₂₇H₂₄N₂NaO⁺: 415.1781 found: 415.1769.

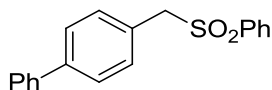
4-([1,1'-Biphenyl]-4-ylmethyl)morpholine 200



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (1.8 mg, 5 mol%) and DPEphos (2.9 mg, 5 mol%), 4-fluoromethyl-1,1'-biphenyl (20 mg, 110 μ mol) reacted with morpholine (0.02 ml, 0.16 mmol, 1.5 equiv) and triethylamine (0.03 ml, 0.16 mmol, 1.5 equiv) in ethanol at 70°C for 24h to give the product after flash chromatography (silica, 5:95 methanol/dichloromethane) as a brown oil (22 mg, 85 μ mol, 79%).

¹H NMR (CHLOROFORM-d, 400MHz): δ = 7.59 (d, J =7.8 Hz, 2 H, *HI*/2), 7.63 (d, J =7.6 Hz, 2 H, *HI*/2), 7.40 - 7.54 (m, 4 H, *o,m*-Ph), 7.37 (t, J =7.6 Hz, 1 H, *p*-Ph), 3.76 (t, J =4.3 Hz, 4 H, OCH₂R), 3.57 (s, 2 H, ArCH₂NR₂), 2.51 ppm (br. s., 4 H, NCH₂R); **¹³C NMR** (CHLOROFORM-d, 101MHz): δ = 140.8, 140.0, 136.8, 129.5, 128.7, 127.1, 127.0, 126.9, 67.0, 63.1, 53.6 ppm.²²⁰

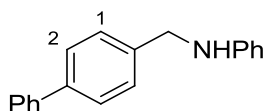
4-([1,1'-Biphenyl]-4-ylmethyl)phenyl sulfone 226



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (1.8 mg, 5 mol%) and *t*BuXPhos (4.6 mg, 10 mol%), 4-fluoromethyl-1,1'-biphenyl (20 mg, 110 μ mol) reacted with sodium phenyl sulfinate (26 mg, 0.16 mmol, 1.5 equiv) in ethanol/water 5:1 at 75°C for 4h to give the product after flash chromatography (silica, gradient 4:1 hexanes/dichloromethane to dichloromethane) as a white solid (22 mg, 70 μ mol, 66%).

$^1\text{H NMR}$ (CHLOROFORM-*d*,400MHz): δ = 7.70 (d, J =7.5 Hz, 2 H, *SO*₂*Ph-ortho*), 7.55 - 7.66 (m, 3 H, *SO*₂*Ph*), 7.41 - 7.54 (m, 6 H, *ArH*), 7.37 (t, J =7.6 Hz, 1 H, *para-Ph*), 7.17 (d, J =8.3 Hz, 2 H), 4.36 ppm (s, 2 H, *ArCH*₂*SO*₂*Ph*); $^{13}\text{C NMR}$ (CHLOROFORM-*d*,101MHz): δ = 141.6, 140.1, 137.9, 133.7, 131.2, 128.9, 128.8, 128.6, 127.6, 127.2, 127.0, 126.9, 62.6 ppm.²²¹

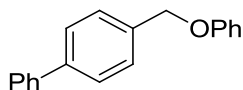
N-(4-Phenylbenzyl)aniline 223



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (3.6 mg, 5 mol%) and DPEphos (12 mg, 10 mol%), 4-fluoromethyl-1,1'-biphenyl (40 mg, 220 μ mol) reacted with aniline (0.04 ml, 0.44 mmol, 2.0 equiv) and triethylamine (0.06 ml, 0.44 mmol, 2.0 equiv) in ethanol at 75°C for 24 h to give the product after flash chromatography (silica, gradient 1:4 to 1:2 dichloromethane/hexanes) as a white solid (49 mg, 190 μ mol, 87%).

$^1\text{H NMR}$ (CHLOROFORM-*d*,400MHz): δ = 7.63 (t, J =7.6 Hz, 4 H, *o,m-Ph*), 7.49 (dt, J =7.8, 3.6 Hz, 4 H, *H1 & H2*), 7.39 (t, J =7.3 Hz, 1 H, *p-Ph*), 7.24 (t, J =7.8 Hz, 2 H, *m-NHPh*), 6.78 (t, J =7.6 Hz, 1 H, *p-NHPh*), 6.71 (d, J =7.8 Hz, 2 H, *o-NHPh*), 4.42 (s, 2 H, *ArCH*₂*NHPh*), 4.01 ppm (br. s., 1 H, *NH*); $^{13}\text{C NMR}$ (101 MHz, CHLOROFORM-*d*): δ = 148.1, 140.8, 140.2, 138.5, 129.3, 128.7, 127.9, 127.3, 127.2, 127.0, 117.6, 112.8, 48.0 ppm.²²²

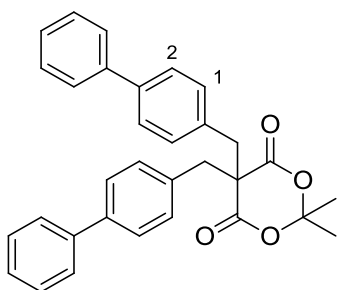
4-Phenylbenzyl phenyl ether 229



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (1.8 mg, 5 mol%) and DPEphos (5.8 mg, 10 mol%), 4-fluoromethyl-1,1'-biphenyl (40 mg, 220 μ mol) reacted with phenol (40 mg, 0.43 mmol, 2.0 equiv) and triethylamine (0.06 ml, 0.43 mmol, 2.0 equiv) in ethanol at 75°C for 24 h to give the product after flash chromatography (silica, gradient 10:1 hexanes/dichloromethane to 4:1) as a white solid (12 mg, 48 μ mol, 22%).

$^1\text{H NMR}$ (CHLOROFORM- d_4 ,400MHz): δ = 7.62 (t, $J=7.5$ Hz, 4 H, ArH), 7.53 (d, $J=7.8$ Hz, 2 H, ArH), 7.46 (t, $J=7.6$ Hz, 2 H, ArH), 7.38 (d, $J=7.3$ Hz, 1 H, ArH), 7.32 (t, $J=8.0$ Hz, 2 H, ArH), 7.02 (d, $J=8.3$ Hz, 2 H, ArH), 6.98 (d, $J=7.6$ Hz, 1 H, ArH), 5.13 ppm (s, 2 H, ArCH₂OPh); $^{13}\text{C NMR}$ (CHLOROFORM- d_4 ,50MHz): δ = 158.7, 140.9, 140.8, 136.0, 129.5, 128.8, 127.9, 127.3, 127.1, 120.9, 114.8, 69.6 ppm.²²³

5,5-Bis(biphenyl-4-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6,dione 219

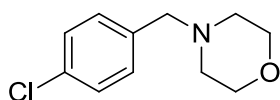


Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (1.8 mg, 5 mol%) and DPEphos (5.8 mg, 10 mol%), 4-fluoromethyl-1,1'-biphenyl (20 mg, 110 μ mol) reacted with Meldrum's acid (31 mg, 0.21 mmol, 2.0 equiv) and triethylamine (0.03 ml, 0.21 mmol, 2.0 equiv) in ethanol at 75°C for 16 h to give the product after flash chromatography (silica, 1:1 hexanes/dichloromethane) as a white solid (21 mg, 44 μ mol, 82%).

$^1\text{H NMR}$ (CHLOROFORM- d_4 ,400MHz): δ = 7.55 (d, $J=7.8$ Hz, 8 H, *o*-Ph & *H*1/2), 7.44 (t, $J=7.6$ Hz, 4 H, *m*-Ph), 7.36 (d, $J=7.3$ Hz, 2 H, *p*-Ph), 7.32 (d, $J=8.1$ Hz, 4 H, *H*1/2), 3.54 (s, 4 H, 2 x ArCH₂R),

0.70 ppm (s, 6 H, 2 x CH₃); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 168.2, 140.7, 140.4, 133.8, 130.6, 128.8, 127.5, 127.4, 126.9, 106.0, 60.1, 44.6, 28.7 ppm; IR: 1734 (C=O stretch), 1354, 1263, 1208 cm⁻¹; mp 183°C; HRMS (ESI+) calc'd for [M+Na]⁺ C₃₂H₂₈NaO₄: 499.1880, found: 499.1868.

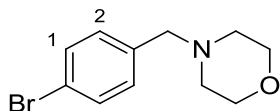
4-(4-Chlorobenzyl)morpholine 250



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (4.8 mg, 5 mol%) and DPEphos (16 mg, 10 mol%), 4-chlorobenzyl fluoride (40 mg, 0.28 mmol) reacted with morpholine (0.04 ml, 0.56 mmol, 2.0 equiv) and triethylamine (0.08 ml, 0.56 mmol, 2.0 equiv) in ethanol at 75°C for 16 h to give the product after acid/base extraction as a brown solid (52 mg, 240 μmol, 88%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.27 (s, 4 H, ArH), 3.70 (t, J=4.4 Hz, 4 H, OCH₂R), 3.45 (s, 2 H, ArCH₂NR₂), 2.42 ppm (br. s., 4 H, NCH₂R); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 136.3, 132.7, 130.3, 128.3, 66.9, 62.6, 53.5 ppm; IR: 2816, 1493, 1451, 1110 cm⁻¹; mp 56 °C; HRMS (ESI+) m/z calc'd for [M+H]⁺ C₁₁H₁₃³⁵ClNO: 212.0837 found: 212.0837.

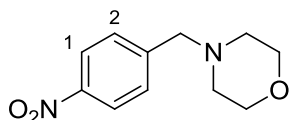
4-(4-Bromobenzyl)morpholine 253



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (3.6 mg, 5 mol%) and DPEphos (11 mg, 10 mol%), 4-bromobenzyl fluoride (20 mg, 0.106 mmol) reacted with morpholine (0.02 ml, 0.21 mmol, 2 equiv) and triethylamine (0.03 ml, 0.21 mmol, 2 equiv) in 1-propanol at 95°C for 16 h to give the product after acid/base extraction as a brown oil (18 mg, 69 μmol, 65%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.43 (d, $J=7.6$ Hz, 2 H, *H1*), 7.21 (d, $J=8.1$ Hz, 2 H, *H2*), 3.70 (t, $J=4.4$ Hz, 4 H, *OCH₂R*), 3.43 (s, 2 H, *ArCH₂NR₂*), 2.42 ppm (br. s., 4 H, *NCH₂R*); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 136.8, 131.3, 130.7, 120.8, 66.9, 62.6, 53.5 ppm.²²⁴

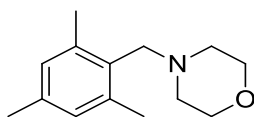
4-(4-Nitrobenzyl)morpholine 251



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (1.8 mg, 5 mol%) and *t*BuXPhos (9.1 mg, 20 mol%), 4-nitrobenzyl fluoride (20 mg, 0.13 mmol) reacted with morpholine (0.03 ml, 0.26 mmol, 2.0 equiv) and triethylamine (0.04 ml, 0.26 mmol, 2.0 equiv) in ethanol at 75°C for 4h to give the product after acid/base extraction (diethyl ether/HCl then NaOH/DCM) as a yellow solid (28 mg, 130 μ mol, 98%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 8.18 (d, $J=8.1$ Hz, 2 H, *H1*), 7.53 (d, $J=8.3$ Hz, 2 H, *H2*), 3.69 (t, $J=4.4$ Hz, 4 H, *OCH₂R*), 3.57 (s, 2 H, *ArCH₂NR₂*), 2.25 - 2.54 ppm (m, 4 H, *NCH₂R*); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 147.0, 145.9, 129.4, 123.4, 66.8, 62.3, 53.5 ppm.²²⁴

4-(2,4,6-Trimethylbenzyl)morpholine 252

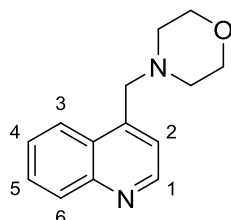


Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (2.3 mg, 5 mol%) and DPEphos (14 mg, 20 mol%), 2-(fluoromethyl)-1,3,5-trimethylbenzene (40 mg, 0.26 mmol) reacted with morpholine (0.05 ml, 0.53 mmol, 2.0 equiv) and triethylamine (0.07 ml, 0.53 mmol, 2.0 equiv) in ethanol at 75°C for 16 h to give the product after acid/base extraction as a yellow oil (23 mg, 100 μ mol, 40%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 6.88 (s, 2 H, *ArH*), 3.68 (t, $J=4.8$ Hz, 4 H, *OCH₂R*), 3.50 (s, 2 H, *ArCH₂NR₂*), 2.48 (t, $J=4.3$ Hz, 4 H, *NCH₂R*), 2.41 (s, 6 H, 2 x *o-CH₃*), 2.31 ppm (s, 3 H,

p-CH₃); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 138.0, 136.3, 131.3, 128.8, 67.2, 56.1, 53.1, 20.8, 20.0 ppm; IR: 2851, 1450, 1115 cm⁻¹; HRMS (ESI+) m/z calc'd for [M+H]⁺ C₁₄H₂₂NO: 220.1696 found: 220.1691.

