Chlorine as an Auxiliary in Asymmetric Aldol Reactions and Photocatalytic Fluorination of C-H Bonds

by

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Abstract

Organohalides are ubiquitous in organic chemistry, with broad utility ranging from their use as building blocks in multistep syntheses, to fluoropharmaceuticals that can oftentimes provide more favourable properties to drug molecules. In this regard, two new synthetic methods have been developed that involve the use or preparation of organohalides: chlorine as an auxiliary for asymmetric aldol reactions, and the photocatalytic fluorination of C-H bonds.

The aldol reaction is an important carbon-carbon bond forming reaction in organic chemistry, the product of which is a β-hydroxyketone, which is a functionality often encountered in drugs and natural products. As many pharmaceuticals, agrochemicals and bioactive compounds have increased activity as single enantiomers, asymmetric variants of aldol reactions are sought. Herein, an auxiliary strategy is demonstrated for the stereoselective addition of lithium enolates to aldehydes in which the auxiliary itself is not chiral, but a single chlorine atom introduced *via* organocatalytic asymmetric α-chlorination. The stereodirecting influence of the chloromethine is then exploited prior to its removal by radical reduction. This strategy is demonstrated in the synthesis of various optically enriched β-hydroxyketones (92-99% *ee*), as well as the natural products (+)-dihydroyashabushiketol and (+)-solistatin.

Fluorination reactions are essential to modern medicinal chemistry, and can provide a means to block site-selective metabolic degradation of drugs and access radiotracers for positron emission tomography imaging. Despite current sophistication in fluorination reagents and processes, the fluorination of unactivated C-H bonds remains a significant challenge. Reported herein is a convenient and economic process for direct fluorination of C-H bonds that exploits the hydrogen abstracting ability of a decatungstate photocatalyst in combination with the mild fluorine atom transfer reagent *N*-fluorobenzenesulfonimide. This operationally straightforward reaction provides direct access to a wide range of fluorinated organic molecules, including structurally complex natural products, acyl fluorides, and fluorinated amino acid derivatives.

Keywords: organic synthesis; halogens; asymmetric aldol reaction; photocatalysis; radical fluorination

Dedication

To my parents Ruth and David Halperin, who have been nothing but extremely loving and supportive throughout all these years, and for showing me the values and work ethic that has made this achievement possible.

To my wonderul husband Darren, who was a constant source of compassion, encouragement, and support, especially when I needed it most. He was always willing to drive me to and from Burnaby Mountain on a Sunday afternoon, which cut hours off my commute time. Having Darren and his tremendously encouraging family in my life these last few years has given me the support to complete my graduate studies.

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List of Abbreviations and Acronyms

°C	Degrees Celsius
δ	Chemical shift in ppm
D	Dextrorotatory
L	Levaorotatory
$[\alpha]_D$	Specific rotation at the sodium D line (589 nm) [deg $dm^{-1}cm^3 g^{-1}$]
Ac	Acetyl, acetate
acac	Acetyl acetonate
AcOH	Acetic acid
Ac_2O	Acetic anhydride
AgOTf	Silver trifluoromethanesulfonate
AIBN	Azo*bis*(isobutyronitrile)
aq	Aqueous
BEt_3	Triethylborane
BF_3•OEt_2	Trifluoroborane Diethyletherate
Bn	Benzyl
Boc	Di-*tert*-butyl dicarbonate
Bu	Butyl
BuLi	Butyllithium
Bz	Benzoyl
c	Concentration in g/mL
cat	Catalyst
CF	Cornforth
CSA	Camphor sulfonic acid
CH_2Cl_2	Dichloromethane
dba	Dibenzylideneacetone
DBDMH	1,3-dibromo-5,5-dimethylhydantoin
DIBAL-H	Diisobutylaluminum hydride
DIPA	*N,N*-Diisopropylamine
DIPEA	*N,N*-Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide

DPP-IV	Dipeptidyl peptidase-4
d.r.	Diastereomeric ratio
E	Entgegen (trans)
e.e.	Enantiomeric excess
equiv.	Equivalents
Et	Ethyl
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOH	Ethanol
EtOAc	Ethyl acetate
FA	Felkin-Anh
FDA	Federal Drug Administration
GC	Gas chromatography
h	Hours
HMBC	Heteronuclear Multiple-Bond Correlation
HMDS	Hexamethyldisilizane
HOMO	Highest Occupied Molecular Orbital
HPLC	High-performance liquid chromatography
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
i	*iso*-
LLB	Lanthanum trilithium*tris*(binapthoxide)
LDA	Lithium diisopropylamide
LUMO	Lowest Unoccupied Molecular Orbital
lut.	Lutidine
M	Molar
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mmol	Millimole(s)
mol	Mole(s)
Ms	Mesylate, methanesulfonate

NCS	*N*-chlorosuccinimide
N.D.	Not determined
NFSI	*N*-fluorobenzenesulfonimide
nm	Nanometre
NMP	*N*-methyl pyrrolidinone
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
N.R.	No reaction
Nu	Nucleophile
OMe	Methoxy
p	Para
PCC	Pyridinium chlorochromate
PET	Positron emission tomography
PFA	Polar-Felkin-Anh
pH	$-\log_{10}[H^+]$
Ph	Phenyl
PhMe	Toluene
phthalimide	1,3-dioxoisoindoline
ppm	Parts-per-million
Pr	Propyl
Pyr	Pyridine
pyromellitimide	Benzene-1,2,4,5-tetracarboxylic diimide
r.t	Room temperature
salen	2,2'-Ethylenebis(nitrilomethylidene)diphenol
SAR	Structure-activity relationship
SOMO	Singly Occupied Molecular Orbital
t	Tertiary, *tert*-
TBADT	tetrabutylammonium decatungstate $[(NBu_4)_4W_{10}O_{32}]$
TBAF	Tetra-*n*-Butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
temp	Temperature
Tf	Triflate (CF_3SO_2)
TFA	Trifluoroacetate

THF	Tetrahydrofuran
TMS	Trimethylsilyl
TREAT-HF	Triethylamine trihydrofluoride
TS	Transition state
Ts	Tosylate (toluenesulfonyl)
TsOH	*p*-Toluenesulfonic acid
TTMSS	Tris(trimethylsilyl)silane

Chapter 1.

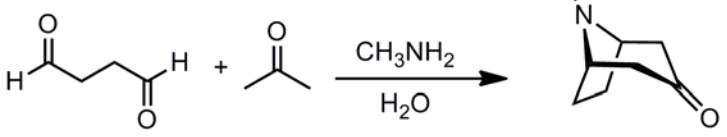
Introduction: Halogens in Organic Synthesis

1.1. Organic Synthesis

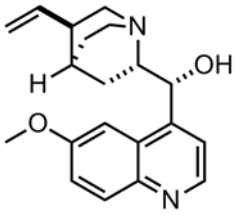
The synthesis of complex, carbon-containing compounds from commodity chemicals, commonly known as organic synthesis, is a continuously evolving area of research. Since Wöhler first described the preparation of the organic compound urea from ammonium cyanate in 1828,[1] the ability to synthesize both natural and unnatural molecules has become critical to our existence and essential for the production of dyes, medicines, agrochemicals, and many materials. Research in the area of organic synthesis can be broadly classified as target-oriented synthesis, where molecules are synthesized for a particular use, or method development, where the primary focus is the identification of new bond-forming reactions.

The strategic and deliberate construction of organic molecules can be dated back to 1845, when Kolbe carefully designed a synthesis of acetic acid from elemental carbon, chlorine, sulfur and water.[2] Notably, in Kolbe's publication of the acetic acid synthesis, the word "synthesis" was used for the first time in referring to a logical series of reactions that lead to a specific target.[3] In addition to the logical synthesis of target molecules for the purpose of discovery or development, the total synthesis of complex natural products is often accomplished with various rationales in mind. For example, natural product synthesis can be undertaken to corroborate a proposed structure or provide proof for relative and absolute stereochemistry of chiral molecules. Additionally, total synthesis can provide access to natural products that are only available in limited quantities from the producing organism. This is particularly important for biologically active natural products, whose development into drugs often relies on total synthesis.

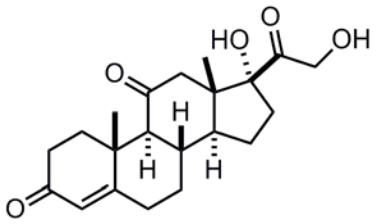
Notably, these efforts can also provide access to unnatural analogues of the target molecule whose biological testing helps establish relationships between structure and biological activity. One of the classic and early examples of target-oriented synthesis of a natural compound is the synthesis of tropinone (**1**, Scheme 1.1) in 1917 by Sir R. Robinson.[4] Robinson identified that three simple starting materials could undergo two tandem Mannich reactions to produce tropinone in a one-pot process.[4] Other historically important examples of the total synthesis of complex natural products include Woodward's total syntheses of quinine (**2**),[5] cortisone (**3**),[6] strychnine (**4**),[7] and erythromycin A (**5**),[8] depicted in Scheme 1.1.



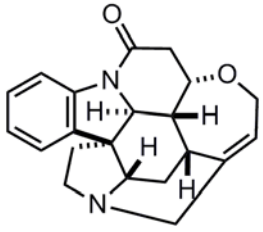
Synthesis of (±)-Tropinone (1)[4]
Robinson 1917[4]



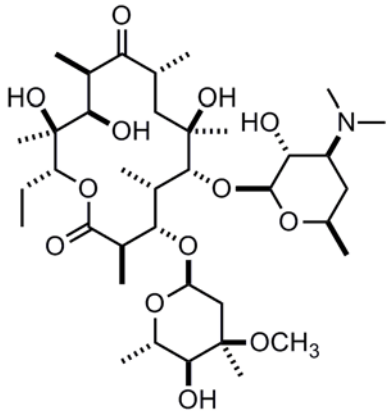
(±)-Quinine (2)
Woodward 1945[5]



(±)-Cortisone (3)
Woodward 1952[6]



(±)-Strychnine (4)
Woodward 1954[7]

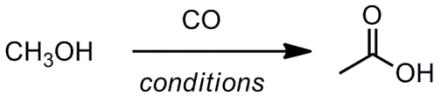


(-)-Erythromycin A (5)
Woodward 1981[8]

Scheme 1.1. Notable Achievements in Target-Oriented Synthesis

In contrast to target oriented synthesis, the discovery and development of new synthetic methods is often motivated by a desire to improve the efficiency of existing processes, or to identify new means to access useful functional groups. As synthetic efficiency is closely linked to the economic and environmental impact of a process, synthetic method development is critical to industries that produce commodity chemicals. For example, more than 150 years after Kolbe first synthesized acetic acid, the annual demand for this chemical is approximately 6 million tonnes.[9] To meet this demand, BASF commercialized an acetic acid synthesis in 1960 that relied on a cobalt-catalyzed carbonylation of methanol (Table 1.1).[10] Within the same decade, Monsanto improved this process through the use of rhodium catalysis.[11] Most recently, BP Chemicals commercialized the Cativa™ process, which employs a less expensive iridium catalyst. Notably, the Cativa™ process has proven superior than the Monsanto process in terms of higher reactor productivity, a more stable catalyst system, and fewer side products.[9,12]

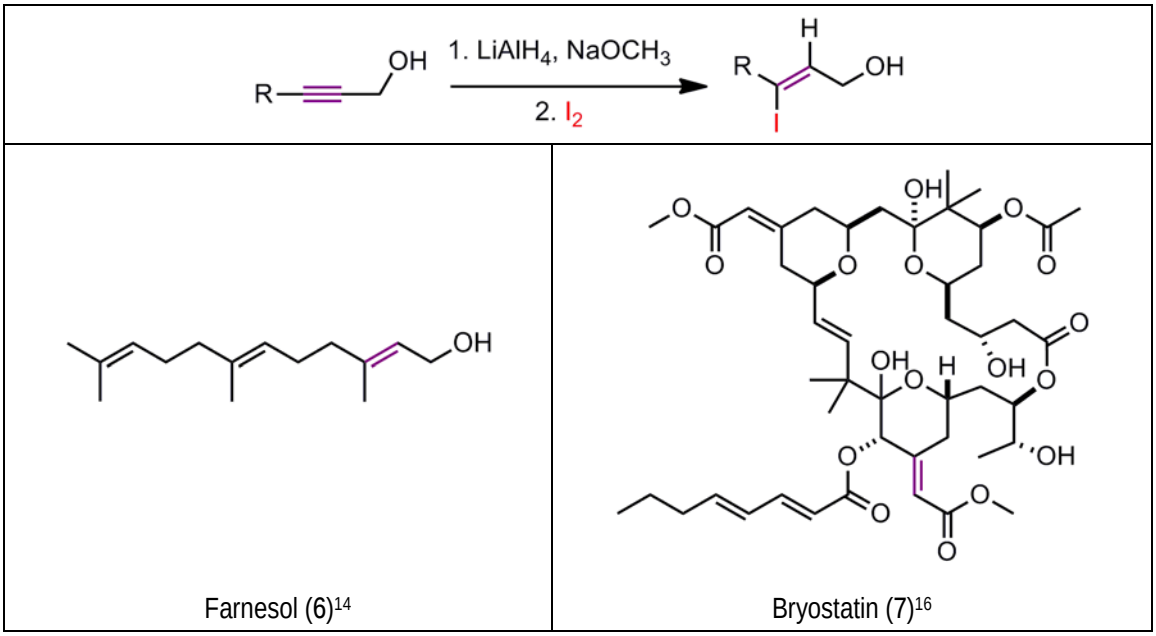
Table 1.1. Industrial Processes for the Carbonylation of Methanol



conditions	process
cobalt catalyst, 230 °C, 600 atm	BASF 1960[13]
$[Rh(CO)_2I_2]^{1-}$, 150-220 °C, 30-60 atm	Monsanto 1966[13]
$[Ir(CO)_2I_2]^{1-}$, 190 °C, 20-30 atm	Cativa™ (BP Chemicals)1996[11]

In addition to improvement of synthetic processes, additional motivation for the development of new synthetic methods includes the enablement of target oriented synthesis campaigns. Oftentimes, the success of a total synthesis is only realized through discovery of a new bond forming reaction. An early example of method development supporting target oriented synthesis is Corey's synthesis of farnesol (**6**), which incorporates a trisubstituted olefin that represented a significant synthetic challenge at the time. Stereoselective olefination reactions were not well known, and in order to complete the synthesis a regio- and stereoselective reduction of propargylic alcohols was developed that employed the combination of lithium aluminum hydride (LAH) and sodium methoxide (Scheme 1.2).[14] This process has since found widespread

use in total syntheses, including applications in the total synthesis of bryostatin (**7**)[15,16] and strychnine (**4**) (see highlighted trisubstituted olefins, Scheme 1.2).[17]



Scheme 1.2. Corey`s Stereoselective Olefination and Use in Total Synthesis

1.2. Chemistry and Reactivity of Carbon-Halogen Bonds

Although many advances in synthetic organic chemistry have been realized over the last two centuries, numerous challenges persist. For example, many natural products and medicines contain densely functionalized carbon skeletons and, consequently, the formation of carbon-carbon bonds remains an important and active area of research.[18] Strategies that address the challenge of carbon-carbon bond formation have often relied on reactions that exploit the enhanced reactivity of carbon-heteroatom bonds. Specifically, carbon-halogen bonds play a key role in the synthesis of organic molecules.[19]

The unique chemistry and reactivity of the organohalides can be readily explained through analysis of the properties of carbon-halogen bonds summarized in Table 1.2. Bond dissociation energy, which is the amount of energy required to homolytically cleave a bond, decreases significantly from carbon-fluorine to carbon-iodine. To further highlight this fact, carbon-fluorine bonds (110 kcal/mol) are one of the

strongest known single bonds that carbon can form,[20] and have a bond dissociation energy almost double that of corresponding carbon-iodine bonds (57 kcal/mol). The length of methyl halide bonds also show a trend that increases from methyl fluoride to methyl iodide, and can be attributed to the increase in atomic size of the halogen. Consequently, the strong carbon-fluorine bond is relatively short and is characterized by the partial ionic character of the carbon and fluorine atoms.[21] Halogens are also amongst the most electronegative atoms, a phenomenon that generally leads to highly polarized carbon-halogen bonds, specfically for fluorinated and chlorinated carbons.[22] Thus, carbon-halogen bonds can greatly affect reactivity, and chlorinated and brominated molecules are often used as intermediates in organic synthesis, especially for the purpose of carbon-carbon bond forming reactions (*vide infra*). Alternatively, due to the very strong bond between carbon and fluorine, the incorporation of a fluorine atom into an organic molecule can suppress reactivity at specific positions or block unwanted reactions. In line with these properties, halogenated molecules represent versatile building blocks for organic synthesis. In particular, organochlorides are widely used due to their ease and low cost of preparation,[23] as well as their stability and resultant simplified storage[24] and handling compared to organobromides and iodides.

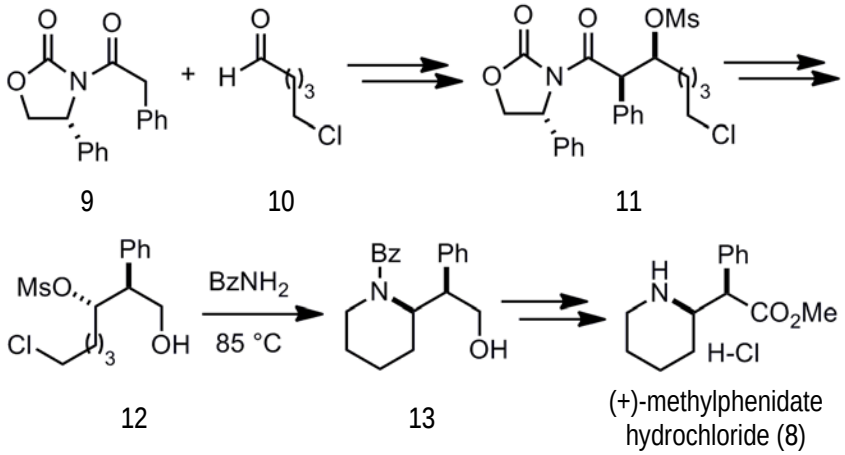
Table 1.2. Properties of Various Halogens vs. Hydrogen

X	H_3C-X BDE (kcal/mol)[25]	H_3C-X Bond Length (Å)[26]	Electronegativity (Pauling)[22]
F	110	1.39	4.0
Cl	85	1.70	3.0
Br	71	1.93	2.8
I	57	2.14	2.5
H	99	1.09	2.1

1.3. Organochlorides in Synthesis

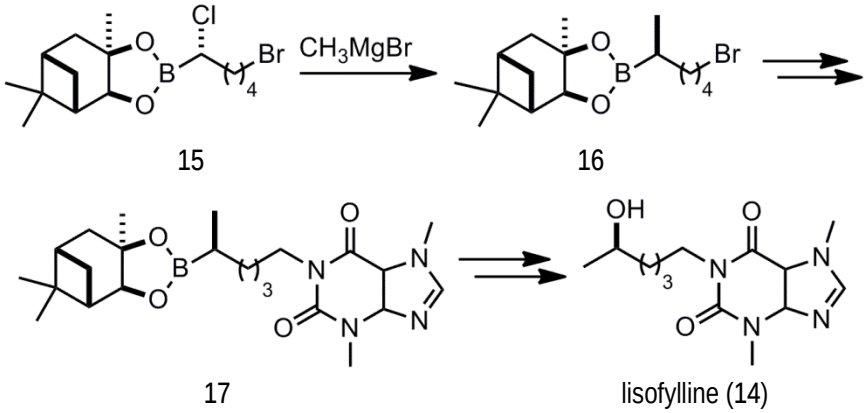
The reactivity of the carbon-chlorine bond has been exploited extensively in organic synthesis and unique examples of reactions of organochlorines within the context of drug discovery are highlighted below. Methylphenidate hydrochloride (**8**, Scheme 1.3) is a drug developed by Novartis for treatment of attention-deficit disorders.[27] The synthesis of **8** relied on a chloroaldehyde building block **10** that was

introduced as a coupling partner in an asymmetric aldol reaction with oxazolidinone **9**. The aldol adduct **11** was converted into the protected chlorodiol **12**, which was treated with benzylamine and heat in order to effect chloride displacement. A subsequent intramolecular nucleophilic attack by the amine resulted in the stereospecific formation of the substituted piperidine ring in **13** that possessed the correct substitution and stereochemistry required for the synthesis of (+)-methylphenidate hydrochloride (**8**).



Scheme 1.3. Novartis Synthesis of (+)-Methylphenidate Hydrochloride (8)[27]

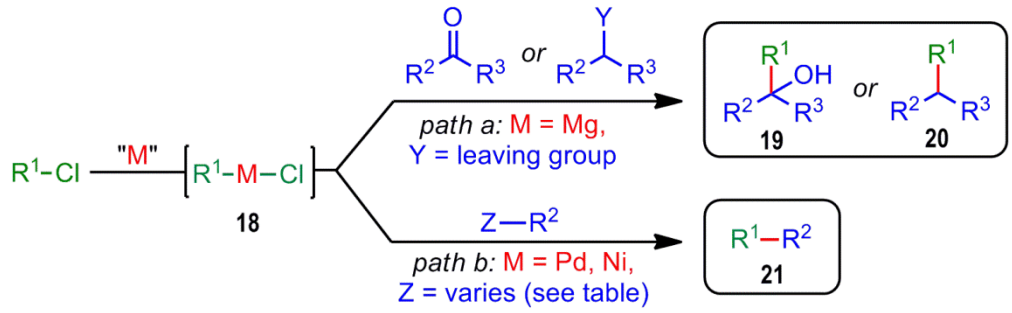
Lisofylline (**14**, Scheme 1.4) is a xanthine derivative developed by Cell Therapeutics[28] that is used as an anti-inflammatory agent and has also shown efficacy in the treatment of type 1 diabetes.[29] The functionalized boronate ester **15** underwent a stereospecific displacement of the chloride with a methyl Grignard reagent to yield **16**, which was converted into lisofylline (**14**) following several transformations.



Scheme 1.4. Synthesis of Lisofylline (14)[28]

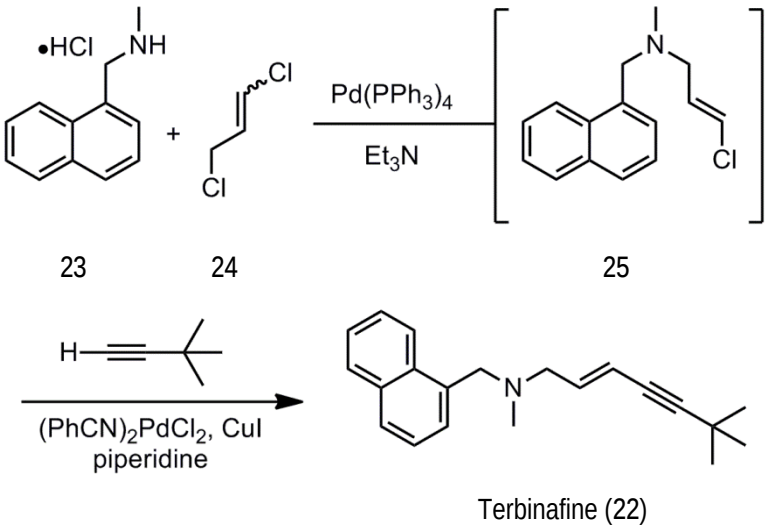
In addition to the syntheses above, which depict S_N2 reactions involving chloromethane/methylenes, the insertion of metals into carbon-chlorine bonds has become an increasingly important means to effect carbon-carbon bond formations. Descriptions of common metal insertion reactions are highlighted in Table 1.3. Reaction of an organochloride with magnesium results in a single electron transfer process to yield intermediate **18**,[30] while palladium and nickel metals undergo oxidative addition[31] of the carbon-chloride bond to produce intermediate **18**. Subsequent addition of an electrophilic species to the alkyl magnesium halide (e.g. **18**, M = Mg, *path a*) can lead to new carbon-carbon bonds.[32] For example, addition to a ketone results in formation of a tertiary alcohol (e.g., **19**),[33] while nucleophilic substitution leads to linear or branched hydrocarbons (e.g., **20**).[34] Alternatively, the palladium or nickel complex (e.g., **18**, M = Pd or Ni, *path b*) can react with an appropriately functionalized coupling partner (e.g., Z-R^2) which results in the formation of a new bond (e.g., **21**),[35] and many adaptations of this cross-coupling have been reported.[36] The significance and utility of these types of reactions was acknowledged by the 2010 Nobel Prize in Chemistry being awarded to Ei-ichi Negishi, Richard F. Heck, and Akira Suzuki, whose names are synonymous with cross coupling reactions. Further highlighting the utility of these metal insertion processes in synthesis of pharmaceuticals, an example of organochloride cross-coupling in the synthesis of terbinafine (Scheme 1.5, **22**)[37] is presented below.

Table 1.3. Metal Insertion into Carbon-Chlorine Bonds and Subsequent Reactions



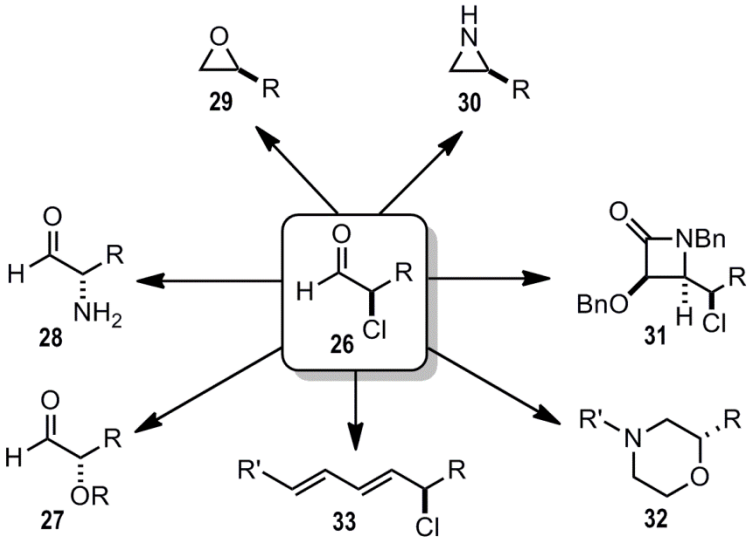
path	Name	M	Coupling Partner
a	Grignard[36]	Mg	R^2COR^3 or R^2CYR^3 (Y = halide, alkoxide, etc.)
b	Heck[36]	Pd	Z-R^2 (Z = H, R^2 = $CHCHR^4$, R^4 = alkyl, aryl)
b	Sonogashira[38]	Pd	Z-R^2 (Z = H, R^2 = CCR^4, R^4 = alkyl, aryl)
b	Suzuki[36]	Pd	Z-R^2 (Z = $B(OR^4)_2$, R^2, R^4= alkyl, aryl)
b	Stille[36]	Pd	Z-R^2 (Z = SnR_3, R^2= alkyl, aryl)
b	Negishi[36]	Pd or Ni	Z-R^2 (Z = ZnX, X = halide, R^2= alkyl, aryl)
b	Buchwald-Hartwig[36]	Pd	Z-R^2 (Z = H, R^2 = NHR^4 or OR^4, R^4 = alkyl, aryl)

Terbinafine is an antifungal agent used in the treatment of skin infections that was first reported by Sandoz in 1980.[37] One efficient synthesis of terbinafine developed by Hansol Pharmaceuticals utilized 1,3-dichloropropene (**24**, Scheme 1.5) in a palladium-catalyzed allylic amination that selectively formed the *E*-alkene **25**.[37] A subsequent Sonogashira cross coupling yielded the desired compound terbinafine (**22**).



Scheme 1.5. Synthesis of Terbinafine (22)[37]

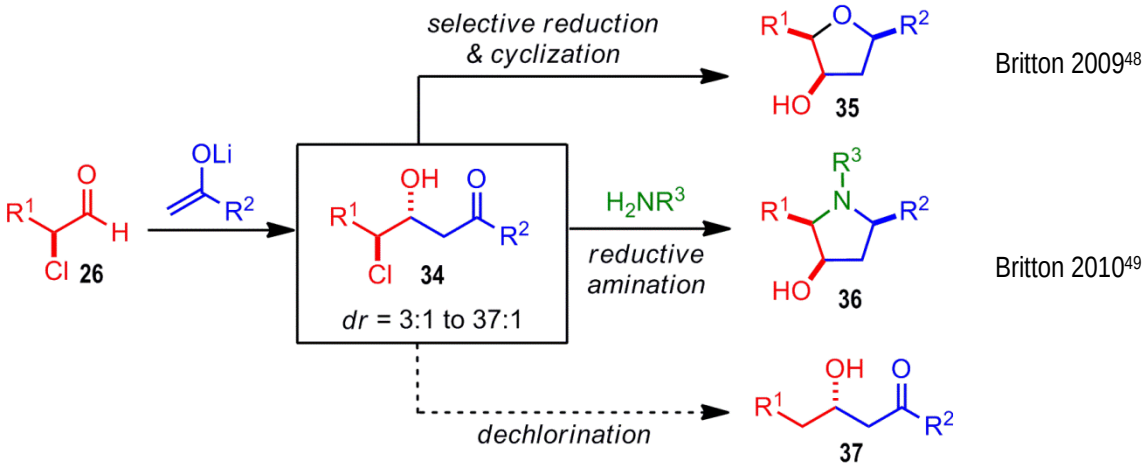
An additional and underutilized class of organochloride building blocks are the α-chloroaldehydes, which have recently been exploited in the synthesis of a variety of natural products and biologically active molecules.[39] Scheme 1.6 depicts the fundamental transformations of α-chloroaldehydes (e.g., **26**).[39] Direct S_N2 substitution of the chloride with a nitrogen or oxygen nucleophile results in the formation of α-oxyaldehydes (e.g., **27**)[40] or α-aminoaldehydes (e.g., **28**).[41] Reduction of the carbonyl functionality can result in epoxides (e.g., **29**)[42] while reductive amination produces the corresponding aziridine (e.g., **30**).[43] The one-step transformation of an α-chloroaldehyde to an α-chloroimine, followed by a Staudinger ketene cycloaddition, can yield functionalized β-lactams (e.g., **31**).[44] Substituted morpholines (e.g., **32**) can also be produced from α-chloroaldehydes via reductive amination of the carbonyl with an appropriately functionalized amine, followed by base-induced cyclization.[45] Finally, subjecting α-chloroaldehydes to Horner-Wadsworth-Emmons reaction conditions can lead to allylic chlorides (e.g., **33**).[46]



Scheme 1.6. α-Chloroaldehydes as Building Blocks

In addition to the reactions discussed above, the development of diastereoselective lithium aldol reactions of α-chloroaldehydes has been described by the Britton group.[42] Importantly, the presence of a chlorine atom adjacent to the carbonyl directs the enolate addition to preferentially form the 1,2-*anti* aldol adducts (Scheme 1.7).[47] The stereochemistry at the newly created carbinol sterocenter (e.g., **34**)

has been further exploited through a 1,3-directed reduction of the ketone function, followed by intramolecular nucleophilic cyclization to yield optically enriched tetrahydrofuranols (e.g., **35**).[48] Alternatively, products of these stereoselective aldol reactions may undergo reductive aminations that enable the rapid construction of enantiomerically enriched 3-hydroxypyrrolidines (e.g., **36**).[49]



Scheme 1.7. Previous Work and Proposed Research Involving α-Chloroaldehydes

1.4. Chapter 2 Overview

The work presented in *Chapter 2* of this thesis describes efforts to further expand the useful reactivity of α-chloroaldehydes. Specifically, the highly diastereoselective nature of lithium aldol reactions of α-chloroaldehydes is combined with a radical dehalogenation process to provide direct access to nonracemic acetate aldol adducts. As discussed in Section 2.1, enantioselective variants of aldols involving methyl ketones are often problematic and many current methods rely on expensive auxiliaries or multistep processes. Importantly, the products of these reactions are enantiomerically enriched β-hydroxyketones (e.g., **37**, Scheme 1.7), a functionality commonly encountered in biologically active organic molecules, including many cholesterol lowering medications. Thus, a key objective was the identification of a suitable method for the dechlorination of sensitive β-ketochlorohydrins. The ultimate development of a sequential α-chloroaldehyde aldol reaction/dechlorination sequence enabled the rapid

construction of a variety of enantiomerically enriched β-hydroxyketones and was applied in the concise total synthesis of the natural products (+)-dihydroyashabushiketol and (+)-solistatin.

1.5. Halogenated Molecules as Pharmaceuticals

A variety of organohalide pharmaceuticals are currently on the market and some examples are described in Figure 1.1. Pipobroman (**38**) is an anti-cancer drug that is proposed to act as an alkylating agent.[50] Pipobroman has shown to inhibit myeloproliferation and is used in treatment for myeloproliferative blood diseases such as polycythemia vera and essential thrombocythemia.[50] Brotizolam (**39**), a potent benzodiazepine analogue, was discovered by Kuwada and coworkers and patented by Takeda Chemical Industries in 1976,[51] and is currently approved in some countries for the treatment of insomnia and anxiety. Chloroquine (**40**) was initially synthesized by Andersag in 1934 and patented under the name Resochin in 1939 as a potent anti-malarial treatment,[52] but the drug did not receive FDA approval until 1949. For the first few decades after its commercialization, it was one of the most widely used drugs for malaria treatment and prevention. Unfortunately, the malaria parasite *Plasmodium falciparum* developed widespread resistance to chloroquine,[53] which deterred its further use. The mechanism of action has been investigated and it was shown that chloroquine enters the blood stream and forms a drug-heme complex, which ultimately results in the disruption of parasitic cell function.[54] Cefaclor (**41**) belongs to a family of antibiotics identified as the cephalosporins, which have similar pharmacology and mechanism of action to the penicillins, and are used against a wide range of gram positive and gram negative bacteria. Cefaclor was discovered by Chauvette and Pennington at Lilly in 1975 and was approved by the FDA in 1979,[55,56] and is still currently in use to treat various ear, skin, and urinary tract infections.

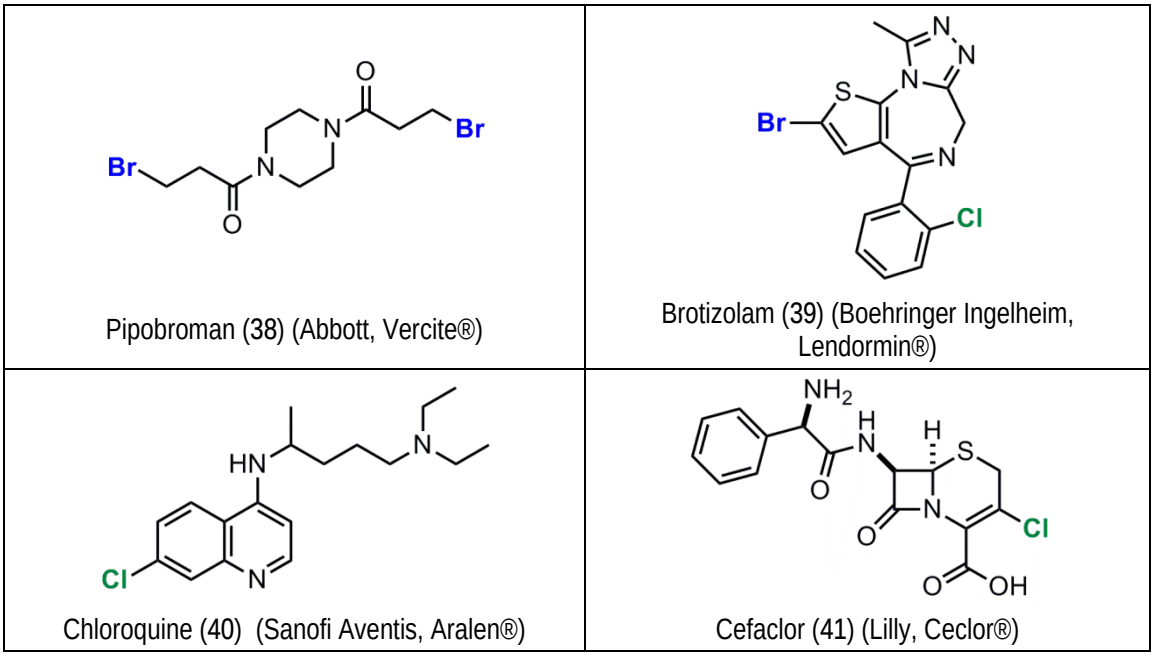
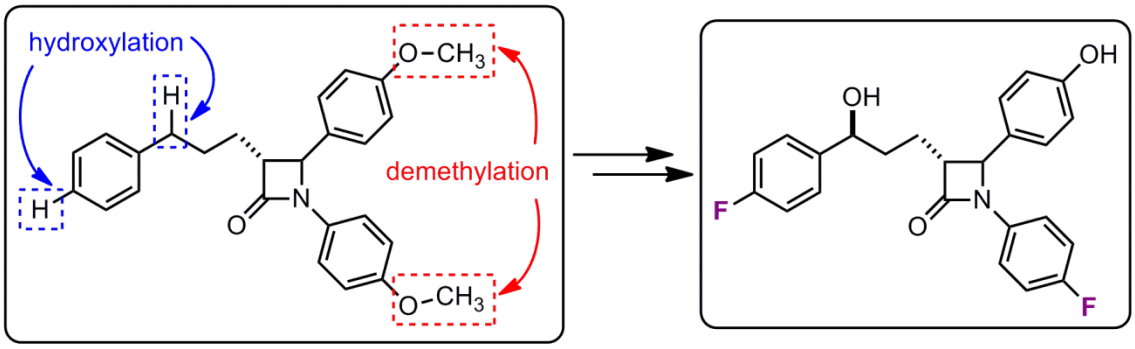


Figure 1.1. Chlorinated and Brominated Pharmaceuticals

In addition to the chlorinated and brominated pharmaceuticals described above, there exists a large number of fluorinated drugs.[57,58,59] The development of fluorinated drugs is often motivated by the fact that the incorporation of a fluorine atom into drug molecules significantly alters the drug's properties, including metabolic stability, pKa, solubility and membrane permeability.[60] One example shown below (Scheme 1.8) is the ezetimibe (**42**), where the site-specific fluorination of metabolically labile sites on an initial drug lead (SCH48461, **43**) ultimately led to SCH58235 (Ezetimibe, **42**), which exhibited a 50-fold increase in potency compared to SCH48461.[61] Further examples of fluorinated drugs are discussed in detail in Section 3.1.1, with a key emphasis on the role that fluorine plays in the activity of the drug molecule.



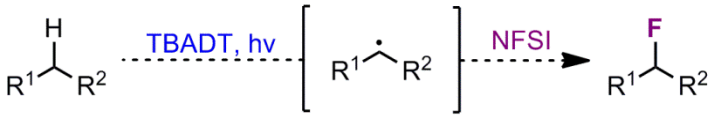
SCH48461 (43)
ED_{50} = 2.2 mg/kg^{-1}

SCH58235, Ezetimibe (42)
ED_{50} = 0.04 mg/kg^{-1}

Scheme 1.8. SCH48461 and Ezetimibe

1.6. Chapter 3 Overview

As the natural abundance of fluorinated molecules is relatively low,[62] the development of new methods to incorporate fluorine atoms into biologically active molecules is an important pursuit.[61] Owing to the advantageous pharmacokinetic and pharmacodynamic changes that can occur when fluorine is introduced to a molecule,[59] various methods for fluorination have recently been disclosed.[63] Unfortunately, and despite much effort, many challenges still exist that complicate the direct incorporation of fluorine into organic molecules. *Chapter 3* of this thesis describes our efforts to develop a practical C-H fluorination reaction. This novel transformation relies on the use of a photoexcited polyoxometalate (TBADT) that is capable of abstracting hydrogen atoms from unactivated carbons, in combination with the fluorine transfer reagent *N*-fluorobenzenesulfonimide (NFSI) (e.g, Scheme 1.9). The optimization of this C-H fluorination reaction, a survey of the substrate scope and limitations, as well as the application to the practical synthesis of fluoroleucine, a key building block used in the synthesis of a potential osteoporosis drug, is described. Additionally, insight into the mechanism of the fluorine transfer process is presented.



Scheme 1.9. Proposed C-H Fluorination

Chapter 2.

Chlorine as an Auxiliary for Asymmetric Aldol Reactions[a,b]

2.1. Introduction: Asymmetric Aldol Reactions

The reaction of an enol or enolate with an aldehyde, also known as the aldol reaction (Figure 2.1), is one of the most important carbon-carbon bond forming reactions in synthetic chemistry.[64] The direct result of this reaction is the formation of a β-hydroxyketone, which is a functional group common to natural products and biologically active molecules. Another consequence of this carbon-carbon bond formation is the construction of one or two contiguous stereogenic centres, and many catalysts and methods have been reported to effect asymmetry to this process.[65,66] Shown below are three biologically active natural compounds that contain chiral nonracemic hydroxyketone moieties (Figure 2.1). Erythromycin (**5**), originally isolated from *Saccharopolyspora erythraea,*[67] is a macrolide antibiotic with a wide antimicrobial spectrum that is commonly prescribed for the treatment of bacterial infections. Analogues of epothilone A (**44**), which was originally identified as a metabolite produced by *Sorangium cellulosum*,[68] are currently in clinical trials as anticancer therapeutics.[69] Lovastatin (**45**), found naturally in red yeast rice and oyster mushrooms, was the first statin to be approved by the FDA for the treatment of hypercholesterolemia.[70]

[a] Research described in this chapter was published in: *Synthesis*, **2011**, 1946-1953; *Org. Biomol. Chem.* **2013**, 1702-1705.

[b] Dr. Baldip Kang assisted with initial synthesis and characterization of ketochlorohydrins, including conducting NOESY experiments.

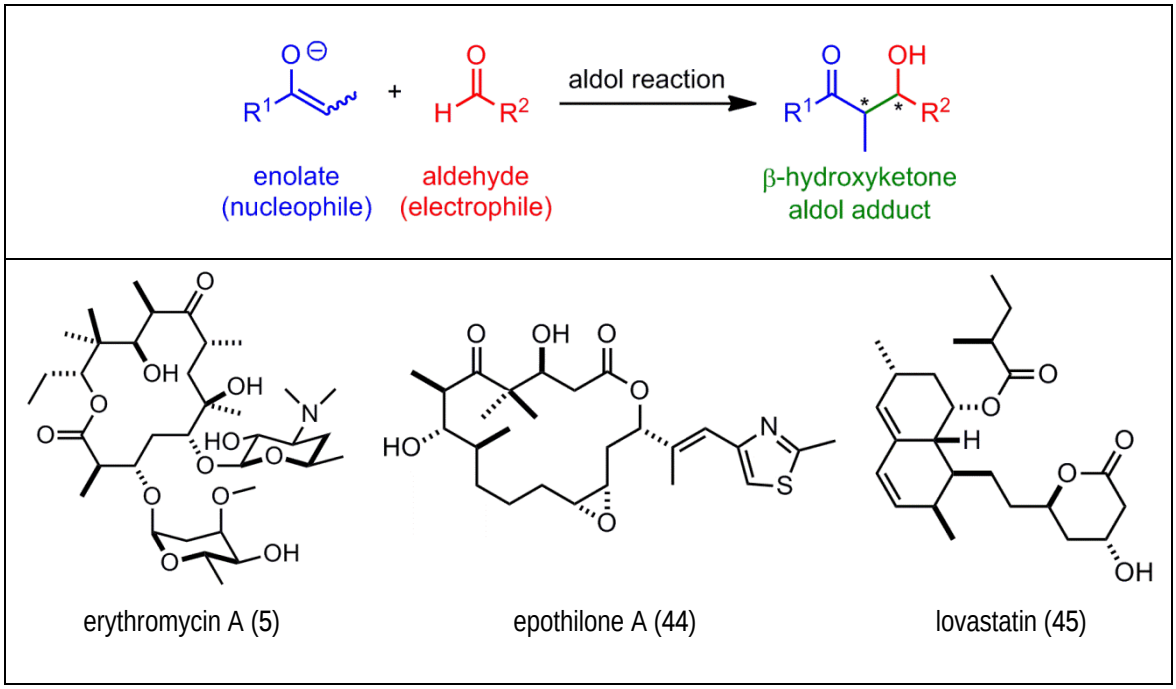


Figure 2.1. Generalized Aldol Reaction & Naturally Occurring β-Hydroxy Ketones and Lactones

As many drugs and bioactive molecules have increased activity as single enantiomers, new methods that impart enantioselectivity to aldol reactions are of high value and continuously sought.[66] While a variety of enantioselective aldol reactions have been reported, many of these asymmetric processes have limitations; including i) reliance on chiral auxiliaries and the consequent necessity for their removal, ii) providing access to only one enantiomer or diastereomer, iii) requirement for a large excess of ketone or aldehyde coupling partners, and iv) low levels of diastereo- or enantioselectivity. For example, Figure 2.2 depicts an aldol reaction with the commonly used Evan's chiral oxazolidinone,[71] where the steric bulk of the isopropyl group is exploited to direct the selectivity of the enolate addition. Despite the popularity of this methodology, the utility of this process is limited to propionate (Figure 2.2, R^1 = Me) and larger amides, as acetate derivatives (Figure 2.2, R^1 = H) are not good substrates for this reaction owing to the fact that the smaller methyl group does not impart sufficient steric influence on the facial selectivity.[72] Although many additional strategies have been developed to address this specific restriction, most enantioselective acetate aldol reactions suffer from the general limitations described above.[64] Several examples of common asymmetric acetate aldol reactions are discussed below.

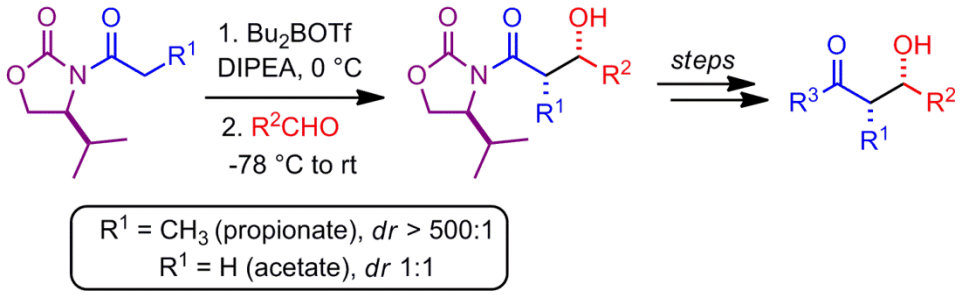
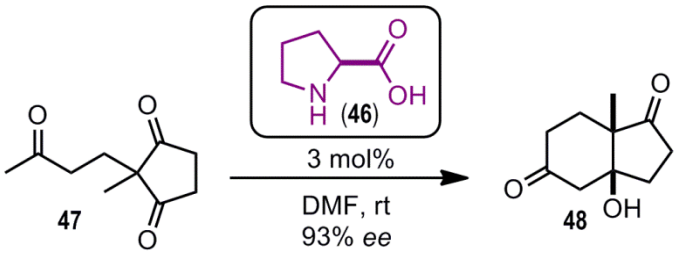


Figure 2.2. Evan's Oxazolidinone Chiral Auxiliary

2.1.1. Background: Catalytic Asymmetric Acetate Aldol Reactions

The majority of catalytic asymmetric aldol reactions are either metal- or organocatalyzed, and there has been a large amount of research in the development of variations of both. Of historical note, the first organocatalyzed asymmetric aldol reaction was developed at Hoffmann La-Roche by Hajos and Parrish in the early 1970's and utilized proline (**46**) as a chiral catalyst to convert an achiral triketone **47** into the optically enriched bicyclic diketoalcohol **48** (Scheme 2.1).[73]



Scheme 2.1. Hajos-Parrish Reaction.

