EXPANSION OF THE APPLICABILITY OF THE TRUCE-SMILES REARRANGEMENT

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BY

LYNDON GREGORY SWICK

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ABSTRACT

EXPANSION OF THE APPLICABILITY OF THE TRUCE-SMILES REARRANGEMENT

Lyndon Swick

Supervisor:

Lakehead University

Dr. C. Gottardo

The Truce-Smiles rearrangement is a synthetically useful and easily performed reaction which can be used to condense multiple steps of a synthesis. The nucleophilic aromatic substitution in this reaction produces a chiral center in the rearrangement product. A variety of rearrangement substrates has been prepared and investigated. Investigations into tether functionalization, tether length, pyridyl ring systems and introduction of a second heteroatom into the tether are reported. It has been shown that the rearrangement prefers nitrile tether functionalization. For ethyl ester tethers that perform the rearrangement, there is a secondary cyclization that results in the formation of an aryl lactone. The rearrangement favours a tether length that proceeds through a 5-membered ring intermediate. Rearrangement was successfully reported for a substrate which utilizes two heteroatoms in the tether, something which has not appeared in the literature previously. Use of a microwave reactor resulted in increased rearrangement yields, in addition to facilitating rearrangements that were previously unsuccessful using conventional heating with an oil bath. Use of chiral ionic liquids (CILs) is an excellent approach toward *green* chemistry due to their high solubility power, coupled with their ability to be recycled and reused over multiple reactions. Over recent years, there has been an increasing interest in investigating the use of CILs as solvent systems to selectively induce chirality in reactions; resulting in the enantioselective formation of products and reduced waste. A variety of CILs have been prepared and tested for their ability to serve as solvents and impart chirality on the reaction. The CILs were successfully used as reaction solvents, however, there is no strong chiral induction observed.

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TABLE OF CONTENTS

CHAPTER ONE: REVIEW OF THE TRUCE-SMILES REARRANGEMENT AND IONIC LIQUIDS

CHAPTER TWO: INVESTIGATION INTO SUBSTRATE DESIGN FOR THE TRUCE-SMILE REARRANGEMENT

CHAPTER THREE: TRUCE-SMILES REARRANGEMENT UTILIZNG CHIRAL IONIC LIQUIRD SOLVENT SYSTEMS

LIST OF TABLES

LIST OF FIGURES

LIST OF REACTION SCHEMES

SYMBOLS AND ABBREVIATIONS

[citBr-me]   1-[(3S)-3,7-dimethyloct-6-enyl]-3-methyl-1H-imidazolium bromide

[citBr-but]   1-butyl-3-[(3S)-3,7-dimethyloct-6-enyl]-1H-imidazolium bromide

[butmetimid][camph-R]   1-butyl-3-methylimidazolium R-camphorsulfonate

[butmetimid][camph-S]   1-butyl-3-methylimidazolium S-camphorsulfonate

CIL   chiral ionic liquid

DCM   dichloromethane

DMF   dimethylformamide

DMSO   dimethyl sulfoxide

% *ee*   enantiomeric excess

FT-IR   Fourier transform - infrared spectroscopy

GC   gas chromatography

HRS   hours

IL   ionic liquid

MS   mass spectrometry

NMR   nuclear magnetic resonance

α_{obs} observed rotation

$[\alpha]_D^{20}$ specific rotation, 20°C using sodium lamp, λ= 589.0 nm

TLC   thin layer chromatography

TS   Truce-Smiles

CHAPTER ONE: REVIEW OF THE TRUCE-SMILES REARRANGEMENT AND IONIC LIQUIDS

1.1 Truce-Smiles Rearrangement

1.1.1 General Overview

Rearrangement reactions represent some of the most efficient and well-designed approaches to a synthesis[1]. By taking advantage of intramolecular reactivity and in some cases selectivity, large structural changes can be performed. They are also an excellent atom economical approach to condense multiple steps in a synthesis[1]. The Truce-Smiles rearrangement is best described as an intramolecular nucleophilic aromatic substitution with a generated carbanion serving as the nucleophile (Scheme 1). It results in the formation of a new sp^3 C-C bond and a new chiral center giving this reaction tremendous synthetic potential. The Truce-Smiles rearrangement was first reported over 60 years ago, and since then various publications have reported on this reaction, however, given its potential utility it has been relatively under studied[1].
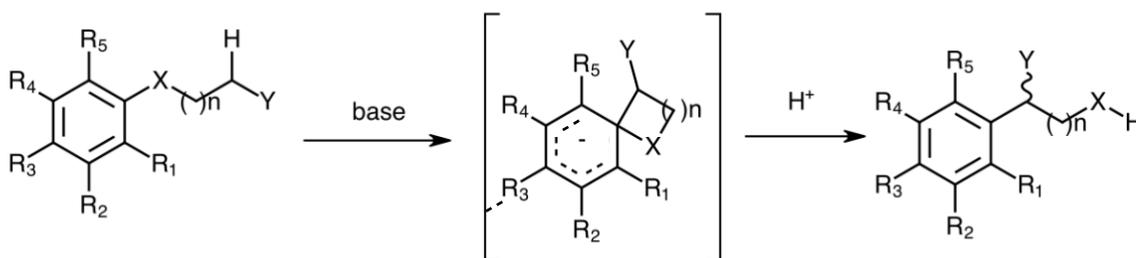
Scheme 1. Truce-Smiles rearrangement.

The Truce-Smiles rearrangement is a modification from a previous reaction, the Smiles rearrangement. First reported on in 1931, Smiles demonstrated the rearrangement of hydroxy-sulfones[2] via an intramolecular nucleophilic aromatic

substitution reaction, where the nucleophile is a heteroatom (Scheme 2). The reaction proceeds in a step wise fashion generating a spiro-bicyclic Meisenheimer adduct as the intermediate; a similar intermediate to that shown in Scheme 1. Since the nucleophile for the Smiles rearrangement must be a heteroatom, functional groups such as alcohols, amines or thiols are excellent choices to perform this reaction[1,3]. In 1958, Truce reported the modified rearrangement utilizing a non-terminal carbanion nucleophile, which would then go on to be called the Truce-Smiles rearrangement (Scheme 1)[1,4].
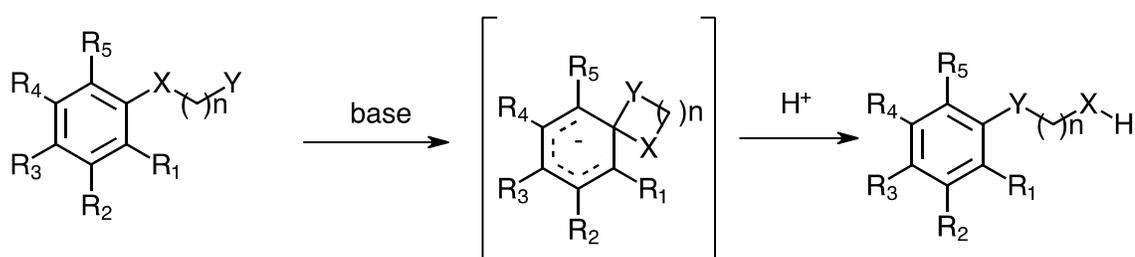
Scheme 2. Smiles rearrangement.

Mechanistic investigations into the Truce-Smiles rearrangement have been completed by multiple groups and all have demonstrated the same findings showing the reaction proceeding through an intramolecular nucleophilic attack (Scheme 1)[1,5,6]. Separate competition experiments performed by Naito et al.[5] and Wood et al.[6] showed that even when a rearrangement substrate is in the presence of other aromatic electrophiles, the intramolecular rearrangement product was exclusively formed. In addition, Wood et al., have performed *in-situ* NMR studies indicating the presence of the spirocyclic Meisenheimer adduct as the intermediate (Scheme 1)[6].

1.1.2 Stabilization of the Meisenheimer Adduct

As shown in Scheme 1, the Truce-Smiles rearrangement proceeds through a negatively charged Meisenheimer adduct. For successful rearrangement to occur, the stabilization of this intermediate is crucial. From reviewing the literature, the stabilization takes the form of either having electron-withdrawing groups attached to the ring, or the presence of electronegative heteroatoms within the ring itself.

1.1.2.1 Electron Withdrawing Groups on Aryl Ring

The presence of electron-withdrawing groups on the aryl ring serves to increase its electrophilicty for nucleophilic attack and stabilization of the generated Meisenheimer adduct. The stabilization of the intermediate through electron-withdrawing groups appears to be critical as no reported cases have been successful without some form of electron withdrawal directly on the aryl ring. Although the current literature is mostly dominated by rearrangements with the electron withdrawing groups at the *para* position, due to resonance stabilization (Scheme 3), and minimal steric hindrance, substitution at the *ortho* position is also very successful[1,6]. Limited examples of *meta* substitution are available since this substitution pattern allows for minimal charge delocalization. In addition to stabilization of the Meisenheimer intermediate, electron-withdrawing groups direct the incoming nucleophile to the desired *ipso* carbon giving the 1,1 adduct intermediate and reduce the likelihood of undesirable side reactions, which would form the 1,2 or 1,3 adduct as the intermediate.
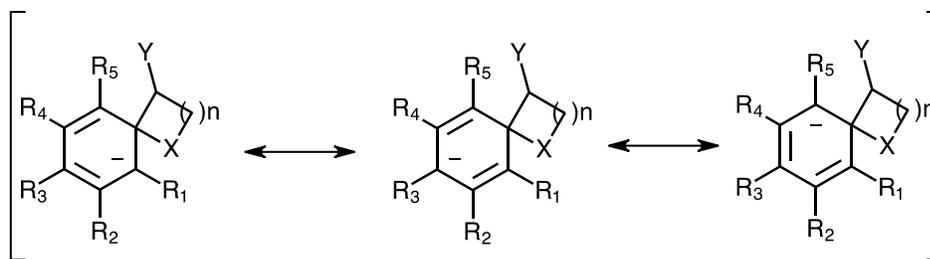
Scheme 3. Major Resonance Structures of Meisenheimer Adduct.

Work done by Wood et al. has outlined how the presence of *ortho* substituents on their own can give higher yields than the *para* substituted analog[6]. In addition, they outlined that for bromo and chloro groups, the presence of *ortho* substituents in a 2,6 fashion facilitated a successful reaction and resulted in higher yields, while for the 2,4-isomer the reaction was not as successful and gave poorer yields for the dibromo and dichloro compounds[6]. From surveying the literature, the steric interactions between the incoming nucleophile and the ring substituents are an important factor for successful rearrangement, however to date there is no systematic review of the effect of these sterics with mono and di *ortho*-substituted substrates.

It was initially thought that only strong electron-withdrawing groups, such as a nitro group, could successfully facilitate the reaction, but research into a broad array of different reaction substrates has shown that moderate and weak withdrawing groups such as cyano, aprotic acyl groups and halides also work[1,6]. The use of halides needs to be in a di- or tri- substituted manner at the *ortho* and *para* positions to allow for successful intermediate stabilization since their electron withdrawing effects are the weakest[6]. To date there is considerable literature with varying electron withdrawing groups on the ring which facilitate a successful reaction. Wood et al. have published a systematic review which outlines functional groups that offer a sufficient electron withdrawing effect to allow rearrangement[6]; however, there are still many groups which are left untested. In addition,

their work was focused on a single tether, which leaves other aspects of substrate design such as the heteroatom, tether length, and functional group on the tether untested systematically.

1.1.2.2 Presence of Heteroatom Within Aryl Ring - Pyridine Substrates

In addition to electron withdrawing functional groups attached directly to the aromatic ring, another way to stabilize the intermediate is use of N-substituted rings. Nitrogen within the ring can withdraw electron density through inductive and mesomeric effects[1]. It was previously discussed that presence of electron-withdrawing groups at the *ortho*, or 2, and *para*, or 4, positions offers the best stabilization due to resonance, and this rational is also applicable for the position of the N atom within the ring. In the literature, there are successful rearrangements of N-substitutions at the 2, 3, or 4 positions (Scheme 4), however the literature is dominated by N in positions 2 and 4[1,7] as the electronegative nitrogen can stabilize the negative charge.

N-2   N-3   N-4
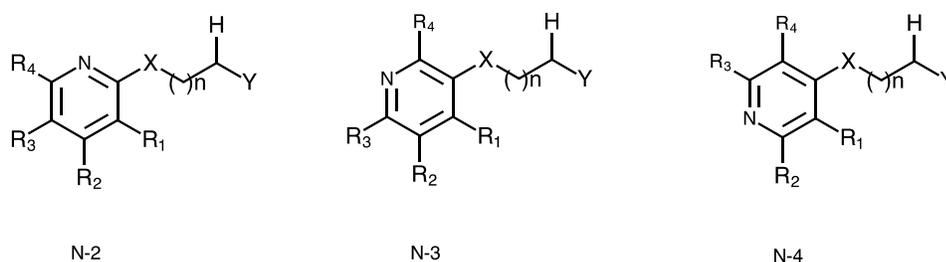
Scheme 4. Pyridine Substrates.

Although N-substitution at the 2-position appears most frequently in the literature, substitution at the 4-position seems to offer the best results in terms of reaction time and higher yields[1,7]. In addition to mono substituted azines, di and tetra substituted analogs have also been reported with success. The Truce-Smiles rearrangement has been

performed using other heterocycle substrates such as benzothiazole, thienopyridine and benzothiophene as well[1,10-12].

1.1.3 Substrate Tether Considerations

In addition to the aryl ring itself, other considerations which play a crucial role in allowing the rearrangement to successfully occur include the presence of a heteroatom and functional group(s) on the tether, in addition to the length of the tether between the nucleophilic carbon and the aryl ring.

1.1.3.1 Presence of Heteroatom Within Tether

The presence of a hetero atom (X in Scheme 1) connects the nucleophilic tether to the ring and then serves as the leaving group to give the rearrangement product. Heteroatom presence is beneficial since it assists in ring activation by reducing electron density on the *ipso* carbon and increasing its electrophilicity. The heteroatom bond cleavage from the ring is favored by its better leaving group ability and decreased nucleophilicity with respect to the incoming carbanion. This prevents the reversal of the rearrangement back to starting material since the carbanion is such a strong nucleophile and an exceptionally poor leaving group. Although the presence of the heteroatom adjacent to the aryl ring greatly helps facilitate the rearrangement, it is not an absolute requirement for the reaction to proceed as there are successful reports of C-C rearrangements, in addition to N-C, P-C, O-C and S-C rearrangements in the literature[1,12-32]. From reviewing the literature there are no published reactions which take advantage of a second heteroatom within the tether. It is unclear how this would affect the reaction

and something which warrants investigation as it could add further complexity to the reaction and allow for a whole other multitude of possible rearrangement precursors. Likely heteroatoms candidates for this should include O, N and S.

1.1.3.2 Electron Withdrawing Group on the Tether

For successful carbanion generation, there is a need for an electron withdrawing group on the adjacent carbon (Y in Scheme 1) to allow a selective deprotonation and stabilization of the anion[31,32]. Examples found in the literature to date show that nitriles give the best results[1]. Currently there is no systematic review of other feasible tether function groups that will work in the Truce-Smiles rearrangement with various substrate combinations. It seems likely that since the functional group is placed in such close proximity to the *ipso* carbon in the transition state there should be some influence. Some functional groups which warrant further investigation include esters, ketones, halides, and sulfonyl groups.

1.1.3.3 Intermediate Spirocyclic Ring Size

The size of the ring formed in the intermediate depends on how far away the carbanion is from the ring (tether length), Scheme 5. There are successful rearrangements reported for the generation of a bicyclic Meisenheimer adduct with secondary ring sizes ranging from three to six, however, ring sizes of three and four are rare[17,32-37].
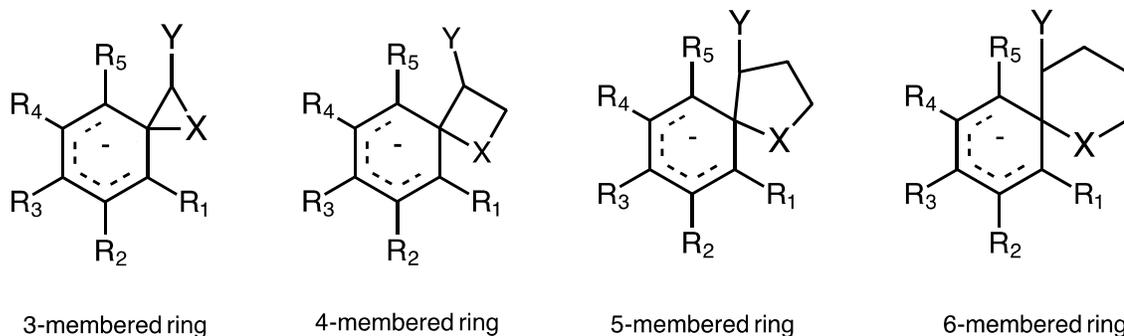
Scheme 5. Illustration of How Tether Length Effects Intermediate Secondary Ring Size.

The scarcity of examples with smaller ring sizes is a result of excessive ring strain formed in the intermediate. It should be noted that the successful rearrangements with secondary ring sizes of three and four which are reported in literature have highly substituted tethers or substitutions with large / steric groups[1]. This suggests that through favourable steric interactions, the nucleophilic carbanion is placed in the desirable and more reactive position[1]. Generation of 6-membered rings are also uncommon in the literature, but have been successful using tethers which have a point of unsaturation present[1,14,38,39]. This suggests that fewer degrees of freedom of rotation are beneficial for the formation of the larger intermediates[1]. Most examples in the literature have focused on the generation of 5-membered ring intermediates[25-28,36]. The 5-membered secondary ring has the lowest activation energy in comparison to the smaller and larger intermediates. This due to a combination of reduced ring strain and proximity of the carbanion relative to the aryl electrophilic carbon[1]. There are no reported examples in the literature for intermediates with ring size greater than six, something which deserves greater attention, although cyclization due to entropic factors may provide difficult.

1.1.4 Tandem Cyclization After Successful Rearrangement

The leaving group which results in the Truce-Smiles product (X in Scheme 1) can further react in tandem cyclization reactions, displacing ortho substituents on the aryl ring or react with the electron withdrawing group on the tether (Y in Scheme 1). In fact, many of the reported examples of Truce-Smiles rearrangement include a tandem cyclization reaction[1]. One example of a tandem reaction following the Truce-Smiles rearrangement was published by Wood et al. where the presence of a bromo substitution at the ortho was a site of a secondary aromatic substitution reaction, forming the bicyclic structure seen in Scheme 6 i)[6]. Interestingly they showed a successful Truce-Smile rearrangement for the 2,4,6-tri chloro and 2,6-di bromo substrate, however those compounds did not undergo tandem cyclization as shown in Scheme 6. Another example of a tandem reaction following the Truce-Smile rearrangement was also published by Wood et al. where the presence of an *ortho* cyano group was the site of a nucleophilic attack, forming the tricyclic structure shown in Scheme 6 ii)[6]. They outlined how through manipulation of solvent - DMF vs DMSO- they were able to either exclusively collect the tandem cyclization product or a combination of the cyclization product and the Truce-Smiles product. This manipulation of solvent was also tested for the reaction shown in Scheme 6i, however it was unsuccessful as the Truce-Smiles rearrangement would not proceed in DMSO for that substrate[6]. This confirms that choice of solvent is crucial for the Truce-Smile rearrangement.

i)

ii) DMF

DMSO

0%

44%

17%

31%
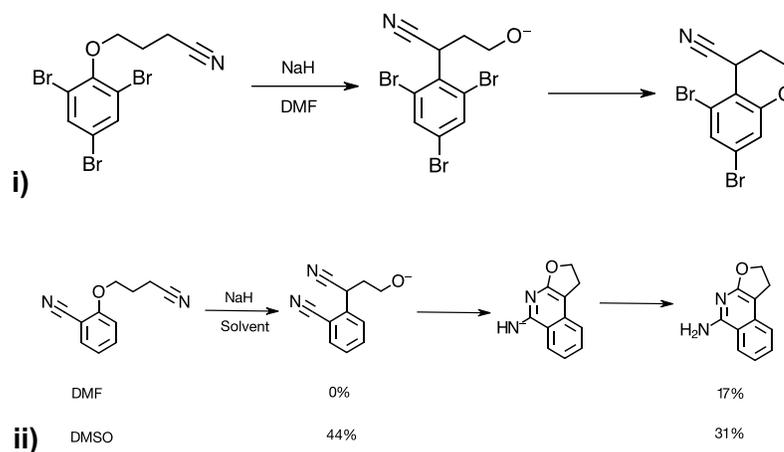
Scheme 6. Tandem Cyclization Following the Truce-Smiles Rearrangement[6].

1.1.5 Chiral Outcomes and Considerations

Scheme 1 shows that the rearrangement product of the Truce-Smiles reaction generates a chiral center adjacent to the aryl ring. Predictable and controllable conditions for chiral control on Truce-Smiles rearrangement have received little attention which might be one reason why it is an underutilized reaction. One study using an enantiomerically pure substrate with the tether containing a chiral center, resulted in relatively high diastereomeric excess[40]. There was no investigation into the mechanism behind this outcome. The limitation to this type of control is the need for an additional functional group on the tether which may cause steric crowding at the transition state, thus limiting its applicability to already crowded substituents. In addition, if the chiral functional group on the tether is not intended to be present in the final product of a multi-step synthesis, an additional step is needed to remove it. Development of chiral control for the Truce-Smiles rearrangement should allow for the use of various ring sized intermediates and multiple substrates.

1.2 Review of Ionic Liquids

1.2.1 History of Ionic Liquids

Ionic liquids (ILs) represent a diverse class of compounds which are highly viscous liquids at room temperature. They are organic salts which consist of an ionic organic group that is complimented with either another oppositely charged organic group or non-organic counter ion. Figure 1 illustrates some common IL cations and anions which can be found in the literature. It is clear there are limitless ILs which can be formed as each one of the charged partners can be modified with different substituents and counter ion partners.

Cationic Portion   **Anionic Portion**
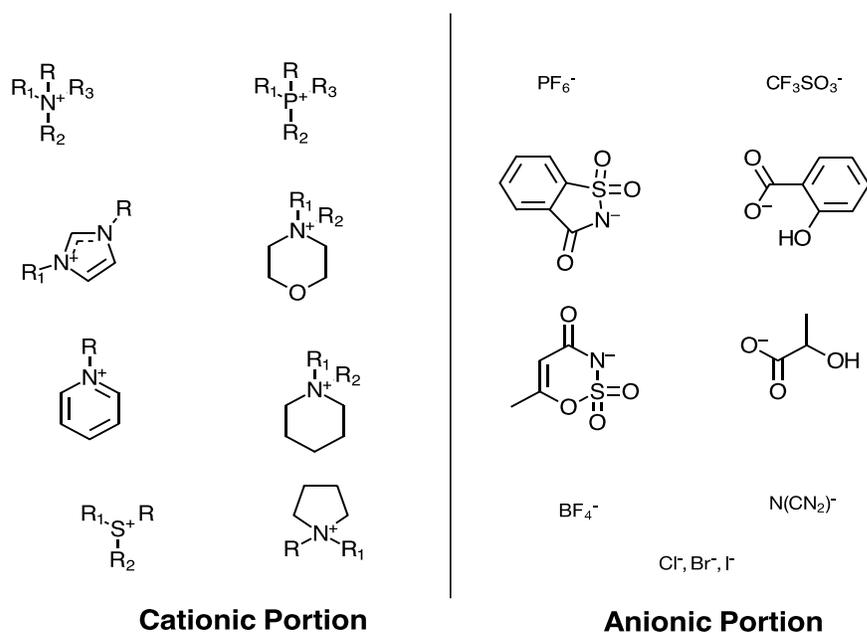
Figure 1. Examples of CIL Counter Ions.

The R group for the cations are usually some form of alkyl group, however it can include hydroxyl or hydrogen substitution[41].

The presence of ILs in literature can be dated as far back as 1888[41,42], however, the first appearances of ILs in literature was brief and they were not thoroughly investigated since their utility was not clear. It was not until the end of the 20th century, in 1996, when Seddon outlined the potential uses for ILs, such as substitutes for

conventional solvents, that the global community began to take an interest in these organic salts. As they are still a relatively new area of research, significant examples in the literature have been seen only recently [43-45]. As research expands, so has the definition of what constitutes an IL; today it is inclusive to any organic salt which has a melting point less than 100°C[41].

1.2.2 Ionic Liquids as Solvents

ILs represent an effective approach toward green chemistry due to their atmospheric stability, very low vapor pressure and high solubility power (able to dissolve organic and inorganic material)[41]. Their robust solubility power is attributed to their ability to interact via hydrogen bonding, hydrophobic interactions, and $\pi-\pi$ or electrostatic interactions[46]. All of these characteristics makes them an excellent replacement for traditional solvents, which unlike ILs, tend to have high vapor pressure and are more selective in their solubility. In addition to green chemistry, this low vapour pressure is also safer for the researcher as they are not exposed to chemical fumes over prolonged careers. With careful choice of an IL solvent that is stable under the reaction conditions, the IL can be completely recycled and reused multiple times without any significant degradation[44,45]. Their solubilizing power is complimented by their diversification since depending on reaction being performed, each ionic partner can be custom made and tuned to meet specific needs. ILs have been referred to as *designer solvents* since slight modification of the structure, or the corresponding counter ion, can drastically change their properties[47]. Work done by Marsh et al. has demonstrated that for the 1-alkyl-3-methylimidazolium cation, changing the anion from PF_6^- to BF_4^-, significantly increases the water solubility, while substituting the anion for Tf_2N^-, decreases the water solubility.

In addition, modification of the organic cation anion from 1-methyl to 1-nonyl, resulted in the IL being immiscible with water[47]. Other properties, such as melting point and viscosity, can be easily altered by modifying the amount of alkyl character and the extent of asymmetry. It has been shown that substituting small organic cations with bulky and asymmetric ions, results in a melting point decrease. Furthermore, the increase of alkyl character increases the viscosity[47]. Since ILs tend to be very viscous, their main limitation in a synthesis is they lack the ability to adequately mix systems[47]. However, by being able to predictably manipulate viscosity, allows researchers to tailor the ILs to their synthetic needs. Systematic investigations of various ILs would allow researchers to have an indication of which ILs would be best suited for their specific needs. Having an initial theoretical approach for which IL would be best suited eliminates the need to then perform multiple reactions to determine the most favourable combination, thus eliminating overall waste in material and time.

1.2.3 Chiral Ionic Liquids

Chiral Ionic Liquids (CILs) meet the above description and contain at least one chiral center in the compound which can be placed on either ionic partner: cation or anion. CILs with multiple chiral centers on either ionic portion can also be synthesized; however, the literature focuses on utilizing a single chiral center in the compound. By varying the number of chiral centers and their location further compounds their complexity. In addition to also encompassing the same advantageous properties and uses of ILs, CILs have other applications due to their specificity which stems from their chirality. Other applications of CILs include organocatalysis in asymmetric aldol reactions, chiral phases

in gas chromatography for enantioselective elution, increased stereoselectivity and reduction of side reactions in polymerizations[48-52].

1.2.4 Chiral Ionic Liquids in a Selective Synthesis

Arguably one of the most practical applications is the use of CILs for selective chiral synthesis. There are many reports of CILs having success at inducing chirality for a variety of different reactions, with varying results of enantiomeric excess (% ee). The first reported success of using CILs to induce chirality was reported by Vo-Thanh et al. who reported a 44% ee in their asymmetric Baylis-Hillman addition (Scheme 7). Protection of the hydroxyl group on their CIL resulted in a significantly lower %ee, which suggests a hydrogen-bonding interaction at this site is crucial for chiral induction in this system[45,48].
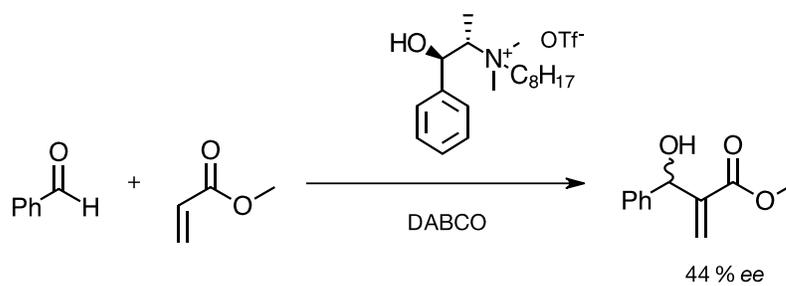
Scheme 7. Asymmetric Baylis-Hillman Addition using CIL.