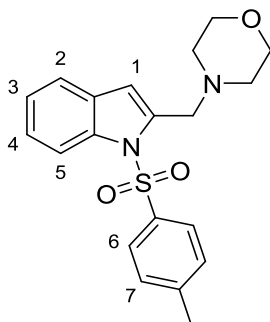
4-(Quinolin-4-ylmethyl)morpholine 245



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (3.2 mg, 5 mol%) and DPEphos (9.8 mg, 10 mol%), 4-fluoromethylquinoline (30 mg, 0.19 mmol) reacted with morpholine (0.03 ml, 0.37 mmol, 2.0 equiv) and triethylamine (0.05 ml, 0.37 mmol, 2.0 equiv) in ethanol at 75°C for 4h to give the product after acid/base extraction as a brown oil (37 mg, 0.16 mmol, 87%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 8.85 (d, *J*=4.3 Hz, 1 H, *H*1), 8.24 (d, *J*=8.3 Hz, 1 H, *H*3/6), 8.12 (d, *J*=8.6 Hz, 1 H, *H*3/6), 7.71 (t, *J*=7.7 Hz, 1 H, *H*4/5), 7.56 (t, *J*=8.1 Hz, 1 H, *H*4/5), 7.42 (d, *J*=4.3 Hz, 1 H, *H*2), 3.91 (s, 2 H, ArCH₂NR₂), 3.71 (t, *J*=4.5 Hz, 4 H, OCH₂R), 2.52 ppm (t, *J*=4.0 Hz, 4 H, NCH₂R); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 150.0, 148.3, 143.4, 129.9, 129.1, 127.6, 126.3, 124.1, 121.3, 66.9, 60.0, 53.8 ppm; IR: 1593, 1508, 1116 cm⁻¹; HRMS (ESI+) m/z calc'd for [M+H]⁺ C₁₄H₁₇N₂O: 229.1335, found: 229.1335.

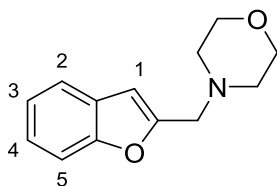
4-((1-Tosyl-1H-indol-2-yl)methyl)morpholine 244



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (1.1 mg, 5 mol%) and DPEphos (3.6 mg, 10 mol%), 2-(fluoromethyl)-1-tosylindole (20 mg, 0.066 mmol) reacted with morpholine (0.01 ml, 0.13 mmol, 2.0 equiv) and triethylamine (0.02 ml, 0.13 mmol, 2.0 equiv) in ethanol at 60°C for 2h to give the product after acid/base extraction (diethyl ether/HCl/NaOH) as a colourless oil (19 mg, 50 μ mol, 76%).

$^1\text{H NMR}$ (CHLOROFORM-d,400MHz): δ = 8.11 (d, J =8.3 Hz, 1 H, *H*6), 7.98 (d, J =8.3 Hz, 2 H, *H*7), 7.47 (d, J =7.6 Hz, 1 H, *H*2/5), 7.29 (t, J =7.3 Hz, 1 H, *H*3/4), 7.19 - 7.26 (m, 2 H, *H*2/5 & *H*3/4), 6.56 (s, 1 H, *H*1), 3.89 (s, 2 H, ArCH₂NR₂), 3.62 (t, J =4.5 Hz, 4 H, CH₂O), 2.48 - 2.62 (m, 4 H, CH₂N), 2.36 ppm (s, 3 H, ArCH₃); $^{13}\text{C NMR}$ (CHLOROFORM-d,101MHz): δ = 144.5, 137.2, 136.7, 129.4, 128.7, 127.0, 124.4, 123.3, 120.5, 114.6, 111.5, 66.8, 55.8, 53.5, 29.7, 21.5 ppm.²²⁵

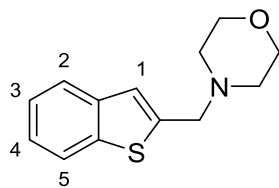
4-(Benzofuran-2-ylmethyl)morpholine 243



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (4.6 mg, 5 mol%) and DPEphos (14 mg, 10 mol%), 2-(fluoromethyl)benzofuran (40 mg, 0.29 mmol) reacted with morpholine (0.05 ml, 0.53 mmol, 2.0 equiv) and triethylamine (0.07 ml, 0.53 mmol, 2.0 equiv) in ethanol at 75°C for 4 h to give the product after acid/base extraction (diethyl ether/HCl then NaOH/DCM) as a pale yellow oil (57 mg, 260 μ mol, 98%).

$^1\text{H NMR}$ (CHLOROFORM-d, 200MHz): δ = 7.40 - 7.61 (m, 2 H, Ar*H*), 7.10 - 7.33 (m, 2 H, Ar*H*), 6.61 (d, J =0.7 Hz, 1 H, *H*1), 3.75 (t, J =4.8 Hz, 4 H, OCH₂R), 3.68 (s, 2 H, ArCH₂NR₂), 2.55 ppm (t, J =4.8 Hz, 4 H, NCH₂R); $^{13}\text{C NMR}$ (CHLOROFORM-d,50MHz): δ = 155.0, 153.9, 128.1, 124.0, 122.6, 120.6, 111.2, 105.8, 66.7, 55.8, 53.4 ppm.²²⁶

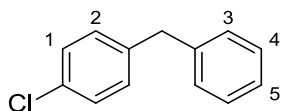
4-(Benzothiophene-2-ylmethyl)morpholine 242



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (4.1 mg, 5 mol%) and DPEphos (13 mg, 10 mol%), 2-(fluoromethyl)benzothiophene (40 mg, 0.24 mmol) reacted with morpholine (0.04 ml, 0.48 mmol, 2.0 equiv) and triethylamine (0.07 ml, 0.48 mmol, 2.0 equiv) in ethanol at 75°C for 4h to give the product after acid/base extraction (diethyl ether/HCl/NaOH) as a pale orange solid (56 mg, 240 μ mol, 99%).

$^1\text{H NMR}$ (CHLOROFORM-d,400MHz): δ = 7.80 (d, $J=7.8$ Hz, 1 H, $H_{2/5}$), 7.70 (d, $J=7.3$ Hz, 1 H, $H_{2/5}$), 7.24 - 7.37 (m, 2 H, $H_{3/4}$), 7.17 (s, 1 H, H_1), 3.79 (s, 2 H, ArCH_2NR_2), 3.75 (t, $J=4.6$ Hz, 4 H, OCH_2R), 2.55 ppm (t, $J=4.0$ Hz, 4 H, NCH_2R); $^{13}\text{C NMR}$ (CHLOROFORM-d,101MHz): δ = 142.8, 140.0, 139.5, 124.1, 123.9, 123.1, 122.3, 122.3, 66.9, 58.2, 53.4 ppm; **IR**: 2957, 2916, 2856, 2800, 1321, 1111, 1006 cm^{-1} ; **mp** 79 °C ; **HRMS** (ESI) m/z calc'd for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{16}\text{NOS}$: 234.0947 found: 234.0946.

(4-Chlorophenyl)phenylmethane 254



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (2.4 mg, 5 mol%) and DPEphos (7.4 mg, 10 mol%), 4-chlorobenzyl fluoride (20 mg, 0.140 mmol) reacted with phenylboronic acid (34 mg, 0.28 mmol, 2.0 equiv) and K_3PO_4 (58 mg, 0.28 mmol, 2.0 equiv) in *n*-propanol at 95°C for 16 h to give the product after flash chromatography (silica, hexanes) as a colourless oil (20 mg, 11wt% mixture with biphenyl, 18 mg product, 88 μ mol, 64%).

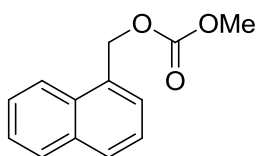
¹H NMR (CHLOROFORM-d,400MHz): $\delta = 7.21 - 7.34$ (m, 5 H, *H3*, *H4* & *H5*), 7.18 ppm (d, $J=7.1$ Hz, 2 H, *H1*), 7.13 (d, $J=8.3$ Hz, 2 H, *H2*), 3.97 ppm (s, 2 H, ArCH₂Ar); **¹³C NMR** (CHLOROFORM-d,101MHz): $\delta = 140.5, 139.6, 131.9, 130.2, 128.8, 128.5, 127.1, 126.3, 41.2$ ppm.²²⁷

5.3.3 Competition Reaction Substrates

Procedure for competition reactions

Palladium precursor and ligand, were added to a vial, solvent added and the mixture was stirred for 30 minutes. This solution was transferred to a vial containing one equivalent of each of benzylic fluoride and and comparison substrate and the mixture was stirred for a further 5 minutes. One equivalent of the nucleophile was added, the vial was purged with argon, and the mixture was then heated. After the time indicated the reaction mixture was poured into water (5 ml). The aqueous layer was extracted with DCM and the combined organics dried (MgSO_4) and concentrated *in vacuo*. The crude mixture was analysed by ^1H NMR, integrating the benzylic peaks to give relative ratios of species present.

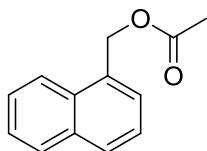
1-Naphthylmethyl carbonate 256d



Methyl chloroformate (1.5 ml, 13 mmol, 2.0 equiv) was added dropwise to a solution of 1-naphthylmethanol (1.0 g, 6.3 mmol) and pyridine (1.5 ml, 19 mmol, 3.0 equiv) in dichloromethane (20 ml) at 0 °C. The mixture was stirred at room temperature for 4 h then quenched by the dropwise addition of aqueous hydrochloric acid. The organic layer was separated and the aqueous layer extracted with dichloromethane. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (silica, 1:9 ethyl acetate : petroleum ether 40-60) to give the product as a yellow oil (0.95 g, 4.4 mmol, 70 %).

^1H NMR (CHLOROFORM- d , 400MHz) δ : 8.06 (m, 1H, ArH), 7.91 (m, 2H, ArH), 7.53 (m, 4H, ArH), 5.65 (s, 2H, ArCH₂O), 3.81 (s, 3H, OCH₃). ^{13}C NMR (CHLOROFORM- d , 101MHz) δ : 155.7, 133.7, 131.5, 130.7, 129.6, 128.7, 127.7, 126.7, 126.0, 125.2, 123.5, 68.0, 53.4 ppm.²²⁸

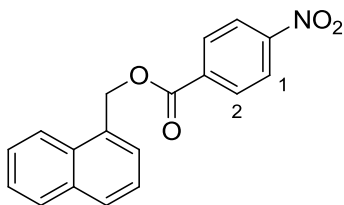
1-Naphthylmethylacetate 256a



Acetic anhydride (0.13 ml, 1.4 mmol, 1.1 equiv) was added to a stirred solution of 1-naphthalenemethanol (0.2 g, 1.3 mmol) and DMAP (16 mg, 0.13 mmol, 0.1 equiv.) in triethylamine (1 ml) at 0 °C and the reaction mixture stirred at room temperature overnight. The mixture was diluted with Et₂O (5 ml), then washed with 1M HCl (10 ml) solution, dried over MgSO₄, filtered, concentrated and purified by flash column chromatography (silica, 1:9, ethyl acetate : hexanes) to give the product as a light yellow oil (0.17 g, 0.83 mmol, 66%).