Initial progress in metal-catalyzed asymmetric acetate aldol reactions was largely restricted to Mukaiyama-type reactions (Figure 2.3). Mukaiyama reported the first asymmetric addition of silyl enol ethers derived from thioesters to various aldehydes using a tin(II) catalyst combined with chiral ligand **49**.[74,75] Since this report, numerous variations to the structure of the enol or metal catalyst have been explored to produce optically enriched aldol adducts in high enantioselectivity.[76] In 1994, Carreira demonstrated an enantioselective aldol reaction involving a silyl enol ether with a chiral titanium(IV) catalyst **50**.[77] This reaction is noteworthy for its wide substrate scope, low catalyst loadings, and consistently high levels of enantioselectivity. Alternatively,

Shibasaki developed a series of heterobimetallic catalysts for aldol reactions that did not require the necessary preformation of the silyl enol ether.[78] Shibasaki reported the use of the lanthanum trilithiumtris(*R*-binapthoxide) [(*R*)-LLB] (**51**) catalyst in the total synthesis of several natural products, including epothilone A (**44**, Scheme 2.1).[79]

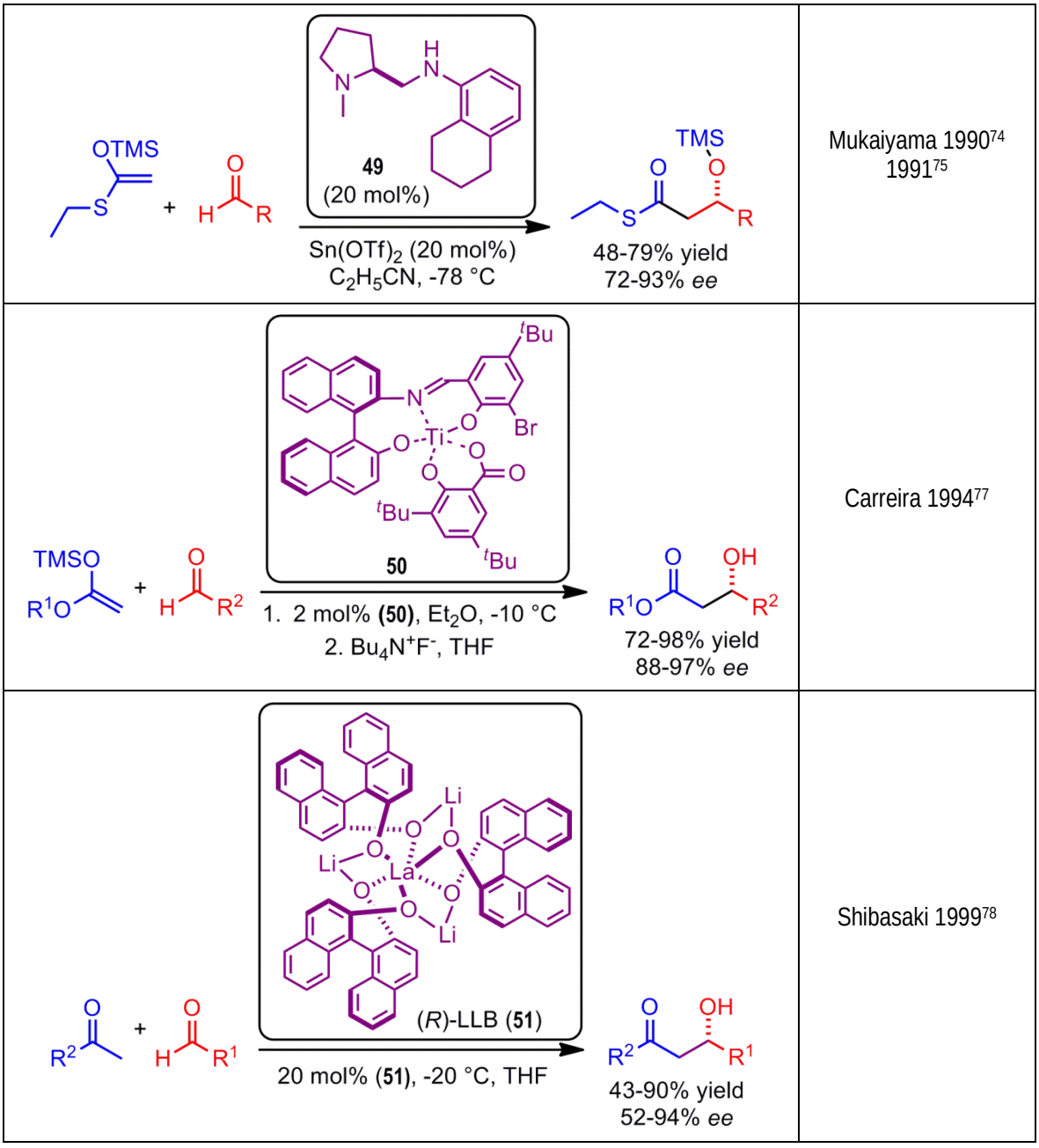


Figure 2.3. Metal-Catalyzed Asymmetric Acetate Aldol Additions

Organocatalysis is another common method of promoting direct asymmetric aldol reactions, and the use of small organic molecules such as proline as chiral catalysts has recently gained popularity.[76] These reactions do not require conversion of a ketone to an silyl enol ether or enolate surrogate, although organocatalyzed aldol reactions usually require an excess of the ketone coupling partner, and can suffer from low yields due to homocoupling of either ketone or aldehyde.[73] However, the ability to perform these reactions with an inexpensive, non-toxic, and readily available catalyst in aqueous solutions has stimulated their widespread use. While the first intramolecular enantioselective proline-catalyzed aldol addition was discovered in the early 1970's (Scheme 2.1), it took almost thirty years until the first proline-catalyzed *inter*molecular direct aldol reaction was demonstrated by List (**52**, Figure 2.4)[80] Since this seminal report, numerous organocatalysts derived from naturally occurring chiral amines have been described.[73] More recently, Zhao disclosed a C_2-symmetric bisprolinamide (**53**) that catalyzed the direct addition of acetone to various aldehydes in high yields and enantioselectivities (Figure 2.4).[81]

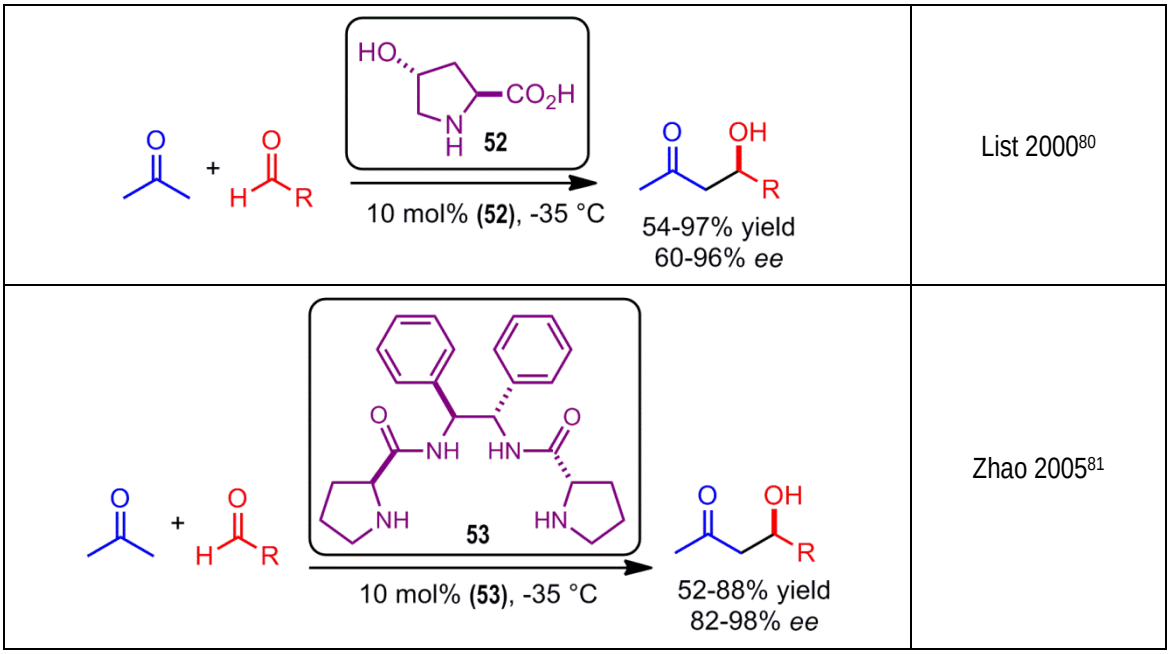


Figure 2.4. Organocatalyzed Asymmetric Acetate Aldol Additions

2.1.2. Background: Chiral Auxiliaries in Acetate Aldol Reactions

The use of chiral auxiliaries to impart stereoselectivity to aldol reactions has been well-studied, and there are numerous reports of auxiliaries appended to carbonyl functions via ester, amide, or thioester linkages that provide aldol adducts in both high yield and diastereoselectivity.[64] The first report of an asymmetric acetate aldol reaction using a chiral enolate was by Braun over 30 years ago (Figure 2.5).[82] In this early work, readily available (*R*)-2-acetoxy-1,1,2-triphenylethanol (**54**) underwent double deprotonation using two equivalents of LDA, and following transmetallation with $MgBr_2$, reacted with various aldehydes in good yield and diastereoselectivity. The ester auxiliary was easily cleaved using base to reveal the β-hydroxyacid. Since this early example, many chiral enolates have been developed, including Oppolzer's use of camphorsultam (e.g., **55**) as a readily cleavable auxiliary.[83] As an extension to Evan's *N*-acyloxazolidinone auxiliary commonly used in diastereoselective propionate aldol additions (e.g., Figure 2.2), Crimmins reported the use of chiral thiazolidinethione derivatives (e.g., **56**) that were able to promote the production of 1,3-diols in good yields and high enantiomeric excess following cleavage of the chiral auxiliary.[72]

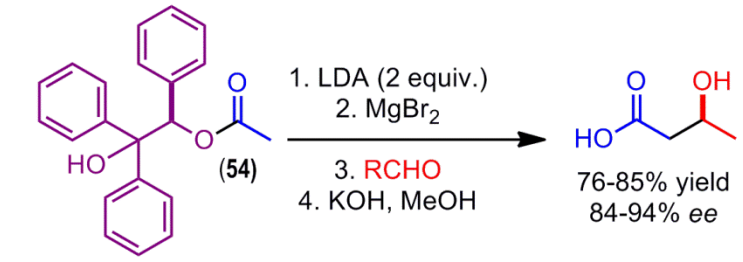
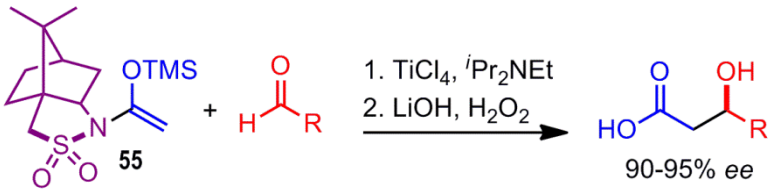
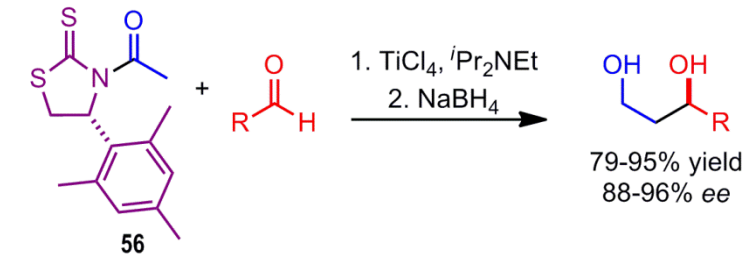
	Braun 1984[82]
	Oppolzer 1992[83]
	Crimmins 2007[72]

Figure 2.5. Chiral Auxiliaries in Acetate Aldol Reactions

Although these chiral auxiliaries promote highly diastereoselective aldol reactions, upon hydrolysis of the auxiliary, the resultant products are β-hydroxyacids or 1,3-diols, not the β-hydroxyketones that are often the desired end product of aldol reactions. Thus, further functional group transformations are required if a β-hydroxyketone is ultimately desired.

2.1.3. Background: Stereoselective Additions to α-Substituted Aldehydes

Most examples of chiral auxiliaries that are used to impart asymmetry in aldol reactions require the auxiliary to be appended to the nucleophilic (enol/enolate) coupling partner. Examples of aldol additions with chiral auxiliaries on the aldehyde are not common, even though the stereoselective addition of enolates to α-substituted aldehydes has been widely studied.[84] In this regard, several models that help predict the sense and magnitude of diastereoelectivity in the nucleophilic addition to α-substituted carbonyl compounds have been established. The Felkin-Anh model (Figure 2.6) was one of the first used to rationalize the preference for 1,2-*anti* adducts that are observed during the addition of nucleophiles to α-substituted aldehydes.[85] In this model, selectivity is attributed to the size of the substituents and avoidance of steric interactions. Thus, the three groups attached to the α-carbon are labelled as small, medium and large. Positioning the largest group perpendicular to the carbonyl, and minimizing eclipsing interactions, the nucleophile is then expected to follow the Bürgi-Dunitz trajectory of attack from the least hindered face of the aldehdye carbonyl, leading to a 1,2-*anti* product.

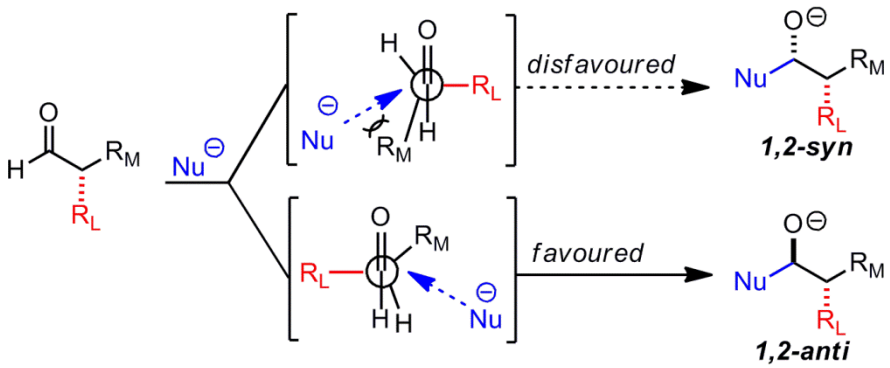


Figure 2.6. Felkin-Anh Model

The Cram chelate model (Figure 2.7) can be used to predict the stereochemical outcome of reactions where the α-substituent on the aldehyde bears a lone pair (i.e., OR, NR_2, SR_2) and a metal capable of chelation is used.[86] Due to the metal chelating to the heteroatom and the carbonyl, the conformation is locked, and following nucleophilic attack via the Bürgi-Dunitz trajectory, very high 1,2-*syn* selectivites will result.

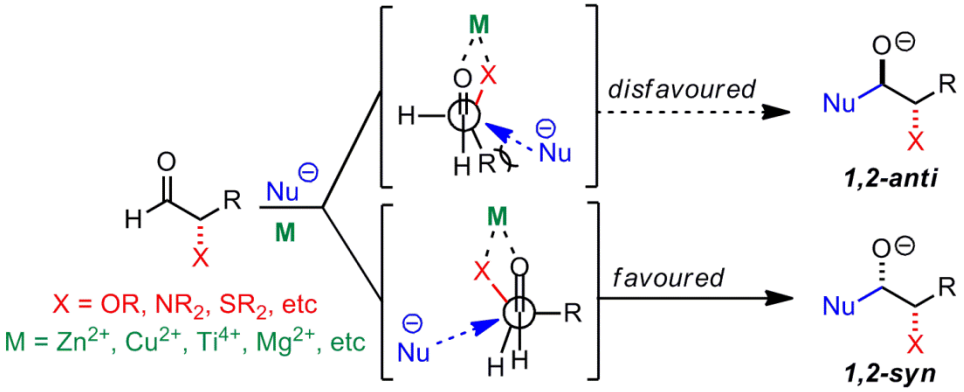


Figure 2.7. Cram Chelate Model

In order to adapt the Felkin-Anh model to situations where polar, electronegative α-substituents are present, the Polar Felkin-Anh (PFA) model was devised (Figure 2.8).[87,88] This model predicts that the electronegative substituent will align perpendicular to the carbonyl, in order to maximize the stabilizing hyperconjugative delocalization between the C-X bond LUMO and the incoming nucleophile HOMO.[89] Employing this model, nucleophilic addition to the least hindered face of the carbonyl following the Bürgi-Dunitz trajectory of attack yields a 1,2-*anti* product.

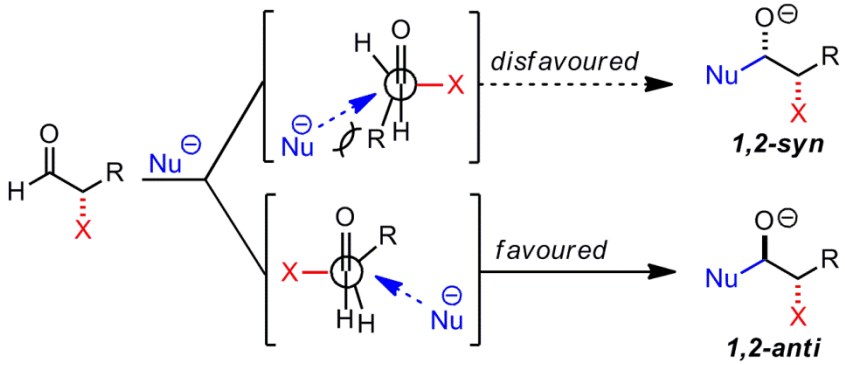


Figure 2.8. Polar-Felkin-Anh Model

The Cornforth model (Figure 2.9) has also been used to rationalize the *anti* preference that is observed in additions to aldehydes bearing an electronegative heteroatom at the α-position.[84,47] In this model, the heteroatomic (C-X) and carbonyl (C=O) bonds are positioned such that their dipoles are opposing, which results in an *anti*-periplanar conformation with respect to the carbonyl and heteroatom. Attack of the nucleophile via the Bürgi-Dunitz trajectory, preferentially from the less hindered face of the aldehyde, then results in the preferred formation of 1,2-*anti* products.

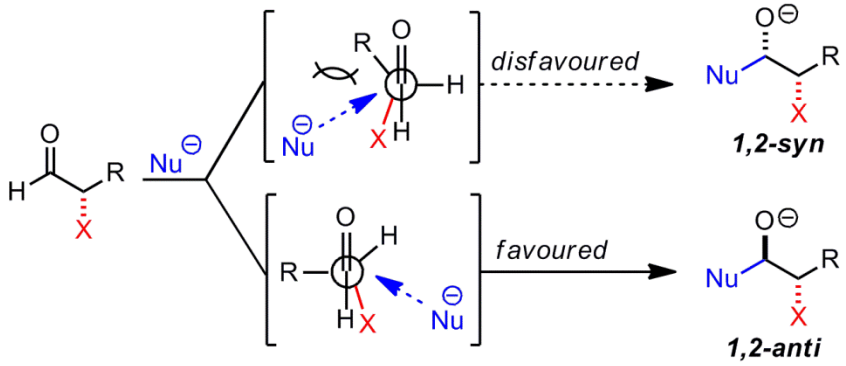


Figure 2.9. Cornforth Model of Nucleophilic Additions to α-Heteroaldehydes

Given that both the Cornforth and Polar Felkin-Anh models predict the formation of 1,2-*anti* products, Evans and coworkers designed an elaborate experiment in order to determine which model was presiding in aldol reactions involving α-polar atom functionalized aldehdyes.[84] Following careful examination of the transition states for both models (Figure 2.10), it was proposed that if the Polar-Felkin-Anh (PFA) model was operative, due to destabilizing steric interactions in the *Z*-enolate (TS-PFA-*Z*), the *E* enolate (TS-PFA-*E*) should give higher 3,4-*anti* selectivity. Conversely, if the Cornforth (CF) model was presiding, the *Z*-enolate (TS CF-*Z*) would give higher 3,4-*anti* selectivity than the sterically destabilized *E*-enolate (TS CF-*E*). In this regard, the hypothesis was tested through the synthesis and reaction of *Z*- and *E*-boron and lithium enolates with various α-oxyaldehydes. From these studies, it was found that *Z*-enolates gave significantly higher 3,4-*anti* selectivity than the analogous *E*-enolates. This experimental evidence supports the use of the Cornforth model in predicting the stereochemical outcome of aldol reactions involving α-heteroatom functionalized aldehydes under non-chelation conditions.

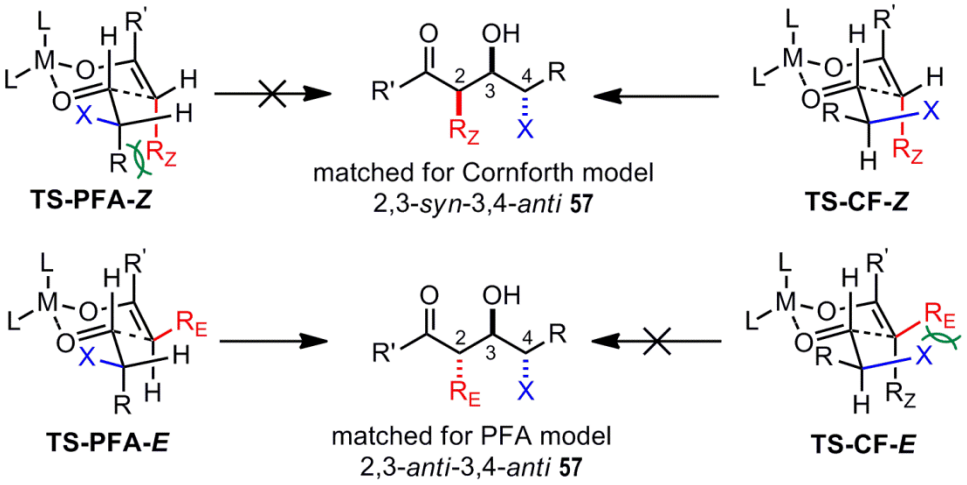


Figure 2.10. Discriminating between Cornforth and Polar-Felkin-Anh Models

Further refinements that involved theoretical investigations by Evans and co-workers have revealed that the Cornforth model should be applied for reactions involving aldehydes with an electronegative heteroatom at the α-position (i.e., F, Cl, OR), while the Polar-Felkin-Anh model should be used to predict stereochemical outcomes of less electronegative heteroatoms (i.e. SR_2, NR_2).[89]

2.1.4. Background: Preparation of Enantioenriched α-Chloroaldehydes

The first report of the racemic chlorination of aldehydes was in 1871, when Shroder described the reaction of chlorine gas with 3-methylbutanal.[90] While additional reports document the racemic α-halogenation of aldehydes,[91] convenient methods for asymmetric chlorination of aldehydes were unknown until the last decade. Jørgensen was one of the first to report the enantioselective organocatalytic α-chlorination of aldehydes, and this seminal publication included a catalyst screen of proline derivatives that, when combined with the electrophilic chlorinating agent *N*-chlorosuccinimide (NCS), provided α-chloroaldehydes in moderate to high enantiomeric excess, with diphenylpyrrolidine (**58**) providing the optimal yield and enantioselectivity (Figure 2.11).[92]

In the same year, MacMillan demonstrated the use of an imidazolidinone organocatalyst **59** combined with an electrophilic chlorinating agent **60** to provide optically enriched α-chloraldehydes.[93] MacMillan subsequently developed a second

generation amino-acid derived imidazolidinone organocatalyst (**61**)[c] with utility in highly enantioselective α-chlorinations, whose proposed mechanism involves 'singly occupied molecular orbital' (SOMO) activation via enamine intermediate **62** (Scheme 2.2).[94,95,96] This methodology facilitates production of α-chloroaldehydes in enantiomeric excess of up to 97% by employing 20 mol% of catalyst, 0.5 equivalents of a copper(II) species, 1.5 equivalents of lithium chloride and stoichiometric oxidant.

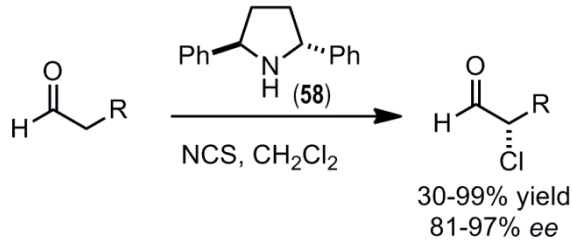
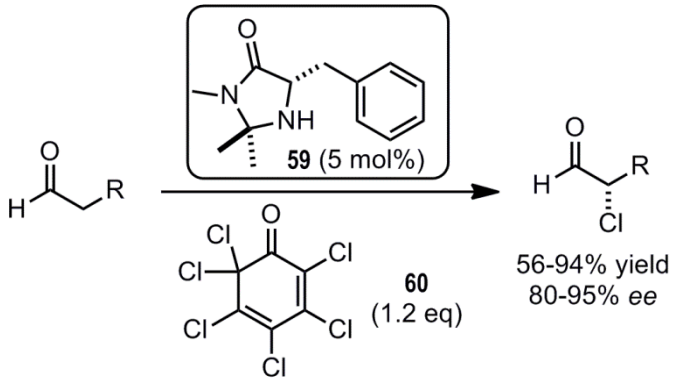
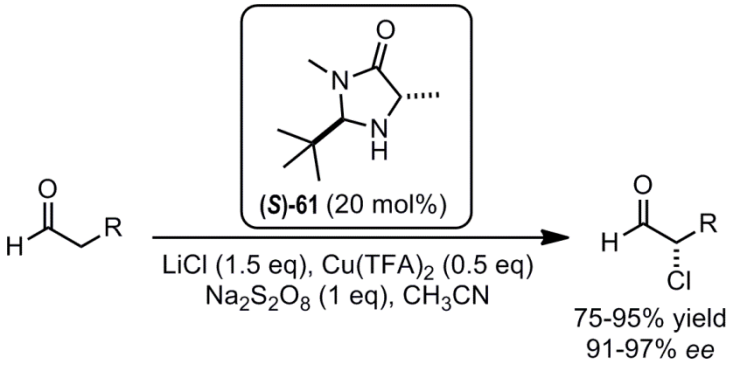
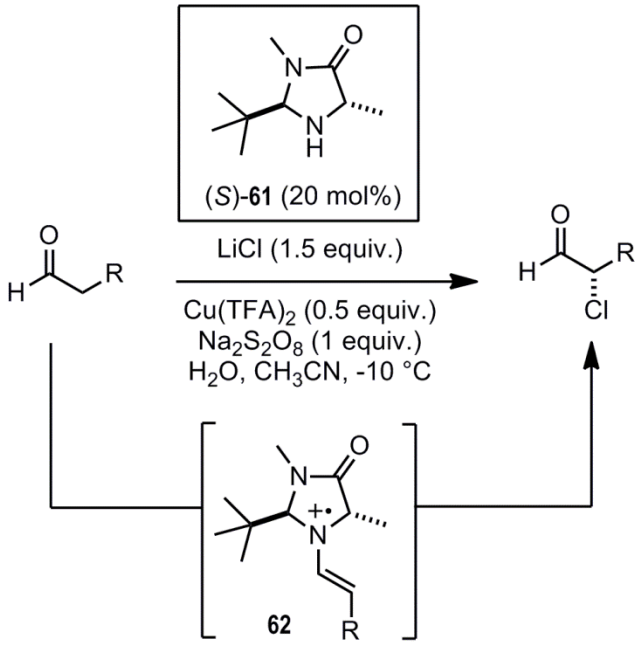
Reaction	Reference
	Jørgensen 2004[92]
	MacMillan 2004[93]
	MacMillan 2007,[94] 2009[96]

Figure 2.11. Enantioselective α-Chlorination Methods

[c] Note on nomenclature in this thesis regarding catalyst **61**: Use of the term "(*R*)-**61**" refers to the enantiomer of the catalyst that results in the (2*R*)-2-chloroaldehyde as the major product, and "(*S*)-**61**" refers to the enantiomer of the catalyst that results in the (2*S*)-2-chloroaldehyde as the major product.



Scheme 2.2. Mechanism for SOMO-catalyzed α-Chlorination of Aldehydes

2.2. Previous Work in the Britton Lab

The α-chlorination of aldehydes, as described above, has been well established by Jørgensen and Macmillan, and many optically enriched α-chloroaldehydes have been prepared in our laboratory using these methods. These substrates react well with lithium enolates to yield β-ketochlorohydrins (e.g., **34**, Figure 2.12) in diastereomeric ratios up to 37:1 (*anti:syn*), as predicted by the Cornforth model described above, with various substituents on both the aldehyde (R^1) and ketone (R^2) starting materials.

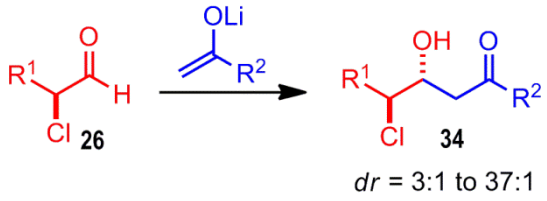
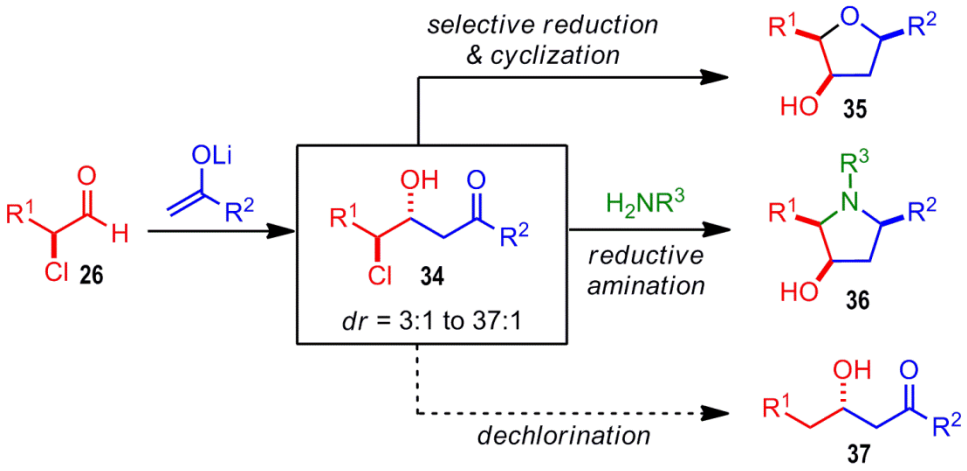


Figure 2.12. Lithium Aldol Additions to α-Chloroaldehydes

Further reactions of the resultant β-ketochlorohydrins have been explored in the Britton group, some of which are described in Scheme 2.3. These include (i) selective

reduction to the *syn* or *anti* chlorodiol, followed by stereospecific intramolecular cyclization to give direct access to all diastereoisomers of substituted tetrahydrofuranols (e.g., **35**),[48] and (ii) reductive amination with substituted primary amines to yield optically enriched hydroxypyrrolidines (e.g., **36**).[49] A notable application of this latter method was the concise 3 step total synthesis of the natural product (+)-preussin.[49] It is also important to note that all the stereocenters formed in these more complex molecules are completely dependent on the absolute configuration of the chloromethine in the α-chloroaldehyde.



Scheme 2.3. Functionalization of β-Ketochlorohydrins

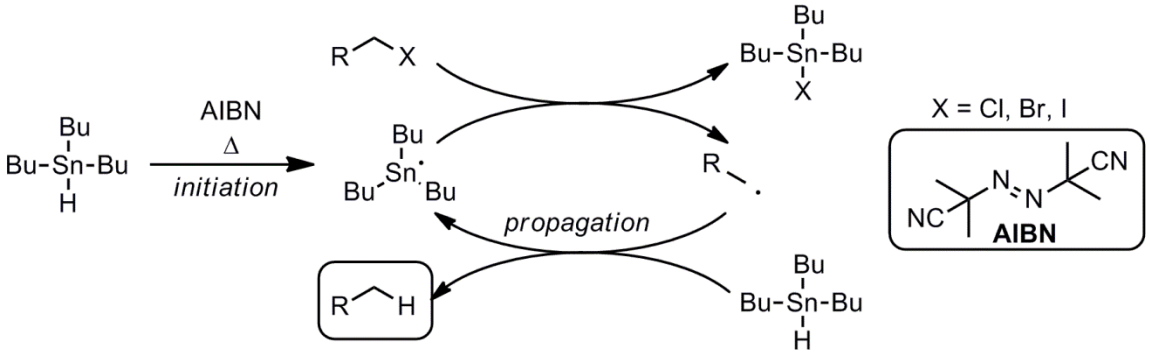
Considering the limitations to acetate aldol reactions discussed above, and the now ready availability of α-chloroaldehydes, we envisaged a process whereby the highly diastereoselective nature of lithium enolate additions to α-chloroaldehydes could be further exploited to yield optically enriched β-hydroxyketones. Given the high degree of selectivity observed in the formation of the new carbinol sterecentre, it was envisioned that removal of the chlorine atom would provide access to optically enriched aldol adducts (e.g., **37**, Scheme 2.3) in three facile steps. As the preparation of β-ketochlorohydrins has been well established in the Britton group, a key aspect of this proposed research would involve the identification of a high yielding and functional group tolerant dechlorination process. A brief survey of reported dehalogenation methods is presented below.

2.3. Radical Dehalogenating Reagents

Trialkyl group 14 compounds such as Bu_3SnH and Et_3SiH are well known for their radical propagating ability. As shown in Table 2.1, their utility in this regard can be attributed to the relatively low Si-H and Sn-H bond dissociation energies, which allows for facile hydrogen abstraction by a radical initiator or intermediate radical, to form a tin or silyl centred-radical. As depicted in Scheme 2.4, a tin radical initially formed by reaction with AIBN is capable of reacting with alkyl halides to form an alkyl radical, which then reacts with another equivalent of the propagator to yield the reduced alkane and tributyltin halide.

Table 2.1. Properties of Radical Reducing Agents

Radical Reducing Agent	Bond Dissociation Energy (kcal/mol)[97]		Rate Constant for Cl Abstraction from $(CH_3)_3CCl$ by Si• or Sn• @298 K[98]
Bu_3Sn-H	Sn-H	74	$2.7 \times 10^4\ M^{-1}s^{-1}$
Et_3Si-H	Si-H	90	$2.5 \times 10^6\ M^{-1}s^{-1}$
$(TMS)_3Si$-H	Si-H	79	$4.0 \times 10^5\ M^{-1}s^{-1}$



Scheme 2.4. Mechanism of Tributyltin Hydride Mediated Radical Dehalogenation

While Bu_3SnH and related alkyltin reagents are some of the most widely used radical propagators for this process, the toxic and environmentally harmful side effects associated with trialkyltins make these reagents undesirable.[99] In the late 1980's, the radical propagating reagent tris(trimethylsilyl)silane (TTMSS (**63**) Figure 2.13) was reported by Chatgilialoglu as an efficient radical reducing agent.[100] As these silyl radicals have been shown to possess greater halogen abstracting ability compared to

trialkyltins (Table 2.1), utilizing TTMSS for the radical dechlorination would be a desirable and effective alternative to tributyltin hydride.

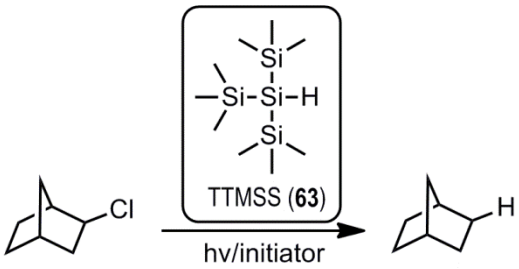
	Chatgilialoglu 1988[100]

Figure 2.13. Tris(trimethylsilyl)silane (TTMSS, 63)

2.3.1. Other Dehalogenation Methodologies

In addition to the silicon and tin promoted radical dehalogenation reactions described above, few reports exist regarding the use of other reagents. These include palladium-catalyzed hydrogenolysis of brominated cyclic ethers (Figure 2.14), and magnesium-promoted reduction of benzylic carbon-chlorine bonds that also resulted in the unsaturated dimer as byproduct.

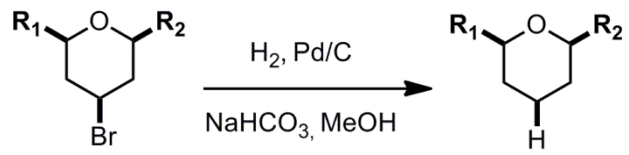
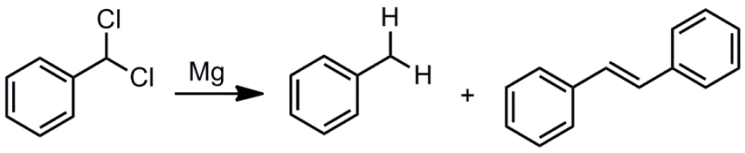
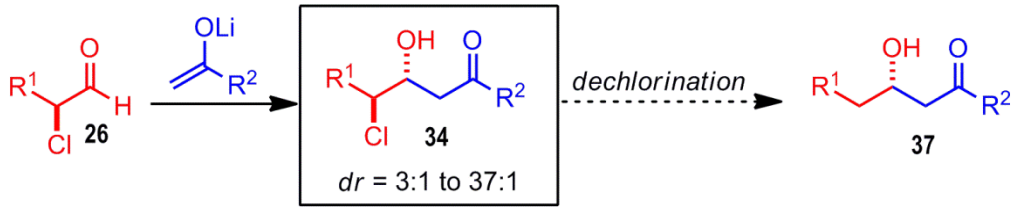
	Loh 2007[101]
	Aitken1997[102]

Figure 2.14. Other Dehalogenation Methods

2.4. Proposal: Chlorine as an Auxiliary in Asymmetric Aldol Reactions

Our primary focus was to develop highly diastereoselective aldol reactions of methyl and cyclic ketones by utilizing a chlorine auxiliary on the aldehyde that imparts diastereoselectivity to the reaction (Scheme 2.5). Following removal of the chlorine atom, the resultant optically active β-hydroxyketones could be utilized as building blocks for natural product synthesis.



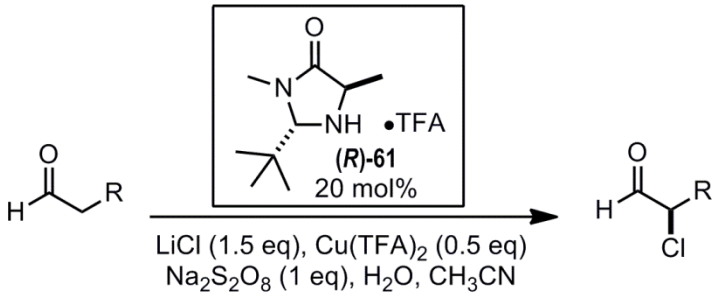
Scheme 2.5. Proposed Methodology for Asymmetric Aldol Reactions

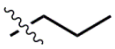
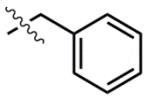
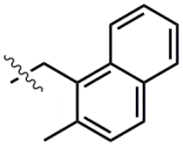
2.5. Results

2.5.1. Synthesis of α-Chloroaldehydes and β-Ketochlorohydrins

The preparation of nonracemic α-chloroaldehydes from aldehydes was accomplished using MacMillan's SOMO catalysis method (e.g., Figure 2.11). As depicted in Table 2.2, a variety of functionalized and substituted α-chloroaldehydes were prepared in good yield following this protocol. The relatively low yields obtained for smaller chain α-chloroaldehydes (entries 1-2) can be attributed to the volatility of these compounds, as product was inevitably lost during workup and purification. Additionally, α-chloroaldehydes were generally reacted immediately following synthesis or partial decomposition occurred.

Table 2.2. Synthesis of α-Chloroaldehydes[a]

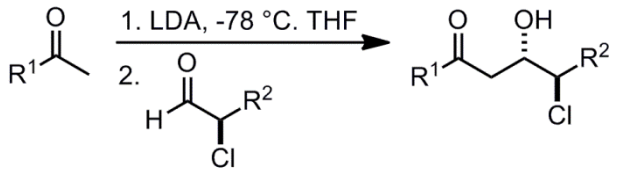


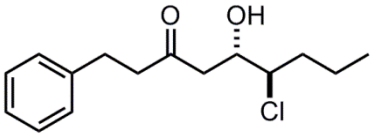
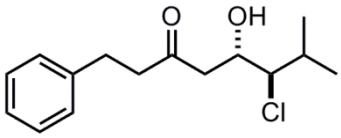
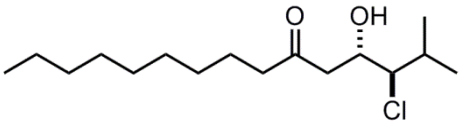
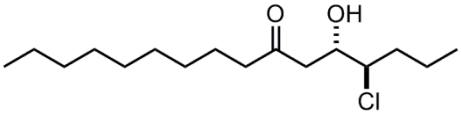
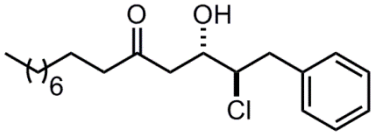
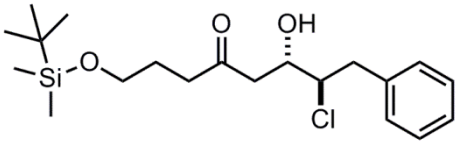
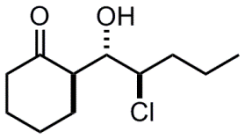
entry	R =		Yield[b]
1		64	60%
2		65	55%
3		66	80%
4		67	66%

[a.] Reaction conditions: A suspension of the SOMO catalyst (20 mol%), $Cu_2(CO_2CF_3)_2$ (0.5 equiv), LiCl (1.5 equiv), $Na_2S_2O_8$ (1 equiv), H_2O (2.2 equiv) in CH_3CN (0.1 M) was stirred at -30° C. See experimental for more information. [b.] Isolated yield

Utilizing previously reported conditions,[48] a variety of nonracemic ketochlorohydrins were prepared by addition of the (*R*)-α-chloroaldehyde to a premixed solution of the ketone or nitrile and lithium diisopropylamide (Table 2.3). A variety of functional groups were tolerated by this process as the lithium enolates that were involved in the aldol reaction included those derived from aliphatic methyl ketones (entries 3-5), protected alcohols (entry 6), and cyclic ketones (entries 7-9). Additionally, utilizing the anion derived from acetonitrile provided β-nitrilechlorohydrins (entries 10-11). Diastereomeric ratios of the aldol products ranged from 2:1 to 20:1 (*anti:syn* chlorohydrins), and were highest for the branched aldehydes (entries 2-3). All keto- or nitrilechlorohydrins depicted in Table 2.3 were isolated in good to excellent yield.[103]

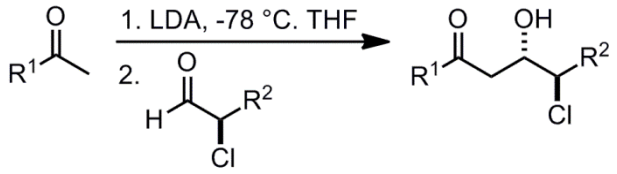
Table 2.3. Synthesis of β-Ketochlorohydrins.

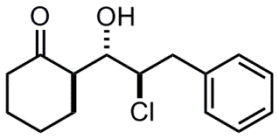
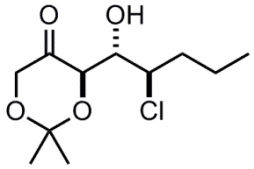
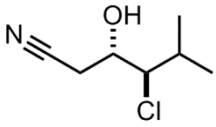
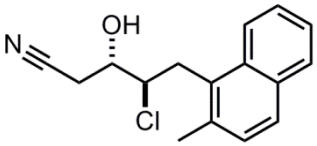


entry	Product		Yield[a]	dr (*anti:syn*)[b]
1		68	80%	7:1
2		69	90%	19:1
3		70	76%	12:1
4		71	74%	7:1
5		72	63%	4:1
6		73	57%	4:1
7		74	76%	9:1

[a.] Isolated yield of single diastereomer. [b.] Diastereomeric ratio determined by analysis of ^{1}H NMR spectra recorded on crude reaction products in $CDCl_3$. ND = not determined.

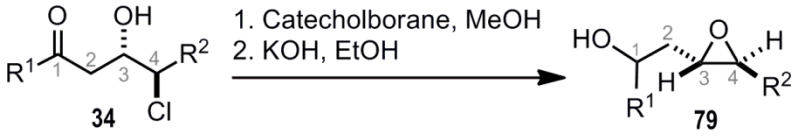
Table 2.3 Continued



entry	Product		Yield[a]	dr (*anti:syn*)[b]
8		75	61%	N.D
9		76	54%	N.D.
10		77	54%	6:1
11		78	53%	2:1

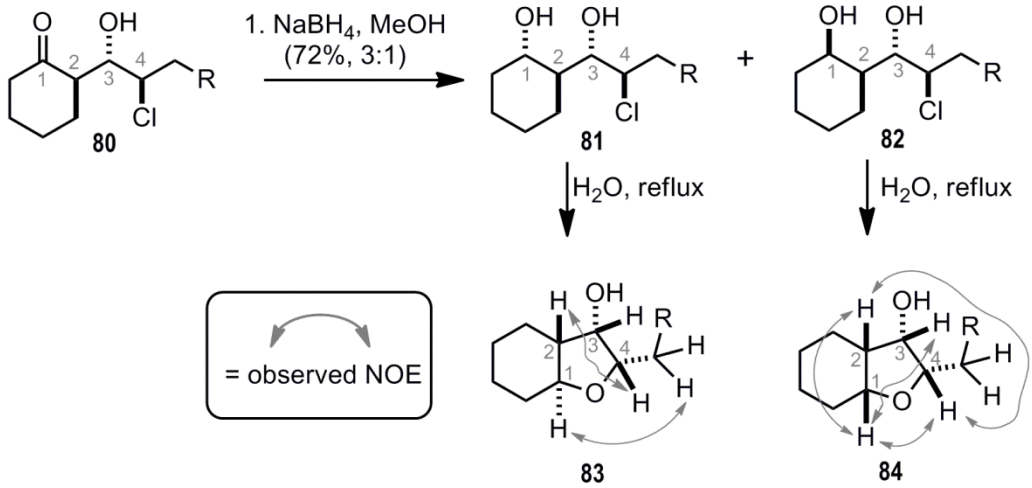
[a.] Isolated yield of single diastereomer. [b.] Diastereomeric ratio determined by analysis of ^{1}H NMR spectra recorded on crude reaction products in $CDCl_3$. ND = not determined.

The *anti* configuration of the product of enolate addition to α-chloroaldehydes was determined by reduction of the ketone **34** (catecholborane) and subsequent conversion of the chlorohydrin into a *trans*-epoxide (e.g., **79**) (KOH) as shown in Scheme 2.6. Analysis of the $^2J_{H\text{-}H}$ coupling constants of the vicinal protons (typically 2 Hz for *trans* vs. 5 Hz for *cis*) on the *trans* epoxide confirmed the relative 3,4-*anti* stereochemistry of the chlorohydrin. Additionally, NOESY experiments did not show a correlation between the two epoxide proton resonances, but did lead to enhancements of proton resonances of the corresponding attached alkyl groups.



Scheme 2.6. Epoxidation of Chlorohydrins

The relative stereochemistry of the three contiguous stereocenters in the aldol products depicted in entries 7-8 was confirmed as follows. The ketone **80** was reduced ($NaBH_4$, MeOH) and the resulting diastereomers **81** and **82** were separated. A subsequent stereospecific cyclization[48] of the resulting chlorodiols **81** and **82** led to a rigid bicylic compound **83** or **84**. NOESY analysis of these tetrahydrofuranols confirmed the relative stereochemistry as depicted and, consequently, that of the originating aldol adduct. Further evidence for the relative stereochemistry is shown in Table 2.6.



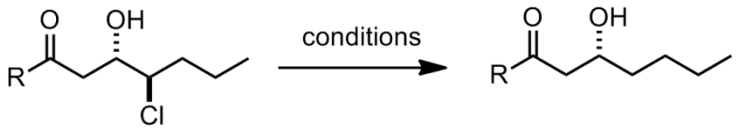
Scheme 2.7. Stereochemical Proof for Cyclic Substrates

2.5.2. Elaboration to Enantioenriched Aldol Adduct

Table 2.4 describes a survey of conditions used to effect the dechlorination of β-ketochlorohydrins. Based on previous reports,[102,101] initial attempts at dehalogenation involved hydrogenolysis, which only resulted in reduction of the ketone function (entry 1) or recovered starting material (entry 2). Alternatively, attempts to form a Grignard reagent and subsequently react with a proton source were similarly not successful (entries 3-6). Preliminary experiments demonstrated that when the ketochlorohydrins

were reacted with a slight excess of tris(trimethylsilyl)silane (entry 7) the dechlorination proceeded in suboptimal yield (35%). By exploring the use of excess amounts of TTMSS, it was found that 5 equivalents of this radical propagator resulted in excellent conversion of the ketochlorohydrin to the reduced product (entries 8-9).

Table 2.4. Preliminary Dechlorination Experiments.

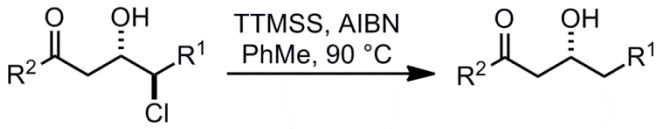


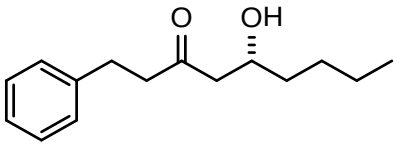
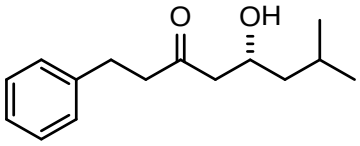
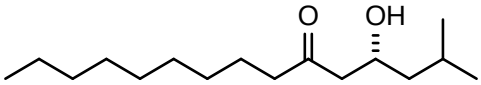
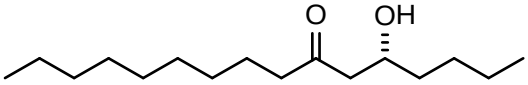
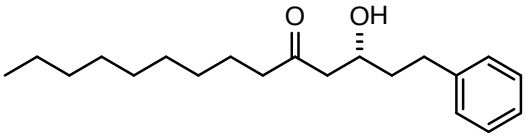
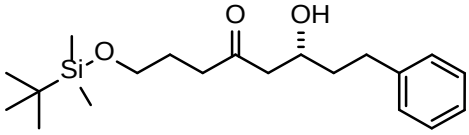
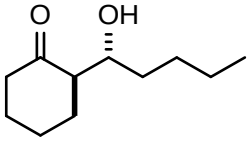
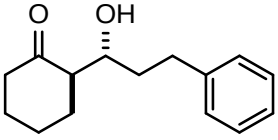
entry	Conditions[a]	R =	Result[b]
1	H_2, Pd/C, MeOH, rt	-Ph	reduction of ketone to CH_2
2	H_2, Pd/C, NEt_3, MeOH, rt	-CH_2-CH_2-Ph	N.R.
3	Mg, I_2 (cat), THF, reflux	-CH_2-CH_2-Ph	N.R.
4	Mg, MeOH, rt	-CH_2-CH_2-Ph	N.R.
5	Mg, I_2 (cat), Et_2O, reflux	-CH_2-CH_2-Ph	N.R.
6	Mg, I_2 (cat), Et_2O, MeOH, reflux	-CH_2-CH_2-Ph	N.R.
7	TTMSS (1.2 equiv.), PhMe, 90 °C	-CH_2-CH_2-Ph	35% yield
8	TTMSS (2.0 equiv.), PhMe, 90 °C	-CH_2-CH_2-Ph	38% yield
9	TTMSS (5.0 equiv.), PhMe, 90 °C	-CH_2-CH_2-Ph	92% yield[c]

[a.] rt = room temperature. [b.] As observed by integration of signals in the crude ^{1}H NMR spectrum. N.R. = no reaction. [c.] isolated yield.