Another example found in the literature which utilized a CIL as the solvent to impose chirality was reported by Bica et al in their Diels-Alder reaction (Scheme 8)[45,49]. Although their CIL did not impose enantioselectivity, it did impose a high degree of diastereoselectivity. It was also reported that the CIL was recycled and used multiples times with consistent yields and selectivities[45,49]. Other examples which have shown success in terms of stereoselective outcome include asymmetric alkylation of aldehydes, Michael additions, and organocatalysis[45, 48,53,54].

endo / exo = 7.3/1
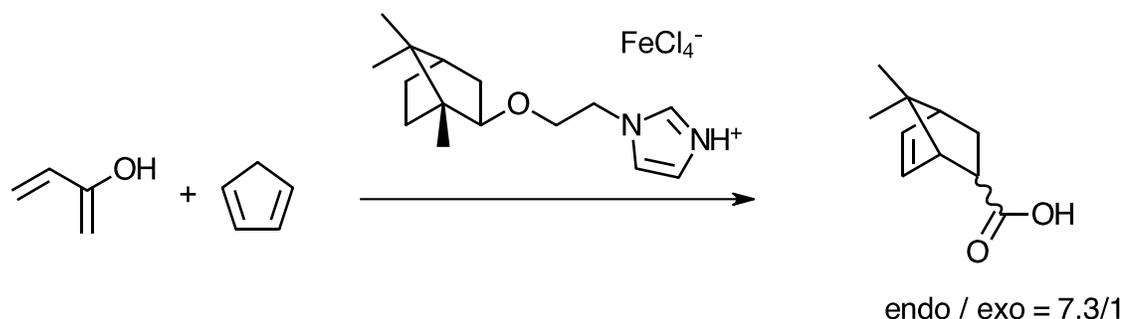
Scheme 8. Diels-Alder Reaction using CIL.

To date, studies have not presented sufficient mechanistic investigations into the method by which CILs cause chiral induction. It seems probable that the CIL interacts with reaction transition states either through non-bonding charge interactions or placement into a chiral pocket that utilizes steric interactions. Performing an in-depth mechanistic investigation for a reaction can potentially lead to the ability to predict which CIL structure will yield the best results. There is a strong correlation between the structure of a CIL and the enantioselective outcome of a reaction as even a slight modification of the structure can have a dramatic effect on enantiomeric excess[45]. Although there is considerable work done on enantioselective syntheses in the literature, such as utilizing organometallic catalysts, CILs offer a unique approach since it is the solvent itself that is imposing the chirality, and, in theory, it can be recycled over many reactions.

1.3 Project Objectives

The main objective of this project is to further expand on the literature regarding the Truce-Smiles rearrangement. This will be accomplished by synthesizing a variety of rearrangement substrates with differing functionalization on both the aromatic ring and the tether. These prepared substrates will then be subjected to a variety of reaction

conditions to determine their feasibility to undergo rearrangement. The successful rearrangement substrates will be tested in a CIL solvent system to determine if they can impart chirality onto the product, which will be determine by comparing optical rotations, and if necessary, using a chiral GC column to determine the %*ee*.

CHAPTER TWO: INVESTIGATION INTO SUBSTRATE DESIGN FOR THE TRUCE-SMILE REARRANGEMENT

2.1 Introduction

Substrate structures chosen for Truce-Smile investigations focus on substituted aromatic ring systems which were prepared separately with four different tethers: 4-bromobutyronitrile, ethyl-4-bromobutyrate, 5-bromovaleronitrile and ethyl-5-bromovalerate. The ester and nitrile group of the tethers sufficiently lowers the pKa of the proton on the α-carbon which allows for selective deprotonation and stabilization of the carbanion which is formed[6]. The aromatic rings, phenyl or pyridyl, were substituted with various electron-withdrawing functional groups at the *ortho*, *meta* and/or *para* positions. The use of electron-withdrawing groups helps activate the aromatic ring for a nucleophilic substitution and delocalization of the negative charge generated in the intermediate[1,6]. Work previously published by Wood et al.[6] has already investigated some of the substrates we present here using the 4-butyronitrile tether. The work previously done has demonstrated that increasing reaction temperature can provide sufficient energy for the rearrangement to occur, however, Wood et al.[6] reported several unsuccessful rearrangements even at elevated temperatures, reaching a maximum of 60°C. Here we report the outcome of subjecting the substrates which were unsuccessfully rearranged by Wood et al.[6], in addition to our own modified substrates, to an increased temperature of 100°C to see if this would provide sufficient energy for the rearrangement to occur. We have followed the same optimized procedure used by Wood et al. which uses NaH as the base (it is strong enough to generate the carbanion and is non-nucleophilic) with DMF as the solvent.

2.2 Results and Discussion

2.2.1.1 Investigations into Phenolic Substrates Which Generate 5-Membered Ring Intermediates

Outlined in Table 1 are aryl ether rearrangement substrates which were prepared via a Williamson ether synthesis. Purity of the collected product after silica gel purification was determined by GC, TLC, MS and ^{1}H NMR. Once the rearrangement substrates were

Table 1. Synthesis of Aryl Ethers with Varying Functional Groups; Nitrile Tether and 5-Membered Ring Intermediate Tether.

Entry	1	R	% Yield 1
1	a	H	61
2	b	2-Br	73
3	c	3-Br	46
4	d	2,4-Br	63
5	e	2-I	46
6	f	3-I	74
7	g	4-I	54
8	h	2-NO$_2$	71
9	i	4-NO$_2$	78
10	j	4-CN	78
11	k	2-CHO	70
12	l	4-CHO	93
13	m	2-COCH$_3$	90
14	n	4-COCH$_3$	91

prepared they were tested for their ability to undergo a Truce-Smiles rearrangement (Table 2). The ethers which were prepared all would proceed through a 5-membered ring intermediate as shown in Scheme 5. It can be seen that compounds **1a-g**, which were not successfully rearranged in previous literature reports, were still unsuccessful at the elevated temperatures.

Table 2. Truce-Smiles Rearrangement of Prepared Aryl Ethers; Nitrile Tether and 5-Membered Ring Intermediate Tether.

Entry	1	R	Temperature / °C	% Yield 2
1	a	H	100	-
2	*b	2-Br	100	-
3	*c	3-Br	100	-
4	*d	2,4-Br	100	-
5	*e	2-I	100	-
6	*f	3-I	100	-
7	*g	4-I	100	-
8	+h	2-NO$_2$	0	47
9	+i	4-NO$_2$	20	80
10	+j	4-CN	60	42
11	k	2-CHO	100	-
12	l	4-CHO	100	-
13	m	2-COCH$_3$	100	-
14	n	4-COCH$_3$	60	30

* Indicates compounds previously tested by Wood e al.[6] that were unsuccessful at 60°C.

+ Indicates compounds previously tested by Wood et al[6]. that were successful.

Compounds **1h-j** yielded desirable rearrangement products (**2h-j**) as expected since they have the strongest electron withdrawing groups. These compounds were previously reported in the literature[6], which served as confirmation that our procedure was working. For substrates, **1k** and **1l**, there was no conversion as only unreacted starting material was collected and the same lack of reactivity is observed with the ortho methyl ketone substrate **1m**. However, **1n** did give a successful rearrangement. This trend of reactivity observed with the carbonyls is expected since the methyl ketone substitution offers a stronger electron withdrawing effect than the formaldehyde. A likely reason why there was no reaction for the ortho substituted ketone, **1m**, is due to increased steric interactions in the transition state. Since the carbonyl presents an electrophilic site on our aromatic ring, it was expected that when a carbonyl group is placed at the ortho position, such as in compounds **1k** and **1m**, the carbanion might attack the carbonyl. This type of reactivity was also reported by Wood et al.[6] when instead of using a methyl ketone, phenyl ketone derivative was used. Interestingly, no such reaction was observed as only starting material was recovered. A potential explanation for this is that the generated carbanion is strong enough to deprotonate the ketone which would then be reprotonated upon reaction work up. For all subsequent Truce-Smile reactions that showed lack of reactivity, starting material was exclusively collected and identity was confirmed using TLC.

In the next part of this project the electron withdrawing group on the tether was modified to an ester, while still maintaining the intermediate secondary ring size at five. Ethyl ester was chosen because in addition to allowing selective deprotonation to generate the carbanion, it will remain stable and unreactive in our reaction conditions. Shown in Table 3 are the prepared aryl ethers which utilize a tether with ethyl ester. In a similar fashion as reported above, the prepared aryl ethers were then tested to determine

their viability to undergo a Truce-Smiles rearrangement. As before, compounds which could not be rearranged successfully at room temperature were heated to a maximum of 100°C. Comparing Table 4 with Table 2, it can be seen that substrate **3d** has a bromo substitution at the *para* position. This analog was not tested using the nitrile tether simply due to the order of which the substrates were originally synthesized. Since the 2,4 dibro-

Table 3. Synthesis of Aryl Ethers with Varying Functional Groups; Ethyl Ester Tether and 5-Membered Ring Intermediate Tether.

Entry	3	R	% Yield 3
1	a	H	77
2	b	2-Br	74
3	c	3-Br	57
4	d	4-Br	69
5	e	2,4-Br	66
6	f	2-I	41
7	g	3-I	51
8	h	4-I	44
9	i	2-NO$_2$	75
10	j	4-NO$_2$	64
11	k	4-CN	83
12	l	2-CHO	77
13	m	4-CHO	77
14	n	2-COCH$_3$	67
15	o	4-COCH$_3$	88

mo analog, **1d**, did not successfully rearrange, we extrapolate that the 4-bromo on its

own still would give the same results, so this combination was not pursued. It can be

seen that **3d**, in addition to the majority of the other substrates, did not yield a Truce-

Smiles product and starting material was recovered (Table 4).

Table 4. Truce-Smiles Rearrangement of Prepared Aryl Ethers; Ethyl Ester Tether and 5-membered ring intermediate.

Entry	3	R	Solven	Temperature /	% Yield 4	
1	a	H	DMF	100	-	
2	b	2-Br	DMF	100	-	
3	c	3-Br	DMF	100	-	
4	d	4-Br	DMF	100	-	
5	e	2,4-Br	DMF	100	-	
6	f	2-I	DMF	100	-	
7	g	3-I	DMF	100	-	
8	h	4-I	DMF	100	-	
9	i	2-NO$_2$	DMF	100	-	
10	j	4-NO$_2$	DMF	60	50	**(5j)**
11*	j	4-NO$_2$	DMSO	60	46	**(5j)**
12	k	4-CN	DMF	100	-	
13	l	2-CHO	DMF	100	-	
14	m	4-CHO	DMF	100	-	
15	n	2-COCH$_3$	DMF	100	-	
16	o	4-COCH$_3$	DMF	100	-	

*Addition performed at room temperature.

The only ester tether substrate which yielded rearrangementproduct was compound **3j** (entries 10 and 11, Table 4). Interestingly the product collected was that of a tandem cyclization to form an aryl gamma lactone, **5**. The proposed reaction path for this reaction is outlined in Scheme 9. As mentioned earlier, the literature provided examples in which a change in solvent prevents intramolecular reactivity of the alkoxide leaving group. To determine if the alkoxide could be trapped and prevent the cyclization into the lactone, the reaction was performed in DMSO (Table 4, entry 10), which still resulted in **5j** as the exclusive product. All other rearrangement attempts resulted in incomplete conversion with collection of starting material.
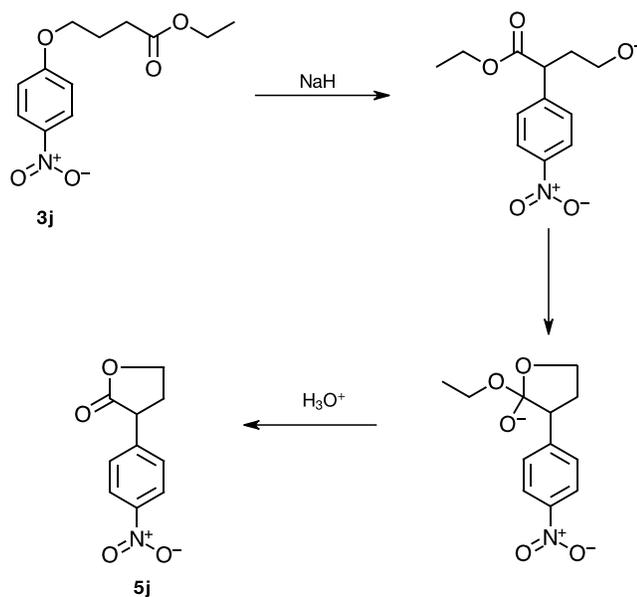
Scheme 9. Proposed Reaction Pathway of Aryl Gamma Lactone **3j** to **5j**.

As mentioned previously, stabilization of the transition state is the most important aspect in determining the success of the rearrangement. Although substrates **3i** and **3j** have the same electron withdrawing group present, NO_2, the location is the only logical explanation for the difference in reactivity. Placing the nitro group at the ortho position increases steric interactions for the incoming nucleophile and the transition state. This

increased steric interference is further supported when considering the relative size of a nitrile vs ethyl ester functional group. The smaller size of the nitrile explains why it could successfully undergo rearrangement for substrate **1h**, but not **3i**. Furthermore, these increased steric interactions provide an explanation as to why there was overall poor reactivity with the other ester substrates shown in Table 4.

2.2.1.2 Conclusions and Future Work

We have shown that for our substrates which generate a 5-membered ring in the intermediate, the product yield is correlated with the strength of the electron withdrawing group. This aligns with what was previously discussed in chapter one, in addition to the available literature. For our nitrile tether substrates, our initial goal for this part of the project was to determine if additional heating could facilitate rearrangement of substrates which were previously unsuccessful in the literature. We report no successful reactions for substrates which were previously unsuccessful in the literature, even at an increased reaction temperature of $100^{\circ}C$. There was overall poor reactivity observed for our ethyl ester tether substrates, as only the 4-NO_2 functionalized ring system rearranged, which was then followed by the secondary cyclization into a gamma lactone. Although we were unable to prevent the cyclization into the gamma-lactone, this warrants further attention since being able to control the product of the reaction, potentially with choice of solvent, may provide synthetically useful products. To try and reduce the steric interference attributed to the ester functional group on the tether, this systematic investigation could be re-done by making use of methyl ester instead of ethyl ester. The reduced steric interactions might allow the Truce-Smile to be successful for other substrates that contain weaker electron withdrawing groups and thus be able to prepare a greater variety of aryl gamma lactones. We have shown that varying the functional group on the tether

significantly alters the feasibility of the rearrangement. Additional future work should include different electron withdrawing groups on the tether, further expanding the scope of this rearrangement.

2.2.2.1 Investigations into Phenolic Substrates Which Generate 6-Membered Ring Intermediates

Up to this point in the project, the prepared substrates all had the same tether length between the aryl ring carbon (*ipso* carbon of the transition state) and the nucleophilic carbanion; 5-atoms long and thus the secondary ring formed in the transition state is a 5-membered ring. The next logical modification to substrate structure was to change the tether length. As mentioned earlier, few examples in the literature have been reported for tether lengths which result in a 6-membered ring intermediate. In this part of the project the various ring substitutions and electron withdrawing groups on the tether were kept the same as in Table 2 and Table 4, while the tether length was increased by one carbon. The decision to extend the tether, rather than decrease it, was based on available work done by Hollett and Wood which suggests transition states with 6-membered ring intermediates are more successful than 4-membered[55]. Considering this, making the tether longer seemed like a logical starting point. Tables 5 and 7 present the results of the synthesis of these aryl ethers which were then tested for their ability to undergo a Truce-Smiles rearrangement (Tables 6 and 8). Work previously done by Hollett and Wood has already tested **6i** (see Table 5) which showed success (collected 51% yield)[55]. However, their work was focused on investigating tether length while maintaining all substrates aspects, such as ring and tether functional groups the same[55]. Here we report the testing of various ring functional groups, in addition to a different tether functional group.

It should be noted that for the prepared compounds in Table 5, some were made using 5-chlorovalernitrile rather than 5-bromovaleronitrile. This was done to use up reagents which were already in the lab before purchasing more. The compounds prepared using 5-chlorovaleronitrile had lower yields; as expected since Cl is not as good

of a leaving group as Br. Similar to the rearrangements described above, the substrates were subjected to a maximum temperature of 100ºC, and all other experimental aspects were maintained.

Table 5. Synthesis of Aryl Ethers with Varying Functional Groups; Nitrile Tether and 6-Membered Ring Intermediate Tether.

Entry	6	R	% Yield 6
1*	a	H	42
2*	b	2-Br	47
3*	c	3-Br	41
4*	d	2,4-Br	49
5*	e	2-I	54
6*	f	3-I	53
7*	g	4-I	44
8	h	2-NO$_2$	76
9*	i	4-NO$_2$	37
10*	j	4-CN	75
11	k	2-CHO	49
12	l	4-CHO	74
13	m	2-COCH$_3$	74
14	n	4-COCH$_3$	94

* Indicates compounds synthesized using 5-chlorovaleronitrile.

Table 6. Truce-Smiles Rearrangement of Prepared Aryl Ethers; Nitrile Tether and 6-Membered Ring Intermediate Tether.
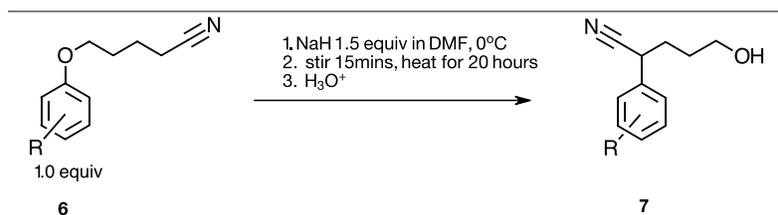
Entry	6	R	Temperature / °C	% Yield 7
1	a	H	100	-
2	b	2-Br	100	-
3	c	3-Br	100	-
4	d	2,4-Br	100	-
5	e	2-I	100	-
6	f	3-I	100	-
7	g	4-I	100	-
8	h	2-NO$_2$	100	-
9	*i	4-NO$_2$	60	51
10	j	4-CN	100	-
11	k	2-CHO	100	-
12	l	4-CHO	100	-
13	m	2-COCH$_3$	100	-
14	n	4-COCH$_3$	100	-

* Indicates compounds previously reported in literature[55].

Table 7. Synthesis of Aryl Ethers with Varying Functional Groups; Ethyl Ester Tether and 6-Membered Ring Intermediate Tether.
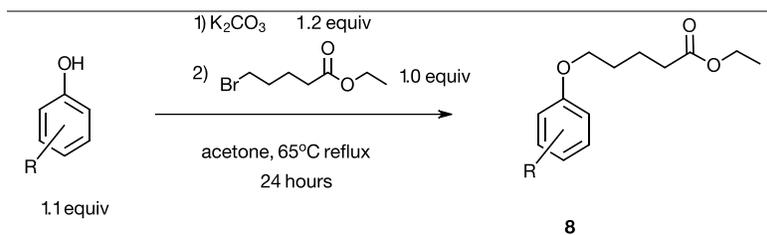
Entry	8	R	% Yield 8
1	a	H	83
2	b	2-Br	55
3	c	3-Br	81
4	d	2,4-Br	74
5	e	2-I	69
6	f	3-I	66
7	g	4-I	75
8	h	2-NO$_2$	84
9	i	4-NO$_2$	53
10	j	4-CN	71
11	k	2-CHO	42
12	l	4-CHO	58
13	m	2-COCH$_3$	63
14	n	4-COCH$_3$	96

Table 8. Truce-Smiles Rearrangement of Prepared Aryl Ethers; Ethyl Ester Tether and 6-Membered Ring Intermediate Tether.

Entry	8	R	Temperature / °C	% Yield 9
1	a	H	100	-
2	b	2-Br	100	-
3	c	3-Br	100	-
4	d	2,4-Br	100	-
5	e	2-I	100	-
6	f	3-I	100	-
7	g	4-I	100	-
8	h	$2\text{-}NO_2$	100	-
9	i	$4\text{-}NO_2$	100	-
10	j	4-CN	100	-
11	k	2-CHO	100	-
12	l	4-CHO	100	-
13	m	$2\text{-}COCH_3$	100	-
14	n	$4\text{-}COCH_3$	100	-

Looking at Tables 6 and 8 we can see that extending the tether length - leading to the 6-membered ring intermediate - gave very limited success. As expected, since previously reported in the literature, substrate **6i** successfully underwent rearrangement and yielded **7i** (Table 6). Except for this substrate, there was an overall lack of rearrangement product observed for our extended tethers and only starting material was collected.

2.2.2.2 Conclusions and Future Work

The theme of the nitrile functionalized tether being more reactive than the esters is observed once again. There was overall poor reactivity for both tether functional groups, however for the nitrile tether we did obtain one product, while for the ester tethers, there was no detected rearrangement. As mentioned earlier, published examples which proceed through 6-membered ring intermediates, favour tethers with a point of saturation, suggesting the rigidity of the tether is important. Our lack of observed reactivity is likely a result of our saturated tether, which does not have a section of rigidity. Future work on these substrates which would proceed through the 6-membered ring intermediate should include tethers which have either a point of unsaturation or a steric functional group within the tether. The point of unsaturation would reduce the degrees of rotation for the tether and make it more likely for the carbanion to contact the electrophilic carbon on the ring, while the steric functional group might assist in ring closure by forcing the carbanion into a more favourable position. Future work which was mentioned in Chapter 2.2.1.2, such as utilizing a methyl ester and other functional groups on the tether is applicable for the extended tether substrates.

2.2.3.1 Pyridine Ring Derivatives

In the next part of this project, we investigated a variety of pyridine derivatives for their ability to undergo a Truce-Smiles rearrangement. Since 2-hydroxypyridine ring systems can shift to their 2-pyridone tautomer when in solution, the synthesis of our pyridine substrates needed to be adapted. As shown in Table 9, greater yields were collected when using a higher temperature, a more polar solvent and letting the reaction proceed for longer (compare entries 1 and 2 in Table 9). Although our investigation to increasing the substrate yields was not thorough, the increase of yield was enough to move forward with the Truce-Smiles rearrangement of the substrates. A more thorough investigation to optimizing the procedure for synthesis of pyridine deviates should be performed to give an enhanced yield. These modifications to the procedure were carried forward with all pyridine substrates which were synthesized. Shown in Tables 9-12 are the substrates which utilize the same tether functional groups and lengths as previously seen. Our derivatives focus on having the nitrogen atom at the N-2 position since this substitution is most commonly seen in the literature. To our knowledge, a systematic review of the choice of electron withdrawing groups on the pyridine ring has yet to be completed and published in the literature; something which would be synthetically useful. Our substrates, which contain the 3-iodo-5-nitro substitutions, were chosen such that the nitro group should have a sufficient electron-withdrawing effect to facilitate the rearrangement, while the iodo substitution could serve as a site for a tandem cyclization; this type of tandem cyclization was previously mentioned in Scheme 6. Although iodine is not typically used as an EWG in aromatic substitutions due to low electronegativity and reactivity compared to other halogens, it was chosen since this substrate was commercially available. Shown in Tables 13-16 are the outcomes of investigating our pyridine substrates for their feasibility to undergo a Truce-Smiles rearrangement.

Table 9. Synthesis of Pyridine Ethers with Varying Functional Groups; Nitrile and 5-Membered Ring Intermediate Tether.

Entry	10	R	Solvent	Temperature / °C	Time / hrs	% Yield 10
1	a	H	Acetone	65	24	16
2	a	H	DMF	85	72	51
3	b	3-I 5-NO$_2$	DMF	85	72	22
4	c	5-CF$_3$	DMF	85	72	51

Table 10. Synthesis of Pyridine Ethers with Varying Functional Groups; Ethyl Ester Tether and 5-Membered Ring Intermediate Tether.

Entry	11	R	% Yield 11
1	a	H	50
2	b	3-I, 5-NO$_2$	36
3	c	5-CF$_3$	37

Table 11. Synthesis of Pyridine Ethers with Varying Functional Groups; Nitrile Tether and 6-Membered Ring Intermediate Tether.

Entry	12	R	% Yield 12
1	a	H	59
2	b	3-I, 5-NO$_2$	30
3	c	5-CF$_3$	21

Table 12. Synthesis of Pyridine Ethers with Varying Functional Groups; Ethyl Ester Tether and 6-Membered Ring Intermediate Tether.

Entry	13	R	% Yield 13
1	a	H	45
2	b	3-I, 5-NO$_2$	28
3	c	5-CF$_3$	37

Table 13. Truce-Smiles Rearrangement of Prepared Pyridine Ethers; Nitrile Tether and 5-Membered Ring Intermediate Tether.
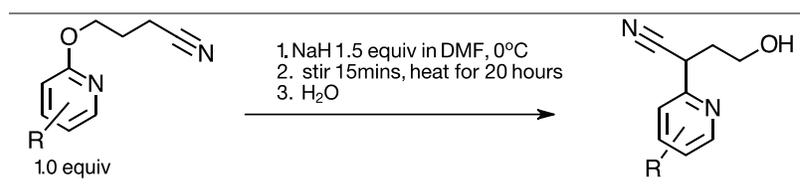
Entry	10	R	Temperature / °C	% Yield 14
1	a	H	100	-
2	b	3-I	60	43
		5-NO$_2$		
3	c	5-CF$_3$	60	39

We can see from Table 13 that **10a** did not yield the desired Truce-Smiles product. Although there were no functional groups directly on the ring, the pyridine ring itself is electron deficient due to the presence 2-N. Considering the incomplete conversion observed, this suggested that the presence of additional functionalization is required for pyridine substrates. Substrates **10b** and **10c** both successfully underwent the rearrangement as expected since they contain strong electron withdrawing groups. The presence of the 3-I within the ring did not result in a tandem cyclization as only compound **14b** was detected. Considering the synthetic potential for this tandem cyclization, future work should include this type of substrate, but with different halogens to further investigate its feasibility.

Since stabilization of the spirocyclic intermediate through use of electron-withdrawing group is crucial for the success of the rearrangement, it was expected that the pyridine derivative **10b** would give higher yields. If we compare the yield if **14b** and **2i** there is a considerable difference in yield. Both substrates are nitro functionalized

either in a *para* or *pseudo-para* manner with respect to the *ipso* carbon of the intermediate. For **14b** it is further functionalized with 2-N and 3-I, which should further increase the ring's ability to stabilize a negative charge. Interestingly, the substrate which theoretically has the better ability to stabilize the transition state, resulted in worse yields. The likely reason for this is due to the presence of the I in a 2- position with respect to the *ipso* carbon, which increases the steric interference in the transition state. This is further supported when considering the elevated reaction temperature which was required in order to successfully facilitate the reaction.

Table 14. Truce-Smiles Rearrangement of Prepared Pyridine Ethers; Ethyl Ester and 5-Membered Ring Intermediate Tether.

Entry	11	R	Solvent	Temperature	% Yield 15
1	a	H	DMF	100	-
2	b	3-I	DMF	100	-
		5-NO$_2$			
3	c	5-CF$_3$	DMF	60	18
4*	c	5-CF$_3$	DMSO	60	-

* Indicates addition performed at room temperature.

Outlined in Table 14 are the outcomes from using an ethyl ester tether. Only substrate **11c** successfully underwent the rearrangement which yielded product **15c**. As was shown before, the product was a result of a tandem cyclization that yielded a gamma-lactone. Comparing this result with the lack of reactivity shown for the cyano group (Table 4, entry 11) we can conclude that the 2-N substitution must be facilitating the intermediate

stabilization since the cyano group is better able to withdraw electron density through resonance, then the trifluoromethyl group that is only able to participate inductively and thus has a weaker electron-withdrawing effect. As was previously seen, the substrate which yielded a gamma-lactone product, was tested using DMSO, to try and stop the secondary cyclization, which interestingly, resulted in no product. It is outlined in the literature that the Truce-Smiles rearrangement is solvent dependent[6], however, this outcome is surprising since DMSO is also a polar aprotic solvent. Substrate **11b** did not undergo rearrangement, which was surprising considering the 4-nitro functionalized compounds in Table 4 could. This lack of reactivity is likely attributed to the presence of the 3-I group which, as mentioned previously, increases steric interactions. This outcome aligns with the lack of reactivity we saw in Table 4 for the 2-nitro functionalized ring, which was also attributed to increased sterics at the transition state. Considering both outcomes, this suggests that although electron-withdrawing group strength is an important factor for facilitating the reaction, the presence of steric interactions at the transition state inhibits the rearrangement.

Table 15. Truce-Smiles Rearrangement of Prepared Pyridine Ethers; Nitrile and 6-Membered Ring Intermediate Tether.

Entry	12	R	Temperature /	% Yield 16
1	a	H	100	-
2	b	3-I	100	-
		5-NO$_2$		
3	c	5-CF$_3$	100	-

Table 16. Truce-Smiles Rearrangement of Prepared Pyridine Ethers; Ethyl Ester and 6-Membered Ring Intermediate Tether.