¹H NMR (CHLOROFORM-d, 400MHz) δ : 8.03 (d, J = 8.1 Hz, 1 H, ArH), 7.93 – 7.84 (m, 2 H, ArH), 7.62 – 7.51 (m, 3 H, ArH), 7.50 – 7.44 (m, 1 H, ArH), 5.59 (s, 2 H, ArCH₂O), 2.13 (s, 3 H, CH₃) ppm;
¹³C NMR (CHLOROFORM-d, 101MHz) δ : 171.0, 133.7, 131.6, 131.4, 129.3, 128.7, 127.5, 126.6, 125.9, 125.3, 124, 65, 21 ppm.²²⁹

1-Naphthylmethyl 4-nitrobenzoate 256b

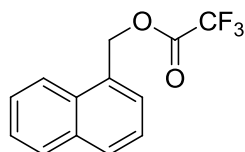


To a stirred solution of 1-naphthylmethanol (1.0 g, 6.3 mmol) and triethylamine (0.97 ml, 7.0 mmol, 1.1 equiv.) in DCM (20 ml), 4-nitrobenzoyl chloride (1.3 g, 7.0 mmol, 1.1 equiv.) was added portionwise at 0 °C. The temperature was increased to 25 °C and the mixture stirred for 1h. The reaction mixture was diluted with DCM (20 ml), washed with water (20 ml), sodium bicarbonate (3 x 20 ml) and brine (20 ml), dried over MgSO₄, filtered and the solvent removed *in vacuo* to give a pure yellow solid (1.8 g, 5.7 mmol, 91 %).

¹H NMR (CHLOROFORM-d, 400MHz) δ : 8.24 (d, J = 8.8 Hz, 2 H, HI/2), 8.20 (d, J = 9.1 Hz, 2 H, HI/2), 8.12 (d, J = 8.3 Hz, 1 H, ArH), 7.93 (d, J = 9.1 Hz, 1 H, ArH), 7.92 (d, J = 8.1 Hz, 1 H, ArH),

7.65 (d, $J = 6.6$ Hz, 1 H, ArH), 7.63 - 7.58 (m, 1 H, ArH), 7.58 - 7.53 (m, 1 H, ArH), 7.51 (dd, $J = 8.1$, 7.1 Hz, 1 H, ArH), 5.88 (s, 2 H, ArCH₂). ¹³C NMR (CHLOROFORM-d, 101MHz) δ : 164.6, 150.6, 135.4, 133.8, 131.7, 130.8, 130.7, 129.8, 128.9, 128.0, 126.9, 126.1, 125.3, 123.5, 123.4, 66.0 ppm; **IR**: 1711 (C=O stretch), 1529 (NO₂ asymmetric stretch) cm⁻¹; **mp** 121°C; **HRMS** (FI) m/z calc'd for [M]⁺ C₁₈H₁₄NO₄: 307.0845, found: 307.0843.

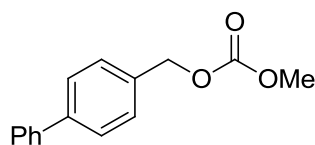
1-Naphthylmethyl trifluoroacetate 256c



To a stirred solution of naphthalenemethanol (0.77 g, 4.9 mmol) and triethylamine (0.74 ml, 5.3 mmol, 1.1 equiv.) in dichloromethane (15 ml) at 0 °C, trifluoroacetic anhydride (1.7 ml, 5.3 mmol, 1.1 equiv.) was added and the mixture stirred for 3h at 25 °C. The reaction mixture was washed with sodium bicarbonate (sat. aq.) (3 x 20 ml) and brine (20 ml), dried over MgSO₄, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (1:9 EtOAc:petrol) gave a yellow oil (1.0 g, 4.0 mmol, 82 %).

¹H NMR (CHLOROFORM-d, 400MHz) δ : 8.00 (d, $J = 8.3$ Hz, 1 H, ArH), 7.94 (d, $J = 8.1$ Hz, 2 H, ArH), 7.66 - 7.55 (m, 3 H, ArH), 7.53 - 7.45 (m, 1 H, ArH), 5.84 (s, 2 H, ArCH₂) ppm; ¹³C NMR (CHLOROFORM-d, 101MHz) δ : 157.5 (q, $J = 42$ Hz), 133.8, 131.5, 130.4, 128.8, 128.8, 128.5, 127.1, 126.3, 125.2, 123.0, 114.6 (q, $J = 286$ Hz), 68.0 ppm; ¹⁹F NMR (377 MHz, CHLOROFORM-d) δ : -74.9 ppm; **IR**: 1785 (C=O stretch), 1338, 1224, 1145, 793, 775 cm⁻¹; **HRMS** (FI) m/z calc'd for [M]⁺ C₁₃H₁₀F₃O₂: 254.0555, found: 254.0553.

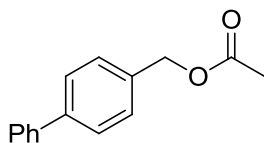
[1,1'-Biphenyl]-4-ylmethyl methyl carbonate 260d



A solution of biphenyl-4-methanol (0.50 g, 2.7 mmol) and pyridine (0.24 ml, 3.0 mmol, 1.1 equiv.) in dichloromethane (5 ml) was cooled to 0°C and methyl chloroformate (0.23 ml, 3.0 mmol, 1.1 equiv.) was added dropwise. The mixture was stirred at this temperature for 4 h and a further equivalent of both pyridine and methyl chloroformate were added, the mixture was stirred at room temperature for 4h, then poured into saturated aqueous sodium bicarbonate solution (10 ml). Dichloromethane was added (10 ml) and the organic layer was extracted with 2 portions of dilute hydrochloric acid. The solvent was removed *in vacuo* to give the product as a white solid (610 mg, 2.5 mmol, 93%).

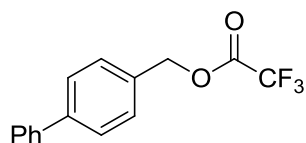
¹H NMR (CHLOROFORM-d,400MHz): δ = 7.54 - 7.66 (m, 4 H, ArH), 7.41 - 7.52 (m, 4 H, ArH), 7.38 (d, $J=7.3$ Hz, 1 H, ArH), 5.22 (s, 2 H, ArCH₂O), 3.83 ppm (s, 3 H, OCH₃); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 155.7, 141.5, 140.6, 134.2, 128.8, 127.5, 127.3, 127.1, 69.4, 54.9 ppm.²³⁰

[1,1'-Biphenyl]-4-ylmethyl acetate 260a



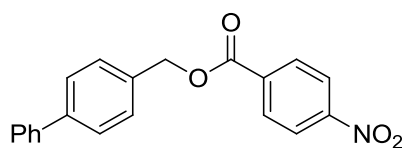
To a solution of 4-biphenylmethanol (0.50 g, 2.7 mmol) and triethylamine (0.41 ml, 3.0 mmol, 1.1 equiv.) in dichloromethane (10 ml) at 0°C was added acetyl chloride (0.21 ml, 3.0 mmol, 1.1 equiv.) and the mixture stirred at this temperature for 1 h. Saturated aqueous sodium bicarbonate solution was added and the mixture transferred to a separating funnel. The aqueous layer was extracted with 2 portions of dichloromethane and the combined organic fractions were dried over MgSO₄. Evaporation of the solvent gave the product as a white solid (0.47 g, 2.1 mmol, 76%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.60 - 7.72 (m, 4 H, ArH), 7.46 - 7.55 (m, 4 H, ArH), 7.42 (t, $J=7.3$ Hz, 1 H, ArH), 5.22 (s, 2 H, ArCH₂O), 2.18 ppm (s, 3 H, OCH₃); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 170.7, 141.0, 140.5, 134.8, 128.7, 128.6, 127.3, 127.1, 126.9, 65.8, 20.8 ppm.²³¹

[1,1'-Biphenyl]-4-ylmethyl trifluoroacetate 260c

To a solution of 4-biphenylmethanol (1.0 g, 5.4 mmol) and pyridine (0.70 ml, 8.7 mmol, 1.6 equiv.) in dichloromethane (10 ml) at 0°C was added trifluoroacetic acid anhydride (1.1 ml, 8.2 mmol, 1.5 equiv.) and the mixture stirred at this temperature for 2h. Methanol (0.5 ml) was added dropwise and the mixture transferred to a separating funnel. The solution was washed with 1 portion of saturated aqueous sodium bicarbonate solution and then dried over MgSO₄. The crude product was purified by flash chromatography (4 parts petrol ether to 1 part ethyl acetate) to give the product as a white solid (0.50 g, 1.8 mmol, 33%).

¹H NMR (CHLOROFORM-*d*, 400 MHz): δ = 7.71 (t, J =8.6 Hz, 4 H, ArH), 7.51 - 7.61 (m, 4 H, ArH), 7.48 (t, J =7.6 Hz, 1 H, ArH), 5.47 ppm (s, 2 H, ArCH₂O); **¹³C NMR** (101 MHz, CHLOROFORM-*d*) δ ppm 157.3 (q, J =42.3 Hz), 142.2, 140.2, 132.2, 129.1, 128.8, 127.7, 127.5, 127.0, 114.6 (q, J =284.4 Hz), 69.3; **IR**: 1785, 1342, 1209, 1142 cm⁻¹; **mp** 62°C; **HRMS** (CI) m/z calc'd for [M+H]⁺ C₁₅H₁₂O₂F₃: 281.0789, found: 281.0794.

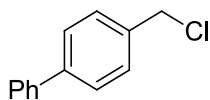
[1,1'-Biphenyl]-4-ylmethyl 4-nitrobenzoate 260b

To a solution of 4-biphenylmethanol (400 mg, 2.2 mmol) and triethylamine (0.33 ml, 2.4 mmol, 1.1 equiv.) in dichloromethane (8 ml) at 0°C was added *para*-nitrobenzoyl chloride (440 mg, 2.4 mmol, 1.1 equiv.) and the mixture was stirred at room temperature for 4h. Dichloromethane was added (10ml) and the organic layer extracted with 2 portions of water, 2 portions of saturated aqueous sodium bicarbonate solution, the solvent was removed *in vacuo* and the residue purified by flash

chromatography (4 parts petroleum ether to 1 part ethyl acetate) to give the product as a pale yellow solid (0.57 g, 1.70 mmol, 78%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 8.23 - 8.33 (m, 4 H, ArH), 7.58 - 7.68 (m, 4 H, ArH), 7.55 (d, J =8.3 Hz, 2 H, ArH), 7.47 (t, J =7.6 Hz, 2 H, ArH), 7.33 - 7.42 (m, J =7.3 Hz, 1 H, ArH), 5.46 ppm (s, 2 H, ArCH₂O); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 164.6, 150.6, 141.6, 140.5, 135.5, 134.2, 130.8, 129.0, 128.8, 127.6, 127.5, 127.1, 123.5, 67.4 ppm; **IR**: 1712 (C=O stretch), 1519, 1260 cm⁻¹; **mp** 126 °C; **HRMS** (FI) m/z calc'd for [M]⁺ C₂₀H₁₅NO₄: 333.1001, found: 333.1005.