With optimized conditions in hand, the radical dechlorination of a series of keto- and nitrilechlorohydrins proceeded in very good yield. Pleasingly, this reaction was tolerant to a variety of functional groups, including aryl, alkyl, keto- and nitrile groups (Table 2.5). Enantiomeric excess of the hydroxyketones was determined by chiral HPLC, unless otherwise noted, and ranged from 90-99% *ee*. Lower enantioselectivities (entries 6,8) can be attributed to the presence of a small amount of *syn*-chlorohydrin that was unable to be separated from the *anti*-chlorohydrin prior to dechlorination. The inclusion of this diastereomer results in the formation of the enantiomeric hydroxyketone after radical reduction of the C-Cl bond, and degradation of the enantiomeric purity of the final product.

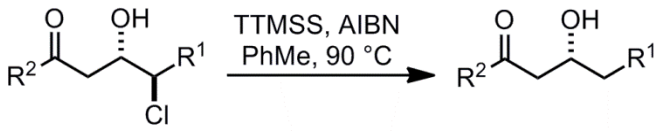
Table 2.5. Radical Dechlorination of Various β-Ketochlorohydrins.[a]

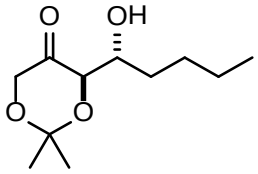
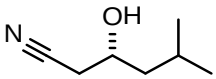
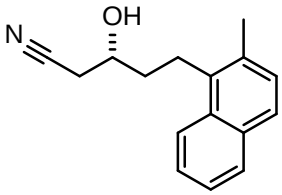


entry	Product		Yield[a]	*ee*[b]
1		85	92%	99%
2		86	95%	96%
3		87	81%	95%[c]
4		88	92%	97%[d]
5		89	95%	96%
6		90	86%	92%
7		91	74%	N.D
8		92	35%	90%[d]

[a.] Isolated yield. [b.] *ee* determined by HPLC (Daicel Chiralpak AD-H). ND = not determined. [c.] *ee* determined by GC. [d.] alcohol was converted to benzoyl ester prior to HPLC detection.

Table 2.5 Continued

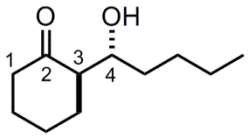
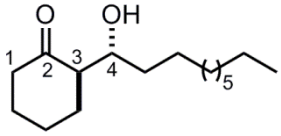
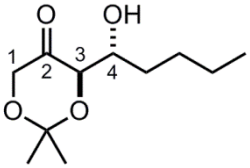
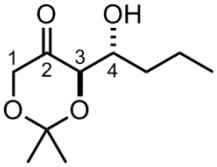


entry	product		yield[a]	ee[b]
9		93	74%	N.D.
10		94	70%	N.D
11		95	88%	N.D.

[a.] Isolated yield. [b.] *ee* determined by HPLC (Daicel Chiralpak AD-H). ND = not determined. [c.] *ee* determined by GC. [d.] alcohol was converted to benzoyl ester prior to HPLC detection.

Further confirmation of the stereochemistry for the compounds depicted in entries 7-9, Table 2.5, is described in Table 2.6. Comparison of key ^{1}H NMR spectral data for **91** and **93** confirmed the 3,4-*anti* stereochemistry as depicted in Table 2.6. The chemical shift of the proton resonances of **91** and **93** were in good agreement (Δ ppm ~ 0.01) with the equivalent resonances reported for the analogous compounds (**96** and **97**) depicted in Table 2.6. Importantly, the spectroscopic data for the corresponding 3,4-*syn* diastereomers (not shown) clearly differentiated these compounds (Δδ ppm ~ 0.5) from the 3,4-*anti* aldol adducts described in Table 2.6.

Table 2.6. Comparison of Spectral Data for 91 and 93 With Known Compounds

Compound (experimental)	^{1}H NMR ($CDCl_3$) ppm	Compound (known)	^{1}H NMR ($CDCl_3$) ppm
 91	H_4: 3.73 (m), OH: 3.42 (d, J = 4.3 Hz)	 96[104]	H_4: 3.72 (m) OH: 3.41 (d, J = 4.0 Hz)
 93	H_1: 4.26, 4.02 H_3: 4.09 H_4: 3.89	 97[105]	H_1: 4.25, 4.01 H_3: 4.08 H_4: 3.89

2.5.3. Total Synthesis of Natural Products

Diarylheptanoids

Diarylheptanoids are a class of plant metabolites that share a common molecular structure that includes a seven carbon chain flanked by two aromatic rings.[106] This family can be further classified as linear or cyclic diarylheptanoids, the latter of which includes aromatic rings that are connected either by a carbon-oxygen or carbon-carbon bond. Biological studies of various diarylheptanoids have shown that some of these molecules exhibit anti-inflammatory or anti-cancer properties.[107] Some examples of naturally occurring diarylheptanoids are shown in Figure 2.15. Curcumin (**98**) is naturally found in turmeric and ginger and is reported to exhibit a large variety of biological activities including ant-inflammatory, anti-cancer and anti-oxidant.[108] Furthermore, due to its yellow colour it is often used in food colouring. Acerogenin A (**99**) is a cyclic diarylheptanoid that has comparable anti-inflammatory properties to the commercially available drug indomethacin.[109]

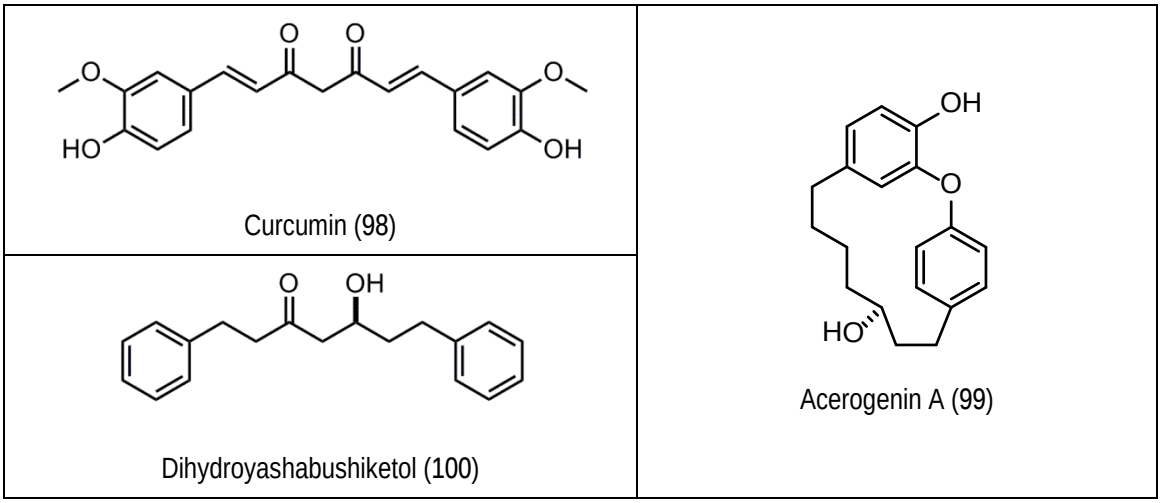
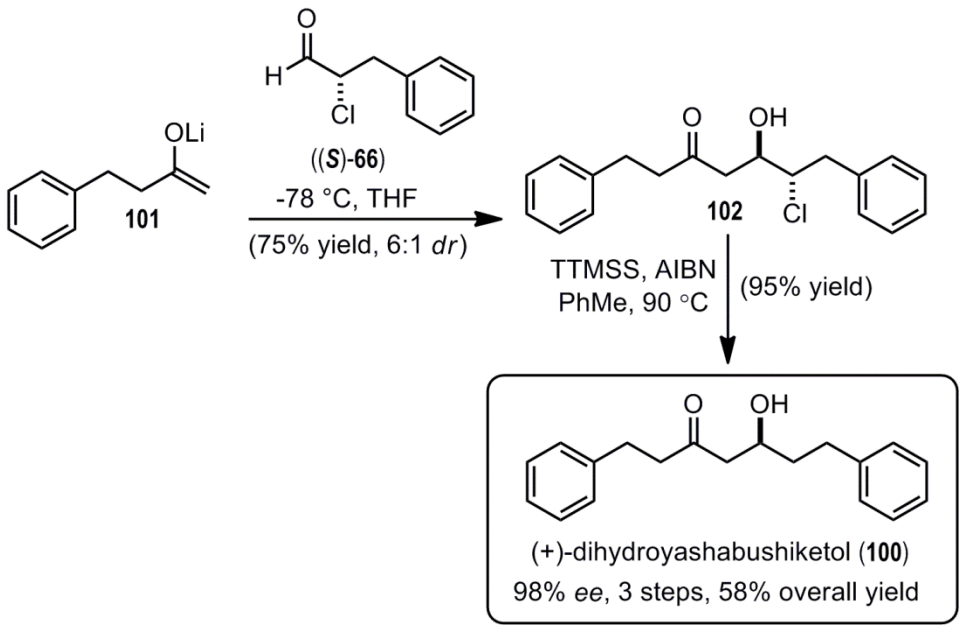


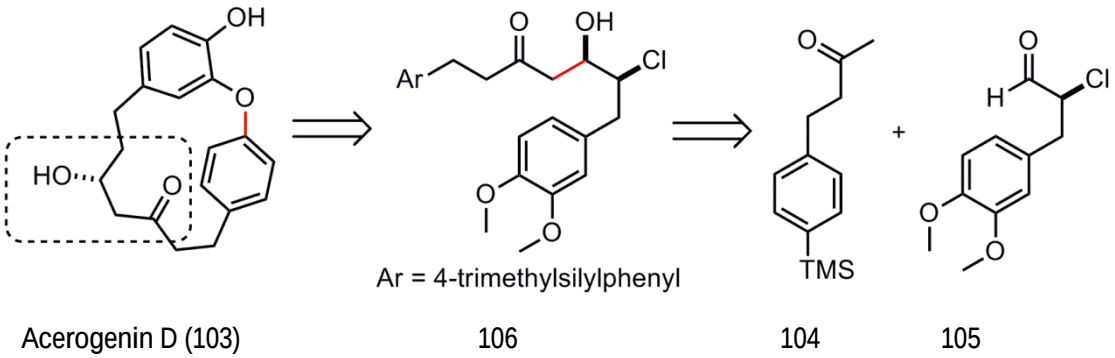
Figure 2.15. Naturally Occurring Diarylheptanoids

Dihydroyashabushiketol (**100**) was originally isolated in 1970 from the plant *Alnus firma* and has demonstrated a variety of potentially useful biological activities.[110,107] The first asymmetric synthesis of **100** was reported in 2011 and required 6 synthetic steps,[111] and utilized Oppolzer's sultam chiral auxiliary (e.g., **55**, Figure 2.5) to direct the absolute stereochemistry of a 1,3-dipolar cycloaddition. Using our chlorine auxiliary strategy (Scheme 2.5) the lithium enolate derived from benzylacetone (**101**) was reacted with (2*S*)-2-chlorohydrocinnamaldehyde ((***S***)**-66**) to yield the 1,2,-*anti* ketochlorohydrin **102** in good yield and diastereoselectivity. The subsequent dechlorination of **102** proceeded in excellent yield to provide (+)-dihydroyashabushiketol (**100**) in a total of 3 steps (Scheme 2.8). This is the shortest reported synthesis of this compound to date, and it was prepared with an enantiomeric excess of 98% and overall yield of 58%.



Scheme 2.8. Synthesis of Dihydroyashabushiketol (100).

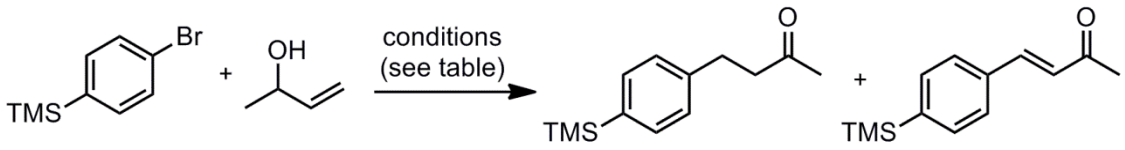
Acerogenin D (**103**, Scheme 2.9) was first isolated in 1993 from a Japanese maple stem extract.[112,109,113] No total synthesis of acerogenin D has been reported and it was envisioned that our asymmetric acetate aldol methodology could be exploited in a synthesis of the β-hydroxyketone core (dashed box, Scheme 2.9). As depicted in the proposed retrosynthesis (Scheme 2.9), it was expected that the natural product could be made via an aryl ether macrocyclization in the final step, utilizing well-established aryl iodide/aryl ether coupling strategies.[114] The key carbon-carbon bond forming reaction would involve a stereoselective aldol reaction between a *para*-functionalized 4-phenyl-2-butanone (e.g., **104**) and the appropriate α-chloroaldehyde **105**.



Scheme 2.9. Retrosynthesis of Acerogenin D

In the forward sense, a palladium-catalyzed Heck reaction between aryl halide **107** and allylic alcohol **108** was utilized to construct the desired *p*-trimethylsilylaryl ketone **104**. Table 2.7 summarizes the results that led to the optimization of this reaction. While use of palladium acetate as a catalyst resulted in good conversion (60%) to the desired product (entry 2), these conditions also led to the production of an undesired enone **109**, derived from oxidation of the ketone **104**. A brief screen of palladium catalysts led to the identification of $Pd(PPh_3)_2Cl_2$ as optimal and also demonstrated that the addition of sodium bicarbonate resulted in the highest yield of desired product **104** (69%) with only a small amount (5%) of the conjugated enone **109**. As the desired product was inseparable from the undesired enone, these inseparable mixtures were subjected to hydrogenation over palladium which resulted in clean conversion to the saturated ketone. Using this method, sufficient amounts of the ketone were made available to explore the key aldol reaction.

Table 2.7. Optimization of the Synthesis of Ketone 102



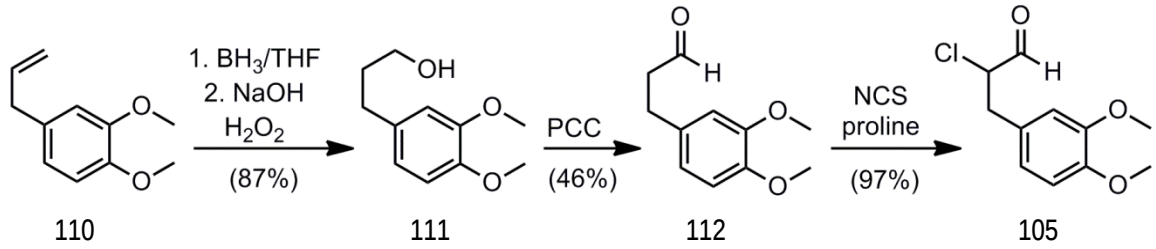
107 108 104 109

entry	Conditions	Yield[a]		
		Starting Material	104	109
1	$Pd(OAc)_2$, NaOAc, NMP, 120°C o/n (reflux)	94%	6%	0%
2	$Pd(OAc)_2$, PPh_3, NEt_3, 75°C o/n (reflux)	0%	60%	40%
3	$Pd(OAc)_2$, LiCl, NEt_3, DMF, 120°C o/n (sealed tube)	38%	61%	trace
4	$Pd(OAc)_2$, LiCl, NEt_3, DMF, 120°C o/n (reflux)	85%	10%	5%
5	$Pd(OAc)_2$, LiCl, NEt_3, DMF, 120°C, 20 min (μwave)	94%	5%	trace
6	$Pd(PPh_3)_2Cl_2$, $NaHCO_3$, NMP, 120°C , 5h (reflux)	26%	69%	5%

[a] As observed by integration of proton resonances in the crude ^1H NMR spectrum. NMP = *N*-methylpyrrolidinone.

Synthesis of the necessary aldehyde **105** began with hydroboration/oxidation of commercially available 4-allyl-1,2-dimethoxybenzene (**110,** Scheme 2.10) to yield the

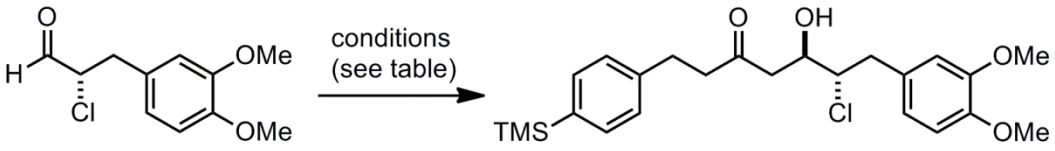
terminal alcohol **111** in good yield. A subsequent oxidation with pyridinium chlorochromate (PCC) afforded the aldehyde **112**. Chlorination of the aldehyde using NCS/proline gave the desired chloroaldehyde **105** as a racemic mixture.



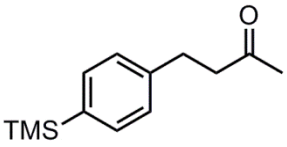
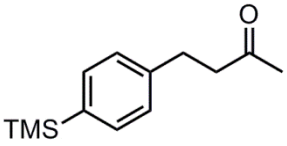
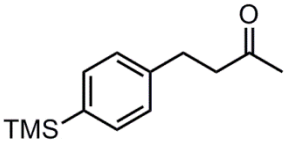
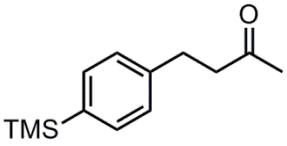
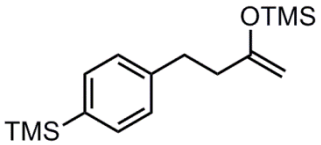
Scheme 2.10. Synthesis of α-Chloroaldehyde 105

With both ketone **104** and aldehyde **105** in hand, the aldol reaction was explored using previously optimized conditions for lithium enolate additions to α-chloroaldehydes. Unfortunately, after multiple repetitions of this reaction, the desired aldol product was not detected by ^{1}H NMR spectroscopic analysis of crude reaction products. A summary of results is shown in Table 2.8. In addition to lithium enolate aldol reactions (entries 1-3), attempts to form and react the corresponding boron enolate with the α-chloroaldehyde **105** only resulted in the recovery of the ketone and α-chloroaldehyde starting materials (entry 4). To isolate the problem with this aldol reaction, the lithium enolate addition was repeated using benzaldehyde in place of the α-chloroaldehyde **105** (not shown). In this test reaction, the desired aldol product was produced in ~ 80% yield, confirming that formation of the lithium enolate was not a complicating factor in the previously unsuccessful aldol reactions. Finally, the silyl enol ether derived from ketone **104** was synthesized and reacted with α-chloroaldehyde **105** using standard Mukaiyama aldol conditions (entry 4), however, none of the desired product **106** was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Based on our inability to effect the desired aldol reaction under a variety of standard conditions, the total synthesis of acerogenin D was abandoned.

Table 2.8. Aldol Additions of Chloroaldehyde 103



105 106

entry	ketone or enol silyl ether	equiv. chloroaldehyde	conditions	result[a]
1		1.3	LDA (1.1 equiv.), THF -78 °C	N.R.
2		1.5	LDA (1.2 equiv.), THF -78 °C	N.R.
3		1.7	LDA (1.1 equiv.), THF -78 °C	N.R.
4		1.3	$B(Cy)_2Cl$ (1.5 equiv.) Et_2O, Et_3N, -78 °C	N.R.
5		1.0	BF_3•OEt_2 (1.5 equiv.) CH_2Cl_2, -60 °C	N.R.

[a] As observed by integration of signals in the crude ^1H NMR spectrum. N.R. = No aldol reaction product; only the ketone starting material was recovered.

Solistatin

Many commercially available cholesterol lowering medications, both natural and synthetic, contain β-hydroxy-γ-lactone functionalities, some of which are depicted in Figure 2.16. Lovastatin (**45**), which occurs naturally in oyster mushrooms and red yeast rice, was the first HMG-CoA reductase inhibitor to be approved by the FDA in 1987.[70] Since this time, a large variety of synthetic LDL-lowering medications have been developed and approved as drugs, including fluvastatin (**113**)[115] and atorvastatin

(**114**).[116] Both atorvastatin and fluvastatin contain β,γ-dihydroxyacids, while the similar functionality in lovastatin is present in the lactone form.

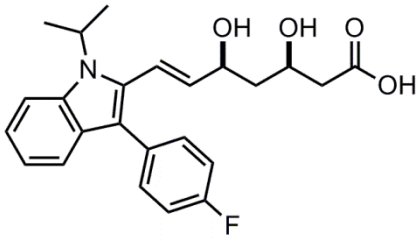
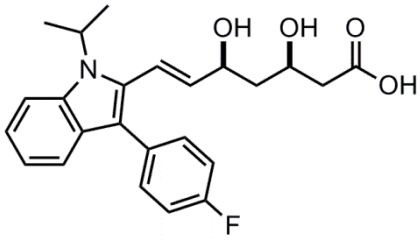
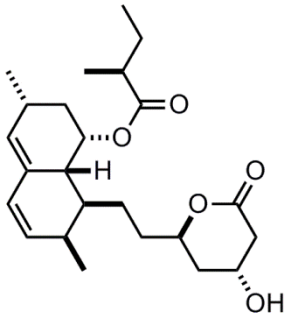
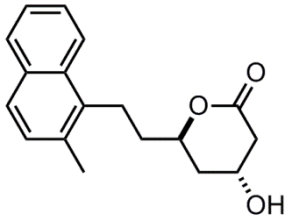
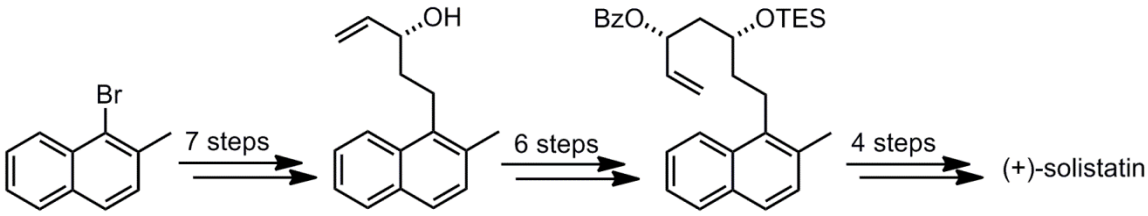
	
Fluvastatin (**113**) (Lescol®)	Atorvastatin (**114**) (Lipitor®)
	
Lovastatin (**45**) (Mevacor®)	(+)-Solistatin (**115**)

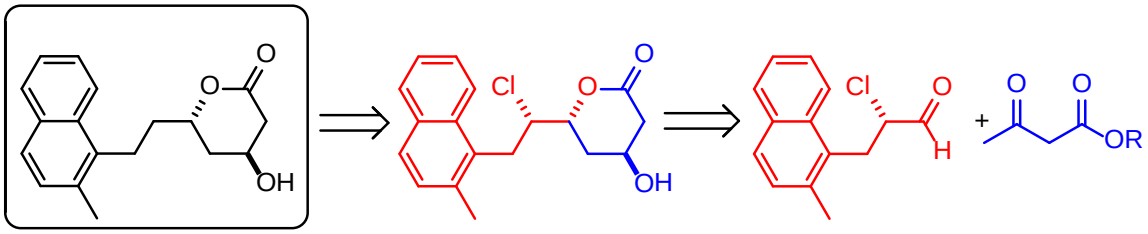
Figure 2.16. Cholesterol Lowering Molecules

Isolated in 1999 from *Penicillium solitum* mold, solistatin (**115**) is an aromatic lovastatin analogue that also possesses cholesterol-lowering activity.[117] Interestingly, decades before being isolated as a natural product, the structure of solistatin was included in a patent describing antihyperlipemic agents.[118] The only previous synthesis of solistatin was reported in 2011 and required 17 synthetic steps,[119] with the absolute and relative stereochemistry of the two oxygen-bearing stereocenters being established via sequential catalytic asymmetric Overman esterification reactions (Scheme 2.11).[120]



Scheme 2.11. Previous Synthesis of (+)-Solistatin

As outlined in Figure 2.16, the structure of (+)-solistatin includes a β-hydroxy-γ-lactone function and it was envisioned that this could be accessed using the asymmetric aldol methodology described above. The retrosynthetic analysis of (+)-solistatin (**115**) is depicted in Scheme 2.12. The β-hydroxylactone could be derived from the diastereoselective reduction and lactonization of β-ketochlorohydrin **116**, which transpires from the aldol reaction of a β-ketoester with the appropriate α-chloroaldehyde. The two key starting materials required for the synthesis of (+)-solistatin are the β-aryl-α-chloroaldehyde **(*S*)-67** and the acetoacetate ester **117**.

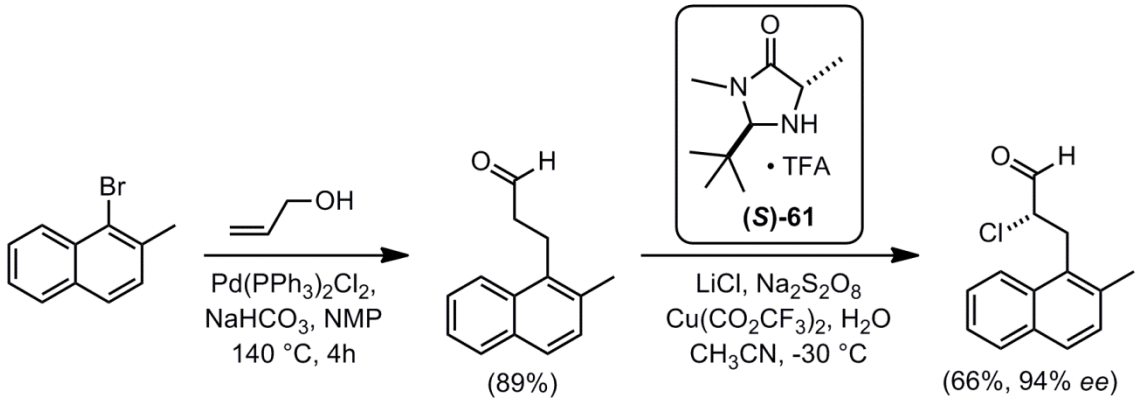


115 116 (*S*)-67 117

Scheme 2.12. Solistatin Retroynthesis

Construction of the necessary aldehyde **(*S*)-67** commenced with a Heck reaction employing conditions similar to those optimized for the synthesis of ketone **104** (Table 2.7). As shown in Scheme 2.13, reaction of 1-bromo-2-methylnapthalene (**118**) with allyl alcohol gave aldehyde **119** in 89% yield. The asymmetric α-chlorination of aldehyde **119** was accomplished using the conditions described by Macmillan[96] to provide the (*S*)-chloroaldehyde **67** in 47% yield and 94% enantiomeric excess. The enantiomeric excess of **(*S*)-67** was determined by reduction of the chloroaldehyde ($NaBH_4$) to the corresponding chlorohydrin and analysis by chiral HPLC. To determine retention times for the two enantiomeric chlorohydrins, 'racemic' chloroaldehyde (±)-**67** was also

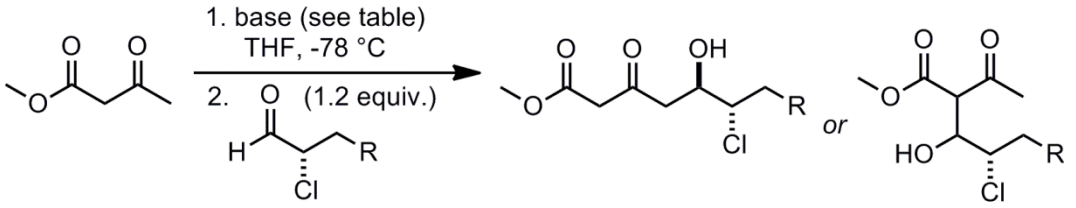
synthesized using proline/NCS chlorination method[119] (0-20% ee), and similarly reduced and analyzed accordingly by chiral HPLC.



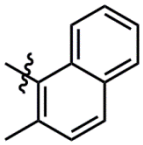
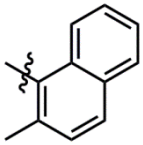
Scheme 2.13. Synthesis of α-Chloroaldehyde (*S*)-67

Efforts that led to the optimization of the aldol reaction required for the synthesis of (+)-solistatin are detailed in Table 2.9. Unfortunately, employing the standard conditions for formation of the sodium lithium dienolate (NaH/*n*-BuLi)[121] and reaction with α-chloroaldehydes **(*S*)-64** or **(*S*)-67** only led to the chlorohydrin aldol product **121** (entries 1 and 3), derived from addition of the monoenolate of methyl acetoacetate to the α-chloroaldehyde, as detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Gratifyingly, using a modified procedure in which 2.4 equivalents of LDA were used for the deprotonation of methyl acetoacetate (**117**), the resulting dianion was reacted with (2*S*)-2-chloropentanal (**(*S*)-64**) to afford the desired product (entry 2). As indicated in entry 4, employing the same conditions but using the α-chloroaldehyde **(*S*)-67** resulted in the formation of the desired aldol adduct **120**, which was isolated in 35% yield and 2:1 diastereoselectivity. As the yield and selectivity for the key step in the synthesis was not optimal, further efforts to optimize the formation of the desired aldol adduct were explored.

Table 2.9. Aldol Additions of Methylacetoacetate with α-Chloroaldehydes



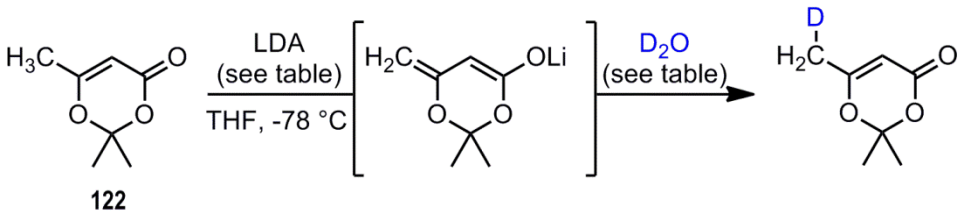
117 120 121

entry	R =		Base	Result [a] (yield) [b]
1	Ethyl	((*S*)-64)	NaH (1.2 equiv) *n*-BuLi (1.2 equiv)	121 (N.D.)
2	Ethyl	((*S*)-64)	LDA (2.4 equiv)	120 (46%)
3		((*S*)-67)	LDA (2.0 equiv)	121 (N.D.)
4		((*S*)-67)	LDA (2.5 equiv)	120 (35%, 2:1 *anti:syn*)

[a.] As observed by analysis of proton resonances in the crude ^{1}H NMR spectrum. [b.] isolated yield.

As an alternative to the lithium dienolate of methylacetoacetate in the aldol reaction, the use of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**122**) as a β-ketoester surrogate was explored. In efforts to optimize the deprotonation of dioxinone **122** with LDA, deuterium quenching experiments were carried out to determine optimal conditions for anion formation (Table 2.10).

Table 2.10. Deuterium Quenching Experiments



122

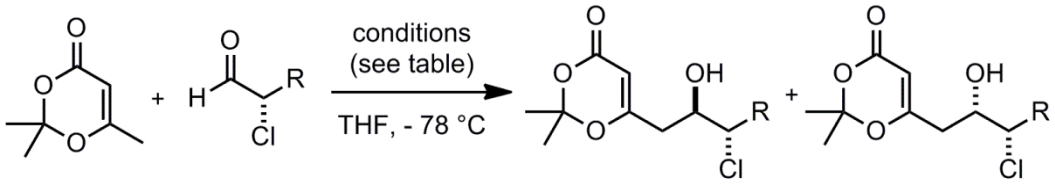
entry	equiv. LDA	reaction time	reaction temperature	%D incorporation[b]
1	2.0 equiv.	0.75 h	-78° C	54%
2	1.5 equiv.	0.75 h	-78° C	50%
3	1.5 equiv.	0.75 h	-78° C → -40° C	50%
4	1.5 equiv.	0.75 h	-78° C → 0° C	65%
5	1.2 equiv.	1 h	-78° C → 0° C	61%
6	1.0 equiv.	0.5 h	-78° C → 0° C	74%
7	1.0 equiv.	0.25 h	-78° C → 0° C	76%
8	1.2 equiv.	1.5 h	-78° C → rt	54%
9	1.2 equiv.	1 h	-78° C → rt	65%
10	1.0 equiv.	0.5 h	-78° C → rt	73%
11	1.0 equiv.	0.25 h	-78° C → rt	78%
12	1.0 equiv.	0.1 h	-78° C → rt	86%

[a.] Reaction conditions: To a cold (-78 ˚C) solution of base in THF was slowly added dioxinone 122. Reaction was stirred for reaction time while warming to reaction temperature and then quenched with excess D_2O.
[b.] As observed by integration of proton resonances (deuterated product and recovered starting material) in the crude ^1H NMR spectrum.

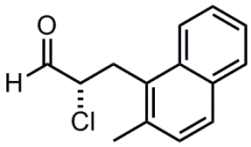
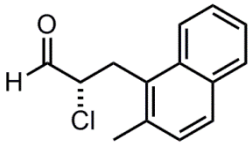
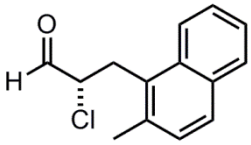
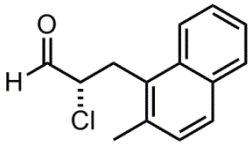
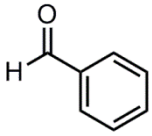
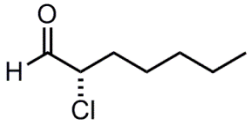
Examining the data obtained from the deuterium quenching experiments, it was found that allowing the reaction to proceed at temperatures above -78 °C resulted in higher deuterium incorporation (entries 1-4). Next, examining the reaction time indicated that shorter reaction times were optimal (entries 5-12). Thus, allowing the enolate to warm to room temperature over 0.1 hours resulted in 86% deuterium incorporation as

observed by integration of proton resonances in the ^{1}H NMR spectrum of the recovered dioxinone (entry 12). As depicted in Table 2.11, these optimized conditions were then used to form the anion of the dioxinone **122**, which was subsequently reacted with the α-chloroaldehyde (**(*S*)-67**). Unfortunately, under these conditions, the desired aldol adduct ((*anti*)-**123**) was isolated in low yield (25-28%) and diastereoselectivity (3:1 *anti:syn)*. Furthermore, a significant amount of the chloroaldehyde and dioxinone starting materials were consistently recovered. Additional experiments indicated that the enolate derived from dioxinone **122** reacted with benzaldehyde (**124**) to give 80% yield of the corresponding aldol product, suggesting that the specific α-chloroaldehyde **67** was problematic under these conditions (entry 5). This supposition was further supported by the fact that the equivalent reaction involving α-chloroheptanal (**125**) resulted in 57% yield of the desired aldol product and 4:1 diastereoselectivity (entry 6).

Table 2.11. Reactions of Dioxinone 122 with Chloroaldehydes.



122 (*anti*)-123 (*syn*)-123

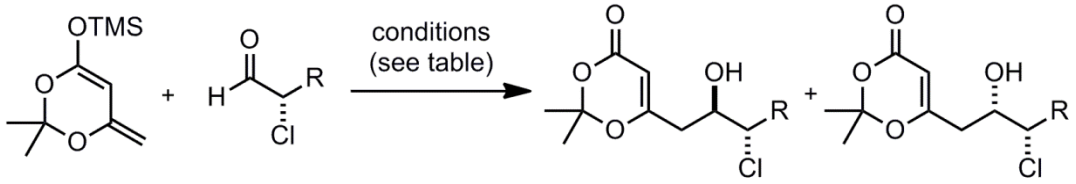
entry	aldehyde		equiv. aldehyde	base (equiv.)[a]	result[b]
1		(*S*)-67	0.5	LDA (1.2 equiv.)	26% yield[c] 3:1 *anti:syn*
2		(*S*)-67	0.8	LiHMDS (1.0 equiv.)	15% yield
3		(*S*)-67	3	LDA (1.0 equiv.)	25% yield 3:1 *anti:syn*
4		(*S*)-67	0.3	LDA (1.0 equiv.)	28% yield 2:1 *anti:syn*
5		124	0.8	LDA (1.0 equiv.)	80% yield
6		125	0.8	LDA (1.0 equiv.)	57% yield 4:1 *anti:syn*

[a.] Reaction conditions (entries 1-6): To a cold (-78 ˚C) solution of base in THF was slowly added dioxinone 120. The cold bath was removed and reaction was stirred for 0.1 h and then quenched with aldehyde. [b.] As observed by integration of proton resonances in the crude ^{1}H NMR spectrum. [c.] Isolated yield.

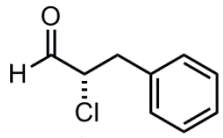
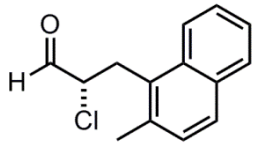
Previously, the silyl enol ether derived from dioxinone **122** has been used in Mukaiyama aldol reactions.[122] Thus, the conversion of dioxinone **122** to the silyl enol ether **126** and subsequent reaction with α-chloroaldehyde **(*S*)-67** was also explored (Table 2.12). Gratifyingly, in the presence of boron trifluoride, the addition of **126** to **(*S*)-**

67 resulted in 94% yield of the aldol product (entry 2). Additionally, this Mukaiyama aldol reaction provided a 2:1 mixture of *anti:syn* chlorohydrins **123** that were separable by column chromatography.

Table 2.12. Reactions of Silyl Enol Ether 126 with α-Chloroaldehydes

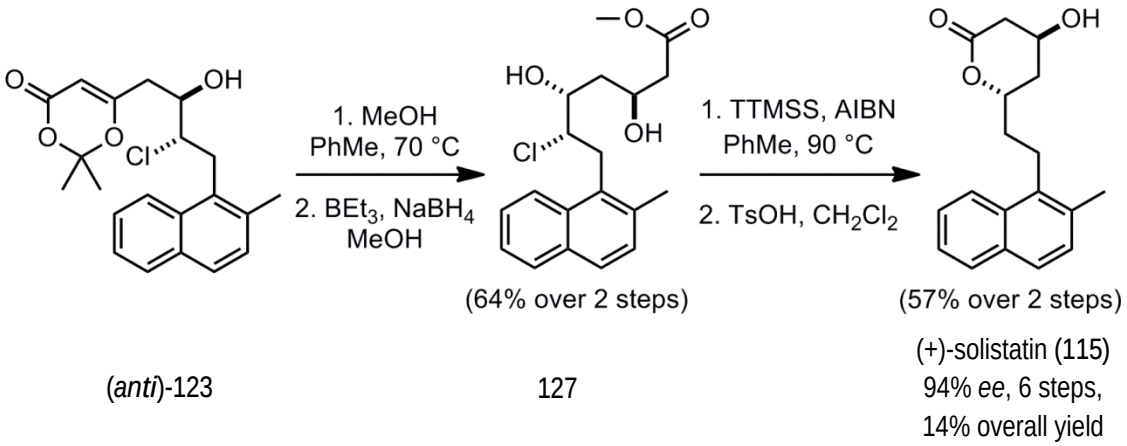


126 (*anti*)-123 (*syn*)-123

entry	α-chloroaldehyde	equiv. aldehyde	conditions[a]	result
1	 (*S*)-66	1.5 equiv.	MeLi (1 equiv.) THF, -78 °C	28% yield[b] 3:1 *anti:syn* dr
2	 (*S*)-67	0.5 equiv.	BF_3•OEt_2 (1.5 equiv.) CH_2Cl_2, -60 °C	94% yield[c] 2:1 *anti:syn* dr

[a.] Conditions (entry 2): To cold (-60 °C), stirred a solution of aldehyde (*S*)-67 in CH_2Cl_2 was added BF_3•OEt_2 and the resultant orange solution was stirred for 10 minutes. Silyl enol ether 126 was then added neat and the resulting colourless solution was stirred at -60 °C for 18 hours. H_2O was then added, and the reaction mixture was allowed to warm to room temperature. [b.] As observed by integration of signals in the crude ^1H NMR spectrum. [c.] Isolated yield.

With chlorohydrin *anti*-**123** in hand, methanolysis of the dioxinone in the presence of methanol led to β-ketoester **120** (Table 2.9), which was subjected to Prasad conditions for diastereoselective reduction of β-keto alcohol.[123] Employing triethylborane followed by sodium borohydride led to the formation of the *syn*-chlorodiol **127** in 64% yield over two steps (Scheme 2.14). Finally, reduction of the chloromethine with TTMSS, and formation of the corresponding lactone from the hydroxyacid gave (+)-solistatin (**115**) in 94% enantiomeric excess. Overall, this total synthesis required six steps and proceeded in 14% overall yield, representing the shortest synthesis of (+)-solistatin.



Scheme 2.14. Synthesis of Solistatin

2.6. Conclusion

As demonstrated above, a new process for the asymmetric synthesis of β-hydroxyketones has been established that uses chlorine for the induction of stereochemistry, further demonstrating the utility of α-chloroaldehydes as building blocks in organic synthesis. While many enantioselective aldol methods are known, this is the first example of an asymmetric aldol reaction that uses a chiral director on the aldehyde, instead of the ketone, that is removed following the aldol reaction. Contrary to current chiral auxiliary strategies, the entire sequence requires only three synthetic steps, and produces the desired hydroxyketone as a final product (Figure 2.17). This methodology was found to be compatible with a variety of substituted ketone and aldehyde substrates. Ease of preparation of the nonracemic α-chloroaldehyde, good diastereoselectivities of the aldol reaction, facile dechlorination, and high enantiopurities of the final aldol adduct highlight the practicality of this method. Finally, this method was also demonstrated in the concise asymmetric total synthesis of two natural products (+)-dihydroyashabushiketol (**100**) and (+)-solistatin (**115**) (Figure 2.17).

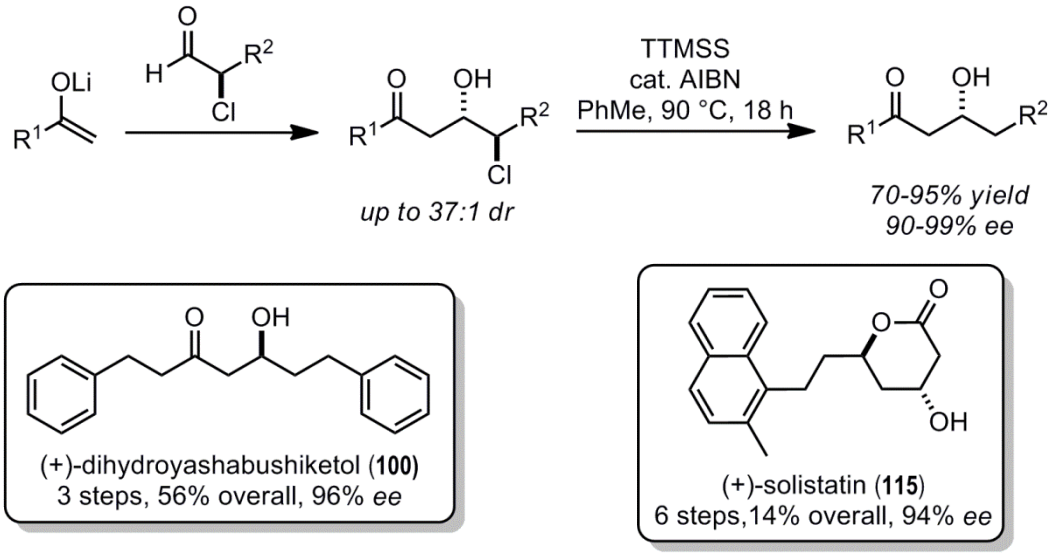


Figure 2.17. Summary: Chlorine as an Auxiliary in Asymmetric Aldol Reactions

2.7. Experimental

2.7.1. General

All reactions described were performed under an atmosphere of dry nitrogen using oven dried glassware unless otherwise specified. THF and Et_2O were freshly distilled from sodium/benzophenone and CH_2Cl_2 was distilled from CaH_2 prior to use. Commercial anhydrous EtOH (reagent grade) was used without further purification. Cold temperatures were maintained by the use of following reaction baths: 0 °C, ice-water; -78 °C, acetone-dry ice; temperatures between -78 °C to -0 °C required for longer reaction times were maintained with a Polyscience VLT-60A immersion chiller.

Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still.[124] Concentration and removal of trace solvents was done via a Buchi rotary evaporator using acetone-dry-ice condenser and a Welch vacuum pump.

Gas chromatography (GC) analysis was performed on an Agilent 6890 gas chromatograph, equipped with a flame ionization detector and a custom-made chiral GC

column coated with a 1:1 mixture of heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-beta-cyclodextrin and OV-1701.

High performance liquid chromatography (HPLC) analysis was performed on an Agilent 1100 HPLC, equipped with a variable wavelength UV-Vis detector and Chiralcel OD-H chiral column (0.46 cm x 25 cm). Retention times for the individual enantiomers were determined on racemic standards. Copies of the HPLC traces for both enantiomerically enriched and racemic samples can be found in: *Org. Biomol. Chem.* **2013**, 1702-1705.

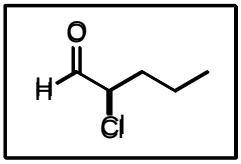
NMR spectra were recorded using deuterochloroform ($CDCl_3$) as the solvent unless otherwise indicated. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR) Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constants, number of protons. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Varian Inova 500 (500 MHz), or Bruker 400 (400 MHz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (150 MHz), Varian Inova 500 (125 MHz), or Bruker 400 (100 MHz). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of ^{1}H-^{1}H COSY, HMBC, HMQC and nOe spectra. Copies of the ^{1}H and ^{13}C NMR spectroscopic data can be accessed free of charge in the supporting information files associated with the following publications: *Synthesis*, **2011**, 1946-1953 and *Org. Biomol. Chem.* **2013**, 1702-1705.Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with internal calibration as films between sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

High resolution mass spectra (HRMS-ESI) were recorded on a Bruker micrOTOF II mass spectrometer.

Optical rotation was measured on a Perkin Elmer Polarimeter 341 at 589 nm. The optical rotation was not measured on chloroaldehydes as these compounds tend to decompose at room temperature.

2.7.2. Preparation and Experimental Data for New Compounds

Preparation of (2*R*)-2-chloropentanal ((*R*)-64):

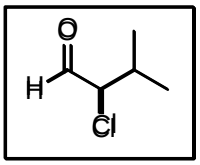


To a solution of (2*S*,5*R*)-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one ((*R*)-**61**) (20 mol%), $Cu(TFA)_2$ (0.5 equiv.), LiCl (1.5 equiv.), and $Na_2S_2O_8$, (1 equiv.) in CH_3CN (0.2 M) and H_2O (2.2 equiv.) at -30 °C was added a solution of pentanal (2.00 g, 23.2 mmol) in CH_3CN (1 mL) and the resultant green-yellow solution was stirred at -30 °C for 5 hours. The reaction mixture was then diluted with H_2O (20 mL) and brine (20 mL), the organic layer extracted with diethyl ether (3 x 50 mL), and the combined extracts washed with brine, dried ($MgSO_4$) filtered and concentrated via rotary evaporator in a cold ice-water bath to yield a yellow oil. Purification via kugelrohr distillation (55 °C, 60 mmHg) gave pure (*R*)-chloropentanal ((*R*)-**64**) (1.68 g,14.0 mmol, 60% yield) which was used directly or stored in -10 °C freezer. The spectral data acquired on this material was in complete agreement with that previously reported.[48]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.51 (d, *J* = 2.4 Hz, 1H), 4.19 (ddd, *J* = 8.2, 5.3, 2.4 Hz, 1H), 1.97 (m, 1H), 1.83 (m, 1H), 1.63-1.45 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.7, 64.0, 34.2, 19.1, 13.6 ppm.

Preparation of (2*R*)-2-chloroisovaleralehyde ((*R*)-65):

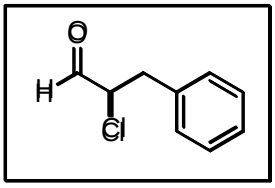


To a solution of (2*S*,5*R*)-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one **((*R*)-61)** (20 mol%), $Cu(TFA)_2$ (0.5 equiv.), LiCl (1.5 equiv.), and $Na_2S_2O_8$, (1 equiv.) in CH_3CN (0.2 M) and H_2O (2.2 equiv.) at -30 °C was added a solution of isovaleraldehyde (2.00 g, 23.2 mmol) in CH_3CN (1 mL) and the resultant green-yellow solution was stirred at -30 °C for 5 hours. The reaction mixture was then diluted with H_2O and brine, the organic layer extracted with diethyl ether, and the combined extracts washed with brine, dried ($MgSO_4$) filtered and concentrated via rotary evaporator in a cold Ice-water bath to yield a yellow oil. Purification via kugelrohr distillation (55 °C, 60 mmHg) gave pure (*R*)-chloroisovaleraldehyde **((*R*)-65)** (1.54 g, 12.8 mmol, 60% yield) which was used directly or stored in -10 °C freezer. The spectral data acquired on this material was in complete agreement with that previously reported.[93]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52 (d, *J* = 2.9 Hz, 1H), 4.04 (dd, *J* = 5.5, 2.9 Hz, 1H), 2.37 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.3, 70.7, 31.2, 20.0, 17.9 ppm.