Entry	13	R	Temperature / °C	% Yield 17
1	a	H	100	-
2	b	3-I	100	-
		5-NO$_2$		
3	c	5-CF$_3$	100	-
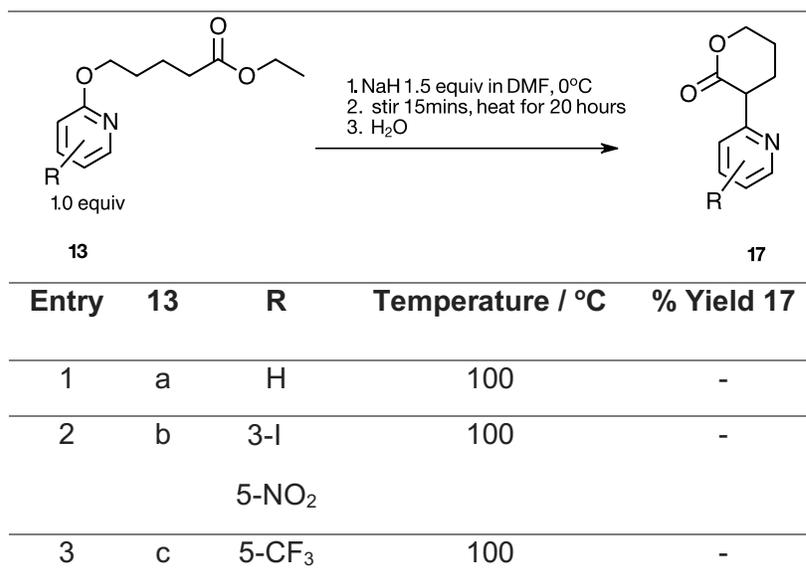
It can be seen in Tables 15 and 16 that for the extended tether length there was only starting material collected for both nitrile and ester tethers. Most notably, substrate **12b** did not undergo the rearrangement. As discussed earlier regarding the poor yield for **14b**, we attribute this lack of reactivity to the steric interference cause by the 3-I substitution.

2.2.3.2 Conclusions and Future Work

Our initial goal of preparing and testing a variety of substrates equipped with a pyridine ring was completed and rearrangement products were collected. We have shown that a pyridine ring on its own is insufficient in facilitating a rearrangement, and required further functionalization. Our choice of ring functionalized with an iodo and nitro functional group, complimented with a nitrile tether that yields a 5-membered ring intermediate, was successfully able to rearrange, however there was no detected secondary cyclization that

took place. As discussed earlier we saw a relatively poor yield for this substrate when comparing the yields collected for the nitro functionalized substrates discussed in chapter 2.2.1. We attribute this to increased sterics, which is further supported by the lack of reactivity for the ester equipped with a tether of the same length. Our trifluoromethyl group substrate did successfully give rearrangement products for both functionalized tethers. Interestingly, when the ethyl ester tether was tested in DMSO to prevent the cyclization into the gamma-lactone, there was no reaction detected, suggesting its enhanced sensitivity to solvent conditions. For our extended tethers, there was a complete lack of reactivity observed. Future work should include a N-2 and 5-NO_2 substrate so accurate comparisons can be made regarding the influence of introduction of a heteroatom into the ring. In addition, weaker electron-withdrawing groups, such as mono-, di-, and tri-halogen substitutions, carbonyls and nitriles should be systematically investigated. Lastly, a systematic review of N-4 ring systems should be performed.

2.2.4.1 Introducing a Second Heteroatom into the Tether

As mentioned earlier one of the important factors of substrate design is the length of the tether connecting the aromatic ring and the nucleophilic carbon. The recent literature, in addition to our own results, favour tether lengths which generate a 5-membered spirocyclic intermediate. To further expand the diversity of substrate scope, while also investigating how to facilitate rearrangement for extended tethers, we report the synthesis of novel compounds which include a second heteroatom within the tether, consisting of a vicinal linkage (Tables 17). Our choice of substrate design was to utilize electron withdrawing groups on the aromatic ring which have either already shown success for a 6-membered ring intermediate ($4-NO_2$), in addition to some of our other strongest electron withdrawing groups ($2-NO_2$ and 4-CN) that have been successful with 5-membered ring intermediates. Our approach was to systematically work our way from strongest to weakest electron withdrawing effects.

To introduce a second oxygen atom, the tether needed to be synthesized in a step-wise fashion. It was decided to build the substrates directly off the aromatic rings, rather than synthesizing the tether first followed by joining them to the rings, for two reasons: i) the starting materials used in the first reaction - aromatic rings and bromoethanol - were less expensive and more readily available than the starting materials used in the final step - bromoacetonitrile and ethyl bromoacetate - so this allowed us to save our most expensive materials for the end to minimize loss and ii) by having the presence of an aromatic ring throughout the entire synthesis allows for easier product identification via UV when purifying the product. It should be noted that protection of the hydroxyl group on bromo ethanol was not required since out choice of potassium carbonate as the base exclusively deprotonates the phenolic rings, which resulted in compounds **18a-c** as the exclusive product. It should be noted that the yields for **19a-f**

were relatively poor, however, procedure optimization was not performed since sufficient product was collected to continue with the rearrangement part of the project. Future work should include procedure optimization to collect better yields.

Table 17. Synthesis of Double-Heteroatom Tether Substrates; 6-Membered Ring Intermediate Tethers.

Entry	R1	18	% Yield	R2	19	% Yield
1	4-NO$_2$	a	73	CN	a	30
2	4-NO$_2$			CO$_2$Et	b	23
3	2-NO$_2$	b	54	CN	c	35
4	2-NO$_2$			CO$_2$Et	d	48
5	4-CN	c	48	CN	e	23
6	4-CN			CO$_2$Et	f	33

Once our substrates were prepared our attention shifted to testing their ability to undergo a Truce-Smiles rearrangement (Table 18). We can see from Table 18 the only substrate which was able to undergo the rearrangement was **19a**, giving **20a**. If we compare Tables 6 and 18, we can see that introduction of the second heteroatom reduced the yield of the collected Truce-Smiles product. Similarly, to what was previously observed for our extended tether substrates, only the 4-nitro ring with the cyano tether substrate successfully rearranged.

Table 18. Truce-Smiles Rearrangement of Double-Heteroatom Tether Substrates; 6-Membered Ring Intermediate Tethers.

Entry	19	R1	R2	Temperature	% Yield 20
1	a	4-NO$_2$	CN	60	30
2	b	4-NO$_2$	CO$_2$Et	100	-
3	c	2-NO$_2$	CN	100	-
4	d	2-NO$_2$	CO$_2$Et	100	-
5	e	4-CN	CN	100	-
6	f	4-CN	CO$_2$Et	100	-

In addition to preparing the above extended tether substrates with vicinal linkages, we also set out to prepare a variety of substrates which utilize our more successful tether length that gives the 5-membered spirocyclic ring intermediate; geminla linkage. We set out to synthesize our substrates by building directly off the ring. Shown in Scheme 10 is the original synthetic approach which was designed.
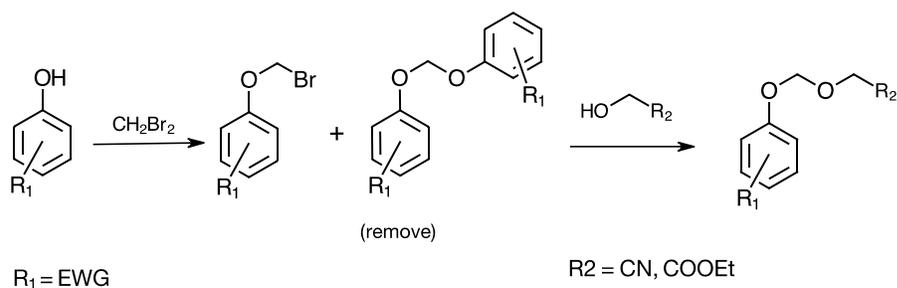
Scheme 10. Initial Synthetic Approach for Double Heteroatom Substrates; 5-Membered Ring Intermediate Tethers.

The first step of this synthesis was to perform an ether synthesis using dibromomethane to generate methyl ether **21**. Since our starting material, dibromomethane, has two sites which it can perform an S_N2 reaction, it was expected that there would be a mixture of products. Our goal was to develop reaction conditions which favour the desirable mono-aryl product, which could then be isolated (Table 19). Our first approach was to react the phenolic reactants with dibromomethane in a 50% excess. Unfortunately, **22** was exclusively collected, even when the reaction time was shortened in an attempt to stop the reaction before the undesirable second ring could be added; compare entry 1 and 2. Since dibromomethane is easy to remove during a separation, our next approach was to try and overwhelm the phenoxide starting material to yield **21** in majority. However, even at three times equivalence of the dibromomethane, **22** was collected exclusively.

Table 19. Synthesis of 4-bromomethoxynitrobenzene.

Entry	Equivalence CH$_2$Br$_2$	Temperature / °C	Time / hrs	% Yield 21	% Yield 22
1	1.5	65	40	-	57
2	1.5	65	2	-	19
3	3.0	65	40	-	51
	Equivalence CH$_2$BrI				
4*	3.0	20	4	-	39

* 4-nitrophenol was dissolved in 5 mL of acetone, and added to a stirring solution of CH$_2$BrI and K$_2$CO$_3$ over 4 hours

After unsuccessful attempts to collect **21** using dibromomethane, we tried the reaction once more using bromoiodomethane instead; see Table 19, entry 4. It was thought that the more reactive iodine would react much faster and thus if reacted in excess, might yield **21**. In an attempt to further increase selectivity, the reaction temperature was decreased to room temperature and the 4-nitrophenol was added dropwise over four hours. As before, this exclusively yielded **22**, with no detectable traces of **21**. Considering the poor selectivity, and our inability to synthesis **21**, the proposed synthetic pathway in Scheme 9 was abandoned. Due to time constraints on the project, no further work was performed on synthesizing double heteroatom substrates with the shortened tethers.

2.2.4.2 Conclusions and Future Work

We have successfully synthesized a variety of rearrangement substrates which contain a second heteroatom within the tether. Our goal of expanding the diversity of potential substrates was successful as we collected a Truce-Smile rearrangement product which contained two heteroatoms within the tether for our tether length which proceeds through a 6-membered ring intermediate. From evaluating the obtained results, it does not appear that the introduction of the second heteroatom is beneficial for facilitating the rearrangement as the collected yield was lower. Future work on optimizing the synthesis of the double heteroatom substrates should be performed to improve product yield.

Further work needs to be performed on synthesizing double heteroatom substrates which consist of the shorter tether length. As discussed earlier, our initial synthetic approach was unsuccessful and needed to be revised. Shown in Scheme 11 is

our updated synthetic approach which needs to be investigated. Aside from being a more selective synthetic approach, the inter mediate methyl ester product can be tested for its ability to perform a Truce-Smile rearrangement. Another benefit of this approach is that after generating our alcohol, we are now able to use the same reagents shown in Table 17; bromoacetonitrile and ethyl bromoacetate. Future work involving double heteroatom substrates should also include varying the heteroatoms; N or S would be good candidates. In addition, the aromatic ring could be replaced with pyridine derivatives, further compounding substrate complexity.
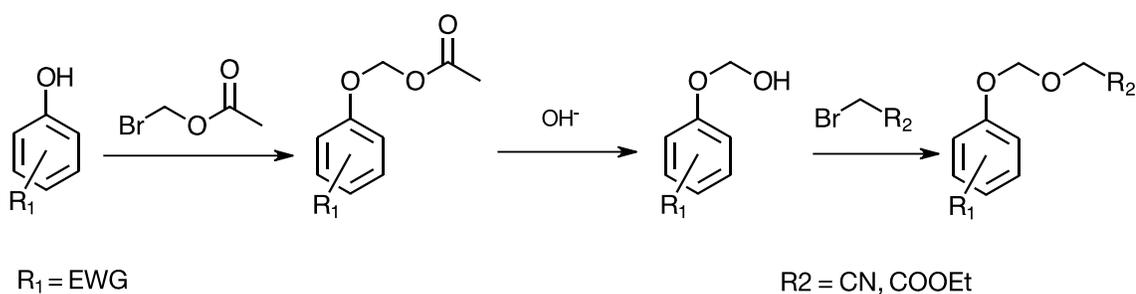
Scheme 11. Revised Synthetic Approach for Double Heteroatom Substrates; 5-Membered Ring Intermediate Tethers.

2.2.5.1 Altering Linking Heteroatom

Up to this point in the project all our substrates have been aromatic ethers which result in the breaking of a C-O bond to form a C-C bond. As discussed in Chapter 1.1.3, an important aspect of substrate design is the presence of this heteroatom which connects the electron deficient aromatic ring to the incoming carbanion tether, as it will serve as the leaving group. Since the heteroatom will be a better leaving group than a carbanion, it facilitates the reaction in the forwards direction to give product. In this portion of the project, we have altered the linking heteroatom from an O to an S and N. Our choice of heteroatom substitution was based on our desire to keep a similar substrate scaffold, and the electron deficient aniline and thiophenol compounds are commercially available. Since amino anions are worse leaving groups than alkoxides, we expect stronger electron withdrawing groups will be required, in addition there will likely be lower yields when compared to the ether analogs. Our choice of aromatic ring systems to start with was based on what was already available in our lab and then purchase more N and S derivatives if time permits.

Shown in Tables 20 and 21 respectively are the synthesis and subsequent testing of our aniline derivatives. The collected yields for compounds **23a-c** are very low, however sufficient product was collected to continue with the Truce-Smiles rearrangement testing. As outlined in Table 21 none of our tested substrates yielded product, and starting material was recovered. These results are not surprising since mono and di bromine functionalization was previously unsuccessful for our ether substrates.

Table 20. Synthesis of Aniline Substrates; 5-membered Ring Intermediate Tether.

Entry	23	R1	% Yield 23
1	a	2-Br	38
2	b	3-Br	22
3	c	4-Br	18

Table 21. Truce-Smiles Rearrangement of Prepared Aniline Substrates; 5- Membered Ring Intermediate Tether.

Entry	23	R	Temperature / °C	% Yield 24
1	a	2-Br	100	-
2	b	3-Br	100	-
3	c	4-Br	100	-

Next, we looked to investigate the effects of changing the heteroatom to sulfur. Shown in Tables 22 and 23 are the substrates which were prepared for our Truce-Smile testing. Our thiophenol compounds were prepared using the same procedure used previously for our ethers shown in chapters 2.2.1 and 2.2.2, while when preparing our mercaptopyridine substrates, we used the same optimized procedure outlined earlier in Chapter 2.2.3. Once our substrates were prepared, we tested their ability to undergo a Truce-Smile rearrangement (Table 24 and 25). There were no successful

rearrangements that occurred, and starting material was collected for trials. Similar with

our aniline substrates, these results are as expected since there was very

Table 22. Synthesis of Thio Substrates; 5-membered Ring Intermediate Tether.

Entry	25	R1	Procedure	R2	% Yield 25
1	a	C-H	A	CN	50
2	b	C-H	A	CO_2Et	51
3	c	N	B	CN	88
4	d	N	B	CO_2Et	67

Table 23. Synthesis of Thio Substrates; 6-membered Ring Intermediate Tether.

Entry	26	R1	Procedure	R2	% Yield 26
1	a	C-H	A	CN	70
2	b	C-H	A	CO_2Et	69
3	c	N	B	CN	67
4	d	N	B	CO_2	48

minimal electron withdrawing effect for our mercaptopyridine substrates, and no electron

withdrawal for our thiphenol substrates. As mentioned earlier, our approach was to utilize

reagents which were already present in our lab, and then if time permits purchase other

analogs with varying electron withdrawing groups so that a more thorough investigation

could be performed. Although the data presented here is a good starting point, there is

still a significant amount of work which needs to be done moving forward.

Table 24. Truce-Smiles Rearrangement of Prepared Thio Substrates; 5-Membered Ring Intermediate Tether.
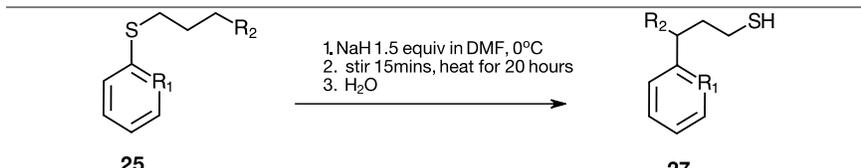
Entry	25	R1	R2	Temperature / °C	% Yield 27
1	a	C-H	CN	100	-
2	b	C-H	CO_2Et	100	-
3	c	N	CN	100	-
4	d	N	CO_2Et	100	-

Table 25. Truce-Smiles Rearrangement of Prepared Thio Substrates; 6-Membered Ring Intermediate Tether.
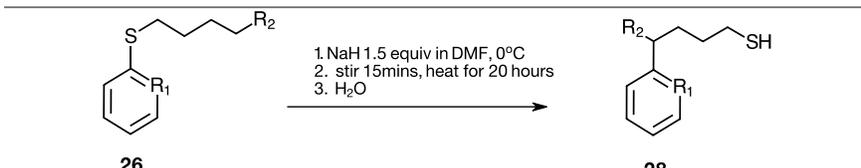
Entry	26	R1	R2	Temperature / °C	% Yield 28
1	a	C-H	CN	100	-
2	b	C-H	CO_2Et	100	-
3	c	N	CN	100	-
4	d	N	CO_2Et	100	-

2.2.5.2 Conclusions and Future Work

Our objective for this part of the project to synthesize a variety of rearrangement substrates with N and S linker heteroatoms was a success. They were then tested for their ability to undergo a Truce-Smiles rearrangement. The substrates tested had very

weak electron withdrawing groups on the aromatic ring, so it is not surprising that they did not yield product. These substrates tested are a good starting point for future work which needs to be done to draw accurate conclusions about the effect of altering the linking heteroatom. Future work should include several more substrates for testing, with similar electron withdrawing groups to what we have seen in previous chapters, so accurate comparisons can be made. In addition, this work of altering the linking heteroatom can be expanded into our double heteroatom substrates; having tethers with two different heteroatoms.

CHAPTER THREE: TRUCE-SMILES REARRANGEMENT UTILIZING CHIRAL IONIC LIQUID SOLVENT SYSTEMS

3.1 Introduction

As shown in Scheme 1, the Truce-Smiles rearrangement generates a chiral center, which to date, there is minimal work done on controlling this outcome. The generation of the negatively charged Meisenheimer adduct presents an interesting approach to this chiral control problem. A CIL with a positively charged chiral portion might allow for transition state stabilization and chiral influence. In this part of this project, we report the synthesis of a variety of compounds through the Truce-Smile rearrangement in a CIL solvent to determine if an enantioselective synthesis can be achieved. Although we have several successful rearrangement substrates, our scope of substrate when using CILs as the solvent was limited to those which gave high yields. In addition, we tested our ethyl ester tether substrates to determine if this solvent system could prevent the tandem cyclization into the gamma-lactone.

3.2 Synthesis of Chiral Ionic Liquids

Before testing of CIL as solvents, they needed to be synthesized. CILs **30a** and **30b** were chosen as their synthesis has already been reported in the literature and they are stable under the strongly basic reaction conditions[56]. In addition, the precursor, *S*-(-)-citronellol, is an inexpensive and readily available starting material. Lastly, the potential for various alkylations on the imidazole ring provides access to numerous other possible CILs that can be synthesized in the future. For the purposes of this project *R-(+)*-citronellol was not used to synthesize enantiomers of the CILs since it is significantly

more expensive. It was decided that if there was favourable results with *S-(-)*, the *R-(+)* compound would be investigated. Citronellol first needed to be converted to citronellyl bromide (**29**) so that a bromide could serve as the counter ion for the CIL. Shown in Table 26 is the synthetic pathway of **29** and **30a,b**, with their respective yields. CIL purity and structure was determined through NMR comparison with the literature[56]. Our CILs specific rotations were obtained and when compared with literature values (Table 26) we can see that they are very close, however what we have prepared has slightly higher specific rotations for each. Considering how close the values lie to that found in literature, and the alignment of NMR structure, our CILs do in fact match.

Table 26. Preparation of Citronellyl Bromide (**29**), CILs **30a** and **30b**.

Compound	R	% Yield	Specific Rotation $[\alpha]_D^{20}$	Literature Specific Rotation[56] $[\alpha]_D^{20}$
29	-	82	-	-
30a	CH_3	90	1.799 ± 0.172	1.4
30b	C_4H_9	83	2.453 ± 0.198	2.2

Other CILs prepared, **31a,b** are derived from a similar cation scaffold, however, the anionic portion is drastically different as it is no longer a halide, but now organic in nature. These CILs were chosen since they have also been reported in the literature, are

inexpensive, simple to make (refer to Table 27 for synthetic scheme followed), and our lab group has previously worked with these CILs with preliminary results having shown moderate effectiveness at chiral induction[57]. It should be noted that unlike our previous CILs, which had no acidic hydrogens, **31a,b** does have acidic sites which are adjacent to the carbonyl on the anionic partner. Considering the relative acidities of this site and the nitrile electron withdrawing groups on our tether, this should not be an issue since the α-hydrogen of the ketone will have a higher pka than that of our acidic site on the tether. It should be noted however since our base is still strong enough to deprotonate the α-hydrogen of the ketone, there will likely be a small amount of deprotonation occurring on the CIL. This generated carbanion on the CIL, however, will still be able to deprotonate the acidic site on our nitrile tether, allowing for the reaction to proceed. Conversely, for our ethyl ester tether substrates the α-hydrogen of the ketone should have a lower pka than that of the α-hydrogen of the ester, and there will be a more significant deprotonation of the CIL. As before, CIL purity and structure was determined through NMR comparison with the literature[57], followed by obtaining specific rotations which were also compared with literature values that match within uncertainty of the polarimeter (Table 27).

Table 27. Preparation of Imidazolium Camphorsulfonate CILs **31a,b**.
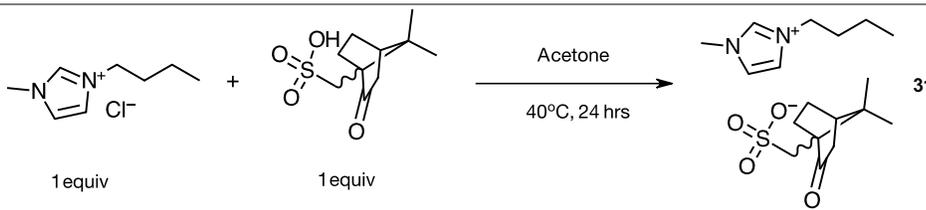
Compound	Enantiomer	% Yield	Specific Rotation $[\alpha]_D^{20}$	Literature Specific Rotation[57] $[\alpha]_D^{20}$
31a	R	97	-21.859 ± 0.372	-22
31b	S	98	22.271 ± 0.333	22

3.3 Testing Chiral Influence on the Truce-Smiles Rearrangement Using CILs

When testing the ability of our CILs to influence chirality on the rearrangement, our strategy was to utilize substrates which had the same tether length so direct comparisons could be made regarding the interactions between the CIL and substrates with varying electron withdrawing groups. The substrates chosen for testing were based upon compounds which previously provided good yields in the conventional solvent system. Before investigating CIL influence on the chirality of our rearrangement products, chirality of the products collected from using a traditional solvent was determined to establish a baseline. This was followed by performing the rearrangement reactions in our CIL solvents and obtaining optical rotations.

3.3.1 Establishing Chirality of Rearrangement Products Using Achiral Solvent Systems

It was expected that collected products would be a racemic mixture of the two enantiomers since there is no chiral influence at the transition state. Shown in Table 28 are specific rotation values for our previously prepared products which will be synthesized again using CILs. It should be noted that **2h** is not included since its corresponding rearrangement substrate **1h**, was not test using CILs as our focus was on ring system with *para* functionalization due to time constraints. The results show that the products formed were in equal molar amounts of the two enantiomers since the specific rotations were found to be zero, within the range of error for the polarimeter. It should be noted that depending on slight differences in sample concentration, the error associated with the specific rotation changed accordingly.

Table 28. Specific Rotations for Truce-Smiles Products - Conventional Solvent.

Product	Solvent	% Yield	Specific Rotation $[\alpha]_D^{20}$
2i	DMF	80	-2.069 ± 0.462
2j	DMF	42	-0.610 ± 1.220
2n	DMF	30	3.906 ± 1.592
5j	DMF	50	2.020 ± 1.015
5j	DMSO	46	1.634 ± 1.095
14b	DMF	43	-2.361 ± 0.093
14c	DMF	39	1.923 ± 1.288
15c	DMF	18	0.777 ± 0.388

Some of our obtained values and associated uncertainties do not fall within zero, which suggests that there are slightly unequal amounts of the two enantiomers. Since there are no literature values indicating whether (+) or (-) corresponds to R or S, it is not possible to comment on the predominant enantiomer in that regard, only the direction to which the product rotates plane polarized light. Since none of these compounds reported appear in the literature with enantiomerically pure rotation values, accurate conclusions about the relative amounts of each enantiomer cannot be made. However, considering how close the values are to zero, in addition to their relatively low rotation values, we are confidently able to continue forward with the assumption of there being limited chiral influence.

3.3.2 Performing Truce-Smiles Rearrangements in CIL Solvent Systems

Once our CILs were prepared and a baseline was established for a conventional solvent system, our focus shifted to using our CILs as reaction solvents. Previous work done by Wood et al. has shown that rearrangement is concentration dependent, favouring dilute conditions[6]. Thus far, all our conditions have been set up such that every 0.5 mmol of substrate is diluted in 10mL of solvent, as this is what the literature has shown to be optimal. Considering the high viscosity of CILs, even at elevated temperatures, the volume to be used needed to be scaled back to allow for easier stirring. In addition, since our CILs need to be synthesized over several days, it allows us to perform more reactions with the CILs at hand. Shown in Table 29 is our investigation outlining a brief procedure optimization using CIL **30a**. This was chosen for optimization for two reasons: i) we predict that since our imidazolium bromide CILs have no acidic sites, this group of CILs should give us the best yield and ii) between our imidazolium bromide CILs, **30a** uses a less expensive imidazolium partner. At room temperature, our CILs are too viscous to permit stirring using magnetic stir bar. In-order to allow for adequate stirring, the reaction needed to be heated to a minimum of 60°C for all substrates tested.

In Table 29 the yields of our rearrangement products using DMF and the CILs as solvents are outlined; we can see that the yields are lower for the latter. A likely reason for lower yield is due to the viscosity of the CILs, preventing adequate mixing of reactants. Another possible reason for this could be that the generated carbanion is interacting with the positive charge on the imidazole ring, hindering its nucleophilicity. We can see that when the reaction was scaled down in size there was negligible difference in obtained yield; compare entry 1 and 3. As what was outlined in the literature, when the reaction is concentrated, the yield was lower; compare entry 1 and 2. The highest yield obtained was for when the reaction time was doubled to 40 hours, however, a similar yield was

obtained when the reaction temperature was increased to 100ºC (entries 3-5). The decision was made to utilize entry 4 as our optimized procedure since it uses less CIL and substrate, while the reaction time shortened by applying a higher temperature with negligible loss to yield. At this point in the project, the main objective was to determine chiral influence from the CILs, which is attainable using entry 4, so further yield optimization of our CIL solvents was not performed.

Table 29. CIL Procedure Optimization Using Substrate **1i** and CIL **30a**.

Entry	Volume of 30a / mL	Amount of 1i / mM	Temperature / °C	Time / hrs	% Yield	Specific Rotation $[\alpha]_D^{20}$
1	10	0.5	60	20	21	-2.000 ± 0.503
2	5	0.5	60	20	15	-1.838 ± 0.738
3	5	0.25	60	20	19	-2.353 ± 1.185
4	5	0.25	100	20	21	-2.234 ± 0.642
5	5	0.25	60	40	22	-1.701 ± 0.490

We can see from Table 29 that all our obtained rotation values are similar and all overlap within their associated uncertainties. It should be noted that reaction time, temperature or concentration did not have an effect the chiral outcome. Furthermore, these rotations are all similar to those presented in Table 28 for product **2i**. This suggests that there is minimal chiral imposition occurring from CIL **30a** when reacted with substrate **1i**. However, there are still several other substrates and CIL combinations which need to be tested for potential chiral imposition (Table 30).

Table 30. Specific Rotations for Truce-Smiles Product - CIL Solvent.

Product	CIL	% Yield	Specific Rotation $[\alpha]_D^{20}$
2i	30a	21	-3.529 ± 1.195
	30b	10	-2.759 ± 0.464
	31a	15	-1.304 ± 1.871
	31b	14	-3.784 ± 1.100
2j	30a	35	-2.444 ± 0.448
	30b	38	0.869 ± 0.870
	31a	20	2.222 ± 1.491
	31b	25	0.851 ± 0.851
2n	30a	26	0.275 ± 0.448
	30b	22	-1.176 ± 1.785
	31a	29	-2.531 ± 0.255
	31b	26	2.857 ± 1.924
14b	30a	22	1.887 ± 0.758
	30b	19	2.308 ± 0.774
	31a	-	-
	31b	-	-
14c	30a	22	-0.870 ± 0.871
	30b	20	1.000 ± 2.003
	31a	-	-
	31b	-	-

Rearrangements products **5j** and **15c** (ester tether substrates) were attempted and no product was obtained and only starting material was collected. Furthermore, we

can also see that for our pyridine substrates, **14b** and **14c**, no product was collected utilizing our camphor sulfonate CILs. Building off what was outlined previously, in addition to the published literature, this further supports the notion of solvent dependency for successful rearrangement. As what was shown for our procedure optimization in Table 29, the collected yields for our Truce-Smiles products were all lower in our CIL solvent; compare Table 28 and 30. We can see that CILs did not affect all the products equally. We see the largest difference for substrate **2i** as the yields ranged from around 70-85% decrease. However, we can see that for substrates **2j** and **2n** that the effect of using our CIL solvents was much less detrimental. In fact, for product **2n** there was minimal difference in the collected yields. This suggests that the CILs are interacting with the electron withdrawing groups on the aromatic rings differently.