4-(Chloromethyl)-1,1'-biphenyl 260e

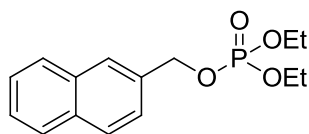


To a solution of 4-biphenylmethanol (1.0 g, 5.4 mmol) and pyridine (0.50 ml, 6.0 mmol, 1.1 equiv.) in dichloromethane (10 ml) at 0°C was added phosphorus pentachloride (1.2 g, 6.0 mmol, 1.1 equiv.) and the mixture stirred at this temperature for 1h. Methanol (0.5 ml) was added dropwise and the mixture transferred to a separating funnel. The solution was washed with 1 portion of saturated aqueous sodium bicarbonate solution and then dried over MgSO₄. The solvent was removed *in vacuo* to give the product as a white solid (1.0 g, 5.0 mmol, 92%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.57 - 7.66 (m, 4 H, ArH), 7.42 - 7.52 (m, 4 H, ArH), 7.35 - 7.42 (m, 1 H, ArH), 4.66 ppm (s, 2 H, ArCH₂Cl); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 141.4, 140.5, 136.4, 129.0, 128.8, 127.5, 127.5, 127.1, 46.0 ppm.²³²

5.3.4 Substrates for Benzylic Fluorination

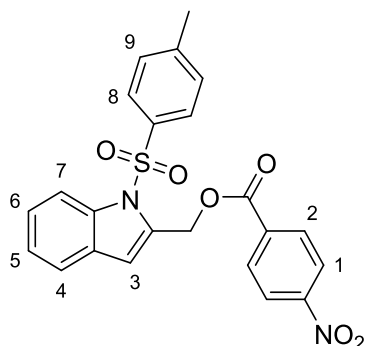
Diethyl (naphthalen-2-ylmethyl) phosphate 258d



Naphthalen-2-yl methanol (0.40 g, 2.0 mmol) was dissolved in DCM (20 ml) and pyridine was added (0.24 ml, 3.0 mmol, 1.5 equiv.). The mixture was cooled to 0°C and diethylchlorophosphate (0.44 ml, 3.0 mmol, 1.5 equiv.) was added dropwise. The mixture was stirred for 4h at RT and then quenched by the addition of NaHCO₃ (sat. aq. soln.). The organic fraction was removed, the aqueous layer extracted with dichloromethane, and the combined organic fractions dried (MgSO₄) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, 2:1 hexane/EtOAc) to give the product as a straw coloured liquid (560 mg, 1.9 mmol, 94%).

¹H NMR (CHLOROFORM-*d*, 400MHz): δ = 7.77 - 7.94 (m, 4 H, ArH), 7.42 - 7.58 (m, 3 H, ArH), 5.24 (d, J =8.1 Hz, 2 H, ArCH₂O), 4.12 (m, 4 H, 2 x OCH₂CH₃), 1.31 ppm (td, J =7.1, 1.0 Hz, 6 H, 2 x CH₃); ¹³C NMR (101 MHz, CHLOROFORM-*d*) δ = 133.4, 133.2, 133.1, 128.4, 128.0, 127.7, 126.9, 126.4, 126.3, 125.4, 69.1 (d, J =5.6 Hz), 63.9 (d, J =5.6 Hz), 16.1 (d, J =7.2 Hz) ppm; ³¹P NMR (162 MHz, CHLOROFORM-*d*) δ = -0.8 ppm.²³³

(1-Tosyl-1H-indol-2-yl)methyl 4-nitrobenzoate 262

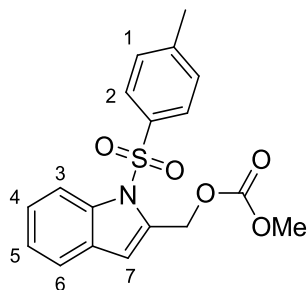


(1-Tosylindol-2-yl)methanol (1.0 g, 3.3 mmol) and Et₃N (0.51 ml, 3.7 mmol, 1.1 equiv) were dissolved in DCM (20 ml). The mixture was cooled to 0 °C and 4-nitrobenzoyl chloride (0.68 g, 3.7

mmol, 1.1 equiv) was added as one portion. The reaction was stirred for 2 h, then quenched by the addition of sat. aq. NaHCO₃. The organic fraction was separated and the aqueous fraction extracted with DCM. The combined organic fractions were dried (MgSO₄) and the solvent removed to give the product as a yellow crystalline solid (1.5 g, quantitative yield).

¹H NMR (CHLOROFORM-d,400MHz): δ = 8.14 - 8.21 (m, 2 H, *H1*), 8.02 - 8.12 (m, 3 H, *H2* & *H4/7*), 7.56 - 7.65 (m, 2 H, *H8*), 7.45 (d, *J*=7.8 Hz, 1 H, *H4/7*), 7.28 (ddd, *J*=8.4, 7.2, 1.2 Hz, 1 H, *H5/6*), 7.14 - 7.22 (m, 1 H, *H5/6*), 7.04 - 7.11 (m, *J*=7.8 Hz, 2 H, *H9*), 6.75 (d, *J*=0.7 Hz, 1 H, *H3*), 5.71 (s, 2 H, ArCH₂O), 2.24 ppm (s, 3 H, ArCH₃); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 164.2, 150.6, 145.1, 137.3, 135.9, 135.2, 134.0, 130.9, 129.9, 128.6, 126.3, 125.5, 123.9, 123.5, 121.3, 114.6, 113.4, 60.6, 21.5 ppm; **IR**: 1729 (C=O stretch), 1520 (NO₂ asymmetric stretch), 1346 (NO₂ symmetric stretch), 1265 cm⁻¹; **mp** 150 °C; **HRMS** (ESI+) *m/z* calc'd for [M+Na]⁺ C₂₃H₁₈N₂O₆S: 473.0778, found: 473.0763.

Methyl ((1-tosyl-1H-indol-2-yl)methyl) carbonate 263



(1-Tosylindol-2-yl)methanol (0.50 g, 1.7 mmol) and pyridine (0.21 ml, 2.7 mmol, 1.6 equiv) was dissolved in DCM (16 ml) and the solution cooled to 0 °C. Methyl chloroformate (0.19 ml, 2.5 mmol, 1.5 equiv) was added dropwise and the mixture stirred at this temperature for 3 h. Sat. aq. NaHCO₃ was added (5 ml) to quench, then the organic fraction separated. The aqueous fraction was extracted with DCM and the combined organic fractions were dried (MgSO₄) and the solvent removed to give the product as an orange oil (0.58 g, 1.6 mmol, 96%).

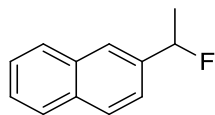
¹H NMR (CHLOROFORM-d,400MHz): δ = 8.12 (dd, *J*=8.3, 0.8 Hz, 1 H, *H3/H6*), 7.84 (d, *J*=8.3 Hz, 2 H, *H2*), 7.49 (d, *J*=7.8 Hz, 1 H, *H3/H6*), 7.34 (ddd, *J*=8.5, 7.2, 1.3 Hz, 1 H, *H4/H5*), 7.22 - 7.26 (m,

1 H, *H4/H5*), 7.20 (d, *J*=8.1 Hz, 2 H, *H1*), 6.76 (d, *J*=0.8 Hz, 1 H, *H7*), 5.60 (s, 2 H, ArCH₂OR), 3.84 (s, 3 H, OCH₃), 2.32 ppm (s, 3 H, ArCH₃); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 155.3, 145.0, 136.8, 135.3, 134.1, 129.7, 128.6, 126.8, 125.2, 123.6, 121.2, 114.4, 112.8, 62.5, 55.0, 21.4 ppm; IR: 1749 (C=O stretch), 1449, 1370, 1255, 1173 cm⁻¹; HRMS (ESI+) m/z calc'd for [M+Na]⁺ C₁₈H₁₇NO₅S: 382.0720, found: 382.0721.

5.4 Experimental Data for Chapter 4

5.4.1 Synthesis of Secondary and Tertiary Benzylic Fluorides

2-(1-Fluoroethyl)naphthalene 265



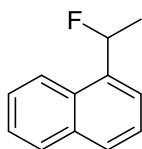
Diethylaminosulfurtrifluoride (2.5 ml, 19 mmol, 3.0 equiv) was added to dichloromethane (8 ml) and the mixture cooled to -78°C . Trimethylsilylmorpholine (3.6 ml, 20 mmol, 3.3 equiv) was added and the mixture stirred at room temperature for 2.5 h. The mixture was cooled to -78°C and a solution of alpha-methyl-2-naphthalenemethanol (1.0 g, 5.9 mmol) in dichloromethane (18 ml) was added slowly, the reaction mixture was allowed to warm to room temperature and then stirred for 16h. The reaction was quenched by the dropwise addition of 1 ml of methanol followed by saturated aqueous sodium bicarbonate solution. After aqueous workup the combined organic fractions were dried (MgSO_4) and the solvent evaporated. The product was isolated by flash chromatography, eluting with pentane. The product was a white solid (0.75 g, 4.3 mmol, 73%) that decomposed violently if stored neat in glass containers – final solvent evaporation was performed in a plastic centrifuge tube and the product stored in a freezer.

$^1\text{H NMR}$ (CHLOROFORM-*d*, 400MHz): δ = 7.81 - 7.97 (m, 4 H, ArH), 7.46 - 7.61 (m, 3 H, ArH), 5.85 (dq, $J=47.5, 6.1$ Hz, 1 H, CHFMe), 1.79 ppm (dd, $J=23.5, 6.1$ Hz, 3 H, CH_3); $^{13}\text{C NMR}$ (101 MHz, CHLOROFORM-*d*) δ ppm 22.90 (d, $J=26$ Hz) 91.07 (d, $J=167$ Hz) 123.07, 124.13, 126.15, 126.27, 127.67, 128.05, 128.33, 133.06, 133.14, 138.79 (d, $J=19$ Hz) ppm; $^{19}\text{F NMR}$ (377 MHz, CHLOROFORM-*d*) δ ppm -166.80 (dq, $J=48, 24$ Hz); **IR**: 1056 (C-F stretch), 827, 753 cm^{-1} ; **mp** 45°C ; **HRMS** (GC-MS CI^+) m/z calc'd for $[\text{M}-\text{HF}+\text{NH}_4]^+$ $\text{C}_{12}\text{H}_{14}\text{N}$: 172.1126 found: 172.1120; **HPLC**: Diacell OJ-H, 98:2 hexane/*i*PrOH, 1 ml/min, retention times: *R*: 10.68 min, *S*: 12.17 min.

For stereospecific deoxyfluorination of enantiopure 2-(1-fluoroethyl)naphthalene the reaction was performed using the same quantities of reagent, with the stir after addition of the alcohol performed at

-78°C for 48h rather than room temperature for 16h – this afforded the product with *ee*'s ranging from 69-77%.¹⁷⁵

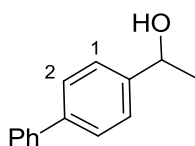
1-(1-Fluoroethyl)naphthalene 295



DAST (2.5 ml, 19 mmol, 3.3 equiv.) was added to DCM (8 ml) and the solution was cooled to -78°C. TMS-morpholine (3.6 ml, 20 mmol, 3.5 equiv.) was added and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was then cooled to -78°C and a solution of 1-(naphthalen-1-yl)ethan-1-ol (1.0 g, 5.8 mmol) in DCM (18 ml) was added dropwise. The mixture was allowed to come to RT, and stirred for 48h. The reaction was quenched by the addition of MeOH (0.5 ml) and then 1M aq. K₂CO₃. The organic phase was separated, and the aqueous fraction extracted with DCM. The combined organic fractions were dried (MgSO₄) and the residue purified by flash chromatography (silica, 30-40 petrol ether) to give the product as a colourless oil (0.60 g, 3.4 mmol, 59 %).