Preparation of (2*R*)-2-chloro-3-phenylpropanal ((*R*)-66)

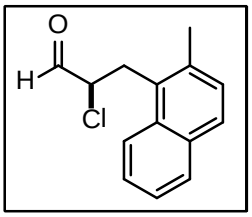


To a solution of (2*S*,5*R*)-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one **((*R*)-61)** (20 mol%), $Cu(TFA)_2$ (0.5 equiv.), LiCl (1.5 equiv.), and $Na_2S_2O_8$, (1 equiv.) in CH_3CN (0.2 M) and H_2O (2.2 equiv.) at -30 °C was added a solution of 3-phenylpropanal (2.00 g,14.9 mmol) in CH_3CN (1 mL) and the resultant green-yellow solution was stirred at -30 °C for 5 hours. The reaction mixture was then diluted with H_2O and brine, the organic layer extracted with ethyl acetate, and the combined extracts washed with brine, dried ($MgSO_4$) filtered and concentrated via rotary evaporator to yield ((2*R*)-2-chloro-3-phenylpropanal **((*R*)-66)** (1.98 g, 11.9 mmol, 80% yield) as an orange oil which was used directly or stored in -10 °C freezer. The spectral data acquired on this material was in complete agreement with that previously reported.[96]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.57 (d, *J* = 2.1 Hz, 1H), 7.38-7.23 m, 5H), 4.41 (ddd, *J* = 8.1, 5.8, 2.1 Hz, 1H), 3.40 (dd, *J* = 14.6, 5.7 Hz, 1H), 3.11 (dd, *J* = 14.6, 8.4 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.8, 135.6, 129.7, 129.0, 127.7, 64.2, 38.6 ppm.

Preparation of (2*R*)-2-chloro-3-(2-methylnaphthalen-1-yl)propanal ((*R*)-67)



To a solution of (2*S*,5*R*)-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one **((*R*)-61)** (42 mg, 0.20 mmol, 20 mol%), $Cu(TFA)_2$ (89 mg, 0.49 mmol, 0.5 equiv.), LiCl (63 mg, 1.5 mmol, 1.5 equiv.), and $Na_2S_2O_8$ (215 mg, 0.98 mmol, 1 equiv.) in CH_3CN (10 mL) and H_2O (0.03 mL, 2.2 equiv.) at -30 °C was added a solution of aldehyde **119** (148 mg, 0.747 mmol) in CH_3CN (1 mL) and the resultant green-yellow solution was stirred at -30 °C for 4 days. The reaction mixture was then diluted with H_2O (1 mL), the organic layer extracted with ethyl acetate (3 x 10 mL) and the combined extracts washed with brine (1 x 20 mL), dried ($MgSO_4$) and concentrated via rotary evaporator to yield an orange oil. Purification by column chromatography (4:1 hexanes:ethyl acetate) gave **((*R*)-67)** (82 mg, 47%) as a yellow oil, which was used directly or stored in a -10 °C freezer in solution.

(2*R*)-2-chloro-3-(2-methylnaphthalen-1-yl)propanal ((*R*)-67) - continued

IR (neat): 3051, 2958, 2929, 2870, 1731, 1623, 1598, 1512, 1443, 1265, 1067 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.63 (d, *J* = 2.3 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.53 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.45 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 4.58 (dt, *J* = 7.6, 2.2 Hz, 1H), 3.89 (dd, *J* = 15.0, 6.2 Hz, 1H), 3.62 (dd, *J* = 15.0, 8.2 Hz, 1H), 2.56 (s, 3H).

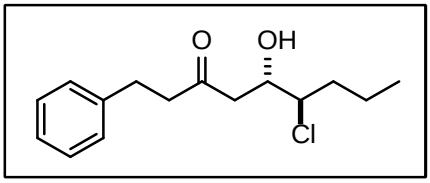
^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.6, 135.2, 132.8, 132.1, 129.4, 129.2, 128.6, 126.8, 125.1, 122.9, 63.8, 31.4, 21.0.

HRMS: *m/z* calcd for $C_{14}H_{13}ClO$: 255.0547 (M+Na); Found: 255.0545 (M+Na).

$[\alpha]_D^{20}$ = + 32.4° (c 0.34, $CHCl_3$)

For the determination of enantiomeric excess, (*R*)-2-chloro-3-(2-methylnaphthalen-1-yl)propanal (**67**) was reduced to the corresponding chloroalcohol (2 equiv. $NaBH_4$, CH_2Cl_2, 1 h, room temperature). The corresponding enantiomeric alcohols of 2-chloro-3-(2-methylnaphthalen-1-yl)propanal (**67**) were separable by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes: IPA 90:10, detection at 227 nm, flow rate = 1.5 mL/min. The retention time of the (+)-enantiomer is 6.6 min; the retention time of the (-)-enantiomer is 8.9 min (94% *ee*).

Preparation of (5*S*,6*R*)-6-chloro-5-hydroxy-1-phenylnonan-3-one (68)



To a cold (0 °C) stirred solution of *i*-Pr_2NH (0.052 mL, 1.2 equiv) in THF (0.1M) was added *n*-BuLi in hexanes (0.137 mL, 2.72 M, 1.2 equiv) and the mixture was stirred at 0 °C for 30 min, then cooled to –78 °C and benzylacetone (0.046 mL, 0.311 mmol, 1 equiv) was added slowly in one portion. The resulting solution was stirred for an additional 30 minutes at –78 °C. After this time, a solution of (2*R*)-2-chloropentanal (**(*R*)-64**) (45 mg, 1.2 equiv) in THF (1.0 M) was added dropwise over 15 min at –78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was added, and the mixture was allowed to warm to r.t. The reaction mixture was then diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes–EtOAc) gave pure (5*R*,6*S*)-6-chloro-5-hydroxy-1-phenylnonan-3-one (**68**). Isolated as a colourless solid (68.8 mg, 80% yield); mp 41–45 °C.

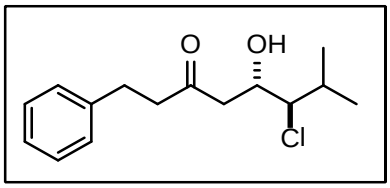
IR (thin film): 3463, 3028, 2964, 2875, 1708, 1614, 1048, cm^{-1}.

^{1}H NMR (400 MHz, CDCl3): δ = 7.26–7.32 (m, 2 H), 7.15–7.23 (m, 3 H), 4.06–4.13 (m, 1 H), 3.88–3.94 (m, 1 H), 3.18 (d, *J* = 5.1 Hz, 1H), 2.88–2.95 (m, 2 H), 2.73–2.85 (m, 4 H), 1.78–1.87 (m, 1H), 1.58–1.68 (m, 1 H), 1.38–1.45 (m, 1 H), 0.95 (t, *J* = 7.2 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl3): δ = 210.5, 140.6, 128.6, 128.3, 126.3, 70.9, 65.8, 45.19, 45.17, 35.8, 29.5, 19.6, 13.5 ppm.

HRMS: *m*/*z* calcd for $C_{15}H_{21}ClO_2$: 291.1122 (M + Na); found: 291.1131 (M + Na).

Preparation of (5*S*,6*R*)-6-chloro-5-hydroxy-7-methyl-1-phenyloctan-3-one (69)



To a cold (0 °C) stirred solution of *i*-Pr_2NH (0.052 mL, 1.2 equiv) in THF (0.1M) was added *n*-BuLi in hexanes (0.137 mL, 2.72 M, 1.2 equiv) and the mixture was stirred at 0 °C for 30 min, then cooled to –78 °C and benzylacetone (0.046 mL, 0.311 mmol, 1 equiv) was added slowly in one portion. The resulting solution was stirred for an additional 30 minutes at –78 °C. After this time, a solution of (2*R*)-2-chloroisovaleraldehyde (**(*R*)-65**) (45 mg, 1.2 equiv) in THF (1.0 M) was added dropwise over 15 min at –78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was added, and the mixture was allowed to warm to r.t. The reaction mixture was then diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes–EtOAc) gave pure (5*S*,6*R*)-6-chloro-5-hydroxy-7-methyl-1-phenyloctan-3-one **(69)**. Isolated as a colorless solid (75.5 mg, 90% yield); mp 30–35 °C.

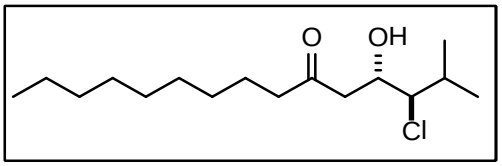
IR (thin film): 3943, 3688, 2685, 1704, 1421 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.36 (m, 2 H), 7.17–7.27 (m, 3 H), 4.09–4.19 (m, 1 H), 3.77 (dd, *J* = 3.6, 8.4 Hz, 1 H), 3.40 (d, *J* = 5.4 Hz, 1 H), 3.02–2.80 (m, 5 H), 2.73 (dd, *J* = 8.4, 17.8 Hz, 1 H), 2.36 (m, 1 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.3, 140.5, 128.5, 128.2, 126.2, 71.4, 69.0, 46.0, 45.1, 29.4, 29.1, 20.6, 15.8 ppm.

HRMS: *m*/*z* calcd for $C_{15}H_{21}ClO_2$: 291.1119 (M + Na); found: 291.1122 (M + Na).

Preparation of (3*R*,4*S*)-3-Chloro-4-hydroxy-2-methylpentadecan-6-one (70)



To a cold (0 °C) stirred solution of *i*-Pr_2NH (0.292 mL,1.2 equiv) in THF (0.1M) was added *n*-BuLi in hexanes (0.761 mL, 2.7 M, 1.2 equiv) and the mixture was stirred at 0 °C for 30 min, then cooled to –78 °C and undecanone (0.357 mL, 1.73 mmol, 1 equiv) was added slowly in one portion. The resulting solution was stirred for an additional 30 minutes at –78 °C. After this time, a solution of (2*R*)-2-chloroisovaleraldehyde (**(*R*)-65**) (250 mg, 1.2 equiv) in THF (1.0 M) was added dropwise over 15 min at –78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was added, and the mixture was allowed to warm to r.t. The reaction mixture was then diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes–EtOAc) gave pure(3*R*,4*S*)-3-Chloro-4-hydroxy-2-methylpentadecan-6-one **(70)**. Isolated as a colorless solid (385 mg, 76% yield); mp 45–50 °C.

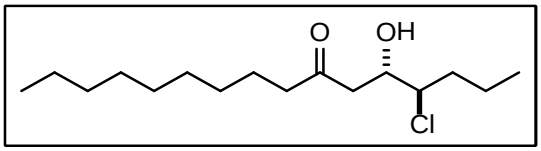
IR (thin film): 3688, 3054, 2685, 1694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.14–4.06 (m, 1 H), 3.78 (dd, *J* = 3.7, 8.7 Hz, 1 H), 3.49 (d, *J* = 5.2 Hz, 1 H), 2.99 (dd, *J* = 2.4, 17.8 Hz, 1 H), 2.71 (dd, *J* = 8.4, 17.8 Hz, 1 H), 2.47 (t, *J* = 7.5 Hz, 2 H), 2.43–2.33 (m, 1 H), 1.64–1.55 (m, 2 H), 1.34–1.22 (m, 12 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.89 (t, *J* = 6.6 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.9, 71.4, 69.1, 45.6, 43.8, 31.8, 29.4, 29.3, 29.2, 29.1, 29.0, 23.6, 22.6, 20.7, 15.7, 14.1 ppm.

HRMS: *m*/*z* calcd for $C_{16}H_{31}ClO_2$: 291.2083 (M + H); found: 291.2085 (M + H).

Preparation of (4*R*,5*S*)-4-chloro-5-hydroxyhexadecan-7-one (71)



To a cold (0 °C) stirred solution of *i*-Pr_2NH (0.292 mL,1.2 equiv) in THF (0.1M) was added *n*-BuLi in hexanes (0.761 mL, 2.7 M, 1.2 equiv) and the mixture was stirred at 0 °C for 30 min, then cooled to –78 °C and undecanone (0.357 mL, 1.73 mmol, 1 equiv) was added slowly in one portion. The resulting solution was stirred for an additional 30 minutes at –78 °C. After this time, a solution of (2*R*)-2-chloropentanal (**(*R*)-64**) (250 mg, 1.2 equiv) in THF (1.0 M) was added dropwise over 15 min at –78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was added, and the mixture was allowed to warm to r.t. The reaction mixture was then diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes–EtOAc) gave pure (4*R*,5*S*)-4-chloro-5-hydroxyhexadecan-7-one **(71)**. Isolated as a white solid (370 mg, 74% yield); mp 35–38 °C.

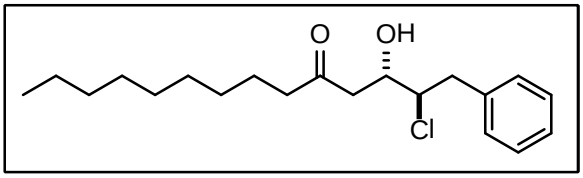
IR (thin film): 3435, 2923, 2859, 1708, 1458, 1374, 1068, cm^{-1}.

^1H NMR (600 MHz, CDCl3): δ = 4.10 (m, 1 H), 3.92 (m, 1 H), 3.32 (d, *J* = 4.8 Hz, 1 H), 2.82 (dd, *J* = 2.9, 17.6 Hz, 1 H), 2.75 (dd, *J* = 8.5, 17.6 Hz, 1 H), 2.46 (t, *J* = 7.5 Hz, 2 H), 1.85 (m, 1 H), 1.68–1.55 (m, 4 H), 1.42 (m, 1 H), 1.33–1.21 (m, 12 H), 0.94 (t, *J* = 7.3 Hz, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.3, 71.2, 65.9, 45.0, 44.1, 36.1, 32.1, 29.6, 29.6, 29.5, 29.3, 23.8, 22.9, 19.8, 14.3, 13.7 ppm.

HRMS: *m*/*z* calcd for $C_{16}H_{31}ClO_2$: 313.1905 (M + Na); found: 313.1901 (M + Na).

Preparation of (2*R*,3*S*)-2-chloro-3-hydroxy-1-phenyltetradecan-5-one (72)



To a cold (0 °C) stirred solution of *i*-Pr_2NH (0.147 mL, 1.2 equiv) in THF (0.1M) was added *n*-BuLi in hexanes (0.378 mL, 2.54 M, 1.2 equiv) and the mixture was stirred at 0 °C for 30 min, then cooled to –78 °C and undecanone (0.180 mL, 0.87 mmol, 1 equiv) was added slowly in one portion. The resulting solution was stirred for an additional 30 minutes at –78 °C. After this time, a solution of (2*R*)-2-chloro-3-phenylpropanal (**(*R*)-66**) (250 mg, 1.7 equiv) in THF (1.0 M) was added dropwise over 15 min at –78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was added, and the mixture was allowed to warm to r.t. The reaction mixture was then diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 9:1 hexanes–EtOAc) gave pure (2*R*,3*S*)-2-chloro-3-hydroxy-1-phenyltetradecan-5-one **(72)**. Isolated as a white solid (185 mg, 63% yield); mp 60.5–61.0 °C.

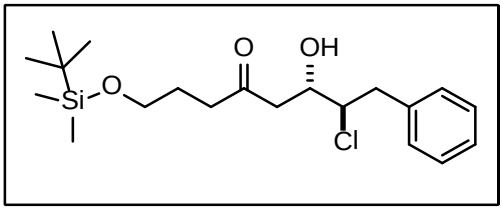
IR (thin film): 3349, 2916, 2849, 1698, cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2 H), 7.27–7.24 (m, 3 H), 4.12–4.07 (m, 2 H), 3.52 (d, *J* = 4.8 Hz, 1 H), 3.32 (dd, *J* = 3.1, 14.4 Hz, 1 H), 2.95 (dd, *J* = 8.6, 14.4 Hz, 1 H), 2.91 (dd, *J* = 2.1, 17.8 Hz, 1 H), 2.78 (dd, *J* = 8.1, 17.8 Hz, 1 H), 2.45 (t, *J* = 7.4 Hz, 2 H), 1.58 (m, 2 H), 0.88 (t, *J* = 7.0 Hz, 3 H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.5, 137.5, 129.8, 128.6, 127.1, 70.8, 65.8, 45.0, 44.1, 40.3, 32.1, 29.6, 29.6, 29.5, 29.3, 23.8, 22.9, 14.3 ppm.

HRMS: *m*/*z* calcd for $C_{20}H_{31}ClO_2$: 339.2085 (M + H); found: 339.2077 (M + H).

(6*S*,7*R*)-1-(*tert*-Butyldimethylsilyloxy)-7-chloro-6-hydroxy-8-phenyloctan-4-one (73)



To a cold (0 °C) stirred solution of *i*-Pr_2NH (0.147 mL, 1.2 equiv) in THF (0.1M) was added *n*-BuLi in hexanes (0.387 mL, 2.5 M, 1.2 equiv) and the mixture was stirred at 0 °C for 30 min, then cooled to –78 °C and 1-(*tert*-butyldimethylsilyloxy)-pentan-4-one (188 mg, 1 equiv) was added slowly in one portion. The resulting solution was stirred for an additional 30 minutes at –78 °C. After this time, a solution of (2*R*)-2-chloro-3-phenylpropanal (**(*R*)-66**) (220 mg, 1.2 equiv) in THF (1.0 M) was added dropwise over 15 min at –78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was added, and the mixture was allowed to warm to r.t. The reaction mixture was then diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 20:1 hexanes–EtOAc) gave pure (6*S*,7*R*)-1-(*tert*-butyldimethylsilyloxy)-7-chloro-6-hydroxy-8-phenyloctan-4-one **(73)**. Isolated as a clear, colorless oil (127 mg, 57% yield).

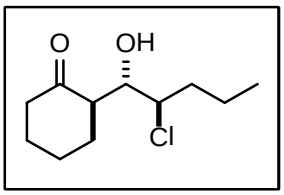
IR (neat): 3446, 2952, 2927, 2851, 2356, 1708, 1249, cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2 H), 7.28–7.24 (m, 3 H), 4.14–4.08 (m, 2 H), 3.62 (t, *J* = 6.0 Hz, 2 H), 3.54 (d, *J* = 4.5 Hz, 1 H), 3.23 (dd, *J* = 3.7, 14.7 Hz, 1 H), 2.97–2.91 (m, 2 H), 2.80 (dd, *J* = 8.1, 17.7 Hz, 1 H), 2.58–2.54 (t, *J* = 7.2 Hz, 2 H), 1.83–1.77 (m, 2 H), .89 (s, 9 H), 0.04 (s, 6 H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.0, 137.5, 129.7, 128.6, 127.0, 70.7, 65.8, 62.2, 45.2, 40.4, 40.3, 26.7, 26.1, 18.5, –5.2 ppm.

HRMS: *m*/*z* calcd for $C_{20}H_{33}ClO_3Si$: 385.1960 (M + H); found: 385.1976 (M + H).

(+/-)-(2*R)-2-[(1'*S**,2'*R**)-2-chloro-1-hydroxypentyl]cyclohexanone (74)**



To a cold (0 °C) stirred solution of *i*-Pr_2NH (0.225 mL, 1.2 equiv) in THF (0.1M) was added *n*-BuLi in hexanes (0.69 mL, 2.5 M, 1.2 equiv) and the mixture was stirred at 0 °C for 30 min, then cooled to –78 °C and cyclohexanone (0.15 mL, 0.0014 mmol, 1 equiv) was added slowly in one portion. The resulting solution was stirred for an additional 30 minutes at –78 °C. After this time, a solution of (2*R*)-2-chloropentanal (**(*R*)-64**) (350 mg, 1.2 equiv) in THF (1.0 M) was added dropwise over 15 min at –78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was added, and the mixture was allowed to warm to r.t. The reaction mixture was then diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 9:1 hexanes–EtOAc) gave pure (+/-)-(2*R**)-2-[(1'*S**,2'*R**)-2-chloro-1-hydroxypentyl]cyclohexanone **(74)**. Isolated as a clear, colorless oil (232 mg, 76% yield).

IR (thin film): 3463, 3305, 2979, 1740, 1651, 1373 $cm^{-1.}$

^1H NMR (400 MHz, $CDCl_3$): δ = 4.07 (dt, *J* = 2.6, 8.9 Hz, 1 H), 3.46–3.32 (m, 2 H), 3.05–2.96 (m, 1 H), 2.4–2.3 (m, 2 H), 2.17–1.55 (m, 9 H), 1.42 (m, 1 H), 0.93 (t, *J* = 7.4 Hz, 3 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.8, 76.9, 64.1, 51.5, 43.1, 35.8, 32.6, 28.2, 25.1, 19.2, 13.5 ppm.

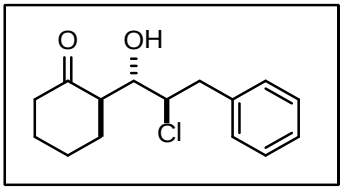
HRMS: *m*/*z* calcd for $C_{11}H_{19}ClO_2$: 241.0967 (M + Na); found: 241.0966 (M + Na).

(+/-)-(2*R)-2-[(1'*S**,2'*R**)-2-chloro-1-hydroxypentyl]cyclohexanone (74) - continued**

Proof of the relative stereochemistry of **74** was accomplished as follows.

A purified sample of **74** was reduced (catecholborane, MeOH) and subsequently converted to the corresponding epoxide (2M KOH (1.2 eq), EtOH). Analysis of the ^{1}H NMR spectrum recorded on the epoxide revealed that the two epoxide protons resonated at 2.94 and 2.82 ppm, and shared a coupling constant of 2.5 Hz, typical of a trans epoxide. Additionally, irradiation of either proton resonance did not result in an enhancement of the other proton resonance in nOe experiments. These results support the proposed anti stereochemistry of the chlorohydrin function in **74**.

(2*R*)-2-[(1'*S*,2'*R*)-2-chloro-1-hydroxy-3-phenylpropyl]cyclohexanone (75)



To a cold (0 °C) stirred solution of *i*-Pr_2NH (0.322 mL, 1.2 equiv) in THF (0.1M) was added *n*-BuLi in hexanes (0.82 mL, 2.32 M, 1.2 equiv) and the mixture was stirred at 0 °C for 30 min, then cooled to –78 °C and cyclohexanone (0.2 mL, 1.9 mmol, 1 equiv) was added slowly in one portion. The resulting solution was stirred for an additional 30 minutes at –78 °C. After this time, a solution of (2*R*)-2-chloro-3-phenylpropanal (**(*R*)-66**) (1.2 equiv) in THF (1.0 M) was added dropwise over 15 min at –78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was added, and the mixture was allowed to warm to r.t. The reaction mixture was then diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 9:1 hexanes–EtOAc) gave pure (2*R*)-2-[(1'*S*,2'*R*)-2-chloro-1-hydroxy-3-phenylpropyl]cyclohexanone **(75)**. Isolated as a clear, colorless oil (308 mg, 61% yield).

IR (thin film): 3689, 3054, 1694, 1421 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H), 4.34 (dt, *J* = 3.1, 8.8 Hz, 1 H), 3.56–3.45 (m, 3 H), 2.96 (dd, *J* = 8.8, 14.5 Hz, 1 H), 3.03–3.10 (m, 1 H), 2.43–2.35 (m, 2 H), 2.18–2.05 (m, 2 H), 1.99–1.91 (m, 2 H), 1.79–1.62 (m, 2 H) ppm.

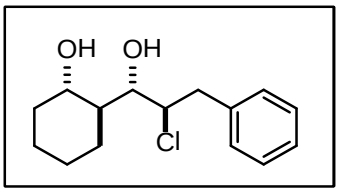
^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.1, 137.6, 129.7, 128.2, 126.6, 76.7, 64.2, 51.2, 43.2, 40.1, 32.8, 28.3, 25.2 ppm.

HRMS: *m*/*z* calcd for $C_{15}H_{19}ClO_2$: 267.1142 (M + H); found: 267.1146 (M + H).

General Procedure: Reduction of Chlorohydrin to Diol

To a cold (0 °C) stirred solution of **75** (68 mg, 0.25 mmol) in MeOH (2.5 mL) was added $NaBH_4$ (19 mg, 0.5 mmol) and the reaction mixture was stirred at 0 °C for 3 h. After this time, H_2O (5 mL) was added and the resulting mixture was then extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated to provide a colorless oil. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes–EtOAc) afforded **81**(36 mg, 54%) and **82** (12 mg, 18%) as colourless oils.

(1*S,2*S**)-2-[(1'*S**,2'*R**)-2'-Chloro-1'-hydroxy-*3*-phenylpropyl]cyclohexan-1-ol (81)**



Isolated in 54% yield.

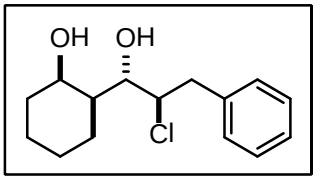
IR (thin film): 3689, 3054, 2936, 1421 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): d = 7.36–7.31 (m, 2 H), 7.30–7.22 (m, 3 H), 4.40 (dt, J = 2.8, 10.8 Hz, 1 H), 4.05–3.94 (m, 1 H), 3.66–3.57 (m, 1 H), 3.45 (d, J = 1.7 Hz, 1 H), 3.20 (dd, J = 2.8, 14.9 Hz, 1 H), 3.00 (dd, J = 10.8, 14.9 Hz, 1 H), 2.08–2.00 (m, 1 H), 1.81–1.62 (m, 3 H), 1.39–1.18 (m, 3 H), 1.14–1.01 (m, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): d = 137.9, 129.3, 128.4, 126.8, 81.2, 75.2, 66.9, 45.9, 36.7, 34.9, 27.3, 25.1, 24.2 ppm.

HRMS: *m/z* calcd for $C_{15}H_{21}ClO_2$: 269.1302 (M + H); found: 269.1303 (M + H).

(1*R,2*S**)-2-[(1'*S**,2'*R**)-2'-Chloro-1'-hydroxy-3-phenylpropyl]cyclohexan-1-ol (82)**



Isolated in 18% yield.

IR (thin film): 3603, 3449, 2935, 2935, 2858, 1732, 1496 cm^{-1}.

1H NMR (400 MHz, CDCl3): d = 7.39–7.23 (m, 5 H), 4.43–4.39 (m, 1 H), 4.18 (dt, J= 2.8, 8.8 Hz, 1 H), 3.76 (d, J = 7.8 Hz, 1 H), 3.64 (dt, J = 4.1, 8.2 Hz, 1 H), 3.55 (dd, J = 2.8, 14.5 Hz, 1 H), 2.95 (dd, J = 9.5, 14.5 Hz, 1 H), 2.06–1.98 (m, 1 H), 1.95–1.74 (m, 4 H), 1.66–1.43 (m, 5 H) ppm.

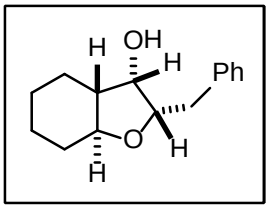
^{13}C NMR (100 MHz, CDCl3): d = 138.2, 129.7, 128.2, 126.6, 77.8, 67.9, 64.6, 40.6, 39.9, 33.7, 25.6, 24.3, 19.9 ppm.

HRMS: *m/z* calcd for $C_{15}H_{21}ClO_2$: 269.1302 (M + H); found: 269.1303 (M + H).

General Procedure: Tetrahydrofuranol Formation

A stirred solution of the diol in H_2O (0.1 M) was heated at reflux for 12 h. After this time, the solution was diluted with Et_2O and the Et_2O layer was washed with brine, dried ($MgSO_4$), and concentrated to provide a white solid, which was purified via flash chromatography (silica gel, hexanes–EtOAc).

(1*S*,6*R*,7*S*,8*S*)-8-Benzyl-7-hydroxy-9-oxabicyclo[4.3.0]nonane (83)



Isolated as a white solid (91% yield); mp 85–88 °C.

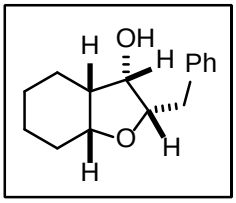
IR (thin film): 3608, 3053, 2937, 1265 cm^{-1}.

1H NMR (400 MHz, C_6D_6): d = 7.30 (d, J = 7.5 Hz, 2 H), 7.20–7.14 (m, 2 H), 7.12–7.07 (m, 1 H), 4.19–4.14 (dt, J = 3.7, 7.2 Hz, 1 H), 3.67 (dt, J= 3.7, 10.9 Hz, 1 H), 3.57–3.53 (m, 1 H), 3.11–3.06 (dd, J = 7.2, 13.7 Hz, 1 H), 3.03–2.96 (dd, J = 7.2, 13.7 Hz, 1 H), 2.20– 2.14 (m, 1 H), 1.57–1.48 (m, 2 H), 1.48–1.41 (m, 1 H), 1.32–0.81 (m, 6 H) ppm.

13C NMR (100 MHz, C_6D_6): d = 129.4, 128.2, 128.0, 125.9, 83.8, 78.9, 72.8, 51.0, 36.3, 32.4, 25.5, 24.1, 23.8 ppm.

HRMS: *m/z* calcd for $C_{15}H_{20}O_2$: 233.1535 (M + H); found: 233.1536 (M+H).

(1*R*,6*R*,7*S*,8*S*)-8-Benzyl-7-hydroxy-9-oxabicyclo[4.3.0]nonane (84)



Isolated as a white solid (86% yield); mp 78–83 °C.

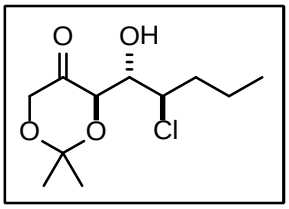
IR (thin film): 3609, 3054, 2934, 1421, 1265 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): d = 7.30 (d, J = 7.2 Hz, 2 H), 7.20–7.16 (m, 2 H), 7.10–7.06 (m, 1 H), 3.93–3.89 (m, 1 H), 3.79–3.76 (t, J = 6.0 Hz, 1 H), 3.65–3.61 (m, 1 H), 3.02–2.93 (m, 2 H), 1.86–1.78 (m, 1 H), 1.76–1.67 (m, 1 H), 1.62–0.71 (m, 8 H).

^{13}C NMR (100 MHz, C_6D_6): d = 140.0, 129.5, 128.3, 126.0, 82.2, 75.2, 42.1, 37.1, 29.8, 29.7, 23.8, 22.1, 21.2.

HRMS: *m/z* calcd for $C_{15}H_{20}O_2$: 233.1536 (M + H); found: 233.1536 (M + H)

(+/-)-(*R)-4-((1*S**,2*R**)-2-chloro-1-hydroxypentyl)-2,2-dimethyl-1,3-dioxan-5-one (76)**



To a cold (-78 °C), stirred 0.2 M solution of *i*-Pr_2NH (0.065 mL, 1.1 equiv) in THF was added *n*-BuLi (0.18 mL, 1.1 equiv, 2.32 M in hexanes). This mixture was allowed to warm to 0 °C and was stirred at this temperature for 20 minutes prior to cooling to -78 °C, at which temperature a solution of 2,2-dimethyl-1,3-dioxan-5-one (0.046 mL, 0.38 mmol, 1.0 equiv) in THF (1 mL) was added. After an additional 5 minutes of stirring at -78 °C, a solution of (+/-)-2-chloropentanal (**64**) (82 mg, 1.3 equiv) in THF was slowly added to the reaction mixture. After a further 15 minutes stirring at -78 °C, the reaction mixture was quenched by the slow addition of water, diluted with EtOAc, the phases were separated, and the aqueous phase was washed with EtOAc (3 x 30 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to provide a crude oil. Purification of the crude product was carried out by flash chromatography (9:2:1 hexanes:CH_2Cl_2:EtOAc) to afford (+/-)-(*R**)-4-((1*S**,2*R**)-2-chloro-1-hydroxypentyl)-2,2-dimethyl-1,3-dioxan-5-one (**76**) (51 mg, 54%) as a colourless oil.

IR (neat) 3512, 2964, 1749, 1374, 1226, 1100 cm^{-1}

^1H NMR (600 MHz, $CDCl_3$): δ = 4.46 (dd, *J* = 6.7, 1.4 Hz, 1H), 4.30 (dd, *J* = 17.4, 1.4 Hz, 1H), 4.27-4.21 (m, 1H,), 4.10-4.05 (m, 1H), 4.06 (d, *J* =17.4 Hz, 1H), 3.08 (d, *J* = 4.0 Hz, 1H), 1.83-1.77 (m, 2H), 1.70-1.59 (m, 2H), 1.49 (s, 3H), 1.45 (s, 3H), 0.95 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 210.1, 101.4, 74.1, 66.9, 62.7, 34.9, 24.0, 23.9, 19.8, 13.6 ppm.

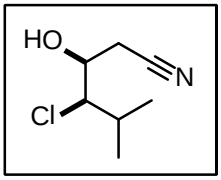
HRMS: *m/z* calcd for $C_{11}H_{19}ClO_4$: 251.1045 (M+H); Found: 251.1036 (M+H).

(+/-)-(*R)-4-((1*S**,2*R**)-2-chloro-1-hydroxypentyl)-2,2-dimethyl-1,3-dioxan-5-one (76) - continued**

Proof of the relative stereochemistry of **76** was accomplished as follows.

A purified sample of **76** was reduced ($NaBH_4$, MeOH (1.2 eq.), THF) and subsequently converted into the corresponding epoxide (2M KOH (1.2 eq), EtOH). Analysis of the ^1H NMR spectrum recorded on the epoxide revealed that the two epoxide protons resonated at 2.96 and 2.93 ppm, and shared a coupling constant of 2.2 Hz, typical of a trans epoxide. Additionally, irradiation of either proton resonance did not result in an enhancement of the other proton resonance in nOe experiments. These results support the proposed anti stereochemistry of the chlorohydrin function in **76**.

Preparation of (+/-)-(4*R,3*S**)-4-chloro-3-hydroxy-5-methylhexanenitrile (77)**



To a cold (0 °C) stirred solution of *i*-Pr_2NH (0.217 mL, 1.2 equiv) in THF (0.1M) was added *n*-BuLi in hexanes (0.594 mL, 2.5 M, 1.2 equiv) and the mixture was stirred at 0 °C for 30 min, then cooled to –78 °C and acetonitrile (0.074 mL, 1.4 mmol, 1 equiv) was added slowly in one portion. The resulting solution was stirred for an additional 30 minutes at –78 °C. After this time, a solution of (+/-)-2-chloroisovaleraldehyde (**65**) (1.2 equiv) in THF (1.0 M) was added dropwise over 15 min at –78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was added, and the mixture was allowed to warm to r.t. The reaction mixture was then diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. The crude product (4:1 *dr*) was purified by flash chromatography (hexanes:EtOAc 9:1) to afford (+/-)-(4*R**,3*S**)-4-chloro-3-hydroxy-5-methylhexanenitrile (**77**) (121 mg, 54%, 8:1 *dr*) as a colourless oil.

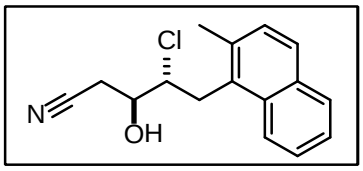
IR (neat): 3443, 2969, 2937, 2878, 2257, 1636, 1464, 1414, 1389, 1371, 1063 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ: 4.08 (dt, *J* = 7.3, 3.8 Hz, 1H), 3.84 (dd, J = 8.1, 4.1 Hz, 1H), 2.88 (dd, *J* = 16.7, 3.6 Hz, 1H), 2.77 (dd, *J* = 16.7, 7.3 Hz, 1H), 2.31 (m, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 117.2, 70.7, 69.1, 29.4, 23.9, 20.5, 16.1 ppm.

HRMS: *m/z* calcd for $C_7H_{12}ClNO$: 184.0500 (M+Na); Found: 184.0504 (M+Na).

(+/-)-(4*R,3*S**)-4-chloro-3-hydroxy-5-(2-methylnaphthalen-1-yl)pentanenitrile** (**78**)



To a cold (-78 °C) stirred solution of LDA (1.2 equiv) was added acetonitrile (0.138 mL, 2.61 mmol, 1 equiv) in one portion. The resulting solution was stirred for an additional 30 minutes at –78 °C. After this time, a solution of (±)-2-chloro-3-(2-methylnaphthalen-1-yl)propanal (**67**) (729 mg,1.2 equiv) in THF (1.0 M) was added dropwise over 15 min at -78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was added, and the mixture was allowed to warm to r.t, diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude orange solid. Analysis of the crude reaction product indicated that the ratio of diastereomeric chlorohydrins was 2:1. The major (1,2-*anti*)-chlorohydrin was purified by flash chromatography (hexanes:EtOAc:CH_2Cl_2,9:1:1) to afford (the title compound (**78**) (378 mg, 53%, 2:1 *dr*) as white solid, mp 132-136 °C.

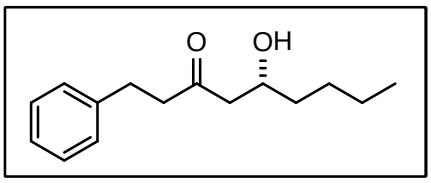
IR (neat): 3425, 3052, 2972, 2930, 2870, 2254, 2211, 1729, 1709, 1624, 1599, 1512, 1265, 1076, 955 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.53 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.44 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 4.4 (m, 1H), 4.27 (m, 1H), 3.84 (dd, *J* = 15.0, 4.4 Hz, 1H), 3.51 (dd, *J* = 15.0, 9.7 Hz, 1H), 2.91 (dd, *J* = 16.9, 4.0 Hz, 1H), 2.79 (dd, *J* = 16.9, 8.0 Hz, 1H), 2.75 (d, *J* = 6.1 Hz, 1H), 2.58 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.9, 132.7, 132.1, 129.8, 129.3, 129.0, 127.7, 126.6, 124.9, 123.1, 117.1, 71.6, 64.9, 32.6, 23.5, 21.0 ppm.

HRMS: *m/z* calcd for $C_{16}H_{16}ClNO$: 274.0993 (M+H); Found: 274.0998 (M+H)

Preparation of (*R*)-5-hydroxy-1-phenylnonan-3-one (85)



To a solution of β-ketochlorohydrin (20 mg, 0.093 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude product was purified by flash chromatography hexanes:EtOAc 9:1) to afford (*R*)-5-hydroxy-1-phenylnonan-3-one (**85**) (16 mg, 92%) as a white solid.

mp 161-165 °C

IR (neat): 3454, 2955, 2928, 2857, 1711, 1604, 1454, 1260, 1032, 841 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.25 (m, 2H), 7.23-7.15 (m, 3H), 4.02 (m, 1H), 2.95-2.88 (m, 3H), 2.79-2.73 (m, 2H), 2.57 (dd, *J* = 3.0, 17.5 Hz, 1H), 2.49 (dd, *J* = 8.9, 17.5 Hz, 1H), 1.43-1.23 (m, 7H), 0.89 (t, *J* = 7.2 Hz, 3H) ppm.

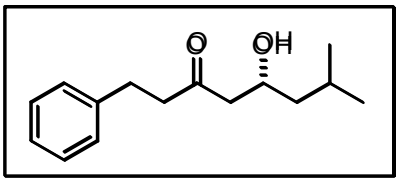
^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.2, 140.7, 128.5, 128.3, 126.2, 67.6, 49.3, 45.1, 36.1, 29.5, 27.6, 22.6, 14.0 ppm.

HRMS: *m/z* calcd for $C_{15}H_{23}O_2$: 235.1693 (M+H); Found: 235.1693 (M+H)

$[\alpha]_D^{20}$ = + 41.2° (c 0.27, $CHCl_3$)

The enantiomeric excess of (*R*)-5-hydroxy-1-phenylnonan-3-one (**85**) was determined by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes:IPA 20:1, detection at 205 nm, flow rate = 1.2 mL/min. The retention time of the (+)-enantiomer is 12.25 min; the retention time of the (-)-enantiomer is 8.10 min, 99% *ee*.

Preparation of (*R*)-5-hydroxy-7-methyl-1-phenyloctan-3-one (86)



To a solution of β-ketochlorohydrin (25 mg, 0.093 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude product was purified by flash chromatography (hexanes:EtOAc 9:1) to afford (*R*)-5-hydroxy-7-methyl-1-phenyloctan-3-one (**86**) (20 mg, 95%) as a white solid.

mp 163-164 °C

IR (neat): 3442, 3027, 2955, 2928, 2869, 1707, 1496, 748, 699 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.26 (m, 2H), 7.23-7.16 (m, 3H), 4.12 (m, 1H), 2.95-2.87 (m, 3H), 2.80-2.75 (m, 2H), 2.56 (dd, *J* = 3.2, 17.4 Hz, 1H), 2.49 (dd, *J* = 8.6, 17.4 Hz, 1H), 1.78 (m, 1H), 1.46 (ddd, *J* = 5.5, 8.6, 13.9 Hz, 1H), 1.12 (dddd, *J* = 0.6, 4.5, 8.6, 13.9 Hz, 1H), 0.93 (d, *J* = 0.6 Hz, 3H), 0.91 (d, *J* = 0.6 Hz, 3H) ppm.

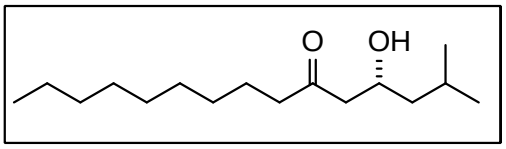
^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.2, 140.7, 128.6, 128.3, 126.2, 65.7, 49.8, 45.6, 45.1, 29.5, 24.4, 23.3, 22.0 ppm.

HRMS: *m/z* calcd for $C_{15}H_{23}O_2$: 235.1693 (M+H); Found: 235.1694 (M+H)

$[\alpha]_D^{20}$ = + 22.6° (c 0.53, $CHCl_3$)

The enantiomeric excess of (*R*)-5-hydroxy-7-methyl-1-phenyloctan-3-one (**86**) was determined by chiral HPLC equipped with a DAICEL-CHIRALCEL-OD column. Eluent = hexanes: IPA 20:1, detection at 205 nm, flow rate = 1.2 mL/min. The retention time of the (+)-enantiomer is 10.21 min; the retention time of the (-)-enantiomer is 6.95 min, 96% *ee*.

Preparation of (*R*)-4-hydroxy-2-methylpentadecan-6-one (87)



To a solution of β-ketochlorohydrin (77 mg, 0.265 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude product was purified by flash chromatography (Hexanes:EtOAc 9:1) to afford (*R*)-4-hydroxy-2-methylpentadecan-6-one (**87**) (57 mg, 81%) as a colourless oil.

IR (neat): 3439, 2955, 2925, 2855, 1707, 1466, 1358, 840 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.12 (m, 1H), 3.06 (d, *J* = 3.3 Hz, 1H), 2.58 (dd, *J* = 2.6, 17.6 Hz, 1H), 2.48 (dd, *J* = 9.1, 17.6 Hz, 1H), 2.41 (t, *J* = 7.4 Hz, 2H), 1.79 (m, 1H), 1.61-1.52 (m, 2H) 1.46 (m, 1H), 1.30-1.20 (m, 12H), 1.11 (m, 1H), 0.91 (d, *J* = 1.8 Hz, 3H), 0.90 (d, *J* = 1.8 Hz, 3H), 0.87 (t, *J* = 6.7 Hz, 3H) ppm.

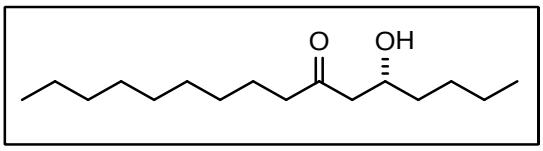
^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.4, 66.5, 50.2, 46.3, 44.5, 31.6, 30.2, 30.1, 30.0, 29.9, 25.1, 24.4, 24.1, 23.4, 22.8 ppm.

HRMS: *m/z* calcd for $C_{16}H_{32}O_2$: 257.2467 (M+H); Found: 257.2475 (M+H).

$[\alpha]_D^{20}$ = + 30.0° (c 0.3, $CHCl_3$)

The enantiomeric excess of (*R*)-4-hydroxy-2-methylpentadecan-6-one (**87**) was determined by an Agilent 6890 gas chromatograph, equipped with a flame ionization detector and a custom-made chiral GC column coated with a 1:1 mixture of heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-beta-cyclodextrin and OV-1701. Temperature program: 140 °C isothermal, split injection. The retention time of the (+)-enantiomer is 89.7 min; the retention time of the (-)-enantiomer is 88.3 min, 95% *ee*.

Preparation of (*R*)-5-hydroxyhexadecan-7-one (88)



To a solution of β-ketochlorohydrin (18 mg, 0.62 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude product was purified by flash chromatography (hexanes:EtOAc 9:1) to afford (*R*)-5-hydroxyhexadecan-7-one (**88**) (21 mg, 92%) as a white solid, mp 41-44 °C

IR (neat): 3333, 2955, 2918, 2849, 1703, 1466, 1118 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.03 (m, 1H), 3.04 (d, *J* = 3.5 Hz, 1H), 2.60 (dd, *J* = 2.8, 17.5 Hz, 1H), 2.49 (dd, *J* = 9.2, 17.5 Hz, 1H), 2.42 (t, *J* = 7.5 Hz, 2H), 1.61-1.20 (m, 20H), 0.93-0.84 (m, 6H) ppm.

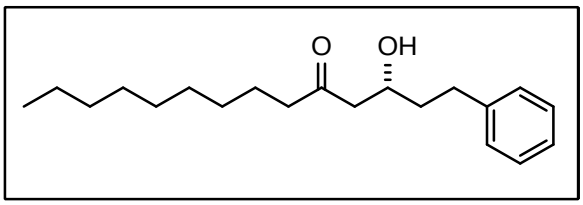
^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.7, 67.7, 48.9, 43.7, 36.1, 31.9, 29.40, 29.38, 29.3, 29.2, 27.6, 23.6, 22.7, 22.6, 14.1, 14.0 ppm.

HRMS: *m/z* calc for $C_{16}H_{32}O_2$: 257.2481 (M+H); Found: 257.2477 (M+H).

$[\alpha]_D^{20}$ = + 29.1° (c 0.28, $CHCl_3$)

For the determination of enantiomeric excess, 5-hydroxyhexadecan-7-one (**88**) was converted into the corresponding benzoyl ester (5 equiv. benzoyl chloride, 10 equiv. pyridine, CH_2Cl_2, 14 h, room temperature). The corresponding enantiomeric benzoyl esters of 5-hydroxyhexadecan-7-one (**88**) were separable by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes: IPA 95:5, detection at 230 nm, flow rate = 1.2 mL/min. The retention time of the (+)-enantiomer is 5.18 min; the retention time of the (-)-enantiomer is 4.14 min, 97% *ee*.

Preparation of (*R*)-3-hydroxy-1-phenyltetradecan-5-one (89)



To a solution of β-ketochlorohydrin (23.6 mg, 0.7 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. AIBN was then added (cat, 1-2mg), and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude product was purified by flash chromatography (hexanes:EtOAc 9:1) to afford (*R*)-3-hydroxy-1-phenyltetradecan-5-one (**89**) (18 mg, 85%) as a white solid, mp 35-38 °C.

IR (neat): 3372, 3273, 3027, 2953, 2917, 2850, 1704, 14468, 1453, 1110 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31-7.28 (m, 2H), 7.22-7.17 (m, 3H), 4.05 (m, 1H), 3.17 (d, *J* = 3.2 Hz, 1H), 2.82 (ddd, *J* = 5.4, 9.8, 14.2 Hz, 1H), 2.69 (ddd, *J* = 6.9, 9.8, 14.2 Hz, 1H), 2.60 (dd, *J* = 3.0, 17.7 Hz, 1H), 2.52 (dd, *J* = 8.9, 17.7 Hz, 1H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.82 (m, 1H), 1.68 (m, 1H), 1.61-1.50 (m, 2H), 1.35-1.20 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm.

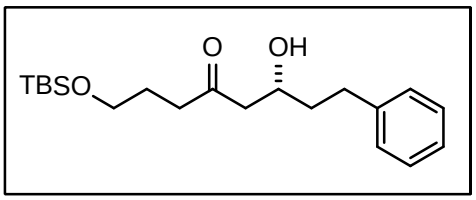
^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.6, 141.9, 128.47, 128.41, 125.9, 66.9, 48.9, 43.7, 38.0, 31.9, 31.8, 29.4, 29.3, 29.2, 29.1, 23.6, 22.7, 14.1 ppm.

HRMS: *m/z* calcd for $C_{20}H_{32}O_2$: 305.2475 (M+H); Found: 305.2476 (M+H).

$[\alpha]_D^{20}$ = + 26.6° (c 0.15, $CHCl_3$)

The enantiomeric excess of (*R*)-3-hydroxy-1-phenyltetradecan-5-one (**89**) was determined by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes: IPA 20:1, detection at 205 nm, flow rate = 1.2 mL/min. The retention time of the (+)-enantiomer is 12.13 min; the retention time of the (-)-enantiomer is 7.83 min, 96% *ee*.

(*R*)-1-(*tert*-butyldimethylsilyloxy)-6-hydroxy-8-phenyloctan-4-one (90)



To a solution of β-ketochlorohydrin (0.1 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude product was purified by flash chromatography (hexanes:EtOAc 10:1) to afford (*R*)-1-(*tert*-butyldimethylsilyloxy)-6-hydroxy-8-phenyloctan-4-one (**90**) (21.5 mg, 86%) as a colourless oil.