Once all our products were collected and purified to remove traces of CILs, the optical rotations were obtained to determine if there was any chiral imposition. By comparing Table 28 and 29, we can see that there is a minimal difference of optical rotations, which suggests the extent of chiral imposition is negligible. The largest difference in optical activity was in product **2n** when CIL **30a** was used, however, it was still relatively small when comparing the rotation found when using an achiral solvent. Furthermore, the change of rotation brings the value closer to zero, which would represent a mixture that is closer to being racemic. Since there are no literature rotation values for enantiomerically pure products, we are unable to calculate any enantiomeric excess. However, based on the data outlined in Table 30, it is unlikely we would find large %ee and the products would be close to a racemic ratio.

3.4 Conclusions and Future Work

For this part of the project we set out to synthesize a variety of CILs and then utilize them as reaction solvents in the Truce-Smiles rearrangement to determine if they could impart chirality. We have synthesized a total of four CILs and successfully tested them as reaction solvents. Upon comparison of specific rotation values for products collected using conventional solvents and then our CILs, there was minimal change in optical activity, suggesting poor chiral imposition. The collected yields from using our CILs were all lower, however it was found that some product yields were impacted more than others. Future work for this part of the project should include the testing of additional CILs with different scaffolds as the imidazolium backbone has not shown success. Our lab group has recently purchased a chiral GC column which will be able to separate the two enantiomers and generate two distinct area peaks on a chromatogram. Further work should include program development with this column, so the impact of chiral imposition can be determined more accurately, and the exact %*ee* can be calculated even without literature rotation values.

CHAPTER FOUR: MICROAVE ASSISTED TRUCE-SMILES REARRANGEMENT

4.1 Introduction

As shown by Wood et al.[6], in addition to our own work previously outlined in this project, applying heat to the Truce-Smiles reaction not only decreases the reaction time, but also provides sufficient energy to facilitate a successful rearrangement. Up to this point all our reactions have been heated using traditional methods, such as a stirred oil bath. However, an alternative method of providing energy to reaction solutions is through use of a microwave reactor. The benefits of microwave heating reactions include: speed, efficiency, and increased product yields[58]. Towards the end of this project our lab group was given access to a microwave reactor to investigate its effects on the Truce-Smiles rearrangement as an alternative method of applying energy to our rearrangement substrates. In this section of the project, no new or novel substrates were prepared or tested, but rather we further investigated substrates which were previously tested that were both successful and unsuccessful. Specifically, we will be investigating if the microwave is able to increase product yields and if it is able to facilitate successful rearrangement for substrates that were previously unsuccessful using an oil bath.

4.2 Results and Discussion

4.2.1 Procedure Optimization

First, we needed to determine optimal microwave conditions to run our reactions. The microwaves internal program calculates new reaction conditions based on the conditions that were used during conventional heating and then converted them to the

comparable microwave conditions. The auto generated programs were the starting point for these investigations. Since in Chapter 2 there were no successful rearrangements that occurred at 100°C, the conditions which we inputted for conversion were: Reaction Time: 20hrs and Temperature: 60°C, which then gave the following conditions which would be comparable under a microwave environment: Reaction Time 37min and Temperature 110°C. Rearrangement substrate **1j** was chosen for procedure optimization since it was already shown to generate relatively good yields, and it could only rearrange successfully at elevated temperatures. Although other substrates such as **1h** and **1i** also had good yields, they were not chosen since they could rearrange at room temperature or below. Since all other substrates required more energy, it made more sense to develop a procedure that would be applicable to all substrates; the substrates which worked at lower temperatures will likely work at elevated conditions also, but not vice versa. Shown in Table 31 is our brief procedure optimization.

Table 31. Microwave Procedure Optimization Using Substrate **1j**.

Entry	Type of Heating	Solvent	Temperature / °C	Time	% Yield 2j
1	Oil bath	DMF	60	20 hrs	42
2	Microwave	DMF	110	37 min	47
3	Microwave	DMSO	110	37 min	28
4	Microwave	DMF	110	1.25 hrs	56
5	Microwave	DMF	110	2.5 hrs	55

We can see that the microwave significantly shortened the reaction time, and also increased product yield. Comparing entry 2 and 3 we can see that when reaction solvent

was substituted for DMSO the yield was decreased. The highest yield obtained was entry 4 when the reaction time was doubled. If we compare this with entry 5 where the reaction time was further increased, there was no yield increase, suggesting that our optimal yield was achieved. Moving forward we used entry 4 as our optimized microwave procedure. It should be noted that this procedure investigation was very brief and not thorough as it did not evaluate choice of base and solvent further. Although this investigation has already been performed by Wood et al.[6] using an oil bath, it should also be completed under microwave conditions.

4.2.2 Microwave Investigations Using Conventional Solvent System

Once optimal reaction conditions were determined our attention then shifted to re-testing our substrates. Not all substrates were tested, but rather we decided to start with our substrates which have the strongest electron withdrawing groups present and systematically work our way down to our weaker electron withdrawing groups. Shown in Tables 32-35 are the results obtained from testing the rearrangement substrates under microwave reaction conditions. For the substrates which proceed through a 5-membered ring intermediate, and utilize a nitrile tether, the microwave increased yields for all products that were previously successful using an oil bath (Table 32). Furthermore, the microwave successfully facilitated rearrangement for substrates **1l** and **1d** that could not be rearranged using an oil bath. It should be noted that substrate **1d** has previously appeared in the literature with no successful rearrangement[6], so we are pleased to present its success under our newly developed conditions. Shown in Scheme 12 is our proposed reaction pathway for product **33**, which proceeds through a tandem cyclization to generate our bicyclic product.

Table 32. Microwave Assisted Truce-Smiles Rearrangement of Prepared Aryl Ethers; Nitrile Tether and 5-Membered Ring Intermediate Tether.

Reaction conditions: 1. NaH 1.5 equiv, 0°C; 2. stir 15, heat for time; 3. H₃O⁺

Entry	1	R	Type of Heating	Solvent	Temperature / °C	Time / hrs	% Yield 2
1	h	2-NO$_2$	Oil bath	DMF	0	20	47
2	h	2-NO$_2$	Microwave	DMF	110	1.25	55
3	i	4-NO$_2$	Oil bath	DMF	110	20	80
4	i	4-NO$_2$	Microwave	DMF	110	1.25	84
5	j	4-CN	Oil bath	DMF	110	20	42
6	j	4-CN	Microwave	DMF	110	1.25	56
7	k	2-CHO	Oil bath	DMF	100	20	-
8	k	2-CHO	Microwave	DMF	110	1.25	-
9	l	4-CHO	Oil bath	DMF	100	20	-
10	l	4-CHO	Microwave	DMF	110	1.25	33
11	m	2-COCH$_3$	Oil bath	DMF	100	20	-
12	m	2-COCH$_3$	Microwave	DMF	110	1.25	-
13	n	4-COCH$_3$	Oil bath	DMF	60	20	30
14	n	4-COCH$_3$	Microwave	DMF	110	1.25	36
15	d	2,4-Br	Oil bath	DMF	100	20	-
16	d	2,4-Br	Microwave	DMF	110	1.25	28 **(33)**
17	*d	2,4-Br	Microwave	DMSO	110	1.25	-
18	b	2-Br	Oil Bath	DMF	100	20	-
19	b	2-Br	Microwave	DMF	110	1.25	-

*Addition performed at room temperature.

As before we tested this reaction again using DMSO as our solvent to prevent the secondary reaction, however it was unsuccessful; compare entries 16 and 17. Substrates

1k and **1m** did not undergo a rearrangement even under the microwave conditions, which further suggests that the presence of electron withdrawing groups at the ortho position generates steric interference at the transition state, hindering rearrangement. From the substrates which we have tested, microwave assisted rearrangement ceased at the mono brominated substrate **1b**, with functionalization at the ortho position. Further work should include bromo functionalization at the para position, in addition to testing mono chlorinated substrates, since the literature has shown it is more successful.
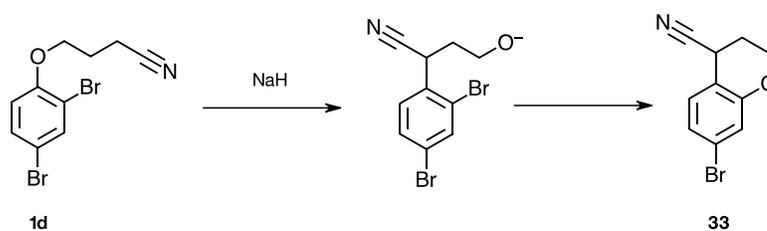
Scheme 12. Synthesis of **33** From **1d**.

Shown in Table 33 is the outcome from testing the ethyl ester tether substrates that also proceed through a 5-membered ring intermediate. The microwave was able to increase yields for products that were also collected using an oil bath (compare entries 3-6), while also facilitating rearrangement to give products that were not collected prior. All collected products were tested in DMSO, which resulted in lower yields and the same product; there was no prevention of the secondary cyclization. For this tether, the rearrangement ceased to proceed at the 2,4-bromo substrate and this was the cut-off for substrate testing. It is clear the microwave is effective in facilitating rearrangement since prior investigations in chapter two resulted in only substrate **3j** giving product, where here there are multiple gamma-lactones collected as a result of a successful Truce-Smiles rearrangement. Although testing ceased at the di-substituted bromo substrate, further work should be inclusive to tri-substitution, into other halides, such as chlorides.

Table 33. Microwave Assisted Truce-Smiles Rearrangement of Prepared Aryl Ethers; Ethyl Ester Tether and 5-Membered Ring Intermediate Tether.


Entry	3	R	Type of Heating	Solvent	Temperature / °C	Time / hrs	% Yield 5
1	i	2-NO$_2$	Oil bath	DMF	100	20	-
2	i	2-NO$_2$	Microwave	DMF	110	1.25	-
3	j	4-NO$_2$	Oil bath	DMF	100	20	50
4	j*	4-NO$_2$	Oil bath	DMSO	100	20	46
5	j	4-NO$_2$	Microwave	DMF	110	1.25	56
6	j*	4-NO$_2$	Microwave	DMSO	110	1.25	49
7	k	4-CN	Oil bath	DMF	100	20	-
8	k	4-CN	Microwave	DMF	110	1.25	31
9	k*	4-CN	Microwave	DMSO	110	1.25	13
10	l	2-CHO	Oil bath	DMF	100	20	-
11	l	2-CHO	Microwave	DMF	110	1.25	-
12	m	4-CHO	Oil bath	DMF	100	20	-
13	m	4-CHO	Microwave	DMF	110	1.25	31
14	m*	4-CHO	Microwave	DMSO	110	1.25	10
15	n	2-COCH$_3$	Oil bath	DMF	100	20	-
16	n	2-COCH$_3$	Microwave	DMF	110	1.25	-
17	o	4-COCH$_3$	Oil bath	DMF	100	20	-
18	o	4-COCH$_3$	Microwave	DMF	110	1.25	34
19	o*	4-COCH$_3$	Microwave	DMSO	110	1.25	9
20	e	2,4-Br	Oil bath	DMF	100	20	-
21	e	2,4-Br	Microwave	DMF	110	1.25	-

*Addition performed at room temperature.

Next, we investigated substrates which are equipped with our extended tethers. In chapter two these substrates were the most unreactive as only two (**6i** and **19a**) yielded product. These substrates which proceeded through a 6-member intermediate, were both 4-NO$_2$ functionalized, giving products **7i** and **20a**. As outlined in Tables 34 and 35 the successful rearrangement for a variety of substrates which use the extended tether are reported, in addition to increased yields for **7i**. The double heteroatom substrates were

Table 34. Microwave Assisted Truce-Smiles Rearrangement of Prepared Aryl Ethers; Nitrile Tether and 6-Membered Ring Intermediate Tether.

Entry	6	R	Type of Heating	Solvent	Temperature / °C	Time / hrs	% Yield 7
1	h	2-NO$_2$	Oil bath	DMF	100	20	-
2	h	2-NO$_2$	Microwave	DMF	110	1.25	-
3	i	4-NO$_2$	Oil bath	DMF	100	20	51
4	i	4-NO$_2$	Microwave	DMF	110	1.25	58
5	j	4-CN	Oil bath	DMF	100	20	-
6	j	4-CN	Microwave	DMF	110	1.25	39
7	k	4-CHO	Oil bath	DMF	100	20	-
8	k	4-CHO	Microwave	DMF	110	1.25	-
9	n	4-COCH$_3$	Oil bath	DMF	100	20	-
10	n	4-COCH$_3$	Microwave	DMF	110	1.25	36

not tested in the microwave due to time constraints, but should be in the future. Product **7i** has previously appeared in the literature[55], however, their investigations were focused on tether length with constant electron-withdrawing groups on the ring and tether. Here

compounds which further expand on this work with varying functionalization on the aromatic ring are presented. The extended nitrile tether substrates rearrangement was unsuccessful for 4-CHO, so this served as the cut-off point for further investigations. As what was mentioned earlier, future work should include functionalization with a variety of di and tri halogenated substrates, including bromo and chloro.

Table 35. Microwave Assisted Truce-Smiles Rearrangement of Prepared Aryl Ethers; Ethyl Ester Tether and 6-Membered Ring Intermediate Tether.

Entry	8	R	Type of Heating	Solvent	Temperature / °C	Time / hrs	% Yield 34
1	h	2-NO$_2$	Oil bath	DMF	100	20	-
2	h	2-NO$_2$	Microwave	DMF	110	1.25	-
3	i	4-NO$_2$	Oil bath	DMF	100	20	-
4	i	4-NO$_2$	Microwave	DMF	110	1.25	23
5	i	4-NO$_2$	Microwave	DMSO	110	1.25	14
6	j	4-CN	Oil bath	DMF	100	20	-
7	j	4-CN	Microwave	DMF	110	1.25	16
8	j	4-CN	Microwave	DMSO	110	1.25	13
9	n	4-COCH$_3$	Oil bath	DMF	100	20	-
10	n	4-COCH$_3$	Microwave	DMF	110	1.25	-

As shown in Table 35, our extended ethyl ester tethers, which were previously unsuccessful, have yielded product under our microwave conditions. As was observed with our shorter tethers, after the Truce-Smile rearrangement the alkoxide proceeded to react and produce a lactone. The mechanism for this pathway was previously outlined in

Scheme 9. Use of DMSO was unable to prevent this cyclization as the lactone was exclusively collected. Although products **34i** and **34j** were collected in relatively poor yield, this is representing a good starting point for future microwave investigations, since this tether was previously completely unreactive.

4.2.3 Microwave Investigations Using CIL Solvent System

As outlined previously, microwave reaction conditions have been shown to be very effective in facilitating the Truce-Smile rearrangement. In the final section of this project, we wanted to test our CIL solvent systems using the optimized microwave reaction conditions. Our choice of substrate **1i** was chosen for testing since it represents the best substrate design due to ideal electronic configuration and tether length, which has resulted in good yields. Shown in Table 36 is the outcome of using CILs as reaction solvents under microwave conditions, and the specific rotations of the products. The same optimized amounts of CIL and substrate, 5mL per 0.25mmol, respectively, were used.

As was observed when using the conventional solvents - DMF and DMSO - the microwave conditions result in better yields with the CIL solvents. The microwave did not affect chiral imposition on the products as the optical rotations for products from using conventional versus CIL solvent system are similar. Due to time constraints, no further substrates were tested in CILs under microwave reaction conditions. This is something which warrants further attention. Currently, it does not appear that there is strong chiral induction, however systematic investigation should be performed to confidently draw conclusions.

Table 36. Microwave Assisted Truce-Smile Rearrangement Using CIL Solvent System.

Entry	CIL	Type of Heating	% Yield 2i	Specific Rotation $[\alpha]_D^{20}$
1	30a	Oil Bath	21	-3.529 ± 1.195
2	30a	Microwave	26	-1.911 ± 0.640
3	30b	Oil Bath	10	-2.759 ± 0.464
4	30b	Microwave	17	-2.128 ± 1.069
5	31a	Oil Bath	15	-1.304 ± 1.871
6	31a	Microwave	19	-2.679 ± 0.901
7	31b	Oil Bath	14	-3.784 ± 1.100
8	31b	Microwave	22	-2.609 ± 0.877

4.3 Conclusions and Future Work

The goal of investigating the effects of microwave reaction conditions on the Truce-Smiles rearrangement was a success. It has been demonstrated that the reactions give increased yields, and also the ability to facilitate reactions that were otherwise unreactive under conventional heating techniques. Although some procedure optimization has been carried out, this should be expanded upon to include testing different bases and solvents. It is likely that DMF and NaH will remain the best choice, but this should still be explored to say with confidence. Not all of the substrates were tested under these reaction conditions due to time constraints, however this also warrants further attention. The pyridine and double heteroatom substrates are excellent microwave

contenders since they previously have shown mixed reactivity even though they contain relatively strong electron withdrawing groups. Lastly, additional substrates should be tested using CIL solvents.

CHAPTER FIVE: EXPERIMENTAL

5.1 General Information

All glassware used for aryl ether, thioether and amine syntheses and subsequent Truce-Smiles rearrangements was oven dried at a temperature of 120 °C. All Truce-Smiles rearrangements were performed under an inert atmosphere of nitrogen gas. All reagents and solvents used were of commercial grade with purities of >99%. All collected organic layers from separatory funnel extraction were dried using $MgSO_4$ and gravity filtered. Aluminum backed silica gel 60 F_{254} TLC plates were used and visualized using UV light (λ = 254 nm). Flash column chromatography was performed using 230-400 mesh silica gel. Melting points were determined using a capillary melting point apparatus and are reported uncorrected. IR data was recorded using a thin film of the purified product between two NaCl plates (Thermo Instruments, Nicolet 380 FT-IR). Low resolution MS data was obtained using an Advion Express-L CMS using atmospheric chemical pressure ionization (APCI). Calculations of mass are presented to one decimal place to match the instrument resolution. Samples were introduced using the atmospheric solid analysis probe (ASAP). ^1H and ^{13}C NMR data was acquired on a Bruker Neo Advance 500 MHz instrument. ^1H NMR was performed using 16 scans, ^{13}C NMR was performed using 64 - 1024 scans with power gated decoupling. Chemical shifts are reported relative to tetramethylsilane (TMS) as an internal standard set to δ 0.00 ppm for ^1H and relative to the $CDCl_3$ solvent residual as an internal standard set to δ 77.16 ppm for ^{13}C. Peak multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations of, or multiplet (m). All NMR data was compared to reported literature values when available. Optical rotations of compounds dissolved in dichloromethane were collected at room temperature (20 ºC) using a polarimeter (Perkin Elmer model 343) set to λ = 589 nm, equipped with a sodium lamp. Microwave reactions were performed

using a CEM Discover 2.0 Synthesizer. Throughout experimental section, compounds associated with an * indicates where literature comparison was available, with the respective reference.

5.2 Synthesis of Aryl Ether Substrates

General Procedure A. In a round bottom flask, the aryl phenol (or aryl thiophenol) (1.2 mmol, 1.2 equiv.), anhydrous potassium carbonate (1.5 mmol, 0.2073 g), alkyl halide (1.0 mmol, 1.0 equiv.) and acetone (10 mL) were combined. The flask was fitted with a reflux condenser and refluxed with stirring at 65°C for 24 hrs using an oil bath. The contents of the flask were concentrated using rotary evaporation, diluted with ethyl acetate (20 mL), washed with 1M $HCl_{(aq)}$ (15 mL), washed with $NaOH_{(aq)}$ (2 x 15 mL) and washed with a saturated NaCl solution (15mL). The organic layer was dried, filtered and concentrated.

(1a) 4-Phenoxybutyronitrile

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.0982 g, 61% yield).; TLC R_f (80 % hexanes, 20 % ethyl acetate): 0.375; IR (neat) v_{max} (cm^{-1}):3055, 2943, 2247, 1590, 1246, 757; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.29 (2H, t, J = 7.50 Hz), 6.97 (1H, t, J = 7.88 Hz), 6.89 (2H, d, J = 7.50 Hz), 4.07 (2H, t, J = 5.60Hz), 3.51 (2H, t, J = 5.90 Hz), 2.13 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 158.3, 129.6, 121.2, 119.2, 114.5, 65.2, 25.53, 14.2; MS m/z: 121.0, [M+H]$^+$ calculated for C$_{10}$H$_{11}$NO: 162.1, found 162.1.

(1b) *4-(2-Bromophenoxy)butyronitrile*

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.1748 g, 73% yield); TLC R_f (60 % hexanes, 40 % ethyl acetate): 0.481; IR (neat) v_{max} (cm^{-1}): 3064, 2942, 2248, 1586, 1467, 1248, 1054, 956, 825, 661, 606; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.53 (1H, d, J = 7.60 Hz), 7.26 (1H, dd, J = 7.60 Hz, J = 7.25), 6.97 (2H, m), 4.11 (2H, t, J = 5.45 Hz), 2.67 (2H, t, J = 6.85 Hz), 2.17 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 154.6, 133.3, 128.7, 112.4, 119.2, 113.4, 112.2, 66.2, 25.5, 14.3; MS m/z: 94.2, 172.9, 175.0, [M+H]$^+$ calculated for C$_{10}$H$_{10}$BrNO: 240.0, found 240.1 and 242.1.

(1c) *4-(3-Bromophenoxy)butyronitrile*

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.1096 g, 46% yield); TLC R_f (60 % hexanes, 40 % ethyl acetate): 0.444; IR (neat) v_{max} (cm^{-1}): 3066, 2942, 2248, 1590, 1468, 1229, 1051, 992, 857, 773, 681; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.15 (1H, dd, J = 8.00 Hz, J = 7.50), 7.10 (1H, d, J = 7.50 Hz), 7.05 (1H, s), 6.83 (1H, d, J = 8.00 Hz), 4.05 (2H, t, J = 5.95 Hz), 2.58 (2H, t, J = 6.85 Hz), 2.13 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 159.1, 130.7, 124.3, 122.9, 119.1, 117.9, 113.4, 65.5, 25.1, 14.1; MS m/z: 94.1, 172.9, 175.0, [M+H]$^+$ calculated for C$_{10}$H$_{10}$BrNO: 240.0, found 240.1 and 242.1.

(1d) *4-(2,4-Dibromophenoxy)butyronitrile*

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.1998 g, 63% yield); TLC R_f (60 %

hexanes, 40 % ethyl acetate): 0.413; IR (neat) v_{max} (cm^{-1}): 3090, 2943, 2248, 1579, 1480, 1248, 1052, 803, 639; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.61 (1H, d, J= 9.10 Hz), 7.27 (1H, s), 6.96 (1H, d, J= 8.55 Hz), 4.14 (2H, t, J= 5.80 Hz), 2.61 (2H, t, J= 7.25 Hz), 2.19 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 161.6, 134.2, 119.0, 118.8, 115.0, 104.6, 65.6, 60.3, 25.2, 14.2; MS m/z: 172.0, 174.0, 239.1, 241.1, [M+H]$^+$ calculated for C$_{10}$H$_9$Br$_2$NO: 317.9, found 318.0 and 320.0.

(1e) 4-(2-Iodophenoxy)butyronitrile

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.1319 g, 46% yield); TLC R$_f$ (60 % hexanes, 40 % ethyl acetate): 0.435; IR (neat) v_{max} (cm^{-1}): 3100, 2944, 2247, 1581, 1465, 1276, 1052, 749, 668; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.76 (1H, dd, J = 7.45 Hz, J = 1.45 Hz), 7.30 (1H, td, J = 8.05 Hz, J = 1.60 Hz), 6.80 (1H, d, J = 7.70 Hz), 6.74 (1H, td, J = 7.45 Hz, J = 1.40 Hz), 4.11 (2H, t, J = 5.25 Hz), 2.711 (2H, t, J = 7.05 Hz), 2.18 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 156.8, 139.5, 129.7, 123.2, 119.2, 112.3, 86.7, 66.3, 25.6, 14.4; MS m/z: 161.1 [M+H]$^+$ calculated for C$_{10}$H$_{10}$INO: 288.0, found 288.0.

(1f) 4-(3-Iodophenoxy)butyronitrile

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.2128 g, 74% yield); TLC R$_f$ (60 % hexanes, 40 % ethyl acetate): 0.524; IR (neat) v_{max} (cm^{-1}): 3060, 2939, 2248, 1584, 1466, 1242, 1049, 846, 773, 653; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.30 (1H, d, J =

8.00), 7.24 (1H, s), 7.00 (1H, dd, J = 8.20, J = 8.00 Hz), 6.86 (1H, d, J = 8.20), 4.03 (2H,

t, J = 5.65 Hz), 2.56 (2H, t, , J = 6.80), 2.11 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm):

158.8, 131.0, 130.8, 123.5, 119.2, 114.1, 94.4, 65.4, 25.3, 14.2; MS m/z: 161.1 [M+H]$^+$

calculated for C$_{10}$H$_{10}$INO: 288.0, found 288.0.

(1g) *4-(4-Iodophenoxy)butyronitrile*

General procedure A was followed. Flash column chromatography (60% hexanes, 40%

ethyl acetate) yields the product as a pale yellow crystalline solid (0.1553 g, 54% yield);

mp =58.0 -59.0 ºC; TLC R$_f$ (60 % hexanes, 40 % ethyl acetate): 0.460; IR (neat) v$_{max}$

(cm^{-1}): 3086, 2942, 2250, 1586, 1421, 1250, 1041, 823, 755, 625; ^{1}H NMR (500 MHz,

CDCl$_3$) δ (ppm): 7.56 (2H, d, J = 8.50 Hz), 6.70 (2H, d, J = 8.00 Hz), 4.03 (2H, t, J = 5.70

Hz), 2.57 (2H, t, J = 7.15 Hz), 2.12 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 158.2,

138.2, 119.2, 116.6, 83.3, 65.4, 25.1, 14.1; MS m/z: 161.1, [M+H]$^+$ calculated for

C$_{10}$H$_{10}$INO: 288.0, found 288.0.

(1h) *4-(2-Nitrophenoxy)butyronitrile*

General procedure A was followed. Flash column chromatography (60% hexanes, 40%

ethyl acetate) yields the product as a pale yellow crystalline solid; (0.1469 g, 71% yield);

mp = 48.8 - 49.6 ºC; TLC R$_f$ (60 % hexanes, 40 % ethyl acetate): 0.462; IR (neat) v$_{max}$

(cm^{-1}): 3060, 2949, 2253, 1609, 1526, 1353; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.85

(1H, dt, J = 6.00 Hz, J = 1.75 Hz), 7.55 (1H, dd, J = 7.45, J = 6.00 Hz), 7.08 (2H, m), 4.24

(2H, t, J = 9.05 Hz), 2.68 (2H, m), 2.19 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm):

151.8, 139.7, 134.6, 125.8, 120.9, 119.2, 114.5, 66.7, 25.2, 14.0; MS m/z: 161.1, 122.1, 68.2, [M+H]$^+$ calculated for $C_{10}H_{10}N_2O_3$: 207.1, found 207.1

(1i) 4-(4-Nitrophenoxy)butyronitrile

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a colourless solid (0.1607 g, 78% yield); mp = 50.6 - 51.7 ºC; TLC R$_f$ (60 % hexanes, 40 % ethyl acetate): 0.235; IR (neat) v$_{max}$ (cm^{-1}): 3086, 2948, 2247, 1593, 1506, 1340, 1173, 1044, 845, 752; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.19 (2H, d, J = 9.20 Hz), 6.98 (2H, d, J = 8.80 Hz), 4.20 (2H, t, J = 5.85 Hz), 2.64 (2H, t, J = 6.75 Hz), 2.22 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 163.3, 141.8, 126.2, 119.0, 114.4, 66.1, 25.5, 14.4; MS m/z: 161.1, 68.2, [M+H]$^+$ calculated for $C_{10}H_{10}N_2O_3$: 207.1, found 207.1.

(1j) 4-(4-Cyanophenoxy)butyronitrile

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a white crystalline solid (0.1447 g, 78% yield); mp = 54.1 - 56.5 ºC; TLC R$_f$ (60 % hexanes, 40 % ethyl acetate): 0.250; IR (neat) v$_{max}$ (cm^{-1}): 3078, 2947, 2248, 2225, 1604, 1259, 1048, 835; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.59 (2H, d, J = 7.85 Hz), 6.97 (2H, d, J = 8.50 Hz), 4.14 (2H, t, J = 5.85 Hz), 2.61 (2H, t, J = 7.30 Hz), 2.18 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 161.9, 134.2, 119.2, 115.4, 104.5, 65.8, 53.6, 25.2, 14.3; MS m/z: 68.2, [M+H]$^+$ calculated for $C_{11}H_{10}N_2O$: 187.1, found 187.1.

(1k) *4-(2-Formylphenoxy)butyronitrile*

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil; (0.1316 g, 70% yield); TLC R_f (60 % hexanes, 40 % ethyl acetate): 0.366; IR (neat) v_{max} (cm^{-1}): 3075, 2943, 2247, 1684, 1599, 1242, 1163; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 10.46 (1H, s), 7.81 (1H, d, J = 9.50 Hz), 7.53 (1H, dd, J = 9.50, J = 7.50 Hz), 7.05 (1H, d, J = 9.50), 6.92 (1H, d, J = 8.00 Hz), 4.20 (2H, t, J = 6.15 Hz), 2.63 (2H, t, J = 8.00 Hz), 2.21 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 189.4, 160.48, 138.2, 136.04, 131.8, 128.7, 124.8, 121.2, 66.2, 25.1, 14.5; MS m/z: 121.1, 95.1, [M+H]$^+$ calculated for C$_{11}$H$_{11}$NO$_2$: 190.1, found 190.1.