¹H NMR (CHLOROFORM-d,400MHz): δ = 8.05 (d, J =8.1 Hz, 1 H, ArH), 7.89 - 7.96 (m, 1 H, ArH), 7.86 (d, J =8.1 Hz, 1 H, ArH), 7.65 (d, J =7.1 Hz, 1 H, ArH), 7.49 - 7.60 (m, 3 H, ArH), 6.39 (dq, J =46.7, 6.4 Hz, 1 H, ArCHFCH₃), 1.87 ppm (dd, J =24.0, 6.6 Hz, 3 H, CHFCH₃); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 137.0 (d, J =18 Hz), 133.7, 129.9, 128.9, 128.7, 126.3, 125.7, 125.3, 123.1, 122.5 (d, J =10 Hz), 88.8 (d, J =167 Hz), 22.4 (d, J =25 Hz) ppm; ¹⁹F NMR (377 MHz, CHLOROFORM-d) δ ppm -170.3 - -169.2 (m).⁸⁰

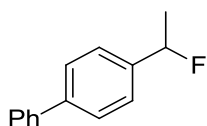
1-([1,1'-Biphenyl]-4-yl)ethanol



LiAlH₄ (0.20 g, 5.1 mmol, 0.5 equiv.) was suspended in Et₂O. The suspension was cooled and 4-acetylbiphenyl (2.0 g, 10 mmol) was added portionwise. The mixture was stirred at RT until complete, then quenched by the dropwise addition of water, until the suspended solids were white and began to clump. The mixture was filtered, washing the solids with EtOAc, and the filtrate was concentrated under vacuum to give the product as a white solid (1.8 g, 9.0 mol, 89%).

¹H NMR (CHLOROFORM-d,400MHZ): δ = 7.56 - 7.66 (m, 4 H, *o*-Ph & *H1/H2*), 7.43 - 7.51 (m, 4 H, *m*-Ph & *H1/H2*), 7.37 (t, *J*=7.1 Hz, 1 H, *p*-Ph), 4.97 (q, *J*=6.2 Hz, 1 H, *CHOHCH*₃), 1.97 (br. s., 1 H, *OH*), 1.56 ppm (d, *J*=6.6 Hz, 3 H, *CHCH*₃); ¹³C NMR (CHLOROFORM-d,101MHZ): δ = 144.8, 140.8, 140.4, 128.7, 127.2, 127.2, 127.1, 125.8, 70.1, 25.1 ppm.²³⁴

4-(1-Fluoroethyl)-1,1'-biphenyl 267

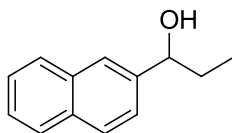


DAST (1.1 ml, 8.2 mmol, 3.3 equiv.) was added to DCM (4 ml) and the solution was cooled to -78°C. TMS-morpholine (1.5 ml, 8.2 mmol, 3.3 equiv.) was added and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was then cooled to -78°C and a solution of 1-([1,1'-biphenyl]-4-yl)ethanol (0.5 g, 2.5 mmol) in DCM (9 ml) was added dropwise. The mixture was allowed to come to RT, and stirred for 48h. The reaction was quenched by the addition of MeOH (0.5 ml) and then 1M aq. K₂CO₃. The organic phase was separated, and the aqueous fraction extracted with DCM. The combined organic fractions were dried (MgSO₄) and the residue purified by flash chromatography (silica, 30-40 petrol ether) to give the product as a colourless oil that solidified on standing in the freezer (0.44 g, 2.2 mmol, 88%).

¹H NMR (CHLOROFORM-d,400MHZ): δ = 7.62 (t, *J*=6.8 Hz, 4 H, *ArH*), 7.42 - 7.50 (m, 4 H, *ArH*), 7.33 - 7.42 (m, 1 H, *PhH*), 5.70 (dq, *J*=47.7, 6.3 Hz, 1 H, *CHFCH*₃), 1.71 ppm (dd, *J*=24.0, 6.6 Hz, 3 H, *CH*₃); ¹³C NMR (101 MHz, CHLOROFORM-d) δ ppm 141.2, 140.7, 140.4 (d, *J*=20 Hz), 128.8, 127.4, 127.3, 127.1, 125.7 (d, *J*=6 Hz), 90.8 (d, *J*=168 Hz), 22.9 (d, *J*=25 Hz); ¹⁹F NMR (376 MHz,

CHLOROFORM-*d*) δ ppm -166.6 (dt, $J=71.7, 23.9$ Hz). **IR** (Diamond ATR): 1484, 1067 (C-F stretch), 1005 cm^{-1} ; **HRMS** (GCT-MS CI+) m/z calc'd for $[\text{M-F}]^+$ $\text{C}_{14}\text{H}_{13}$: 181.1017 found: 181.1018.

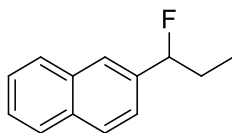
1-(Naphthalen-2-yl)propan-1-ol



A solution of ethylmagnesium bromide (3 M in Et_2O , 2.6 ml, 7.8 mmol, 1.2 equiv.) was added dropwise to a solution of 2-naphthaldehyde (1.0 g, 6.5 mmol) in tetrahydrofuran (13 ml) at 0°C and the mixture stirred at this temperature for 2h, then for a further 1h at room temperature. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution, then the solvent removed *in vacuo*. Water was added to the residue and the mixture extracted with 3 portions of dichloromethane. The combined organic fractions were dried (MgSO_4) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (4:1 Hexane/EtOAc) to give the product as a white solid (0.85 g, 4.6 mmol, 71%).

^1H NMR (CHLOROFORM-*d*, 400MHz): δ = 7.80 - 7.92 (m, 3 H, ArH), 7.76 (s, 1 H, ArH), 7.51 - 7.58 (m, 2 H, ArH), 7.48 (dd, $J=8.5, 1.4$ Hz, 1 H, ArH), 4.71 (t, $J=6.6$ Hz, 1 H $\text{CHOHCH}_2\text{CH}_3$), 2.88 (s, 1 H, OH), 1.89 (qt, $J=13.7, 6.9$ Hz, 2 H, $\text{CHOHCH}_2\text{CH}_3$), 0.97 ppm (t, $J=7.5$ Hz, 3 H, CH_3); **^{13}C NMR** (CHLOROFORM-*d*, 101MHz): δ = 141.8, 133.1, 132.8, 128.0, 127.8, 127.5, 125.9, 125.6, 124.6, 124.1, 75.8, 31.5, 10.0 ppm ²³⁵

2-(1-Fluoropropyl)naphthalene 291

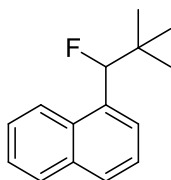


DAST (0.93 ml, 7.1 mmol, 3.3 equiv) was added to DCM (3ml) and the solution cooled to -78°C . TMS-morpholine (1.3 ml, 7.1 mmol, 3.3 equiv) was added dropwise, and the mixture stirred at RT for 2.5 h. The mixture was cooled to -78°C and a solution of 1-(naphthalen-2-yl)propan-1-ol (0.40 g, 2.2

mmol) in DCM (7 ml) was added dropwise. The mixture was allowed to come to RT and stirred for 48 h, then quenched with MeOH (1 ml) and saturated K₂CO₃ solution (10 ml). The organic phase was separated and the aqueous layer extracted with DCM. The combined organic fractions were dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (hexane) to give the product as a low melting white solid (300 mg, 1.6 mmol, 75%).

¹H NMR (CHLOROFORM-*d*,400MHz): δ = 7.84 - 7.93 (m, 3 H, ArH), 7.81 (s, 1 H, ArH), 7.50 - 7.58 (m, 2 H, ArH), 7.48 (d, *J*=8.6 Hz, 1 H, ArH), 5.56 (ddd, *J*=47.5, 7.1, 5.6 Hz, 1 H, CHF), 1.90 - 2.19 (m, 2 H, CHFCH₂), 1.04 ppm (t, *J*=7.5 Hz, 3 H, CH₃); **¹³C NMR** (101 MHz, CHLOROFORM-*d*) δ ppm 137.6 (d, *J*=20.0 Hz), 133.2, 133.0, 128.3, 128.0, 127.7, 126.3, 126.1, 124.8 (d, *J*=8.0 Hz), 123.3 (d, *J*=6.4 Hz), 95.9 (d, *J*=171.0 Hz), 30.1 (d, *J*=24.0 Hz), 9.4 (d, *J*=5.6 Hz); **IR**: 1509, 1463, 1271, 1086 (C-F stretch), 1043 cm⁻¹; **HRMS** (GCT - MS CI+) *m/z* calc'd for [M-F]⁺ C₁₃H₁₃ 169.1017, found 169.1010.

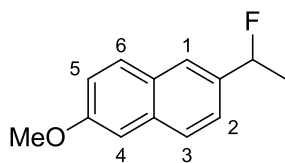
1-(1-Fluoro-2,2-dimethylpropyl)naphthalene 296



DAST (0.40 ml, 3.0 mmol, 3.3 equiv) was added to DCM (2 ml) and cooled to -78°C. TMS-morpholine (0.54 ml, 3.1 mmol, 3.3 equiv) was added dropwise and the mixture was stirred at RT for 2.5 h. 2,2-dimethyl-1-(naphthalen-1-yl)propan-1-ol²³⁶ (0.20 g, 0.94 mmol) in DCM (5 ml) was added dropwise to the solution of DAST at -78°C, and the mixture was stirred at RT for 48 h. MeOH (0.5 ml) was added to quench the reaction, followed by 1 M K₂CO₃ (aq.). The aqueous layer was extracted with DCM and the combined organic fractions were dried (MgSO₄). The solvent was removed and the product purified by flash chromatography (silica, hexanes) to give a colourless oil (140 mg, 0.63 mmol, 67%).

¹H NMR (CHLOROFORM-*d*, 400 MHz): δ = 8.05 (d, J =8.6 Hz, 1 H, ArH), 7.87 - 7.92 (m, 1 H, ArH), 7.86 (d, J =8.1 Hz, 1 H), 7.64 (d, J =7.3 Hz, 1 H, ArH), 7.45 - 7.58 (m, 3 H, ArH), 6.10 (d, J =45.0 Hz, 1 H, ArCHFR), 1.07 ppm (s, 9 H, 3 x CH₃); **¹³C NMR** (101 MHz, CHLOROFORM-*d*) δ ppm 134.0 (d, J =20.0 Hz), 133.3, 131.3 (d, J =4.8 Hz), 128.8, 128.5 (d, J =1.6 Hz), 125.8, 125.6 (d, J =10.4 Hz), 125.2, 124.8, 123.8, 97.0 (d, J =175.8 Hz), 37.0 (d, J =22.4 Hz), 26.0 (d, J =4.8 Hz); **IR**: 1477, 1395, 1364, 1051 (C-F stretch), 984 cm⁻¹; **HRMS** (GC - MS CI⁺) m/z calc'd for [M-F]⁺ C₁₅H₁₇: 197.1330, found: 197.1322.

2-(1-Fluoroethyl)-6-methoxynaphthalene 288

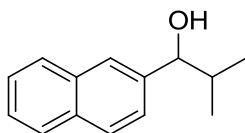


DAST (0.42 ml, 3.2 mmol, 3.3 equiv) was added to DCM (2 ml) and the solution cooled to -78°C. TMS-morpholine (0.57 ml, 3.2 mmol, 3.3 equiv) was added dropwise and the mixture was stirred at RT for 2.5 h. The mixture was cooled to -78°C and 1-(6-methoxynaphthalen-2-yl)ethanol²³⁷ (0.20 g, 0.99 mmol) in DCM (5 ml) was added dropwise. The reaction mixture was stirred at RT for 16h, then quenched by the careful addition of MeOH (0.5 ml) and NaHCO₃ (5 ml sat. aq.). The organic fraction was separated, and the aqueous fraction extracted with DCM. The combined organic fractions were dried (MgSO₄) and the residue purified by flash chromatography (silica, 3% EtOAc in hexane) to give the product as a white solid (160 mg, 0.78 mmol, 79%).