IR (neat): 3453, 3026, 3027, 2953, 2928, 2857, 1708, 1496, 1256, 1100, 1032, 836 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.28 (m, 2H), 7.23-7.17 (m, 3H), 4.06 (m, 1H), 3.62 (t, *J* = 6.1 Hz, 2H), 3.19 (s, 1H), 2.83 (m, 1H), 2.69 (m, 1H), 2.63 (dd, *J* = 2.7, 17.6 Hz, 1H), 2.55 (dd, *J* = 9.1, 17.6 Hz, 1H), 2.51 (t, *J* = 7.4 Hz, 2H), 1.88-1.76 (m, 3H), 1.69 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H) ppm.

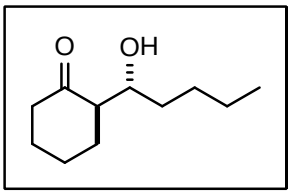
^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.2, 141.9, 128.5, 128.4, 125.9, 66.9, 62.0, 49.1, 40.0, 38.1, 31.8, 26.6, 25.9, 25.9, 18.3, -5.4 ppm.

HRMS: *m/z* calcd for $C_{20}H_{34}O_3Si$: 351.2311 (M+H); Found: 351.2357 (M+H)

$[\alpha]_D^{20}$ = + 26.2° (c 0.11, $CHCl_3$)

The enantiomeric excess of (*R*)-1-(*tert*-butyldimethylsilyloxy)-6-hydroxy-8-phenyloctan-4-one (**90**) was determined by HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes: IPA 95:5, detection at 205 nm, flow rate = 1.2 mL/min. The retention time of the (+)-enantiomer is 18.06 min; the (-)-enantiomer is 10.22 min, 92% *ee*.

Preparation of (+/-)-(*R*)-2-(1*R*)-(1-hydroxypentyl)cyclohexanone (91)



To a solution of β-ketochlorohydrin (24 mg, 0.11 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude product was purified by flash chromatography (hexanes:EtOAc 9:1) to afford (+/-)-(*R**)-2-(1*R**)-(1-hydroxypentyl)cyclohexanone (**91**) (15 mg, 74%) as a colourless oil.

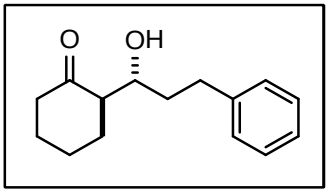
IR (neat): 3528, 2936, 2861, 1697, 1449, 1403, 1312, 969 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.73 (m, 1H), 3.42 (d, *J* = 4.3 Hz, 1H), 2.44-2.26 (m, 3H), 2.14-2.05 (m, 2H), 1.91 (m, 1H), 1.74-1.61 (m, 2H), 1.56-1.24 (m, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 215.9, 71.5, 55.9, 42.9, 33.3, 30.8, 27.8, 27.4, 25.0, 22.8, 14.1 ppm.

HRMS: *m/z* calcd for $C_{11}H_{20}O_2$: 185.1497 (M+H); Found: 185.1536 (M+H).

Preparation of (*R*)-2-((*R*)-1-hydroxy-3-phenylpropyl)cyclohexanone (92)



To a solution of β-ketochlorohydrin (0.2 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude product was purified by flash chromatography (hexanes:EtOAc 9:1) to afford (*R**)-2-((*R*)-1-hydroxy-3-phenylpropyl)cyclohexanone (**92**) (17 mg, 35%) as a colourless oil.

IR (neat): 3448, 3026, 2936, 2862, 1698, 1603, 1495, 1453, 1251, 1075, 1066, 843 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.27 (m, 2H), 7.21-7.16 (m, 3H), 3.77 (m, 1H), 3.54 (d, *J* = 4.4 Hz, 1H), 2.88 (m, 1H), 2.70 (m, 1H), 2.44-2.23 (m, 3H), 2.14-2.05 (m, 2H), 1.89 (m, 1H), 1.83-1.60 (m, 4H), 1.44 (m, 1H) ppm.

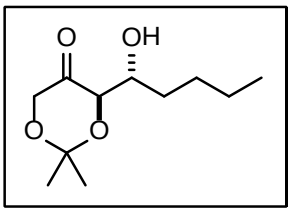
^{13}C NMR (100 MHz, $CDCl_3$) δ: 215.7, 142.3, 128.5, 128.3, 125.7, 70.9, 56.0, 42.9, 35.5, 31.6, 30.7, 27.8, 25.0 ppm.

HRMS: *m/z* calcd for $C_{15}H_{20}O_2$: 233.1352 (M+Na); Found: 255.1356 (M+Na)

$[\alpha]_D^{20}$ = + 21.2° (c 0.18, $CHCl_3$)

The enantiomeric excess of (*R*)-2-((*R*)-1-hydroxy-3-phenylpropyl)cyclohexanone (**92**) was determined by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes: IPA 20:1, detection at 205 nm, flow rate = 1.2 mL/min. The retention time of the (+)-enantiomer is 10.32 min; the retention time of the (-)-enantiomer is 12.79 min, 90% *ee*.

Preparation of (+/-)-(*R)-4-((*R**)-1-hydroxypentyl)-2,2-dimethyl-1,3-dioxan-5-one (93)**



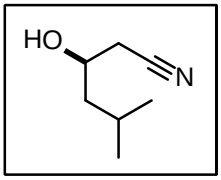
To a solution of β-ketochlorohydrin (0.15 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude product was purified by flash chromatography (hexanes:EtOAc 9:1) to afford (+/-)-(*R**)-4-((*R**)-1-hydroxypentyl)-2,2-dimethyl-1,3-dioxan-5-one (**93**) (24 mg, 74%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.26 (dd, *J* = 17.2, 1.3 Hz, 1H), 4.09 (dd, *J* = 7.1, 1.3 Hz, 1H), 4.02 (d, *J* = 17.2 Hz, 1H), 3.89 (m, 1H), 2.94 (d, *J* = 3.9 Hz, 1H), 1.64 (m, 1H), 1.54-1.51 (m, 2H), 1.49 (s, 3H), 1.45 (s, 3H), 1.41-1.30 (m, 3H), 0.92 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.5, 100.9, 75.9, 70.9, 66.8, 31.9, 27.4, 24.0, 23.5, 22.6, 14.4 ppm.

HRMS: *m/z* calcd for $C_{11}H_{20}O_4$: 217.1434 (M+H); found: 217.1430 (M+H)

Preparation of (+/-)-(3*R)-3-hydroxy-5-methylhexanenitrile (94)**



To a solution of β-ketochlorohydrin (0.37 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude product was purified by flash chromatography (hexanes:EtOAc 4:1) to afford (+/-)-(3*R**)-3-hydroxy-5-methylhexanenitrile (**94**) (33 mg, 70%) as a colourless oil.

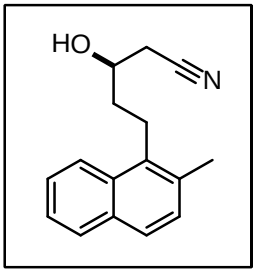
IR (neat): 3437, 2959, 2932, 2872, 2252, 1469, 1416, 1369, 1224, 1078, 1023cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.02 (m, 1H), 2.57 (dd, *J* = 16.7, 4.7 Hz, 1H), 2.47 (dd, *J* = 16.7, 6.3 Hz, 1H), 2.29 (s, 1H) 1.79 (m, 1H), 1.57 (m, 1H), 1.36 (m, 1H), 0.97-0.91 (m, 6H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ: 117.8, 65.9, 45.5, 26.6, 24.5, 23.1, 21.8 ppm.

HRMS: *m/z* calcd for $C_7H_{13}NO$: 150.0889 (M+Na); Found: 150.0893 (M+Na).

Preparation of (+/-)-3-hydroxy-5-(2-methylnaphthalen-1-yl)pentanenitrile (95)



To a solution of β-ketochlorohydrin (148 mg, 0.54 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The crude product was purified by flash chromatography (hexanes:EtOAc 4:1) to afford (+/-)-(3*R**)-3-hydroxy-5-(2-methylnaphthalen-1-yl)pentanenitrile (**95)** (113 mg, 88%) as a colourless oil.

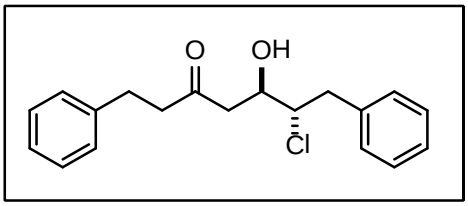
IR (neat): 3453, 3050, 2955, 2924, 2251, 1730, 1707, 1597, 1511, 1414, 1265, 1087, 813 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.52 (dt, *J* = 7.24, 1.15 Hz, 1H), 7.43 (t, *J* = 7.24 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 4.11 (m, 1H), 3.31 (m, 1H), 3.16 (m, 1H), 2.60-2.55 (m, 2H), 2.53 (s, 3H), 1.94-1.88 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.0, 133.2, 132.8, 132.06, 129.4, 126.7, 126.3, 124.8, 123.3, 117.7, 67.9, 60.6, 36.6, 26.5, 24.4, 20.3 ppm.

HRMS: *m/z* calcd for $C_{16}H_{17}NO$: 240.1383 (M+H); Found: 240.1355 (M+H).

Preparation of (5*R*,6*S*)-6-chloro-5-hydroxy-1,7-diphenylheptan-3-one (102)



To a cold (0 °C) stirred solution of *i*-Pr_2NH (0.325 mL, 1.2 equiv) in THF (0.1M) was added *n*-BuLi in hexanes (0.837 mL, 2.5 M, 1.2 equiv) and the mixture was stirred at 0 °C for 30 min, then cooled to -78 °C and benzylacetone (0.286 mL, 1.91 mmol, 1 equiv) was added slowly in one portion. The resulting solution was stirred for an additional 30 minutes at -78 °C. After this time, a solution of (2*S*)-2-chloro-3-phenylpropanal ((***S***)-**66**) (420 mg, 1.2 equiv) in THF (1.0 M) was added dropwise over 15 min at –78 °C, and the resulting mixture was stirred for an additional 30 minutes. Sat. aq NH_4Cl (25 mL) was added, and the mixture was allowed to warm to r.t. , then diluted with EtOAc (10 mL), the aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, hexanes–EtOAc) gave pure (5*R*,6*S*)-6-chloro-5-hydroxy-1,7-diphenylheptan-3-one (**102**), Isolated as a colorless solid (453 mg, 75% yield); mp 56–60 °C.

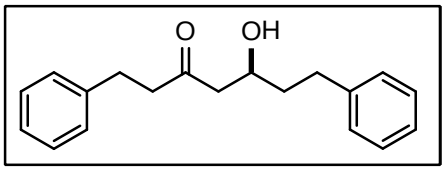
IR (thin film): 3463, 3028, 2924, 2360, 1704, 1491, 1455 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.16 (m, 10 H), 4.15–4.07 (m, 2 H), 3.41 (d, *J* = 4.7 Hz, 1 H), 3.30 (dd, *J* = 3.8, 15 Hz, 1 H), 2.98–2.75 (m, 7 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.7, 129.5, 128.6, 128.4, 128.3, 126.9, 126.3, 70.5, 65.5, 45.2, 45.1, 40.0, 29.5 ppm.

HRMS: *m*/*z* calcd for $C_{19}H_{21}ClO_2$: 317.1300 (M + H); found: 317.1303 (M + H).

Preparation of (+)-dihydroyashabushiketol (100)



To a solution of β-ketochlorohydrin (80 mg, 0.25 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2. AIBN was added (cat., 1-2 mg), and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The reaction mixture was cooled to room temperature and concentrated, and the crude product was purified by flash chromatography (hexanes:EtOAc 9:1) to afford (+)-dihydroyashabushiketol (**100**) (68 mg, 96%) as a white solid, mp 62-65 °C. The spectral data acquired on this material was in complete agreement with that reported.[111]

IR (neat): 3439, 3026, 2926, 2860, 1709, 1603, 1495, 1453, 1406, 1371, 1096, 748 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.30 (m, 4H), 7.26-7.19 (m, 6H), 4.10 (m, 1H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.89-2.67 (m, 5H), 2.60-2.56 (m, 2H), 1.89-1.80 (m, 1H), 1.77-1.67 (m, 1H) ppm.

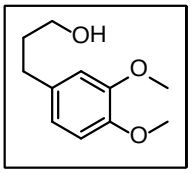
^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.1, 141.8, 140.7, 128.6, 128.5, 128.4, 128.3, 126.3, 125.9, 66.9, 49.3, 45.0, 38.0, 31.7, 29.5 ppm.

HRMS: *m/z* calcd for $C_{19}H_{22}O_2$: 305.1509 (M+Na); Found: 305.1512 (M+Na).

$[\alpha]_D^{20}$ = + 14.6° (c 0.75, $CHCl_3$)

For the determination of enantiomeric excess, (+)-dihydroyashabushiketol (**100**) was converted into the benzoyl ester (5 equiv. BzCl, 10 equiv. pyr., CH_2Cl_2, rt). The benzoyl esters of dihydroyashabushiketol (**100**) were separable by chiral HPLC using a DAICEL-CHIRALCEL-OD column. Eluent = hexanes: IPA 90:10, detection at 230 nm, flow rate = 1.5 mL/min. The retention time of the (+)-enantiomer is 8.39 min; the retention time of the (-)-enantiomer is 9.54 min (98% *ee*).

3-(3,4-dimethoxyphenyl)propan-1-ol (111)



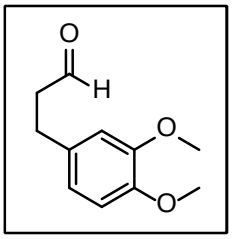
To solution of 1-allyl-2,3-dimethoxybenzene (**110**) (4.83 mL, 28.1 mmol) in THF (150 mL) at 0 °C was added BH_3•THF (9.35 mL, 1M in THF) and the resulting solution was stirred at room temperature for 1.5 hours. Following this time, the solution was cooled to 0 °C, and a solution of NaOH (3.10 mL, 3M in H_2O) was slowly added, followed by H_2O_2 (2.85 mL, 30% in H_2O), and the resulting mixture was allowed to warm to room temperature and stirred for a further 1.5 hours. The reaction solution was poured into water and extracted with ethyl acetate. The combined organic extracts were dried (MgSO4), filtered and concentrated to yield a colourless oil. Purification by vacuum distillation (130 °C, 0.5 torr) provided the pure alcohol (**111**) (4.79 g, 87%)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.94-6.75 (m, 3H), 3,90 (s, 3H), 3.88 (s, 3H), 3.73-3.69 (m, 2H), 2.71-2.67 (dd, *J* = 7.5, 9.4 Hz, 2H), 1.94-1.87 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.9, 147.2, 134.4, 120.2, 111.8, 111.3, 62.3, 55.9, 5.8, 34.3, 31.7 ppm.

HRMS: *m/z* calcd for $C_{11}H_{16}NaO_3$: 219.0987 (M+Na); Found: 219.0992 (M+Na).

3-(3,4-dimethoxyphenyl)propanal (112)



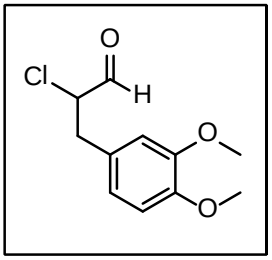
A round-bottom flask containing crushed molecular sieves (~5 g) was flame dried under vacuum and cooled under a constant stream of nitrogen. To the flask was then added PCC (4.20 g, 2 equiv.) and the mixture was diluted with CH_2Cl_2 (25 mL) and cooled to 0 °C. A solution of **111** (1.90 g, 9.72 mmol) in CH_2Cl_2 (5 mL) was added to the suspension, and the reaction mixture was stirred at room temperature for 2 hours. After this time, the suspension was filtered through a cake of celite, concentrated, and purified via column chromatography to yield the title compound **111** as a colourless oil (0.861 g, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.83 (t, *J* = 1.4 Hz, 1H), 6.84-6.71 (m, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 2.92 (t, *J* = 7.8 H, 2H), 2.78 (t, *J* = 7.8 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.7, 149.0, 147.5, 132.9, 120.1, 111.7, 111.4, 55.94, 55.85, 45.5 ppm.

HRMS: *m/z* calcd for $C_{11}H_{14}NaO_3$: 217.0831 (M+Na); Found: 217.0835 (M+Na).

(+/-)-2-chloro-3-(3,4-dimethoxyphenyl)propanal (105)

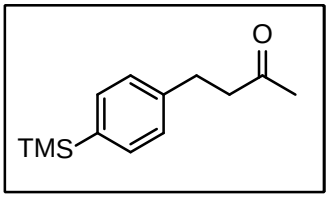


A solution of aldehyde **112** (1.54 g, 7.93 mmol) in CH_2Cl_2 (60 mL) was cooled to 0 °C. *l*-proline (**46**) (91 mg, 0.1 equiv.) was added to the reaction mixture, followed by the addition of *N*-chlorosuccinimide (1.00 g, 7.53 mmol). The reaction mixture was stirred for 4 hours at room temperature. Pentane (100 mL) was added and the reaction mixture was cooled to -78° C, and the suspension was filtered and the mother liquor concentrated, dissolved in pentane (100 mL), cooled to -78 °C and the suspension filtered again. The mother liquor was concentrated to yield the α-chloroaldehyde (**105**) as a yellow oil (1.70 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.53 (d, *J* = 2.4 Hz, 1H), 6.83-6.73 (m, 3H), 4.36 (ddd, = 6.0, 8.0, 2.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.31 (dd, *J* = 14.5, 6.0 Hz, 1H), 3.05 (dd, *J* = 14.5, 8.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.6, 149.0, 148.4, 127.8, 121.6, 112.6, 111.3, 64.1, 55.91, 55.89, 38.1 ppm.

4-(4-(trimethylsilyl)phenyl)butan-2-one (104)



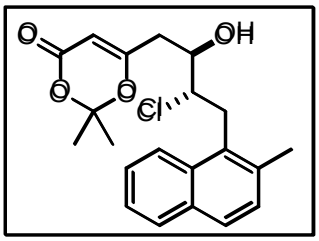
A solution containing (4-bromophenyl)trimethylsilane (**107**) (1.0 g, 4.36 mmol), 2-hydroxybutene (**108**) (0.62 mL, 1.5 equiv.), $Pd(PPh_3)_2Cl_2$ (0.150 g, 5 mol%), NaHCO3 (0.439 g, 1.2 equiv.) in NMP (40 mL) was refluxed (130 °C) for 5 hours. After this time, the solution was cooled and H_2O was added (50 mL). Ethyl acetate was added, and the organic layer was extracted (3 x 50 mL).The combined organic extracts were washed with brine (3 x 50 mL), dried (MgSO4), filtered and concentrated, and purified via column chromatography (hexanes/ethyl acetate) to provide the title ketone **104** (0.61 g, 64%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 7.8 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 2.94 (dd, *J* = 7.8, 7.3 Hz, 2H), 2.81 (dd, *J* = 7.8, 7.3 Hz, 2H), 2.19 (s, 3H), 0.30 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.8, 141.6, 137.9, 133.6, 127.8, 45.1, 30.0, 29.7, -1.05 ppm.

HRMS: *m/z* calcd for $C_{13}H_{20}NaOSi$: 243.1176 (M+Na); Found: 243.1175 (M+Na).

Preparation of 6-((1*S*,2*R*)-2-chloro-1-hydroxy-3-(2-methylnaphthalen-1-yl)propyl)-2,2-dimethyl-4*H*-1,3-dioxin-4- one (123)



To cold (-60 °C), stirred a solution of (2*R*)-2-chloro-3-(2-methylnaphthalen-1-yl)propanal ((***R***)-**67**) (76 mg, 0.33 mmol, 1 equiv.) in dry CH_2Cl_2 (3 mL) was added BF_3•OEt_2 (0.12 mL, 3 equiv.) and the resultant orange solution was stirred for 10 minutes. Silyl enol ether **126**[122] was then added neat (140 mg, 2 equiv.), and the resulting colourless solution was stirred at -60 °C for 18 hours. H_2O (5 mL) was then added, and the reaction mixture was allowed to warm to room temperature. The phases were separated and extracted with CH_2Cl_2 (3 x 10 mL), the combined organic extracts were washed with brine (1 x 10 mL), dried ($MgSO_4$), and concentrated to provide a mixture of 1,2-*anti* and 1,2-*syn* chlorohydrins **123** in a 1.5:1 ratio. Purification by flash chromatography (9:2:1 hexanes:CH_2Cl_2:EtOAc; 2 columns required to separate diastereomers) afforded the title compound (***anti*-123**) as a white solid, mp 32-35 °C (89 mg, 73 %) as well as the 1,2-syn diastereomer (***syn*-123**) (26 mg, 21%) (combined isolated yield = 94%).

IR (neat): 3413, 3057, 2992, 2948, 1709, 1634, 1511, 1391, 1378, 1275, 1203, 1015cm^{-1}

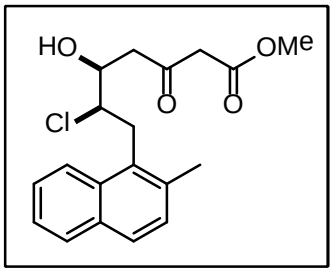
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 5.39 (s, 1H), 4.44 (m, 1H), 4.22 (m, 1H), 3.76 (dd, *J* = 14.9, 4.5 Hz, 1H), 3.54 (dd, *J* = 9.5, 14.9 Hz, 1H), 2.80 (dd, *J* = 14.9, 2.7 Hz, 2H), 2.66-2.57 (m, 2H), 2.59 (s, 3H), 1.72 (s, 3H), 1.71 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 160.9, 134.9, 132.7, 132.1, 130.3, 129.3, 129.0, 127.5, 126.4, 124.8, 123.1, 106.9, 95.8, 72.0, 66.8, 37.6, 32.3, 25.5, 24.7 ppm.

HRMS: *m/z* calcd for $C_{21}H_{23}ClO_4$: 375.1358 (M+H); Found: 3375.1391 (M+H).

$[\alpha]_D^{20}$ = - 43.3° (c 0.06, $CHCl_3$)

Preparation of (5*S*,6*R*)-methyl-6-chloro-5-hydroxy-7-(2-methylnaphthalen-1-yl)-3-oxoheptanoate (120)



To a stirred solution of anhydrous methanol (0.034 mL, 4 eq.) in toluene (3 mL, 0.07 M) at room temperature was added 6-((1*S*,2*R*)-2-chloro-1-hydroxy-3-(2-methylnaphthalen-1-yl)propyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (**123**) (79 mg, 0.21 mmol, 1 eq.) and the sealed reaction vial was heated to 65 °C in an oil bath for 18 h. Concentration of the crude reaction mixture and purification by silica gel chromatography (4:1 hexanes:ethyl acetate) gave (5*S*,6*R*)-methyl-6-chloro-5-hydroxy-7-(2-methylnaphthalen-1-yl)-3-oxoheptanoate (**120**) as a colourless oil (61 mg, 83%).

IR (neat): 3477, 3050, 3003, 2955, 2925, 1747, 1713, 1654, 1512, 1437, 1363, 1223, 1092 cm^{-1}

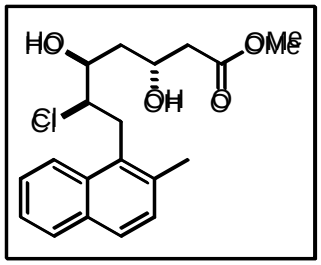
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 4.41-4.30 (m, 2H), 3.91 (dd, *J* = 15.2, 3.5 Hz, 1H), 3.77 (s, 3H), 3.54 (d, *J* = 2.0 Hz, 2H), 3.45 (dd, *J* =15.2, 9.8 Hz, 1H), 3.18 (dd, *J* = 17.8, 2.1 Hz, 1H), 2.97 (dd, *J* = 17.8, 8.5 Hz, 1H), 2.58 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.0, 167.2, 134.9, 132.6, 132.2, 130.7, 129.3, 128.8, 127.3, 126.2, 124.7, 123.5, 71.4, 65.6, 52.6, 49.6, 46.2, 32.7, 21.0 ppm.

HRMS: *m/z* calcd for $C_{19}H_{21}ClO_4$: 349.1201(M+H); Found: 349.1196 (M+H).

$[\alpha]_D^{20}$ = - 22.6° (c 0.15, $CHCl_3$)

Preparation of (3*R*,5*S*,6*R*)-methyl 6-chloro-3,5-dihydroxy-7-(2-methylnaphthalen-1-yl)heptanoate (127)



To a stirred solution of triethylborate (0.17 mL, 1.0 M in THF, 1.2 eq) in THF (5 mL) at room temperature was added methanol (0.4 mL). The resulting solution was stirred for 20 minutes and then cooled to -78 °C. A solution of **120** (51 mg, 0.15 mmol) in THF (1 mL) was then added slowly, and the resultant yellow solution was stirred for one hour at this temperature. $NaBH_4$ (11 mg, 2 eq.) was then added and the reaction mixture was stirred for one hour at -78 °C. The reaction mixture was then treated with glacial acetic acid (0.2 mL) followed by water (6 mL), and then slowly warmed to room temperature. The phases were separated and the aqueous layer was extracted with EtOAc (4 x 15 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (2 x 10 mL) and brine (1 x 10 mL), then dried ($MgSO_4$), filtered, and concentrated. The crude product was dissolved in methanol and concentrated (5 x 10 mL) (to ensure complete removal of boron reagents via trimethylborate) to give the crude diol as a single diastereomer. Purification of the crude product by column chromatography (3:1 hexanes:ethyl acetate) gave the title compound **127** as a colourless oil (39 mg, 77%).

IR (neat): 3437, 3051, 2953, 2853, 1732, 1512, 1438, 1375, 1250, 1072, 1050, 813 cm^{-1}

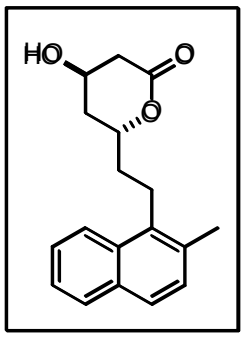
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 4.37 (m, 1H) 4.28 (m, 1H), 4.15 (m, 1H) 4.11 (d, *J* = 2.1 Hz, 1H)), 3.89 (dd, *J* = 15.0, 3.6 Hz, 1H), 3.82 (m, 1H), 3.75 (s, 3H) 3.45 (dd, *J* = 15.0, 10.1 Hz, 1H), 2.58 (s, 3H), 2.56 (d, *J* = 1.68 Hz, 1H) 2.10 (m, 1H), 1.78 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 134.9, 132.6, 132.3, 131.2, 129.3, 128.8, 127.2, 126.2, 124.6, 123.6, 75.6, 68.9, 67.0, 52.0, 41.2, 38.5, 29.7, 21.0 ppm.

HRMS: *m/z* calcd for $C_{19}H_{23}ClO_4$: 351.1358 (M+H); Found: 351.1361 (M+H).

$[\alpha]_D^{20}$ = - 26.9° (c 0.13, $CHCl_3$)

Prepration of (+)-solistatin (115):



To a solution of β-ketochlorohydrin **127** (0.1 mmol) in toluene (1 mL) was added tris(trimethylsilyl)silane (5 eq) and the resultant solution was sparged with N_2 for 20 minutes. A catalytic amount (1-2 mg) of AIBN was then added, and the reaction vessel was sealed and heated to 110 °C in an oil bath and maintained at this temperature for 18 hours. The crude product was flushed through a short plug of silica gel (2:1 hexanes:EtOAc) to provide a mixture of diol (14 mg) and solistatin (6 mg), which was immediately dissolved in CH_2Cl_2 (2 mL), treated with a catalytic amount of *p*-TsOH and stirred for 4 hours at room temperature. The resulting solution was then treated with saturated $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 5 mL), washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography (2:1 hexanes:EtOAc) to provide (+)-solistatin (**115**) (18 mg, 57% yield over 2 steps) as a colourless oil. The spectral data acquired on this material was in complete agreement with that reported.[117]

IR (neat): 3422, 3049, 2956, 2922, 2851, 1709, 1511, 1388, 1256, 1056, 1069 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.5 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.3 (d, *J* = 8.3 Hz, 1H),4.85 (m, 1H), 4.42 (m, 1H), 3.41 (m, 1H), 3.19 (m, 1H), 2.80 (dd, *J* = 17.0, 5.0 Hz, 1H), 2.67 (ddd, *J* = 17.0, 3.6, 1.6 Hz, 1H), 2.52 (s, 3H), 2.03-1.98 (m, 2H), 1.93 (m, 1H), 1.86 (dt, *J* = 12.9, 3.3 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 134.2, 133.2, 132.6, 132.0, 129.3, 128.7, 126.5, 126.2, 124.6, 123.4, 75.5, 63.0, 38.8, 36.2, 35.7, 24.1, 20.2 ppm.

HRMS: *m/z* calcd for $C_{18}H_{20}O_3$: 307.1305 (M+Na); Found: 307.1309 (M+Na).

$[\alpha]_D^{20}$ = + 29.1° (c 0.17, $CHCl_3$)

Chapter 3.

Photocatalytic Fluorination of Unactivated C-H Bonds[d,e]

3.1. Introduction: Fluorination of C-H Bonds

The incorporation of a fluorine atom into an advanced drug candidate is a common strategy in medicinal chemistry.[125,126] Oftentimes, a single hydrogen to fluorine substitution improves drug-like properties by blocking undesired metabolism at a specific site, increasing lipophilicity or binding affinity, or altering drug absorption, distribution, or excretion.[125] In addition to the medicinal advantages often presented by fluorination, valuable pharmacokinetic information can be gleaned from non-invasive positron emission tomography (PET) imaging of ^{18}F-labeled drugs *in vivo*.[127] The critical role fluorine plays in the drug discovery process is highlighted by the fact that one-third of the so-called blockbuster drugs are fluorinated in at least one position.[58] Since the fluorination of cortisone[128] signalled a new era of fluoropharmaceuticals (*vide infra*), further advances have relied on the discovery of mild fluorination reagents that can be handled safely and obviate the use of fluorine gas or its surrogates.[126,129] While present sophistication in the field includes the addition of electrophilic fluorine to alkenes, [129,130] and fluorination of aryltriflates[131] and palladium aryl complexes,[132] there is much interest in the development of reactions that effect the direct fluorination of C-H bonds. In this context, the identification of reagent systems that effect selective fluorination of

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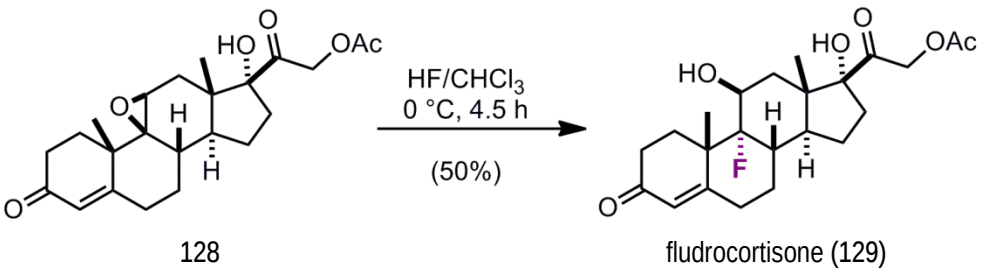
[e] Hope Fan and Stanley Chang assisted in the fluorination and characterization of some compounds described in this chapter. Duane Hetland assisted in the construction of the flow apparatus.

unactivated C(sp^3)-H bonds, or those not adjacent to functional groups which facilitate the formation of radicals or anions, remains a significant challenge.

3.1.1. Fluorine in Medicinal Chemistry

As discussed in Section 1.2, fluorine-carbon bonds are extremely strong and polarized, and the substitution of a carbon-hydrogen bond for a carbon-fluorine bond can modify the electronics of a molecule.[22] From a medicinal chemistry perspective, this allows for modification of the polarity of a drug candidate with minimal perturbation in size. The incorporation of a fluorine atom into a bioactive molecule can lead to a more favourable pharmacokinetic and pharmacodynamic profile;[61] it has been shown that fluorine can alter properties such as lipophilicity, acidity, bioavailability and metabolic stability.[59,61,126] A significant application of the latter phenomenon is the site-specific incorporation of fluorine atoms at metabolically labile positions, where the strong carbon-fluorine bond is much less prone to metabolism, and can thus block metabolic degradation of a drug in the body.[20,133]

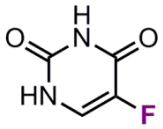
The first reported fluorination of a drug molecule appeared in 1954, when Fried and Sabo disclosed the hydrogen fluoride promoted fluorination of a hydrocortisone acetate derivative **128** (Figure 3.1).[128] They also demonstrated that the fluorinated hydrocortisone acetate **129** was almost 11 times more potent as a glucocorticoid receptor agonist than the parent molecule **128**. Unfortunately, mineralocorticoid activity also increased by over 300 fold, causing undesirable sodium and water retention. More recently, fludrocortisone has found utility as an aldosterone analogue used in the treatment of Addison's disease and salt-wasting forms of congential adrenal hyperplasia.[134]



128 fludrocortisone (129)

Figure 3.1. Fludrocortisone Synthesis.

In 1957, Heidelberger and coworkers synthesized 5-fluorouracil[135] (**130**, Figure 3.2) and subsequently reported that the fluorinated pyrimidine analogue led to inhibition of tumour growth in mice.[136] As a result, 5-fluorouracil quickly became commercially available as an anti-cancer treatment and is currently still in use for this purpose. The mechanism of action of 5-fluorouracil (**130**) has been extensively studied, and it is now known that **130** is a suicide inhibitor of thymidylate synthase, with the carbon-fluorine bond being a key component of the potent irreversible inhibition by blocking the reactive site.[137]



5-fluorouracil (130)

Figure 3.2. 5-fluorouracil

Following these important discoveries, the use of site-specific fluorine incorporation into bioactive molecules to produce more favourable physiochemical properties has been widely studied.[126,125,138] Some notable examples of fluorinated pharmaceuticals are depicted in Figure 3.3. Fluticasone propionate (**131**), an analogue of fludrocortisone (**129**, Figure 3.1) with two additional fluoromethine bonds, was developed as an anti-inflammatory agent used in the treatment of respiratory diseases. As many corticosteroidal therapies available at the time were associated with undesirable side effects in children such as adrenal suppression and osteoporosis,[139] structure activity relationships reported by Phillips at Glaxo led to the development of fluticasone propionate,[140] which was shown to possess the optimal physicochemical and pharmacokinetic properties for use as both a topical and inhaled treatment for asthma and other chronic respiratory illnesses. Specifically, as lipophilicity was shown to be an important property in the uptake and retention of the corticosteroids in lung tissue,[141] fluticasone propionate showed the highest deposition in lung tissue and affinity for the glucocorticoid receptor compared to previous therapies, which can be attributed to the relatively high lipophilicity of the fluorinated molecule.

Norfloxacin (**132**) was the first quinolone to be modified by the incorporation of a fluorine atom, which was shown to increase the antibacterial activity. Compared to the

parent quinolone, norfloxacin showed a 63-fold increase in potency against *Esherichia coli* H560, and an 18-fold increase in DNA gyrase-inhibitory potency.[57] Following the publication of the norfloxacin patent, multiple drug companies initiated fluoroquinolone programs, and researchers at Bayer discovered that a slight modification at the *N*-alkyl site could further increase the potency.[142] Ciprofloxacin (**133**), marketed as Cipro, was soon approved as an effective gram-negative antibacterial therapeutic.

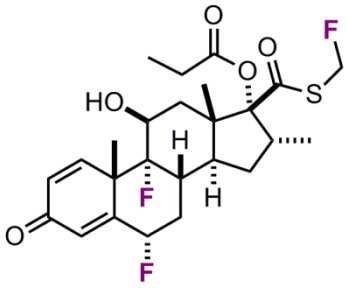
Atorvastatin (**114**) was approved by the FDA in 1996, and when compared to statin therapeutics available at the time it was found to be the most effective at lowering undesired LDL levels. The discovery and SAR of atorvastatin was conducted by Roth and coworkers at Parke-Davis,[143] later acquired by Pfizer, who found that fluorination of the aryl ring gave a 5-fold increase in potency compared to the unfluorinated version.[116] The importance of the aryl fluoride functionality is highlighted by its incorporation into the majority of related statin drugs. With almost $15 billion USD in sales in 2006 alone,[144] atorvastatin has been described as the top selling drug of all time and boasts over $140 billion USD in global sales in over 16 years.[145]

Sitagliptin (**134**) is an oral dipeptidyl peptidase-4 (DPP-IV) inhibitor that was developed by Merck for treatment of type II diabetes.[138] Rigorous SAR studies on a sitagliptin analogue showed that the substitution of hydrogen for fluorine on the benzene ring led to increased potency, with a 2,4,5-trifluorinated benzene ring leading to greater potency and selectivity for inhibition of DPP-IV.[146] Additionally, incorporation of a trifluoromethyl group on the triazole ring resulted in a significant increase in the oral bioavailability of the molecule.[125]

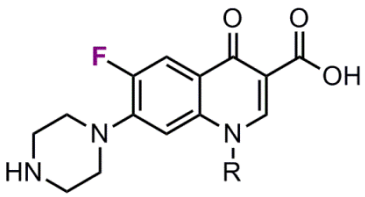
Gemcitabine (**135**) is a gem-difluoro analogue of deoxycytidine that was shown to exhibit a narrow therapeutic index for many cancer types. The mechanism of action, similar to that of 5-fluorouracil described above, is the potent and irreversible inhibition of processes required for DNA synthesis.[147] Gemcitabine is currently marketed as Gemzar by Eli Lilly and is used in chemotherapy for non-small cell lung, pancreatic, bladder, and breast cancers.

Odanacatib (**136**) is a potent and selective Cathepsin K inhibitor that recently concluded clinical trials for treatment of osteoporosis.[148,149] Through various SAR

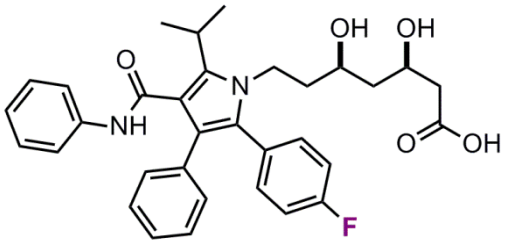
studies, it was found that a trifluoroethylamine moiety was a suitable isostere for an amide, and this substitution led to 10-20 fold increase in selectivity for Cathepsin K.[150] Additionally, site-specific fluorination of the tertiary isopropyl carbon was necessary in order to minimize undesired metabolites arising from the oxidation of that site *in vivo*.[151]



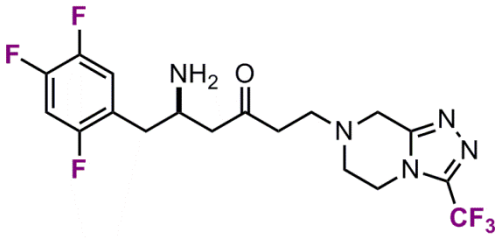
fluticasone propionate (131) (Glaxo, Flovent®)



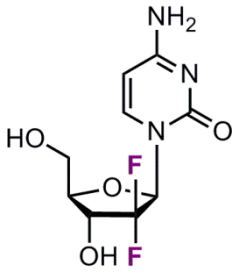
R = ethyl, norfloxacin (132) (Merck, Noroxin®)
R = cyclopropyl, ciprofloxacin (133) (Bayer, Cipro®)



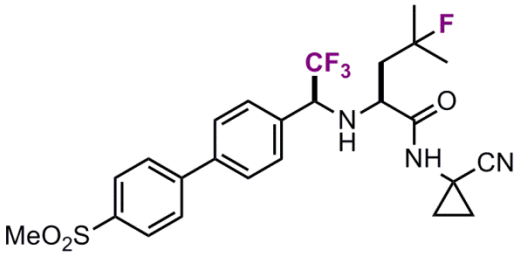
atorvastatin (114) (Pfizer, Lipitor®)



sitagliptin (134) (Merck, Januvia®)



gemcitabine (135) (Lilly, Gemzar®)



odanacatib (136) (Merck)

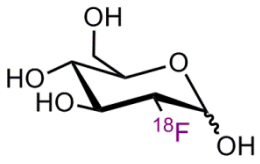
Figure 3.3. Fluorinated Pharmaceuticals

3.1.2. ^{18}F and PET

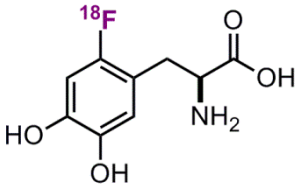
Positron emission tomography (PET) is a commonly used non-invasive method of imaging through detection of positron emitting radiopharmaceuticals. Following administration of the PET radionuclide to a patient, positrons (β) are emitted that travel a certain distance before colliding with an electron. The resultant annihilation event

produces two gamma ray photons (γ) that emit in 180° opposing directions, and it is the detection of these gamma rays that allow for approximate location of the radionuclide in the body.[152,127] Although there are a number of positron-emitting radioisotopes whose stable isotopes are commonly encountered in organic molecules (e.g. carbon, oxygen), fluorine has been identified as the most clinically relevant PET-radioisotope.[132] This is largely due to its favourable physical and nuclear characteristics; a short positron range which correlates to highest resolution PET images available, and a half-life of 110 minutes which allows for quick but manageable radiosynthesis.[152,127]

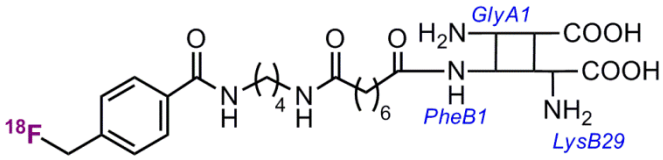
Examples of ^{18}F radiolabelled imaging agents are depicted in Figure 3.4. The radiolabelled glucose analogue [^{18}F]fluorodeoxyglucose ([^{18}F]-FDG, **137**) is the most commonly used PET agent for the detection of tumour cells. Exploiting the fact that cancerous cells show increased glucose metabolism compared to noncancerous cells, [^{18}F]-FDG is able to quickly enter the glycolysis pathway of tumours as an analogue of glucose, and the gradient build-up of radiolabelled [^{18}F]-FDG metabolites is observable by PET.[153] The amino acid derivative [^{18}F]-F-DOPA (**138**) was the first ^{18}F- radiolabelled substrate developed for investigations of Parkinson's disease and other movement disorders.[154] F-DOPA is a dopamine precursor that is clinically used to examine and follow dopaminergic pathways, where defects often occur in patients with movement or neurodegenerative disorders.[154,155] In the late 1980's, Shai and coworkers described the modification of insulin, a peptide hormone used to regulate sugar and fat metabolism, to incorporate a radiochemically fluorinated prosthetic group at the phenylalanine B1 amino acid site.[156] The same researchers subsequently reported that the binding of [^{18}F]-fluoroinsulin (**139**) to receptor cells was equal in affinity to native insulin, and utilized this probe to monitor insulin receptor-ligand interactions *in vivo* in rhesus monkeys.[157]



[18F]fluorodeoxyglucose
([18F]-FDG, 137)



3,4-dihydroxy-6-[18F]fluorophenylalanine
([18F]-FDOPA, 138)

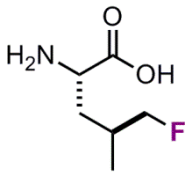


B1-[[[(4-[18F]fluoromethylbenzamido)butyl]amino]suberoyl]insulin
([18F]-fluoroinsulin, 139)

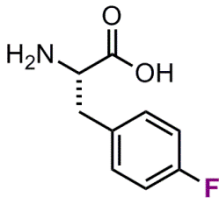
Figure 3.4. ^{18}F-radiolabelled PET imaging agents

3.1.3. ^{19}F NMR Spectroscopy

Due to the high natural abundance of the spin-active ^{19}F isotope, fluorine NMR spectroscopy has recently become an extremely useful probe for investigating the metabolism, binding, and structure of proteins and other biomolecules.[158] The sensitivity of ^{19}F for NMR spectroscopy observation is 83% that of ^{1}H NMR spectroscopy, and distinct coupling patterns and chemical shifts of fluorinated molecules allows for facile detection and characterization of the probe.[159] The fluorination of biomolecules can give insight to enzyme mechanism,[160] metabolic pathways,[158] and biomolecular interactions,[159] as the small changes in the physical and chemical environment of the molecule are detectable by ^{19}F NMR spectroscopy. Owing to these favourable properties, many fluorinated amino acids have been incorporated into biologically relevant molecules. One of the first synthetic fluoro- amino acids to be used as an ^{19}F NMR spectroscopy probe was (2*S*,4*S)*-5-fluoroleucine (**140**, Figure 3.5) which was incorporated into the enzyme dihydrofolate reductase from *Lactobacillus casei.*[161] ^{19}F NMR spectroscopy was also utilized to monitor the interactions of 4-fluorophenylalanine (**141**) in *Escherichia coli* and it was reported that 4-fluorophenylalanine was binding to a receptor previously described as being specific to *I*-leucine.[162]



5-fluoroleucine (140)



4-fluorophenylalanine (141)

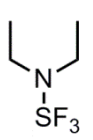
Figure 3.5. Fluorinated Amino Acids

3.2. Methods of C-F Bond Formation

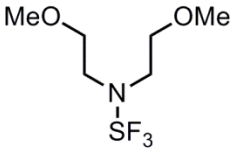
3.2.1. Nucleophilic F^- Sources

The simplest fluorinating agents are the alkali fluoride salts that provide a nucleophilic source of F^-; they include lithium, sodium, potassium, and cesium fluoride. However, due to the high electronegativity of fluorine and the tendency for fluoride to form hydrogen bonds and solvation shells, the inorganic fluorides decrease in nucleophilicity when dissolved in polar solvents.[163] Furthermore, owing to the relative basicity of F^-, oftentimes elimination reactions compete with direct displacement processes. Additionally, the poor solubility of the inorganic fluoride salts in nonpolar solvents has limited the use of these reagents.[163]

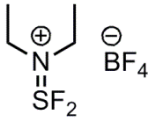
More versatile nucleophilic fluorinating agents include the sulfur fluorides shown in Figure 3.6, and (diethylamino)sulfur trifluoride (DAST, **142**) is one of the most common reagents used for nucleophilic displacement of a hydroxyl group with fluoride.[164] The proposed mechanism involves initial S_N2 attack of the hydroxyl oxygen onto sulfur, displacing fluoride, which in turn acts as a nucleophile in displacing a sulfoxide.[163,165] Disadvantages to the use of DAST include moisture sensitivity and explosions that may occur upon heating. Safer and more thermally stable analogues of DAST, with similar reactivities, were subsequently developed (Deoxofluor, **143**, and X-Tal Fluor, **144**, Figure 3.6).[163]



DAST (142)



Deoxo-Fluor (143)

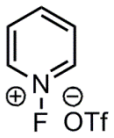


X-Tal Fluor (144)

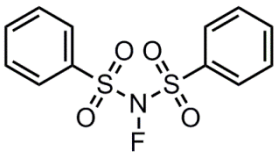
Figure 3.6. Nucleophilic Fluoride Sources

3.2.2. Electrophilic F^+ Sources

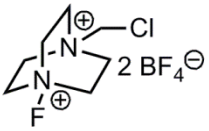
N-fluoropyridinium salts (e.g. **145**, Figure 3.7) were first developed in the 1980's as a source of electrophilic fluorine.[166] It was identified that substitution on the pyridine ring of **145** could dramatically alter the fluorinating potential, and a variety of substituted *N*-fluoropyridinium salts have been developed that are capable of reacting with carbon nucleophiles to form new carbon-fluorine bonds.[63] In 1984 Barnette disclosed the utility of *N*-fluorosulfonamides, prepared from the treatment of *N*-alkylsulfonamides with dilute F_2 gas. *N*-fluorobenzenesulfonimide (NFSI, (**146**), Figure 3.7) and related compounds were quickly developed and commercialized as effective, bench stable F^+ sources.[167] In 1992, Banks described the effective electrophilic fluorinating agent 1-chloromethyl-4-fluoro-1,4-diazonobicyclo[2.2.2]octane bis (tetrafluoroborate), (F-TEDA-BF_3, (**147**), Figure 3.7), which was commercialized by Air Products and Chemicals under the name Selectfluor®. Initial studies conducted by Banks showed that the incorporation of an electron withdrawing substituent on a nitrogen of the diazobicyclo[2.2.2]octane core was found to increase the oxidation potential of the F-TEDA complex.[168]



N-fluoropyridinium triflate (145)



NFSI (146)



Selectfluor® (147)

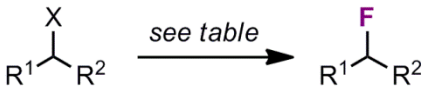
Figure 3.7. Electrophilic Fluorinating Agents

3.2.3. Decarboxylative Fluorinations

Substrates that incorporate a carboxylic acid or perester have been shown to undergo decarboxylative fluorinations; the first example of this transformation was reported in 1983 by Patrick who demonstrated that a combination of xenon difluoride

and hydrofluoric acid effected the decarboxylative fluorination of various alphatic and benzylic carboxylic acids.[169] Mallouk later described a photochemical fluorination in 1990 with a limited substrate scope.[170] This fluorination method was revisited and optimized in 2012 independently by Sammis[171,172] and Li,[173] utilizing more bench-stable fluorinating agents such as Selectfluor (**147**) and NFSI (**146**).