(1l) *4-(4-Formylphenoxy)butyronitrile*

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a white crystalline solid; (0.1787 g, 93% yield); mp = 44.4 - 46.5 °C; TLC R_f (60 % hexanes, 40 % ethyl acetate): 0.395; IR (neat) v_{max} (cm^{-1}): 3070, 2944, 2247, 1687, 1601, 1257, 1161; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 9.90 (1H, s), 7.85 (2H, dd, J = 7.50 Hz, J = 2.35 Hz), 7.01 (2H, dd, J = 8.20 Hz, J = 2.15 Hz), 4.18 (2H, t, J = 4.85 Hz), 2.63 (2H, t, J = 7.30 Hz), 2.19 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 190.8, 163.2, 132.1, 130.3, 119.1, 114.7, 65.8, 25.3, 14.1; MS m/z: 121.1, 95.1, [M+H]$^+$ calculated for C$_{11}$H$_{11}$NO$_2$: 190.1, found 190.1.

(1m) *4-(2-Acetylphenoxy)butyronitrile*

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.1894 g, 90% yield); TLC R_f

(60 % hexanes, 40 % ethyl acetate): 0.375; IR (neat) v_{max} (cm^{-1}): 3073, 2942, 2247, 1674, 1597, 1237; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.70 (1H, dd, *J*= 8.50 Hz, *J* = 1.80 Hz), 7.45 (1H, ddd, *J* = 8.50, *J*= 7.95 Hz, *J* = 1.75 Hz), 7.01 (1H, dd, *J* = 8.55 Hz, *J* = 7.25 Hz), 6.96 (1H, d, *J*= 8.55 Hz), 4.18 (2H, t, *J*= 5.65 Hz), 2.62 (2H, t, *J*= 7.25 Hz), 2.59 (3H, s), 2.20 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 199.3, 157.5, 133.9, 130.3, 128.6, 121.2, 119.1, 112.5, 66.3, 31.8, 25.6, 14.5; MS m/z: 119.1, [M+H]$^+$ calculated for C$_{12}$H$_{13}$NO$_2$: 204.1, found 204.1.

(1n) 4-(4-Acetylphenoxy)butyronitrile

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.1894 g, 91% yield); TLC R$_f$ (60 % hexanes, 40 % ethyl acetate): 0.310; IR (neat) v_{max} (cm^{-1}): 3073, 2945, 2248, 1675, 1601, 1255; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.93 (2H, d, *J*= 8.10 Hz), 6.93 (2H, d, *J* = 8.15 Hz), 4.14 (2H, t, *J* = 4.15 Hz), 2.61 (2H, t, *J* = 7.10 Hz), 2.55 (3H, s), 2.17 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 196.7, 162.2, 130.7, 130.6, 119.2, 114.0, 65.6, 26.4, 25.3, 14.2; MS m/z: 149.1, [M+H]$^+$ calculated for C$_{12}$H$_{13}$NO$_2$: 204.1, found 204.1.

(3a) Ethyl-4-phenoxybutyrate

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.1597 g, 77% yield); TLC R$_f$ (80 % hexanes, 20 % ethyl acetate): 0.375; IR (neat) v_{max} (cm^{-1}): 3063, 2980, 1734, 1601, 1246, 1043, 755, ; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.27 (2H, m), 6.95 (1H, tt, *J* = 7.45 Hz, *J* = 1.10 Hz), 6.89 (2H, dd, *J* = 8.75 Hz, *J* = 1.05 Hz), 4.14 (2H, q, *J* = 7.20 Hz),

4.0 (2H, t, J = 6.36 Hz), 2.52 (2H, t, J = 7.40 Hz), 2.11 (2H, m), 1.26 (3H, t, J = 7.10 Hz)

; ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.4, 158.8, 129.6, 120.8, 114.6, 66.6, 60.7, 31.0,

24.6, 14.2; MS m/z: 163.0, 87.1, [M+H]$^+$ calculated for C$_{12}$H$_{16}$O$_3$: 209.1 found 209.0.

(3b) Ethyl-4-(2-bromophenoxy)butyrate

General procedure A was followed. Flash column chromatography (80% hexanes, 20%

ethyl acetate) yields the product as a clear colourless oil (0.2113 g, 74% yield); TLC R$_f$

(80 % hexanes, 20 % ethyl acetate): 0.407; IR (neat) v$_{max}$ (cm^{-1}): 3064, 2980, 1734, 1586,

1249, 1030, 749, 664; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.52 (1H, dd, J = 7.90 Hz, J

= 1.50 Hz), 7.24 (1H, m), 6.88 (1H, d, J = 8.30 Hz), 6.82 (1H, td, J = 7.25 Hz, J = 1.45

Hz), 4.14 (2H, q, J = 7.75 Hz, Hz), 4.07 (2H, t, J = 6.75 Hz), 2.59 (2H, t, J = 7.25 Hz),

2.15 (2H, m), 1.26 (3H, t, J = 7.1 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.4, 155.3,

133.3, 128.4, 122.0, 113.26, 112.4, 68.0, 60.4, 30.7, 24.5, 14.2; MS m/z: 241.0, 243.0,

115.0, [M+H]$^+$ calculated for C12H$_{15}$BrO$_3$: 287.0, found 287.0 and 289.0.

(3c) Ethyl-4-(3-bromophenoxy)butyrate

General procedure A was followed. Flash column chromatography (80% hexanes, 20%

ethyl acetate) yields the product as a clear colourless oil (0.1641 g, 57% yield); TLC R$_f$

(80 % hexanes, 20 % ethyl acetate): 0.407; IR (neat) v$_{max}$ (cm^{-1}): 3050, 2980, 1734, 1590,

1245, 1040, 772, 681; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.26 (1H, s), 7.12 (1H, t, J =

7.95), 6.07 (1H, d, J = 7.95 Hz), 6.82 (1H, dd, J = 7.95 Hz, J = 2.65 Hz), 4.15 (2H, q, J

= 7.25 Hz), 3.99 (2H, t, J = 6.4 Hz), 2.50 (2H, t, J = 7.1 Hz), 2.10 (2H, m), 1.26 (3H, t,

J = 7.4 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.2, 159.8, 130.6, 123.83, 122.8,

117.7, 113.5, 67.01, 60.6, 30.8, 24.6, 14.3, ; MS m/z: 241.0, 243.0 178.0, 115.1, $[M+H]^+$

calculated for $C_{12}H_{15}BrO_3$: 287.0, found 287.0 and 289.0.

(3d) *Ethyl-4-(4-bromophenoxy)butyrate*

General procedure A was followed. Flash column chromatography (80% hexanes, 20%

ethyl acetate) yields the product as a clear colourless oil (0.1982 g, 69% yield); TLC R_f

(80 % hexanes, 20 % ethyl acetate): 0.293; IR (neat) v_{max} (cm^{-1}): 3050, 2980, 1734, 1591,

1489, 1245, 1071, 822 ;^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.35 (2H, d, J = 8.75 Hz),

6.76 (2H, d, J = 9.15 Hz), 4.14 (2H, q, J = 7.30 Hz), 3.97 (2H, t, J = 5.85 Hz), 2.49 (2H,

t, J = 7.30 Hz), 2.09 (2H, m), 1.25 (3H, t, J = 8.00 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ

(ppm): 173.2, 158.0, 132.4, 116.5, 113.0, 67.23, 60.5, 30.7, 24.6, 14.2; MS m/z: 241.0,

243.0, 115.1,$[M+H]^+$ calculated for $C_{12}H_{15}BrO_3$: 287.0, found 287.0 and 289.0.

(3e) *Ethyl 4-(2,4-dibromophenoxy)butyrate*

General procedure A was followed. Flash column chromatography (80% hexanes, 20%

ethyl acetate) yields the product as a clear colourless oil (0.2415 g, 66% yield); TLC R_f

(80 % hexanes, 20 % ethyl acetate): 0.341; IR (neat) v_{max} (cm^{-1}): 3075, 2979, 1734, 1579,

1481, 1247, 1049, 638; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.65 (1H, d, J = 2.45 Hz),

7.34 (1H, dd, J = 8.80 Hz, J = 2.35 Hz), 6.75 (1H, d, J = 8.85 Hz), 4.15 (2H, q, J = 7.50

Hz), 4.04 (2H, t, J = 6.00 Hz), 2.56 (2H, t, J = 7.30 Hz), 2.14 (2H, m), 2.56 (3H, t, J = 7.30

Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.0, 154.6, 135.5, 131.2, 114.6, 113.3, 113.0,

68.3, 60.5, 30.6, 24.5, 14.3; MS m/z: 319.0, 321.0 323.0, 115.1, $[M+H]^+$ calculated for

$C_{12}H_{14}Br_2O_3$: 364.9, found 365.0, 366.0, 367.0 and 369.0.

(3f) Ethyl-4-(2-iodophenoxy)butyrate

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a pale-yellow oil (0.1368 g, 41% yield); TLC R_f (80 % hexanes, 20 % ethyl acetate): 0.275; IR (neat) v_{max} (cm^{-1}): 3057, 2980, 1732, 1582, 1248, 1051, 741, 650 ; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.76 (1H, dd, J = 5.90, 1.90 Hz), 7.28 (1H, m), 6.80 (1H, dd, J = 7.2, 1.30 Hz), 6.70 (1H, ddd, J = 7.55, J = 5.90, 1.40 Hz), 4.15 (2H, q, J = 7.15 Hz), 4.07 (2H, t, J = 6.0 Hz), 2.62 (2H, t, J = 6.85 Hz), 2.16 (2H, m), 1.26 (3H, t, J = 4.65 Hz) ; ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.4, 157.3, 139.4, 129.5, 122.51, 112.1, 86.8, 68.1, 60.7, 31.0, 24.7, 14.1; MS m/z: 288.9, 162.0, 115.1, [M+H]$^+$ calculated for C$_{12}$H$_{15}$IO$_3$: 335.0, found 335.0.

(3g) Ethyl-4-(3-iodophenoxy)butyrate

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a pale yellow oil (0.1670 g, 51% yield); TLC R_f (80 % hexanes, 20 % ethyl acetate): 0.395; IR (neat) v_{max} (cm^{-1}): 3050, 2978, 1734, 1584, 1243, 1037, 773, 681 ; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.26 (1H, dt, J = 7.60, 1.10 Hz), 7.23 (1H, dd, J = 7.60, J = 2.0 Hz), 6.97 (1H, t, J = 8.35 Hz), 6.84 (1H, dd, J = 8.10, 2.75 Hz), 4.14 (2H, q, J = 7.35, J = 6.45 Hz), 3.97 (2H, t, J = 5.7 Hz), 2.49 (2H, t, J = 6.7 Hz), 2.09 (2H, m), 1.26, (3H, t, 7.3 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 173.0, 159.4, 130.7, 129.9, 123.6, 114.2, 94.4, 66.8, 60.5, 30.7, 24.5, 14.2; MS m/z: 288.9, 162, [M+H]$^+$ calculated for C12H$_{15}$IO$_3$: 335.0, found 335.0.

(3h) Ethyl-4-(4-iodophenoxy)butyrate

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a pale-yellow oil (0.1469 g, 44% yield); TLC R_f (80 % hexanes, 20 % ethyl acetate): 0.316; IR (neat) v_{max} (cm^{-1}): 3050, 2978, 1734, 1586, 1244, 1037, 820, 631; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.53 (2H, d, $J =$ 8.65 Hz), 6.67 (2H, d, $J =$ 8.80 Hz), 4.14 (2H, q, $J =$ 7.00 Hz), 3.97 (2H, t, $J =$ 5.96 Hz), 2.50 (2H, t, $J =$ 7.35), 2.10 (2H, m), 1.26 (3H, t, 7.20 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.0, 158.8, 138.3, 117.0, 83.1, 67.3, 60.6, 30.6, 24.6, 14.6; MS m/z: 288.9, 162.0, 115.1, [M+H]$^+$ calculated for C12H$_{15}$IO$_3$: 335.0, found 335.0.

(3i) Ethyl-4-(2-nitrophenoxy)butyrate

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.1761 g, 75% yield); TLC R_f (60 % hexanes, 40 % ethyl acetate): 0.592; IR (neat) v_{max} (cm^{-1}): 3040, 2981, 1734, 1609, 1527, 1353, 1280, 1182; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.81 (1H, dd, $J =$ 7.95 Hz, $J =$ 1.75 Hz), 7.52 (1H, dd, $J =$ 8.50, $J =$ 8.10 Hz), 7.10 (1H, d, $J =$ 8.50 Hz), 7.02 (1H, t, $J =$ 7.80 Hz), 4.18 (2H, t, $J =$ 6.60 Hz), 4.14 (2H, q, $J =$ 7.45 Hz), 2.57 (2H, t, $J =$ 6.85 Hz), 2.15 (2H, m), 1.25 (3H, t, $J =$ 7.45 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm):173.0, 152.1, 139.8, 134.1, 125.5, 120.4, 114.7, 68.2, 60.7, 30.4, 24.2, 14.3; MS m/z: 208.0, 180, 115.0, [M+H]$^+$ calculated for C$_{12}$H$_{15}$NO$_5$: 254.1, found 254.1.

(3j) Ethyl-4-(4-nitrophenoxy)butyrate

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear crystalline solid(0.1611 g, 64% yield); mp = 47.2 - 48.9 °C; TLC R_f (80 % hexanes, 20 % ethyl acetate): 0.279; IR (neat) v_{max} (cm^{-1}): 3050, 2980, 1734, 1608, 1341, 1174, 1245, 1040, 753; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.19 (2H, d, J = 9.40 Hz), 6.95 (2H, d, J = 9.30 Hz), 4.16 (2H, q, J = 7.00 Hz), 4.12 (2H, t, J = 6.35 Hz), 2.53 (2H, t, 7.25 Hz), 2.16 (2H, m), 1.27 (3H, t, J = 7.20 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 172.9, 163.9, 141.5, 126.0, 114.4, 67.7, 60.7, 30.5, 24.3, 14.2; MS m/z: 208, 115.0, [M+H]$^+$ calculated for C$_{12}$H$_{15}$NO$_5$: 254.1, found 254.1.

(3k) Ethyl-4-(4-cyanophenoxy)butyrate

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a white crystalline solid (0.1932 g, 83% yield); mp = 51.5 - 53.4 °C; TLC R_f (80 % hexanes, 20 % ethyl acetate): 0.175; IR (neat) v_{max} (cm^{-1}): 3097, 2951, 2220, 1731, 1605, 715; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.59 (2H, d, J = 8.75 Hz), 6.94 (2H, d, J = 9.10 Hz), 4.15 (2H, q, J = 7.15 Hz), 4.07 (2H, t, J = 6.15 Hz), 2.51 (2H, t, J = 7.25 Hz), 2.14 (2H, m), 1.26 (3H, t, J = 7.05 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.1, 162.0, 134.0, 119.4, 115.3, 104.2, 67.0, 60.3, 30.6, 24.4, 14.1; MS m/z: 188, 115, [M+H]$^+$ calculated for C$_{13}$H$_{15}$NO$_3$: 234.1, found 234.1.

(3l) Ethyl 4-(2-formylphenoxy)butyrate

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.1320 g, 56% yield); TLC R_f (60%

hexanes, 40% ethyl acetate): 0.568; IR (neat) v_{max} (cm^{-1}): 3076, 2981, 1735, 1688, 1600, 1244, 1183; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 10.45 (1H, s), 7.82 (1H, d, J = 8.70 Hz), 7.53 (1H, m), 7.00 (2H, m), 4.15, (4H, m), 2.55 (2H, t, J = 7.50 Hz), 2.19 (2H, m), 1.26 (3H, t, J = 8.80 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 189.6, 173.0, 161.1, 136.1, 128.2, 124.9, 120.8, 112.7, 67.3, 60.6, 30.7, 24.5, 14.2; MS m/z: 191.1, 115.1, 87.1 [M+H]$^+$ calculated for C$_{13}$H$_{16}$O$_4$: 237.1, found 237.1.

(3m) Ethyl 4-(4-formylphenoxy)butyrate

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear yellow oil (0.1826 g, 77% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.568; IR (neat) v_{max} (cm^{-1}): 3075, 2981, 1734, 1700, 1600, 1256, 1160; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 9.87 (1H, s), 7.82 (2H, d, J = 7.85 Hz), 6.99 (2H, d, J = 8.75 Hz), 4.15 (2H, t, J = 6.96 Hz), 4.10 (2H, t, J = 6.60 Hz), 2.53 (2H, t, J = 7.95 Hz), 2.15 (2H, m), 1.26 (3H, t, J = 7.25 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 190.9, 173.2, 164.1, 132.1, 129.9, 114.7, 67.2, 60.3, 30.7, 24.5, 14.3; MS m/z: 191.1, 115.1, [M+H]$^+$ calculated for C$_{13}$H$_{16}$O$_4$: 237.1, found 237.1.

(3n) Ethyl 4-(2-acetylphenoxy)butyrate

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.1676 g, 67% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.488; IR (neat) v_{max} (cm^{-1}): 3100, 2955, 1725, 1675, 1550, 1240; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.67 (1H, d, J = 8.00 Hz), 7.46 (1H, d, J = 8.00 Hz), 7.01 (1H, t, J = 8.00 Hz), 6.95 (1H, d, J = 9.00 Hz), 4.14 (4H, m) 3.20 (3H,

s), 2.54 (2H, t, J = 7.00 Hz), 2.19 (2H, m), 1.26 (3H, t, J = 6.90 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 204.8, 172.8, 157.8, 134.2, 130.3, 129.0, 120.9, 112.5, 70.1, 60.7, 30.8, 29.5, 24.8, 14.3; MS m/z: 207.0, 205.0, 131.1, 115.1, [M+H]$^+$ calculated for C$_{14}$H$_{18}$O$_4$: 251.1, found 251.0.

(3o) Ethyl 4-(4-acetylphenoxy)butyrate

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.2210 g, 88% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.488; IR (neat) v$_{max}$ (cm^{-1}): 3040, 2980, 1735, 1676, 1601, 1257, 1172; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.92 (2H, d, J = 8.35 Hz), 6.91 (2H, d, J = 8.30 Hz), 4.14 (2H, q, J = 7.25 Hz), 4.07 (2H, t, J = 5.75 Hz) 2.54 (3H, s), 2.52 (2H, t, J = 6.80 Hz), 2.13 (2H, m), 1.25 (3H, t, J = 7.60 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 196.6, 173.0, 162.7, 130.6, 130.3, 114.1, 67.03, 60.4, 30.7, 26.4, 24.5, 14.3; MS m/z: 205.1, 115.1, 87.1, [M+H]$^+$ calculated for C$_{14}$H$_{18}$O$_4$: 251.1, found 251.1.

(6a) 5-Phenoxyvaleronitrile

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.0733 g, 42% yield); TLC R$_f$ (60 % hexanes, 40 % ethyl acetate): 0.463; IR (neat) v$_{max}$ (cm^{-1}): 3050, 2942, 2245, 1582, 1466, 1277, 1245, 1017, 751, 650; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.29 (2H, t, J = 8.65 Hz), 6.95 (1H, t, J = 7.15 Hz), 6.89 (2H, d, J = 8.05 Hz), 4.01 (2H, t, J = 6.05 Hz), 2.45 (2H, t, J = 6.80 Hz), 1.86 (4H, m); ^{13}C NMR

(125 MHz, CDCl$_3$) δ (ppm): 159.2, 129.7, 120.9, 119.2, 114.4, 66.5, 28.2, 22.7, 16.6 ; MS

m/z: 82.2 [M+H]$^+$ calculated for C$_{11}$H$_{13}$NO: 176.1, found 176.1.

(6b) *5-(2-Bromophenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column

chromatography (60% hexanes, 40% ethyl acetate) yields the product as a colourless oil

(0.1204 g, 47% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.471; IR (neat) v$_{max}$

(cm^{-1}): 3075, 2959, 2249, 1587, 1468, 1278, 912, 732, 675; ^{1}H NMR (500 MHz, CDCl$_3$)

δ (ppm): 7.53 (1H, d, *J* = 8.35 Hz), 7.26 (1H, dd, *J* = 8.53, Hz *J* = 7.90 Hz), 6.89 (1H, d,

J = 8.35 Hz), 6.85 (1H, dd, *J* = 8.35 Hz, *J* = 7.90 Hz), 4.07 (2H, t, *J* = 5.95), 2.51 (2H, t, *J*

= 6.35 Hz), 1.95 (2H, m), 1.85 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 155.02,

133.4, 128.6, 122.1, 119.7, 119.4, 113.1, 112.2, 31.21, 22.8, 16.6; MS m/z: 82.1, [M+H]$^+$

calculated for C$_{11}$H$_{12}$BrNO: 354.0, found 253.9 and 255.9.

(6c) *5-(3-Bromophenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column

chromatography (60% hexanes, 40% ethyl acetate) yields the product as a colourless oil

(0.1034 g, 41% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.420; IR (neat) v$_{max}$

(cm^{-1}): 3050, 2960, 2247, 1590, 1470, 1244, 992, 650; ^{1}H NMR (500 MHz, CDCl$_3$) δ

(ppm): 7.14 (1H, dd, *J* = 8.15Hz, *J* = 8.15 Hz), 7.08 (1H, d, *J* = 8.15 Hz), 7.04 (1H, s),

6.82 (1H, d, *J* = 8.15 Hz), 3.98 (2H, t, *J* = 5.85 Hz), 3.59 (2H, t, *J* = 6.05 Hz), 1.94 (2H,

m), 1.86 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 159.4, 130.7, 124.0, 119.2, 117.7,

113.5, 66.9, 43.6, 31.0, 28.2, 22.8, 16.62; MS m/z: 82.1, [M+H]$^+$ calculated for C$_{11}$H$_{12}$BrNO: 254.0, found 254.0 and 256.0.

(6d) *5-(2,4-Dibromophenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.1601 g, 49% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.410; IR (neat) v$_{max}$ (cm^{-1}): 3100, 2945, 2225, 1579, 1480, 1284, 1049, 803, 692; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.66 (1H, s), 7.36 (1H, dd, J = 9.00 Hz, J = 1.80 Hz), 6.74 (1H, d, J = 8.85 Hz), 4.03 (2H, t, J = 5.80 Hz), 2.50 (2H, t, J = 7.25 Hz), 1.99 (2H, m), 1.93 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 154.5, 135.7, 131.3, 119.7, 114.4, 113.2, 68.4, 43.6, 28.1, 22.5, 17.2; MS m/z: 82.2, [M+H]$^+$ calculated for C$_{11}$H$_{11}$Br$_2$NO: 331.9, found 332.0 and 334.0, 336.0.

(6e) *5-(2-Iodophenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale-yellow oil (0.1622 g, 54% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.420; IR (neat) v$_{max}$ (cm^{-1}): 3075, 2960, 2247, 1600, 1498, 1245, 1172, 758; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.76 (1H, d, J = 7.80), 7.29 (1H, dd, 8.70 Hz, J = 8.00 Hz), 6.79 (1H, d, J = 8.70 Hz), 6.71 (1H, t, J = 7.55 Hz), 4.04 (2H, t, J = 5.40 Hz), 2.50 (2H, t, J = 6.50 Hz), 1.98 (4H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 157.1, 139.5, 129.5, 122.8, 119.6, 112.0,

86.5, 67.9, 27.9, 22.6, 17.0; MS m/z: 175.1 [M+H]$^+$ calculated for $C_{11}H_{12}INO$: 302.0, found 302.1.

(6f) *5-(3-Iodophenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale-yellow oil (0.1592 g, 53% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.289; IR (neat) v_{max} (cm^{-1}): 3025, 2961, 2247, 1585, 1467, 1243, 990, 650; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.28 (1H, d, *J* = 7.80 Hz), 7.24 (1H, s), 7.00 (1H, dd, *J* = 8.30 Hz, *J* = 7.80 Hz), 6.85 (1H, d, *J* = 8.30 Hz), 3.97 (2H, t, *J* = 5.60 Hz), 2.45 (2H, t, *J* = 7.00 Hz), 1.94 (2H, m), 1.85 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 159.4, 130.9, 130.0, 123.60, 119.3, 114.1, 94.5, 43.8, 31.2, 22.8, 16.6; MS m/z: 175.0 [M+H]$^+$ calculated for $C_{11}H_{12}INO$: 302.0, found 301.9.

(6g) *5-(4-Iodophenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale brown oil (0.1333 g, 44% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.521; IR (neat) v_{max} (cm^{-1}): 3100, 2944, 2245, 1585, 1243, 1056, 630; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.54 (2H, d, *J* = 8.70 Hz), 6.66 (2H, d, *J* = 8.35 Hz), 3.96 (2H, t, *J* = 5.95 Hz), 2.43 (2H, t, *J* = 6.85 Hz), 1.94 (2H, m), 1.86 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 158.8, 138.2, 119.5, 117.0, 83.0, 66.8, 28.1, 22.38, 17.0; MS m/z: 175.1, [M+H]$^+$ calculated for $C_{11}H_{12}INO$: 302.0, found 302.0.

(6h) *5-(2-Nitrophenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as pale yellow oil (0.1680 g, 76% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.400; IR (neat) v_{max} (cm^{-1}): 3080, 2948, 2247, 1608, 1525, 1353, 1280; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.82 (1H, dd, *J* = 7.95 Hz, *J* = 1.90 Hz), 7.54 (1H, ddd, *J* = 7.95 Hz, *J* = 7.75 Hz, *J* = 1.70 Hz), 7.08 (1H, dd, *J* = 8.15 Hz, 1.25 Hz), 7.04 (1H, td, *J* = 7.95 Hz, *J* = 1.50 Hz), 4.16 (2H, t, *J* = 5.35 Hz), 2.49 (2H, t, *J* = 6.70 Hz), 2.00 (2H, m), 1.93 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 152.1, 139.8, 134.4, 125.7, 120.5, 119.7, 114.4, 68.3, 27.8, 22.3, 16.9; MS m/z: 122.1, 82.1, [M+H]$^+$ calculated for C$_{11}$H$_{12}$N$_2$O$_3$: 221.1, found 221.1.

(6i) *5-(4-Nitrophenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale-yellow oil (0.0817 g, 37% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.262; IR (neat) v_{max} (cm^{-1}): 3075, 2946, 2245, 1607, 1512, 1341, 1299, 1111, 753; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.20 (2H, d, *J* = 9.50 Hz), 6.95 (2H, d, *J* = 9.20 Hz), 4.11 (2H, t, *J* = 5.95 Hz), 2.48 (2H, t, *J* = 6.90 Hz), 2.02 (2H, m), 1.91 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 164.0, 142.0, 126.0, 119.3, 114.4, 67.5, 28.0, 22.4, 17.1; MS m/z: 175.1 [M+H]$^+$ calculated for C$_{11}$H$_{12}$N$_2$O$_3$: 221.1, found 221.1.

(6j) *5-(4-Cyanophenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a white crystalline solid (0.1504 g, 75% yield); mp = 72.8 - 73.7 ℃; TLC R_f (60% hexanes, 40% ethyl acetate): 0.214; IR (neat) v_{max} (cm^{-1}):3100, 2959, 2230, 2225, 1607, 1509, 1254, 1034, 847, 712;^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.58 (2H, d, *J* = 8.70 Hz), 6.94 (2H, d, *J* = 8.95 Hz), 4.06 (2H, t, *J* = 6.15 Hz), 2.47 (2H, t, *J* = 6.75 Hz), 1.99 (2H, m), 1.89 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 162.0, 134.0, 119.3, 115.1, 104.0, 67.2, 28.1, 22.3, 17.1; MS m/z: [M+H]$^+$ calculated for C$_{12}$H$_{12}$N$_2$O: 201.1, found 201.1.

(6k) *5-(2-Formylphenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as white crystalline solid (0.1001 g, 49% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.429; IR (neat) v_{max} (cm^{-1}): 3055, 2943, 2244, 1685, 1599, 1243; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 10.48 (1H, s), 7.83 (1H, dd, *J* = 7.45 Hz, *J* = 1.75 Hz), 7.36 (1H, ddd, *J* = 7.95 Hz, *J* = 7.45 Hz, *J* = 1.70 Hz), 7.04 (1H, dd, *J* = 8.60 Hz, *J* = 7.75 Hz), 6.91 (1H, d, *J* = 8.60 Hz), 4.14 (2H, t, *J* = 5.30 Hz), 2.48 (2H, td, *J* = 9.30 Hz, *J* = 2.35 Hz), 2.04 (2H, m), 1.92 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 198.9, 189.4, 138.2, 136.0, 128.6, 124.9, 121.1, 119.4, 67.2, 28.1, 22.2, 17.0; MS m/z: 95.1, 82.2, [M+H]$^+$ calculated for C$_{12}$H$_{13}$NO$_2$: 204.1, found 204.1.