¹H NMR (BENZENE-*d*₆, 400 MHz): δ = 7.58 (d, J =8.6 Hz, 1 H, H₃), 7.54 (s, 1 H, H₁), 7.48 (d, J =9.0 Hz, 1 H, H₆), 7.37 (dd, J =8.3, 1.7 Hz, 1 H, H₂), 7.19 (dd, J =9.0, 2.4 Hz, 1 H, H₅), 6.91 (d, J =2.4 Hz, 1 H, H₄), 5.49 (dq, J =47.7, 6.6 Hz, 1 H, CHFCH₃), 3.38 (s, 3 HOCH₃), 1.46 ppm (dd, J =23.2, 6.4 Hz, 3 H, CHFCH₃); **¹³C NMR** (101 MHz, BENZENE-*d*₆) δ = 158.8, 137.5 (d, J =20 Hz), 135.3, 130.3, 129.0, 127.8, 125.0 (d, J =8 Hz) 124.4 (d, J =6 Hz), 119.9, 106.3, 91.4 (d, J =168 Hz), 55.1, 23.4 ppm (d, J =25 Hz); **¹⁹F NMR** (377 MHz, BENZENE-*d*₆) δ = -165.75 ppm (dq, J =46.8, 24.0 Hz); **IR**: 1607,

1484, 1264, 1119 (C-F stretch) cm^{-1} ; **mp** 59 °C (decomposed); **HRMS** (GC - MS CI^+) m/z calc'd for $[\text{M-F}]^+$ $\text{C}_{13}\text{H}_{13}\text{O}$: 185.0966 found: 185.0958.

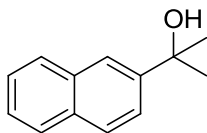
2-Methyl-1-(naphthalen-2-yl)propan-1-ol



iso-propylmagnesium chloride solution (2M in THF) (9.6 ml, 19 mmol, 3.0 equiv) was added to a solution of 2-naphthaldehyde (1.0 g, 6.4 mmol) at 0°C and the mixture allowed to warm to RT, then stirred for 4 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution, then the solvent removed *in vacuo*. The residue was extracted with 3 portions of Et_2O and the solvent removed. The residue was purified by flash chromatography (silica, 20% EtOAc in Hexane) to give the product as a yellowish solid (0.58 g, 2.9 mmol, 45%).

^1H NMR (CHLOROFORM- d , 200MHz): δ = 7.79 - 7.95 (m, 3 H, ArH), 7.75 (s, 1 H, ArH), 7.48 - 7.61 (m, 3 H, ArH), 4.49 (d, $J=6.9$ Hz, 1 H, ArCHOHR), 2.68 (s, 1 H, OH), 2.10 (m, 1 H, $\text{CH}(\text{CH}_3)_2$), 1.11 (d, $J=6.7$ Hz, 3 H, CH_3), 0.88 ppm (d, $J=6.8$ Hz, 3 H, CH_3); **^{13}C NMR** (CHLOROFORM- d , 50MHz): δ = 141.0, 133.0, 132.8, 127.8, 127.7, 127.5, 125.9, 125.5, 125.3, 124.6, 79.9, 35.0, 18.9, 18.2 ppm.²³⁸

2-(Naphthalen-2-yl)propan-2-ol

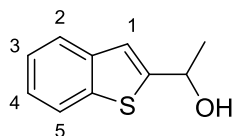


2-acetonaphthone (2.0 g, 12 mmol) was dissolved in THF (20 ml), the solution was cooled to 0°C and methylmagnesium bromide (5.9 ml of a 3M solution in Et_2O , 18 mmol, 1.5 equiv) was added dropwise. The mixture was allowed to warm to room temperature over 2 h and the reaction was then quenched by the addition of NH_4Cl (sat. aq.). THF was removed under reduced pressure and the residue diluted with water. Et_2O was added and the mixture transferred to a separating funnel. The

aqueous layer was extracted with 3 portions of Et₂O, the combined extracts were dried (Na₂SO₄) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, Hexane/EtOAc 10:1) to give the product as a colourless oil that solidified to a white solid on standing (1.1 g, 5.9 mmol, 50%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.94 - 7.97 (m, 1 H, ArH), 7.81 - 7.88 (m, 3 H, ArH), 7.63 (dd, *J*=8.8, 2.0 Hz, 1 H, ArH), 7.45 - 7.52 (m, 2 H, ArH), 1.70 ppm (s, 6 H, 2 x CH₃); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 146.4, 133.1, 132.3, 128.1, 127.9, 127.5, 126.1, 125.7, 123.5, 122.4, 72.7, 31.7 ppm.²³⁹

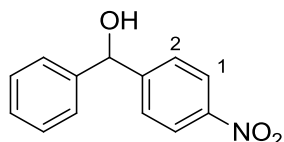
2-(1-Hydroxyethyl)benzo[b]thiophene



To a solution of benzo[b]thiophene-2-carboxaldehyde (1.0 g, 6.2 mmol) in tetrahydrofuran (12 ml) at 0 °C was added a 3 molar solution of methylmagnesium bromide in diethyl ether (2.5 ml, 7.4 mmol, 1.2 equiv). The mixture was allowed to come to room temperature and stirred for 3 h, at which time saturated aqueous ammonium chloride solution was added (5 ml), the mixture transferred to a separating funnel and the organic layer separated. The aqueous layer was extracted with diethyl ether and the combined organic fractions washed with brine and dried over magnesium sulfate. The solvent was removed *in vacuo* to give the product as a yellow solid (1.1 g, 5.9 mmol, 96%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.82 (d, *J*=7.8 Hz, 1 H, H₅), 7.72 (d, *J*=7.3 Hz, 1 H, H₂), 7.28 - 7.40 (m, 2 H, H₃ & H₄), 7.18 (s, 1 H, H₁), 5.19 (q, *J*=6.4 Hz, 1 H, ArCHOHCH₃), 1.66 ppm (d, *J*=6.6 Hz, 3 H, CHCH₃); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 150.5, 139.5, 139.2, 124.2, 124.1, 123.4, 122.4, 119.4, 66.7, 25.0 ppm.²⁴⁰

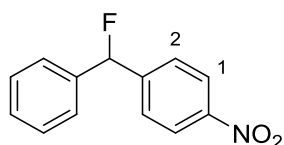
(4-Nitrophenyl)(phenyl)methanol



4-nitrobenzaldehyde (2.0 g, 13 mmol) was dissolved in THF (100 ml) and the solution was cooled to 0°C. PhMgBr (4.4 ml of 3.0 M solution in Et₂O, 13 mmol, 1.0 equiv) was added slowly and the mixture stirred at this temperature for 2 h. The reaction was then quenched by the addition of sat. aq. NH₄Cl solution. THF was removed under reduced pressure and the aqueous mixture extracted with 3 portions of Et₂O. The combined fractions were dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (silica, 6 parts hexanes : 1 part EtOAc) to give the product as a yellow solid that darkened on exposure to air (1.1 g, 4.9 mmol, 37%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 8.12 - 8.23 (m, *J*=8.8 Hz, 2 H, *H1*), 7.54 - 7.63 (m, *J*=8.6 Hz, 2 H, *H2*), 7.28 - 7.42 (m, 5 H, *Ph*), 5.92 (s, 1 H, *CHOH*), 2.52 ppm (br. s., 1 H, *OH*); ¹³C NMR (CHLOROFORM-d,101MHz): δ = 150.7, 147.1, 142.6, 128.9, 128.3, 127.0, 126.6, 123.6, 75.5 ppm.²⁴¹

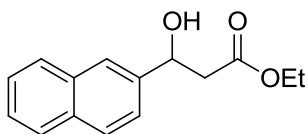
1-(Fluoro(phenyl)methyl)-4-nitrobenzene 294



(4-nitrophenyl)(phenyl)methanol (0.4 g, 1.8 mmol) in DCM (20 ml) was added and the cooling bath allowed to warm to RT. The mixture was stirred at RT for 16 h, then quenched by the addition of MeOH (0.5 ml) and sat. aq. NaHCO₃ (20 ml). The organic fraction was separated and the aqueous fraction extracted with 2 portions of DCM. The combined organic fractions were dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 40% DCM in hexanes) to give the product as a pale yellow oil that solidified on standing in the freezer (stored in plastic) (0.35 g, 1.5 mmol, 87%).

¹H NMR (BENZENE-*d*, 400MHz): δ = 7.72 (d, J =8.1 Hz, 2 H, *HI*), 6.94 - 7.13 (m, 5 H, *Ph*), 6.84 (d, J =9.1 Hz, 2 H, *H2*), 5.95 ppm (d, J =47.4 Hz, 1 H, *Ar*₂*CHF*); **¹³C NMR** (101 MHz, BENZENE-*d*) δ = 148.3, 146.8 (d, J =22 Hz), 139.4 (d, J =21 Hz), 129.5 (d, J =2 Hz), 129.3, 127.4 (d, J =6 Hz), 127.1 (d, J =7 Hz), 124.0, 93.8 ppm (d, J =176 Hz); **¹⁹F NMR** (377 MHz, CHLOROFORM-*d*) δ -169.3 ppm (d, J =46.9 Hz).²⁴²

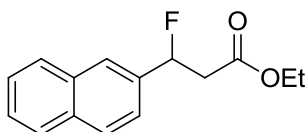
Ethyl 3-hydroxy-3-(naphthalen-2-yl)propanoate



NaBH₄ (130 mg, 3.3 mmol, 1.5 equiv) was added to MeOH (15 ml) at 0 °C. Ethyl 3-(naphthalen-2-yl)-3-oxopropanoate²⁴³ (0.50 g, 2.2 mmol) in MeOH (5 ml) was added dropwise and stirred at this temperature for 1 h. The reaction was quenched with 1.0 M HCl aq. (5 ml) and the solvent removed *in vacuo*. The residue was dissolved in water and extracted with 3 portions of EtOAc. The combined organic fractions were dried (MgSO₄) and the solvent removed. The residue was purified by flash chromatography (silica, Hexanes/EtOAc gradient 5:1 to 3:1) to give the product (0.37 g, 1.5 mmol, 74%).

¹H NMR (CHLOROFORM-*d*, 400MHz): δ = 7.70 - 7.83 (m, 4 H, *ArH*), 7.35 - 7.47 (m, 3 H, *ArH*), 5.24 (dt, J =7.7, 3.7 Hz, 1 H, *CHOH*), 4.13 (q, J =7.1 Hz, 2 H, *CH*₂*CH*₃), 3.33 (d, J =3.2 Hz, 1 H, *OH*), 2.72 - 2.77 (m, 2 H, *CHOHCH*₂*COOR*), 1.20 ppm (t, J =7.1 Hz, 3 H, *CH*₂*CH*₃); **¹³C NMR** (CHLOROFORM-*d*, 101MHz): δ = 172.4, 139.8, 133.3, 133.0, 128.4, 128.0, 127.7, 126.2, 126.0, 124.4, 123.7, 70.4, 60.9, 43.3, 14.1 ppm.²⁴⁴

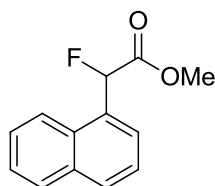
Ethyl 3-fluoro-3-(naphthalen-2-yl)propanoate 292



Ethyl 3-hydroxy-3-(naphthalen-2-yl)propanoate (0.30 g, 1.3 mmol) was dissolved in DCM (15 ml) and the solution was cooled to -78°C . DAST (0.21 ml, 1.6 mmol, 1.2 equiv) was added dropwise and the mixture stirred for 20 minutes. MeOH (1 ml) was added, followed by solid NaHCO_3 . The mixture was warmed to RT over 30 min with stirring, then filtered. The solvent was removed *in vacuo* and the residue purified by flash chromatography (silica, 2% EtOAc in hexanes) to give the product as a white solid (130 mg, 0.52 mmol, 40%).

$^1\text{H NMR}$ (CHLOROFORM- d , 400 MHz): $\delta = 7.81 - 7.92$ (m, 4 H, ArH), 7.43 - 7.58 (m, 3 H, ArH), 6.11 (ddd, $J=46.9, 9.0, 4.2$ Hz, 1 H, ArCHF), 4.22 (qd, $J=7.1, 3.1$ Hz, 2 H, OCH_2CH_3), 3.13 (ddd, $J=16.0, 13.5, 8.9$ Hz, 1 H, CH_2CHF), 2.90 (ddd, $J=32.0, 16.0, 4.4$ Hz, 1 H, CH_2CHF), 1.28 ppm (t, $J=7.2$ Hz, 3 H, CH_3CH_2); $^{13}\text{C NMR}$ (101 MHz, CHLOROFORM- d) δ 169.6 (d, $J=5.6$ Hz), 136.0 (d, $J=19.9$ Hz), 133.4, 133.0, 128.6, 128.1, 127.7, 126.5, 126.5, 125.0 (d, $J=8$ Hz), 123.0 (d, $J=5$ Hz), 90.8 (d, $J=173$ Hz), 61.0, 42.5 (d, $J=28$ Hz), 14.1 ppm; $^{19}\text{F NMR}$ (377 MHz, CHLOROFORM- d) δ ppm -173.0 (ddd, $J=46.9, 32.0, 14.0$ Hz); IR 1734 (C=O stretch), 1177, 1021 (C-F stretch) cm^{-1} ; mp: 48°C ; HRMS (ESI+) m/z calc'd for $[\text{M}+\text{Na}]^+$ $\text{C}_{15}\text{H}_{15}\text{FO}_2$: 269.0948, found 269.0941.