Table 3.1. Decarboxylative Fluorinations



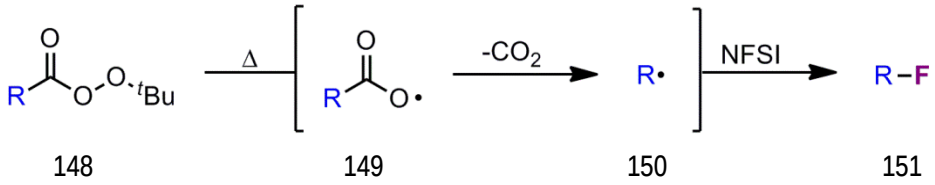
X	R^1	conditions	reference
-COOH	various	XeF_2, HF	Patrick 1983[169]
-COOH	$R^1 = R^2 = Ph$	TiO_2, hv, AgF	Mallouk 1990[169]
-COO^{t}Bu	various	NFSI, CH_3CN, reflux	Sammis 2012[171]
-COOH	-OPh or -Ph	Selectfluor, NaOH, hv	Sammis 2012[172]
-COOH	various	Selectfluor, $AgNO_3$, acetone, reflux	Li 2012[173]

As most previously known methods of carbon-fluorine bond formations involved either nucleophilic or electrophilic carbon atoms reacting with a complementary source of fluorine, Sammis, Paquin and Kennepohl were the first to report on the use of electrophilic fluorinating agents to effect the fluorination of alkyl radicals.[171] Using alkyl radicals formed via decarboxylative processes,[174] Sammis and coworkers proposed that commercially available and bench-stable electrophilic fluorinating agents could serve as fluorine transfer reagents. In addition to the analyses of reported mechanisms for these fluorinating agents,[175] DFT calculations of the bond dissociation energies of *N*-fluorobenzenesulfonimide (NFSI), *N*-fluoropyridinium triflate and Selectfluor were compared (Table 3.2), and it was proposed that the relatively low N-F bond dissociation energies of these agents (specifically, NFSI and Selectfluor) could allow for facile homolytic bond cleavage and facilitate fluorine atom transfer to alkyl radicals. Thus, due to its superior solubility in organic solvents, Sammis and coworkers initially used NFSI as a fluorine radical transfer agents,[171] It was subsequently demonstrated that Selectfluor was also suitable in this regard.[172,173]

Table 3.2. Bond Dissocation Energies of Electrophilic Fluorinating Agents

Electrophilic Fluorinating Agent	DFT-Calculated Bond Dissociation Energy (N-F, in CH_3CN)[171]
NFSI (146)	63.1 kcal/mol
N-fluoropyridinium triflate	75.1 kcal/mol
Selectfluor (147)	60.9 kcal/mol

The proposed mechanism for the peroxyester decarboxylative fluorination as described by Sammis is shown in Scheme 3.4.[171] Light or heat mediated decarboxylation of a peroxyester (e.g., **148**) leads to an alkyl radical (e.g., **150**) that subsequently reacts with a fluorine transfer agent to produce a new carbon-fluorine bond. The precise mechanistic details of how the fluorine transfer agent reacts with the alkyl radical are still under investigation.

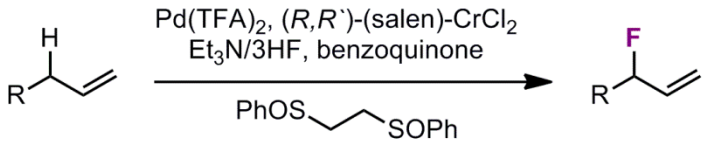


148 149 150 151

Scheme 3.1. Proposed Mechanism of Fluorodecarboxylation

3.2.4. *sp*^{2}-Adjacent C-H Fluorination

As carbon-hydrogen bonds adjacent to sp^2 hybridized carbons (i.e., allylic or benzylic positions) have a significantly lower bond-dissociation energy than that of alkyl C-H bonds (i.e., 101 kcal/mol for CH_3CH_2-H vs. ca. 90 kcal/mol for CH_2CHCH_2-H and $PhCH_2$-H),[176] they are considered activated and generally require a distinct set of conditions for functionalization. The first direct catalytic fluorination of allylic carbon-hydrogen bonds was reported in 2013 by Doyle and Braun (Scheme 3.2),[177] who used an electrophilic Pd^{II}-sulfoxide system originally developed by White[178] for C-H activation. This palladium-catalyzed fluorination relied on triethylamine trihydrogen fluoride as nucleophilic source of fluoride, and a high ratio of branched to linear regioisomers were formed in good yield.

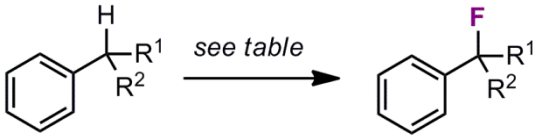


Doyle & Braun 2013[177]

Scheme 3.2. Direct Allylic Fluorination

The fluorination of benzylic carbon-hydrogen bonds has had a recent surge of interest, although the first report was almost twenty-five years ago. This early account by Mallouk and Wang was limited in scope to triphenylmethyl substrates, and yields ranged from 7% to 57% (Table 3.3).[170] In 2012, Lectka disclosed a polycomponent copper-catalyzed fluorination, however, once again the substrate scope was limited to ethylbenzene.[179] More recent accounts of benzylic fluorination are shown in Section 3.3.7.

Table 3.3. Benzylic Fluorination.



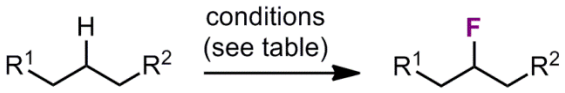
conditions	R	reference
TiO_2, AgF, CH_3CN, hv	$R^1 = R^2 = Ph$	Mallouk and Wang 1990[170]
$KB(C_6F_5)_4$, Selectfluor, Cu(I)I, *N*,*N*-(bisphenylmethylene)-1,2-ethanediamine, *N*-hydroxyphtalimide, KI, CH_3CN, reflux.	$R^1 = CH_3$ $R^2 = H$	Lectka 2012[179]

3.2.5. Unactivated C-(sp^3)-H Fluorination

The direct conversion of unactivated C-H bonds to C-F bonds is a desirable process, as oftentimes site-specific fluorination of unactivated carbons is desired. One of the first reports of this transformation appeared in 1976, when Kollonitsch and co-workers at Merck irradiated a combination of fluoroxytrifluoromethane and hydrofluoric acid to convert *d*-alanine into 3-fluoro-*d*-alanine (Table 3.4).[180] Similarly, Barton and coworkers reported the single-site fluorination of a steroid substrate uitlizing fluoroxytrifluoromethane.[181] Throughout the 1980's several reports by Rozen describe the use of fluorine gas to effect C-H fluorination on a range of aliphatic substrates,[182,183,184,185] and an electrophilic mechanism was proposed rather than the

radical mechanism that is known to occur with equivalent reactions of chlorine and bromine gas. A few decades later, Chambers compared the fluorinating abilities of fluorine gas, as reported by Rozen, with Selectfluor combined with heating, and the two methods gave comparable selectivities and yields.[186,187] Notably, in this work, Chambers proposed mechanism is in agreement with that posited by Rozen involving electrophilic fluorination. More recently, Groves reported a manganese porphoryin catalyzed aliphatic fluorination, and proposed a radical carbon-hydrogen abstraction by an oxomanganese(V) catalytic intermediate.[188] Additionally, Lectka's polycomponent copper-mediated conditions described previously (Table 3.3) are also capable of fluorinating unactivated carbon-hydrogen bonds.[179]

Table 3.4. Examples of C-H Fluorination



conditions	reference
HF/CF_3OF, hv	Kollonitsch and Barash 1976[180]
CF_3OF, NaF, nitrobenzene	Barton 1976[181]
F_2/N_2	Rozen 1980,[182] 1985,[183] 1987,[184] 1988[185]
Selectfluor, CH_3CN, reflux	Chambers 2000,[186] 2002[187]
Mn(TMP)Cl, TBAF-$3H_2O$, PhIO, AgF, 50 °C	Groves 2012[188]
$KB(C_6F_5)_4$, Selectfluor, CuI, *N*,*N*-(bisphenylmethylene)-1,2-ethanediamine, *N*-hydroxyphtalimide, KI, CH_3CN, reflux.	Lectka 2012[179]

Considering the scarcity of examples involving C-H fluorination, there remain many limitations that preclude the fluorination of carbon-hydrogen bonds. These include the use of harsh or non-bench stable chemicals (i.e., HF, F_2,), variety of metals or bimetallic reagent mixtures, or require prefunctionalization at the site where fluorination is desired (e.g., decarboxylative fluorination). Ideally, a process could be developed that incorporates the fluorine transfer capabilities of electrophilic fluorinating agents with a catalytic carbon radical formation reaction, ultimately providing a new method of C-H fluorination.

3.2.6. Alkyl Radicals from C-H Bonds: Decatungstate Photocatalysis

The utility of tungsten-based polyoxometalates as photocatalysts have been well-documented since the early 1980's.[189] Although initially employed for oxidative transformations,[190] the decatungstate ($W_{10}O_{32}^{4-}$) anion and salts thereof have received much attention as efficient hydrogen abstracting agents.[191] Specifically, the (tetra)tetrabutylammonium salt of decatungstate, known as TBADT (**152**, Figure 3.8), has been shown to photocatalytically abstract hydrogen atoms from various carbon-hydrogen bonds, yielding carbon centred radicals as intermediates. In the presence of an appropriate radical acceptor, new carbon-carbon bonds can be formed.[192]

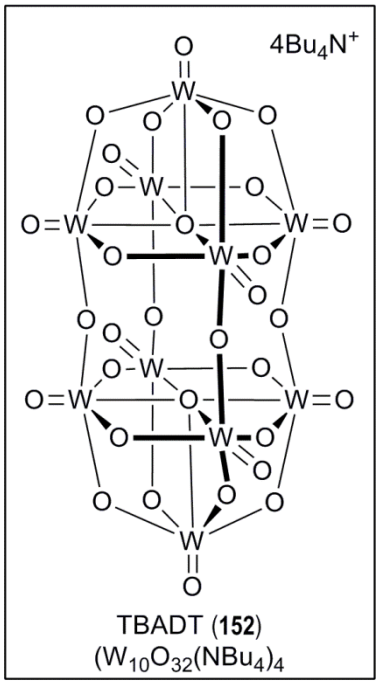
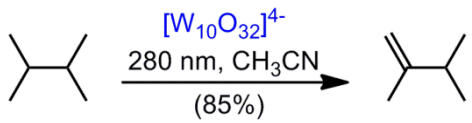
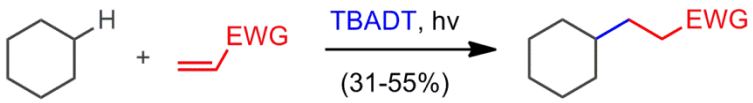
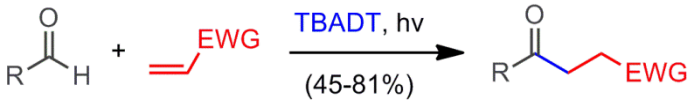
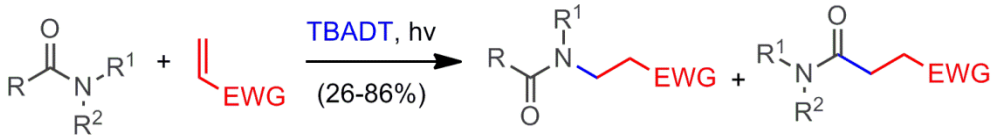
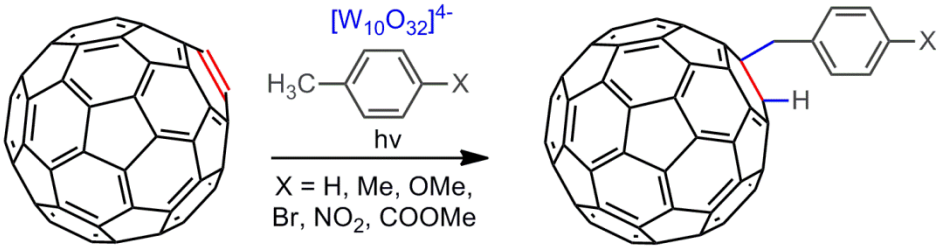


Figure 3.8. Structure of TBADT (152).

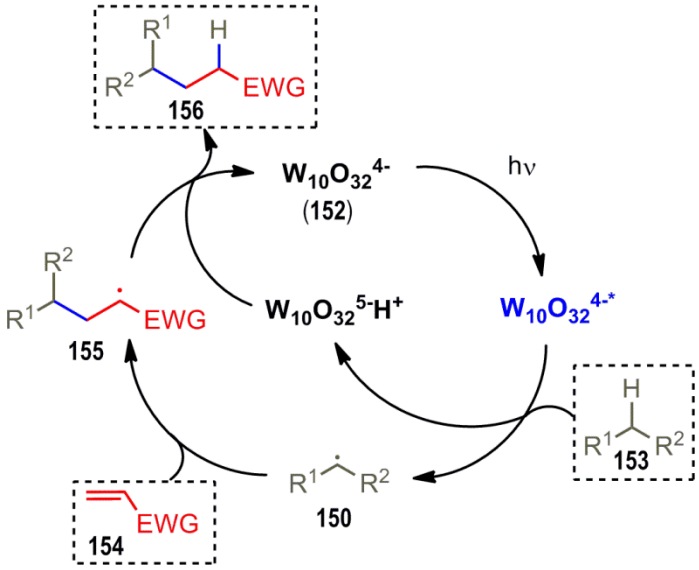
Some notable examples involving the use of decatungstate photocatalysis are shown in Table 3.5. Hill has made a number of advances in this area including the decatungstate-promoted dehydrogenation of 2,3-dimethylbutane that resulted in the formation of the less thermodynamically stable alkene.[190] Fagnoni and coworkers have extensively investigated the utility of TBADT in C-H functionalization reactions, and have demonstrated the TBADT-catalyzed hydrogen abstraction of alkyl, [193] aldehydic, [194] and

amide[195] substrates and subsequent reaction of the resulting radical with electron-poor alkenes. Recently, the functionalization of fullerenes has been disclosed via trapping of a benzylic radical, produced by decatungstate, with C_{60}.[196]

Table 3.5. Decatungstate Photocatalyzed Reactions.

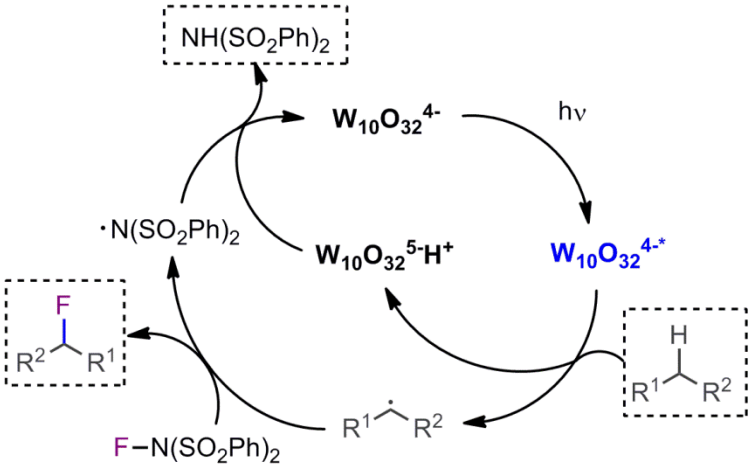
Reaction	Reference
	Hill 1990[197]
	Fagnoni 2006[193]
	Fagnoni 2007[194] 2010[198]
	Fagnoni 2008[195]
	Tzirakis 2008[196]

The proposed mechanism of the decatungstate photocatalyzed carbon-carbon bond formation is shown in Scheme 3.3.[194] As described above, photoexcited decatungstate is capable of abstracting hydrogen atoms from carbon-hydrogen bonds (e.g., **153**), producing a reduced decatungstate and alkyl radical. The carbon centred radical **150** can then react with a radical acceptor (e.g., **154**), yielding a new carbon-carbon bond and transferring the unpaired electron to the carbon nearest the electron withdrawing group (e.g., **155**). In the final step, decatungstate completes its catalytic cycle by returning the hydrogen atom back to the substrate (e.g., **156**).



Scheme 3.3. Mechanism of Decatungstate Photocatalyzed Carbon-Carbon Bond Formation.

Considering the above, it was envisioned that exploiting the hydrogen abstracting capabilities of TBADT, coupled with the fluorine transfer potential of electrophlilic fluorinating reagents,[171] a photocatalyzed C-H fluorination could be accomplished. A proposed mechanism for this novel transformation is depicted in Scheme 3.4 and forms the basis for the research discussed in this chapter.



Scheme 3.4. Proposed Mechanism for TBADT-Photocatalyzed C-F Bond Formation

3.3. Results: Fluorination of Unactivated C-H Bonds[f]

In line with the ultimate objectives discussed above, it was crucial to identify a light source that would selectively excite the TBADT catalyst but not the fluorinating agent NFSI. UV-Vis absorbance spectra were acquired for TBADT and NFSI and are shown in Appendix A. As NFSI is not excited by UV light above ~250 nm, a lamp with emission range of 300-400 nm would be suitable for selectively activating TBADT in the presence of NFSI. Specifically, a UVB-black light blue lamp, centred around 365 nm, was utilized in all experiments. The emission spectrum for the lamp is shown in Appendix A.

3.3.1. Aliphatic and Benzylic Fluorinations

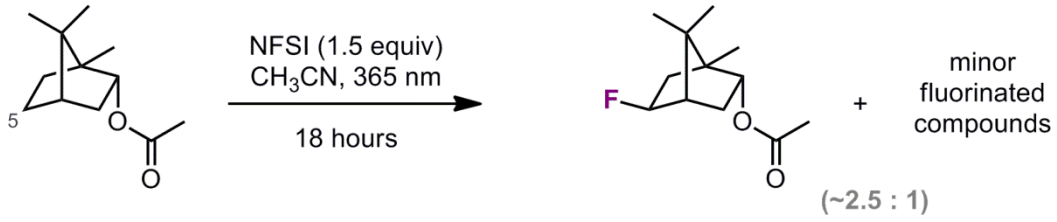
The fluorination of aliphatic substrates was initiated and optimized using bornyl acetate (**157**, Table 3.6) as a model substrate. Although bornyl acetate contains 16 unique and unactivated c-(sp^3)-H bonds, all fluorination attempts utilizing bornyl acetate (**157**) gave one major fluorinated compound, 5-*exo*-fluorobornyl acetate (**158**), in addition to several minor compounds, in a 2.5:1 ratio (5-fluoro:minor). Characterization data for 5-*exo*-fluorobornyl acetate (**158**) was in complete agreement with that previously reported for the same compound.[188]

Optimization efforts for the fluorination of bornyl acetate are shown in Table 3.6. When the catalyst loading of the TBADT catalyst was evaluated it was found that 2 mol% was optimal (entries 1-3). Additionally, no reaction occurred in the absence of the TBADT catalyst (entry 4). Increasing the overall concentration of the reaction from 0.2 M to 1 M increased the yield from 32% to 43%, and further increasing the concentration to 2 M had a slight further increase on the overall yield (43% to 46%, entries 5-6). Finally, since small amounts of hydrofluoric acid could be forming in these reactions via

[f] Note on Results: S.D.H. was the primary researcher in the Britton lab conducting C-H fluorination experiments. To assist with optimization, other students (Hope Fan and Stanley Chang) supported the development of this methodology. Reactions that were not solely performed by S.D.H. are annotated as such in the corresponding Results table.

elimination processes, we evaluated the addition of various inorganic bases (entries 7-9), in efforts to consume any coincident hydrofluoric acid. Optimally, the addition of substoichiometric amounts of base, specifically 10% $NaHCO_3$, led to an overall yield of 59%. Irradiation of the reaction mixture for longer than 18 hours did not result in improved conversion (not shown). When reactions were monitored by ^1H NMR spectroscopy it was found that >90% of the NFSI is consumed within 18 hours and that TBADT also catalyzed the gradual decomposition of NFSI. This was further confirmed by control reactions containing only NFSI and TBADT, whereafter 18 hours of irradiation ~20% of the NFSI had been degraded to dibenzenesulfonimide (not shown). Irradiation of a solution of NFSI without TBADT did not result in degradation.

Table 3.6. Fluorination of Bornyl Acetate.



157 158

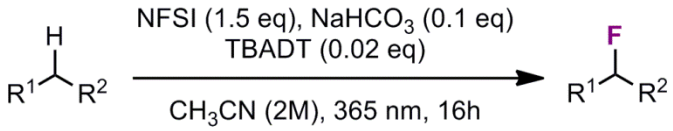
entry	TBADT (mol %)	[reaction] (M)	additive (0.1 equiv)	yield (%)[a,b]
1	2	0.2	none	32
2	1	0.2	none	12
3	5	0.2	none	25
4	0	0.2	none	0
5	2	1.0	none	43
6	2	2.0	none	46
7	2	2.0	K_2CO_3	55
8	2	2.0	Na_2CO_3	52
9	2	2.0	$NaHCO_3$	59

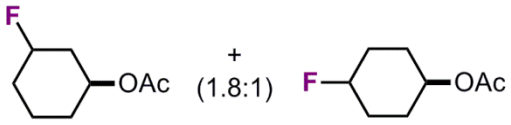
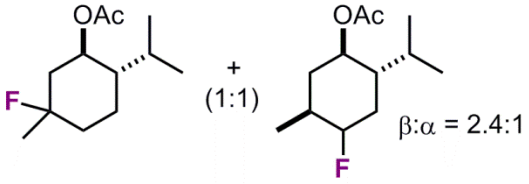
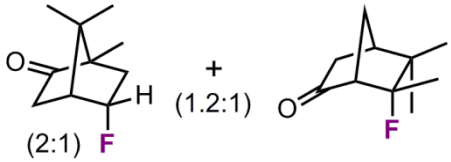
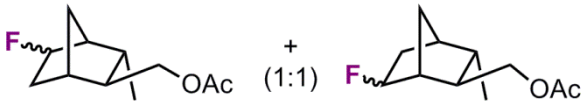
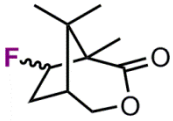
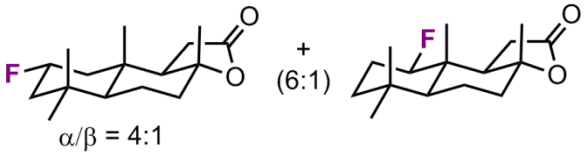
[a.] combined isolated yield of fluorinated products. [b.] initial experiment conducted by S.D.H., optimization completed by H.F.

Employing the conditions that were optimized for the fluorination of bornyl acetate (Table 3.6, entry 9), a variety of functionalized cycloalkanes were fluorinated with reasonable conversion (Table 3.7). These fluorinations were generally selective for the most sterically accessible sites that are also remote from electron withdrawing groups. In addition, no difluorinated products were observed in any of these reactions. Fluorination of cyclohexyl acetate (Table 3.7, entry 1) led to a statistical mixture of two fluorinated regioisomers at the methylenes most remote from the acetoxy function (**159** and **160**). Subjecting menthyl acetate to the fluorination conditions (entry 2) resulted in two fluorinated compounds (**161** and **162**) that were produced in a 1:1 ratio. The products formed in this latter reaction provides further information about the selectivity of this fluorination protocol, as fluorination occurred predominantly at two positions: (i) the branched position on the cyclohexyl ring, which indicates the formation of a stable 3° radical intermediate, and (ii) the CH_2 most remote from the electron-withdrawing acetoxy function and the bulky *tert*-butyl group (entry 2). Structural assignment of fluorination product **161** was confirmed by analysis of the NMR spectral data acquired on this material. Specifically, no fluoromethine resonances were observed in the ^{1}H NMR spectrum, and the presence of a doublet (3H, $^3J_{H\text{-}F}$ = 21.1 Hz) at δ 1.35 ppm was consistent with known values for $^3J_{H\text{-}F}$ coupling.[199] This resonance was assigned to the protons on the methyl group attached to the cyclohexane ring. The assignment of α-**162** and β-**162** was based on the presence of distinct fluoromethine resonances ($^2J_{HF}$ ~ 50 Hz) and analysis of $^3J_{H\text{-}H}$ coupling constants in the ^{1}H NMR spectrum (see Scheme 3.5). Specifically, the ^{1}H NMR spectra of the α-anomer assigned to **162** showed a fluoromethine resonance at δ 4.11 ppm ($^2J_{HF}$ = 48.7 Hz, $^3J_{HH}$ = 11.4, 2.6 Hz), with a large $^3J_{H\text{-}H}$ coupling constant indicating a 1,2-diaxial relationship between the fluoromethine hydrogen and its coupling partner. Similarly, the **162** β-anomer was assigned based on the observation of a fluoromethine resonance at δ 4.66 ppm ($^2J_{HF}$ = 49.8 Hz, no other coupling observed). Furthermore, the lack of any $^3J_{HH}$ coupling suggested an equatorial conformation on the cyclohexane ring for the fluoromethine proton. Fluorination of camphor (entry 3) yielded 5-fluorocamphor (**163**) (2:1 ratio of β:α isomers) in addition to the rearranged fluoroisocamphonone (**164**). A possible mechanistic rational for the formation of this latter compound is discussed in Section **3.3.6**. The relative configuration of the fluoromethine in 5-fluorocamphor (**163**) was determined by NOESY experiments (Scheme 3.5). Fluorination of another bicyclic compound (entry 4)

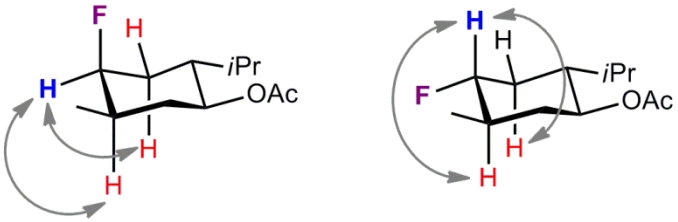
produced a 1:1 mixture of regioisomers (**165** and **166**), with fluorination occurring at the two methines most remote from the acetoxy group. The fluorination of a lactone (entry 6) produced one fluorinated product as a single stereoisomer (**167**), although the relative configuration of the fluoromethine could not be determined. Subjecting the natural product sclareolide to the optimized fluorination conditions resulted in a 6:1 ratio of two fluorinated regioisomers (**168** and **169**) in 68% combined yield, with a 4:1 mixture of α:β isomers at the major site of fluorination. The selectivity demonstrated here for C-H fluorination of sclareolide is comparable to previous reports.[188]

Table 3.7. Fluorination of Cyclic Substrates.



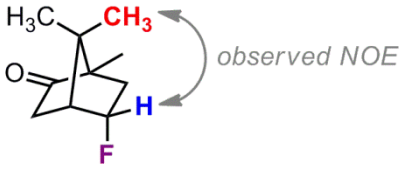
entry	Product	Conversion[a] (Yield)
1	 159 + (1.8:1) 160	50% (49%)[b,e]
2	 161 + (1:1) 162, β:α = 2.4:1	47% (28%)[c,d]
3	 163 (2:1) + (1.2:1) 164	48% (31%)[b,d]
4	 165 + (1:1) 166	53% (40%)[c,e]
5	 167	30% (14%)[c,e]
6	 α/β = 4:1 168 + (6:1) 169	N.D. (68%)[c,d]

[a.] based on integration of resonances (starting material & product) in the crude ^{1}H NMR spectrum. [b.] combined yield calculated based on integration of resonances using internal standard (1,3,5-(tris)trifluoromethylbenzene) in crude ^{19}F NMR spectrum. [c.] combined isolated yield. [d.] initial reactions & characterization conducted by S.D.H and optimized by H.F/S.C. [e.] Reactions & optimization conducted by H.F/S.C., characterization conducted by H.F/S.D.H.



β-162
small $^{3}J_{Heq\text{-}Hax}$ coupling
(assigned as β-fluoro)

α-162
large $^{3}J_{Hax\text{-}Hax}$ coupling
(assigned as α-fluoro)

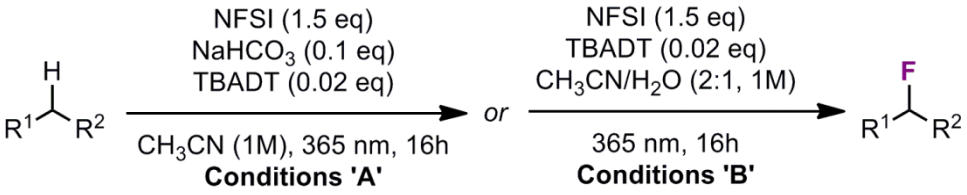


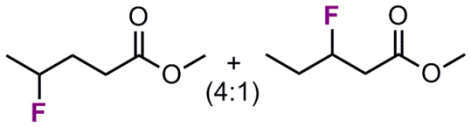
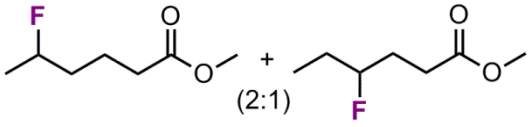
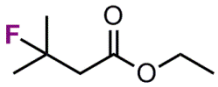
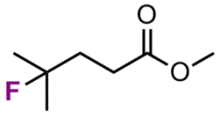
163

Scheme 3.5. Stereochemical Assignment of New Compounds.

The fluorination of aliphatic esters was also investigated, in order to assess the influence of substitution and proximity to the electron withdrawing carbonyl function on selectivity. As depicted in (Table 3.8), the conversion of the aliphatic esters to the corresponding fluoroesters proceeded with reasonable yield. In most cases the yield was necessarily calculated based on analysis of ^{1}H NMR spectra following the addition of an internal standard to the crude reaction mixture, due to the volatility of the products. Comparison of the five and six carbon chain esters (entries 1 and 2) demonstrated that increasing the chain length led to a decrease in selectivity. Additionally, in the case of methyl-branched aliphatic esters, the fluorination was selective for the branched position, although the standard conditions described above led to suboptimal yields (conditions A, entries 3-4, 28% and 31%). Notably, employing water as an additive (in place of $NaHCO_3$) led to an increase in yield for both branched substrates **174** and **175** (conditions B, entries 3-4, 45% and 40%). As observed with the cyclic aliphatic substrates, fluorination occurred at positions remote from the carbonyl, and complement the standard fluorination reactions of esters, which occur exclusively at the α-position via the intermediacy of enolates.

Table 3.8. Aliphatic Ester Fluorination



entry	product	conditions	conversion[a] (yield)[b]
1	 170 + (4:1) 171	A	70% (42%)
2	 172 + (2:1) 173	A	51% (50%)
3	 174	A	60% (31%)
		B	75% (45%)[c]
4	 175	A	33% (28%)
		B	49% (40%)[c]

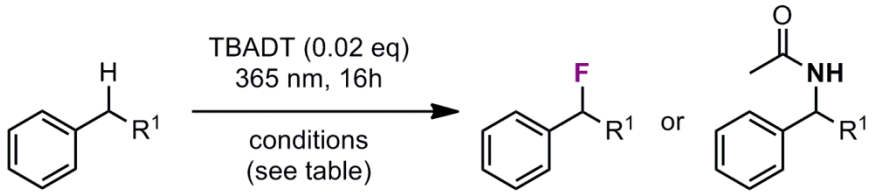
[a.] based on integration of resonances (starting material & product) in the crude ^{1}H NMR spectrum. [b.] combined yield calculated based on integration of resonances using internal standard (1,3,5-(tris)trifluoromethylbenzene) in crude ^{19}F NMR spectrum. [c.] combined yield of fluorinated ester and acid (hydrolysis product).

3.3.2. Benzylic and Allylic Fluorinations

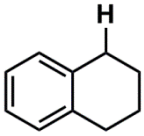
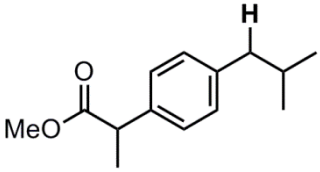
Benzylic fluorination was also explored using tetrahydronapthalene and ibuprofen methyl ester as substrates. Use of the methyl ester of ibuprofen was necessary as decarboxylative fluorination was observed with the parent carboxylic acid, and has been reported by Sammis[172] and Li.[173] Employing the optimized conditions (Table 3.6, entry 9) on tetrahydronapthalene (Table 3.9, entries 1-2) resulted in the formation of a variety of undesired byproducts, including benzylic oxidation to the alcohol or ketone (not shown), and formation of an acetamide (e.g., **177**). The formation of acetamides from

the reaction of an alkylnitrile and carbocation has been well documented and was first reported by Ritter in 1948.[200] In our case, it was reasoned that the benzylic carbocation could be arising from either (i) S_N1 reaction from an initially formed benzylic carbon-fluorine bond, or (ii) oxidation of the carbon-centred radical to carbocation by NFSI (see Section **3.3.6**). Although no fluorinated product was observed in the reaction of tetrahydronapthylenene with NFSI and TBADT (entries 1-2), subjection of ibuprofen methyl ester to these conditions produced a 1:1 mixture of acetamide (**177**) and fluorinated product (**176**), with fluorination occurring at the least hindered benzylic position (entry 3). Examining several variations to the reaction conditions (e.g., concentration, amount of NFSI or additive), indicated that increasing the equivalents of NFSI had the most positive effect on conversion (i.e., entries 4-5). As described in entry 8, using two equivalents of NFSI and a reaction concentration of 1M, near quantitative fluorination of ibuprofen methyl ester was achieved, with a single fluorinated product isolated in 84% yield. Importantly, reactions performed in the absence of light (entry 9) gave no product and starting material was completely recovered. Building on these initial results, the fluorination of a wide range of benzylic substrates has recently been accomplished in the Britton lab.

Table 3.9. Benzylic Fluorinations



176 177

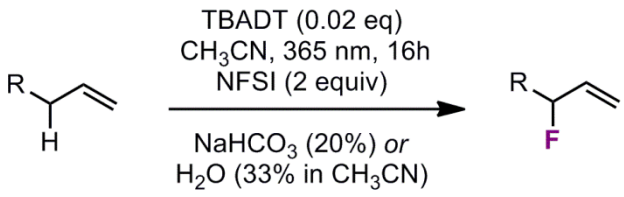
entry	substrate	$NaHCO_3$ (equiv.)	NFSI (equiv.)	solvent (M)	result (conversion,[a] yield)
1	 tetrahydronapthalene	0	1.2	CH_3CN (0.2 M)	177 (N.D., 58%[b])
2		0.1	1.2	CH_3CN (2 M)	177 (61%, N.D)
3	 ibuprofen methyl ester	0	1.2	CH_3CN (0.4 M)	176/177(1:1) (60%, N.D)
4		0.1	1.2	CH_3CN (1 M)	176 (65%, N.D)
5		0.1	2	CH_3CN (2 M)	176 (80%, N.D)
6		0.1	2	CH_3CN (1 M)	176 (90%, N.D)
7		1.0	2	CH_3CN (1 M)	176 (95%, 61%[c])
8		0	2	CH_3CN/H_2O (2:1, 1 M)	176 (100%, 84%[b])
9[d]		0	1.2	CH_3CN (0.2 M)	(0%, N.D.)

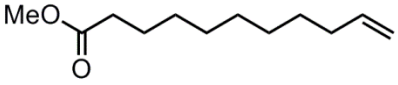
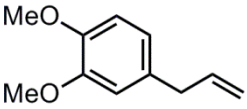
[a.] based on integration of resonances (starting material & product) in the crude ^1H NMR spectrum [b.] isolated yield. [c.] yield calculated based on integration of resonances using internal standard (1,3,5-(tris)trifluoromethylbenzene) in crude ^{19}F NMR spectrum. [d.] no irradiation

With the ability to successfully fluorinate benzylic C-H bonds demonstrated, it was posited that allylic C-H bonds, which possess similar bond dissociation energies to benzylic C-H bonds,[176] could also be fluorinated via the same method. Initial efforts to fluorinate various allylic substrates are described in Table 3.10, using the two unique sets of conditions that provided the highest conversion in benzylic fluorinations (entries 7 and 8, Table 3.9).

Unfortunately, subjecting undecene (**178**) and methyl undec-10-enoate (**179**) to either of the fluorination conditions depicted in Table 3.10 resulted in mostly recovered starting material, along with a small amount of a product that decomposed rapidly during workup (entries 1-2). Analysis of the crude ^{1}H NMR spectra from these reactions indicated that the product did not match characterization data for either the branched or linear allylic fluorides. Furthermore, the lack of a distinct fluoromethine doublet in the ^{1}H NMR spectrum ($^{2}J_{F\text{-}H}$ = 45-55 Hz), or identifiable resonances in the ^{19}F NMR spectrum, indicated that fluorination had not occurred at any other site on the substrate (See A3, Appendix A). Additionally, 4-allyl-1,2-dimethoxybenzene (**180**), which contains an allylic hydrogen that is also in a benzylic position, did not fluorinate under these conditions (entry 3). As no identifiable fluorinated compounds were obtained with allylic substrates, attempts to adapt the C-H fluorination method to allylic C-H bonds was abandoned.

Table 3.10. Allylic Fluorinations



entry	substrate	result[a]
1	 178	recovered starting material and unidentified product (see text)
2	 179	recovered starting material and unidentified product
3	 180	N.R.

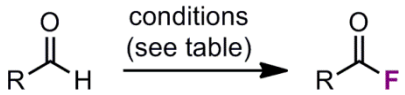
[a] based on integration of resonances in the crude ^{1}H and ^{19}F NMR spectrum. N.R. = no reaction.

3.3.3. Aldehydic Fluorination

Acyl Fluorides from Aldehydes: Previous Work

The direct conversion of aldehydes to acyl fluorides is limited to few known accounts, the first of which was reported in 1989 by Stavber using cesium fluoroxysulfate (Table 3.11).[201,202] In 1994, Yoneda disclosed an electrochemical fluorination of several aliphatic aldehydes using HF-base solutions.[203] Banks and coworkers, who are credited with the invention of the electrophiic fluorinating agent Selectfluor,[168] utilized their reagent with heating to effect the conversion of *p*-chlorobenzaldehyde to *p*-chlorobenzoyl fluoride.[204] Chambers described the fluorine gas promoted fluorination of heptanal in 2006.[205] Lastly, an aryl(difluoro)-λ^3-bromane reagent that was capable of converting primary aliphatic aldehydes into the corresponding acyl fluorides was reported by Ochiai in 2011.[206]

Table 3.11. Acyl Fluorides from Aldeydes.

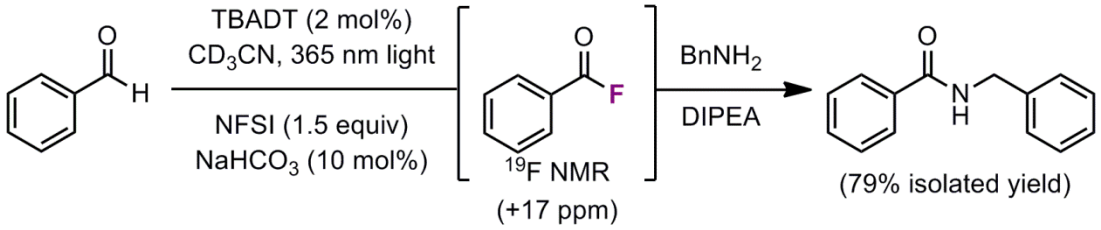


conditions	R	reference
$CsSO_4F$, CH_3CN, 35 °C	aryl, alkyl	Stavber 1989[201]
Et_3N-5HF, CH_3CN/electrolysis (20 F/mol)	alkyl	Yoneda 1994[203]
Selectfluor, CH_3CN, reflux	*p*-ClC_6H_4	Banks 1994[204]
F_2/N_2, CH_3CN, 0 °C	C_6H_{13}	Chambers 2006[205]
p-trifluoromethylphenyl(difluoro)- λ^3-bromane CH_2Cl_2, 0°C	alkyl	Ochiai 2011[206]

Acyl Fluorides from Aldehydes: Results

As TBADT has been shown to selectively abstract aldehydic hydrogens to yield acyl radicals,[194] it was hypothesized that the reaction of NFSI with the resulting acyl radical could give rise to acyl fluorides. Subjecting benzaldehyde (**181**) to the optimized reaction conditions (Table 3.6, entry 9) showed clean conversion to the acyl fluoride **182** after 18 hours as observed by ^{19}F NMR spectroscopy (Scheme 3.6). The crude reaction

mixture containing benzoyl fluoride (**182**) in acetonitrile-d_3 was reacted directly with benzylamine, in order to isolate the bench-stable amide **183**. Following this protocol, *N*-benzylbenzamide (**183**) was isolated in 79% yield, indicating relatively high conversion of benzaldehyde to benzoyl fluoride. Although this is not the first report of direct conversion of an aldehyde to an acyl fluoride, this is one of the first methods that employ bench-stable and commercially available reagents, allowing for general and widespread use.



Scheme 3.6. Fluorination of Benzaldehyde

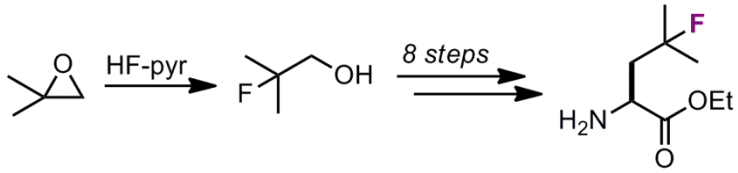
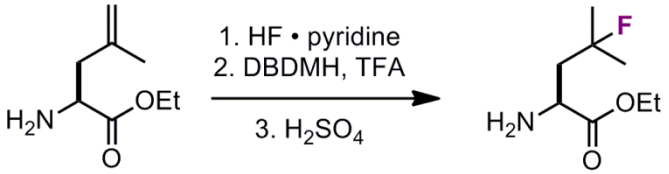
3.3.4. Fluorination of Amino Acids

Synthesis of Fluorinated Amino Acids: Previous Work

The fluorination of the canonical amino acids has been shown to adjust the physical, chemical, and biological properties of these molecules.[207] Carbon-hydrogen to carbon-fluorine modifications that lead to changes in hydrophobicity, acidity, stability and conformation can vary greatly depending on the substrate, and the consequent change in properties is not always predictable. Despite this fact, a large amount of effort has been devoted to the fluorination of amino acids and the study of the physical properties of these molecules. As described in Section 3.1.3, fluorinated amino acids and peptides have found increased used as mechanistic probes, biological tracers, pharmaceuticals, and enzyme inhibitors.[207]

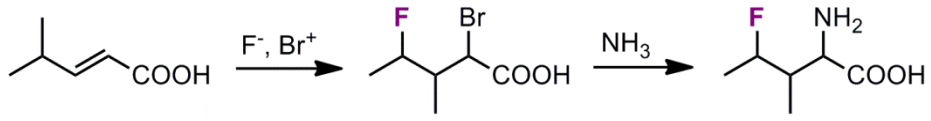
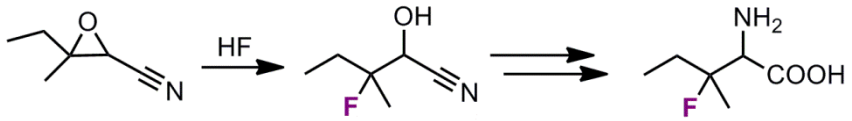
The synthesis of fluorinated amino acids is a broad and well-documented area of research, with many comprehensive reviews on this topic.[208,207] Thus, only the synthesis of fluorinated amino acids relevant to the research described in this section will be introduced. With the discovery of Odanacatib (**136**, Figure 3.3), a facile synthesis of γ-fluoroleucine was required. Towards this goal, in 2005 Merck & Co. disclosed their first

synthesis of γ-fluoroleucine (**184**), which required 9 steps and utilized a chemoenzymatic reaction to establish the required absolute stereochemistry.[209] The key carbon-fluorine bond formation was accomplished via nucleophilic fluoride attack onto an appropriately functionalized epoxide **185**, to yield the 1,2-fluorohydrin **186** that was converted into fluoroleucine ethyl ester (**184**) following further transformations (Scheme 3.7). Eight years later, Merck revealed a shorter, 3-step synthesis of γ-fluoroleucine ethyl ester (**184**), employing a chiral phase-transfer catalyst to provide the desired enantiomer, and a fluorination of terminal alkene **187** to construct the required tertiary alkyl fluoride.[210]

Reaction	Reference
 185 186 γ-fluoroleucine ethyl ester (184)	Merck 2005[209]
 187 γ-fluoroleucine ethyl ester (184)	Merck 2013[210]

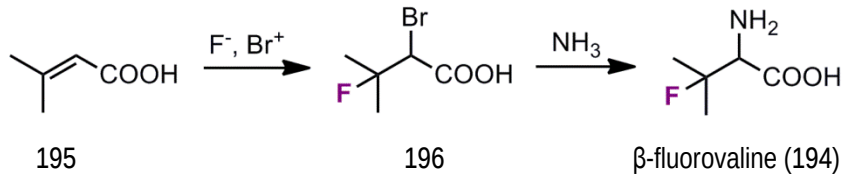
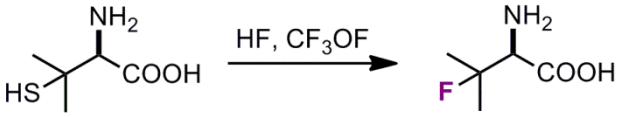
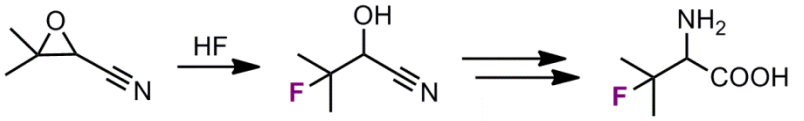
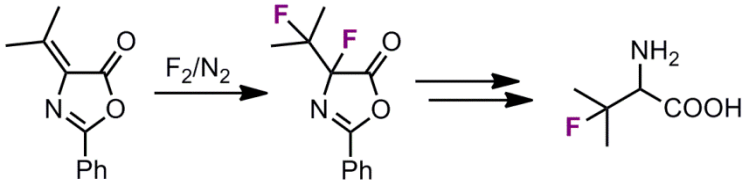
Scheme 3.7. Merck γ-Fluoroleucine Syntheses

The first synthesis of γ-fluoroisoleucine (**188**) was an efficient 2-step protocol reported by Gershon and coworkers in 1978.[211] Starting with 4-methyl-2-pentenoic acid (**189**, Scheme 3.8), hydrogen fluoride and *n*-bromoacetamide were used to produce the rearranged bromo-fluoroacid **190**. Lastly, ammonolysis of the carbon-bromide bond produced racemic γ-fluoroisoleucine (**188**) as a single isomer, although the relative configuration was not determined. A method to construct β-fluorinated α-amino acids was developed by Ayi and coworkers in the early 1980`s.[212] Beginning with nitrile **191**, HF-mediated ring opening gave the tertiary alkyl fluoride **192**. Further functional group interconversions were required to convert β-hydroxynitrile **192** into β-fluoroisoleucine (**193**).

Reaction	Reference
 189 190 γ-fluoroisoleucine (188)	Gershon 1978[211]
 191 192 β-fluoroisoleucine (193)	Ayi 1980[212]

Scheme 3.8. Synthesis of β- and γ-fluoroisoleucine

Strategies for the synthesis of β-fluorovaline (**194**) include similar methods to those described for isoleucine, including the two-step protocol developed by Gershon[213] and epoxynirile derivitization reported by Ayi (Scheme 3.9).[212] Additionally, Kollonitsch and coworkers at Merck in 1976 utilized the nucleophilic displacement of sulfur by fluoride in a one-step β-fluorovaline synthesis.[214] Finally, a 1995 report by Kaneko described the addition of fluorine gas to functionalized alkene **200**, the product of which was then further modified to yield β-fluorovaline (**194**).[215]

Reaction	Reference
 195 196 β-fluorovaline (194)	Gershon 1973[213]
 197 β-fluorovaline (194)	Kollonitsch 1976[214]
 198 199 β-fluorovaline (194)	Ayi 1980[212]
 200 201 β-fluorovaline (194)	Kaneko 1995[215]

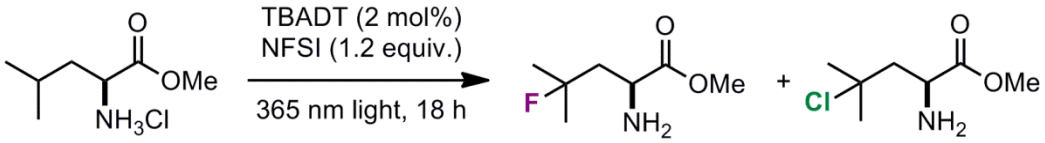
Scheme 3.9. Syntheses of β-fluorovaline

Synthesis of Fluorinated Amino Acids: Results

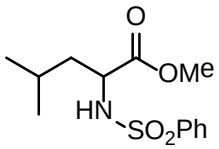
The fluorination of amino acids was explored using our previously employed conditions with leucine as an initial substrate (Table 3.12). The methyl ester of *l*-leucine was utilized, as 4-fluoroleucine is known to engage in defluorolactonization reactions.[209] As indicated in entry 1, reaction of *l*-leucine methyl ester (**202**) with TBADT and NFSI did not lead to any fluorinated product, and instead resulted in nearly quantitative conversion to an *N*-functionalized compound, presumably resulting from reaction of NFSI with the nucleophilic primary amine function of leucine. Analysis of the spectroscopic data collected from this product led to proposed structure **204**, indicating that the basic amine function in leucine methyl ester had engaged in nucleophilic attack onto the sulfur atom of NFSI.[216] Considering this unexpected result, all further reactions were carried out using *l*-leucine methyl ester hydrochloride salt, which proved to be a suitable substrate for fluorination. As detailed in entries 2-3, using 100% acetonitrile as solvent for the

fluorination reaction resulted in a considerable amount of chloroleucine (**203**), in addition to the desired fluorinated product **184**. A proposed mechanism explaining the formation of chloroleucine is discussed in Scheme 3.10 (Section **3.3.6**). Observing that the addition of a small amount of water aided in the solubility of the hydrochloride salt in acetonitrile, this slight adjustment was found to suppress the formation of the chlorinated byproduct (entry 4), and using solvent mixtures varying from 2:1 to 4:1 acetonitrile:water resulted in complete elimination of this undesired product (entries 5-6). Optimally, a 2:1 acetonitrile:water solvent mixture and an overall reaction concentration of 0.2M resulted in the complete consumption of starting material and 83% yield of 4-fluoroleucine methyl ester (entry 7). Attempts to purify and isolate 4-fluoroleucine methyl ester (**184**) led to a significant loss in yield due to the high aqueous solubility of the fluorinated product. Additionally, hydrolysis of the ester to the acid, which occurs at low (<2) or high (>10) pH and on column chromatography, is followed rapidly by lactonization via fluoride displacement.[209] Despite the suboptimal results with respect to purification and isolation, the one-step protocol for conversion of leucine to 4-fluoroleucine is the most efficient synthesis of fluoroleucine to date. The enantiomeric excess of the product resulting from the fluorination of *l*-leucine ethyl ester hydrochloride salt was 95%. The *ee* was determined by chiral GC (Cyclodex B) using the fluorination product of *dl*-leucine ethyl ester hydrochloride salt as a racemic standard.