(6l) *5-(4-Formylphenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as pale yellow oil (0.1507 g, 74% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.391; IR (neat) v_{max} (cm^{-1}): 3075, 2945, 2246, 1688, 1602, 1257, 1161; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 9.86 (1H, s), 7.82 (2H, d, *J* = 9.00 Hz), 6.99 (2H, d, *J* = 8.50 Hz), 4.08 (2H, t, *J* = 5.70 Hz), 2.47 (2H, t, *J* = 6.90 Hz), 1.97 (2H, m), 1.88 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 191.1, 163.7, 131.8, 130.2, 119.5, 114.6, 67.1, 28.0, 22.1, 16.9; MS m/z: 95.1, 82.2, [M+H]$^+$ calculated for C$_{12}$H$_{13}$NO$_2$: 204.1, found 204.1.

(6m) *5-(2-Acetylphenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as white crystalline solid (0.1602 g, 74% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.308; IR (neat) v_{max} (cm^{-1}): 3070, 2955, 2246, 1705, 1600, 1248; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.70 (1H, dd, *J* = 6.15 Hz, *J* = 1.70 Hz), 7.44 (1H, ddd, *J* = 7.85 Hz, *J* = 6.15 Hz, *J* = 1.80), 6.98 (1H, dd, *J* = 8.30 Hz, *J* = 7.85 Hz), 6.94 (1H, d, *J* = 8.30 Hz), 4.09 (2H, t, *J* = 6.10 Hz), 2.60 (3H, s), 2.45 (2H, t, *J* = 7.05 Hz), 2.00 (2H, M), 1.87 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 199.4, 157.9, 133.6, 130.3, 128.2, 120.8, 119.5, 112.3, 67.4, 32.2, 28.3, 22.5, 16.7; MS m/z: 119.1, 82.2, [M+H]$^+$ calculated for C$_{13}$H$_{15}$NO$_2$: 218.1, found 218.1.

(6n) *5-(4-Acetylphenoxy)valeronitrile*

General procedure A was followed; refluxed time changed to 4 days. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.2048 g, 94% yield); TLC R_f (60% hexanes, 40 % ethyl acetate): 0.333; IR (neat) v_{max} (cm^{-1}): 3050, 2946, 2248, 1700, 1602, 1255; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.90 (2H, d, *J* = 7.50 Hz), 6.91 (2H, d, *J* = 8.30 Hz), 4.05 (2H, t, *J* = 4.70 Hz), 2.53 (3H, s), 2.45 (2H, t, *J* = 4.50 Hz), 1.95 (2H, m), 1.86 (2H, m) ; ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 196.8, 162.8, 130.6, 130.3, 119.7, 114.2, 66.8, 28.0, 26.3, 22.5, 16.8; MS m/z: 179.1, 82.2, [M+H]$^+$ calculated for C$_{13}$H$_{15}$NO$_2$: 218.1, found 218.1.

(8a) *Ethyl-5-phenoxyvalerate*

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.1853 g, 83% yield).; TLC R_f (80% hexanes, 20% ethyl acetate): 0.400; IR (neat) v_{max} (cm^{-1}): 3025, 2941, 1734, 1600, 1246, 1172, 755; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.26 (2H, td, *J* = 6.70 Hz, *J* = 2.65 Hz), 6.92 (1H, tt, *J* = 7.25 Hz, *J* = 1.10 Hz), 6.89 (2H, dt, *J* = 8.15, *J* = 1.25 Hz), 4.13 (2H, q, *J* = 6.85 Hz), 3.97 (2H, t, *J* = 5.90 Hz), 2.38 (2H, t, *J* = 7.35), 1.893 (2H, m), 1.78 (2H, m), 1.25 (3H, t, *J* = 7.10 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.7, 159.2, 129.5, 120.7, 114.8, 67.3, 60.3, 34.06, 28.74, 21.72, 14.26; MS m/z: 177.1, 129.1, [M+H]$^+$ calculated for C$_{13}$H$_{18}$O$_3$: 223.1, found 223.2.

(8b) Ethyl 5-(2-bromophenoxy)valerate

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.1610 g, 55% yield).; TLC R_f (80% hexanes, 20% ethyl acetate): 0.390; IR (neat) v_{max} (cm^{-1}): 3050, 2939, 1734, 1587, 1484, 1248, 1052, 749, 665; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.52 (1H, d, J = 8.00 Hz), 7.24 (1H, dd, J = 8.00 Hz, J = 8.00 Hz), 6.87 (1H, d, J = 8.00 Hz), 6.82 (1H, dd, J = 8.00 Hz, J = 7.50 Hz), 4.13 (2H, q, J = 6.85 Hz), 4.03 (2H, t, J = 5.45 Hz), 2.41 (2H, t, J = 6.85 Hz), 1.88 (4H, m), 1.26 (3H, t, J = 7.10 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.5, 155.3, 133.3 128.4, 121.7, 113.1, 112.2, 68.5, 60.3, 33.9, 28.5, 21.6, 14.2; MS m/z: 255.1, 257.1, 129.1, [M+H]$^+$ calculated for C$_{13}$H$_{17}$BrO$_3$: 301.0, found 301.1 and 303.1.

(8c) Ethyl 5-(3-bromophenoxy)valerate

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.2448 g, 81% yield).; TLC R_f (80% hexanes, 20% ethyl acetate): 0.435; IR (neat) v_{max} (cm^{-1}): 3050, 2939, 1735, 1590, 1470, 1229, 1168, 773, 681; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.08 (2H, m), 7.03 (1H, t, J = 8.10 Hz, J = 1.85), 6.81 (1H, dd, J = 8.10 Hz, J = 1.65 Hz), 4.13 (2H, q, J = 7.00 Hz), 3.94 (2H, t, J = 5.90 Hz), 2.37 (2H, t, J = 7.05 Hz), 1.80 (4H, m), 1.26 (3H, t, J = 7.50 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.3, 159.7, 130.5, 123.7, 122.8, 117.7, 113.5, 67.6, 60.3, 33.9, 28.6, 21.6, 14.3; MS m/z: 255.0, 257.0, 129.1, [M+H]$^+$ calculated for C$_{13}$H$_{17}$BrO$_3$: 301.0, found 301.1 and 303.1.

(8d) *Ethyl 5-(2,4-dibromophenoxy)valerate*

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.2811 g, 74% yield); TLC R_f (80% hexanes, 20% ethyl acetate): 0.310; IR (neat) v_{max} (cm^{-1}): 3053, 2934, 1734, 1589, 1480, 1286, 1174, 1047, 802, 694, 637; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.65 (1H, d, J = 2.40 Hz), 7.34 (1H, dd, J = 8.95 Hz, J = 2.35 Hz), 6.74 (1H, d, J = 8.95 Hz), 4.13 (2H, q, J = 7.20 Hz), 3.99 (2H, t, J = 5.65 Hz), 2.41 (2H, t, J = 6.60 Hz), 1.86 (4H, m), 1.26 (3H, t, J = 6.90 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.4, 154.8, 135.4, 131.2, 114.1, 113.1, 112.8, 68.9, 60.4, 33.9, 28.4, 21.6, 14.3; MS m/z: 333.0, 335.0, 337.0, 129.1, [M+H]$^+$ calculated for C$_{13}$H$_{16}$Br$_2$O$_3$: 379.0, found 379.0, 381.0 and 383.0.

(8e) *Ethyl 5-(2-iodophenoxy)valerate*

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.2393 g, 69% yield).; TLC R_f (80% hexanes, 20 % ethyl acetate): 0.381; IR (neat) v_{max} (cm^{-1}): 3025, 2939, 1734, 1582, 1247, 1162, 749, 650 ; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.75 (1H, dd, J = 7.75 Hz, J = 1.55 Hz), 7.26 (1H, ddd, J = 7.75 Hz, J = 7.50, Hz J = 1.70 Hz), 6.78 (1H, dd, J = 8.25 Hz, J = 1.20 Hz), 6.68 (1H, ddd, J = 8.25 Hz, J = 7.65 Hz, J = 1.55 Hz), 4.13 (2H, q, J = 7.25 Hz), 4.02 (2H, t, J = 6.00 Hz), 2.41 (2H, t, J = 7.00 Hz), 1.88 (4H, m), 1.25 (3H, t, J = 7.20 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.6, 157.7, 139.8, 129.5, 122.7, 112.3, 86.9, 68.7, 60.5, 34.0, 28.7, 22.0, 14.4; MS m/z: 303.0, 176.1, 129.1, [M+H]$^+$ calculated for C$_{13}$H$_{17}$IO$_3$: 349.0, found 349.1.

(8f) *Ethyl 5-(3-iodophenoxy)valerate*

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.2265 g, 66% yield).; TLC R_f (80% hexanes, 20% ethyl acetate): 0.472; IR (neat) v_{max} (cm^{-1}): 3025, 2938, 1733, 1584, 1466, 1243, 1170, 774, 681; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.26 (1H, dd, J = 7.85 Hz, J = 1.20 Hz), 7.23 (1H, m) 6.97 (1H, dd, J = 8.40 Hz, J = 7.85 Hz), 6.84 (1H, dd, J = 8.40 Hz, J = 2.70 Hz), 4.13 (2H, q, J = 7.40 Hz), 3.93 (2H, t, J = 5.45 Hz), 2.37 (2H, t, J = 7.10 Hz), 1.80 (4H, m), 1.25 (3H, t, J = 7.10 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.3, 159.6, 130.7, 129.8, 123.7, 114.2, 94.3, 67.6, 60.3, 33.9, 28.6, 21.6, 14.3; MS m/z: 303.1, 176.1, 129.1, [M+H]$^+$ calculated for C$_{13}$H$_{17}$IO$_3$: 349.0, found 349.1.

(8g) *Ethyl 5-(4-iodophenoxy)valerate*

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.2596 g, 75% yield).; TLC R_f (80% hexanes, 20% ethyl acetate): 0.419; IR (neat) v_{max} (cm^{-1}): 3050, 2938, 1735, 1586, 1487, 1244, 1175, 821, 650; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.53 (2H, d, J = 8.96 Hz), 6.65 (2H, d, J = 8.45 Hz), 4.13 (2H, q, J = 7.25 Hz), 3.92 (2H, t, J = 6.00 Hz), 2.37 (2H, t, J = 8.10 Hz), 1.8022 (4H, m), 1.25 (3H, t, J = 7.25); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.4, 158.7, 138.4, 116.9, 82.8, 67.6, 60.33, 33.8, 28.49, 21.5, 14.2; MS m/z: 303.0, 176.1, 129.1, [M+H]$^+$ calculated for C$_{13}$H$_{17}$IO$_3$: 349.0, found 349.1.

(8h) Ethyl 5-(2-nitrophenoxy)valerate

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a yellow oil (0.2253 g, 84% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.600; IR (neat) v_{max} (cm^{-1}): 3078, 2943, 1732, 1609, 1527, 1353, 1281, 1166; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.79 (1H, dd, J = 8.05 Hz, J = 1.90 Hz), 7.52 (1H, td, J = 8.20, J = 1.75 Hz), 7.09 (1H, dd, J = 8.65 Hz, J = 1.05 Hz), 7.01 (1H, t, J = 8.05), 4.12 (4H, m), 2.39 (2H, t, J = 6.70 Hz), 1.86 (4H, m), 1.25 (3H, t, J = 7.20 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.3, 152.4, 139.8, 134.3, 125.5, 120.2, 114.5, 69.0, 60.3, 33.7, 28.4, 21.5, 14.3; MS m/z: 222.1, 129, 122.1, 101.1, [M+H]$^+$ calculated for C$_{13}$H$_{17}$NO$_5$: 268.1, found 268.0.

(8i) Ethyl 5-(4-nitrophenoxy)valerate

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.1370 g, 53% yield)); mp = 31.2 - 32.0 ºC; TLC R_f (80% hexanes, 20% ethyl acetate): 0.204; IR (neat) v_{max} (cm^{-1}): 3086, 2941, 1734, 1607 1513, 1342, 1262, 1111, 1034, 847, 753, 654; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.19 (2H, d, J = 9.00 Hz), 6.95 (2H, d, J = 9.1 Hz), 4.14 (2H, q, J = 7.00 Hz), 4.08 (2H, t, J = 6.15 Hz), 2.41 (2H, t, J = 6.85), 1.87 (4H, m), 1.27 (3H, t, J = 7.00 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.1, 164.0, 141.3, 126.2, 114.6, 68.2, 60.8, 34.1, 28.3, 21.6, 14.4; MS m/z: 222.1, 129.1, [M+H]$^+$ calculated for C$_{13}$H$_{17}$NO$_5$: 268.1, found 268.1.

(8j) *Ethyl 5-(4-cyanophenoxy)valerate*

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.1764 g, 71% yield); mp = 46.2 - 47.2 ℃; TLC R_f (80% hexanes, 20% ethyl acetate): 0.209; IR (neat) v_{max} (cm^{-1}): 3053, 2950, 2226, 1735, 1607, 1455, 1263, 1176, 1062, 839, 740; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.57 (2H, d, J = 9.20 Hz), 6.94 (2H, d, J = 9.15 Hz), 4.13 (2H, q, J = 7.10 Hz), 4.03 (2H, t, J = 5.70 Hz), 2.39 (2H, t, J = 6.35 Hz), 1.85 (4H, m), 1.26 (3H, t, 7.55Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.2, 162.3, 134.0, 119.3, 115.2, 103.7, 67.8, 60.4, 33.8, 28.4, 21.5, 14.3; MS m/z: 202.1, 129.1, [M+H]$^+$ calculated for C$_{14}$H$_{17}$NO$_3$: 248.1, found 248.2.

(8k) *Ethyl 5-(2-formylphenoxy)valerate*

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.1058 g, 42% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.324; IR (neat) v_{max} (cm^{-1}): 3076, 2941, 1734, 1689, 1599, 1286, 1243, 1162; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 10.51 (1H, s), 7.82 (1H, d, J = 6.40 Hz), 7.53 (1H, dd, J = 7.90 Hz, J = 6.40 Hz), 7.00 (2H, m), 4.12 (4H, m), 2.40 (2H, t, J = 6.00 Hz), 1.89 (4H, m), 1.26 (3H, t, J = 8.00 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 189.7, 173.3, 161.4, 135.9, 128.3, 124.9, 120.7, 112.5, 68.1, 60.5, 33.9, 28.5, 21.6, 14.4; MS m/z: 205.1, 129.1, 101.1, [M+H]$^+$ calculated for C$_{14}$H$_{18}$O$_4$: 251.1, found 251.1.

(8l) *Ethyl 5-(4-formylphenoxy)valerate*

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow solid (0.1444 g, 58% yield); mp = 36.1 - 37.5 °C; TLC R_f (60% hexanes, 40% ethyl acetate): 0.700; IR (neat) v_{max} (cm^{-1}): 3076, 2945, 1732, 1689, 1602, 1257, 1161; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 9.88 (1H, s), 7.82 (2H, dd, J = 8.80 Hz, J = 2.80 Hz), 6.98 (2H, dd, J = 8.80 Hz, J = 2.15 Hz), 4.13 (2H, q, J = 6.85 Hz), 4.06 (2H, t, J = 6.10 Hz), 2.40 (2H, t, J = 7.25), 1.85 (4H, m), 1.26 (3H, t, J = 8.30 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 190.9, 173.4, 164.0, 131.9, 129.9, 114.7, 67.7, 60.4, 33.9, 28.5, 21.6, 14.2; MS m/z: 205.1, 129.1, 101.1, [M+H]$^+$ calculated for C$_{14}$H$_{18}$O$_4$: 251.1, found 251.1.

(8m) *Ethyl 5-(2-acetylphenoxy)valerate*

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.1655 g, 63% yield).; TLC R_f (60% hexanes, 40% ethyl acetate): 0.461; IR (neat) v_{max} (cm^{-1}): 3022, 2980, 1734, 1676, 1597, 1242; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.67 (1H, d, J = 8.30 Hz), 7.46 (1H, dd, J = 8.30, Hz J = 7.35 Hz), 7.00 (1H,m), 6.82 (1H, d, J = 8.75 Hz), 4.14 (2H, q, J = 7.30 Hz), 4.08 (2H, t, J = 5.90 Hz), 3.21 (3H, s), 2.40 (2H, t, J = 6.50 Hz), 1.88 (4H, m), 1.26 (3H, t, J = 7.25 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 204.4, 173.2, 158.1, 134.1, 130.2, 128.7, 120.9, 112.3, 70.1, 60.6, 33.9, 29.3, 28.6, 21.8, 14.2; MS m/z: 129.1, 101.1, [M+H]$^+$ calculated for C$_{15}$H$_{20}$O$_4$: 265.1, found 265.0.

(8n) Ethyl 5-(4-acetylphenoxy)valerate

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.2538 g, 96% yield).; TLC R_f (60% hexanes, 40% ethyl acetate): 0.561; IR (neat) v_{max} (cm^{-1}): 3033, 2984, 1734, 1700, 1602, 1257; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.92 (2H, d, J = 9.00 Hz), 6.91 (2H, d, J = 9.00 Hz), 4.13 (2H, q, J = 7.85 Hz), 4.04 (2H, t, J = 5.80 Hz), 2.55 (3H, s), 2.39 (2H, t, J = 6.20 Hz), 1.84 (4H, m), 1.26 (3H, t, J = 7.25 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 196.9, 173.3, 163.0, 130.6, 130.2, 114.2, 67.6, 60.4, 33.9, 28.5, 26.4, 21.6, 14.3; MS m/z: 219.1, 129.1, 101.1, [M+H]$^+$ calculated for C$_{15}$H$_{20}$O$_4$: 265.1, found 265.2.

5.3 Synthesis of Pyridine Substrates

General Procedure B. In a round bottom flask, the pyridine derivatives (1.2 mmol, 1.2 equiv.) and alkyl halide with electron withdrawing group (1.0 mmol, 1.0 equiv.) and DMF (10 mL) were combined. The flask was fitted with a reflux condenser heated with stirring under nitrogen at 85ºC for 72 hrs using an oil bath. The contents of the flask were combined with water (15 mL) and then diluted with ethyl acetate (20 mL), and extracted. Aqueous phase was washed with additional ethyl acetate (10mL). 1M NaOH was added make the organic layer basic (checked with pH strip), which was then extracted, washed with 1M NaOH$_{(aq)}$ (2 x 15 mL) and washed with a saturated NaCl solution (15mL). The organic layer was dried, filtered and concentrated.

(10a) *4-(2-Pyridyloxy)butyronitrile*

General procedure B was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil; (0.0829 g, 51% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.478; IR (neat) v_{max} (cm^{-1}): 3058, 2952, 2248, 1596, 1467, 1143; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.13 (1H, d, J = 4.85 Hz), 7.58 (1H, dd, J = 8.00 Hz, J = 4.85 Hz), 6.88 (1H, m), 6.74 (1H, d, J = 8.40 Hz), 4.40 (2H, t, J = 5.90 Hz), 2.54 (2H, t, J = 7.25 Hz), 2.13 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 163.4, 146.8, 138.7, 119.2, 116.9, 111.1, 63.4, 25.3, 14.1; MS m/z: 78.1, 68.1, [M+H]$^+$ calculated for C$_9$H$_{10}$N$_2$O: 163.1, found 163.1.

(10b) *4-(3-Iodo-5-nitro-2-pyridyloxy)butyronitrile*

General procedure B was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow crystalline solid; (0.0720 g, 22% yield); mp = 91.2 - 93.5 °C; TLC R_f (60% hexanes, 40% ethyl acetate): 0.565; IR (neat) v_{max} (cm^{-1}): 3070, 2955, 2250, 1585, 1512, 1337, 1045, 610; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 9.01 (1H, s), 8.82 (1H, s), 4.59 (2H, t, J = 5.75 Hz), 2.65 (2H, t, J = 6.60 Hz), 2.23 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 164.6, 143.7, 143.1, 139.7, 118.9, 79.1, 66.5, 25.0, 14.4; MS m/z: 266.9, [M+H]$^+$ calculated for C$_9$H$_8$IN$_3$O$_3$: 334.0, found 334.1.

(10c) *4-[5-(Trifluoromethyl)-2-pyridyloxy]butyronitrile*

General procedure B was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil; (0.1175 g, 51% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.610; IR (neat) v_{max} (cm^{-1}): 3072, 2960, 2251, 1615, 1501,

1152; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.43 (1H, s), 7.79 (1H, d, J = 7.50 Hz), 6.84 (1H, m), 4.49 (2H, m), 2.56 (2H, m), 2.16 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 165.4, 145.2, 136.2, 123.3, 120.5 (q, J = 35.00 Hz), 119.3, 111.4, 64.4, 25.3, 14.6; MS m/z: 146.1, 68.2, [M+H]$^+$ calculated for C$_{10}$H$_9$F$_3$N$_2$O: 231.1, found 231.1.

(11a) Ethyl 4-(2-pyridyloxy)butyrate

General procedure B was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.1048 g, 50% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.667; IR (neat) v$_{max}$ (cm^{-1}): 3057, 2980, 1734, 1609, 1469, 1288, 1179, 1048; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.14 (1H, m), 7.56 (1H, m), 6.85 (1H, d, J = 6.00 Hz), 6.72 (1H, m), 4.33 (2H, m), 4.14 (2H, m), 2.49 (2H, m), 2.12 (2H, m), 1.26 (3H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.3, 163.9, 146.8, 138.4, 116.7, 111.3, 64.6, 60.4, 31.1, 24.8, 14.3; MS m/z: 180.1, 115.1, 87.1, [M+H]$^+$ calculated for C$_{11}$H$_{15}$NO$_3$: 210.1, found 210.0.

(11b) Ethyl 4-(3-iodo-5-nitro-2-pyridyloxy)butyrate

General procedure B was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow crystalline solid (0.1364 g, 36% yield); mp = 57.1 - 58.9 °C; TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.721; IR (neat) v$_{max}$ (cm^{-1}): 3066, 2979, 1734, 1586, 1440,1338, 1042, 644, 601; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.99 (1H, s), 8.81 (1H, s), 4.52 (2H, t, J = 6.30 Hz), 4.16 (2H, q, J = 6.95 Hz), 2.51 (2H, t, J = 7.85 Hz), 2.18 (2H, m), 1.27 (2H, t, J = 7.10 Hz); ^{13}C NMR (125 MHz, CDCl$_3$)

δ (ppm): 173.1, 164.9, 144.0, 143.2, 139.4, 79.0, 68.3, 60.8, 30.7, 24.0, 14.1; MS m/z: 115.1, 87.1, [M+H]$^+$ calculated for $C_{11}H_{13}IN_2O_5$: 381.0, found 381.1.

(11c) Ethyl 4-[5-(trifluoromethyl)-2-pyridyloxy]butyrate

General procedure B was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a pale yellow oil (0.1016 g, 37% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.744; IR (neat) v_{max} (cm^{-1}): 3024, 2983, 1736, 1616, 1502, 1328, 1126; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.42 (1H, s), 7.76 (1H, dd, J = 8.75 Hz, J = 2.50 Hz), 6.80 (1H, d, J = 8.75 Hz), 4.41 (2H, t, J = 6.35 Hz), 4.15 (2H, q, J = 7.15 Hz), 2.49 (2H, t, J = 7.45 Hz), 2.14 (2H, m), 1.26, (3H, t, J = 7.15 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.1, 165.8, 145.1, 135.6, 125.16, 120.03 (q, J = 32.50 Hz), 111.2, 65.7, 60.5, 31.0, 24.3, 14.3; MS m/z: 115.1, 87.1, [M+H]$^+$ calculated for $C_{12}H_{14}F_3NO_3$: 278.1, found 278.1.

(12a) 5-(2-Pyridyloxy)valeronitrile

General procedure B was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.1045 g, 59% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.525; IR (neat) v_{max} (cm^{-1}): 3057, 2951, 2245, 1609, 1469, 1288, 1143, 1050; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.14 (1H, dd, J = 5.20 Hz, J = 1.75 Hz), 7.57 (1H, ddd, J = 7.80 Hz, J = 5.20, Hz J = 2.05 Hz), 6.87 (1H, m), 6.72 (1H, d, J = 8.15 Hz), 4.34 (2H, t, J = 6.35 Hz), 2.44 (2H, t, J = 7.00 Hz), 1.94 (2H, m), 1.86 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 163.4, 146.9, 138.7, 119.5, 116.9,

111.3, 64.5, 28.0, 22.5, 16.7; MS m/z: 82.2, 78.1, [M+H]$^+$ calculated for $C_{10}H_{12}N_2O$: 177.1, found 177.1.

(12b) 5-(3-Iodo-5-nitro-2-pyridyloxy)valeronitrile

General procedure B was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow solid (0.1045 g, 30% yield); mp = 97.2 - 97.9 °C; TLC R_f (60% hexanes, 40% ethyl acetate): 0.884; IR (neat) v_{max} (cm^{-1}): 3078, 2934, 2245, 1586, 1508, 1447, 1340, 1045, 710; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 9.00 (1H, d, J = 2.30 Hz), 8.81 (1H, d, J = 2.45 Hz), 4.52 (2H, t, J = 6.20 Hz), 2.51 (2H, t, J = 6.60 Hz), 2.03 (2H, m), 1.93 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 164.7, 143.8, 142.9, 139.6, 119.4, 79.1, 68.1, 27.6, 22.5, 17.3; MS m/z: 266.9, 82.2, [M+H]$^+$ calculated for $C_{10}H_{10}IN_3O_3$: 348.1, found 348.1.

(12c) 5-[5-(Trifluoromethyl)-2-pyridyloxy]valeronitrile

General procedure B was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.0508 g, 21% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.633; IR (neat) v_{max} (cm^{-1}): 3048, 2957, 2247, 1615, 1502, 1326, 1125; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.42 (1H, s), 7.78 (1H, dd, J = 7.90 Hz, J = 2.95 Hz), 6.81 (1H, d, J = 8.40 Hz), 4.41 (2H, t, J = 5.15 Hz), 2.45 (2H, t, J = 6.55 Hz), 1.97 (2H, m), 1.86 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 165.7, 145.0, 135.8, 122.9, 120.2, (q, J = 35.00 Hz),119.9, 111.1, 65.2, 28.0, 22.1, 17.0 ; MS m/z: 164.0, 82.2, [M+H]$^+$ calculated for $C_{11}H_{11}F_3N_2O$: 245.1, found 245.1.

(13a) Ethyl 5-(2-pyridyloxy)valerate

General procedure B was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.0996 g, 45% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.674; IR (neat) v_{max} (cm^{-1}): 3070, 2957, 1733, 1596, 1433, 1288, 1176; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.14 (1H, dd, J = 5.10 Hz, J = 2.0 Hz), 7.55 (1H, ddd, J = 7.75 Hz, J = 5.10, Hz 1.95 Hz), 8.84 (1H,m), 6.72 (1H, d, J = 8.40 Hz), 4.30 (2H, t, J = 6.05 Hz), 4.13 (2H, q, J = 7.40 Hz), 2.38 (2H, t, J = 7.30 Hz), 1.81 (4H, m), 1.25 (3H, t, J = 7.15 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.5, 164.1, 147.1, 138.6, 116.6, 111.1, 65.1, 60.2, 33.9, 28.6, 21.8, 14.3; MS m/z: 179.1, 129.1, 87.1, [M+H]$^+$ calculated for C$_{12}$H$_{17}$NO$_3$: 224.1, found 224.1.

(13b) Ethyl 5-(3-iodo-5-nitro-2-pyridyloxy)valerate

General procedure B was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a brown oil (0.1116 g, 28% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.702; IR (neat) v_{max} (cm^{-1}): 3067, 2958, 1735, 1604, 1441, 1337, 1273, 1167, 650; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 9.00 (1H, d, J = 2.70 Hz), 8.80 (1H, d, J = 2.55 Hz), 4.48 (2H, t, J = 6.65 Hz), 4.14 (2H, q, J = 7.10 Hz), 2.42 (2H, t, J = 7.95 Hz), 1.86 (4H, m), 1.26 (3H, t, J = 7.15 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.5, 165.3, 144.8, 143.8, 142.8, 69.1, 67.5, 60.4, 33.9, 27.9, 21.4, 14.3; MS m/z: 129.1, 101.1, 87.1, [M+H]$^+$ calculated for C$_{12}$H$_{15}$IN$_2$O$_5$: 395.1, found 395.1.

(13c) Ethyl 5-[5-(trifluoromethyl)-2-pyridyloxy]valerate

General procedure B was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.1081 g, 37% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.766; IR (neat) v_{max} (cm^{-1}): 3020, 2960, 1736, 1614, 1502, 1327, 1294, 1125; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.42 (1H, s), 7.76 (1H, dd, J = 8.90 Hz, J = 2.55 Hz), 6.80 (1H, d, J = 8.50 Hz), 4.38 (2H, t, J = 5.95 Hz), 4.14 (2H, q, J = 7.00 Hz), 2.39 (2H, t, J = 7.00 Hz), 1.83 (4H, m), 1.26 (3H, t, J = 7.00 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.3, 165.8, 144.9, 135.5, 125.3, 119.5 (q, J = 36.25 Hz), 111.3, 66.2, 60.3, 34.1, 28.4, 21.6, 14.3; MS m/z: 246.1, 129.1, 101.1, [M+H]$^+$ calculated for C$_{13}$H$_{16}$F$_3$NO$_3$: 292.1, found 292.1.