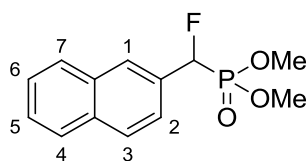
Eethyl 2-fluoro-2-(naphthalen-1-yl)acetate 298



Methyl 1-naphthaleneacetate (0.44 ml, 2.5 mmol) was added dropwise to a solution of lithium diisopropylamide (1.4 ml of 2M solution in THF/heptane/ethylbenzene, 2.8 mmol, 1.1 equiv.) in THF (25 ml) at -78°C . The solution was stirred at this temperature for 1h, then NFSI (0.87 g, 2.8 mmol, 1.1 equiv.) was added portionwise. The mixture was stirred at RT for 16h, then quenched by the addition of saturated aqueous ammonium chloride solution. The THF was removed *in vacuo* and the aqueous remnants were extracted with 3 portions of diethyl ether. The combined organic fractions were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica, hexane/ethyl acetate 12:1) to give the product as a yellow oil (0.37 g, 1.7 mmol, 67%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 8.19 (d, J =8.3 Hz, 1 H, ArH), 7.92 (t, J =7.8 Hz, 2 H, ArH), 7.57 - 7.64 (m, 2 H, ArH), 7.53 - 7.57 (m, 1 H, ArH), 7.48 - 7.53 (m, 1 H, ArH), 6.39 (d, J =47.0 Hz, 1 H, CHF₂CO₂Me), 3.77 ppm (s, 3 H, OCH₃); **¹³C NMR** (101 MHz, CHLOROFORM-d) δ ppm 169.4 (d, J =27.2 Hz), 133.8, 130.6 (d, J =2.4 Hz), 130.0 (d, J =18.4 Hz), 128.8, 127.1, 126.9, 126.8, 126.2, 125.1, 123.6, 88.6 (d, J =187.0 Hz), 52.7.⁶³

Dimethyl (fluoro(naphthalen-2-yl)methyl)phosphonate 300



2-Bromomethylnaphthalene (0.50 g, 2.3 mmol) was added to trimethylphosphite (2.7 ml, 23 mmol, 10 equiv) and the mixture was stirred at 100 °C for 16h. The mixture was filtered through silica eluting with DCM, DCM was removed by rotary evaporation and excess trimethylphosphite removed by evaporation under high vacuum. The crude phosphonate product was used directly in the next step.

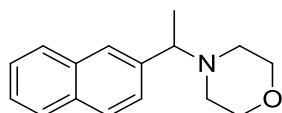
The crude product was dissolved in THF (5 ml) and cooled to -78 °C. LDA (1.1 ml of a commercial 2M solution in THF/heptane/ethylbenzene, 2.3 mmol, 1.0 equiv) was added dropwise and the mixture stirred at this temperature for 2h. NFSI (0.71 g, 2.3 mmol, 1.0 equiv) was added portionwise and the mixture allowed to warm to room temperature. NH₄Cl (5 ml, sat. aq.) was added and the organic solvents removed *in vacuo*. The mixture was extracted with 3 portions of DCM and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (silica, EtOAc) to give the product as a beige solid (240 mg, 0.90 mmol, 40% over 2 steps).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.96 (s, 1 H, H1), 7.82 - 7.93 (m, 3 H, H2 & ArH), 7.61 (d, J =8.6 Hz, 1 H, H3), 7.47 - 7.57 (m, 2 H, ArH), 5.90 (dd, J =44.5, 8.1 Hz, 1 H), 3.75 ppm (dd, J =10.6, 4.0 Hz, 6 H); **¹³C NMR** (101 MHz, CHLOROFORM-d) δ = 133.5, 132.8 (d, J =2 Hz), 130.0 (d, J =19 Hz), 128.4, 128.2, 127.7, 126.8, 126.5, 126.3 (t, J =8 Hz), 123.8 (t, J =5 Hz), 89.4 (dd, J =185, 170 Hz), 53.9 (d, J =45 Hz), 54.0 ppm (d, J =45 Hz); **¹⁹F NMR** (377 MHz, CHLOROFORM-d) δ = -199.8 ppm (dd, J =84.7, 45.0 Hz); **³¹P NMR** (162 MHz, CHLOROFORM-d) δ = 17.2 ppm (d, J =85.5

Hz); **IR**: 1261, 1031 (C-F stretch); **mp** 73 °C; **HRMS** (ESI+) m/z calc'd for $[M+Na]^+$ $C_{13}H_{14}FNaO_3P$: 291.0557, found: 291.0559.

5.4.2 Secondary and Tertiary Fluoride Defluorination Products

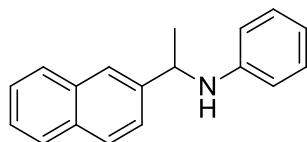
N-[1-(2-Naphthyl)ethyl]morpholine 283



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (2.0 mg, 5 mol%) and dppf (6.4 mg, 10 mol%), 2-(1-fluoroethyl)naphthalene (20 mg, 0.12 mmol) reacted with morpholine (0.02 ml, 0.23 mmol, 2.0 equiv) and triethylamine (0.03 ml, 0.23 mmol, 2.0 equiv) in ethanol at 60°C for 1.5h to give the product after acid/base extraction (diethyl ether/HCl then NaOH/DCM) as a brownish oil (24 mg, 98 μ mol, 85%).

¹H NMR (CHLOROFORM-*d*,400MHz): δ = 7.78 - 7.88 (m, 3 H, *ArH*), 7.73 (s, 1 H, *ArH*), 7.54 (dd, $J=8.6, 1.5$ Hz, 1 H, *ArH*), 7.41 - 7.50 (m, 2 H, *ArH*), 3.64 - 3.81 (m, $J=5.9, 3.0, 3.0$ Hz, 4 H, 2 x CH_2O), 3.48 (q, $J=6.8$ Hz, 1 H, $CHNR_2CH_3$), 2.48 - 2.65 (m, 2 H, CH_2N), 2.42 (dt, $J=10.5, 5.1$ Hz, 2 H, CH_2N), 1.45 ppm (d, $J=6.6$ Hz, 3 H, $CHNR_2CH_3$); **¹³C NMR** (CHLOROFORM-*d*,101MHz): δ = 141.5, 133.3, 132.8, 128.0, 127.7, 127.6, 126.2, 125.9, 125.8, 125.6, 67.2, 65.6, 51.4, 19.8 ppm.²⁴⁵

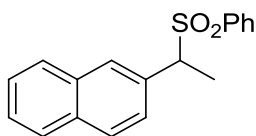
N-(1-(Naphthalen-2-yl)ethyl)aniline 286



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (4.2 mg, 5 mol%) and DPEphos (13 mg, 10 mol%), 2-(1-fluoroethyl)naphthalene (40 mg, 0.23 mmol) reacted with aniline (0.04 ml, 0.46 mmol, 2.0 equiv) and triethylamine (0.07 ml, 0.46 mmol, 2.0 equiv) in ethanol at 40°C for 16 h to give the product after flash chromatography (silica, gradient 10:1 to 1:1 hexanes/DCM) as a colourless oil (38 mg, 150 μ mol, 67%).

¹H NMR (CHLOROFORM-d,400MHz): $\delta = 7.78 - 7.90$ (m, 4 H, ArH), 7.54 (dd, $J=8.5, 1.4$ Hz, 1 H, ArH), 7.41 - 7.52 (m, 2 H, ArH), 7.12 (t, $J=7.8$ Hz, 2 H, *m*-Ph), 6.68 (t, $J=7.3$ Hz, 1 H, *p*-Ph), 6.60 (d, $J=7.6$ Hz, 2 H, *o*-Ph), 4.68 (q, $J=6.7$ Hz, 1 H, ArCHNR₂CH₃), 4.17 (br. s., 1 H, NH), 1.63 ppm (d, $J=6.8$ Hz, 3 H, CH₃); **¹³C NMR** (CHLOROFORM-d,101MHz): $\delta = 147.2, 142.7, 133.5, 132.7, 129.1, 128.4, 127.8, 127.6, 126.0, 125.5, 124.4, 124.2, 117.3, 113.4, 53.7, 25.0$ ppm.²⁴⁶

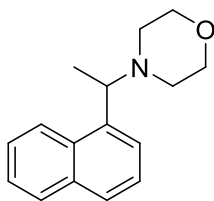
2-(1-(Phenylsulfonyl)ethyl)naphthalene 287



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (2.1 mg, 5 mol%) and DPEphos (6.4 mg, 10 mol%), 2-(1-fluoroethyl)naphthalene (40 mg, 0.23 mmol) reacted with sodium phenylsulfinate (76 mg, 0.46 mmol, 2.0 equiv) in ethanol/water (4:1) at 60°C for 16 h to give the product after flash chromatography (silica, 2:1 hexanes/EtOAc) as a white solid (44 mg, 130 μ mol, 86 %).

¹H NMR (CHLOROFORM-d,400MHz): $\delta = 7.79 - 7.84$ (m, 1 H, ArH), 7.69 - 7.77 (m, 2 H, ArH), 7.54 - 7.60 (m, 3 H, *o*-Ph & *p*-Ph), 7.53 (d, $J=7.6$ Hz, 1 H, ArH), 7.43 - 7.51 (m, 2 H, ArH), 7.35 (t, $J=8.2$ Hz, 2 H, *m*-Ph), 7.30 (dd, $J=8.3, 1.8$ Hz, 1 H, ArH), 4.42 (q, $J=7.2$ Hz, 1 H, CHCH₃), 1.87 ppm (d, $J=7.1$ Hz, 3 H, CHCH₃); **¹³C NMR** (CHLOROFORM-d,101MHz): $\delta = 136.7, 133.5, 133.2, 132.8, 131.1, 129.1, 129.0, 128.6, 128.0, 128.0, 127.5, 126.6, 126.5, 126.3, 66.1, 14.2$ ppm.²⁴⁷

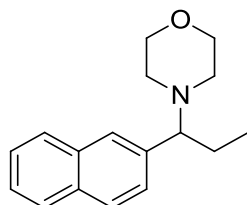
4-(1-(Naphthalen-1-yl)ethyl)morpholine 302



Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (2.0 mg, 5 mol%) and dppf (6.4 mg, 10 mol%), 1-(1-fluoroethyl)naphthalene (40 mg, 0.23 mmol) reacted with morpholine (0.04 ml, 0.46 mmol, 2.0 equiv) and triethylamine (0.06 ml, 0.46 mmol, 2.0 equiv) in ethanol at 60°C for 24 h to give the product after acid/base extraction (diethyl ether/HCl then NaOH/DCM) as a brown oil (36 mg, 98 μ mol, 65%).

^1H NMR (CHLOROFORM- d ,400MHz): δ = 8.47 (d, J =7.8 Hz, 1 H, ArH), 7.88 (dd, J =7.3, 2.2 Hz, 1 H, ArH), 7.77 (d, J =8.1 Hz, 1 H, ArH), 7.64 (d, J =6.8 Hz, 1 H, ArH), 7.42 - 7.56 (m, 3 H, ArH), 4.08 (q, J =5.9 Hz, 1 H, ArCHCH₃NR₂), 3.59 - 3.83 (m, 4 H, 2 x CH₂OR), 2.62 (br. s., 2 H, CH₂NR₂), 2.40 - 2.51 (m, 2 H, CH₂NR₂), 1.50 ppm (d, J =6.6 Hz, 3 H, CHCH₃); **^{13}C NMR** (CHLOROFORM- d ,101MHz): δ = 134.0, 131.5, 128.8, 127.4, 125.5, 125.4, 125.3, 124.8, 124.0, 67.2, 62.2, 51.5, 18.9 ppm; **IR**: 1453, 1265, 1118 cm⁻¹; **HRMS** (ESI+) m/z calc'd for [M+H]⁺ C₁₆H₁₉NO: 242.1539, found: 242.1539.