Table 3.12. Optimization of the Fluorination of *l*-Leucine



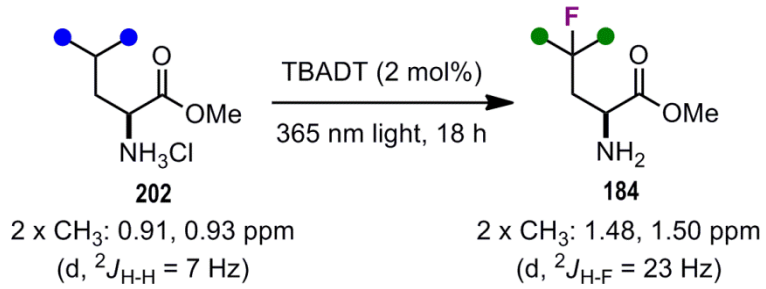
202 184 203

entry	substrate	solvent (M)	result (conversion,[a] yield[b])
1	*l*--leucine methyl ester	CH_3CN (0.3 M)	 204
2	*l*--leucine methyl ester HCl salt	CH_3CN (2 M)	184: 203 = 1:2 (55%, N.D.)
3	*l*--leucine methyl ester HCl salt	CH_3CN (0.2 M)	184: 203 = 4:5 (78%, N.D.)
4	*l*--leucine methyl ester HCl salt	CH_3CN/H_2O (12:1, 0.06 M)	184: 203 = 7:1 (90%, N.D.)
5	*l*--leucine methyl ester HCl salt	CH_3CN/H_2O (4:1, 0.06 M)	184 (>95%, N.D.)
6	*l*--leucine methyl ester HCl salt	CH_3CN/H_2O (2:1, 0.68 M)	184 (87%, N.D.)
7	*l*--leucine methyl ester HCl salt	CH_3CN/H_2O (2:1, 0.2 M)	184 (97%, 83%)

[a.] combined for both products based on integration of signals (starting material & product) in the crude ^1H NMR spectrum. [b.] yield calculated based on integration of signals using internal standard (1,3,5-(tris)trifluoromethylbenzene) in crude ^1H or ^{19}F NMR spectrum. N.D. = no data.

The fluorination of *l*-leucine methyl ester could also be monitored directly by ^1H NMR spectroscopy when the reaction was repeated in a standard sample tube using CD_3CN/D_2O as solvent. As depicted in Figure 3.9, clean conversion of leucine methyl ester to 4-fluoroleucine methyl ester occurred over an 18 hour period. The chemical shift and coupling constant corresponding to the hydrogens on the two CH_3 groups bound to the tertiary carbon of leucine show a significant change in chemical shift and coupling constants due to the presence of the fluorine atom. Specifically, the protons on the two methyl groups in the starting material resonate at 0.91 and 0.93 ppm (blue dots),

and appear as doublets ($^3J_{H\text{-}H}$ = 7 Hz). The protons corresponding to the methyl groups in 4-fluoroleucine resonate at 1.48 and 1.50 ppm (green dots), and are split by the vicinal fluorine atom with a distinct and relatively large coupling constant ($^3J_{H\text{-}F}$ = 23 Hz). Furthermore, quantitative conversion of NFSI (pink dots) to the reduced dibenzenesulfonimide is indicated in the aromatic region of the ^{1}H spectra.



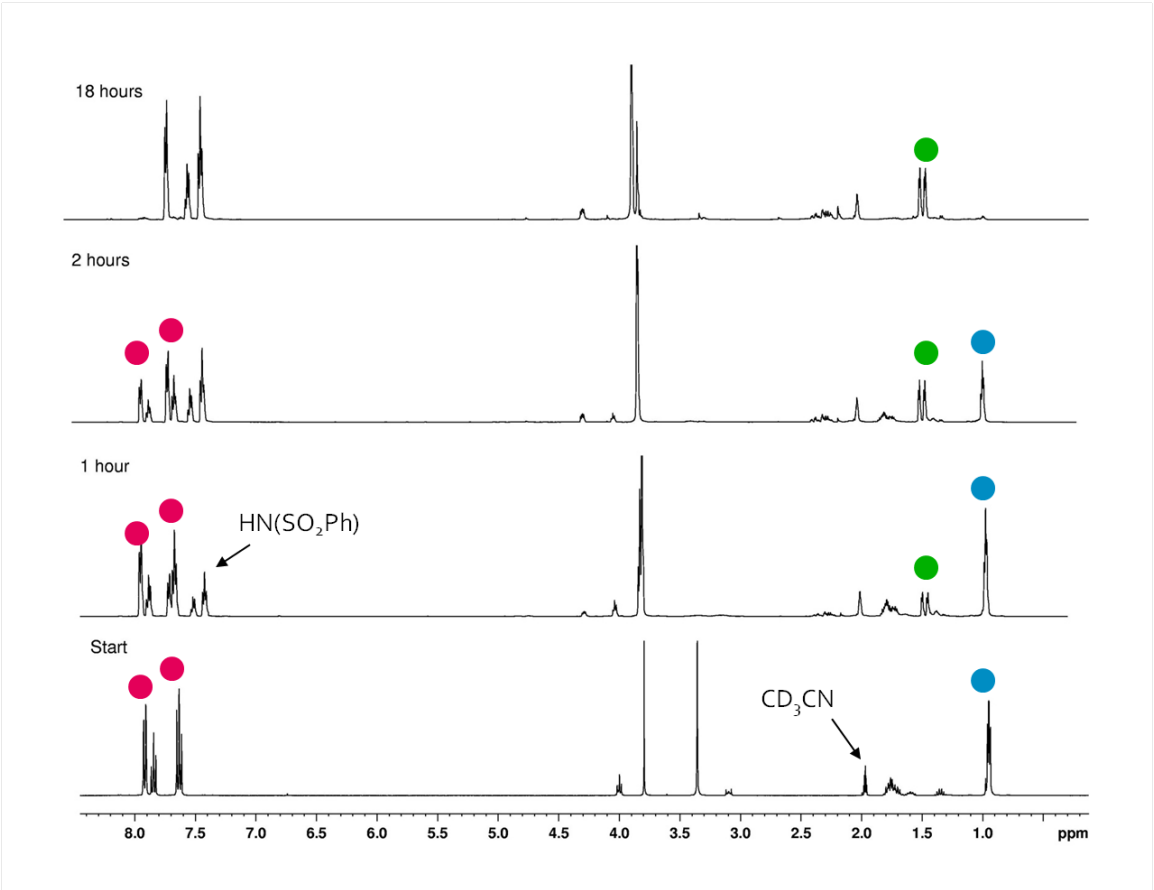
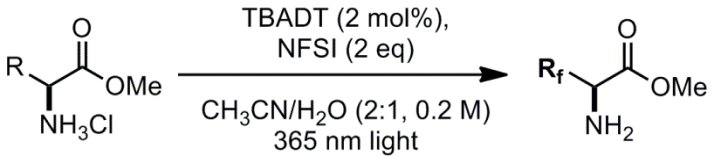


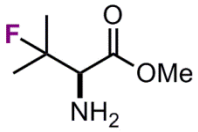
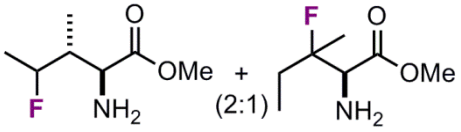
Figure 3.9. ^{1}H NMR spectra (CD_3CN, 500 MHz) monitoring the fluorination of *l*-leucine methyl ester hydrochloride salt

With the high yielding fluorination of leucine methyl ester established, the fluorination of a variety of other amino acids was evaluated. The results are shown in

Table 3.13. Subjecting *l*-valine methyl ester hydrochloride salt to the reaction conditions optimized for leucine (Table 3.12, entry 7) led to a single product (**205**), but required longer reaction time in order to achieve higher yields of the fluorinated product (entry 1). It was postulated that the closer proximity of the abstractable hydrogen to the electron withdrawing amino ester functionality in valine (compared to leucine) led to the reduced reactivity of this substrate. *l*-Isoleucine methyl ester hydrochloride salt (entry 2) was also reacted under the same conditions (Table 3.12, entry 7) to yield two fluorinated products in reasonable yield after 48 hours of irradiation. The fluorinated regioisomers **206** and **207** were formed in a 2:1 ratio, with 1:1 diastereoselectivity at the fluorinated position (entry 2). Unfortunately, for the substrates depicted in entries 3-6, under a variety of reaction conditions, analysis of crude reaction mixtures by ^{1}H and ^{19}F NMR spectroscopy did not indicate any identifiable resonances corresponding to the desired fluorinated product.

Table 3.13. Fluorination of Amino Acids



entry	amino acid	time	product	conversion,[a] yield[b]
1	*l*-valine OMe HCl salt	120 hours	 205	88%, 56%
2	*l*-isoleucine OMe HCl salt	48 hours	 206 (1:1 *dr*) (2:1) 207 (1:1 *dr*)	N.D., 60%
3	*d*-alanine OMe HCl salt	18 hours	N.R.	-
4	*d*-phenylalanine OMe HCl salt	18 hours	N.R.	-
5	*l*-proline OMe HCl salt	18 hours	N.R.	-
6	methyl 1-aminocyclobutane carboxylate HCl salt	18 hours	N.R.	-

[a.] based on integration of signals (starting material & product) in the crude ^{1}H NMR spectrum [b.] combined yield calculated based on integration of signals using internal standard (1,3,5-(tris)trifluoromethylbenzene) in crude ^{1}H or ^{19}FNMR spectrum. N.R. = no reaction

3.3.5. Fluorination in Flow

Flow chemistry has been shown to decrease reaction times by aiding in the uniformity of reagent dispersion, temperature and solubility.[217,218] In order for this newly described fluorination method to be applicable towards ^{18}F chemistry, reaction times must be compatible with the half-life of the radionuclide. Furthermore, recent accounts on the preparation of ^{18}F-radiopharmeceuticals for human use via continuous flow apparatus has demonstrated the viability of this method.[219] Thus, a flow reaction setup was developed to gauge the feasibility of the photocatalytic C-H fluorination

methodology towards flow chemistry. Towards this end, a 10-metre stretch of FEP tubing (~1.4 mL volume) was wrapped around one 365nm blacklight blue bulb and placed inside a large cardboard box lined with aluminum foil ("photochamber").[g] On one end of the tubing, a syringe connected to a syringe pump was attached, and a collecting flask was placed at the other end. Before each trial, the entire system was flushed with degassed acetonitrile (~5 mL), and after the reagent solution (1 mL) is passed through the photochamber, the system is subsequently flushed with degassed acetonitrile (~2 mL).

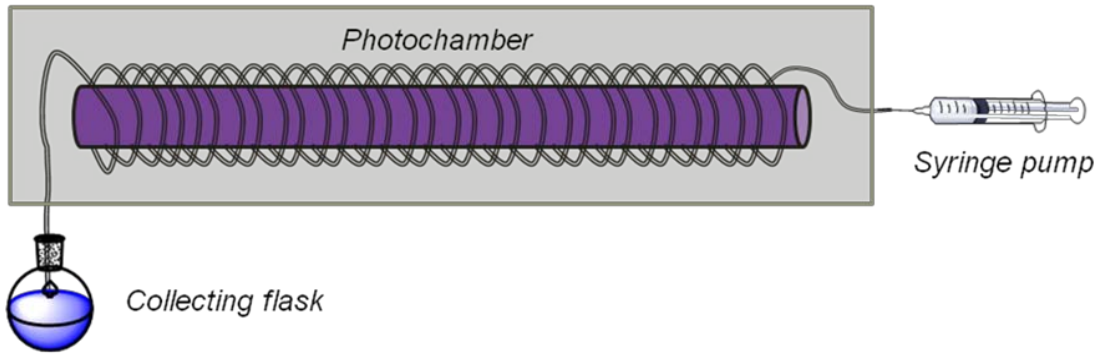
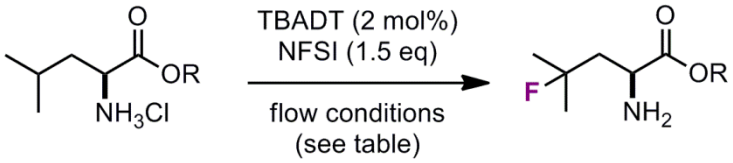


Figure 3.10. Flow Reaction Setup

A brief summary of fluorination results are shown in Table 3.14. Gratifyingly, subjecting a solution of leucine methyl ester, TBADT and NFSI in acetonitrile/water to the flow irradiation conditions described above (Figure 3.10) resulted in conversion to 4-fluoroleucine (entry 1). Not surprisingly, increasing or decreasing the irradiation time had a significant effect on the conversion (entries 2-3).

[g] Undergraduate student Duane Hetland assisted with the construction of the flow apparatus.

Table 3.14. Fluorination of Leucine Methyl Ester Hydrochloride Salt Under Flow Conditions



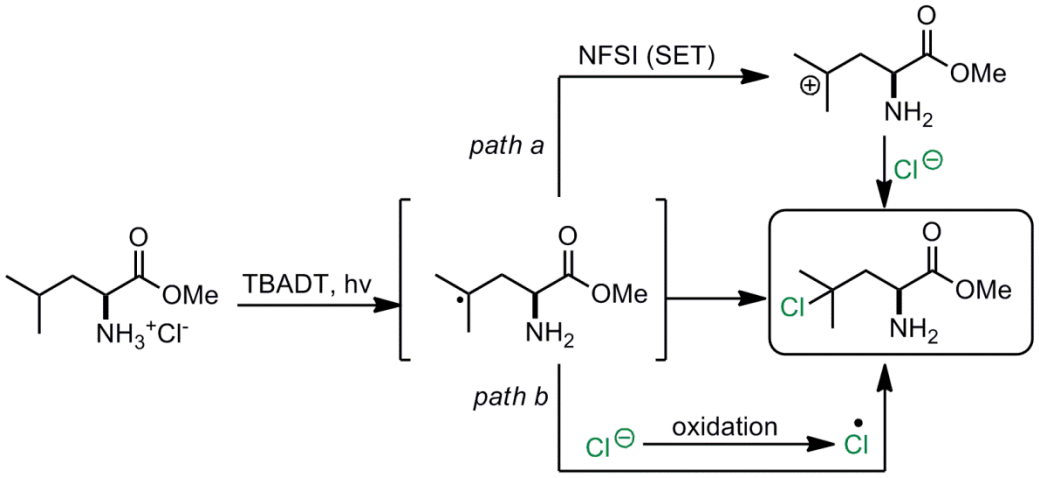
202 184

entry	[CH_3CN+H_2O] (~4:1)	flow rate	irradiation time	conversion[a]
1	0.10 M	0.8 mL / hour	2 hours	38%
2	0.17 M	2 mL / hour	0.75 hour	25%
3	0.14 M	0.4 mL / hour	4.5 hours	62%

[a.] Based on integration of proton resonances (starting material & product) in the crude ^{1}H NMR spectrum.

3.3.6. Mechanistic Insight

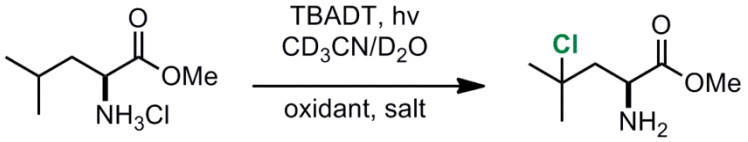
Throughout these initial investigations, it was assumed that the mechanism for the TBADT-catalyzed fluorination of C-H bonds abided by that proposed in Scheme 3.4, however, several unexpected results indicated that the mechanism of fluorination may differ from that initially posited. The isolation of chloroleucine as a byproduct in the fluorination of leucine (Table 3.12, entries 2-4) indicated that the NFSI present in the reaction was not reacting solely as a source of fluorine. Two mechanisms are proposed that utilize NFSI as an oxidant that could lead to the formation of the chlorinated product (Scheme 3.10). If NFSI oxidizes the carbon-centred radical (**208**) produced by TBADT to a carbocation (**209**), then the chlorinated product **203** may result from nucleophilic attack of chloride ion (present in the solution) onto the carbocation (**209**, Scheme 3.10, *path a*). Alternatively, if the chloride ion is oxidized to a chlorine radical by TBADT ($E°_{Cl^{\bullet}/Cl^-}$ = 2.59 V,[220] $E°_{(W_{10}O_{32}^{4-}/W_{10}O_{32}^{5-})}$ = 2.85 V,[221] both vs. SHE)the chlorine radical could recombine with the carbon-centred radical (**208**) produced by TBADT to yield the chlorinated product (*path b*). While differentiating between the two mechanisms is not trivial, this interesting result was further investigated by exploring the ability of other oxidants to promote halogenations on leucine (Table 3.15).



Scheme 3.10. Proposed Mechanism for the Chlorination of Leucine Methyl Ester Hydrochloride Salt Under TBADT-Photocatalyzed Conditions

Gratifyingly, in most cases, the presence of TBADT, light source, and an oxidant were sufficient to convert leucine methyl ester hydrochloride salt into chloroleucine methyl ester, albeit in lower conversions than were observed for the fluorination of leucine methyl ester. The chlorination of leucine methyl ester hydrochloride salt proceeded with various bench-stable and commercially available oxidants, although the use of sodium persulfate as oxidant led to the highest yields of chloroleucine (**203**) (entries 1, 4 and 5). Initially, sodium fluoride was added as an external fluoride source, in attempts to produce fluorinated compounds in the absence of NFSI, but the reaction conditions produced only chloroleucine methyl ester (entries 1-3). This result suggests that the actual mechanism involves oxidation of the chloride anion to the chlorine radical by NFSI. Interestingly, when the amount of TBADT was increased to 10 mol%, none of the chlorinated product **203** was observed (entry 6). The combination of TBADT and other oxidants and salts for halogenations is being further investigated in the Britton lab.

Table 3.15. Results: Chlorination of Leucine Methyl Ester Hydrochloride Salt



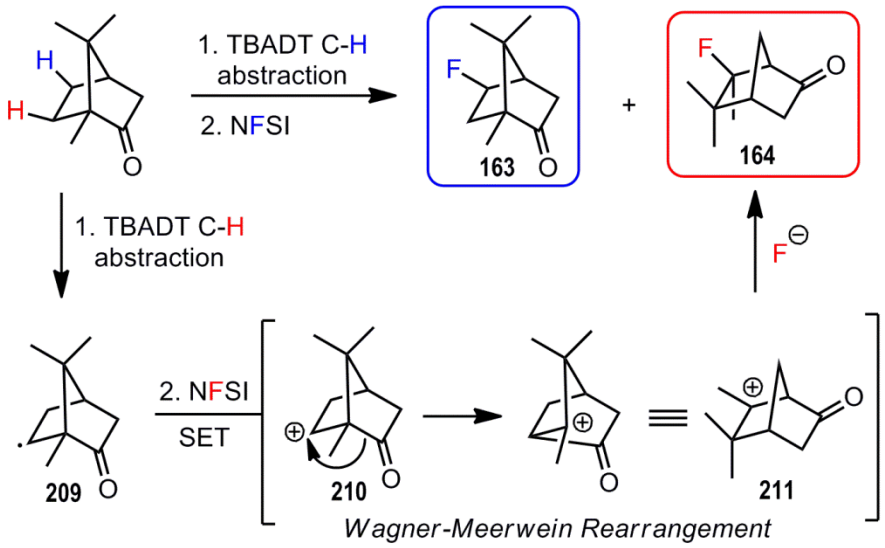
202 203

entry	Oxidant (1.2 equiv.)	salt (1.2 equiv.)	TBADT mol%	$CH_3CN:H_2O$, [M]	conversion[a]
1	$Na_2S_2O_8$	NaF	2%	4:1, 0.4 M	33%
2	$K_2S_2O_8$	NaF	2%	4:1, 0.4 M	25%
3	$FeCl_3H_2O$	NaF	2%	4:1, 0.4 M	18%
4	$Na_2S_2O_8$	none	2%	4:1, 0.4 M	31%
5	$Na_2S_2O_8$	none	2%	8:1, 0.25 M	37%
6	$Na_2S_2O_8$	none	10%	4:1, 0.4 M	0%
7	$Na_2S_2O_8$	none	2%	no H_2O, 0.25 M	26%
8	$Na_2S_2O_8$	none	2%	12:1, 0.17 M	37%

[a.] As determined by integration of resonances (starting material & product) in the crude ^1H NMR spectrum.

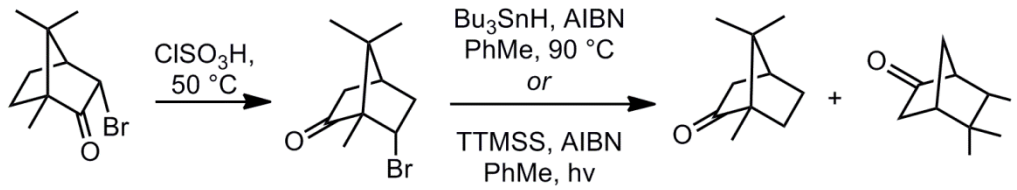
In addition to the evidence described above, the rearranged product fluoroisocamphonone **164** that resulted from the fluorination of camphor (Table 3.7, entry 3) also gave insight into a mechanism that could utilize NFSI as an oxidant. As depicted in Scheme 3.11, employing the fluorination conditions previously described, hydrogen abstraction of camphor by TBADT occurs at the two methines furthest away from the carbonyl. When abstraction occurs at the position closer to the quaternary carbon, oxidation of the carbon radical **211** to the carbocation **212** followed by a Wagner-Meerwein (W.M.) rearrangement could produce intermediate **213**, which can be trapped by fluoride to give fluoroisocamphonone **164** (Scheme 3.11). Given that almost all known Wagner-Meerwein[222] rearrangements are reported to abide by cationic, not radical, mechanisms, this result indicated that NFSI could be participating as an oxidant,

simultaneously oxidizing the carbon-centred radical to a cation, and producing a fluoride anion. Furthermore, it has been previously reported that the radical produced by 6-bromocamphor (**215**, Scheme 3.12) does not rearrange,[223] suggesting that our rearranged product was derived from a cationic intermediate.



Scheme 3.11. Proposed Mechanism for the Formation of Fluoroisocamphanone (164)

In efforts to further probe the ability of camphor radicals to undergo rearrangements, a radical reduction was performed directly on 6-bromocamphor (**215**) using previously reported conditions for carbon-bromine radical reduction (Scheme 3.12). Surprisingly, both the tin- and silyl-promoted radical reduction of 6-bromocamphor resulted in variable mixtures of camphor (**216**) and isocamphonone (**217**), indicating that a radical mechanism for this Wagner-Meerwein rearrangement cannot be ruled out. A radical mechanism for the Wagner-Meerwein rearrangement of camphor-derived substrates has been described by Jana *et. al*.[224]



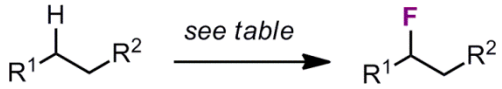
214 215 216 217

Scheme 3.12. Radical Reduction of 6-Bromocamphor

3.3.7. Current State in the Field

As there continues to be demand for the site-specific fluorination of carbon-hydrogen bonds, a variety of new methods that effect this transformation have been disclosed since the start of this research, and are depicted in Table 3.16.

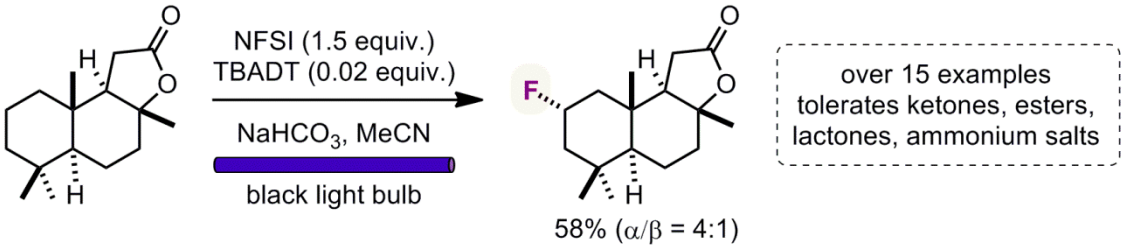
Table 3.16. Current State in the Field: C-H Fluorination.



conditions	reference	substrate
Selectfluor, BEt_3, CH_3CN	Lectka 2013[225]	aliphatic
Selectfluor, 1,2,4,5-tetracyanobenzene, CH_3CN, hv	Lectka 2014[226]	aliphatic
Selectfluor, anthraquinone, CH_3CN, fluorescent light	Tan 2014[227]	aliphatic (R^2 = EWG)
N,N'-dihydroxy-pyromellitimide, Selectfluor, 50 °C	Inoue 2013[228]	benzylic (R^1 = Ph)
Mn(salen)Cl, TREAT-HF, PhIO, AgF, 50 °C	Groves 2013[229]	benzylic (R^1 = Ph)
$Fe(acac)_2$, Selectfluor, CH_3CN, 23 °C	Lectka 2013[230]	benzylic (R^1 = Ph)
Fluorenone, Selectfluor	Chen 2013[231]	benzylic (R^1 = Ph)
AgF, PhSeCl, NFPy•BF_4, CH_2Cl_2	Lectka 2014[232]	allylic (R^1 = $CHCH_2$)

3.4. Conclusion

The fluorination of unactivated C-H bonds has been achieved, using an inexpensive, bench-stable polyoxometallate catalyst together with NFSI as a fluorine transfer agent. This new methodology tolerates a variety of functional groups including ketone, ester, lactone, aldehyde and ammonium salts, and the reaction can be carried out in the presence of water or wet solvents. This C-H fluorination allows direct access to novel fluorinated molecules that had not been previously reported. Furthermore, this is one of the first reports that describe a one-step transformation of aldehydes to acyl fluorides using commercially available and bench-stable reagents. The utility of this method has also been extended to the one step fluorination of amino esters. Notably, the fluorination of leucine methyl ester hydrochloride salt to yield γ-fluoroleucine methyl ester in a single transformation is a significant improvement upon previous approaches to γ-fluoroleucine. The majority of the fluorination results described in this chapter were published in early 2014.[233]



Scheme 3.13. Summary of C-H Fluorination

3.5. Experimental

3.5.1. General

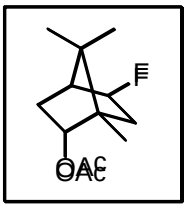
Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still.[124] Concentration and removal of trace solvents was done via a Buchi rotary evaporator using acetone-dry-ice condenser and a Welch vacuum pump.

NMR spectra were recorded using deuterochloroform ($CDCl_3$) as the solvent unless otherwise indicated. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent or standard ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR; δ -37.7 (NFSI), ^{19}F NMR) Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constants, number of protons. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Bruker 500 (500 MHz), or Bruker 400 (400 MHz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (150 MHz), Bruker 500 (125 MHz), or Bruker 400 (100 MHz). ^{19}F NMR spectra were recorded on a Bruker 500 (470 MHz). Assignments of ^{1}H, ^{19}F and ^{13}C NMR spectra are based on analysis of ^{1}H-^{1}H COSY, HMBC, HMQC, TOCSY and nOe spectra.

High resolution mass spectra (HRMS-ESI) were recorded on a Bruker micrOTOF II mass spectrometer.

3.5.2. Characterization of Compounds Described in This Chapter

(5*S*)-5-Fluorobornyl acetate (158)



Bornyl acetate (59 mg, 1.0 equiv) was dissolved in a solution of acetonitrile (2M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (1.2 equiv) and $NaHCO_3$ (10 mol%) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 17 hours. Following this time, the resulting blue solution was treated with solid saturated $NaHCO_3$ solution (1 mL) and extracted 3 times with CH_2Cl_2 (5 mL). The combined organic washes were dried over $MgSO_4$, filtered and concentrated to afford the crude fluorinated product. Purification by flash column chromatography (4% EtOAc/pentane) afforded the fluorination products in a combined yield of 56%. (5*S*)-5-Fluorobornyl acetate (**158**) was obtained as a colourless oil (26 mg, 40%). The spectral data derived from 5-fluorobornyl acetate was in complete agreement with that reported previously for this material.[188]

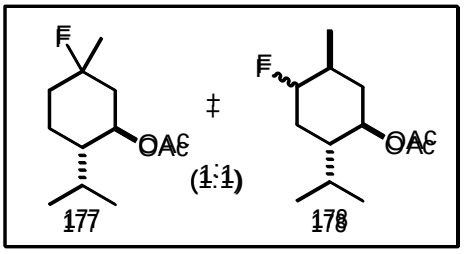
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.79 (d, *J* = 9.7 Hz, 1H), 4.62 (ddd, *J* = 60.0, 7.6, 2.3 Hz, 1H), 2.46-2.34 (m, 2H), 2.09-2.00 (m, 1H), 2.07 (s, 3H), 1.69 (dd, *J* = 35.3, 15.4 Hz, 1H), 1.07 (d, *J* = 2.1 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.75 (dd, *J* = 14.5, 3.4 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2, 95.8 (d, $^1J_{C\text{-}F}$ = 186 Hz), 77.6, 50.5 (d, $^2J_{C\text{-}F}$ = 18.1 Hz), 49.5, 47.3, 37.6 (d, $^2J_{C\text{-}F}$ = 18.1 Hz), 32.2 (d, $^3J_{C\text{-}F}$ = 11.3 Hz), 21.2, 20.3 (d, $^4J_{C\text{-}F}$ = 5.5 Hz), 19.4, 12.6 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -157.8 ppm.

HRMS (EI) calc'd for $C_{12}H_{19}FNaO_2$ $[M+Na]^+$: 237.1261, found 237.1288

5-Fluoro menthyl acetate and (4*S*)- and (4*R*)-4-fluoro menthyl acetate (161 and 162)



Menthyl acetate (60 mg, 1.0 equiv) was dissolved in a solution of acetonitrile (2M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (1.2 equiv) and $NaHCO_3$ (10 mol%) were added. The resulting suspension was sparged for 5 minutes with N_2. The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, 365 nm) at room temperature for 17 hours. Following this time, the resulting blue solution was treated with saturated $NaHCO_3$ solution (1 mL) and extracted 3 times with CH_2Cl_2 (5 mL). The combined organic washes were dried over $MgSO_4$, filtered and concentrated to afford the crude fluorinated product. Purification by flash column chromatography (hexanes to 6% EtOAc/hexanes gradient) afforded the fluorination as an inseparable mixture (as a colourless oil, 18 mg, 28% combined yield), with the 5-fluoro isomer as the major product. The products were analyzed by ^{1}H NMR spectroscopy, and the yield for 5-fluoro menthyl acetate (**161**) was calculated to be 13%, the yield for (4*S*)-4-fluoro menthyl acetate (**162**β) was calculated to be 11%, and the yield for (4*R*)-4-fluoro menthyl acetate (**162**α) was calculated to be 4%. In addition, a further 50% of starting material remained unreacted.

The structural assignment for each of the products present in the mixture was based on analysis of 1D TOCSY spectra, COSY, HSQC, and HMBC spectra.

5-Fluoro menthyl acetate (**161**): no fluoromethine present in ^{1}H NMR spectra and the presence of a doublet (3H) at δ 1.35 ppm ($^2J_{HF}$ = 21.1 Hz). (4*S*)-4-fluoro menthyl acetate (**162-**β): a fluoromethine resonance at δ 4.66 ppm ($^1J_{HF}$ = 49.8 Hz, no other coupling observed). (4*R*)-4-fluoro menthyl acetate (**162-**α): a fluoromethine resonance at δ 4.11 ppm ($^1J_{HF}$ = 48.7 Hz, $^3J_{HH}$ = 11.4, 2.6 Hz).

5-fluoromenthyl acetate (161) continued:

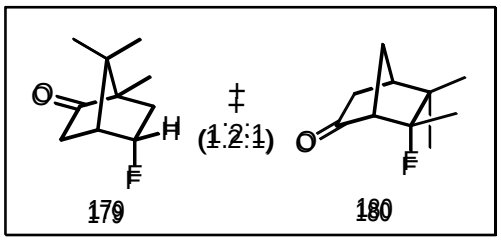
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (ddd, *J* = 10.8, 10.8, 4.7 Hz, 1H), 2.30 (m, 1H), 1.93-1.89 (m, 4H), 1.46-1.30 (m, 6H), 1.35 (d, *J* = 21.1 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 94.6 (d, $^{1}J_{C\text{-}F}$ = 169.2 Hz), 70.6, 46.1, 41.9 (d, $^{2}J_{C\text{-}F}$ = 21.1 Hz), 39.5, 35.6 (d, $^{2}J_{C\text{-}F}$ = 22.4 Hz), 26.9 (d, $^{2}J_{C\text{-}F}$ = 24.1 Hz), 25.3, 25.7, 20.3, 15.6 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -150.0 ppm.

HRMS (EI) calc'd for $C_{12}H_{21}FNaO_2$ $[M+Na]^+$: 239.1418, found 239.1439.

(5*S*)-5-fluorocamphor (163) and and fluoroisocamphanone (164)



Camphor (46 mg, 1.0 equiv) was dissolved in a solution of acetonitrile (2M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (1.2 equiv) and $NaHCO_3$ (10 mol%) were added. The resulting suspension was sparged for 5 minutes with N_2. The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, 365 nm) at room temperature for 17 hours. Following this time, the resulting blue solution was treated with saturated $NaHCO_3$ solution (1 mL) and extracted with CH_2Cl_2 (3x 5 mL). The combined organic washes were dried over $MgSO_4$, filtered and concentrated to afford the crude fluorinated products. Based on analysis of a ^{1}H NMR spectrum recorded on the crude reaction mixture following addition of an internal standard, the yield of (5*S*)-5-fluorocamphor was calculated to be 11%, the yield of (5*R*)-5-fluorocamphor was calculated to be 6%, and the yield of fluoroisocamphanone was calculated to be 14%. In addition, 52% of starting material remained unreacted. Purification by flash column chromatography (8% EtOAc/hexane) afforded a fraction containing a purified sample of fluoroisocamphanone **164** and (5*S*)-5-fluorocamphor (**163**) as an inseparable 1:1 mixture (white solid, 4.5 mg).

(5*S*)-5-fluorocamphor (163) and and fluoroisocamphanone (164) - continued

The structural assignment of the fluorination products was determined following analysis of COSY, HSQC, and HMBC NMR spectra. The relative stereochemistry of (5*S*)-5-fluorocamphor (**163**) was determined by NOESY shown in Scheme 3.5.

^{1}H NMR (500 MHz, $CDCl_3$):

(5*S*)-5-fluorocamphor (**163**): δ = 5.35 (dm, *J* = 56.6 Hz, 1H), 2.56 (d, *J* = 18.6 Hz, 1H), 2.43 (m, 1H), 2.26 (dd, *J* = 18.6, 4.5 Hz, 1H), 2.23 (m, 1H), 1.55 (ddd, *J* = 27.4, 14.8, 3.2 Hz, 1H), 1.01 (s, 3H), 0.93 (s, 3H), 0.87 (s, 3H) ppm.

fluoroisocamphanone (**164**): δ = 2.69 (d, *J* = 7.5 Hz, 1H), 2.41 (dm, *J* = 10.9 Hz, 1H), 2.27 (m, 1H), 2.20 (m, 1H), 1.98 (dd, *J* = 18.8, 4.4 Hz, 1H), 1.66 (d, J = 10.9 Hz, 1H), 1.27 (d, *J* = 24.2 Hz, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 0.94 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$):

(5*S*)-5-fluorocamphor (**163**): δ = 217.0, 91.8 (d, $^{1}J_{C\text{-}F}$ = 184.8 Hz), 58.5, 47.4 (d, $^{2}J_{C\text{-}F}$ = 15.9 Hz), 38.4 (d, $^{2}J_{C\text{-}F}$ = 21.9 Hz), 34.6 (d, $^{3}J_{C\text{-}F}$ = 11.2 Hz), 23.5, 20.2, 13.7, 8.7 ppm.

fluoroisocamphanone (**164**): δ = 214.9 ($^{3}J_{C\text{-}F}$ = 10.0 Hz), 100.9 ($^{1}J_{C\text{-}F}$ = 196.9 Hz), 65.1 (d, $^{2}J_{C\text{-}F}$ = 24.7 Hz), 46.9, 41.6 (d, $^{3}J_{C\text{-}F}$ = 3.6 Hz), 34.1, 23.9 (d, $^{2}J_{C\text{-}F}$ = 22.4 Hz), 23.4, 23.5, 20.0 (d, $^{2}J_{C\text{-}F}$ = 25.1 Hz).

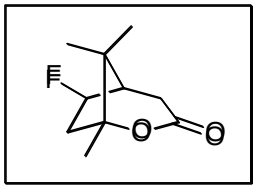
^{19}F NMR (470 MHz, $CDCl_3$):

(5*S*)-5-fluorocamphor (**163**): δ = -190.1 ppm.

fluoroisocamphanone (**164**): δ = -139.1 ppm

HRMS (EI) calc'd for $C_{10}H_{15}FNaO$ $[M+Na]^+$: 193.0999, found 193.1023.

(1*S*,5*R*)-6-fluoro-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (165)



(1*S*,5*R*)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (50 mg, 1.0 equiv) was dissolved in a solution of acetonitrile (2M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (1.2 equiv) and $NaHCO_3$ (10 mol%) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 17 hours. Following this time, the resulting blue solution was treated with solid saturated $NaHCO_3$ solution (1 mL) and extracted 3 times with CH_2Cl_2 (5 mL). The combined organic washes were dried over $MgSO_4$, filtered and concentrated to afford the crude fluorinated product. Following addition of an internal standard (1,3,5-trimethoxybenzene), the crude product was analyzed by 1H NMR spectroscopy and the yield for (1*S*,5*R*)-6-fluoro-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**165**) was calculated to be 14%. In addition, 53% of starting material remained unreacted. Purification by flash column chromatography (16% EtOAc/hexane) afforded the title compound as a white solid (6.5 mg, 12%) isolated as a mixture containing an additional 7.5 mg of starting material.

The structural assignment for **165** was determined following analysis of COSY, HSQC, and HMBC ^{1}H NMR spectra. We were not able to unambiguously assign the relative stereochemistry at the fluoromethine stereocenter.

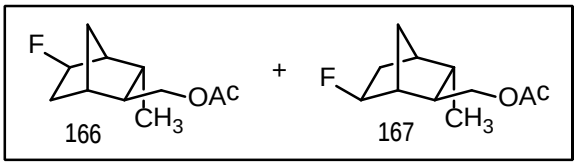
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.92 (ddd, *J* = 54.3, 7.4, 2.3 Hz, 1H), 2.88 (dt, *J* = 19.3, 6.2 Hz, 1H), 2.71 (ddd, *J* = 16.2, 16.2, 7.4 Hz, 1H), 2.42 (d, *J* = 19.3 Hz, 1H), 2.30 (dd, *J* = 39.2, 16.8 Hz, 1H), 2.27 (d, *J* = 16.2 Hz, 1H), 1.34 (s, 3H), 1.18 (s, 3H), 1.07 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 96.5 (d, $^1J_{C\text{-}F}$ = 183.8 Hz), 92.9 (d, $^3J_{C\text{-}F}$ = 3.4 Hz), 48.7 (d, $^2J_{C\text{-}F}$ = 20.9 Hz), 46.7 (d, $^2J_{C\text{-}F}$ = 20.9 Hz), 42.2 (d, $^4J_{C\text{-}F}$ = 1.8 Hz), 34.5 (d, $^3J_{C\text{-}F}$ = 11.5 Hz), 24.1 (d, $^3J_{C\text{-}F}$ = 4.4 Hz), 18.1, 18.0 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -160.2 ppm.

HRMS (EI) calc'd for $C_{10}H_{15}FNaO_2$ $[M+Na]^+$: 209.0948, found 209.0969.

5- and 6-fluoro bicyclo[2.2.1]heptanes 166 and 167



Bicyclo[2.2.1]heptane (0.3 mmol, 1.0 equiv) was dissolved in a solution of acetonitrile (2M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (1.2 equiv) and $NaHCO_3$ (10 mol%) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 17 hours. Following this time, the resulting blue solution was treated with saturated $NaHCO_3$ solution (1 mL) and extracted 3 times with CH_2Cl_2 (5 mL). The combined organic washes were dried over $MgSO_4$, filtered and concentrated to afford the crude fluorinated product. Purification by flash column chromatography (4% EtOAc/hexane) afforded the major fluorination products **166** and **167** as an inseparable 1:1 mixture (colourless oil, 24 mg, 40% combined yield). In addition, a further 23% of starting material remained unreacted.

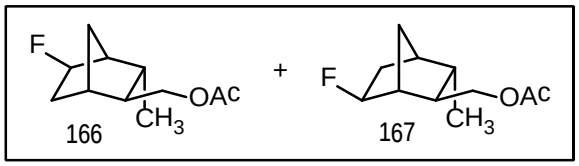
The structural assignment for **166** and **167** were determined following analysis of COSY, HSQC, and HMBC NMR spectra. We were not able to unambiguously assign the relative stereochemistry at the fluoromethine stereocenters.

^{1}H NMR (500 MHz, $CDCl_3$):

5-fluoro (**166**): δ = 4.55 (dd, *J* = 55.9, 6.4 Hz, 1H), 3.87 (m, 2H), 2.28 (d, *J* = 8.6 Hz, 1H), 2.10 (m, 1H), 2.04 (s, 3H), 1.60 (d, *J* = 10.6 Hz, 1H), 1.53-1.41 (m, 3H), 1.38 (d, *J* = 8.8 Hz, 1H), 1.11 (dt, *J* = 7.1, 6.7 Hz, 1H),0.89 (d, *J* = 6.9 Hz, 3H).

6-fluoro (**167**): δ = 4.93 (dm, *J* = 55.2 Hz, 1H), 3.98-3.88 (m, 2H), 2.35 (m, 1H), 2.15 (m, 1H), 2.06 (s, 3H), 1.75-1.69 (m, 2H), 1.60 (d, *J* = 10.6 Hz, 1H), 1.53 (m, 1H), 1.39 (d, *J* = 8.8 Hz, 1H), 0.98 (d, *J* = 7.3 Hz, 3H), 0.92 (dt, *J* = 8.0, 6.6 Hz, 1H) ppm.

5- and 6-fluoro bicyclo[2.2.1]heptanes - continued



^{13}C NMR (APT, 125 MHz, $CDCl_3$):

5-fluoro (**166**): δ = 95.2 (d, $^{1}J_{C\text{-}F}$ = 182.8 Hz), 67.2, 48.2, 45.7 (d, $^{2}J_{C\text{-}F}$ = 20.3 Hz), 40.3, 37.5, 33.7, 32.7 (d, $^{2}J_{C\text{-}F}$ =19.0 Hz), 20.9, 15.8 ppm.

6-fluoro (**167**): δ = 92.5 (d, $^{1}J_{C\text{-}F}$ = 177.7 Hz), 66.3 (d, $^{4}J_{C\text{-}F}$ = 3.4 Hz), 47.6 (d, $^{2}J_{C\text{-}F}$ = 19.5 Hz), 43.3 (d, $^{3}J_{C\text{-}F}$ = 10.3 Hz), 40.5 (d, $^{2}J_{C\text{-}F}$ = 20.1 Hz), 38.5, 35.5, 33.8, 20.9, 16.1 ppm.

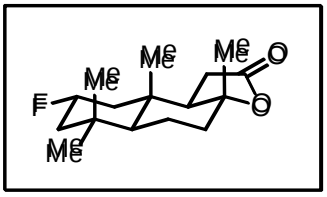
^{19}F NMR (470 MHz, $CDCl_3$):

5-fluoro (**166**): δ = -160.6 ppm.

6-fluoro (**167**): δ = -171.3 ppm.

HRMS (EI) calc'd for $C_{11}H_{17}FNaO_2$ $[M+Na]^+$: 223.1105, found 223.1118.

2-fluoro-(3α-*R*)-(+)-Sclareolide (168)



Sclareolide (75 mg, 1.0 equiv) was dissolved in a solution of acetonitrile (2M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (1.2 equiv) and $NaHCO_3$ (10 mol%) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 17 hours. Following this time, the resulting blue solution was treated with solid saturated $NaHCO_3$ solution (1 mL) and extracted 3 times with CH_2Cl_2 (5 mL). The combined organic washes were dried over $MgSO_4$, filtered and concentrated to afford the crude fluorinated product. Purification by flash column chromatography (hexanes to 20% ethyl acetate/hexanes gradient) afforded the fluorination products [^{19}F NMR: -179.9 ppm (2α), -187.3 ppm (2β), -180.9 ppm (3β)] in a combined yield of 68%. The major 2α-fluoro isomer (**168**) was obtained as a white solid, mixed with a small amount of the β-anomer (47 mg, 58% combined). The spectroscopic data derived from **168** was in agreement with that reported previously for this compound.

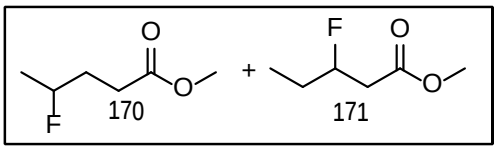
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.84 (dtt, *J* = 48.0, 11.3, 4.6 Hz, 1H), 2.46 (dd. *J* = 16.2, 14.7 Hz, 1H), 2.28 (dd, *J* = 15.7, 6.5 Hz, 1H), 2.13-1.86 (m, 4H), 1.71 (td, *J* = 12.6, 4.1 Hz, 1H), 1.44-1.31 (m, 6H), 1.23 (m, 2H), 1.00 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.1, 87.6 (d, *J* = 168 Hz), 58.8, 56.0 (d, *J* = 2.0 Hz), 51.3, 47.9 (d, $^3J_{C\text{-}F}$ = 15 Hz), 45.2 (d, $^3J_{C\text{-}F}$ = 17.4 Hz), 38.4, 37.3, 35.0 33.2, 28.7, 21.6, 21.8, 20.1, 16.1 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -179.9 ppm

HRMS (EI) m/z calc'd for $C_{16}H_{25}FNaO_2$ $[M+Na]^+$: 291.1731, found 291.1744

Methyl 4-fluorovalerate (170) and methyl 3-fluorovalerate (171)



Methyl valerate (0.46 mmol, 1.0 equiv) was dissolved in a solution of acetonitrile (1M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (1.2 equiv) and $NaHCO_3$ (10 mol%) were added. The resulting suspension was sparged for 5 minutes with N_2. The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, 365 nm) at room temperature for 19 hours. Following this time, the reaction mixture was treated with solid $NaHCO_3$ (10 mg), $MgSO_4$, filtered (celite), and the filter cake was washed with CD_3CN. Following addition of an internal standard, the crude product was analyzed by ^1H NMR spectroscopy and the yield of methyl 4-fluorovalerate (**171**) was calculated to be 34%, and the yield of methyl 3-fluorovalerate (**170**) was calculated to be 8%, for a combined yield of 42%. In addition, 30% of starting material remained unreacted.

^1H NMR (600 MHz, CD_3CN):

4-fluoro (**170**): δ = 4.72 (dm, *J* = 48.6 Hz, 1H), 3.66 (s, 3H), 2.47-2.42 (m, 2H), 1.95-1.84 (m, 2H) 1.32 (dd, *J* = 24.2, 6.3 Hz, 3H) ppm. 3-fluoro (**171**): δ = 4.87 (dm, *J* = 48.9 Hz, 1H), 3.69 (s, 3H), 2.69-2.61 (m, 2H), 1.77-1.63 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (150 MHz, CD_3CN):

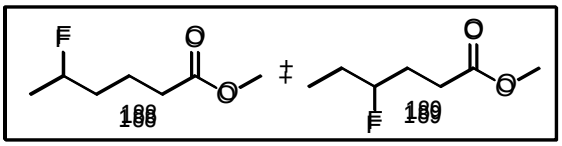
4-fluoro (**170**): δ = 173.4, 90.1 (d, $^1J_{C\text{-}F}$ = 165 Hz), 51.1, 31.7 (d, $^2J_{C\text{-}F}$ = 20.3 Hz), 29.3 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 20.1 (d, $^2J_{C\text{-}F}$ = 22.4 Hz) ppm. 3-fluoro (**171**): δ = 170.8 (d, $^3J_{C\text{-}F}$ = 4.7 Hz), 91.9 (d, $^1J_{C\text{-}F}$ = 170 Hz), 51.3, 39.4 (d, $^2J_{C\text{-}F}$ = 23.1 Hz), 27.5 (d, $^2J_{C\text{-}F}$ = 20.5 Hz), 8.5 ppm.

^{19}F NMR(565 MHz, CD_3CN):

4-fluoro (**170**): δ = -175.1 ppm, 3-fluoro (**171**): δ = -181.0 ppm.