5.4 Synthesis of Double Heteroatom Substrates

General Procedure C. In a round bottom flask, the aryl phenol (10.5 mmol, 1.05 equiv.), anhydrous potassium carbonate (10.6 mmol, 1.4511 g), 2-bromoethanol (10.0 mmol, 1.0 equiv.) and acetone (100 mL) were combined. The flask was fitted with a reflux condenser and refluxed with stirring at 50ºC for 48 hrs using an oil bath. The contents of the flask were concentrated using rotary evaporation, diluted with ethyl acetate (200 mL), washed with 1M HCl$_{(aq)}$ (150 mL), washed with NaOH$_{(aq)}$ (2 x 150 mL) and washed with a saturated NaCl solution (150mL). The organic layer was dried, filtered and concentrated.

(18a) 2-(4-Nitrophenoxy)ethanol

General procedure C was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as white crystalline solid (0.1340 g, 73% yield); mp =

86.9 - 89.1 °C; TLC R_f (60% hexanes, 40% ethyl acetate): 0.279; IR (neat) v_{max} (cm^{-1}): 3269, 2950, 1607, 1506, 1346, 1270, 158; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.22 (2H, d, J = 9.00 Hz), 7.00 (2H, d, J = 8.00 Hz), 4.19 (2H, t, J = 4.50 Hz), 4.03 (2H, q, J = 3.00 Hz) 1.98 (1H, t, J = 5.50 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 163.9, 141.9, 126.1, 114.8, 70.1, 60.9; MS m/z: 123.0, 166.1, 167.0, [M+H]$^+$ calculated for C$_8$H$_9$NO$_4$: 184.1, found 184.1.

(18b) 2-(2-Nitrophenoxy)ethanol

General procedure C was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow crystalline solid (0.1003 g, 54% yield);mp = 35.5 - 38.9 °C; TLC R_f (60% hexanes, 40% ethyl acetate): 0.180; IR (neat) v_{max} (cm^{-1}): 3402, 3112, 2946, 1609, 1525, 1353, 1280, 1041; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.88 (1H, dd, J = 8.20 Hz, J = 1.75 Hz), 7.55 (1H, ddd, J = 8.20 Hz J = 7.80 Hz, J = 1.35 Hz), 7.11 (1H, d, J = 8.05 Hz), 7.07 (1H, m), 4.25 (2H, t, J = 4.40 Hz), 3.99 (2H, q, J = 5.35 Hz), 2.54 (1H, t, J = 5.50 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 152.1, 139.7, 134.5, 126.0, 120.8, 115.2, 71.3, 60.9; MS m/z: 123.0, 166.1, 167.0, [M+H]$^+$ calculated for C$_8$H$_9$NO$_4$: 184.1, found 184.1.

(18c) 2-(4-Cyanophenoxy)ethanol

General procedure C was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a white crystalline solid (0.0726g, 48% yield);mp = 85.5 - 86.8 °C; TLC R_f (60 % hexanes, 40 % ethyl acetate): 0.136; IR (neat) v_{max} (cm^{-1}): 3509, 3103, 2940, 2229, 1608, 1121; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.60 (2H, d, J

= 9.58 Hz), 6.98 (2H, d, J = 8.00 Hz), 4.13 (2H, t, J = 5.35 Hz), 4.01 (2H, q, J = 4.90 Hz),

2.03 (1H, t, J = 5.85 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 162.1, 134.2, 119.2, 115.3,

104.6, 69.7, 61.2; MS m/z: 61.1, [M+H]$^+$ calculated for C$_9$H$_9$NO$_2$: 164.1, found 164.0.

General Procedure D. In a round bottom flask, 3.0 mmol of sodium hydride (60%

dispersion in oil) (1.5 equiv.) was added to 10 mL of anhydrous DMF and allowed to stir

under nitrogen at 0°C on ice bath under an N$_2$ atmosphere. The aryl ethanol derivate (2.0

mmol, 1.0 equiv.) was dissolved in anhydrous DMF and added to flask. The contents

were allowed to stir for 10 mins, followed by the addition of alkyl halide (2.4 mmol, 1.2

equiv.) dissolved in 5 mL of anhydrous DMF. The contents were stirred at room

temperature for 10 minutes, then 60°C for 48 hours using an oil bath. The solution was

quenched with 1M HCl, checked with pH strip to ensure acidic, diluted with ethyl acetate

(40 mL), washed with 1M HCl (30 mL), water (2 x 40 mL) and then washed with a

saturated NaCl solution (30mL). The organic layer from the extraction was dried, filtered

and concentrated.

(19a) [2-(4-Nitrophenoxy)ethoxy]acetonitrile

General procedure D was followed. Flash column chromatography (60% hexanes, 40%

ethyl acetate) yields the product as yellow oil (0.1340 g, 30% yield); TLC R$_f$ (60%

hexanes, 40% ethyl acetate): 0.297; IR (neat) v$_{max}$ (cm^{-1}): 3085, 2938, 2258, 1609, 1342,

1262, 1176, 1111; ^{1}H NMR (500 MHz, CD$_3$CN) δ (ppm): 8.20 (2H, d, J = 7.40 Hz), 7.07

(2H, d, J = 8.75 Hz), 4.40 (2H, s,) 4.27 (2H, t, J = 3.75 Hz) 3.94 (2H, t, J = 3.55 Hz); ^{13}C

NMR (125 MHz, CD$_3$CN) δ (ppm): 171.5, 164.7, 142.3, 126.4, 115.7, 70.2, 68.3, 57.2;

MS m/z: 166, [M+H]$^+$ calculated for C$_{10}$H$_{10}$N$_2$O$_4$: 223.1, found 223.0

(19b) Ethyl-[2-(4-Nitrophenoxy)ethoxy]acetate

General procedure D was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a light yellow oil (0.0947 g, 23% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.333; IR (neat) v_{max} (cm^{-1}): 3085, 2982, 1751, 1594, 1516, 1339, 1261, 1058, 926; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.21 (2H, d, J = 8.60 Hz), 7.00 (2H, d, J = 9.10 Hz), 4.28 (2H, t, J = 4.10 Hz), 4.22 (4H, m), 3.99 (2H, t, J = 4.30 Hz), 1.29 (3H, t, J = 7.05 Hz);^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 170.1, 163.7, 141.7, 126.1, 114.5, 69.8, 68.8, 68.2, 61.1, 14.2; MS m/z: 166.1, [M+H]$^+$ calculated for C$_{12}$H$_{15}$NO$_6$: 270.1, found 270.1.

(19c) [2-(2-Nitrophenoxy)ethoxy]acetonitrile

General procedure D was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as dark yellow oil (0.1562 g, 35% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.290; IR (neat) v_{max} (cm^{-1}): 3040, 2979, 2257, 1608, 1353, 1280, 1044; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.88 (1H, d, J = 8.40 Hz), 7.56 (1H, dd, J = 8.40, Hz J = 8.00 Hz), 7.09 (2H, d, J = 8.00 Hz), 4.46 (2H, s,) 4.31 (2H, t, J = 4.15 Hz) 4.02 (2H, t, J = 4.45 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 152.0, 139.9, 134.4, 125.9, 121.3, 116.2, 114.9, 69.5, 69.2, 57.0; MS m/z: 166.0, 122.1, [M+H]$^+$ calculated for C$_{10}$H$_{10}$N$_2$O$_4$: 223.1, found 223.0.

(19d) Ethyl-[2-(2-Nitrophenoxy)ethoxy]acetate

General procedure D was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a dark yellow oil (0.2584 g, 48% yield); TLC R_f (60%

hexanes, 40% ethyl acetate): 0.380; IR (neat) v_{max} (cm^{-1}): 3077, 2983, 1751, 1607, 1524, 1354, 1143, 1032, 852; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.85 (1H, d, J = 8.20 Hz), 7.53 (1H, m), 7.08 (2H, m), 4.31 (2H, t, J = 4.45 Hz), 4.23 (4H, m), 4.00 (2H, t, J = 4.05 Hz), 1.29 (3H, t, J = 7.30 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 170.4, 160.7, 152.2, 134.2, 125.8, 120.9, 114.8, 69.7, 68.2, 67.5, 61.1, 14.2; MS m/z: 166.0, 122.1, [M+H]$^+$ calculated for C$_{12}$H$_{15}$NO$_6$: 270.1, found 270.1.

(19e) [2-(4-Cyanophenoxy)ethoxy]acetonitrile

General procedure D was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.0947 g, 23% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.245; IR (neat) v_{max} (cm^{-1}): 3020, 2939, 2253, 1606, 1509, 1260, 1126; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.61 (2H, d, J = 9.05 Hz), 6.98 (2H, d, J = 9.10 Hz), 4.39 (2H, s,) 4.24 (2H, t, J = 5.00 Hz), 3.993 (2H, t, J = 4.00 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm):161.7, 134.1, 119.1, 115.7, 115.2, 104.8, 69.8, 67.2, 56.9; MS m/z: 162, 146.0, 118.1, [M+H]$^+$ calculated for C$_{11}$H$_{10}$N$_2$O$_2$: 203.1, found 203.0.

(19f) Ethyl-[2-(4-cyanophenoxy)ethoxy]acetate

General procedure D was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.1651 g, 33% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.434; IR (neat) v_{max} (cm^{-1}): 3100, 2981, 2225, 1752, 1606, 1509, 1261, 1058, 837; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.59 (2H, d, J = 8.70 Hz), 6.98 (2H, d, J = 8.30 Hz), 4.21 (6H, m), 3.97 (2H, t, J = 4.50 Hz), 1.29 (3H, t, J = 7.05 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 170.1, 162.1, 133.8, 119.2, 115.4, 104.2,

69.7, 68.9, 67.8, 61.1, 14.3; MS m/z: 147.1, 103.1, [M+H]$^+$ calculated for C$_{13}$H$_{15}$NO$_4$: 250.1, found 250.1.

(22) 1,1-Bis(4-nitrophenxoy)methane

In a round bottom flask, anhydrous potassium carbonate (1.2 mmol, 0.1658 g) and bromoiodomethane (3.0 mmol, 0.6625g) was stirred in acetone (15 mL) at room temperature. 4-nitrophenol (1.0 mmol, 0.1391g) was dissolved in acetone (5 mL) and was placed in a dropping funnel. Over a four-hour period, the dissolved 4-nitrophenol was allowed to drop into the round bottom flask. After 4 hours the contents of the flask were concentrated using rotary evaporation, diluted with ethyl acetate (20 mL), washed with 1M HCl$_{(aq)}$ (15 mL), washed with NaOH$_{(aq)}$ (2 x 15 mL) and washed with a saturated NaCl solution (15mL). The organic layer was dried, filtered and concentrated. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale-yellow crystalline sold (0.0566 g, 39% yield); m.p. = 145.2 - 147.3°C; TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.556; IR (neat) v$_{max}$ (cm^{-1}): 3116, 2995, 1610, 1508, 1346, 1221, 1177, 1210, 845; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.24 (4H, d, *J* = 9.20 Hz), 7.22 (4H, *J* = 9.45 Hz), 5.91 (2H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 161.0, 143.1, 125.9, 116.2, 89.92; MS m/z: 152.2, [M+H]$^+$ calculated for C$_{13}$H$_{10}$N$_2$O$_6$: 291.1, found 291.1.

5.5 Synthesis of Amine Substrates

General Procedure E. In a round bottom flask, the aryl aniline (1.2 mmol, 1.2 equiv.) and alkyl halide with electron withdrawing group (1.0 mmol, 1.0 equiv.) and acetone (10 mL) were combined. The flask was fitted with a reflux condenser and refluxed

with stirring at 65ºC for 72 hrs using an oil bath. The contents of the flask were concentrated using rotary evaporation, diluted with ethyl acetate (20 mL) and water (15 mL). 1M NaOH was added make the organic layer basic (checked with pH strip), which was then extracted, washed with 1M NaOH$_{(aq)}$ (2 x 15 mL) and washed with a saturated NaCl solution (15mL). The organic layer was dried, filtered and concentrated.

(23a) 4-(2-bromophenylamino)butyronitrile

General procedure E was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a pale brown oil (0.0904 g, 38% yield); TLC R$_f$ (80% hexanes, 20% ethyl acetate): 0.111; IR (neat) v$_{max}$ (cm^{-1}): 3397, 3050, 2958, 2247, 1597, 745; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.43 (1H, dd, J = 7.90 Hz, J = 1.65 Hz), 7.19 (1H, m), 6.65 (1H, dd, J = 8.35 Hz, J = 1.40 Hz), 6.60 (1H, m), 4.34 (1H, s), 3.52 (2H, t, J = 6.25), 2.58 (2H, t, J = 7.20), 2.20 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 132.6, 128.6, 118.4, 111.2, 42.11, 30.1, 28.2, 25.0, 16.0, 14.8; MS m/z: [M+H]$^+$ calculated for C$_{10}$H$_{11}$BrN$_2$: 239.0, found 239.1 and 241.0.

(23b) 4-(3-Bromophenylamino)butyronitrile

General procedure E was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a pale brown oil (0.0515 g, 22% yield).; TLC R$_f$ (80% hexanes, 20% ethyl acetate): 0.111; IR (neat) v$_{max}$ (cm^{-1}): 3386, 3050, 2936, 2246, 1597, 683; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.02 (1H, m), 6.84 (1H, dd, J = 8.25 Hz, J = 1.90 Hz), 6.74 (1H, dd, J = 8.25 Hz J = 7.65 Hz), 6.52 (1H, dd, J = 7.65 Hz, J = 2.50 Hz), 3.79 (1H, s), 3.30 (2H, t, J = 6.00 Hz), 2.47 (2H, t, J = 6.65 Hz), 1.97 (2H, m); ^{13}C NMR

(125 MHz, CDCl$_3$) δ (ppm): 148.9, 130.6, 123.5, 120.7, 119.3, 115.5, 111.7, 42.3, 25.3, 14.9; MS m/z: [M+H]$^+$ calculated for C$_{10}$H$_{11}$BrN$_2$: 239.0, found 239.0 and 241.0.

(23c) 4-(4-Bromophenylamino)butyronitrile

General procedure E was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a pale brown oil (0.0434 g, 18% yield); TLC R$_f$ (80% hexanes, 20% ethyl acetate): 0.289; IR (neat) v$_{max}$ (cm^{-1}): 3367, 3050, 2939, 2246, 1592, 751; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.26 (2H, d, *J* = 8.55 Hz), 6.50 (2H, d, *J* = 8.5 Hz), 3.74 (1H, s), 3.29 (2H, t, *J* = 6.90 Hz), 2.47 (2H, t, *J* = 7.2 Hz), 1.96 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 146.9, 132.2, 119.5, 114.4, 110.0, 42.5, 25.1, 15.1; MS m/z: [M+H]$^+$ calculated for C$_{10}$H$_{11}$BrN$_2$: 239.0, found 239.1 and 241.0.

5.6 Synthesis of Thio Substrates

(25a) 4-Phenylthiobutyronitrile

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a clear colourless oil (0.0887 g, 50% yield). ; TLC R$_f$ (80% hexanes, 20 % ethyl acetate): 0.333; IR (neat) v$_{max}$ (cm^{-1}): 3058, 2926, 2246, 1583, 691; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.36 (2H, d, *J* = 7.50 Hz), 7.30 (2H, t, *J* = 7.95 Hz), 7.23 (1H, d, *J* = 7.10 Hz), 3.03 (2H, t, *J* = 6.65Hz), 2.50 (2H, t, *J* = 7.05 Hz), 1.95 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 134.8, 130.2, 129.2, 126.8, 119.0, 32.7, 24.8, 16.0; MS m/z: 109.0, 68.1, [M+H]$^+$ calculated for C$_{10}$H$_{11}$NS: 178.1, found 178.0.

(25b) Ethyl-4-(Phenylthio)butyrate

General procedure A was followed. Flash column chromatography (80% hexanes, 20% ethyl acetate) yields the product as a pale-yellow oil (0.1148 g, 51% yield); TLC R_f (80% hexanes, 20 % ethyl acetate): 0.385; IR (neat) v_{max} (cm^{-1}): 3050, 2980, 1735, 1583, 1205, 1025, 739, 691; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.34 (2H, d, *J* = 7.20 Hz), 7.28 (2H, t, *J* = 6.85 Hz), 7.18 (1H, d, *J* = 7.95 Hz), 4.12 (2H, q, *J* = 7.55 Hz), 2.97 (2H, t, *J* = 6.85 Hz), 2.46 (2H, t, *J* = 7.25), 1.96 (2H, m), 1.25 (3H, t, *J* = 7.60 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.3, 136.1, 129.4, 129.0, 126.1, 60.5, 33.1, 32.9, 24.4, 14.3; MS m/z: 179.0, 151.0, [M+H]$^+$ calculated for C$_{12}$H$_{16}$O$_2$S: 225.1, found 225.1.

(25c) 4-(2-Pyridylthio)butyronitrile

General procedure C was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil; (0.1562 g, 88% yield); TLC R_f (60% hexanes, 40% ethyl acetate): 0.576; IR (neat) v_{max} (cm^{-1}): 3040, 2927, 2247, 1579, 1414, 1125; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.40 (1H, d, *J* = 4.45 Hz), 7.46 (1H, dd, *J* = 8.00 Hz, *J* = 4,45 Hz), 7.16 (1H, d, *J* = 8.00 Hz), 6.98 (1H, m), 3.27 (2H, m), 2.49 (2H, m), 2.05 (2H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 157.7, 149.5, 136.07, 122.4, 119.7, 119.4, 28.3, 25.65, 16.2; MS m/z: 78.1, 68.2, [M+H]$^+$ calculated for C$_9$H$_{10}$N$_2$S: 179.1, found 179.1.

(25d) Ethyl 4-(2-pyridylthio)butyrate

General procedure C was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.1514 g, 67% yield); TLC R_f

(60% hexanes, 40% ethyl acetate): 0.717; IR (neat) v_{max} (cm^{-1}): 3020, 2980, 1731, 1579, 1454, 1414, 1124, 1043 ; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.40 (1H, d, J = 4.20 Hz), 7.46 (1H, dd, J = 7.95 Hz, J = 4.20 Hz), 7.17 (1H, d, J = 7.95 Hz), 6.96 (1H, m), 4.13 (2H, q, J = 7.25 Hz), 3.22 (2H, t, J = 7.00 Hz), 2.47 (2H, t, J = 7.80 Hz), 2.04 (2H, m), 1.25 (3H, t, J = 7.15 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.1, 158.9, 149.6, 135.7, 122.5, 119.3, 60.3, 33.3, 29.2, 25.1, 14.4; MS m/z: 180.0, 115.0, [M+H]$^+$ calculated for C$_{11}$H$_{15}$NO$_2$S: 226.1, found 226.1.

(26a) 5-(Phenylthio)valeronitrile

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a clear colourless oil (0.1337 g, 70% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.592; IR (neat) v_{max} (cm^{-1}): 3058, 2936, 2246, 1583, 1480, 1025, 741; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.34 (2H, d, J = 8.15 Hz), 7.28 (2H, m), 7.19 (1H, m), 2.94 (2H, t, J = 5.95 Hz), 2.33 (2H, t, J = 6.30 Hz), 1.78 (4H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 135.8, 129.5, 129.0, 126.3, 119.4, 32.9, 27.9, 24.3, 16.9; MS m/z: 111.1 [M+H]$^+$ calculated for C$_{11}$H$_{13}$NS: 192.1, found 192.1.

(26b) Ethyl-5-(phenylthio)valerate

General procedure A was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale-yellow oil (0.1651 g, 69% yield); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.609; IR (neat) v_{max} (cm^{-1}): 3059, 2936, 1734, 1584, 1481, 1180, 739; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.32 (2H, d, J = 8.30 Hz), 7.27 (2H, m), 7.17 (1H, m), 4.11 (2H, q, J = 7.20 Hz), 2.92 (2H, t, J = 7.85 Hz), 2.31 (2H, t, J = 7.05

Hz), 1.77 (2H, m), 1.67 (2H, m), 1.24 (3H, t, *J* = 7.30 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ

(ppm): 173.4, 136.6, 129.1, 128.9, 125.9, 30.4, 33.8, 33.2, 28.6, 24.1, 14.3; MS m/z:

165.1, 193.1[M+H]$^+$ calculated for C$_{13}$H$_{18}$O$_2$S: 239.1, found 239.0.

(26c) *5-(2-Pyridylthio)valeronitrile*

General procedure C was followed. Flash column chromatography (60% hexanes, 40%

ethyl acetate) yields the product as pale yellow oil (0.1286 g, 67% yield); TLC R$_f$ (60%

hexanes, 40% ethyl acetate): 0.542; IR (neat) v$_{max}$ (cm^{-1}): 3046, 2937, 2246, 1578, 1415,

1124; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.39 (1H, dd, *J* = 5.05 Hz, *J* = 2.45 Hz), 7.44

(1H, dd, *J* = 7.85 Hz, *J* = 1.00 Hz), 7.14 (1H, d, *J* = 8.05 Hz), 6.95 (1H, m), 3.18 (2H, t, *J*

= 6.75 Hz), 2.36 (2H, t, *J* = 6.75 Hz), 1.83 (2H, m), 1.76 (2H, m); ^{13}C NMR (125 MHz,

CDCl$_3$) δ (ppm): 158.4, 149.4, 135.9, 122.2, 119.6, 119.4, 28.6, 28.5, 24.3, 16.6; MS m/z:

114.1, [M+H]$^+$ calculated for C$_{10}$H$_{12}$N$_2$S: 193.1, found 193.1.

(26d) *Ethyl-5-(2-pyridylthio)valerate*

General procedure C was followed. Flash column chromatography (60% hexanes, 40%

ethyl acetate) yields the product as a pale yellow oil (0.1148 g, 48% yield); TLC R$_f$ (60%

hexanes, 40% ethyl acetate): 0.775; IR (neat) v$_{max}$ (cm^{-1}): 3070, 2938, 1734, 1578, 1414,

1125; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.40 (1H, dd, *J* = 4.80 Hz, *J* = 0.90 Hz), 7.44

(1H, dd, *J* = 7.70 Hz, *J* = 1.95 Hz), 7.14 (1H, d, *J* = 8.20 Hz), 6.94 (1H, m), 4.11 (2H, q, *J*

= 7.00 Hz), 3.17 (2H, t, *J* = 7.25 Hz), 2.34 (2H, t, *J* = 7.55), 1.77 (4H, m), 1.23 (3H, t, *J* =

7.30 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 173.3, 159.1, 149.5, 135.8, 122.2, 119.2,

60.2, 33.7, 29.5, 28.8, 24.3, 14.3; MS m/z: 194.1, 166.1, 129.1, [M+H]$^+$ calculated for C$_{12}$H$_{17}$NO$_2$S: 240.1, found 240.1.

5.7 Truce-Smiles Rearrangement of Prepared Substrates

NOTE: For all Truce-Smile reactions which did not generate a rearrangement product, starting material was recovered in the organic layer and identify was confirmed via TLC using Hexanes : Ethyl Acetate as describe in the synthesis of each rearrangement substrate. No yield of recollected rearrangement was obtained.

General Procedure F (achiral environment, oil bath). In a round bottom flask sodium hydride (60% dispersion in oil) (0.0300 g, 0.75 mmol) was added, evacuated and backfilled with nitrogen, sealed and placed on an ice water bath. Anhydrous DMF (7 mL) was added to flask and stirred. The prepared aryl substrate **(n)** (0.5 mmol, 1.0 equiv) dissolved in anhydrous DMF (3 mL) was added to the flask, let stir on the ice water bath for 10 minutes, then stirred at temperature and time as described. The solution was quenched with 1M HCl, checked with pH strip to ensure acidic, diluted with ethyl acetate (20 mL), washed with 1M HCl (15 mL), water (2 x 20 mL) and then washed with a saturated NaCl solution (15 mL). The organic layer from the extraction was dried, filtered and concentrated.

General Procedure G (achiral environment, oil bath). In a round bottom flask, at room temperature, sodium hydride (60% dispersion in oil) (0.0300 g, 0.75 mmol) was added, evacuated and backfilled with nitrogen, sealed. Anhydrous DMSO (7 mL) was added to flask and stirred. The prepared aryl substrate **(n)** (0.5 mmol, 1.0 equiv) dissolved in anhydrous DMSO (3 mL) was added to the flask, let stir at room temperature for 10 minutes, then stirred at temperature and time as described. The solution was quenched

with 1M HCl, checked with pH strip to ensure acidic, diluted with ethyl acetate (20 mL), washed with 1M HCl (15 mL), water (2 x 20 mL) and then washed with a saturated NaCl solution (15 mL). The organic layer from the extraction was dried, filtered and concentrated.

General Procedure H (achiral environment, microwave). In a glass reaction vial sodium hydride (60% dispersion in oil) (0.0300 g, 0.75 mmol) was added, evacuated and backfilled with nitrogen, sealed and placed on an ice water bath. Anhydrous DMF (7 mL) was added to flask and stirred. The prepared aryl substrate **(n)** (0.5 mmol, 1.0 equiv) dissolved in anhydrous DMF (3 mL) was added to the flask, let stir on the ice water bath for 10 minutes, then using a microwave reactor the sample was stirred at temperature and time as described. The solution was quenched with 1M HCl, checked with pH strip to ensure acidic, diluted with ethyl acetate (20 mL), washed with 1M HCl (15 mL), water (2 x 20 mL) and then washed with a saturated NaCl solution (15 mL). The organic layer from the extraction was dried, filtered and concentrated.

General Procedure I (chiral environment, oil bath). In a round bottom flask sodium hydride (60% dispersion in oil) (0.0150 g, 0.375 mmol), the described chiral ionic liquid, along with the rearrangement substrate was added in the listed order. The flask was evacuated and backfilled with nitrogen, sealed and gradually warmed up to the described temperature. The solution was quenched with 1M HCl, checked with pH strip to ensure acidic, diluted with ethyl acetate (20 mL), washed with 1M HCl (15 mL), water (2 x 20 mL) and then washed with a saturated NaCl solution (15 mL). The organic layer from the extraction was dried, filtered and concentrated.

General Procedure J (chiral environment, microwave). In a glass reaction vial sodium hydride (60% dispersion in oil) (0.0150 g, 0.375 mmol), the described chiral ionic liqud, along with the rearrangement substrate was added in the listed order. The flask was evacuated and backfilled with nitrogen, sealed and gradually warmed up to the described temperature. The solution was quenched with 1M HCl, checked with pH strip to ensure acidic, diluted with ethyl acetate (20 mL), washed with 1M HCl (15 mL), water (2 x 20 mL) and then washed with a saturated NaCl solution (15 mL). The organic layer from the extraction was dried, filtered and concentrated.

(2h) 4-Hydroxy-2-(2-nitrophenyl)butanenitrile

Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as an orange oil; TLC R_f (60% hexanes, 40% ethyl acetate): 0.143; IR (neat) v_{max} (cm^{-1}): 3446, 3020, 2932, 2220, 1609, 1527, 1350, 1042; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.05 (1H, dd, J = 8.20 Hz, J = 0.95 Hz), 7.81 (1H, dd, J = 7.75 Hz, J = 1.30 Hz), 7.72 (1H, ddd, J = 7.75 Hz, J = 7.65 Hz, J = 1.20 Hz), 7.55 (1H, ddd, J = 7.95 Hz, J = 7.65 Hz, J = 1.40 Hz), 4.96 (1H, dd, J = 9.45 Hz, J = 4.80 Hz), 3.89 (2H, m), 2.21 (2H, m), 1.66 (1H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 134.5, 130.4, 129.4, 126.3, 59.4, 37.9, 31.8, 30.3, 22.6, 14.2; MS m/z: 190.0, [M+H]$^+$ calculated for C$_{10}$H$_{10}$N$_2$O$_3$: 207.0, found 207.1.

General Procedure F: 0.0517 g, 47% yield

General Procedure H: 0.0567 g, 55% yield

(2i) *4-Hydroxy-2-(4-nitrophenyl)butanenitrile*

Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as an orange oil; TLC R_f (60% hexanes, 40% ethyl acetate): 0.190 IR (neat) v_{max} (cm^{-1}): 3438, 3025, 2925, 2245, 1608, 1524, 1347, 1047, 851; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.27 (2H, d, *J* = 8.00 Hz), 7.59 (2H, d, *J* = 7.50 Hz), 4.29 (1H, dd, *J* = 7.50, *J* = 2.70 Hz), 3.91 (1H, m), 3.75 (1H, m), 2.21 (1H, m), 2.13 (1H, m), 1.60 (1H, s) ; ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 147.9, 142.7, 128.6, 124.5, 119.7, 58.8, 37.9, 33.5; MS m/z: 190.0, [M+H]$^+$ calculated for C$_{10}$H$_{10}$N$_2$O$_3$: 207.0, found 207.1.

General Procedure F: 0.0839 g, 80% yield; $[\alpha]_D^{20}$= -2.069 ± 0.462 (c = 0.0044 g/mL in CHCl$_3$).