4-(1-(Naphthalen-2-yl)propyl)morpholine 301



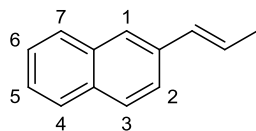
Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (1.8 mg, 5 mol%) and dppf (5.9 mg, 10 mol%), 2-(1-fluoropropyl)naphthalene (20 mg, 0.11 mmol) reacted with morpholine (0.02 ml, 0.22 mmol, 2.0 equiv) and triethylamine (0.03 ml, 0.22 mmol, 2.0 equiv) in ethanol at 50°C for 16 h to give the product after acid/base extraction (diethyl ether/HCl then NaOH/DCM) as a brown oil (12 mg, 48 μ mol, 45%).

^1H NMR (CHLOROFORM- d ,400MHz): δ = 7.76 - 7.90 (m, 3 H, ArH), 7.67 (s, 1 H, ArH), 7.47 (td, J =6.2, 3.2 Hz, 3 H, ArH), 3.71 (br. s., 4 H, 2 x OCH₂), 3.28 (br. s., 1 H, ArCHNR₂), 2.56 (br. s., 2 H, NCH₂R), 2.44 (br. s., 2 H, NCH₂R), 2.06 (br. s., 1 H, CH₂CH₃), 1.81 (br. s., 1 H, CH₂CH₃), 0.73 ppm (t, J =7.3 Hz, 3 H, CH₂CH₃); **^{13}C NMR** (CHLOROFORM- d ,101MHz): δ = 133.1, 132.9, 127.9, 127.9,

127.8, 127.7, 127.6, 126.4, 126.0, 125.6, 72.5, 67.1, 51.5, 25.2, 10.6 ppm; **IR**: 1452, 1271, 1117 cm^{-1} ;

HRMS (ESI) m/z calc'd for $[\text{M}+\text{H}]^+$ ($\text{C}_{17}\text{H}_{22}\text{NO}$): 256.1696, found: 256.1689.

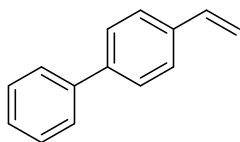
(*E*)-2-(Prop-1-en-1-yl)naphthalene



Isolated either as a byproduct of synthesis of 2-(1-fluoropropyl)naphthalene or 4-(1-(naphthalen-2-yl)propyl)morpholine by flash chromatography (silica, hexanes)

^1H NMR (CHLOROFORM- d , 400 MHz): δ = 7.75 - 7.84 (m, 3 H, *H*3, *H*4 & *H*7), 7.68 (s, 1 H, *H*1), 7.59 (dd, J =8.6, 1.7 Hz, 1 H, *H*2), 7.39 - 7.49 (m, 2 H, *H*5 & *H*6), 6.59 (dd, J =15.8, 1.3 Hz, 1 H, ArCHCHR), 6.40 (dq, J =15.7, 6.6 Hz, 1 H, CHCH₃), 1.96 ppm (dd, J =6.6, 1.5 Hz, 3 H, CH₃); **^{13}C NMR** (CHLOROFORM- d , 101 MHz): δ = 135.4, 133.7, 132.6, 131.1, 128.0, 127.8, 127.6, 126.2, 126.1, 125.4, 125.1, 123.5, 18.6 ppm.²⁴⁸

4-Vinyl-1,1'-biphenyl

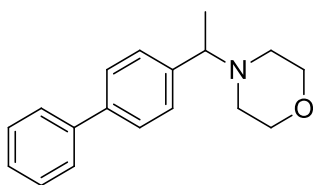


Following general procedure I, using a catalyst prepared *in situ* from palladium allyl cyclooctadiene tetrafluoroborate (1.7 mg, 5 mol%) and DPEphos (5.4 mg, 10 mol%), 4-(1-fluoroethyl)-1,1'-biphenyl (20 mg, 0.10 mmol) reacted with morpholine (0.02 ml, 0.20 mmol, 2.0 equiv) and triethylamine (0.03 ml, 0.20 mmol, 2.0 equiv) in 1-propanol at 95 °C for 24 h to give the product after aqueous work up and chromatography (silica, hexanes) as a white solid (18 mg, quantitative yield).

^1H NMR (CHLOROFORM- d , 400 MHz): δ = 7.55 - 7.67 (m, 4 H, ArH), 7.42 - 7.55 (m, 4 H, ArH), 7.32 - 7.40 (m, 1 H, ArH), 6.78 (dd, J =17.6, 11.0 Hz, 1 H, ArCH=CH₂), 5.82 (dd, J =17.6, 0.7 Hz, 1

H, ArCH=CH₂), 5.30 ppm (dd, $J=10.9, 0.9$ Hz, 1 H, ArCH=CH₂); ¹³C NMR (CHLOROFORM-d,101MHz): $\delta = 140.7, 140.6, 136.6, 136.4, 128.8, 127.3, 127.2, 126.9, 126.6, 113.9$ ppm.²⁴⁹

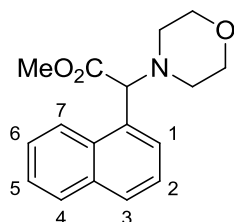
4-(1-([1,1'-Biphenyl]-4-yl)ethyl)morpholine 308



Isolated as a trace product in the defluorination of 4-(1-fluoroethyl)-1,1'-biphenyl.

¹H NMR (CHLOROFORM-d,400MHz): $\delta = 7.52 - 7.66$ (m, 4 H, ArH), 7.31 - 7.49 (m, 5 H, ArH), 3.74 (t, $J=4.6$ Hz, 4 H, 2 x CH₂O), 3.39 (q, $J=6.8$ Hz, 1 H, ArCHCH₃NR₂), 2.54 (br. s., 2 H, CH₂NR₂), 2.44 (s, 2 H, CH₂NR₂), 1.42 ppm (d, $J=6.6$ Hz, 3 H, CHCH₃); ¹³C NMR (CHLOROFORM-d,101MHz): $\delta = 140.9, 140.0, 128.7, 128.1, 127.1, 127.0, 127.0, 126.5, 67.1, 65.1, 51.2, 19.7$ ppm; IR: 1486, 1118 cm⁻¹; HRMS (ESI+) m/z calc'd for [M+H]⁺ C₁₈H₂₁NO: 268.1696, found: 268.1696.

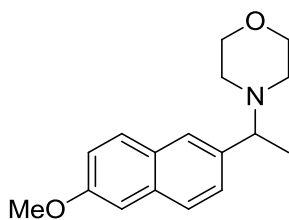
Methyl 2-morpholino-2-(naphthalen-1-yl)acetate 304



Following general procedure I, using a catalyst prepared *in situ* from from palladium allyl cyclooctadiene tetrafluoroborate (1.6 mg, 5 mol%) and DPEphos (5.7 mg, 10 mol%), methyl 2-fluoro-2-(naphthalen-1-yl)acetate (20 mg, 92 μ mol) reacted with morpholine (16 μ l, 180 μ mol, 2.0 equiv.) and Et₃N (25 μ l, 180 μ mol, 2.0 equiv.) in MeOH at 90°C for 60h to give the product after flash chromatography (silica, EtOAc) and acid/base extraction (HCl/Et₂O then NaOH/DCM) as a yellowish oil (14 mg, 50 μ mol, 54%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 8.52 (d, J =8.6 Hz, 1 H, *H7*), 7.87 (d, J =8.1 Hz, 1 H, *H4*), 7.84 (d, J =8.3 Hz, 1 H, *H3*), 7.69 (d, J =7.0 Hz, 1 H, *H1*), 7.49 - 7.60 (m, 2 H, *H5* & *H6*), 7.47 (dd, J =8.1, 7.3 Hz, 1 H, *H7*), 4.78 (s, 1 H, ArCHNR₂CO₂Me), 3.72 (t, J =4.3 Hz, 4 H, OCH₂R), 3.66 (s, 3 H, OCH₃), 2.57 - 2.65 (m, 2 H, NCH₂R), 2.49 - 2.57 ppm (m, 2 H, NCH₂R); **LRMS** (ESI+) calc'd for [M+H]⁺ C₁₇H₂₀NO₃⁺: 286.1 found: 286.1.²⁵⁰

4-(1-(6-Methoxynaphthalen-2-yl)ethyl)morpholine 307

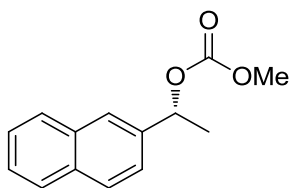


Following general procedure I, 2-(1-fluoroethyl)-6-methoxynaphthalene (40 mg, 200 μ mol) reacted with morpholine (34 μ l, 390 μ mol, 2.0 equiv.) and Et₃N (54 μ l, 390 μ mol, 2.0 equiv.) in the presence of a catalyst derived from Pd(allyl)(COD).BF₄ (3.4 mg, 5 mol%) and dppf (11 mmol, 10 mol%) to give the product as a pale brown oil after flash chromatography (silica, DCM then 5% Et₃N in EtOAc) (41 mg, 160 μ mol, 76%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.62 (d, J =8.6 Hz, 2 H, Ar*H*), 7.55 (s, 1 H, Ar*H*), 7.39 (d, J =8.3 Hz, 1 H, Ar*H*), 6.96 - 7.12 (m, 2 H, Ar*H*), 3.83 (s, 3 H, OCH₃), 3.62 (br. s., 4 H, 2 x OCH₂CH₂), 3.34 (q, J =6.3 Hz, 1 H, ArCHNR₂CH₃), 2.44 (br. s., 2 H, NCH₂CH₂), 2.21 - 2.37 (m, 2 H, NCH₂CH₂), 1.34 ppm (d, J =6.4 Hz, 3 H, CHCH₃); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 157.4, 139.2, 133.8, 129.2, 128.7, 126.9, 126.3, 126.0, 118.7, 105.6, 67.2, 65.4, 55.3, 51.4, 19.7 ppm; **IR**: 1607, 1264, 1119 cm⁻¹; **HRMS** (ESI+) m/z calc'd for [M+H]⁺ C₁₇H₂₂NO₂: 272.1645, found: 272.1636.

5.4.3 Substrates for Stereochemical Investigation

Methyl (1-(naphthalen-2-yl)ethyl) carbonate 285



A solution of 1-(naphthalen-2-yl)ethanol (0.30 g, 1.7 mmol) and pyridine (0.45 ml, 5.2 mmol, 3.0 equiv) in dichloromethane (10 ml) was cooled to °C and methyl chloroformate (0.45 ml, 5.2 mmol, 3.0 equiv) was added slowly. The mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution and the aqueous layer was extracted with dichloromethane. The combined organic fractions were dried over magnesium sulfate and the solvent removed *in vacuo* to give the product as a colourless oil that solidified on standing (0.30 g, 1.3 mmol, 75%).

¹H NMR (CHLOROFORM-d,400MHz): δ = 7.79 - 7.91 (m, 4 H, ArH), 7.44 - 7.56 (m, 3 H, ArH), 5.91 (q, $J=6.6$ Hz, 1 H, ArCHORCH₃), 3.78 (s, 3 H, OCH₃), 1.69 ppm (d, $J=6.6$ Hz, 3 H, CH₃); **¹³C NMR** (CHLOROFORM-d,101MHz): δ = 155.2, 138.4, 133.1, 128.5, 128.1, 127.7, 126.3, 126.1, 125.1, 123.8, 76.6, 54.7, 22.3 ppm.¹⁵⁰

5.5 References

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