HRMS (EI) calcd for $C_6H_{11}FNaO_2$ $[M+Na]^+$: 157.0635, found: 157.0631

Methyl 5-fluorohexanoate (172) and methyl 4-fluorohexanoate (173)



Methyl hexanoate (0.46 mmol, 1.0 equiv) was dissolved in a solution of acetonitrile (1M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (1.2 equiv) and $NaHCO_3$ (10 mol%) were added. The resulting suspension was sparged for 5 minutes with N_2. The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 19 hours. Following this time, the reaction mixture was treated with solid $NaHCO_3$ (10 mg), $MgSO_4$, filtered over Celite, and the filter cake was washed with CD_3CN. Following addition of an internal standard (1,3,5-tris(trifluoromethyl)benzene), the crude product was analyzed by ^{1}H NMR spectroscopy and the yield of methyl 5-fluorohexanoate (**172**) was calculated to be 33%, and the yield of methyl 4-fluorohexanoate (**173**) was calculated to be 17%, for a combined yield of 50%. In addition, 49% of starting material remained unreacted.

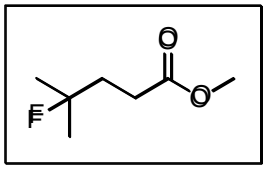
^{1}H NMR (500 MHz, CD_3CN): <u>5-fluoro:</u> δ = 4.69 (dm, *J* = 48.6 Hz, 1H), 3.66 (s, 3H), 2.36 (t, *J* = 7.0 Hz, 2H), 1.77-1.62 (m, 4H), 1.32 (dd, *J* = 24.2, 6.3 Hz, 3H) ppm. <u>4-fluoro:</u> δ = 4.47 (dm, *J* = 49.5 Hz, 1H), 3.65 (s, 3H), 2.45-2.38 (m, 2H), 1.96-1.83 (m, 2H), 1.68-1.58 (m, 2H). 0.96 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, CD_3CN: <u>5-fluoro</u>: δ = 173.4, 90.6 (d, $^1J_{C\text{-}F}$ = 162.0 Hz), 51.0, 35.8 (d, $^2J_{C\text{-}F}$ = 21.7Hz), 33.1, 20.2 (d, $^2J_{C\text{-}F}$ = 22.5 Hz), 19.7 (d, $^3J_{C\text{-}F}$ = 5.2 Hz ppm. <u>4-fluoro</u>: δ = 173.6, 94.7 (d, $^1J_{C\text{-}F}$ = 165.4 Hz), 51.1, 29.6 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 28.3 (d, $^3J_{C\text{-}F}$ = 4.9 Hz), 27.6 (d, $^2J_{C\text{-}F}$ = 21.2 Hz), 8.6 (d, $^3J_{C\text{-}F}$ = 5.5 Hz) ppm.

^{19}F NMR (470 MHz, $CDCl_3$): <u>5-fluoro:</u> δ = -173.2 ppm. <u>4-fluoro:</u> δ = -183.9 ppm.

HRMS (EI) calcd for $C_7H_{13}NaO_2$ $[M+Na]^+$: 171.0792, found: 171.0791.

Methyl 4-fluoro-4-methylvalerate (174)

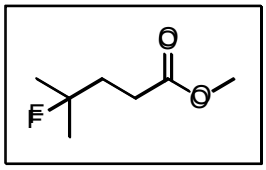


Methyl 4-methylvalerate (0.46 mmol, 1.0 equiv) was dissolved in a solution of acetonitrile (1M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (1.2 equiv) and $NaHCO_3$ (10 mol%) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 20 hours. Following this time, the reaction mixture was treated with solid $NaHCO_3$ (10 mg), $MgSO_4$, filtered over celite, and the filter cake was washed with CD_3CN. Following addition of an internal standard (1,3,5-tris(trifluoromethyl)benzene), the crude product was analyzed by ^1H NMR spectroscopy and the yield of methyl 4-fluoro-4-methylvalerate (**174**) was calculated to be 28%. In addition, 66% of starting material remained unreacted.

or

methyl 4-methylvalerate (0.2 mmol, 1.0 equiv) was dissolved in a solution of acetonitrile-H_2O (2:1, 1M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%) and NFSI (1.2 equiv) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 20 hours. Following this time, an additional amount of NFSI (50 mg, 0.16 mmol) was added, and the solution was degassed and irradiated for a further 24 hours. Following this time, the reaction mixture was treated with solid $NaHCO_3$ (10 mg), $MgSO_4$, filtered over celite, and the filter cake was washed with CD_3CN. Following addition of an internal standard (1,3,5-tris(trifluoromethyl)benzene), the crude product was analyzed by ^1H NMR spectroscopy and the combined yield of methyl 4-fluoro-4-methylvalerate and 4-fluoro-4-methylvaleric acid (hydrolysis product) was calculated to be 40%. In addition, 51% of the starting material remained unreacted.

Methyl 4-fluoro-4-methylvalerate (174) - continued



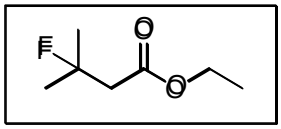
^{1}H NMR (500 MHz, CD_3CN): δ = 3.66 (s, 3H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.94 (m, 2H), 1.35 (d, *J* = 21.4 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5, 95.7 (d, $^{1}J_{C\text{-}F}$ = 163.8 Hz), 52.0, 36.7 (d, $^{2}J_{C\text{-}F}$ = 23.2 Hz), 29.4 (d, $^{3}J_{C\text{-}F}$ = 4.8 Hz), 26.6 (d, $^{2}J_{C\text{-}F}$ = 24.9 Hz), 25.7 (d, $^{2}J_{C\text{-}F}$ = 20.4 Hz) ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -140.1 ppm.

HRMS (EI) calcd for $C_7H_{14}FO_2$ $[M+H]^+$: 149.0972, found: 149.0960

Ethyl 3-fluoroisovalerate (175)

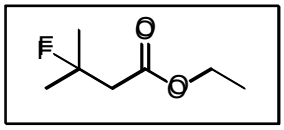


Ethyl isovalerate (0.46 mmol, 1.0 equiv) was dissolved in a solution of acetonitrile (1M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (1.2 equiv) and $NaHCO_3$ (10 mol%) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 24 hours. Following this time, an additional amount of NFSI (50mg, 0.16 mmol) was added, and the solution was degassed and irradiated for a further 24 hours. Following this time, the reaction mixture was treated with solid $NaHCO_3$ (10 mg), $MgSO_4$, filtered over celite, and the filter cake was washed with CD_3CN. Following addition of an internal standard (1,3,5-tris(trifluoromethyl)benzene), the crude product was analyzed by ^1H NMR spectroscopy and the yield of ethyl 3-fluoroisovalerate (**175**) was calculated to be 31%. In addition, 25% of starting material remained unreacted.

or

Ethyl isovalerate (0.2 mmol, 1.0 equiv) was dissolved in a solution of acetonitrile-H_2O (2:1, 1M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%) and NFSI (1.2 equiv) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 20 hours. Following this time, an additional amount of NFSI (25mg, 0.08 mmol) was added, and the solution was degassed and irradiated for a further 24 hours. Following this time, the reaction mixture was treated with solid $NaHCO_3$ (10 mg), $MgSO_4$, filtered over celite, and the filter cake was washed with CD_3CN. Following addition of an internal standard (1,3,5-trimethoxybenzene), the crude product was analyzed by ^1H NMR spectroscopy and the combined yield of ethyl 3-fluoroisovalerate and 3-fluoroisovaleric acid (hydrolysis product) was calculated to be 45%. In addition, 40% of the starting material remained unreacted.

Ethyl 3-fluoroisovalerate (175) – continued



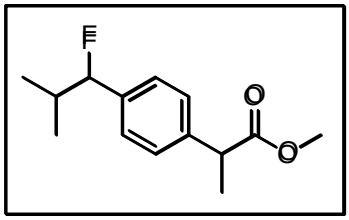
^{1}H NMR (500 MHz, CD_3CN): δ = 4.14 (q, *J* = 7.0 Hz, 2H), 2.67 (d, *J* = 17.3 Hz, 2H), 1.48 (d, *J* = 21.2 Hz, 6H), 1.25 (t, *J* = 8.6 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 93.4 (d, $^{1}J_{C\text{-}F}$ = 166.6 Hz), 59.7, 45.0 (d, $^{2}J_{C\text{-}F}$ = 24.9 Hz), 25.6 (d, $^{2}J_{C\text{-}F}$ = 23.4Hz), 13.0 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -134.5 ppm.

HRMS (EI) calcd for $C_7H_{13}NaFO_2$ $[M+Na]^+$: 171.0791, found: 171.0790.

fluoroibuprofen methyl ester



Ibuprofen methyl ester (44 mg, 1.0 equiv) was dissolved in a solution of acetonitrile-H_2O (2:1, 1M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%) and NFSI (1.2 equiv) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 18 hours. The resulting blue solution was then diluted with $CHCl_3$ and saturated $NaHCO_3$, the organic layer was extracted with $CHCl_3$ (3 x 10 mL) the organic layer washed with brine, dried ($MgSO_4$) and concentrated. Purification by column chromatography (2% MeOH in CH_2Cl_2) gave the title product as a colourless oil (40 mg, 84%).

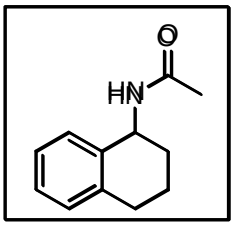
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32-7.28 (m, 2H), 7.27-7.24 (m, 2H), 5.08 (dd, *J* = 47.0, 6.7 Hz, 1H), 3.75 (q, *J* = 7.0 Hz, 1H), 3.67 (s, 3H), 2.10 (m, 1H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9, 140.4, 138.3 ($^{2}J_{CF}$ = 20.5 Hz) 127.3, 126.5 ($^{3}J_{CF}$ = 7.0 Hz), 99.2 ($^{1}J_{CF}$ = 173.3 Hz), 52.1, 45.2, 34.2 ($^{2}J_{CF}$ = 22.5 Hz), 18.6, 18.3 ($^{3}J_{CF}$ = 5.5 Hz), 17.5 ($^{3}J_{CF}$ = 5.5 Hz) ppm

^{19}F NMR (470 MHz, $CDCl_3$): δ = -179.6 ppm.

HRMS (EI) calcd for $C_{14}H_{19}FNaO_2$ $[M+Na]^+$: 261.1287; found: 261.1261.

N-(1,2,3,4-tetrahydronaphthalen-1-yl)acetamide



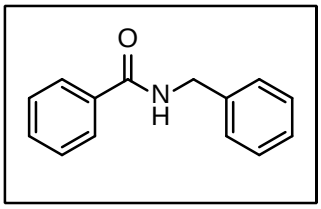
Tetrahydronapthalene (0.2 mmol, 1.0 equiv) was dissolved in a solution of acetonitrile (0.2M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%) and NFSI (2 equiv) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 17 hours. Following this time, the resulting blue solution was treated with saturated $NaHCO_3$ solution (1 mL) and extracted 3 times with CH_2Cl_2 (5 mL). The combined organic washes were dried over $MgSO_4$, filtered and concentrated to afford the crude fluorinated product. Purification by flash column chromatography (10% EtOAc/hexane) afforded the *N*-(1,2,3,4-tetrahydronaphthalen-1-yl)acetamide as a white solid, mp = 142 °C (22 mg, 58%). The spectral data derived for *N*-(1,2,3,4-tetrahydronaphthalen-1-yl)acetamide was in complete agreement with previously reported.[234]

IR (neat) = 3243, 3062, 2924, 2853, 1634, 155, 1371, 1092, 739.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29-7.27 (m, 1H), 7.21-7.17 (m, 2H), 7.12-7.09 (m, 1H) 5.71 (d, *J* = 6.1 Hz, 1H) 5.19 (m, 1H) 2.88-2.73 (m, 2H) 2.09-2.03 (m, 1H) 2.02 (s, 3H) 1.87-1.78 (m, 3H)

HRMS (EI) calcd for $C_{12}H_{16}NO$ $[M+H]^+$: 190.1222, found: 190.1226

_N_-Benzylbenzamide (183)



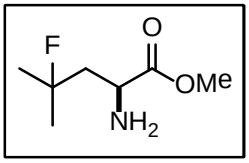
Benzaldehyde (1 mmol, 1.0 equiv) was dissolved in a solution of acetonitrile (1M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (1.2 equiv) and $NaHCO_3$ (10 mol%) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 18 hours. The reaction mixture was then treated with a solution of benzylamine (0.22 mL, 2 mmol) and diisopropylethylamine (0.35 mL, 2 mmol) in CH_3CN (1 mL) and stirred for an additional 30 minutes (without irradiation). The resulting solution was added to a mixture of saturated $NaHCO_3$ solution and EtOAc in a separatory funnel and the organic layer was removed. The aqueous layer was extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (gradient from 100% CH_2Cl_2 to 2% MeOH in CH_2Cl_2) gave *N*-benzylbenzamide (**183**) as a white solid (166 mg, 79% yield). The spectral data derived from *N*-benzylbenzamide (**183**) was in complete agreement with that reported.[235]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.8 (d, *J* = 7.5 Hz, 2H), 7.51 (m, 1H), 7.45-7.40 (m, 2H), 7.39-7.33 (m, 4H), 7.31 (m, 1H), 6.52 (bs, 1H), 4.65 (d, *J* = 5.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.4, 138.2, 134.4, 131.6, 128.8, 128.6, 127.9, 127.6, 127.0, 44.1.

HRMS (EI) calcd for $C_{14}H_{14}NO$ $[M+H]^+$: 212.1058 (M+H); found 212.1070.

Fluoroleucine methyl ester (184)



l-leucine methyl ester hydrochloride salt (36 mg, 1.0 equiv) was dissolved in a solution of acetonitrile-H_2O (2:1, 1M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%) and NFSI (1.2 equiv) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 17 hours. Following this time, the reaction mixture was treated with solid $NaHCO_3$ (10 mg), $MgSO_4$, filtered over celite, and the filter cake was washed with CD_3CN. Following addition of an internal standard (1,3,5-tris(trifluoromethyl)benzene), the crude product was analyzed by ^1H NMR spectroscopy and the yield of fluoroleucine (**184**) was determined to be 83%. In addition, no starting material remained unreacted. Data is reported for fluoroleucine ethyl ester:

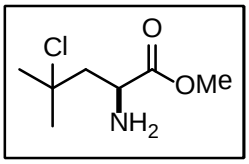
^1H NMR (600 MHz, $CDCl_3$): δ = 4.18 (q, *J* = 7 Hz, 2H), 3.69 (m, 1H), 2.14 (ddd, *J* = 23.6, 14.8, 4.8 Hz, 1H), 1.85 (ddd, *J* = 25.5, 14.8, 7.9 Hz, 1H), 1.44 (d, *J* = 21.5 Hz, 3H), 1.43 (d, *J* = 21.4 H, 3H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.8, 95.2 (d, *J* = 165.8 Hz), 61.2, 51.7, 45.9 (d, *J* = 21.3 Hz), 27.3 (d, *J* = 90.5 Hz) 27.2 (d, *J* = 90.8 Hz), 14.3 ppm.

^{19}F (470 MHz, $CDCl_3$): δ = -139.1 ppm

HRMS *m/z* $[M+H]^+$ calcd for $C_8H_{17}FNO_2$: 178.1238; found: 178.1222.

Chloroleucine methyl ester (203)

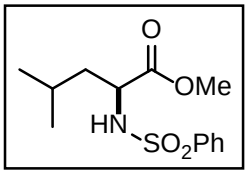


^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.47 (t, *J* = 5.5 Hz, 1H), 3.78 (s, 3H), 2.61 (dd, *J* = 15.6, 5.5 Hz, 1H), 2.52 (dd, *J* = 15.6, 5.5 Hz, 1H), 1.65 (s, 3H), 1.62 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.4, 67.7, 53.4, 51.1, 45.8, 32.3, 32.6 pm.

HRMS (EI) calcd for $C_7H_{15}ClNO_2$ $[M+H]^+$: 180.0785 $[M+H]^+$; found: 180.0786.

Methyl (phenylsulfonyl) leucinate (204)



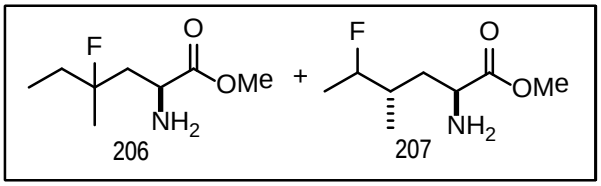
IR (neat): 3269, 2956, 1737, 1447, 1331, 1212, 1147, 1163, 1092, 754, 589 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.0 Hz, 2H), 7.64-7.50 (m, 3H), 5.04 (d, *J* = 10.1 Hz, 1H), 3.95 (m, 1H), 3.41 (s, 3H), 1.78 (m, 1H), 1.48 (dt, *J* = 3.1, 7.2 Hz, 2H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.2, 132.4, 129.0, 128.6, 126.9, 54.0, 51.8, 42.0, 24.0, 22.2, 20.9 ppm.

HRMS (EI) calcd for $C_{13}H_{20}NO_4S$ $[M+H]^+$: 286.1113 $[M+H]^+$; found: 286.1107.

δ-fluoroisoleucine methyl ester (207)



l-isoleucine methyl ester hydrochloride salt (53 mg, 1.0 equiv) was dissolved in a solution of acetonitrile-H_2O (2:1, 1M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%) and NFSI (1.2 equiv) were added. The resulting suspension was sparged for 5 minutes with N_2. The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, 365 nm) at room temperature for 24 hours. An additional 0.5 equivalents (60 mg) of NFSI was added after this time, and irradiation continued for a total of 48 hours. Following this time, the reaction mixture was treated with solid $NaHCO_3$ (10 mg), $MgSO_4$, filtered over celite, and the filter cake was washed with CD_3CN. Following addition of an internal standard (1,3,5-tris(trifluoromethyl)benzene), the crude product was analyzed by ^1H NMR spectroscopy and the yield of δ-fluoroisoleucine methyl ester (**207**) was determined to be 40% (1:1 *dr*), along with a small amount of γ-fluoroisoleucine methyl ester (**206**) in 19% (1:1 *dr*). Purification via Combiflash (C18 Reverse-Phase Redisep Gold) gave δ-fluoroisoleucine methyl ester (**207**) as a 1:1 mixture of diastereomers at the δ-fluorinated position. Data is reported for the mixture of diastereomers:

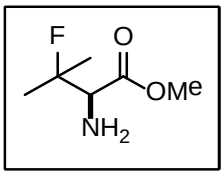
^1H NMR (600 MHz, $CDCl_3$): δ = 4.80 (dm, *J* = 41.9 Hz, 1H), 4.72 (dm, *J* = 44.1 Hz, 1H), 4.46 (d, *J* = 3.1 Hz, 1H), 4.35 (d, *J* = 4.9 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 2.49 (m, 1H), 2.35 (m, 1H), 1.29 (dd, *J* = 24.5, 6.2 Hz, 3H), 1.27 (dd, *J* = 25.5, 5.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.53, 168.48, 90.4 (d, $^1J_{C\text{-}F}$ = 167.4 Hz), 90.1 (d, $^1J_{C\text{-}F}$ = 168.0 Hz), 55.8, 54.5, 52.7, 52.6, 40.6 (d, $^2J_{C\text{-}F}$ = 18.2 Hz), 39.0 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 18.6 (d, $^2J_{C\text{-}F}$ = 23.2 Hz), 17.9 (d, $^2J_{C\text{-}F}$ = 22.5 Hz), 11.4 (d, $^3J_{C\text{-}F}$ = 7.4 Hz), 8.9 (d, $^3J_{C\text{-}F}$ = 5.6 Hz).

^{19}F NMR (564 MHz, $CDCl_3$): δ = -172.7, -186.3 ppm.

HRMS (EI) calcd for $C_7H_{15}FNO_2$ $[M+H]^+$: 164.1081 (M+H); found 164.1086

β-fluorovaline methyl ester (205)



l-valine methyl ester hydrochloride salt (35 mg, 1.0 equiv) was dissolved in a solution of acetonitrile-H_2O (2:1, 1M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%) and NFSI (1.2 equiv) were added. The resulting suspension was sparged for 5 minutes with N_2 (through a septic needle). The reaction vessel was then sealed, and the mixture was stirred and irradiated (two 15-Watt UVB-BLB lamps, centered at 365 nm) at room temperature for 120 hours. An additional 1.2 equivalents (100 mg total; 50 mg per addition) of NFSI was added after 48 and 72 hours, and the reaction was irradiated for a total of 120 hours. Following addition of an internal standard (1,3,5-tris(trifluoromethyl)benzene), the crude product was analyzed by ^{1}H NMR spectroscopy and the yield of β-fluorovaline (**205**) was determined to be 56%. In addition, 40% of the starting material was recovered unreacted. Attempts to purify β-fluorovaline methyl ester hydrochloride by normal or reverse phase chromatography resulted largely in decomposition, and only small amounts of mixtures containing β-fluorovaline methyl ester and valine methyl ester could be recovered following chromatography.

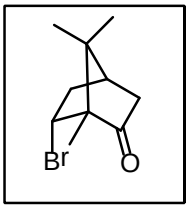
^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.43 (d, J = 11.9 Hz, 1H), 3.76 (s, 3H), 1.62 (d, J = 22.1 Hz, 3H), 1.51 (d, J = 22.1 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.9 (d, $^3J_{C\text{-}F}$ = 6.8 Hz), 92.9 (d, $^1J_{C\text{-}F}$ = 177.8 Hz), 59.9 (d, $^2J_{C\text{-}F}$ = 23.2 Hz), 53.1, 25.0 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 22.8 (d, $^2J_{C\text{-}F}$ = 24.1 Hz) ppm.

^{19}F NMR (564 MHz, $CDCl_3$): δ = -142.9 ppm.

HRMS (EI) calcd for $C_6H_{13}FNO_2$ $[M+H]^+$: 150.0947 (M+H); found 150.0925.

(6R)-6-bromocamphor (215)



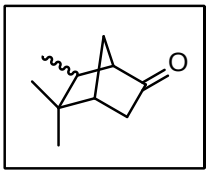
A solution of 3-bromocamphor (**214**) (3.5 g) in chlorosulfonic acid (10 mL) was heated to 50 °C for 30 minutes. The reaction mixture was cooled to room temperature and then slowly poured into a beaker of ice (careful!). The water was extracted with dichloromethane (3 x 30 mL), and the combined organic extracts were washed with saturated $NaHCO_3$ (2 x 20 mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered and concentrated to yield a yellow oil that was purified by flash chromatography (9:1 hexanes:ethyl acetate) to yield white crystals that would turn yellow upon standing at room temperature. The spectral data derived for 6-bromocamphor (**215**) is in complete agreement with previously reported.[223] Additionally, crystal structure was conducted to confirm the stereochemistry at the carbon-bromine center (see Appendix B). The CIF file for the crystal structure has been deposited in the Cambridge Crystallographic Data Centre. Deposition number: CCDC 1045645

^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.24 (dd, *J* = 10.0, 3.1 Hz, 1H), 2.87 (m, 1H), 2.47 (dt, *J* = 18.5, 2.5 Hz, 1H), 2.24 (t, *J* = 4.5 Hz, 1H), 2.08 (d, *J* =18.5 Hz, 1H), 1.92 (dd, *J* = 14.5, 3.2 Hz, 1H), 1.02 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 213.5, 63.6, 51.0, 47.9, 42.9, 42.4, 40.1, 21.0, 19.3, 7.7 ppm.

HRMS (EI) calcd for $C_{10}H_{16}BrO$ [M+H]: 231.0378; found: 231.0379

Isocamphanone (217)



To a solution of 6-bromocamphor (**215**) (0.3 mmol, 1 equiv) in toluene (1 mL) was added tributyltin hydride (2 equiv) and AIBN (cat.). The reaction mixture was sparged with N_2 (5 minutes) then the reaction vessel was sealed and heated to 90 °C for 18 hours. The reaction was cooled to room temperature and the solvent was removed. The crude material was dissolved in diethyl ether (10 mL) and washed with 1M HCl (10 mL), saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was subsequently dried (MgSO4), filtered, and concentrated to yield a mixture of two compounds; camphor and isocamphanone in an approximately 6:1 ratio. Attempts to isolate isocamphanone from camphor via flash chromatography led to degradation.. Analysis of the spectral data derived from a purified mixture of isocamphanone and camphor (1:6) confirmed the presence of the former compound and is in complete agreement with previously reported.[236]

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.40 (m, 1H), 2.21 (m, 2H), 2.03 (dd, *J* = 10.5, 4.0 Hz, 1H), 1.91 (m, 2H), 1.64 (d, *J* = 10.5 Hz, 1H), 1.16 (s, 3H), 0.89 (s, 3H), 0.87 (d, *J* = 7.7 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.9, 58.6, 47.5, 43.7, 42.1, 36.9, 36.1, 31.9, 21.2, 13.3 ppm.

GC/MS: MS calcd for $C_{10}H_7O$ [M+H]: 153; found: 153.

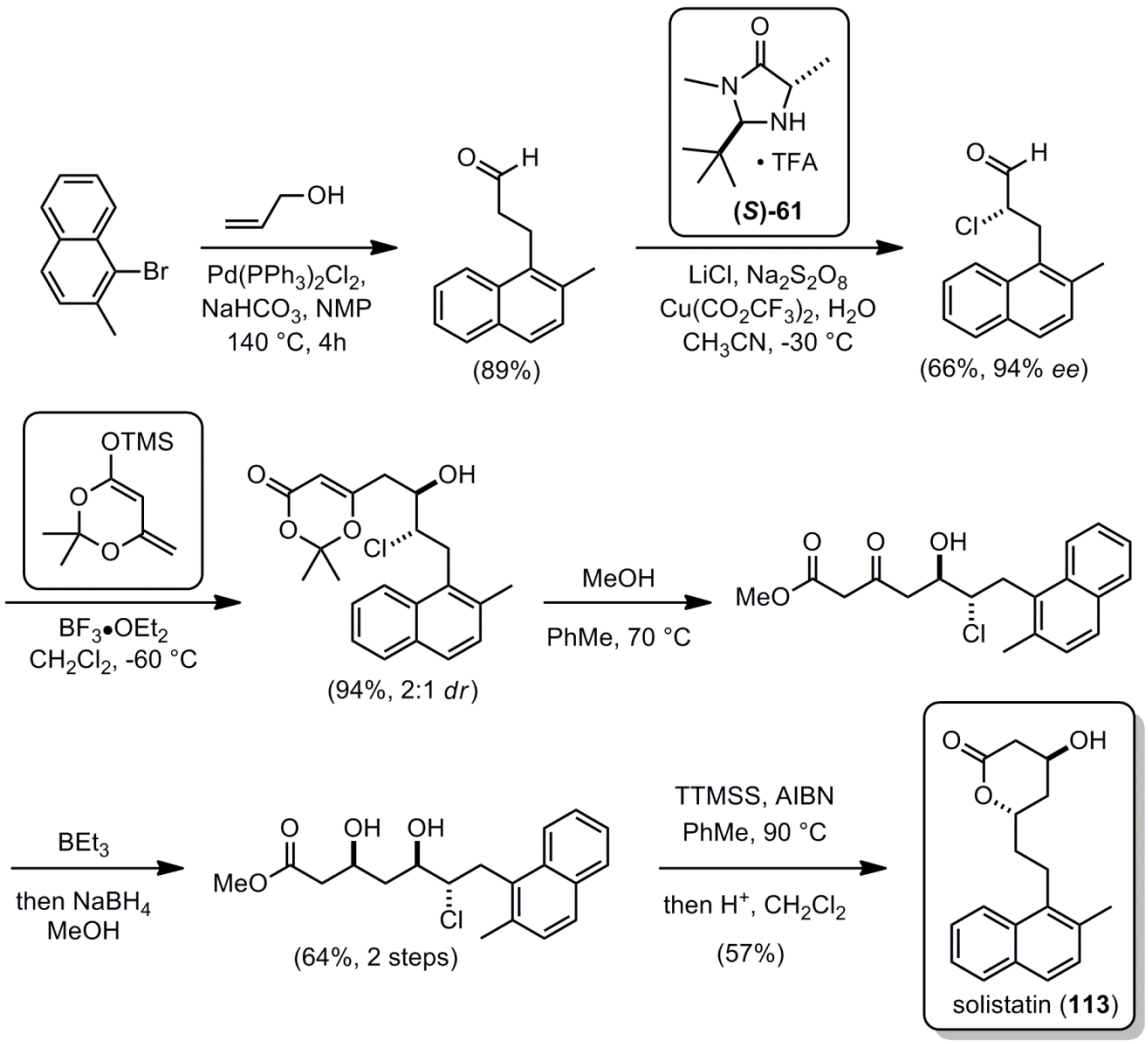
Chapter 4.

Conclusion

4.1. Chlorine as an Auxiliary in Asymmetric Aldol Reactions

In summary, the utility of α-chloroaldehydes has been extended to include their use in asymmetric aldol reactions. Lithium enolates have been shown to engage in stereoselective additions to α-chloroaldehydes that result in the preferential formation of 1,2-*anti* chlorohydrins, due to the directing effects of the chlorine atom. The scope of this reaction was explored through the construction of a variety of β-ketochlorohydrins from the appropriate enolate and α-chloroaldehyde, with various functional groups being tolerated on both coupling partners. Rapid and facile dechlorination of the intermediate β-ketochlorohydrin with the radical hydrogen transfer reagent tris(trimethylsilylsilane) produced a collection of nonracemic β-hydroxyketones in excellent yield and enantiomeric excess (90-99% *ee*). Notably, this methodology provides access to optically enriched aldol adducts, which is a functionality found in many drugs and bioactive natural products, in only three synthetic transformations: chlorination of the aldehyde, aldol reaction between the ketone and α-chloroaldehyde, and radical dechlorination of the chlorohydrin.

This new methodology for the synthesis of asymmetric aldol adducts was utilized in the nonracemic total syntheses of two natural products: (+)-dihydroyashabushiketol and (+)-solistatin. (+)-Dihydroyashabushiketol was synthesized in three synthetic steps, 57% overall yield and 98% *ee*, compared to the only previous nonracemic synthesis in 2011 that required 6 steps. A previous asymmetric synthesis of (+)-solistatin required 17 synthetic steps, however, using our asymmetric aldol methodology, the natural product was prepared in 6 steps, 14% overall yield and 94% *ee* (Scheme 4.1).

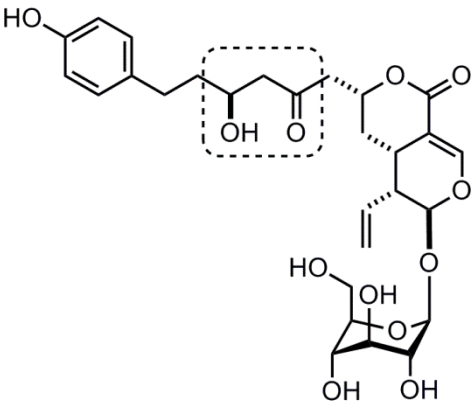


Scheme 4.1. Six-Step Synthesis ofSolistatin

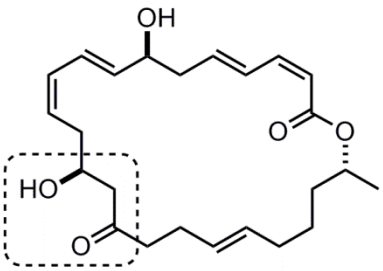
4.2. Future Work

As the development of this methodology is complete, and two total syntheses have been achieved, the future work involving this research may involve its application in the total syntheses of more complex natural products that contain β-hydroxyketone functionalities (e.g., Figure 4.1). Hydromacroside A was originally isolated in 1994 from the leaves of *Hydrangea macrophylla* and was shown to exhibit anti-allergenic properties.[237] Importantly, the structure of this natural product has not been confirmed by total synthesis and possesses a β-hydroxyketone moiety. Macolactin F was isolated in 1989 from a deep-sea marine bacterium[238] and while efforts towards its synthesis

have been reported,[239] no total synthesis currently exists. In this regard, our methodology to construct asymmetric β-hydroxyketones could be employed in a total synthesis of either of these natural products.



Hydramacroside A

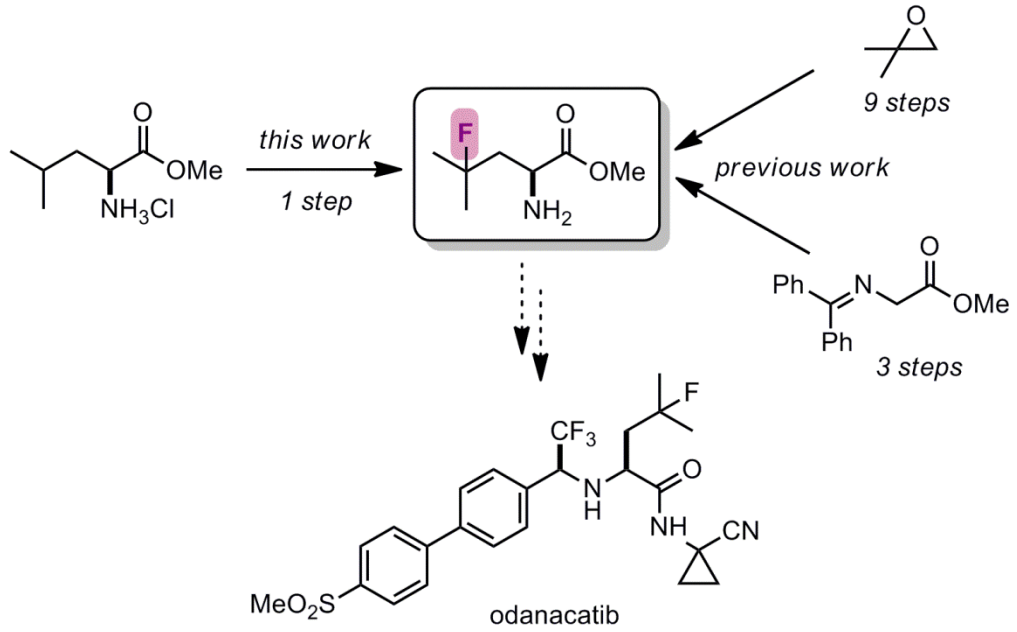


Macrolactin F

Figure 4.1. Future Work: Potential Synthetic Targets

4.3. Photocatalytic Fluorination of C-H Bonds

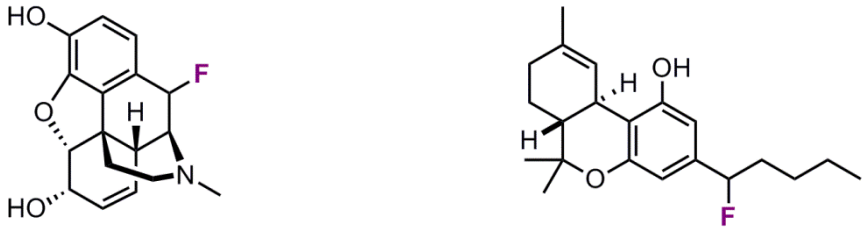
A new methodology that combines that hydrogen abstracting abilities of a decatungstate polyoxometallate, with the fluorine radical transfer ability of electrophilic fluorinating agents, has been described. This one-step fluorination of carbon-hydrogen bonds utilizes TBADT as a photocatalyst and hydrogen abstraction agent and NFSI as a source of fluorine radical. The fluorination that results from the combination of these two reagents under the appropriate conditions is tolerant to a variety of functional groups, as the fluorination of various esters, ammonium salts, aldehydes, ketones and lactones was achieved. Furthermore, the one step C-H fluorination of amino esters has provided quick access to fluorinated amino acids (e.g., Scheme 4.2), which have significant pharmaceutical and medicinal utility. As not all the substrates successfully fluorinated, insights into the mechanism could be useful in order to adapt the methodology to a broader range of substrates.



Scheme 4.2. Syntheses of Fluoroleucine

4.4. Future Work

Future work involving the fluorination of C-H bonds includes exploration of the substrate scope for benzylic fluorinations, as this research only reported the benzylic fluorination of a single substrate. The fluorination of benzylic positions on various biologically active compounds can be achieved to produce new fluorinated analogues (e.g., Figure 4.2). As the benzylic fluorination of morphine and tetrahydrocannabinol have never been reported, the synthesis of these novel compounds depicted in Figure 4.2 could provide leads to more potent pharmaceuticals. Furthermore, these ^{19}F labeled bioactive compounds could allow for metabolic, binding, and enzymatic studies using ^{19}F NMR spectroscopy. Additionally, the fluorination of benzylic substrates with various electron-donating and electron-withdrawing groups situated *para* to the site of C-H abstraction can potentially provide insight into the mechanism of the benzylic fluorination via Hammett plots. Finally, as recent reports of metal-free benzylic fluorination have been described, other methods of benzylic C-H abstraction should be investigated in order to potentially obviate the use of the TBADT photocatalyst.



fluoro-morphine fluoro-tetrahydrocannabinol

Figure 4.2. Potential New Targets for Benzylic Fluorination

In addition to the future work regarding benzylic fluorinations, the synthesis of ^{18}F radiolabelled compounds can be achieved as the synthesis of [^{18}F]-NFSI has been reported.[240] In this regard, with collaborations from TRIUMF, this C-H fluorination methodology could be applied towards the ^{18}F-fluorination of molecules with applications in PET imaging.

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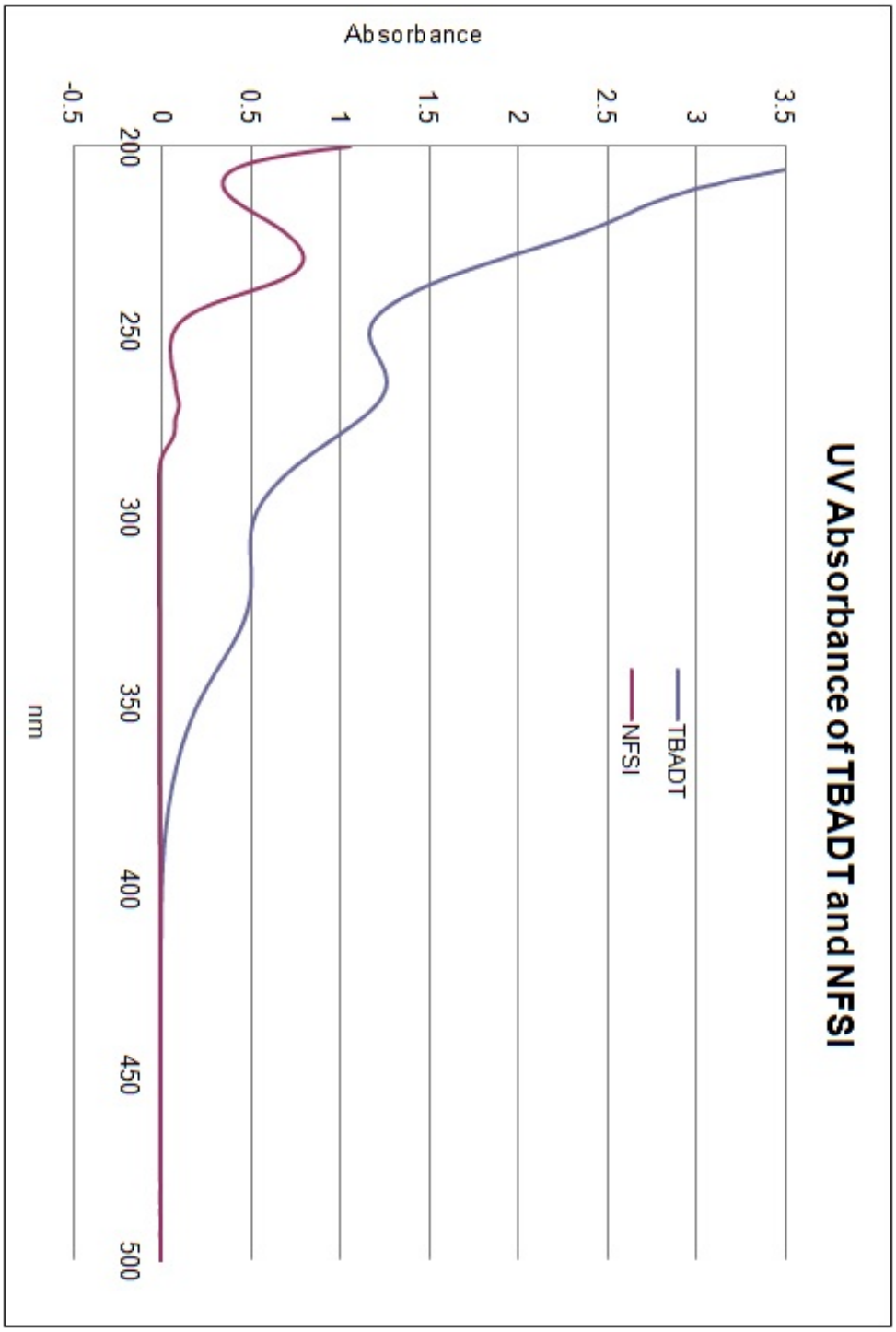
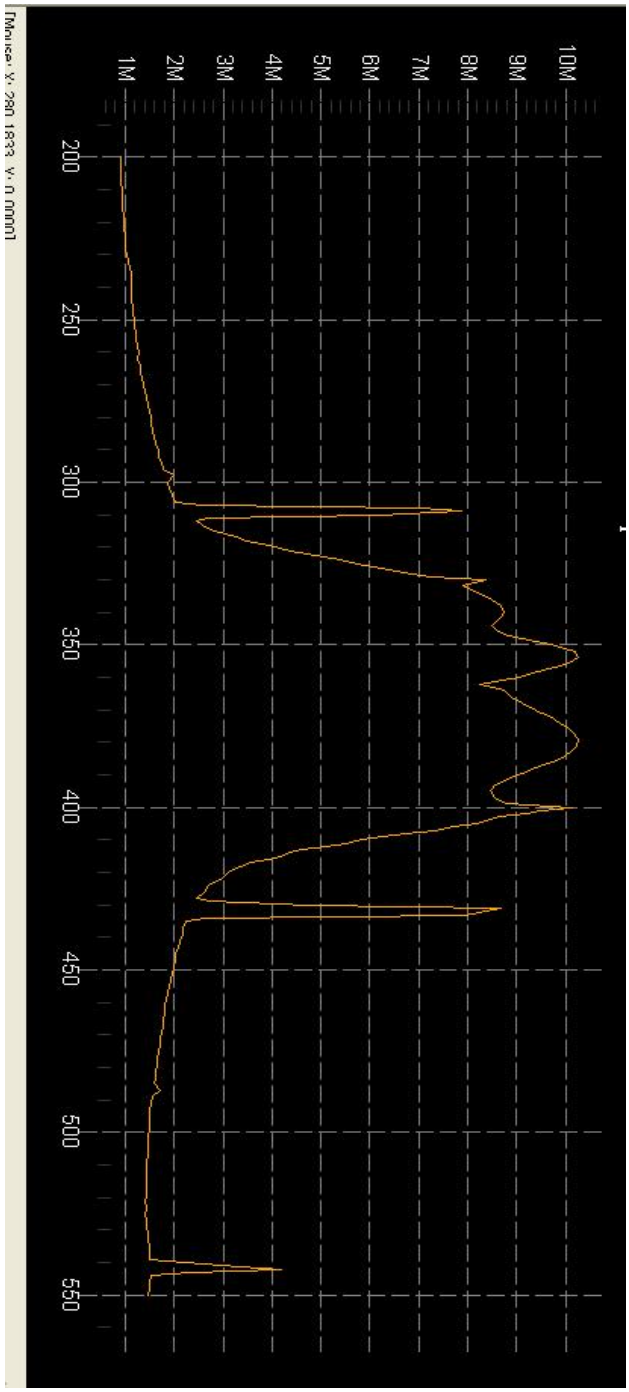
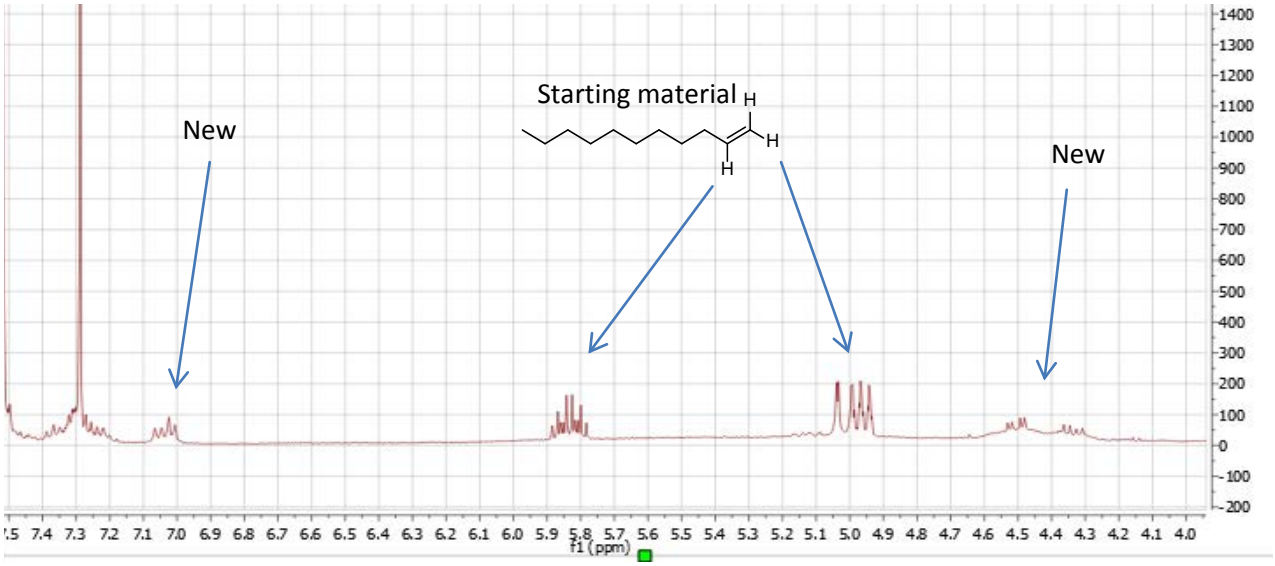
Appendix A. Absorbance, Emission and NMR Spectra



Spectrum A1. UV spectrum of TBADT and NFSI



Spectrum A2. Emission spectrum for UV-BLB lamp



Spectrum A3. Crude ^{1}H NMR spectrum ($CDCl_3$; expanded 7.5-4.0 ppm) for allylic fluorination of undecene.

Appendix B. X-Ray Structure of 6-Bromocamphor

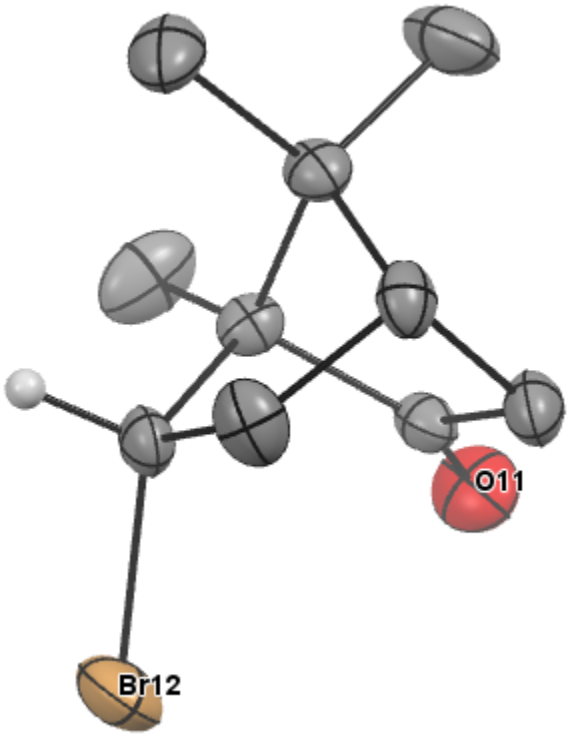


Figure B1. **ORTEP representation of 6-bromocamphor (20% probability, hydrogen atoms omitted for clarity)**

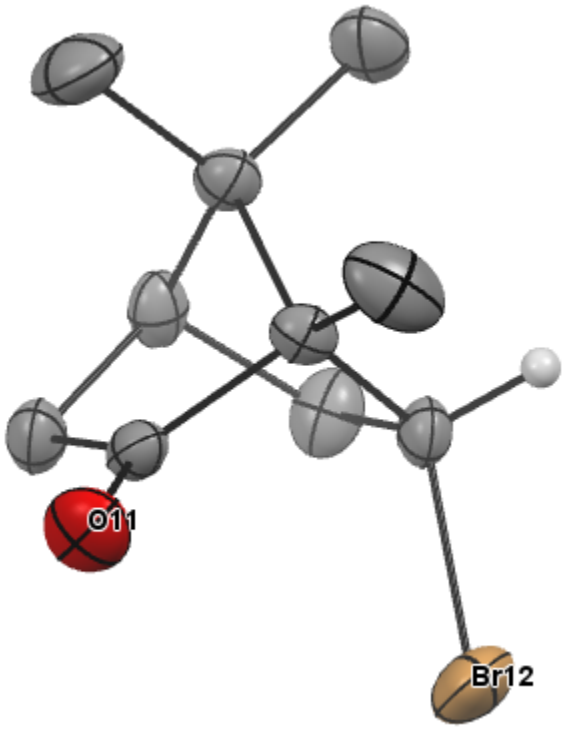


Figure B2. **ORTEP representation of 6-bromocamphor (20% probability, hydrogen atoms omitted for clarity)**