General Procedure H: 0.0865 g, 84% yield

General Procedure I: [CitBr-Me] - 0.0108 g, 21% yield; $[\alpha]_D^{20}$= -3.529 ± 1.195 (c = 0.0017 g/mL in CHCl$_3$), [CitBr-But] - 0.0051 g, 10 % yield; $[\alpha]_D^{20}$= -2.759 ± 0.464 (c = 0.0044 g/mL in CHCl$_3$), [ButMetImid][Camph-R] - 0.0079 g, 15 % yield; $[\alpha]_D^{20}$= -1.304 ± 1.871 (c = 0.0023 g/mL in CHCl$_3$), [ButMetImid][Camph-S] - 0.0019 g, 14 % yield; $[\alpha]_D^{20}$= -3.784 ± 1.100 (c = 0.0023 g/mL in CHCl$_3$).

General Procedure J: [CitBr-Me] - 0.0134 g, 26% yield; $[\alpha]_D^{20}$=-1.911 ± 0.640 (c = 0.0031 g/mL in CHCl$_3$), [CitBr-But] - 0.0088 g, 17 % yield; $[\alpha]_D^{20}$= -2.128 ± 1.069 (c = 0.0019 g/mL in CHCl$_3$), [ButMetImid][Camph-R] - 0.0098 g, 19 % yield; $[\alpha]_D^{20}$= -2.679 ± 0.901 (c = 0.0022 g/mL in CHCl$_3$), [ButMetImid][Camph-S] - 0.0113 g, 22 % yield; $[\alpha]_D^{20}$= -2.609 ± 0.877 (c = 0.0023 g/mL in CHCl$_3$).

(2j) *4-Hydroxy-2-(4-cyanophenyl)butanenitrile*

Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as an orange oil; TLC R_f (60% hexanes, 40% ethyl acetate): 0.200; IR (neat) v_{max} (cm^{-1}): 3498, 3025, 2935, 2230, 1606, 1506, 1259, 1049, 834; ^{1}H NMR (500 MHz, CDCl$_3$) δ

(ppm): 7.71 (2H, d, J = 7.95 Hz), 7.59 (2H, d, J = 7.85 Hz), 4.23 (1H, m), 3.88 (1H, m), 3.72 (1H, m), 2.18 (1H, m), 2.09 (1H, m), 1.91 (1H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 140.8, 132.9, 128.4, 118.2, 115.3, 112.4, 58.8, 38.0, 33.7; MS m/z: [M+H]$^+$ calculated for C$_{11}$H$_{10}$N$_2$O: 187.1, found 187.1.

General Procedure F: 0.0446 g, 42% yield; $[\alpha]_D^{20}$= -0.610 ± 1.220 (c = 0.0016 g/mL in CHCl$_3$).

General Procedure H: 0.0511 g, 56% yield

General Procedure I: [CitBr-Me] - 0.0162 g, 35% yield; $[\alpha]_D^{20}$= -2.444 ± 0.448 (c = 0.0045 g/mL in CHCl$_3$), [CitBr-But] - 0.0184 g, 38 % yield; $[\alpha]_D^{20}$= 0.869 ± 0.870 (c = 0.0023 g/mL in CHCl$_3$), [ButMetImid][Camph-R] - 0.0094 g, 20 % yield; $[\alpha]_D^{20}$= 2.222 ± 1.491 (c = 0.0014 g/mL in CHCl$_3$), [ButMetImid][Camph-S] - 0.0116 g, 25 % yield; $[\alpha]_D^{20}$= 0.851 ± 0.851 (c = 0.0024 g/mL in CHCl$_3$).

(2l) 2-(4-Formylphenyl)-4-hydroxybutyronitrile

General procedure H was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a light orange oil (0.0308 g, 33%); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.102; IR (neat) v$_{max}$ (cm^{-1}): 3449, 2927, 2222, 1700, 1607, 1426, 1211, 1051, 828; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 10.03 (1H, s), 7.92 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.06 Hz), 4.23 (1H, dd, J = 8.10 Hz, J = 2.30 Hz), 3.89 (1H, m), 3.74 (1H, m), 2.19 (1H, m), 2.12 (1H, m), 1.62 (1H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 191.4, 142.1, 136.1, 132.3, 130.5, 114.2, 60.4, 31.5, 14.1; MS m/z: 174.1, [M+H]$^+$ calculated for C$_{11}$H$_{11}$NO$_2$: 190.1, found 190.2.

(2n) *2-(4-Acetylphenyl)-4-hydroxybutyronitrile*

Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a dark yellow oil; TLC R_f (60% hexanes, 40% ethyl acetate): 0.100; IR (neat) v_{max} (cm^{-1}): 3448, 2930, 2884, 2243, 1684, 1608, 1286, 1049, 830; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.99 (2H, d, J = 8.25 Hz), 7.49 (2H, d, J = 7.75 Hz), 4.20 (1H, t, J = 7.65 Hz), 3.89 (1H, m), 3.74 (1H, m), 2.62 (3H, s), 2.19 (1H, m), 2.11 (1H, m), 1.69 (1H, s) ;^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 197.3, 140.5, 137.2, 129.3, 127.8, 120.0, 58.7, 38.1, 33.8, 26.8; MS m/z: 186.1, 147.1, [M+H]$^+$ calculated for C$_{12}$H$_{13}$NO$_2$: 204.1, found 204.0.

General procedure F: 0.0303 g, 30% yield; $[\alpha]_D^{20}$= 3.906 ± 1.592 (c = 0.0013 g/mL in CHCl$_3$).

General Procedure H: 0.0369 g, 36% yield.

General Procedure I: [CitBr-Me] - 0.0132 g, 26% yield; $[\alpha]_D^{20}$= 0.275 ± 0.448 (c = 0.0073 g/mL in CHCl$_3$), [CitBr-But] - 0.0113 g, 22 % yield; $[\alpha]_D^{20}$=-1.176 ± 1.785 (c = 0.0017 g/mL in CHCl$_3$), [ButMetImid][Camph-R] - 0.0145 g, 29 % yield; $[\alpha]_D^{20}$= -2.531 ± 0.255 (c = 0.0079 g/mL in CHCl$_3$), [ButMetImid][Camph-S] - 0.0132 g, 26% yield; $[\alpha]_D^{20}$= 2.857 ± 1.924 (c = 0.0011 g/mL in CHCl$_3$).

(5j) *3-(4-Nitrophenyl)-4,5-dihydro-3H-furan-2-one*

Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as an orange oil; TLC R_f (60% hexanes, 40% ethyl acetate): 0.200; IR (neat) v_{max} (cm^{-1}): 3025, 2917, 1772, 1606, 1519, 1349, 1156, 749; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.24 (2H, d, J = 8.40 Hz), 7.51 (2H, d, J = 8.30 Hz), 4.54 (1H, td, J = 9.00 Hz, J = 2.65 Hz), 4.41 (1H, td, J = 9.85 Hz, J = 6.40 Hz), 3.96 (1H, dd, J = 10.15 Hz, J = 2.40 Hz),

2.80 (1H, m), 2.50 (1H, m);^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 175.9, 147.3, 129.0, 126.0, 124.0, 66.5, 45.5, 31.2; MS m/z: 164.1, 149.1, [M+H]$^+$ calculated for C$_{10}$H$_9$NO$_4$: 208.1, found 208.1.

General Procedure F: 0.0339 g, 50% yield; $[\alpha]_D^{20}$= 2.020 ± 1.015 (c = 0.0020 g/mL in CHCl$_3$).

General procedure G: 0.0319 g, 46% yield; $[\alpha]_D^{20}$= 1.634 ± 1.095 (c = 0.0018 g/mL in CHCl$_3$).

General Procedure H: 0.0590 g, 56% yield.

(5k) *4-(2-Oxo-4,5-dihydro-3H-fur-3-yl)benzonitrile*

General procedure H was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a yellow oil (0.0365 g, 31%); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.250; IR (neat) v$_{max}$ (cm^{-1}): 3015, 2915, 2229, 1770, 1609, 1508, 1374, 1157, 1023, 950; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.68 (2H, d, J = 8.60 Hz), 7.44 (2H, d, J = 8.40 Hz), 4.52 (1H, td, J = 8.80 Hz, J = 2.55 Hz), 4.39 (1H, m), 3.89 (1H, dd, J = 10.20 Hz, J = 2.35 Hz), 2.77 (1H, m), 2.46 (1H, m);^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 177.1, 132.6, 128.8, 126.1, 118.4, 111.7, 45.4, 31.1, 14.1; MS m/z: 144.1, 89.0, [M+H]$^+$ calculated for C$_{11}$H$_9$NO$_2$: 188.1, found 188.1.

(5m) *4-(2-Oxo-4,5-dihydro-3H-fur-3-yl)benzaldehyde*

General procedure H was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a yellow oil (0.0368 g, 31%); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.195; IR (neat) v$_{max}$ (cm^{-1}): 3025, 2914, 1768, 1701, 1609, 1374,

1212, 1157, 1024, 949, 821; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 10.02 (1H, s), 7.90 (2H, d, J = 8.55 Hz), 7.49 (2H, d, J = 8.30 Hz), 4.52 (1H, td, J = 8.85 Hz, J= 2.80 Hz), 4.40 (1H, m), 3.92 (1H, dd, J = 9.70 Hz, J = 1.75 Hz), 2.78 (1H, m), 2.49 (1H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm):192.0, 171.1, 143.6, 135.7, 130.1, 128.7, 60.4, 45.8, 31.2; MS m/z: 163.0, 87.2, [M+H]$^+$ calculated for C$_{11}$H$_{10}$O$_3$: 191.1, found 191.0.

(5o) 3-(4-Acetylphenyl)-4,5-dihydro-3H-furan-2-one

General procedure H was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a yellow oil (0.0425 g, 34%); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.167; IR (neat) v$_{max}$ (cm^{-1}): 3020, 2919, 1770, 1684, 1609, 1360, 1268, 1158, 1023, 958, 828; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.97 (2H, d, J = 8.15 Hz), 7.41 (2H, d, J = 8.50 Hz), 4.52 (1H, m), 4.38 (1H, m), 4.25 (1H,m), 2.76 (1H, m),2.60 (3H, s), 2.48 (1H, m); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 197.6, 176.9, 136.7, 129.0, 128.2, 125.7, 66.6, 45.6, 31.5, 26.6 ; MS m/z: 163.1, [M+H]$^+$ calculated for C$_{12}$H$_{12}$O$_3$: 205.1, found 205.1.

(7i) 5-Hydroxy-2-(4-nitrophenyl)valeronitrile

Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale red oil; TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.120; IR (neat) v$_{max}$ (cm^{-1}): 3388, 3025, 2956, 2243, 1600, 1522, 1348, 1111, 858; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.27 (2H, d, J = 7.90 Hz), 7.56 (2H, d, J = 7.65 Hz), 4.05 (1H, t, J = 7.20 Hz), 3.74 (2H, m), 2.075 (2H, m), 1.77 (2H, m), 1.60 (1H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm):

147.9, 142.8, 128.5, 124.7, 119.5, 60.3, 36.8, 32.8, 29.4; MS m/z: 203.0, [M+H]$^+$ calculated for $C_{11}H_{12}N_2O_3$: 221.1, found 221.0.

General Procedure F: 0.0561 g, 51% yield.

General Procedure H: 0.0644 g, 58% yield.

(7j) *2-(4-Cyanophenyl)-5-hydroxyvaleronitrile*

General procedure H was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a yellow oil (0.0391 g, 39%); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.100; IR (neat) v_{max} (cm^{-1}): 3508, 3040, 2934, 2230, 1606, 1506, 1404, 1259, 1054, 839 ; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.70 (2H, d, *J* = 8.30 Hz), 7.49 (2H, d, *J* = 8.35 Hz), 3.98 (1H, t, *J* = 7.65 Hz), 3.74 (3H, m), 3.15 (1H, t, *J* = 7.00 Hz), 1.71 (2H, m), 1.65 (1H, s);^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 140.9, 132.9, 128.9, 119.6, 118.1, 112.4, 60.4, 29.6, 20.7, 14.2; MS m/z: 172.0, 130.1, [M+H]$^+$ calculated for $C_{12}H_{12}N_2O$: 201.1, found 201.1.

(7n) *2-(4-Acetylphenyl)-5-hydroxyvaleronitrile*

General procedure H was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as an orange oil (0.0389 g, 36%); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.0638; IR (neat) v_{max} (cm^{-1}): 3493, 3040, 2941, 2244, 1683, 1601, 1511, 1251, 1171, 1054, 838, 735; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.04 (2H, d, *J* = 5.70 Hz), 6.93 (2H, d, *J* = 7.25 Hz), 3.94 (2H, m), 3.76 (1H, t, *J* = 6.20 Hz), 3.71 (1H, m), 3.16 (1H, t, *J*= 7.00 Hz), 2.76 (3H, s), 1.75 (2H, m), 1.62 (1H, s);^{13}C NMR (125 MHz,

CDCl$_3$) δ (ppm): 197.6, 129.1, 128.6, 128.3, 128.26, 127.6, 60.5, 22.4, 21.1, 17.0, 14.2; MS m/z: 202.1, 189.1, 147.1, [M+H]$^+$ calculated for C$_{13}$H$_{15}$NO$_2$: 218.1, found 218.2.

(14b) *4-Hydroxy-3-(3-iodo-5-nitro-2-pyridyl)butyronitrile*

Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a brown oil (0.0716 g, 43%); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.157; IR (neat) v$_{max}$ (cm^{-1}): 3415, 3055, 2937, 2275, 1608, 1520, 1332, 1293, 710; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 9.40 (1H, d, *J* = 2.55 Hz), 8.91 (1H, d, *J* = 2.60 Hz), 4.87 (1H, dd, *J* = 6.15 Hz, *J* = 2.80 Hz), 3.98 (1H, m), 3.89 (1H, m), 2.28 (2H, m), 1.62 (1H, s);^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 162.5, 144.2, 131.5, 127.8, 113.2, 60.6, 53.3, 36.3, 22.5; MS m/z: 316.0, [M+H]$^+$ calculated for C$_9$H$_8$IN$_3$O$_3$: 334.0, found 334.0. NOTE: With respect to general procedures F, when quenching the reaction mixture water was used, following by a washing with water, not HCl.

General procedure F: 0.0717 g, 43% yield; $[\alpha]_D^{20}$= -2.361 ± 0.093 (c = 0.0216 g/mL in CHCl$_3$).

General Procedure I: [CitBr-Me] - 0.0154 g, 22% yield; $[\alpha]_D^{20}$= 1.887 ± 0.758 (c = 0.0027 g/mL in CHCl$_3$), [CitBr-But] - 0.0145 g, 19 % yield; $[\alpha]_D^{20}$= 2.308 ± 0.774 (c = 0.0017 g/mL in CHCl$_3$).

(14c) *4-Hydroxy-3-[5-(trifluoromethyl)-2-pyridyl]butyronitrile*

Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as an orange oil; TLC R$_f$ (60 % hexanes, 40 % ethyl acetate): 0.109; IR (neat) v$_{max}$ (cm^{-1}): 3403, 2930, 2225, 1610, 1329, 1131, 1802, 1018; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.88 (1H, s), 8.01 (1H, dd, *J* = 8.20, 2.45 Hz), 7.65 (1H, d, *J* = 8.15 Hz), 4.40 (1H, t, *J* =

7.35 Hz), 3.98 (1H, m), 3.77 (1H, m), 2.30 (2H, m), 1.60 (1H, s);^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 171.9, 158.7, 146.9 (q, J = 4.1 Hz), 134.8, 121.8, 119.4, 59.0, 35.9, 21.0, 14.3; MS m/z: 213, 186, [M+H]$^+$ calculated for C$_{10}$H$_9$F$_3$N$_2$O: 231.1, found 231.0. NOTE: With respect to general procedures F, when quenching the reaction mixture water was used, following by a washing with water, not HCl.

General procedure F: 0.0450 g, 39% yield; $[\alpha]_D^{20}$= 1.923 ± 1.288 (c = 0.0016 g/mL in CHCl$_3$).

General Procedure I: [CitBr-Me] - 0.0136 g, 22% yield; $[\alpha]_D^{20}$= -0.870 ± 0.871 (c = 0.0023 g/mL in CHCl$_3$), [CitBr-But] - 0.0124 g, 20% yield; $[\alpha]_D^{20}$= 1.000 ± 2.003 (c = 0.0010 g/mL in CHCl$_3$).

(15c) 5-[5-(Trifluoromethyl)-2-pyridyl]-4,5-dihydro-3H-furan-2-one

General Procedure F was followed. NOTE: With respect to general procedures F, when quenching the reaction mixture water was used, following by a washing with water, not HCl. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a brown oil (0.0211 g, 18% yield); TLC Rf (60% hexanes, 40% ethyl acetate): 0.262; IR (neat) vmax (cm-1): 3055, 2919, 1772, 1607, 1328, 1130, 1081, 1011, 850; 1H NMR (500 MHz, CDCl3) δ (ppm): 8.84 (1H, s), 7.94 (1H, dd, J = 8.35 Hz, J = 2.60 Hz), 7.57 (1H, d, J = 8.00 Hz), 4.61 (1H, m), 4.44 (1H, m), 4.03 (1H, t, J = 8.80 Hz), 2.89 (1H, m), 2.72 (1H, m);13C NMR (125 MHz, CDCl3) δ (ppm): 175.9, 159.9, 146.6, 138.1, 134.1, (q, J = 3.50 Hz), 125.9, 123.3, 67.4, 47.5, 28.7; MS m/z: 186.0, 174.0, [M+H]+ calculated for C10H8F3NO2: 232.1, found 232.0. $[\alpha]_D^{20}$= 0.777 ± 0.388 (c = 0.0052 g/mL in CHCl$_3$).

(20a) *(2-Hydroxyethoxy)(4-nitrophenyl)acetonitrile*

General procedure F was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a yellow oil (0.0337 g, 30%); TLC R_f (60% hexanes, 40% ethyl acetate): 0.133; IR (neat) v_{max} (cm^{-1}): 3450, 3020, 2923, 2225, 1594, 1507, 1458, 1340, 1262, 1111, 858; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 8.31 (2H, J = 9.15 Hz), 7.00 (2H, J = 8.70 Hz), 4.53 (1H, m), 4.39 (1H, s), 4.27 (1H, m), 4.01 (2H, m), 1,91 (1H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 170.9, 130.7, 125.9, 123.5, 114.7, 60.2, 20.9, 14.3; MS m/z: 205.1, 177.0, 61.0, [M+H]$^+$ calculated for $C_{10}H_{10}N_2O_4$: 223.1, found 223.1.

(33) *7-Bromo-4-chromancarbonitrile*

General procedure H was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a red oil (0.0447 g, 28%); TLC R_f (60% hexanes, 40% ethyl acetate): 0.697; IR (neat) v_{max} (cm^{-1}): 3075, 2924, 2224, 1597, 1473, 1280, 1182, 1058, 812, 683; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.32 (1H, dd, J = 8.55 Hz), 7.26 (1H, s), 6.90 (1H, d, J = 8.80 Hz), 4.33 (1H, m), 3.22 (1H, m), 2.48 (1H, m), 2.34 (1H, m), 2.19 (1H, m) ;^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 171.2, 134.1, 132.1, 130.4, 124.7, 122.0, 117.5, 60.5, 21.2, 14.2; MS m/z: 227.1, 205.1, 187.2, 163.1, 149.1, [M+H]$^+$ calculated for $C_{10}H_8BrNO$: 238.0, found 238.1, 240.1.

(34i) *3-(4-Nitrophenyl)-3,4,5,6-tetrahydro-2-pyranone*

General procedure H was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a pale yellow oil (0.0218 g, 16%); TLC R_f (60% hexanes, 40% ethyl acetate): 0.133; IR (neat) v_{max} (cm^{-1}): 3055, 2946, 1744, 1592, 1517,

1346, 1263, 1173, 1111, 847, 733; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.43 (2H, d, J = 8.40 Hz), 6.94 (2H, d, J = 8.80 Hz), 4.51 (2H, m), 3.89 (1H, t, J = 8.75 Hz), 2.35 (1H, m), 2.09 (3H, m);^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 178.2, 163.9, 129.4, 125.9, 123.9, 69.3, 46.9, 28.0, 14.2; MS m/z: 176.0, 150.1, 101.1, [M+H]$^+$ calculated for C$_{11}$H$_{11}$NO$_4$: 222.1, found 222.1.

(34j) 4-(2-Oxo-3,4,5,6-tetrahydro-3-pyranyl)benzonitrile

General procedure H was followed. Flash column chromatography (60% hexanes, 40% ethyl acetate) yields the product as a yellow oil (0.0283 g, 23%); TLC R$_f$ (60% hexanes, 40% ethyl acetate): 0.0625; IR (neat) v$_{max}$ (cm^{-1}): 3040, 2961, 2223, 1708, 1606, 1511, 1274, 1178, 1008, 840; ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.65 (2H, d, J = 8.05 Hz), 7.37 (2H, 8.90 Hz), 4.48 (2H, m), 3.82 (1H, m), 2.33 (1H, m), 2.07 (3H, m);^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 178.4, 134.1, 132.8, 129.6, 115.1, 103.9, 67.8, 33.1, 28.3, 21.4; MS m/z: 172.1, 101.2, [M+H]$^+$ calculated for C$_{12}$H$_{11}$NO$_2$: 202.1, found 202.2.

5.8 Synthesis of Chiral Ionic Liquids

(29) *S-Citronellyl Bromide*

 In a round bottom flask triphenyl phosphine (5.036 g, 19.2 mmol), imidazole (1.307 g, 19.2 mmol) and bromine (0.983 mL, 19.2 mmol) were combined with anhydrous dichloromethane (75.0 mL). *S*-(-)-citronellol (2.92 mL, 16.0 mmol) in anhydrous dichloromethane (5.0 mL) was added to the stirring solution. The flask was back filled with nitrogen and to stirred for 3.0 hrs at room temperature, then concentrated. Flash column chromatography (100% hexanes) yielded the product as a clear liquid (2.8750 g,

82%); TLC R$_f$ (80% hexanes, 20% ethyl acetate): 0.577; IR (neat) v$_{max}$ (cm^{-1}): 2965, 2925,

1451, 1378, 648; ^{1}H NMR (500 MHz, CDCl3) δ (ppm): 5.08 (1H, tt, J = 7.0 Hz, J = 1.30

Hz), 3.43 (2H, m), 1.99 (2H, m), 1.89 (1H, m), 1.70 (3H,s), 1.62 (3H, s), 1.35 (2H, m),

1.20 (2H, m), 0.913 (3H, d, J = 6.0 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 131.6, 124.4,

40.0, 36.5, 32.1, 25.8, 25.3, 18.6, 17.8; MS m/z: 151.1, 137.0, 83.2, 69.2, [M+H]$^+$

calculated for C$_{10}$H$_{19}$Br: 219.1, found 219.0 and 221.0.

General Procedure K. Equal molar amounts of citronellyl bromide (2.4108 g, 11.0 mmol,

1.0 equiv) and the respective 1-alkyl-1H-imidazole (11.0 mmol, 1.0 equiv) were combined

into a heavy walled round bottom flask, backfilled with nitrogen, sealed and heated at 40

ºC for 5 days. Contents were transferred to a round bottom flask and placed under

vacuum (0.1-0.001 Torr) at 40 ºC 2 days.

(30a) 1-[(3S)-3,7-Dimethyloct-6-enyl]-3-methyl-1H-imidazolium bromide / [citBr-me]

General procedure K was followed yielding a pale yellow, viscous oil (3.0689 g, 90%);

IR (neat) v$_{max}$ (cm^{-1}): 3137, 2959, 1571,1456, 1377, 1171, 732; ^{1}H NMR (500 MHz,

CDCl3) δ (ppm): 10.28 (1H,s), 7.80 (1H, s), 7.57 (1H,s), 5.05 (1H, t, J = 8.5 Hz), 4.35

(2H, m), 4.15 (3H,s) 2.05 (3H, m), 1.67 (3H, s), 1.57 (3H, s), 1.38 (2H, m), 1.22 (2H, m),

0.99 (3H, d, J = 7.0 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 136.9, 131.7, 124.1, 122.1,

48.2, 37.3, 36.8, 36.6, 29.9, 25.7, 25.2, 19.1, 17.8; optical rotation: $[\alpha]_D^{20}$= 1.799 ± 0.172

(c = 0.0117 g/mL in CHCl$_3$).

(30b) *1-Butyl-3-[(3S)-3,7-dimethyloct-6-enyl]-1H-imidazolium Bromide / [citBr-but]*

General procedure K was followed yielding a clear viscous oil, (3.1409 g, 83%); IR (neat) v_{max} (cm⁻¹): 3052, 2960, 1563, 1459, 1377, 1167, 752; ¹H NMR (500 MHz, CDCl3) δ (ppm): 10.44 (1H, s), 7.725 (1H, t, *J* = 2.0 Hz), 7.60 (1H, t, *J* = 2.05 HZ), 5.05 (1H, tt, *J* = 7.40 Hz, 1.35 Hz), 4.38 (4H, m), 1.94 (5H, m), 1.76 (1H, m), 1.67 (3H, s), 1.59 (3H, s), 1.51 (1H, m), 1.39 (3H, m), 1.22 (1H, m), 0.99 (3H, d, *J* = 6.35 Hz), 0.963 (3H, t, *J* = 7.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 134.0, 131.8, 124.1, 122.5, 122.0, 49.8, 48.3, 37.4, 36.7, 32.3, 29.9, 25.7, 25.2, 19.4, 19.1, 17.7, 13.5; optical rotation: $[\alpha]_D^{20}$ = 2.453 ± 0.198 (c = 0.0102 g/mL in CHCl₃).

General Procedure L. Equal molar amounts of (1*S* or 1*R*)-10-camphorsulfonic acid (0.9292g, 4.0 mmol, 1.0 equiv) and 1-butyl-3-methylimidazolium chloride (0.6987 g, 4.0 mmol, 1.0 equiv) were combined into a heavy walled reaction flask with 4mL of acetone, backfilled with nitrogen, sealed and heated at 50 ºC for 24 hours. Contents were transferred to a round bottom flask and acetone as removed using rotary evaporation.

(31a) *1-Butyl-3-methylimidazolium R-camphorsulfonate / [butmetimid][camph-R]*

General procedure L was followed yielding a reddish-brown, viscous oil (1.4375 g, 97%); IR (neat) v_{max} (cm⁻¹): 3147, 3096, 2959, 1742, 1573, 1456, 1169, 1037, 914 ; ¹H NMR (500 MHz, CDCl3) δ (ppm): 9.71 (1H, s), 7.48 (1H, t, *J* = 1.90 Hz), 7.39 (1H, t, *J* = 1.87 Hz), 4.29 (2H, t, *J* = 7.50 Hz), 4.06 (3H, s), 3.47 (1H, d, *J* = 14.90 Hz), 3.01 (1H, d, *J* = 14.90 Hz), 2.56 (1H, m), 2.37 (1H, dt, *J* = 19.65 Hz, *J* = 4.25 Hz), 2.08 (1H, t, *J* = 4.75 Hz), 2.02 (1H, m), 1.88 (3H, m), 1.72 (1H, m), 1.38 (3H, m), 1.10 (3H, s), 0.95 (3H, t, *J* =

7.45 Hz), 0.86 (3H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 216.6, 137.5, 123.7, 122.0, 58.3, 49.8, 48.1, 48.0, 42.6, 42.7, 36.6, 32.1, 27.0, 24.9, 19.9, 19.8, 19.5, 13.5; $[\alpha]_D^{20}$ = -21.859 ± 0.372 (c = 0.0080 g/mL in CHCl$_3$).

(31b) *1-Butyl-3-methylimidazolium S-camphorsulfonate / [butmetimid][camph-S]*

General procedure L was followed yielding a reddish-brown, viscous oil (1.4478 g, 98%); IR (neat) ν$_{max}$ (cm^{-1}): 3147, 3099, 2960, 1742, 1573, 1456, 1170, 1038, 915; ^{1}H NMR (500 MHz, CDCl3) δ (ppm): 9.78 (1H, s), 7.45 (1H, t, *J* = 1.90 Hz), 7.36 (1H, t, *J* = 1.87 Hz), 4.29 (2H, t, *J* = 8.40 Hz), 4.07 (3H, s), 3.45 (1H, d, *J* = 14.70 Hz), 3.02 (1H, d, *J* = 15.00 Hz), 2.56 (1H, m), 2.37 (1H, dt, *J* = 18.20 Hz, *J* = 4.61 Hz), 2.08 (1H, t, *J* = 4.80 Hz), 2.03 (1H, m), 1.89 (3H, m), 1.74 (1H, m), 1.39 (3H, m), 1.10 (3H, s), 0.95 (3H, t, *J* = 7.25 Hz), 0.86 (3H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 216.6, 137.7, 123.6, 121.9, 58.3, 49.8, 48.1, 48.0, 42.8, 42.6, 36.7, 32.1, 27.0, 24.9, 19.8, 19.7, 19.5, 13.5; $[\alpha]_D^{20}$ = 22.271 ± 0.333 (c = 0.0089 g/mL in CHCl$_3$).

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